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Catalytic Synthesis of Alpha-Tetrasubstituted Homoallylamines and Their Use in the Construction of 1-Azaspirocyclic Scaffolds

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in

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by

Keegan Gregory Nelson

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Dissertation Committee:
Dr. Catharine H. Larsen, Chairperson
Dr. Richard J. Hooley
Dr. David B.C. Martin

The Dissertation of Keegan Gregory Nelson is approved:

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Committee Chairperson

University of California, Riverside

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Chapter 1:

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DEDICATION

This section is dedicated to those who have offered support and guidance over these past five years.

Thank you to my advisor Catharine for providing me with the opportunity to do this research. It has felt like a privilege to do this work even at times full of frustration and setback. Your advice has been invaluable, and your mentorship has helped me come into my own as scientist.

To my friends in the Larsen lab, it has been an intense five years, but you made it not only survivable but outright enjoyable. From beers at group meetings to morning coffee runs and late-night vent sessions, I've always felt like I had a solid group of friends and allies I could rely on.

Finally, I'd like to thank my parents. I cannot even begin to account for everything you've done for me and the unwavering support I've always felt. How far I've gotten and have yet to go owes so much to you and the person you've raised me to be.

ABSTRACT OF THE DISSERTATION

Catalytic Synthesis of Alpha-Tetrasubstituted Homoallylamines and Their Use in the Construction of 1-Azaspirocyclic Scaffolds
by

Keegan Gregory Nelson

Doctor of Philosophy, Graduate Program in Chemistry
University of California, Riverside, March 2019
Dr. Catharine H. Larsen, Chairperson

Alpha-tetrasubstituted amines are found in numerous natural products and drug therapies. Variants are typically accessed through the synthesis and isolation of the appropriate ketimine followed by reaction with stoichiometric organometallic reagents. The first direct three-component coupling of a ketone, amine, and allyl nucleophile proceeds efficiently under green, solvent-free conditions to provide the hindered amine building blocks in a single catalytic step. The terminal olefin possessed in the products demonstrates utility for further modification by readily undergoing cross-metathesis in the presence of Grubbs' catalysts.

The resultant alpha-tetrasubstituted homoallyl amines provide a synthetic platform for producing a wide variety of structurally complex small molecules through the formation of a spirocyclic ring system. A streamlined methodology allows for the protection of the free amine through either allylation or acrylation,

and ring-closing metathesis to give both electron-rich and poor ring systems while only requiring column chromatography for a single step.

Table of Contents

List of Schemes

List of Figures

List of Tables

Chapter One: Catalytic Tandem Condensation-Allylation for the Synthesis of Alpha-Tetrasubstituted Amines

1.1 Introduction

Similar to quaternary carbon centers, tetrasubstituted carbons bearing amines form the core of many bioactive compounds and often require multiple steps to synthesize.[1] In addition to a collection of natural products including lycopodium alkaloids[2], insect feeding deterrents like (-)-adaline[1], these structures are found in a number of compounds with therapeutic value (Figure 1.1). Salinosporamide A is a metabolite of a genus of marine bacteria with notable cytotoxic properties toward a variety of cancer cell lines including breast, lung, and

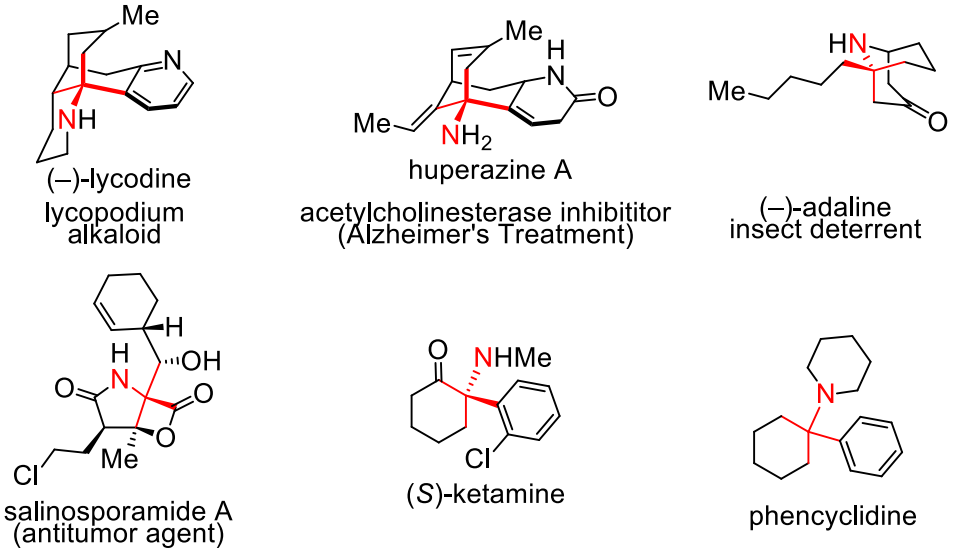


Figure 1.1: Natural products and therapeutics containing alpha-tetrasubstituted amines

melanoma.[3] One can also find these structures in more common compounds such as ketamine, or the dissociative hallucinogenic phencyclidine. Figure 1.2 shows the most common synthetic approach to preparing these compounds. The HIV reverse transcriptase inhibitor candidate DPC 961 is prepared from the addition of stoichiometric amounts of a lithium acetylide to a synthesized and isolated ketimine.[4]

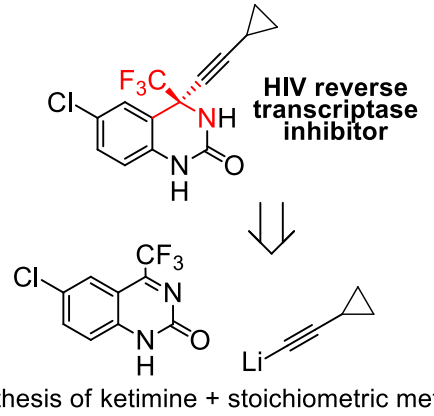


Figure 1.2: Typical synthetic approach requires addition of organometallic reagent to isolated ketimine.

The presence of the tetrasubstituted carbon bearing an amine is not simply a necessary structural novelty, but in some instances these compounds have shown significantly enhanced activity when compared to trisubstituted analogs. One of the most notable examples of this trend is that of fentanyl, an opioid analgesic with a potency 80-100 times greater than morphine. When the trisubstituted center (at the 4-position on the piperidine ring) is converted into a tetrasubstituted center as is seen in carfentanil the activity is observed to increase by 100-fold (Figure 1.3).[5] This gives carfentanil a potency greater than 10,000 times that of morphine, making it

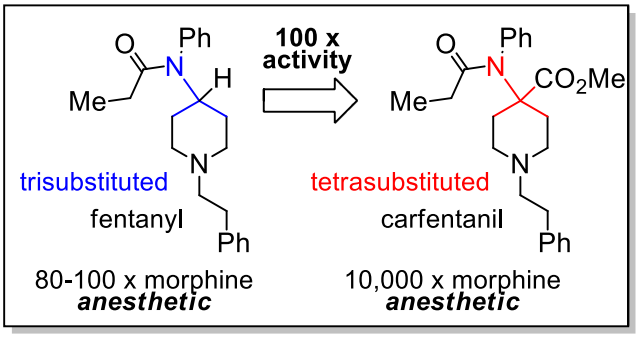
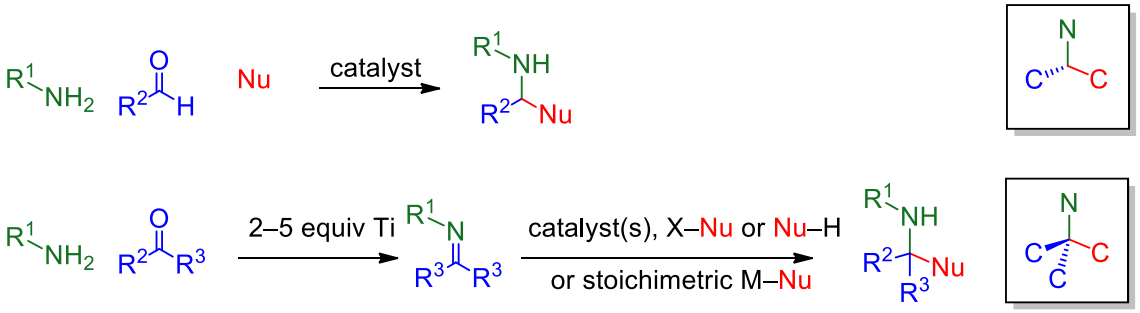


Figure 1.3: Tetrasubstituted carfentanil demonstrates 100-fold increase in potency compared to trisubstituted fentanyl.

bioactive in humans in as little as 1 μg. Due to its potency, the risk of overdose is so high in humans carfentanil is predominantly used as a wildlife anesthetic.

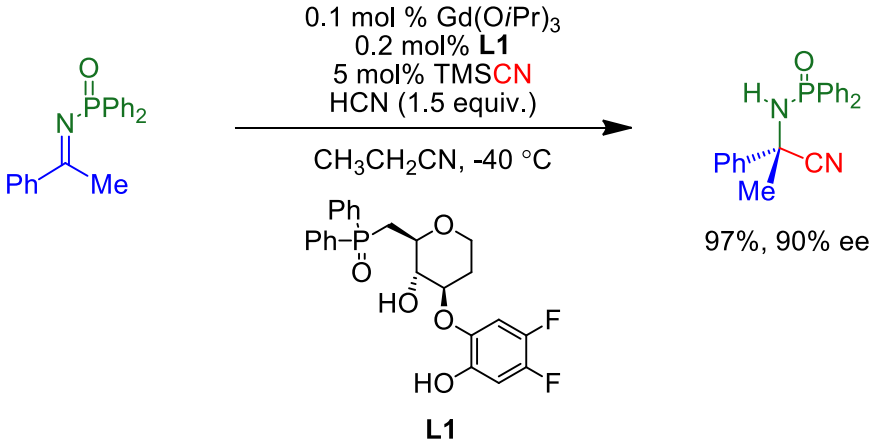
Trisubstituted carbons bearing amines are readily formed by a wide array of three-component couplings of an aldehyde and an amine with a nucleophile.[6] The rapid condensation of aldehyde and amine allows for in situ formation of aldimine followed by nucleophilic attack (Scheme 1.1). As the aldehydes lack both the added steric hinderance of another carbon as well as its donating effect their reactivity is ~300 fold greater than that of a simple acyclic ketone.



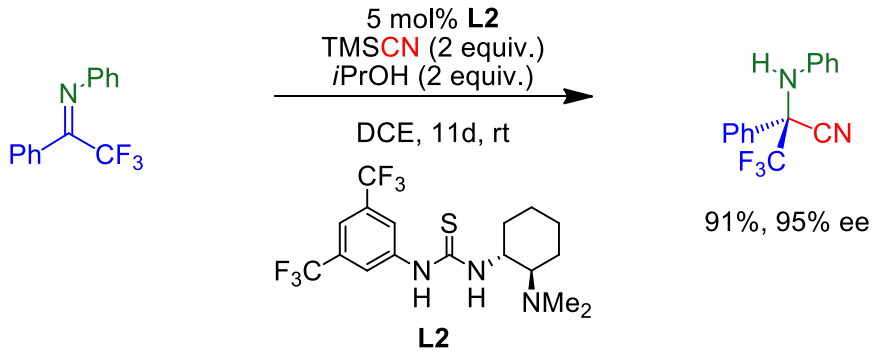
Scheme 1.1: Comparison of general synthetic approaches to tri- and tetrasubstituted carbons bearing amines

In contrast, the handful of examples incorporating less-reactive ketone electrophiles[7] require an extra step to synthesize and isolate the ketimine.[8] Furthermore, unless this ketimine starting material is activated, for example by electron-withdrawing and/or chelating groups, co-catalysts and other additives are required to promote nucleophilic attack, especially in enantioselective variants.[9]

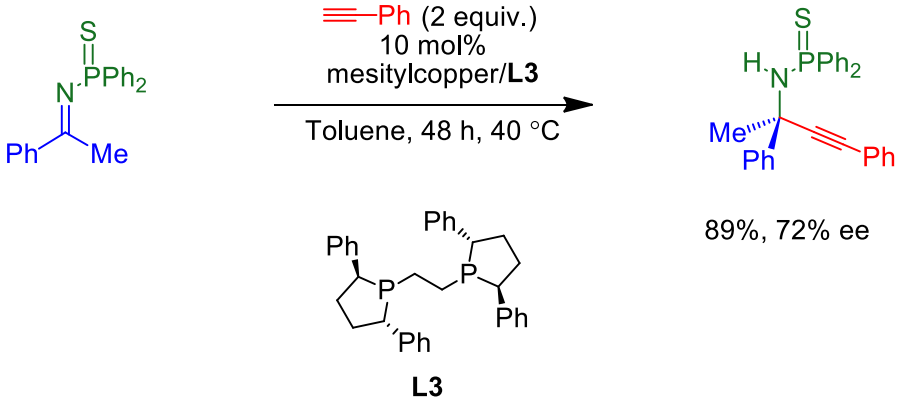
Shibasaki's Enantioselective Ketimine Cyanation (2004):



Enders's Enantioselective Ketimine Cyanation (2010):



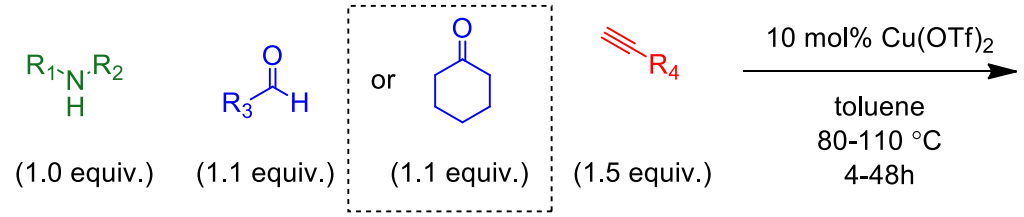
Shibasaki's Enantioselective Ketimine Alkynylation (2013):



Scheme 1.2: Enantioselective addition to isolated ketimines require additional additives, ligands, and activated substrates.

Shibasaki and Kanai devised a generalized synthetic approach to alpha-

aminonitriles through a catalytic enantioselective Strecker reaction. This was accomplished through the usage of a gadolinium(III) alkoxide catalyst along with a chiral ligand derived from D-glucose. Their methodology demonstrated excellent reactivity with aromatic, alkyl, and cyclic *N*-phosphinoylketimines (Scheme 1.2). Enders and co-workers designed a simpler enantioselective Strecker reaction to



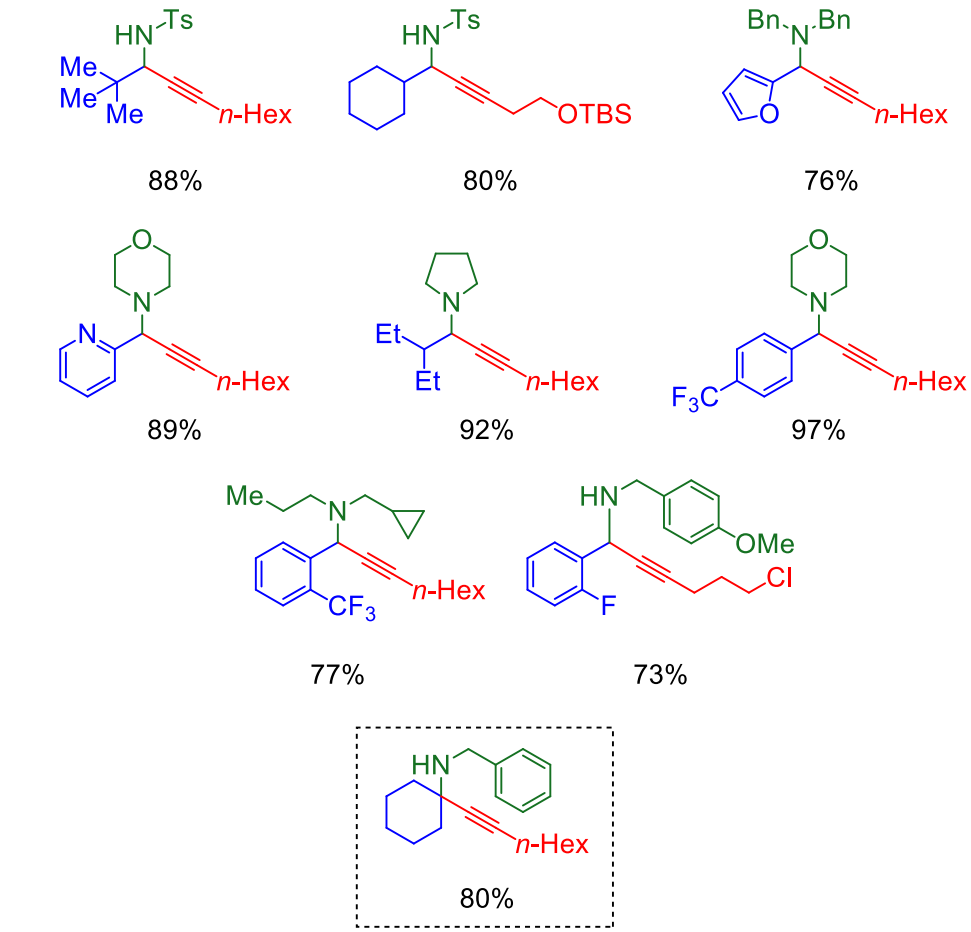
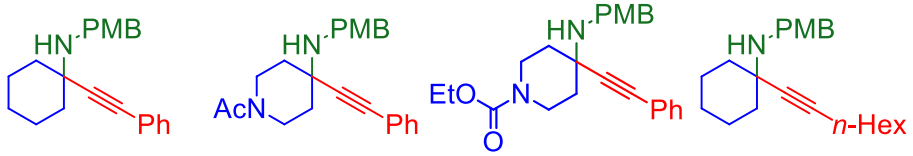


Table 1.1: Aldehydes and cyclohexanone react with amines and terminal alkynes under the same conditions.

produce alpha-trifluoromethyl nitriles. However, these are produced from the corresponding alpha-trifluoromethyl ketimine which are inherently more electrophilic. Terminal alkynes have also been shown to be suitable nucleophiles for catalytic enantioselective additions to ketimines. In addition to the above discussed asymmetric cyanation, Shibasaki and co-workers developed the first catalytic asymmetric alkynylation of ketimines, which relied on a catalytic system to both generate the copper-acetylide and active the ketimine towards attack (Scheme 1.2). It is of note that the soft Lewis basicity of the thiophosphinoyl group on the ketimine is essential to the activity, as the corresponding phosphinoyl substrate did not undergo any reaction. The importance of these hindered compounds warrants this expenditure of extra time, energy, and materials, but the problem remains to be solved: ketones are not readily substituted into three-component couplings designed to incorporate aldehydes.[8]

Special classes of activated ketones can react under conditions developed for aldehydes. Cyclohexanones are a particularly reactive class of cyclic ketones

(1.0 equiv.) (1.2 equiv.) (1.5 equiv.)

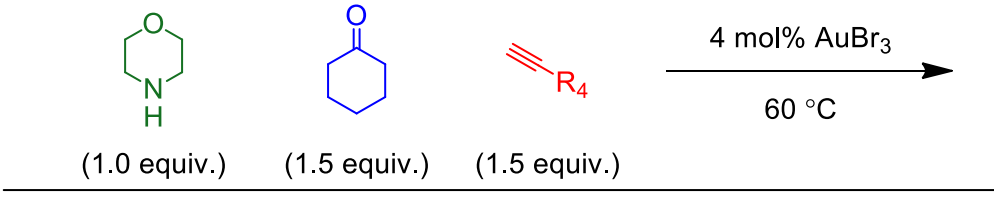


76% 64% 82% 31%

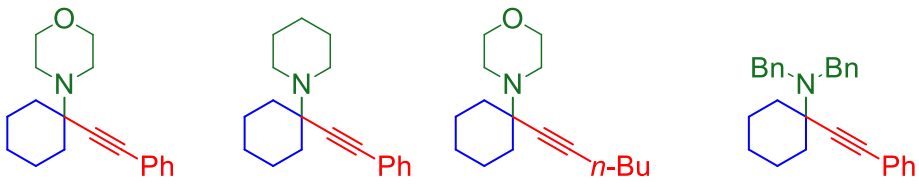
Table 1.2: The first method developed for the three-component coupling of cyclohexanones with amines and terminal alkynes was reported by the Van der Eycken group.

due to the torsional strain released when the sp^2 carbonyl carbon is converted into sp^3 by the attack of a nucleophile.[10] Cyclohexanone can be converted into the corresponding tetrasubstituted propargylamine under the same conditions that convert aldehydes, amines, and alkynes into trisubstituted propargylamines (Table 1.1).[11] Combinations of electron-poor to electron-rich, cyclic or acyclic, and alkyl or aryl aldehyde, amines, and alkynes provide good to excellent yields. Under the same set of conditions, it was found that cyclohexanone reacts with benzylamine and 1-octyne in 80% yield.

Van der Eycken and co-workers published the first example of a catalytic method developed specifically for cyclohexanones.[12] With 20 mol% copper(I) iodide and 25 minutes of microwave heating without solvent, *p*-methoxybenzylamine, phenylacetylene, and cyclohexanones produce *p*-methoxybenzyl (PMB) protected propargylic amines in up to 82% yield (Table 1.2). However, even with two equivalents of 1-octyne reacting with cyclohexanone and *p*-methoxybenzylamine, the yield of the corresponding alkyl-substituted



(1.0 equiv.) (1.5 equiv.) (1.5 equiv.)



89% 75% 45% 29%

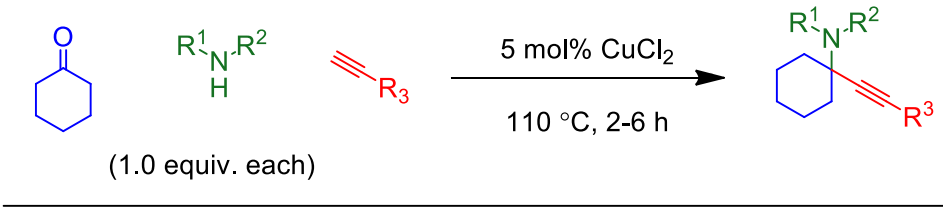
Table 1.3: Cyclic amines and cyclohexanone react efficiently with phenylacetylene under solvent-free gold(III) catalysis as reported by Ji and co-workers.

propargylamine is 31%. This is a stark contrast to the 76% yield of the corresponding aryl-substituted propargylamine using phenylacetylene.[12]

Gold(III) catalysis enables a 40 °C reduction in temperature in the three-component coupling of cyclic amines with cyclohexanone and alkynes (Table 1.3).[13] Ji and coworkers observe the same unexplained trend of lower yields with alkyl alkynes. Compared to the reaction of morpholine with cyclohexanone and phenylacetylene, acyclic *N*,*N*-dibenzylamine results in a threefold drop in yield to 29%.[13]

Both of the processes devised by Ji (Table 1.2)[13] and Van der Eycken (Table 1.3)[12] reduce waste by operating without solvent. The catalyst loading is five times lower in Ji's methodology, but $AuBr_3$ costs 200 times more than CuI. As our conditions in Scheme 1.2 produce an alkyl-substituted propargylic amine in 80% yield, it was reasoned that removing solvent from our copper(II) catalyst would be the first step to an improved, green process.[14] If the excess starting materials could also be excised, then the sole byproduct of this reaction would be one equivalent of water. Thus, the goals were to reduce the loading of an economical catalyst, remove solvent and excess starting material, and expand amine and alkyne scope. A survey of copper catalysts under solvent-free conditions with equimolar amounts of cyclohexanone, benzylamine, and 1-octyne showed that copper halides were superior catalysts.[15] A loading of 5 mol% copper(II) chloride provides high yields of cyclohexanone- derived propargylic amines from both cyclic and acyclic amines and alkyl and aryl alkynes. Published in *Green Chemistry*, this

process gives a higher yield (91% vs. 80% of product in Scheme 1.2) with no solvent or excess starting material in one-quarter the time. The yields of problematic substrates increase significantly as well. Whereas 20 mol% CuI provides PMB-protected *n*-hexyl propargylic amine in 31% yield (Scheme 1.3), 5 mol% $CuCl_2$ provides 87% yield. The combination of morpholine, cyclohexanone, and alkyl alkyne improves from 45% yield to 92% yield. In fact, these conditions are sufficiently mild for acid-sensitive silyl groups and sufficiently activating to form a



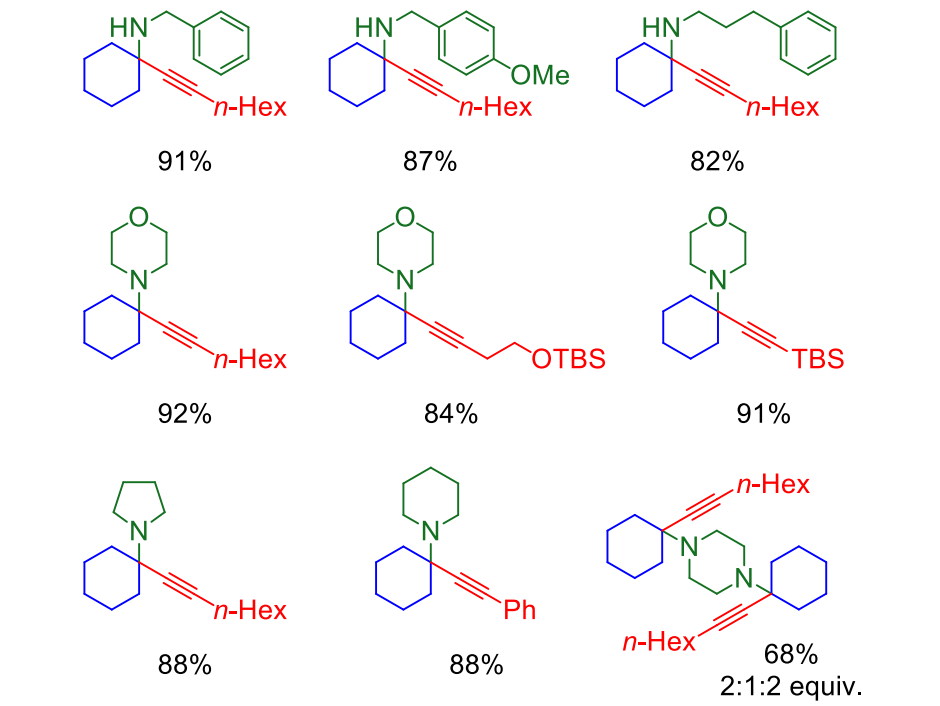


Table 1.4: Green solvent-free conditions proved to be optimal conditions, giving products derived from both primary and secondary amines.

double condensation-alkynylation product from piperazine in 68% yield (Table 1.4).[15]

Although these conditions are highly successful with cyclohexanone, acyclic 2-butanone does not react. Neither ketimine intermediate nor propargylamine product is observed. Once again, whereas the strain released upon addition to cyclohexanone allows it to react under conditions developed for aldehydes, the barrier to ketimine formation and attack from unactivated acyclic ketones is significantly higher.[15]

Surprisingly, the body of literature indicates that a racemic three-component coupling that incorporates a ketone electrophile is a greater challenge

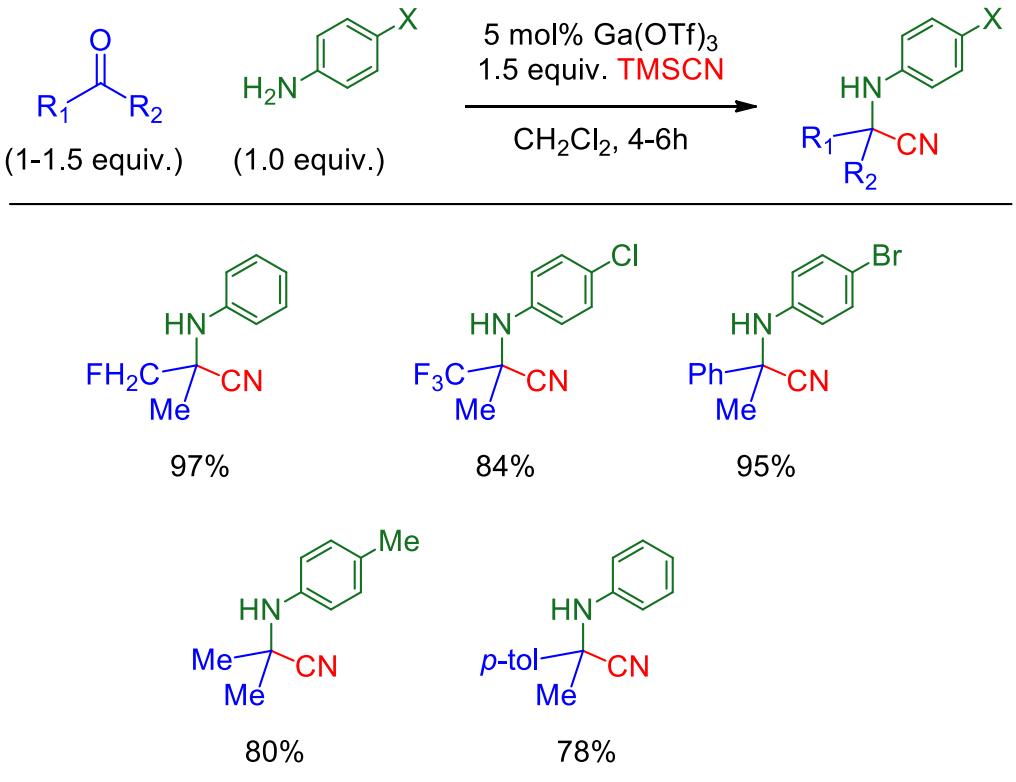


Table 1.5: First catalytic three-component coupling with a ketone, amine, and carbon nulceophile reported by Prakash and Olah.

than an asymmetric addition to a preformed ketimine.[8] The first asymmetric Strecker additions of cyanide to ketimines[16] were reported seven years before the first racemic Strecker reaction operating directly from ketones.[17] This seminal report by Prakash and Olah stood as the sole type of catalytic ketone-amine-nucleophile coupling until the work described herein.

Prakash and Olah's methodology employed the use of catalytic gallium(III) triflate for the multicomponent coupling of an acyclic ketone, aniline and trimethylsilyl cyanide (TMSCN). While the amine source was limited to various substituted anilines both aromatic and alkyl ketones were shown to be viable starting materials (Table 1.5). Along with simple acyclic ketones, they were also able to incorporate fluorinated acetone derivatives as well, though it should be noted that these are technically activated ketones. This was in fact shown to be a problem as when 1,1,1-trifluoroacetophenone was used as the starting ketone the desired product was not observed. Instead a TMS-protected cyanohydrin was obtained, a product of the direct nucleophilic addition to the ketone. This competition between the various electrophilic species was also an issue that arose in our own work.

The key to activating acyclic ketones was the addition of titanium(IV) ethoxide, a Lewis acid known for clean condensation of amines with ketones.[18] A 25-50 mol% loading of titanium cocatalyst added to the green conditions employing 5 mol% $CuCl_2$ catalyzes both ketimine formation and alkynylation (Table 1.6).[19] As $Ti(OEt)_4$ is inexpensive and forms benign titanium dioxide and

ethanol as byproducts, it is practical to utilize 50 mol% to ensure complete conversion into product. Interestingly, excess titanium (i.e., the 2–5 equivalents $Ti(OEt)_4$ originally reported for optimal ketimine formation[18]) inhibits conversion. Presumably, the equilibrium for titanium-bound amine shifts towards amine sequestration. It is important to note that all of the tetrasubstituted propargylic amines synthesized via cooperative catalysis were formed from equimolar amounts of all three starting materials without the addition of solvents, ligands, or other additives.

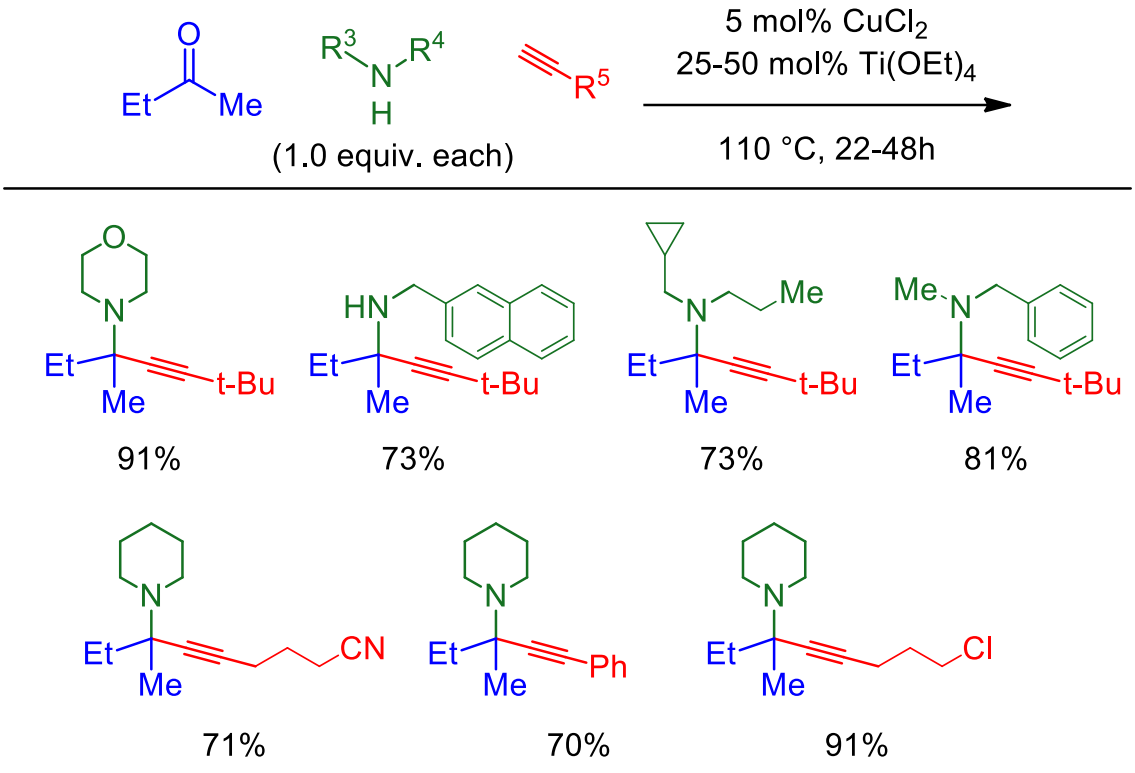


Table 1.6: Dual Cu(II)–Ti(IV) catalysis incorporates acyclic ketones into fully substituted propargylic amines as reported by the Larsen group.

Table 1.6 exhibits a subset of the amines and alkynes that react efficiently in the dual Cu–Ti process.[19] The product from the three-component coupling of

morpholine, 2-butanone and *tert*-butylacetylene is isolated in 91% yield. Primary benzylic, secondary alkyl, and secondary mixed alkyl/benzylic amines produce fully substituted propargylamines in 73–81% yield. Additionally, the methodology demonstrates good functional group tolerance with piperidine and 2-butanone reacting with terminal alkynes bearing phenyl, chlorine, and nitrile groups in 70–91% yield.[19]

Additional nonsymmetric ketones react with 1-octyne and various amines (Table 1.7).[19] Only 25 mol% $Ti(OEt)_4$ is required to convert morpholine, 2-butanone, and 1-octyne into product in 84% yield. Ketones bearing cyclopropyl,

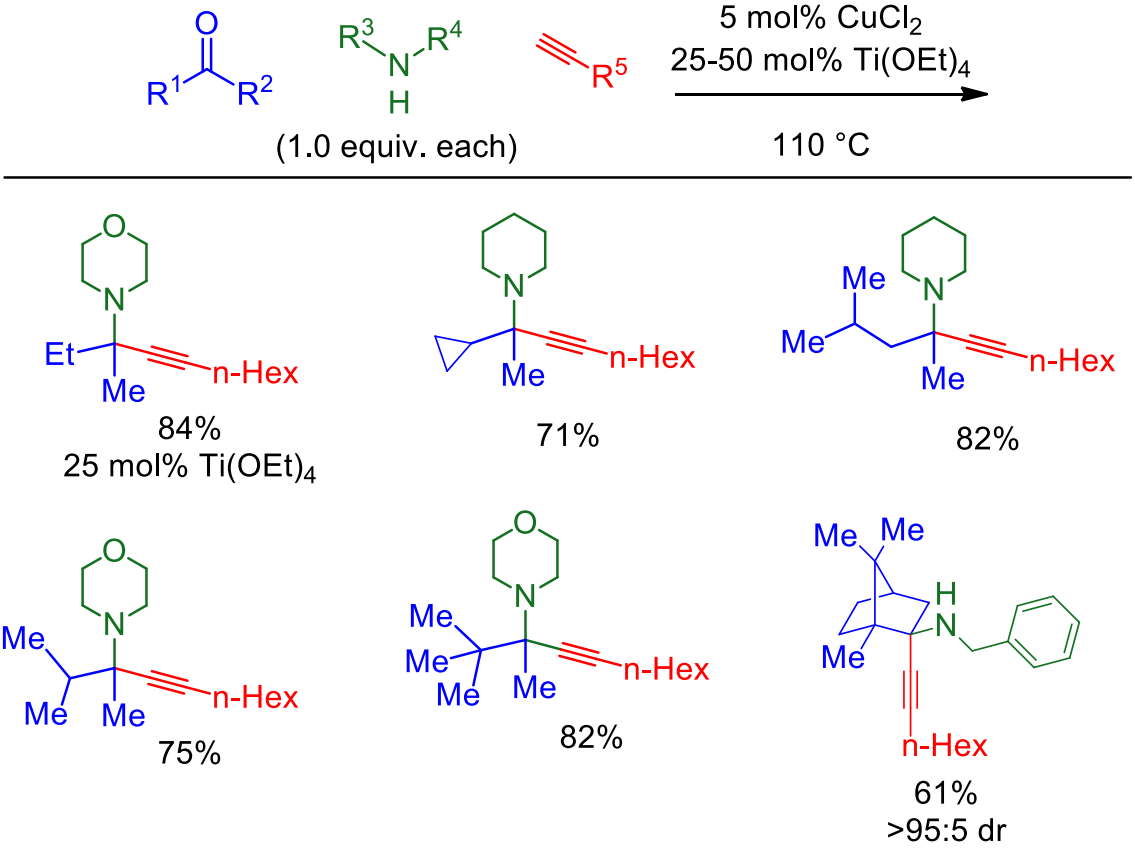


Table 1.7: Dual Cu(II)–Ti(IV) catalysis incorporates acyclic ketones into fully substituted propargylic amines

isopropyl, isobutyl, and *tert*-butyl groups provide the corresponding hindered products in 71–82% yield. (1*R*)-(+)-Camphor reacts in the first diastereoselective ketone–amine–alkyne coupling to provide a single diastereomer by ^{1}H-NMR in 61% yield.[19]

Titanium appears to accelerate imine formation and to activate the resultant ketimine for nucleophilic attack. The rate of production of propargylamine product does not differ significantly under the following two conditions: 1) *in situ* preformation of ketimine upon heating in the presence of $Ti(OEt)_4$ followed by the addition of 5 mol% $CuCl_2$ and alkyne, and 2) standard simultaneous addition of copper, titanium, ketone, amine, and alkyne. However, the reaction of purified ketimine heated solely with 5 mol% $CuCl_2$ proceeds at half the rate of the three-component coupling.

The development of systems whose high activity arises from cooperative catalysis in conjunction with solvent free conditions provides a one-step green synthesis of these challenging molecules. However, the reaction times require 1–3 days. The high barrier to ketimine formation from the condensation of ketones and amines could be bypassed with an alternate mode of forming these key intermediates.

The synthesis of hindered organic amines remains a challenge in part because the reactivity difference between aldehydes and cyclohexanone is drastically smaller than the gulf between cyclohexanone and acyclic ketones.

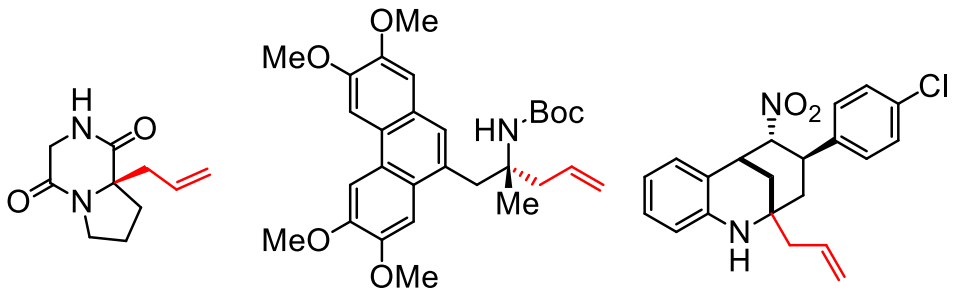
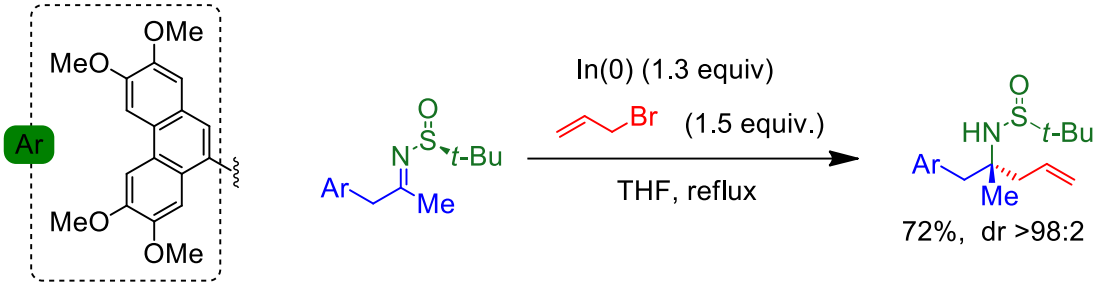


Figure 1.4: Bioactive and synthetic targets containing alpha-tetrasubstituted homoallyl amines.

The turning point for the incorporation of ketones as electrophiles in reactions with amines and alkynes arose from the investigation of a greener solvent-free system in conjunction with copper catalysis. Inexpensive copper(II) chloride catalyzes the reaction of cyclohexanone[15] with the widest range of both amines and terminal alkynes. As a bonus, with no solvents or wasted starting materials, the byproduct is one equivalent of water. However, simple, acyclic ketones remained unreactive under these conditions. The discovery of a dual copper–titanium catalyst system overcomes the barrier to in situ ketimine formation and attack to give the first catalytic coupling of unactivated ketones, amines, and alkynes.[19]

When it comes to potential therapeutics alpha-tetrasubstituted homoallyl amines are no exception, more importantly however, they possess a great deal of utility as the terminal olefin is a useful synthetic handle (Figure 1.4).[20] The corresponding trisubstituted centers can be constructed directly from aldehydes through known multicomponent couplings.[21] Direct access to the tetrasubstituted center from ketones is less convenient. In addition to isolation of the ketimine intermediate, common synthetic approaches require harsher conditions, more

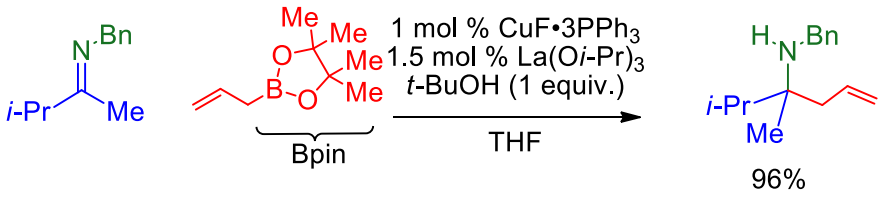


Scheme 1.3: Common asymmetric synthetic approaches find success in using an Ellman auxiliary.

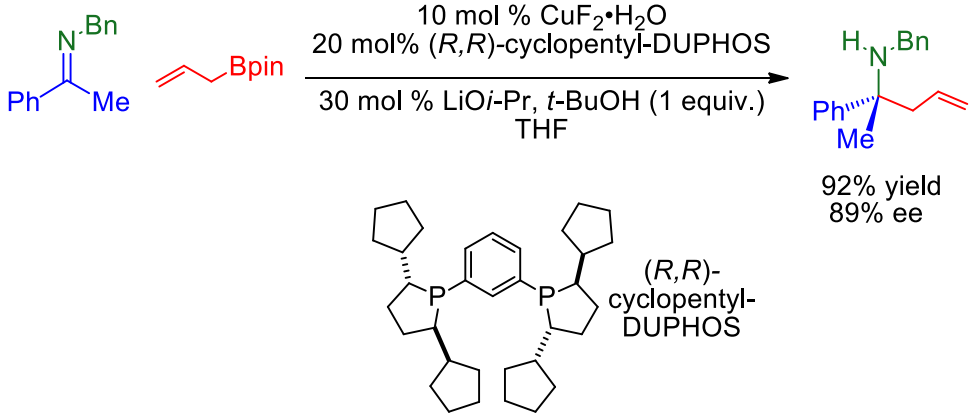
aggressive carbon nucleophiles, give toxic byproducts, or require stoichiometric transition metals. Common examples include Grignard reagents for racemic reactions and asymmetric approaches often opt to use Ellman auxiliaries in conjunction with an allyl nucleophile generated from allyl bromide and stoichiometric amounts of metals like indium (0) (Scheme 1.3).[20a]

In recent years boronic acid derivatives have become a popular route for forming carbon-carbon bonds as they demonstrate excellent reactivity, possess stability towards air and water, have low toxicity, and are widely available. Their greatest popularity likely comes from their use in Suzuki-Miyaura couplings, but their synthetic utility stretches beyond that into allylboration, Petasis-borono Mannich reactions, and rhodium-catalyzed additions to alkenes and carbonyl compounds.[22] One set of derivatives, allylboronate esters, has been shown to undergo nucleophilic addition to ketimines.[23] In 2006 Kanai and Shibasaki

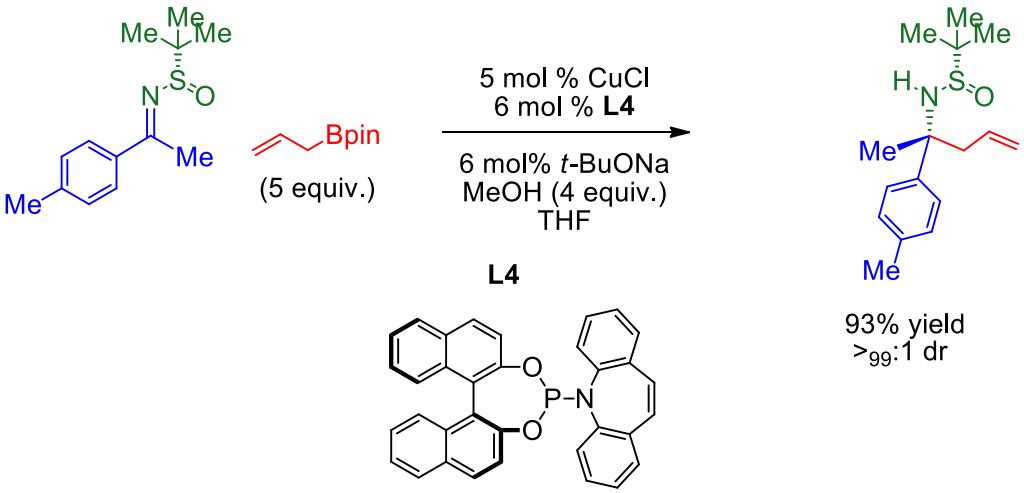
Shibasaki's Racemic Ketimine Allylation (2006):



Shibasaki's Enantioselective Reaction (2006):



Tao's Diastereoselective Ketimine Allylation (2015):

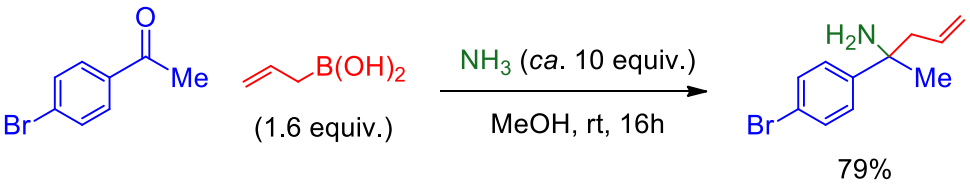


Scheme 1.4: Shibasaki and Kanai demonstrated the successful catalytic allylboration of isolated ketimine (top) and the first catalytic enantioselective allylation of ketimines (middle). Tao's group utilizes both chiral auxiliaries and ligands to achieve excellent diastereoselectivity (bottom).

developed a general catalytic methodology for the allylation of ketimines using $CuF•3PPh_3$ with a $La(O\textit{i}\text{-}Pr)_3$ cocatalyst and allyl boronic acid pinacol ester (Allyl

Bpin) as their nucleophile. They were able to achieve excellent yields as well a low loading for both catalysts by using an equivalent of *t*-BuOH as a protic additive (Scheme 1.4). Additionally, they reported the first catalytic enantioselective allylation of ketimines using a CuF catalyst derived from reduced $CuF_2 \bullet H_2O$, Li*O*i*P*r co-catalyst, and a DuPHOS ligand. Since then only a handful methodologies have been developed for the asymmetric allylation of ketimines.[24,25] Nearly a decade after Shibasaki and Kanai's work, Tao and co-workers reported a diastereoselective allylation of *N*-*tert*-butanesulfinyl ketimines. They were able to achieve both excellent yields and dr through dual stereocontrol approach by using both an Ellman auxiliary and a bulky phosphoramidite ligand (Scheme 1.4).[25] In both of these methodologies it is important to note that an excess of the Allyl Bpin is required for complete conversion of the starting material, as much as 5 equivalents in the case of Tao's work. Along with large excesses of the nucleophile, both methodologies utilize a copper catalyst along with some protic additive such as *t*-BuOH or MeOH.

Thadani and co-workers were able to devise a three-component coupling procedure for the construction of *N*-unsubstituted homoallyl amines, however it relies on a large excess of inorganic ammonia (10 equiv.) as its sole nitrogen

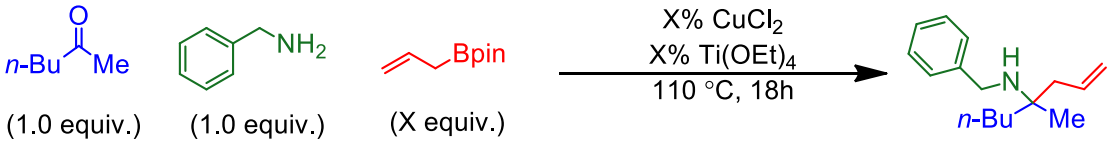


Scheme 1.5: Thadani and co-workers work requires the use of methanolic ammonia to produce N-unsubstituted alpha-tetrasubstituted homoallyl amines.

source.[26] Their group had screened a number of different allylboron nucleophile sources including Allyl Bpin and other boronic acid esters. They discovered however that the free allylboronic acid was the superior nucleophile under their conditions. It is important to note that the allylboronic acid cannot be isolated as a pure substance (due to decomposition) but must be stored dissolved in a typically alcoholic solvent. This is fortuitous in the case of this methodology as it requires methanol for the dissolution of ammonia as well (Scheme 1.5).

1.2 Preliminary Results and Reaction Optimization

The initial goal was to apply the same reaction conditions previously developed for the propargylamine synthesis through tandem condensation-alkynylation[19] and discern if a different nucleophile could be substituted for the *in situ* generated copper acetylide. This tracked logically as the titanium would still



(1.0 equiv.) (1.0 equiv.) (X equiv.)

Entry	$CuCl_2$ (mol%)	$Ti(OEt)_4$ (mol%)	Allyl Bpin (equiv.)	Atmosphere	GC Yield(%)
1	10	25	2.0	Argon	36
2	10	25	3.0	Argon	64
3	0	25	2.0	Argon	>95
4	0	5	2.0	Argon	86
5	0	5	2.0	air	>95
6	0	5	1.5	air	66
7	0	25	2.0	air	>95
8	10	25	2.0	air	33

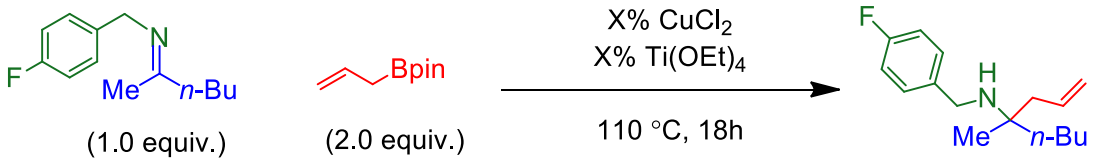
Table 1.8: Optimization of tandem condensation-allylation reaction conditions.

be needed for initial condensation and previous work had shown the necessity for a copper catalyst for the allylation.[23-25] For screening purposes, the copper catalyst loading was increased from 5 to 10 mol% as no difference was observed in conversion by GC, and this allowed for better reproducibility on smaller scale reactions. Using a simple acyclic ketone (2-butanone), we were able to obtain the desired tetrasubstituted product however only at a 38% isolated yield. The higher boiling 2-hexanone provided a higher yield and was thus selected as the standard ketone for optimization (Table 1.2).

Despite reports of increased yields in ketimine allylation,[23] protic additives such as *t*-BuOH were found to have no effect. Increasing the equivalents of Allyl Bpin from 2 to 3 was found to have little effect on overall conversion and almost no effect on isolated yield: 53% versus 55%. Alternate copper(I) and (II) sources were screened, but copper(II) chloride was still found to give the best conversion. There was no observable trend when it came to the oxidation state of the copper catalyst, as copper(I) iodide was shown to perform only slightly worse than copper(II) chloride, but both gave better yields than any other copper source. These reactions were monitored by GC and it was found that by 6 hours no Allyl Bpin remained despite its excess. To determine the source of the degradation several control reactions were run. Initially it was posited that either the copper or titanium catalyst was responsible. The first controls involved heating the Allyl Bpin in the presence of either copper or titanium. These reactions, as well as the combined reaction with both catalysts, showed no change in the amount of

boronate ester after 18 hours. The three-component reaction was then run omitting either copper or titanium. As expected, when only $CuCl_2$ is present, there is no reaction as the condensation of ketone and amine to ketimine does not occur. When only $Ti(OEt)_4$ is present, instead of ketimine and no product, a greater conversion of imine to product was seen by GC and excess Allyl Bpin was seen. This led us to believe that the source of the Allyl Bpin degradation was due to a combination of the copper with either the amine or ketone. Upon testing it was discovered that it was in fact a combination of the copper and amine responsible. Knowing this, our test reaction of 2-hexanone, benzylamine, and Allyl Bpin was repeated and gave an isolated yield of 84%, an increase of more than 30%.

While good yields were achieved for a few substrates, a lower catalyst load was explored. GC conversions for the test substrate were found to be nearly identical for both 5 and 50 mol% titanium. Interestingly it was observed that



Entry	$CuCl_2$ (mol%)	$Ti(OEt)_4$ (mol%)	GC Yield(%)	Remaining Bpin (%)
1	0	0	17	79
2	0	5	15	83
3	10	0	4	63
4	10	5	4	37

Table 1.9: Effects of catalyst presence on the addition of Allyl Bpin to isolated ketimine.

increasing the titanium catalyst loading beyond 50% up to 100% caused a drop in

the yield of 5-10%. This could be due in part to product sequestration by the excess catalyst and titanium alkoxides known azaphilicity. Furthermore, additional screening showed that the reaction could not only be run in air without issue, but was observed as running, nearly a 10% increase in GC yield. Along with this the solvent-free conditions could be maintained. The results of the optimization screening are summarized in Table 1.8. The first two entries were observed by GC to have no remaining nucleophile at 6 hours, and no further conversion was observed at later time points. Using the finalized conditions an array of substrates (Tables 1.10-1.13) were synthesized. While a lower equivalence of the Allyl Bpin would be desirable, reducing the equivalence to 1.5 causes a notable drop in yield (Table 1.8, entry 6). It is possible that the boronate ester has a secondary solvodynamic effect, allowing for more thorough and homogeneous mixing. It is surprising that this reaction not only proceeds in the absence of copper but more efficiently. This contrasts with Shibasaki and Kanai's need for both a copper source and a lanthanide cocatalyst for effective allylation of an isolated ketimine.[23]

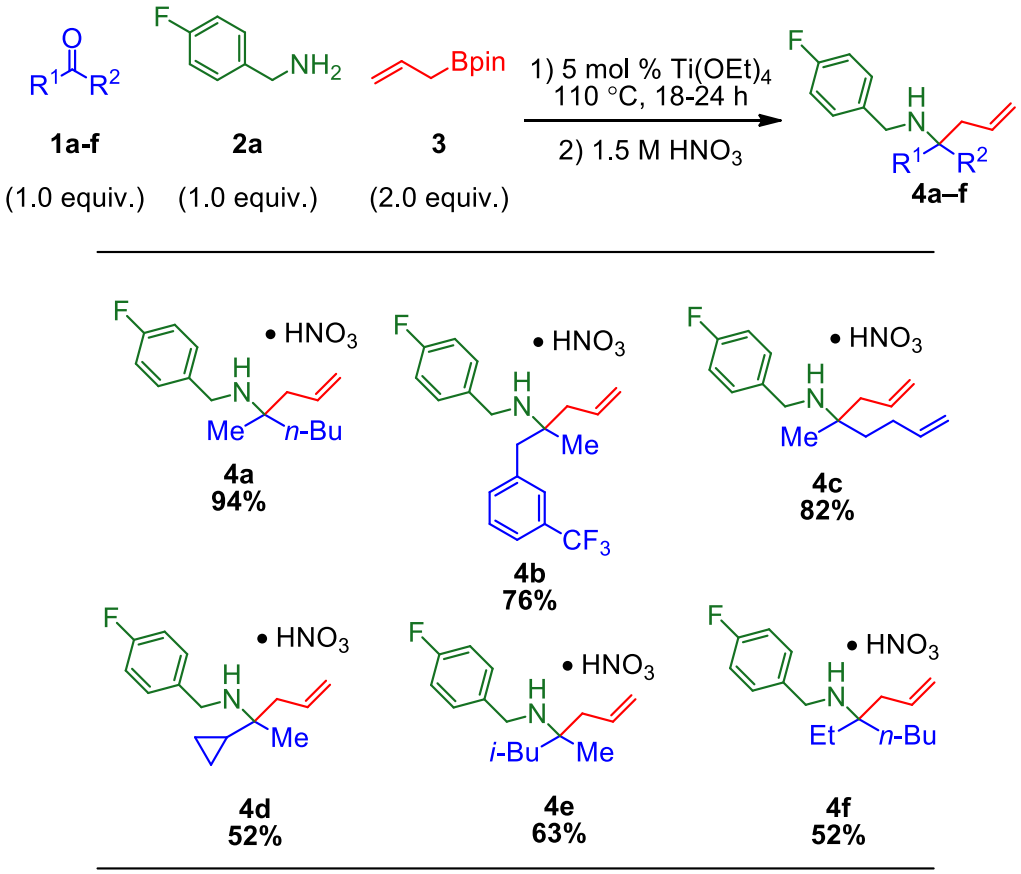
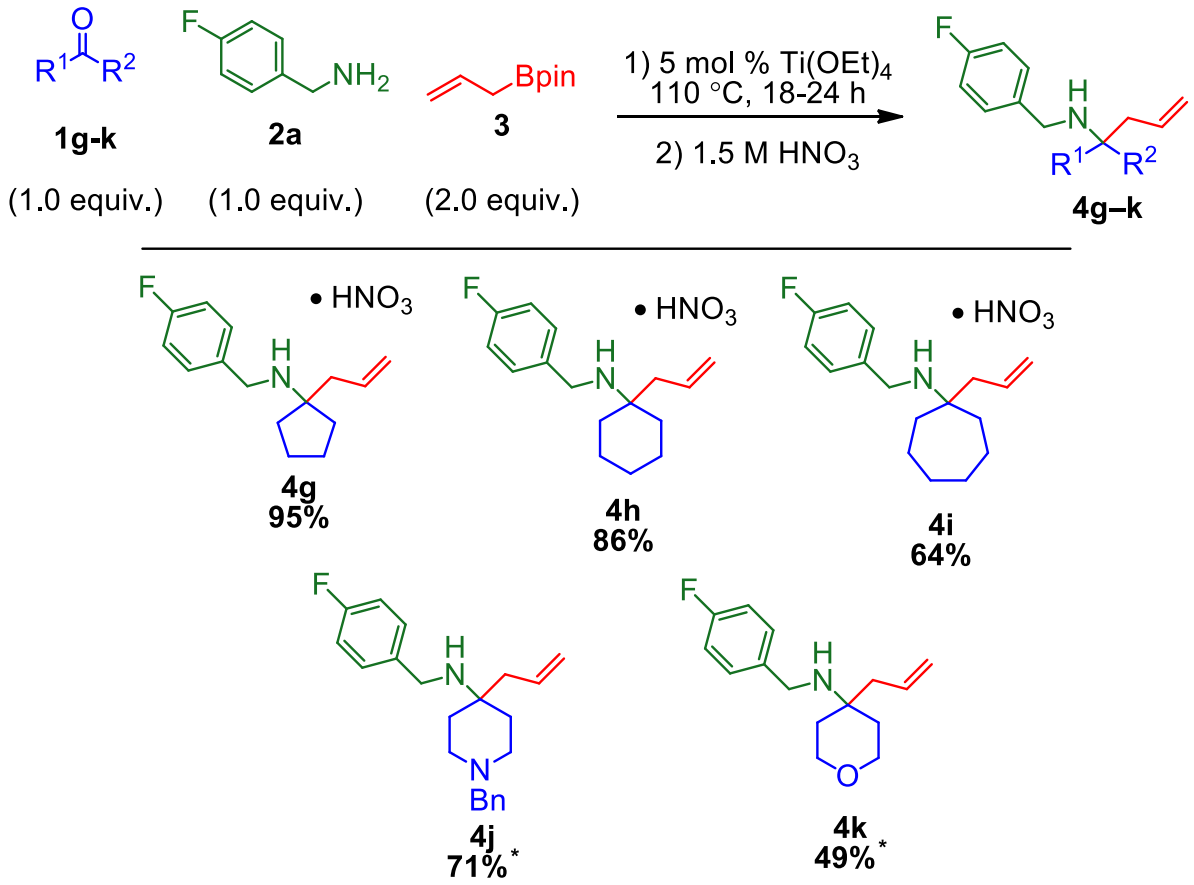


Table 1.10: Acyclic ketone scope of tandem-condensation allylation.

They posit (based on NMR evidence) that the active nucleophile in their system is an allylcopper species. While this cannot be the case for our system, it does provide a possible explanation for our loss of excess nucleophile. It could be that the amine binds the copper and induces the transmetalation of the allyl group to the copper. If this is the case the resulting species might either be inactive or further decay under our conditions.

With the removal of the copper catalyst from the system and therefore any intermediates resulting from it, the observed ineffectiveness of alcoholic additives such as *t*-BuOH to increase yield begins to make sense. Shibasaki and Kanai



*Isolated as the free amine by column chromatography

Table 1.11: Cyclic ketone scope of tandem condensation-allylation.

propose that the *t*-BuOH in their system acts to facilitate catalysis by protonating a copper-amide intermediate formed when the allylcopper (the active nucleophile) adds to the imine.[19]

Further catalytic controls show a more complex interplay between the reagents and catalysts. A series of control reactions were run on the addition of Allyl Bpin to the isolated ketimine (Table 1.9). It was hypothesized that one of the reasons previous work[23,25] had required such a high equivalents of Allyl Bpin (as much as 5 equivalents in some cases[25]) was that the imine in conjunction with a

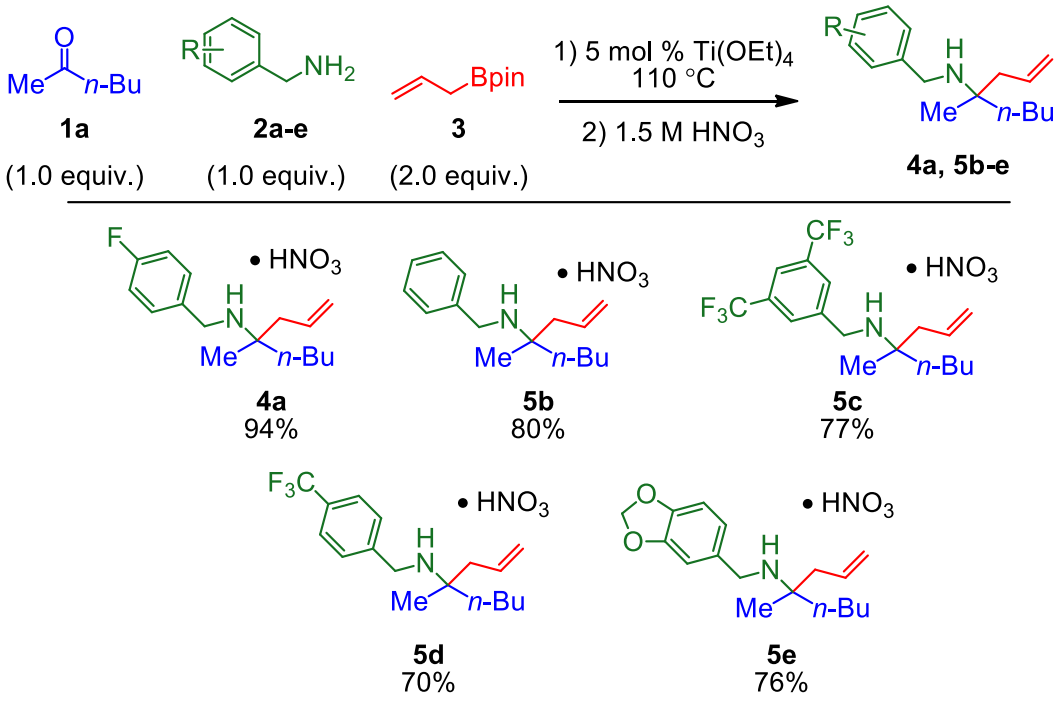


Table 1.12: Benzylamines used for tandem condensation-allylation allow for column free purification.

copper catalyst could be leading a similar degradation pathway that was observed with the amine and copper source. The addition of Allyl Bpin to isolated ketimine in absence of either catalyst shows a meager 17% yield at 18 hours (entry 1). When 5% $Ti(OEt)_4$ is added a similar yield of 15% is observed (entry 2). This is not surprising as the titanium's primary function is to encourage the condensation of the amine with the ketone. In both entries 1 and 2 the majority of the 2 equivalents of Allyl Bpin is remaining, 79 and 83% respectively. The addition of copper shows a drop to only 4% yield at 18 hours and a loss of one of third of the Allyl Bpin (entry 3). This suggests that the presence of the imine along with the copper catalysts acts to degrade Allyl Bpin, albeit slower than the amine and copper which showed complete loss of Ally Bpin within 6 hours. It could be that the imine acts in a similar

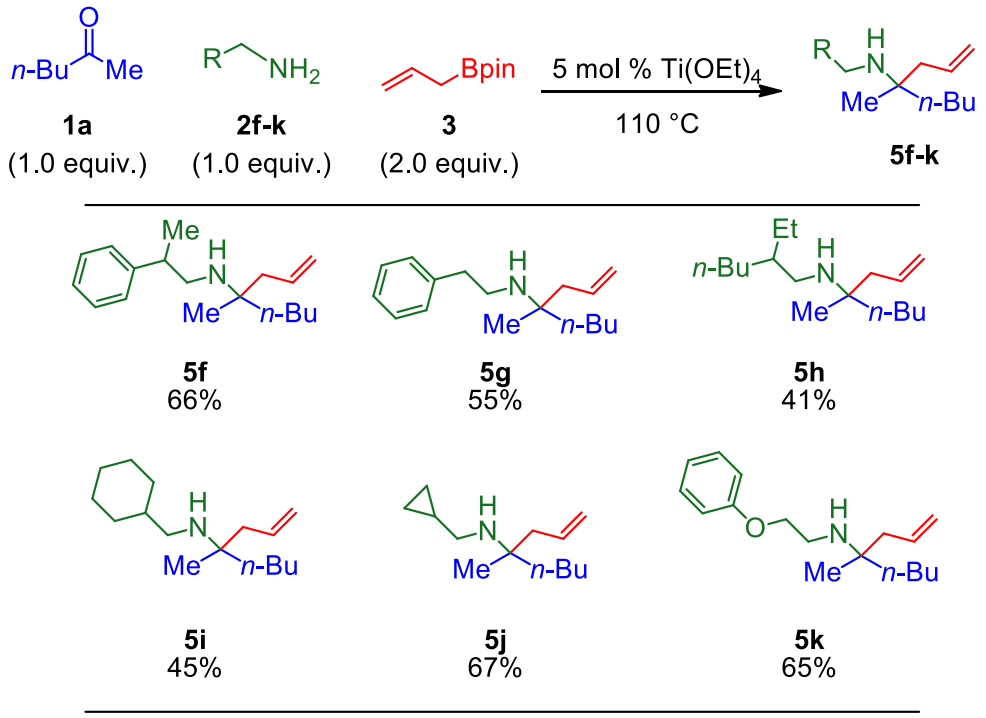


Table 1.13: Non-benzylamines, both alkyl and aryl provide modest yields.

manner to that of the free amine but activates the copper more poorly. The most intriguing entry however is 4 in which both catalysts were added. A similar yield to entry 3 is observed, but only 37% of the Allyl Bpin is left in solution. This suggests that there are two separate degradation pathways occurring in the dual catalyst system. One through the combination of the amine and copper and a second caused by the imine and copper that appears to be accelerated by the presence of titanium. One explanation of this might be that if the imine does not coordinate and activate the copper as strongly the Allyl Bpin might be activated by the $Ti(OEt)_4$. An ethoxide ligand could be liberated and serve to form the tetracoordinate boronate complex and thus accelerate transmetalation to the allyl copper species.

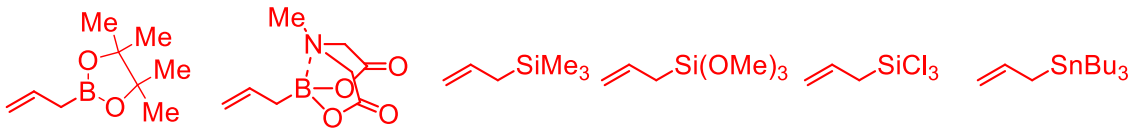


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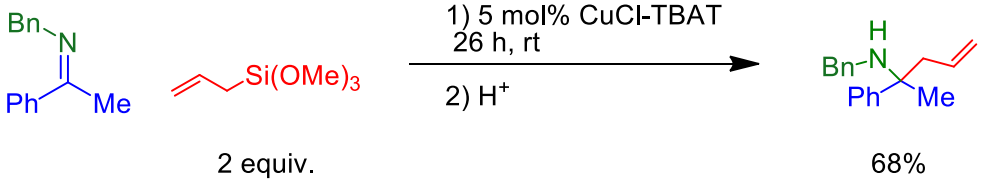
Figure 1.5: Screened allylic nucleophile sources.

While the boronic acid pinacol ester proved to be a capable nucleophile under our conditions, we opted to examine other allylic nucleophile sources. Allyl Bpin was screened against the MIDA ester, as well as three allyl silyl nucleophiles, and allyl tributyltin (Figure 1.5), which have been shown to add to pre-formed imine under a variety of conditions.[8,27] While the pinacol ester delivered the expected quantitative yield GC the MIDA ester gave only a meager 6%. Neither the silyl nucleophiles nor the allyl tin showed any presence of the expected product and returned largely unreacted starting materials. The meager performance of the MIDA ester could be a result of several factors but the greatest of which is likely due to the unique nature of the ester. As the nitrogen of the MIDA ligand folds over, there is a dative interaction of the lone pair with the empty orbital on the boron. This prevents the Lewis acid-base interaction of the boron with the ketimine which is required for the formation of the posited 6-membered transition state required to allow allylation. Allyltrimethoxysilane has been successfully used in the catalytic addition to isolated ketimines, giving products in modest yields (Scheme 1.6).[28]

A brief screen was performed to test the tolerance of our methodology in the presence of additional water. While under our optimized conditions our best substrate gives nearly quantitative yield by GC, the addition of a single equivalent of water drops the yield to 79%. A second equivalent drops it to 44%. This trend continues with only trace product (5%) being observed at 10 equivalents of water.



Scheme 1.6: Catalytic allylation of isolated ketimines proceeds in the presence of allyltrimethoxysilane, copper catalyst, and a fluoride source.

This sensitivity to water is intriguing as the initial condensation of the ketone and amine produces an equivalent of water and the addition of extra drying agents e.g. mol sieves showed no improvement in performance. Along with reduced yield, a simultaneous decrease is seen in the remaining Allyl Bpin. Among other possibilities, excess water may be causing the drop in yield by hydrolysis of the boronate ester and thus removal of the active nucleophile.

1.3 Substrate Scope and Mechanistic Considerations

The substrate scope of this reaction has demonstrated some limitation. Secondary amines displayed no reactivity, only returning starting materials with no evidence of condensation to form ketiminium or nucleophilic attack on it. The proposed Zimmerman-Traxler transition state may account for this (Figure 1.6).[31] As the reaction in this case would have to proceed through a ketiminium intermediate the nitrogen lone pair required to interact with the boron would be

largely unavailable. This issue is not observed with the previous ketone-amine-alkyne coupling as the copper acetylide acts as an external nucleophile.[15] This limited the amine scope to primary amines with both alkyl and aryl amine showing reactivity. As benzylamines demonstrated high reactivity, alpha-methylbenzylamine was tested. However, the reaction proceeded fully to the ketimine intermediate but allylation did not occur. Upon examination of the proposed transition state there is the possibility of 1,3-diaxial interactions between the methyl group from the amine and the hydrogens from the terminal olefin. Similar results were seen with cyclohexylamine and cyclopentylamine. It appears that only primary amines that are also primary at the alpha position are viable

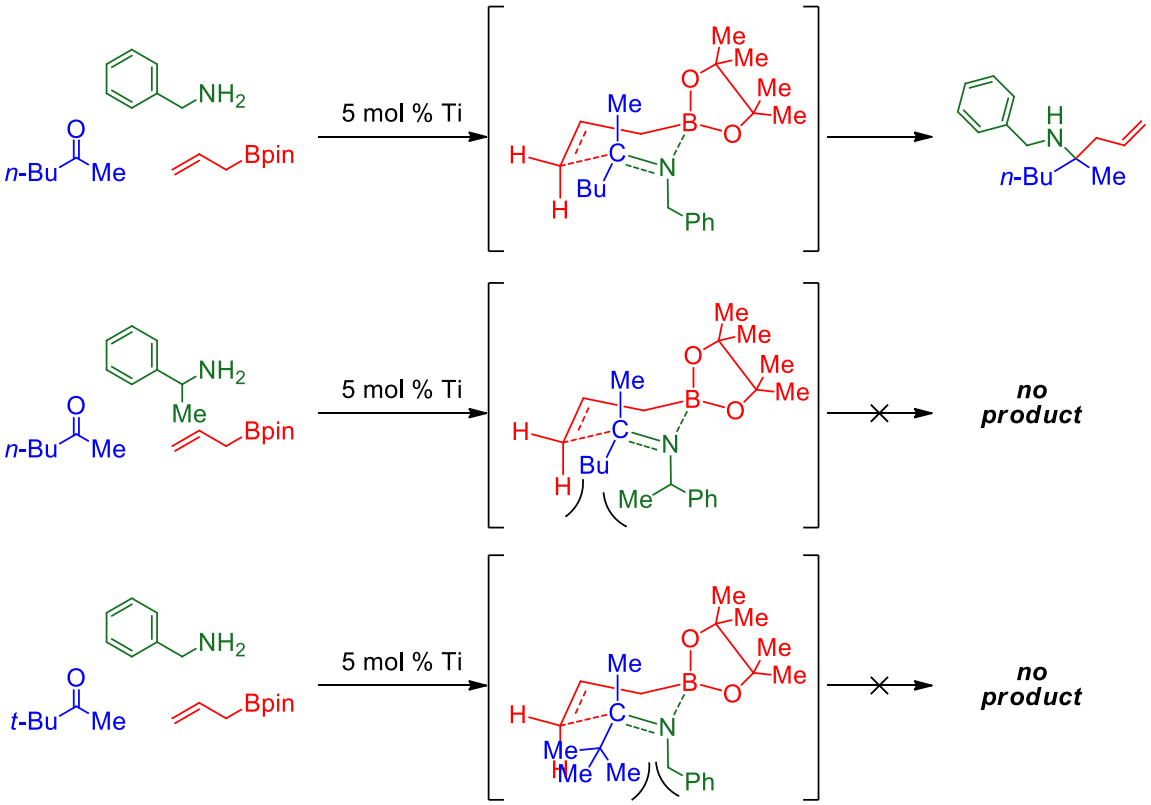


Figure 1.6: Proposed Zimmerman-Traxler transition state for the allylation of the *in situ* formed ketimine.

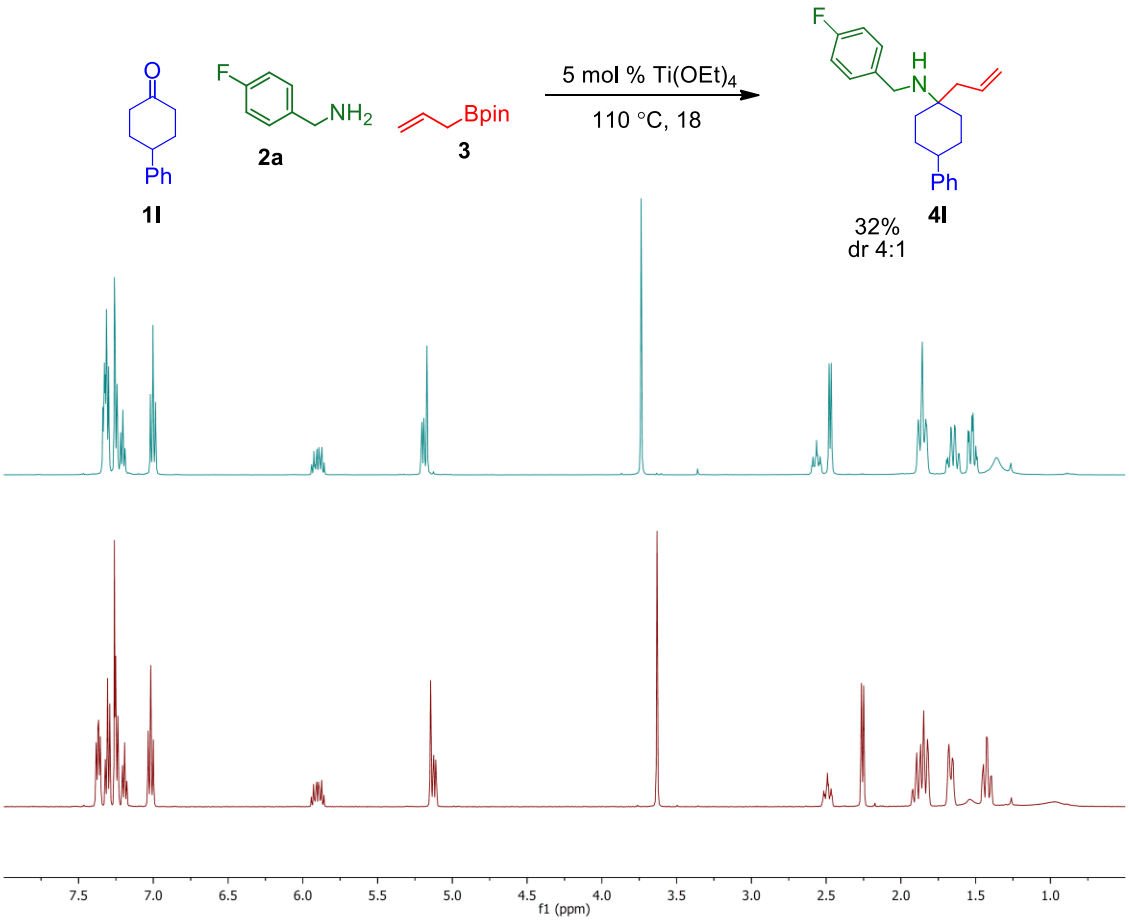


Figure 1.7: Stacked ^{1}H-NMR spectra of product **4l** which yielded two isomers which were isolable by simple column chromatography. All samples taken in $CDCl_3$.

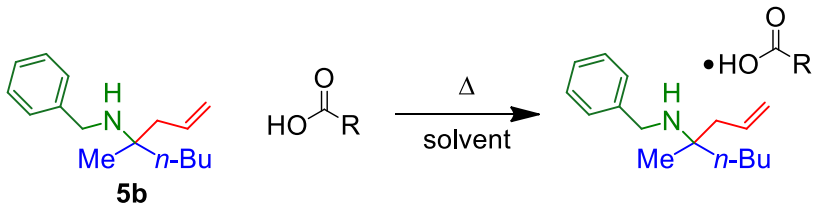
components under the current conditions. Exploration into the ketone scope has demonstrated that both simple acyclic and cyclic ketones can be utilized. There is a notable drop in yield as the steric bulk about the carbonyl is increased. Even the subtle change from 2-hexanone (**4a**) to 3-heptanone (**4f**) leads to more than a 30% drop in yield. More hindered ketones such as pinacolone and *R*-(+)-camphor gave full conversion to the ketimine but no nucleophilic attack by the Allyl Bpin. In the case of both pinacolone and camphor there is a quaternary carbon at the alpha position. This could lead to possible allylic strain between the quaternary carbon

and the benzyl group of the amine (Figure 1.6). As the ketimine is observed to form attempted formation of this transition state could increase the interactions preventing addition. Due to the steric hinderance and the resulting 1,3-diaxial interactions with the boronate ester, it's unlikely the tert-butyl group would occupy the axial position of the transition state.

In addition to the cyclic ketones trialed for this methodology (Table 1.11), 4-phenylcyclohexanone was attempted (Figure 1.7). Though a low yield was obtained, the resulting cis-trans isomers could not only be resolved by GC, but they were easily separated by column chromatography. Both by GC and isolated mass, the cis-trans ratio was found to be 4:1. The likely cause of the low yield (32%) in this case is that a large amount of the 4-phenylcyclohexanone is directly allylated by the Allyl Bpin. While the exact configuration of the dominant isomer has not been confirmed at this time, Gaussian calculations[32] of the two possible isomers show that the cis-isomer possesses a slightly lower ground state energy. Using the B3LYP DFT computational method and the 6-311+G(d,p) basis set the trans-isomer was calculated to have a ground state energy 1.3 kcal/mol higher than that of the cis-isomer.

Another curious aspect to this reaction is the low loading of the $Ti(OEt)_4$ catalyst. As was previously stated, in most instances $Ti(OEt)_4$ is used in super-stoichiometric amounts to achieve condensation.[14] The catalytic ketone-amine-alkyne reaction discussed above was able to lower that to only 50%, with 25% being sufficient to give product (though highest yields were reported at 50%). One

possible explanation for this catalytic activity could be the participation of the Allyl Bpin in the initial condensation. In addition to its primary purpose as the active nucleophile, there exists the possibility it plays a secondary role as a Lewis acid either by encouraging the condensation directly or aiding the titanium itself. This would also fall in line with why the Allyl MIDA ester showed such poor activity. The absence of an empty orbital on the boron would not only impedes ability to form the transition state with the imine but would also prevent it from effectively acting as a Lewis acid during the condensation.



5b

entry	Salt	Solvent Mixtures: EtOAc:Acetone:H_2O 7:2:1	MeCN:H_2O 9:1	iPrOH:H_2O 9:1	pKa of free acid
1	(*R*)-Camsylate	X	X	-	1.2
2	Maleate	X	X	-	1.92
3	D-Glutamate	-	-	-	2.10
4	2-NO_2-Benzoate	X	X	X	2.16
5	Malonate	X	X	-	2.83
6	L-Tartrate	-	-	-	2.89
7	Salicylate	-	-	-	2.97
8	Citrate	-	-	-	3.13
9	Ascorbate	-	-	-	4.10
10	Benzoate	-	-	-	4.20
11	Stearate	-	-	-	10.15

Table 1.14: Attempted formation of salts using a selection of acids used in pharmaceutical salt formulations. "X" denotes the formation of an amorphous or crystalline solid, while "-" means an oil was recovered upon evaporation.

1.4 Salt Formation

Looking to make access to these compounds more rapid and improve the overall “greenness” of the reaction, alternatives to column chromatography were explored. One popular approach to the isolation of free amine compounds is to form the corresponding ammonium salt by the addition of a strong acid. Ideally, the acid can be added to a suspension of the free amine oil in solvent in which the solid is insoluble. However, there is no reliable way of predicting the behavior of these salts or what effect the counter ion will have on the physicochemical properties like solubility and stability.[29] The purified oil of **4a** was taken up in a number of different non-polar solvents (e.g. hexanes, toluene, petroleum ether), and to this was added various acids in hopes of forming a solid. The screen of acids included mineral acids like HCl, H_2SO_4, HNO_3, and H_3PO_4, and organic acids including AcOH, TFA, TsOH, MsOH, and TfOH. From this it was determined that the addition of diethyl ether acidified with nitric acid to a hexanes suspension of the free amine gave a white solid. The addition of pure nitric acid to the hexanes suspension did not produce the same solid due to miscibility issues. The solid ammonium can be washed with ether to remove other solid organic impurities like

pinacol. Due to the solids non-existent aqueous solubility it can even be rinsed with water to remove titanium dioxide or boric acid should any remain. The ability to salt out these products as the ammonium salts only works when benzylamine and its derivatives were used as the amine source. Despite attempts at recrystallization out of variety of solvents, only an amorphous solid was recovered. These salts could be easily converted back to the free amine by simple basic aqueous workup if desired. This allowed for a chromatography-free synthesis of substrates **4a**-**4i** and **5b**-**5e**.

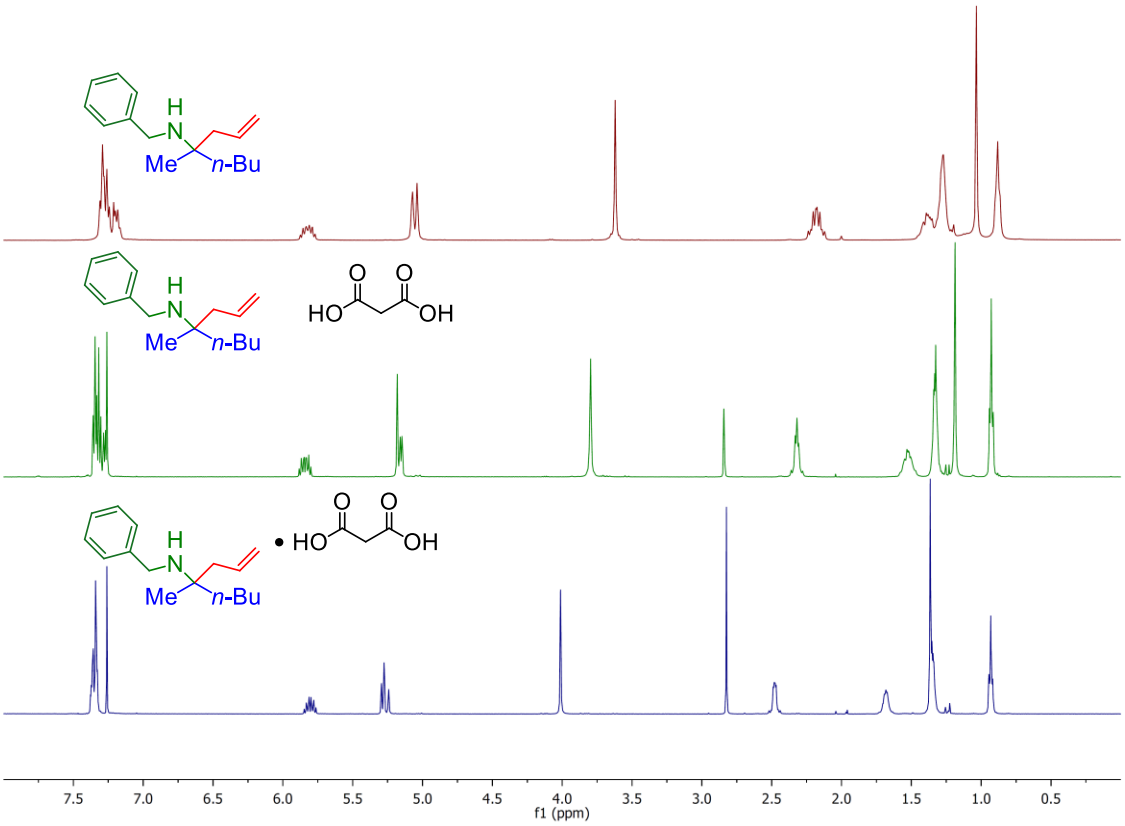


Figure 1.8: Stacked ^{1}H-NMR spectra of free amine **5b** (top), **5b** and malonic acid (middle), crystalline solid recovered from the slow-evaporation of equimolar **5b** and malonic acid (bottom). All samples taken in $CDCl_3$.

A diverse array of organic acids was tested to see if it were possible to isolate them as a cocrystal/salt with free amine **5b**. The carboxylic acids tested were chosen due to their presence in pharmaceutical formulations (Table 1.14).[29] This approach relies not on the ability to precipitate out the desired product from a suspension but by formation of a salt ion pair and then isolation by slow evaporation of the solvent mixture. Initial attempts to form these salts relied on heating hexanes, but the carboxylic acids low solubility did not permit full solvation. Published methods use combination of the water and water-miscible organic solvents, with alcoholic solvents being the most common.[30] Fully aqueous conditions were not conducive due to the low miscibility of the free amine oil and the longer evaporation time. It was determined that only 10% water was needed to solvate the carboxylic acids. A list of tested solvent mixtures can be found in Table 1.14. Equimolar amounts of **5b** and the corresponding acid were heated to reflux in each mixture until no solid remained. These were then allowed to evaporate at ambient conditions until sufficiently dry (10-15 days).

The majority of these trials returned a high viscosity syrup or heterogeneous mixture of solid and oil. Malonic, 2-nitrobenzoic, maleic, and camphorsulfonic acid resulted in either a crystalline or a homogeneous amorphous solid. ^{1}H-NMR confirms the formation of the new salt pair in both cases. Comparison of the ^{1}H-NMRs of free amine, free amine and malonic acid, and the new salt can be seen in Figure 1.7. The benzylic and allylic resonances display a distinct downfield shift going from the equimolar mixture of amine and acid to the cocrystal formed by slow

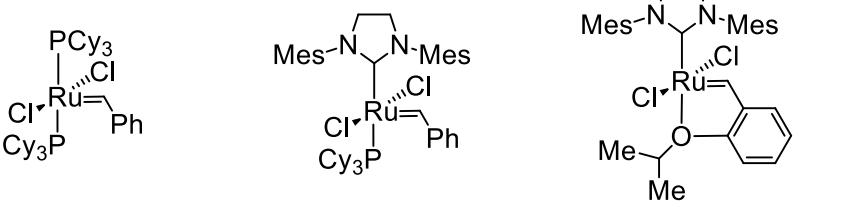
evaporation. The only definitive trend in the nature of acids is that all acids that were capable of protonating the free amine and forming the cocrystal/salt possessed pKa's less than 3. For example, benzoic acid (pKa ~4.2) did not give a solid salt however 2-nitrobenzoic acid (pKa ~2.2) did. However, not all acids with a pKa in this range gave an isolable solid. Neither salicylic acid (pKa ~ 2.97) nor L-tartaric acid (pKa ~2.89) formed a usable solid, though this could be due to other mitigating factors such as the free OH groups present in both acids. While stearic acid did not form a salt pair with free amine **5b**, a solid was observed to form. Upon analysis by ^{1}H-NMR it was observed that this was predominantly recrystallized stearic acid along with a trace amount of **5b**. The complete inability of D-glutamic acid (entry 3) to form a salt pair is most likely attributed to the fact the acid was insoluble in the combination of solvents tried. Increasing the amount of water to 50% aided in solubilizing it but still did not allow for complete solvation even after refluxing, additionally at this ratio of water miscibility issues were observed with **5b**.

1.5 Modification of Homoallyl Amine Products

While alpha-tetrasubstituted homoallylamines are found in a collection bioactive compounds, their greatest utility is as synthetic building blocks. With these substrates in hand it was then investigated as to how they could be readily modified. One of the most widely used and versatile ways to modify a terminal alkene is through olefin metathesis. Grubbs' catalysts readily allow for the

formation of carbon-carbon double bonds while tolerating a wide-variety of functional groups.[24]

Substrates containing free amines often require prior protection in order to prevent coordination and deactivation of the catalyst. However, the alpha-tetrasubstituted homoallylamines are hindered and it was posited this might be sufficient to prevent the previously mentioned coordination. Initial trials proved this to be ineffective. Compound **5b** (as the free amine) was reacted with 5 mol% of various Grubbs' catalysts (Figure 1.8) and 2 equivalents of crotonaldehyde. The reaction was monitored by GC and no product formation was observed, only starting materials. First attempts at protecting these substrates involved utilizing them in their nitrate salt form. Deactivation of the amine by addition Bronsted or Lewis acids has been shown to be effective for both ring-closing metathesis (RCM) as well as cross-metathesis (CM).[33] These substrates also display no activity under these conditions, so much so in fact the starting ammonium salts could even be recovered. As it was unknown which protecting groups would work or could be effectively installed, a wide variety were screened.

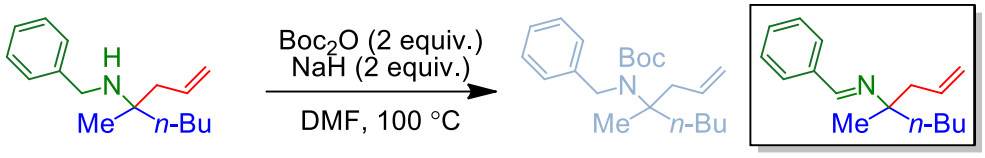


Grubbs Catalyst 1st Generation | Grubbs Catalyst 2nd Generation | Hoveyda-Grubbs Catalyst 2nd Generation

Figure 1.9: Grubbs Catalysts screened for olefin metathesis.

