

Convenient Lanthanum-Mediated Synthesis of Bulky *tert*-Alkyl Amines from Nitriles

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General Experimental Considerations

Reactions were run under nitrogen in an IT Glove box, using oven-dried glassware or scintillation vials and stir bars unless otherwise specified. All reactions were conducted at ambient temperature. ^1H , ^{13}C , and ^{31}F NMR data were collected at 300K on a Bruker AV-500 or AV-400 NMR spectrometer in CDCl_3 using standard NMR tubes and caps. ^1H NMR spectra are referenced to tetramethylsilane ($\text{Si}(\text{CH}_3)_4 = 0.00$ ppm) standard in the CDCl_3 NMR solvent. ^{13}C NMR spectra are referenced to the central CDCl_3 peak (77.16 ppm). Mass spectrometric data were acquired by Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University).

Solvents

Diethyl ether for product work-ups and chromatography was purchased as ACS grade from Fisher, and was used as is. Diethyl ether for reactions was purchased as anhydrous ACS grade from Sigma Aldrich, and stored over activated 3\AA molecular sieves under nitrogen.

2-Methyltetrahydrofuran was purchased from Sigma-Aldrich in a Sure/seal® bottle (anhydrous, catalogue number 155810).

Tetrahydrofuran was purchased as anhydrous >99% ACS grade from Sigma Aldrich and stored over 3\AA molecular sieves under nitrogen.

Toluene was purchased from Sigma-Aldrich in a Sure/seal® bottle (anhydrous, catalogue number 244511).

Trifluorotoluene was purchased from Sigma-Aldrich in a Sure/seal® bottle (anhydrous, catalogue number 547948). Trifluorotoluene was stored over activated 3\AA molecular sieves under nitrogen.

Reagents

2-Fluoroisonicotinonitrile, 3-isoquinolinecarbonitrile, 3-thiophenecarbonitrile, benzo[b]thiophene-3-carbonitrile were purchased from AmBeed and used directly as received.

4-(Trifluoromethyl)benzonitrile, 4-methoxybenzonitrile were purchased from Oakwood Chemical and used directly as received.

Benzonitrile, 2-pyridinecarbonitrile, α,α,α -trifluoro-*m*-tolunitrile, ethylmagnesium bromide solution in diethyl ether (3.0 M), propylmagnesium chloride solution in diethyl ether (2.0 M), and lanthanum (III) chloride bis(lithium chloride) complex solution in tetrahydrofuran were purchased from Sigma-Aldrich and used directly as received.

3-Methoxybenzonitrile was prepared by K&K Laboratories and obtained from Dalhousie's Legacy Chemical Program. Purity was verified by Nuclear Magnetic Resonance spectroscopy before use.

2-Naphthonitrile, thiophene-2-carbonitrile, 3-phenylpropionitrile, 4-phenylbenzonitrile were purchased from Combi-Blocks and used directly as received.

X-Ray Crystallography

The crystal chosen was attached to the tip of a MicroLoop with paratone-N oil. Measurements were made on a Bruker D8 VENTURE diffractometer equipped with a PHOTON III CMOS detector using monochromated Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$) for hydrate 1 and Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$) for hydrate 2 from Incoatec microfocus sealed tubes at 150 K [1]. The initial orientation and unit cell were indexed using a least-squares analysis of the reflections collected from a complete 180° phi-scan, 5 seconds per frame and 1° per frame. For data collection, a strategy was calculated to maximize data completeness and multiplicity, in a reasonable amount of time, and then implemented using the Bruker Apex 4 software suite [1]. The data were collected with 40 sec (0.5° per frame) for hydrate 1 and 20 second (0.50°) frame times for hydrate 2; the crystal to detector distance was set to 4 cm. Cell refinement and data reduction were performed with the Bruker SAINT [2] software, which corrects for beam inhomogeneity, possible crystal decay, and Lorentz and polarisation effects. A multi-scan absorption correction was applied in each case (SADABS [3]). The structures were solved using SHELXT-2014 [4] and were refined using a full-matrix least-squares method on F^2 with SHELXL-2019 [4]. The refinements were unremarkable. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms bonded to carbon were included at geometrically idealized positions and were allowed to ride on the atoms to which they were bonded. The isotropic thermal parameters of these hydrogen atoms were fixed at $1.2U_{\text{eq}}$ of the parent carbon atom or $1.5 U_{\text{eq}}$ for hydrogen atoms in methyl groups. The positions of the hydrogen atoms bonded to oxygen in the water molecules and to nitrogen in the cations were located in a near final difference Fourier map. They were added to the atom list and refined with $U_{\text{iso}}\text{H}$ equal to $-1.5 U_{\text{eq}}\text{O/N}$, with restraints placed on their geometries to keep them reasonable.

Deposition Numbers 2394325 (hydrate 1) and 2394326 (hydrate 2) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures Service, www.ccdc.cam.ac.uk/structures.

Hydrate 1

Data was collected to try and reach a resolution of 0.75 \AA , however during processing this was cut to 0.77 \AA ($\theta_{\text{max}} = 27.48^\circ$) to give a full set of data of reasonable completeness and intensity. One reflection ($-1\ 0\ 2$) was removed from the final refinement because of poor agreement between F_{obs}^2 and F_{calc}^2 ; it was partially obscured by the beam stop.

The compound was found to crystallize in the centrosymmetric Monoclinic space group $P2_1/c$, with two cations, 1 anion and 4 water molecules in the asymmetric unit. The hydrogen atoms of the water molecules were all clearly visible in near final Fourier difference maps. In the case of the molecule containing O7, there were 3 Fourier peaks near the central oxygen atom, all with reasonable positions to represent hydrogen atoms. Refinement as hydrogen atoms, including refining their occupancies, starting from all three possible positions, showed a water molecule with

two different orientations. One hydrogen atom (HO7A) refined with an occupancy of one and is present in both orientations. The second (HO7B) refined with an occupancy of 0.80 (which was then fixed), defining the geometry of the major component of this disordered molecule. The minor component of the disorder was defined by the position of HO7C and had a refined occupancy of 0.20 (which was also fixed in the final refinement). The two components had reasonable total occupancies, geometries and contacts even with the application of only minimal restraints. The hydrogen bond of HO7C occupies the same region of space (with opposite directionality) as that of HO6B but the former is present only 20 % of the time. If HO7C was removed from the refinement the statistics were worse and a new Fourier peak would appear in its former location. The distance of HO7C from O7 was long enough that it did not appear to represent a lone pair of electrons, but rather an alternate true position for the second hydrogen atom on O7.

Both CF₃ groups in the structure (one per cation) were disordered, spinning around the C-CF₃ bond axes. This was modelled with three parts used to describe the disorder in both cases. The anisotropic displacement parameters of all of the fluorine atoms were restrained to be similar. In addition, the C-F bond lengths in all of the groups were restrained to be similar. Finally, enhanced rigid bond restraints were placed over all of the heavy atoms in the structure. In each CF₃ group a different free variable was used to describe the occupancy of each part of the disorder (3 in total for each CF₃ group). The total of the three refined occupancies was set to one using a different SUMP instruction for each cation. The final occupancies obtained were 44.4(3), 39.3(3) and 16.3(3) % for Parts A, B and C, respectively in cation1. In the second cation the same three values refined to 51.5(3), 28.4(3) and 20.1(3) % for Parts A, B and C, respectively.

One of the isopropyl chains in cation 1 (C9 to C11) also showed minor disorder, which could be modelled using two parts. The geometries of the parts were restrained to be similar, as were the bond lengths from the ordered part of the cation to the disordered parts. The occupancies of the two parts were restrained to total one and refined to final values of 97.4(3) and 2.6 %, for Parts A and B, respectively.

Hydrate 2

Data was collected and integrated to a maximum resolution of 0.80 Å ($\theta_{max} = 74.57^\circ$). All of this data was used in the refinement except for one reflection (2 0 0) which was removed from the final refinement because of poor agreement between F_{obs}^2 and F_{calc}^2 ; it was partially obscured by the beam stop.

The molecule crystallized in the non-centrosymmetric Orthorhombic space group *Cmc2*₁, with one cation, one half of the anion and two water molecules, each only half occupied, defining the asymmetric unit. The moiety formula for the structure is thus C₁₄H₂₁F₃N, 0.5(SO₄), H₂O and with $Z = 8$ there are 8 cations, 4 anions and 4 water molecules in each unit cell. In the unit cell, the anion and the water molecules lie either on, or in the case of one of the water molecules slightly off, the mirror plane defined by the *A* face of the unit cell.

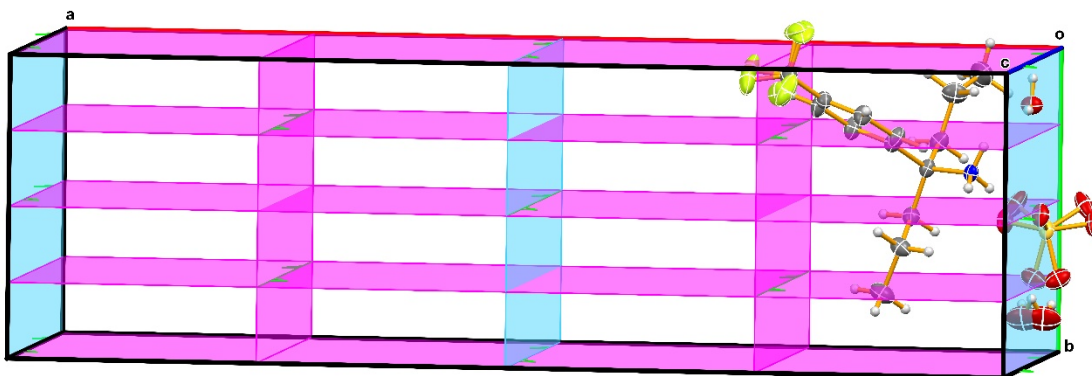


Figure S1: Unit cell showing the symmetry elements for the space group $Cmc2_1$. While the cation occupies general positions, the anion and water molecules lie on the mirror plane, shown in blue, defined by the A face of the unit cell.

For the cation this means that S1 and O1 lie directly on the mirror plane, O3 lies just slightly off of it and is doubled by symmetry, and O2 and O4 are generated by reflection in the mirror at positions close to their opposite partner on the other side of the mirror. The result can be described as a disordered anion. All of the atoms in the second water molecule lie directly on the mirror plane and show reasonable anisotropic displacement parameters. For the first water molecule, if the oxygen atom is left on the mirror plane its displacement ellipsoid is large and elongated. Moving it slightly off of the mirror plane improves the refinement statistics and the shape of its displacement parameters (similar to O3 of the anion). To overcome some of these issues, the anisotropic displacement parameters of all of the oxygen atoms in the structure were restrained to be similar.

The positions of the hydrogen atoms of both water molecules were clearly visible as the top peaks in the difference Fourier maps near the end of the refinement. If both of the hydrogen atom positions are also moved off of the mirror plane with O5 in the water molecule, one refines nicely but the second moves back onto the mirror plane, where it was left in the final refinement. In the final checkcif file there remains one level B alert and it involves this particular hydrogen atom: PLAT420_ALERT_2_B D-H Bond Without Acceptor O5 --HO5A.

The oxygen atom O5 still has relatively large anisotropic displacement parameters even after being moved off of the mirror plane (disordered) but its occupancy refines to one. The position of both hydrogen atoms on O5 were visible in the Fourier map and could be refined. The oxygen atom O5 accepts one hydrogen bond from HO6B and donates two. In addition to O6 (symmetry $x, y-1, z$), O1 and O3 (with its symmetry related partner) of one anion are the only close contacts made by O5. These atoms can accept hydrogen bonds from the two hydrogen atoms of the O5 water molecule but the angles formed are too acute if both contacts are to be maximized at the same time. It seems more likely that the hydrogen bonds average somewhere between maximizing one

extreme or the other. This would help to explain the large anisotropic displacement parameters observed for O5, particularly in contrast to those observed for the other water molecule. In addition, refinement of HO5A, at the given position on the mirror plane, does give it a hydrogen acceptor at a linear angle but long distance (see Figure S11).

The CF₃ group in the cation is disordered, spinning around the C-CF₃ bond axes. It could be modelled with two parts of equal occupancies used to describe the disorder. The geometries of the two parts were restrained to be similar, as were the anisotropic displacement parameters of all of the fluorine atoms.

The structure was refined as an inversion twin since the Flack parameter was not close to zero. The value of BASF refined to 0.11(2) giving the contribution of the minor twin component.

Comparison of the structures of the two hydrates

The sample was provided as colourless crystals still in the recrystallization solvent. Under the microscope a smaller sample placed in Paratone oil showed the majority of the crystals to be larger plates that were visibly built up from multiple layers. These crystals were by far the majority of the sample. However, amongst these crystals were a few much smaller (yet cleaner and nicer looking) thin flat rods with pointed ends. Being so visually different, unit cells were determined for each of these types of crystals and they proved to be different. Initial structure solutions from the unit cell data showed these to be different hydrates of the same salt. Full data collections were carried out for each type of crystal, the major product – (C₁₄H₂₁F₃N)₂SO₄•4H₂O and the minor product – (C₁₄H₂₁F₃N)₂SO₄•2H₂O, hereafter referred to as hydrate 1 and hydrate 2, respectively. The unit cell of hydrate 1 has a volume of 3483.67(18) Å³ and contains a total of 8 cations, 4 anions and 16 water molecules. The contents of one unit cell for hydrate two differ only in the water content, where 8 less water molecules are found per unit cell. The volume of the unit cell in hydrate 2 is slightly smaller, 3249.3(3) Å³, but its greater density (1.334 versus 1.313 Mg/m³ for 1) suggests that the packing is also more efficient in the higher symmetry space group. In very broad terms, the unit cells of hydrates 1 and 2 are similar in length along the *B* axis, while hydrate 2 is twice as long on *A* and half as long on *C* as hydrate 1 resulting in their similar volumes, even though the first cell is Monoclinic and the second is Orthorhombic.

Comparison of the hydrogen bonded network in the two crystals (Figure S12) gives a good indication of the broad similarities and differences in the packing of the two hydrates. The orientation of the axes in the unit cells differ between the two structures, with the hydrogen bonding viewed down the *B* axis in structure 1 being similar to that down the *C* axis in structure 2 and vice versa; this leaves the *A* axis view equivalent in both cells. There are columns of hydrogen bonded anions and water molecules (O-H...O) visible in both the views down *B* and *C* in each structure. In hydrate 1 the columns run parallel to the *C* axis at 1/2*A*. In hydrate 2, where the *A* axis is roughly

twice as long, the columns are oriented parallel to the B axis and are found at both zero and one-half along A .

In both structures every cation has 3 N-H donor groups and these groups all participate in hydrogen bonds, with the acceptors always being oxygen of the anion (two) and an oxygen of a water molecule (one). Similarly, in both structures the anion can only accept hydrogen bonds. In hydrate 1 the anion accepts four N-H (cation) and four O-H (water) hydrogen bonds. The anion in hydrate 2 accepts 2 unique N-H (cation) and 2 O-H (water) bonds but expanding this to the full anion gives the same number and distribution of interactions as found for hydrate 1. The cation...anion hydrogen bonding is the same in both structures, with the network varying only slightly in the participation of the water atoms in the anion channels.

In hydrate 1 the view down the C axis and the view down the B axis in hydrate 2 shows that the cations on each side of the central column are hydrogen bonded into the network (via N-H...O) in a repeating pattern. However, the repeating order is different in the two hydrates; in the first, the CF_3 groups of the cations are oriented in opposite directions on each side of the column while in hydrate 2 they are all aligned in the same direction. There is the least visible order in the hydrogen bonded network in the third projection for each structure (down the A axis) but here an important difference is evident. In hydrate 2 there is a single layer which repeats down this axis, while in hydrate 1 there are two interleaving layers with different orientations of the cations. The same patterns are again apparent if the packing diagrams in the two hydrates are considered (Figure S13). Since the distribution of the cation...anion interactions is the same in the two structures, shifting of the orientations of the layers when packing must result in the observed structural differences.

References

- [1] APEX 4 (Bruker, 2018) Bruker AXS Inc., Madison, Wisconsin, USA.
- [2] SAINT (Bruker, 2019) Bruker AXS Inc., Madison, Wisconsin, USA.
- [3] SADABS (Bruker, 2016) Bruker AXS Inc., Madison, Wisconsin, USA.
- [4] Sheldrick, G.M. (2015) *Acta Cryst.*, A71, 3-8; Sheldrick, G.M. (2015) *Acta Cryst.*, C71, 3-8.

Table S1: Crystal data and structure refinement details.

	Hydrate 1	Hydrate 2
Identification code		
CCDC deposit number	2394325	2394326
Radiation	Mo	Cu
Empirical formula	C ₂₈ H ₅₀ F ₆ N ₂ O ₈ S	C ₁₄ H ₂₃ F ₃ NO ₃ S _{0.5}
Chemical formula	(C ₁₄ H ₂₁ F ₃ N) ₂ SO ₄ ·4H ₂ O	0.5[(C ₁₄ H ₂₁ F ₃ N) ₂ SO ₄ ·2H ₂ O]
Formula weight	688.76	326.36
Crystal system	Monoclinic	Orthorhombic
Space group	<i>P2₁/c</i>	<i>Cmc2₁</i>
Unit cell dimensions (Å and °)	<i>a</i> = 15.9823(5) <i>b</i> = 10.6216(3) <i>c</i> = 21.5922(6) α = 90 β = 108.1193(10) γ = 90	<i>a</i> = 29.6157(17) <i>b</i> = 8.9695(5) <i>c</i> = 12.2342(7) α = 90 β = 90 γ = 90
Volume (Å ³)	3483.67(18)	3249.9(3)
<i>Z</i>	4	8
Density (calculated, Mg/m ³)	1.313	1.334
Absorption coefficient (mm ⁻¹)	0.171	1.560
F(000)	1464	1384
Crystal size (mm ³)	0.216x0.094x0.020	0.157x0.047x0.024
Theta range of data (°)	1.985 to 27.484	5.152 to 74.571
Index ranges (<i>h</i> , <i>k</i> , <i>l</i>)	-20/20, -13/13, -26/28	-36/36, -9/11, -15/15
Reflections collected	104065	17526
Independent reflections	7991	3303
R(int)	0.0604	0.0366
Completeness (%)	100.0	99.8
Max. and min. transmission	0.7457 and 0.7091	0.7538 and 0.6610
Data / restraints / parameters	7991 / 761 / 604	3303 / 42 / 265
Goodness-of-fit on F ²	1.103	1.073
Final R indices [<i>I</i> >2σ(<i>I</i>)]	R1 = 0.0415 wR2 = 0.0981	R1 = 0.0275 wR2 = 0.0691
R indices (all data)	R1 = 0.0718 wR2 = 0.1235	R1 = 0.0289 wR2 = 0.0704
Absolute structure parameter	n.a.	0.11(2)
Largest diff. peak and hole (e.Å ⁻³)	0.225 and -0.557	0.144 and -0.225

Table S2: Hydrogen bonds in Hydrates 1 and 2 [\AA and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
Hydrate 1				
N(1)-HN1A...O(6)#1	0.916(15)	2.039(16)	2.936(2)	166.2(19)
N(1)-HN1B...O(3)	0.921(15)	1.838(16)	2.735(2)	163.8(19)
N(1)-HN1C...O(1)#1	0.920(16)	1.919(17)	2.814(2)	164(2)
N(2)-HN2A...O(7)#1	0.916(15)	2.056(16)	2.953(2)	166.1(19)
N(2)-HN2B...O(2)#1	0.915(16)	1.924(17)	2.804(2)	160(2)
N(2)-HN2C...O(4)#2	0.932(16)	1.822(16)	2.741(2)	168(2)
O(5)-HO5A...O(2)	0.873(16)	1.875(17)	2.7451(19)	174(3)
O(5)-HO5B...O(3)#1	0.876(16)	2.004(18)	2.834(2)	158(2)
O(6)-HO6A...O(5)	0.878(17)	1.842(18)	2.707(2)	168(3)
O(6)-HO6B...O(7)#3	0.865(17)	2.308(18)	3.172(3)	177(3)
O(7)-HO7A...O(8)	0.877(17)	1.834(18)	2.703(2)	171(3)
O(7)-HO7B...O(6)	0.870(18)	2.49(2)	3.303(3)	155(3)
O(7)-HO7C...O(6)#4	0.86(2)	2.45(9)	3.172(3)	142(13)
O(8)-HO8A...O(4)#5	0.859(16)	1.980(18)	2.7843(19)	156(2)
O(8)-HO8B...O(1)	0.862(16)	1.896(17)	2.7528(19)	172(2)
Hydrate 2				
N(1)-HN1A...O(6)	0.875(18)	2.06(2)	2.871(2)	155(3)
N(1)-HN1B...O(1)	0.872(18)	1.902(19)	2.754(2)	165(3)
N(1)-HN1C...O(2)#6	0.872(18)	1.94(2)	2.754(7)	155(3)
N(1)-HN1C...O(4)#7	0.872(18)	1.93(2)	2.753(7)	156(3)
O(5)-HO5B...O(3)	0.80(2)	2.07(3)	2.845(5)	164(10)
O(6)-HO6A...O(3)#6	0.79(2)	2.05(2)	2.793(4)	157(4)
O(6)-HO6A...O(3)#7	0.79(2)	2.05(2)	2.793(4)	157(4)
O(6)-HO6B...O(5)#8	0.80(2)	2.01(2)	2.788(5)	167(4)
O(6)-HO6B...O(5)#9	0.80(2)	2.01(2)	2.788(5)	167(4)

Symmetry transformations used to generate equivalent atoms:

Hydrate 1 #1 $-x+1, -y+1, -z+1$ #2 $x, y+1, z$ #3 $-x+1, y+1/2, -z+1/2$ #4 $-x+1, y-1/2, -z+1/2$ #5 $-x+1, -y, -z+1$

Hydrate 2 #6 $-x, -y+1, z+1/2$ #7 $x, -y+1, z+1/2$ #8 $x, y-1, z$ #9 $-x, y-1, z$

Hydrate 1

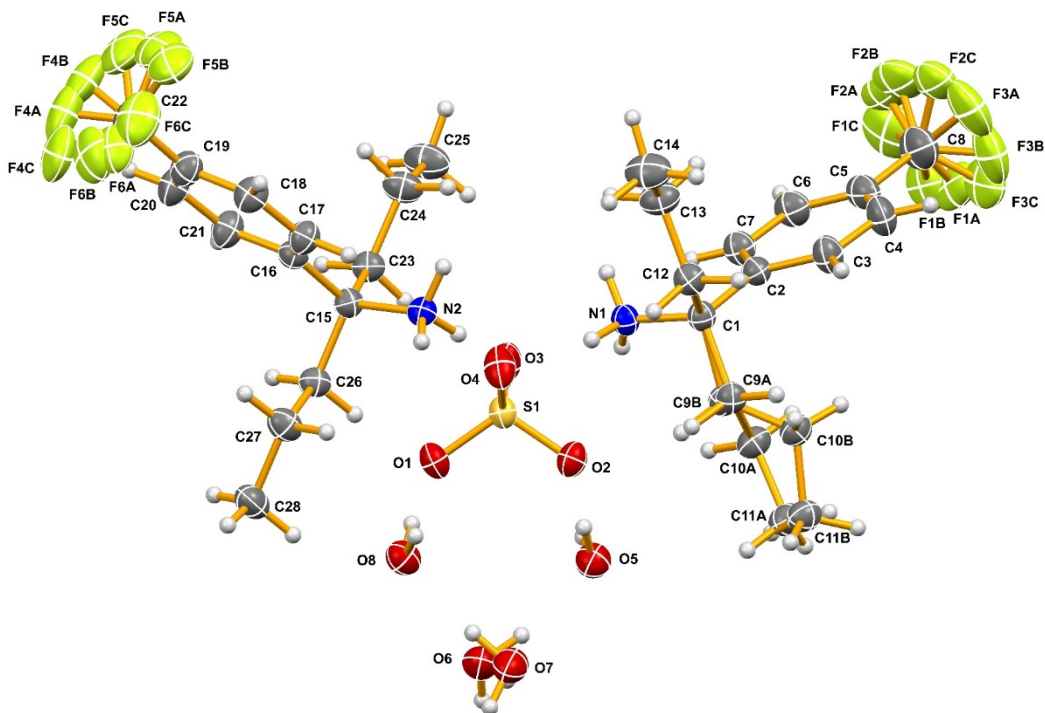


Figure S2. Structure of hydrate 1. Disorder has not been removed. Thermal ellipsoids are drawn at the 50 % probability level. Hydrogen atoms are included but have not been labelled.

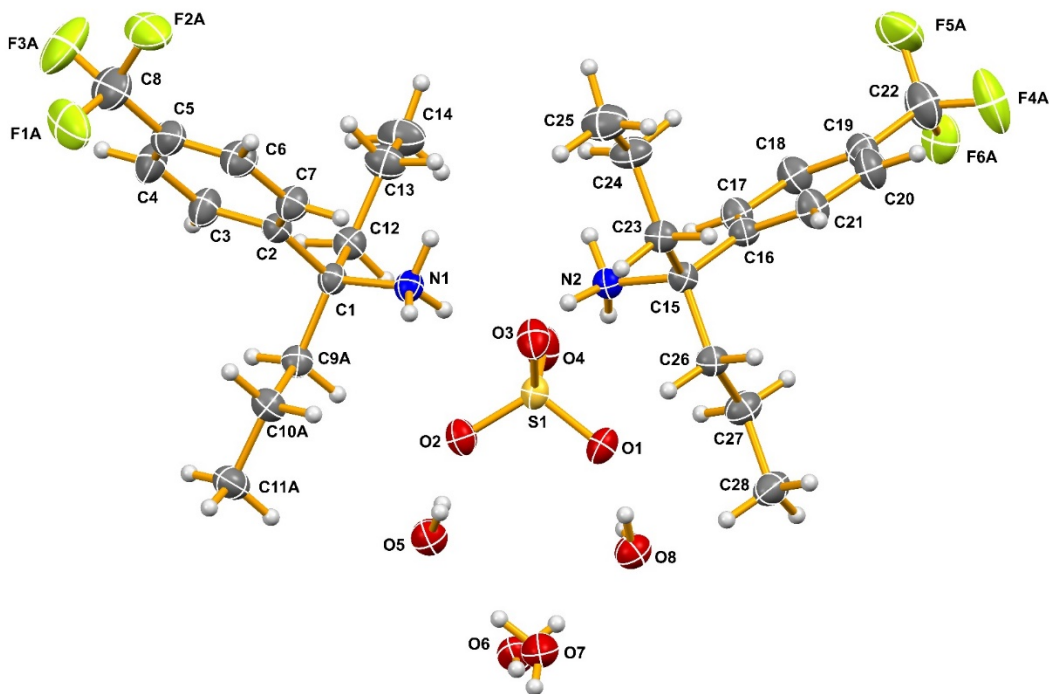


Figure S3. Structure of hydrate 1. Disorder has been removed. Thermal ellipsoids are drawn at the 50 % probability level. Hydrogen atoms are included but have not been labelled.

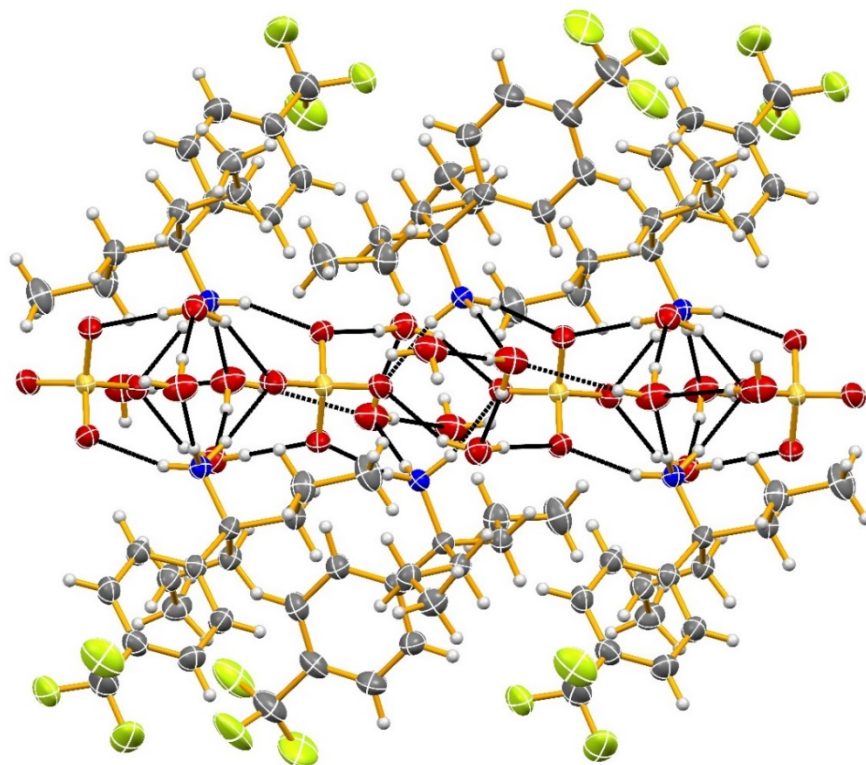


Figure S4. N-H...O and O-H...O hydrogen bonds in the structure of hydrate **1** (see Table S2). Disorder has been removed. Atoms have not been labelled.

