Supporting Information for

Asymmetric Cu-Catalyzed 1,4-Dearomatization of Pyridines and Pyridazines without Preactivation of the Heterocycle or Nucleophile

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1. General Information

1.1 General Reagent Information

Unless noted otherwise, reagents and starting materials were purchased from commercial vendors and used as supplied. The (+)-(2*S*,5*S*) and (-)-(2*R*,5*R*) isomers of 1,2-bis(2,5-diphenylphospholano)ethane (i.e., Ph-BPE) were obtained from Namëna Chemicals.

$Cu(OAc)_2$ was anhydrous and obtained from Strem as an amorphous powder (97% minimum purity).[1] Dimethoxy(methyl)silane (DMMS, CAS #16881-77-9) was obtained from TCI America and stored in an N_2-atmosphere glovebox. Caution: several vendors (TCI, Alfa Aesar) assign a GHS hazard code of H318 to DMMS,[2] indicating that it is a Category I serious eye-damage hazard (i.e., causes serious eye damage). Other vendors (Gelest, AK Scientific) assign DMMS a GHS hazard code of H319, indicating that it is a category II Eye Irritant. DMMS should be handled in a well-ventilated fumehood using proper precautions as outlined for the handling of hazardous materials in "Prudent Practices in the Laboratory."[3] In the general oxidation procedure, as well as in the procedure for characterizing crude 1,4-dihydropyridines (DHPs) by ^{1}H NMR, excess DMMS is evaporated using a vacuum manifold once the dearomatization has gone to completion. This operation must be performed inside a well-ventilated chemical fumehood using a vacuum manifold with two liquid-nitrogen-cooled traps in order to prevent release of DMMS into the atmosphere. After the oxidation step, the reaction mixture is stirred in the presence of saturated methanolic NH_4F for 2 h inside a fumehood prior to other manipulations. In the reduction protocol, the dearomatization reaction mixtures are aged in the presence of a large excess of glacial AcOH for ca. 16 h in a procedure that is carried out in a fumehood. This operation destroys any DMMS left over from the dearomatization prior to concentration of the reaction mixtures with the aid of a rotary evaporator (see section 2.2 for procedural details and discussion of additional safety considerations). Pyridine (Aldrich) was anhydrous and stored under nitrogen in a dry Schlenk storage tube sealed with a screw-in PTFE plug. Molecular O_2 used in oxidation experiments was obtained from Airgas in a cylinder pressurized to ca. 2500 psi. THF and PhMe were obtained from J.T. Baker in CYCLE-TAINER® delivery kegs and purified by successive filtrations though packed columns of neutral alumina and CuO under Ar pressure; CH_2Cl_2 used as a reaction solvent was purified in the same manner. EtOAc used in chromatography eluents was HPLC grade (Aldrich HPLC plus, 99.9%, Aldrich catalog number 650528); EtOAc used in all other applications was ACS reagent grade (Aldrich, 99.5%). Flash chromatography was performed on wet-loaded, manually eluted silica columns using SiliCycle SiliaFlash® F60 silica gel (40-63 μm, 230-400 mesh, 60 Å pore diameter). Preparative TLC separations used Silicycle glass-backed extra-hard-layer plates (60 Å pore-diameter, 1.0-mm-thick silica layer, F-254 indicator, 20x20 cm). Dearomatization reactions were performed in glass culture tubes with threaded ends (oven dried at 140 °C for at least 16 h prior to use) that were sealed with screw-thread caps fitted with PTFE/silicone septa (see general procedures for sizes and part numbers). A photograph of a representative reaction vessel is provided in Figure SI-1.

1.2 General Analytical Information

Proton and Carbon NMR spectra of new compounds were recorded on Bruker 400 MHz, Bruker 600 MHz, and Varian 500 MHz instruments. The ^{1}H NMR spectrum of cinnamyl methyl ether was recorded on a Varian 300 MHz instrument. The Varian 500 was used for all HBMC, HSQC, g-COSY and 1D-NOESY experiments. Chemical shifts of ^{1}H NMR signals are referenced to the indicated residual solvent peak ($CDCl_3$, δ = 7.26; CD_2Cl_2, δ = 5.32; benzene-*d6*, δ = 7.16; acetone-*d6*, δ = 2.05) and reported in ppm

relative to tetramethylsilane. Chemical shift values for the crude dihydropyridines (DHPs) described in Section 3.3 are an exception; the C_6D_6 signal was usually obscured in their ^1H NMR spectra, and consequently their shifts are referenced to the known value

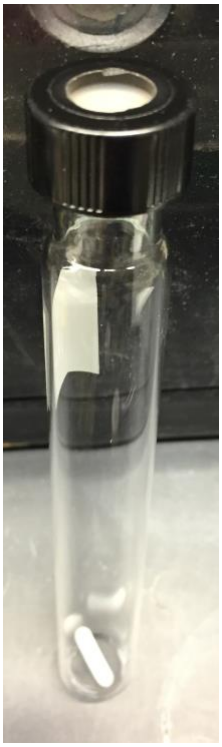


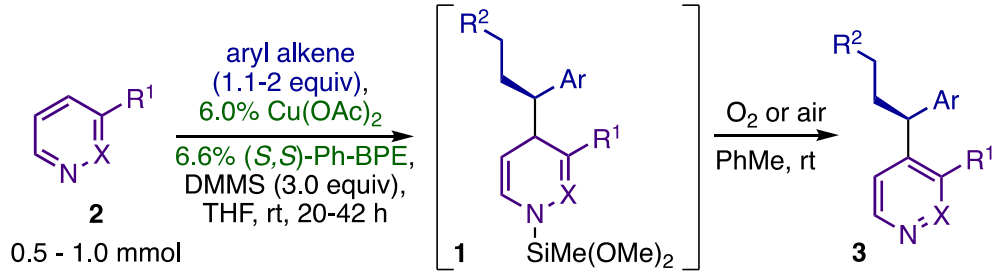
Figure SI-1. Reaction apparatus for dearomatization reactions: glass culture tube with threaded end (20 x 125 mm; Fisher scientific part # 14-959-35A), phenolic screw-thread open-top cap (Kimble-Chase part # 73804-15425), PTFE-lined silicone septum (Thermo Fisher scientific part # B7995-15), and a small PTFE-coated stir bar. Note that some dearomatization procedures call for a slightly longer culture tube (20 x 150 mm; Fisher scientific part # 14-959-37C).

for a resonance of an internal standard (δ = 6.33 ppm for C4-H of 3,5-dimethoxy-1-chlorobenzene, δ = 6.36 for C(3,5)-H of 2,6-dimethoxytoluene, δ = 6.24 for C(2,4,6)-H of 1,3,5-trimethoxybenzene, δ = 6.75 for C(2,3,5,6)-H of 1,4-dimethoxybenzene). All ^{13}C spectra are proton-decoupled, and ^{13}C shifts are reported in ppm relative to the indicated solvent shifts at δ = 77.16 ($CDCl_3$) or 53.84 ppm (CD_2Cl_2). Fluorine NMR shifts were recorded on a 300 MHz Varian instrument and indirectly referenced to $CFCl_3$ by way of neat external trifluorotoluene (δ = -63.72). $CDCl_3$, CD_2Cl_2, and C_6D_6 were obtained from Cambridge Isotope Laboratories; the $CDCl_3$ was stored over activated 3 Å molecular sieves for 48 h prior to use. Benzene-d_6 used for ^1H NMR observation of crude DHPs was degassed inside an oven-dried Schlenk storage tube sealed with a screw-in PTFE plug by subjecting it to a freeze-pump-thaw sequence on a vacuum manifold. This was accomplished by freezing the solvent in liquid nitrogen while the vessel was sealed, evacuating the Schlenk tube until the internal pressure was ca. 20 mTorr, resealing the vessel, and then allowing the frozen solvent to thaw under static vacuum at ambient temperature. This process was repeated twice. The benzene-d_6 was then stored in an N_2-atmosphere glovebox over 4 Å molecular sieves. Gas Chromatography (GC) analyses

were performed with internal dodecane using an Agilent 7890A gas chromatograph equipped with an FID detector and a J&W DB-1 column (10 mm, 0.1 mm I.D.). TLC analyses employed Silicycle SiliaPlate® glass-backed extra-hard-layer TLC plates (60 Å, 250 µm thickness, 20x20 cm, UV-254 indicator) and visualization with 254 nm light or I_2/SiO_2. Diastereomer separations for examples **4s-u** were performed by preparative HPLC using an Agilent 1260 Infinity instrument equipped with a ZORBAX CN PreHT (normal phase) column (21.2 mm x 250 mm, 7 μm). Melting ranges (uncorrected) were determined using a Mel-Temp capillary melting point apparatus. IR spectra were acquired from neat samples using a Thermo Scientific Nicolet iS5 spectrometer equipped with an iD5 diamond laminate ATR accessory, and representative peaks are reported as wavenumbers in units of cm^{-1}. Specific optical rotation measurements were obtained from $CHCl_3$ solutions having concentrations of 5 mg/mL (examples **3a-k**) or 10 mg/mL (examples **4a-u**) using a Jasco 1010 polarimeter operating at 589 nm. High-resolution mass spectrometry was performed using an Agilent 6510 QToF LC/MS instrument with a dual ESI source and B.05.01 MassHunter software. Elemental analyses were performed for carbon and hydrogen by Atlantic Microlabs Inc., Norcross, GA. Enantiomeric excesses (ee's) were determined by chiral SFC analysis using a Waters Acquity UPC^2 instrument; specific columns and analytic methods are provided in the experimental details for individual compounds. LC-MS analysis was performed with a Thermo Scientific Accucore C18 column (30 x 2.1 mm, 2.6 μm particle size) maintained at 45 ºC within an instrument consisting of Agilent 1260 series binary pump, degasser and sample manager modules, Agilent 1100 series COLCOM and DAD modules, and an Agilent 6120 quadrupole MS operating in positive MM-ES+APCI ionization mode.

2. General Procedural Information

2.1 General Procedures for Dearomatization/Oxidation



Caution: *oxygenated solvents and reaction mixtures such as those used in Procedure A (see below) are extremely flammable*[4] *and can undergo potentially violent combustion if exposed to sources of ignition.* These reaction mixtures must be stored in a well-ventilated fumehood. In addition, we note that the tubing and other apparatus used for delivery of compressed oxygen to reaction mixtures (see Figures SI-3 through SI-7) must be free of oil, grease, or other combustibles.[5]

Procedure A: *Oxidation with O_2.*

I. Dearomatization of the heterocycle. Inside a N_2-atmosphere-filled glovebox, a 20 x 150 mm borosilicate glass culture tube with a threaded end (Fisher Scientific part # 14-959-37C) was charged with $Cu(OAc)_2$ (10.9 mg, 0.060 mmol) and (*S*,*S*)-Ph-BPE (33.5 mg, 0.066 mmol) and equipped with a small PTFE-coated stir bar. Then 1.0 mL THF (anhydrous, degassed, stored over molecular sieves) was added followed by DMMS (0.37 mL, 3.0 mmol), the tube was sealed with a phenolic screw-thread open-top cap fitted with a PTFE-lined silicone septum (see figure S-1 for details), and the resulting mixture was stirred at rt. Dissolution of all solids and a color change from pale blue to vivid orange was noted within ca. 15 min. The reaction mixture was removed from the glovebox and stirred at rt for an additional 15 min, during which time the orange color deepened and acquired a reddish hue. The heterocycle substrate **2** (1.00 mmol, measured volumetrically) was added to the reaction mixture by piercing the septum with a 100 μL gas-tight microsyringe at the end of the 30 min catalyst-generation period, and stirring was continued for an additional 15 min. The vinyl arene (2.00 mmol; Exceptions noted in individual procedures) was then added through the septum using a disposable plastic 1 mL syringe fitted with a disposable stainless steel needle, the septum-cap was copiously wrapped with parafilm, and the reaction mixture was stirred at rt in the dark for the indicated period of time.

Figure SI-2. Apparatus for concentrating dearomatization reaction mixtures.

II. Removal of Volatiles. The septum-cap was removed and the threaded end of the tube was wrapped with PTFE tape and outfitted with a connecting adapter (Chemglass part numbers CG-1318-10 and CG-1318-23) joined to a 24/40 gas-adapter with a greased ground-glass stopcock (see Fig. SI-2 for a picture of the apparatus). Copper wire and rubber bands were used to ensure a tight seal between the gas adapter and the connecting adapter (this became important later, primarily when the vacuum was relieved, and particularly in Procedure E [*vide infra*], in which it was necessary to ensure that the apparatus was not pulled apart by vacuum while it was being introduced into a glovebox

Figure SI-3. Gas regulator setup.

Figure SI-4. Anti-suck-back trap**.**

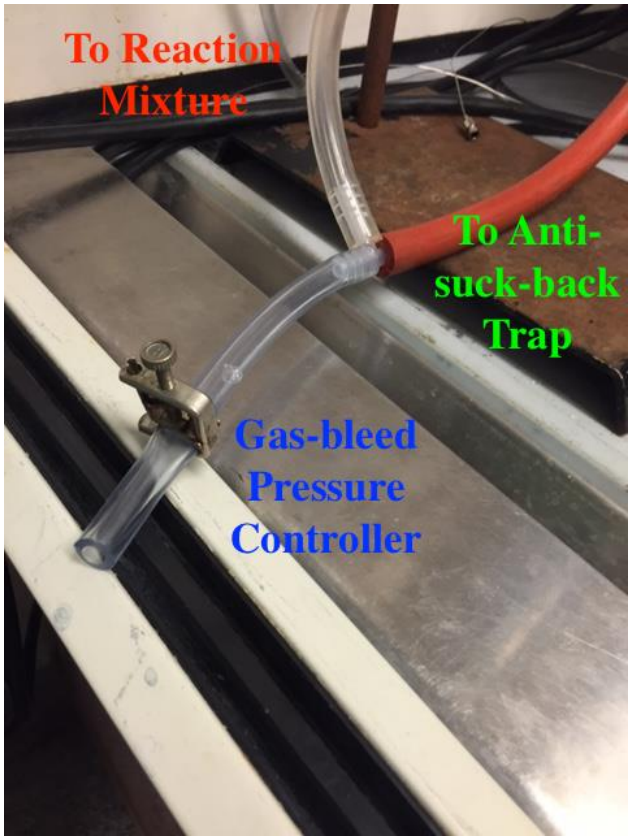


Figure SI-5. Secondary pressure-control system.

Figure SI-6. O_2-Delivery needle**.**

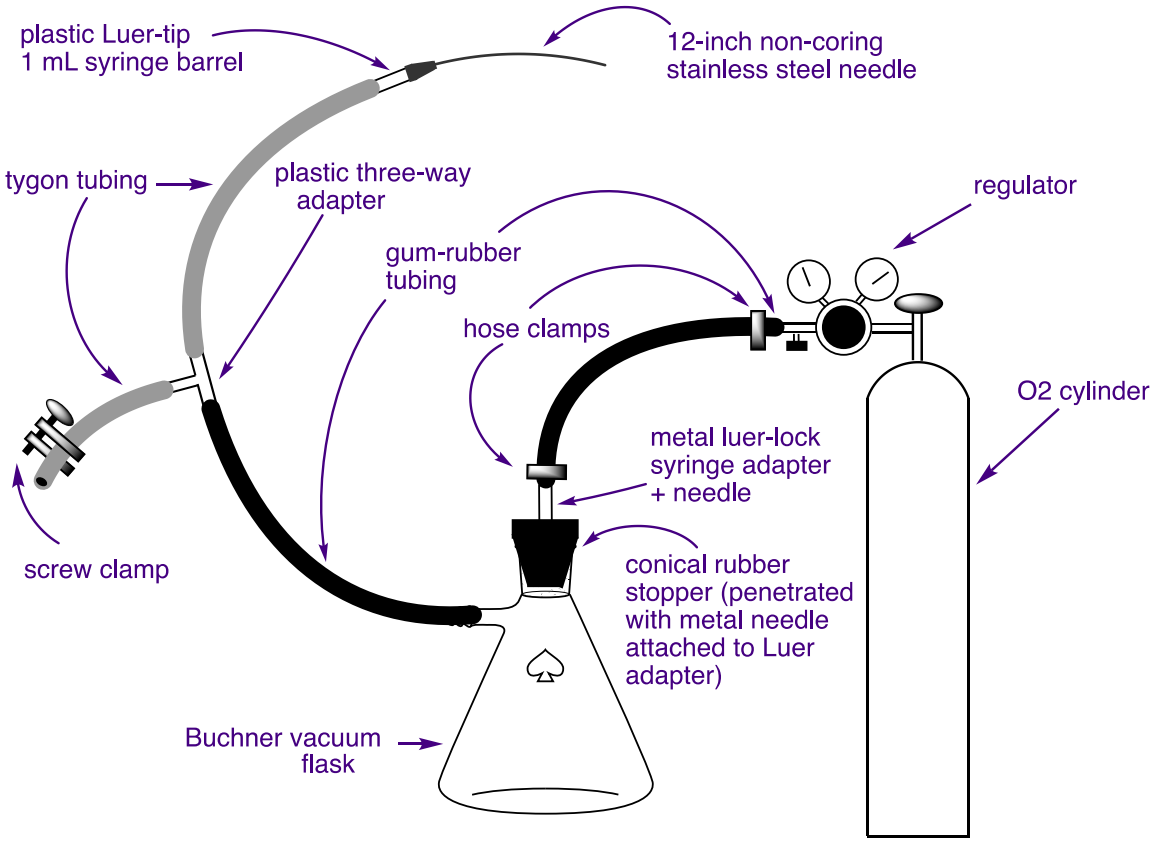


Figure SI-7. Schematic diagram of apparatus for delivering O_2 to the oxidation reaction mixtures.

via the antechamber for preparation of the NMR sample). Using a length of gum-rubber hose, the gas adapter was attached to a Schlenk dual-manifold with two liquid-nitrogen-cooled traps, and vacuum was carefully applied to the sample by quickly opening and closing the stopcock while the reaction tube was gently manually agitated (this was necessary to prevent flash-boiling of the sample, which can cause mechanical product loss). A viscous orange-brown residue was obtained once most of the volatiles had been removed. This material was evenly distributed over the inner wall of the tube so as to provide maximal surface area for evaporation, and the mixture was maintained under vacuum for ca. 2 h. Finally, the reaction tube containing the crude residue was closed to the vacuum line and back-filled with nitrogen, unscrewed from the connecting adapter, and sealed with a phenolic screw-thread open-top cap fitted with a PTFE-lined silicone septum. While the trap was maintained inside a well-ventilated chemical fumehood, its contents were allowed to thaw at ambient temperature, and then they were diluted with acetone and poured into a container designated for organic liquid waste. *Caution: this waste contains DMMS – see above for details on safety considerations in handling this material.* Both traps were rinsed several times with acetone, which was subsequently disposed of in the same manner. Finally, the traps were allowed to air-dry inside the fumehood for several hours before being used again.

Figure SI-8. A 0.5-mmol scale Oxidation.

III. Dihydroheterocycle Oxidation with O_2. A pressurized cylinder of O_2 equipped with an O_2-specific regulator (CGA-540 inlet, Fig SI-3) was connected to an anti-suck-back trap constructed from a Buchner filter flask, a Luer-tip syringe adapter, and a thick rubber stopper (see Fig. SI-4).[6] The side arm of the filter flask was fitted with a length of rubber tubing leading to a three-way plastic connector. One arm of the plastic connector was equipped with a Tygon tube closed with an adjustable screw-clamp that was used as a bleed-valve for obtaining very fine control over the O_2 pressure delivered to the sample (see Fig. SI-5). The third arm of the connector led to a length of Tygon tubing terminating in a plastic 1-mL Luer-tip syringe (Fig. SI-6). The syringe was equipped with a 12" stainless steel needle that was used to introduce O_2 bubbles into the reaction mixture. For a complete schematic depiction of the apparatus used for introducing oxygen into the reaction mixtures, see Fig. SI-7. Anhydrous PhMe was gently sparged inside a dry glass reaction tube of the type described in Part I for ca. 20 min immediately prior to use. A plastic syringe was used to transfer the oxygenated PhMe (6 mL for 1 mmol-scale examples; 3 mL for 0.5 mmol-scale examples) to the crude DHP residue obtained at the end of Part II. The septum-cap was pierced with a vent needle (see Fig.

SI-8) and the O_2 inlet needle pictured in Figure SI-6 was inserted through the septum. The reaction mixture was very slowly stirred while a gentle stream of O_2 was bubbled through it for the indicated period of time. In most cases, a color change to green was observed as the oxidation progressed (although this was not generally true for pyridazine examples).

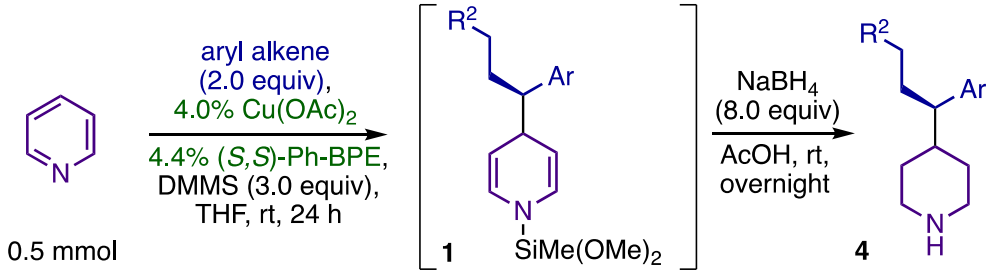
After the indicated period of time, the O_2 inlet needle was removed from the reaction tube and the stirred mixture was maintained under an O_2 balloon overnight. On the subsequent day, the balloon was replaced with a vent needle, and saturated methanolic NH_4F (6 mL for 1 mmol-scale reactions; 3 mL for 0.5 mmol-scale reactions) and MeOH (1.5 mL for 1 mmol-scale reaction; 1 mL for 0.5 mmol-scale reactions) were added to the tube using syringes. The resulting mixture was vigorously stirred at rt for ca. 2 h. The mixture was then diluted with EtOAc and concentrated with the aid of a rotary evaporator to provide a residue that was taken up into CH_2Cl_2, loaded onto a plug of silica gel (see individual procedures for specific amounts) that had been transferred as a slurry in organic solvent (see individual procedures) to a plastic filter-funnel and allowed to settle. The plug was then eluted with the indicated solvent, and the filtrate obtained was concentrated to give an oily crude residue that was promptly purified by flash column chromatography to provide the C4-functionalized heteroarene.

Procedure B: *Oxidation with Air.*

The crude DHP was prepared as described in Parts I and II of Procedure A. Dry PhMe (6 mL) was added and the resulting solution was slowly stirred while a stream of air was gently bubbled through it using a tank of compressed air and Tygon tubing equipped with a stainless steel syringe (as shown in Figure SI-6). After 4 h, bubbling was terminated and the reaction mixture was stirred overnight under an atmosphere of air. It was then subjected to the NH_4F workup, filtration and purification operations described in Part III of Procedure A.

2.2. General Procedures for Dearomatization/Reduction

Procedure C: *Dearomatization/Reduction of Pyridine with Styrene Derivatives.*

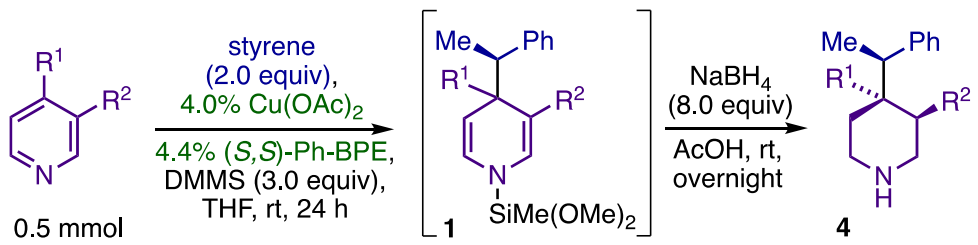


I. In-situ Preparation of $NaHB(OAc)_3$. An oven-dried 25 mL round-bottom flask containing a dry PTFE stir bar was charged with $NaBH_4$ (152 mg, 4 mmol) and maintained under an Ar atmosphere with the aid of an inlet needle. The flask was cooled in an ice bath, and glacial AcOH (6.0 mL, sparged with Ar for ca. 60 min immediately

before use), was carefully added to the borohydride reagent dropwise using a syringe over the course of ca. 2 min. *CAUTION: very vigorous gas evolution occurs at this stage; the rate of addition must be slow enough to allow pressure-equalization via the inlet needle).* The ice bath was removed and stirring was continued while the mixture was allowed to warm to rt. Once gas evolution ceased and all of the starting borohydride had been consumed, the reagent was deemed ready for use. We noted that this step can take varying lengths of time depending on the form the $NaBH_4$ is supplied in.

II. Dearomatization with in-situ DHP Reduction. Inside an N_2-atmosphere-filled glovebox, a borosilicate glass culture tube with a threaded end (Fisher Scientific part # 14-959-35C); oven-dried at 140 ºC for 16 h and then allowed to cool to rt prior to use) was charged with $Cu(OAc)_2$ (3.6 mg, 0.020 mmol), (*S,S*)-Ph-BPE (11.1 mg, 0.022 mmol) and equipped with a small PTFE-coated stir bar. THF (0.5 mL) and DMMS (1.5 mmol, 3 equiv) were then added via syringe. The tube was sealed with a phenolic screw-thread cap with a PTFE/silicone septum (Thermo Scientific part number C4015-66A) and brought outside the glovebox. The reaction mixture was stirred for approximately 20 min at rt, during which time it acquired an orange color. The styrene derivative (1.0 mmol, 2.0 equiv.) was added via syringe, pyridine (0.41 μL, 0.5 mmol, 1.0 mmol) was added using a microsyringe, and the reaction mixture was stirred at rt for 24 h in the dark. After this period, the freshly prepared $NaBH(OAc)_3$/AcOH mixture (6 mL, 4.0 mmol $NaHB(OAc)_3$, 8.0 equiv) was added into the reaction mixture, using an Ar inlet needle to allow for pressure-equalization during the addition (*CAUTION: gas evolution occurs during this step and can continue to occur after the addition is completed; venting through an Ar inlet needle should be carried out to mitigate pressure-buildup during the reaction).* The resulting mixture was stirred at room temperature overnight and then concentrated *in vacuo* until the AcOH had been *completely removed* (*failure to remove all of the AcOH can significantly lower the yield by resulting in a buffered aqueous phase in the subsequent workup that is not sufficiently basic to allow complete extraction of the free base into the organic layer. It can be useful to check the pH of the aqueous layer at that stage*). The residue obtained was neutralized with saturated Na_2CO_3 (20 mL), and the resulting aqueous mixture was extracted with EtOAc (3x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to provide a crude residue that was further purified by flash column chromatography. The silica column used in the purification was prepared by wet-loading a slurry of silica gel (12 g) in CH_2Cl_2 inside a narrow (ca. 1 cm outer-diameter) column. Additional chromatography conditions specific to individual examples are provided in section 3.2.

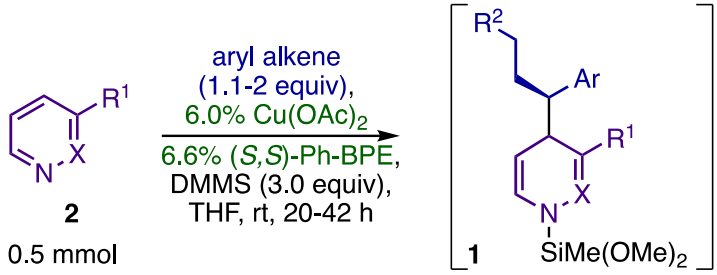
Procedure D: *Dearomatization/Reduction of Pyridine Derivatives with Styrene.*



The borohydride reducing agent used here was prepared as in Part I of Procedure C. The dearomatization reaction was conducted as described in Part II of Procedure C. After the 24 h reaction period, the reaction mixture was transferred dropwise using a plastic 1 mL syringe to the freshly-prepared $NaHB(OAc)_3$/AcOH mixture described in Part I while the latter was stirred at rt under Ar (*CAUTION: gas evolution can occur at this stage*). The resulting reduction mixture was stirred at rt for 8 h and then subjected to the evaporation, workup, and purification operations described in Procedure C.

2.3. General Procedure for ^{1}H NMR Observations of the Crude DHPs

Procedure E: ^{1}H NMR *Observation of the Crude N-Silyl 1,4-DHPs*



Dearomatization Reactions were set up on 0.5 mmol scale as described in part I of Procedure A (section 2.1). After the period of time indicated below, volatiles were removed as in part II of Procedure A. While the gas adapter (see Figure SI-2) was still connected to the vacuum hose, the apparatus was back-filled with dry nitrogen and the stopcock was closed. In this state, the apparatus was disconnected from the manifold and taken inside a nitrogen-atmosphere glovebox. The reaction tube was unscrewed from the connecting adapter, and the indicated internal standard was weighed into it by difference. At this juncture, the glovebox circulator was temporarily shut off. A ca. 0.6 mL aliquot of dry, degassed C_6D_6 was transferred to the reaction tube, which was then immediately sealed with a septum-cap of the type used described in Procedure A, Part I. The mixture inside the sealed tube was agitated until all of the crude product and internal standard dissolved and a brown solution was obtained. The septum-cap was removed and the entire crude product C_6D_6 solution was transferred to an oven-dried NMR tube using an oven-dried glass pipette. The tube was quickly sealed with a plastic NMR tube cap and the edges of the cap were sealed with a strip of electrical tape. The NMR tube was removed from the glovebox and analyzed by ^{1}H NMR immediately. NMR yields were determined by comparing product dihydroheterocycle integrals to integrals of well-resolved internal-standard resonances.[7]

2.4. Assignment of Diastereomers

Our conclusion that the asymmetric dearomatization exhibits general (Cα,C4)-*anti* diastereoselectivity (See Fig. SI-9 for explanation of stereodescriptor conventions) was based on a series of observations that began with our determination of the stereochemical outcomes for the syntheses of piperidines **4s-u** (structures are reproduced in Figure SI-9, (C) below). By large margins, the major product in each case was the **4 (a,s)**

diastereomer. (See specific procedural information and spectral attachments for structure-determination data). For **4u**, we confirmed that the second-most prevalent piperidine in the intial product mixture was **4u (s,s)**. As our work had previously suggested that the Cα and C4 stereocenters of the 1,4-DHPs should be configurationally stable during the reduction, we expected that we should see a correspondence between these diastereomeric piperidines and their diastereomeric 1,4-DHP precursors. The ^{1}H NMR spectrum of the sample of crude DHP **1u** that was used in the reduction showed two principal nicotinamide-derived species (See excerpt in Figure SI-10 and complete spectrum in the spectral attachments). **Major species:** δ 6.50 (s), 6.01 (d, J = 7.9 Hz), and 4.76 (dd, J = 7.9, 4.6 Hz) ppm (1:1:1 integral ratio); **minor species:** δ 6.64 (s, 1H), 6.13 (d, J = 8.0 Hz, 1H), 4.56 (dd, J = 8.0, 4.4 Hz, 1H) ppm (1:1:1 integral ratio). That the corresponding signals in each set had similar shifts, identical multiplicities, and very similar coupling constants strongly supported their assignments as corresponding to ***anti*-1u** and ***syn*-1u**, respectively. In addition, a multiplet appearing at δ 4.10 – 4.04 ppm was clearly a composite of signals coming from both the major and minor species (See Figure SI-10 for structures and assignments). Comparing the integrals for the major and minor components of the H_2- and H_6-proton diagnostic pairs gave an approximate ratio of 4.6:1 for ***anti*-1u**:***syn*-1u** (the two higher-field multiplets were known to be subject to interference from baseline distortion or overlap with minor impurities; hence they were not used in the calculation).

There were two other notable products present in the **4u** diastereomer mixture, and the most chemically reasonable assignment for these derives from the assumption that the reduction does not exert perfect control over the C3 stereocenter generated in that step. Assigning these minor species as **4u (a,a)** and **4u (s,a)** gave us an [all (Cα,C4)-*anti*-piperidines]:[all (Cα,C4)-*syn*-piperidines] (i.e., [**4u (a,s)** + **4u (a,a)**]:[**4u (s,s)** + **4u (s,a)**]) ratio of 4.4:1 (i.e., 81:19) as measured by SFC analysis of the crude product, closely matching the 4.6:1 ratio (i.e., 82:18) estimated for ***anti*-1u**:***syn*-1u** by NMR. Other observations also supported these assignments for the minor reduction products. For the closely related substrate **2s** (i.e., 3-phenylpyridine), we were able to isolate and confirm the structure of the **4s (a,a)** piperidine diastereomer, and in our ^{1}H NMR analysis of the diastereomer mixture **4t** (derived from *tert*-butyl nicotinate), a key diagnostic resonance of **4t (a,a)** was clearly evident. We have never succeeded in isolating a **4 (s,a)** diastereomer, as this species is always present in very small amounts, but we noted in our NMR analysis of the **4t** mixture that the least prevalent component exhibits a signal that we predicted would be a key diagnostic for **4t (s,a)**. For **1s** and **1t**, the dr*'s* we measured based on ^{1}H NMR by analogy to example **1u** were again in good agreement with the [**4 (a,s)** + **4 (a,a)**]:[**4 (s,s)** + **4 (s,a)**] ratios independently estimated for their piperidine product mixtures, corroborating our anti/syn assignments for those dihydropyridines as well.

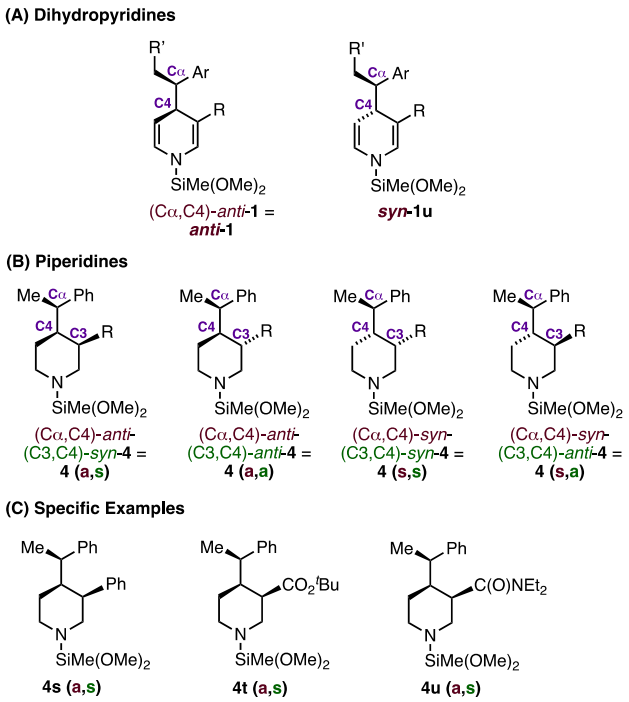


Figure SI-9. Stereochemical conventions for (A) dihydropyridines, and (B) piperidines, and (C) structures of piperidine examples relevant to this discussion.

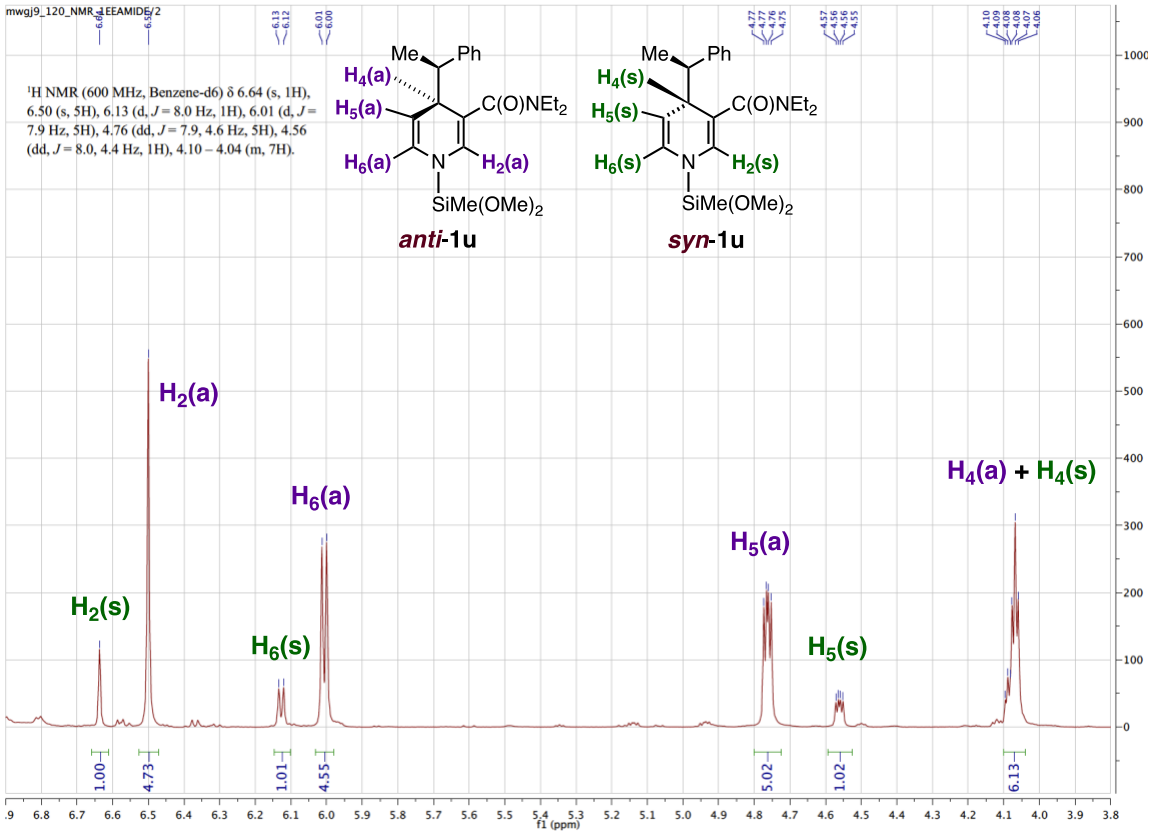


Figure SI-10. Excerpt of the ^{1}H NMR spectrum of crude 1,4-dihydropyridine **1u**.

In addition to the DHPs **1s-u** above, we also used ^{1}H NMR spectroscopy to observe crude DHPs obtained from a set of heterocycle substrates having more widely varied C3-substituents (F, Me, MeO, CCTES, CO_2Me; additional heterocycles included 3-MeO-pyridazine). For all of the examples, whenever both signals of a given diagnostic resonance pair were observable in the ^{1}H NMR spectrum of the crude DHP, they exhibited the same qualitative relationships observed for the corresponding diagnostic pair of **1u**. In Particular:

1. *The major and minor H_5 signals were always observable, and the minor H_5 signal was always shifted upfield (0.1 – 0.5 ppm) relative to the major H_5 signal – often significantly so.* Qualitative Conformational analysis of the DHPs predicts this reliable difference in the H_5 shifts (See Figure SI-11). The C4-Cα bond possesses three staggered rotamers, but only one of these avoids a syn-pentane interaction between the DHP C3-substituent and one of the organic groups on Cα (the benzylic carbon). This rotamer should be appreciably more stable than the other two. In ***anti*-1**, the most stable staggered conformer is expected to display the benzylic phenyl group gauche to both of the ring-carbon substituents on C4. In contrast, avoidance of a syn-pentane clash in ***syn*-1** situates a face of the benzylic Ph near H_5, where it should selectively engage that proton in an anisotropic shielding interaction.

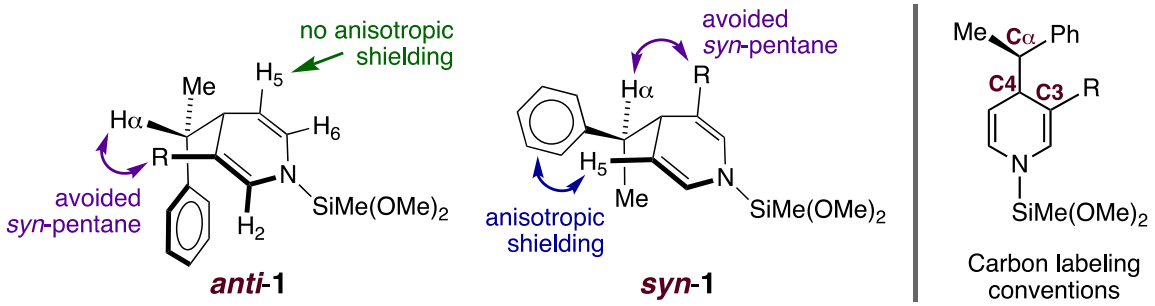


Figure SI-11. Conformational Models for ***anti*-1** and ***syn*-1**.

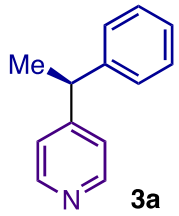
2. *The major and minor H_6 signals were also always observable, and the minor H_6 signal was always shifted downfield relative to the major signal. Both H_2 signals were observable in the large majority of cases, and whenever this was true, the minor signal was also found downfield relative to the major.* These differences in shift can also be understood using the conformational models above: display of the benzylic Ph ring in ***anti*-1** face-to-face with the nearby DHP-ring could anisotropically shield H_2 and H_6 in that diastereomer. Traditional physical models of ***anti*-1** suggest that the two ring faces should be close one another.

Thus, when we considered all of the DHPs we had observed by NMR but not derivatized, we found that we could rationalize the conserved relationships between the major and minor components of the diagnostic resonance pairs if we assigned the major DHP diastereomer as *anti*. Conversely, in order for the major diastereomer *not* to be *anti* for some of these DHPs, the relationships between the minor and major components of all of the diagnostic resonance-pairs would have to be coincidentally reversed for just those

examples, despite our conformational models' implication that the basic structural features of the DHPs should be conserved across the series.

3. Specific Procedural Information and Characterization Data for Preparative Examples

3.1 Oxidation Examples

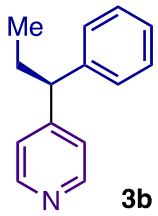


3a

(*S*)-4-(1-Phenylethyl)pyridine (3a): Prepared according to Procedure A on 1.0 mmol scale. In this case, a reduced catalyst loading of 4.0% $Cu(OAc)_2$ (7.2 mg, 0.04 mmol) and 4.4% (*S*,*S*)-Ph-BPE (11.2 mg, 0.044 mmol) was used. The dearomatization reaction mixture was stirred at rt for 20 h before being concentrated. O_2 was bubbled through the oxidation mixture for 4 h, after which it was stirred overnight under an O_2 balloon. The residue obtained after treatment with methanolic NH_4F and concentration *in vacuo* (as described in Part III) was filtered through a 10 g plug of silica gel using 75% EtOAc/Hexanes as the eluent. Concentrating the resulting filtrate gave a crude residue that was purified on a 40 g silica column wet-loaded as a slurry in 15% EtOAc:hexanes and eluted with 1:2 EtOAc:hexanes. Product fractions were combined and concentrated *in vacuo* to provide the title compound as a yellow oil, 117.8 mg (64% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.62 – 8.31 (m, 2H), 7.31 (apparent t, J = 7.6 Hz, 2H), 7.25 – 7.17 (m, 3H), 7.15 – 7.11 (m, 2H), 4.12 (q, J = 7.2 Hz, 1H), 1.64 (d, J = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 155.20, 149.94, 144.54, 128.76, 127.75, 126.77, 123.10, 44.37, 21.19. **IR** (neat) 3062.13, 3025.29, 2968.74, 2932.91, 2874.24, 1594.01, 1555.62, 1492.79, 1451.07, 1412.01, 994.10, 828.30, 813.44, 768.74, 745.98, 698.34, 625.73, 615.82 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{15}H_{13}N + H]^+$: 184.1121, Found: 184.1118. **Specific Rotation** $[\alpha]_D^{24}$ +2.32 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 8 min elution on a Daicel OJ-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ (i.e., supercritical CO_2) containing 5.0% of a 0.1% solution (v/v) of diethylamine (DEA) in MeOH, flow rate (fr) = 2.5 mL/min, column temperature (ct) = 40 ºC, simultaneous detection from 210-400 nm with a photodiode array (chosen quantitation wavelength = 210 nm), Retention times t_M (major enantiomer) = 3.38 min, t_m (minor enantiomer) = 3.85 min. *90% ee*. **Duplicate Experiment** 65% yield, *91% ee*.

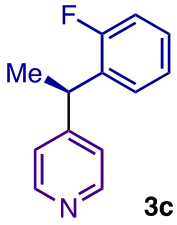
Alternative Method The crude DHP residue was prepared as above, but the oxidation was instead performed according to Procedure B. The work-up, filtration and chromatography steps were performed in the same manner as before. The product was

isolated as a yellow oil, 118.2 (65% yield, *89% ee*). The ^{1}H NMR spectrum of this sample was identical to the one obtained from material generated using Procedure A. **Duplicate Experiment** 60% yield, *91% ee*.



3b

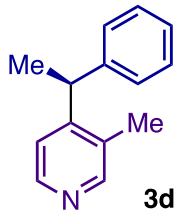
(*S*)-4-(1-Phenylpropyl)pyridine (3b): Prepared according to Procedure A on 1.0 mmol scale. In this example, the dearomatization reaction mixture was stirred at rt for 42 h prior to removal of volatiles. All subsequent manipulations were identical to those described in example **3a**. The title compound was obtained as a pale-orange oil, 135.9 mg (69% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.49 (d, J = 4.2 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.23 – 7.19 (m, 3H), 7.17 – 7.13 (m, 2H), 3.77 (t, J = 7.7 Hz, 1H), 2.08 (apparent p, J = 7.4 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 154.09, 149.94, 143.30, 128.75, 128.05, 128.04, 126.77, 123.42, 77.16, 52.76, 28.04, 12.68. **IR** (neat) 3062.34, 3025.15, 2961.49, 2931.11, 2873.14, 1594.57, 1556.72, 1493.83, 1451.69, 1411.27, 993.34, 801.59, 764.47, 744.16, 698.41, 632.93, 585.70 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{14}H_{15}N + H]^+$: 198.1277, Found: 198.1277. **Specific Rotation** $[\alpha]_D^{23}$ +0.07 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 8 min elution on a Daicel OD-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 5.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 254 nm), t_M = 5.66 min, t_m = 6.25 min. *95% ee*. **Duplicate Experiment** 63% yield, *96% ee*.



3c

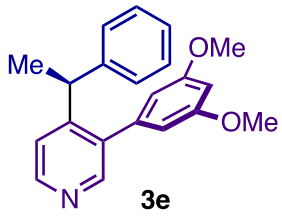
(*R*)-4-(1-(2-Fluorophenyl)ethyl)pyridine (3c): Prepared according to Procedure A on 1.0 mmol scale using a reduced catalyst loading of 4% $Cu(OAc)_2$ and 4.4% (*S*,*S*)-Ph-BPE. All details of the procedure were the same as in example **3a**. The title compound was obtained as a pale-orange oil, 138.2 mg (69% yield). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.56 – 8.37 (m, 2H), 7.29 – 7.20 (m, 2H), 7.19 – 7.10 (m, 3H), 7.04 (ddd, J = 10.5, 8.2, 1.3 Hz, 1H), 4.43 (q, J = 7.3 Hz, 1H), 1.64 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 161.78, 160.15, 154.27, 150.18, 131.89, 131.79, 128.88, 128.86, 128.76, 128.70, 124.72, 124.70, 123.10, 115.87, 115.73, 37.67, 20.03. Note that all of the fluoroarene resonance appear as doublets due to J_{CF} coupling. *Ispo* carbon signal centered on δ 160.97 ppm ($^{1}J_{CF}$ = 245.4 Hz). C2 at δ 131.84 ppm ($^{2}J_{CF}$ = 14.7 Hz). C6 at

115.80 ppm ($^2J_{CF}$ = 22.0 Hz). C4 at δ 124.71 ppm ($^4J_{CF}$ = 3.4 Hz). C3 and C5 resonances (order arbitrary) at δ 128.87 ($^3J_{CF}$ = 8.4 Hz) and 128.73 ($^3J_{CF}$ = 4.4 Hz) ppm. **^{19}F NMR** (282 MHz, C_6D_6) δ -117.59. **IR** (neat) 3027.40, 2973.18, 2934.67, 2878.54, 1595.98, 1488.78, 1451.80, 1413.53, 1221.51 1112.07, 823.23, 793.83, 753.75, 653.27 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{12}FN + H]^+$: 202.1027, Found: 202.1021. **Specific Rotation** $[\alpha]_D^{23}$ +3.03 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 8 min elution on a Daicel OD-H column (4.6 x 250 mm, 5 μM particle size) with supercritical CO_2 containing 4.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 256 nm), t_M = 5.10 min, t_m = 5.56 min. *93% ee*. **Duplicate Experiment** 75% yield, *93% ee*.



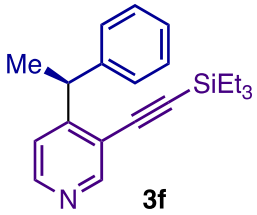
3d

(*S*)-3-Methyl-4-(1-Phenylethyl)pyridine (3d): Prepared according to Procedure A on 1.0 mmol scale. The dearomatization mixture was stirred for 20 h prior to removal of volatiles. All other procedural details were the same as in example **3a**. The product was obtained as a pale-orange oil that solidified as a waxy, cream-colored crystalline solid upon storage in a -35 ºC freezer overnight, 124.0 mg (63% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.1 Hz, 1H), 8.33 (s, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.17 (d, *J* = 5.1 Hz, 1H), 7.14 – 7.10 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 1H), 2.19 (s, 3H), 1.60 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.70, 151.09, 147.98, 144.33, 131.71, 128.69, 127.74, 126.53, 121.55, 40.92, 21.42, 16.58. **IR** (neat) 3024.63, 2965.95, 2927.87, 2871.40, 1589.78, 1491.65, 1446.42, 1402.09, 1302.29 1196.19, 1149.22, 1083.67, 1029.43, 837.36, 764.16, 705.96, 640.80, 602.35, 558.44 cm^{-1}. **EA** Calcd. for $C_{14}H_{15}N$: C, 85.24; H, 7.66, Found: C, 84.97; H, 7.75. **Melting Range** 47-55 °C. This melting range was unusually broad despite the apparently high chemical purity of the compound. This may have been due to the presence of distinct homo- and hetero-chiral crystal forms having significantly different melting points. In theory, a heterochiral crystal form could make up ca. 20% of the material. **Specific Rotation** $[\alpha]_D^{23}$ +34.56 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 8 min elution on a Daicel OD-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 7.5% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 260 nm), t_M = 3.91 min, t_m= 4.73 min. *82% ee*. **Duplicate Experiment** 60% yield, *82% ee*.



3e

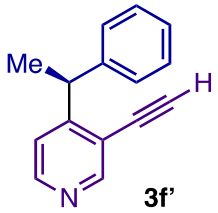
(*S*)-3-(3,5-Dimethoxyphenyl)-4-(1-Phenylethyl)pyridine (3e): Performed according to Procedure A on 0.529 mmol scale. The dearomatization mixture was stirred for 36 h prior to removal of volatiles. The oxidation was performed as described in example **3a**, except here 3.0 mL of PhMe was used rather than 6.0 mL. The fluoride workup was omitted in this example. The crude product was distributed over two preparative TLC plates, and both of these were eluted twice with 40% EtOAc/hexanes. The product bands were stripped away from the plates with an industrial flat-razor and the silica was pulverized and stirred in the presence of EtOAc for ca. 1 h. The extraction slurry was then transferred to a disposable plastic filter-cup and the silica filter-cake was rinsed with the aid of a vacuum using HPLC-grade EtOAc until fresh filtrate showed no UV-quenching activity. The filtrate was concentrated and dried under high vacuum to give the title compound as a very viscous pale-orange oil, 125.3 mg (74% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.55 (d, J = 5.2 Hz, 1H), 8.46 (s, 1H), 7.29 – 7.23 (m, 2H), 7.21 – 7.15 (m, 1H), 7.09 – 7.05 (m, 2H), 6.52 – 6.50 (m, 1H), 6.34 (d, J = 2.2 Hz, 2H), 4.32 (q, J = 7.2 Hz, 1H), 3.74 (s, 6H), 1.57 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.90, 152.72, 150.44, 149.28, 145.26, 140.03, 137.76, 128.76, 127.86, 126.61, 122.50, 107.99, 100.25, 77.37, 55.66, 40.50, 22.16. **IR** (neat) 3024.84, 3000.66, 2966.19, 2934.77, 2835.62, 1590.63, 1451.21, 1422.45, 1396.69, 1350.68, 1339.06, 1203.76, 1152.22, 1062.38, 1024.76, 835.47, 759.09, 698.40, 682.93 cm^{-1}. **EA** Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63, Found: C, 78.71; H, 6.64. **Specific Rotation** $[\alpha]_D^{23}$ -112.34 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 12-min elution on a Daicel OJ-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 3.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 215 nm), t_M= 7.40 min, t_m = 8.40 min. *95% ee*. **Duplicate Experiment** 73% yield, *94% ee*.



3f

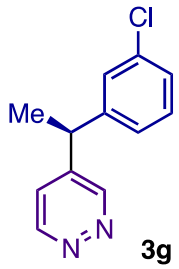
(*S*)-4-(1-Phenylethyl)-3-((triethylsilyl)ethynyl)pyridine (3f): Prepared according to Procedure A on 0.50 mmol scale. The dearomatization, oxidation and isolation of crude product were as described in example **3e**. The crude residue was distributed over two preparative TLC plates, both of which were eluted with 4% acetone/hexanes (1x) and then with 5% acetone/hexanes (3x). The product-containing silica was extracted as

described in example **3a** to provide the title compound as a viscous pale-orange oil, 86.9 mg (54% yield). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.60 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.27 – 7.24 (m, 2H), 7.23 – 7.19 (m, 1H), 7.10 (dt, J = 5.2, 0.7 Hz, 1H), 4.69 (q, J = 7.2 Hz, 1H), 1.63 (d, J = 7.2 Hz, 3H), 1.05 (t, J = 7.9 Hz, 9H), 0.71 (q, J = 7.9 Hz, 6H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 157.04, 153.64, 149.31, 144.26, 128.80, 128.15, 126.89, 121.66, 120.21, 101.95, 100.21, 42.39, 20.62, 7.68, 4.68. **IR** (neat) 3027.47, 2953.94, 2910.19, 2873.44, 2154.22, 1580.59, 1451.24, 1397.35, 1235.44, 1192.31, 1003.96, 973.15, 853.60, 836.37, 798.08, 723.00, 696.87, 626.32 cm^{-1}. **EA** Calcd. for $C_{21}H_{27}NSi$: C, 78.44; H, 8.46, Found: C, 78.65; H, 8.53. **Specific Rotation** $[\alpha]_D^{23}$ -165.69 (*c* 0.50, $CHCl_3$). **Chiral Analysis** Direct determination of the enantiomeric excess of this compound was challenging. The terminal alkyne **3f'** obtained upon silyl deprotection was easy to analyze. We expect the ee's of the precursors of **3f** to be similar to those values. **Duplicate Experiment** 57% yield.



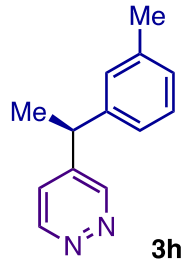
3f'

(*S*)-3-Ethynyl-4-(1-phenylethyl)pyridine (3f'): TES-alkyne **3f** (25.0 mg, 0.078 mmol) was taken up into MeOH (0.6 mL) and added to a solution of K_2CO_3 (54 mg, 5.0 equiv) in water (0.2 mL). The resulting mixture was vigorously stirred in a small vial overnight. On the following day, THF (0.1 mL) and MeOH (0.2 mL) were added to the mixture, and stirring was continued for an additional 4 h. The reaction mixture was neutralized with pH 7 phosphate buffer, and the product was extracted into ether. The organics were concentrated *in vacuo* and purified by preparative TLC, eluting once with 5% acetone/hexanes and then with 5.8% acetone/hexanes to provide the product as an orange oil, 13.7 mg (85% yield). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.63 (s, 1H), 8.44 (d, J = 5.3 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.24 (m, 2H), 7.23 – 7.19 (m, 1H), 7.13 (d, J = 5.2 Hz, 1H), 4.67 (q, J = 7.2 Hz, 1H), 3.47 (s, 1H), 1.63 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 157.46, 153.82, 149.79, 144.13, 128.84, 128.14, 126.95, 121.80, 119.05, 84.60, 79.62, 42.24, 20.71. **IR** (neat) 3287.47, 3027.29, 2969.90, 2931.57, 2873.83, 1583.17, 1546.77, 1493.03, 1450.37, 1398.37, 1054.24, 1027.60, 838.61, 775.33, 752.45, 723.95, 697.60, 633.92, 594.34 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{15}H_{13}N + H]^+$: 208.1121, Found: 208.1115. **Specific Rotation** $[\alpha]_D^{23}$ -171.10 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 8 min elution on a Daicel OD-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 7.5% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 235 nm), t_M= 3.89 min, t_m = 5.03 min. *83% ee*. **Duplicate Experiment** 97% yield, *82% ee*.



