Supporting Information

Utilizing Biocatalysis and a Sulfolane-mediated Reductive Acetal Opening to Access Nemtabrutinib from Cyrene

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1. General Experimental Details

Unless otherwise noted, all reactions were performed under N_2-atmosphere. Heating of reaction mixtures was performed using a temperature-controlled hotplate equipped with stirring and an active thermocouple. Stirring of reaction mixtures was performed using magnetic stirring, unless noted otherwise. Evaporation and concentration *in vacuo* steps were performed using variable vacuum *via* a vacuum-controlled (ca. 400–40 mmHg) rotary evaporator. Column chromatography was performed using a Teledyne ISCO CombiFlash® Rf+ chromatography system using prepacked single-use silica packed cartridges (RediSep Rf Gold Normal-Phase Silica, 20–40 micron average particle size, 60 Å average pore size).

Materials.

Reagents were purchased in reagent grade from commercial suppliers and used without further purification, unless otherwise described. Cyrene™ was purchased from Sigma-Aldrich or Circa Group directly. Sulfolane was purchased from Sigma-Aldrich or Alfa Aesar and used as received. Anhydrous solvents (acetonitrile, anisole, cyclopentyl methyl ether, dichloromethane, 1,4-dioxane, DMSO, and 1,2-dichloroethane, *N*,*N*-dimethylacetamide, *N*-methyl-2-pyrrolidone, 1,2-dimethoxyethane) were obtained from Sigma-Aldrich as part of their Sure/Seal™ bottles product line. NMR kinetic experiments utilized anisole-d_8 which was purchased from Sigma-Aldrich. CD_2Cl_2, CD_3OD, and DMSO-d_6 were purchased from Cambridge Isotope Laboratories in sealed ampules and used as received.

Instrumentation.

Nuclear Magnetic Resonance Spectroscopy (NMR). Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra, and proton-decoupled fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded at 25 °C on a Bruker 500 MHz AVANCE III HD spectrometer equipped with a SmartProbe. Chemical shifts for proton and carbon are reported in parts per million downfield from tetramethylsilane and are referenced to residual proton resonances of the NMR solvent according to values reported in the literature.[1] ^{19}F NMR spectra are not calibrated by an internal reference. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) quoted in hertz (Hz) and integration.

Analysis of crude reaction mixtures during the reaction optimization for amine **3a** and **1a** and wt% purity analysis of isolated products was performed by quantitative ^{1}H NMR using the following parameters: D1 = 60 s, NS = 8, and either maleic acid, CH_2Br_2 or 1,3,5-trimethoxybenzene as the internal standard.

Analysis of reaction profiles, and quantification of starting material, product, and byproducts, was done using quantitative ^{1}H NMR (D1 = 20 seconds, number of scans = 8, 10-degree flip angle), and ^{19}F NMR (D1 = 10 seconds, number of scans = 4, 10-degree flip angle) analysis. Octafluoronaphthalene (0.49 equiv) was used as an internal standard for ^{19}F NMR.

Gas Chromatography (GC). GC-FID analysis was performed using a DB-624 (6% cyanopropylphenyl/94% dimethyl polysiloxane) GC column (20 m x 0.18 mm, 1 μm) and operating at an injection port temperature of 220 °C and an FID detector temperature of 250 °C. The oven temperature was increased at a rate of 20 °C/minute from 80 °C at t = 0 to 250 °C, and then held for 10 minutes using a constant hydrogen flow of 1 mL/minute. Typical Retention Times: Compound **3a** (4.8 minutes), Compound **3b** (4.7 minutes).

UPLC. Analysis of reactions to optimize the reaction conditions to access amine **Bn-1a** was performed by UPLC analysis using an Agilent 1290 system equipped with a UV detector (λ = 210 nm) and an Eclipse

[1] Fulmer, G. R.; Miller, A. J. M. Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M. Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.

Plus C18 column (50 mm x 2.1 mm, 1.8 µm) operating at 35 °C with a flow of 1 mL/min. The binary eluent mixture of eluent A = 0.5 mM $Na_2B_4O_7$ in H_2O and eluent B = acetonitrile was used with a 1.5-2 min gradient starting from 95%A and 5%B to 5%A and 95% B.

UPLC Method for HRMS. HRMS sample analysis was performed using a Waters Acquity UPLC system interfaced with Thermo Scientific Orbitrap Mass Analyzer and an ESI source temperature set to 263 °C. Samples were dissolved in acetonitrile at a 0.01 mM concentration, and 2 µL injection volumes were used for analysis. The Waters UPLC was equipped with an ACQUITY UPLC™ CSH Column (130 Å pore size, 1.7 µm particle size, 2.1 mm internal diameter, 150 mm length; part number 186005408) operating at a 0.4 mL/min flow rate of a binary eluent mixture (eluent A and B, prepared as described below). A column temperature of 45 °C was used for all analytes. A column temperature of 60 °C was used for compound **4**. The 5 min method used the following eluent gradient: a gradient from 90% A/10% B at t = 0 min held until 0.5 min, to 10% A/90% B at t = 1.0 min held until 4.0 min, and a subsequent gradient to achieve 90% A and 10% B at t = 4.1 min and final hold until t = 5.0 min. Eluent Preparation: A = 0.1% v/v formic acid in H_2O, B = 0.1% v/v formic acid in acetonitrile.

Abbreviations. ATA = Amine Transaminase, Bn = Benzyl, Boc = *tert*-butyloxycarbonyl, calc. = calculation, Cyrene™ = (1S,5R)-6,8-dioxabicyclo[3.2.1]octan-4-one, DMSO = dimethyl sulfoxide, ESI = electrospray ionization, equiv = equivalents, GC = gas chromatography, UPLC = ultra-high pressure liquid chromatography, HRMS = high resolution mass spectrometry, PLP = (4-Formyl-5-hydroxy-6-methylpyridin-3-yl)methyl dihydrogen phosphate or pyridoxal-5′-phosphate, QToF = quadrupole time of flight, Tf = Trifluoromethanesulfonate, 2-MeTHF = 2-methyltetrahydrofuran, THF = tetrahydrofuran, Ts = *para*-toluenesulfonate.

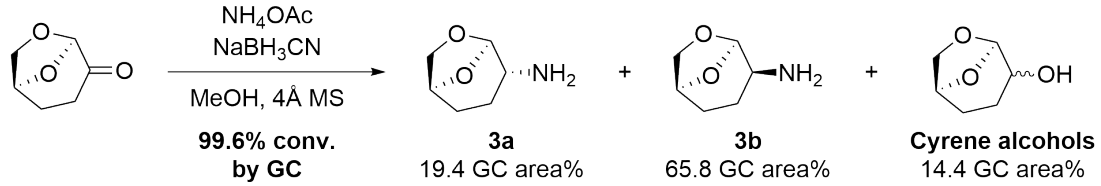
Safety. Please note that reaction conditions to form **Bn-1a** and **1a·TsOH** require handling of BH_3·THF or involve the *in-situ* generation of H_2 and diborane gas. H_2 gas is flammable, BH_3·THF and diborane are highly reactive, flammable and acutely toxic. Appropriate PPE and engineering controls should be used when performing those reactions. Adequate process safety analysis and equipment selection should be performed prior to scaling-up those reaction conditions. For more information see reference 22 in the manuscript.

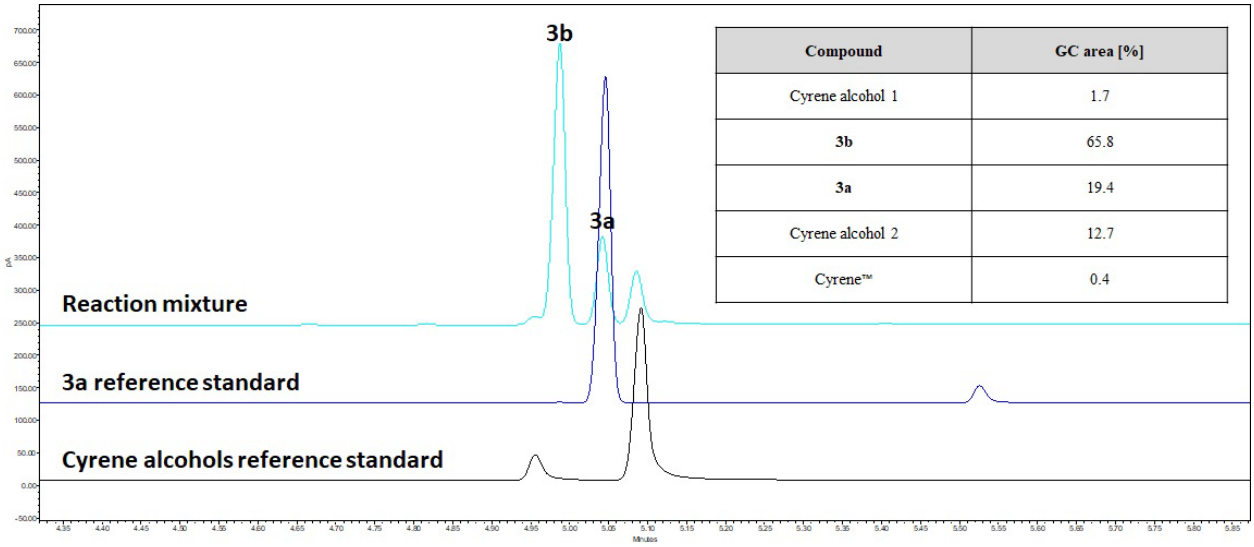
2. Biocatalytic Transamination

2.1. Reductive Amination of Cyrene™

A 40 mL vial equipped with a stir bar was charged with Cyrene™ (500 mg, 0.4 mL, 3.9 mmol, 1.0 equiv). A solution of NH_4OAc (3.0 g, 39.0 mmol, 10.0 equiv) in methanol (8 mL) was added followed by heat-activated 3 Å molecular sieves (MS) (550 mg). Sodium cyanoborohydride (245 mg, 3.9 mmol, 1.0 equiv) was added and the reaction was stirred at room temperature for 5.5 hours until full conversion was observed by ^1H NMR. An aliquot was diluted 4 times with methanol, filtered, and analyzed by GC to determine the product distribution (Scheme S1, Figure S1).

Scheme S1. Reductive amination of Cyrene™ with $NaBH_3CN$.





Compound	GC area [%]
Cyrene alcohol 1	1.7
3b	65.8
3a	19.4
Cyrene alcohol 2	12.7
Cyrene™	0.4

Figure S1. Gas chromatogram (GC) of the reductive amination of Cyrene™ with $NaBH_3CN$.

2.2. Screening of Transaminase Enzymes

General Procedure 1. Cyrene™ (500 mg, 0.4 mL, 3.9 mmol, 1.0 equiv) and (4-formyl-5-hydroxy-6-methylpyridin-3-yl)methyl dihydrogen phosphate (PLP, 10 mg, 40 µmol, 1 mol%) were dissolved in 9.6 mL buffer solution (0.1 M $Na_2B_4O_7$ 10·H_2O, 1 M isopropylamine, 2.5 equiv relative to Cyrene™, pH 9.5) to reach a total volume of about 10 mL and a Cyrene™ concentration of 50 g/L. 500 µL (25 mg, 0.39 mmol, 1.0 equiv of Cyrene™) of this solution were added to 2.5 mg of transaminase variant (lyophilized cell-free powder, 10 wt% relative to Cyrene™) in vials and incubated at 35 °C with shaking. After 20 hours, 100 µL of each reaction was diluted with 600 µL of 0.5% maleic acid (internal standard) in D_2O for analysis by quantitative ^1H NMR (see Figure S2 for a representative ^1H NMR and Table S1 and S2 for results.)

Scheme S2. Biocatalytic transaminase reaction.

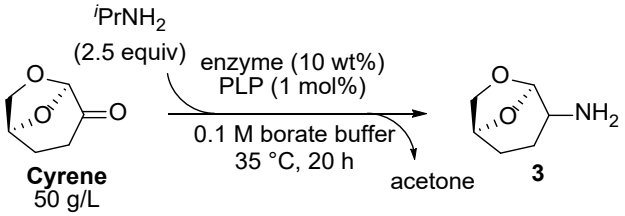


Table S1. Screening of Codexis® transaminase enzymes.

Entry	Transaminase Enzyme	Assay Yield [%]	3a:3b d.r.
1	ATA-007	11	1:1
2	ATA-009	10	1.1:1
3	ATA-013	65	2.5:1
4	ATA-014	74	2.3:1
5	ATA-015	68	1.8:1
6	ATA-016	100	1.7:1
7	ATA-024	100	1.3:1
8	ATA-036	67	1:1.6
9	ATA-234	86	1:6.9
10	ATA-273	100	1:4.8
11	ATA-303[2]	95	1.9:1
12	**ATA-426[3]**	**57**	**17:1**
13	CDX-010	91	1.5:1
14	CDX-017[4]	72	1.1:1

Table S2. ATA-426 enzyme loading study.

Entry[a]	ATA-426 Loading [wt%]	Assay Yield [%]	3a:3b d.r.
1	**20**	**71%**	**17:1**
2	15	62%	18:1
3	10	57%	17:1
4	5	42%	>20:1

[a] *Reaction conditions according to general protocol 1, above.*

[2] Limanto, J. et al. *Org. Lett.* **2014**, *16*, 2716–2719.
[3] Yasuda, N. et al. *Org. Process Res. Dev.* **2017**, *21*, 1851–1858.
[4] Savile, C. K. et al. *Science* **2010**, *329*, 305–309.

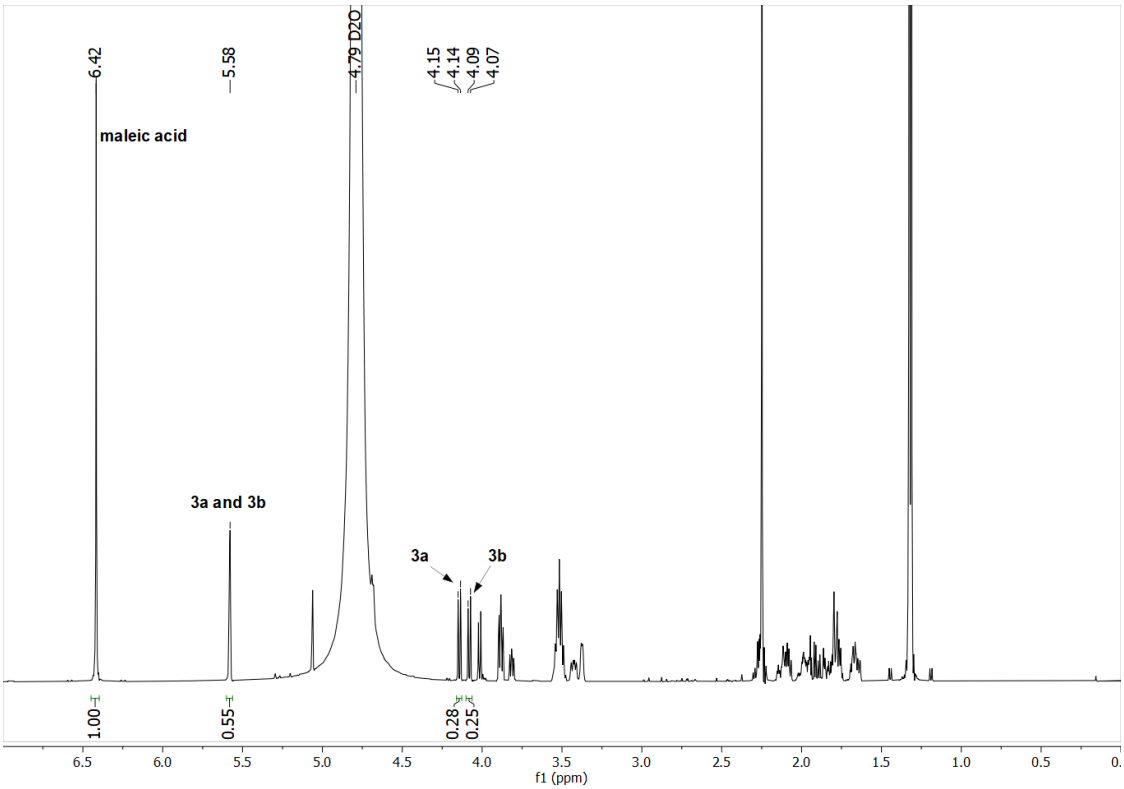


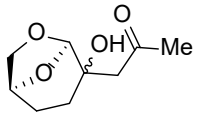
Figure S2. ^{1}H NMR at 500 MHz in D_2O of the crude reaction mixture for entry 14 of Table S1. Integration of the singlet at 5.58 ppm was used to calculate the combined assay yield of **3a** and **3b**. The diastereomeric ratio was determined via integration of the doublets at 4.15 ppm (**3a**) and 4.08 ppm (**3b**).

2.3. Transaminase Reactions on Gram-Scale

Representative procedure for Entry 7 of Table 1. In a 100 mL Mettler Toledo EasyMax vessel equipped with an overhead stirrer, (4-formyl-5-hydroxy-6-methylpyridin-3-yl)methyl dihydrogen phosphate (PLP) (41 mg, 160 µmol, 0.7 mol%) was dissolved in 0.1 M $Na_2B_4O_7 \cdot 10\ H_2O$ buffer (60 mL, pH 9.5) containing isopropylamine (4.4 mL, 51.5 mmol, 2.2 equiv). Cyrene™ (3.0 g, 23.4 mmol, 1.0 equiv) and transaminase enzyme ATA-426 (600 mg, 20 wt%) were then added at room temperature. The mixture was heated to 45 ºC and agitated for 21 h. During the reaction, vacuum (400-450 mbar) and airflow were applied to remove the acetone generated. The pH was monitored throughout the reaction using a pH probe. The pH was adjusted manually over the course of the reaction to keep the pH above 7.5 (with 5 N aqueous NaOH) yielding a solution of **3a** (2.76 g, 21.4 mmol, 91% assay yield, 24:1 d.r.). The assay yield was determined by diluting an aliquot of the reaction mixture by a factor of 6 using a 0.5% solution of maleic acid (internal standard) in D_2O.

Higher concentrations of the borate buffer, 0.25 M and 0.40 M concentrations were also explored following the reaction conditions above using a 100 g/L Cyrene concentration. The assay yields were 95% and 94%, respectively, and a pH adjustment was still required. Using a 0.1 M borate buffer at 100 g/L Cyrene yielded **3a** in 93% assay yield, see Section 2.5). Therefore, higher buffer concentrations did not provide a significant benefit.

2.4. Characterization of Compound 4

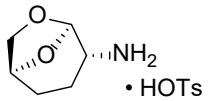


4

1-((1*S*,5*R*)-4-hydroxy-6,8-dioxabicyclo[3.2.1]octan-4-yl)propan-2-one (4). A 2.5 M solution of *n*-butyllithium in hexanes (62.3 mL, 156 mmol, 0.95 equiv) was added over 2 h and 15 minutes to a solution of diisopropylamine (21.8 mL, 156 mmol, 0.95 equiv) in cyclopentyl methyl ether (210 mL) in a 500 mL round bottom flask at 0 °C. The resulting solution was stirred for 1 h and then cooled to −78 °C. Acetone (10.8 mL, 148 mmol, 0.9 equiv) was added slowly to maintain the reaction temperature below −68 °C and the resulting mixture was stirred for an additional 2 h at −78 °C. Cyrene™ (16.8 mL, 164 mmol, 1.00 equiv) in cyclopentyl methyl ether (10 mL) was added and the reaction was allowed to stir overnight at −78 °C. The reaction was then quenched with a saturated aqueous solution of NH_4Cl (200 mL) at room temperature. The phases were separated, and the organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain the crude product as an oil. The crude product was purified by column chromatography using hexanes/ethyl acetate to yield compound **4**, a mixture of two diastereomers, as a pale-yellow oil (8.8 g, 94.5 wt% purity, 44.7 mmol, 27% yield, 1.2:1 d.r.). The isolated material contained 4.2 GC area% Cyrene™ that could not be separated.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.10 (s, 1H), 5.08 (s, 1H), 4.46 (br s, 2H), 3.84 – 3.79 (m, 2H), 3.76 – 3.70 (m, 2H), 3.17 (br s, 2H), 2.85 (d, *J* = 16.3 Hz, 1H), 2.63 (d, *J* = 16.3 Hz, 1H), 2.56 (s, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 2.09 – 2.01 (m, 1H), 1.88 – 1.57 (m, 6H), 1.55 – 1.49 (m, 1H), 1.45 – 1.40 (m, 1H) ppm. **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 210.18 (CO), 209.47 (CO), 104.37 (CH), 103.90 (CH), 73.73 (CH), 73.33 (CH), 72.17 (C_q), 71.19 (C_q), 68.32 (CH_2), 67.38 (CH_2), 49.93 (CH_2), 47.43 (CH_2), 32.32 (CH_3), 32.30 (CH_3), 29.85 (CH_2), 28.40 (CH_2), 27.34 (CH_2), 25.64 (CH_2) ppm. **HRMS** m/z calc. for $[C_9H_{15}O_4]$ ($[M+H]^+$): 187.0965, found: 187.0961.

2.5. Synthesis and Characterization of 3a·TsOH and 3b·TsOH



3a•HOTs

(1*S*,4*R*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-4-aminium 4-methylbenzene-1-sulfonate (3a·TsOH). In a 1 L jacketed round bottom flask, (4-formyl-5-hydroxy-6-methylpyridin-3-yl)methyl dihydrogen phosphate (PLP) (1.0 g, 4.0 mmol, 1.0 mol%) was dissolved in 0.1 M $Na_2B_4O_7 \cdot 10\ H_2O$ buffer (500 mL, pH 9.5) containing 1.56 M isopropylamine (67 mL, 778 mmol, 2 equiv). Transaminase enzyme ATA-426 (10 g, 20 wt%) was then added and dissolved at room temperature. Cyrene™ (49.9 g, 389 mmol, 1.0 equiv) was then added, and the mixture was heated to 33-37 ºC and agitated with overhead stirring for 27 h. During the reaction, vacuum (400-450 mbar) and airflow were applied to remove the acetone generated. The pH was monitored at various points during the reaction using a pH probe and was adjusted if needed to keep the pH between 7.9 and 8.6 (four additions of a total of 17.5 mL of 50 wt% aqueous NaOH) yielding a solution of **3a** (46.8 g, 362 mmol, 93% assay yield, 17:1 d.r.). The assay yield was determined by diluting an aliquot of the reaction mixture by a factor of 6 using a 0.5% solution of maleic acid (internal standard) in D_2O.

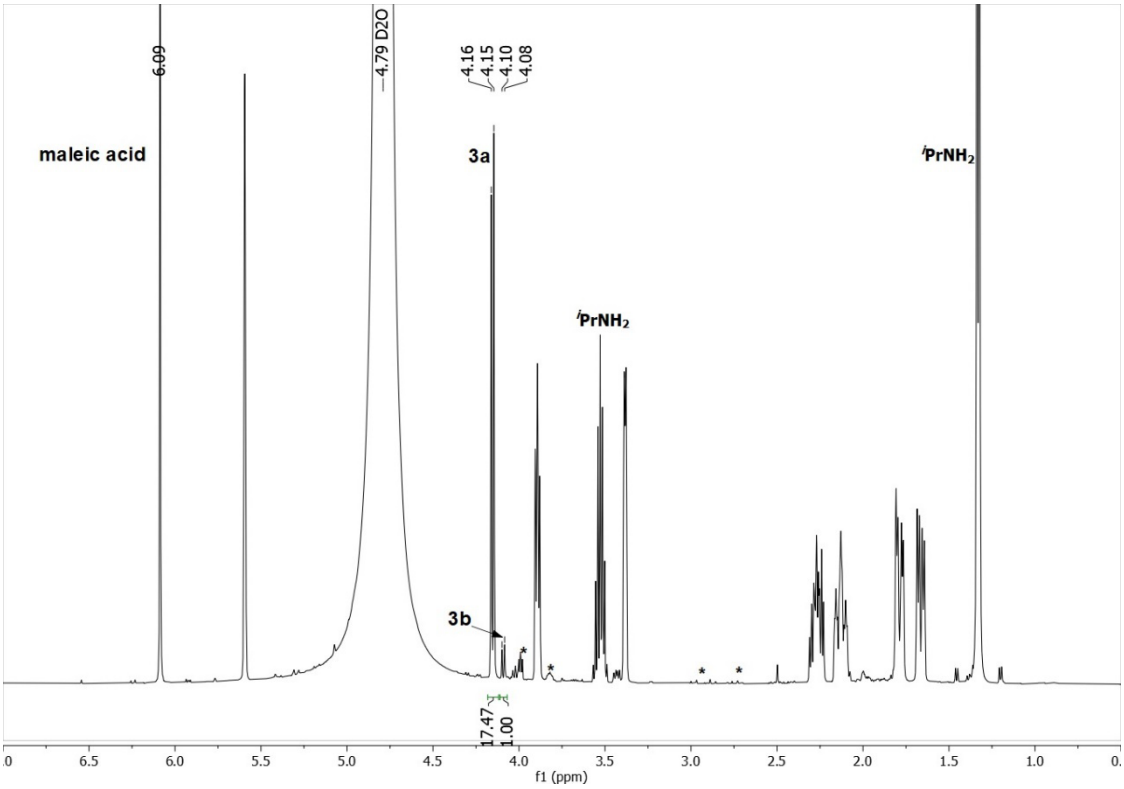


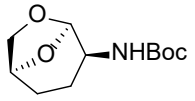
Figure S3. ^{1}H NMR at 500 MHz in D_2O of the crude reaction mixture. The * indicates compound **4**.