While the free amine **5b** was not hindered enough to prevent interaction and deactivation of the Grubbs' catalyst, the steric hinderance was enough to require somewhat aggressive conditions to protect it. Exploration of the literature led to a sampling of protecting groups try that were successfully used in metathesis reactions[34b], including tosyl (Ts), Boc, trityl (Tr), *p*-nitrobenzyl (PNB), acetyl (Ac), and benzyl carbamate (Cbz). Early attempts at acylation of the substrate showed that previously established conditions were not sufficient for these compounds. Whereas standard procedures advocate for running acylations with acetic anhydride at either reduced or ambient temperature, it was discovered that in order to acylate **5b** the reaction had to be refluxed in order to ensure complete conversion. The hinderance of the amine is the most likely culprit in this instance. Taking a cue from these early attempts at acylation it was determined that installation of protecting groups would more than likely require elevated temperatures. All protecting group candidates were screened across a variety of solvents typically used for their installment. A sampling of bases was tested including inorganic bases such as potassium or cesium carbonate and sodium hydride, amine bases like triethylamine and diazabicycloundecene (DBU) as well as the alkoxide base sodium ethoxide. The tosyl protecting group gave incomplete conversion in all cases with both starting materials observed at the end of reaction regardless of conditions. These reactions were also not consistent from trial to trial and the tosyl group appeared to be rather labile. The tritylation reactions proceeded more cleanly however, even under optimized conditions (1,4-dioxane

solvent, and sodium hydride) the reaction still did not reach completion, and the final product was largely inseparable from the free amine. The Boc protecting group which under best conditions only gave 40% conversion did however produce an unexpected side product. Upon spectroscopic analysis of the product mixture it was discovered that instead of protection of the free nitrogen there was instead formation of the benzyl imine (Scheme 1.7). This was confirmed by the imine proton resonance at 8.2 ppm as well as the imine carbon resonance at 155.9 ppm. Along with the appearance of these unique resonances is the disappearance of both benzylic protons and the benzylic carbon in the proton and carbon NMR spectra respectively. Greater success was seen with the PNB protection which after screening was determined to proceed ideally in dioxane using sodium hydride as the base. The benzyl carbamate however was shown to be the most successful,



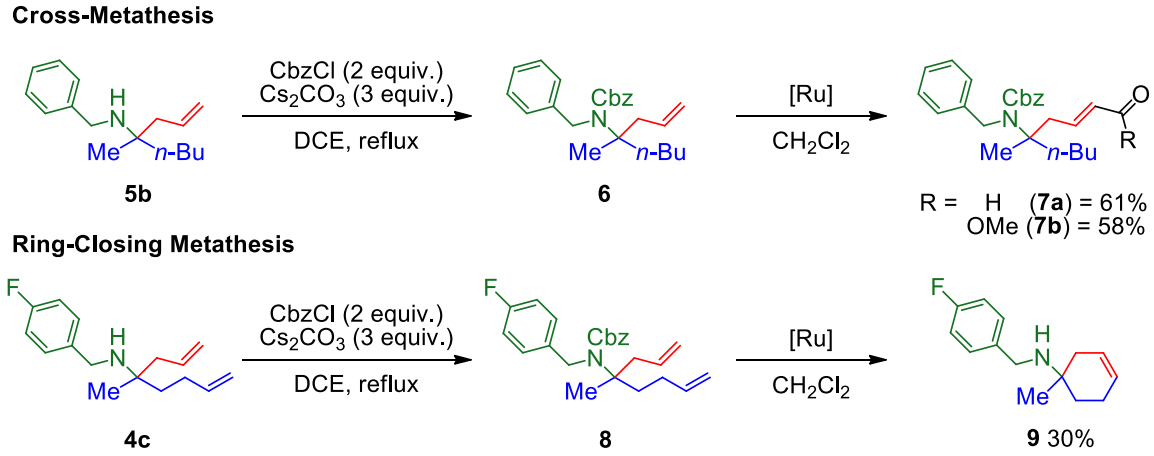
Scheme 1.7: Attempted Boc-protection of the **5b** does not yield expected product but instead generates the benzylidene imine.

with the cleanest reactions and best overall yields. In order to achieve complete conversion **5b** had to be reacted with four equivalents of benzyl chloroformate along with two to three equivalents of cesium carbonate. By in large the greatest difficulty experienced with these reactions was separation of side products generated by the large excesses of the protecting group reagent used. This was most notable with the synthesis of the benzyl carbamate **6**. As benzyl alcohol is also present in the reaction it can react with an equivalent of benzyl chloroformate

to give dibenzyl carbonate which requires careful separation by chromatography to fully remove.

Homoallyl amine **5b** was shown to be readily protectable as the corresponding carbamate (**6**) with benzyl chloroformate (CbzCl) using the modified established protocols described previously. This newly protected substrate was then again screened against the previously mentioned Grubbs' catalysts (Figure 1.8) in the three most common solvents (DCM, MTBE, and toluene) with crotonaldehyde as the CM partner. Only Grubbs 2nd Gen. and Hoveyda-Grubbs 2nd Gen. showed any activity. Product (**7a**) was confirmed in all trials for those two catalysts across all solvents. However complete conversion to product was only observed for Hoveyda-Grubbs 2nd Gen. in DCM. The dearth of reactivity of the Grubbs 1st Gen. catalyst might be due in part to the lower relative stability of the phosphine ligands compared to that of the NHCs present in the other two catalysts. The protected substrate also readily underwent cross-metathesis under these conditions with methyl acrylate as well to yield the stable α,β-unsaturated methyl ester **7b** (Scheme 1.8). Other common CM partners, like styrene, were also screened however the rate of homodimerization was so much greater than that of the cross-metathesis that the desired product was never observed, and in the case of styrene only protected substrate and *trans*-stilbene were recovered. Similar results were seen with allyl acetate. When similar trials were performed with the PNB protected **5b** a noticeable lack of activity was observed. These trials either failed to go to meaningful conversion or only returned starting materials.

Moving forward from the success with the cross-metathesis reaction, a ring-closing metathesis (RCM) reaction was considered. This bis-olefin product **4c** was suitable for this purpose. The substrate was protected as the benzyl carbamate in the same manner as **4a** without issue. The previously known to work catalysts

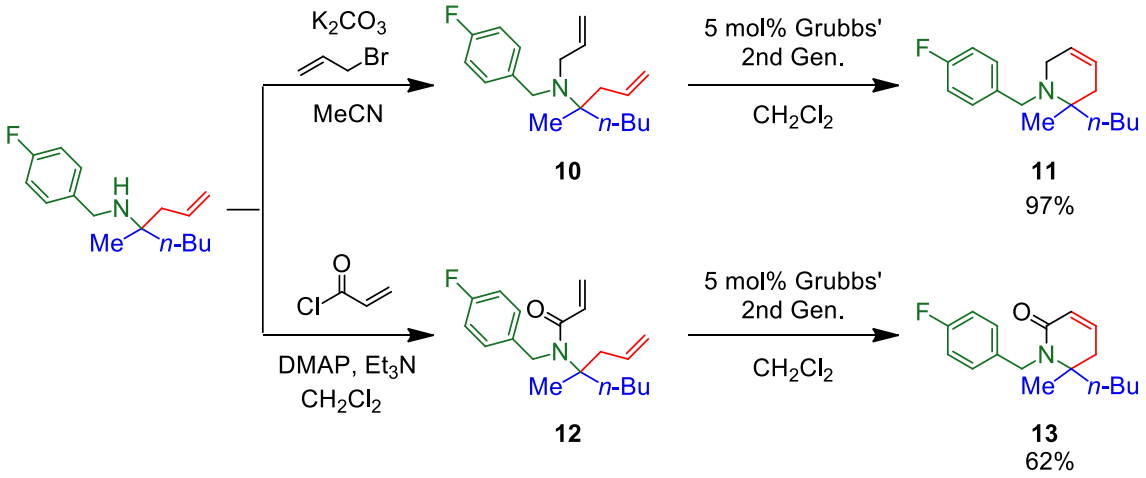


Scheme 1.8: Cross/ring-closing metathesis of Cbz-protected substrates using ruthenium catalysts.

Grubbs 2nd Gen. and Hoveyda-Grubbs 2nd Gen. were screened again with the same solvents. It was discovered that in this case that while all reactions ran to completion, all those utilizing Grubbs 2nd Gen. catalyst were cleaner by both TLC and ^{1}H-NMR (Scheme 1.8). All reactions were run at 0.1 M in order to avoid homodimerization of the starting material. Despite full conversion under these conditions, yields were low at 30%.

Despite success with the cross and RCM reactions of the protected substrates, other methods of substrate modification were explored that did not require the installment and removal of a protecting group. Instead the idea of a

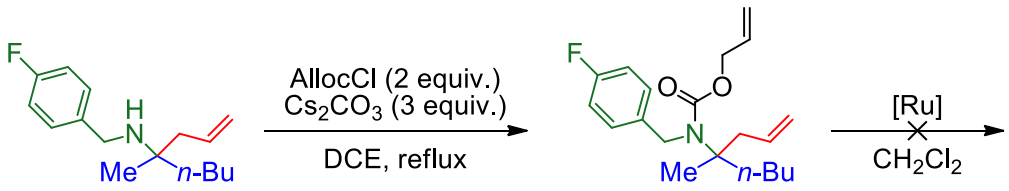
nitrogen protecting group that could be incorporated into the final structure was considered. The first option considered was allylation of the free amine then using Grubbs catalyst for ring-closing metathesis, thus giving an alpha-tetrasubstituted piperidine. Free amine **4a** was protected using allyl bromide and potassium carbonate in acetonitrile. As it had been previously observed that Grubbs 2nd Gen. catalyzed RCM reactions most cleanly it was chosen, and the desired product was obtained in 97% yield (Scheme 1.9).



Scheme 1.9: Protection of the free amine **4a** with an additional terminal olefin (either allyl or acryl) gave substrates that readily under went ring-closing metathesis with Grubbs catalyst to provide both electron rich and poor ring systems.

With the ability to successfully install an additional olefin handle on the nitrogen known, the next pathway considered was acrylation. The resultant acrylamide would upon RCM yield an alpha-tetrasubstituted lactam. Free amine **4a** could be readily reacted with acryloyl chloride, triethylamine, and catalytic dimethylaminopyridine (DMAP) to give the desired acrylamide. When reacted under the same RCM conditions as above, the expected lactam was produced in a 62% yield (Scheme 1.10). Further trials of both RCM reactions showed that the reactions reached completion after only 2 hours. From this success, additional

olefin-containing protecting groups were attempted to further broaden the scope of this avenue of modification. For the purposes of forming a larger ring system, the Alloc protecting group was considered. Ring-closing metathesis would in theory yield the 8-membered cyclic carbamate. Installation of the protecting group was carried out using standard conditions, 4 equivalents of both allyl chloroformate and cesium carbonate were added to **4a** which were allowed to reflux in dichloroethane. The final product had to be separated from the primary byproduct diallyl carbonate. When treated under RCM conditions, none of the desired product was formed. ^{1}H-NMR of the resultant reaction gave broad proton resonances similar to that of the starting allyl carbamate. As GC confirmed the consumption of starting material but no product formation, one possible explanation is polymerization of the Alloc protecting group.



4a **14**

Scheme 1.10: Alloc-protected substrate was successfully prepared but failed to undergo ring-closing metathesis under any conditions.

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1.7 Supporting Information

General Reagent Information:

All reactions were set up on the benchtop in test tubes equipped with magnetic stir bars and closed with screw caps. Flash column chromatography was performed using basic alumina gel or silica gel from Silicycle. Titanium(IV) tetraethoxide was purchased from Strem Chemical and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, Aldrich, or Oakwood and distilled before use. All ketones were purchased from Acros Organics, Alfa Aesar or TCI America and were purified by distillation before use. Allyl Bpin was purchased from Boron Molecular.

General Analytical Information.:

1H, 13C, and 19F NMR spectra were measured on a 500 and 400 MHz spectrometer using $CDCl_3$ as a solvent at room temperature. Some spectra include tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. Gas chromatography spectra were obtained using dodecane as an internal standard. For IR spectra, attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm-1). No sample preparation was necessary for ATR analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive index, and its reflection at the interface between the crystal and the solid material.

Mass spectrometric data was recorded on a ToF instrument using direct injection of samples in methanol into the electrospray source (ESI) and either positive or negative ionization.

Procedure for the synthesis of α-tetrasubstituted homoallyl amines A:

To an oven-dried test tube equipped with a magnetic stir bar was added 5 mol% Ti(OEt)4, ketone (1.0 equiv.), amine (1.0 equiv.), and allylboronic acid pinacol ester (2.0 equiv.). The reaction was then stirred at 110 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop an alumina gel column. Chromatography with 5-20% ethyl acetate (EtOAc) in hexanes as eluent afforded product, identified by its brown spot from permanganate stain ($KMnO_4$) on TLC.

Procedure for the synthesis of α-tetrasubstituted homoallyl amines B:

To an oven-dried test tube equipped with a magnetic stir bar was added 5 mol% Ti(OEt)4, ketone (1.0 equiv.), benzylamine (or substituted benzylamine) (1.0 equiv.), and allylboronic acid pinacol ester (2.0 equiv.). The reaction was then stirred at 110 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and rinsed with hexanes and diethyl ether (Et_2O). The mixture was then filtered through a short silica plug to remove the solid titanium dioxide. The resulting solution was then concentrated *in vacuo*. The crude oil was taken up in hexanes. To this a 1.5 M HNO_3 solution in Et_2O was added dropwise until no further product precipitated. The solution was then vacuum filtered, and the filter paper rinsed twice with hexanes. Additionally, the filtrate was

tested with excess acidified ether to verify no product remained. The nitrate salts could be readily converted to free amine upon solvation with methylene chloride and washing with a satd. sodium bicarbonate solution.

Procedure for the benzyl carbamate protection:

To an oven dried test tube equipped with a magnetic stir bar was added three-component product (1.0 equiv.), cesium carbonate (3.0 equiv.), and dichloroethane (0.5 M). While stirring at room temperature benzyl chloroformate (4.0 equiv.) was added dropwise. After addition, the reaction mixture was heated to reflux for 18 hours. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop a silica gel column. Chromatography with 1-5% ethyl acetate (EtOAc) in hexanes as eluent afforded product. Shallow gradient is required to achieve acceptable separation from the primary side product, dibenzyl carbonate.

General Allylation Procedure:

To an oven-dried test tube equipped with a magnetic stir bar was added either free amine or ammonium salt (1.0 equiv.), potassium carbonate (3.0 equiv.), and acetonitrile (2M). While stirring, to this was added allyl bromide (2.0 equiv.). After addition, the reaction mixture was stirred at 50 °C for 4 hours. Upon completion the mixture concentrated *in vacuo,* dissolved in 5% Et_2O/Hexanes then flushed through a Florisil plug. The mixture was then concentrated *in vacuo* again and used without further purification.

Procedure for Alloc protection:

To an oven dried test tube equipped with a magnetic stir bar was added three-component product (1.0 equiv.), cesium carbonate (3.0 equiv.), and dichloroethane (0.5 M). While stirring at room temperature allyl chloroformate (2.0 equiv.) was added dropwise. After addition, the reaction mixture was heated to reflux for 18 hours. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop a silica gel column. Chromatography with 0-1% ethyl acetate (EtOAc) in hexanes as eluent afforded product. Shallow gradient is required to achieve acceptable separation from the primary side product, diallyl carbonate.

General Cross-Metathesis Procedure:

To an oven-dried test tube equipped with a stir bar was added Hoveyda-Grubb's 2nd Generation catalyst (0.05 equiv.), and half the total volume of methylene chloride (0.25 M). The tube was then purged with argon for 5 minutes. While stirring, CM partner (2.0 equiv.) and Cbz-protected substrate dissolved in the remaining methylene chloride are added dropwise. After addition the reaction was heated for 18 hours at 50 °C. The resultant product mixture was concentrated *in vacuo* and then loaded directly atop a silica column and eluted with EtOAc/Hexanes.

N-(4-fluorobenzyl)-4-methyloct-1-en-4-aminium nitrate (4a):

Prepared according to general procedure B: 2-hexanone (123 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0

mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 94% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.39 (broad, d, *J* = 38.3 Hz, 2H), 7.51-7.34 (m, 2H), 6.97 (t, *J* = 7.9 Hz, 2H), 5.76 (td, *J* = 16.4, 8.1 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 5.20 (d, *J* = 16.9 Hz, 1H), 3.98 (s, 2H), 2.36 (ddd, *J* = 52.0, 14.3, 7.4 Hz, 2H), 1.39-1.26 (m, 6H), 1.21 (s, 3H), 0.91 (t, *J* = 6.2 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) 163.3 (d), 132.2 (d), 130.7, 126.8, 121.4, 116.1 (d), 62.8, 45.0, 40.7, 35.2, 25.0, 23.0, 21.9, 13.9. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -111.8. IR (neat): 3056.0 (w), 2959.4 (w), 2863.5 (w), 1514.6 (m), 1366.2 (s), 1314.6 (s), 1226.8 (m), 835.2 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 250.1966 found 250.1953.

N-(4-fluorobenzyl)-2-methyl-1-(3-(trifluoromethyl)phenyl)pent-4-en-2-aminium nitrate (4b):

Prepared according to general procedure B: 3-(trifluoromethyl)phenylacetone (168 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 76% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 91.8 Hz, 2H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.41-7.30 (m, 4H), 6.80 (t, *J* = 8.2 Hz, 2H), 6.04 (dt, *J* = 16.1, 8.0 Hz, 1H), 5.46 (d, *J* = 10.1 Hz, 1H), 5.35 (d, *J* = 16.7 Hz, 1H), 4.02 (t, *J* = 9.6 Hz, 2H), 2.86 (dd, *J* = 87.7, 13.3 Hz, 2H), 2.36 (ddd, *J* = 68.8, 15.4, 7.3 Hz, 2H), 1.21 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.1 (d), 135.3, 134.3 (d), 132.1 (d), 131.0 (q), 130.0 (d), 129.1, 127.3 (d), 126.1, 124.4, 123.9 (q), 122.2, 115.9 (d), 62.5, 45.2,

42.2, 39.4, 21.2. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -63.2, -111.2. IR (neat): 3033.3 (w), 2822.6 (w), 1394.4 (m), 1325.9 (s), 1296.7 (m), 1229.4 (m), 1136.3 (s), 1074.8 (m), 704.6 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 352.1683 found 352.1703.

N-(4-fluorobenzyl)-4-methylocta-1,7-dien-4-aminium nitrate (4c):

Prepared according to general procedure B: 5-hexen-2-one (116 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 82% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.44 (broad, s, 2H), 7.41 (dd, *J* = 8.3, 5.3 Hz, 2H), 6.98 (t, *J* = 8.3 Hz, 2H), 5.85-5.64 (m, 2H), 5.28 (d, *J* = 10.1 Hz, 1H), 5.22 (d, *J* = 16.9 Hz, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 5.01 (d, *J* = 10.1 Hz, 1H), 3.99 (s, 2H), 2.38 (ddd, *J* = 44.2, 14.4, 7.5 Hz, 1H), 2.21-2.06 (m, 2H), 1.73 (t, *J* = 8.5 Hz, 2H), 1.24 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.3 (d), 136.7, 132.2 (d), 130.5, 121.6, 116.2 (d), 116.0, 62.5, 45.1, 40.8, 34.7, 27.2, 21.9. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -111.7. IR (neat): 3077.1 (w), 2829.0 (w), 1513.4 (m), 1369.2 (s), 1308.7 (s), 1227.2 (m), 911.8 (m), 834.5 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 248.1809 found 248.1802.

2-cyclopropyl-N-(4-fluorobenzyl)pent-4-en-2-aminium nitrate (4d):

Prepared according to general procedure B: cyclopropyl methyl ketone (99 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 52% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.46 (broad, s, 2H), 7.42 (dd, *J* = 8.5, 5.2 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 5.80

(dt, *J* = 16.8, 8.0 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 5.15 (d, *J* = 17.7 Hz, 1H), 4.13 (dd, *J* = 35.3, 12.1 Hz, 2H), 2.37 (ddd, *J* = 21.8, 13.6, 7.5 Hz, 2H), 1.19-1.10 (m, 1H), 0.86 (s, 3H), 0.69-0.60 (m, 1H), 0.56 (dt, *J* = 13.9, 5.7 Hz, 2H), 0.38 (dt, *J* = 15.1, 5.5 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.3 (d), 132.3 (d), 131.0, 127.0, 121.1, 116.1 (d), 63.1, 45.3, 43.0, 16.5, 16.1, 2.8, 1.2. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -111.9. IR (neat): 3017.6 (w), 2814.8 (w), 1514.7 (m), 1393.4 (s), 1313.5 (s), 1226.2 (m), 826.2 (m), 523.3 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 234.1653 found 234.1665.

N-(4-fluorobenzyl)-4,6-dimethylhept-1-en-4-aminium nitrate (4e):

Prepared according to general procedure B: 4-methyl-2-pentanone (125 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 63% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.37 (broad, d, *J* = 45.4 Hz, 2H), 7.40 (dd, *J* = 8.0, 5.4 Hz, 2H), 6.97 (t, *J* = 8.4 Hz, 2H), 5.84 (dt, *J* = 16.9, 7.2, 1H), 5.31 (d, *J* = 10.1 Hz, 1H), 5.24 (d, *J* = 16.9 Hz, 1H), 3.99 (s, 2H), 2.44 (qd, *J* = 14.5, 7.4 Hz, 2H), 1.81 (dt, *J* = 12.4, 6.2 Hz, 1H), 1.71-1.57 (m, 2H), 1.20 (s, 3H), 0.98 (d, *J* = 6.5 Hz, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.3 (d), 132.2 (d), 130.8, 126.8, 121.7, 116.2 (d), 66.0, 63.3, 45.0, 44.4, 41.4, 25.1, 23.7, 22.3, 15.4. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -111.9. IR (neat): 3013.1 (w), 2853.0 (w), 1512.7 (m), 1383.0 (s), 1310.4 (s), 1224.8 (m), 829.0 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 250.1966 found 250.1976.

4-ethyl-N-(4-fluorobenzyl)oct-1-en-4-aminium nitrate (4f):

Prepared according to general procedure B: 3-heptanone (140 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 52% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (br, s, 2H), 7.44 (dd, *J* =8.2, 5.3 Hz, 2H), 7.01 (t, *J* = 8.5 Hz, 2H), 5.83 (dt, *J* = 17.3, 7.4 Hz, 1H), 5.28 (dd, *J* = 18.1, 13.8 Hz, 2H), 4.03 (s, 2H), 2.45 (d, *J* = 7.3 Hz, 2H), 1.78-1.61 (m, 4H), 1.39-1.22 (m, 4H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.3 (d), 132.1, 130.4, 121.7, 116.1 (t), 65.9, 45.3, 38.6, 33.4, 27.1, 24.6, 23.0, 13.9, 7.4. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -111.5. IR (neat): 3013.3 (w), 2961.2 (w), 2861.3 (w), 1600.25 (m), 1512.2 (m), 1392.4 (s), 1313.8 (s), 1222.9 (m), 828.9 (m), 523.6 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 264.2122 found 264.2105.

1-allyl-N-(4-fluorobenzyl)cyclopentanaminium nitrate (4g):

Prepared according to general procedure B: cyclopentanone (88 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 95% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.52 (br, s, 2H), 7.44-7.37 (m, 2H), 6.98 (t, *J* = 7.8 Hz, 2H), 5.91 (td, *J* = 16.2, 8.0 Hz, 1H), 5.36 (d, *J* = 10.0 Hz, 1H), 5.29 (d, *J* = 16.8 Hz, 1H), 3.99 (s, 2H), 2.48 (d, *J* = 6.9 Hz, 2H), 1.74-1.48 (m, 8H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.3 (d), 132.3 (d), 131.2, 126.7, 121.4, 116.0 (d), 69.0, 46.4, 40.6, 35.0, 24.4. ^{19}F-NMR (376 MHz,

$CDCl_3$) δ -112.1. IR (neat): 3054.0 (w), 2958.5 (w), 2865.3 (w), 1587.2 (m), 1511.7 (m), 1409.0 (m), 1299.6 (s), 1223.8 (s), 841.8 (m), 535.8 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 234.1653 found 234.1654.

1-allyl-N-(4-fluorobenzyl)cyclohexanaminium nitrate (4h):

Prepared according to general procedure B: cyclohexanone (104 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 86% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 2H), 7.40 (dd, *J* = 8.5, 5.4 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 5.99 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.52 – 5.14 (m, 2H), 4.10 – 3.90 (m, 2H), 2.57 (d, *J* = 7.3 Hz, 2H), 1.74 (d, *J* = 12.6 Hz, 2H), 1.63 (d, *J* = 11.2 Hz, 3H), 1.51 – 1.25 (m, 4H), 1.22-1.06 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.2 (d), 132.5 (d), 130.6, 126.9, 121.4, 115.9 (d), 62.2, 44.1, 36.0, 32.4, 24.7, 21.7. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -112.9. IR (neat): 3028.9 (w), 2926.6 (w), 2866.4 (w), 1600.2 (m), 1510.0 (m), 1301.8 (s), 1223.4 (s), 821.1 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 248.1809 found 248.1820.

1-allyl-N-(4-fluorobenzyl)cycloheptanaminium nitrate (4i):

Prepared according to general procedure A: cycloheptanone (118 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 64% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.41 (dd, *J* = 8.5, 5.3 Hz, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 5.91 (ddt, *J* = 17.3,

10.2, 7.3 Hz, 1H), 5.40 – 5.17 (m, 2H), 4.02 (s, 2H), 2.50 (d, *J* = 7.3 Hz, 2H), 1.92 – 1.73 (m, 4H), 1.70 – 1.60 (m, 2H), 1.60-.146 (m, 4H), 1.44-1.32 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.2 (d), 138.8, 137.3, 134.2 (d), 129.8, 129.4, 128.4, 127.1, 118.0, 115.1 (d), 63.5, 52.4, 49.4, 44.6, 42.3, 35.2. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -112.7. IR (neat): 2929.0 (w), 1600.6 (w), 1511.2 (m), 1359.6 (s), 1310.8 (s), 1224.8 (s), 824.3 (m), 516.9 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 262.1966 found 262.1980.

4-allyl-1-benzyl-N-(4-fluorobenzyl)piperidin-4-amine (4j):

Prepared according to general procedure A: 1-benzyl-4-piperidone (185 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 71% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 6H), 6.92 (t, *J* = 8.7 Hz, 2H), 5.78 (ddt, *J* = 17.7, 10.5, 7.4 Hz, 1H), 5.07 – 5.01 (m, 2H), 3.53 (s, 2H), 3.46 (s, 2H), 2.50 – 2.32 (m, 4H), 2.18 (d, *J* = 7.4 Hz, 2H), 1.61 – 1.48 (m, 4H), 0.93 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 162.0 (d), 138.8, 137.3, 134.2 (d), 129.8, 129.4, 128.4, 127.1, 118.0, 115.1 (d), 63.5, 52.4, 49.4, 44.6, 42.3, 35.2. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -117.7. IR (neat): 2930.1 (w), 2810.2 (w), 1507.8 (s), 1219.2 (s), 912.6 (m), 823.9 (s), 733.0 (s), 697.2 (s). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 339.2231 found 339.2228.

4-allyl-N-(4-fluorobenzyl)tetrahydro-2H-pyran-4-amine (4k):

Prepared according to general procedure A: tetrahydro-4*H*-pyran4-one (92 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 49% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.83 (ddt, *J* = 16.7, 10.4, 7.4 Hz, 1H), 5.19-5.05 (m, 2H), 3.86 (ddd , J = 11.2, 9.9, 2.9 Hz, 2H), 3.66 (dt, *J* = 11.4, 4.1 Hz, 2H), 3.63 (s, 2H), 2.30 (d, *J* = 7.5 Hz, 2H), 1.68-1.45 (m, 4H), 0.93 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.0 (d), 137.0, 133.3, 129.9 (d), 118.7, 115.3 (d), 63.7, 52.1, 44.7, 42.5, 36.0. IR (neat): 2936.1 (w), 2860.9 (w), 1602.1 (w), 1507.7 (s), 1446.3 (w), 1302.3 (w), 1218.7 (s), 1154.4 (m), 1085.6 (m), 1015.0 (m), 914.2 (m), 824.9 (s), 744.8 (m), 586.6 (m), 488.2 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 250.1602 found 250.1735.

N-benzyl-4-methyloct-1-en-4-aminium nitrate (5b):

Prepared according to general procedure B: 2-hexanone (123 µL, 1.0 mmol), benzylamine (109 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 80% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (br, d, *J* = 30.8 Hz, 2H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.33-7.24 (m, 3H), 5.76 (dt, *J* = 17.1, 8.7 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 5.21 (d, *J* = 16.5 Hz, 1H), 4.00 (s, 2H), 2.38

(ddd, *J* = 47.5, 14.1, 7.3 Hz, 2H), 1.66-1.59 (m, 2H), 1.38-1.26 (m, 4H), 1.25 (s, 3H), 0.90 (t, *J* = 6.9 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 131.0, 130.9, 130.1, 130.0, 129.2, 121.4, 63.0, 46.0, 40.8, 35.4, 25.0, 23.0, 22.0, 13.9. IR (neat): 3064.4 (w), 3026.9 (w), 2957.2 (m), 2929.6 (m), 2859.4 (m), 1466.1 (m), 911.0 (m), 696.3 (s). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 232.2060 found 232.2083.

N-(3,5-bis(trifluoromethyl)benzyl)-4-methyloct-1-en-4-aminium nitrate (5c):

Prepared according to general procedure B: 2-hexanone (123 µL, 1.0 mmol), 3,5-bis(trifluoromethyl)benzylamine (243 mg, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 77% yield. **1**H-NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 59.8 Hz, 2H), 8.01 (s, 2H), 7.81 (s, 1H), 5.71 (td, *J* = 17.4, 7.5 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 16.8 Hz, 1H), 4.16 (s, 2H), 2.41-2.19 (m, 2H), 1.65-1.58 (m, 2H), 1.28 (s, 4H), 1.11 (s, 3H), 0.90 (t, *J* = 6.8 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 133.5, 132.3 (q), 131.0, 130.4, 123.4, 122.9 (q), 121.6, 63.4, 44.8, 40.6, 35.2, 25.0, 22.9, 21.9, 13.8. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -63.5. IR (neat): 3020.6 (w), 2962.7 (w), 2873.1 (w), 1597.1 (w), 1383.2 (m), 1278.5 (s), 1169.1 (m), 1133.2 (s), 896.3 (m), 717.2 (m), 703.3 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 368.1808 found 368.1847.

4-methyl-N-(4-(trifluoromethyl)benzyl)oct-1-en-4-aminium nitrate (5d):

Prepared according to general procedure B: 2-hexanone (123 µL, 1.0 mmol), 4-(trifluoromethyl)benzylamine (143 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound

after precipitation as the nitrate salt in 70% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 57.1 Hz, 2H), 7.56 (q, *J* = 8.4 Hz, 4H), 5.76 (td, *J* = 17.2, 7.4 Hz, 1H), 5.25 (d, *J* = 10.1 Hz, 1H), 5.20 (d, *J* = 16.9 Hz, 1H), 4.04 (s, 2H), 2.38 (ddd, *J* = 39.5, 14.1, 7.2, 2H), 1.68-1.58 (m, 2H), 1.29 (s, 4H), 1.12 (s, 3H), 0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 134.9, 131.5 (q), 130.7, 125.9, 124.9, 123.8 (q), 121.5, 63.1, 45.2, 40.8, 35.3, 25.1, 23.0, 21.9, 13.9. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -63.3. IR (neat): 3018.8 (w), 2968.1 (w), 2873.3 (w), 1596.3 (w), 1394.0 (m), 1327.7 (s), 1162.8 (m), 1125.6 (s), 1069.1 (m), 925.8 (w), 846.5 (w), 594.8 (w). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 300.1934 found 300.1969.

N-(benzo[d][1,3]dioxol-5-ylmethyl)-4-methyloct-1-en-4-aminium nitrate (5e): Prepared according to general procedure B: 2-hexanone (123 µL, 1.0 mmol), piperonylamine (125 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 76% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 25.2 Hz, 2H), 6.94-6.87 (m, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 5.85 (s, 2H), 5.78 (dt, *J* = 17.3, 7.4 Hz, 1H), 5.24 (dd, *J* = 20.0, 13.4 Hz, 2H), 3.96 (t, *J* = 5.9 Hz, 2H), 2.43 (ddd, *J* = 21.3, 14.3, 7.5, 2H), 1.69-1.61 (m, 2H), 1.39-1.25 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 148.6, 148.2, 130.7, 124.7, 124.1, 110.2, 108.8, 101.5, 62.8, 45.9, 40.8, 35.5, 25.1, 23.0, 22.0, 13.9. IR (neat): 3061.5 (w), 2940.4 (w), 2861.9 (w), 1584.6 (w), 1493.5 (m), 1447.7 (s), 1373.7 (s), 1306.2 (s), 1248.4 (s), 1042.1 (s), 933.9 (m), 812.1 (m), 717.3 (w). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 276.1958 found 276.1953.

4-methyl-N-(2-phenylpropyl)oct-1-en-4-amine (5f):

Prepared according to general procedure A: 2-hexanone (123 µL, 1.0 mmol), β-methylphenethylamine (145 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 66% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.24-7.18 (m, 3H), 5.71-5.60 (m, 1H), 4.99 (s, 1H), 4.96 (d, *J* = 5.1 Hz, 1H), 2.81 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.71-2.60 (m, 2H), 2.03 (qd, *J* = 13.6, 7.5 Hz, 2H), 1.26 (m, 7H), 1.06 (m, 2H), 0.94 (d, *J* = 5.3 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 145.9, 134.9, 128.6, 127.4, 126.5, 117.44, 54.3, 49.2, 43.5, 40.9, 38.2, 25.6, 24.8, 23.5, 20.3, 14.3. IR (neat): 3072.5 (w), 3027.2 (w), 2957.4 (m), 2928.8 (m), 2870.8 (m), 1638.2 (w), 1452.2 (m), 1375.2 (m), 996.5 (w), 910.6 (m), 760.8 (m), 697.9 (s), 553.6 (w). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 260.2373 found 260.2407.

4-methyl-N-phenethyloct-1-en-4-amine (5g):

Prepared according to general procedure A: 2-hexanone (123 µL, 1.0 mmol), phenethylamine (126 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 55% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (tdd, *J* = 15.3, 11.1, 4.4 Hz, 5H), 5.71 (ddt, *J* = 17.8, 10.4, 7.4 Hz, 1H), 5.07-4.94 (m, 2H), 2.75 (s, 4H), 2.20-2.00 (m, 2H), 1.41-1.05 (m, 7H), 0.97 (s, 3H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (100 MHz,

$CDCl_3$) δ 140.4, 134.7, 128.8, 128.4, 126.2, 117.5, 54.5, 43.3, 43.2, 38.4, 37.2, 25.6, 24.7, 23.4, 14.2. IR (neat): 3073.0 (w), 3026.9 (w), 2956.7 (m), 2929.1 (m), 2858.8 (m), 1638.0 (w), 1453.8 (m), 1375.5 (w), 996.4 (w), 911.1 (m), 748.3 (m), 696.9 (s). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 246.2216 found 246.2228.

N-(2-ethylhexyl)-4-methyloct-1-en-4-amine (5h):

Prepared according to general procedure A: 2-hexanone (123 μL, 1.0 mmol), 2-ethyl-1-hexylamine (164 μL, 1.0 mmol), allyl boronic acid pinacol ester (375 μL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 45% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 17.8, 7.5 Hz, 1H), 5.10-5.01 (m, 2H), 2.37 (s, 2H), 2.12 (qd, *J* = 13.6, 7.0 Hz, 2H), 1.45-1.17 (m, 15H), 0.98 (s, 3H), 0.94-0.82 (m, 9H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 135.3, 117.4, 54.3, 44.4, 43.5, 40.5, 38.7, 31.7, 29.2, 25.8, 24.9, 24.8, 23.6, 23.3, 14.4, 14.3, 11.1. IR (neat): 3074.7 (w), 2957.0 (s), 2926.6 (s), 2858.6 (s), 1638.4 (w), 1460.2 (s), 1377.0 (m), 996.0 (m), 911.4 (s), 698.6 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 254.2842 found 254.2844.

N-(cyclohexylmethyl)-4-methyloct-1-en-4-amine (5l):

Prepared according to general procedure A: 2-hexanone (123 μL, 1.0 mmol), cyclohexylmethlamine (130 μL, 1.0 mmol), allyl boronic acid pinacol ester (375 μL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 45% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 17.3, 7.6 Hz,

1H), 5.10-5.00 (m, 2H), 2.30 (d, *J* = 6.2 Hz, 2H) 2.11 (td, *J* = 21.1, 13.7 Hz, 2H), 1.80-1.61 (m, 5H), 1.43-1.11 (m, 10H), 0.98 (s, 3H), 0.94-0.79 (m, 5H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 135.1, 117.5, 54.2, 48.4, 43.3, 39.0, 38.6, 32.0, 26.9, 26.3, 25.8, 24.9, 23.5, 14.3. IR (neat): 3074.3 (w), 2920.2 (s), 2851.3 (m), 1638.1 (w), 1447.8 (m), 1376.0 (w), 995.8 (w), 910.8 (m), 710.1 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 238.2529 found 238.2518.

N-(cyclopropylmethyl)-4-methyloct-1-en-4-amine (5j):

Prepared according to general procedure A: 2-hexanone (123 µL, 1.0 mmol), 1-cyclopropylmethanamine (87 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 67% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 17.4, 7.4 Hz, 1H), 5.06 (t, *J* = 13.2 Hz, 2H), 2.34 (d, *J* = 6.6 Hz, 2H), 2.11 (qd, *J* = 13.8, 7.4 Hz, 2H), 1.41-1.19 (m, 6H), 0.99 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 4H), 0.46 (q, *J* = 4.9 Hz, 2H), 0.07 (q, *J* = 4.8 H, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 135.2, 117.9, 54.4, 47.3, 43.5, 38.9, 26.1, 25.2, 23.8, 14.6, 12.2, 3.8. IR (neat): 3076.1 (w), 3002.5 (m), 2957.6 (m), 2860.3 (m), 1638.3 (w), 1466.9 (m), 1373.8 (m), 1162.8 (m), 1093.8 (m), 1015.5 (m), 995.9 (m), 910.9 (s), 825.7 (m), 703.1 (m), 640.1 (m), 490.9 (w). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 196.2060 found 196.2056.

4-methyl-N-(2-phenoxyethyl)oct-1-en-4-amine (5k):

Prepared according to general procedure A: 2-hexanone (123 µL, 1.0 mmol), 2-phenoxyethylamine (131 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL,

2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 65% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (m, 2H), 7.00-6.86 (m, 3H), 5.85 (dt, *J* = 17.6, 7.5 Hz, 1H), 5.17-5.03 (m, 2H), 4.07 (t, *J* = 5.4 Hz, 2H), 2.91 (t, *J* = 5.4 Hz, 2H), 2.24-2.11 (m, 2H), 1.47-1.24 (m, 6H), 1.05 (s, 3H), 0.93 (t, *J* = 6.7 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.0, 134.7, 129.5, 120.8, 117.8, 114.7, 68.3, 54.5, 43.4, 41.0, 38.6, 25.7, 24.9, 23.5, 14.3. IR (neat): 3072.6 (w), 2957.0 (m), 2928.8 (m), 2860.5 (m), 1599.2 (m), 1496.2 (m), 1458.9 (m), 1243.1 (s), 1171.0 (m), 1044.9 (m), 911.7 (m), 750.9 (s), 689.7 (s), 508.7 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 262.2165 found 262.2145.

benzyl benzyl(4-methyloct-1-en-4-yl)carbamate (6):

Prepared according to carbamate protection procedure: N-benzyl-4-methyloct-1-en-4-amine (231 mg, 1.0 mmol), cesium carbonate (977 mg, 3.0 mmol), and benzyl chloroformate (571 µL, 4.0 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 61% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.45-7.18 (m, 10H), 5.70 (dt, *J* = 17.0, 7.4 Hz, 1H), 5.14 (q, *J* = 12.5 Hz, 2H), 4.98 (m, 2H), 4.57 (s, 2H), 2.85 (dd, *J* = 13.5, 7.4 Hz, 1H), 2.36 (dd, *J* = 13.5, 7.4 Hz, 1H), 2.14 (m, 1H), 1.51 (m, 2H), 1.20 (m, 6H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 156.4, 140.6, 137.0, 134.7, 128.5, 128.3, 128.1, 127.9, 127.0, 118.0, 66.9, 62.4, 49.6, 43.8, 39.1, 26.6, 24.4, 23.2, 14.3. IR (neat): 2955.7 (m), 1697.7 (s), 1453.0 (m), 1392.9 (m), 1353.0 (m),

1201.8 (s), 1065.9 (m), 1026.8 (m), 913.9 (m), 727.3 (m), 696.0 (s). HRMS (ESI) *m/z* calcd for $[M+Na]^+$ requires 388.2247 found 388.2264.

(E)-benzyl benzyl(5-methyl-1-oxonon-2-en-5-yl)carbamate (7a):

Prepared according to general cross-metathesis procedure: benzyl benzyl(4-methyloct-1-en-4-yl)carbamate (73 mg, 0.2 mmol), crotonaldehyde (28 µL, 0.4 mmol), and Hoveyda-Grubb's 2nd gen. (6 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 61% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.15 (d, *J* = 7.9 Hz, 1H), 7.19 (m, 10H), 6.45 (dt, *J* = 15.3, 7.6 Hz, 1H), 5.92 (dd, *J* = 15.5, 7.9 Hz, 1H), 5.11 (q, *J* = 12.3 Hz, 2H), 4.72 (d, *J* = 16.7 Hz, 1H), 4.29 (d, *J* = 16.7 Hz, 1H), 3.28 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.40 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.16 (dd, *J* = 16.6, 8.4 Hz, 1H), 1.44 (td, *J* = 12.5, 3.5 Hz, 1H), 1.14 (m, 7H), 0.79 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 156.2, 155.1, 140.0, 136.6, 135.2, 128.6, 128.5, 128.2, 127.4, 127.1, 67.3, 62.4, 49.4, 43.0, 39.5, 26.3, 24.7, 23.0, 14.2. IR (neat): 2956.3 (m), 1686.5 (s), 1453.3 (m), 1394.7 (m), 1353.7 (m), 1198.5 (m), 1066.5 (m), 1027.1 (m), 976.4 (m), 729.9 (m), 696.9 (s). HRMS (ESI) *m/z* calcd for $[M+Na]^+$ requires 416.2196 found 416.2189.

(E)-methyl 5-(benzyl((benzyloxy)carbonyl)amino)-5-methylnon-2-enoate (7b):

Prepared according to general cross-metathesis procedure: benzyl benzyl(4-methyloct-1-en-4-yl)carbamate (73 mg, 0.2 mmol), methacrylate (36 µL, 0.4

mmol), and Hoveyda-Grubb's 2nd gen. (6 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 58% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40-7.14 (m, 10H), 6.85 (dt, *J* = 15.6, 7.8 Hz, 1H), 5.79 (d, *J* = 15.5 Hz, 1H), 5.17 (q, *J* = 12.4 Hz, 2H, 4.67 (d, *J* = 17.0 Hz, 1H), 4.51 (d, *J* = 17.0 Hz, 1H), 3.73 (s, 3H), 3.13 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.50 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.19 (td, *J* = 12.7, 4.4 Hz, 1H), 1.54 (td, *J* = 12.7, 4.4 Hz, 1H), 1.36-1.07 (m, 7H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.8, 156.3, 145.6, 140.1, 136.8, 128.5, 128.5, 128.1, 128.0, 127.0, 126.8, 123.8, 67.1, 62.4, 51.5, 49.5, 42.4, 39.3, 26.5, 24.5, 23.1, 14.2. IR (neat): 2954.4 (m), 1696.8 (s), 1453.1 (m), 1394.5 (m), 1354.4 (m), 1198.1 (m), 908.0 (m), 728.2 (s), 697.1 (s). HRMS (ESI) *m/z* calcd for $[M+Na]^+$ requires 446.2302 found 446.2369.

benzyl 4-fluorobenzyl(4-methylocta-1,7-dien-4-yl)carbamate (8):

Prepared according to carbamate protection procedure: N-(4-fluorobenzyl)-4-methylocta-1,7-dien-4-amine (247 mg, 1.0 mmol), cesium carbonate (977 mg, 3.0 mmol), and benzyl chloroformate (571 µL, 4.0 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 40% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 7.17 (dd, *J* = 8.4, 5.4 Hz, 2H), 6.95 (t, *J* = 8.6 Hz, 2H) 5.79-5.61 (m, 2H), 5.19-5.11 (m, 2H), 5.02-4.87 (m, 4H), 4.59-4.45 (m, 2H), 2.86 (dd, *J* = 13.6, 7.4 Hz, 1H), 2.37-2.25 (m, 2H), 1.91 (q, *J* = 7.7 Hz, 2H), 1.63-1.54 (m, 2H), 1.23 (s, 3H).

benzyl 4-fluorobenzyl(1-methylcyclohex-3-en-1-yl)carbamate (9):

Prepared according to general ring closing-metathesis procedure**:** benzyl 4-fluorobenzyl(4-methylocta-1,7-dien-4-yl)carbamate (76 mg, 0.2 mmol), and Grubb's 2nd gen. (6 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 30% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.38-7.25 (m, *5*H), 7.14 (dd, *J* = 8.2, 5.4 Hz, 2H), 6.97 (t, *J* = 8.4 Hz, 2H), 5.80-5.67 (m, 1H), 5.63-5.50 (m, 1H), 5.16 (s, 2H), 4.80 (d, *J* = 17.2 Hz, 1H), 4.46 (d, *J* = 17.2 Hz, 1H), 2.48 (dt, *J* = 12.7, 6.2 Hz, 1H), 2.41 (d, *J* = 18.1 Hz, 1H), 2.27 (d, *J* = 18.0 Hz, 1H), 2.05 (s, 2H), 1.68 (dt, *J* = 12.9, 6.5 Hz, 1H), 1.40 (s, 3H). Substrate not fully characterized.

N-allyl-N-(4-fluorobenzyl)-4-methyloct-1-en-4-amine (10):

Prepared according to general allylation procedure: N-(4-fluorobenzyl)-4-methyloct-1-en-4-aminium nitrate (312 mg, 1.0 mmol), and Grubb's 2nd gen. (6 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 74% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.3, 5.6 Hz, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 5.89 (ddt, *J* = 15.8, 11.1, 7.3 Hz, 1H), 5.77 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.09 – 5.00 (m, 2H), 4.94 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.87 (dd, *J* = 10.1, 1.8 Hz, 1H), 3.72 (d, *J* = 3.3 Hz, 2H), 3.21 (d, *J* = 6.5 Hz, 2H), 2.30 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.20 (dd, *J* = 14.0, 7.5 Hz, 1H), 1.56 – 1.21 (m, 6H), 1.02 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

2-butyl-1-(4-fluorobenzyl)-2-methyl-1,2,3,6-tetrahydropyridine (11):

Prepared according to general ring closing-metathesis procedure: N-allyl-N-(4-fluorobenzyl)-4-methyloct-1-en-4-amine (52 mg, 0.2 mmol), and Grubb's 2nd gen. (6 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 97% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.3, 5.5 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 5.73 – 5.62 (m, 1H), 5.54 (dt, *J* = 10.1, 2.8 Hz, 1H), 3.68 (d, *J* = 13.3 Hz, 1H), 3.43 (d, *J* = 13.3 Hz, 1H), 3.01 – 2.89 (m, 1H), 2.83 (dt, *J* = 17.7, 2.8 Hz, 1H), 2.22 (dt, *J* = 17.4, 2.9 Hz, 1H), 1.82 (ddd, *J* = 17.4, 4.7, 2.4 Hz, 1H), 1.58 – 1.25 (m, 6H), 1.09 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H).

N-(4-fluorobenzyl)-N-(4-methyloct-1-en-4-yl)acrylamide (12):

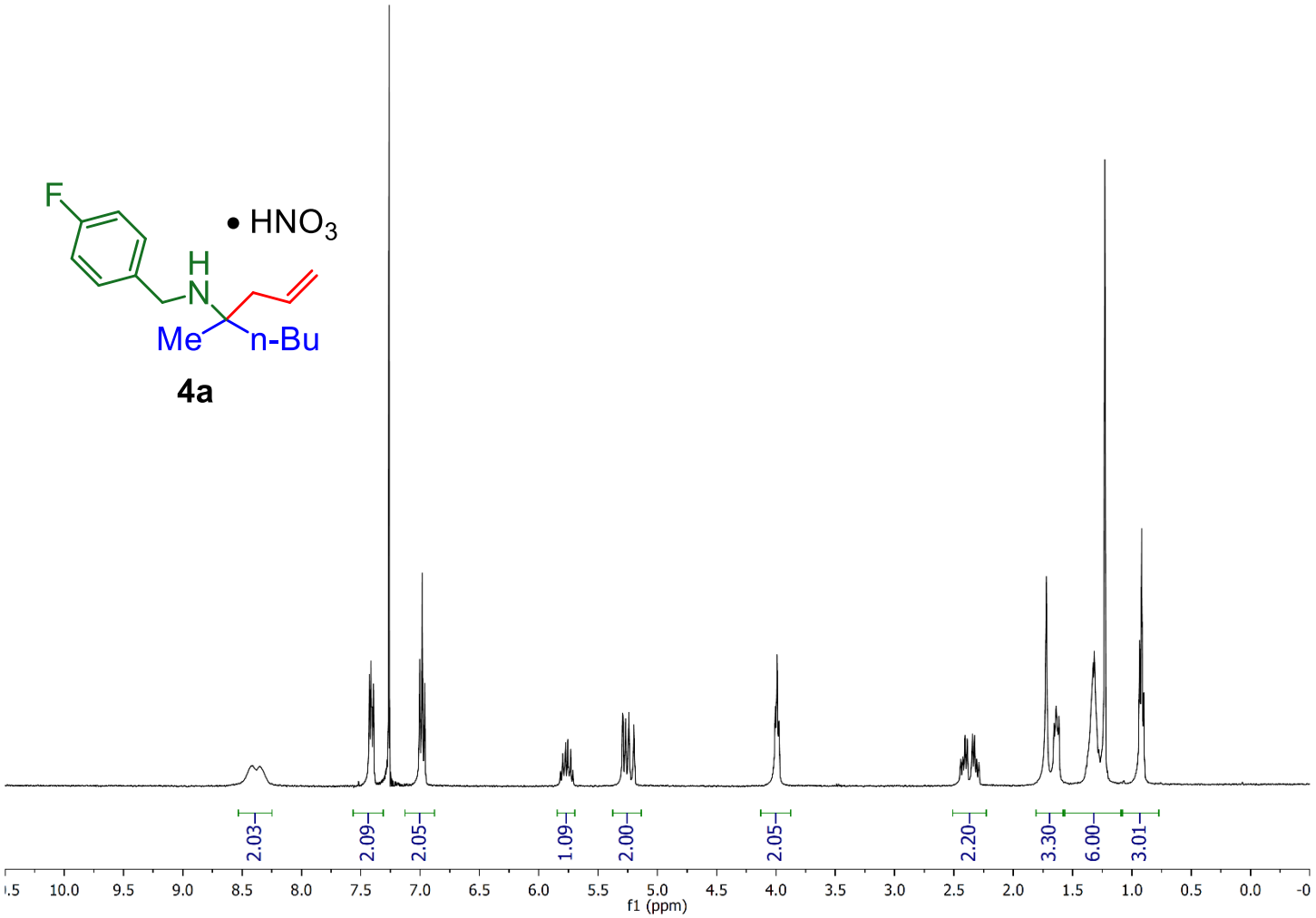
Prepared according to general acrylation procedure: N-(4-fluorobenzyl)-4-methyloct-1-en-4-aminium nitrate (312 mg, 1.0 mmol), and Grubb's 2nd gen. (6 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 42% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.04 (t, *J* = 8.6 Hz, 1H), 6.43 – 6.28 (m, 1H), 5.77 (ddt, *J* = 19.6, 9.3, 7.5 Hz, 0H), 5.56 (dd, *J* = 9.8, 2.6 Hz, 1H), 5.13 – 5.01 (m, 1H), 4.53 (s, 1H), 3.05 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.45 (dd, *J* = 13.4, 7.4 Hz, 0H), 2.27 (ddd, *J* = 13.3, 11.2, 5.5 Hz, 1H), 1.79 – 1.60 (m, 1H), 1.35 – 1.14 (m, 3H), 0.88 (t, *J* = 7.1 Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.6, 162.1 (d), 135.2 (d), 134.8, 131.4, 127.8, 127.7, 118.3, 115.7 (d), 63.6, 49.3, 42.8, 38.5, 26.8, 23.9, 23.3, 14.3.

6-butyl-1-(4-fluorobenzyl)-6-methyl-5,6-dihydropyridin-2(1H)-one (13):

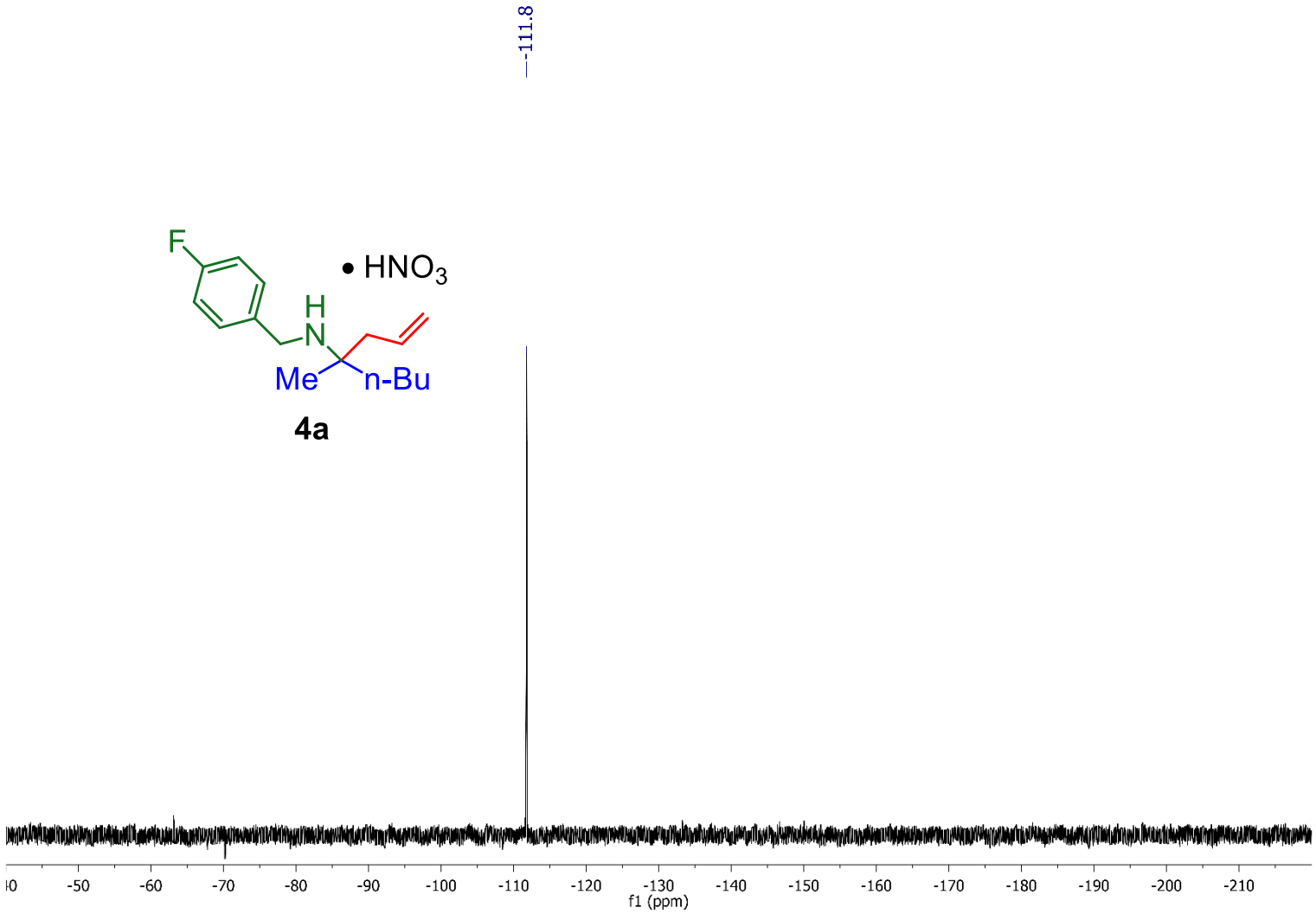
Prepared according to general ring closing-metathesis procedure: N-(4-fluorobenzyl)-N-(4-methyloct-1-en-4-yl)acrylamide (61 mg, 0.2 mmol, and Grubb's 2nd gen. (6 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 62% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.47 (ddd, *J* = 9.8, 5.0, 3.5 Hz, 1H), 6.03 (dt, *J* = 9.7, 1.8 Hz, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.34 (d, *J* = 15.7 Hz, 1H), 2.43 – 2.29 (m, 2H), 1.64 (ddd, *J* = 13.6, 11.2, 5.0 Hz, 1H), 1.54 (ddd, *J* = 13.6, 11.3, 4.6 Hz, 1H), 1.31 – 1.08 (m, 7H), 0.84 (t, *J* = 7.0 Hz, 3H).^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.6, 161.8 (d), 137.5, 135.9, 128.8 (d), 125.1, 115.3 (d), 59.7, 43.8, 38.7, 36.0, 27.2, 25.8, 23.3, 14.1.

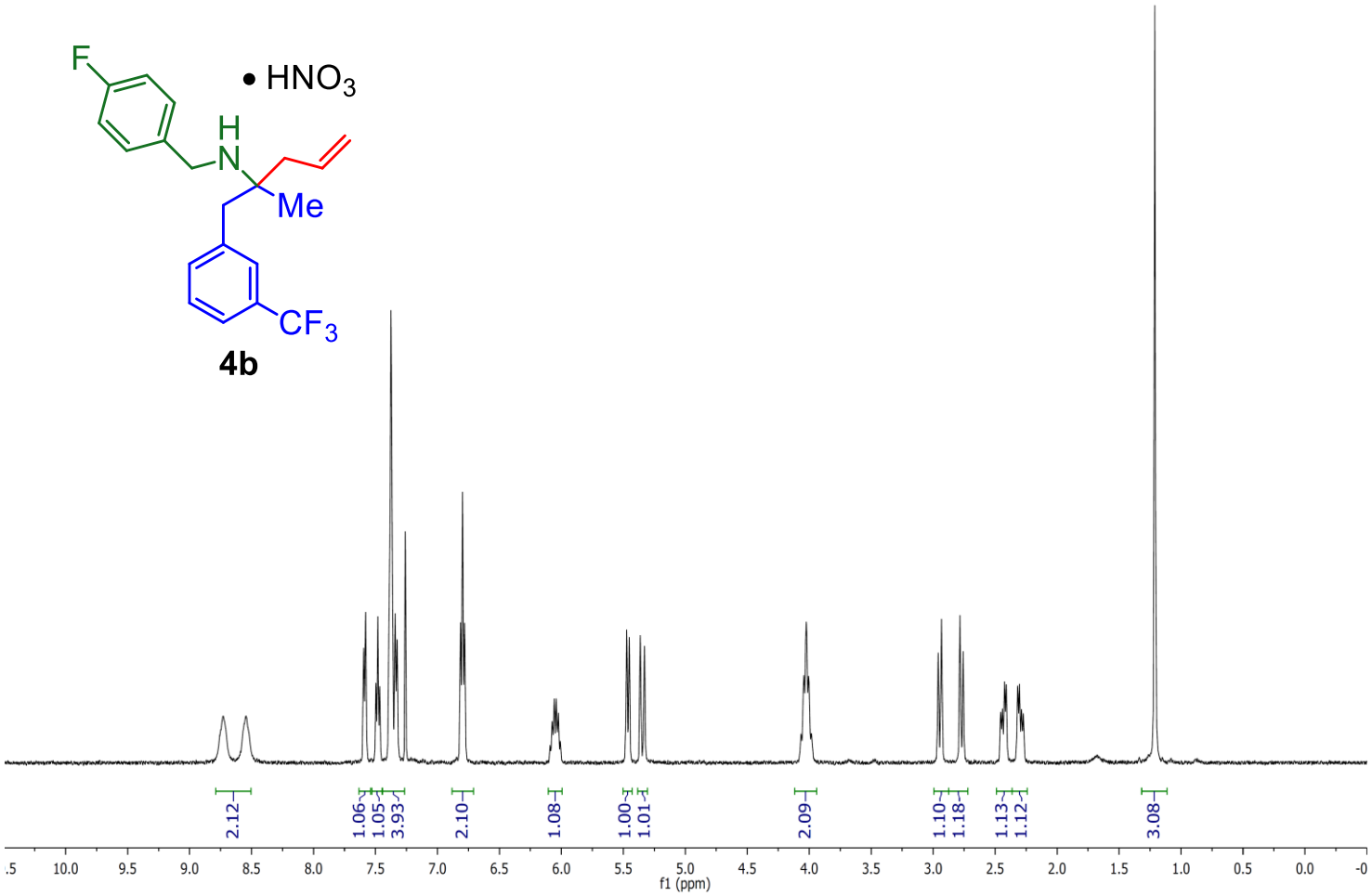
Allyl 4-fluorobenzyl(4-methyloct-1-en-4-yl)carbamate (14):

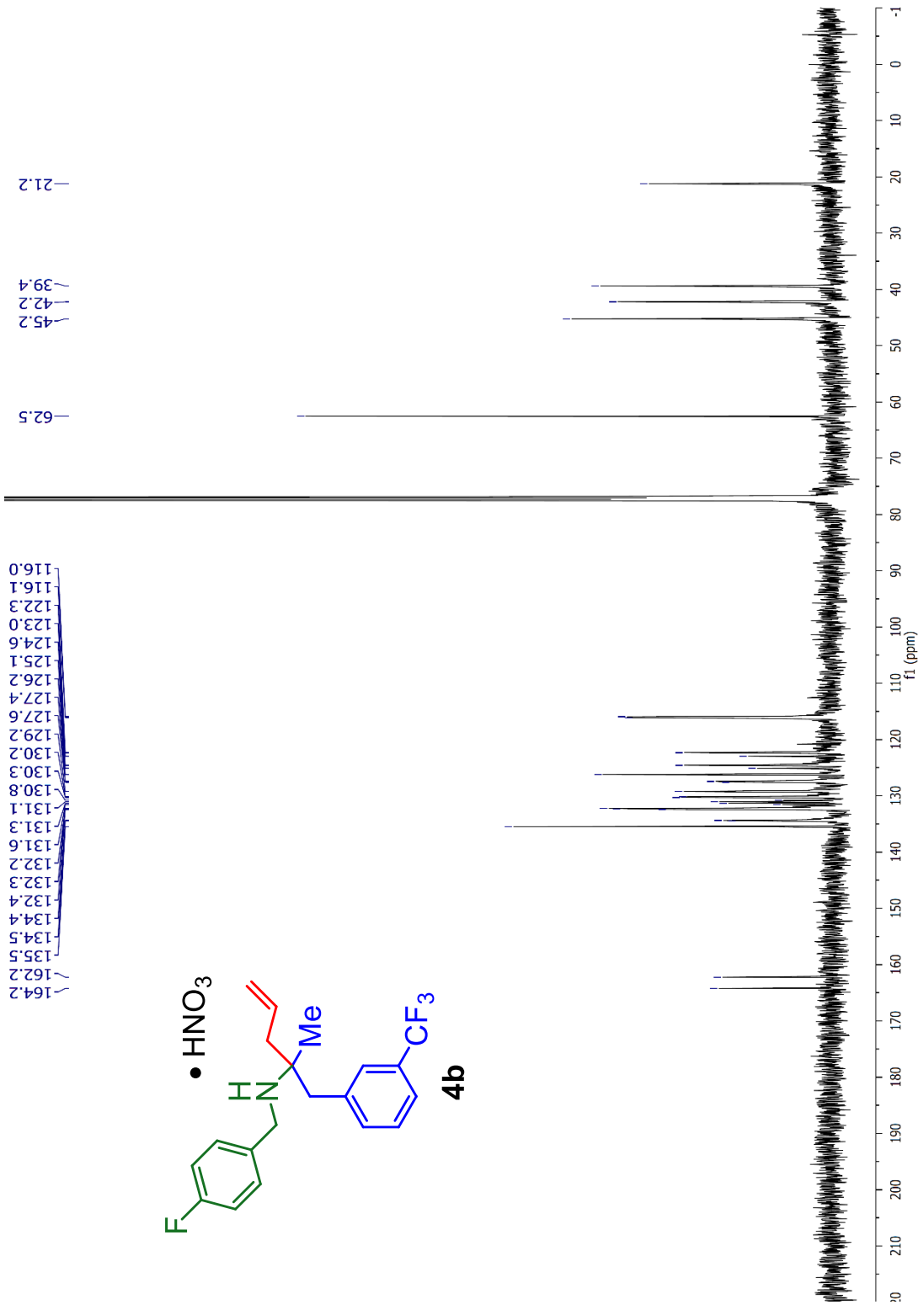
Prepared according to alloc protection procedure: N-(4-fluorobenzyl)-4-methylocta-1,7-dien-4-amine (247 mg, 1.0 mmol), allyl chloroformate (213 µL, 2.0 mmol), and cesium carbonate (977 mg, 3.0 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 64% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.3, 5.3 Hz, 2H), 6.98 (t, *J* = 8.6 Hz, 2H), 5.91 (ddt, *J* = 16.4, 10.8, 5.6 Hz, 1H), 5.70 (dq, *J* = 19.0, 7.7 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 5.05 – 5.00 (m, 2H), 4.66 – 4.56 (m, 2H), 4.52 (s, 2H), 2.87 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.32 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.51 (ddd, *J* = 13.5, 10.8, 6.0 Hz, 1H), 1.35 – 1.04 (m, 7H), 0.86 (t, *J* = 7.3 Hz, 3H).

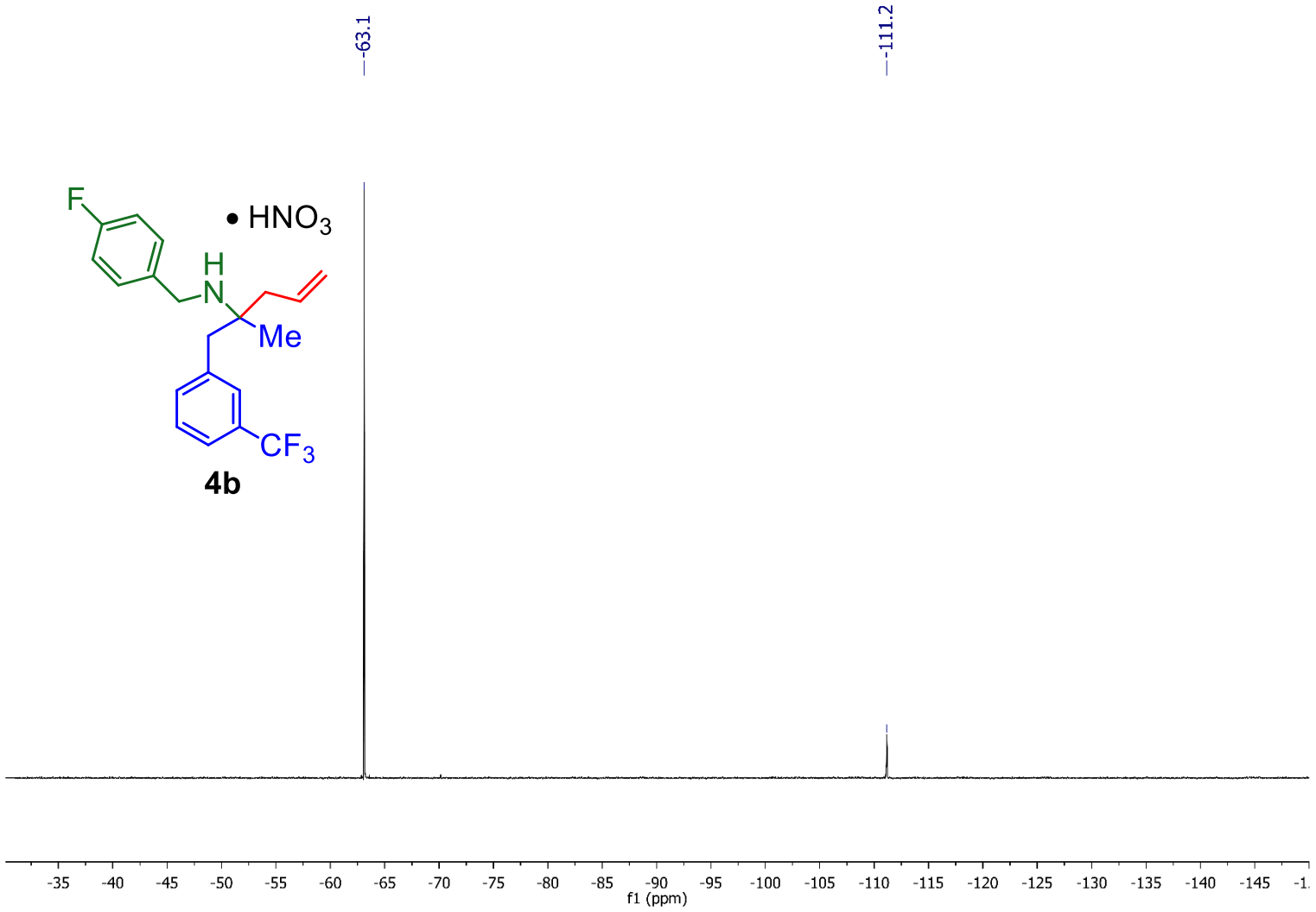

F
• HNO3
H
N
Me
n-Bu
4a
2.03
2.09
2.05
1.09
2.00
2.05
2.20
3.30
6.00
3.01
f1 (ppm)

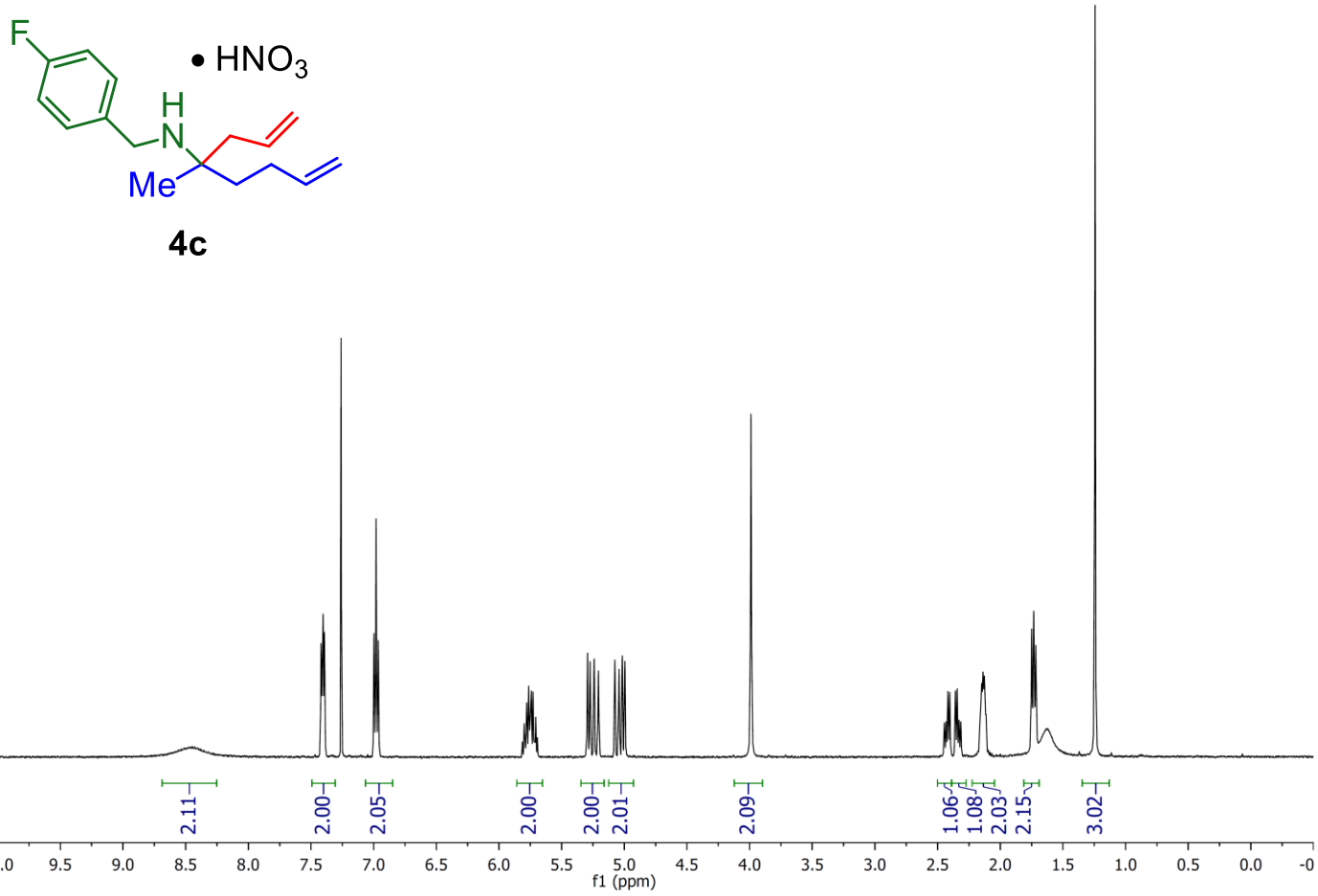
164.3
162.3
132.3
132.2
130.7
126.8
121.4
116.2
116.0
62.8
45.0
40.7
35.2
25.0
23.0
21.9
13.9
F
H
N
Me
n-Bu
• HNO3
4a
f1 (ppm)


-111.8
F
• HNO3
H
N
Me
n-Bu
4a
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

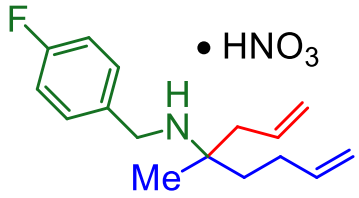

F
• HNO3
H
N
Me
CF3
4b
2.12
1.06
1.05
3.93
2.10
1.08
1.00
1.01
2.09
1.10
1.18
1.13
1.12
3.08
f1 (ppm)


21.2
39.4
42.2
45.2
62.5
116.0
116.1
122.3
123.0
124.6
125.1
126.2
127.4
127.6
129.2
130.2
130.3
130.8
131.1
131.3
131.6
132.2
132.3
132.4
134.4
134.5
135.5
162.2
164.2
f1 (ppm)
• HNO3
Me
CF3
F
4b


-63.1
-111.2
F
• HNO3
H
N
Me
CF3
4b
-35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145
f1 (ppm)


F
• HNO3
H
N
Me
4c
2.11
2.00
2.05
2.00
2.00
2.01
2.09
1.06
1.08
2.03
2.15
3.02
f1 (ppm)

164.3
162.3
136.7
132.2
132.2
130.5
121.6
116.3
116.1
116.0
62.5
45.1
40.7
34.7
27.2
21.9
• HNO3
H
N
Me
F
4c
f1 (ppm)

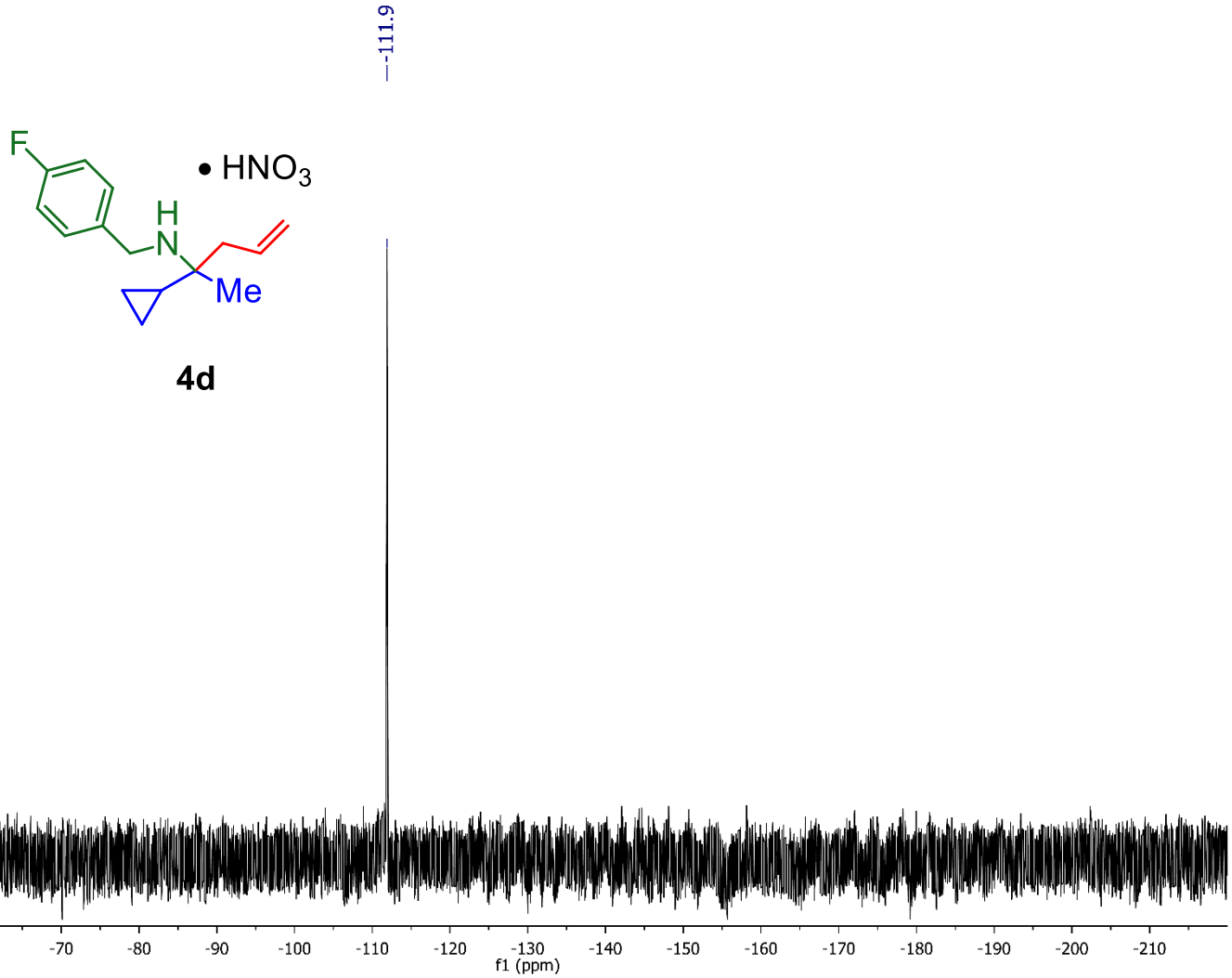

F
• HNO3
H
N
Me

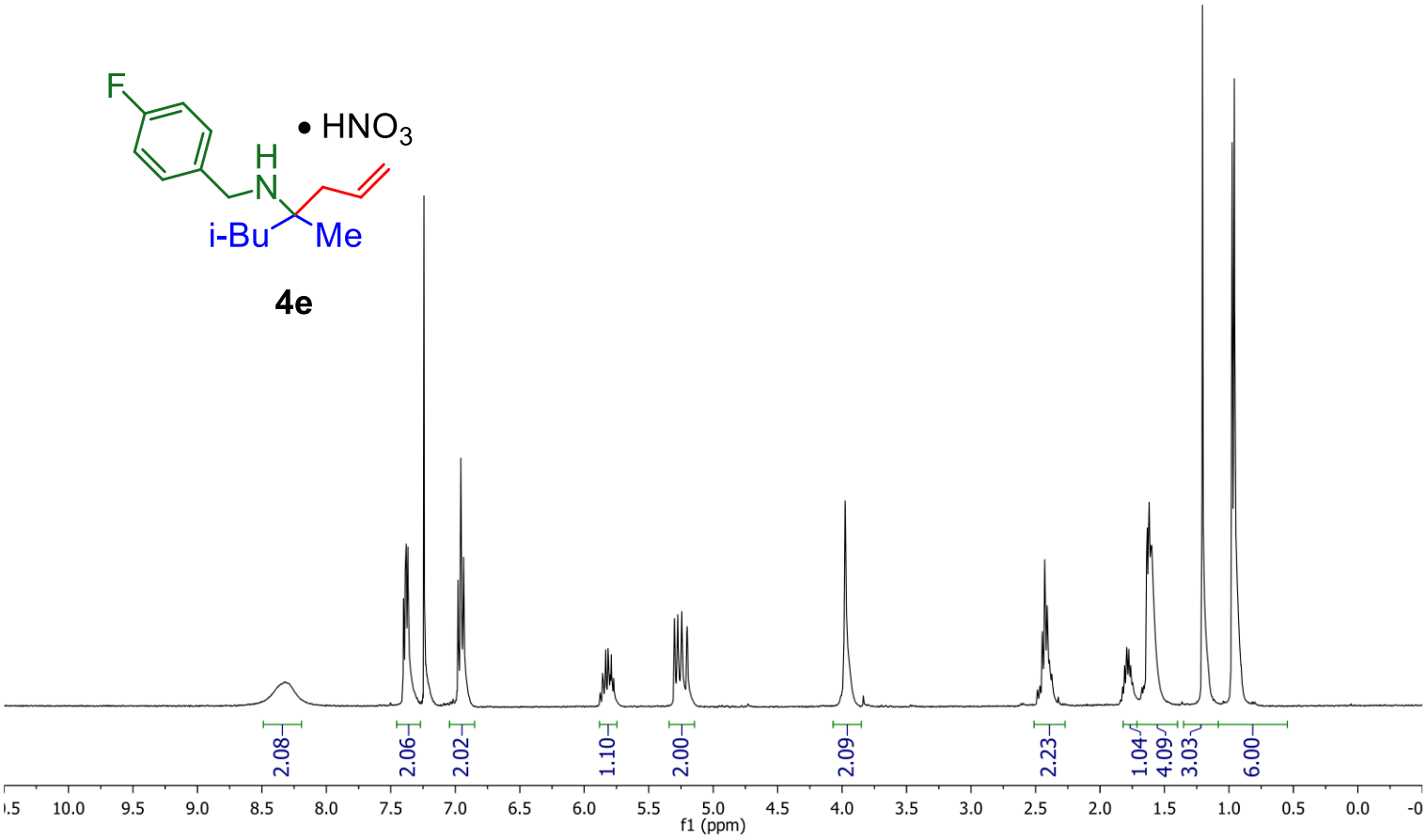
4c

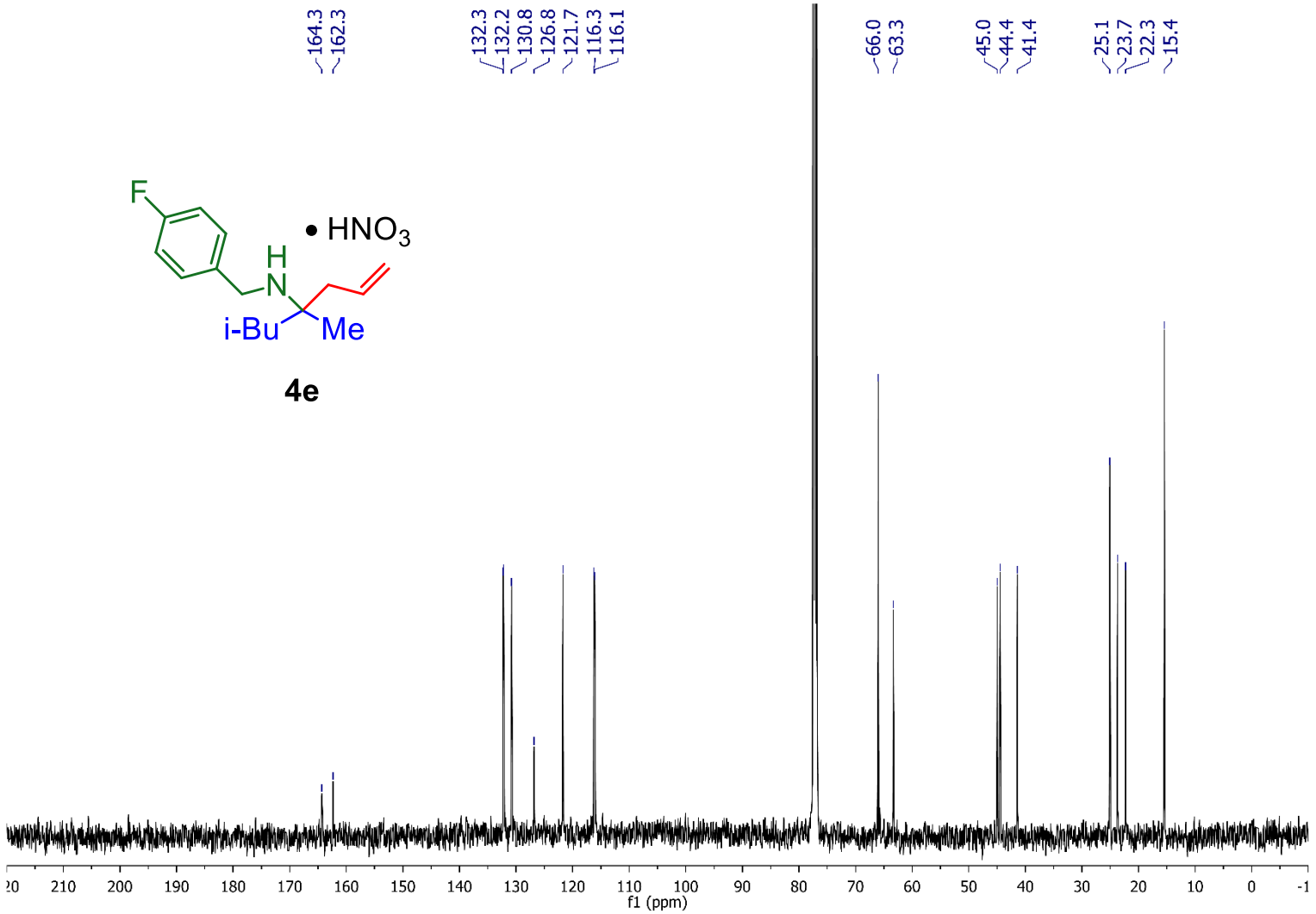
-111.7
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

• HNO3
H
N
Me
F
4d
2.12
2.02
2.09
1.09
1.00
1.08
2.06
2.13
1.07
3.00
1.08
2.01
1.08
f1 (ppm)

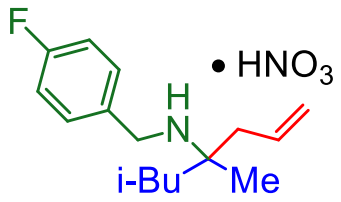
164.3
162.3
132.3
132.3
131.0
127.0
121.0
116.2
116.0
63.1
45.3
42.9
16.5
16.1
2.8
1.2
• HNO3
H
N
Me
F
4d
f1 (ppm)


-111.9
F
• HNO3
H
N
Me
4d
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


F
• HNO3
H
N
i-Bu
Me
4e
2.08
2.06
2.02
1.10
2.00
2.09
2.23
1.04
4.09
3.03
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

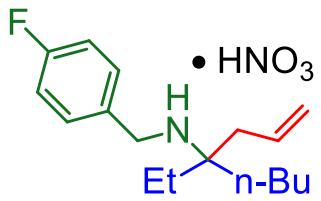

164.3
162.3
132.3
132.2
130.8
126.8
121.7
116.3
116.1
66.0
63.3
45.0
44.4
41.4
25.1
23.7
22.3
15.4
F
• HNO3
H
N
i-Bu
Me
f1 (ppm)

4e

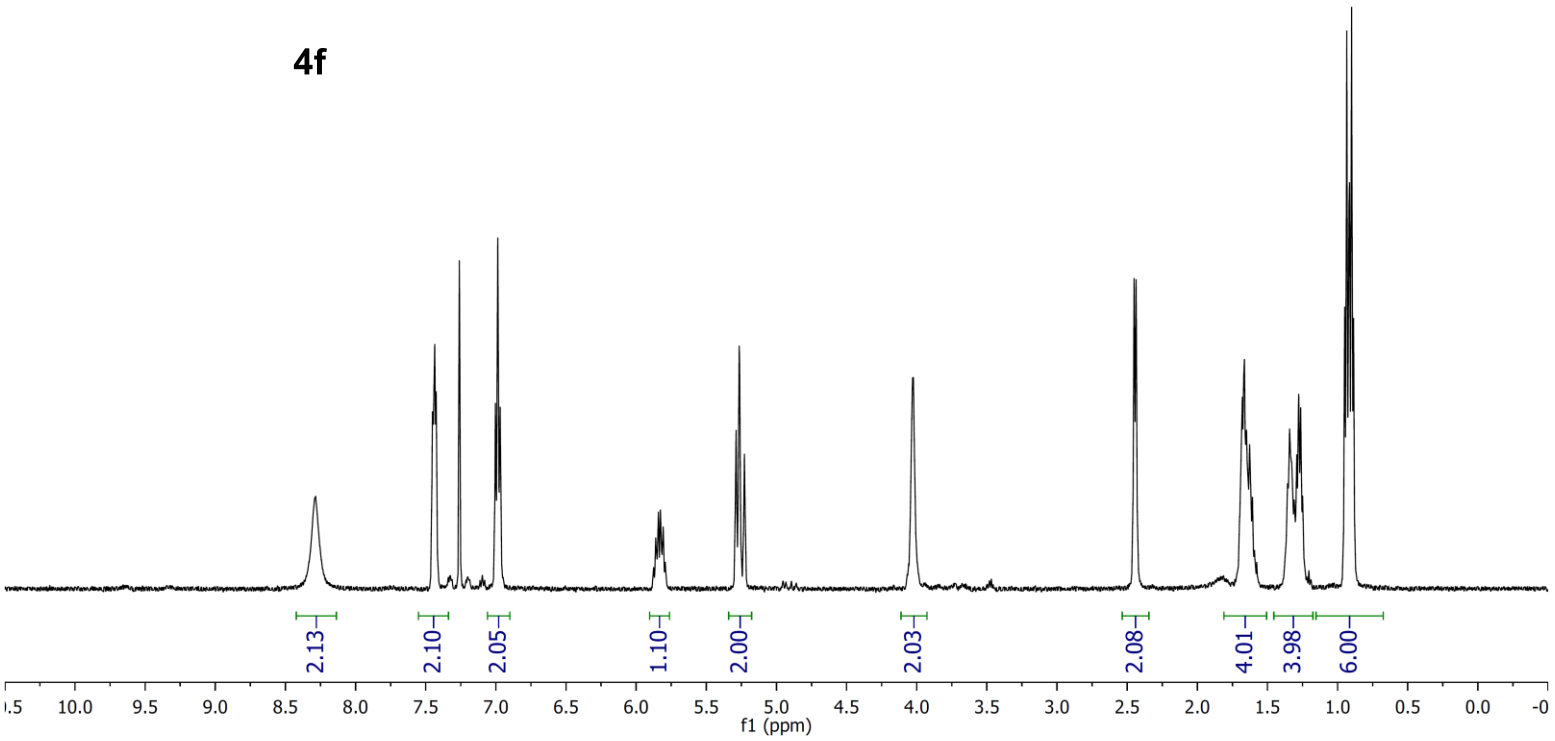

F
• HNO3
H
N
i-Bu
Me

4e

-111.9
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

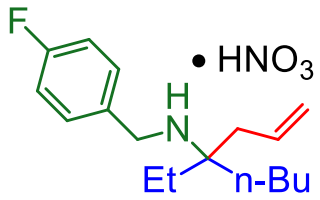

F
• HNO3
H
N
Et
n-Bu

4f


2.13
2.10
2.05
1.10
2.00
2.03
2.08
4.01
3.98
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

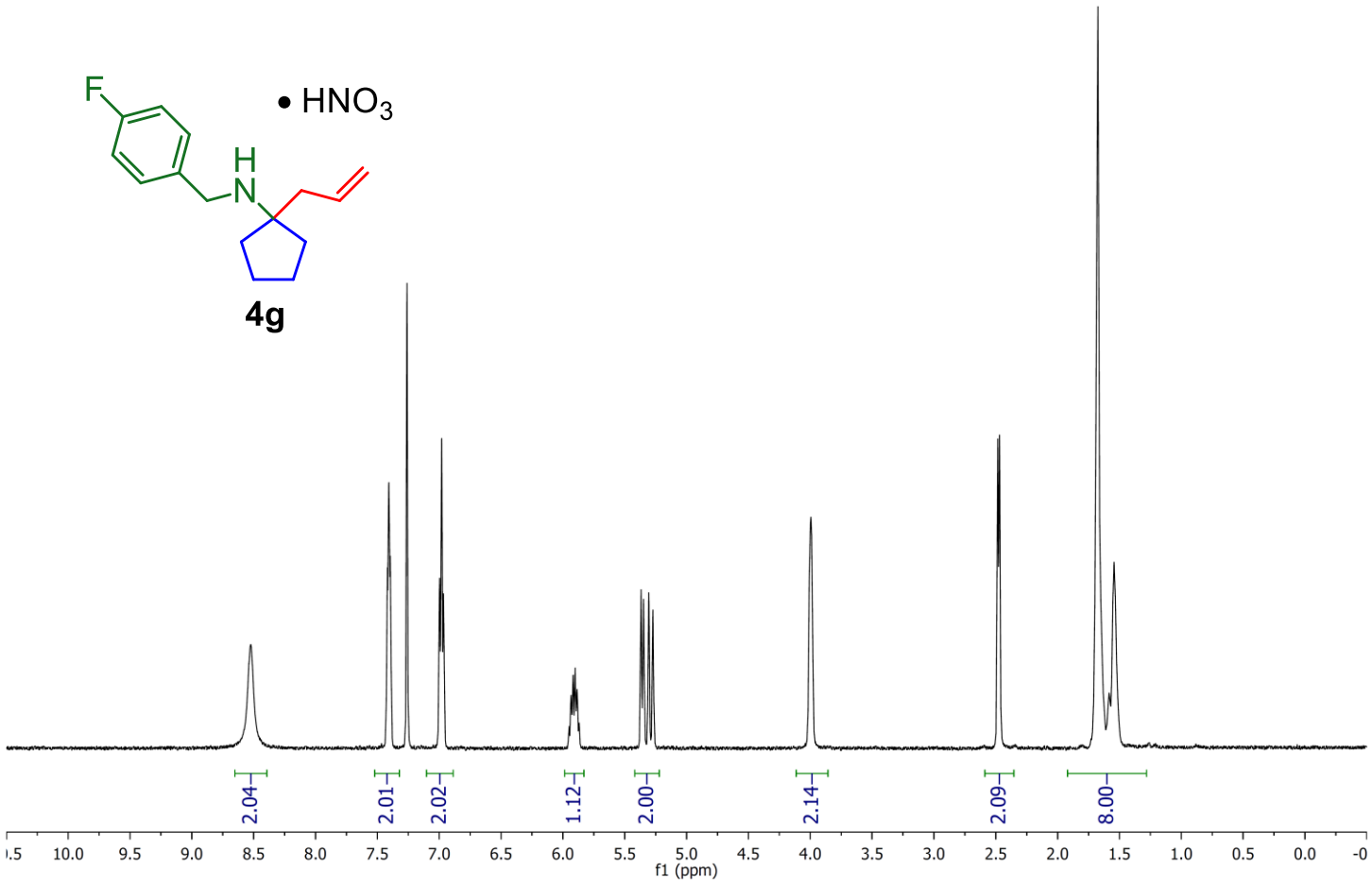
164.3
162.3
132.2
132.1
130.6
127.0
121.4
116.3
116.1
65.9
45.4
38.7
33.4
27.1
24.5
23.0
13.9
7.3
f1 (ppm)
F
H
N
Et
n-Bu
• HNO3