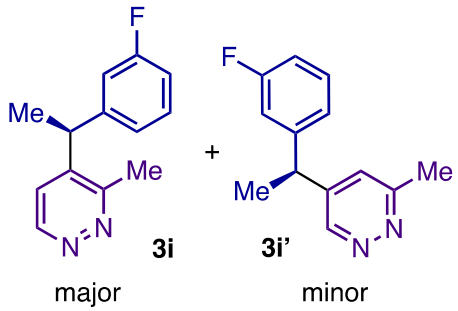
3g

(*S*)-4-(1-(3-Chlorophenyl)ethyl)pyridazine (3g): Prepared according to Procedure A on l.0 mmol scale. This example employed a 36 h dearomatization time, and O_2 was gently bubbled through the oxidation reaction mixture for 8 h prior to stirring it overnight under an O_2 balloon. After the fluoride workup, the residue was filtered through a 10 g plug of silica with EtOAc (200 mL). The crude product was purified on a 40 g silica column that was wet-loaded as a slurry in 75% EtOAc/hexanes and eluted with EtOAc. Product fractions were combined and concentrated *in vacuo* to give the product as an orange oil, 121.6 mg (55% yield). Analysis by ^{1}H NMR indicated the presence of a 3-pyridazinone impurity at the level of ca. 3 mol%. Assignment of this species as the pyridazinone was corroborated by LC-MS analysis (6 min method with 5.5 min linear gradient from 7% to 95% MeCN in water (0.1% TFA) followed by a 30 s hold time, fr = 0.9 mL/min; pyridazinone t_R = 1.66 min, m/z = $(M+H)^+$ = 235.0 amu; the pyridazine product eluted at t_R = 1.87 min showing the expected m/z = $(M+H)^+$ = 219.0 amu peak). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.13 – 9.04 (m, 2H), 7.31 – 7.23 (m, 3H), 7.19 – 7.17 (m, 1H), 7.07 (dt, *J* = 7.1, 1.7 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 1H), 1.68 (d, *J* = 7.2 Hz, 3H). Observable signals from the pyridazinone impurity: δ 12.97 (s, 1H), 7.92 (s, 1H), 7.71 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 1H), 1.53 (d, *J* = 7.2 Hz, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.09, 151.29, 144.77, 144.65, 134.97, 130.36, 127.86, 127.59, 125.94, 124.78, 41.94, 20.57. **IR** (neat) 3048.68, 2972.39, 2934.57, 2875.08, 1580.81, 1475.50, 1456.22, 1429.00, 1380.46, 1193.56, 1081.42, 1050.38, 968.38, 857.19, 779.13, 757.47, 699.87, 682.32, 667.93 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{12}H_{11}ClN_2 + H]^+$: 219.0684, Found: 219.0681. **Specific Rotation** $[\alpha]_D^{23}$ -6.44 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 8 min elution on a Daicel AS-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 10.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 210 nm), t_M = 3.49 min, t_m = 3.81 min. *96% ee*. **Reproducibility Experiments** This preparative example was performed on two other occasions using 4% $Cu(OAc)_2$ and 4.4% (*S*,*S*)-Ph-BPE, all other conditions were the same. Those experiments provided similar to those described above: 53% yield, *97% ee* for the first run, 50% yield, *97% ee* for the second.



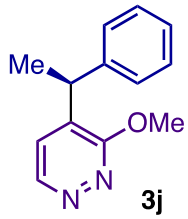
3h

(*S*)-4-(1-(*m*-Tolyl)ethyl)pyridazine (3h): Prepared according to Procedure A on 0.50 mmol scale. The dearomatization and oxidation steps were as described in example **3g**. The fluoride workup was conducted as described in Step III for 0.5-mmol-scale reactions. After the workup, the residue was filtered through a 2.5 g plug of silica gel using EtOAc. The crude product was distributed over two preparative TLC plates that were subsequently eluted with 70% EtOAc/hexanes (3x). The product-containing silica was extracted as described in example **3e** to provide the product as a gummy orange oil, 47.3 mg (48% yield). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 9.07 – 8.98 (m, 2H), 7.28 (ddd, J = 5.4, 2.5, 0.8 Hz, 1H), 7.22 (apparent t, J = 7.4, 1H), 7.09 – 7.05 (m, 1H), 7.04 – 6.96 (m, 2H), 4.11 (q, J = 7.2 Hz, 1H), 2.31 (d, J = 0.8 Hz, 3H), 1.65 (d, J = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 152.60, 151.50, 145.74, 143.45, 139.05, 129.07, 128.75, 128.11, 124.97, 42.46, 21.52, 20.72. **IR** (neat) 3043.97, 2969.64, 2931.82, 2874.59, 1606.03, 1580.59, 1488.88, 1455.93, 1378.25, 1050.00, 968.44, 857.55, 783.85, 758.81, 704.03, 668.37 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{14}N_2 + Na]^+$: 221.1049, Found: 221.1048. **Specific Rotation** $[\alpha]_D^{23}$ +7.07 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 10 min elution on a Daicel AS-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 4.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 210 nm), t_M= 6.22 min, t_m = 6.90 min. *94% ee*. **Duplicate Experiment** 49% yield, *94% ee*.



(*S*)-4-(1-(3-Fluorophenyl)ethyl)-3-Methylpyridazine (3i)[8] **and (*S*)-5-(1-(3-Fluorophenyl)ethyl)-3-Methylpyridazine (3i'), 7:1 Regioisomer Mixture:** Prepared according to Procedure A on 1.0 mmol scale. The dearomatization step in this procedure used 1.51 equiv of the styrene (0.18 mL) rather than 2.0 equiv, and the oxidation and fluoride workup steps were preformed as described in example **3g**. The residue obtained after the fluoride workup was filtered through a 5 g plug of silica gel with EtOAc and the filtrate was concentrated to provide a crude residue that was purified using the chromatography conditions described in example **3g** (albeit here using 50 g of silica rather than 40 g) to provide a 7:1 mixture of **3i** and **3i'** as a pale-orange oil, 104.1 mg (48% total yield). **^{1}H NMR** (600 MHz, $CDCl_3$) Major regioisomer δ 9.05 (d, J = 5.1 Hz, 1H), 7.31 – 7.26 (m, 2H), 6.94 (tdd, J = 8.5, 2.6, 1.0 Hz, 1H), 6.89 – 6.85 (m, 1H), 6.80 (dt, J = 9.8, 2.1 Hz, 1H), 4.23 (q, J = 7.2 Hz, 1H), 2.62 (s, 3H), 1.63 (d, J = 7.2 Hz, 3H). Observable signals of the minor regioisomer: δ 8.91 (d, J = 2.2 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 4.11 (q, J = 7.2 Hz, 1H), 2.69 (s, 3H), 1.66 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) **Major Regioisomer:** δ 164.00, 162.37, 159.81, 150.25, 145.47, 145.43,

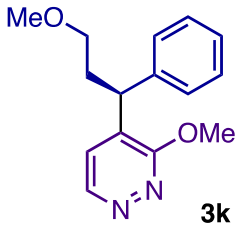
143.03, 130.56, 130.51, 123.94, 123.41, 123.39, 114.73, 114.59, 114.18, 114.04, 77.37, 40.36, 20.98, 20.54. **Minor Regioisomer:** ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.02, 162.38, 159.95, 149.92, 145.53, 144.57, 130.60, 130.54, 125.07, 123.46, 123.44, 114.76, 114.61, 114.30, 114.16, 41.85, 22.50, 20.62. All fluoroarene resonances of both regioisomers are observable and exhibit J_{CF} coupling. **Major regioisomer:** C1: doublet at δ 163.18 ppm ($^1J_{CF}$ = 253.1 Hz). C2 and C6 (arbitrary order): doublets at δ 114.11 ppm ($^2J_{CF}$ = 21.0 Hz) and 114.66 ppm ($^2J_{CF}$ = 21.9 Hz). C3: doublet at δ 145.45 ppm ($^3J_{CF}$ = 6.7 Hz). C4: doublet at δ 123.40 ppm ($^4J_{CF}$ = 2.7 Hz). C5: doublet at δ 130.53 ppm ($^3J_{CF}$ = 8.4 Hz). **Minor regioisomer:** C1: doublet at δ 163.20 ppm ($^1J_{CF}$ = 247.0 Hz. C2 and C6 (arbitrary order): doublets at δ 114.24 ppm ($^2J_{CF}$ = 21.2 Hz) and 114.68 ppm ($^2J_{CF}$ = 21.7 Hz). C3: doublet at δ 145.50 ppm ($^3J_{CF}$ = 7.3 Hz; high-field spike overlaps C3 signal of major regioisomer). C4: doublet at δ 12 3.45 ppm ($^4J_{CF}$ = 3.0 Hz). C5: doublet at δ 130.57 ppm ($^3J_{CF}$ = 8.3 Hz). In addition to the doublets, 8 singlets are observed in the aromatic region, as required by the presence of two distinct disubstituted pyridazines. **^{19}F NMR** (282 MHz, C_6D_6) δ -112.32. **IR** (neat) 3044.87, 2971.01, 2932.63, 1612.05, 1588.23, 1484.99, 1446.48, 1427.22, 1376.08, 1355.04, 1260.90, 1239.60, 1140.47, 1033.66, 910.72, 868.21, 787.33, 752.13, 696.71 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{13}FN_2 + H]^+$: 217.1135, Found: 217.1137. **Specific Rotation** $[\alpha]_D^{23}$ +39.48 (*c* 0.50, $CHCl_3$). **Chiral Analysis** *Method for the major regioisomer*: 8 min elution on a Daicel OD-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 7.5% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 256 nm), t_M= 6.74 min, t_m= 6.23 min. <u>*98.5% ee*</u>. *Method for the minor regioisomer:* eight-min elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ containing 5.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, quantitation wavelength = 256 nm, t_M = 3.58 min, t_m = 3.25 min. <u>*97% ee.*</u> **Duplicate Experiment** 51% yield, 7:1 regioisomer ratio; *98% ee* (major regioisomer), *95% ee* (minor regioisomer).



3j

(*S*)-3-Methoxy-4-(1-Phenylethyl)pyridazine (3j)[8]: Prepared according to Procedure A on 1 mmol scale. The dearomatization, oxidation, fluoride workup and crude-product-isolation steps were as described in example **3g**. The crude product was purified on a 40 g silica column that was wet-loaded as a slurry in 15% EtOAc/hexanes and eluted with 2:1 hexanes:EtOAc (450 mL) → 45% EtOAc/hexanes (sufficient for complete elution of product). The title compound was obtained as a yellow-orange oil, 114.4 mg (54% yield). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.70 (d, *J* = 4.7 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.21 (m, 1H), 7.21 – 7.18 (m, 2H), 7.14 (dd, *J* = 4.7, 0.9 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 1H), 4.07 (s, 3H), 1.57 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 163.80,

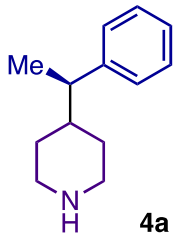
147.89, 143.47, 135.87, 128.87, 128.07, 127.02, 126.12, 54.92, 37.92, 19.85. **IR** (neat) 3060.42, 3026.83, 2971.50, 2950.29, 1586.81, 1555.14, 1493.92, 1452.62, 1414.48, 1365.51, 1323.53, 1284.39, 1011.25, 859.11, 759.33, 734.92, 698.74 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{14}N_2O + H]^+$: 215.1179. Found: 215.1184. **Specific Rotation** $[\alpha]_D^{23}$ -33.90 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 8 min elution on a Daicel OJ-H (4.6 x 250 mm, 5 μM particle size) column with $scCO_2$ containing 10.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 267 nm), t_M= 2.54 min, t_m = 2.38 min. *98% ee.* **Duplicate Experiment** 55% yield, *98% ee*.



3k

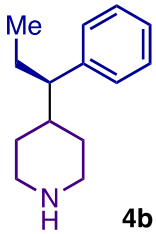
(*S*)-3-Methoxy-4-(3-Methoxy-1-Phenylpropyl)pyridazine (3k): Prepared according to Procedure A on 1.0 mmol scale. The dearomatization step in this example used 1.12 equiv of the olefin (166 mg) rather than 2.0 equiv. The dearomatization mixture was stirred at rt for 42 h prior to removal of volatiles. The oxidation, fluoride workup, filtration and chromatography steps were as in example **3g**. The title compound was obtained as an extremely viscous yellow-orange oil (153.5 mg, 60% yield). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.26 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.24 – 7.19 (m, 3H), 4.34 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.07 (s, 2H), 3.32 – 3.21 (m, 5H), 2.29 (ddt, *J* = 13.9, 7.5, 6.5 Hz, 1H), 2.18 (dddd, *J* = 13.7, 9.2, 6.1, 5.5 Hz, 1H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 163.88, 147.81, 141.52, 134.43, 128.89, 128.64, 127.17, 126.19, 70.34, 58.70, 54.95, 40.26, 33.83. **IR** (neat) 2949.45, 2872.71, 1586.48, 1555.49, 1459.70, 1369.27, 1289.58, 1118.22, 1011.67, 866.97, 758.64, 736.31, 700.24 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{15}H_{18}N_2O_2 + H]^+$: 259.1441. Found: 259.1444. **Specific Rotation** $[\alpha]_D^{23}$ -14.14 (*c* 0.50, $CHCl_3$). **Chiral Analysis** 5 min elution on a Daicel AD-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ containing 10.0% of a 0.1% solution (v/v) of DEA in MeOH, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 269 nm), t_M = 3.22 min, t_m = 2.97 min. *93% ee*. **Duplicate Experiment** 56 %yield, *93% ee*.

3.2 Reduction Examples



4a

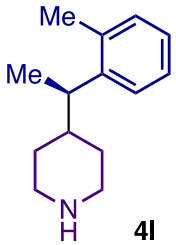
(*R*)-4-(1-Phenylethyl)piperidine (4a): Prepared according to Procedure C. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 7:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 7:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil (82.0 mg, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.24 – 7.11 (m, 3H), 3.27 – 2.95 (m, 1H), 2.70 – 2.54 (m, 1H), 2.47 (dq, *J* = 8.3, 7.1 Hz, 2H), 2.03 – 1.72 (m, 1H), 1.52 (ddt, *J* = 11.8, 8.3, 5.9 Hz, 1H), 1.45 – 1.33 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.23 – 1.12 (m, 1H), 1.11 – 0.94 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.79, 128.32, 127.52, 126.12, 45.74, 45.72, 45.44, 42.01, 30.15, 29.32, 18.67. **IR** (neat) 2935, 2848, 2733, 1492, 1451,1373, 1320, 1271, 1144, 1021, 760, 699 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{19}N + H]^+ = [M + H]^+$: 190.1596, Found: 190.1586. **Specific Rotation** $[\alpha]_D^{23}$ +26.5 (*c* 1.0, $CHCl_3$). **Chiral analysis** 18 min elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ containing 7.5% of a 0.1% (v/v) solution of DEA in MeOH, 210-400 nm detection (quantitation wavelength = 210 nm), fr = 2.5 mL/min, ct = 40 °C, t_M = 13.16 min, t_m = 14.47 min. *90% ee*. **Duplicate experiment** 85% yield, *90% ee.*



4b

(*R*)-4-(1-Phenylpropyl)piperidine (4b): Prepared according to Procedure C. The silica column used in the purification was prepared from a slurry of silica gel (12 g) in CH_2Cl_2 inside a narrow (ca. 1 cm outer-diameter) column. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 7:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 7:1 mixture

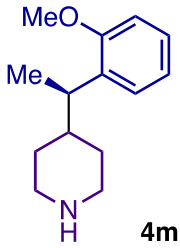
was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil (75.0 mg, 74% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (ddd, J = 7.6, 6.4, 1.3 Hz, 2H), 7.24 – 7.17 (m, 1H), 7.15 – 7.07 (m, 2H), 3.28 (s, 1H), 3.20 – 3.10 (m, 1H), 3.02 (dt, J = 12.5, 3.3 Hz, 1H), 2.62 (td, J = 12.3, 2.8 Hz, 1H), 2.49 (td, J = 12.2, 2.8 Hz, 1H), 2.23 (ddd, J = 10.8, 8.3, 4.0 Hz, 1H), 2.01 – 1.78 (m, 2H), 1.68 – 1.45 (m, 2H), 1.37 (dq, J = 13.3, 2.8 Hz, 1H), 1.29 – 1.12 (m, 1H), 1.06 (dtd, J = 13.2, 12.0, 4.1 Hz, 1H), 0.71 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.72, 128.49, 128.07, 125.93, 53.80, 46.51, 46.49, 41.40, 31.17, 31.09, 25.04, 12.26. **IR** (neat) 2928, 2871, 1493, 1452, 1320, 1263, 1144, 1030, 747, 700 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{14}H_{21}N + H]^+$ ($[M + H]^+$): 204.1752, Found: 204.1746. **Specific Rotation** $[\alpha]_D^{23}$ -2.5 (*c* 1.0, $CHCl_3$). **Chiral analysis** Elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ and a 15 min linear gradient from 5% to 12% MeOH (0.1% DEA v/v) followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 210 nm), t_M = 10.79 min, t_m = 11.59 min. *95% ee*. **Duplicate experiment** 76% yield, *92% ee*.



4l

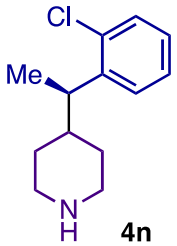
(*R*)-4-(1-(*o*-Tolyl)ethyl)piperidine (4l): Prepared according to Procedure C. The silica column used in the purification was prepared from a slurry of silica gel (12 g) in CH_2Cl_2 inside a narrow (ca. 1 cm outer-diameter) column. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 10:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 10:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil (85.0 mg, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 – 7.10 (m, 3H), 7.06 (ddd, J = 7.6, 6.0, 2.4 Hz, 1H), 3.15 (ddt, J = 12.1, 3.7, 1.9 Hz, 1H), 2.98 (ddt, J = 12.2, 3.8, 1.9 Hz, 1H), 2.80 – 2.65 (m, 2H), 2.59 (td, J = 12.2, 2.8 Hz, 1H), 2.47 (td, J = 12.2, 2.7 Hz, 1H), 2.30 (s, 3H), 2.03 – 1.80 (m, 1H), 1.55 (tdt, J = 12.1, 8.8, 3.6 Hz, 1H), 1.37 (dt, J = 13.3, 2.9 Hz, 1H), 1.31 – 1.20 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 1.08 (dtd, J = 13.0, 12.0, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.81, 135.52, 130.11, 125.98, 125.87, 125.33, 46.72, 46.70, 42.39, 39.99, 31.51, 30.71, 19.90, 18.43. **IR** (neat) 2931, 2847, 1488, 1458, 1373, 1320, 1272, 1142, 1101, 1022, 757, 727 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{14}H_{21}N + H]^+$ = ($[M + H]^+$): 204.1752, Found: 204.1744. **Specific Rotation** $[\alpha]_D^{23}$ -17.9 (*c* 1.0, $CHCl_3$). **Chiral analysis** Elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ and a 10 min linear gradient from 5% to 15% MeOH (0.1% DEA v/v) followed by a 1 min hold time, fr = 2.5 mL/min, ct = 40

ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 220 nm), t_M = 6.77 min, t_m = 7.31 min). *92% ee*. **Duplicate experiment** 85% yield, *92% ee*.



4m

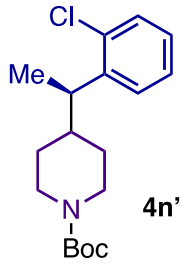
(*R*)-4-(1-(2-Methoxyphenyl)ethyl)piperidine (4m): Prepared according to Procedure C. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 10:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 10:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil (82.0 mg, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 – 7.13 (m, 1H), 7.11 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.91 (td, *J* = 7.4, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.79 (s, 3H), 3.33 (s, 1H), 3.20 (d, *J* = 12.2 Hz, 1H), 3.11 – 2.91 (m, 2H), 2.70 – 2.37 (m, 2H), 1.88 (d, *J* = 13.5 Hz, 1H), 1.59 (dtd, *J* = 11.6, 8.3, 4.4 Hz, 1H), 1.40 (d, *J* = 13.2 Hz, 1H), 1.34 – 1.04 (m, 2H), 1.19 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.12, 134.36, 127.64, 126.68, 120.49, 110.54, 55.37, 46.17, 41.26, 37.18, 30.66, 29.96, 17.51. **IR** (neat) 2933, 2834, 1598, 1491, 1462, 1238, 1028, 753, 734 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{14}H_{21}NO + H]^+$ = $[M + H]^+$): 220.1701, Found: 220.1694. **Specific Rotation** $[\alpha]_D^{23}$ 1.5 (*c* 1.0, $CHCl_3$). **Chiral analysis** Elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ and a 15 min linear gradient from 5% to 12% MeOH (0.1% DEA v/v) followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 220 nm), t_M = 12.08 min, t_m = 12.91 min). *93% ee*. **Duplicate Experiment** 76% yield, *97% ee*.



4n

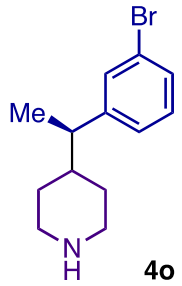
(*R*)-4-(1-(2-Chlorophenyl)ethyl)piperidine (4n): Prepared according to Procedure C. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1

CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 10:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 10:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil 83.0 mg (75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (dt, J = 8.0, 1.0 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.09 (ddd, J = 7.9, 5.3, 3.6 Hz, 1H), 3.19 – 3.04 (m, 2H), 3.02 – 2.91 (m, 1H), 2.55 (td, J = 12.2, 2.7 Hz, 1H), 2.47 (td, J = 12.1, 2.8 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.58 (tdt, J = 11.8, 8.3, 3.6 Hz, 1H), 1.43 – 1.30 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H), 1.26 – 1.06 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.72, 134.01, 129.40, 127.93, 126.77, 126.69, 46.86, 46.84, 42.09, 40.61, 31.55, 30.62, 17.57. **IR** (neat) 2916, 2848, 1475, 1436, 1374, 1321, 1266, 1033, 752, 731, 687 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{18}ClN + H]^+ = [M + H]^+$: 224.1206, Found: 224.1201. **Specific Rotation** $[\alpha]_D^{23}$ 7.4 (*c* 1.0, $CHCl_3$). **Duplicate Experiment** 75% yield.



4n'

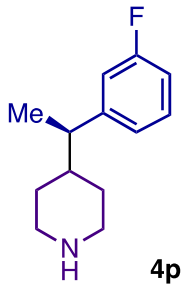
***Tert*-butyl (*R*)-4-(1-(2-Chlorophenyl)ethyl)piperidine-1-Carboxylate (4n'):** Piperidine **4n** (20 mg, 0.082 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). Triethylamine (25 mg, 0.246 mmol) and di-*tert*-butyl dicarbonate (35 mg, 0.164 mol) were added to the resulting solution. After stirring at room temperature for 1 h, saturated Na_2CO_3 was added, and the resulting mixture was extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (Hexane : EtOAc = 5 : 1) to give the title compound as a colorless oil, 28 mg (100% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 7.9, 1.2 Hz, 1H), 7.22 (dd, J = 6.7, 1.7 Hz, 2H), 7.11 (ddd, J = 8.1, 6.3, 2.6 Hz, 1H), 4.14 (d, J = 13.4 Hz, 1H), 4.01 (d, J = 13.3 Hz, 1H), 3.29 – 2.99 (m, 1H), 2.64 (td, J = 12.9, 2.8 Hz, 1H), 2.56 (td, J = 12.9, 2.9 Hz, 1H), 1.81 (dt, J = 13.0, 2.9 Hz, 1H), 1.68 – 1.55 (m, 2H), 1.44 (s, 9H), 1.37 – 1.31 (m, 1H), 1.21 (d, J = 7.1 Hz, 3H), 1.20 – 1.09 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.78, 143.46, 133.99, 129.54, 127.91, 127.01, 126.99, 126.85, 79.23, 44.02, 41.95, 40.14, 30.25, 29.28, 28.47, 17.71. **IR** (neat) 2972, 2931, 2851, 1693, 1476, 1422, 1365, 1283, 1173, 1149, 1033, 754 cm^{-1}. **EA** Calcd. for $C_{18}H_{26}ClNO_2$: C, 66.76; H, 8.09, Found: C, 66.48; H, 8.39. **Specific Rotation** $[\alpha]_D^{23}$ - 6.0 (*c* 1.0, $CHCl_3$). **Chiral analysis** Elution on a Daicel OJ-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ and an 8 min linear gradient from 5% to 10% ^{i}PrOH followed by a 1 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 220 nm), t_M = 2.81 min, t_m = 3.16 min. *81% ee*. **Duplicate experiment** *82% ee*.



4o

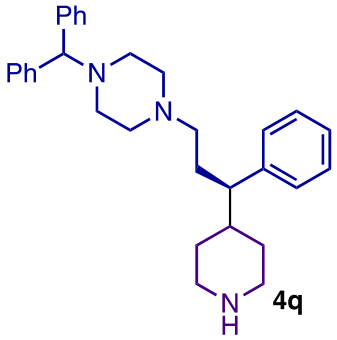
(*R*)-4-(1- (3-Bromophenyl)ethyl)piperidine (4o): Prepared according to Procedure C. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 10:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 10:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil (119.0 mg, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 2H), 7.14 (t, J = 7.7 Hz, 1H), 7.06 (dt, J = 7.7, 1.4 Hz, 1H), 3.12 (d, J = 11.5 Hz, 1H), 2.99 (d, J = 12.1 Hz, 1H), 2.64 – 2.32 (m, 4H), 1.91 – 1.68 (m, 1H), 1.55 – 1.41 (m, 1H), 1.39 – 1.30 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.20 – 1.10 (m, 1H), 1.09 – 0.92 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.76, 130.59, 129.75, 129.01, 126.40, 122.37, 46.63, 45.68, 42.66, 31.61, 30.86, 18.52. **IR** (neat) 2932, 2849, 2733, 1592, 1565, 1473, 1426, 1280, 1072, 996, 810, 783, 698, 669 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{17}BrN + H]^+ = [M + H]^+$: 268.0701, Found: 268.0695. **Specific Rotation** $[\alpha]_D^{23}$ -16.6 (*c* 1.0, $CHCl_3$). **Chiral Analysis** Elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ and a 15 min linear gradient from 5% to 12% MeOH (0.1% DEA v/v) followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 220 nm), t_M = 13.03 min, t_m = 13.84 min. *68% ee*. **Duplicate experiment** 88% yield, *68% ee*.

Recrystallization of the Hydrochloride Salt of 4o: Piperidine **4o** (45 mg, 0.17 mmol) was dissolved in methanolic HCl (0.5 mL, 1.25 M) at 0 ºC, and the resulting mixture was stirred at room temperature for 20 min. The solvent was removed *in vacuo* and the residue was dissolved in a 2:1 mixture of hot EtOAc:hexanes (about 2 mL total). The solution was cooled in a refrigerator (4 ºC) overnight. The crystalline hydrochloride salt was obtain by filtration. These crystals were dissolved in NaOH (1.0 mL, 1 M), and the resulting solution was extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 28 mg (62% recovery) of **4o** having *94% ee* by the analytical method described in the previous procedure.



4p

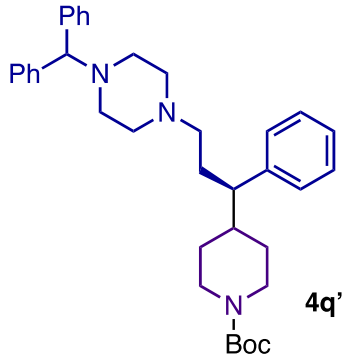
(*R*)-4-(1-(3-Fluorophenyl)ethyl)piperidine (4p): Prepared according to Procedure C. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 10:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 10:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil (92.0 mg, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (td, J = 7.9, 6.1 Hz, 1H), 6.94 – 6.75 (m, 3H), 3.20 – 3.06 (m, 1H), 3.06 – 2.89 (m, 2H), 2.63 – 2.53 (m, 1H), 2.52 – 2.36 (m, 2H), 1.88 – 1.79 (m, 1H), 1.47 (tdt, J = 11.8, 8.3, 3.5 Hz, 1H), 1.40 – 1.29 (m, 1H), 1.22 (d, J = 7.1 Hz, 3H), 1.24 – 1.13 (m, 1H), 1.12 – 1.00 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.88 (d, J = 245.0 Hz), 148.95 (d, J = 6.7 Hz), 129.53 (d, J = 8.2 Hz), 123.38 (d, J = 2.7 Hz), 114.24 (d, J = 20.7 Hz), 112.75 (d, J = 21.1 Hz), 46.49 , 45.62 , 45.61 , 42.56 , 31.37 , 30.62 , 18.54. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -114.27. **IR** (neat) 2933, 1615, 1586, 1483, 1444, 1376, 1321, 1270, 1139, 870, 782, 749, 661 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{13}H_{18}FN + H]^+$ = $[M + H]^+$: 208.1502, Found: 208.1504. **Specific Rotation** $[\alpha]_D^{23}$ -25.7 (*c* 1.0, $CHCl_3$). **Chiral Analysis** Elution on a Daicel AD-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ and a 10 min linear gradient from 5% to 15% MeOH (0.1% DEA v/v) followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 210 nm), t_M = 6.56 min, t_m = 6.98 min. *91% ee*. **Duplicate experiment** 90% yield, *92% ee*. **10 mmol scale reaction** 1.68 g, 81% yield, *89% ee*.



4q

(*R*)-1-Benzhydryl-4-(3-Phenyl-3-(Piperidin-4-yl)propyl)piperazine (4q): Prepared according to Procedure C. The crude product mixture was loaded onto the column as a

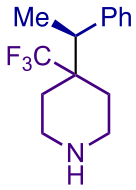
solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 6:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 6:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a white solid, 140 mg (62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H), 7.22 – 7.13 (m, 6H), 7.13 – 7.04 (m, 3H), 7.03 – 6.95 (m, 2H), 4.12 (s, 1H), 3.62 (s, 2H), 3.19 – 3.04 (m, 1H), 2.96 (dt, *J* = 12.3, 3.3 Hz, 1H), 2.53 (td, *J* = 12.3, 2.7 Hz, 1H), 2.45 – 2.14 (m, 9H), 2.12 – 1.75 (m, 4H), 1.61 (ddd, *J* = 14.2, 10.9, 5.5 Hz, 1H), 1.54 – 1.42 (m, 1H), 1.32 – 1.10 (m, 2H), 1.10 – 0.92 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.19, 142.73, 128.37, 128.22, 128.20, 127.86, 126.79, 126.15, 76.19, 56.96, 53.46, 51.83, 49.96, 46.02, 41.41, 30.46, 30.41, 29.44. **Melting Point:** 68 - 70 ºC. **IR** (neat) 3060, 3024, 2936, 2848, 2807, 1492, 1451, 1268, 1137, 1008, 758, 704, 618 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{31}H_{39}N_3 + H]^+ = [M + H]^+$: 454.3222, Found: 454.3217. **Specific Rotation** $[\alpha]_D^{23}$ 5.3 (*c* 1.0, $CHCl_3$). **Duplicate Experiment** 67% yield.



4q'

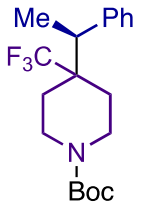
***Tert*-butyl (*R*)-4-(3-(4-Benzhydrylpiperazin-1-yl)-1-Phenylpropyl)piperidine-1-Carboxylate (4q'):** Piperidine 4q (20 mg, 0.044 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). Triethylamine (13.4 mg, 0.132 mmol) and di-*tert*-butyl dicarbonate (19 mg, 0.088 mol) were added to the resulting solution. After stirring at room temperature for 1 h, saturated Na_2CO_3 was added, and the resulting mixture was extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (CH_2Cl_2 : MeOH = 20 : 1) to give the title compound as a colorless oil (24 mg, 100% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 3H), 7.23 – 7.13 (m, 6H), 7.12 – 7.04 (m, 3H), 7.01 (d, *J* = 7.3 Hz, 2H), 4.12 (s, 1H), 4.09 – 3.77 (m, 2H), 2.63 – 2.13 (m, 10H), 2.15 – 1.85 (m, 4H), 1.81 – 1.58 (m, 2H), 1.55 – 1.41 (m, 1H), 1.34 (s, 9H), 1.28 – 1.13 (m, 1H), 1.04 (tt, *J* = 12.5, 6.2 Hz, 1H), 0.90 (tt, *J* = 13.4, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.69, 143.16, 142.66, 128.38, 128.21, 127.84, 127.82, 126.82, 126.17, 79.14, 76.15, 56.96, 53.41, 51.69, 49.73, 43.93, 41.81, 30.37, 30.22, 29.44, 28.40, 27.37. IR (neat) 2916, 2848, 1664, 1451, 1426, 1366, 1265, 1165, 1008, 735 cm^{-1}. HR-MS (m/z, ESI)

Calcd. For $[C_{36}H_{47}N_3O_2 + H]^+ = [M + H]^+$: 554.3747, Found: 554.3740. Specific Rotation $[\alpha]_D^{23}$ 15.0 (*c* 1.0, $CHCl_3$). Chiral Analysis Elution on a Daicel AD-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ and an 8 min linear gradient from 5% to 40% ^{i}PrOH followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 220 nm), t_M = 6.83 min, t_m = 6.40 min. *84% ee*. Duplicate experiment: *86% ee*.



4r

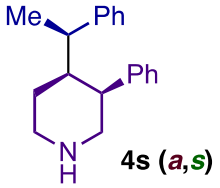
(*S*)-4-(1-Phenylethyl)-4-(Trifluoromethyl)piperidine (4r): Prepared according to Procedure C. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using a gradient of 40:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL) → 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 20:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide the title compound as a colorless oil, 115.0 mg (89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 6.82 (m, 5H), 3.14 (q, *J* = 7.4 Hz, 1H), 3.04 – 2.69 (m, 4H), 1.90 – 1.50 (m, 5H), 1.34 (dd, *J* = 7.4, 1.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.23, 129.62, 129.49 (q, *J* = 286.0 Hz), 127.81, 126.70, 44.60 (q, *J* = 21.4 Hz), 42.27, 41.42, 29.25, 27.88, 16.16. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -66.92. **IR** (neat) 2948, 1495, 1453, 1384, 1336, 1242, 1217, 1162, 1124, 1068, 1040, 770, 702, 638, 610 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{14}H_{18}F_3N + H]^+ = [M + H]^+$): 258.1461, Found: 258.1462. **Specific Rotation** $[\alpha]_D^{23}$ -2.1 (*c* 1.0, $CHCl_3$). **Duplicate Experiment** 91% yield.



4r'

***Tert*-butyl (*S*)-4-(1-Phenylethyl)-4-(Trifluoromethyl)piperidine-1-Carboxylate (4r'):** Piperidine **4r** (20 mg, 0.077 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). Triethylamine (24 mg, 0.231 mmol) and di-*tert*-butyl dicarbonate (33 mg, 0.154 mol) were added to the resulting solution. After stirring at room temperature for 1 h, saturated Na_2CO_3 was added, and the resulting mixture was extracted with CH_2Cl_2 (3x). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (Hexanes : EtOAc = 5 : 1) to give the title compound as a colorless oil, 27 mg (100% yield). **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 7.27 – 7.02 (m, 5H), 3.60 – 3.45 (m, 1H), 3.40 - 3.25 (m, 3H), 3.05 (q, J = 7.4 Hz, 1H), 1.88 – 1.59 (m, 4H), 1.37 – 1.29 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.87, 141.80, 129.50, 129.52 (q, J = 287.9 Hz), 127.96, 126.90, 126.89, 79.63, 44.35 (q, J = 21.2 Hz), 42.72, 39.45, 28.36, 28.18, 26.37, 16.26. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -67.15. **IR** (neat) 2974, 2916, 1693, 1453, 1407, 1365, 1283, 1250, 1215, 1156, 1116, 1064, 1039, 985, 863, 769, 703 cm^{-1}. **EA** Calcd. for $C_{18}H_{26}ClNO_2$: C, 63.85; H, 7.33, Found: C, 64.11; H, 7.50. **Specific Rotation** $[\alpha]_D^{23}$ 5.2 (*c* 1.0, $CHCl_3$). **Chiral Analysis** Elution on a Daicel OJ-H column (4.6 x 250 mm, 5 μM particle size) with $scCO_2$ and an 8 min linear gradient from 5% to 10% ^{i}PrOH followed by a 1 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 215 nm), t_M = 1.94 min, t_m = 2.72 min. *75% ee*. **Duplicate experiment:** *78% ee*.



4s (*a*,*s*)

(3*S*,4*S*)-3-Phenyl-4-((*R*)-1-Phenylethyl)piperidine (4s (a,s)): Prepared according to Procedure D. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The major isomer **4s (a,s)** (a colorless oil, 91 mg, 70% yield) was then eluted from the column with 20:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (200 mL). The second fraction (26 mg) was eluted with 10:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (100 mL). The total isolated yield was 91%. Based on chiral SFC analysis of the crude product mixture, the ratio of the four diastereomers was 12.6 : 2.4 : 1 : 0.10 (See spectral attachments for details of the calculation). The diastereomer **4s (a,a)** was isolated by preparative HPLC from the second fraction above (ZORBAX CN PreHT, dimensions 21.2 mm x 250 mm., 10 : 90 IPA(1% DEA): Hexane for 60 min, 245 nm and 220 nm detection, 20 mL/min flow rate). **^{1}H NMR (4s (a,s))** (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.2 Hz, 2H), 7.26 (t, J = 7.4 Hz, 2H), 7.17 (dd, J = 16.8, 7.5 Hz, 3H), 7.07 (t, J = 7.3 Hz, 1H), 6.99 (d, J = 6.9 Hz, 2H), 3.13 – 2.85 (m, 4H), 2.50 (td, J = 12.3, 3.4 Hz, 1H), 2.19 (dq, J = 10.8, 6.8 Hz, 1H), 1.99 – 1.76 (m, 2H), 1.50 (qd, J = 12.7, 4.6 Hz, 1H), 1.07 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 14.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.60, 143.20, 130.12, 128.21, 128.08, 127.50, 126.10, 125.81, 53.27, 46.81, 45.86, 42.69, 42.41, 27.55, 19.82. **IR** (neat) 3026, 2929, 1600, 1492, 1451, 1373, 1321, 1265, 1144, 1080, 1031, 764, 735, 699 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{19}H_{23}N + H]^+$ = $[M + 1]^+$: 266.1909, Found: 266.1908. **Specific Rotation** $[\alpha]_D^{23}$ -25.6 (*c* 1.0, $CHCl_3$). **Chiral Analysis** Elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ and a 15 min linear gradient from 5% to 15% MeOH (0.1% DEA v/v) followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 215 nm)**,** t_M = 9.75 min, t_m = 8.49 min. *97% ee*. **Duplicate experiment:** 88% total yield, 66% yield of **4s (a,s)** (*98% ee)*.

Procedure for recrystallization of the hydrochloride salt of 4s (a,s):
Piperidine **4s(a,s)** (180 mg, 0.68 mmol) was dissolved in methanolic HCl (1.5 mL, 1.25 M) at 0 ºC and the resulting mixture was stirred at room temperature for 20 min. The solvent was removed *in vacuo* and the residue was dissolved in a hot 2:1 mixture of EtOH:Et_2O (about 4 mL). The solution was cooled to room temperature. After 3 days, needle-like crystals of [**4s (a,s)**]•HCl were present. These crystals were submitted to X-ray diffraction analysis without further manipulation. An ORTEP diagram of **4s (a,s)**•HCl is provided in Figure SI-12.

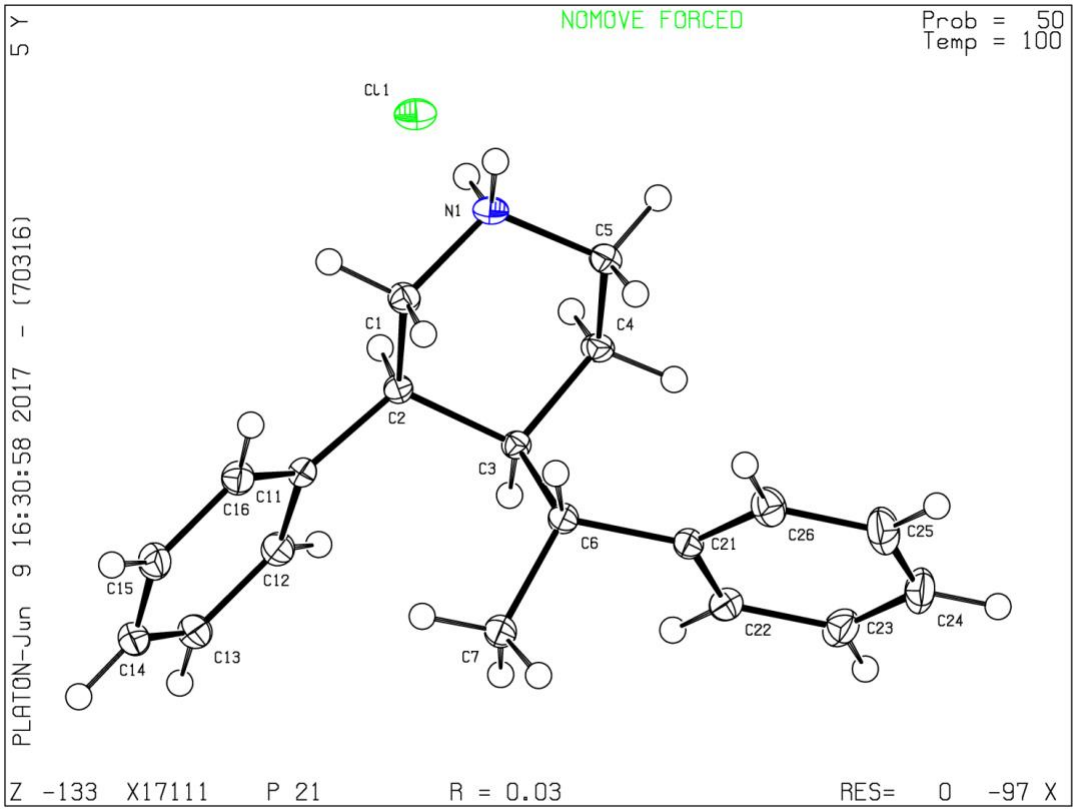
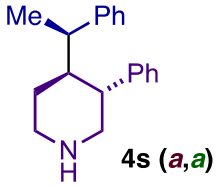


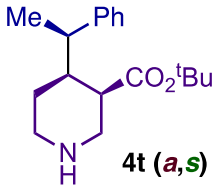
Fig. SI-12. Crystal Structure of [**4s (a,s)**]•HCl[9]



4s (*a*,*a*)

(3*R*,4*S*)-3-Phenyl-4-((*R*)-1-Phenylethyl)piperidine (4s (a,a))[8]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 7.5 Hz, 2H), 7.18 – 7.01 (m, 6H), 6.87 (d, J = 6.9 Hz, 2H), 3.03 (d, J = 12.5 Hz, 1H), 2.96 – 2.83 (m, 1H), 2.73 (tt, J = 7.3, 3.6 Hz, 1H), 2.64 – 2.50 (m, 1H), 2.45 (t, J = 11.8 Hz, 1H), 2.19 (td, J = 11.2, 4.0 Hz, 1H), 1.98 – 1.84 (m, 1H), 1.81 (d, J =

13.1 Hz, 1H), 1.12 (d, J = 7.3 Hz, 3H), 0.99 (qd, J = 12.5, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.42, 142.99, 128.85, 128.59, 128.25, 127.53, 126.30, 125.93, 55.96, 48.54, 47. 06, 46.17, 39.48, 27.25, 19.17. **IR** (neat) 3026, 2931, 1601, 1492, 1452, 1376, 1216, 1142, 1071, 748, 699 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{19}H_{23}N + H]^+$ = $[M + H]^+$): 266.1909, Found: 266.1908. **Specific Rotation** $[\alpha]_D^{23}$ -114.4 (*c* 1.0, $CHCl_3$).



4t (*a*,*s*)

***Tert*-butyl (3*R*,4*S*)-4-((*R*)-1-Phenylethyl)piperidine-3-Carboxylate (4t (a,s))[8]:** Prepared according to procedure D. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using 15:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 15:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide a mixture of diastereomers containing **4t (a,s)** as the major component, 114.0 mg (77% total yield). Based on ^{1}H-NMR analysis of this mixture, the ratio of four diastereomers was 5 : 1 : 0.7 : 0.35. (see below for details of the calculation). The major isomer **4t (a,s)** was isolated by preparative HPLC (ZORBAX CN PreHT, dimensions 21.2 mm x 250 mm. 15 : 85 IPA(1% DEA) : Hexane for 60 min, 245nm and 220 nm detection, 20 mL/min flow rate). Thus, 73 mg of **4t (a,s)** (51% yield) was obtained as a colorless oil. **^{1}H NMR (4t (a,s))** (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H), 7.26 – 7.16 (m, 1H), 7.19 – 7.12 (m, 2 H), 3.52 – 3.12 (m, 1H), 3.01 (ddt, J = 13.5, 3.6, 1.7 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.64 (dq, J = 10.8, 6.9 Hz, 1H), 2.49 – 2.32 (m, 1H), 2.01 (s, 1H), 1.89 – 1.64 (m, 1H), 1.55 (s, 9H), 1.56 – 1.39 (m, 1H), 1.33 (d, J = 6.9 Hz, 3H), 1.03 – 0.89 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.53, 146.33, 128.34, 127.47, 126.06, 80.52, 49.45, 46.82, 45.06, 43.69, 42.03, 28.27, 27.47, 19.53. **IR** (neat) 2932, 2850, 1713, 1453, 1366, 1231, 1148, 1020, 847, 750, 699 cm^{-1}. **EA** Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40, Found: C, 74.44; H, 9.55. **Specific Rotation** $[\alpha]_D^{23}$ 19.5 (*c* 1.0, $CHCl_3$). **Chiral Analysis** Elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ and a 10 min linear gradient from 5% to 15% MeOH (0.1% DEA v/v) followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 210 nm), t_M = 4.80 min, t_m = 5.77 min. *99% ee*. **Duplicate experiment:** 75% total yield, 44% yield of **4t (a,s)** (*99% ee)*.

Dr-Determination and Absolute Diastereomer Structural Assignments for Example 4t:

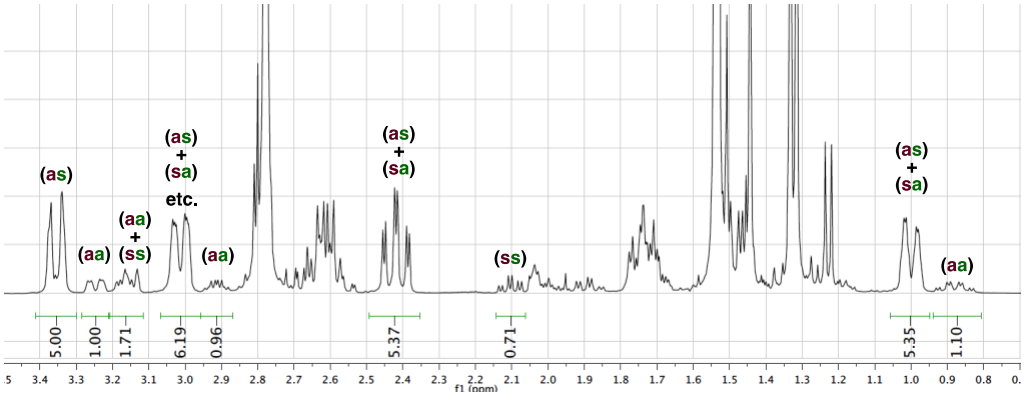


Fig SI-13. Excerpt of the ^{1}H NMR spectrum of the **4t** diastereomer mixture.

Unlike the other 3,4-disubstituted piperidines, the dr for the crude diastereomer mixture from which **4t (a,s)** was obtained could not be directly determined by SFC due to peak overlap. Further, signals present in the ^{1}H NMR spectrum obtained from the crude reduction mixture were much too broad to permit quantitation. Thus, the mixture was eluted on a silica column in such a way as to give total recovery of the diastereomers while separating them from both very polar and very non-polar impurities. After this manipulation, we obtained interpretable ^{1}H NMR spectra (See, e.g., Fig. SI-13).

We were able to independently assign the absolute configuration of purified **4t (a,s)** by 1-D ^{1}H NMR, 1-D NOESY and g-COSY analyses, and a fully resolved signal due to **4t (a,s)** is readily identifiable in the spectrum for the diastereomer mixture (δ = ca. 3.35 ppm); the integral for this signal is normalized to 5.0 in our analysis. We noted that the ^{1}H NMR spectrum of **4t (a,s)** indicates a substantial shielding interaction involving the H_5e proton, and we postulate that it is a conformation-driven anisotropic interaction between H_5e and the benzylic Ph ring (Fig SI-14). In 4-benzylpiperidine, which has less conformational incentive to display the phenyl ring near a specific piperidine proton, the H_3e (= H_5e) proton resonates at 1.62 ppm,[10] whereas H_5e in our compound resonates at 0.99 ppm. A conformational analysis of **4t (a,s)** indicates that the only way this molecule can simultaneously achieve a staggered conformation about the C4-Cα bond *and* avoid a *syn*-pentane interaction between the ester and the organic benzyl substituents is by situating the benzylic phenyl ring near H_5e (see Figure SI-14) – hence, the conformational model correctly predicts the strong shielding of H_5e.

Further, the H_5e shielding is abolished upon proceeding from the **(a,s)** to the **(a,a)** diastereomer in the closely related 3-Ph-piperidine series (**4s**, above). Working in this series, we were able to spectroscopically characterize a highly purified sample of the latter. Our conformational model correctly predicted that the H_5e resonance of **4s (a,a)** [δ = 1.81, versus 0.97 for H_5e in **4s (a,s)**] should be similar to the H_5e resonance of 4-benzylpiperidine. This loss of shielding is not easily rationalized as resulting from

changes in the orientations of other substituents; H_5e should not experience steric deshielding when the Ph is axial, and the presence of the 3-Ph group on the opposite side of the ring from H_5e should mitigate anisotropic interactions between them, regardless of the configuration at C3. These observations further support the notion that the shielding effect in **4 (a,s)** is due to an anisotropic interaction with the benzylic Ph group.

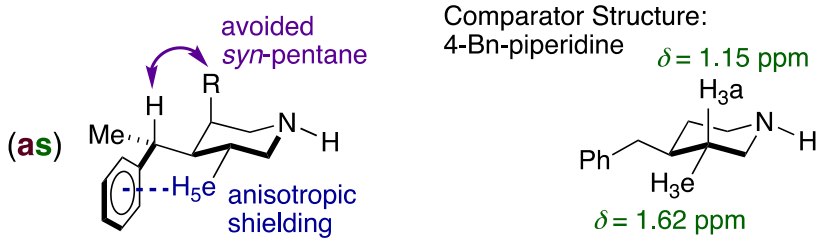


Fig SI-14. Conformation analysis correctly predicts anisotropic shielding of H_5e in **4 (a,s)**.

We can infer from the spectrum of purified **4s (a,s)** that its H_3e resonance must be between δ 2.95 – 3.15 ppm, whereas the H_3a resonance of **4s (a,a)** occurs at 2.19 ppm. In addition, upon progressing from **4s (a,s)** to **4s (a,a)**, the shift of the H_5a proton decreases from 1.50 to 0.99 ppm, suggesting the presence of a different shielding interaction. The latter differences could arise partly from elimination of axial-H steric-deshielding when the Ph substituent is transposed to an equatorial site, while the former may also reflect the intrinsically greater shielding of axial than equatorial protons. However, our model of **4 (a,a)** (Fig. SI-15) suggests that anisotropic interactions of H_3a and H_5a with a proximal benzylic Ph-face may also contribute to the pronounced shielding observed for both protons. In either case, our model for **4s (a,a)** qualitatively predicts the observed changes. Since the structural features causing these changes are preserved in **4t (a,a)**, we expect that its H_5a proton will be similarly shielded. It is clear from the 1-D ^{1}H NMR spectrum of the **4t** diastereomer mixture that a piperidine-containing species

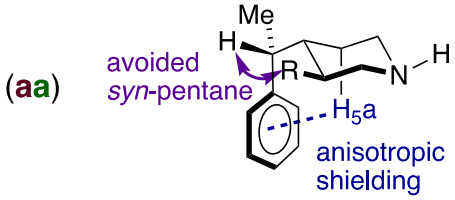


Figure SI-15. Conformation analysis predicts anisotropic shielding of axial protons in **4 (a,a)**.

is present (integrating at 1.0) possessing an axial H that resonates near δ 0.9 ppm (similar to the chemical shift observed for the strongly shielded H_5a of **4s (a,a)**). We therefore attribute this signal to **4t (a,a)**, setting the **4t (a,s)**:**(a,a)** ratio at 5:1.

A third diastereomer is present with integrals normalized at 0.7. This species does *not* place signals in the strongly-shielded aliphatic region containing H_5 resonances of **4t (a,s)** and **4t (a,a)**. Working with the analogous 3-carbamoyl-piperidine series (**4u**, *vide infra*), we were able to spectroscopically characterize the purified **(s,s)** diastereomer and confirm

that neither H_5a nor H_5e is strongly shielded in this compound (H_5e and H_5a in **4u (s,s)** resonate at 1.78 and 2.27 ppm, respectively). Rather, H_3e (the α-proton of the 3-carbamoyl substituent) is shifted ca. 0.55 ppm upfield relative to the corresponding H_3e resonance of **4u (a,s)**, despite the fact that the carbamoyl groups are axial and the benzyl substituents and H_5e's are *trans*-diequatorial in both structures. Conformational analysis (Fig. SI-16) correctly indicates that there should be a selective shielding of the H_3e proton in **4 (s,s)** and not in **4 (a,s)**. Our conformational model also predicts that **(s,s)** is the *only* diastereomer that should fail to strongly shield one of the H_5 protons (see further explanation below). Consequently, the piperidine species integrating at 0.7 is assigned as **(s,s)**, and the diastereomer ratio is set to 5.0:1.0:0.7 **(a,s)**:**(a,a)**:**(s,s)**.

We knew that **4t (s,a)** had to be present in the diastereomer mixture, but we had not previously characterized any analogous **4 (s,a)** species and were not able to observe any fully resolved resonances for **4t (s,a)** in the ^{1}H NMR spectrum of the mixture. However, in our model of **4t (s,a)**, (Fig. SI-17) the requirements for C4-Cα staggering and *syn*-pentane avoidance restore the strongly-shielding relationship between the benzylic Ph

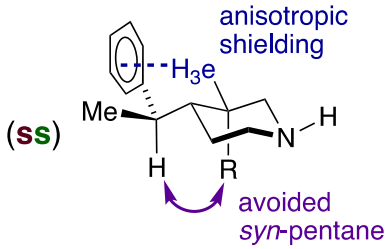


Fig. SI-16. Selective anisotropic shielding of H_3e in **4 (s,s)**.

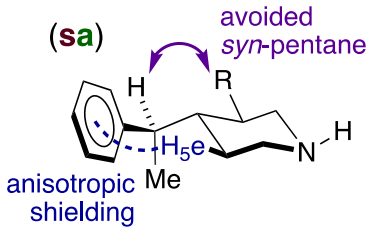
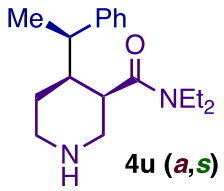


Fig. SI-17: Prediction of H_5e anisotropic shielding in **4 (s,a)** diastereomers.

ring and H_5e that we previously noted for **4t (a,s)** (cf. Fig. SI-14). Consequently, we predict that the H_5e resonance of **4t (s,a)** should be very similar to the H_5e resonance of **4t (a,s)**. Indeed, integration of the 1-D ^{1}H NMR spectrum of the **4t** diastereomer mixture indicates the presence of a fourth species, integrating at 0.35, two of whose signals are degenerate, respectively, with the H_5e and H_6a resonances of **4t (a,s)**. We therefore attribute these 0.35 integral contributions to the **4t (s,a)** diastereomer and arrive at the final diastereomer ratio of **(a,s)**:**(a,a)**:**(s,s)**:**(s,a)** = 5:1:0.7:0.35.