Next, the solution pH was adjusted to 13.4 by adding 50 wt% aqueous NaOH solution (28 mL). The mixture was cooled to 10-15 °C and potassium carbonate (83.3 g) was added in 3 portions to the stirring solution maintaining the temperature below 25 °C. 2-MeTHF (300 mL) was added, and the resulting mixture was stirred at room temperature overnight to allow for enzyme denaturing. The denatured protein solids were then filtered off. The filter cake was washed with 2-MeTHF (3 x 50 mL). The two phases of the filtrate were separated, and the aqueous phase was extracted with 2-MeTHF (75 mL). The combined organic layers were then concentrated under reduced pressure to remove isopropylamine to <0.5 mol% with respect to the Cyrene™ amine. The resulting crude solution was then diluted with 2-MeTHF to a total volume of 200 mL, and the water content (KF) was adjusted to 3-3.6 wt% by adding water. A solution of *para*-toluenesulfonic

acid monohydrate (73.6 g, 387 mmol, 0.99 equiv) in 2-MeTHF (150 mL) was added dropwise over 4 h at 40 °C, the resulting slurry was cooled to room temperature and aged for 2 h. The solids were filtered, washed with wet 2-MeTHF (50 mL, KF = 2 wt%) followed by dry 2-MeTHF (50 mL), and then dried overnight at 50 °C under vacuum with nitrogen sweep to yield **3a·TsOH** as a white solid (92.1 g, 99.4 wt% purity, 306 mmol, 79% yield, >20:1 d.r.).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.02 (br s, 3H), 7.57 – 7.39 (m, 2H), 7.14 – 7.13 (m, 2H), 5.40 (s, 1H), 4.59 – 4.58 (m, 1H), 3.97 (d, *J* = 7.4 Hz, 1H), 3.74 – 3.56 (m, 1H), 3.17 – 2.99 (m, 1H), 2.29 (s, 3H), 2.14 – 1.94 (m, 2H), 1.62 – 1.50 (m, 1H), 1.49 – 1.35 (m, 1H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 145.24 (C_q), 137.94 (C_q), 128.17 (CH), 125.47 (CH), 98.61 (CH), 73.07 (CH), 66.99 (CH_2), 47.44 (CH), 23.21 (CH_2), 20.78 (CH_3), 18.59(CH_2) ppm. **HRMS** m/z calc. for [$C_6H_{12}NO_2$] ([M+H]$^+$): 130.0863, found: 130.0861.

The relative and absolute stereochemistry of **3a·TsOH** was confirmed by X-ray crystallography, see Section 6.1.

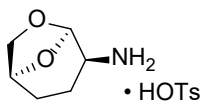


Boc-3b

***tert*-Butyl ((1*S*,4*S*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-4-yl)carbamate (Boc-3b).** In a 1 L 3-necked vessel equipped with an overhead stirrer, (4-formyl-5-hydroxy-6-methylpyridin-3-yl)methyl dihydrogen phosphate (PLP) (600 mg, 2.4 mmol, 1.0 mol%) was dissolved in 0.1 M $Na_2B_4O_7 \cdot 10\ H_2O$ buffer (600 mL, pH 9.5) containing 1.50 M isopropylamine (50 mL, 585 mmol, 2.5 equiv). ATA-234 (4.5 g, 15 wt%) was then added and dissolved at room temperature. Cyrene™ (30 g, 234 mmol, 1.0 equiv) was added, and the mixture was heated to 45 ºC and agitated for 22 h. During the reaction, vacuum (400 mbar) and nitrogen flow were applied to remove the acetone generated. The stream was then cooled to room temperature and the pH was adjusted to pH 12 using 50 wt% aqueous NaOH. To remove isopropylamine, the reaction mixture was distilled at 80 mbar and 48 °C jacket temperature using an air sweep. During the distillation additional 50 wt% aqueous NaOH was charged to maintain the pH at 12. THF (200 mL) was charged, and the distillation was continued until isopropylamine was < 0.5 wt% by ^{1}H NMR. The remaining aqueous solution was filtered over celite to remove the denatured enzyme yielding an aqueous solution of **3b** (195 mmol, 83% assay yield, 5:1 d.r.).

To the aqueous solution at pH 12 was then added to a solution of di-*tert*-butyl dicarbonate (Boc_2O, 51.1 g, 234 mmol, 1.0 equiv.) in THF (70 mL) *via* syringe pump over 40 min upon which the pH dropped to pH 7.55. The pH was adjusted to pH 12 using 50 wt% aqueous NaOH and the reaction was stirred at room temperature for 22 h. Methyl *tert*-butyl ether (500 mL) was then charged, and the mixture was stirred for 30 min. The mixture was filtered using methyl *tert*-butyl ether, the layers of the filtrate were separated, and the aqueous layer was extracted with methyl *tert*-butyl ether (300 mL). The combined organic layers were washed with 20 wt% aqueous NaCl solution (300 mL) and then concentrated. The isolated solid was recrystallized twice from methylcyclohexane to yield **Boc-3b** as a white solid (32.3 g, 141 mmol, 60% yield, 44:1 d.r).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 6.71 (d, *J* = 7.5 Hz, NH, 1H), 5.14 (s, 1H), 4.47 (s, 1H), 3.76 (d, *J* = 7.1 Hz, 1H), 3.61- 3.59 (m, 1H), 3.38 – 3.34 (m, 1H), 1.77 – 1.67 (m, 1H), 1.67 – 1.47 (m, 3H), 1.37 (s, 9H) ppm; **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 154.95 (CO), 101.06, 77.77 ($C(CH_3)_3$), 72.12, 67.51 (CH_2), 50.59, 28.18 (CH_3), 27.46 (CH_2), 21.42 (CH_2) ppm. **HRMS** m/z calc. for [$C_{11}H_{20}NO_4$] ([M+H]$^+$): 230.1387, found: 230.1383.

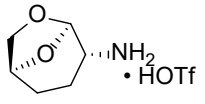


3b•HOTs

(1*S*,4*S*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-4-aminium 4-methylbenzene-1-sulfonate (3b·TsOH). Boc-3b (31.7 g, 138 mmol, 1.0 equiv) was dissolved in a solution of *para*-toluenesulfonic acid monohydrate (79 g, 415 mmol, 3 equiv) in 2-MeTHF (159 mL) and the reaction was heated to 35 °C overnight. The resulting slurry was cooled to room temperature and the solids were filtered, washed with 2-MeTHF (100 mL), and then dried under vacuum yielding **3b·TsOH** as a white solid (35.1 g, 99.2 wt% purity, 116 mmol, 84% yield, >20:1 d.r.).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.91 (s, 3H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 5.39 (s, 1H), 4.60 (s, 1H), 3.90 (d, *J* = 7.3 Hz, 1H), 3.70 (t, *J* = 6.2 Hz, 1H), 3.15 (br s, 1H), 2.29 (s, 3H), 1.91 – 1.74 (m, 2H), 1.66 - 1.57 (m, 2H) ppm; **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 145.65 (C_q), 137.62 (C_q), 128.04 (CH), 125.46 (CH), 98.88 (CH), 72.39 (CH), 67.84 (CH_2), 49.68 (CH), 26.56 (CH_2), 20.76 (CH_3), 20.66 (CH_2) ppm. **HRMS** m/z calc. for [$C_6H_{12}NO_2$] ([M+H]$^+$): 130.0863, found: 130.0861.

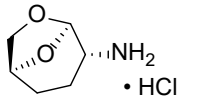
2.6. Synthesis of Cyrene Amine Salts



3a•HOTf

(1*S*,4*R*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-4-aminium trifluoromethanesulfonate (3a·HOTf). A 9.86 wt% solution of **3a** (78.4 g, 59.9 mmol, 1.0 equiv.) in 2-MeTHF was charged into a 250 mL round bottom flask and then concentrated under vacuum (100-150 mbar) at a heating bath temperature of 40 °C. 2-MeTHF (50 mL) was added, and the process was repeated to remove water and isopropylamine. The residue was dissolved in dichloromethane (50 mL) and the resulting solution was cooled in an ice bath. A solution of TfOH (5.3 mL, 59.9 mmol, 1.0 equiv) in dichloromethane (70 mL) was added slowly *via* an addition funnel and the mixture was allowed to warm to room temperature overnight. The resulting slurry was filtered under nitrogen atmosphere and the solid was washed with dichloromethane and dried under vacuum to yield **3a·HOTf** as a light yellow solid (16.5 g, 98.3 wt% purity, 58.2 mmol, 97% yield, >20:1 d.r.).

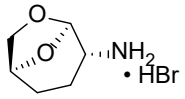
^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.93 (s, NH_3, 3H), 5.38 (s, 1H), 4.72 - 4.48 (m, 1H), 3.98 (d, *J* = 7.3 Hz, 1H), 3.77 - 3.60 (m, 1H), 3.12 (s, 1H), 2.20 - 1.87 (m, 2H), 1.60 - 1.47 (m, 1H), 1.50 - 1.38 (m, 1H) ppm; **^{19}F{^{1}H} NMR (471 MHz, DMSO-*d*$_6$)** δ −77.74 ppm; **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 120.67 (q, *J* = 322.4 Hz, CF_3), 98.60 (C6), 73.07 (C2), 66.99 (C1), 47.39 (C5), 23.21 (C3), 18.60 (C4) ppm.



3a•HCl

(1*S*,4*R*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-4-aminium hydrochloride (3a·HCl). A 250 mL 3-neck round bottom equipped with an overhead stirrer was charged with a 1.15 M solution of **3a** (20 mL, 23 mmol, 1 equiv) in 2-MeTHF. 2-MeTHF (24 mL) was added, and the solution was heated to 50 °C. HCl in cyclopentyl methyl ether (7.7 ml, 23.0 mmol, 1.0 equiv) was added at 48 °C over 1 hour. The resulting slurry was cooled to room temperature and aged overnight. The slurry was filtered and the solid was washed with EtOH (2 x 10 mL). After drying under vacuum, **3a·HCl** was obtained as a white crystalline solid (2.89 g, 99.8 wt% purity, 17.4 mmol, 76% yield, >20:1 d.r.).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.30 (s, 3H, NH_3, 3H), 5.45 (s, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.11 - 3.87 (m, 1H), 3.77 - 3.55 (m, 1H), 3.15 - 2.92 (m, 1H), 2.19 - 1.89 (m, 2H), 1.69 - 1.53 (m, 1H), 1.45-1.42 (m, 1H) ppm; **^{13}C NMR (126 MHz, DMSO-d$_6$)** δ 98.61, 72.99, 66.95, 47.31, 23.25, 18.55 ppm.

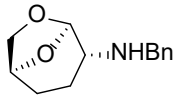


3a•HBr

(1*S*,4*R*,5*R*)-6,8-Dioxabicyclo[3.2.1]octan-4-aminium hydrobromide (3a·HBr). A 9.86 wt% solution of **3a** (87.9 g, 67.1 mmol, 1.0 equiv.) in 2-MeTHF was charged into a 250 mL round bottom flask and then concentrated under vacuum (100-150 mbar) at 40 °C. 2-MeTHF (50 mL) was added, and the process was repeated to remove water and isopropylamine. 2-MeTHF (70 mL) was added followed by a slow addition of aqueous HBr (9.1 mL, 81.0 mmol, 1.2 equiv.) over 5-10 minutes at 40 °C. The biphasic mixture was then concentrated at 40 °C, 2-MeTHF (50 mL) was then added, and the process was repeated to remove excess water. The residue was dissolved in 2-MeTHF (50 mL) and heated to 40 °C. Methanol (5 mL) was added and the solution was allowed to cool to room temperature overnight. The resulting slurry was filtered and washed 2-MeTHF (2 x 20 mL). The isolated solid was recrystallized from 2-MeTHF (60 mL) and methanol (6 mL) at 40 °C, followed by a recrystallization in methanol (25 mL) at 60 °C. 2-MeTHF (10 mL) was added at room temperature to improve the recovery. The resulting solid was filtered, washed with 2-MeTHF (2 x 20 mL), and dried under vacuum to yield **3a·HBr** as a white solid (7.86 g, 100 wt% purity, 37.4 mmol, 56% yield, >20:1 d.r.).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.09 (s, 3H), 5.42 (s, 1H), 4.60 (d, *J* = 4.6 Hz, 1H), 3.98 (dd, *J* = 7.3 Hz, *J* = 0.6 Hz, 1H), 3.74 - 3.60 (m, 1H), 3.16 - 3.03 (m, 1H), 2.19 - 1.83 (m, 2H), 1.67 - 1.50 (m, 1H), 1.49 - 1.36 (m, 1H) ppm; **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 98.52, 73.02, 67.00, 47.36, 23.24, 18.54 ppm.

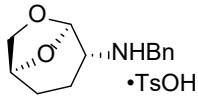
2.7. Synthesis of Bn-3a and Bn-3b



Bn-3a

(1*S*,4*R*,5*R*)-*N*-benzyl-6,8-Dioxabicyclo[3.2.1]octan-4-amine (Bn-3a). A 250 mL round bottom flask was charged with **3a·TsOH** (6.0 g, 19.9 mmol, 1.0 equiv.) and methanol (7 mL). Sodium acetate (3.3 g, 39.8 mmol, 2.0 equiv) and $MgSO_4$ (1.2 g, 10.0 mmol, 0.5 equiv) were added under nitrogen atmosphere. Benzaldehyde (2.0 mL, 19.9 mmol, 1.0 equiv) was added and the slurry was stirred at room temperature for 1 hour. Sodium cyanoborohydride (2.5 g, 39.8 mmol, 2.0 equiv) was added in one portion and the reaction was heated to 50 °C overnight. The cooled reaction was filtered using ethyl acetate and the filtrated was concentrated under vacuum. The resulting residue was dissolved in ethyl acetate (50 mL), washed with water (50 mL), and then with a 2 M aqueous K_2CO_3 solution (2 x 25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude oil was then purified by column chromatography using dichloromethane/methanol to yield **Bn-3a** as a colorless oil (3.79 g, 96.7 wt% purity, 16.73 mmol, 84% yield, >20:1 d.r.).

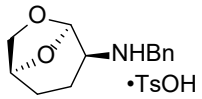
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.37 – 7.33 (m, 2H), 7.33 – 7.28 (m, 2H), 7.26 – 7.20 (m, 1H), 5.34 – 5.30 (s, 1H), 4.42 (s, 1H), 3.89 (d, *J* = 7.0 Hz, 1H), 3.87 (d, *J* = 13.3 Hz, 1H), 3.76 (d, *J* = 13.3 Hz, 1H), 3.71 (ddd, *J* = 7.0 Hz, *J* = 5.2 Hz, *J* = 1.3 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.05 – 1.93 (m, 1H), 1.84 (tt, *J* = 13.4 Hz, *J* = 5.4 Hz, 1H), 1.75 – 1.63 (m, 2H), 1.45 – 1.33 (m, 1H) ppm; **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 141.55, 128.80, 128.55, 127.31, 103.39, 73.82, 67.39, 55.44, 51.62, 25.73, 20.02 ppm. **LCMS** m/z calc. for $[C_{13}H_{18}NO_2]$ ($[M+H]^+$): 220.1, found: 220.2.



Bn-3a•TsOH

(1*S*,4*R*,5*R*)-*N*-benzyl-6,8-Dioxabicyclo[3.2.1]octan-4-aminium 4-methylbenzene-1-sulfonate (Bn-3a·TsOH). A 500 mL round bottom flask was charged with **3a·TsOH** (10.0 g, 33.2 mmol, 1.0 equiv.) and methanol (120 mL). Sodium acetate (5.4 g, 66.4 mmol, 2.0 equiv) and $MgSO_4$ (2.0 g, 16.6 mmol, 0.5 equiv) were added under nitrogen atmosphere. Benzaldehyde (3.4 mL, 33.2 mmol, 1.0 equiv) was added and the slurry was stirred

at room temperature for 1.5 hours. Sodium cyanoborohydride (4.2 g, 66.4 mmol, 2.0 equiv) was added in one portion and the reaction was heated to 50 °C overnight. The cooled reaction was filtered using ethyl acetate and the filtrated was concentrated under vacuum. The resulting residue was dissolved in ethyl acetate (100 mL), washed with water (50 mL), and then with a 2 M aqueous K_2CO_3 solution (2 x 50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude oil was dissolved in 2-MeTHF (15 mL) and a solution of *para*-toluenesulfonic acid monohydrate (6.3 g, 33.2 mmol, 1.0 equiv) in 2-MeTHF (15 mL) was added at room temperature over 30 minutes using an addition funnel. Additional 2-MeTHF (40 mL) was added *via* the addition funnel and the resulting slurry was stirred overnight at room temperature. The solid was filtered, washed with 2-MeTHF (20 mL, then 30 mL), and dried under vacuum to yield **Bn-3a·TsOH** as a white solid (10.2 g, 93.1 wt% purity, 24.3 mmol, 73% yield).
^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.95 (br s, NH_2, 2H), 7.56 - 7.50 (m, 2H), 7.50 - 7.40 (m, 5H), 7.18 - 7.05 (m, 2H), 5.63 (s, 1H), 4.64 (br s, 1H), 4.28 (d, *J* = 13.1 Hz, 1H), 4.22 (d, *J* = 13.1 Hz, 1H), 3.99 (d, *J* = 7.0 Hz, 1H), 3.68 (ddd, *J* = 7.0 Hz, *J* = 5.1 Hz, *J* = 1.1 Hz, 1H), 3.09 (br s, 1H), 2.29 (s, 3H), 2.19 - 2.06 (m, 1H), 2.05 - 1.95 (m, 1H), 1.85 - 1.76 (m, 1H), 1.45 (dd, *J* = 13.7 Hz, *J* = 5.8 Hz, 1H) ppm; **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 145.77 (C_q), 137.54 (C_q), 131.61 (C_q), 130.24 (CH), 129.08 (CH), 128.67 (CH), 128.01 (CH), 125.47 (CH), 97.55 (CH), 73.16 (CH), 67.20 (CH_2), 53.84 (CH), 48.88 (CH_2), 23.32 (CH_2), 20.75 (CH_3), 16.78 (CH_2) ppm. **LCMS** m/z calc. for [$C_{13}H_{18}NO_2$] ([M+H]$^+$): 220.1, found: 220.2. **HRMS** m/z calc. for [$C_{13}H_{18}NO_2$] ([M+H]$^+$): 220.1332, found: 220.1330.



Bn-3b•TsOH

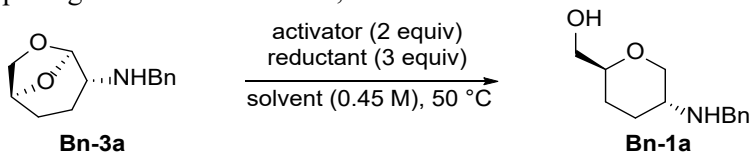
(1*S*,4*S*,5*R*)-*N*-benzyl-6,8-Dioxabicyclo[3.2.1]octan-4-aminium 4-methylbenzene-1-sulfonate (Bn-3b·TsOH). A 500 mL round bottom flask was charged with **3b·TsOH** (10.0 g, 33.2 mmol, 1.0 equiv.) and methanol (120 mL). Sodium acetate (5.4 g, 66.4 mmol, 2.0 equiv) and $MgSO_4$ (2.0 g, 16.6 mmol, 0.5 equiv) were added under nitrogen atmosphere. Benzaldehyde (3.4 mL, 33.2 mmol, 1.0 equiv) was added and the slurry was stirred at room temperature for 1 hour. Sodium cyanoborohydride (4.2 g, 66.4 mmol, 2.0 equiv) was added in one portion and the reaction was heated to 50 °C overnight. The cooled reaction was filtered using ethyl acetate and the filtrated was concentrated under vacuum. The resulting residue was dissolved in ethyl acetate (100 mL), washed with water (100 mL), and then with a 2 M aqueous K_2CO_3 solution (2 x 50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude oil was dissolved in 2-MeTHF (15 mL) and a solution of *para*-toluenesulfonic acid monohydrate (6.3 g, 33.2 mmol, 1.0 equiv) in 2-MeTHF (15 mL) was added at room temperature over 30 minutes using an addition funnel. Additional 2-MeTHF (40 mL) was added *via* the addition funnel and the resulting slurry was stirred overnight at room temperature. The solid was filtered, washed with 2-MeTHF (2 x 20 mL), and dried under vacuum to yield **Bn-3b·TsOH** as a white solid (11.4 g, 93.4 wt% purity, 27.2 mmol, 82% yield).
^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.92 (d, J = 28.2 Hz, NH_2, 2H), 7.55 – 7.38 (m, 7H), 7.11 (d, *J* = 7.8 Hz, 2H), 5.63 (s, 1H), 4.62 (d, *J* = 4.6 Hz, 1H), 4.20 (d, *J* = 13.8 Hz, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.94 (d, *J* = 7.4 Hz, 1H), 3.78 – 3.67 (m, 1H), 3.21 (br s, 1H), 2.29 (s, 3H), 2.09 – 1.96 (m, 1H), 1.83 – 1.64 (m, 3H) ppm; **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 145.76 (C_q), 137.55 (C_q), 131.73 (C_q), 130.09 (CH), 129.04 (CH), 128.68 (CH), 128.01 (CH), 125.47 (CH), 97.85 (CH), 72.60 (CH), 67.97 (CH_2), 56.13 (CH), 47.79 (CH_2), 26.62 (CH_2), 20.75 (CH_3), 19.02 (CH_2) ppm. **LCMS** m/z calc. for [$C_{13}H_{18}NO_2$] ([M+H]$^+$): 220.1, found: 220.2. **HRMS** m/z calc. for [$C_{13}H_{18}NO_2$] ([M+H]$^+$): 220.1332, found: 220.1330.

3. Reductive Acetal Opening

3.1. Reaction Optimization using Bn-3a

General Procedure 2. A tared 4 mL vial equipped with a stir bar was charged with **Bn-3a** (50 mg, 225 µmol, 1 equiv.) followed by 0.5 mL of the respective solvent under N_2 atmosphere. The reductant, either triethylsilane (108 µl, 674 µmol, 3 equiv.) or BH_3·THF (1.0 M, 674 µl, 674 µmol, 3 equiv), was added followed by the addition of the Lewis or Bronsted Acid such as BF_3·OEt_2 (57 µl, 449 µmol, 2 equiv). The vial was then placed into a heating block and heated to 50 °C for 18 h before it was carefully quenched with methanol (200 µL) and heated again to 50 °C for 2 hours. The reactions were analyzed by HPLC after diluting a weighed aliquot (80 µL) into a 50 mL volumetric flask using acetonitrile.

Scheme S3. Acetal opening of **Bn-3a**. For results, see Table 2.



Bn-3a **Bn-1a**

3.2. Solvent Screening using Bn-3a

Microscale high-throughput experimentation was conducted as previously described[5] in aluminum 96-well microtiter plates containing 8×30 mm glass vial inserts in a nitrogen-purged glovebox with O_2 < 10 ppm.

Survey of Silanes and Solvents for the Ring Opening of Bn-3a.

To each well in a 96-well plate, 100 µL of a 0.1 M stock solution of **Bn-3a** free base (2.19 mg, 10 µmol) in 1,2-dichloroethane (DCE) was added followed by removal of the volatiles under a flow of nitrogen. 100 µL of the desired solvent was added to each well, followed by 60 µmol (6 equiv) of the desired silane (9.58 µL Et_3SiH, 12.29 µL $^{i}Pr_3SiH$, 11.07 µL $(EtO)_3SiH$, 9.61 µL $(EtO)_2MeSiH$, 8.26 µL $(EtO)Me_2SiH$, 7.40 µL $PhSiH_3$, 10.60 µL TMDSO, or 6.66 µL Me_2SiHCl) and 7.40 µL (60 µmol, 6 equiv.) of $BF_3{\cdot}OEt_2$. The plate was sealed, stirred using magnetic tumble stirring, and heated to 40 °C overnight (Figure S4).

AY	MeCN	DMSO	DMA	NMP	sulfolane	PC	DME	DCE	2-MeTHF	CPME	$PhCF_3$	PhMe
Et_3SiH	25.7	0.0	0.0	0.0	93.2	28.0	0.6	3.0	0.3	0.7	1.7	1.2
$^{i}Pr_3SiH$	12.4	0.5	0.6	0.6	5.1	6.0	0.6	1.0	0.6	0.4	0.5	0.5
$(EtO)_3SiH$	62.7	0.6	1.3	1.0	50.0	44.7	13.8	0.9	1.1	0.6	0.9	0.6
$(EtO)_2MeSiH$	1.1	0.0	0.7	0.0	1.2	1.0	0.0	0.0	0.0	0.0	0.0	0.0
$(EtO)Me_2SiH$	37.1	0.0	0.0	0.0	30.2	16.2	0.0	0.5	0.0	0.0	0.3	0.3
$PhSiH_3$	23.5	0.0	0.0	0.0	83.4	13.7	0.4	1.2	0.0	0.0	0.0	0.5
TMDSO	22.3	0.6	1.0	0.3	92.2	8.6	1.5	4.9	0.4	0.4	1.9	3.0
Me_2SiHCl	47.1	0.0	1.8	1.8	32.3	42.3	19.2	2.8	10.6	1.7	3.0	1.4

Product d.r.	MeCN	DMSO	DMA	NMP	sulfolane	PC	DME	DCE	2-MeTHF	CPME	$PhCF_3$	PhMe
Et_3SiH	5				599	22						
$^{i}Pr_3SiH$	19				2	2						
$(EtO)_3SiH$	121				14	19	91					
$(EtO)_2MeSiH$												
$(EtO)Me_2SiH$	92				6	5						
$PhSiH_3$	30				542	88						
TMDSO	51				601	56		22				
Me_2SiHCl	6				7	6	0	1	0	0	1	0

Figure S4. *Top:* Assay yields (AY) as determined by UPLC analysis against an internal standard for the silane and solvent combination tested. *Bottom:* **Bn-1a**:**Bn-1b** ratio as determined by UPLC analysis. MeCN = acetonitrile, DMA = *N*,*N*-dimethylacetamide, NMP = *N*-methyl-2-pyrrolidone, PC = propylene carbonate, DME = 1,2-dimethoxyethane, CPME = cyclopentyl methyl ether, TMDSO = 1,1,3,3-tetramethyldisiloxane.

Survey of Cosolvents for the Ring Opening of Bn-3a·TsOH.

To each well in a 96-well plate, 100 µL of a well-stirred 0.1 M stock slurry of **3a·TsOH** (3.91 mg, 10 µmol) in 1,2-dichloroethane (DCE) was added followed by removal of the volatiles under a flow of nitrogen. 10, 25, 50, or 75 µL of gently warmed sulfolane was added to the desired wells followed by 90, 75, 50, or 25 µL of the desired cosolvents. 9.58 µL (60 µmol, 6 equiv.) of Et_3SiH or 10.60 µL (60 µmol, 6 equiv.) of

[5] Shevlin, M. Practical High-Throughput Experimentation for Chemists. *ACS Med. Chem. Lett.* **2017**, *8*, 601–607.

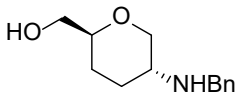
TMDSO was added to the desired wells, followed by 7.40 µL (60 µmol, 6 equiv.) of $BF_3 \cdot OEt_2$ to each well. The plate was sealed, stirred using magnetic tumble stirring, and heated to 40 °C overnight (Figure S5).