4f


F
• HNO3
H
N
Et
n-Bu

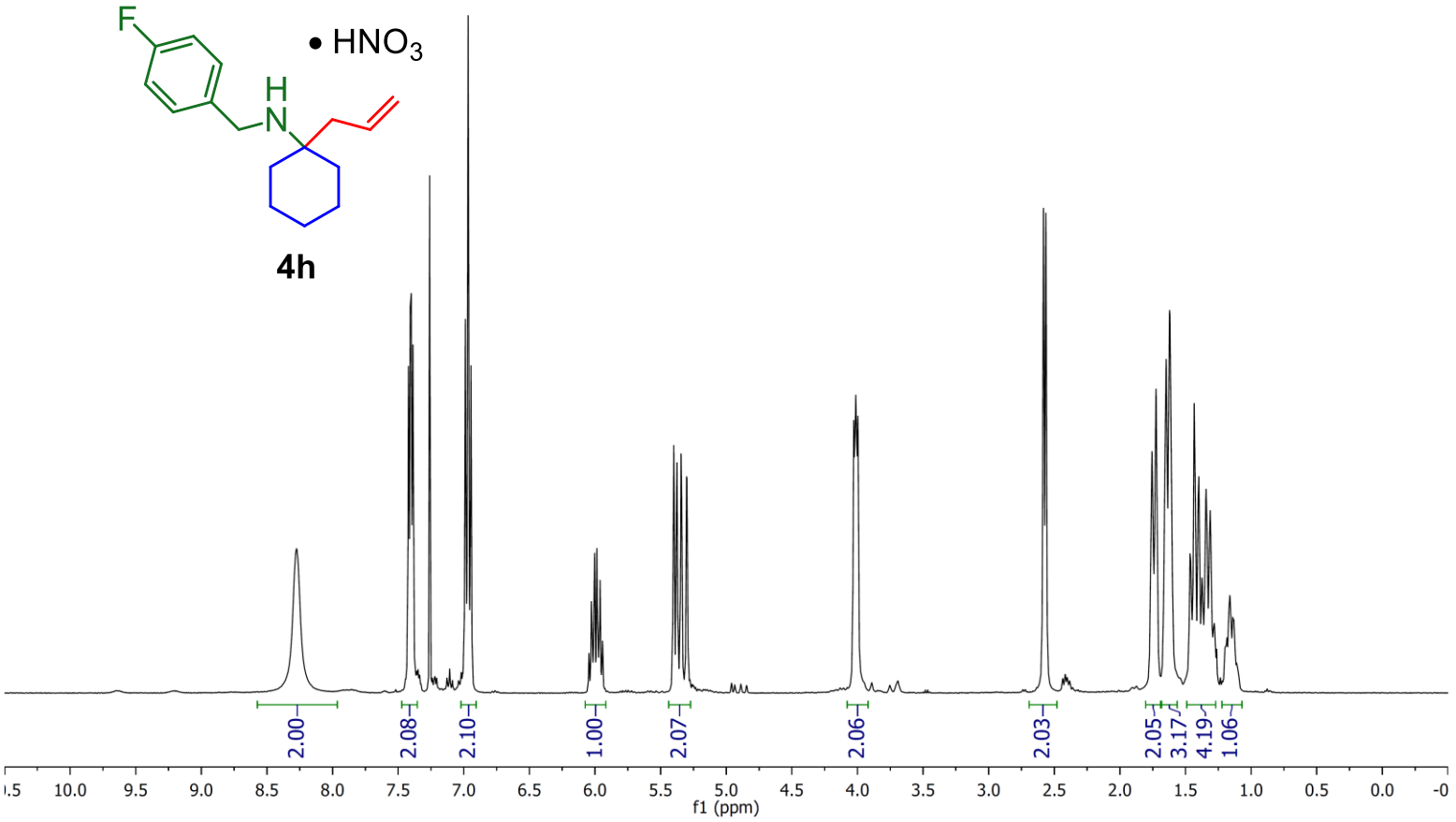
4f

--111.5
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

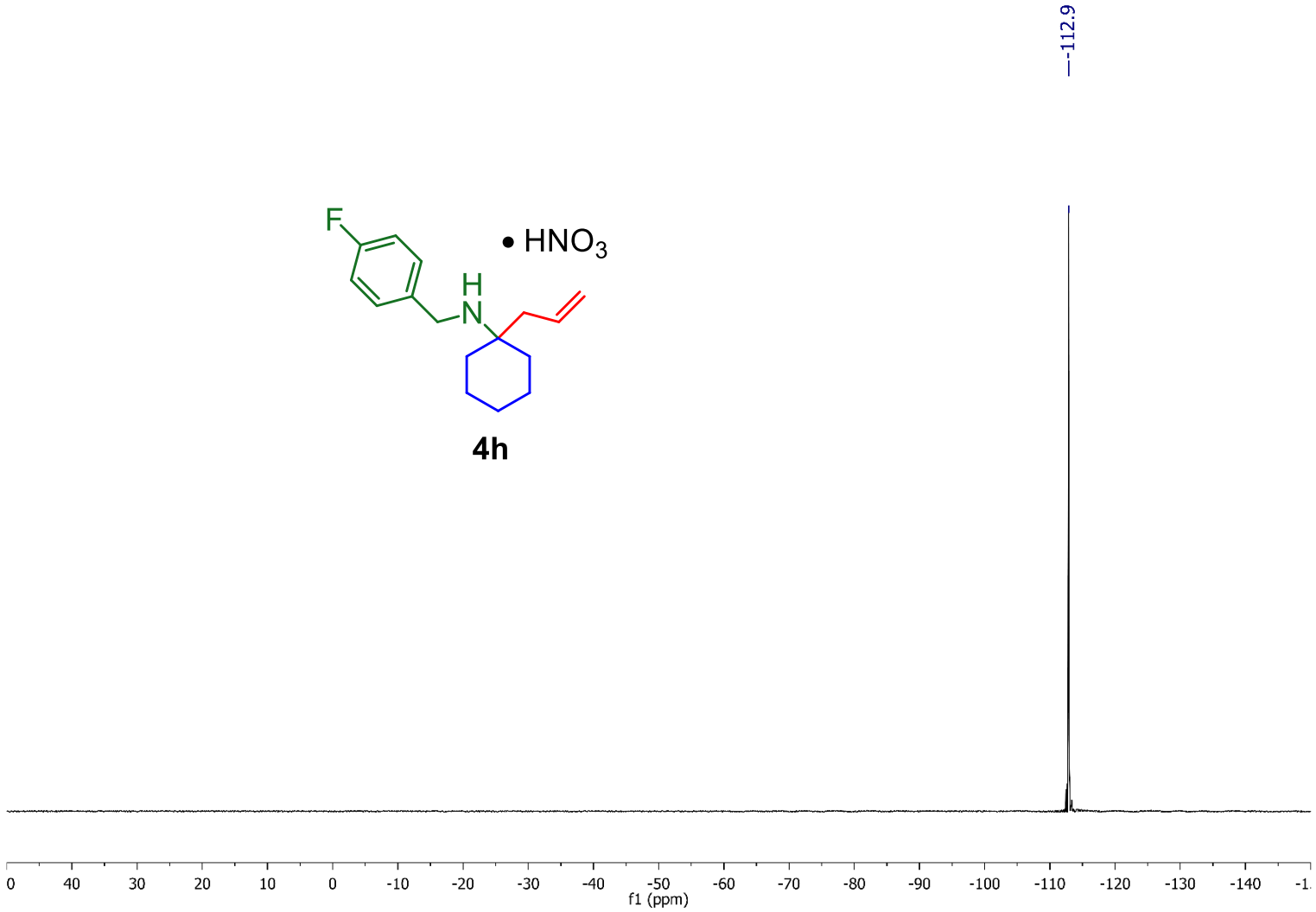

F
H
N
• HNO3
4g
2.04
2.01
2.02
1.12
2.00
2.14
2.09
8.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

164.3
162.3
132.4
132.3
131.2
126.7
121.4
116.1
115.9
69.0
46.4
40.6
34.9
24.4
f1 (ppm)
• HNO3
H
N
F
4g

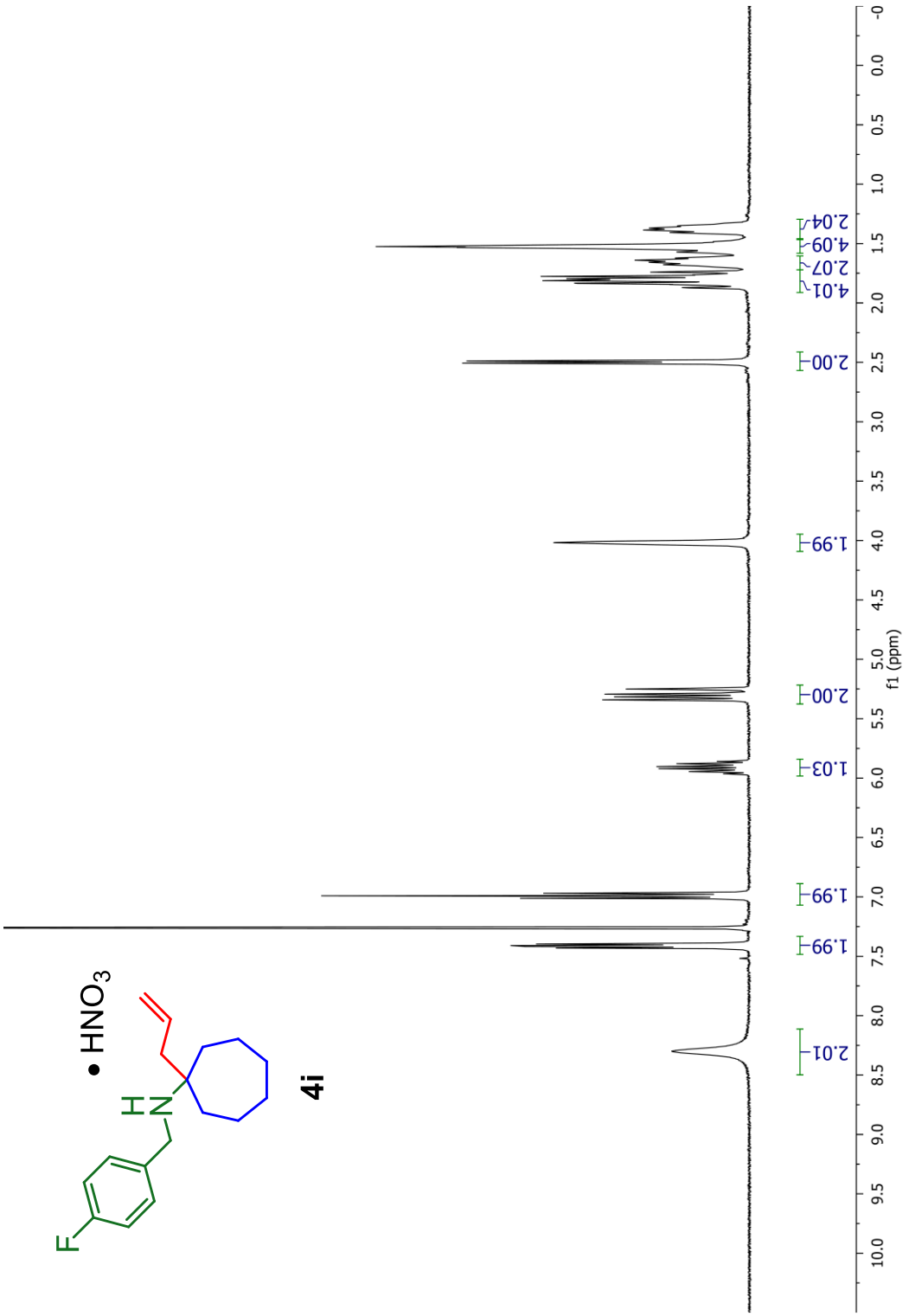
-112.1
• HNO3
H
N
F
4g
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


F
• HNO3
H
N
4h
2.00
2.08
2.10
1.00
2.07
2.06
2.03
2.05
3.17
4.19
1.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

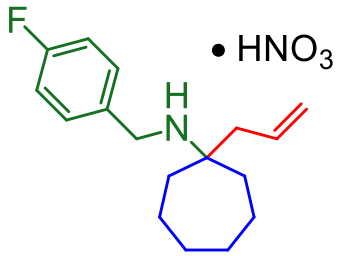
164.4
161.9
132.5
132.4
130.6
126.9
121.4
116.0
115.7
62.2
44.1
36.0
32.4
24.7
21.7
• HNO3
H
N
F
4h
f1 (ppm)


-112.9
F
• HNO3
H
N
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

4h

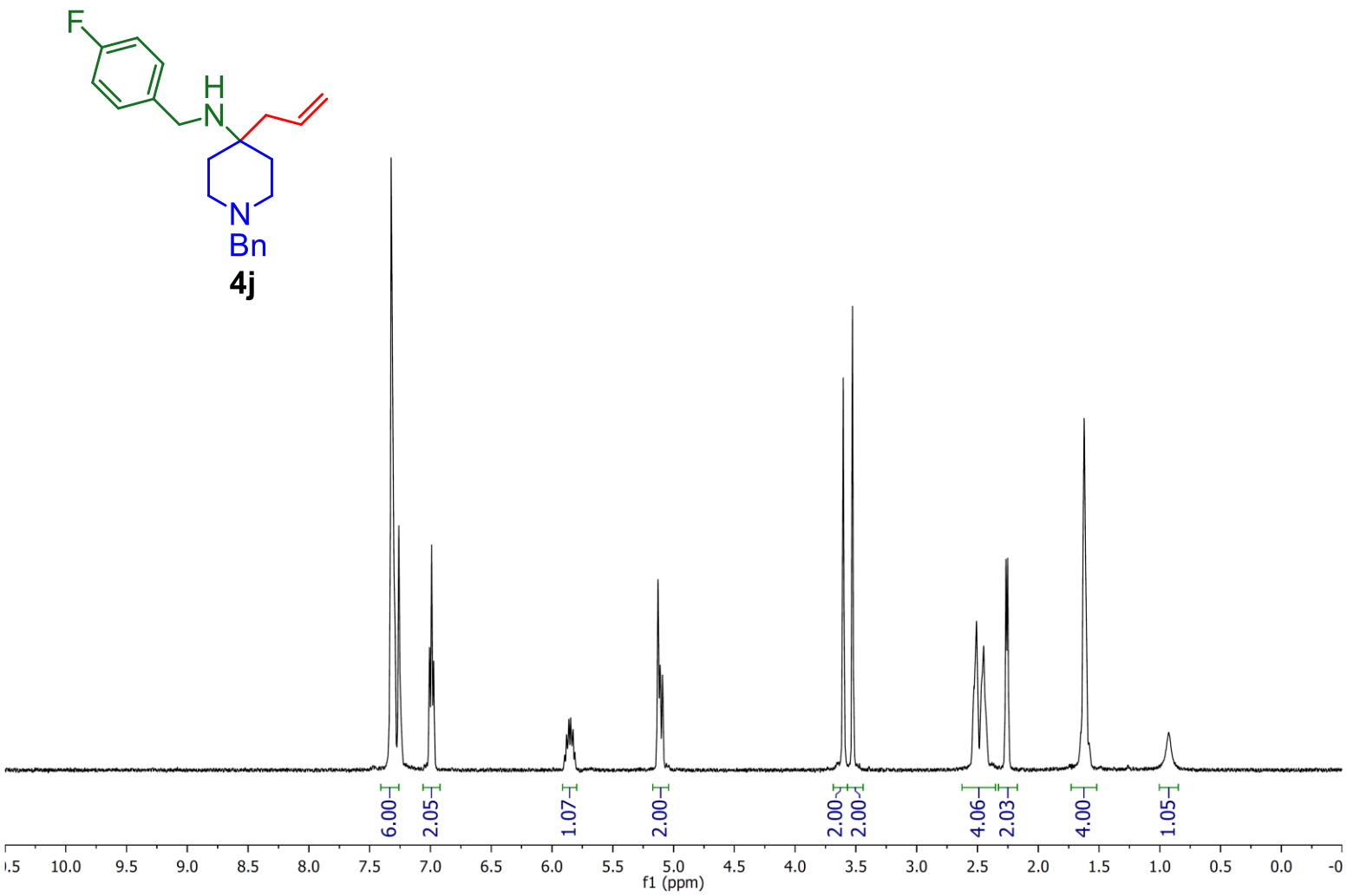

• HNO3
H
N
F
4i
2.01
1.99
1.99
1.03
2.00
1.99
2.00
4.01
2.07
4.09
2.04
f1 (ppm)

164.2
162.2
132.2
132.2
130.9
127.0
121.5
116.1
115.9
66.4
45.2
41.6
35.8
29.8
22.2
F
H
N
• HNO3
4i
f1 (ppm)

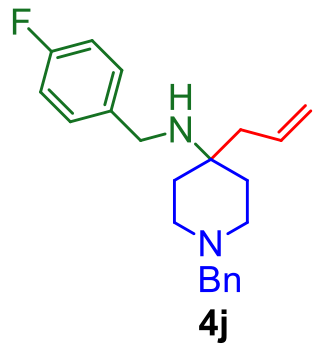

F
• HNO3
H
N

4i

-112.7
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

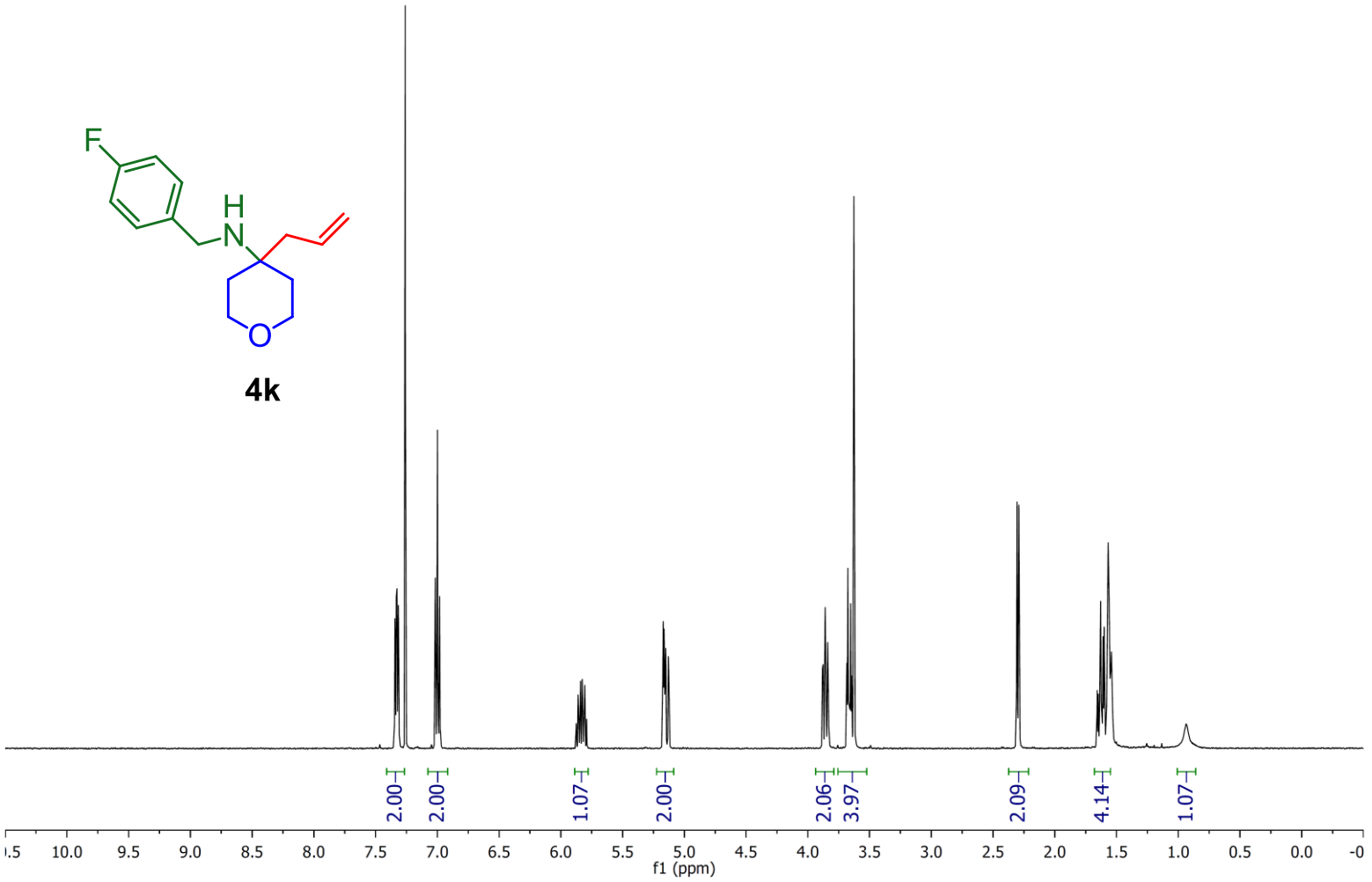

F
H
N
N
Bn
4j
6.00
2.05
1.07
2.00
2.00
2.00
4.06
2.03
4.00
1.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

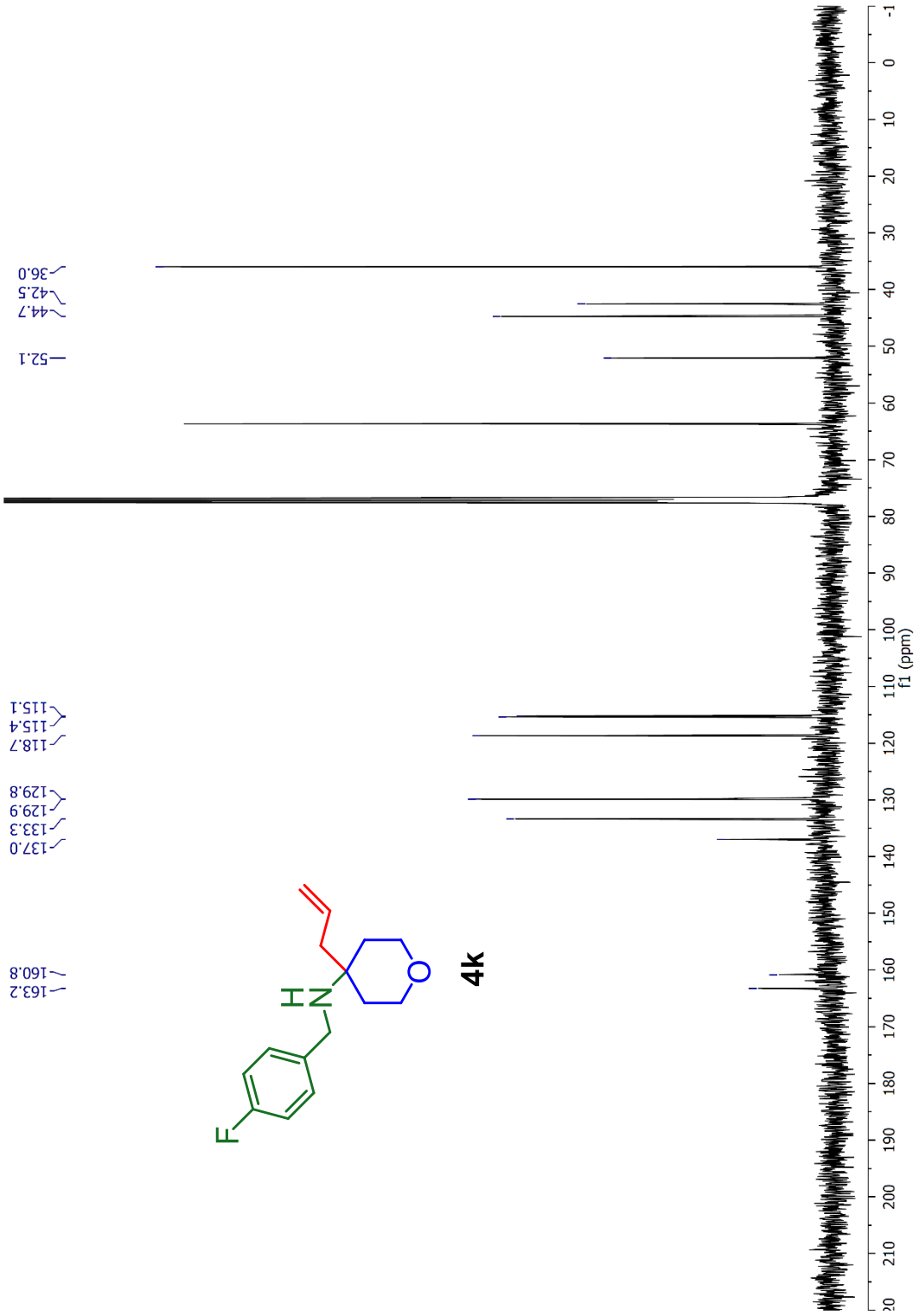
162.9
161.0
138.8
137.3
134.2
134.1
129.8
129.4
128.4
127.1
118.0
115.2
115.0
63.5
52.4
49.4
44.6
42.3
35.2
f1 (ppm)
4j

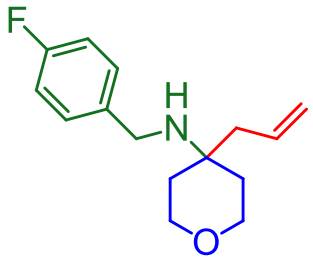

F
H
N
N
Bn

4j

-117.7
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

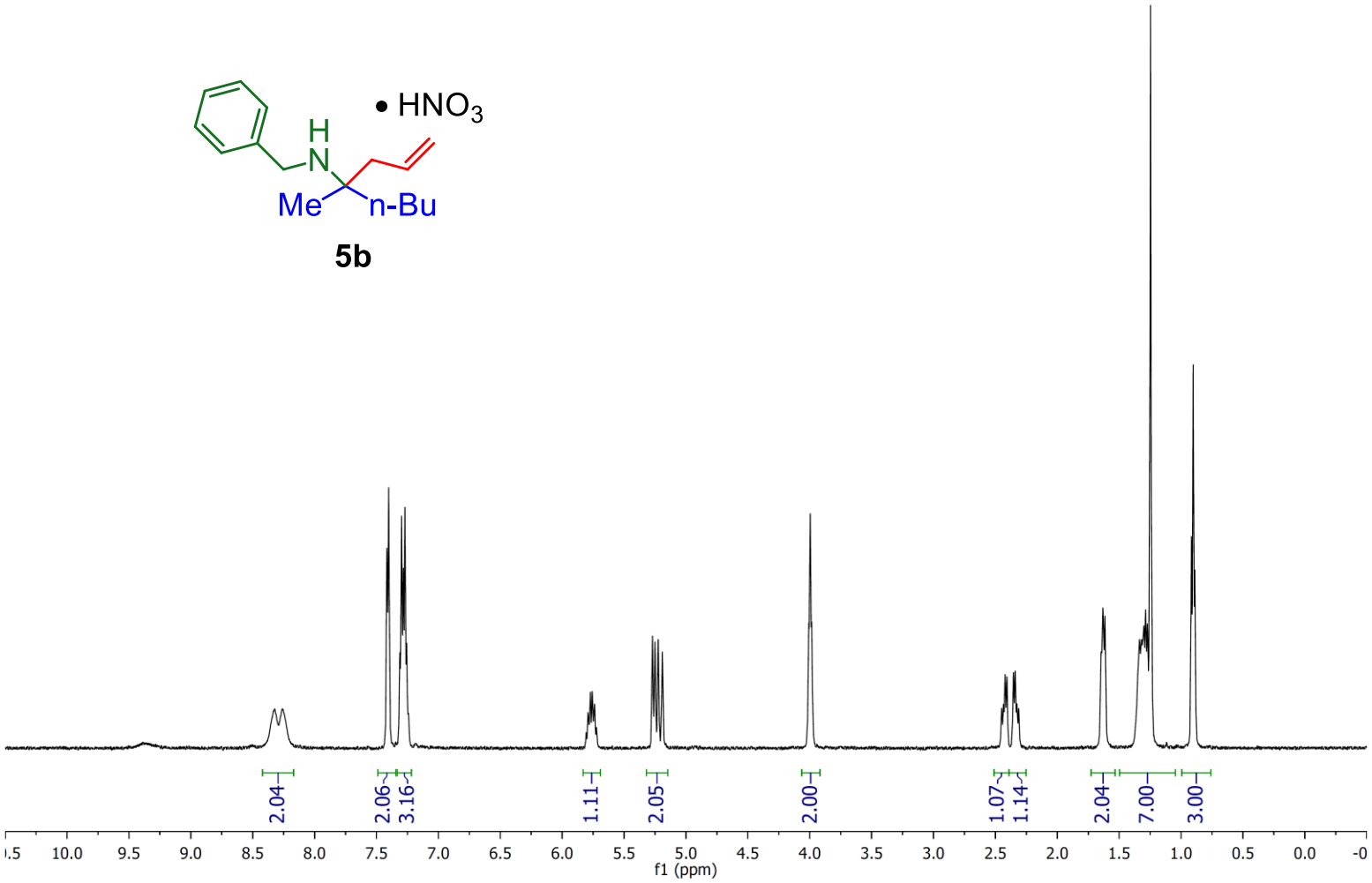

F
H
N
O
4k
2.00
2.00
1.07
2.00
2.06
3.97
2.09
4.14
1.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

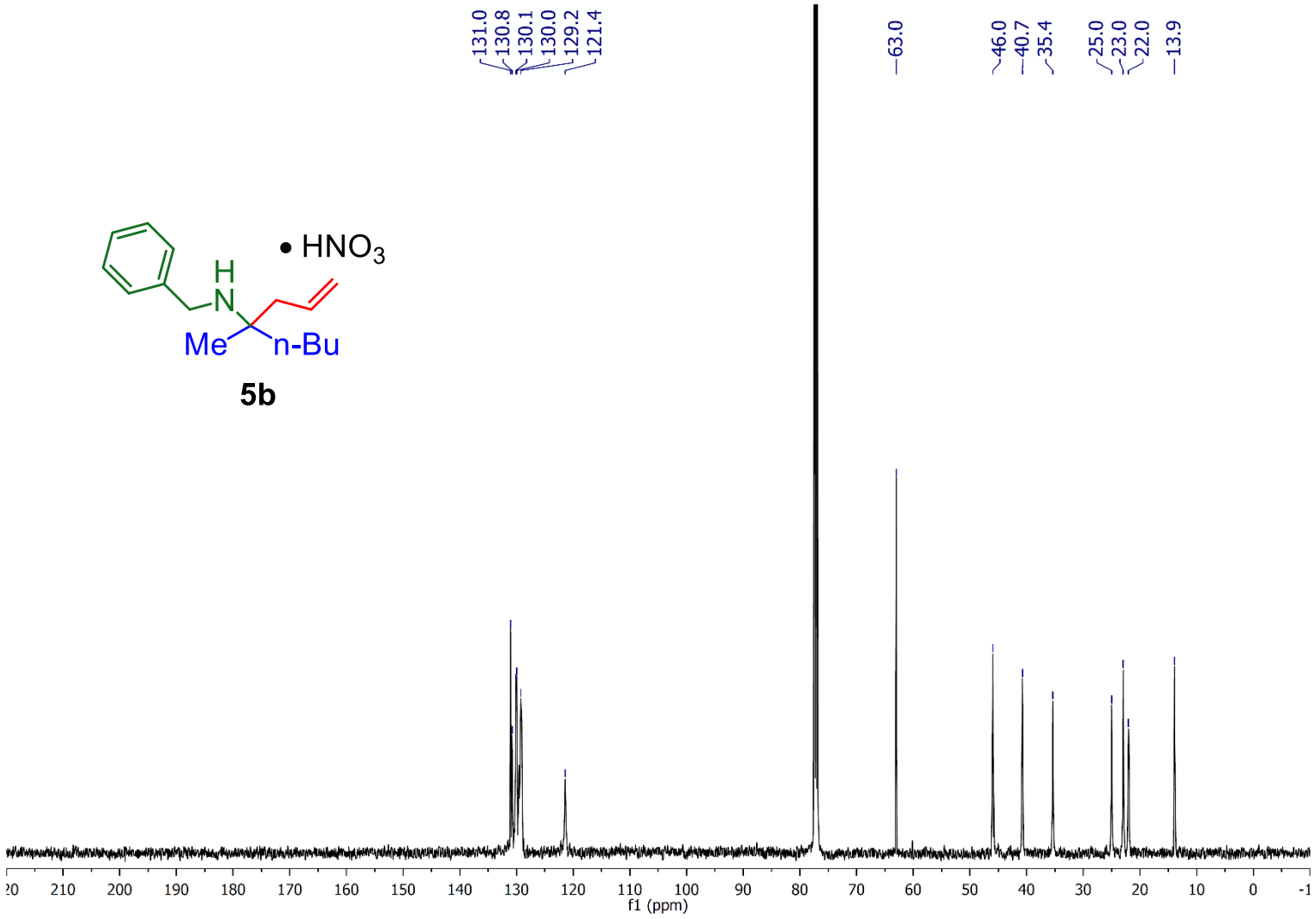

163.2
160.8
137.0
133.3
129.9
129.8
118.7
115.4
115.1
52.1
44.7
42.5
36.0
H
N
F
4k
f1 (ppm)

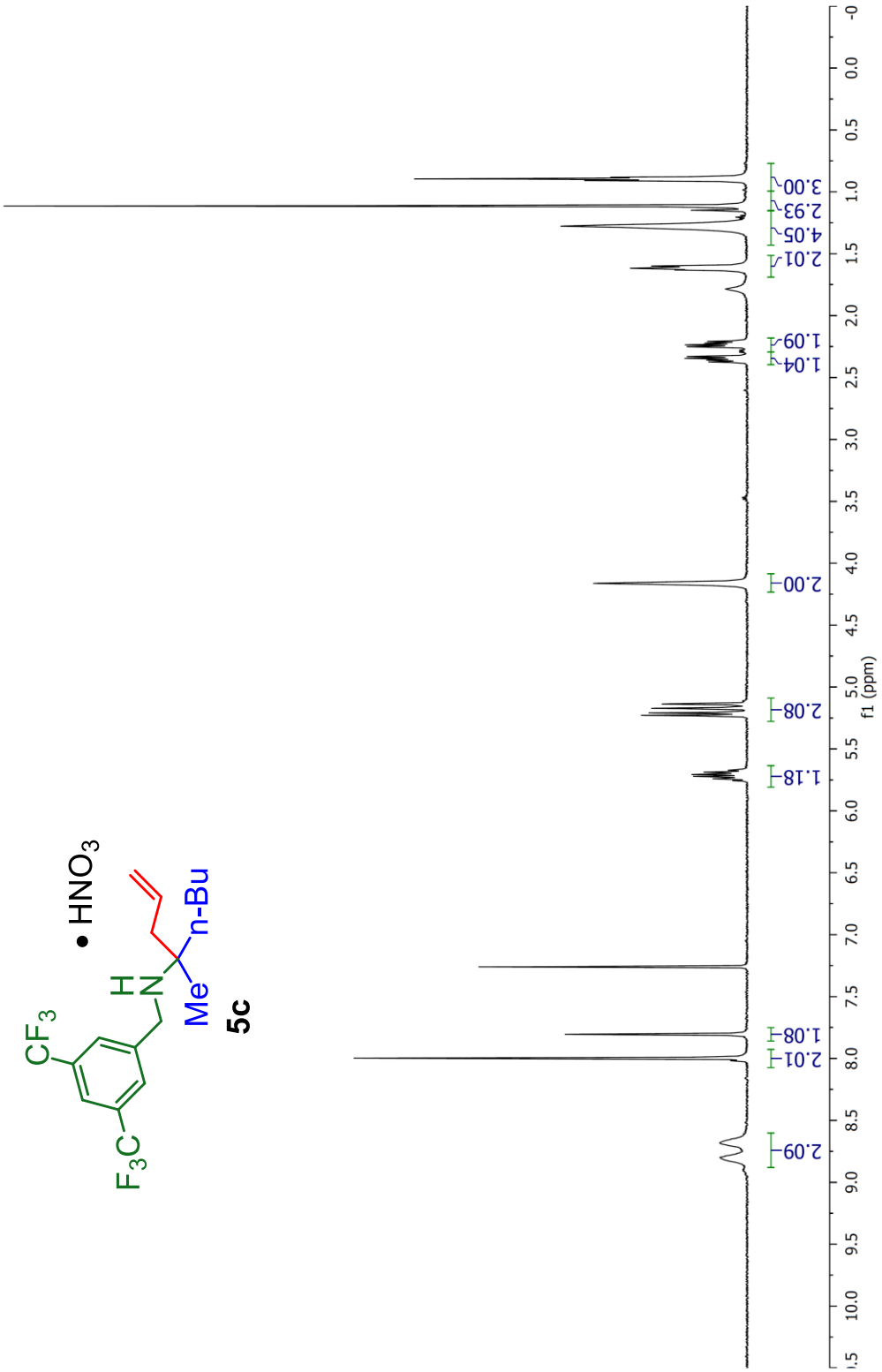

F
H
N
O

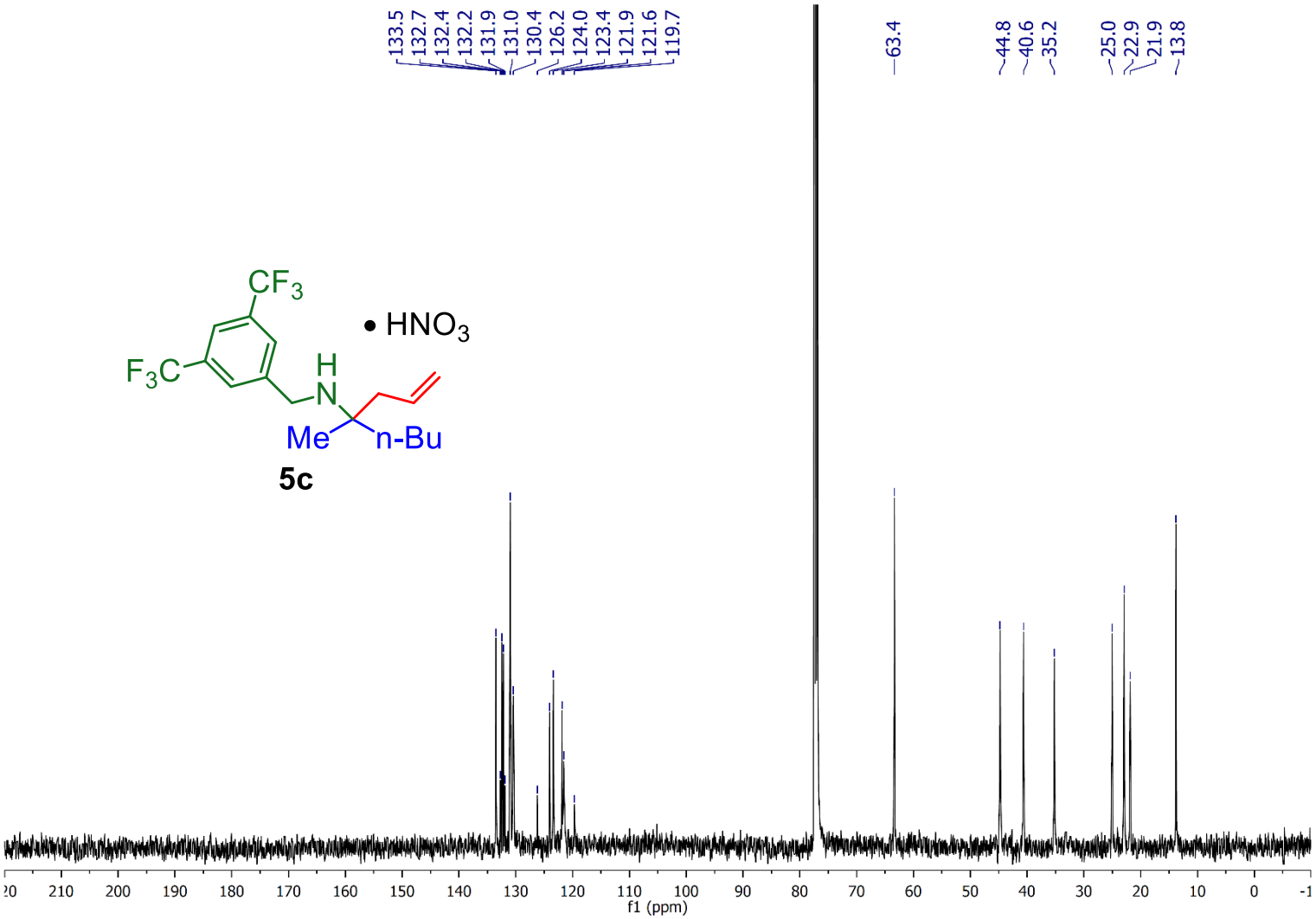
4k

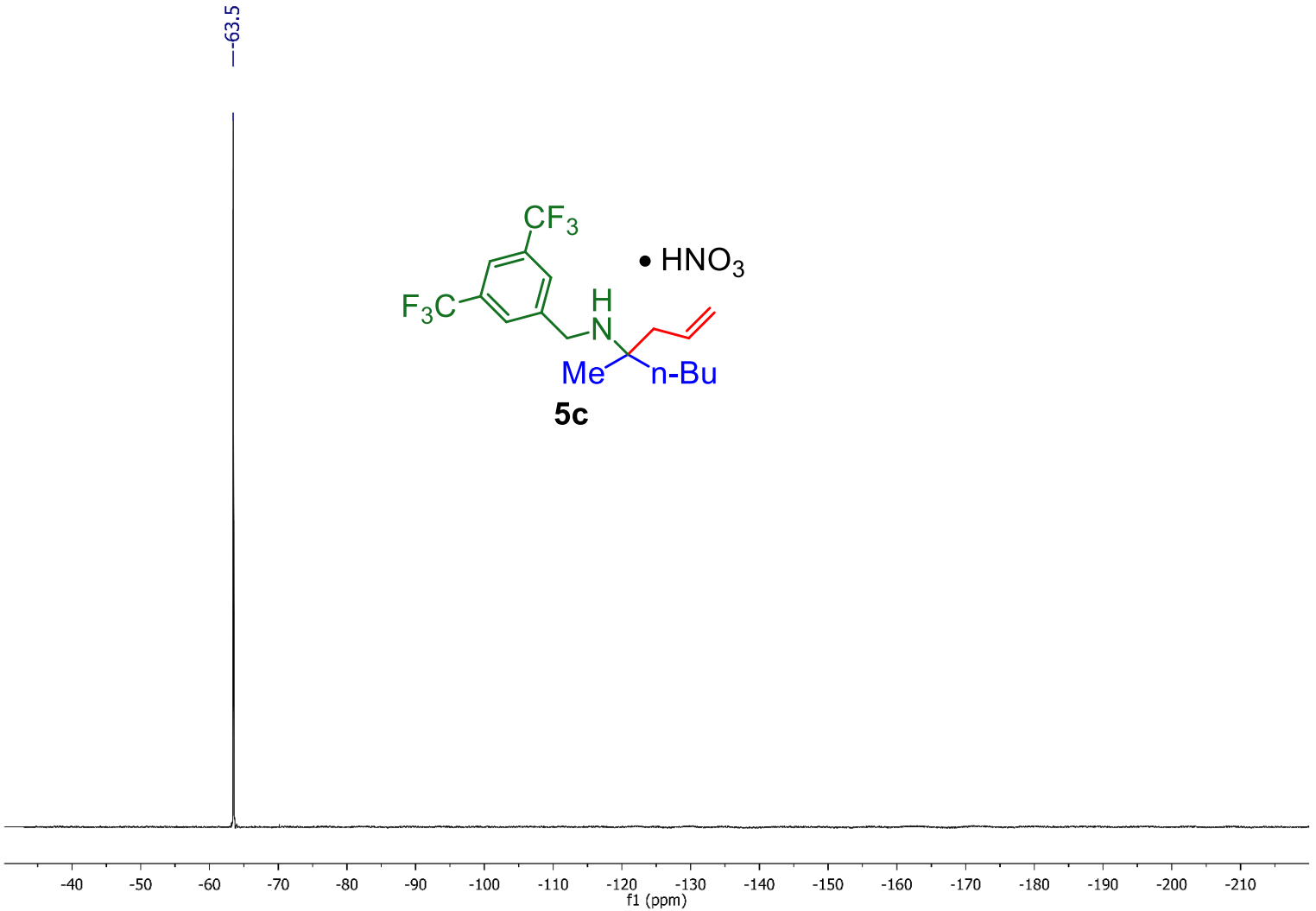
-117.5
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-1
f1 (ppm)


• HNO3
H
N
Me
n-Bu
5b
2.04
2.06
3.16
1.11
2.05
2.00
1.07
1.14
2.04
7.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

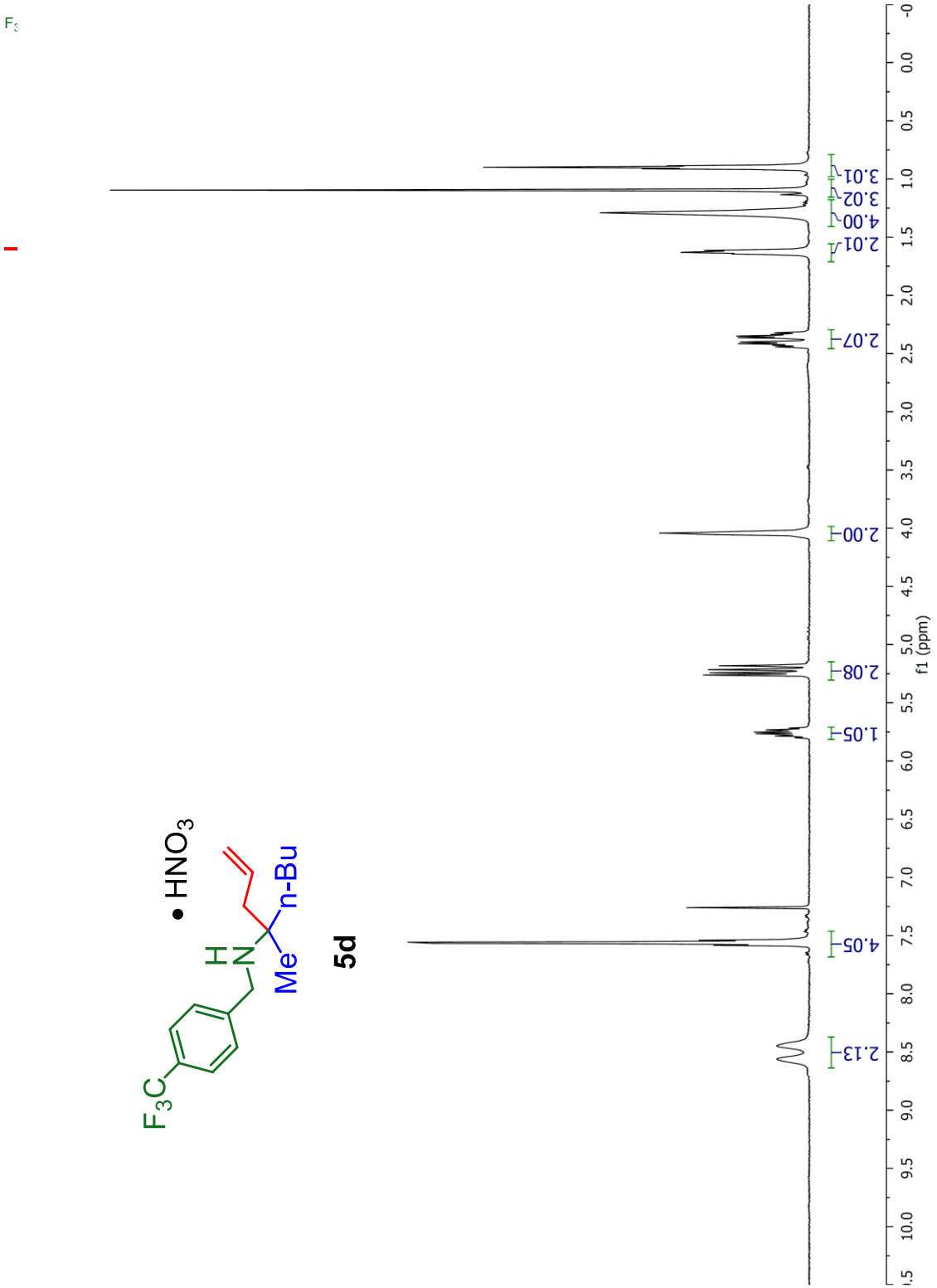

131.0
130.8
130.1
130.0
129.2
121.4
63.0
46.0
40.7
35.4
25.0
23.0
22.0
13.9
• HNO3
H
N
Me
n-Bu
5b
f1 (ppm)

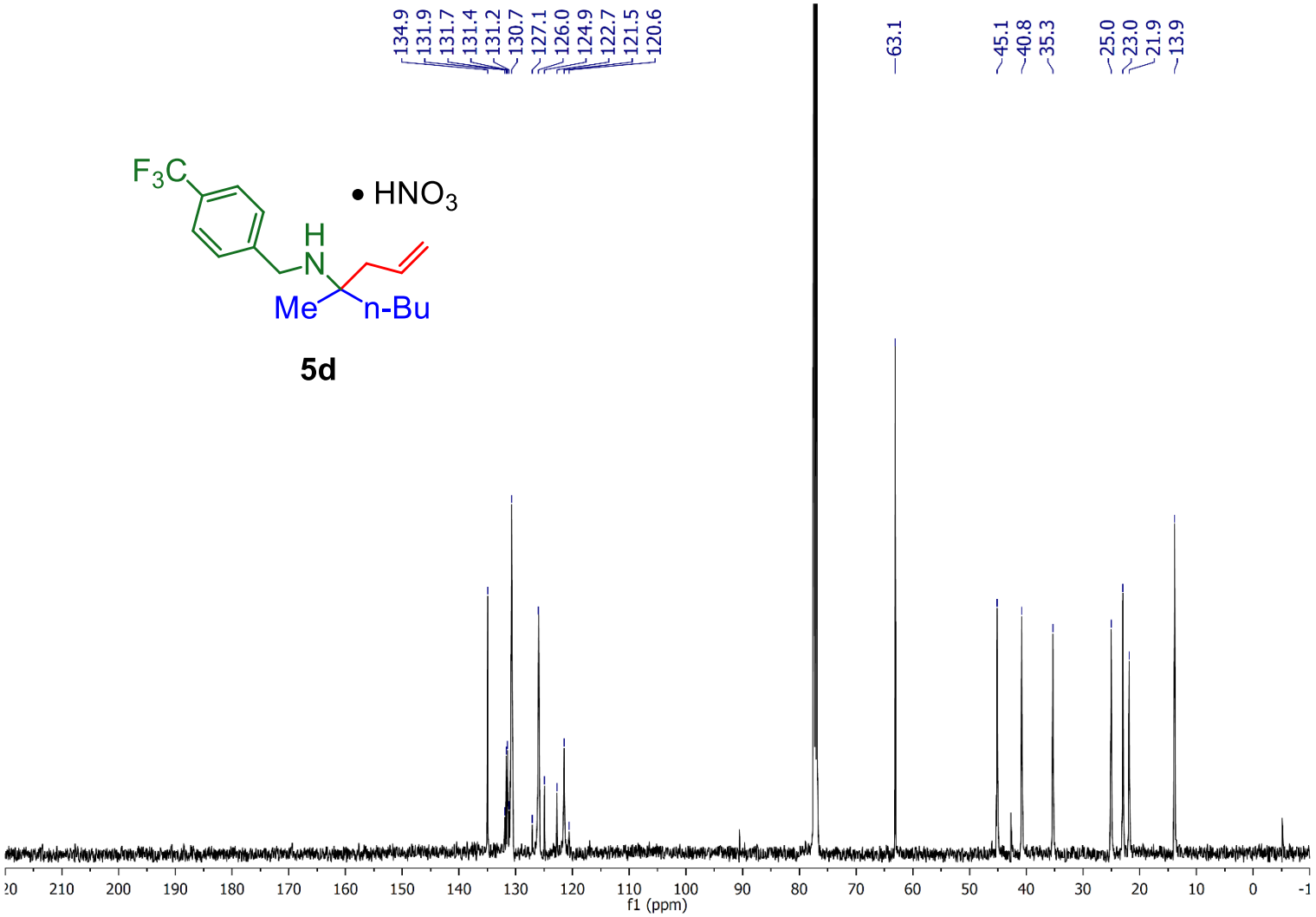

• HNO3
CF3
F3C
H
N
Me
n-Bu
5c
3.00
2.93
4.05
2.01
1.09
1.04
2.00
2.08
1.18
1.08
2.01
2.09
f1 (ppm)

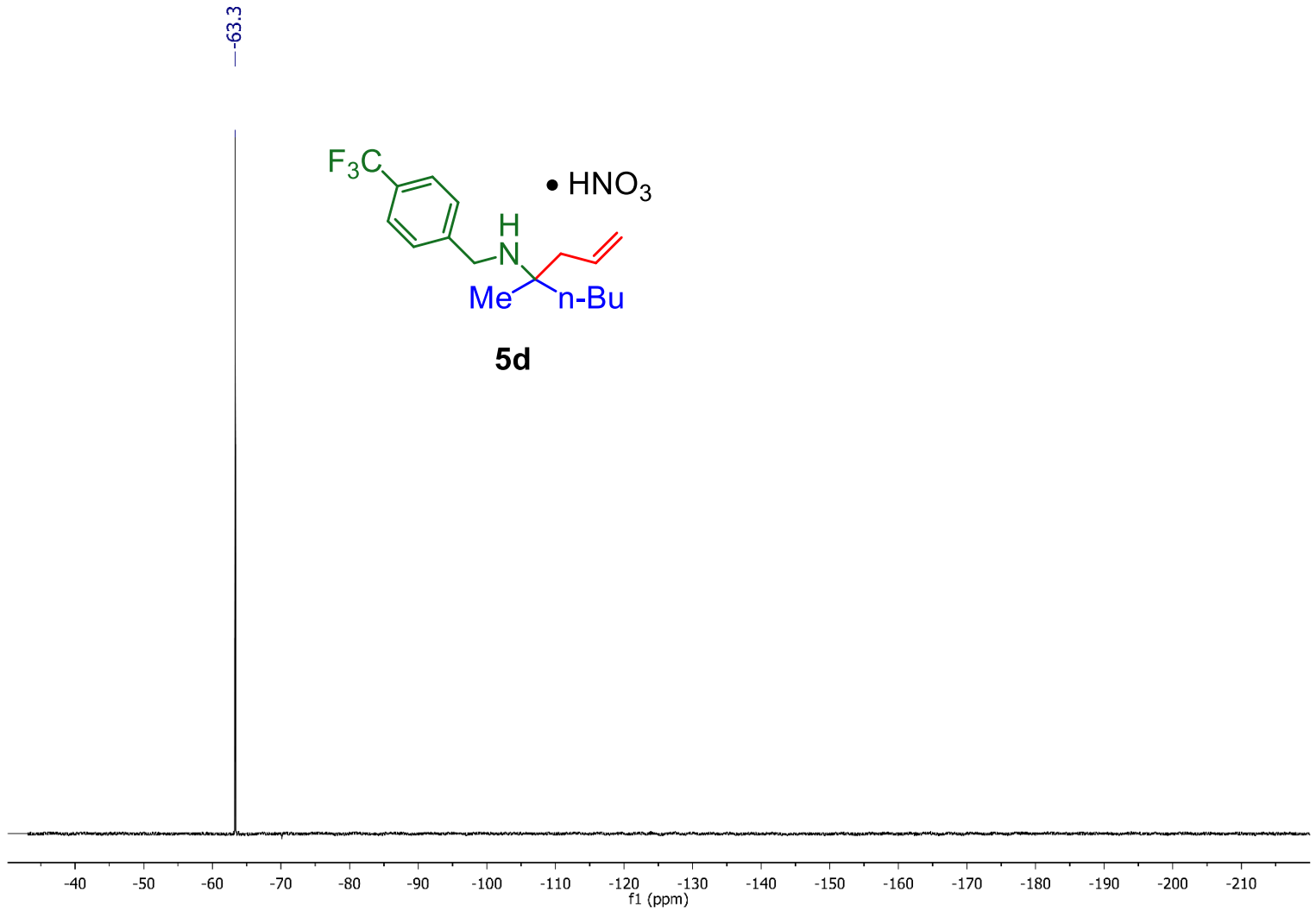

133.5
132.7
132.4
132.2
131.9
131.0
130.4
126.2
124.0
123.4
121.9
121.6
119.7
63.4
44.8
40.6
35.2
25.0
22.9
21.9
13.8
CF3
F3C
• HNO3
H
N
Me
n-Bu
5c
f1 (ppm)


-63.5
CF3
• HNO3
F3C
H
N
Me
n-Bu
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

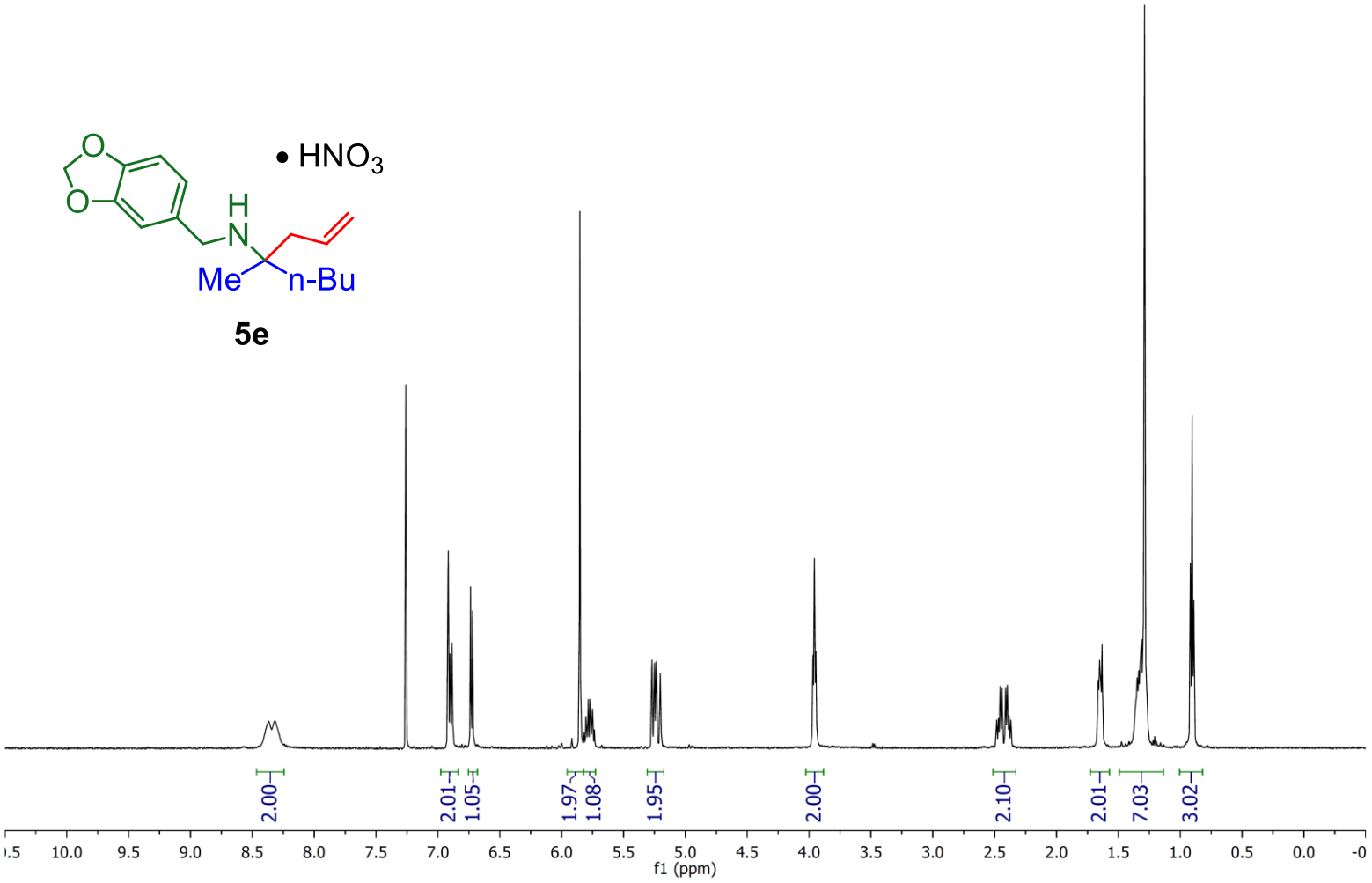
5c

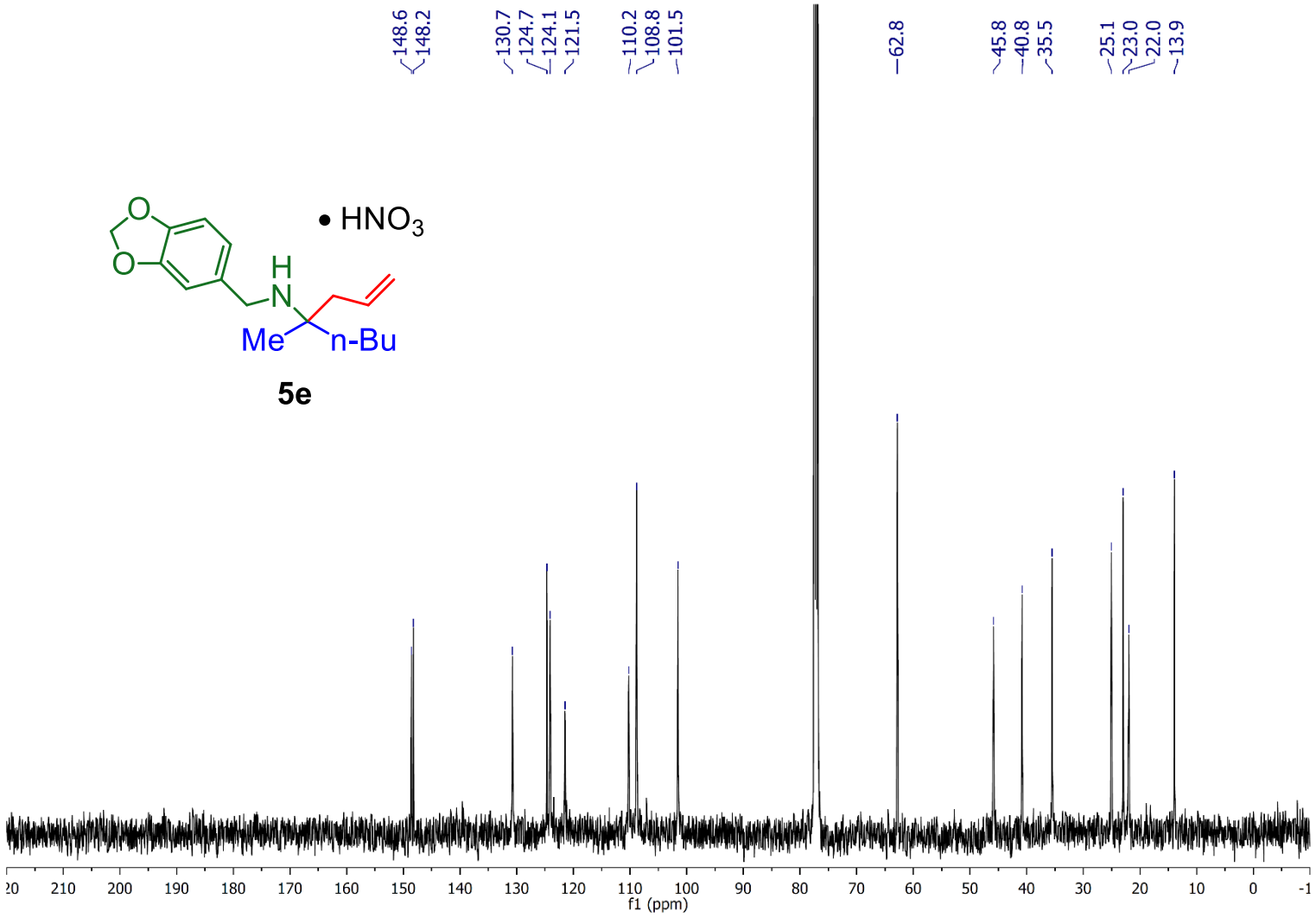

F3
• HNO3
H
N
Me
n-Bu
F3C
5d
2.13
4.05
1.05
2.08
2.00
2.07
2.01
4.00
3.02
3.01
f1 (ppm)

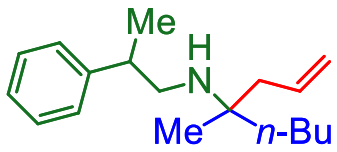

134.9
131.9
131.7
131.4
131.2
130.7
127.1
126.0
124.9
122.7
121.5
120.6
63.1
45.1
40.8
35.3
25.0
23.0
21.9
13.9
F3C
• HNO3
H
N
Me
n-Bu
5d
f1 (ppm)


-63.3
F3C
• HNO3
H
N
Me
n-Bu
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

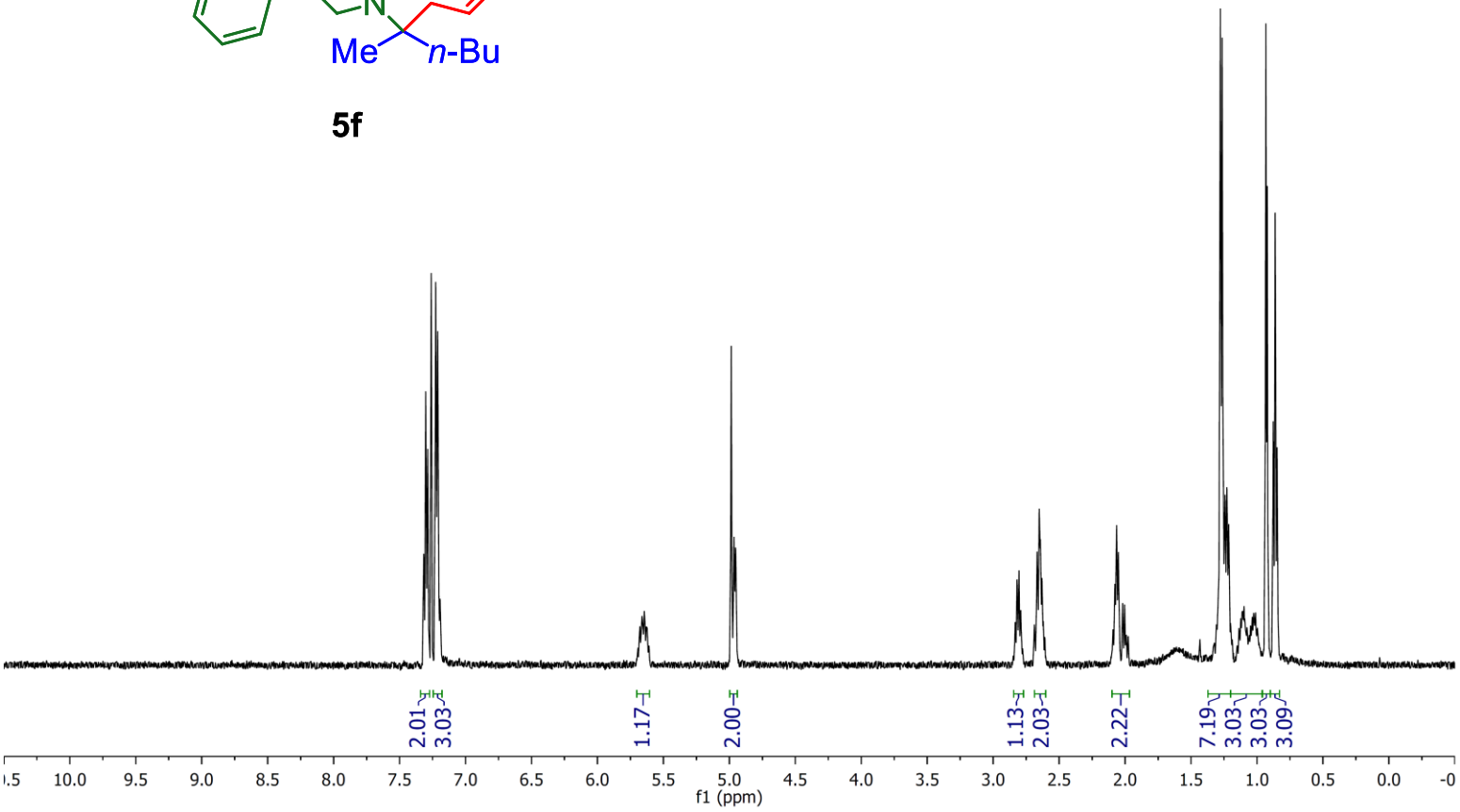
5d

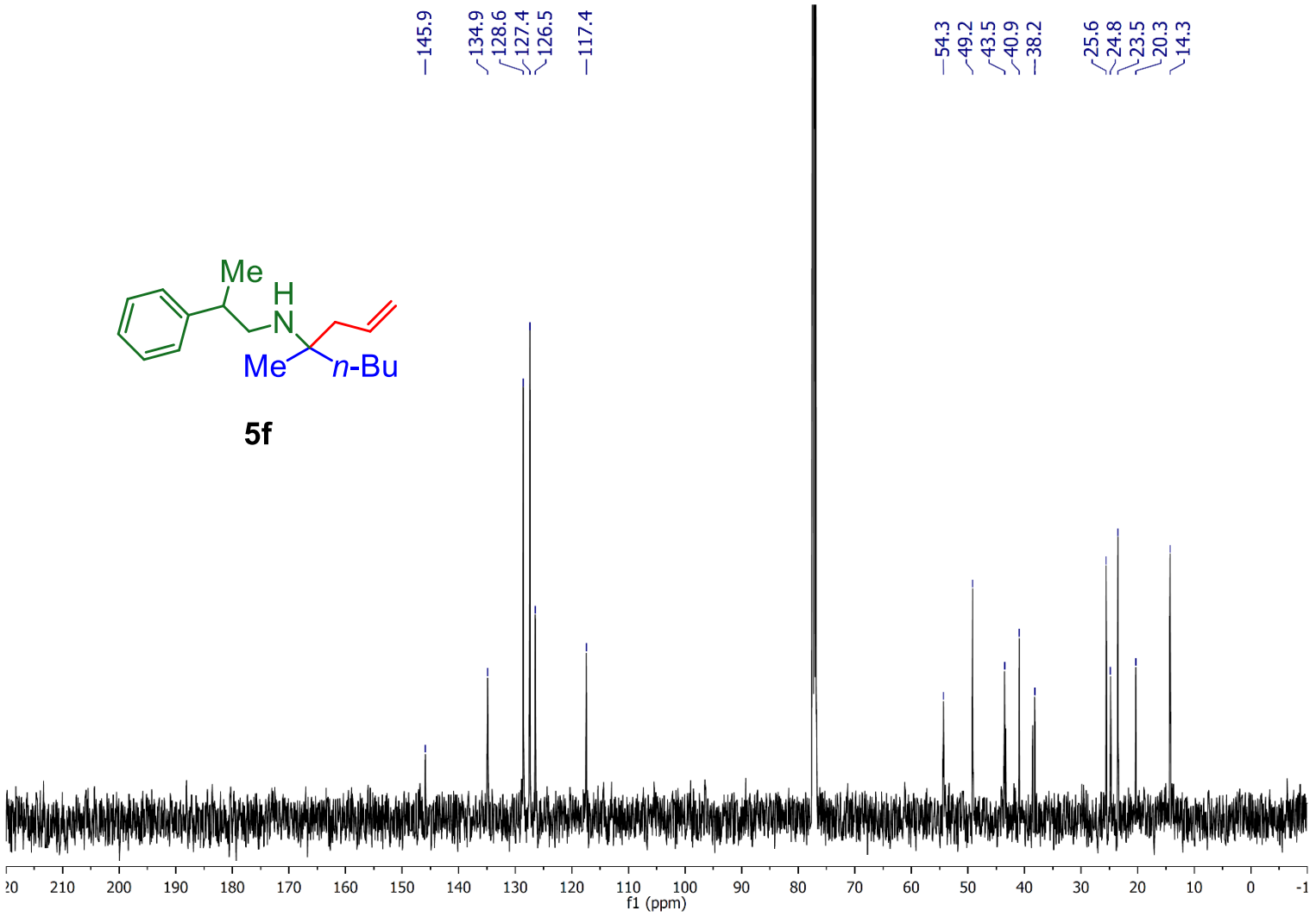

• HNO3
H
N
Me
n-Bu
5e
2.00
2.01
1.05
1.97
1.08
1.95
2.00
2.10
2.01
7.03
3.02
f1 (ppm)

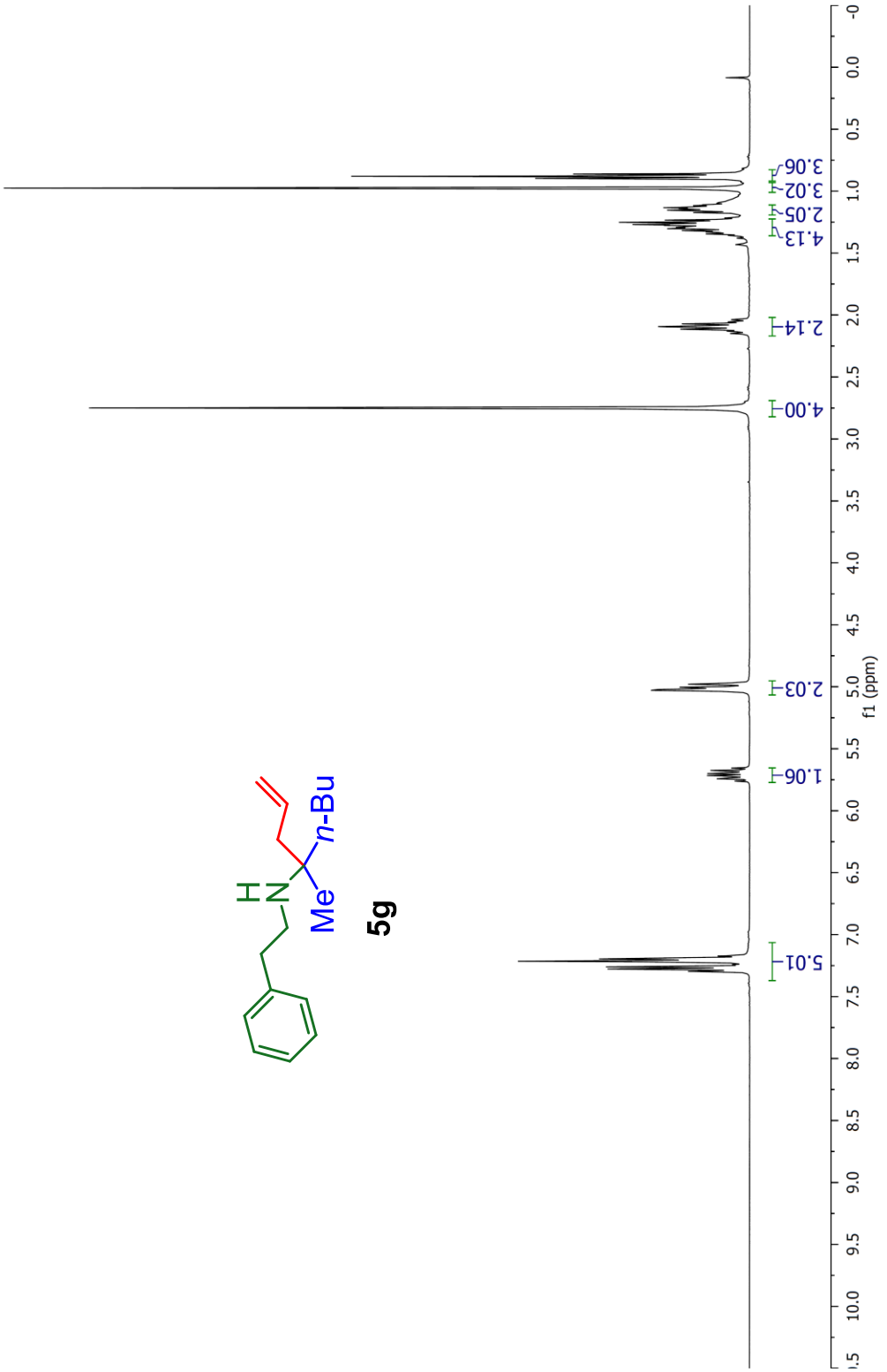

148.6
148.2
130.7
124.7
124.1
121.5
110.2
108.8
101.5
62.8
45.8
40.8
35.5
25.1
23.0
22.0
13.9
• HNO3
H
N
Me
n-Bu
5e
f1 (ppm)


Me
H
N
Me
n-Bu

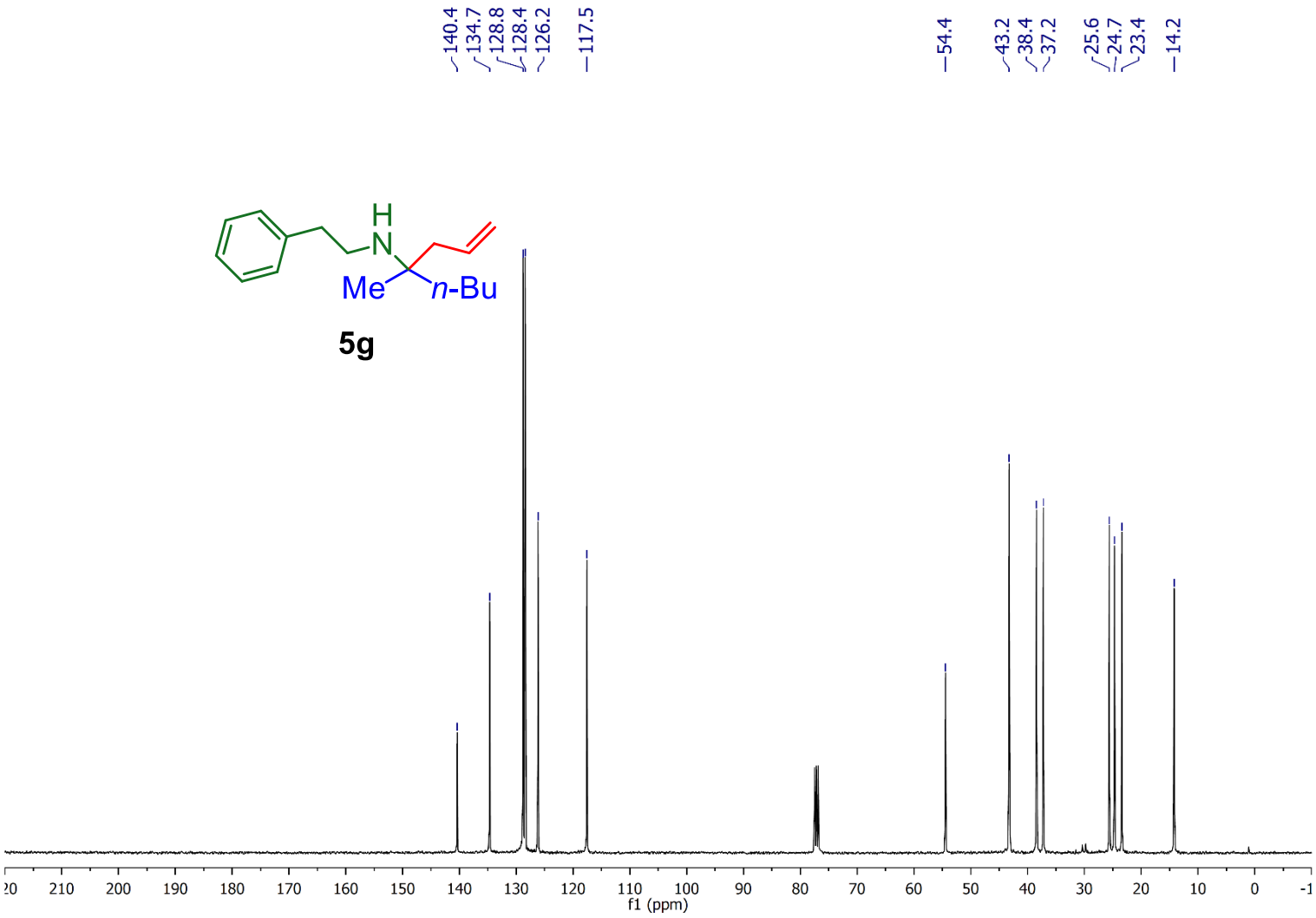
5f

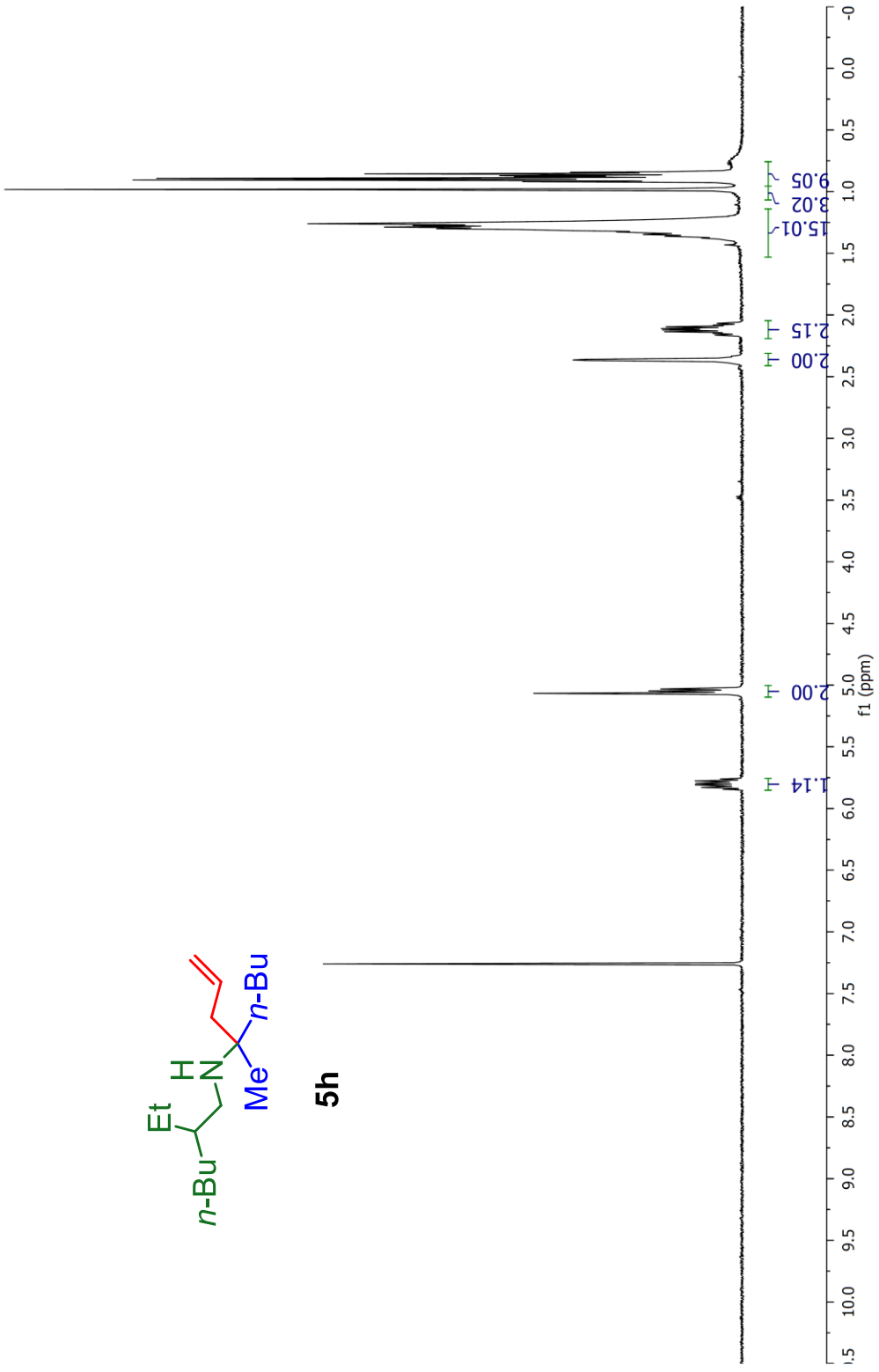

2.01
3.03
1.17
2.00
1.13
2.03
2.22
7.19
3.03
3.03
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

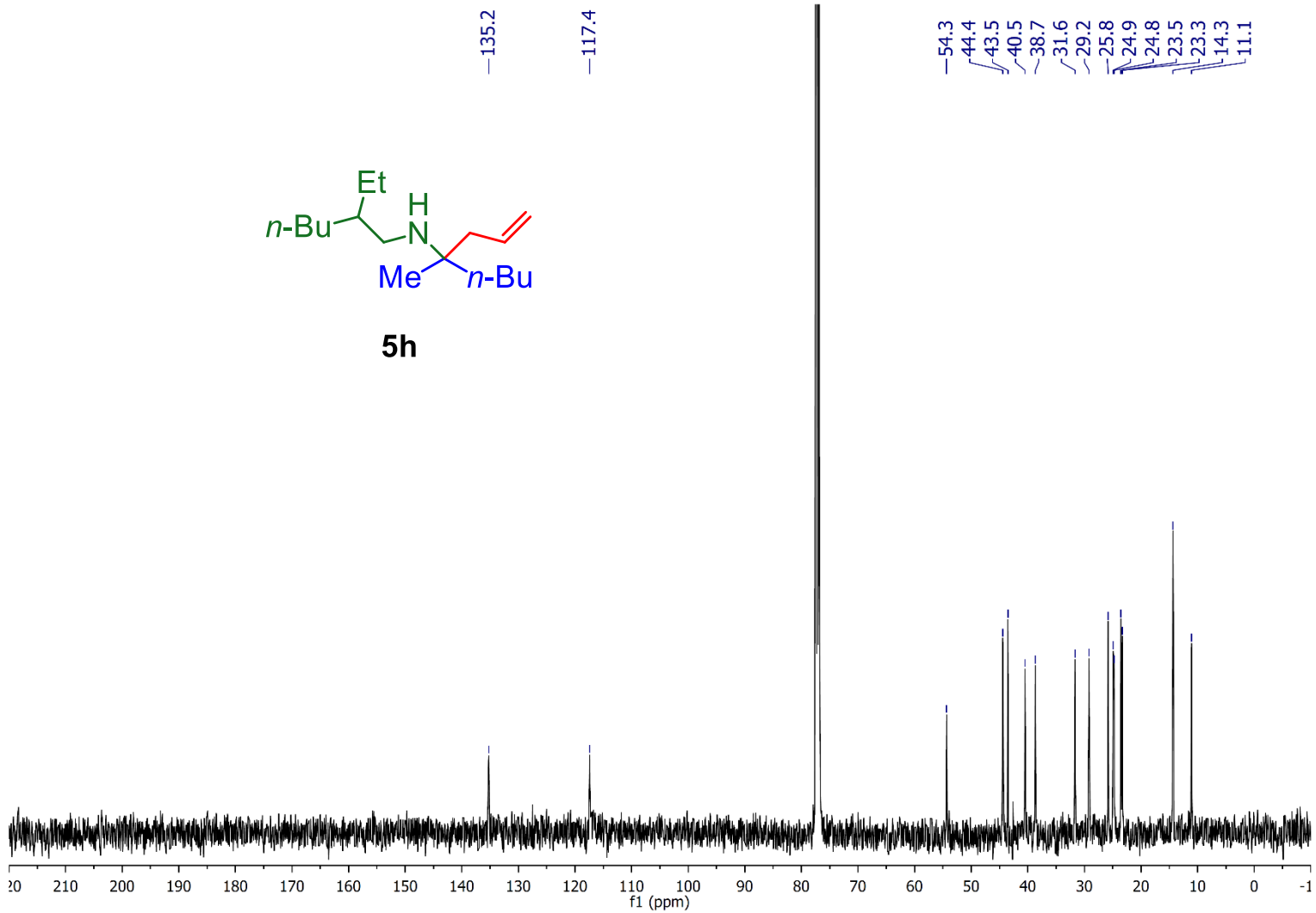

145.9
134.9
128.6
127.4
126.5
117.4
54.3
49.2
43.5
40.9
38.2
25.6
24.8
23.5
20.3
14.3
Me
H
N
Me
n-Bu
5f
f1 (ppm)

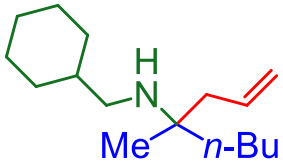


5g


140.4
134.7
128.8
128.4
126.2
117.5
54.4
43.2
38.4
37.2
25.6
24.7
23.4
14.2
H
N
Me
n-Bu
5g
f1 (ppm)


Et
H
N
Me
n-Bu
n-Bu
5h
9.05
3.02
15.01
2.15
2.00
2.00
1.14
f1 (ppm)


135.2
117.4
54.3
44.4
43.5
40.5
38.7
31.6
29.2
25.8
24.9
24.8
23.5
23.3
14.3
11.1
Et
H
N
n-Bu
Me
n-Bu
5h
f1 (ppm)

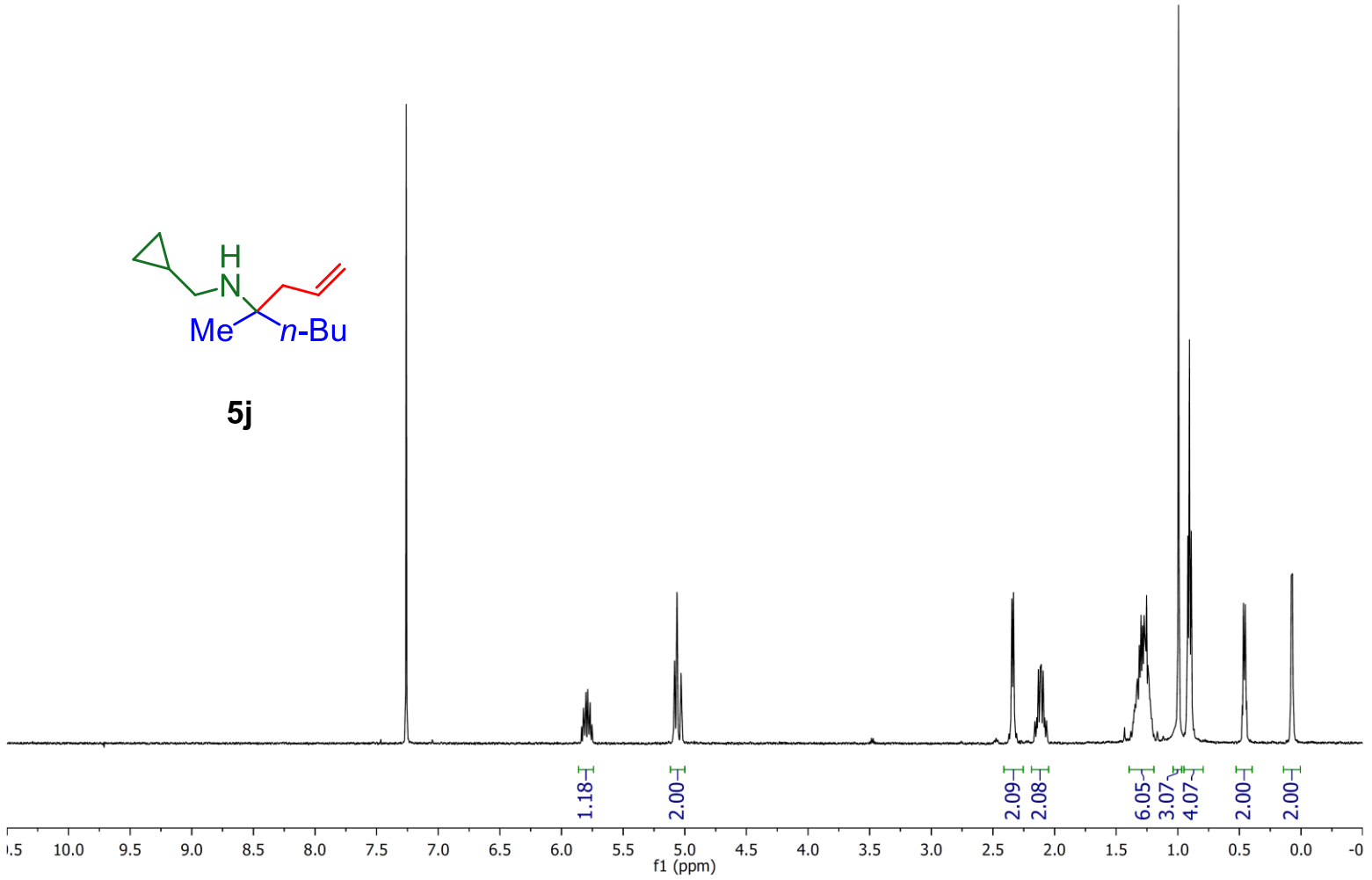

H
N
Me
n-Bu

5i

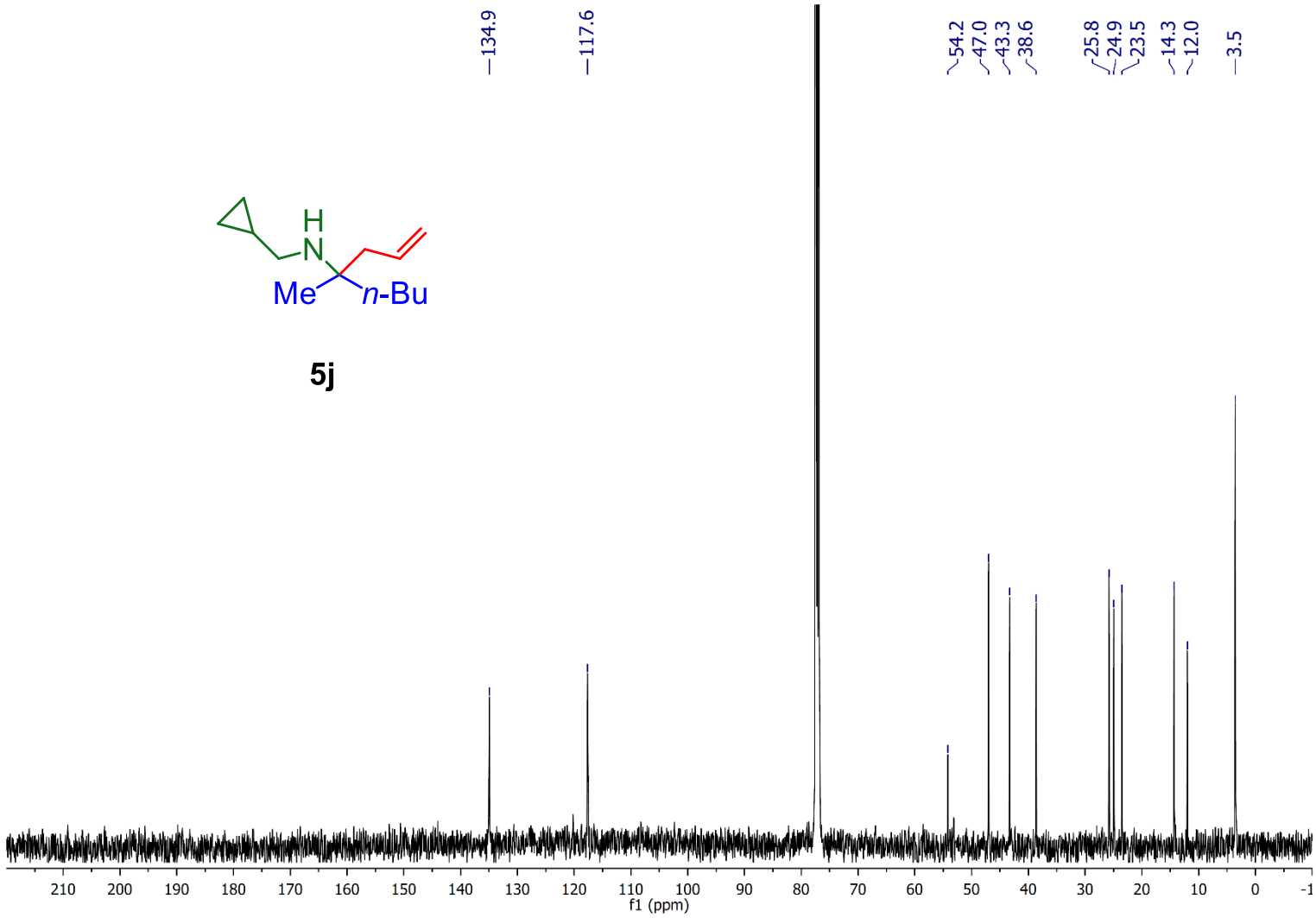
1.14
2.00
2.11
2.16
5.02
10.04
3.00
5.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