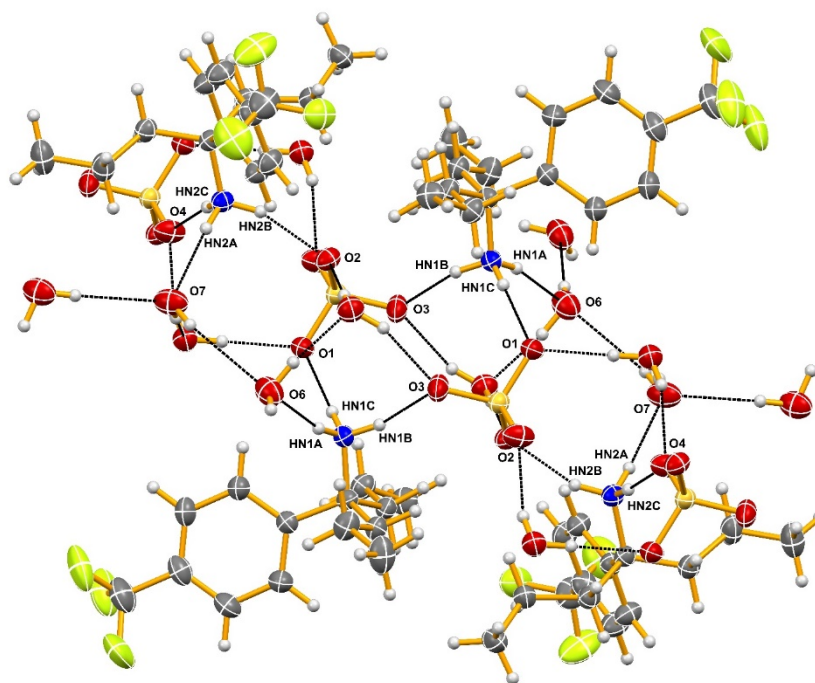


Figure S5. Hydrogen bonds in the structure of hydrate **1** drawn to emphasize the N-H...O interactions (see Table S2). Disorder has been removed. Only select atoms have been labelled.

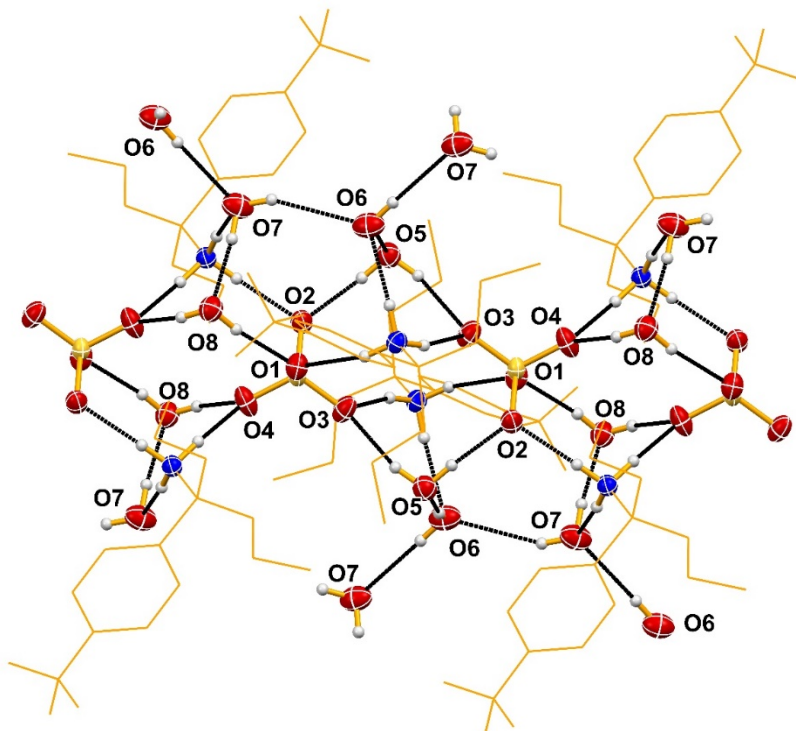


Figure S6. Hydrogen bonds in the structure of hydrate **1** drawn to emphasize the O-H...O interactions (see Table S2). Disorder has been removed. The cation atoms other than the NH donors are drawn in wireframe for clarity. Only select atoms have been labelled.

Hydrate 2

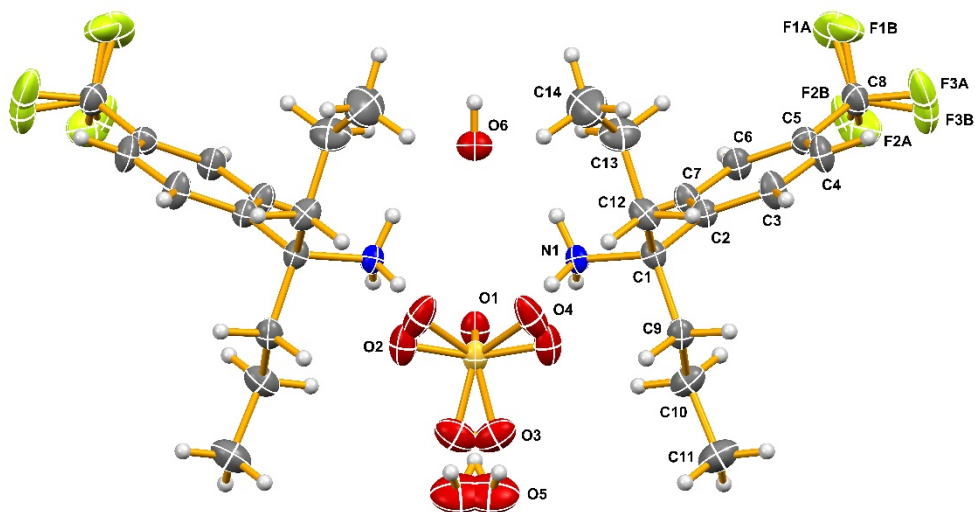


Figure S7. Structure of hydrate **2**, shown with the independent unit doubled. Only the unique atoms defining the independent unit have been labelled. Disorder has not been removed. Thermal ellipsoids are drawn at the 50 % probability level. Hydrogen atoms are included but have not been labelled.

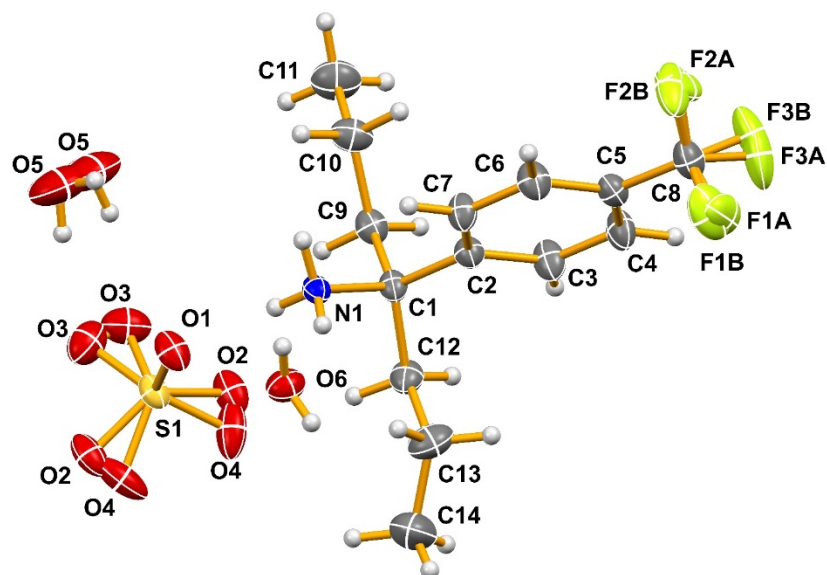


Figure S8. Structure of hydrate **2**. Disorder has not been removed. The atoms in the cation are fully occupied unless disordered, but the atoms of the anion and the water molecules (all of which lie on or across a mirror plane) have only half occupancies. Thermal ellipsoids are drawn at the 50 % probability level. Hydrogen atoms are included but have not been labelled.

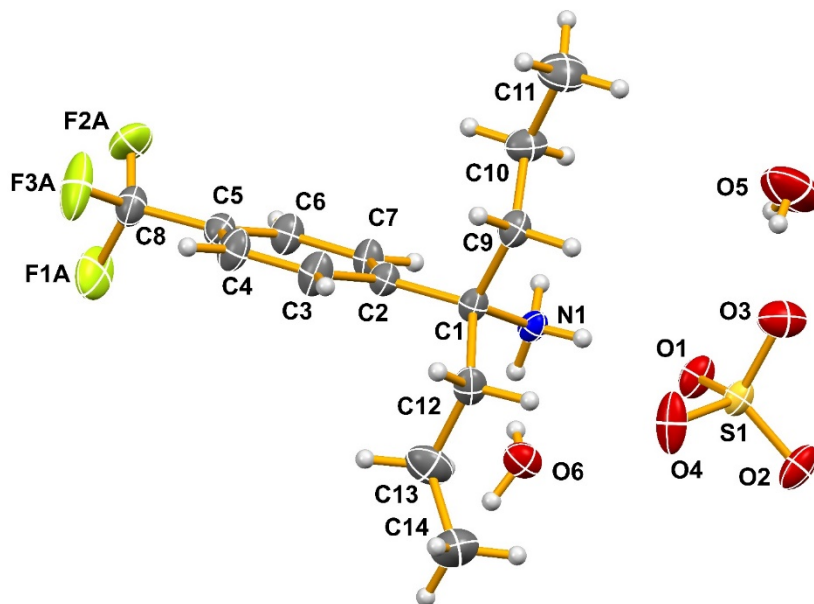


Figure S9. Structure of hydrate **2**. Disorder has been removed. The atoms in the cation are fully occupied unless disordered, but the atoms of the anion and the water molecules (all of which lie on or across a mirror plane) have only half occupancies. Thermal ellipsoids are drawn at the 50 % probability level. Hydrogen atoms are included but have not been labelled.

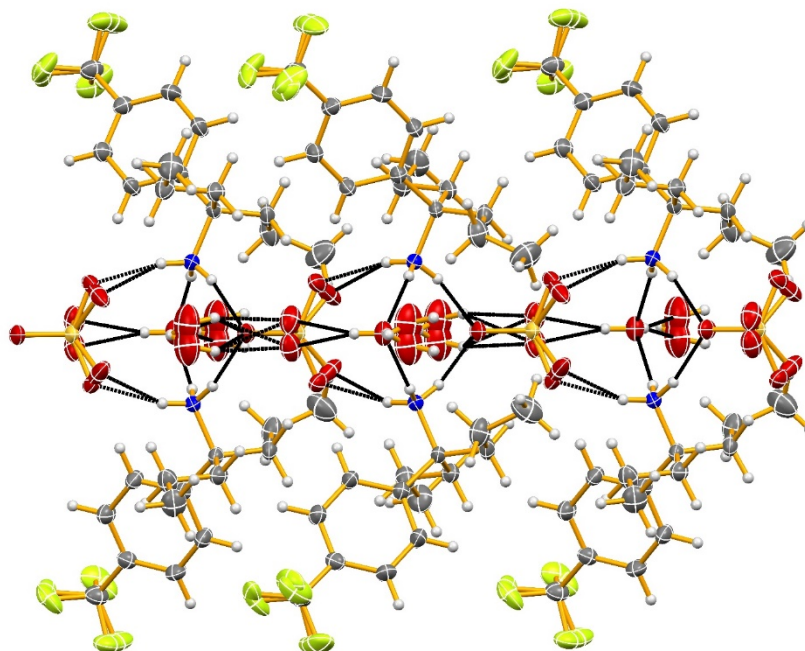


Figure S10. N-H...O and O-H...O hydrogen bonds in the structure of hydrate **2** (see Table S2). Disorder has not been removed. Atoms have not been labelled.

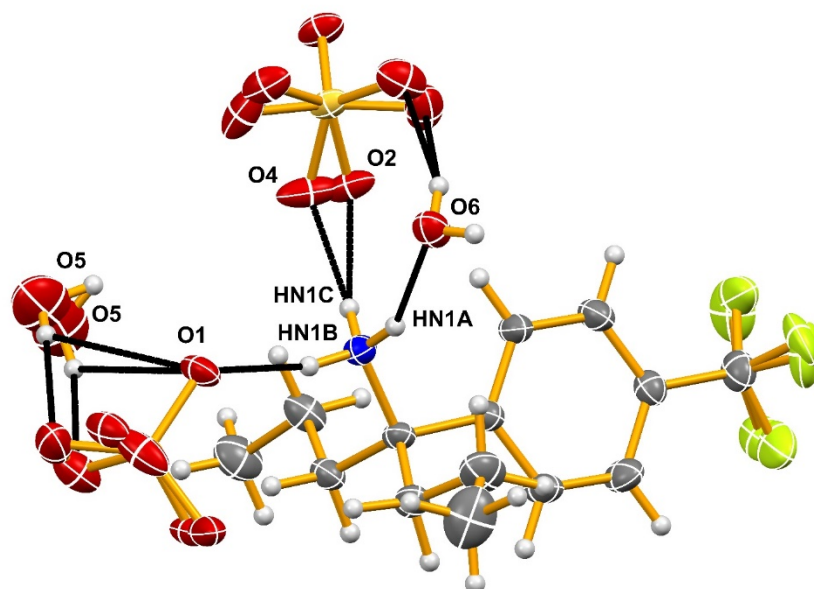


Figure S11. Hydrogen bonds in the structure of hydrate **2** drawn to emphasize the N-H...O interactions (see Table S2). Disorder has not been removed. Only select atoms have been labelled.

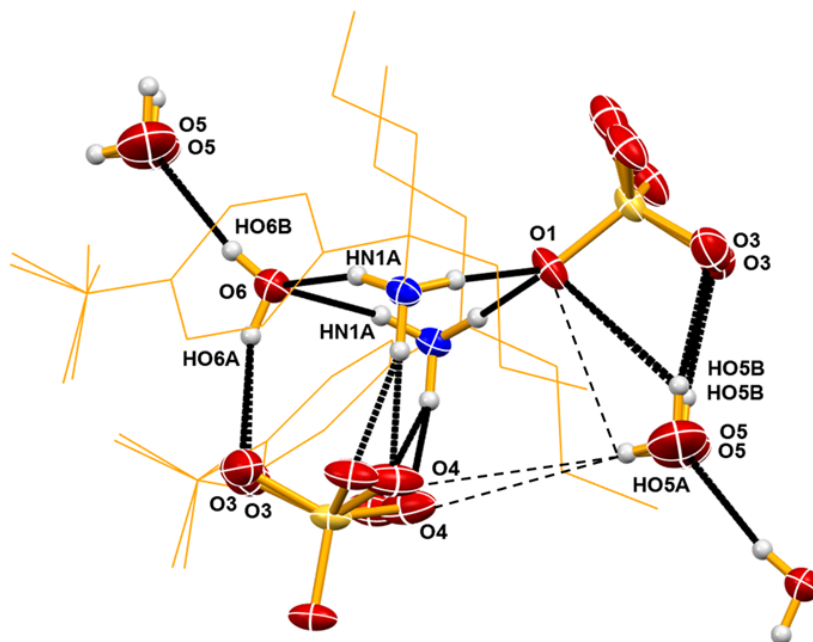


Figure S12. Hydrogen bonds in the structure of hydrate 2 drawn to emphasize the O-H...O interactions (see Table S2). Disorder has been removed. The cation atoms other than the NH donors are drawn in wireframe for clarity. Only select atoms have been labelled. The longer or less favorable potential hydrogen bonds involving HO5A are shown by the lighter dashed lines.

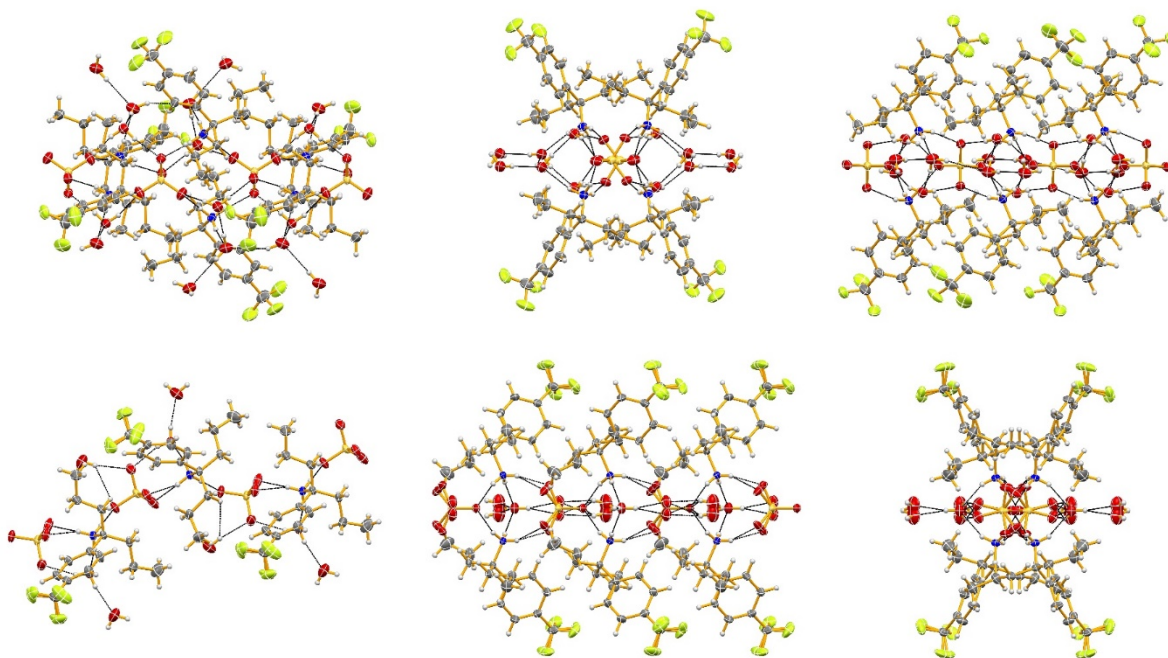


Figure S13. Composite diagram showing the hydrogen bonding network in the two hydrates (top – hydrate 1 and bottom – hydrate 2). In order from left to right are the views down the *A*, *B* and *C* axes.

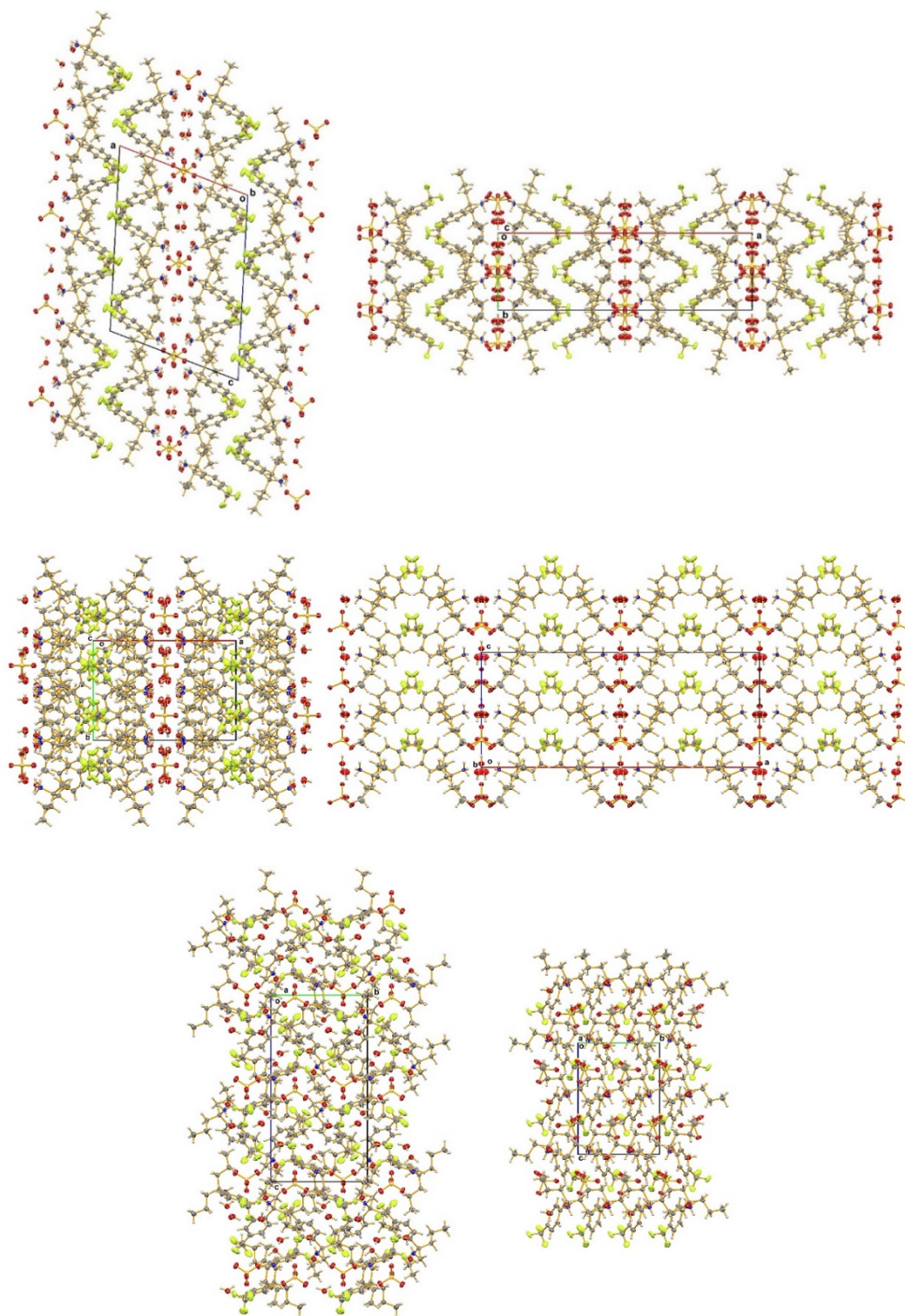


Figure S14. Composite diagram showing the packing in the two hydrates. Hydrate 1 is on the left and hydrate 2 is on the right. Orientations with similar packing are shown together. Top hydrate 1 viewed down *B* and hydrate 2 viewed down *C*. Middle 1 viewed down *C* and 2 viewed down *B*. Bottom 1 and 2 viewed down *A*.

Experimental Procedures and Tabulated Data

General Procedure A for synthesis of amines: Nitrile (2 mmol, 1 equiv.) was dissolved in toluene (2 mL) in a 4-dram vial equipped with a stir bar. Grignard reagent (2 mmol, 1 equiv.) was added, and the mixture was left to stir for 1 hour. Lanthanum chloride bis(lithium chloride) (1 mL, 0.6 mmol, 0.6 M solution, 0.3 equiv.) was added followed immediately by the addition of Grignard reagent (4 mmol, 2 equiv.) and left to stir for 18 hours. The vessel was removed from the glovebox and quenched dropwise with 4 mL of 2 M HCl. The mixture was left to stir for 1 hour and then 5 mL of 2 M NaOH was added leading to the formation of sludgy lanthanum salts. The lanthanum salts were filtered out of solution over celite, rinsed with diethyl ether and the filtrate was transferred to a separatory funnel where an additional 10 mL of 2 M NaOH was added. The aqueous layer was extracted with 3 x 10 mL of diethyl ether, the combined organic layers were dried over Na₂SO₄ and concentrated via rotary evaporator, then dried under vacuum.

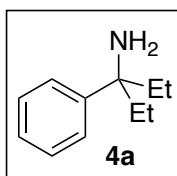
General Procedure B for synthesis of amines: Nitrile (2 mmol, 1 equiv.) was dissolved in trifluorotoluene (4 mL) in a 4-dram vial equipped with a stir bar. Grignard reagent (2 mmol, 1 equiv.) was added, and the mixture was left to stir for 1 hour. Lanthanum chloride bis(lithium chloride) (1.0 mL, 0.6 mmol, 0.6 M, 0.3 equiv.) was added followed immediately by the addition of Grignard reagent (4 mmol, 2 equiv.) and left to stir for 48 hours. The vessel was removed from the glovebox and quenched dropwise with 4 mL of 2 M HCl. The mixture was left to stir for 1 hour and then 5 mL of 2 M NaOH was added leading to the formation of sludgy lanthanum salts. The lanthanum salts are filtered out of solution over celite, rinsed with diethyl ether and the filtrate was transferred to a separatory funnel where an additional 10 mL of 2 M NaOH was added. The aqueous layer was extracted with 3 x 10 mL of diethyl ether, the combined organic layers were dried over Na₂SO₄ and concentrated via rotary evaporator.

Purification Method A: This is for compounds where the amine-sulfate salt is soluble in water, and insoluble in diethyl ether. The crude amine/ketone mixture was redissolved in diethyl ether (10 mL) and transferred to a separatory funnel where the organic layer was extracted with 3 x 10 mL of 2M NaHSO₄. The combined aqueous layers were made basic using 2 M NaOH and then extracted with 3 x 10 mL of diethyl ether. The combined organic layers were dried over Na₂SO₄ and concentrated via rotary evaporator to afford the freebase amine.

Purification Method B: This is for compounds where the amine sulfate salt is soluble in water, but also soluble in diethyl ether. The crude amine/ketone mixture was redissolved in hexanes (10 mL) and transferred to a separatory funnel where the organic layer was extracted with 3 x 10 mL of 2M NaHSO₄. The combined aqueous layer was basified using 2 M NaOH and then extracted with 3 x 10 mL of diethyl ether. The combined organic layers were dried over Na₂SO₄ and concentrated via rotary evaporator to afford the freebase amine.

Purification Method C: This is for compounds where the amine sulfate salt has limited solubility in water. 20 mL of 2 M NaHSO₄ was added to the unpurified crude reaction mixture to form a

precipitated amine salt. The solid was collected via a Buchner funnel suction filtration and rinsed thoroughly with hexanes. Setting the salt collected aside, the filtrate was transferred to a separatory funnel and the organic layer was extracted with another 5 mL of 2 M NaHSO₄. The aqueous layer was basified with 2 M NaOH, transferred to a separatory funnel and extracted with 3 x 10 mL of diethyl ether. The combined organic layers from this extraction were dried over Na₂SO₄ and concentrated via rotary evaporator to afford an oil. 20 mL of 2 M NaOH was added to the previously collected salt and then transferred to a separatory funnel, rinsing the flask with diethyl ether. The aqueous layer was extracted with 3 x 10 mL of diethyl ether and the combined organic layers were dried over Na₂SO₄ and concentrated via rotary evaporator to afford an oil. Both the freebase oils originating from the basification and extraction on the solid salt and the initial aqueous filtrate were combined for recorded yields.

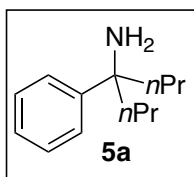


4a Prepared according to the **General Procedure A** using benzonitrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **4a** (138 mg, 0.84 mmol, 42% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.40–7.38 (m, 2H), 7.34–7.30 (m, 2H), 7.21–7.18 (m, 1H), 1.84 (dq, *J* = 14.0 Hz, 7.5 Hz, 2H), 1.68 (dq, *J* = 13.8 Hz, 7.5 Hz, 2H), 1.45 (br. s, 2H), 0.72 (t, *J* = 7.5 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 146.9, 128.1, 126.1, 125.9, 58.2, 36.2, 8.2.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₁H₁₈N: 164.1434 found: 164.1435.

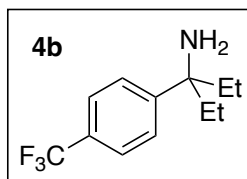


5a Prepared according to the **General Procedure B** using benzonitrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **5a** (177 mg, 0.92 mmol, 46% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.40–7.38 (m, 2H), 7.33–7.29 (m, 2H), 7.21–7.17 (m, 1H), 1.77 (ddd, *J* = 13.3 Hz, 12.4 Hz, 4.2 Hz, 2H), 1.63 (ddd, *J* = 13.8 Hz, 12.2 Hz, 4.6 Hz, 2H), 1.47 (br. s, 2H), 1.29–1.18 (m, 2H), 1.05–0.95 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 147.6, 128.1, 128.9, 125.8, 57.9, 46.7, 17.1, 14.7.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₃H₂₂N: 192.1747 found: 192.1754.