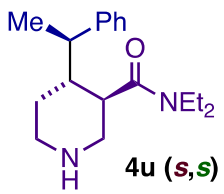
Notably, this analysis stipulates that the other piperidine protons of **4t (s,a)** overlap signals from the other diastereomers over the range δ 3.1 – 1.4. This requires shielding of the H_1e proton of **4t (s,a)** relative to the analogous resonance in **4t (a,s)**. The implied

shift difference can be rationalized as resulting from display of H_1e in **4t (s,a)** near the shielding region of the adjacent equatorial carbonyl function; the carbonyl occupies an axial site in **4t (a,s)**.



4u (*a*,*s*)

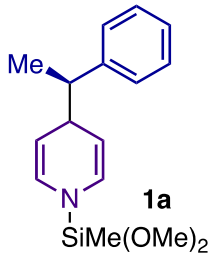
(3*R*,4*S*)-*N*,*N*-Diethyl-4-((*R*)-1-Phenylethyl)piperidine-3-Carboxamide (4u (a,s))[8]: Prepared according to Procedure D. The crude product mixture was loaded onto the column as a solution in CH_2Cl_2, and then nonpolar impurities were separated from the sample by flushing the column with CH_2Cl_2 (100 mL). The product was then eluted from the column using 10:1 CH_2Cl_2:(1.5 M NH_3 in MeOH) (typically about 200 mL of the 10:1 mixture was sufficient for complete elution of the product). Fractions containing the purified product were combined and concentrated to provide a diastereomer mixture containing **4u (a,s)** as the major product as a colorless oil, 128.0 mg (89% total yield). Based on chiral SFC of the crude product mixture, the ratio of four diastereomers was 11.4 : 2.7 : 1 : 0.11. See spectral attachments for details of the calculation. The major isomer **4u (a,s)** and **4u (s,s)** were isolated by preparative HPLC (ZORBAX CN PreHT, dimensions 21.2 mm x 250 mm. 20 : 80 IPA(1% DEA) : Hexane for 60 min, 245 nm and 220 nm detection, 20 mL/min flow rate). Thus, 70 mg of **4u (a,s)** (49% yield) and 15 mg of **4u (a,s)** (10% yield) were obtained as colorless oils. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.21 – 7.12 (m, 3H), 3.41 (dtt, J = 43.3, 14.2, 7.0 Hz, 4H), 3.23 - 3.12 (m, 1H), 3.11 – 2.96 (m, 2H), 2.88 (dd, J = 13.6, 4.3 Hz, 1H), 2.74 (dq, J = 10.4, 7.0 Hz, 1H), 2.40 (td, J = 13.1, 3.4 Hz, 1H), 2.23 – 1.97 (m, 2H), 1.75 (ddt, J = 12.1, 10.3, 4.4 Hz, 1H), 1.33 – 1.05 (m, 9H), 0.93 (dq, J = 13.3, 1.8 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.01, 146.64, 128.28, 127.57, 125.97, 50.10, 46.89, 45.10, 42.99, 42.30, 40.04, 36.49, 27.37, 19.77, 14.76, 13.10. **IR** (neat) 2930, 1622, 1493, 1453, 1431, 1380, 1262, 1216, 1134, 747, 700, 664 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{18}H_{28}N_2O + H]^+$ = $[M + H]^+$: 289.2280, Found: 289.2287. **Specific Rotation** $[\alpha]_D^{23}$ 52.1 (*c* 1.0, $CHCl_3$). **Chiral Analysis** Elution on a Waters Trefoil Cel-2 column (3.0 x 150 mm, 2.5 μM particle size) with $scCO_2$ and a 25 min linear gradient from 5% to 15% MeOH (0.1% DEA v/v) followed by a 2 min hold time, fr = 2.5 mL/min, ct = 40 ºC, simultaneous detection from 210-400 nm (quantitation wavelength = 215 nm), t_M = 16.48 min, t_m = 18.85 min. *99% ee*. **Duplicate experiment:** 85% total yield, 48% yield of **4u (a,s)** (*99% ee*).



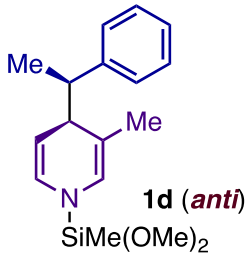
4u (*s*,*s*)

(3*R*,4*R*)-*N*,*N*-Diethyl-4-((*R*)-1-Phenylethyl)piperidine-3-Carboxamide (4u (s,s))[8]: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.23 – 7.17 (m, 1H), 7.16 – 7.08 (m, 2H), 3.62 – 3.48 (m, 1H), 3.32 (dd, *J* = 13.6, 4.6 Hz, 1H), 3.00 (dq, *J* = 12.1, 7.1 Hz, 1H), 2.83 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.74 – 2.62 (m, 2H), 2.56 – 2.44 (m, 1H), 2.44 – 2.37 (m, 1H), 2.28 (qd, *J* = 12.7, 4.8 Hz, 1H), 2.22 – 2.11 (m, 1H), 2.00 – 1.89 (m, 1H), 1.80 – 1.72 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.44, 146.58, 128.65, 127.63, 126.19, 50.12, 46.81, 43.61, 43.49, 41.70, 40.17, 36.40, 26.37, 21.39, 14.21, 12.96. **IR** (neat) 2931, 1620, 1451, 1430, 1360, 1259, 1143, 1015, 925, 729, 701 cm^{-1}. **HR-MS** (m/z, ESI) Calcd. For $[C_{18}H_{28}N_2O + H]^+ = [M + H]^+$: 289.2280. Found: 289.2287.

3.3 Crude N-Silyl-1,4-Dihydropyridines

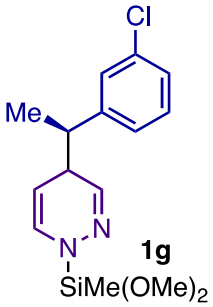


(*R*)-1-(Dimethoxy(methyl)silyl)-4-(1-Phenylethyl)-1,4-Dihydropyridine (1a): The dearomatization used 40 μL pyridine (0.495 mmol) and a catalyst loading of 4% $Cu(OAc)_2$ (3.6 mg) and 4.4% (*S*,*S*)-Ph-BPE (11.2 mg). It was conducted according to Procedure A, Part I as described for example **3a**. Upon concentration, the NMR sample was prepared according to Procedure E using 2,6-dimethoxytoluene (44.8 mg, 0.294 mmol) as the internal standard. The NMR yield was estimated to be 92%. See spectral attachments for details. **^{1}H NMR** (600 MHz, C_6D_6) δ 7.19 (t, *J* = 7.6 Hz, 2H), 7.17 – 7.11 (m, 3H), 7.11 – 7.02 (m, 2H), 6.19 (dt, *J* = 8.1, 1.2 Hz, 1H), 6.15 (dt, *J* = 8.0, 1.1 Hz, 1H), 4.57 (ddd, *J* = 8.1, 3.8, 2.5 Hz, 1H), 4.50 (ddd, *J* = 8.1, 3.8, 2.5 Hz, 1H), 3.39 (dtt, *J* = 5.8, 3.7, 1.0 Hz, 1H), 3.24 (s, 6H), 2.71 (apparent p, apparent *J* = 6.9 Hz, 1H), 1.34 (d, *J* = 7.1 Hz, 3H), -0.01 (s, 3H). Small signals due to the 1,2-dihydropyridine regioisomer were discernable in the spectrum: **^{1}H NMR** (600 MHz, C_6D_6) δ 6.27 (dd, *J* = 7.0, 1.1 Hz, 1H), 6.04 (dd, *J* = 9.2, 5.4 Hz, 1H), 5.29 (ddd, *J* = 7.2, 5.5, 1.0 Hz, 1H),5.26 (ddt, *J* = 9.4, 5.9, 1.0 Hz, 1H), 4.06 (ddd, *J* = 8.4, 5.9, 1.1 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), -0.35 (s, 3H). The ratio between the 1,4-DHP and the 1,2-DHP in this experiment was about 17.9:1 (corresponding to a ca. 5% NMR yield of the 1,2-DHP). The NMR spectrum recorded in this experiment provided the most accurate quantitation of the yield available to us, but the MeO-resonance of 2,6-dimethoxytoluene obscured the multiplet due to the C4-H proton of **1a**. Thus, in a separate experiment, we recorded another spectrum using a less obtrusive internal standard (3,5-dimethoxy-1-chlorobenzene). In this new spectrum, we were able to see the C4-H multiplet, and we have incorporated this feature into the list of signals reported above, for simplicity. The chemical shifts for resonances observable in both spectra were in very good agreement (most shifts differed by 0.01 ppm). The ratio between the 1,4-dihydropyridine and 1,2-dihydropyridine in the second experiment was about 25.6:1 (average regioisomer ratio for the two runs = 22:1)



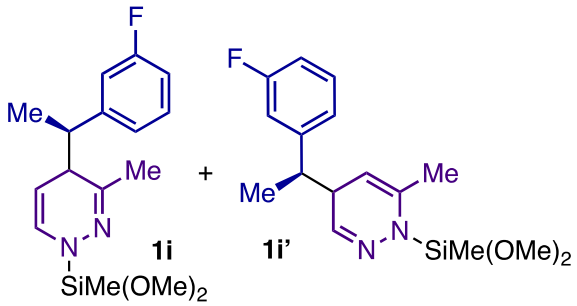
1d (***anti***)

(*R*)-1-(Dimethoxy(methyl)silyl)-3-Methyl-4-((*R*)-1-Phenylethyl)-1,4-Dihydropyridine (1d): The dearomatization used 49.0 μL of 3-picoline (0.504 mmol) and a catalyst loading of 6.0% $Cu(OAc)_2$ (5.4 mg) and 6.6% (*S*,*S*)-Ph-BPE (16.8 mg). The reaction mixture was prepared as described in Part I of Procedure A and stirred at rt for 24 h prior to removal of volatiles. The NMR sample was prepared using 2,6-dimethoxytoluene (49.2 mg, 0.323 mmol) as the internal standard. The ratio of *anti* to *syn* diastereomers was estimated to be 25:1. The NMR yield was estimated to be 92%. See spectral attachments for details. **Major (*anti*) Diastereomer: ^{1}H NMR** (600 MHz, C_6D_6) δ 7.25 – 7.17 (m, 2H), 7.12 (t, J = 7.6 Hz, 2H), 7.03 (dt, J = 7.8, 2.3 Hz, 1H), 6.15 (dd, J = 7.9, 1.2 Hz, 1H), 5.88 (t, J = 1.5 Hz, 1H), 4.66 (dd, J = 7.8, 4.4 Hz, 1H), 3.26 (t, J = 4.2 Hz, 1H), 3.16 (apparent d, apparent J = 3.2 Hz, 6H), 2.95 (qd, J = 7.2, 3.7 Hz, 1H), 1.54 (s, 3H), 1.26 (d, J = 7.2 Hz, 3H), -0.07 (s, 3H). **Observable Minor Diastereomer Signals:** ^{1}H NMR (600 MHz, C_6D_6) δ 6.26 (d, J = 8.1 Hz, 1H), 4.30 (dd, J = 8.0, 4.1 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H).

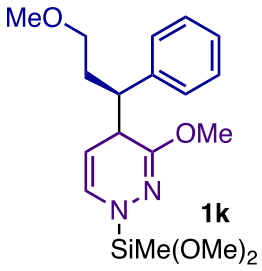


1g

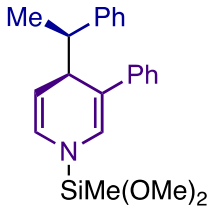
4-((*R*)-1-(3-Chlorophenyl)ethyl)-1-(Dimethoxy(methyl)silyl)-1,4-Dihydropyridazine (1g): The dearomatization was performed as described in example **3g**, albeit here on half-scale (specifically, this experiment used 0.497 mmol pyridazine) and with a slightly extended reaction time of 42 h. The NMR sample was prepared using 1,3,5-trimethoxybenzene (40.5 mg, 0.241 mmol) as the internal standard. The NMR yield was estimated to be 98%. See spectral attachments for details. **^{1}H NMR** (600 MHz, C_6D_6) δ 7.14 (d, J = 2.3 Hz, 1H), 7.06 (dd, J = 8.1, 2.0 Hz, 1H), 6.88 (t, J = 7.7 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.53 (d, J = 2.9 Hz, 1H), 6.44 (d, J = 8.1 Hz, 1H), 4.26 (dt, J = 7.3, 3.3 Hz, 1H), 3.40 (br. s, 6H), 2.82 (dt, J = 6.7, 3.7 Hz, 1H), 2.45 (apparent p, J = 6.8 Hz, 1H), 1.07 (d, J = 7.1 Hz, 3H), 0.29 (s, 3H).



1-(Dimethoxy(methyl)silyl)-4-((*R*)-1-(3-Fluorophenyl)ethyl)-3-Methyl-1,4-Dihydropyridazine (1i) and 1-(Dimethoxy(methyl)silyl)-4-((*R*)-1-(3-fluorophenyl)ethyl)-6-Methyl-1,4-Dihydropyridazine (1i'): The dearomatization was performed as described in the preparative example for these compounds, albeit here on half-scale (specifically, this experiment used 46 μL [0.504 mmol] 3-methylpyridazine). The NMR sample was prepared using 1,3,5-trimethoxybenzene (85.1 mg, 0.506 mmol) as the internal standard. The total NMR yield was estimated to be 96%. The ratio of **1i** to **1i'** was estimated to be 8:1. See spectral attachments for detail. **Major Regioisomer:** ^{1}H NMR (600 MHz, C_6D_6) δ 7.03 – 6.91 (m, 2H), 6.84 – 6.73 (m, 3H), 6.49 (d, J = 7.8 Hz, 1H), 4.42 (dd, J = 7.7, 4.9 Hz, 1H), 3.39 (s, 3H), 3.33 (s, 3H), 2.99 (t, J = 4.8 Hz, 1H), 2.80 (qd, J = ca. 6.8, 4.9 Hz, 1H), 1.79 (s, 3H), 1.09 (d, J = 7.2 Hz, 3H), 0.21 (s, 3H). **Minor Regioisomer:** ^{1}H NMR (600 MHz, C_6D_6) δ 6.62 (t, J = 2.7 Hz, 1H), 4.12 (d, J = 4.0 Hz, 1H), 2.87 (dt, J = 7.3, 3.9 Hz, 1H), 2.54 (p, J = 6.8 Hz, 1H), 1.89 (s, 3H), 1.12 (d, J = 7.1 Hz, 3H), 0.39 (s, 3H).

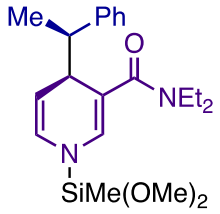


1-(Dimethoxy(methyl)silyl)-3-Methoxy-4-((*R*)-3-Methoxy-1-Phenylpropyl)-1,4-Dihydropyridazine (1k): The dearomatization was performed as described in example **3k**, albeit here on half-scale (specifically, using 54.6 mg [0.496 mmol] of 3-methoxypyridazine and 83.5 mg [0.563 mmol, 1.14 equiv] cinnamyl methyl ether). The NMR sample was prepared using 1,3,5-trimethoxybenzene (40.2 mg,0.239 mmol) as the internal standard. The *anti*:*syn* ratio was estimated to be 13:1. The NMR yield appeared to be quantitative (average yield estimate = 102%). **Major Diastereomer:** ^{1}H NMR (600 MHz, C_6D_6) δ 7.18 (d, J = 7.3 Hz, 2H), 7.12 (t, J = 7.5 Hz, 2H), 7.06 – 6.99 (m, 1H), 6.46 (d, J = 7.8 Hz, 1H), 4.49 (dd, J = 7.8, 4.0 Hz, 1H), 3.57 – 3.54 (m, 1H), 3.50 (s, 3H), 3.45 – 3.39 (m, 1H), 3.33 (s, 3H), 3.21 (s, 3H), 3.17 (dt, J = 9.6, 6.0 Hz, 1H), 3.09 (dt, J = 9.3, 7.2 Hz, 1H), 3.04 (s, 3H), 2.02 – 1.92 (m, 2H), 0.12 (s, 3H). **Minor Diastereomer:** ^{1}H NMR (600 MHz, C_6D_6) δ 6.57 (d, J = 7.7 Hz, 1H), 4.38 (dd, J = 7.9, 4.1 Hz, 1H), 0.28 (d, J = 1.1 Hz, 3H).



1s (***anti***)

(*R*)-1-(Dimethoxy(methyl)silyl)-3-Phenyl-4-((*R*)-1-Phenylethyl)-1,4-Dihydropyridine (1s (*anti*)): The dearomatization reaction was performed as described in example **3s**. For spectral clarity, an internal standard was not included in the NMR sample for this experiment. However, chemical shifts for diagnostic resonances of the product were already known from ^{1}H NMR spectra acquired in the presence of 1,4-dimethoxybenzene. Thus, we have set the C2-H resonance to its previously measure value of δ = 6.46 in tabulating spectral data here. The *anti*:*syn* ratio was estimated to be ca. 11:1. **Major Diastereomer:** ^{1}H NMR (600 MHz, C_6D_6) δ 7.39 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.5 Hz, 3H), 7.12 – 7.04 (m, 6H), 7.00 (t, J = 7.1 Hz, 1H), 6.46 (s, 1H), 6.12 (d, J = 7.8 Hz, 1H), 4.83 (dd, J = 7.8, 4.7 Hz, 1H), 4.06 (t, J = 4.4 Hz, 1H), 3.13 (s, 6H), 3.06 (dt, J = 7.4, 3.8 Hz, 1H), 1.20 (d, J = 7.3 Hz, 3H), -0.09 (s, 3H). **Minor Diastereomer:** ^{1}H NMR (600 MHz, C_6D_6) δ 7.49 (d, J = 7.8 Hz, 2H), 6.71 (s, 1H), 6.29 (d, J = 8.0 Hz, 1H), 4.52 (dd, J = 8.0, 4.2 Hz, 1H), 4.19 (t, J = 3.9 Hz, 1H), 1.38 (d, J = 7.1 Hz, 3H), 0.05 (s, 3H)

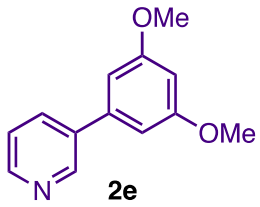


1u (***anti***)

(*R*)-1-(Dimethoxy(methyl)silyl)-*N*,*N*-Diethyl-4-((*R*)-1-Phenylethyl)-1,4-Dihydropyridine-3-Carboxamide (1u (*anti*): For spectral clarity, an internal standard was not included in the NMR sample for this experiment. However, chemical shifts for diagnostic resonances of the product were already known from ^{1}H NMR spectra acquired in the presence of 1,4-dimethoxybenzene. Thus, we have set the C2-H resonance to its previously measure value of δ = 6.50 in tabulating spectral data here. Preliminary estimated value for the *anti*:*syn* ratio was 4.8. Excluding signals from the calculation that were thought to lead to overestimation due to signal overlap or baseline distoration gave a refined average estimated value of 4.6. **Major diastereomer (anti)** ^{1}H NMR (600 MHz, C_6D_6) δ 7.31 (d, J = 7.6 Hz, 3H), 7.13 (t, J = 7.5 Hz, 2H), 7.03 (t, J = 7.4 Hz, 1H), 6.50 (s, 1H), 6.01 (d, J = 7.9 Hz, 1H), 4.76 (dd, J = 7.9, 4.6 Hz, 1H), 4.07 (t, J = 5.2 Hz, 1H), 3.36 (dp, J = 14.6, 7.3 Hz, 3H), 3.22 (d, J = 7.0 Hz, 1H), 3.14 (apparent d, apparent J = 3.9 Hz, 6H), 3.09 – 3.03 (m, 1H), 3.00 (dq, J = 13.9, 6.9 Hz, 2H), 1.27 (d, J = 7.2 Hz, 3H), 0.96 (t, J = 7.0 Hz, 6H), -0.09 (s, 3H). **Observable signals of the syn diastereomer** ^{1}H NMR (600 MHz, Benzene-d6) δ 6.64 (s, 1H), 6.13 (d, J = 8.0 Hz, 1H),

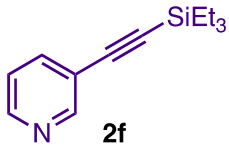
4.56 (dd, J = 8.0, 4.4 Hz, 1H), 3.22 (apparent d, apparent J = 7.0 Hz, 6H), 1.45 (d, J = 7.1 Hz, 3H), -0.02 (s, 3H).

4. Synthesis of Starting Materials



2e

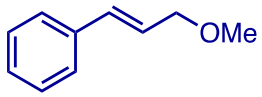
3-(3,5-Dimethoxyphenyl)pyridine (2e): $Pd(OAc)_2$ (67 mg, 0.30 mmol), SPhos (250 mg, 0.60 mmol), K_3PO_4 (9.6 g, 45 mmol), 3,5-dimethoxyphenylboronic acid (3.82 g, 21.0 mmol), and a dry PTFE-coated stir bar were transferred to a dry round-bottom flask that was subsequently purged with Ar and charged with 30 mL dry, degassed PhMe. The resulting mixture was stirred at rt for 5 min. The heterocycle 3-bromopyridine (1.45 mL, 15 mmol) was added via syringe, the reaction vessel was equipped with a reflux condenser fitted with a gas adapter leading to an Ar manifold, and the stirred mixture was heated in a 90 ºC oil bath overnight. On the subsequent day, after cooling to rt, the reaction mixture was filtered through celite, and the filtrate was concentrated to give a crude residue that was purified on a 120 g silica column eluted with 1:1 EtOAc:hexanes. Product fractions were combined and concentrated to give the title compound as a faintly peach-colored viscous oil, 2.65 g (82% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.83 (dd, J = 2.4, 0.8 Hz, 1H), 8.59 (dd, J = 4.9, 1.6 Hz, 1H), 7.84 (dt, J = 7.9, 2.0 Hz, 1H), 7.34 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 6.70 (d, J = 2.2 Hz, 2H), 6.50 (t, J = 2.2 Hz, 1H), 3.85 (s, 6H). The 1H NMR spectrum was virtually identical to one reported previously.[11]



2f

3-((Triethylsilyl)ethynyl)pyridine (2f): A dry reaction tube of the type described in Procedure A, Part I containing a dry PTFE-coated stir bar was charged with *trans*-dichlorobis(triphenylphosphine)palladium(II) (70 mg, 2 mol%, 0.10 mmol), triphenylphosphine (53 mg, 4 mol%, 0.20 mmol), and CuI (19 mg, 2 mol%, 0.10 mmol). The tube was sealed with a septum-cap and purged with Ar using an inlet needle and a vent needle. The heterocycle (3-Br-pyridine, 0.79 g, 0.48 mL), diisopropylamine (1.25 mL, 1.8 equiv), and degassed, dry PhMe (9 mL) were added to the tube via syringe. The resulting mixture was stirred at rt for ca. 15 min, and then TES-acetylene (1.08 mL, 846 mg, 6.03 mmol) was added. The reaction mixture was heated in an 80 ºC oil bath for ca. 18 h. After cooling to rt, the reaction mixture was partitioned between EtOAc and

saturated NH_4Cl. The combined organics were sequentially washed with water, saturated sodium bicarbonate, and brine. They were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude residue that was purified on a 50 g silica column eluted with 10 to 20 % EtOAc/hexanes. Product fractions were concentrated in the presence of 8.7 mg tert-butyl catechol to provide the title compound as an orange-red oil, 982 mg (973 mg after correction for inhibitor present, 90% yield). **^{1}H NMR** (500 MHz, acetone-d_6) δ 8.71 – 8.61 (m, 1H), 8.56 (dd, J = 4.9, 1.7 Hz, 1H), 7.85 (dt, J = 7.9, 1.9 Hz, 1H), 7.39 (ddd, J = 7.9, 4.8, 0.9 Hz, 1H), 1.06 (t, J = 7.9 Hz, 9H), 0.71 (q, J = 7.9 Hz, 6H). The ^{1}H NMR data were consistent with those reported previously.[12]



Cinnamyl Methyl Ether: Inside a nitrogen-atmosphere glovebox, a dry round-bottom flask containing a dry PTFE-coated stir bar was charged with sodium hydride (1.75 g, 95% by weight, 69 mmol, 1.2 equiv). The flask was sealed with a septum and removed from the glovebox and its contents were suspended in 60 mL dry, degassed THF. The resulting mixture was stirred under an N_2 atmosphere while cooling in an ice-water bath. Cinnamyl alcohol (8.39 g, 62.5 mmol, 1.1 equiv) was carefully added to the mixture via syringe (*CAUTION: vigorous hydrogen evolution occurs at this stage*) followed by iodomethane (3.5 mL, 56 mmol, 1.0 equiv). The mixture was stirred in the ice-water bath for ca. 5 min and then allowed to gradually warm to rt. After 24 h, the excess MeI was quenched by adding diethylamine (3 mL) via syringe and and continuing stirring for ca. 1 h. The reaction mixture was then partitioned between EtOAc and saturated NH_4Cl, and the aqueous layer was back-extracted. The combined organics were sequentially washed with 2 M HCl (2 x 100 mL), water, 1 M Na_2CO_3, and brine. The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a crude residue that was purified on a 300 g silica column eluted with 5 to 10% EtOAc/hexanes. Product fractions were concentrated in the presence of 40 mg tert-butyl-catechol to provide the title compound, 6.21 g (6.17 g adjusted for inhibitor present; 75% corrected yield). **^{1}H NMR** (300 MHz, acetone-d_6) δ 7.48 – 7.41 (m, 2H), 7.37 – 7.29 (m, 2H), 7.28 – 7.21 (m, 1H), 6.63 (dt, J = 16.0, 1.6 Hz, 1H), 6.34 (dt, J = 16.0, 5.8 Hz, 1H), 4.05 (dd, J = 5.8, 1.5 Hz, 2H), 3.32 (s, 3H). The ^{1}H NMR data for this compound were consistent with those reported previously.[13]

5. References and Notes

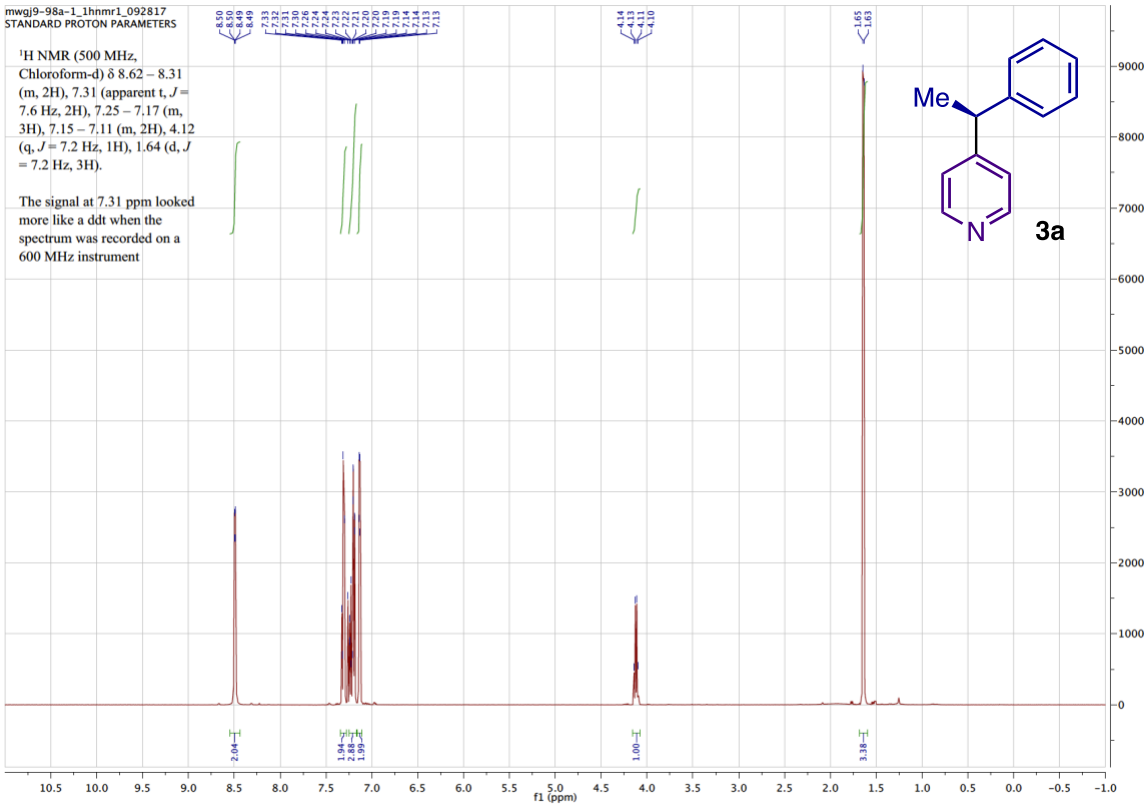
1. In addition to the form described above and used in this work, anhydrous $Cu(OAc)_2$ can be obtained as a microcrystalline solid having very high metals-basis purity. In our experience, this crystalline form of $Cu(OAc)_2$ is not generally equivalent to the amorphous powder. Researchers wishing to use the Cu-catalyzed dearomatization are advised to use the amorphous powder.

2. For more information of hazard classifications specific to eye injury, see: United Nations. Serious Eye Damage/Eye Irritation. *Globally Harmonized System of Classification and Labeling of Chemicals (GHS), Third Revised Edition*, New York and Geneva, 2009, pp 133-144. available at: http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev03/English/03e_part3.pdf (accessed October 13, 2017).
3. "Prudent Practices in the Laboratory [electronic resource]: Handling and Management of Chemical Hazards / Committee on Prudent Practices in the Laboratory: An Update." Board on Chemical Sciences and Technology, Division of Earth and Life Studies, National Research Council of the National Academies. Washington, D.C.: National Academies Press, 2011.
4. Osterberg, P. M.; Niemeier, J. K.; Welch, C. J.; Hawkins, J. M.; Martinelli, J. R.; Johnson, T. E.; Root, T. W.; Stahl, S. S. *Org. Process Res. Dev.* **2015**, *19*, 1537-1543.
5. See https://www.airgas.com/msds/001043.pdf (accessed December 14, 2017).
6. The anti-suck-back trap is a safety feature designed to prevent introduction of liquid into the gas cylinder in the event that liquid is unintentionally aspirated into the tubing (e.g., by depressurizing the system while the gas-delivery needle is inserted in a solvent or reaction mixture).
7. For some dihydropyridines, the α and α' proton signals gave significantly smaller integrals than other diagnostic protons, we presume due to idiosyncratic relaxation times. When this was true, these resonances were not used in NMR-yield calculations. The siloxane methyl signals also consistently under-integrated and were not used.
8. See spectral attachments for NMR structure-determination experiments.
9. See CIF file included with supporting information for crystal data.
10. NMR data and assignments for 4-benzylpiperidine are available in the AIST database. SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, accessed November 17, 2017).
11. Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649-2652.
12. Carril, M.; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 4862-4865.
13. Kasashima, Y.; Uzawa, A.; Hashimoto, K.; Nishida, T.; Murakami, K.; Mino, T.; Sakamoto, M.; Fujita, T. *J. Oleo. Sci.* **2010**, *59*, 549-555.

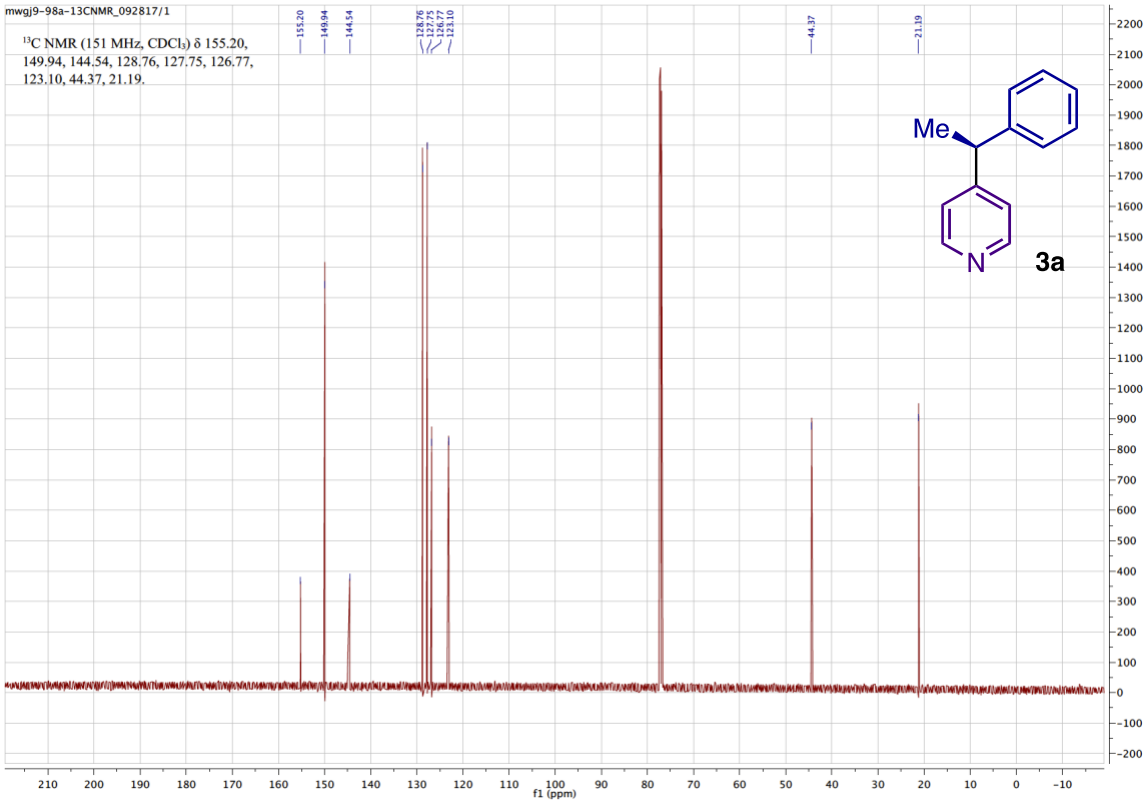
6. Spectral Attachments

6.1. NMR Spectra of New Compounds

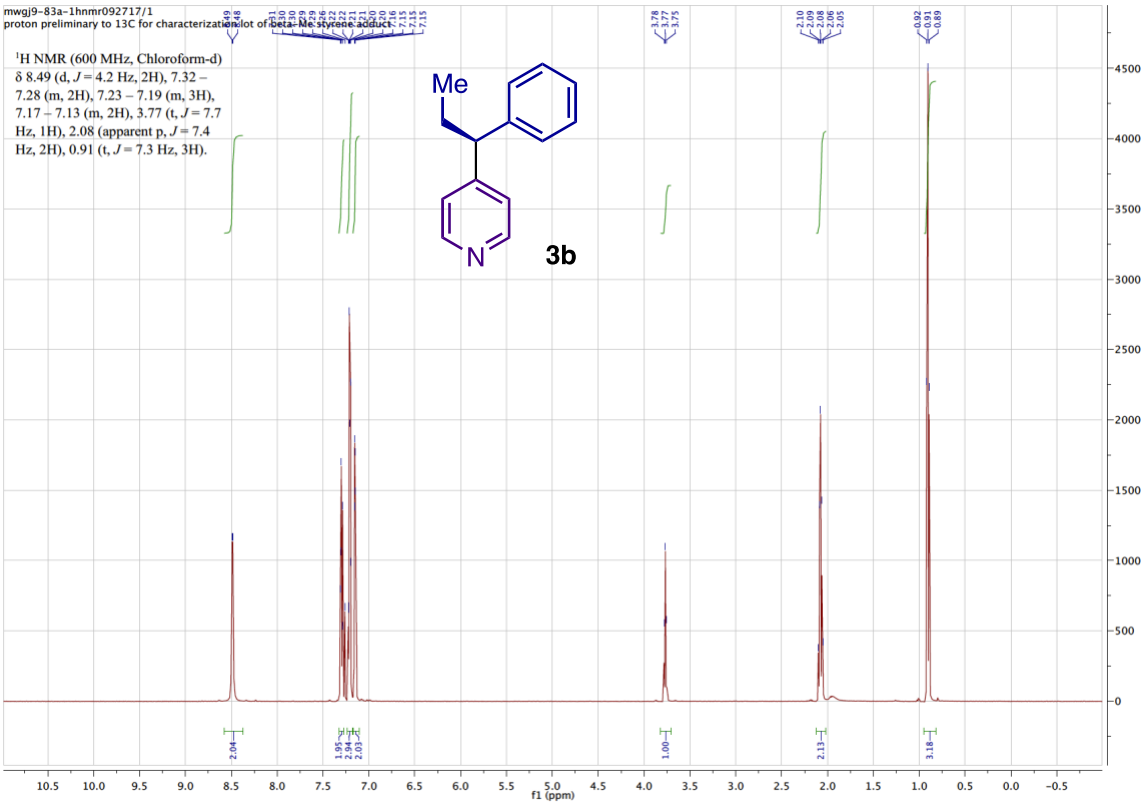
^{1}H NMR Spectrum of 3a



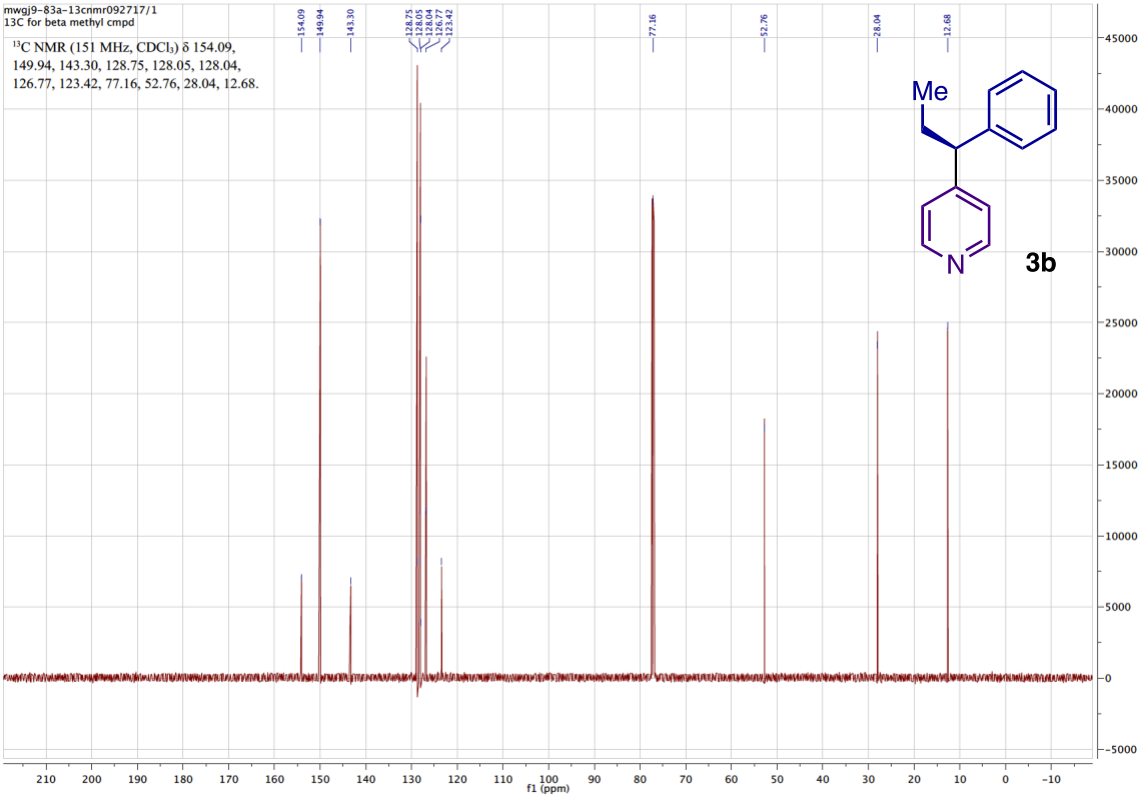
^{13}C NMR Spectrum of 3a



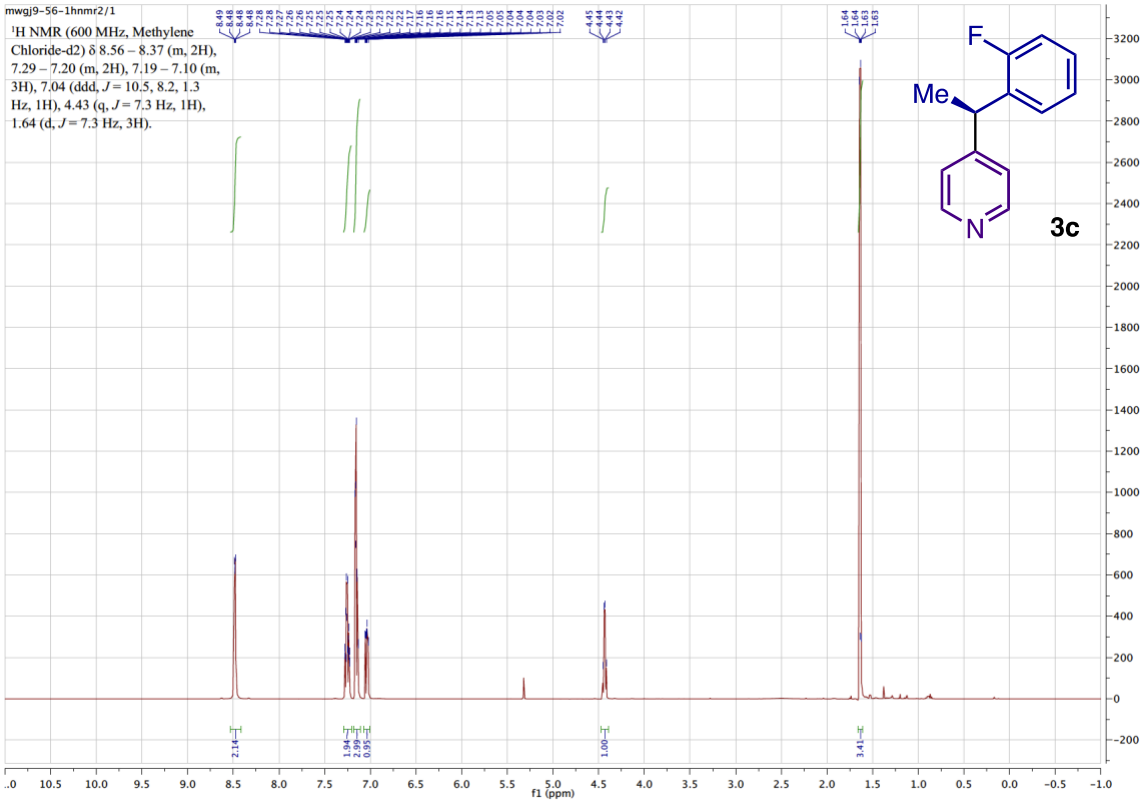
^{1}H NMR Spectrum of 3b



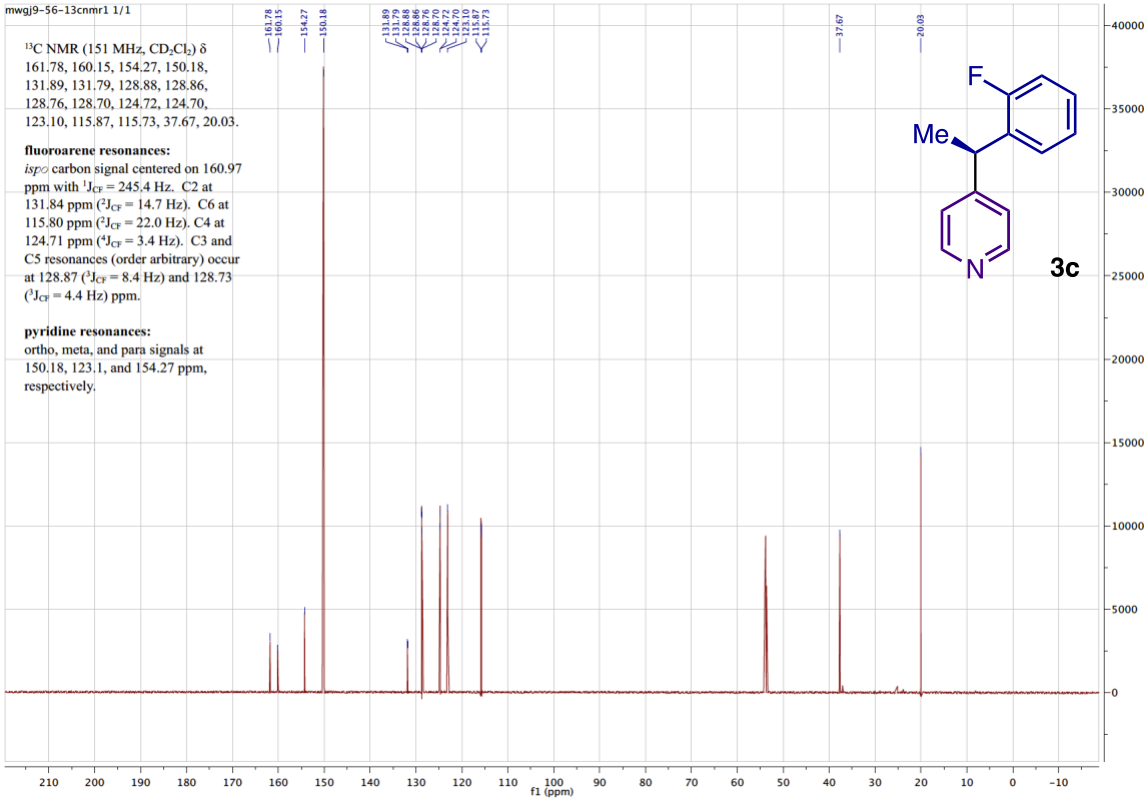
^{13}C NMR Spectrum of 3a



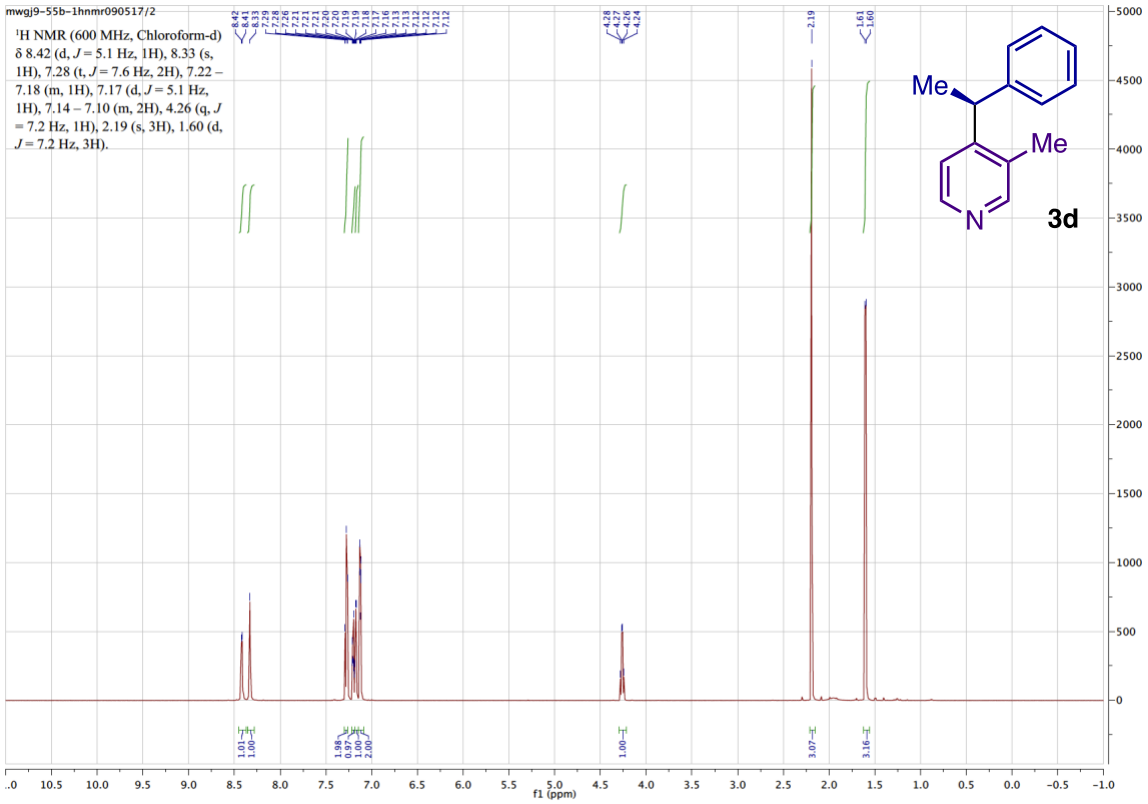
^{1}H NMR Spectrum of 3c



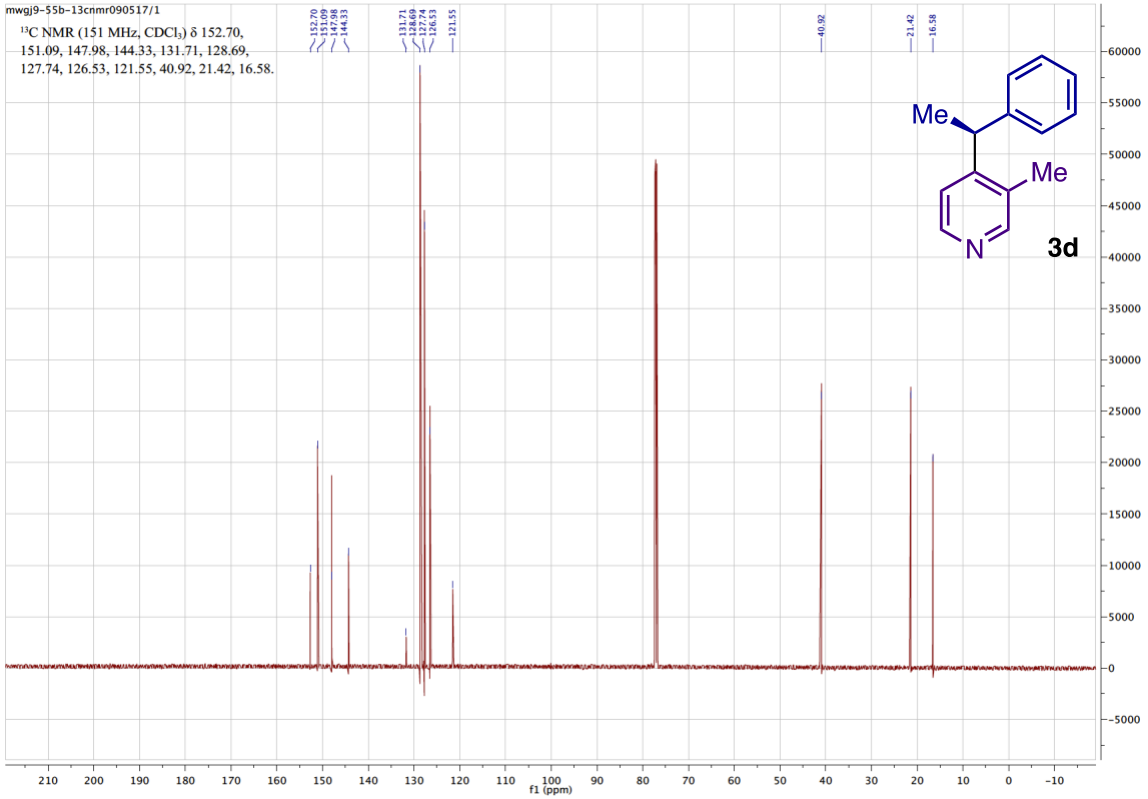
^{13}C NMR Spectrum of 3c



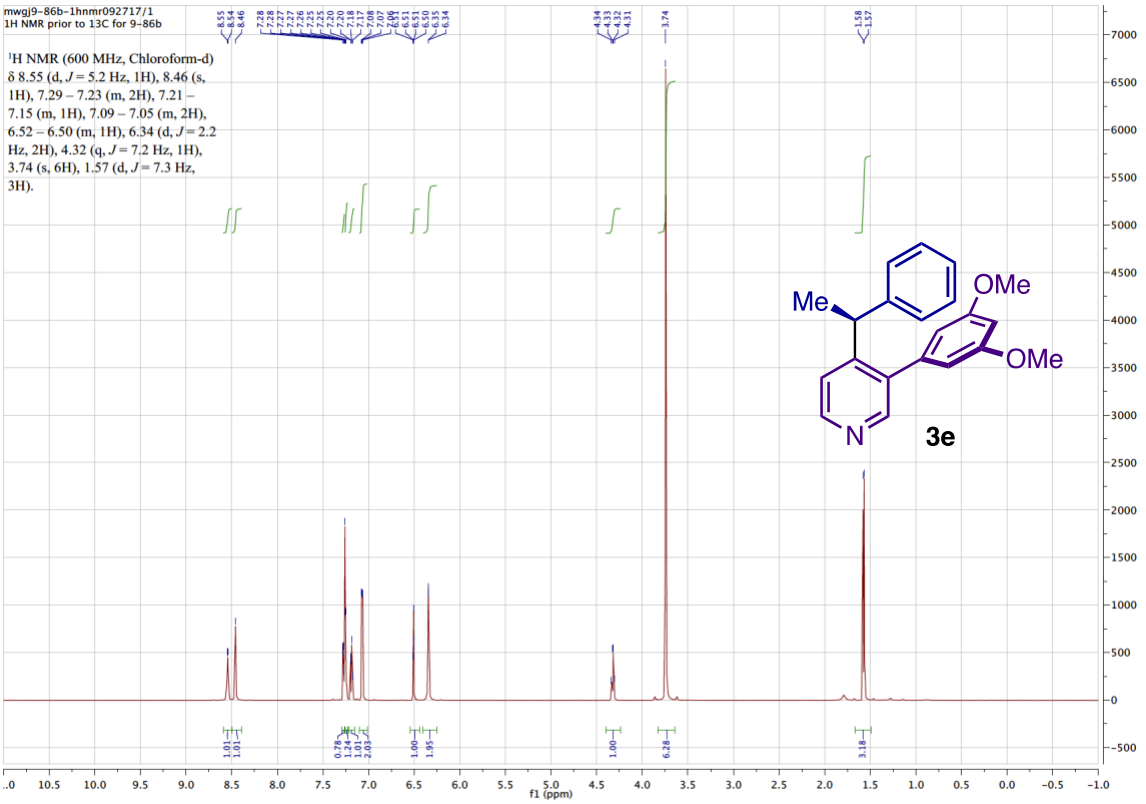
^{1}H NMR Spectrum of 3d



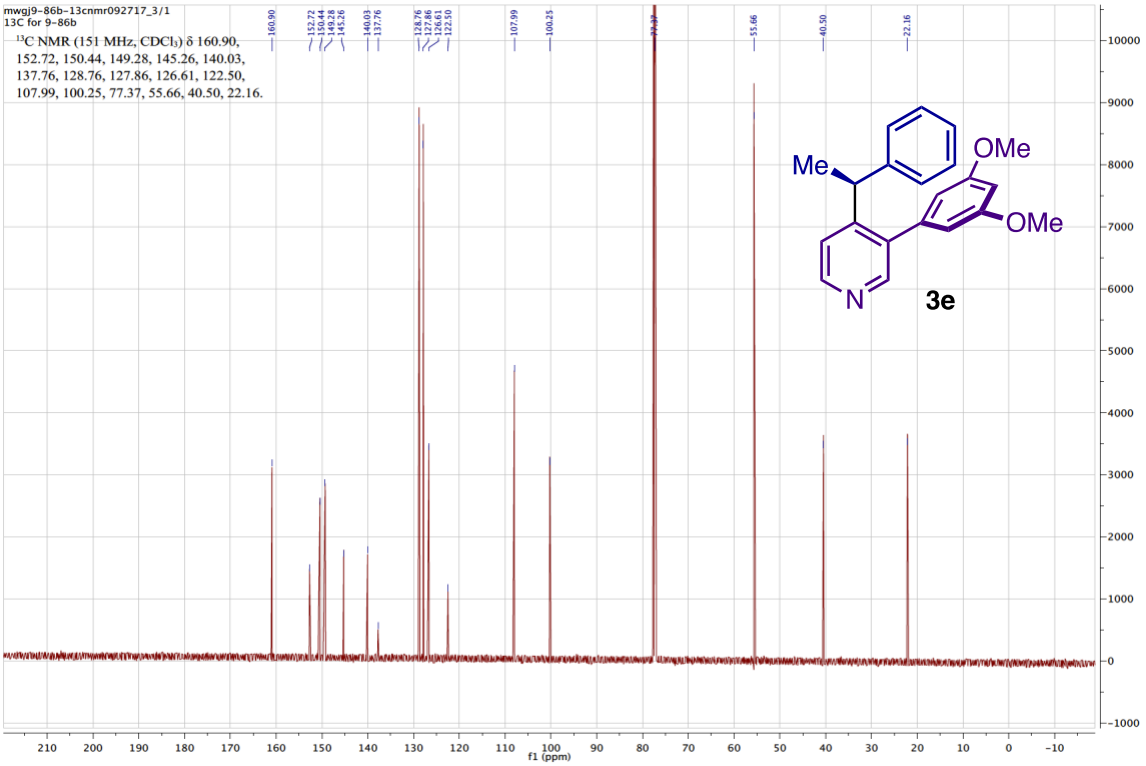
^{13}C NMR Spectrum of 3d



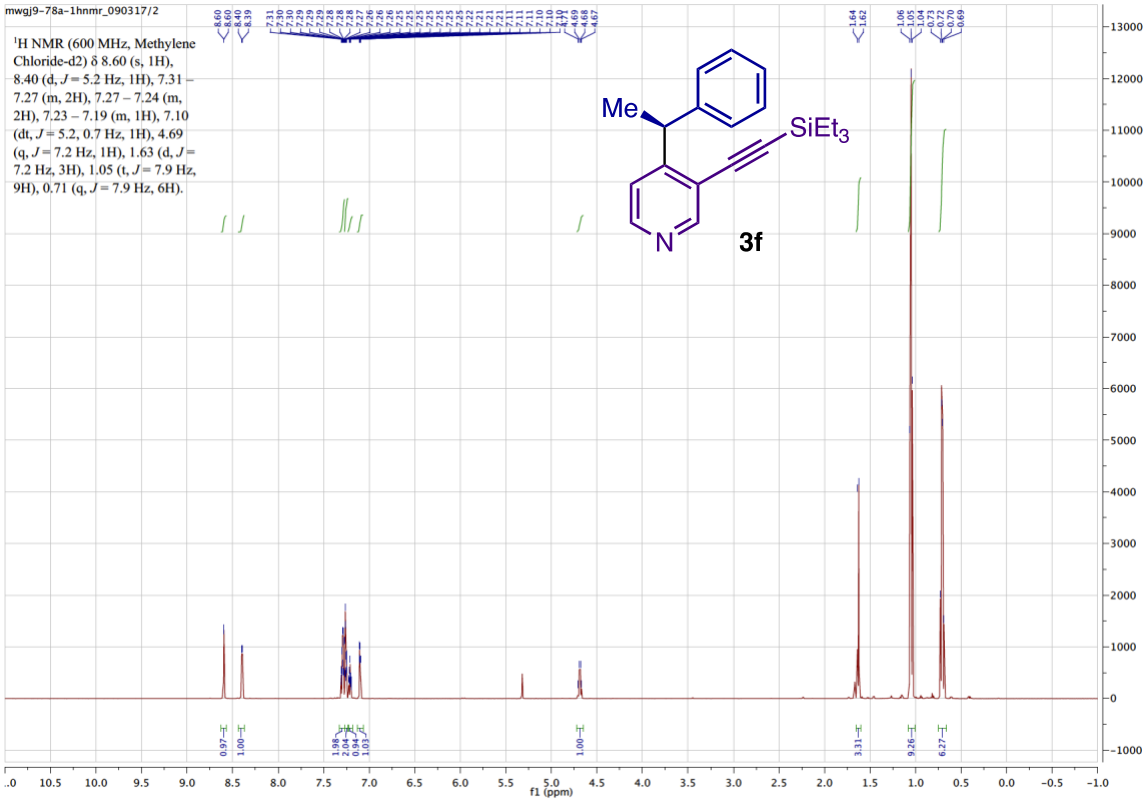
^{1}H NMR Spectrum of 3e



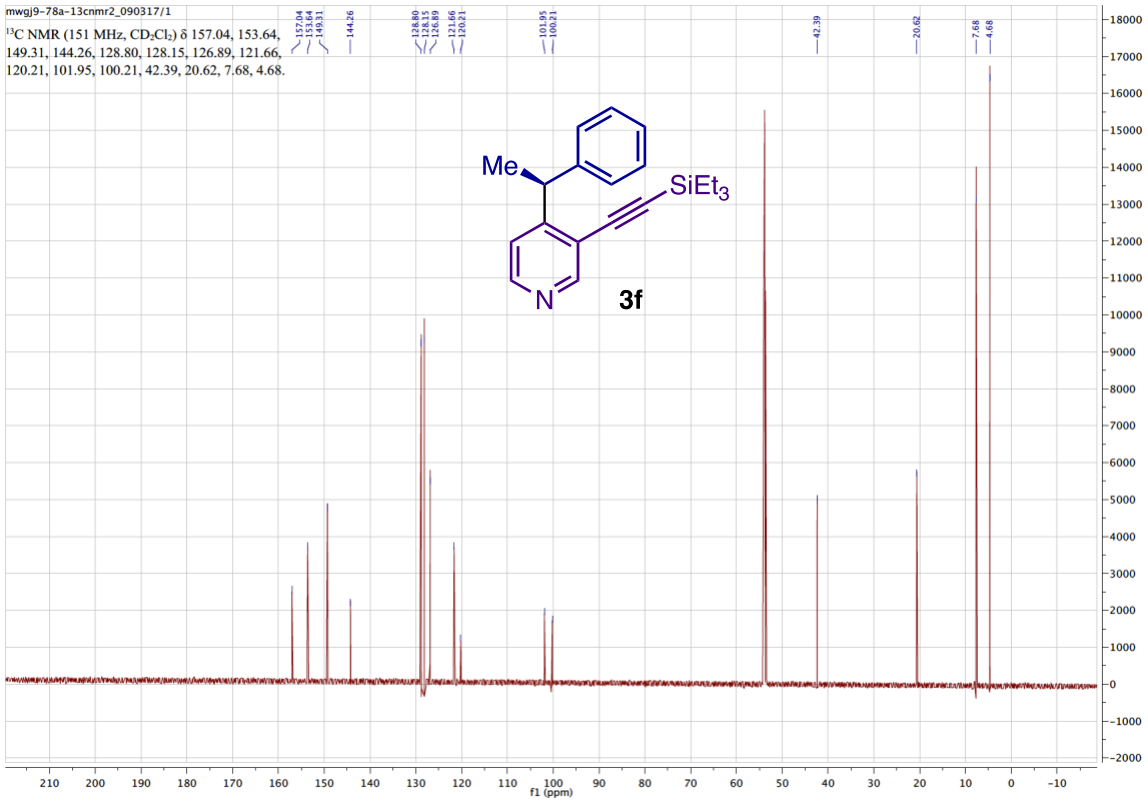
^{13}C NMR Spectrum of 3e



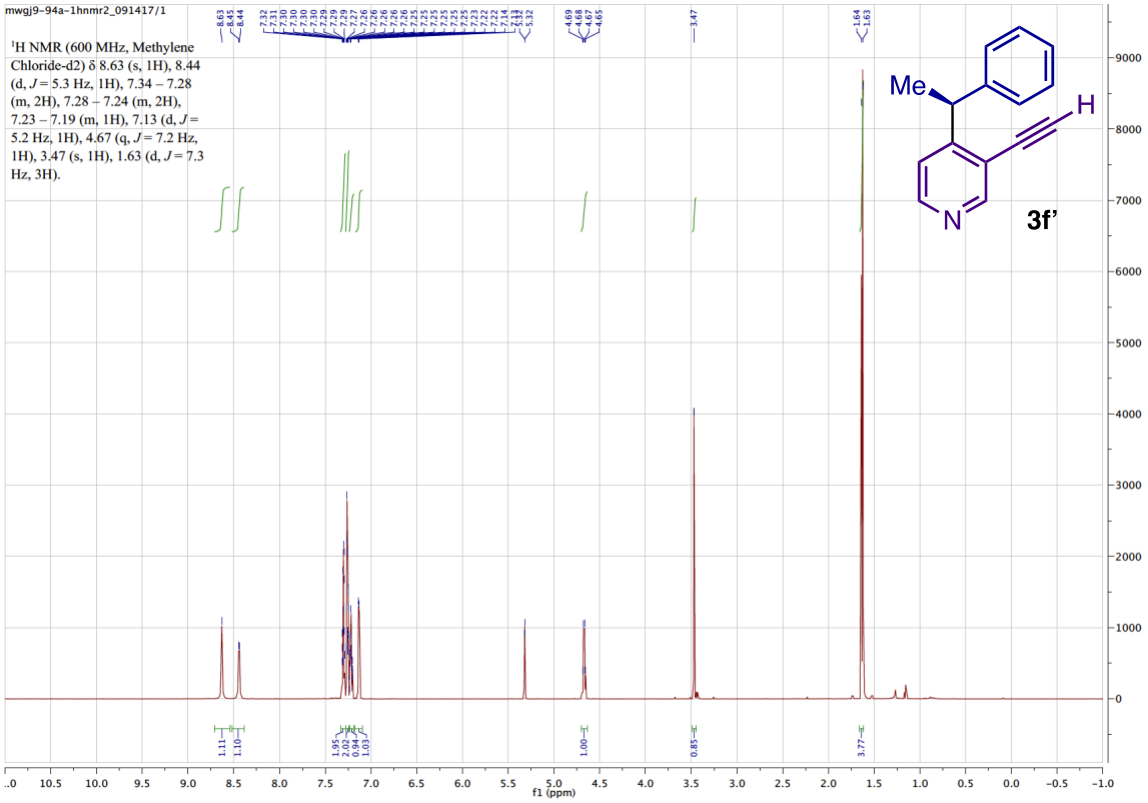
^{1}H NMR Spectrum of 3f



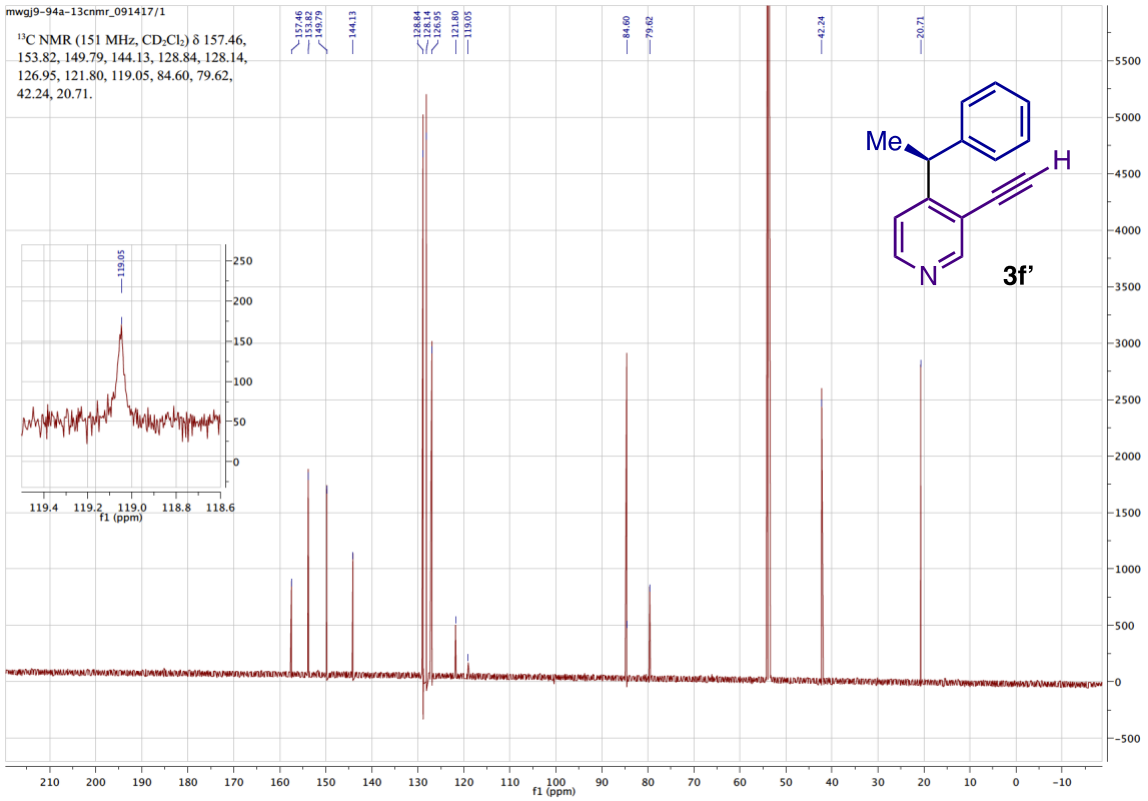
^{13}C NMR Spectrum of 3f



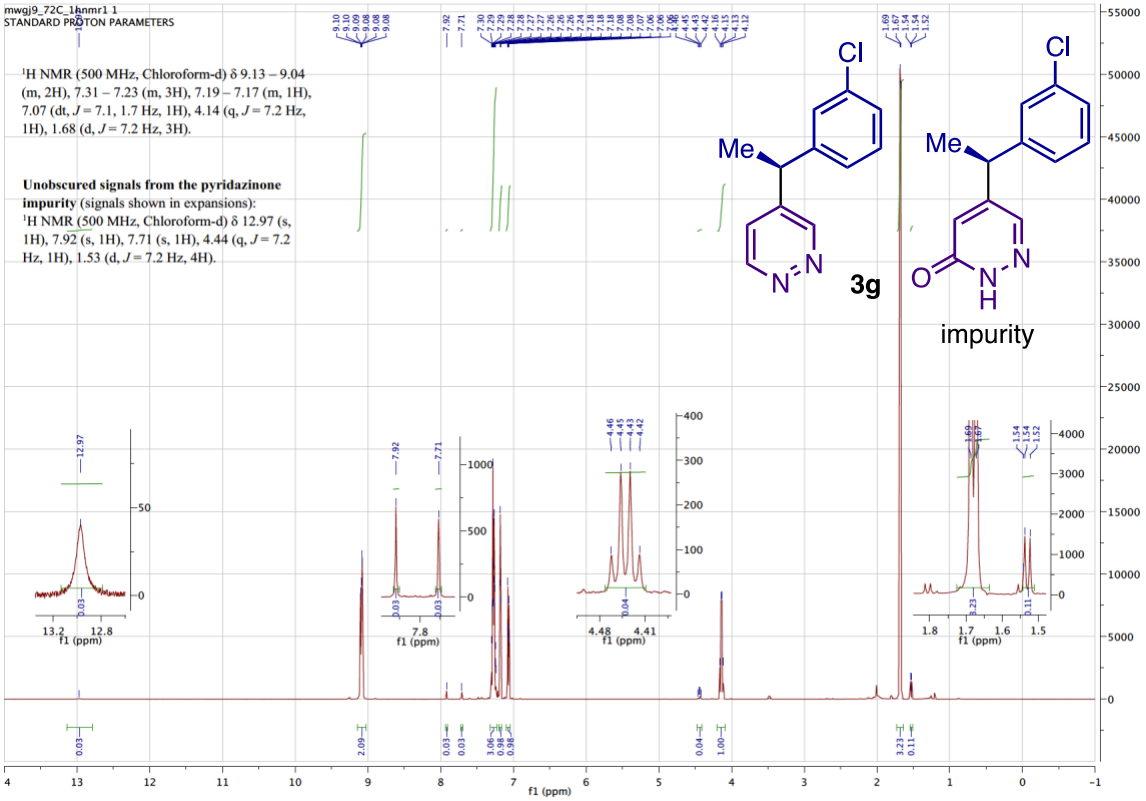
^{1}H NMR Spectrum of 3f'



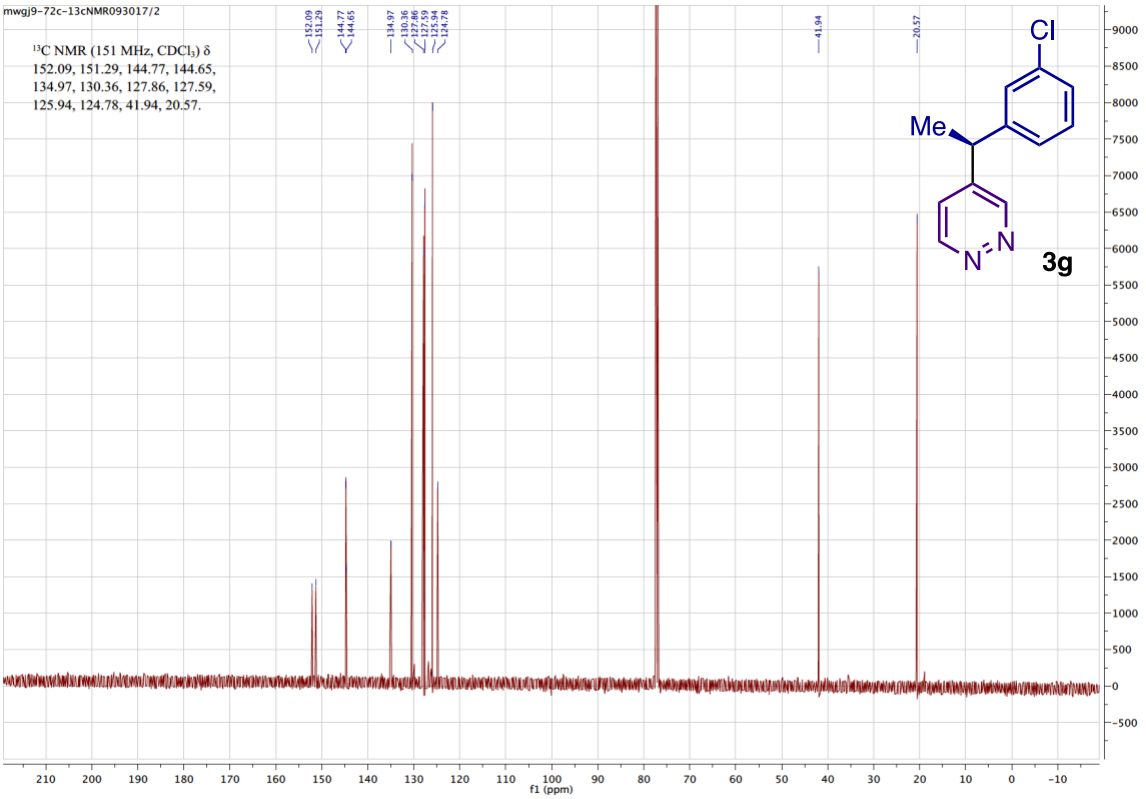
^{13}C NMR Spectrum of 3f'



^{1}H NMR Spectrum of 3g

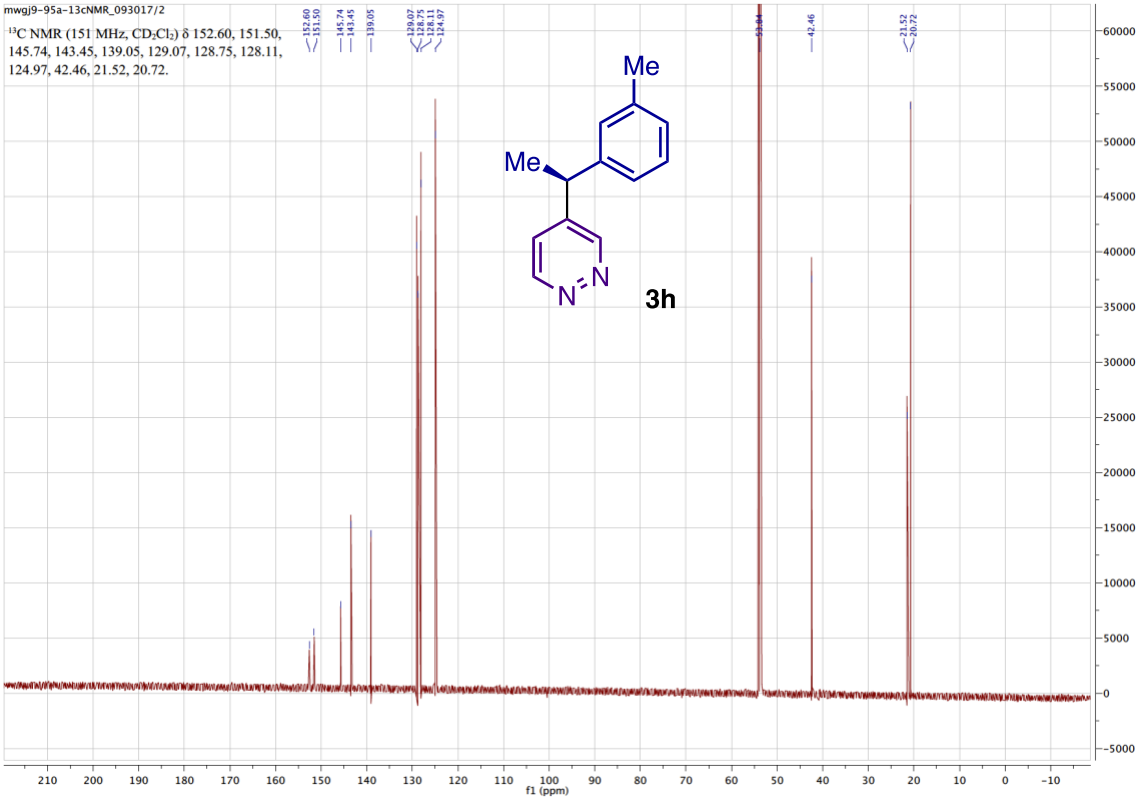


^{13}C NMR Spectrum of 3g

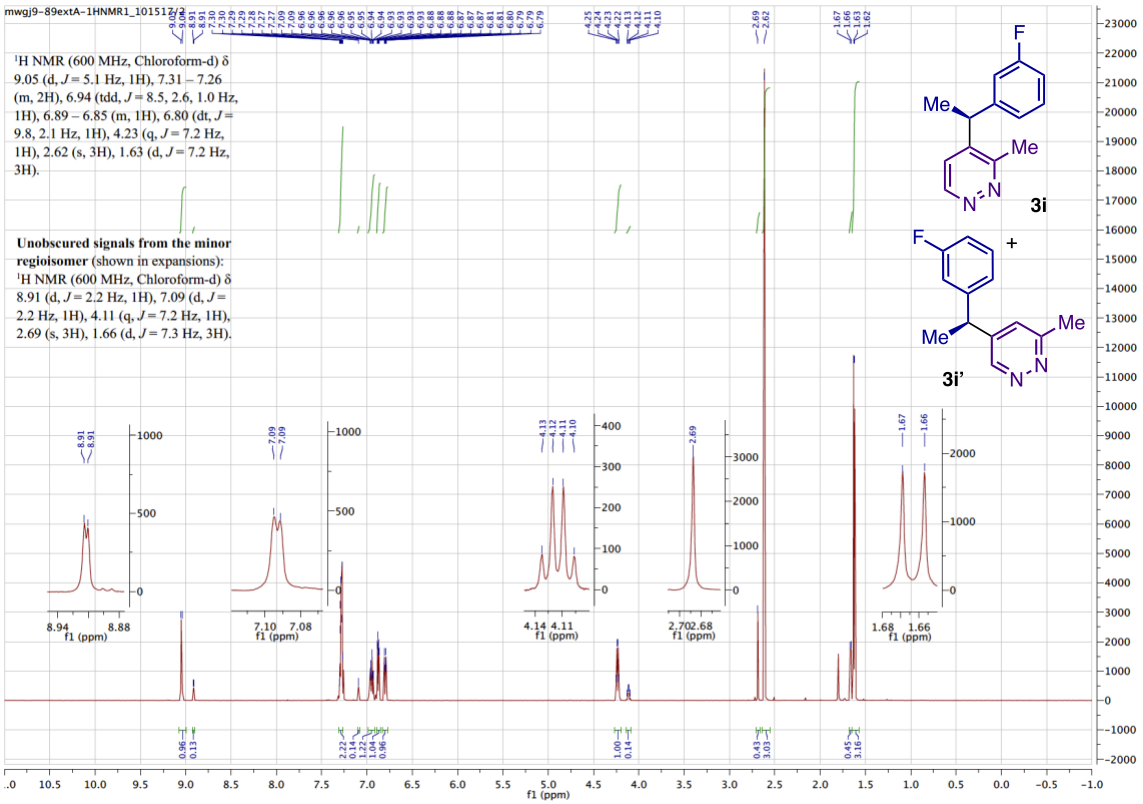


^{1}H NMR Spectrum of 3h

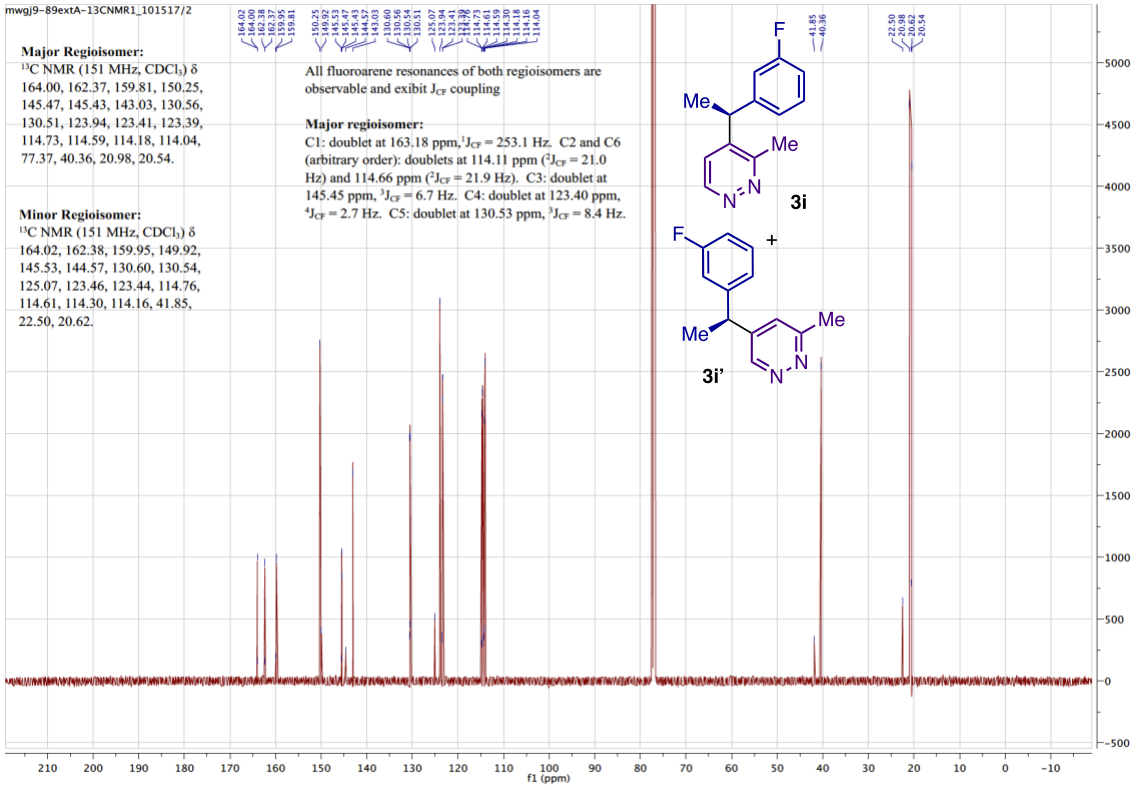
^{13}C NMR Spectrum of 3h



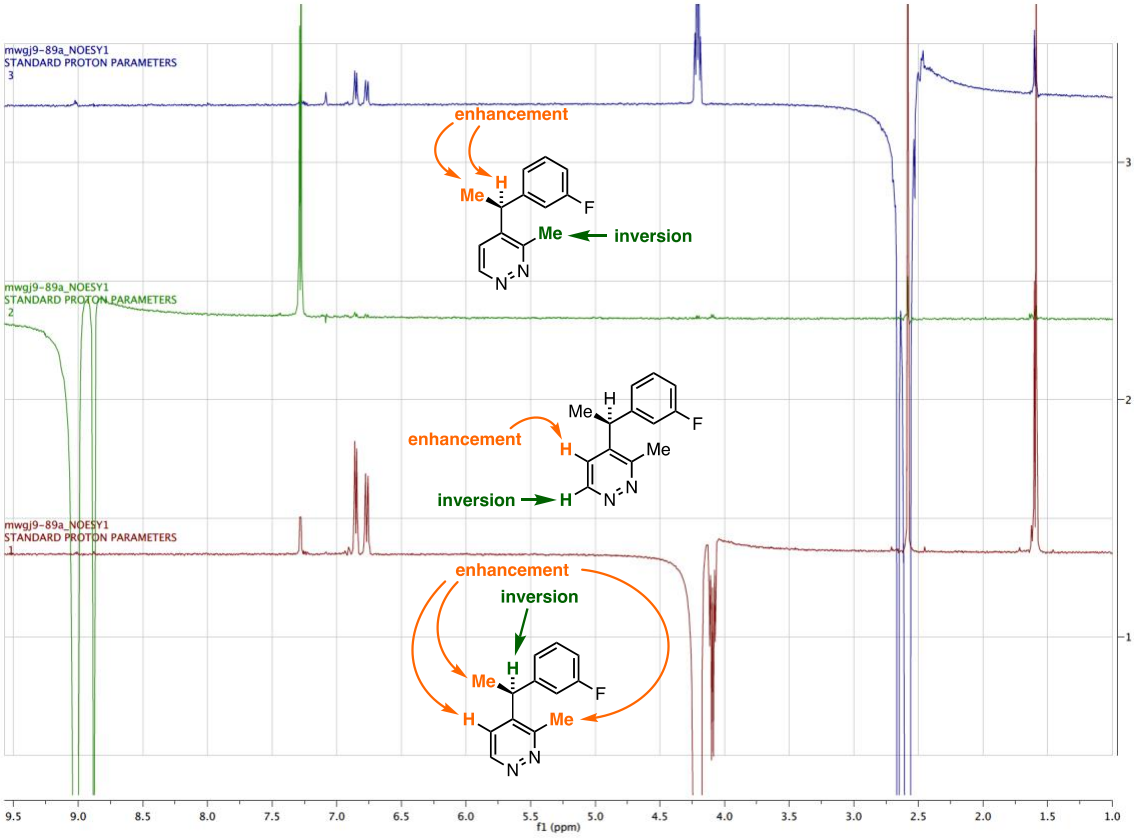
^{1}H NMR Spectrum of 3i + 3i' (7:1)



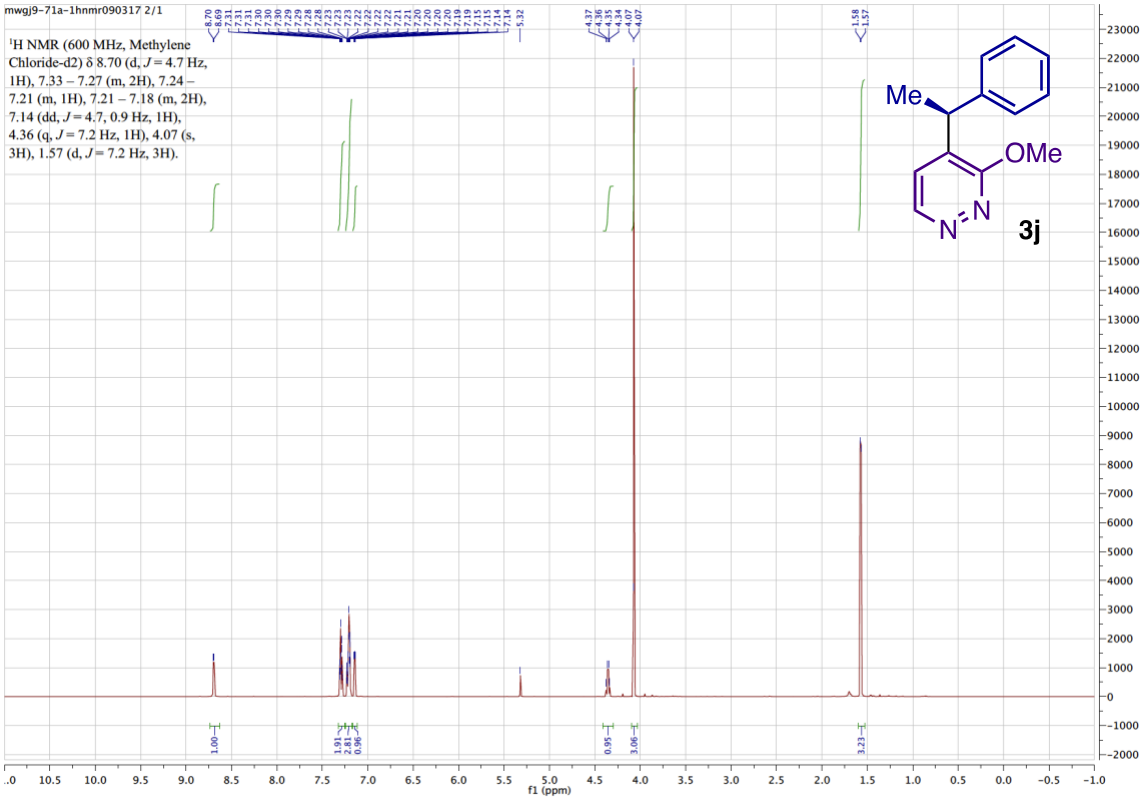
^{13}C NMR Spectrum of 3i + 3i' (7:1)



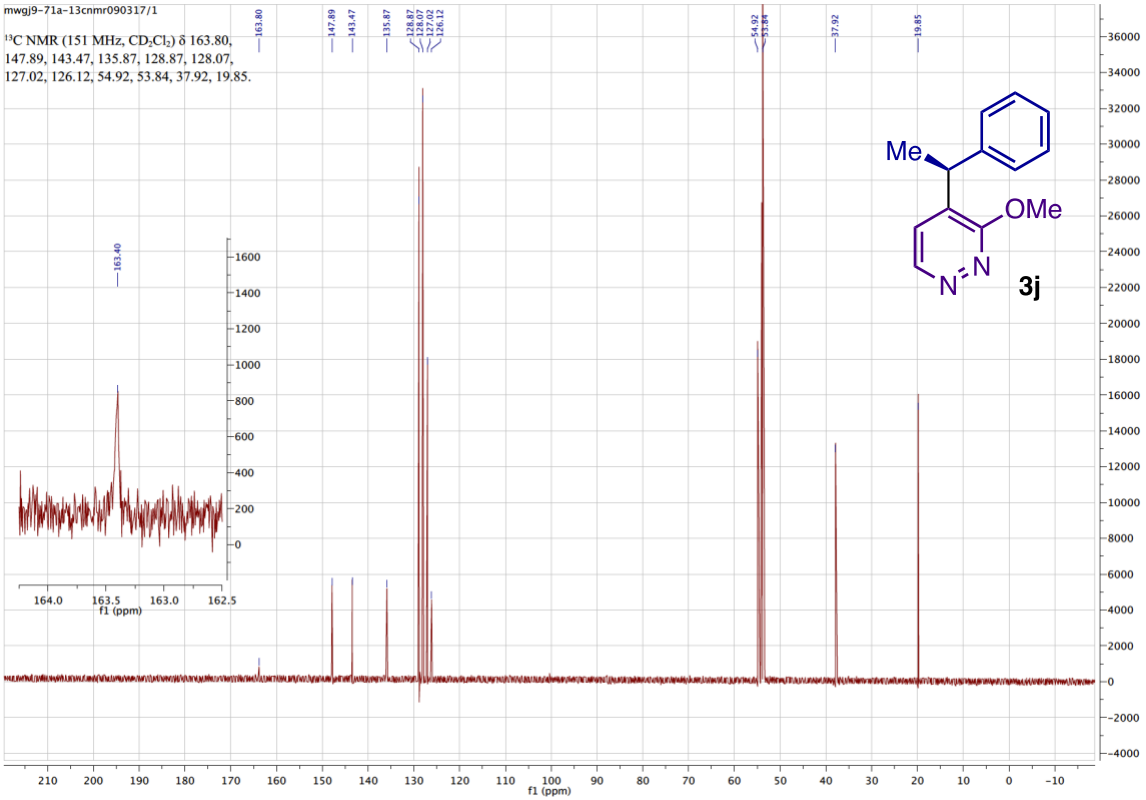
1-D NOESY Spectrum of 3i (as present in mixture)



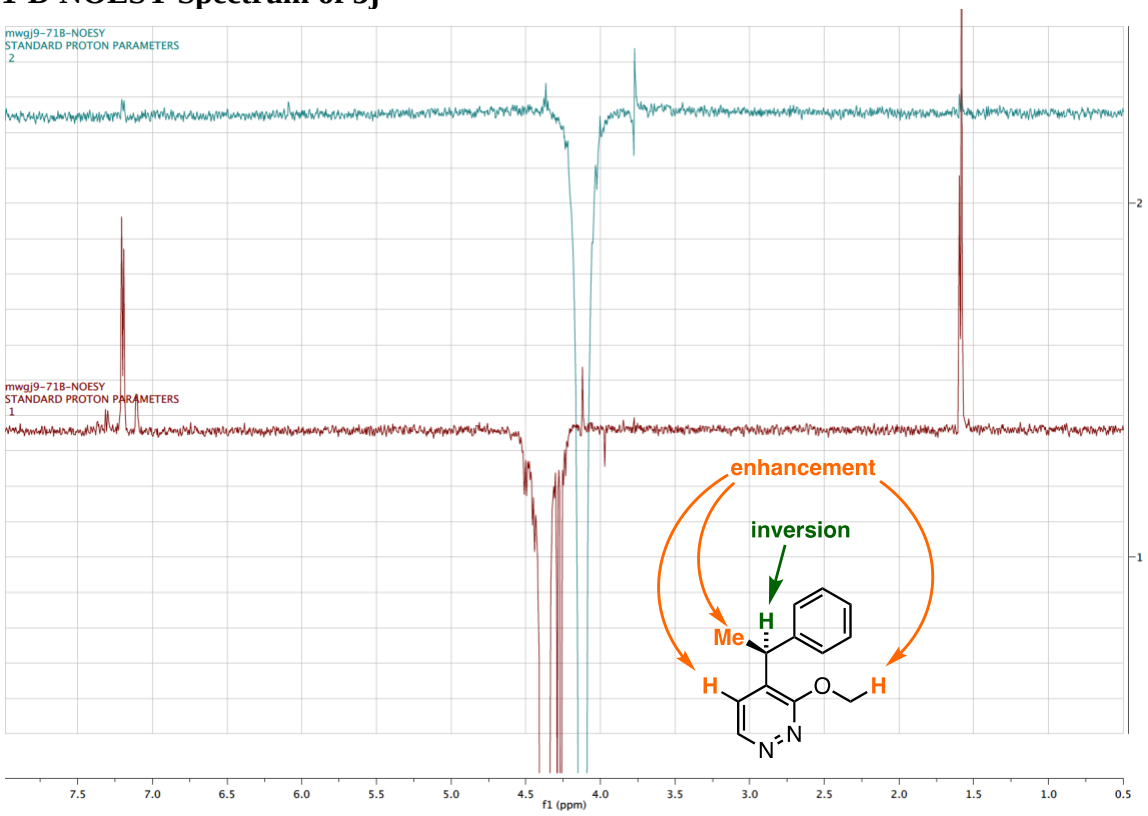
^{1}H NMR Spectrum of 3j



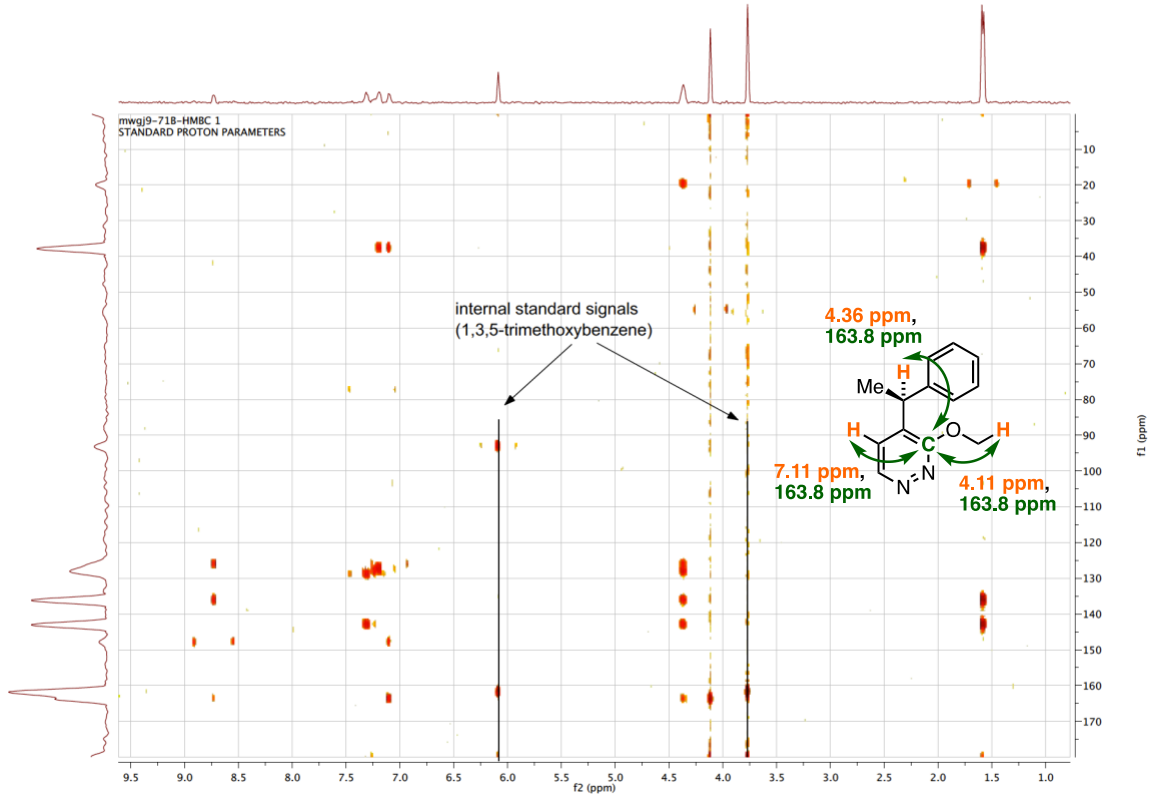
^{13}C NMR Spectrum of 3j



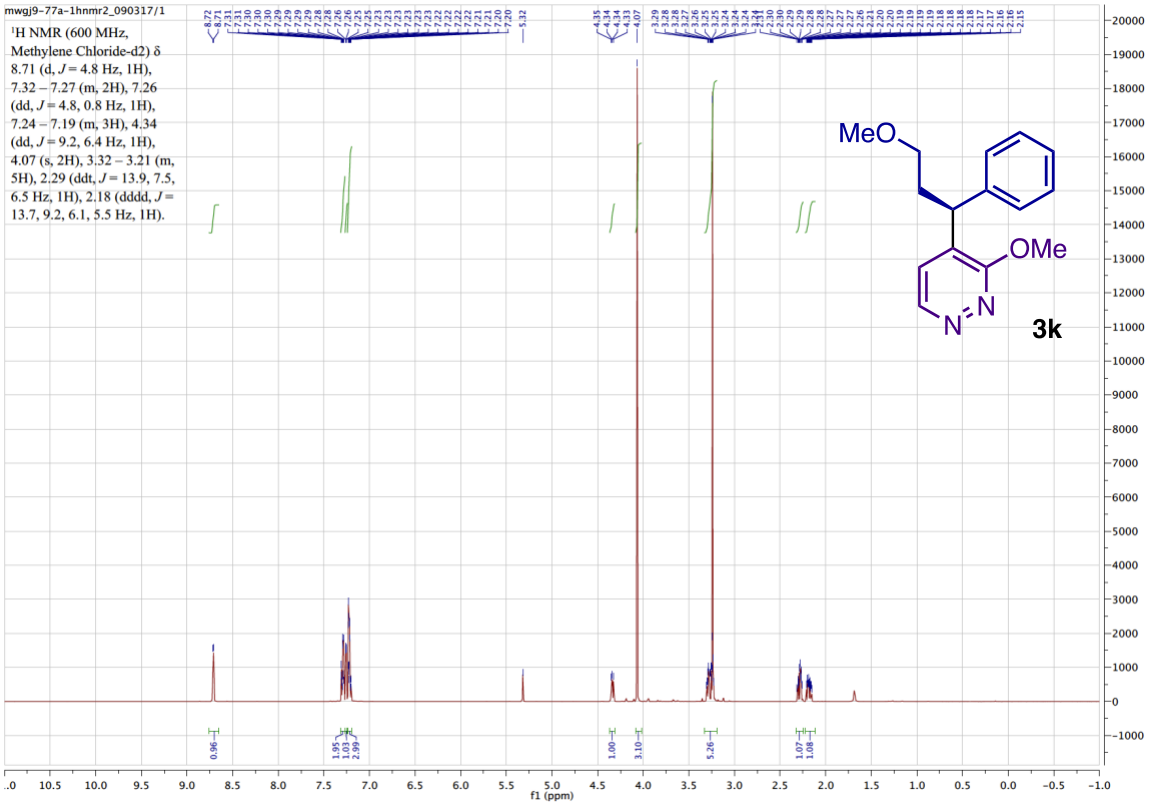
1-D NOESY Spectrum of 3j



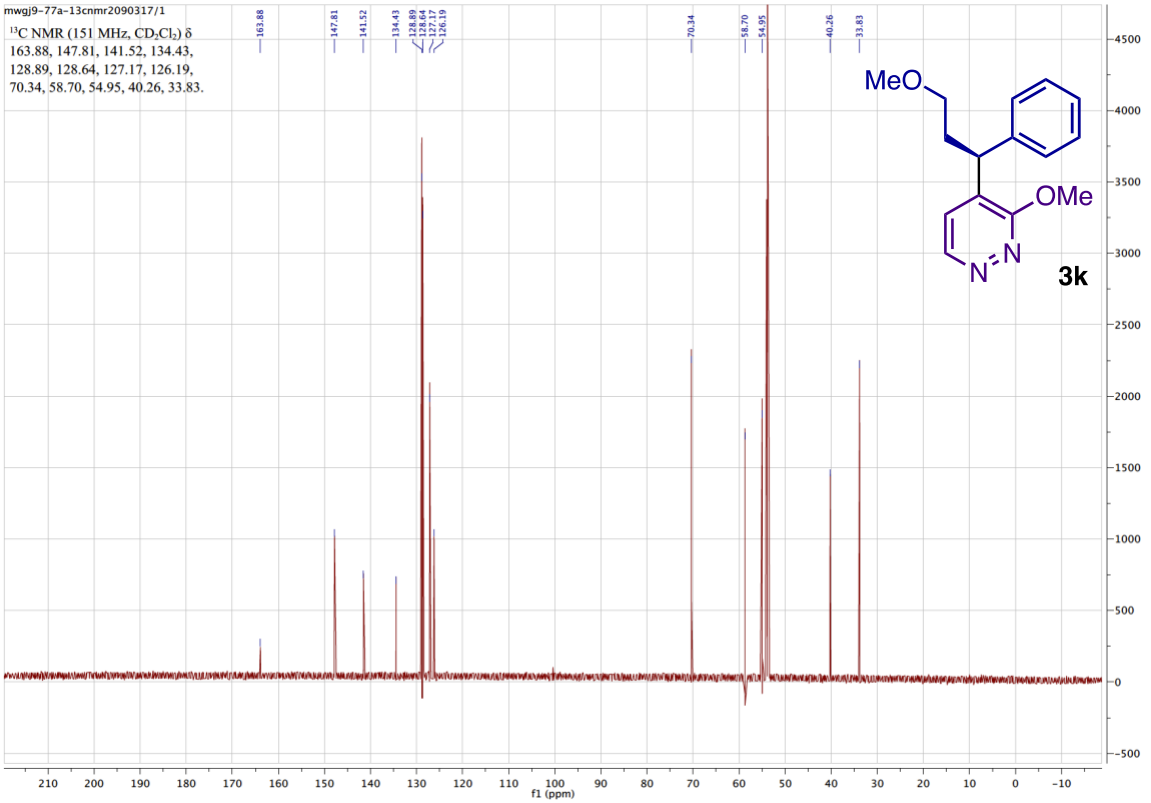
HMBC Spectrum of 3j



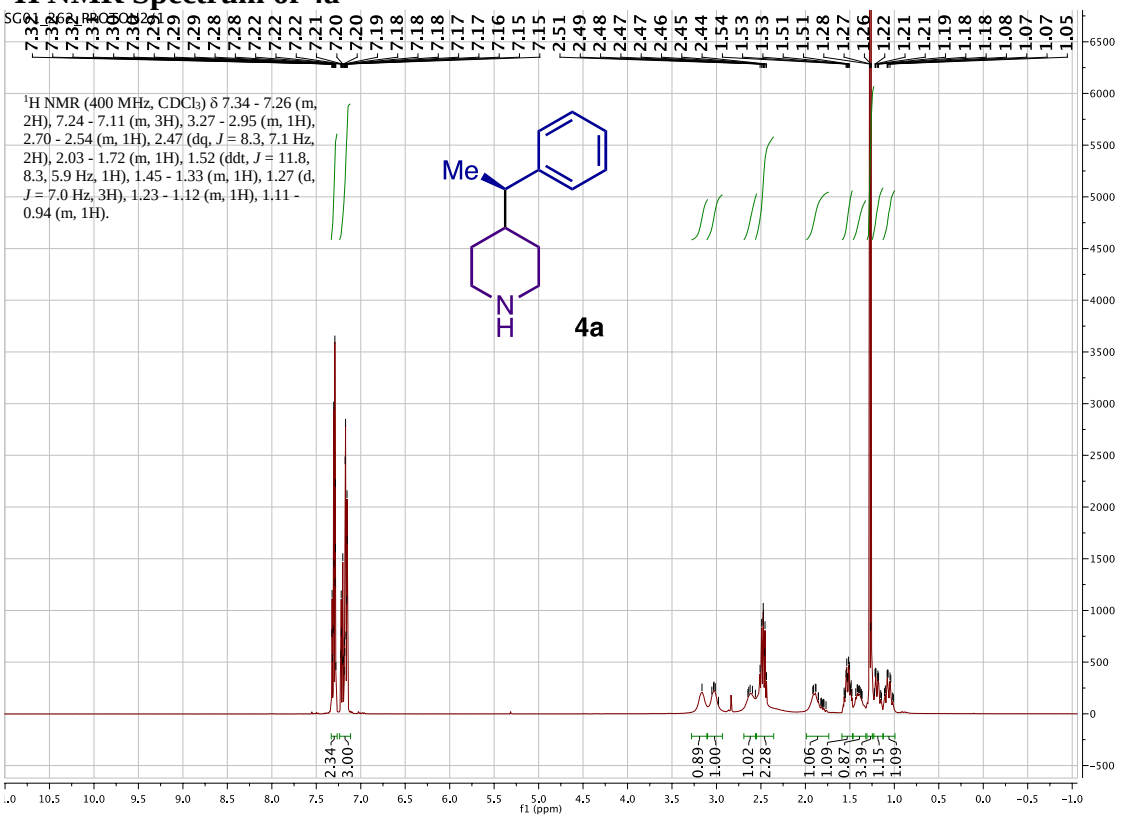
^{1}H NMR Spectrum of 3k



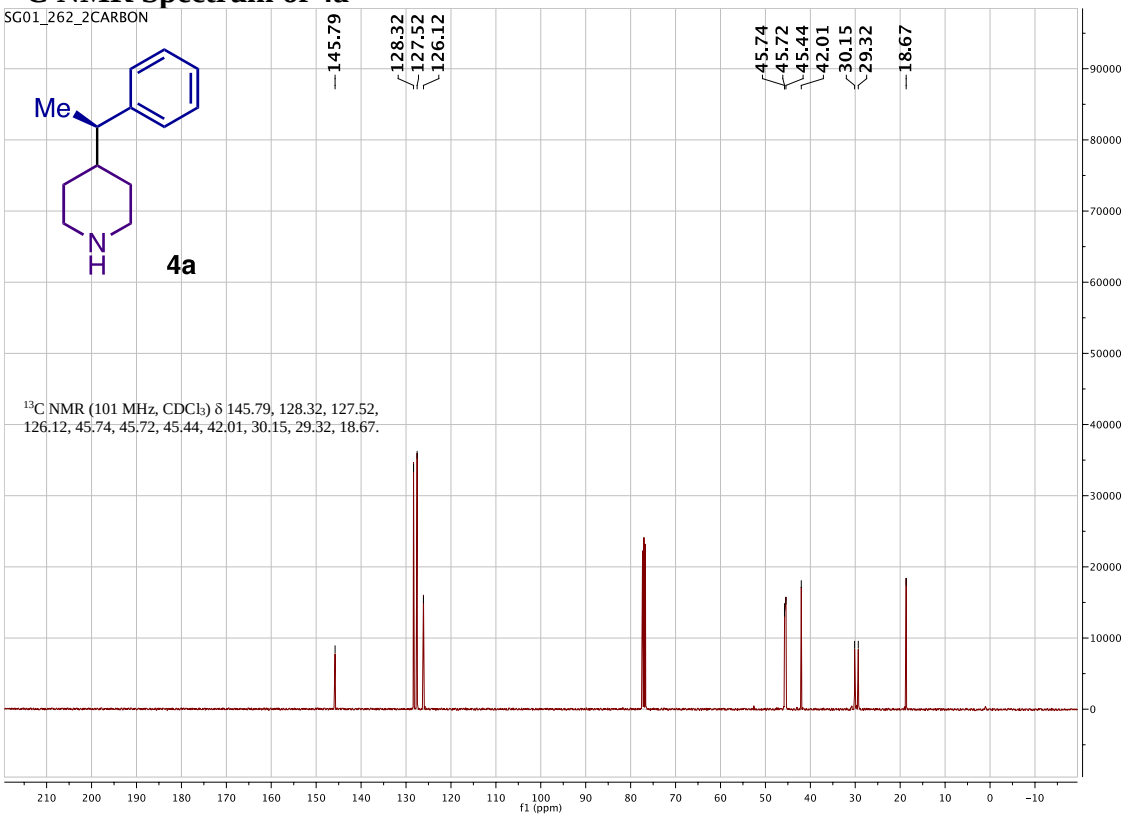
^{13}C NMR Spectrum of 3k



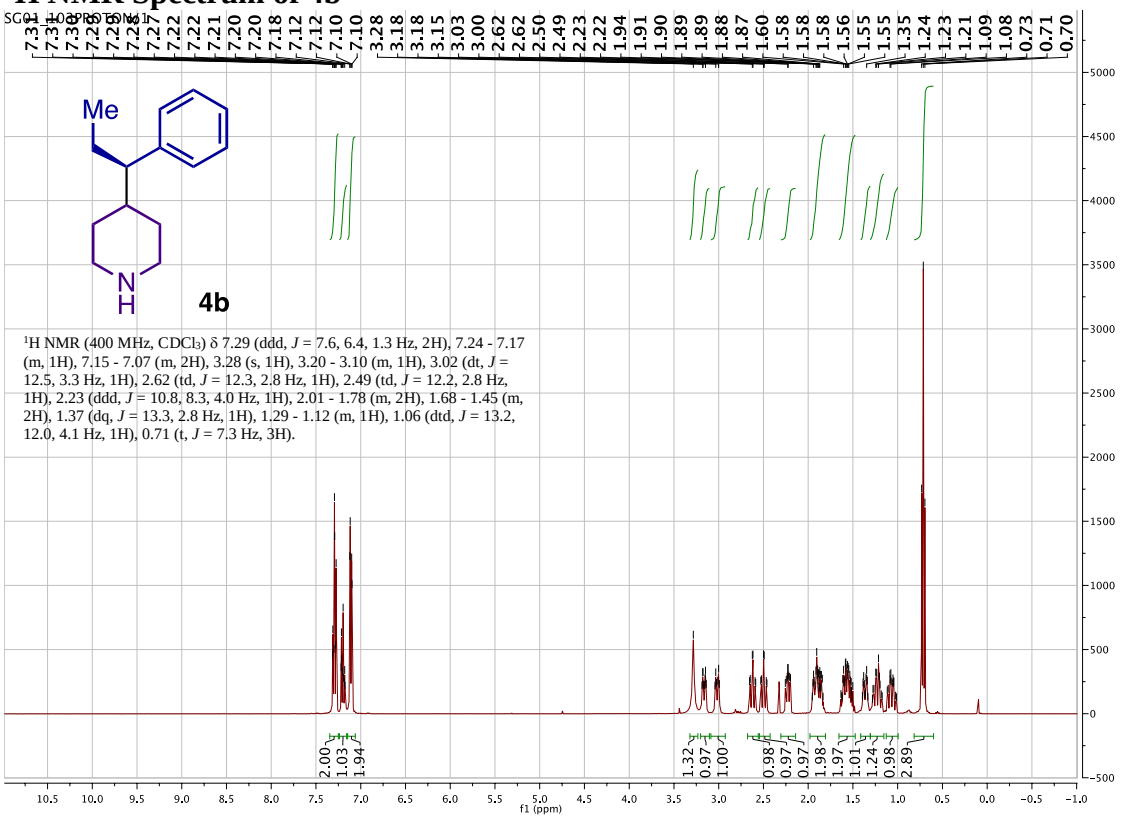
^{1}H NMR Spectrum of 4a



^{13}C NMR Spectrum of 4a

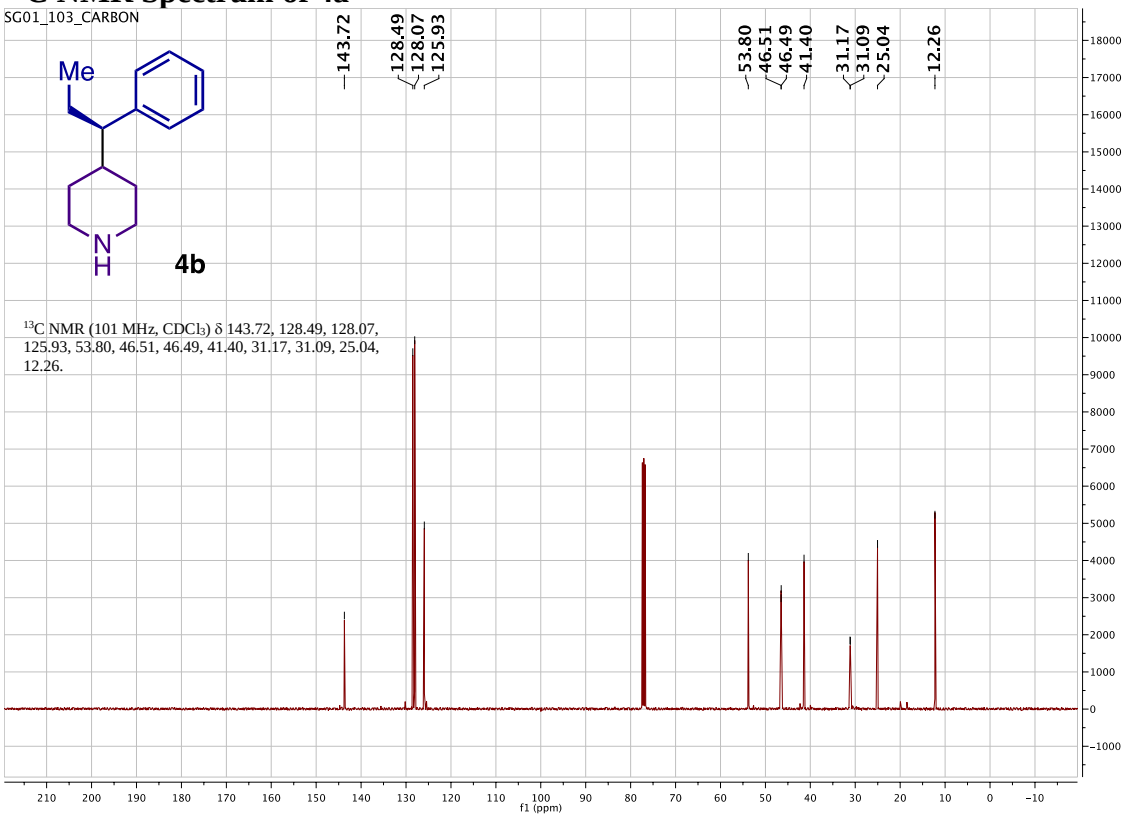


^{1}H NMR Spectrum of 4b



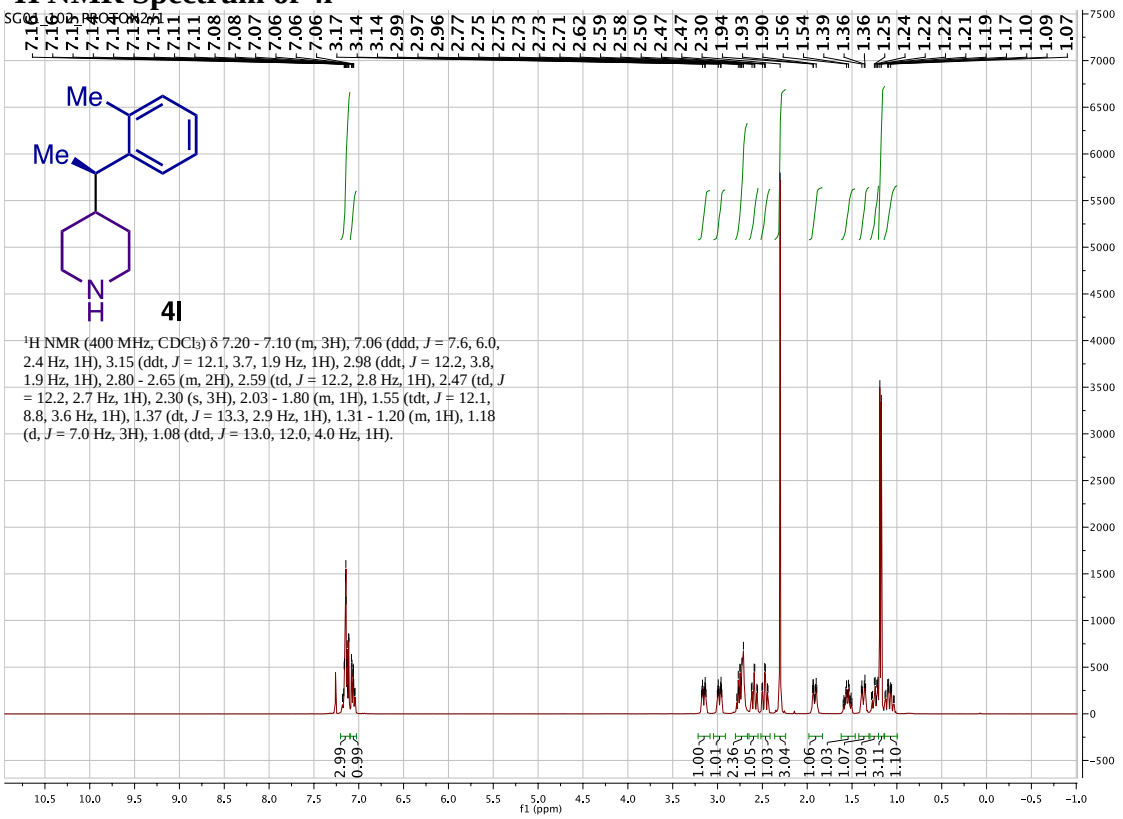
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (ddd, *J* = 7.6, 6.4, 1.3 Hz, 2H), 7.24 - 7.17 (m, 1H), 7.15 - 7.07 (m, 2H), 3.28 (s, 1H), 3.20 - 3.10 (m, 1H), 3.02 (dt, *J* = 12.5, 3.3 Hz, 1H), 2.62 (td, *J* = 12.3, 2.8 Hz, 1H), 2.49 (td, *J* = 12.2, 2.8 Hz, 1H), 2.23 (ddd, *J* = 10.8, 8.3, 4.0 Hz, 1H), 2.01 - 1.78 (m, 2H), 1.68 - 1.45 (m, 2H), 1.37 (dq, *J* = 13.3, 2.8 Hz, 1H), 1.29 - 1.12 (m, 1H), 1.06 (dtd, *J* = 13.2, 12.0, 4.1 Hz, 1H), 0.71 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR Spectrum of 4a

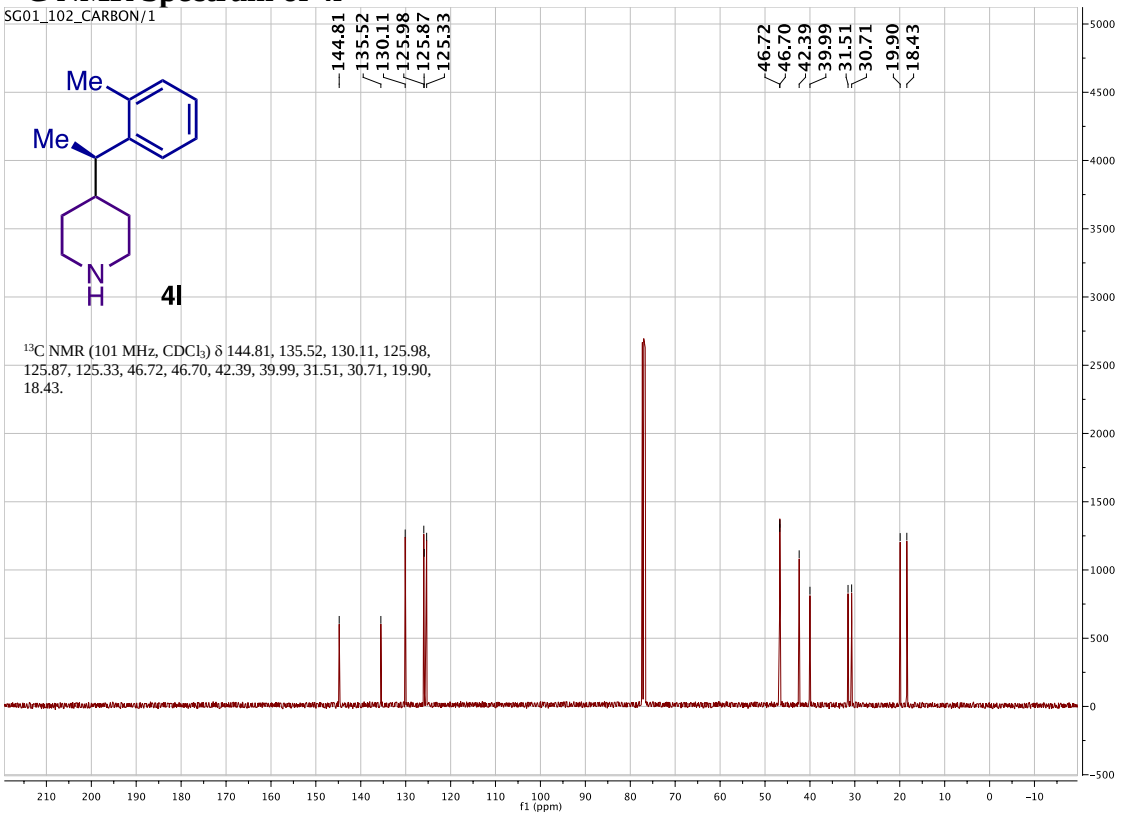


^{13}C NMR (101 MHz, $CDCl_3$) δ 143.72, 128.49, 128.07, 125.93, 53.80, 46.51, 46.49, 41.40, 31.17, 31.09, 25.04, 12.26.

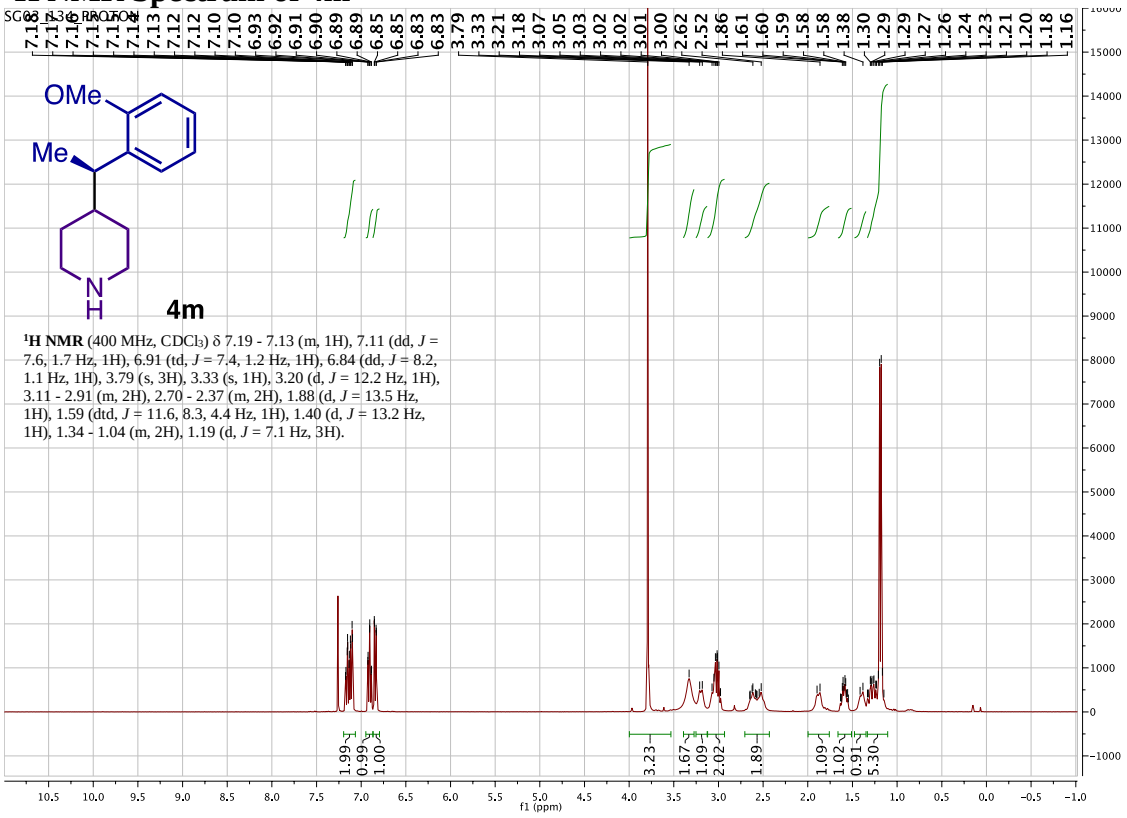
^{1}H NMR Spectrum of 4l



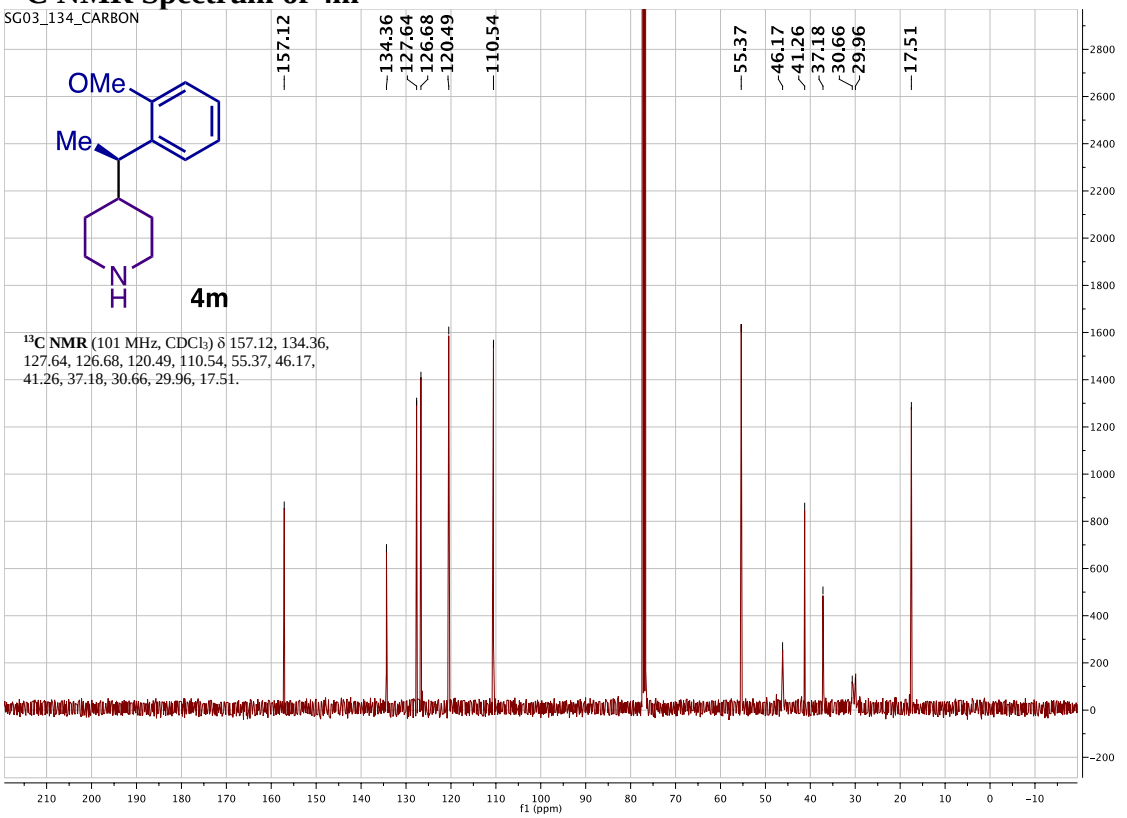
^{13}C NMR Spectrum of 4l



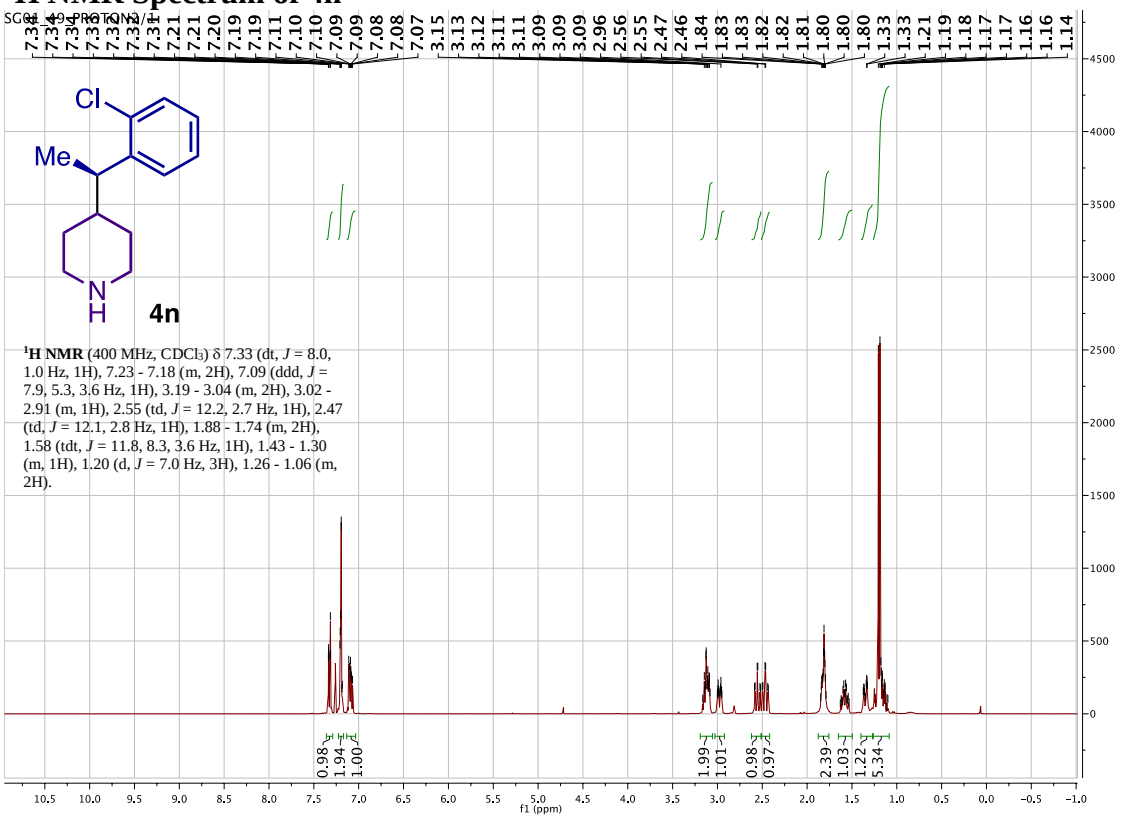
^{1}H NMR Spectrum of 4m



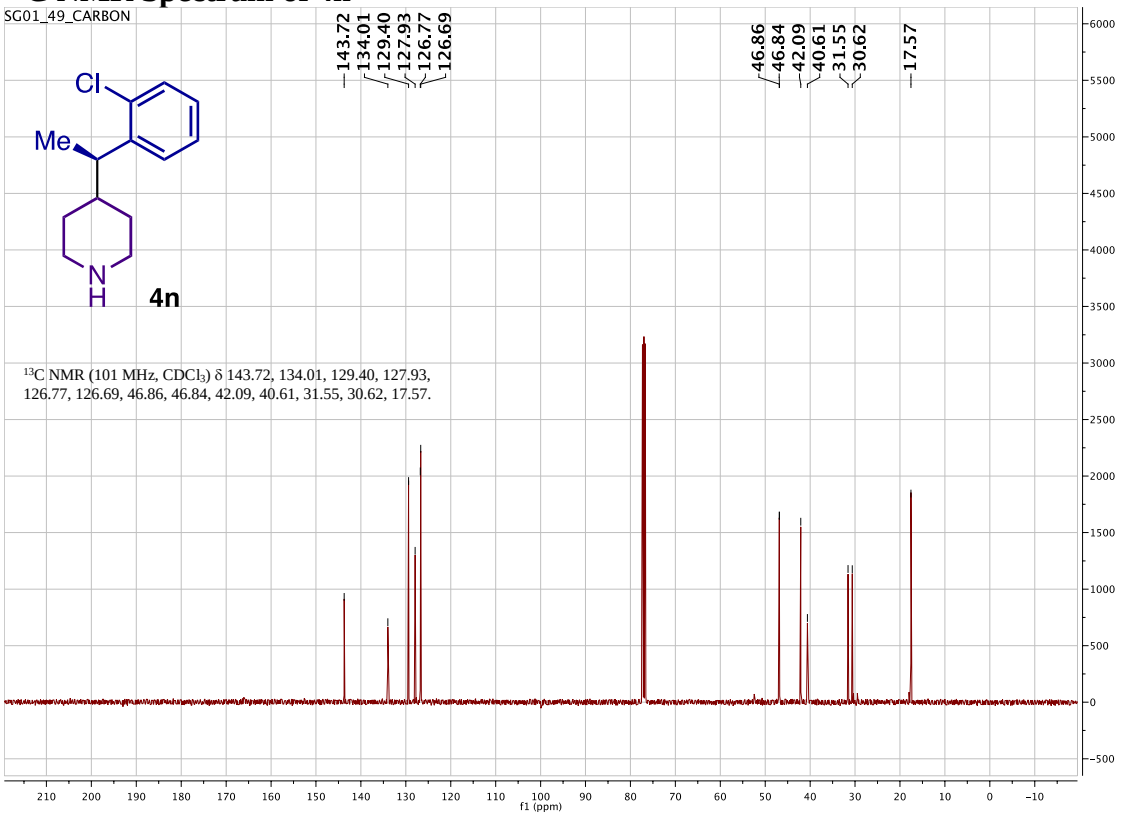
^{13}C NMR Spectrum of 4m



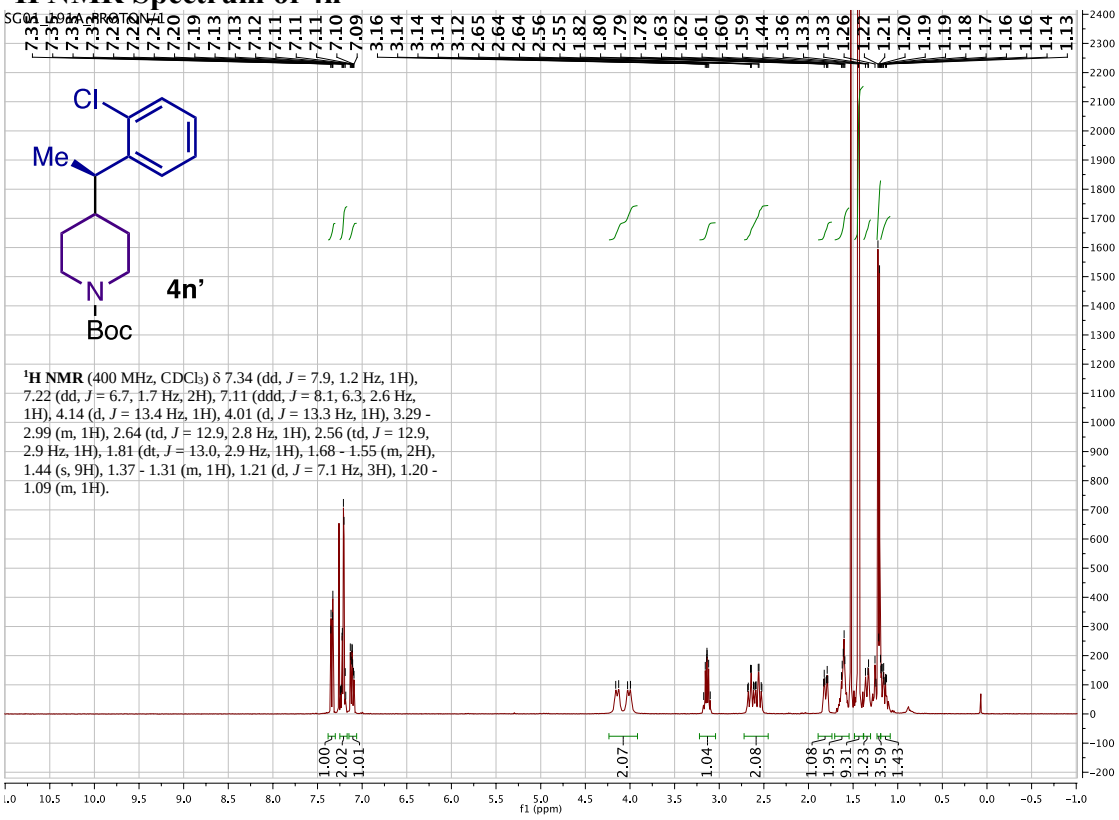
^{1}H NMR Spectrum of 4n



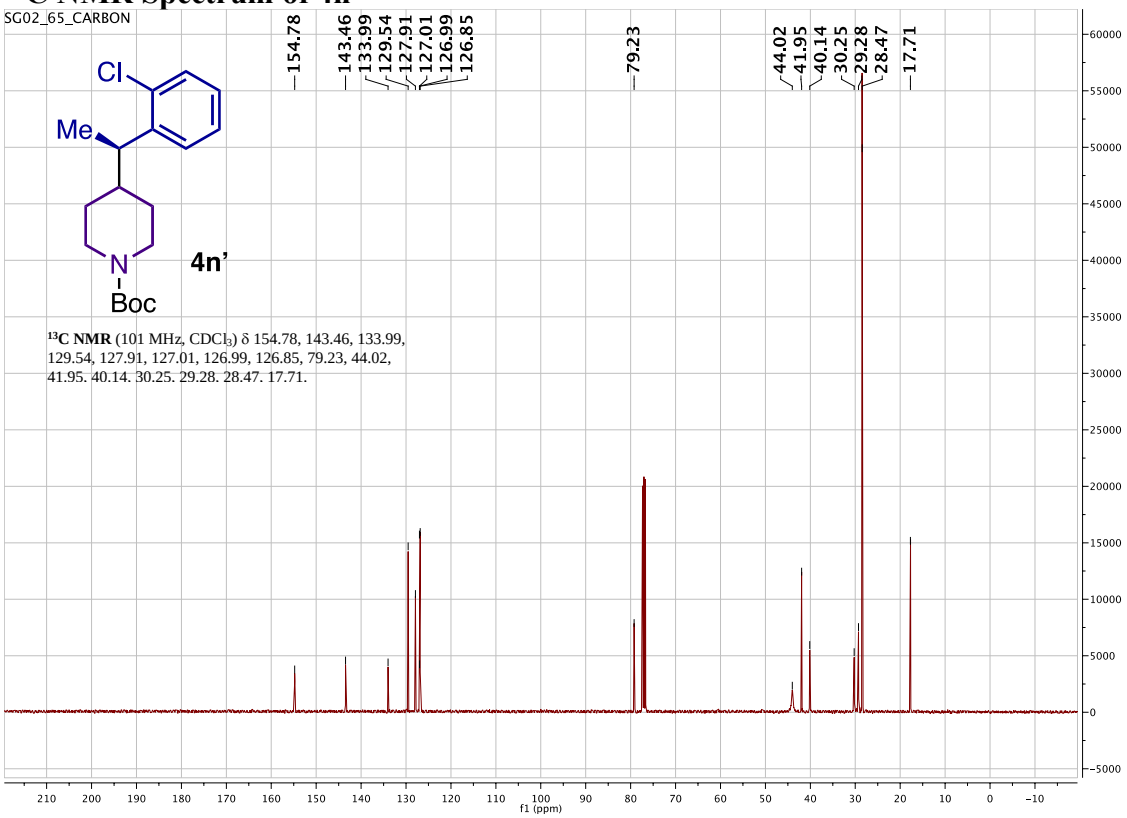
^{13}C NMR Spectrum of 4n



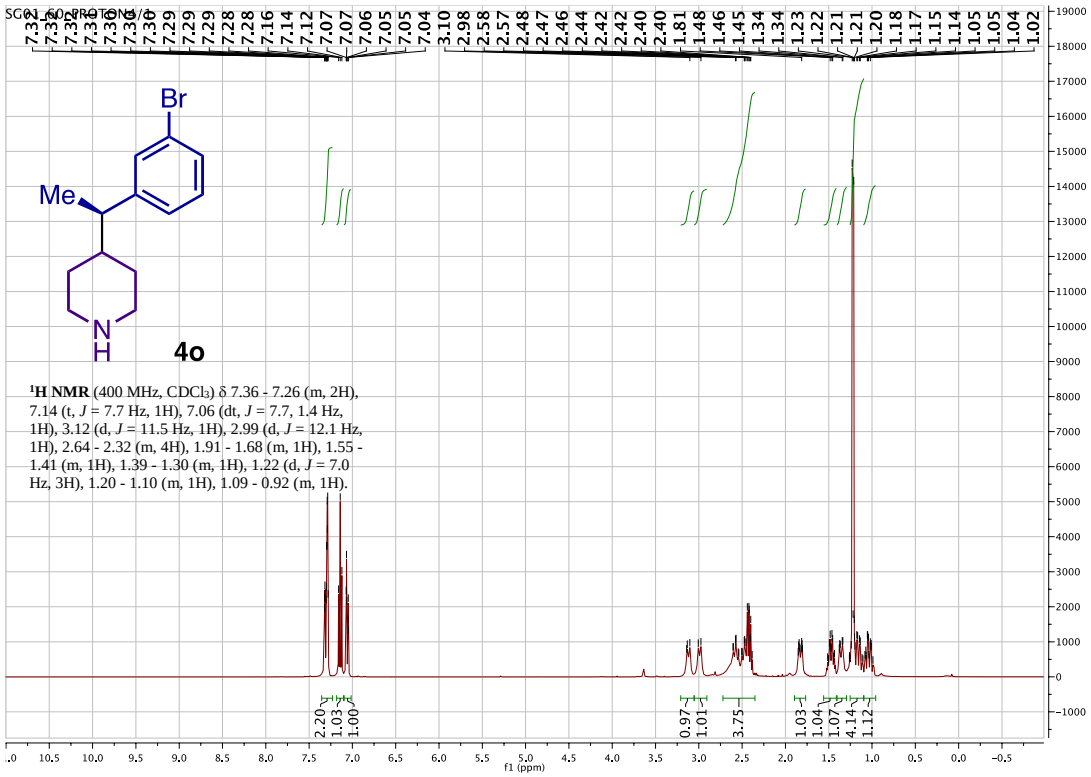
^{1}H NMR Spectrum of 4n’



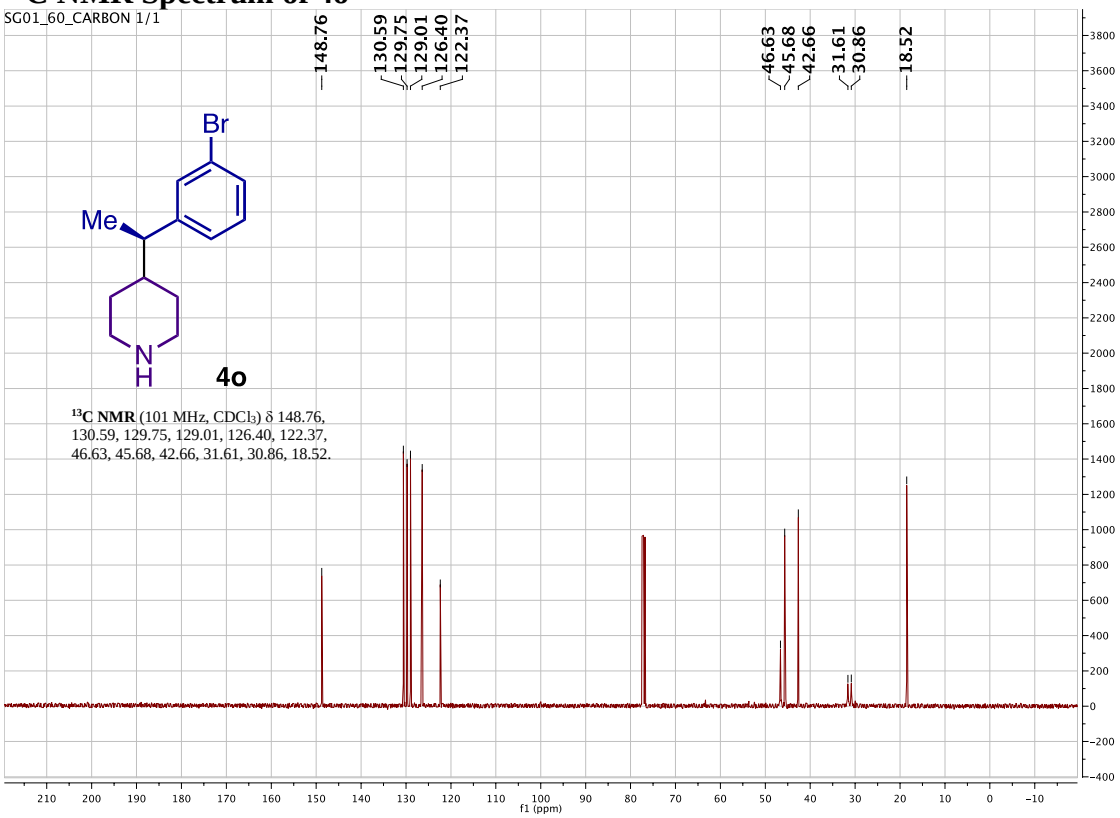
^{13}C NMR Spectrum of 4n’



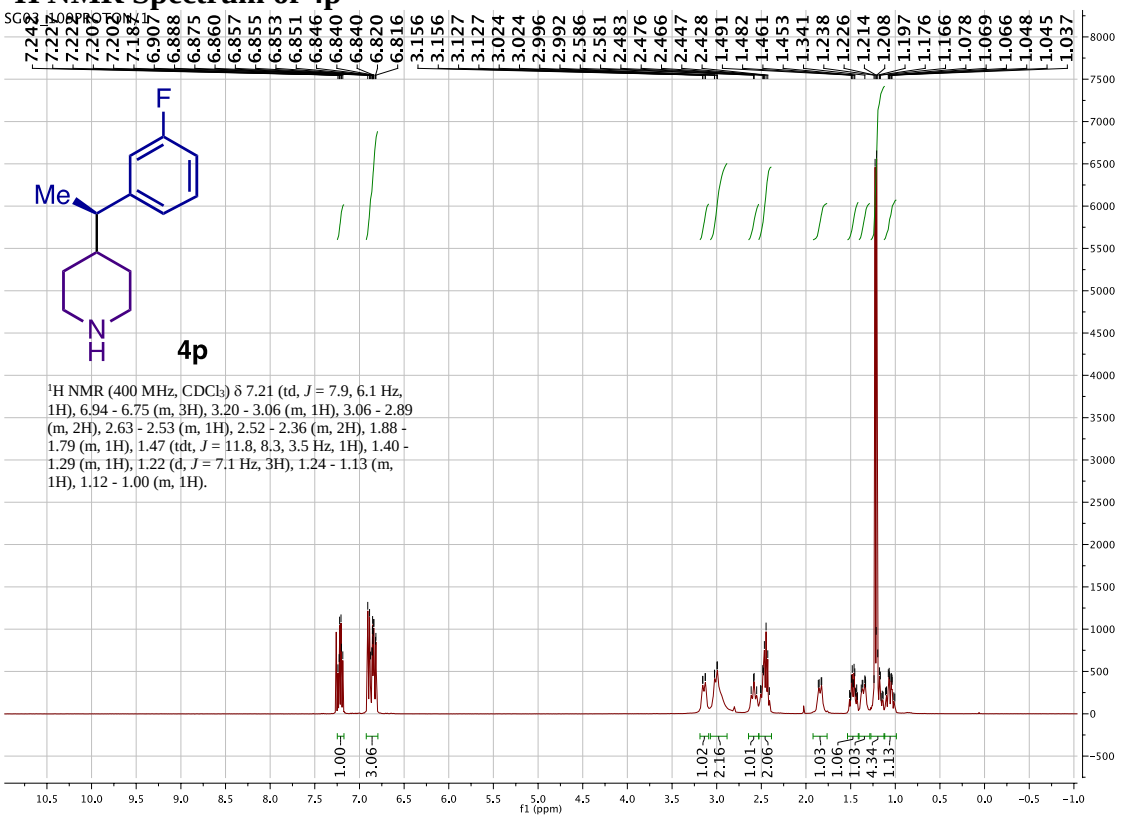
^{1}H NMR Spectrum of 4o



^{13}C NMR Spectrum of 4o

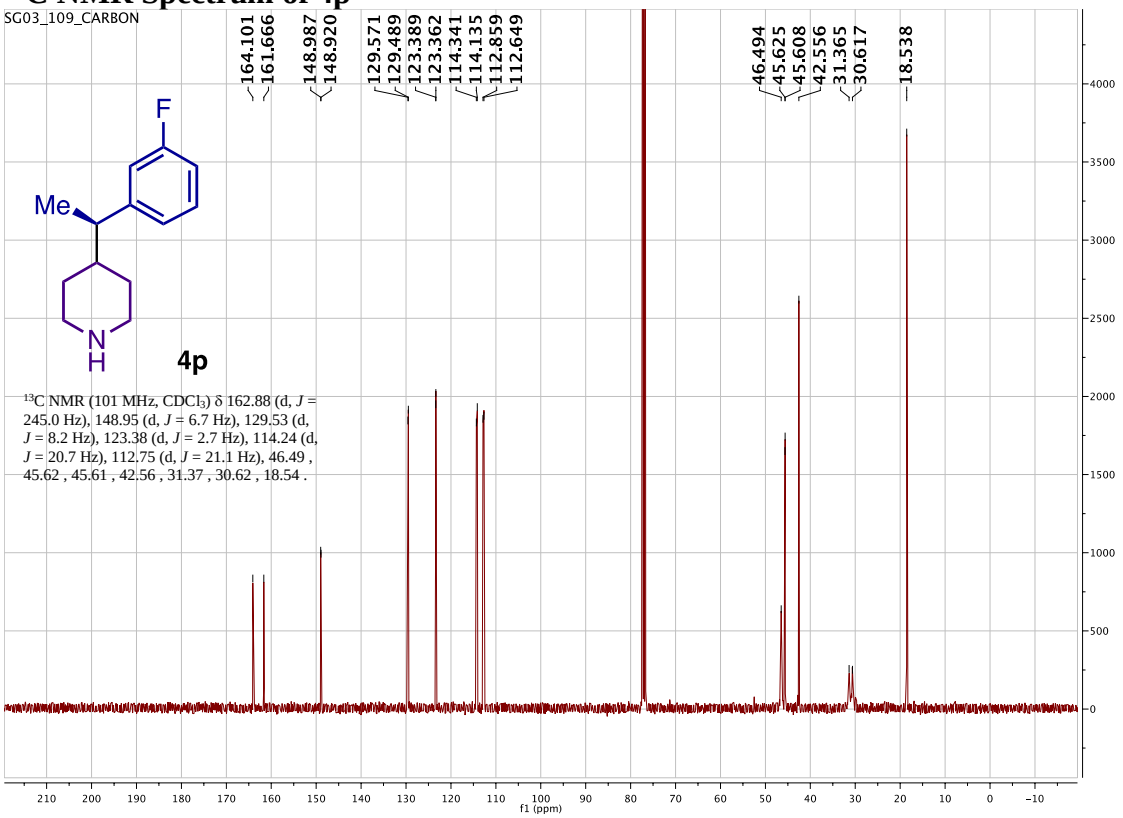


^{1}H NMR Spectrum of 4p



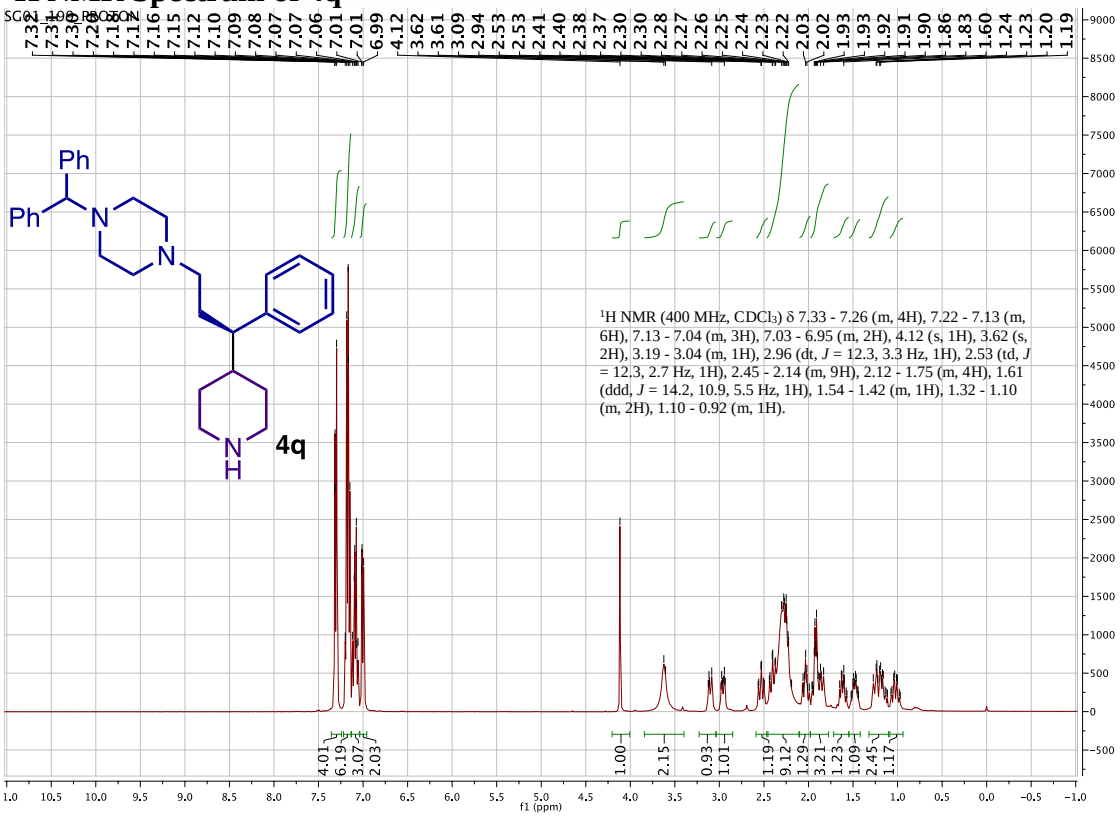
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (td, *J* = 7.9, 6.1 Hz, 1H), 6.94 - 6.75 (m, 3H), 3.20 - 3.06 (m, 1H), 3.06 - 2.89 (m, 2H), 2.63 - 2.53 (m, 1H), 2.52 - 2.36 (m, 2H), 1.88 - 1.79 (m, 1H), 1.47 (tdt, *J* = 11.8, 8.3, 3.5 Hz, 1H), 1.40 - 1.29 (m, 1H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.24 - 1.13 (m, 1H), 1.12 - 1.00 (m, 1H).

^{13}C NMR Spectrum of 4p

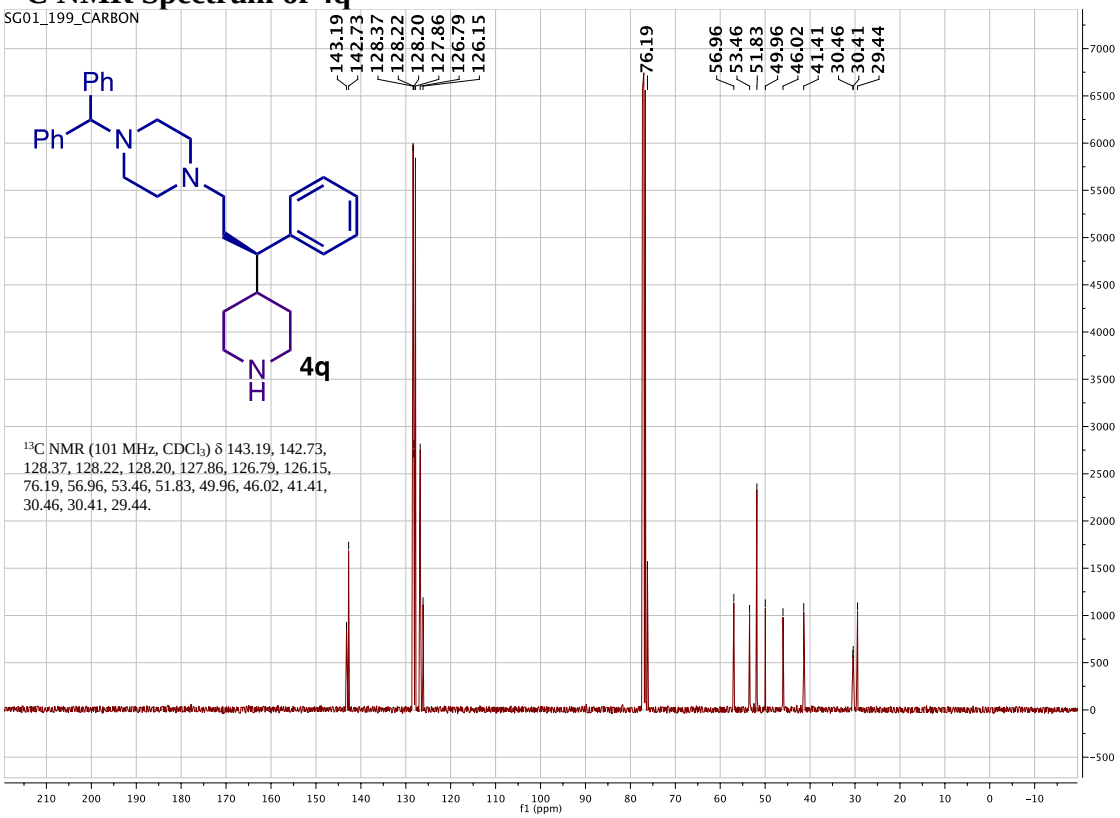


^{13}C NMR (101 MHz, $CDCl_3$) δ 162.88 (d, *J* = 245.0 Hz), 148.95 (d, *J* = 6.7 Hz), 129.53 (d, *J* = 8.2 Hz), 123.38 (d, *J* = 2.7 Hz), 114.24 (d, *J* = 20.7 Hz), 112.75 (d, *J* = 21.1 Hz), 46.49 , 45.62 , 45.61 , 42.56 , 31.37 , 30.62 , 18.54 .

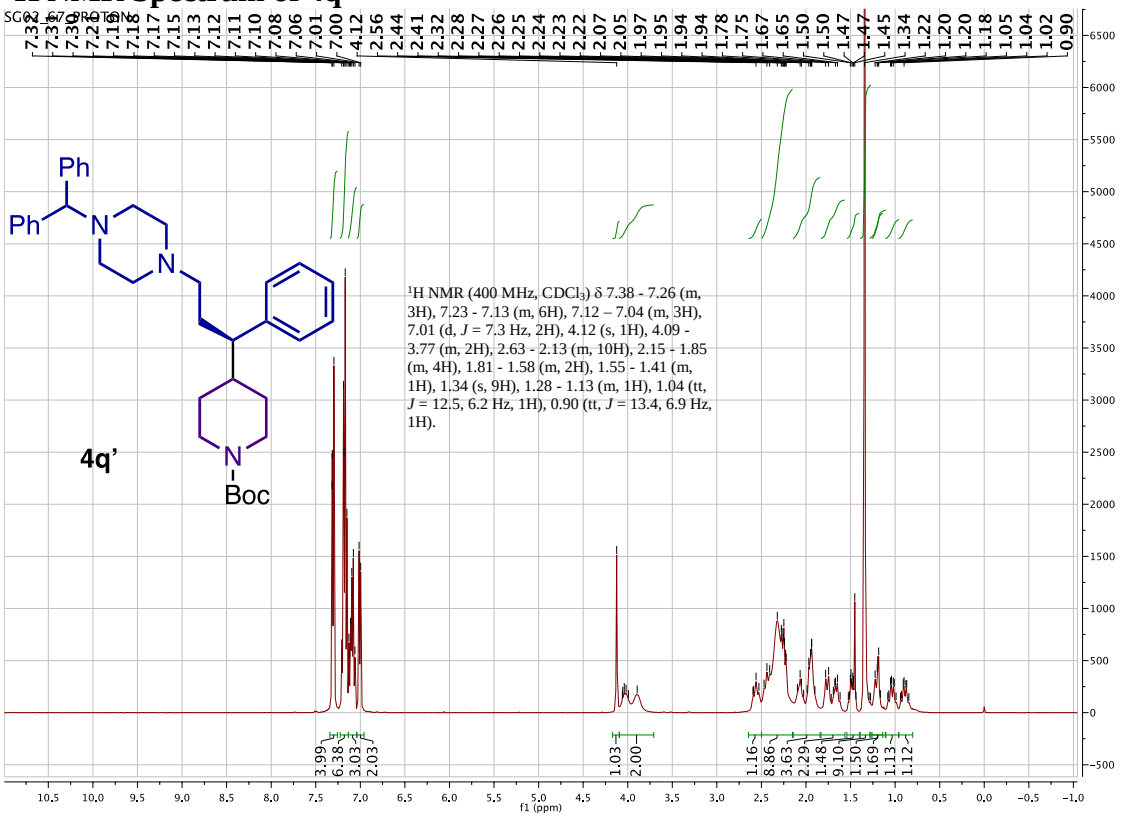
^{1}H NMR Spectrum of 4q



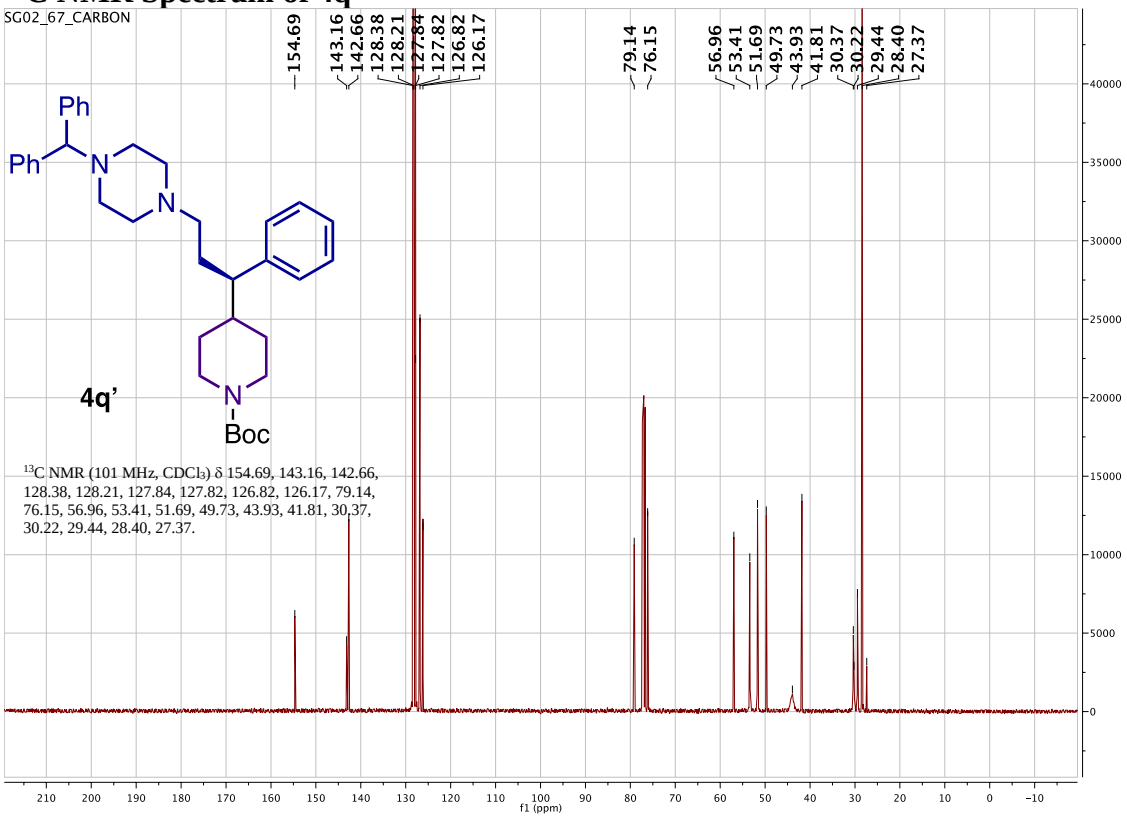
^{13}C NMR Spectrum of 4q



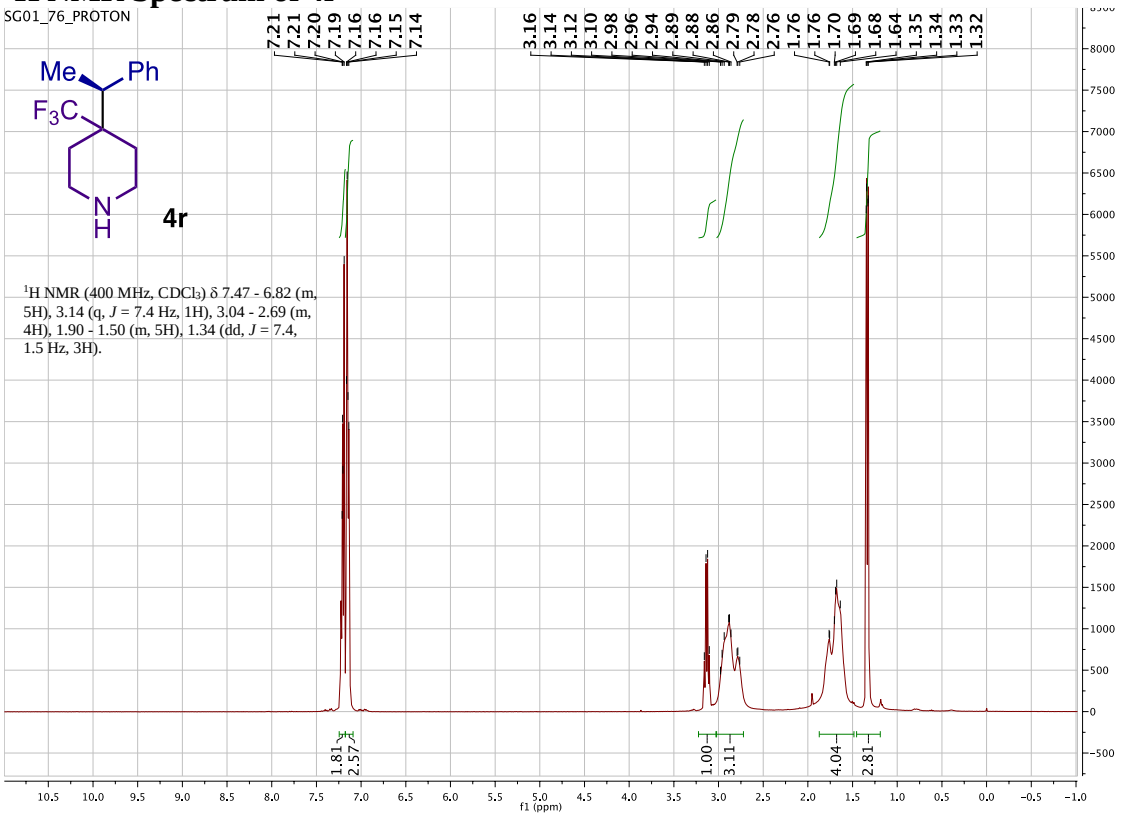
^{1}H NMR Spectrum of 4q'



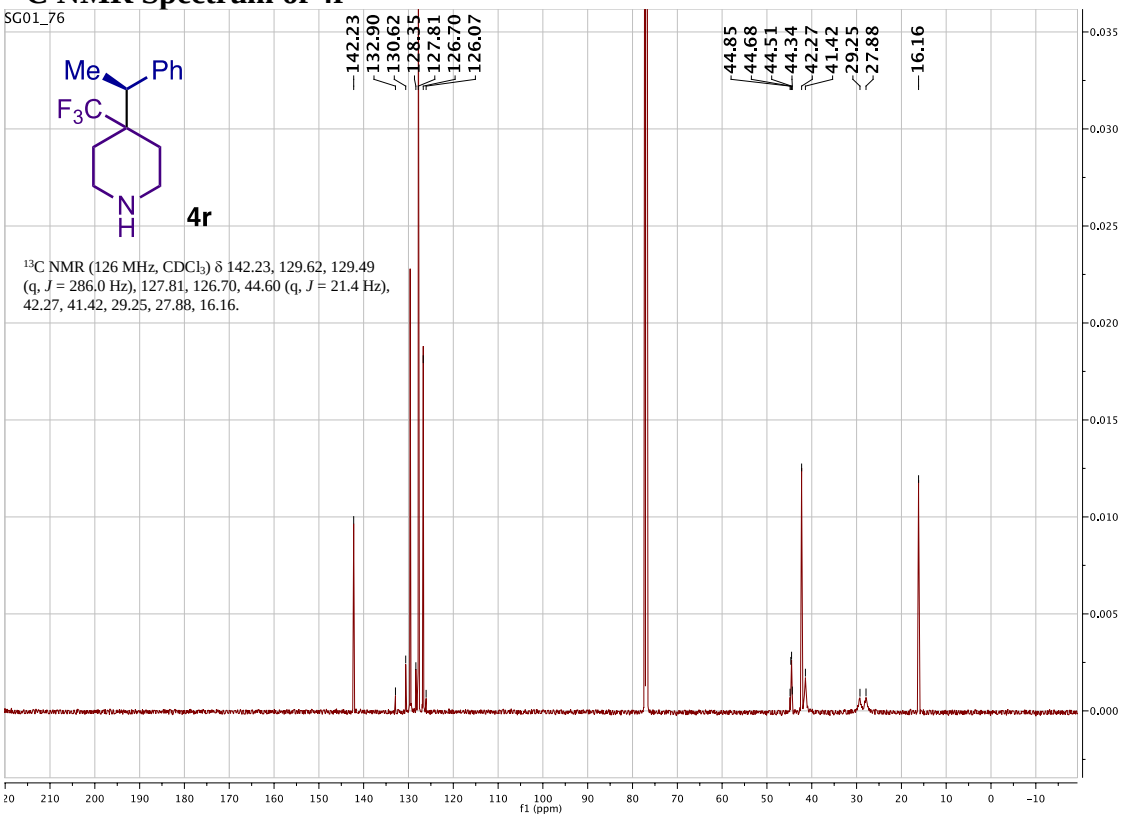
^{13}C NMR Spectrum of 4q'



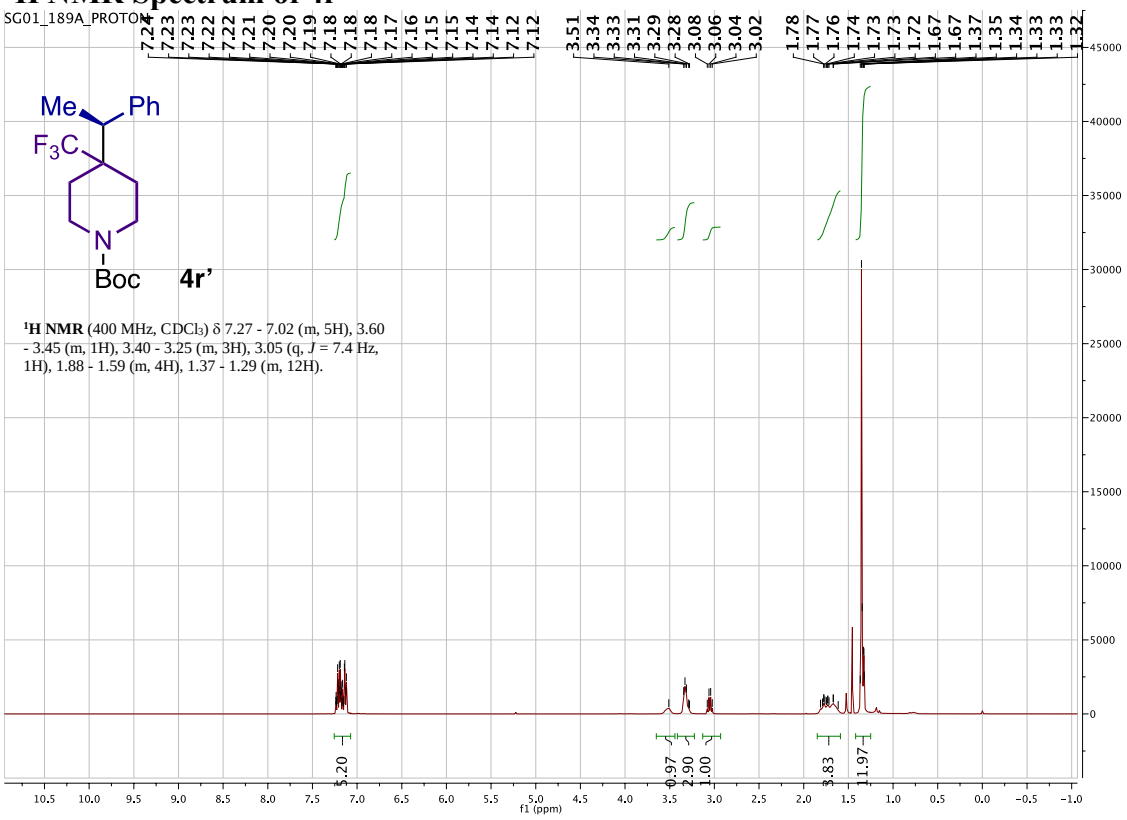
^{1}H NMR Spectrum of 4r



^{13}C NMR Spectrum of 4r

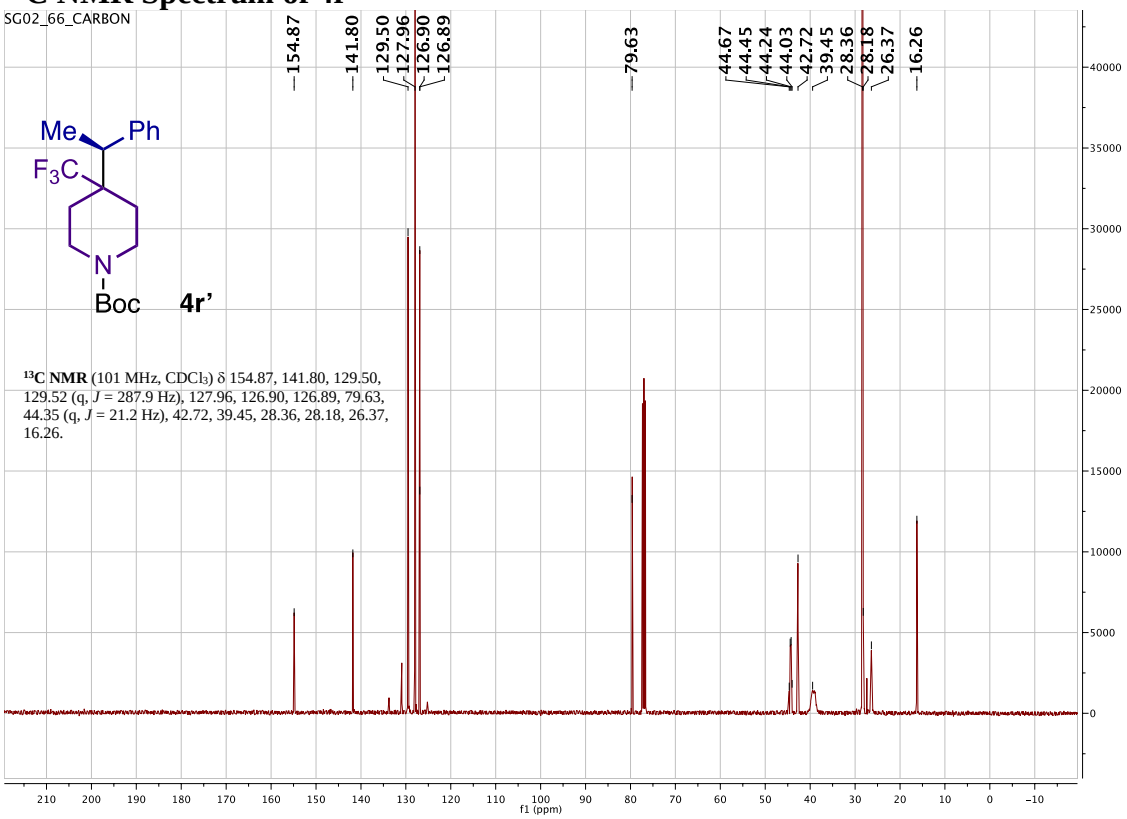


^{1}H NMR Spectrum of 4r’



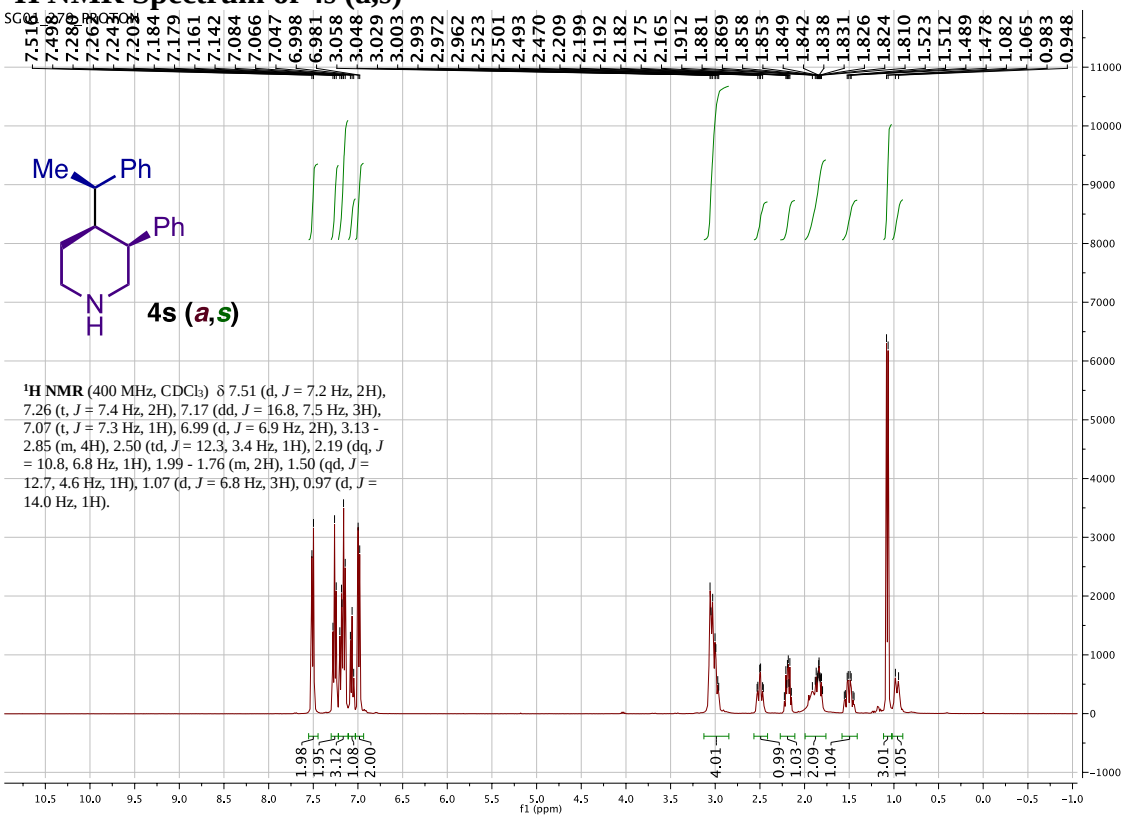
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.02 (m, 5H), 3.60 - 3.45 (m, 1H), 3.40 - 3.25 (m, 3H), 3.05 (q, *J* = 7.4 Hz, 1H), 1.88 - 1.59 (m, 4H), 1.37 - 1.29 (m, 12H).

^{13}C NMR Spectrum of 4r’

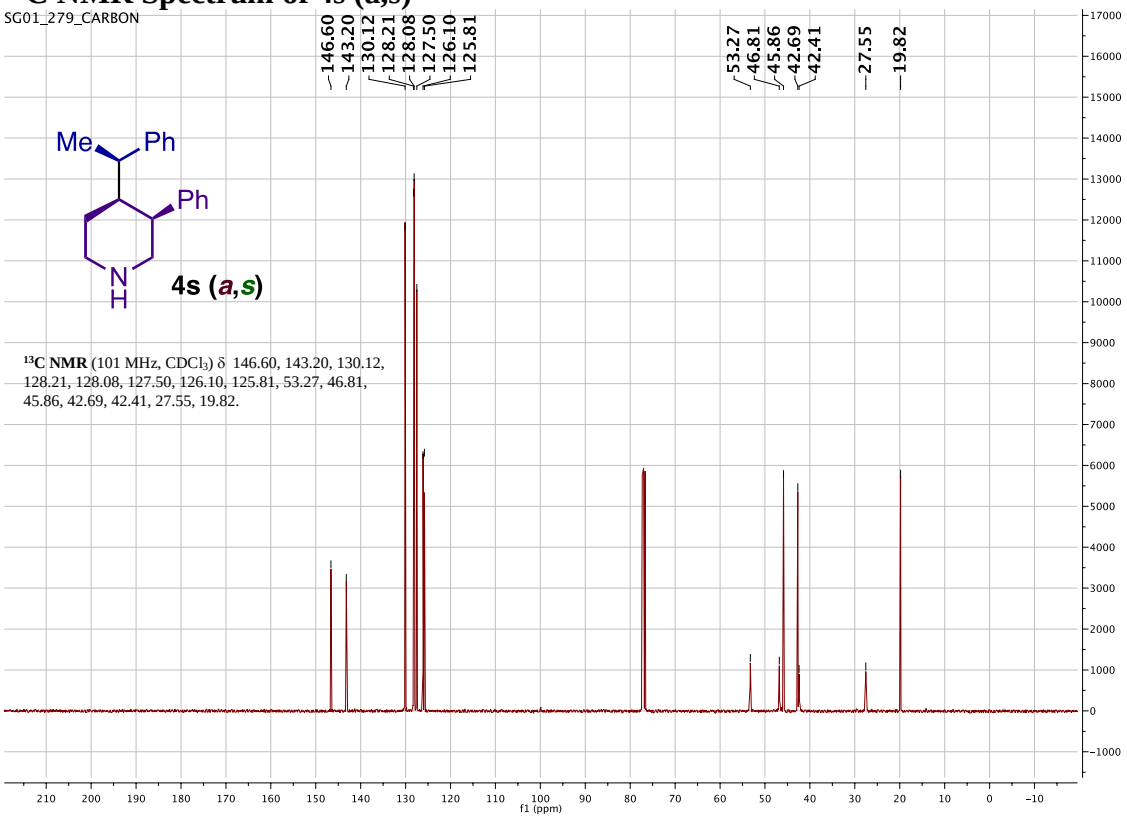


^{13}C NMR (101 MHz, $CDCl_3$) δ 154.87, 141.80, 129.50, 129.52 (q, *J* = 287.9 Hz), 127.96, 126.90, 126.89, 79.63, 44.35 (q, *J* = 21.2 Hz), 42.72, 39.45, 28.36, 28.18, 26.37, 16.26.

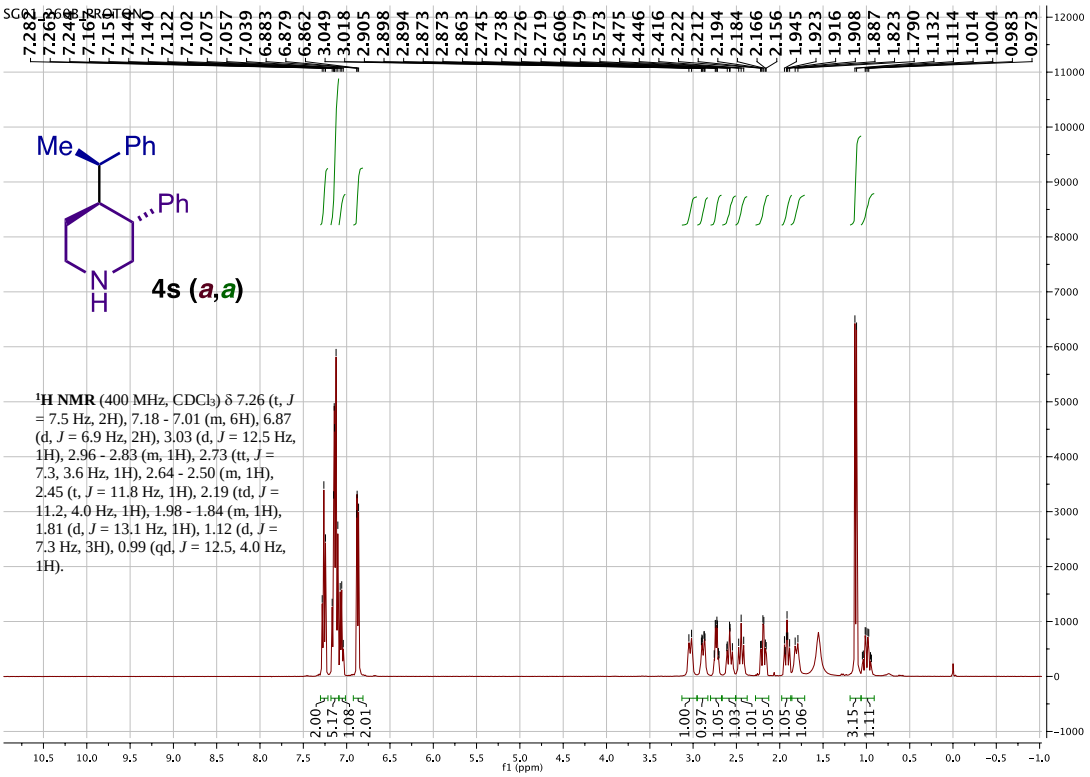
^{1}H NMR Spectrum of 4s (a,s)



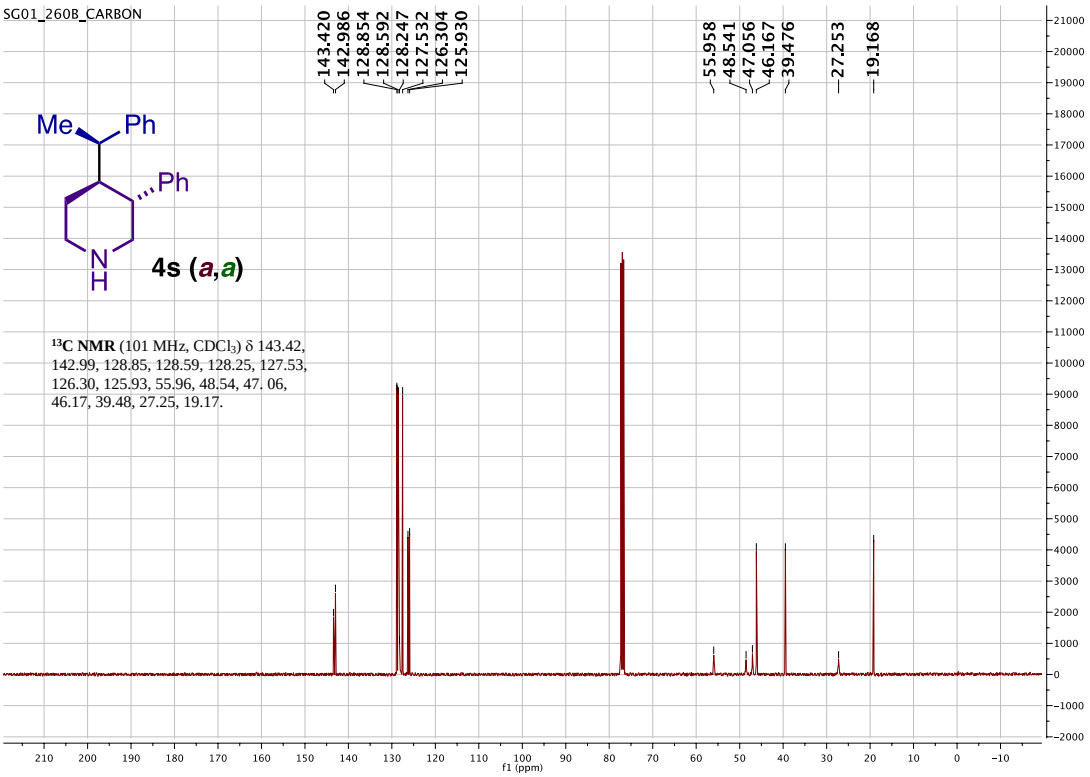
^{13}C NMR Spectrum of 4s (a,s)



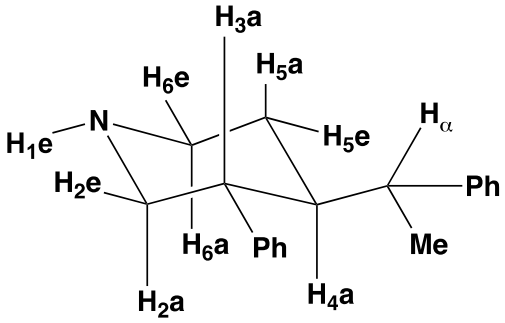
^{1}H NMR Spectrum of 4s (a,a)

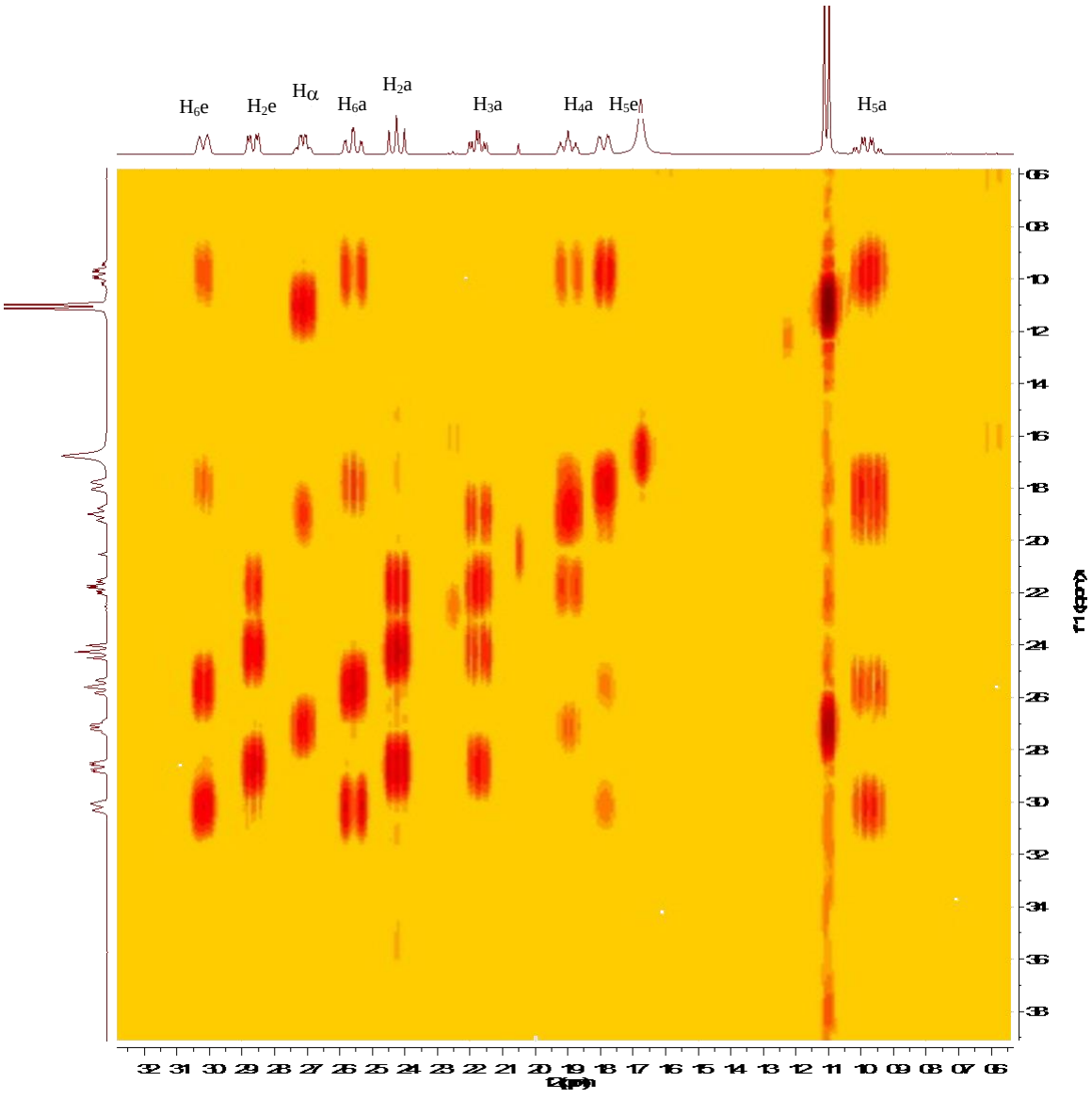


^{13}C NMR Spectrum of 4s (a,a)

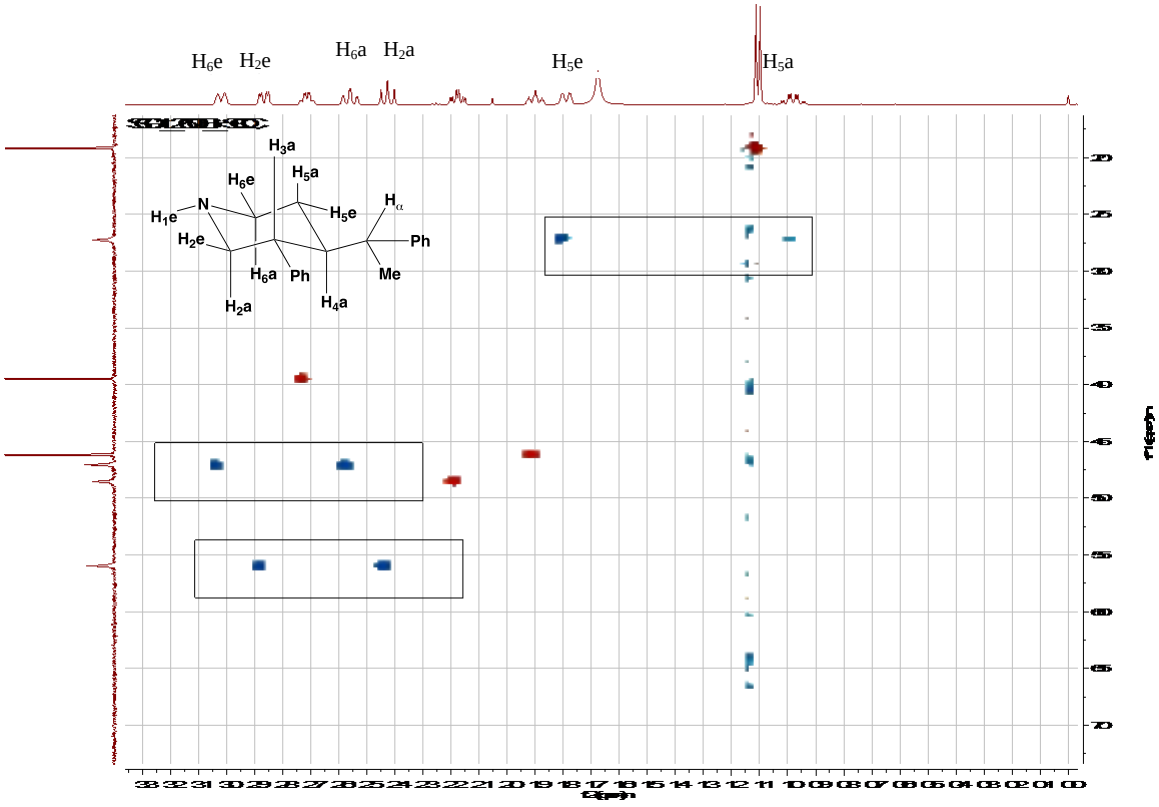


g-COSY Spectrum of 4s (a,a)

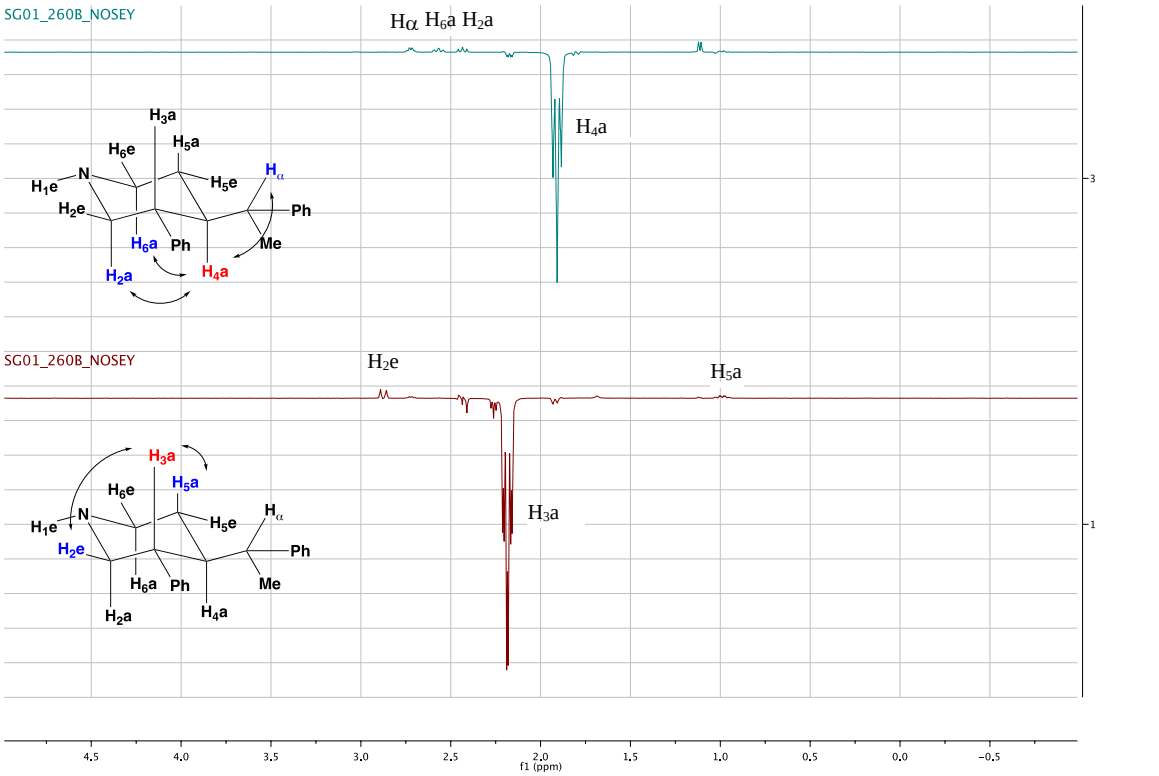




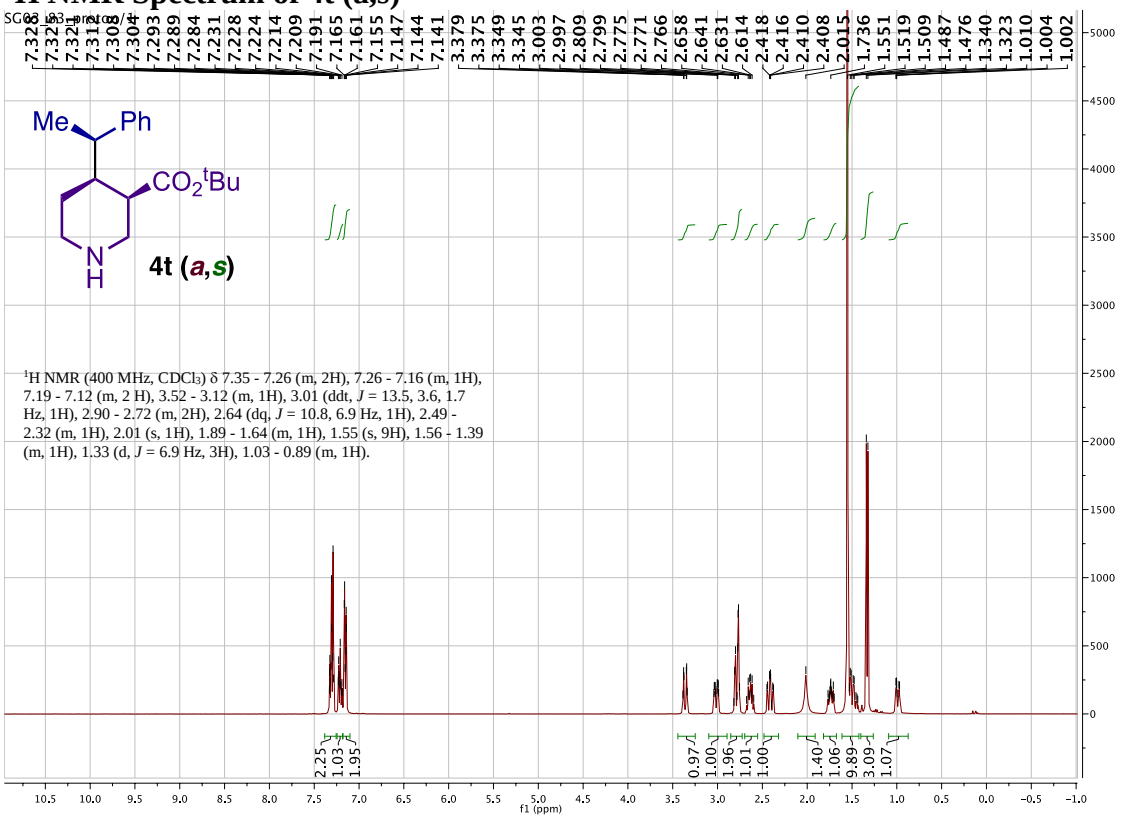
HSQC Spectrum of 4s (a,a)



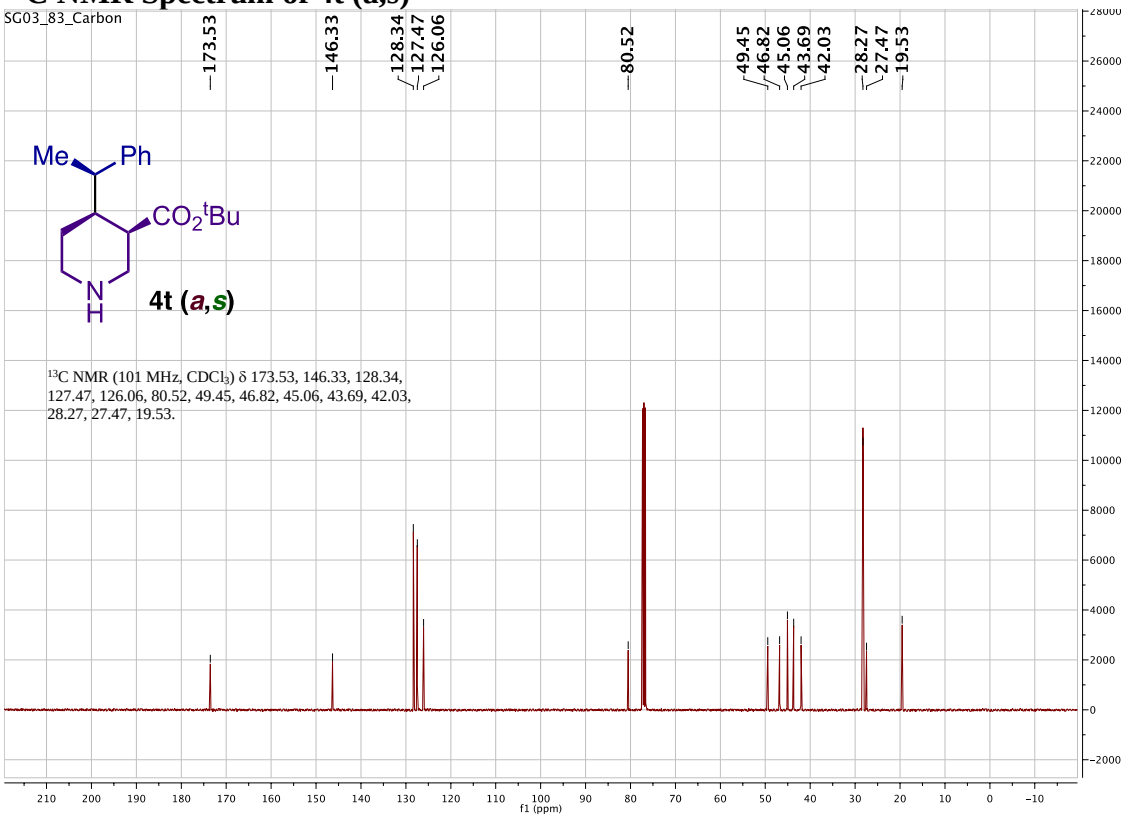
1-D NOESY Spectrum of 4s (a,a)



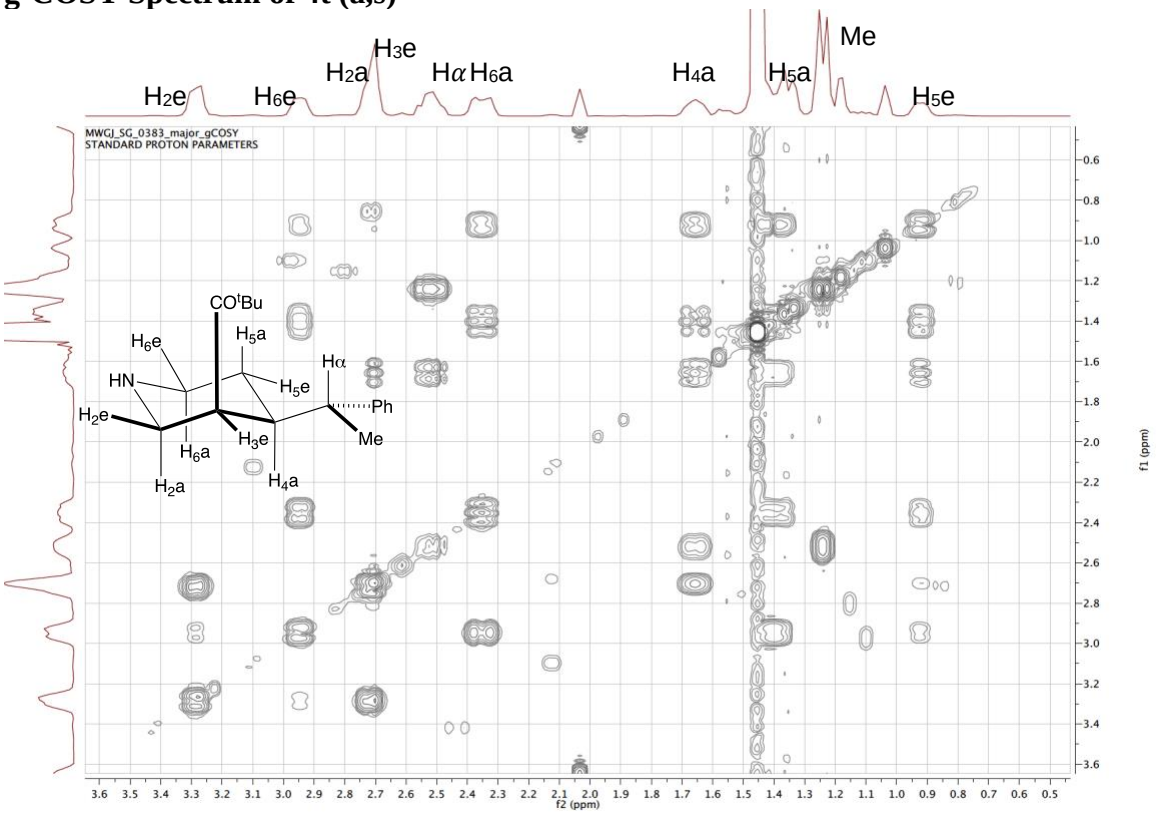
^{1}H NMR Spectrum of 4t (a,s)



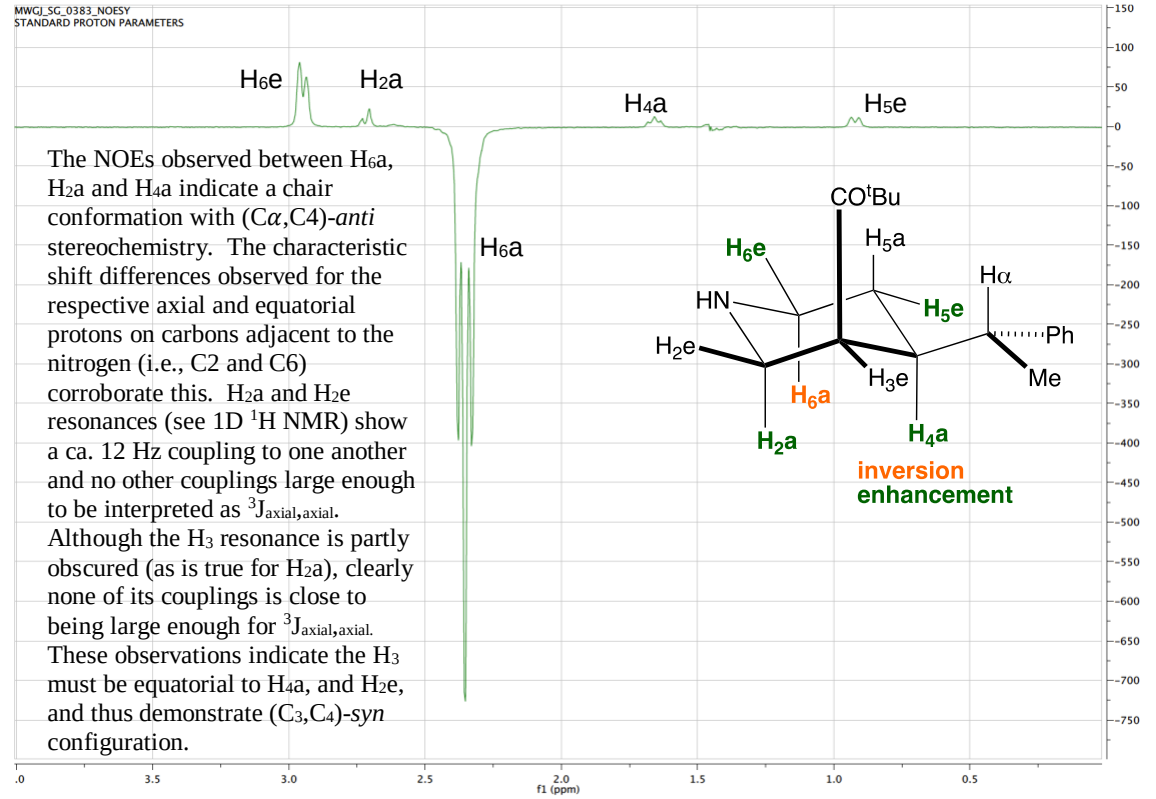
^{13}C NMR Spectrum of 4t (a,s)



g-COSY Spectrum of 4t (a,s)

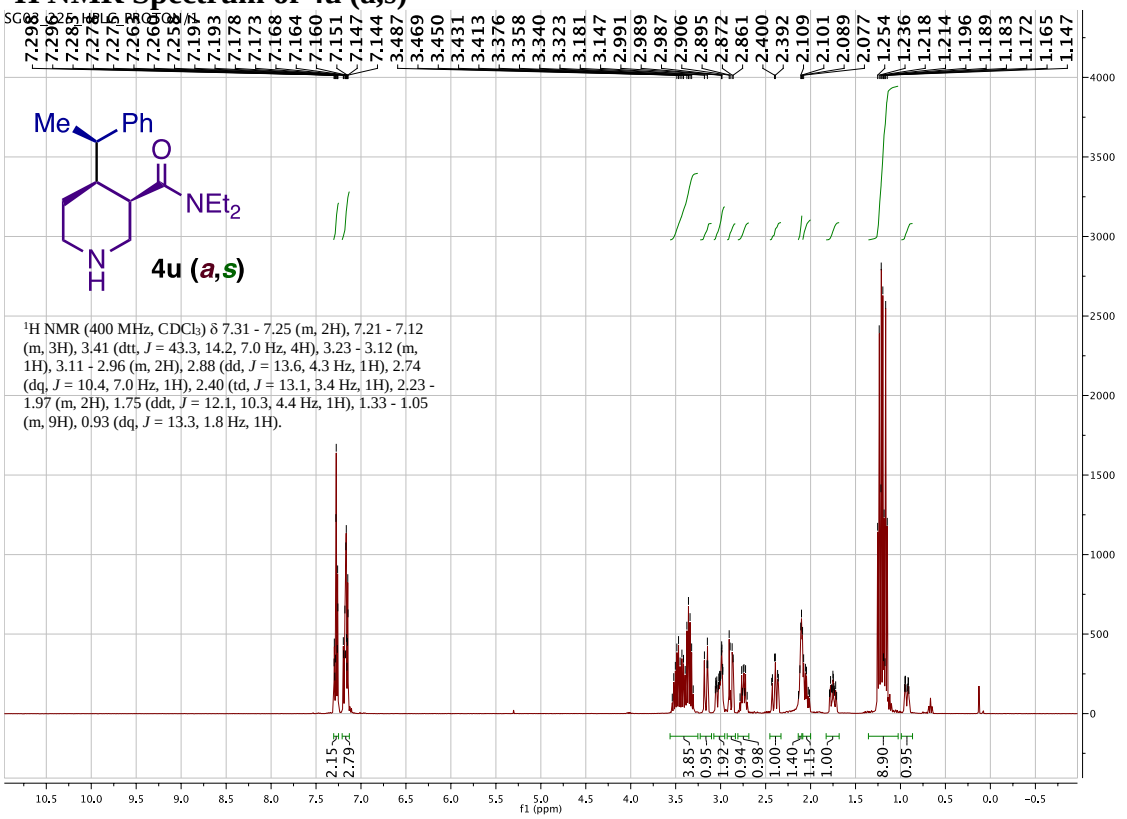


1-D NOESY Spectrum of 4t (a,s)

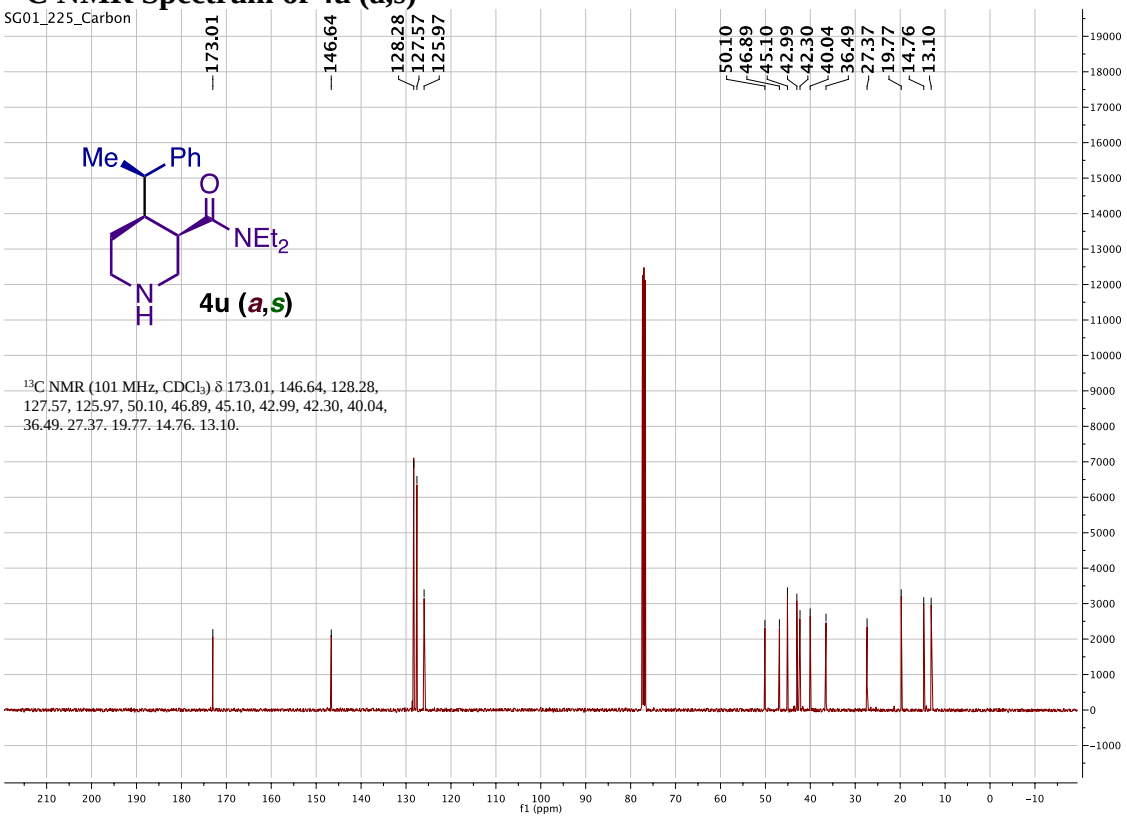


The NOEs observed between H_6a, H_2a and H_4a indicate a chair conformation with (Cα,C4)-*anti* stereochemistry. The characteristic shift differences observed for the respective axial and equatorial protons on carbons adjacent to the nitrogen (i.e., C2 and C6) corroborate this. H_2a and H_2e resonances (see 1D ^{1}H NMR) show a ca. 12 Hz coupling to one another and no other couplings large enough to be interpreted as $^3J_{axial,axial}$. Although the H_3 resonance is partly obscured (as is true for H_2a), clearly none of its couplings is close to being large enough for $^3J_{axial,axial}$. These observations indicate the H_3 must be equatorial to H_4a, and H_2e, and thus demonstrate (C_3,C_4)-*syn* configuration.

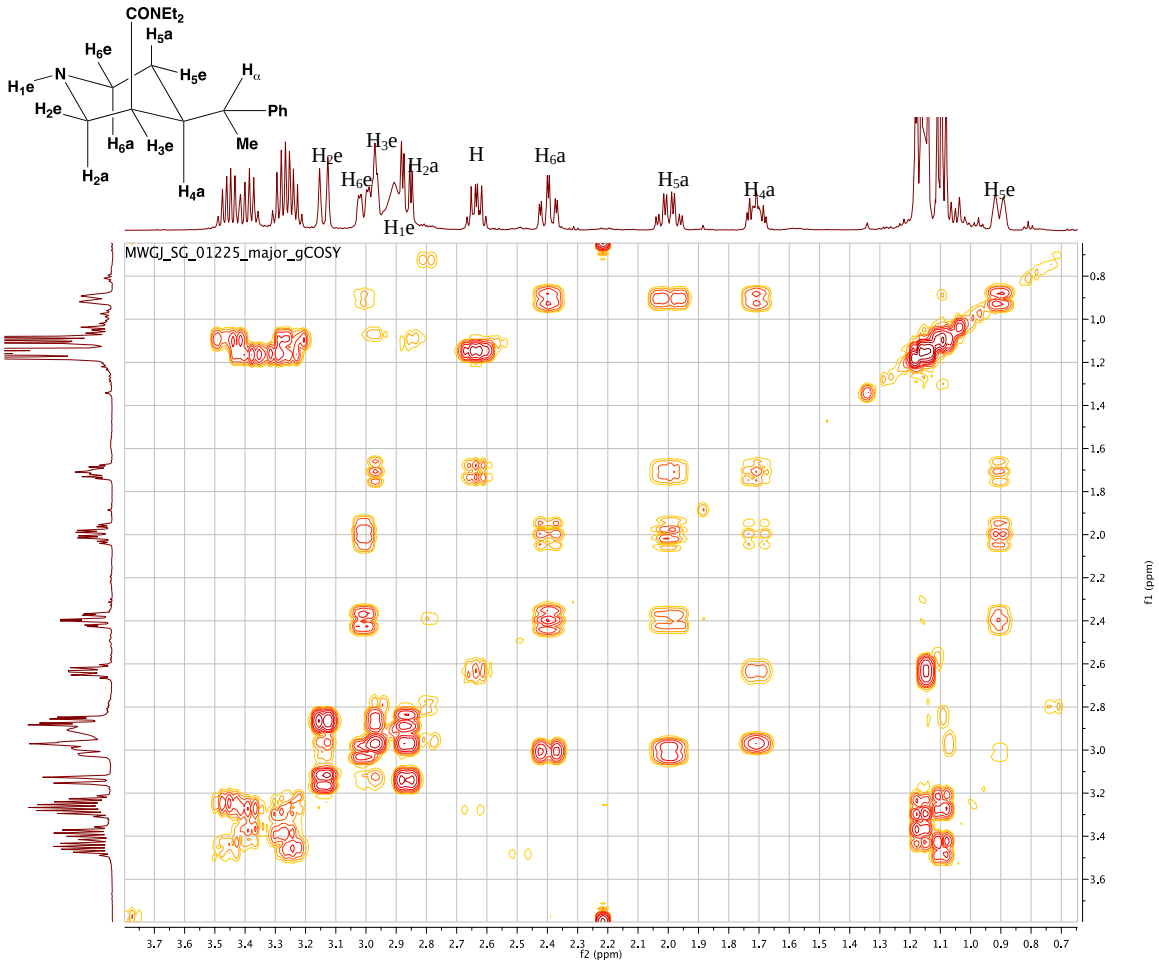
^{1}H NMR Spectrum of 4u (a,s)



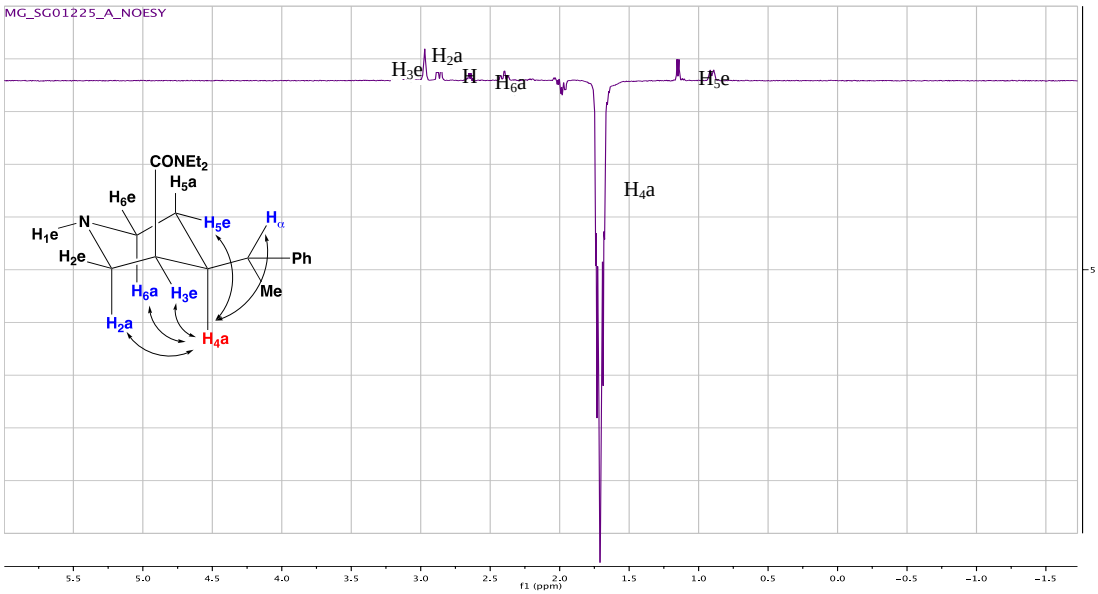
^{13}C NMR Spectrum of 4u (a,s)



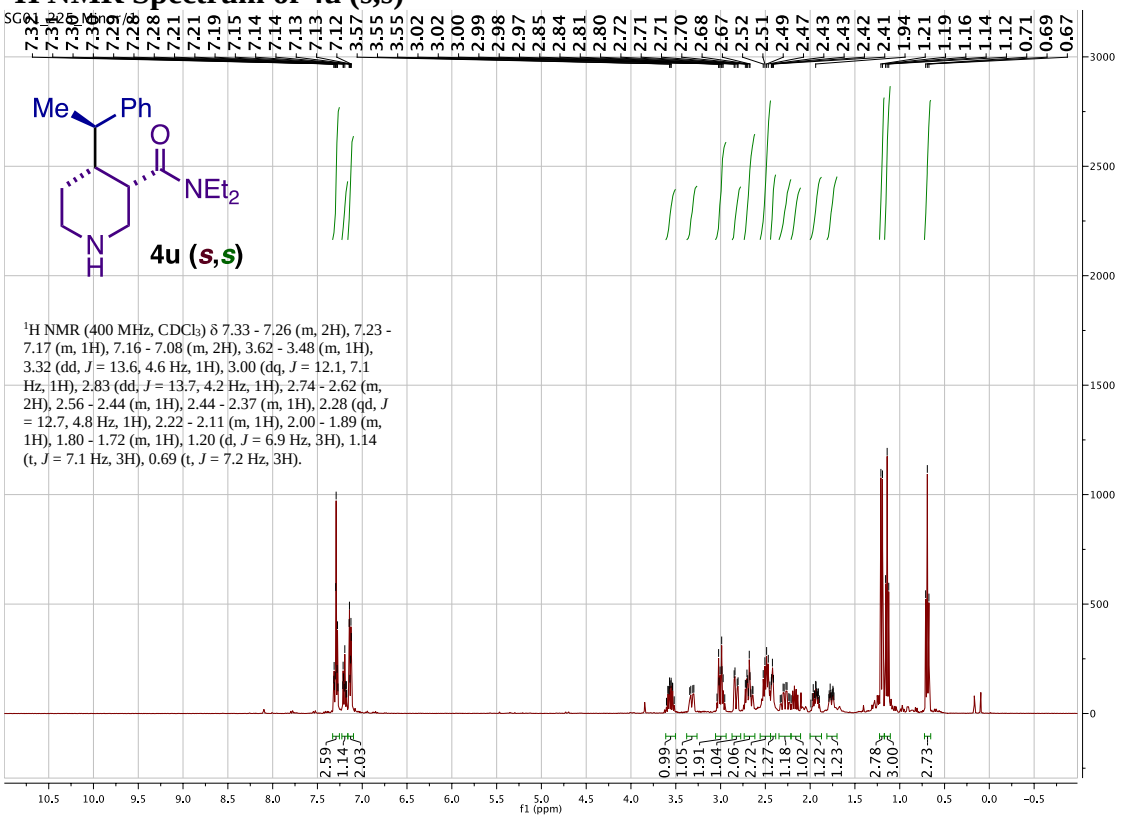
g-COSY Spectrum of 4u (a,s)



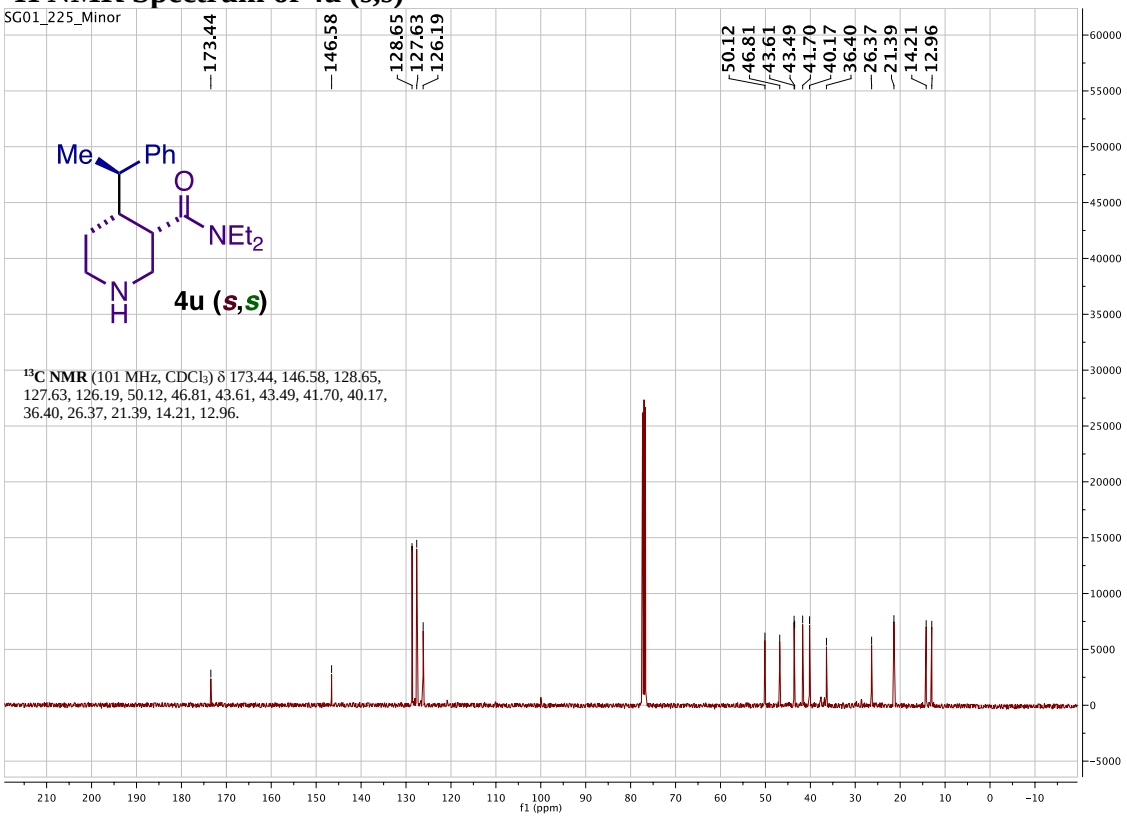
1-D NOESY Spectrum of 4u (a,s)



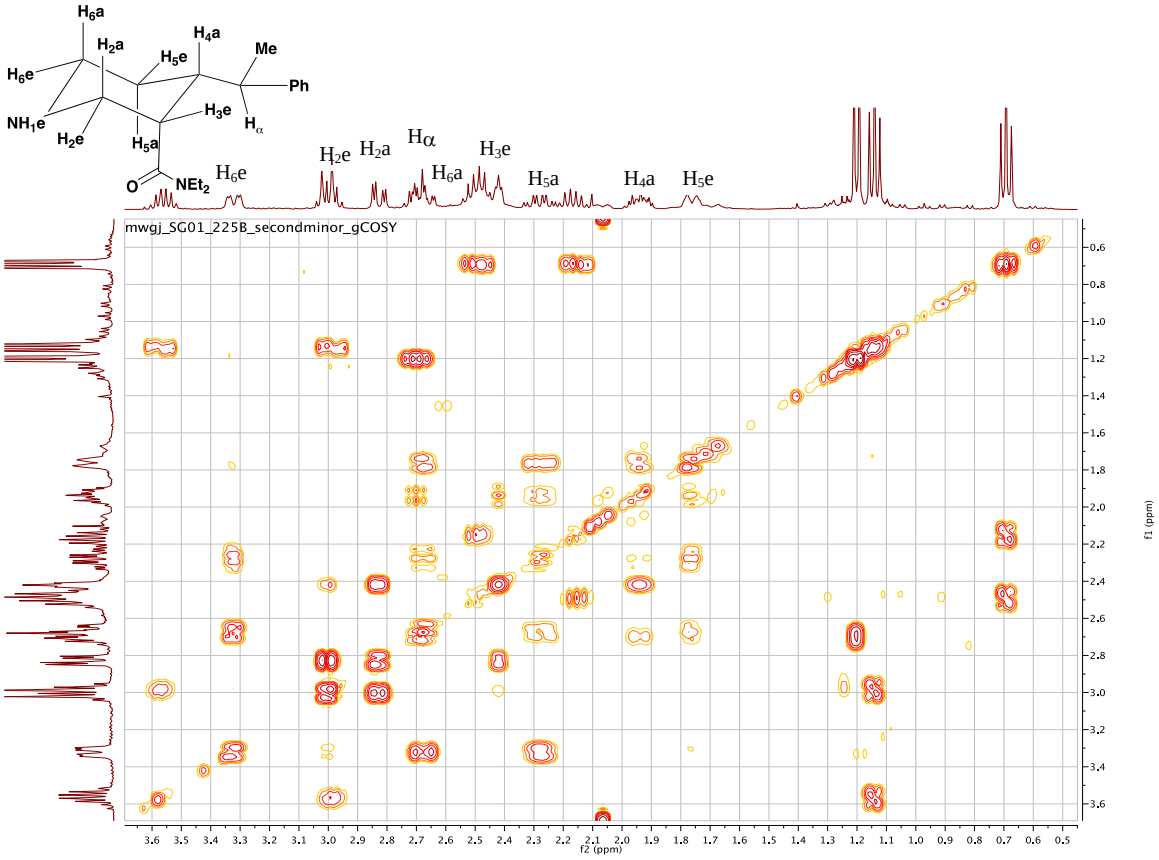
^{1}H NMR Spectrum of 4u (s,s)



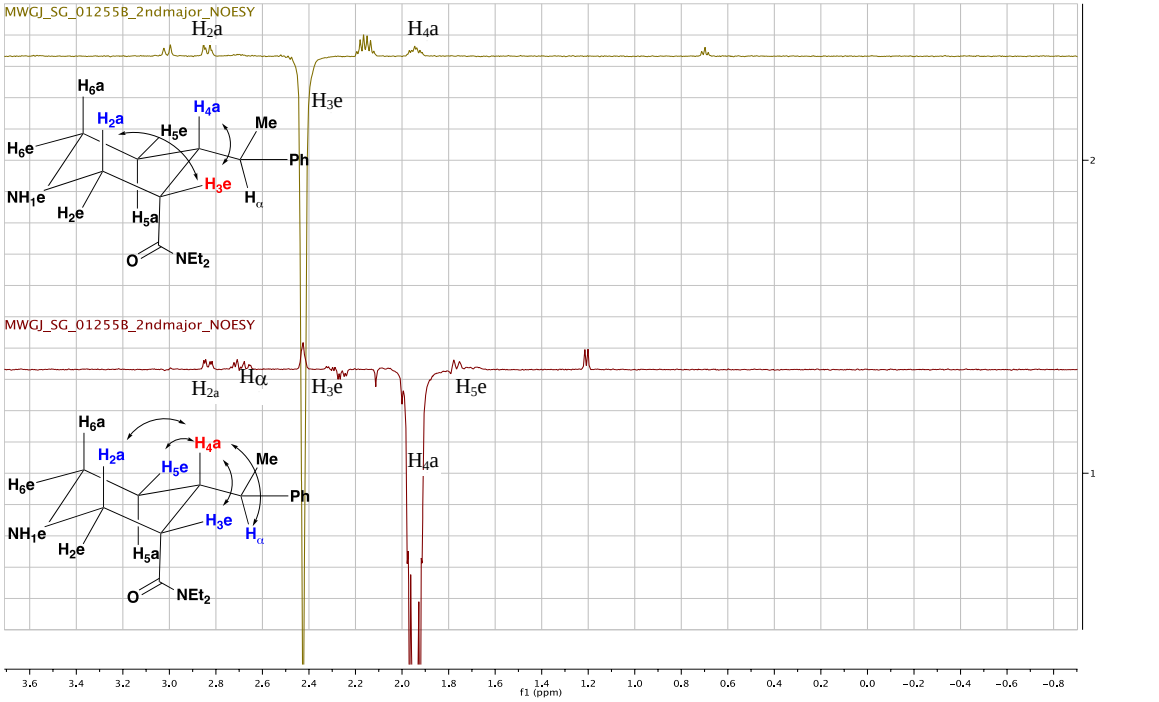
^{1}H NMR Spectrum of 4u (s,s)



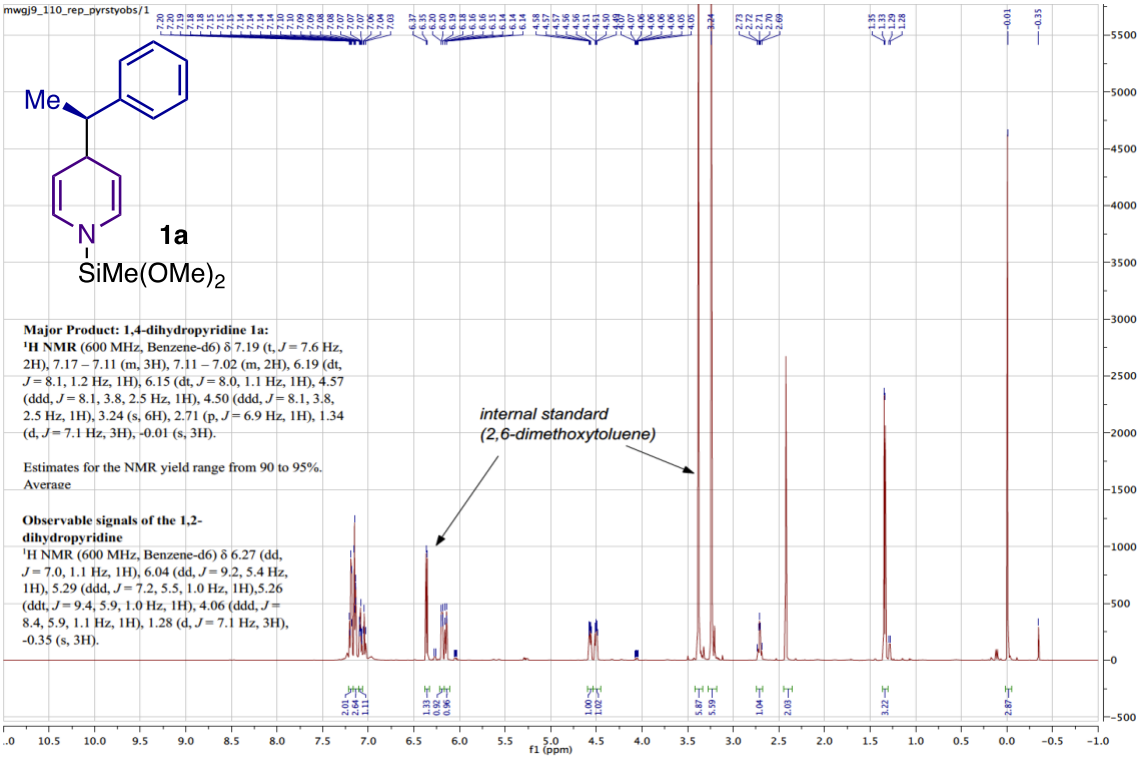
g-COSY Spectrum of 4u (s,s)



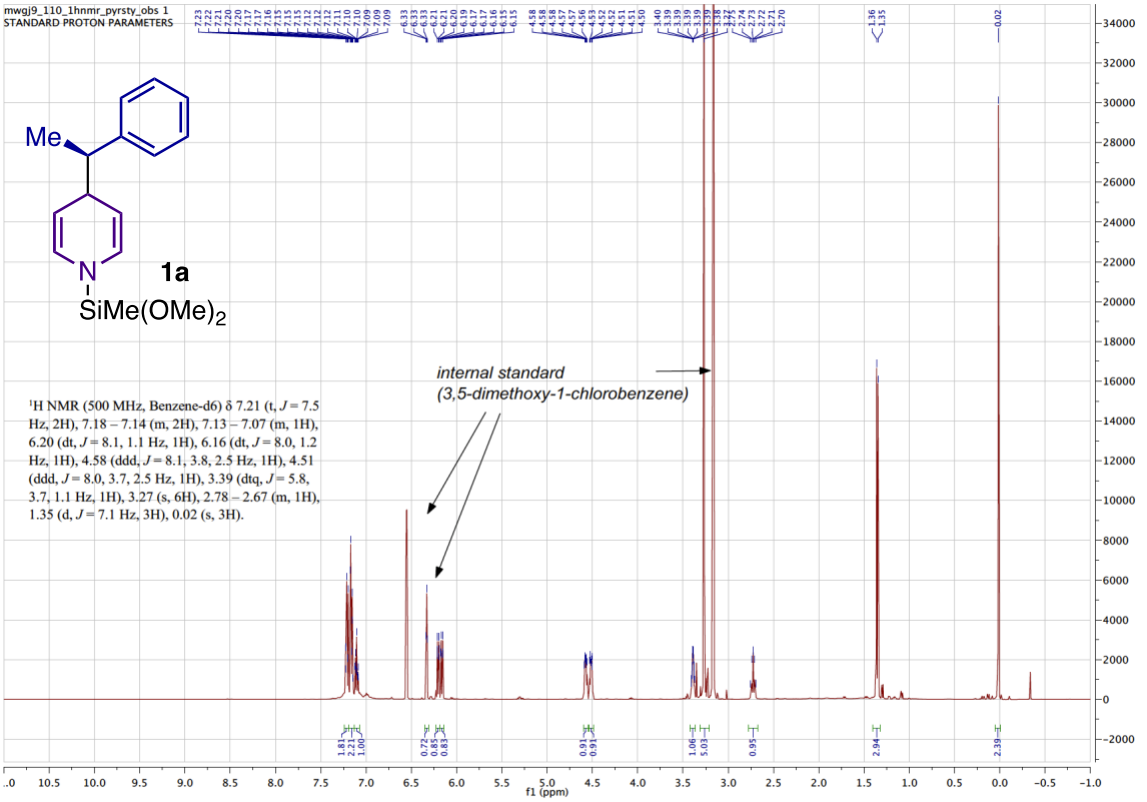
1-D NOESY Spectrum of 4u (s,s)



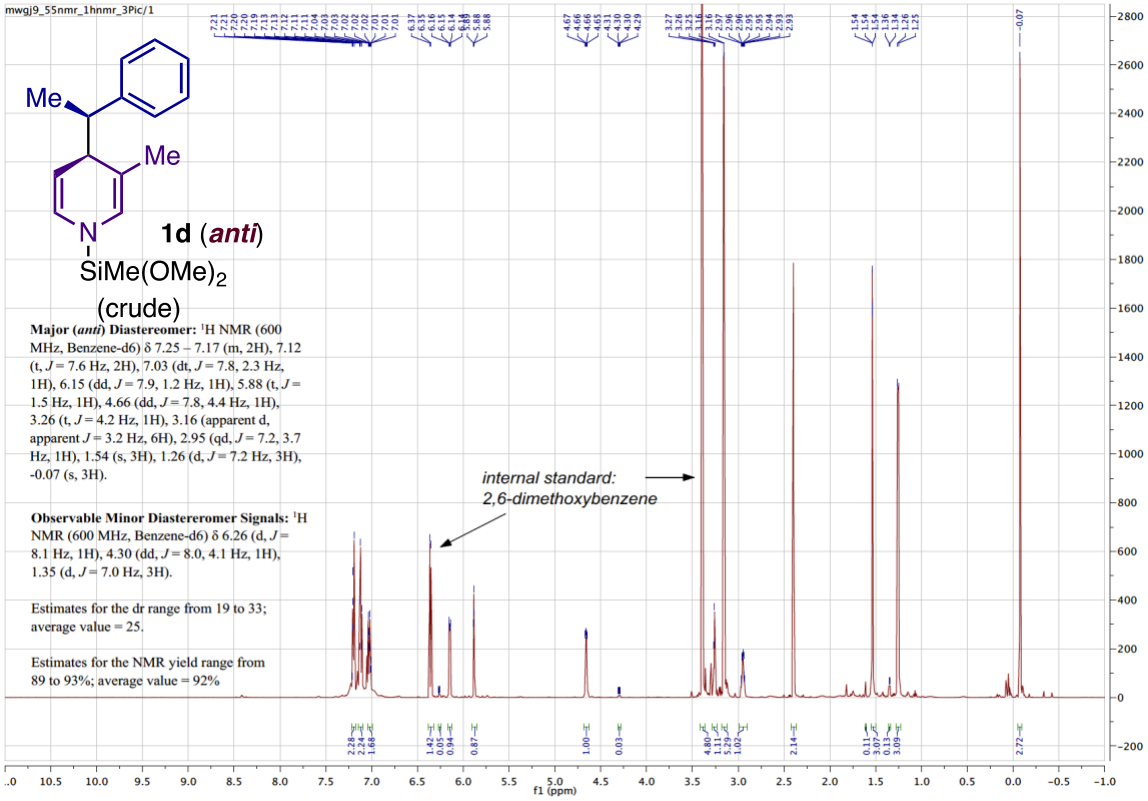
^{1}H NMR Spectrum of Crude 1a with 2,6-dimethoxytoluene Internal Standard



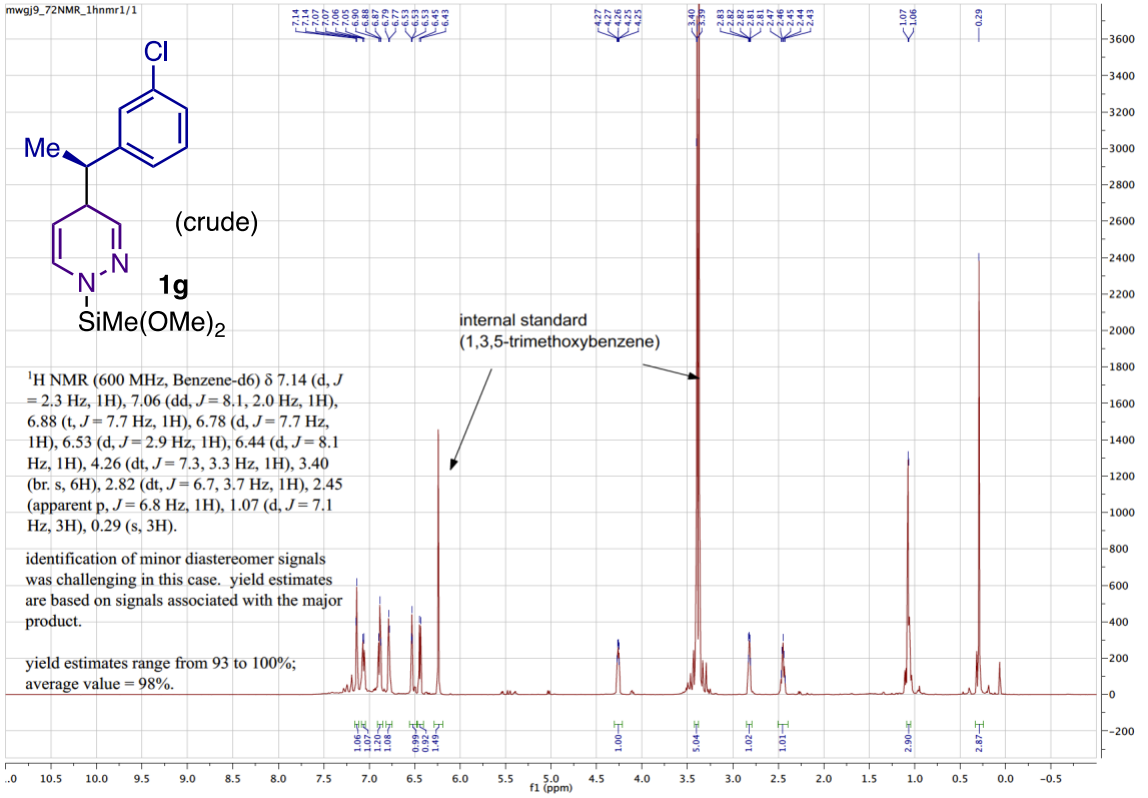
^{1}H NMR Spectrum of Crude 1a with 3,5-dimethoxy-1-chlorobenzene



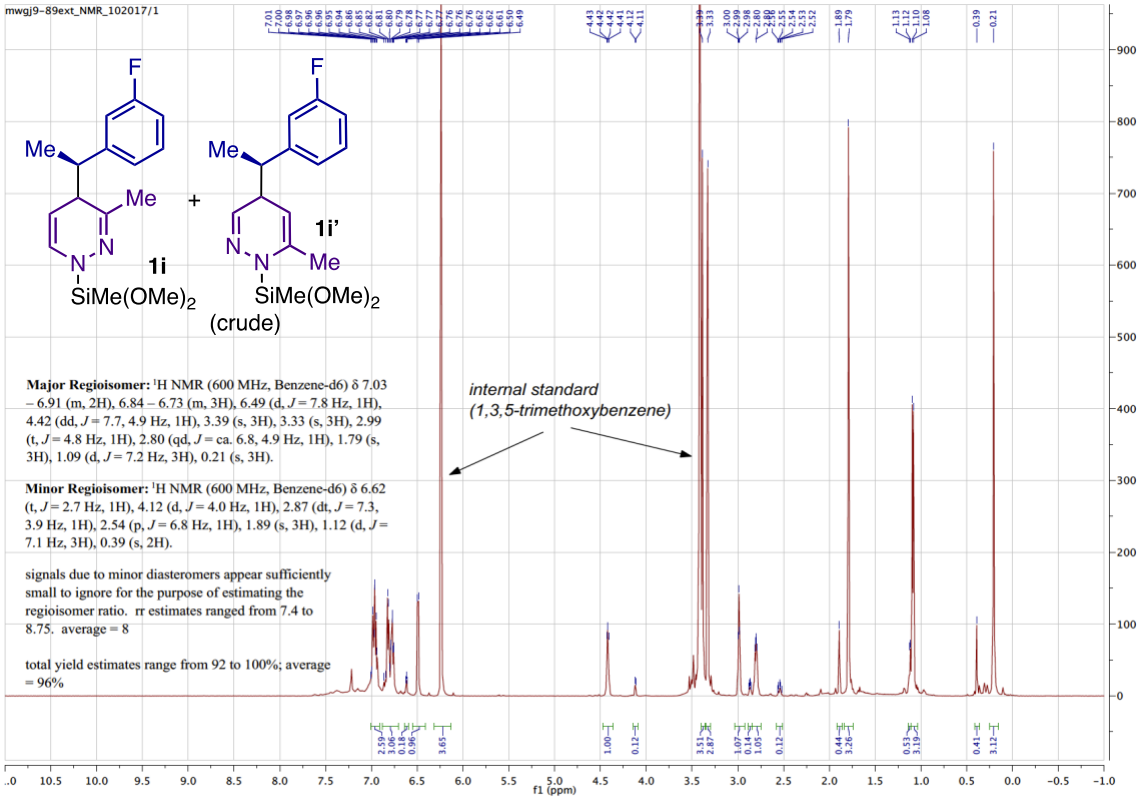
^{1}H NMR Spectrum of Crude 1d



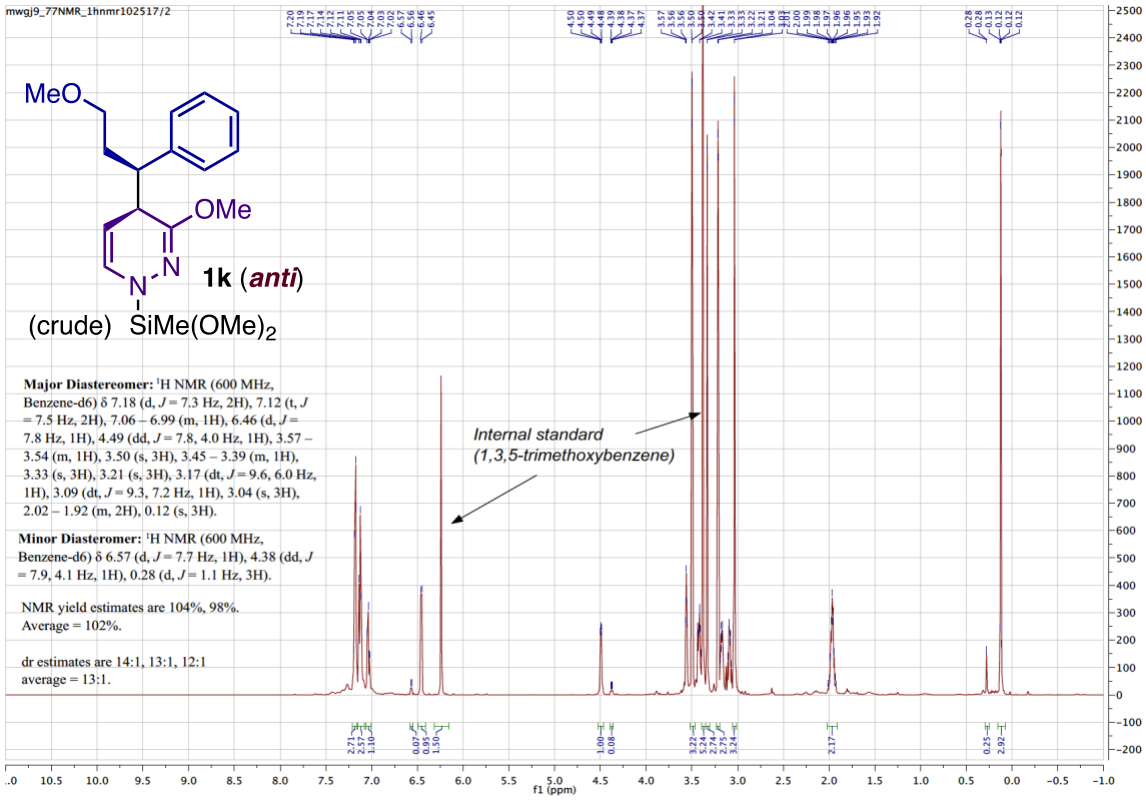
^{1}H NMR Spectrum of Crude 1g



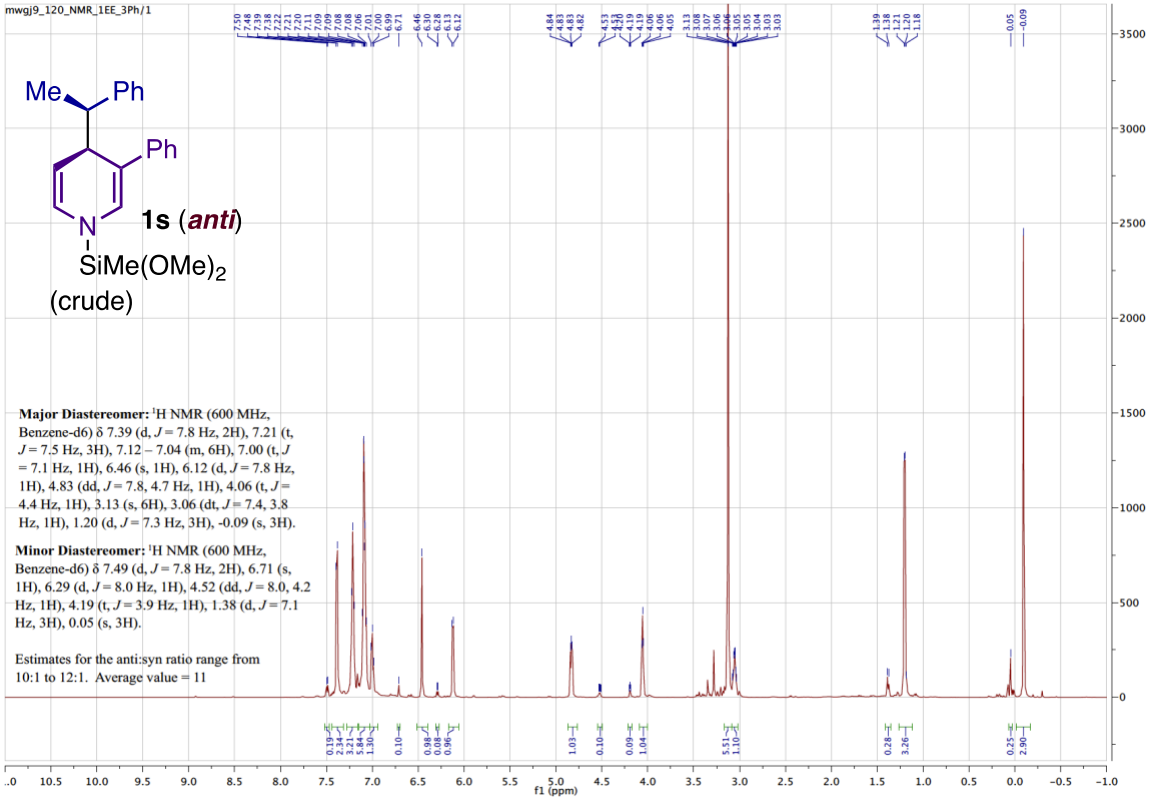
^{1}H NMR Spectrum of Crude 1i + 1i' (8:1 Mixture)



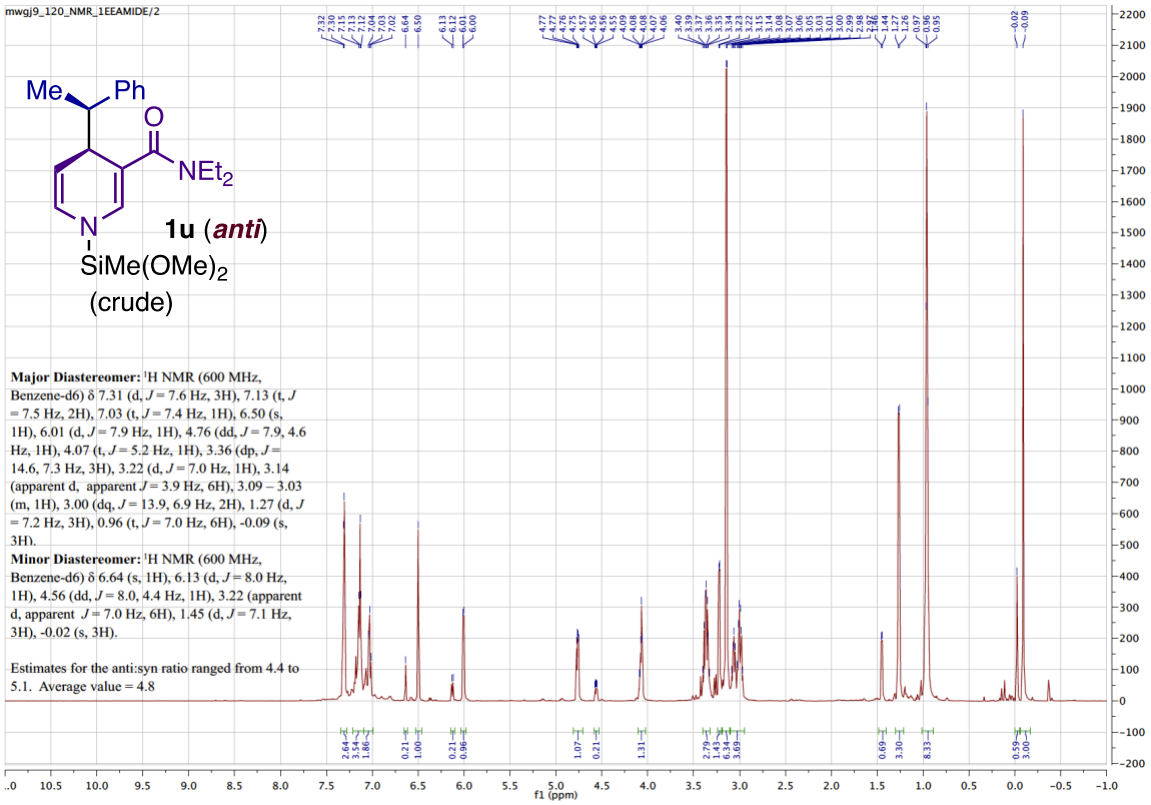
^{1}H NMR Spectrum of Crude 1k



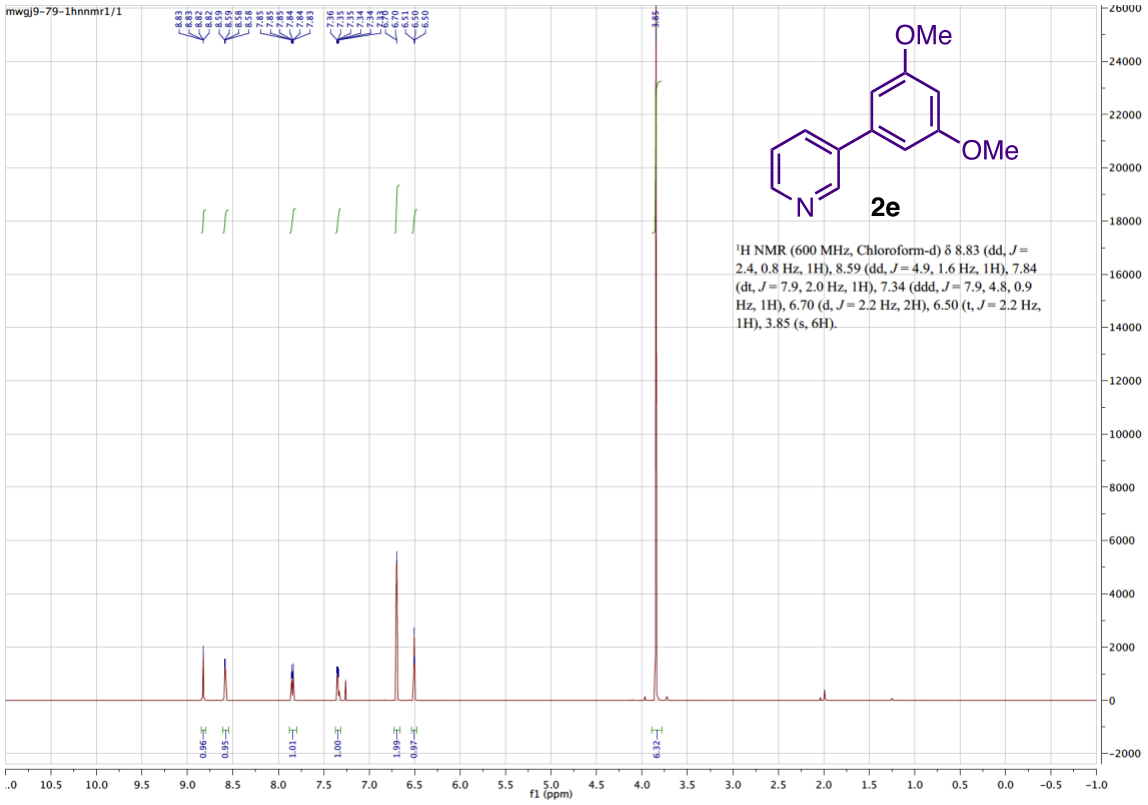
^{1}H NMR Spectrum of Crude 1s



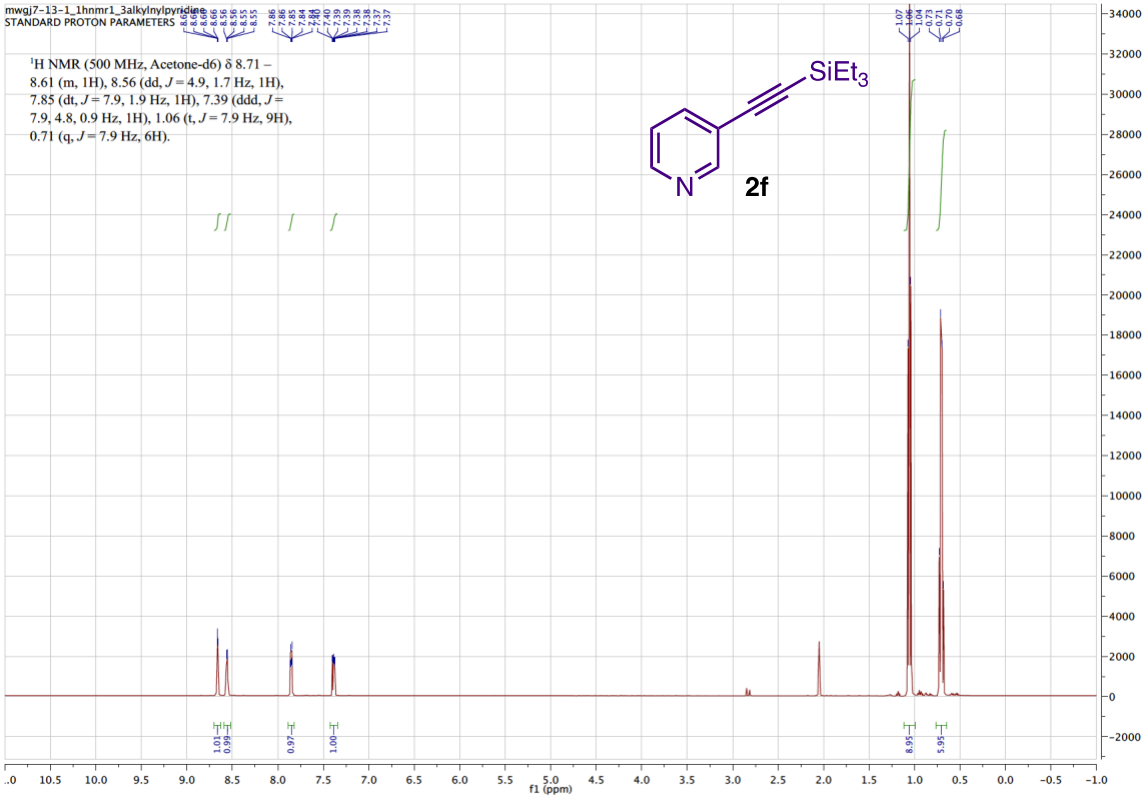
^{1}H NMR Spectrum of Crude 1u



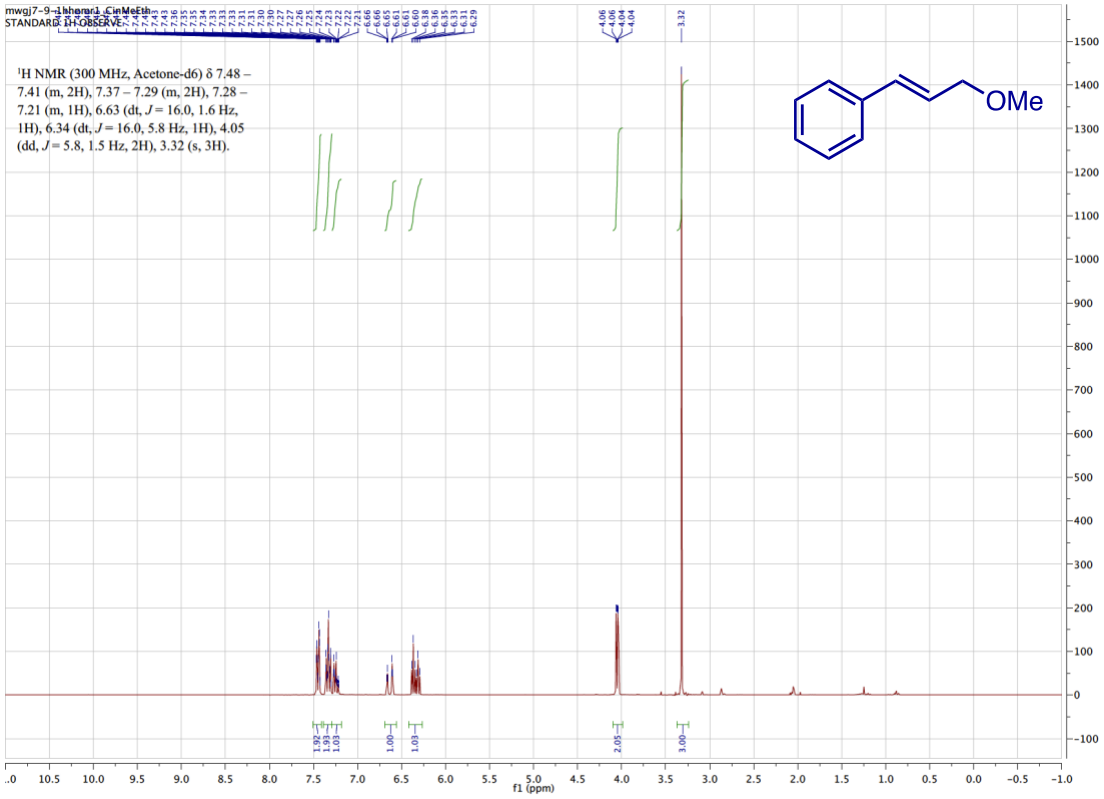
^{1}H NMR Spectrum of 2e



^{1}H NMR Spectrum of 2f

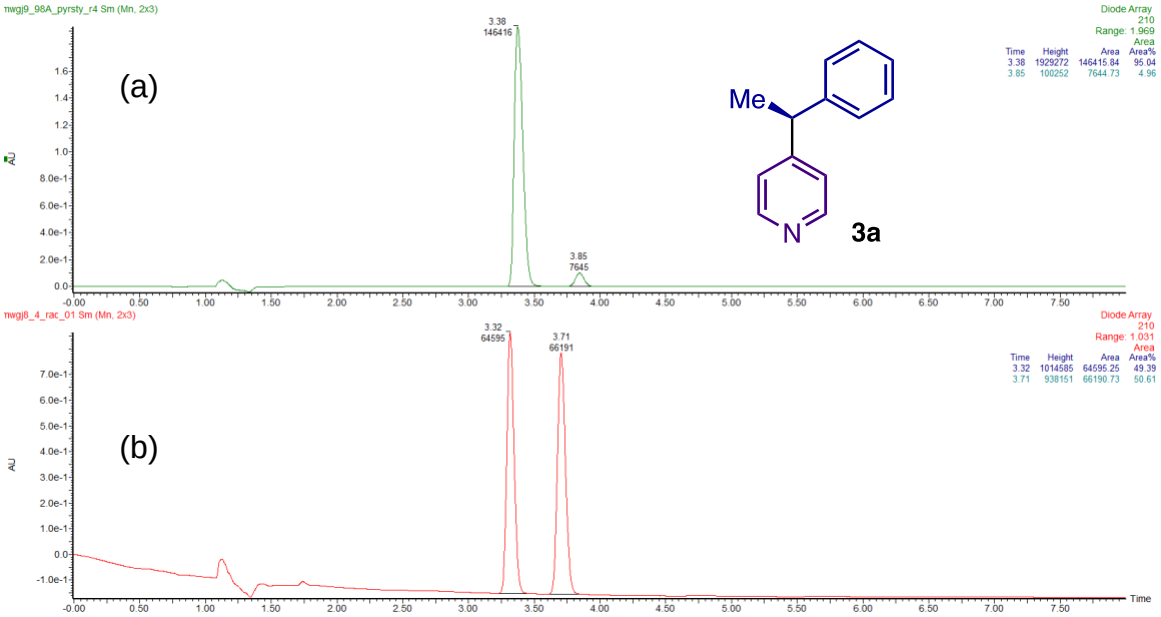


^{1}H NMR Spectrum of Cinnamyl Methyl Ether



6.2. Chiral SFC Chromatograms

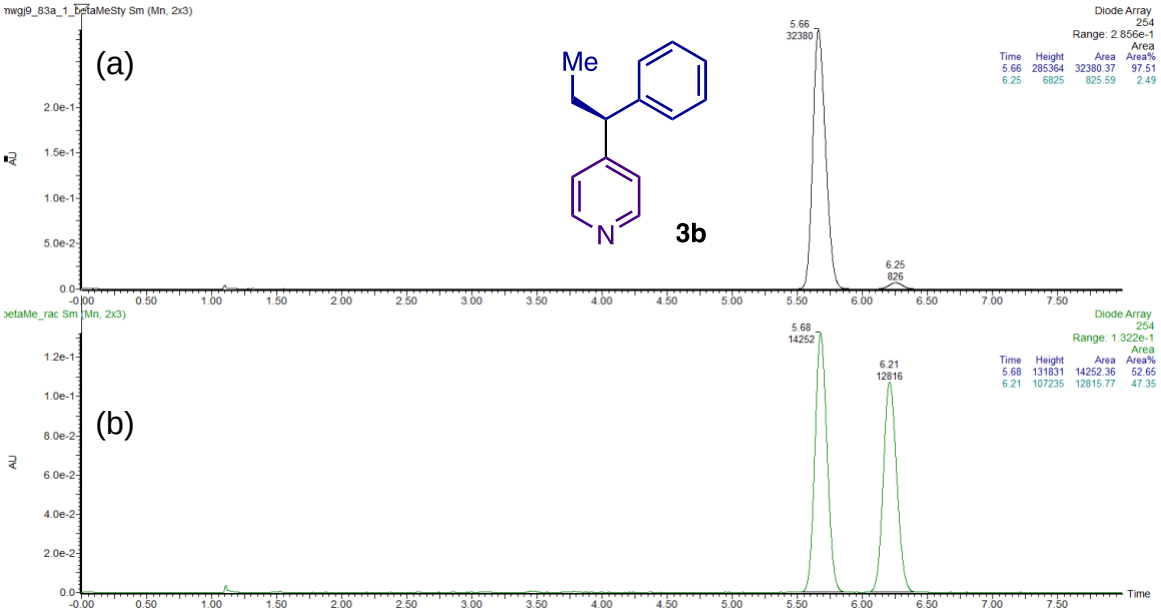
ee Determination for 3a



(a) t_M = 3.38 min, area% (210 nm) = 95.04
t_m = 3.85 min, area% (210 nm) = 4.96

(b) t_M = 3.32 min, area% (210 nm) = 49.39
t_m = 3.85 min, area% (210 nm) = 50.61

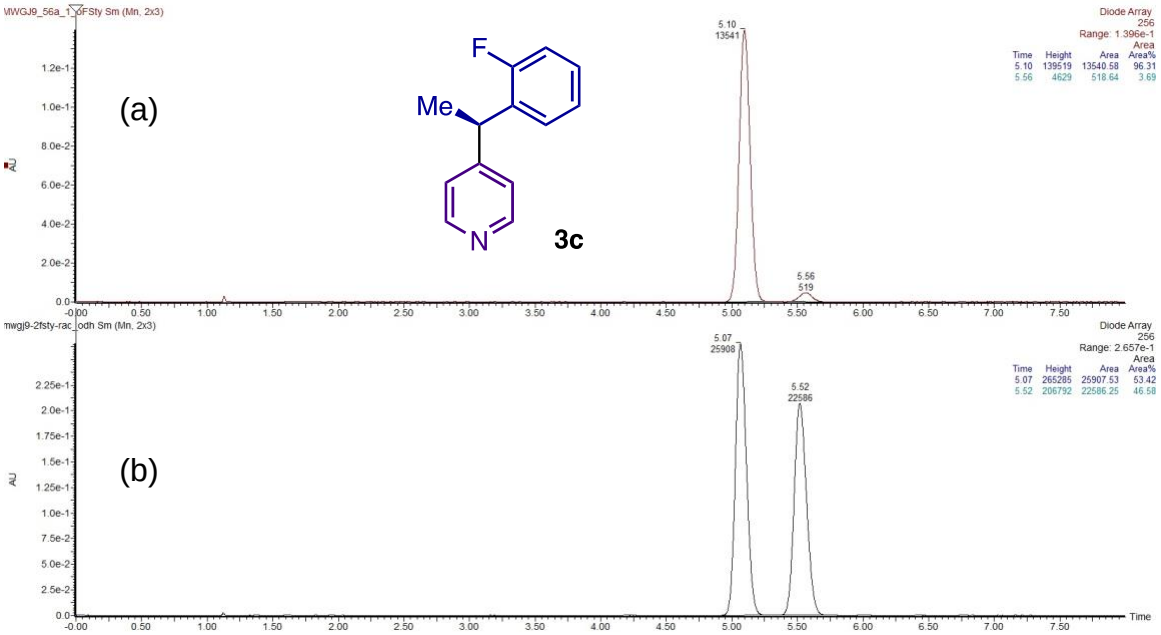
ee Determination for 3b



(a) t_M = 5.66 min, area% (254 nm) = 97.51
t_m = 6.25 min, area% (254 nm) = 2.49

(b) t_M = 5.68 min, area% (254 nm) = 52.65
t_m = 6.21 min, area% (254 nm) = 47.35

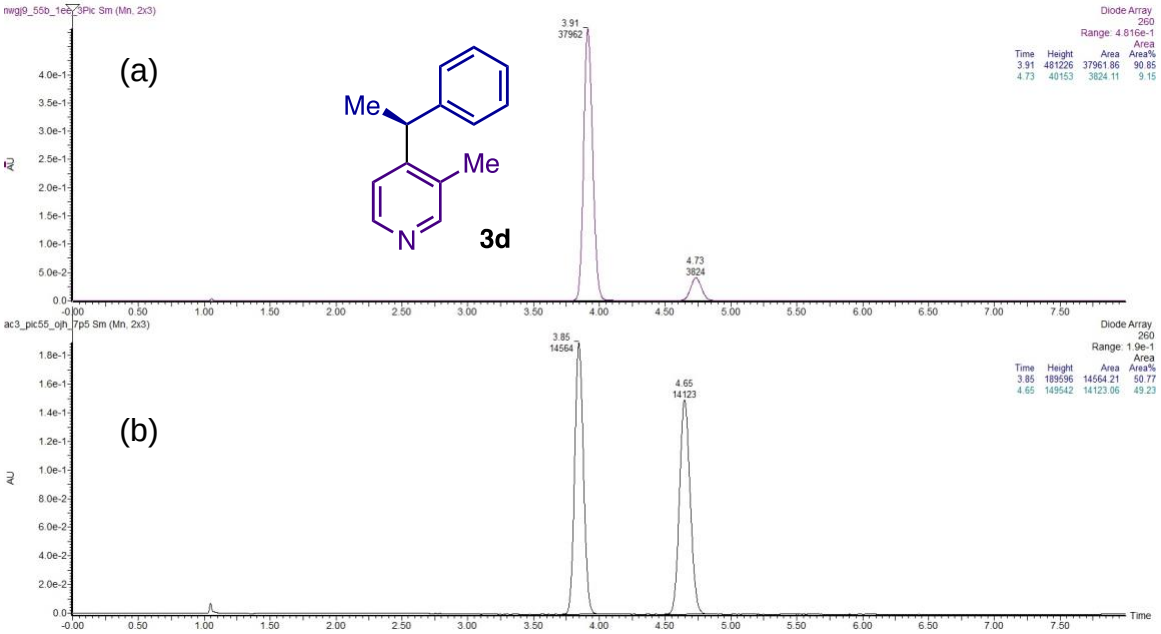
ee Determination for 3c



(a) t_M = 5.10 min, area% (256 nm) = 96.31
t_m = 5.56 min, area% (256 nm) = 3.69

(b) t_M = 5.07 min, area% (256 nm) = 53.42
t_m = 5.52 min, area% (256 nm) = 46.58

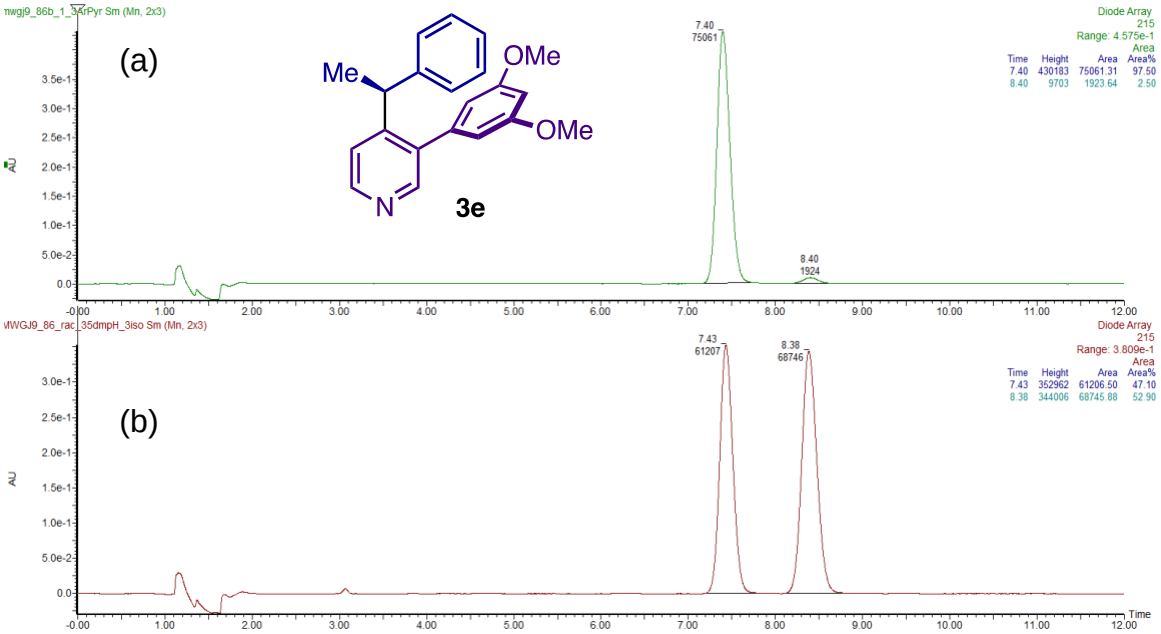
ee Determination for 3d



(a) t_M = 3.91 min, area% (260 nm) = 90.85
t_m = 4.73 min, area% (260 nm) = 9.15

(b) t_M = 5.07 min, area% (260 nm) = 50.77
t_m = 5.52 min, area% (260 nm) = 49.23

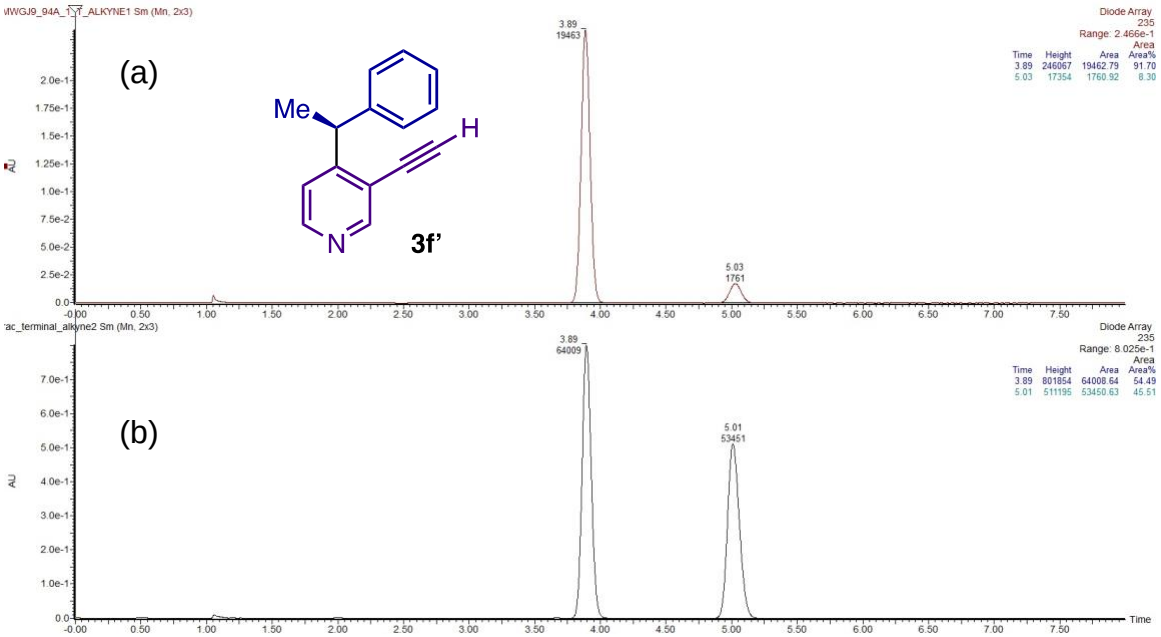
ee Determination for 3e



(a) t_M = 7.40 min, area% (215 nm) = 97.50
t_m = 8.40 min, area% (215 nm) = 2.50

(b) t_M = 7.43 min, area% (215 nm) = 47.10
t_m = 8.38 min, area% (215 nm) = 52.90

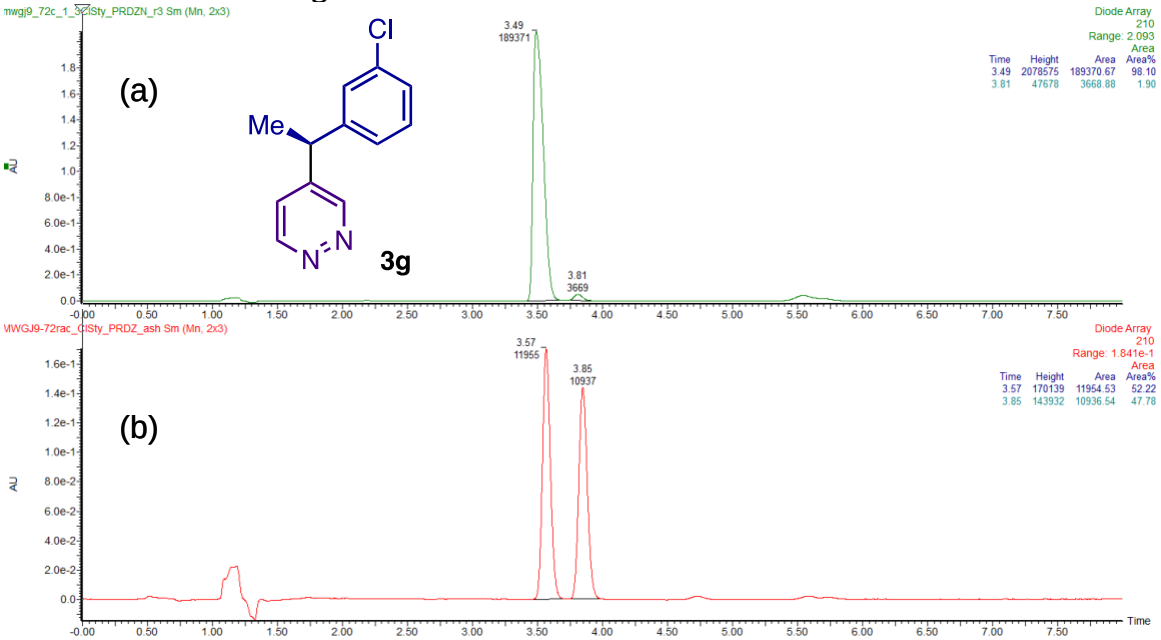
ee Determination for 3f'



(a) t_M = 3.89 min, area% (235 nm) = 91.70
t_m = 5.03 min, area% (235 nm) = 8.30

(b) t_M = 3.89 min, area% (235 nm) = 54.49
t_m = 5.01 min, area% (235 nm) = 45.51

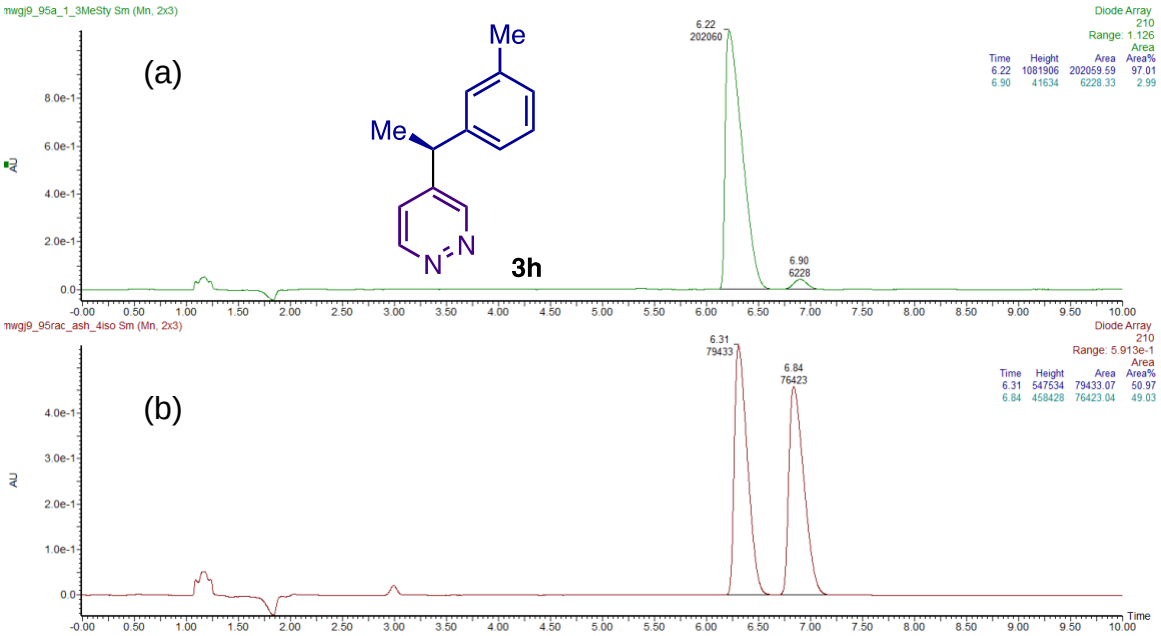
ee Determination for 3g



(a) t_M = 3.49 min, area% (210 nm) = 98.10
t_m = 3.81 min, area% (210 nm) = 1.90

(b) t_M = 3.57 min, area% (210 nm) = 52.22
t_m = 3.85 min, area% (210 nm) = 47.78

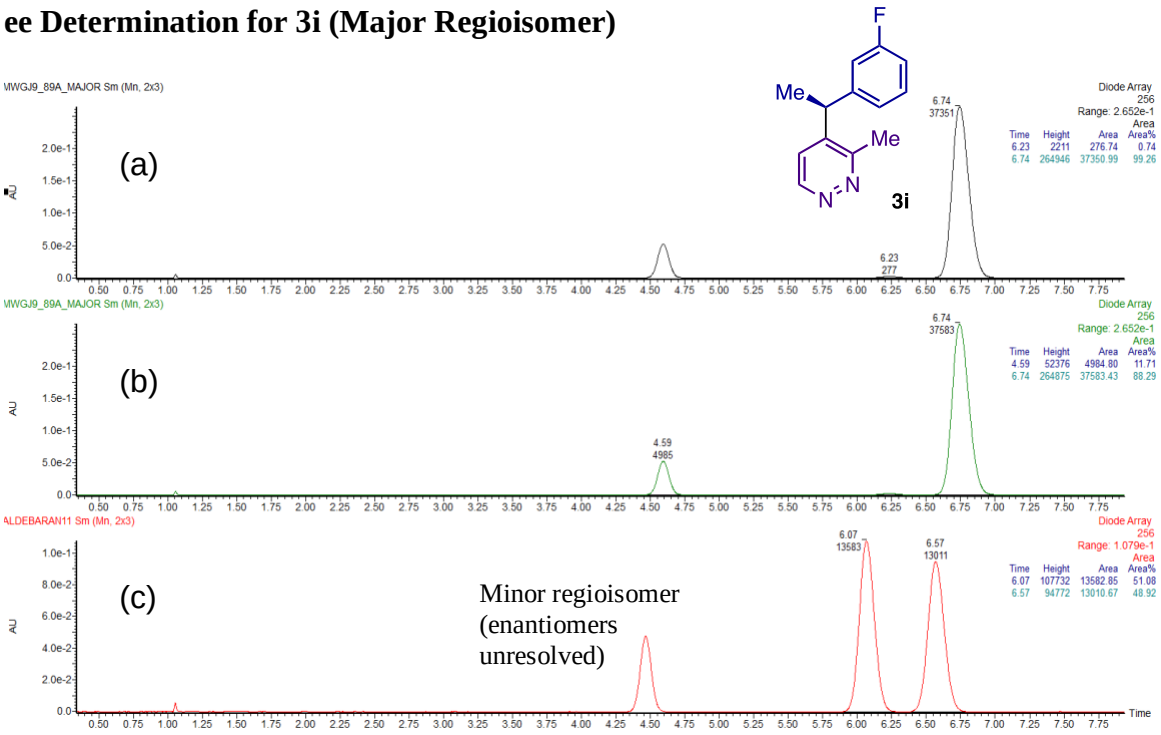
ee Determination for 3g



(a) t_M = 6.22 min, area% (210 nm) = 97.01
t_m = 6.90 min, area% (210 nm) = 2.99

(b) t_M = 6.31 min, area% (210 nm) = 50.97
t_m = 6.84 min, area% (210 nm) = 49.03

ee Determination for 3i (Major Regioisomer)

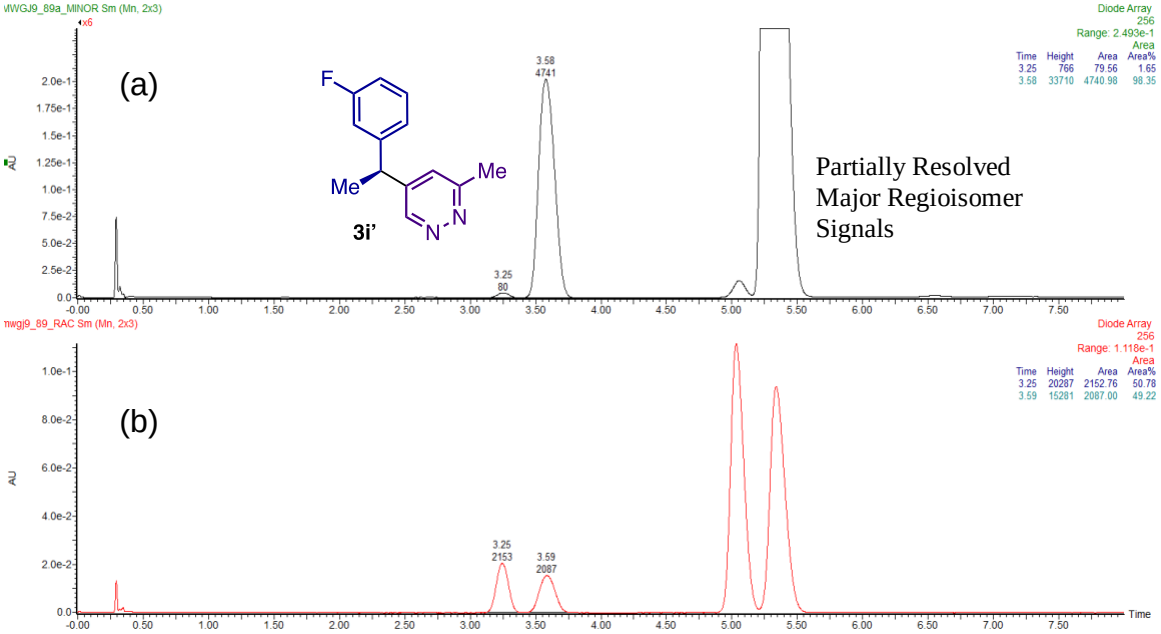


(a) t_M = 6.74 min, area% (256 nm) = 99.26
t_m = 6.23 min, area% (256 nm) = 0.74

(b) minor regioisomer (both enantiomers) area% (256 nm) = 11.71
major regioisomer (both enantiomers) area% (256 nm) = 88.29
(Regioisomer ratio = 7:1 assuming all isomers have the same extinction coefficient)

(c) t_M = 6.57 min, area% (256 nm) = 48.92
t_m = 6.05 min, area% (256 nm) = 51.08

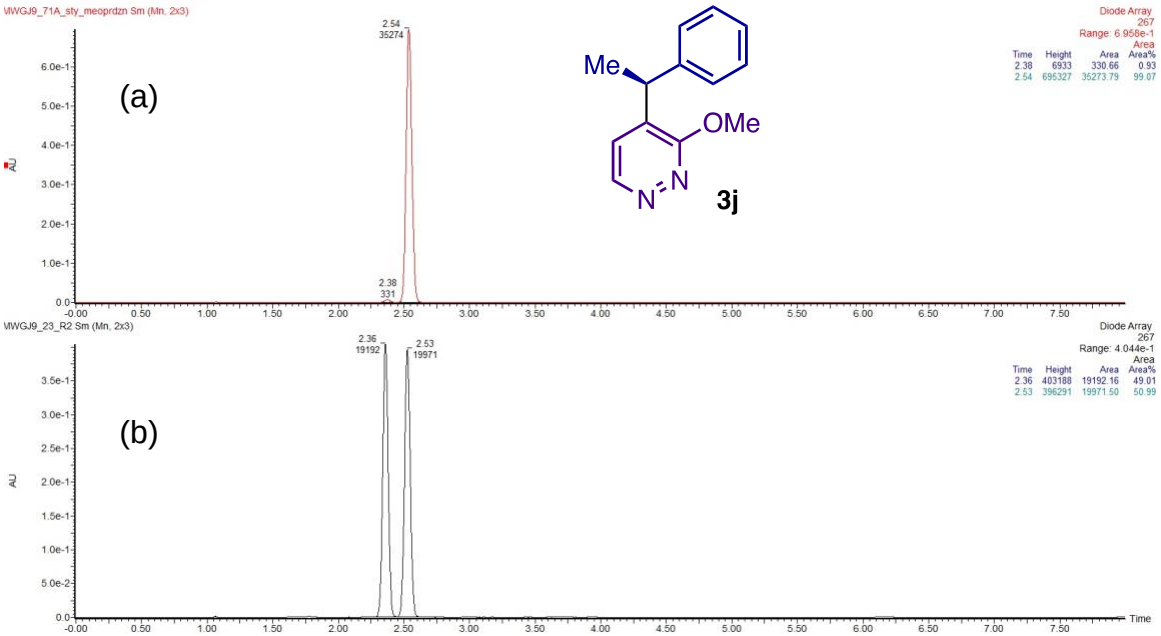
ee Determination for 3i' (Minor Regioisomer)



(a) t_M = 3.58 min, area% (256 nm) = 98.35
t_m = 3.25 min, area% (256 nm) = 1.65

(b) t_M = 3.59 min, area% (256 nm) = 49.22
t_m = 3.25 min, area% (256 nm) = 50.78

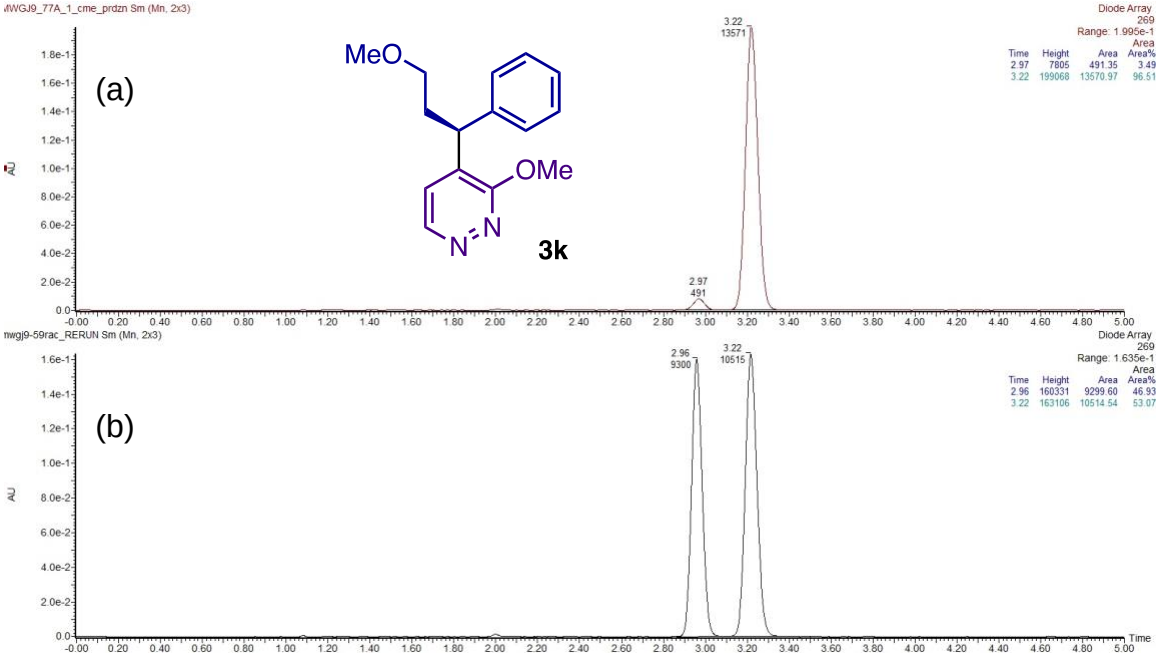
ee Determination for 3j



(a) t_M = 2.54 min, area% (267 nm) = 99.07
t_m = 2.38 min, area% (267 nm) = 0.93

(b) t_M = 3.59 min, area% (267 nm) = 50.99
t_m = 2.36 min, area% (267 nm) = 49.01

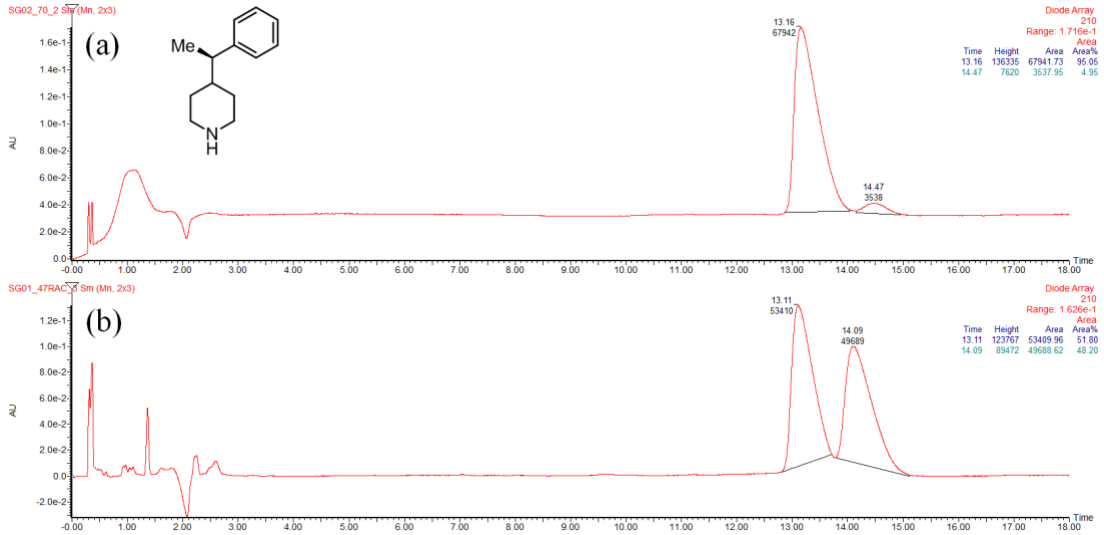
ee Determination for 3k



(a) t_M = 3.22 min, area% (267 nm) = 96.51
t_m = 2.97 min, area% (267 nm) = 3.49

(b) t_M = 3.22 min, area% (267 nm) = 53.07
t_m = 2.96 min, area% (267 nm) = 46.93

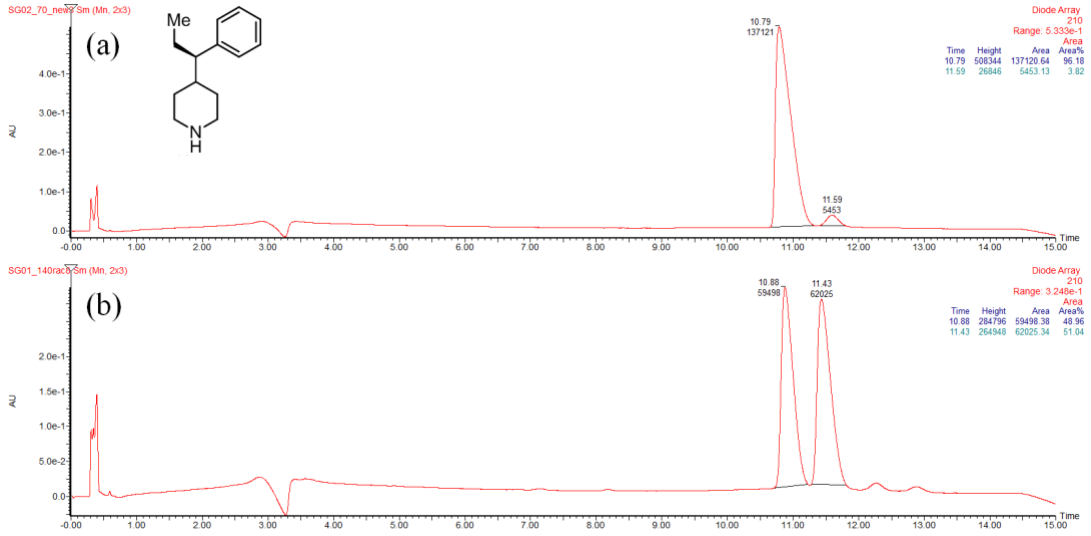
ee Determination for 4a



(a) t_M = 13.16 min, area% (210 nm) = 95.05
t_m = 14.47 min, area% (210 nm) = 4.95

(b) t_M = 13.11 min, area% (210 nm) = 51.80
t_m = 14.09 min, area% (210 nm) = 48.20

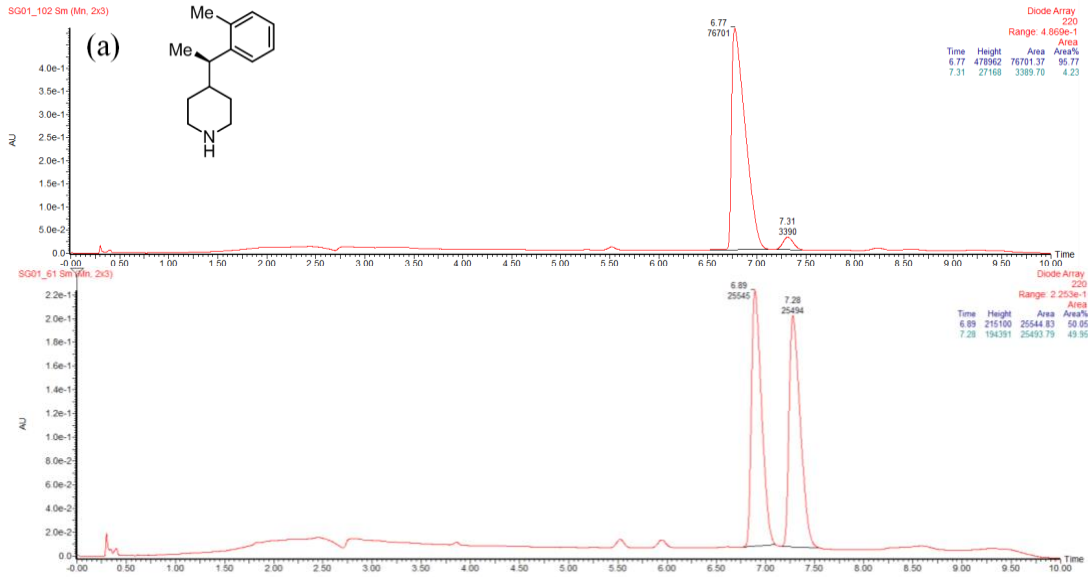
ee Determination for 4b



(a) t_M = 10.79 min, area% (210 nm) = 96.18
t_m = 11.59 min, area% (210 nm) = 3.82

(b) t_M = 10.88 min, area% (210 nm) = 48.96
t_m = 11.43 min, area% (210 nm) = 51.04

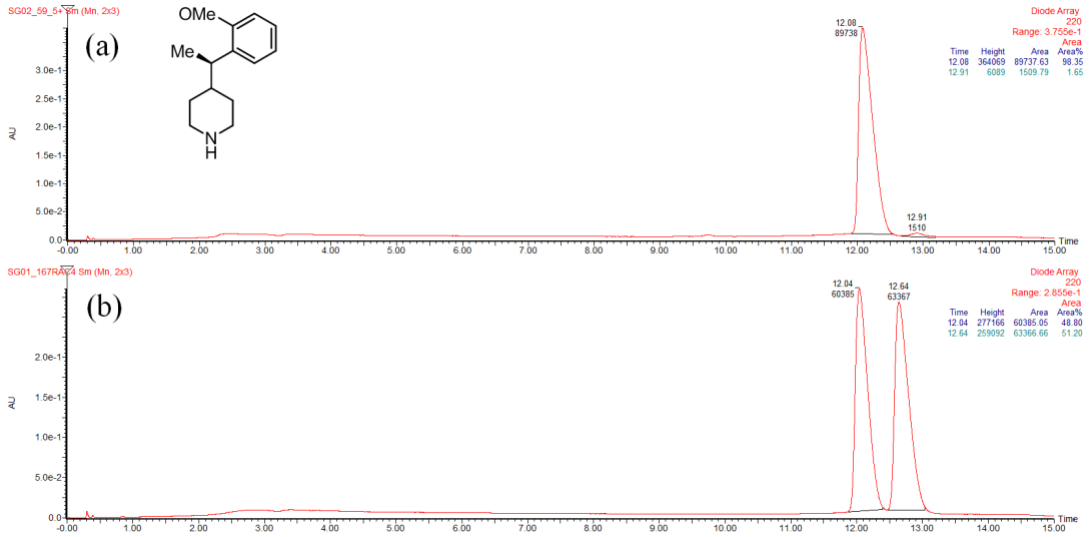
ee Determination for 4l



(a) t_M = 6.77 min, area% (220 nm) = 95.77
t_m = 7.31 min, area% (220 nm) = 4.23

(b) t_M = 6.89 min, area% (220 nm) = 50.02
t_m = 7.28 min, area% (220 nm) = 49.98

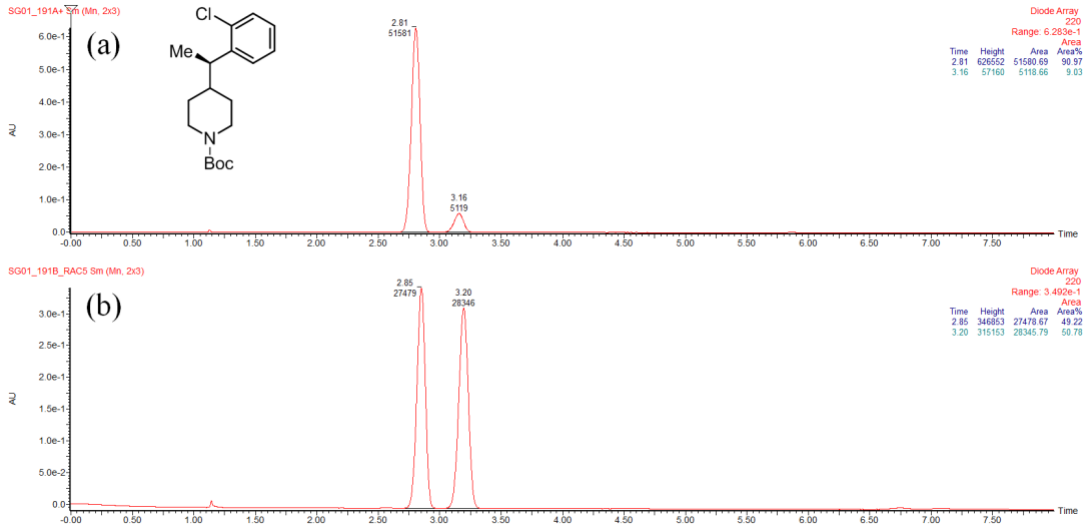
ee Determination for 4m



(a) t_M = 12.08 min, area% (220 nm) = 98.35
t_m = 12.91 min, area% (220 nm) = 1.65

(b) t_M = 12.04 min, area% (220 nm) = 48.80
t_m = 12.64 min, area% (220 nm) = 51.20

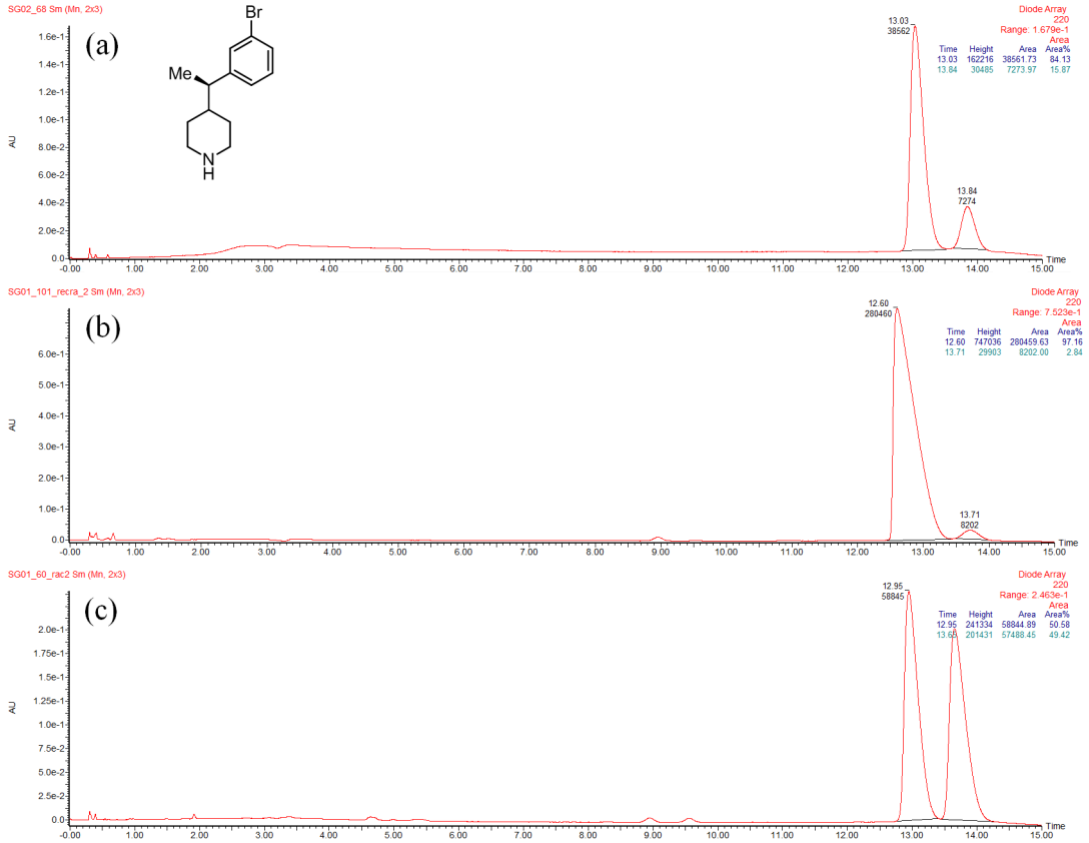
ee Determination for 4n'



(a) t_M = 2.81 min, area% (220 nm) = 90.97
t_m = 3.16 min, area% (220 nm) = 9.03

(b) t_M = 2.85 min, area% (220 nm) = 49.22
t_m = 3.20 min, area% (220 nm) = 50.78

ee Determination for 4o

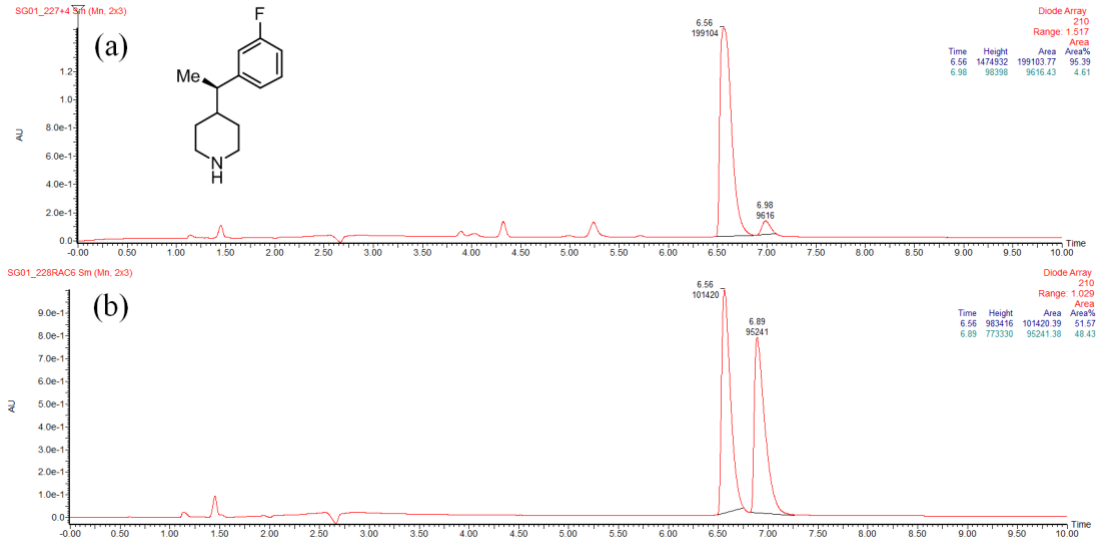


(a) t_M = 13.03 min, area% (220 nm) = 84.13
t_m = 13.84 min, area% (220 nm) = 15.87

(b) *After Recrystallization*
t_M = 12.60 min, area% (220 nm) = 97.16
t_m = 13.71 min, area% (220 nm) = 2.84

Racemate
(c) t_M = 12.95 min, area% (220 nm) = 50.58
t_m = 13.65 min, area% (220 nm) = 49.42

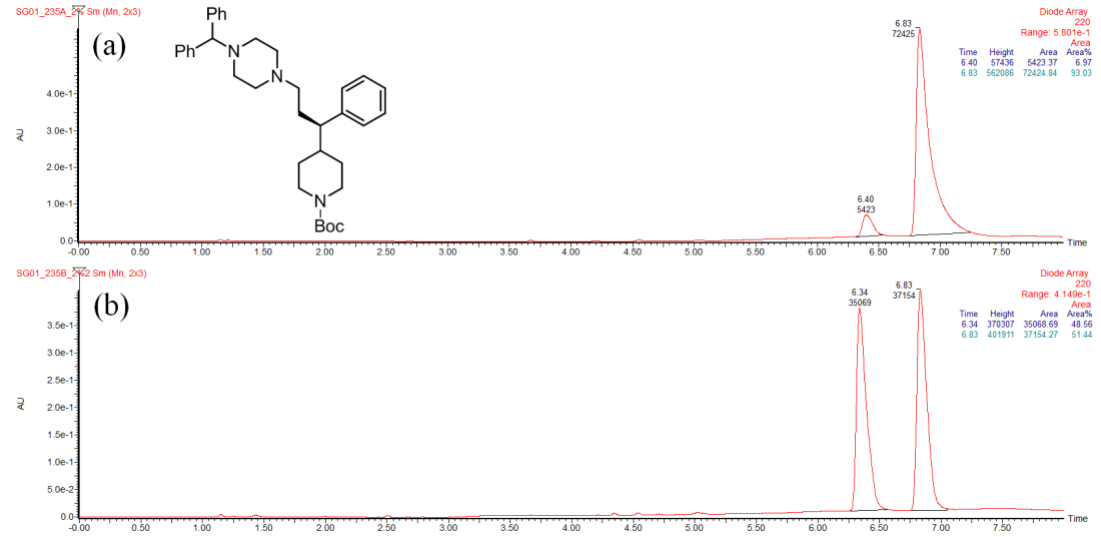
ee Determination for 4p



(a) t_M = 6.56 min, area% (210 nm) = 95.39
t_m = 6.98 min, area% (210 nm) = 4.61

(b) t_M = 6.56 min, area% (210 nm) = 51.57
t_m = 6.89 min, area% (210 nm) = 48.43

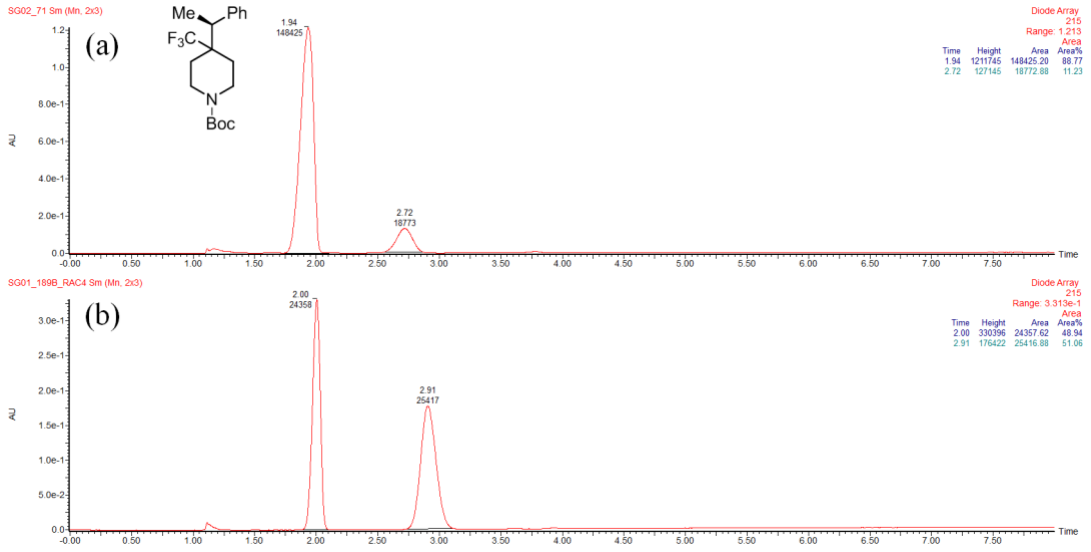
ee Determination for 4q'



(a) t_M = 6.83 min, area% (220 nm) = 93.03
t_m = 6.40 min, area% (220 nm) = 6.97

(b) t_M = 6.83 min, area% (220 nm) = 51.44
t_m = 6.34 min, area% (220 nm) = 48.56

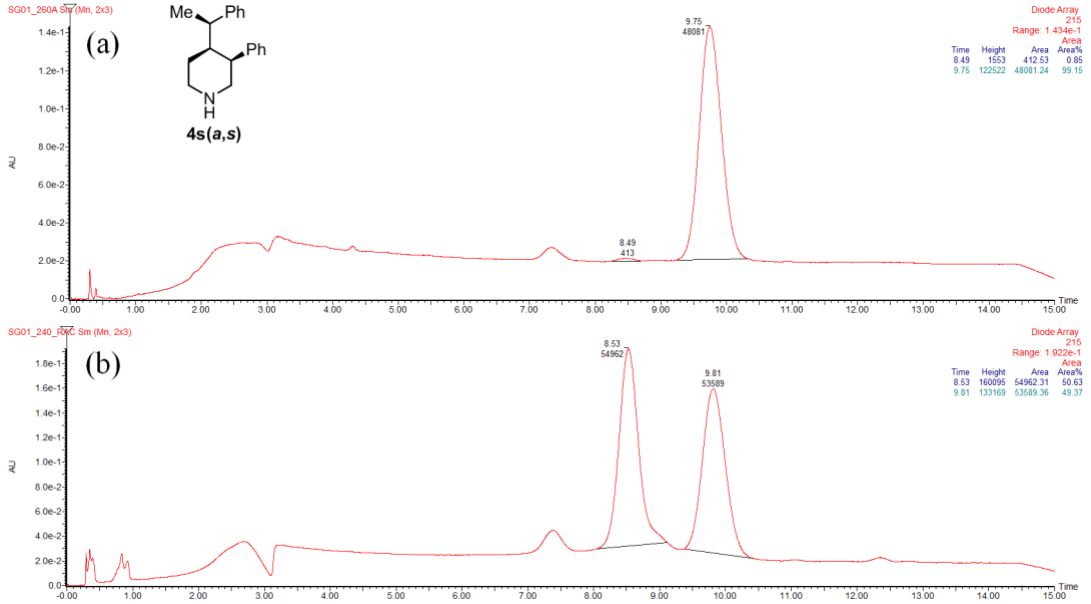
ee Determination for 4r'



(a) t_M = 1.94 min, area% (215 nm) = 88.77
t_m = 2.72 min, area% (215 nm) = 11.23

(b) t_M = 2.00 min, area% (215 nm) = 48.94
t_m = 2.91 min, area% (215 nm) = 51.06

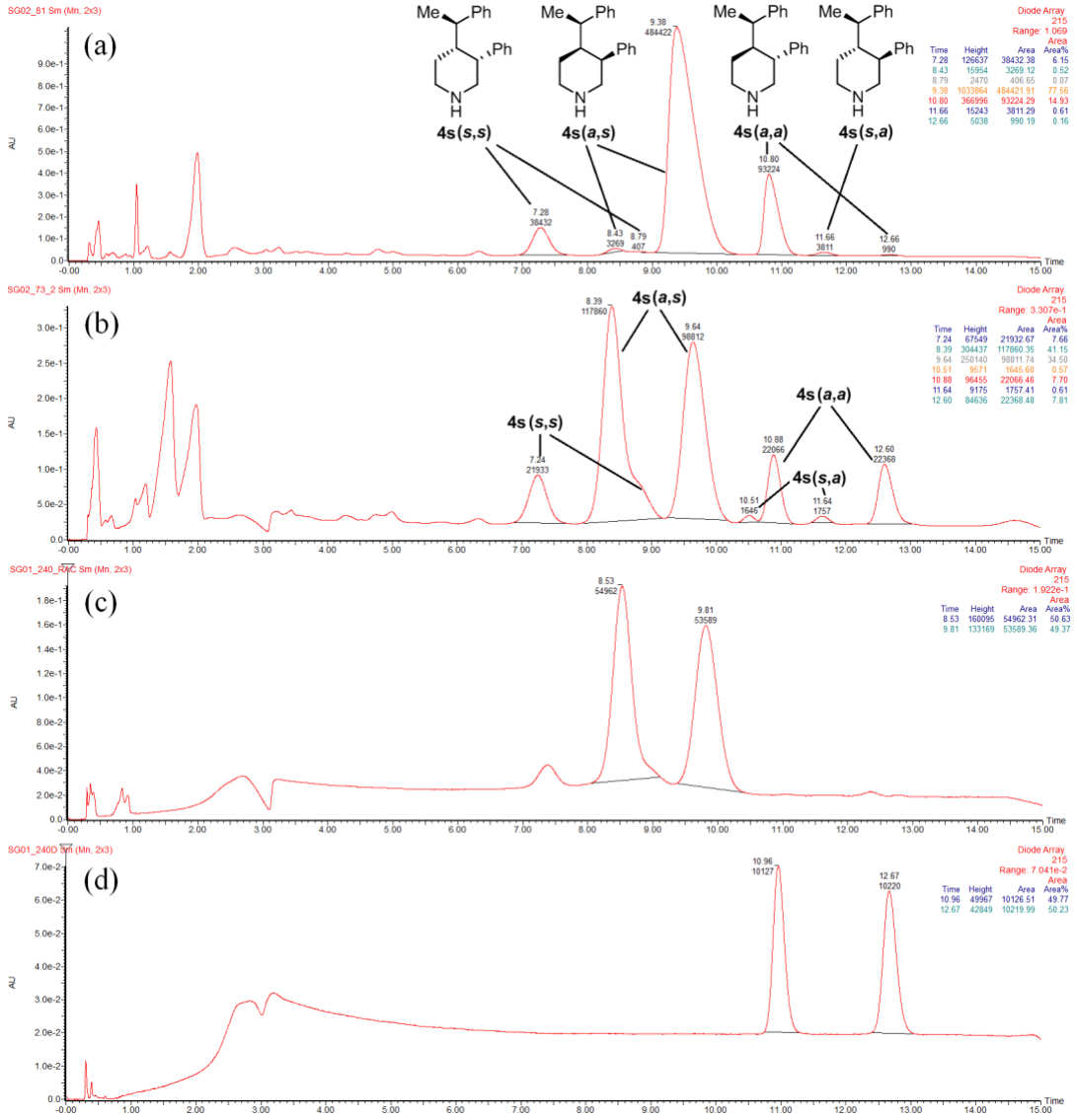
ee Determination for 4s (a,s)



(a) t_M = 9.75 min, area% (215 nm) = 99.15
t_m = 8.49 min, area% (215 nm) = 0.85

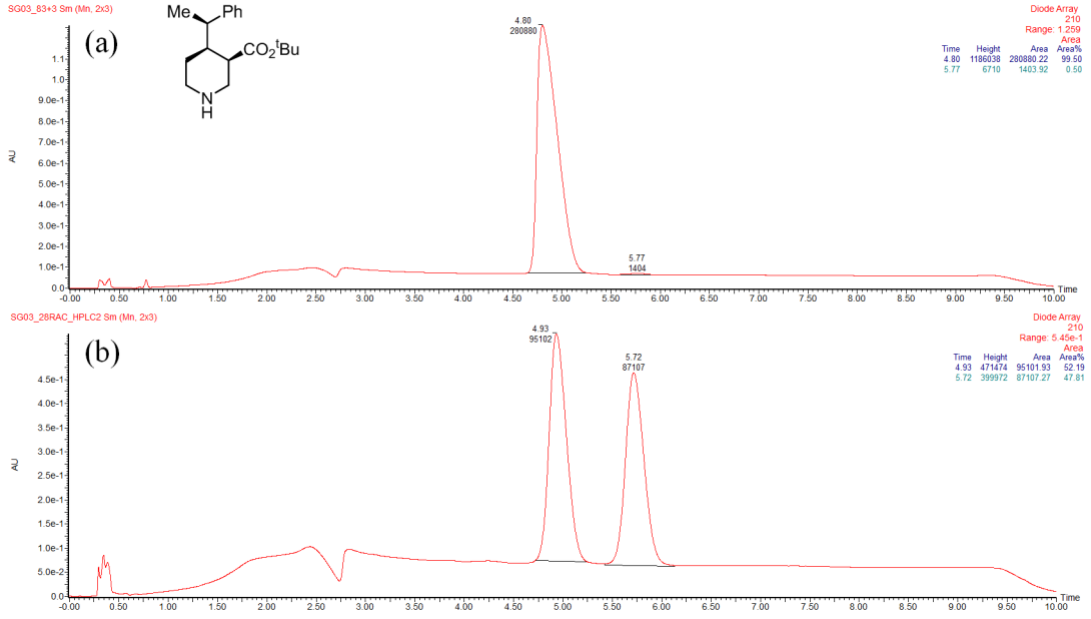
(b) t_M = 9.81 min, area% (215 nm) = 49.37
t_m = 8.53 min, area% (215 nm) = 50.63

dr Determination of Crude 4s



(a) the crude product obtained with (*S*,*S*)-Ph-BPE (after workup)
4s (a,s): t_M = 9.38, t_m = 8.43; area% (215 nm) = 78.08
4s (a,a): t_M = 10.80, t_m = 12.66; area% (215 nm) = 15.09
4s (s,s): t_M = 7.28, t_m = 8.79; area% (215 nm) = 6.22
4s (s,a): t_M = 11.66; area% (215 nm) = 0.61
dr = 12.6 : 1 : 2.4 : 0.1 (***a***,***s***):(***s***,***s***):(***a***,***a***):(***s***,***a***)
(b) the crude obtained with racemic Ph-BPE
(c) racemate of **4s (a,s)**
(d) racemate of **4s (a,a)**

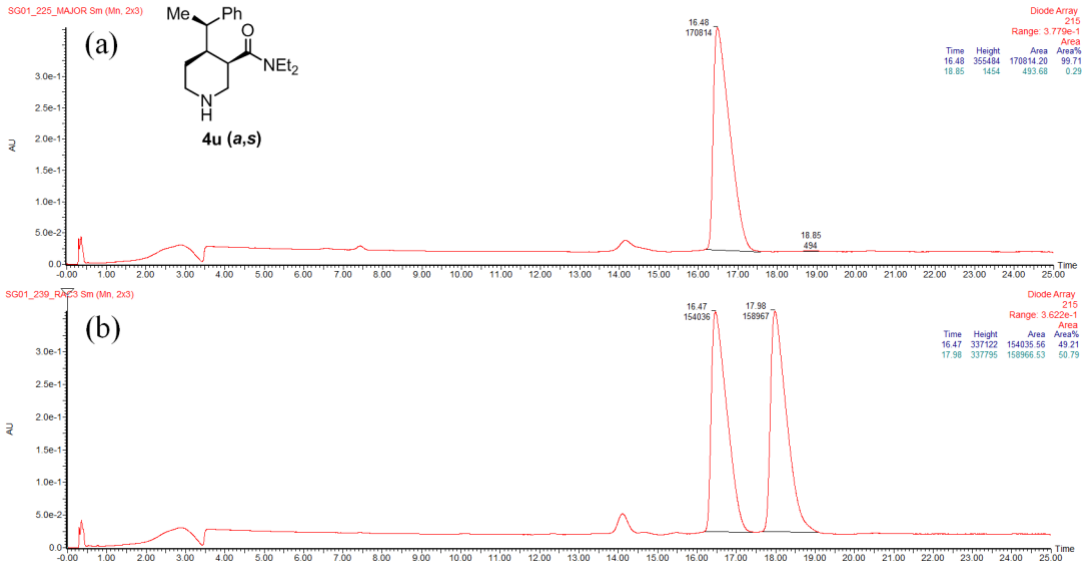
ee Determination for 4t (a,s)



(a) t_M = 4.80 min, area% (210 nm) = 99.50
t_m = 5.77 min, area% (210 nm) = 0.50

(b) t_M = 4.93 min, area% (210 nm) = 52.19
t_m = 5.72 min, area% (210 nm) = 47.81

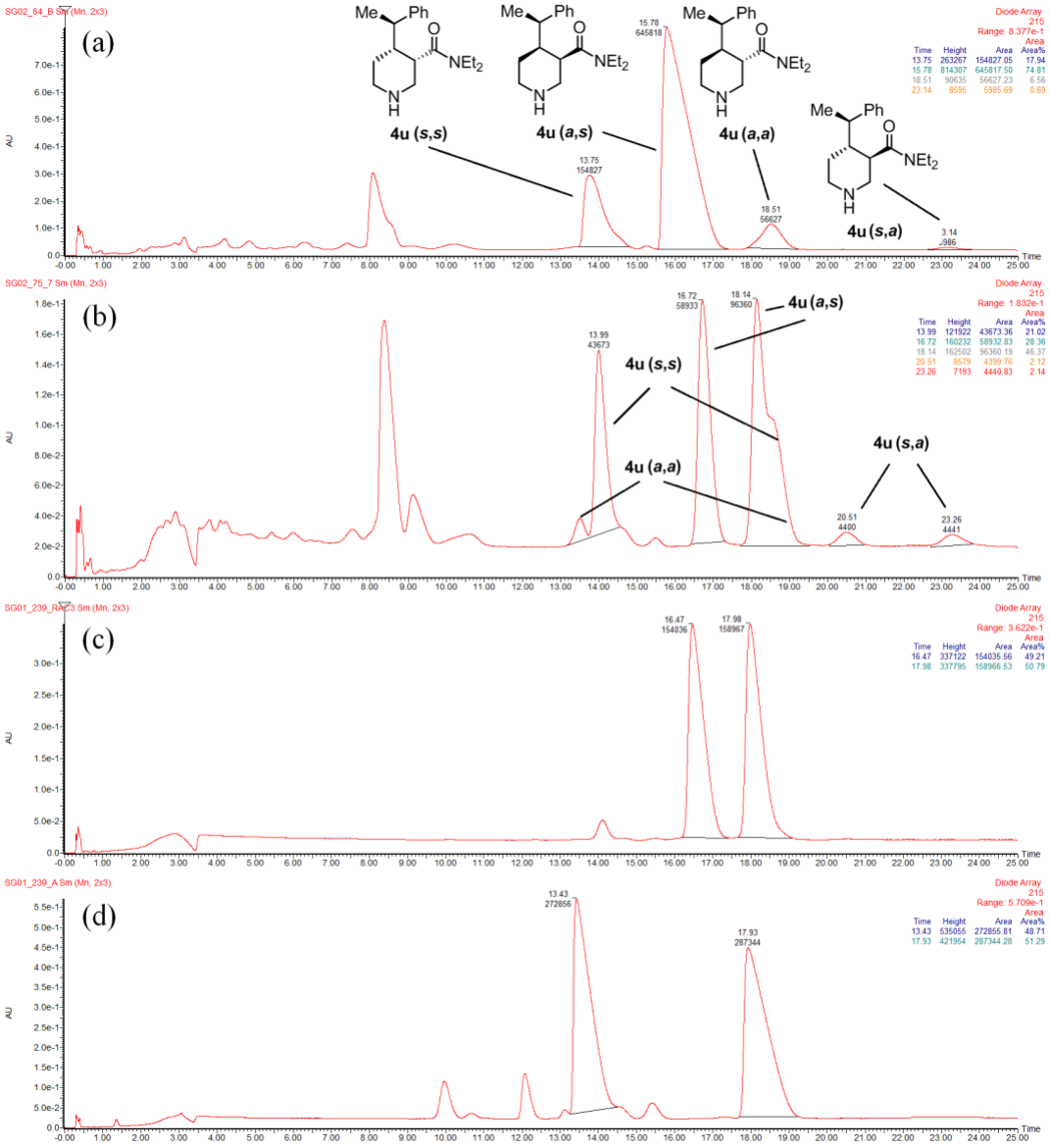
ee Determination for 4u (a,s)



(a) t_M = 16.48 min, area% (215 nm) = 99.71
t_m = 18.85 min, area% (215 nm) = 0.29

(b) t_M = 16.47 min, area% (215 nm) = 49.21
t_m = 17.98 min, area% (215 nm) = 50.79

dr Determination of Crude 4u



(a) the crude product obtained with (*S*,*S*)-Ph-BPE
4u (a,s) : t_M = 15.78, area% (215 nm) = 74.81
4u (a,a) : t_M = 10.80, area% (215 nm) = 6.56
4u (s,s) : t_M = 18.51, area% (215 nm) = 17.94
4u (s,a) : t_M = 23.14; area% (215 nm) = 0.69
dr = 11.4 : 2.7 : 1 : 0.11 (***a*,*s***):(***s*,*s***):(***a*,*a***):(***s*,*a***)
(b) the crude product obtained with racemic Ph-BPE
(c) racemate of **4u (a,s)**
(d) racemate of **4u (s,s)**