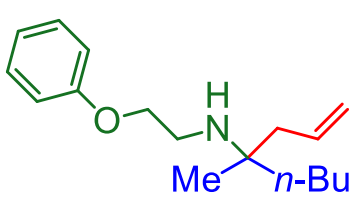
135.1
117.5
54.2
48.4
43.3
39.0
38.6
32.0
26.9
26.3
25.8
24.9
23.5
14.3
f1 (ppm)
H
N
Me
n-Bu

5i


H
N
Me
n-Bu
1.18
2.00
2.09
2.08
6.05
3.07
4.07
2.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

5j


134.9
117.6
54.2
47.0
43.3
38.6
25.8
24.9
23.5
14.3
12.0
3.5
H
N
Me
n-Bu
5j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

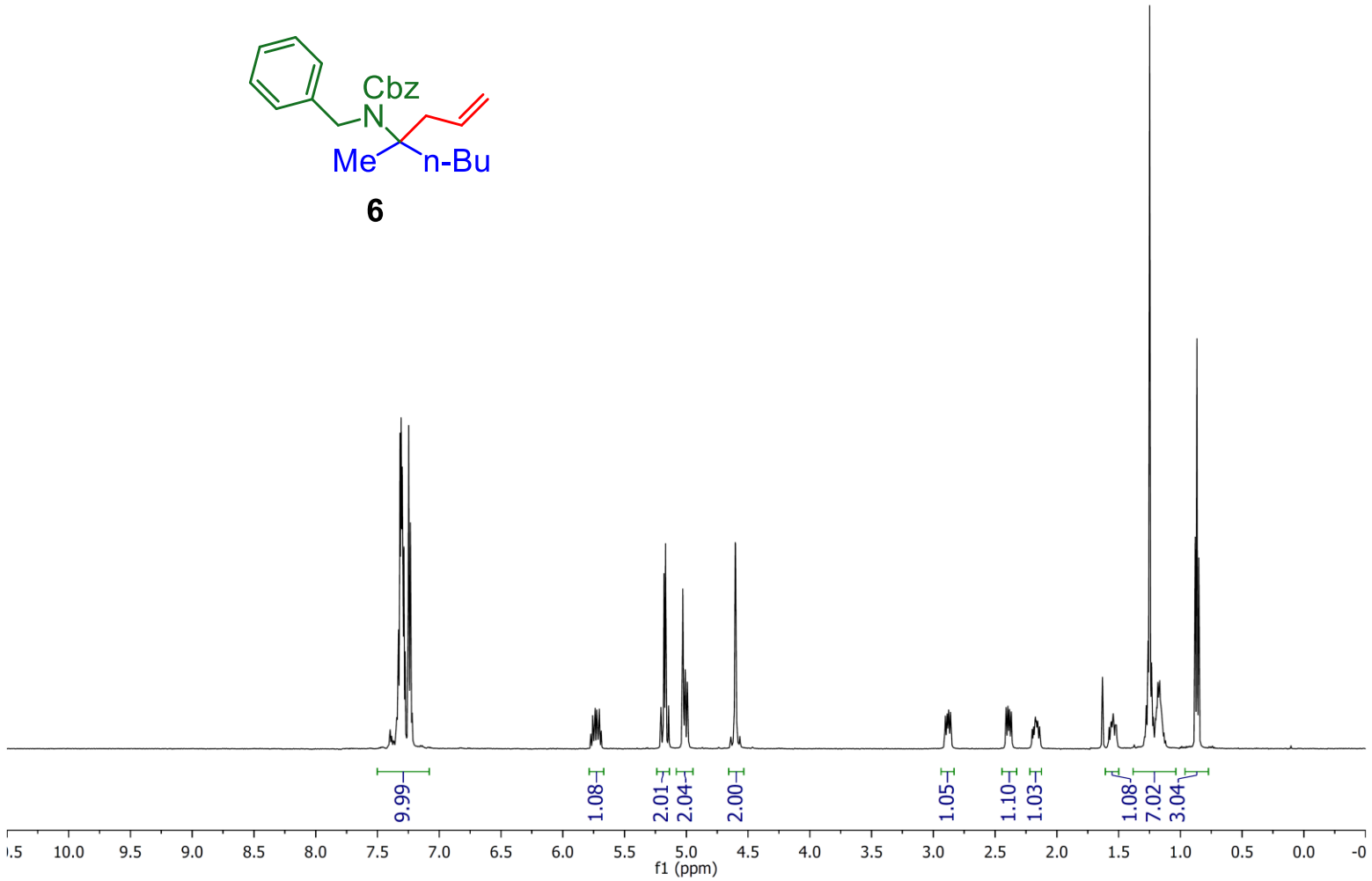

H
N
O
Me
n-Bu

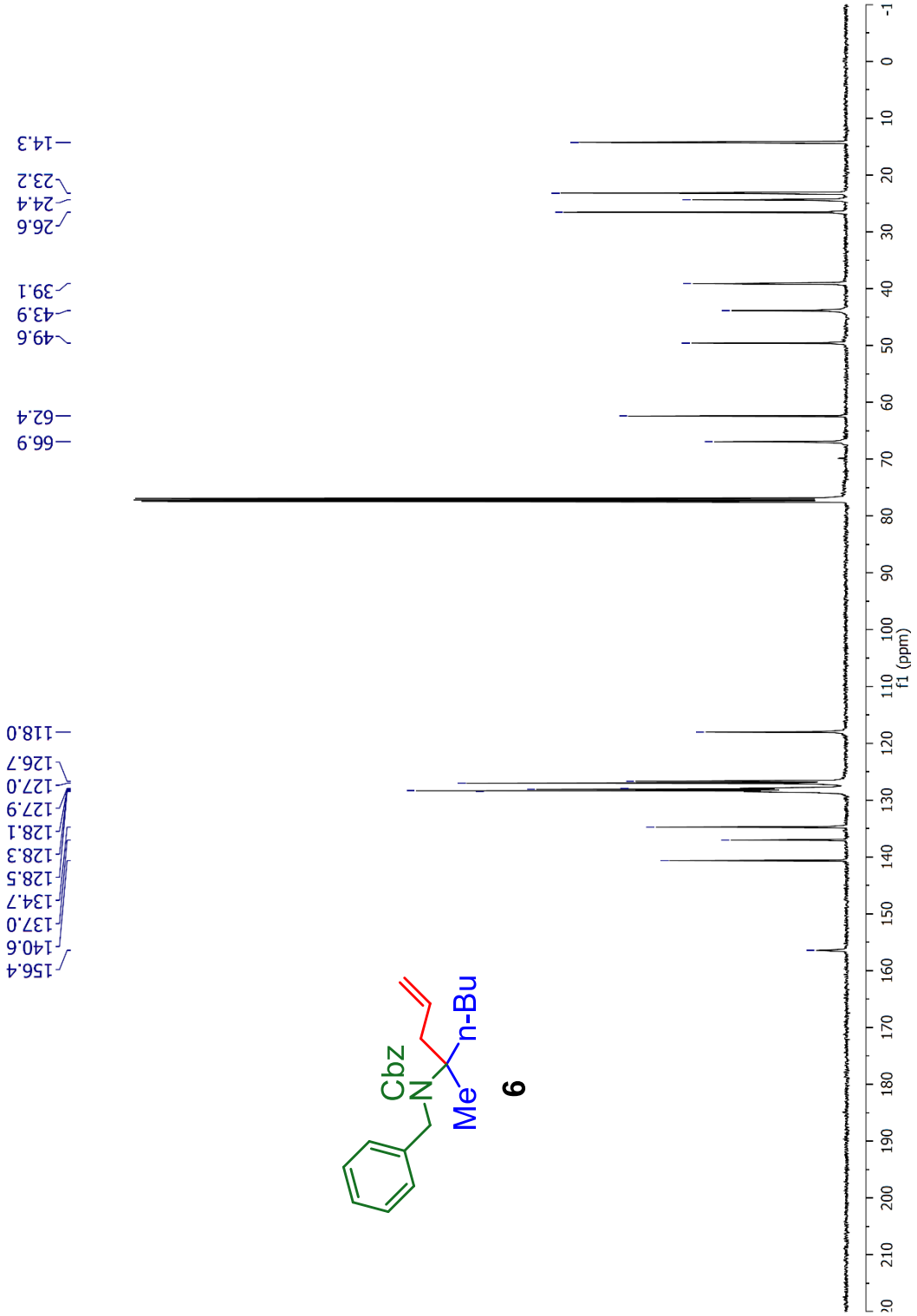
5k

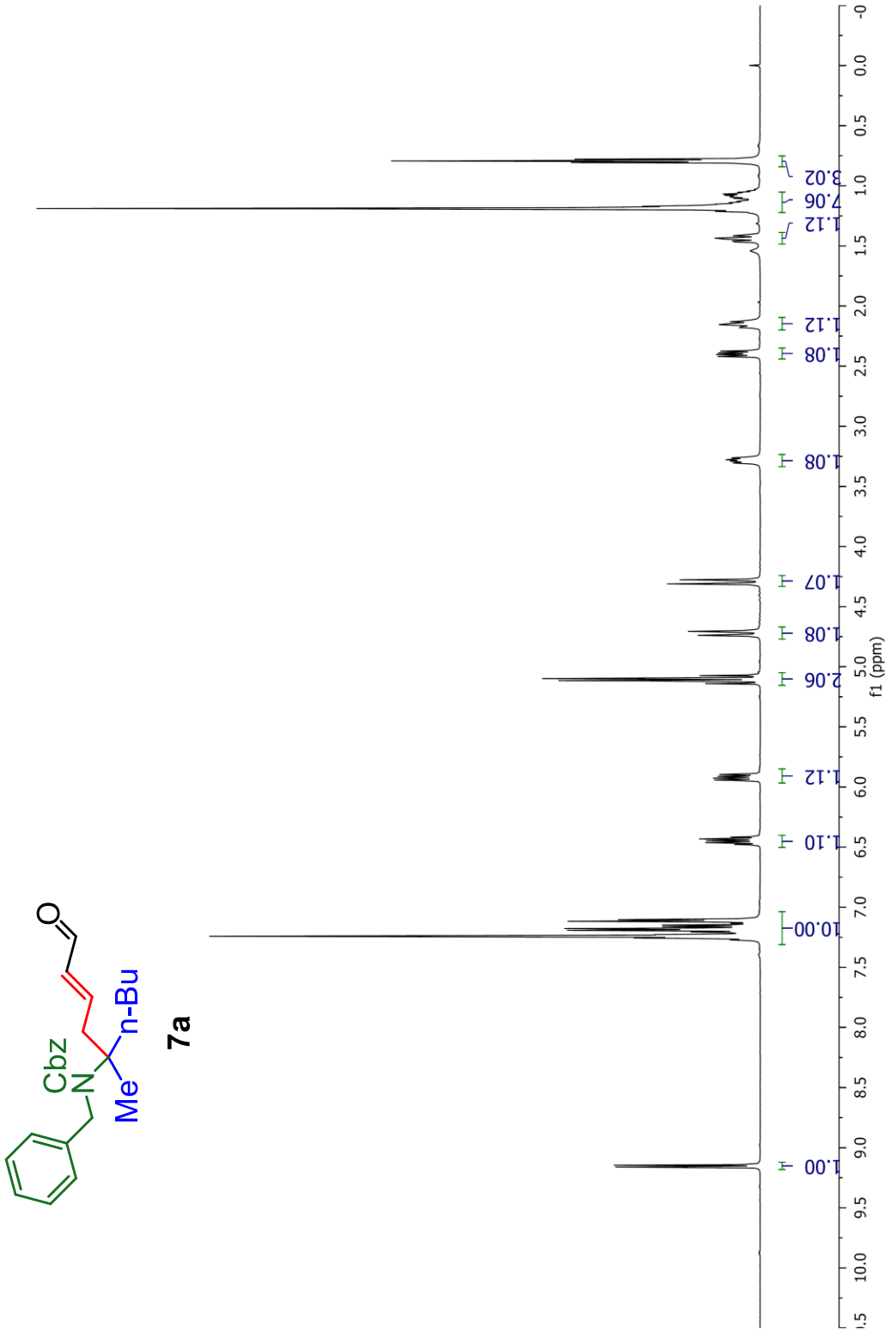
2.63
2.90
1.11
2.00
2.09
2.02
2.00
6.09
3.01
3.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

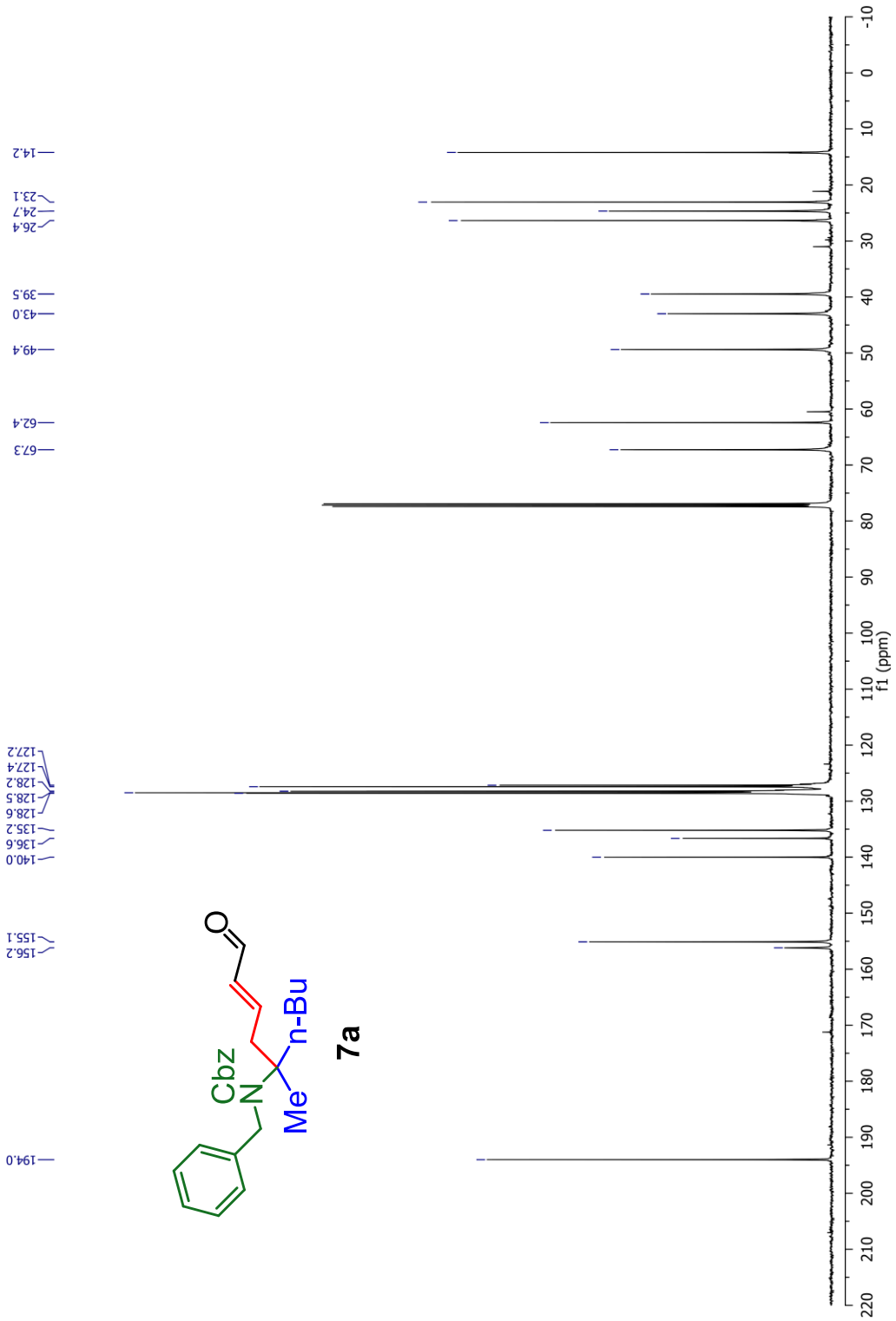
159.0
134.7
129.5
120.8
117.8
114.7
68.3
54.5
43.4
41.0
38.6
25.7
24.9
23.5
14.3
H
N
Me
n-Bu
O
f1 (ppm)

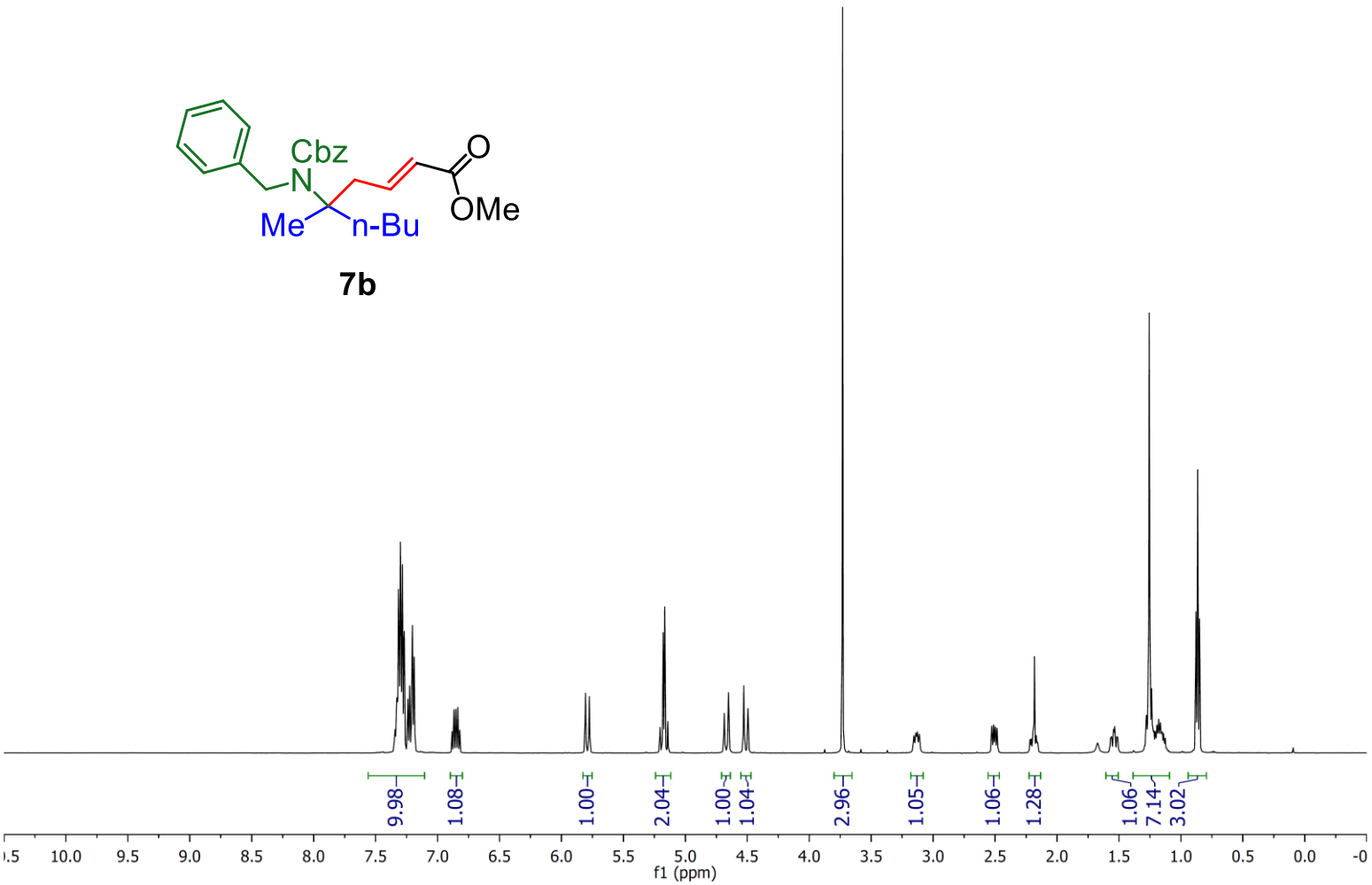
5k


Cbz
N
Me
n-Bu
6
9.99
1.08
2.01
2.04
2.00
1.05
1.10
1.03
1.08
7.02
3.04
f1 (ppm)

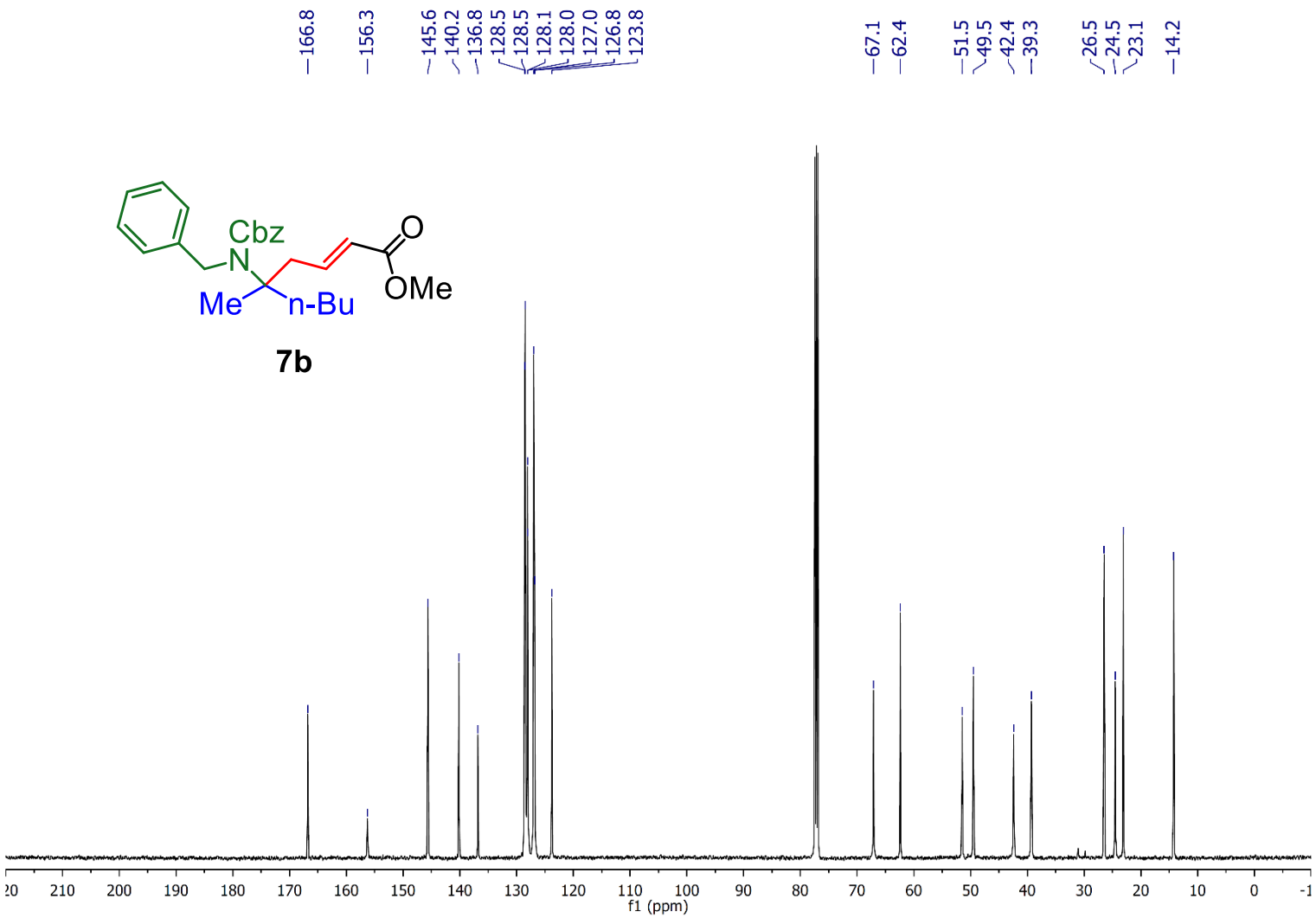

156.4
140.6
137.0
134.7
128.5
128.3
128.1
127.9
127.0
126.7
118.0
66.9
62.4
49.6
43.9
39.1
26.6
24.4
23.2
14.3
f1 (ppm)
Cbz
N
Me
n-Bu
6

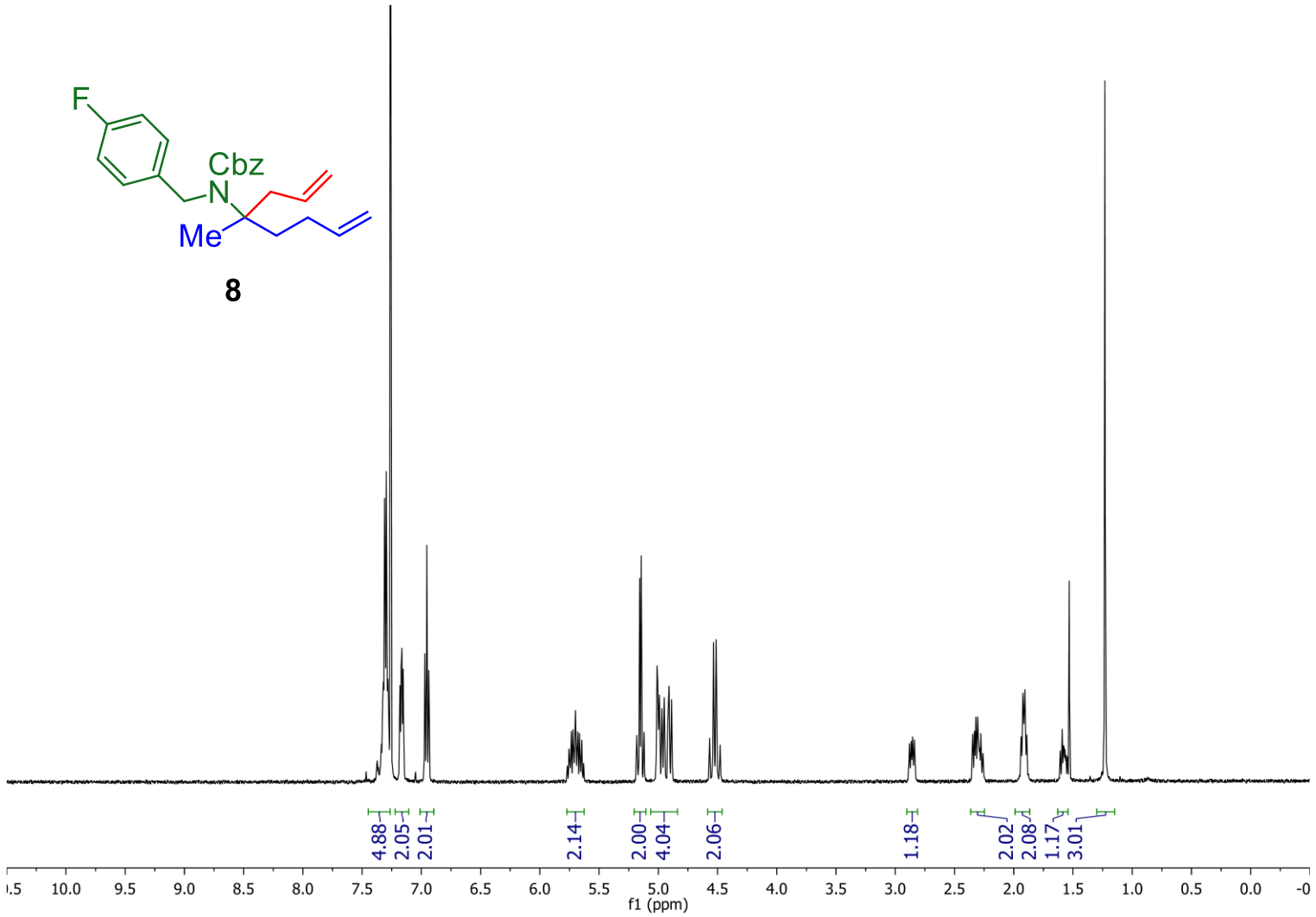

O
Cbz
N
Me
n-Bu
7a
10.00
1.10
1.12
2.06
1.08
1.07
1.08
1.08
1.12
1.08
7.06
1.12
3.02
f1 (ppm)

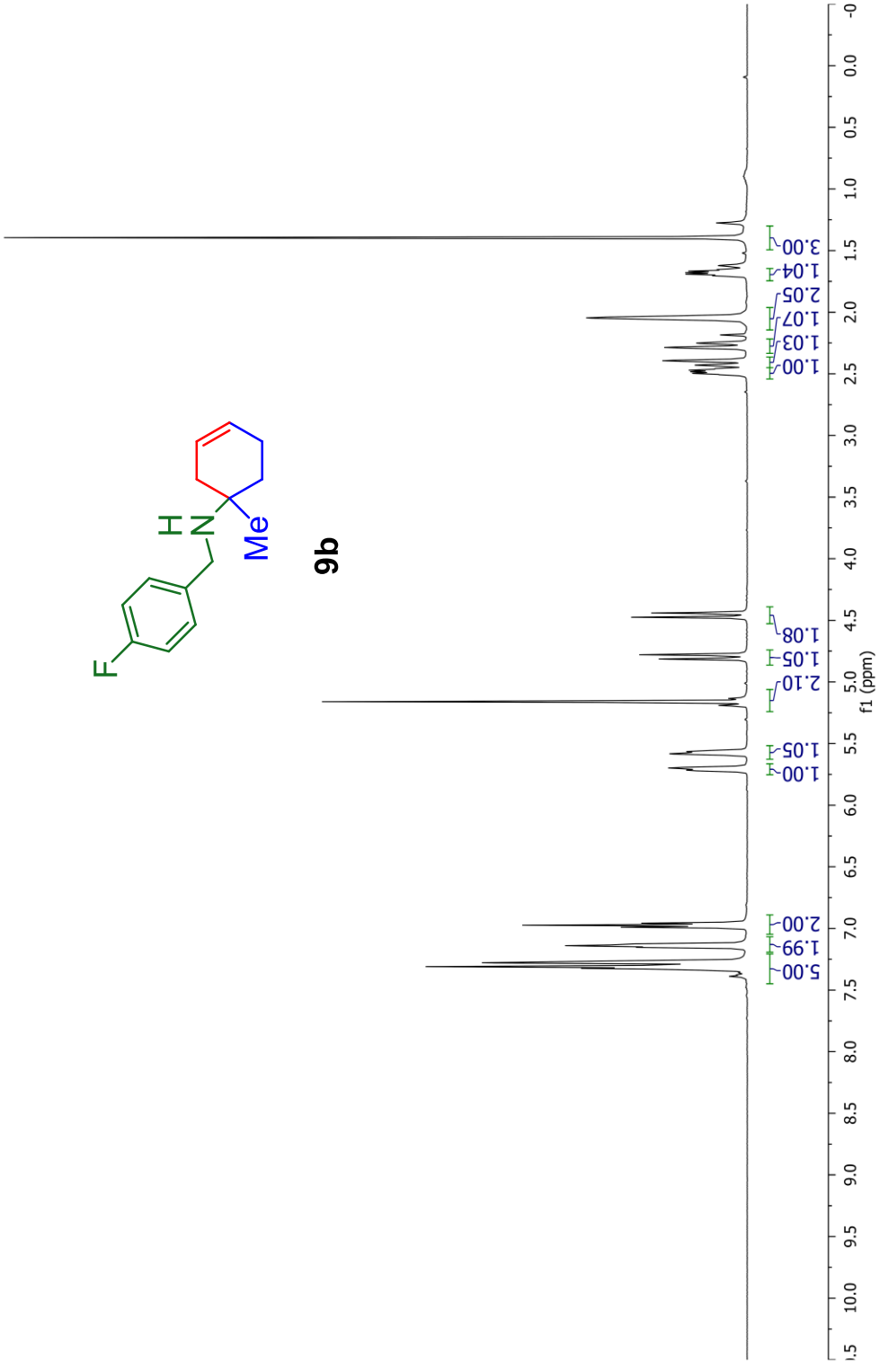

14.2
23.1
24.7
26.4
39.5
43.0
49.4
62.4
67.3
127.2
127.4
128.2
128.5
128.6
135.2
136.6
140.0
155.1
156.2
194.0
Cbz
N
Me
n-Bu
7a
f1 (ppm)

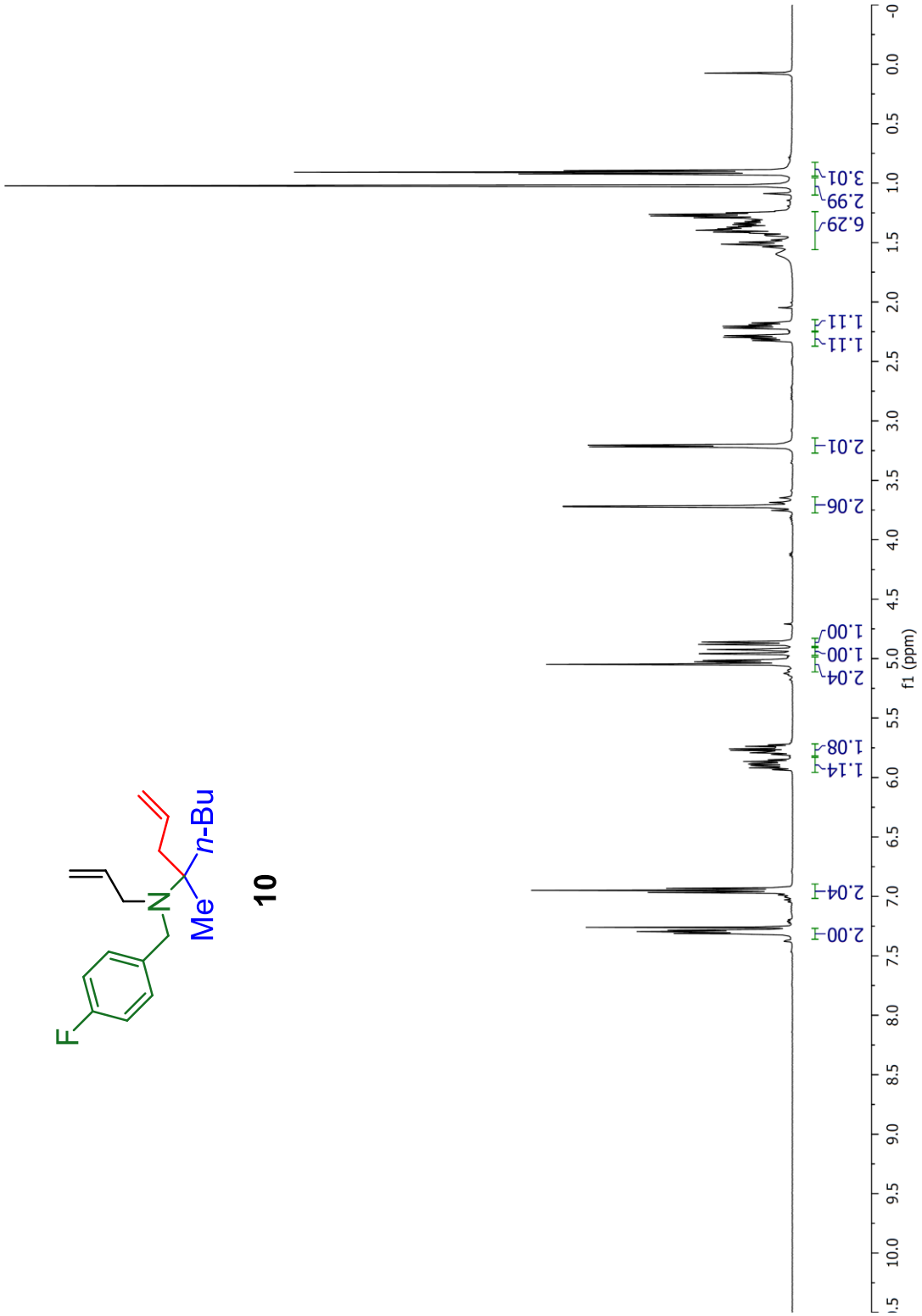

Cbz
N
Me
n-Bu
O
OMe
9.98
1.08
1.00
2.04
1.00
1.04
2.96
1.05
1.06
1.28
1.06
7.14
3.02
f1 (ppm)

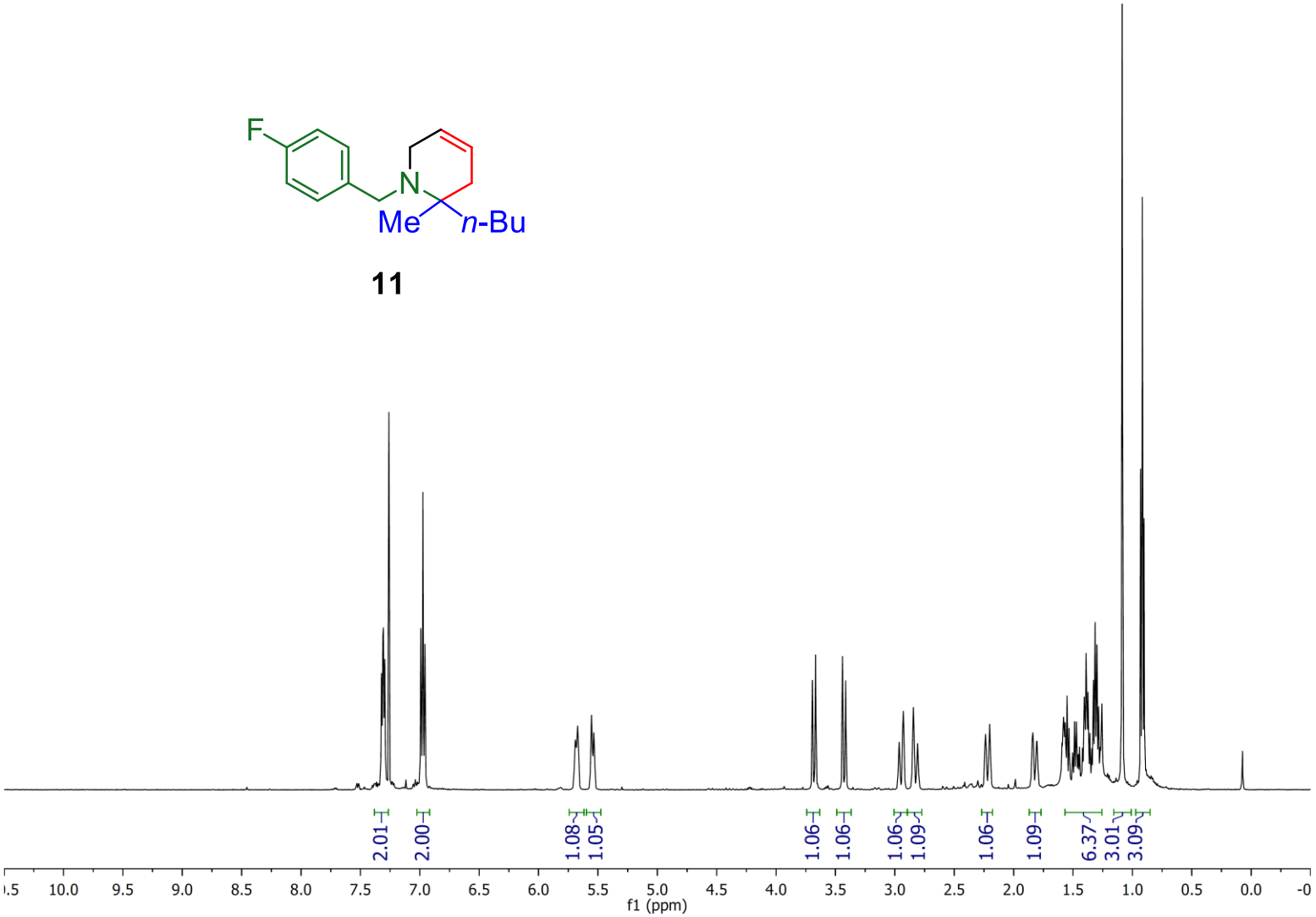
7b


166.8
156.3
145.6
140.2
136.8
128.5
128.5
128.1
128.0
127.0
126.8
123.8
67.1
62.4
51.5
49.5
42.4
39.3
26.5
24.5
23.1
14.2
Cbz
N
Me
n-Bu
O
OMe
7b
f1 (ppm)

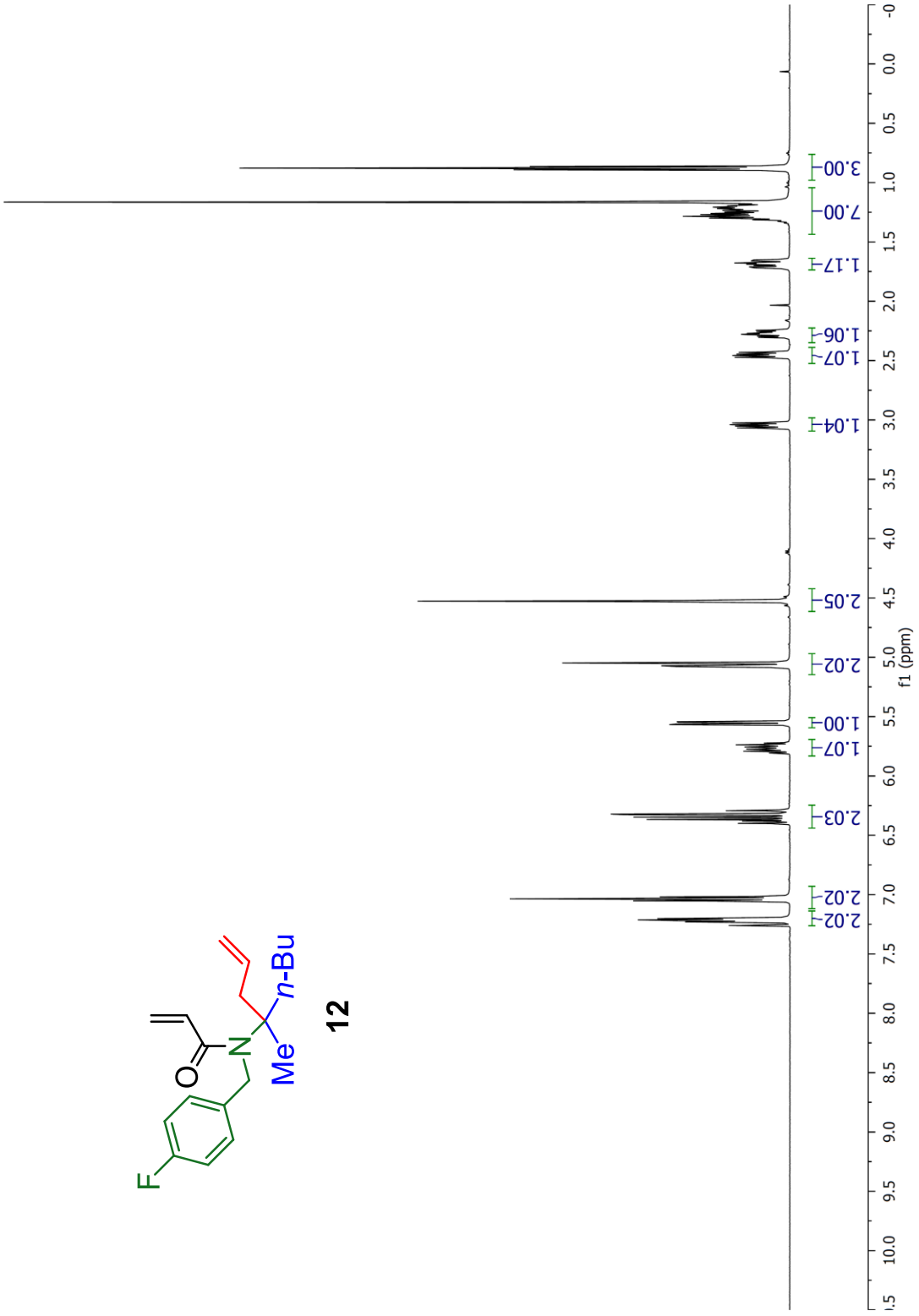

F
Cbz
N
Me
8
4.88
2.05
2.01
2.14
2.00
4.04
2.06
1.18
2.02
2.08
1.17
3.01
f1 (ppm)


H
N
Me
F
9b
3.00
1.04
2.05
1.07
1.03
1.00
1.08
1.05
2.10
1.05
1.00
2.00
1.99
5.00
f1 (ppm)

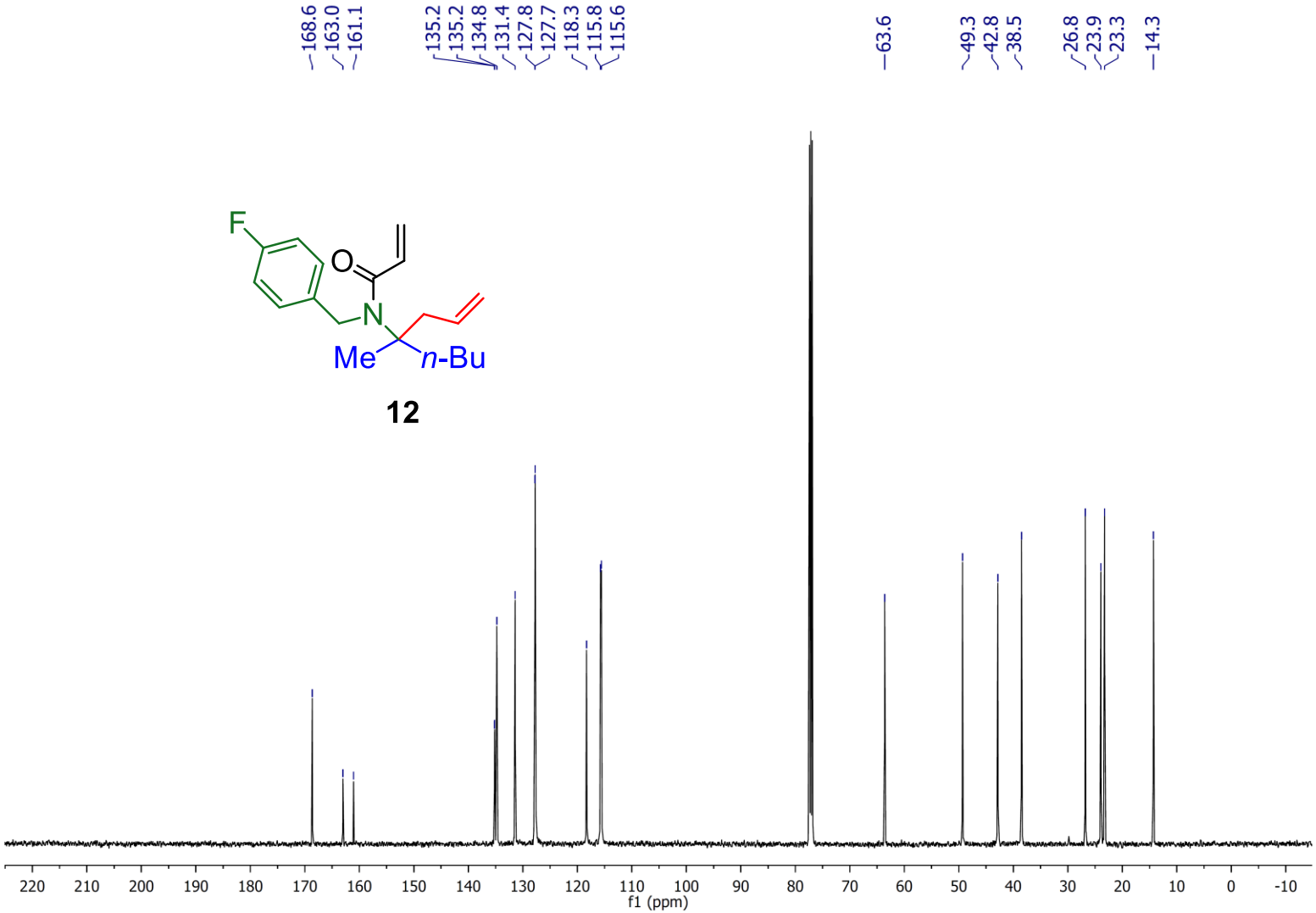

F
N
Me
n-Bu
10
3.01
2.99
6.29
1.11
1.11
2.01
2.06
1.00
1.00
2.04
1.08
1.14
2.04
2.00
f1 (ppm)


F
N
Me
n-Bu
2.01
2.00
1.08
1.05
1.06
1.06
1.06
1.09
1.06
1.09
6.37
3.01
3.09
f1 (ppm)

11


F
O
N
Me
n-Bu
3.00
7.00
1.17
1.06
1.07
1.04
2.05
2.02
1.00
1.07
2.03
2.02
2.02
f1 (ppm)

12


168.6
163.0
161.1
135.2
135.2
134.8
131.4
127.8
127.7
118.3
115.8
115.6
63.6
49.3
42.8
38.5
26.8
23.9
23.3
14.3
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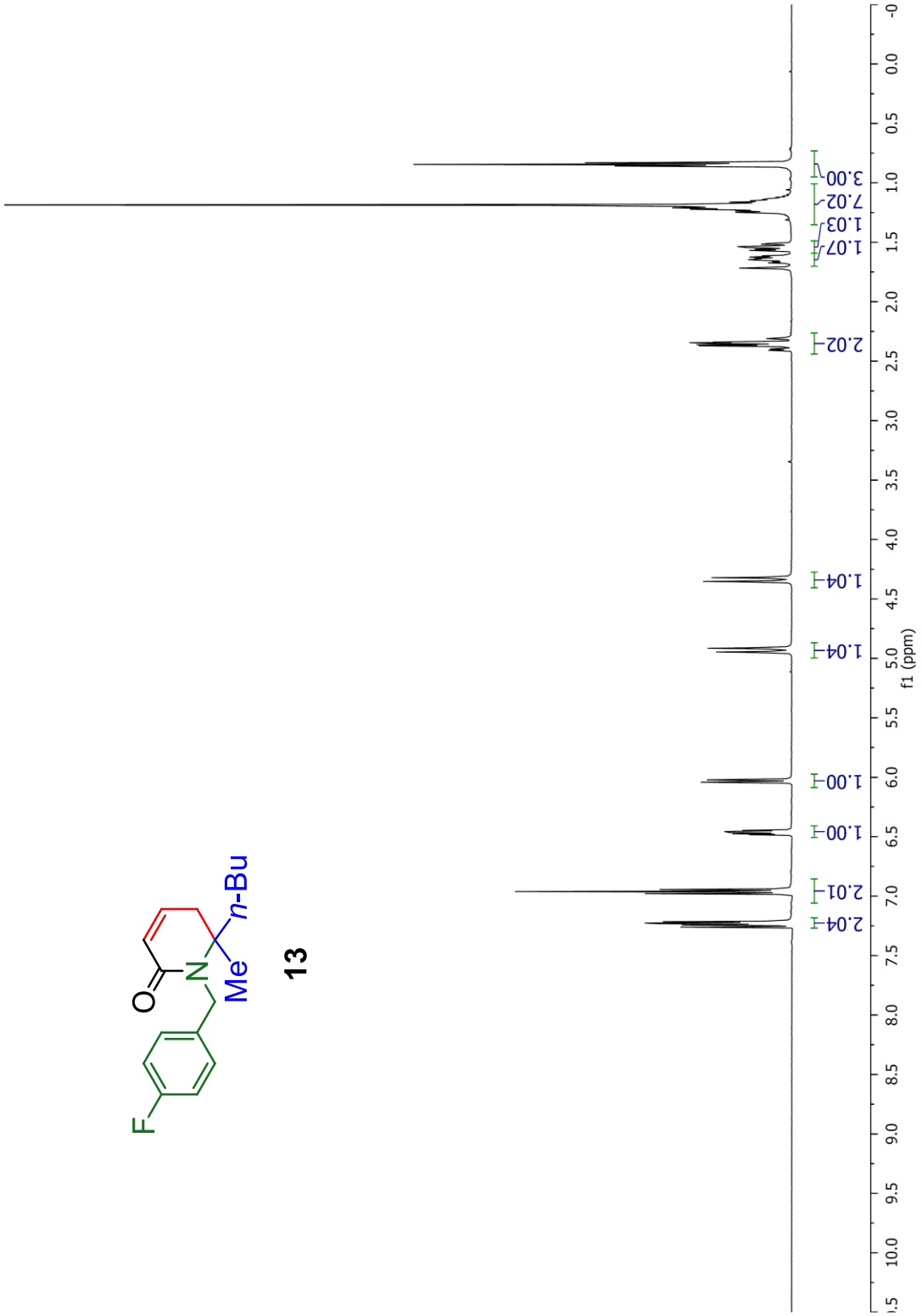
12
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



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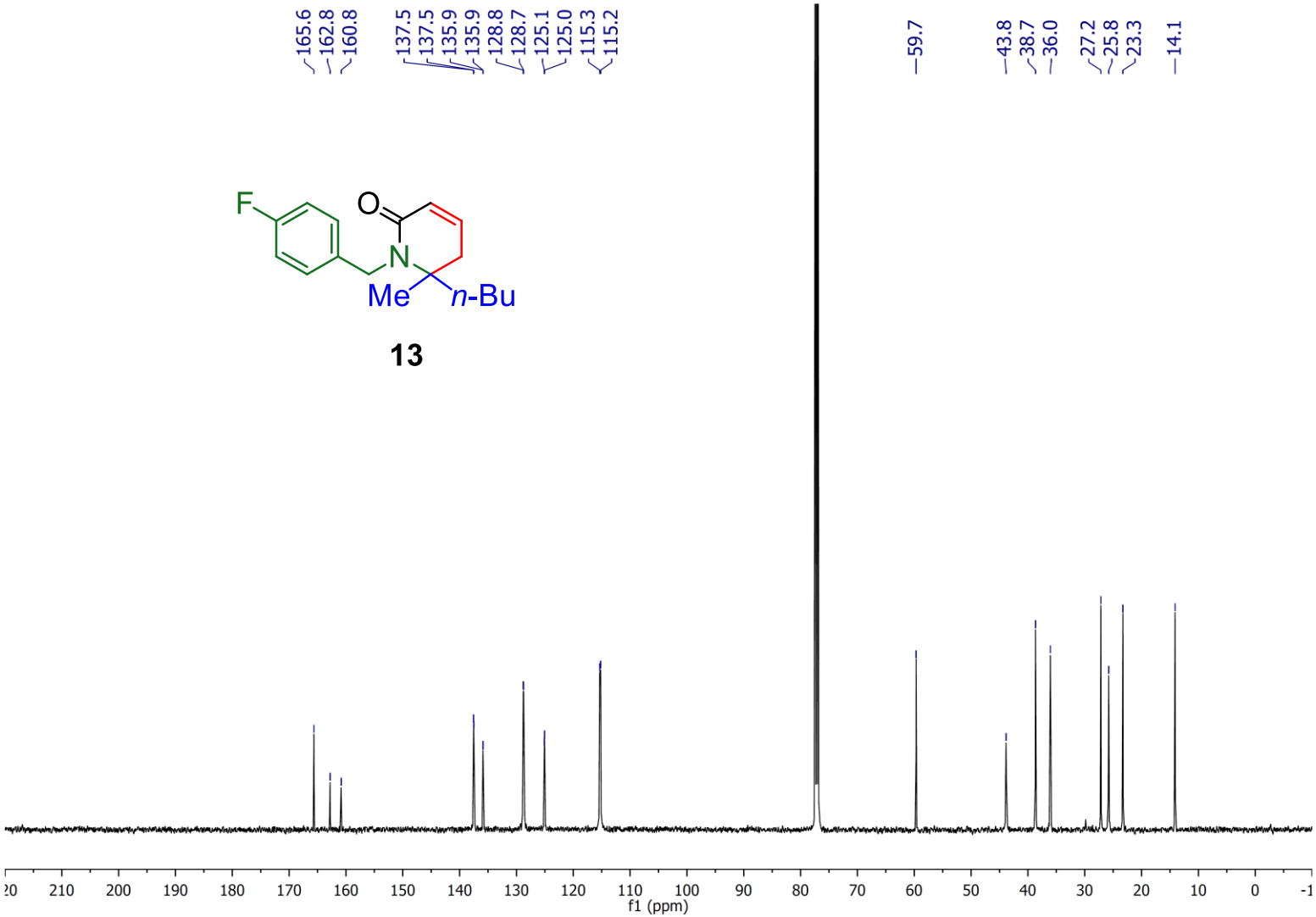
165.6
162.8
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n-Bu
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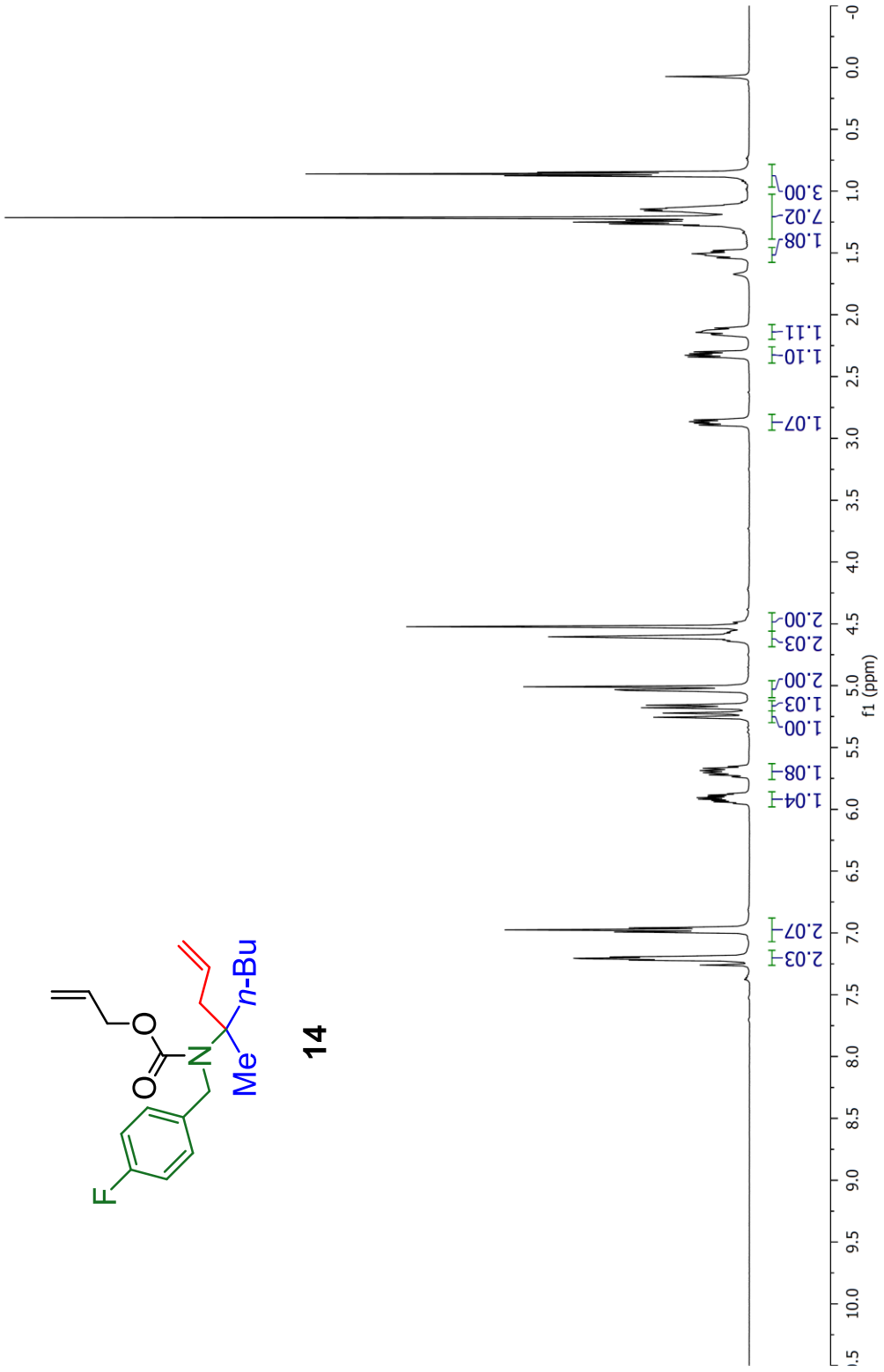
f1 (ppm)


F
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14
2.03
2.07
1.04
1.08
1.00
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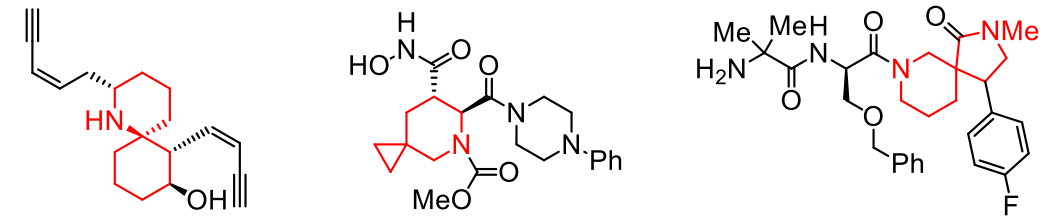
2.03
2.00
1.07
1.10
1.11
1.08
7.02
3.00
f1 (ppm)

Chapter Two: Synthesis of 1-Azaspirocyclic Scaffolds

2.1 Introduction

Spirocycles, especially those containing heteroatoms, have long been considered privileged scaffolds in medicinal chemistry.[1] As drug targets these structures possess a significant advantage in that they have a lower conformational entropy cost to binding. This is due to the geometric nature of the tetrasubstituted carbon at the heart of the structure, that forms the orthogonal ring system which enforces three-dimensionality.[2] This inherent rigidity allows for the tuning of specific structural features to enhance π-stacking, H-bonding, and hydrophobic interactions of a pharmacophore in biological space. There are notable examples in the development of specific therapeutics that have shown enhanced activity due to their presence when compared to similar fused bicyclic systems.[3] Additionally substrates containing spirocycles can not only demonstrate enhanced activity but also possess better off-target selectivity. There has been



Histrionicotoxin 283A — **A**

Aderbasib
ADAM10/17 Inhibitor — **B**

US 20120302540
Ghrelin Receptor Agonist — **C**

Figure 2.1: Bioactive and synthetic targets containing azaspirocycles.

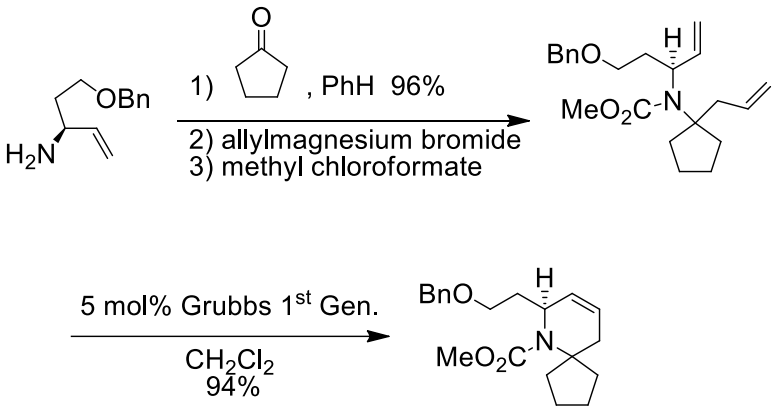
increased interest in exploring spirocycles as it is an underexplored area that offers structural complexity and patentability in the field of drug discovery.[1]

The largest class of bioactive spirocyclic compounds are those that contain a nitrogen heteroatom (Figure 2.1).[1] 2-Spiropiperdines are a largely uncharted subset of this class but include compounds with notable biological potency like histrionicotoxin (**A**), a nicotinic acetylcholine receptor inhibitor found in poison frogs. While approaches to these structural features are known[4] there are few known methodologies that provide direct access to these structural features from commercially available starting materials.[5]

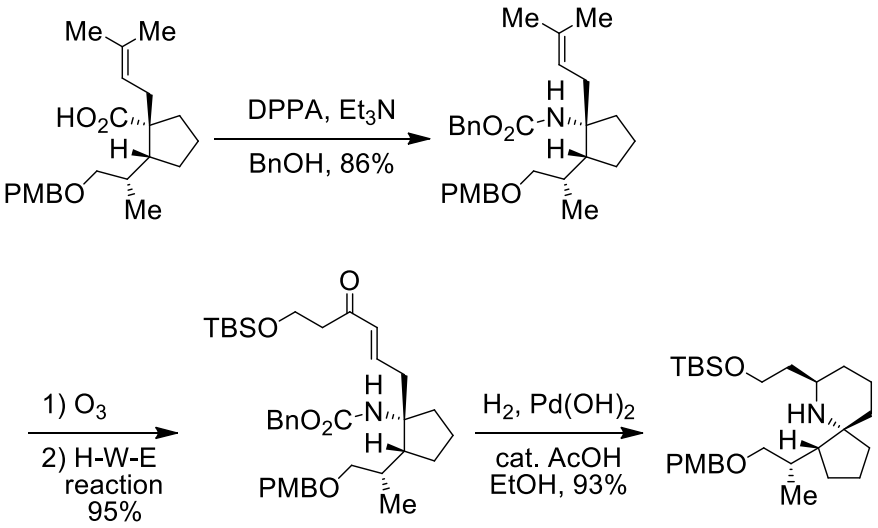
Synthesis of 1-azaspirocycles typically follow one of three different general synthetic pathways. The difference results from the order in which the primary structural features are formed. The first pathway involves the formation of the tetrasubstituted carbon center followed by the closing of the heterocycle, the second the formation of the tetrasubstituted center followed by the closing of the carbocycle, and finally the third involves simultaneous formation of both the tetrasubstituted carbon center along with the spirocycle.

Utilizing the first pathway in which the tetrasubstituted center is formed first followed by the heterocycle, one of the most common ways to do this is introduction of the carbocycle by condensation of amine onto a cyclic ketone then addition into the imine followed by ring-closing metathesis (Scheme 2.1).[6] This was shown by Wright and co-workers to be an effective route in the preparation of the halichlorine and pinnaic acid core. Another popular approach is to perform a Curtius

Wright's Imine addition-RCM:



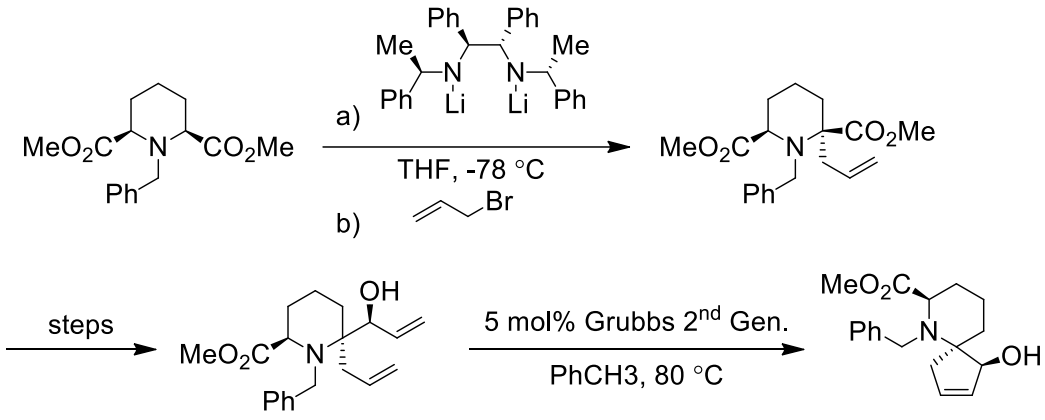
Arimoto's Curtius Rearrangement-Reductive Amination:



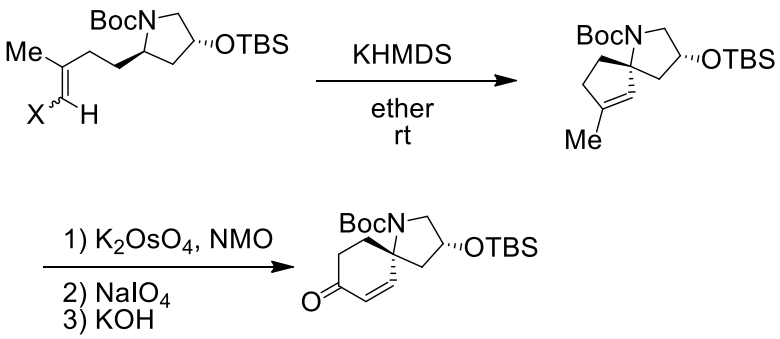
Scheme 2.1: Common examples of 1-azaspirocycle formation carried out by construction of the tetrasubstituted carbonfollowed by closure of the heterocycle.

rearrangement to convert a quaternary carbon center to a tetrasubstituted carbon bearing an amine, followed by either reductive amination[7] or *N*-alkylation[8] to close the heterocycle. The use of conjugate additions is also an effective pathway. Both Stella[9] and Heathcock[10] prepared cylindricine A through similar approaches that involve the conjugate addition of ammonia to a bis-enone. The resultant piperidone can undergo radical cyclization using NCS to close the heterocycle.

Simpkins Enolate Alkylation-RCM:

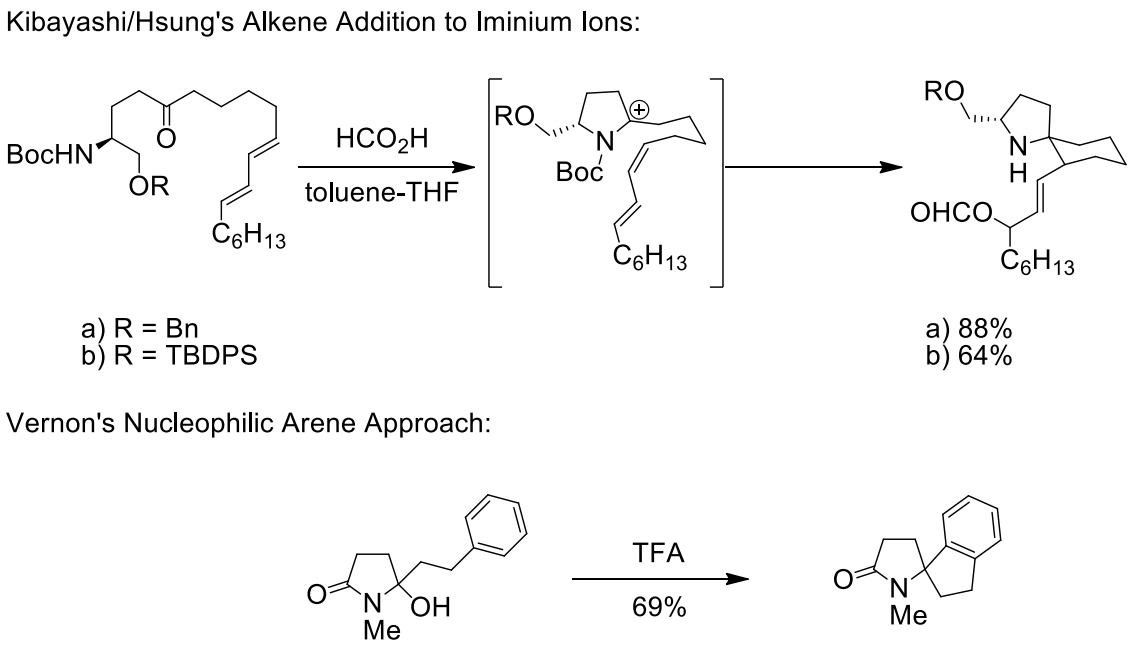


Hayes C-H insertion - Aldol Condensation:



Scheme 2.2: Common examples of 1-azaspirocycle formation carried out by construction of the tetrasubstituted carbon followed by closure of the carbocycle.

In the second pathway in which the tetrasubstituted center is set followed by the formation of the carbocycle there is another synthesis of the halichlorine core mentioned above. In this instance Simpkins and co-workers perform an enolate alkylation on a meso diester with allyl bromide. Further synthetic steps install an additional allyl group at the alpha position and ring-closing metathesis forms the carbocycle (Scheme 2.2).[11] Another popular approach for this pathway is that of C-H insertion. Hayes et al. report the formation of a 1-aza[4.4]nonane upon treatment of the starting compound with KHMDS to generate a carbene

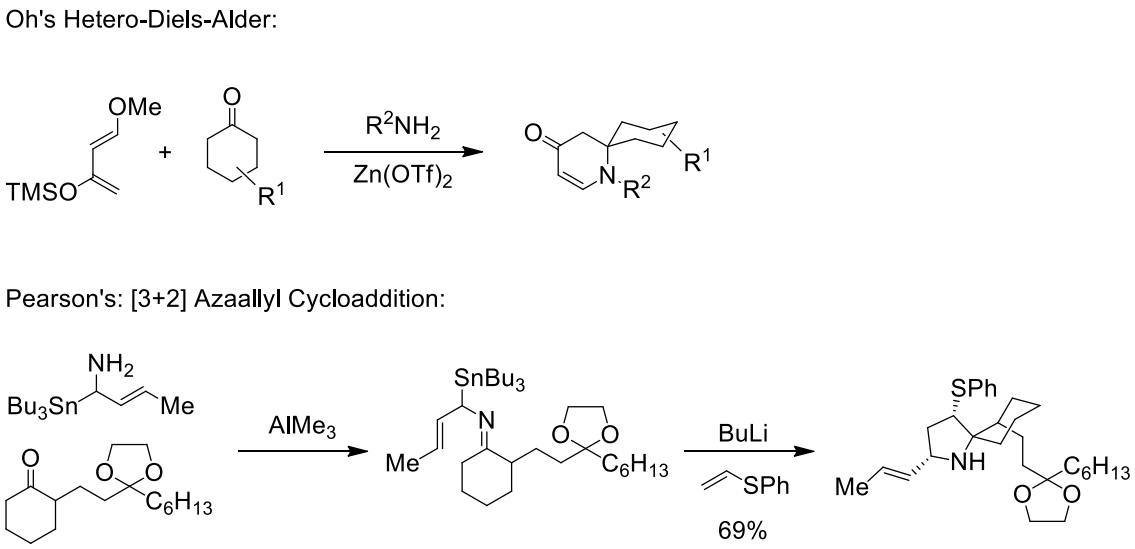


Scheme 2.3: Examples of spirocycles formed through the attack on an in situ formed iminium.

intermediate which then undergoes C-H insertion. This spirocycles is further modified by oxidative cleavage then followed by an aldol condensation to produce the cyclohexanone.[12]

The final category involves the simultaneous formation of the tetrasubstituted center as well as the spirocycles. Since these pathways only require a single synthetic step they have the added benefit of efficiency. However, there is a notable trade off in that there are significant limitations in the scope of the reaction.[4] This is the most varied area but the various methodologies can be sorted into general categories, the most notable and relevant of which will be mentioned.

The largest category is the addition to *in situ* formed iminium ions. Both the Kibayashi[13] and Hsung[14] groups showed the viability of nucleophilic alkene

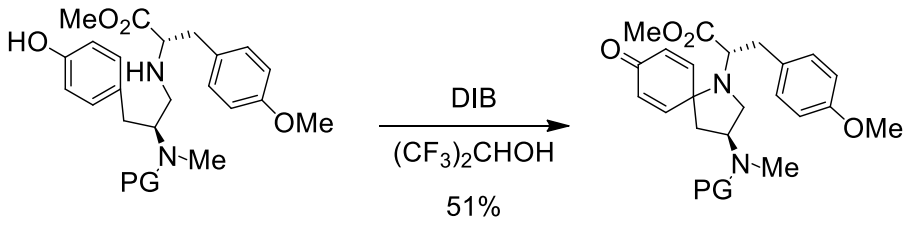


Scheme 2.4: Cycloadditions provide a useful approach to spirocycles for the synthesis of the heterocycle.

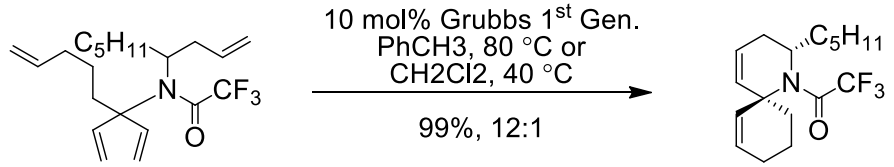
addition to an *in situ* iminium/azacarbenium in the synthetic pursuit of lepadiformine (Scheme 2.3). Both groups discovered that simple alkenes were not sufficient for capturing the transient azacarbenium species. Another useful example is that of nucleophilic arenes. Vernon and co-workers were able to show that nucleophilic arenes were capable of adding into *N*-acyliminium ions generated from the substrate shown in Scheme 2.3.[15]

Cycloadditions represent another useful approach to the simultaneous formation of the desired structural features for these substrates. The Oh group pursued a hetero Diels-Alder pathway by reacting Danishefsky's diene with the imines formed from a chosen amine and cyclic ketone. The performance of this reaction was found not to be dependent on whether or not the imine was isolated or formed *in situ* but rather on the size of the substituent on the nitrogen (Scheme

Sorensen's Oxidation w/ Hypervalent Iodine:



Harrity's Dual Ring-Closing Metathesis:

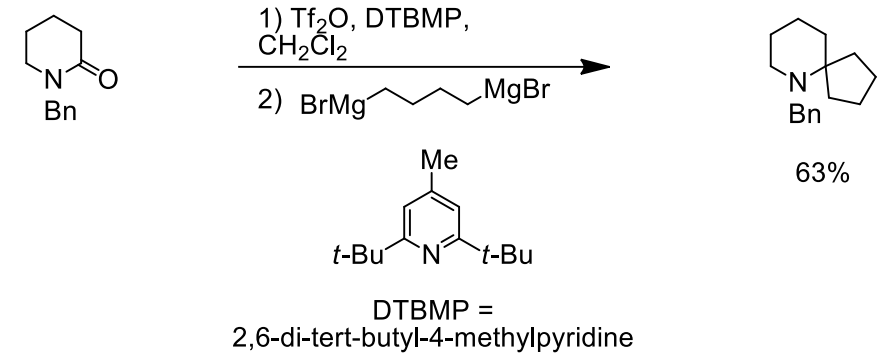


Scheme 2.5: Other more unique approaches can yield structurally complex products in a single-step forming multiple crucial bonds, but are limited by the starting substrate

2.4).[16] Pearson and co-workers reported a unique approach which involved the [3+2] cycloaddition strategy.[17] The initial imine is generated from the starting ketone and amine shown in Scheme 2.4 using trimethylaluminum. After the imine undergoes a tin-lithium exchange using *n*-butylithium to generate the 2-azaallyl anion, vinyl phenyl sulfide is introduced to facilitate the cycloaddition.

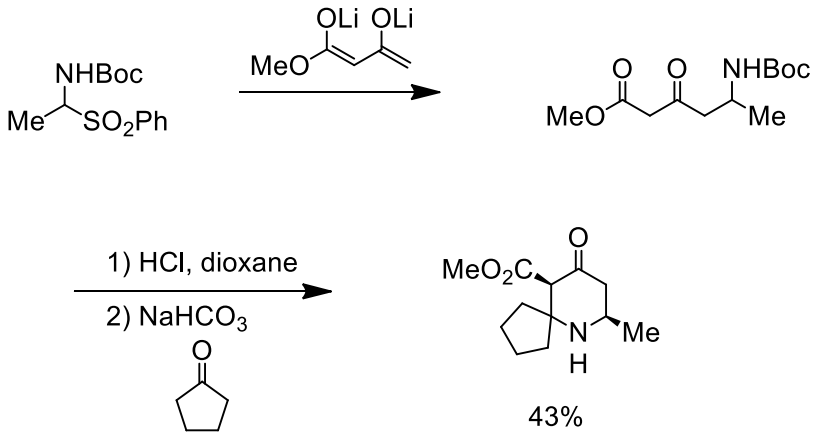
A common approach of which there are several variants and reagents is the usage of hypervalent iodine species. This is reaction is contingent on the presence of a *para*-substituted phenol or anisole in order for it to undergo dearomatization and give the resultant dienone as part of the spirocycle.[4] The majority of example use primary amines, however secondary amines do work, but typically report lower yields. Additionally, the choice of solvent is critical for these reactions, Sorensen

and Huang's Bis-Grignard Addition to Activated Lactams : co-



DTBMP =
2,6-di-tert-butyl-4-methylpyridine

Clarke's aza-Maitland-Japp Reaction:



Scheme 2.6: Recent advances in generalized synthetic approaches to 1-azaspirocycles.

workers showed that in the case of their substrate hexafluoroisopropanol gave the best results (Scheme 2.5).[18]

One last notable method uses Grubbs' catalyst induced ring-closing metathesis to close both the carbocycle and heterocycle in a single catalytic step. Harrity's group demonstrate the effectiveness of this approach on the trifluoroacetamide in Scheme 2.5. The reaction gives excellent yield and good diastereoselectivity (12:1). The authors did remark however that the

diastereoselectivity was enhanced when each of the cycles was closed in a stepwise fashion.[19]

Synthesizing histrionicotoxin and other members of that alkaloid family has been met with such difficulty that there are 52 formal or total syntheses of histrionicotoxin and related alkaloids and 19 partial synthesis of the azaspirocyclic core with little to no advancement towards synthesis of the remaining structure.[20] Due to this, exploration into the facile synthesis of these and similar azaspirocyclic cores is a worthwhile pursuit. More recent, and generalized, synthetic methodologies require synthesis of starting materials and harsh reaction conditions.[5]

Huang and co-workers designed an approach that relied on the activation of pre-formed lactams and treatment with multiple equivalents of organometallic reagents.[5a] A tertiary amide would be activated using triflic anhydride, then successively treated with two organometallic reagents (Scheme 2.6). Using this they were able to prepare 1-azaspirocycles through two different approaches. In the first case the activated lactam was reacted with a bis-Grignard reagent in order to form the carbocycle. The other was through a reaction of the activated lactam with two equivalents of either allyl or homoallyl magnesium bromide. This bis-olefin could then undergo ring-closing metathesis using Grubbs' catalyst.

Clarke et al recently published a somewhat more stepwise approach which involves *N*-Boc sulfone precursors undergoing an aza-Maitland-Japp reaction (Scheme 2.6).[5b] The sulfone precursors act like masked imines, removal of the

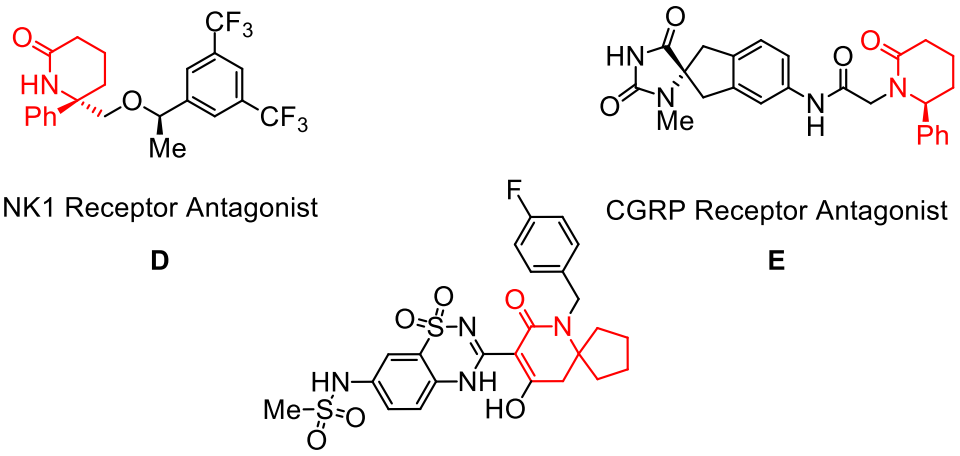
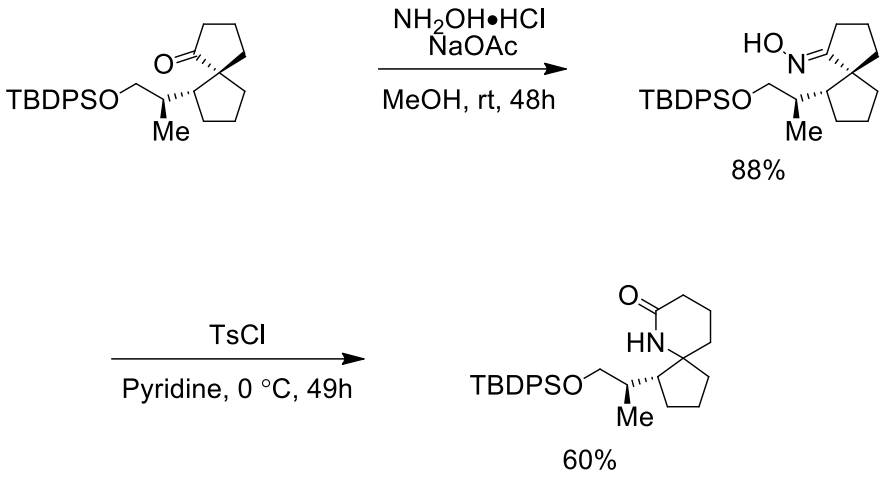


Figure 2.2: Bioactive and synthetic targets containing δ-lactams.

phenyl sulfonyl yields the aldimine which can react with the Weiler dianion. This results in the Boc-protected δ-amino-β-ketoester. This can then undergo deprotection using HCl in dioxane. Free basing of the ammonium salt with $NaHCO_3$ in the presence of a commercially available cyclic ketone, induces the final cyclization.

α,β-Unsaturated lactams as well as their fully saturated cousins are well known pharmacophores. **D** has shown activity as an NK1 receptor antagonist and use as an antiemetic for patients suffering from nausea due to chemotherapy. While **E** is a CGRP receptor antagonist being explored as a possible treatment for migraines.[21] Not surprisingly the spirocyclic variants of these lactams have also been explored in recent years for their bioactivity. The α,β-unsaturated spirolactam **F** demonstrated inhibition of HCV NS5B polymerase at nanomolar levels.[22] Despite their synthetic potential and utility, there are fewer reported approaches to these structures than the aforementioned 2-spiropiperdines.

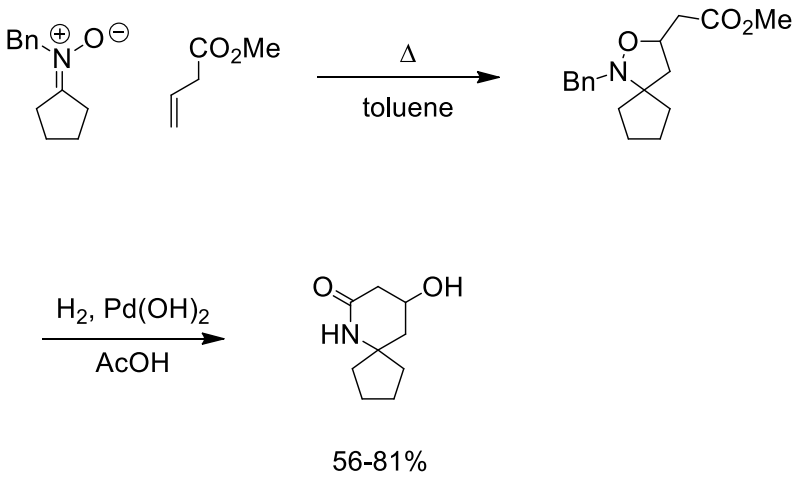


Scheme 2.7: Utilizing a Beckmann rearrangement to synthesize the spirolactam can be useful it does however require the construction of the quaternary carbon center and both carbocycles of a spirocyclic system.

Typical procedures for accessing these [5.X]-spirolactams require the formation and isolation of the ketimine and treatment with an allyl Grignard to give the homoallyl amine. The free amine could then be acrylated then followed with olefin metathesis.[23] Previous approaches however have required the use of extra Lewis acid catalysts to facilitate the formation of product. This approach is similar to the first category of pathways shown for the 2-spiropiperdines above in which the tetrasubstituted center is formed then the heterocycle is closed afterwards.[4]

Other approaches take advantage of the utility of the Beckmann rearrangement to convert the carbocycle to the heterocycle. Pilli and co-workers sought synthetic routes to a familiar azaspirocyclic core, that of halichlorine and related marine alkaloids.[24] Upon synthesis of the required ketone, it was reacted with hydroxylamine to give the oxime. The oxime was then reacted with *p*-TsCl and pyridine to give the desired spirolactam following rearrangement (Scheme 2.7).

Funk's [3+2] Cycloaddition of a Nitrone and Olefin :

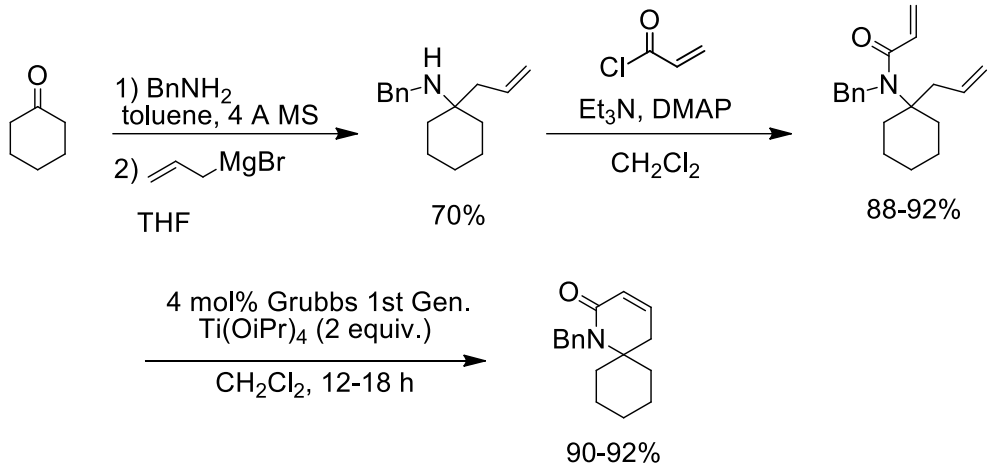


Scheme 2.8: A cycloaddition of a nitrone with an olefin gives a spirocyclic isoxazolidine that upon hydrogenolysis of N-O bond gives the lactam.

While a useful route, it does require the synthesis of a quaternary carbon center first.

Less common routes include a [3+2] cycloaddition followed by amide bond formation. Funk and co-workers showed that a [3+2] dipolar cycloaddition of a nitrone derived from a cyclic ketone with an olefin to give the spirocyclic isoxazolidine. Hydrogenolysis of N-O bond then leads to spontaneous formation of the lactam to give the product (Scheme 2.8).[25]

Finally Marco's group reported a synthetic pathway to these spirolactams most similar to what is reported herein (Scheme 2.9).[23] An imine can be formed from the condensation of a cyclic ketone and amine. This ketimine is then treated with ally Grignard reagent to give the alpha-tetrasubstituted homoallyl amine, similar to the traditional pathways used for preparing substrates discussed in Chapter 1. The free amine is acrylated then undergoes ring-closing metathesis. It



Scheme 2.9: Marco and co-workers approach requires the formation and isolation of an imine which is then reacted with allylmagnesium bromide. The free amine is then acrylated then undergoes ring-closing metathesis.

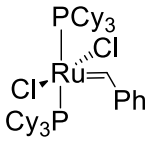
is notable that the 1st generation Grubbs catalyst was successful in inducing this reaction, but only in the presence of two equivalents of a titanium Lewis acid.

Given previous success with constructing these alpha-tetrasubstituted homoallyl amines, this synthetic pathway offered a new opportunity to create a library of structurally interesting small molecules.

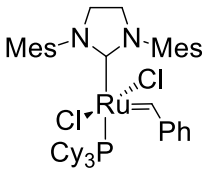
2.2 Synthesis of 2-Spiropiperdines

The previously established methodology for the tandem condensation-allylation of ketones and amines (Chapter 1), allowed for a convenient starting point for the synthesis of these spirocycles. Simple cyclic ketones (cyclopentanone, cyclohexanone etc.) had originally been shown to be incorporated into the reaction without major issue. Cyclopentanone was shown to give the best yields with no noticeable side products. While cyclohexanone is often a convenient choice as it does not require the presence of Lewis Acid to undergo condensation, the inherent nucleophilicity of the boronate ester led to a competitive

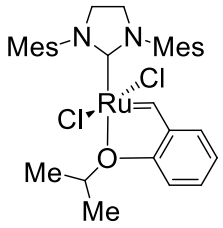
side reaction in which the ketone was directly allylated. This problem was not observed with cyclopentanone.



Grubbs Catalyst
1st Generation



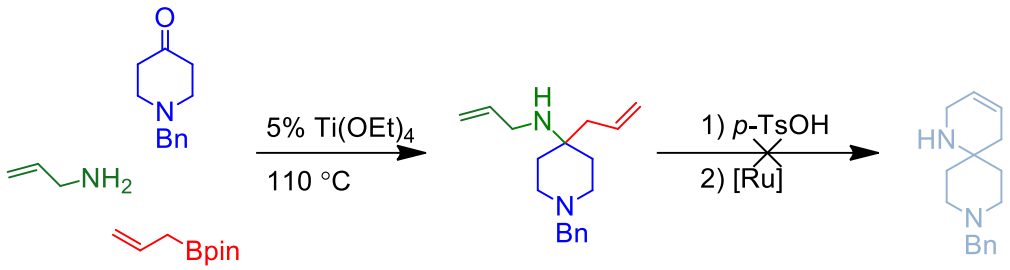
Grubbs Catalyst
2nd Generation



Hoveyda-Grubbs Catalyst
2nd Generation

Figure 2.3: Grubbs Catalysts screened for olefin metathesis.

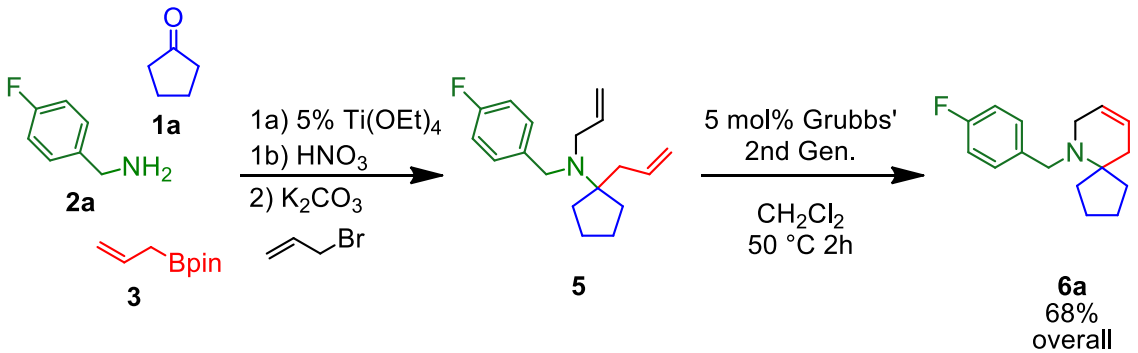
First attempts at making these spirocycles were done using a substrate made from the three-component reaction of *N*-benzylpiperidone, allylamine, and Allyl Bpin (Scheme 2.10). Gracias and co-workers had shown a multi-step one-pot synthesis of diazaspirocycles by protection of the free amine using p-toluenesulfonic acid (TsOH) followed by RCM using Grubbs 1st Gen.[26] These reaction conditions were replicated to the fullest possible extent, including using one of the reported substrates, however no reactivity was observed. As there had been no previous activity observed with the first-generation Grubbs catalyst, both the 2nd generation and Hoveyda-Grubbs 2nd Gen. were tried as well. The same lack of activity was again observed with only starting materials observed by both TLC and GC. It should be noted there was a concern that the dearth of reactivity on the part of the 1st Gen. Grubbs catalyst across various the reaction conditions mentioned here and in the previous chapter was possibly due to an aged batch of the catalyst. Two additional sources of the catalyst were tested to no avail,



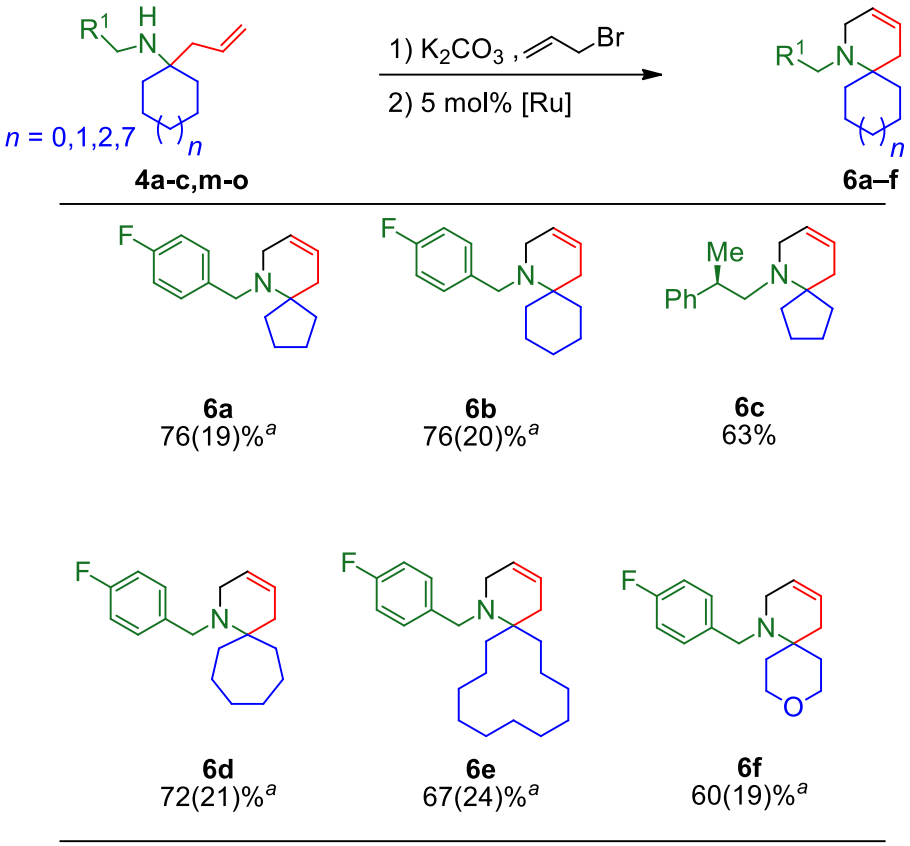
Scheme 2.10: First attempts at the synthesis of spirocycles utilized a published methodology and substrate. The free amine was to be protected via a Bronsted acid. No product formation was observed using the suggested catalyst or any others screened.

additionally a control cross-metathesis reaction with styrene and acrolein produced cinnamaldehyde without issue.

As the initial idea of synthesizing these 2-spiropiperdines failed the next approach would involve allylating the products of the three-component reaction to give the respective bis-allyl substrate (Scheme 2.11). These allylations could be carried out easily using allyl bromide and potassium carbonate and went to full conversion without issue. These bis-allyl substrates could be readily separated from any starting material (should any remain) by column chromatography. It was discovered early on that providing the reactions showed full consumption of the free a mine the product mixture could be run through a simple plug and used



Scheme 2.11: Synthetic approach to 2-spiropiperdine **5a** from commercially available starting materials requiring minimal column chromatography.

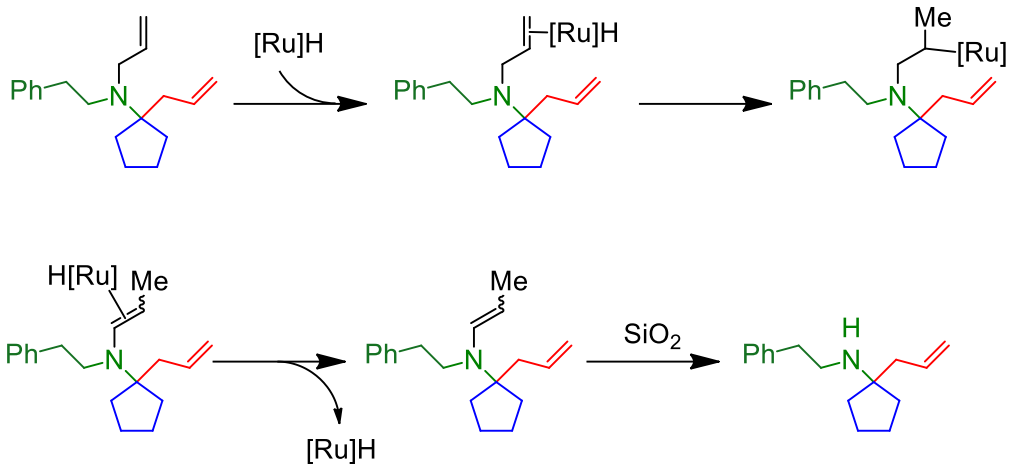


[a] Yields in parantheses are for the corresponding hydrochloride salt

Table 2.1: 2-Spiropiperdines prepared in two steps from condensation-allylation products. Yields given are over two steps.

without further purification in the following step. The ring-closing metathesis (RCM) was carried out with a Grubb's 2nd Generation catalyst (Figure 2.3). Hoveyda-Grubb's 2nd Generation catalyst was also shown to work, giving full conversion, but the reactions were observed to be not as clean by GC. When Grubb's 1st Generation catalyst was tested no activity was observed. A number of cyclic ketones were shown to work (Table 2.1).

In test cases it was discovered that some of the final products could be prepared with only a single column as the three-component substrates could be isolated via salting out with nitric acid and the allyl amines only required a simple



Scheme 2.12: Substrates undergo N-deallylation induced by ruthenium catalysts, and possibly by hydride impurities in them.

plug before RCM (Scheme 2.11). 2-Spiropiperdine **6a** could be prepared in 72% yield over three-steps. Of additional utility was the fact the three-component products could be used directly from their salt forms, requiring no free basing prior to allylation. It was observed that unless the column-purified spirocycles were then isolated as their corresponding hydrochloride salt and kept cold, there was notable degradation. This is possibly due to N-oxide formation but has not been confirmed.

Following the success of 4-fluorobenzylamine the substrate scope was expanded to other amines. Phenethylamines were attempted as this family of compounds (both simple and complex) are found in numerous biological molecules, and therapeutics. The three-component products could also be isolated with relative ease using hydrochloric acid to form the corresponding salt. While the allylations proceeded normally upon attempted RCM low conversion was

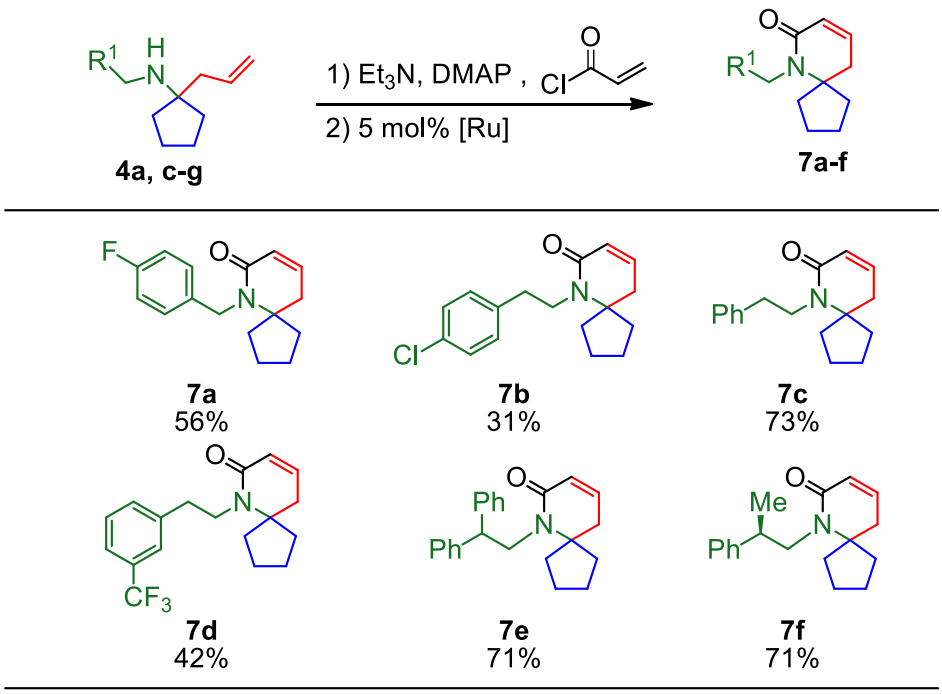


Table 2.2: α,β-Unsaturated δ-spirolactams are synthesized in two steps from condensation-allylation products. Yields shown are over two steps.

observed. Upon further investigation it was determined that under these conditions the ring-closing reaction was in competition with a de-allylation reaction of the starting material. This is not unknown and has been observed before.[27] After initial addition into the metal center the double bond can be isomerized, initially to the 1,2-di-substituted olefin and eventually the imine at which point it can be hydrolyzed upon column chromatography with silica (Scheme 2.12). Liberated free amine then leads to deactivation of the catalyst. This ruthenium-induced *N*-deallylation was optimized by Alcaide and co-workers for the purposes of selective deallylation of substrates in the presence of O-allylated functional groups. Attempting more vigorously dry conditions did not abate the problem. This variety of *N*-deallylation is more typically seen with either palladium(0) or (II) species.[28]

However, if instead of simple phenethylamines, a phenethylamine possessing an extra substituent at the 2-position hindered this side reaction (Table 2.1 **6c**).

2.3 Synthesis of δ-Spirolactams

Initial combinations showed that the 4-fluorobenzylamine derived substrates were tolerated without issue when it came to both acrylation and ring-closing metathesis. As with the corresponding allylation reactions the acrylamides could be flushed through a silica plug and used without further purification. Early attempts were met with success when trying to use the simple phenethylamine three-component products. The switch from an allylamine to an acrylamide omits the β-hydrogens required to undergo the isomerization of the side reaction and allow the reaction to proceed to completion. Yields of the final δ-spirolactams were

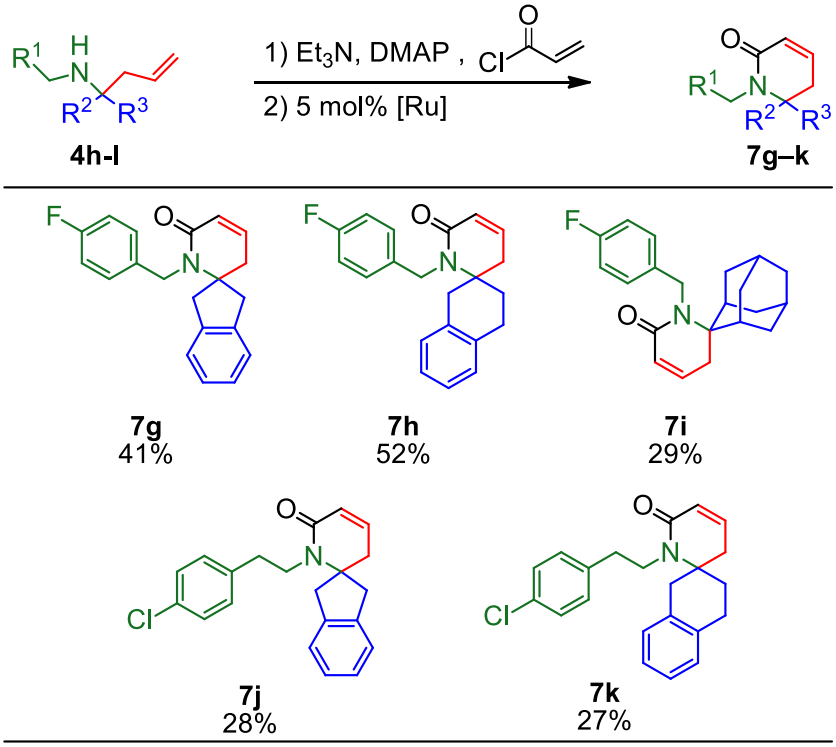
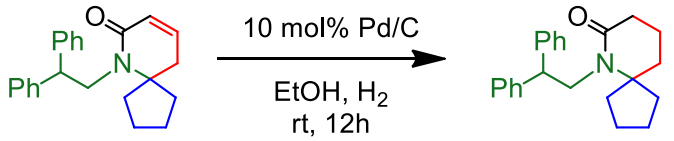


Table 2.3: α,β-Unsaturated δ-spirolactams were synthesized in two steps from condensation-allylation products from hindered ketones though in lower yields. Yields shown are over two steps.

ok to good (Table 2.2-2.3). Unlike previous approaches no additional Lewis acid is required for the reaction to proceed, and the reactions go to completion in 2 hours instead of 12-18.[8] Additionally, the α,β-unsaturated system offers a synthetic handle suitable for further transformations. Catalytic hydrogenation of **7e** was carried out to give the corresponding saturated δ-spirolactam, which was afforded in excellent yield and without column chromatography (Scheme 2.11). Unlike the corresponding 2-spiropiperdines the δ-spirolactams display considerably more bench top stability and can be left in ambient conditions in their free base form without any observed degradation.

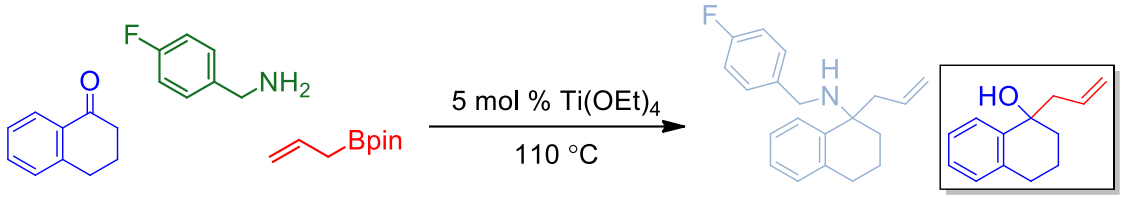
When compared to the methodology put forth by Marco and co-workers this methodology proceeds in only 2 hours compared to the, albeit standard, 12 hours reported by them. Their choice of catalyst (first generation Grubbs catalyst) was shown only to work in the presence of 2 equivalents of Ti(O*i*Pr)$_4$. The final ring-closing metathesis step in this case doesn't require the use of stoichiometric Lewis acid in order to proceed and more importantly the starting homoallyl amine is prepared without the use of organometallic reagents. Additionally (as with the 2-spiropiperdines) both the three-component coupling and *N*-protection reactions can be purified without the use of column chromatography.



7e **8** 94%

Scheme 2.13: α,β-Unsaturated spirolactam readily undergoes catalytic hydrogenation to give the saturated spirolactam.

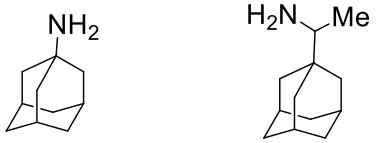
Along with simple cyclic ketones, more exotic and structurally diverse candidates could be incorporated including 2-tetralone, 2-



Scheme 2.14: Attempting to incorporate 1-tetralone into condensation-allylation results in production of homoallyl alcohol side product.

indanone, and adamantanone (Table 2.3). The other constitutional isomers of tetralone and indanone were attempted however failed to produce the desired product. While ketimine formation was not observed, allylation of the ketone and the resultant alcohol was the primary product formed (Scheme 2.14). While not surprising as aromatic ketones like acetophenone, had previously shown not be compatible with condensation-allylation reaction, it was posited that the release of torsional strain might be able to help drive the reaction.

The 2-adamantanone derived substrate **7i**, is of note not simply due to its structural novelty but reduced variants have shown notable antiviral activity, specifically against certain strains of the flu.[29] Simple aminoadamantanes such as amantadine and rimantadine (Figure 2.4) were previously prescribed as antiviral treatments for influenza, however in the last decade studies have shown that common strains of the flu responsible for large scale outbreaks have developed resistance rendering them ineffective.[30] As a result exploration into new therapeutics of this type are essential for the development of new treatments. The only other published synthesis for a delta-spirolactam skeleton containing the

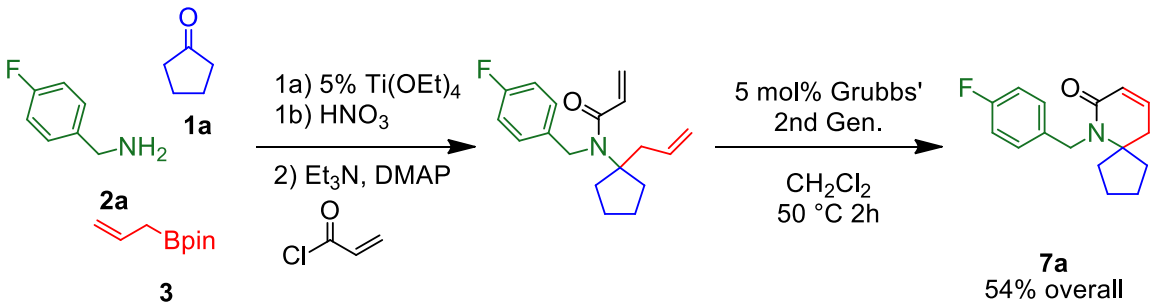


Amantadine Rimantadine

Figure 2.4: Simple aminoadamantanes like amantadine and rimantadine were previously prescribed for influenza treatment and prophylaxis.

adamantyl scaffold, is an 8-step synthesis from 2-nitroadamantane which was prepared in 3 steps from the oxime of 2-adamanatanone.[29] This approach requires multiple functional group interconversions along with use of aggressive reagents including hydride reducing agents, Raney nickel, and thionyl chloride. The resultant saturated spirolactam could then be reduced to the spiropiperidine and modified further for anti-viral screening. As this synthesis was published in 1996 before the popularization and wide-spread implementation of synthetic routes using ring-closing metathesis the lengthy construction of the heterocycle portion of the spirocycles is not surprising.

The above synthesis of the spirolactam and subsequent reduction to the spiropiperidine is emblematic of a more useful synthetic approach. While the lactam can be readily reduced to the piperidine, the reverse reaction does not occur as readily. Allylic oxidation of the carbon contiguous to the nitrogen does not occur with complete regioselectivity and has been shown in partially unsaturated piperidines to give the 4-piperidone instead of the α,β-unsaturated delta-lactam.[31] Furthermore Marco's group attempted allylic oxidation of an *N*-acylated 2-spiropiperidine without success. Reagents for both allylic oxidation



Scheme 2.15: Synthetic approach to delta-spirolactam **7a** from commercially available starting materials requiring minimal column chromatography.

(SeO_2/tBuOOH, PDC/tBuOOH, CrO_3-3,5-dimethylpyrazole etc.) as well as amine/amide oxidation (RuO_2/$NaIO_4$) were screened.[32] The authors note that the desired position did not undergo oxidation, and partial decomposition was observed along with recovery of some starting material. With these details in mind the rapid synthesis of delta-spirolactams shown herein offers a rapid and modular pathway to the synthesis of these spirocycles that involves minimal chromatography, harsh reagents, and yields products that possess benchtop stability. Additionally, the documented ability to reduce the lactam down to the piperidine offers an alternate route to the 2-spiropiperidine compounds discussed earlier.

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2.5 Supporting Information:

General Reagent Information:

All reactions were set up on the benchtop in test tubes equipped with magnetic stir bars and closed with screw caps. Flash column chromatography was performed using basic alumina gel or silica gel from Silicycle. Titanium(IV) tetraethoxide was purchased from Strem Chemical and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, Aldrich, or Oakwood and distilled before use. All ketones were purchased from Acros Organics, Alfa Aesar or TCI America and were purified by distillation before use. Allylboronic acid pinacol ester was purchased from Boron Molecular and purified by distillation before use.

General Analytical Information:

1H, 13C, and 19F NMR spectra were measured on a 500 and 400 MHz spectrometer using $CDCl_3$ as a solvent at room temperature. Some spectra include tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. Gas chromatography spectra were obtained using dodecane as an internal standard. For IR spectra, attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm-1). No sample preparation was necessary for ATR analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive

index, and its reflection at the interface between the crystal and the solid material. Mass spectrometric data was recorded on a ToF instrument using direct injection of samples in methanol into the electrospray source (ESI) and either positive or negative ionization.

Procedure for the synthesis of α-tetrasubstituted homoallyl amines A:

To an oven-dried test tube equipped with a magnetic stir bar was added 5 mol% $Ti(OEt)_4$, ketone (1.0 equiv.), amine (1.0 equiv.), and allylboronic acid pinacol ester (2.0 equiv.). The reaction was then stirred at 110 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop an alumina gel column. Chromatography with 5-20% ethyl acetate (EtOAc) in hexanes as eluent afforded product, identified by its brown spot from permanganate stain ($KMnO_4$) on TLC.

Procedure for the synthesis of α-tetrasubstituted homoallyl amines B:

To an oven-dried test tube equipped with a magnetic stir bar was added 5 mol% $Ti(OEt)_4$, ketone (1.0 equiv.), benzylamine (or substituted benzylamine) (1.0 equiv.), and allylboronic acid pinacol ester (2.0 equiv.). The reaction was then stirred at 110 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and rinsed with hexanes and diethyl ether (Et_2O). The mixture was then filtered through a short silica plug to remove the solid titanium dioxide. The resulting solution was then concentrated *in vacuo*. The crude oil was taken up in hexanes. To this a 1.5 M HNO_3 solution in Et_2O was added dropwise until no further product precipitated out. The solution was then vacuum

filtered, and the filter paper rinsed twice with hexanes. Additionally, the filtrate was tested with excess acidified ether to verify no product remained. The nitrate salts could be readily converted to free amine upon solvation with methylene chloride and washing with a satd. sodium bicarbonate solution.

Procedure for the synthesis of α-tetrasubstituted homoallyl amines C:

To an oven-dried test tube equipped with a magnetic stir bar was added 5 mol% $Ti(OEt)_4$, ketone (1.0 equiv.), phenethylamine (or substituted phenethylamine) (1.0 equiv.), and allylboronic acid pinacol ester (2.0 equiv.). The reaction was then stirred at 110 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and rinsed with hexanes and diethyl ether (Et_2O). The mixture was then filtered through a short silica plug to remove the solid titanium dioxide. The resulting solution was then concentrated *in vacuo*. The crude oil was taken up in hexanes. To this a 1.5 M HCl solution in Et_2O was added dropwise until no further product precipitated out. The solution was then vacuum filtered and the filter paper rinsed twice with hexanes. Additionally, the filtrate was tested with excess acidified ether to verify no product remained. The hydrochloride salts could be readily converted to free amine upon solvation with methylene chloride and washing with a satd. sodium bicarbonate solution.

General Allylation Procedure:

To an oven-dried test tube equipped with a magnetic stir bar was added either free amine or ammonium salt (1.0 equiv.), potassium carbonate (3.0 equiv.), and acetonitrile (2M). While stirring, to this was added allyl bromide (2.0 equiv.). After

addition, the reaction mixture was stirred at 50 °C for 4 hours. Upon completion the mixture concentrated *in vacuo,* dissolved in 5% Et_2O/Hexanes then flushed through a Florisil plug. The mixture was then concentrated *in vacuo* again and used without further purification.

General Acrylation Procedure:

To an oven-dried test tube equipped with a magnetic stir bar was added either free amine or ammonium salt (1.0 equiv.), triethylamine (3.0 equiv.), *N*,*N*-dimethylpyridine (0.1 equiv.), and methylene chloride (0.5 M). The tube was then purged with argon for 5 minutes. The mixture was cooled to 0 °C then acryloyl chloride (2.0 equiv.) was added dropwise. The reaction was warmed up to room temperature then stirred at 50 °C overnight. Upon completion the mixture concentrated *in vacuo,* dissolved in 5% Et_2O/Hexanes then flushed through a silica plug. The mixture was then concentrated *in vacuo* again and used without further purification.

General Catalytic Hydrogenation Procedure:

To an oven-dried test tube equipped with a magnetic stir bar was added δ-lactam (1.0 equiv.), palladium on carbon 10% wt. (0.1 equiv.), and ethanol (0.125 M). The tube was then vacuum and purged three times, and then equipped with a balloon of H_2. The reaction mixture was then allowed to stir for 18 hours at room temperature under H_2 atmosphere. The mixture was then filtered and washed through a short silica gel plug with a 50/50 EtOAc/Hexanes mixture.

General Ring-Closing Metathesis Procedure:

To an oven-dried test tube equipped with a stir bar was added Grubb's 2nd Generation catalyst (0.05 equiv.), and half the total volume of methylene chloride (0.1 M). The tube was then purged with argon for 5 minutes. While stirring, either allylamine or acrylamide (1.0 equiv.) was dissolved in the remaining methylene chloride and added dropwise. After addition the reaction was heated for 2 hours at 50 °C. The resultant product mixture was concentrated *in vacuo* and then loaded directly atop a silica column and eluted with EtOAc/Hexanes. Substrates (**4a** and **4b**) were then taken up in hexanes and treated with 1.5 M HCl in Et_2O to give the corresponding hydrochloride salt which was then vacuum filtered, rinsed with hexanes, and immediately dried *in vacuo* to remove any remaining solvent.

1-allyl-N-(4-fluorobenzyl)cyclopentanaminium nitrate (4a):

Prepared according to general procedure B: cyclopentanone (88 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 95% yield. See Chapter 1, substrate **4g** for spectroscopic data.

1-allyl-N-(4-fluorobenzyl)cyclohexanaminium nitrate (4b):

Prepared according to general procedure B: cyclohexanone (104 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after

precipitation as the nitrate salt in 86% yield. See Chapter 1, substrate **4h** for spectroscopic data.

(R)-1-allyl-N-(2-phenylpropyl)cyclopentanamine (4c):

Prepared according to general procedure A: cyclopentanone (88 µL, 1.0 mmol), R-(+)-β-methylphenethylamine (143 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 85% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H), 7.24-7.17 (m, 3H), 5.69 (ddt, *J* = 16.3, 10.7, 7.3 Hz, 1H), 5.05-4.94 (m, 2H), 2.81 (h, J = 6.9 Hz, 1H), 2.73-2.61 (m, 2H), 2.18 (ddt, *J* = 7.4, 2.5, 1.2 Hz, 2H), 1.66-1.37 (m, 8H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.9, 135.3, 128.6, 127.4, 126.4, 117.3, 64.3, 50.3, 42.0, 41.0, 37.2, 37.1, 24.2, 24.1, 20.3. IR (neat): 3027.5 (w), 2955.1 (m), 2868 (w), 1493.5 (w), 1450.9 (m), 1102.9 (w), 994.6 (w), 909.9 (m), 760.6 (m), 697.7 (s), 539.6 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 244.2060 found 244.2005.

1-allyl-N-(4-chlorophenethyl)cyclopentanaminium chloride (4d):

Prepared according to general procedure C: cyclopentanone (88 µL, 1.0 mmol), 2-(4-chlorophenyl)ethylamine (140 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the chloride salt in 85% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ

9.61 (s, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.97 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.30 (d, *J* = 10.1 Hz, 1H), 5.22 (dd, *J* = 16.9, 1.7 Hz, 1H), 3.44 – 3.34 (m, 2H), 3.16 – 2.97 (m, 2H), 2.50 (d, *J* = 7.1 Hz, 2H), 2.26 – 2.14 (m, 2H), 2.06-1.94 (m, 2H), 1.92-1.82 (m, 2H), 1.70 – 1.54 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.7, 133.1, 131.4, 130.2, 129.1, 121.1, 69.1, 44.6, 40.4, 35.2, 32.3, 24.4. IR (neat): 2943.8 (w), 2713.3 (w), 1585.7 (w), 1473.1 (w), 1091.0 (w), 1013.9 (w), 917.3 (m), 835.3 (w), 813.1 (w), 531.6 (w).HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 264.1514 found 264.1414.

1-allyl-N-phenethylcyclopentanamine (4e):

Prepared according to general procedure C: cyclopentanone (88 µL, 1.0 mmol), phenethylamine (126 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the chloride salt in 85% yield. Spectroscopic data is for the free amine. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 2H), 7.24-7.17 (m, 3H), 5.74 (ddt, *J* = 16.0, 11.5, 7.4 Hz, 1H), 5.08-4.88 (m, 2H), 2.83-2.70 (m, 4H), 2.21 (d, *J* = 7.4 Hz, 2H), 1.72-1.42 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ140.5, 135.3, 128.9, 128.5, 126.2, 117.5, 64.5, 44.5, 42.0, 37.4, 37.3, 24.3. IR (neat): 2951.9 (w), 2688.4 (w), 1588.7 (w), 1455.8 (w), 993.1 (w), 922.1 (w), 753.7 (w), 694.4 (m), 508.2 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 230.1903 found 230.1814.

1-allyl-N-(3-(trifluoromethyl)phenethyl)cyclopentanaminium chloride (4f):

Prepared according to general procedure C: cyclopentanone (88 µL, 1.0 mmol), 2-(3-trifluoromethylphenyl)ethylamine (160 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the chloride salt in 43% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 2H), 7.55-7.38 (m, 4H), 5.98 (ddt, *J* = 17.1, 10.0, 7.1 Hz, 1H), 5.32 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.24 (dd, *J* = 16.7, 1.7 Hz, 1H), 3.55-3.48 (m, 2H), 3.19-3.09 (m, 2H), 2.51 (d, *J* = 7.1 Hz, 2H), 2.23 (dt, *J* = 13.6, 7.1 Hz, 2H), 2.08-1.95 (m, 2H), 1.89 (dt, *J* = 13.2, 6.1 Hz, 2H), 1.71-1.58 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.2, 132.3, 131.6, 131.5 (q), 129.5, 124.1, 122.7, 121.1, 69.2, 44.4, 40.4, 35.2, 32.7, 24.5. IR (neat): 2950.2 (w), 2704.2 (w), 1586.7 (w), 1455.2 (w), 1329.2 (m), 1165.6 (m), 1119.8 (m), 1072.6 (m), 995.5 (w), 922.5 (m), 804.4 (m), 751.7 (w), 703.3 (m), 508.8 (w). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 298.1777 found 298.1740.

1-allyl-N-(2,2-diphenylethyl)cyclopentanamine (4g):

Prepared according to general procedure A: cyclopentanone (88 µL, 1.0 mmol), 2,2-diphenylethylamine (197 mg, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 68% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 8H), 7.24-7.15 (m, 2H), 5.70 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.10-4.95 (m, 2H), 4.09 (t, *J* = 7.5

Hz, 1H), 3.16 (d, *J* = 7.5 Hz, 2H), 2.23 (d, *J* = 7.3 Hz, 2H), 1.63-1.40 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.4, 135.3 ,128.7, 128.2, 126.6, 117.4, 64.5, 52.2, 47.9, 42.1, 37.1, 24.1. IR (neat): 3061.0 (w), 3026.0 (w), 2952.3 (m), 2966.1 (w), 1599.6 (w), 1493.3 (m), 1448.9 (m), 1102.0 (w), 994.6 (w), 911.0 (m), 738.5 (m), 696.2 (s), 661.7 (m), 474.5 (w). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 306.2216 found 306.2053.

2-allyl-N-(4-fluorobenzyl)-2,3-dihydro-1H-inden-2-amine (4h):

Prepared according to general procedure A: 2-indanone (132 mg, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 56% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H), 7.20-7.10 (m, 4H), 7.01-6.92 (m, 2H), 6.00 – 5.89 (m, 1H), 5.19 – 5.10 (m, 2H), 3.69 (s, 2H), 3.05 – 2.88 (m, 4H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.41 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 162.0 (d), 142.0, 136.9, 134.8, 129.8 (d), 126.5, 124.9, 118.2, 115.2 (d), 65.4, 46.9, 44.3, 42.5. IR (neat): 3069.5 (w), 2912.4 (w), 2838.1 (w), 1601.4 (m), 1507.3 (s), 1459.4 (m), 1292.0 (m), 1218.3 (s), 1154.0 (m), 1089.2 (m), 915.4 (m), 824.0 (m), 738.4 (s), 663.5 (m), 498.3 (m), 416.9 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 282.1653 found 282.1600.

2-allyl-N-(4-fluorobenzyl)-1,2,3,4-tetrahydronaphthalen-2-amine (4i):

Prepared according to general procedure A: 2-tetralone (132 µL, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 61% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.20 (m, 3H), 7.13 – 7.08 (m, 2H), 7.04 (d, *J* = 5.7 Hz, 1H), 6.94 (t, *J* = 8.7 Hz, 2H), 5.96 (ddt, *J* = 17.5, 10.3, 7.3 Hz, 1H), 5.21-5.09 (m, 2H), 3.73 (s, 2H), 2.96 – 2.87 (m, 1H), 2.84 – 2.76 (m, 3H), 2.39 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.29 (dd, *J* = 14.3, 7.4 Hz, 1H), 1.92 (dt, *J* = 12.8, 6.1 Hz, 1H), 1.76 (ddd, *J* = 13.9, 8.5, 6.0 Hz, 1H), 1.16 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.0 (d), 137.0, 136.0, 135.1, 134.3, 130.0, 129.9, 129.8, 128.8, 125.9, 118.1, 115.2 (d), 53.8, 45.3, 41.1, 40.7, 31.8, 26.1. IR (neat): 3068.9 (w), 2923.1 (w), 2841.2 (w), 1602.0 (w), 1507.3 (s), 1452.4 (m), 1218.7 (s), 1153.2 (m), 1089.5 (m), 1014.7 (w), 913.4 (m), 824.3 (s), 742.3 (s), 505.1 (m), 433.1 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 296.1809 found 296.1748.

(1R,3S,5r,7r)-2-allyl-N-(4-fluorobenzyl)adamantan-2-aminium nitrate (4j): Prepared according to general procedure B: 2-adamantanone (150 mg, 1.0 mmol), 4-fluorobenzylamine (114 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after precipitation as the nitrate salt in 40% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 2H), 7.48 (t *J* = 6.6 Hz, 2H), 7.00 (t, *J* = 8.3 Hz, 2H), 5.97 (dq, J = 16.6, 8.0 Hz,

1H), 5.42-5.20 (m, 2H), 4.16 (s, 2H), 2.79 (d, *J* = 7.0 Hz, 2H), 2.22-1.60 (m, 14H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.3 (d), 132.1 (d), 129.9, 127.2, 121.5, 116.2 (d), 67.7, 44.8, 38.4, 36.5, 33.6, 32.4, 31.5, 26.7, 26.4. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -112.6. IR (neat): 2976.2 (w), 2901.0 (m), 2858.1 (w), 1602.4 (w), 1507.8 (m), 1438.5 (m), 1325.0 (m), 1219.6 (m), 1139.0 (s), 1032.1 (m), 911.0 (m), 851.5 (m), 822.4 (m), 734.5 (m), 671.4 (m), 505.1 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 300.2122 found 300.2412.

2-allyl-N-(4-chlorophenethyl)-2,3-dihydro-1H-inden-2-amine (4k):

Prepared according to general procedure A: 2-indanone (132 mg, 1.0 mmol), 2-(4-chlorophenyl)ethylamine (140 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 87% yield. **1**H-NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 2H), 7.14 – 7.09 (m, 6H), 5.79 (ddt, *J* = 15.4, 11.3, 7.3 Hz, 1H), 5.10 – 5.01 (m, 2H), 2.92-2.84 (m, 4H), 2.79 (t, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.35 (d, *J* = 7.3 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.6, 138.4, 134.2, 132.1, 130.2, 128.7, 126.6, 124.8, 118.5, 65.3, 44.4, 43.8, 42.4, 36.1. IR (neat): 3069.5 (w), 2916.9 (w), 2845.3 (w), 1637.9 (w), 1490.4 (m), 1287.5 (m), 1089.8 (m), 1014.5 (m), 912.5 (m), 814.3 (m), 739.3 (s), 520.6 (m), 417.1 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 312.1514 found 312.1451.

2-allyl-N-(4-chlorophenethyl)-1,2,3,4-tetrahydronaphthalen-2-amine (4l): Prepared according to general procedure A: 2-tetralone (132 µL, 1.0 mmol), 2-(4-chlorophenyl)ethylamine (140 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 77% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2H), 7.13-6.95 (m, 6H), 5.80 (ddt, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.11-5.01 (m, 2H), 2.86-2.75 (m, 2H), 2.72-2.64 (m, 6H), 2.29-2.14 (m, 2H), 1.79 (dt, *J* = 12.7, 6.1 Hz, 1H), 1.65 (dt, *J* = 13.9, 7.3 Hz, 1H), 1.03 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.6, 135.7, 134.9, 133.9, 132.1, 130.2, 129.8, 128.8, 128.6, 125.9, 118.3, 70.6, 53.7, 53.7, 45.8, 42.9, 42.0, 40.8, 40.2, 36.3, 33.9, 31.5, 25.9. IR (neat): 3063.1 (w), 3018.9 (w), 2923.6 (m), 2842.4 (w), 1637.4 (w), 1491.4 (m), 1089.6 (m), 1014.4 (m), 913.5 (m), 810.5 (m), 742.7 (s), 630.0 (m), 517.9 (m), 432.6 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 326.1670 found 326.1438.

1-allyl-N-(4-fluorobenzyl)cycloheptanaminium nitrate (4m):

See Chapter 1, substrate **4i** for preparation procedure and spectroscopic data.

1-allyl-N-(4-fluorobenzyl)cyclododecanamine (4n): Prepared according to general procedure A: cyclododecanone (182 mg, 1.0 mmol), 2-(4-chlorophenyl)ethylamine (140 µL, 1.0 mmol), allyl boronic acid pinacol ester (375 µL, 2.0 mmol), and $Ti(OEt)_4$ (11.4 mg, 0.05 mmol) afforded the title compound after column chromatography on alumina gel (100% hexanes -> 20% EtOAc in hexanes) in 70% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.

97 (t, *J* = 8.7 Hz, 2H), 5.87 (ddt, *J* = 17.4, 10.2, 7.3 Hz, 1H), 5.23-5.09 (m, 2H), 3.61 (s, 2H), 2.49-2.43 (m, 1H), 2.18 (d, *J* = 7.1 Hz, 2H), 1.71 (p, *J* = 6.5 Hz, 1H), 1.48-1.14 (m, 20H), 0.89 (s, 1H). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 332.2748 found 332.2790.

4-allyl-N-(4-fluorobenzyl)tetrahydro-2H-pyran-4-amine (4o):

See Chapter 1, substrate **4k** for preparation procedure and spectroscopic data.

N,1-diallyl-N-(4-fluorobenzyl)cyclopentanamine (5):

Prepared according to general allylation procedure: 1-allyl-N-(4-fluorobenzyl)cyclopentanaminium nitrate (296 mg, 1.0 mmol), potassium carbonate (415 mg, 3.0 mmol), and allyl bromide (173 µL, 2.0 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 20% EtOAc in hexanes) in 78% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.4, 5.8 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 5.97 (ddt, *J* = 17.6, 10.4, 7.3 Hz, 1H), 5.67 (ddt, *J* = 16.6, 10.1, 6.4 Hz, 1H), 5.09 (d, 6.8 Hz, 1H), 5.06 (s, 1H), 4.93 (dd, 17.1, 1.6 Hz, 1H), 4.82 (10.1, 1.2 Hz, 1H), 3.73 (s, 2H), 3.26 (d, *J* = 6.4 Hz, 2H), 2.35 (d, *J* = 7.3 Hz, 2H), 1.77-1.65 (m, 4H), 1.65-1.49 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 161.7 (d), 138.8, 138.6, 136.5, 129.4 (d), 116.8, 115.1, 114.7 (d), 70.3, 54.5, 54.1, 41.0, 36.5, 24.6. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -118.8 IR (neat): 3073.0 (w), 2953.8 (m), 2869.9 (w), 1637.3 (w), 1603.0 (w), 1506.1 (s), 1218.0 (s), 1151.0 (m), 1088.1 (w), 994.0 (m), 909.5 (s), 820.4 (s), 500.3 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 274.1966 found 274.1911.

6-(4-fluorobenzyl)-6-azaspiro[4.5]dec-8-en-6-ium chloride (6a):

Prepared according to general ring closing-metathesis procedure: N,1-diallyl-N-(4-fluorobenzyl)cyclopentanamine (**5**, 55 mg, 0.2 mmol), and Grubb's 2nd gen. (9 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 97% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 12.43 (s, 1H), 7.73 (dd, *J* = 7.7, 5.4 Hz, 2H), 7.08 (t, *J* = 8.2 Hz, 2H), 5.97 (d, *J* = 9.8 Hz, 1H), 5.64 (d, *J* = 9.2 Hz, 1H), 4.46 (dd, *J* = 12.6, 2.4 Hz, 1H), 3.78 (dd, *J* = 12.0, 8.8 Hz, 1H), 3.67 (d, *J* = 17.4 Hz, 1H), 3.19 (dd, *J* = 17.8, 2.9 Hz, 1H), 2.70 (td, *J* = 21.1, 9.0 Hz, 2H), 2.39 (s, 2H), 2.16-1.95 (m, 3H), 1.85-1.60 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.6 (d), 133.9 (d), 125.8, 125.0, 118.7, 116.3 (d), 70.3, 52.2, 44.0, 35.9, 34.2, 31.8, 23.2, 22.5. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -111.9. IR (neat): 2963.2 (w), 2328.2 (m), 1459 (m), 1212.8 (m), 777.9 (m), 666.3 (m), 550.8 (m), 493.9 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 246.1653 found 246.1670.

1-(4-fluorobenzyl)-1-azaspiro[5.5]undec-3-en-1-ium chloride (6b):

Prepared according to general ring closing-metathesis procedure: N,1-diallyl-N-(4-fluorobenzyl)cyclohexanamine (prepared by allylation of **4b**, 57 mg, 0.2 mmol), and Grubb's 2nd gen. (9 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 84% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 12.75 (s, 1H), 7.74 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.00 (d, *J* = 8.7 Hz, 1H), 5.63 (dd, *J* = 10.4, 2.2 Hz, 1H), 4.63 (dd, *J* = 12.5, 3.7 Hz, 1H), 4.04 (ddd, *J* = 22.4, 12.1, 5.2 Hz, 2H), 3.70 – 3.60

(m, 2H), 3.52 (dtd, *J* = 26.7, 12.3, 2.0 Hz, 2H), 3.13 (d, *J* = 18.1 Hz, 1H), 2.95 (dd, *J* = 18.6, 4.4 Hz, 1H), 2.85 (tt, *J* = 12.2, 5.1 Hz, 2H), 2.42 (d, *J* = 19.2 Hz, 1H), 1.84 (t, *J* = 9.1 Hz, 2H).^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.6 (d), 134.0 (d), 125.8, 125.3, 118.2, 116.3 (d), 64.0, 49.6, 41.6, 32.9, 30.3, 28.0, 24.3, 22.5, 22.2. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -112.4. IR (neat): 2955.0 (m), 2421.4 (m), 1600.4 (w), 1508.6 (m), 1447.0 (m), 1218.8 (s), 665.7 (s), 533.3 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 260.1809 found 260.1820.

(R)-6-(2-phenylpropyl)-6-azaspiro[4.5]dec-8-ene (6c):

Prepared according to general ring closing-metathesis procedure: (R)-N,1-diallyl-N-(2-phenylpropyl)cyclopentanamine (prepared by allylation of **4c**, 128 mg, 0.45 mmol), and Grubb's 2nd gen. (19 mg, 0.02 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 64% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.6 Hz, 2H), 7.22-7.15 (m, 3H), 5.71 (dtt, *J* = 9.6, 3.9, 2.0 Hz, 1H), 5.57 (dt, *J* = 10.1, 2.6 Hz, 1H), 3.28 (dt, *J* = 18.1, 2.7 Hz, 1H), 3.09 (dt, *J* = 18.1, 2.6 Hz, 1H), 2.81 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.62-2.39 (m, 2H), 1.90 (dq, *J* = 4.9, 2.5 Hz, 2H), 1.74-1.40 (m, 8H), 1.29 (d, *J* = 6.9 Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 146.9, 128.3, 127.5, 126.0, 125.7, 125.3, 64.6, 58.8, 49.1, 39.6, 37.3, 36.8, 33.1, 24.3, 19.8. IR (neat): 3024.5 (w), 2954.0 (m), 2870.0 (m), 1450.8 (m), 1052.5 (m), 907.4 (w), 758.0 (m), 697.1 (s), 655.8 (m), 541.7 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 255.1987 found 255.1970.

1-(4-fluorobenzyl)-1-azaspiro[5.6]dodec-3-en-1-ium chloride (6d):

Prepared according to general ring closing-metathesis procedure: 1-allyl-N-(4-fluorobenzyl)cycloheptanaminium nitrate (prepared by allylation of **4m**, 128 mg, 0.45 mmol), and Grubb's 2nd gen. (19 mg, 0.02 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 72% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 12.22 (s, 1H), 7.79 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 5.87 (dq, *J* = 7.6, 2.4 Hz, 1H), 5.54 (d, *J* = 10.4 Hz, 1H), 4.67 (dd, *J* = 12.5, 3.9 Hz, 1H), 3.69 (dd, *J* = 12.6, 8.8 Hz, 1H), 3.39 (d, *J* = 17.4 Hz, 1H), 3.13-3.00 (m, 1H), 2.90 (d, *J* = 18.8 Hz, 1H), 2.79-2.69 (m, 1H), 2.34 (ddd, *J* = 18.7, 4.6, 2.1 Hz, 1H), 2.11-1.96 (m, 3H), 1.89 (dd, *J* =14.4, 8.9 Hz, 1H), 1.82-1.42 (m, 7H) . HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 274.1966 found 274.1950.

1-(4-fluorobenzyl)-1-azaspiro[5.6]dodec-3-en-1-ium chloride (6e):

Prepared according to general ring closing-metathesis procedure: 1-allyl-N-(4-fluorobenzyl)cyclododecanamine (prepared by allylation of **4n**, 128 mg, 0.45 mmol), and Grubb's 2nd gen. (19 mg, 0.02 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 67% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.6, 5.2, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 5.92 (d, *J* = 10.2 Hz, 1H), 5.57 (d, *J* = 10.4 Hz, 1H), 4.70 (dd, *J* = 12.6, 3.9 Hz, 1H), 3.76 (dd, *J* = 12.6, 8.8 Hz, 1H), 3.65 (d, *J* = 18.4 Hz, 1H), 3.16 (d, *J* = 17.9 Hz, 1H), 2.71 (d, *J* = 19.3 Hz, 1H), 2.28 (t, *J* = 15.6 Hz, 2H), 2.07-1.76 (m,

4H), 1.71-1.28 (m, 17H). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 344.2748 found 344.2799.

1-(4-fluorobenzyl)-9-oxa-1-azaspiro[5.5]undec-3-en-1-ium chloride (6f):

Prepared according to general ring closing-metathesis procedure: 4-allyl-N-(4-fluorobenzyl)tetrahydro-2H-pyran-4-amine (prepared by allylation of **4o**, 128 mg, 0.45 mmol), and Grubb's 2nd gen. (19 mg, 0.02 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 61% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 12.75 (s, 1H), 7.74 (dd, *J* = 8.5, 5.4, 2H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.00 (q, *J* = 4.4 Hz, 1H), 5.63 (ddd, *J* = 22.4, 12.1, 5.2 Hz, 1H), 4.63 (dd, *J* = 12.5, 3.7 Hz, 1H), 4.04 (ddd, *J* = 22.4, 12.1, 5.2 Hz, 1H), 3.73-3.60 (m, 2H), 3.52 (dtd, *J* = 26.7, 12.3, 2.0 Hz, 2H), 3.19-3.07 (m, 1H), 2.95 (dd, *J* = 18.6, 4.4 Hz, 1H), 2.86 (td, *J* = 12.5, 6.3 Hz, 2H), 2.42 (d, *J* = 19.2 Hz, 1H) 1.93-1.80 (m, 2H). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 262.1602 found 262.1598.

6-(4-fluorobenzyl)-6-azaspiro[4.5]dec-8-en-7-one (7a):

Prepared according to general ring closing-metathesis procedure: N-(1-allylcyclopentyl)-N-(4-fluorobenzyl)acrylamide (prepared by acrylation of **4a**, 142 mg, 0.5 mmol), and Grubb's 2nd gen. (21 mg, 0.025 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 50% EtOAc in hexanes) in 57% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.3,

5.3 Hz, 2H), 6.97 (t, *J* = 8.5 Hz, 2H), 6.50 (dd, *J* = 9.5, 4.6 Hz, 1H), 6.05 (d, *J* = 9.8 Hz, 1H), 4.59 (s, 2H), 2.39 (d, *J* = 4.3 Hz, 2H), 1.91 – 1.49 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9, 161.8 (d), 138.1, 135.5, 128.1 (d), 125.5, 115.3 (d), 67.2, 44.1, 37.3, 36.2, 23.8. ^{19}F-NMR (376 MHz, $CDCl_3$) δ -117.9. IR (neat): 2954.0 (m), 2873.5 (w), 1662.8 (s), 1604.4 (s), 1404.7 (s), 1217.3 (s), 477.1 (s). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 260.1445 found 260.1440.

6-(4-chlorophenethyl)-6-azaspiro[4.5]dec-8-en-7-one (7b):

Prepared according to general ring closing-metathesis procedure: N-(1-allylcyclopentyl)-N-(4-chlorophenethyl)acrylamide (prepared by acrylation of **4d**, 86 mg, 0.27 mmol), and Grubb's 2nd gen. (12 mg, 0.014 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 32% yield. **^{1}**H-NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.44 (dt, *J* = 9.7, 4.2 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 3.45 (t, *J* = 7.9 Hz, 2H), 2.86 (t, *J* = 7.9 Hz, 2H), 2.32 (dd, *J* = 4.2, 1.8 Hz, 2H), 1.69 (m, 8H), 3.19 (dd, *J* = 17.8, 2.9 Hz, 1H), 2.70 (td, *J* = 21.1, 9.0 Hz, 2H), 2.39 (s, 2H), 2.16-1.95 (m, 3H), 1.85-1.60 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.7, 138.2, 137.7, 132.1, 130.4, 128.6, 125.7, 66.9, 43.7, 37.2, 36.3, 35.6, 23.9. IR (neat): 2953.1 (m), 2871.1 (w), 1663.7 (s), 1608.3 (s), 1491.0 (m), 1410.9 (s), 1090.8 (m), 810.0 (s), 516.8 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 290.1306 found 290.1256.

6-phenethyl-6-azaspiro[4.5]dec-8-en-7-one (7c):

Prepared according to general ring closing-metathesis procedure: N-(1-allylcyclopentyl)-N-phenethylacrylamide (prepared by acrylation of **4e**, 139 mg, 0.49 mmol), and Grubb's 2nd gen. (21 mg, 0.025 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 15% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.38-7.12 (m, 5H), 6.43 (dq, *J* = 10.6, 3.6 Hz, 1H), 5.98 (dd, *J* = 9.9, 2.5 Hz, 1H), 3.49 (td, *J* = 7.9, 2.4 Hz, 2H), 2.90 (td, *J* = 7.9, 2.3 Hz, 2H), 2.32 (s, 2H), 1.85-1.37 (m, 8H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.6, 139.8, 137.5, 129.0, 128.5, 126.4, 125.9, 66.9, 43.9, 37.3, 36.4, 36.3, 23.9. IR (neat): 2949.6 (m), 2869.9 (w), 1662.6 (s), 1608.7 (s), 1412.2 (s), 1125.3 (m), 821.2 (m), 745.9 (m), 699.2 (s), 505.0 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 256.1696 found 256.1503.

6-(3-(trifluoromethyl)phenethyl)-6-azaspiro[4.5]dec-8-en-7-one (7d):

Prepared according to general ring closing-metathesis procedure: N-(1-allylcyclopentyl)-N-(3-(trifluoromethyl)phenethyl)acrylamide (prepared by acrylation of **4f**, 127 mg, 0.36 mmol), and Grubb's 2nd gen. (15 mg, 0.018 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 50% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.51-7.34 (m, 4H), 6.44 (dt, *J* = 9.0, 4.2 Hz, 1H), 5.97 (d, *J* = 9.7 Hz, 1H), 3.70-3.20 (m, 2H), 3.09-2.80 (m, 2H), 2.30 (dd, *J* = 4.2, 1.8 Hz, 2H), 1.76-1.45 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.8, 140.7, 137.8, 132.5, 130.8 (q), 128.9, 125.6, 124.3 (q),

123.2, 66.9, 43.5, 37.2, 36.3, 36.0, 23.8. IR (neat): 2955.6 (m), 2878.4 (w), 1665.6 (s), 1611.0 (s), 1440.6 (s), 1329.7 (s), 1120.2 (s), 703.9 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 324.1570 found 324.1349.

6-(2,2-diphenylethyl)-6-azaspiro[4.5]dec-8-en-7-one (7e):

Prepared according to general ring closing-metathesis procedure: N-(1-allylcyclopentyl)-N-(2,2-diphenylethyl)acrylamide (prepared by acrylation of **4g**, 200 mg, 0.56 mmol), and Grubb's 2nd gen. (24 mg, 0.03 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 86% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30-7.23 (m, 8H), 7.22-7.17 (m, 2H), 6.41 (dt, *J* = 9.7, 4.2 Hz, 1H), 5.96 (dd, 9.7, 1.9 Hz, 1H), 4.53 (t, *J* = 7.7 Hz, 1H), 3.89 (d, *J* = 7.7 Hz, 2H), 2.09 (dd, *J* = 4.2, 1.8 Hz, 2H), 1.66-1.54 (m, 2H), 1.54-1.41 (m, 4H), 1.39-1.32 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.6, 142.9, 138.1, 128.8, 128.3, 126.6, 125.8, 67.3, 49.2, 47.0, 36.6, 35.8, 23.4. IR (neat): 2964.4 (w), 2872.2 (w), 1663.1 (m), 1606.7 (m), 1494.7 (m), 1449.5 (m), 1406.5 (m), 1327.0 (m), 1259.2 (w), 1128.5 (m), 1035.5 (m), 910.4 (w), 825.7 (m), 789.5 (m), 739.8 (m), 700.4 (s), 546.6 (m), 480.9 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 332.2009 found 332.1962.

(R)-6-(2-phenylpropyl)-6-azaspiro[4.5]dec-8-en-7-one (7f):

Prepared according to general ring closing-metathesis procedure: (R)-N-(1-allylcyclopentyl)-N-(2-phenylpropyl)acrylamide (prepared by acrylation of **4c**, 119

mg, 0.4 mmol), and Grubb's 2nd gen. (17 mg, 0.02 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 84% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 6.42 (dt, *J* = 9.1, 4.2, 1H), 5.96 (d, *J* = 9.7 Hz, 1H), 3.77 (dd, *J* = 13.5, 7.1 Hz, 1H), 3.17 (h, *J* = 7.2 Hz, 1H), 3.03 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.21 (d, *J* = 4.3 Hz, 2H), 1.85-1.79 (m, 1H), 1.67-1.45 (m, 6H), 1.31 (d, *J* = 7.0 Hz, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.4, 145.0, 137.7, 128.3, 127.5, 126.4, 125.8, 67.1, 48.8, 39.4, 36.6, 36.1, 35.3, 23.4, 23.0, 18.4. IR (neat); 2960.3 (m), 2873.5 (w), 1664.5 (s), 1606.0 (s), 1409.2 (s), 1095.3 (m), 909.0 (m), 728.1 (s), 699.6 (s), 534.8 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 270.1852 found 270.1814.

1'-(4-fluorobenzyl)-1,3-dihydro-1'H-spiro[indene-2,2'-pyridin]-6'(3'H)-one (7g):

Prepared according to general ring closing-metathesis procedure: N-(2-allyl-2,3-dihydro-1H-inden-2-yl)-N-(4-fluorobenzyl)acrylamide (prepared by acrylation of **4h**, 117 mg, 0.35 mmol), and Grubb's 2nd gen. (15 mg, 0.017 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 55% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21-7.10 (m, 6H), 6.99 (t, *J* = 8.6 Hz, 2H), 6.58 (dt, *J* = 9.1, 4.3 Hz, 1H), 6.15 (d, *J* = 9.8 Hz, 1H), 4.66 (s, 2H), 3.28 (d, *J* = 16.5 Hz, 2H), 2.99 (d, *J* = 16.5 Hz, 2H), 2.58 (d, *J* = 2.3 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9, 161.9 (d), 140.1, 138.2, 135.2, 128.1 (d), 127.2, 125.6, 124.8, 115.5 (d), 67.3, 44.7, 43.6, 37.6. ^{19}F-NMR (376 MHz,

$CDCl_3$) δ -117.6. IR (neat): 2934.4 (w), 1663.4 (m), 1606.6 (m), 1508.5 (m), 1405.6 (m), 1220.2 (m), 905.8 (s), 723.9 (s). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 307.1372 found 307.1385.

1'-(4-fluorobenzyl)-3,4-dihydro-1H,1'H-spiro[naphthalene-2,2'-pyridin]-6'(3'H)-one (7h):

Prepared according to general ring closing-metathesis procedure: N-(2-allyl-1,2,3,4-tetrahydronaphthalen-2-yl)-N-(4-fluorobenzyl)acrylamide (prepared by acrylation of **4i**, 157 mg, 0.45 mmol), and Grubb's 2nd gen. (19 mg, 0.023 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 73% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.24-7.19 (m, 2H), 7.17-7.06 (m, 3H), 7.01-6.94 (m, 3H), 6.47 (ddd, *J* = 9.7, 5.1, 3.6 Hz, 1H), 6.14 (dt, *J* = 9.8, 1.8 Hz, 1H), 4.83 (d, *J* = 16.0 Hz, 1H), 4.58 (d, *J* = 15.9 Hz, 1H), 3.11-2.66 (m, 4H), 2.47 (ddd, *J* = 17.9, 5.1, 1.5 Hz, 1H), 2.38 (dt, *J* = 18.1, 3.2 Hz, 1H), 2.15 (ddd, *J* = 12.8, 11.2, 6.4 Hz, 1H), 1.79 (dddd, *J* = 12.7, 5.5, 3.4, 1.9, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ165.0, 161.8 (d), 137.4, 135.7, 134.3 (d), 129.5, 128.8, 128.6, 128.5, 126.5, 126.4, 125.1, 115.4 (d). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -117.5. IR (neat): 2934.8 (w), 1664.8 (s), 1603.4 (s), 1507.4 (s), 1406.6 (s), 1218.1 (s), 898.9 (m), 749.0 (s), 728.8 (s), 530.6 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 321.1529 found 321.1520.

(1R,3S,5r,7r)-1'-(4-fluorobenzyl)-1'H-spiro[adamantane-2,2'-pyridin]-6'(3'H)-one (7i):

Prepared according to general ring closing-metathesis procedure: N-((1R,3S,5r,7r)-2-allyladamantan-2-yl)-N-(4-fluorobenzyl)acrylamide (prepared by acrylation of **4j**, 65 mg, 0.18 mmol), and Grubb's 2nd gen. (9 mg, 0.01 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 63% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 8.4, 5.4 Hz, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.49 (dt, *J* = 9.2, 4.5 Hz, 1H), 6.13 (d, *J* = 9.5 Hz, 1H), 4.98 (s, 2H), 2.68-2.59 (m, 2H), 2.12 (s, 4H), 1.95 (d, *J* = 13.5 Hz, 2H), 1.83 (s, 2H), 1.70-1.54 (m, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 167.8, 161.5 (d), 136.9, 136.2, 128.4 (d), 127.4, 115.0 (d), 64.2, 46.9, 39.1, 35.4, 35.2, 34.5, 33.8, 27.2, 27.0. IR (neat): 2911.4 (m), 1710.7 (m), 1655.4 (m), 1605.0 (m), 1508.2 (m), 1397.6 (m), 1358.8 (m), 1218.9 (s), 1156.3 (m), 1089.0 (m), 984.6 (m), 921.6 (m), 816.4 (s), 730.0 (m), 542.9 (m), 500.6 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 326.1915 found 326.1858.

1'-(4-chlorophenethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-pyridin]-6'(3'H)-one (7j):

Prepared according to general ring closing-metathesis procedure: N-(2-allyl-2,3-dihydro-1H-inden-2-yl)-N-(4-chlorophenethyl)acrylamide (prepared by acrylation of **4k**, 164 mg, 0.44 mmol), and Grubb's 2nd gen. (19 mg, 0.02 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5%

EtOAc in hexanes) in 40% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.14 (m, 6H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.52 (dt, *J* = 9.1, 4.2 Hz, 1H), 6.05 (d, *J* = 9.7 Hz, 1H), 3.52-3.41 (m, 2H), 3.21 (d, J = 16.5 Hz, 2H), 3.02 (d, *J* = 16.5 Hz, 2H), 2.81-2.69 (m, 2H), 2.53 (d, *J* = 2.4 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.5, 140.3, 138.0, 137.7, 132.1, 130.4, 128.6, 127.3, 125.9, 124.8, 67.1, 44.5, 44.1, 37.6, 35.2. IR (neat): 2935.7 (w), 1662.5 (s), 1606.7 (s), 1408.0 (s), 1090.8 (m), 1015.0 (m), 908.2 (m), 726.1 (s). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 337.1233 found 337.1240.

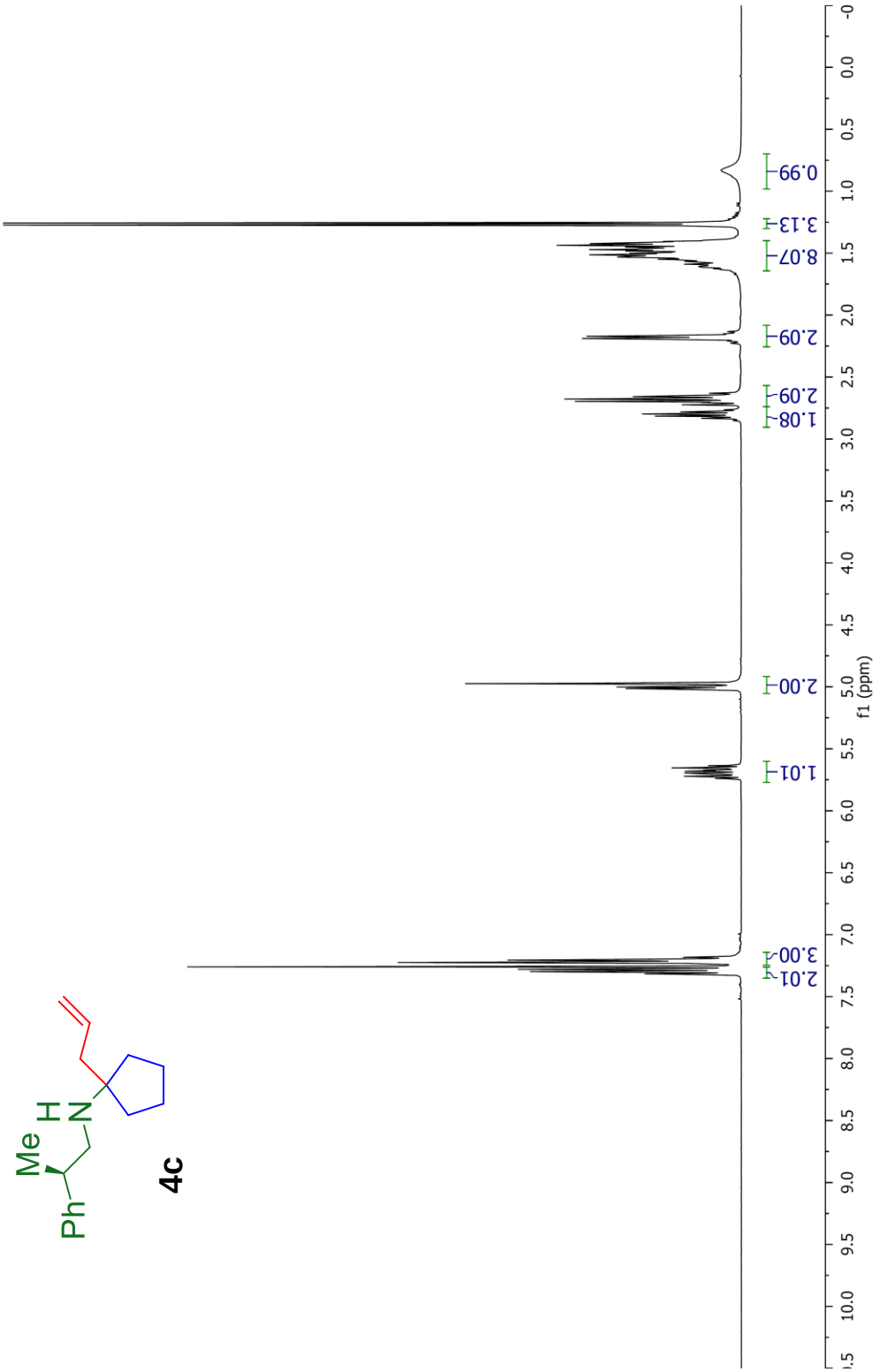
1'-(4-chlorophenethyl)-3,4-dihydro-1H,1'H-spiro[naphthalene-2,2'-pyridin]-6'(3'H)-one (7k):

Prepared according to general ring closing-metathesis procedure: N-(2-allyl-1,2,3,4-tetrahydronaphthalen-2-yl)-N-(4-chlorophenethyl)acrylamide (prepared by acrylation of **4l**, 194 mg, 0.51 mmol), and Grubb's 2nd gen. (21 mg, 0.025 mmol) afforded the title compound after column chromatography on silica gel (100% hexanes -> 5% EtOAc in hexanes) in 41% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.2 Hz, 2H), 7.18-7.08 (m, 5H), 7.03-6.98 (m, 1H), 6.41 (dt, *J* = 9.1, 4.3 Hz, 1H), 6.05 (dd, *J* = 9.6, 2.1 Hz, 1H), 3.67-3.46 (m, 2H), 3.02-2.70 (m, 6H), 2.41 (dd, *J* = 18.4, 4.5 Hz, 1H), 2.31 (dt, *J* = 17.6, 3.0 Hz, 1H), 2.27-2.17 (m, 1H), 1.86 (dt, *J* = 12.7, 4.1 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.2, 138.2, 136.7, 134.4, 134.3, 132.2, 130.4, 129.4, 128.8, 128.6, 126.5, 125.5, 57.9, 43.2, 37.5, 35.8, 33.6, 32.5, 26.7. IR (neat): 2929.9 (m), 1665.4 (s), 1609.6 (s), 1492.0 (m), 1415.6 (s),

1091.2 (m), 812.7 (m), 750.4 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 352.1463 found 352.1135.

6-(2,2-diphenylethyl)-6-azaspiro[4.5]decan-7-one (8) :

Prepared according to general catalytic hydrogenation procedure: 6-(2,2-diphenylethyl)-6-azaspiro[4.5]dec-8-en-7-one (**7e**, 33 mg, 0.1 mmol), palladium on carbon 10% wt (11 mg, 0.01 mmol), and EtOH (0.8 mL) afforded the title compound after filtration on silica gel (50% EtOAc in hexanes) in 94% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 10H), 4.80 (t, *J* = 7.5 Hz, 1H), 3.77 (d, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 6.7 Hz, 2H), 1.74 – 1.66 (m, 2H), 1.61 – 1.49 (m, 4H), 1.47 – 1.40 (m, 2H), 1.39 – 1.29 (m, 2H), 1.18 – 1.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.3, 143.1, 128.9, 128.3, 126.5, 68.3, 48.7, 47.6, 36.4, 36.1, 33.4, 24.0, 17.9. IR (neat): 2944.6 (m), 1629.0 (m), 1598.6 (m), 1445.7 (m), 1401.7 (m), 1365.8 (m), 699.2 (s), 549.8 (m). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 334.2165 found 334.1889.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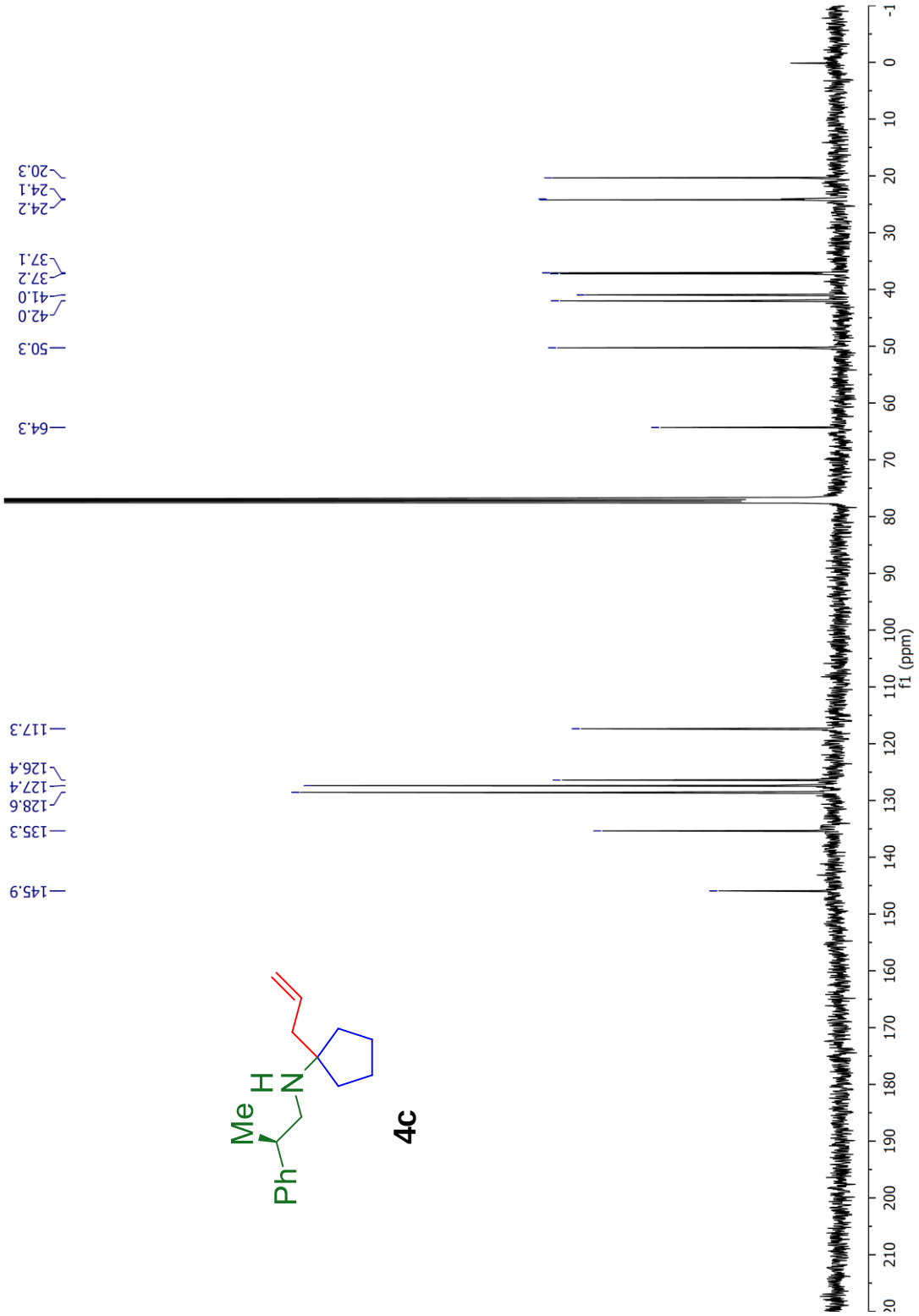
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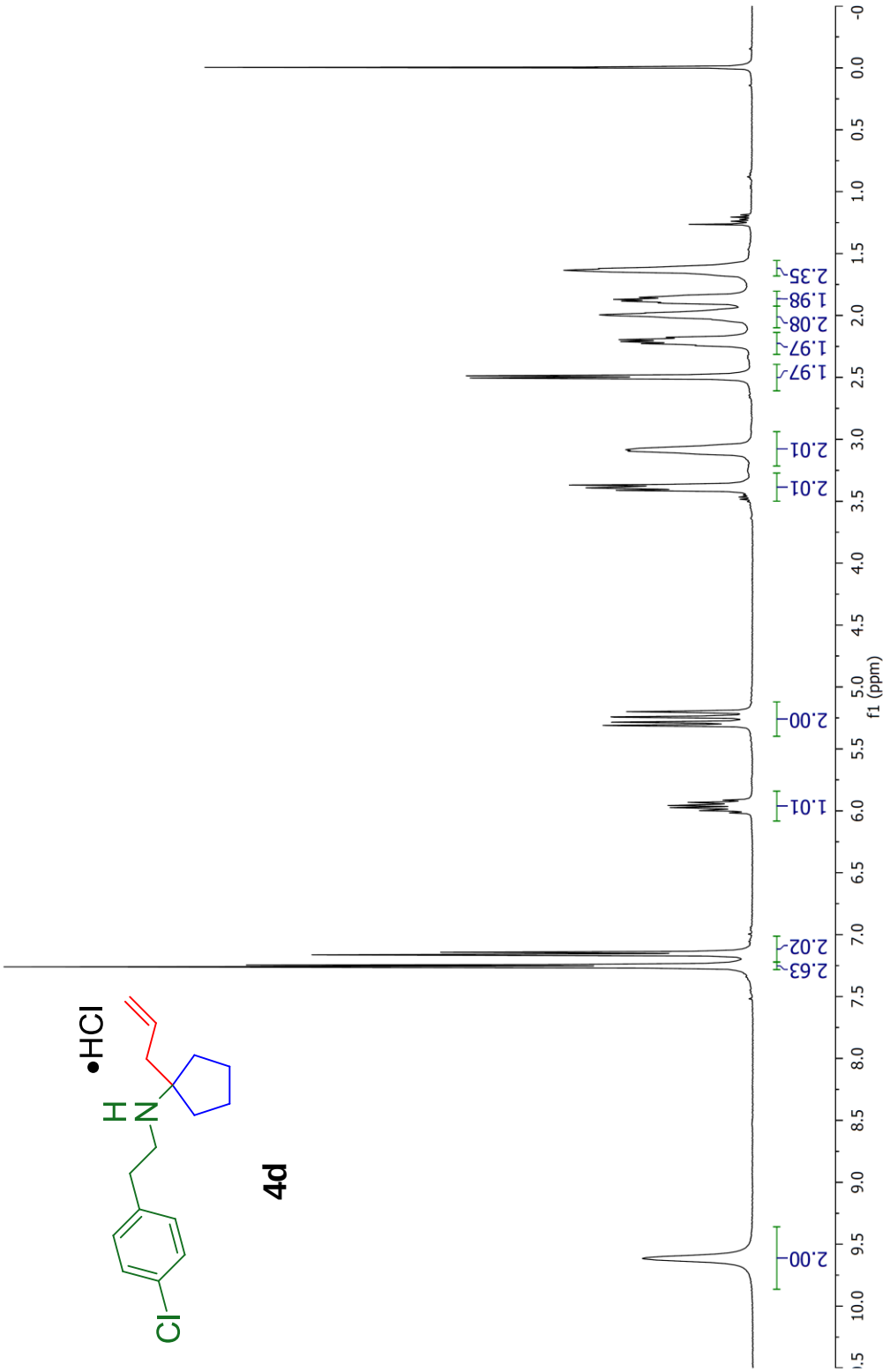
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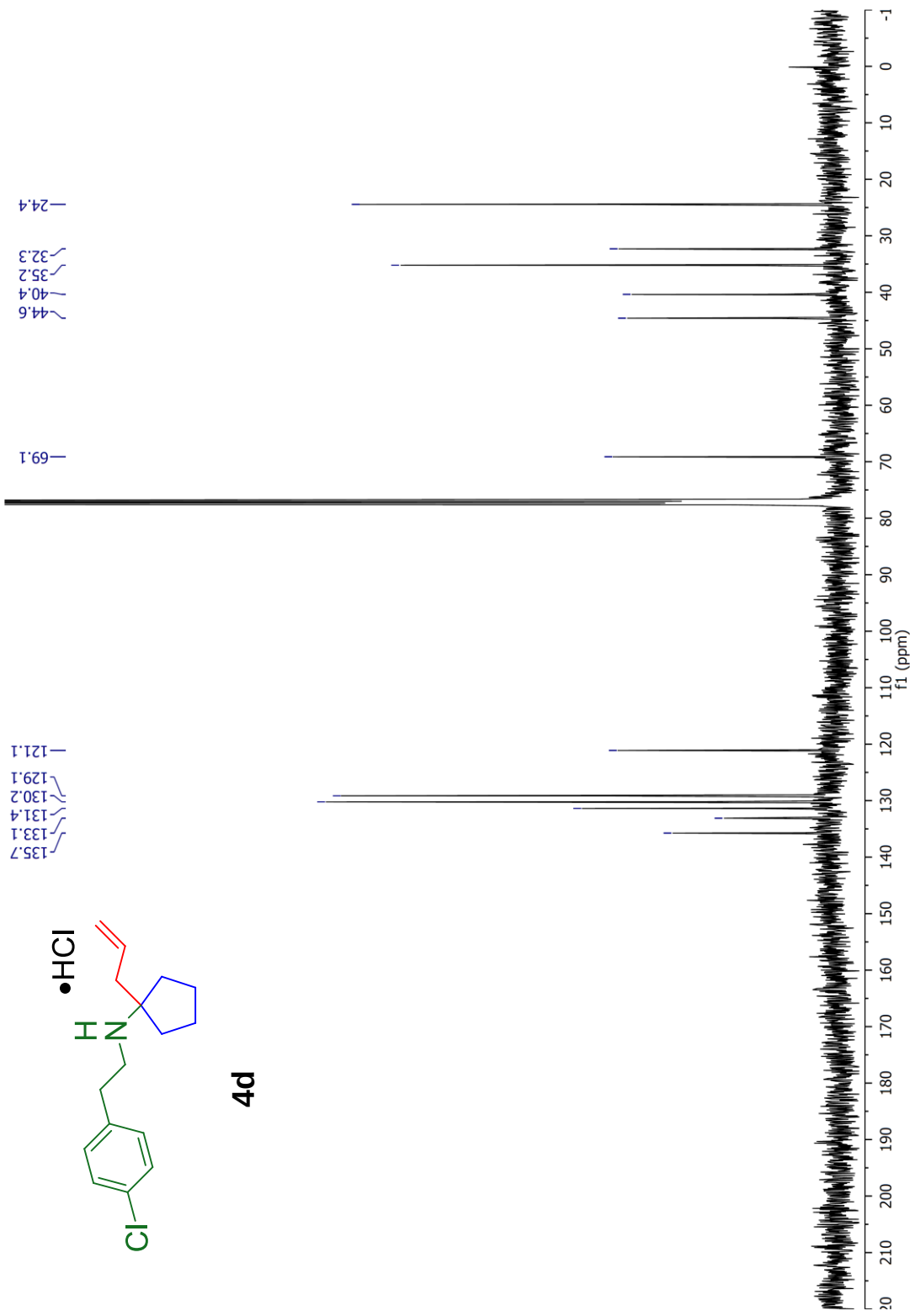
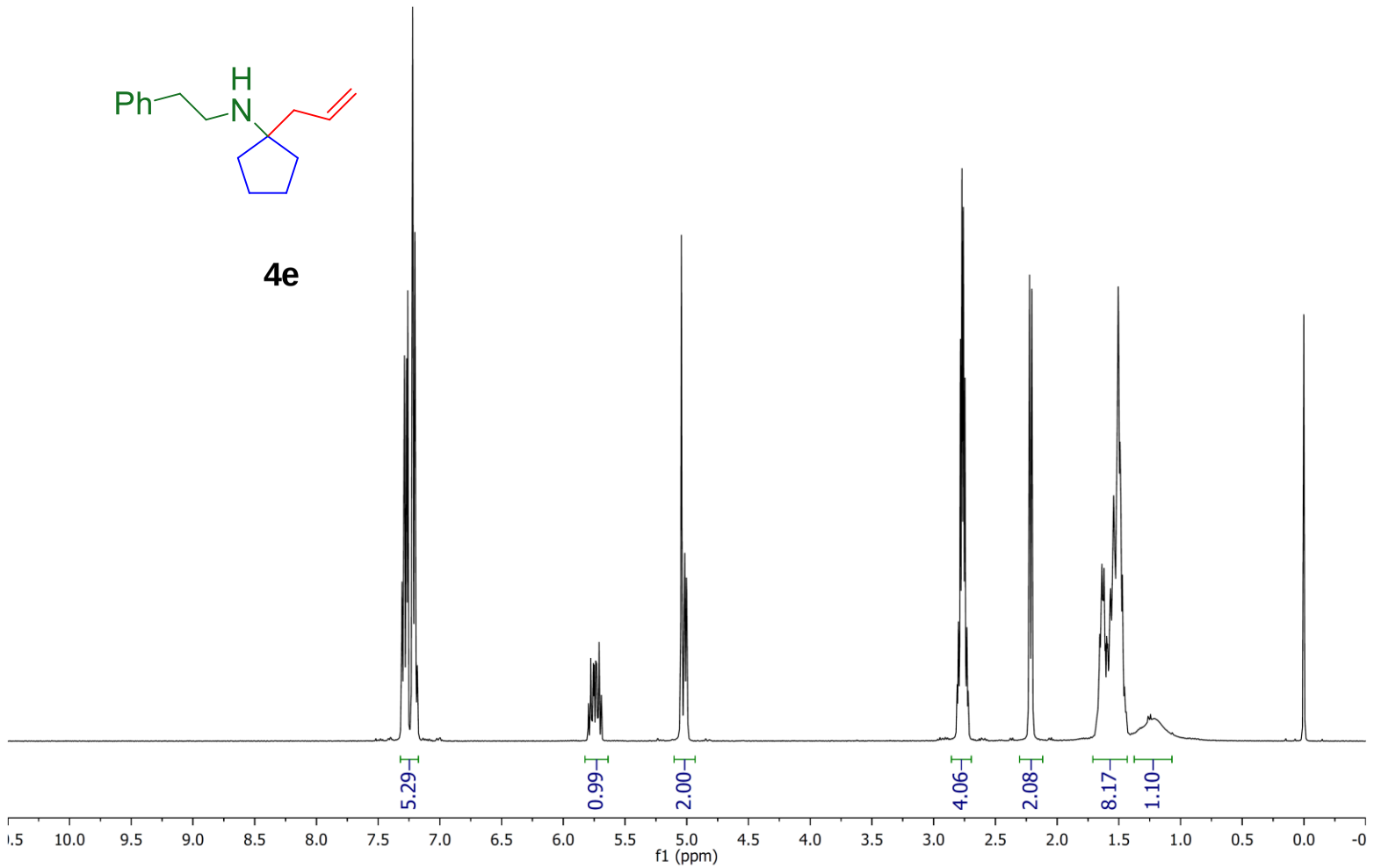
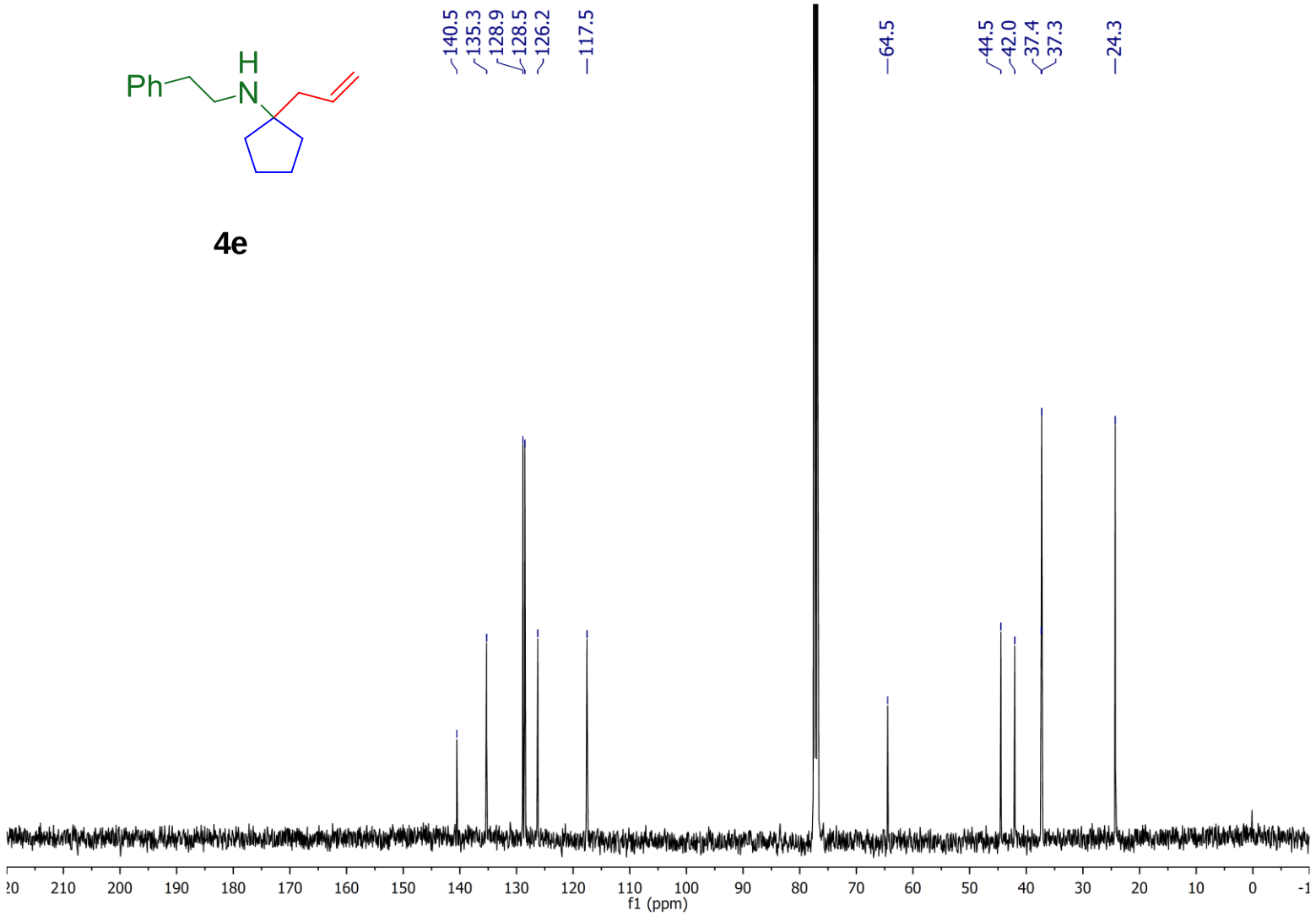
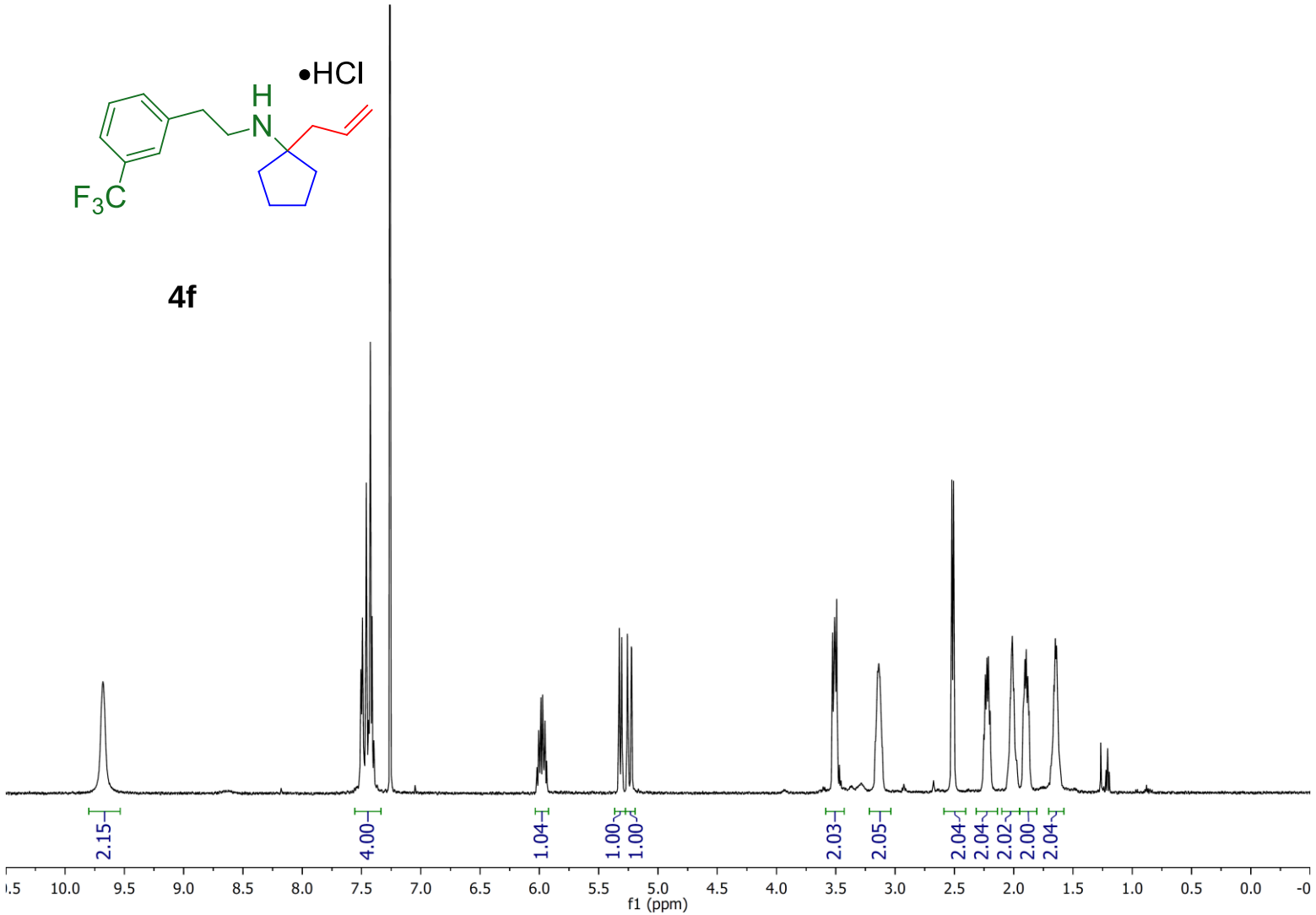
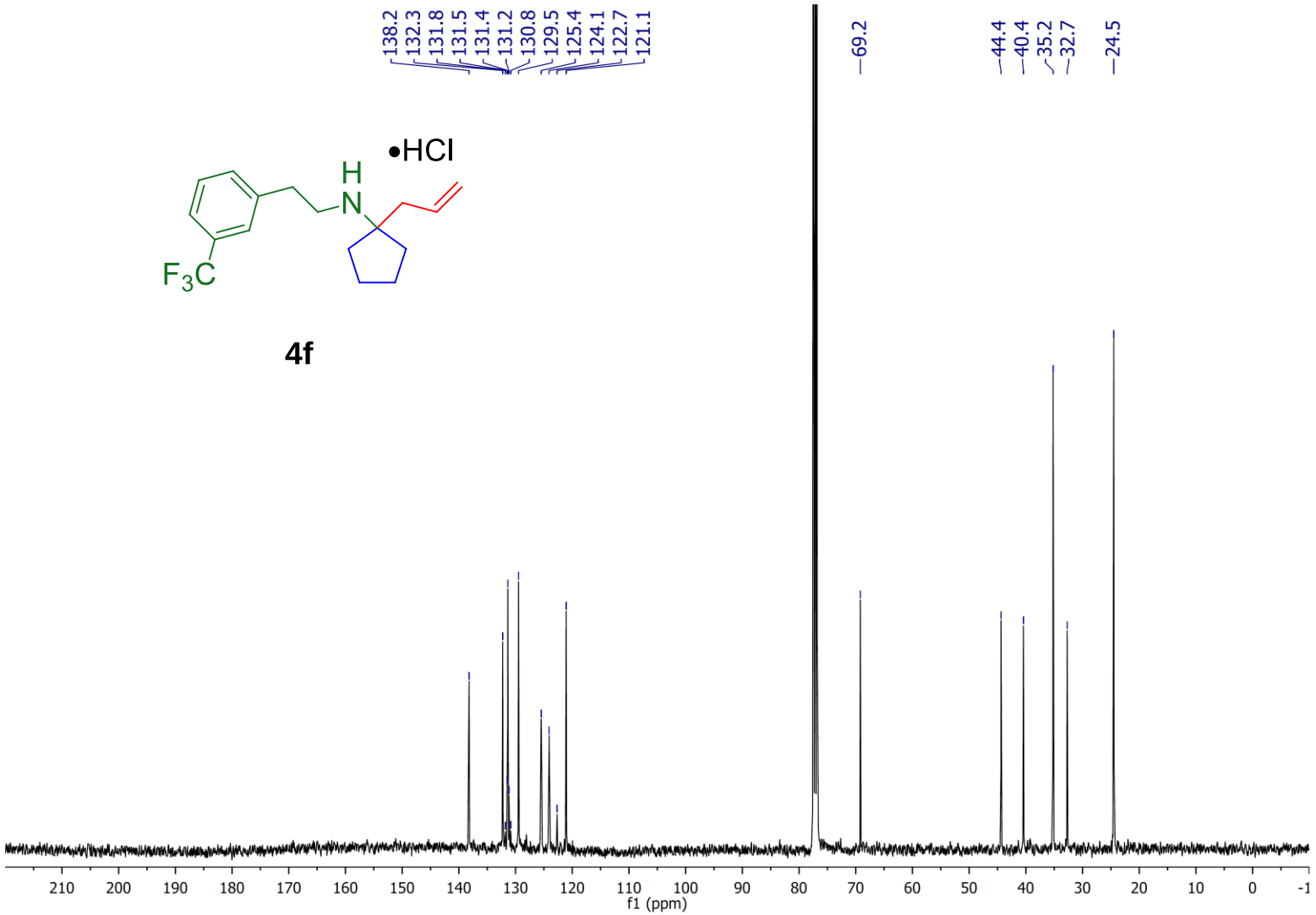
2.35
f1 (ppm)

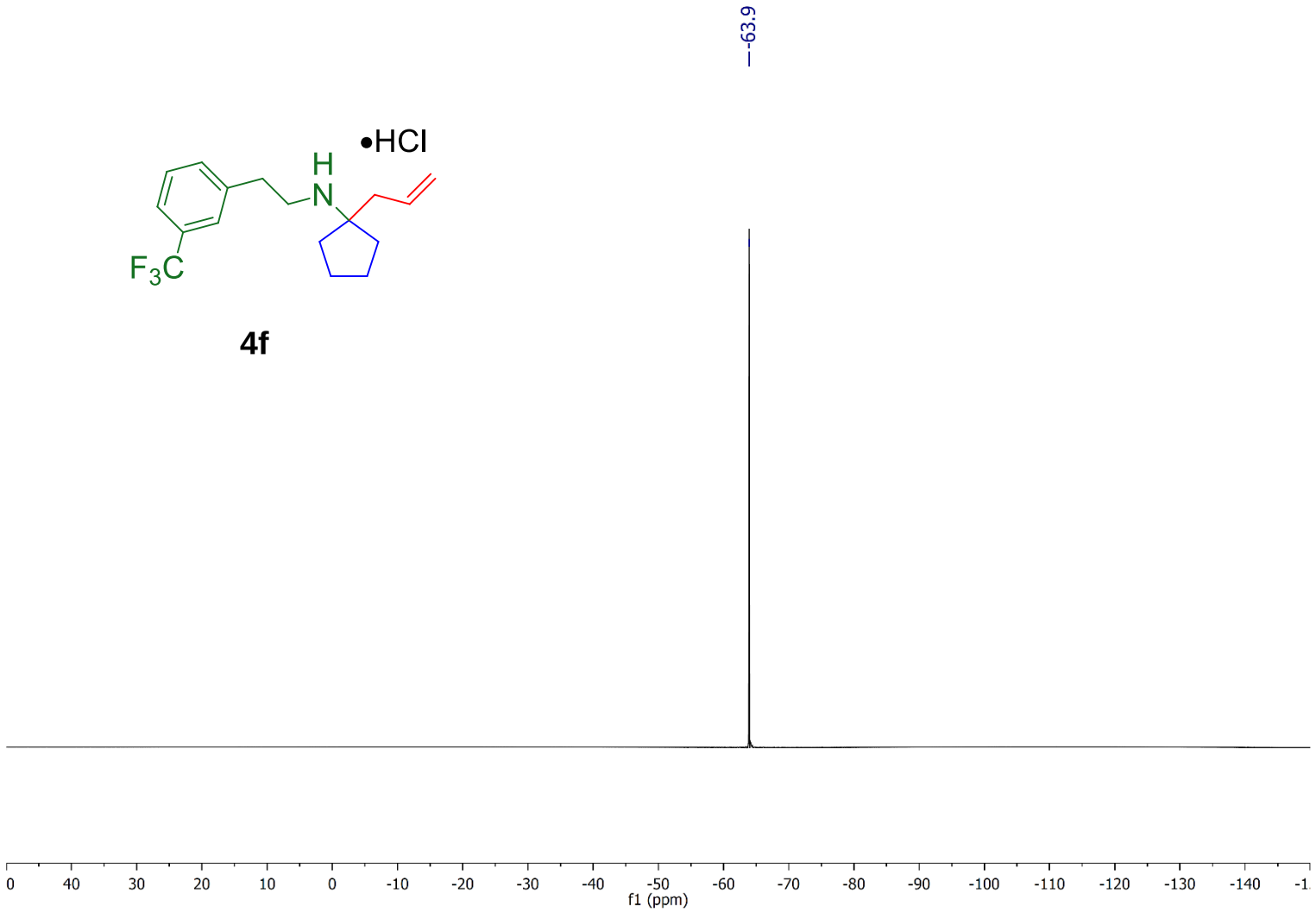

•HCl
H
N
Cl
4d
135.7
133.1
131.4
130.2
129.1
121.1
69.1
44.6
40.4
35.2
32.3
24.4
f1 (ppm)

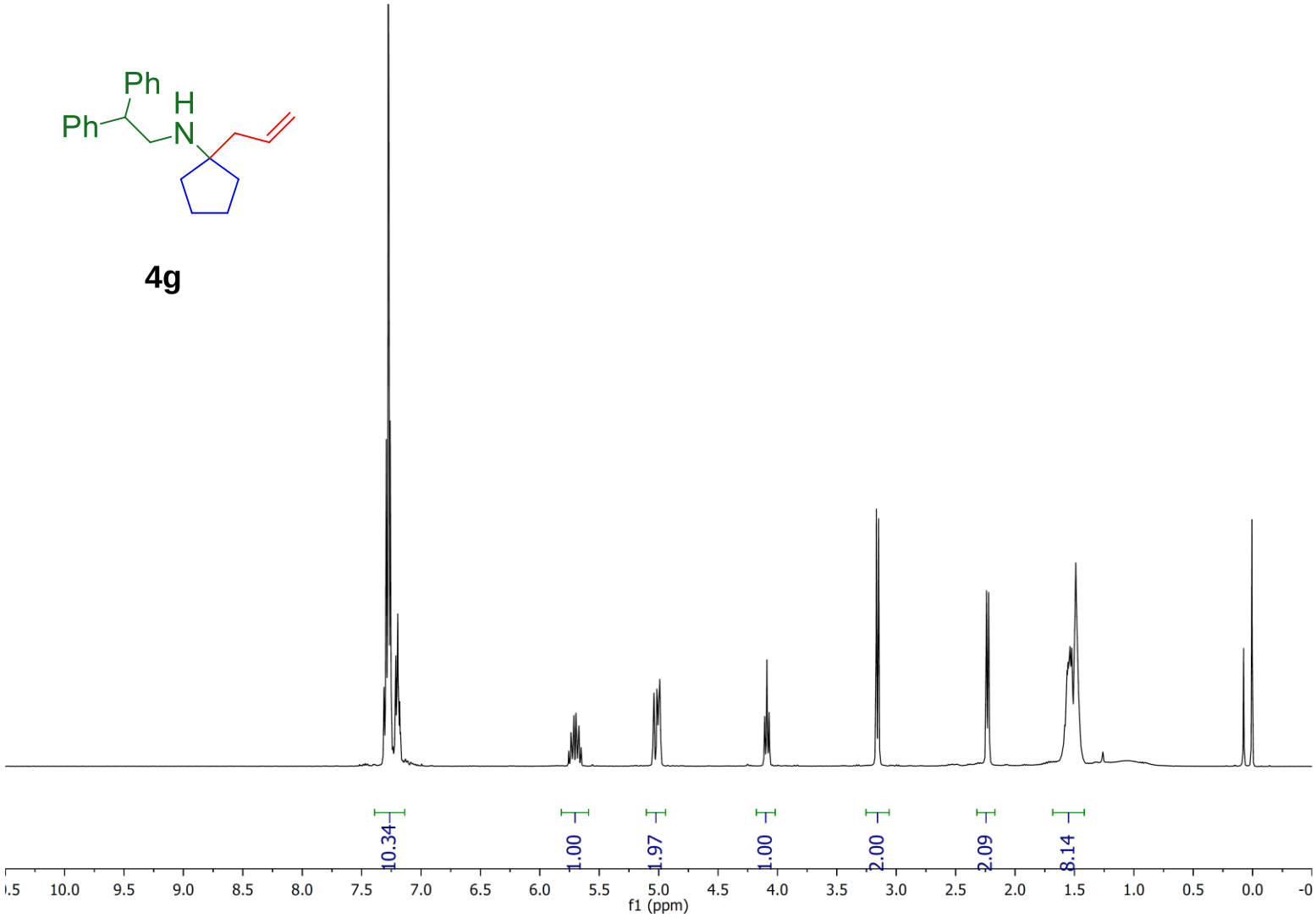

Ph
H
N
4e
5.29
0.99
2.00
4.06
2.08
8.17
1.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

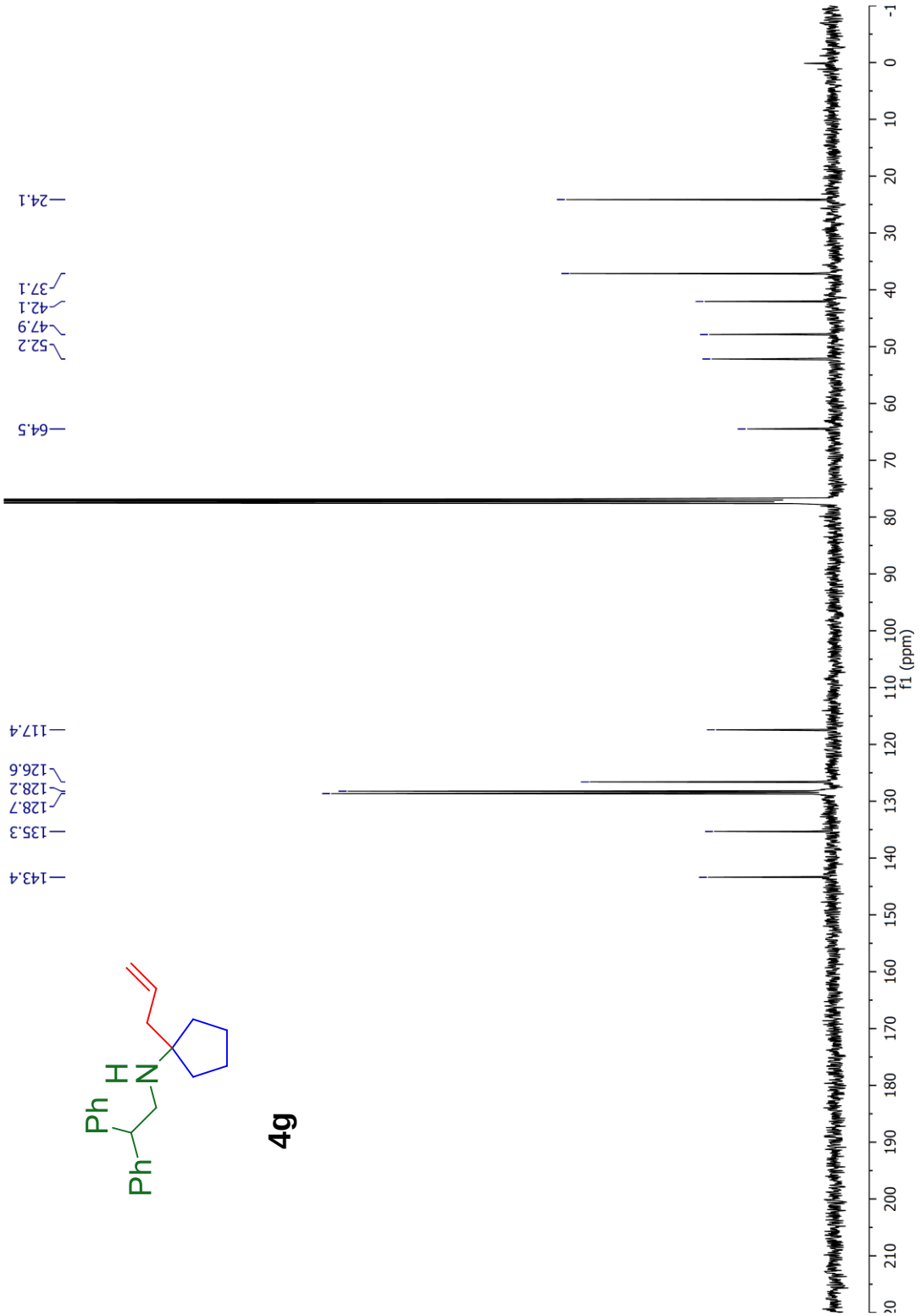

Ph
H
N
4e
140.5
135.3
128.9
128.5
126.2
117.5
64.5
44.5
42.0
37.4
37.3
24.3
f1 (ppm)


•HCl
H
N
F3C
4f
2.15
4.00
1.04
1.00
1.00
2.03
2.05
2.04
2.04
2.02
2.00
2.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

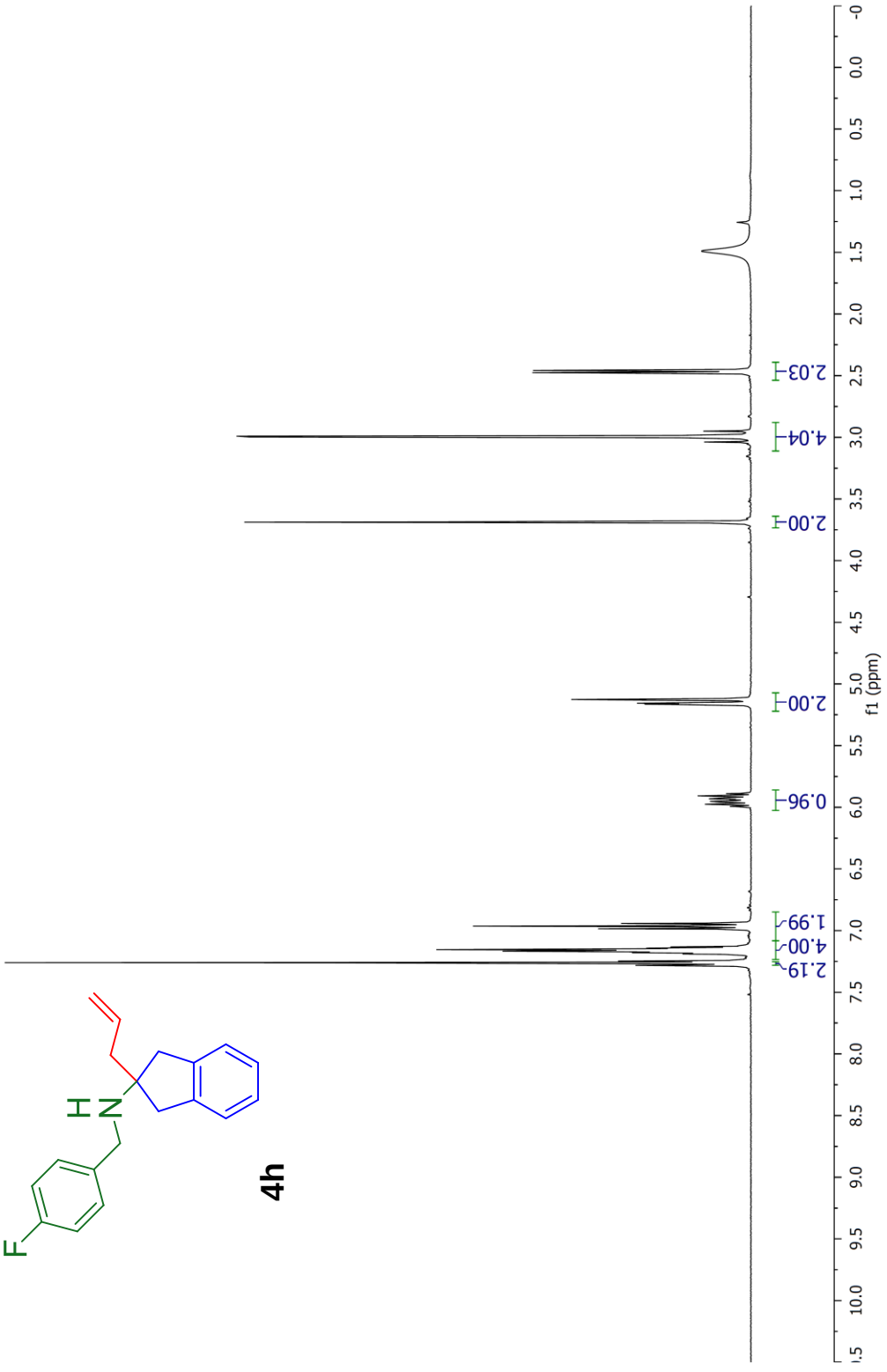

138.2
132.3
131.8
131.5
131.4
131.2
130.8
129.5
125.4
124.1
122.7
121.1
69.2
44.4
40.4
35.2
32.7
24.5
•HCl
H
N
F3C
4f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


•HCl
H
N
F3C
4f
-63.9
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

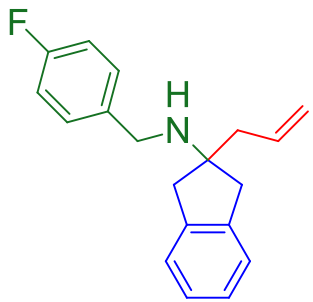

Ph
Ph
H
N
4g
10.34
1.00
1.97
1.00
2.00
2.09
8.14
f1 (ppm)


143.4
135.3
128.7
128.2
126.6
117.4
64.5
52.2
47.9
42.1
37.1
24.1
f1 (ppm)
Ph
H
N
Ph

4g

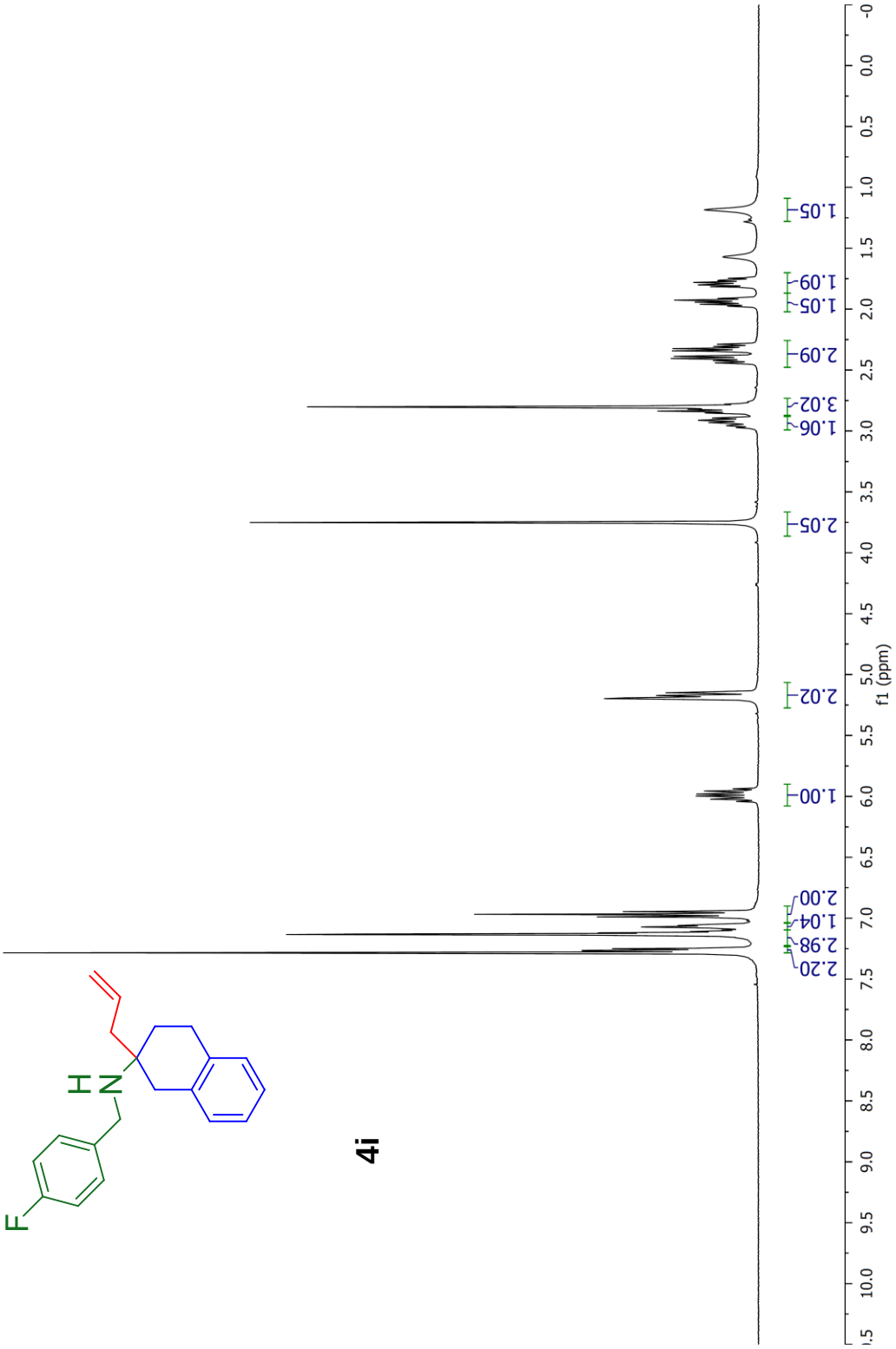

4h
F
H
N
2.19
4.00
1.99
0.96
2.00
2.00
4.04
2.03
f1 (ppm)

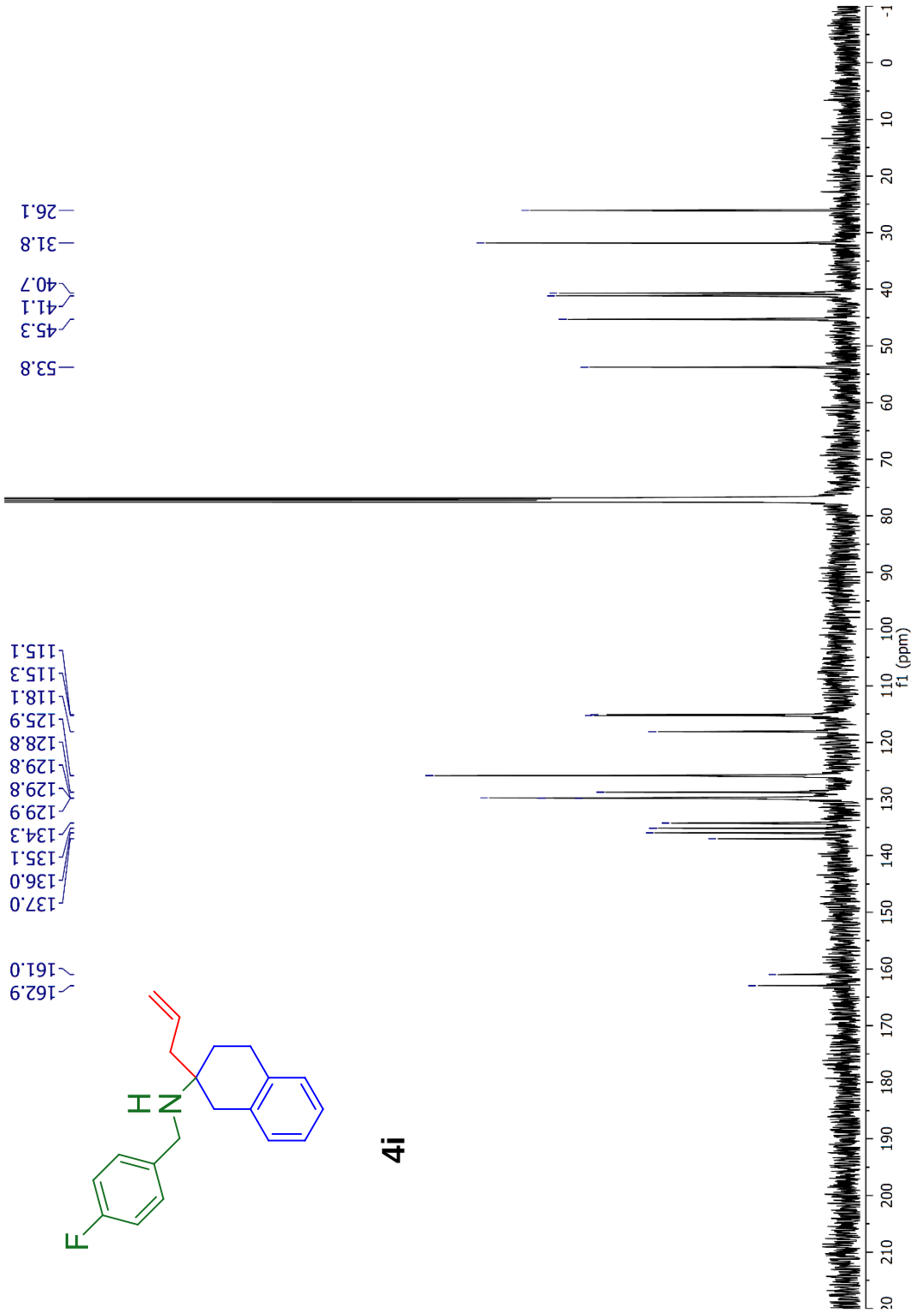
42.5
44.3
46.9
65.4
115.1
115.3
118.2
124.9
126.5
129.8
129.8
134.8
136.9
142.0
161.0
163.0
f1 (ppm)
4h
H
N
F

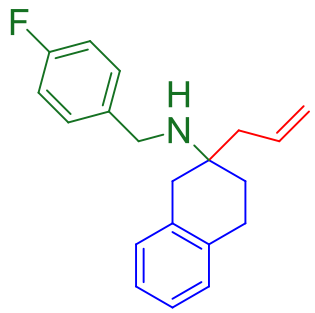

F
H
N

4h

-117.6
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

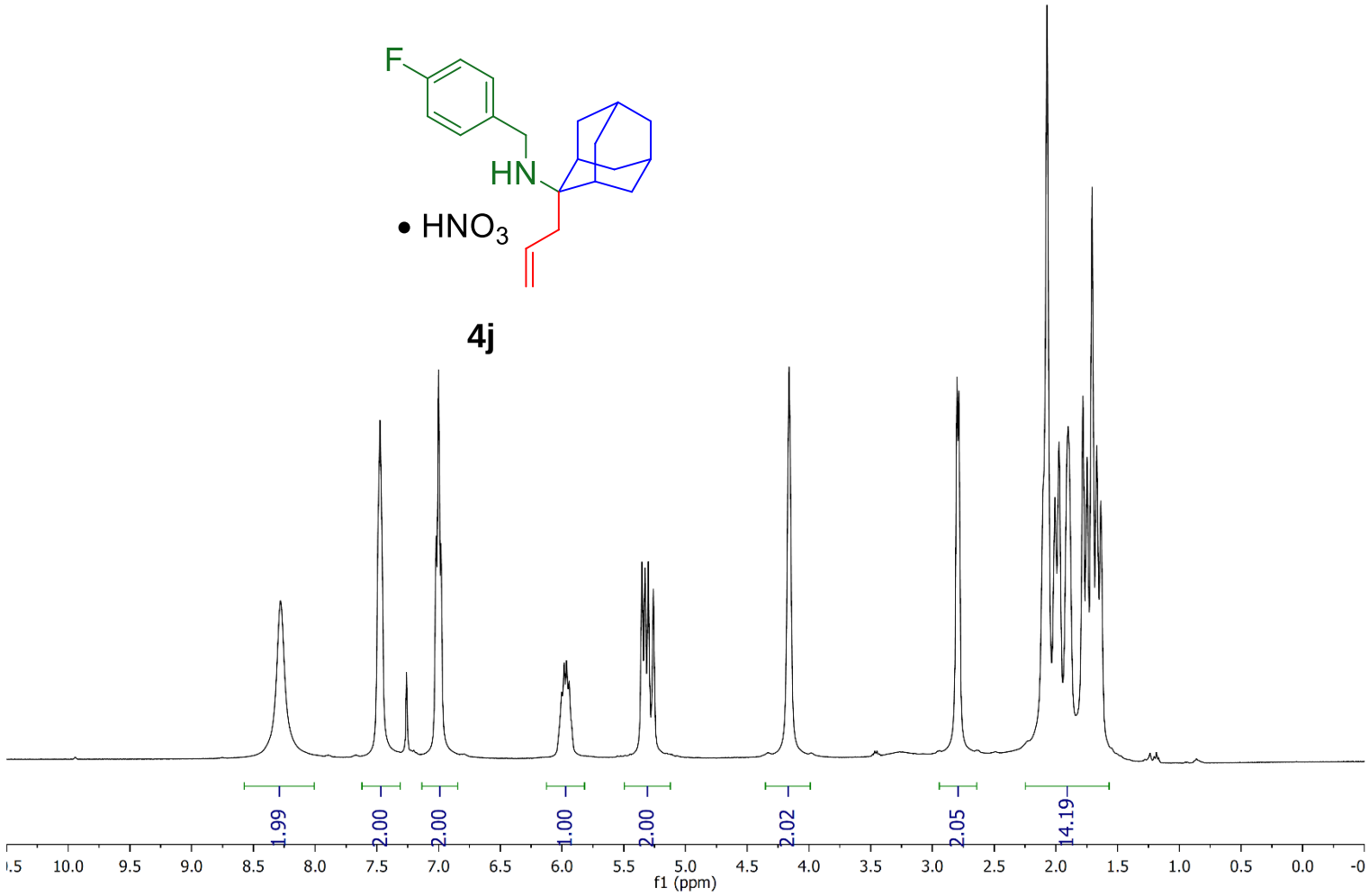

4i
H
N
F
2.20
2.98
1.04
2.00
1.00
2.02
2.05
1.06
3.02
2.09
1.05
1.09
1.05
f1 (ppm)

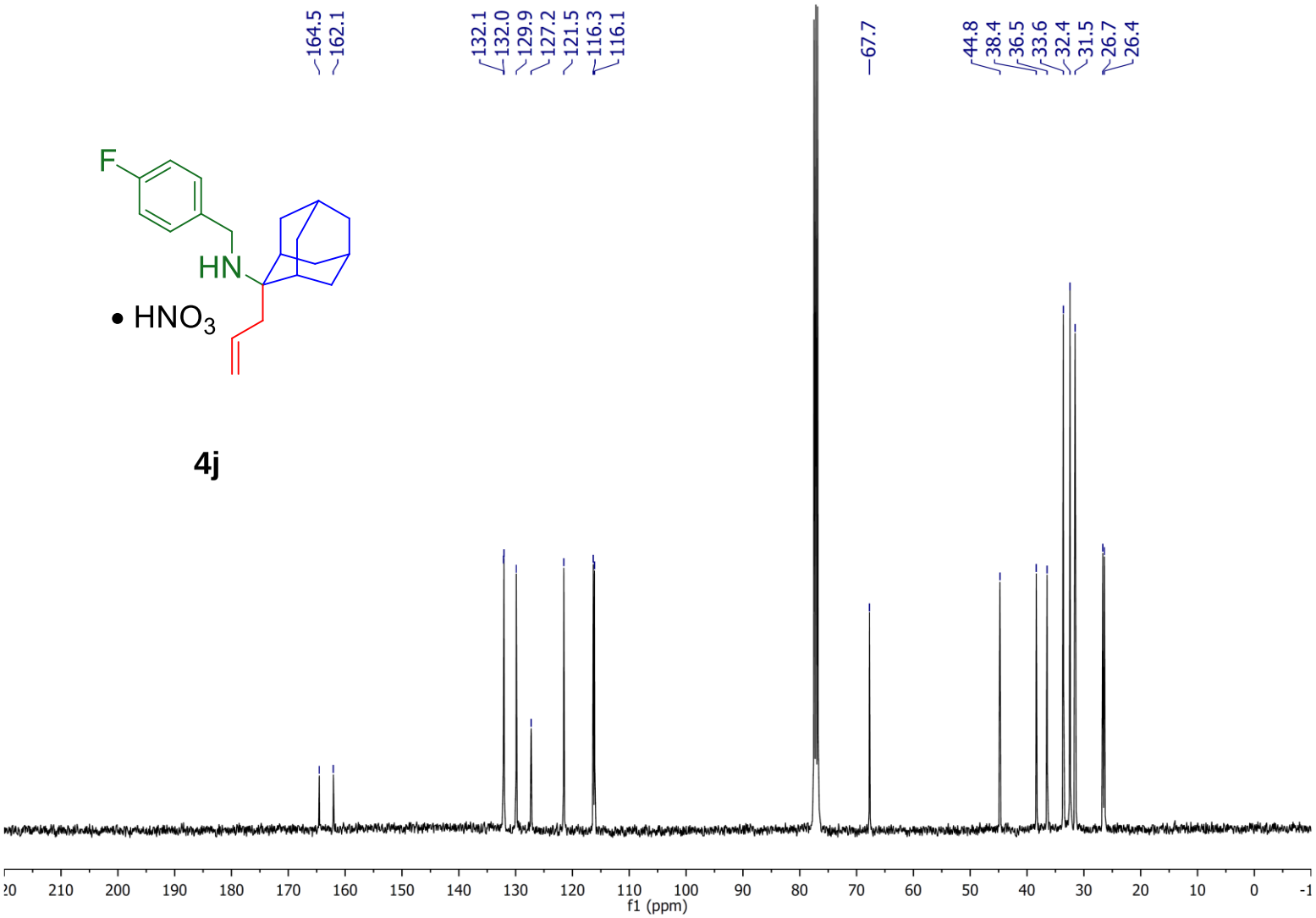

4i
F
H
N
162.9
161.0
137.0
136.0
135.1
134.3
129.9
129.8
129.8
128.8
125.9
118.1
115.3
115.1
53.8
45.3
41.1
40.7
31.8
26.1
f1 (ppm)


F
H
N

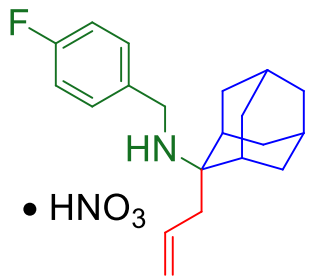
4i

-117.7
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)


F
HN
• HNO3
4j
1.99
2.00
2.00
1.00
2.00
2.02
2.05
14.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

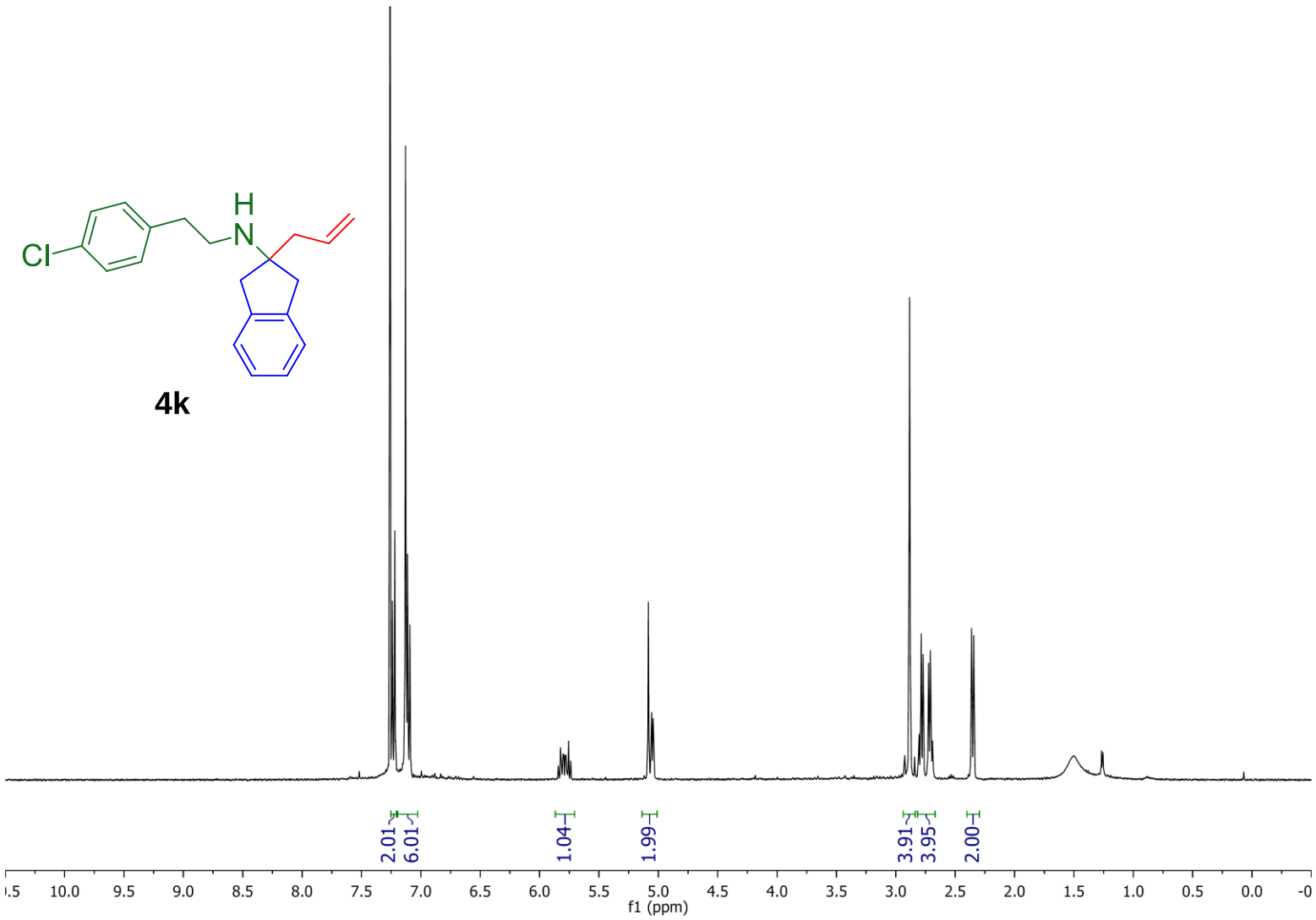

164.5
162.1
132.1
132.0
129.9
127.2
121.5
116.3
116.1
67.7
44.8
38.4
36.5
33.6
32.4
31.5
26.7
26.4
F
HN
• HNO3
f1 (ppm)

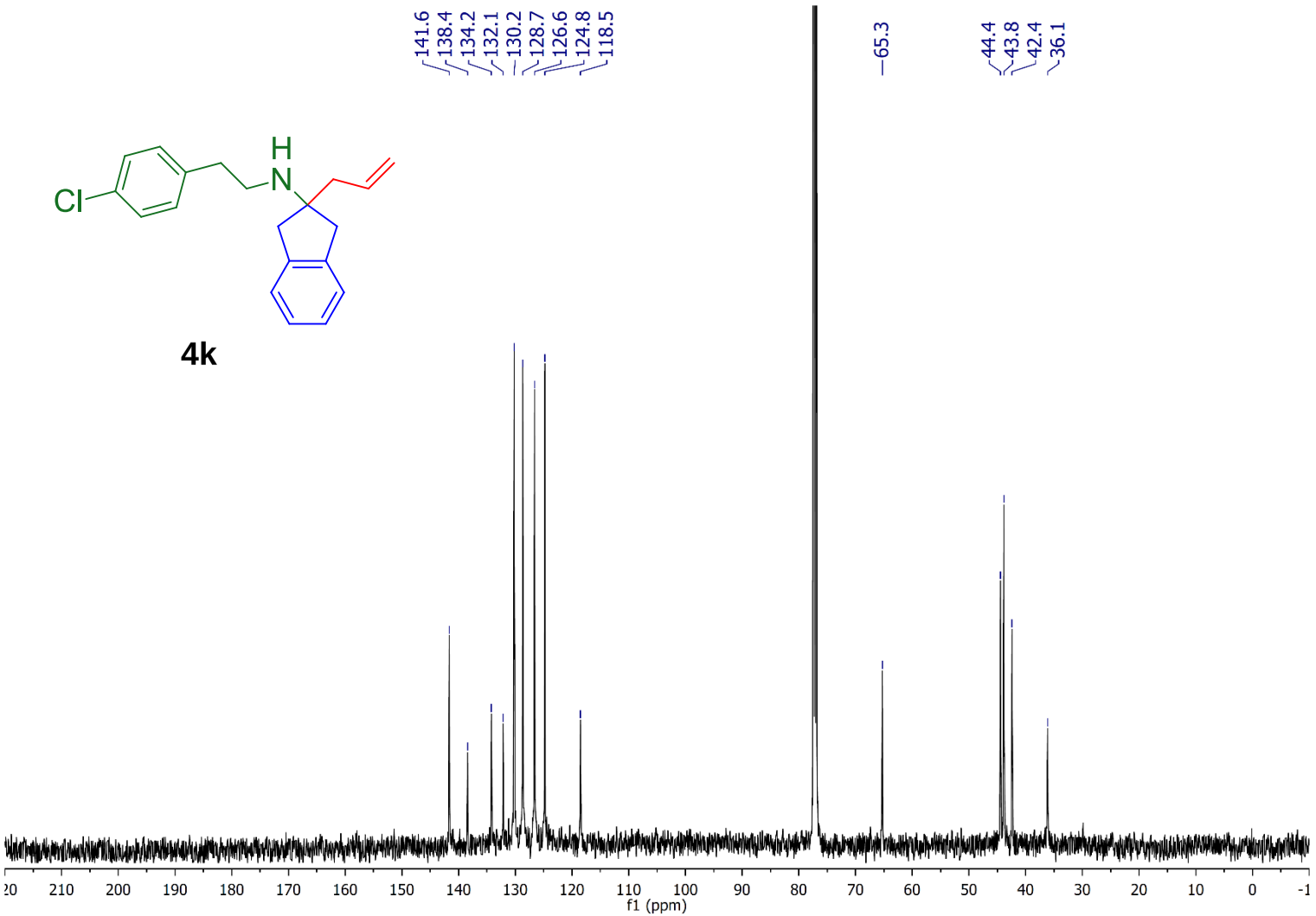
4j

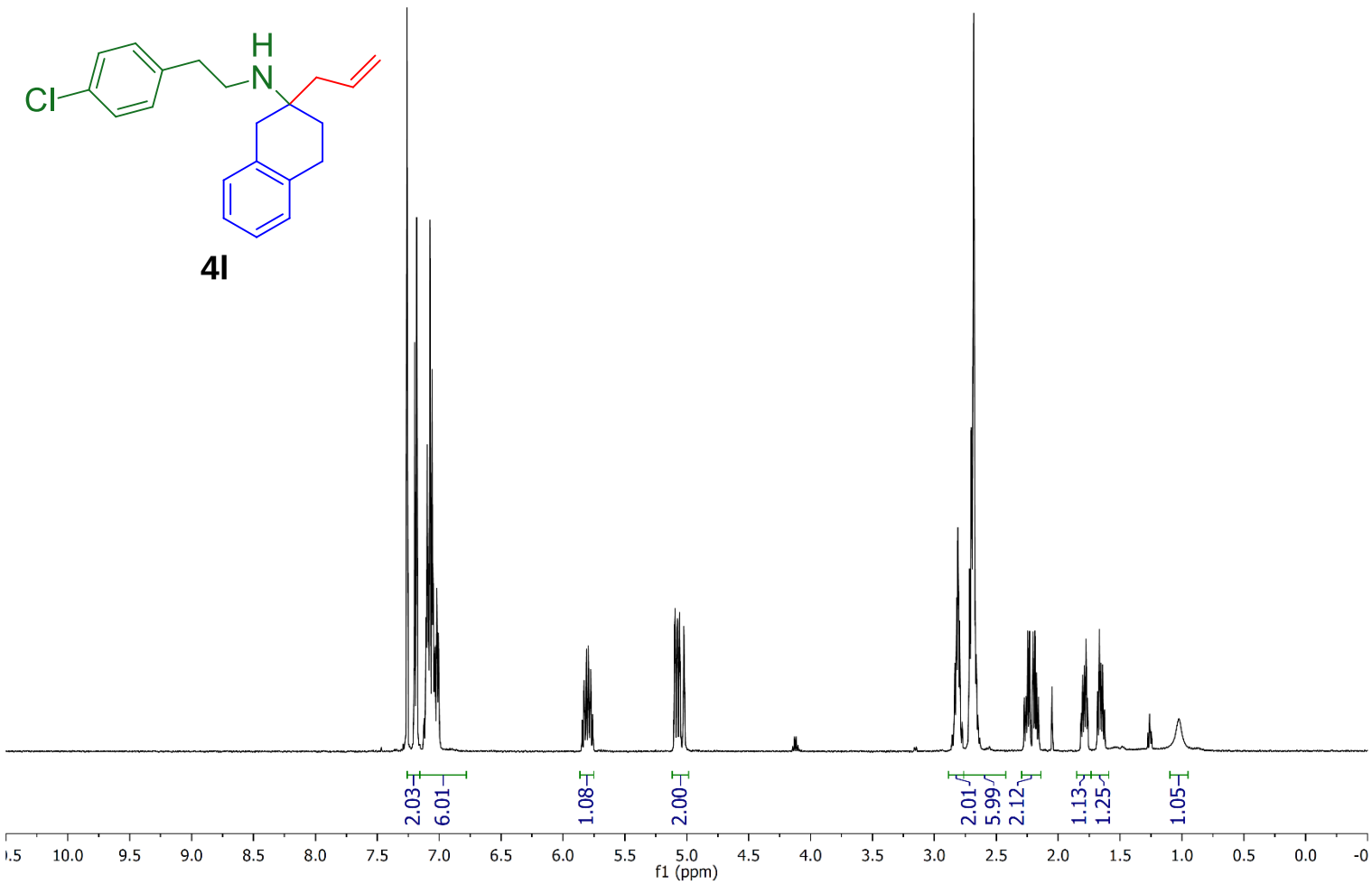

F
HN
• HNO3

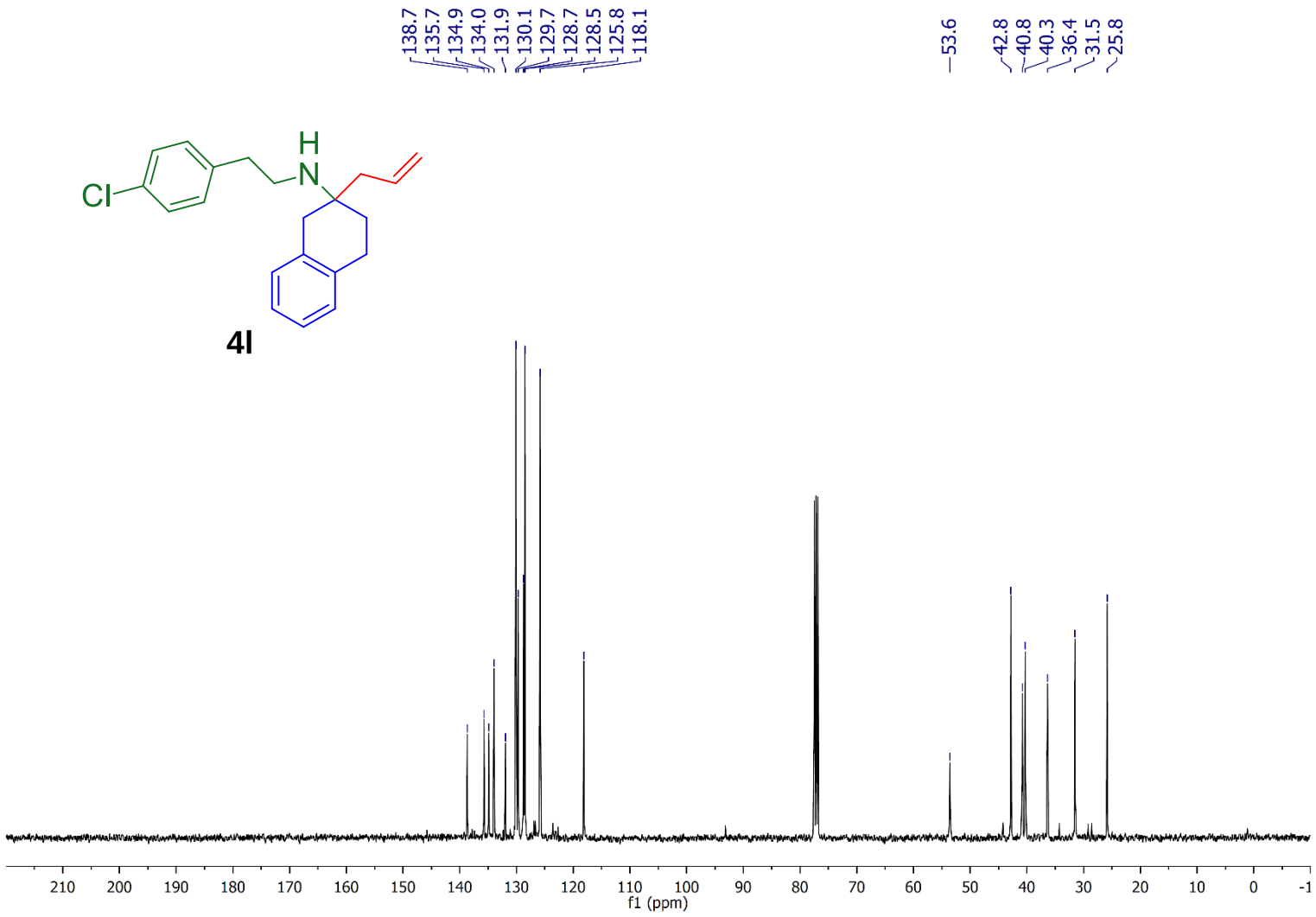
4j

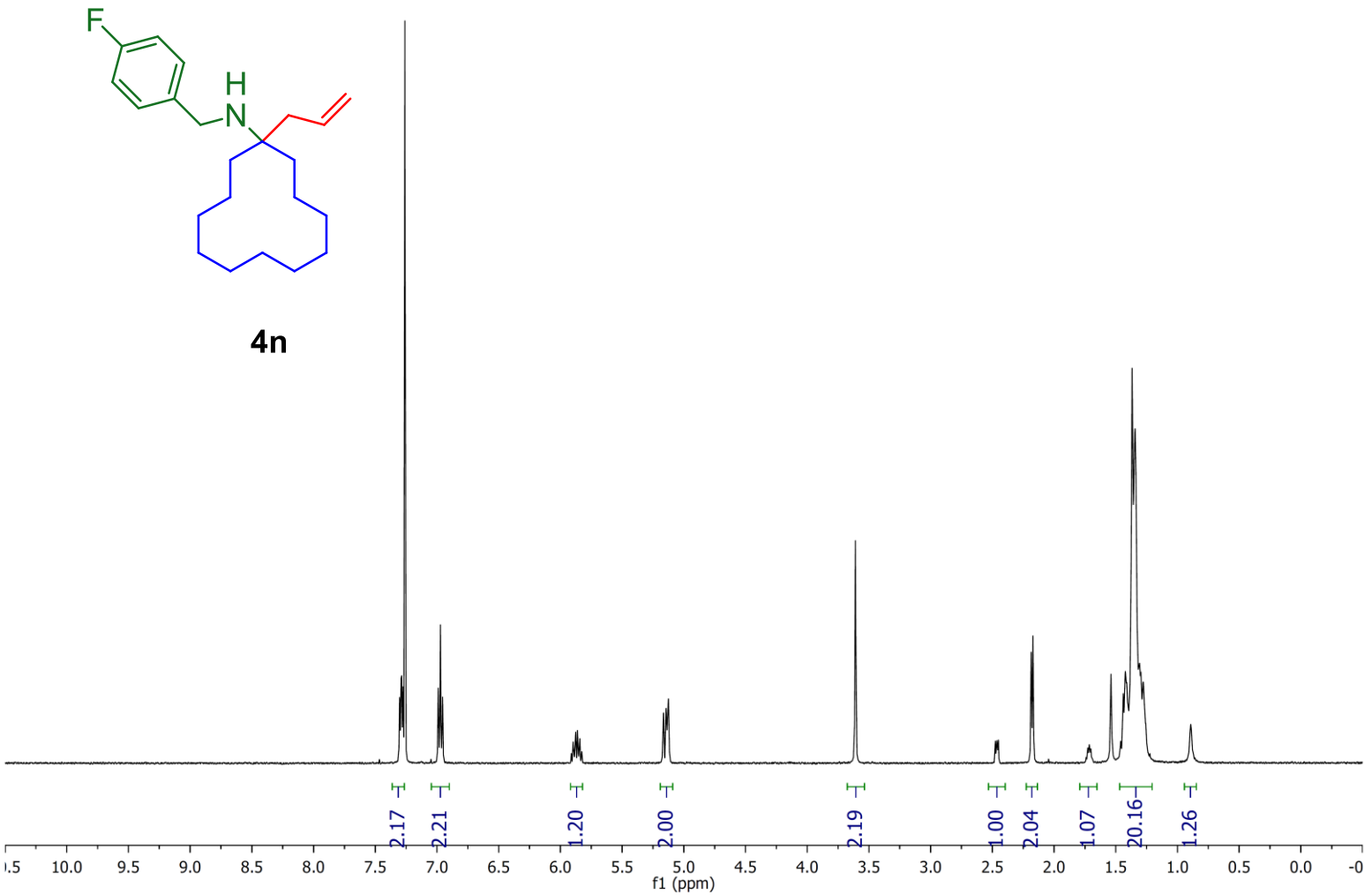
-112.6
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

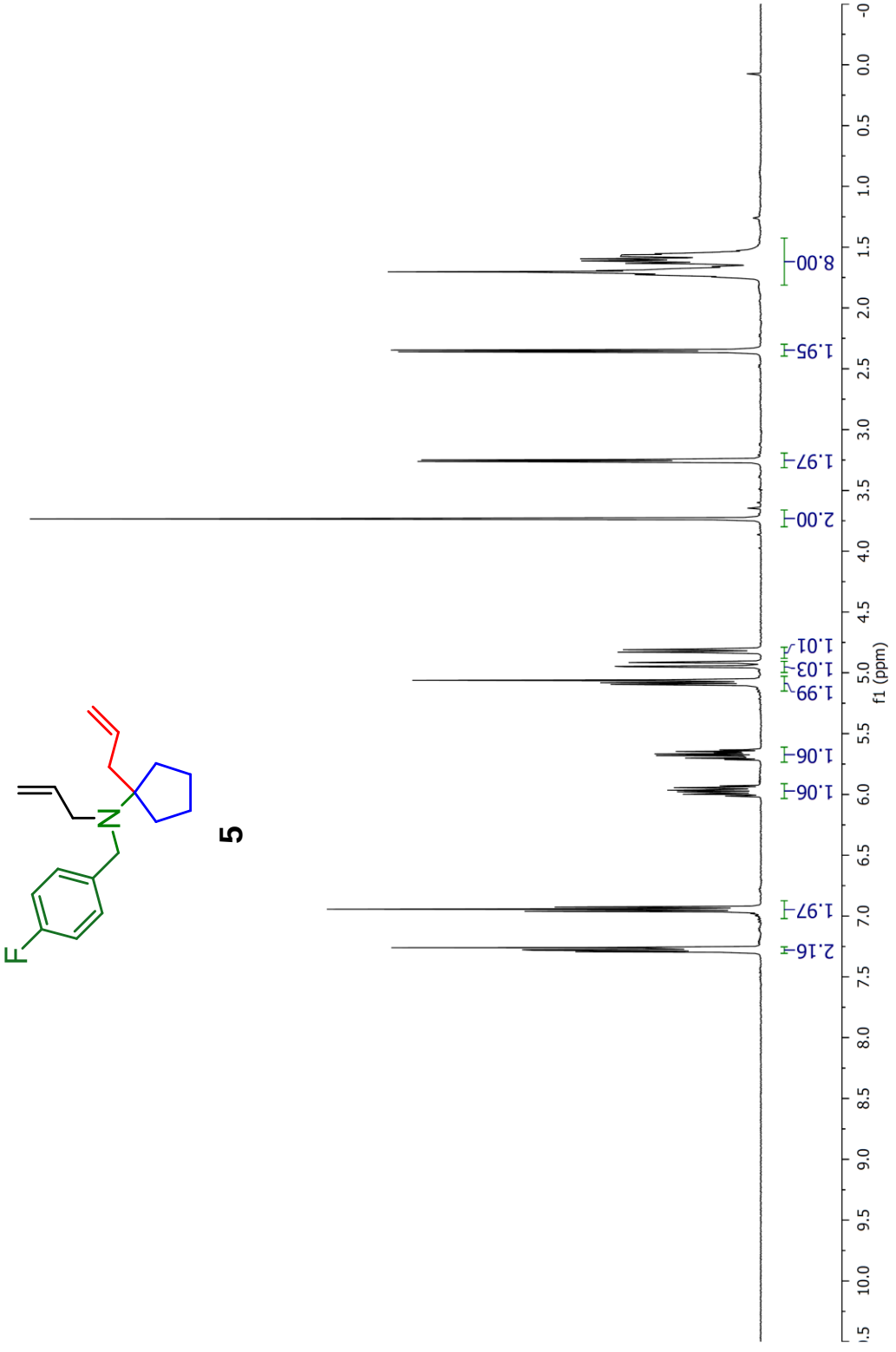

Cl
H
N
4k
2.01
6.01
1.04
1.99
3.91
3.95
2.00
f1 (ppm)


141.6
138.4
134.2
132.1
130.2
128.7
126.6
124.8
118.5
65.3
44.4
43.8
42.4
36.1
Cl
H
N
4k
f1 (ppm)

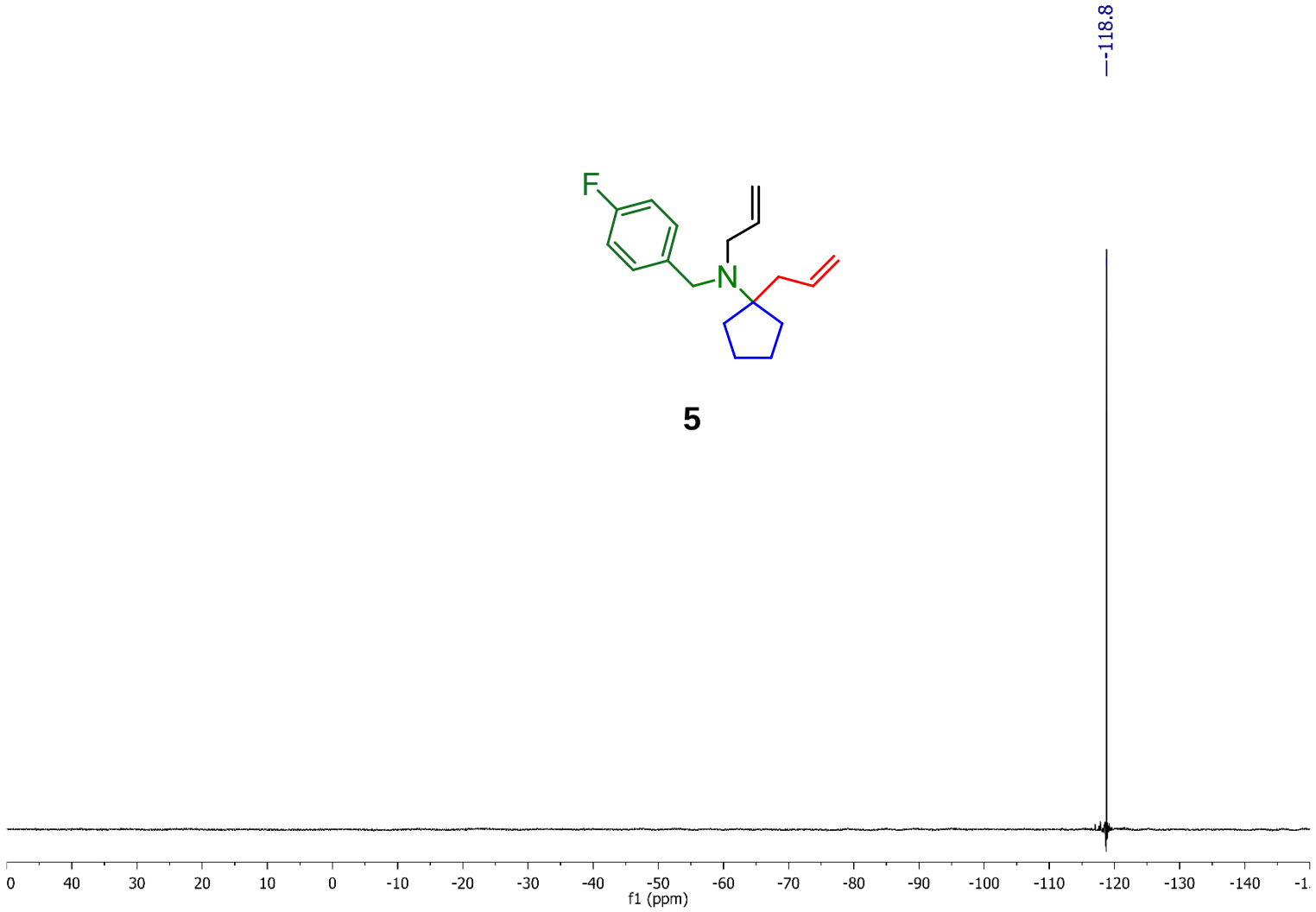

Cl
H
N
4l
2.03
6.01
1.08
2.00
2.01
5.99
2.12
1.13
1.25
1.05
f1 (ppm)


138.7
135.7
134.9
134.0
131.9
130.1
129.7
128.7
128.5
125.8
118.1
53.6
42.8
40.8
40.3
36.4
31.5
25.8
Cl
H
N
4l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

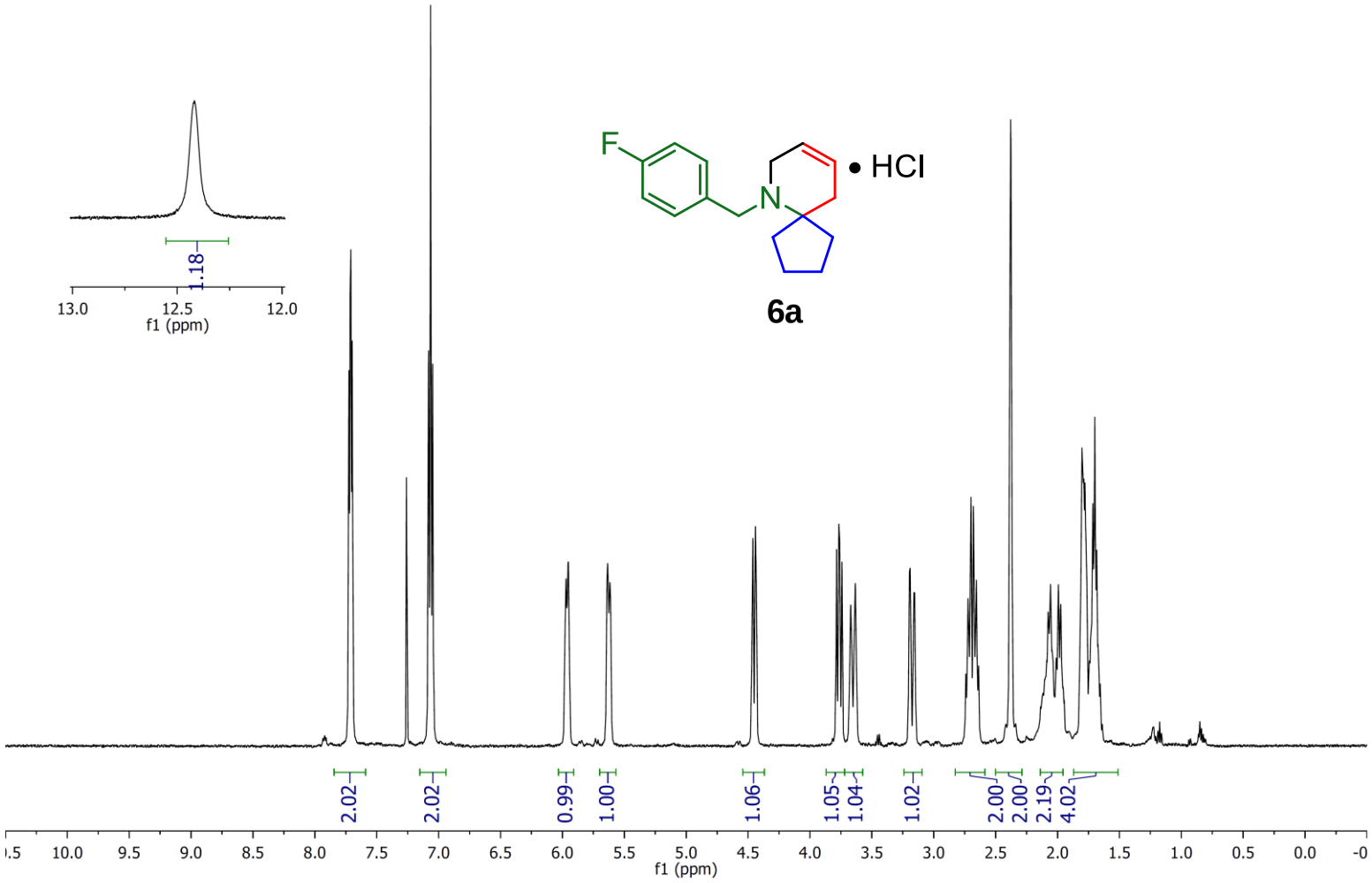

F
H
N
4n
2.17
2.21
1.20
2.00
2.19
1.00
2.04
1.07
20.16
1.26
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


F
N
5
8.00
1.95
1.97
2.00
1.01
1.03
1.99
1.06
1.06
1.97
2.16
f1 (ppm)

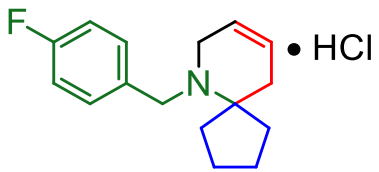
24.6
36.5
41.0
54.1
54.5
70.3
114.6
114.8
115.1
116.8
129.4
129.4
136.5
138.5
138.8
160.7
162.6
F
N
5
f1 (ppm)


F
N
-118.8
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

5

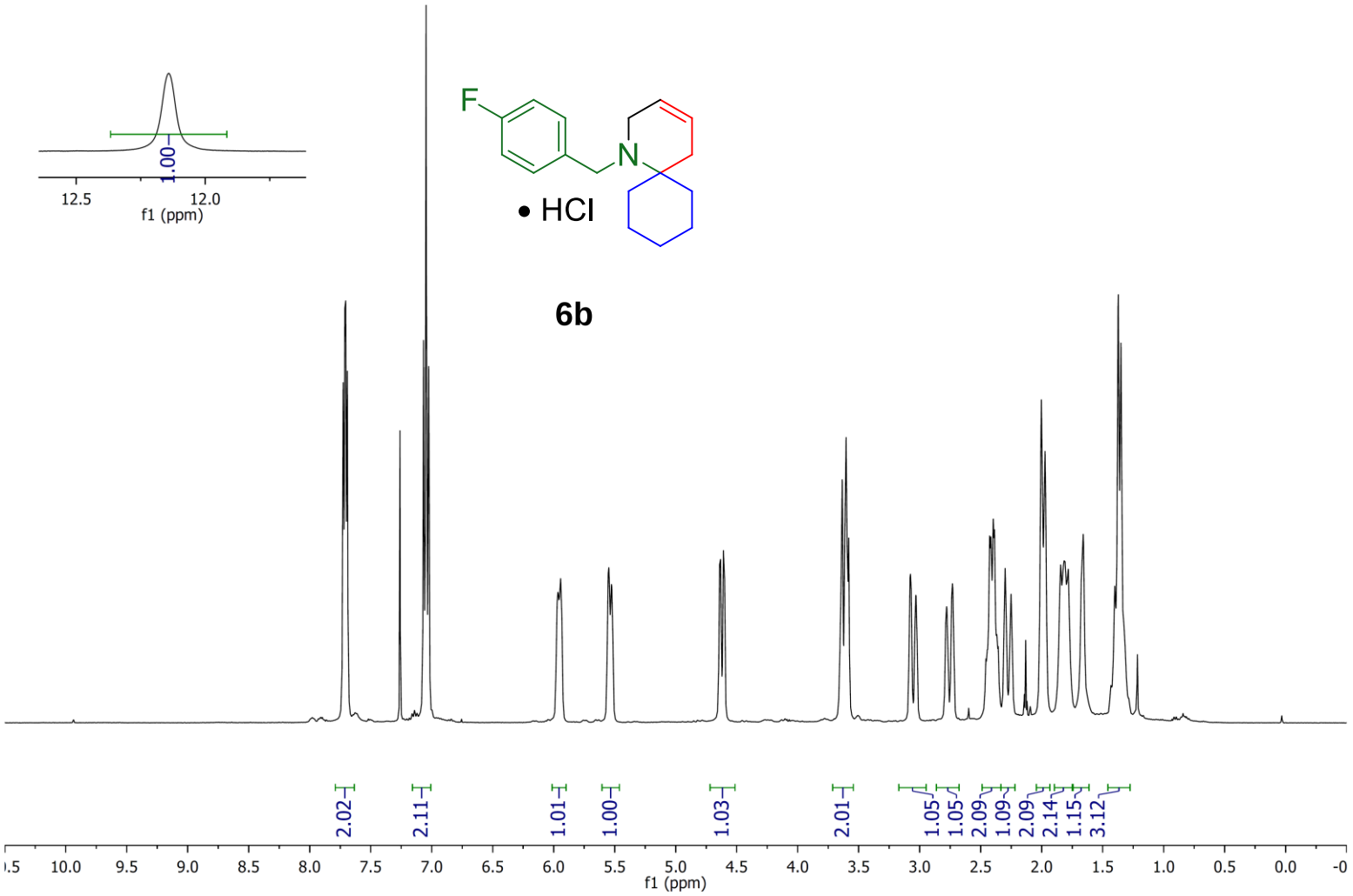

F
N
• HCl
6a
1.18
13.0
12.5
12.0
f1 (ppm)
2.02
2.02
0.99
1.00
1.06
1.05
1.04
1.02
2.00
2.00
2.19
4.02
f1 (ppm)

164.6
162.6
133.9
125.8
125.0
118.7
116.4
116.2
70.3
52.2
44.0
35.9
34.2
31.8
23.2
22.5
• HCl
F
N
6a
f1 (ppm)

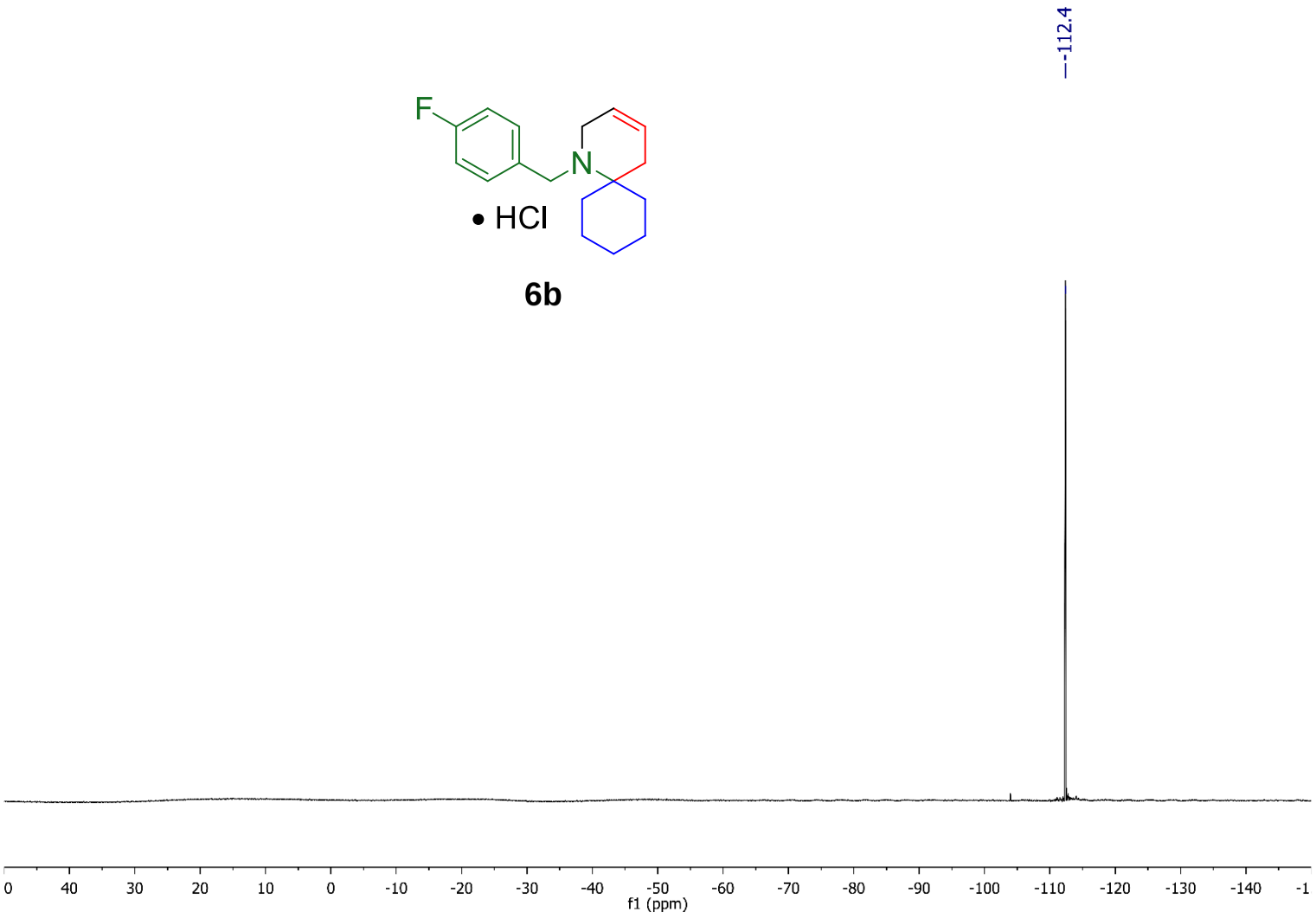

F
N
• HCl

6a

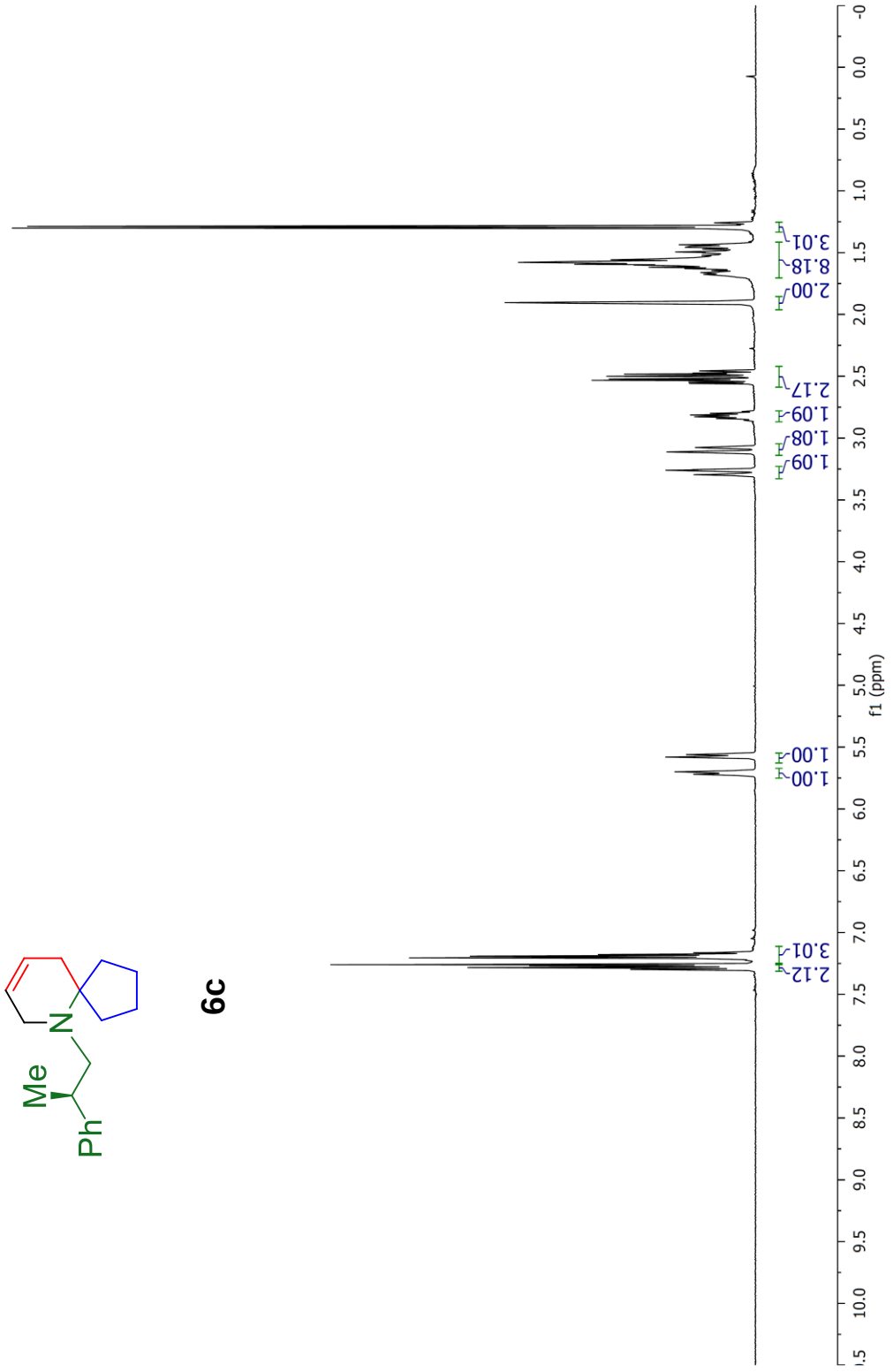
-111.9
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

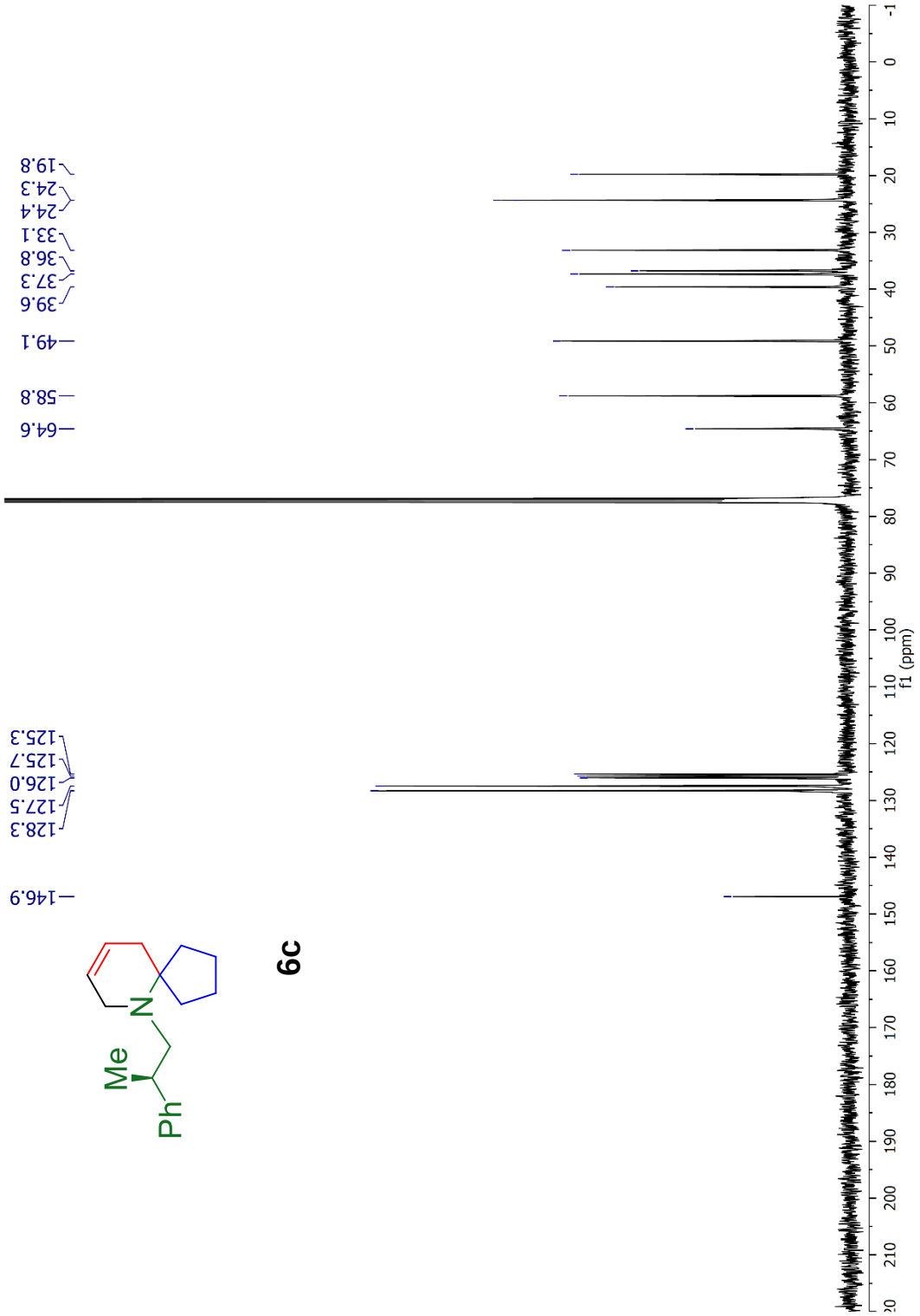

F
N
• HCl
6b
1.00
12.5
12.0
f1 (ppm)
2.02
2.11
1.01
1.00
1.03
2.01
1.05
1.05
2.09
1.09
2.09
2.14
1.15
3.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

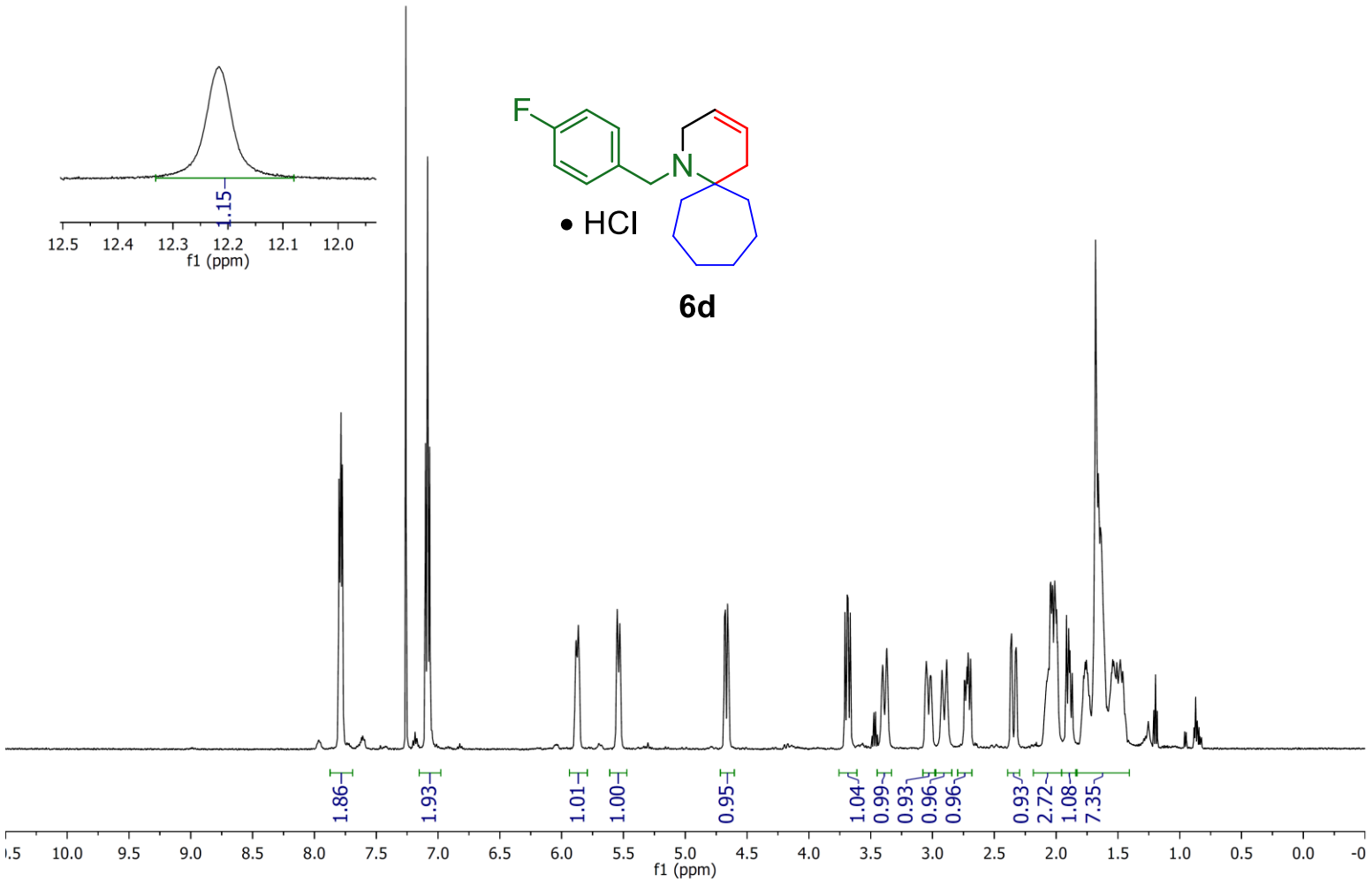
164.8
162.3
134.0
133.9
125.8
125.3
118.2
116.4
116.2
64.0
49.6
41.6
32.9
30.3
28.0
24.3
22.5
22.2
F
N
• HCl
6b
f1 (ppm)

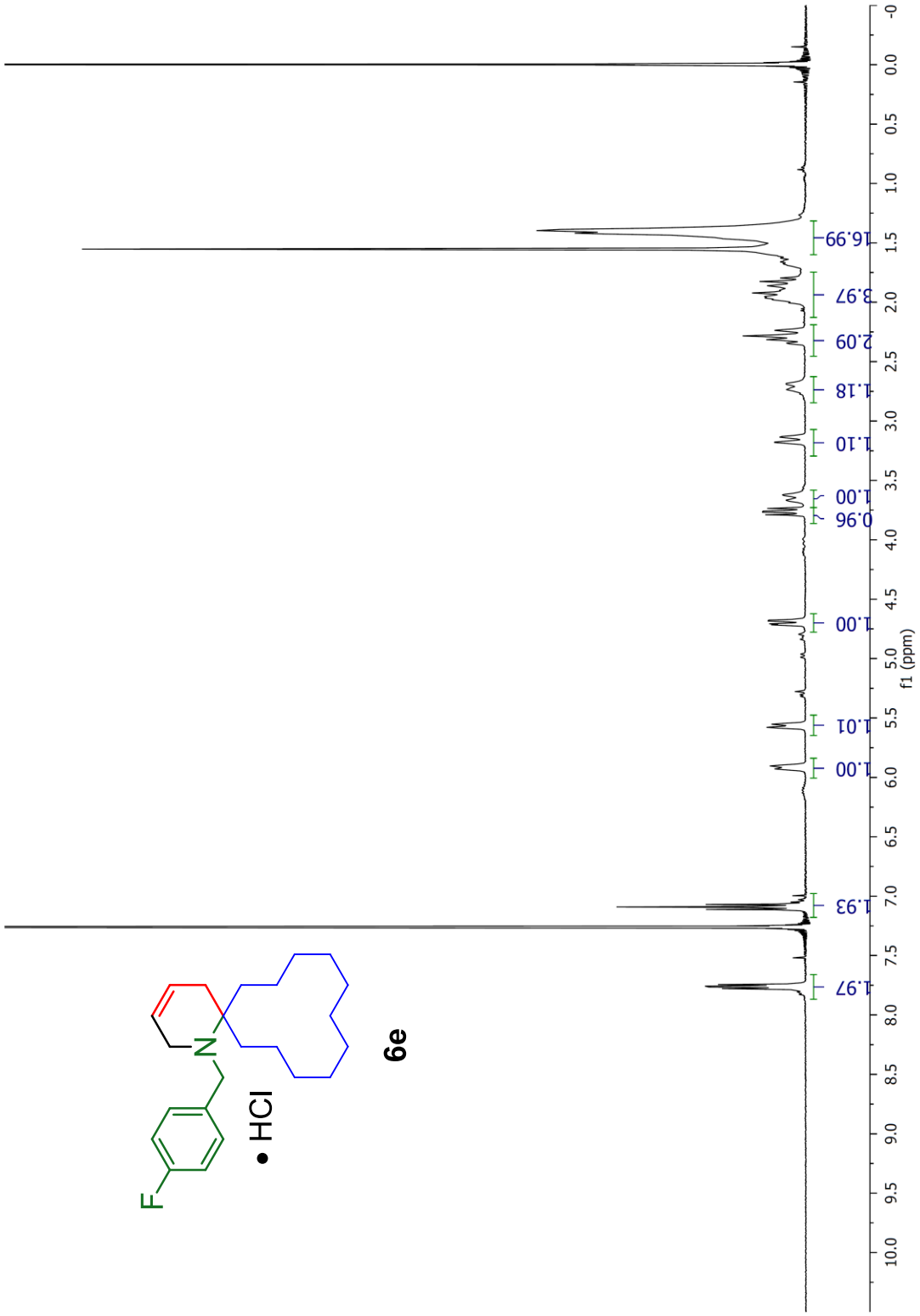

F
N
• HCl
-112.4
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

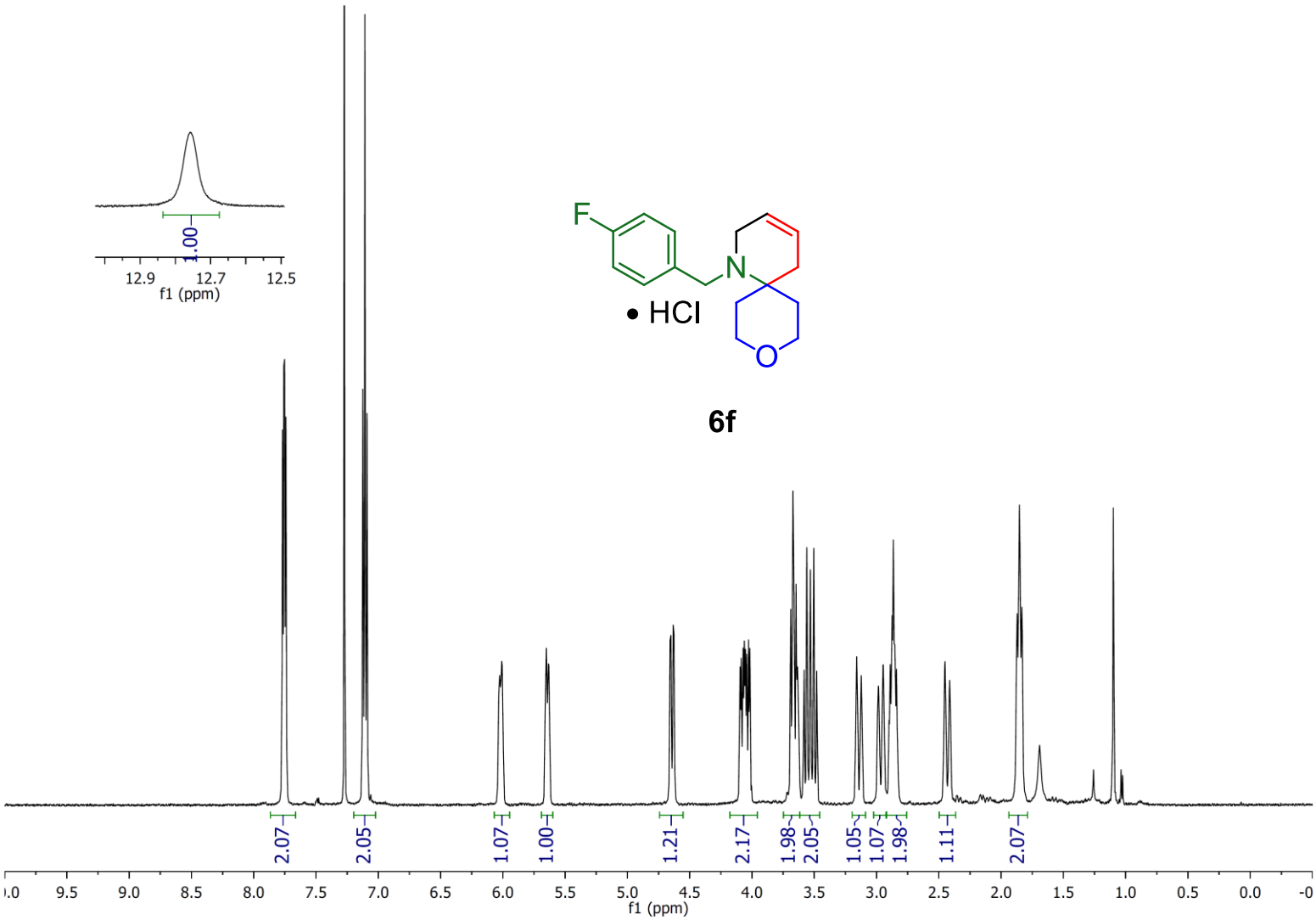
6b

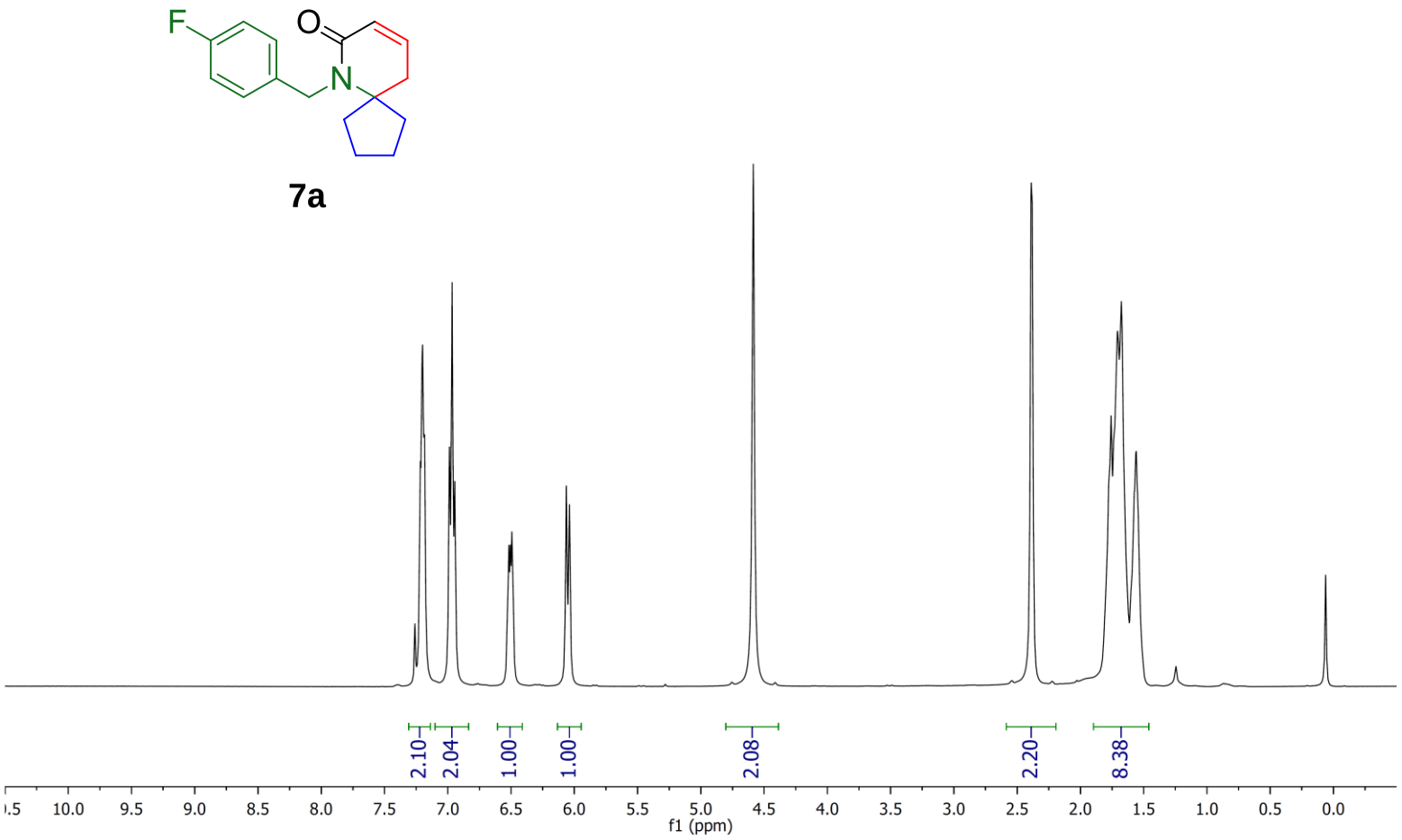

Me
N
Ph
6c
3.01
8.18
2.00
2.17
1.09
1.08
1.09
1.00
1.00
3.01
2.12
f1 (ppm)


19.8
24.3
24.4
33.1
36.8
37.3
39.6
49.1
58.8
64.6
128.3
127.5
126.0
125.7
125.3
146.9
N
Me
Ph
6c
f1 (ppm)

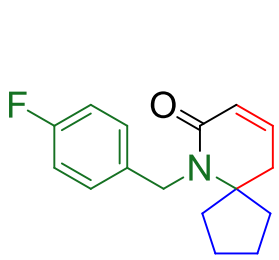

F
N
• HCl
6d
1.15
12.5 12.4 12.3 12.2 12.1 12.0
f1 (ppm)
1.86 1.93 1.01 1.00 0.95 1.04 0.99 0.93 0.96 0.96 0.93 2.72 1.08 7.35
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


16.99
3.97
2.09
1.18
1.10
1.00
0.96
1.00
1.01
1.00
1.93
1.97
f1 (ppm)
• HCl
6e


F
N
O
• HCl
6f
1.00
12.9
12.7
12.5
f1 (ppm)
2.07
2.05
1.07
1.00
1.21
2.17
1.98
2.05
1.05
1.07
1.98
1.11
2.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

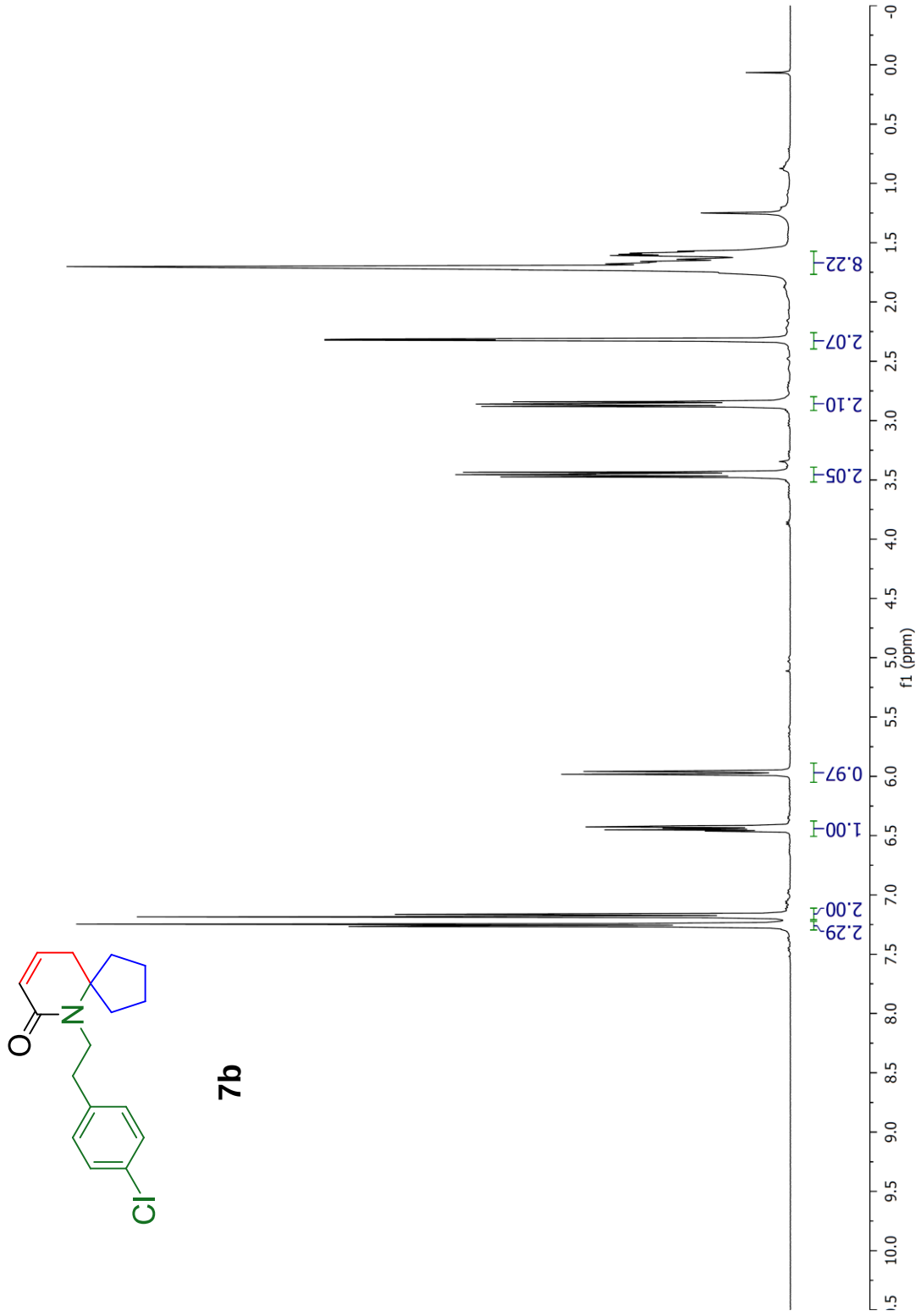

F
O
N
7a
2.10
2.04
1.00
1.00
2.08
2.20
8.38
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

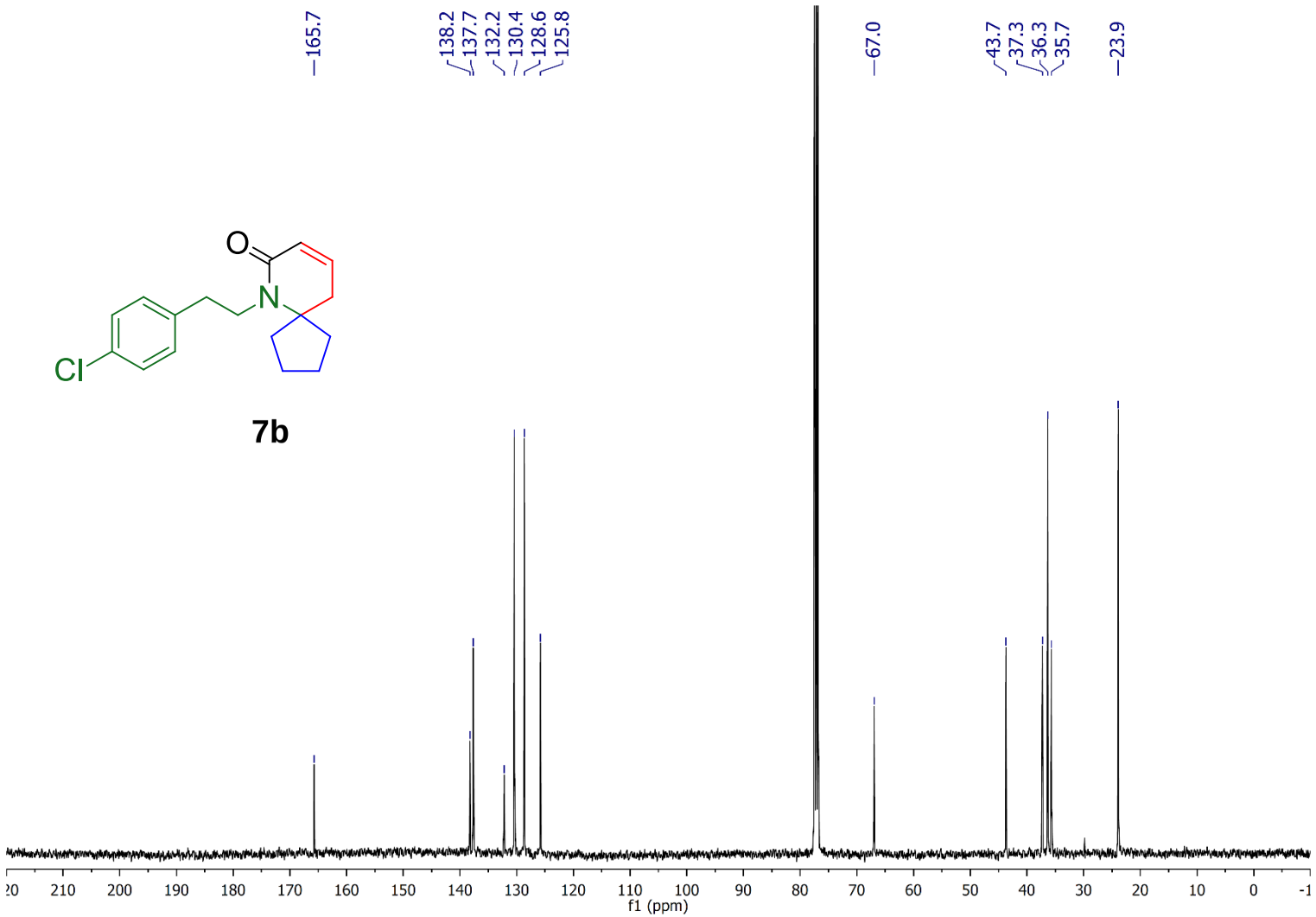
23.8
36.2
37.3
44.1
67.2
115.2
115.4
125.5
128.0
128.1
135.5
138.1
160.6
163.0
165.9
O
N
F
7a
f1 (ppm)

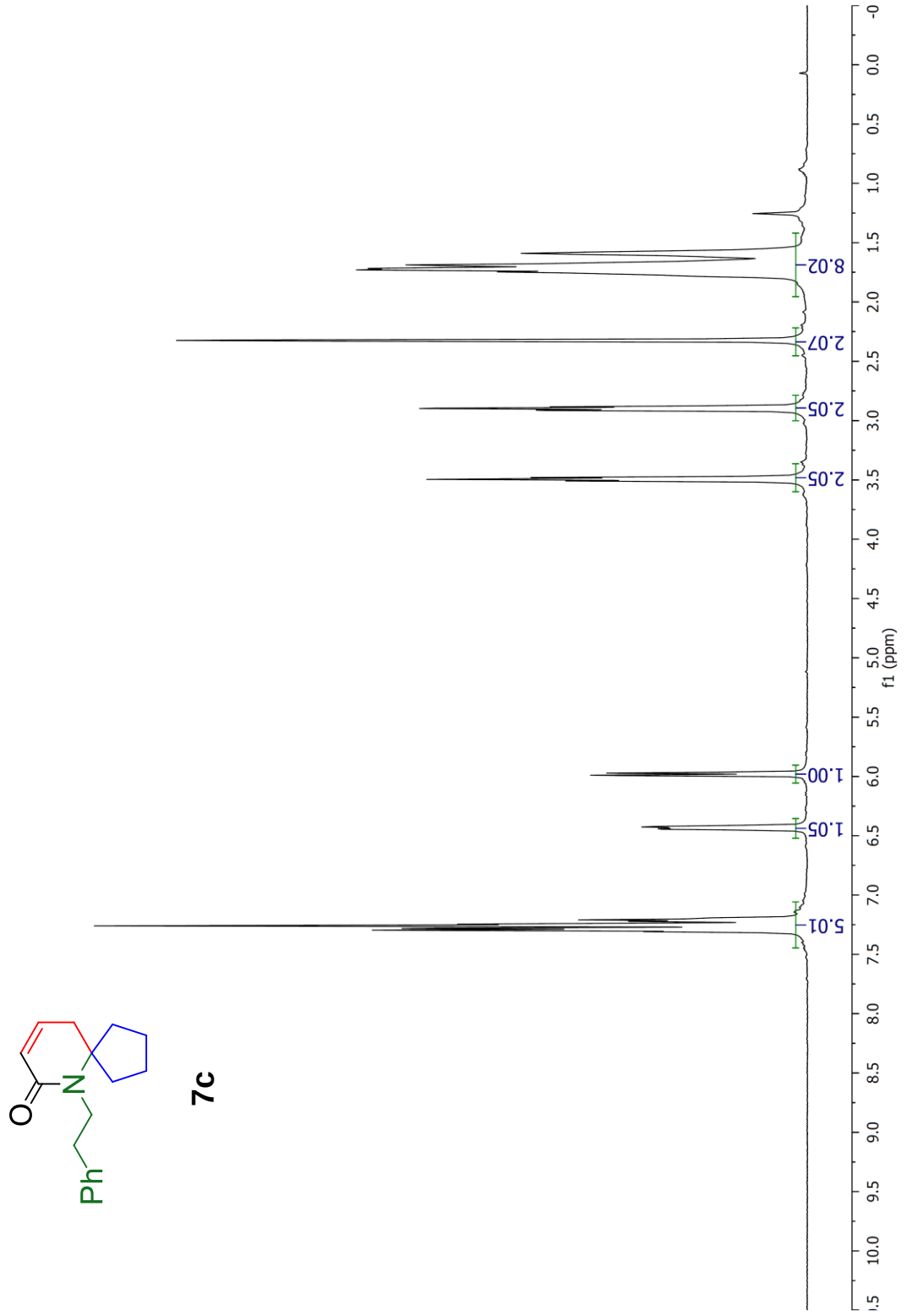

F
O
N

7a

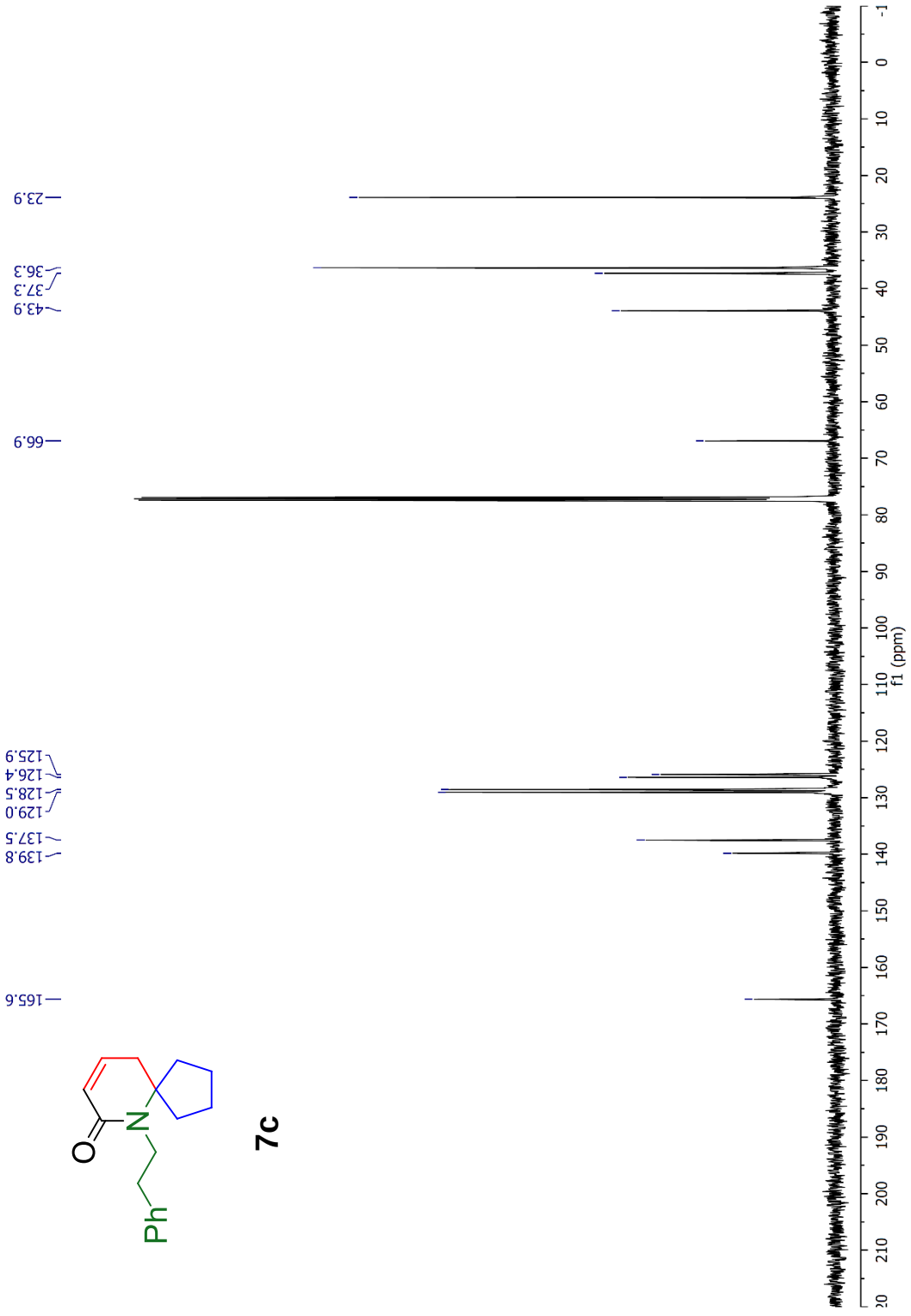
-117.9
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)


7b
O
N
Cl
8.22
2.07
2.10
2.05
0.97
1.00
2.29
2.00
f1 (ppm)

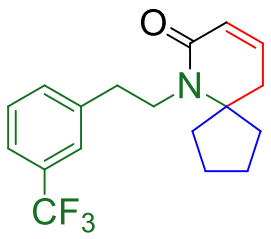

165.7
138.2
137.7
132.2
130.4
128.6
125.8
67.0
43.7
37.3
36.3
35.7
23.9
O
N
Cl
7b
f1 (ppm)



7c

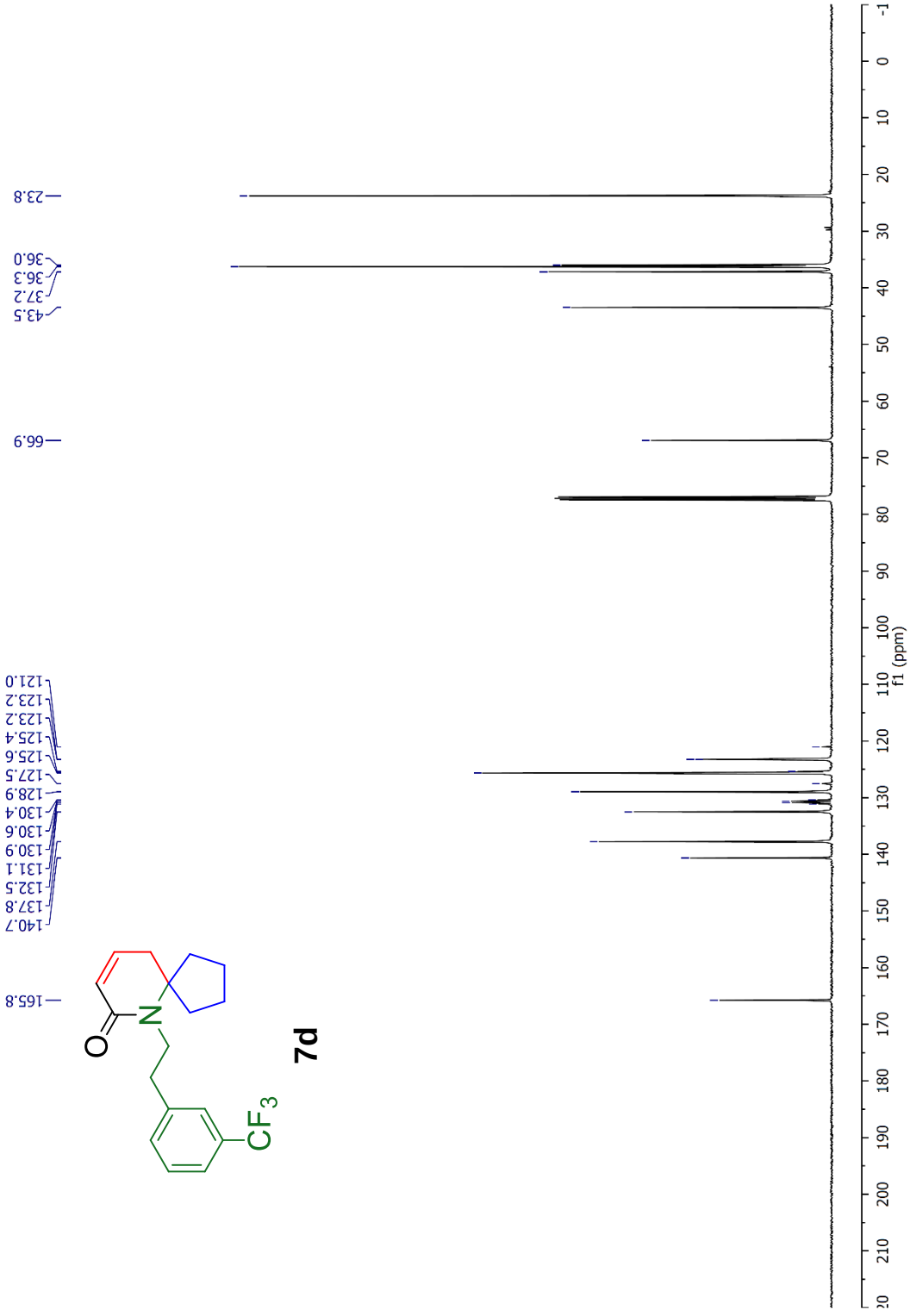

165.6
139.8
137.5
129.0
128.5
126.4
125.9
66.9
43.9
37.3
36.3
23.9
f1 (ppm)
O
N
Ph

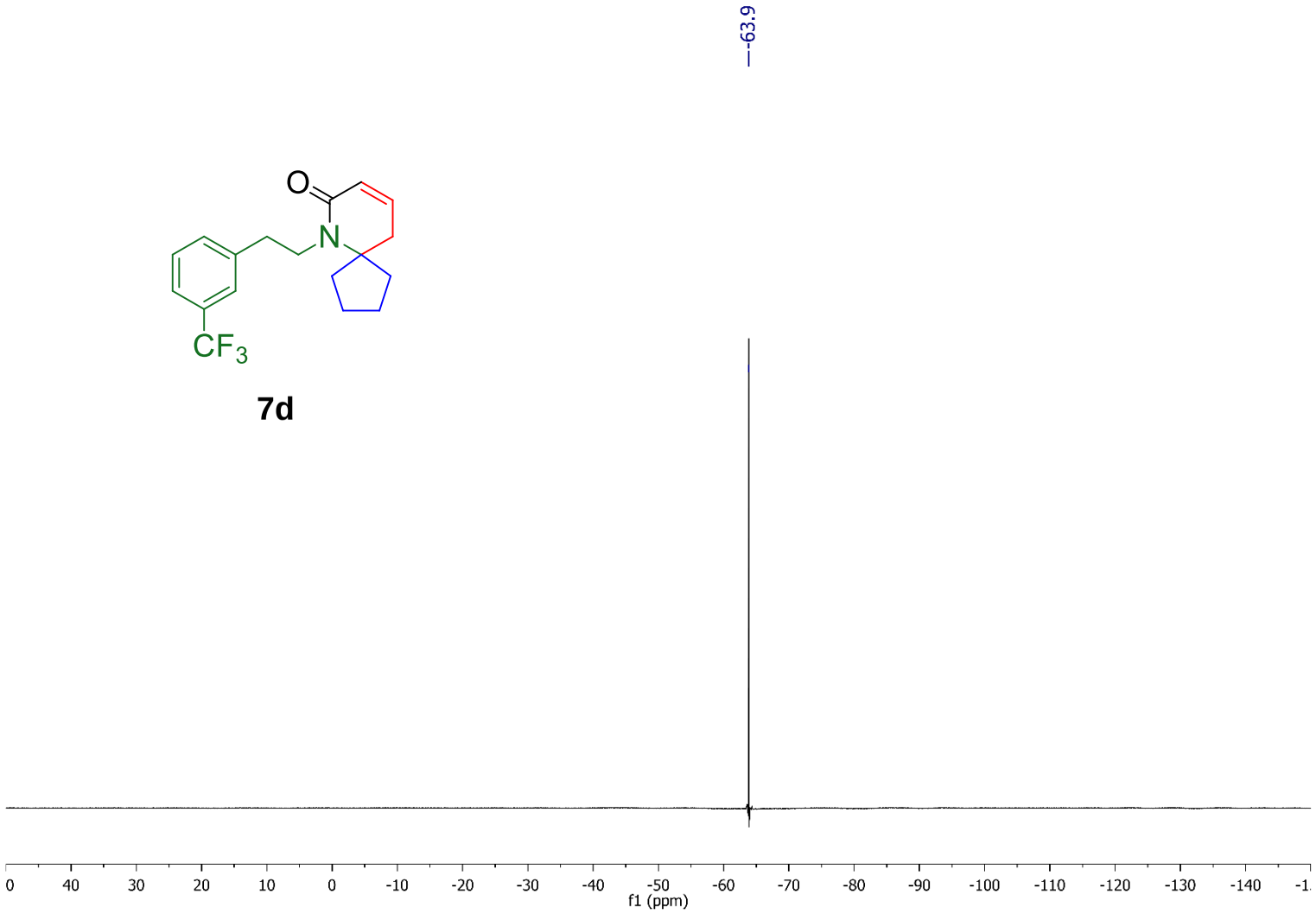
7c

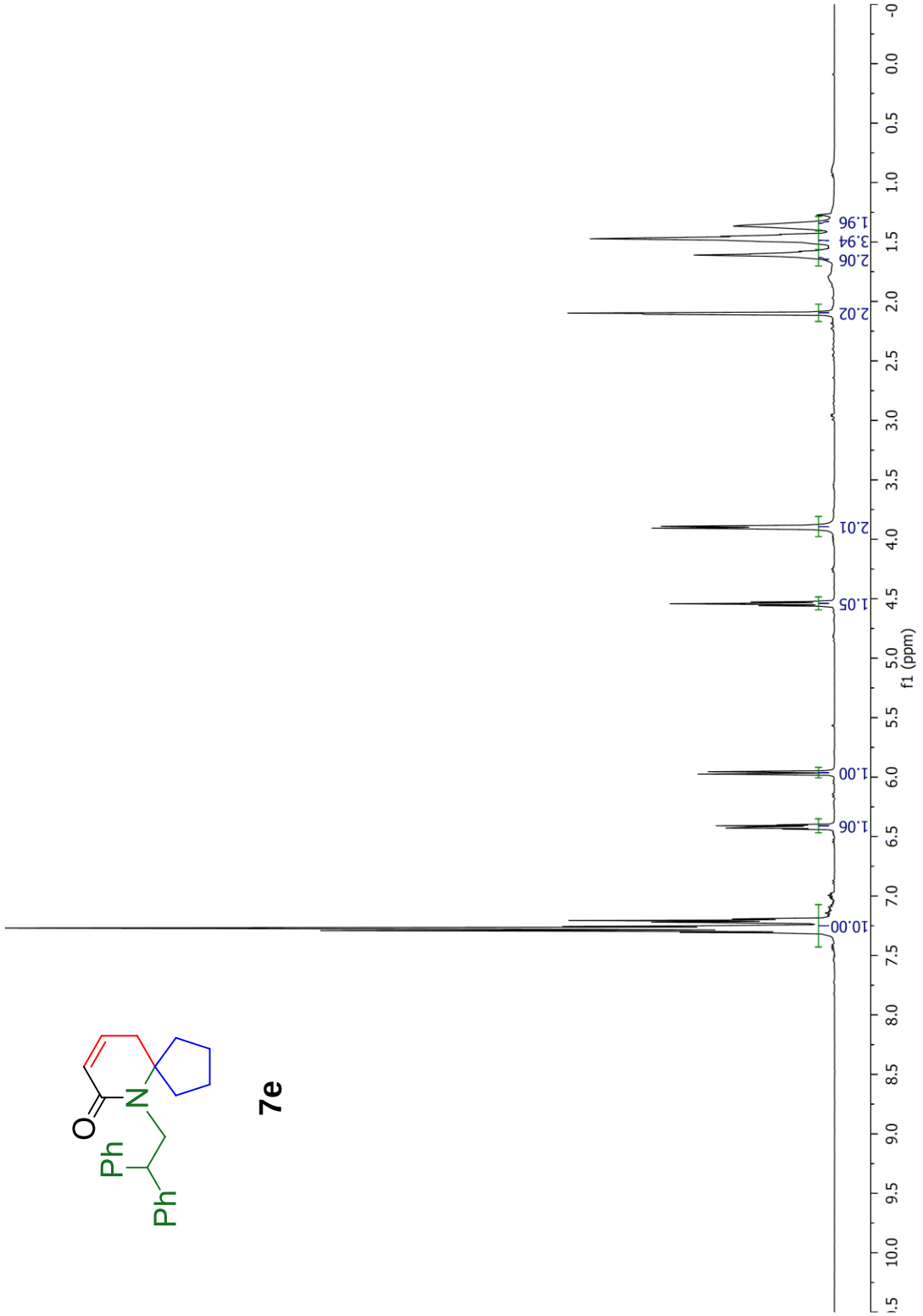

O
N
CF3

7d

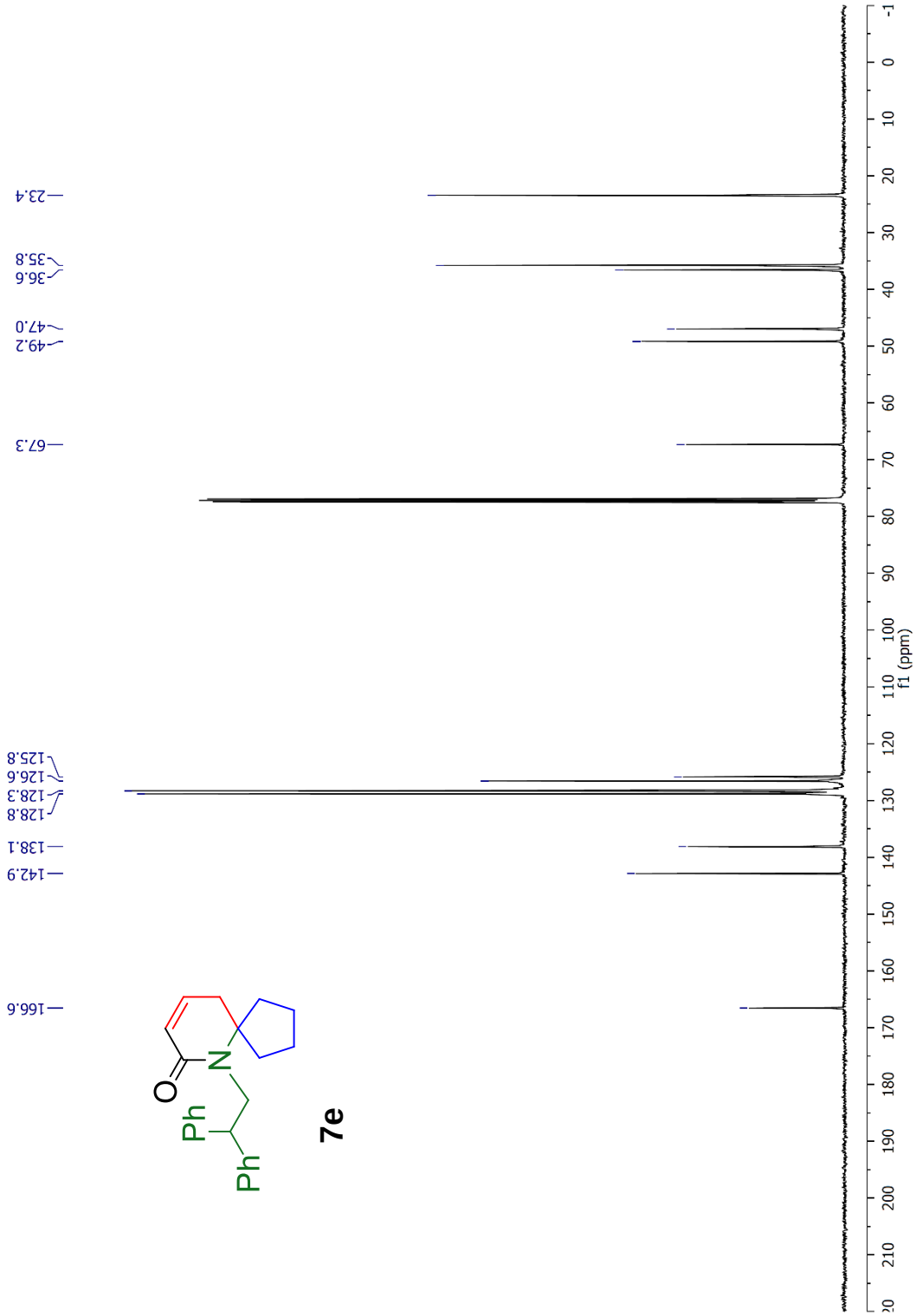
3.92
1.04
1.00
2.07
2.09
2.07
8.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

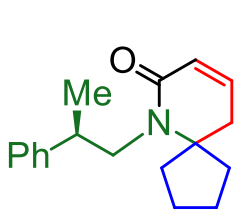

7d
f1 (ppm)


-63.9
O
N
CF3
7d
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)



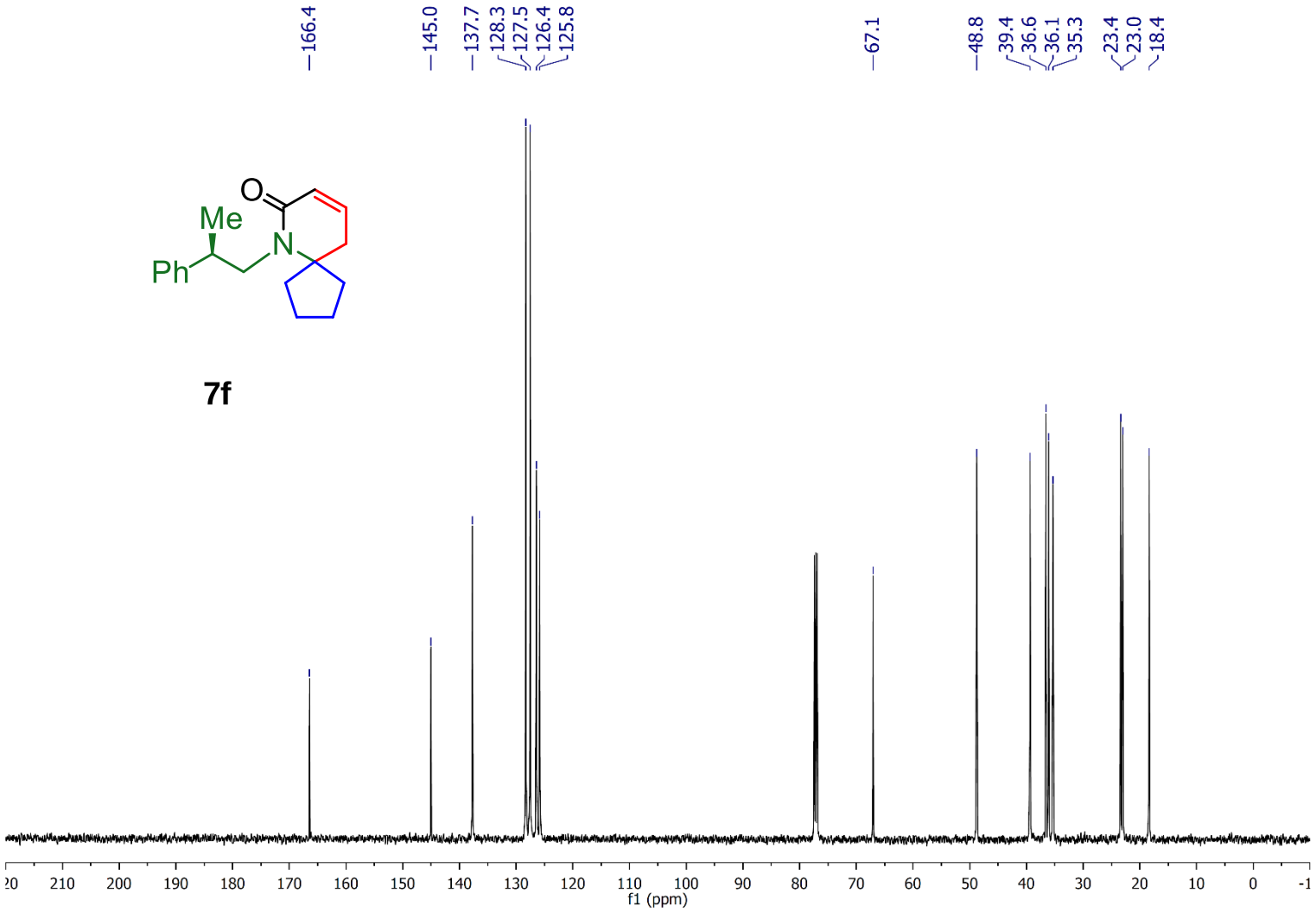
7e

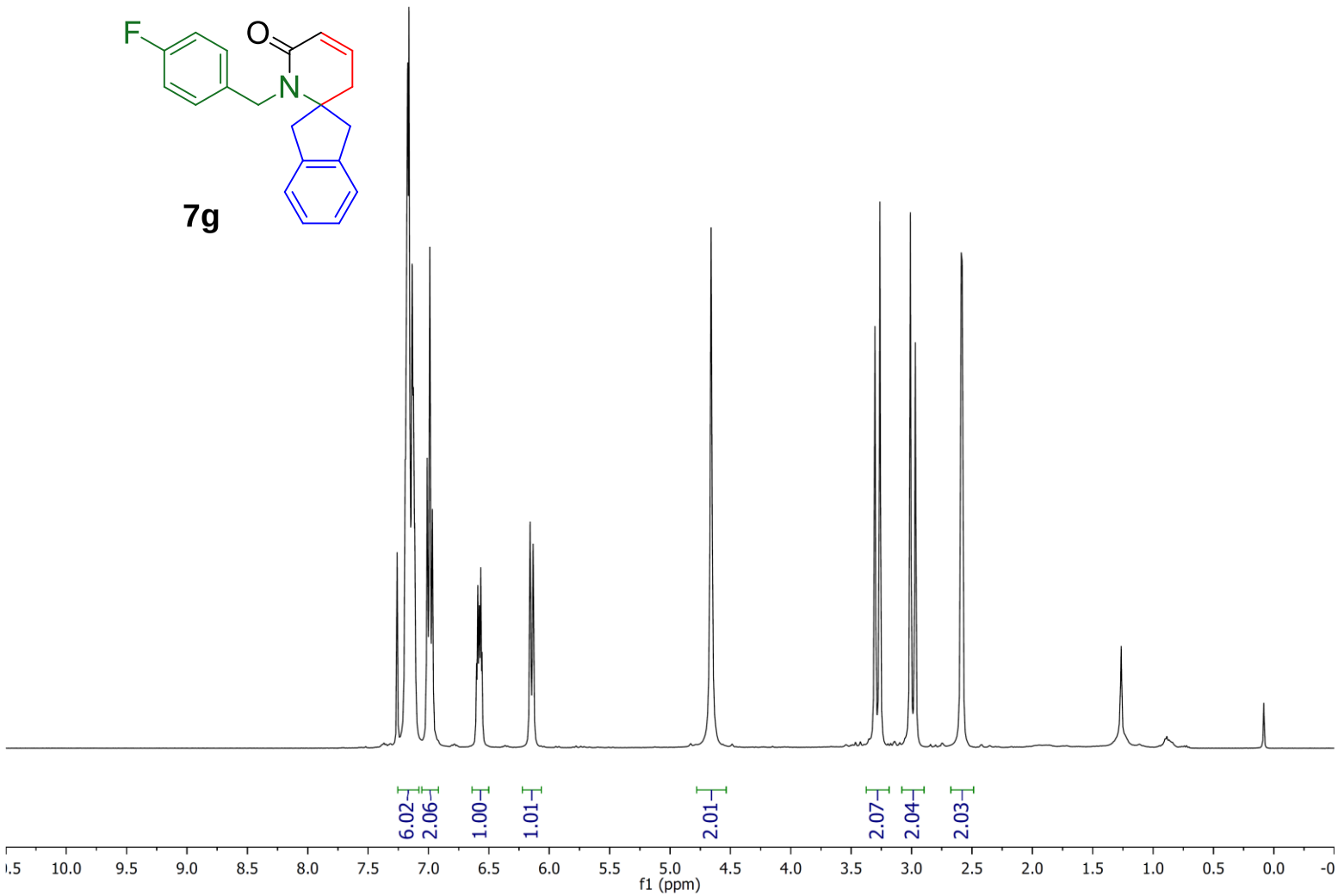

166.6
142.9
138.1
128.8
128.3
126.6
125.8
67.3
49.2
47.0
36.6
35.8
23.4
f1 (ppm)
O
N
Ph
Ph
7e


O
Me
N
Ph

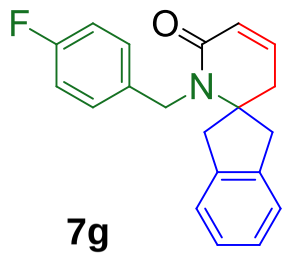
7f

5.07
1.02
1.00
1.04
1.02
1.05
2.12
1.04
6.05
4.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


166.4
145.0
137.7
128.3
127.5
126.4
125.8
67.1
48.8
39.4
36.6
36.1
35.3
23.4
23.0
18.4
O
Me
N
Ph
7f
f1 (ppm)

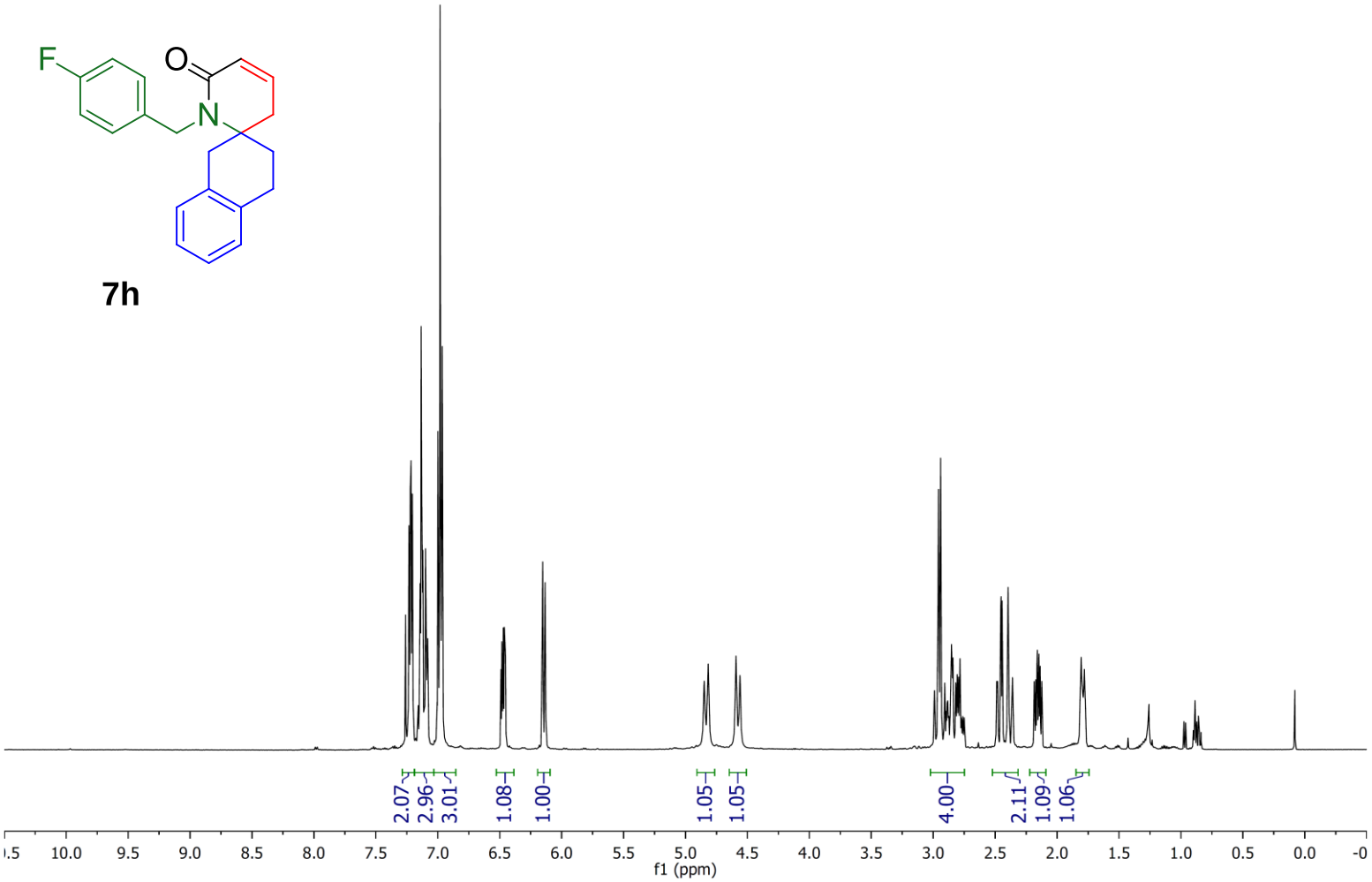

F
O
N
7g
6.02
2.06
1.00
1.01
2.01
2.07
2.04
2.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

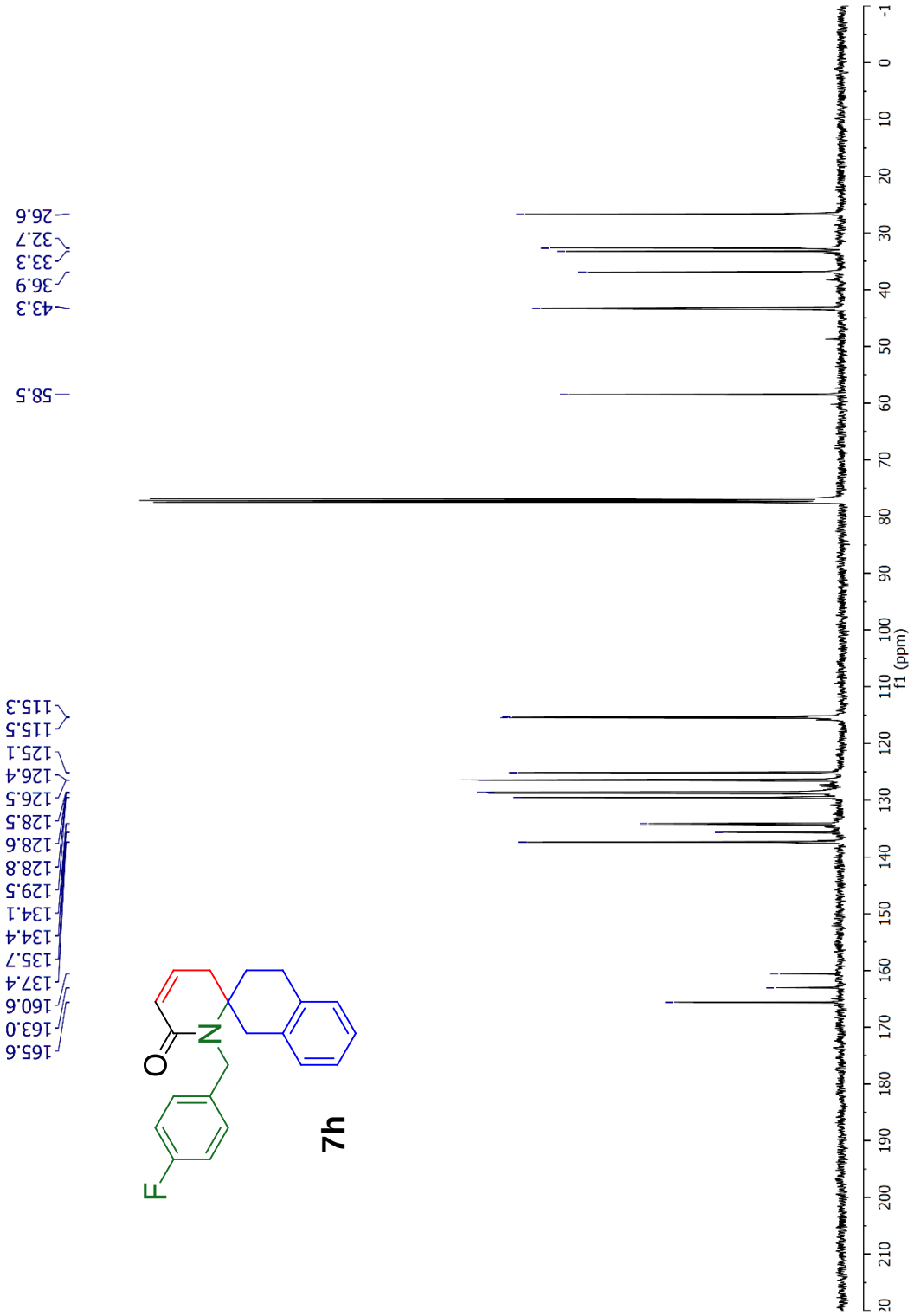
165.9
163.1
160.7
140.1
138.2
135.2
128.1
128.0
127.2
125.6
124.8
115.6
115.4
67.3
44.7
43.6
37.6
O
N
F
7g
f1 (ppm)

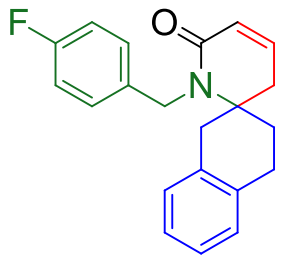

F
O
N

7g

-117.6
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-1
f1 (ppm)

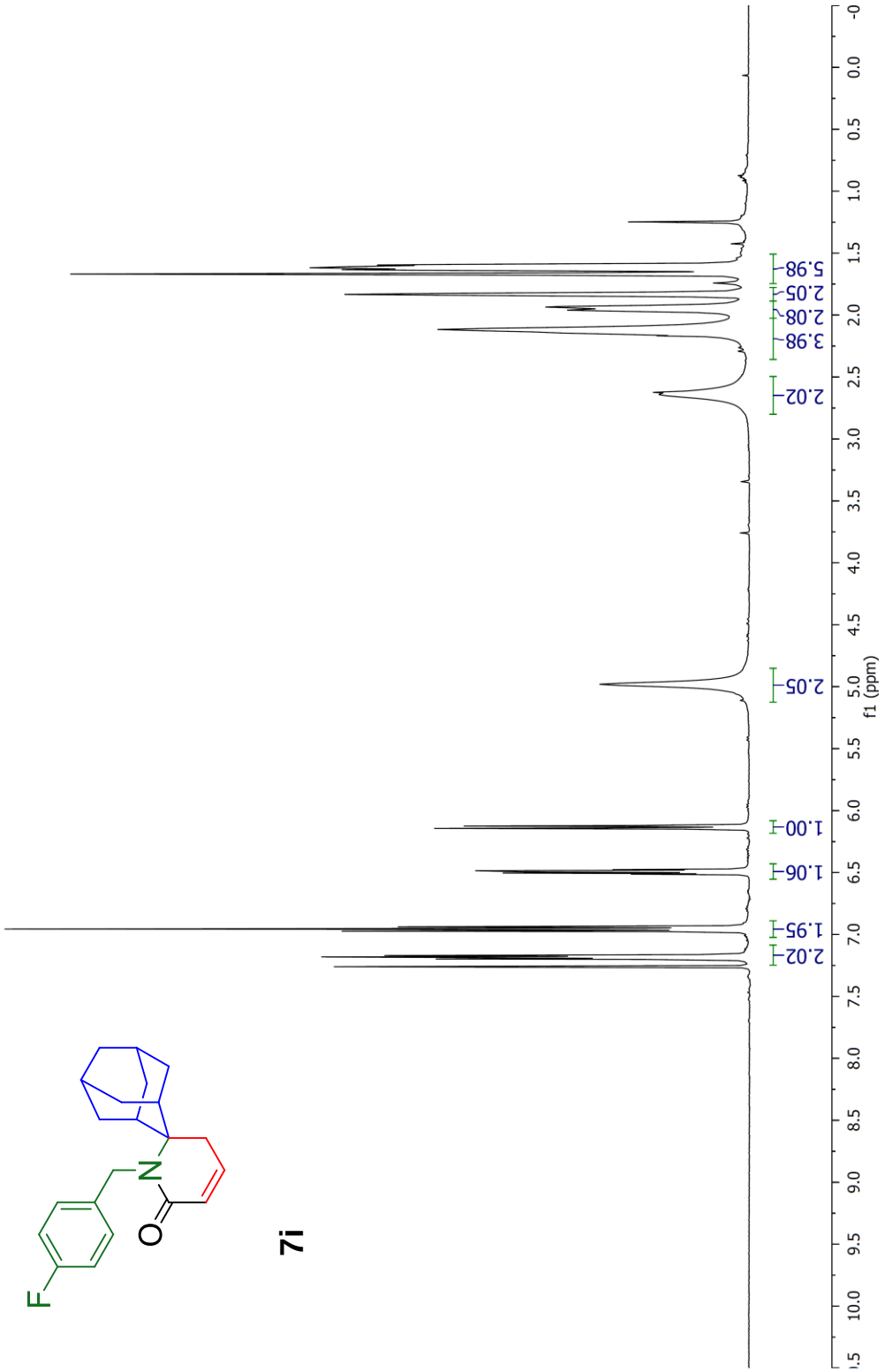

F
O
N
7h
2.07
2.96
3.01
1.08
1.00
1.05
1.05
4.00
2.11
1.09
1.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

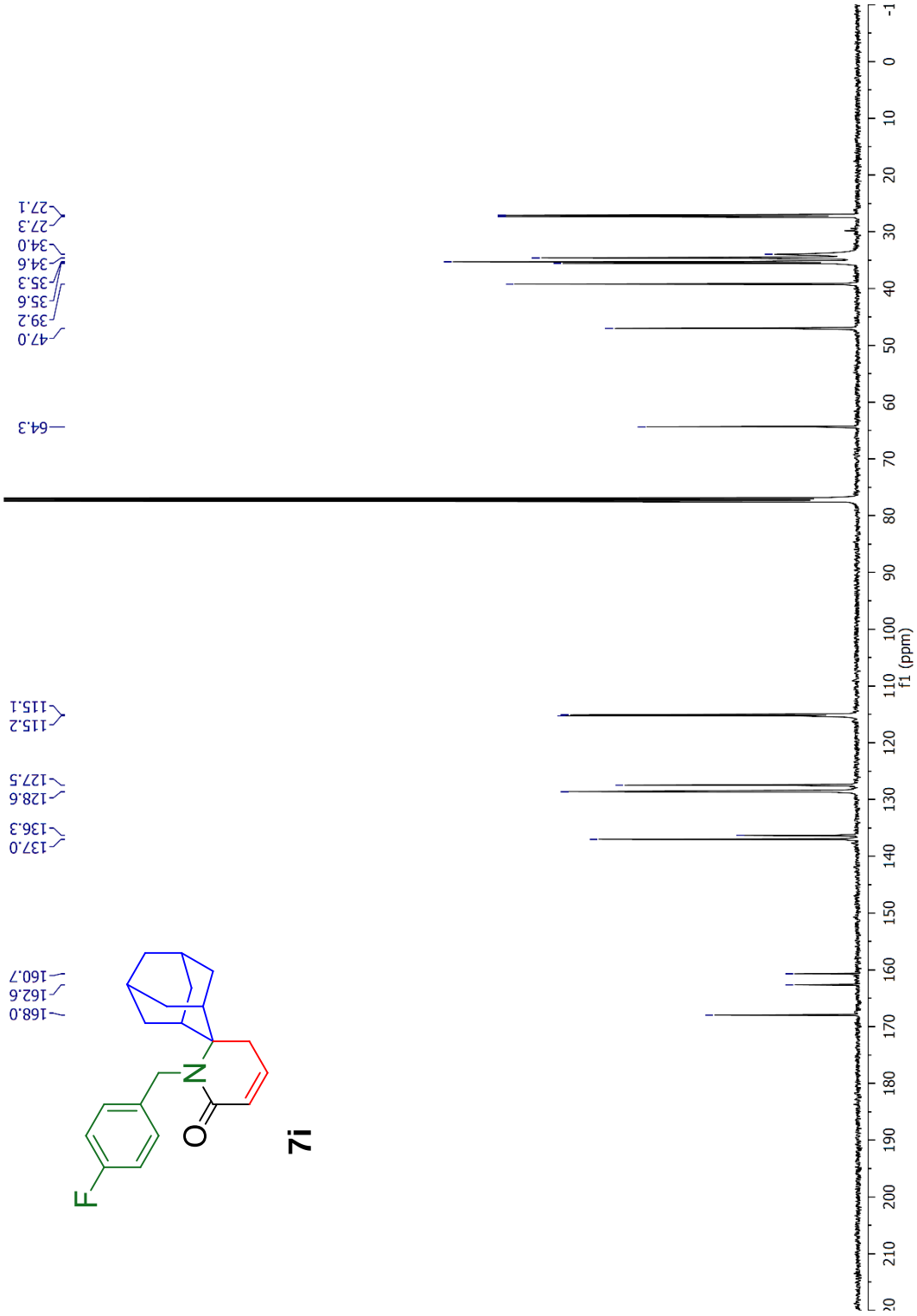

165.6
163.0
160.6
137.4
135.7
134.4
134.1
129.5
128.8
128.6
128.5
126.5
126.4
125.1
115.5
115.3
58.5
43.3
36.9
33.3
32.7
26.6
O
N
F
7h
f1 (ppm)

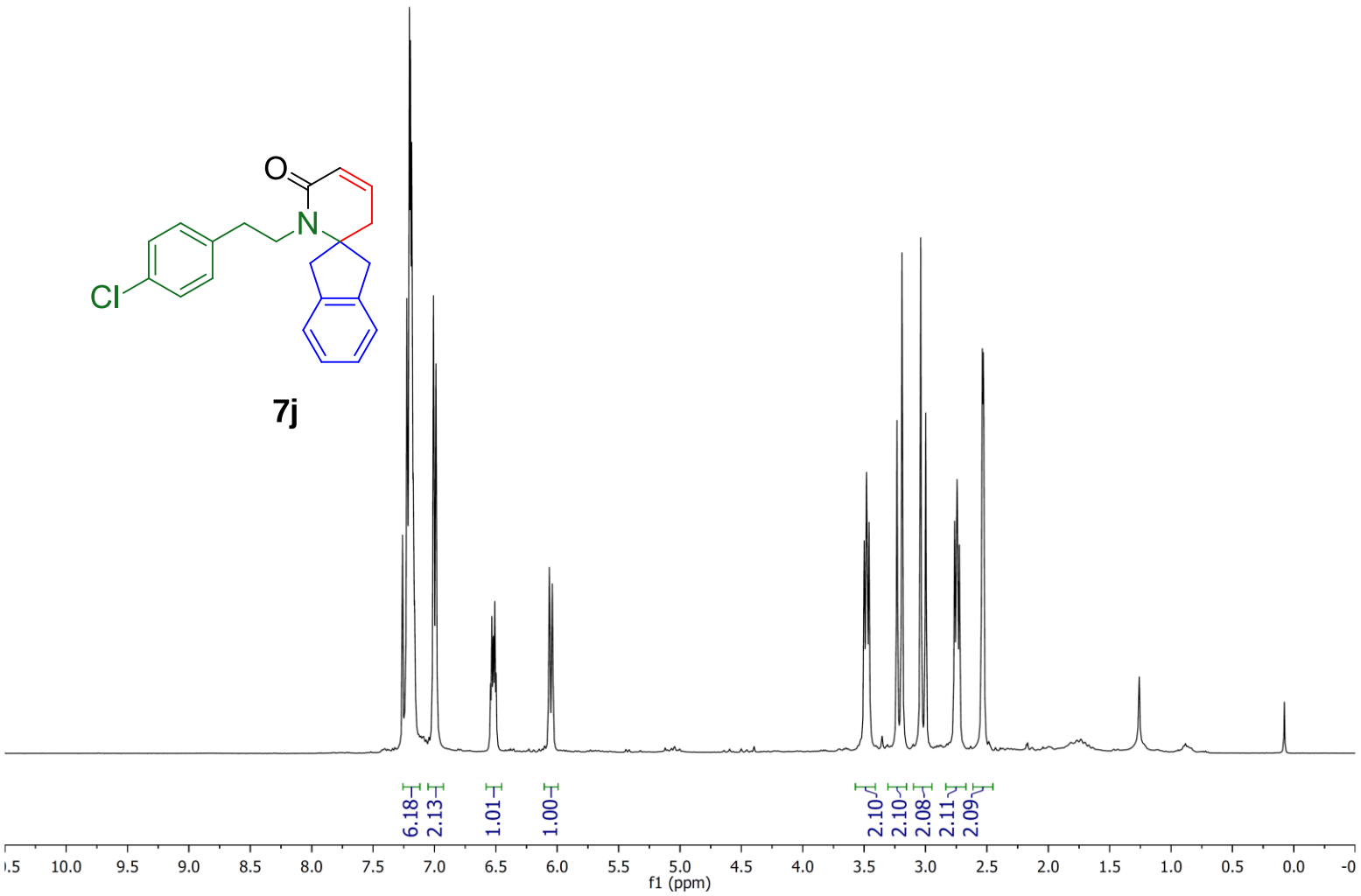

F
O
N

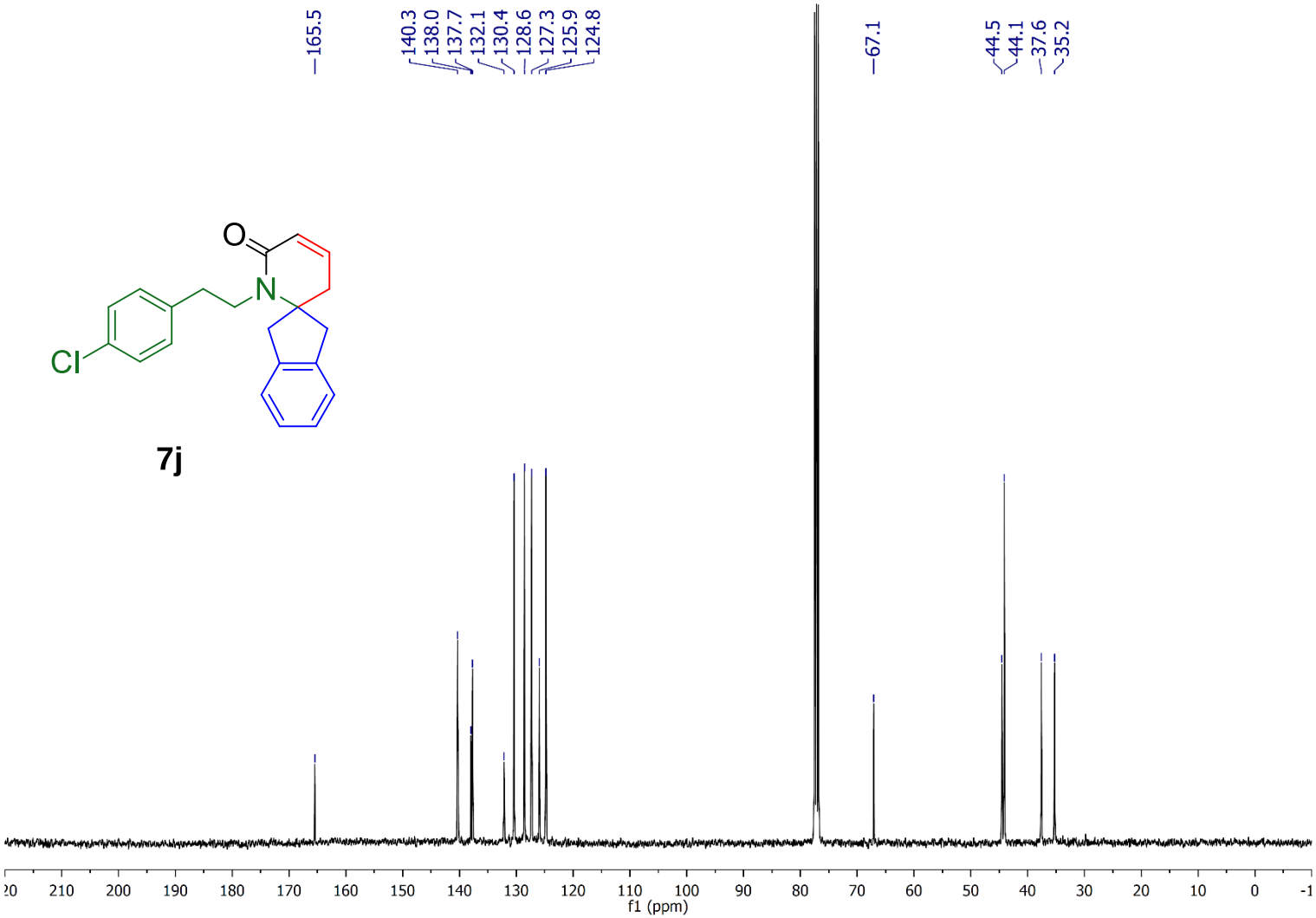
7h

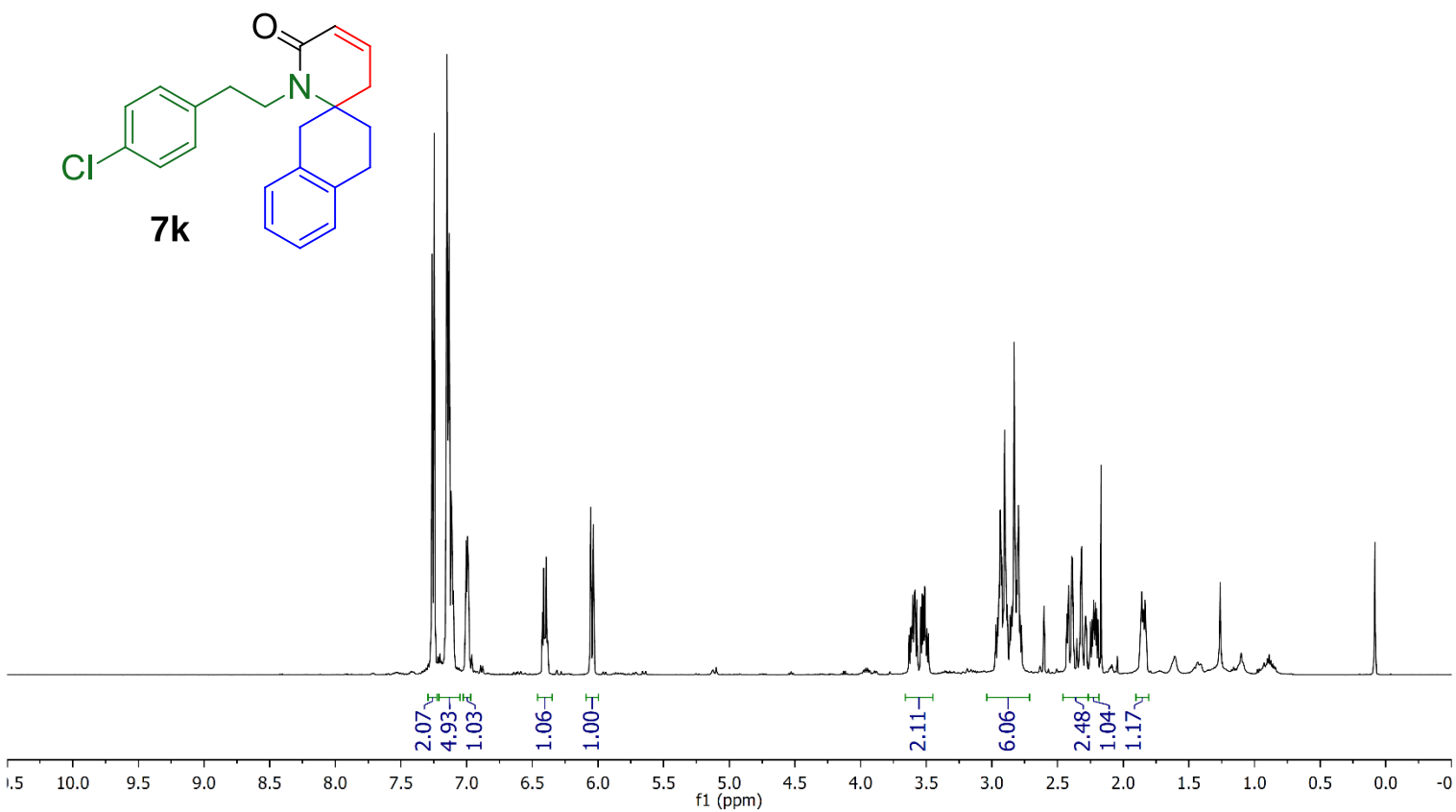
117.5
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

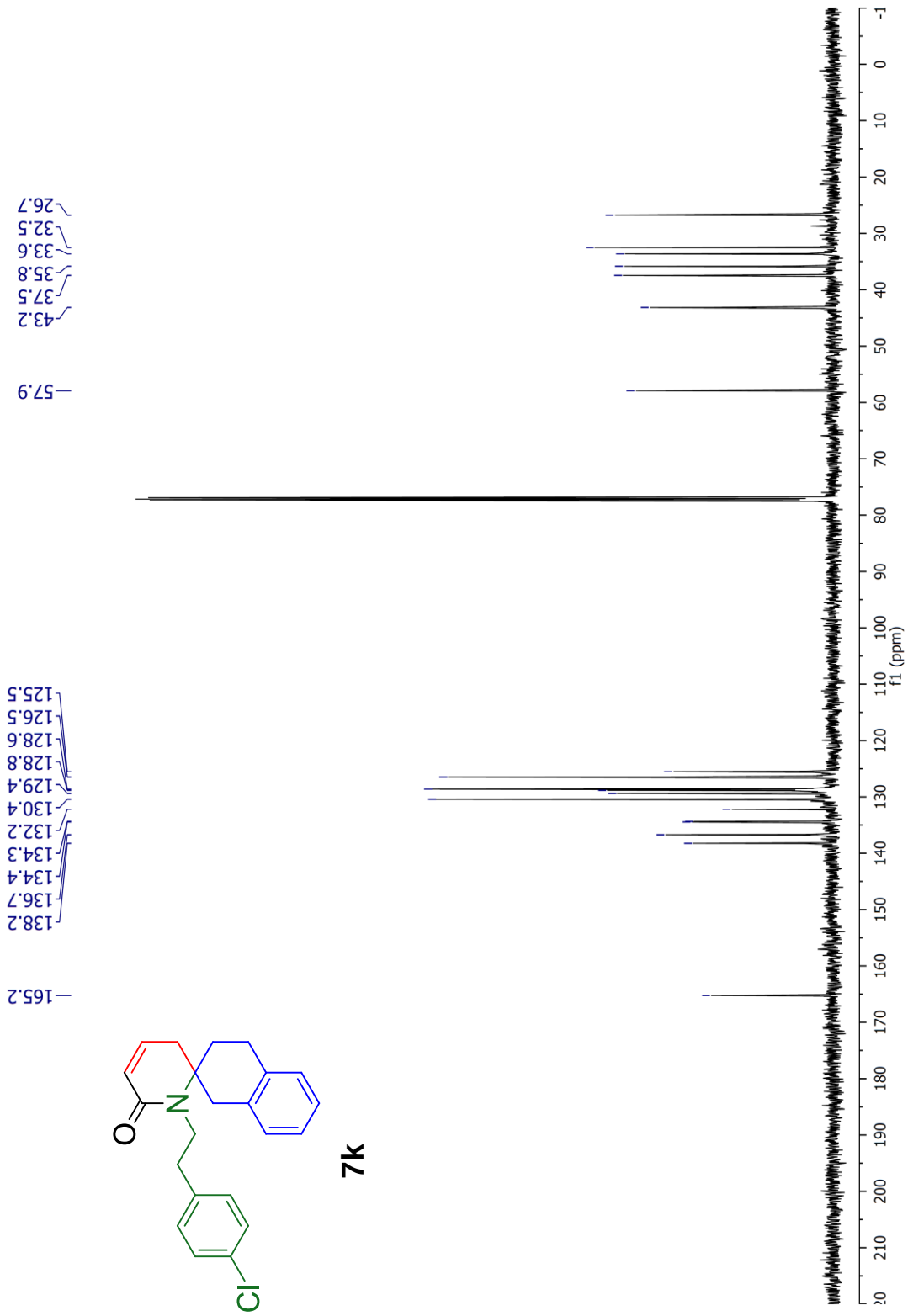

F
O
N
7i
2.02
1.95
1.06
1.00
2.05
5.98
2.05
2.08
3.98
2.02
f1 (ppm)

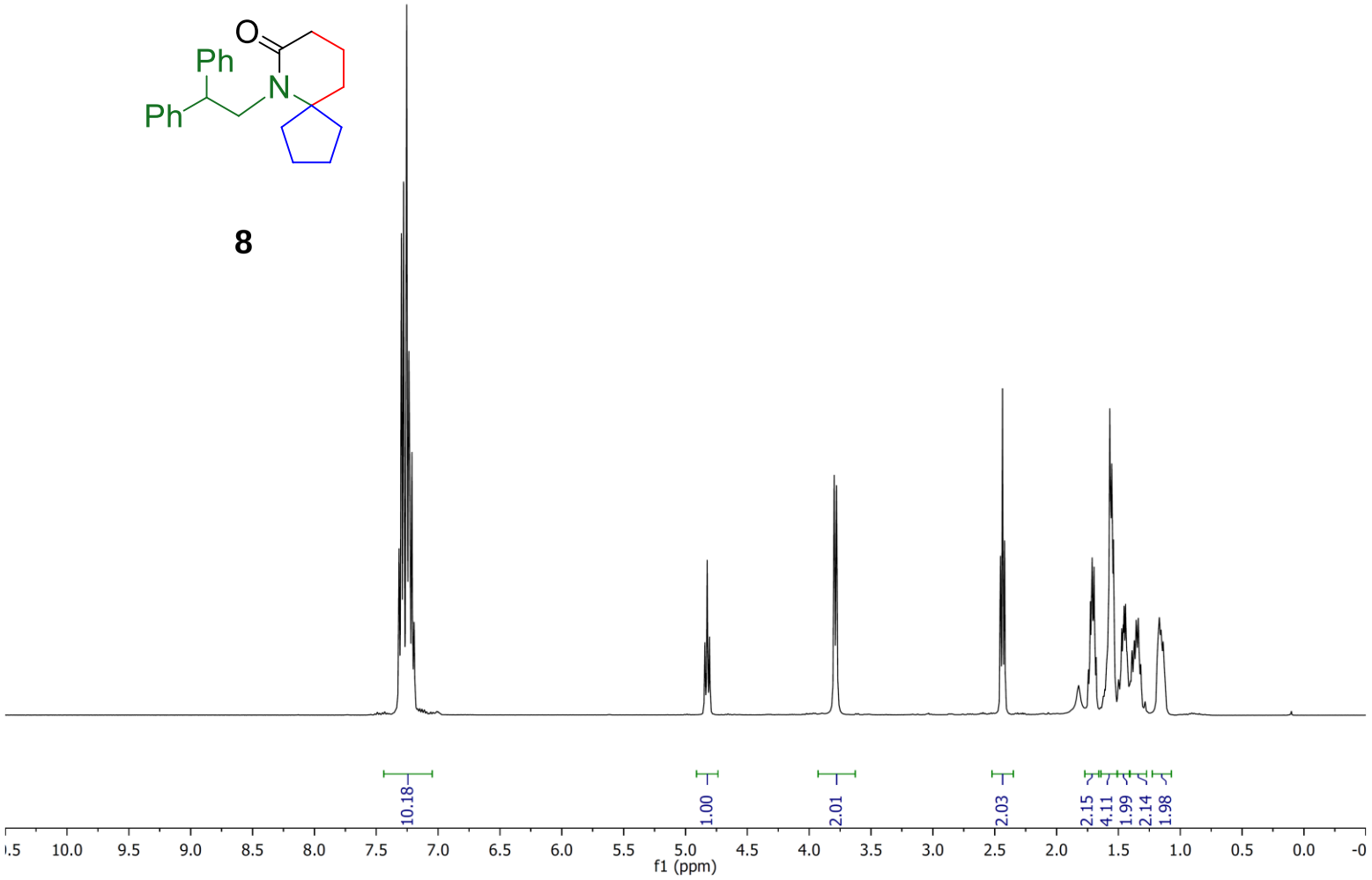

168.0
162.6
160.7
137.0
136.3
128.6
127.5
115.2
115.1
64.3
47.0
39.2
35.6
35.3
34.6
34.0
27.3
27.1
F
N
O
7i
f1 (ppm)

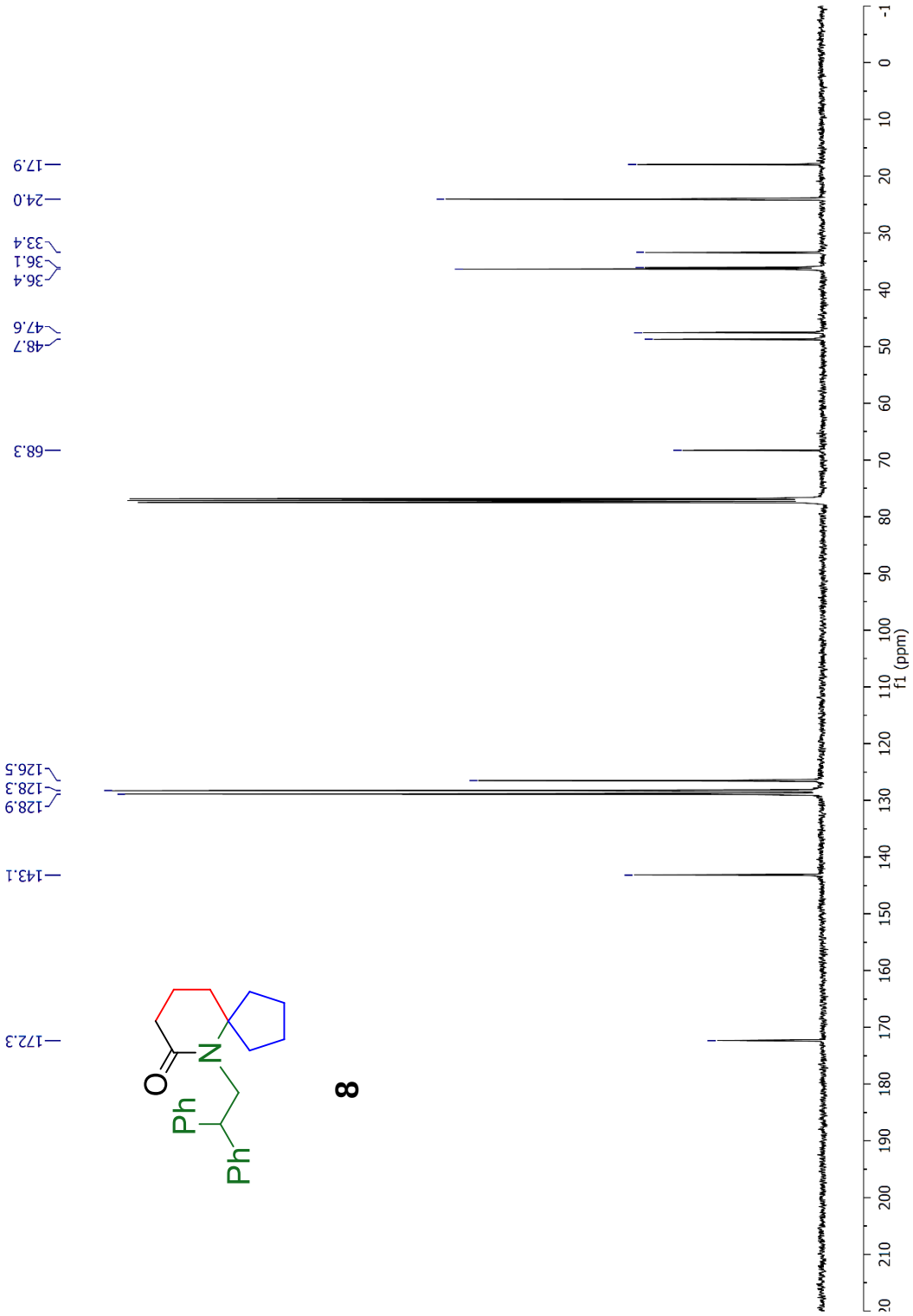

O
N
Cl
7j
6.18
2.13
1.01
1.00
2.10
2.10
2.08
2.11
2.09
f1 (ppm)


165.5
140.3
138.0
137.7
132.1
130.4
128.6
127.3
125.9
124.8
67.1
44.5
44.1
37.6
35.2
O
N
Cl
7j
f1 (ppm)


O
N
Cl
7k
2.07
4.93
1.03
1.06
1.00
2.11
6.06
2.48
1.04
1.17
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


165.2
138.2
136.7
134.4
134.3
132.2
130.4
129.4
128.8
128.6
126.5
125.5
57.9
43.2
37.5
35.8
33.6
32.5
26.7
O
N
Cl
7k
f1 (ppm)


O
Ph
N
Ph
8
10.18
1.00
2.01
2.03
2.15
4.11
1.99
2.14
1.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.3
143.1
128.9
128.3
126.5
68.3
48.7
47.6
36.4
36.1
33.4
24.0
17.9
f1 (ppm)
O
N
Ph
Ph

8

Chapter Three: Transition-Metal Free Electrophilic Cyclizations of Alpha-Tetrasubstituted Homoallylamines to Form Substituted Pyrrolidines

3.1 Introduction

Pyrrolidines are ranked 4th in the top ten list of heterocycles found in known drugs and natural products under 500 Da,[1] making synthetic approaches to substituted variants useful for the purposes of drug discovery and design. Beyond their biological importance substituted pyrrolidines have synthetic utility as chiral

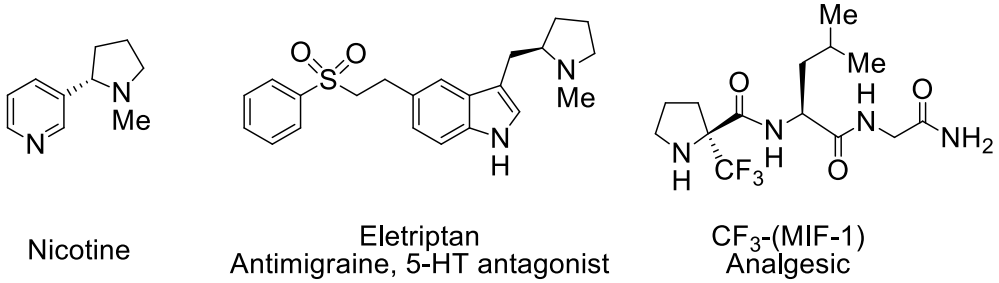
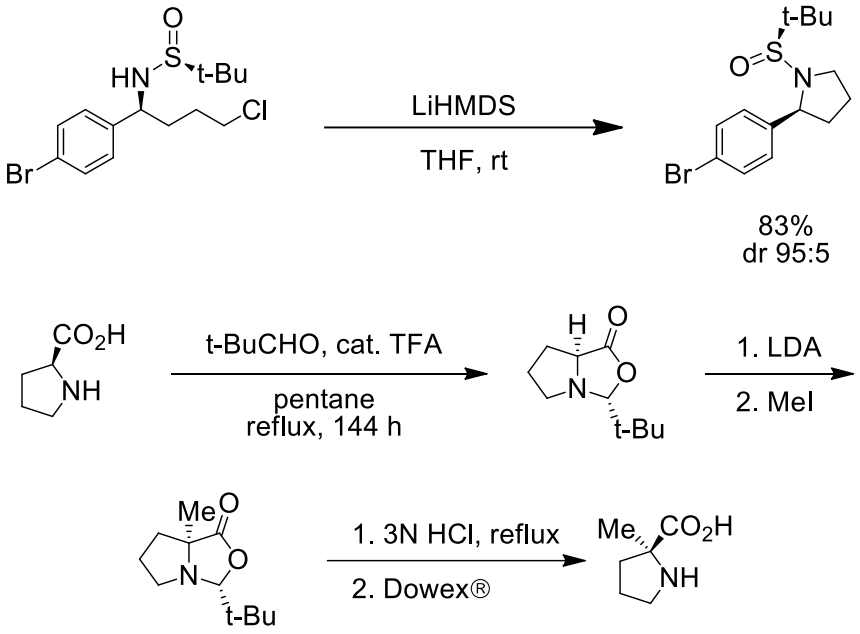


Figure 3.1: Natural products and bioactive compounds containing substituted pyrrolidines.

auxiliaries. Ring systems possess a similar advantage to that of spirocycles mentioned in Chapter 2 in that they have a lower conformational entropy cost to binding. Figure 3.1 shows a small sample of bioactive compounds containing substituted pyrrolidines.[1,2] CF_3-(MIF-1) is a trifluoromethylated analogue of the melanocyte-stimulating hormone release inhibition factor (MIF-1), an endogenous brain tripeptide involved in a variety of physiological processes. The replacement of the terminal proline residue with the synthetic tetrasubstituted proline variant was shown to enhance its potency over MIF-1. Synthesis of the modified proline is an 8-step process from ethyl trifluoropyruvate. More direct synthetic pathways

to alpha-tetrasubstituted, and other diversely substituted pyrrolidines is a worthwhile endeavor.

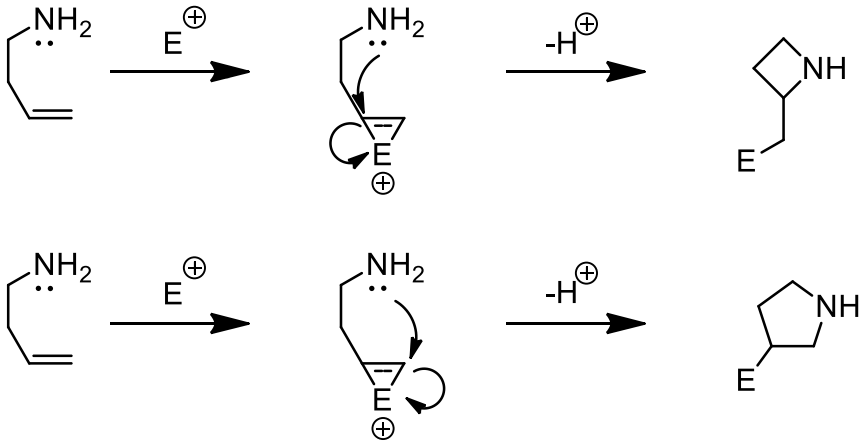


Scheme 3.1: General synthetic pathways to substituted pyrrolidines include diastereoselective intramolecular nucleophilic substitution aided by an Ellman auxiliary (top) and methylation of proline by the Seebach method (bottom).

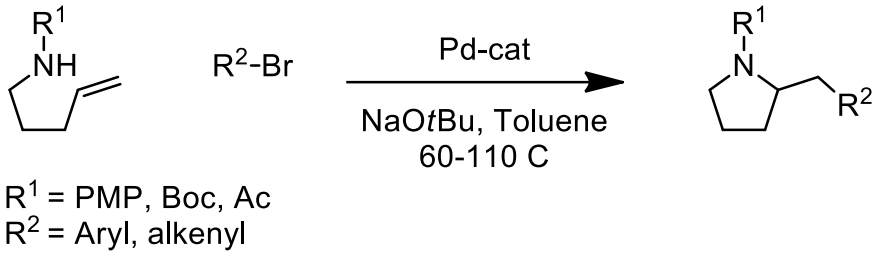
Typical synthetic approaches to substituted pyrrolidines can be as simple as intramolecular nucleophilic attack of a 4-halobutanamine (Scheme 3.1).[3a] This sort of approach is somewhat limited when it comes to the desired stereocontrol needed for particular products when using racemic starting materials. Additionally, if tetrasubstitution is required at the alpha-position, the efficiency of such reactions becomes limited as you either end up with a hindered electrophile or amine. More popular approaches draw on the utility of proline as a naturally-occurring chiral synthon.[3b,c] One of the most commonly utilized synthetic strategies is pictured in Scheme 3.1. Unprotected proline can be converted via condensation/cyclization with pivaldehyde into a pyrrolizidine. This can then be treated with strong base and

methyl iodide to methylate the alpha position. Hydrolysis of the pyrrolizidine with HCl and treatment with a cationic exchange resin returns the modified proline free acid. There is a two-fold advantage to this method as it draws from nature's chiral pool, making the starting material readily available, and the method is stereoselective. The drawback to this approach is the limitation of the library of substituted prolines. It also only facilitates further substitution of the alpha position and requires the free amine to form the pyrrolizidine intermediate. In order to have more flexibility in the patterns of substitution and with substituents at the alpha-position other approaches can be taken. One of those is the synthesis of an allyl amine, followed by cyclization through the generation of a transient electrophilic species and its attack by the free amine.

Intramolecular cyclization of allylamines provide a synthetic route to substituted pyrrolidines as well as piperidines and azetidines. In the simplest instance electrophilic addition across the pi-system and subsequent nucleophilic attack by the nitrogen produces either the 4- or 5-membered ring system (Scheme



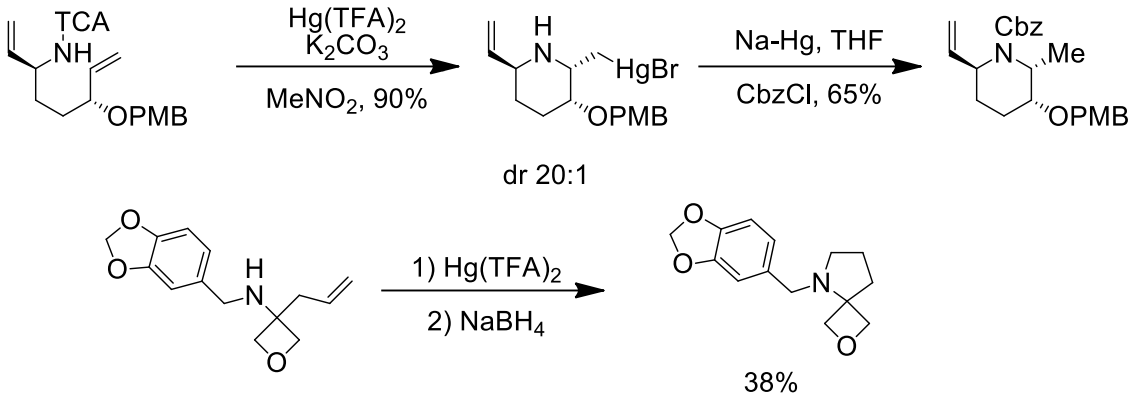
Scheme 3.2: Cyclization pathways of homoallyl amines induced by electrophilic addition to the pi-system.



Scheme 3.3: General conditions for Wolfe's palladium-catalyzed carboamination.

3.2). Most modern approaches to electrophile-induced cyclization of aminoalkenes use either transition metals (catalytically or stoichiometrically)[4] or electrophilic halogen and chalcogen species.[5] Choice of approach is contingent upon starting substrate, desired stereoselective control, and further synthetic considerations.

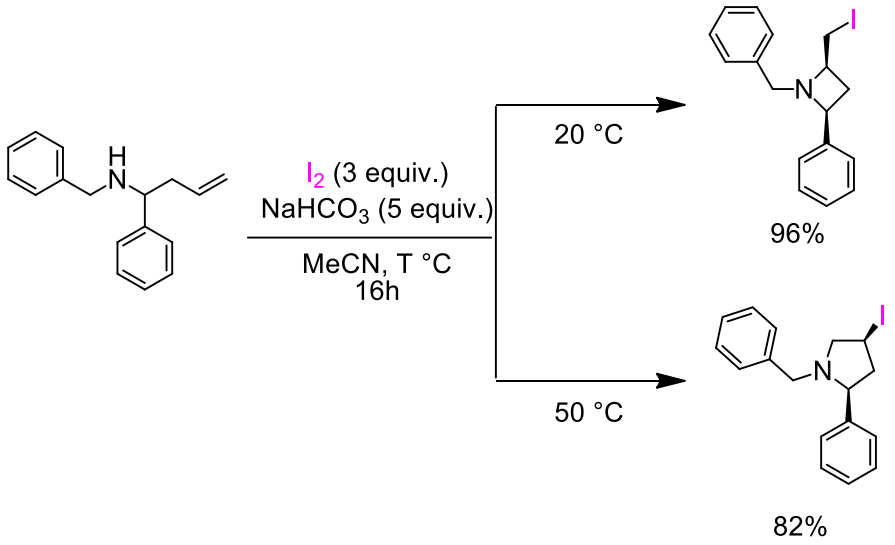
One of the most widely used transition metals used for these transformations is palladium. Palladium (II) salts effectively afford the desired cyclized products under mild conditions and in some cases performed better catalytically than stoichiometrically.[6] These cyclization reactions found a synthetic niche in the preparation of complex nitrogen containing alkaloids. [6,7a] Wolfe's palladium-catalyzed carboamination chemistry has been shown to be a flexible approach to intramolecular nitrogen-carbon bond formation and secondary functionalization of the alkene.[8] Scheme 3.2 shows the general approach. Among the many synthetic uses for this methodology include the synthesis the synthesis of saturated 1,4-benzodiazepines[8b], tetrahydroquinolines, and tetrahydroisoquinolines.[8c] Additionally, using diallyl aniline derivatives Wolfe and coworkers were able to use cascade aminopalladation/carbopalladation reactions to synthesize polycyclic nitrogen heterocycles.[8d] It is worth noting that in order to obtain the substituted pyrrolidines it is necessary to start with the δ-aminoalkene



Scheme 3.4: Amidomercuration carried out with stoichiometric mercury (II) salts affords the desired heterocycle following reductive demercuration.

as the reaction proceeds through an *exo*-cyclization. While palladium makes up the wealth of this carboamination chemistry, similar alkene functionalization has also been carried out with gold (I) salts as well.[9] Zhang's group demonstrated the ability to perform carboaminations on terminal olefins using a gold (I) catalyst to both create the heterocycle and through a cross-coupling like manner introduce functionality from an aryl boronic acid.

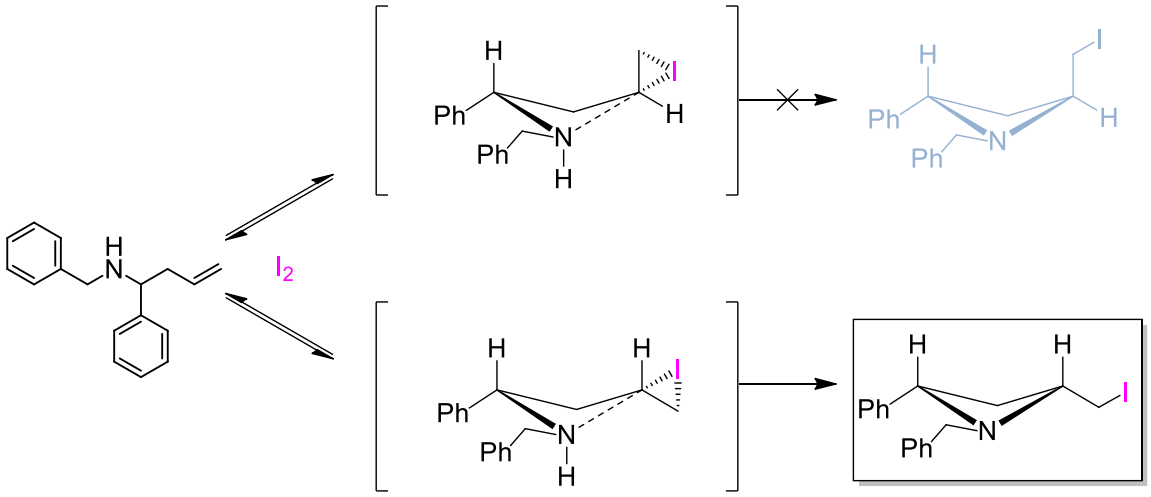
Other common transition metal routes require the use of stoichiometric amounts of mercury salts. Han et al utilized intramolecular amidomercuration to perform a stereoselective synthesis of (+)-*iso*-6-casine.[10a] The size of the mercury ion and its interaction with an *N*-trichloroacetyl protecting group allowed for a stereoselective cyclization with a diastereoselectivity of >20:1 (Scheme 3.3). Sequential treatment with $Hg(TFA)_2$ then $NaBH_4$ has also been used to prepare azaspirocycles, including those containing heavily strained oxetane rings.[10b,c] Unlike the above mentioned methodologies utilizing palladium, the mercury is still present following the initial cyclization and can be further manipulated through either ionic or free radical processes.



Scheme 3.5: Fossey and co-workers iodocyclization methodology affords the *cis*-azetidine exclusively when run at 20 °C, slight elevation of the temperature alternatively gives the *cis*-pyrrolidine.

Halogen and chalcogen species present a metal-free pathway to access these heterocycles. These reactions can be carried out using an elemental halogen (I_2, Br_2), *N*-halosuccinimides (NCS, NBS, and NIS), or phenylselenyl halides; specifically PhSeBr and PhSeCl. In most cases the halogen is not retained, but rather removed by either elimination or nucleophilic substitution by water or an alcoholic solvent.

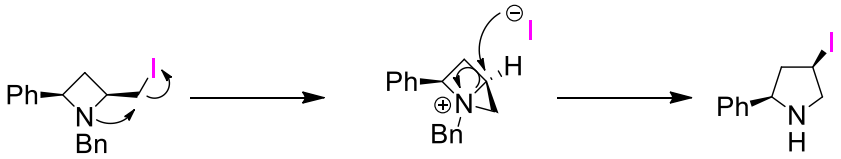
Elemental iodine and bromine have been used in the synthesis of heterocycles found in natural products. Standout examples include William's total synthesis of (+)-croomine[10a] and Backvall's stereoselective synthesis of perhydronicotoxin[11b]. Ward's work on the synthesis of virantmycin analogues compared the effectiveness of diatomic iodide and bromide towards the cyclization of 2-allylanilline species.[10c] In the majority of cases it appears that iodine is the



Scheme 3.6: Fossey's proposed transition state for the iodine-mediated cyclization suggests the *cis*-selectivity results from the disfavored transition state the *trans* isomer would have to proceed through.

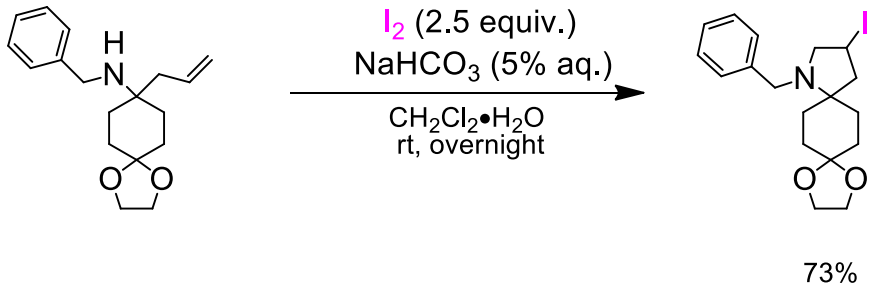
more effective of the pair, giving higher yields, requiring milder conditions, and yielding fewer side products (dibromination is often observed).

As mentioned above typically the halogen is removed in the following steps. In the case of iodocyclizations the resultant substrate makes a useful electrophile. Fossey and co-workers were able to develop a generalized methodology for the iodocyclization of homoallyl amines (Scheme 3.4).[12] By the addition of elemental iodine and a large excess of sodium bicarbonate to an alpha-trisubstituted homoallylamine at ambient conditions the corresponding iodoazetidine was afforded in excellent yields. Despite the more strained ring system the 4-*exo* cyclization is more favored than the 5-*endo*.[13] Of additional interest is the fact that



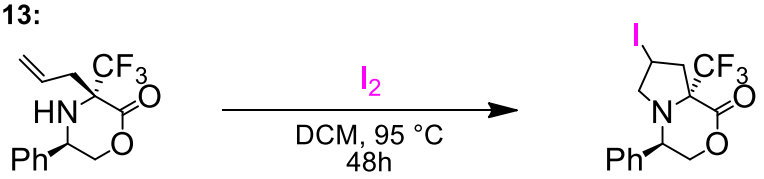
Scheme 3.7: The rearrangement of the iodoazetidine to the iodopyrrolidine is proposed to go through the highly strained bicyclic intermediate.

Bonjoch 2007:



73%

Brigaud 2013:



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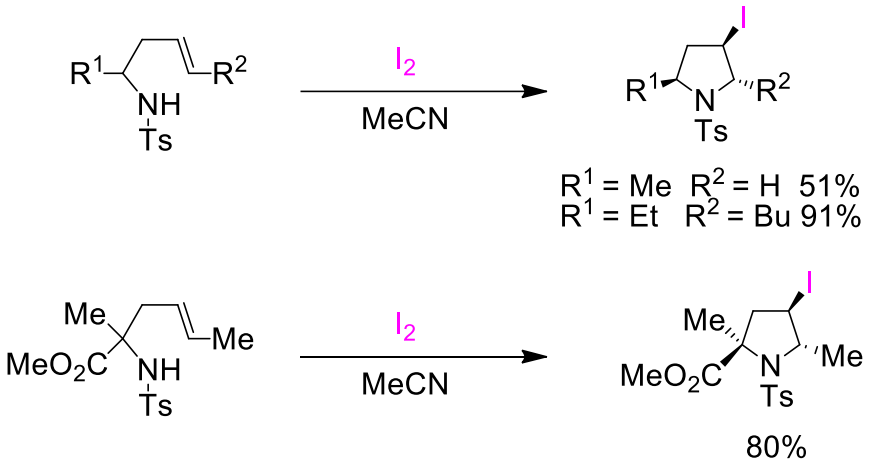
Scheme 3.8: Previous attempts at the iodocyclization of alpha-tetrasubstituted homoallylamines.

only the *cis* product is observed. Examination of the proposed mechanism shows that in order to obtain the *trans* product a heavily disfavored transition state with significant pseudo 1,3-diaxial interactions is required (Scheme 3.5). When the reaction was run at elevated temperature (50 °C), the iodopyrrolidine was instead observed having undergone thermal isomerization with complete stereocontrol. DFT calculations support that the rearrangement occurs through a highly strained bicyclic intermediate (Scheme 3.6).[14] Fossey et al were able to take both iodoazetidines and iodopyrrolidines and treat them with an excess of primary or secondary amine and obtain the new diamine in good yields. These diamines are of synthetic interest as they were tested for rudimentary biological activity in zebrafish assays and were shown to be active in the micromolar range. Additional nucleophiles were shown to be useful as they were also able to use sodium azide.



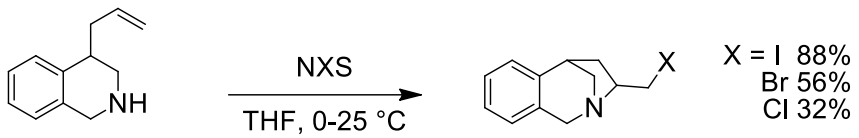
Scheme 3.9: Knight's group only obtained the iodopyrrolidine upon iodocyclization of homoallyl tosylamides.

The resultant azide would readily undergo a click reaction with phenylacetylene and stoichiometric copper (I) iodide to give the corresponding triazole.

The 4-exo cyclization selectivity of Fossey's substrates was observed to be consistent throughout various substrates as far as variation at the alpha-position was concerned, though more electron-deficient substituents were shown to slightly erode that selectivity. This includes 15 examples of substrates reported with >99% yields by ^{1}H-NMR. However, when the substitution off the nitrogen was changed to something non-benzylic (cyclohexyl and *n*-propyl were reported) the selectivity was reversed and only the 5-endo cyclization product was observed though with much lower yields, <40% in both cases. This is similar to other attempts at the iodocyclization of alpha-trisubstituted homoallyl amines. Knight and co-workers showed that under similar conditions a homoallyl tosylamide solely produced the iodopyrrolidine instead of the azetidine (Scheme 3.9).[15] This was seen also with a number of 1,2-disubstituted alkenes, and it is noteworthy that the monosubstituted

alkene had far and away the lowest yield of the attempted substrates at 51% (more than 30% less than the next lowest yield). This along with the trend observed by Fossey's group suggests that the cyclization pathway is heavily dependent on the overall nucleophilicity of the nitrogen species present. In addition to these two instances Komatsu and Minakata had performed the iodocyclization of the unsubstituted homoallyl tosylamide.[16] They reported a low yield of 8%. Furthermore, the product was said to be a mixture of both the 4-exo and 5-endo cyclization pathways. The conditions utilized by Komatsu and Minakata were slightly different in that they used elemental iodine in conjunction with chloramine-T which would have provided a more aggressive iodonium source. This combined with the electron-poor tosylamide could logically provide the mixture of both cyclization pathways.

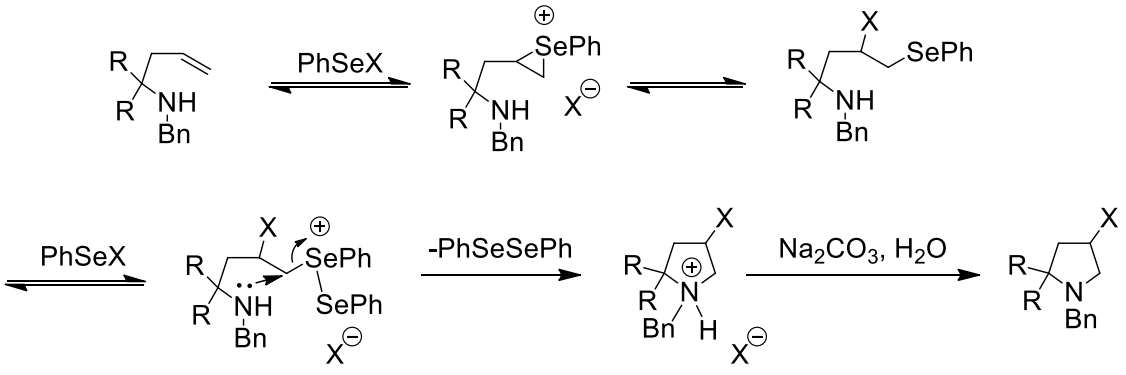
Knight's group continuing their work a decade later went on to take their methodology and apply it to alpha-tetrasubstituted homoallyl tosylamides.[15] They reported obtaining solely the 5-endo pyrrolidine product. The group only reports the results of the cyclizations of 1,2-disubstituted alkenes. No mention or reference is made to the corresponding reaction with a terminal alkene as they had shown previously with the alpha-trisubstituted homoallyl tosylamides (Scheme 3.9).



Scheme 3.10: N-halosuccinimides were screened for the purposes of constructing an azabicyclic core found in possible N-methyl-D-aspartic acid (NMDA) noncompetitive antagonists.

Similar reactions with alpha-tetrasubstituted homoallylamines have afforded only the iodopyrrolidine, though with somewhat disparate approaches. Bonjoch's conditions[17] required the use of water as a co-solvent with dichloromethane, likely to avoid solubility issues with the sodium bicarbonate base used, but these reactions proceeded at ambient conditions. The other unique incidence of this reaction was demonstrated by Brigaud and co-workers in 2013 (Scheme 3.8).[2] Unlike Bonjoch's substrates, Brigaud's do not possess a ring system at the alpha-position but rather the amine is fixed in a ring. Brigaud's conditions did not require the use of water as a co-solvent and omitted the base entirely. The other noticeable difference is that the reaction was run at 95 °C.

Despite the alluring simplicity of using elemental halogens for this purpose, *N*-halosuccinimides have shown wider use for the purposes of introducing



Scheme 3.11: Outurquin's proposed mechanism for the phenylselenyl halide induced cyclization of secondary homoallylamines.

electrophilic halogen species. This is especially true in the case of chlorine where working with the elemental gas is not as convenient. As with the elemental halides, *N*-iodosuccinimide is shown to be the most effective of these reagents. In one case Carroll et al demonstrated a significantly higher yield for azabicycloheptanes when using NIS over NBS or NCS, 88% vs 56 and 32% respectively (Scheme 3.8).[18] There are several notable examples where these reagents were used for the purposes of creating/extending polycyclic systems as well as bridged cyclic structures found in natural products.[18,19]

The last and least used route, though arguably one of the most interesting, is the use of phenylselenyl halides. Dependent on the conditions of the reaction and the substrate these reagents can be used to provide the halogenated heterocycle, the selenylated compound, or the disubstituted product. High equivalence of the phenylselenyl halide along with high reaction temperatures gives predominantly the halopyrrolidine whereas lower equivalency and ambient conditions yield either the selenylated compound or the disubstituted product. The high heat and selenium equivalency is likely required for the oxidation of the phenylselenyl functional group and its subsequent removal.

Outurquin and co-workers have shown across a series of publications that through stoichiometry and temperature these phenylselenyl halides can be reacted with alpha-tetrasubstituted amines and yield either the selenylated azetidine or pyrrolidine or the halogenated pyrrolidine. The proposed mechanism suggests that the phenylselenyl halide adds across the pi-system and then there's an *anti*-

addition by the halide to produce the disubstituted intermediate. The selenium bound to the substrate can now act as a nucleophile and react with another equivalent of phenylselenyl halide. At this point the selenide is a good leaving group encouraging the intramolecular cyclization by the free amine (Scheme 3.9). This 5-*endo* cyclization pathway does not display any pronounced diastereoselectivity.

3.2 Electrophilic Cyclization to Form Beta-Chloropyrrolidines and Beta-Bromopyrrolidines

The initial approach used to synthesize beta-halopyrrolidines was the use of phenylselenyl halide species. Outurquin's conditions[20] were initially screened on substrate **1a** alongside an identical reaction run in dichloroethane. The dichloroethane reaction displayed a greater overall conversion to product by GC. The

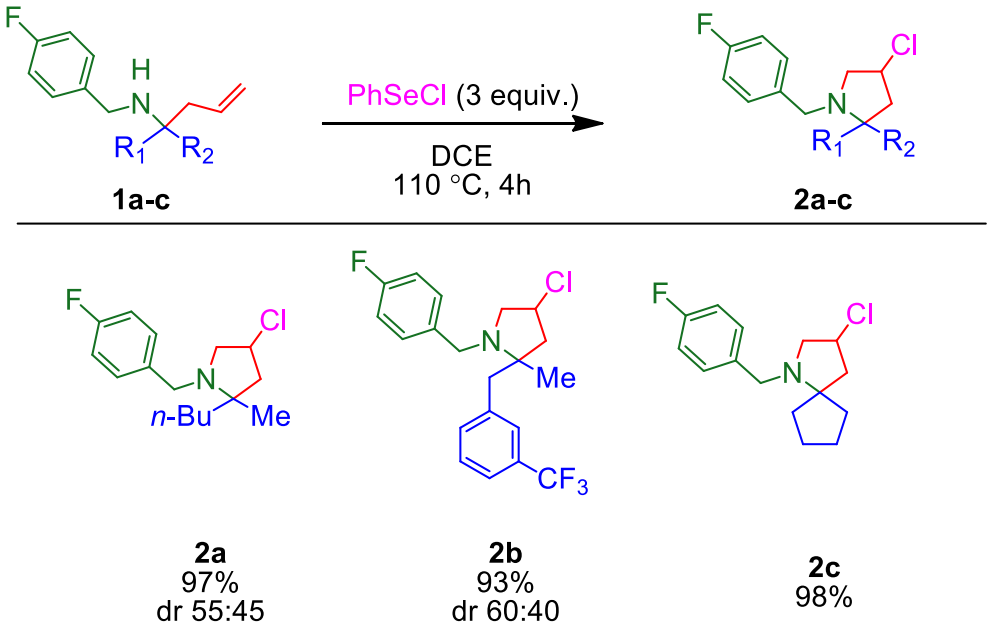
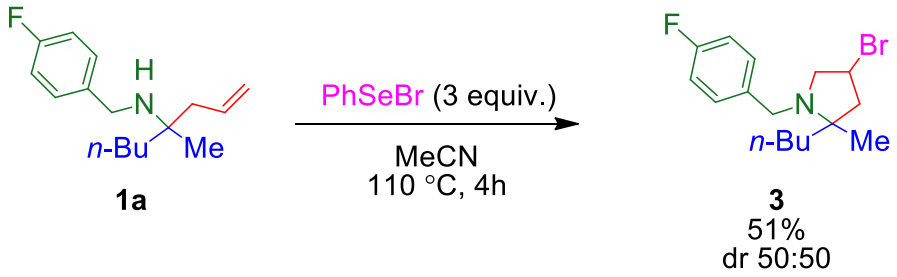


Table 3.1: Phenylselenyl chloride induced cyclization of homoallyl amines gives products in excellent yields and minimal diastereoselectivity.

reaction in DCE proceeded to completion in 18 hours gave product in excellent yield (Table 3.1). ^{1}H-NMR of the purified product shows the presence of both diastereomers, with a dr of 55:45. Repeated trials showed that the reaction proceeds to completion in only 4 hours with comparable yield. Cyclic substrate **1c** also reacted under these conditions to give the corresponding 1-azaspriocycle in quantitative yield. In an attempt to enhance the dr, a substrate possessing more steric bulk off the tetrasubstituted carbon was selected. Substrate **1b** gave the expected beta-chloropyrrolidine in 93% yield but with only a slight enhancement in the diastereoselectivity (60:40). In this case of this substrate diastereoselectivity could be measured both by ^{1}H-NMR as well as GC as the diastereomers were resolvable. Despite best efforts the diastereomers did not resolve by column chromatography.

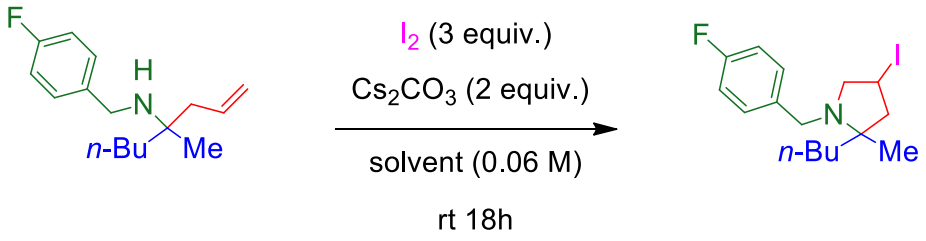


Scheme 3.12: Cyclization with phenylselenyl bromide gives product though in a lower yield than that of the correspoding chloride.

Due to toxicity of the phenylselenyl halide species, there were attempts to lower the equivalency of the reagent. According to the proposed mechanism (Scheme 3.9)[20] only two equivalents should be necessary, for the initial addition to the π-system and the formation of the diphenyl diselenide leaving group. Screening of lower equivalences of phenylselenyl chloride in the presence of **1a**

show that even slight reductions cause a significant drop in overall conversion as monitored by GC (Table 3.1). Within 4 hours the standardized conditions show complete conversion to product. Lowering the equivalence by 0.5 drops the conversion by 30%, and only 2 equivalents shows a minimal conversion of only 15%. This suggests an appreciable amount of degradation of the phenylselenyl chloride or possibly a more complex mechanism than what has been proposed.[17]

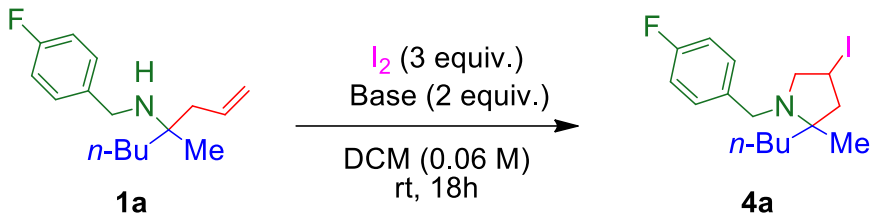
Using the optimized conditions phenylselenyl bromide was utilized next to form the beta-bromopyrrolidine. Upon reaction with **1a** full conversion observed in 4 hours, however confirmation by product by ^{1}H, ^{19}F-NMR, and MS showed only trace amount of the desired product. Aforementioned methods revealed that the primary product was in fact the beta-chloropyrrolidine than the desired brominated species. This is likely due to halogen exchange with the dichloroethane solvent



Solvent	%GC conv.
DCM	78
MeCN	16
Toluene	76
1,4-Dioxane	24
DMF	3
THF	20
DMSO	6
Et_2O	18

Table 3.2: Solvent screen for iodocyclization of **1a** showed that DCM gave the best overall conversion and more polar solvents performed far more poorly.

(Scheme 3.10). This issue was resolved by changing the solvent back to acetonitrile. The resulting the beta-bromopyrrolidine product was produced in a far more modest yield of 51%. Despite the greater size of the bromine there was negligible change in the observed dr. The reaction was attempted with **1b** and while full conversion was observed the isolated product was largely inscrutable by ^{1}H-NMR. The minimal change in the diastereomeric ratio going from chloride to bromide is not surprising. The regioselectivity is determined by the initial facial selectivity of the selenium as it adds across the pi-system, and the halide addition is secondary.



1a **4a**

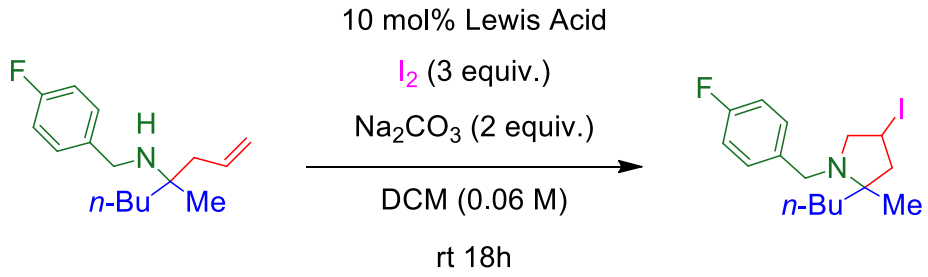
entry	Base	%GC conv.
1	-	44
2	$NaHCO_3$	49
3	Na_2CO_3	75
4	Cs_2CO_3	71
5	K_2CO_3	74
6	NaOAc	52
7	K_3PO_4	61
8	NaOH	66
9	KOtBu	39
10	Et_3N	<1

Table 3.3: Base screen for iodocyclization of **1a** shows that carbonate bases provide the best overall conversion to product with minimal difference between entries.

Seeking an alternative to the toxic phenylselenyl bromide, electrophilic cyclization was attempted on **1a** by using elemental bromine in glacial acetic acid.[18] The reaction, run in acetic acid, proceeds at room temperature and goes to completion in the 30 minutes. Despite this the resultant product mixture contains a mixture of products, including the desired pyrrolidine. ^{1}H-NMR of the product mixture shows resonances consistent with the desired product but also those of what is posited to be the dibrominated product. A number of variations were then run to see if the reaction could be driven the towards the formation of the pyrrolidine

instead of the dibrominated product. Raising or lowering the equivalency (1.5-3.0 equivalents) was shown to have no effect on the observed ratio of the products. Additionally, the rate of addition, whether all at once or in multiple aliquots showed no change. Lowering the temperature of the reaction to 0 °C also proved ineffective.

3.3 Iodocyclization of the Alpha-Tetrasubstituted Amines

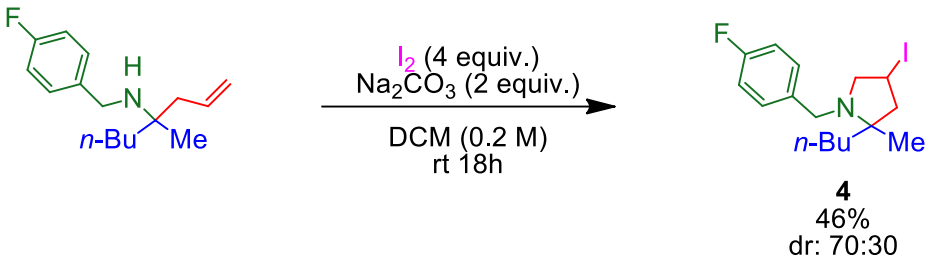


Lewis Acid	% conv. @ 4h	% conv. @ 18h
$AuCl_3$	50	80
AuCl	56	83
CuCl	60	87
$CuCl_2$	58	88
$Cu(OTf)_2$	44	76

Table 3.4: Addition of Lewis acid shows only marginal increase in maximum conversion, but appears to lower overall reaction rate.

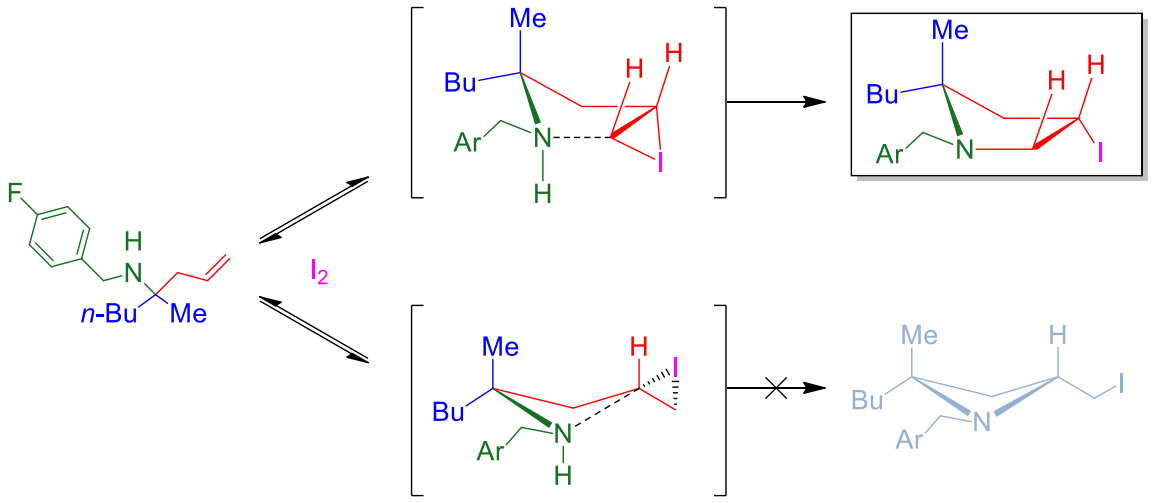
The synthetic approach to forming beta-iodopyrrolidines is a lot milder than that of the chloride or bromide variants. It is worth noting that Outurquin and co-workers reported attempts to utilize phenylselenyl iodide to perform the analogous electrophilic cyclization, but reported only the production of selenlylated product and no evidence of iodide addition.[20] One possible explanation for this is that the

iodinated/selenylated intermediate produced rapidly undergoes cyclization by nucleophilic attack iodine bearing carbon, faster than the selenium can be oxidized by another equivalent of phenylselenyl iodide. Using conditions optimized by Fossey et al[11] initial trials run on **1a** showed no reaction. Reactions were also run at elevated temperatures (60 and 110 °C) concurrently, and both these reactions showed consumption of starting material by TLC. However, upon examination of ^{1}H and ^{19}F-NMR it was determined that a number of different products were produced, most notably was the presence 9 distinct resonances in the ^{19}F-spectra. One possible explanation for this is that at elevated temperatures any iodopyrrolidine formed is a susceptible electrophile for any unreacted substrate.



Scheme 3.13: Iodocyclization under modified conditions goes to complete conversion though at low yield but with a higher dr than the other halopyrrolidines.

Alternative solvents were tested along with the addition of water as a co-solvent. Previous iodocyclizations of alpha-tetrasubstituted amines have used water as co-solvent when using sodium bicarbonate[6], likely for the increase in solubility. The initial screen tested DCM, acetonitrile, toluene, and THF. Only the reaction run in toluene showed full consumption of the starting material, but other side products are observed by GC. However, when this reaction is run in toluene without water as a co-solvent the reaction does not go to completion but there are no observed side-products. Knowing this, further reactions would be carried out in



Scheme 3.14: Proposed transition state for the iodocyclization of homoallyl amine **1a** to iodopyrrolidine **4** compared to the disfavored transition state required to form the iodoazetidine.

anhydrous conditions. Testing of base equivalency showed that 5 equivalents of sodium bicarbonate gave identical conversion to 2, ~50%.

With these current conditions a new solvent screen was run (Table 3.2). sodium bicarbonate was replaced with cesium carbonate which showed a 20% increase in conversion. The best conversions were observed in DCM and Toluene, 78 and 76% respectively. It is notable that, with the exception of diethyl ether, the lowest conversions were observed when using solvents miscible with water. In addition to low conversions, reactions run in DMSO and ether show formation of a side product suspected to be the benzylidene imine, which was also observed by Fossey and co-workers.[11]

With these conditions in place a broad spectrum base screen was conducted (Table 3.3). A series of weak and strong inorganic bases along with amine and alkoxide bases were tested. In addition, a control reaction was also run without base under the theory that unreacted substrate could act as a base to

deprotonate the final cyclized product. Under these conditions carbonate bases gave the best conversions regardless of the counter ion. Interestingly, sodium bicarbonate only performed slightly better than the control reaction. Also, upon closer observation it was observed that majority conversion is observed at 4 hours. Interestingly, when an amine base like triethylamine was utilized, all reactivity was seemingly nullified.

The addition of a sampling of metal Lewis Acids was tried in order to drive this reaction to completion (Table 3.4). Among the metal salts tested include both gold (I) and gold (III) salts along with copper (I) and (II) salts as well. While there was negligible increase in conversion observed at 18 hours, the conversion to product at 4 hours was lower by at least 20% across the board. As the only observed change was a slower overall rate of reaction in these cases, it's possible the metal salts were reacting with the excess iodine and lowering the overall abundance available for the reaction.

Due to its reactive nature, it was posited that the large excess of iodine might degrading under these conditions before it can fully react with the substrate. In order to probe this, the 3 equivalents of iodine were added in two parts, with the first 1.5 equivalents added at the start and second half added after 4 hours. Rather than a positive change, the overall conversion after 18 hours was half than what it was under otherwise optimized conditions. Therefore, the large excess of iodine is required at the start of the reaction for optimum conversion, with this in mind further testing was performed, and it was discovered that increasing the concentration

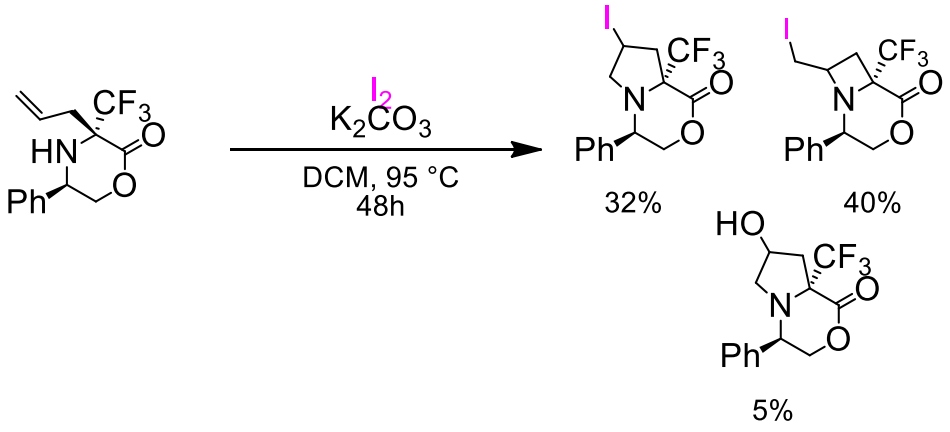
upwards of 0.1 M and using a total of 4 equivalents of iodine gave full conversion to product (Scheme 3.11). The resultant beta-iodopyrrolidine show a slightly enhanced diastereoselectivity over the chloride and bromide with a dr of 70:30. Unlike Fossey et al, the pyrrolidine is the primary product with no evidence of azetidine formation. This is not surprising as the transition state required for formation of the 4-membered ring would be significantly hindered. It is also likely this reaction proceeds through a different mechanistic pathway than Fossey's work (Scheme 3.12). The mixture of diastereomers observed suggests that this reaction goes through the 5-*exo*-trig cyclization pathway exclusively while proceeding at room temperature. At this point in time the absolute configuration of the major isomer has not been confirmed. As was noted earlier when these reactions are heated the product mixtures contain a variety of different compounds, possibly from free amine attacking the secondary iodide generated. There exists the additional possibility that at elevated temperatures the azetidine might form, but the resultant primary iodide would be an even more reactive electrophile and could undergo nucleophilic attack by unreacted substrate.

In contrast to previous attempts at the iodocyclization of alpha-tetrasubstituted homoallyl amines these conditions are simpler and milder (Scheme 3.7). While water was reported by Bonjoch[13] as a useful co-solvent in the case of this reaction it was only shown to create side products without aiding overall conversion to product. Elevating the temperature as in the case of Brigaud's work[2] only led to multiple side products likely due to the formation of product and

secondary attack by another equivalent of free amine. This problem can be partially avoided by running the reaction in more dilute conditions, hence being run at 0.06 M initially. However, increasing the concentration an order of magnitude was a contributing factor in allowing this reaction to go to completion.

Overall the formation of the pyrrolidine during the iodocyclization of these substrates suggests that while Baldwin's Rules favor the 4-*exo* cyclization pathway there are a myriad of factors that affect the regioselectivity. These factors include the significant steric interactions present in the transition state of the 4-*exo* pathway, presence and strength of base, and the nucleophilicity of the amine present.

The alpha-tetrasubstituted homoallyl amines encounter significant pseudo-1,3-diaxial interactions when attempting to proceed through the 4-*exo* cyclization pathway, unlike the trisubstituted variants in which the larger substituent can be oriented in a fashion to minimize said interaction (resulting in the *cis* selectivity observed by Fossey). Review of the literature shows a single instance in which a



Scheme 3.15: When base is added to the reaction methodology used by Brigaud et al, a mixture of products is obtained with the iodoazetidine being the major product.

tetrasubstituted homoallyl amine gives the azetidine. Brigaud and co-workers in their attempts to create the modified proline mentioned above discovered that the 4-membered ring could in fact be produced (Scheme 3.15).[2b] When their substrate was heated to 95 °C in the presence of iodine but the absence of base the pyrrolidine resulted as the sole product. However, when base is present, either potassium or sodium carbonate, a mixture of products was obtained including the iodopyrrolidine, iodoazetidine, as well as the hydroxylated pyrrolidine believed to have resulted from the fact that wet solvent was used (Scheme 3.15). When attempting to heat the substrate reported herein a complex mixture of products was obtained. This was evidenced by ^{19}F-NMR displaying at least 9 distinct resonances and an inscrutable ^{1}H-NMR spectrum. The absence, presence, or nature of the base did not appear to affect our products produced under these conditions but only the overall conversion to the iodopyrrolidine. In the complete absence of base approximately 50% conversion to product is observed.

Knight and co-worker's research is the most comparable as a number of alpha-tetrasubstituted amines were used. The electron-poor tosylamides do change the nature of the reaction and inhibit a direct comparison. Knight does make note that the toslyamides were chosen over other protecting groups such as the benzyl carbamate (Cbz) specifically to avoid the formation of undesired 4-exo-trig cyclization product. It was also reported that through a number of control reactions that this was shown to be the case. As was previously noted Fossey's group saw the opposite regioselectivity when less nucleophilic amines were used

for the iodocyclization. Knight's group solely observed the formation of the iodopyrrolidine and the less nucleophilic amines likely prevent the 4-*exo* pathway. However only 1,2-disusbstituted or trisubstituted olefins were used which Knight had previously shown with the trisubstituted homoallyl tosylamides to have markedly higher yields than monosubstituted alkenes. It's possible that the monosubstituted alkenes like **1a** may not only be susceptible to nucleophilic attack following cyclization by another equivalent of free amine, there is the additional possibility that the iodonium intermediate (formed upon additional of the iodine across the pi-system) could also be a suitable target for the free amine present. This could account for the low yield and possibly the complex mixture of products observed at higher temperatures.

Direct comparisons of yields and diastereoselectivities between the chloro/bromopyrrolidines and iodopyrrolidines cannot be drawn due to the different reaction conditions and nature of the electrophile. If the proposed mechanism by Outurquin (Scheme 3.9) is correct the phenylselenyl halides proceed through a more complex mechanism in which the regioselectivity of the reaction is dictated by the initial addition of the phenylselenyl halide across the pi-system. This contrasts with the iodocyclization where the attack on the iodonium complex at either the terminal or internal position by the amine dictates the product.

The phenylselenyl halide cyclizations do not appear to suffer from the production of any detectable side-products, as the only other compound observed in the reaction mixture is the diphenyl diselenide byproduct. This suggests that the

initial intermediate formed when the selenyl halide adds to the pi-system is a transient species almost immediately attacked by the halide anion present. Additionally, the resultant chloro/bromopyrrolidine will not be as potent an electrophile as the iodopyrrolidine, therefore reaction with free amine is not as likely even at the higher temperatures used.

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3.5 Supporting Information:

General Reagent Information:

All reactions were set up on the benchtop in test tubes equipped with magnetic stir bars and closed with screw caps. Flash column chromatography was performed using basic alumina gel or silica gel from Silicycle. Titanium(IV) tetraethoxide was purchased from Strem Chemical and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, Aldrich, or Oakwood and distilled before use. All ketones were purchased from Acros Organics, Alfa Aesar or TCI America and were purified by distillation before use.

General Analytical Information:

1H, 13C, and 19F NMR spectra were measured on a 500 and 400 MHz spectrometer using $CDCl_3$ as a solvent at room temperature. Some spectra include tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. Gas chromatography spectra were obtained using dodecane as an internal standard. For IR spectra, attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm-1). No sample preparation was necessary for ATR analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive index, and its reflection at the interface between the crystal and the solid material. Mass spectrometric data was recorded on a ToF instrument using direct injection

of samples in methanol into the electrospray source (ESI) and either positive or negative ionization.

Procedure for the synthesis of beta-halopyrrolidines using phenylselenyl selenides:

To an oven-dried test tube equipped with a magnetic stir bar was added free amine (1.0 equiv.), dichloroethane or acetonitrile (0.2 M) and allowed to stir. Phenylselenyl halide (3.0 equiv.) was dissolved in dichloroethane or acetonitrile (0.6 M). This solution was then added dropwise to the solution of free amine while stirring. Following addition the reaction was then stirred at 110 °C for 18 hours. Upon completion the mixture was cooled to room temperature and quenched with a saturated solution of sodium carbonate. The mixture was then extracted with 3 portions of dichloromethane. The resulting solution was then concentrated *in vacuo*. The crude oil was then purified by column chromatography on silica. The column was flushed with pure hexanes until the diphenyl diselenide was eluted (bright yellow band). The product was then eluted using a 1-3% EtOAc in Hexanes mixture.

Procedure for the synthesis of beta-iodopyrrolidines using elemental iodine:

To an oven-dried test tube equipped with a magnetic stir bar was added free amine (1.0 equiv.), sodium carbonate (2 equiv.), and dichloromethane (0.2 M) and allowed to stir. Iodine (4.0 equiv.) was dissolved in dichloromethane (0.8 M). This solution was then added dropwise to the solution of free amine while stirring. Following addition the reaction was then allowed to stir at ambient temperature for 18 hours.

Upon completion the mixture was washed with a saturated solution of sodium thiosulfate. The mixture was then extracted with 3 portions of dichloromethane. The resulting solution was then concentrated *in vacuo*. The crude oil was then purified by column chromatography on silica. The product was eluted using a 1-3% EtOAc in Hexanes mixture.

N-(4-fluorobenzyl)-4-methyloct-1-en-4-ammonium nitrate (1a):

See Chapter 1, substrate **4a** for preparation procedure and spectroscopic data.

N-(4-fluorobenzyl)-2-methyl-1-(3-(trifluoromethyl)phenyl)pent-4-en-2-amine nitrate (1b):

See Chapter 1, substrate **4b** for preparation procedure and spectroscopic data.

1-allyl-N-(4-fluorobenzyl)cyclopentanaminium nitrate (1c):

See Chapter 1, substrate **4g** for preparation procedure and spectroscopic data.

2-butyl-4-chloro-1-(4-fluorobenzyl)-2-methylpyrrolidine (2a):

Prepared according to general procedure for the synthesis of beta-chloropyrrolidines: **1a** (125 mg, 0.5 mmol), phenylselenyl chloride (287 mg, 1.5 mmol), and dichloroethane (5 mL) afforded the title compound after column chromatography on silica in 97% yield with a dr of 55:45. Product was an inseparable mixture of *cis*/*trans*-isomers. HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 283.1503 found 283.1531.

4-chloro-1-(4-fluorobenzyl)-2-methyl-2-(3-(trifluoromethyl)benzyl)pyrrolidine (2b):

Prepared according to general procedure for the synthesis of beta-chloropyrrolidines: **1b** (176 mg, 0.5 mmol), phenylselenyl chloride (287 mg, 1.5 mmol), and dichloroethane (5 mL) afforded the title compound after column chromatography on silica in 93% yield with a dr of 60:40. Product was an inseparable mixture of *cis*/*trans*-isomers. HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 385.1220 found 385.1266.

3-chloro-1-(4-fluorobenzyl)-1-azaspiro[4.4]nonane (2c):

Prepared according to general procedure for the synthesis of beta-chloropyrrolidines: **1c** (117 mg, 0.5 mmol), phenylselenyl chloride (287 mg, 1.5 mmol), and dichloroethane (5 mL) afforded the title compound after column chromatography on silica in 98% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.5, 5.7 Hz, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 4.31 (ddt, *J* = 8.3, 7.2, 4.8 Hz, 1H), 3.55 (s, 2H), 3.07 (dd, J = 10.6, 7.3 Hz, 1H), 2.77 (dd, *J* = 10.6, 4.9 Hz, 1H), 2.38 (dd, *J* = 13.6, 4.5 Hz, 1H), 1.90-1.58 (m, 7H), 1.48-1.36 (m, 1H). HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 267.1190 found 267.1201.

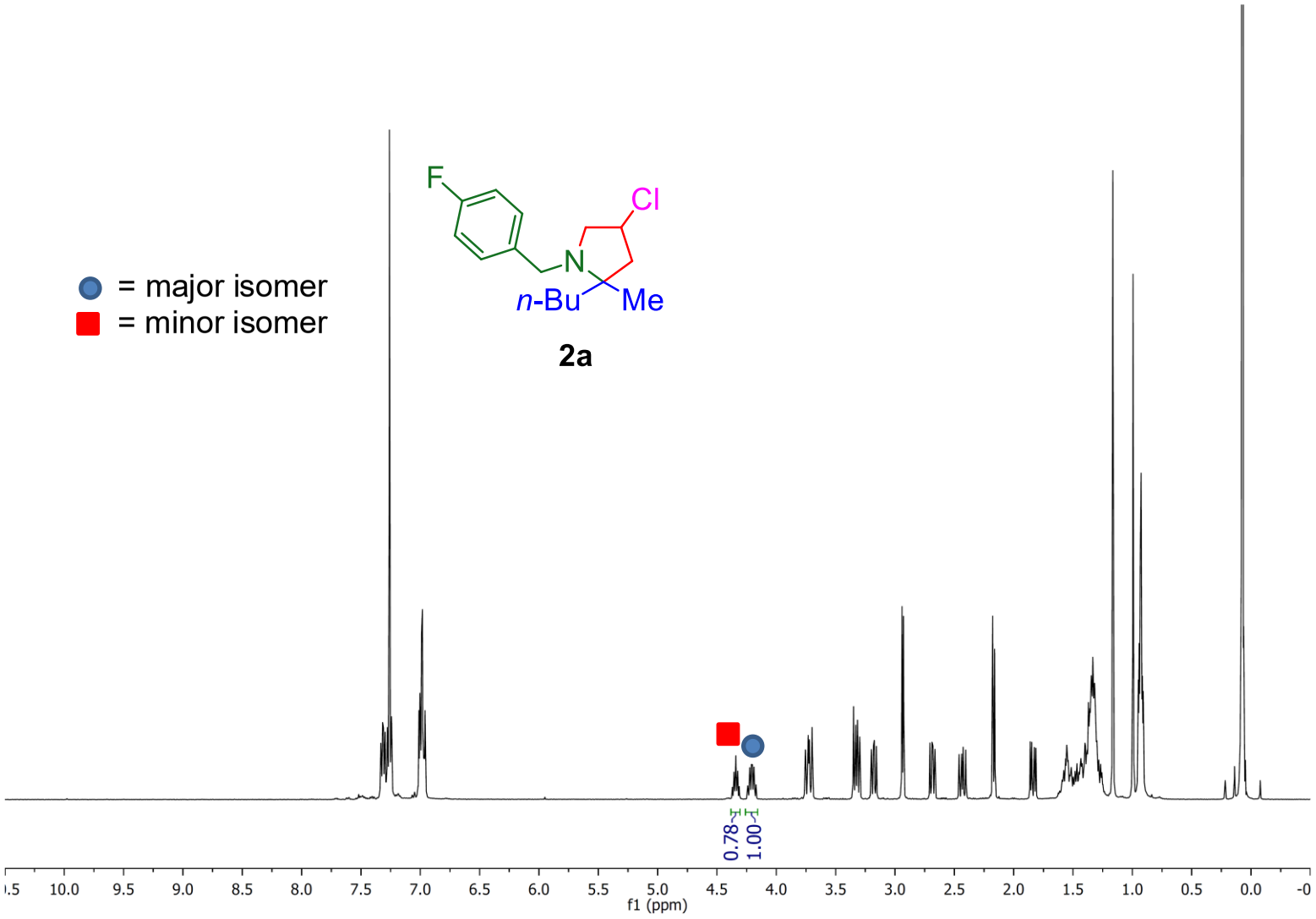
4-bromo-2-butyl-1-(4-fluorobenzyl)-2-methylpyrrolidine (3):

Prepared according to general procedure for the synthesis of beta-bromopyrrolidines: **1a** (125 mg, 0.5 mmol), phenylselenyl bromide (354 mg, 1.5 mmol), and acetonitrile (5 mL) afforded the title compound after column chromatography on silica in 51% yield with a dr of 50:50. Product was an

inseparable mixture of *cis*/*trans*-isomers. HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 327.0998 found 327.0990.

2-butyl-1-(4-fluorobenzyl)-4-iodo-2-methylpyrrolidine (4):

Prepared according to general procedure for the synthesis of beta-iodopyrrolidines: **1a** (125 mg, 0.5 mmol), iodine (506 mg, 2.0 mmol), and dichloromethane (5 mL) afforded the title compound after column chromatography on silica in 46% yield with a dr of 70:30. Product was an inseparable mixture of *cis*/*trans*-isomers. HRMS (ESI) *m/z* calcd for $[M+H]^+$ requires 375.0859 found 375.0883.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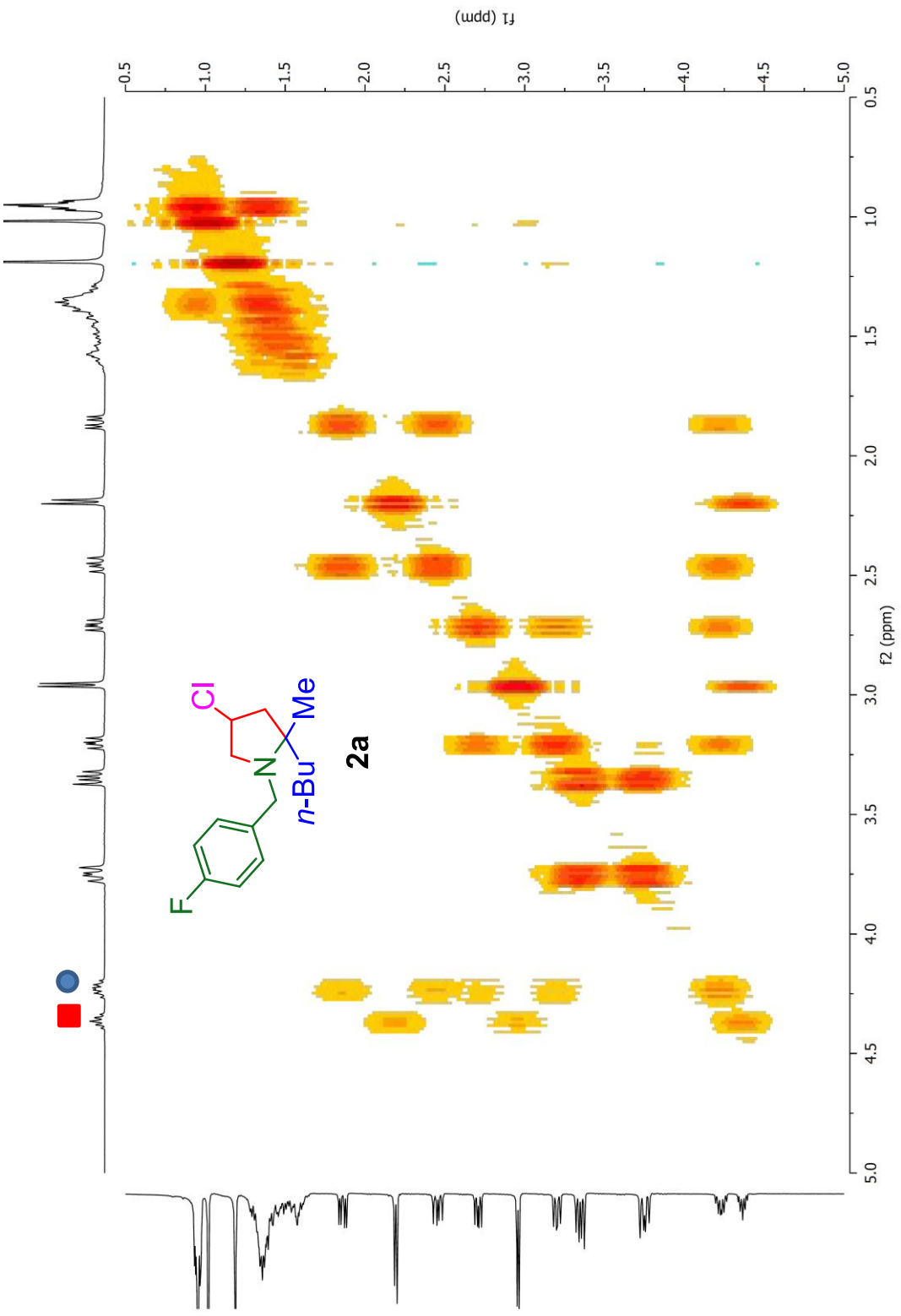
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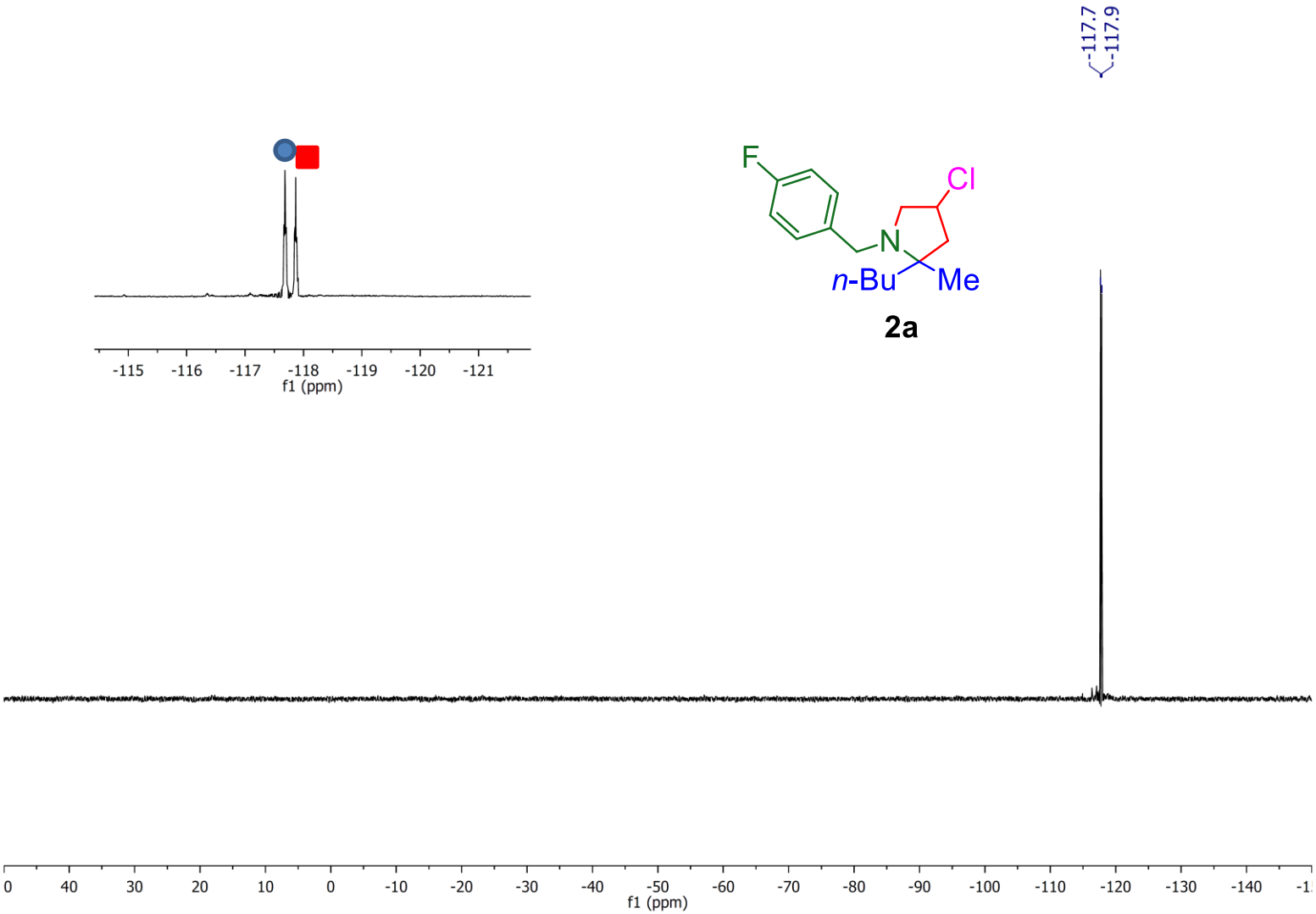
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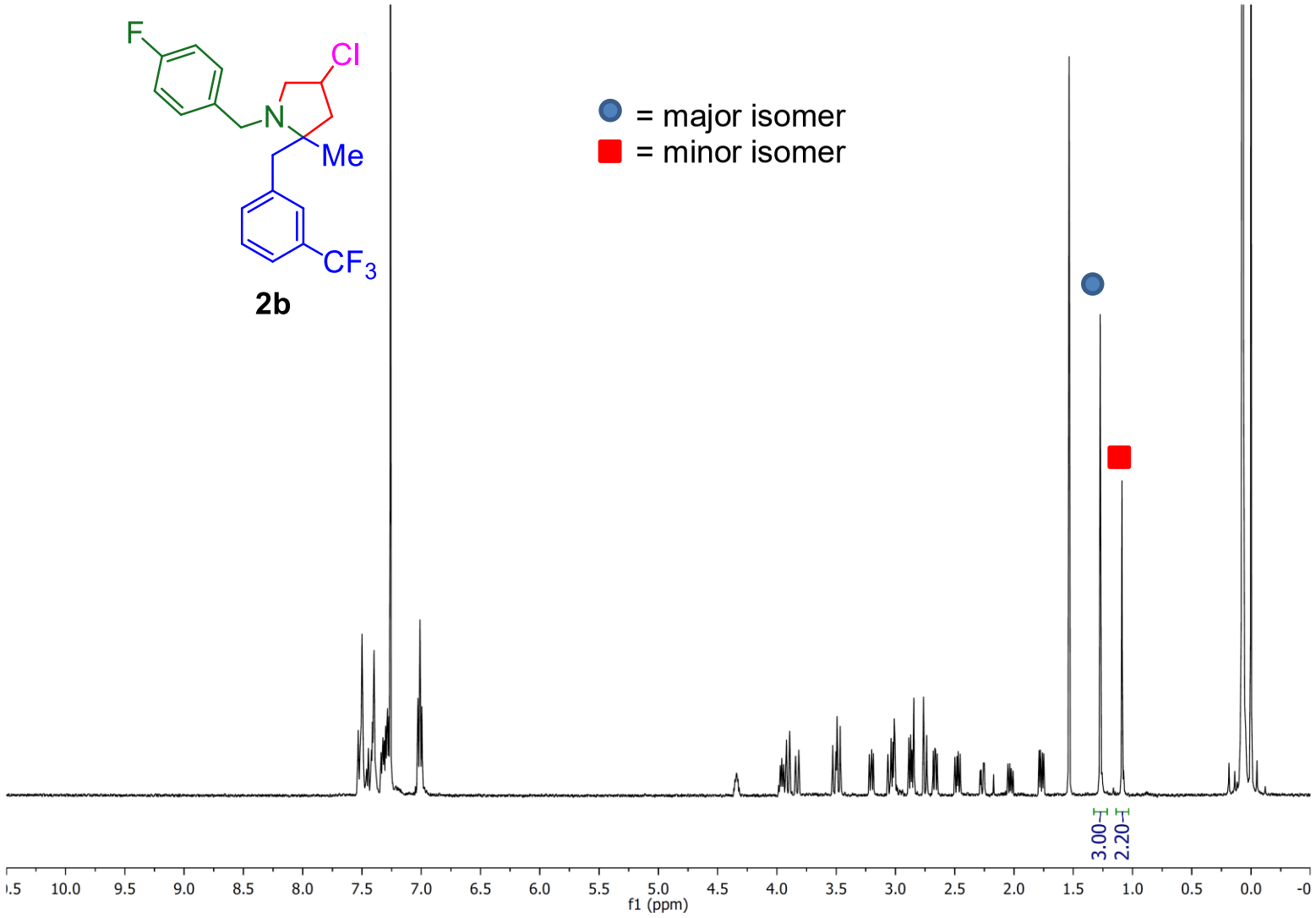
f1 (ppm)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6.5
6.0
5.5
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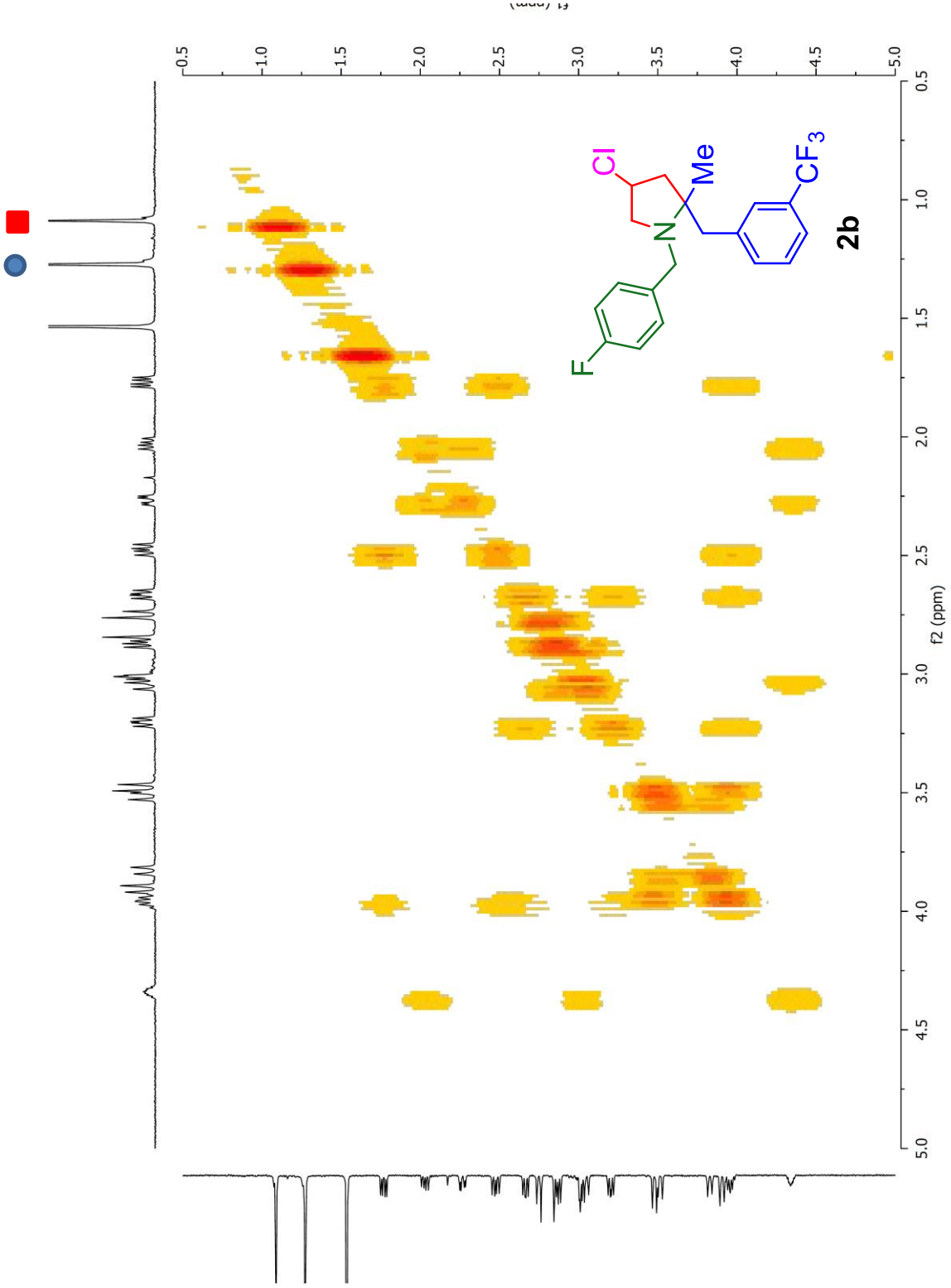
f1 (ppm)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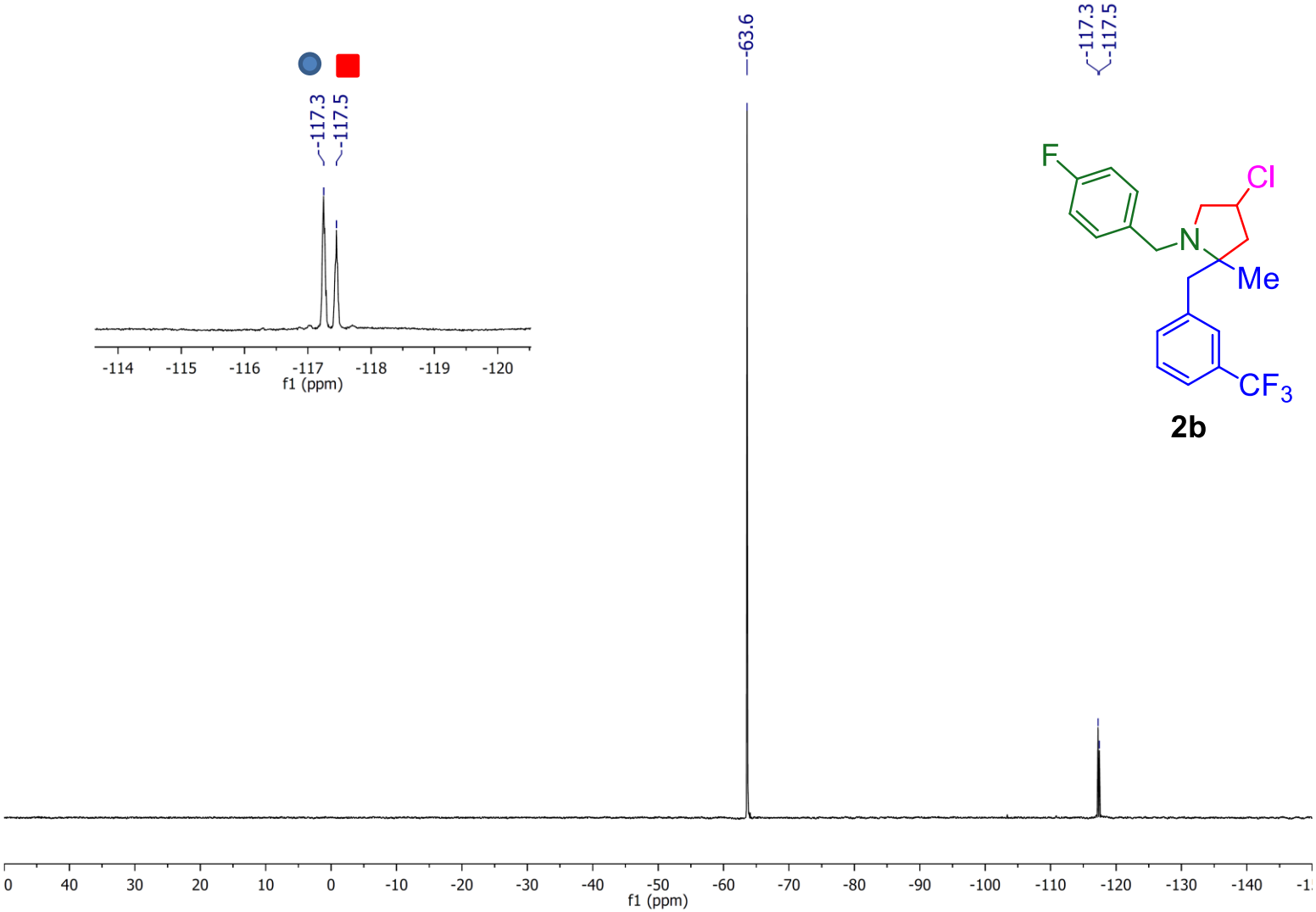
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f1 (ppm)
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30
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10
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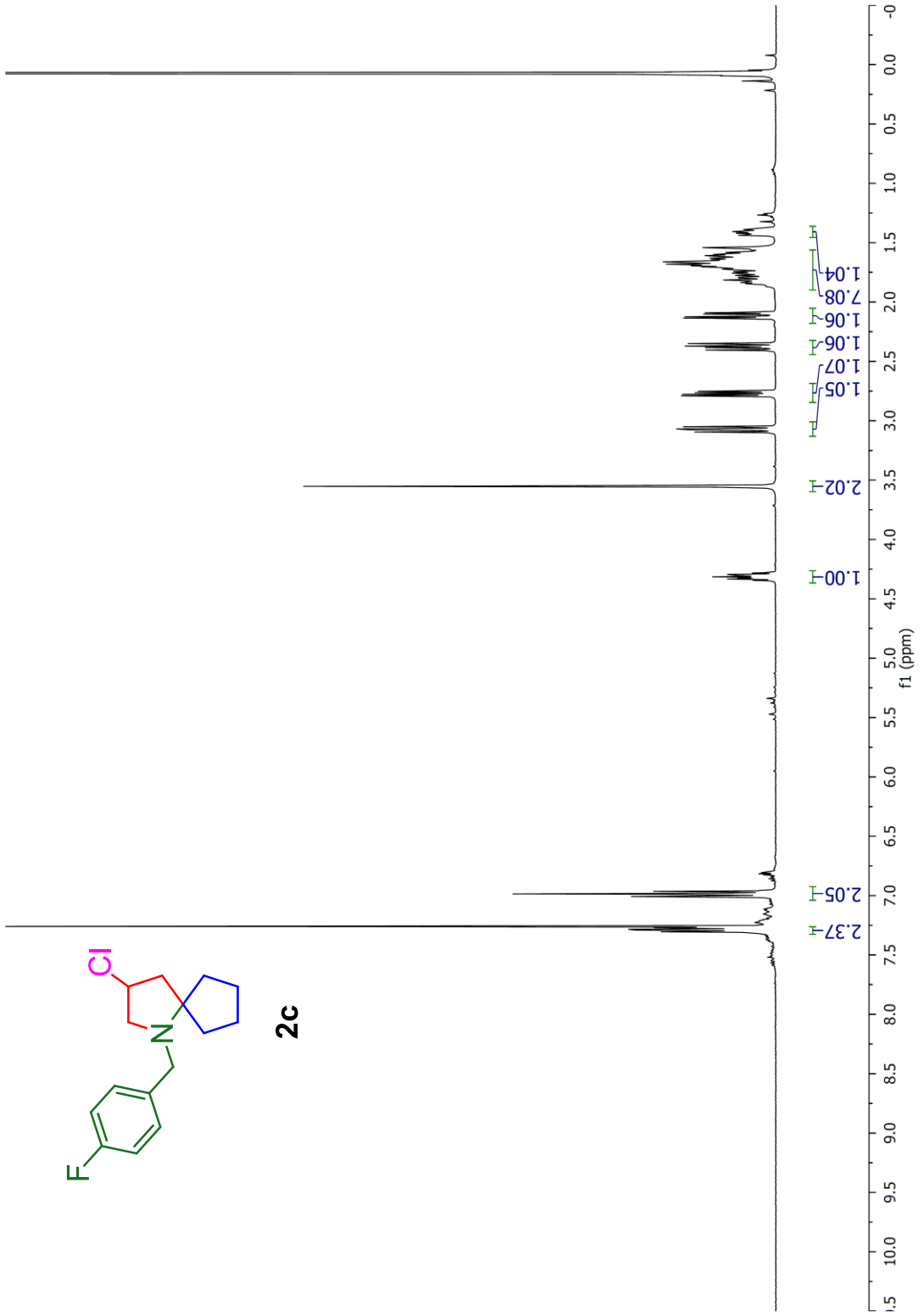
f1 (ppm)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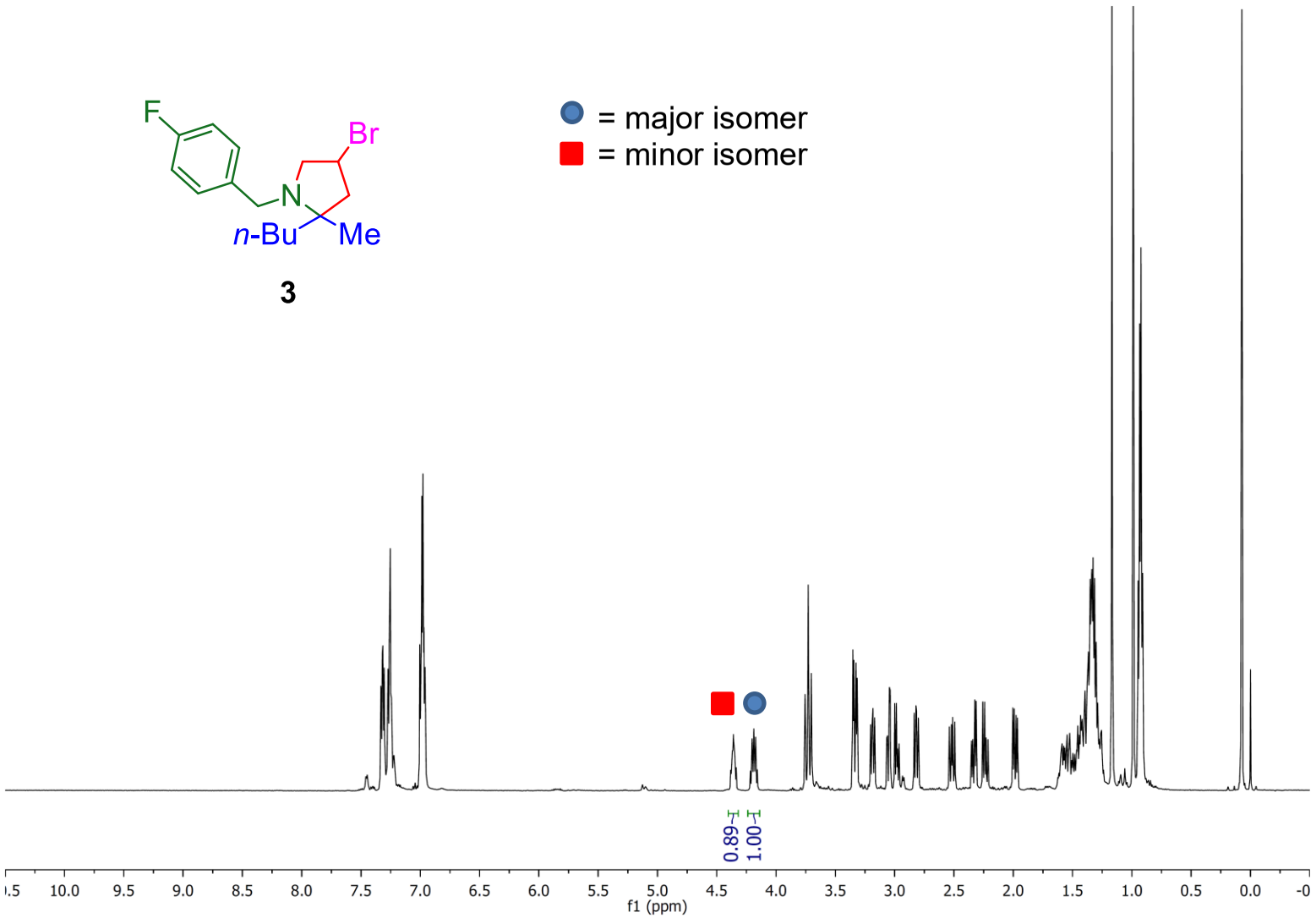
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= minor isomer
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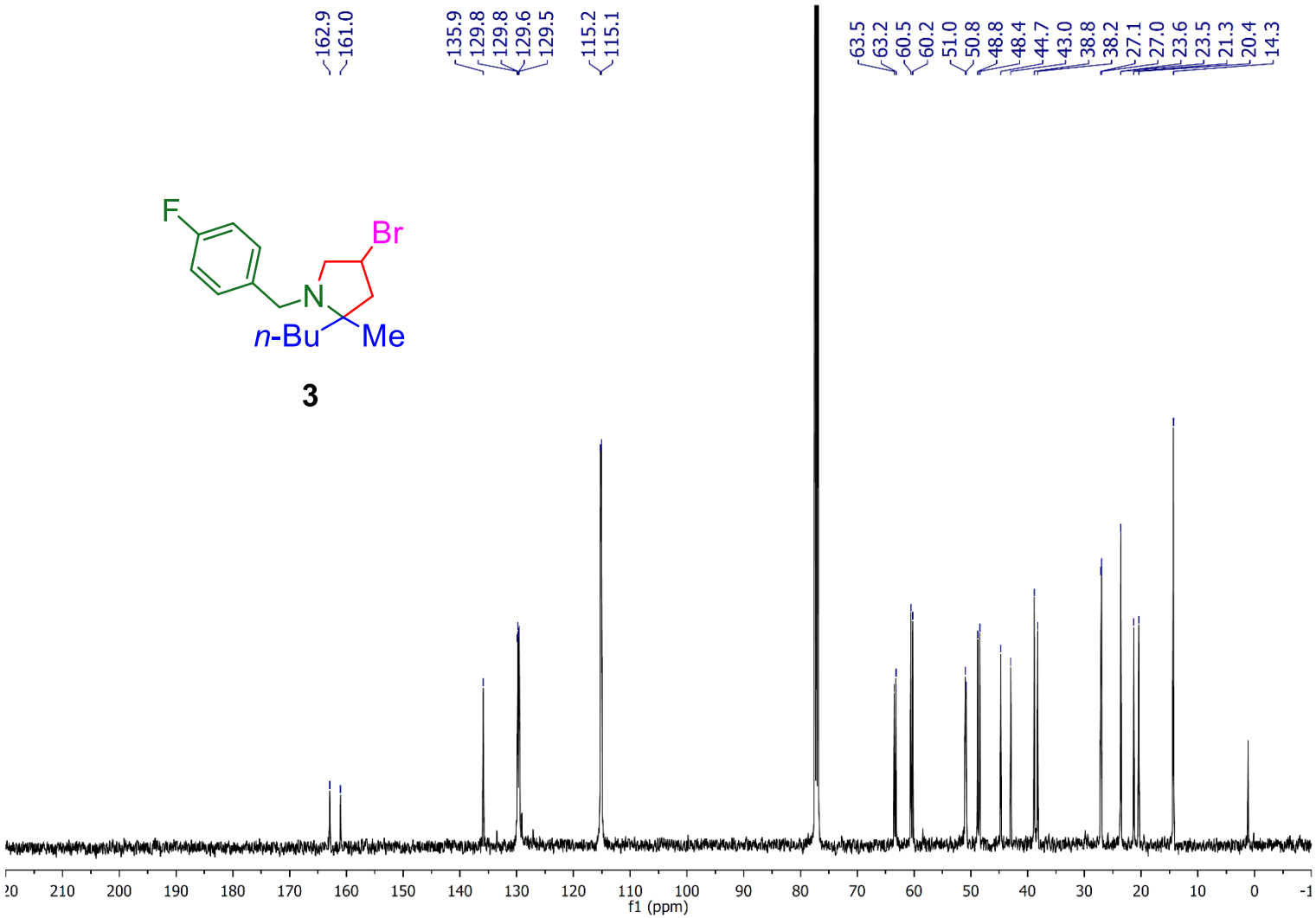
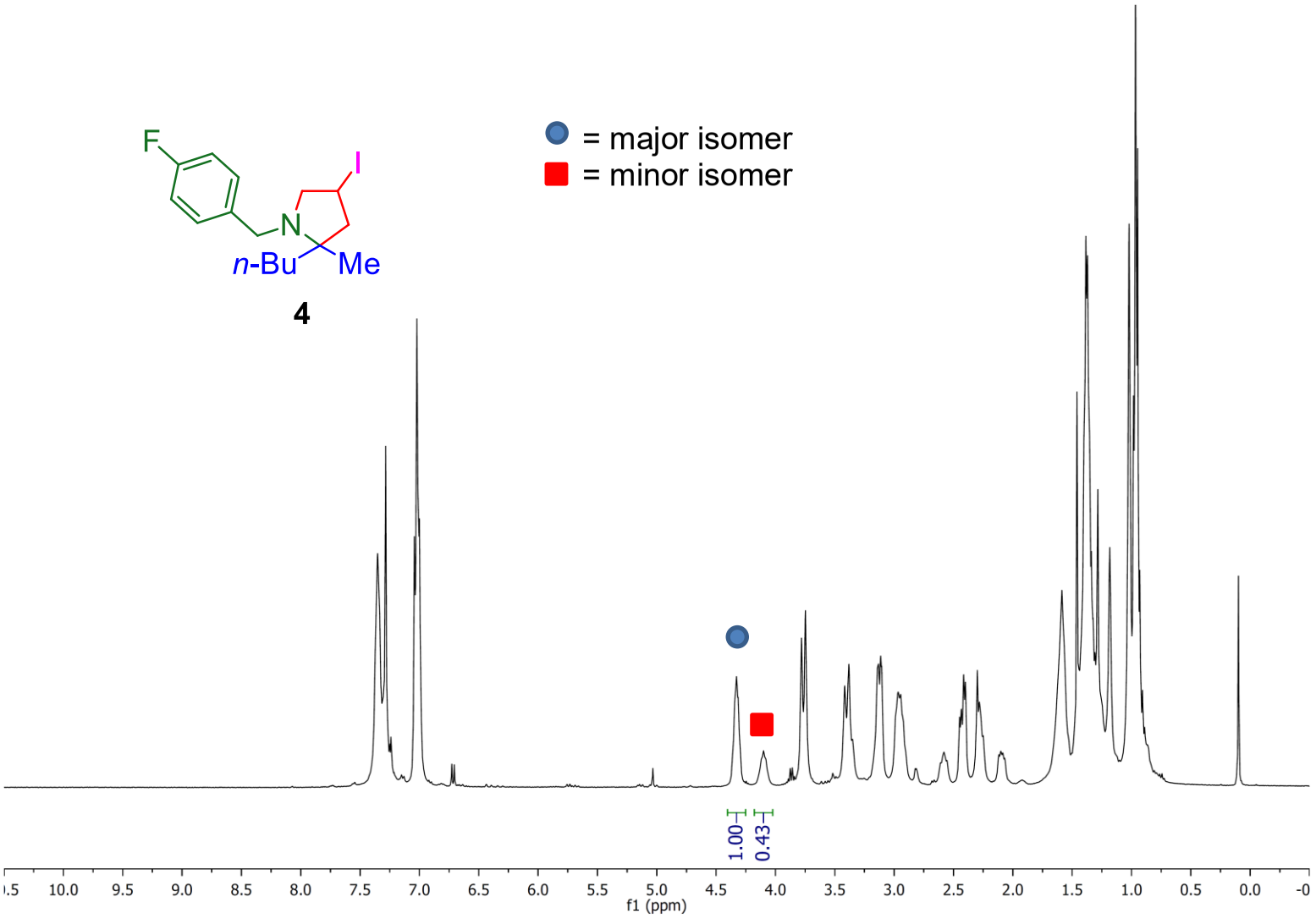
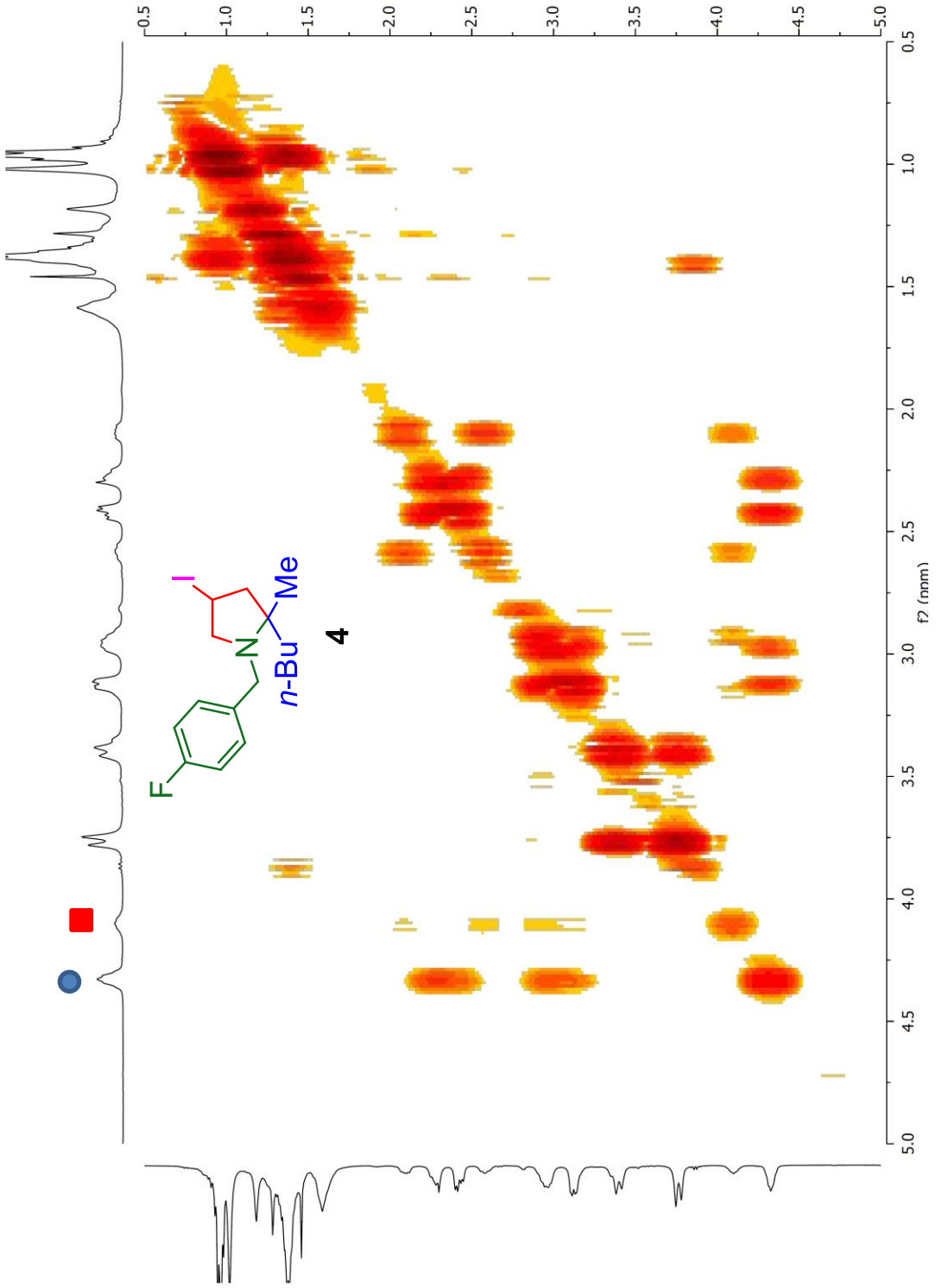
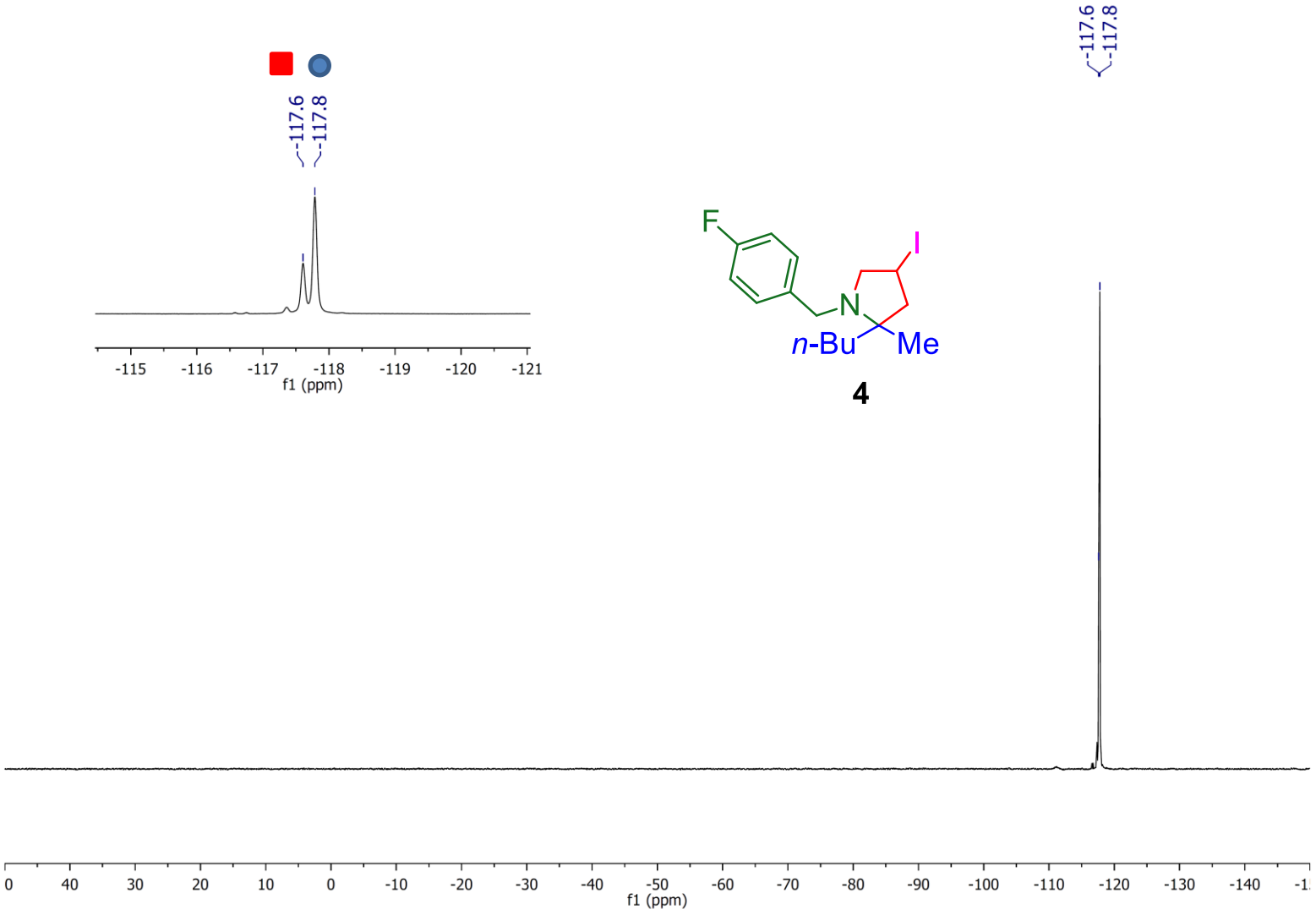
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


162.9
161.0
135.9
129.8
129.8
129.6
129.5
115.2
115.1
63.5
63.2
60.5
60.2
51.0
50.8
48.8
48.4
44.7
43.0
38.8
38.2
27.1
27.0
23.6
23.5
21.3
20.4
14.3
F
Br
N
n-Bu
Me
3
f1 (ppm)


F
I
N
n-Bu
Me
4
= major isomer
= minor isomer
1.00
0.43
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
f2 (ppm)
I
N
n-Bu
Me
F
4


-117.6
-117.8
-115
-116
-117
-118
-119
-120
-121
f1 (ppm)
F
I
N
n-Bu
Me
4
-117.6
-117.8
0
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)