AY	DME	2-MeTHF	CPME	MTBE	PhOMe	$PhCF_3$	PhCl	CH_2Cl_2	PhMe	DMSO	DMA	NMP	
10%	0.0	0.0	0.0	0.0	93.7	94.1	96.0	93.2	87.9	0.0	0.0	0.0	
25%	0.2	0.0	0.0	0.0	>99	>99	>99	>99	>99	0.8	0.6	0.5	Et_3SiH
50%	0.6	0.4	0.4	0.3	95.2	>99	>99	>99	>99	0.8	0.5	0.5	
75%	>99	0.3	0.0	0.0	26.4	3.8	>99	>99	>99	0.8	0.9	0.8	
10%	0.5	0.2	0.8	0.4	0.6	0.2	0.7	22.1	3.8	0.0	0.5	0.2	
25%	0.2	0.4	0.3	0.0	88.1	0.5	84.3	98.5	78.5	0.5	0.3	0.0	TMDSO
50%	0.4	0.4	0.6	0.4	>99	>99	>99	>99	0.7	0.6	0.6	0.5	
75%	0.5	0.5	0.5	0.4	0.4	>99	>99	>99	>99	0.6	0.4	0.3	

Product d.r.	DME	2-MeTHF	CPME	MTBE	PhOMe	$PhCF_3$	PhCl	CH_2Cl_2	PhMe	DMSO	DMA	NMP	
10%					>500	>500	>500	>500	>500				
25%					>500	>500	>500	>500	>500				Et_3SiH
50%					135.6	>500	>500	>500	>500				
75%	70.5				>500		>500	>500	>500				
10%								17.1					
25%					125.2		63.5	117.4	33.7				TMDSO
50%					>500	>500	>500	>500					
75%						>500	>500	>500	>500				

Figure S5. *Top:* Assay yields (AY) as determined by UPLC analysis against an internal standard for the sulfolane-solvent mixtures tested. *Bottom:* **Bn-1a**:**Bn-1b** ratio as determined by UPLC analysis. DMA = *N*,*N*-dimethylacetamide, NMP = *N*-methyl-2-pyrrolidone, DME = 1,2-dimethoxyethane, CPME = cyclopentyl methyl ether, MTBE = methyl *tert*-butyl ether, TMDSO = 1,1,3,3-tetramethyldisiloxane.

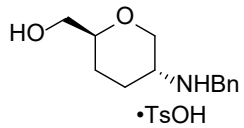
3.3. Synthesis and Characterization of Bn-1a and Bn-1b



Bn-1a

((2*S*,5*R*)-5-(benzylamino)tetrahydro-2*H*-pyran-2-yl)methanol (Bn-1a). Bn-3a (1.0 g, 4.6 mmol, 1.0 equiv) was weight into a 100 mL 2-neck round bottom flask followed by acetonitrile (10 mL) and 2,2,2-trifluoroacetic acid (1.0 mL, 13.8 mmol, 3.0 equiv). BH_3·THF (1.0 M, 13.8 mL, 13.8 mmol, 3.0 equiv) was added and the mixture was stirred at room temperature until no gas evolution was observed. The reaction was heated to 50 °C for 6 h. The reaction was quenched *via* the dropwise addition of methanol (1.7 mL, 41.5 mmol, 9.0 equiv) and then stirred for 45 min before allowing the reaction to cool to room temperature (95% assay yield determined by UPLC). The reaction was concentrated to dryness and the residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with 20 wt% aqueous Na_2CO_3 solution (15 mL) and H_2O (10 mL). The aqueous phases were back extracted with ethyl acetate (10 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude oil was purified by column chromatography (dichloromethane/methanol 100/1–9/1) yielding **Bn-1a** as a colorless oil (824 mg, 3.7 mmol, 81% yield, >20:1 d.r.).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.32 – 7.29 (m, 4H), 7.26 - 7.22 (m, 1H), 4.06 (ddd, *J* = 10.7 Hz, *J* = 4.5 Hz, *J* = 2.3 Hz, 1H), 3.82 (d, *J* = 13.1 Hz, 1H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.53 (dd, *J* = 11.4 Hz, *J* = 3.2 Hz, 1H), 3.43 (dd, *J* = 11.4 Hz, *J* = 7.1 Hz, 1H), 3.37 – 3.32 (m, 1H), 3.06 (t, *J* = 10.7 Hz, 1H), 2.64 (tt, *J* = 10.5 Hz, *J* = 4.2 Hz, 1H), 2.10 – 2.06 (m, 1H), 1.62 – 1.54 (m, 1H), 1.44 – 1.21 (m, 2H) ppm. **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 141.50 (C_q), 128.87 (CH), 128.53 (CH), 127.41 (CH), 78.56 (CH), 72.97 (CH_2), 66.32 (CH_2), 53.85 (CH), 51.66 (CH_2), 31.20 (CH_2), 27.24 (CH_2) ppm. **LCMS** m/z calc. for [$C_{13}H_{20}NO_2$] ([M+H]$^+$): 222.15, found: 222.2.



Bn-1a•TsOH

((2*S*,5*R*)-5-(benzylamino)tetrahydro-2*H*-pyran-2-yl)methanol 4-methylbenzenesulfonate (Bn-1a·TsOH). A 40 mL vial equipped with a stir bar was charged with **Bn-3a·TsOH** (1.89 g, 4.49 mmol, 1.00 equiv), sulfolane (4.0 mL), anisole (6.0 mL) and triethylsilane (3.6 mL, 22.5 mmol, 5.0 equiv). BF_3·OEt_2 (1.1 mL, 9.0 mmol, 2.0 equiv) was added and the reaction was heated to 50 °C for 18 h. Methanol (4 mL) was added carefully, and the mixture was heated to 50 °C for 2 h. The mixture was then allowed to cool to room temperature overnight. The resulting slurry was filtered and the solid was washed with 2-MeTHF (4 mL, 6 mL, and 2 mL) and dried under vacuum to yield **Bn-1a·TsOH** as a white solid (943 mg, 2.40 mmol, 53% yield, >20:1 d.r.).

^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.51 - 7.46 (m, 5H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.28 (d, *J* = 12.9 Hz, 1H), 4.28-4.25 (ddd, *J* = 10.6 Hz, *J* = 4.5 Hz, *J* = 2.4 Hz, 1H), 4.21 (d, *J* = 12.9 Hz, 1H), 3.55 - 3.49 (m, 2H), 3.43 - 3.39 (m, 2H), 3.31 - 3.26 (m, 1H), 2.40-2.35 (m, 1H), 2.37 (s, 3H), 1.83 (dt, *J* = 13.6 Hz, *J* = 4.7 Hz, 1H), 1.66 (qd, *J* = 12.4 Hz, *J* = 4.2 Hz, 1H), 1.51 - 1.43 (m, 1H) ppm. **^{13}C NMR (126 MHz, Methanol-*d*$_4$)** δ 143.60 (C_q), 141.67 (C_q), 132.60 (C_q), 130.91 (CH), 130.80 (CH), 130.39 (CH), 129.81 (CH), 126.97 (CH), 79.51 (CH), 68.18 (CH_2), 65.54 (CH_2), 54.70 (CH), 50.01(CH_2), 27.22 (CH_2), 27.13 (CH_2), 21.29 (CH_3) ppm. **LCMS** m/z calc. for [$C_{13}H_{20}NO_2$] ([M+H]$^+$): 222.2, found: 222.2. **HRMS** m/z calc. for [$C_{13}H_{20}NO_2$] ([M+H]$^+$): 222.1489, found: 222.1486.

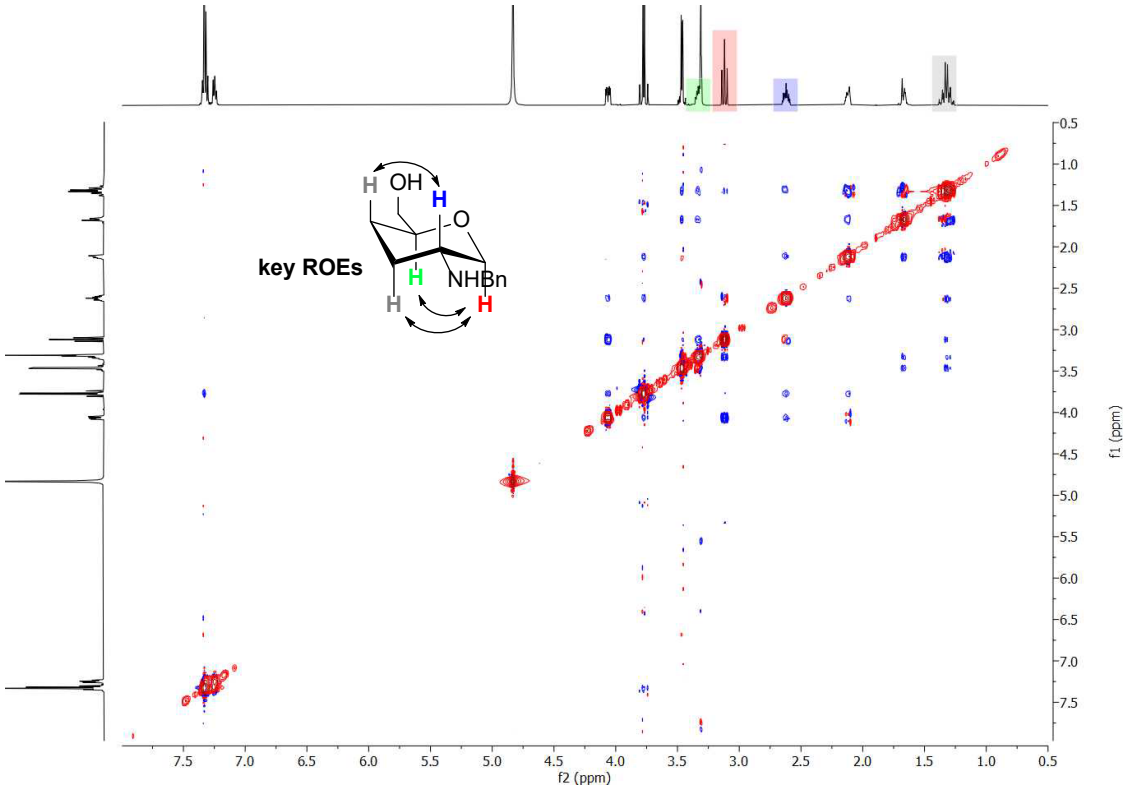
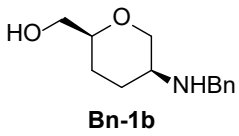


Figure S6. The relative stereochemistry of **Bn-1a** was assigned by rotating-frame nuclear Overhauser effect spectroscopy (ROESY) NMR in methanol-d_4 at 500 MHz. The key through-space correlations are highlighted.



Bn-1b

((2*S*,5*S*)-5-(benzylamino)tetrahydro-2*H*-pyran-2-yl)methanol (Bn-1b). A 100 mL round bottom flask was charged with **Bn-3b·TsOH** (1.2 g, 2.9 mmol, 1.0 equiv) and methanol (10 mL). A 50 wt% solution of NaOH (0.15 mL, 2.9 mmol, 1.0 equiv) was added and the mixture was stirred at room temperature for 1 h. The solution was concentrated to dryness, the residue was suspended in 2-MeTHF (10 mL), $MgSO_4$ was added, and the obtained slurry was filtered. The filtrate was concentrated to dryness to obtain **Bn-3b** as a crude oil (647 mg, 95.1 wt% purity, 2.8 mmol, 98% yield). **Bn-3b** (621 mg, 2.8 mmol, 1.0 equiv) was dissolved in acetonitrile (6 mL) in a 40 mL vial equipped with a stir bar. 2,2,2-trifluoroacetic acid (0.7 mL, 8.5 mmol, 3.0 equiv) was added followed by BH_3·THF (1.0 M, 8.5 mL, 3.0 equiv) and the mixture was stirred at room temperature until gas evolution subsided. The reaction was heated to 50 °C for 23 h. The reaction was quenched *via* the dropwise addition of methanol (1.0 mL, 24.7 mmol, 8.7 equiv) and then stirred for 35 minutes before allowing the reaction to cool to room temperature. The reaction was concentrated to dryness and the residue was dissolved in ethyl acetate (10 mL). The organic layer was washed with 20 wt% aqueous Na_2CO_3 solution (10 mL) and H_2O (6 mL). The aqueous phases were back extracted with ethyl acetate (3 x 8 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude oil was purified twice by column chromatography (dichloromethane/methanol 100/0 – 9/1, then 4 vol% isopropylamine in dichloromethane) yielding **Bn-1b** as a colorless oil (447 mg, 91.1 wt% purity, 1.9 mmol, 66% yield based on **Bn-3b**, >20:1 d.r.).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.37 – 7.35 (m, 2H), 7.33 – 7.31 (m, 2H), 7.25 – 7.22 (m, 1H), 3.96 (dt, J = 11.6 Hz, J = 2.1 Hz, 1H), 3.79 (s, 2H), 3.56 – 3.38 (m, 4H), 2.69 – 2.57 (m, 1H), 2.14 (br s, 2H), 1.99 –

1.94 (m, 1H), 1.72 – 1.53 (m, 2H), 1.37 – 1.33 (m, 1H) ppm. **^{13}C NMR (126 MHz, CD_2Cl_2)** δ 141.33, 128.65, 128.47, 127.14, 78.73, 70.59, 66.24, 51.22, 51.13, 27.06, 22.61 ppm. **HRMS** m/z calc. for $[C_{13}H_{20}NO_2]$ ($[M+H]^+$): 222.1489, found: 222.1469.

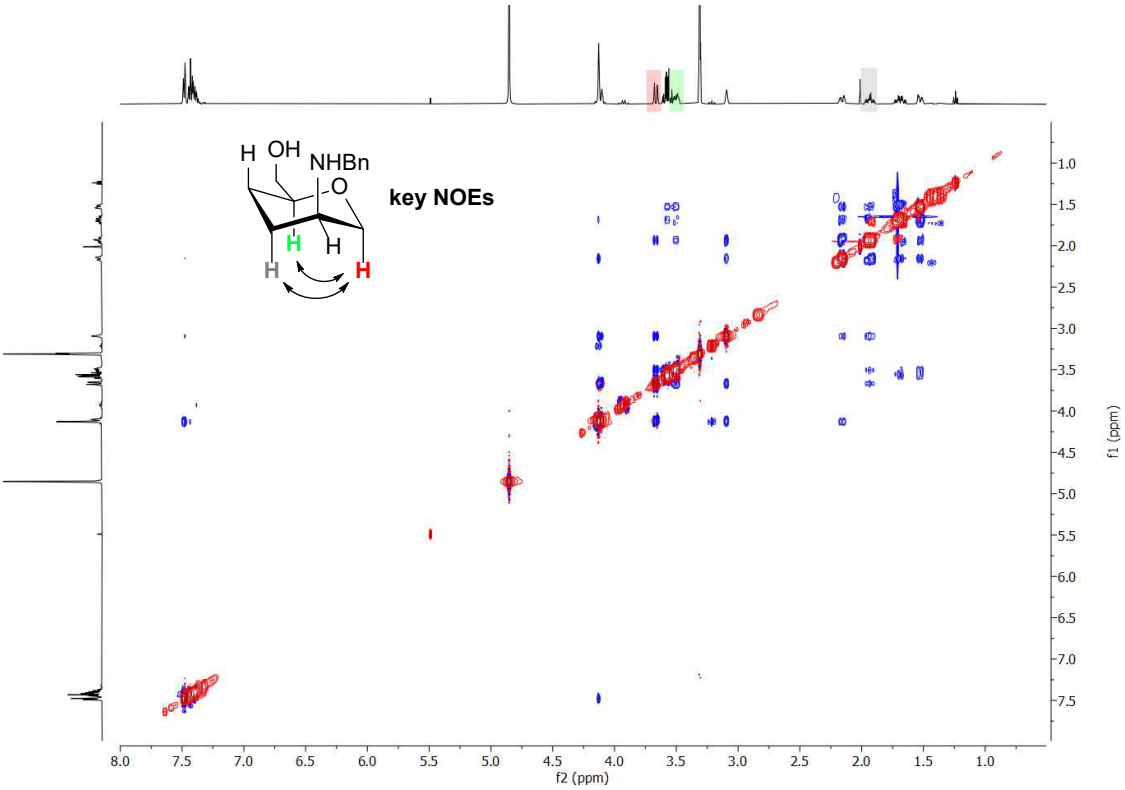


Figure S7. The relative stereochemistry of **Bn-1b** was assigned by nuclear Overhauser effect spectroscopy (NOESY) NMR in methanol-d_4 at 500 MHz. The key through-space correlations are highlighted.

3.4. Screening of Cyrene Amine Salts

General Procedure 3. A 4 mL vial equipped with a stir bar was charged with the requisite salt of **3a** (664 µmol, 1.0 equiv) and suspended in sulfolane (0.4 mL) and anisole (0.6 mL) under N_2 atmosphere. Triethylsilane (318 µl, 1.99 mmol, 3.0 equiv) and $BF_3{\cdot}OEt_2$ (168 µl, 1.33 mmol, 2.0 equiv) were then charged and the vial was placed into a heating block and heated to 50 °C for 18 h before it was carefully quenched with methanol (400 µL) and heated again to 50 °C for 2 hours. Maleic acid (664 µmol, 1.0 equiv) was then added as an internal standard and the mixture was analyzed by quantitative ^{1}H NMR in methanol-*d*$_4$.

Scheme S4. Salt screen of **3a.**

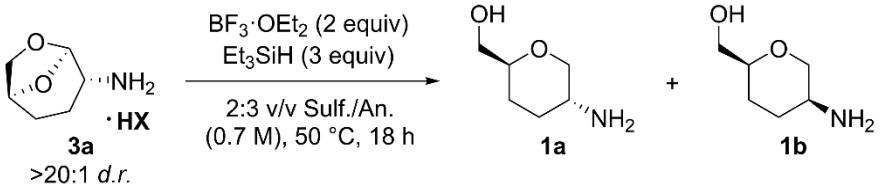
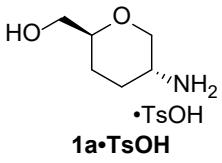


Table S3. Results of **3a** salt screen.

		Solvent KF = 300 ppm		Solvent KF = 1500 ppm	
Entry	**3a Salt**	**1a [%]**	**1a:1b d.r.**	**1a [%]**	**1a:1b d.r.**
1	None	85	>20:1	78	>20:1
2	**TsOH**	**90**	**>20:1**	**91**	**>20:1**
3	TfOH	64	>20:1	54	18:1
4	HCl	81	>20:1	41	6:1
5	HBr	68	10:1	44	4:1

3.5. Synthesis and Characterization of 1a·TsOH



1a•TsOH

((2*S*,5*R*)-5-(aminotetrahydro-2*H*-pyran-2-yl)methanol 4-methylbenzenesulfonate (1a·TsOH). A 100 mL jacketed reactor equipped with an overhead stirrer was charged with **3a·TsOH** (6.0 g, 19.9 mmol, 1.0 equiv.) and suspended in sulfolane (12 mL) and anisole (18 mL) under N_2 atmosphere. Triethylsilane (16 mL, 100 mmol, 5 equiv.) and $BF_3{\cdot}OEt_2$ (5.1 mL, 39.8 mmol, 2.0 equiv) were then charged sequentially and the mixture was heated to 40 °C for 18 hours. The resulting homogenous solution was quenched with methanol (12 mL) at such a rate to maintain the internal temperature below 45 °C before the subsequent quenched solution was heated to 60 °C for *ca.* 2 hours. To this mixture was charged crystalline **1a·TsOH** (60 mg, 1 wt%) and the resulting seed bed was aged for *ca.* 1 hour at 60 °C before being cooled to 20 °C over 6 hours and then aged a further 18 hours at this temperature. The slurry was filtered, and the wet cake was washed with a solution of 9:1 v/v 2-MeTHF:methanol (2 x 12 mL). The cake was dried under vacuum with an N_2 sweep for *ca.* 18 hours to provide **1a·TsOH** as a white solid (4.55 g, 15.0 mmol, 75% yield, >20:1 d.r.).

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.85 (s, 3H), 7.50 – 7.49 (m, 2H), 7.14 – 7.12 (m, 2H), 4.65 (br s, 1H), 3.96 (ddd, *J* = 10.7 Hz, *J* = 4.4 Hz, *J* = 2.2 Hz, 1H), 3.36 (dd, *J* = 11.3 Hz, *J* = 5.9 Hz, 1H), 3.30 (dd, *J* =

11.3 Hz, *J* = 4.7 Hz, 1H), 3.24 – 3.19 (m, 1H), 3.21 (t, *J* = 10.7 Hz, 1H), 3.05 (s, 1H), 2.29 (s, 3H), 2.06 – 2.01 (m, 1H), 1.75 – 1.64 (m, 1H), 1.48 (qd, *J* = 12.6 Hz, *J* = 4.2 Hz, 1H), 1.34 – 1.19 (m, 1H) ppm. **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 145.37 (C_q), 137.84 (C_q), 128.13 (CH), 125.46 (CH), 77.80 (CH), 67.61 (CH_2), 63.84 (CH_2), 46.18 (CH), 27.17 (CH_2), 26.06 (CH_2), 20.77 (CH_3) ppm. **HRMS** m/z calc. for $[C_6H_{14}NO_2]$ ($[M+H]^+$): 132.1019, found: 132.1017.

The relative and absolute stereochemistry was confirmed by X-ray crystallography, see Section 6.2.

4. Mechanistic Experiments

4.1. Reaction Profile for the Synthesis of 1a·TsOH by ^{1}H NMR Spectroscopy

General Procedure 4. A 1 mL volumetric flask was charged with **3a·TsOH** (65 mg, 0.216 M, 1.0 equiv) and octafluoronaphthalene (30 mg, 0.4 equiv), 0.4 mL of a 2:3 (v:v) mixture of sulfolane:anisole-d_8 was added followed by addition of Et_3SiH (106 µL, 3 equiv). Another 0.2 mL of the solvent mixture was added, followed by $BF_3{\cdot}OEt_2$ (55 µL, 2 equiv). The mixture was diluted up to the 1 mL mark of the volumetric flask using the 2:3 (v:v) sulfolane:anisole-d_8 mixture. The solution became homogenous after agitation. A 0.6 mL aliquot from this solution was transferred into a 5 mm NMR tube. The NMR tube was capped and sealed using Parafilm M, where the cap and tube meet. The sample was brought out of the N_2-filled glovebox for NMR analysis.

Scheme S5. Acetal Opening of **3a·TsOH.**

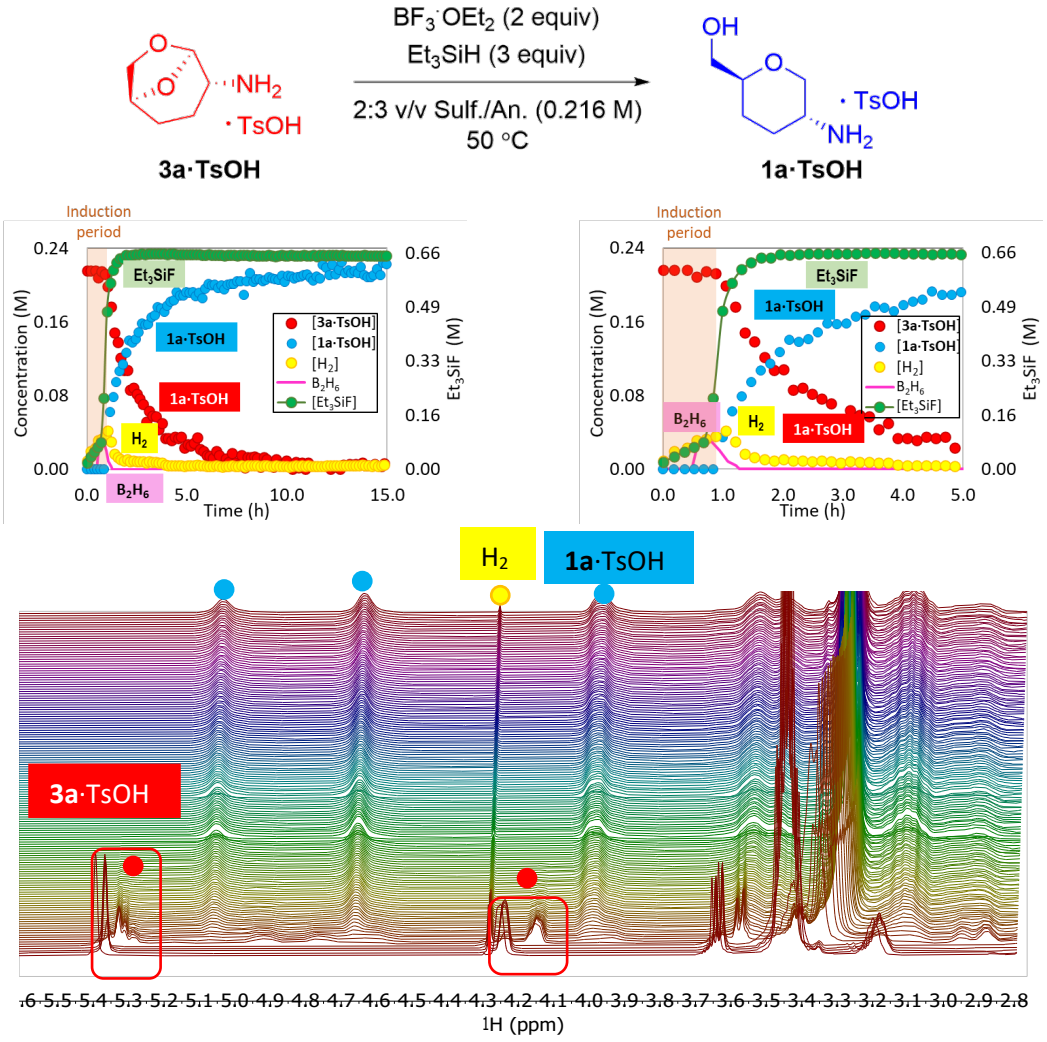


Figure S8. Following general procedure 4, temporal concentration profiles monitored by ^{1}H NMR spectroscopy for the reaction in Scheme S5 were recorded. [**3a·TsOH**]$_0$ = 0.216 M, $BF_3{\cdot}OEt_2$ (2 equiv, 0.431 M), Et_3SiH (3 equiv, 0.656 M), 2:3 (v/v) sulfolane:anisole-d_8, and 50 ˚C.