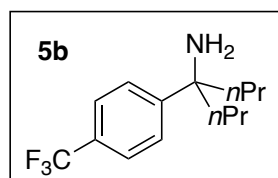
4b Prepared according to the **General Procedure A** using 4-(trifluoromethyl)benzotrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method C** which produced **4b** (343 mg, 1.48 mmol, 74% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.58 (ap. d, *J* = 8.7 Hz, 2H), 7.53 (ap. d, *J* = 8.7 Hz, 2H), 1.85 (dq, *J* = 14.0 Hz, 7.8 Hz, 2H), 1.70 (dq, *J* = 14.0 Hz, 7.4 Hz, 2H), 1.39 (br. s, 2H), 0.71 (t, *J* = 7.5 Hz, 6H).

¹³C{¹H} NMR (125 MHz, CDCl₃): δ 151.2, 128.3 (q, ²*J*_{CF} = 32.3 Hz), 126.6, 125.0 (q, ³*J*_{CF} = 3.5 Hz), 124.5 (q, ¹*J*_{CF} = 271.7 Hz), 58.5, 36.3, 8.1.

¹⁹F NMR (470 MHz, CDCl₃): δ -62.3 (s).

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₂H₁₇F₃N: 232.1308 found: 232.1302.



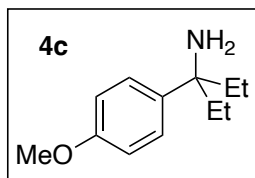
5b prepared according to the **General Procedure B** using 4-(trifluoromethyl)benzotrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method C** which produced **5b** (301 mg, 1.16 mmol, 58% yield). A portion of the solid sulfate/bisulfate salt collected during the Purification Method C was dissolved in acetone, and the crystals for X-ray analysis were obtained by slow evaporation of that solution.

¹H NMR (500 MHz, CDCl₃): δ 7.57 (ap. d, *J* = 8.5 Hz, 2H), 7.53 (ap. d, *J* = 8.5 Hz, 2H), 1.78 (ddd, *J* = 13.8 Hz, 12.5 Hz, 4.3 Hz, 2H), 1.64 (ddd, *J* = 13.9 Hz, 12.0 Hz, 4.4 Hz, 2H), 1.45 (br. s, 2H), 1.30–1.19 (m, 2H), 1.01–0.91 (m, 2H), 0.84 (t, *J* = 7.1, 6H).

¹³C{¹H} NMR (125 MHz, CDCl₃): δ 151.9, 128.2 (q, ²*J*_{CF} = 32.3 Hz), 126.3, 125.0 (q, ³*J*_{CF} = 3.9 Hz), 124.5 (q, ¹*J*_{CF} = 271.6 Hz), 58.2, 46.7, 17.0, 14.6.

¹⁹F NMR (470 MHz, CDCl₃): δ -62.3 (s).

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₄H₂₁F₃N: 260.1621 found: 260.1628.

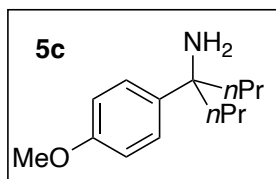


4c Prepared according to the **General Procedure A** using 4-methoxybenzotrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **4c** (156 mg, 0.80 mmol, 40 % yield).

¹H NMR (500 MHz, CDCl₃): δ 7.31 (ap. dt, *J* = 9.0 Hz, 2.2 Hz, 2H), 6.86 (ap. dt, *J* = 8.9 Hz, 2.2 Hz, 2H), 3.80 (s, 3H), 1.80 (dq, *J* = 13.8 Hz, 7.8 Hz, 2H), 1.66 (dq, *J* = 13.8 Hz, 7.3 Hz, 2H), 1.47 (br. s, 2H), 0.72 (t, *J* = 7.4, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 157.7, 138.9, 127.2, 113.4, 57.8, 55.3, 36.1, 8.2.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₂H₂₀NO: 194.1539 found: 194.1543.

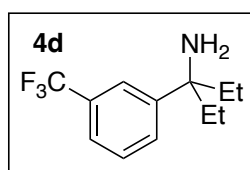


5c prepared according to the **General Procedure B** using 4-methoxybenzotrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **5c** (200 mg, 0.90 mmol, 45% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.30 (ap. dt, *J* = 8.9 Hz, 2.2 Hz, 2H), 6.85 (ap. dt, *J* = 8.9 Hz, 2.2 Hz, 2H), 3.80 (s, 3H), 1.73 (ddd, *J* = 13.5 Hz, 12.3 Hz, 4.3 Hz, 2H), 1.60 (ddd, *J* = 13.5 Hz, 12.1 Hz, 4.7 Hz, 2H), 1.45 (br. s, 2H), 1.28–1.17 (m, 2H), 1.07–0.97 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 157.7, 139.8, 126.9, 113.4, 57.5, 55.3, 46.7, 17.1, 14.7.

LRMS(ESI): *m/z* (M-NH₂)⁺ calculated for C₁₄H₂₁O: 205.1582 found: 205.2



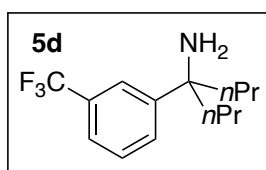
4d Prepared according to the **General Procedure A** using α,α,α-trifluoro-*m*-tolunitrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method C** which produced **4d** (267 mg, 1.16 mmol, 58% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (ap. s, 1H), 7.60–7.58 (m, 1H), 7.48–7.42 (m, 2H), 1.84 (dq, *J* = 14.0 Hz, 7.5 Hz, 2H), 1.70 (dq, *J* = 13.8 Hz, 7.5 Hz, 2H), 1.43 (br. s, 2H), 0.72 (t, *J* = 7.5 Hz, 6H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 148.1, 130.5 (q, ²*J*_{CF} = 30.4 Hz), 129.7, 128.5, 124.6 (q, ¹*J*_{CF} = 272.2 Hz), 123.02–122.9 (m), 58.4, 36.2, 8.1.

¹⁹F NMR (470 MHz, CDCl₃): δ -62.4 (s).

HRMS(ESI): *m/z* (M-NH₂)⁺ calculated for C₁₂H₁₄F₃: 215.1042 found: 215.1049.



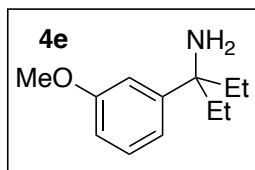
5d Prepared according to the **General Procedure B** using α,α,α-trifluoro-*m*-tolunitrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride). Crude reaction mixture was purified via **Purification Method C** which produced **5d** (268 mg, 1.03 mmol, 52% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70–7.69 (m, 1H), 7.59–7.58 (m, 1H), 7.47–7.41 (m, 2H), 1.78 (ddd, *J* = 13.7 Hz, 12.3 Hz, 4.3 Hz, 2H), 1.65 (ddd, *J* = 13.8 Hz, 12.1 Hz, 4.5 Hz, 2H), 1.42 (br. s, 2H), 1.30–1.19 (m, 2H), 1.02–0.92 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 6H).

¹³C{¹H} NMR (125 MHz, CDCl₃): δ 148.9, 133.4 (q, ²*J*_{CF} = 31.6 Hz), 129.4, 128.5, 124.5 (q, ¹*J*_{CF} = 272.4 Hz), 122.9 (q, ³*J*_{CF} = 4.0 Hz), 122.7 (q, ³*J*_{CF} = 3.9 Hz), 58.1, 46.6, 17.0, 14.6.

¹⁹F NMR (470 MHz, CDCl₃): δ -62.4 (s).

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₄H₂₁F₃N: 260.1621 found: 260.1630.

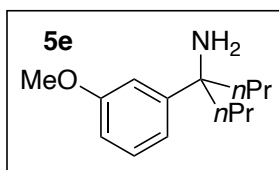


4e Prepared according to the **General Procedure A** using 3-methoxybenzotrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **4e** (188 mg, 0.97 mmol, 49% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.26–7.22 (m, 1H), 6.98–6.95 (m, 2H), 6.76–6.73 (m, 1H), 3.82 (s, 3H), 1.83 (dq, *J* = 14.0 Hz, 7.5 Hz, 2H), 1.67 (dq, *J* = 14.0 Hz, 7.5 Hz, 2H), 1.46 (br. s, 2H), 0.72 (t, *J* = 7.4 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 159.6, 148.9, 129.0, 118.6, 112.6, 110.7, 58.3, 55.3, 36.2, 8.2.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₂H₂₀NO: 194.1539 found: 194.1545.

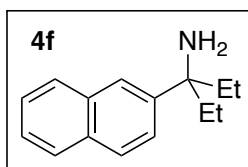


5e Prepared according to the **General Procedure B** using 3-methoxybenzotrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **5e** (236 mg, 1.06 mmol, 53% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.25–7.22 (m, 1H), 6.97–6.95 (m, 2H), 6.75–6.72 (m, 1H), 3.81 (s, 3H), 1.75 (ddd, *J* = 13.4 Hz, 12.2 Hz, 4.1 Hz, 2H), 1.61 (ddd, *J* = 13.4 Hz, 12.2 Hz, 4.4 Hz, 2H), 1.49 (br. s, 2H), 1.29–1.19 (m, 2H), 1.06–0.96 (m, 2H), 0.84 (t, *J* = 7.0 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 159.6, 149.7, 129.0, 118.4, 112.4, 110.5, 58.0, 55.3, 46.7, 17.1, 14.7.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₄H₂₄NO: 222.1852 found: 222.1848.

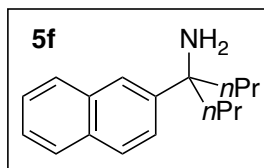


4f Prepared according to the **General Procedure A** using 2-naphthonitrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **4f** (289 mg, 1.36 mmol, 68% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.87–7.86 (m, 1H), 7.84–7.79 (m, 3H), 7.50–7.42 (m, 3H), 1.95 (dq, *J* = 13.9 Hz, 7.3 Hz, 2H), 1.76 (dq, *J* = 14.0 Hz, 7.5 Hz, 2H), 1.60 (br. s, 2H), 0.73 (t, *J* = 7.6 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 144.3, 133.3, 132.0, 128.1, 127.8, 127.5, 126.0, 125.5, 124.8, 124.7, 58.5, 36.1, 8.2.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₅H₂₀N: 214.1590 found: 214.1588.

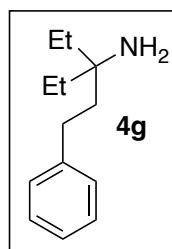


5f Prepared according to the **General Procedure B** using 2-naphthonitrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via column chromatography (1% isopropylamine, 15% ethyl acetate, and 84% hexanes) to afford **5f** (252 mg, 1.04 mmol, 52% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.86–7.86 (m, 1H), 7.84–7.78 (m, 3H), 7.50 (dd, *J* = 8.6 Hz, 2.0 Hz, 1H), 7.48–7.42 (m, 2H), 1.87 (ddd, *J* = 13.6 Hz, 12.6 Hz, 4.3 Hz, 2H), 1.71 (ddd, *J* = 13.7 Hz, 12.2 Hz, 4.5 Hz, 2H), 1.56 (br. s, 2H), 1.32–1.22 (m, 2H), 1.04–0.94 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 145.2, 133.3, 132.0, 128.1, 127.8, 127.5, 126.0, 125.5, 124.7, 124.2, 58.2, 46.6, 17.1, 14.7.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₇H₂₄N: 242.1903 found: 242.1911.

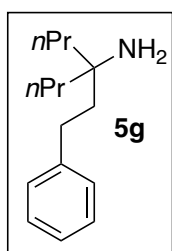


4g Prepared according to the **General Procedure A** using 3-phenylpropionitrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method A** which produced **4g** (185 mg, 0.97 mmol, 48% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.29–7.26 (m, 2H), 7.20–7.16 (m, 2H), 2.60–2.57 (m, 2H), 1.62–1.59 (m, 2H), 1.43 (ap. q, *J* = 7.6 Hz, 4H), 1.18 (br. s, 2H), 0.88 (t, *J* = 7.6 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 143.2, 128.5, 128.4, 125.8, 53.6, 41.5, 32.0, 30.2, 8.0.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₃H₂₂N: 192.1747 found: 192.1751.

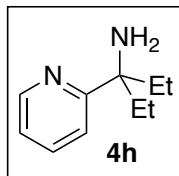


5g Prepared according to the **General Procedure B** using 3-phenylpropionitrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride). The crude reaction mixture was purified via **Purification Method B** which produced **5g** (283 mg, 1.29 mmol, 65% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.29–7.26 (m, 2H), 7.20–7.16 (m, 3H), 2.60–2.57 (m, 2H), 1.63–1.59 (m, 2H), 1.39–1.29 (m, 8H), 0.93 (t, *J* = 7.0 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 143.1, 128.5, 128.4, 125.8, 53.5, 42.9, 42.6, 30.3, 16.9, 15.0.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₅H₂₆N: 220.2060 found: 220.2065.

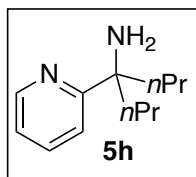


4h Prepared according to the **General Procedure A**, except using 4 mL of toluene instead of 2 mL. 2-Pyridinecarbonitrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride) produced **4h** (222 mg, 1.35 mmol, 68% yield) with no further purification required.

¹H NMR (500 MHz, CDCl₃): δ 8.57 (ap. d, *J* = 4.6 Hz, 1H), 7.65 (ap. t, *J* = 7.5, 1H), 7.41 (ap. d, *J* = 8.1 Hz, 1H), 7.12–7.09 (m, 1H), 1.97–1.89 (m, 2H), 1.79 (br. s, 2H), 1.79–1.70 (m, 2H), 0.71 (t, *J* = 7.6, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 165.9, 148.6, 136.0, 121.1, 120.5, 59.9, 35.1, 8.2.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₀H₁₇N₂: 165.1386 found: 165.1386.

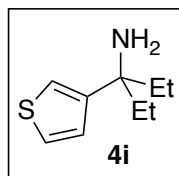


5h Prepared according to the **General Procedure B**. 2-pyridinecarbonitrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride) produced **5h** (264 mg, 1.37 mmol, 69% yield) with no further purification required.

¹H NMR (500 MHz, CDCl₃): δ 8.56 (ddd, *J* = 4.8 Hz, 1.9 Hz, 1.0 Hz, 1H), 7.62 (ddd, *J* = 9.4 Hz, 7.5 Hz, 1.8 Hz, 1H), 7.41 (ap. dt, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.10 (ddd, *J* = 7.5 Hz, 4.8 Hz, 1.1 Hz, 1H), 1.85 (ddd, *J* = 13.6 Hz, 12.5 Hz, 4.5 Hz, 2H), 1.78 (br. s, 2H), 1.70 (ddd, *J* = 13.6 Hz, 12.1 Hz, 4.6 Hz, 2H), 1.31–1.21 (m, 2H), 1.01–0.89 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 166.5, 148.6, 136.0, 121.0, 120.2, 59.6, 45.5, 17.1, 14.7.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₂H₂₁N₂: 193.1699 found: 193.1697.

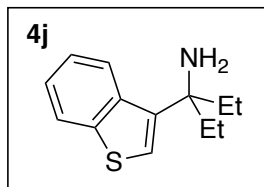


4i Prepared according to the **General Procedure A**, with the exception of using 4 mL of trifluorotoluene instead of 2 mL of toluene. 3-Thiophenecarbonitrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride) produced **4i** (266 mg, 1.57 mmol, 79% yield) with no purification needed.

¹H NMR (500 MHz, CDCl₃): δ 7.27 (dd, *J* = 5.0 Hz, 3.0 Hz, 1H), 7.07 (dd, *J* = 3.0 Hz, 1.4 Hz, 1H), 6.99 (dd, *J* = 5.0 Hz, 1.4 Hz, 1H), 1.77 (dq, *J* = 13.9 Hz, 7.8 Hz, 2H), 1.67 (dq, *J* = 13.9 Hz, 7.7 Hz, 2H), 1.47 (br. s, 2H), 0.76 (t, *J* = 7.5 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 149.7, 126.3, 125.4, 120.0, 57.4, 35.7, 8.3.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₉H₁₆NS: 170.0998 found: 170.1002.

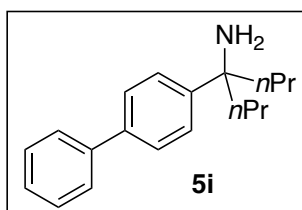


4j Prepared according to the **General Procedure A**, except using 4 mL of trifluorotoluene instead of 2 mL of toluene. Benzo[b]thiophene-3-carbonitrile, ethylmagnesium bromide solution and lanthanum chloride bis(lithium chloride) produced **4j**. The crude reaction mixture was purified via column chromatography (1% isopropylamine, 15% ethyl acetate, and 84% hexanes) to further afford **4j** (337 mg, 1.54 mmol, 77% yield).

¹H NMR (500 MHz, CDCl₃): δ 8.14–8.12 (m, 1H), 7.86–7.84 (m, 1H), 7.35–7.30 (m, 2H), 7.27 (s, 1H), 2.12 (dq, *J* = 14.0 Hz, 7.5 Hz, 2H), 1.87 (dq, *J* = 14.0 Hz, 7.6 Hz, 2H), 1.57 (br. s, 2H), 0.73 (t, *J* = 7.5 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): δ 142.3, 141.8, 137.3, 124.3, 123.8, 123.6, 123.3, 122.7, 58.8, 34.0, 8.3.

HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₇H₂₄N: 220.1154 found: 220.1159.



5i Prepared according to the **General Procedure B**. 4-phenylbenzotrile, propylmagnesium chloride solution and lanthanum chloride bis(lithium chloride) produced **4k**. The crude reaction mixture was purified via column chromatography (1% isopropylamine, 15% ethyl acetate, and 84% hexanes) to further afford **5i** (331 mg, 1.24 mmol, 62% yield).

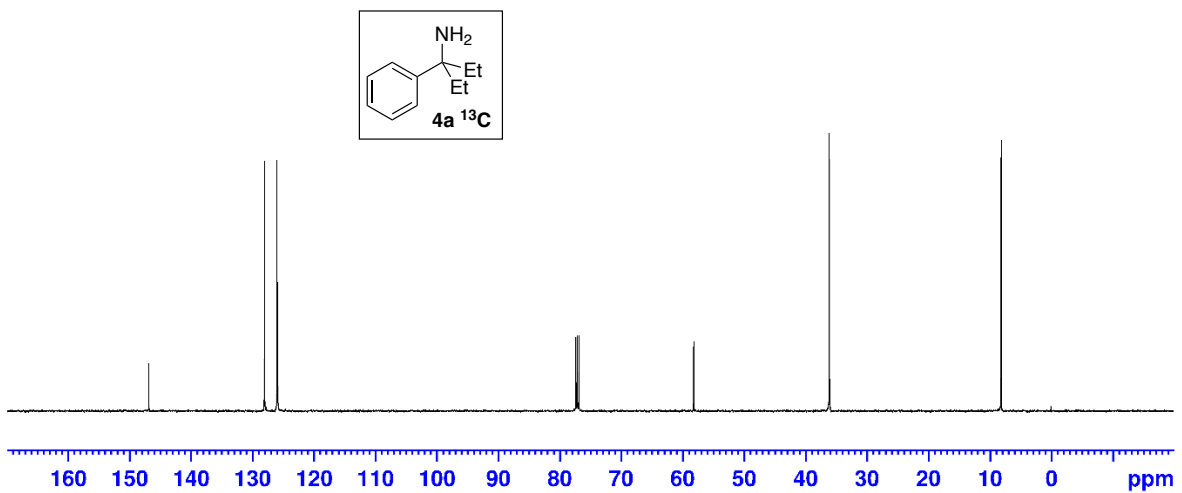
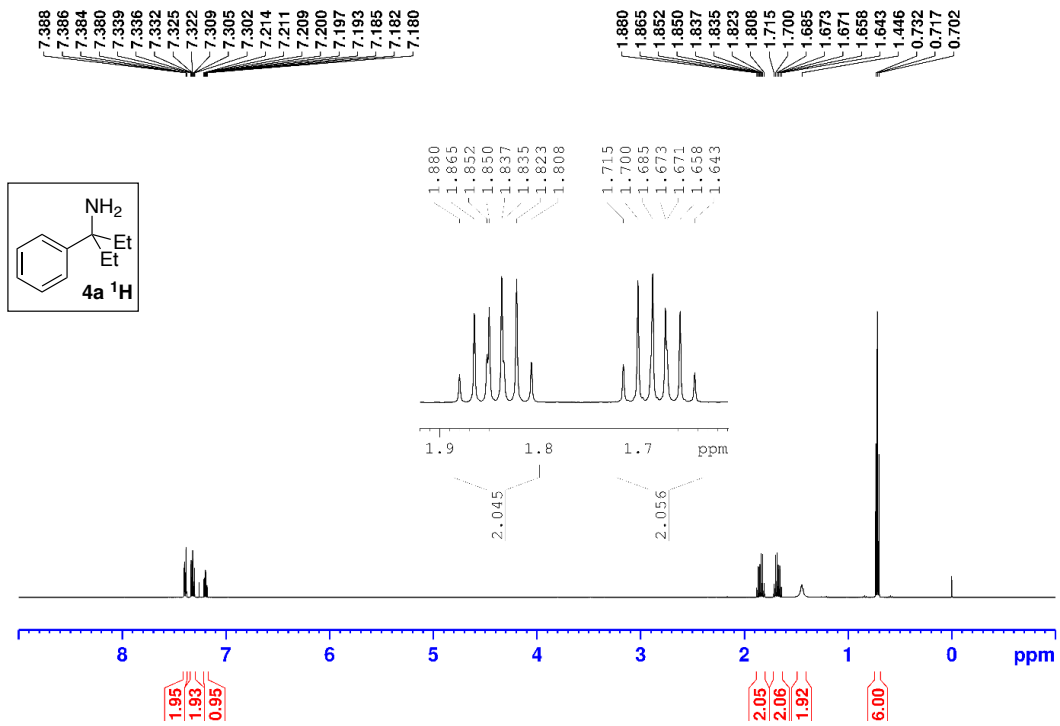
¹H NMR (500 MHz, CDCl₃): 7.61–7.59 (m, 2H), 7.57–7.53 (m, 2H), 7.47–7.41 (m, 4H), 7.34–7.1 (m, 1H), 1.80 (ddd, *J* = 13.5 Hz, 12.5 Hz, 4.3 Hz, 2H), 1.66 (ddd, *J* = 13.6 Hz, 12.3 Hz, 4.7 Hz, 2H), 1.48 (br. s, 2H), 1.31–1.22 (m, 2H), 1.11–1.01 (m, 2H), (t, *J* = 7.4 Hz, 6H).

¹³C NMR (UDEFT) (125 MHz, CDCl₃): 146.9, 141.0, 138.7, 128.8, 127.2, 127.1, 126.8, 126.3, 57.9, 46.7, 17.1, 14.7.

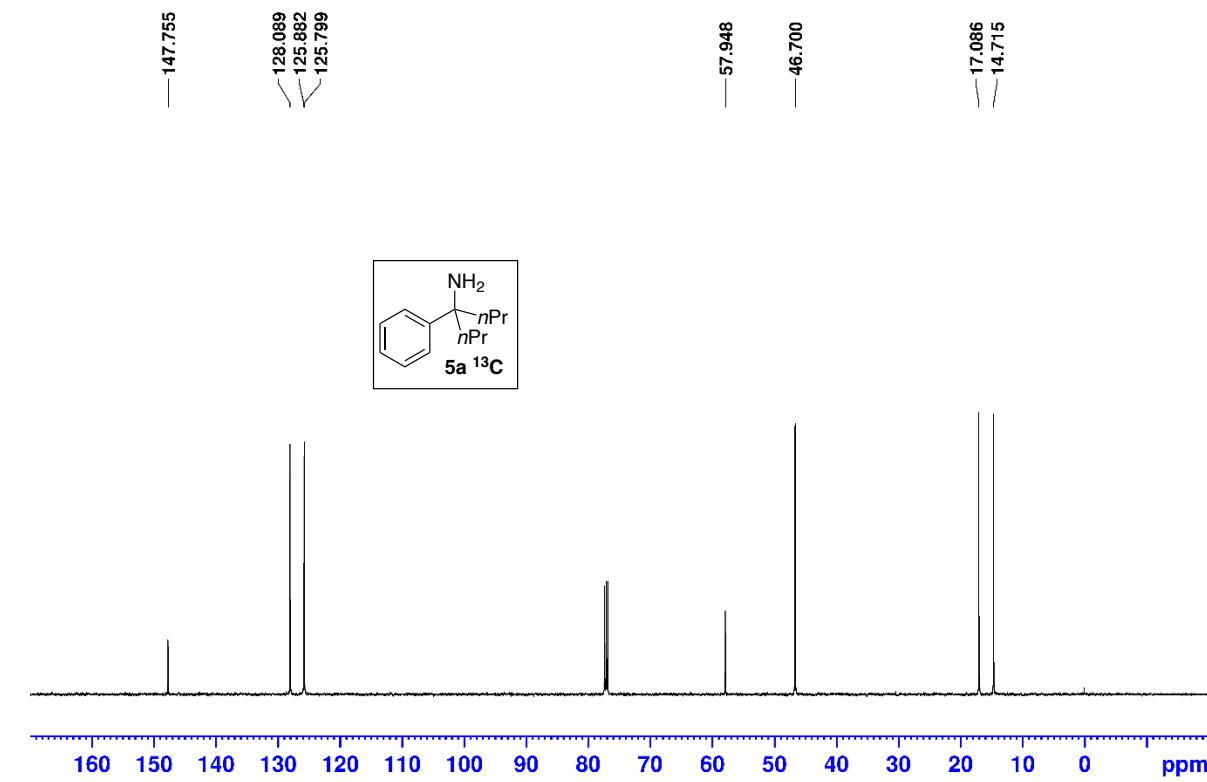
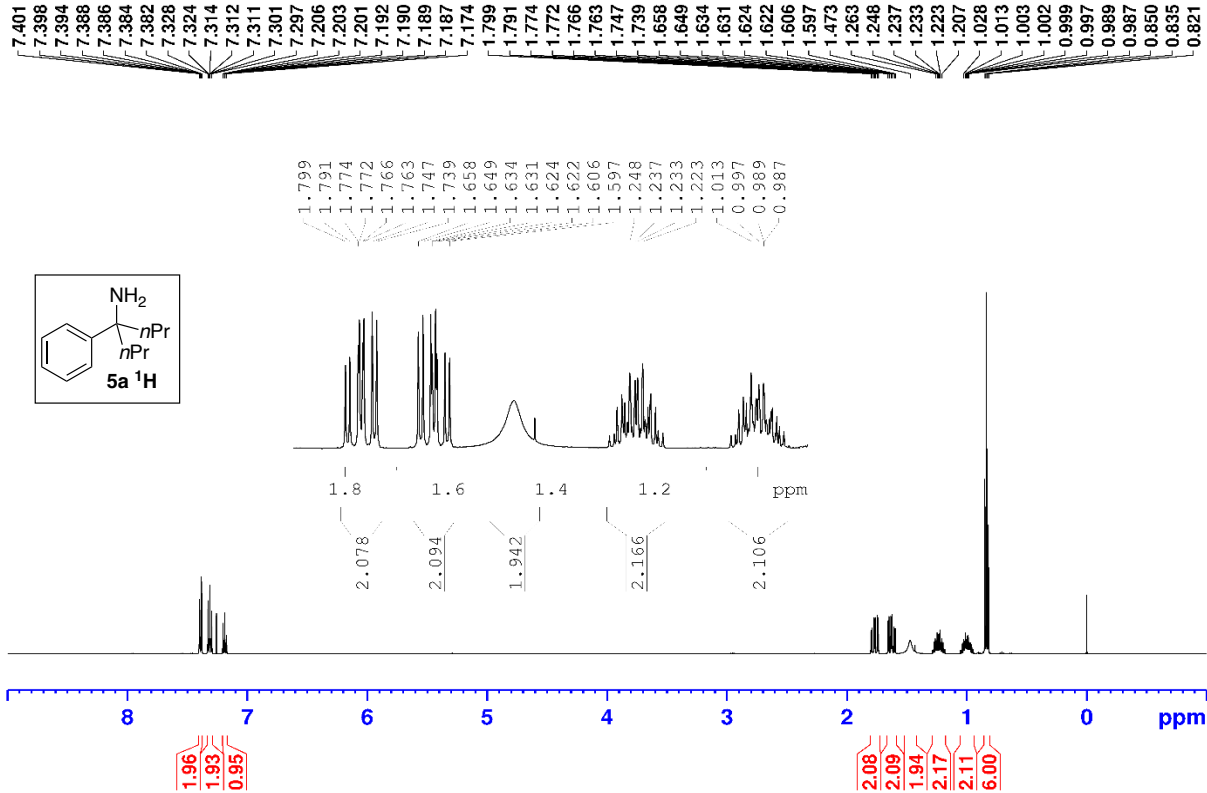
HRMS(ESI): *m/z* (M+H)⁺ calculated for C₁₇H₂₄N: 268.2060 found: 268.2060.

NMR Spectra for Product Amines:

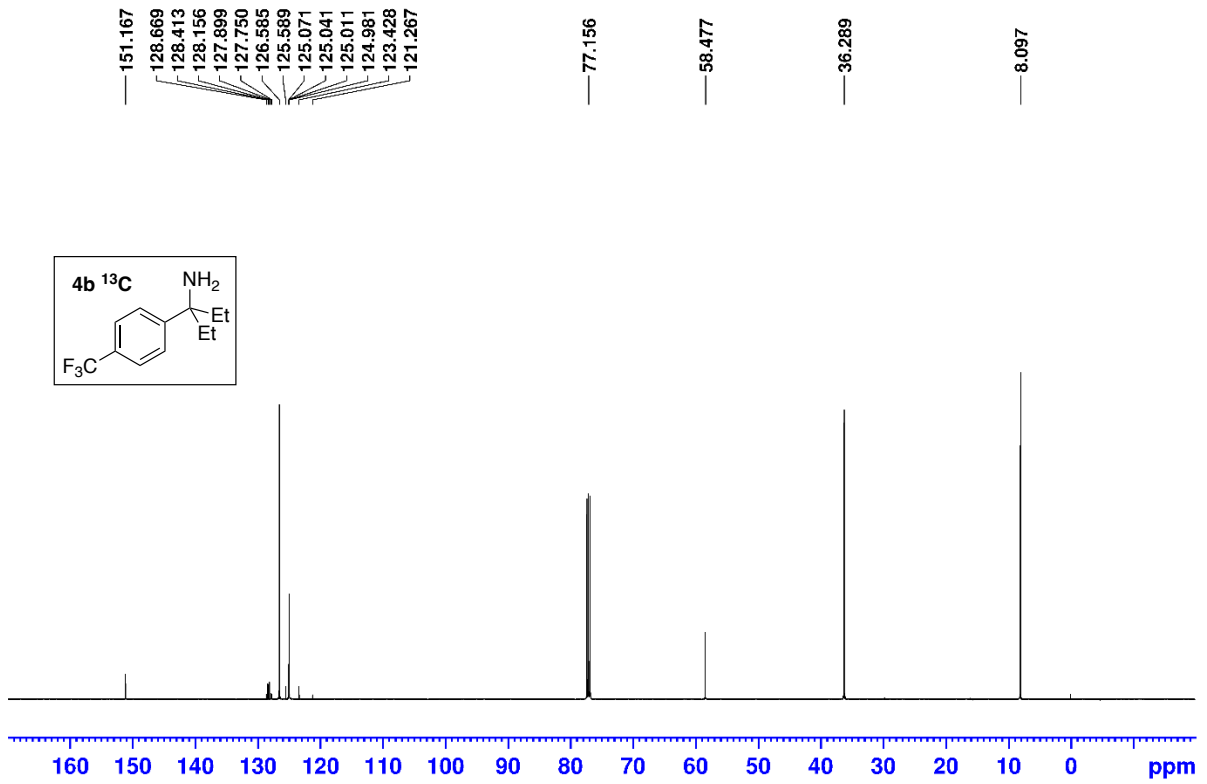
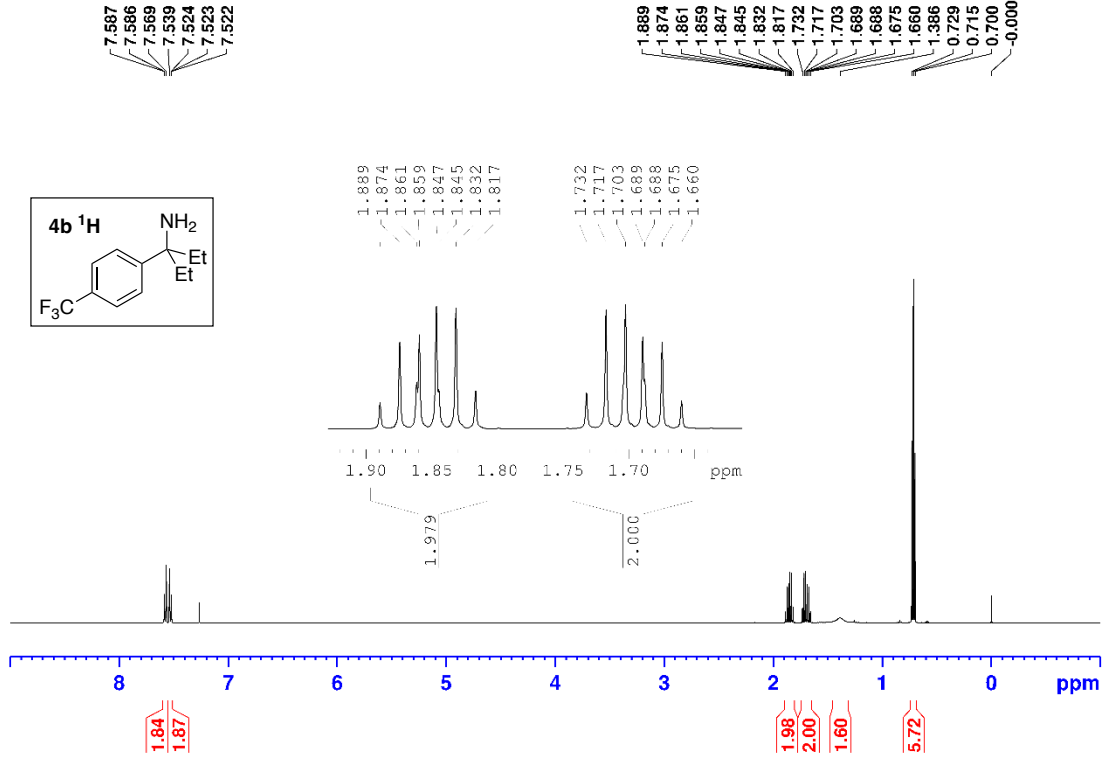
4a

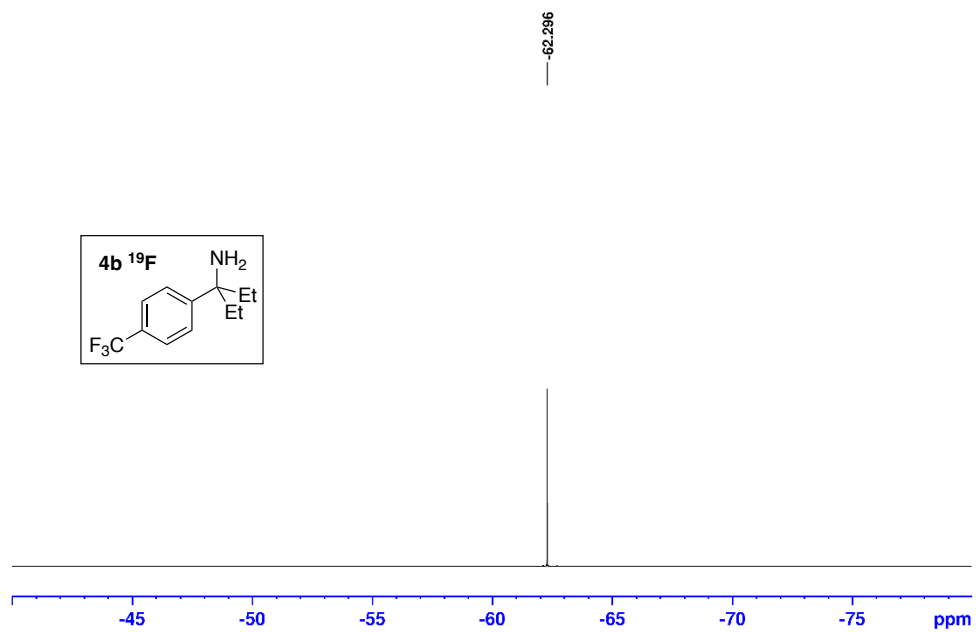
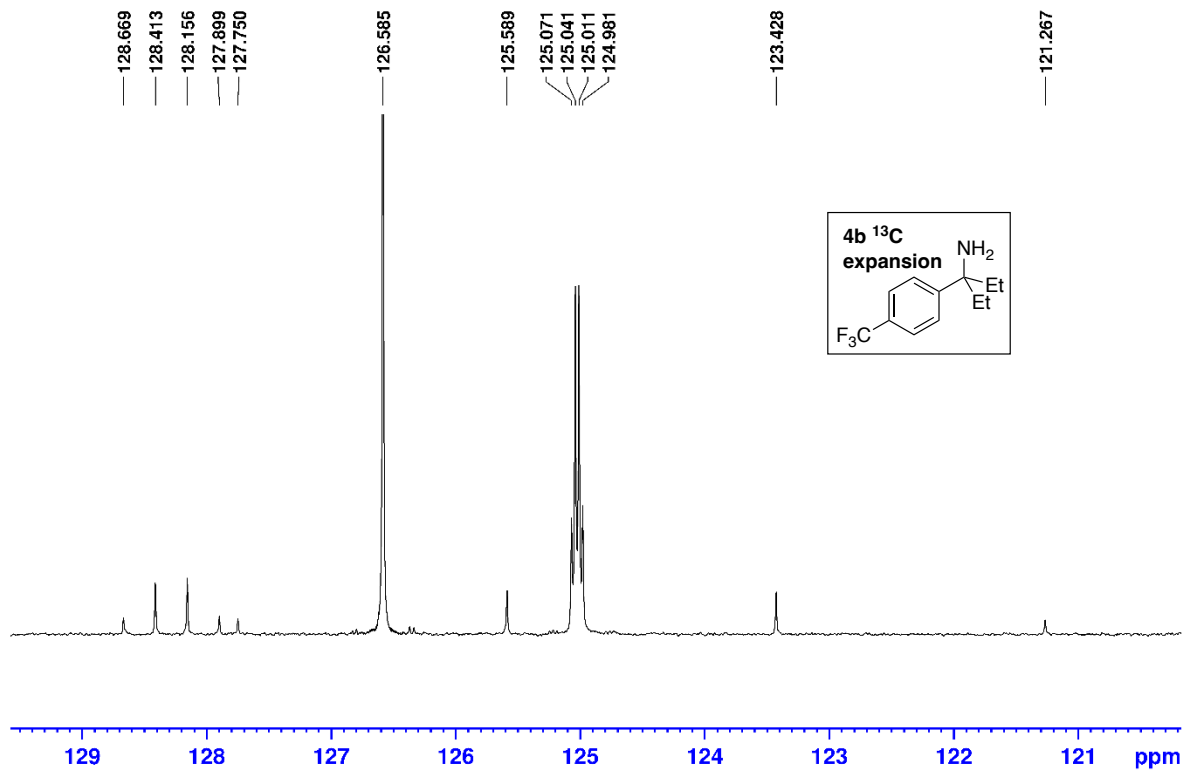


5a

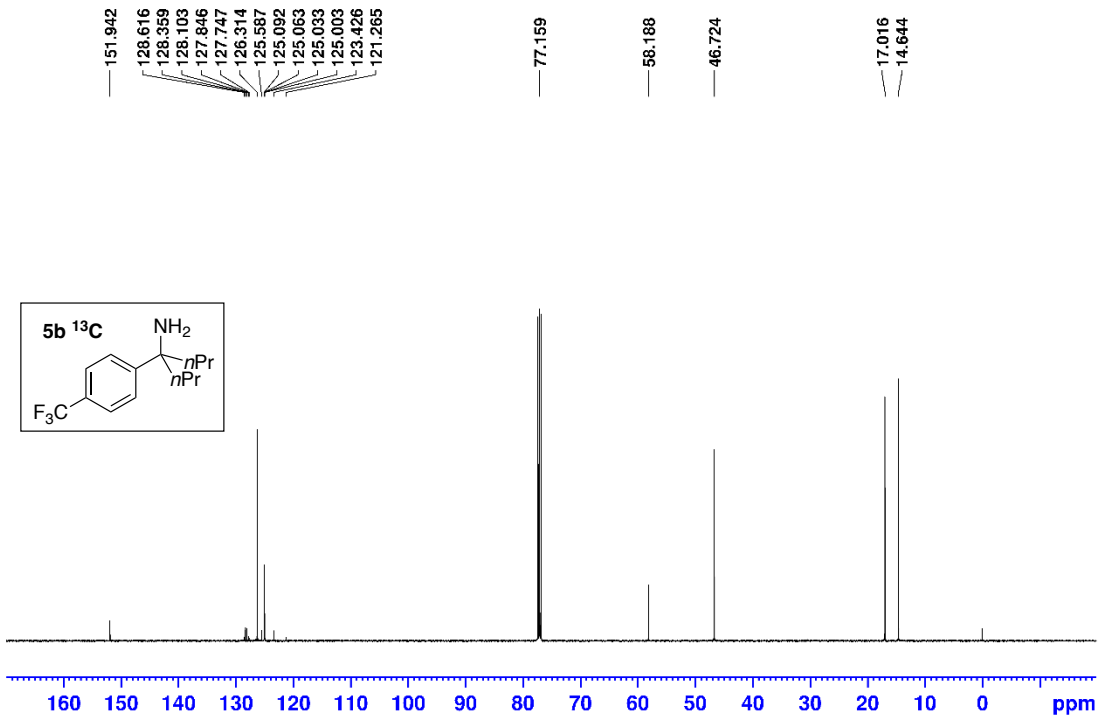
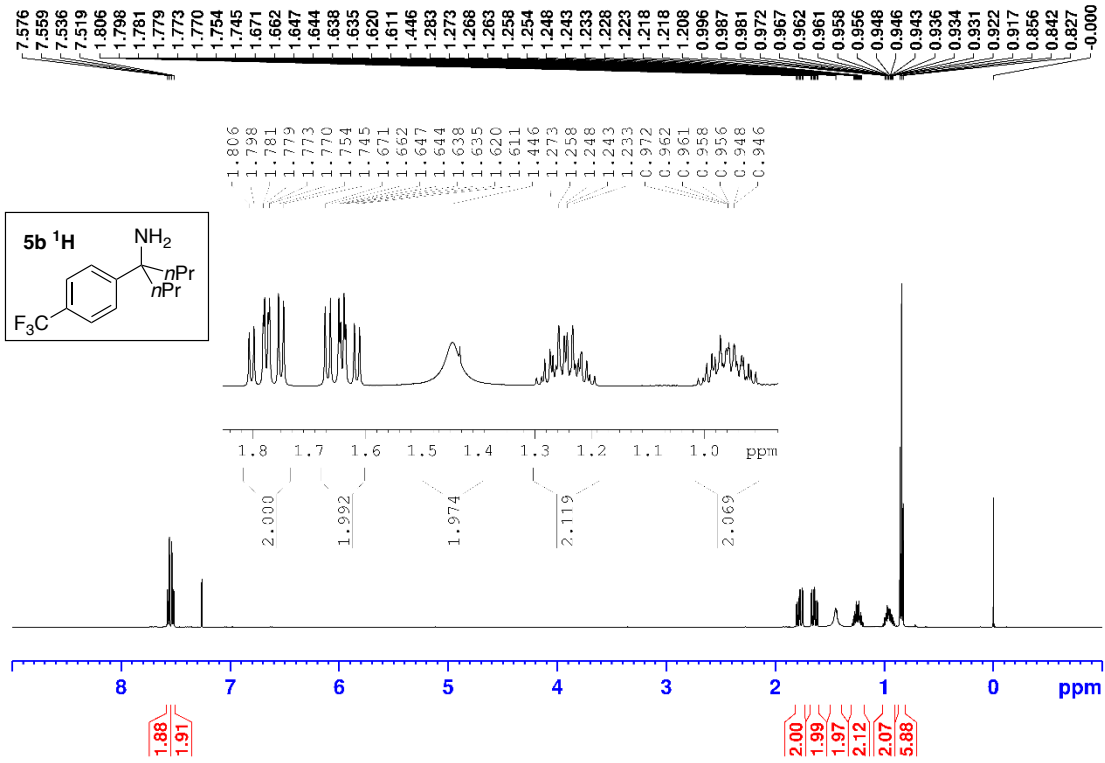


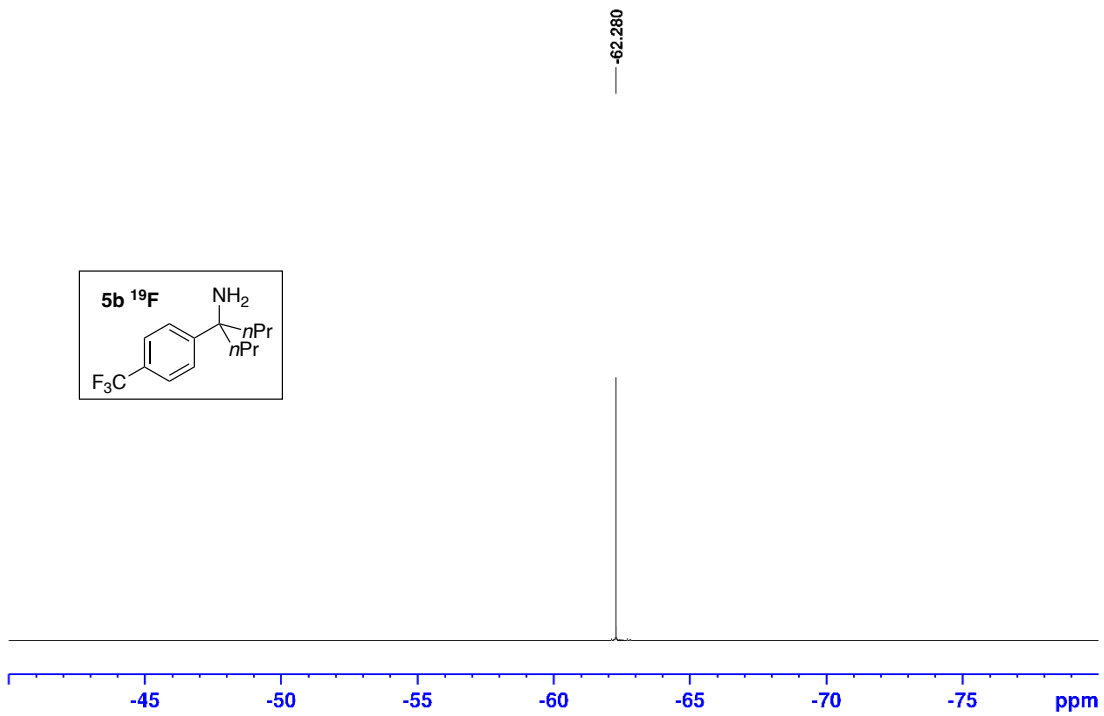
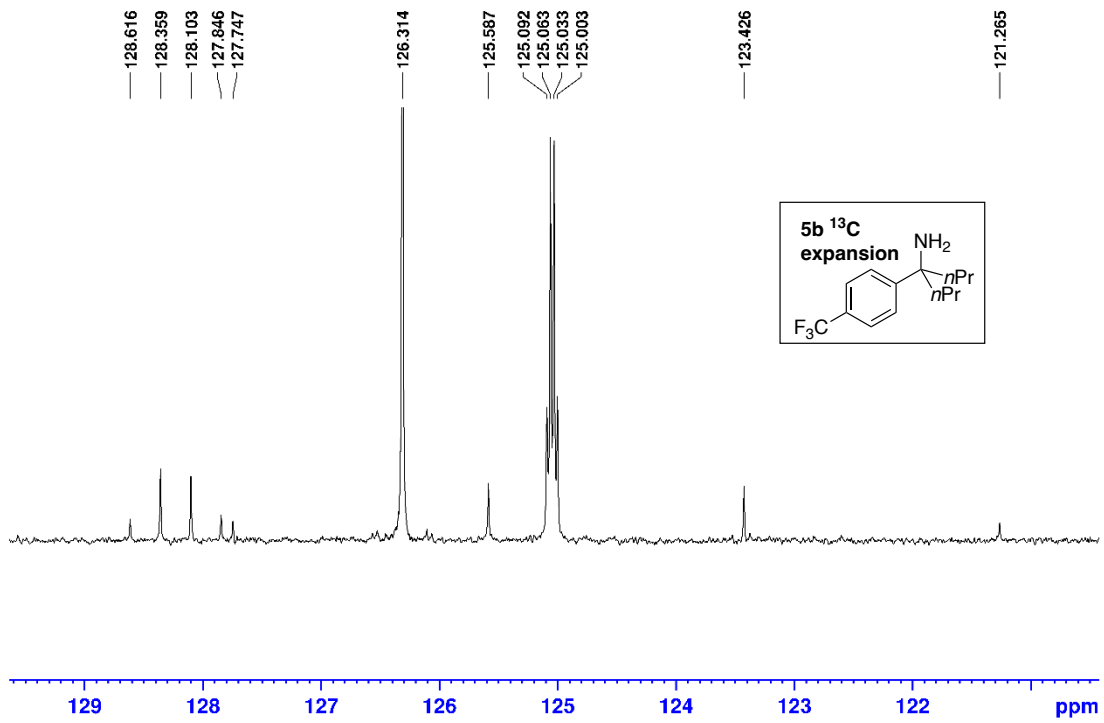
4b



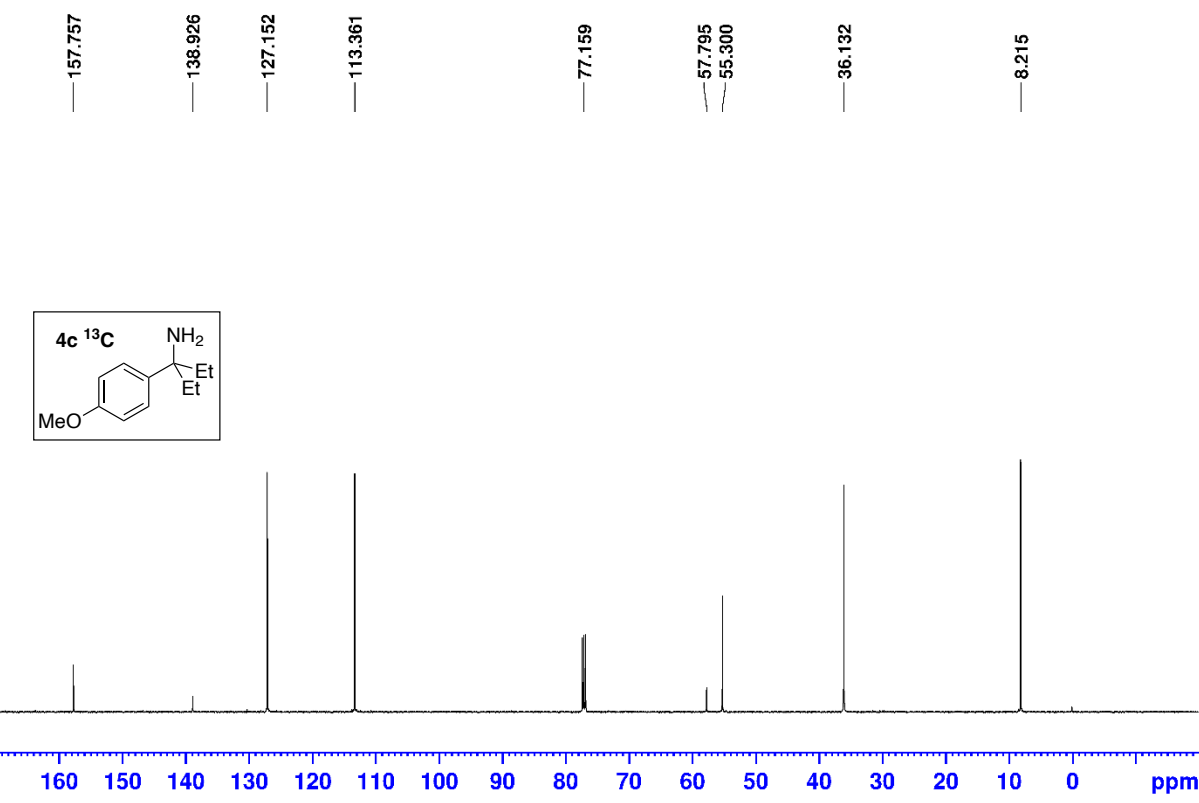
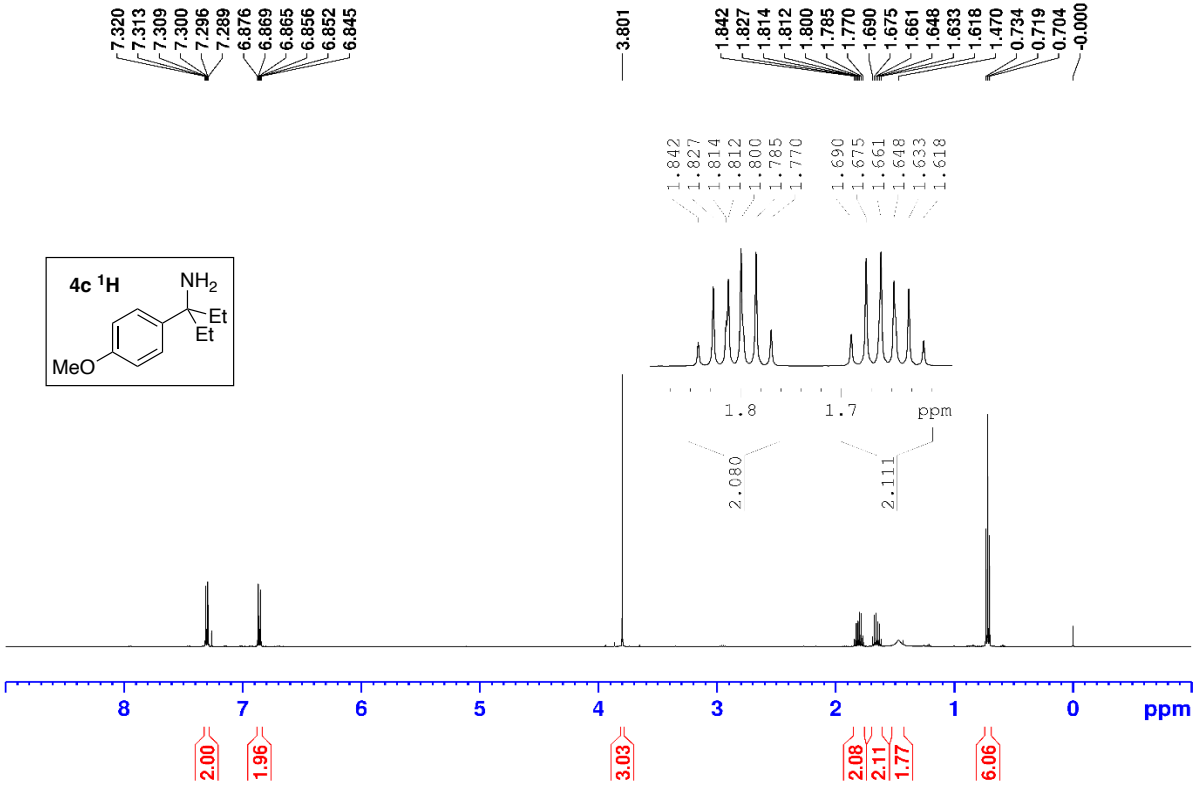


5b

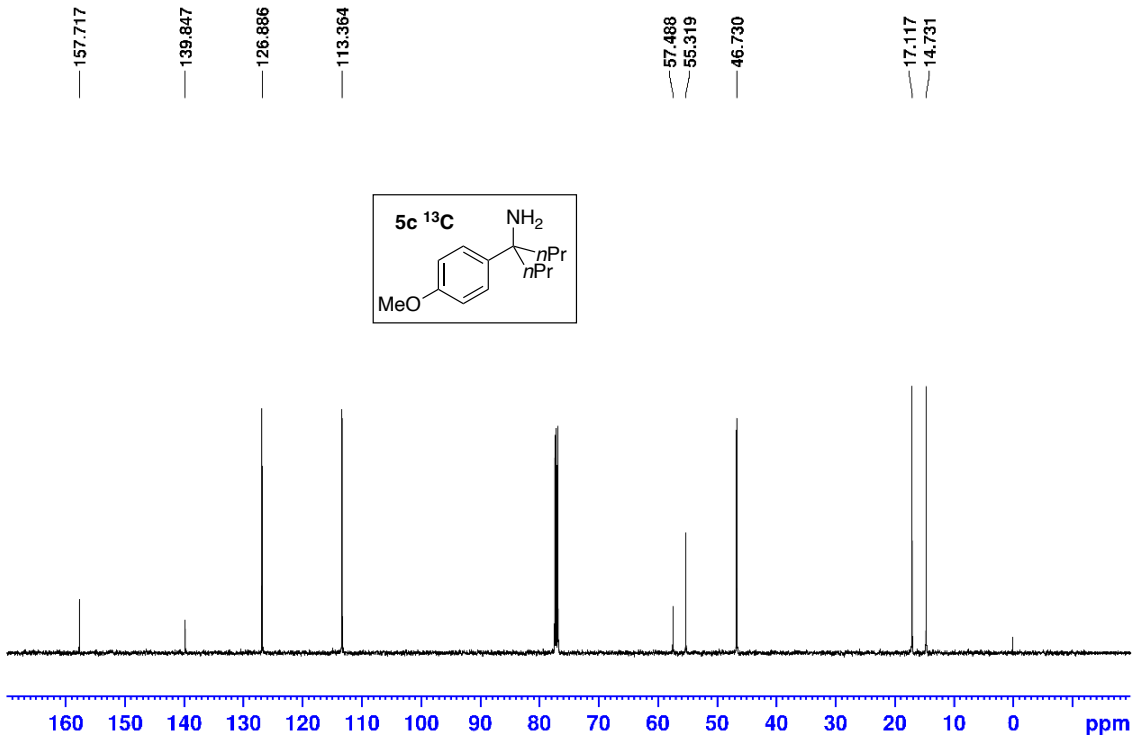
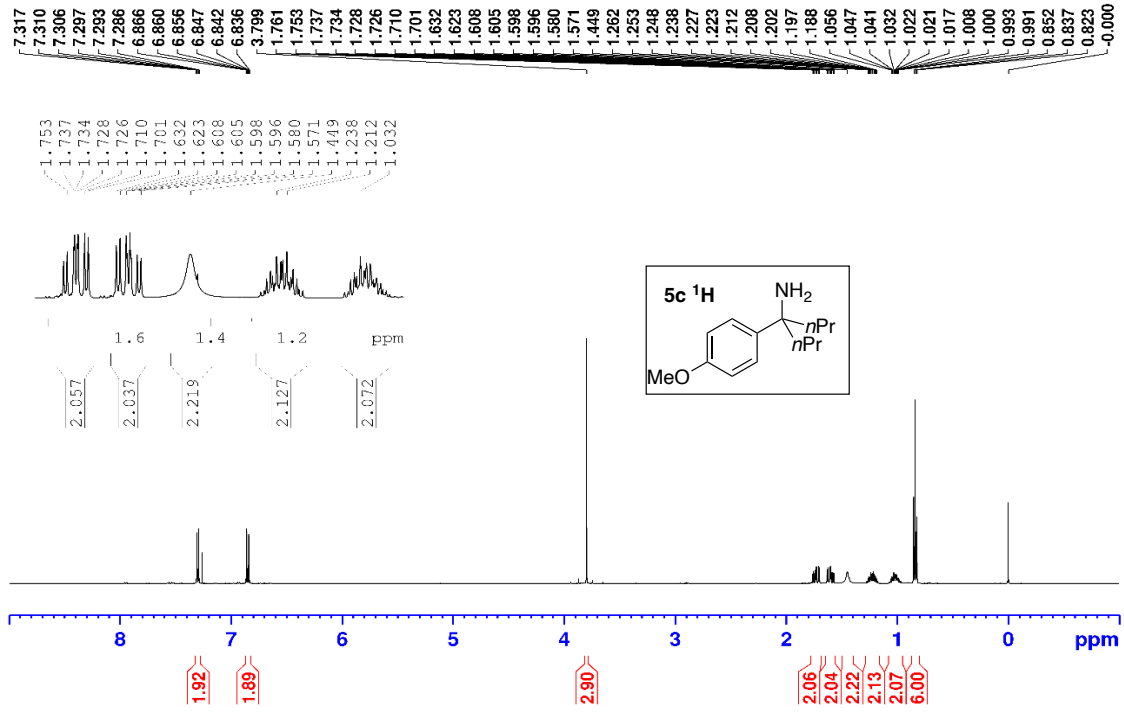




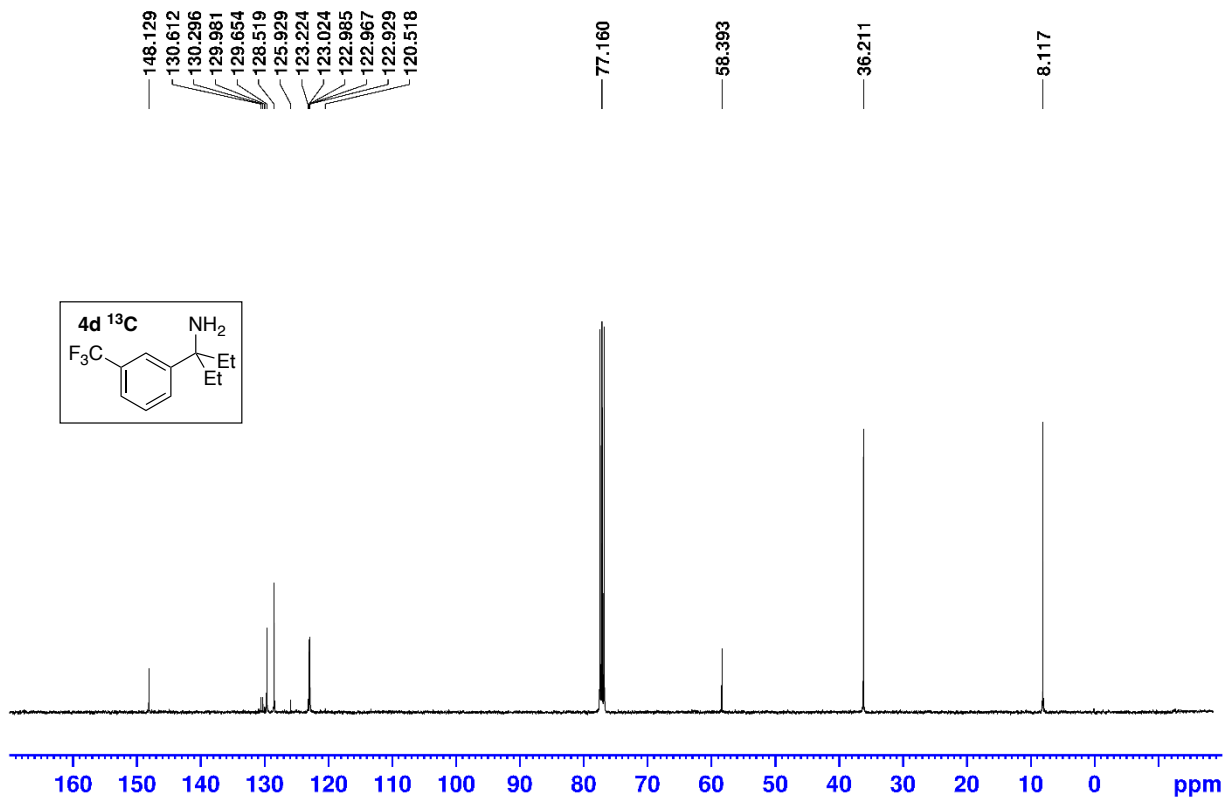
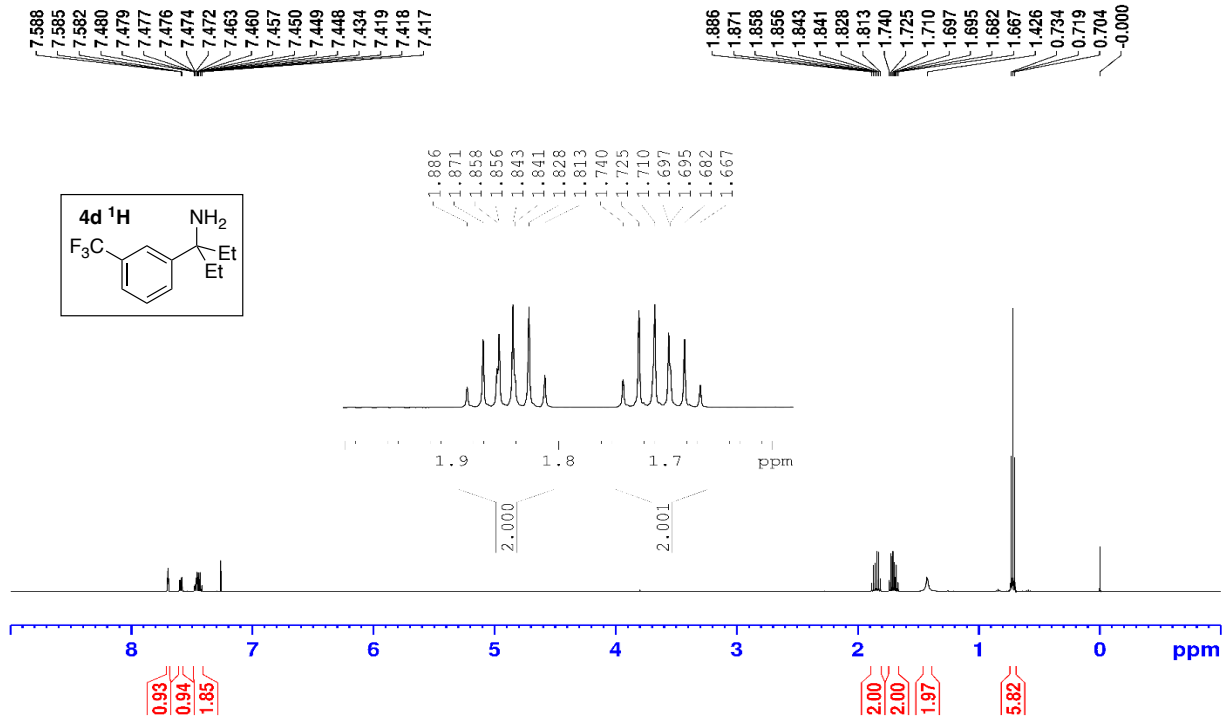
4c

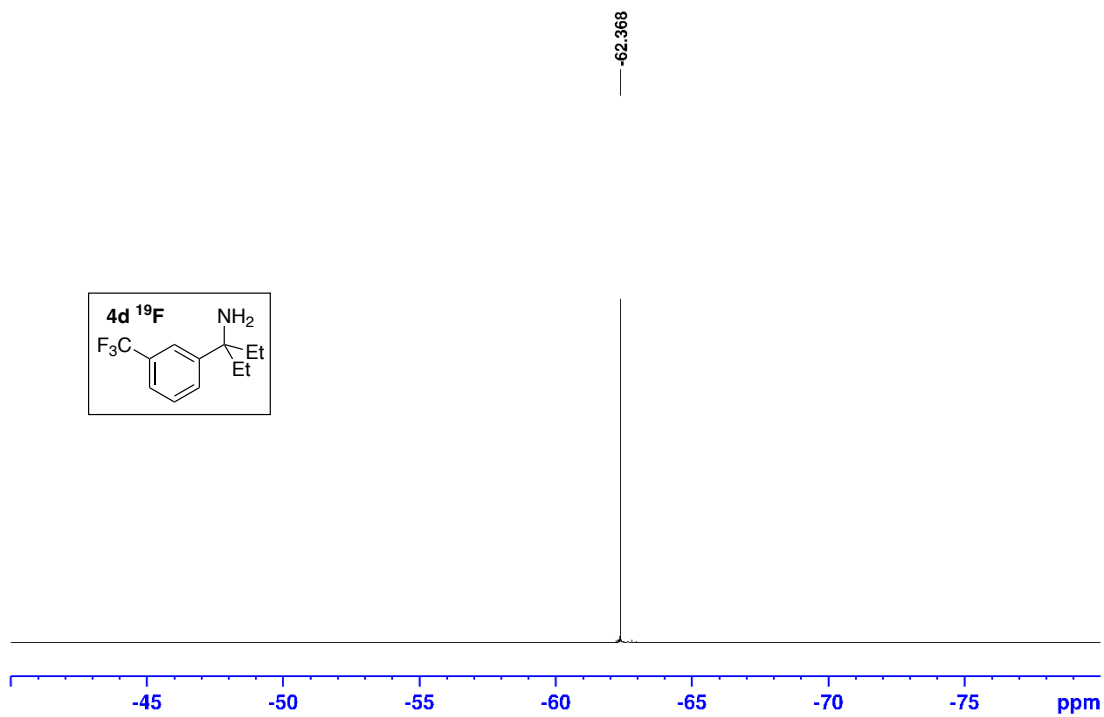
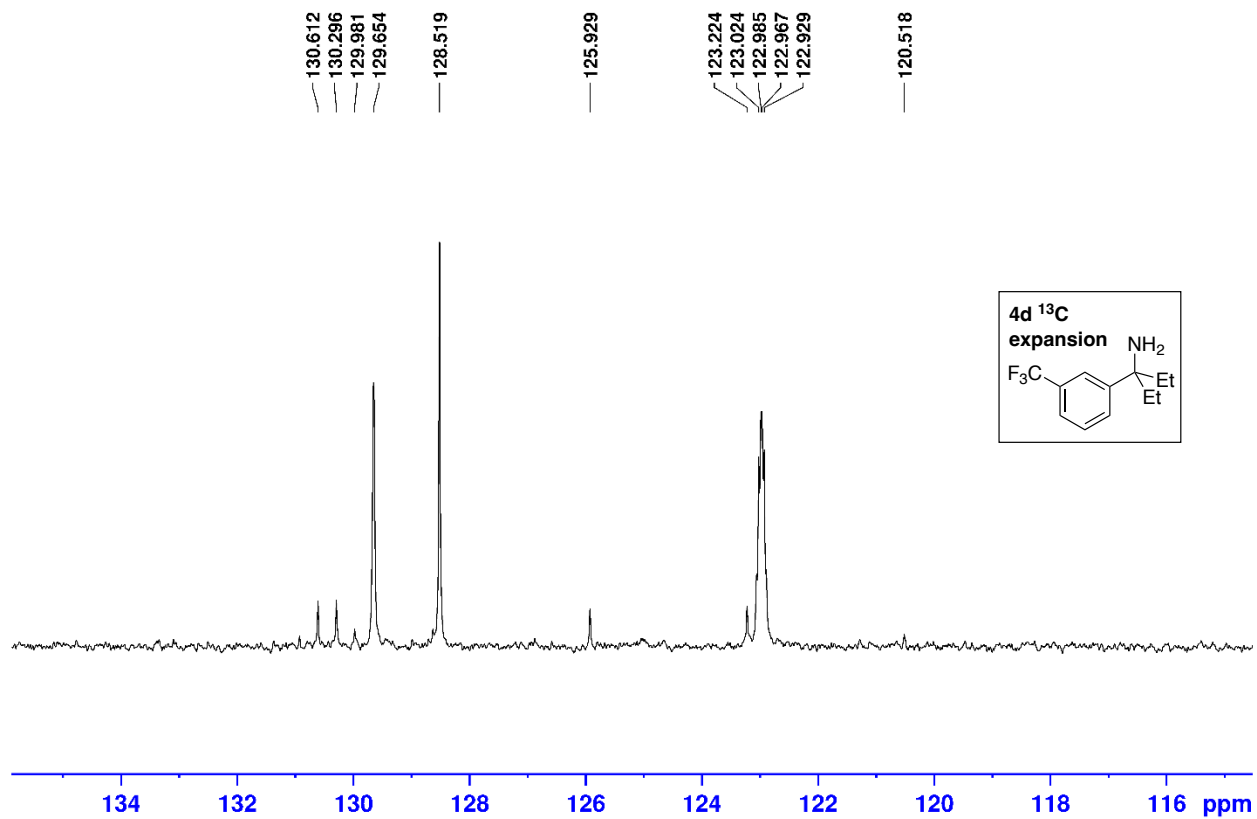


5c

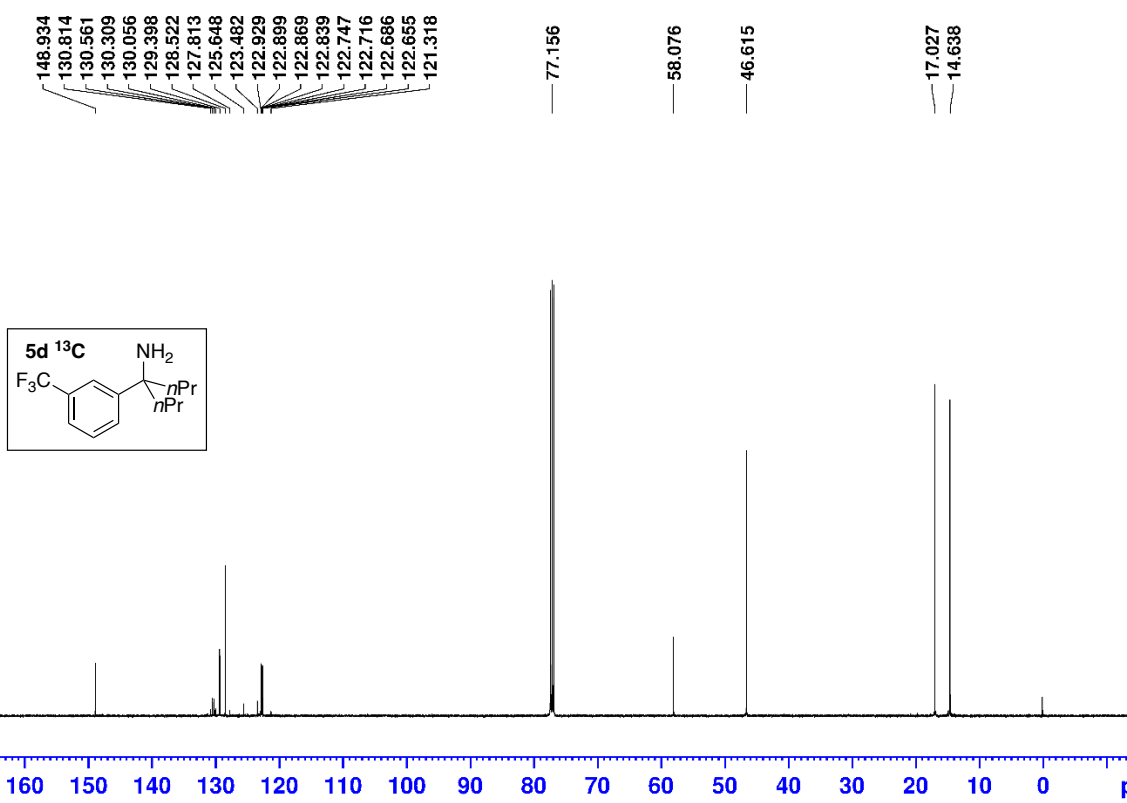
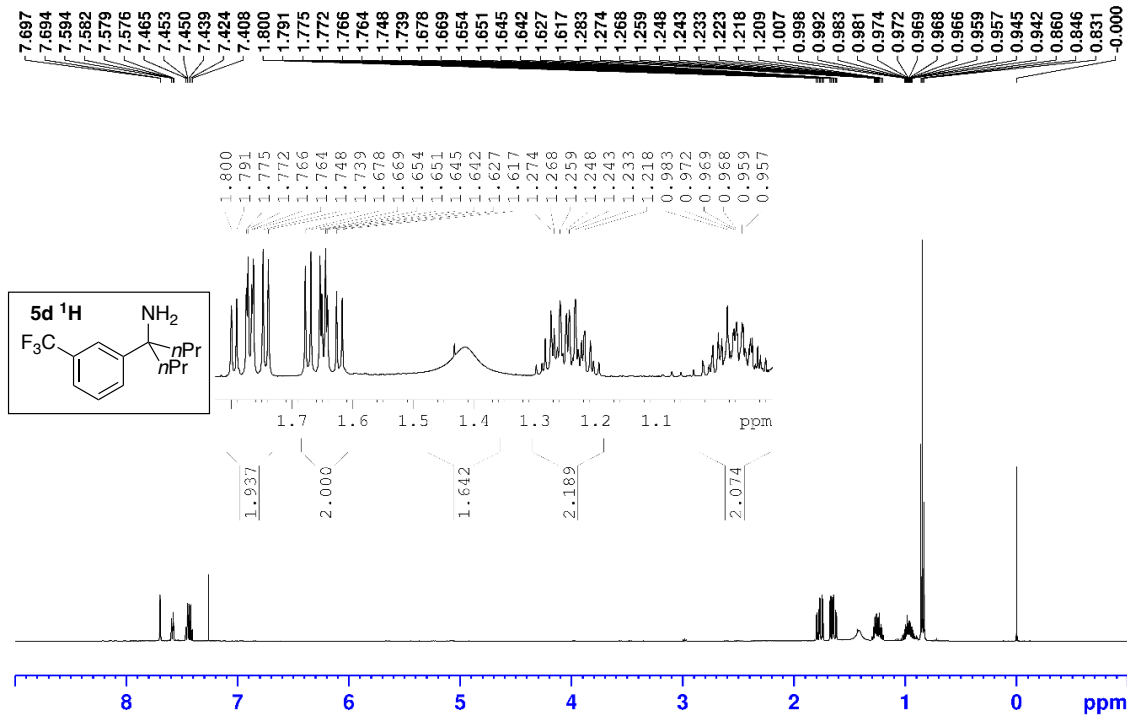


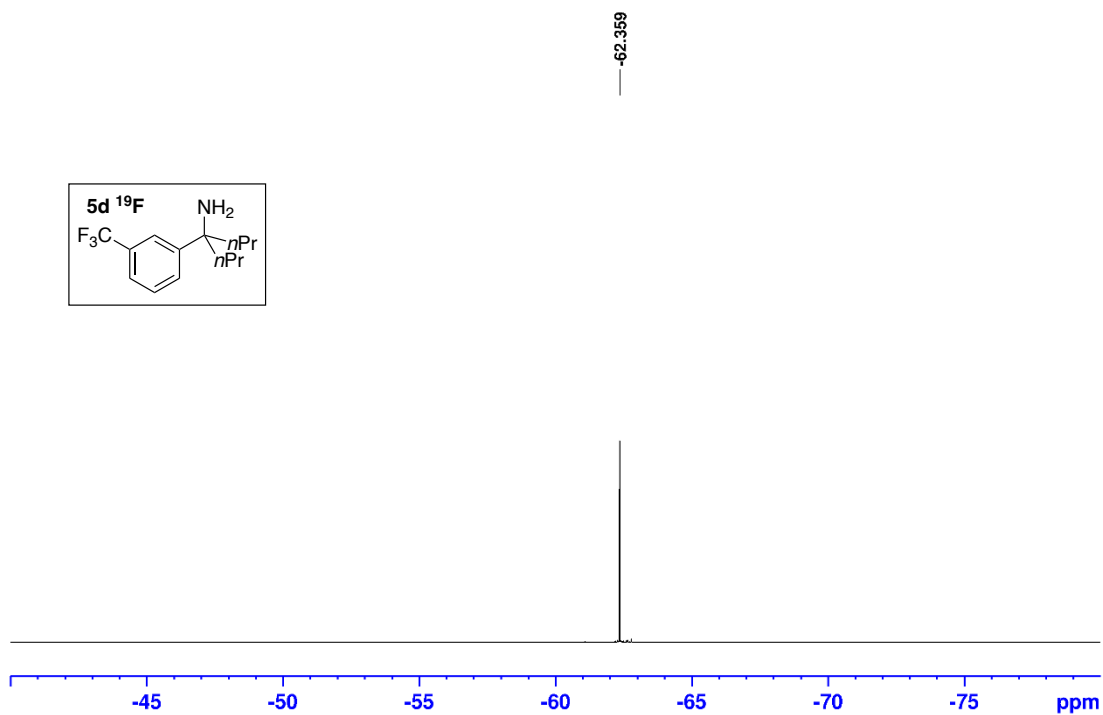
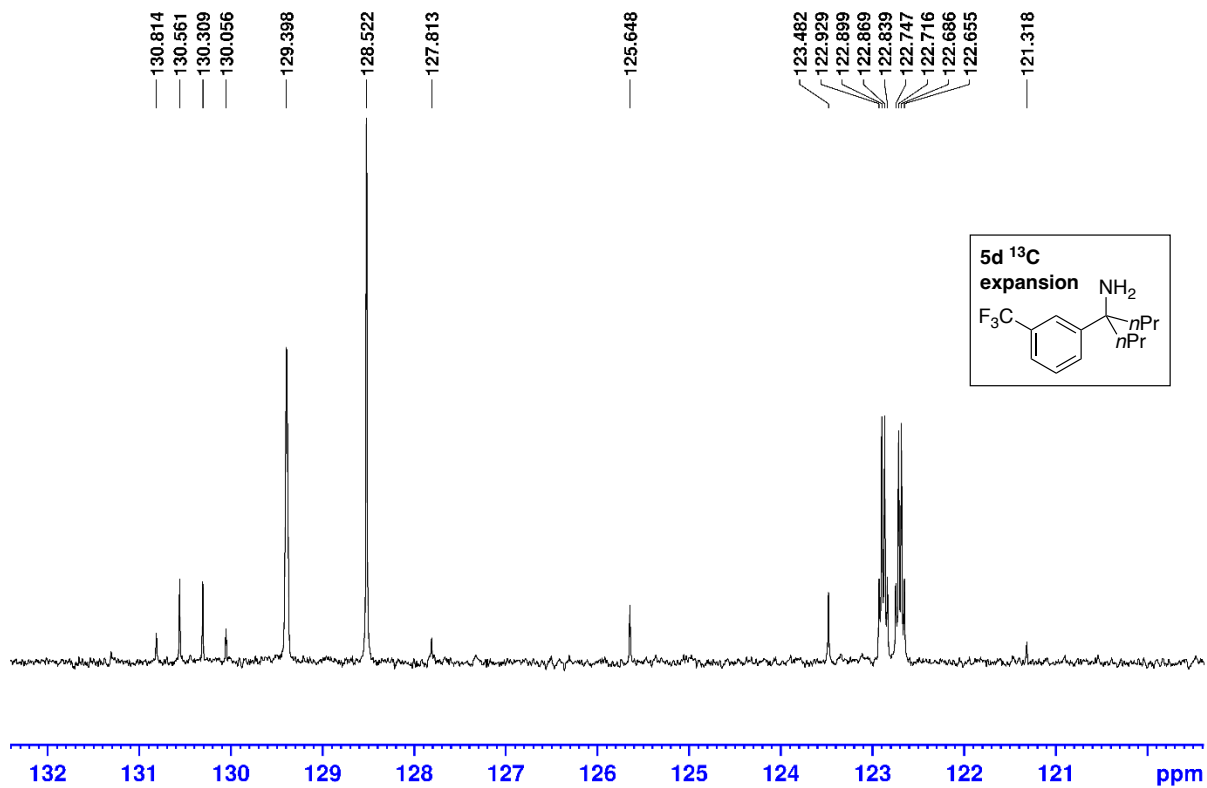
4d



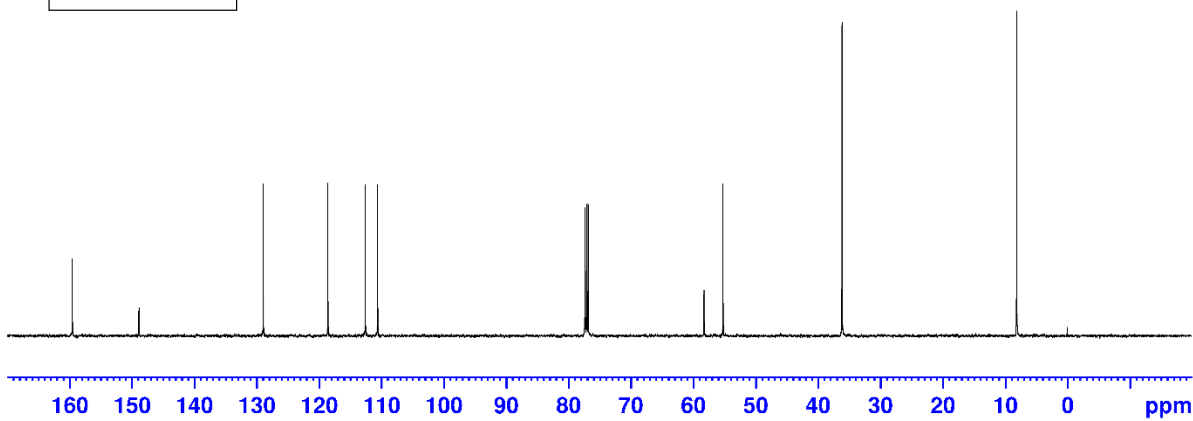
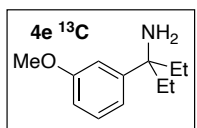
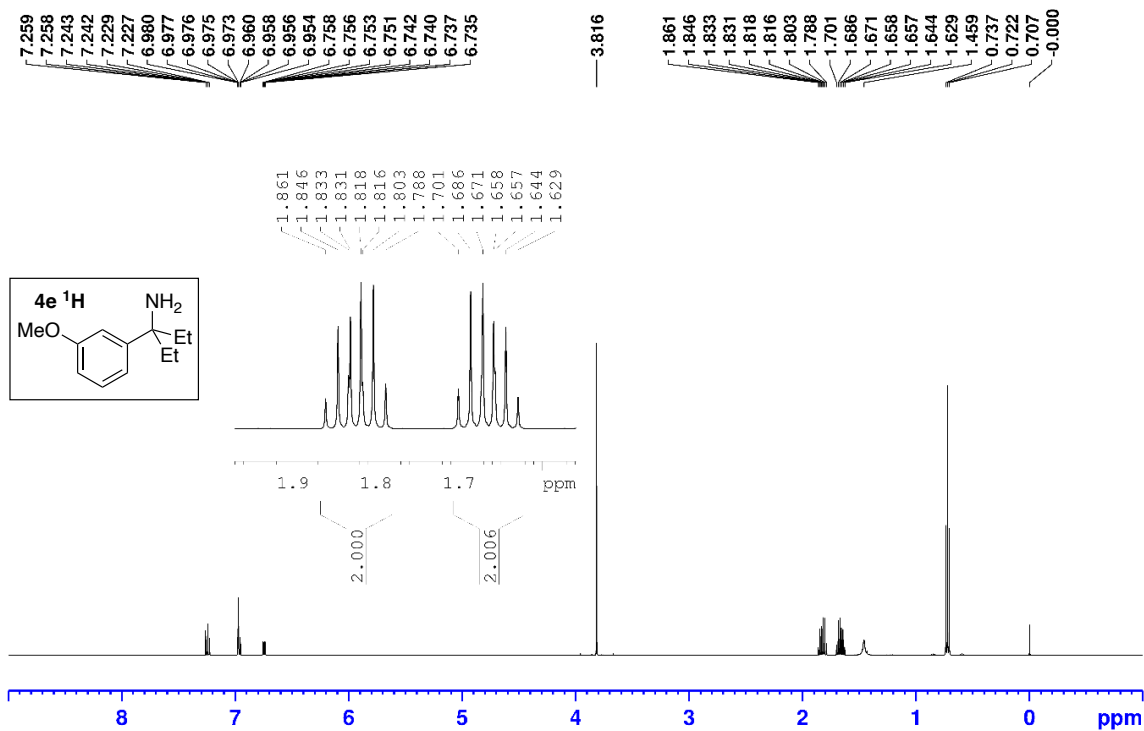


5d

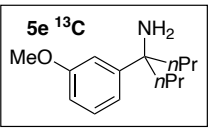
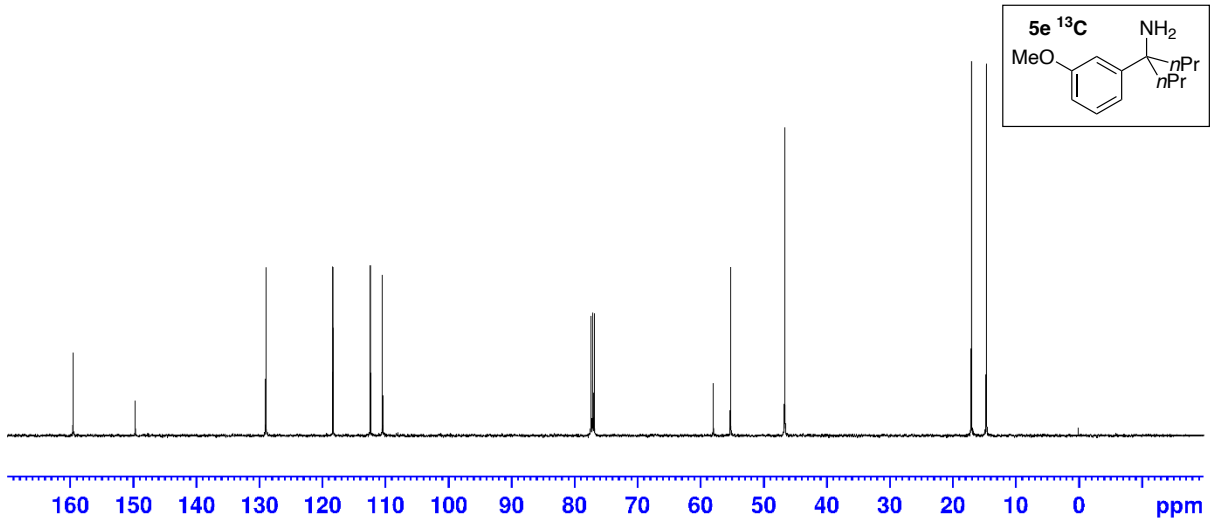
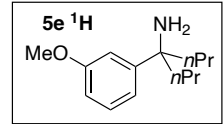
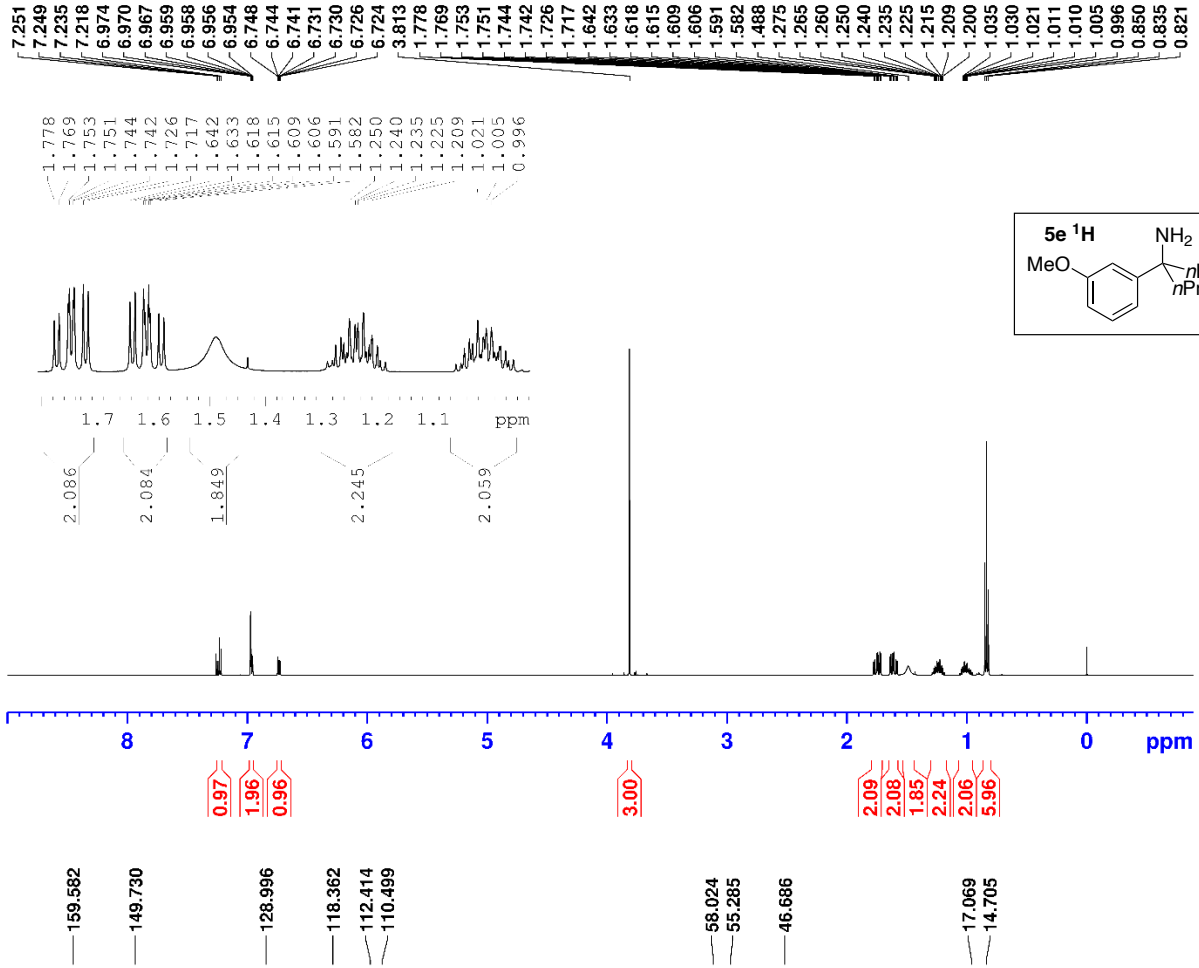




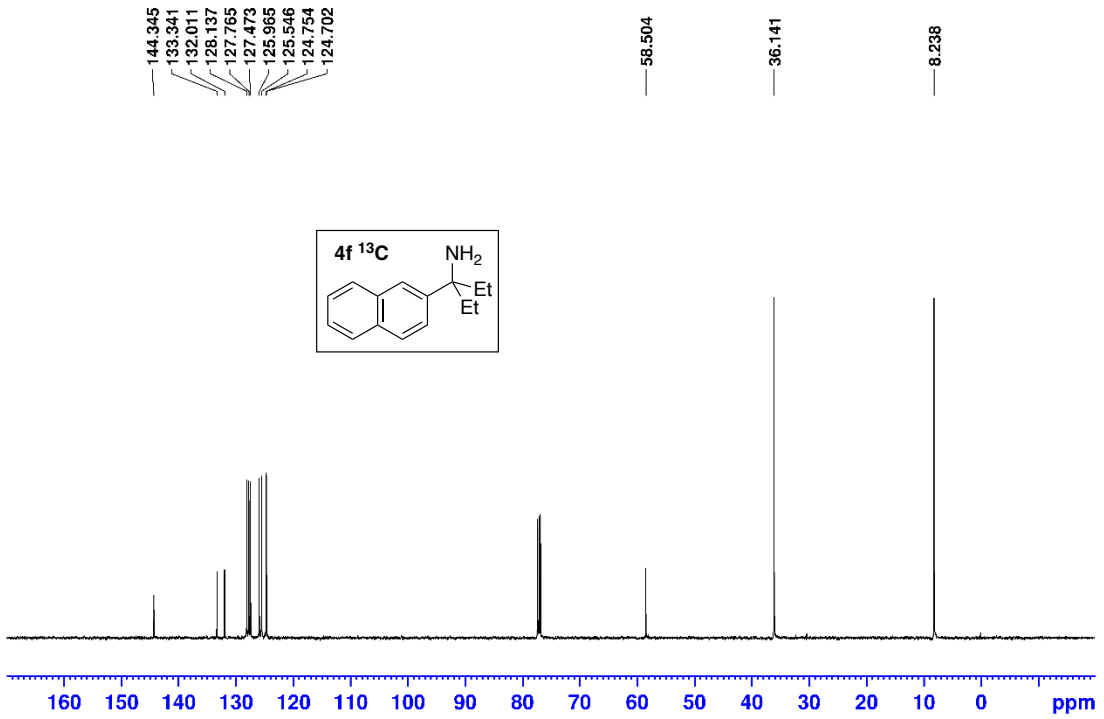
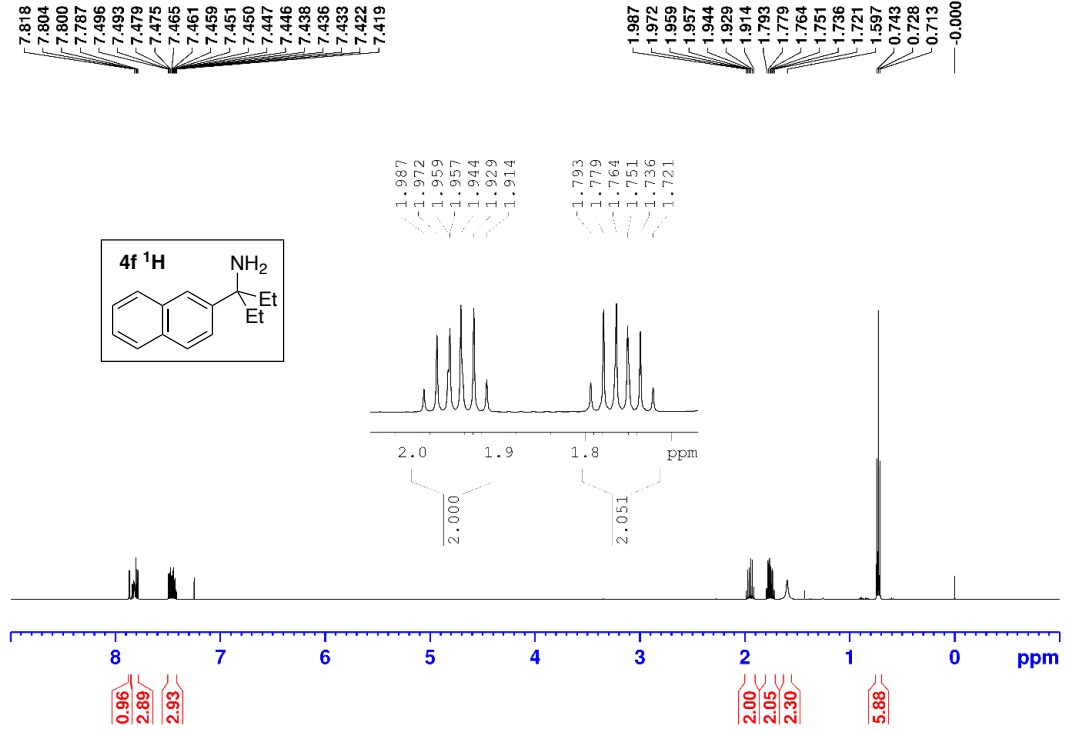
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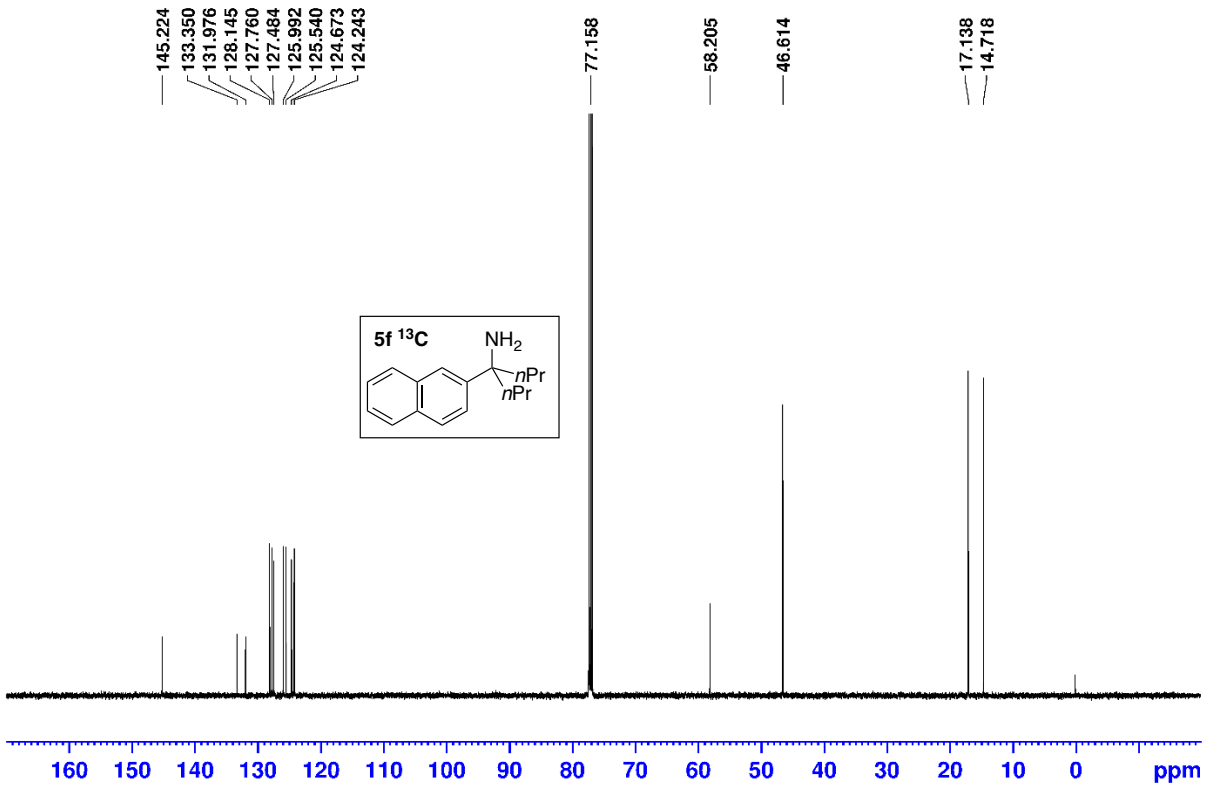
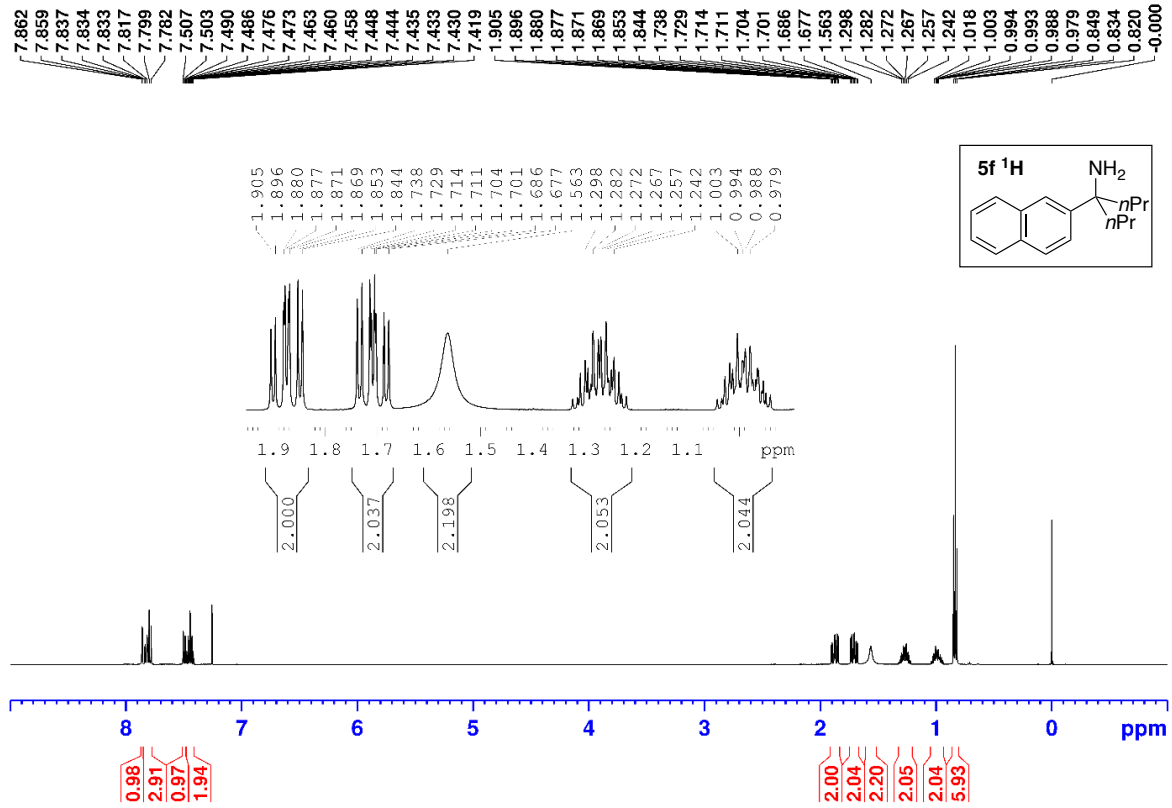
5e



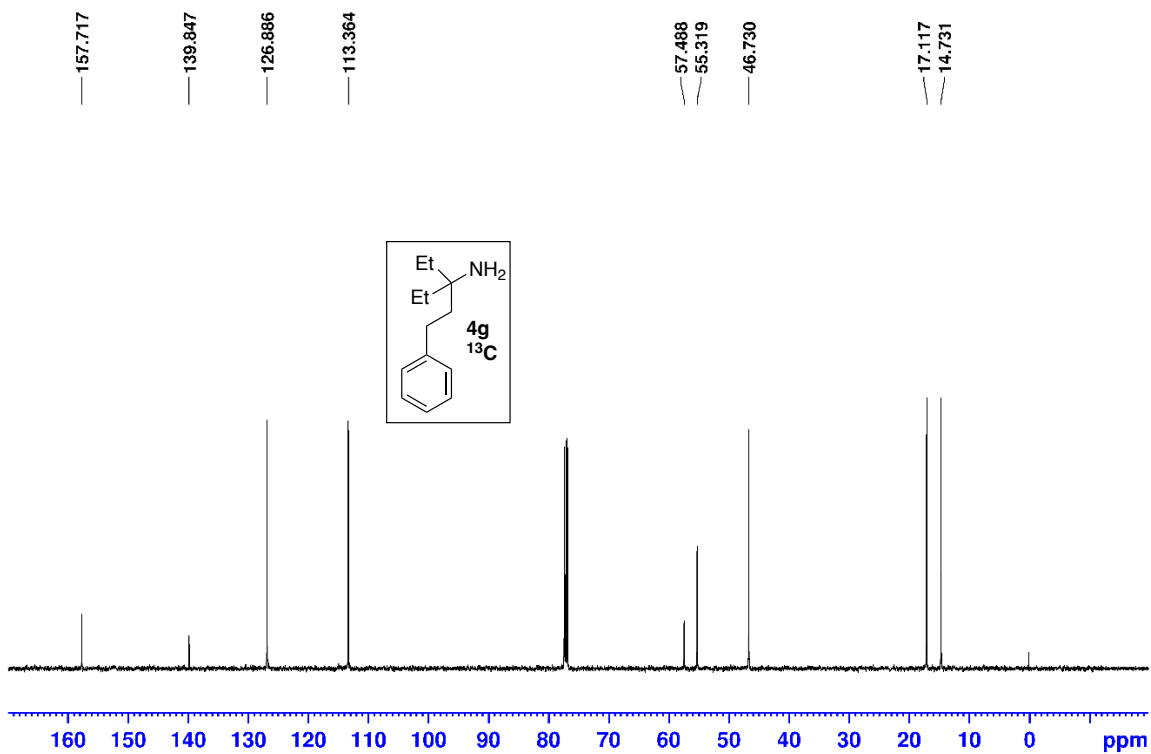
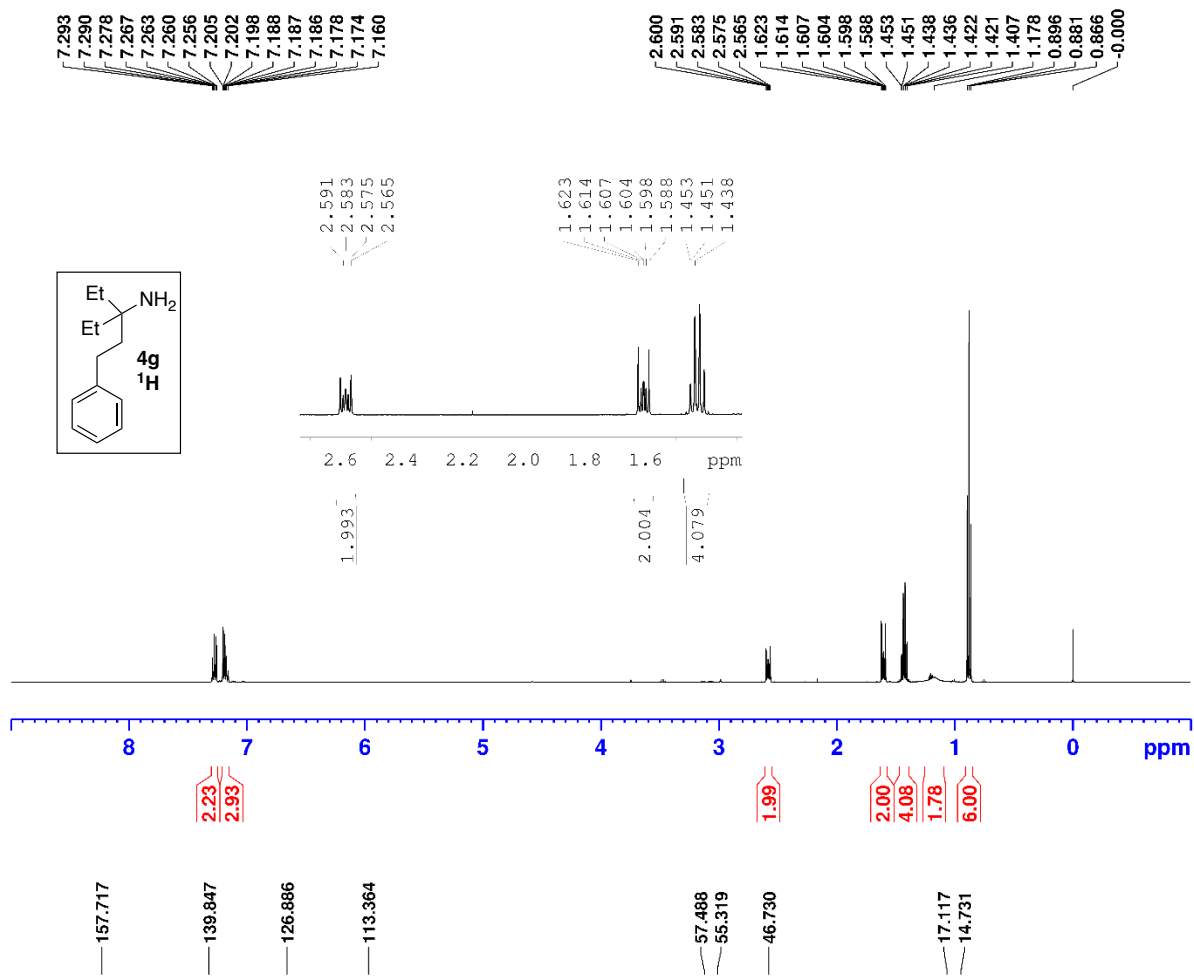
4f

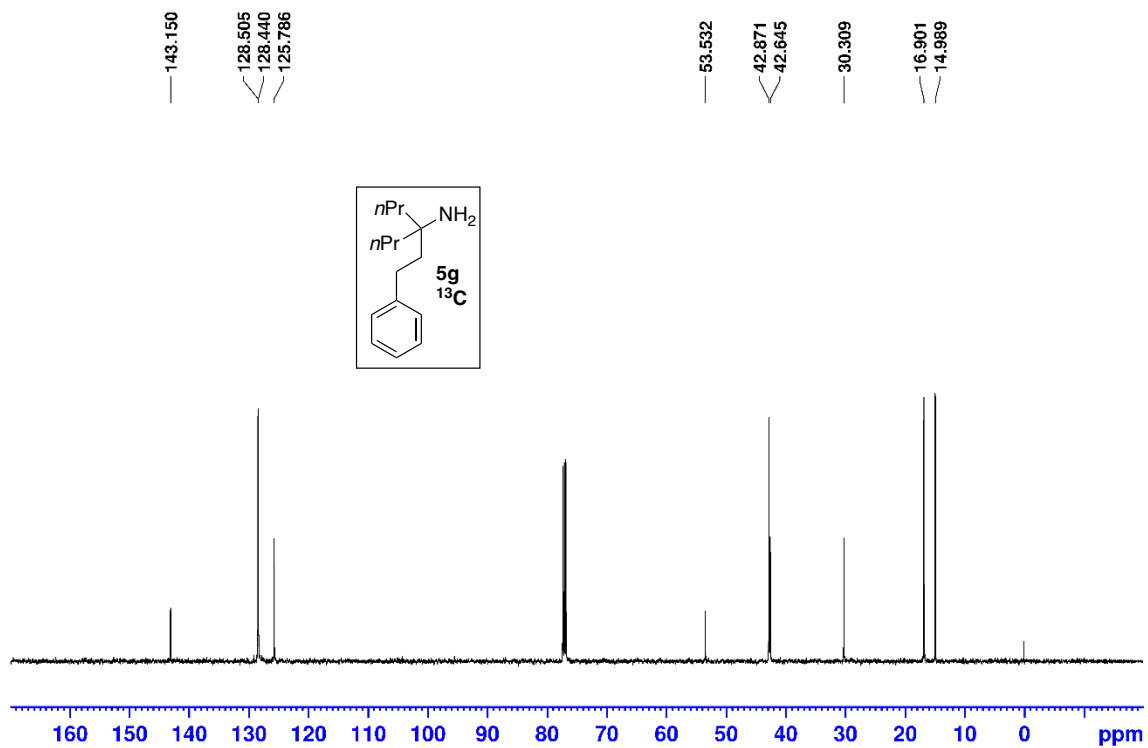
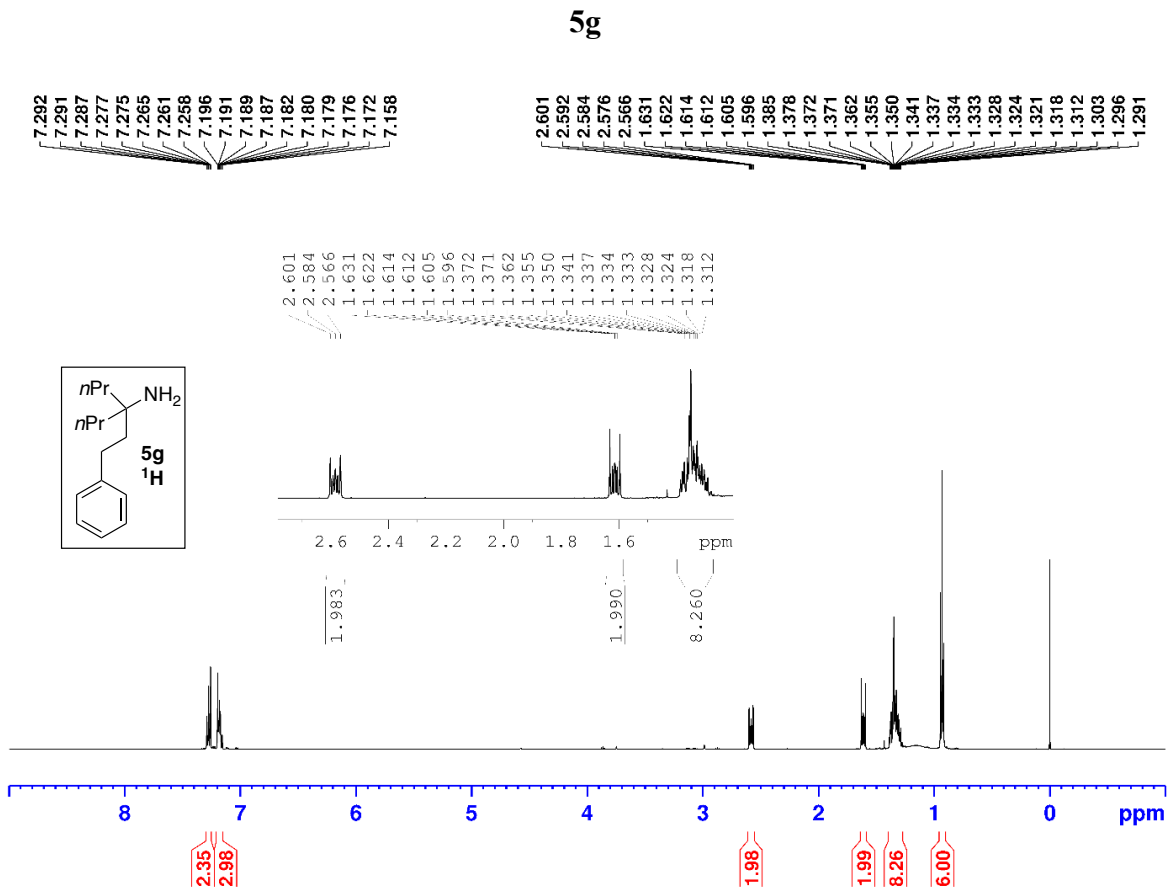


5f

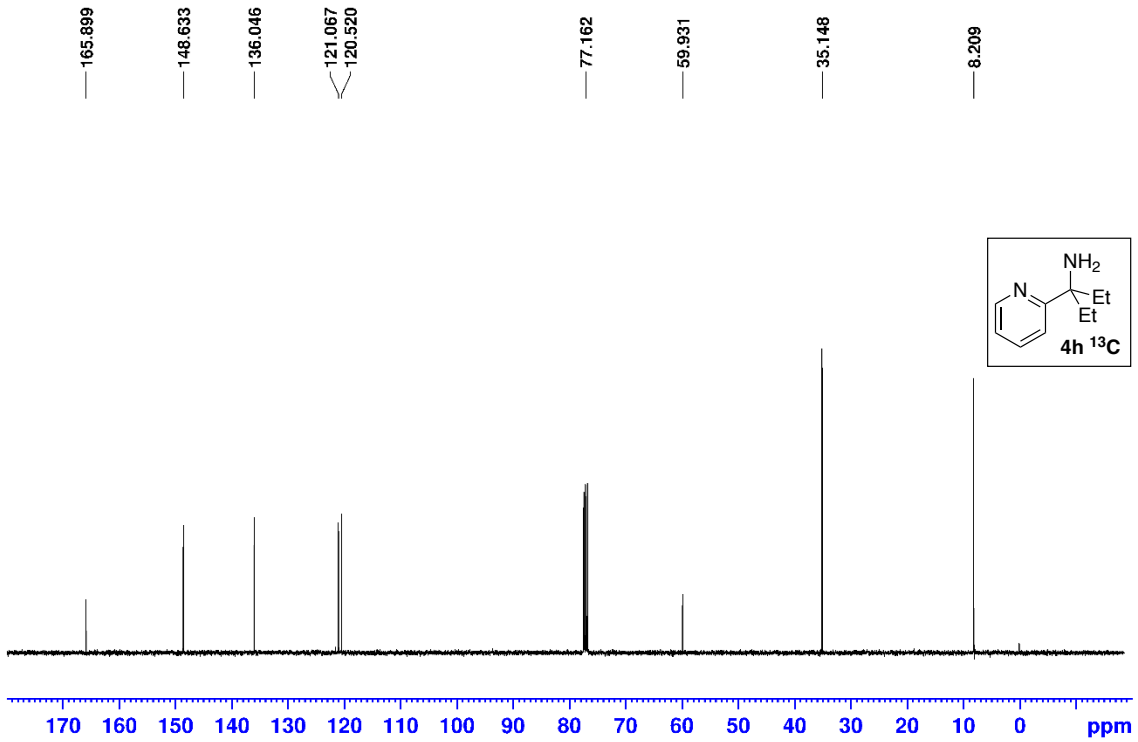
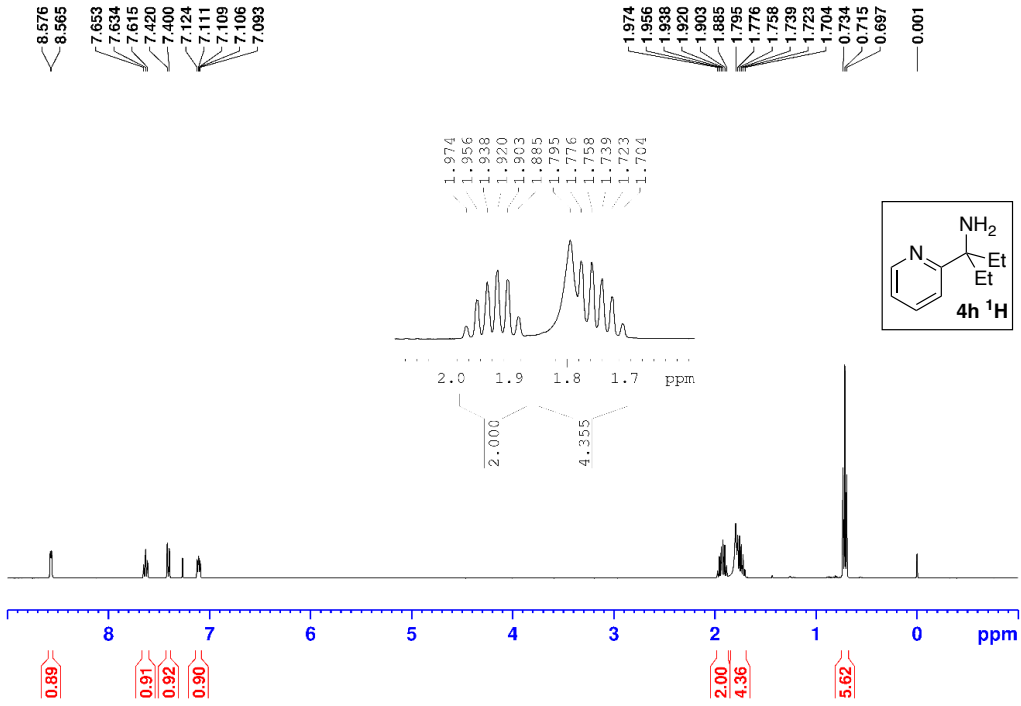


4g

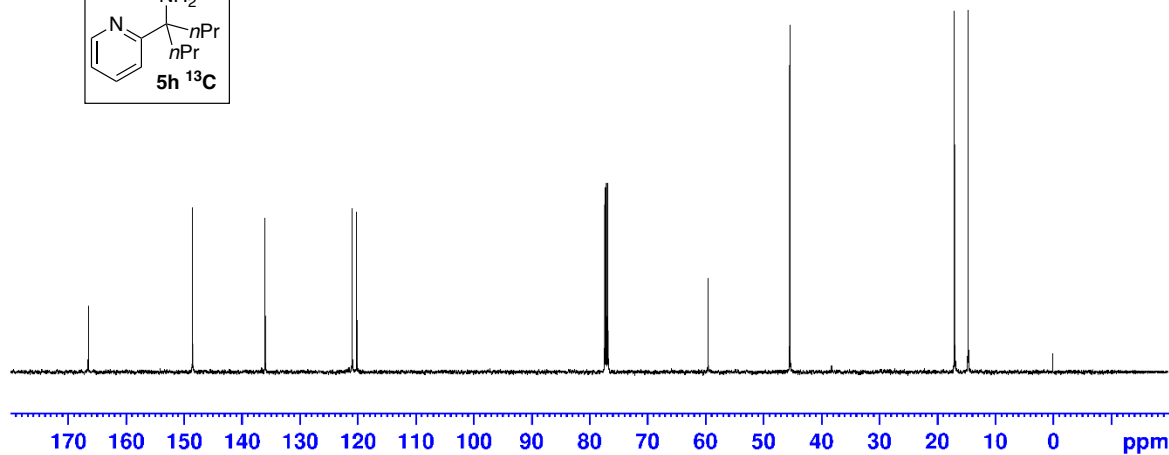
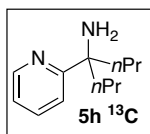
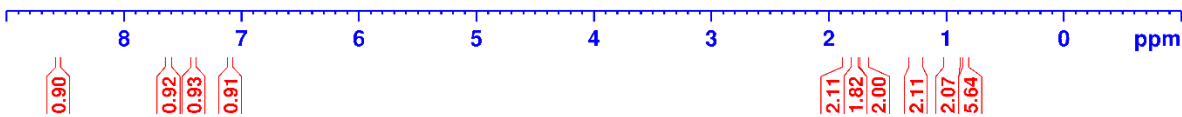
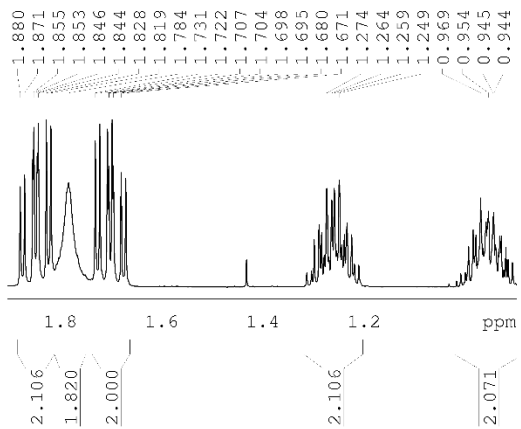
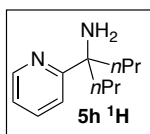
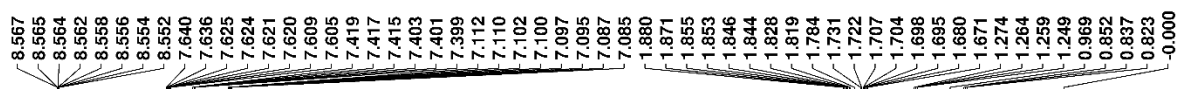




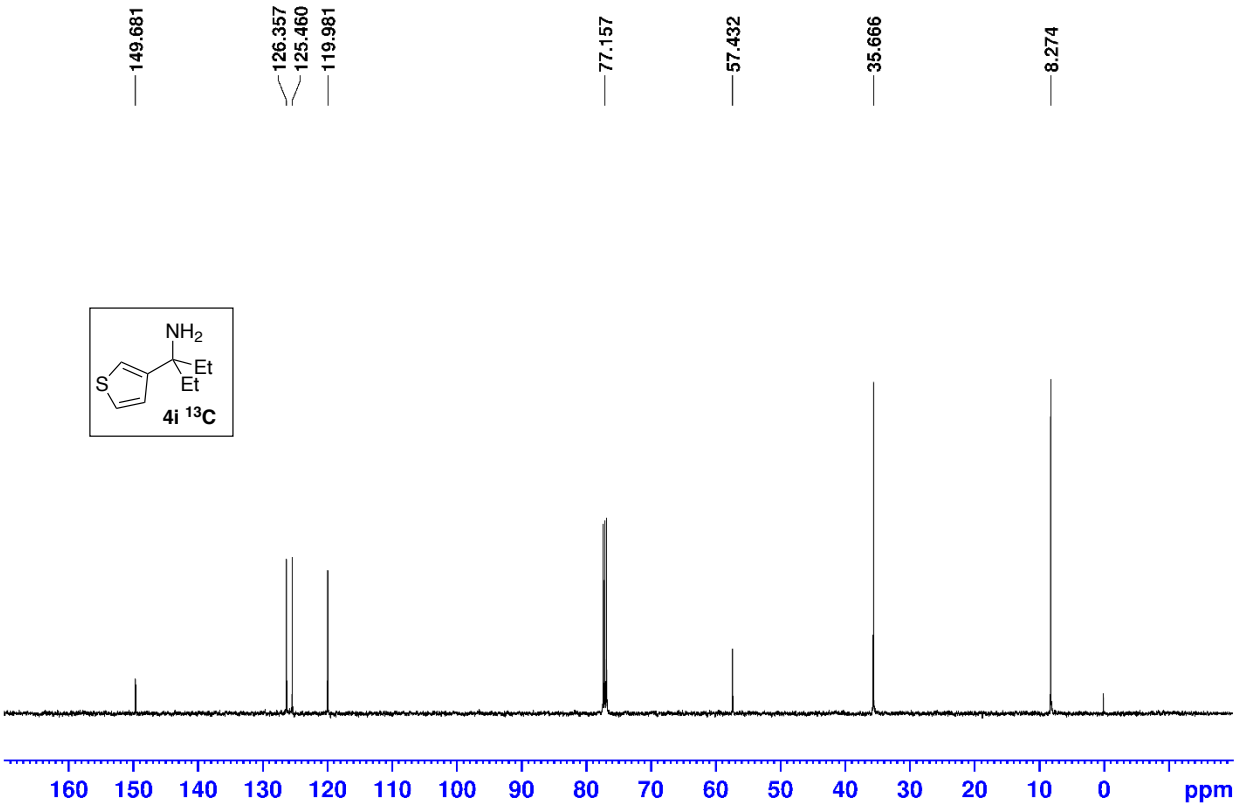
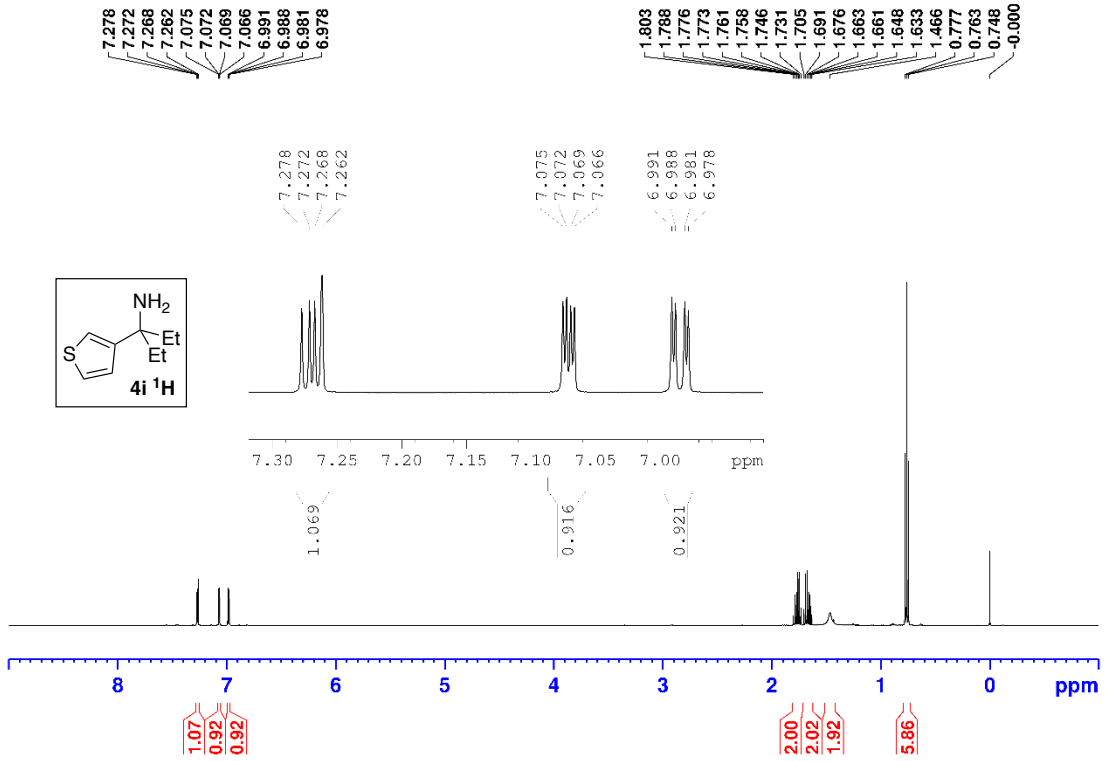
4h



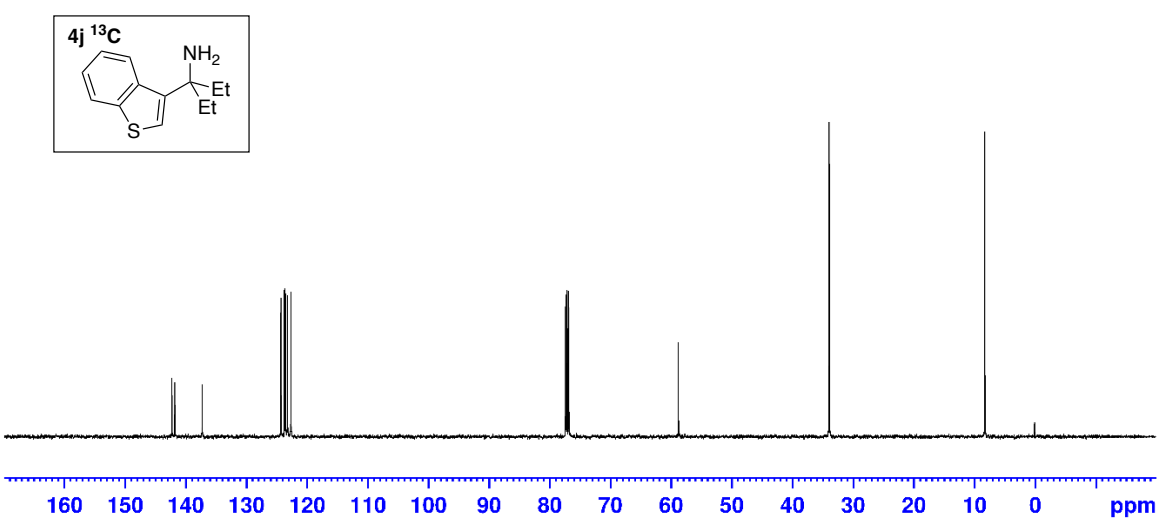
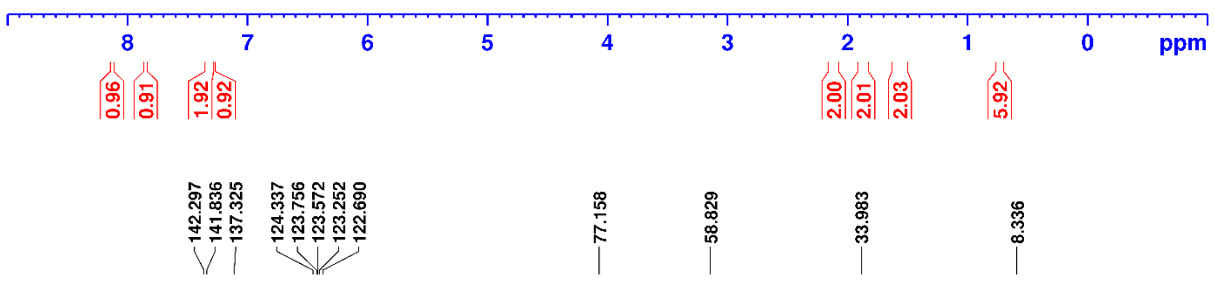
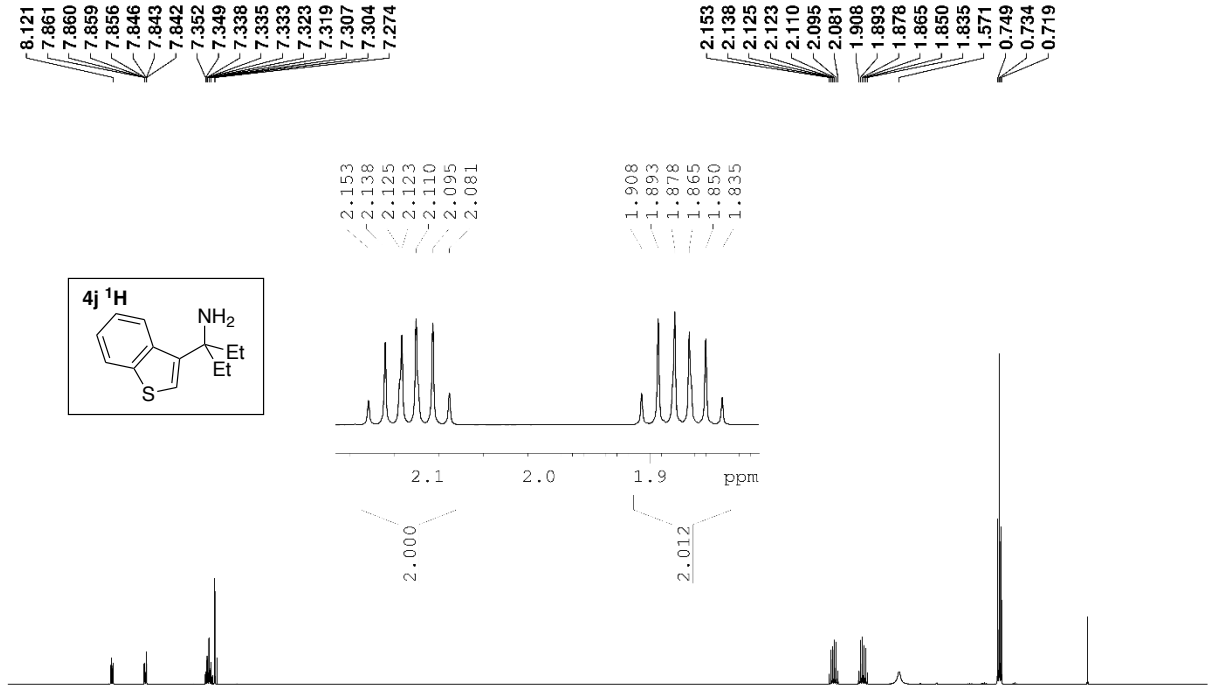
5h



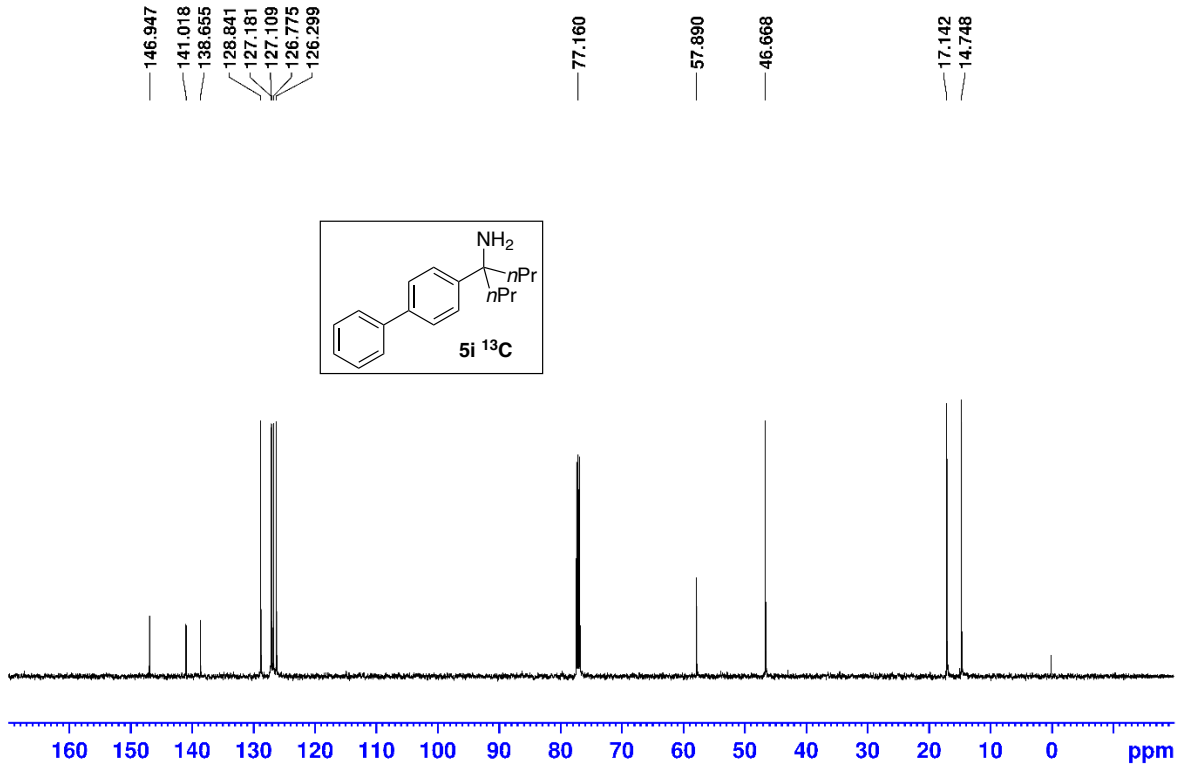
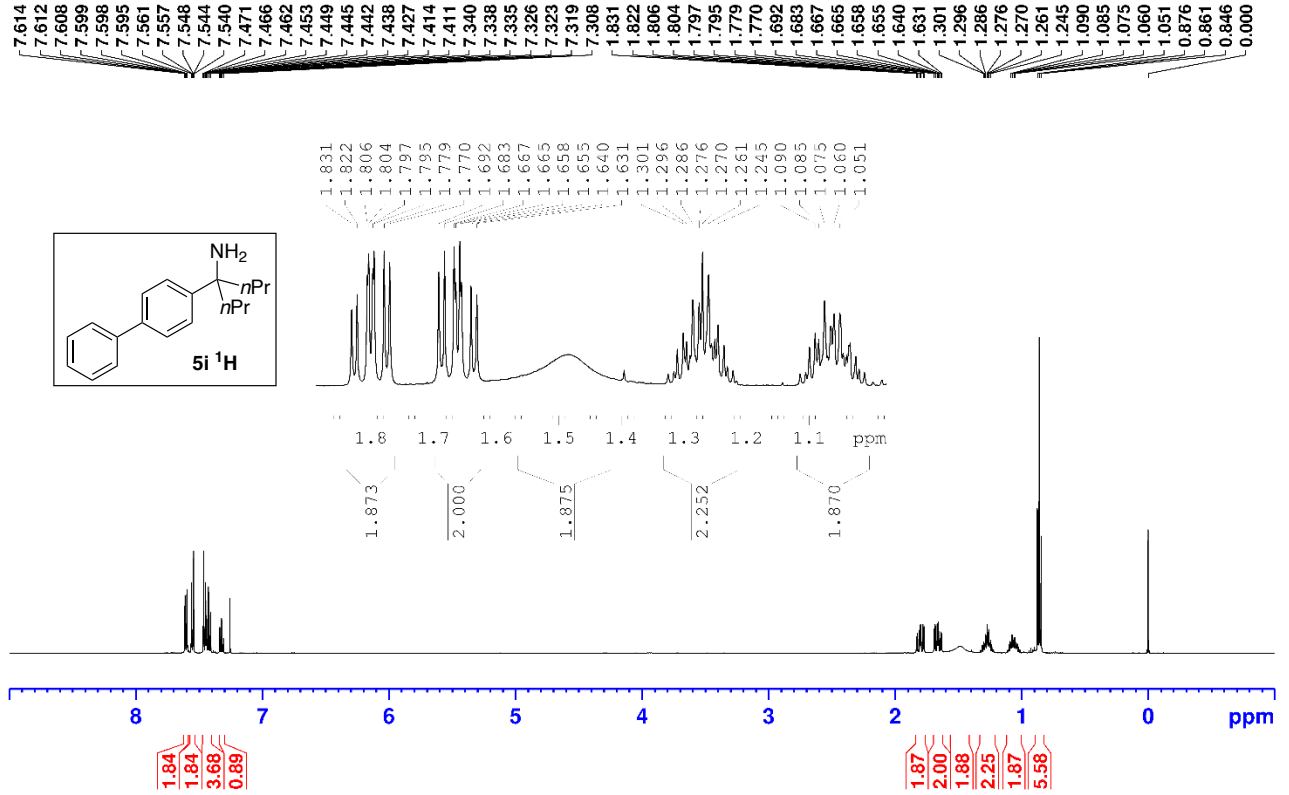
4i



4j

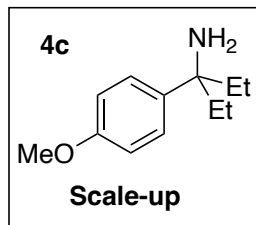


5i



Scale up procedures and NMR spectra for **4c** and **4g**

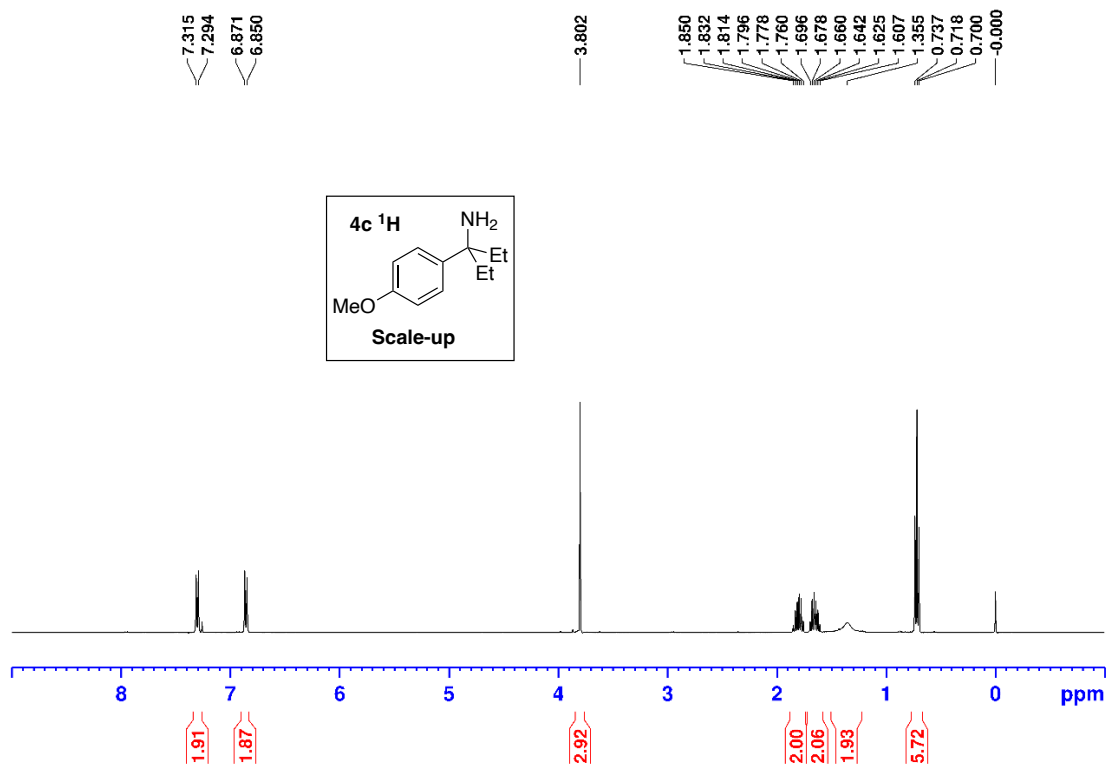
Scale up synthesis of 4c: In the glove box, 4-methoxybenzonitrile (1.0 g, 7.5 mmol, 1 equiv.) was dissolved in toluene (20 mL) in a 500 mL round bottom flask equipped with a stir bar. The flask was removed from the glove box and placed under N₂ atmosphere on a Schlenk line. Ethylmagnesium bromide (2.5 mL, 7.5 mmol, 3 M solution, 1 equiv.) was added dropwise, and the mixture was left to stir for 2 hours. Lanthanum chloride bis(lithium chloride) (3.75 mL, 2.25 mmol, 0.6 M solution, 0.3 equiv.) was added and followed immediately by



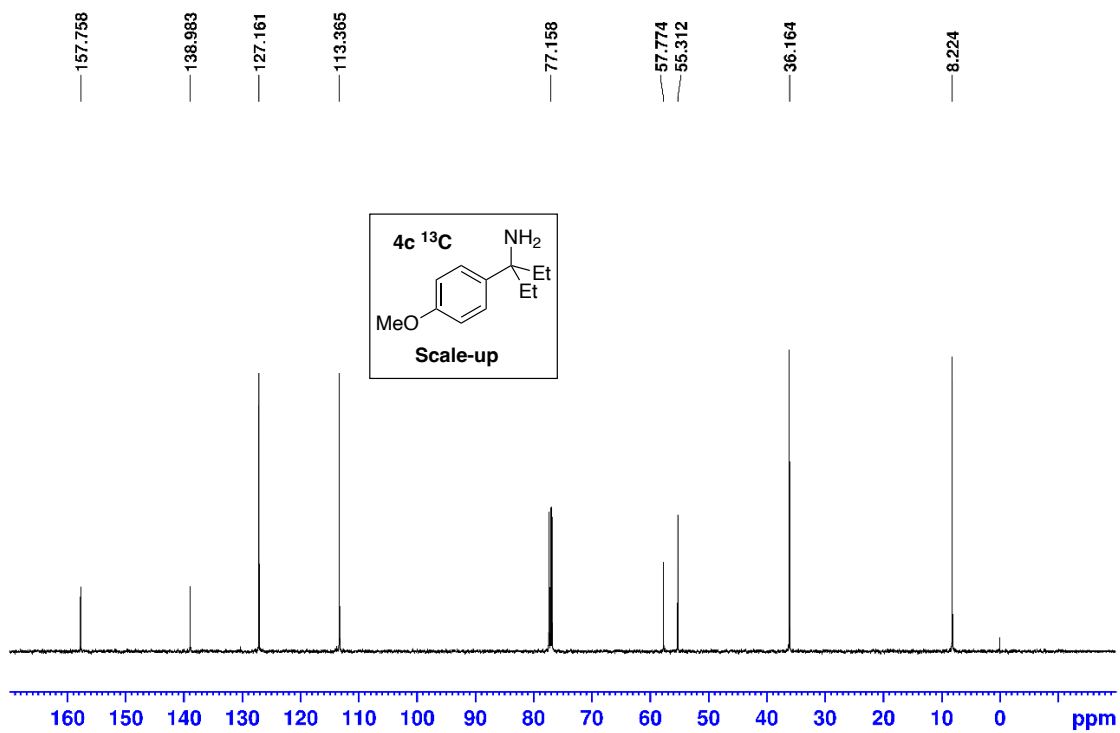
the dropwise addition of ethylmagnesium bromide (5.0 mL, 15 mmol, 3 M solution, 2 equiv.). The reaction was stirred for 2 hours, the N₂ was then turned off and the mixture was left to stir for 48 hours. The mixture was quenched dropwise with 20 mL of 2 M HCl. The mixture was left to stir for 3 hours and then 35 mL of 2 M NaOH was added leading to the formation of sludgy lanthanum salts. The lanthanum salts were filtered out of solution via a filtration over celite, rinsed with diethyl ether and the filtrate was transferred to a separatory funnel where an additional 10 mL of 2 M NaOH was added. The aqueous layer was extracted with 3 x 10 mL of diethyl ether, the combined organic layers were dried over Na₂SO₄ and concentrated via rotary evaporator, then dried under vacuum.

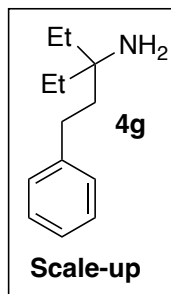
Purification: The crude amine/ketone mixture was redissolved in hexanes (20 mL) and transferred to a separatory funnel where the organic layer was extracted with 3 x 15 mL of 2 M NaHSO₄. The combined aqueous layer was basified using 2 M NaOH and then extracted with 3 x 25 mL of diethyl ether. The combined organic layers were dried over Na₂SO₄, concentrated via rotary evaporator and then dried under vacuum to afford **4c** (1.03 g, 5.3 mmol, 71% yield) as a yellow liquid.

¹H NMR (400 MHz, CDCl₃):



¹³C NMR (UDEFT) (125 MHz, CDCl₃):



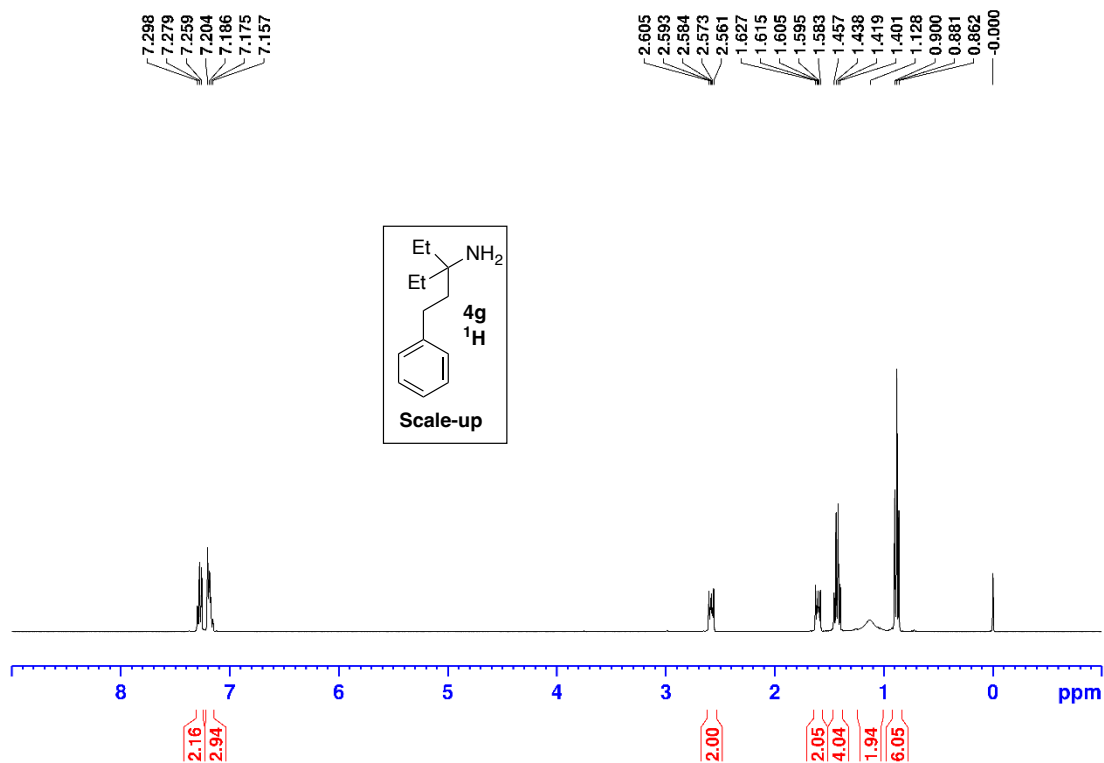


Scale up synthesis of 4g: In the glove box, 3-phenylpropionitrile (1.0 mL, 7.6 mmol, 1 equiv.) was dissolved in toluene (20 mL) in a 500 mL round bottom flask equipped with a stir bar. The flask was removed from the glove box and placed under N₂ atmosphere on a Schlenk line. Ethylmagnesium bromide (2.54 mL, 7.6 mmol, 3 M solution, 1 equiv.) was added dropwise, and the mixture was left to stir for 2 hours. Lanthanum chloride bis(lithium chloride) (3.81 mL, 2.29 mmol, 0.6 M solution, 0.3 equiv.) was added followed immediately by the dropwise addition of ethylmagnesium bromide (5.08 mL, 15.3 mmol, 3 M solution, 2 equiv.). The

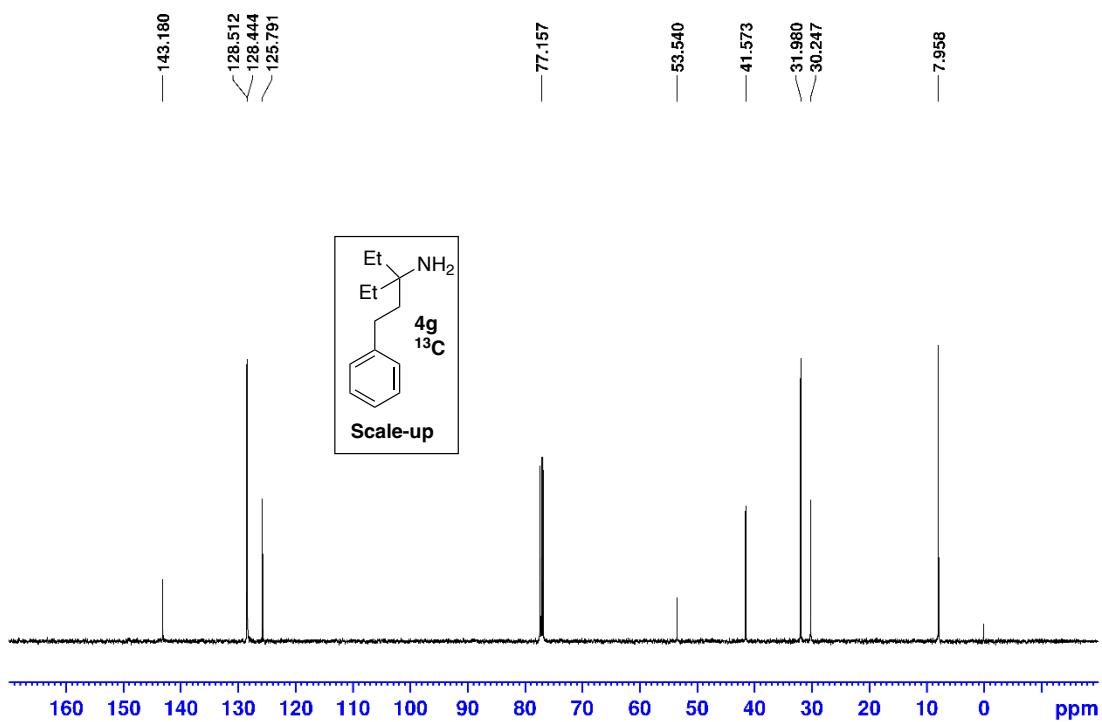
reaction was stirred for 2 hours, the N₂ was then turned off and the mixture was left to stir for 48 hours. The mixture was quenched dropwise with 20 mL of 2 M HCl. The mixture was left to stir for 3 hours and then 35 mL of 2 M NaOH was added leading to the formation of sludgy lanthanum salts. The lanthanum salts were filtered out of solution via a filtration over celite, rinsed with diethyl ether and the filtrate was transferred to a separatory funnel where an additional 10 mL of 2 M NaOH was added. The aqueous layer was extracted with 3 x 10 mL of diethyl ether, the combined organic layers were dried over Na₂SO₄ and concentrated via rotary evaporator, then dried under vacuum.

Purification: The crude amine/ketone mixture was redissolved in hexanes (20 mL) and transferred to a separatory funnel where the organic layer was extracted with 3 x 20 mL of 2 M NaHSO₄. The combined aqueous layer was basified using 2 M NaOH and then extracted with 3 x 25 mL of diethyl ether. The combined organic layers were dried over Na₂SO₄, concentrated via rotary evaporator and then dried under vacuum to afford **4g** (733 mg, 3.83 mmol, 50% yield) as a yellow liquid.

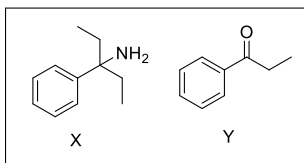
¹H NMR (400 MHz, CDCl₃):



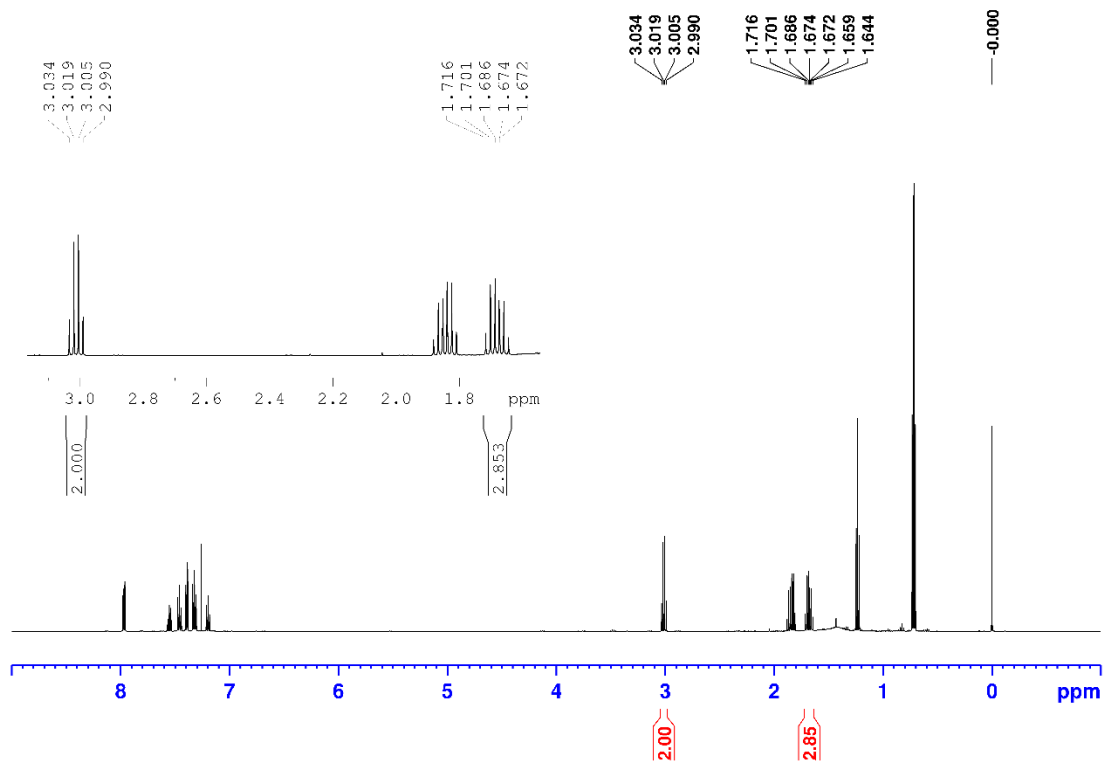
¹³C NMR (UDEFT) (125 MHz, CDCl₃):



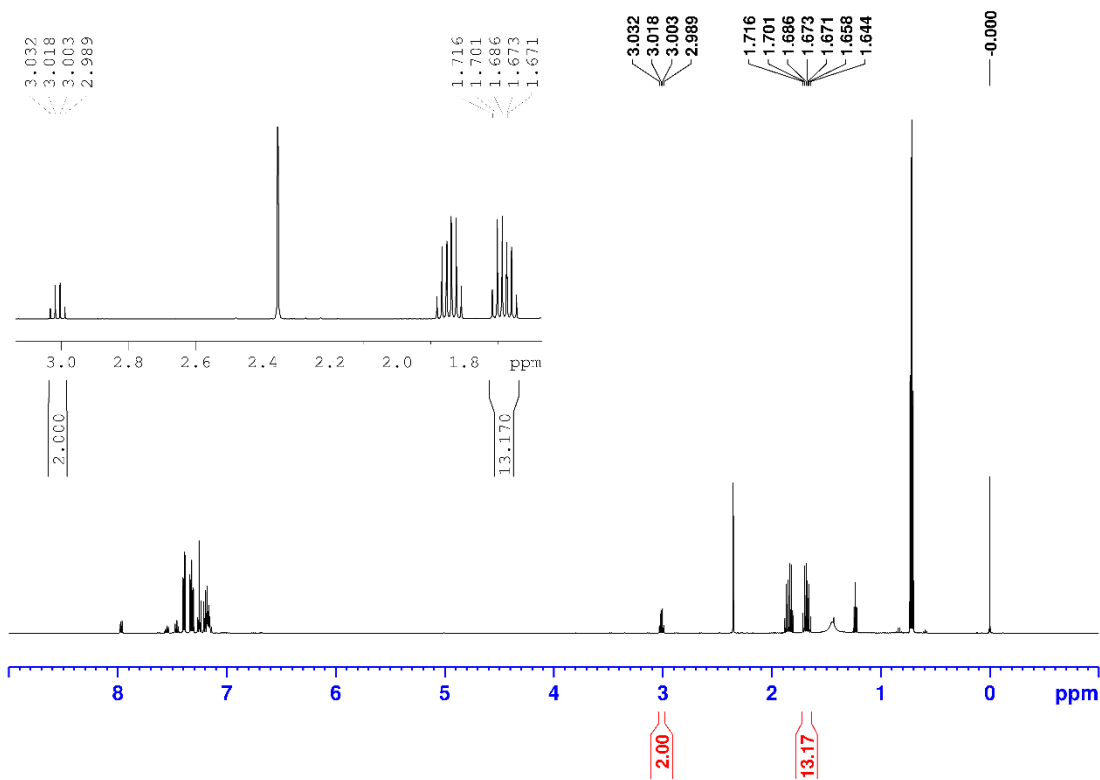
NMR Spectra for **4a** conversion integration:



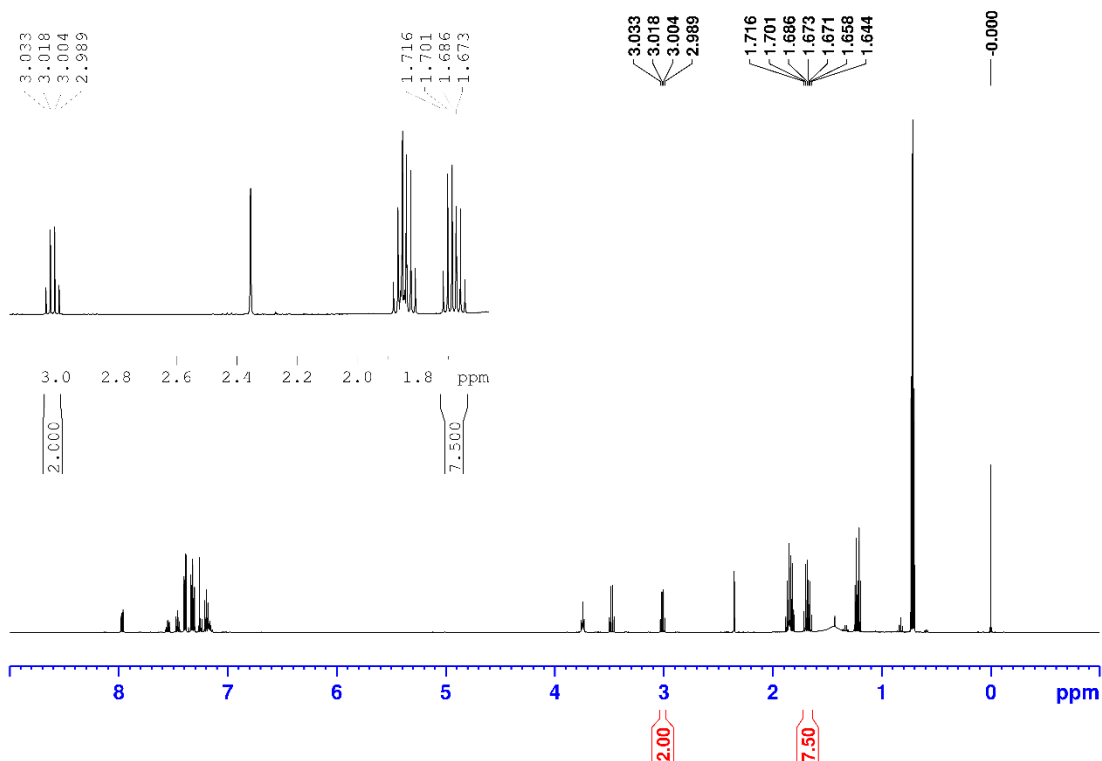
Ketone 3a: Amine 4a using THF as a reaction solvent



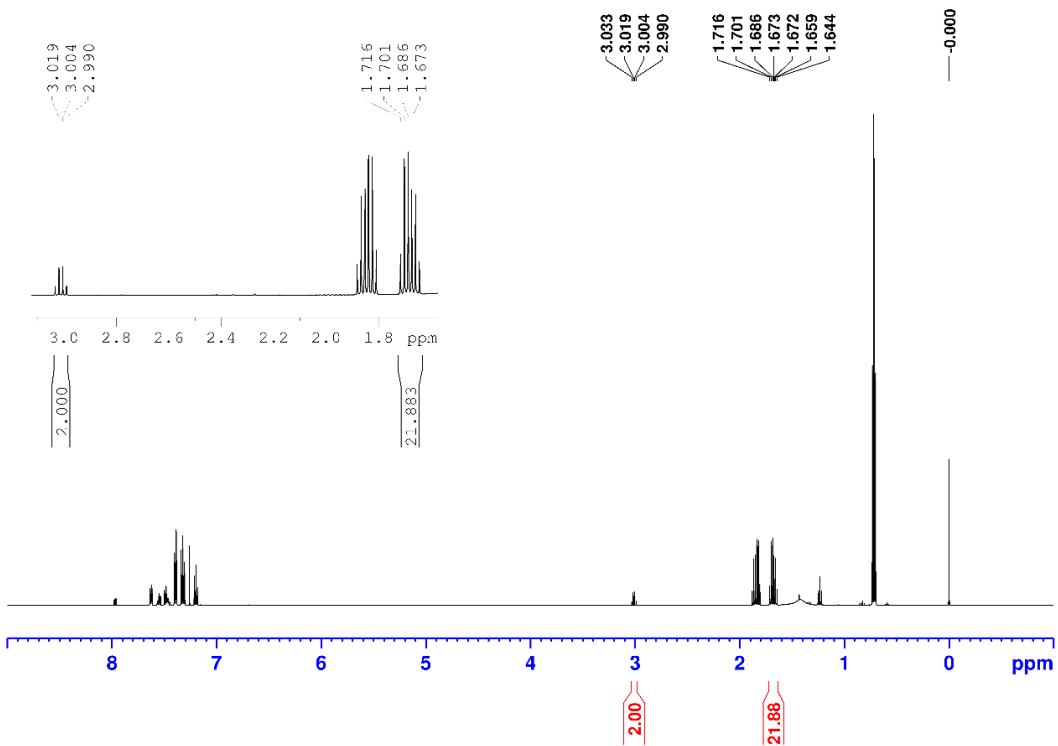
Ketone **3a**: Amine **4a** using toluene as a reaction solvent



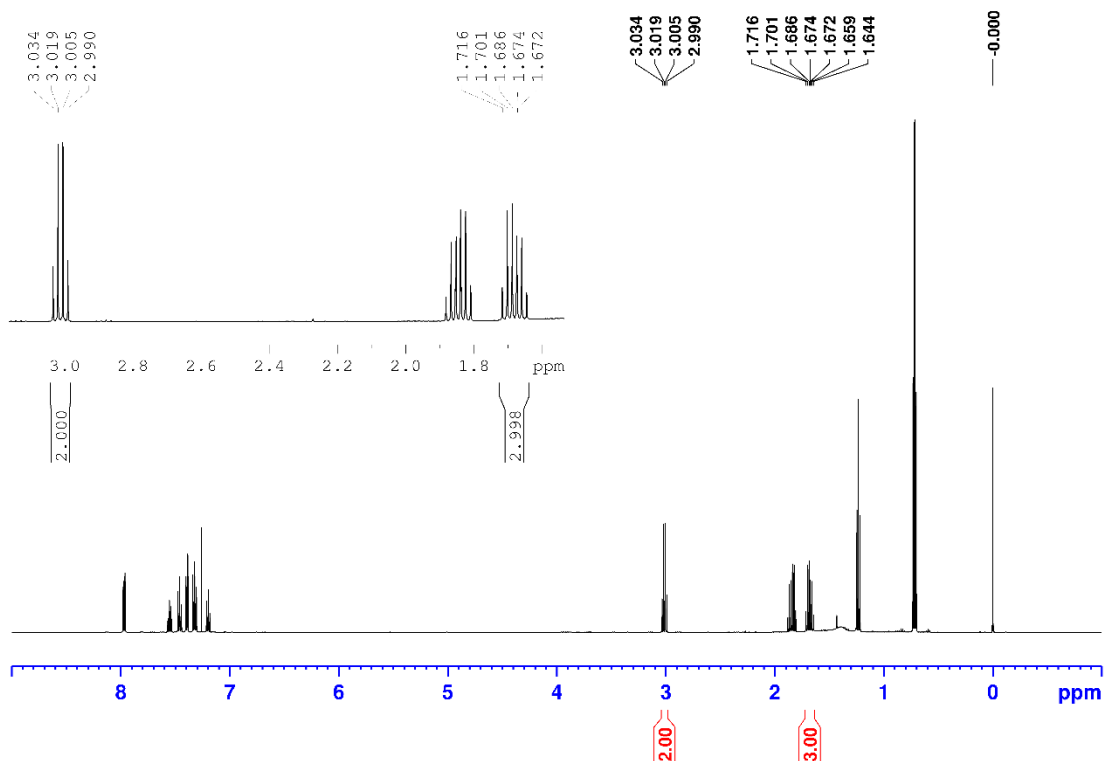
Ketone **3a**: Amine **4a** using diethyl ether as a reaction solvent



Ketone **3a**: Amine **4a** using Trifluorotoluene (TFT) as a reaction solvent



Ketone **3a**: Amine **4a** using Methyl-THF as a reaction solvent



Ketone **3a**: Amine **4a** using pentane as a reaction solvent