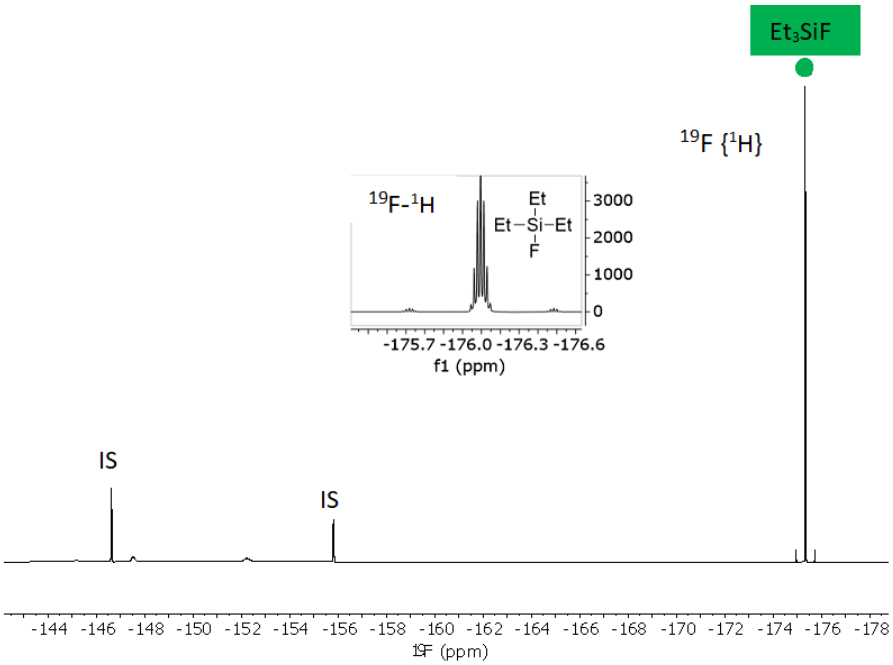


Figure S9. $^{19}F\{^{1}H\}$ NMR spectrum of the end of the reaction mixture in Scheme S5. [**3a·TsOH**]$_0$ = 0.216 M, $BF_3{\cdot}OEt_2$ (2 equiv, 0.431 M), Et_3SiH (3 equiv, 0.656 M), 2:3 (v/v) sulfolane:anisole-d_8 and 50 ˚C. Octafluoronaphthalene (0.49 equiv) was used as an internal standard (IS) for $^{19}F\{^{1}H\}$ NMR. The singlet at ca. −176 ppm is identified as Et_3SiF by ^{19}F-^{1}H NMR spectroscopy, with $J_{Si\text{-}F}$ = 288 Hz (d) and $J_{Si\text{-}H}$ = 6.4 Hz (hept). The chemical shifts match with commercially available Et_3SiF (CAS: 358-43-0).

4.2. Identification and Characterization of Diborane by NMR Spectroscopy

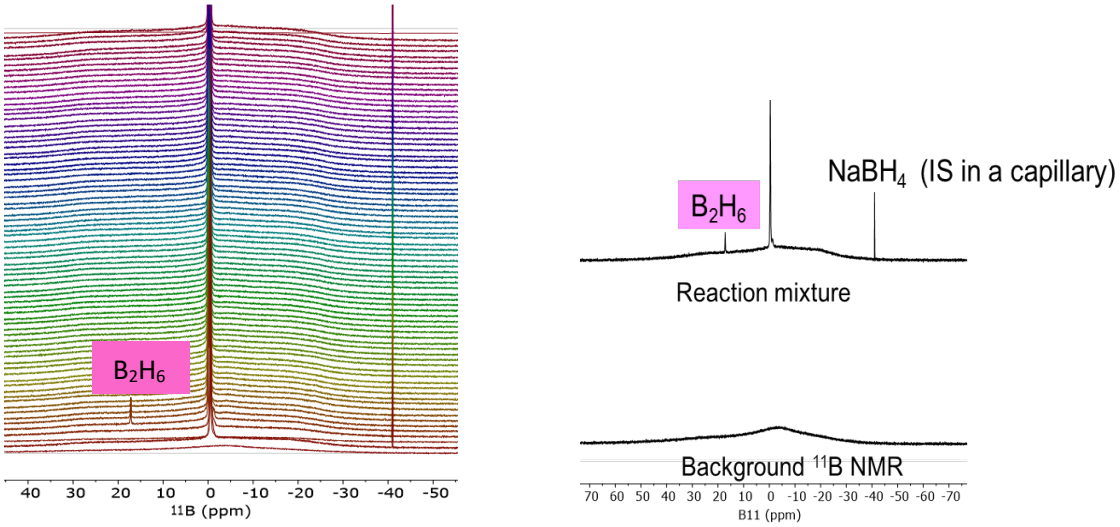


Figure S10. Following general procedure 4, temporal concentration profiles monitored by $^{11}B\{^{1}H\}$ NMR spectroscopy for the reaction in Scheme S5 were recorded. [**3a·TsOH**]$_0$ = 0.216 M, $BF_3{\cdot}OEt_2$ (2 equiv, 0.431 M), Et_3SiH (3 equiv, 0.656 M), 2:3 (v/v) sulfolane:anisole-d_8, and 50 ˚C. A known solution of $NaBH_4$ in methanol-d_4 in a capillary was used as an internal standard (IS) for ^{11}B NMR. *Note:* Quantification of boron species is semiquantitative due to a non-flat baseline caused by the probe and tube glass background signal.

All diborane NMR structure elucidation experiments have been performed on a Bruker 600 MHz instrument equipped with a 5mm Prodigy broadband cryoprobe (LN_2-cooled) and an Avance III HD console. All NMR spectra have been acquired at 3 °C of a sample generated as per general procedure 4 but without substrate **3a·TsOH**. Band-selective ^{1}H decoupling in ^{11}B spectra has been achieved using a low-power (0.001W) single-frequency continuous-wave (cw) irradiation.

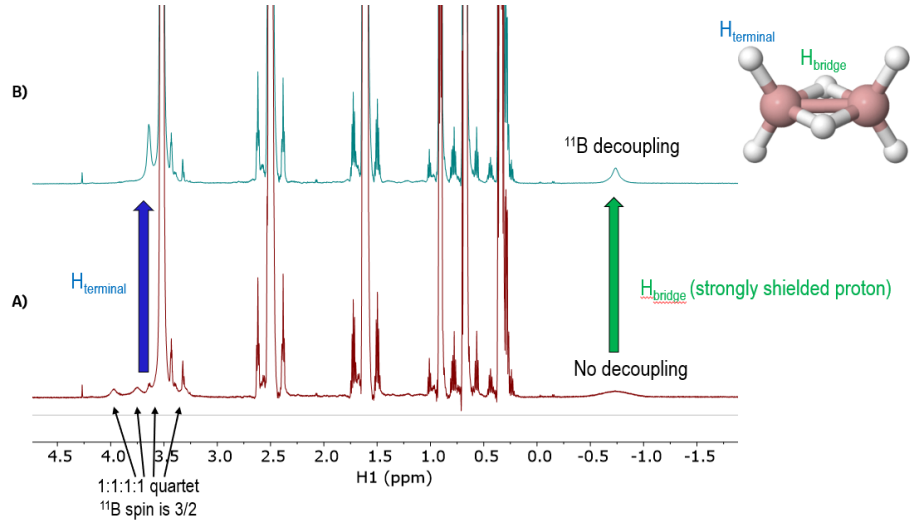


Figure S11. A. ^{1}H spectrum without ^{11}B decoupling; resonances at 3.64 ppm (1:1:1:1 quartet with J = 132.9 Hz) and −0.73 ppm (very broad peak) are detected. **B.** $^{1}H\{^{11}B\}$ spectrum; both resonances at 3.64 ppm and −0.73 ppm become singlets.

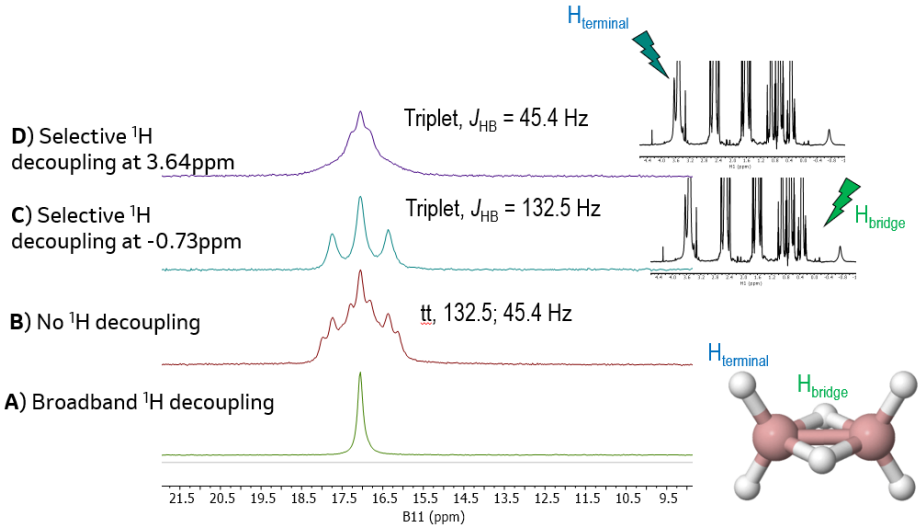


Figure S12. ^{11}B NMR spectra recorded with and without ^{1}H decoupling. **A.** $^{11}B\{^{1}H\}$ spectrum; the boron resonance of interest is a singlet. **B.** ^{11}B spectrum without ^{1}H decoupling; the boron resonance is a tt with J_{HB} = 132.5 Hz and 45.4 Hz. **C.** ^{11}B spectrum with band-selective ^{1}H decoupling at −0.73 ppm; the boron resonance is a triplet with J_{HB} = 132.5 Hz. **D.** ^{11}B spectrum with band-selective ^{1}H decoupling at 3.64 ppm; the boron resonance is a triplet with J_{HB} = 45.4 Hz.

Based on the ^{1}H and ^{11}B peak multiplicity analysis in Figures S11 and S12, as well as the corresponding ^{1}H and ^{11}B chemical shifts, it was concluded that J_{HB} coupling constants and chemical shifts match those reported in reference 27 of the manuscript for the B_2H_6 diborane molecule.

4.3. Delayed Cyrene Amine Addition Experiment

420 µL of 2:3 (v/v) sulfolane/anisole-d_8, $BF_3{\cdot}OEt_2$ (27.3 µL), and Et_3SiH (52 µL) were added to an NMR tube. The solution was heated at 50 °C and the reaction progress was monitored by NMR spectroscopy over time. Once the formation of B_2H_6 was detected by $^{11}B\{^1H\}$ NMR (with a characteristic signal around 17 ppm), **3a·TsOH** (46.4 mg) was immediately added. The subsequent NMR monitoring revealed immediate product formation.

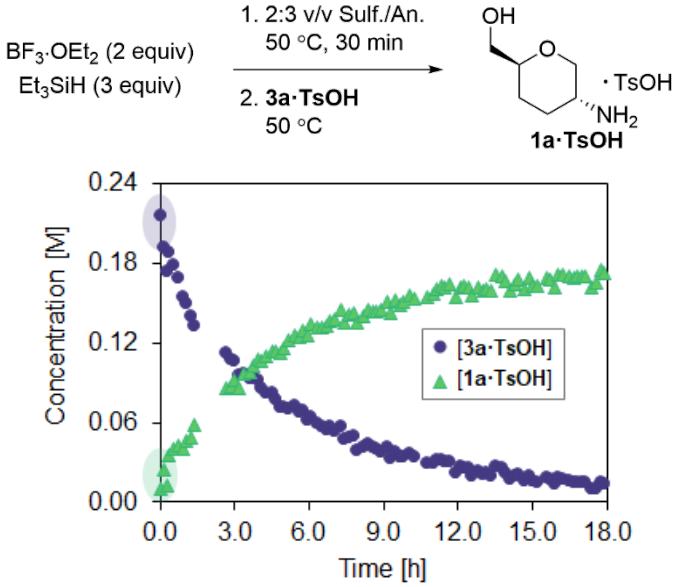


Figure S13. Reaction profiles monitored by ^1H NMR spectroscopy for the reductive acetal opening of **3a·TsOH**, with a delayed addition of **3a·TsOH**. [**3a·TsOH**] = 0.216 M, [$BF_3{\cdot}OEt_2$] = 0.431 M, [Et_3SiH] = 0.656 M, 2:3 (v/v) sulfolane:anisole-d_8, 50 ˚C.

4.3. Dependence of the Induction Period on Water Content

We found that the duration of the induction period increased with increased water content in the reaction mixture (Figure S14A). With the observation of H_2 generation during the induction period, we thus concluded that residual water is quenched during the induction period *via* the release of H_2 before an increase in diborane concentration can be observed. A linear correlation between the water content and the Et_3SiF concentration at the end of the induction period further suggested that an intermediate species generated from Et_3SiH and $BF_3{\cdot}OEt_2$ is the active species reacting with residual water.

General procedure 4 was followed by adding the corresponding additional amount of water: no additional water (460 ppm), 0.1 equiv (974 ppm water), and 0.2 equiv (1529 ppm).

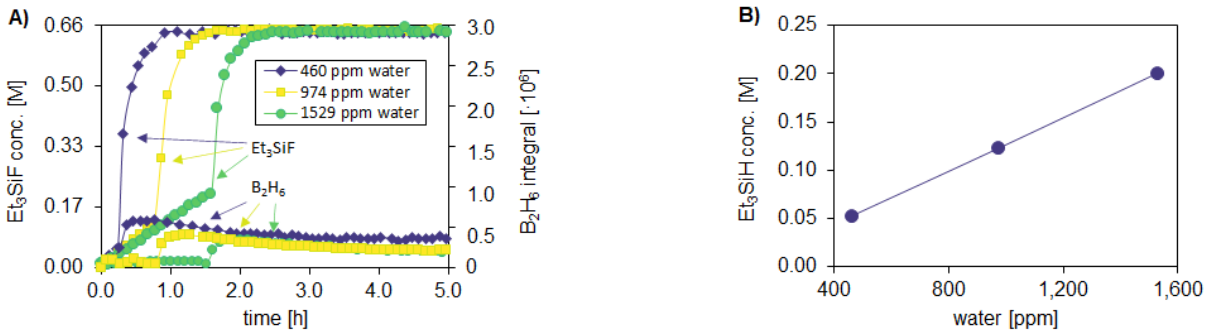


Figure S14. A. Et_3SiF and B_2H_6 concentration profiles monitored by $^{11}B\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectroscopy for the reaction of $BF_3{\cdot}OEt_2$ (0.431 M) with Et_3SiH (0.656 M) to probe the water effect (0, 0.1 and 0.2 equiv). **B.** Linear correlation between water equivalents and the concentration of Et_3SiH at the end of the induction period. Octafluoronaphthalene (0.49 equiv) was used as an internal standard for $^{19}F\{^1H\}$ NMR.

4.4 Importance of Sulfolane for Diborane Formation

Sulfolane appears essential for the productive reaction between $BF_3{\cdot}OEt_2$ and Et_3SiH to form diborane, which is required for the reductive acetal opening. Strong coordinating solvents such as THF, dioxane and DMSO were shown to suppress the benefit of sulfolane in the acetal opening reaction (Table S4).

Table S4. Solvent effects of the acetal opening of **3a·TsOH** (see Scheme S5).

Entry	Solvent	B_2H_6 Formation	Et_3SiF Formation	1a Formation
1	Anisole	No	No	No
2	Anisole:Sulfolane	Yes	Yes	Yes
3	DCM:Sulfolane	Yes	Yes	Yes
4	DCM	No	No	No
5	THF	No	No	No
6	THF:Sulfolane	No	No	No
7	Dioxane:Sulfolane	No	No	No
8	DMSO	No	No	No
9	DMSO:Sulfolane	No	No	No

[a]*Experiments were performed following general procedure 4 using the solvent systems listed.*

In non-coordinating solvents such as anisole and dichloromethane, the addition of sulfolane is crucial for reactivity. The formation of B_2H_6 from $BF_3{\cdot}OEt_2$ and Et_3SiH was not feasible in pure anisole and only occurred upon addition of sulfolane.

Delayed Sulfolane Addition Procedure: To a 1 mL volumetric flask was added Et_3SiH (106 µL, 1.5 equiv), 0.4 mL of anisole-d_8 was added, followed by $BF_3{\cdot}OEt_2$ (55 µL, 1 equiv). The mixture was diluted up to 1 mL mark of the volumetric flask using anisole-d_8. A 0.5 mL aliquot from this solution was transferred into a 5 mm NMR tube. The NMR tube was capped and sealed using Parafilm M, where the cap and tube meet. The sample was brought out of the N_2-filled glovebox for NMR analysis at 50 °C. No diborane formation was observed until upon the later sulfolane addition (0.1 mL).

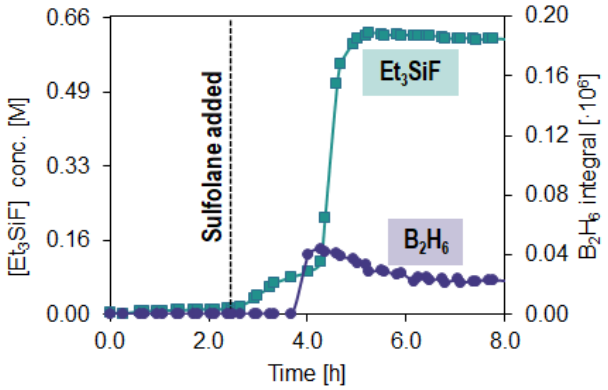


Figure S15. Temporal concentration profiles monitored by ^1H and $^{119}F\{^1H\}$ NMR spectroscopy for the reaction of $BF_3{\cdot}OEt_2$ (0.431 M) with Et_3SiH (0.656 M) in anisole-d_8 with a late addition of sulfolane.

4.5. Reaction Kinetics – Reaction Rate Dependence on Sulfolane

The ratio between anisole and sulfolane dictates the homogeneity of the final reaction mixture. A high ratio of sulfolane seems to lead to biphasic mixtures due to the low solubility of Et_3SiH in the mixture.

Table S5. Effect of the solvent ratio on the homogeneity of the reaction mixture.

Entry	Anisole (mL)	Sulfolane (mL)	Notes
1	0.2	0.8	Biphasic (low solubility of Et_3SiH)
2	0.4	0.6	Biphasic (low solubility of Et_3SiH)
3	0.6	0.4	homogeneous
4	0.8	0.2	homogeneous
5	0.9	0.1	homogeneous
6	1	0	low solubility of **3a·TsOH**

For homogeneous mixtures (anisole:sulfolane 0.6:0.4, 0.8:0.2, and 0.9:0.1; v:v), the acetal opening reaction was performed following general procedure 4 (Scheme S5). The solvent ratio was shown to significantly impact the length of the induction period and the overall conversion rate of **3a·TsOH**. The induction period increased significantly for lower sulfolane concentrations while the reaction rate for Et_3SiF formation as well as the conversion of **3a·TsOH** decreased. These results further corroborate the important role of sulfolane to initiate the formation of diborane and Et_3SiF.

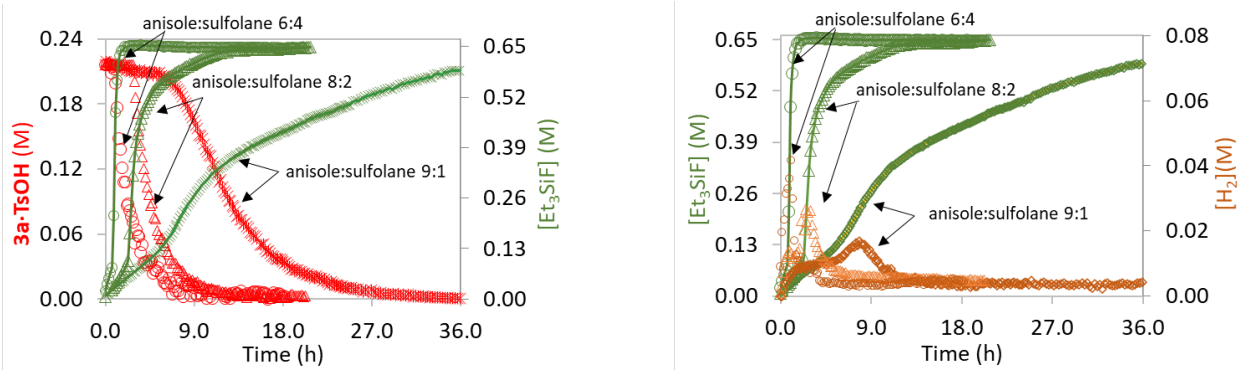


Figure S16. Temporal concentration profiles monitored by ^1H and $^{19}F\{^1H\}$ NMR spectroscopy for the reaction in Scheme S5 using different ratios of anisole-d_8:sulfolane (0.6:0.4, 0.8:0.2, and 0.9:0.1; v:v). [**3a·TsOH**]$_0$ = 0.216 M, $BF_3{\cdot}OEt_2$ (2 equiv), Et_3SiH (3 equiv), and 50 ˚C.

4.6. Reductive Acetal Opening with other Sulfones

General Procedure 6. A 4 mL vial equipped with a stir bar was charged with **3a·TsOH** (200 mg, 664 µmol, 1 equiv.) and suspended in the reaction solvent (0.6 mL) under N_2 atmosphere and the respective sulfone (4.2 mmol, 6.3 equiv) was added followed by triethylsilane (0.32 mL, 1.99 mmol, 3.00 equiv) and $BF_3{\cdot}OEt_2$ (0.17 mL, 1.33 mmol, 2.00 equiv). The reaction vials were then placed into a heating block and heated to 50 °C for 18 h before it was carefully quenched with methanol (0.4 mL) and heated again to 50 °C for 2 hours. CH_2Br_2 (46 µL, 664 µmol, 1 equiv) was then added as an internal standard and the mixture was analyzed by quantitative ^1H NMR in methanol-d_4.

Scheme S6. Acetal opening of **3a·TsOH** with different sulfones.

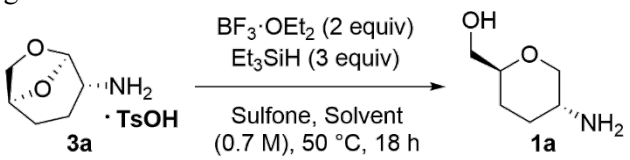


Table S6. Acetal opening of **3a·TsOH** with different sulfones.

Entry	Sulfone	Solvent	1a [%]
1	sulfolane	anisole	93
2	$^{i}PrSO_2Me$	anisole	92
3	$^{i}Pr_2SO_2$[6]	anisole	87
4	Ph_2SO_2[a]	1,2-dichloroethane	20
5	Tol_2SO_2[a]	1,2-dichloroethane	47

[a] *Reactions were performed on a 100 mg (332 µmol) scale.*

4.7. Reaction with BF_3·THF

When BF_3·THF was used instead of BF_3·OEt_2, the induction period was found to be about 1.7 days long. 90% conversion of **3a·TsOH** was eventually observed after heating at 50 °C for 8 days.

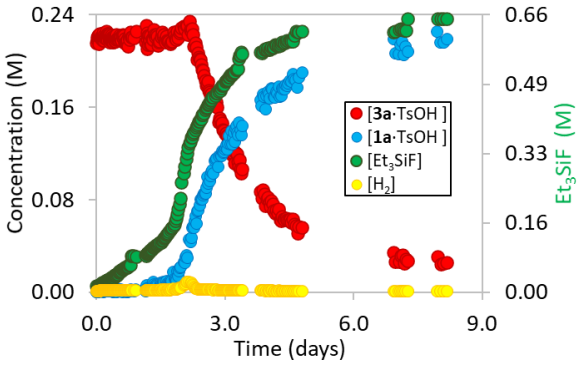


Figure S17. Following general procedure 4, temporal concentration profiles were monitored by ^{1}H NMR spectroscopy for the reaction in Scheme S5 using BF_3·THF. [**3a·TsOH**]$_0$ = 0.216 M, BF_3·THF (2 equiv, 0.431 M), Et_3SiH (3 equiv, 0.656 M), 2:3 (v/v) sulfolane:anisole-d_8, and 50 °C.

[6] $^{i}Pr_2SO_2$ was synthesized following a literature procedure: Balicki, R. *Synth. Commun.* **1999**, *29*, 2235−2239.

5. Computational Studies

5.1. Computational Methods

All density functional theory (DFT) calculations were performed using Gaussian 16 [7]. Geometry optimizations and frequency calculations were performed at the M06-2X/6-31+G(d,p) level of theory[8,9], with the SMD model[10] to account for solvation effects. Normal vibrational mode analysis confirmed the optimized structures are minima or transition structures. Transition structures are verified by intrinsic reaction coordinate (IRC) calculations. Truhlar's quasiharmonic correction was used to compute molecular entropies to reduce the error caused by the breakdown of the harmonic oscillator approximation, by setting all positive frequencies that are less than 100 cm^{-1} to 100 cm^{-1}.[11] M06-2X/6-311+G(d,p) single-point energies were computed on the M06-2X-optimized structures. MacroModel [12] was used to perform conformational searches with the OPLS3e force field.[13] 3D renderings of stationary points were generated using CYLview 1.0[14] and PyMOL 2.3[15].

5.2. Calculated Activation Free Energy Difference for the Reduction of Cyrene™ with BH_4^-

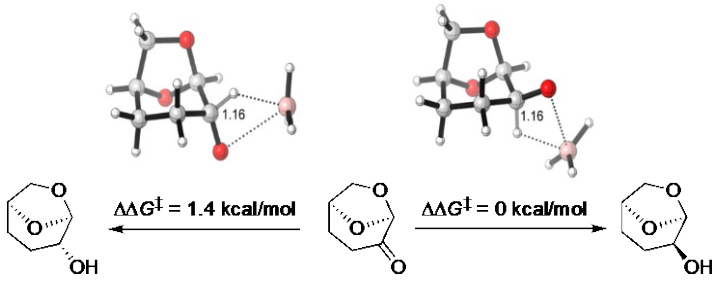
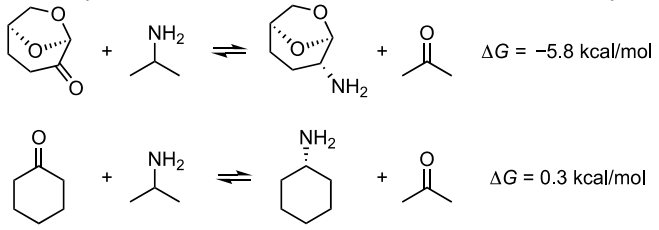


Figure S18. Reaction of Cyrene™ with BH_4^-.

[7] Gaussian 16, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.
[8] Zhao, Y.; Truhlar, D. G. Theor. *Chem. Acc.* **2008**, *120*, 215.
[9] Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.
[10] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.
[11] Zhao, Y.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813.
[12] Schrödinger Release 2019-3: MacroModel, Schrödinger, LLC, New York, NY, 2019.
[13] Roos, K.; Wu, C.; Damm, W.; Reboul, M.; Stevenson, J. M.; Lu, C.; Dahlgren, M. K.; Mondal, S.; Chen, W.; Wang, L.; Abel, R.; Friesner, R. A.; Harder, E. D. *J. Chem. Theory Comput.* **2019**, 1863–1874.
[14] Legault, C. Y. CYLview, version 1.0b; Université de Sherbrooke: Quebec, Canada, 2009; http://www.cylview.org.
[15] The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.

5.3. Calculated Thermodynamics for the Reaction of Cyrene™ with Isopropylamine

Scheme S7. Calculated thermodynamics for the transamination reaction of Cyrene™.



5.4. Calculated Solvent-Sulfolane Displacement Equilibria

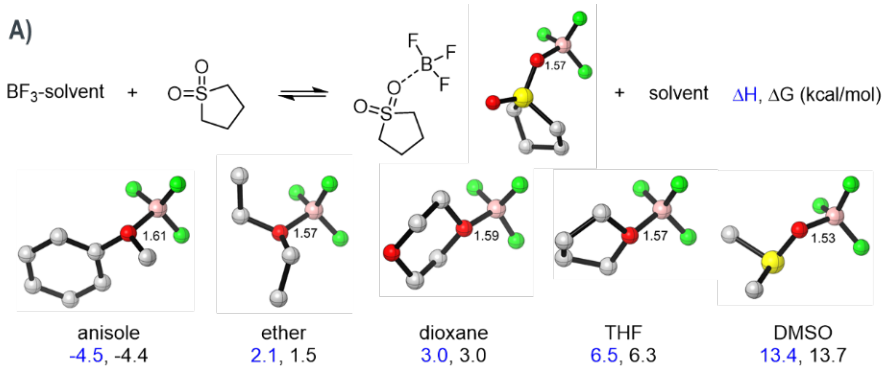


Figure S19. A. Computed enthalpies and free energies of reaction with BF_3. M06-2X/6-311+G(d,p)/SMD(anisole) // M06-2X/6-31+G(d,p)/SMD(anisole). Energies are in kcal/mol.

To understand the solvation effects of this reaction, we computed the reaction equilibria between sulfolane, and each coordinating solvent screened experimentally to BF_3 (Figure S19A). The results show that anisole is the easiest to displace by sulfolane, with a strong energy preference of 4.4 kcal/mol favoring the sulfolane-BF_3 complex. This contrasts with the DMSO equilibrium, which has a ΔG of 13.7 kcal/mol preferring coordination to DMSO. This trend is consistent with the experimental solvent screen (Table S4), where anisole and dichloromethane are the only solvents in which B_2H_6 forms in the presence of sulfolane.

Cartesian Coordinates

Sulfolane

S	0.76706	0.00000	0.00000	H	-0.10003	2.22046	-0.09293
C	-0.44348	1.29841	0.37868	H	-0.44829	1.40742	1.46593
C	-1.77018	0.75399	-0.14979	H	-1.83968	0.91965	-1.23028
C	-1.77017	-0.75400	0.14979	H	-2.61017	1.26439	0.32614
C	-0.44347	-1.29840	-0.37872	H	-2.61016	-1.26442	-0.32611
O	1.51797	0.35081	-1.21516	H	-1.83962	-0.91967	1.23029
O	1.51791	-0.35082	1.21520	H	-0.10000	-2.22046	0.09284
				H	-0.44830	-1.40735	-1.46598

BF_3-sulfolane

B	-1.87323	-0.22466	0.01353
F	-2.09313	-0.32970	1.37240
F	-1.22686	-1.35636	-0.47836
F	-2.99269	0.10897	-0.69713
O	-0.88506	0.97275	-0.19673
S	0.63689	0.85005	-0.05710
O	1.27673	2.15743	0.00049
C	1.31749	-0.18598	-1.37431
C	1.87541	-1.41917	-0.65215
C	2.26660	-0.98919	0.77299
C	1.08060	-0.20148	1.33323
H	2.09643	0.43328	-1.82713
H	0.52477	-0.39039	-2.09504
H	2.73469	-1.80756	-1.20138
H	1.10810	-2.19502	-0.60940
H	3.16178	-0.35896	0.75528
H	2.46938	-1.85130	1.41064
H	0.22196	-0.83936	1.55745
H	1.29885	0.45903	2.17471

BF_3-anisole

B	1.83807	0.04672	-0.51972
F	1.98426	1.40425	-0.35460
F	1.27690	-0.31215	-1.71220
F	2.96324	-0.66062	-0.18396
O	0.75390	-0.40948	0.58402
C	1.12130	-0.14912	1.97031
H	0.45815	-0.74261	2.59860
H	1.01900	0.91685	2.17797
C	-3.27517	0.18702	-0.29027
C	-2.74773	-1.10356	-0.25007
C	-1.39893	-1.29958	0.04378
C	-0.61616	-0.18372	0.28864
C	-1.10693	1.11283	0.25543
C	-2.45819	1.28980	-0.03992
H	-4.32513	0.33471	-0.52174
H	-3.38204	-1.96052	-0.45169
H	-0.95484	-2.28916	0.07314
H	-0.45150	1.95761	0.44082
H	-2.86824	2.29364	-0.07917
H	2.15435	-0.47355	2.07792

BF_3-dioxane

B	1.66239	-0.00000	-0.03870
F	1.88971	0.00008	1.32074
F	2.08032	1.15114	-0.65731
F	2.08033	-1.15121	-0.65718
C	-2.02651	1.16276	-0.24322
C	-0.59879	1.20681	0.25355
C	-0.59881	-1.20683	0.25355
C	-2.02652	-1.16275	-0.24322
H	-2.04188	1.19481	-1.34229
H	-2.56777	2.02780	0.14579
H	-0.54543	1.21297	1.34686
H	-0.04817	2.04840	-0.16487
H	-0.04821	-2.04843	-0.16488
H	-0.54545	-1.21299	1.34686
H	-2.04189	-1.19479	-1.34229
H	-2.56780	-2.02778	0.14578
O	0.08113	-0.00001	-0.21614
O	-2.68798	0.00001	0.22143

BF_3-DMSO

B	-1.44999	-0.03794	0.03579
F	-1.70607	-1.02137	-0.91394
F	-1.42029	1.22269	-0.57179
F	-2.32458	-0.09018	1.09882
O	-0.06316	-0.28586	0.62847
S	1.13596	-0.05767	-0.38895
C	2.32578	-1.23523	0.23915
C	1.84910	1.47931	0.19090
H	3.26808	-1.07335	-0.29002
H	1.93983	-2.23246	0.02185
H	2.02119	1.40923	1.26674
H	1.13401	2.26999	-0.04167
H	2.44354	-1.08561	1.31406
H	2.78239	1.64673	-0.35261

BF_3-Et_2O_1

B	0.94755	-0.69851	-0.02473
F	1.82909	-0.20855	-0.95932
F	0.59725	-2.01499	-0.22712
F	1.35017	-0.46130	1.27536
O	-0.38103	0.11043	-0.25097
C	-1.50469	-0.22706	0.62189
C	-0.30031	1.51273	-0.65795
H	-1.69027	0.63900	1.26220
H	-1.16191	-1.05521	1.24218
H	0.20636	1.50232	-1.62230
C	-2.70162	-0.60808	-0.21616
H	-3.53404	-0.85920	0.44728
H	-3.01945	0.21385	-0.86385
H	-2.47214	-1.47988	-0.83356
C	0.42534	2.35912	0.36350
H	-0.04325	2.29338	1.34943
H	0.38543	3.40192	0.03573
H	1.47311	2.06440	0.44911
H	-1.33424	1.83189	-0.80269

BF_3-THF

B	1.35424	0.00651	0.04125
F	1.29236	-0.25056	1.39986
F	1.86619	1.25208	-0.23911
F	1.94791	-1.01614	-0.66141
O	-0.12472	0.05159	-0.46938
C	-0.91196	-1.19006	-0.34465
C	-2.17851	-0.75266	0.36871
C	-0.92901	1.21749	-0.06734
H	-0.30517	-1.91123	0.20194
H	-1.08931	-1.53740	-1.36371
H	-3.02242	-1.39444	0.11025
H	-2.02995	-0.78041	1.45232
H	-0.61721	1.49787	0.94207
H	-0.70229	2.01323	-0.77489
C	-2.35042	0.69189	-0.10911
H	-2.73803	0.71844	-1.13198
H	-3.00775	1.28039	0.53311

6. X-Ray Crystallography data for 3a·TsOH and 1a·TsOH

6.1. Crystal Data and Structure Refinement for Compound 3a·TsOH (CCDC 2215969)

A single crystal, grown from a water and 2-MeTHF solution, was selected for single crystal X-ray data analysis. The crystal was a colorless rod with dimensions of 0.15 mm x 0.09 mm x 0.09mm. Data collection was performed on a Bruker Apex II system at 293K. The unit cell was determined to be orthorhombic in space group $P2_12_12_1$. The structure contained one molecule of *para*-toluenesulfonic acid and one molecule of **3a** in the crystallographic asymmetric unit.

The absolute configuration was established by anomalous-dispersion effects in diffraction measurements on the crystal and confirmed that the stereochemistry was as shown.
Crystallographic data is summarized in Table S8. Figure S20 shows a thermal ellipsoid representation of Compound **3a·TsOH** with thermal ellipsoids set at the 30% probability level. Significant disorder was observed for the oxygens of *para*-toluenesulfonic acid. Coordinates, refinement details, and structure factors have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2215969).

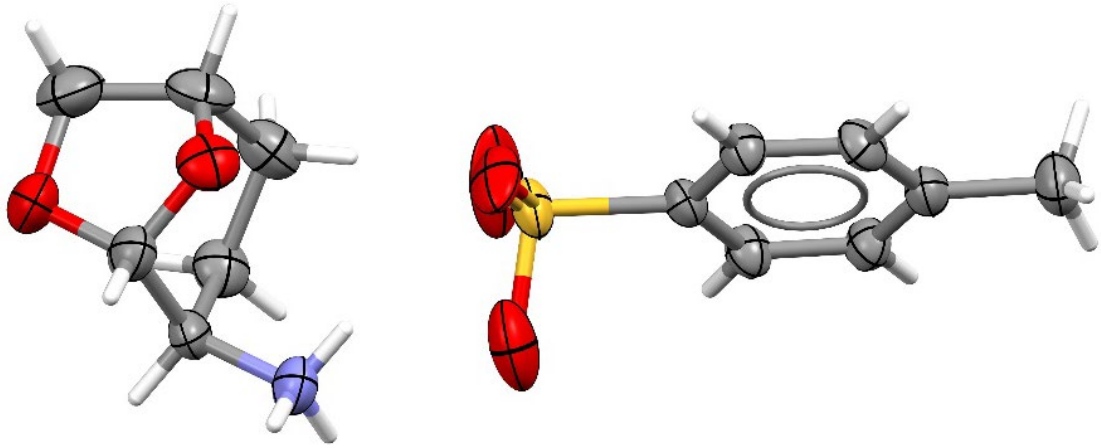


Figure S20. Thermal ellipsoid representation of Compound **3a·TsOH** with thermal ellipsoids set at the 30% probability level. Disorder in the *para*-toluenesulfonic acid was removed for clarity.

Table S7. Crystal data and structure refinement for Compound **3a·TsOH** [CCDC 2215969].

Identification code	mdp019
Empirical formula	$C_{13}H_{19}NO_5S$
Formula weight	301.35
Temperature	293(2) K
Radiation	CuKα (λ = 1.54178)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit Cell Dimensions	a = 6.1009(3) Å α = 90°
	b = 12.5179(6) Å β = 90°
	c = 19.3009(11) Å γ = 90°
Volume	1474.02(13) ($Å^3$)
Z	4
Density	1.358 (g/cm^3)
Absorption coefficient	2.129 mm^{-1}
F(000)	640.0
Crystal size	0.15 × 0.09 × 0.09 mm^3
2Θ range for data collection	8.418° to 133.232°
Index ranges	$-5 \leq h \leq 7$, $-14 \leq k \leq 14$, $-22 \leq l \leq 22$
Reflections collected	9588
Independent reflections	2602 [R_{int} = 0.0306, R_{sigma} = 0.0291]
Completeness to Θ=66.616°	0.999
Absorption correction	multi-scan
Max. and min. transmission	0.7528 and 0.6754
Refinement Method	Full-matrix least-squares on F^2
Data/restraints/parameters	2602/0/211
Goodness-of-fit on F^2	1.077
Final R indexes [I>=2σ (I)]	R_1 = 0.0431, wR_2 = 0.1072
Final R indexes [all data]	R_1 = 0.0479, wR_2 = 0.1108
Flack parameter	0.064(11)
Largest diff. peak/hole	0.24/-0.28 $eÅ^{-3}$

6.2. Crystal Data and Structure Refinement for Compound 1a·TsOH (CCDC 2215968)

A single crystal, grown from a saturated solution of acetonitrile and water, was selected for single crystal X-ray data analysis. The crystal was a colorless irregular shape with dimensions of 0.1 mm x 0.09 mm x 0.09mm. Data collection was performed on a Bruker Apex II system at 100K. The unit cell was determined to be orthorhombic in space group $P2_12_12_1$. The structure contains one molecule **1a**, one molecule of *para*-toluenesulfonic acid, and two water molecules in the crystallographic asymmetric unit.

The absolute configuration was established by anomalous-dispersion effects in diffraction measurements on the crystal and confirmed that the stereochemistry was as shown.
Crystallographic data is summarized in Table S9. Figure S21 shows a thermal ellipsoid representation of Compound **1a·TsOH** with thermal ellipsoids set at the 30% probability level. Coordinates, refinement details, and structure factors have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2215968).

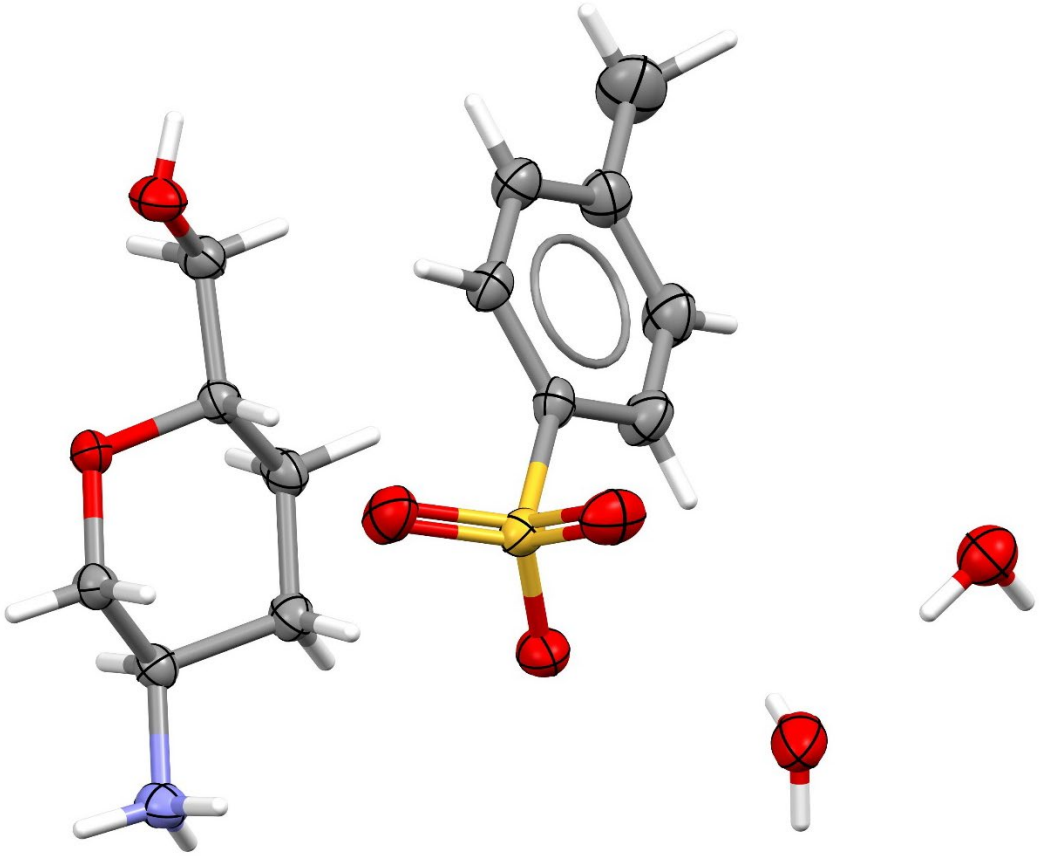


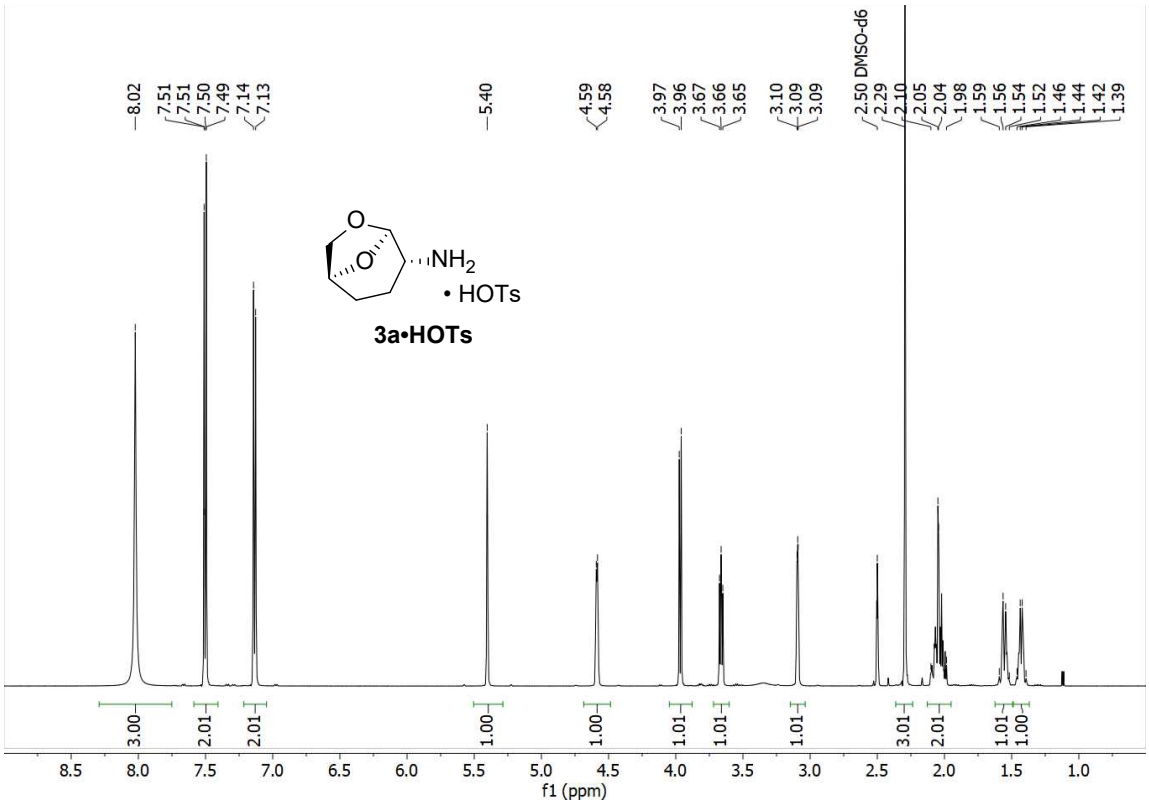
Figure S21. Thermal ellipsoid representation of Compound **1a·TsOH** with thermal ellipsoids set at the 30% probability level.

Table S8. Crystal data and structure refinement for **1a·TsOH** [CCDC 2215968].

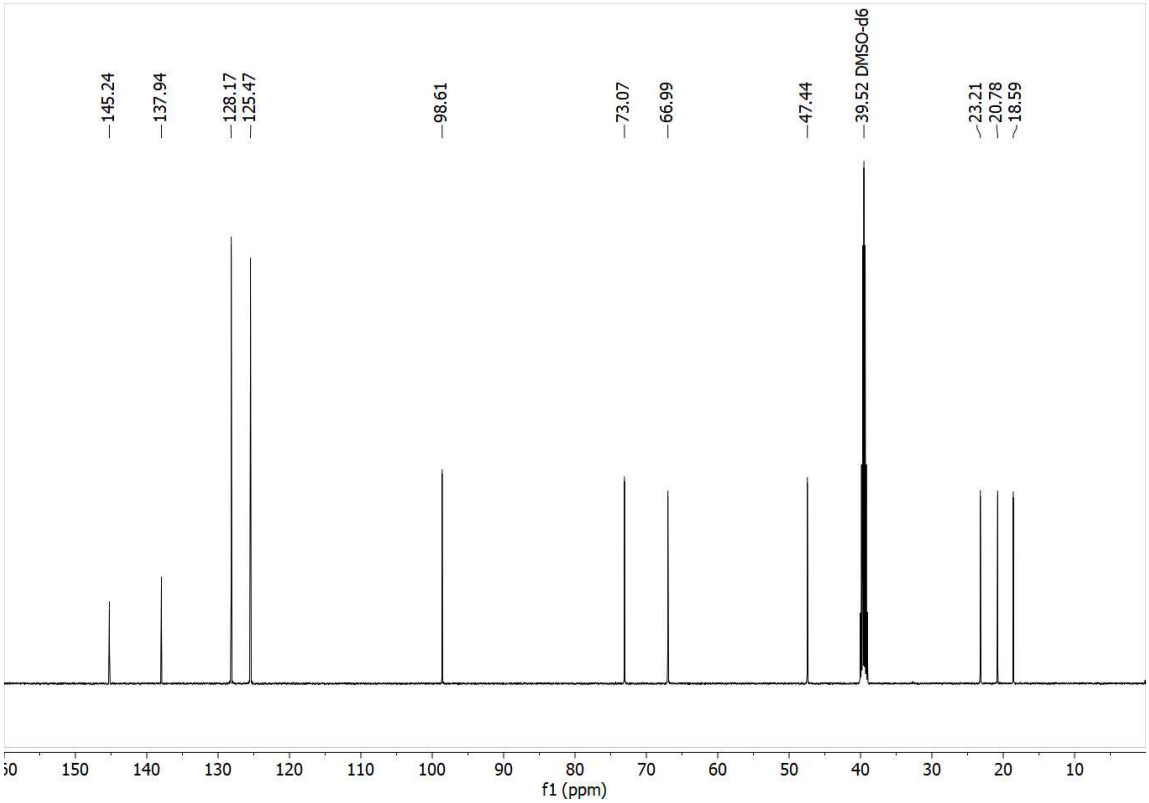
Identification code	mdq012
Empirical formula	$C_{13}H_{25}NO_7S$
Formula weight	339.40
Temperature	296.15 K
Radiation	CuKα (λ = 1.54184)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit Cell Dimensions	a = 7.9459(9) Å α = 90°
	b = 13.5525(12) Å β = 90°
	c = 15.5352(9) Å γ = 90°
Volume	1672.9(3) ($Å^3$)
Z	4
Density	1.348 (g/cm^3)
Absorption coefficient	2.022 mm^{-1}
F(000)	728.0
Crystal size	0.1 × 0.09 × 0.09 mm^3
2Θ range for data collection	8.658° to 133.028°
Index ranges	$-9 \le h \le 9$, $-16 \le k \le 13$, $-18 \le l \le 9$
Reflections collected	9594
Independent reflections	2943 [R_{int} = 0.0435, R_{sigma} = 0.0440]
Completeness to Θ=66.514°	1.000
Absorption correction	multi-scan
Max. and min. transmission	0.7528 and 0.6738
Refinement Method	Full-matrix least-squares on F^2
Data/restraints/parameters	2943/0/293
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0311, wR_2 = 0.0810
Final R indexes [all data]	R_1 = 0.0334, wR_2 = 0.0831
Flack parameter	0.031(12)
Largest diff. peak/hole	0.23/-0.17 $eÅ^{-3}$

7. NMR Spectra

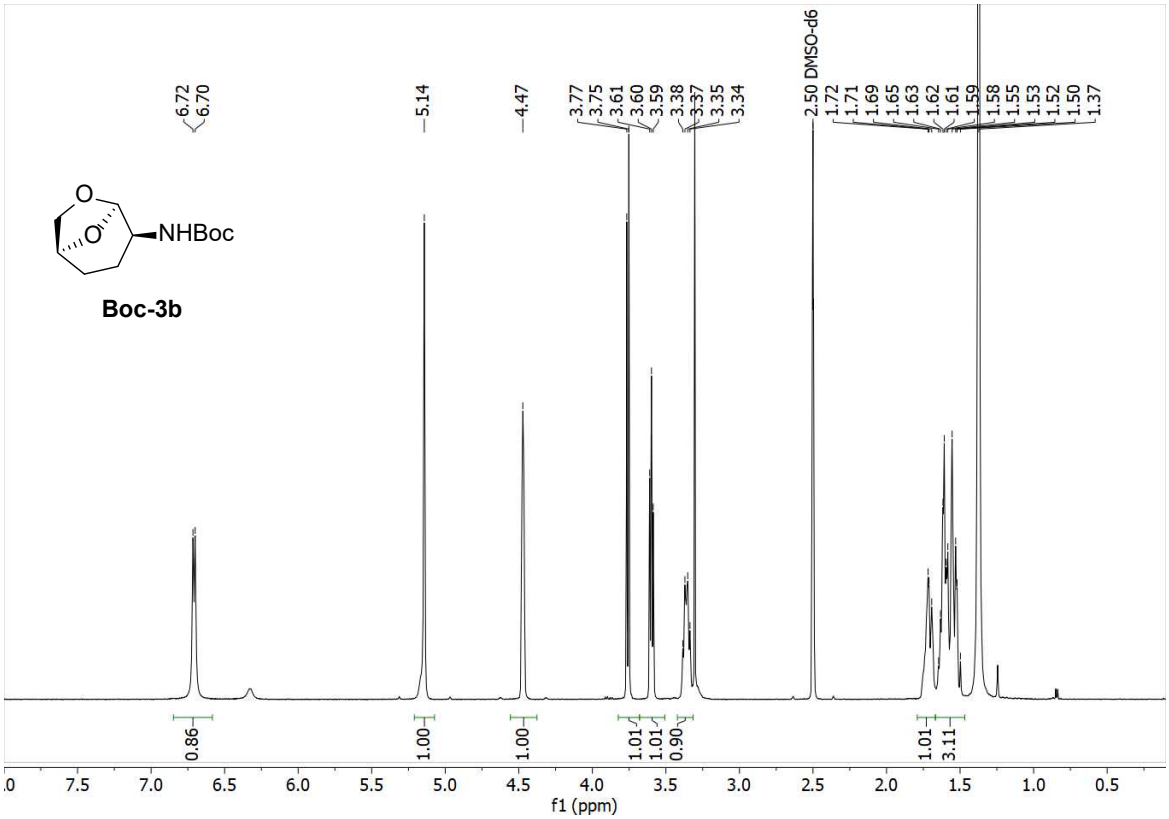
^{1}H NMR at 500 MHz of 3a·HOTs in DMSO-d_6:



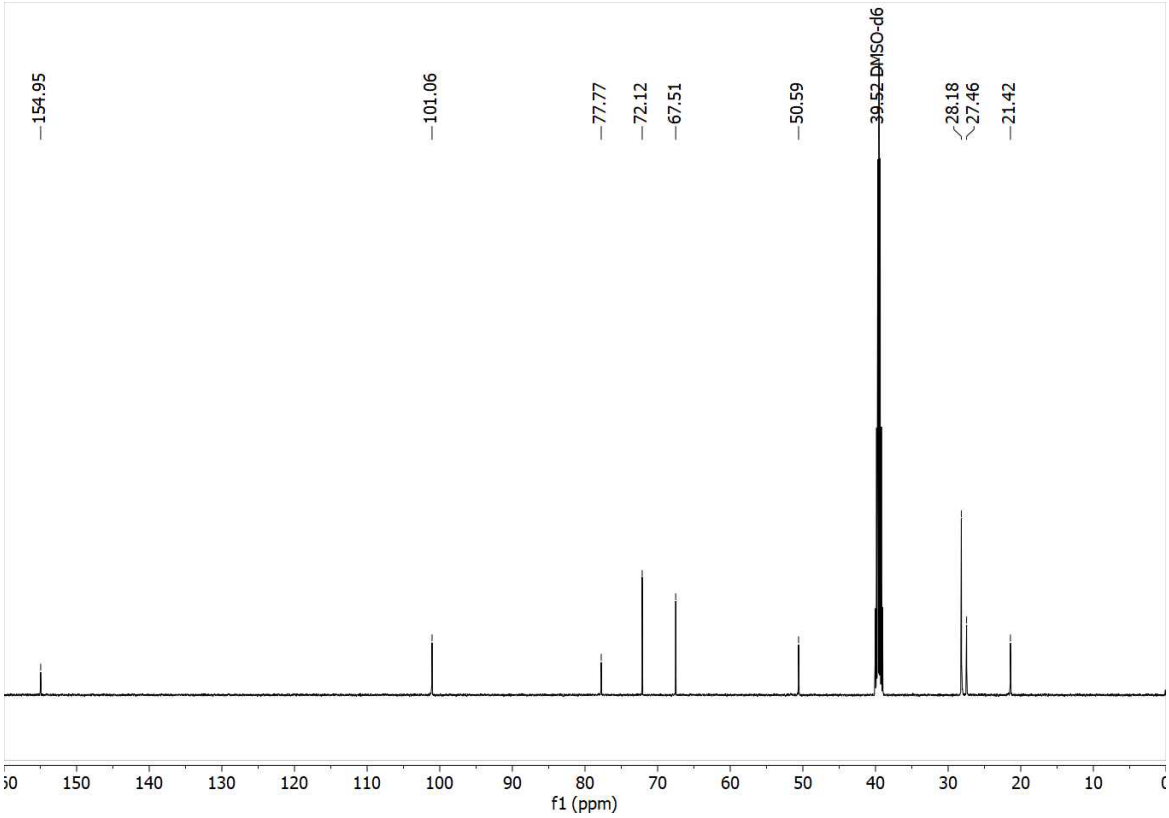
^{13}C NMR at 126 MHz of 3a·HOTs in DMSO-d_6:



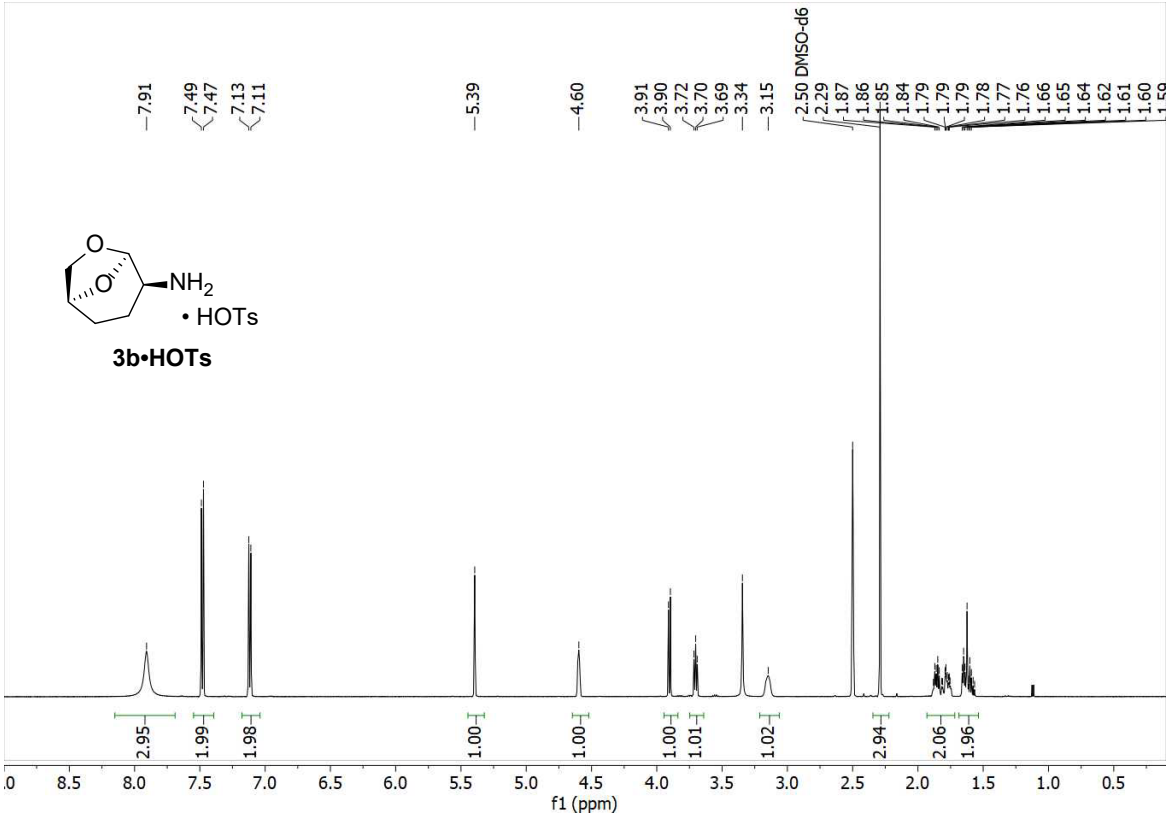
^{1}H NMR at 500 MHz of Boc-3b in DMSO-d_6:



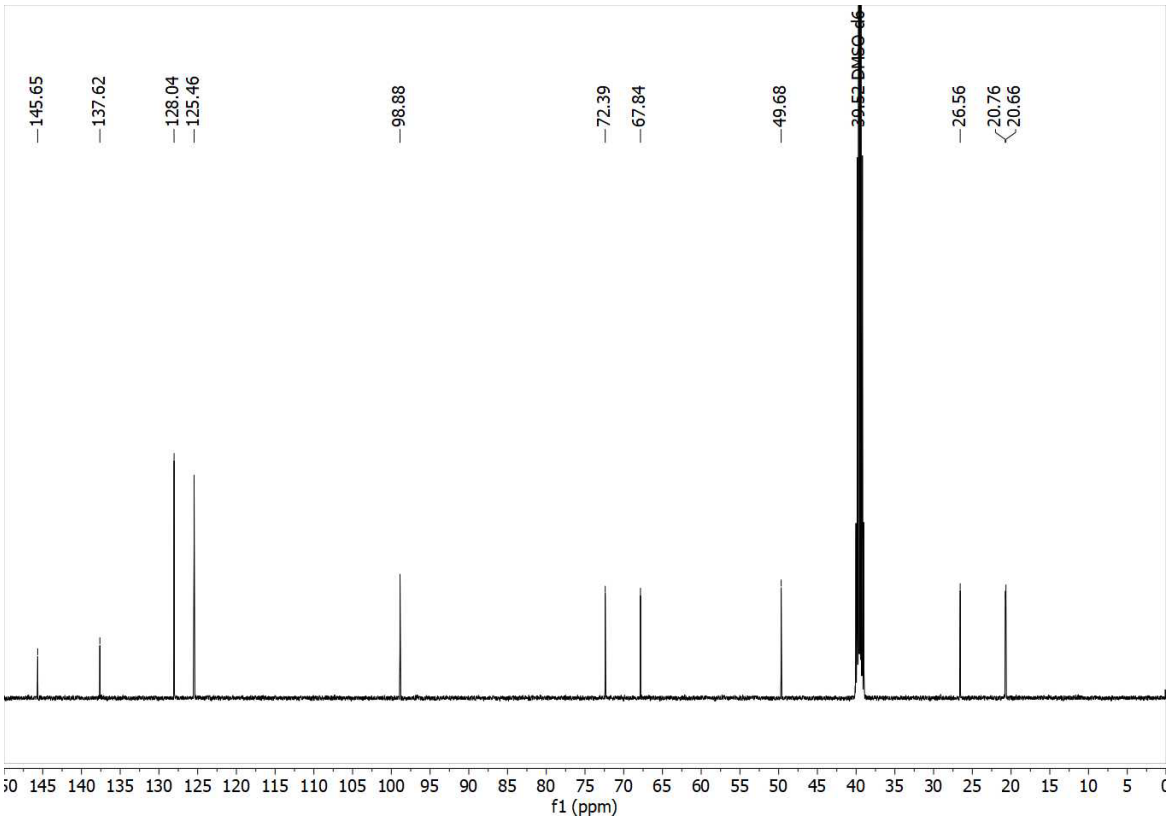
^{13}C NMR at 126 MHz of Boc-3b in DMSO-d_6:



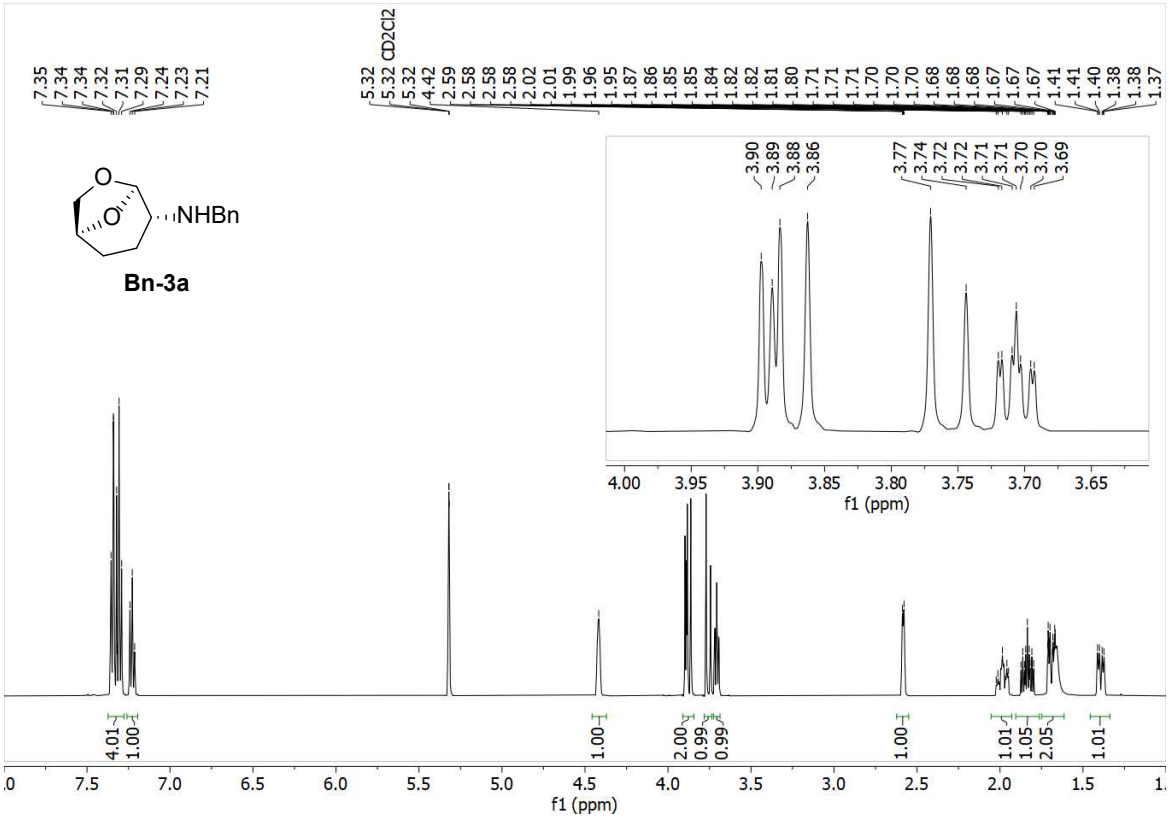
^{1}H NMR at 500 MHz of 3b·HOTs in DMSO-*d*$_6$:



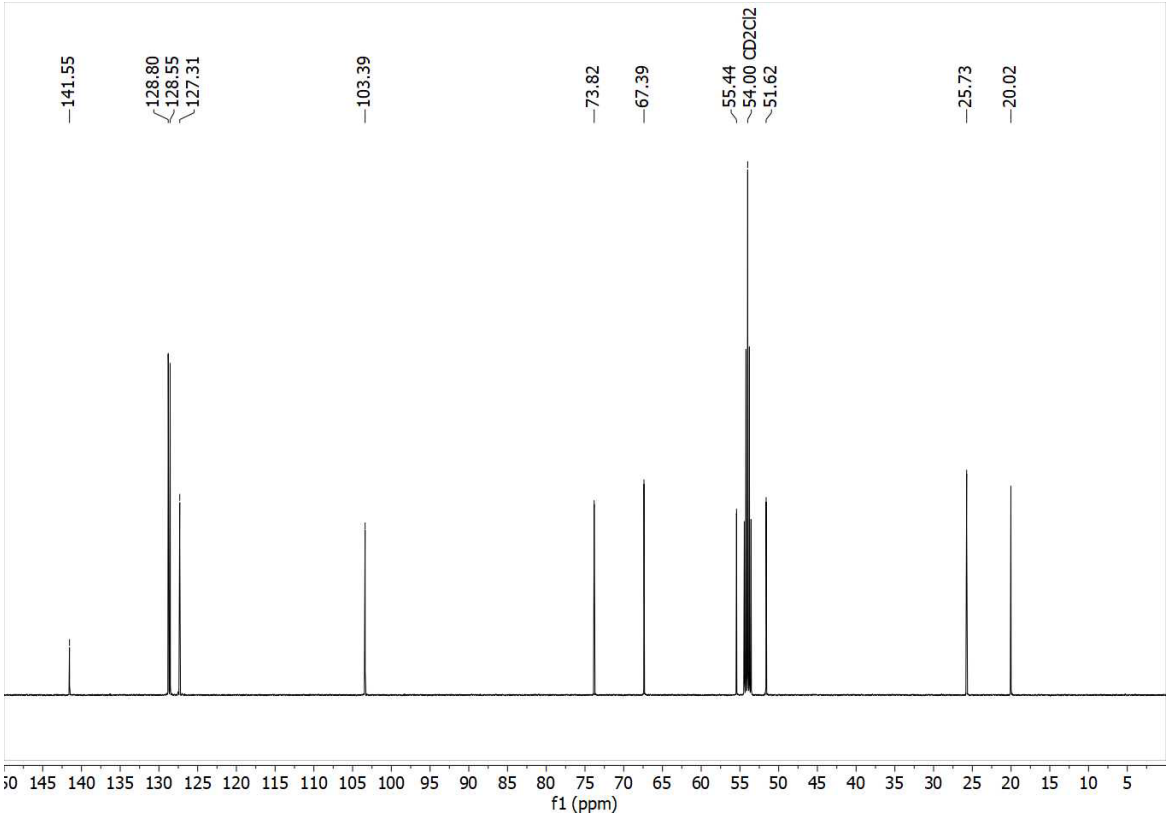
^{13}C NMR at 126 MHz of 3b·HOTs in DMSO-*d*$_6$:



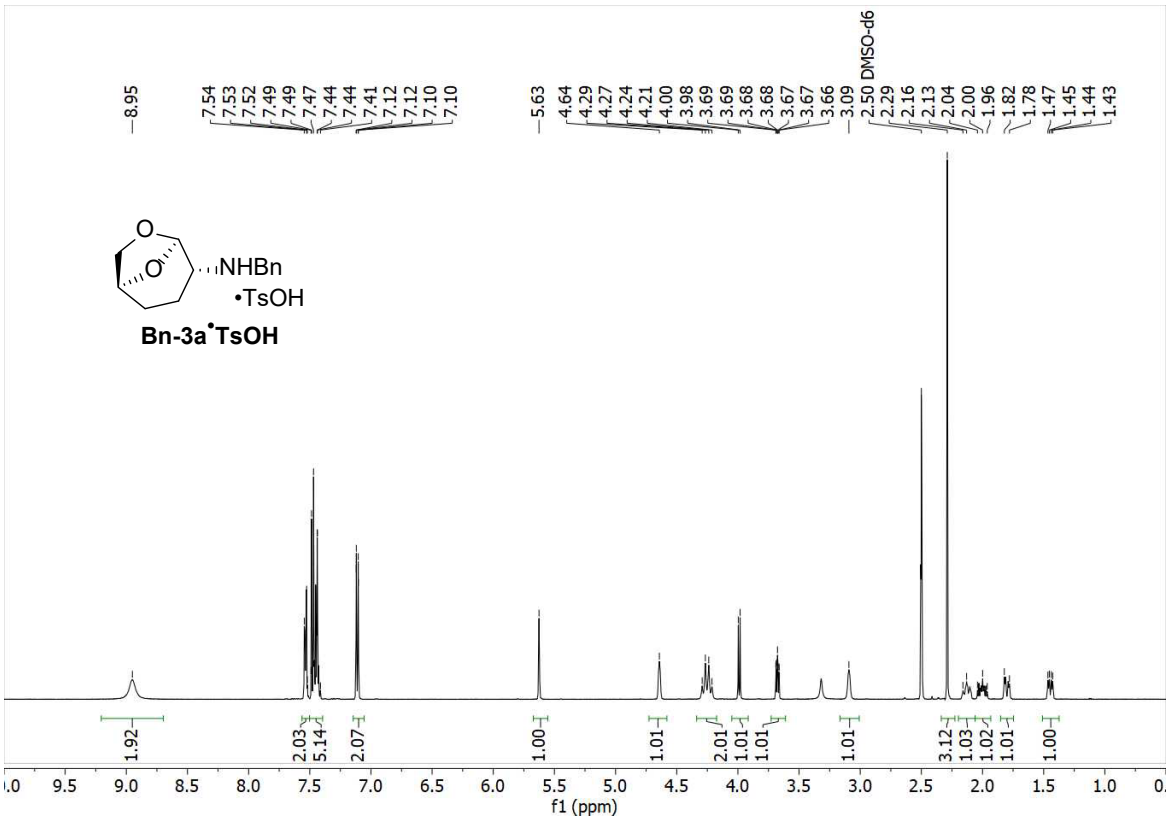
^{1}H NMR at 500 MHz of Bn-3a in CD_2Cl_2:



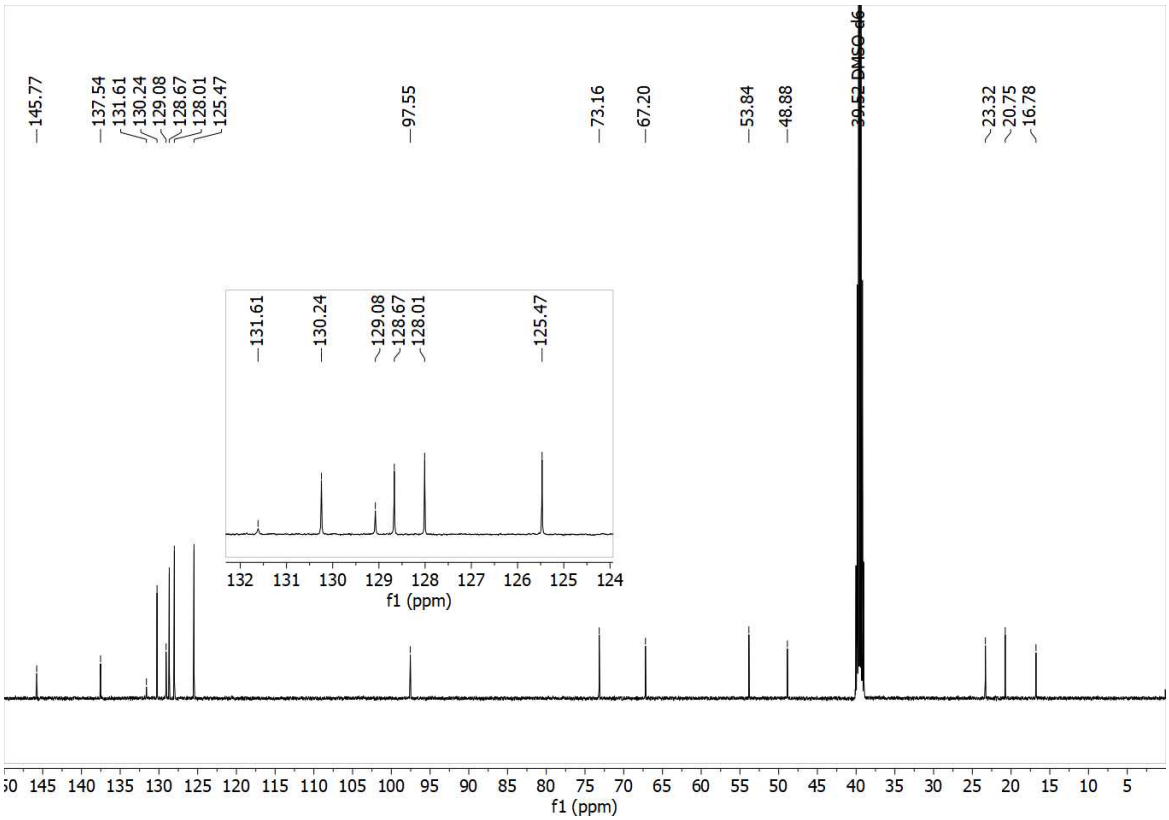
^{13}C NMR at 126 MHz of Bn-3a in CD_2Cl_2:



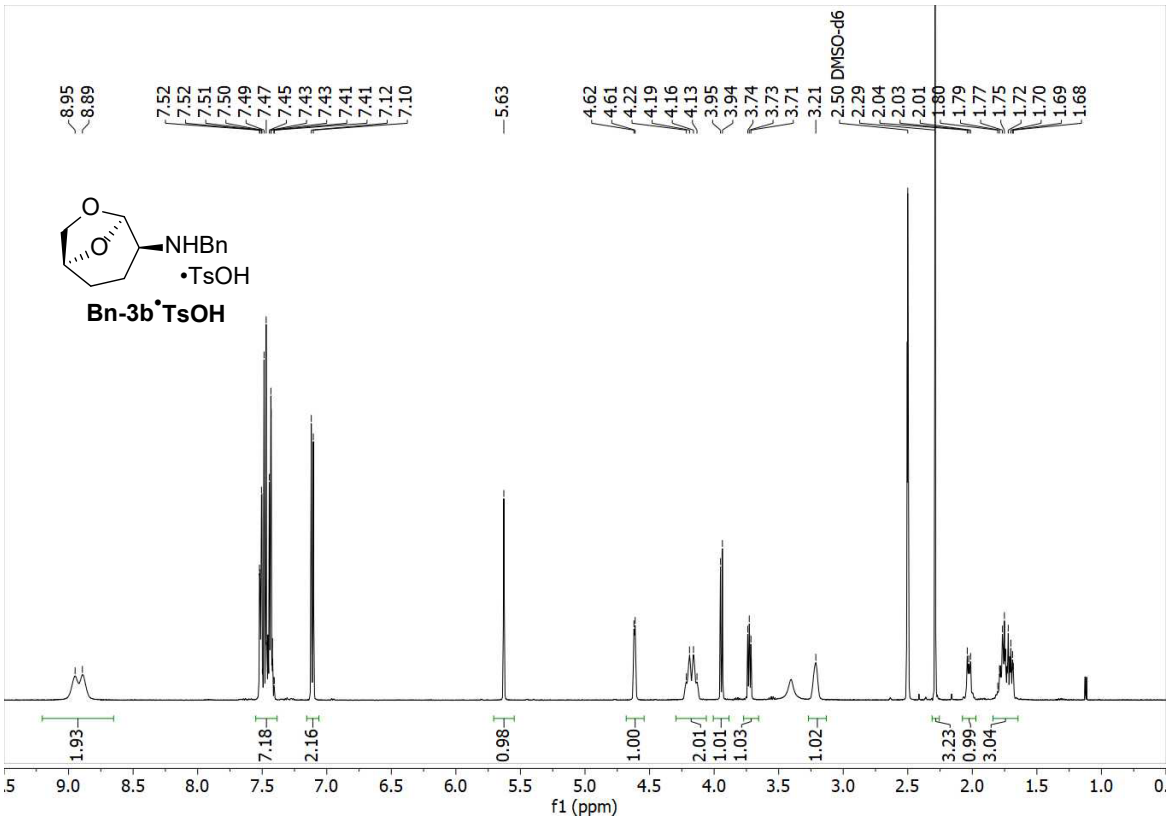
^{1}H NMR at 500 MHz of Bn-3a·HOTs in DMSO-*d*$_6$:



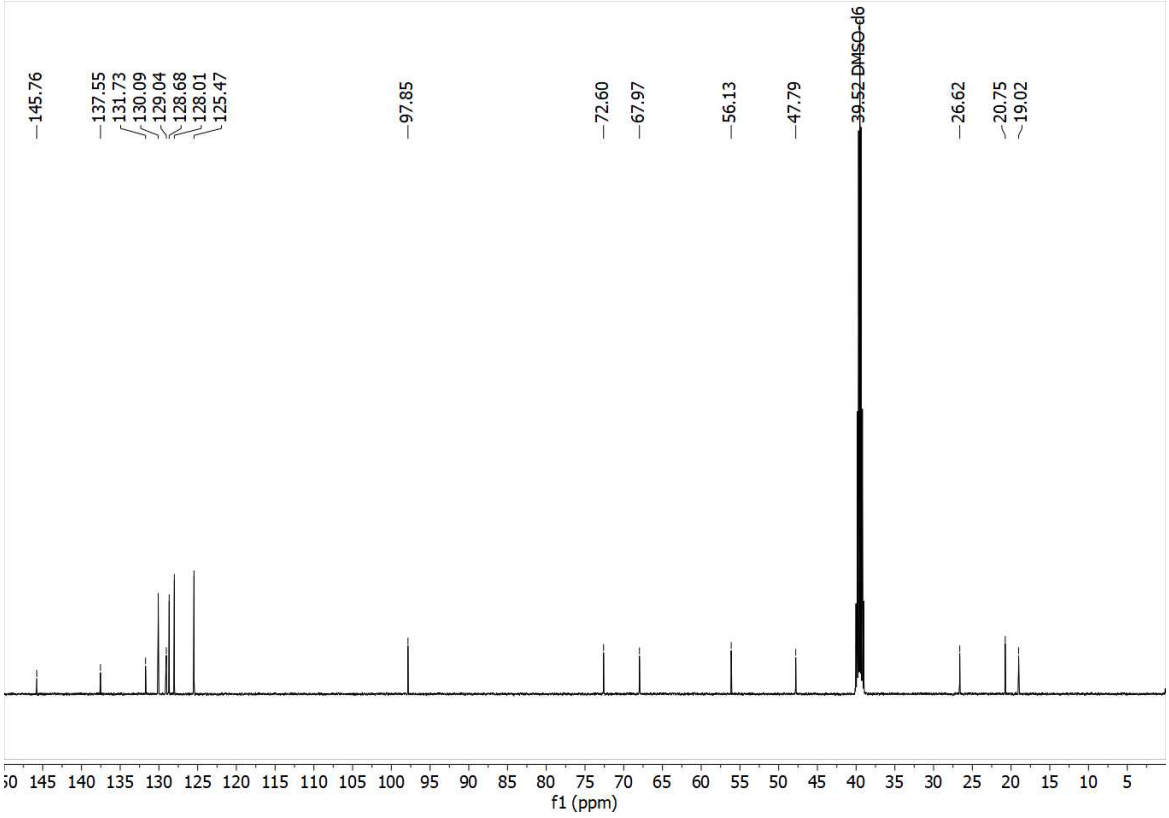
^{13}C NMR at 126 MHz of Bn-3a·HOTs in DMSO-*d*$_6$:



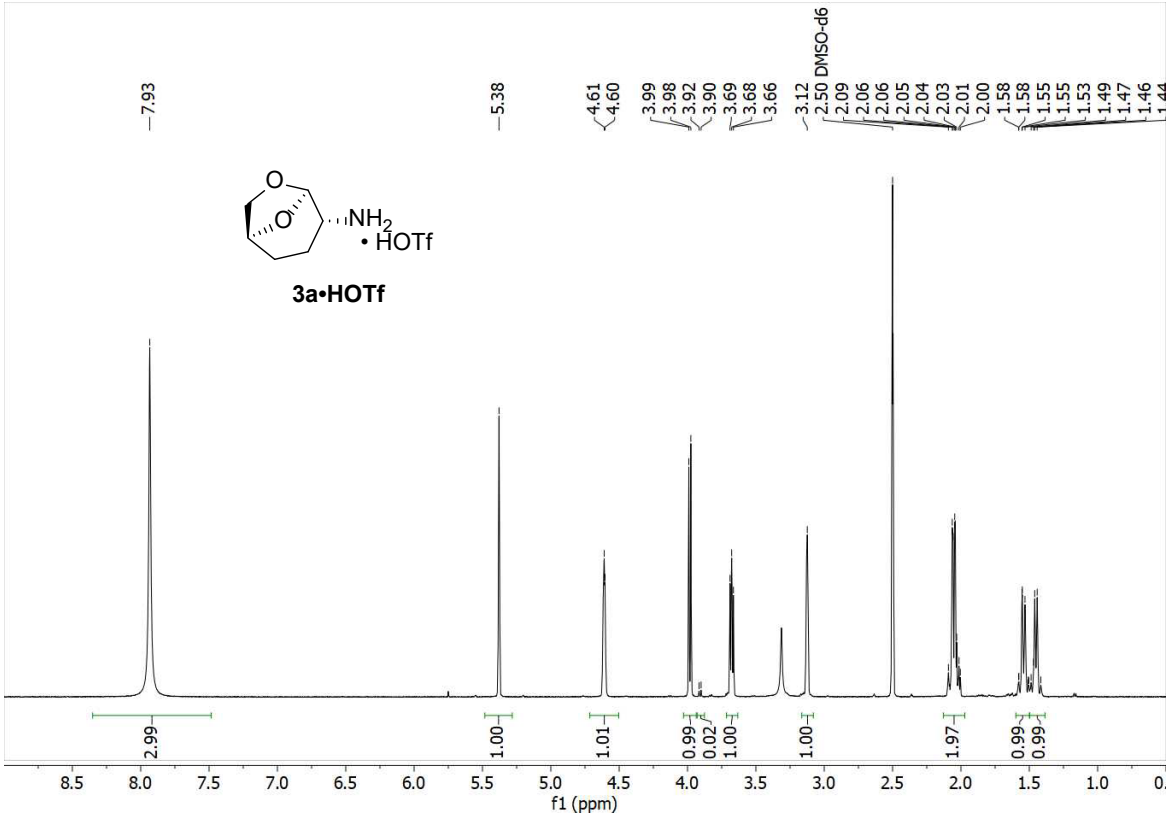
^{1}H NMR at 500 MHz of Bn-3b·HOTs in DMSO-*d*$_6$:



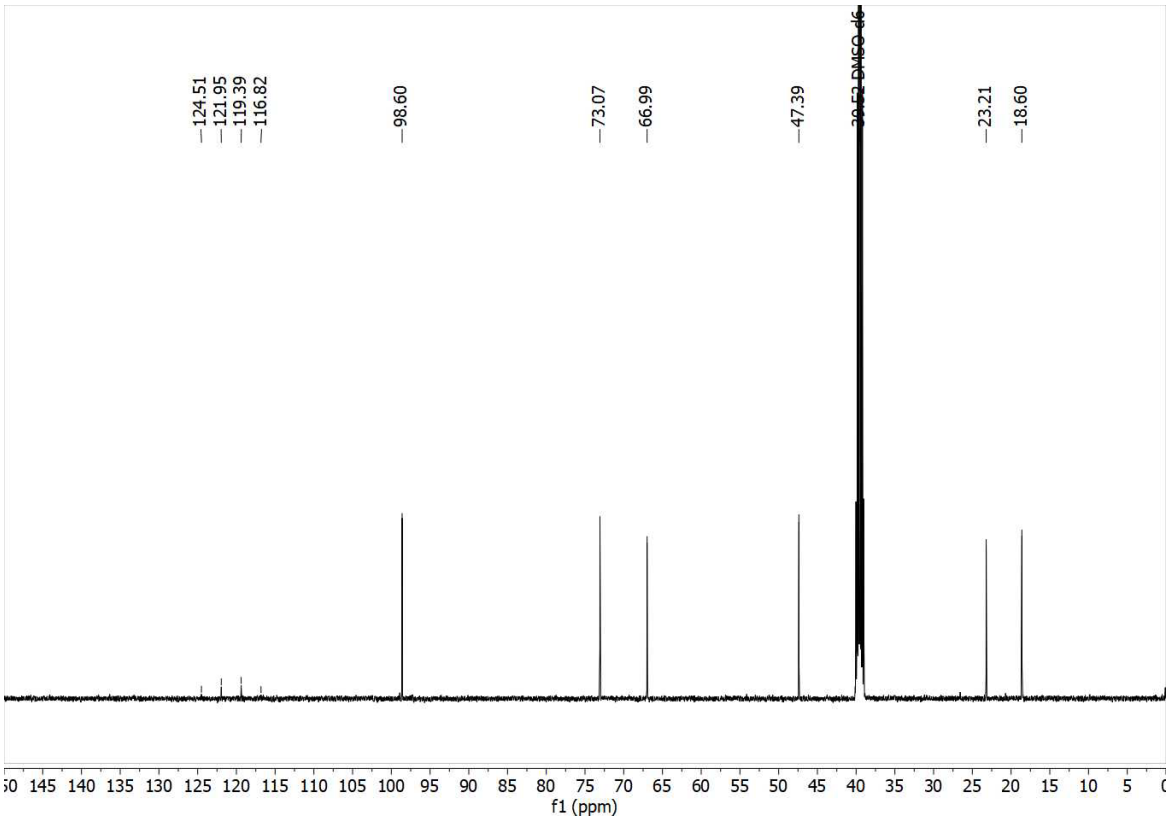
^{13}C NMR at 126 MHz of Bn-3b·HOTs in DMSO-*d*$_6$:



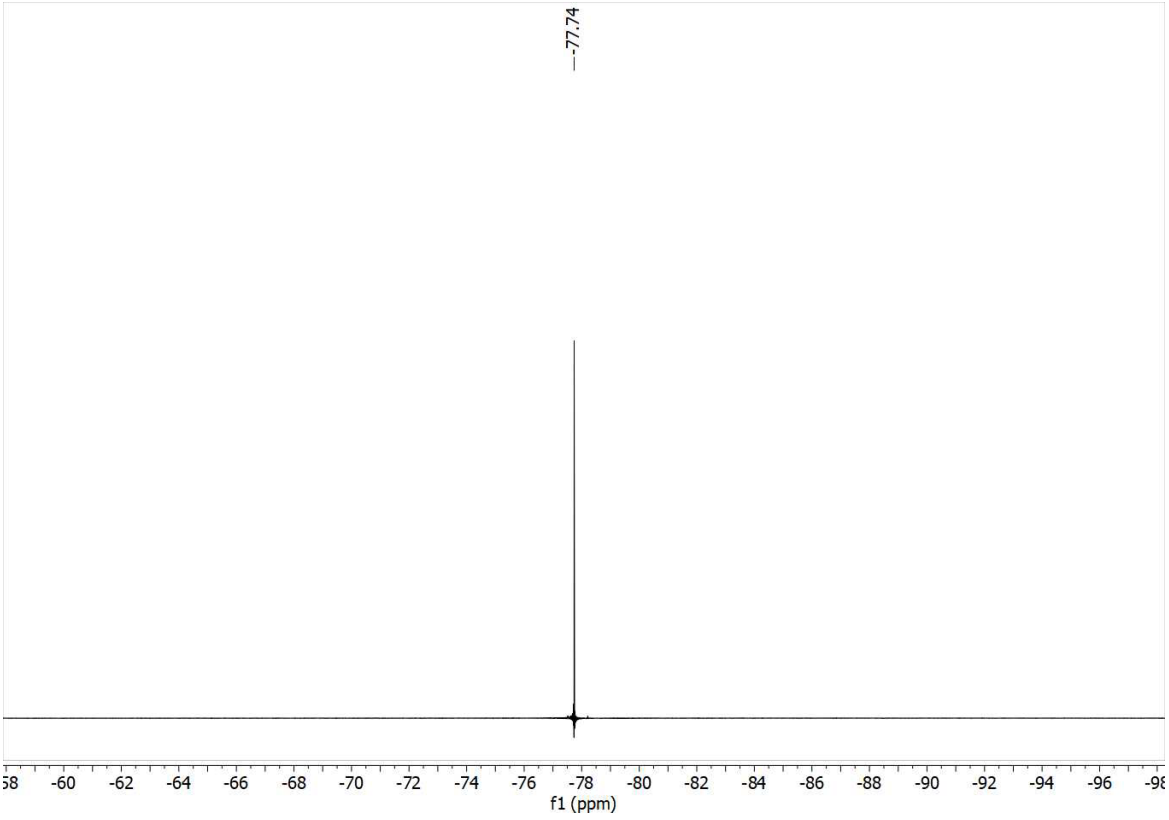
^{1}H NMR at 500 MHz of 3a·HOTf in DMSO-*d*$_6$:



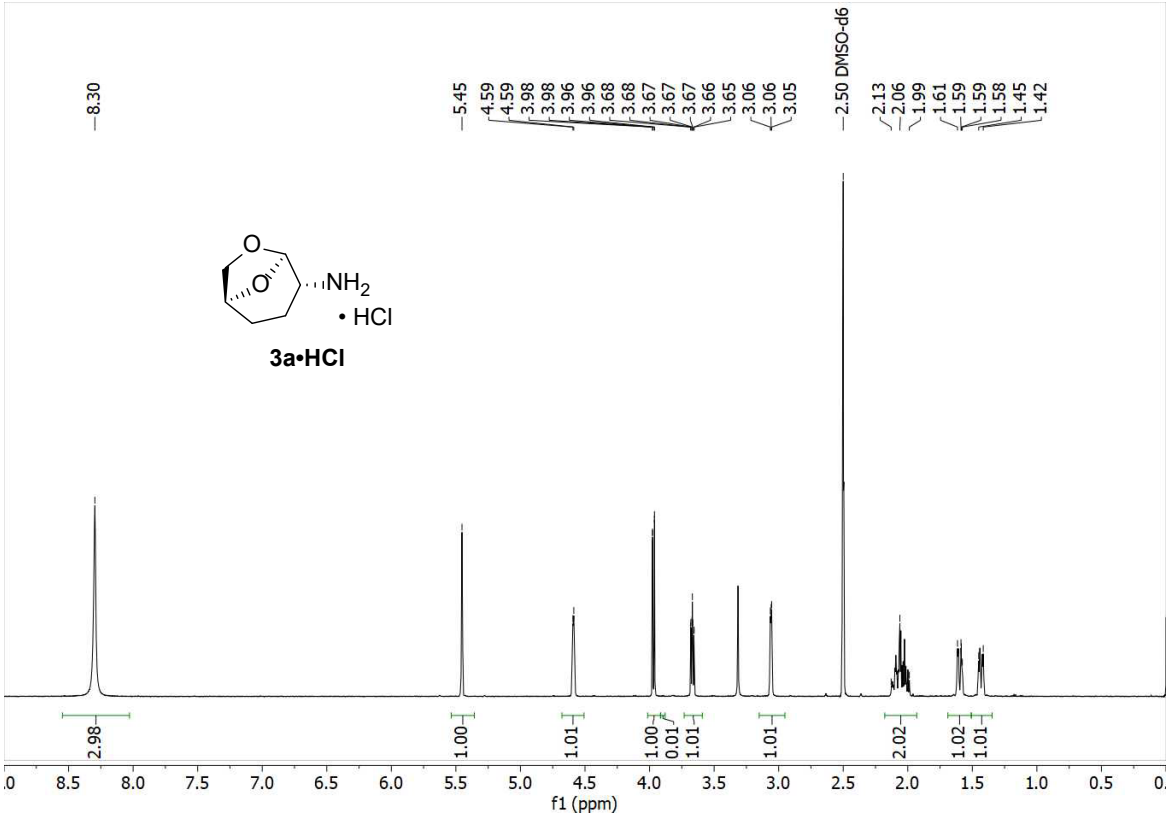
^{13}C NMR at 126 MHz of 3a·HOTf in DMSO-*d*$_6$:



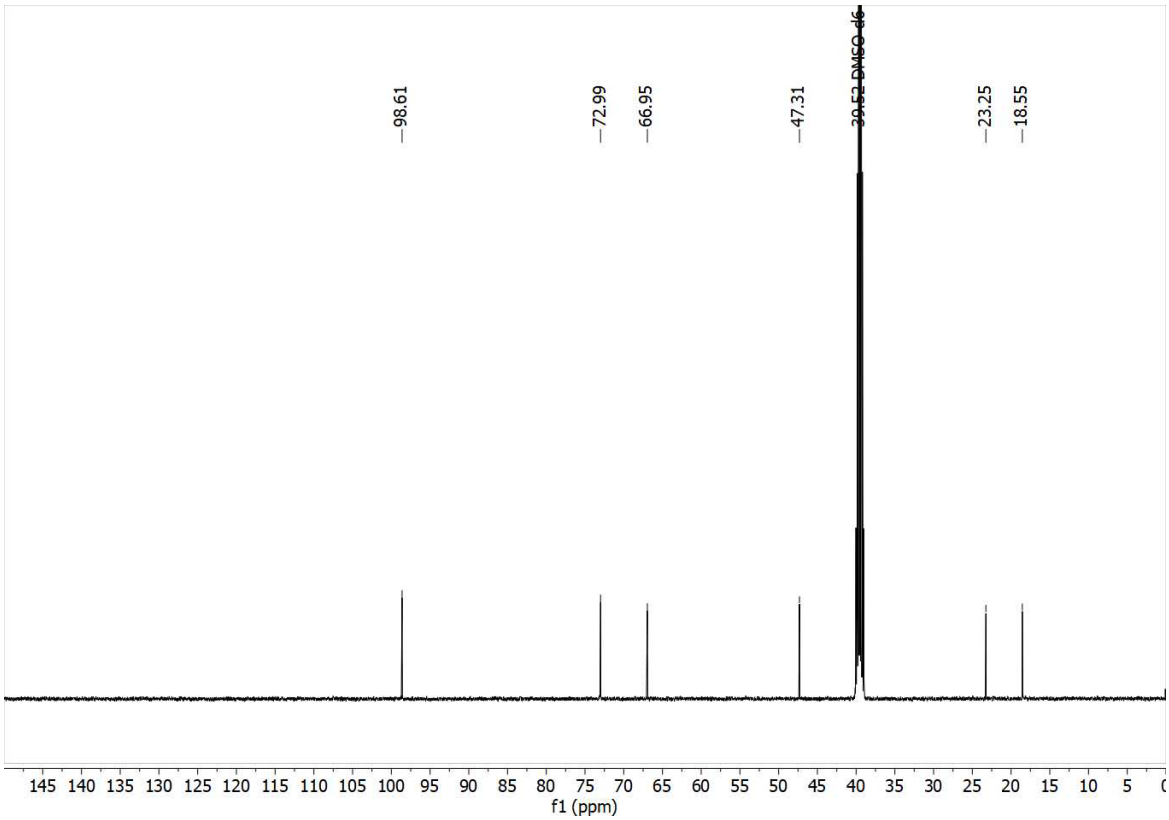
^{19}F NMR at 471 MHz of 3a·HOTf in DMSO-*d*$_6$:



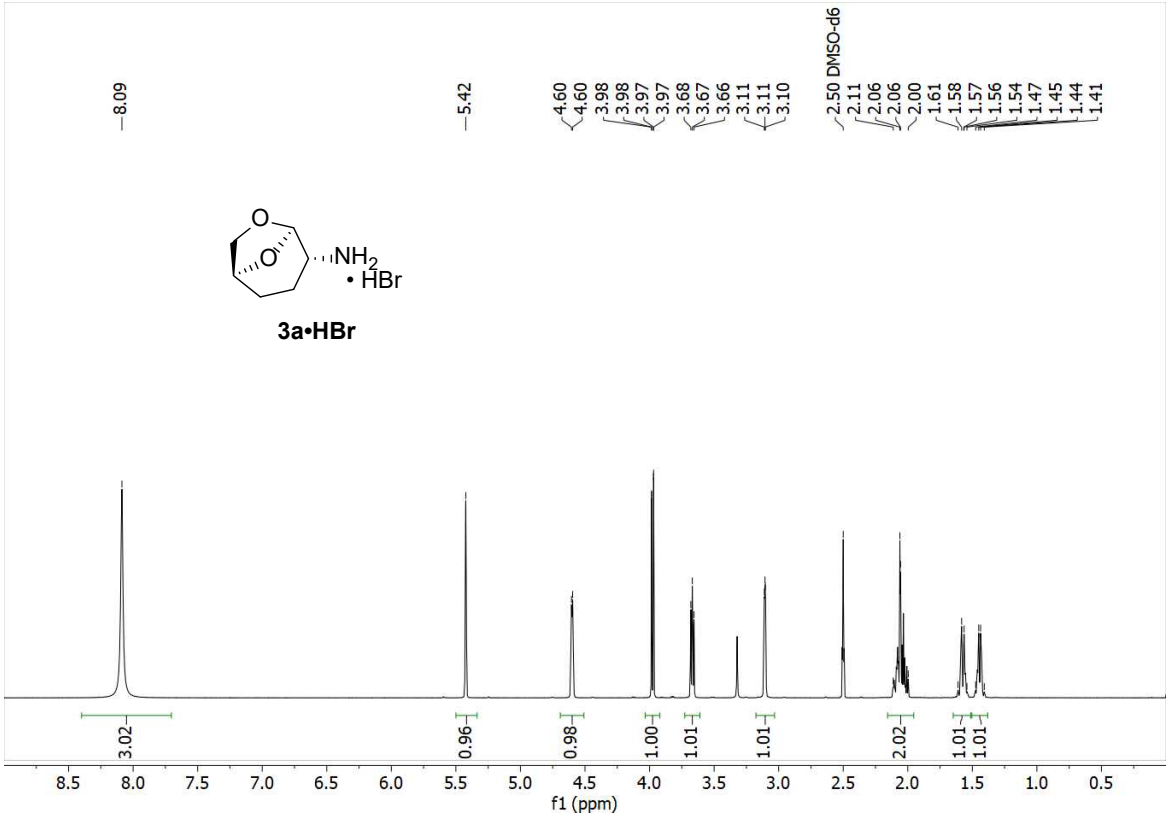
^{1}H NMR at 500 MHz of 3a·HCl in DMSO-*d*$_6$:



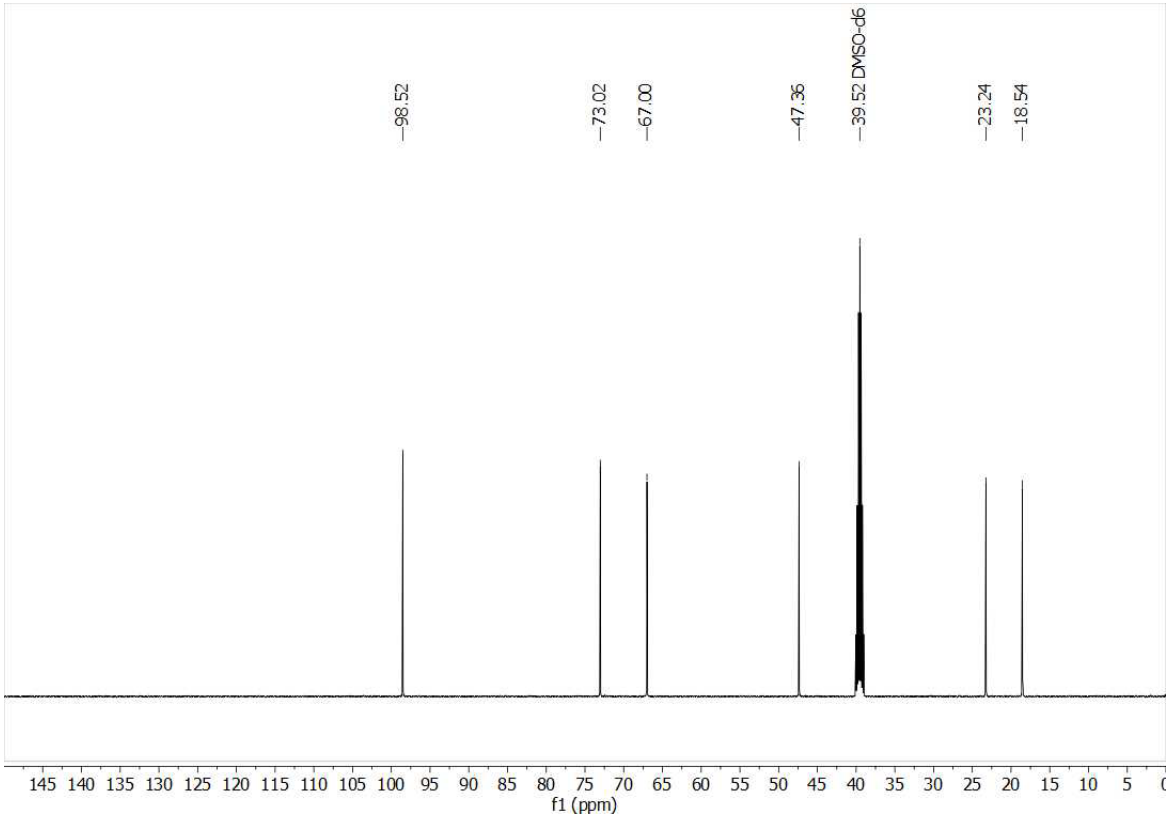
^{13}C NMR at 126 MHz of 3a·HCl in DMSO-*d*$_6$:



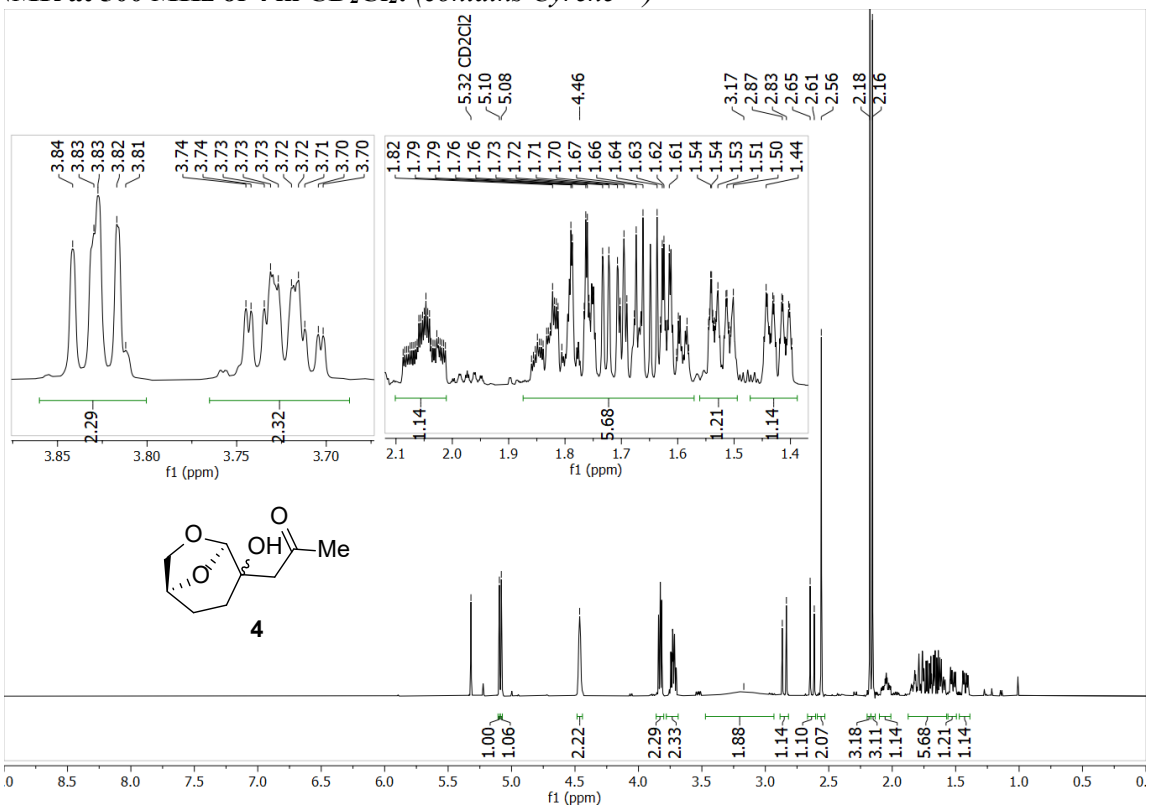
^{1}H NMR at 500 MHz of 3a·HBr in DMSO-d_6:



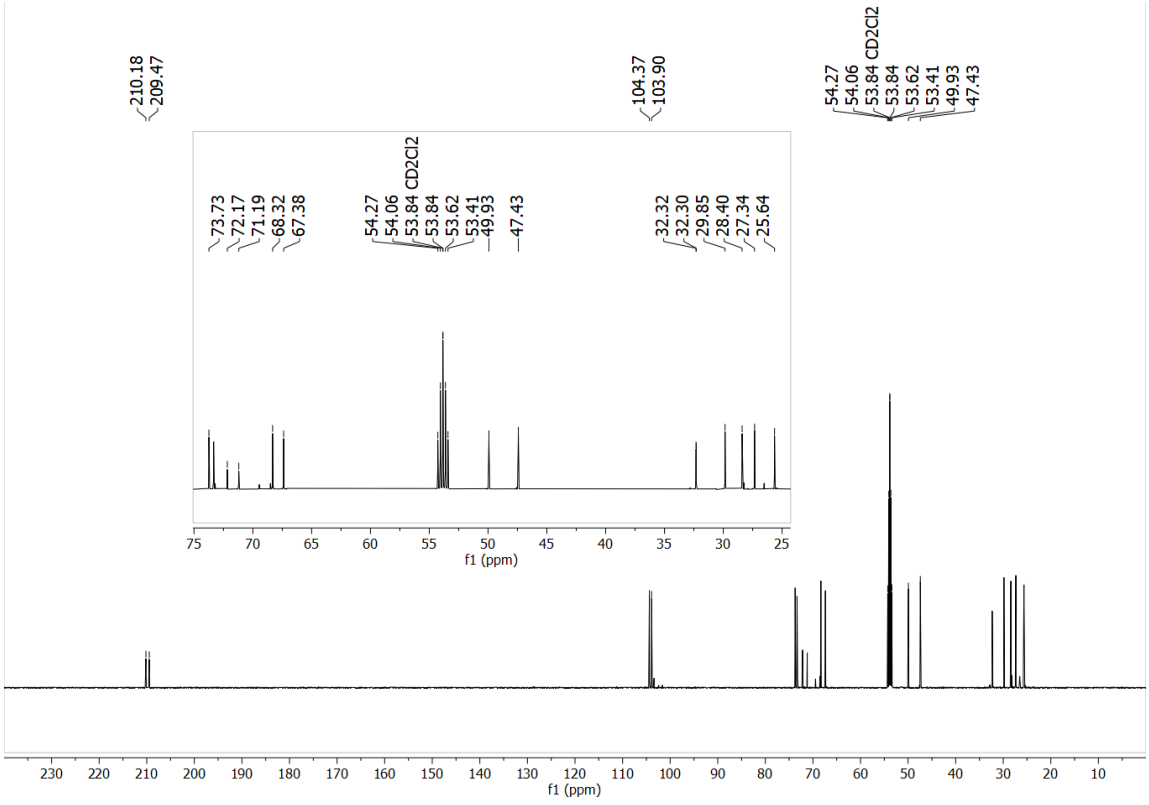
^{13}C NMR at 126 MHz of 3a·HBr in DMSO-d_6:



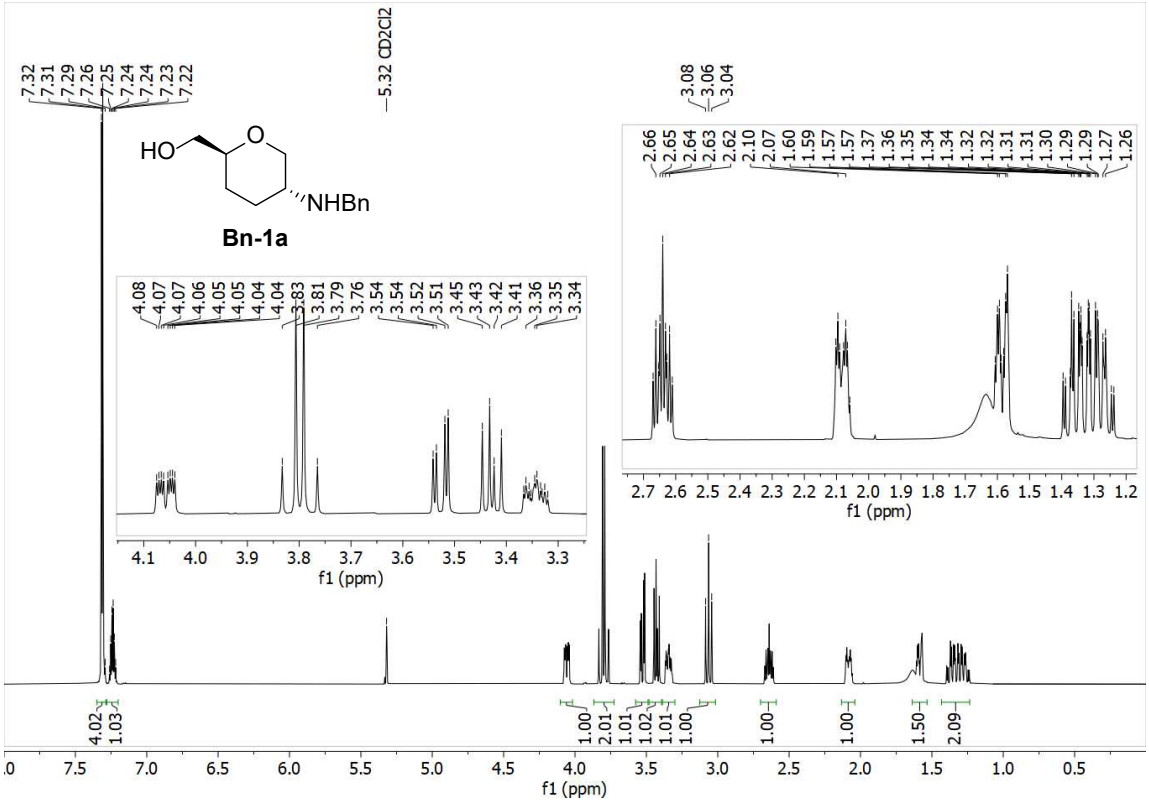
^{1}H NMR at 500 MHz of 4 in CD_2Cl_2: *(contains Cyrene™)*



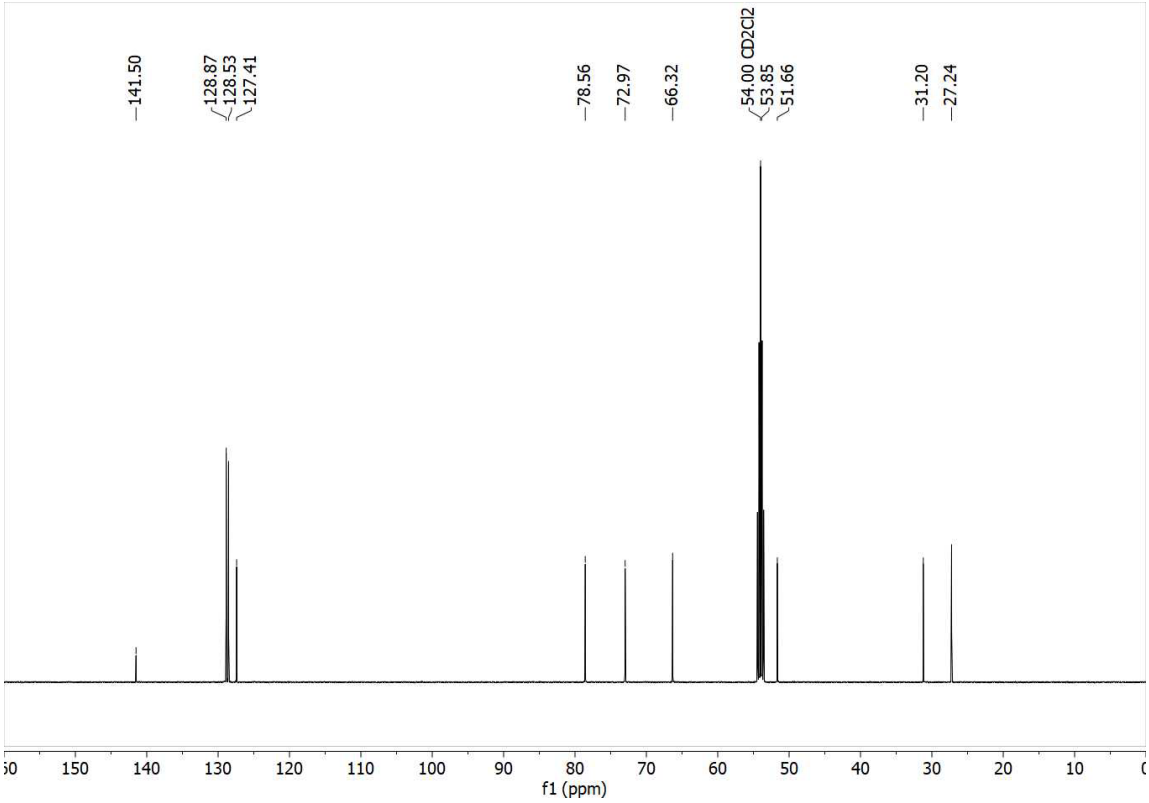
^{13}C NMR at 126 MHz of 4 in CD_2Cl_2: *(contains Cyrene™)*



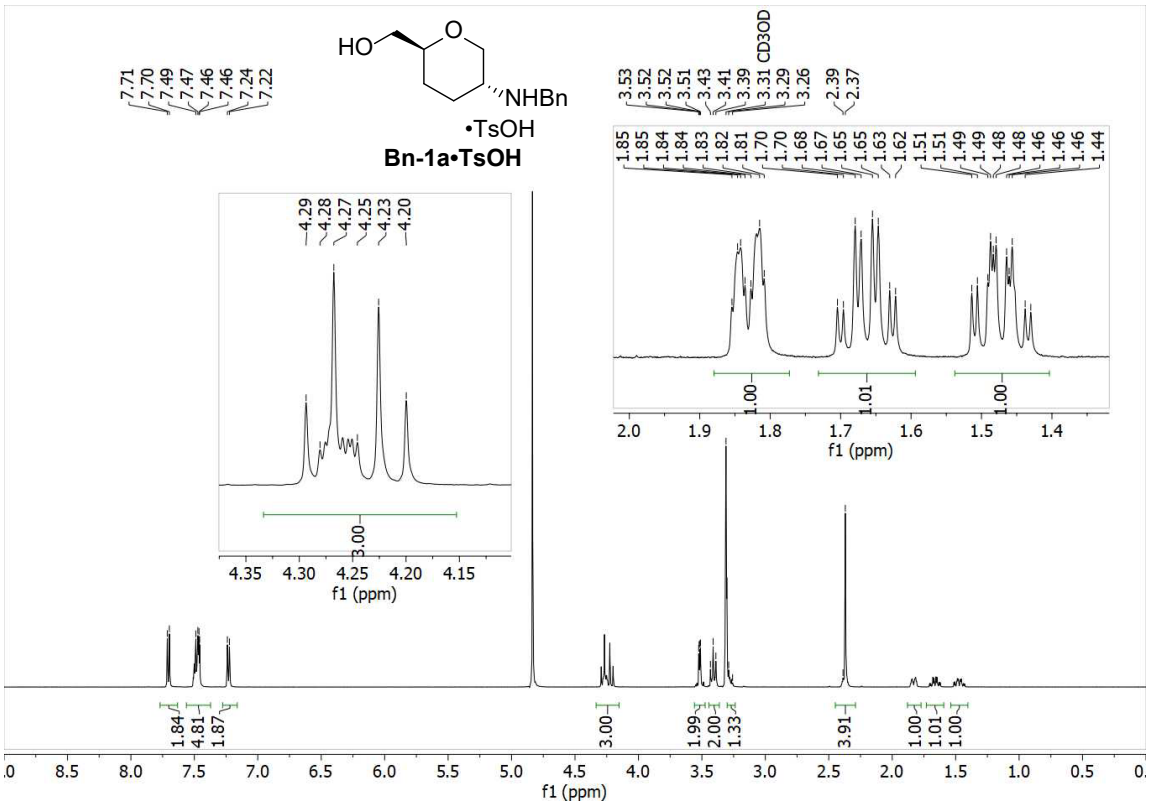
^{1}H NMR at 500 MHz of Bn-1a·in CD_2Cl_2:



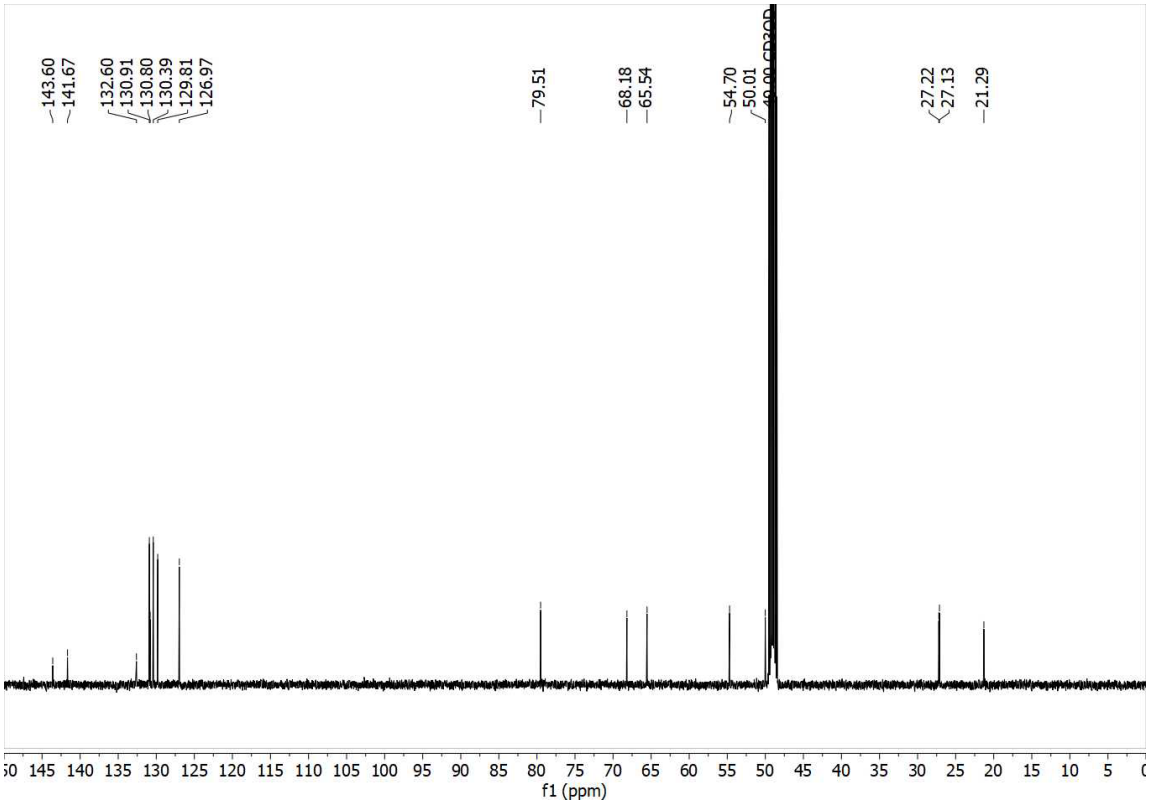
^{13}C NMR at 126 MHz of Bn-1a in CD_2Cl_2:



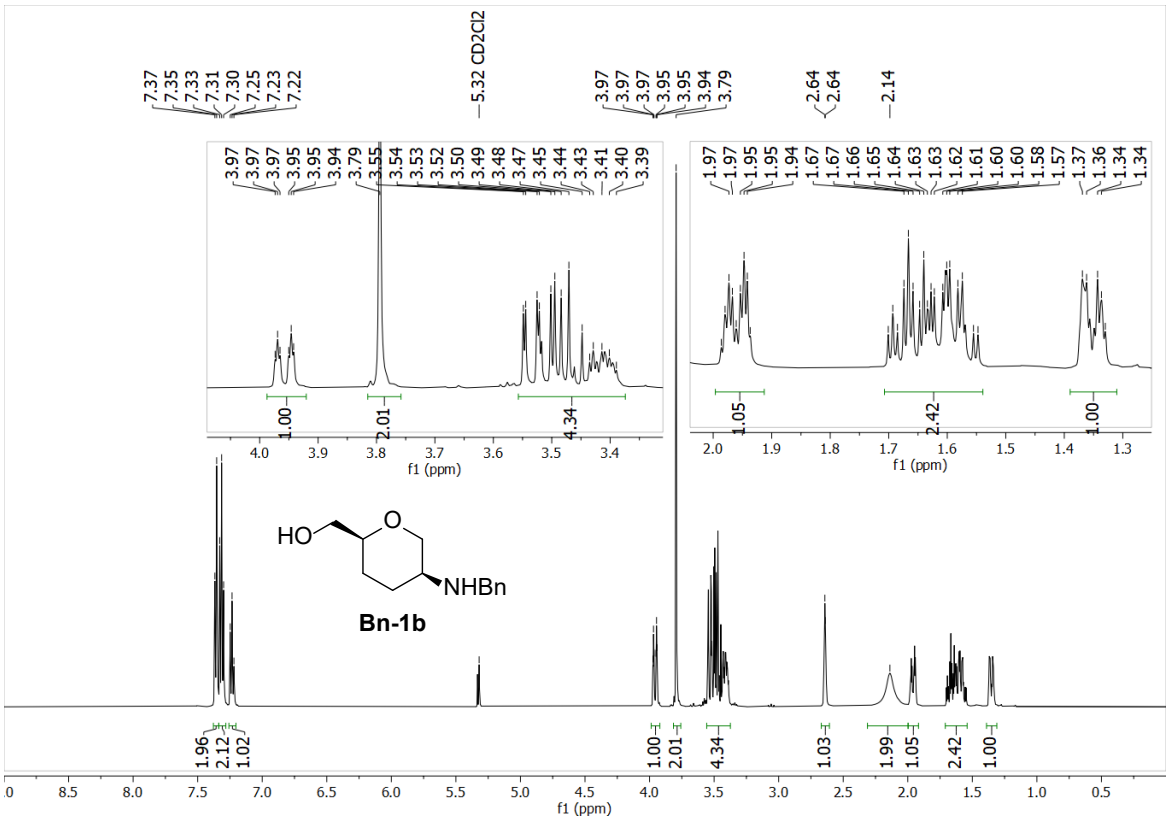
^{1}H NMR at 500 MHz of Bn-1a·TsOH·in methanol-*d*$_4$:



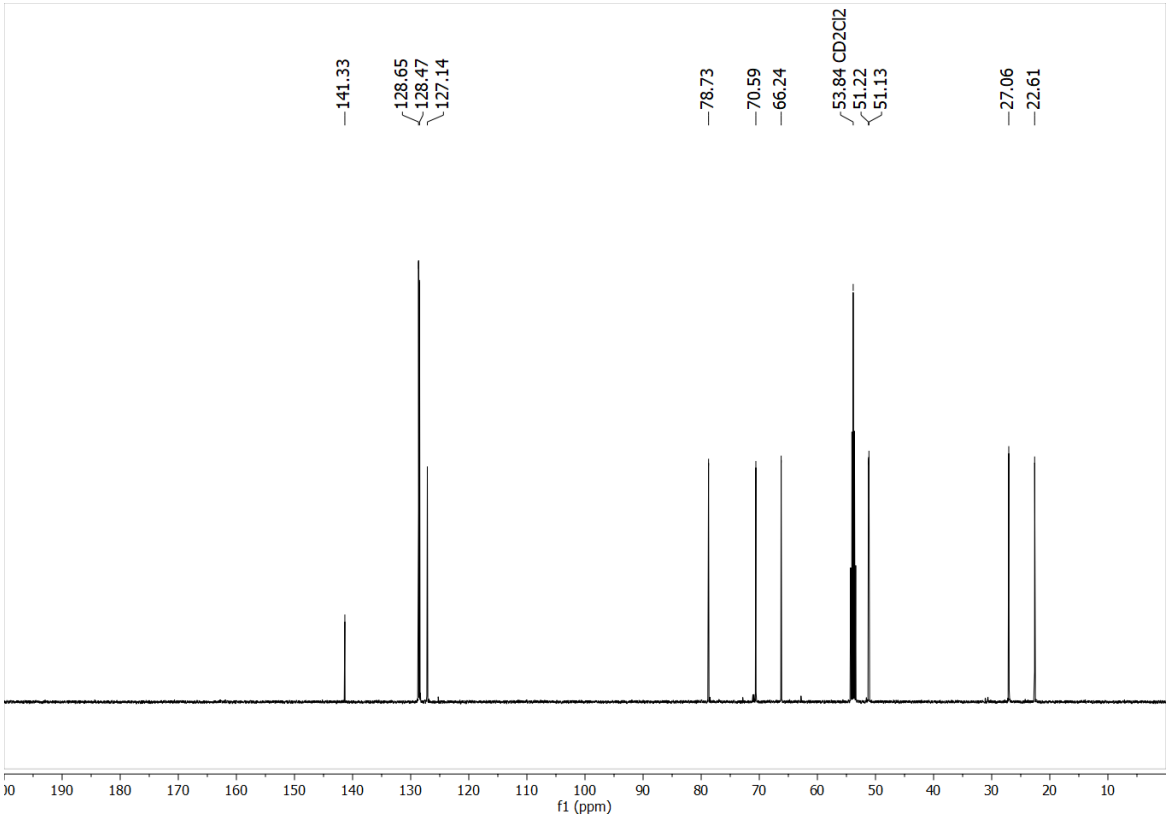
^{13}C NMR at 126 MHz of Bn-1a·TsOH in methanol-*d*$_4$:



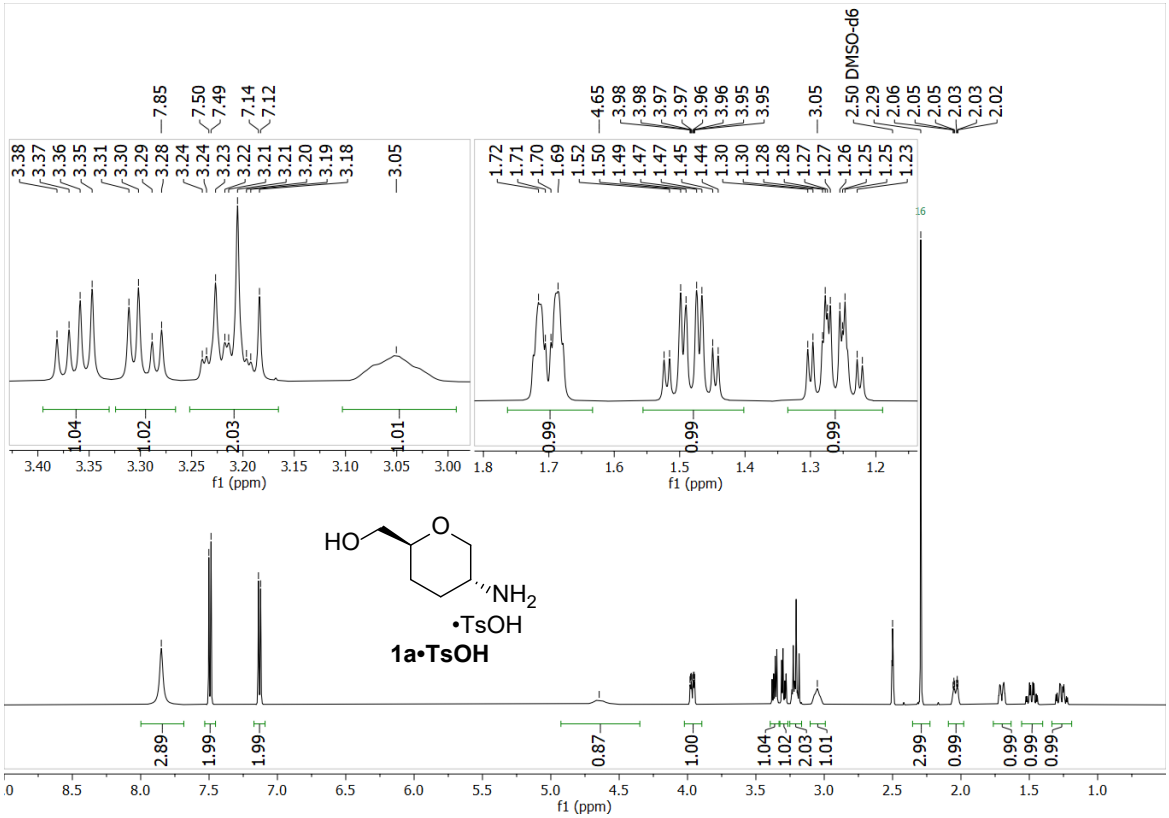
^{1}H NMR at 500 MHz of Bn-1b·in CD_2Cl_2:



^{13}C NMR at 126 MHz of Bn-1b in CD_2Cl_2:



^{1}H NMR at 500 MHz of 1a·TsOH in DMSO-*d*$_6$:



^{13}C NMR at 126 MHz of 1a·TsOH in DMSO-*d*$_6$: