Developments and Applications of Methods for Palladium- and Copper-Catalyzed Carbon–Nitrogen Bond Formation

by

Jeffrey Chih-Yeh Yang

B.S., Chemistry, 2011
B.S., Biochemistry, 2011
University of Washington

Submitted to the Department of Chemistry
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DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

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Signature of Author..... Signature redacted ...
Department of Chemistry
May 18, 2018

Certified by..... Signature redacted .....
Stephen L. Buchwald
Camille Dreyfus Professor of Chemistry
Thesis Supervisor

Accepted by..... Signature redacted
Robert W. Field
Haslam and Dewey Professor of Chemistry
Chairman, Departmental Committee on Graduate Students

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Alexander T. Radosevich: Signature redacted
Thesis Committee Chair

Professor Stephen L. Buchwald: Signature redacted
Thesis Supervisor

Professor Timothy F. Jamison: Signature redacted
Thesis Committee

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Abstract

The studies presented in this dissertation are aimed at the development and application of methodologies that enable carbon-nitrogen (C–N) bond formation catalyzed by late transition metals such as palladium and copper. The first part of this thesis focuses on the use of palladium catalysis for the construction of a carbon(sp^2)–nitrogen bond in the context of a biphasic continuous-flow system (Chapter 1). The second part of this thesis describes the recent developments of copper-hydride (CuH) catalyzed asymmetric hydroamination for the formation of α-chiral carbon(sp^3)–nitrogen bonds from olefins. This work includes the application of CuH catalysis to the synthesis of chiral *N*-alkyl aziridines (Chapter 2), and the discovery and development of novel electrophilic amines to enable CuH-catalyzed asymmetric hydroamination to directly access primary amines (Chapter 3).

Part I.

Chapter 1. Use of a "Catalytic" Cosolvent, *N*,*N*-Dimethyl Octanamide, Allows the Flow Synthesis of Imatinib with no Solvent Switch

A general, efficient method for C–N cross-coupling has been developed using *N*,*N*-dimethyloctanamide as a cosolvent for biphasic continuous-flow applications. In addition to utilizing a proper co-solvent, the described method harnesses the superior mixing abilities of a stainless-steel powder packed tube reactor to efficiently couple a wide range of aryl/heteroaryl halides and aryl/heteroaryl/alkyl amines in a short period of time (< 15 min). The method was also integrated into a two-step sequence that converted phenols into biarylamines via the intermediate of either triflates or tosylates. Lastly, this method was applied to a telescoped three-step continuous-flow synthesis of imatinib, the API of Gleevec®, in good yield without the need of solvent switches, purification of intermediates, or aqueous extraction.

Part II.

Chapter 2. CuH-Catalyzed Regioselective Intramolecular Hydroamination for the Synthesis of Alkyl-Substituted Chiral Aziridines

A general and enantioselective method for the synthesis of *N*-alkyl-substituted aziridines has been developed. This protocol offers a direct route for the synthesis of alkyl-substituted chiral aziridines from achiral starting materials. A convergent synthesis of allylic hydroxylamine esters has been developed from readily accessed allylic alcohols. The allylic hydroxylamine esters undergo copper hydride-catalyzed intramolecular hydroamination with a high degree of regio- and enantiocontrol to afford the aziridine products in good to excellent yields in highly enantioenriched form. The utility of the products derived from this method is further demonstrated through derivatization of the chiral aziridine products to obtain a diverse array of functionalized enantioenriched amines.

Chapter 3. A Novel Electrophilic Nitrogen Source for Copper-Catalyzed Asymmetric Hydroamination for the Synthesis of Chiral Primary Amines

A mild and practical method for the catalytic installation of the amino group across olefins has long been recognized as a significant challenge in synthetic chemistry. Despite substantial efforts in this area, to our knowledge, no effective strategy has been developed to directly access chiral primary amines from unsaturated hydrocarbons. While the direct hydroamination of olefins requires harsh conditions, the lack of suitable nitrogen sources has limited the development of potentially more practical formal hydroamination methods for the synthesis of primary amines. Here, we describe a mild and general protocol for the copper-catalyzed hydroamination of olefins to primary amines, utilizing commercially available isoxazole and its derivatives as novel nitrogen sources. This method provides a powerful means to access a broad range of α-chiral branched primary amines and linear primary amines, as demonstrated by the efficient synthesis of Maraviroc and the formal synthesis of other pharmaceutical agents including DMP 777, Rasagiline, Dapoxetine and Bifemelane.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

ACKNOWLEDGMENTS

It is to my advisor – Steve, that I owe my thanks to, not just for financially supporting me, but also for picking and choosing some of the best people to fill his lab with. These people were the ones who I also owe my thanks to, as they are the friends, companions, gurus, savants, specialists, spiritual and moral guides, as well as inspirational figures, who have been by me throughout this physically and mentally challenging task.

Steve, thank you. It has been a memorable four years, especially since most of the conversations that we have had are something of the following:
SLB: "You're a fourth year. You should start thinking about postdocs and getting a job."
Me: "Um Steve I'm a third year."
SLB: "Oh… Well, you should start early then."
In the past four years, you have continuously reminded me to not mumble (by an unintelligible imitation of my mumbling), to get a haircut (by calling me Cousin Itt), and to be happy (I'm sure telling people to be happy is the key to making everyone happier). All jokes aside, you have been an extremely understanding advisor, and I am truly grateful for what you have done for me.

I would also like to thank my committee members – Profs. Timothy Jamison, Alexander Radosevich, and Jeffrey Van Humbeck for being helpful and informative, humorously blunt and straight to the point, and knowledgeable and professional during my time at MIT.

To say the very least, I owe everything that I have accomplished to my parents and the rest of my family. Regardless of how aimlessly I have shuffled around in my life, they have always been supportive and willing to give me the freedom to make my own mistakes. I couldn't have asked for a better sibling than my sister Jean, who I know will always be there for me if I need her. I would also like to thank my brother-in-law Brian Chae, whose good nature and generosity helped put me through some harder times during graduate school.

If it were not for Hona Jang, Profs. Alex Jen and Gojko Lalic, and most importantly Dr. Sei-hum Jang, I don't think I would have ever come to MIT. Not only did Sei-hum instill in me how to become an experimentalist, his Bob Ross-esque attitude on both chemistry and life has also made a tremendous impact on my perspective on many things. I also owe tremendous gratitude to my friends Shelley Sakuda, Michael Yamamoto, Monica Huang, Harrison Pham, Connie Phan, Richard Maneze, Huy Ta, Ahn Nguyen, Tina Hung, 大頭, 昀融, 小豬, 賀陳, 葉帝, 謙哥, 阿杜, 朱妹, 瑋伯, 關, 阿達, and many others who have not only been great companions throughout the years, but more importantly have had my back pretty much anytime and anywhere.

Notwithstanding the huge amount of support from family and friends that I have made prior to graduate school, I don't think I would have been able to make it through relatively unscathed, if

not for the postdocs, graduate students, and the DCIF folks at MIT. One great thing about being in a huge lab like the one that Steve (or should I say Christine?) runs, is that there is almost guaranteed someone to befriend. I owe enormous amounts of thanks to the people that I have come to know throughout graduate school, for teaching me chemistry, life skills, perspective, and even just companionship.

Beginning with the graduate students, my most sincere thank you to all the "fifth years", who will stay to me as "fifth years" forever, specifically Nootaree Niljianskul, Phillip Milner, Nathan Park, Nicholas Bruno, and James Colombe, who facilitated my smooth integration into the Buchwald lab. Paula Ruiz-Castillo and her mannerisms that drive me bananas, Pedro Arrechea and his late night discussions on species six, Yang Yang and his vast chemistry knowledge, Spencer Shinabery whose steaks I still dream about, Yuxuan Ye whose degree of laziness still amazes me, Bryan Ingoglia who accompanied me in the transition from bitter, cynical, and grumpy to impartial, Saki Ichikawa who always brings me a gift whenever she travels, Anthony Rojas who has kept my coffee addiction cheap to maintain throughout the years, Julian Cooper who has made the daily excursions with me to Panda Express or to commiserate over coffee, Tho Tran and Liam Kelly who help me out whenever I go chemical hunting in the Jamison Lab, Joseph Dennis who has been a responsible and upstanding citizen of the lab, Michael Gribble who I initially found eccentric but turned out to be extremely knowledgeable and quite fun to talk to, Richard Liu and his undying sarcasm, Yujing Zhou and her relentless pursue of working harder, better, and faster, Erica Tsai and the constant bickering that we get into, Aaron Mallek who drunkenly tried to show me how to tie a tie, and Claudia Keller whose good nature is unmatched, will be dearly missed.

In comparison to the list of graduate students that I am grateful to, there are even more postdocs that I am indebted to as mentors, friends, and great colleagues – Liela Bayeh, Scott Mccann, Klaus Speck, Andy Thomas, Aaron Sather, Hong Geun Lee, Vasudev Bhonde, Mao Chen, Dawen Niu, Shaolin Zhu, Shi-Liang Shi, Wenliang Huang, Daniel Cohen, Stig Friis, Kashif Khan, Esben Olsen, Boyoung Park, Nicholas White, Yang Zhao, Thierry Leon, Stefan Roesner, and Michael Pirnot. In particular, I want to thank my collaborators – Haoxuan Wang and Sheng Guo – for sharing both the chemistry burden and the emotional stress that we have experienced, Yiming Wang who has probably taught me more chemistry knowledge than anyone else, John Nguyen who taught me what it means to appreciate life, Kurt Armbrust who I have always gone to seek wisdom from, Gary Zhang who has been a great friend and hoodmate, Sandra King and Timothy Senter who have been of utmost help while I was frantically looking for a job, and Mycah Uehling who I look forward to going fishing with once I move to Delaware. Of course, there is also Christine Nguyen who has not only kept this lab running, but also been essentially another older sister to me.

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me to not lose sight of the big picture, and for making the latter half of my graduate school experience so much more enjoyable. I don't think I would have made it as easily as I did without you. Also thank you for proofreading this Acknowledgement and giving yourself a full paragraph.

I am sure that there are people who I have missed in this list, but if you know me, you will also know that my memory tends to be bad. This has been a remarkable experience that I have had and thank you all for helping me prepare for it, going through it with me, and joining me to look forward to life after graduate school.

PREFACE

Parts of this thesis have been adapted from the following published articles co-written by the author.

"Use of a "Catalytic" Cosolvent, *N,N*-Dimethyl Octanamide, Allows the Flow Synthesis of Imatinib with no Solvent Switch" Yang, J. C.; Niu, D.; Karsten, B. P.; Lima, F.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 2531-2535.

"CuH Catalyzed Regioselective Intramolecular Hydroamination for the Synthesis of Alkyl Substituted Chiral Aziridines" Wang, H.*; Yang, J. C.*; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8424-8431

RESPECTIVE CONTRIBUTIONS

This thesis contains work that is the result of collaborative efforts between the author and other colleagues at MIT. The specific contributions are detailed below.

The work in Chapter 1 was a collaborative effort between Dr. Dawen Niu, Dr. Bram P. Karsten, Fabio Lima (Ley Group), and the author. Dr. Karsten, with assistance from Fabio, performed the initial studies to identify *N*,N-dimethyloctanamide as the ideal solvent. Dr. Niu is credited with the discovery of using *N*,*N*-dimethyloctanamide as a co-solvent with toluene and for useful discussions.

The work disclosed in Chapter 2 resulted from collaboration between Dr. Haoxuan Wang and the author. Dr. Wang is credited with discovering the initial reaction. Dr. Wang and the author collaborated on the optimization and exploration of the scope of this method.

The work disclosed in Chapter 3 resulted from collaboration between Dr. Sheng Guo and the author. Dr. Nootaree Niljianskul is credited with the initial discovery of using *O*-acyl oximes as primary amine surrogates for CuH-catalyzed hydroamination. The author is responsible for all optimization with the oxime reagents. Dr. Guo is credited with discovering the use of isoxazole derivatives as an electrophilic amine source. Dr. Guo and the author collaborated on the optimization and exploration of the scope of this method.

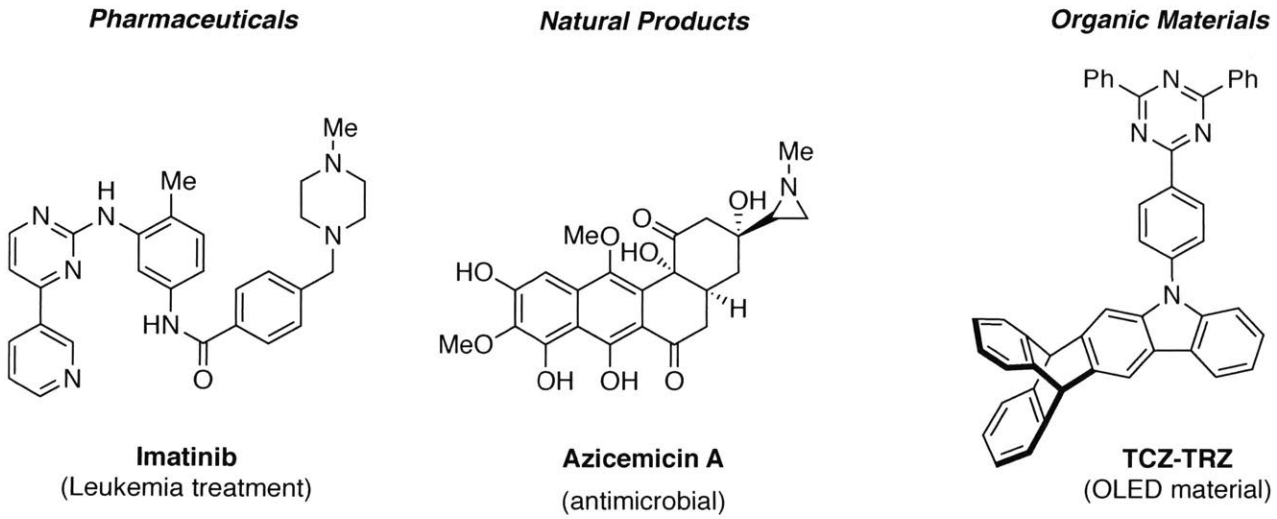
Table of Contents

Chapter 3. Copper-Catalyzed Asymmetric Hydroamination for the Synthesis of Primary Amines using a Novel Electrophilic Nitrogen Source

INTRODUCTION

The formation of a carbon-nitrogen (C–N) bonds is central to the preparation of pharmaceutical agents, in natural product synthesis, and materials science research.[1] In the past 20 to 30 years, the arsenal of methods for the construction of such bonds have been drastically expanded by the use of transition-metal catalyzed reactions. In particular, palladium (Pd)- and copper (Cu)-catalyzed transformations have emerged as one of the most powerful tools for the construction of a C–N in both industrial and academic research.[2-3]

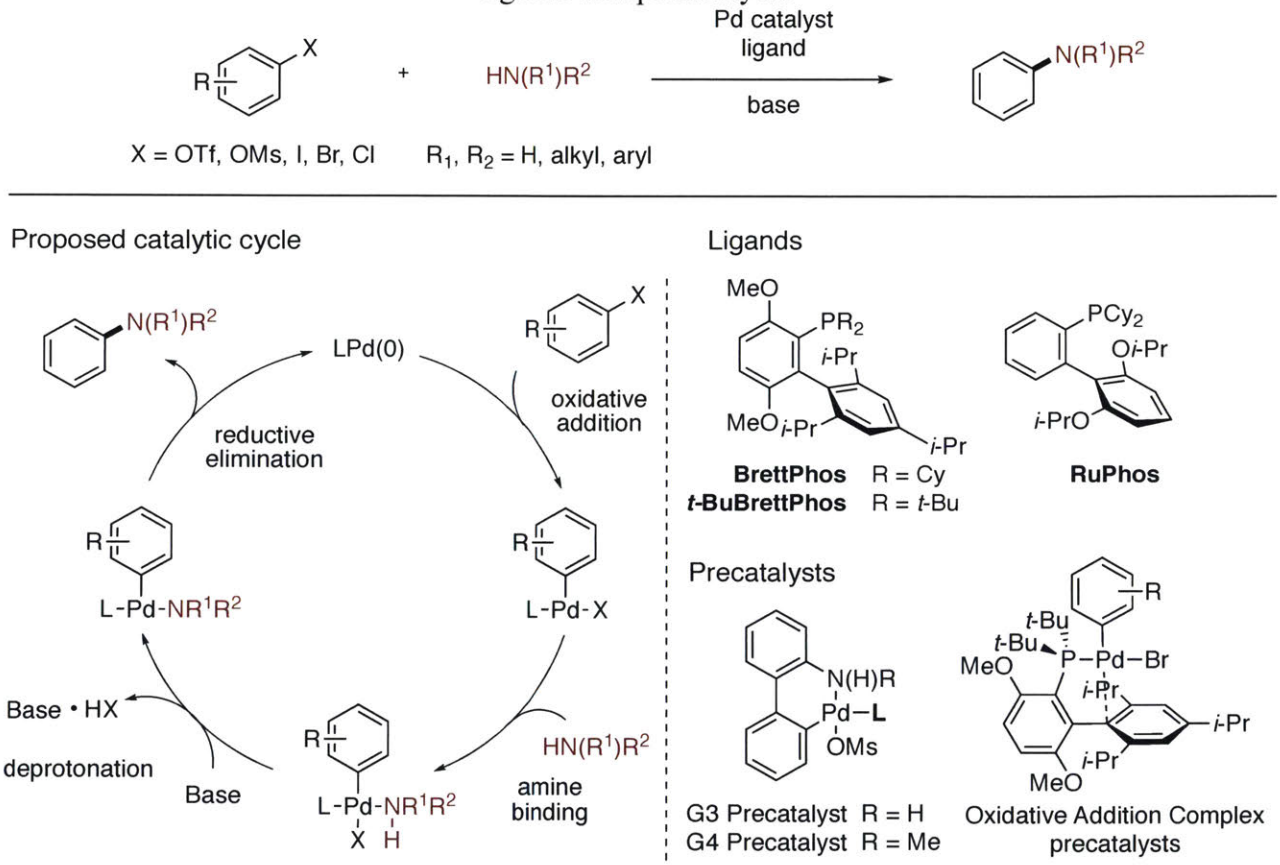
Figure 1. *Selected compounds containing C(sp^2)–N or α-chiral C(sp^3)–N bonds*



A key to the success of Pd-catalyzed cross-coupling methods has been the design of novel ligands. In particular, the biaryl and triaryl monophosphine ligands developed by the Buchwald group have enabled Pd-catalyzed C–N cross-coupling of diverse aryl electrophiles with a wide range of amine nucleophiles (Figure 1).[4-5] Additionally, the practicality of these reactions has been significantly advanced by the development of a series of air- and moisture-stable palladacycle precatalysts that rapidly and quantitatively generate catalytically active $L_1Pd(0)$ species in the presence of a base.[6-7] Supplementing improvements in ligand design, catalyst generation, and optimizing reaction conditions, a concurrent research focus of the Buchwald lab has also been the development of new enabling technologies.[8-9] Continuous-flow technology has received significant attention in recent years as a complementary approach to traditional batch methods.[10-12] In comparison to batch methods, continuous-flow systems are a highly attractive alternative in

the cases where reactions at high temperature and pressure, unstable intermediates, and when multiple synthetic steps can be stream-lined into a single process without the need of purification or isolation. However, the restrictive selection of solvents compatible with cross-coupling conditions and problems arising from the stoichiometric amounts of inorganic solids generated as a byproduct have severely retarded the implementation of Pd-catalyzed cross-coupling to multistep continuous-flow processes.[8]

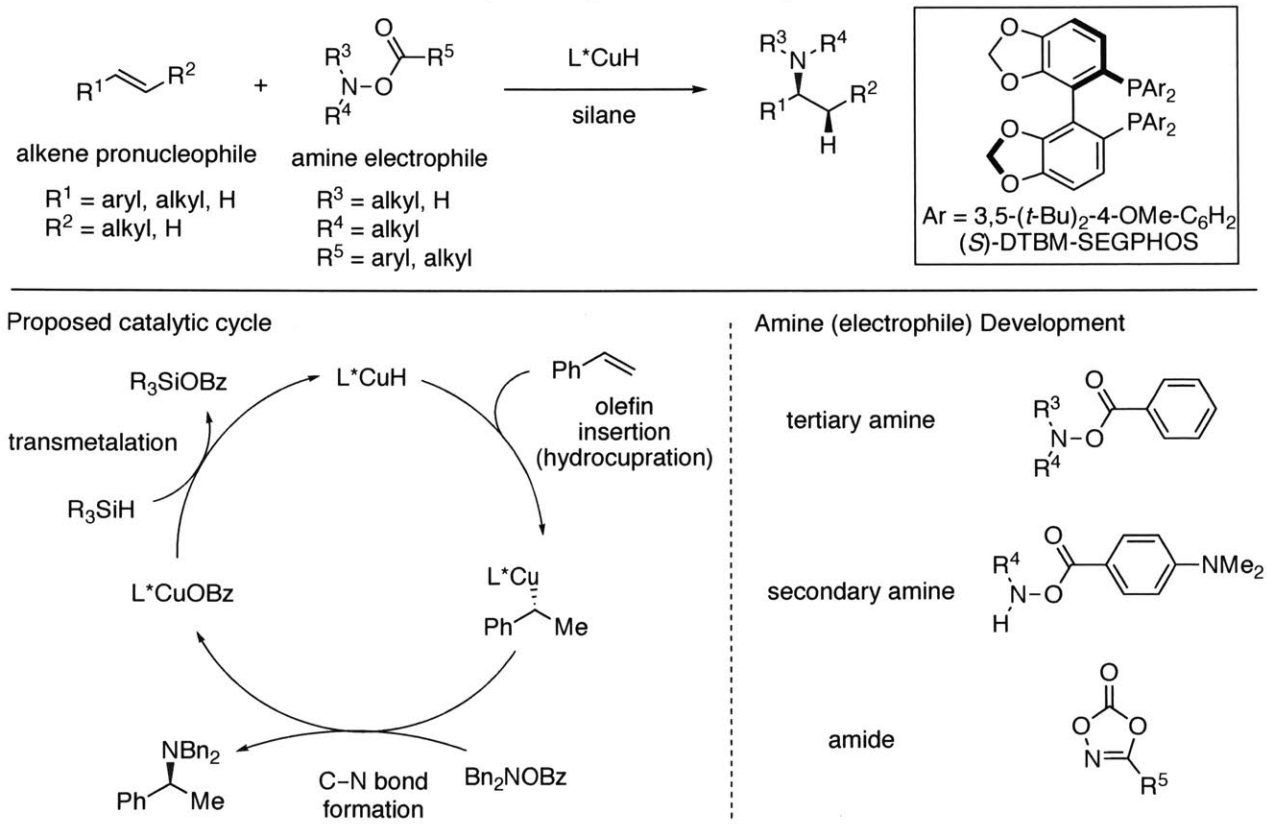
Figure 2. Proposed catalytic cycle for Pd-catalyzed C–N cross-coupling, representative ligands and precatalysts



In addition to the development of Pd-catalyzed cross-coupling processes, the Buchwald lab has also held a long-standing interest in copper hydride(CuH)-catalyzed transformations.[13] Recently, our laboratory[14] and the Miura[15] lab have independently reported the use of copper-hydride catalysis for the asymmetric hydroamination of alkenes.[16] In contrast to traditional methods for the preparation of highly enantioenriched α-chiral amines (*e.g.*, nucleophilic substitution, reductive amination, or metal-catalyzed allylic substitution), CuH-based strategies allow for the direct formation of nitrogen-containing compounds from alkenes by harnessing the *Umpolung*-type

reactivity of electrophilic amines.[17-18] Given the high abundance, general accessibility, and high relative chemical inertness of the carbon–carbon double bond, olefin-hydroamination strategies represent a highly desirable transformation that can bypass the need for a pre-existing carbon–heteroatom bond as the handle for amine-installation. However, due to the lack of suitable electrophiles, this method has been restricted to the synthesis of tertiary amines, secondary α-chiral benzyl amines[19], and α-chiral benzyl amides[20]. Furthermore, the application of this transformation to intramolecular hydroamination strategies for the synthesis of α-chiral nitrogen-containing heterocycles has been met with the challenge of low regioselectivity for the hydrocupration of 1,2-dialkyl alkenes.[21-22]

Figure 3. *Proposed catalytic cycle for CuH-catalyzed asymmetric hydroamination and the development of amine electrophiles*



Overall, the results in this thesis represent the design of novel transition-metal catalyzed systems for the formation of C–N bonds. Chapter 1 details the development of a new continuous-flow method for Pd-catalyzed C–N bond formation. This method uses a combination of an industrial-friendly co-solvent in addition to an aqueous-organic biphasic system to addresses the

issues resulting from byproduct. Chapter 2 describes the application of CuH-catalyzed enantio- and regioselective hydroamination for the synthesis of chiral *N*-alkyl aziridines from allylic hydroxylamine esters. Chapter 3 focuses on the discovery of a novel class of electrophilic isoxazole electrophiles and their application to CuH-catalyzed asymmetric synthesis of primary amines.

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Part I. Palladium-Catalyzed C–N Bond Formation in Continuous-Flow

Chapter 1. Use of a "Catalytic" Cosolvent, *N*,*N*-Dimethyl Octanamide, Allows the Flow Synthesis of Imatinib with no Solvent Switch

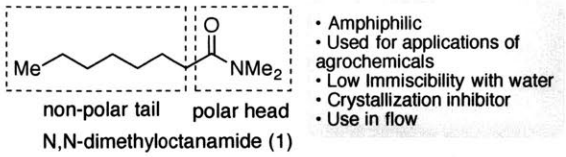
1.1 Introduction

The use of continuous-flow technology in synthesis has received an increasing amount of attention over the past decade in both academia and industry.[1] Compared to traditional batch methods, continuous-flow offers many benefits, including enhanced mass and heat transfer, the safer manipulation of reactions at high-pressure, and the in situ generation and consumption of unstable intermediates. Continuous-flow technology also offers the ability to scale chemical reactions in a more straightforward manner than traditional batch chemistry and to eliminate the need for the isolation of intermediates, thus combining multiple synthetic steps into a single process.[1,2]

The importance of aromatic amines and their derivatives is demonstrated by their prevalence in pharmaceutical agents and organic materials. Palladium catalyzed C–N cross-coupling has become a widely applied method for the preparation of these compounds.[3] As a continuation of our interest in developing practical methods for C–N bond construction, we initiated a program for the development of general methods to perform palladium-catalyzed amination in continuous-flow reactors.[4] Previous studies by us and other research groups have revealed several difficulties with transitioning C–N cross-coupling to continuous-flow conditions.[5] The formation and precipitation of crystalline products and inorganic salts during cross-coupling reactions often results in clogging of the continuous-flow reactor, a nontrivial difficulty to overcome. Moreover, downstream solvent switches are often required due to the limited range of solvents suitable for cross-coupling under continuous-flow conditions. The formation of byproducts may also impact downstream reactions, thus complicating multistep synthesis in a continuous-flow reactor. As a consequence, multistep continuous-flow processes that utilize a C–N cross-coupling step remain rare.

A large body of work has demonstrated the advantages of amphiphilic organic solvents and additives in batch chemistry. Amphiphilic solvents facilitate contact between organic- and water-soluble components of a reaction while maintaining a high local concentration of the organic reactants, thereby accelerating mass transfer and overall reaction rates. In addition to these benefits, amphiphilic solvents are capable of solubilizing a wide range of compounds, which may mitigate crystallization and minimize the need for solvent switches in a multistage continuous-flow process. As a result, we believed that the use of organic amphiphiles in biphasic solvent systems might permit a broader range of C–N cross-coupling reactions to be performed under continuous-flow conditions.

Figure 1. *Properties of N,N-dimethyloctanamide*



Here we report the identification and use of *N,N*-dimethyloctanamide (DMO, **1**, Figure 1) as an amphiphilic organic co-solvent that enabled the synthesis of a wide range of (hetero)arylamines via palladium catalyzed C–N cross-coupling reaction under continuous-flow conditions. Furthermore, we demonstrate that this method could be integrated into a two-step sequence for the direct conversion of phenols to amines, as well as a three-step synthesis of the anti-cancer agent imatinib (Gleevec®) under continuous-flow conditions. Notably, these multistep reaction syntheses were performed without in-line purification of any intermediates or solvent exchanges between steps.

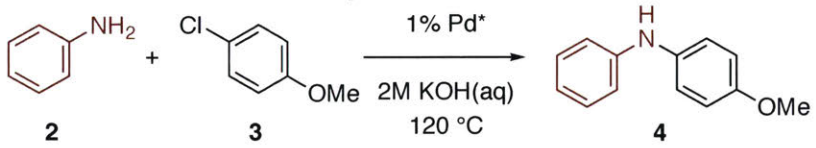
We have previously reported a system where biphasic conditions were utilized for C–N cross-coupling. However, even though phase-transfer catalyst additives were able to greatly increase the efficiency of the reaction, the generality of such a system was still severely impaired by the solubility of reagents in toluene. We envisioned that DMO would be a practical solution for continuous-flow chemistry due to its similar Hansen solubility parameters to dichloromethane,[6b] low solubility in water (4.3 g/L),[6c] reported toxicological profile comparable to common laboratory solvents, ready availability as a high production volume chemical, and previous use as a crystallization inhibitor and for crop protection formulations.[6,7]

1.2 Results and Discussion

We commenced our study by evaluating the use of DMO in the cross-coupling of aniline (2) and 4-chloroanisole (3) in the presence of XPhos-based[8] precatalyst **7** under biphasic conditions with aqueous KOH as the base. When the reaction was performed in a perfluoroalkoxyalkane (PFA) tube reactor with neat DMO as the solvent, low conversion was observed, presumably due to inefficient mixing of the two phases (Table 1, entry 1). The use of a stainless-steel packed bed reactor apparatus, a device previously described for achieving efficient mixing in a biphasic flow system,[4a] improved the yield significantly (Table 1, entry 2). Full conversion and excellent yield were obtained when the BrettPhos-based[9] precatalyst **8** was used instead of **7** (entry 3). Further

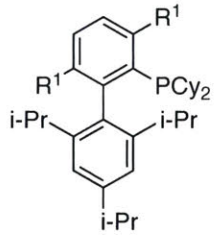
optimization revealed that it is not necessary to use DMO as neat solvent under these conditions. Toluene/DMO mixtures containing as little as 10% DMO gave similar results (entry 4 and 5). In addition, we found that 2-methyltetrahydrofuran (2-MeTHF), a solvent derived from renewable sources and suitable for large-scale production,[10] also gave comparable results when 10% DMO was utilized as an additive (entry 6).

Table 1. *Optimization of the palladium-catalyzed C–N cross-coupling reaction under continuous-flow conditions*[a]

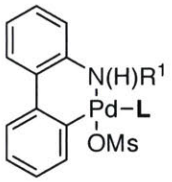


2 **3** **4**

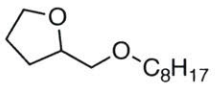
Entry	Solvent	Pd*	Yield	Conversion	t_R [min]
1[b]	**1**	**7**	7	11	15
2	**1**	**7**	68	74	15
3	**1**	**8**	97	>95	15
4	PhMe:**1** = 1:1	**8**	98	>95	7.5
5	PhMe:**1** = 9:1	**8**	95	>95	7.5
6	2-MeTHF:**1** = 9:1	**8**	93	>95	7.5
7	PhMe	**8**	70	71[c]	7.5
8	2-MeTHF	**8**	80	84	7.5
9	**9**	**8**	93	94[c]	7.5



5, XPhos, R^1 = H
6, BrettPhos, R^1 = OMe



7; L = **5**, R = H
8; L = **6**, R = Me



9

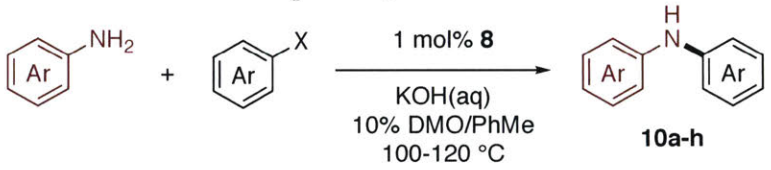
[a]Conversions and yields were determined by GC analysis of the crude reaction mixture. See Experimental for details. [b]0.04" PTFE tubing was used as the reaction vessel. [c]Prolonged reaction times resulted in full conversion along with clogging of the reaction vessel due to the low solubility of the product.

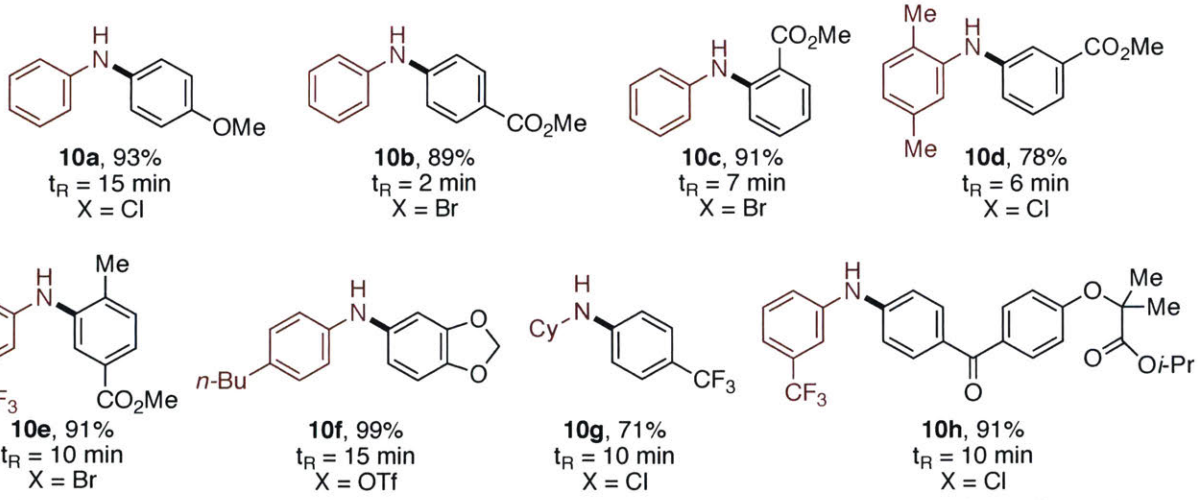
Control experiments showed that the use of toluene or 2-MeTHF in the absence of DMO resulted in incomplete conversion of starting material within the designated reaction times. Upon

extended reaction times to achieve full conversion in toluene (entry 7), the reaction vessel clogged due to the poor solubility of the product. Although the use of amphiphilic solvent **9** also gave high conversion of starting material and yield of product **4**, clogging of the reactor occurred after prolonged reaction times. Therefore, the conditions in entry 5 or 6 of this table were selected for most of the following studies.

Using the above-described conditions, we explored the generality applicability (Table 2). A wide variety of aryl bromides and chlorides, bearing electron-donating or -withdrawing substituents, were efficiently coupled with aniline partners (**10a-b**, and **g-h**).

Table 2. *Substrate scope of C–N cross-coupling reaction between arylamines and aryl (pseudo)halides*[a]





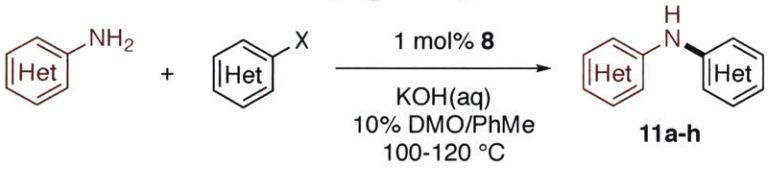
[a]All yields represent average isolated yields of two runs conducted on approximately 1–4 mmol scale. See Experimental for details.

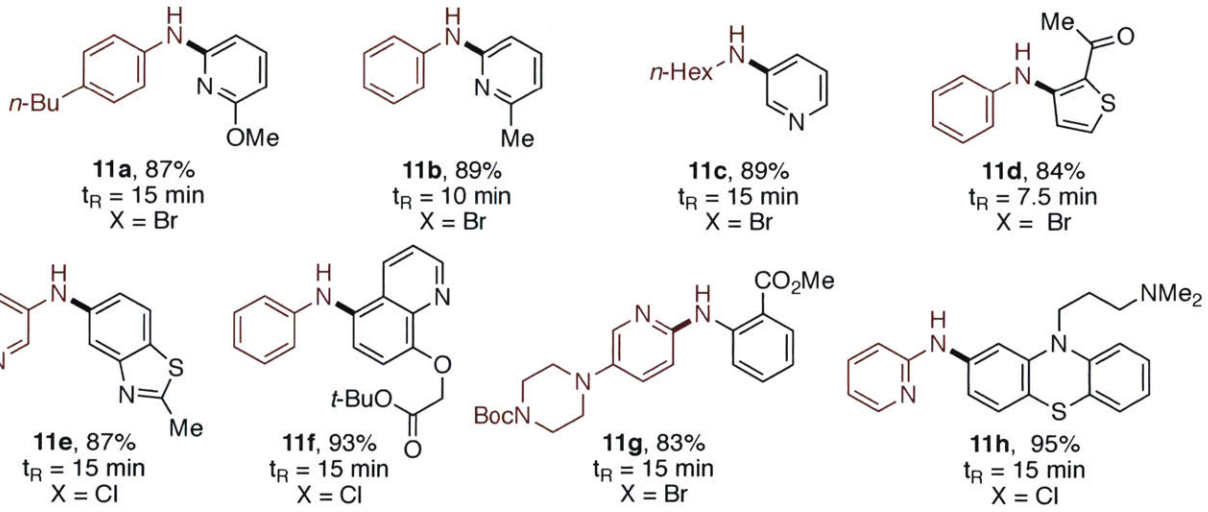
Ortho-substitution in either aryl halide or arylamine reaction partner was accommodated (**10c-e**). In addition, aryl triflates (**10f**) were also excellent substrates under these conditions, with minimal hydrolysis observed. Besides aryl amines, primary alkyl amines could also be successfully converted to product (**10g**). As a consequence of the precise control of reaction times under continuous-flow conditions, even readily hydrolyzed methyl esters provided high yield of desired product (**10b-e**, and **10h**). To demonstrate the potential applicability of this method,

fenofibrate, a medicine used to reduce cholesterol levels, was subjected to the reaction conditions and coupled with 3-trifluoromethylaniline to give **10h** in excellent yield.

Next, we turned our attention to expanding the scope of this method to include heteroaromatic compounds. The results are summarized in Table 3.

Table 3. *Substrate scope of C–N cross-coupling reaction between heteroarylamines and heteroaryl (pseudo)halides*[a]





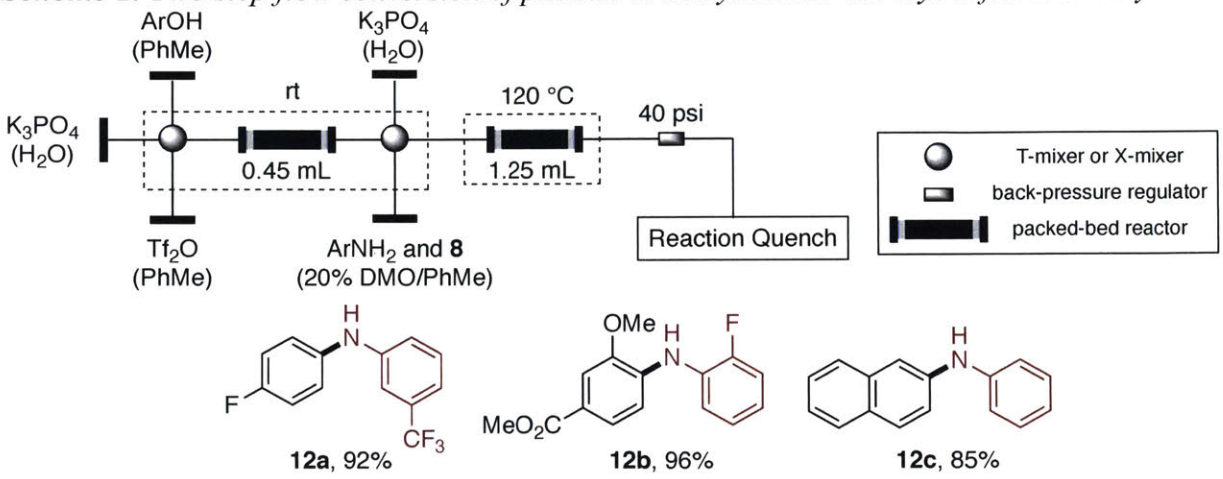
[a]All yields represent average isolated yields of two runs conducted on approximately 1–4 mmol scale. See Experimental for details.

A variety of heterocycles, including pyridines (**11a-c**), thiophene (**11d**), benzothiazole (**11e**), quinoline (**11f**), piperazine (**11g**), and phenothiazine (**11h**), were efficiently coupled with aromatic, heteroaromatic, or aliphatic amine partners. Notably, chlorpromazine, an anti-psychotic drug, could be coupled with 2-aminopyridine under these conditions to give **11h** in excellent yield. Substrates containing base-sensitive functional groups like ketones (**11d**) and esters (**11g**) were again well tolerated under these continuous-flow conditions.

In light of the broad scope demonstrated by our reaction conditions, we next explored the potential of integrating this C–N cross-coupling reaction into multistep sequences in flow. In this context, we were interested in converting phenols to biarylamines via aryl triflate intermediates (Scheme 1). Aryl triflates are recognized as highly reactive coupling partners in C–N cross-

coupling reactions.[3f] However, the lack of commercially available triflates and their instability necessitate their preparation prior to their use, which significantly hampers their application. We reasoned that the two-step conversion of phenols to arylamines without isolating the triflate intermediate would be of considerable interest. We have previously reported a similar sequence in flow, the complete removal of methylene chloride from the first step via microfluidic distillation and solvent exchange to dimethylformamide was required for a subsequent Heck coupling.[2f] After experimentation, we found that this could be accomplished in a flow system as shown in Scheme 1. While the triflation of a phenol often is carried out at low temperature and with the slow addition of triflic anhydride in a batch reactor,[11] this transformation could be performed at room temperature in minutes using aqueous K_3PO_4 as the base in a continuous-flow reactor. The reaction mixture from the first step was directly introduced into another packed-bed reactor with an aryl amine substrate, Pd precatalyst **8**, and additional K_3PO_4 to give the desired biarylamine product in excellent yields over two steps (**12a-b**). In contrast to previous reports of the use of in situ generated aryl triflates in continuous-flow, no in line purification or solvent switch were required in this process. In addition, we found that a phenol tosylation/C–N cross-coupling sequence could also be similarly accomplished (**12c**).[12]

Scheme 1. *Two step flow conversion of phenols to biarylamines via aryl triflates or tosylates*[a]



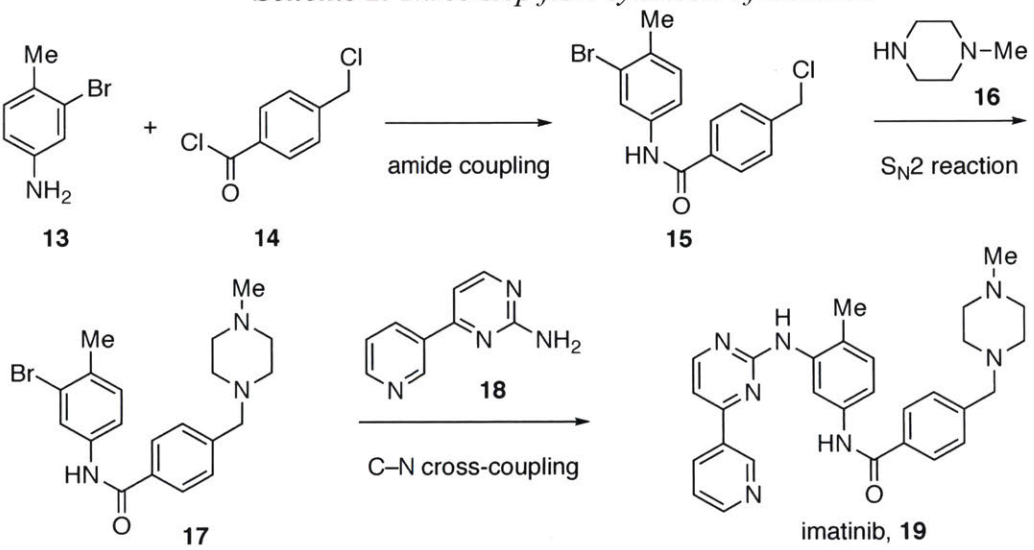
12a, 92% **12b**, 96% **12c**, 85%

[a]All yields represent average isolated yields of two runs conducted on approximately 1–4 mmol scale. See Experimental for details.

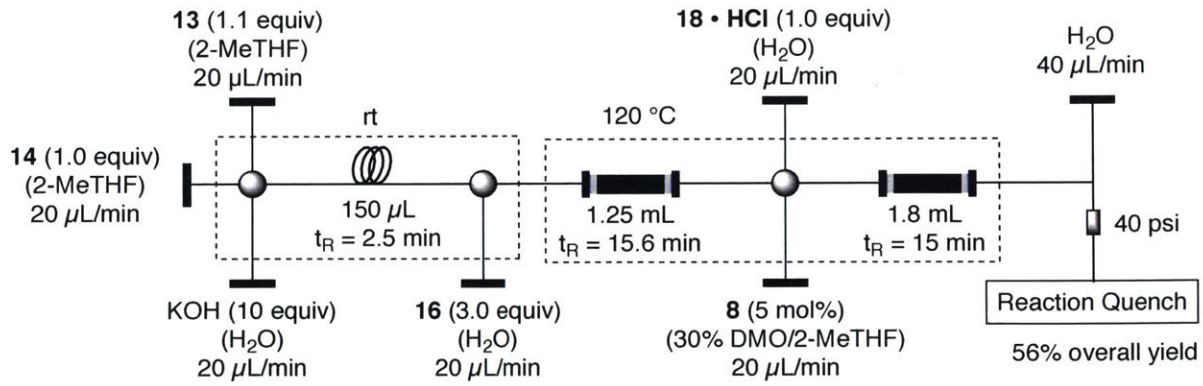
To further demonstrate the utility of this C–N cross-coupling technology, we applied it in a flow-based synthesis of imatinib (**19**, Scheme 3), a tyrosine kinase inhibitor widely used in the treatment of chronic myeloid leukemia.[13] In an elegant demonstration of the power of flow

methodology in the preparation of important pharmaceutical substances, Ley[2g,h] described the flow synthesis of imatinib, as depicted in Scheme 2. Based on this synthetic sequence, Ley reported a flow synthesis of imatinib featuring the sophisticated use of an in-line solvent switching apparatus, solid supported reagents, and purification cartridges to provide imatinib with minimal manual handling of intermediates. The final product was purified by chromatography to provide pure imatinib in 32% overall yield.

Scheme 2. *Three step flow synthesis of imatinib*



Scheme 3. *Flow synthesis for imatinib*[a]



[a]Averaged isolated yields of two runs is reported. See Experimental for details.

We have also reported on the synthesis of imatinib using batch protocols.[14] Using our new C–N cross-coupling technology, a more streamlined continuous-flow process for the synthesis of imatinib is depicted in Scheme 3. The first step, coupling of 3-bromo-4-methylaniline (**13**) with 4-chloromethyl-benzoyl chloride (**14**) to form amide (**15**), was performed in a 2-MeTHF/H_2O

biphasic system with KOH as the base (Schotten-Baumann conditions).[15] Complete conversion was achieved within three minutes at room temperature and the product **15** could be isolated in 87% yield. The next reaction step, the nucleophilic substitution of the benzylic chloride **15** with 1-methylpiperazine (**16**), was implemented by directly using the output of the first reactor. An aqueous solution of **16** was injected into the system and the mixture was pumped through a packed-bed reactor at 120 °C. The residence time in the second reactor was 15 minutes and the reaction yield over the first two steps was 84% as determined by ^{1}H-NMR of the crude reaction mixture. The last step in the synthesis of imatinib is the C–N cross-coupling of **15** with 2-aminopyrimidine **18** using precatalyst **8** (5 mol %). The outlet of the previous reactor was again used directly. Due to the high selectivity of BrettPhos for the coupling of primary amines,[9] it was not necessary to remove the excess 1-methylpiperazine (**16**) from the reaction mixture. To address the low solubility of **18** in organic solvents, it was converted to its conjugate acid, and injected into the system as an aqueous solution. As was done for C–N couplings described earlier, the reaction was performed in a packed-bed reactor in order to maximize mixing of the two phases. The residence time in the last reactor was 15 minutes. Imatinib was isolated in 56% overall yield from the crude reaction mixture via acid/base extraction followed by trituration in acetonitrile.[16] No solvent exchange or purification of intermediates was necessary throughout the whole synthesis.[17]

1.3 Conclusion

In conclusion, we have demonstrated the generality of a flow-based C–N cross-coupling reaction featuring the use of DMO as an organic co-solvent in a biphasic system. The use of the biphasic system serves as a convenient solution to address the precipitation of inorganic byproduct generated during C–N cross-coupling reactions. A wide range of biarylamines, including those derived from commercial drugs has been made in short reaction times. This C–N cross-coupling methodology employed KOH as the inorganic base and yet was compatible with sensitive functional groups. To further illustrate the utility of this method, we have integrated this method into a two-step flow sequence that converts phenols into biarylamines, via the intermediacy of triflates or tosylates. We have also showcased this technology in the three-step synthesis of the anti-cancer agent imatinib. Compared with previous synthetic routes, our synthesis does not require in-line manipulation of reaction intermediates or solvent exchange, uses lower catalyst loading, and produces the target product in higher overall yield. We expect this strategy of using

DMO as a co-solvent in biphasic systems to be applicable to other multistep flow sequences, especially those involving cross-coupling reactions.

1.4 Experimental

I. General Information

General Reagent Information

Anhydrous toluene was dried and deoxygenated by passage through packed columns of neutral alumina and copper(II) oxide under a positive pressure of argon. Palladium precatalysts were made in-house following literature procedure. BrettPhos and XPhos were obtained from Sigma Aldrich. All aryl halides, amines, and phenols were purchased from Alfa Aesar, Sigma Aldrich, Acros, Combi-Blocks, Enamine BB and used as received without further purification. *N,N*-dimethyloctanamide (DMO) was prepared according to literature procedure.[1] Compounds were purified by flash column chromatography using Silicycle SiliaFlash P60 (230–400 mesh) silica gel.

General Material Information for Continuous-flow

All stainless-steel tubing for connectors, PFA tubing, fittings, connectors, nuts, frits, and back-pressure regulators were purchased from IDEX Health and Science. Stainless-steel powder (-100 mesh, Type 304-L) for packed-bed reactors was purchased from Strem Chemicals. Stainless-steel tubing for reactors and relate tube fittings were purchased from Swagelok. Stainless-steel syringes (70-2267, 8 mL Stainless Steel Syringe with 1/16 inch Swagelock; 70-2251, 20 mL Stainless Steel Syringe with 1/16 inch Swagelock) and syringe pumps (PHD 2000) were purchased from Harvard Apparatus. The configurations used for the continuous-flow reactions are depicted in Figures S-1 to S-7. The packed-bed reactors (0.25" OD × 0.0035" wall) were packed with stainless-steel powder (Type 304-L, 100 mesh). Connections for all reactors were made using stainless steel frits (20 μm), stainless reducing unions (0.25" OD to 0.0625" OD), and stainless-steel tubing (0.0625" OD × 0.04" ID × 10 cm). Connections for the stainless-steel tubing for lower temperature (< 120 °C) reactions were made using super flangeless ferrules with stainless-steel rings (IDEX P-259, Tefzel ETFE, 1/4-28 Flat-Bottom, for 1/16" OD) and flangeless PEEK/Tefzel nuts (IDEX XP-141, PEEK, 5/16-24 Flat-Bottom port configuration for 1/16" OD). Connections for the stainless-steel tubing for high temperature (≥ 120 °C) reactions were made using super flangeless ferrules with stainless-steel rings (IDEX P-250X, PEEK/Stainless-steel, 1/4-28 Flat-Bottom, for 1/16"

[1] Lee, W. S.; Park, K. H.; Yoon, Y.-J. *Synth. Commun.* **2000**, *30*, 4241.

OD). All connecting tubing was made of PFA capillary tubing (0.04" ID × 0.0625" OD). Apart from reactions concerning triflic anhydride, which required the use of Tefzel (ETFE) connectors for higher chemical resistance, all Y-mixers, cross-mixers (0.02" ID) used in this work were made out of PEEK.

General Analytical Information

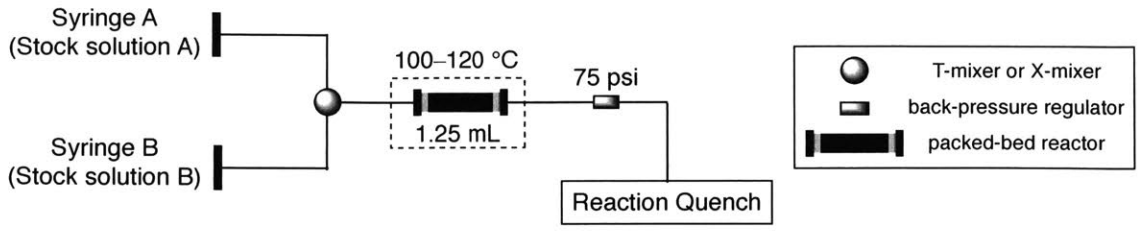
All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR (if appropriate), IR spectroscopy, elemental analysis (or high-resolution mass spectroscopy), and melting point (if solids). NMR spectra were recorded on a Bruker AMX 400 spectrometer or Varian Inova-500 NMR spectrometer and measured relative to the residual deuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). All ^{13}C NMR spectra are ^{1}H decoupled. All IR spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and are reported in terms of frequency of absorption (cm^{-1}). Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. HRMS spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). GC analyses were performed with dodecane as an internal standard on an Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). Thin-layer chromatography (TLC) was performed on Silicycle 250 μm silica gel plates (60 μm). Compounds were visualized by irradiation with UV light, or stained with iodine/silica gel.

General Procedure for the Preparation of the Packed-Bed Reactor

The packed-bed reactors were assembled according to literature procedure.[2] The effective volume of each packed-bed reactor was determined after packing with stainless-steel powder by examining the difference between the dry volume and wet (water) volume. The reactor was immersed in an oil bath (100–120 °C) and flushed with acetone (8 mL), and water (8 mL) successively for a minimum of 2 times each after each use.

[2] Naber, J. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9469.

Figure S-1. General Flow Setup



II. Experimental Procedures and Characterization Data

General Procedure for Table 1

All reagents were added to oven-dried, screw-top volumetric flasks that were fitted with Teflon screw-caps.

Using the reactors described in the general procedure of the preparation of packed-bed reactors, the continuous-flow C–N cross-coupling setup is as depicted in Figure S-1. The organic stock solution (Stock solution A) was prepared by charging a 5 mL volumetric flask with 4-chloroanisole (1.42 g, 10 mmol, 1.0 equiv), aniline (1.12 g, 12 mmol, 1.2 equiv), precatalyst (1 mol%), and dodecane (340 mg, 2 mmol, 0.2 equiv), and diluting to a total volume of 5.0 mL with 10% DMO in. In cases where solid reagents were used, the volumetric flask was sonicated until the solution was homogeneous. The base stock solution (Stock solution B) was prepared by charging a 5 mL volumetric flask was charge with sodium hydroxide (1.12 g, 20 mmol, 2.0 equiv) and diluting with to a total volume to 5.0 mL with deionized water. An 8 mL stainless-steel syringe was loaded with stock solution, connected to the appropriate feeder line as indicated in Figure S-1, and locked into the syringe pump. This process was repeated for each of the stock solutions.

The flow rate for each syringe was set according to the desired residence time. 2–3 reactor volumes were allowed to pass through for the flow reactor to reach steady state. After equilibration, samples were collected in test tubes. The amount of solution collected was measured according to the volumes displayed on the syringe pumps and the yields were calculated from the amount collected. The crude reaction mixture was diluted with brine and EtOAc, then filtered through silica gel before GC analysis.

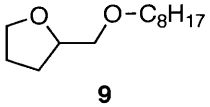
General Procedure for Tables 2 and 3

All reagents were added to oven-dried, screw-top volumetric flasks that were fitted with Teflon screw-caps.

Using the reactors described in the general procedure of the preparation of packed-bed reactors, the continuous-flow C–N cross-coupling setup is as depicted in Figure S-1. The organic stock solution (Stock solution A) was prepared by charging a 10 mL volumetric flask with ArX (X = Br, Cl, OTf) (2 - 10 mmol, 0.2 - 1 M, 1.0 equiv), Ar/R-NH_2 (1.2 equiv), BrettPhos G4 Precatalyst (1-2 mol%), and diluting to a total volume of 10 mL with 10% DMO in. The volumetric flask was then sealed with a screw-cap and shaken vigorously to ensure a homogenous solution. In cases where solid reagents were used, the volumetric flask was sonicated until the solution was homogeneous. The base stock solution (Stock solution B) was prepared by charging a 10 mL volumetric flask was charge with inorganic base (2-5 equiv.) and diluting with to a total volume to 10 mL with deionized water. An 8 mL stainless-steel syringe was loaded with stock solution, connected to the appropriate feeder line as indicated in Figure S-1, and locked into the syringe pump. Prior to the reaction, all reactors and the connecting tubing to mixers and back-pressure regulators were filled with water. The connecting tubing between independent syringes the T-mixer were filled with solutions identical to that of the syringe. This process was repeated for each of the stock solutions.

The flow rate for each syringe was set according to the desired residence time. 2 – 3 reactor volumes were allowed to pass through for the flow reactor to reach steady state. After equilibration, samples were collected in test tubes. The crude reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). Using a separation funnel, the aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layers were rinsed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude reaction mixture was purified by flash silica gel chromatography to give the corresponding compound. The amount of solution collected was measured according to the volumes displayed on the syringe pumps and used to calculate yields.

Characterization Data for Table 1



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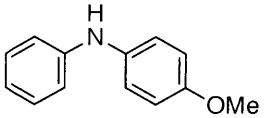
2-((octyloxy)methyl)tetrahydrofuran (**9**): An oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with sodium hydroxide (NaOH, 5.90 g, 0.15 mol) and tetrahydrofurfuryl alcohol (37.8 mL, 0.39 mol). The reaction mixture was stirred at 150 °C for 30 min until all NaOH was dissolved. The reaction mixture was cooled to 100 °C and chlorooctane (16.5 mL, 98 mmol) was added dropwise via

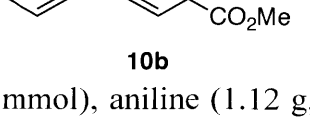
syringe. The reaction mixture was then stirred for 2.5 h at 100 °C and then cooled to room temperature. The mixture was diluted with ether (50 mL), then washed with water (50 mL). The organic layer was separated, rinsed with brine (50 mL × 2), dried with $MgSO_4$, filtered, then concentrated under reduced pressure. The title compound was afforded as a clear oil (17.51 g, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.93 (ddd, J = 12.5, 7.0, 5.3 Hz, 1H), 3.77 (dt, J = 8.1, 6.6 Hz, 1H), 3.69 – 3.59 (m, 1H), 3.35 (q, J = 3.4 Hz, 2H), 3.31 (d, J = 5.3 Hz, 2H), 1.92 – 1.65 (m, 3H), 1.57 – 1.39 (m, 3H), 1.30 – 1.06 (m, 10H), 0.77 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl3) δ 77.8, 77.8, 77.7, 73.4, 71.6, 68.1, 31.7, 29.6, 29.3, 29.2, 28.0, 26.0, 25.5, 22.5, 13.9. **IR** (neat, cm^{-1}) 2924, 2853, 1458, 1116, 1074, 920. **EA** Anal. Calcd. for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 72.68; H, 12.33.

Characterization Data for Table 2



10a

4-methoxy-*N*-phenylaniline (10a): Following the general procedure with a 1.7 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 4-chloroanisole (713 mg, 5.0 mmol), aniline (559 mg, 6.0 mmol), BrettPhos G4 precatalyst (46.1 mg, 50 μmol, 1 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (561 mg, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 113.3 μL/min each. After equilibration, the sample solution was collected into a test tube for 19.1 min (2.16 mL, 2.16 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–10% EtOAc in hexanes) the title compound was obtained as an off-white solid (1st run: 420 mg, 97% of 2.16 mmol; 2nd run: 352 g, 98% of 1.81 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 8.5, 7.3 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.01 – 6.95 (m, 2H), 6.95 – 6.85 (m, 3H), 5.54 (br s, 1H), 3.85 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.4, 145.6, 135.8, 129.4, 122.3, 119.7, 115.8, 114.8, 55.7. Spectral data were in accordance with those in literature.[3]

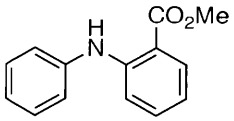


10b

Methyl 4-(phenylamino)benzoate (10b): Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of methyl 4-bromobenzoate (2.15 g, 10.0 mmol), aniline (1.12 g, 12.0 mmol), BrettPhos G4 precatalyst (92.1 mg, 0.1 mmol, 1 mol%) in

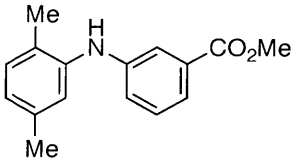
[3] Bruno, N, C; Niljianskul, N.; Buchwald, S. L. *J. Org. Chem.* **2014**, *79*, 4161.

10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (2.81 g, 50 mmol) in H_2O (25 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 375 μL/min each. After equilibration, the sample solution was collected into a test tube for 13.3 min (5 mL, 5 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–10% EtOAc in hexanes) the title compound was obtained as a beige solid (1st run: 925 mg, 84%; 2nd run: 1.17 g, 94% of 5.5 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.6 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.07 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 6.44 (s, 1H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1, 148.3, 140.9, 131.4, 129.4, 122.9, 120.7, 120.3, 114.5, 51.7. Spectral data were in accordance with those in literature.[4]



10c

Methyl 2-(phenylamino)benzoate (10c): Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of methyl 2-bromobenzoate (2.15 g, 10.0 mmol), aniline (1.12 g, 12.0 mmol), BrettPhos G4 precatalyst (138 mg, 0.15 mmol, 1.5 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of K_3PO_4 (10.61 g, 50 mmol) in H_2O (25 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 107 μL/min each. After equilibration, the sample solution was collected into a test tube for 51.4 min (5.5 mL, 5.5 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–10% EtOAc in hexanes) the title compound was obtained as a yellow oil (1st run: 1.15 g, 92%; 2nd run: 1.10 g, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.52 (br s, 1H), 8.01 (dt, J = 8.2, 1.7 Hz, 1H), 7.37 (dtd, J = 14.7, 7.0, 1.8 Hz, 3H), 7.32 – 7.25 (m, 3H), 7.13 (tt, J = 7.2, 1.2 Hz, 1H), 6.77 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 3.94 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.0, 148.1, 140.9, 134.2, 131.7, 129.5, 123.7, 122.6, 117.2, 114.1, 112.0, 51.9. Spectral data were in accordance with those in literature.[5]

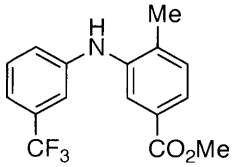


10d

Methyl 3-((2,5-dimethylphenyl)amino)benzoate (10d): Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of methyl 3-chlorobenzoate (1.71 g, 10.0 mmol), 2,5-dimethylaniline (1.45 g, 12.0 mmol), BrettPhos G4

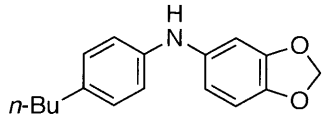
[4] Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.
[5] Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.

precatalyst (92.1 mg, 0.10 mmol, 1.0 mol %) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (2.81 g, 50 mmol) in H_2O (25 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 125 μL/min each. After equilibration, the sample solution was collected into a test tube for 46.6 min (5.83 mL, 5.83 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–25% EtOAc in hexanes) the title compound was obtained as a red oil (1st run: 1.15 g, 78%; 2nd run: 1.25 g, 79% of 6.22 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.51 (m, 2H), 7.30 (t, J = 7.8 Hz, 1H), 7.15 – 7.07 (m, 2H), 7.07 – 7.03 (m, 1H), 6.87 – 6.80 (m, 1H), 5.49 (br s, 1H), 3.91 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3, 144.8, 140.3, 136.7, 131.4, 131.0, 129.3, 126.6, 123.9, 121.1, 120.9, 120.8, 117.7, 52.2, 21.2, 17.6. **IR** (neat, cm^{-1}) 3376, 2949, 1707, 1603, 1575, 1435, 1316, 1282, 1223, 1105, 1003, 803, 750. **EA** Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 74.97; H, 6.82.



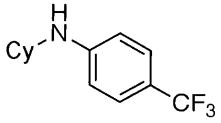
10e

Methyl 4-methyl-3-((3-(trifluoromethyl)phenyl)amino)benzoate (10e): Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of methyl 3-bromo-4-methylbenzoate (1.15 g, 5.0 mmol), 3-(trifluoromethyl)aniline (967 mg, 6 mmol), BrettPhos G4 precatalyst (46.1 mg, 50 μmol, 1.0 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (561 mg, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 75.0 μL/min each. After equilibration, the sample solution was collected into a test tube for 80.1 min (6.01 mL, 3.0 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–25% EtOAc in hexanes) the title compound was obtained as a white solid (1st run: 848 mg, 91%; 2nd run: 885 mg, 92% of 3.1 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.7 Hz, 1H), 7.69 (dd, J = 7.9, 1.7 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.07 (dd, J = 8.1, 2.2 Hz, 1H), 5.41 (br s, 1H), 3.88 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.0, 144.5, 140.3, 135.4, 132.0 (q, J_{CF} = 32.3 Hz), 131.4, 130.0, 129.3, 124.6, 124.2 (q, J_{CF} = 272.7 Hz), 121.3, 119.6, 117.1 (q, J_{CF} = 2.02 Hz), 113.4 (q, J_{CF} = 2.02 Hz), 52.2, 18.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.8. **IR** (neat, cm^{-1}) 3372, 2952, 1704, 1576, 1334, 1118, 1068, 758, 698. **EA** Anal. Calcd. for $C_{16}H_{14}F_3NO_2$: C, 62.13; H, 4.56. Found: C, 62.13; H, 4.60.



10f

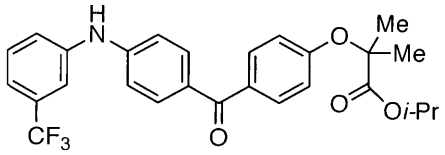
***N*-(4-butylphenyl)benzo[d][1,3]dioxol-5-amine (10f)**: Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate (540 mg, 2.0 mmol), 4-butylaniline (358 mg, 2.4 mmol), BrettPhos G4 precatalyst (18.4 mg, 0.02 mmol, 1.0 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of $K_3PO_4 \cdot H_2O$ (2.30 g, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 50.0 μL/min each. After equilibration, the sample solution was collected into a test tube for 49.7 min (2.48 mL, 0.49 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–10% EtOAc in hexanes) the title compound was obtained as a brown oil (1st run: 137 mg, 99%; 2nd run: 337 mg, 100% of 1.24 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.5, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 8.2, 2.2 Hz, 1H), 5.94 (s, 1H), 5.44 (br s, 1H), 2.60 (t, J = 7.7 Hz, 2H), 1.74 – 1.54 (m, 2H), 1.42 (p, J = 7.5 Hz, 2H), 0.99 (td, J = 7.2, 3.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.3, 142.4, 142.1, 138.3, 135.1, 129.3, 117.2, 111.8, 108.6, 101.7, 101.0, 35.0, 34.0, 22.4, 14.1. **IR** (neat, cm^{-1}) 3394, 2955, 2926, 2856, 1611, 1500, 1483, 1229, 1187, 1036, 930, 795. **EA** Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.73; H, 7.12.



10g

***N*-cyclohexyl-4-(trifluoromethyl)aniline (10g)**: Following the general procedure with a 1.7 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 1-chloro-4-(trifluoromethyl)benzene (1.8 g, 10.0 mmol), cyclohexylamine (1.09 g, 11.0 mmol), BrettPhos G4 precatalyst (140 mg, 0.15 mmol, 1.5 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (2.24 g, 40 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 110 °C at a flow rate of 56.7 μL/min each. After equilibration, the sample solution was collected into a test tube for 93.6 min (5.31 mL, 5.31 mmol). After workup and purification by flash chromatography (Biotage, 100 g SNAP column, 0–2% EtOAc in hexanes) the title compound was obtained as a white crystalline solid (1st run: 912 mg, 71%; 2nd run: 933 mg, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 3.89 (br s, 1H), 3.34 (tt, J = 9.6, 3.6 Hz, 1H), 2.10 (dt, J = 13.1, 3.1 Hz, 2H), 1.82

(dp, J = 11.7, 3.9 Hz, 2H), 1.72 (dp, J = 12.0, 3.7 Hz, 1H), 1.52 – 1.36 (m, 2H), 1.36 – 1.13 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.0, 126.7 (q, J_{CF} = 4.04 Hz), 124.0, 118.0 (q, J_{CF} = 32.6 Hz), 112.1, 51.4, 33.2, 25.9, 25.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -60.7. Spectral data were in accordance with those in literature.[6]

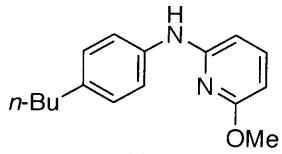


10h

Isopropyl 2-methyl-2-(4-(4-((3(trifluoromethyl)phenyl)amino)benzoyl)phenoxy)propanoate (10h): Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (fenofibrate) (1.8 g, 5.0 mmol), 3-(trifluoromethyl)aniline (967 mg, 6 mmol), BrettPhos G4 precatalyst (46.1 mg, 50 μmol, 1.0 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting K_2CO_3 (1.38 g, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 110 °C at a flow rate of 50.0 μL/min each. After equilibration, the sample solution was collected into a test tube for 38.4 min (1.92 mL, 0.96 mmol). After workup the product was isolated by removing the solvent under reduced pressure. The concentrate was then triturated with hexane and filtered to give the title compound was obtained as a white solid (1st run: 413 mg, 90%; 2nd run: 1.24 g, 91% of 2.82 mmol collected). mp = 116–118 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.64 (tt, 4H), 7.45 – 7.32 (m, 3H), 7.26 (d, J = 8.0 Hz, 1H), 7.12 – 7.00 (m, 2H), 6.92 – 6.80 (dt, 2H), 6.43 (br s, 1H), 5.09 (hept, J = 6.3 Hz, 1H), 1.66 (s, 6H), 1.21 (d, J = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3, 173.4, 159.2, 146.7, 142.0, 132.5, 132.1 (q, J_{CF} = 32.32 Hz), 131.8, 131.5, 130.4, 130.2, 124.0 (q, J_{CF} = 273.71 Hz), 122.5, 119.1 (d, J_{CF} = 4.04 Hz), 117.4, 116.1 (q, J_{CF} = 4.04 Hz), 115.5, 79.5, 69.4, 25.5, 21.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.8. **IR** (neat, cm^{-1}) 3309, 1726, 1635, 1600, 1564, 1436, 1341, 1287, 1248, 1170, 1150, 1130, 1102, 926, 892, 850, 799, 763, 603. **EA** Anal. Calcd. for $C_{27}H_{26}F_3NO_4$: C, 66.80; H, 5.40. Found: C, 66.89; H, 5.42.

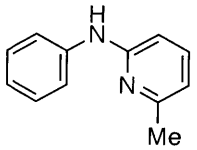
[6] Barker, T. J.; Jarzo, E. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 8325.

Characterization Data for Table 3



11a

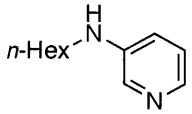
***N*-(4-butylphenyl)-6-methoxypyridin-2-amine (11a)**: Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 2-bromo-6-methoxypyridine (940 mg, 5.0 mmol), 4-butylaniline (895 mg, 6.0 mmol), BrettPhos G4 precatalyst (46.1 mg, 50 μmol, 1.0 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (561 mg, 10 mmol) in H_2O (25 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 50.0 μL/min each. After equilibration, the sample solution was collected into a test tube for 125 min (6.24 mL, 3.12 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–5% EtOAc in hexanes) the title compound was obtained as a red oil (1st run: 713 mg, 90%; 2nd run: 536 mg, 85% of 2.459 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (td, J = 7.9, 1.3 Hz, 1H), 7.30 (dd, J = 8.5, 2.2 Hz, 2H), 7.16 (dd, J = 8.5, 2.1 Hz, 2H), 6.42 (br s, 1H), 6.37 (dd, J = 7.9, 1.6 Hz, 1H), 6.25 – 6.13 (m, 1H), 3.94 (s, 3H), 2.62 (td, J = 7.8, 2.3 Hz, 2H), 1.80 – 1.50 (m, 2H), 1.41 (ddd, J = 12.3, 5.3, 3.1 Hz, 2H), 1.05 – 0.87 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 154.9, 140.2, 138.2, 137.3, 129.1, 120.5, 99.7, 99.4, 53.4, 35.1, 33.9, 22.5, 14.1. **IR** (neat, cm^{-1}) 3393, 2954, 2927, 2856, 1583, 1513, 1456, 1416, 1258, 1146, 1120, 779. **EA** Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86. Found: C, 74.99; H, 7.88.



11b

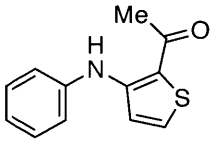
6-methyl-*N*-phenylpyridin-2-amine (11b): Following the general procedure with a 1.5 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 2-bromo-6-methylpyridine (860 mg, 5.0 mmol), aniline (559 mg, 6.0 mmol), BrettPhos G4 precatalyst (46.1 mg, 50 μmol, 1.0 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (561 mg, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 75.0 μL/min each. After equilibration, the sample solution was collected into a test tube for 83 min (6.23 mL, 3.12 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, hexanes/acetone/Et_3N 9:1:0.1 v/v) the title compound was obtained as a yellow oil (1st run: 508 mg, 88%; 2nd run: 502 mg, 91% of 3.0 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.38 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 4.3 Hz, 4H), 7.22 (br s, 1H), 7.05 (p, J = 4.3 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 7.3 Hz, 1H),

2.47 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.1, 155.6, 140.7, 137.9, 129.1, 122.4, 120.2, 114.2, 104.8, 24.1. Spectral data were in accordance with those in literature.[7]



11c

***N*-hexylpyridin-3-amine (11c)**: Following the general procedure with a 1.7 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 3-bromopyridine (1.58 g, 10.0 mmol), *n*-hexylamine (1.2 g, 12.0 mmol), BrettPhos G4 precatalyst (184 mg, 0.2 mmol, 2.0 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (2.24 g, 40 mmol) in H_2O (25 mL total volume). The two solutions were infused into the packed-bed reactor at 110 °C at a flow rate of 56.7 μL/min each. After equilibration, the sample solution was collected into a test tube for 94 min (5.32 mL, 5.32 mmol). The organic layer was washed with 2.0 M HCl (20 mL) to remove residual *n*-hexylamine, neutralized with saturated K_2CO_3, then extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure to provide the title compound was obtained as an off-white powder (1st run: 790 mg, 83%; 2nd run: 268 mg, 89% of 1.68 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, J = 2.8 Hz, 1H), 7.92 (dd, J = 4.7, 1.4 Hz, 1H), 7.06 (m, 1H), 6.84 (ddd, J = 8.3, 2.9, 1.3 Hz, 1H), 3.69 (br s, 1H), 3.10 (td, J = 7.2, 5.7 Hz, 2H), 1.61 (p, J = 7.2 Hz, 2H), 1.47 – 1.35 (m, 2H), 1.35 – 1.23 (m, 4H), 0.89 (s, J = 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.4, 138.4, 135.9, 123.7, 118.3, 43.6, 31.6, 29.4, 26.8, 22.6, 14.0.

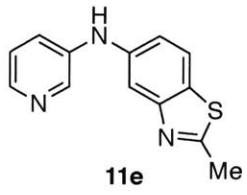


11d

1-(3-(phenylamino)thiophen-2-yl)ethan-1-one (11d): Following the general procedure with a 1.7 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 2-acetyl-6-bromothiophene (2.05 g, 10.0 mmol), aniline (1.1 g, 12.0 mmol), BrettPhos G4 precatalyst (92.1 mg, 0.1 mmol, 1.0 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (1.12 g, 20 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 120 °C at a flow rate of 113.3 μL/min each. After equilibration, the sample solution was collected into a test tube for 8.8 min (1.0 mL, 1.0 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–10% EtOAc in hexanes) the title compound was obtained as a yellow oil (1st run: 189 mg, 87%; 2nd run: 375 mg, 82% of

[7] Dhayalan, V.; Sämann, C.; Knochel, P. *Chem. Commun.* **2015**, *51*, 3239.

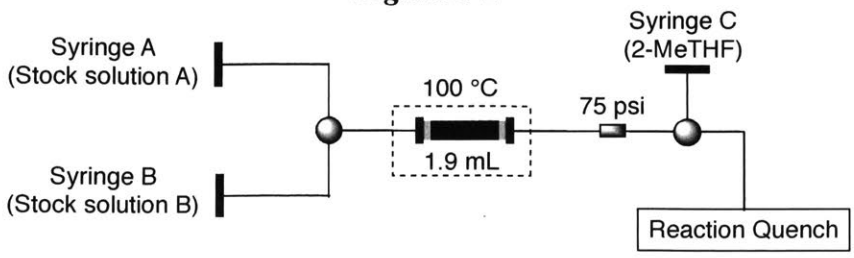
2.1 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.30 – 7.18 (m, 3H), 7.08 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 5.6 Hz, 1H), 6.97 (t, *J* = 8 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.4, 151.7, 141.0, 132.4, 129.4, 123.6, 120.9, 117.9, 113.4, 28.7. **IR** (neat, cm^{-1}) 3256, 1588, 1549, 1375, 1242, 944, 725. **EA** Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.33; H, 5.1. Found: C, 66.07; H, 5.1.

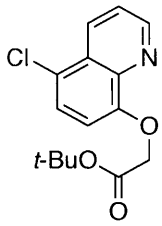


11e

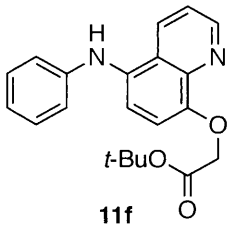
2-methyl-*N*-(pyridin-3-yl)benzo[d]thiazol-5-amine (11e): Following the general procedure with a 1.9 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 5-chloro-2-methylbenzothiazole (367 mg, 2.0 mmol), 3-aminopyridine (226 mg, 2.4 mmol), BrettPhos G4 precatalyst (27.6 mg, 30 μmol, 1.5 mol%) in 10% DMO/2-MeTHF (10 mL total volume). Syringe B was loaded with stock solution B consisting of KOH (561 mg, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 63.3 μL/min each. Syringe C was loaded with 2-MeTHF and connected to the continuous-flow setup as depicted in Figure S-2. Syringe C was infused at a rate of 140 μL/min. After equilibration, the sample solution was collected into a test tube for 89.1 min (5.64 mL, 1.13 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 1% Et_3N in EtOAc) the title compound was obtained as an off-white solid (1st run: 231 mg, 85%; 2nd run: 243 mg, 89% of 1.13 mmol collected). mp = 183–189 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.17 (s, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 2.2 Hz, 1H), 7.46 (ddd, *J* = 8.4, 2.8, 1.3 Hz, 1H), 7.16 (dd, *J* = 8.3, 4.5 Hz, 1H), 7.11 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.11 (s, 1H), 2.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6, 154.8, 142.2, 140.9, 140.3, 129.0, 123.9, 123.4, 122.2, 117.4, 111.4, 20.3. **IR** (neat, cm^{-1}) 3250, 3037, 2993, 1606, 1581, 1480, 1429, 1338, 1157, 847, 800, 641. **EA** Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.71; H, 4.59. Found: C, 64.42; H, 4.62.

Figure S-2





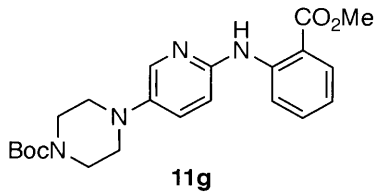
***tert*-butyl 2-((5-chloroquinolin-8-yl)oxy)acetate**: An oven-dried round bottom flask was charged with 5-chloroquinolin-8-ol (3.59 g, 20.0 mmol), *tert*-butyl 2-bromoacetate (4.68 g, 24.0 mmol), K_2CO_3 (8.28 g, 60 mmol), and acetone (0.4 M) and stirred at 50 °C overnight. The resulting mixture was then concentrated under reduced pressure and diluted with EtOAc (25 mL). Using a separation funnel, the organic layer was extracted with H_2O (25 mL × 2) and brine (25 mL), then dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The concentrate was then triturated with hexane and filtered to give the title compound was obtained as a pale white solid (5.53 g, 94%). mp = 93–96 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 – 8.79 (m, 1H), 8.44 (d, J = 8.5 Hz, 1H), 7.47 (dd, J = 8.5, 4.1 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 4.80 (s, 2H), 1.39 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 153.0, 149.9, 140.7, 132.9, 127.1, 126.0, 123.2, 122.4, 109.2, 82.5, 66.5, 28.0. **IR** (neat, cm^{-1}) 2969, 1751, 1591, 1501, 1468, 1364, 1315, 1229, 1148, 1103, 937, 820, 782. **EA** Anal. Calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49. Found: C, 61.16; H, 5.35.



11f

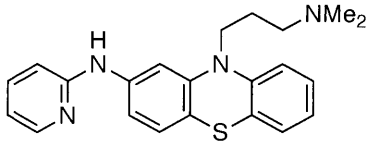
***tert*-butyl 2-((5-chloroquinolin-8-yl)oxy)acetate (11f)**: Following the general procedure with a 1.8 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of *tert*-butyl 2-((5-chloroquinolin-8-yl)oxy)acetate (588 mg, 2.0 mmol), aniline (224 mg, 2.4 mmol), BrettPhos G4 precatalyst (36.8 mg, 40 μmol, 2 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of K_2CO_3 (1.38 g, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 60.0 μL/min each. After equilibration, the sample solution was collected into a test tube for 71.9 min (4.31 mL, 0.86 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–50% EtOAc in hexanes) the title compound was obtained as a yellow solid (1st run: 294 mg, 97%; 2nd run: 371 mg, 89% of 1.20 mmol collected). mp = 148–155 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.85 (m, 1H), 8.24 (dq, J = 8.6, 1.8 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.23 – 7.16 (m, 1H), 7.10 (t, J = 7.2 Hz, 2H), 6.82 (dd, J = 8.4, 1.9 Hz, 1H), 6.79 – 6.70 (m, 1H), 6.70 – 6.59 (m, 2H), 5.70 (br s, 1H), 4.76 (s, 2H), 1.39 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.0, 151.1, 149.6, 146.5, 140.8, 131.8, 129.4, 126.1, 121.5, 120.6, 119.6, 115.5, 109.6, 82.5, 66.7, 28.1. **IR** (neat, cm^{-1}) 3221, 2968, 1751, 1594, 1497, 1469, 1312, 1221,

1145, 1119, 817, 785, 748, and 695. **HRMS** (DART+) calcd. For $C_{21}H_{22}N_2O_3$ $[M+H]^+$ 351.1703, found 351.1670.



11g

***tert*-butyl 4-(6-((2-(methoxycarbonyl)phenyl)amino)pyridin-3-yl)piperazine-1-carboxylate (11g)**: Following the general procedure with a 1.7 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of *tert*-butyl 4-(6-bromopyridin-3-yl)piperazine-1-carboxylate (684 mg, 2.0 mmol), methyl 2-aminobenzoate (380 mg, 2.4 mmol), BrettPhos G4 precatalyst (36.8 mg, 40 μmol, 2 mol%) in 10% DMO/toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of K_3PO_4 (2.12 g, 10 mmol) in H_2O (10 mL total volume). The two solutions were infused into the packed-bed reactor at 100 °C at a flow rate of 56.7 μL/min each. After equilibration, the sample solution was collected into a test tube for 88.2 min (5.0 mL, 1.0 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–30% EtOAc in hexanes) the title compound was obtained as a yellow solid (1st run: 334 mg, 81%; 2nd run: 349 mg, 85% of 0.99 mmol collected) mp = 120–123 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.13 (d, *J* = 2.7 Hz, 1H), 7.94 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.42 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.25 (ddd, *J* = 8.6, 7.4, 2.0 Hz, 1H), 6.83 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.71 – 6.63 (m, 2H), 3.90 (s, 3H), 3.60 – 3.54 (m, 4H), 3.51 (dd, *J* = 7.1, 3.9 Hz, 4H), 1.49 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.2, 157.1, 155.0, 149.9, 145.4, 135.6, 134.4, 131.7, 127.9, 116.5, 113.2, 111.1, 107.7, 80.1, 51.9, 45.6, 28.6. **IR** (neat, cm^{-1}) 3313, 2973, 2834, 1684, 1582, 1516, 1409, 1306, 1231, 1160, 1083, 935, 746, 704. **EA** Anal. Calcd. for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84. Found: C, 64.08; H, 6.90.

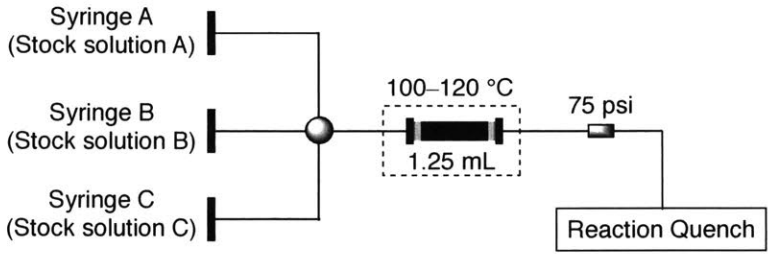


11h

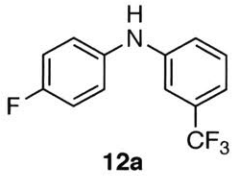
10-(3-(dimethylamino)propyl)-*N*-(pyridin-2-yl)-10H-phenothiazin-2-amine (11h): Following the general procedure with a 1.7 mL packed-bed reactor. Syringe A was loaded with stock solution A consisting of 3-(2-chloro-10H-phenothiazin-10-yl)-*N,N*-dimethylpropan-1-amine (Chlorpromazine, 710 mg, 2.0 mmol) in H_2O (10 mL total volume). Syringe B was loaded with stock solution B consisting of 2-aminopyridine (226 mg, 2.4 mmol), BrettPhos G4 precatalyst (36.8 mg, 40 μmol, 2 mol%) in 10% DMO/toluene (10 mL total volume). Syringe C was loaded with stock solution C consisting of KOH (561 mg, 10 mmol) in H_2O (10 mL total volume). The three solutions were infused into the packed-bed reactor at 110 °C at a flow

rate of 37.8 μL/min each as depicted in Figure S-3. After equilibration, the sample solution was collected into a test tube for 165.4 min (6.25 mL, 1.25 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–100%, (10% Et_3N in EtOAc) in hexanes) the title compound was obtained as an off-white powder (1st run: 460 mg, 97%; 2nd run: 433 mg, 92% of 1.25 mmol collected). mp = 155–157 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (ddd, J = 5.0, 2.0, 0.9 Hz, 1H), 7.48 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 7.18 – 7.11 (m, 2H), 7.05 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 2.1 Hz, 1H), 6.95 – 6.87 (m, 2H), 6.85 (dd, J = 8.2, 2.1 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.75 – 6.70 (m, 1H), 6.60 (br s, 1H), 3.89 (t, J = 8 Hz, 2H), 2.40 (t, J = 7.1 Hz, 2H), 2.19 (s, 6H), 1.97 (p, J = 7.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.2, 148.5, 146.4, 145.2, 140.3, 137.8, 127.8, 127.5, 127.3, 125.5, 122.6, 118.4, 115.7, 115.1, 114.7, 108.7, 108.7, 57.3, 45.7, 45.7, 25.3. **IR** (neat, cm^{-1}) 2970, 2942, 2816, 2764, 1606, 1456, 1436, 767, 739, 721. **EA** Anal. Calcd. for $C_{22}H_{24}N_4S$: C, 70.18; H, 6.43. Found: C, 69.94; H, 6.46.

Figure S-3



Characterization Data for Scheme 1

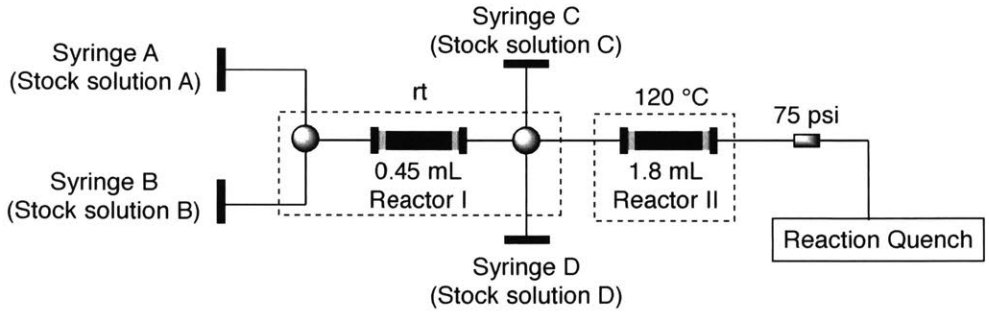


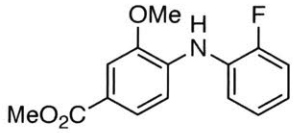
12a

***N*-(4-fluorophenyl)-3-(trifluoromethyl)aniline (12a)**: As depicted in Figure S-4, syringe A was loaded with stock solution A consisting of 4-fluorophenol (504 mg, 4.5 mmol) and K_3PO_4 (3.82 g, 18 mmol) in H_2O (10 mL total volume). Syringe B was loaded with stock solution B consisting of Tf_2O (1.51 mL, 9.0 mmol) in anhydrous toluene (10 mL total volume). Syringe C was loaded with stock solution C consisting of K_3PO_4 (5.09 g, 24 mmol) in H_2O (10 mL total volume). Syringe D was loaded with stock solution D consisting of 4-fluoroaniline (800 mg, 7.2 mmol), BrettPhos G4 precatalyst (82.9 mg, 90 μmol, 1.5 mol%) in 30% DMO/toluene (10 mL total volume). Syringe E was loaded with stock solution D consisting of K_3PO_4 (5.09 g, 24 mmol) in H_2O (10 mL total volume). Syringes A, B, and C were infused into the packed-bed reactor I at a flow rate of 40.0 μL/min each. Syringes D and E were infused into packed-bed reactor II at a flow rate of 40.0

μL/min. After equilibration, the sample solution was collected into a test tube for 58.1 min (2.33 mL, 1.40 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–10% EtOAc in hexanes) the title compound was obtained as a tan oil (1st run: 372 mg, 97%; 2nd run: 315 mg, 96% of 0.96 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (tt, J = 7.9 Hz, 1H), 7.21-7.02 (m, 7H), 5.72 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.9 (d, J_{CF} = 241 Hz), 144.9, 137.7 (d, J_{CF} = 2.7 Hz), 131.8 (q, J_{CF} = 32 Hz), 130.0, 124.2 (q, J_{CF} = 272 Hz), 122.1 (d, J_{CF} = 8.0 Hz), 118.9 (q, J_{CF} = 1.5 Hz), 116.6 (q, J_{CF} = 3.9 Hz), 116.3 (d, J_{CF} = 22.7 Hz), 118.9 (q, J = 3.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.2, -120.4.

Figure S-4



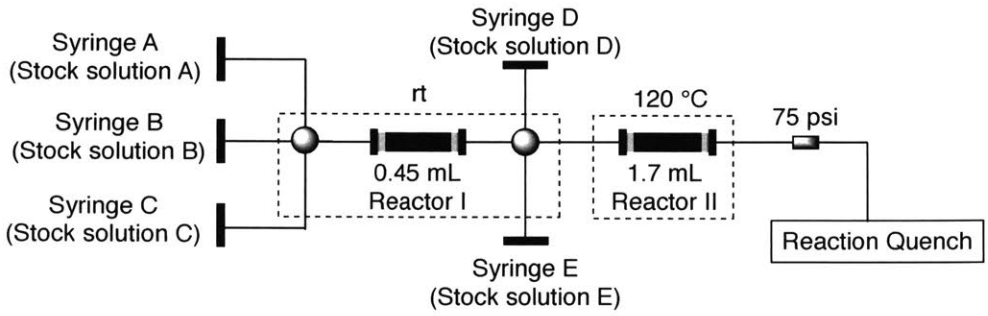


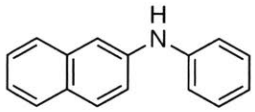
12b

Methyl 4-((2-fluorophenyl)amino)-3-methoxybenzoate (12b): As depicted in Figure S-5, syringe A was loaded with stock solution A consisting of methyl 4-hydroxy-3-methoxybenzoate (1.09 g, 6.0 mmol) in toluene (10 mL total volume). Syringe B was loaded with stock solution B consisting of Tf_2O (1.51 mL, 9 mmol) in anhydrous toluene (10 mL total volume). Syringe C was loaded with stock solution C consisting of 3-trifluoromethylaniline (870 mg, 5.4 mmol), BrettPhos G4 precatalyst (62.2 mg, 67.5 μmol, 1.5 mol%) in 10% DMO/toluene (10 mL total volume). Syringe D was loaded with stock solution D consisting of K_3PO_4 (3.82 g, 18 mmol) in H_2O (10 mL total volume). Syringes A and B were infused into the packed-bed reactor I at a flow rate of 40.0 μL/min each. Syringes C and D were infused into packed-bed reactor II at a flow rate of 40.0 μL/min. After equilibration, the sample solution was collected into a test tube for 96.0 min (3.84 mL, 1.73 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–5% EtOAc in hexanes) the title compound was obtained as a yellow oil (1st run: 415 mg, 94%; 2nd run: 654 mg, 91% of 5.78 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.4, 1.8 Hz, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.46 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.17–7.08 (m, 3H), 7.03–6.97 (m, 1H), 6.54 (br

s, 1H), 3.97 (s, 3H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.1, 154.6 (d, J_{CF} = 243 Hz), 147.1, 137.3, 129.1 (d, J_{CF} = 11 Hz), 124.4 (d, J_{CF} = 3.7 Hz), 123.7, 123.2 (d, J_{CF} = 7.4 Hz), 121.0, 120.9 (d, J_{CF} = 12 Hz), 116.0 (d, J_{CF} = 20 Hz), 111.4, 111.0, 55.9, 51.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -128.4. **IR** (neat, cm^{-1}) 2947, 1705, 1600, 1525, 1500, 1273, 1229, 1127, 1097, 1032, 989, 870. **EA** Anal. Calcd. for $C_{15}H_{14}FNO_3$: C, 65.45; H, 5.13. Found: C, 65.16; H, 5.09.

Figure S-5



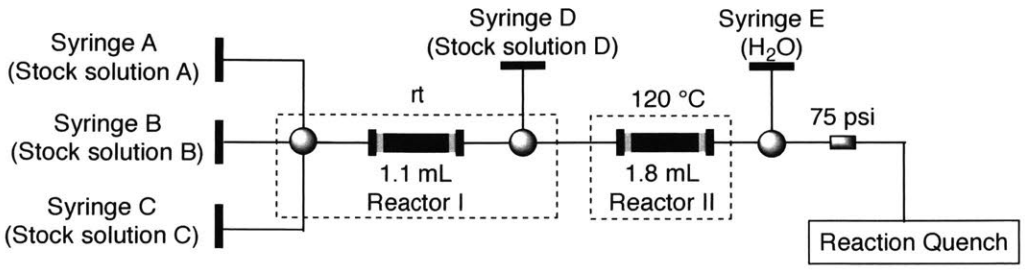


12c

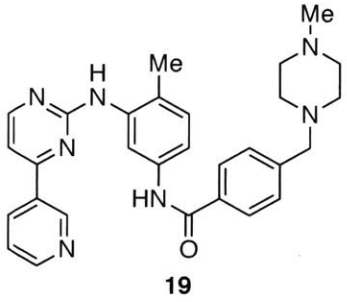
***N*-phenylnaphthalen-2-amine (12c)**: As depicted in Figure S-6, syringe A was loaded with stock solution A consisting of 2-naphthol (720 mg, 5.0 mmol, 1.0 equiv) in 15% DMO/toluene (5 mL total volume). Syringe B was loaded with stock solution B consisting of TsCl (1.0 g, 5.3 mmol) in 15% DMO/toluene (5 mL total volume). Syringe C was loaded with stock solution C consisting of KOH (1.12 g, 20 mmol) in H_2O (5 mL total volume). Syringe D was loaded with stock solution D consisting of aniline (512 mg, 5.5 mmol), BrettPhos G4 precatalyst (92.1 mg, 0.1 mmol, 2.0 mol%) in toluene (5 mL total volume). Syringe E was loaded with H_2O (10 mL total volume). Syringes A, B, and C were infused into the packed-bed reactor I at a flow rate of 30.0 μL/min each. Syringe D was infused into packed-bed reactor II at a flow rate of 30.0 μL/min. Syringe E was infused into the flow system after packed-bed reactor II at a flow rate of 50.0 μL/min. After equilibration, the sample solution was collected into a test tube for 34.4 min (1.03 mL, 1.03 mmol). After workup and purification by flash chromatography (Biotage, 50 g SNAP column, 0–10% EtOAc in hexanes) the title compound was obtained as a tan crystalline solid (1st run: 183 mg, 83%; 2nd run: 194 mg, 88% of 1.01 mmol collected). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (br t, J = 8 Hz, 2H), 7.60 (d, J = 8.2 Hz, 1H), 7.40-7.33 (m, 2H), 7.28 (dd, J = 7.6, 7.6 Hz, 3H), 7.16 (dd, J = 8.7, 2.4 Hz, 1H), 7.11 (*d*, J = 7.6 Hz, 2H), 6.95 (tt, J = 7.3, 1.0 Hz, 1H), 5.73 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.0,

140.9, 134.7, 129.5, 129.3, 129.3, 127.8, 126.6, 126.6, 123.6, 121.5, 120.2, 118.4, 111.7. Spectral data were in accordance with those in literature.[8]

Figure S-6



Procedure and Characterization Data for Schemes 2 and 3



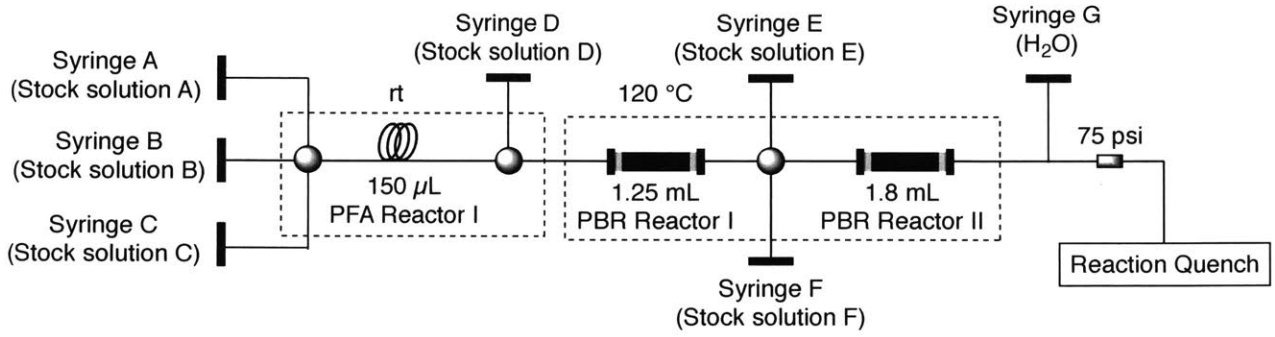
19

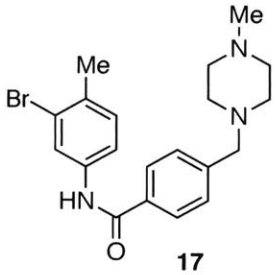
Imatinib (19): As depicted in Figure S-7, syringe A was loaded with stock solution A consisting of 3-bromo-4-methylaniline (936 mg, 5.0 mmol) in 2-MeTHF (10 mL total volume). Syringe B was loaded with stock solution B consisting of 4-(chloromethyl)benzoyl chloride (837 mg, 4.5 mmol) in 2-MeTHF (10 mL total volume). Syringe C was loaded with stock solution C consisting of KOH (1.26 g, 22.5 mmol) in H_2O (10 mL total volume). Syringe D was loaded with stock solution D consisting of *N*-methylpiperazine (1.35 g, 13.5 mmol) in H_2O (10 mL total volume). Syringe E was loaded with stock solution E consisting of 4-(pyridin-3-yl)pyrimidin-2-amine (775 mg, 4.5 mmol) in H_2O with 1 equivalent of HCl (10 mL total volume). Syringe F was loaded with stock solution F consisting of BrettPhos G4 precatalyst (207 mg, 0.225 mmol, 5.0 mol%) in 30% DMO/2-MeTHF (10 mL total volume). Syringe G was loaded with H_2O (25 mL total volume). Syringes A, B, and C were infused into PFA tubing reaction I at a flow rate of 20.0 μL/min each. Syringe D was infused into packed-bed reactor I at a flow rate 20.0 μL/min. Syringe E and F were infused into packed-bed reactor II at a flow rate of 20.0 μL/min each. Syringe G was infused into the flow system after packed-bed reactor II at a flow rate of 40.0 μL/min. After equilibration, the sample solution was collected into a test tube for 53.5 min (1.07 mL, 0.48 mmol). Using a separation funnel, the organic layer was extracted with 0.5 M HCl (25 mL × 2). The aqueous layer was neutralized with saturated K2CO3, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and then concentrated

[8] Kim, M.; Chang, S. *Org. Lett.* **2010**, *12*, 1640.

under reduced pressure. The concentrate was then triturated with a minimal amount of MeCN and filtered to give the title compound as an off-white powder (1st run: 124 mg, 52%; 2nd run: 300 mg, 60% of 1.02 mmol collected), mp 204-208 °C (lit. mp 207-210). **^{1}H NMR** (400 MHz, DMSO – d6) δ 10.17 (s, 1H), 9.28 (s, 1H), 8.98 (s, 1H), 8.68 (d, J = 8 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H), 8.48 (dt, J = 9.7, 1.8 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.50 (m, 2H), 7.46 – 7.37 (m, 3H), 7.21 (d, J = 8.2 Hz, 1H), 3.51 (s, 2H), 2.47 – 2.25 (m, 8H), 2.23 (s, 3H), 2.14 (s, 3H). **^{13}C NMR** (101 MHz, DMSO – d6) δ 165.2, 161.6, 161.2, 159.4, 151.4, 148.2, 142.1, 137.8, 137.2, 134.4, 133.8, 132.2, 130.0, 128.6, 127.6, 127.6, 123.8, 117.2, 116.7, 107.5, 61.6, 54.7, 52.6, 45.7, 17.7. Spectral data were in accordance with those in literature.[9]

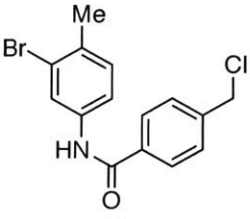
Figure S-7





17

***N*-(3-bromo-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (17)**: **^{1}H NMR** (400 MHz, DMSO – d6) δ10.27 (s, 1H), 8.14 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.74 – 7.60 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.3 Hz, 1H), 3.52 (s, 2H), 2.37 (br s, 8H), 2.32 (s, 3H), 2.15 (s, 3H). **^{13}C NMR** (101 MHz, DMSO – d6) δ 165.4, 142.4, 138.4, 133.2, 131.9, 130.8, 128.6, 127.6, 123.6, 123.3, 119.4, 61.6, 54.7, 52.6, 45.7, 21.7. Spectral data were in accordance with those in literature.[9]



15

***N*-(3-bromo-4-methylphenyl)-4-(chloromethyl)benzamide (15)**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.51 – 7.42 (m, 3H), 7.20 (d, J = 8.2 Hz, 1H), 4.62 (s, 2H), 2.37 (s, 3H) **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.1, 141.3, 136.6, 134.5, 134.2, 130.9,

[9] Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2013**, *11*, 1822.

128.9, 127.5, 124.8, 124.0, 119.3, 45.3, 22.3. Spectral data were in accordance with those in literature.[9]

1.5 References and Notes

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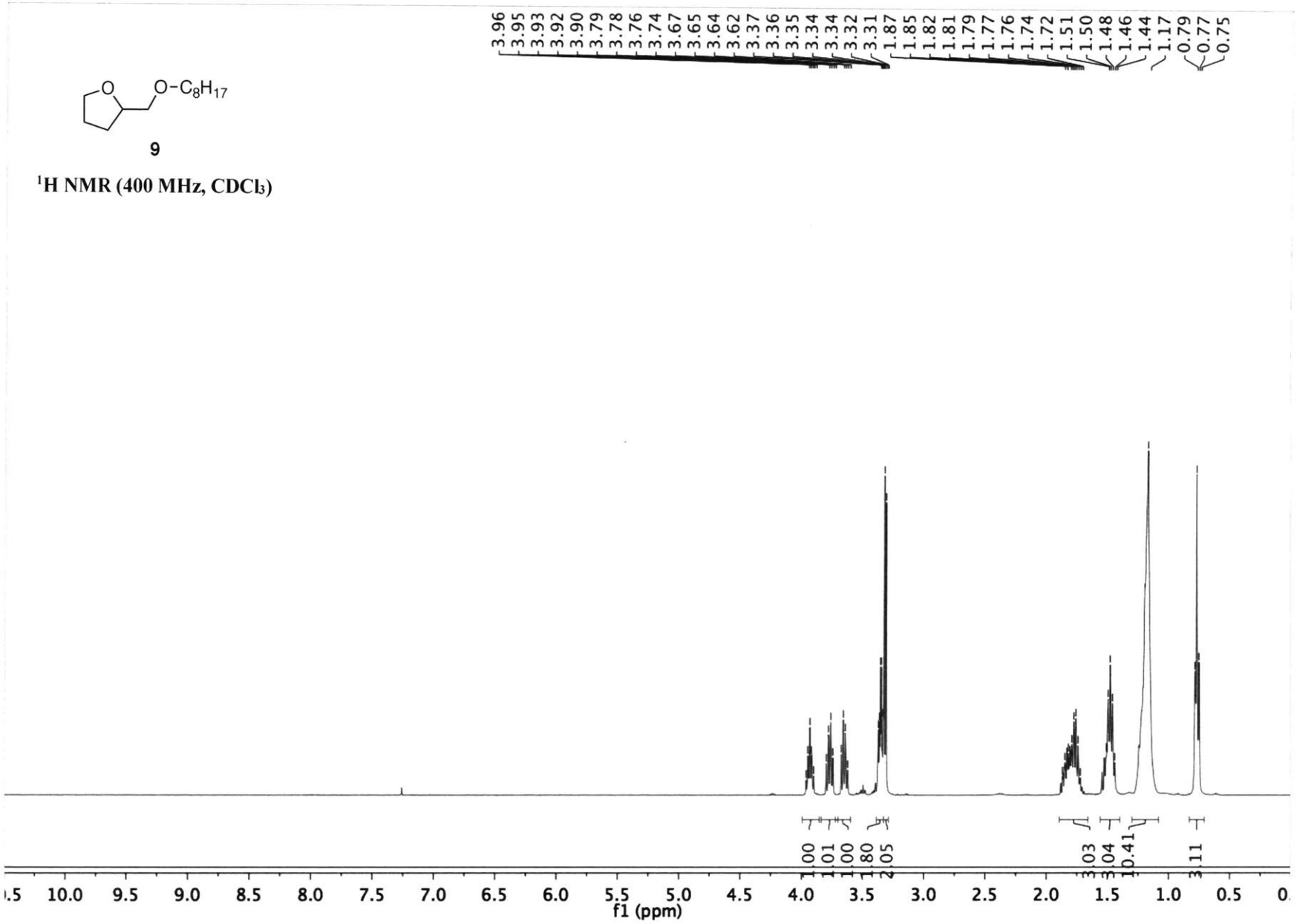
[17] The output of imatinib in our current system is 2.5 mg/min. For comparison, see references 2g, h

1.6 ^{1}H, ^{13}C, and ^{19}F NMR Spectra



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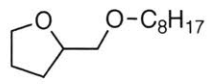

9

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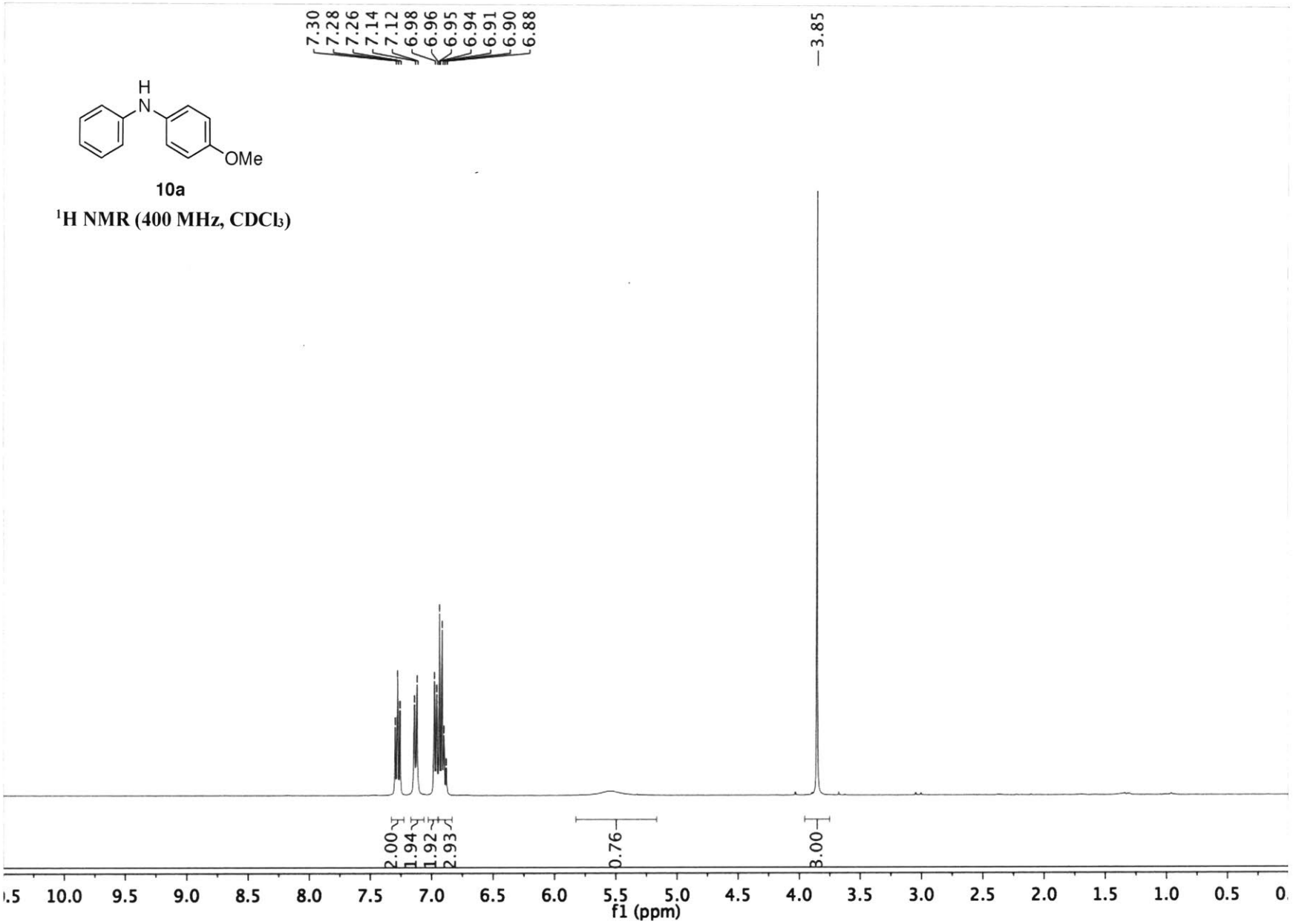
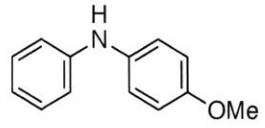


10a

^{1}H NMR (400 MHz, $CDCl_3$)



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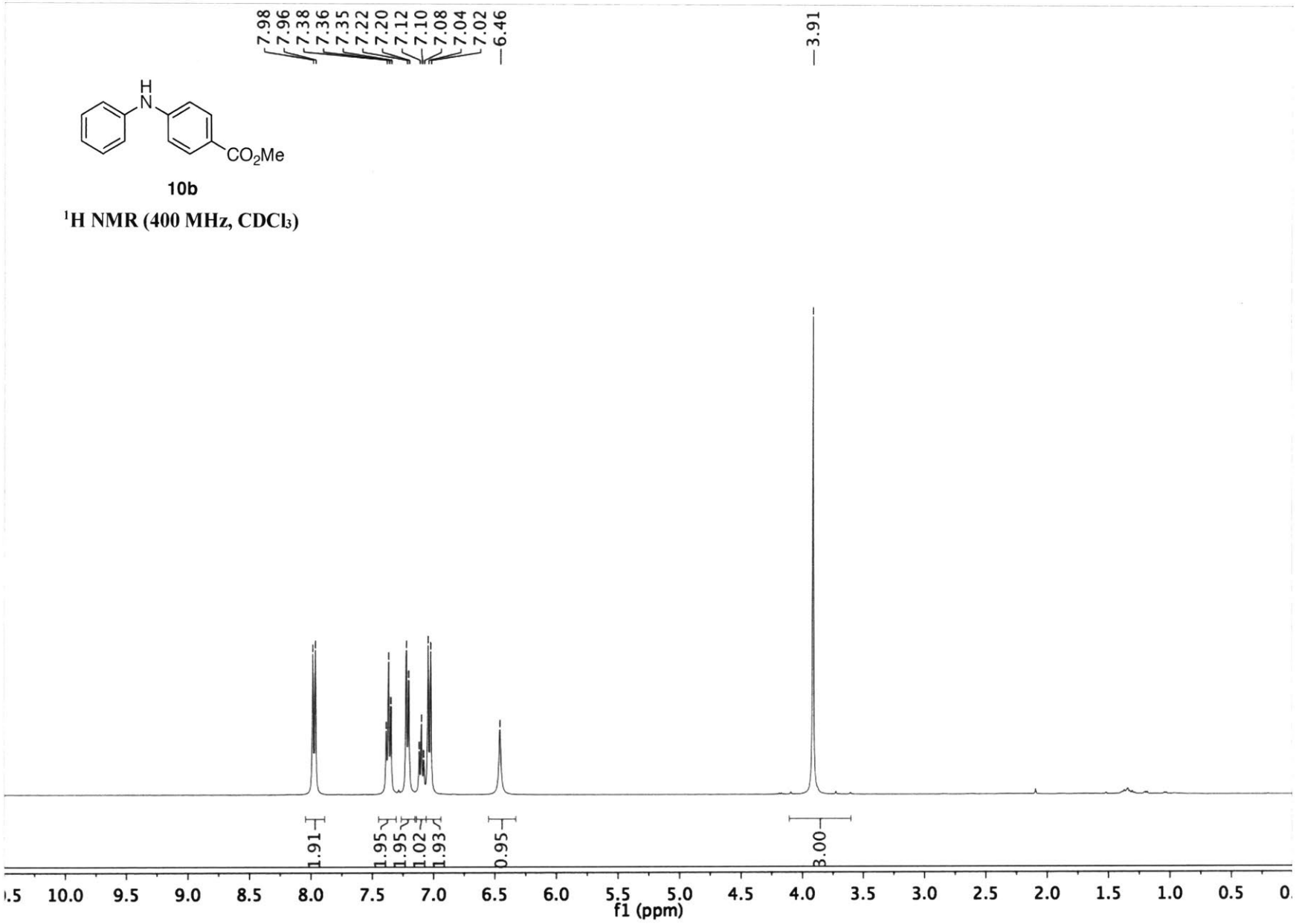

10b

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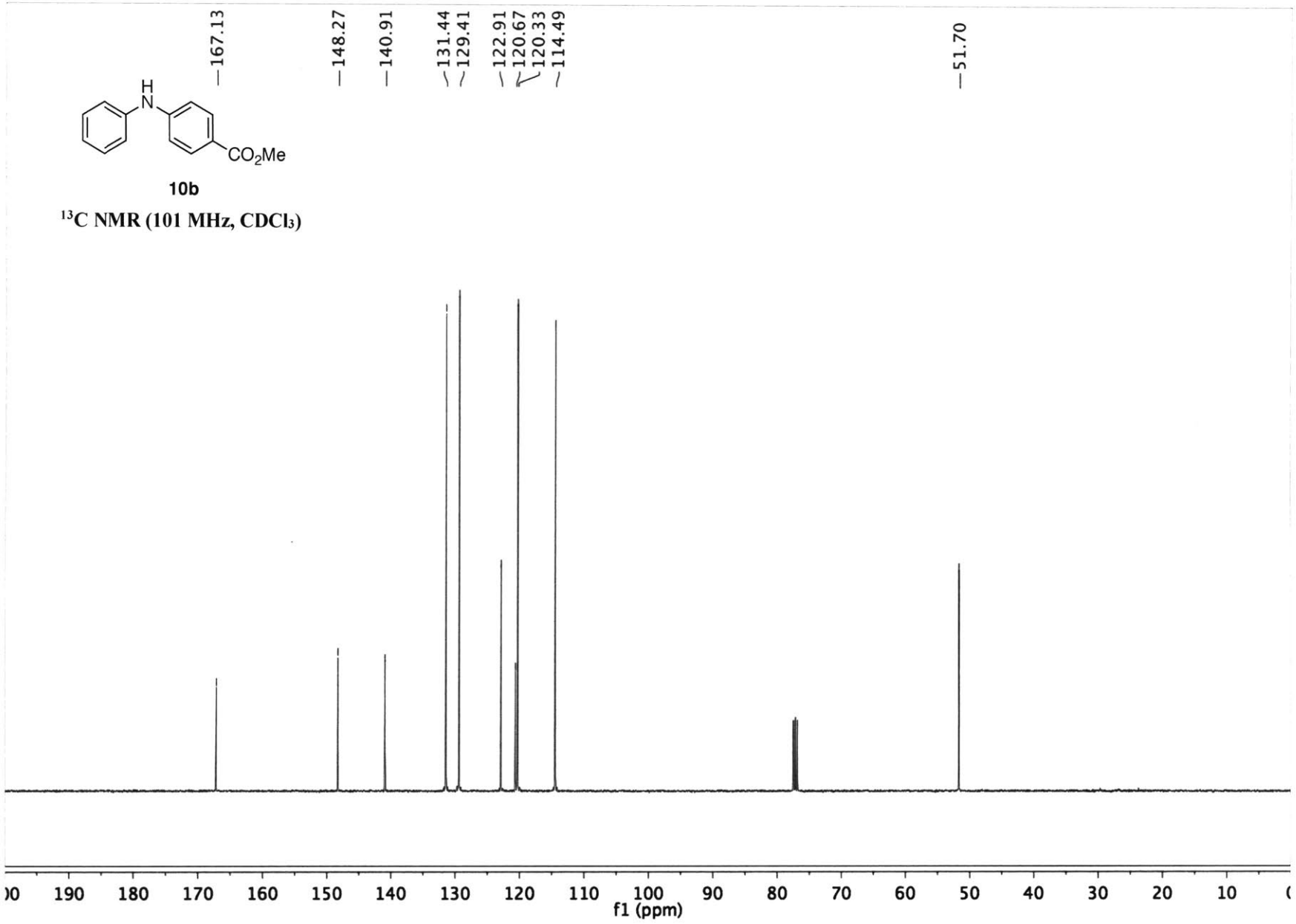
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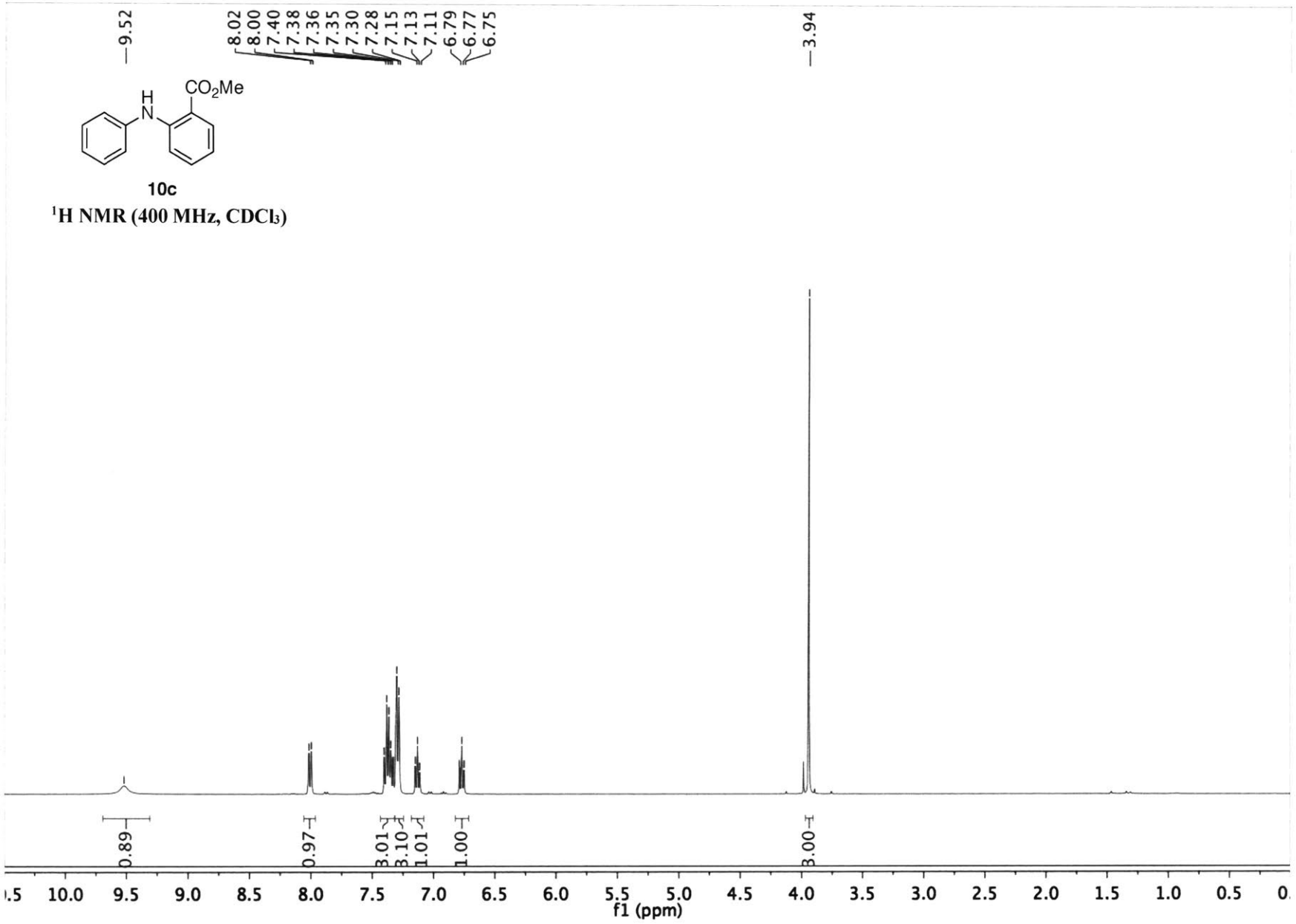
131.44
129.41
122.91
120.67
120.33
114.49
51.70
H
N
CO2Me
10b
13C NMR (101 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



10c

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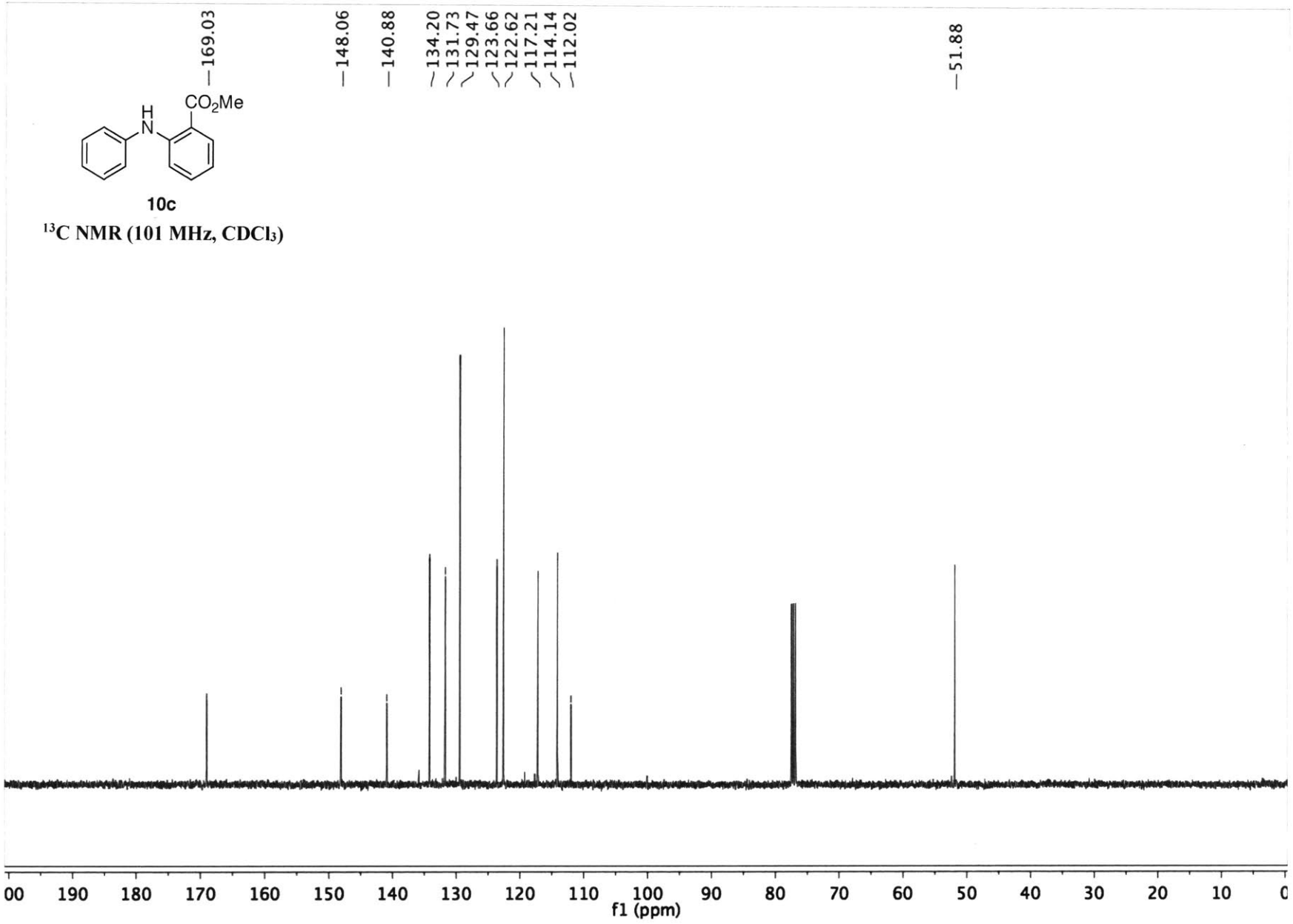
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114.14
112.02
51.88
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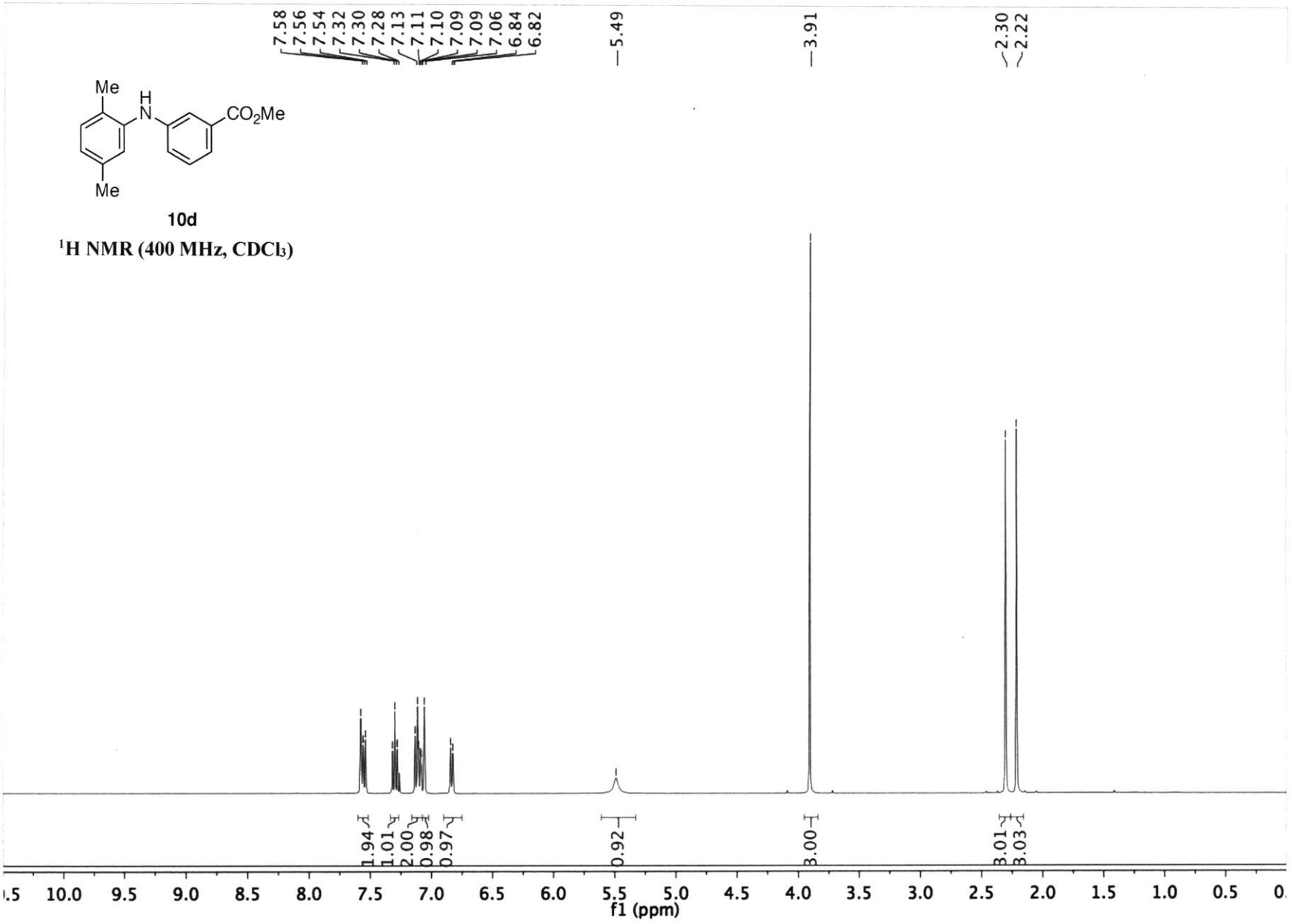
H
N
10c
13C NMR (101 MHz, CDCl3)
f1 (ppm)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7.54
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7.30
7.28
7.13
7.11
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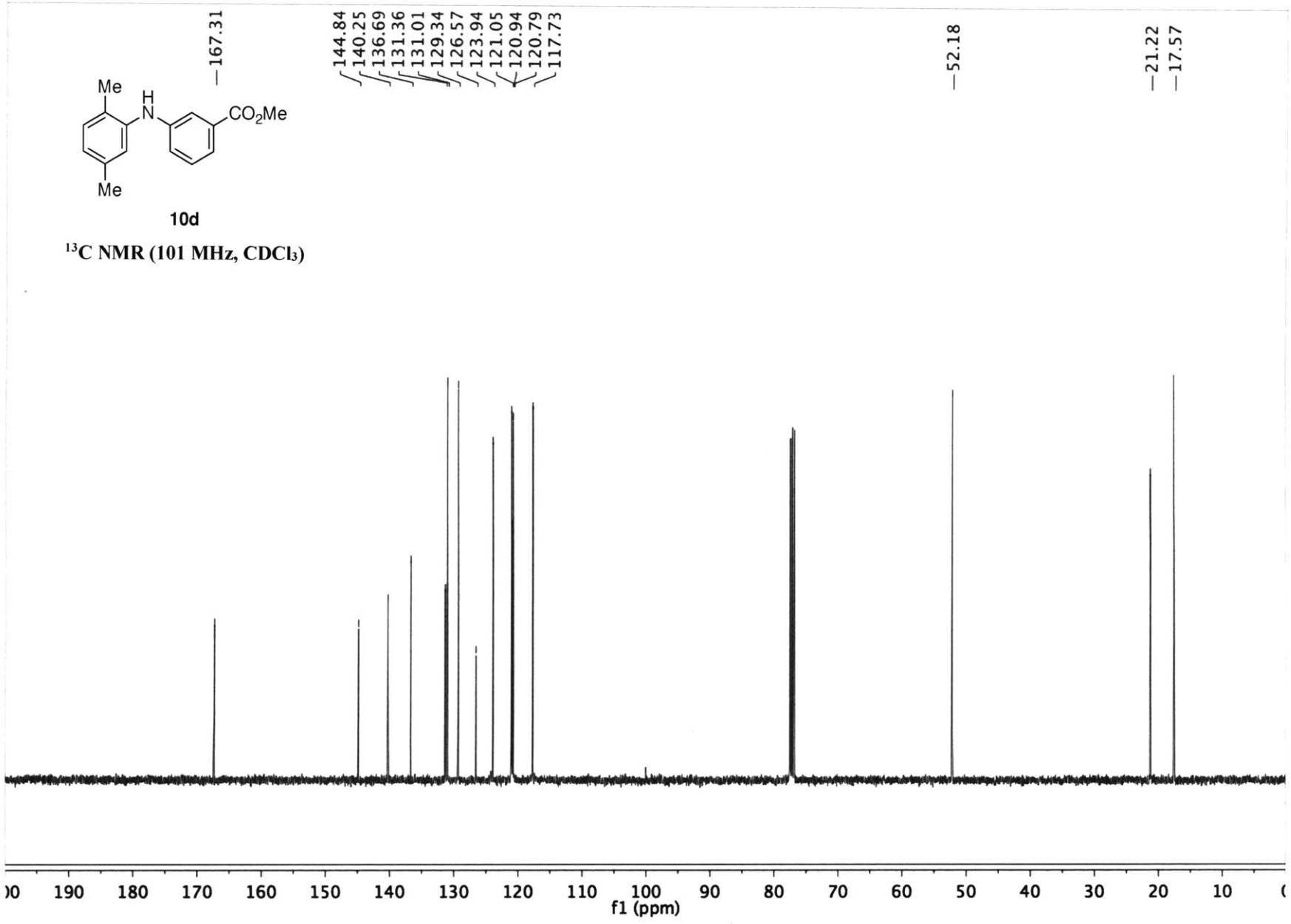
7.09
7.09
7.06
6.84
6.82
5.49
3.91
2.30
2.22
Me
H
N
CO2Me
Me
10d
1H NMR (400 MHz, CDCl3)
1.94
1.01
2.00
0.98
0.97
0.92
3.00
3.01
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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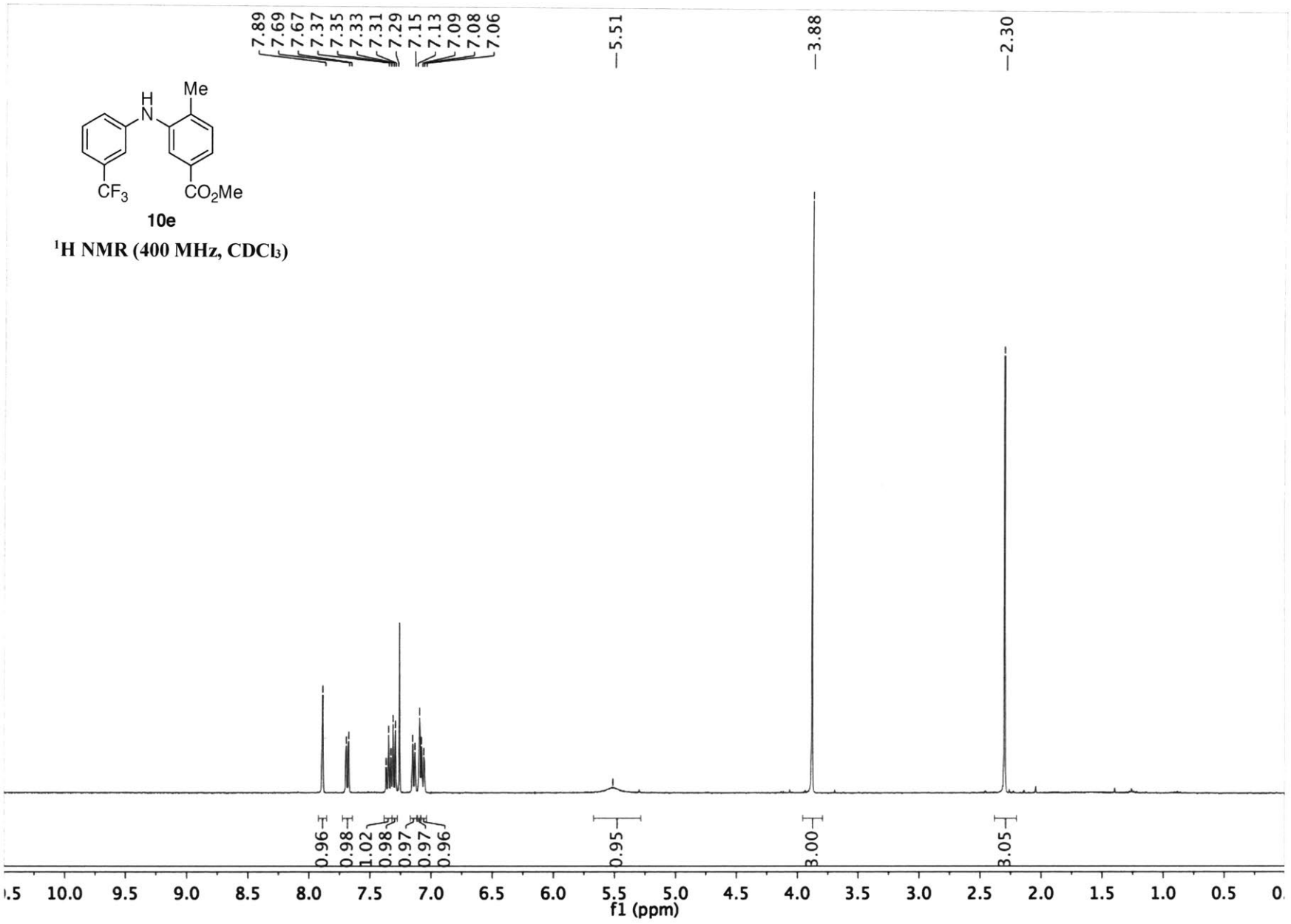
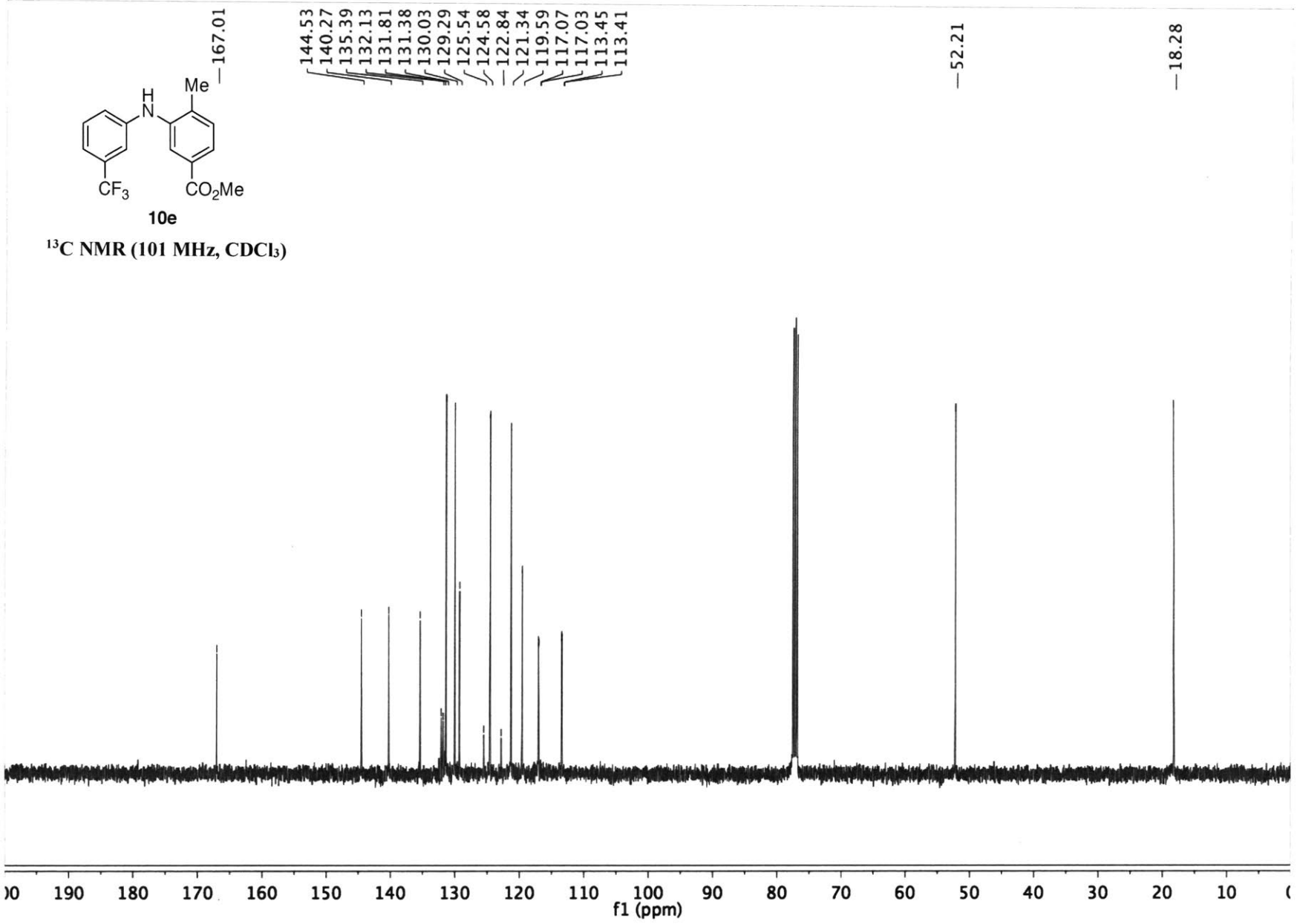
144.84
140.25
136.69
131.36
131.01
129.34
126.57
123.94
121.05
120.94
120.79
117.73
52.18
21.22
17.57
Me
H
N
CO2Me
Me
10d
13C NMR (101 MHz, CDCl3)
f1 (ppm)



10e

^{1}H NMR (400 MHz, $CDCl_3$)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135.39
132.13
131.81
131.38
130.03
129.29
125.54
124.58
122.84
121.34
119.59
117.07
117.03
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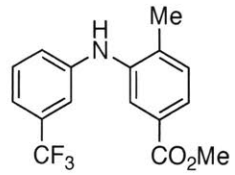
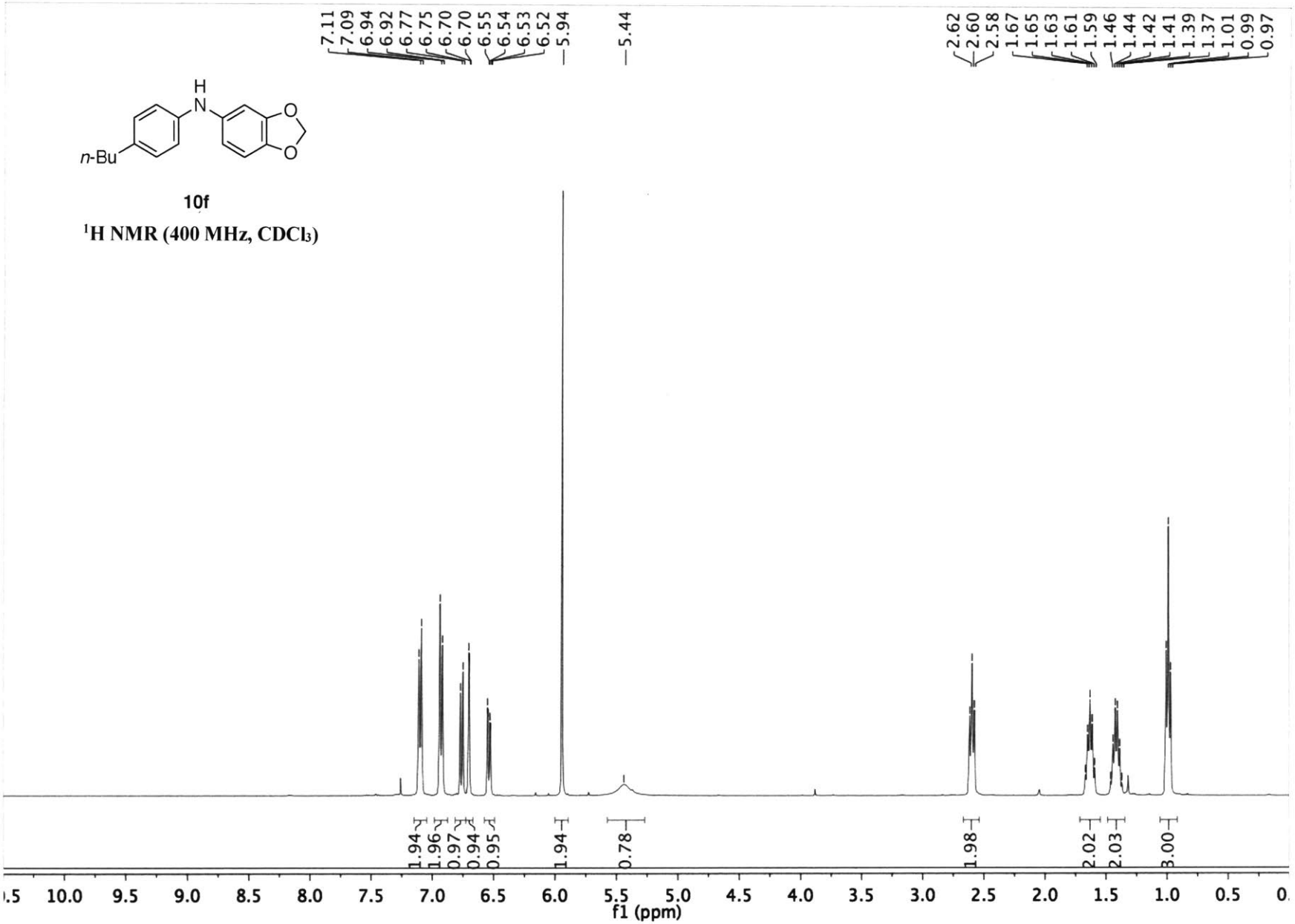
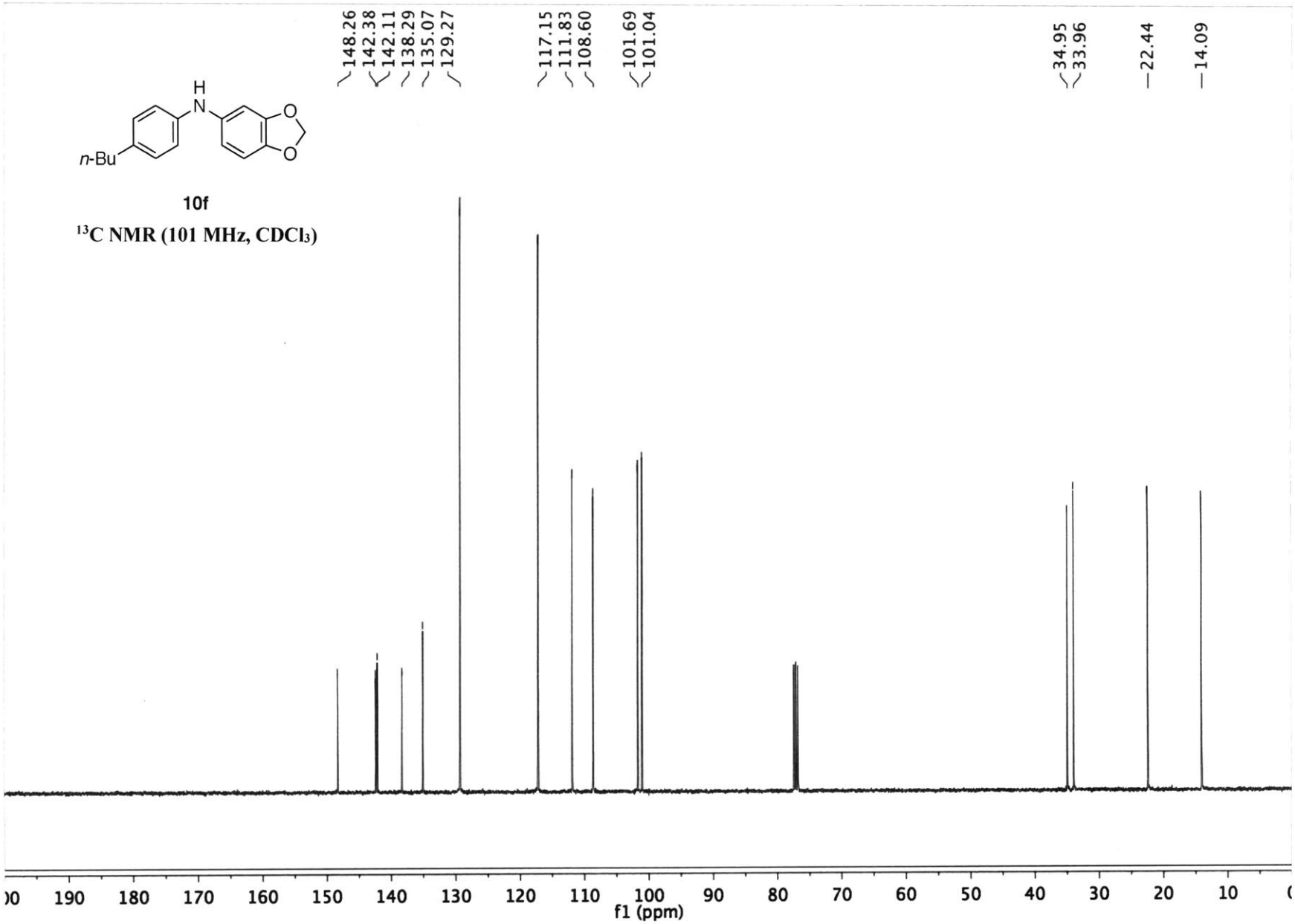
CO2Me
10e
13C NMR (101 MHz, CDCl3)
f1 (ppm)



10e

^{19}F NMR (376 MHz, $CDCl_3$)


7.11
7.09
6.94
6.92
6.77
6.75
6.70
6.70
6.55
6.54
6.53
6.52
5.94
5.44
2.62
2.60
2.58
1.67
1.65
1.63
1.61
1.59
1.46
1.44
1.42
1.41
1.39
1.37
1.01
0.99
0.97
H
N
O
O
n-Bu
10f
1H NMR (400 MHz, CDCl3)
1.94
1.96
0.97
0.94
0.95
1.94
0.78
1.98
2.02
2.03
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
f1 (ppm)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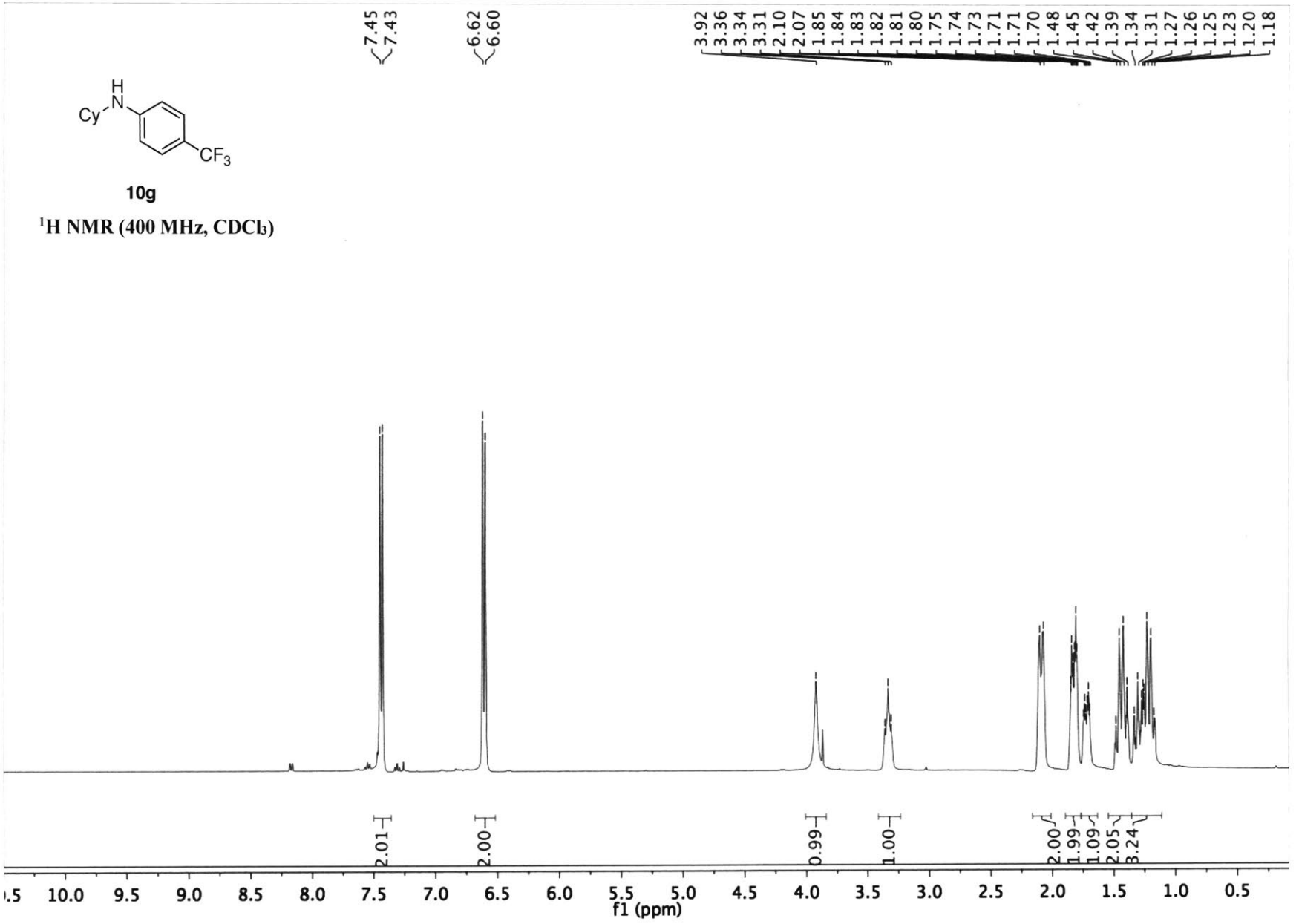
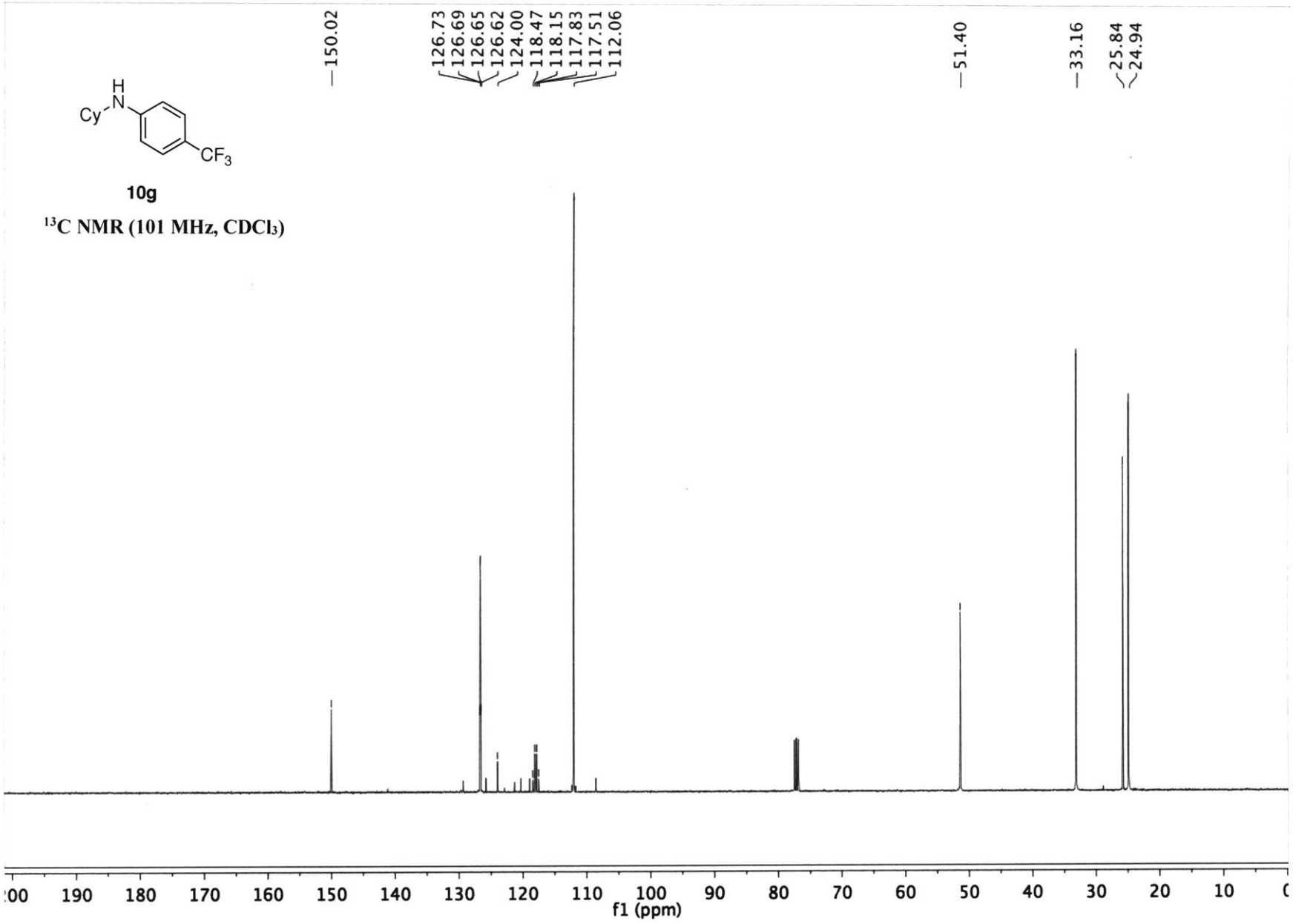
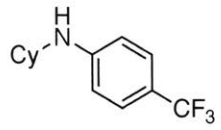
142.38
142.11
138.29
135.07
129.27
117.15
111.83
108.60
101.69
101.04
34.95
33.96
22.44
14.09
n-Bu
H
N
O
O
10f
13C NMR (101 MHz, CDCl3)
f1 (ppm)



10g

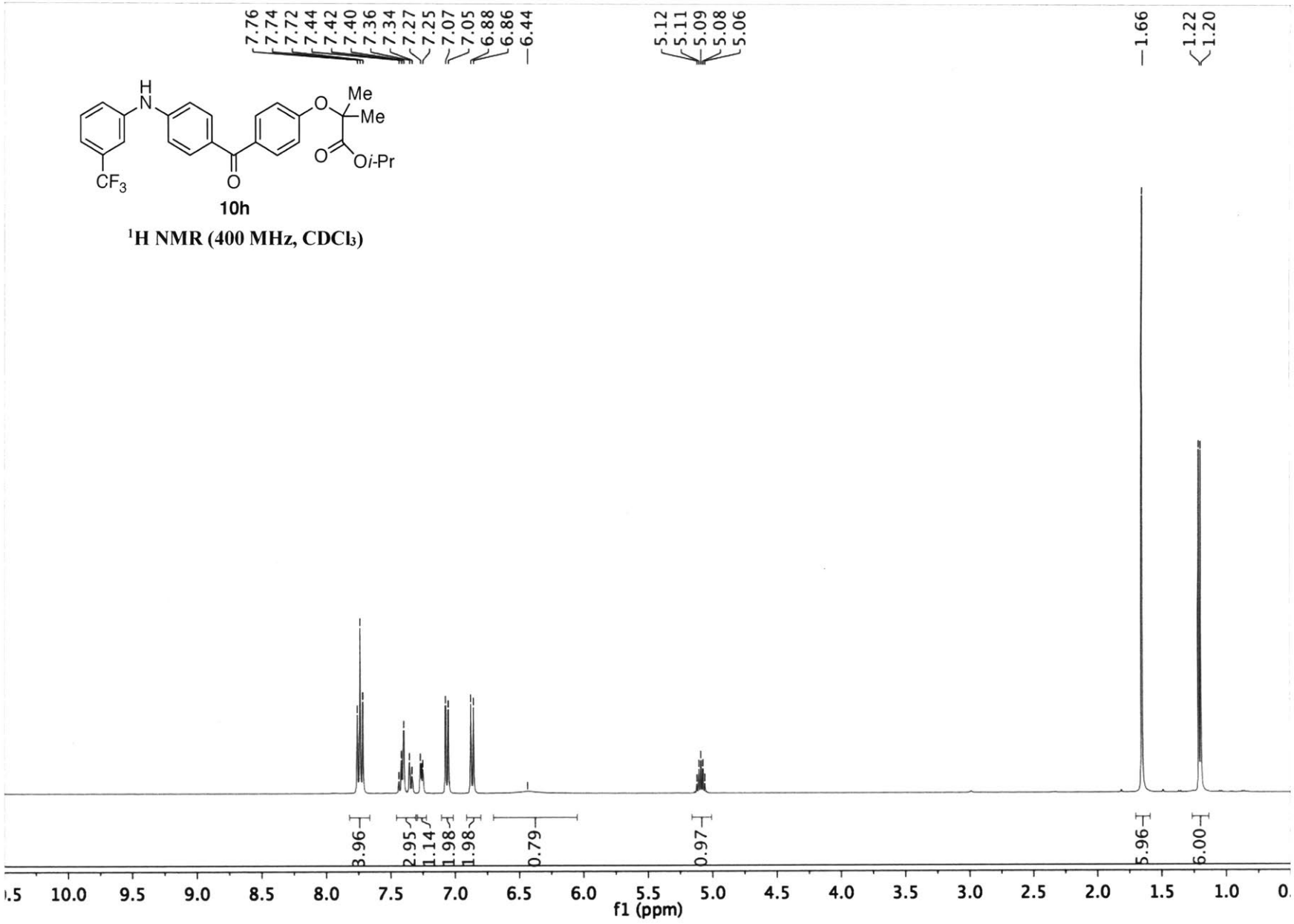
^{1}H NMR (400 MHz, $CDCl_3$)

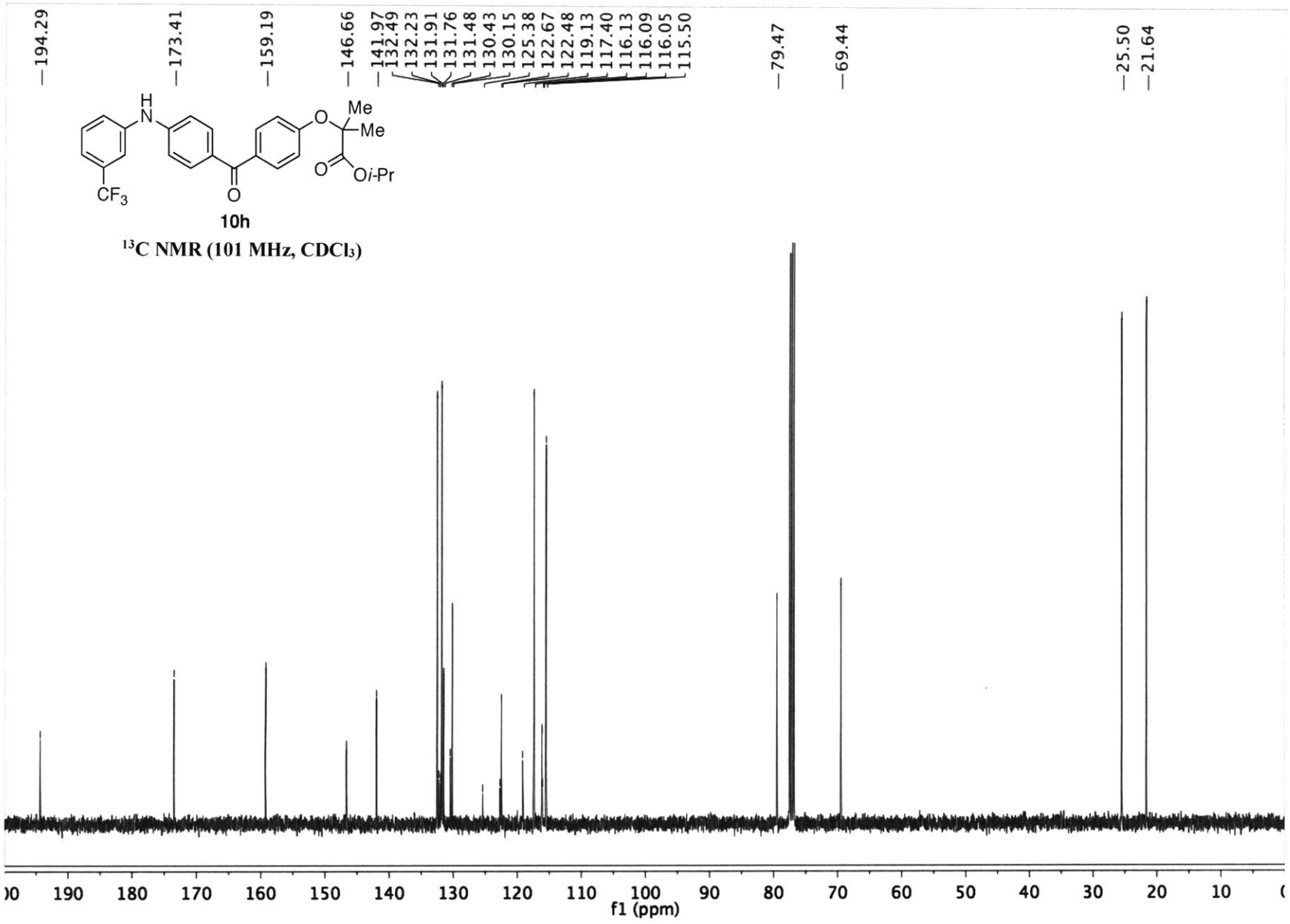

150.02
126.73
126.69
126.65
126.62
124.00
118.47
118.15
117.83
117.51
112.06
51.40
33.16
25.84
24.94
Cy
H
N
CF3
10g
13C NMR (101 MHz, CDCl3)
f1 (ppm)



10g

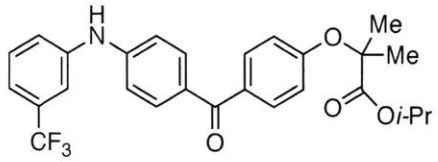
^{19}F NMR (376 MHz, $CDCl_3$)


7.76
7.74
7.72
7.44
7.42
7.40
7.36
7.34
7.27
7.25
7.07
7.05
6.88
6.86
6.44
5.12
5.11
5.09
5.08
5.06
1.66
1.22
1.20
H
N
Me
Me
O
O
O
O*i*-Pr
CF_3
O
10h
^{1}H NMR (400 MHz, $CDCl_3$)
3.96
2.95
1.14
1.98
1.98
0.79
0.97
5.96
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
f1 (ppm)



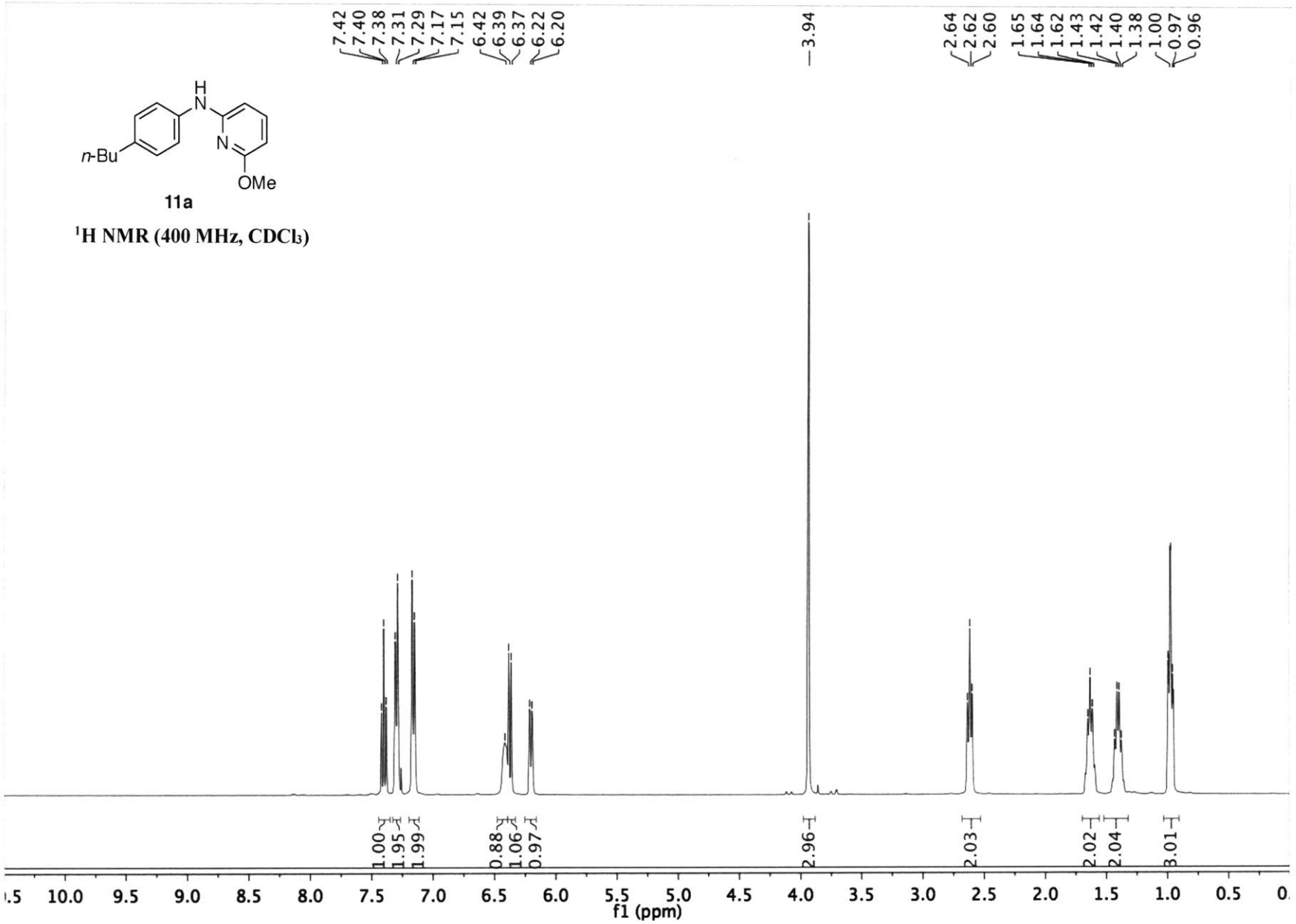
10h

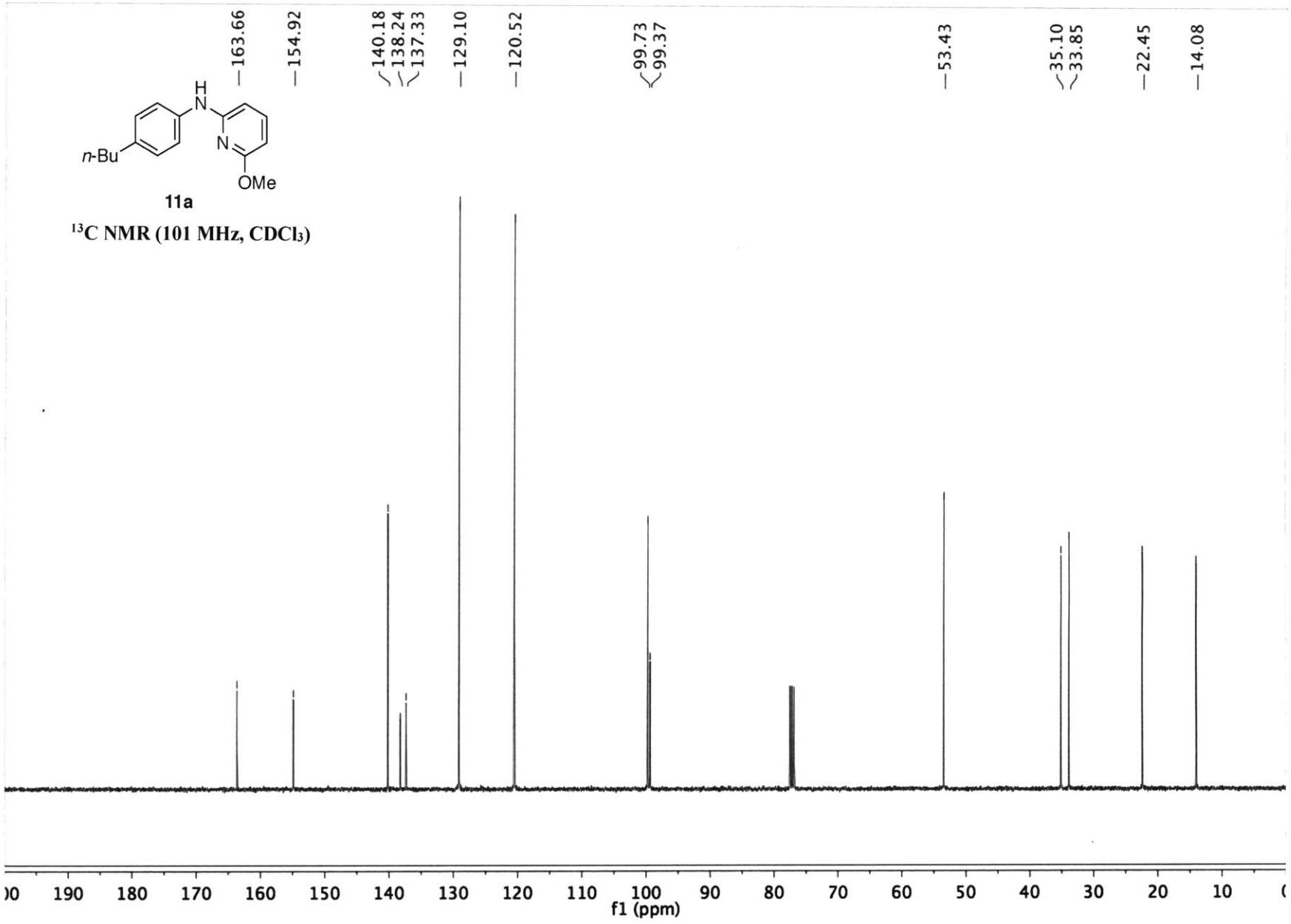
^{13}C NMR (101 MHz, $CDCl_3$)

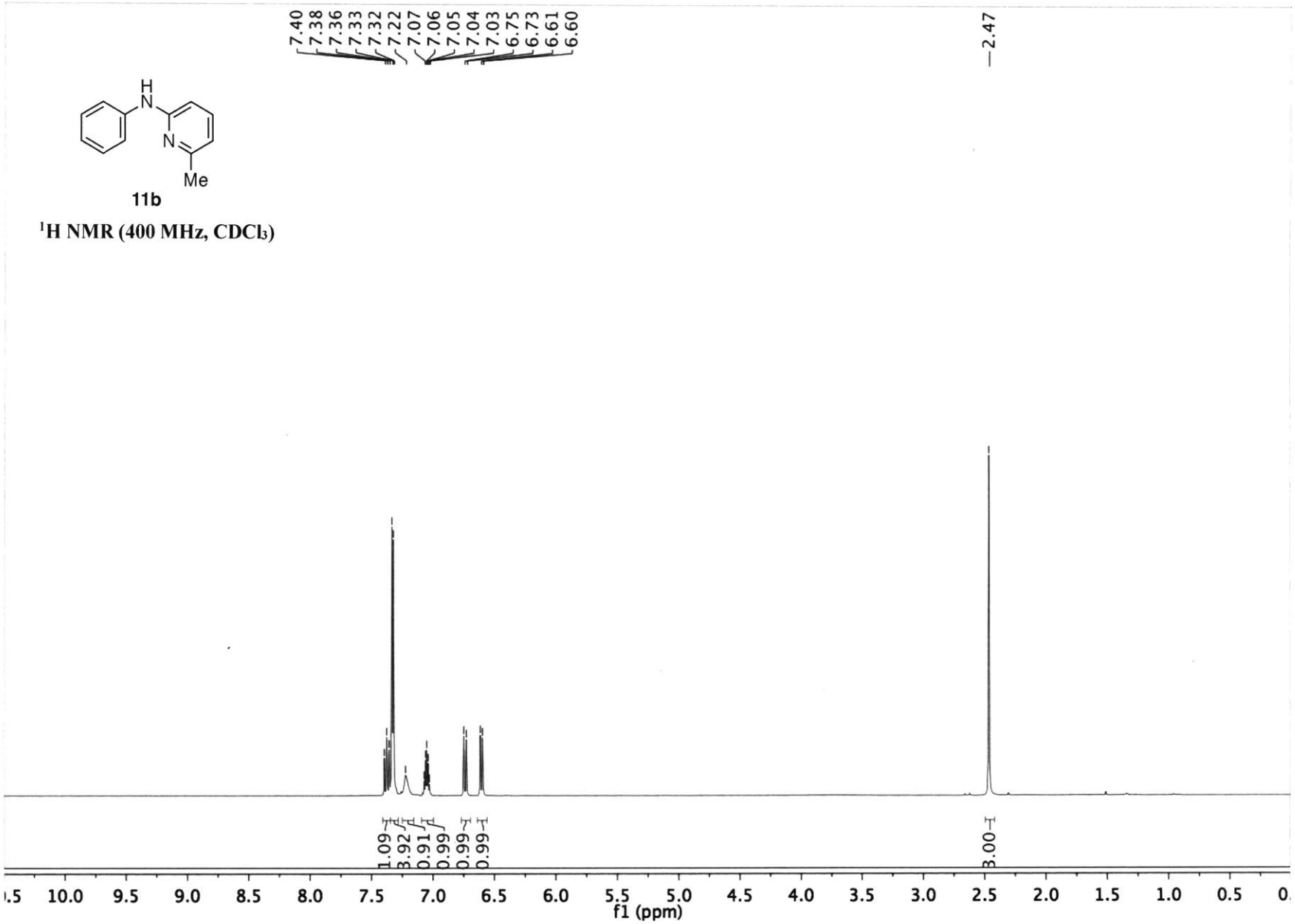


10h

^{19}F NMR (376 MHz, $CDCl_3$)

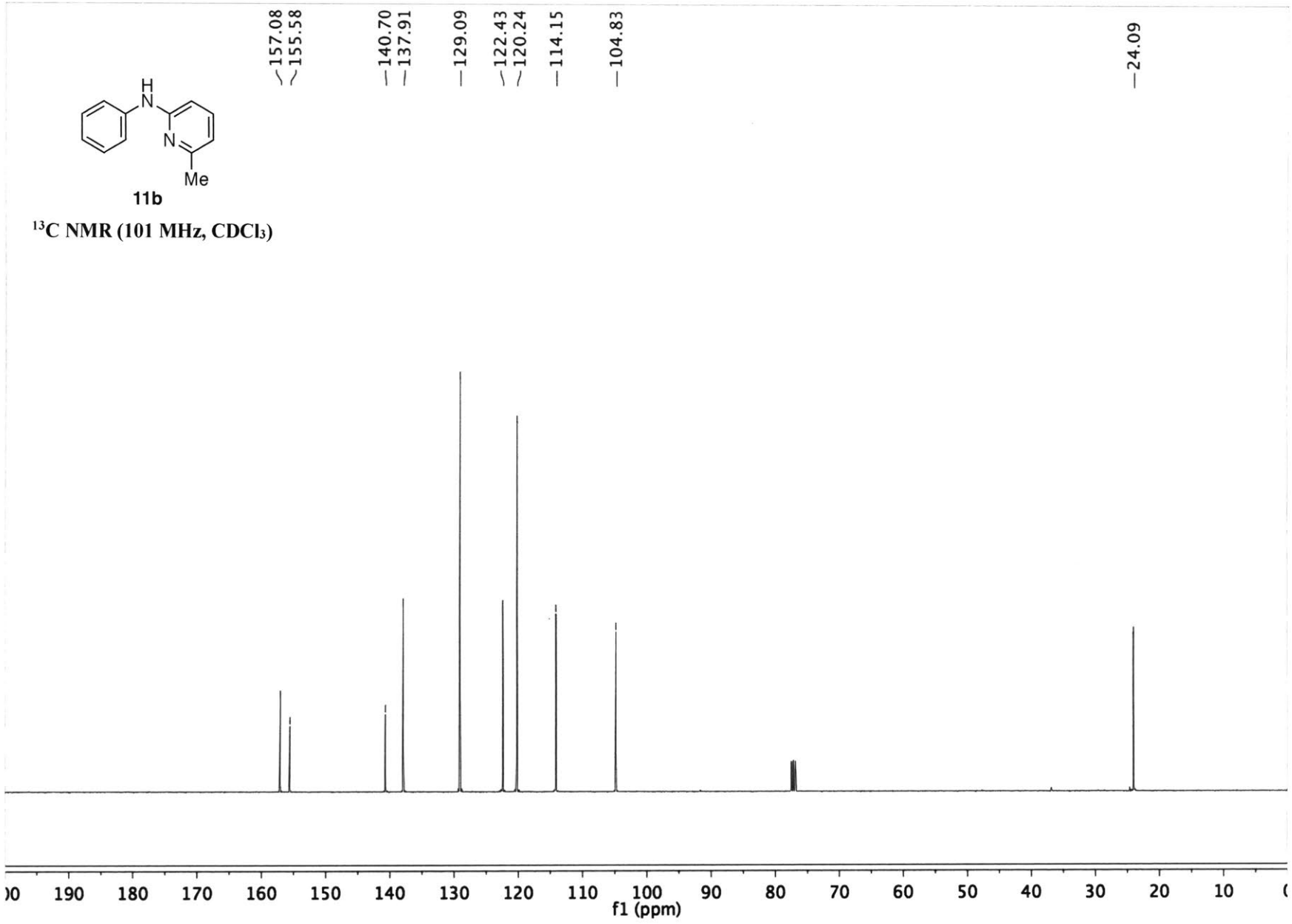

7.42
7.40
7.38
7.31
7.29
7.17
7.15
6.42
6.39
6.37
6.22
6.20
3.94
2.64
2.62
2.60
1.65
1.64
1.62
1.43
1.42
1.40
1.38
1.00
0.97
0.96
n-Bu
H
N
N
OMe
11a
1H NMR (400 MHz, CDCl3)
1.00
1.95
1.99
0.88
1.06
0.97
2.96
2.03
2.02
2.04
3.01
f1 (ppm)

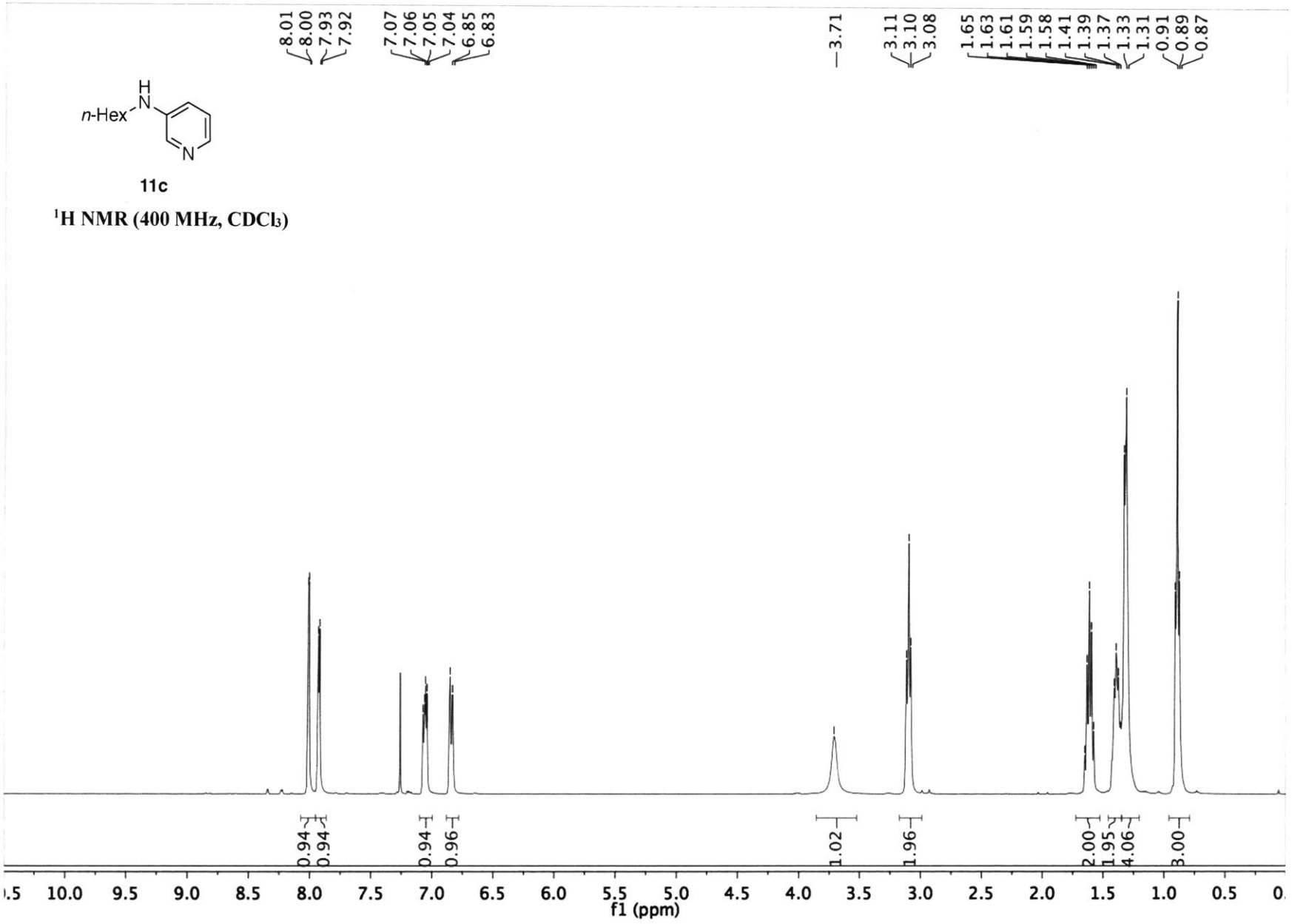

163.66
154.92
140.18
138.24
137.33
129.10
120.52
99.73
99.37
53.43
35.10
33.85
22.45
14.08
n-Bu
N
N
OMe
11a
13C NMR (101 MHz, CDCl3)
f1 (ppm)



11b

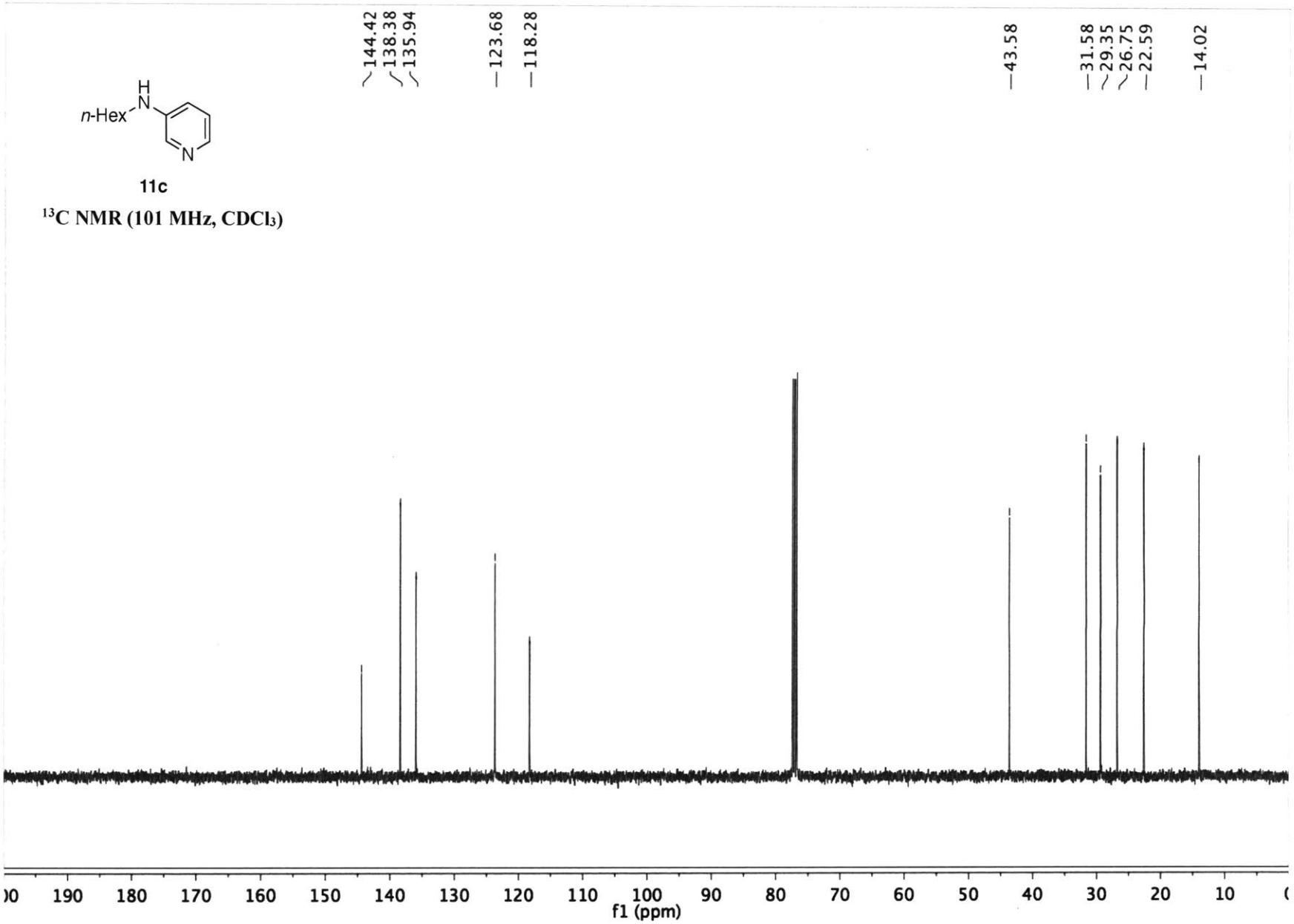
^{1}H NMR (400 MHz, $CDCl_3$)

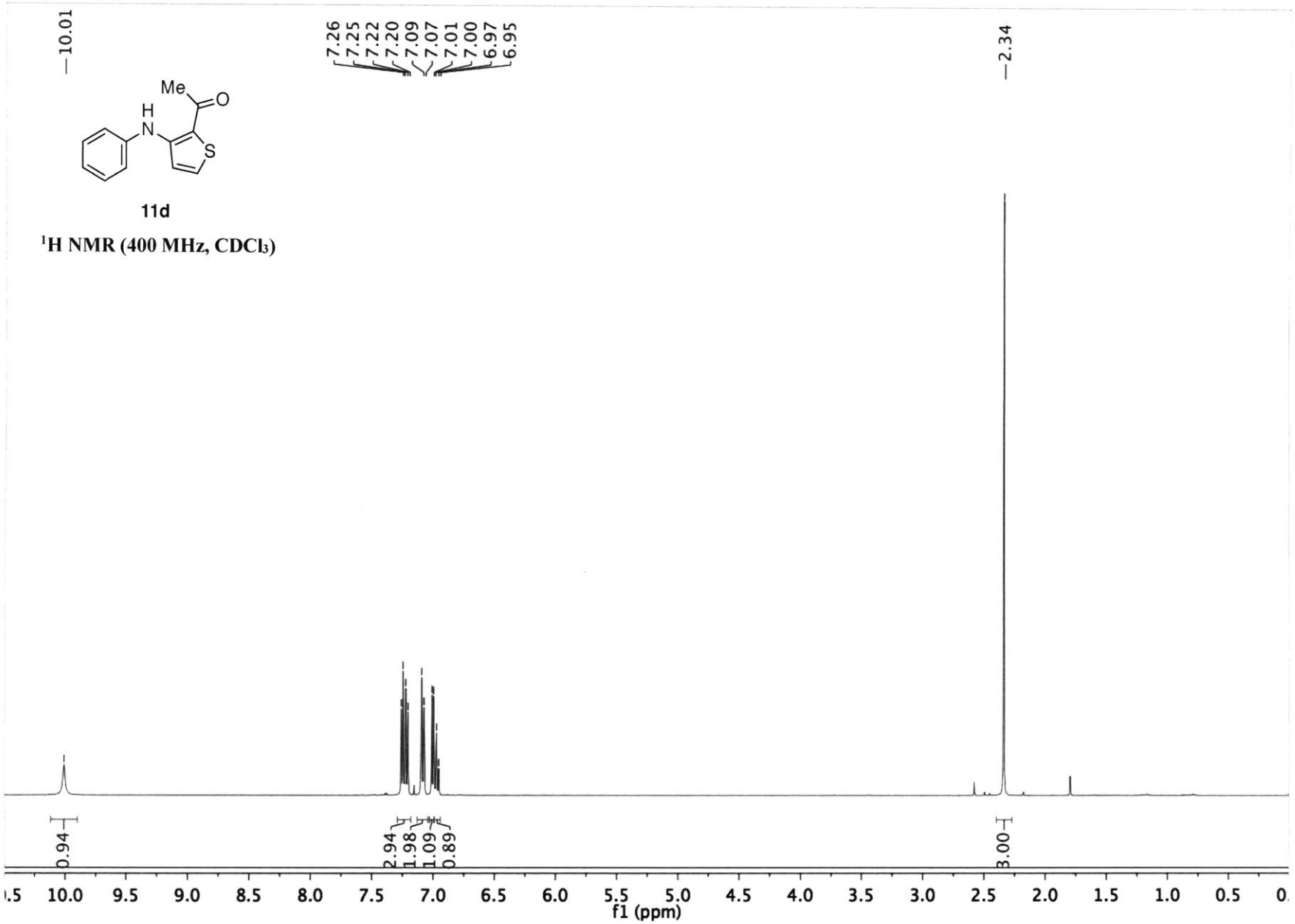

157.08
155.58
140.70
137.91
129.09
122.43
120.24
114.15
104.83
24.09
H
N
N
Me
11b
^{13}C NMR (101 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

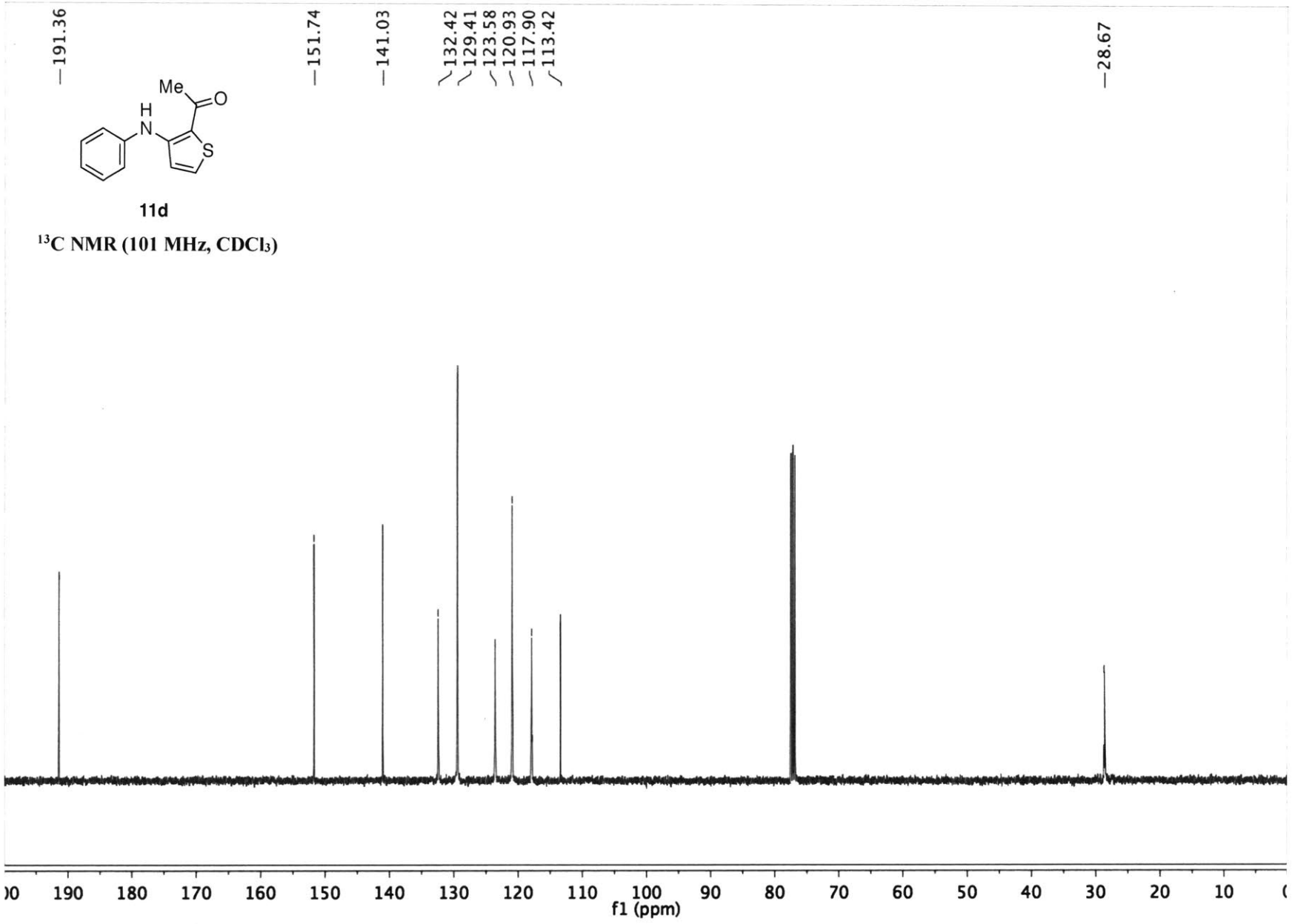


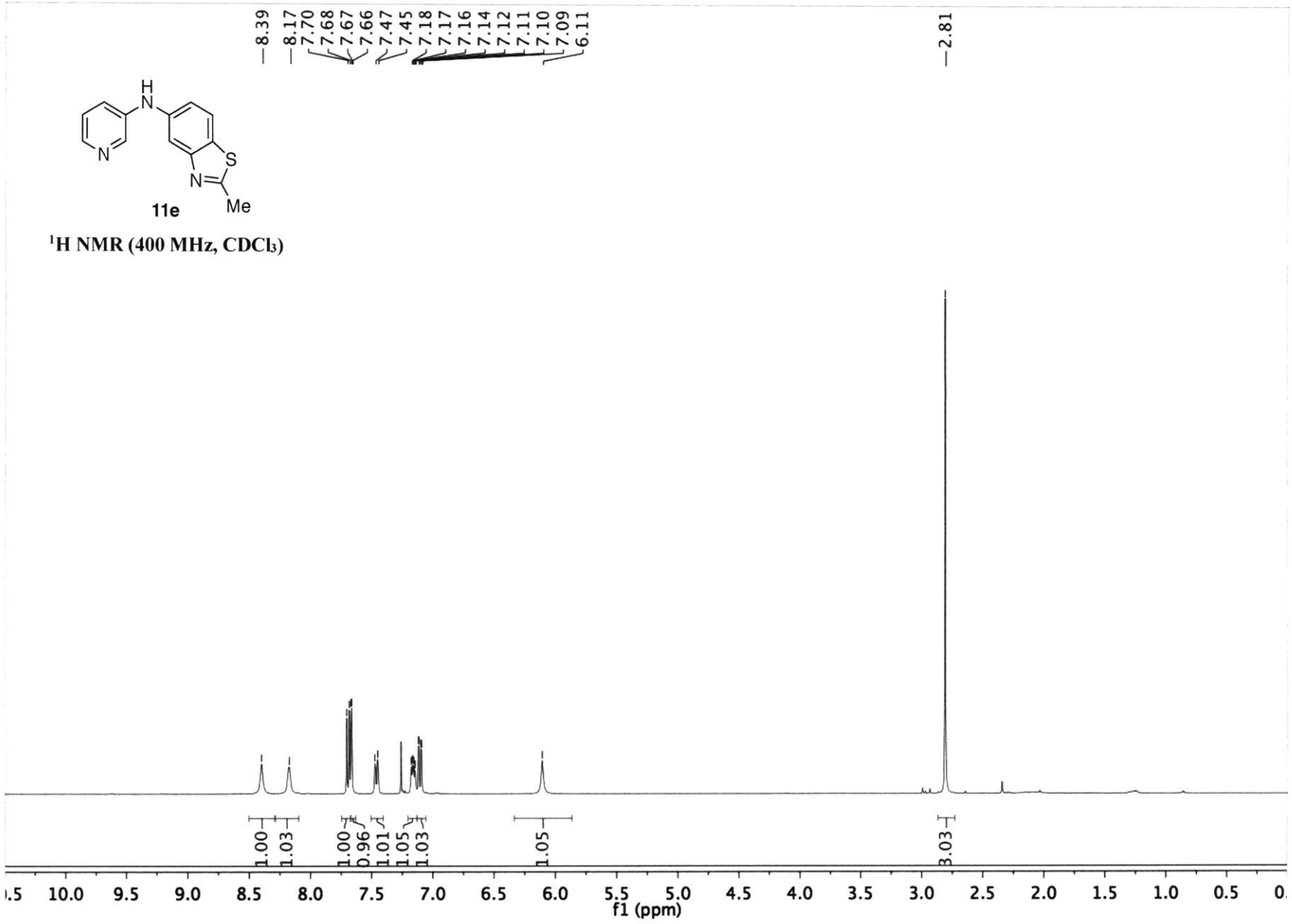
11c

^{1}H NMR (400 MHz, $CDCl_3$)

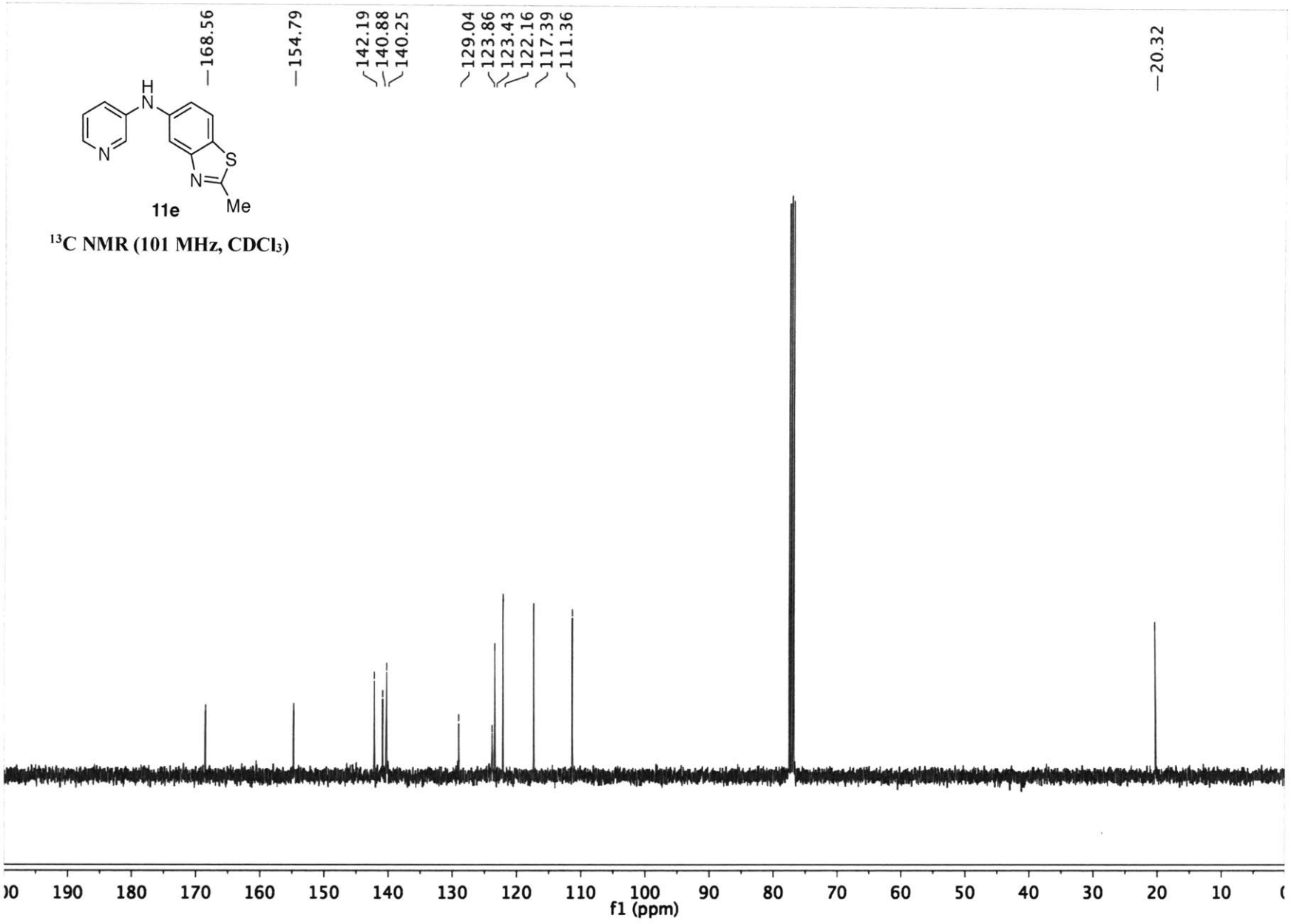

144.42
138.38
135.94
123.68
118.28
43.58
31.58
29.35
26.75
22.59
14.02
n-Hex
H
N
N
11c
13C NMR (101 MHz, CDCl3)
f1 (ppm)

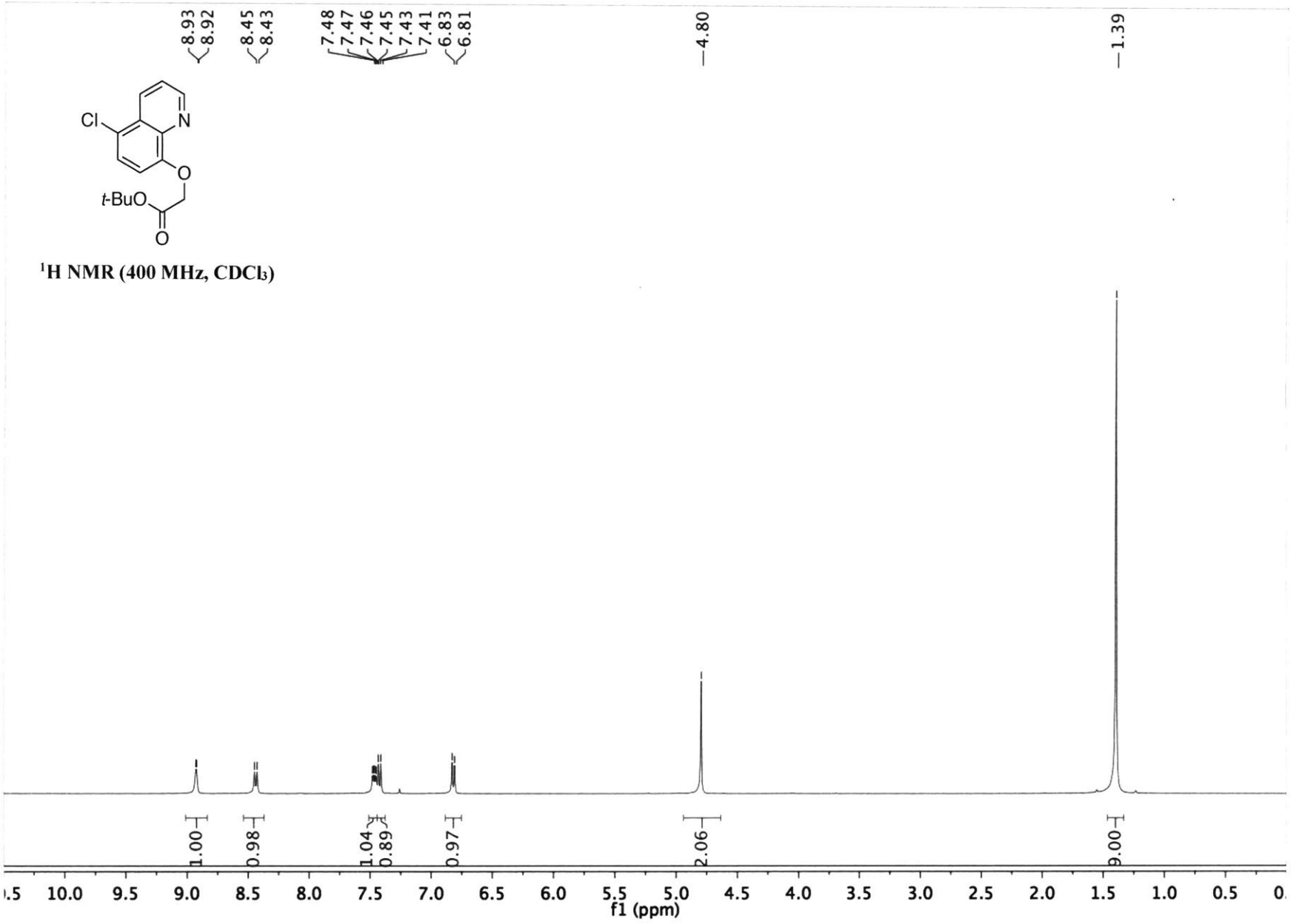

10.01
7.26
7.25
7.22
7.20
7.09
7.07
7.01
7.00
6.97
6.95
2.34
Me
O
H
N
S
11d
¹H NMR (400 MHz, CDCl₃)
0.94
2.94
1.98
1.09
0.89
3.00
f1 (ppm)


191.36
151.74
141.03
132.42
129.41
123.58
120.93
117.90
113.42
28.67
Me
O
H
N
S
11d
13C NMR (101 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

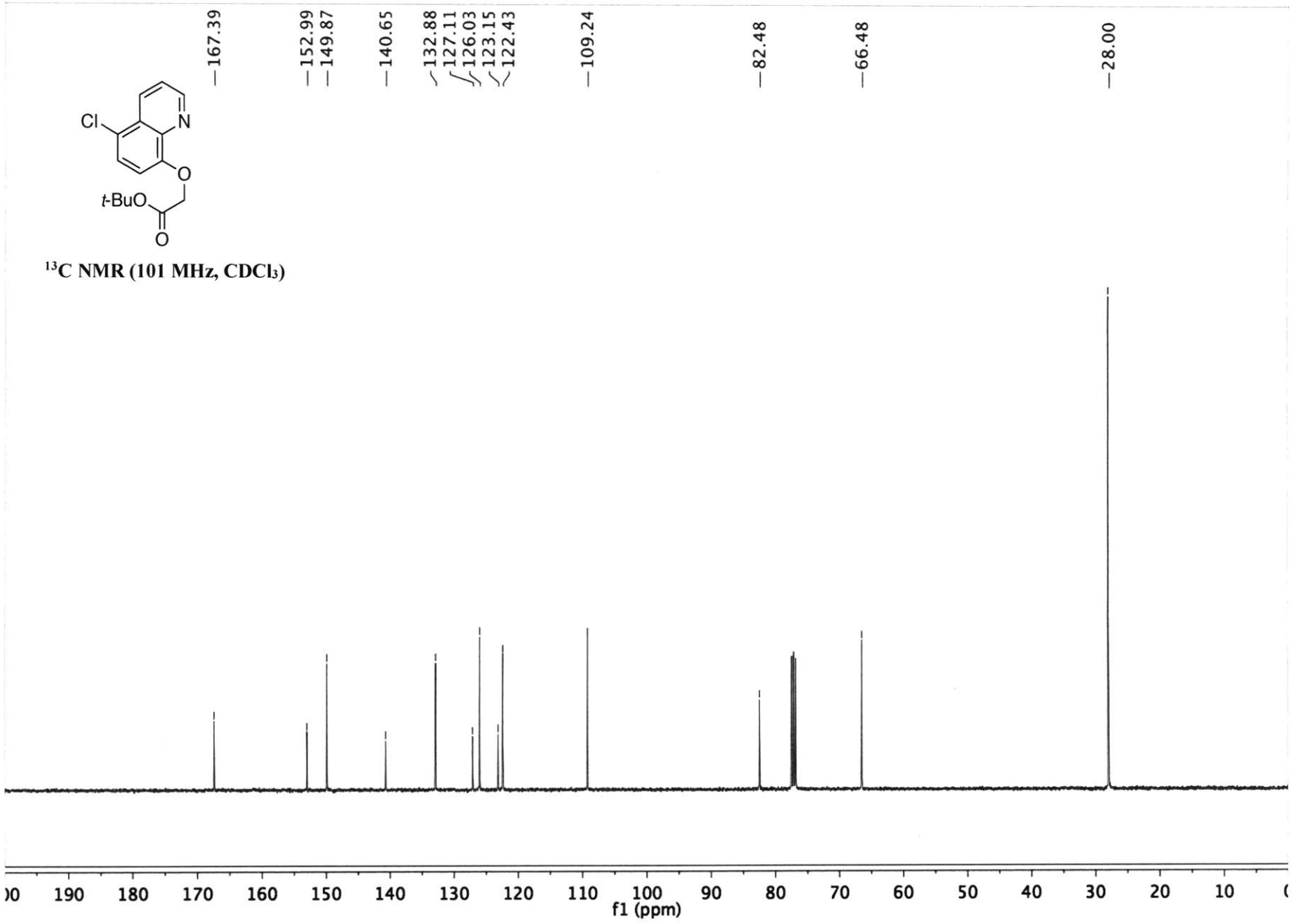


^{1}H NMR (400 MHz, $CDCl_3$)

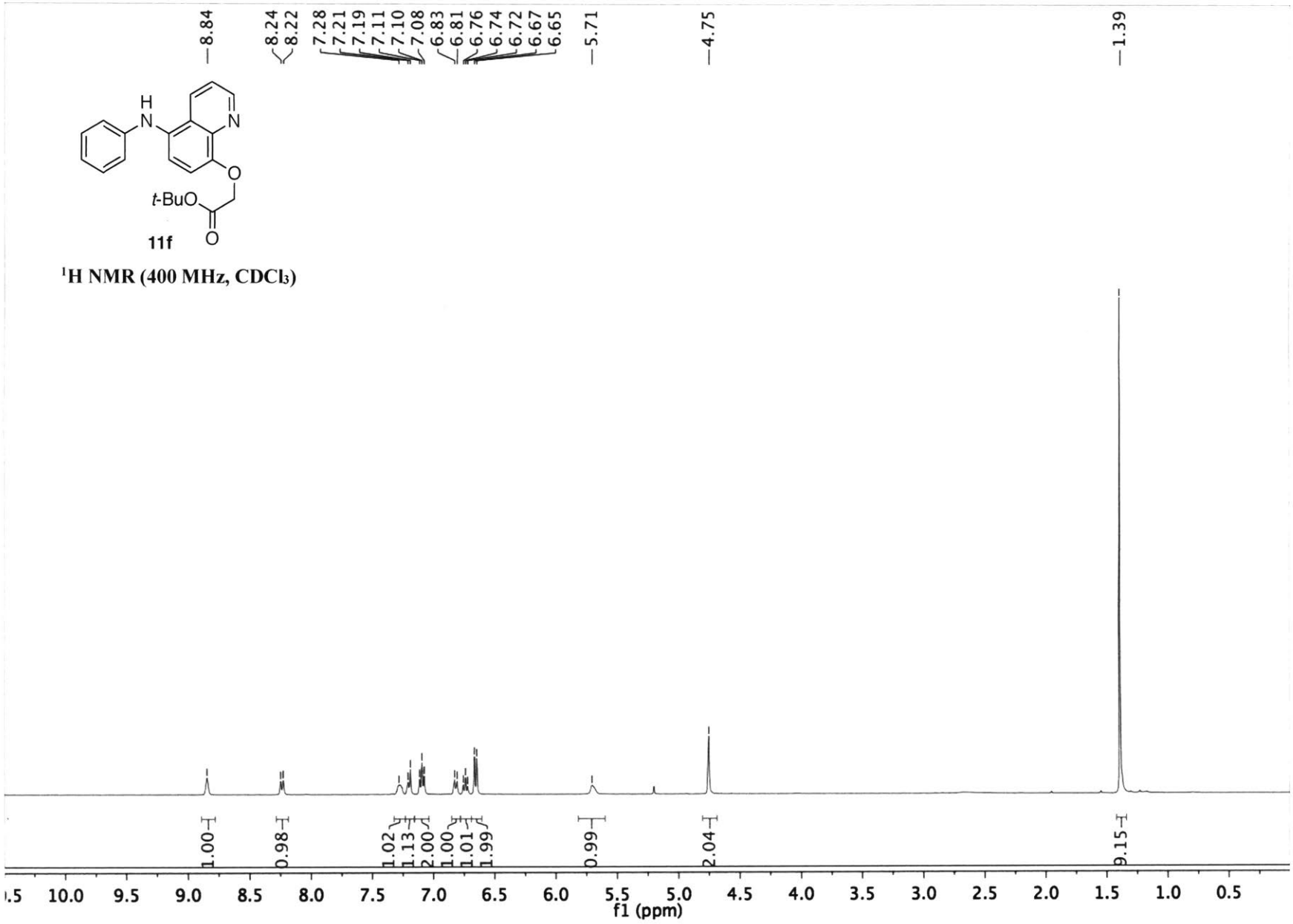

168.56
154.79
142.19
140.88
140.25
129.04
123.86
123.43
122.16
117.39
111.36
20.32
N
H
N
S
N
Me
11e
13C NMR (101 MHz, CDCl3)
f1 (ppm)



^{1}H NMR (400 MHz, $CDCl_3$)

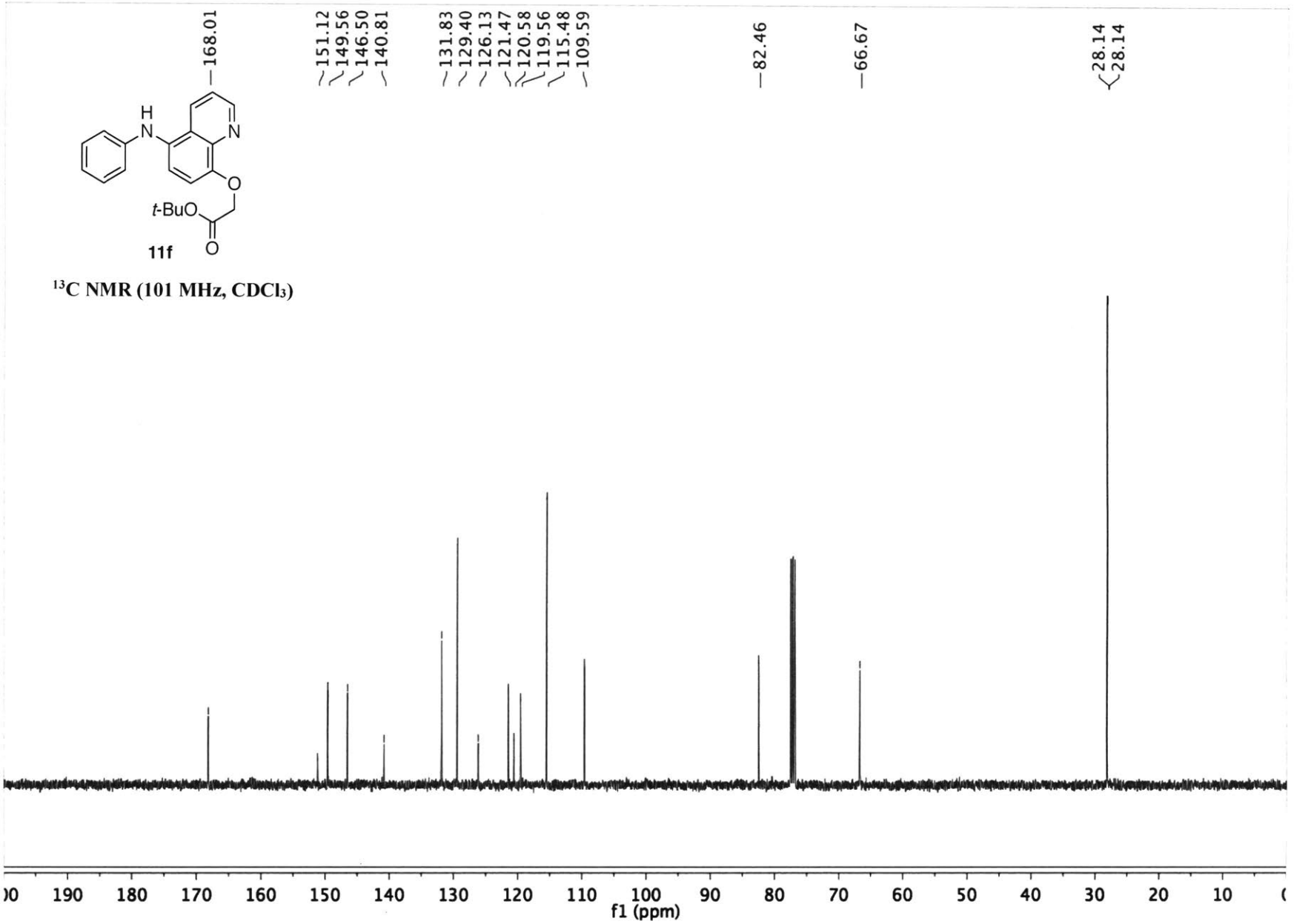


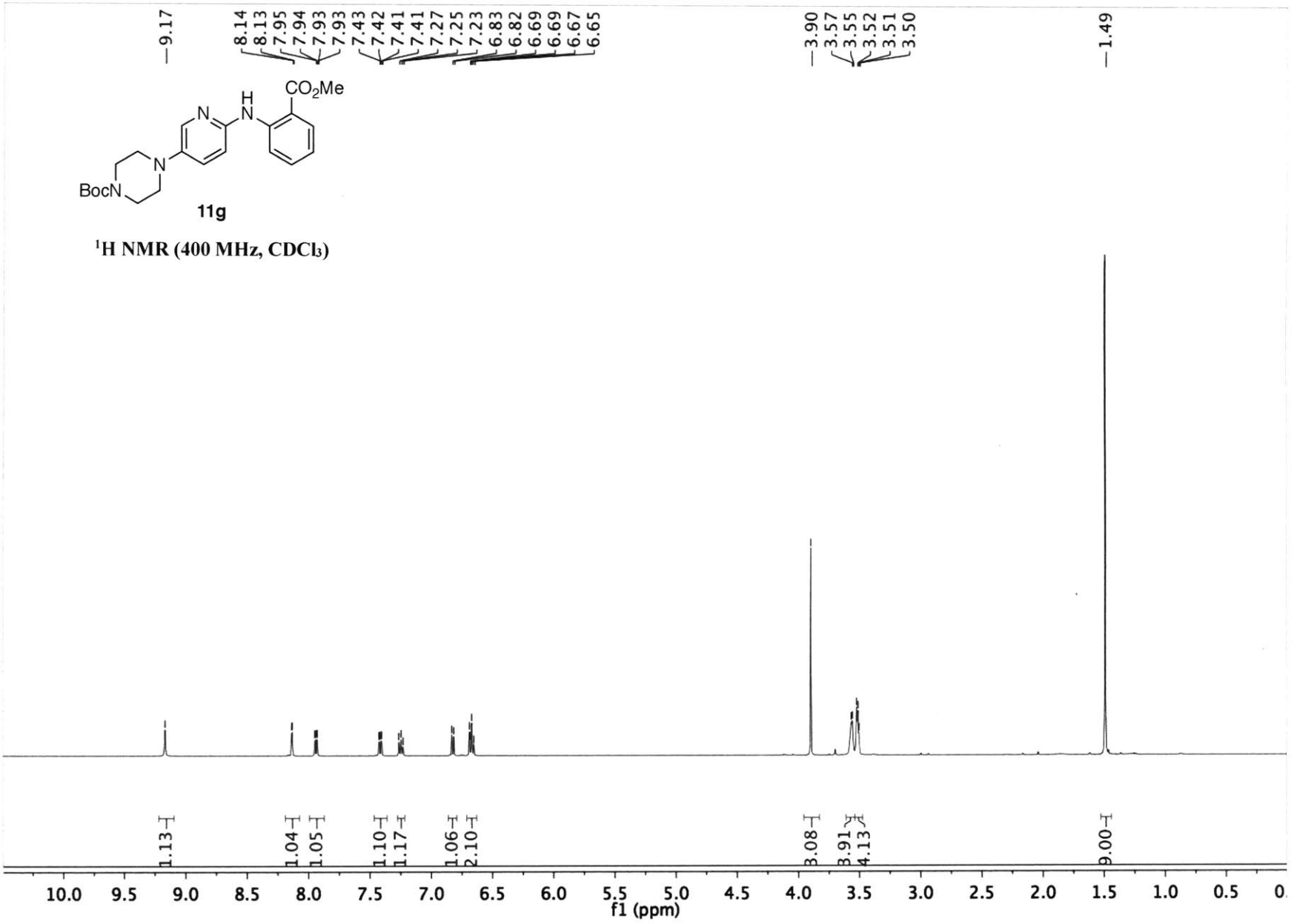
^{13}C NMR (101 MHz, $CDCl_3$)

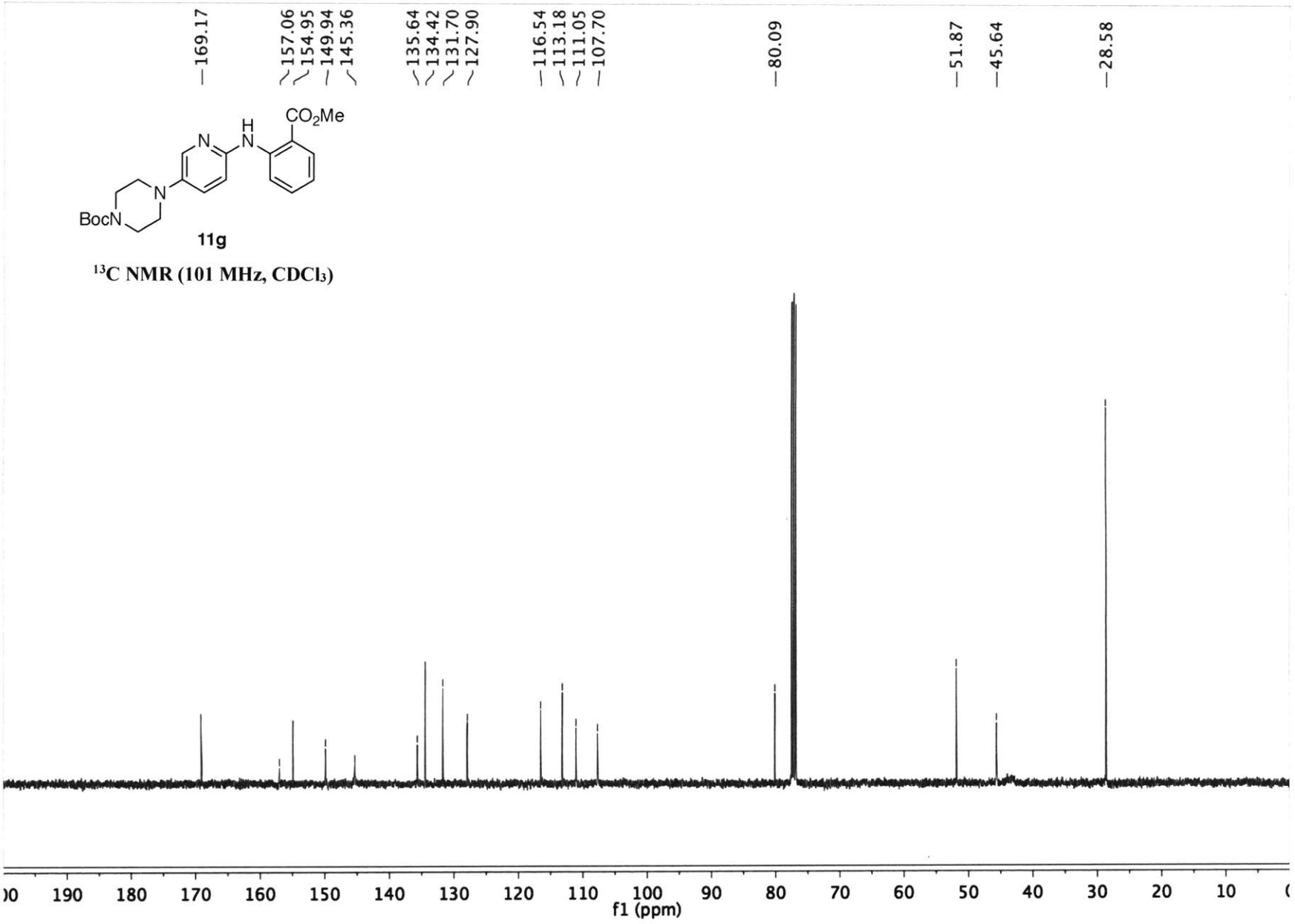


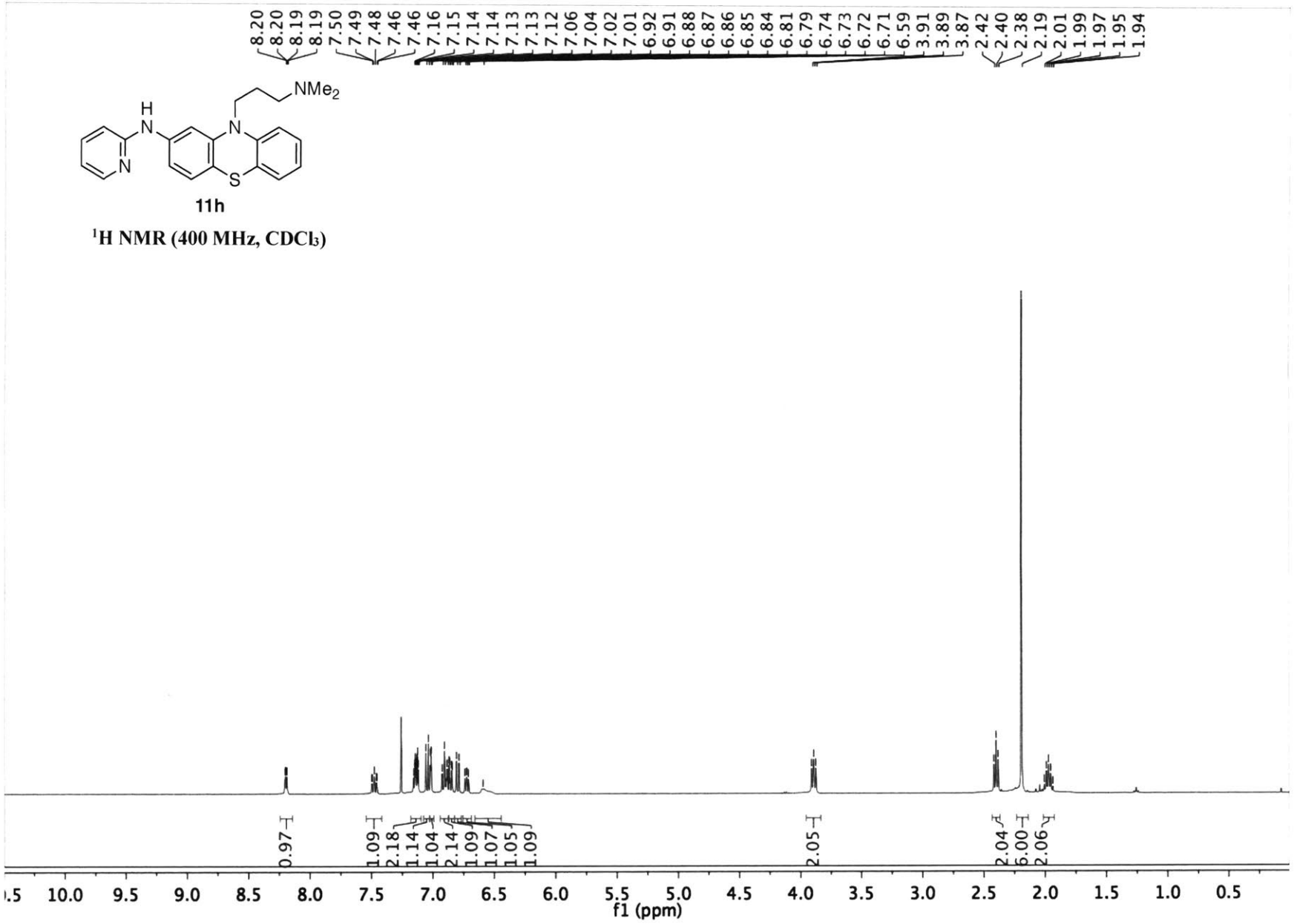
11f

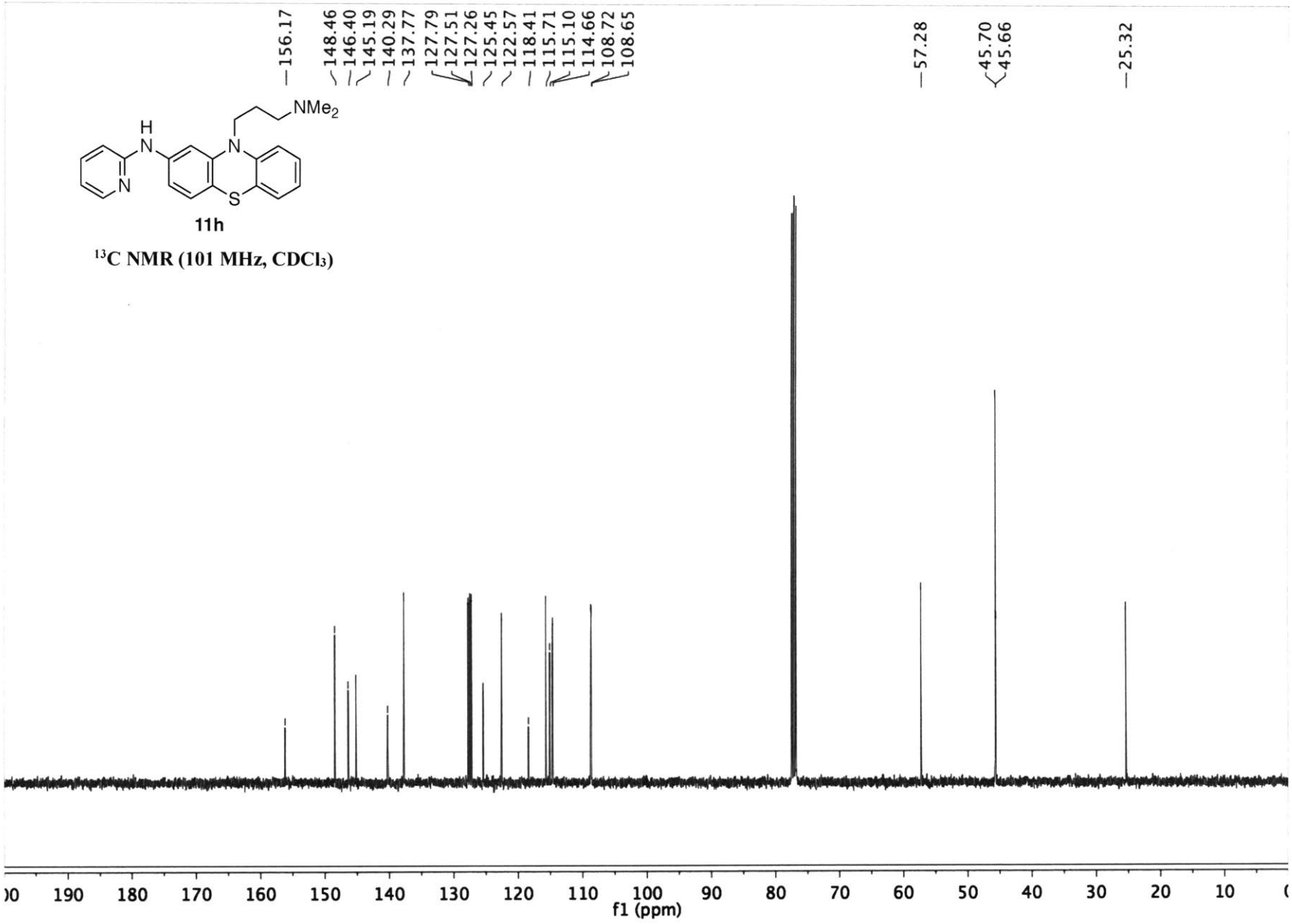
^{1}H NMR (400 MHz, $CDCl_3$)

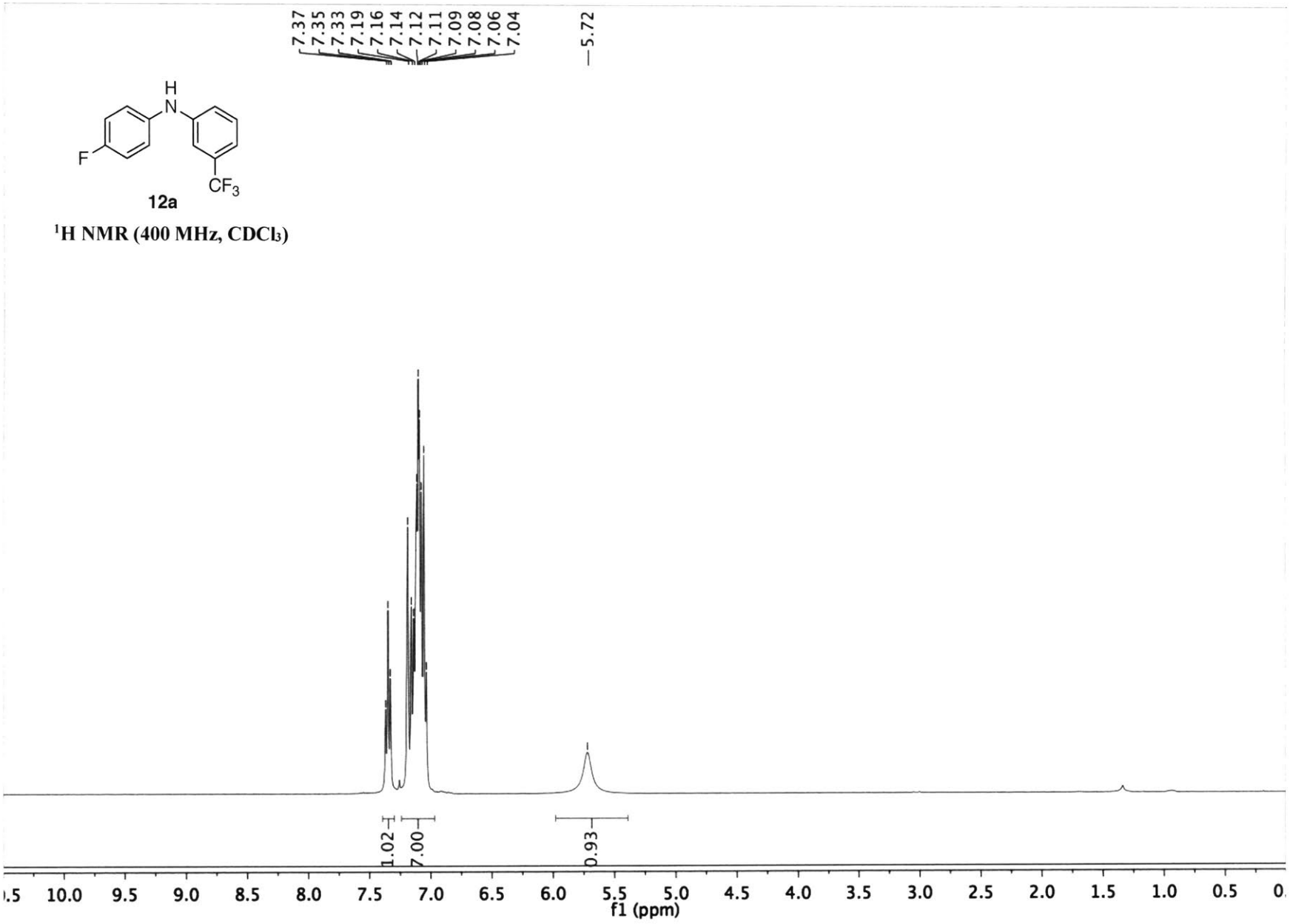

168.01
151.12
149.56
146.50
140.81
131.83
129.40
126.13
121.47
120.58
119.56
115.48
109.59
82.46
66.67
28.14
28.14
H
N
N
O
t-BuO
O
11f
13C NMR (101 MHz, CDCl3)
f1 (ppm)

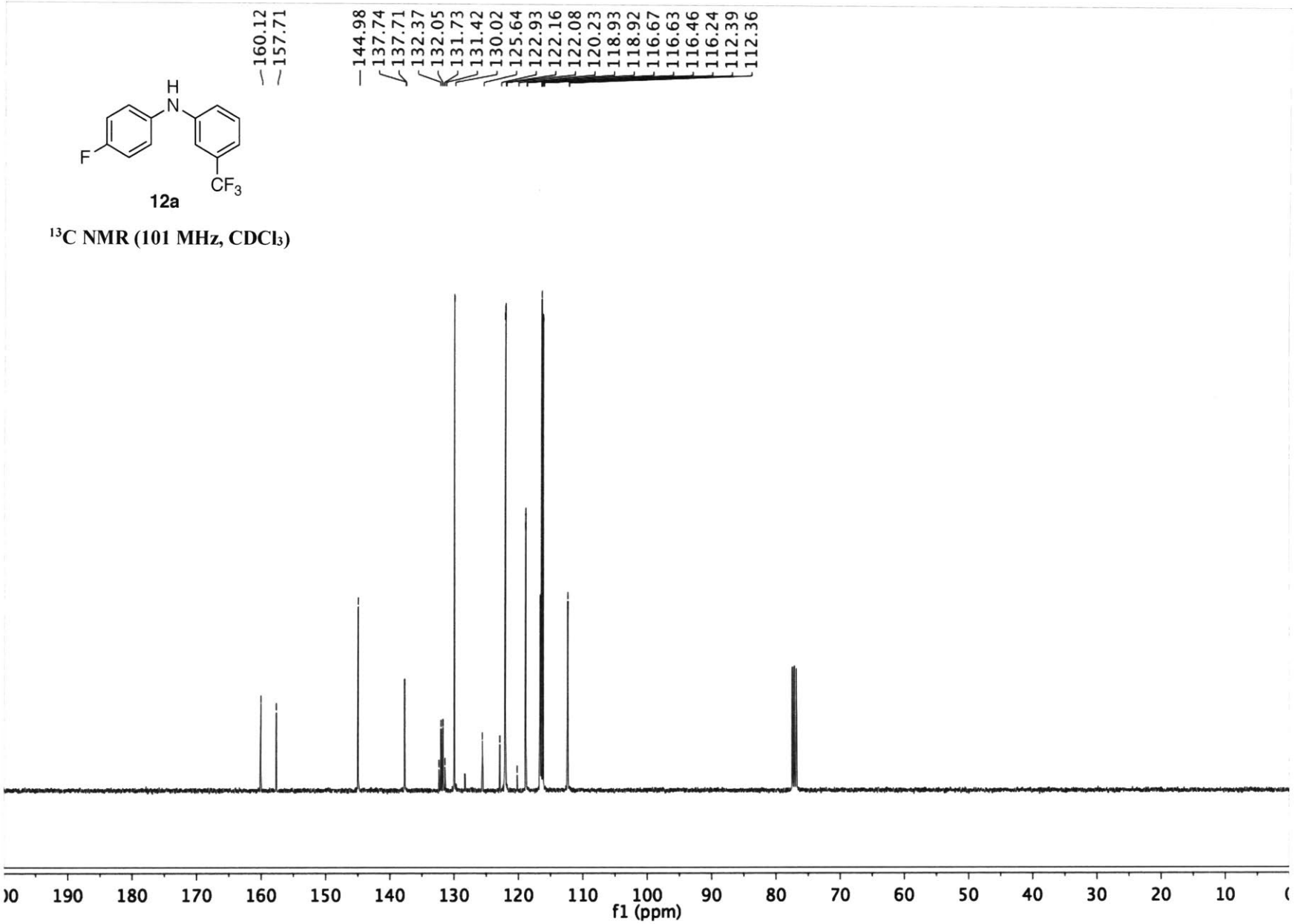

9.17
8.14
8.13
7.95
7.94
7.93
7.93
7.43
7.42
7.41
7.41
7.27
7.25
7.23
6.83
6.82
6.69
6.69
6.67
6.65
3.90
3.57
3.55
3.52
3.51
3.50
1.49
CO2Me
H
N
N
N
BocN
11g
1H NMR (400 MHz, CDCl3)
1.13
1.04
1.05
1.10
1.17
1.06
2.10
3.08
3.91
4.13
9.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


169.17
157.06
154.95
149.94
145.36
135.64
134.42
131.70
127.90
116.54
113.18
111.05
107.70
80.09
51.87
45.64
28.58
CO2Me
H
N
N
N
BocN
11g
13C NMR (101 MHz, CDCl3)
f1 (ppm)


8.20
8.20
8.19
8.19
7.50
7.49
7.48
7.46
7.46
7.16
7.15
7.14
7.14
7.13
7.13
7.12
7.06
7.04
7.02
7.01
6.92
6.91
6.88
6.87
6.86
6.85
6.84
6.81
6.79
6.74
6.73
6.72
6.71
6.59
3.91
3.89
3.87
2.42
2.40
2.38
2.19
2.01
1.99
1.97
1.95
1.94
NMe2
H
N
N
N
S
11h
1H NMR (400 MHz, CDCl3)
0.97
1.09
2.18
1.14
1.04
2.14
1.09
1.07
1.05
1.09
2.05
2.04
6.00
2.06
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
f1 (ppm)

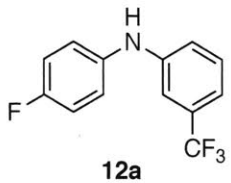

156.17
148.46
146.40
145.19
140.29
137.77
127.79
127.51
127.26
125.45
122.57
118.41
115.71
115.10
114.66
108.72
108.65
57.28
45.70
45.66
25.32
NMe2
H
N
N
N
S
11h
13C NMR (101 MHz, CDCl3)
f1 (ppm)


7.37
7.35
7.33
7.19
7.16
7.14
7.12
7.11
7.09
7.08
7.06
7.04
5.72
H
N
F
CF3
12a
1H NMR (400 MHz, CDCl3)
1.02
7.00
0.93
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
f1 (ppm)



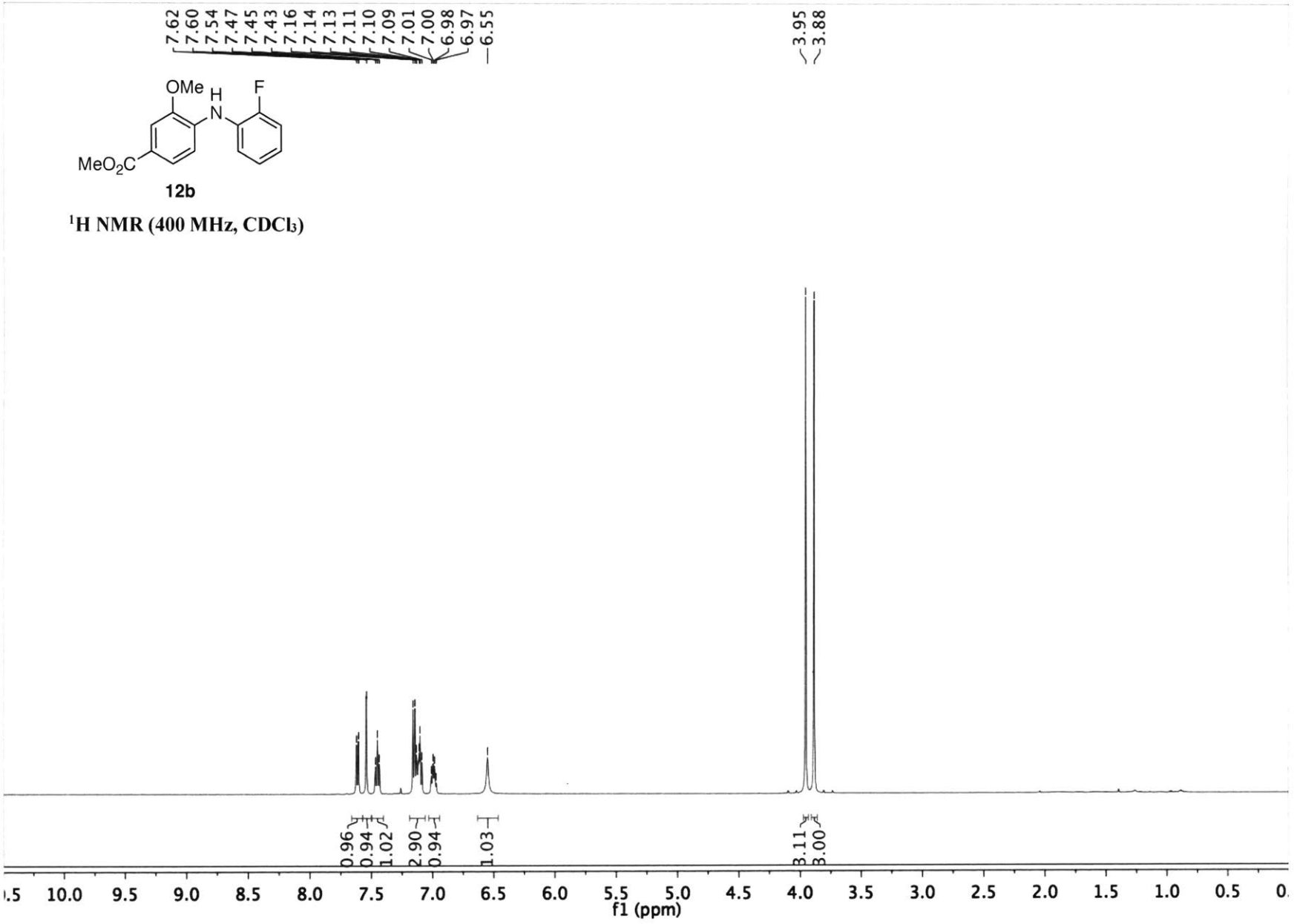
12a

^{13}C NMR (101 MHz, $CDCl_3$)



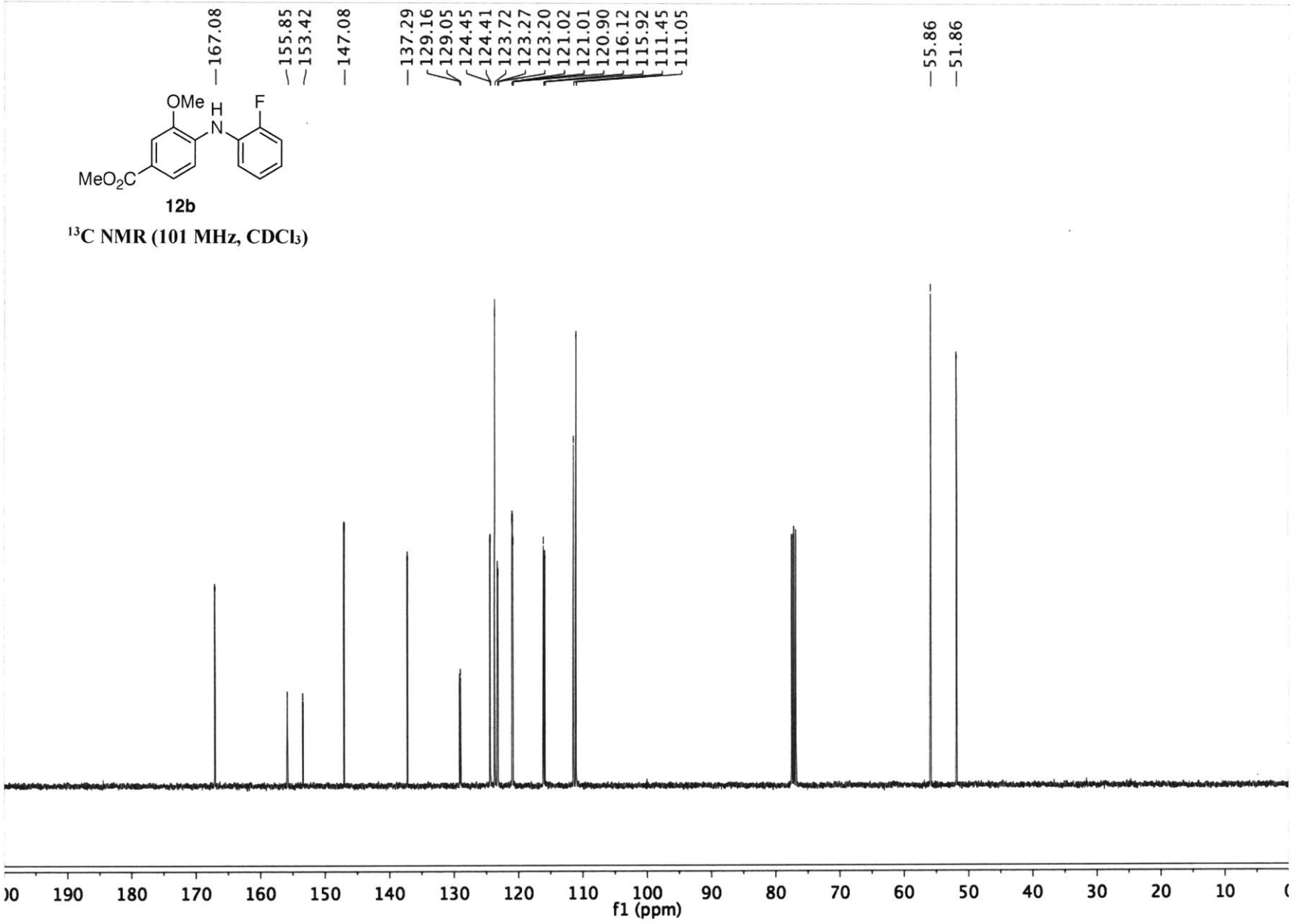
12a

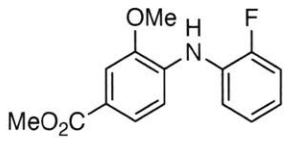
^{19}F NMR (376 MHz, $CDCl_3$)



12b

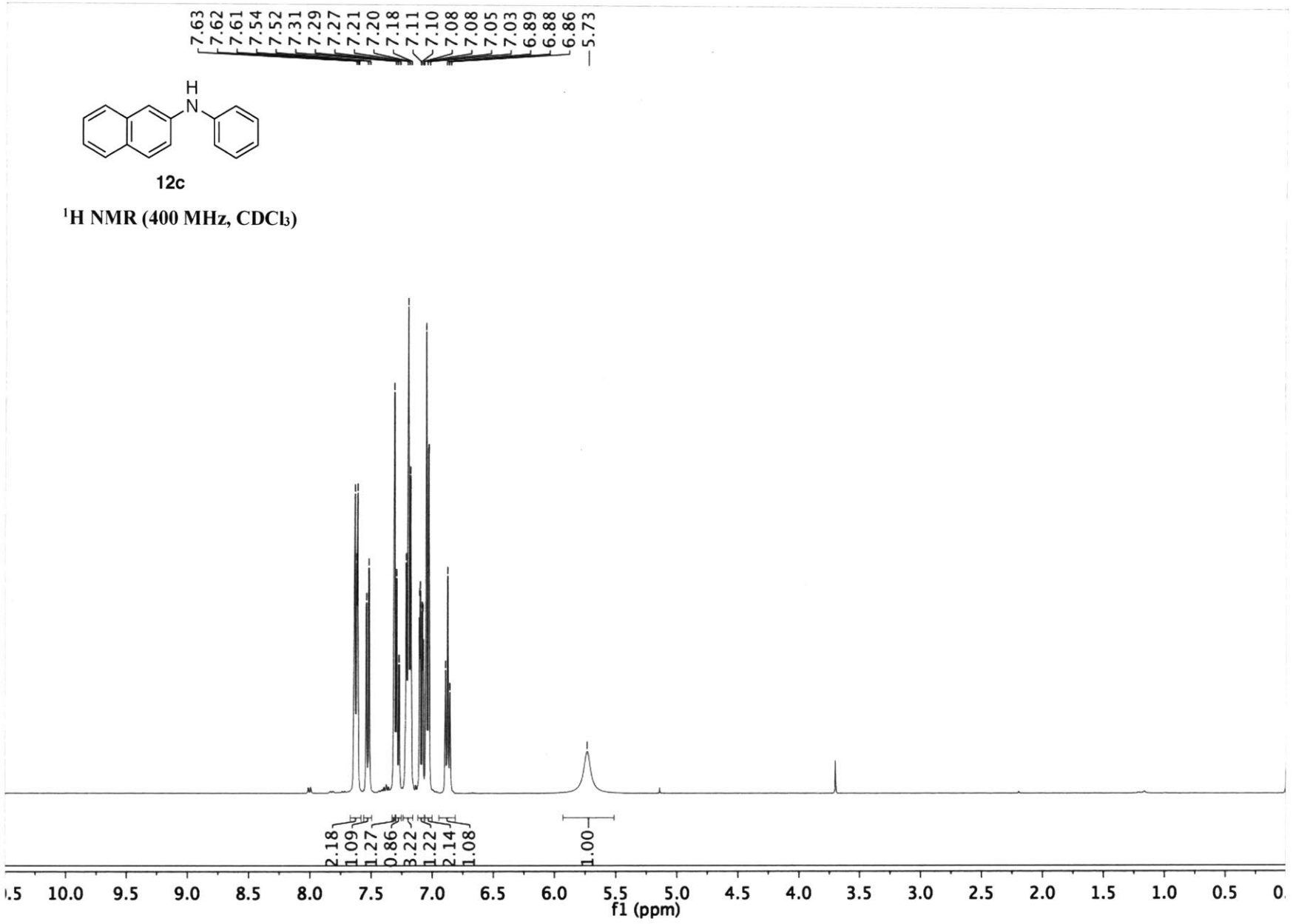
^{1}H NMR (400 MHz, $CDCl_3$)


167.08
155.85
153.42
147.08
137.29
129.16
129.05
124.45
124.41
123.72
123.27
123.20
121.02
121.01
120.90
116.12
115.92
111.45
111.05
55.86
51.86
OMe
H
N
F
MeO2C
12b
13C NMR (101 MHz, CDCl3)
f1 (ppm)



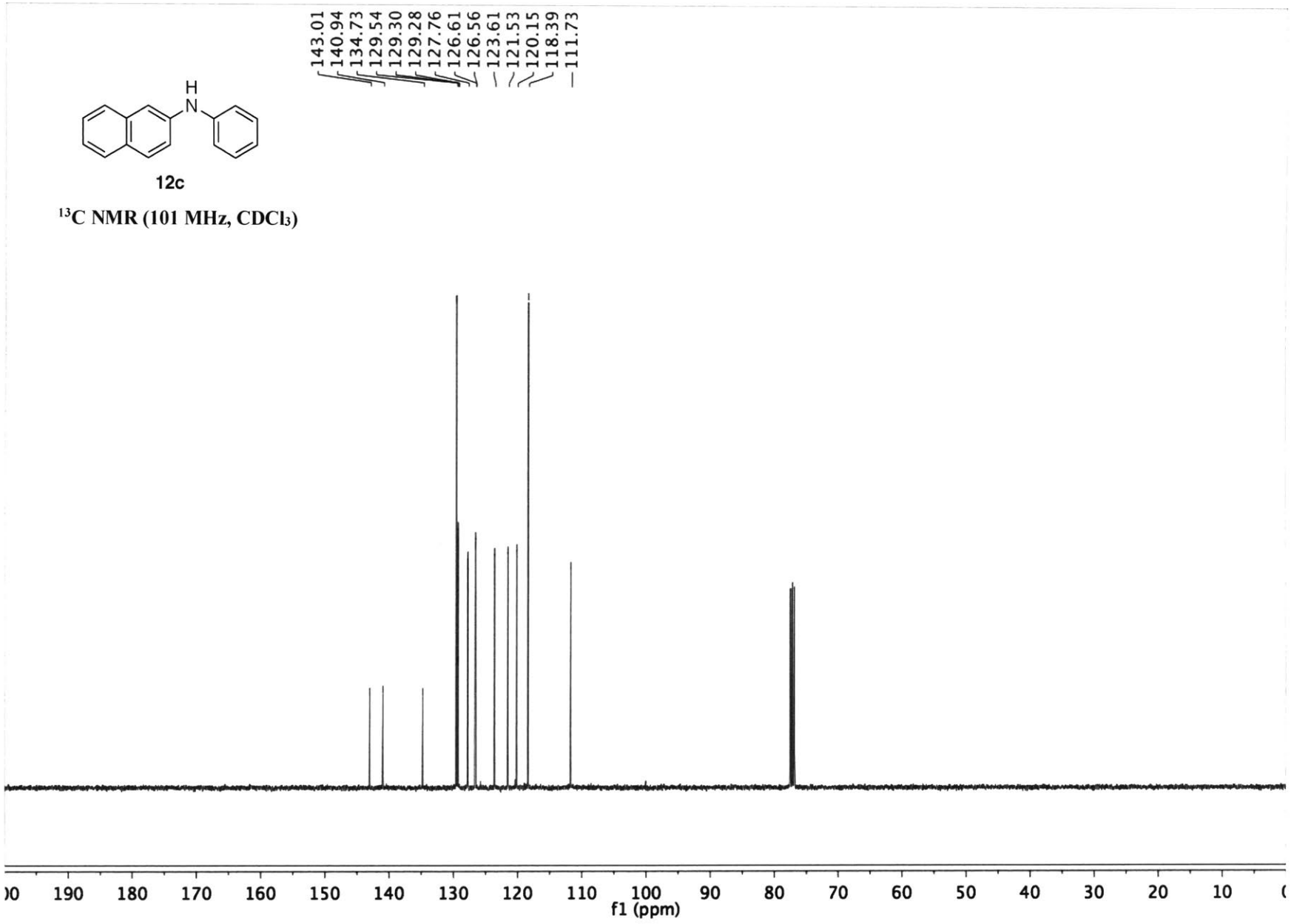
12b

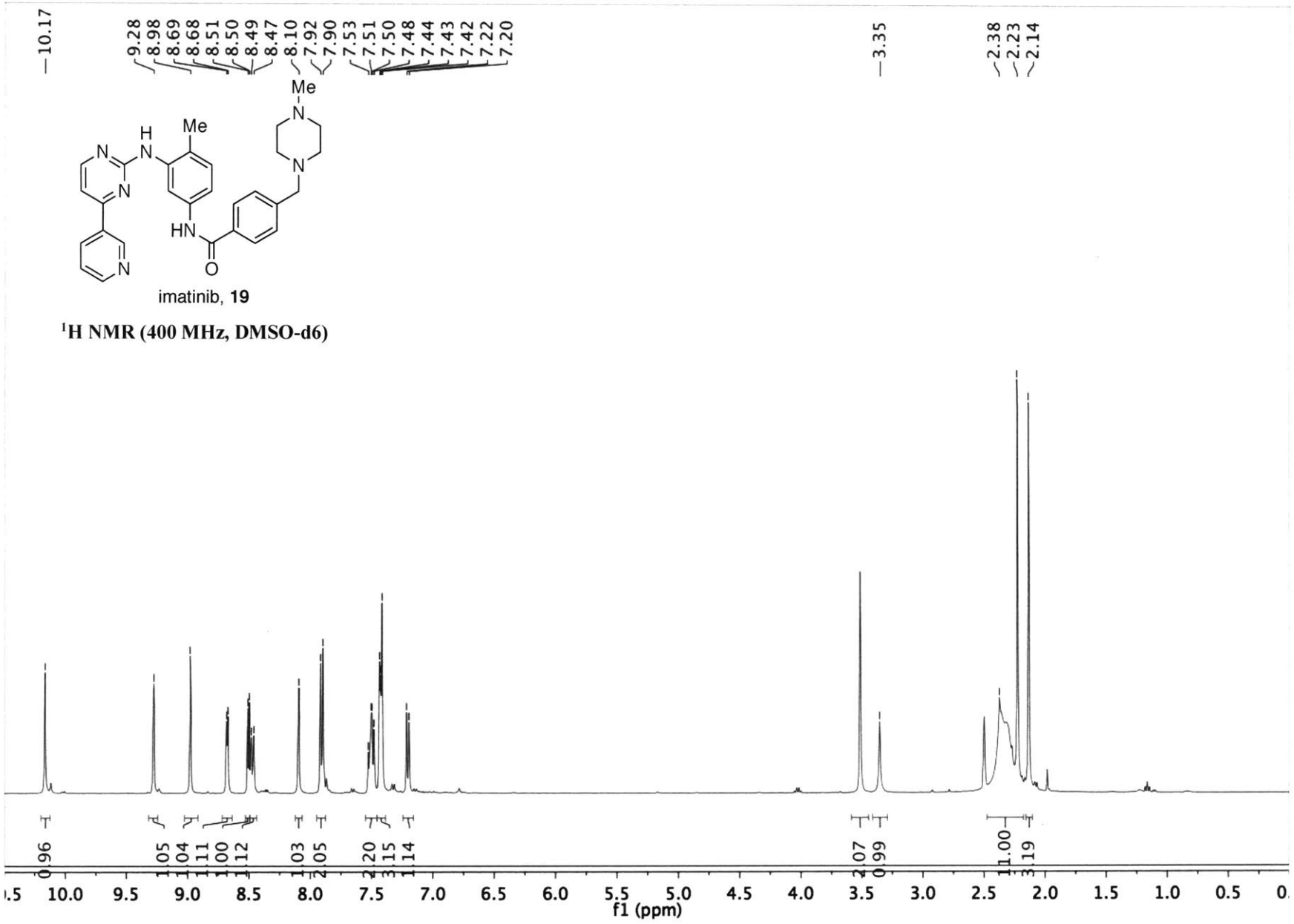
^{19}F NMR (376 MHz, $CDCl_3$)



12c

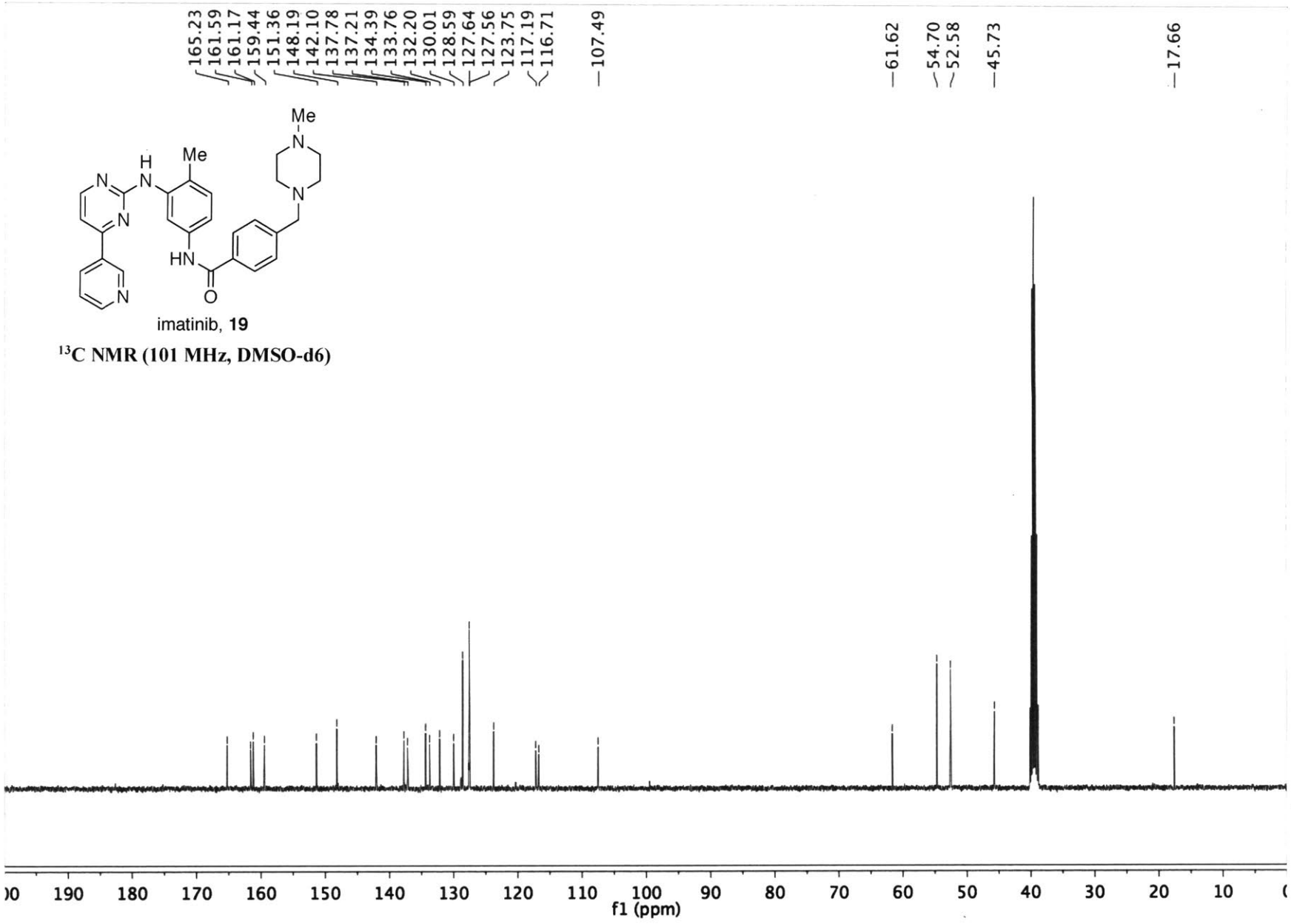
^{1}H NMR (400 MHz, $CDCl_3$)


143.01
140.94
134.73
129.54
129.30
129.28
127.76
126.61
126.56
123.61
121.53
120.15
118.39
111.73
H
N
12c
^{13}C NMR (101 MHz, CDCl$_3$)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



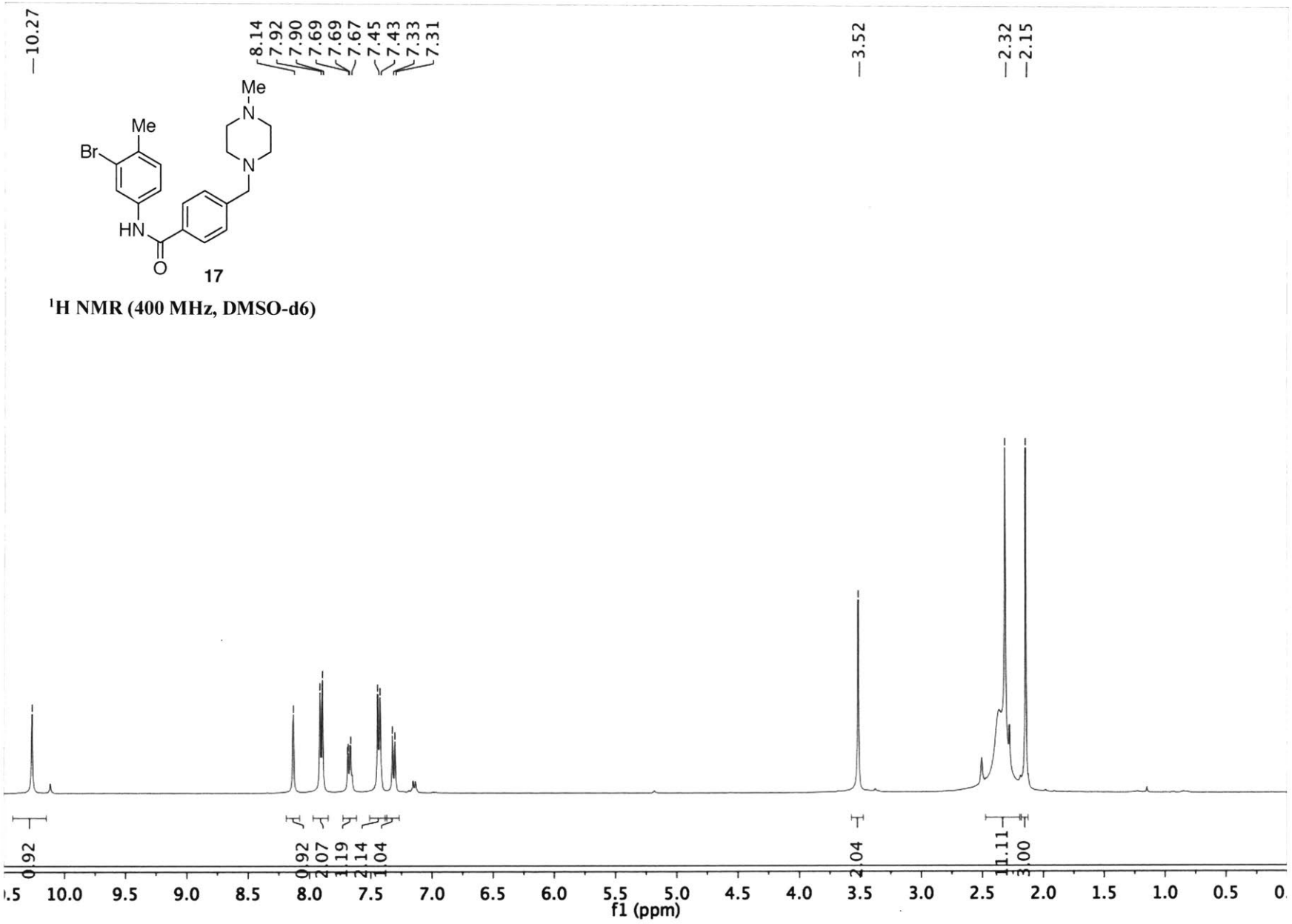
imatinib, **19**

^{1}H NMR (400 MHz, DMSO-d6)

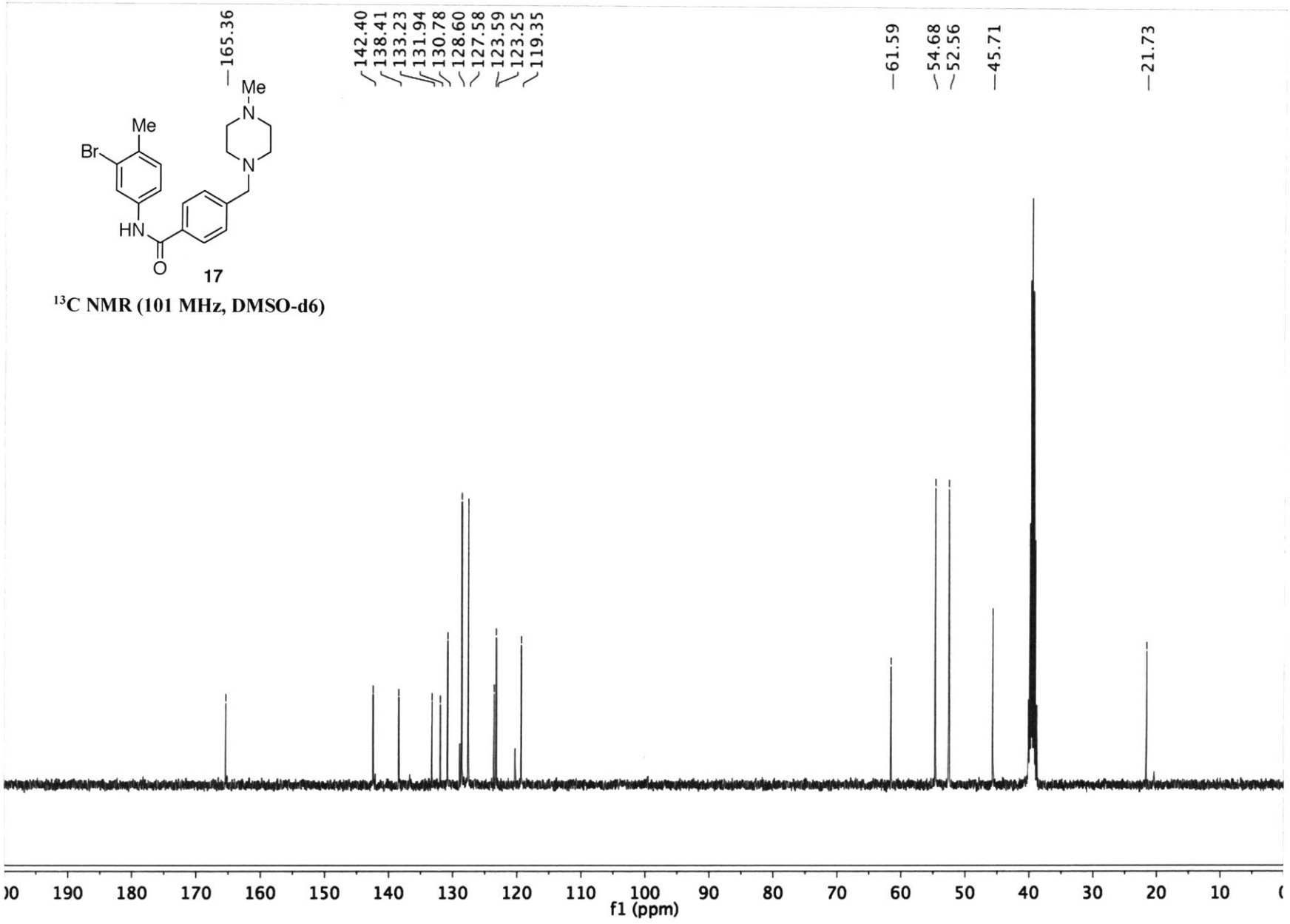


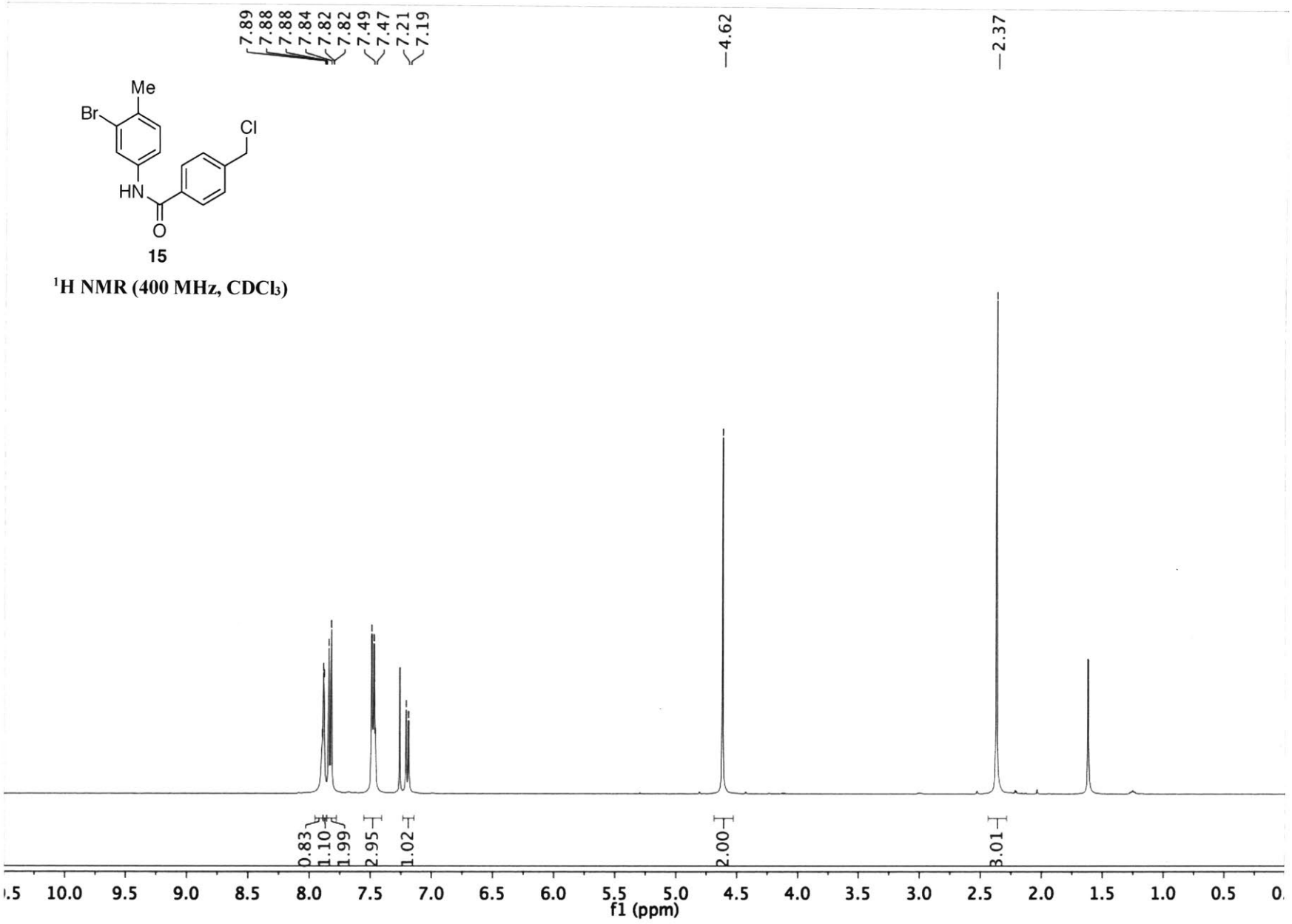
imatinib, **19**

^{13}C NMR (101 MHz, DMSO-d6)



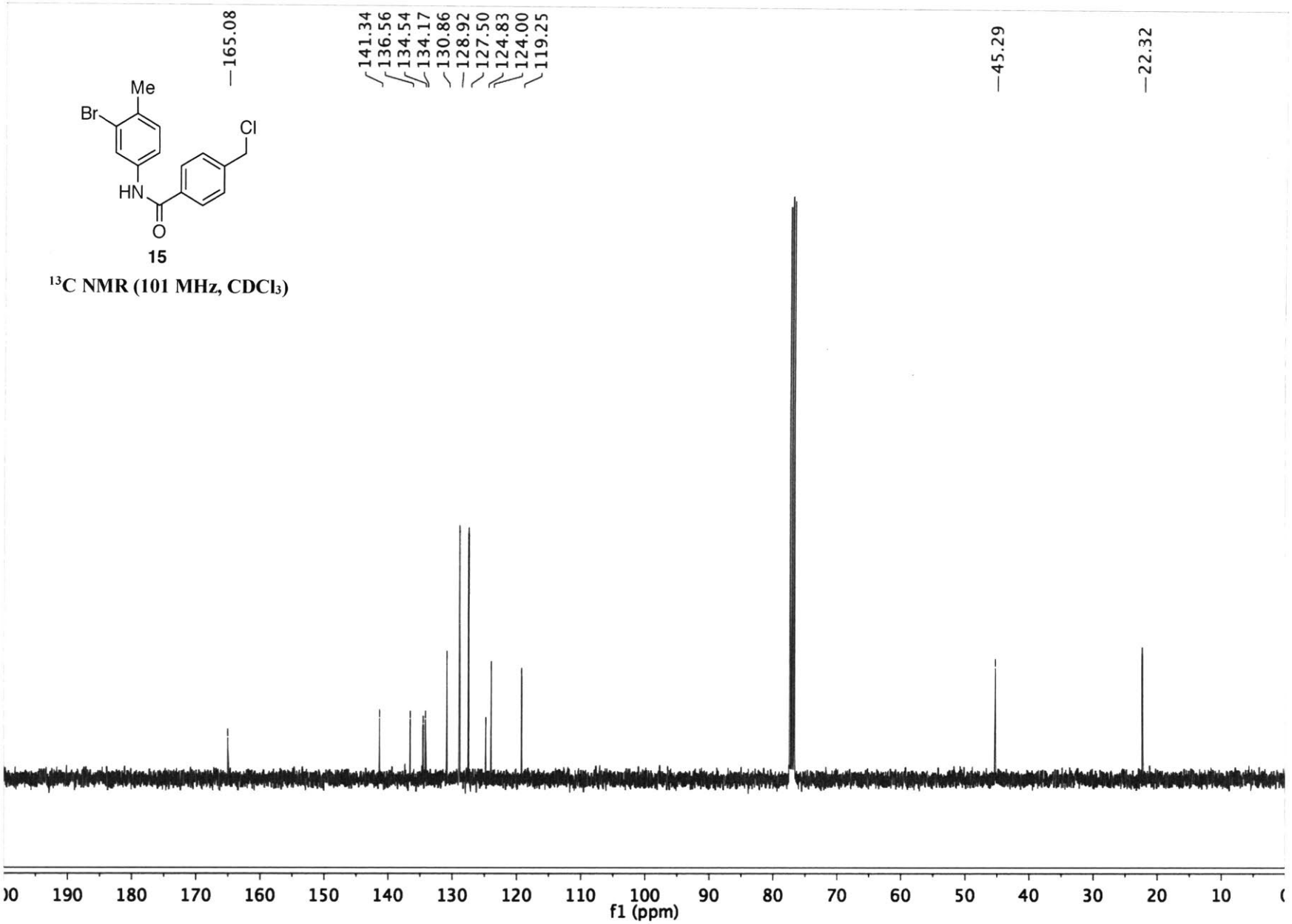
^{1}H NMR (400 MHz, DMSO-d6)


165.36
142.40
138.41
133.23
131.94
130.78
128.60
127.58
123.59
123.25
119.35
61.59
54.68
52.56
45.71
21.73
Me
Br
Me
N
N
HN
O
17
13C NMR (101 MHz, DMSO-d6)
f1 (ppm)



15

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

Part II. Copper-Catalyzed Asymmetric Hydroamination for the Synthesis of Chiral Amines

Chapter 2. CuH-Catalyzed Regioselective Intramolecular Hydroamination for the Synthesis of Alkyl-Substituted Chiral Aziridines

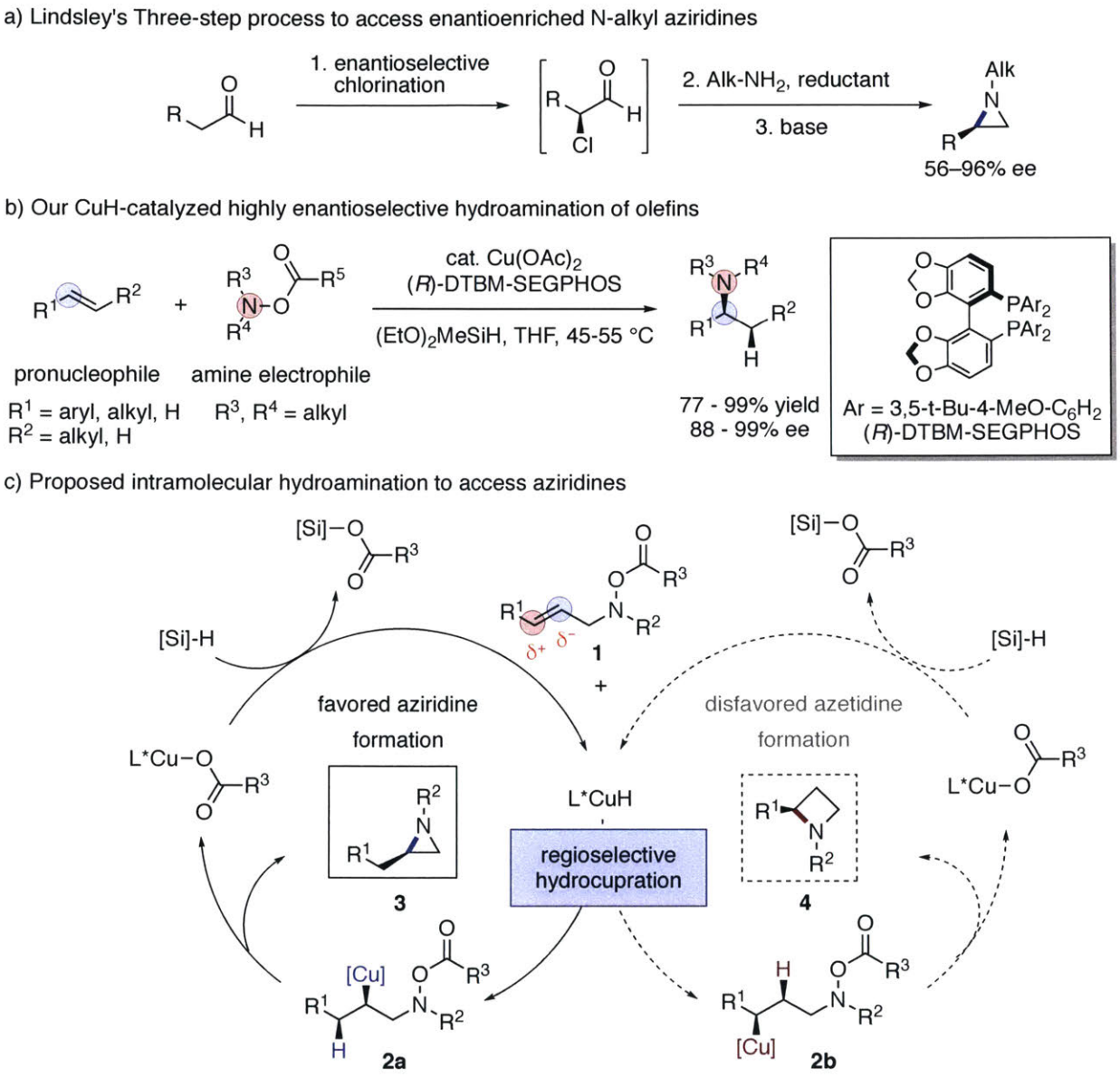
2.1 Introduction

Optically active aziridines constitute a key functional group present in several classes of natural products and pharmaceutical agents.[1] Stereochemically well-defined aziridines also serve as useful building blocks or intermediates for the synthesis of a range of biologically active, nitrogen-containing compounds.[2] For instance, aziridines readily participate in nucleophilic ring opening and ring expansion reactions, as well as in cycloadditions with dipolarophiles.[2] Importantly, the stereochemistry embedded in the heterocycle can often be transferred to the final product to provide configurationally-pure amines. Consequently, a number of synthetic strategies for the stereoselective synthesis of aziridines have been developed.[3] Prominent techniques include metal-catalyzed nitrene cycloadditions with olefins,[4] carbene additions to imines,[5] the aza-Darzens reaction,[6] stereoselective azirine reductions[7] and C–H activation-based approaches.[8] Despite the utility of these methods, they are generally limited to the preparation of aziridines with electron-withdrawing *N*-substituents or require particular substitution patterns for productive reactivity. In general, alkyl-substituted aziridines, are especially challenging to access in a catalytic, enantioselective manner. One recent approach, disclosed by Lindsley, leverages the previously established enantioselective α-chlorination[9] of aldehydes in a three-step one-pot protocol (Figure 1a).[10] Nevertheless, no synthetic method allows for the direct preparation of chiral *N*-alkyl aziridines from achiral starting materials in a catalytic and asymmetric manner. We hypothesized that this synthetic challenge could be addressed through the intramolecular hydroamination of an allylic hydroxylamine ester **1**, enabled by a catalytically generated chiral-phosphine ligated copper(I) hydride (CuH) species.

Recently, our group and others have adopted CuH catalysis as a general platform for the enantioselective hydrofunctionalization of olefins.[11] Among these transformations, the enantioselective hydroamination was successfully applied to symmetric and unactivated internal olefins (Figure 1b).[11e] However, regioselectivity became problematic when unsymmetrical olefins were employed as substrates. Our own experience[11c,e-k] and an example from the recent literature[11m] suggested that a proximal polar substituent on alkenes could influence the regioselectivity of hydrocupration of the alkene by polarizing the C=C double bond. In the proposed aziridine synthesis (Figure 1c), we postulated that the presence of an allylic hydroxylamine ester would enforce the hydrocupration of the internal alkene to provide high regioselectivity for the desired regioisomer (favoring **2a** over **2b**). Following hydrocupration, the

organocopper intermediate would undergo intramolecular amination to furnish chiral aziridine **3**, in preference to the regioisomeric azetidine **4**.

Figure 1. *Lindsley's approach for the synthesis of chiral N-alkyl aziridines and the development of our strategy*

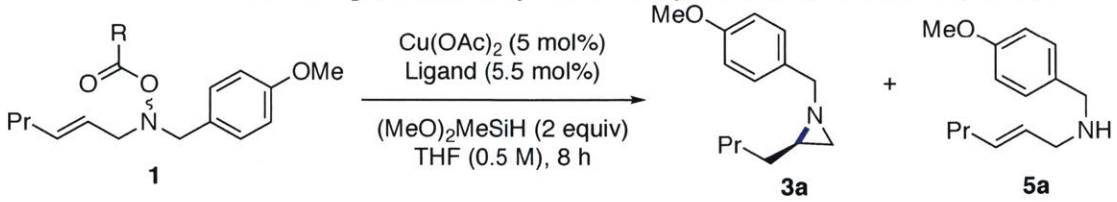


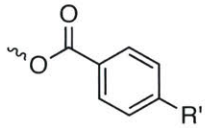
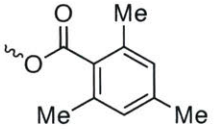
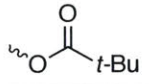
1.2 Results and Discussion

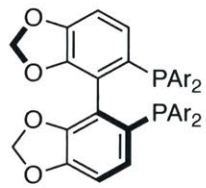
We commenced our study by selecting allylic hydroxylamine ester **1aa** (Table 1) as a model substrate. Subjecting **1aa** to a solution of CuH catalyst (generated from $Cu(OAc)_2$, (*S*)-DTBM-SEGPHOS (**L1**)) and a stoichiometric amount of dimethoxymethylsilane as the hydride source,

resulted in the formation of the desired aziridine product **3a**[12] in 74% yield and 88% ee. Competing N–O bond reduction by the CuH catalyst accounted for the major side product, amine **5a**. In order to suppress this deleterious reduction pathway, the reaction of substrates containing different hydroxylamine esters were examined. While use of electron-deficient *p*-trifluoromethyl benzoate **1ab** exhibited a higher tendency towards reduction, sterically hindered 2,4,6-trimethylbenzoate **1ad** provided **3a** in comparable yield but lower enantioselectivity (entries 2 and 4). The incorporation of electron-rich *p*-*N*,*N*-dimethylamino benzoate **1ac** gave **3a** in higher yield and improved enantioselectivity (80% yield, 94% ee, entry 3). By switching to pivalate **1ae**, the enantioselectivity was further improved to 96% ee (entry 5). These last two results are in line with

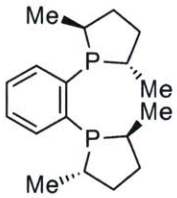
Table 3. *Optimization of CuH-catalyzed chiral aziridine synthesis*[a]



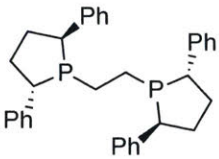
Entry	Substrate	Ligand	Temperature	Yield[a]	ee	Leaving Groups
1	**1aa**	**L1**	40 °C	74%	88%	 **1aa**, R' = H **1ab**, R' = CF_3 **1ac**, R' = NMe_2
2	**1ab**	**L1**	40 °C	57%	66%	
3	**1ac**	**L1**	40 °C	80%	94%	
4	**1ad**	**L1**	40 °C	77%	20%	 **1ad**
5	**1ae**	**L1**	40 °C	78%	96%	
6	**1ae**	**L2**	40 °C	9%	–44%	
7	**1ae**	**L3**	40 °C	4%	–94%	
8	**1ae**	**L4**	40 °C	68%	–94%	
9	**1ae**	(*S*)-CuCatMix[b]	40 °C	82%	96%	 **1ae**
10[c]	**1ae**	(*S*)-CuCatMix[b]	4 °C	89% (80%)[d]	98%	



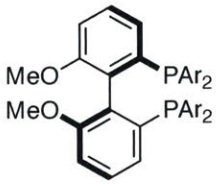
L1
(*S*)-DTBM-SEGPHOS
Ar = 3,5-*t*-Bu-4-MeO-C_6H_2



L2
(*S*,*S*)-Me-DUPHOS



L3
(*S*,*S*)-Ph-BPE

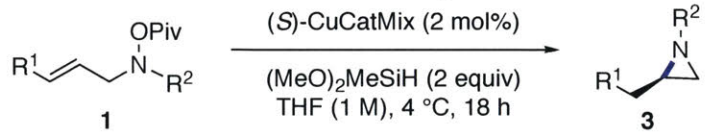


L4
(*R*)-DTBM-BIPHEP
Ar = 3,5-*t*-Bu-4-MeO-C_6H_2

[a]Yields determined by GC analysis of the crude reaction mixture. See Experimental for details. [b]Prepared from $Cu(OAc)_2$/**L1**/PPh_3 (1:1.1:1.1). [c]2 mol% catalyst loading, 1 M concentration, 18 h. [d]Isolated yield on a 0.5 mmol scale.

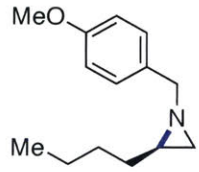
what we have seen in olefin hydroamination processes.[13] In all cases, only a trace amount of the analogous azetidine was seen.[14] Use of other commercially available chiral bisphosphine ligands (**L2-L4**) did not result in any enhancement over our initial choice of ligand, DTBM-SEGPHOS (**L1**) (entries 5-8). The bench-stable precomplexed copper catalyst (*S*)-CuCatMix[13], consisting of a mixture of Cu(OAc)2/**L1**/PPh3 in a 1:1.1:1.1 ratio, offered a slightly improved yield and also simplified the reaction protocol (entry 9). Lastly, further optimization of reaction temperature (4 °C) and concentration (1 M) allowed the desired product to be obtained in 89% yield by GC analysis (81% isolated yield) with an excellent level of enantioselectivity (98% ee, entry 10).

Table 4. *Substrate scope of CuH-catalyzed chiral aziridine synthesis – variation of substitution on the nitrogen atom*[a]

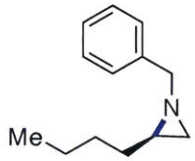


1 **3**

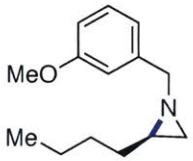
- *Variation of substitution on the nitrogen atom*



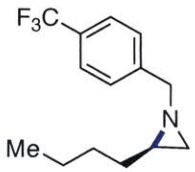
3a
80% yield, 98% ee
from (*Z*)-1ae[b]:
12% yield, 71% ee



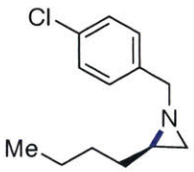
3b
79% yield
97% ee



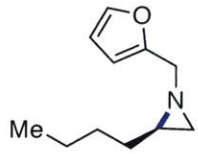
3c
92% yield
95% ee



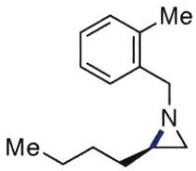
3d
82% yield
94% ee



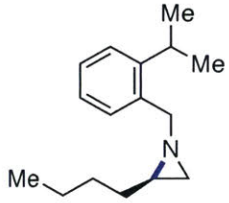
3e
84% yield
94% ee



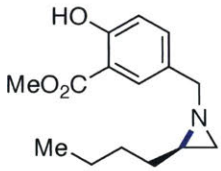
3f
85% yield[c]
99% ee



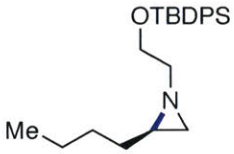
3g
80% yield
90% ee



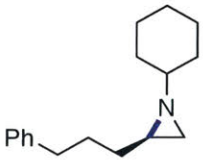
3h
87% yield
79% ee



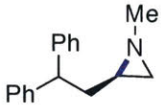
3i
90% yield[d]
97% ee



3j
88% yield
90% ee



3k
86% yield
97% ee



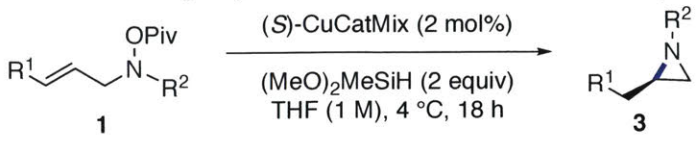
3l
79% yield
>99% ee

[a]All yields represent average isolated yields of two runs conducted on a 0.5 mmol scale. See Experimental for details. [b]40 °C reaction temperature. [c]5 mol% catalyst used. [d]3 equivalents of $(MeO)_2MeSiH$ were used.

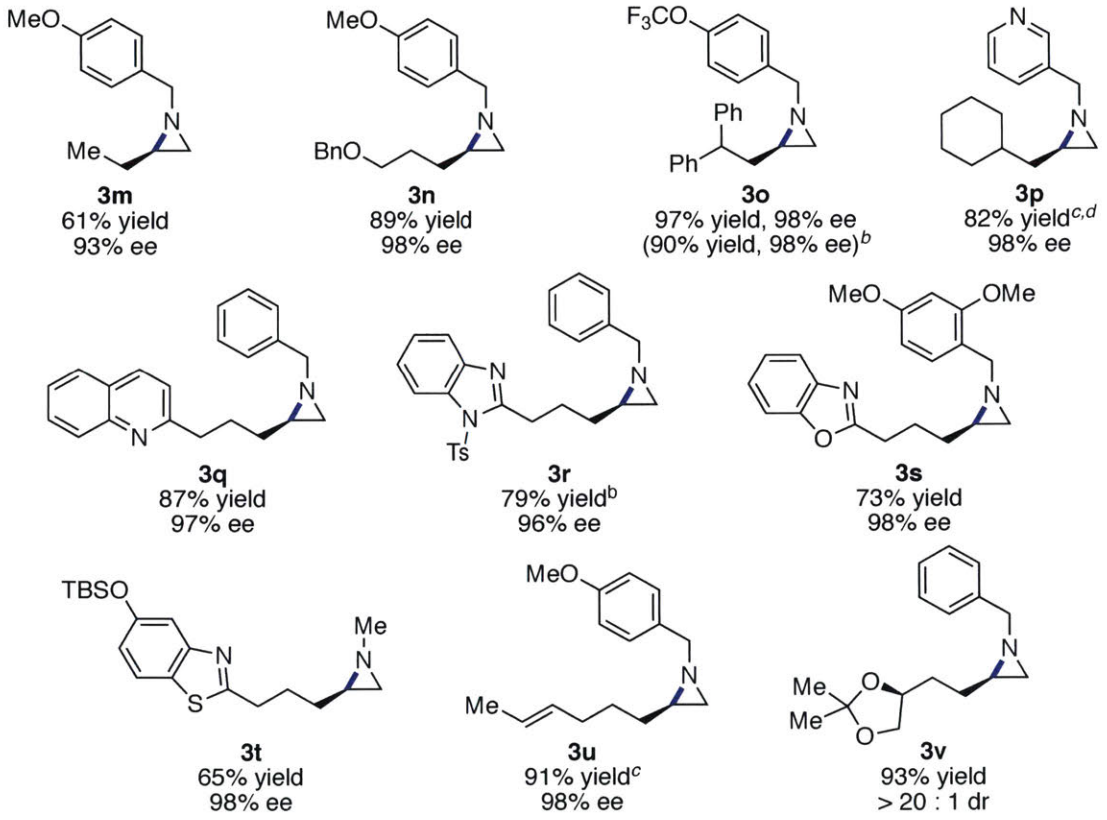
Having identified optimized conditions, the substrate scope of the *N*-substituent was explored (Table 2). In most cases, substituents on the nitrogen atom of varying electronic and steric properties were well-tolerated and their transformation proceeded with high yields and excellent enantioselectivities. In addition, an aziridine with a pendant aryl chloride (**3e**) was successfully prepared, allowing cross-coupling technology to be considered for downstream derivatization. A substrate containing a methyl ester and a free phenol (**3i**) was transformed to product with excellent efficiency and stereoselectivity. Moreover, structurally diverse *N*-alkyl groups including a silyloxyethyl (**3j**), a cyclohexyl (**3k**) and a simple methyl group (**3l**) could all be employed using our procedure. The presence of an *ortho*-isopropyl group on the *N*-benzyl substituent (**3h**) resulted in diminished enantioselectivity and represents a limitation of the current procedure, although a smaller *ortho*-methyl group (**3g**) was readily accommodated.

We next examined the scope of substituents that could be appended to the olefin (Table 3). The analogous 3-ethylaziridine **3m** was successfully obtained from the corresponding crotyl hydroxylamine ester in 62% isolated yield and 93% ee. A benzyl ether (**3n**), an *N*-tosylate (**3r**), a silylether (**3t**), and a ketal (**3v**) were also compatible with the reaction conditions. Furthermore, high yields and enantioselectivities were observed in products derived from substrates that contained heterocyclic fragments. Among the substrates tested, a pyridine (**3p**), a quinoline (**3q**), a furan (**3f**, Table 2), a benzoxazole (**3s**), a benzothiazole (**3t**), and a tosyl-protected benzimidazoles (**3r**) were all well-tolerated under this CuH-catalyzed protocol. Substrates bearing large alkene substituents such as a diphenylmethyl (**3l** and **3o**) and a cyclohexyl (**3p**) group also underwent the desired aziridination reaction without loss of efficiency or selectivity. Notably, other C=C double bonds in positions distal to the hydroxylamine ester (**3u**) were left intact, suggesting that the hydroxylamine ester group not only controls the regioselectivity but also activates the adjacent alkene for chemoselective hydrocupration. The presence of a homoallylic benzyl ether did not perturb the regioselectivity of the reaction (**3n**). Also, a hydroxylamine ester containing a chiral ketal group (**1v**) can be converted to aziridine **3v** with greater than 20 : 1 diastereoselectivity. To demonstrate the scalability of this procedure, product **3o** was synthesized on a 5.0 mmol scale. Full conversion of the substrate was achieved with a reduced catalyst loading of 0.5 mol% to efficiently provide aziridine **3o** (1.78 g of **3o**, 90% yield, 98% ee).

Table 3. *Substrate scope of alkene substituents and heterocyclic substituents*[a]



▪ *Variation of substitution on the alkene and heterocyclic substituents*

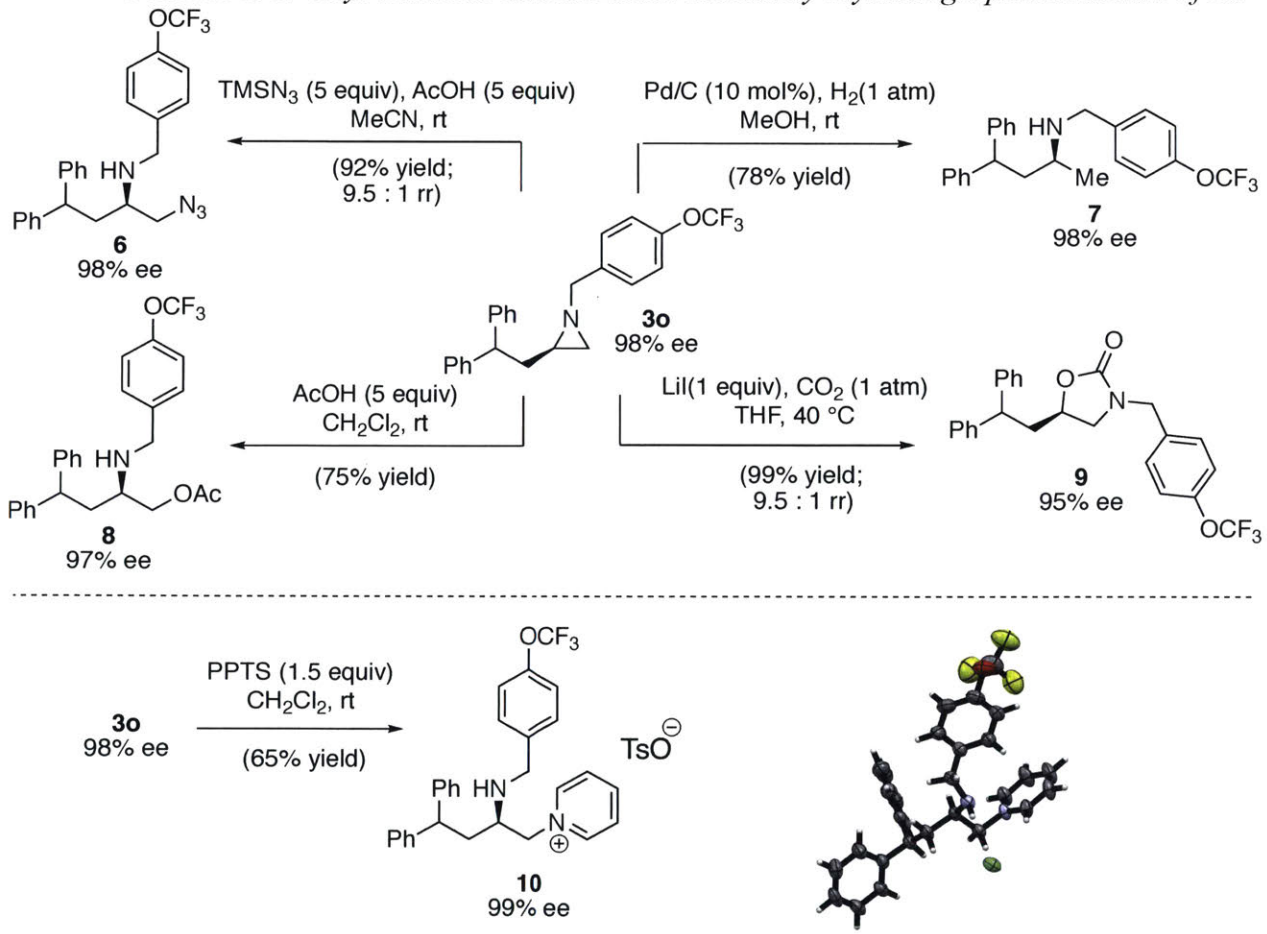


[a]All yields represent average isolated yields of two runs conducted on a 0.5 mmol scale. See Experimental for details. [b]5.0 mmol scale, 0.5 mol% catalyst used, 40 h reaction time. [c]5 mol% catalyst used. [d]48 h reaction time.

During the course of our studies, we found that the nature of olefin geometry had a significant influence on reactivity and enantioselectivity. Under the optimized aziridination conditions, a low conversion of (Z)-**1ae** (Table 2) was observed, with only trace amounts of aziridine product **3a** detected. Although full conversion could be achieved by raising the reaction temperature to 40 °C, the aziridine product **3a** was obtained in only 12% isolated yield and 71% ee. The majority of the mass balance was accounted for by reductive cleavage of the N–O bond **5a**, a side reaction exacerbated by the low reactivity of the (Z)-configured alkene.[11g]

Chiral aziridines are well known as versatile intermediates in organic synthesis.[2] To showcase the synthetic utility of *N*-alkyl aziridines, aziridine **3o** was converted into a series of chiral amines (Scheme 1). Terminal aziridine **3o** underwent regioselective ring opening with azide[15] and acetic acid[16] to provide chiral azido amine **6** and amino alcohol **8**, respectively. Subjecting **3o** to hydrogenation conditions provided chiral secondary amine **7**. Further, LiI-catalyzed insertion of carbon dioxide into **3o** afforded oxazolidones **9** as a 9.5 : 1 mixture of regioisomers.[17] In a reaction for which we could find no precedent, treatment of **3o** with PPTS afforded chiral pyridinium salt **10·OTs**, which allowed the absolute stereochemistry of aziridine product **3o** to be established by X-ray crystallography.[18]

Scheme 1. *N-alkyl aziridine derivatization and X-ray crystallographic structure of* ***10***



2.3 Conclusion

In summary, a highly enantioselective aziridination reaction was achieved through CuH-catalyzed intramolecular hydroamination of allylic hydroxylamine esters. The hydroxylamine ester serves as both the electrophilic amine and to enforce the regioselective hydrocupration of the internal alkene. The high selectivity for the formation of the alkyl copper species with the copper proximal to the hydroxylamine provides the desired aziridines in good to excellent yield in highly enantioenriched forms. The utility of the products derived from this method is further demonstrated through the derivatization of chiral aziridine products to a diverse array of functionalized enantioenriched amines. The mild reaction conditions of this protocol allow for compatibility of a wide range of functional groups and heterocyclic substituents. Additionally, several convergent synthetic routes for accessing allylic hydroxylamines were also developed. Efforts to extend this intramolecular hydroamination strategy to encompass more types of nitrogen-containing heterocycles are currently under way.

2.4 Experimental

I. General Information

General Reagent Information

Unless otherwise noted, reactions were conducted under protection of nitrogen using standard Schlenk line techniques. THF was dried and deoxygenated by passage through packed columns of neutral alumina and copper(II) oxide under a positive pressure of argon and stored in a nitrogen-filled glovebox over 4Å molecular sieves. Copper(II) acetate (99.999% Cu) was purchased from Strem Chemicals Inc. and Sigma Aldrich. Both enantiomers of DTBM-SEGPHOS were purchased from Strem Chemicals Inc. and Takasago International Co. and used as received. Dimethoxy(methyl)silane was purchased from Tokyo Chemical Industry Co. (TCI) and stored at –20 °C for long term storage. DMMS was also stored at rt in a desiccator for up to 3 months with no observable decrease in reagent purity. Caution: Dimethoxy(methyl)silane(DMMS, CAS #16881-77-9) is listed by several vendors (TCI, Alfa Aeser) SDS or MSDS as a H318, a category I Causes Series Eye Damage. Other vendors (Sigma Aldrich, Gelest) list DMMS as a H319, a category II Eye Irritant. DMMS should be handled in a well-ventilated fume hood using proper precaution as outlined in "Prudent Practices in the Laboratory"[1]. At the end of the reaction aqueous sat. Na_2CO_3 was carefully added to the reaction mixture. This was allowed to stir for at least 30 min. All other reagents and solvents were obtained from commercial sources and used as received. Compounds were purified by flash column chromatography using 40-63 μm silica gel (SiliCycle SiliaFlash® F60) unless otherwise indicated.

General Analytical Information

All substrates and products were characterized by ^1H NMR, ^{13}C NMR, ^{19}F NMR (if appropriate), IR spectroscopy, elemental analysis (or high-resolution mass spectroscopy) and melting point analysis (if solids). NMR spectra were recorded with a Bruker 400 MHz (Avance III-400), Varian 500 MHz (Inova-500), JOEL 500 MHz (ECZ-500) or Bruker 600 MHz (Avance-600) instrument. All NMR data are reported in δ units, parts per million (ppm), and were measured relative to the

[1] "Prudent Practices in the Laboratory [electronic resource]: Handling and Management of Chemical Hazards / Committee on Prudent Practices in the Laboratory: An Update."Board on Chemical Sciences and Technology, Division of Earth and Life Studies, National Research Council of the National Academies. Washington, D.C.: National Academies Press, 2011.

residual proton signal in the deuterated solvent ($CDCl_3$: 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR; CD_2Cl_2: 5.32 ppm for ^1H NMR and 54.00 ppm for ^{13}C NMR). All ^{13}C NMR spectra are ^1H decoupled. All IR spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and are reported in terms of frequency of absorption (cm^{-1}). Melting points (m.p.) were measured on a Mel-Temp capillary melting point apparatus. Optical rotations were measured using a Jasco P-1010 digital polarimeter using a cell of 100-mm length under the wavelength of 589 nm. The enantiomeric excesses (ee) of the products were determined by high-performance liquid chromatography (HPLC) analysis performed on Agilent 1200 Series chromatographs using a Chiralpak® columns (25 cm) as noted for each. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High resolution mass spectra were obtained using a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Achiral gas chromatography (GC) analyses were performed on an Agilent 7890A gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). Thin-layer chromatography (TLC) was performed on Silicycle 250 μm silica gel plates (60 μm). Compounds were visualized by irradiation with UV light, or stained with iodine/silica gel, potassium permanganate, or ceric ammonium molybdate (CAN). Preparatory thin-layer chromatography (Prep-TLC) was performed on silica gel GF with UV 254 (20 × 20 cm, 1000 microns, catalog # 02013 from Analtech) and visualized with UV light.

II. Experimental Procedures and Characterization Data

General Procedure for Table 1 – Reaction Optimization

*For entries 1-8 of Table 1, the following procedure was used to prepare a solution of L*CuH:* In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) was charged with a magnetic stir bar (10 mm × 5 mm, egg-shaped), ligand (5.5 μmol, 5.5 mol%) and $Cu(OAc)_2$ (0.9 mg, 5 μmol, 5 mol%). THF (0.2 mL) and dimethoxy(methyl)silane (25 μL, 0.2 mmol, 2.0 equiv) were added sequentially via microsyringes. The vial was capped and the reaction mixture was stirred for 10 min to afford a pale yellow to orange (color was dependent on the ligand) solution of L*CuH.

Aziridination: In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) was charged with a magnetic stir bar (10 mm × 5 mm, egg-shaped) and the substrate (0.1 mmol, 1.0 equiv). The L*CuH solution (prepared above) was added

via a syringe and the reaction tube was sealed with a Teflon/silicone septum screw cap (National, part # C4015-66A). The reaction tube was then removed from the glovebox, placed in a 40 °C oil bath and stirred for 8 h. The reaction was then allowed to cool to rt, and the reaction mixture was quenched by addition of sat. $NaHCO_3$ (2 mL) and dilution with EtOAc (2 mL). 1-Dodecane (10 μL, 0.095 mmol) was added as an internal standard, and the resealed reaction tube was shaken to ensure homogeneity. An aliquot of the organic phase was used for determination of the conversion, yield, and amount of 1-(4-methoxybenzyl)-2-propylazetidine (**4a**) formed by GC analysis of the crude reaction mixture. Another portion of the crude reaction mixture was purified by preparative thin layer chromatography for determination of the enantiomeric excess.

*For entries 9 and 10 of Table 1, general procedure **A** (scaled down to 0.1 mmol) was used for the reaction setup. Reaction workup was performed as described above.*

Preparation of Racemic Samples

To obtain racemic samples of the aziridination products, (±)-CuCatMix was used as the catalyst. (±)-CuCatMix was prepared following a reported procedure using a 1:1 mixture of antipodes of DTBM-SEGPHOS.[2]

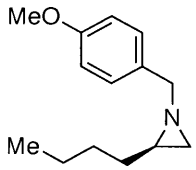
*General Procedure **A** for Tables 2 and 3 – Aziridination of Allylic Hydroxylamine Ester*

An oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) equipped with a magnetic stir bar (10 mm × 5 mm, egg-shaped) was capped with a Teflon/silicone septum screw cap (National, part # C4015-66A). The reaction tube was charged with the allylic hydroxylamine ester substrate (0.5 mmol, 1.0 equiv) and (*S*)-CuCatMix[1] (17.7 mg, 10 μmol, 2 mol%). The reaction tube was recapped, the septum was punctured with a needle attached to a Schlenk line and the tube was evacuated and backfilled with argon (this process was repeated a total of three times). THF (0.4 mL) was added via syringe and the reaction mixture was allowed to stir at rt for 5 min. The reaction tube was then cooled to 0 °C in an ice/water bath and dimethoxy(methyl)silane (125 μL, 1.0 mmol, 2.0 equiv) was added using a syringe. The reaction tube was kept in the ice bath for 5 – 15 min to afford a yellow, orange, or red color. The reaction tube was then transferred to a refrigerator and left at 4 °C without stirring for the time period indicated for each substrate (18 – 48 h). After the time indicated for each reaction, the reaction

[2] Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

tube was removed from the refrigerator, slowly quenched by addition of sat. Na_2CO_3 solution (5 mL) (*Caution: gas evolution!*) and diluted with EtOAc (5 mL). The mixture was then separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The crude reaction mixture was purified by flash silica gel column chromatography to give the corresponding compound.

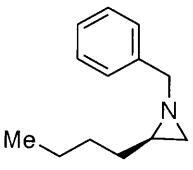
Characterization Data for Tables 2 and 3



3a

(R)-2-Butyl-1-(4-methoxybenzyl)aziridine (3a): Prepared following General Procedure **A** with hydroxylamine ester **1ae** (160 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5–40% EtOAc in hexanes) the title compound was obtained as a colorless oil. (1st run: 89 mg, 81%; 2nd run: 87 mg, 79%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 3.41 (d, J = 12.9 Hz, 1H), 3.25 (d, J = 13.1 Hz, 1H), 1.57 (d, J = 3.4 Hz, 1H), 1.43 (ddt, J = 9.6, 6.1, 3.5 Hz, 1H), 1.40 – 1.34 (m, 3H), 1.32 – 1.21 (m, 4H), 0.83 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.7, 131.8, 129.5, 113.8, 64.5, 55.4, 39.8, 34.0, 32.8, 29.7, 22.5, 14.2. **IR** (neat, cm^{-1}) 2955, 2930, 1512, 1244, 1172, 1037, 818. **HRMS** (DART+) Calcd. for $C_{14}H_{21}NO$ $[M+H]^+$ 220.1696, found 220.1698. **Specific rotation** $[\alpha]_D^{22}$ = 4.16 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 6.6 min, t_m = 7.6 min) indicated 98% ee.

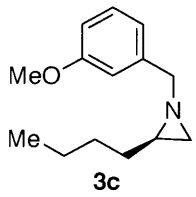
Synthesis of **3a** from **(*Z*)-1ae**: Prepared following General Procedure **A** with hydroxylamine ester **(*Z*)-1ae** (160 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was placed in a 40 °C oil bath and quenched after 18 h. After workup and purification by preparative thin layer chromatography (60% EtOAc in hexanes) the title compound was obtained as a yellow oil. (1st run: 12 mg, 11%; 2nd run: 14 mg, 13%). **HPLC analysis** indicated 71% ee.



3b

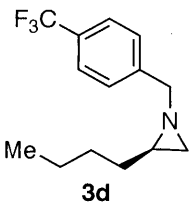
***(R)*-1-Benzyl-2-butylaziridine (3b)**: Prepared following General Procedure **A** with hydroxylamine ester **1b** (289 mg, 1 mmol, 1.0 equiv), (*S*)-CuCatMix (35.4 mg, 0.02 mmol, 2 mol%), dimethoxy(methyl)silane (250 μL, 2.0 mmol, 2.0 equiv), and THF (0.8 mL), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (2–20% EtOAc in hexanes × 2) the title compound was obtained as a light-yellow oil. (1st run: 156 mg, 82%; 2nd run: 143 mg, 76%; *product is volatile*). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.29 – 7.22 (m, 1H), 3.49 (d, J = 13.4 Hz, 1H), 3.33 (d, J = 13.4 Hz, 1H), 1.62 (d, J = 3.2 Hz, 1H), 1.46 (ddt, J = 9.3, 5.8, 3.3 Hz, 1H), 1.42 – 1.34 (m, 3H), 1.34 – 1.18 (m, 4H), 0.91 – 0.77 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.6, 128.4, 128.3, 127.1, 65.1, 39.9, 34.2, 32.8, 29.7, 22.6, 14.2. **IR** (neat, cm^{-1}) 2956, 2929, 1495, 1453, 1355, 730, 696. **HRMS** (DART+) Calcd. for $C_{13}H_{19}N$ $[M+H]^+$ 190.1590, found

190.1582. **Specific rotation** $[\alpha]_D^{22} = -4.68$ ($c = 1.0$, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 0.8 mL/min, $t_M = 5.8$ min, $t_m = 6.5$ min) indicated 97% ee.



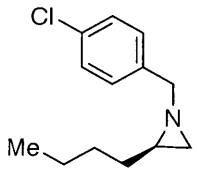
3c

(*R*)-2-Butyl-1-(3-methoxybenzyl)aziridine (3c): Prepared following General Procedure **A** with hydroxylamine ester **1c** (160 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–60% EtOAc in hexanes) the title compound was obtained as a colorless oil. (1st run: 94 mg, 86%; 2nd run: 105 mg, 96%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (t, $J = 7.8$ Hz, 1H), 6.96 – 6.92 (m, 1H), 6.92 – 6.89 (m, 1H), 6.80 (ddd, $J = 8.3$, 2.7, 1.0 Hz, 1H), 3.81 (s, 3H), 3.49 (d, $J = 13.4$ Hz, 1H), 3.29 (d, $J = 13.3$ Hz, 1H), 1.62 (d, $J = 3.0$ Hz, 1H), 1.49 – 1.41 (m, 2H), 1.40 – 1.35 (m, 2H), 1.32 – 1.25 (m, 4H), 0.84 (t, $J = 7.0$ Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7, 141.2, 129.3, 120.6, 113.6, 112.7, 65.0, 55.3, 39.4, 34.2, 32.8, 29.7, 22.6, 14.1. **IR** (neat, cm^{-1}) 2955, 2929, 2857, 1602, 1585, 1263, 1152, 1043, 774, 692. **HRMS** (DART+) Calcd. for $C_{14}H_{21}NO$ $[M+H]^+$ 220.1696, found 220.1697. **Specific rotation** $[\alpha]_D^{22} = 5.79$ ($c = 1.0$, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, $t_m = 7.5$ min, $t_M = 8.6$ min) indicated 95% ee.



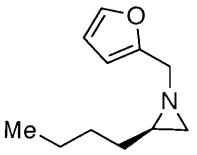
3d

(*R*)-2-Butyl-1-(4-(trifluoromethyl)benzyl)aziridine (3d): Prepared following General Procedure **A** with hydroxylamine ester **1d** (179 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h After workup and purification by flash column chromatography (2–20% EtOAc in hexanes) the title compound was obtained as a pale yellow oil. (1st run: 106 mg, 82%; 2nd run: 106 mg, 82%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 3.51 (d, $J = 13.8$ Hz, 1H), 3.39 (d, $J = 13.8$ Hz, 1H), 1.64 (d, $J = 3.2$ Hz, 1H), 1.45 (tt, $J = 8.2$, 4.0 Hz, 1H), 1.42 – 1.34 (m, 3H), 1.33 – 1.21 (m, 4H), 0.84 (t, $J = 7.0$ Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.7 (q, $J = 1.3$ Hz), 129.3 (q, $J_{CF} = 32.2$ Hz), 128.4, 125.3 (q, $J_{CF} = 3.8$ Hz), 124.40 (q, $J_{CF} = 271.9$ Hz), 64.5, 40.1, 34.3, 32.8, 29.7, 22.6, 14.1. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.29. **IR** (neat, cm^{-1}) 2958, 2929, 1323, 1161, 1122, 1066, 1018, 820. **HRMS** (DART+) Calcd. for $C_{14}H_{18}F_3N$ $[M+H]^+$ 258.1464, found 258.1454. **Specific rotation** $[\alpha]_D^{22} = -4.66$ ($c = 1.0$, $CHCl_3$). **HPLC analysis** (AD-H column, hexanes, 0.5 mL/min, $t_M = 27.8$ min, $t_m = 34.8$ min) indicated 94% ee.



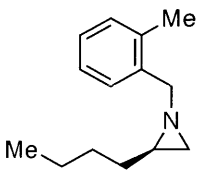
3e

(*R*)-2-Butyl-1-(4-chlorobenzyl)aziridine (3e): Prepared following General Procedure **A** with hydroxylamine ester **1e** (162 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5–25% EtOAc in hexanes) the title compound was obtained as a pale yellow oil. (1st run: 99 mg, 88%; 2nd run: 90 mg, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 3.43 (d, J = 13.4 Hz, 1H), 3.29 (d, J = 13.5 Hz, 1H), 1.61 (d, J = 3.2 Hz, 1H), 1.43 (td, J = 7.1, 6.5, 4.0 Hz, 1H), 1.40 – 1.33 (m, 3H), 1.33 – 1.16 (m, 4H), 0.85 (td, J = 7.2, 6.1, 3.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.1, 132.8, 129.6, 128.5, 64.4, 40.0, 34.2, 32.8, 29.7, 22.6, 14.2. **IR** (neat, cm^{-1}) 2957, 2929, 1490, 1086, 1015, 802. **EA** Calcd. for $C_{13}H_{18}ClN$: C, 69.79; H, 8.11. Found: C, 69.52; H, 8.12. **Specific rotation** $[\alpha]_D^{22}$ = 5.41 (c = 1.0, $CHCl_3$). **HPLC analysis** (OJ-H column, 350:1 hexanes/2-propanol, 0.8 mL/min, t_M = 7.0 min, t_m = 7.6 min) indicated 94% ee.



3f

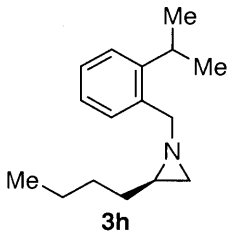
(*R*)-2-Butyl-1-(furan-2-ylmethyl)aziridine (3f): Prepared following General Procedure **A** with hydroxylamine ester **1f** (140 mg, 0.5 mmol, 1.0 equiv) and (*S*)-CuCatMix (44.3 mg, 0.025 mmol, 5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–40% EtOAc in hexanes) the title compound was obtained as a pale yellow oil. (1st run: 75 mg, 84%; 2nd run: 77 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, J = 1.6 Hz, 1H), 6.30 (dd, J = 3.2, 1.9 Hz, 1H), 6.20 (d, J = 3.1 Hz, 1H), δ 3.42 (d, J = 13.9 Hz, 1H), 3.35 (d, J = 13.8 Hz, 1H), 1.58 (d, J = 3.6 Hz, 1H), 1.48 (d, J = 3.9 Hz, 1H), 1.43 – 1.21 (m, 7H), 0.86 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 142.0, 110.2, 107.2, 56.9, 39.7, 33.8, 32.8, 29.7, 22.6, 14.2. **IR** (neat, cm^{-1}) 2957, 2927, 2859, 1727, 1505, 1466, 1342, 1148, 1012, 727. **HRMS** (DART+) Calcd. for $C_{11}H_{17}NO$ $[M+H]^+$ 180.1383, found 180.1385. **Specific rotation** $[\alpha]_D^{22}$ = –12.18 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 5.7 min, t_m = 6.9 min) indicated 99% ee.



3g

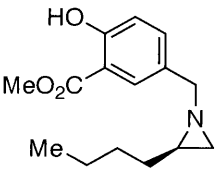
(*R*)-2-Butyl-1-(2-methylbenzyl)aziridine (3g): Prepared following General Procedure **A** with hydroxylamine ester **1g** (152 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (2–10% EtOAc in hexanes × 2) the title compound was

obtained as a colorless oil. (1st run: 83 mg, 82%; 2nd run: 79 mg, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 1H), 7.21 (td, J = 7.3, 2.0 Hz, 1H), 7.19 – 7.12 (m, 2H), 3.41 (s, 2H), 2.31 (s, 3H), 1.66 (d, J = 3.3 Hz, 1H), 1.58 – 1.35 (m, 5H), 1.35 – 1.23 (m, 3H), 0.88 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.9, 135.8, 130.0, 128.0, 126.9, 125.9, 62.6, 39.9, 34.3, 32.8, 29.7, 22.6, 19.2, 14.2. **IR** (neat, cm^{-1}) 2956, 2928, 1460, 740. **HRMS** (DART+) Calcd. for $C_{14}H_{21}N$ $[M+H]^+$ 204.1747, found 204.1744. **Specific rotation** $[\alpha]_D^{22}$ = –18.07 (c = 0.99, $CHCl_3$). **HPLC analysis** (AD-H column, hexanes, 0.5 mL/min, t_M = 24.1 min, t_m = 32.7 min) indicated 90% ee.



3h

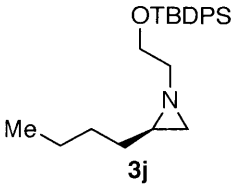
(*R*)-2-Butyl-1-(2-isopropylbenzyl)aziridine (3h): Prepared following General Procedure **A** with hydroxylamine ester **1h** (166 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (1–8% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. (1st run: 98 mg, 85%; 2nd run: 104 mg, 90%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.6 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 3.59 (d, J = 13.9 Hz, 1H), 3.37 (d, J = 13.9 Hz, 1H), 3.21 (hept, J = 6.9 Hz, 1H), 1.64 (d, J = 3.0 Hz, 1H), 1.53 – 1.41 (m, 2H), 1.41 – 1.33 (m, 2H), 1.33 – 1.25 (m, 4H), 1.23 (dd, J = 7.0, 1.7 Hz, 6H), 0.91 – 0.81 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.7, 136.3, 128.6, 127.3, 125.7, 125.0, 62.2, 39.7, 34.4, 32.8, 29.7, 28.5, 23.9, 23.8, 22.6, 14.2. **IR** (neat, cm^{-1}) 2959, 2926, 1456, 1035, 758. **HRMS** (DART+) Calcd. for $C_{16}H_{25}N$ $[M+H]^+$ 232.2060, found 232.2050. **Specific rotation** $[\alpha]_D^{22}$ = –2.90 (c = 1.01, $CHCl_3$). **HPLC analysis** (AD-H column, hexanes, 0.5 mL/min, t_M = 14.1 min, t_m = 16.4 min) indicated 79% ee.



3i

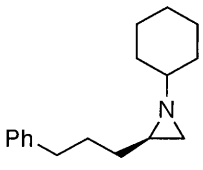
Methyl (*R*)-5-((2-butylaziridin-1-yl)methyl)-2-hydroxybenzoate (3i): Prepared following General Procedure **A** with hydroxylamine ester **1i** (182 mg, 0.5 mmol, 1.0 equiv) and dimethoxymethylsilane (185 μL, 1.5 mmol, 3.0 equiv), the reaction mixture was quenched after 18 h and the phenol was desilylated by addition of 1M HCl (5 mL) and stirring for 15 min. After workup and purification by flash column chromatography (0–40% EtOAc in hexanes) the title compound was obtained as a colorless oil. (1st run: 118 mg, 90%; 2nd run: 119 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.81 (s, 1H), 7.43 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 3.94 (s, 3H), 3.41 (d, J = 13.1 Hz, 1H), 3.23 (d, J = 13.1 Hz, 1H), 1.59 (d, J = 3.2 Hz, 1H), 1.43 (m, 1H), 1.40 – 1.34

(m, 3H), 1.29 – 1.24 (m, 4H), 0.87 – 0.79 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 160.8, 136.0, 130.5, 129.5, 117.6, 112.1, 64.3, 52.3, 40.0, 34.2, 32.8, 29.8, 22.6, 14.2. **IR** (neat, cm^{-1}) 2955, 2928, 2858, 1675, 1489, 1440, 1205, 1088, 795. **EA** Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04. Found: C, 68.19; H, 8.21. **Specific rotation** $[\alpha]_D^{22} = 6.79$ (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99.5:0.5 hexanes/2-propanol, 1.0 mL/min, t_M = 16.0 min, t_m = 19.3 min) indicated 97% ee.



3j

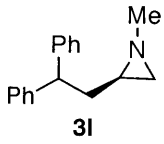
(*R*)-2-Butyl-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)aziridine (3j): Prepared following General Procedure **A** with hydroxylamine ester **1j** (241 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (2–20% EtOAc in hexanes) the title compound was obtained as a pale yellow oil. (1st run: 167 mg, 88%; 2nd run: 168 mg, 88%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.45 – 7.35 (m, 6H), 3.84 (td, J = 6.2, 2.2 Hz, 2H), 2.47 (dt, J = 12.6, 6.4 Hz, 1H), 2.39 (dt, J = 12.2, 6.2 Hz, 1H), 1.50 (d, J = 3.0 Hz, 1H), 1.47 – 1.28 (m, 7H), 1.27 (d, J = 5.8 Hz, 1H), 1.06 (s, 9H), 0.88 (t, J = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.7, 135.7, 133.9, 133.8, 129.7, 127.8, 64.0, 63.0, 39.4, 33.8, 32.9, 29.7, 27.0, 22.7, 19.3, 14.2 (two signals missing due to overlap). **IR** (neat, cm^{-1}) 2956, 2929, 2857, 1427, 1111, 822, 736, 699, 614. **EA** Calcd. for $C_{25}H_{37}NOSi$: C, 75.89; H, 9.43. Found: C, 75.71; H, 9.29. **Specific rotation** $[\alpha]_D^{22} = -12.08$ (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 3.9 min, t_m = 4.5 min) indicated 90% ee.



3k

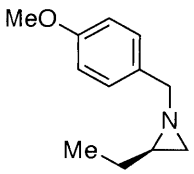
(*R*)-1-Cyclohexyl-2-(3-phenylpropyl)aziridine (3k): Prepared following General Procedure **A** with hydroxylamine ester **1k** (172 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5–30% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. (1st run: 100 mg, 82%; 2nd run: 110 mg, 90%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.5 Hz, 2H), 7.21 – 7.15 (m, 3H), 2.64 (ddt, J = 13.7, 9.8, 4.9 Hz, 2H), 1.90 – 1.78 (m, 3H), 1.77 – 1.66 (m, 3H), 1.66 – 1.47 (m, 2H), 1.49 (d, J = 3.0 Hz, 1H), 1.42 – 1.25 (m, 4H), 1.23 (d, J = 6.2 Hz, 1H), 1.24 – 1.05 (m, 3H), 1.01 (tt, J = 10.7, 3.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 128.5, 128.4, 125.8, 69.1, 38.3, 36.1, 33.3, 33.2, 32.6, 30.0, 26.2, 25.2, 25.1 (one signal missing due to overlap). **IR** (neat, cm^{-1}) 2924, 2852, 1451, 1367, 1073, 868, 745, 697. **EA** Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 83.59; H, 10.35.

Specific rotation $[\alpha]_D^{22}$ = –16.30 (*c* = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 4.7 min, t_m = 5.1 min) indicated 97% ee.



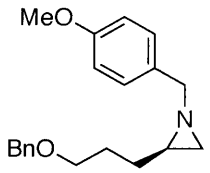
3l

(*R*)-2-(2,2-Diphenylethyl)-1-methylaziridine (3l): Prepared following General Procedure **A** with hydroxylamine ester **1l** (169 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (10–100% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. (1st run: 94 mg, 79%; 2nd run: 95 mg, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 8H), 7.17 (dtd, *J* = 9.1, 6.4, 2.6 Hz, 2H), 4.13 (dd, *J* = 8.7, 6.9 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.15 (s, 3H), 2.05 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.50 (d, *J* = 3.2 Hz, 1H), 1.13 (dq, *J* = 11.4, 6.2, 4.9 Hz, 1H), 1.08 (d, *J* = 6.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.9, 144.6, 128.6, 128.5, 128.1, 127.9, 126.3, 126.2, 50.0, 47.8, 39.26, 39.25, 35.4. **IR** (neat, cm^{-1}) 3026, 2939, 1493, 1450, 747, 736, 697. **HRMS** (DART+) Calcd. for $C_{17}H_{19}N$ $[M+H]^+$ 238.1590, found 238.1598. **Specific rotation** $[\alpha]_D^{24}$ = –25.74 (*c* = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 199:1 hexanes/2-propanol, 0.8 mL/min, t_m = 23.0 min, t_M = 24.4 min) indicated >99% ee.



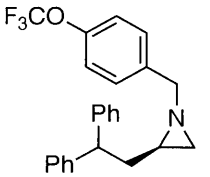
3m

(*R*)-2-Ethyl-1-(4-methoxybenzyl)aziridine (3m): Prepared following General Procedure **A** with hydroxylamine ester **1m** (146 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5–50% EtOAc in hexanes; followed by second purification via flash column chromatography with 2–12% acetone in hexanes) the title compound was obtained as a pale-yellow oil. (1st run: 60 mg, 63%; 2nd run: 59 mg, 62%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 6.89 – 6.83 (m, 2H), 3.79 (s, 3H), 3.46 (d, *J* = 13.0 Hz, 1H), 3.23 (d, *J* = 13.0 Hz, 1H), 1.59 (d, *J* = 3.0 Hz, 1H), 1.46 – 1.33 (m, 4H), 0.90 – 0.81 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.8, 131.7, 129.5, 113.8, 64.5, 55.4, 41.4, 33.8, 26.2, 11.7. **IR** (neat, cm^{-1}) 2962, 2834, 1612, 1511, 1464, 1301, 1243, 1173, 1034, 808. **HRMS** (DART+) Calcd. for $C_{12}H_{17}NO$ $[M+H]^+$ 192.1383, found 192.1380. **Specific rotation** $[\alpha]_D^{22}$ = 12.15 (*c* = 0.55, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 7.3 min, t_m = 8.4 min) indicated 93% ee.



3n

(*R*)-2-(3-(Benzyloxy)propyl)-1-(4-methoxybenzyl)aziridine (3n): Prepared following General Procedure **A** with hydroxylamine ester **1n** (206 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (10–100% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. (1st run: 139 mg, 89%; 2nd run: 140 mg, 90%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 4.45 (d, J = 2.6 Hz, 2H), 3.80 (s, 3H), 3.47 – 3.36 (m, 3H), 3.22 (d, J = 12.9 Hz, 1H), 1.65 (tdd, J = 8.8, 7.1, 4.3 Hz, 2H), 1.60 (d, J = 3.4 Hz, 1H), 1.54 (ddt, J = 10.3, 8.5, 5.2 Hz, 1H), 1.49 – 1.40 (m, 2H), 1.38 (d, J = 6.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.8, 138.7, 131.7, 129.5, 128.4, 127.7, 127.6, 113.8, 72.9, 70.0, 64.5, 55.4, 39.4, 34.1, 29.8, 27.8. **IR** (neat, cm^{-1}) 1611, 1511, 1243, 1173, 1100, 1034, 818, 734, 697. **EA** Calcd. for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09. Found: C, 76.99; H, 8.09. **Specific rotation** $[\alpha]_D^{22}$ = 5.21 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 97:3 hexanes/2-propanol, 1.0 mL/min, t_M = 9.2 min, t_m = 10.7 min) indicated 98% ee.

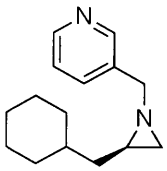


3o

(*R*)-2-(2,2-Diphenylethyl)-1-(4-(trifluoromethoxy)benzyl)aziridine (3o): Prepared following General Procedure **A** with hydroxylamine ester **1o** (249 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5–30% EtOAc in hexanes) the title compound was obtained as a yellow oil. (1st run: 191 mg, 96%; 2nd run: 196 mg, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 12H), 7.13 (d, J = 7.5 Hz, 2H), 4.02 (dd, J = 9.4, 6.6 Hz, 1H), 3.33 (d, J = 13.4 Hz, 1H), 3.21 (d, J = 13.4 Hz, 1H), 2.26 (ddd, J = 14.1, 9.3, 4.9 Hz, 1H), 2.08 (dt, J = 13.8, 6.8 Hz, 1H), 1.64 (d, J = 3.3 Hz, 1H), 1.43 (ddq, J = 11.2, 7.6, 4.6, 3.5 Hz, 1H), 1.36 (d, J = 6.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.4, 145.0, 144.2, 138.3, 129.7, 128.57, 128.55, 128.1, 127.9, 126.4, 126.3, 121.1, 120.7 (q, J_{CF} = 256.8 Hz), 64.0, 49.9, 39.2, 38.4, 34.5. **^{19}F NMR** (376 MHz, $CDCl_3$) -57.86. **IR** (neat, cm^{-1}) 1256, 1221, 1195, 1159, 748, 737, 698. **EA** Calcd. for $C_{24}H_{22}F_3NO$: C, 72.53; H, 5.58. Found: C, 72.36; H, 5.53. **Specific rotation** $[\alpha]_D^{22}$ = – 0.45 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99.5:0.5 hexanes/2-propanol, 0.8 mL/min, t_m = 14.5 min, t_M = 16.2 min) indicated 98% ee.

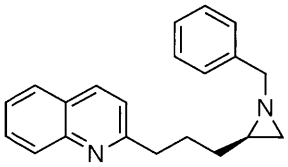
Large-scale synthesis of **3o**: Prepared following General Procedure **A** with hydroxylamine ester **1o** (2.5 g, 5.0 mmol, 1.0 equiv) and (*S*)-CuCatMix (44.3 mg, 25 μmol, 0.5 mol%), the reaction mixture was quenched after 40 h. After workup and purification by flash column chromatography

(0–30% EtOAc in hexanes) the title compound was obtained as a yellow oil. (1.78 g, 90%). **HPLC analysis** 98% ee.



3p

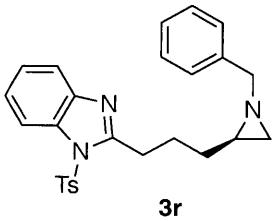
(*R*)-3-((2-(Cyclohexylmethyl)aziridin-1-yl)methyl)pyridine (3p): Prepared following General Procedure **A** with hydroxylamine ester **1p** (165 mg, 0.5 mmol, 1.0 equiv) and (*S*)-CuCatMix (44.3 mg, 25 μmol, 5 mol%), the reaction mixture was quenched after 48 h. After workup and purification by flash column chromatography (1–8% MeOH in CH_2Cl_2) the title compound was obtained as a yellow oil. (1st run: 89 mg, 77%; 2nd run: 99 mg, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.49 (d, J = 2.2 Hz, 1H), 8.45 (dd, J = 4.9, 1.7 Hz, 1H), 7.66 (dt, J = 7.8, 2.0 Hz, 1H), 7.20 (dd, J = 7.8, 4.8 Hz, 1H), 3.43 (d, J = 13.4 Hz, 1H), 3.25 (d, J = 13.4 Hz, 1H), 1.66 – 1.50 (m, 6H), 1.47 (qd, J = 6.2, 3.5 Hz, 1H), 1.36 (d, J = 6.4 Hz, 1H), 1.31 – 1.12 (m, 3H), 1.12 – 0.96 (m, 3H), 0.88 – 0.70 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.6, 148.6, 135.9, 135.1, 123.6, 62.4, 40.7, 38.3, 36.7, 34.7, 33.7, 33.0, 26.6, 26.34, 26.27. **IR** (neat, cm^{-1}) 2918, 2849, 1448, 1423, 1026, 791, 712. **HRMS** (DART+) Calcd. for $C_{15}H_{22}N_2$ $[M+H]^+$ 231.1856, found 231.1851. **Specific rotation** $[\alpha]_D^{22}$ = 1.92 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 98.8:1:0.2 hexanes/2-propanol/Et_2NH, 1.0 mL/min, t_m = 15.6 min, t_M = 16.5 min) indicated 98% ee.



3q

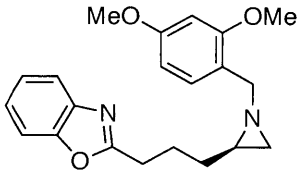
(*R*)-2-(3-(1-Benzylaziridin-2-yl)propyl)quinolone (3q): Prepared following General Procedure **A** with hydroxylamine ester **1q** (201 mg, 0.5 mmol, 1.0 equiv). the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–30% acetone in hexanes) the title compound was obtained as a yellow oil. (1st run: 126 mg, 83%; 2nd run: 124 mg, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.6, 3.8 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.24 – 7.21 (m, 1H), 7.17 (d, J = 8.5 Hz, 1H), 3.47 (d, J = 13.3 Hz, 1H), 3.32 (d, J = 13.3 Hz, 1H), 2.92 (t, J = 7.9 Hz, 2H), 1.83 (dd, J = 7.8, 3.9 Hz, 2H), 1.61 (s, 1H), 1.56 – 1.45 (m, 3H), 1.44 – 1.37 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6, 147.9, 139.4, 136.2, 129.3, 128.8, 128.3, 128.2, 127.5, 127.0, 126.7, 125.7, 121.3, 65.0, 39.5, 38.9, 34.1, 32.8, 27.7. **IR** (ncat, cm^{-1}) 3055, 3039, 2923, 2856, 1600, 1503, 1355, 825, 731, 696. **HRMS** (DART+) Calcd. for $C_{21}H_{22}N_2$ $[M+H]^+$ 303.1856, found

303.1856. **Specific rotation** $[\alpha]_D^{22} = -7.63$ (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 98:2 hexanes/2-propanol, 1.0 mL/min, t_M = 20.2 min, t_m = 23.1 min) indicated 97% ee.



3r

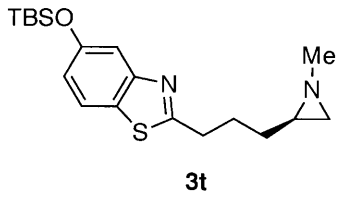
(*R*)-2-(3-(1-Benzylaziridin-2-yl)propyl)-1-tosyl-1*H*-benzo[*d*]imidaz-ole (3r): Prepared following General Procedure **A** with hydroxylamine ester **1r** (273 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–50% acetone in hexanes) the title compound was obtained as a red oil. (1st run: 180 mg, 81%; 2nd run: 174 mg, 78%; *product is not stable upon standing at rt*). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 8.05 – 7.98 (m, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.64 – 7.57 (m, 1H), 7.41 – 7.15 (m, 9H), 3.49 (d, J = 13.4 Hz, 1H), 3.32 (d, J = 13.4 Hz, 1H), 3.14 (td, J = 7.0, 1.0 Hz, 2H), 2.36 (s, 3H), 1.94 (ttd, J = 10.2, 5.4, 4.7, 2.1 Hz, 2H), 1.62 – 1.46 (m, 4H), 1.36 (d, J = 5.7 Hz, 1H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 155.50, 146.70, 142.69, 140.44, 135.94, 133.72, 130.74, 128.72, 128.57, 127.30, 127.23, 125.06, 124.95, 120.17, 114.04, 65.25, 39.77, 34.04, 32.99, 30.00, 25.71, 21.91. **IR** (neat, cm^{-1}) 3027, 2925, 1645, 1596, 1494, 1451, 1372, 1161, 1088, 1042, 764. **HRMS** (DART+) Calcd. for $C_{26}H_{27}N_3O_2S$ $[M+H]^+$ 446.1897, found 446.1889. **Specific rotation** $[\alpha]_D^{23} = -84.11$ (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 90:10 hexanes/2-propanol, 1.0 mL/min, t_m = 14.8 min, t_M = 18.7 min) indicated 96% ee.



3s

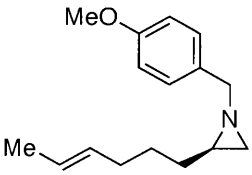
(*R*)-2-(3-(1-(2,4-Dimethoxybenzyl)aziridin-2-yl)propyl)ben-zo[*d*]-ox-azole (3s): Prepared following General Procedure **A** with hydroxylamine ester **1s** (226 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–80% acetone in hexanes) the title compound was obtained as red oil. (1st run: 130 mg, 74%; 2nd run: 126 mg, 72%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 1H), 7.45 – 7.39 (m, 1H), 7.29 – 7.22 (m, 3H), 6.44 – 6.37 (m, 2H), 3.76 (s, 3H), 3.70 (s, 3H), 3.44 (d, J = 13.3 Hz, 1H), 3.25 (d, J = 13.3 Hz, 1H), 2.84 (hept, J = 8.2, 7.7 Hz, 2H), 1.95 – 1.83 (m, 2H), 1.59 (d, J = 3.1 Hz, 1H), 1.57 – 1.41 (m, 3H), 1.38 (d, J = 5.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 160.1, 158.2, 150.9, 141.5, 130.3, 124.5, 124.1, 120.3, 119.6, 110.4, 103.9, 98.4, 58.6, 55.4, 55.4, 39.0, 33.9, 32.5, 28.2, 24.8. **IR** (neat, cm^{-1}) 2936, 2834, 1612, 1506, 1455, 1206, 1154, 1034, 831, 745. **HRMS** (DART+) Calcd. for $C_{21}H_{42}N_2O_3$ $[M+H]^+$ 353.1860, found 353.1874. **Specific**

rotation $[\alpha]_D^{23}$ = 8.81 (*c* = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 90:10 hexanes/2-propanol, 1.0 mL/min, t_M = 11.0 min, t_m = 14.4 min) indicated 98% ee.



3t

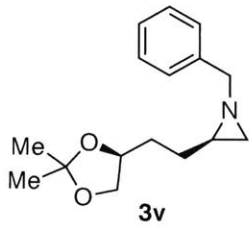
(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-(3-(1-methylaziridin-2-yl)-propyl)benzo[*d*]thiazole (3t): Prepared following General Procedure **A** with hydroxylamine ester **1t** (231 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0.5–5% MeOH in CH_2Cl_2) the title compound was obtained as a dark green oil. (1st run: 111 mg, 61%; 2nd run: 123 mg, 68%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.6 Hz, 1H), 7.41 (d, *J* = 2.3 Hz, 1H), 6.90 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.31 (s, 3H), 2.11 – 1.91 (m, *J* = 6.7 Hz, 2H), 1.66 – 1.42 (m, 3H), 1.28 (br s, 1H), 1.17 (br s, 1H), 0.99 (s, 9H), 0.21 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.2, 154.64, 154.58, 127.8, 121.7, 119.1, 113.0, 47.9, 40.3, 34.9, 34.3, 32.6, 27.8, 25.8, 18.4, -4.3. **IR** (neat, cm^{-1}) 2929, 2857, 1454, 1274, 1254, 1168, 970, 872, 838, 780. **EA** Calcd. for $C_{19}H_{30}N_2OSSi$: C, 62,94; H, 8.34. Found: C, 62.76; H, 8.18. **Specific rotation** $[\alpha]_D^{22}$ = –12.57 (*c* = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 10.0 min, t_m = 12.5 min) indicated 98% ee.



3u

(*R*,*E*)-2-(Hex-4-en-1-yl)-1-(4-methoxybenzyl)aziridine (3u): Prepared following General Procedure **A** with hydroxylamine ester **1u** (173 mg, 0.5 mmol, 1.0 equiv) and (*S*)-CuCatMix (44.3 mg, 25 μmol, 5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–35% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. (1st run: 112 mg, 91%; 2nd run: 113 mg, 92%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.35 (dt, *J* = 5.0, 2.8 Hz, 2H), 3.80 (s, 3H), 3.44 (d, *J* = 12.8 Hz, 1H), 3.26 (d, *J* = 12.9 Hz, 1H), 1.98 – 1.82 (m, 2H), 1.67 – 1.57 (m, 4H), 1.45 – 1.82 (dd, *J* = 6.2, 3.5 Hz, 1H), 1.42 – 1.33 (m, 4H), 1.19 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.8, 131.6, 131.3, 129.5, 125.0, 113.8, 64.3, 55.3, 39.7, 34.0, 32.5, 32.3, 27.4, 18.0. **IR** (neat, cm^{-1}) 2929, 2854, 2834, 1612, 1512, 1243, 1173, 1036, 965, 818. **HRMS** (DART+) Calcd. for $C_{16}H_{23}NO$ $[M+H]^+$ 246.1852, found 246.1848. **Specific rotation** $[\alpha]_D^{23}$ = 7.24 (*c* = 1.0, $CHCl_3$). **HPLC**

analysis (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 6.9 min, t_m = 8.3 min) indicated 98% ee.

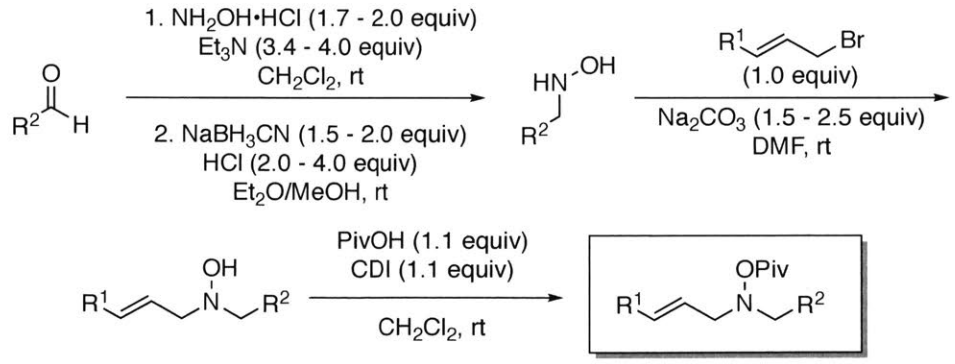


3v

(*R*)-1-Benzyl-2-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl) aziridine (3v): Prepared following General Procedure **A** with hydroxylamine ester **1v** (181 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–30% acetone in hexanes) the title compound was obtained as a pale-yellow oil. (1st run: 121 mg, 93%; 2nd run: 124 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.07 (m, 5H), 3.89 (q, J = 6.2 Hz, 1H), 3.84 (q, J = 6.6 Hz, 1H), 3.38 (d, J = 13.2 Hz, 1H), 3.31 (t, J = 7.2 Hz, 1H), 3.20 (d, J = 13.1 Hz, 1H), 1.60 – 1.34 (m, 5H), 1.29 (d, J = 6.3 Hz, 1H), 1.27 – 1.17 (m, 7H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.4, 128.5, 128.4, 127.2, 108.9, 76.0, 69.6, 65.1, 39.6, 34.2, 31.6, 29.6, 27.1, 25.9. **IR** (neat, cm^{-1}) 2981, 2934, 2867, 1453, 1378, 1368, 1213, 1158, 1056, 754, 731, 697. **HRMS** (DART+) Calcd. for $C_{16}H_{23}NO_2$ $[M+H]^+$ 262.1802, found 262.1793. **Specific rotation** $[\alpha]_D^{23}$ = 8.03 (c = 1.0, $CHCl_3$). > 20 : 1 dr as determined by NMR analysis of the crude reaction mixture.

*Synthetic Procedures and Characterization Data for Aziridination Substrates and Azetidine **4a***

*General Procedure **B** – Preparation of O-pivaloyl Allylic Hydroxylamine Esters*



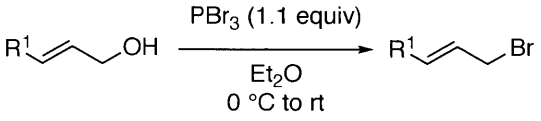
B1. Preparation of hydroxylamine:

An oven-dried round-bottom flask was charged with aldehyde (1.0 equiv), hydroxylamine hydrochloride (1.7 – 2.0 equiv), Et_3N (3.4 – 4.0 equiv), and CH_2Cl_2 (0.5 M). The reaction mixture was stirred vigorously under nitrogen at rt for 12 h. The reaction mixture was quenched by addition of water. The aqueous layer was separated and extracted twice with EtOAc using a separatory funnel. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated

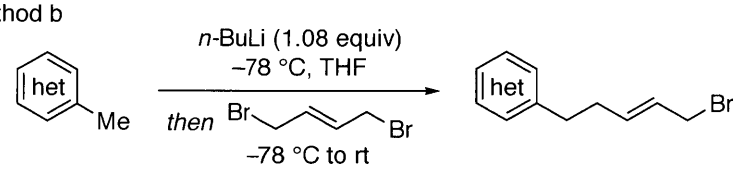
under reduced pressure. The resultant crude oxime material was diluted with MeOH (1.0 M) and methyl orange (~1 mg per 10 mmol of aldehyde) was added as a pH indicator. $NaBH_3CN$ (1.5 – 2.5 equiv) was added as a solid in small portions over 10 min, and the reaction mixture was maintained at pH < 3 (pink) with slow addition of HCl solution via syringe (2.0 M in Et_2O, 2.0 – 4.0 equiv). The reaction mixture was allowed to stir at rt for 1 – 12 h and then quenched by the addition of aqueous NaOH 2 M solution. The mixture was concentrated *under reduced pressure* until half of the original volume remained, and the mixture was extracted with EtOAc (× 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude hydroxylamine, which was directly used in subsequent reactions without further purification.

B2. Preparation of allylic bromides:

Method a



Method b



[Method a] (For substrates **1a-p**, **1u-v**): An oven-dried round-bottom flask equipped with a large stir bar was charged with the allylic alcohol (1.0 equiv) and Et_2O (0.5 M). The reaction flask was cooled to 0 °C in an ice/water bath and PBr_3 (1.1 equiv) was added dropwise via a syringe. The reaction flask was removed from the ice bath once the addition was complete and the reaction mixture was allowed to stir for 1.5 h at rt. The reaction was quenched by addition of sat. $NaHCO_3$ solution (*Caution: gas evolution!*) and the resulting solution was transferred to a separatory funnel where the aqueous layer was separated and extracted twice with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude allylic bromide was used in subsequent reactions without further purification.

[Method b] (For substrates **1q-t**): An oven-dried round-bottom flask equipped with a large stir bar was charged with the heteroarene (1.0 equiv). The reaction flask was capped with a rubber septum, the septum was punctured with a needle attached to a Schlenk line and the flask was evacuated and backfilled with argon (this process was repeated a total of three times). THF (0.2 M) was added and the reaction flask was cooled to –78 °C in a dry ice/acetone bath. *n*-BuLi (1.6 M in hexanes,

1.08 equiv) was added in one portion via syringe and the reaction was allowed to stir for 30 min at –78 °C under nitrogen atmosphere. A solution of (*E*)-1,4-dibromo-2-butene (1.0 – 1.5 equiv) in THF (3.0 M) was added in one portion via syringe and the reaction mixture was stirred at –78 °C for 45 min. The cold bath was then removed and the reaction mixture was allowed to warm to rt. The reaction was quenched by addition of sat. NH_4Cl and transferred to a separatory funnel. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography to provide the desired allylic bromide (22–57% yield).

B3. Preparation of allylic hydroxylamines:

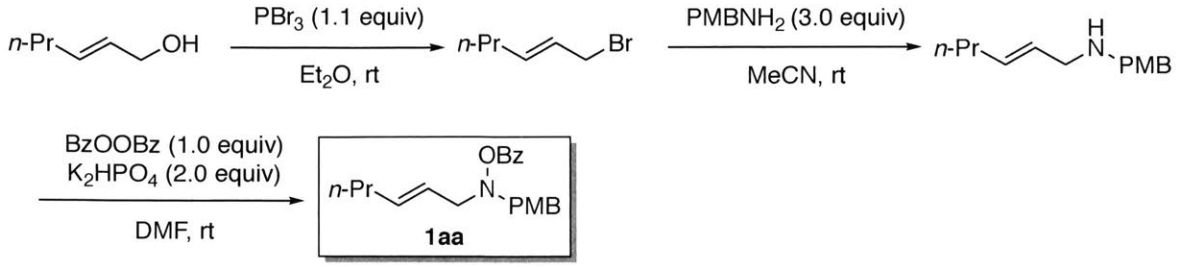
An oven-dried round-bottom flask equipped with a large magnetic stir bar was charged with allylic bromide (1.0 equiv; prepared according to General Procedure **B2**), hydroxylamine (1.0 – 8.2 equiv; prepared according to General Procedure **B1**), Na_2CO_3 (1.5 – 2.85 equiv), and DMF (0.5 M). The reaction mixture was stirred vigorously at rt until complete consumption of the starting material (2–23 h, as determined by TLC analysis). The reaction was quenched by addition of water then transferred into a separatory funnel. The aqueous layer was separated and extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography to provide the desired allylic hydroxylamines (29–88% yield).

B4. Preparation of O-pivaloyl allylic hydroxylamine ester:

An oven-dried reaction flask equipped with a magnetic stir bar was charged with pivalic acid (1.1 – 1.2 equiv) and CH_2Cl_2 (0.5 M). Carbonyldiimidazole (1.1 – 1.2 equiv) was carefully added in several small portions directly into the flask (*Caution: gas evolution!*). The mixture was allowed to stir for 15 min at rt until the reaction ceased to effervesce. Allylic hydroxylamine (1.0 equiv; prepared according to General Procedure **B3**) was added as a solution in CH_2Cl_2 (~2 M) via a syringe, and the reaction mixture was allowed to stir at rt until complete consumption of the hydroxylamine (1–24 h, as determined by TLC analysis). The reaction was quenched by addition of sat. $NaHCO_3$ solution. The aqueous layer was separated and extracted twice with EtOAc using a separatory funnel. The combined organic layers were washed with brine. The mixture was then separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under

reduced pressure, and purified via flash column chromatography to provide *O*-pivaloyl allylic hydroxylamine ester (76–99% yield).

(*E*)-*O*-Benzoyl-*N*-(hex-2-en-1-yl)-*N*-(4-methoxybenzyl) hydroxylamine (1aa)



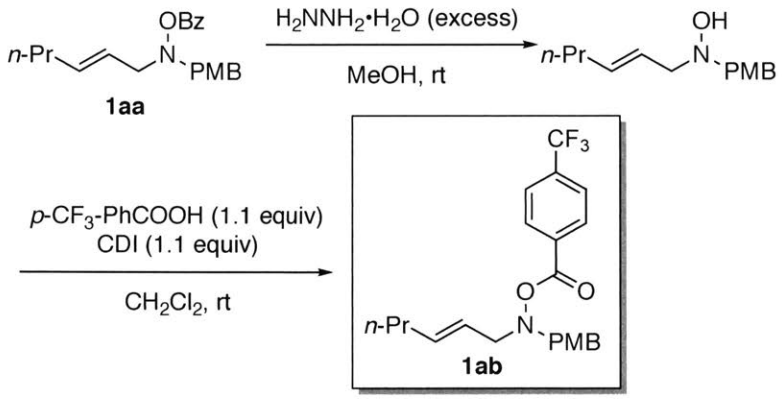
(*E*)-1-Bromohex-2-ene was prepared according to General Procedure **B2** (Method a) from (*E*)-hex-2-en-1-ol (5.9 mL, 50.0 mmol, 1.0 equiv), PBr_3 (5.2 mL, 55 mmol, 1.1 equiv), and Et_2O (100 mL). Following an aqueous workup, the crude (*E*)-1-bromohex-2-ene mixture was used in the next part of the procedure without further purification.

A 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*E*)-1-Bromohex-2-ene (6.8 g, 41.7 mmol, 1.0 equiv) and MeCN (52 mL). Using a syringe, the solution was added dropwise into a vigorously stirred solution of *p*-methoxybenzylamine (16.3 mL, 125 mmol, 3.0 equiv) in MeCN (10 mL) at rt in a 250 mL oven-dried round-bottom flask. After stirring for 12 h, the reaction mixture was washed with sat. $NaHCO_3$ solution (500 mL) using a separatory funnel. The aqueous layer was separated and extracted with EtOAc (300 mL × 2). The combined organic layers were washed with brine (500 mL). The mixture was then separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (10–60% EtOAc/hexanes) to provide (*E*)-*N*-(4-methoxybenzyl)hex-2-en-1-amine as a yellow oil. **Yield:** 4.64 g, 51%. This material was used directly in the next part of the procedure.

A 50 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*E*)-*N*-(4-Methoxybenzyl)hex-2-en-1-amine (4.64 g, 21 mmol, 1.2 equiv; prepared above) and DMF (20 mL). Using a glass pipette, the solution was slowly added to a slurry of benzoyl peroxide (5.64 g, 17.5 mmol, 1 equiv) and K_2HPO_4 (6.09 g, 35 mmol, 2.0 equiv) in DMF (20 mL) at rt in a 500 mL oven-dried round-bottom flask. After 9 h, the reaction was quenched by the addition of water (200 mL). The aqueous layer was separated and extracted with EtOAc (150 mL × 2) using a

separatory funnel. The combined organic layers were washed with brine (300 mL). The mixture was then separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, under reduced pressure, and purified via flash column chromatography (4–16% EtOAc in hexanes) to provide the title compound as a yellow oil. **Yield:** 5.20 g, 88%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 – 7.81 (m, 2H), 7.56 – 7.46 (m, 1H), 7.38 (td, J = 7.8, 1.5 Hz, 2H), 7.35 – 7.30 (m, 2H), 6.88 – 6.69 (m, 2H), 5.66 (td, J = 3.7, 1.8 Hz, 2H), 4.11 (s, 2H), 3.75 (d, J = 2.6 Hz, 3H), 3.61 (d, J = 3.4 Hz, 2H), 2.03 – 1.90 (m, 2H), 1.30 (h, J = 7.4 Hz, 2H), 0.80 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.2, 159.1, 136.3, 132.9, 130.9, 129.5, 129.4, 128.3, 127.9, 124.3, 113.7, 61.8, 60.6, 55.2, 34.5, 22.3, 13.6. **IR** (neat, cm^{-1}) 1741, 1512, 1241, 1173, 1083, 1062, 1025, 969, 812, 706. **EA** Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42. Found: C, 74.23; H, 7.38.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-(4-(trifluoromethyl)benzoyl)hydroxyl amine (1ab)

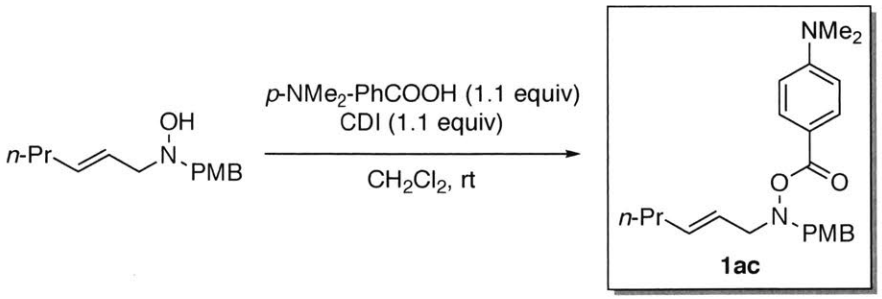


A 500 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with allylic hydroxylamine ester **1aa** (4.62 g, 13.6 mmol, 1.0 equiv) and MeOH (130 mL; degassed by repeated sonication under light vacuum for 0.5 min and refilling the atmosphere with argon). Using a syringe, hydrazine hydrate (6.85 mL) was added at rt (*Note: employ caution when using hydrazine. All hydrazine-containing wastes should be dealt with properly*). After 38 h, the reaction was concentrated under reduced pressure, then redissolved in water (100 mL) and EtOAc (100 mL). The aqueous layer was separated using a separatory funnel and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with brine (300 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (5–25% EtOAc in hexanes) to provide (*E*)-*N*-(hex-2-

en-1-yl)-*N*-(4-methoxybenzyl) hydroxylamine as a light-yellow oil. **Yield:** 3.23 g, >99%. A portion of this material was used in the next part of the procedure.

A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with *p*-trifluoromethylbenzoic acid (194 mg, 1.02 mmol, 1.2 equiv) and CH_2Cl_2 (1.0 mL). Carbonyldiimidazole (168 mg, 1.02 mmol, 1.2 equiv) was added carefully as several portions directly into the flask (*Caution: gas evolution!*). The mixture was allowed to stir for 15 min at rt until the reaction ceased to effervesce. Using a syringe, (*E*)-*N*-(Hex-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (200 mg, 0.85 mmol, 1.0 equiv; prepared above) was added as a CH_2Cl_2 solution (0.7 mL) and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (2–10% EtOAc in hexanes) to provide the title compound as a yellow oil. **Yield:** 318 mg, 92%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 7.4 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 7.8 Hz, 2H), 5.74 – 5.52 (m, 2H), 4.12 (s, 2H), 3.76 (d, J = 3.0 Hz, 3H), 3.63 (d, J = 4.7 Hz, 2H), 2.03 – 1.87 (m, 2H), 1.29 (dtd, J = 15.6, 8.3, 7.8, 6.7 Hz, 2H), 0.80 (td, J = 7.4, 1.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.0, 159.3, 136.6, 134.4 (q, J_{CF} = 32.6 Hz), 132.9, 130.9, 129.8, 127.8, 125.4 (q, J_{CF} = 3.7 Hz), 124.2, 123.7 (q, J_{CF} = 272.7 Hz), 113.9, 62.0, 60.9, 55.30, 34.5, 22.3, 13.6. **^{19}F NMR** (376 MHz, $CDCl_3$) -63.16. **IR** (neat, cm^{-1}) 1745, 1513, 1323, 1246, 1172, 1128, 1078, 1065, 1016, 769, 699. **EA** Calcd. for $C_{22}H_{24}F_3NO_3$: C, 64.86; H, 5.94. Found: C, 65.15; H, 6.09.

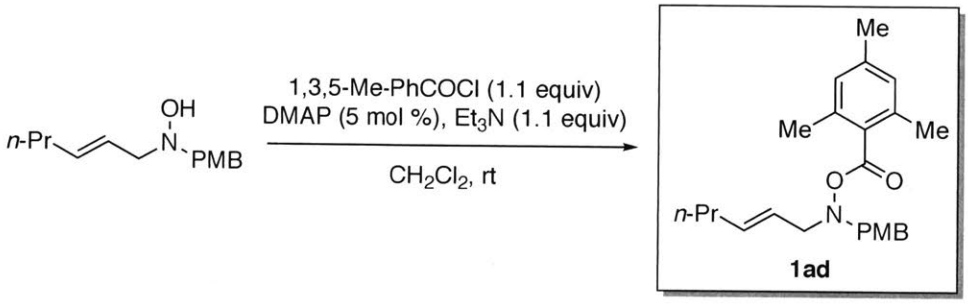
(*E*)-4-(((Hex-2-en-1-yl(4-methoxybenzyl)amino)oxy)carbonyl)-*N*,*N*-dimethylaniline (1ac)



An oven-dried screw-cap reaction tube (13 mm × 100 mm) equipped with a magnetic stir bar was charged with *p*-dimethylaminobenzoic acid (182 mg, 1.1 mmol, 1.1 equiv) and CH_2Cl_2 (1 mL). Carbonyldiimidazole (178 mg, 1.1 mmol, 1.1 equiv) was added carefully as several portions directly into the tube (*Caution: gas evolution!*). The mixture was allowed to stir for 15 min at rt

until the reaction ceased to effervesce. Using a syringe, (*E*)-*N*-(Hex-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (235 mg, 1.0 mmol, 1.0 equiv; see **1ab** for the preparation procedure) was added as a CH_2Cl_2 solution (1.0 mL) and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (10–30% EtOAc in hexanes) to provide the hydroxylamine ester **1ac** as a pale-yellow oil. **Yield:** 393 mg, >99%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 5.65 (td, J = 5.4, 4.0 Hz, 2H), 4.09 (s, 2H), 3.76 (s, 3H), 3.57 (d, J = 4.8 Hz, 2H), 3.01 (s, 6H), 1.97 (td, J = 7.3, 5.1 Hz, 2H), 1.32 (h, J = 7.4 Hz, 2H), 0.82 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.6, 159.0, 153.3, 136.0, 131.1, 131.0, 128.2, 124.5, 116.1, 113.6, 110.7, 61.5, 60.3, 55.2, 40.1, 34.6, 22.3, 13.7. **IR** (neat, cm^{-1}) 1721, 1604, 1512, 1366, 1265, 1248, 1179, 1171, 1069, 763. **EA** Calcd. for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91. Found: C, 71.94; H, 7.89.

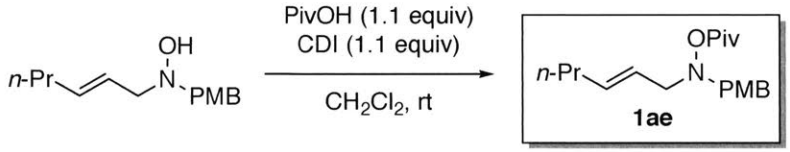
(*E*)-4-(((Hex-2-en-1-yl(4-methoxybenzyl)amino)oxy)carbonyl)-*N*,*N*-dimethylaniline (1ad)



An oven-dried screw-cap reaction tube (13 mm × 100 mm) tube equipped with a magnetic stir bar was charged with (*E*)-*N*-(hex-2-en-1-yl)-*N*-(4-methoxybenzyl)-hydroxylamine (150 mg, 0.64 mmol, 1.0 equiv; see **1ab** for its preparation procedures), DMAP (3.9 mg, 30 μmol, 5 mol%) and CH_2Cl_2 (0.4 mL), followed by Et_3N (98 μL, 0.70 mmol, 1.1 equiv). The reaction tube was cooled to 0 °C in an ice/water bath, and a solution of 2,4,6-trimethyl benzoyl chloride (117 μL, 0.70 mmol, 1.1 equiv) in CH_2Cl_2 (0.4 mL) was slowly added to the reaction mixture using a syringe. The reaction mixture was warmed to rt. After 2 h, the reaction was quenched by addition of sat. $NaHCO_3$ solution (2 mL). Using a separatory funnel, the aqueous layer was separated and extracted with EtOAc (2 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (0–15% EtOAc in hexanes) to provide the title compound as a colorless oil. **Yield:** 196 mg, 81%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H),

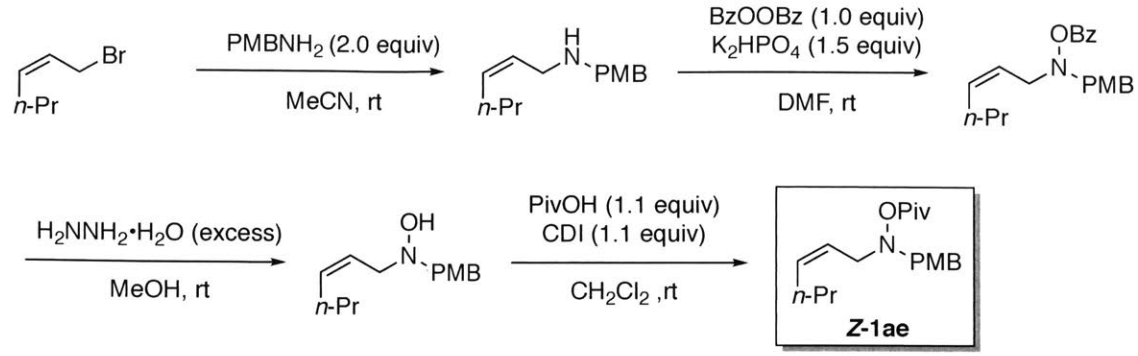
6.77 (s, 2H), 5.76 – 5.64 (m, 2H), 4.06 (s, 2H), 3.79 (s, 3H), 3.68 (d, J = 5.0 Hz, 2H), 2.24 (s, 3H), 2.07 – 1.98 (m, 8H), 1.41 (h, J = 7.3 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.8, 159.3, 139.3, 136.2, 135.2, 130.7, 129.9, 128.6, 128.2, 124.4, 113.8, 61.5, 60.9, 55.4, 34.6, 22.3, 21.2, 19.4, 13.9. **IR** (neat, cm^{-1}) 2956, 2926, 1747, 1612, 1513, 1243, 1161, 1057, 1035, 971, 850. **EA** Calcd. for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19. Found: C, 75.44; H, 8.31.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (1ae)



(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (**1ae**) was prepared according to General Procedure **B4** with (*E*)-*N*-(hex-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (1.0 g, 4.25 mmol, 1.0 equiv; see **1ab** for its preparation procedures), carbonyldiimidazole (758 mg, 4.67 mmol, 1.1 equiv), pivalic acid (477 mg, 4.67 mmol, 1.1 equiv), and CH_2Cl_2 (4.5 mL), the reaction mixture was quenched after 24 h. After workup and purification by flash column chromatography (2–10% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. **Yield:** 1.24 g, 92%. **^{1}H NMR** (500 MHz, $CDCl_3$) 7.26 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.78 – 5.37 (m, 2H), 3.94 (s, 2H), 3.77 (s, 3H), 3.47 (d, J = 5.5 Hz, 2H), 1.98 (q, J = 6.8 Hz, 2H), 1.37 (h, J = 7.4 Hz, 2H), 1.03 (s, 9H), 0.88 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.4, 159.1, 135.9, 130.9, 128.2, 124.4, 113.6, 61.9, 60.7, 55.3, 38.5, 34.6, 27.2, 22.3, 13.8. **IR** (neat, cm^{-1}) 2958, 2930, 2870, 2835, 1750, 1612, 1513, 1246, 1118, 1035, 968, 821. **EA** Calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.68; H, 9.21.

(*Z*)-*N*-(Hex-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (*Z*-1ae)



A 100 mL oven-dried round-bottom flask was charged with (*Z*)-1-bromohex-2-ene (~10 mmol, 1.0 equiv; see **1aa** for a similar preparation procedure from (*Z*)-hex-2-en-1-ol) and MeCN (30 mL). Using a syringe, the solution was added dropwise into a vigorously stirred solution of 4-methoxybenzylamine (2.6 mL, 20 mmol, 2.0 equiv) in MeCN (10 mL) in a 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar at rt. After stirring for 18 h, the reaction mixture was concentrated under reduced pressure to ~25% the original volume. After workup and purification by flash column chromatographyy (10–60% EtOAc in hexanes) (*Z*)-*N*-(4-methoxybenzyl)hex-2-en-1-amine was obtained as a yellow oil. **Yield:** 1.0 g, 46%. A portion of this material was used in the next part of the procedure.

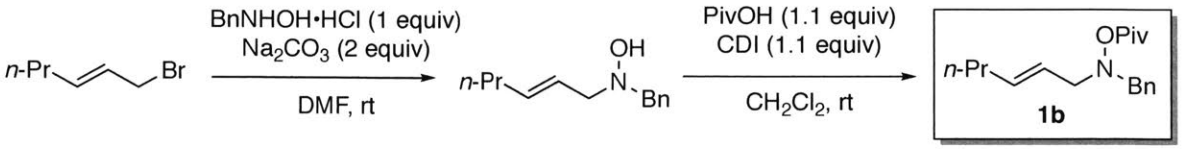
A 100 mL oven-dried round-bottom flask equipped with a large magnetic stir bar was charged with (*Z*)-*N*-(4-methoxybenzyl)hex-2-en-1-amine (576 mg, 2.63 mmol, 1.05 equiv; prepared above), benzoyl peroxide (865 mg, 2.5 mmol, 1.0 equiv), K_2HPO_4 (653 mg, 3.75 mmol, 1.5 equiv), and DMF (5.0 mL). The reaction mixture was stirred vigorously at rt for 7 h and the reaction was quenched by addition of water (75 mL). After workup and purification by flash column chromatographyy (10–14% EtOAc in hexanes) (*Z*)-*O*-benzoyl-*N*-(hex-2-en-1-yl)-*N*-(4-methoxybenzyl)-hydroxylamine was obtained as a pale-yellow oil. **Yield:** 768 mg, 90%. A portion of this material was used in the next part of the procedure.

A 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*Z*)-*O*-benzoyl-*N*-(hex-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (689 mg, 2.03 mmol, 1.0 equiv; prepared above) and MeOH (20 mL; degassed by repeated sonication under light vacuum for 0.5 min and refilling the atmosphere with argon). Using a syringe, hydrazine hydrate (1 mL) was added at rt (*Note: employ caution when using hydrazine. All hydrazine-containing wastes*

should be dealt with properly.). After 24 h, the reaction was concentrated under reduced pressure and redissolved in sat. $NaHCO_3$ solution (50 mL) and EtOAc (50 mL). The aqueous layer was separated using a separatory funnel and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (5–25% EtOAc in hexanes) to provide (*Z*)-*N*-(hex-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine as a yellow solid. **Yield:** 459 mg, 96%. This material was used directly in the next part of this procedure.

(*Z*)-*N*-(Hex-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (***Z*-1ae**) was prepared according to General Procedure **B4** with (*Z*)-*N*-(hex-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (459 mg, 1.95 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (348 mg, 2.14 mmol, 1.1 equiv), pivalic acid (219 mg, 2.14 mmol, 1.1 equiv), and CH_2Cl_2 (2 mL), the reaction mixture was quenched after 3 h. After workup and purification by flash column chromatographyy (1–8% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. **Yield:** 572 mg, 92%. **^{1}H NMR** (500 MHz, $CDCl_3$) 7.28 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.63 – 5.53 (m, 2H), 3.96 (s, 2H), 3.78 (s, 3H), 3.59 (d, J = 4.5 Hz, 2H), 2.03 (q, J = 6.8 Hz, 2H), 1.38 (h, J = 7.5 Hz, 2H), 1.03 (s, 9H), 0.90 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.5, 159.2, 134.0, 130.8, 128.3, 124.0, 113.6, 62.0, 55.4, 55.3, 38.5, 29.8, 27.3, 22.8, 13.9. **IR** (neat, cm^{-1}) 2957, 2932, 2871, 2837, 1750, 1613, 1513, 1246, 1115, 1035, 819, 769. **EA** Calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.48; H, 9.21.

(*E*)-*N*-Benzyl-*N*-(hex-2-en-1-yl)-*O*-pivaloylhydroxylamine (1b)



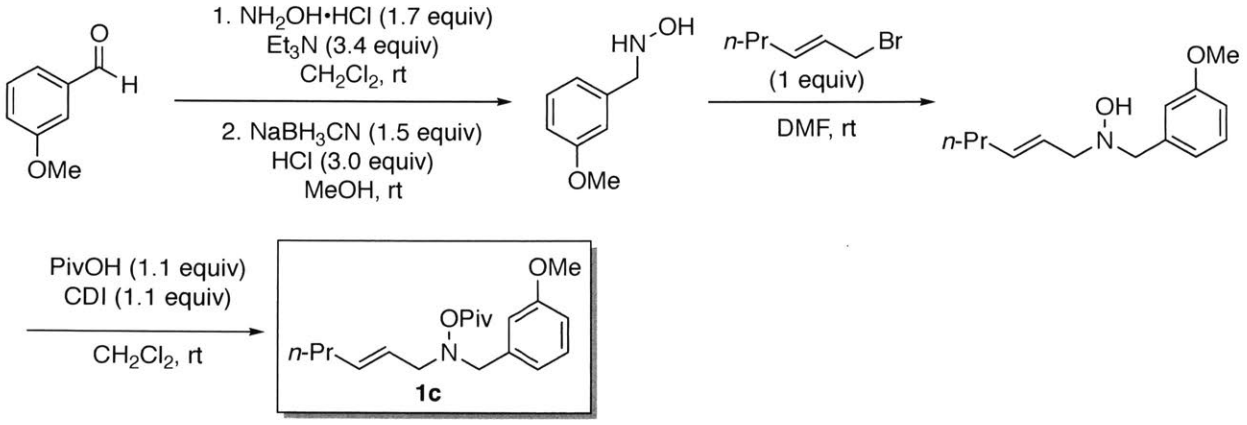
The title compound was prepared following General Procedure **B**.

(*E*)-*N*-Benzyl-*N*-(hex-2-en-1-yl)hydroxylamine was prepared according to General Procedure **B3** from the benzyl hydroxylamine hydrochloride salt (883 mg, 5.53 mmol, 1.0 equiv), the crude (*E*)-1-bromohex-2-ene mixture (902 mg, 5.53 mmol, 1.0 equiv; see **1aa** for the preparation procedure), Na_2CO_3 (1.17 g, 11.06 mmol, 2.0 equiv), and DMF (11 mL), the reaction mixture was quenched after 5 h. After workup and purification by flash column chromatographyy (2–12% EtOAc in

hexanes) (*E*)-*N*-benzyl-*N*-(hex-2-en-1-yl)hydroxylamine was obtained as a pale yellow oil. **Yield:** 745 mg, 65%. A portion of this material was used in the next part of the procedure.

(*E*)-*N*-Benzyl-*N*-(hex-2-en-1-yl)-*O*-pivaloylhydroxylamine (**1b**) was prepared according to General Procedure **B4** with (*E*)-*N*-benzyl-*N*-(hex-2-en-1-yl)hydroxylamine (700 mg, 3.41 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (608 mg, 3.75 mmol, 1.1 equiv), pivalic acid (383 mg, 3.75 mmol, 1.1 equiv), and CH_2Cl_2 (3.4 mL), the reaction mixture was quenched after 3 h. After workup and purification by flash column chromatographyy (2–12% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. **Yield:** 916 mg, 93%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 2H), 7.29 (ddt, *J* = 7.9, 6.3, 1.2 Hz, 2H), 7.26 – 7.19 (m, 1H), 5.71 – 5.48 (m, 2H), 4.01 (s, 2H), 3.51 (d, *J* = 5.3 Hz, 2H), 2.16 – 1.86 (m, 2H), 1.38 (h, *J* = 7.3 Hz, 2H), 1.01 (s, 9H), 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 136.3, 136.1, 129.6, 128.3, 127.6, 124.4, 62.5, 61.1, 38.5, 34.6, 27.2, 22.4, 13.9. **IR** (neat, cm^{-1}) 2958, 2929, 2872, 1751, 1113, 967, 737, 697. **EA** Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40. Found: C, 74.78; H, 9.56.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(3-methoxybenzyl)-*O*-pivaloylhydroxylamine (1c)



The title compound was prepared following General Procedure **B**.

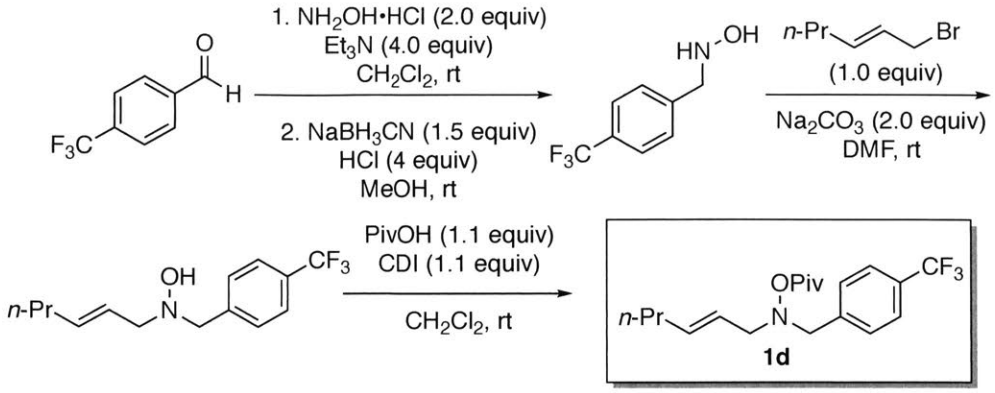
(*E*)-3-Methoxybenzaldehyde oxime was prepared according to General Procedure **B1** from 3-methoxybenzaldehyde (2.44 mL, 20 mmol, 1.0 equiv), hydroxylamine hydrochloride (2.36 g, 34 mmol, 1.7 equiv), Et_3N (9.4 mL, 68 mmol, 3.4 equiv), and CH_2Cl_2 (40 mL). Following an aqueous workup, the crude (*E*)-3-methoxybenzaldehyde oxime material was reduced to *N*-(3-methoxybenzyl)hydroxylamine using $NaBH_3CN$ (1.89 g, 30 mmol, 1.5 equiv), methyl orange (~1 mg), HCl (30 mL, 60 mmol, 3.0 equiv; 2.0 M in Et_2O), and MeOH (20 mL). Following an aqueous

workup, the crude *N*-(3-methoxybenzyl)hydroxylamine mixture was used in the next part of this procedure without further purification.

The allylic hydroxylamine was prepared according to General Procedure **B3** from the crude *N*-(3-methoxybenzyl)hydroxylamine mixture (~20 mmol, 1.0 equiv; prepared above), the crude (*E*)-1-bromohex-2-ene mixture (~20 mmol, 1.0 equiv; see **1aa** for the preparation procedure), Na_2CO_3 (3.2 g, 30 mmol, 1.5 equiv), and DMF (40 mL), the reaction mixture was quenched after 12 h. After workup and purification by flash column chromatographyy (0–25% EtOAc in hexanes) (*E*)-*N*-(hex-2-en-1-yl)-*N*-(3-methoxybenzyl)hydroxylamine was obtained as a pale yellow oil. **Yield:** 3.45 g, 73%. A portion of this material was used in the next part of the procedure.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(3-methoxybenzyl)-*O*-pivaloylhydroxylamine (**1c**) was prepared according to General Procedure **B4** with (*E*)-*N*-(hex-2-en-1-yl)-*N*-(3-methoxybenzyl)hydroxylamine (941 mg, 4.0 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (713 mg, 4.4 mmol, 1.1 equiv), pivalic acid (450 mg, 4.4 mmol, 1.1 equiv), and CH_2Cl_2 (8.0 mL), the reaction mixture was quenched after 7 h. After workup and purification by flash column chromatography (0–30% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. **Yield:** 973 mg, 76%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (t, J = 7.9 Hz, 1H), 6.95 (s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.84 – 6.72 (m, 1H), 5.62 (q, J = 5.3 Hz, 2H), 4.00 (s, 2H), 3.79 (s, 3H), 3.51 (d, J = 5.1 Hz, 2H), 2.00 (td, J = 7.7, 7.3, 5.1 Hz, 2H), 1.38 (h, J = 7.4 Hz, 2H), 1.01 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4, 159.6, 137.9, 136.1, 129.1, 124.4, 121.7, 114.3, 113.7, 62.4, 61.1, 55.4, 38.5, 34.6, 27.2, 22.4, 13.9. **IR** (neat, cm^{-1}) 2958, 2930, 2872, 2836, 1750, 1603, 1264, 1113, 1042, 968, 778. **EA** Calcd. for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.19; H, 9.19.

(*E*)-*N*-(Hex-2-en-1-yl)-*O*-pivaloyl-*N*-(4-(trifluoromethyl)benzyl)hydroxylamine (1d)



The title compound was prepared following General Procedure **B**.

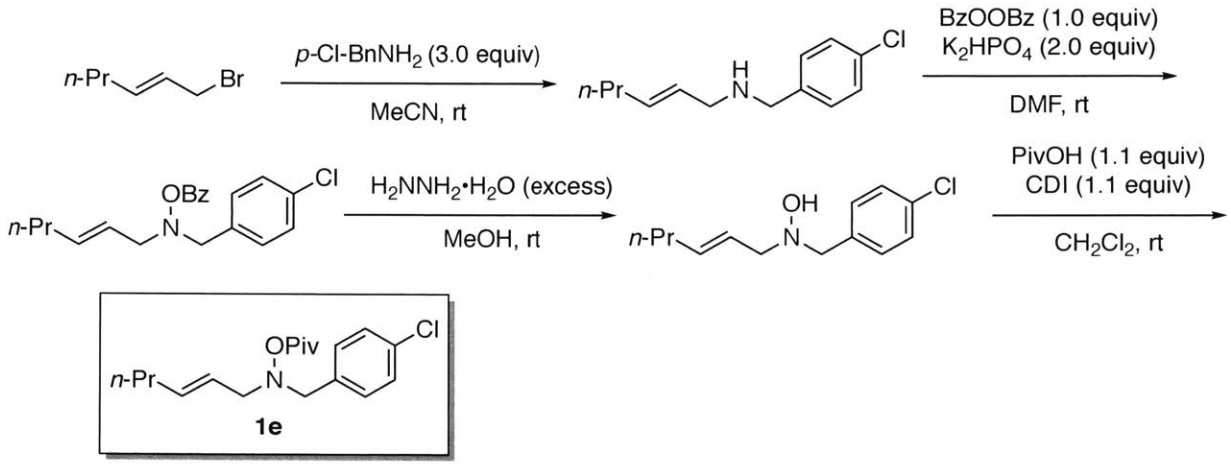
(*E*)-4-(Trifluoromethyl)benzaldehyde oxime was prepared according to General Procedure **B1** from *p*-trifluoromethylbenzaldehyde (1.12 g, 6.43 mmol, 1.0 equiv), hydroxylamine hydrochloride (894 mg, 12.86 mmol, 2.0 equiv), Et_3N (3.6 mL, 25.7 mmol, 4.0 equiv), and CH_2Cl_2 (9.5 mL). Following an aqueous workup, the crude (*E*)-4-(trifluoromethyl)benzaldehyde oxime (793 mg, 4.2 mmol, 1.0 equiv) was reduced to *N*-(4-(trifluoromethyl)benzyl)hydroxylamine using $NaBH_3CN$ (395 mg, 6.3 mmol, 1.5 equiv), methyl orange (0.5 mg), HCl (4.2 mL, 16.8 mmol, 4.0 equiv; 4.0 M in dioxane), and MeOH (4.2 mL). Following an aqueous workup, the crude *N*-(4-(trifluoromethyl) benzyl)hydroxylamine mixture was used in the next part of this procedure without further purification.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(4-(trifluoromethyl)benzyl)hydroxylamine was prepared according to General Procedure **B3** from the crude *N*-(4-(trifluoromethyl)benzyl) hydroxylamine mixture (607 mg, 3.18 mmol, 1.0 equiv; prepared above), the crude (*E*)-1-bromohex-2-ene mixture (518 mg, 3.18 mmol, 1.0 equiv; see **1aa** for the preparation procedure), Na_2CO_3 (674 mg, 6.35 mmol, 2.0 equiv), and DMF (6 mL), the reaction mixture was quenched after 13 h. After workup and purification by flash column chromatography (1–16% EtOAc in pentane) (*E*)-*N*-(hex-2-en-1-yl)-*N*-(4-(trifluoromethyl)benzyl)hydroxylamine was obtained as a white solid. **Yield:** 660 mg, 76%. This material was directly used in the next part of this procedure.

(*E*)-*N*-(Hex-2-en-1-yl)-*O*-pivaloyl-*N*-(4-(trifluoromethyl)benzyl)hydroxylamine (**1d**) was prepared according to General Procedure **B4** with (*E*)-*N*-(hex-2-en-1-yl)-*N*-(4-(trifluoromethyl)benzyl)hydroxylamine (660 mg, 2.41 mmol, 1.0 equiv; prepared above),

carbonyldiimidazole (431 mg, 2.66 mmol, 1.1 equiv), pivalic acid (271 mg, 2.66 mmol, 1.1 equiv), and CH_2Cl_2 (2.4 mL), the reaction mixture was quenched after 21 h. After workup and purification by flash column chromatography (1–8% EtOAc/hexanes) the title compound was obtained as a pale-yellow oil. **Yield:** 833 mg, 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 5.62 (qt, J = 15.3, 6.3 Hz, 2H), 4.05 (s, 2H), 3.53 (d, J = 6.1 Hz, 2H), 2.00 (q, J = 6.9 Hz, 2H), 1.38 (h, J = 7.3 Hz, 2H), 0.97 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.3, 140.6, 136.5, 129.8 (q, J_{CF} = 32.3, 31.6 Hz), 129.53, 125.2 (q, J_{CF} = 4.0 Hz), 124.3 (q, J_{CF} = 272.8, 271.8 Hz), 124.0, 61.8, 61.4, 38.4, 34.6, 27.1, 22.3, 13.8. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.40. **IR** (neat, cm^{-1}) 2960, 1751, 1323, 1163, 1113, 1066, 1019, 968, 820. **EA** Calcd. for $C_{19}H_{26}F_3NO_2$: C, 63.85; H, 7.33. Found: C, 64.05; H, 7.40.

(*E*)-*N*-(4-Chlorobenzyl)-*N*-(hex-2-en-1-yl)-O-pivaloylhydroxylamine (1e)



A 100 mL oven-dried round-bottom flask was charged with (*E*)-1-bromohex-2-ene (~15 mmol, 1.0 equiv; see **1aa** for the preparation procedure) and MeCN (45 mL). Using a syringe, the solution was added dropwise into a vigorously stirred solution of 4-chlorobenzylamine (5.47 mL, 45 mmol, 3.0 equiv) in MeCN (3.0 mL) in a 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar at rt. After stirring for 12 h, the reaction mixture was concentrated under reduced pressure to ~25% the original volume. After workup and purification by flash column chromatography (0–60% EtOAc in hexanes) (*E*)-*N*-(4-chlorobenzyl)hex-2-en-1-amine was obtained as a yellow oil. **Yield:** 1.2 g, 36%. A portion of this material was used for the next part of this procedure.

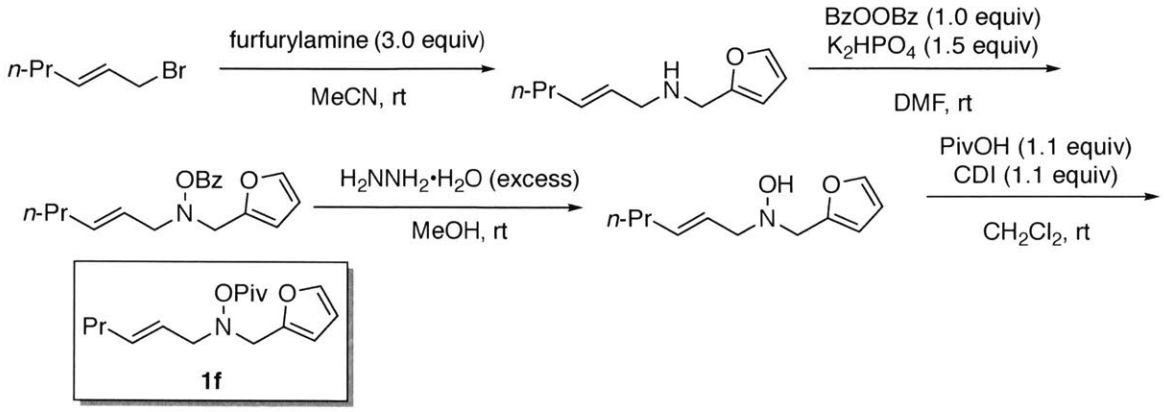
A 100 mL oven-dried round-bottom flask equipped with a large magnetic stir bar was charged with (*E*)-*N*-(4-chlorobenzyl)hex-2-en-1-amine (685 mg, 3.06 mmol, 1.02 equiv; prepared above), benzoyl peroxide (969 mg, 3.0 mmol, 1.0 equiv), K_2HPO_4 (784 mg, 4.5 mmol, 3.0 equiv), and DMF (6.0 mL), the reaction mixture was stirred vigorously at rt for 7 h and the reaction was quenched by addition of water (20 mL). After workup and purification by flash column chromatography (0–15% EtOAc/hexanes) (*E*)-*O*-benzoyl-*N*-(4-chlorobenzyl)-*N*-(hex-2-en-1-yl)-hydroxylamine was obtained as a yellow oil. **Yield:** 825 mg, 78%. This material was directly used for the next part of this procedure.

A 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*E*)-*O*-benzoyl-*N*-(4-chlorobenzyl)-*N*-(hex-2-en-1-yl)hydroxylamine (825 mg, 2.4 mmol, 1.0 equiv; prepared above) and MeOH (24 mL; degassed by repeated sonication under light vacuum for 0.5 min and refilling the atmosphere with argon). Using a syringe, hydrazine hydrate (1.2 mL) was added at rt (*Note: employ caution when using hydrazine. All hydrazine-containing wastes should be dealt with properly.)*. After 24 h, the reaction was concentrated under reduced pressure and redissolved in sat. $NaHCO_3$ solution (30 mL) and EtOAc (30 mL). The aqueous layer was separated using a separatory funnel and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (4–20% EtOAc in hexanes) to provide (*E*)-*N*-(4-chlorobenzyl)-*N*-(hex-2-en-1-yl)hydroxylamine as a pale yellow oil. **Yield:** 418 mg, 73%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(4-Chlorobenzyl)-*N*-(hex-2-en-1-yl)-*O*-pivaloylhydroxylamine (**1e**) was prepared according to General Procedure **B4** with (*E*)-*N*-(4-chlorobenzyl)-*N*-(hex-2-en-1-yl)-hydroxylamine (418 mg, 1.74 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (311 mg, 1.92 mmol, 1.1 equiv), pivalic acid (196 mg, 1.92 mmol, 1.1 equiv), and CH_2Cl_2 (2.0 mL), the reaction mixture was quenched after 5 h After workup and purification by flash column chromatography (2–6% EtOAc in hexanes) the title compound was obtained as a pale yellow oil. **Yield:** 530 mg, 94%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 5.61 (qt, J = 15.5, 6.3 Hz, 2H), 3.96 (s, 2H), 3.50 (d, J = 6.1 Hz, 2H), 2.00 (q, J = 6.9 Hz, 2H), 1.38 (h, J = 7.4 Hz, 2H), 1.01 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$)

δ 176.3, 136.3, 134.9, 133.4, 130.8, 128.4, 124.1, 61.6, 61.2, 38.5, 34.6, 27.2, 22.3, 13.9. **IR** (neat, cm^{-1}) 2958, 2930, 2873, 1753, 1492, 1247, 1114, 1016, 968, 807. **EA** Calcd. for $C_{18}H_{26}ClNO_2$: C, 66.76; H, 8.09. Found: C, 66.87; H, 8.20.

(*E*)-*N*-(Furan-2-ylmethyl)-*N*-(hex-2-en-1-yl)-*O*-pivaloylhydroxylamine (1f)



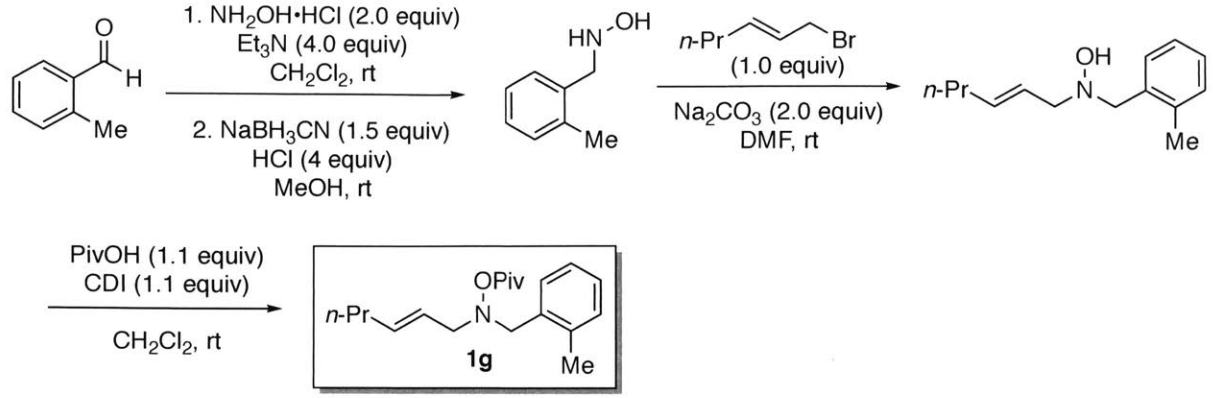
A 100 mL oven-dried round-bottom flask was charged with (*E*)-1-bromohex-2-ene (~25 mmol, 1.0 equiv; see **1aa** for the preparation procedure) and MeCN (75 mL). Using a syringe, the solution was added dropwise into a vigorously stirred solution of furan-2-ylmethanamine (6.63 mL, 75 mmol, 3.0 equiv) in MeCN (5.0 mL) in a 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar at rt. After stirring for 18 h, the reaction mixture was concentrated under reduced pressure to ~25% the original volume. After workup and purification by flash column chromatography (0–50% acetone/hexanes) (*E*)-*N*-(furan-2-ylmethyl)hex-2-en-1-amine was obtained as a colorless oil. **Yield:** 2.30 g, 51%. This material was directly used for the next part of this procedure.

A 100 mL oven-dried round-bottom flask equipped with a large magnetic stir bar was charged with (*E*)-*N*-(furan-2-ylmethyl)hex-2-en-1-amine (2.30 g, 12.8 mmol, 1.01 equiv; prepared above), benzoyl peroxide (4.093 g, 12.67 mmol, 1.0 equiv), K_2HPO_4 (3.31 g, 19.0 mmol, 3.0 equiv), and DMF (24 mL). The reaction mixture was stirred vigorously at rt for 15 h and the reaction was quenched by addition of water (50 mL). After workup and purification by flash column chromatography (10% EtOAc in hexanes) (*E*)-*O*-benzoyl-*N*-(furan-2-ylmethyl)-*N*-(hex-2-en-1-yl)-hydroxylamine was obtained as a colorless oil. **Yield:** 2.73 g, 83%. A portion of this material was used for the next part of this procedure.

A 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*E*)-*O*-benzoyl-*N*-(furan-2-ylmethyl)-*N*-(hex-2-en-1-yl)hydroxylamine (1.31 g, 5.0 mmol, 1.0 equiv; prepared above) and MeOH (50 mL; degassed by repeated sonication under light vacuum for 0.5 min and refilling the atmosphere with argon). Using a syringe, hydrazine hydrate (2.5 mL) was added at rt (*Note: employ caution when using hydrazine. All hydrazine-containing wastes should be dealt with properly.)*. After 20 h, the reaction was concentrated under reduced pressure and partitioned between sat. $NaHCO_3$ solution (50 mL) and EtOAc (50 mL). The aqueous layer was separated using a separatory funnel and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (25% EtOAc in hexanes) to provide (*E*)-*N*-(furan-2-ylmethyl)-*N*-(hex-2-en-1-yl)hydroxylamine as a colorless oil. **Yield:** 812 mg, 83%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(Furan-2-ylmethyl)-*N*-(hex-2-en-1-yl)-*O*-pivaloylhydroxylamine (**1f**) was prepared according to General Procedure **B4** using (*E*)-*N*-(furan-2-ylmethyl)-*N*-(hex-2-en-1-yl)hydroxylamine (812 mg, 4.16 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (742 mg, 4.58 mmol, 1.1 equiv), pivalic acid (467 mg, 4.58 mmol, 1.1 equiv) and CH_2Cl_2 (9 mL), the reaction mixture was quenched after 15 h. The crude residue was purified by flash column chromatography (0–20% EtOAc in hexanes) to provide the title compound as a colorless yellow oil. **Yield:** 1.10 g, 95%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 1.1 Hz, 1H), 6.31 (dd, J = 3.2, 1.8 Hz, 1H), 6.25 (d, J = 2.9 Hz, 1H), 5.70 – 5.51 (m, 2H), 4.03 (s, 2H), 3.48 (d, J = 6.3 Hz, 2H), 1.99 (q, J = 7.6, 6.9 Hz, 2H), 1.37 (h, J = 7.4 Hz, 2H), 1.11 (s, 9H), 0.88 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 149.9, 142.4, 136.3, 124.2, 110.4, 109.7, 60.5, 54.1, 38.5, 34.6, 27.3, 22.3, 13.9. **IR** (neat, cm^{-1}) 2958, 2931, 2873, 1750, 1480, 1115, 732. **EA** Calcd. for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02. Found: C, 68.95; H, 9.19.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(2-methylbenzyl)-*O*-pivaloylhydroxylamine (1g)



The title compound was prepared following General Procedure **B**.

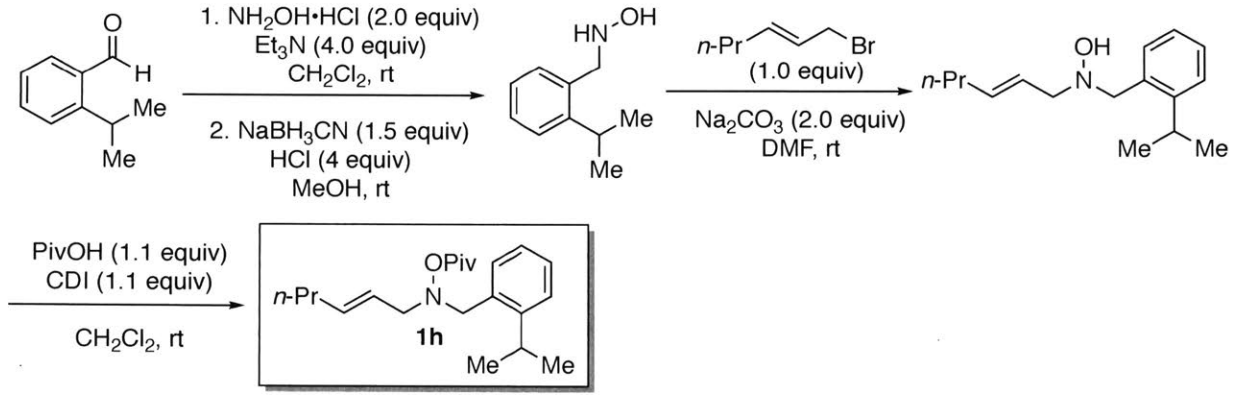
(*E*)-2-Methylbenzaldehyde oxime was prepared according to General Procedure **B1** from *o*-methylbenzaldehyde (2.40 g, 20.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (2.78 g, 40.0 mmol, 2.0 equiv), Et_3N (11.1 mL, 80.0 mmol, 4.0 equiv), and CH_2Cl_2 (28 mL). Following an aqueous workup, the crude oxime was reduced to the corresponding hydroxylamine using $NaBH_3CN$ (1.89 g, 30 mmol, 1.5 equiv), methyl orange (2.4 mg), HCl (20 mL, 80 mmol, 4.0 equiv; 4.0 M in dioxane), and MeOH (20 mL). Following an aqueous workup, the crude *N*-(2-methylbenzyl)hydroxylamine mixture was directly used for the next part of this procedure without further purification.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(2-methylbenzyl)hydroxylamine was prepared according to General Procedure **B3** from the crude *N*-(2-methylbenzyl)hydroxylamine mixture (686 mg, 5.0 mmol, 1.0 equiv; prepared above), the crude (*E*)-1-bromohex-2-ene mixture (815 mg, 5.0 mmol, 1.0 equiv; see **1aa** for the preparation procedure), Na_2CO_3 (1.06 g, 10.0 mmol, 2.0 equiv), and DMF (10 mL), the reaction mixture was quenched after 14 h. After workup and purification by flash column chromatography (2–10% EtOAc in hexanes) (*E*)-*N*-(hex-2-en-1-yl)-*N*-(2-methylbenzyl)hydroxylamine was obtained as a yellow oil. **Yield:** 956 mg, 87%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(2-methylbenzyl)-*O*-pivaloylhydroxylamine (**1g**) was prepared according to General Procedure **B4** with (*E*)-*N*-(hex-2-en-1-yl)-*N*-(2-methylbenzyl)hydroxylamine (956 mg, 4.36 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (777 mg, 4.80 mmol, 1.1 equiv), pivalic acid (490 mg, 4.80 mmol, 1.1 equiv),

and CH_2Cl_2 (4.5 mL), the reaction mixture was quenched after 4 h. After workup and purification by flash column chromatography (1–4% EtOAc in hexanes) the title compound was obtained as a yellow oil. **Yield:** 1.17 g, 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (d, J = 7.4 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.10 (td, J = 7.1, 2.4 Hz, 1H), 5.62 (qt, J = 15.6, 6.3 Hz, 2H), 3.99 (s, 2H), 3.50 (d, J = 6.1 Hz, 2H), 2.45 (s, 3H), 2.01 (q, J = 6.9 Hz, 2H), 1.39 (h, J = 7.4 Hz, 2H), 1.03 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.3, 137.9, 135.8, 134.4, 130.5, 130.3, 127.7, 125.5, 124.6, 61.1, 60.4, 38.4, 34.6, 27.2, 22.4, 19.6, 13.9. **IR** (neat, cm^{-1}) 2958, 2929, 2872, 1751, 1110, 967, 759, 742 cm^{-1}. **EA** Calcd. for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63. Found: C, 75.51; H, 9.74.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(2-isopropylbenzyl)-*O*-pivaloylhydroxylamine (1h)



The title compound was prepared following General Procedure **B**.

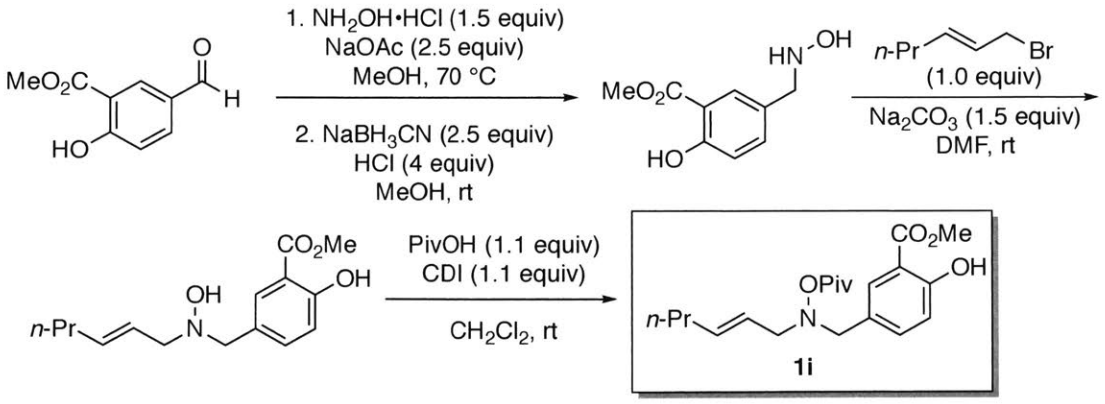
(*E*)-2-Isopropylbenzaldehyde oxime was prepared according to General Procedure **B1** from *o*-isopropylbenzaldehyde (2.53 g, 17.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (2.37 g, 34.1 mmol, 2.0 equiv), Et_3N (9.5 mL, 68.3 mmol, 4.0 equiv), and CH_2Cl_2 (25 mL). Following an aqueous workup, the crude (*E*)-2-isopropylbenzaldehyde oxime mixture was reduced to *N*-(2-isopropylbenzyl)hydroxylamine using $NaBH_3CN$ (1.60 g, 25.5 mmol, 1.5 equiv), methyl orange (2.0 mg), HCl (34 mL, 68 mmol, 4.0 equiv; 2.0 M in Et_2O), and MeOH (17 mL). After workup and purification by flash column chromatography (10–60% EtOAc in hexanes) to provide *N*-(2-isopropylbenzyl)hydroxylamine as a pale yellow oil. **Yield:** 2.80 g, 99%. A portion of this material was used for the next part of this procedure.

N-(2-Isopropylbenzyl)hydroxylamine was prepared according to General Procedure **B3** from *N*-(2-isopropylbenzyl)hydroxylamine (826 mg, 5.0 mmol, 1.0 equiv; prepared above), the crude (*E*)-1-bromohex-2-ene mixture (815 mg, 5.0 mmol, 1.0 equiv; see **1aa** for the preparation procedure),

Na_2CO_3 (1.06 g, 10.0 mmol, 2.0 equiv), and DMF (10 mL), the reaction mixture was quenched after 6 h. After workup and purification by flash column chromatography (2–12% EtOAc in hexanes) *N*-(2-isopropylbenzyl) hydroxylamine was obtained as a white solid. **Yield:** 815 mg, 66%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(Hex-2-en-1-yl)-*N*-(2-isopropylbenzyl)-*O*-pivaloylhydroxylamine (**1h**) was prepared according to General Procedure **B4** with *N*-(2-isopropylbenzyl)hydroxylamine (815 mg, 3.29 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (588 mg, 3.62 mmol, 1.1 equiv), pivalic acid (370 mg, 3.62 mmol, 1.1 equiv), and CH_2Cl_2 (4.0 mL), the reaction mixture was quenched using an aqueous workup after 2 h. After workup and purification by flash column chromatography (1–4% EtOAc in hexanes) title compound was obtained as a yellow oil. **Yield:** 1.03 g, 94%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.10 (td, J = 7.2, 1.4 Hz, 1H), 5.62 (qt, J = 15.3, 6.3 Hz, 2H), 4.04 (s, 2H), 3.52 – 3.43 (m, 3H), 2.00 (q, J = 6.9 Hz, 2H), 1.38 (h, J = 7.4 Hz, 2H), 1.25 (d, J = 6.9 Hz, 6H), 1.04 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.2, 148.4, 135.7, 133.0, 130.8, 128.1, 125.4, 125.3, 124.7, 60.9, 59.8, 38.4, 34.6, 28.6, 27.2, 24.0, 22.4, 13.8. **IR** (neat, cm^{-1}) 2959, 2928, 2869, 1751, 1456, 1271, 1114, 1027, 968, 759. **EA** Calcd. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03. Found: C, 76.31; H, 10.07.

Methyl (*E*)-5-((hex-2-en-1-yl(pivaloyloxy)amino)methyl)-2-hydroxybenzoate (1i)



The title compound was prepared following General Procedure **B**.

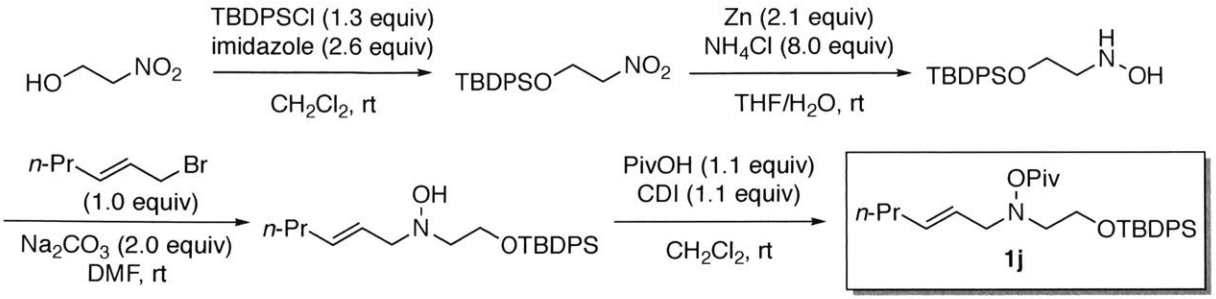
An oven-dried 50 mL round-bottom flask was charged with methyl 5-formyl-2-hydroxybenzoate (1.80 g, 10.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.04 g, 15.0 mmol, 1.5 equiv), NaOAc (2.1 g, 25 mmol, 2.5 equiv), and MeOH (20 mL). The mixture was heated at 70 °C for 15

h then cooled to rt. Following an aqueous workup, the crude methyl (*E*)-2-hydroxy-5-((hydroxyimino)methyl)benzoate mixture was reduced to the corresponding hydroxylamine according to General Procedure **B1** using $NaBH_3CN$ (1.50 g, 25.0 mmol, 2.5 equiv), methyl orange (~1.0 mg), HCl (20 mL, 40 mmol, 4.0 equiv; 2.0 M in Et_2O), and MeOH (20 mL). Following an aqueous workup, the crude methyl 2-hydroxy-5-((hydroxyamino)methyl)benzoate mixture was directly used for the next part of this procedure without further purification.

Methyl (*E*)-5-((hex-2-en-1-yl(hydroxy)amino)methyl)-2-hydroxybenzoate was prepared according to General Procedure **B3** from the crude methyl 2-hydroxy-5-((hydroxyamino)methyl)benzoate (~10.0 mmol, 1.0 equiv; prepared above), the crude (*E*)-1-bromohex-2-ene mixture (~10.0 mmol, 1.0 equiv; see **1aa** for the preparation procedure), Na_2CO_3 (1.60 g, 15.0 mmol, 1.5 equiv), and DMF (25 mL), the reaction mixture was quenched after 15 h. After workup and purification by flash column chromatography (20% EtOAc in hexanes) methyl (*E*)-5-((hex-2-en-1-yl(hydroxy)amino)methyl)-2-hydroxybenzoate was obtained as a colorless oil. **Yield:** 1.84 g, 66%. A portion of this material was used for the next part of this procedure.

Methyl (*E*)-5-((hex-2-en-1-yl(pivaloyloxy)amino)methyl)-2-hydroxy-benzoate (**1i**) was prepared according to General Procedure **B4** with methyl (*E*)-5-((hex-2-en-1-yl(hydroxy)amino)methyl)-2-hydroxybenzoate (1.12 g, 4.0 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (714 mg, 4.4 mmol, 1.1 equiv), pivalic acid (450 mg, 4.4 mmol, 1.1 equiv), and CH_2Cl_2 (8.0 mL), the reaction mixture was quenched after 3 h. After workup and purification by flash column chromatography (10% EtOAc in hexanes) the title compound was obtained as a white crystalline solid, **m.p.** 69–71 °C. **Yield:** 1.21 g, 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 7.82 (s, 1H), 7.46 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 5.74 – 5.49 (m, 2H), 4.02 – 3.85 (m, 5H), 3.49 (d, J = 5.8 Hz, 2H), 2.00 (q, J = 6.9 Hz, 2H), 1.38 (q, J = 7.4 Hz, 2H), 1.04 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 170.5, 161.0, 137.1, 136.1, 130.9, 126.9, 124.1, 117.4, 111.9, 61.3, 60.7, 52.2, 38.4, 34.4, 27.1, 22.2, 13.7. **IR** (neat, cm^{-1}) 3228, 2960, 2928, 2868, 1755, 1668, 1489, 1439, 1336, 1119, 1083. **EA** Calcd. for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04. Found: C, 65.81; H, 8.18.

(*E*)-*N*-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-*N*-(hex-2-en-1-yl)-*O*-pivaloyl hydroxyl-amine (1j)



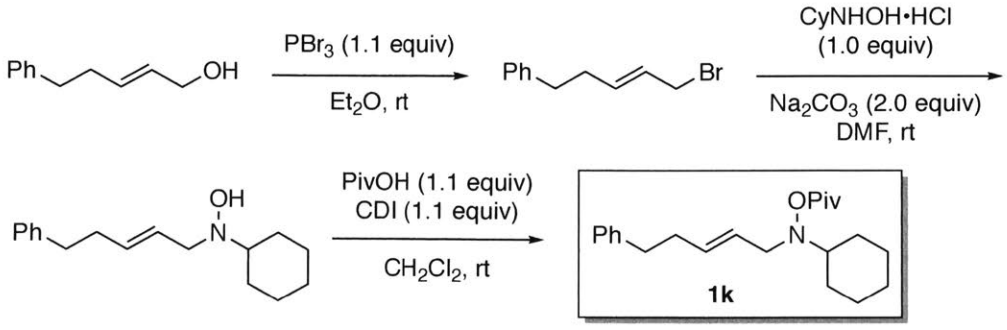
An oven-dried 250 mL round bottom flask equipped with a magnetic stir bar was charged with 2-nitroethan-1-ol (2.15 mL, 30.0 mmol, 1.0 equiv), and CH_2Cl_2 (60 mL). TBDPSCl (10.1 mL, 39.0 mmol, 1.3 equiv) was added using a syringe, followed by the addition of imidazole (5.31g, 78.0 mmol, 2.6 equiv) as one portion. The flask was then sealed with a rubber septum and purged with nitrogen for 10 minutes, then allowed to stir for 16 h at rt. The reaction mixture was quenched by addition of water (100 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (100 mL × 2) using a separatory funnel. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (1–20% EtOAc in hexanes) to provide *tert*-butyl(2-nitroethoxy)diphenylsilane as a white solid. **Yield:** 8.04 g, 82%. A portion of this material was used for the next part of this procedure.

An oven-dried 100 mL round bottom flask equipped with a magnetic stir bar was charged with *tert*-butyl(2-nitroethoxy)diphenylsilane (2.0 g, 6.1 mmol, 1.0 equiv; prepared above), THF (18 mL) and water (3.0 mL). The reaction flask was cooled to 0 °C using an ice/water bath. Zn powder (836 mg, 12.7 mmol, 2.1 equiv) was added portion-wise, followed by slow addition of a solution of NH_4Cl (2.6 g, 48.6 mmol, 8.0 equiv) in water (9 mL) via syringe over 10 min. The mixture was allowed to stir for 1 h at 0 °C and then warmed to rt. After 16 h, the reaction mixture was quenched by addition of sat. $NaHCO_3$ solution (60 mL). The reaction mixture was then poured into a separatory funnel and extracted with EtOAc (60 mL). The aqueous layer was separated and extracted with EtOAc (60 mL × 2). The combined organic layers were washed with brine (200 mL). The organic layer was separated, dried with anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (10–80% EtOAc in hexanes) to provide the title compound as a yellow solid. **Yield:** 1.04 g, 54%. A portion of this material was used for the next part of this procedure.

(*E*)-*N*-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-*N*-(hex-2-en-1-yl)hydroxylamine was prepared according to General Procedure **B3** from *N*-(2-((*tert*-butyldiphenyl-silyl)oxy)ethyl)hydroxylamine (880 mg, 2.79 mmol, 1.0 equiv; prepared above), the crude (*E*)-1-bromohex-2-ene mixture (450 mg, 2.79 mmol, 1.0 equiv; see **1aa** for the preparation procedure), Na_2CO_3 (590 mg, 5.58 mmol, 2.0 equiv), and DMF (5.6 mL), the reaction mixture was quenched after 3 h 30 min. After workup and purification by flash column chromatography (4–16% EtOAc/hexanes) (*E*)-*N*-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-*N*-(hex-2-en-1-yl)hydroxylamine was obtained as a colorless oil. **Yield:** 641 mg, 58%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-*N*-(hex-2-en-1-yl)-*O*-pivaloylhydroxyl-amine (**1j**) was prepared according to General Procedure **B4** with (*E*)-*N*-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-*N*-(hex-2-en-1-yl)hydroxylamine (641 mg, 1.61 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (288 mg, 1.77 mmol, 1.1 equiv), pivalic acid (181 mg, 1.77 mmol, 1.1 equiv), and CH_2Cl_2 (2.0 mL), the reaction mixture was quenched after 2 h. After workup and purification by flash column chromatography (2–6% EtOAc in hexanes) the title compound was obtained as a pale-yellow oil. **Yield:** 648 mg, 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 4H), 7.46 – 7.32 (m, 6H), 5.70 – 5.37 (m, 2H), 3.82 (dd, *J* = 7.7, 6.5 Hz, 2H), 3.50 (d, *J* = 6.3 Hz, 2H), 3.11 (t, *J* = 7.1 Hz, 2H), 1.99 (q, *J* = 6.8 Hz, 2H), 1.38 (h, *J* = 7.4 Hz, 2H), 1.07 (s, 9H), 1.05 (s, 9H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4, 135.9, 135.6, 133.6, 129.7, 127.8, 124.2, 62.0, 61.1, 59.8, 38.4, 34.5, 27.2, 26.9, 22.3, 19.2, 13.8. **IR** (neat, cm^{-1}) 2957, 2931, 2857, 1753, 1105, 823, 737, 700, 689, 614. **EA** Calcd. for $C_{29}H_{43}NO_3Si$: C, 72.30; H, 9.00. Found: C, 72.48; H, 9.04.

(*E*)-*N*-Cyclohexyl-*N*-(5-phenylpent-2-en-1-yl)-*O*-pivaloylhydroxylamine (1k)



The title compound was prepared following General Procedure **B**.

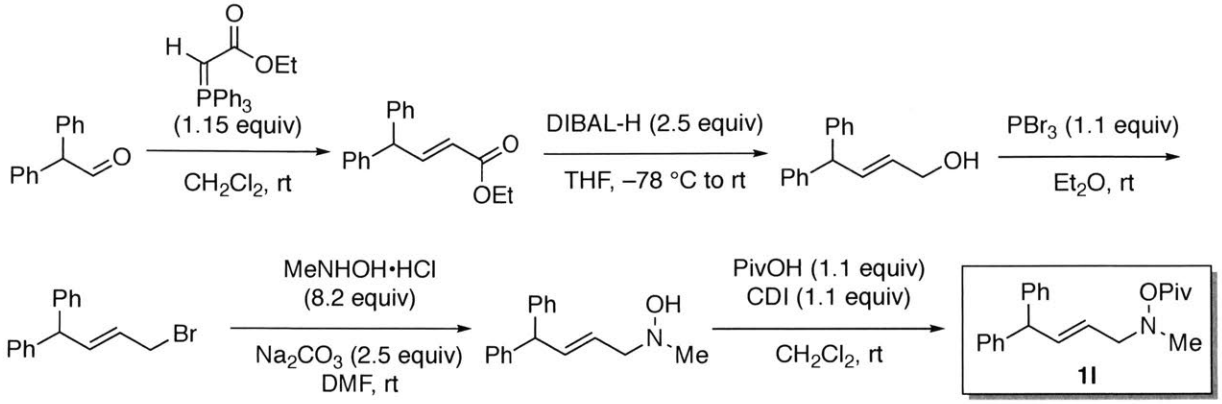
(*E*)-(5-Bromopent-3-en-1-yl)benzene was prepared according to General Procedure **B2** (Method a) from (*E*)-5-phenylpent-2-en-1-ol (630 mg, 3.9 mmol, 1.0 equiv; prepared according to literature)[3], PBr_3 (0.40 mL, 4.3 mmol, 1.1 equiv), and Et_2O (8.0 mL). Following an aqueous workup, the crude (*E*)-(5-bromopent-3-en-1-yl)benzene mixture was directly used for the next part of this procedure without further purification.

(*E*)-*N*-Cyclohexyl-*N*-(5-phenylpent-2-en-1-yl)hydroxylamine was prepared according to General Procedure **B3** from the *N*-cyclohexyl hydroxylamine hydrochloride salt (591 mg, 3.9 mmol, 1.0 equiv), the crude (*E*)-(5-bromopent-3-en-1-yl)benzene mixture (1.0 equiv; prepared above), Na_2CO_3 (823 mg, 7.8 mmol, 2.0 equiv), and DMF (10 mL), the reaction mixture was quenched after 2 h. After workup and purification by flash column chromatography (5–40% EtOAc in hexanes) (*E*)-*N*-cyclohexyl-*N*-(5-phenylpent-2-en-1-yl)hydroxylamine was obtained as a pale-yellow oil. **Yield:** 497 mg, 49%. This material was directly used for the next part of this procedure.

(*E*)-*N*-Cyclohexyl-*N*-(5-phenylpent-2-en-1-yl)-*O*-pivaloylhydroxylamine (**1k**) was prepared according to General Procedure **B4** with (*E*)-*N*-cyclohexyl-*N*-(5-phenylpent-2-en-1-yl)hydroxylamine (497 mg, 1.92 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (342 mg, 2.11 mmol, 1.1 equiv), pivalic acid (215 mg, 2.11 mmol, 1.1 equiv), and CH_2Cl_2 (2.5 mL), the reaction mixture was quenched after 4 h. After workup and purification by flash column chromatography (4–16% EtOAc in hexanes) the title compound was obtained as a yellow oil. **Yield:** 573 mg, 87%. = **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.6 Hz, 2H), 7.22 – 7.08 (m, 3H), 5.76 – 5.50 (m, 2H), 3.49 (d, J = 5.6 Hz, 2H), 2.74 (ddd, J = 10.7, 7.3, 2.9 Hz, 1H), 2.67 (t, J = 7.9 Hz, 2H), 2.37 – 2.28 (m, 2H), 1.89 (d, J = 10.2 Hz, 2H), 1.78 (d, J = 11.3 Hz, 2H), 1.62 (d, J = 12.3 Hz, 1H), 1.31 – 1.19 (m, 4H), 1.19 (s, 9H), 1.16 – 1.05 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.8, 141.9, 134.2, 128.5, 128.4, 125.9, 125.6, 64.6, 57.4, 38.8, 35.6, 34.2, 29.0, 27.5, 26.0, 25.3. **IR** (neat, cm^{-1}) 2930, 2855, 1752, 1453, 1117, 969, 744, 698. **EA** Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 77.15; H, 9.70.

[3] Race, N. J.; Bower, J. F. *Org. Lett.* **2013**, *15*, 4616.

(*E*)-*N*-(4,4-Diphenylbut-2-en-1-yl)-*N*-methyl-*O*-pivaloylhydroxylamine (1l)



A 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 2,2-diphenylacetaldehyde (7.1 mL, 40.0 mmol, 1.0 equiv) and CH_2Cl_2 (80 mL). Ethyl (triphenylphosphoranylidene)acetate (16.0 g, 46.0 mmol, 1.15 equiv) was added as a solid in one portion and the resulting reaction mixture was stirred for 20 h at rt. The reaction mixture was then diluted with 60% EtOAc in hexanes (100 mL) and filtered through a plug of silica gel. The silica gel plug was washed with additional 60% EtOAc in hexanes (800 mL). The filtrate was concentrated under reduced pressure and purified via flash column chromatography (1–8% EtOAc in hexanes) to provide ethyl (*E*)-4,4-diphenylbut-2-enoate as a white solid. **Yield:** 6.76 g, 64%. This material was used for the next part of this procedure.

A 500 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with ethyl (*E*)-4,4-diphenylbut-2-enoate (6.76 g, 25.4 mmol, 1.0 equiv; prepared above) and THF (25 mL). The reaction flask was capped with a rubber septum and purged with argon by puncturing the septum with a needle attached to an argon-filled Schlenk manifold and kept under an argon atmosphere. The reaction flask was cooled to –78 °C using a dry ice/acetone bath and DIBAL-H (63 mL, 63.0 mmol, 2.5 equiv; 1.0 M solution in hexanes) was added slowly using a syringe into the reaction flask. After 40 min, the reaction flask was warmed to 0 °C using an ice/water bath and kept at 0 °C for 2 h. The reaction was worked up following Fieser workup[4] procedures: first diluted with Et_2O (150 mL) at 0 °C using an ice/water bath; water (2.5 mL) was slowly added via syringe, followed by addition of 15% NaOH solution (2.5 mL); another portion of water (6.3 mL) was added; and the reaction mixture was warmed to rt and stirred for 15 min; $MgSO_4$ was added and

[4] Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1; Wiley: New York, 1967; pp 581–595.

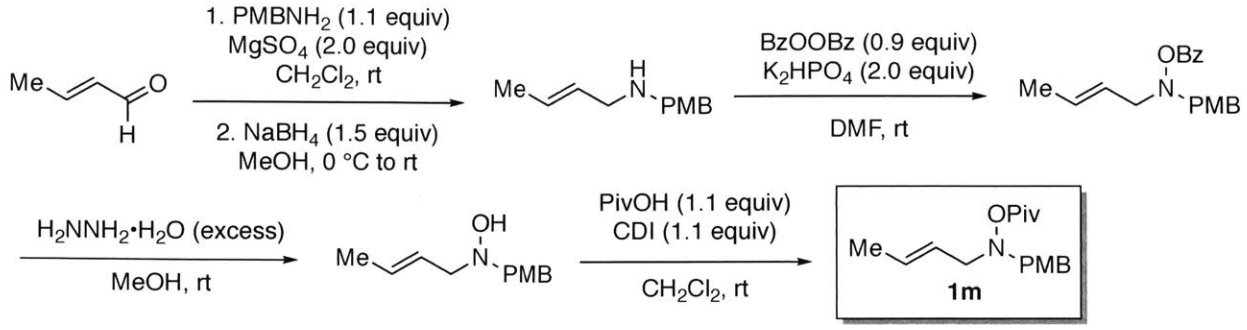
the reaction mixture was stirred for an additional 15 min; The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to provide (*E*)-4,4-diphenylbut-2-en-1-ol as a colorless oil. **Yield:** 5.45 g, 96%. A portion of this material was directly used for the next part of this procedure.

(*E*)-(4-Bromobut-2-ene-1,1-diyl)dibenzene was prepared according to General Procedure **B2** (Method a) from (*E*)-4,4-diphenylbut-2-en-1-ol (2.24 g, 10.0 mmol, 1.0 equiv; prepared above), PBr_3 (1.0 mL, 11.0 mmol, 1.1 equiv) and Et_2O (20 mL). Following an aqueous workup, the crude (*E*)-(4-bromobut-2-ene-1,1-diyl)dibenzene mixture was directly used for the next part of this procedure without further purification.

(*E*)-*N*-(4,4-Diphenylbut-2-en-1-yl)-*N*-methylhydroxylamine was prepared according to General Procedure **B3** with modified reagent amounts from the *N*-methyl hydroxylamine hydrochloride salt (4.6 g, 55.1 mmol, 8.2 equiv), the crude (*E*)-(4-bromobut-2-ene-1,1-diyl)dibenzene mixture (1.93 g, 6.72 mmol, 1.0 equiv; prepared above), Na_2CO_3 (1.78 g, 16.8 mmol, 2.5 equiv), and DMF (13 mL), the reaction mixture was quenched after 2 h. After workup and purification by flash column chromatography (10–60% EtOAc in hexanes) (*E*)-*N*-(4,4-diphenylbut-2-en-1-yl)-*N*-methylhydroxylamine was obtained as a yellow oil. **Yield:** 551 mg, 33%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(4,4-Diphenylbut-2-en-1-yl)-*N*-methyl-*O*-pivaloylhydroxylamine (**1l**) was prepared according to General Procedure **B4** with (*E*)-*N*-(4,4-diphenylbut-2-en-1-yl)-*N*-methylhydroxylamine (551 mg, 2.17 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (387 mg, 2.39 mmol, 1.1 equiv), pivalic acid (244 mg, 2.39 mmol, 1.1 equiv), and CH_2Cl_2 (2.2 mL), the reaction mixture was quenched after 1 h. After workup and purification by flash column chromatography (10–20% EtOAc in hexanes) the title compound was obtained as a yellow oil. **Yield:** 644 mg, 88%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.6 Hz, 4H), 7.20 (d, J = 7.3 Hz, 2H), 7.17 (d, J = 7.9 Hz, 4H), 6.15 (dd, J = 15.3, 7.6 Hz, 1H), 5.56 (dt, J = 15.6, 6.6 Hz, 1H), 4.72 (d, J = 7.5 Hz, 1H), 3.52 (d, J = 6.6 Hz, 2H), 2.72 (s, 3H), 1.10 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.4, 143.3, 137.4, 128.6, 128.5, 126.5, 126.4, 62.7, 54.0, 46.0, 38.4, 27.2. **IR** (neat, cm^{-1}) 2969, 1748, 1493, 1452, 1273, 1120, 1070, 1028, 975, 756, 740, 698. **EA** Calcd. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06. Found: C, 78.24; H, 8.11.

(*E*)-*N*-(But-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (1m)



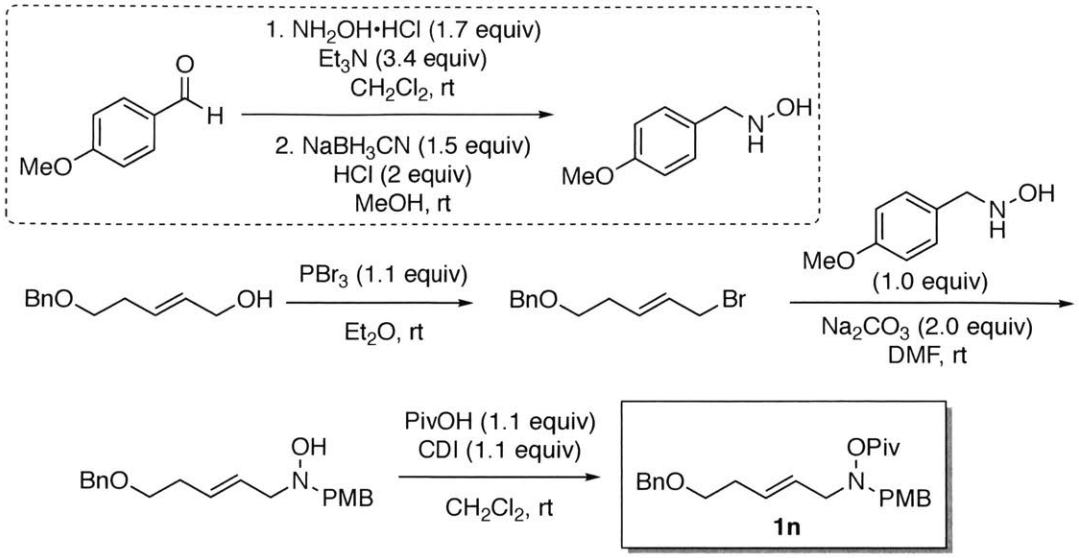
A 250 mL oven-dried flask was charged with crotonaldehyde (4.2 mL, 50.0 mmol, 1.0 equiv), $MgSO_4$ (12.0 g, 100.0 mmol, 2.0 equiv) and CH_2Cl_2 (50 mL). *p*-Methoxybenzyl amine (7.2 mL, 55 mmol, 1.1 equiv) was added dropwise using a syringe. The resulting mixture was allowed to stir at rt for 15 min before it was filtered and concentrated under reduced pressure. The resulting reaction crude material was dissolved in MeOH (50 mL) and the reaction flask was cooled to 0 °C using an ice/water bath. $NaBH_4$ (2.85 g, 75 mmol, 1.5 equiv) was added in several portions directly into the reaction flask. The reaction mixture was warmed to rt after 1 h and quenched with sat. $NaHCO_3$ solution (200 mL). The resulting mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (200 mL × 3). The combined organic layers were washed with brine (500 mL). The mixture was then separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (10–100% EtOAc in hexanes with 1% Et_3N) to provide (*E*)-*N*-(4-methoxybenzyl)but-2-en-1-amine. **Yield:** 5.81 g, 61%. A portion of this material was used for the next part of this procedure.

A 50 mL oven-dried round-bottom flask was charged wih (*E*)-*N*-(4-Methoxybenzyl)but-2-en-1-amine (1.91 g, 10.0 mmol, 1.0 equiv; prepared above) and DMF (15 mL). The solution was added dropwise using a glass pipette to a slurry of benzoyl peroxide (2.91 g, 9.0 mmol, 0.9 equiv; 75 wt%) and K_2HPO_4 (3.48 g, 20.0 mmol, 2.0 equiv) in DMF (10 mL) in a 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar at rt. After 6 h, the reaction was quenched by the addition of water (200 mL). After workup and purification by flash column chromatography (2–16% EtOAc in hexanes) (*E*)-*O*-benzoyl-*N*-(but-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine was obtained as a yellow oil. **Yield:** 2.31 g, 82%. This material was directly used for the next part of this procedure.

A 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*E*)-*O*-benzoyl-*N*-(but-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (2.31 g, 7.42 mmol, 1.0 equiv; prepared above) and MeOH (74 mL; degassed by repeated sonication under light vacuum for 0.5 min and refilling the atmosphere with argon). Using a syringe, hydrazine hydrate (3.7 mL) was added at rt (*Note: employ caution when using hydrazine. All hydrazine-containing wastes should be dealt with properly.)*. After 22 h, the reaction was concentrated under reduced pressure and redissolved in EtOAc (80 mL) and sat. $NaHCO_3$ solution (80 mL). The aqueous layer was separated using a separatory funnel and extracted with EtOAc (80 mL × 2). The combined organic layers were washed with brine (150 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (5–40% EtOAc in hexanes) to provide (*E*)-*N*-(but-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine as a pale-yellow oil. **Yield:** 1.34 g, 87%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(But-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (**1m**) was prepared according to General Procedure **B4** with (*E*)-*N*-(but-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (1.34 g, 6.47 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (1.15 g, 7.11 mmol, 1.1 equiv), pivalic acid (726 mg, 7.11 mmol, 1.1 equiv) and CH_2Cl_2 (6.5 mL), the reaction mixture was quenched after 3 h. After workup and purification by flash column chromatography (2–16% EtOAc in hexanes) the title compound was obtained as a colorless oil. **Yield:** 1.63 g, 87%, 21 : 1= *E/Z* ratio. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.61 (p, J = 5.8 Hz, 2H), 3.94 (s, 2H), 3.78 (s, 3H), 3.46 (d, J = 5.8 Hz, 2H), 1.67 (d, J = 5.1 Hz, 3H), 1.03 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.4, 159.1, 130.9, 130.8, 128.2, 125.6, 113.6, 62.0, 60.8, 55.4, 38.5, 27.3, 18.0. **IR** (neat, cm^{-1}) 1755, 1610, 1509, 1236, 1174, 1105, 1037, 970, 818, 757. **EA** Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65. Found: C, 70.25; H, 8.76.

(*E*)-*N*-(5-(Benzyloxy)pent-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (1n)



The title compound was prepared following General Procedure **B**.

(*E*)-4-Methoxybenzaldehyde oxime was prepared according to General Procedure **B1** from 4-methoxybenzaldehyde (1.4 mL, 11.6 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.39 g, 20.0 mmol, 1.7 equiv), Et_3N (5.5 mL, 40.0 mmol, 3.4 equiv), and CH_2Cl_2 (30 mL). Following an aqueous workup, the crude (*E*)-4-methoxybenzaldehyde oxime material (920 mg, 6.09 mmol, 1.0 equiv) was reduced to *N*-(4-methoxybenzyl)hydroxylamine using $NaBH_3CN$ (574 mg, 9.14 mmol, 1.5 equiv), methyl orange (0.7 mg), HCl (3 mL, 12 mmol, 2.0 equiv; 4.0 M in dioxane), and MeOH (6 mL). Following an aqueous workup, the crude residue was purified by flash column chromatography (20–80% EtOAc in hexanes) to provide *N*-(4-methoxybenzyl)-hydroxylamine as a white solid. **Yield:** 829 mg, 89%. A portion of this material was used for the preparation of (*E*)-*N*-(5-(benzyloxy)pent-2-en-1-yl)-*N*-(4-methoxybenzyl)-hydroxylamine.

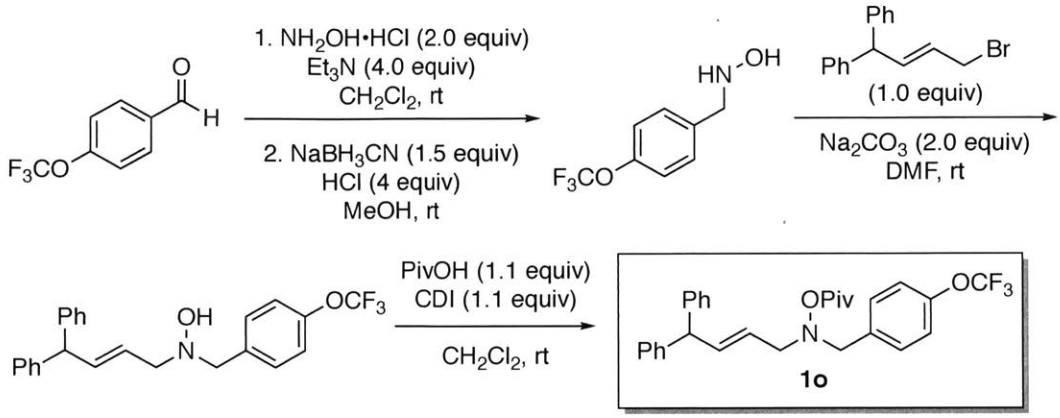
(*E*)-(((5-Bromopent-3-en-1-yl)oxy)methyl)benzene was prepared according to General Procedure **B2** (Method a) from (*E*)-5-(benzyloxy)pent-2-en-1-ol (1.05 g, 5.46 mmol, 1.0 equiv; prepared according to literature[5]), PBr_3 (0.57 mL, 6.0 mmol, 1.1 equiv) and Et_2O (10 mL). Following an aqueous workup, the crude (*E*)-(((5-bromopent-3-en-1-yl)oxy)methyl)benzene mixture was used without further purification. A portion of this material was used for the next part of this procedure.

[5] Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996.

(*E*)-*N*-(5-(Benzyloxy)pent-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine was prepared according to General Procedure **B3** with modified reagent amounts from the *N*-(4-methoxybenzyl)hydroxylamine (762 mg, 5.0 mmol, 1.0 equiv; prepared above), the crude (*E*)-(((5-bromopent-3-en-1-yl)oxy)methyl)benzene mixture (1.27 g, 5.0 mmol, 1.0 equiv; prepared above), Na_2CO_3 (1.06 g, 10.0 mmol, 2.0 equiv), and DMF (10 mL), the reaction mixture was quenched after 4 h. After workup and purification by flash column chromatography (5–60% EtOAc in hexanes) (*E*)-*N*-(5-(benzyloxy)pent-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine was obtained as a pale-yellow oil. **Yield:** 1.07 g, 65%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(5-(Benzyloxy)pent-2-en-1-yl)-*N*-(4-methoxybenzyl)-*O*-pivaloylhydroxylamine (**1n**) was prepared according to General Procedure **B4** with (*E*)-*N*-(5-(benzyloxy)pent-2-en-1-yl)-*N*-(4-methoxybenzyl)hydroxylamine (1.07 g, 3.27 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (584 mg, 3.6 mmol, 1.1 equiv), pivalic acid (367 mg, 3.6 mmol, 1.1 equiv), and CH_2Cl_2 (3.3 mL), the reaction mixture was quenched after 2 h. After workup and purification by flash column chromatography (5–30% EtOAc in hexanes) the title compound was obtained as a yellow oil. **Yield:** 1.19 g, 88%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 4H), 7.24 – 7.13 (m, 3H), 6.77 (d, J = 7.9 Hz, 2H), 5.68 – 5.55 (m, 2H), 4.44 (s, 2H), 3.89 (s, 2H), 3.72 (d, J = 1.6 Hz, 3H), 3.44 (td, J = 6.7, 1.5 Hz, 4H), 2.30 (q, J = 6.2 Hz, 2H), 0.97 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4, 159.2, 138.5, 132.1, 130.9, 128.5, 128.2, 127.8, 127.7, 126.5, 113.6, 73.0, 69.8, 61.9, 60.6, 55.4, 38.5, 32.9, 27.3. **IR** (neat, cm^{-1}) 1749, 1512, 1246, 1108, 1028, 969, 819, 735, 697. **EA** Calcd. for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08. Found: C, 72.97; H, 8.09.

(*E*)-*N*-(4,4-Diphenylbut-2-en-1-yl)-*O*-pivaloyl-*N*-(4-(trifluoromethoxy)benzyl) hydroxylamine (1o)



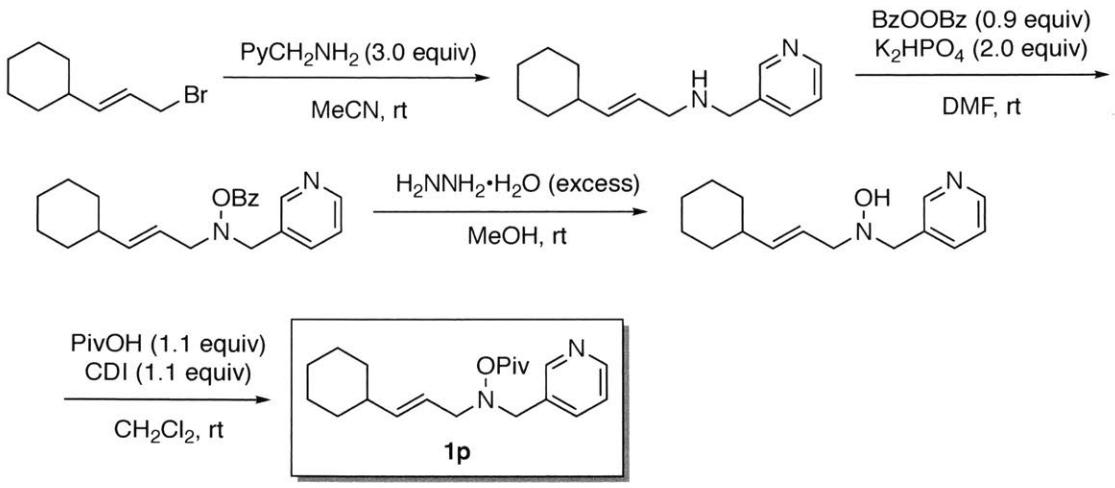
The title compound was prepared following General Procedure **B**.

(*E*)-4-(Trifluoromethoxy)benzaldehyde oxime was prepared according to General Procedure **B1** from 4-trifluoromethoxybenzaldehyde (2.14 mL, 15.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (2.08 g, 30.0 mmol, 2.0 equiv), Et_3N (8.4 mL, 60.0 mmol, 4.0 equiv), and CH_2Cl_2 (20 mL). Following an aqueous workup, the crude (*E*)-4-(trifluoromethoxy)benzaldehyde oxime material (2.08 g, 10.1 mmol, 1.0 equiv) was reduced to *N*-(4-(trifluoromethoxy)benzyl)hydroxylamine using $NaBH_3CN$ (956 mg, 15.2 mmol, 1.5 equiv), methyl orange (1.2 mg), HCl (6.2 mL, 24.8 mmol, 2.5 equiv; 4.0 M in dioxane), and MeOH (10 mL). Following an aqueous workup, the crude residue was purified by flash column chromatography (10–80% EtOAc in hexanes) to provide *N*-(4-(trifluoromethoxy)benzyl)hydroxylamine as a white solid. **Yield:** 1.88 g, 90%. A portion of this material was used for the next part of this procedure.

(*E*)-*N*-(4,4-Diphenylbut-2-en-1-yl)-*N*-(4-(trifluoromethoxy)benzyl)hydroxylamine was prepared according to General Procedure **B3** from the *N*-(4-(trifluoromethoxy)-benzyl)hydroxylamine (1.16 g, 5.6 mmol, 1.0 equiv; prepared above), the crude (*E*)-(4-bromobut-2-ene-1,1-diyl)dibenzene mixture (1.61 g, 5.6 mmol, 1.0 equiv; see **1l** for the preparation procedure), Na_2CO_3 (1.19 g, 11.2 mmol, 2.0 equiv), and DMF (12 mL), the reaction mixture was quenched after 4 h. After workup and purification by flash column chromatography (2–20% EtOAc in hexanes) (*E*)-*N*-(4,4-diphenylbut-2-en-1-yl)-*N*-(4-(trifluoromethoxy)benzyl)hydroxylamine was obtained as a white solid. **Yield:** 1.63 g, 71%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(4,4-Diphenylbut-2-en-1-yl)-*O*-pivaloyl-*N*-(4-(trifluoromethoxy)benzyl)hydroxyl amine (**1o**) was prepared according to General Procedure **B4** with (*E*)-*N*-(4,4-diphenylbut-2-en-1-yl)-*N*-(4-(trifluoromethoxy)benzyl)hydroxylamine (2.86 g, 6.92 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (1.23 g, 7.61 mmol, 1.1 equiv), pivalic acid (776 mg, 7.61 mmol, 1.1 equiv), and CH_2Cl_2 (14 mL), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (0–10% EtOAc in hexanes) the title compound was obtained as a white solid, **m.p.** 94 – 96 °C. **Yield:** 3.25 g, 94%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.7 Hz, 2H), 7.29 (t, J = 7.6 Hz, 4H), 7.21 (d, J = 7.4 Hz, 2H), 7.20 – 7.16 (m, 4H), 7.14 (d, J = 8.2 Hz, 2H), 6.16 (dd, J = 15.3, 7.6 Hz, 1H), 5.64 (dt, J = 15.4, 6.7 Hz, 1H), 4.74 (d, J = 7.5 Hz, 1H), 4.01 (s, 2H), 3.63 (d, J = 6.6 Hz, 2H), 0.90 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.2, 148.7, 143.3, 137.8, 135.0, 130.8, 128.6, 126.5, 126.2, 120.5 (q, J_{CF} = 256.8 Hz), 120.8, 61.8, 60.8, 54.0, 38.3, 27.0. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -57.80. **IR** (neat, cm^{-1}) 1752, 1258, 1221, 1196, 1164, 1110, 758, 742, 699. **EA** Calcd. for $C_{29}H_{30}F_3NO_3$: C, 70.01; H, 6.08. Found: C, 69.79; H, 6.08.

(*E*)-*N*-(3-Cyclohexylallyl)-*O*-pivaloyl-*N*-(pyridin-3-ylmethyl)hydroxylamine (1p)



(*E*)-(3-Bromoprop-1-en-1-yl)cyclohexane was prepared according to General Procedure **B2** (Method a) from (*E*)-3-cyclohexylprop-2-en-1-ol (1.68 g, 12.0 mmol, 1.0 equiv; prepared according to literature[6]), PBr_3 (1.24 mL, 13.2 mmol, 1.1 equiv) and Et_2O (24 mL). Following an aqueous workup, the crude (*E*)-(5-bromopent-3-en-1-yl)benzene mixture was directly used without further purification for the next part of this procedure.

[6] Tosatti, P.; Horn, J.; Campbell, A. J.; House, D.; Nelson, A.; Marsden, S. P. *Adv. Synth. Catal.* **2010**, *352*, 3153.

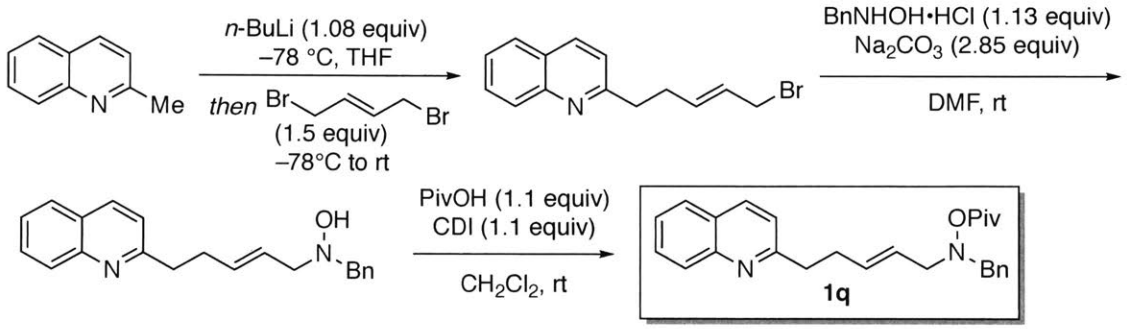
A 100 mL oven-dried round-bottom flask was charged with (*E*)-(3-bromoprop-1-en-1-yl)cyclohexane (~12 mmol, 1.0 equiv; prepared above) and MeCN (40 mL). Using a syringe, the solution was added dropwise into a vigorously stirred solution of pyridin-3-ylmethanamine (4.9 mL, 48 mmol, 4 equiv) in MeCN (4.0 mL) in a 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar at rt. After stirring for 7.5 h, the reaction mixture was concentrated under reduced pressure to ~25% the original volume. After workup and purification by flash column chromatography (0–10% MeOH in CH_2Cl_2) (*E*)-3-cyclohexyl-*N*-(pyridin-3-ylmethyl)prop-2-en-1-amine was obtained as a yellow oil. **Yield:** 1.2 g, 43%. A portion of this material was used for the next part of this procedure.

A 100 mL oven-dried round-bottom flask equipped with a large magnetic stir bar was charged with (*E*)-3-cyclohexyl-*N*-(pyridin-3-ylmethyl)prop-2-en-1-amine (846 mg, 3.68 mmol, 1.05 equiv; prepared above), benzoyl peroxide (1.13 g, 3.5 mmol, 1.0 equiv), K_2HPO_4 (914 mg, 5.25 mmol, 1.5 equiv), and DMF (7.0 mL), the reaction mixture was stirred vigorously at rt for 15 h and the reaction was quenched by addition of water (25 mL). After workup and purification by flash column chromatography (25–50% EtOAc in hexanes) (*E*)-*O*-benzoyl-*N*-(3-cyclohexylallyl)-*N*-(pyridin-3-ylmethyl)hydroxylamine was obtained as an orange solid. **Yield:** 1.06 g, 87%. A portion of this material was used for the next part of this procedure.

A 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*E*)-*O*-benzoyl-*N*-(3-cyclohexylallyl)-*N*-(pyridin-3-ylmethyl)hydroxylamine (876 mg, 2.5 mmol, 1.0 equiv; prepared above) and MeOH (25 mL; degassed by repeated sonication under light vacuum for 0.5 min and refilling the atmosphere with argon). Using a syringe, hydrazine hydrate (1.25 mL) was added at rt (*Note: employ caution when using hydrazine. All hydrazine-containing wastes should be dealt with properly.)*. After 18 h, the reaction was concentrated under reduced pressure, and partitioned between sat. $NaHCO_3$ solution (25 mL) and EtOAc (25 mL). The aqueous layer was separated using a separatory funnel and extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (33% acetone in hexanes) to provide (*E*)-*N*-(3-cyclohexylallyl)-*N*-(pyridin-3-ylmethyl)-hydroxylamine as an off-white solid. **Yield:** 520 mg, 84%. A portion of this material was used for the next part of this procedure.

(E)-*N*-(3-Cyclohexylallyl)-*O*-pivaloyl-*N*-(pyridin-3-ylmethyl)hydroxylamine (**1p**) was prepared according to General Procedure **B4** with (*E*)-*N*-(3-cyclohexylallyl)-*N*-(pyridin-3-ylmethyl)hydroxylamine (493 mg, 2.0 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (357 mg, 2.2 mmol, 1.1 equiv), pivalic acid (225 mg, 2.2 mmol, 1.1 equiv), and CH_2Cl_2 (4.0 mL), the reaction mixture was quenched after 2 h. After workup and purification by flash column chromatography (20% acetone in hexanes) the title compound was obtained as a yellow solid, **m.p.** 39 – 41 °C. **Yield:** 660 mg, 99%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.49 – 8.43 (m, 1H), 7.75 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.21 (ddd, *J* = 6.9, 4.8, 1.5 Hz, 1H), 5.64 – 5.43 (m, 2H), 3.97 (s, 2H), 3.50 (d, *J* = 5.8 Hz, 2H), 1.93 (tt, *J* = 11.1, 3.9 Hz, 1H), 1.75 – 1.54 (m, 5H), 1.30 – 0.98 (m, 5H), 0.96 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 150.5, 149.1, 142.3, 137.1, 131.9, 123.3, 121.3, 61.4, 59.6, 40.5, 38.4, 32.8, 27.1, 26.2, 26.0. **IR** (neat, cm^{-1}) 2926, 2849, 1746, 1123, 1027, 962, 779, 713. **EA** Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15. Found: C, 72.69; H, 9.24.

(*E*)-*N*-Benzyl-*O*-pivaloyl-*N*-(5-(quinolin-2-yl)pent-2-en-1-yl)hydroxylamine (1q)



The title compound was prepared following General Procedure **B**.

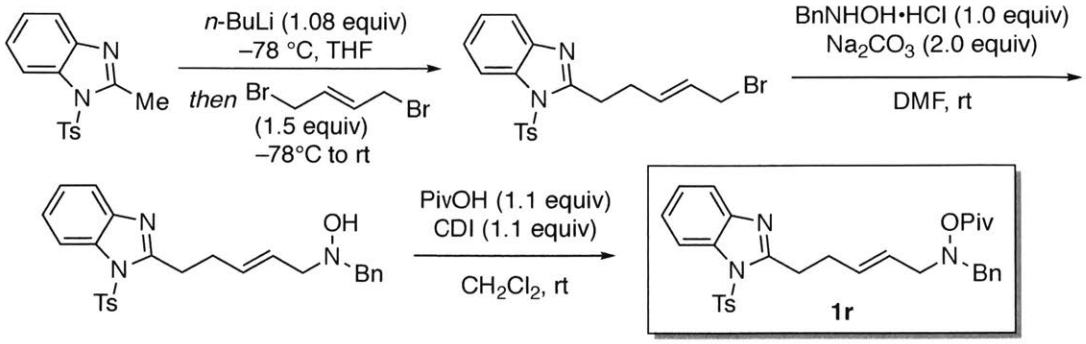
(*E*)-2-(5-Bromopent-3-en-1-yl)quinoline was prepared according to General Procedure **B2** (Method b) from quinaldine (1.35 mL, 10 mmol, 1.0 equiv), (*E*)-1,4-dibromobut-2-ene (3.21 g, 15 mmol, 1.5 equiv) and *n*-BuLi (6.75 mL, 10.8 mmol, 1.08 equiv; 1.6 M in hexanes). The crude residue was purified by flash column chromatography (10% EtOAc in hexanes) to provide (*E*)-2-(5-bromopent-3-en-1-yl)quinoline as a dark red oil. **Yield:** 1.20 g, 44%. This material was directly used for the next part of this procedure.

(*E*)-*N*-Benzyl-*N*-(5-(quinolin-2-yl)pent-2-en-1-yl)hydroxylamine was prepared according to General Procedure **B3** from (*E*)-2-(5-bromopent-3-en-1-yl)quinoline (1.20 g, 4.4 mmol, 1.0 equiv; prepared above), *N*-benzylhydroxylamine hydrochloride (800 mg, 5.0 mmol, 1.13 equiv) and

Na_2CO_3 (1.33 g, 12.5 mmol, 2.85 equiv), and DMF (10 mL), the reaction mixture was quenched after 15 h. After workup and purification by flash column chromatography (50% EtOAc in hexanes) (*E*)-*N*-benzyl-*N*-(5-(quinolin-2-yl)pent-2-en-1-yl)hydroxylamine was obtained as an off-white solid. **Yield:** 955 mg, 68%. This material was used for the next part of this procedure.

(*E*)-*N*-Benzyl-*O*-pivaloyl-*N*-(5-(quinolin-2-yl)pent-2-en-1-yl)hydroxylamine (**1q**) was prepared according to General Procedure **B4** with (*E*)-*N*-benzyl-*N*-(5-(quinolin-2-yl)pent-2-en-1-yl)hydroxylamine (955 mg, 3.0 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (535 mg, 3.3 mmol, 1.1 equiv), pivalic acid (337 mg, 3.3 mmol, 1.1 equiv), and CH_2Cl_2 (6.0 mL), the reaction mixture was quenched after 4 h. After workup and purification by flash column chromatography (25% EtOAc in hexanes) the title compound was obtained as an off-white solid, **m.p.** 70–73 °C. **Yield:** 1.03 g, 85%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.79 – 7.72 (m, 1H), 7.66 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.47 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.34 – 7.16 (m, 6H), 5.81 – 5.62 (m, 2H), 3.92 (s, 2H), 3.51 (d, *J* = 6.2 Hz, 2H), 3.06 (dd, *J* = 8.8, 6.8 Hz, 2H), 2.59 (dd, *J* = 14.2, 7.4 Hz, 2H), 0.99 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 161.9, 148.1, 136.4, 136.2, 134.8, 129.5, 129.0, 128.2, 127.6, 127.6, 126.9, 125.9, 125.3, 121.5, 62.3, 60.8, 38.8, 38.5, 32.5, 27.2 (one signal missing due to overlap). **IR** (neat, cm^{-1}) 2957, 2866, 1753, 1600, 1115, 962, 643 cm^{-1}. **EA** Calcd. for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51. Found: C, 77.47; H, 7.58.

(*E*)-*N*-Benzyl-*O*-pivaloyl-*N*-(5-(1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)pent-2-en-1-yl)hydroxylamine (1r)



The title compound was prepared following General Procedure **B**.

(*E*)-2-(5-Bromopent-3-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole was prepared according to General Procedure **B2** (Method b) from 2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole (2.86 g, 10.0 mmol, 1.0

equiv; prepared according to literature[7]), (*E*)-1,4-dibromobut-2-ene (3.21 g, 15.0 mmol, 1.5 equiv) and *n*-BuLi (6.75 mL, 10.8 mmol, 1.08 equiv; 1.6 M in hexanes). The crude residue was purified by flash column chromatography (33% EtOAc in hexanes) to provide (*E*)-2-(5-bromopent-3-en-1-yl)-1-tosyl-1*H*-benzo[*d*]-imidazole as a yellow oil. **Yield:** 2.38 g, 57%. This material was used for the next part of this procedure.

(*E*)-*N*-Benzyl-*N*-(5-(1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)pent-2-en-1-yl)hydroxylamine was prepared according to General Procedure **B3** from (*E*)-2-(5-bromopent-3-en-1-yl)-1-tosyl-1*H*-benzo[*d*]imidazole (2.38 g, 5.7 mmol, 1.0 equiv; prepared above), the crude *N*-benzylhydroxylamine hydrochloride (914 mg, 5.7 mmol, 1.0 equiv) and Na_2CO_3 (1.51 g, 14.3 mmol, 2.0 equiv), and DMF (12 mL), the reaction mixture was quenched after 6 h. After workup and purification by flash column chromatography (20% EtOAc in CH_2Cl_2) (*E*)-*N*-benzyl-*N*-(5-(1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)pent-2-en-1-yl)hydroxylamine was obtained as a viscous yellow oil. **Yield:** 1.89 g, 80%. This material was used directly for the next part of this procedure.

(*E*)-*N*-Benzyl-*O*-pivaloyl-*N*-(5-(1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)pent-2-en-1-yl)-hydroxylamine (**1r**) was prepared according to General Procedure **B4** with (*E*)-*N*-benzyl-*N*-(5-(1-tosyl-1*H*-benzo[*d*]imidazol-2-yl)pent-2-en-1-yl)hydroxylamine (1.89 g, 4.1 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (803 mg, 4.95 mmol, 1.2 equiv), pivalic acid (505 mg, 4.95 mmol, 1.2 equiv), and CH_2Cl_2 (10 mL), the reaction mixture was quenched after 1 h, After workup and purification by flash column chromatography (0–25% EtOAc in hexanes) the title compound was obtained as a viscous pale-yellow oil. **Yield:** 1.95 g, 88%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.68 – 7.60 (m, 1H), 7.37 – 7.24 (m, 9H), 5.86 – 5.65 (m, 2H), 3.99 (s, 2H), 3.53 (d, *J* = 6.0 Hz, 2H), 3.29 – 3.16 (m, 2H), 2.65 (dd, *J* = 15.1, 6.2 Hz, 1H), 2.37 (s, 3H), 1.01 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4, 154.4, 146.1, 142.1, 136.1, 135.7, 133.9, 133.3, 130.4, 129.6, 128.3, 127.7, 126.9, 125.9, 125.0, 124.8, 120.0, 113.8, 62.6, 60.9, 38.5, 30.3, 29.5, 27.2, 21.9. **IR** (neat, cm^{-1}) 2972, 2870, 1748, 1451, 1376, 1119, 742. **HRMS** (DART+) Calcd. for $C_{31}H_{35}N_3O_4S$ $[M+H]^+$ 546.2421, found 546.2418.

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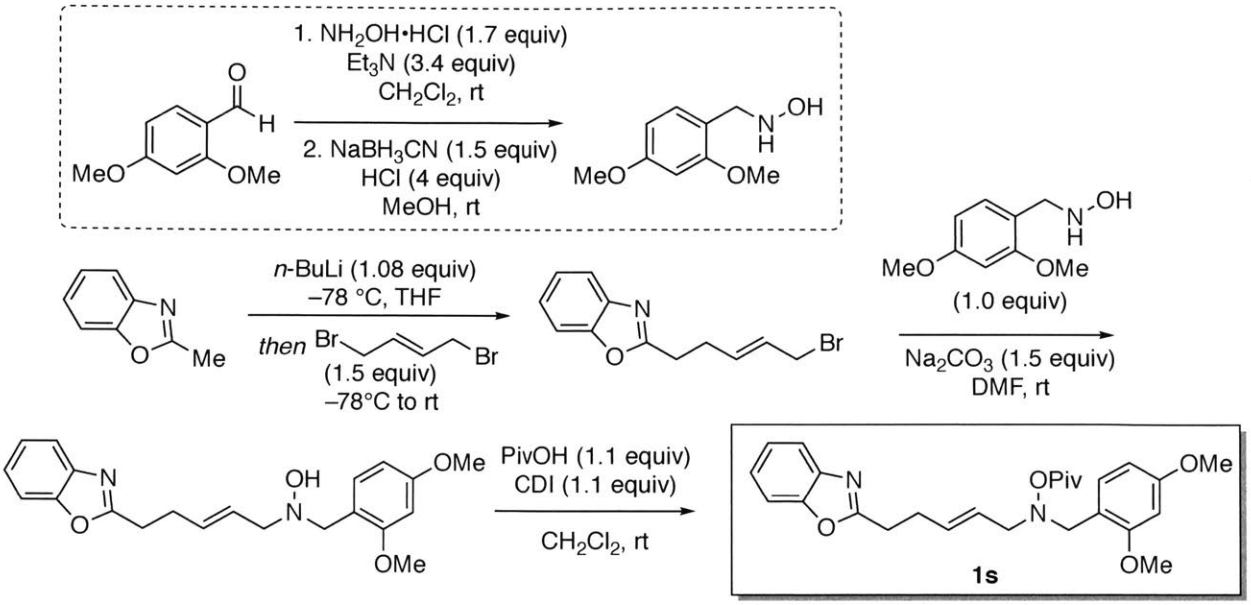
[7] Abdireimov, K. B.; Mukhamedov, N. S.; Aiymbetov, M. Zh.; Shakhidoyatov, Kh. M. *Chem. Heterocyclic. Cmpd.* **2010**, *46*, 941

(*E*)-*N*-(5-(Benzo[*d*]oxazol-2-yl)pent-2-en-1-yl)-*N*-(2,4-dimethoxybenzyl)-*O*-pivaloyl-hydroxylamine (1s)



The title compound was prepared following General Procedure **B**.

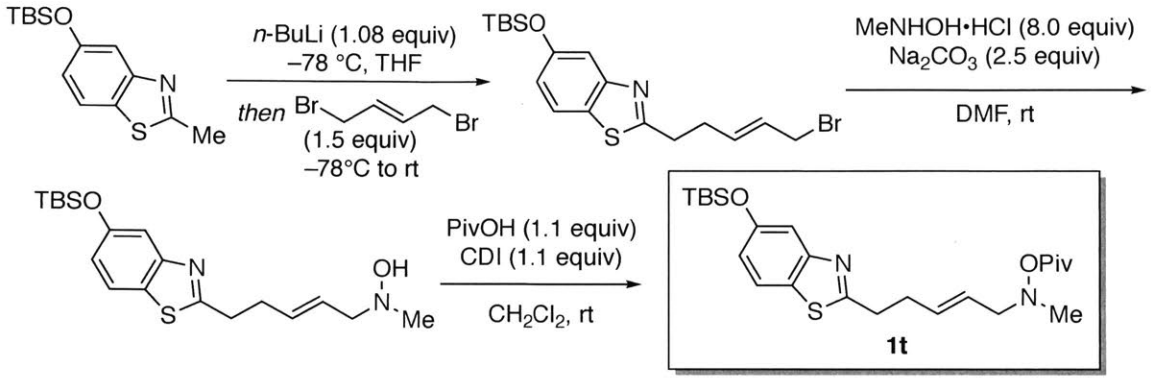
(*E*)-2,4-Dimethoxybenzaldehyde oxime was prepared according to General Procedure **B1** from 2,4-dimethoxybenzaldehyde (1.66 g, 10 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.18 g, 17 mmol, 1.7 equiv), Et_3N (4.7 mL, 34 mmol, 3.4 equiv), and CH_2Cl_2 (20 mL). Following an aqueous workup, the crude (*E*)-2,4-dimethoxybenzaldehyde oxime was reduced to the corresponding hydroxylamine using $NaBH_3CN$ (942 mg, 15 mmol, 1.5 equiv), methyl orange (~1.0 mg), HCl (20 mL, 40 mmol, 4.0 equiv; 2.0 M in Et_2O), and MeOH (20 mL). Following an aqueous workup, the crude *N*-(2,4-dimethoxybenzyl)hydroxylamine mixture was used for the preparation of (*E*)-*N*-(5-(benzo[*d*]oxazol-2-yl)pent-2-en-1-yl)-*N*-(2,4-dimethoxybenzyl)hydroxylamine without further purification.

(*E*)-2-(5-Bromopent-3-en-1-yl)benzo[*d*]oxazole was prepared according to General Procedure **B2** (Method b) from 2-methylbenzo[*d*]oxazole (1.19 mL, 10.0 mmol, 1.0 equiv), (*E*)-1,4-dibromobut-2-ene (3.21 g, 15.0 mmol, 1.5 equiv) and *n*-BuLi (6.75 mL, 10.8 mmol, 1.08 equiv; 1.6 M in hexanes). Following an aqueous workup, the crude (*E*)-2-(5-bromopent-3-en-1-yl)benzo[*d*]oxazole mixture was used without further purification. This material was used for the next part of this procedure.

(*E*)-*N*-(5-(Benzo[*d*]oxazol-2-yl)pent-2-en-1-yl)-*N*-(2,4-dimethoxybenzyl)hydroxylamine was prepared according to General Procedure **B3** from the crude (*E*)-2-(5-bromopent-3-en-1-yl)benzo[*d*]oxazole (~10 mmol, 1.0 equiv; prepared above), the crude *N*-(2,4-dimethoxybenzyl)hydroxylamine (~10 mmol, 1.0 equiv; prepared above) and Na_2CO_3 (1.6 g, 15 mmol, 1.5 equiv), and DMF (25 mL), the reaction mixture was quenched after 23 h. After workup and purification by flash column chromatography (0–33% EtOAc in hexanes) (*E*)-*N*-(5-(benzo[*d*]oxazol-2-yl)pent-2-en-1-yl)-*N*-(2,4-dimethoxybenzyl)hydroxylamine was obtained as a viscous yellow oil. **Yield:** 1.35 g, 36%. This material was directly used for the next part of this procedure.

(*E*)-*N*-(5-(Benzo[*d*]oxazol-2-yl)pent-2-en-1-yl)-*N*-(2,4-dimethoxybenzyl)-*O*-pivaloyl-hydroxylamine (**1s**) was prepared according to General Procedure **B4** with (*E*)-*N*-(5-(benzo[*d*]oxazol-2-yl)pent-2-en-1-yl)-*N*-(2,4-dimethoxybenzyl)hydroxylamine (1.35 g, 3.6 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (642 mg, 3.96 mmol, 1.1 equiv), pivalic acid (404 mg, 3.96 mmol, 1.1 equiv), and CH_2Cl_2 (15 mL), the reaction mixture was quenched after 15 h. After workup and purification by flash column chromatography (0–33% EtOAc in hexanes) to provide the title compound as a viscous pale-yellow oil. **Yield:** 1.57 g, 96%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 1H), 7.45 (dt, *J* = 6.4, 1.8 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 1H), 6.46 – 6.33 (m, 2H), 5.80 – 5.62 (m, 2H), 3.99 (s, 2H), 3.78 (s, 6H), 3.52 – 3.39 (m, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.68 – 2.51 (m, 2H), 1.06 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3, 166.3, 160.4, 158.8, 150.8, 141.3, 132.5, 132.1, 126.8, 124.5, 124.1, 119.6, 116.5, 110.3, 103.9, 98.2, 60.1, 55.4, 55.4, 55.3, 38.4, 29.3, 28.3, 27.2. **IR** (neat, cm^{-1}) 2957, 2934, 2836, 1746, 1613, 1508, 1455, 1207, 1121, 1035, 745. **EA** Calcd. for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13. Found: C, 68.75; H, 7.09.

(*E*)-*N*-(5-(5-((*tert*-Butyldimethylsilyl)oxy)benzo[*d*]thiazol-2-yl)pent-2-en-1-yl)-*N*-methyl-*O*-pivaloylhydroxylamine (1t)



The title compound was prepared following General Procedure **B**.

(*E*)-2-(5-Bromopent-3-en-1-yl)-5-((*tert*-butyldimethylsilyl)oxy)benzo[*d*]thiazole was prepared according to General Procedure **B2** (Method b) from 5-((*tert*-butyldimethylsilyl)oxy)-2-methylbenzo[*d*]thiazole (4.64 g, 16.6 mmol, 1.0 equiv; prepared according to literature procedure[8]), (*E*)-1,4-dibromobut-2-ene (3.55 g, 16.6 mmol, 1.0 equiv) and *n*-BuLi (11.2 mL, 17.9 mmol, 1.08 equiv; 1.6 M in hexanes). After workup and purification by flash column chromatography (1–10% EtOAc in hexanes) (*E*)-2-(5-bromopent-3-en-1-yl)-5-((*tert*-butyldimethylsilyl)oxy)benzo[*d*]-thiazole was obtained as a brown oil. **Yield:** 1.51 g, 22%. A portion of this material was used for the next part of this procedure.

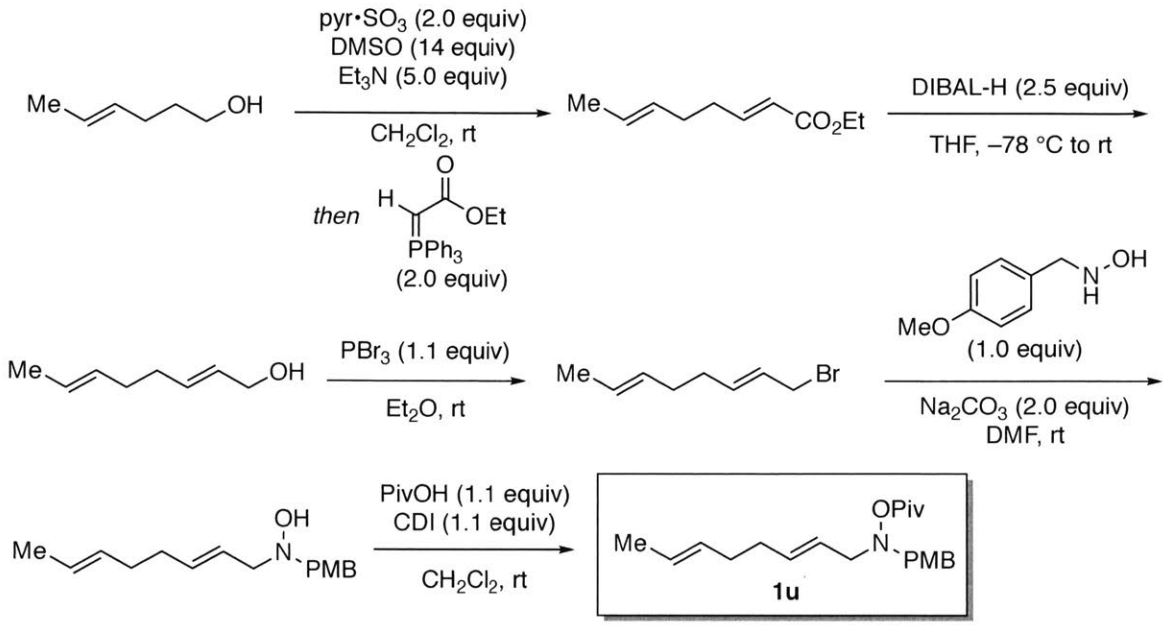
(*E*)-*N*-(5-(5-((*tert*-Butyldimethylsilyl)oxy)benzo[*d*]thiazol-2-yl)pent-2-en-1-yl)-*N*-methyl hydroxylamine was prepared according to General Procedure **B3** from *N*-methylhydroxylamine hydrochloride (1.48 g, 17.7 mmol, 8.0 equiv) and (*E*)-2-(5-bromopent-3-en-1-yl)-5-((*tert*-butyldimethylsilyl)oxy)benzo[*d*]thiazole (915 mg, 2.22 mmol, 1.0 equiv; prepared above), Na_2CO_3 (589 mg, 5.55 mmol, 2.5 equiv), and DMF (4.5 mL), the reaction mixture was quenched after 2 h 30 min. After workup and purification by flash column chromatography (1–8% MeOH in CH_2Cl_2) (*E*)-*N*-(5-(5-((*tert*-butyldimethylsilyl)oxy)benzo[*d*]thiazol-2-yl)pent-2-en-1-yl)-*N*-methylhydroxyl-amine was obtained as an orange oil. **Yield:** 244 mg, 29%. This material was used for the next part of this procedure.

(*E*)-*N*-(5-(5-((*tert*-Butyldimethylsilyl)oxy)benzo[*d*]thiazol-2-yl)pent-2-en-1-yl)-*N*-methyl-*O*-pivaloylhydroxylamine (**1t**) was prepared according to General Procedure **B4** with (*E*)-*N*-(5-(5-

[8] Sidhu, P. S.; Zhou, Q.; Desai, U. R. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5716

((*tert*-butyldimethylsilyl)oxy)benzo[*d*]thiazol-2-yl)pent-2-en-1-yl)-*N*-methyl hydroxylamine (438 mg, 1.16 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (206 mg, 1.27 mmol, 1.1 equiv), pivalic acid (130 mg, 1.27 mmol, 1.1 equiv), and CH_2Cl_2 (1.2 mL), the reaction mixture was quenched after 3 h. After workup and purification by flash column chromatography (5–40% EtOAc in hexanes) the title compound was obtained as a yellow oil. **Yield:** 428 mg, 80%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 6.90 (dd, J = 8.5, 2.3 Hz, 1H), 5.68 (qt, J = 15.6, 6.4 Hz, 2H), 3.41 (d, J = 6.2 Hz, 2H), 3.14 (dd, J = 8.6, 6.7 Hz, 2H), 2.66 (s, 3H), 2.59 (q, J = 7.2 Hz, 2H), 1.15 (s, 9H), 0.99 (s, 9H), 0.21 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.5, 172.3, 154.7, 154.4, 133.2, 127.8, 126.3, 121.7, 119.2, 113.0, 62.8, 45.8, 38.4, 34.0, 32.2, 27.3, 25.8, 18.4, -4.3. **IR** (neat, cm^{-1}) 2956, 2929, 2858, 1752, 1455, 1274, 1168, 1119, 970, 874, 839, 781.. **EA** Calcd. for $C_{24}H_{38}N_2O_3SSi$: C, 62.30; H, 8.28. Found: C, 62.40; H, 8.45.

_N_-(4-Methoxybenzyl)-_N_-((2_E_,6_E_)-octa-2,6-dien-1-yl)-_O_-pivaloylhydroxylamine (1u)



A 100 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with (*E*)-hex-4-en-1-ol (1.84 mL, 15 mmol, 1.0 equiv), DMSO (15 mL, 211 mmol, 14 equiv), Et_3N (10.6 mL, 75 mmol, 5.0 equiv), and CH_2Cl_2 (150 mL). The reaction flask was capped with a rubber septum and purged with nitrogen by puncturing the septum with a needle attached to a nitrogen-filled Schlenk manifold and kept under nitrogen atmosphere. The reaction flask was cooled to 0 °C using an ice/water bath and the rubber septum was removed to allow pyr·SO_3 (4.8 g, 30 mmol, 2.0 equiv) to be added in one portion as a solid. The reaction flask was resealed with the rubber septum, removed from the ice/water bath, and allowed to warm up to rt. After stirring at rt for 3 h, the septum was removed and ethyl (triphenylphosphoranylidene)acetate (10.4 g, 30 mmol, 2.0 equiv) was added in one portion as a solid and the resulting reaction mixture was stirred for 18 h

at rt. The reaction mixture was quenched by addition of water (75 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (75 mL × 2) using a separatory funnel. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (0–20% EtOAc in hexanes) to provide ethyl (2*E*,6*E*)-octa-2,6-dienoate as a colorless oil. **Yield:** 2.07 g, 82%. This material was used for the next part of this procedure.

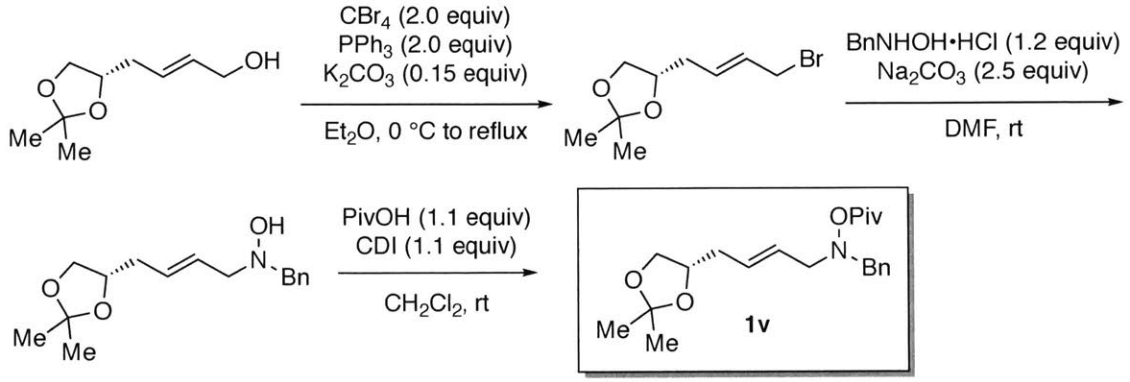
A 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with ethyl (2*E*,6*E*)-octa-2,6-dienoate (2.07 g, 12 mmol, 1.0 equiv; prepared above) and CH_2Cl_2 (24 mL). The reaction flask was purged with nitrogen using a nitrogen-filled manifold and kept under nitrogen atmosphere. DIBAL-H (30 mL, 30 mmol, 2.5 equiv; 1.0 M solution in hexanes) was added slowly using a syringe into the reaction flask and the resulting reaction mixture was stirred for 5 h at rt. The reaction was worked up by a dropwise addition of sat. Na_2SO_4 (~5 mL); the reaction mixture was stirred at rt for 15 min until it gelled, then EtOAc (50 mL) was added, followed by anhydrous $MgSO_4$. The resulting slurry was stirred at rt for 30 min then filtered. The filtrate was concentrated under reduced pressure then purified via flash column chromatography (0–16% EtOAc in hexanes) to provide (2*E*,6*E*)-octa-2,6-dien-1-ol as a colorless oil. **Yield:** 740 mg, 50%. This material was used for the next part of this procedure.

(2*E*,6*E*)-1-Bromoocta-2,6-diene was prepared according to General Procedure **B2** (Method a) from (2*E*,6*E*)-octa-2,6-dien-1-ol (740 mg, 5.84 mmol, 1.0 equiv; prepared above), PBr_3 (610 μL, 6.42 mmol, 1.1 equiv), and Et_2O (12 mL). Following an aqueous workup, the crude (2*E*,6*E*)-1-bromoocta-2,6-diene mixture was used immediately in the next step without further purification.

N-(4-Methoxybenzyl)-*N*-((2*E*,6*E*)-octa-2,6-dien-1-yl)hydroxylamine was prepared according to General Procedure **B3** from the crude *N*-(4-methoxybenzyl)hydroxylamine (1.07 g, ~7 mmol, 1.2 equiv; prepared above), the crude (2*E*,6*E*)-1-bromoocta-2,6-diene (~5.84 mmol, 1.0 equiv; prepared above), Na_2CO_3 (1.02 g, 9.64 mmol, 1.5 equiv), and DMF (12 mL), the reaction mixture was quenched after 20 h. After workup and purification by flash column chromatography (0–33% EtOAc in hexanes) *N*-(4-methoxybenzyl)-*N*-((2*E*,6*E*)-octa-2,6-dien-1-yl)hydroxylamine was obtained as a colorless oil. **Yield**: 1.0 g, 66%. This material was directly used for the next part of this procedure.

N-(4-Methoxybenzyl)-*N*-((2*E*,6*E*)-octa-2,6-dien-1-yl)-*O*-pivaloylhydroxylamine (**1u**) was prepared according to General Procedure **B4** with *N*-(4-methoxybenzyl)-*N*-((2*E*,6*E*)-octa-2,6-dien-1-yl)hydroxylamine (1.0 g, 3.83 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (682 mg, 4.21 mmol, 1.1 equiv), pivalic acid (430 mg, 4.21 mmol, 1.1 equiv), and CH_2Cl_2 (8.0 mL), the reaction mixture was quenched after 4 h. After workup and purification by flash column chromatography (0–25% EtOAc in hexanes) the title compound was obtained as a yellow oil. **Yield:** 1.06 g, 80%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.71 – 5.58 (m, 2H), 5.49 – 5.39 (m, 2H), 3.97 (s, 2H), 3.81 (s, 3H), 3.50 (d, *J* = 4.9 Hz, 2H), 2.19 – 1.99 (m, 4H), 1.69 – 1.61 (m, 3H), 1.06 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4, 159.2, 135.5, 130.9, 130.7, 128.3, 125.4, 124.7, 113.6, 61.8, 60.7, 55.4, 38.5, 32.5, 32.2, 27.3, 18.1. **IR** (neat, cm^{-1}) 2959, 2932, 2836, 1750, 1612, 1512, 1246, 1116, 965, 820. **HRMS** (DART+) Calcd. for $C_{21}H_{31}NO_3$ $[M+H]^+$ 346.2377, found 346.2375.

(*S*,*E*)-*N*-Benzyl-*N*-(4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-yl)-*O*-pivaloyl-hydroxylamine (1v)



The title compound was prepared following General Procedure **B**.

A 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar was purged with argon using an argon-filled manifold, then charged with (*S*,*E*)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (1.57 g, 9.1 mmol, 1.0 equiv; prepared according to literature procedure[9]), PPh_3 (4.77 g, 18.2 mmol, 2.0 equiv), K_2CO_3 (188 mg, 1.37 mmol, 0.15 equiv), and Et_2O (70 mL). The reaction flask was cooled to 0 °C using an ice/water bath. CBr_4 (5.67 g, 18.2 mmol, 2.0 equiv) was added directly into the reaction flask in six portions over 5 min. The reaction mixture was warmed to rt by removing the ice/water bath and stirred at rt for 2 h. The reaction flask was then equipped with

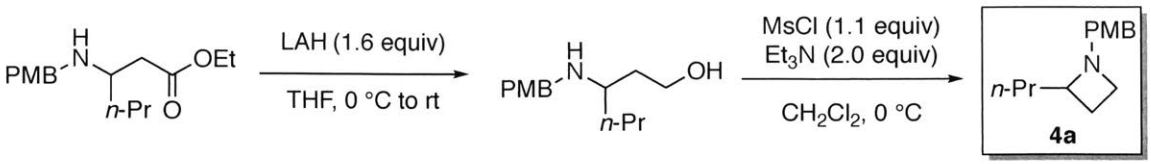
[9] Ramana, C. V.; Mallik, R.; Sahoo, G. *Tetrahedron Lett.* **2009**, *50*, 4844

a refluxing condenser connected with chilled water and was heated to reflux for 15 min in an oil bath. The reaction flask was then removed from the oil bath and cooled to rt. The reaction mixture was diluted with pentane (150 mL) and filtered. The precipitate was rinsed with Et_2O (300 mL). The combined filtrate was concentrated under reduced pressure, and purified via flash column chromatography (10–30% Et_2O in hexanes) to provide (*S*,*E*)-4-(4-bromobut-2-en-1-yl)-2,2-dimethyl-1,3-dioxolane as a pale yellow oil. **Yield:** 880 mg, 41%. A portion of this material was used for the next part of this procedure.

(*S*,*E*)-*N*-Benzyl-*N*-(4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-yl)hydroxylamine was prepared according to General Procedure **B3** from *N*-benzylhydroxylamine hydrochloride (670 mg, 4.2 mmol, 1.2 equiv), (*S*,*E*)-4-(4-bromobut-2-en-1-yl)-2,2-dimethyl-1,3-dioxolane (822 mg, 3.5 mmol, 1 equiv; prepared above), Na_2CO_3 (930 mg, 8.75 mmol, 2.5 equiv), and DMF (7 mL), the reaction mixture was quenched after 5 h. After workup and purification by flash column chromatography (0–50% EtOAc in hexanes) (*S*,*E*)-*N*-benzyl-*N*-(4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-yl)hydroxyl-amine was obtained as a pale yellow oil. **Yield:** 858 mg, 88%. This material was used directly for the next part of this procedure.

(*S*,*E*)-*N*-Benzyl-*N*-(4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-yl)-*O*-pivaloyl-hydroxylamine (**1v**) was prepared according to General Procedure **B4** with (*S*,*E*)-*N*-benzyl-*N*-(4-(2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-yl)hydroxylamine (858 mg, 3.09 mmol, 1.0 equiv; prepared above), carbonyldiimidazole (551 mg, 3.4 mmol, 1.1 equiv), pivalic acid (347 mg, 3.4 mmol, 1.1 equiv), and CH_2Cl_2 (6 mL), the reaction mixture was quenched after 4 h. After workup and purification by flash column chromatography (0–25% EtOAc in hexanes) the title compound was obtained as a colorless oil. **Yield:** 978 mg, 87%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.5 Hz, 2H), 7.33 – 7.23 (m, 3H), 5.68 (dtd, J = 22.0, 15.5, 7.8 Hz, 2H), 4.13 (q, J = 6.1 Hz, 1H), 4.06 – 3.98 (m, 3H), 3.61 – 3.47 (m, 3H), 2.32 (ddd, J = 38.4, 14.4, 7.5 Hz, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.25 (s, 1H), 1.02 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 135.9, 130.5, 129.4, 128.2, 127.5, 127.4, 109.0, 75.2, 68.9, 62.5, 60.7, 38.3, 36.7, 27.1, 26.9, 25.6. **IR** (neat, cm^{-1}) 2981, 2934, 2872, 1750, 1368, 1213, 1114, 1059, 739, 698. **EA** Calcd. for $C_{21}H_{31}NO_4$: C, 69.78; H, 8.64. Found: C, 69.58; H, 8.72.

1-(4-Methoxybenzyl)-2-propylazetidine (4a)



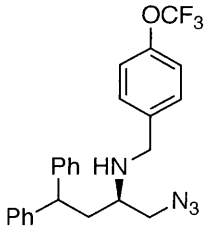
A 250 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with ethyl 3-((4-methoxybenzyl)amino)hexanoate (1.92 g, 6.9 mmol, 1.0 equiv; prepared according to literature procedure[10]) and THF (27 mL). The reaction flask was cooled to 0 °C using an ice/water bath and LAH (0.42 g, 11.0 mmol, 1.6 equiv) was added portion-wise. The reaction was worked up following Fieser workup procedures[3]: first diluted with Et_2O (70 mL) at 0 °C using an ice/water bath; water (0.42 mL) was slowly added, followed by addition of 15% NaOH solution (0.42 mL); another portion of water (1.26 mL) was added; and the reaction mixture was warmed to rt and stirred for 15 min; $MgSO_4$ was added and the reaction mixture was stirred for another 15 min. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to provide 3-(benzylamino)hexan-1-ol as a colorless oil (1.59 g). A portion of this material was used for the next part of this procedure without purification.

A 50 mL oven-dried round-bottom flask equipped with a magnetic stir bar was charged with 3-(benzylamino)hexan-1-ol (119 mg, 0.5 mmol, 1.0 equiv), mesyl chloride (43 μL, 0.55 mmol, 1.1 equiv), and CH_2Cl_2 (2.5 mL). The reaction flask was cooled to 0 °C using an ice/water bath. Et_3N (140 μL, 1.0 mmol, 2.0 equiv) was added slowly to the reaction mixture. The reaction was stirred at 0 °C for 70 min before it was quenched carefully by addition of sat. $NaHCO_3$ solution (10 mL) and EtOAc (10 mL). The aqueous layer was separated and extracted with EtOAc (10 mL × 2) using a separatory funnel. The combined organic layers were washed with brine (30 mL) and 1.0 M NaOH solution (20 mL × 2). The mixture was then separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, concentrate under reduced pressure, and purified via preparative thin layer chromatography (10% MeOH in CH_2Cl_2) to provide the title compound as a colorless oil. **Yield:** 51 mg, 46%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.65 (d, J = 12.4 Hz, 1H), 3.38 (d, J = 12.4 Hz, 1H), 3.33 – 3.19 (m, 1H), 3.08 (qd, J = 8.0, 5.3 Hz, 1H), 2.82 – 2.69 (m, 1H), 2.01 (dtd, J = 10.0, 7.8, 2.2 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.50 – 1.40 (m, 1H), 1.40 – 1.33 (m, 1H), 1.23 (h, J = 7.5 Hz, 2H), 0.86 (t, J = 7.3

[10] N'Goka, V.; Schlewer, G.; Linget, J. M.; Chambon, J. P.; Wermuth, C. G. *J. Med. Chem.* **1991**, *34*, 2547.

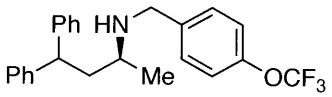
Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.8, 130.2, 113.8, 66.9, 62.3, 55.3, 51.4, 38.5, 24.3, 18.8, 14.3 (one signal missing due to overlap). **IR** (neat, cm^{-1}) 2955, 2930, 1612, 1511, 1300, 1244, 1180, 1170, 1037, 821. **EA** Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.38; H, 9.74.

Synthetic Procedures and Characterization Data for Aziridine Derivatization Reactions



6

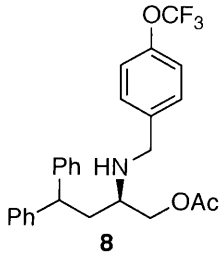
(*R*)-1-Azido-4,4-diphenyl-*N*-(4-(trifluoromethoxy)benzyl)butan-2-amine (6): A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar was capped with a rubber septum and purged with argon by puncturing the septum with a needle attached to an argon-filled Schlenk manifold and kept under argon atmosphere. The flask was charge with $TMSN_3$ (350 μL, 2.5 mmol, 5.0 equiv) and CH_2Cl_2 (1 mL). Using a syringe, acetic acid (143 μL, 2.5 mmol, 5.0 equiv) was added dropwise *(Note: use caution when employing or preparing alkyl azides.)* The reaction mixture was stirred for 20 min at rt. A solution of aziridine **3o** (199 mg, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was added via syringe to the reaction mixture. After 24 h, the reaction was quenched by addition of sat. $NaHCO_3$ solution (10 mL). The aqueous layer was separated and extracted with EtOAc (10 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (5–50% EtOAc in hexanes) to provide the title compound as a pale yellow oil as a 9.5 : 1 mixture of regioisomers. **Yield:** 203 mg, 92%. The mixture of regioisomers was separated using preparative HPLC (Agilent preparative C18 column, 21.2 × 150 mm, 5 micron) with acetonitrile and water as eluents (5% acetonitrile in water – 95% acetonitrile in water) for NMR analysis of the major isomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 8H), 7.24 – 7.17 (m, 4H), 7.16 (d, J = 8.3 Hz, 2H), 4.15 (t, J = 7.9 Hz, 1H), 3.79 (d, J = 13.3 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H), 3.47 (dd, J = 12.4, 4.4 Hz, 1H), 3.28 (dd, J = 12.4, 4.8 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.22 (dd, J = 7.9, 6.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.3 (d, J_{CF} = 2.2 Hz; two of the quartet peaks are obscure), 144.6, 144.2, 139.0, 129.6, 128.8, 128.7, 127.9, 127.8, 126.54, 126.52, 121.1, 120.6 (q, J_{CF} = 256.9 Hz), 54.7, 54.3, 50.2, 48.0, 39.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -57.83. **IR** (neat, cm^{-1}) 2097, 1254, 1220, 1160, 751, 739, 697. **EA** Calcd. for $C_{24}H_{23}F_3N_4O$: C, 65.44; H, 5.26. Found: C, 65.57; H, 5.40. **Specific rotation** $[\alpha]_D^{21}$ = 19.1 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 99:1 hexanes/2-propanol, 1.0 mL/min, t_M = 7.4 min, t_m = 14.9 min) indicated 98% ee.



7

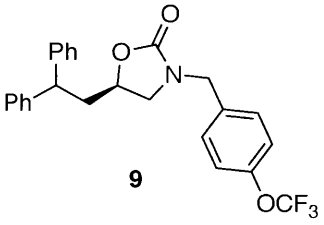
(*S*)-4,4-Diphenyl-*N*-(4-(trifluoromethoxy)benzyl)butan-2-amine (7): An oven-dried screw-cap reaction tube (13 mm × 100 mm) equipped with a magnetic stir bar was charged with aziridine **3o** (199 mg, 0.5 mmol, 1.0 equiv) and Pd/C (53 mg, 0.05 mmol, 10 mol%). The reaction tube was recapped, the septum was punctured with a needle attached to a Schlenk line and the tube was evacuated and backfilled with argon (this process was repeated a total of three times). MeOH (2 mL) was then added using a syringe and the reaction mixture was bubbled with H_2 for 10 min by immersing a needle attached to a H_2-filled balloon under the solvent surface *(Note: employ caution when using hydrogen)*. The reaction mixture was stirred at rt for 25 h under 1 atm pressure of H_2 before it was filtered through a plug of celite and eluted with EtOAc (100 mL). The filtrate was concentrated under reduced pressure, and purified via preparative thin layer chromatography (50% EtOAc in hexanes) to provide the title compound as a pale yellow oil. **Yield:** 156 mg, 78%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 6H), 7.24 (d, J = 7.8 Hz, 4H), 7.20 (d, J = 7.2 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 4.24 – 4.07 (m, 1H), 3.79 (d, J = 13.2 Hz, 1H), 3.64 (d, J = 13.2 Hz, 1H), 2.57 (q, J = 6.8 Hz, 1H), 2.25 (dt, J = 15.3, 7.8 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.84 – 1.54 (m, 1H), 1.15 (d, J = 5.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1, 144.9, 139.5, 129.5, 128.63, 128.59, 128.0, 126.33, 126.30, 121.0, 120.6 (q, J_{CF} = 256.5 Hz), 50.4, 50.3, 48.2, 43.5, 20.8 (two signals missing due to overlap). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -57.73. **IR** (neat, cm^{-1}) 1255, 1220, 1159, 751, 738, 697. **EA** Calcd. for $C_{24}H_{24}F_3NO$: C, 72.16; H, 6.06. Found: C, 72.21; H, 6.22. **Specific rotation** $[\alpha]_D^{22}$ = 20.3 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 97:3 hexanes/2-propanol, 1.0 mL/min, t_M = 4.9 min, t_M = 6.4 min) indicated 98% ee.

(*R*)-4,4-Diphenyl-2-((4-(trifluoromethoxy)benzyl)amino)butyl acetate (8): A 25 mL oven-dried round bottom flask equipped with a magnetic stir bar, purged with argon using an argon-filled manifold, was charged with aziridine **3o** (199 mg, 0.5 mmol, 1.0 equiv) and CH_2Cl_2 (1 mL). Acetic acid (143 µL, 2.5 mmol, 5.0 equiv) was added dropwise using a syringe. The reaction mixture was stirred for 48 h at rt before it was quenched carefully by addition of sat. $NaHCO_3$ solution (10 mL) and EtOAc (10 mL). The aqueous layer was separated and extracted with EtOAc (10 mL × 2) using a separatory funnel. The combined organic layers were washed with brine (30 mL). The mixture was then separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography



8

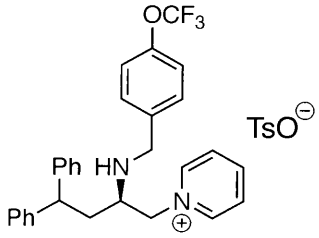
(4–20% acetone in hexanes) to provide the title compound as a pale-yellow oil. **Yield:** 172 mg, 75%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 8H), 7.26 – 7.19 (m, 4H), 7.17 (d, J = 8.1 Hz, 2H), 4.27 – 4.18 (m, 2H), 4.10 (dd, J = 11.3, 4.8 Hz, 1H), 3.82 (d, J = 13.4 Hz, 1H), 3.69 (d, J = 13.4 Hz, 1H), 2.71 (dq, J = 7.6, 4.8 Hz, 1H), 2.30 – 2.17 (m, 2H), 2.09 (s, 3H), 1.58 (br s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.3, 148.4 (q, J_{CF} = 1.8 Hz), 145.0, 144.5, 139.4, 129.7, 128.85, 128.81, 128.1, 128.0, 126.61, 126.59, 121.1, 120.8 (q, J_{CF} = 256.7 Hz), 65.8, 53.8, 50.3, 48.0, 38.6, 21.2. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -57.76. **IR** (neat, cm^{-1}) 1736, 1255, 1221, 1160, 699 cm^{-1}. **EA** Calcd. for $C_{26}H_{26}F_3NO_3$: C, 68.26; H, 5.73. Found: C, 68.29; H, 5.75. **Specific rotation** $[\alpha]_D^{21}$ = 18.4 (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 97:3 hexanes/2-propanol, 1.0 mL/min, t_M = 7.3 min, t_m = 9.6 min) indicated 97% ee.



9

(*R*)-4-(2,2-Diphenylethyl)-3-(4-(trifluoromethoxy)-benzyl)-oxazolidin-2-one (9): An oven-dried screw-cap reaction tube (13 mm × 100 mm) equipped with a magnetic stir bar was charged with aziridine **3o** (199 mg, 0.5 mmol, 1.0 equiv). The reaction tube was transferred into a nitrogen-filled glovebox and anhydrous LiI (66.6 mg, 0.5 mmol, 1.0 equiv), and THF (2.5 mL) were added. The reaction tube was resealed with a new screw cap with a Teflon septum and removed from the glovebox. Using a Schlenk manifold, the reaction tube was evacuated and back-filled with CO_2 using 2 balloons filled with CO_2. The reaction mixture was stirred for 20 h at 40 °C, with an additional balloon filled with CO_2 being added after the first two deflated. The reaction mixture was cooled to rt, then quenched by addition of water (10 mL) and EtOAc (10 mL). The aqueous layer was separated and extracted with EtOAc (10 mL × 2) using a separatory funnel. The combined organic layers were washed with brine (30 mL). The mixture was then separated using a separatory funnel and the organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (0–35% EtOAc in hexanes) to provide the title compound and the corresponding regioisomer in a 9.5 : 1 ratio as a pale yellow oil. **Yield:** 219 mg, 99%. The mixture of regioisomers was separated using preparative HPLC (Agilent preparative C18 column, 21.2 × 150 mm, 5 micron) with acetonitrile and water as eluents (5% acetonitrile in water – 80% acetonitrile in water) for NMR analysis of the major isomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 6.92 (m, 15H), 4.46

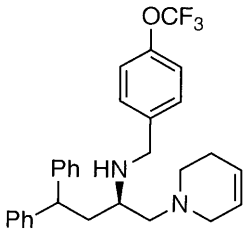
(d, J = 15.1 Hz, 1H), 4.36 (d, J = 15.3 Hz, 1H), 4.34 – 4.24 (m, 2H), 3.41 (t, J = 8.5 Hz, 1H), 3.05 (t, J = 7.8 Hz, 1H), 2.47 (ddd, J = 14.3, 9.1, 5.2 Hz, 1H), 2.33 (ddd, J = 14.3, 10.6, 4.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.0, 149.0 (q, J_{CF} = 1.7 Hz), 143.8, 142.9, 134.6, 129.7, 128.9, 128.8, 128.2, 127.6, 126.9, 126.7, 121.5, 120.54 (q, J_{CF} = 257.4 Hz), 71.8, 49.6, 47.7, 46.7, 41.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -57.87. **IR** (neat, cm^{-1}) 3027, 2928, 1742, 1253, 1220, 1198, 1161, 757, 697 cm^{-1}. **HRMS** (DART+) Calcd. for $C_{25}H_{22}F_3NO_3$ $[M+H]^+$ 442.1625, found 442.1628. **Specific rotation** $[\alpha]_D^{22}$ = 63.4 (c = 0.95, $CHCl_3$). **HPLC analysis** (AD-H column, 90:10 hexanes/2-propanol, 1.0 mL/min, major isomer: t_M = 20.0 min, t_m = 19.1 min, minor isomer: t_M = 10.8 min, t_m = 10.4 min) indicated 95% ee.



10

(*R*)-1-(4,4-Diphenyl-2-((4-(trifluoromethoxy)benzyl)amino)-butyl)-pyridin-1-ium 4-methylbenzenesulfonate (10): An oven-dried screw-cap reaction tube (13 mm × 100 mm) equipped with a magnetic stir bar, purged with argon using an argon-filled manifold, was charged with aziridine **3o** (199 mg, 0.5 mmol, 1.0 equiv) and CH_2Cl_2 (1 mL). Tosylic acid (188 mg, 0.75 mmol, 1.5 equiv) was added as one portion. The reaction tube was then sealed with a screw cap with a Teflon septum. The reaction mixture was stirred for 6 h at rt and then quenched by addition of sat. $NaHCO_3$ solution (5 mL) and EtOAc (5 mL). The aqueous layer was separated and extracted with EtOAc (5 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via trituration using hexanes (30 mL) to provide the title compound as a yellow solid, **m.p.** 47–53 °C. **Yield:** 211 mg, 65%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (d, J = 5.8 Hz, 2H), 8.04 (t, J = 7.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 6.9 Hz, 2H), 7.38 – 7.24 (m, 8H), 7.24 – 7.14 (m, 4H), 6.78 (d, J = 8.0 Hz, 2H), 6.48 (d, J = 8.1 Hz, 2H), 5.03 (d, J = 12.4 Hz, 1H), 4.80 (t, J = 11.2 Hz, 1H), 4.20 (dd, J = 9.5, 6.4 Hz, 1H), 3.63 (d, J = 13.3 Hz, 1H), 3.26 (d, J = 13.3 Hz, 1H), 2.44 – 2.29 (m, 2H), 2.38 (s, 3H), 2.22 (dt, J = 13.8, 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7 (d, J_{CF} = 1.8 Hz), 145.9, 144.5, 144.08, 144.06, 143.8, 139.5, 138.8, 129.6, 128.9, 128.8, 128.7, 128.1, 128.0, 126.7, 126.5, 126.1, 120.5, 120.5 (q, J_{CF} = 256.8 Hz), 63.9, 55.6, 49.1, 47.5, 37.8, 21.4 (one signal missing due to overlap). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -57.77. **IR** (neat, cm^{-1}) 1492, 1260, 1194, 1120, 1033, 1011, 816, 731, 679. **HRMS** (DART+) Calcd. for

$C_{36}H_{35}F_3N_2O_4S$ $[M–OTs]^+$ 477.2148, found 477. 2132. **Specific rotation** $[\alpha]_D^{22} = -57.9$ (c = 1.02, $CHCl_3$). **HPLC analysis** was performed on its reduction product see below.



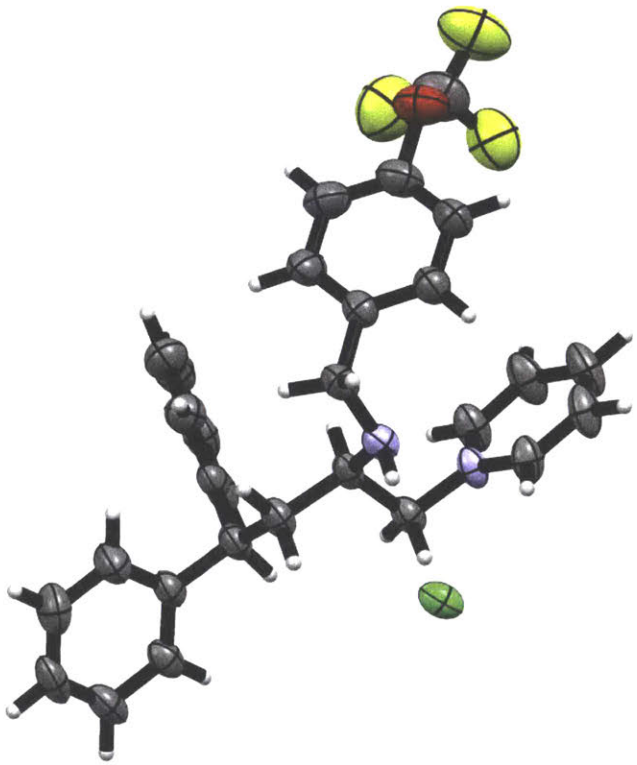
SI-1

(*R*)-1-(3,6-dihydropyridin-1(2*H*)-yl)-4,4-diphenyl-*N*-(4-(trifluoromethoxy)benzyl)butan-2-amine (SI-1): A 25 mL oven-dried round-bottom flask equipped with a magnetic stir bar, the crude reaction material of (*R*)-1-(4,4-diphenyl-2-((4-(trifluoromethoxy)benzyl)amino)butyl)-pyridin-1-ium 4-methylbenzene-sulfonate **10** (0.5 mmol, 1.0 equiv; prepared above) was dissolved in MeOH (2.5 mL). $NaBH_4$ (76 mg, 2.0 mmol, 4 equiv) was added as one portion and the reaction mixture was allowed to stir for 15 h at rt, before it was quenched carefully by addition of sat. $NaHCO_3$ solution (10 mL) and EtOAc (10 mL). The aqueous layer was separated and extracted with EtOAc (10 mL × 2) using a separatory funnel. The combined organic layers were washed with brine (40 mL). The mixture was then separated and the organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified via flash column chromatography (10–40% acetone in hexanes) to the title compound as a yellow oil. **Yield:** 151 mg, 63% over 2 steps. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 6H), 7.24 – 7.14 (m, 4H), 7.04 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.2 Hz, 2H), 5.68 (dt, J = 10.0, 3.1 Hz, 1H), 5.54 (dt, J = 10.0, 2.6 Hz, 1H), 4.03 (dd, J = 9.9, 5.9 Hz, 1H), 3.77 (d, J = 13.7 Hz, 1H), 3.53 (d, J = 13.8 Hz, 1H), 2.71 (dt, J = 16.5, 2.8 Hz, 1H), 2.65 (dt, J = 16.2, 2.9 Hz, 1H), 2.51 (tt, J = 8.4, 4.2 Hz, 1H), 2.43 – 2.36 (m, 2H), 2.32 (ddd, J = 14.3, 9.9, 4.2 Hz, 1H), 2.29 – 2.22 (m, 2H), 2.05 (dt, J = 14.2, 7.2 Hz, 1H), 2.03 – 1.87 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.0, 145.2, 145.0, 139.6, 129.7, 128.7, 128.6, 128.1, 127.9, 126.4, 126.3, 125.4, 125.3, 120.9, 120.6 (q, J_{CF} = 256.8 Hz), 62.6, 53.1, 50.4, 50.1, 50.0, 48.0, 39.3, 26.2. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -57.79. **IR** (neat, cm^{-1}) 1256, 1221, 1160, 735, 697, 653. **HRMS** (DART-TOF) Calcd. for $C_{29}H_{31}F_3N_2O$ $[M+H]^+$ 481.2461, found 481. 2476. **Specific rotation** $[\alpha]_D^{21} = -76.3$ (c = 1.0, $CHCl_3$). **HPLC analysis** (AD-H column, 97:3 hexanes/2-propanol, 1.0 mL/min, t_M = 7.3 min, t_m = 11.3 min) indicated 99% ee.

X-ray Crystal Information of Compound 10•Cl

Crystal data and structure refinement for **10•Cl**.

Identification code	X17068_sq	
Empirical formula	C29 H29 Cl F3 N2 O1.50	
Formula weight	521.99	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 16.4745(13) Å	a= 90°.
	b = 10.3337(8) Å	b= 112.448(5)°.
	c = 18.463(2) Å	g = 90°.
Volume	2905.0(5) $Å^3$	
Z	4	
Density (calculated)	1.194 Mg/m^3	
Absorption coefficient	1.537 mm^{-1}	
F(000)	1092	
Crystal size	0.260 x 0.145 x 0.007 mm^3	
Theta range for data collection	2.589 to 68.246°.	
Index ranges	-19<=h<=19, -12<=k<=12, -22<=l<=22	
Reflections collected	34400	
Independent reflections	5341 [R(int) = 0.0638]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5341 / 1022 / 455	
Goodness-of-fit on F^2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1278	
R indices (all data)	R1 = 0.0613, wR2 = 0.1398	
Absolute structure parameter	0.061(9)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.198 and -0.179 $e.Å^{-3}$	



Single crystal X-ray structure of **10•Cl**. ORTEP representation, 50% probability level.

2.5 References and Notes

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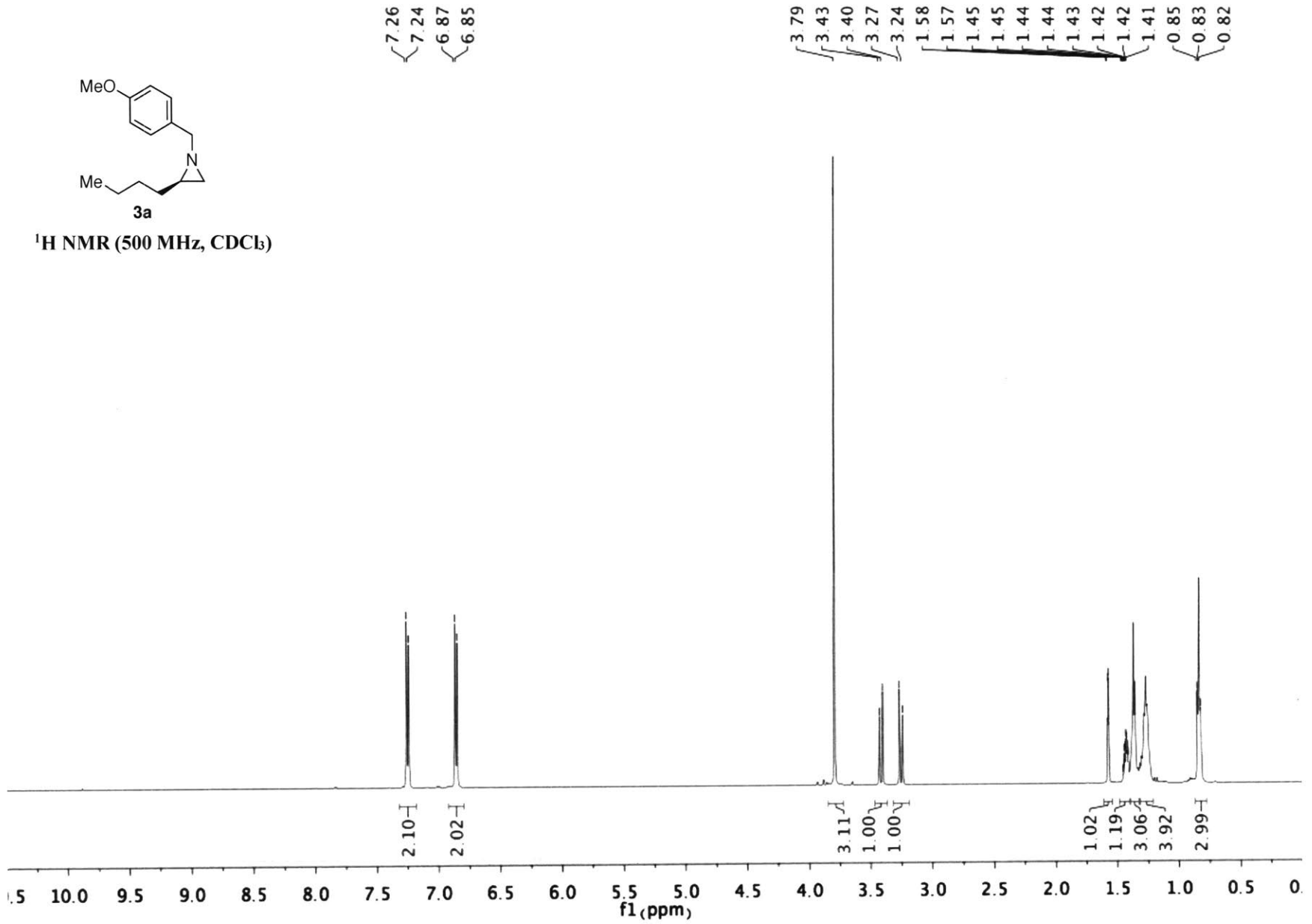
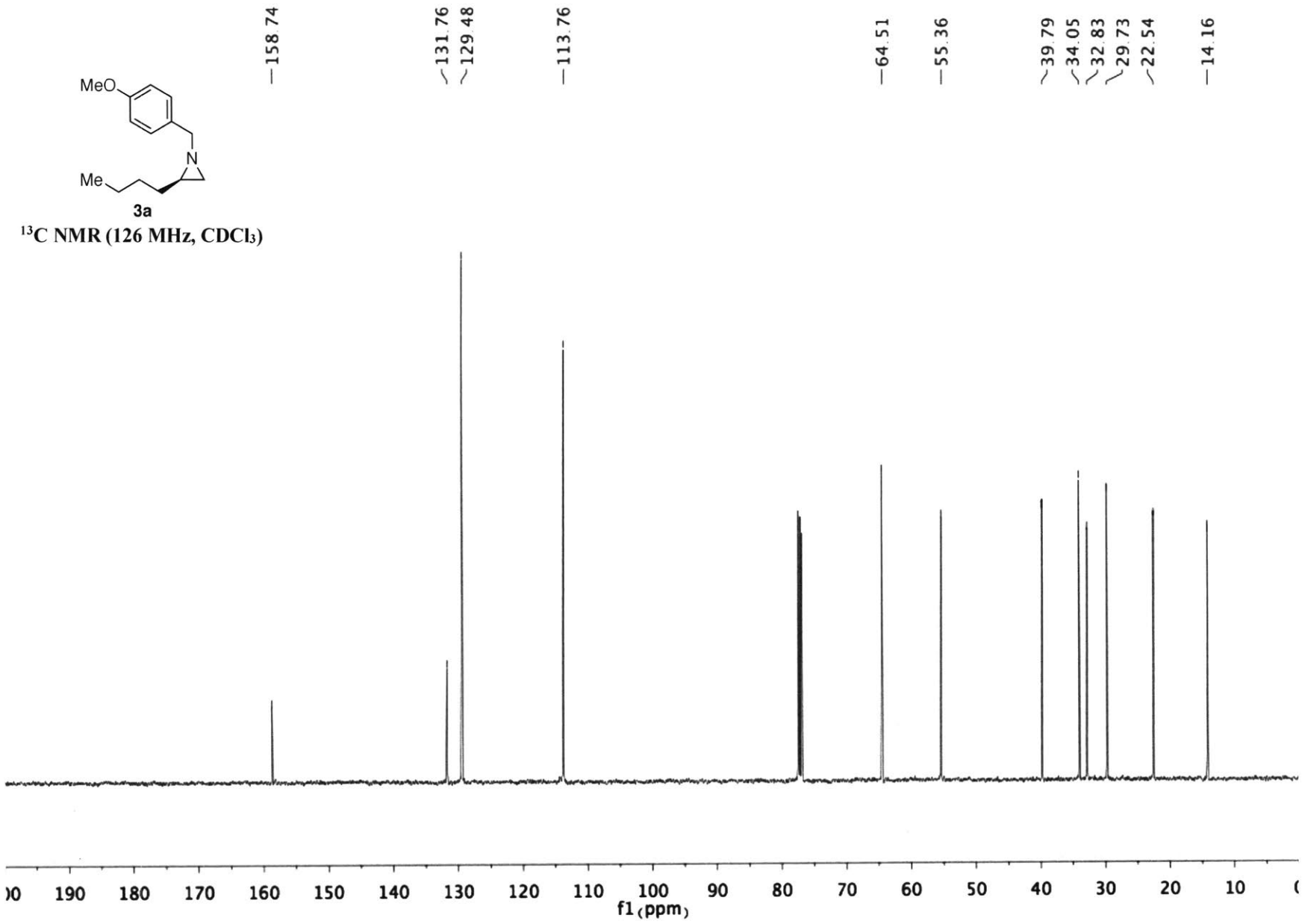
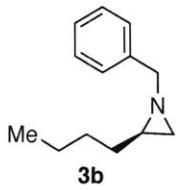
[18] The crystal structure obtained was that of **10**·Cl. Pyridinium salt **10**·OTs was crystallized from a solvent mixture containing dichloromethane, which is presumed to be the source of the chloride anion observed by X-ray crystallography.

2.6 ^{1}H, ^{13}C, and ^{19}F NMR Spectra



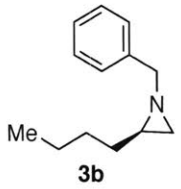
^{1}H NMR (500 MHz, $CDCl_3$)


158.74
131.76
129.48
113.76
64.51
55.36
39.79
34.05
32.83
29.73
22.54
14.16
MeO
N
Me
3a
^{13}C NMR (126 MHz, CDCl$_3$)
f1 (ppm)



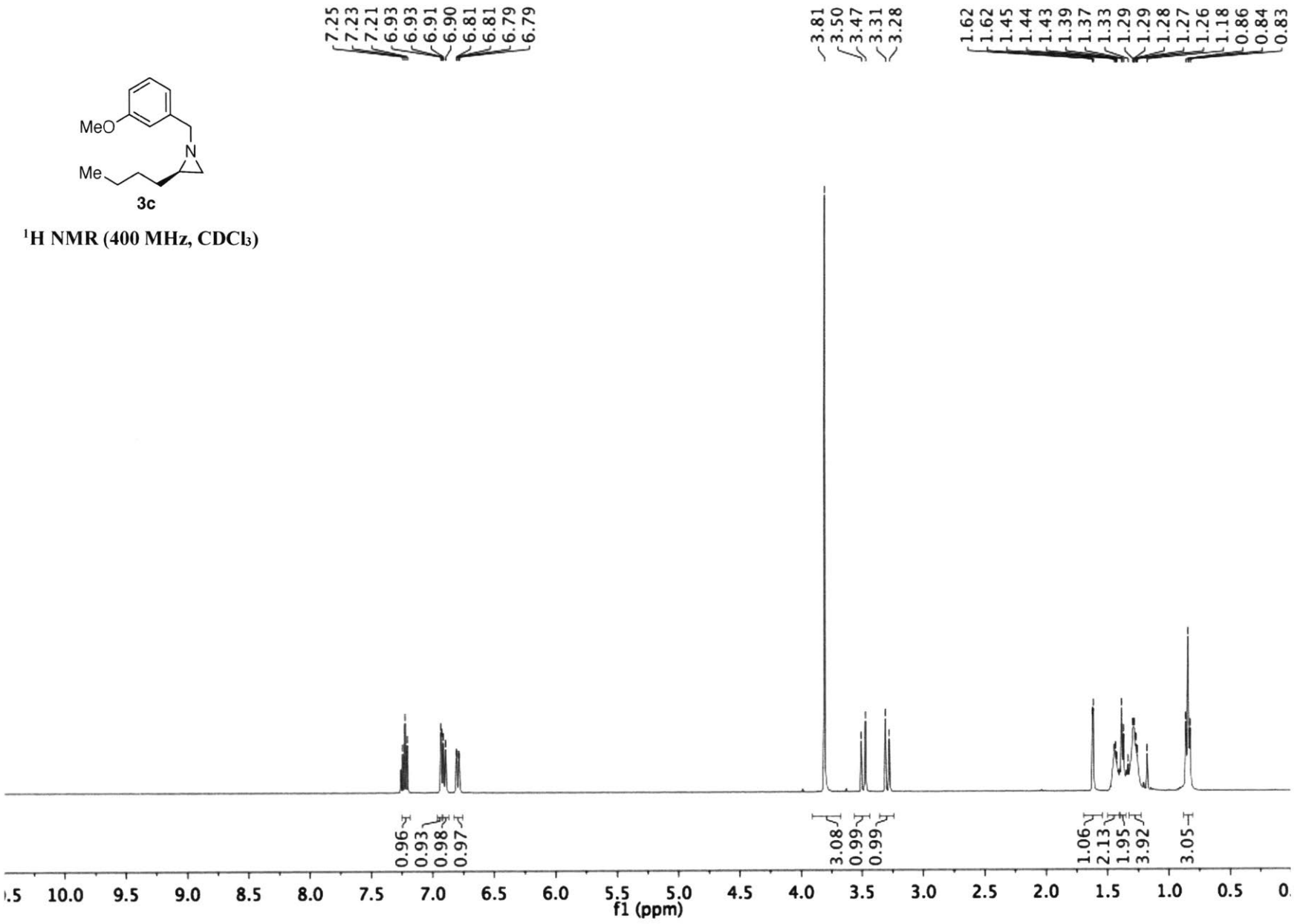
3b

^{1}H NMR (500 MHz, $CDCl_3$)

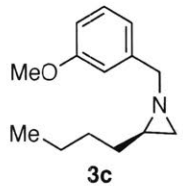


3b

^{13}C NMR (126 MHz, $CDCl_3$)

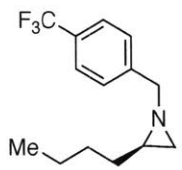


^{1}H NMR (400 MHz, $CDCl_3$)



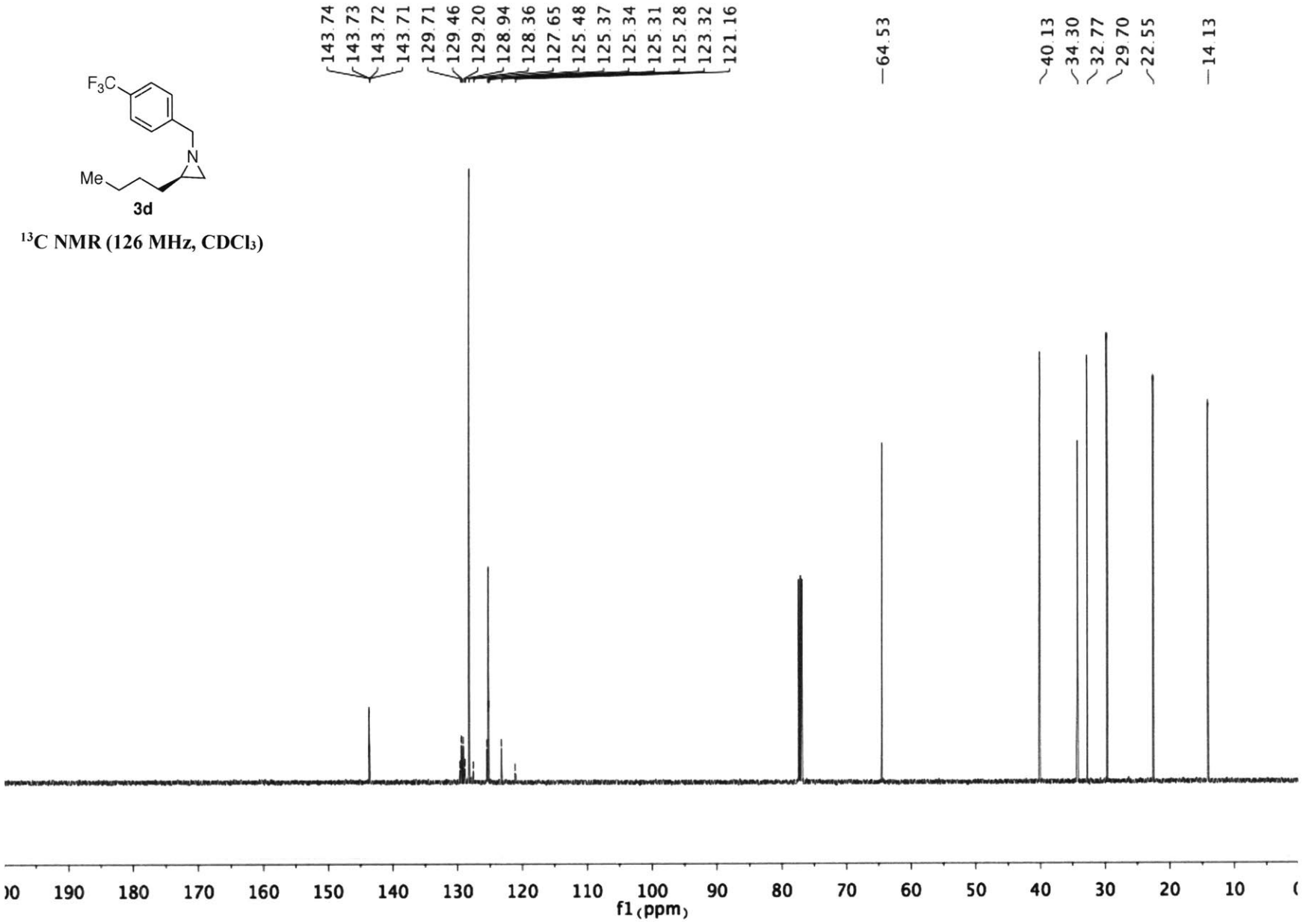
3c

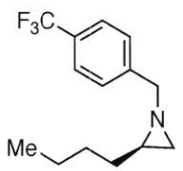
^{13}C NMR (101 MHz, $CDCl_3$)



3d

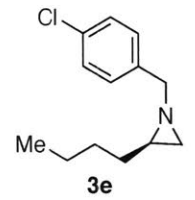
^{1}H NMR (500 MHz, $CDCl_3$)


143.74
143.73
143.72
143.71
129.71
129.46
129.20
128.94
128.36
127.65
125.48
125.37
125.34
125.31
125.28
123.32
121.16
64.53
40.13
34.30
32.77
29.70
22.55
14.13
F3C
N
Me
3d
13C NMR (126 MHz, CDCl3)
f1 (ppm)



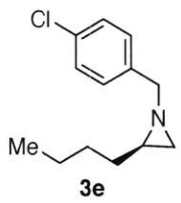
3d

^{19}F NMR (471 MHz, $CDCl_3$)



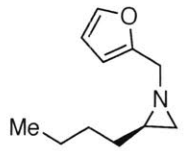
3e

^{1}H NMR (500 MHz, $CDCl_3$)



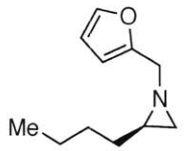
3e

^{13}C NMR (126 MHz, $CDCl_3$)



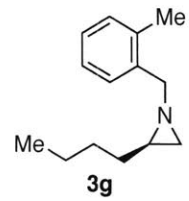
3f

^{1}H NMR (400 MHz, $CDCl_3$)



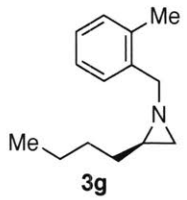
3f

^{13}C NMR (101 MHz, $CDCl_3$)



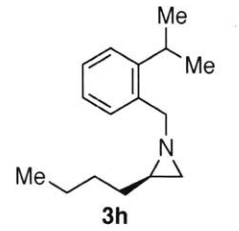
3g

^{1}H NMR (500 MHz, $CDCl_3$)



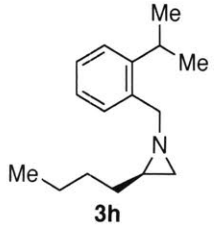
3g

^{13}C NMR (126 MHz, $CDCl_3$)



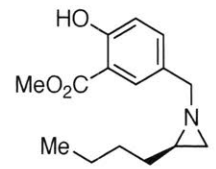
3h

^{1}H NMR (500 MHz, $CDCl_3$)



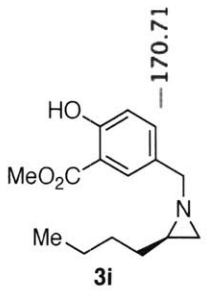
3h

^{13}C NMR (126 MHz, $CDCl_3$)



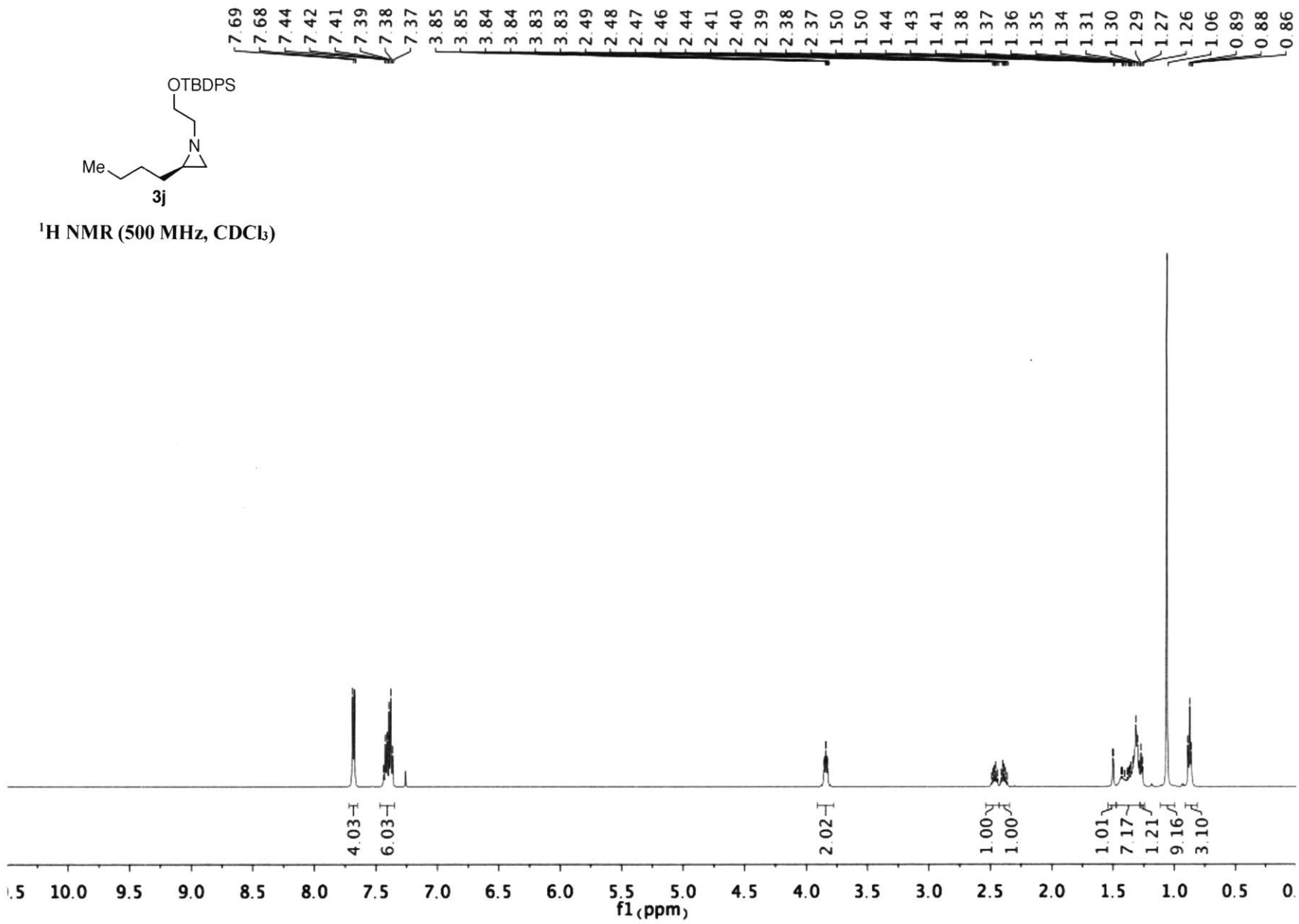
3i

^{1}H NMR (400 MHz, $CDCl_3$)



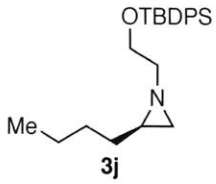
3i

^{13}C NMR (101 MHz, $CDCl_3$)



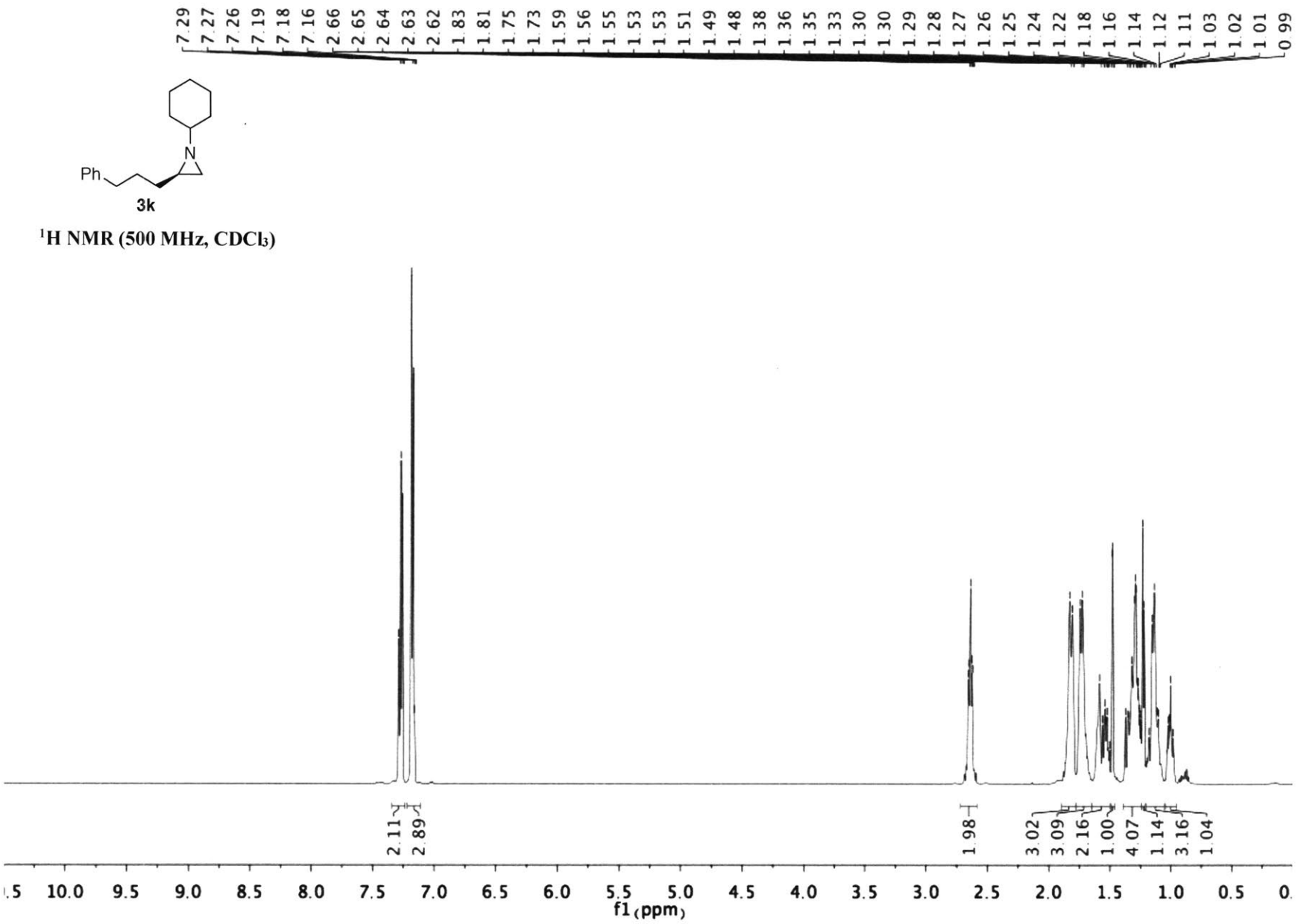
3j

^{1}H NMR (500 MHz, $CDCl_3$)

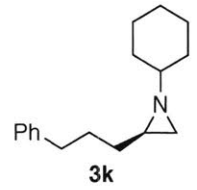


3j

^{13}C NMR (126 MHz, $CDCl_3$)

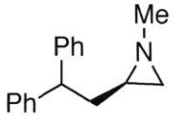


^{1}H NMR (500 MHz, $CDCl_3$)



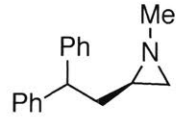
3k

^{13}C NMR (126 MHz, $CDCl_3$)



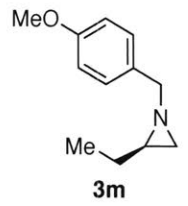
3l

^{1}H NMR (500 MHz, $CDCl_3$)



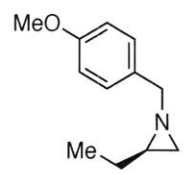
3l

^{13}C NMR (126 MHz, $CDCl_3$)



3m

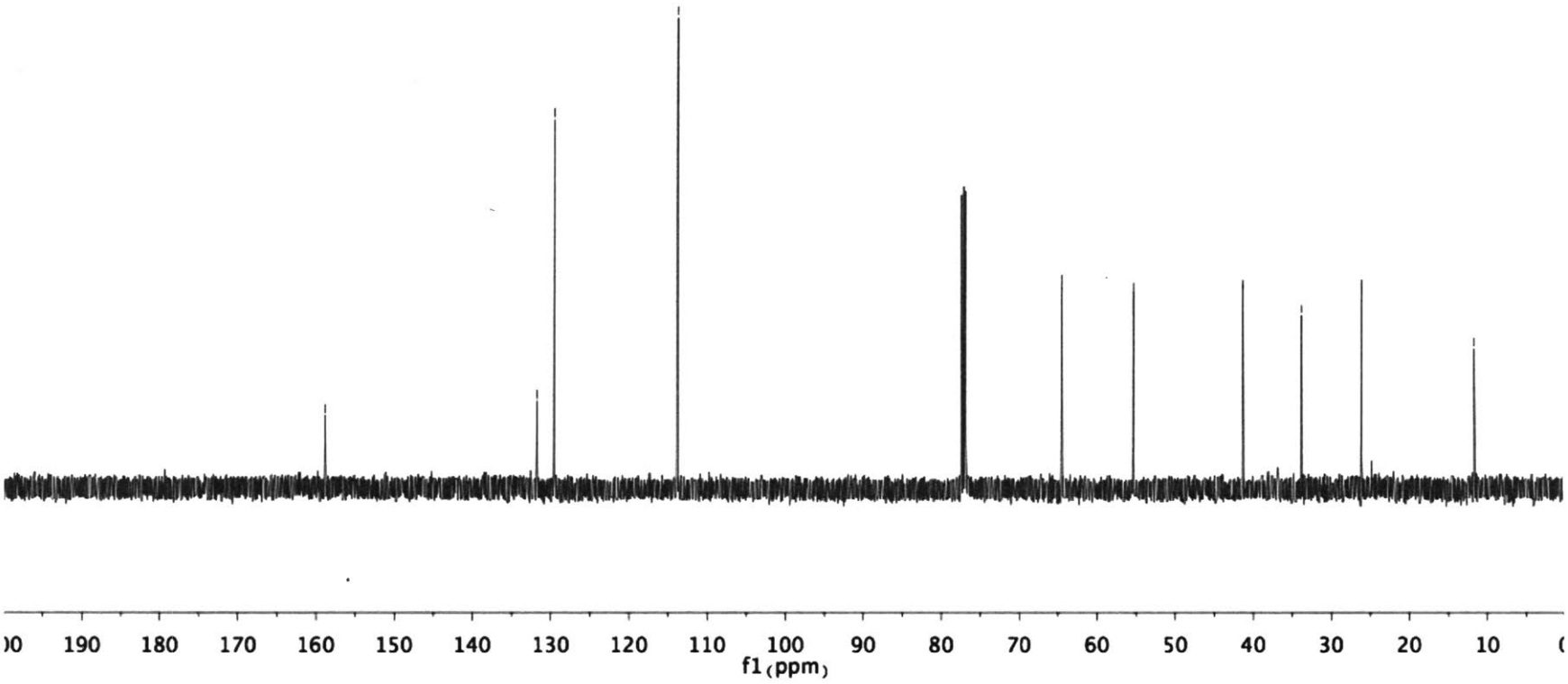
^{1}H NMR (500 MHz, $CDCl_3$)

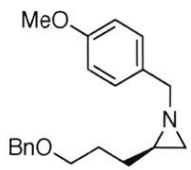


3m

^{13}C NMR (126 MHz, $CDCl_3$)

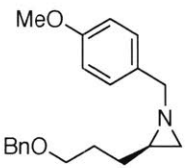
158.75
131.74
129.50
113.77
64.47
55.37
41.37
33.84
26.20
11.69





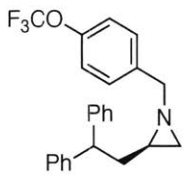
3n

^{1}H NMR (500 MHz, $CDCl_3$)



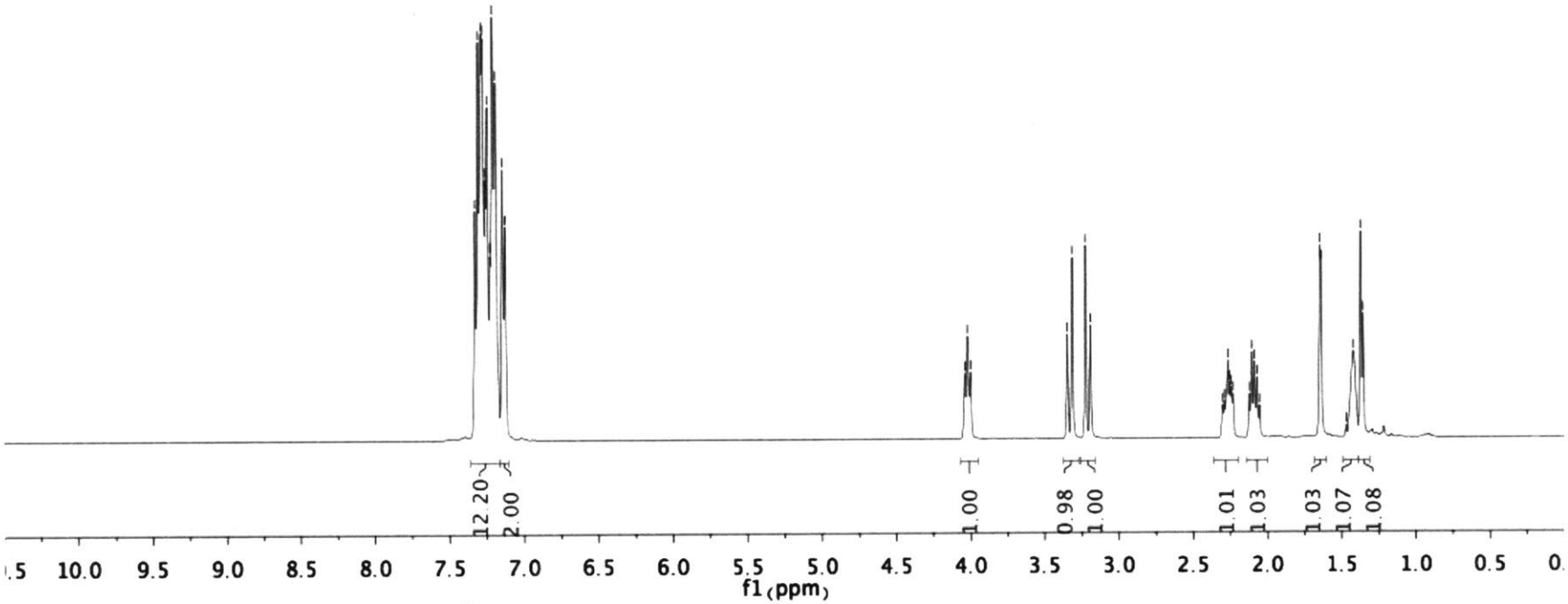
3n

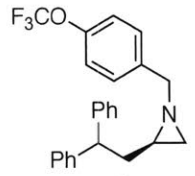
^{13}C NMR (126 MHz, $CDCl_3$)



3o

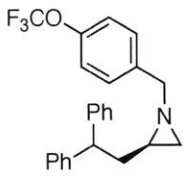
^{1}H NMR (400 MHz, $CDCl_3$)





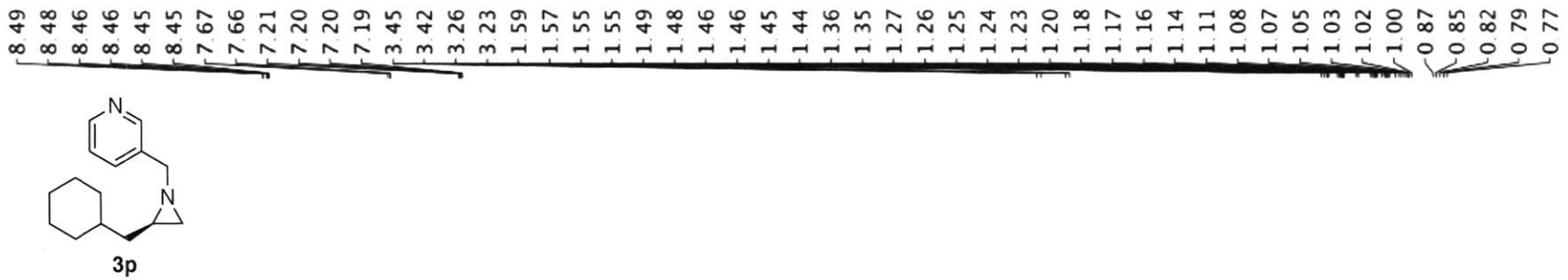
3o

^{13}C NMR (101 MHz, $CDCl_3$)



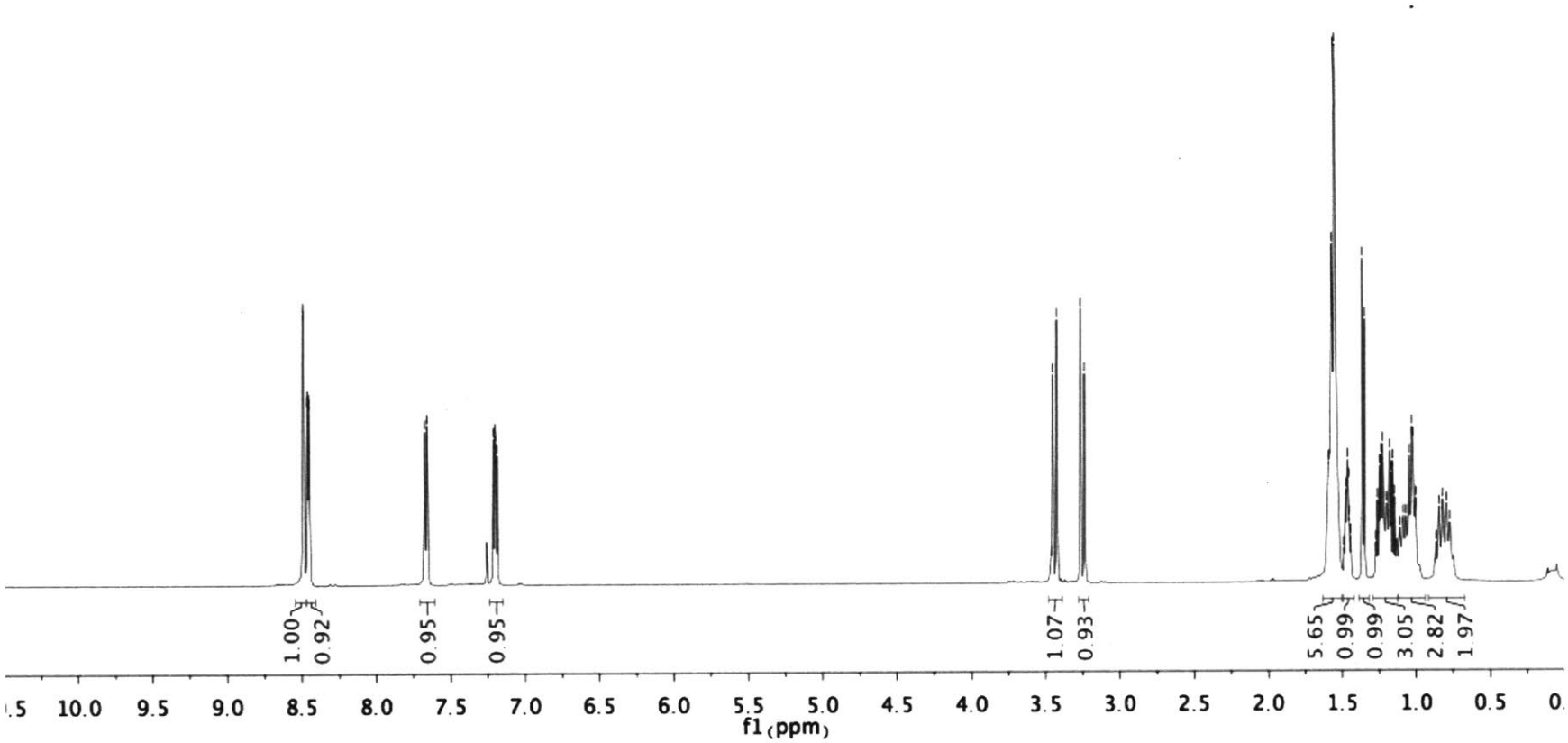
3o

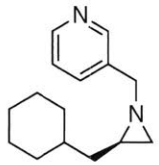
^{19}F NMR (376 MHz, $CDCl_3$)



3p

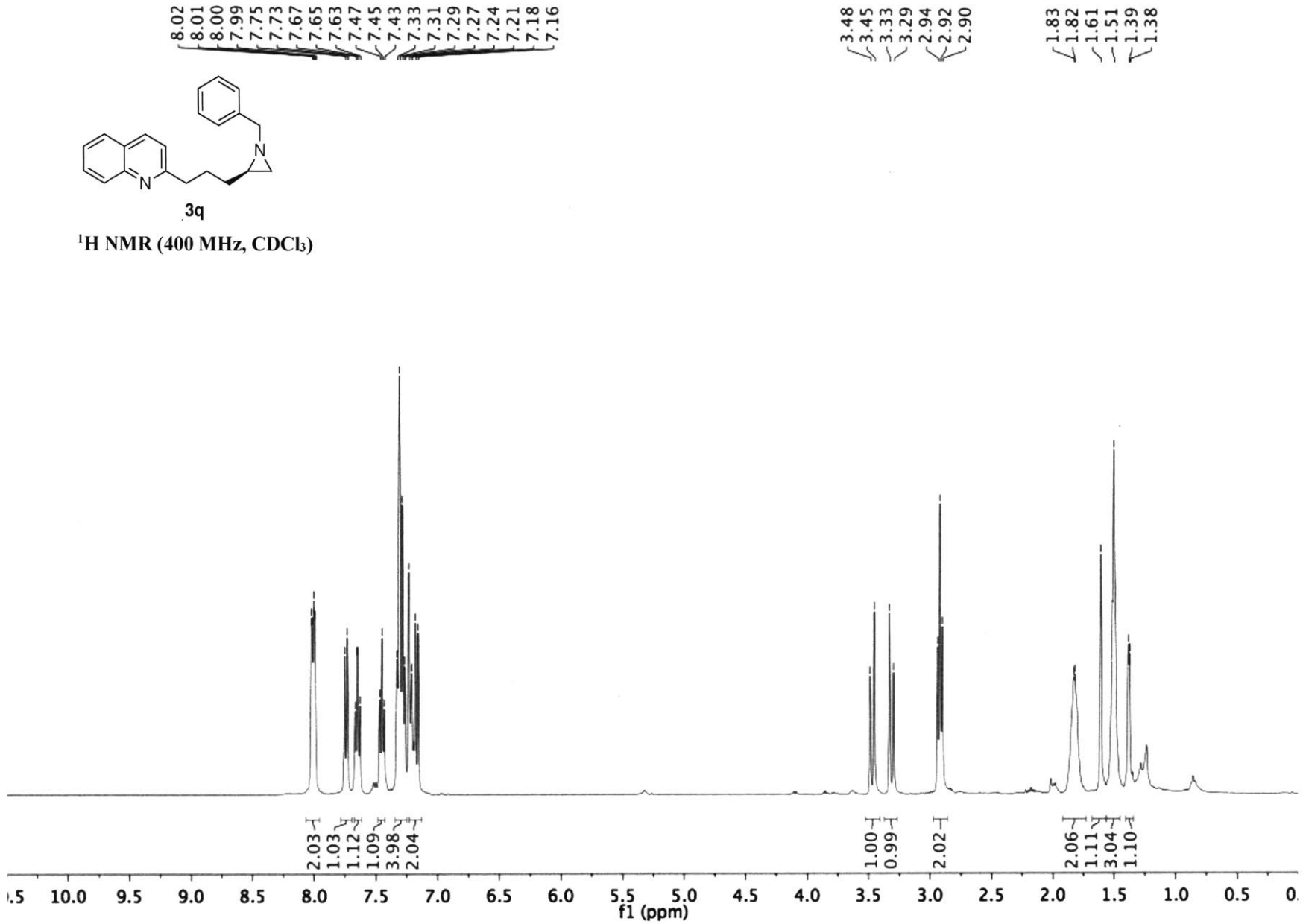
^{1}H NMR (500 MHz, $CDCl_3$)





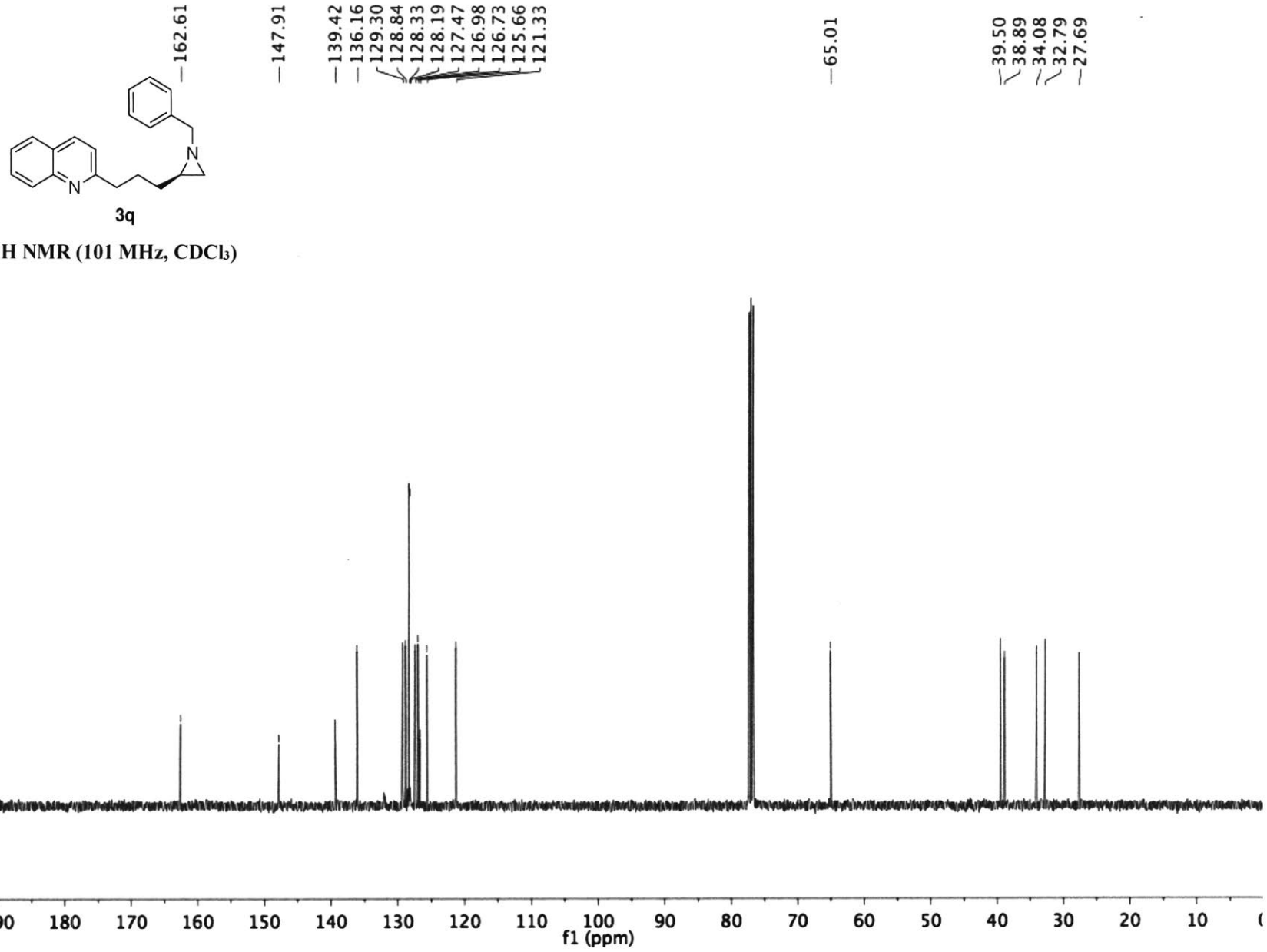
3p

^{13}C NMR (126 MHz, $CDCl_3$)



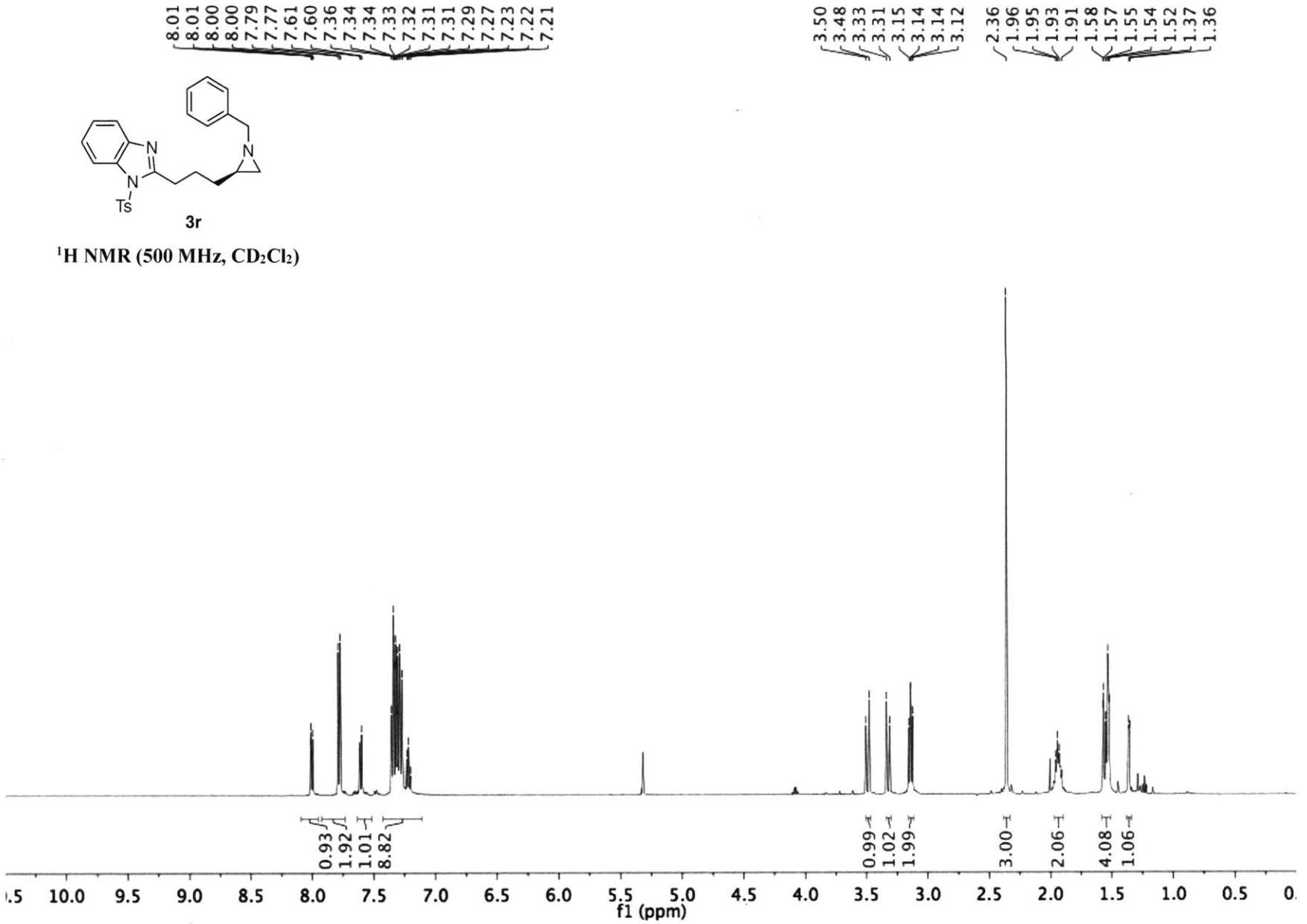
3q

^{1}H NMR (400 MHz, $CDCl_3$)



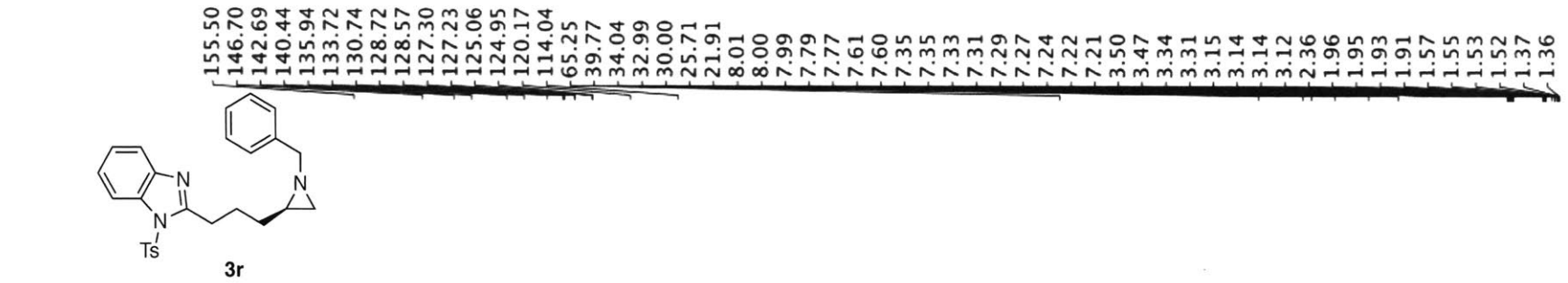
3q

^{1}H NMR (101 MHz, $CDCl_3$)



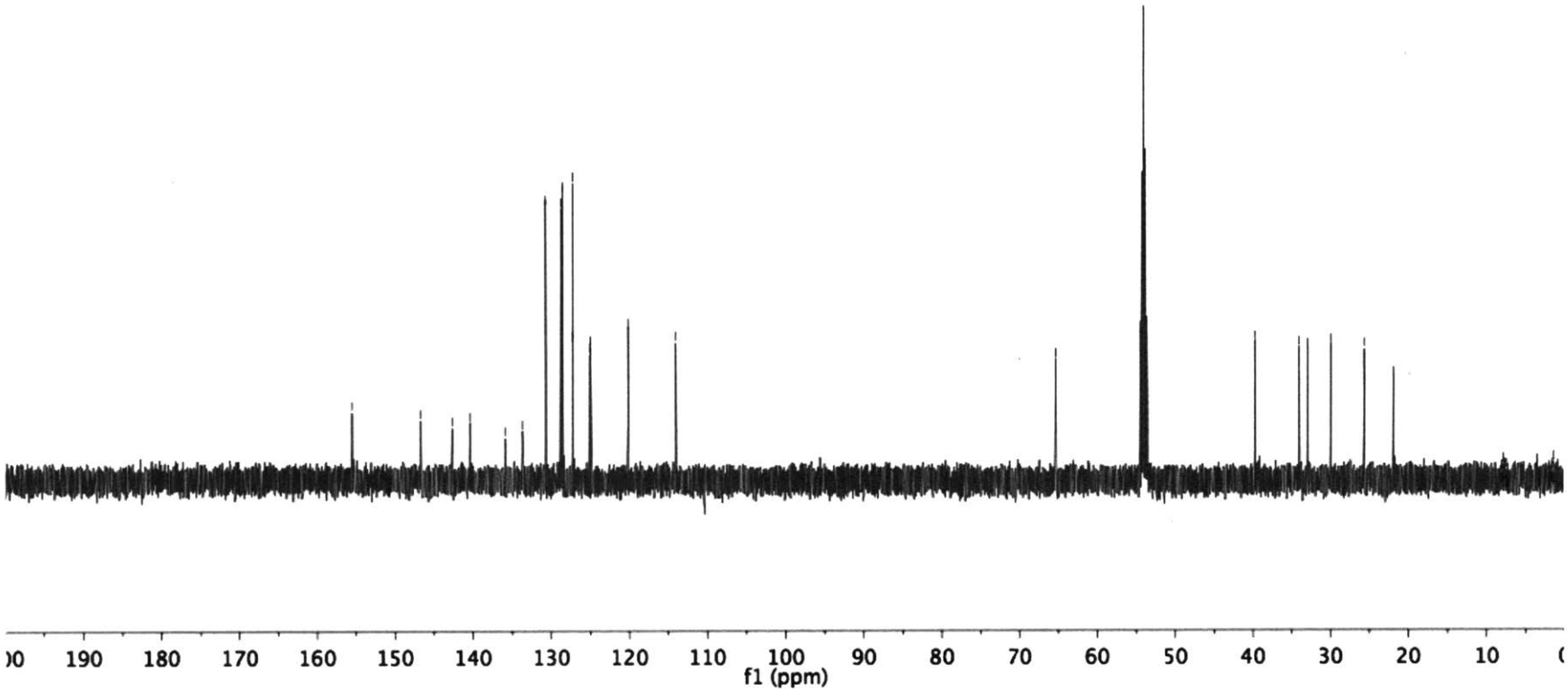
3r

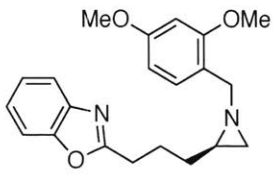
^{1}H NMR (500 MHz, CD_2Cl_2)



3r

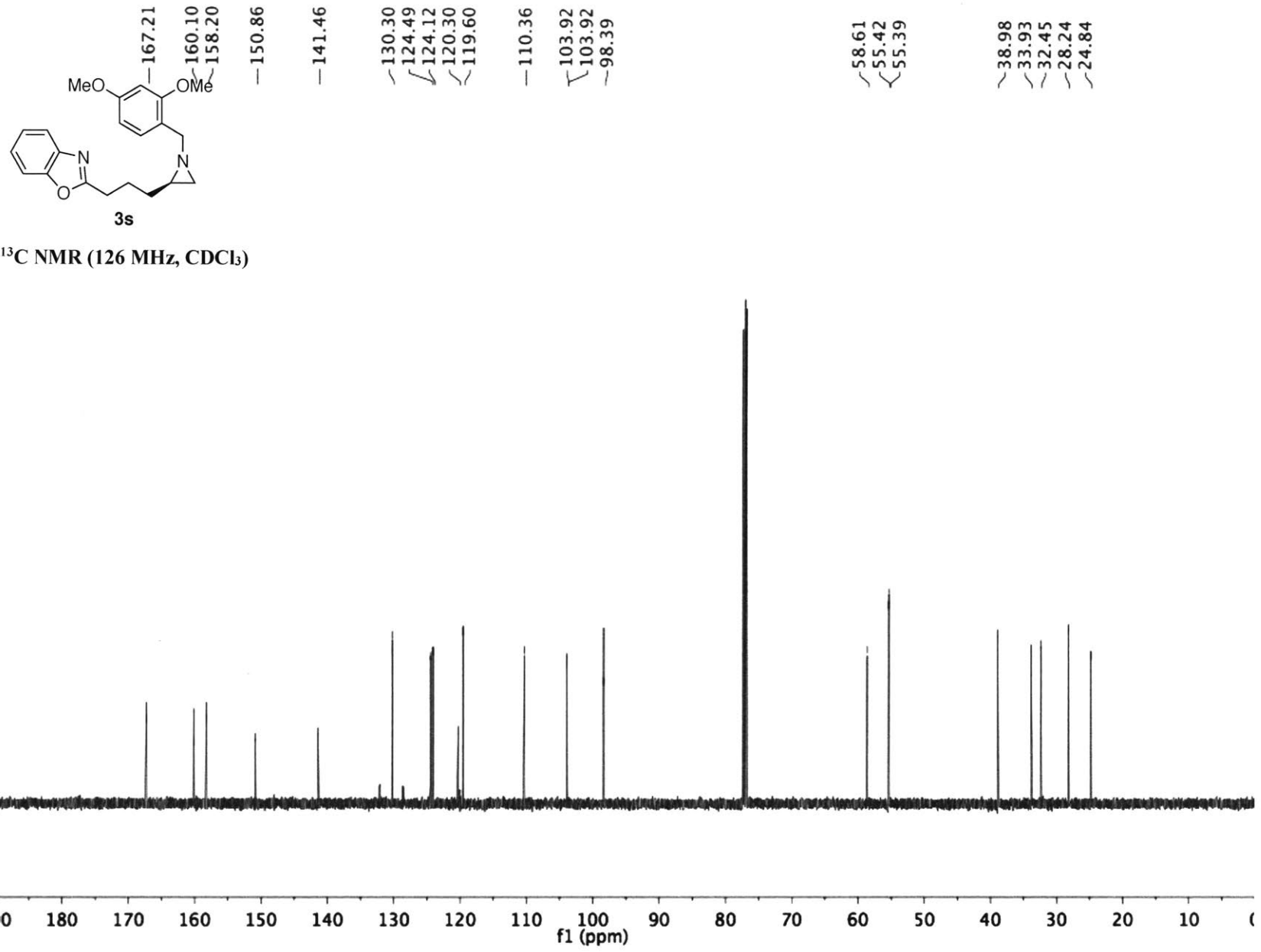
^{13}C NMR (126 MHz, CD_2Cl_2)



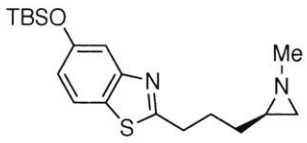


3s

^{1}H NMR (500 MHz, $CDCl_3$)

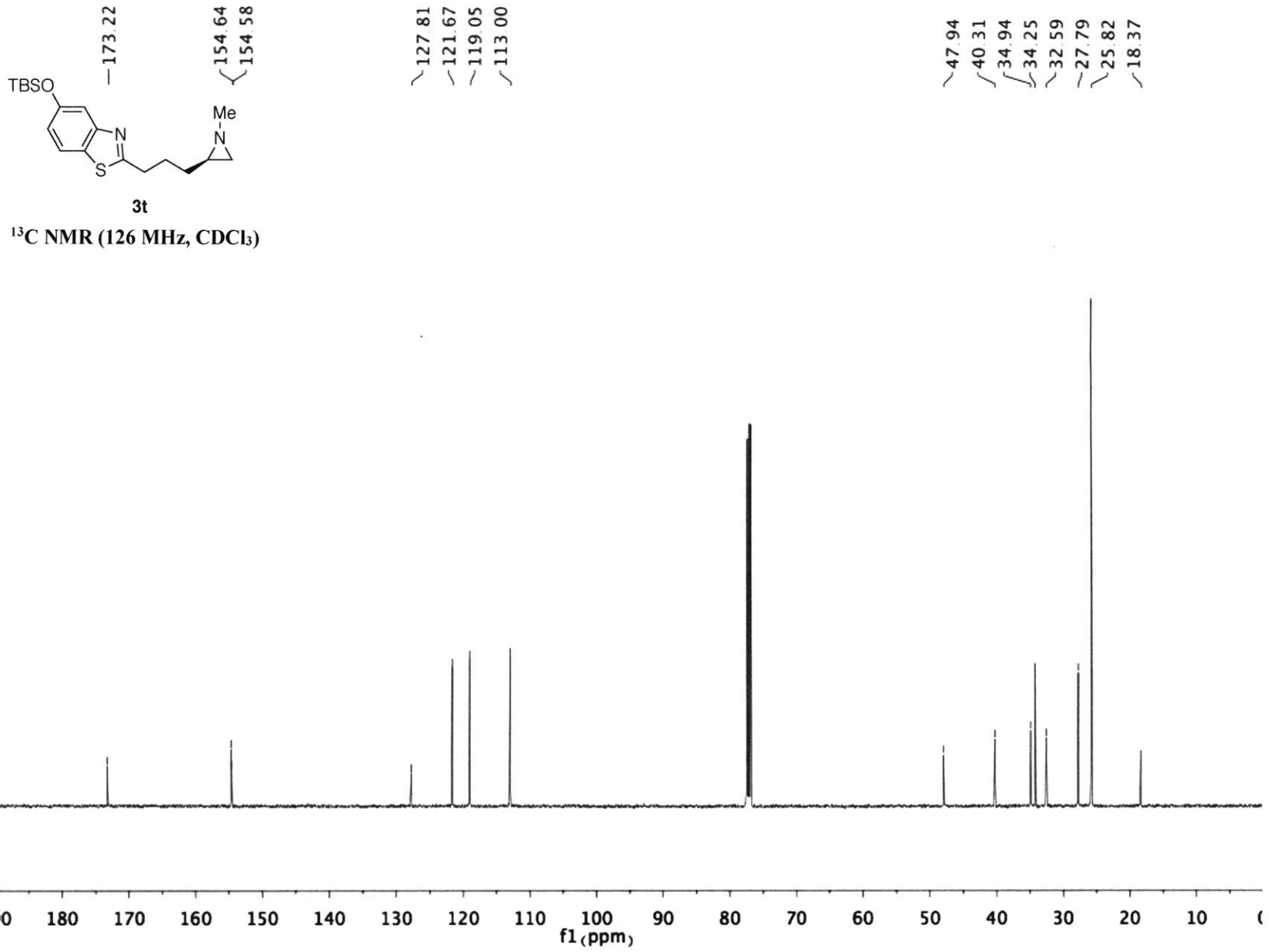


^{13}C NMR (126 MHz, $CDCl_3$)



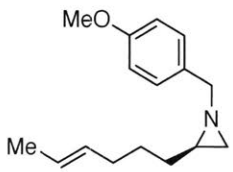
3t

^{1}H NMR (500 MHz, $CDCl_3$)



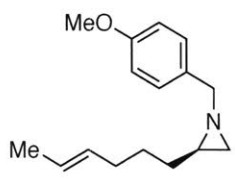
3t

^{13}C NMR (126 MHz, $CDCl_3$)



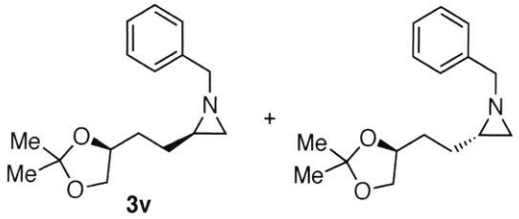
3u

^{1}H NMR (500 MHz, $CDCl_3$)



3u

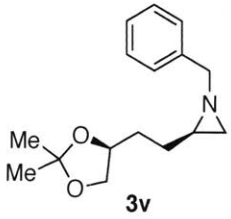
^{13}C NMR (126 MHz, $CDCl_3$)



3v

^{1}H NMR (500 MHz, $CDCl_3$)

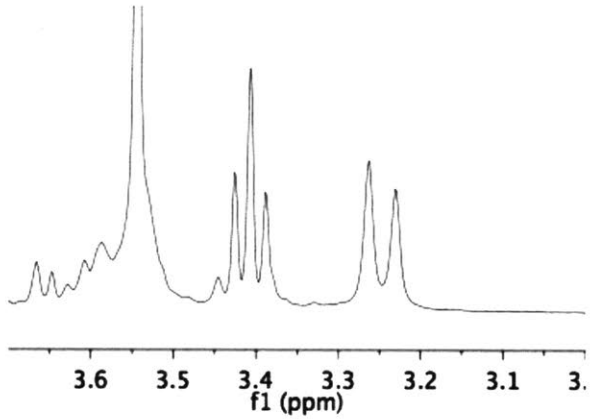
^{1}H NMR spectra of the crude reaction mixture containing 3v and its diastereomer (reaction conducted with (*rac*)-CuCatMix

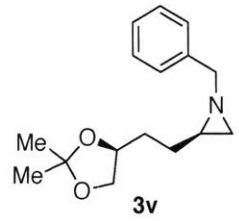


3v

^{1}H NMR (400 MHz, $CDCl_3$)

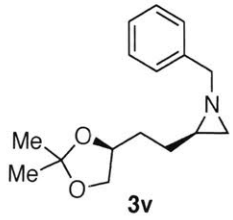
^{1}H NMR spectra of the crude reaction mixture (reaction conducted with (*S*)-CuCatMix





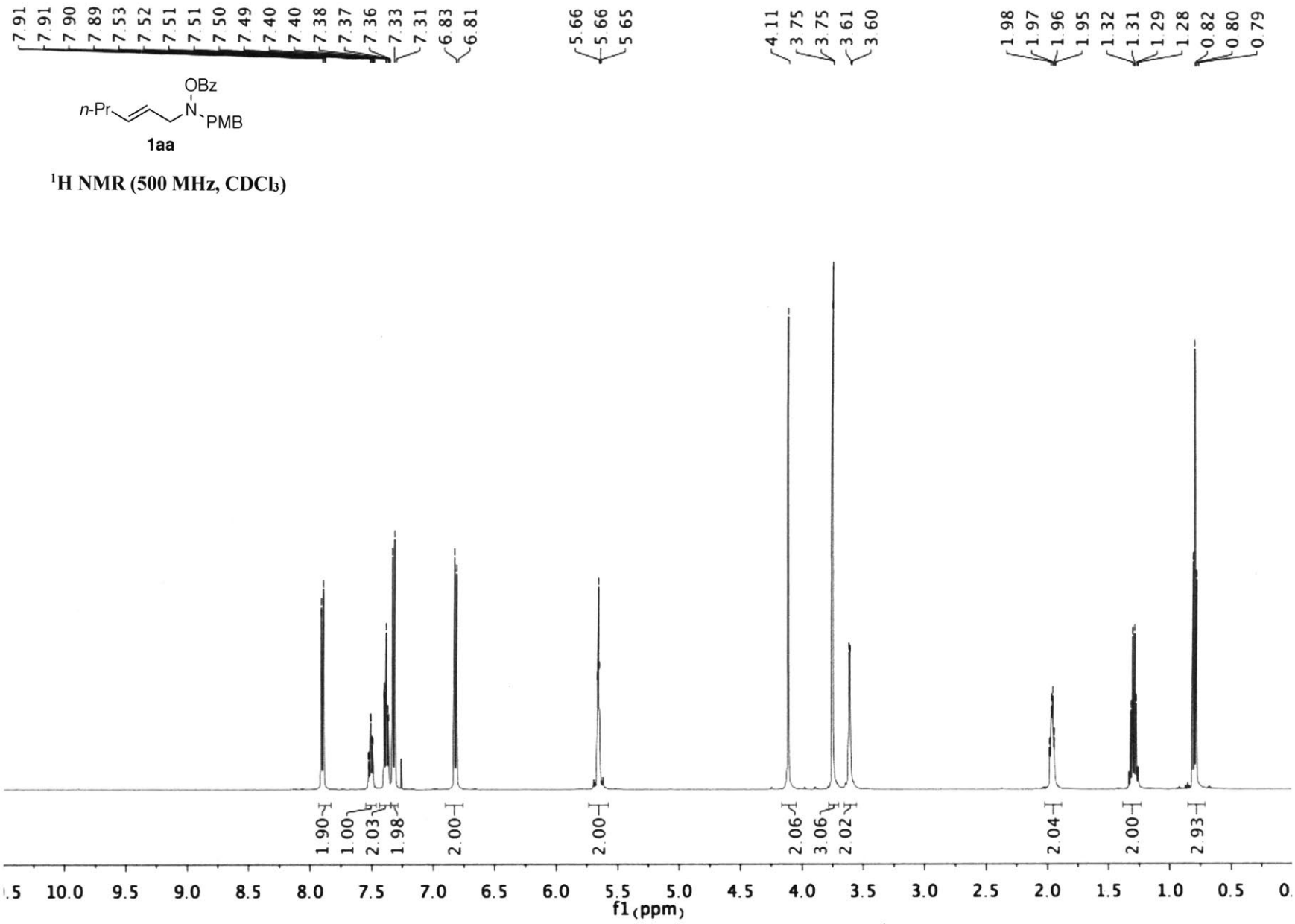
3v

^{1}H NMR (400 MHz, $CDCl_3$)

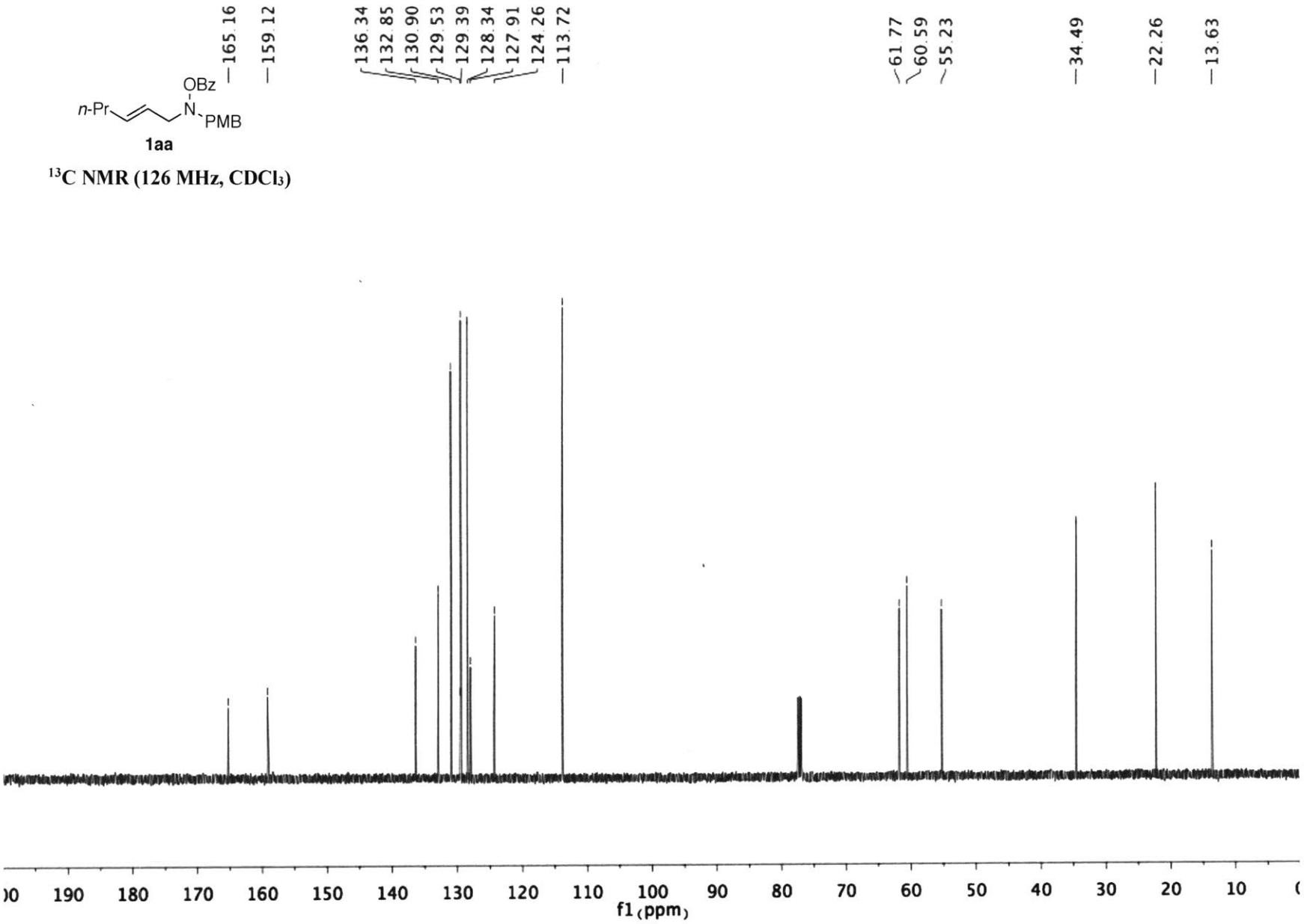


3v

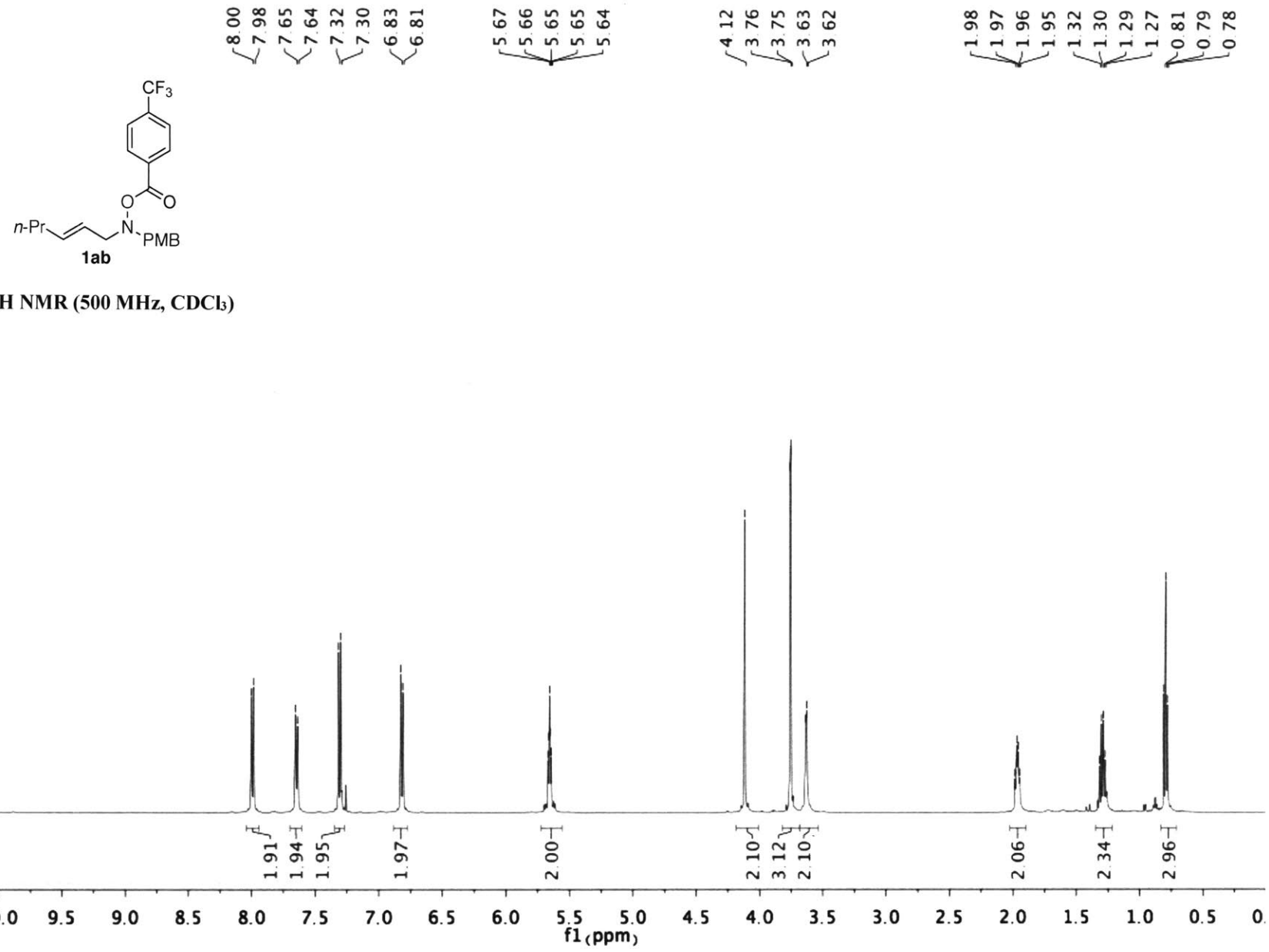
^{1}H NMR (101 MHz, $CDCl_3$)



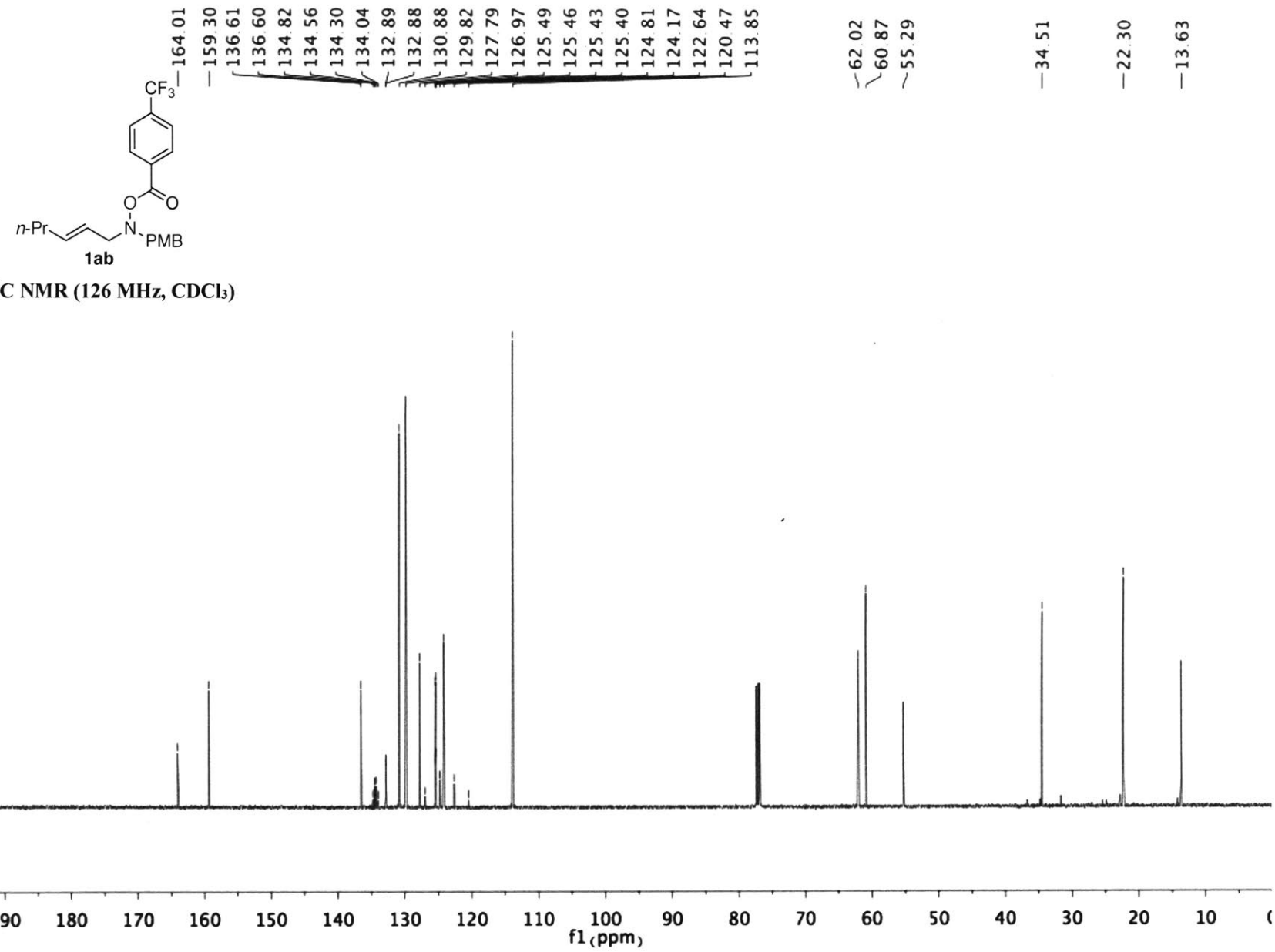
^{1}H NMR (500 MHz, $CDCl_3$)



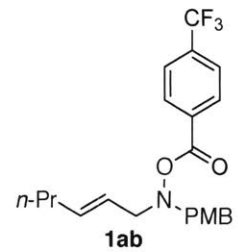
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

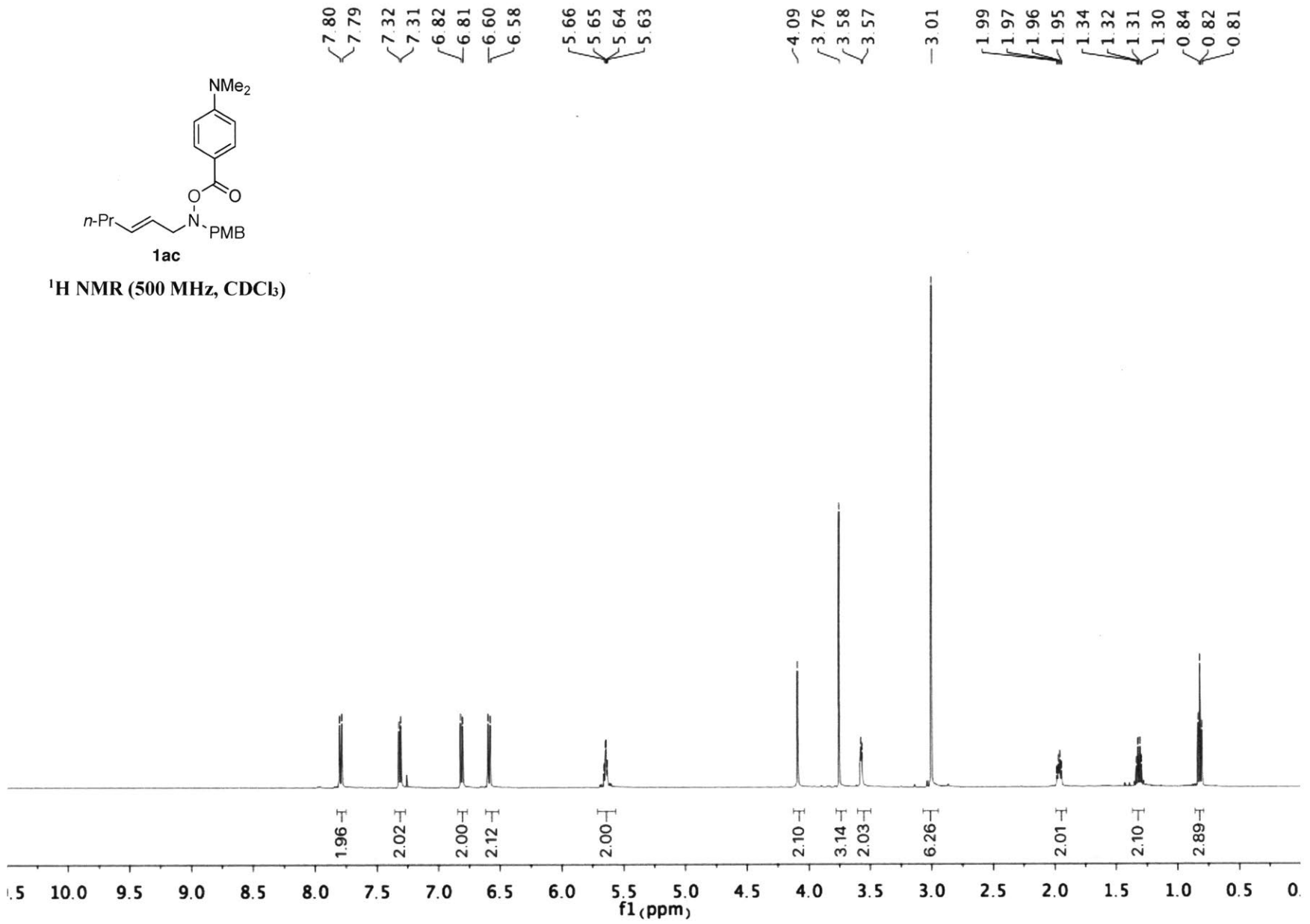


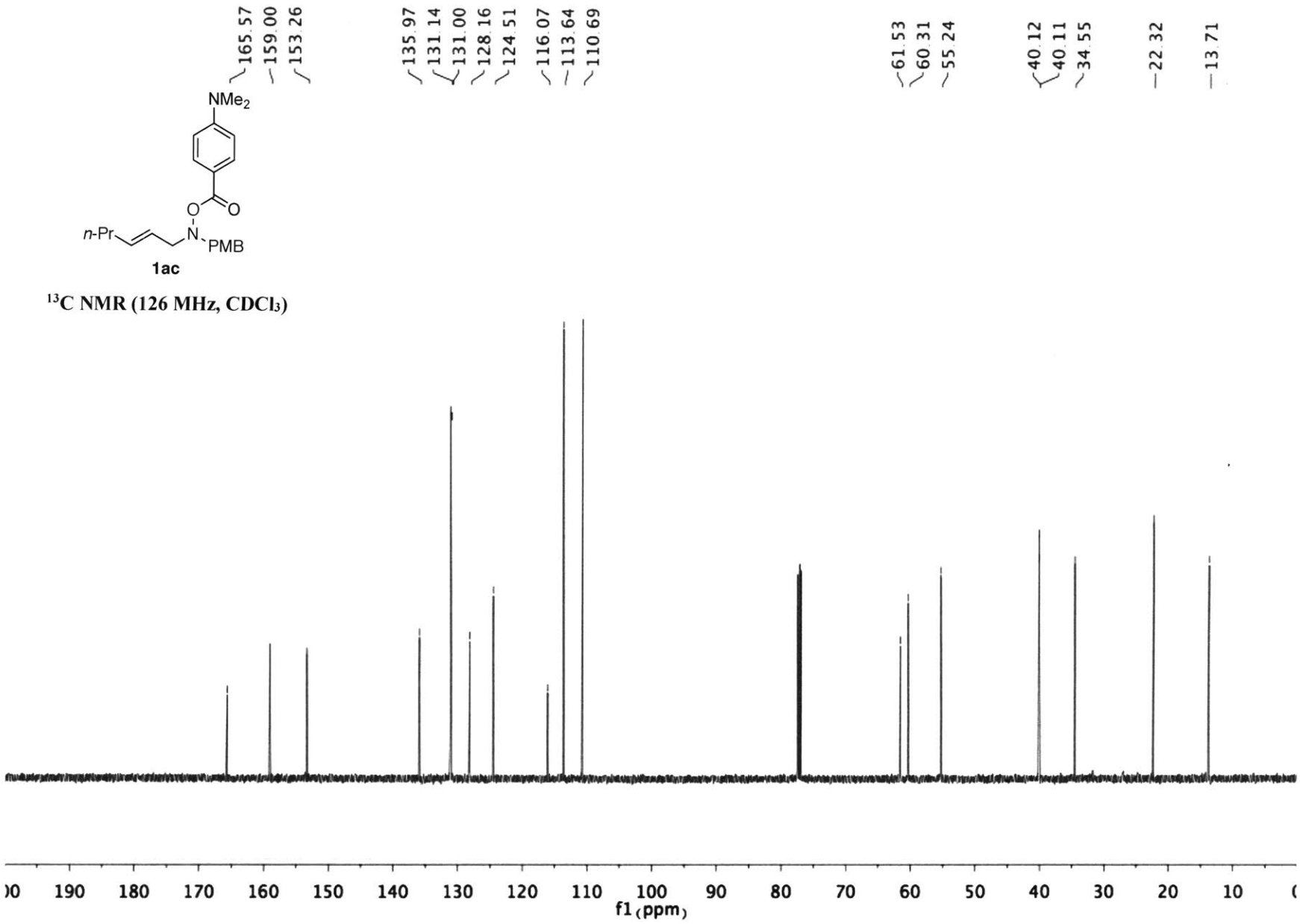
^{13}C NMR (126 MHz, $CDCl_3$)

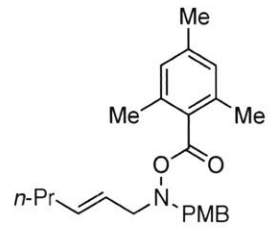


1ab

^{19}F NMR (376 MHz, $CDCl_3$)

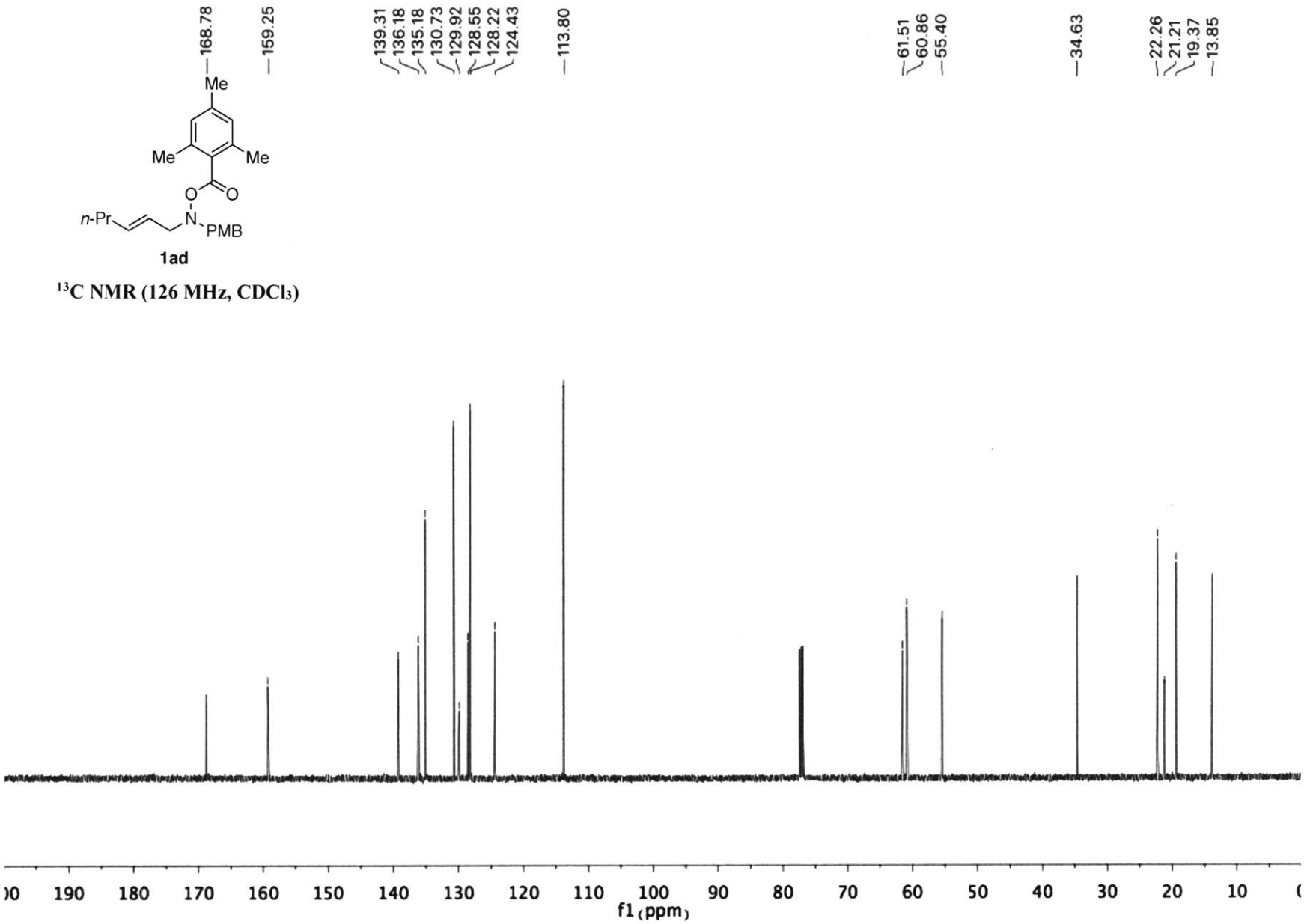

7.80
7.79
7.32
7.31
6.82
6.81
6.60
6.58
5.66
5.65
5.64
5.63
4.09
3.76
3.58
3.57
3.01
1.99
1.97
1.96
1.95
1.34
1.32
1.31
1.30
0.84
0.82
0.81
NMe2
O
O
n-Pr
N
PMB
1ac
1H NMR (500 MHz, CDCl3)
1.96
2.02
2.00
2.12
2.00
2.10
3.14
2.03
6.26
2.01
2.10
2.89
f1 (ppm)


165.57
159.00
153.26
135.97
131.14
131.00
128.16
124.51
116.07
113.64
110.69
61.53
60.31
55.24
40.12
40.11
34.55
22.32
13.71
NMe2
n-Pr
N
PMB
O
O
1ac
13C NMR (126 MHz, CDCl3)
f1 (ppm)

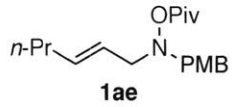


1ad

^{1}H NMR (500 MHz, $CDCl_3$)

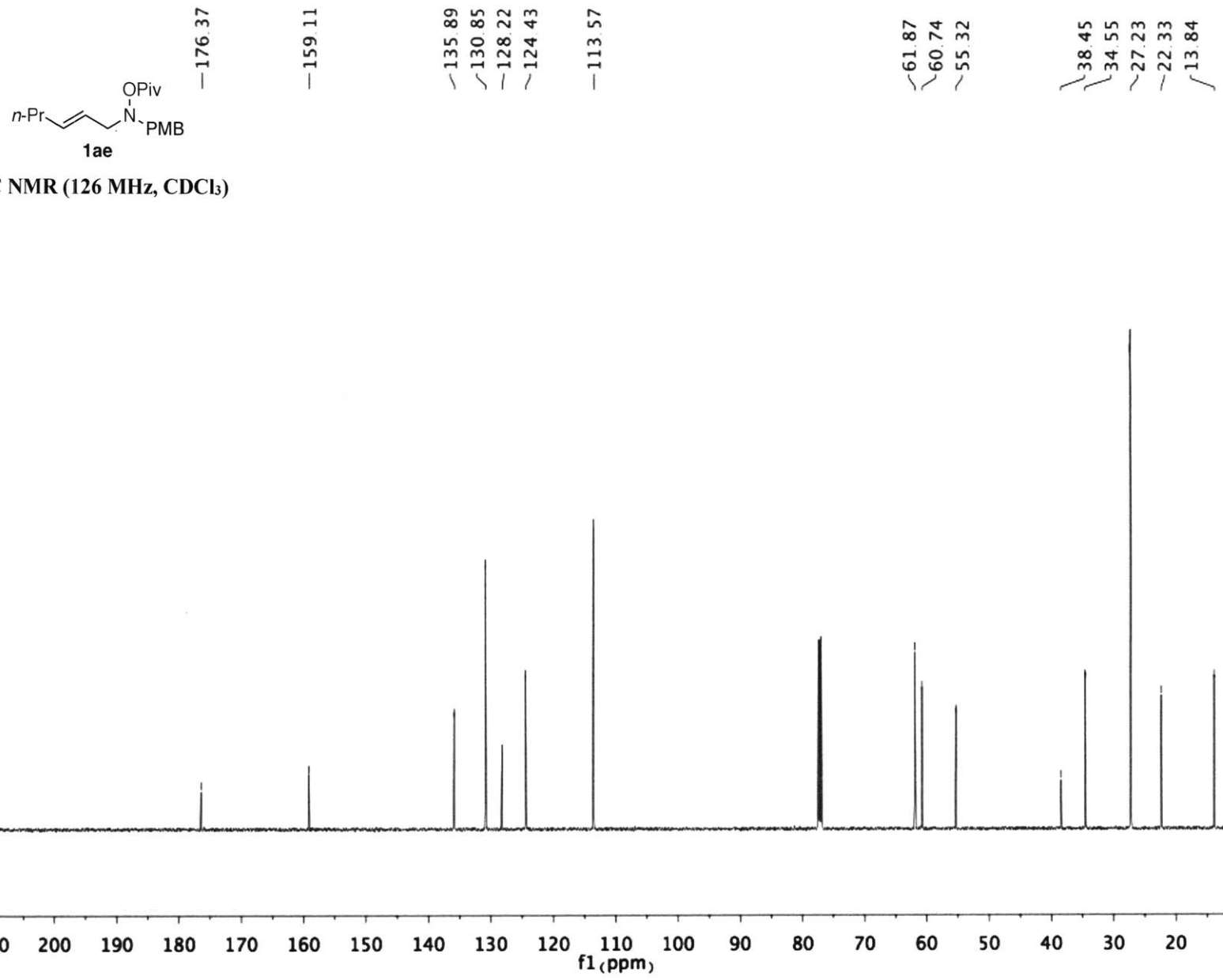


^{13}C NMR (126 MHz, $CDCl_3$)

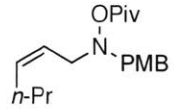


1ae

^{1}H NMR (500 MHz, $CDCl_3$)

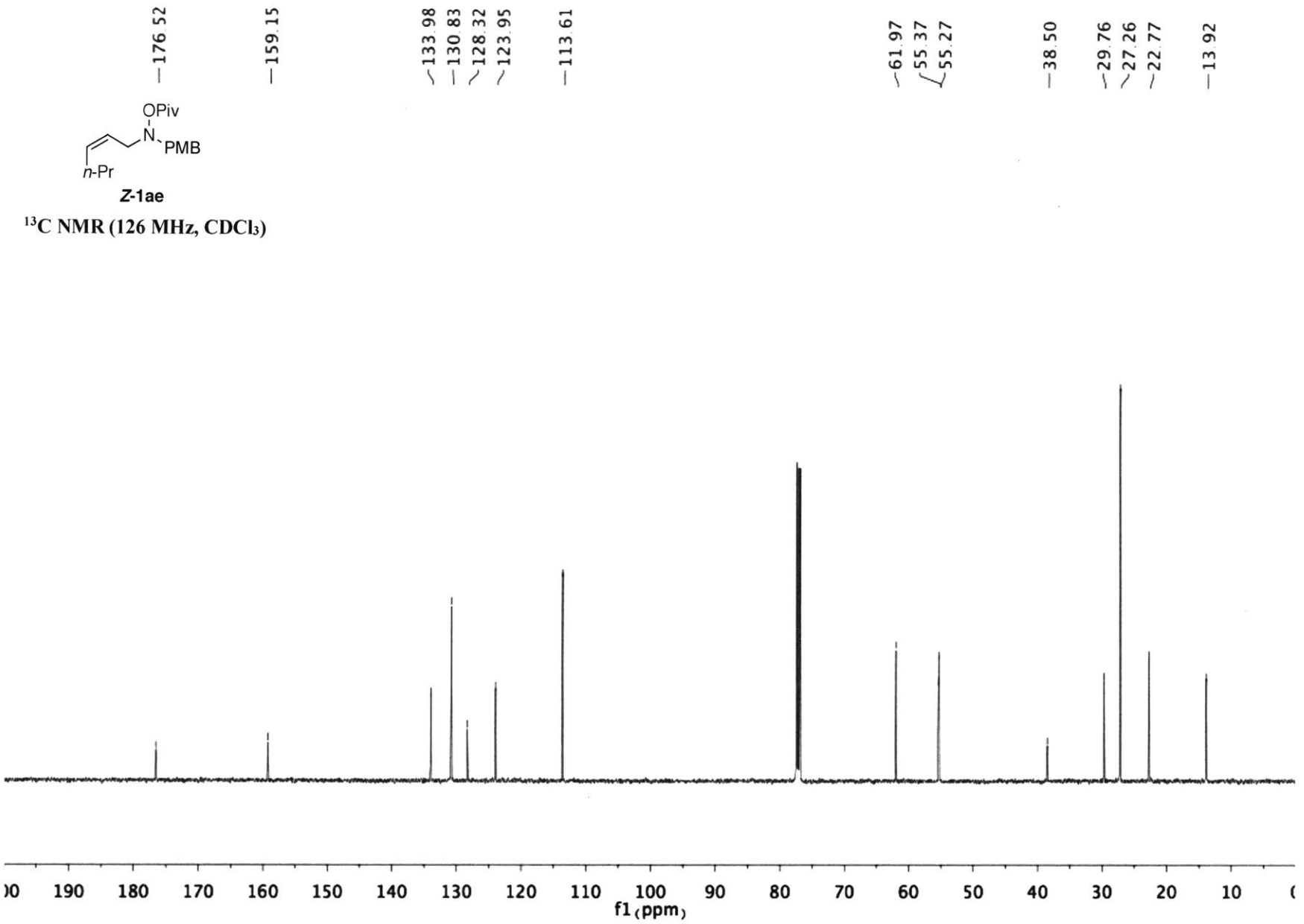


^{13}C NMR (126 MHz, $CDCl_3$)



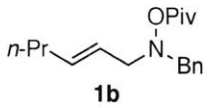
***Z*-1ae**

^{1}H NMR (500 MHz, $CDCl_3$)



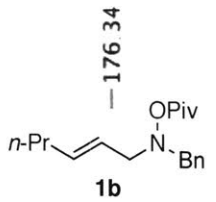
***Z*-1ae**

^{13}C NMR (126 MHz, $CDCl_3$)



1b

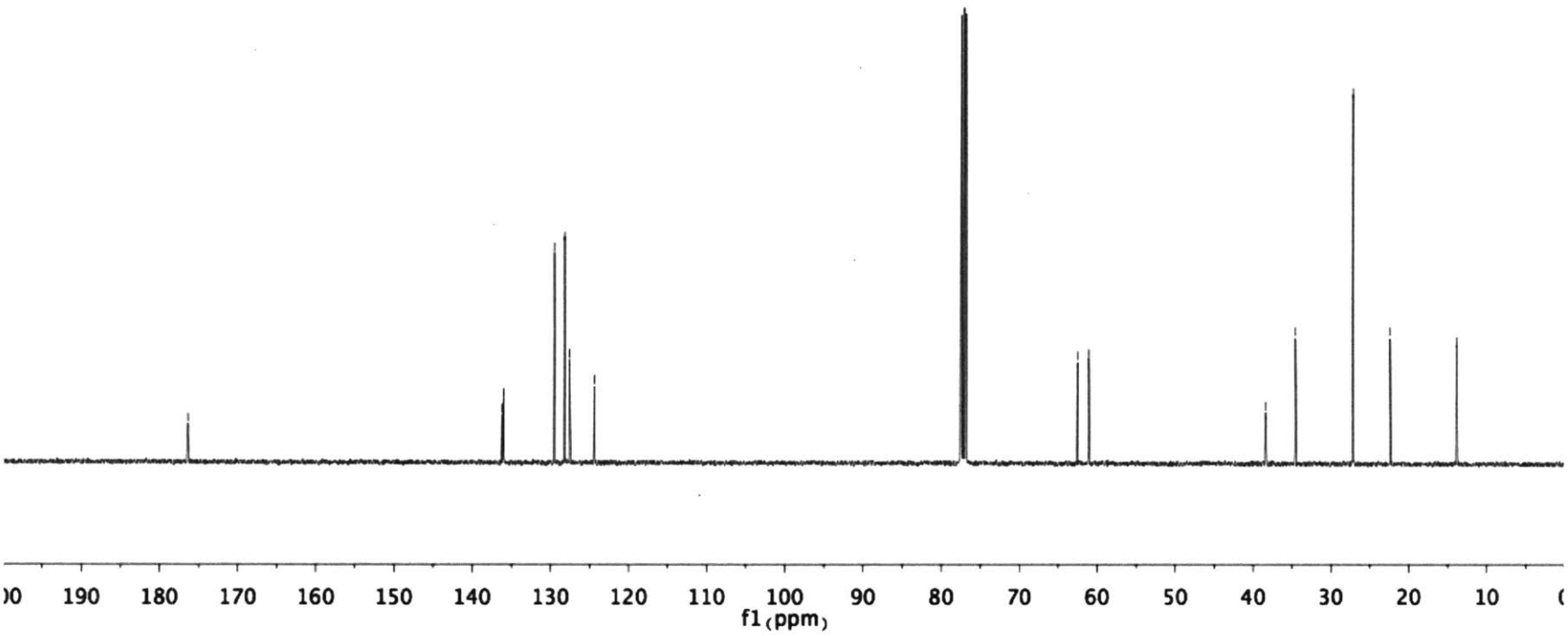
^{1}H NMR (400 MHz, $CDCl_3$)

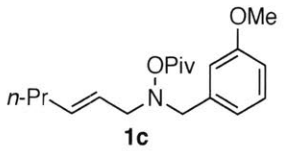


1b

136.28
136.05
129.57
128.26
127.60
124.40
62.51
61.05
38.48
34.59
27.21
22.38
13.87

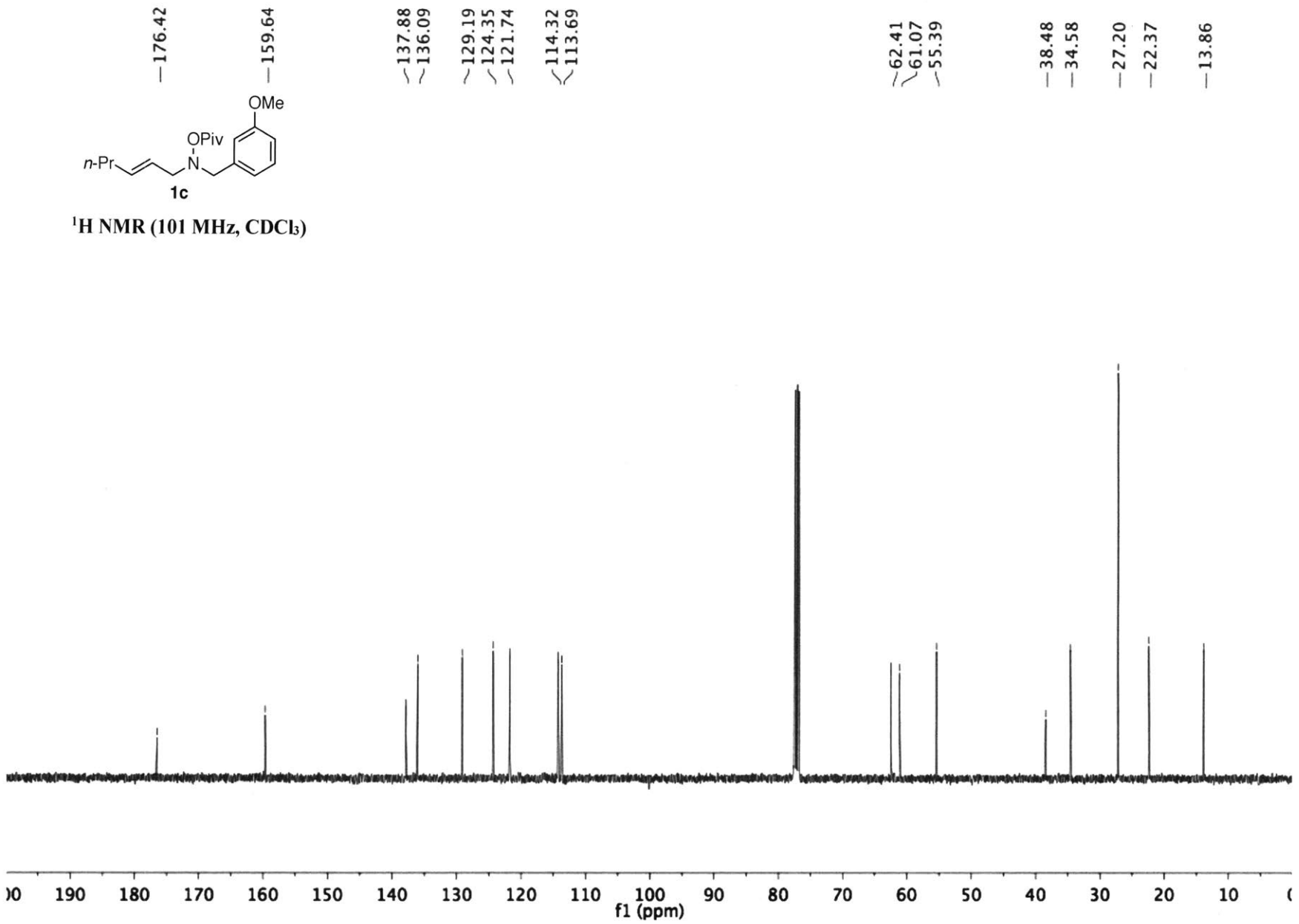
^{13}C NMR (101 MHz, $CDCl_3$)



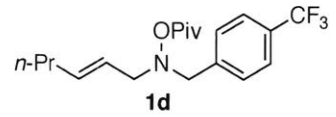


1c

^{1}H NMR (400 MHz, $CDCl_3$)

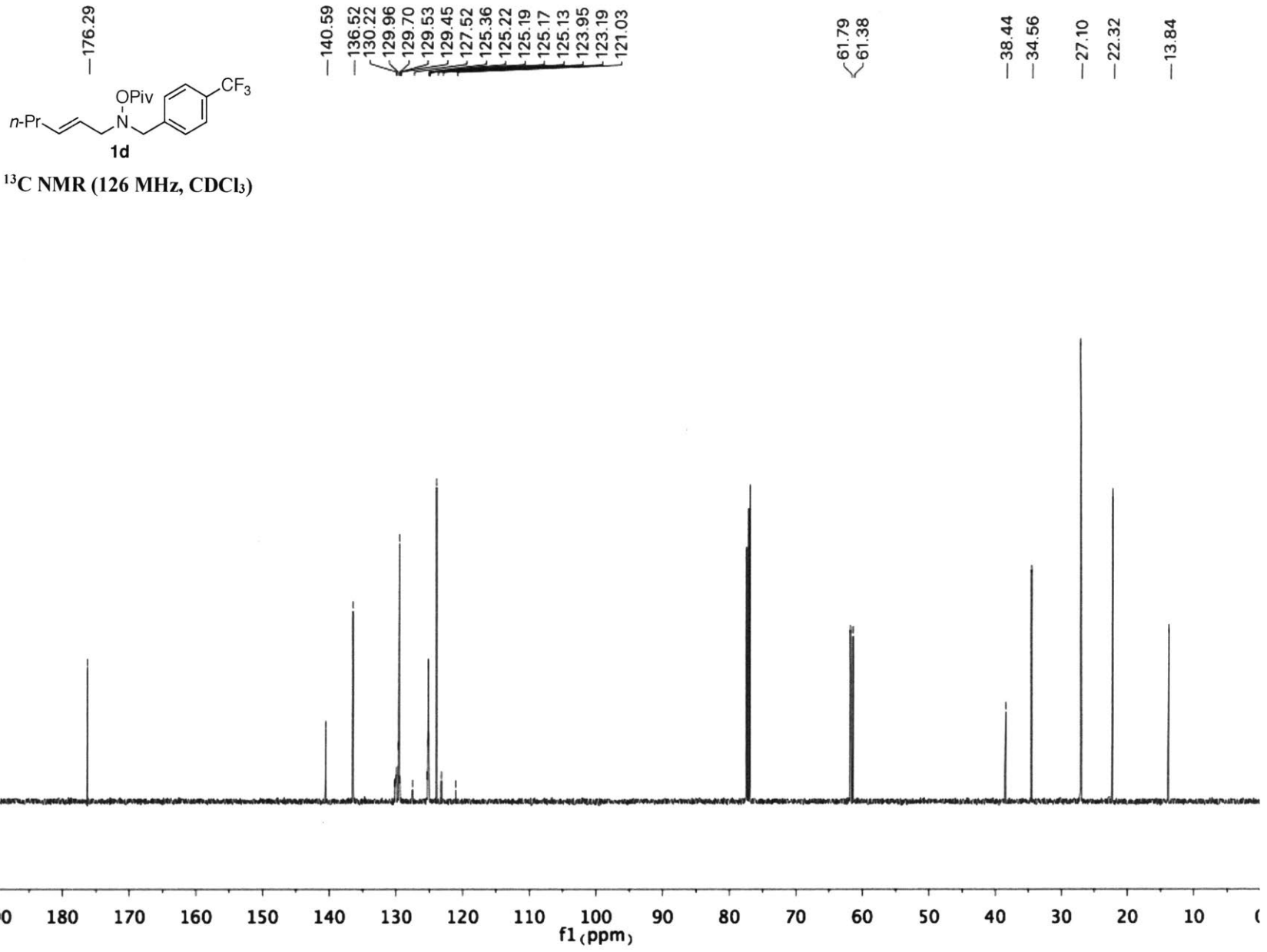


^{1}H NMR (101 MHz, $CDCl_3$)

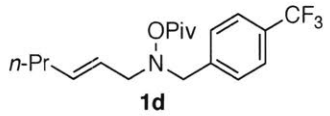


1d

^{1}H NMR (500 MHz, $CDCl_3$)

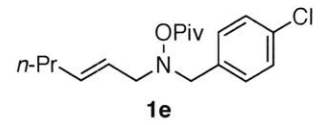


^{13}C NMR (126 MHz, $CDCl_3$)



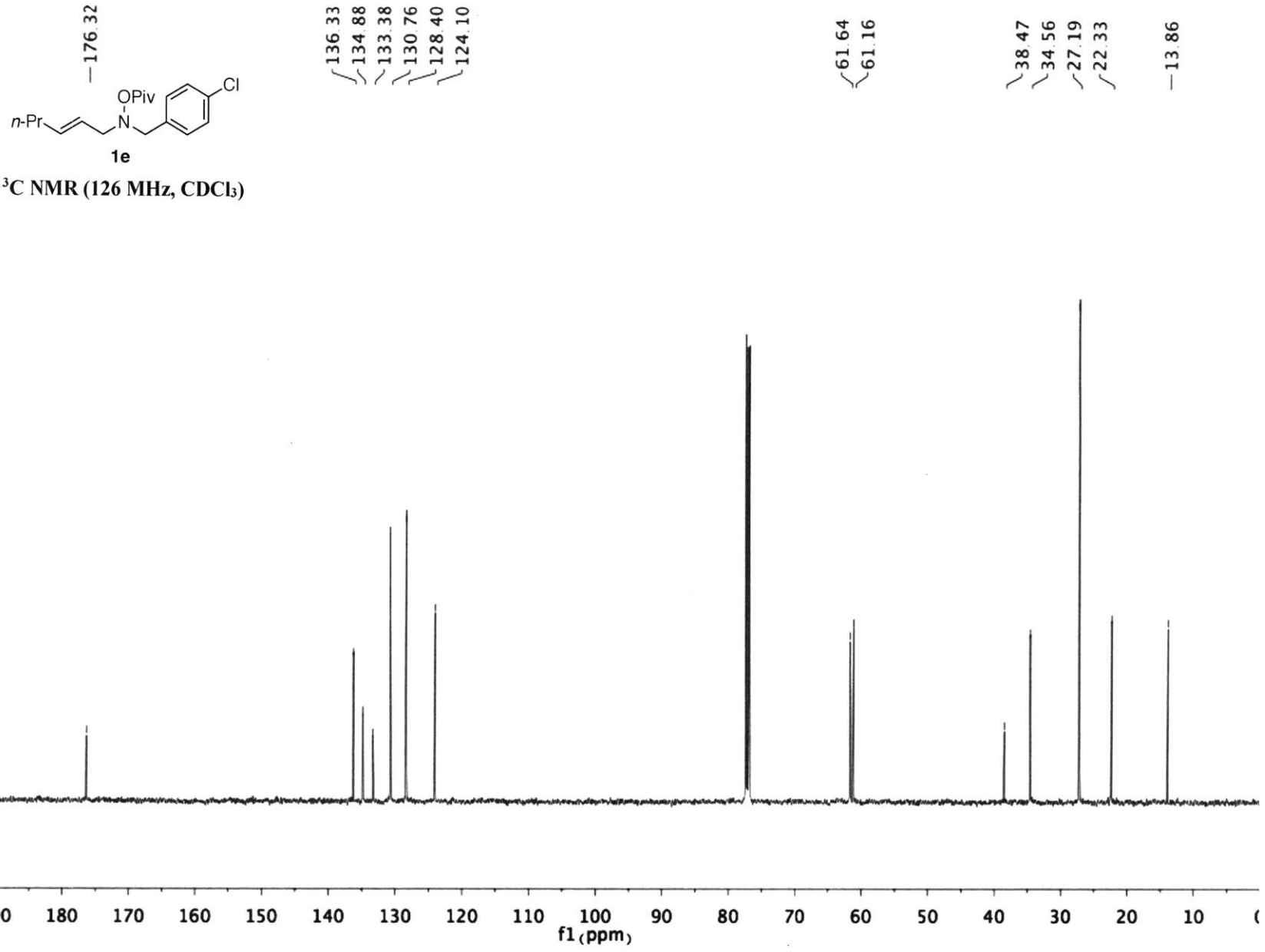
1d

^{19}F NMR (471 MHz, $CDCl_3$)

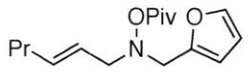


1e

^{1}H NMR (500 MHz, $CDCl_3$)

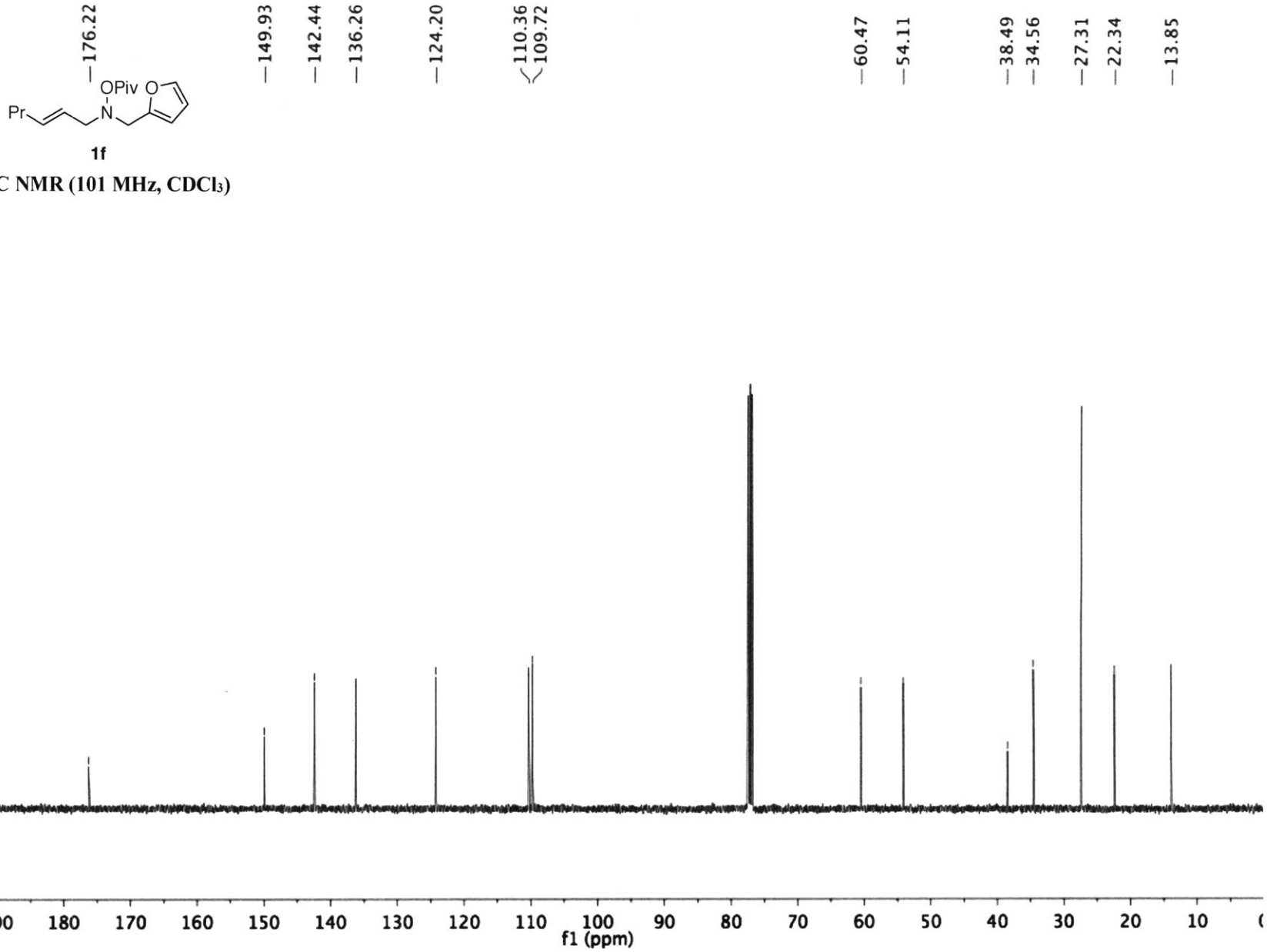


^{13}C NMR (126 MHz, $CDCl_3$)



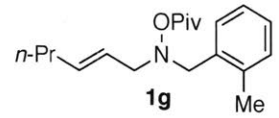
1f

^{1}H NMR (400 MHz, $CDCl_3$)



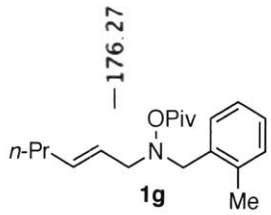
1f

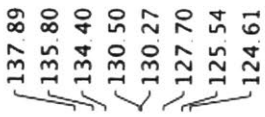
^{13}C NMR (101 MHz, $CDCl_3$)



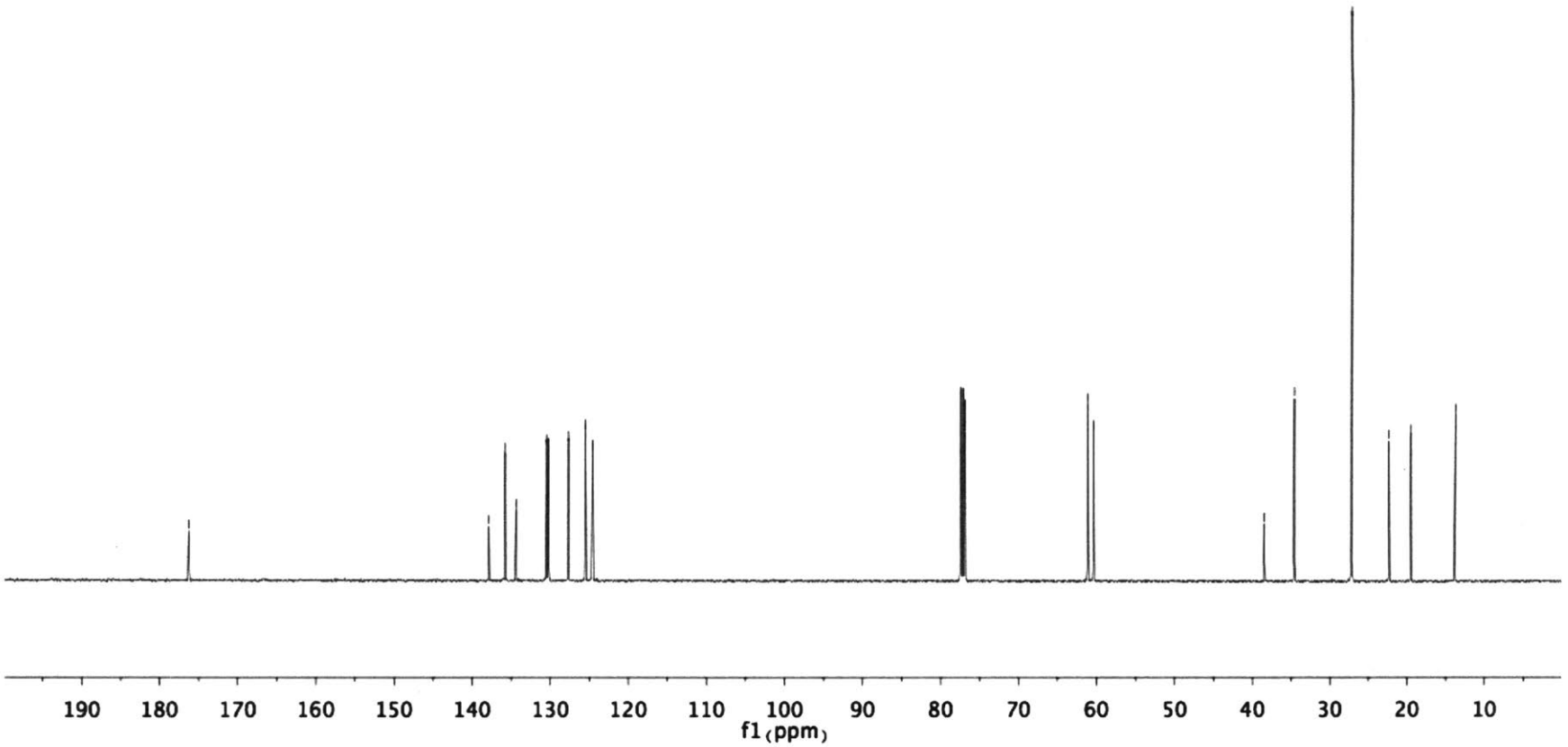
1g

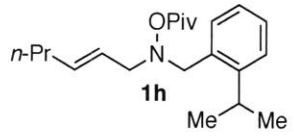
^{1}H NMR (500 MHz, $CDCl_3$)



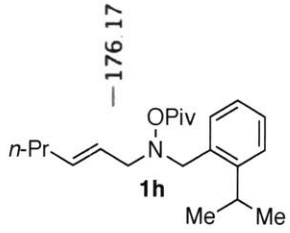


^{13}C NMR (1260 MHz, $CDCl_3$)

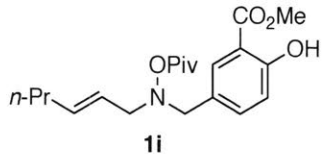




^{1}H NMR (500 MHz, $CDCl_3$)

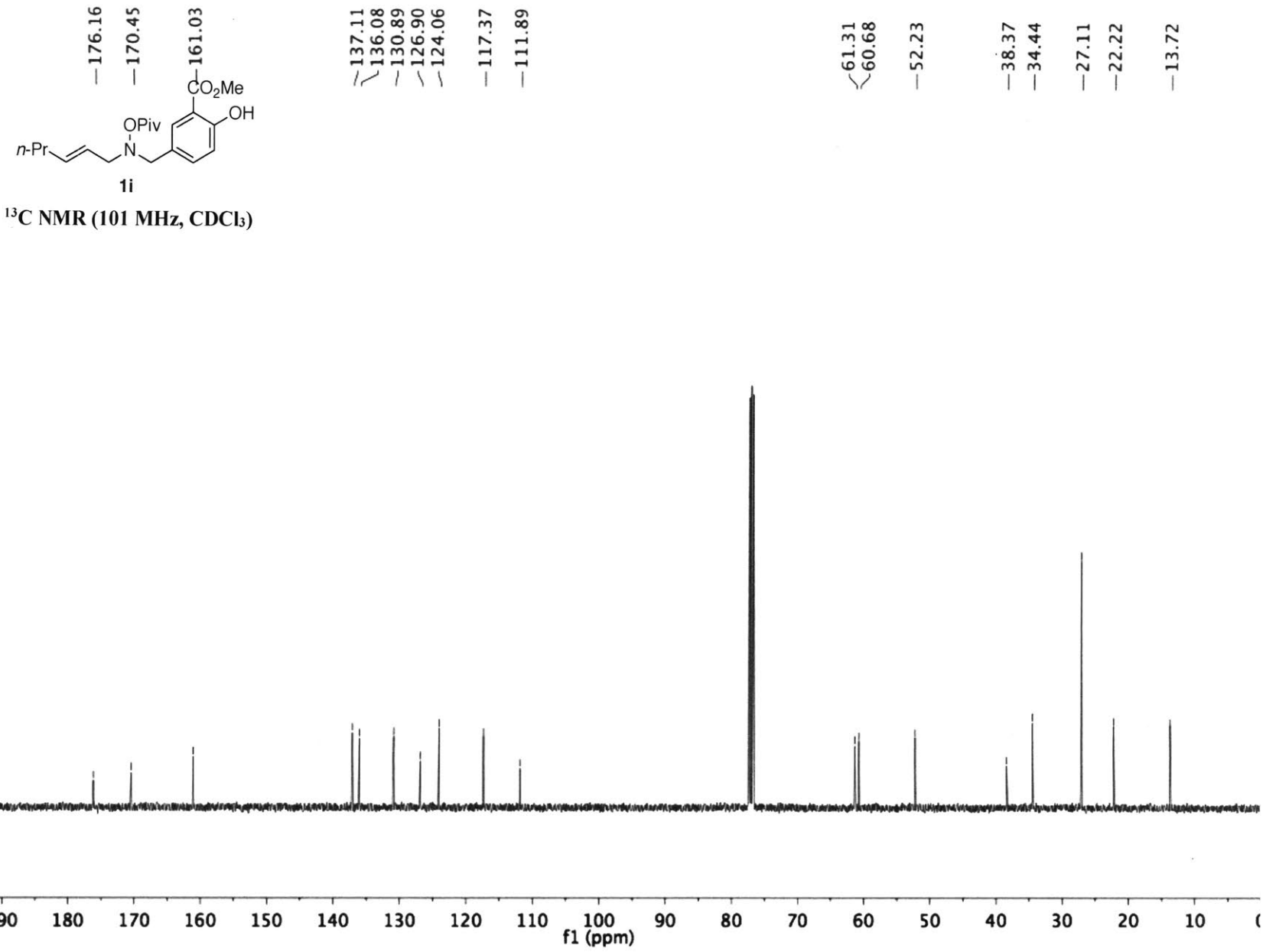


^{13}C NMR (126 MHz, $CDCl_3$)

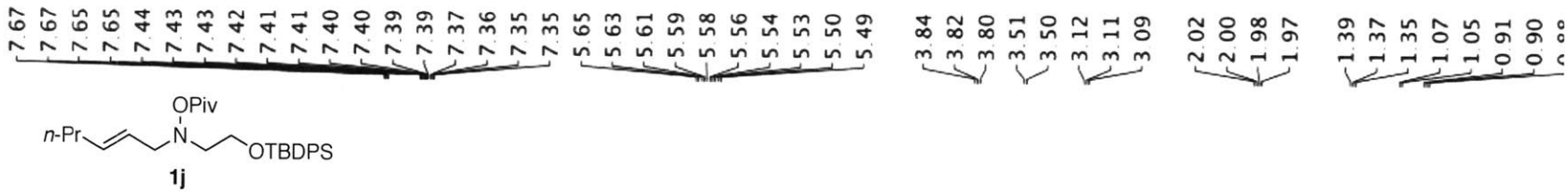


1i

^{1}H NMR (400 MHz, $CDCl_3$)

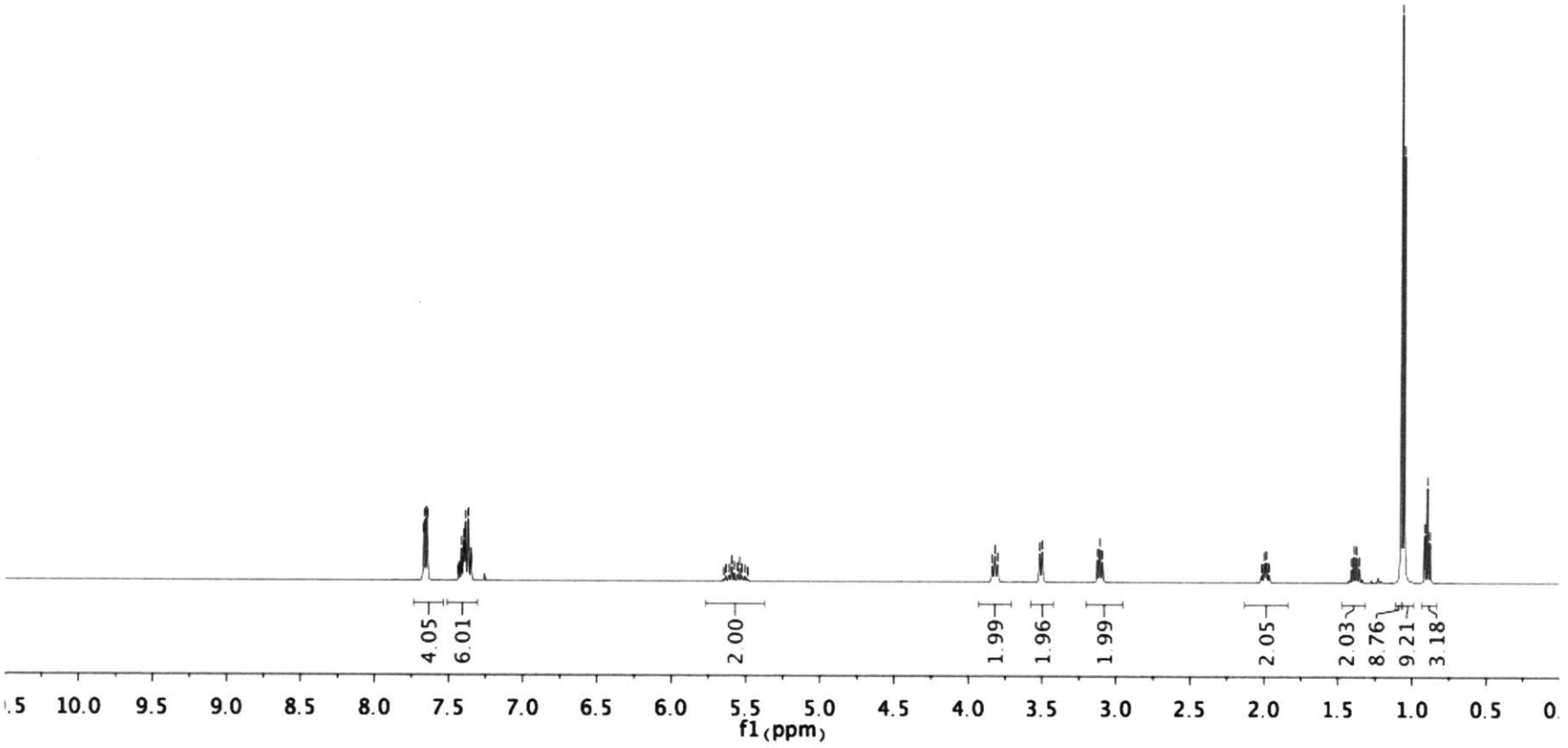


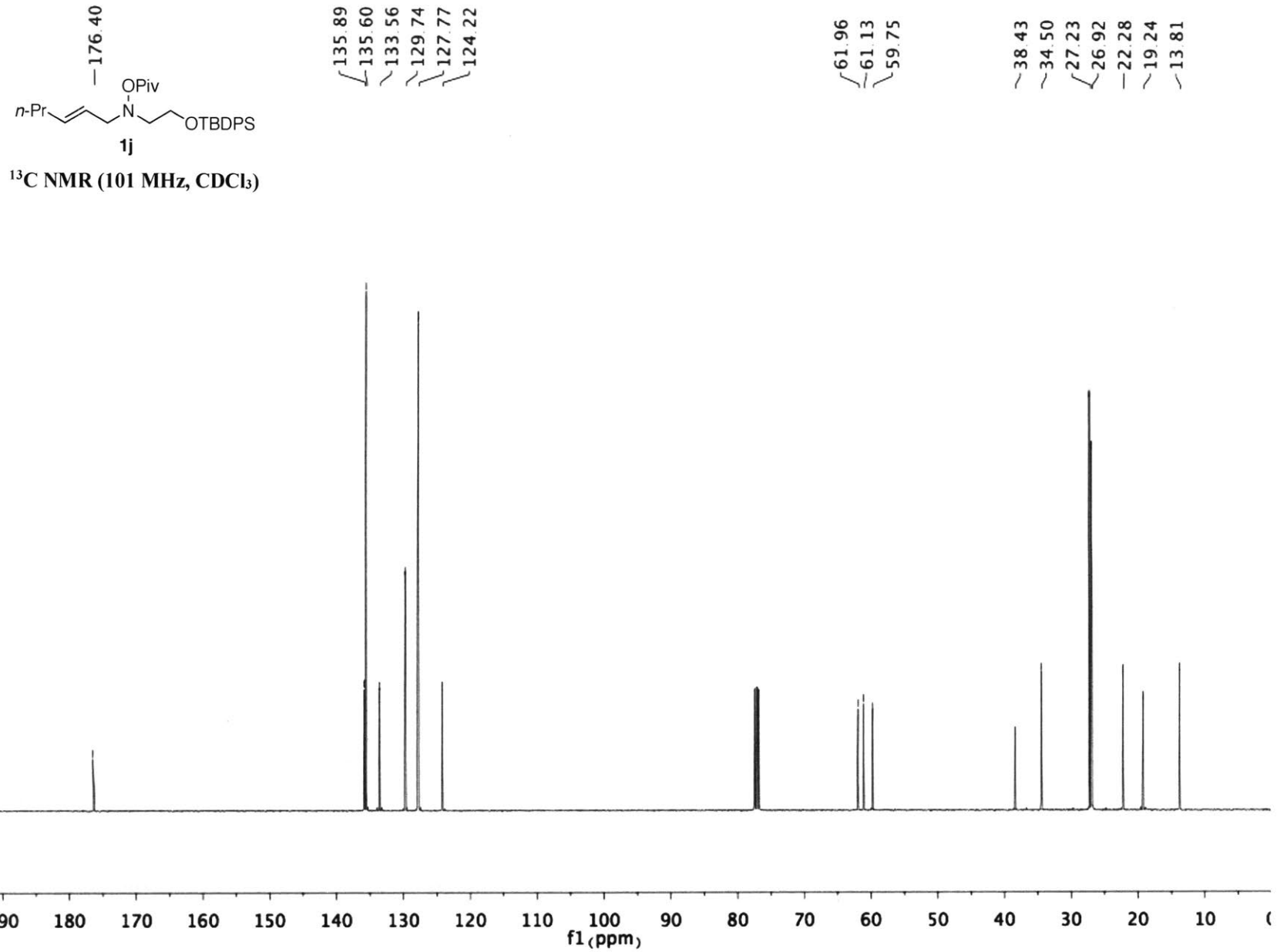
^{13}C NMR (101 MHz, $CDCl_3$)



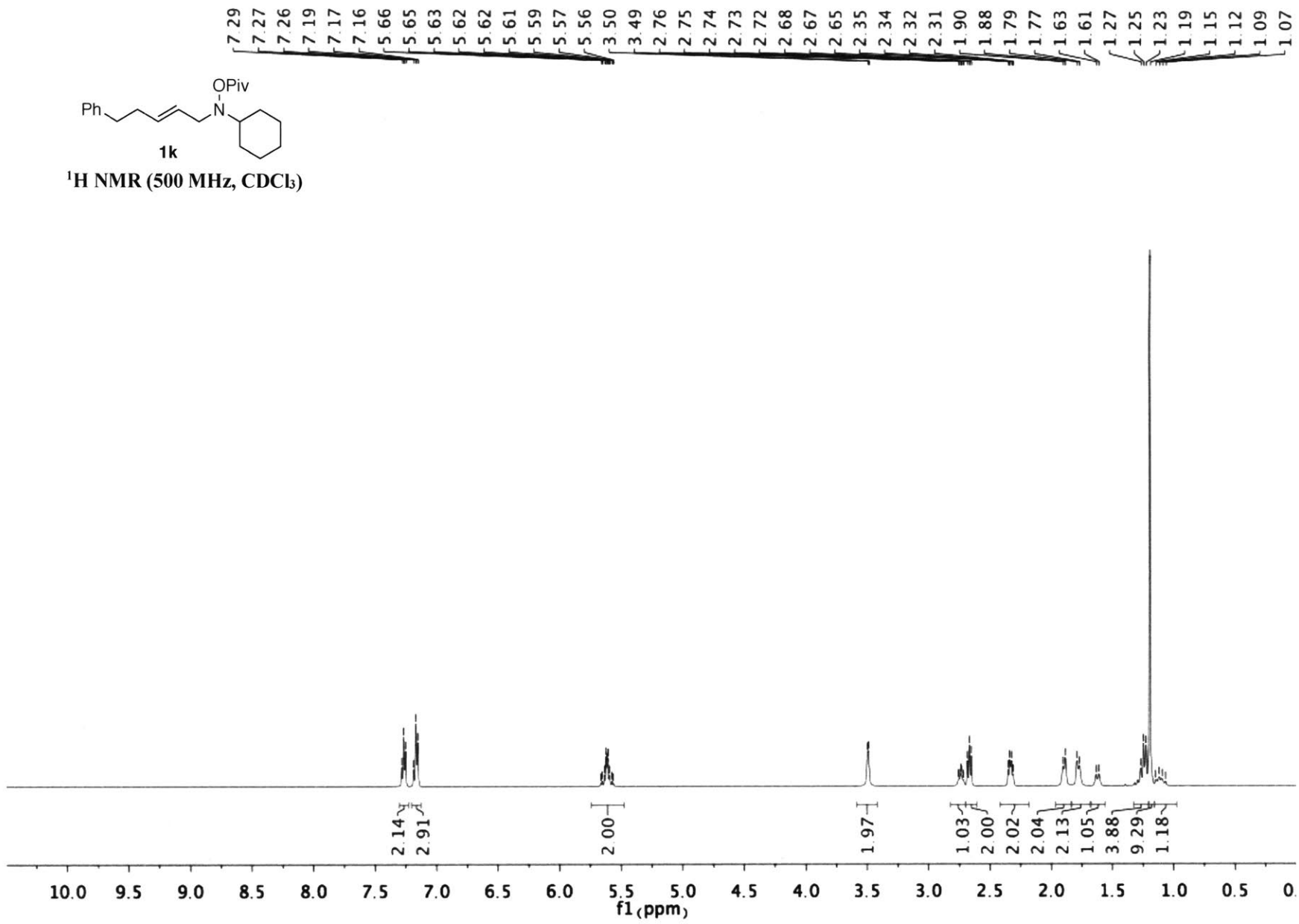
1j

^{1}H NMR (400 MHz, $CDCl_3$)

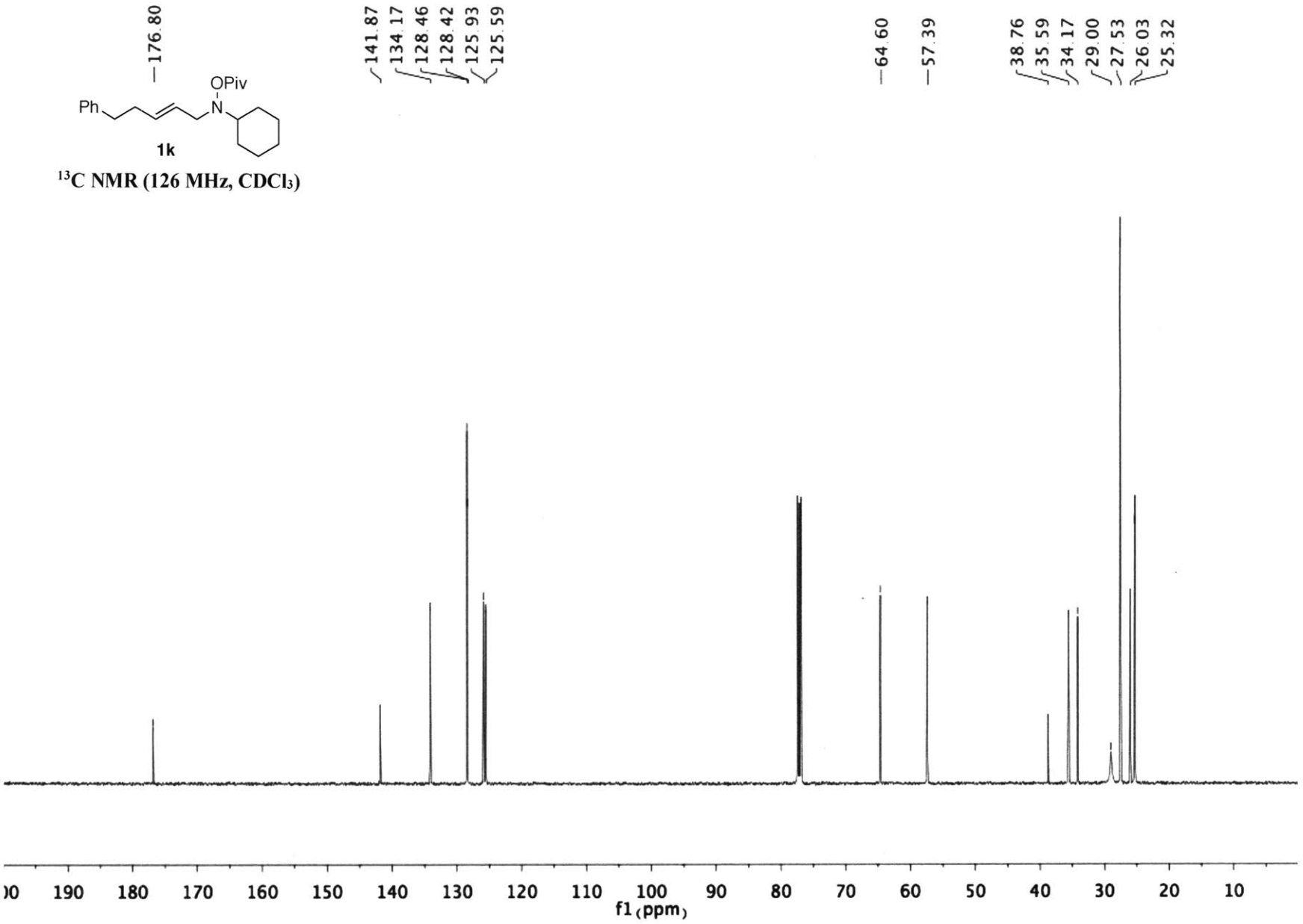




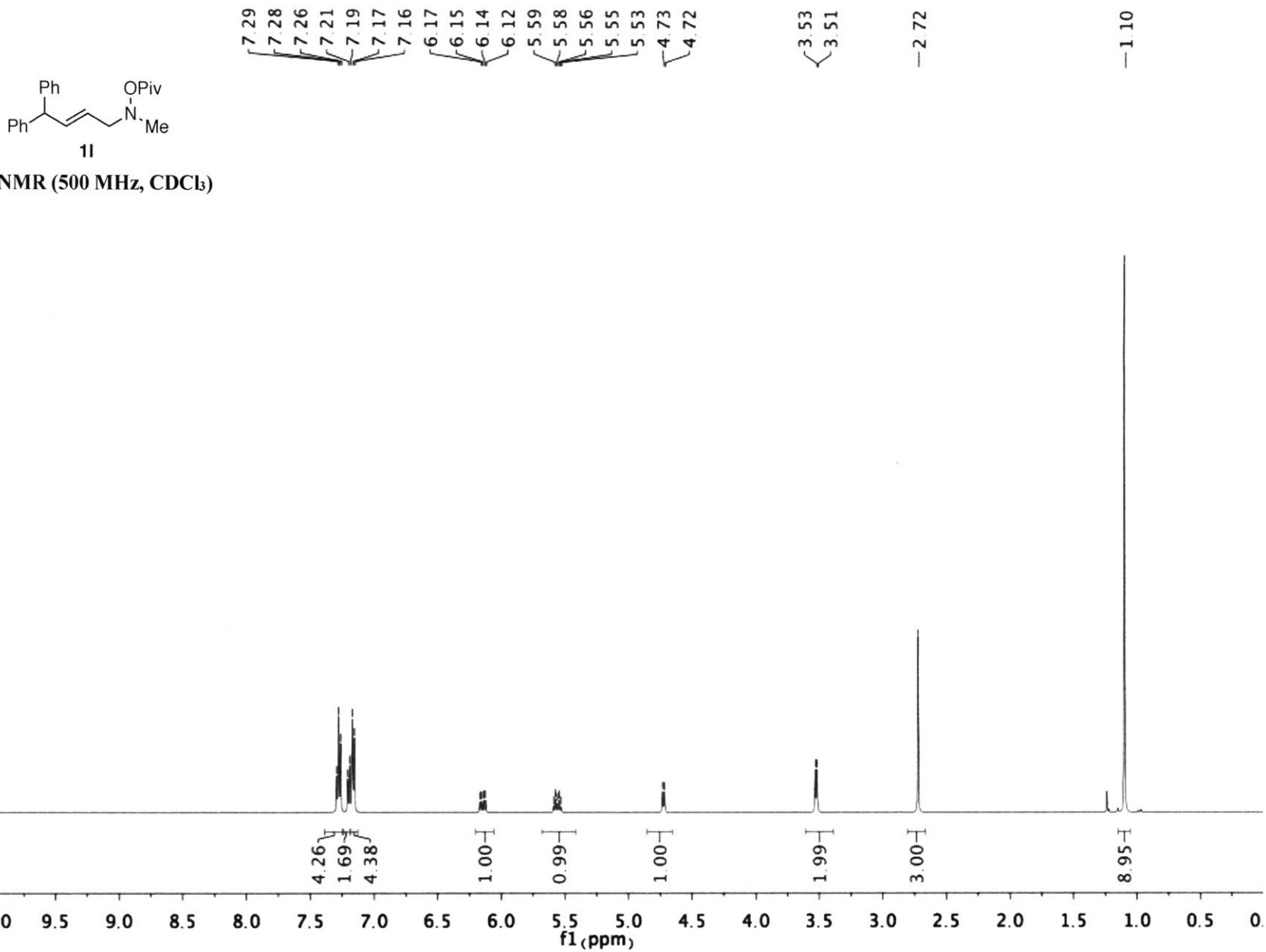
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

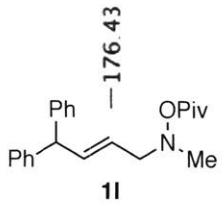


^{13}C NMR (126 MHz, $CDCl_3$)



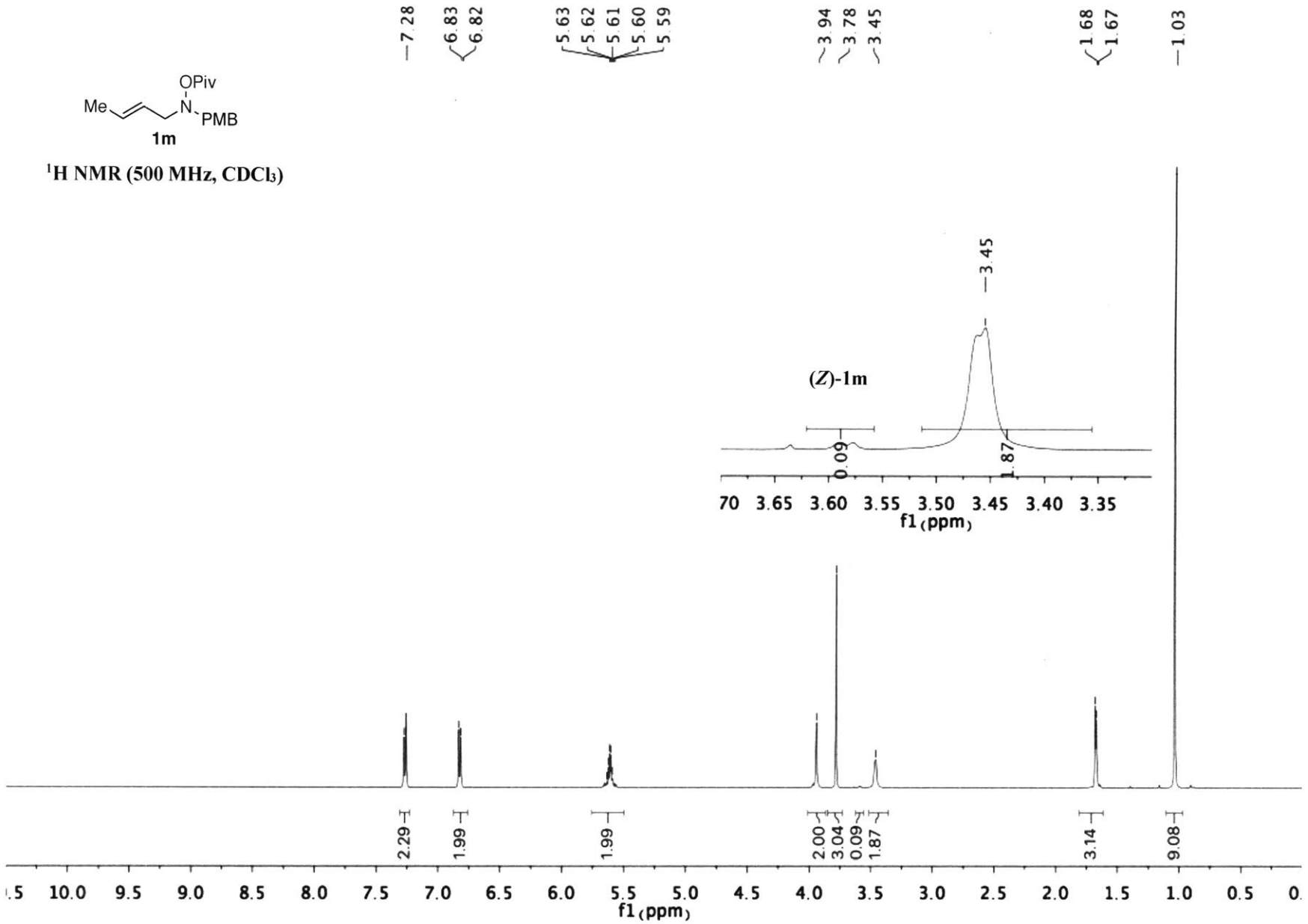
1l

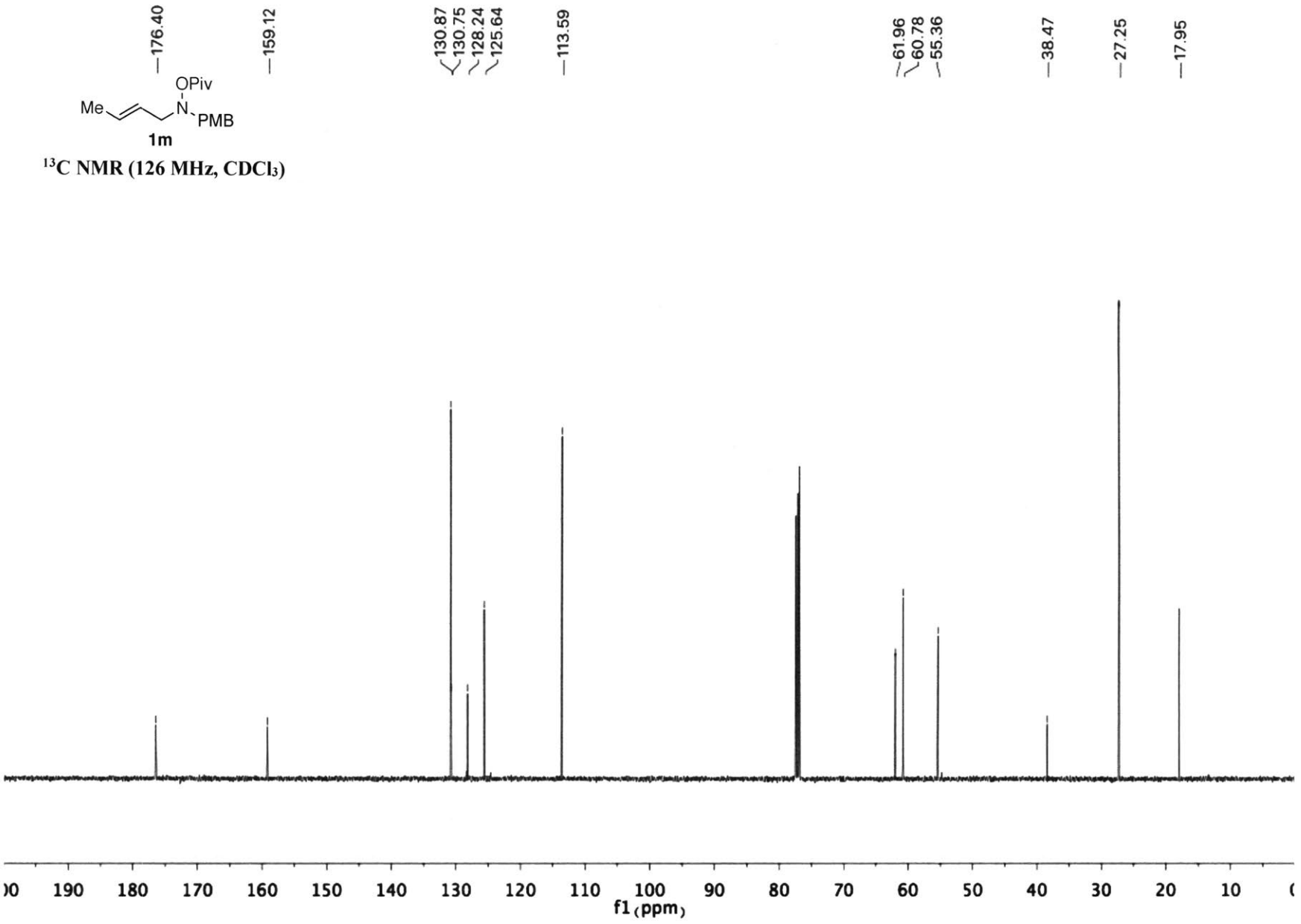
^{1}H NMR (500 MHz, $CDCl_3$)



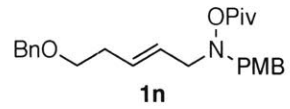
1l

^{13}C NMR (126 MHz, $CDCl_3$)


OPiv
Me
N
PMB
1m
1H NMR (500 MHz, CDCl3)
7.28
6.83
6.82
5.63
5.62
5.61
5.60
5.59
3.94
3.78
3.45
1.68
1.67
1.03
(Z)-1m
3.45
0.09
1.87
f1 (ppm)
2.29
1.99
1.99
2.00
3.04
0.09
1.87
3.14
9.08
f1 (ppm)

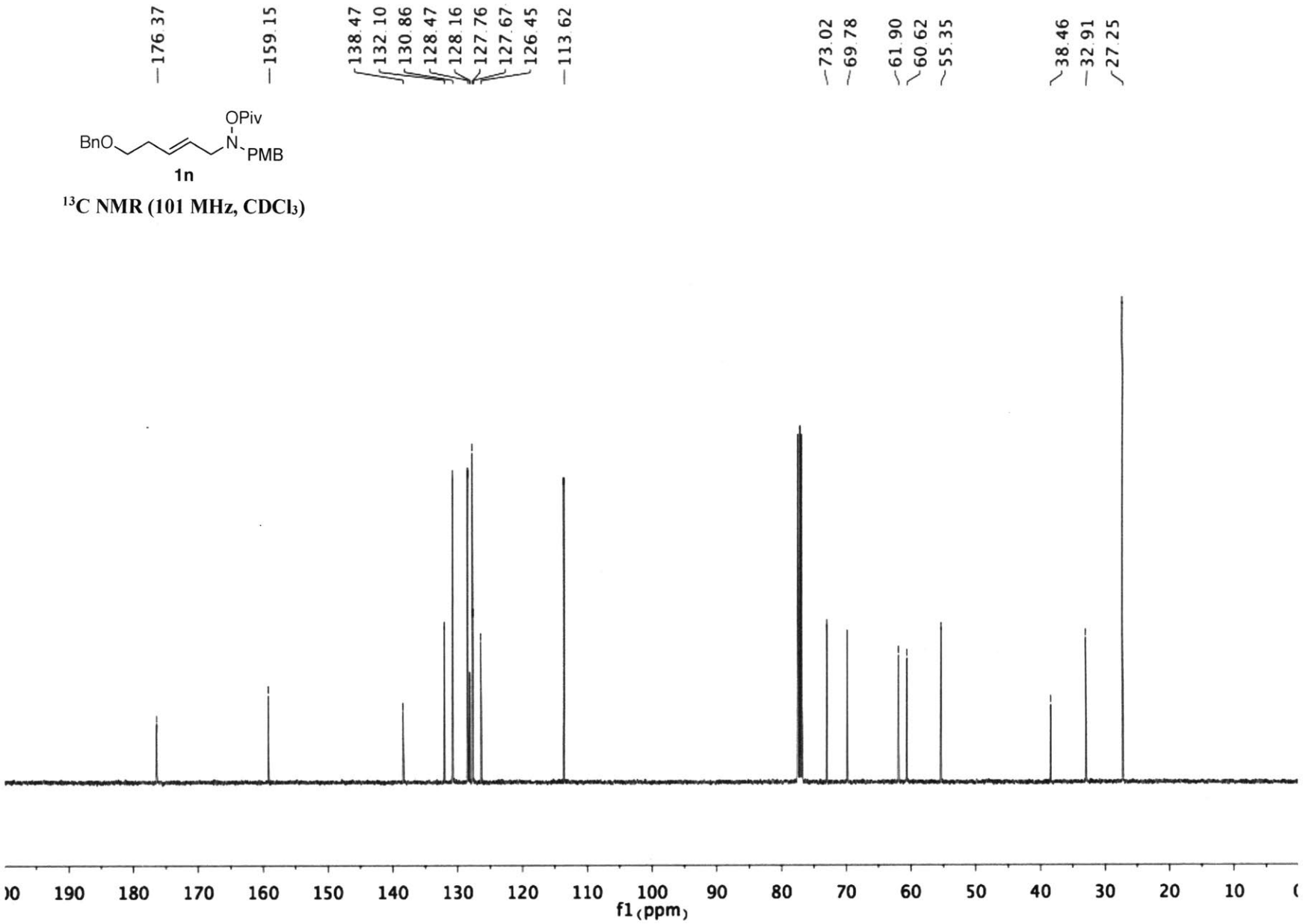


^{13}C NMR (126 MHz, $CDCl_3$)

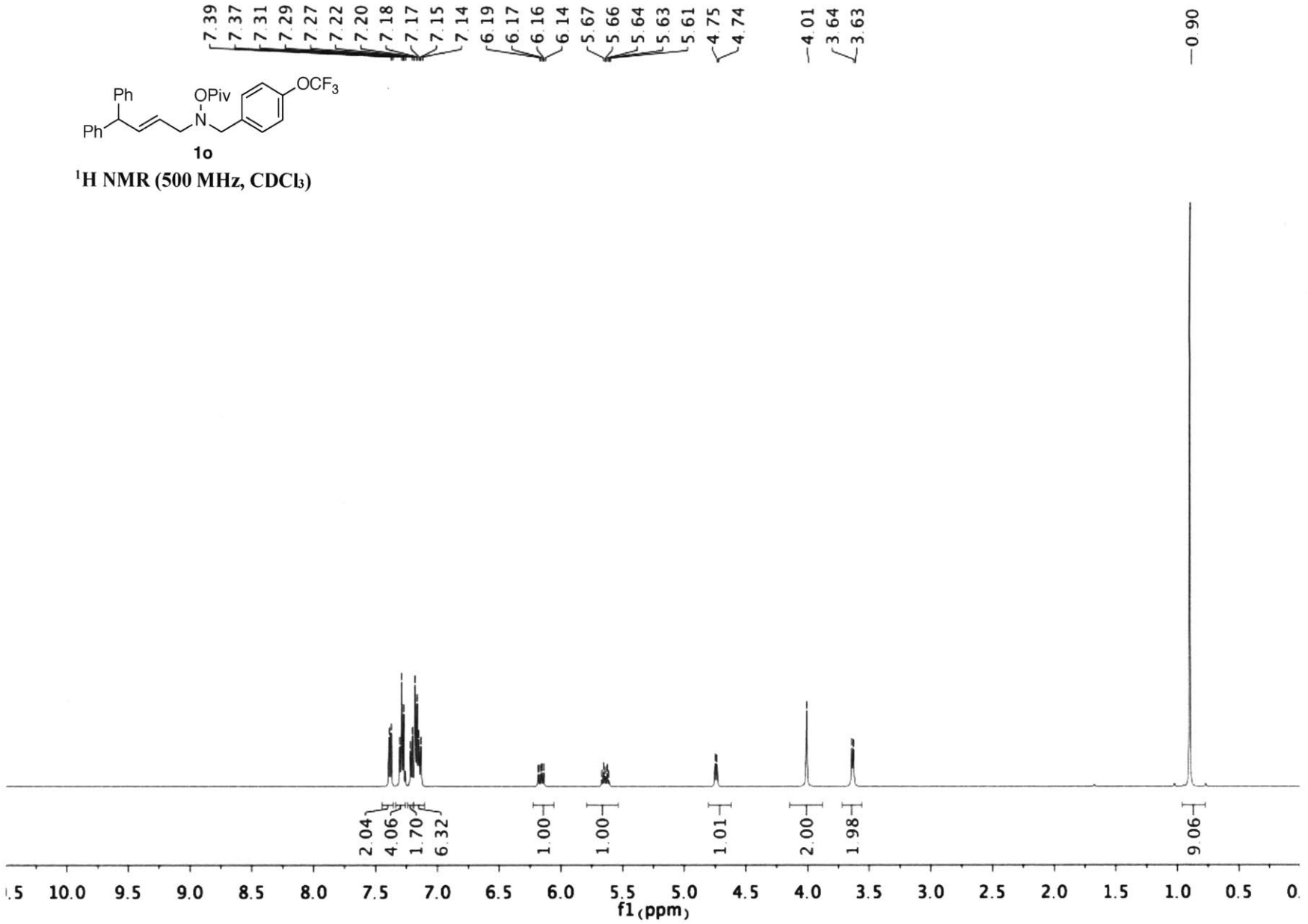


1n

^{1}H NMR (400 MHz, $CDCl_3$)

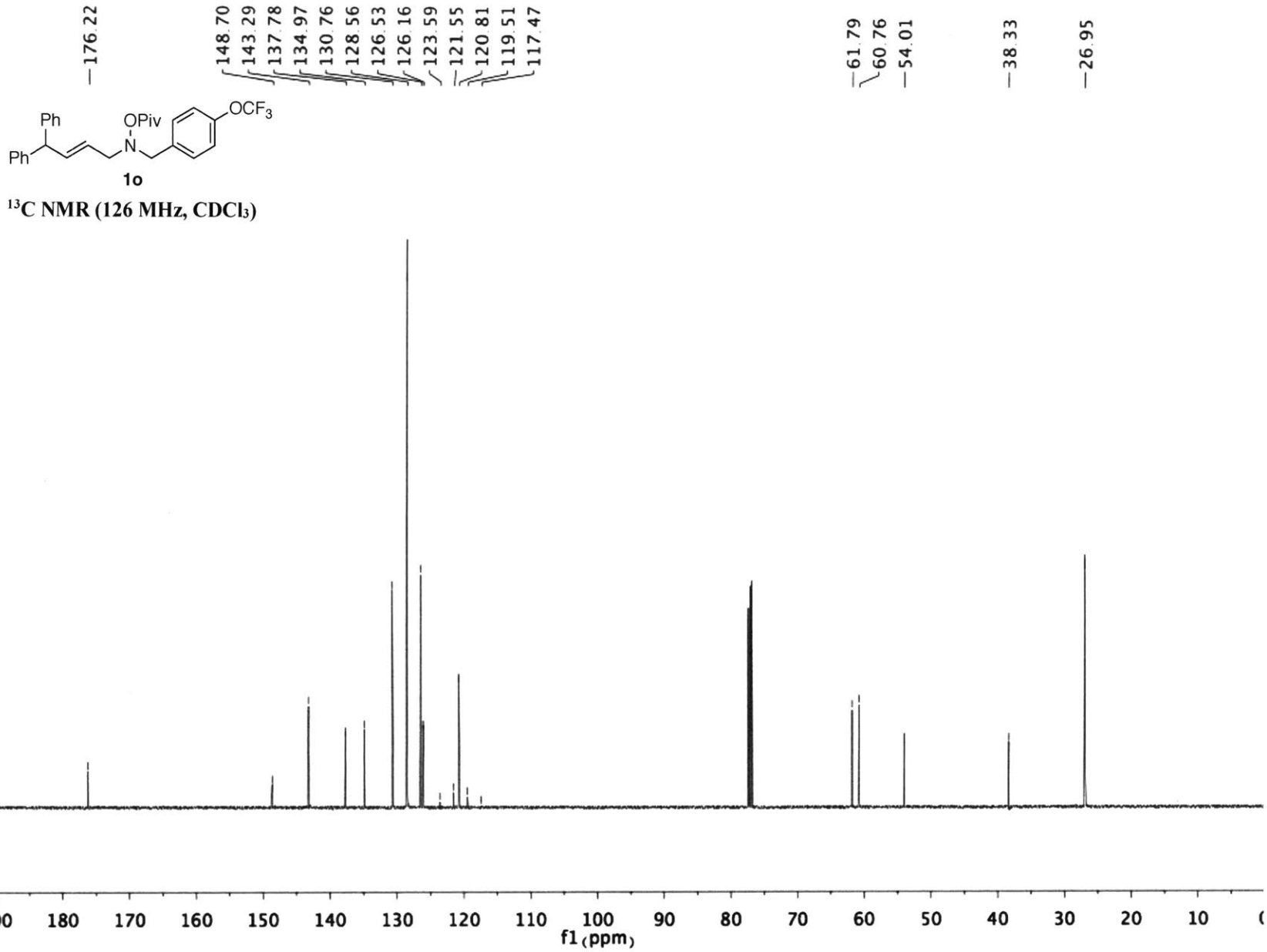


^{13}C NMR (101 MHz, $CDCl_3$)

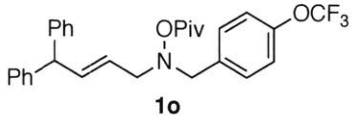


1o

^{1}H NMR (500 MHz, $CDCl_3$)

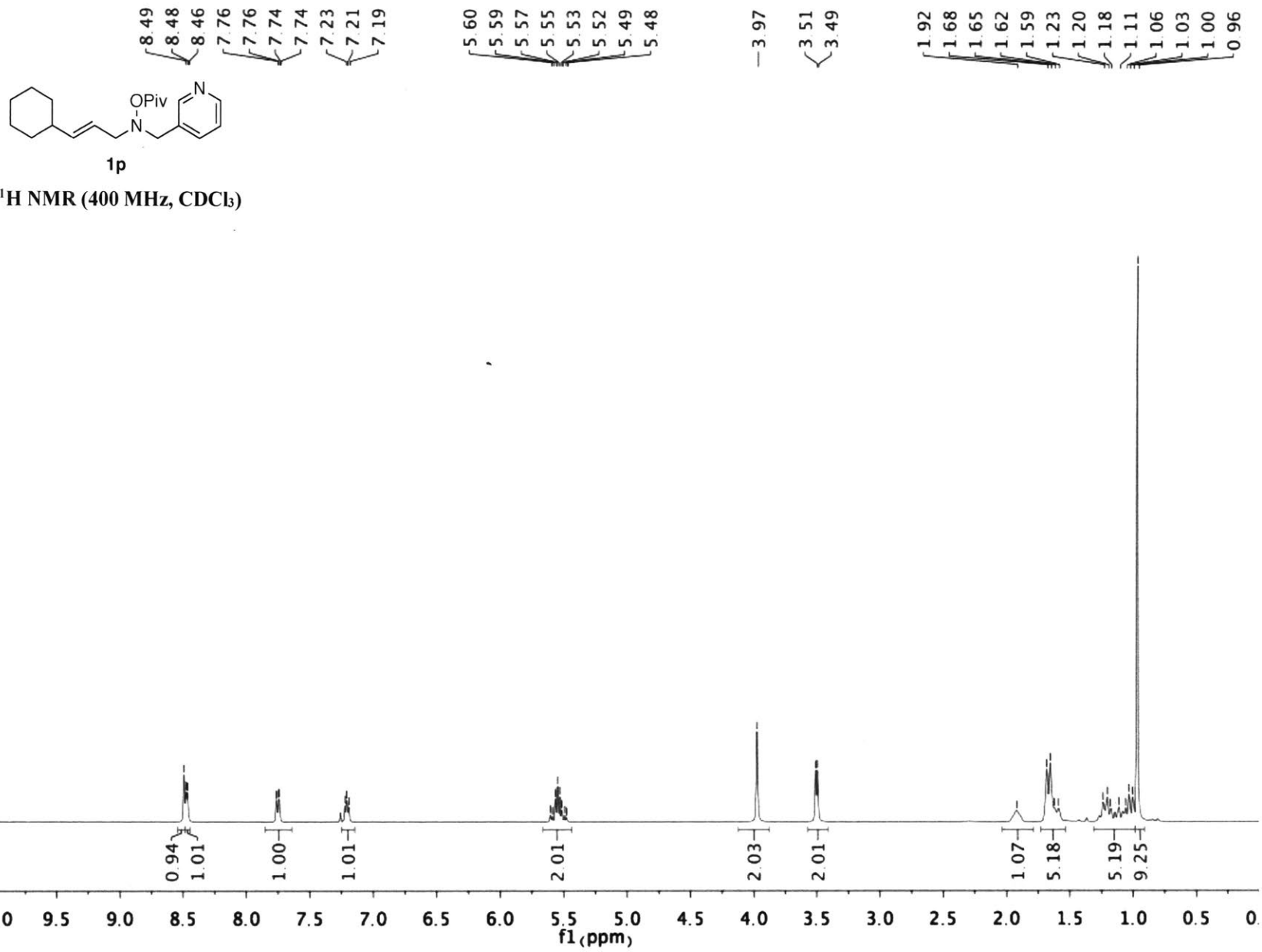


^{13}C NMR (126 MHz, $CDCl_3$)



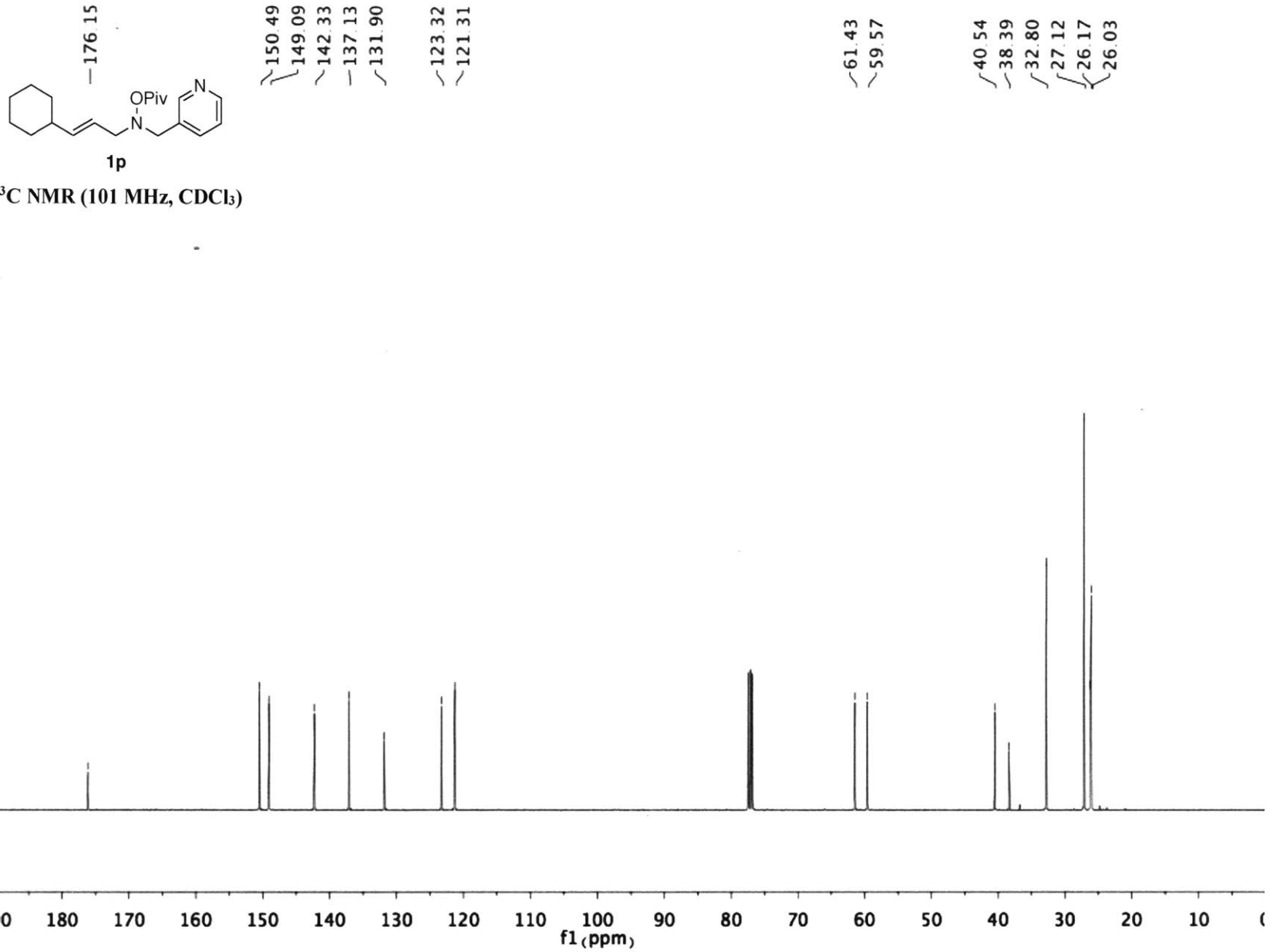
1o

^{19}F NMR (471 MHz, $CDCl_3$)

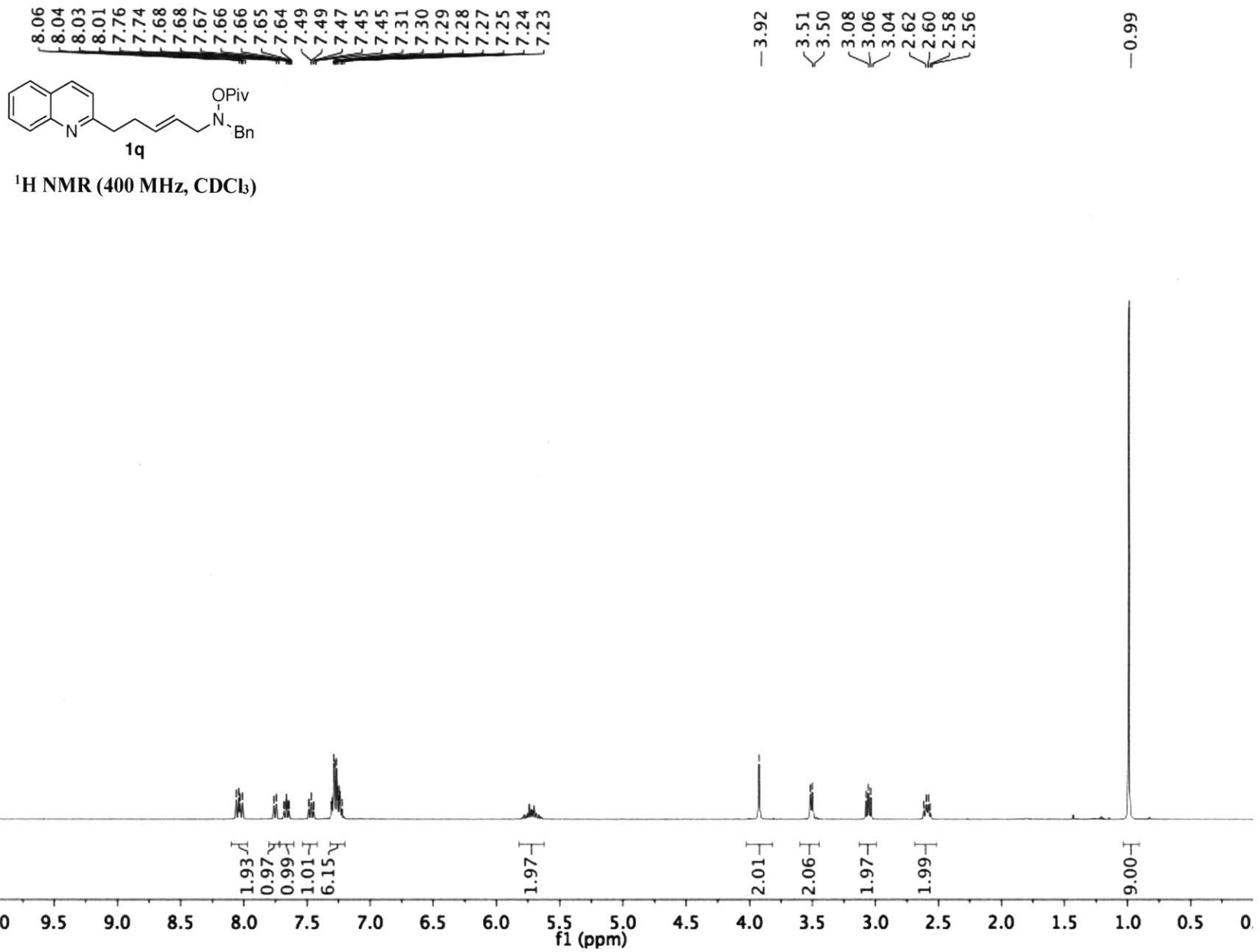


1p

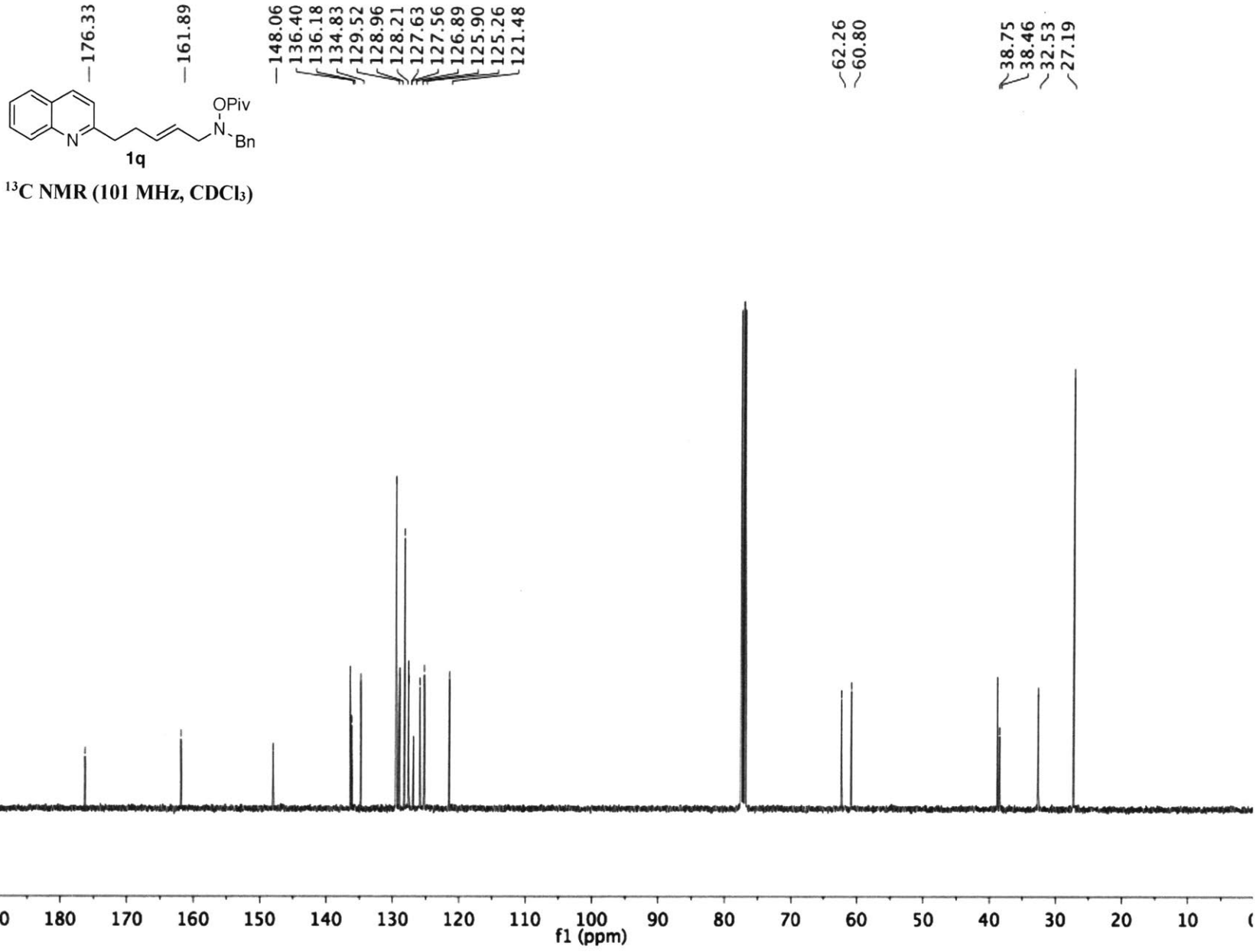
^{1}H NMR (400 MHz, $CDCl_3$)



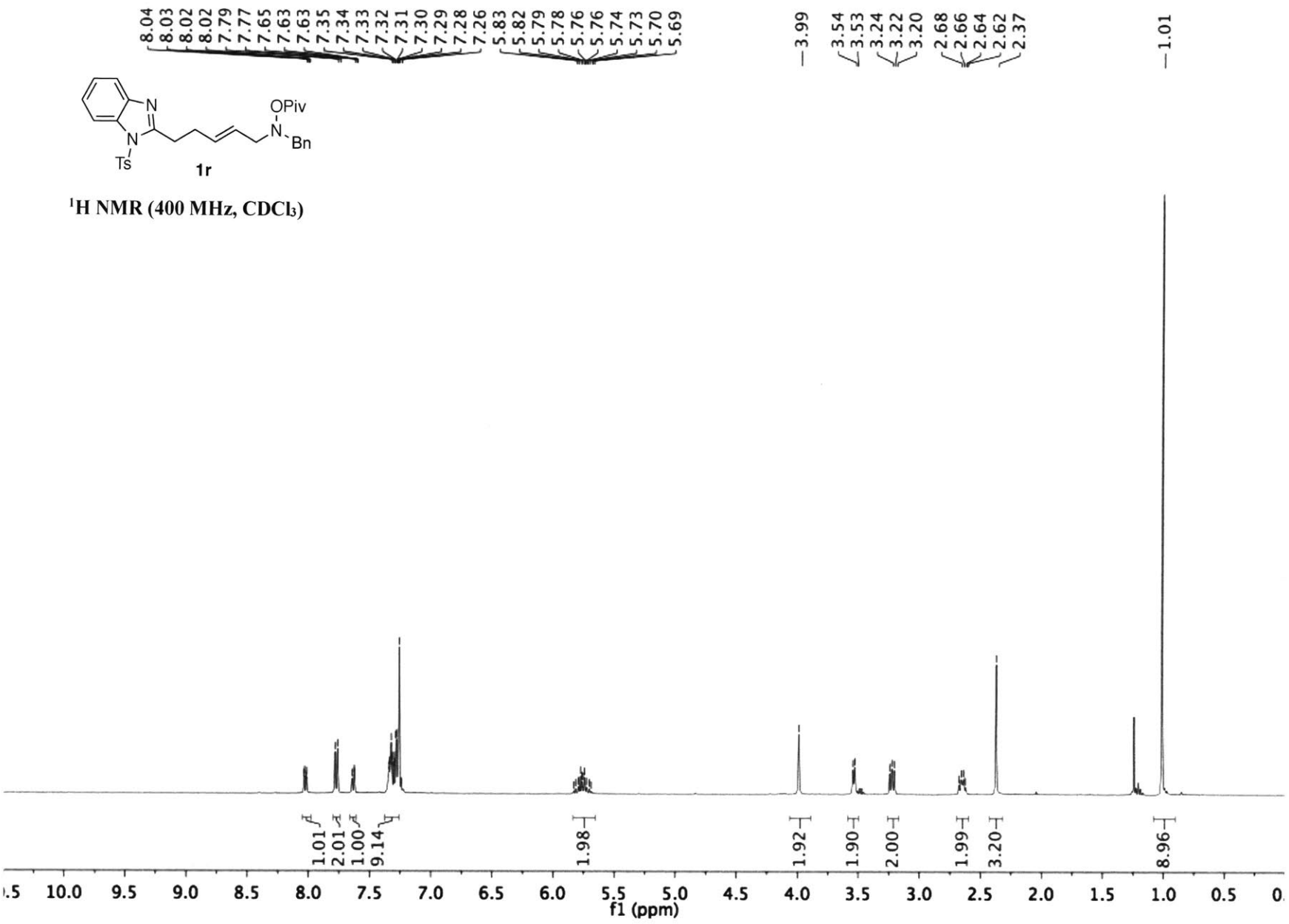
^{13}C NMR (101 MHz, $CDCl_3$)



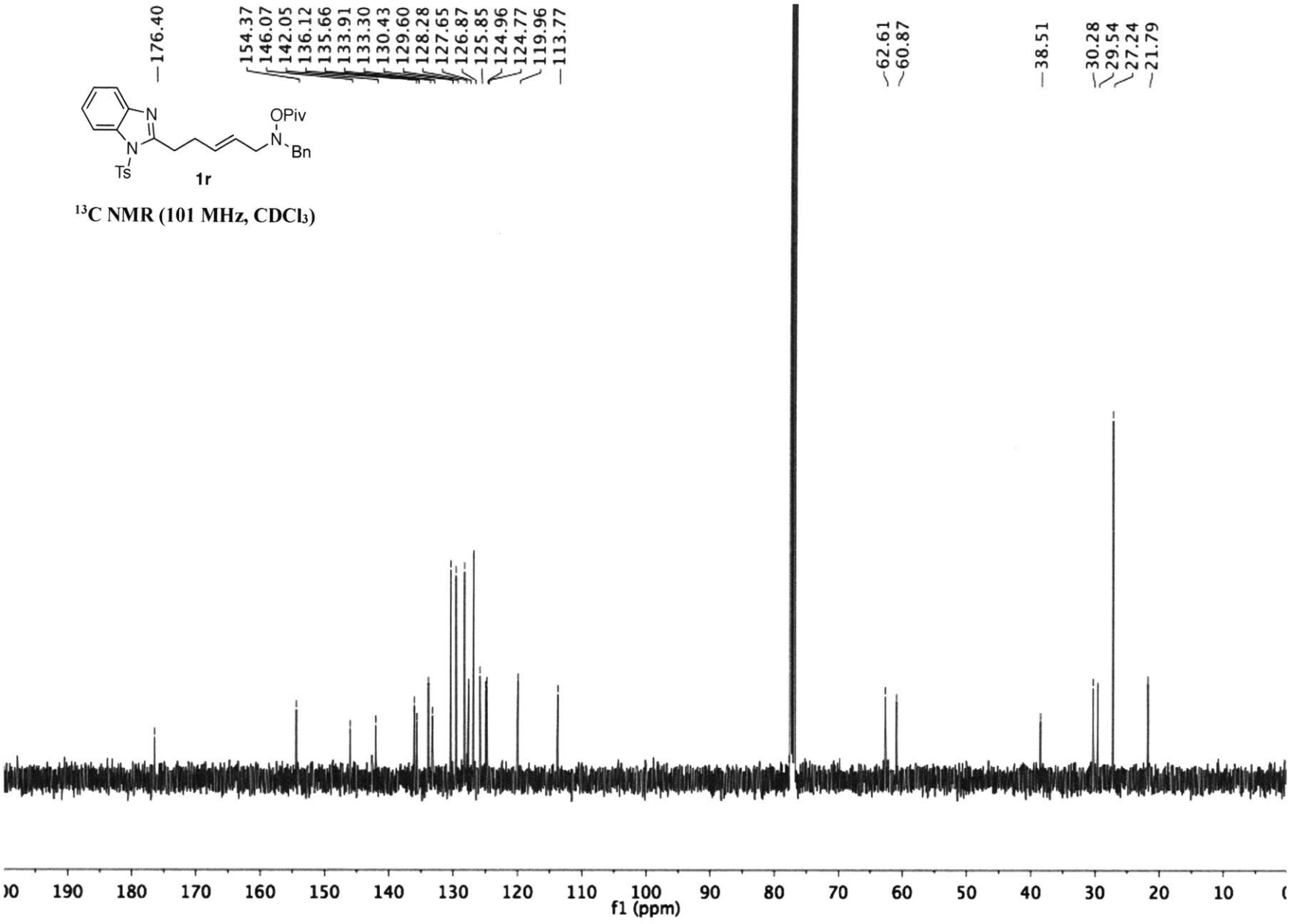
^{1}H NMR (400 MHz, $CDCl_3$)



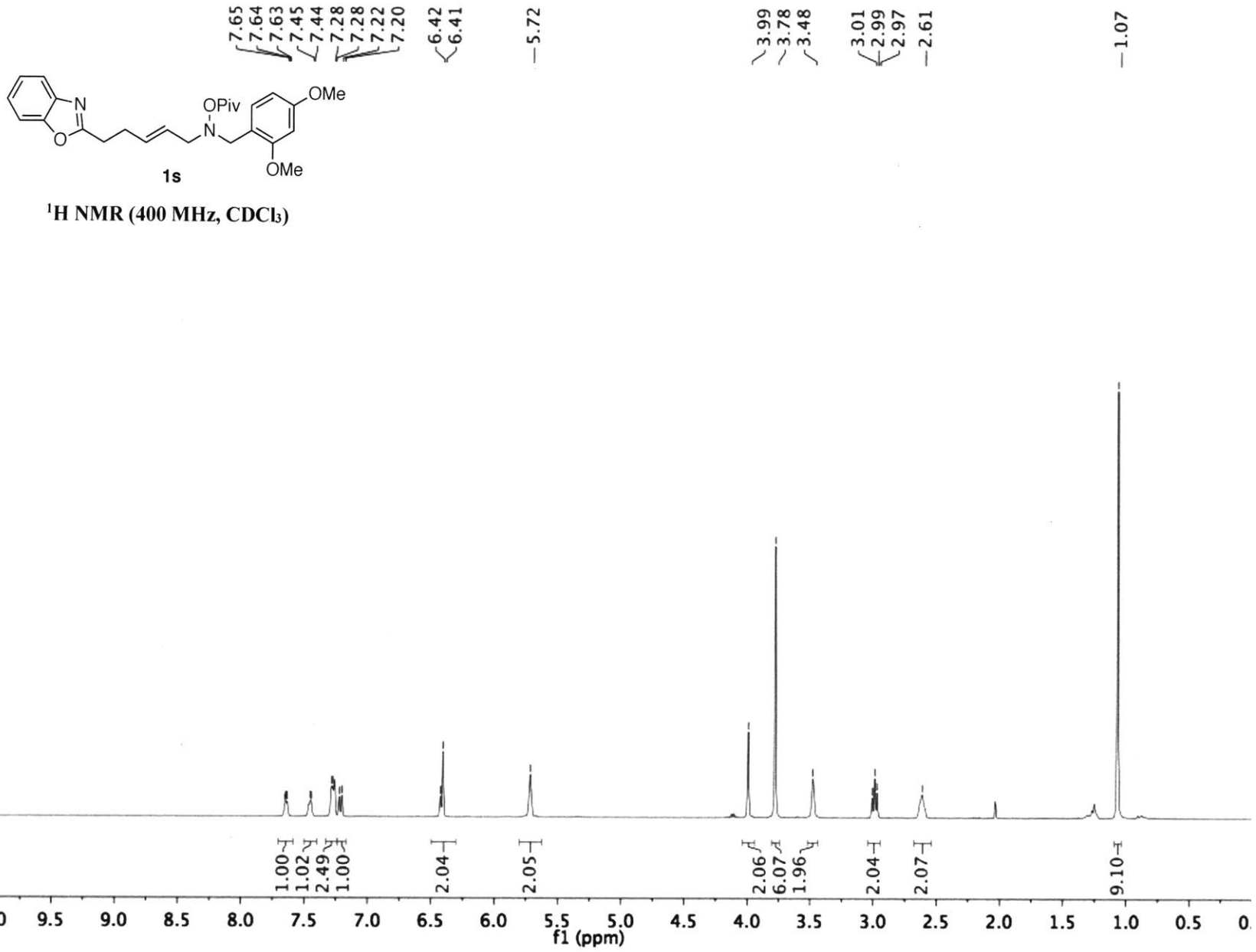
^{13}C NMR (101 MHz, $CDCl_3$)



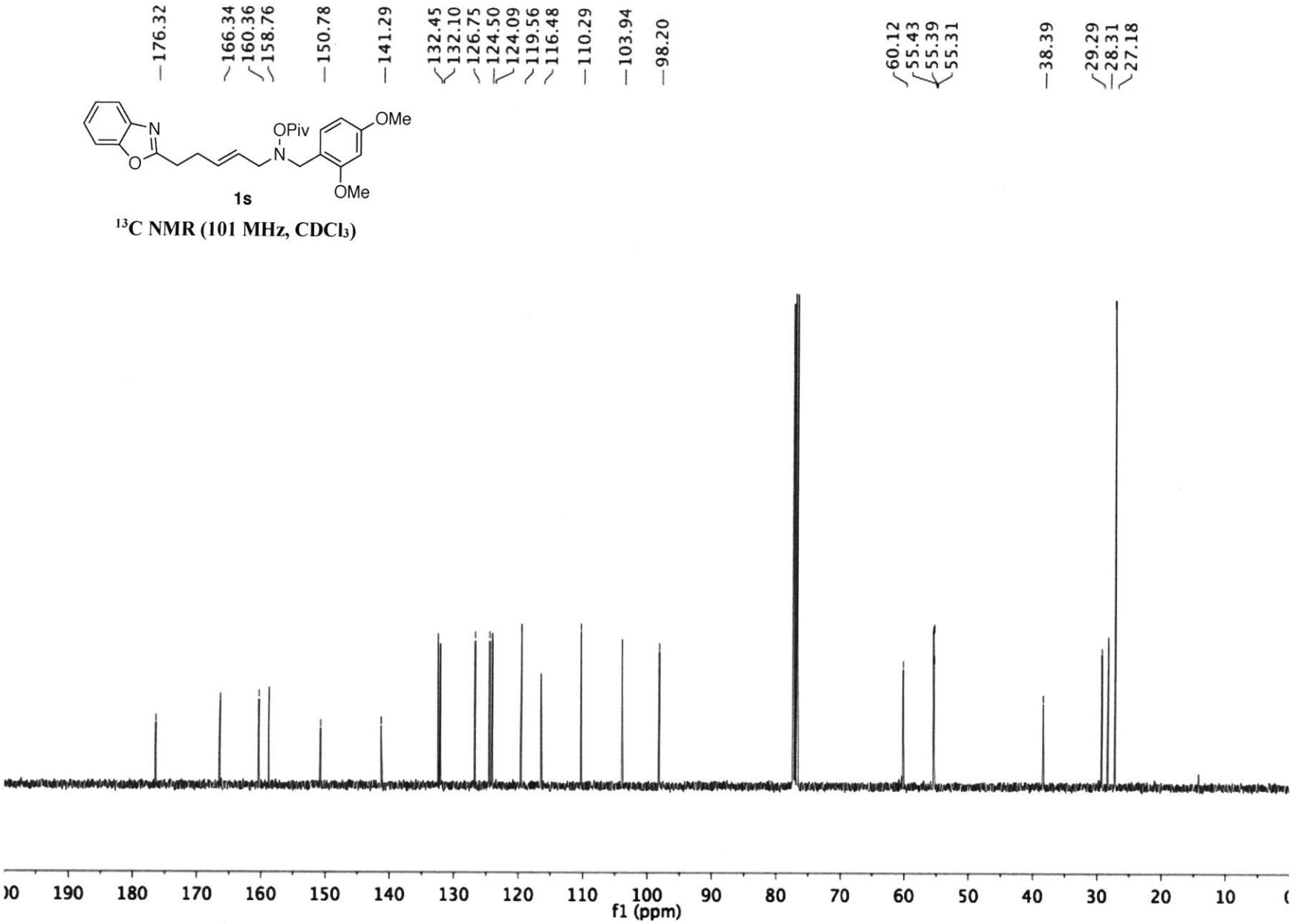
^{1}H NMR (400 MHz, $CDCl_3$)



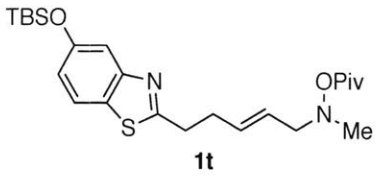
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)

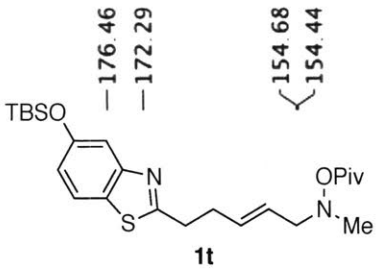


^{13}C NMR (101 MHz, $CDCl_3$)



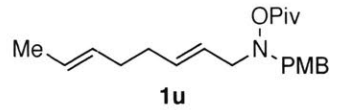
1t

^{1}H NMR (500 MHz, $CDCl_3$)



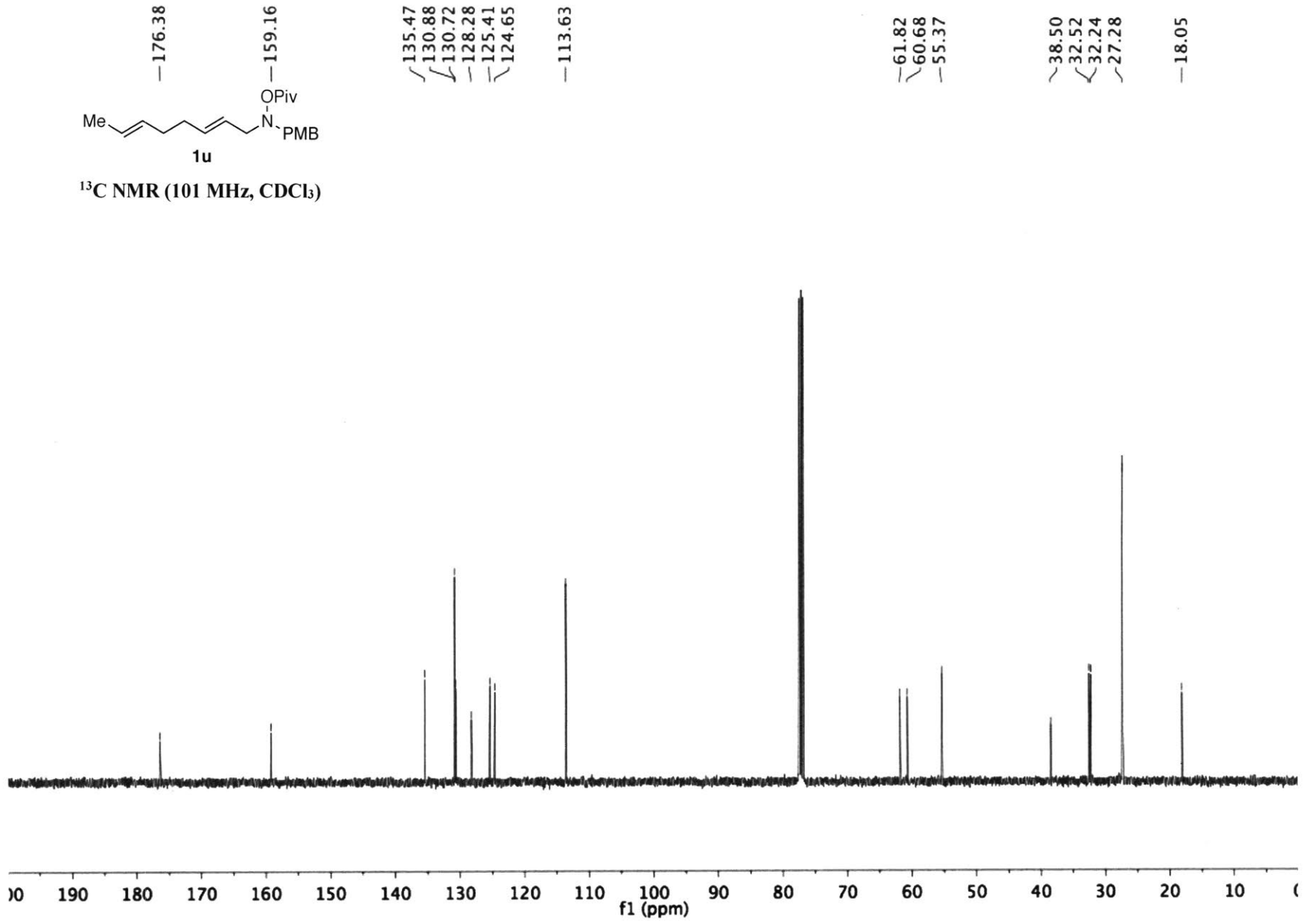
1t

^{13}C NMR (126 MHz, $CDCl_3$)

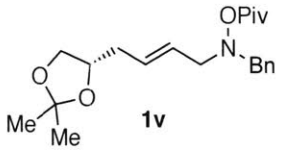


1u

^{1}H NMR (400 MHz, $CDCl_3$)

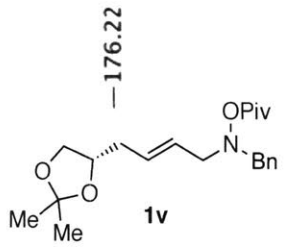


^{13}C NMR (101 MHz, $CDCl_3$)



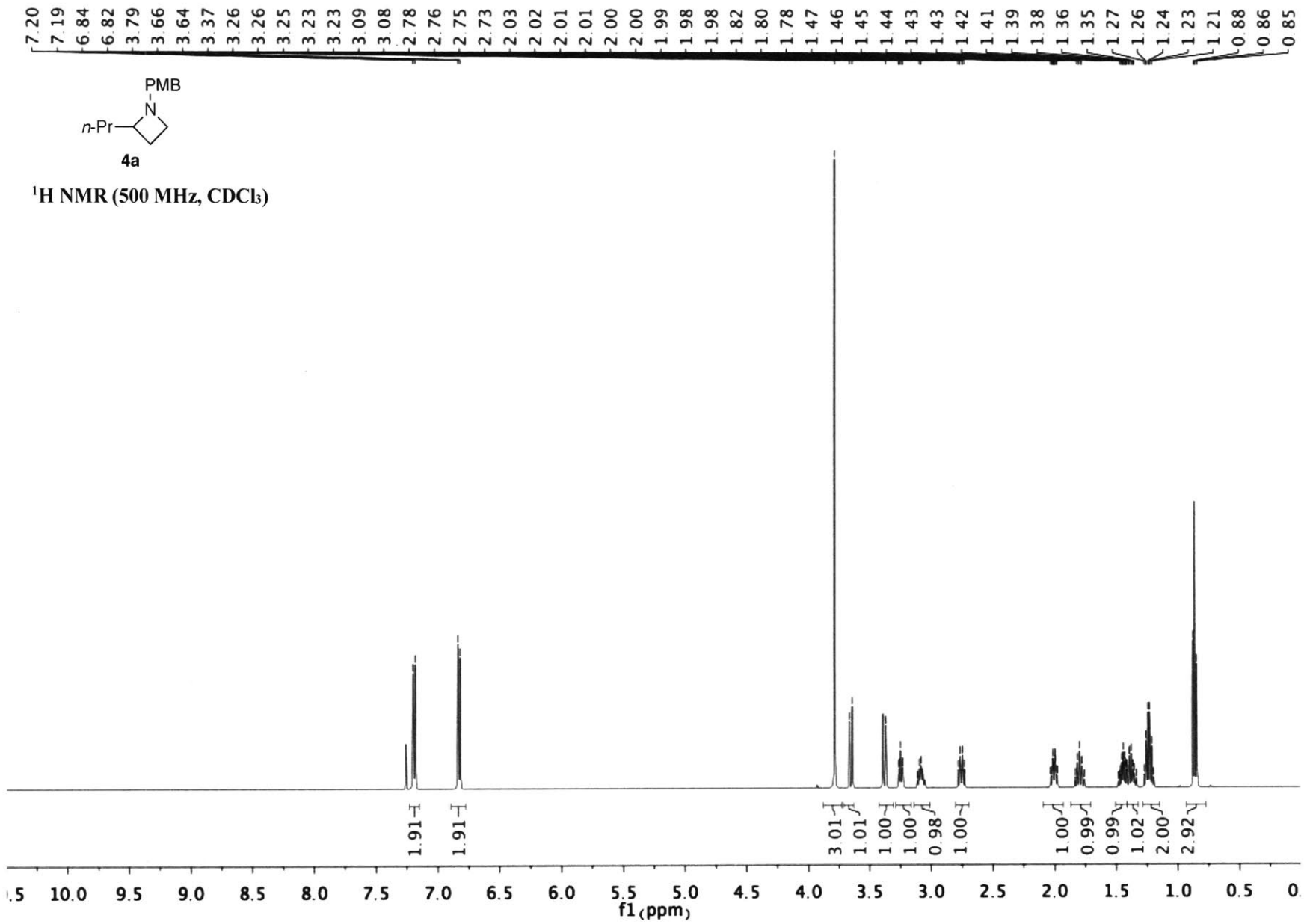
1v

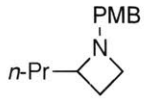
^{1}H NMR (400 MHz, $CDCl_3$)



1v

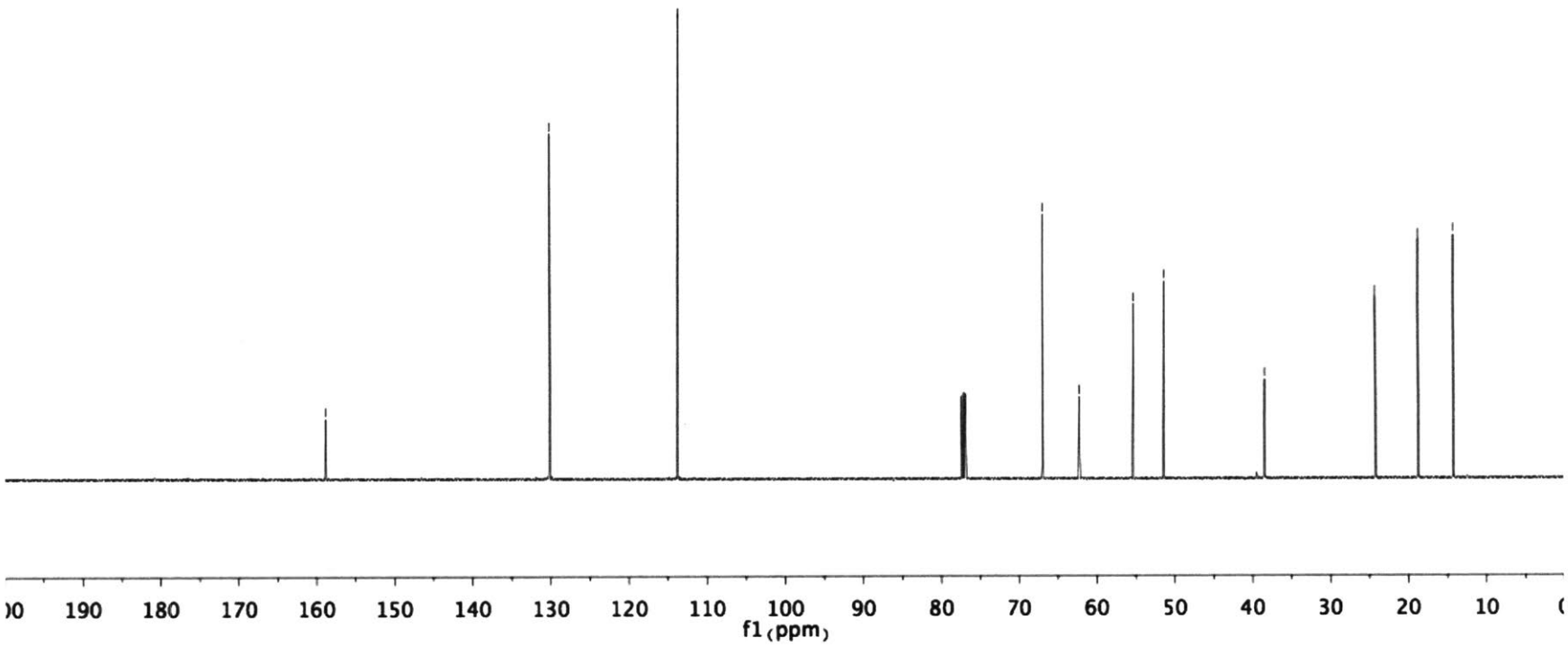
^{13}C NMR (101 MHz, $CDCl_3$)


7.20 7.19 6.84 6.82 3.79 3.66 3.64 3.37 3.26 3.26 3.25 3.23 3.23 3.09 3.08 2.78 2.76 2.75 2.73 2.03 2.02 2.01 2.01 2.00 2.00 1.99 1.98 1.98 1.82 1.80 1.78 1.47 1.46 1.45 1.44 1.43 1.43 1.42 1.41 1.39 1.38 1.36 1.35 1.27 1.26 1.24 1.23 1.21 0.88 0.86 0.85
PMB
N
n-Pr
4a
1H NMR (500 MHz, CDCl3)
1.91 1.91 3.01 1.01 1.00 1.00 0.98 1.00 1.00 0.99 0.99 1.02 2.00 2.92
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
f1 (ppm)

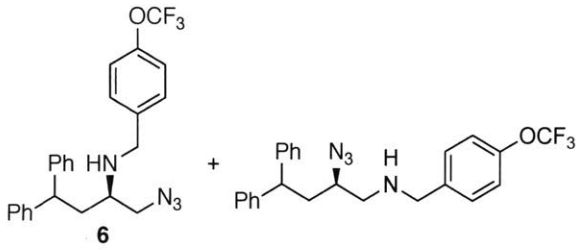


4a

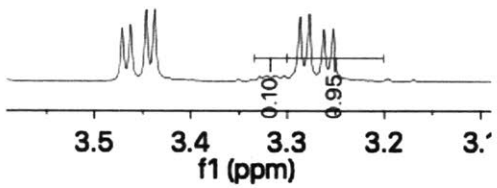
^{13}C NMR (126 MHz, $CDCl_3$)

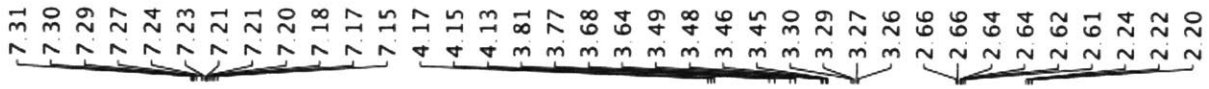


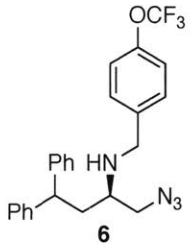
^{1}H NMR spectra of the crude reaction mixture containing 6 and its regioisomer



^{1}H NMR (400 MHz, $CDCl_3$)

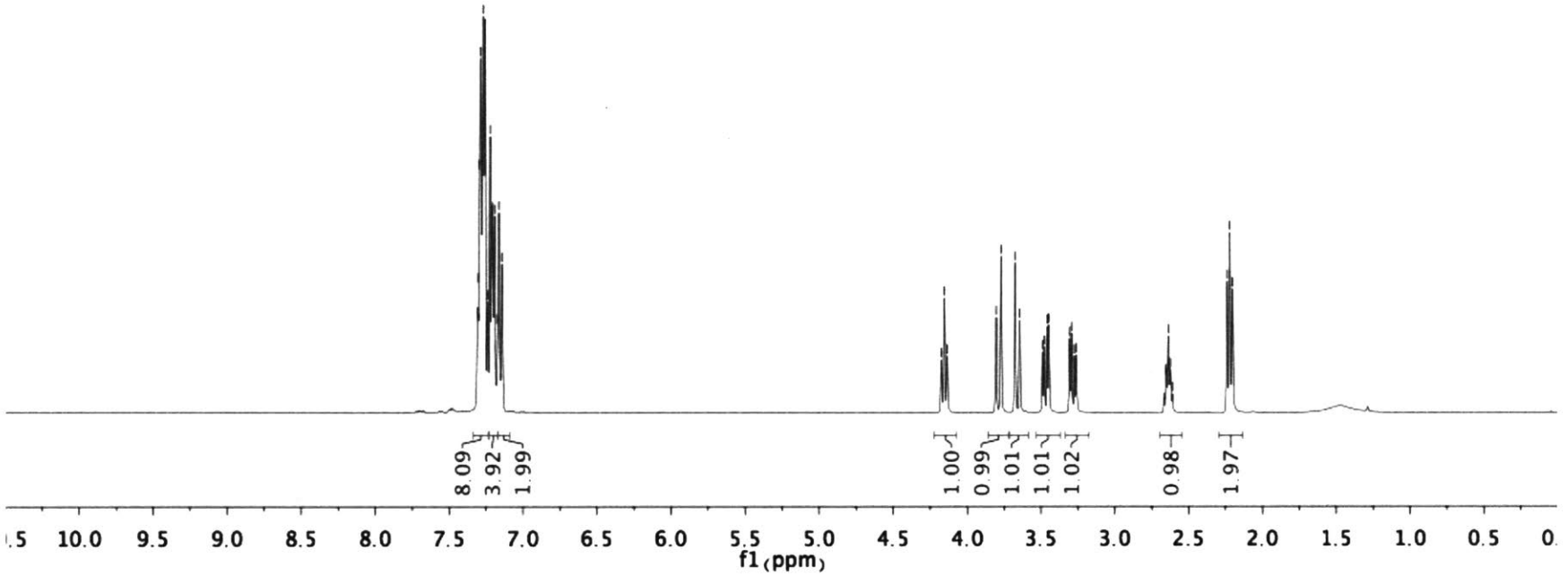


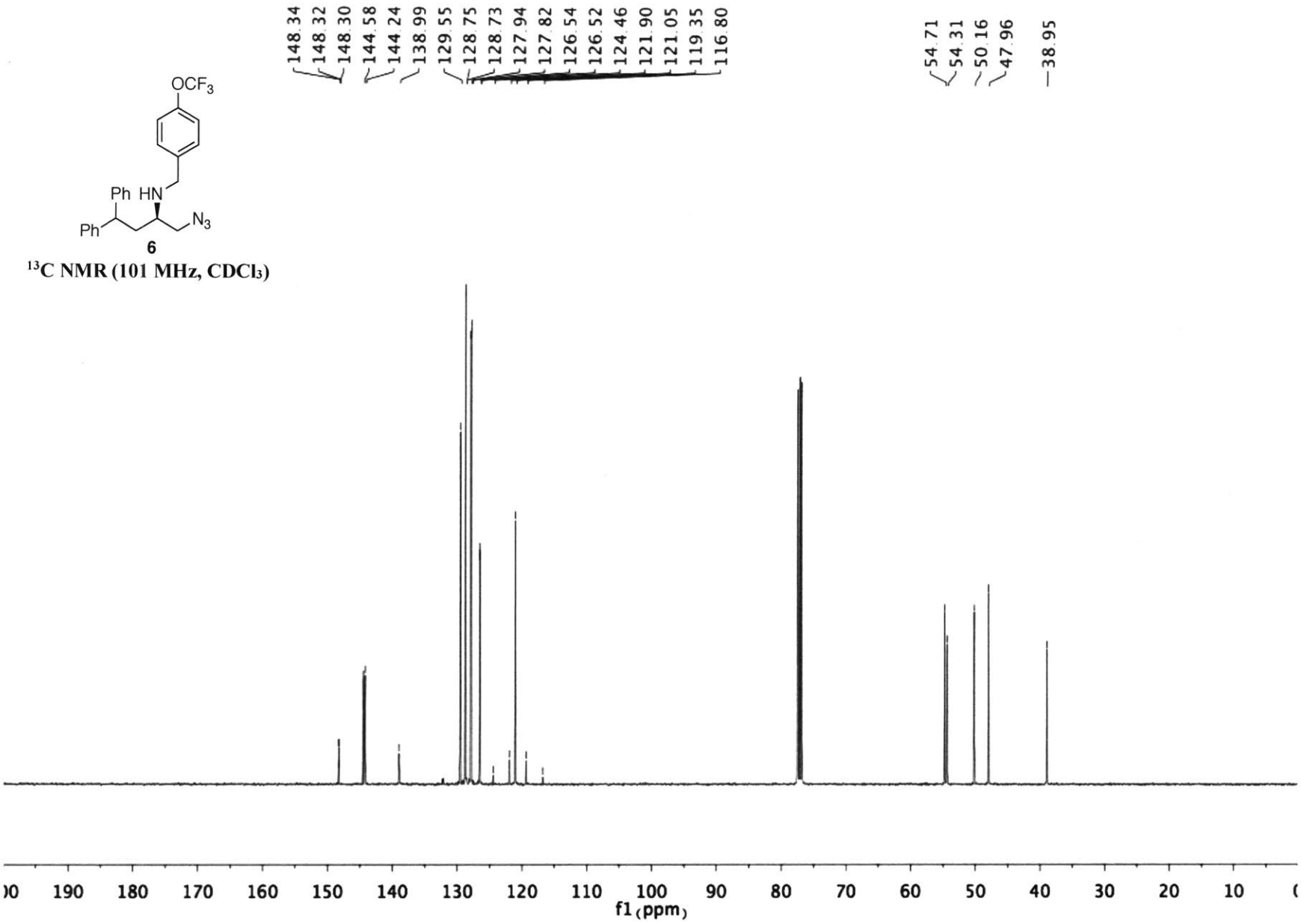


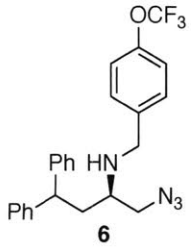


6

^{1}H NMR (400 MHz, $CDCl_3$)

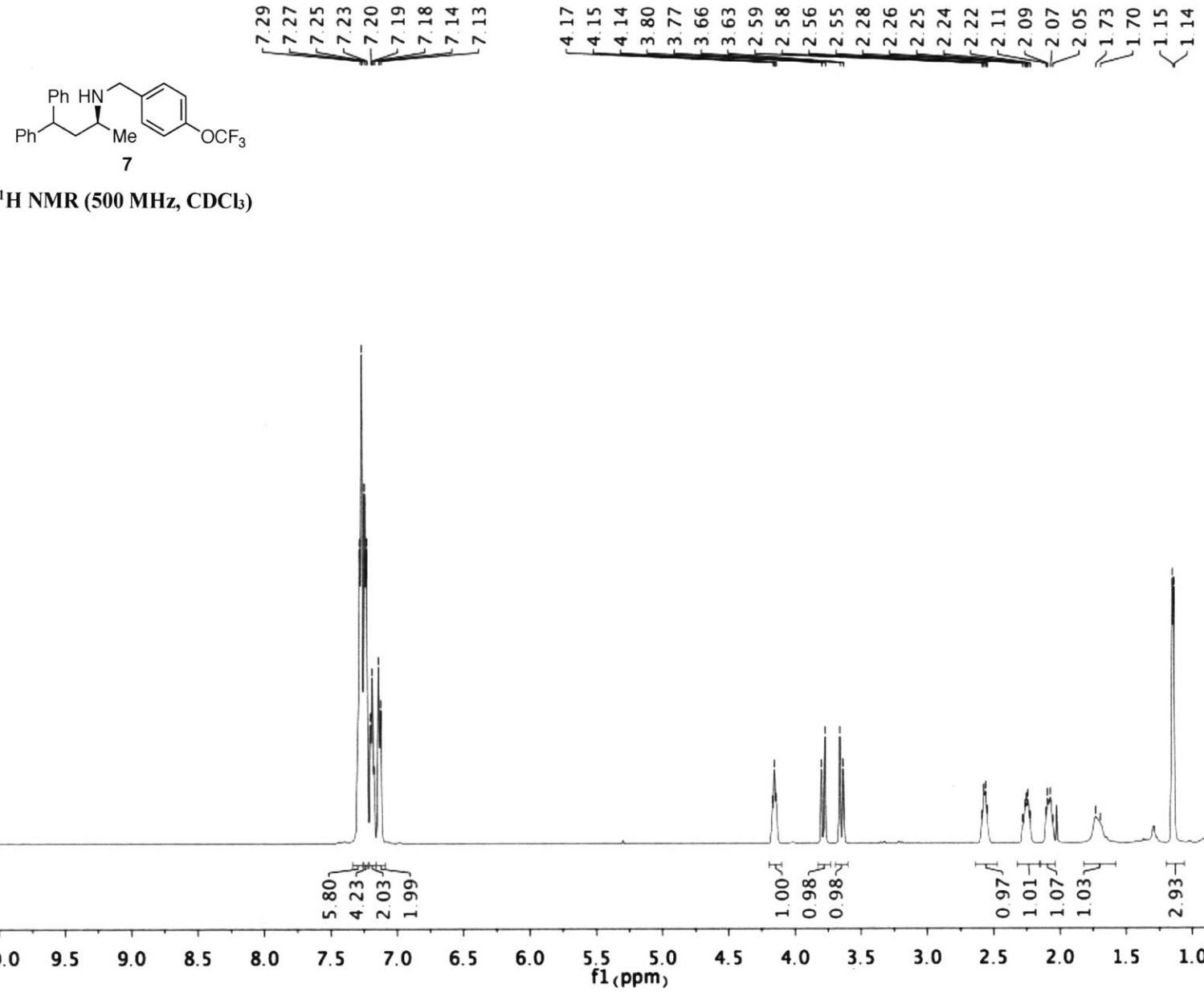



148.34
148.32
148.30
144.58
144.24
138.99
129.55
128.75
128.73
127.94
127.82
126.54
126.52
124.46
121.90
121.05
119.35
116.80
54.71
54.31
50.16
47.96
38.95
OCF3
Ph HN
Ph
N3
6
13C NMR (101 MHz, CDCl3)
f1 (ppm)

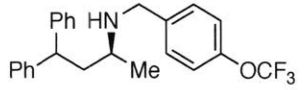


6

^{19}F NMR (376 MHz, $CDCl_3$)

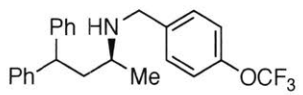


^{1}H NMR (500 MHz, $CDCl_3$)



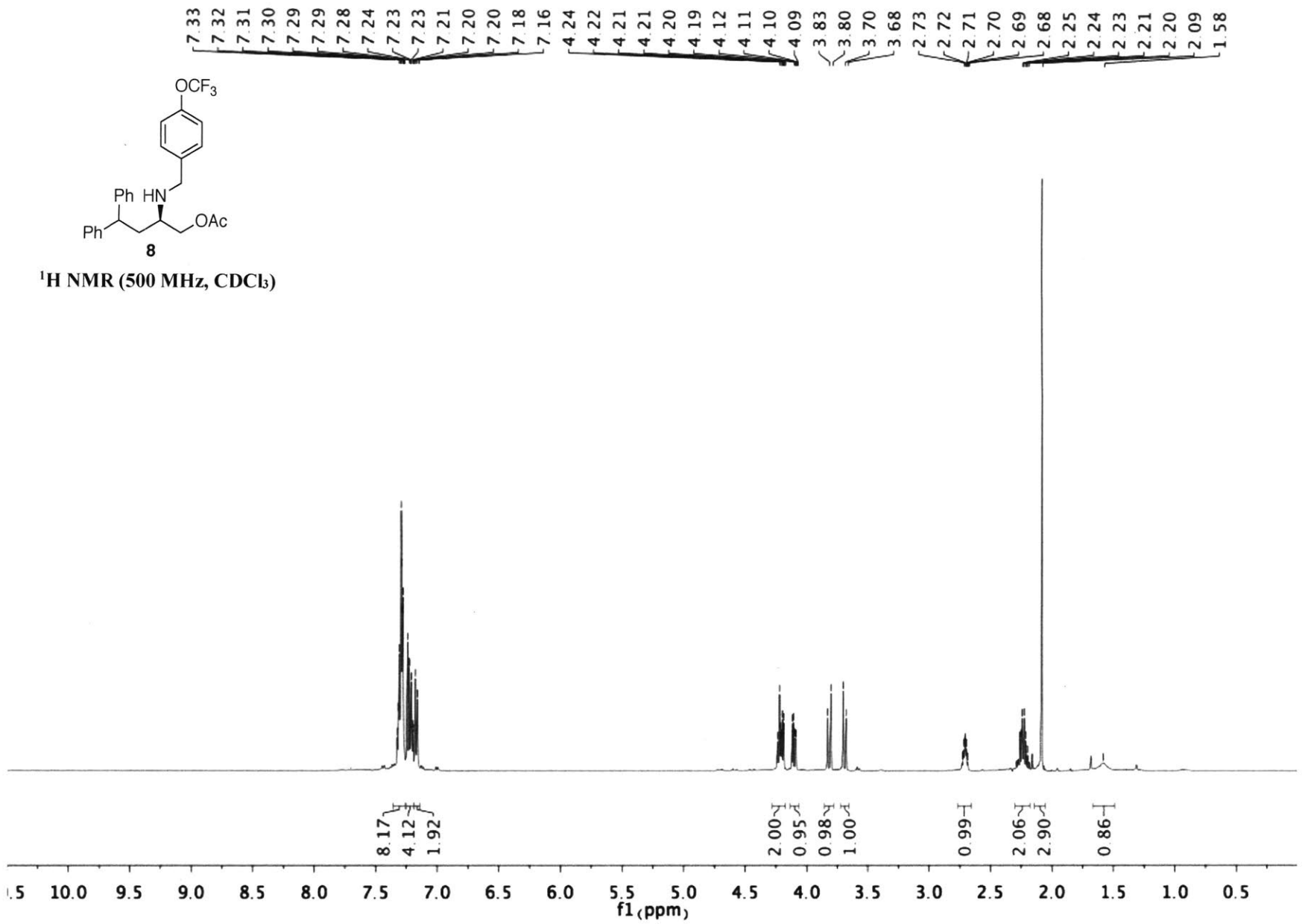
7

^{13}C NMR (126 MHz, $CDCl_3$)

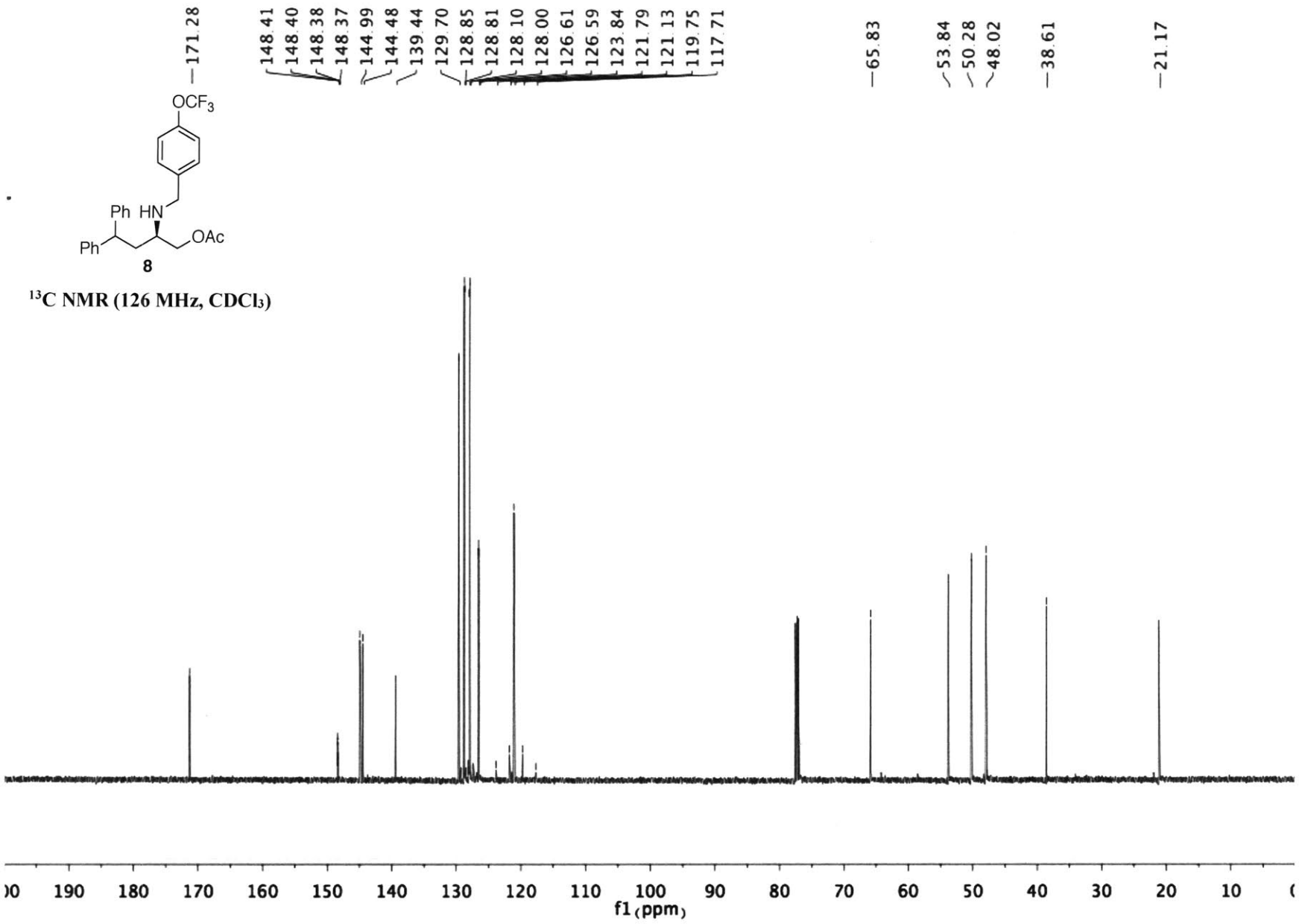


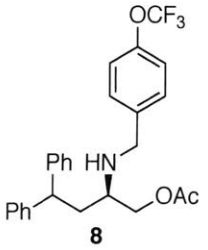
7

^{19}F NMR (471 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)

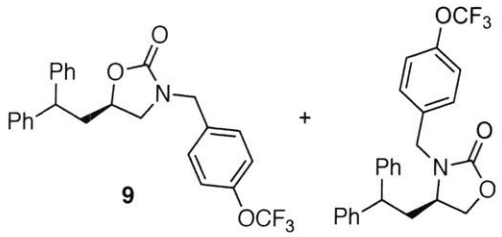

171.28
148.41
148.40
148.38
148.37
144.99
144.48
139.44
129.70
128.85
128.81
128.10
128.00
126.61
126.59
123.84
121.79
121.13
119.75
117.71
65.83
53.84
50.28
48.02
38.61
21.17
OCF3
Ph HN
Ph
OAc
8
13C NMR (126 MHz, CDCl3)
f1 (ppm)



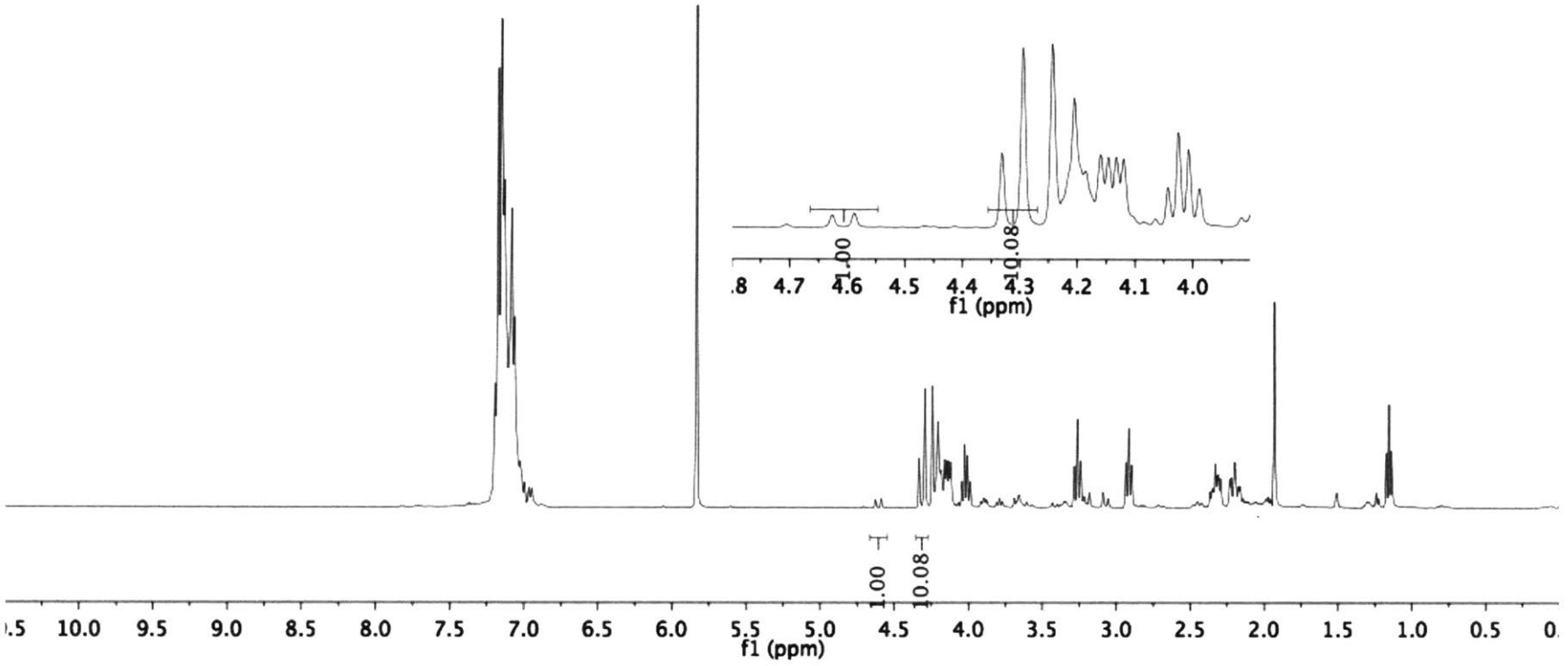
8

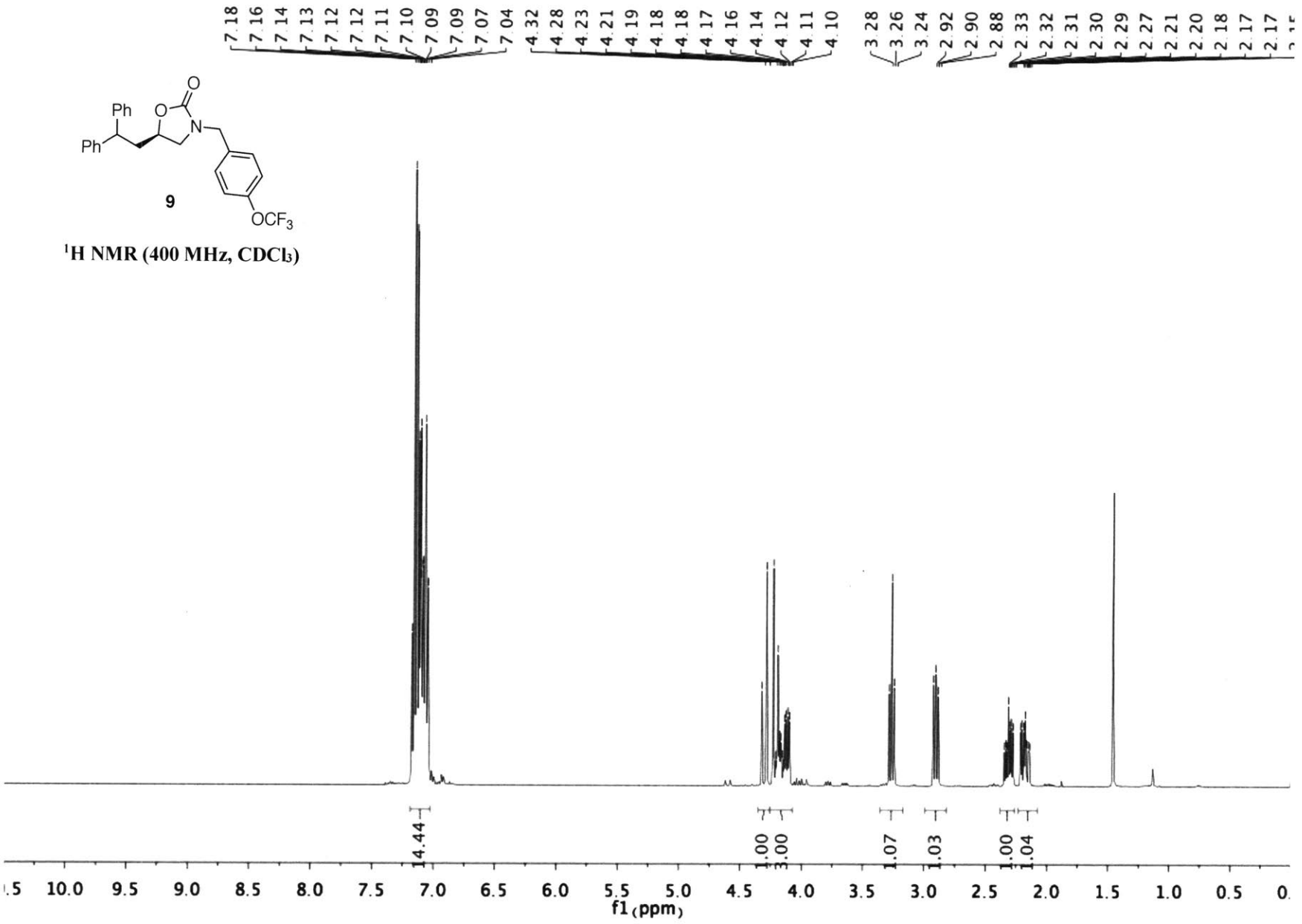
^{19}F NMR (471 MHz, $CDCl_3$)

^{1}H NMR spectra of the crude reaction mixture containing 9 and its regioisomer

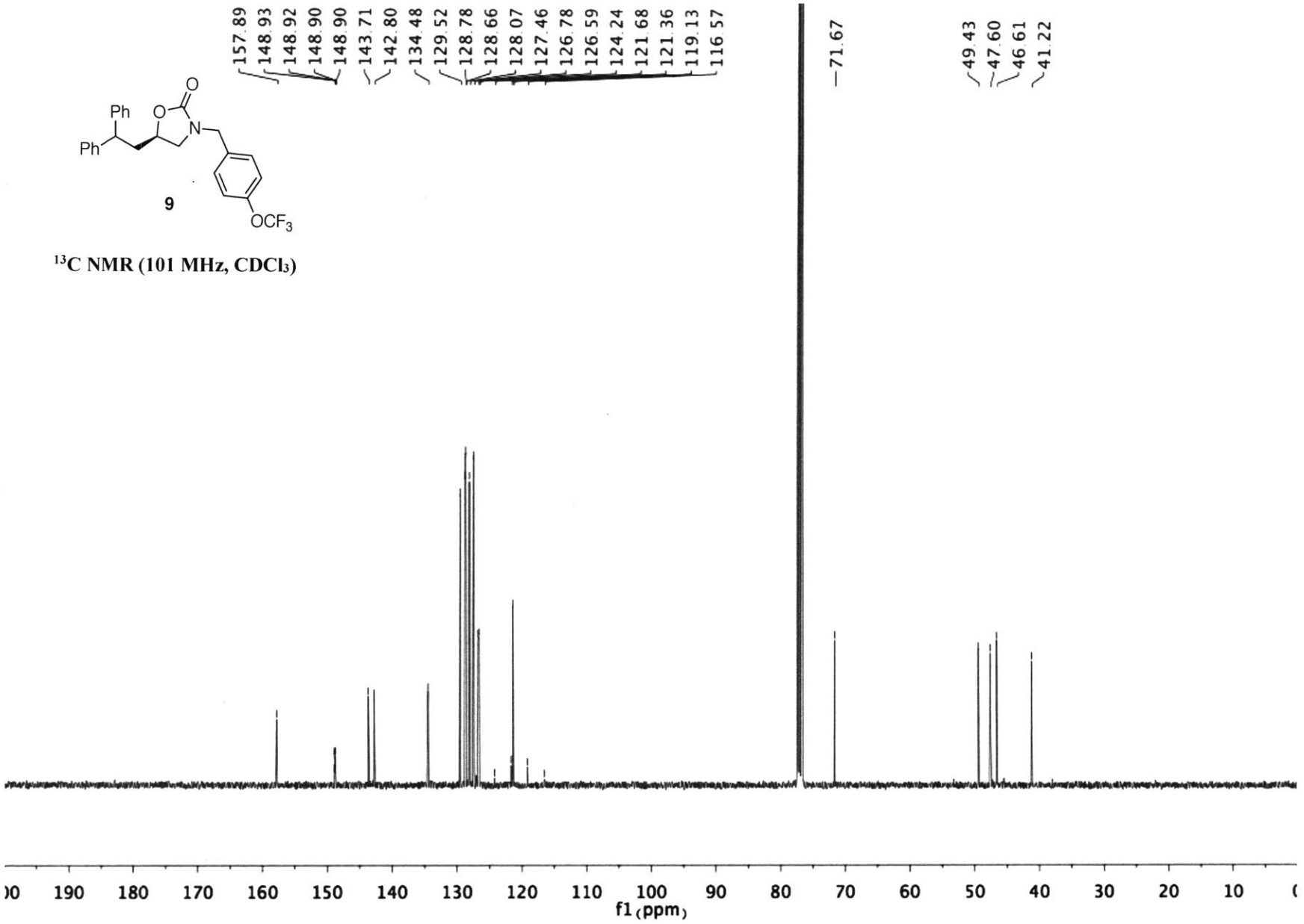


^{1}H NMR (400 MHz, $CDCl_3$)

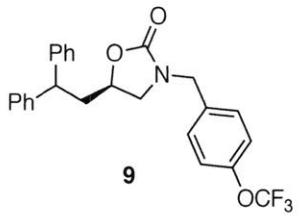




^{1}H NMR (400 MHz, $CDCl_3$)

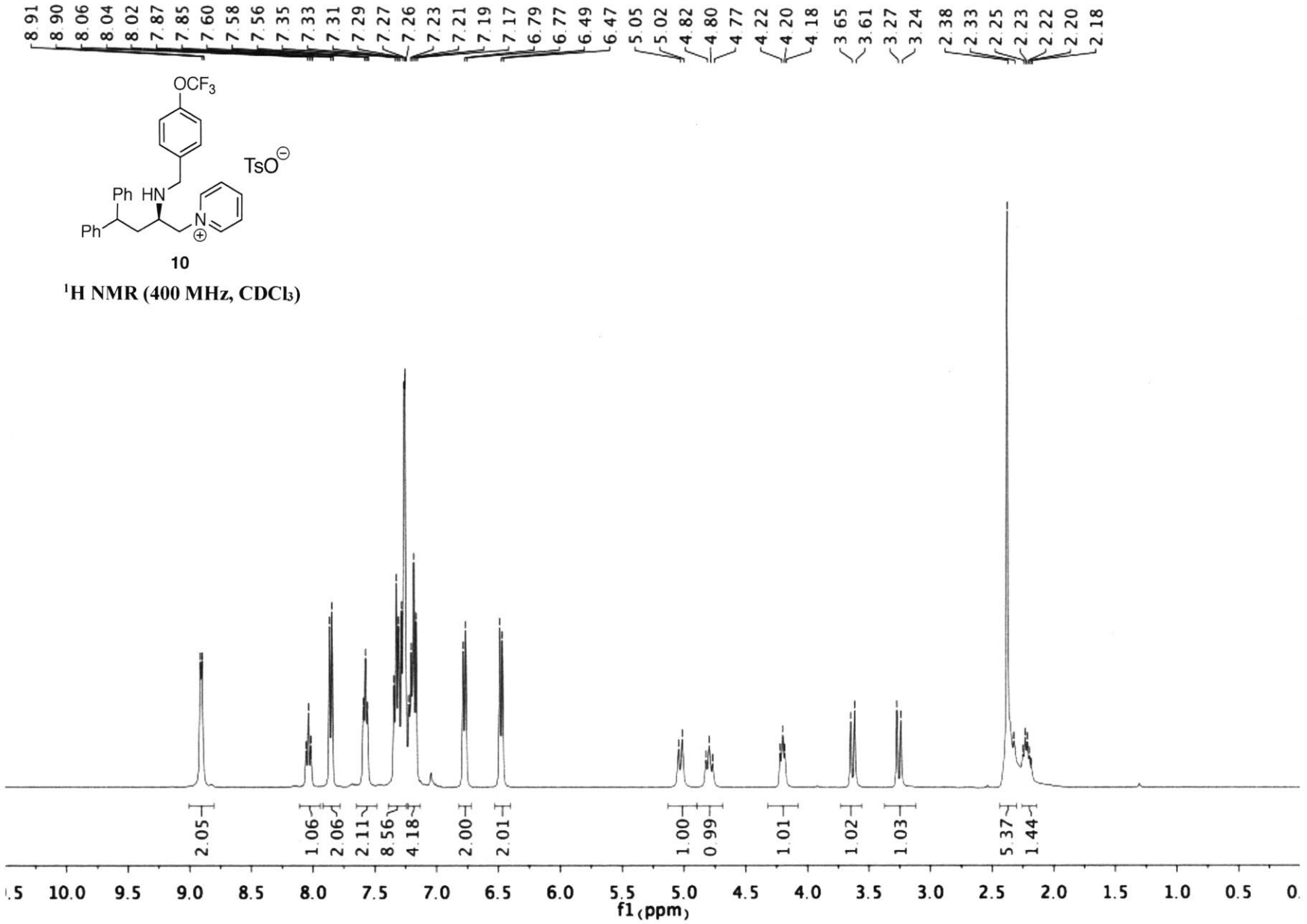


^{13}C NMR (101 MHz, $CDCl_3$)



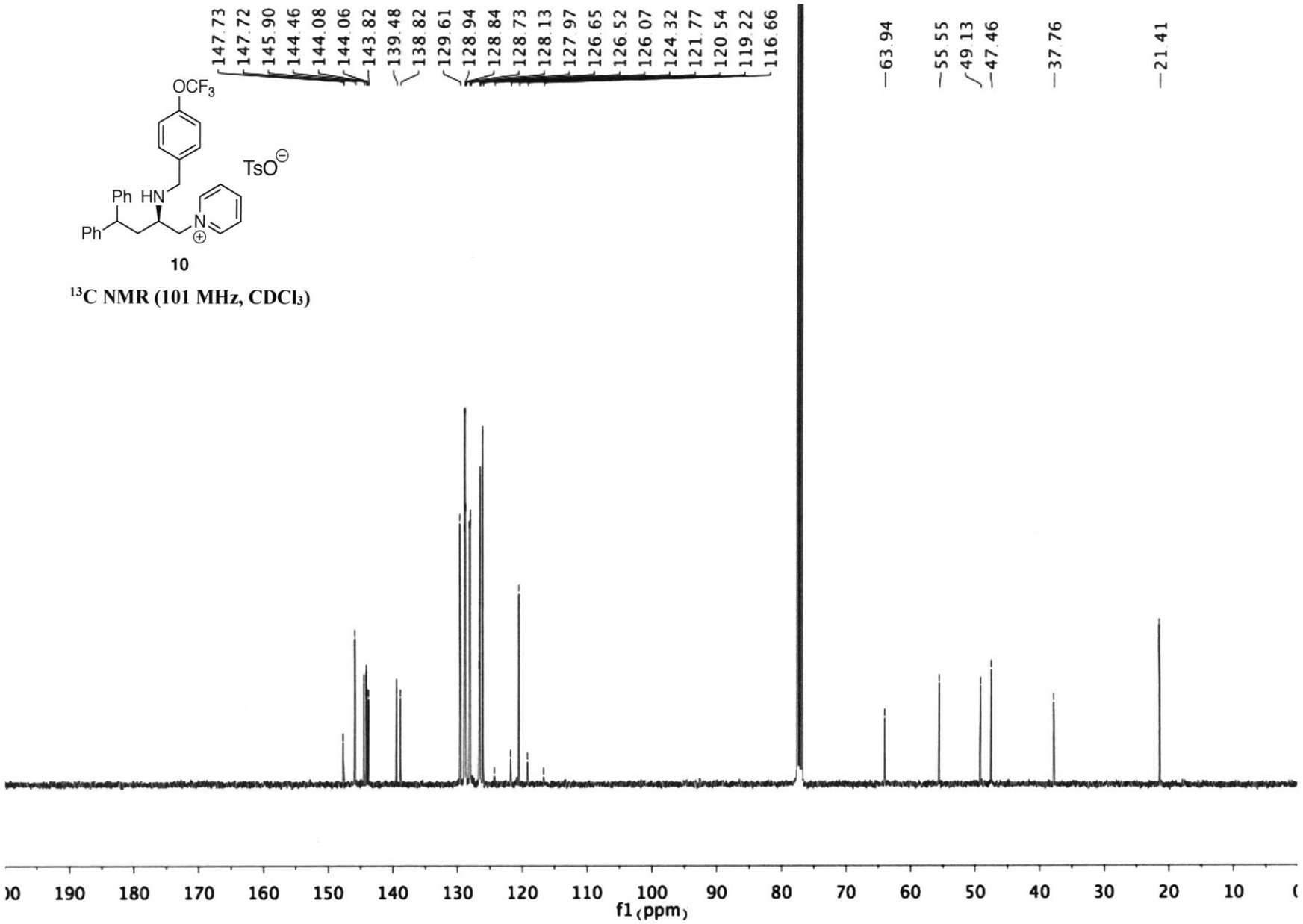
9

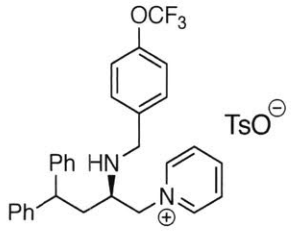
^{19}F NMR (376 MHz, $CDCl_3$)



10

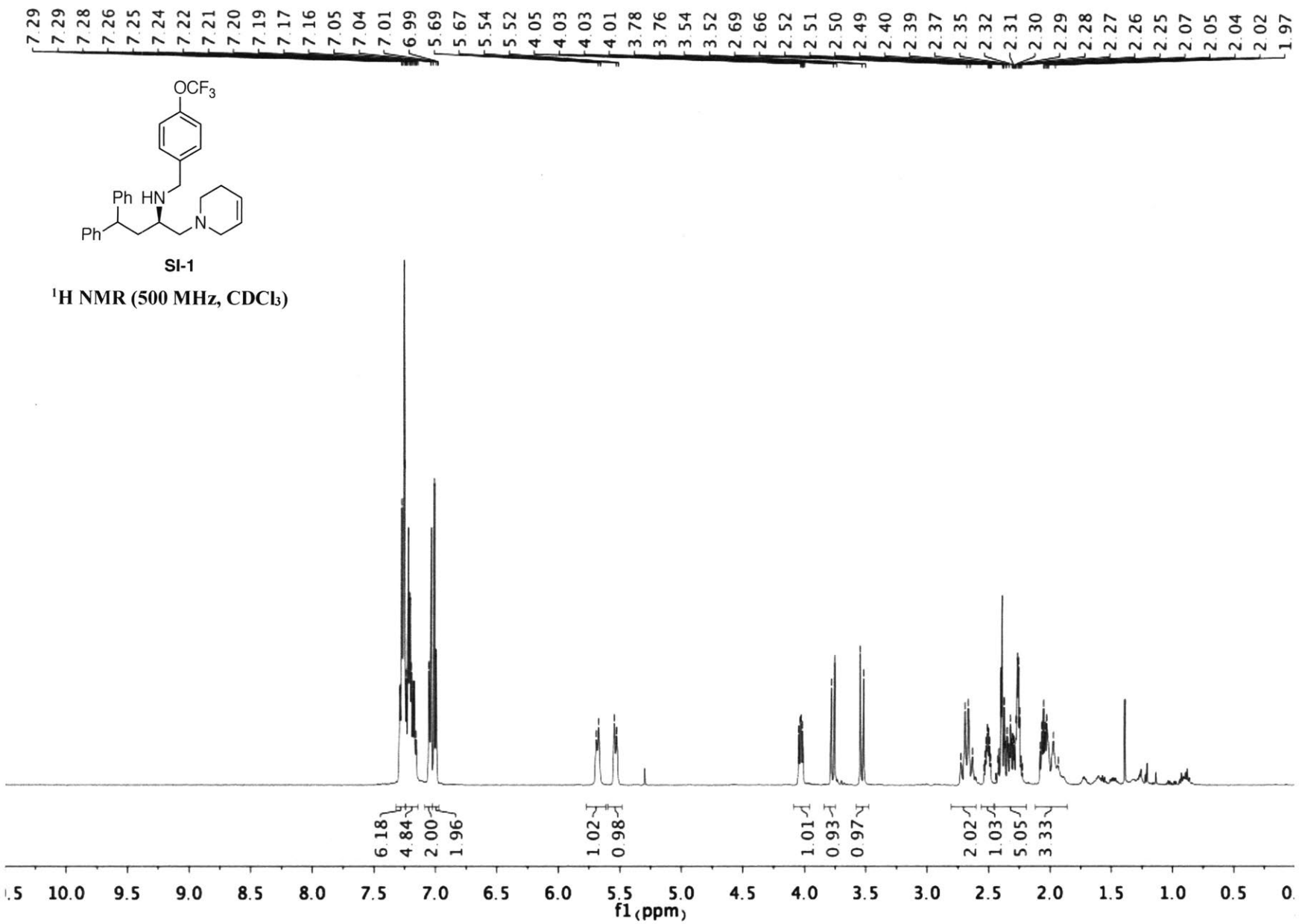
^{1}H NMR (400 MHz, $CDCl_3$)

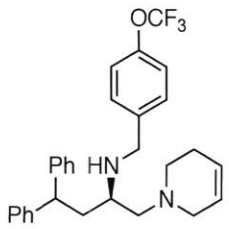

147.73
147.72
145.90
144.46
144.08
144.06
143.82
139.48
138.82
129.61
128.94
128.84
128.73
128.13
127.97
126.65
126.52
126.07
124.32
121.77
120.54
119.22
116.66
63.94
55.55
49.13
47.46
37.76
21.41
OCF3
TsO⊖
Ph HN
Ph
N⊕
10
13C NMR (101 MHz, CDCl3)
f1 (ppm)



10

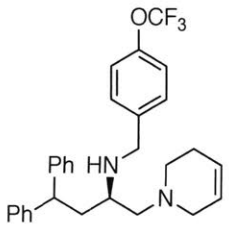
^{19}F NMR (471 MHz, $CDCl_3$)


7.29 7.29 7.28 7.26 7.25 7.24 7.22 7.21 7.20 7.19 7.17 7.16 7.05 7.04 7.01 6.99 5.69 5.67 5.54 5.52 4.05 4.03 4.03 4.01 3.78 3.76 3.54 3.52 2.69 2.66 2.52 2.51 2.50 2.49 2.40 2.39 2.37 2.35 2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.25 2.07 2.05 2.04 2.02 1.97
OCF3
Ph HN
Ph
N
SI-1
1H NMR (500 MHz, CDCl3)
6.18 4.84 2.00 1.96 1.02 0.98 1.01 0.93 0.97 2.02 1.03 5.05 3.33
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
f1 (ppm)



SI-1

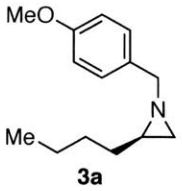
^{13}C NMR (126 MHz, $CDCl_3$)



SI-1

^{19}F NMR (471 MHz, $CDCl_3$)

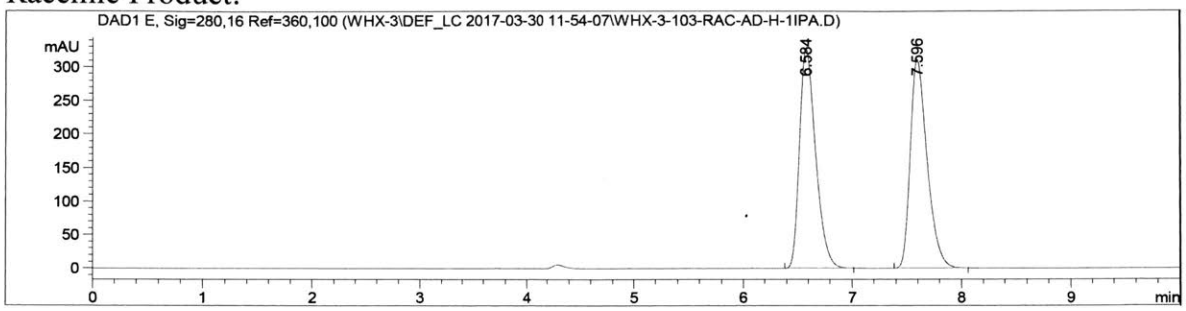
2.7 Chiral HPLC Spectra



3a

(*R*)-2-Butyl-1-(4-methoxybenzyl)aziridine (3a): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 280 nm): t_R(major) = 6.6 min, t_R (minor) = 7.6 min.

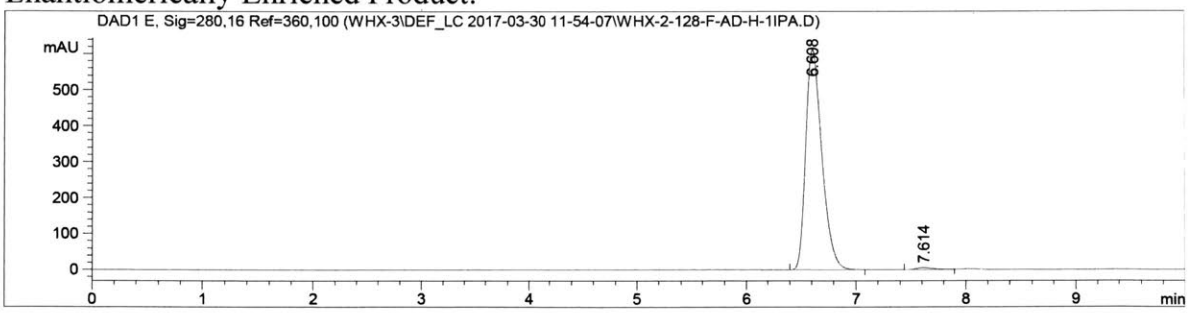
Racemic Product:



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

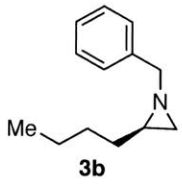
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.584	BB	0.1574	3352.12671	327.45602	50.0477
2	7.596	BB	0.1633	3345.73877	311.59991	49.9523

Enantiomerically Enriched Product:



Signal 5: DAD1 E, Sig=280,16 Ref=360,100

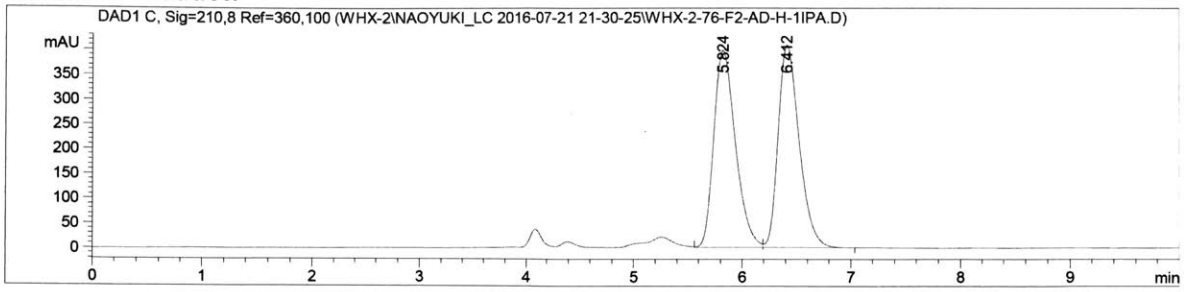
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.608	BB	0.1563	6221.67432	613.35010	98.9660
2	7.614	BV	0.1716	65.00283	5.51003	1.0340



3b

(*R*)-1-Benzyl-2-butylaziridine (3b): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 0.8 mL/min, 210 nm): t_R(major) = 5.8 min, t_R(minor) = 6.5 min.

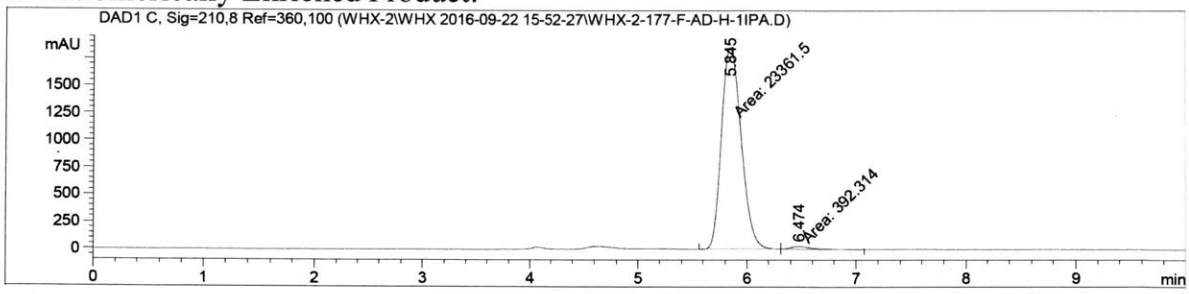
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

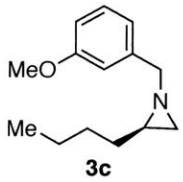
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.824	VV	0.2139	5516.53711	397.49734	50.1265
2	6.412	VB	0.2071	5488.68359	407.64963	49.8735

Enantiomerically Enriched Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

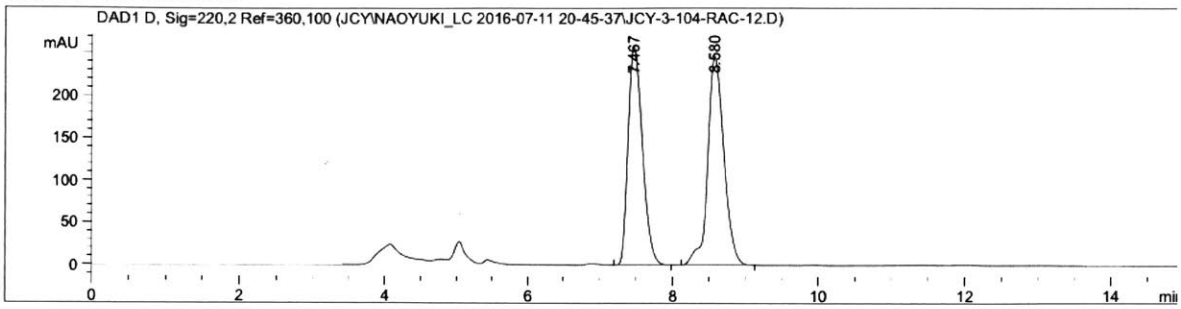
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.845	MF	0.2098	2.33615e4	1855.98645	98.3484
2	6.474	FM	0.2385	392.31387	27.41751	1.6516



3c

(*R*)-2-Butyl-1-(3-methoxybenzyl)aziridine (3c): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 210 nm): t_R (minor) = 7.5 min, t_R (major) = 8.6 min.

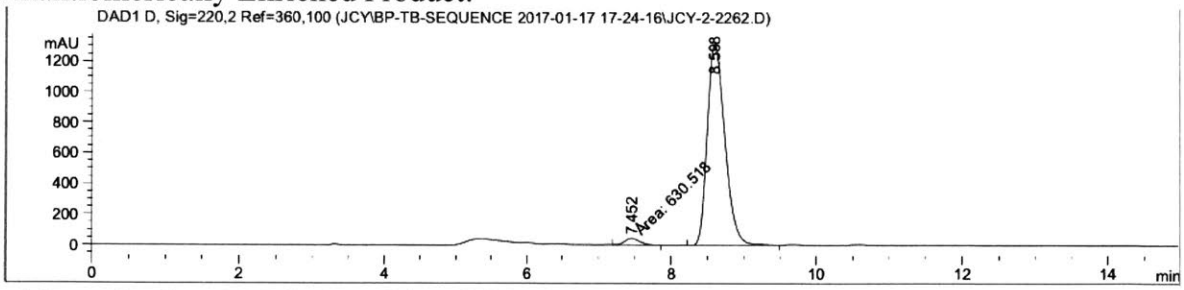
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

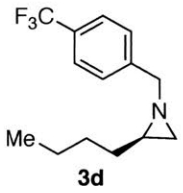
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.467	VB	0.2169	4092.42651	296.74838	46.7344
2	8.578	MM	0.2733	4664.35498	284.49326	53.2656

Enantiomerically Enriched Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

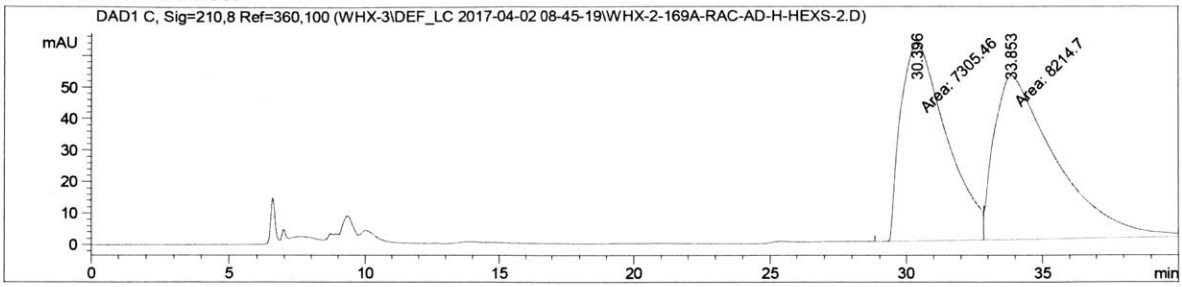
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.452	MM	0.2427	630.51843	43.30308	2.7513
2	8.598	VV	0.2641	2.22865e4	1312.74329	97.2487



3d

(*R*)-2-Butyl-1-(4-(trifluoromethyl)benzyl)aziridine (3d): HPLC analysis (AD-H column, hexanes, 0.5 mL/min, 210 nm): t_R (major) = 27.8 min, t_R (minor) = 34.8 min.

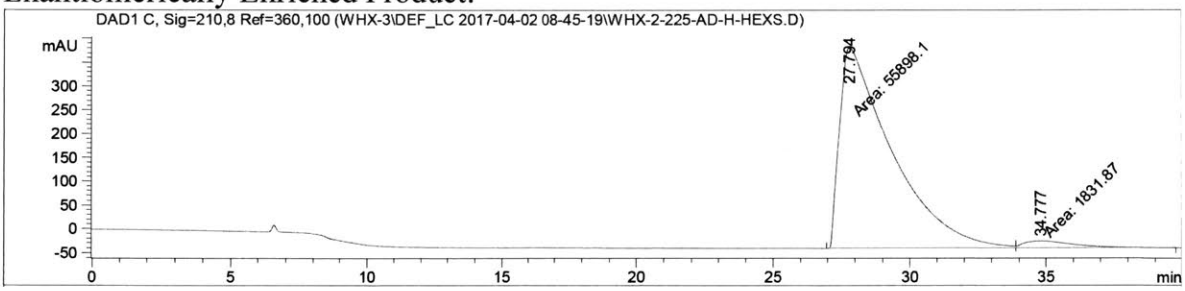
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

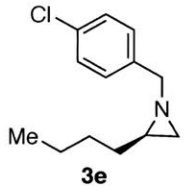
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.396	MF	1.9440	7305.45654	62.63379	47.0708
2	33.853	MM	2.6338	8214.70117	51.98301	52.9292

Enantiomerically Enriched Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

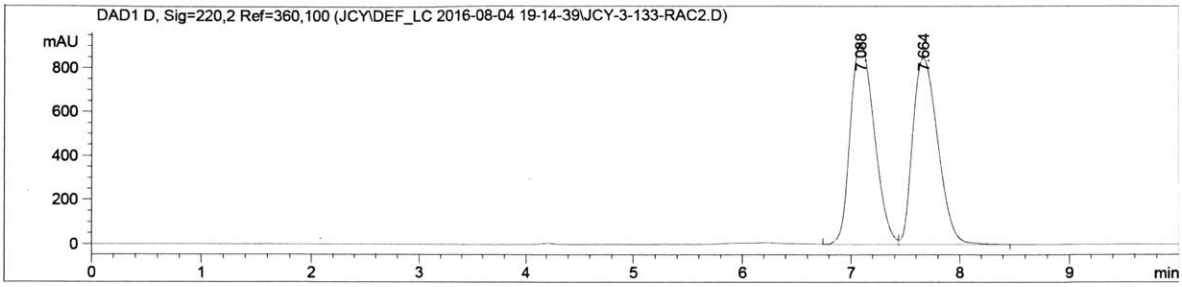
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.794	MF	2.2013	5.58981e4	423.22705	96.8268
2	34.777	FM	2.0958	1831.87305	14.56755	3.1732



3e

(*R*)-2-Butyl-1-(4-chlorobenzyl)aziridine (3e): HPLC analysis (OJ-H column, 0.3% 2-propanol in hexanes, 0.8 mL/min, 220 nm): t_R (major) = 7.0 min, t_R (minor) = 7.6 min.

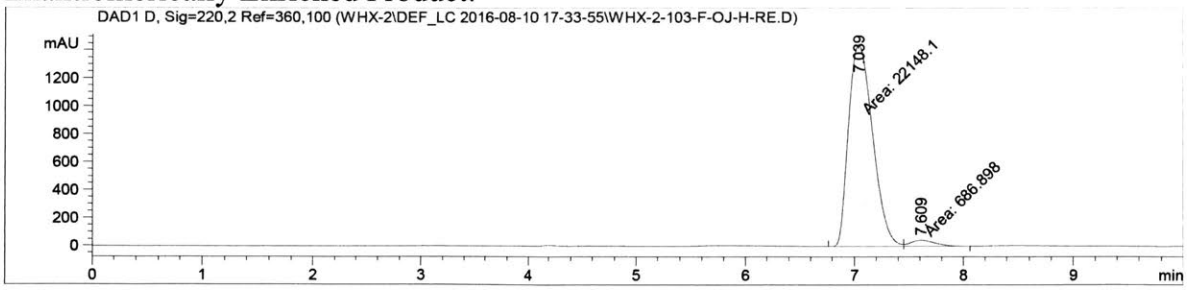
Racemic Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

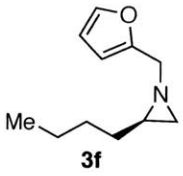
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.088	VV	0.2451	1.40275e4	913.65875	50.9076
2	7.664	VB	0.2549	1.35273e4	844.35760	49.0924

Enantiomerically Enriched Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

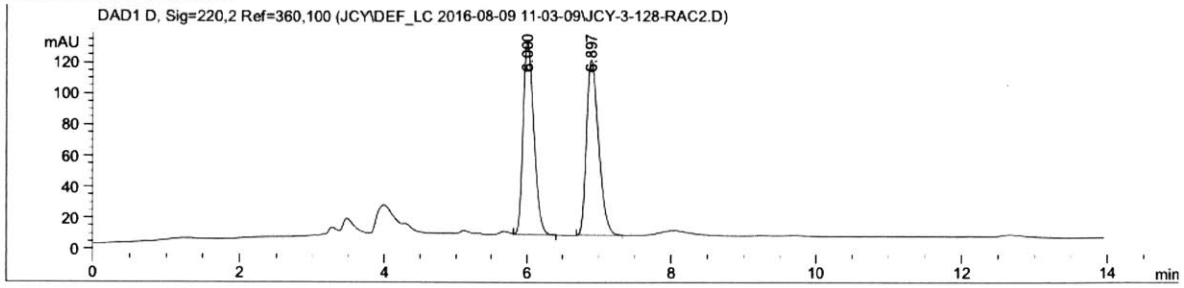
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.039	MF	0.2556	2.21481e4	1444.43884	96.9919
2	7.609	FM	0.2663	686.89789	42.98613	3.0081



3f

(*R*)-2-Butyl-1-(furan-2-ylmethyl)aziridine (3f): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 220 nm): t_R (major) = 5.7 min, t_R (minor) = 6.9 min.

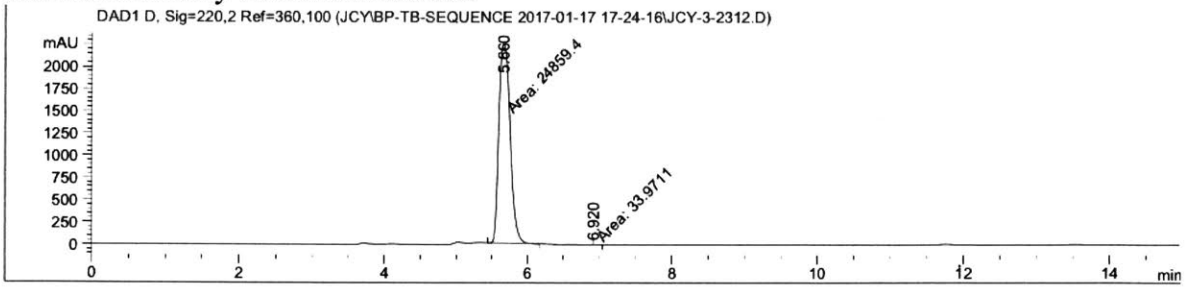
Racemic Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

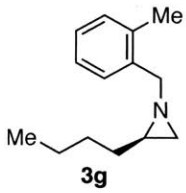
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.000	VB	0.1661	1310.90674	123.27050	50.2595
2	6.897	BB	0.1787	1297.36816	112.38988	49.7405

Enantiomerically Enriched Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

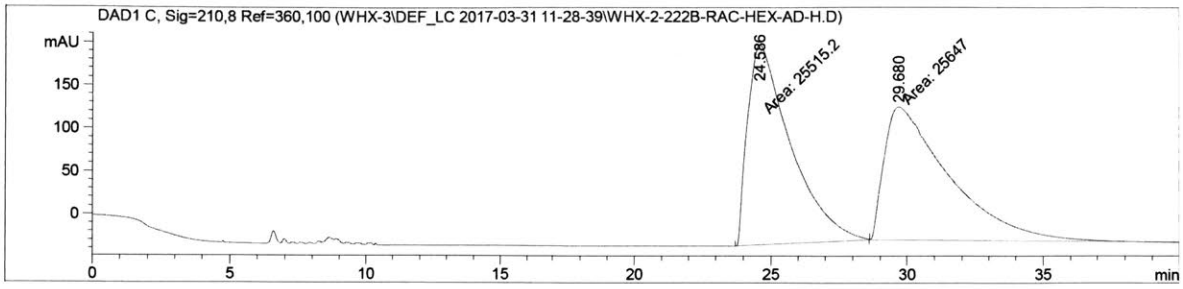
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.660	MM	0.1844	2.48594e4	2247.26245	99.8635
2	6.920	MM	0.0869	33.97112	6.50850	0.1365



3g

(*R*)-2-Butyl-1-(2-methylbenzyl)aziridine (3g): HPLC analysis (AD-H column, hexanes, 0.5 mL/min, 210 nm): t_R (major) = 24.1 min, t_R (minor) = 32.7 min.

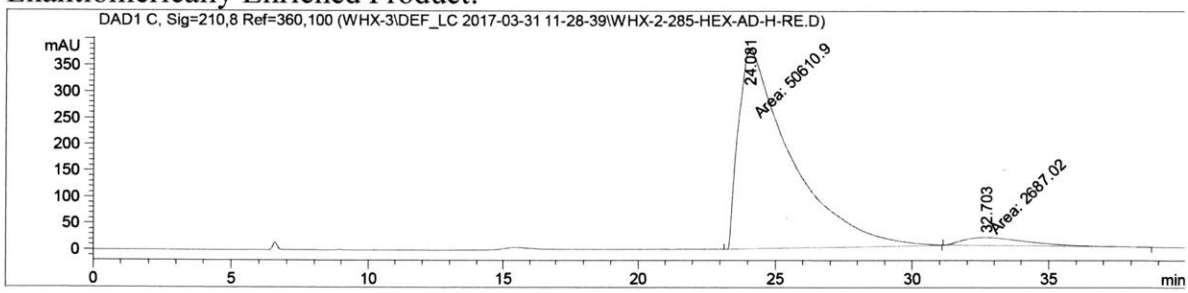
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

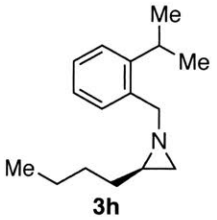
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.586	MM	1.8228	2.55152e4	233.30225	49.8711
2	29.680	MM	2.7608	2.56470e4	154.82697	50.1289

Enantiomerically Enriched Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

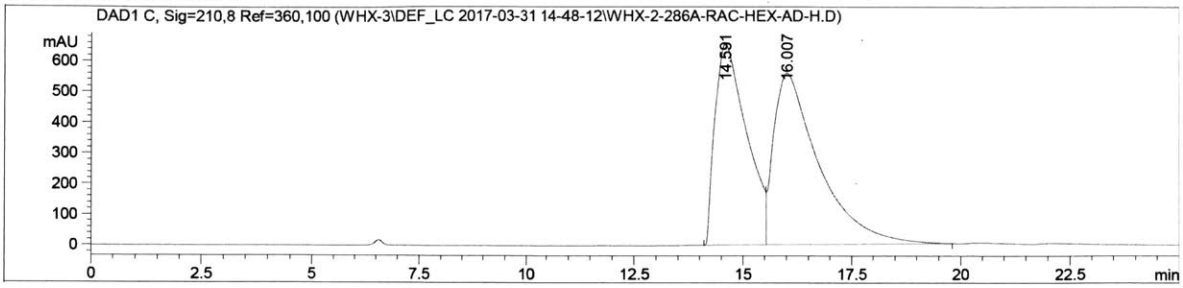
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.081	MM	2.2160	5.06109e4	380.64536	94.9585
2	32.703	MM	2.8206	2687.01929	15.87717	5.0415



3h

(*R*)-2-Butyl-1-(2-isopropylbenzyl)aziridine (3h): HPLC analysis (AD-H column, hexanes, 0.5 mL/min, 210 nm): t_R(major) = 14.1 min, t_R(minor) = 16.4 min.

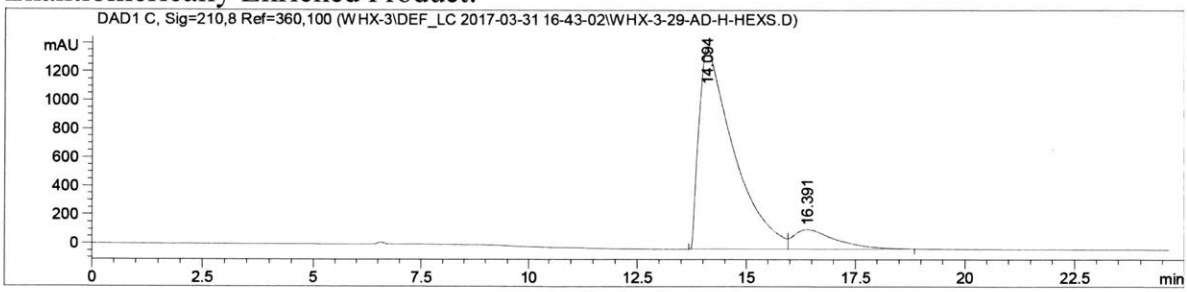
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

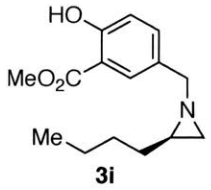
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.591	BV	0.7501	3.29187e4	655.25531	44.8207
2	16.007	VB	1.0393	4.05266e4	558.02533	55.1793

Enantiomerically Enriched Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

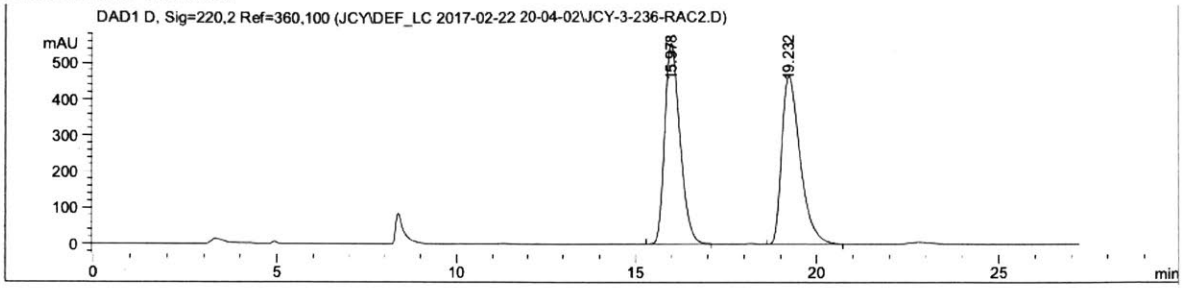
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.094	BV	0.7861	7.81977e4	1412.12219	89.3503
2	16.391	VB	0.9717	9320.37891	137.68842	10.6497



3i

Methyl (*R*)-5-((2-butylaziridin-1-yl)methyl)-2-hydroxybenzoate (3i): HPLC analysis (AD-H column, 0.5% 2-propanol in hexanes, 1.0 mL/min, 220 nm): t_R(major) = 16.0 min, t_R(minor) = 19.3 min.

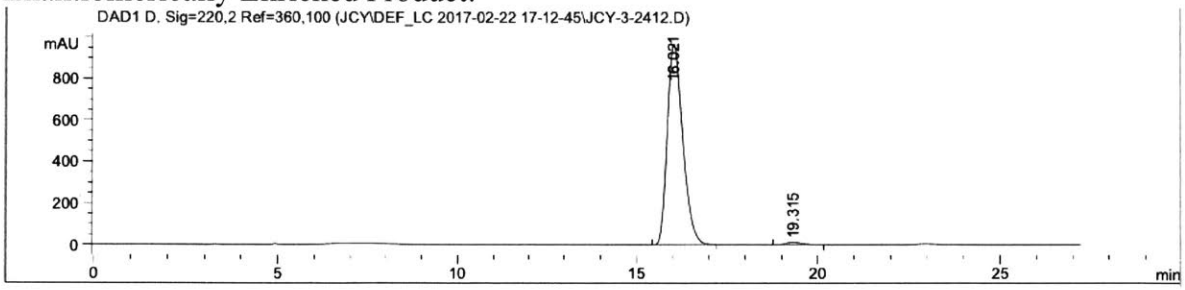
Racemic Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

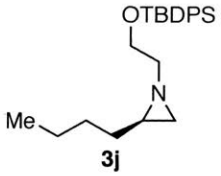
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.978	BB	0.4529	1.62696e4	553.49152	49.9151
2	19.232	VB	0.5390	1.63249e4	463.36023	50.0849

Enantiomerically Enriched Product:



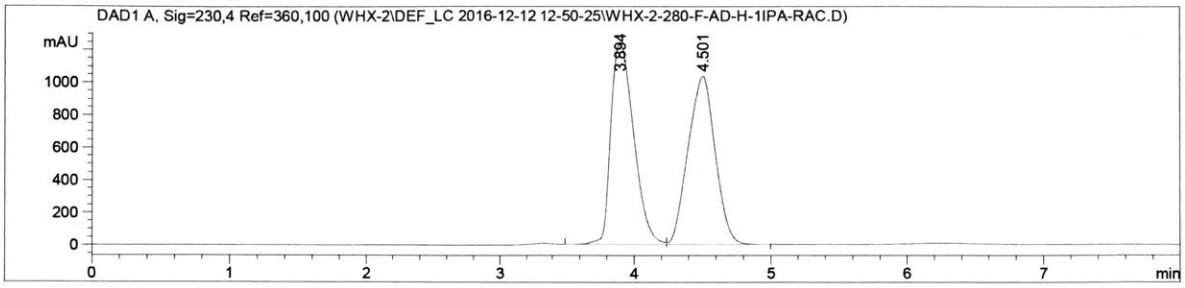
Signal 4: DAD1 D, Sig=220,2 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.021	BB	0.4608	2.89130e4	966.95270	98.5461
2	19.315	BB	0.4823	426.55322	13.08692	1.4539



(*R*)-2-Butyl-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)aziridine (3j): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm): t_R(major) = 3.9 min, t_R(minor) = 4.5 min.

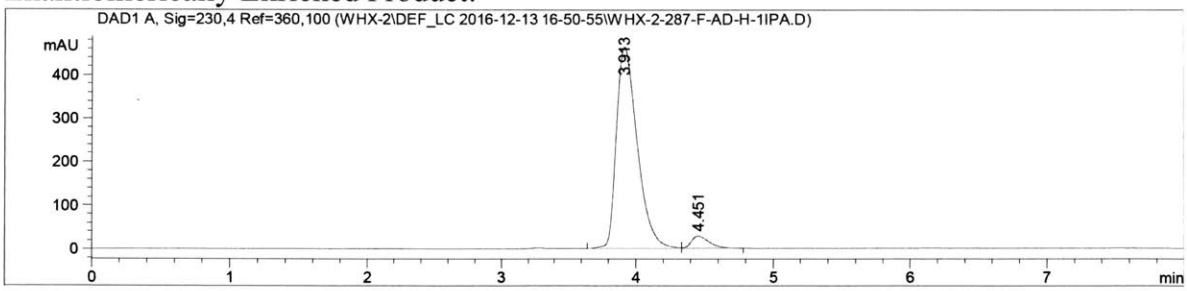
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

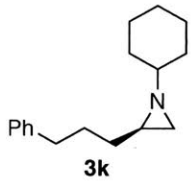
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.894	VV	0.1862	1.44372e4	1236.66138	50.3404
2	4.501	VB	0.2186	1.42419e4	1034.49927	49.6596

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

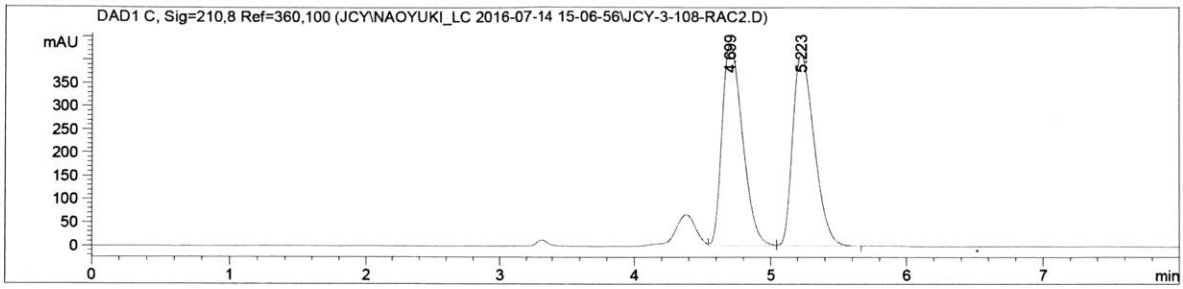
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.913	BV	0.1634	4898.55518	462.94653	94.9652
2	4.451	VB	0.1410	259.70639	28.32160	5.0348



3k

(*R*)-1-Cyclohexyl-2-(3-phenylpropyl)aziridine (3k): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 210 nm): t_R(major) = 4.7 min, t_R(minor) = 5.1 min.

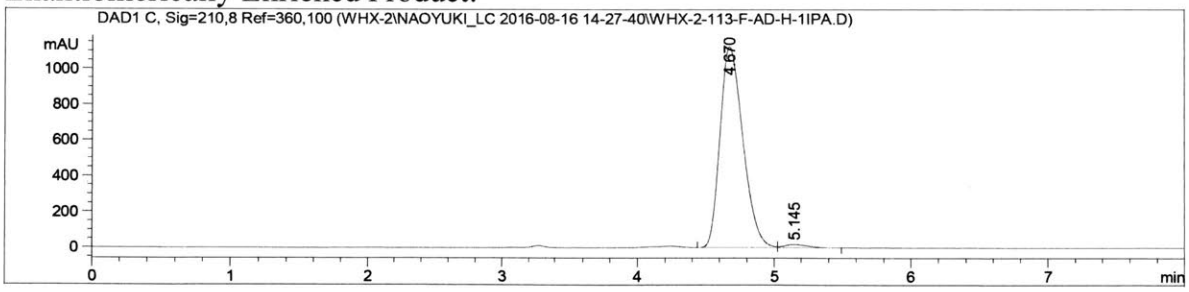
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

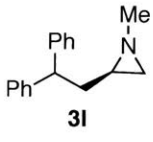
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.699	VV	0.1670	4579.69092	434.56323	50.2093
2	5.223	VB	0.1744	4541.50195	412.57312	49.7907

Enantiomerically Enriched Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

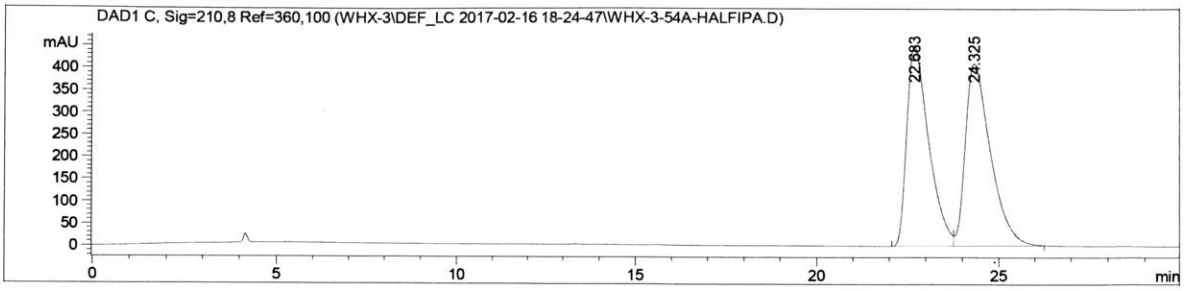
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.670	VV	0.1817	1.31117e4	1127.02832	98.3423
2	5.145	VB	0.1832	221.01056	18.51809	1.6577



3l

(*R*)-2-(2,2-Diphenylethyl)-1-methylaziridine (3l): HPLC analysis (AD-H column, 0.5% 2-propanol in hexanes, 0.8 mL/min, 210 nm): t_R(minor) = 23.0 min, t_R(major) = 24.4 min.

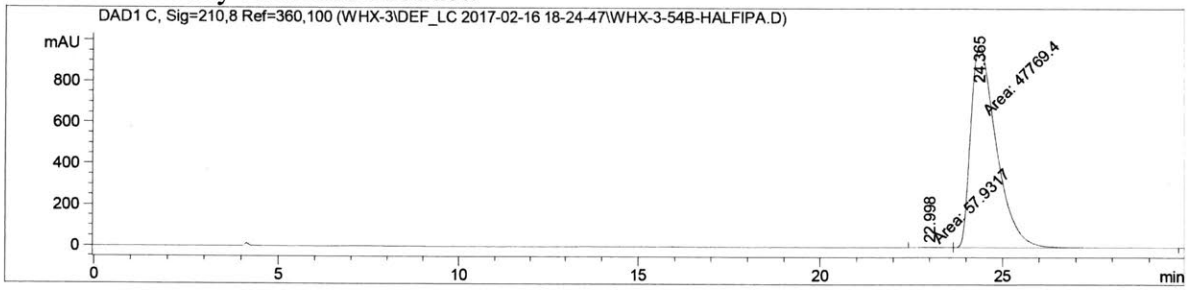
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

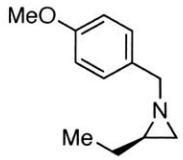
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.683	BV	0.6308	1.89436e4	450.26019	49.1944
2	24.325	VB	0.7168	1.95641e4	409.92502	50.8056

Enantiomerically Enriched Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

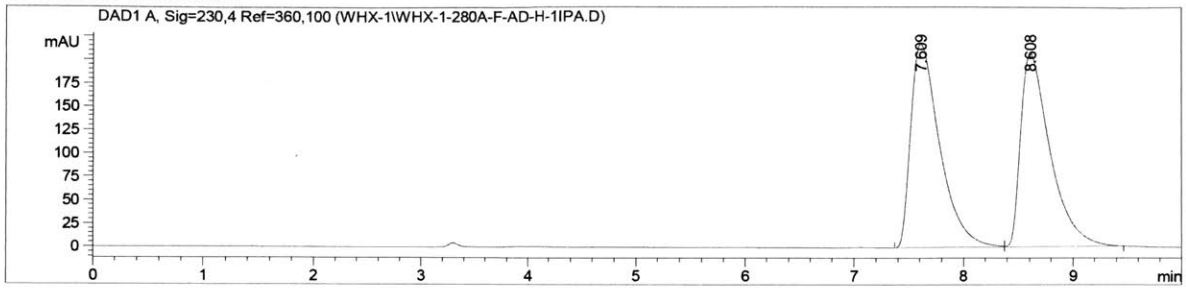
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.998	MF	0.6857	57.93169	1.40804	0.1211
2	24.365	FM	0.8120	4.77694e4	980.51855	99.8789



3m

(*R*)-2-Ethyl-1-(4-methoxybenzyl)aziridine (3m): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm). t_R(major) = 7.3 min, t_R(minor) = 8.4 min.

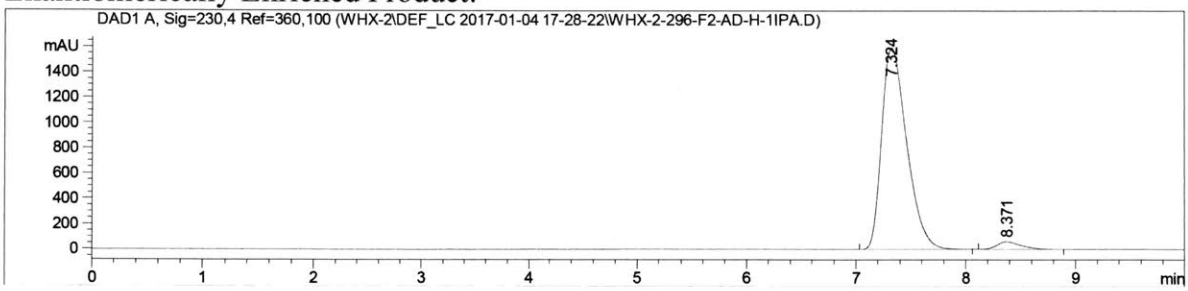
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

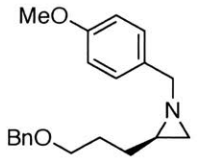
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.609	BV	0.2816	4011.31763	217.04893	50.8322
2	8.608	VB	0.2836	3879.97900	206.15500	49.1678

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

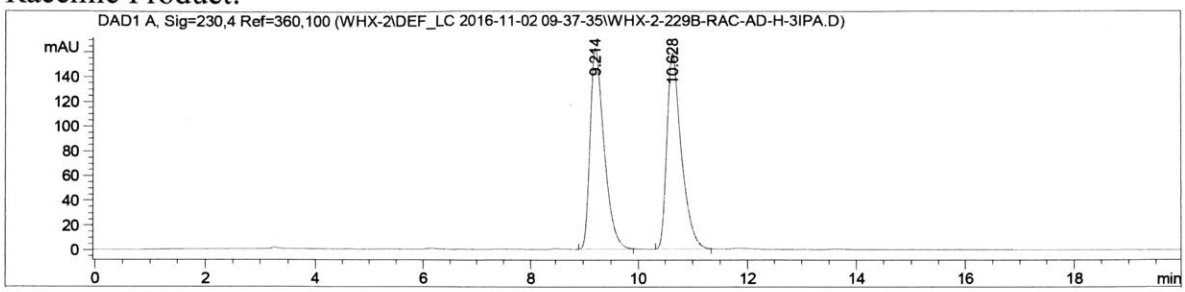
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.324	BB	0.2453	2.52981e4	1593.06177	96.5037
2	8.371	BB	0.2302	916.54028	59.34445	3.4963



3n

(*R*)-2-(3-(Benzyloxy)propyl)-1-(4-methoxybenzyl)aziridine (3n): HPLC analysis (AD-H column, 3% 2-propanol in hexanes, 1.0 mL/min, 230 nm): t_R(major) = 9.2 min, t_R(minor) = 10.7 min.

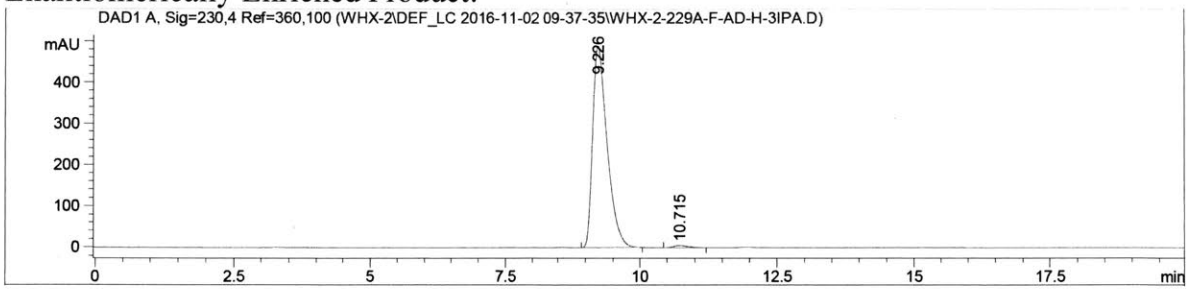
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

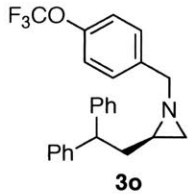
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.214	BB	0.2712	2911.25659	162.34746	50.1401
2	10.628	BB	0.2738	2894.98828	157.97168	49.8599

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

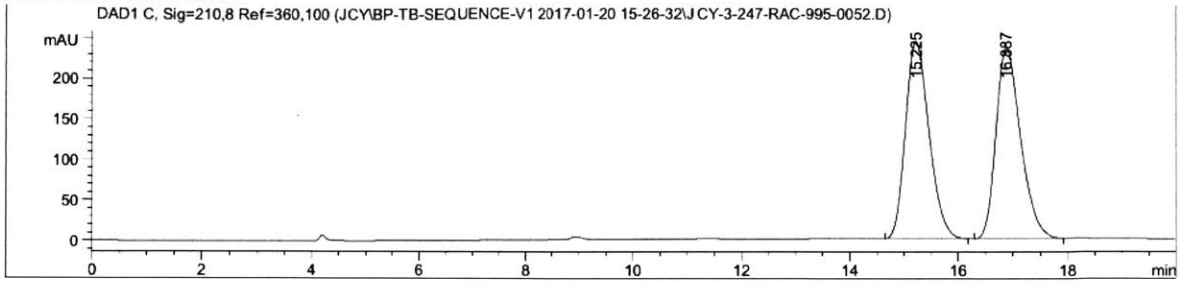
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.226	BB	0.2805	9085.20410	489.53833	98.9239
2	10.715	BB	0.2764	98.82854	5.42796	1.0761



3o

(*R*)-2-(2,2-Diphenylethyl)-1-(4-(trifluoromethoxy)benzyl)aziridine (3o): HPLC analysis (AD-H column, 0.5% 2-propanol in hexanes, 0.8 mL/min, 210 nm): t_R(minor) = 14.5 min, t_R(major) = 16.2 min.

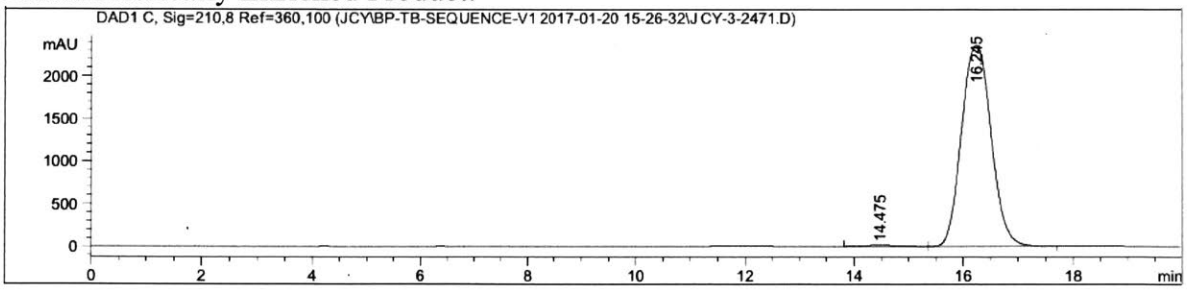
Racemic Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

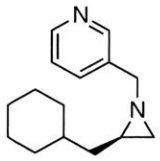
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.225	BB	0.4636	7332.85645	243.29607	49.9398
2	16.887	BB	0.4792	7350.53516	234.83517	50.0602

Enantiomerically Enriched Product:



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

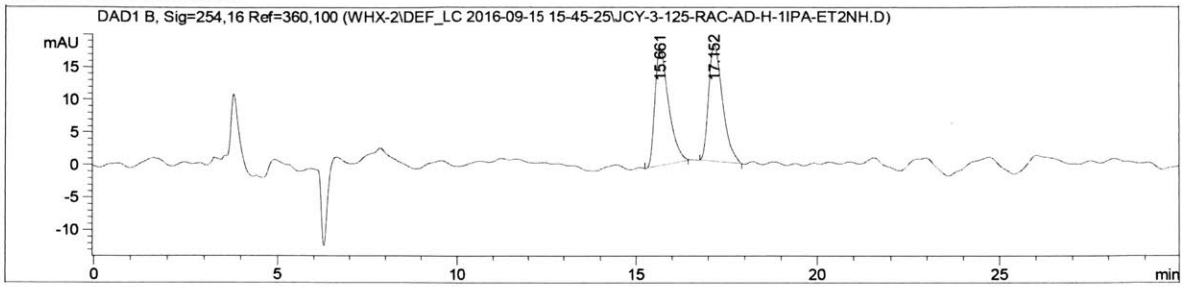
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.475	BV	0.5635	560.09918	15.14312	0.6285
2	16.245	VB	0.5924	8.85617e4	2356.81128	99.3715



3p

(*R*)-3-((2-(Cyclohexylmethyl)aziridin-1-yl)methyl)pyridine (3p): HPLC analysis (AD-H column, 1% 2-propanol, 0.2% Et_2NH in hexanes, 1.0 mL/min, 254 nm): t_R(minor) = 15.6 min, t_R(major) = 16.5 min)

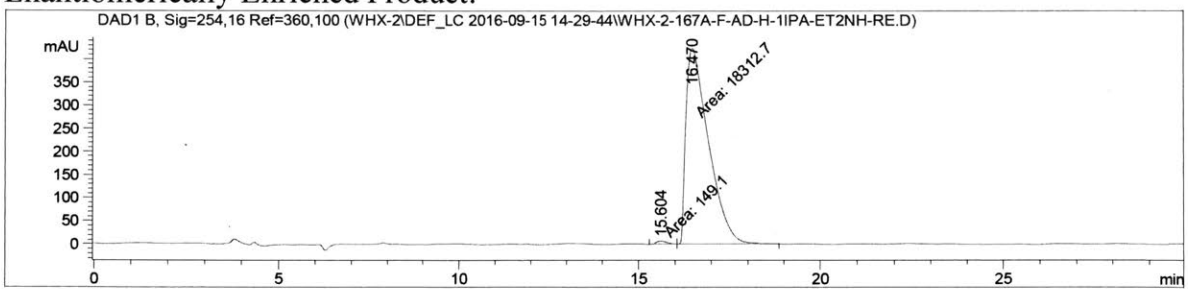
Racemic Product:



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

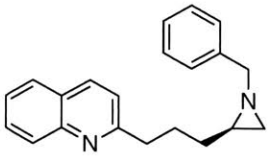
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.661	BB	0.4007	475.09561	17.95465	49.5853
2	17.152	BB	0.4061	483.04190	18.05738	50.4147

Enantiomerically Enriched Product:



Signal 2: DAD1 B, Sig=254,16 Ref=360,100

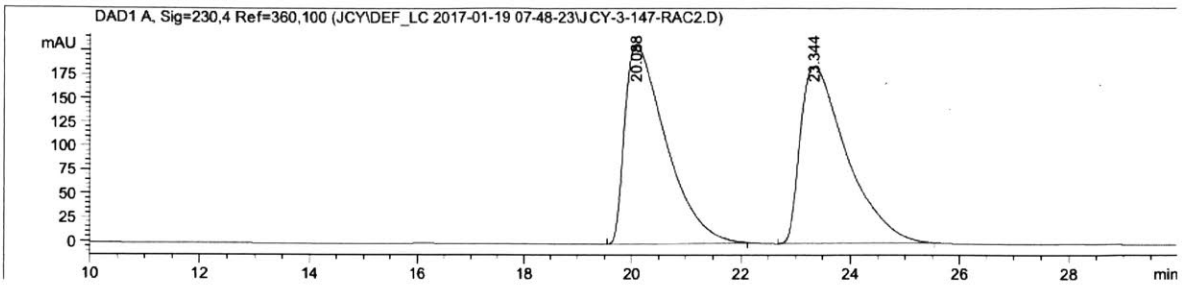
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.604	MF	0.3511	149.09972	7.07793	0.8076
2	16.470	FM	0.7196	1.83127e4	424.12607	99.1924



3q

(*R*)-2-(3-(1-Benzylaziridin-2-yl)propyl)quinolone (3q): HPLC analysis (AD-H column, 2% 2-propanol in hexanes, 1.0 mL/min, 230 nm): t_R(major) = 20.2 min, t_R(minor) = 23.1 min.

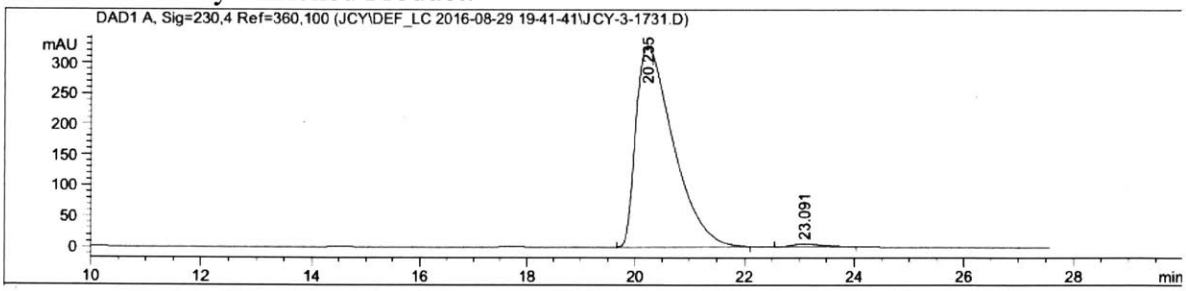
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

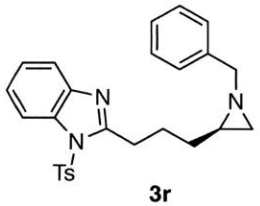
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.088	BB	0.7982	1.10480e4	209.18555	50.1035
2	23.344	BB	0.8829	1.10023e4	186.33034	49.8965

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

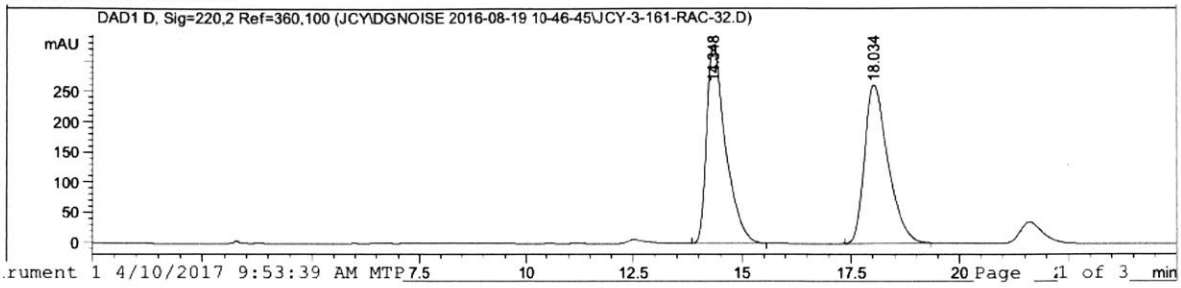
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.235	BB	0.7261	1.56081e4	327.44113	98.7101
2	23.091	BB	0.5636	203.95461	5.02450	1.2899



3r

(*R*)-2-(3-(1-Benzylaziridin-2-yl)propyl)-1-tosyl-1*H*-benzo[*d*]imidaz- ole (3r): HPLC analysis (AD-H column, 10% 2-propanol in hexanes, 1.0 mL/min, 220 nm): t_R (minor) = 14.8 min, t_R(major) = 18.7 min.

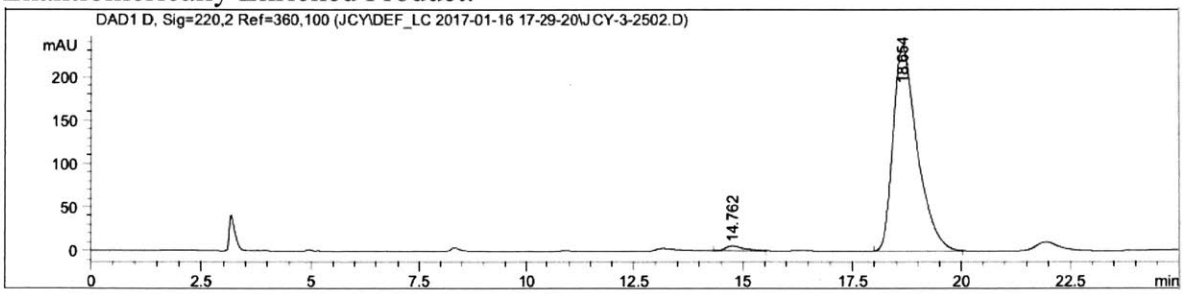
Racemic Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

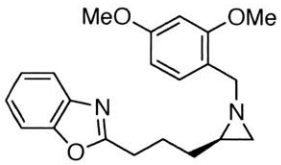
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.348	BB	0.4405	9879.10645	328.81531	50.2539
2	18.034	BB	0.5600	9779.29688	261.70404	49.7461

Enantiomerically Enriched Product:



Signal 2: DAD1 D, Sig=220,2 Ref=360,100

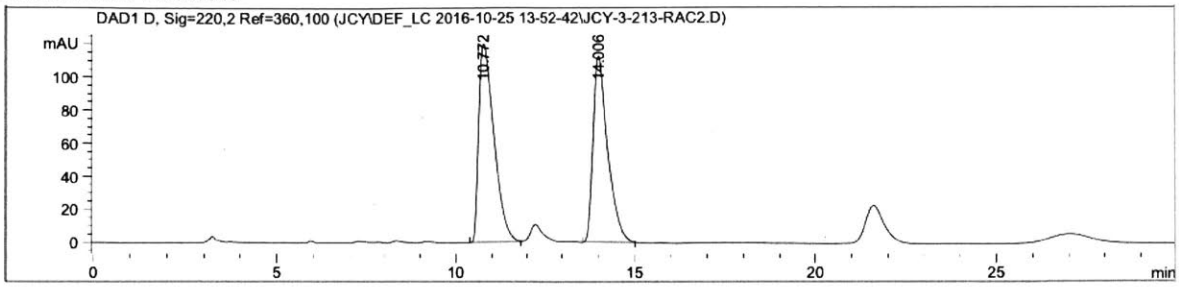
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.762	BB	0.4198	168.22278	5.67561	1.8064
2	18.654	BB	0.5762	9144.49219	235.95003	98.1936



3s

(*R*)-2-(3-(1-(2,4-Dimethoxybenzyl)aziridin-2-yl)propyl)ben-zo[*d*]- oxazole (3s): HPLC analysis (AD-H column, 10% 2-propanol in hexanes, 1.0 mL/min, 220 nm): t_R(major) = 11.0 min, t_R(minor) = 14.4 min.

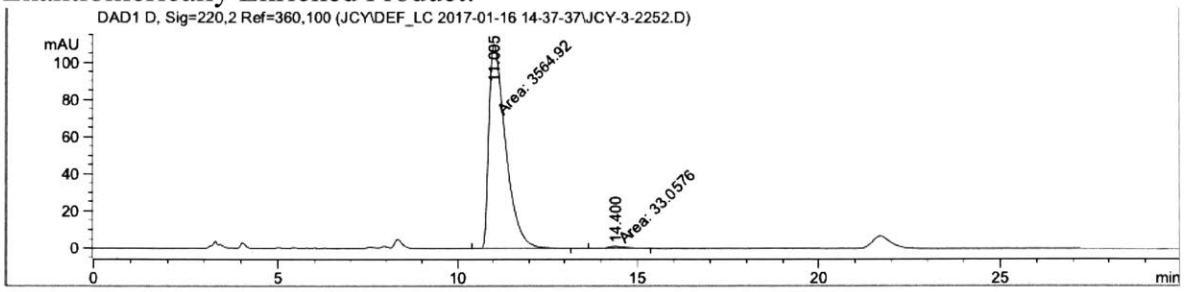
Racemic Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

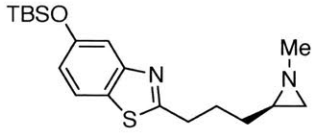
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.772	BB	0.4691	3570.25903	119.98804	53.0790
2	14.006	BB	0.4134	3156.05566	112.47490	46.9210

Enantiomerically Enriched Product:



Signal 2: DAD1 D, Sig=220,2 Ref=360,100

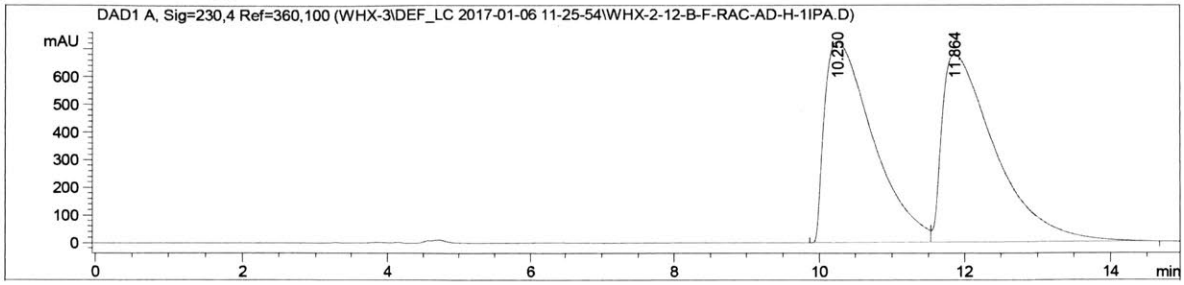
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.005	MF	0.5415	3564.91553	109.72578	99.0812
2	14.400	FM	0.5236	33.05755	1.05235	0.9188



3t

(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-(3-(1-methylaziridin-2-yl)-propyl)benzo[*d*]thiazole (3t): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm): t_R(major) = 10.0 min, t_R(minor) = 12.5 min.

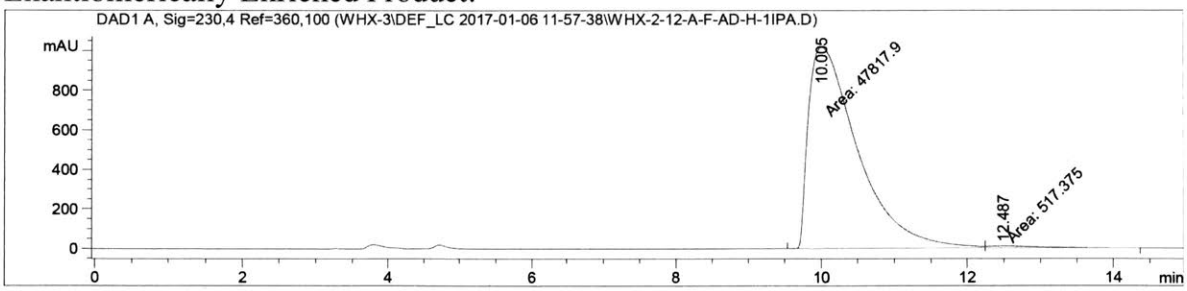
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

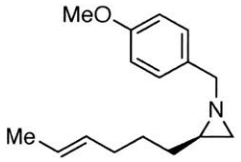
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.250	BV	0.7090	3.33656e4	724.88947	49.1801
2	11.864	VB	0.7692	3.44781e4	678.06396	50.8199

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

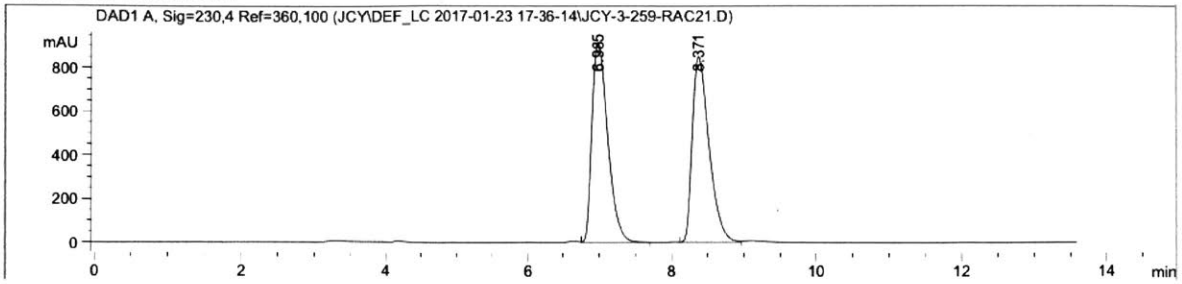
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.005	MF	0.7822	4.78179e4	1018.86353	98.9296
2	12.487	FM	0.8376	517.37476	10.29501	1.0704



3u

(*R*,*E*)-2-(Hex-4-en-1-yl)-1-(4-methoxybenzyl)aziridine (3u): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm): t_R(major) = 6.9 min, t_R(minor) = 8.3 min.

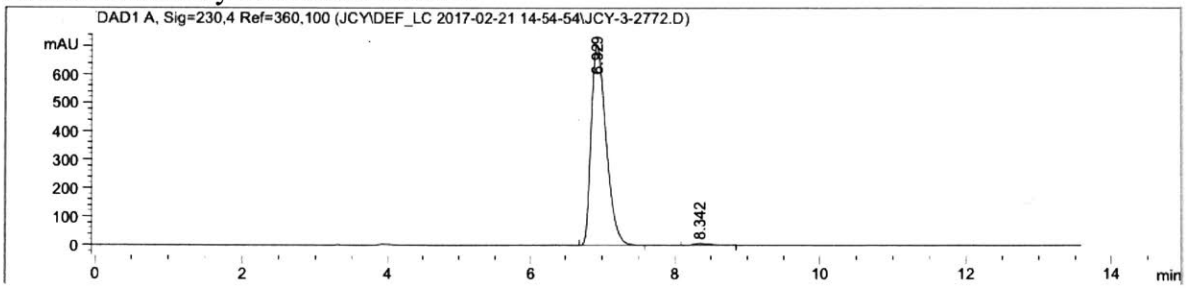
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

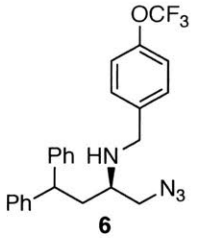
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.985	VB	0.2350	1.38776e4	914.96259	50.2528
2	8.371	VV	0.2466	1.37380e4	849.76483	49.7472

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

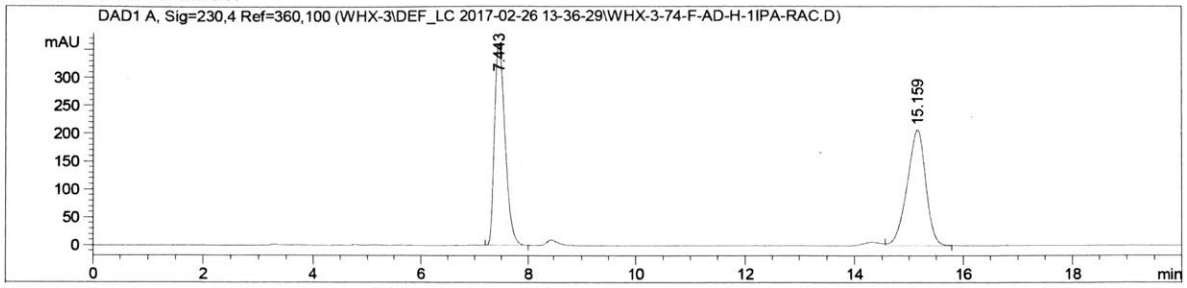
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.929	BB	0.2206	1.00759e4	705.67517	99.0362
2	8.342	BB	0.2395	98.06073	6.23584	0.9638



6

(*R*)-1-Azido-4,4-diphenyl-*N*-(4-(trifluoromethoxy)benzyl)butan-2- amine (6): HPLC analysis (AD-H column, 1% 2-propanol in hexanes, 1.0 mL/min, 230 nm): t_R(major) = 7.4 min, t_R(minor) = 14.9 min.

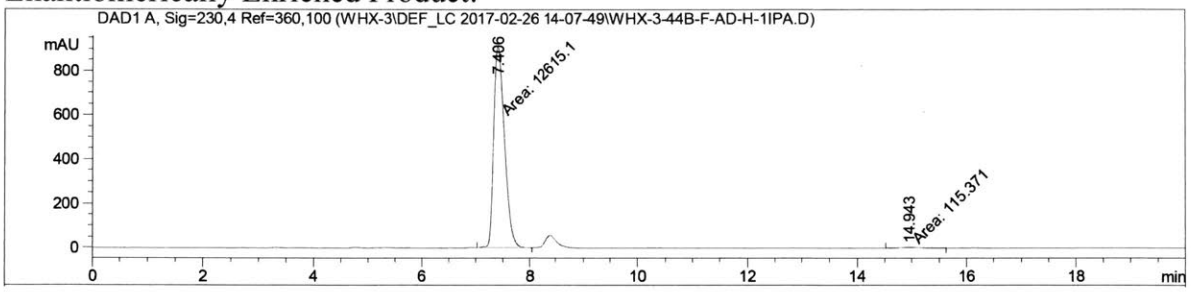
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

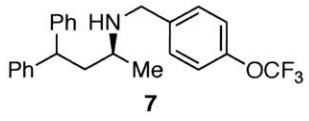
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.443	BB	0.2097	4885.87061	361.39709	49.7034
2	15.159	VB	0.3584	4944.18213	207.21404	50.2966

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

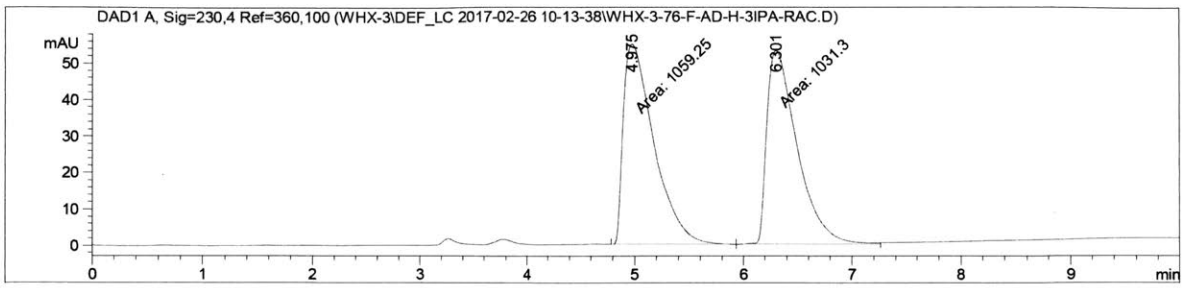
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.406	MM	0.2303	1.26151e4	912.93347	99.0937
2	14.943	MM	0.4245	115.37129	4.52929	0.9063



7

(*S*)-4,4-Diphenyl-*N*-(4-(trifluoromethoxy)benzyl)butan-2-amine (7): HPLC analysis (AD-H column, 3% 2-propanol in hexanes, 1.0 mL/min, 230 nm): t_R(major)= 4.9 min, t_R(minor) = 6.4 min.

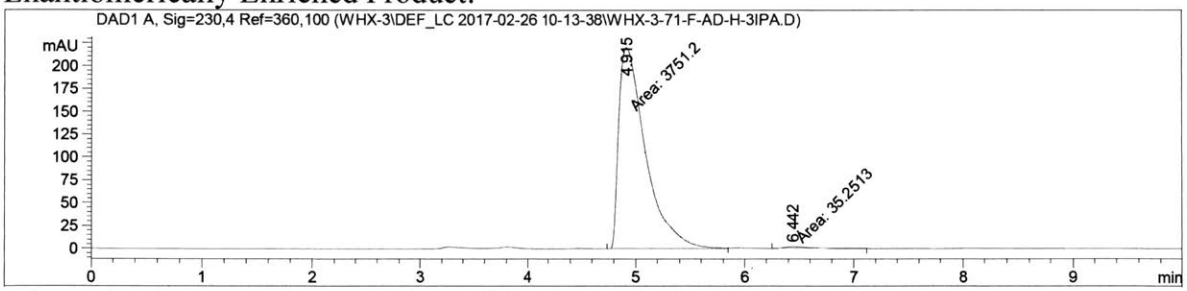
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

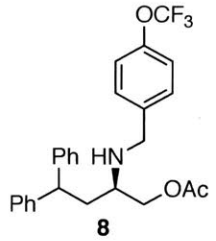
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.975	MF	0.3223	1059.24609	54.76748	50.6683
2	6.301	FM	0.3243	1031.30420	52.99949	49.3317

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

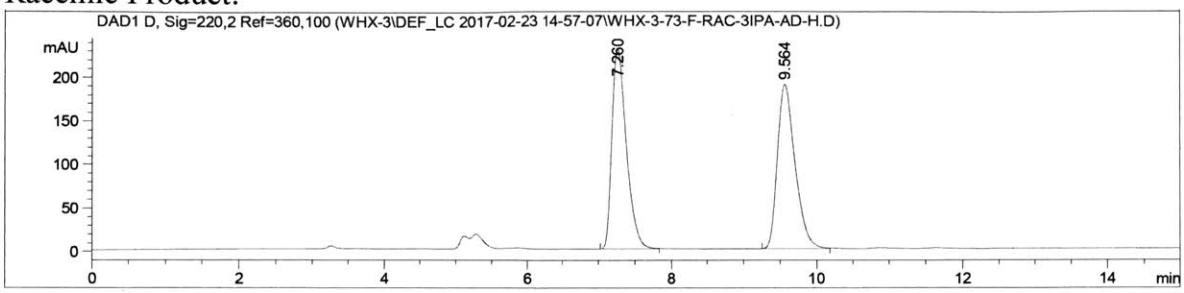
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.915	MM	0.2836	3751.19702	220.47542	99.0690
2	6.442	MM	0.3074	35.25129	1.91111	0.9310



8

(*R*)-4,4-Diphenyl-2-((4-(trifluoromethoxy)benzyl)amino)butyl acetate (8): HPLC analysis (AD-H column, 3% 2-propanol in hexanes, 1.0 mL/min, 220 nm):t_R(major) = 7.3 min, t_R(minor) = 9.6 min.

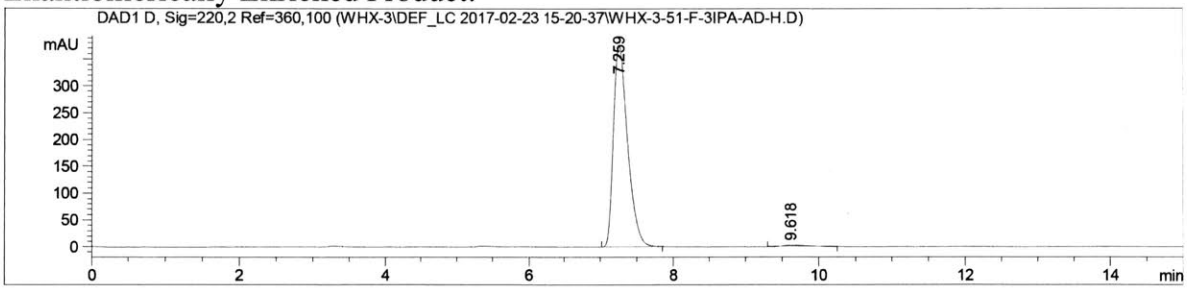
Racemic Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

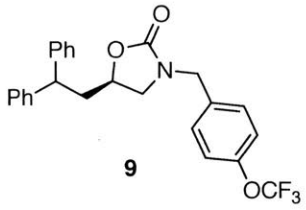
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.260	BB	0.2110	3167.40503	229.50046	50.1110
2	9.564	BB	0.2574	3153.37354	188.30408	49.8890

Enantiomerically Enriched Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

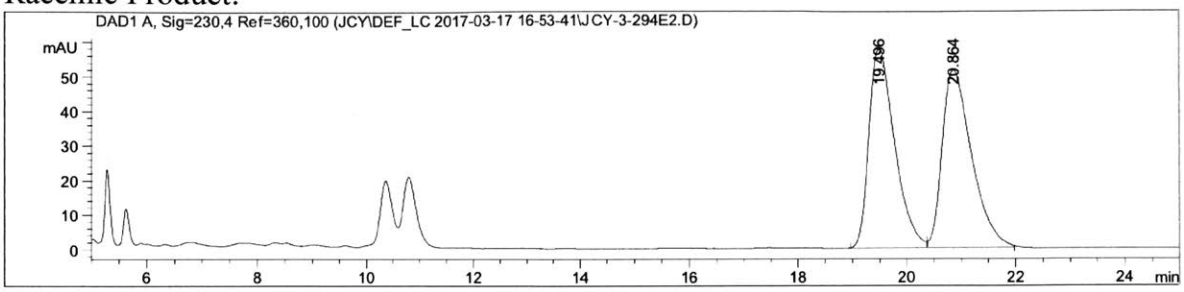
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.259	BB	0.2083	5099.11572	375.74362	98.5118
2	9.618	BB	0.3595	77.03160	2.86676	1.4882



9

(*R*)-4-(2,2-Diphenylethyl)-3-(4-(trifluoromethoxy)-benzyl)-oxazolidin-2-one (9): HPLC analysis (AD-H column, 10% 2-propanol in hexanes, 1.0 mL/min, 230 nm): major isomer: t_R(major) = 20.0 min, t_R(minor) = 19.1 min; minor isomer: t_R(major) = 10.8 min, t_R(minor) = 10.4 min.

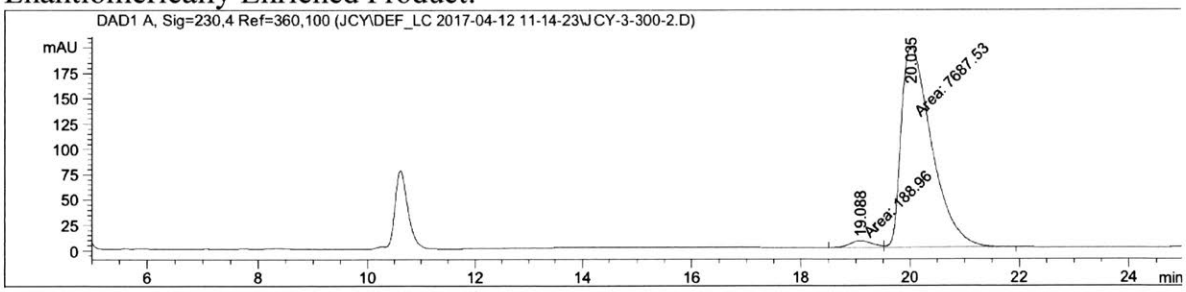
Racemic Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

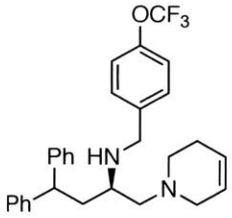
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.496	BB	0.5051	1914.42188	57.99331	49.8584
2	20.864	BB	0.5736	1925.29663	51.56508	50.1416

Enantiomerically Enriched Product:



Signal 1: DAD1 A, Sig=230,4 Ref=360,100

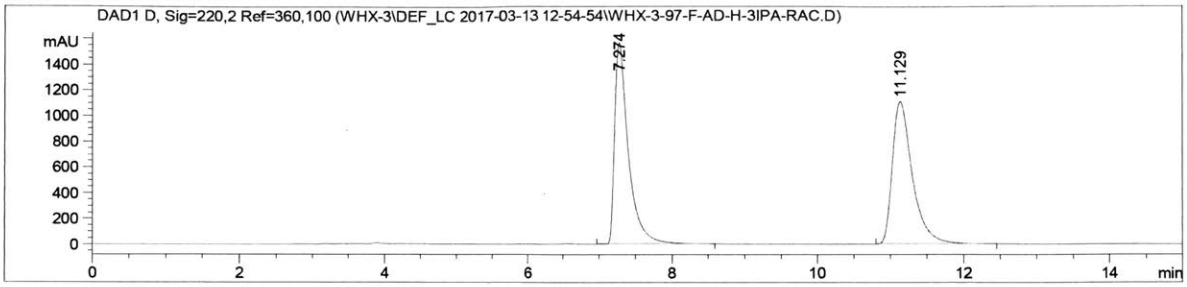
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.088	MF	0.4787	188.95967	6.57835	2.3990
2	20.035	FM	0.6461	7687.53027	198.31697	97.6010



SI-1

(*R*)-1-(3,6-dihydropyridin-1(2*H*)-yl)-4,4- diphenyl-*N*-(4-(trifluoromethoxy)benzyl)butan-2-amine (SI-1): HPLC analysis (AD-H column, 3% 2-propanol in hexanes, 1.0 mL/min, 220 nm): t_R(major) = 7.3 min, t_R(minor) = 11.3 min.

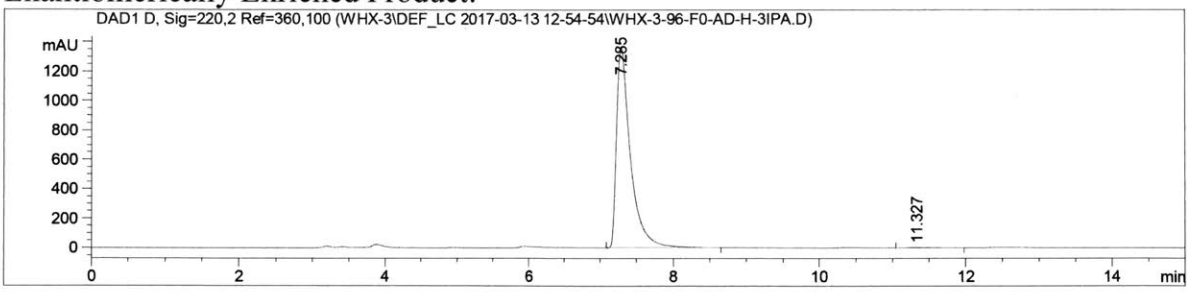
Racemic Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.274	VB	0.1964	2.06873e4	1562.73218	49.4636
2	11.129	BB	0.2872	2.11360e4	1104.93542	50.5364

Enantiomerically Enriched Product:



Signal 4: DAD1 D, Sig=220,2 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.285	BB	0.1960	1.82883e4	1367.76794	99.5467
2	11.327	BB	0.3742	83.28120	3.03450	0.4533

Chapter 3. Copper-Catalyzed Asymmetric Hydroamination for the Synthesis of Primary Amines using a Novel Electrophilic Nitrogen Source

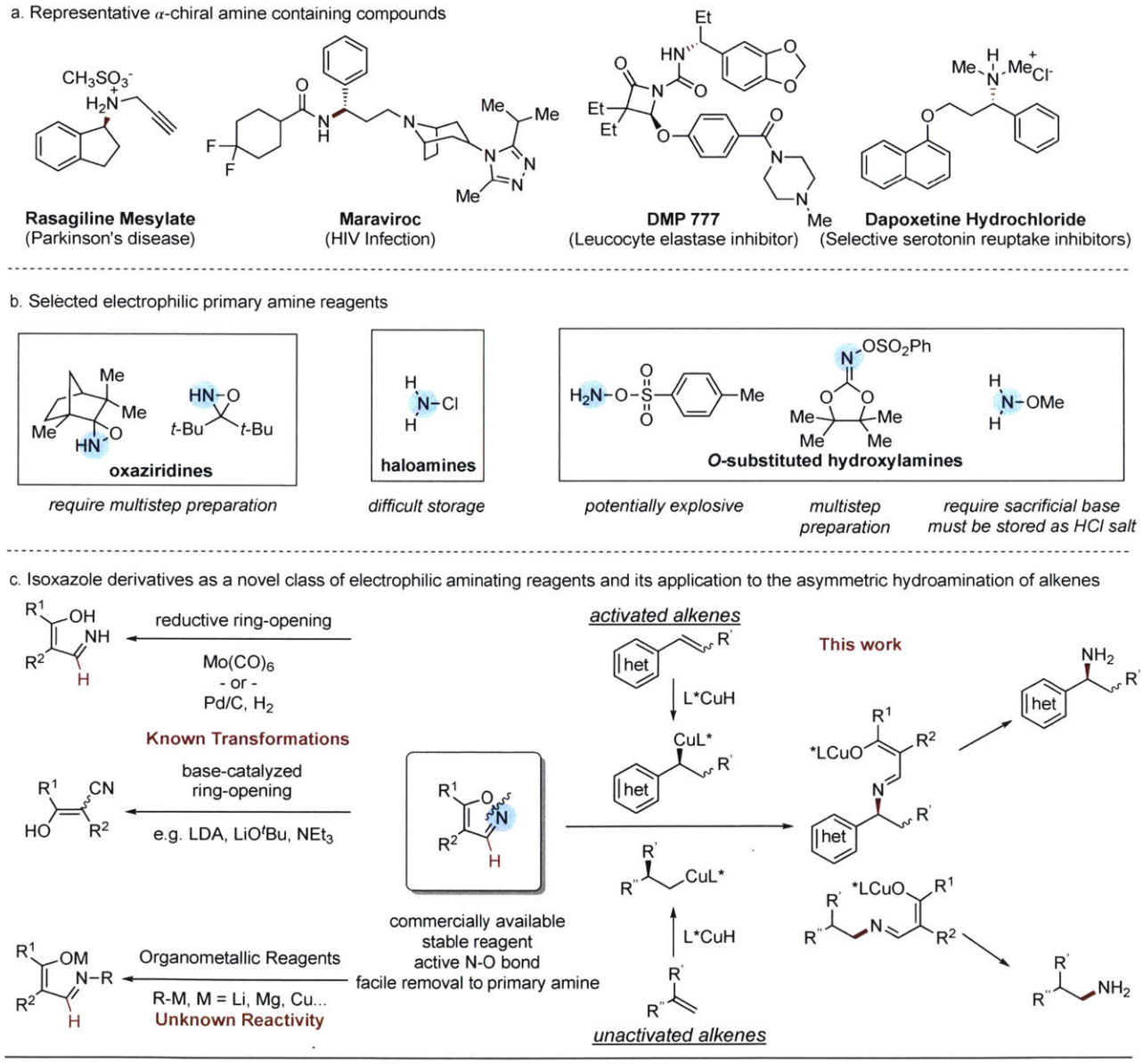
3.1 Introduction

Chiral primary amines are an important structural unit in natural products, pharmaceutical agents, agrochemicals and materials.[1] As versatile intermediates, chiral primary amines are frequently used for the preparation of drug candidates, activate pharmaceutical ingredients, and other analogous compounds via simple transformations (Figure 1a). Consequently, the preparation of primary amines in enantioenriched forms has been of long-standing interest to synthetic organic chemists. Enantiopure primary amines are traditionally prepared by enantioselective reductive amination of ketones and aldehydes,[2-3] asymmetric hydrogenation of imines and enamines,[4] the stereoselective addition of a carbon nucleophile to imines,[5] the asymmetric addition of a nitrogen nucleophile to allylic alcohols or carbonates,[6] biocatalytic reactions,[7] and the kinetic[8] or dynamic kinetic resolution[9] of racemic primary amines or their derivatives. Although various methods exist for the installation of primary amines, all current methods require a pre-existing carbon–heteroatom bond as the handle for functionalization. In comparison, the net addition of an ammonia across an unfunctionalized alkene (hydroamination) represents a highly desirable transformation given the high abundance, general accessibility, and relative chemical inertness of the carbon–carbon double bond. Despite substantial progress in the field of alkene hydrofunctionalization reactions,[10-11] to our knowledge, there have not been reports of enantioselective transformations that allow for the synthesis of primary amines from olefins in one step.

In 2013, our lab[12] and the lab of Miura[13] independently reported the use of catalytic amounts of a chiral bisphosphine-ligated copper(I) hydride (CuH) for the hydroamination of alkenes to tertiary amines. Since the initial reports, this protocol has been applied to a wide range of olefins.[14] However, due to the lack of suitable amine electrophiles[15-16], this strategy has been restricted to the synthesis of tertiary amines, secondary α-chiral benzyl amines[17], and α-chiral benzyl amides.[18] While electrophilic amines containing free NH_2 groups allow for the direct formation of a primary amine in principle, these reagents suffer from instability (in the case of haloamines[19]) and have been reported to be hazardous upon purification and isolation (in the case of *O*-tosyl hydroxylamines[20]). In contrast, reagents such as methoxyamine may be stable as the corresponding hydrochloride salt, but these reagents require a minimal of two equivalents of sacrificial organometallic reagents (neutralization and deprotonation) to access the active form, which is capable of forming the desired C–N bond. Although protected primary amine surrogates

such as oxime derivatives[21] or the creatively engineered oxaziridines[22] may circumvent the challenge of competitive amine-deprotonation and difficult deprotections, most of these electrophiles require multistep synthesis and are not atom economical.[23] The development or discovery of a simple, stable, atom-economic, and commercially available electrophilic amine source thus remains a goal for synthetic chemists.

Figure 1. *Representative α-chiral amines, selected electrophilic primary amine reagents, and our discovery of the novel reactivity of isoxazole derivatives*



Our work on the use of nitrogen-containing heterocycles as electrophiles in the copper-hydride catalyze dearomative coupling with styrenes,[24] led us to surmise that isoxazole may be used as a potential electrophilic nitrogen source due to its relatively weak N–O bond (55 kcal/mol) and its lower aromaticity. We envisioned that the combination of this novel electrophilic primary amine surrogate with copper-hydride catalyzed hydroamination strategies may directly provide access to chiral primary amines from alkenes (Figure 1c, right). Additionally, the field of complex natural product synthesis has in particular exploited the comparatively weak N–O bond of isoxazoles for its use as a masked 1,3-dicarbonyl synthon (Figure 1c, left).[25]

Mechanistically, such as approach would require isoxazole, a naturally electron-rich heterocycle to undergo electrophilic addition with an *in-situ* formed alkyl-copper species. However, as 3-H isoxazole derivatives have been reported to undergo Kemp elimination (ring-opening) reactions in the presence of catalytic amounts of weak bases such as triethylamine,[26] the desired transformation would necessitate that C–N bond formation be much faster than ring-opening via deprotonation of the isoxazole from the alkyl-copper species. Although we were aware that substituents on the 3-position of the isoxazole prevent the reagent from undergoing base-catalyzed Kemp elimination,[27] we postulated that a 3-substitutent could be electronically and sterically counterproductive for reactivity at the nitrogen atom. The inertness of 3,5-disubstituted isoxazoles can be further deduced by their prevalence in transition-metal catalyzed reactions.[28] Nonetheless, we anticipated that the exceptionally mild conditions of copper-hydride-catalyzed reactions would be compatible with isoxazole and its derivatives.[29] If successful, isoxazole and its derivatives would represent highly desirable nitrogen sources in organic synthesis as they are commercially available, stable under ambient conditions, and the imine product may be hydrolyzed to the corresponding primary amine during a hydrolytic workup.

Herein, we describe the use of isoxazole and its derivatives as electrophilic sources for the installation of primary amines. These electrophiles were applied to CuH-catalyzed hydroamination for the enantioselective synthesis of chiral primary amines from alkenes. This strategy overcomes the limitation of previous copper-catalyzed hydroamination protocols that are limited to the formation of secondary and tertiary amine products. It proceeds under mild reaction conditions to afford good to excellent yields and high levels of stereoinduction. Using this method, a series of α-branched chiral primary amines (from styrenes) and linear primary amines (from alkyl-substituted terminal alkenes) could be prepared (Figure 1d). Lastly, the potential of this

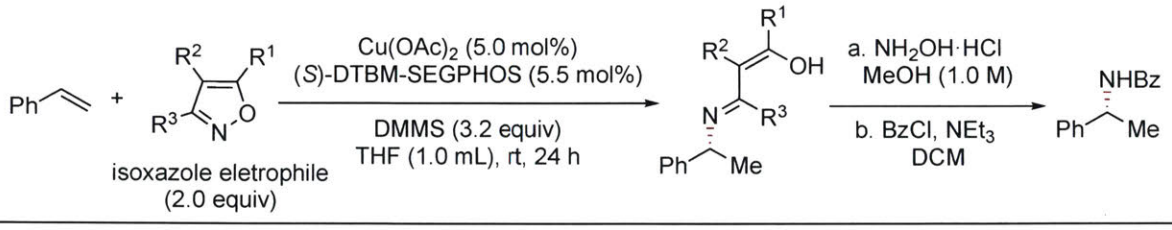
transformation was further demonstrated by the synthesis of several important pharmaceuticals, as well as the one-step conversion of low cost abundant starting materials into valuable synthetic intermediates.

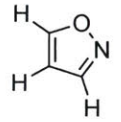
3.2 Results and Discussion

Effect of substitution pattern of isoxazole derivatives

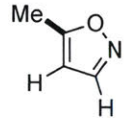
We commenced our study by assessing the reactivity of a wide range of commercially-available isoxazole derivatives with varying electronic and steric properties. In the presence of 5 mol% copper acetate, 5.5 mol% (*S*)-DTBM-SEGPHOS, an excess of dimethoxymethylsilane (DMMS), and using styrene as the pronucleophile with isoxazole afforded moderate yield of product with excellent levels of enantioselectivity. Further investigation revealed that, in agreement with our original hypothesis, substitution at the 3-position shut down the hydroamination process regardless

Table 1. *Effect of substitution pattern of isoxazole derivatives*

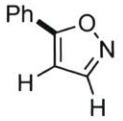




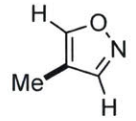
2a
60% yield, 97% *ee*[a]



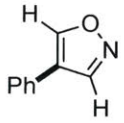
2b
32% yield, 96% *ee*[a]



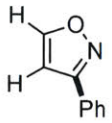
2c
66% yield, 99% *ee*[a]



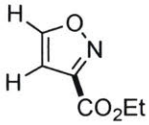
2d
27% yield, 95% *ee*[a]



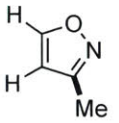
2e
25% yield, 95% *ee*[a]



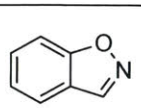
2f
0% yield



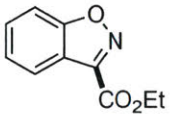
2g
0% yield



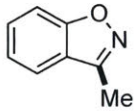
2h
0% yield



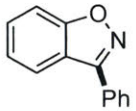
2
94% yield, 98% *ee*[b]



2i
0% yield



2j
0% yield

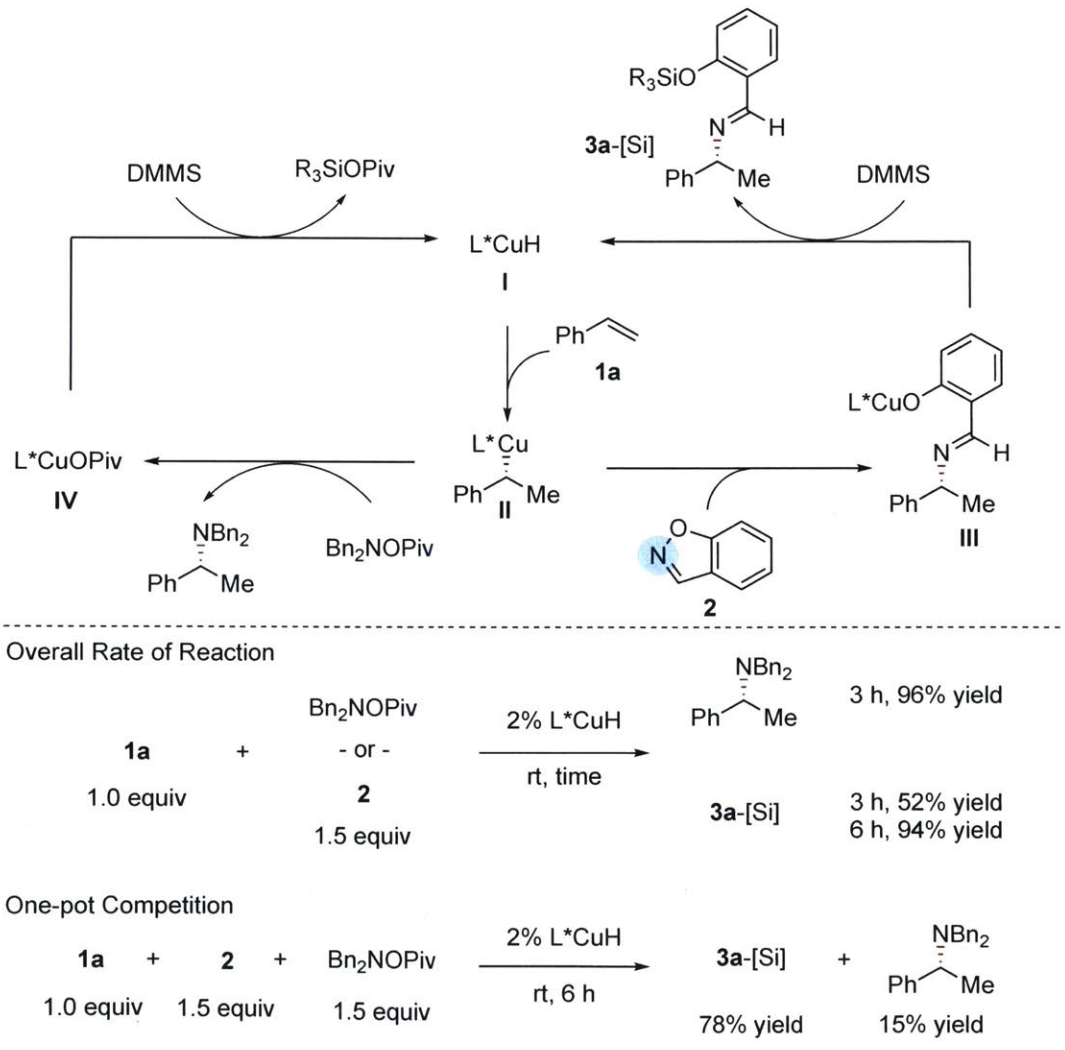


2k
Trace

[a]Yields and *ee* were determined from the N-benzoyl amine derivative. [b]Yield and *ee* were determined from the initial Schiff base product.

of steric and electronic properties of the heterocycle (**2f**, **2g**, **2h**). In contrast, a comparison between substituents at the 4- and 5- positions (**2b-2e)** showed that although substituents at these positions promote the ring-opening decomposition of the electrophile,[27] the extension of the π-system proved to be beneficial for reaction efficiency. Indeed, the use of 1,2-benzisoxazole afforded the chiral Schiff base product in excellent yield and with a high level of enantiopurity. Additional experiments confirmed that 3-substituted benzisoxazoles (**2i, 2j, 2k**) also were not suitable electrophiles for this system.

Figure 2*. Comparison of benzisoxazole with state-of-art electrophilic amine reagents for CuH-catalyzed hydroamination*[a]



[a]Yields are ^{1}H-NMR yields as determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. See Experimental for details.

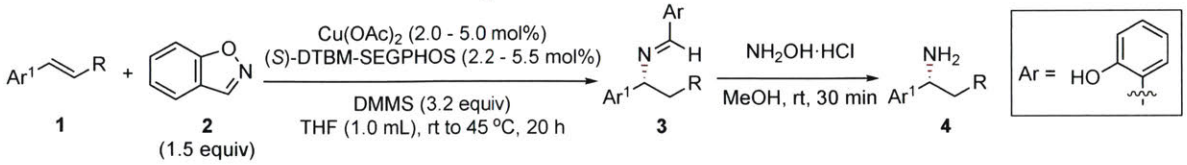
The effectiveness of 1,2-benzisoxazole as a novel electrophilic amine source was benchmarked against *N*,*N*-dibenzyl-*O*-pivaloylhydroxylamine (Bn_2NOPiv), which was previously reported to be the state-of-the-art electrophilic amine reagent for CuH-catalyzed hydroamination reactions (Figure 2).[30] Although the overall rate of reaction with Bn_2NOPiv was about twice as fast as with 1,2-benzisoxazole, a one-pot competition experiment revealed that the alkyl-copper species **II** reacts preferentially with 1,2-benzisoxazole over Bn_2NOPiv. Based on previous mechanistic studies that have shown the rate-determining-step of CuH-catalyzed hydroamination to be the regeneration of CuH catalyst, it is reasonable to suggest that the slow overall rate of reaction with 1,2-benzisoxazole is due to the comparatively slower regeneration of activate CuH species from copper-phenolate (Figure 2, **III**). These results in combination with the exceptionally high initial chemoselectivity observed, (see Experimental for details) have led us to conclude that 1,2-benzisoxazole is a significantly more reactive electrophilic amine source, which can be utilized for the development of a mild hydroamination protocol for the synthesis of chiral Schiff base products or chiral primary amines from readily available alkenes.

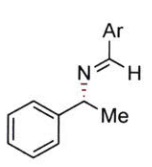
Hydroamination of alkenes to furnish primary amines

Having identified 1,2-benzisoxazole as an excellent electrophilic nitrogen source, we set out to examine the scope of the alkene coupling partner in this hydroamination protocol (Table 2). While the chiral Schiff base products derived from this strategy are in themselves a class of asymmetric ligands,[31] they may also be quantitatively converted, in a one-pot procedure, to the corresponding primary amine without erosion of enantiomeric excess. Both the Schiff base products (**3a-m**) and the primary amines (**4a-f**) from this protocol can be obtained in good yields and high enantioselectivity (≥91% ee). Styrenes bearing either electron-donating (**3h**) and electron-withdrawing (**3g**) substituents were converted to products with good efficiency. Similarly, substrates with electronically diverse set of *ortho*-substituents (**3b**, **3c**) as well as β-substitution were also suitable coupling partners (**3i-k**). Due to the mild reaction conditions, a variety of functional groups such as esters (**3k**), sulfonamides (**4a**), carbamates (**4b**), aryl chlorides (**3d**) and bromides (**3e**), and acetals (**3l**) were tolerated. Notably, the chiral Schiff base product **3j** can be obtained in highly enantioenriched form and may be hydrolyzed to the chiral primary amine intermediate for the synthesis of human leukocyte elastase inhibitor, DMP 777 (Figure 1a).[32]

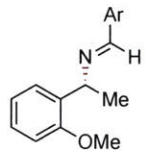
Although this method requires the use of an electron-rich heterocycle as the electrophile, a wide range of vinyl-substituted heteroarenes including electron-deficient pyridines (**3l**), 7-azaindoles

Table 2. *Substrate scope of hydroamination of vinyl arenes using benzisoxazole as the electrophilic amine source*[a,33]

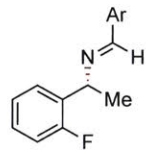




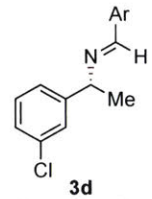
3a
85% yield, 98% *ee*[a]
Condition A with 2.0% 'Cu'



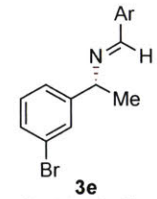
3b
81% yield, 97% *ee*[a]
Condition B with 2.0% 'Cu'



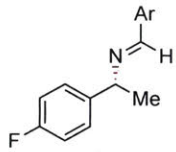
3c
73 % yield, 98% *ee*[a]
Condition A with 2.0% 'Cu'



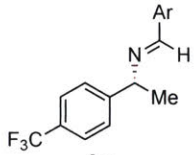
3d
79% yield, 98% *ee*[a]
Condition A with 2.0% 'Cu'



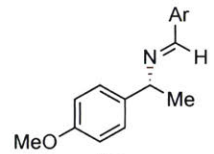
3e
81% yield, 95% *ee*[a]
Condition A with 2.0% 'Cu'



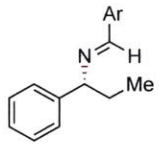
3f
82% yield, 96% *ee*[a]
Condition A with 2.0% 'Cu'



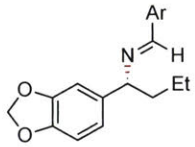
3g
76% yield, 93% *ee*[a]
Condition A with 2.0% 'Cu'



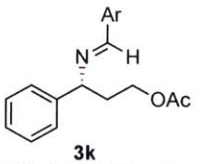
3h
77% yield, 98% *ee*[a]
Condition A with 5.0% 'Cu'



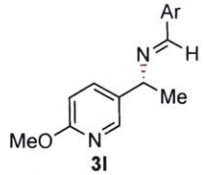
3i
73% yield, 96% *ee*[a]
Condition B with 2.0% 'Cu'



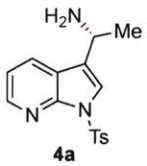
3j
81% yield, 99% *ee*[a]
Condition B with 2.0% 'Cu'



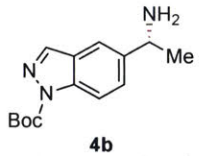
3k
75% yield, 98% *ee*[a]
Condition B with 2.0% 'Cu'



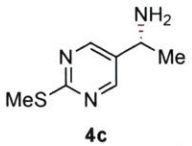
3l
73% yield, 98% *ee*[a]
Condition A with 5.0% 'Cu'



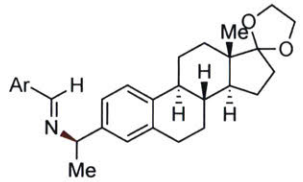
4a
73% yield, 91% *ee*[a]
Condition A with 5.0% 'Cu'



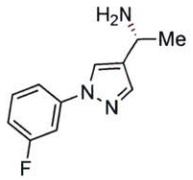
4b
78% yield, 96% *ee*[a]
Condition A with 5.0% 'Cu'



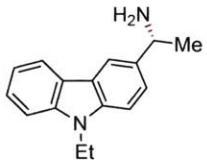
4c
62% yield, 97% *ee*[a]
Condition A with 5.0% 'Cu'



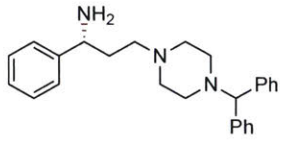
3m
81% yield, 99 : 1 d.r.[a]
Condition B with 5.0% 'Cu'



4d
70% yield, 97% *ee*[a]
Condition B with 5.0% 'Cu'



4e
77% yield, 98% *ee*[a]
Condition A with 5.0% 'Cu'



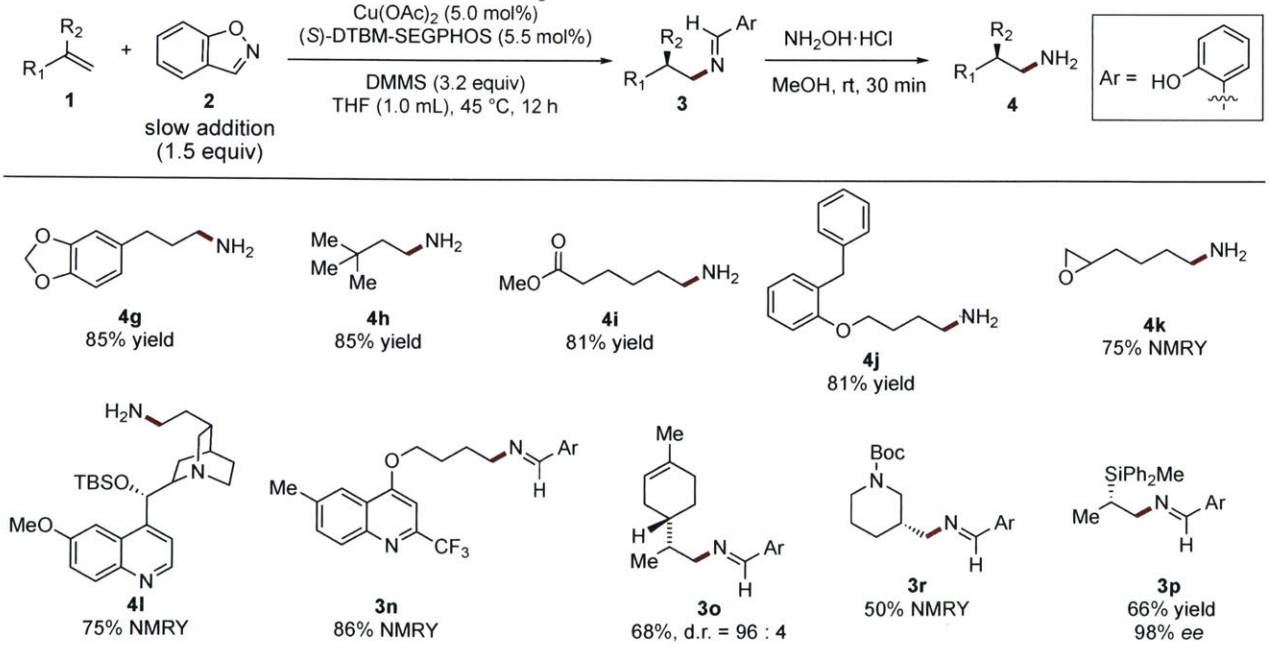
4f
86% yield, 98% *ee*[a]
Condition A with 5.0% 'Cu'[b]

Condition A : (2.0 - 5.0 mol%) Cu(OAc)2, (2.2 - 5.5 mol%) (*S*)-DTBM-SEGPHOS, rt
Condition B; (2.0 - 5.0 mol%) Cu(OAc)2, (2.2 - 5.5 mol%) (*S*)-DTBM-SEGPHOS, 1,2 - benzisoxazole (0.5 equiv) was added every 2 h, 45 °C

[a]All yields represent average isolated yields of two runs conducted on a 1.0 mmol scale and the enantioselectivity was determined from the Schiff base product. See Experimental for details. [b]Cyclohexane as reaction solvent, 1,2-benzisoxazole was added using a syringe pump.

(4a) and pyrimidines (**4c**), electron-rich indazoles (**4b**), pyrroles (**4d**), and carbazoles (**4e**) were all readily accommodated and provided the α-chiral primary amine with high levels of enantioselectivity. This approach can also be applied to the hydroamination of complex aryl alkenes such as estrone to provide rapid access to the structurally complex Schiff base **3m** or applied to the late-stage enantioselective attachment of an amino group to pharmaceutical compounds such as the antihistamine cinnarizine to provide **4f**. It should be noted that significant amounts of reduced alkene side product were observed during the hydroamination of cinnarizine using the standard reaction conditions. The lack of an obvious proton source, combined with our observation of salicylonitrile in the crude reaction mixture led us to postulate that the large steric hindrance of the β-substitution had sufficiently retarded the formation of the C–N bond, resulting in competitive Kemp elimination through deprotonation by the alkyl copper species. We were aware that the efficiency of Kemp elimination could be influenced by overall solvent polarity[34] and reasoned that the use of a less polar solvent could limit the non-productive consumption of alkene starting material. Upon switching the reaction solvent from tetrahydrofuran to cyclohexane and using a syringe pump addition to limit the amount of 1,2-benzisoxazole present, cinnarizine

Table 3. *Substrate scope of hydroamination of unactivated alkenes using benzisoxazole as the electrophilic amine source*[a]



[a]Work in progress, yields are a combination of ^{1}H-NMR yields and isolated yields.

enantioselectivity. This simple modification of the reaction system later proved to be crucial during our synthesis of Maraviroc (see below).

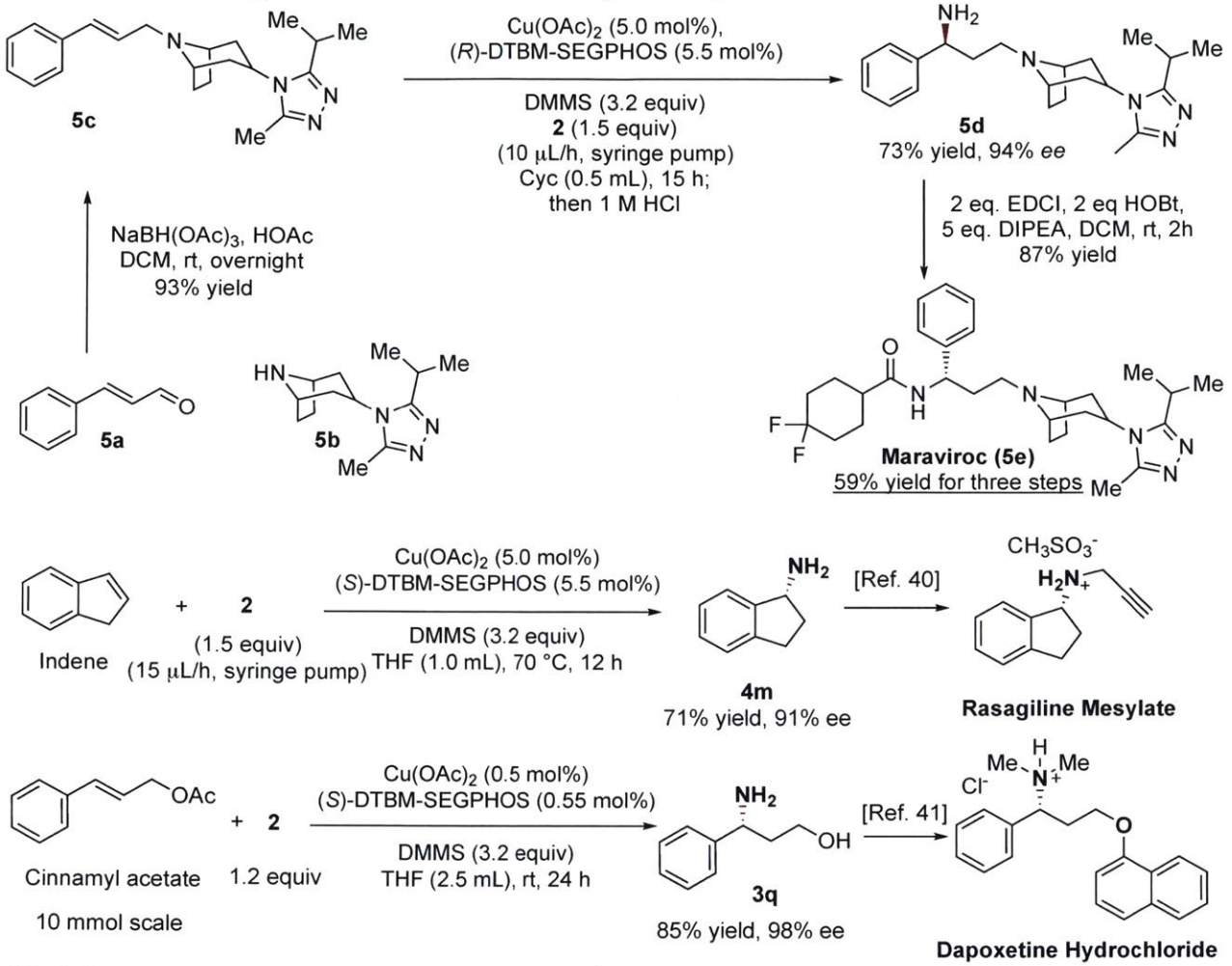
Having confirmed the effectiveness of our method for the synthesis of chiral Schiff bases and primary amines, we continued our investigation into the hydroamination of unactivated alkenes (Table 3). Due to the slower rate of hydrocupration of unactivated alkenes,[14, 35] slightly elevated temperatures (≥ 45 °C) and the slow addition of the electrophile using a syringe pump were required for good yields and levels of enantioselectivity. This protocol was successfully applied to terminal alkenes as well as 1,1-disubstituted olefins. Despite the large steric hindrance, *tert*-butylethylene successfully underwent hydroamination to yield the primary amine **4h** in 85% yield. The increased temperature did not negatively impact the functional group tolerance of this protocol, as methyl esters (**4i**), silyl-protected alcohols (**4l**), epoxides (**4k**), and carbamates (**3r**) were again well tolerated under reaction conditions. Both electron-rich and electron-deficient heterocycles such as quinoline (**3n, 4l**), were also readily accommodated. Finally, the one-pot synthesis of primary amine **4j** provided an alternative route for the preparation of bifemelane,[36] a cerebral activator used for the treatment of senile dementia and glaucoma, demonstrating the potential utility of this method for the synthesis or late-stage functionalization of moderately complex molecules (**4l**).

Application towards the synthesis of pharmaceuticals

A key advantage of this mild enantioselective hydroamination strategy using 1,2-benzisoxazole as a primary amine surrogate lies in its ability to install a chiral primary amine group at a late stage in the synthesis of highly functionalized synthetic intermediates. To illustrate this point, a convergent three-step synthesis of the antiretroviral drug for the treatment of HIV infections, Maraviroc,[37] is described through the hydroamination of a moderately complex alkene (Figure 3). The β-substituted, 1,2,4-triazole containing aryl alkene **5c** was synthesized in excellent yield from the highly efficient reductive amination of cinnamyl aldehyde **5a** with the complex secondary amine **5b**. Using similar conditions to those developed for the hydroamination of cinnarizine, the core chiral primary amine fragment **5d** was constructed in 73% yield and 94% ee after a one-pot hydrolysis. Subsequent amidation then provided Maraviroc in 59% overall yield over three steps. Given the ease of synthesis of α,β-unsaturated aldehyde precursors, this hydroamination strategy presents a method to rapidly obtain analogous compounds, in contrast to the three literature

reports[38-40] for the synthesis of Maraviroc, which call for the early installation of the chiral amino group from simple starting materials.

***Figure 3**. Concise routes to important synthetic intermediates*[a]



[a]Work in progress, yields are a combination of ^{1}H-NMR yields and isolated yields.

As a further demonstration of this method, we have converted a simple feedstock olefin – indene, to 1-aminoindane (**4m**), a highly valuable synthetic precursor for important pharmaceuticals such as Rasagiline[41] and Dapoxetine[42]. Although cis-alkenes have been both computationally and experimentally[30] determined to be challenging substrates for efficient hydrocupration, previous CuH-catalyzed hydroamination systems have demonstrated their successful incorporation as viable starting materials.[12] By simply increasing the reaction temperature to 70 °C, and following the protocol developed for unactivated alkenes, **4m** was obtained in 71% yield and 91% ee. To evaluate the scalability of this procedure, we have also

synthesized another widely used intermediate (*R*)-3-amino-3-phenylpropan-1-ol (**3q**) from the hydroamination of cinammyl acetate on a 10 mmol scale with 0.5 mol% catalyst loading, decreased equivalents of 1,2-benzisoxazole, and a 24 h reaction time to provide **3q** without any significant erosion in either yield or level of enantioselectivity (85% yield, 98% ee).

3.3 Conclusion

In summary, we have discovered the use of isoxazole and its commercially available derivatives as electrophilic nitrogen sources for copper-catalyzed C–N bond formations. Using these reagents in conjunction with CuH-catalyzed hydroamination reactions, we describe the first report of enantioselective conversion of alkenes to primary amines. In a single operation, this method provides the efficient synthesis of α-branched chiral primary amines and linear amines under mild reaction conditions. Good yields and uniformly high to excellent levels of enantioselectivity were observed across a range of substrates with high functional group tolerance. Furthermore, this method was applied to the convergent synthesis of Maraviroc as well as the preparation of several core structures of pharmaceutically-relevant compounds from simple alkenes. We believe that the use of isoxazole derivatives as an electrophilic amine source will directly address the current limitations in the fields of electrophilic amination as well as CuH-catalyzed hydroamination. The expansion of this strategy to other classes of alkenes are currently under way and will be reported in due course.

3.4 Experimental

I. General Information

General Reagent Information

Unless otherwise noted, reactions were conducted under nitrogen or argon using standard Schlenk line techniques. THF and toluene were dried and deoxygenated by passage through packed columns of neutral alumina and copper(II) oxide under a positive pressure of argon and stored in a nitrogen-filled glovebox over 4Å molecular sieves. Copper(II) acetate (99.999% Cu) was purchased from Strem Chemicals Inc. and Sigma Aldrich. Both enantiomers of DTBM-SEGPHOS were purchased from Strem Chemicals Inc. or Takasago International Co. and used as received. Dimethoxy(methyl)silane was purchased from Tokyo Chemical Industry Co. (TCI) and stored at –20 °C for long term storage. Dimethoxy(methyl)silane (DMMS) was also stored in a refrigerator at 4 °C for up to 3 months with no observable decrease in reagent purity. Caution: DMMS (CAS: 16881-77-9) is listed by several vendors (TCI, Alfa Aeser) SDS or MSDS as a H318, a category 1 Causes Serious Eye Damage. Other vendors (Sigma Aldrich, Gelest) list DMMS as a H319, a category II Eye Irritant. DMMS should be handled in a well-ventilated fume hood using proper precaution as outlined for the handling of hazardous materials in "Prudent Practices in the Laboratory."[1] At the end of the reaction either ammonium fluoride in methanol, aqueous sat. sodium bicarbonate ($NaHCO_3$), or hydroxylamine hydrochloride in methanol should be carefully added to the reaction mixture. This should be allowed to stir for at least 30 min or the time indicated in the detailed reaction procedure. 1,2-Benzisoxazole was purchased from Tokyo Chemical Industry Co. (TCI) and stored in a refrigerator at 4 °C. All other reagents and solvents were obtained from commercial sources and used as received. Compounds were purified by flash column chromatography using silica gel (SiliCycle SiliaFlash® F60, 230-400 mesh), basic aluminum oxide (Alfa Aeser, activated, basic, Brockmann Grade I, 60 mesh), or neutral aluminum oxide (Alfa Aeser, activated, Brockmann Grade I, 60 mesh) unless otherwise indicated.

[1] "Prudent Practices in the Laboratory [electronic resource]: Handling and Management of chemical Hazards / Committee on Prudent Practices in the Laboratory: An Update."Board on Chemical Sciences and Technology, Division of Earth and Life Studies, National Research Council of the National Academies. Washington, D.C.: National Academies Press, 2011.

General Analytical Information

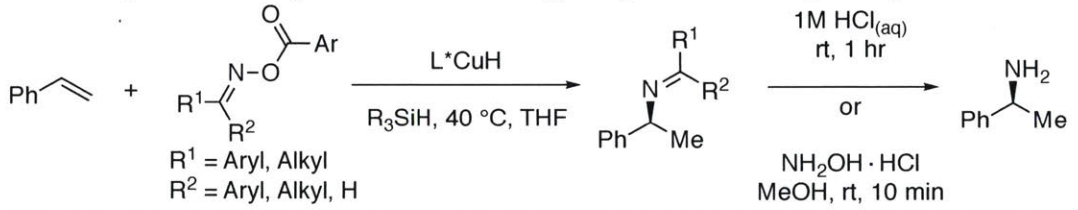
All substrates and products were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR (if appropriate), IR spectroscopy, elemental analysis (or high-resolution mass spectroscopy) and melting point analysis (if solids). NMR spectra were recorded with a Bruker 400 MHz (Avance III-400). All NMR data are reported in δ units, parts per million (ppm), and were measured relative to the residual proton signal in the deuterated solvent ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; CD_2Cl_2: 5.32 ppm for ^{1}H NMR and 54.00 ppm for ^{13}C NMR). All ^{13}C NMR spectra are ^{1}H decoupled. All IR spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and are reported in terms of frequency of absorption (cm^{-1}). Melting points (m.p.) were measured on a Mel-Temp capillary melting point apparatus. Optical rotations were measured using a Jasco P-1010 digital polarimeter using a cell of 100-mm length under the wavelength of 589 nm. Enantiomeric excesses (ee) of the products were determined by chiral SFC analysis using a Waters Acquity UPC2 instrument; specific columns and analytical methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analysis are provided with the associated chromatograms. High-performance liquid chromatography (HPLC) analysis performed on Agilent 1200 Series chromatographs using a Chiralpak® columns (25 cm) as noted for each. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High resolution mass spectra were obtained using a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Achiral gas chromatography (GC) analyses were performed on an Agilent 7890A gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). Thin-layer chromatography (TLC) was performed on Silicycle 250 μm silica gel plates (60 μm) or Millipore 250 μm aluminum oxide plates (60 Å). Compounds were visualized by irradiation with UV light, or stained with iodine/silica gel, or potassium permanganate. Preparatory thin-layer chromatography (Prep-TLC) was performed on silica gel GF with UV 254 (20 × 20 cm, 250 microns, catalog # TLG-R10014B-323 from Silicycle) and visualized with UV light.

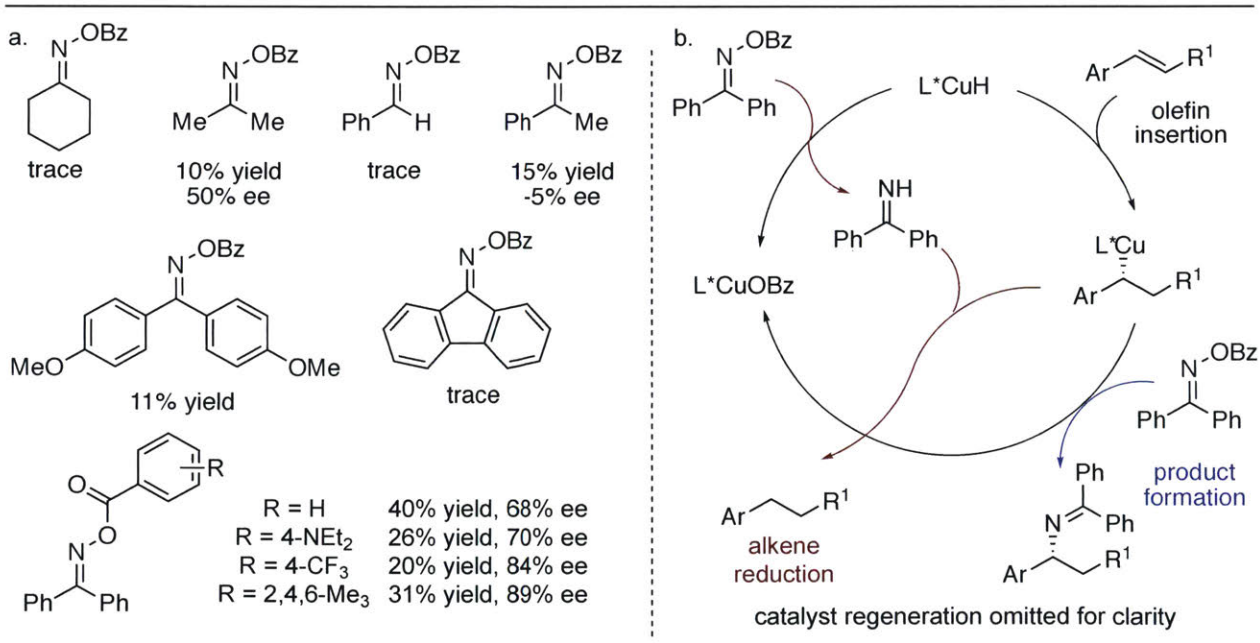
II. Optimization of *O*-ester oxime electrophiles

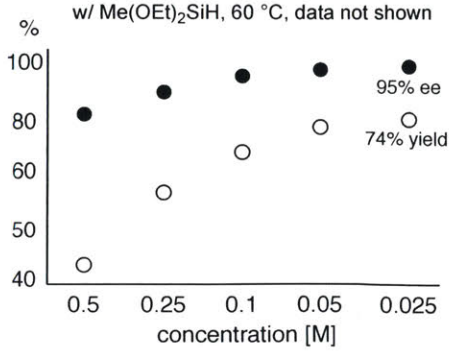
A range of ketoxime and aldoxime esters were evaluated with styrene as the pronucleophile. A series of electron rich- and deficient, as well as sterically hindered leaving groups were simultaneously evaluated. However, no obvious trends were observed and *O*-benzoyl

benzophenone oxime was chosen as the primary amine surrogate for subsequent optimization due to its low cost to synthesize and ease of purification (recrystallization for both steps starting from benzophenone). We reasoned that the increased steric hindrance of the oxime reagents impeded the efficiency of C–N bond formation, thus resulting poor yields and moderate levels of stereoinduction. Furthermore, the presence of reduced alkene suggested that the competitive reduction of the oxime ester to the corresponding imine produced a sufficiently acidic proton source for the deprotonation of alkyl cuprates (Table S–1). Indeed, increased reaction temperatures

***Table S-1**. Optimization of O-ester oxime reagents for CuH-catalyzed hydroamination*







Entry	T (°C)	Silane	Concentration (M)	%yield	%ee
1	40	$Me(OEt)_2SiH$	0.5	40	68
2	60	$Me(OEt)_2SiH$	0.5	42	85
3	85	$Me(OEt)_2SiH$	0.5	48	88
4	85	$Me(OMe)_2SiH$	0.5	56	90
5	85	$Me(OMe)_2SiH$	0.1	76	94
6	85	$Me(OMe)_2SiH$	0.05	88	95
7	85	$Me(OMe)_2SiH$*	0.05	88	97

*2% $Cu(OAc)_2$, 4.4% (*R*)-DTBM-SEGPHOS

to facilitate the C–N bond formation were found to simultaneously increased yield and enantioselectivity of the reaction. (Table S-1 entries 1-3) Further optimization also revealed that decreased concentration also benefited reaction efficiency. The optimized conditions are highlighted in blue and can provide the desired product in 88% yield and 97% ee.

III. Experimental Procedures and Characterization Data

General Procedure for Table SI-1 – Hydroamination of O-ester oxime reagents

An oven-dried screw-cap reaction tube (20 mm × 125 mm, Fisherbrand, part # 1495937A) was charged with oxime ester (0.6 mmol, 1.5 equiv), $Cu(OAc)_2$ (2.91 mg, 16 μmol, 4 mol%) and (*S*)-DTBM SEGPHOS (20.7 mg, 17.6 μmol, 4.4 mol%). An oven-dried magnetic stir bar (10 mm × 5 mm, egg-shaped) was then added and the reaction tube was capped with a Teflon/silicone septum screw cap (National, part # B7995-18; Kimble Chase, part # 73804-15425). The septum was punctured with a needle attached to a Schlenk line and the reaction tube was evacuated and backfilled with either argon or nitrogen (this process was repeated a total of three times). Styrene (45 μL, 0.4 mmol, 1.0 equiv), THF, and silane (1.2 mmol, 3.0 equiv) were added sequentially using a syringe and the reaction mixture was placed in a preheated oil bath. The reaction was stirred for roughly 12 h, then cooled to rt and diluted with dodecane (40 μL, 0.18 mmol, 0.44 equiv) and EtOAc (4 mL). An aliquot of this mixture was analyzed by gas chromatograph (GC) to determine the yield. To the remaining mixture was added 1.0 M HCl solution (5 mL) and the mixture was stirred at rt for 30 min. The mixture was then pour into a separatory funnel containing brine (5 mL) and CH_2Cl_2 (5 mL) and the organic layer removed. The aqueous layer was then extract with CH_2Cl_2 (5 mL) for another two times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. To the concentrated residue was added CH_2Cl_2 (2 mL), Et_3N (110 μL, 0.8 mmol, 2.0 equiv), and benzoyl chloride (70 μL, 0.6 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 30 min, then a fraction of this solution was purified using preparative thin layer chromatography (20% EtOAc in hexanes) to determine the enantiomeric excess.

Procedure for Comparison of Electrophilic Amine Reagents

Copper-Hydride Solution: An oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) was charged with $Cu(OAc)_2$ (4.0 mg, 22 μmol, 2 mol% for 2.2 reactions), (*S*)-DTBM-SEGPHOS (28.6 mg, 24.2 μmol, 2.2 mol% for 2.2 reactions) and a magnetic stir bar (10

mm × 5 mm, egg-shaped). The reaction tube was loosely capped and transferred into a nitrogen-filled glovebox. Inside the glovebox, THF (1.1 mL) and DMMS (440 μL, 3.63 mmol, 3.2 equiv for 2.2 reactions) were added sequentially. The reaction tube was capped and stirred for 30 min to afford a red solution. To each reaction was added 0.7 mL of this solution.

Hydroamination with N,N-dibenzyl-O-pivaloylhydroxylamine: An oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) was charged with 1,3,5-trimethoxybenzene (14.5 mg, 8.6 μmol, 0.17 equiv), *N,N-dibenzyl-O-pivaloylhydroxylamine* (223 mg, 0.75 mmol, 1.5 equiv), and a magnetic stir bar (10 mm × 5 mm, egg-shaped). The reaction tube was loosely capped and transferred into a nitrogen-filled glovebox. Inside a nitrogen-filled glovebox, styrene (57.5 μL, 0.5 mmol, 1.0 equiv) was added, followed by 0.7 mL of the copper-hydride solution. After stirring for 2–5 min (until the reaction was homogeneous), the reaction mixture was partition into a series of oven-dried vials (15 mm × 45 mm, VWR, part # 66011-041) 25 μL per vial. The vials were capped and removed from the glovebox. At each given time point, a vial was uncapped and $CDCl_3$ (0.5 mL) was added. The vial was recapped, shaken, then the solution transferred to an oven-dried NMR tube for NMR analysis of the crude reaction mixture.

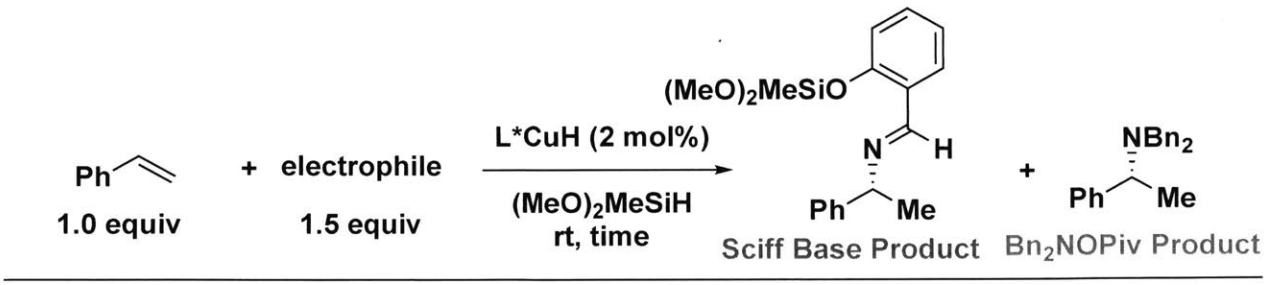
Hydroamination with 1,2-benzisoxazole: An oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) was charged with 1,3,5-trimethoxybenzene (18.0 mg, 10.7 μmol, 0.21 equiv) and a magnetic stir bar (10 mm × 5 mm, egg-shaped). The reaction tube was loosely capped and transferred into a nitrogen-filled glovebox. Inside the glovebox, styrene (57.5 μL, 0.5 mmol, 1.0 equiv) was added, followed by 0.7 mL of the copper-hydride solution. After stirring for 2–5 min, 1,2-benzisoxazole (75 μL, 0.75 mmol, 1.5 equiv) was added dropwise at a rate of ~ 2 drops/s using a microsyringe. The reaction mixture was stirred for another 2 min, then partitioned into a series of oven-dried vials (15 mm × 45 mm, VWR, part # 66011-041) 25 μL per vial. The vials were capped and removed from the glovebox. At each given time point, a vial was uncapped and $CDCl_3$ (0.5 mL) was added. The vial was recapped, shaken, then the solution transferred to an oven-dried NMR tube for NMR analysis of the crude reaction mixture.

One-pot Competition between electrophilic amines: An oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) was charged with 1,3,5-trimethoxybenzene (14.5 mg, 8.6 μmol, 0.17 equiv), *N,N-dibenzyl-O-pivaloylhydroxylamine* (223 mg, 0.75 mmol, 1.5

equiv), and a magnetic stir bar (10 mm × 5 mm, egg-shaped). The reaction tube was loosely capped and transferred into a nitrogen-filled glovebox. Inside the glovebox, styrene (57.5 μL, 0.5 mmol, 1.0 equiv) and 1,2-benzisoxazole (75 μL, 0.75 mmol, 1.5 equiv) were added, followed by 0.7 mL of the copper-hydride solution. After stirring for 2–5 min (until the reaction was homogeneous), the reaction mixture was partition into a series of oven-dried vials (15 mm × 45 mm, VWR, part # 66011-041) 25 μL per vial. The vials were capped and removed from the glovebox. At each given time point, a vial was uncapped and $CDCl_3$ (0.5 mL) was added. The vial was recapped, shaken, then the solution transferred to an oven-dried NMR tube for NMR analysis of the crude reaction mixture.

The peaks used for ^{1}H-NMR analysis are indicated in the representative spectra (Figure S-1) and compared to spectra of purified products.

Chart S-1. *Time Points of One-Pot Competition Experiment of Electrophilic Amine Reagents (Conversion, % Yield of Schiff Base, % Yield tertiary amine product, % conversion of benzisoxazole, Product ratio vs time)*



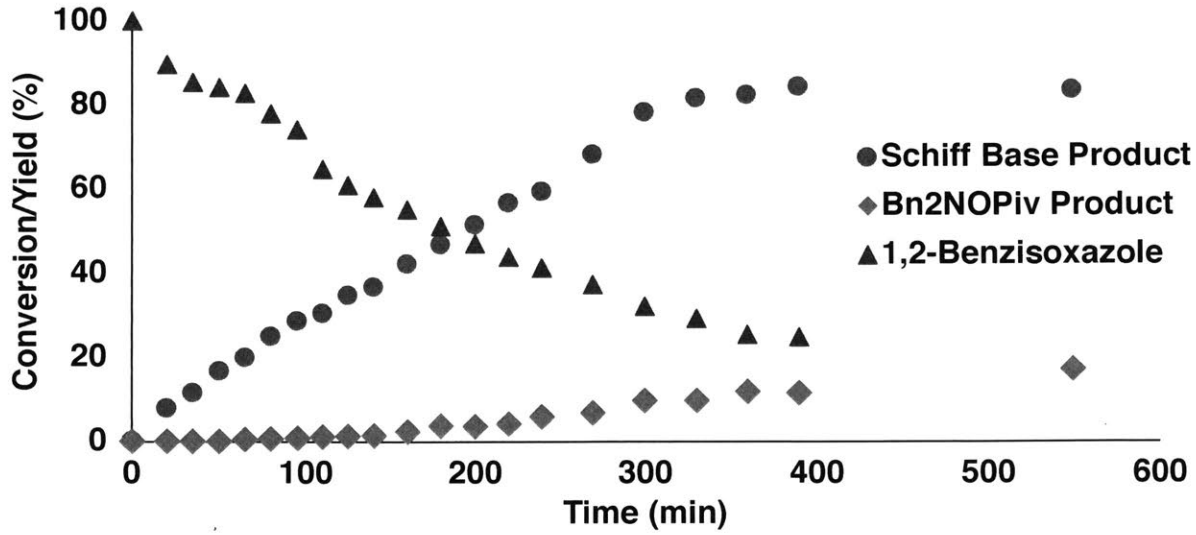
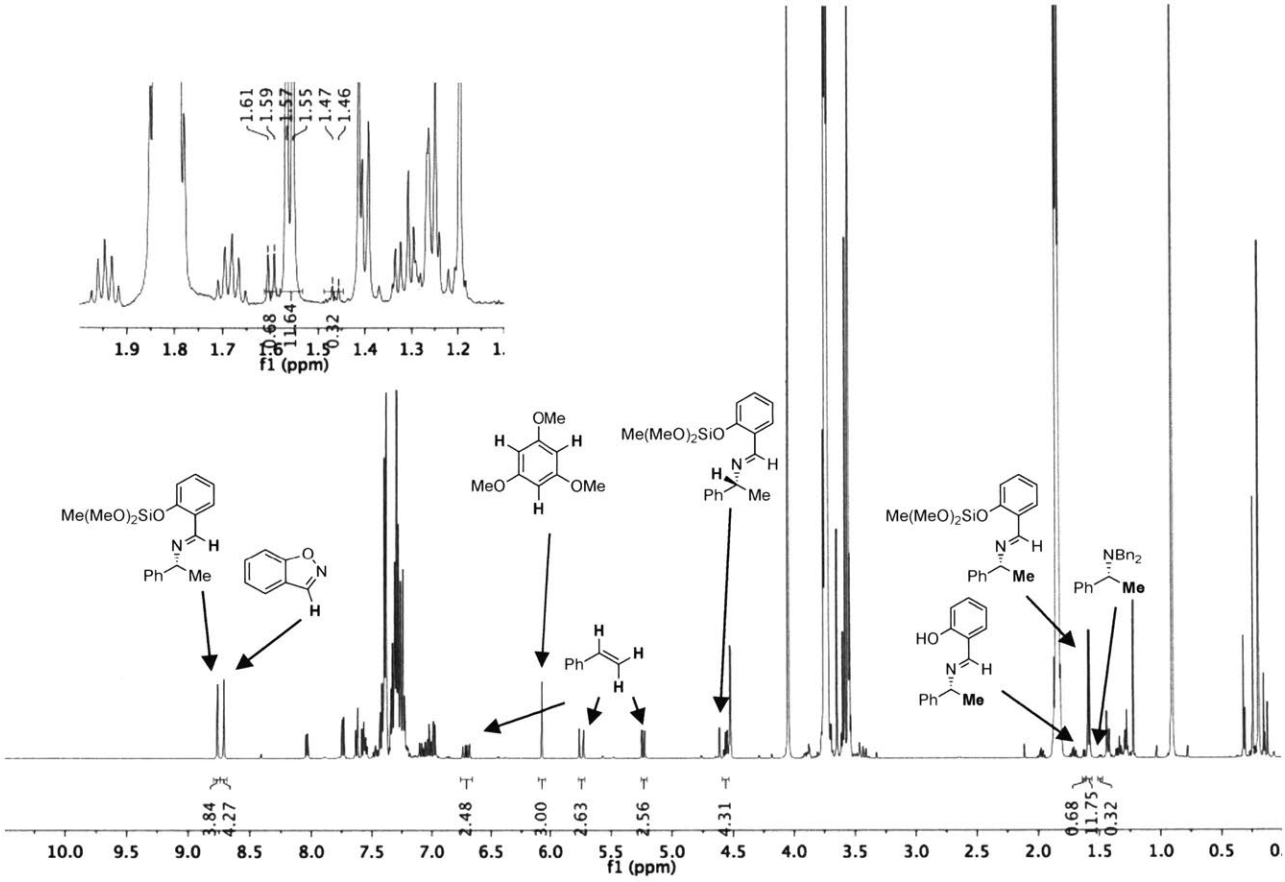


Figure S-1. *Representative ^{1}H-NMR Spectra for one-pot competition of electrophiles (220 min)*



General Procedure for Table 1 – Evaluation of Isoxazole Derivatives

An oven-dried screw-cap reaction tube (13 mm × 100 mm, Fisherbrand, part # 14-959-35C) was charged with $Cu(OAc)_2$ (4.6 mg, 25 μmol, 5 mol%) and (*S*)-DTBM SEGPHOS (32.5 mg, 27.5 μmol, 5.5 mol%), and a magnetic stir bar (10 mm × 5 mm, egg-shaped). The reaction tube was loosely capped and transferred into a nitrogen-filled glovebox. Inside the glovebox, THF (0.5 mL) and DMMS (0.2 mL, 1.6 mmol, 3.2 equiv) were added sequentially using a syringe and the reaction mixture was allowed to stir at rt for 30 min, at which the solution appeared as a dark-red color. Styrene (57.5 μL, 0.5 mmol, 1.0 equiv) and 1,2-benzisoxazole (100 μL, 1.0 mmol, 2.0 equiv) were added sequentially and the reaction tube was capped and removed from the glovebox.

For electrophiles **2a-k**: After 20 h, the reaction tube was cooled to 0 °C in an ice/water bath. To the crude reaction mixture was added dropwise 4 mL methanolic $NH_2OH{\cdot}HCl$ (0.5 M) solution. After around 30 min, as determined by TLC analysis, the crude reaction mixture was concentrated under reduced pressure and the residue was neutralized with sat. $NaHCO_3$. Using a separatory

funnel, the aqueous layer was extract with CH_2Cl_2 until no primary amine remained in the aqueous layer (as determined by TLC analysis). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the concentrated residue was added CH_2Cl_2 (2 mL), Et_3N (110 μL, 0.8 mmol, 2.0 equiv), and benzoyl chloride (70 μL, 0.6 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 30 min, then a fraction of this solution was purified using preparative thin layer chromatography (20% EtOAc in hexanes) to determine the enantiomeric excess.

For electrophile **2**: After 20 h, the reaction tube was quenched by diluting with DCM (3 mL) then concentrated under reduced pressure. 1,3,5-Trimethoxybenzene was then added as an internal standard and $CDCl_3$ (5 mL) was added to the concentrated residue. The vial was recapped, shaken, then the solution transferred to an oven-dried NMR tube for NMR analysis of the crude reaction mixture. A fraction of this solution was s purified using preparative thin layer chromatography (10% EtOAc in hexanes) to determine the enantiomeric excess.

*General Procedure **A** for Table 2 – Hydroamination of Activated Alkenes*

Copper-Hydride Solution: An oven-dried screw-cap reaction tube (20 mm × 125 mm, Fisherbrand, part # 1495937A) was charged with $Cu(OAc)_2$ (3.63 mg, 20 μmol, 2 mol%) and (*S*)-DTBM SEGPHOS (26.0 mg, 22 μmol, 2.2 mol%). An oven-dried magnetic stir bar (10 mm × 5 mm, egg-shaped) was then added and the reaction tube was capped with a Teflon/silicone septum screw cap (National, part # B7995-18; Kimble Chase, part # 73804-15425). The septum was punctured with a needle attached to a Schlenk line and the reaction tube was evacuated and backfilled with either argon or nitrogen (this process was repeated a total of three times). THF (1.0 mL) and DMMS (0.4 mL, 3.2 mmol, 3.2 equiv) were added sequentially using a syringe and the reaction mixture was allowed to stir at rt for 30 min, at which the solution appeared as a dark-red color.

Hydroamination: Vinyl arene (1.0 mmol, 1.0 equiv) added to the copper-hydride solution using a microsyringe. After stirring for 2–5 min, benzisoxazole (0.15 mL, 1.5 mmol, 1.5 equiv) was added dropwise at a rate of ~2 drops/s using a microsyringe. The cap of the reaction tube was then wrapped with parafilm and allowed to stir at rt.

Note: If the vinyl arene is a solid (**4b-f**), 1.2 equiv of the CuH solution was made and 1.4 mL of this solution was transferred to a reaction tube containing the vinyl arene.

*Workup for Schiff Base Products (**3a-q**)*: After 18 h, the reaction tube was quenched by diluting with EtOAc (3 mL), cooling to 0 °C in an ice/water bath, and the dropwise addition of 1.0 M NaOH solution (1.5 mL) (*Caution: gas evolution!*). The ice/water bath was removed after 5 min and the mixture was stirred at rt for another 25 min, then 0.1 mL of 30% H_2O_2 in H_2O was added to remove the ligand and the mixture was stirred for another 10 min. The mixture was then pour into a separatory funnel containing brine (10 mL) and EtOAc (10 mL) and the organic layer was removed. The aqueous layer was then extract with EtOAc (20 mL) two additional times. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the title compound. For the purification of imines **3**, silica gel was neutralized with 2–3% Et_3N in hexanes prior to packing the column, then column was then flushed with either hexanes or 0.1% Et_3N in hexanes to remove excess Et_3N prior to sample loading.

*Workup for Primary Amine Products (**4a-4m**)*: After the indicated reaction time, the reaction tube was cooled to 0 °C in an ice/water bath. To the crude reaction mixture was added dropwise 4 mL methanolic $NH_2OH{\cdot}HCl$ (0.5 M) solution. (*Caution: gas evolution observed*) Following the color change from yellow to colorless (around 30 min, as determined by TLC analysis), the crude reaction mixture was concentrated under reduced pressure and the residue was neutralized with sat. $NaHCO_3$. Using a separatory funnel, the aqueous layer was extract with CH_2Cl_2 until no primary amine remained in the aqueous layer (as determined by TLC analysis). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the title compound.

*General Procedure **B** for Table 3 – Hydroamination of Unactivated Alkenes*

An oven-dried screw-cap reaction tube (20 mm × 125 mm, Fisherbrand, part # 1495937A) was charged with $Cu(OAc)_2$ (9.08 mg, 50 μmol, 5 mol%), (*S*)-DTBM SEGPHOS (64.9 mg, 55 μmol, 5.5 mol%), and alkene (1.0 mmol, 1.0 equiv). An oven-dried magnetic stir bar (10 mm × 5 mm, egg-shaped) was then added and the reaction tube was capped with a Teflon/silicone septum screw

cap (National, part # B7995-18; Kimble Chase, part # 73804-15425). The septum was punctured with a needle attached to a Schlenk line and the reaction tube was evacuated and backfilled with either argon or nitrogen (this process was repeated a total of three times).

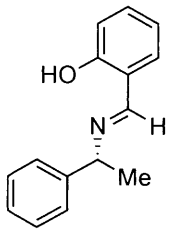
Hydroamination of Terminal Alkenes (**4g-l, 3n**): THF (1.0 mL) and DMMS (0.4 mL, 3.2 mmol, 3.2 equiv) were added sequentially using a syringe and the reaction mixture was allowed to stir at rt for 30 min. The Teflon cap was then wrapped with parafilm, then placed in a 45 °C oil bath. Using a syringe pump, benzisoxazole (0.15 mL, 1.5 mmol, 1.5 equiv) was added dropwise at a rate of 15 μL/h. After the indicated reaction time, the reaction was worked up following that of General Procedure A - *Workup for Schiff Base Products* or *Workup for Primary Amine Products*.

Hydroamination of 1,1-disubstituted alkenes (**3o-3p**): THF (0.1 mL) and DMMS (0.7 mL, 5.7 mmol, 5.7 equiv) were added sequentially using a syringe and the reaction mixture was allowed to stir at rt for 30 min. The Teflon cap was then wrapped with parafilm, then placed in a 45 °C oil bath. Using a syringe pump, benzisoxazole (0.15 mL, 1.5 mmol, 1.5 equiv) was added dropwise at a rate of 10 μL/h. After the indicated reaction time, the reaction was worked up following that of General Procedure A - *Workup for Schiff Base Products* or *Workup for Primary Amine Products*.

*General Procedure for Determination of Enantiomeric Excess of Primary Amine Products **4X***

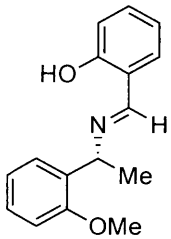
An oven-dried screw-cap reaction tube (20 mm × 125 mm, Fisherbrand, part # 1495937A) was charged with the corresponding primary (0.1 mmol, 1.0 equiv), salicylaldehyde (21 μL, 0.2 mmol, 2.0 equiv), and *i*-PrOH (0.2 mL). The reaction tube was capped and shaken to ensure a homogenous solution, then placed in a pre-heated 60 °C oil bath. After an hour, the reaction tube was removed from the oil bath and allowed to cool to rt. The corresponding Schiff base product (**4X-SB**) was purified using preparative thin layer chromatography (20% EtOAc in hexanes) to determine the enantiomeric excess of the primary amine product **4X**.

Characterization Data for Tables 2, 3, and Figure 3



3a

(*R*,*E*)-2-(((1-phenylethyl)imino)methyl)phenol (3a): Prepared following General Procedure **A** with styrene (115 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (3% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow solid. (1st run: 195 mg, 87%; 2nd run: 194 mg, 86%). **m.p.** 75–77 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.45 (s, 1H), 8.30 (s, 1H), 7.27 – 7.10 (m, 7H), 6.86 (d, *J* = 8.2 Hz, 1 H), 6.76 (td, *J* = 7.5, 1.1 Hz, 1H), 4.44 (q, *J* = 6.7 Hz, 1H), 1.53 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6, 161.2, 144.0, 132.4, 131.5, 128.8, 127.4, 126.5, 119.0, 118.8, 117.1, 68.7, 25.1. **IR** (neat, cm^{-1}) 2974, 2867, 1639, 1582, 1493, 1453, 1418, 1378, 1278, 1205, 1151, 1068, 755, 699. **Specific rotation** $[\alpha]_D^{24}$ = -138.51 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 7.4 min, t_m = 8.1 min) indicated 98% ee. Spectral data were in accordance with those in literature.[2]



3b

(*R*,*E*)-2-(((1-(2-methoxyphenyl)ethyl)imino)methyl)phenol (3b): Prepared following General Procedure **A** with 2-vinylanisole (134 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (3% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 209 mg, 82%; 2nd run: 208 mg, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.71 (s, 1H), 8.30 (s, 1H), 7.32 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.23 – 7.1 (m, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.81 – 6.70 (m, 2H), 4.89 (q, *J* = 6.6 Hz, 1H), 3.74, 1.48 (d, *J* = 6.6 Hz, 3Hf). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.6, 161.5, 156.4, 132.2, 131.9, 131.5, 128.3, 127.0, 121.0, 119.1, 118.5, 117.1, 110.6, 61.7, 55.4, 23.3. **IR** (neat, cm^{-1}) 2969, 2836, 1627, 1600, 1582, 1491, 1462, 1278, 1241, 1151, 1088, 1030, 813, 752. **Specific rotation** $[\alpha]_D^{24}$ = -197.36 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 7.4 min, t_m = 6.9 min) indicated 97% ee. Spectral data were in accordance with those in literature.[3]

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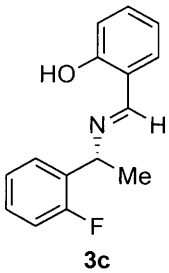
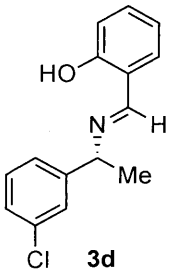
[2] Jaworska, M.; Wełniak, Zięciak, J.; Kozakiewicz, A.; Wojtczak, A. *Arkovic.* **2011**, *ix*, 189

[3] Yeşilel, O. Z., Akdağb, K., Paşaoğlu, H., & Büyükgüngör, O. *Zeitschrift für Naturforschung B.* **2007**, *62*, 818



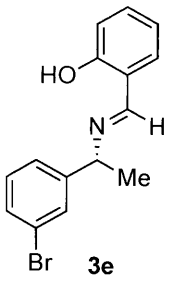
3c

(*R*,*E*)-2-(((1-(2-fluorophenyl)ethyl)imino)methyl)phenol (3c): Prepared following General Procedure **A** with 2-fluorostyrene (119 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (3% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow solid. (1st run: 179 mg, 74%; 2nd run: 170 mg, 69%). **m.p.** 60–65 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.48 (s, 1H), 8.46 (s, 1H), 7.49 (td, *J* = 7.6, 2.0 Hz, 1H), 7.32 (ddd, *J* = 8.6, 7.3, 1.8 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.16 (td, *J* = 7.6, 1.5 Hz, 1H), 7.06 (ddd, *J* = 10.5, 8.1, 1.4 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 4.91 (q, *J* = 6.7 Hz, 1H), 1.65 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 161.1, 160.1 (d, *J* = 245.8 Hz), 132.5, 131.7, 130.8 (d, *J* = 13.9 Hz), 128.8 (d, *J* = 8.8 Hz), 127.8 (d, *J* = 4.4 Hz), 124.6 (d, *J* = 3.7 Hz), 118.9, 118.8, 117.1, 115.7 (d, *J* = 22.7 Hz), 61.7 (d, *J* = 2.2 Hz), 23.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -119.3. **IR** (neat, cm^{-1}) 2975, 2870, 1629, 1582, 1489, 1456, 1411, 1382, 1275, 1228, 1151, 1083, 828, 753. **HRMS** (m/z, ESI) Calcd. for $[C_{15}H_{14}FNO+H]^+$ 244.1138, found 244.1136. **Specific rotation** $[\alpha]_D^{24}$ = -147.81 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 7.8 min, t_m = 7.1 min) indicated 97% ee.



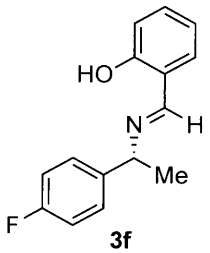
3d

(*R*,*E*)-2-(((1-(3-chlorophenyl)ethyl)imino)methyl)phenol (3d): Prepared following General Procedure **A** with 3-chlorostyrene (127 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 204 mg, 79%; 2nd run: 217 mg, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.29 (s, 1H), 8.42 (s, 1H), 7.34 (s, 1H), 7.34 – 7.22 (m, 5H), 6.98 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.89 (td, *J* = 7.5, 1.1 Hz, 1H), 4.52 (q, *J* = 6.7 Hz, 1H), 1.62 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.1, 161.1, 146.0, 134.6, 132.7, 131.7, 130.1, 127.6, 126.8, 124.7, 118.9, 118.9, 117.2, 68.3, 25.0. **IR** (neat, cm^{-1}) 2972, 2866, 1627, 1575, 1276, 1199, 1079, 829, 753, 696. **EA** Calcd. for $C_{15}H_{14}ClNO$: C, 69.37; H, 5.43. Found: C, 69.12; H. 5.63. **Specific rotation** $[\alpha]_D^{23}$ = -151.52 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 7.8 min, t_m = 7.1 min) indicated 98% ee.



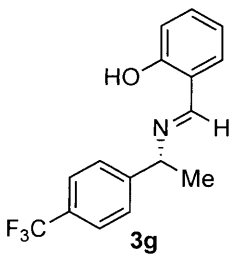
3e

(*R*,*E*)-2-(((1-(3-bromophenyl)ethyl)imino)methyl)phenol (3e): Prepared following General Procedure **A** with 3-bromostyrene (130 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 245 mg, 81%; 2nd run: 251 mg, 82%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.19 (s, 1H), 8.33 (s, 1H), 7.42 (s, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.25 – 7.10 (m, 4H), 6.90 (d, J = 8.3 Hz, 1H), 6.81 (t, J = 7.4 Hz, 1H), 4.42 (q, J = 6.7 Hz, 1H), 1.53 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.1, 161.1, 146.3, 132.7, 131.7, 130.5, 130.4, 129.7, 125.2, 122.8, 118.9, 118.8, 117.2, 68.3, 25.0. **IR** (neat, cm^{-1}) 2971, 2863, 1627, 1593, 1579, 1568, 1276, 752. **EA** Calcd. for $C_{15}H_{14}BrNO$: C, 59.23; H, 4.64. Found: C, 59.32; H. 4.81. **Specific rotation** $[\alpha]_D^{23}$ = -133.02 (c = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 9.3 min, t_m = 8.4 min) indicated 95% ee.



3f

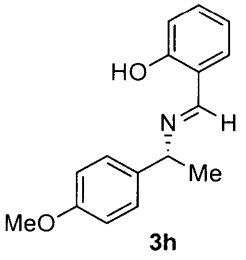
(*R*,*E*)-2-(((1-(4-fluorophenyl)ethyl)imino)methyl)phenol (3f): Prepared following General Procedure **A** with 4-fluorostyrene (120 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 197 mg, 81%; 2nd run: 202 mg, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.42 (s, 1H), 8.43 (s, 1H), 7.39 – 7.29 (m, 3H), 7.28 (s, 1H), 7.06 (t, J = 8.7 Hz, 2H), 6.99 (d, J = 8.3 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 4.56 (q, J = 6.7 Hz, 1H), 1.63 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 162.1 (d, J_{CF} = 245.4 Hz), 161.1, 139.7 (d, J_{CF} = 3.1 Hz), 132.6, 131.6, 128.1 (d, J_{CF} = 8.0 Hz), 115.6 (d, J_{CF} = 21.4 Hz), 68.0, 25.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.5. **IR** (neat, cm^{-1}) 2973, 2863, 1627, 1602, 1577, 1508, 1495, 1276, 1220, 832, 753. **EA** Calcd. for $C_{15}H_{14}FNO$: C, 74.06; H, 5.80. Found: C, 73.78; H. 5.89. **Specific rotation** $[\alpha]_D^{23}$ = -106.00 (c = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 5.8 min, t_m = 7.4 min) indicated 96% ee.



3g

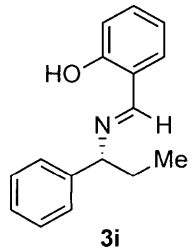
(*R*,*E*)-2-(((1-(4-(trifluoromethyl)phenyl)ethyl)imino)methyl)phenol (3g): Prepared following General Procedure **A** with 4-(trifluoromethyl)styrene (148 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow solid.

(1st run: 230 mg, 78%; 2nd run: 214 mg, 73%). **m.p.** 46–49 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.22 (s, 1H), 8.43 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.32 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.26 (d, *J* = 1.6 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 4.59 (q, *J* = 6.7 Hz, 1H), 1.63 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 161.1, 148.0, 133.8 (d, *J* = 159.6 Hz), 132.8, 131.7, 126.9, 125.8 (q, *J* = 3.9 Hz), 119.0, 119.0 (d, *J* = 29.3 Hz), 117.7, 117.2, 68.4, 25.2. (product unstable for prolonged periods of time in $CDCl_3$) **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.5. **IR** (neat, cm^{-1}) 2974, 2867, 1628, 1581, 1322, 1277, 1118, 1098, 1066, 839, 753. **EA** Calcd. for $C_{16}H_{14}F_3NO$: C, 65.52; H, 4.81. Found: C, 65.24; H. 4.93. **Specific rotation** $[\alpha]_D^{23}$ = -106.00 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 3.9 min, t_m = 4.6 min) indicated 93% ee.



3h

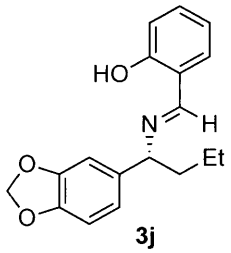
(*R*,*E*)-2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenol (3h): Prepared following General Procedure **A** with 4-methoxystyrene (133 μL, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.1 mg, 50 μmol, 5 mol%), and (*S*)-DTBM-SEGPHOS (65.0 mg, 55 μmol, 5.5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow solid. (1st run: 190 mg, 75%; 2nd run: 201 mg, 79%). **m.p.** 66–68 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.59 (s, 1H), 8.38 (s, 2H), 7.34 – 7.27 (m, 3H), 7.23 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.91 – 6.83 (m, 3H), 4.52 (q, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 1.61 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.3, 161.2, 158.9, 136.0, 132.4, 131.5, 127.7, 119.0, 118.7, 117.1, 114.2, 67.9, 55.5, 25.0. **IR** (neat, cm^{-1}) 2967, 2834, 1627, 1611, 1581, 1511, 1495, 1276, 1243, 829, 753. **EA** Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.00; H. 6.64. **Specific rotation** $[\alpha]_D^{23}$ = -136.53 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 8.9 min, t_m = 10.8 min) indicated 98% ee.



3i

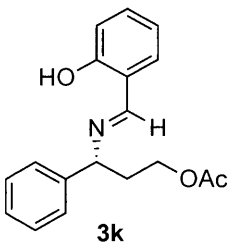
(*R*,*E*)-2-(((1-phenylpropyl)imino)methyl)phenol (3i): Prepared following General Procedure A with *trans*-β-methylstyrene (130 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (3% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 171 mg, 72%; 2nd run: 173 mg,

73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.52 (s, 1H), 8.29 (s, 1H), 7.26 – 7.12 (m, 7H)), 6.88 (d, *J* = 8.3 Hz, 1H), 6.77 (td, *J* = 7.5, 1.2 Hz, 1H), 4.11 (t, *J* = 6.8 Hz, 1H), 1.88 (p, *J* = 7.4 Hz, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0, 161.3, 143.1, 132.4, 131.5, 128.8, 127.4, 127.0, 118.9, 118.7, 117.1, 75.9, 31.9, 11.1. **IR (neat, cm^{-1})** 2964, 2930, 2872, 1628, 1581, 1493, 1461, 1415, 1277, 1151, 755, 699. **Specific rotation** $[\alpha]_D^{24}$ = 157.48 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 6.3 min, t_m = 7.7 min) indicated 98% ee.



3j

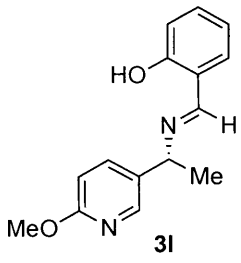
(*R*,*E*)-2-(((1-(benzo[*d*][1,3]dioxol-5-yl)butyl)imino)methyl)phenol (3j): Prepared following General Procedure **A** with (*E*)-5-(but-1-en-1-yl)benzo[*d*][1,3]dioxole (176 mg, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (3% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 230 mg, 78%; 2nd run: 233 mg, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.53 (s, 1H), 8.34 (s, 1H), 7.30 (t, *J* = 8.7 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 1.7 Hz, 2H), 5.94 (d, *J* = 2.6 Hz, 2H), 4.22 (t, *J* = 7.0 Hz, 1H), 1.88 (dddd, *J* = 11.7, 9.7, 7.0, 3.9 Hz, 2H), 1.46 – 1.18 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 161.2, 148.0, 146.8, 137.2, 132.4, 131.5, 120.1, 118.9, 118.8, 117.1, 108.3, 107.4, 101.2, 73.8, 41.0, 19.7, 13.9. **IR** (neat, cm^{-1}) 2957, 2932, 2872, 1627, 1605, 1502, 1487, 1442, 1244, 1205, 1151, 1039, 931, 811, 757. **EA** Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44. Found: C, 72.46; H. 6.50. **Specific rotation** $[\alpha]_D^{24}$ = -74.37 (*c* = 1.0, $CHCl_3$). **SFC analysis** (AD-H column, see spectra for details, t_M = 8.5 min, t_m = 7.0 min) indicated 99% ee.



3k

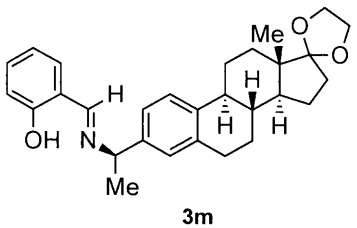
(*R*,*E*)-3-((2-hydroxybenzylidene)amino)-3-phenylpropyl acetate (3k): Prepared following General Procedure **A** with cinnamyl acetate (167 μL, 1.0 mmol, 1.0 equiv). After 18 h, the reaction was quenched by cooling to 0°C in an ice/water bath and the dropwise-addition of sat. NH_4F in MeOH (0.5 mL). The mixture was then removed from the ice/water bath and stirred uncapped for 30 min. The mixture was then pour into a separatory funnel containing sat. $NaHCO_3$ (20 mL) and EtOAc (20 mL) and the organic layer was removed. The aqueous layer was then extract with EtOAc (20 mL) for another two times. The combined organic layers were dried over anhydrous

Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the title compound. (10% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 231 mg, 78%; 2nd run: 213 mg, 73%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.30 (s, 1H), 8.40 (s, 1H), 7.36 (d, *J* = 4.4 Hz, 4H), 7.34 – 7.27 (m, 1H), 7.29 – 7.26 (m, 1H), 7.24 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.88 (td, *J* = 7.5, 1.1 Hz, 1H), 4.47 (dd, *J* = 8.1, 6.0 Hz, 1H), 4.10 (td, *J* = 6.3, 2.4 Hz, 2H), 2.37 – 2.22 (m, 2H), 2.04 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 165.0, 161.1, 142.2, 132.7, 131.7, 129.0, 127.8, 126.9, 118.9, 118.8, 117.1, 71.0, 61.6, 37.5, 21.0. **IR** (neat, cm^{-1}) 2957, 2877, 1736, 1627, 1580, 1493, 1277, 1232, 1043, 1032, 754, 699. **EA** Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44. Found: C, 72.56; H. 6.53. **Specific rotation** $[\alpha]_D^{23}$ = -83.61 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 7.2 min, t_m = 7.5 min) indicated 98% ee.



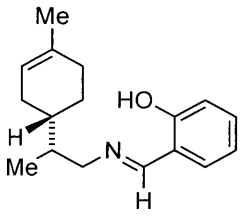
3l

(*R*,*E*)-2-(((1-(6-methoxypyridin-3-yl)ethyl)imino)methyl)phenol (3l): Prepared following General Procedure **A** with 2-methoxy-5-vinylpyridine (135 mg, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.1 mg, 50 μmol, 5 mol%), and (*S*)-DTBM-SEGPHOS (65.0 mg, 55 μmol, 5.5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (5% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 178 mg, 69%; 2nd run: 190 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.26 (s, 1H), 8.41 (s, 1H), 8.13 (d, *J* = 2.6 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.31 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H), 7.24 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.96 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.88 (td, *J* = 7.5, 1.2 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 4.53 (q, *J* = 6.7 Hz, 1H), 3.92 (s, 3H), 1.62 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8, 163.7, 161.1, 144.9, 137.1, 132.6, 132.1, 131.6, 118.9, 118.8, 117.1, 111.2, 65.8, 53.6, 24.7. **IR** (neat, cm^{-1}) 2973, 2944, 2846, 1627, 1606, 1490, 1276, 1025, 829, 753. **EA** Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29. Found: C, 70.40; H. 6.29. **Specific rotation** $[\alpha]_D^{23}$ = -133.88 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 6.8 min, t_m = 7.3 min) indicated 98% ee.



3m

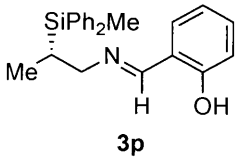
2-((*E*)-(((*R*)-1-((8*S*,9*S*,13*S*,14*S*)-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthren-e-17,2'-[1,3]dioxolan]-3-yl)-ethyl)imino)methyl)phenol (3m): Prepared following General Procedure **A** with (8R,9S,13S,14S)-13-methyl-3-vinyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] (162 mg, 0.5 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (10% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow foam. (1st run: 180 mg, 81%; 2nd run: 190 mg, 85%). **m.p.** 70–74 °C. **^{1}H NMR** (500 MHz, C_6D_6) δ 13.90 (s, 1H), 7.92 (s, 1H), 7.23 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.14 – 7.11 (m, 2H), 7.08 – 7.02 (m, 2H), 6.88 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.67 (td, *J* = 7.4, 1.2 Hz, 1H), 4.13 (q, *J* = 6.6 Hz, 1H), 3.63 – 3.46 (m, 4H), 2.73 – 2.62 (m, 2H), 2.29 – 2.16 (m, 2H), 2.09 (ddd, *J* = 14.5, 11.6, 3.2 Hz, 1H), 1.96 – 1.82 (m, 2H), 1.80 – 1.60 (m, 3H), 1.54 (ddd, *J* = 12.5, 4.1, 2.4 Hz, 1H), 1.51 – 1.40 (m, 1H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.37 – 1.26 (m, 1H), 1.25 – 1.09 (m, 2H), 0.96 (s, 3H).**^{13}C NMR** (126 MHz, C_6D_6) δ 163.6, 162.1, 141.5, 139.7, 137.2, 132.5, 131.7, 127.3, 126.2, 124.1, 119.5, 119.4, 118.6, 117.6, 68.7, 65.3, 64.6, 49.7, 46.4, 44.5, 39.2, 34.7, 31.1, 29.9, 27.4, 26.5, 25.0, 22.7, 14.7. **IR** (neat, cm^{-1}) 3010, 2968, 2939, 2872, 1630, 1497, 1459, 1379, 1279, 1216, 1180, 1161, 1105, 1045, 891, 753, 667. **HRMS** (m/z, ESI) Calcd. for $[C_{29}H_{35}NO_3+H]^+$ 446.2695, found 446.2689. **Specific rotation** $[\alpha]_D^{24}$ = -82.47 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 5.7 min, t_m = 6.2 min) indicated 98% ee.



3o

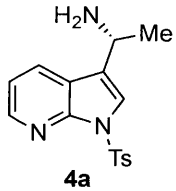
2-((*E*)-(((*R*)-2-((*S*)-4-methylcyclohex-3-en-1-yl)propyl)imino)methyl)phenol (3o)**:** Prepared following General Procedure **B** with (*S*)-(−)-Limonene (161 μL, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (3% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow foam. (1st run: 102 mg, 63%; 2nd run: 172 mg, 67%). **^{1}H NMR** (400 MHz, C_6D_6) δ 13.80 (s, 1H), 7.79 (d, *J* = 1.4 Hz, 1H), 7.13 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.10 – 7.03 (m, 1H), 6.94 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.76 – 6.67 (m, 1H), 5.39 (s, 1H), 3.22 (ddd, *J* = 12.0, 4.9, 1.5 Hz, 1H), 2.99 (ddt, *J* = 12.0, 7.6, 1.1 Hz, 1H), 1.97 – 1.81 (m, 3H), 1.78 – 1.67 (m, 1H), 1.62 (s, 3H), 1.58 (ddd, *J* = 12.8, 5.3, 2.6 Hz, 1H), 1.53 – 1.26 (m, 2H), 1.13 (dtd, *J* = 12.4, 11.3, 5.7 Hz, 1H), 0.78 (dd, *J* = 6.7, 0.7 Hz,

3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 165.2, 162.2, 133.8, 132.4, 131.4, 121.1, 119.4, 118.5, 117.6, 63.9, 38.7, 36.9, 30.8, 29.9, 26.0, 23.7, 15.2. **IR** (neat, cm^{-1}) 2963, 2912, 1634, 1582, 1498, 1456, 1280, 1215, 1151, 1042, 754. **EA** Calcd. for $C_{17}H_{23}NO$: C, 79.33; H, 9.01. Found: C, 79.06; H. 9.12. **Specific rotation** $[\alpha]_D^{24}$ = -28.87 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OD-H column, see spectra for details, t_M = 5.7 min, t_m = 5.4 min) indicated 96:4 d.r.



3p

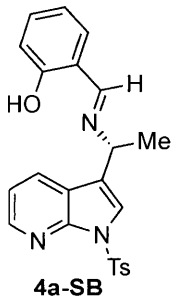
(*S*,*E*)-2-(((2-(methyldiphenylsilyl)propyl)imino)methyl)phenol (3p): Prepared following General Procedure **B** with methyldiphenyl(prop-1-en-2-yl)silane (238 mg, 1.0 mmol, 1.0 equiv), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography (3% EtOAc in hexanes with 0.1% Et_3N) the title compound was obtained as a yellow oil. (1st run: 238 mg, 67%; 2nd run: 260 mg, 72%). **^{1}H NMR** (500 MHz, C_6D_6) δ 13.72 (s, 1H), 7.56 (s, 1H), 7.44 (dd, *J* = 6.3, 3.1 Hz, 4H), 7.22 – 7.16 (m, 4H), 7.14 – 7.10 (m, 3H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.67 (t, *J* = 7.4 Hz, 1H), 3.52 (dd, *J* = 12.1, 3.6 Hz, 1H), 2.98 (t, *J* = 11.4 Hz, 1H), 1.55 (dtt, *J* = 14.3, 7.3, 3.6 Hz, 1H), 0.93 (d, *J* = 7.3 Hz, 3H), 0.43 (s, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 165.1, 162.2, 136.0, 135.2, 135.2, 132.4, 131.5, 129.7, 119.3, 118.5, 117.6, 62.6, 20.7, 13.3, -5.8. **IR** (neat, cm^{-1}) 2068, 1954, 2866, 1629, 1581, 1496, 1461, 1427, 1280, 1253, 1111, 1018, 787, 756, 737, 700. **EA** Calcd. for $C_{23}H_{25}NOSi$: C, 76.83; H, 7.01. Found: C, 76.71; H. 7.15. **Specific rotation** $[\alpha]_D^{24}$ = -10.06 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OD-H column, see spectra for details, t_M = 9.1 min, t_m = 8.7 min) indicated 98% ee.



4a

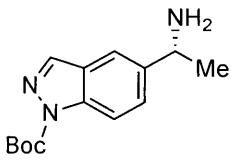
(*R*)-1-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethan-1-amine (4a): Prepared following General Procedure **A** with 1-tosyl-3-vinyl-1H-pyrrolo[2,3-b]pyridine (298 mg, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.1 mg, 50 μmol, 5 mol%), and (*S*)-DTBM-SEGPHOS (65.0 mg, 55 μmol, 5.5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography with neutral alumina (0–6% 2M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained as a white foam. (1st run: 206 mg, 65%; 2nd run: 188 mg, 60%). **m.p.** 58–65 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.96 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.65 (s, 1H), 7.24 (s, 1H), 7.16 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.36 (q, *J* = 6.6 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 2H), 1.51 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.9, 145.2, 145.1, 135.7, 129.7, 128.8,

128.1, 121.8, 121.7, 118.6, 44.3, 24.4, 21.8 (one peak missing due to overlap). **IR** (neat, cm^{-1}) 2964, 2921, 1595, 1553, 1396, 1368, 1173, 1157, 1091, 801, 772, 667. **EA** Calcd. for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43. Found: C, 60.66; H. 5.50. **Specific rotation** $[\alpha]_D^{23}$ = 3.20 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by the corresponding Schiff base product (**4a-SB**) with salicylaldehyde



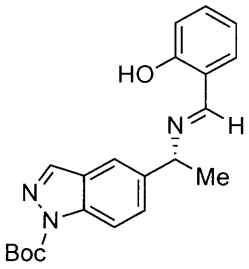
4a-SB

(*R*,*E*)-2-(((1-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl)imino)methyl)phenol (4a-SB): yellow foam. **^{1}H NMR** (400 MHz, C_6D_6 δ 13.45 (s, 1H), 8.28 – 8.19 (m, 3H), 7.78 (d, *J* = 18.6 Hz, 2H), 7.48 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.11 – 7.00 (m, 2H), 6.81 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.69 – 6.62 (m, 1H), 6.61 (d, *J* = 8.3 Hz, 2H), 6.56 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.12 (q, *J* = 6.7 Hz, 1H), 1.68 (s, 3H), 1.24 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 164.5, 161.9, 148.2, 145.0, 144.8, 136.4, 132.9, 131.9, 129.6, 128.8, 128.6, 122.9, 121.4, 120.9, 119.1, 118.8, 118.7, 117.6, 61.2, 22.8, 21.1. **IR** (neat, cm^{-1}) 2953, 2924, 2853, 1627, 1397, 1373, 1278, 1175, 1160, 756, 664, 580. **HRMS** (m/z, ESI) Calcd. for $[C_{23}H_{21}N_3O_3S+H]^+$ 420.1376, found 420.1378. **Specific rotation** $[\alpha]_D^{23}$ = -73.85 (*c* = 1.0, $CHCl_3$). **SFC analysis** (AD-H column, see spectra for details, t_M = 6.9 min, t_m = 7.2 min) indicated 91% ee.



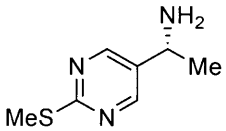
4b

***tert*-butyl (*R*)-5-(1-aminoethyl)-1*H*-indazole-1-carboxylate (4b)**: Prepared following General Procedure **A** with tert-butyl 5-vinyl-1H-indazole-1-carboxylate (244 mg, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.1 mg, 50 μmol, 5 mol%), and (*S*)-DTBM-SEGPHOS (65.0 mg, 55 μmol, 5.5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography with neutral alumina (0–5% 2M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained as a beige waxy solid (1st run: 209 mg, 79%; 2nd run: 214 mg, 83%). **m.p.** 46–40 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 – 8.08 (m, 2H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 8.8, 1.7 Hz, 1H), 4.28 (q, *J* = 6.5 Hz, 1H), 1.72 (s, 9H), 1.57 (s, 2H), 1.43 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.4, 143.7, 139.7, 139.1, 127.7, 126.2, 117.6, 114.7, 84.9, 51.2, 28.3, 26.2. **IR** (neat, cm^{-1}) 2973, 2931, 1733, 1385, 1368, 1246, 1161, 1148, 1028, 847. **HRMS** (m/z, ESI) Calcd. for $[C_{14}H_{19}N_3O_2+H]^+$ 262.155, found 262.1544. **Specific rotation** $[\alpha]_D^{23}$ = 19.21 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by the corresponding Schiff base product (**4b-SB**) with salicylaldehyde.



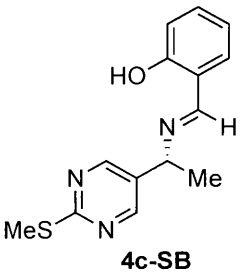
4b-SB

***tert*-butyl (*R*,*E*)-5-(1-((2-hydroxybenzylidene)amino)ethyl)-1*H*-indazole-1-carboxylate (4b-SB)**: yellow oil. **^{1}H NMR** (400 MHz, C_6D_6) δ 13.66 (s, 1H), 8.40 (d, *J* = 8.7 Hz, 1H), 7.83 (s, 1H), 7.67 (s, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.18 (d, *J* = 1.7 Hz, 1H), 7.13 (d, *J* = 1.1 Hz, 1H), 7.07 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 6.91 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.69 (td, *J* = 7.5, 1.3 Hz, 1H), 4.08 (q, *J* = 6.7 Hz, 1H), 1.46 (s, 9H), 1.32 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 164.0, 162.0, 149.8, 139.8, 139.7, 139.3, 132.8, 131.8, 126.7, 119.3, 118.7, 118.4, 117.6, 115.3, 83.9, 68.4, 28.0, 25.1 (one peak missing due to overlap). **IR** (neat, cm^{-1}) 2975, 2932, 2868, 1755, 1733, 1627, 1383, 1369, 1141, 1028, 782. **HRMS** (m/z, ESI) Calcd. for $[C_{21}H_{23}N_3O_3+H]^+$ 366.1812, found 366.1815. **Specific rotation** $[\alpha]_D^{23}$ = -118.63 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 2.7 min, t_m = 5.4 min) indicated 96% ee.



4c

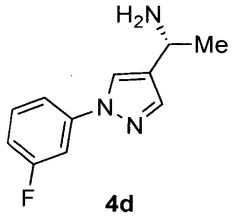
(*R*)-1-(2-(methylthio)pyrimidin-5-yl)ethan-1-amine (4c): Prepared following General Procedure **A** with 2-(methylthio)-5-vinylpyrimidine (152 mg, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.1 mg, 50 μmol, 5 mol%), and (*S*)-DTBM-SEGPHOS (65.0 mg, 55 μmol, 5.5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography with neutral alumina (0–7% 2M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained as a thick oil that became a dark brown solid upon standing. (1st run: 113 mg, 67%; 2nd run: 120 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 2H), 4.13 (q, *J* = 6.7 Hz, 1H), 2.55 (d, *J* = 1.7 Hz, 3H), 1.51 (s, 2H), 1.40 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.26, 155.67, 155.64, 134.78, 47.10, 25.62, 14.24. **IR** (neat, cm^{-1}) 2963, 2926, 2870, 1627, 1584, 1538, 1395, 1172, 775, 642. **HRMS** (m/z, ESI) Calcd. for $[C_7H_{11}N_3S+H]^+$ 170.0746, found 170.0739. **Specific rotation** $[\alpha]_D^{23}$ = 38.76 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by the corresponding Schiff base product (**4c-SB**) with salicylaldehyde.



4c-SB

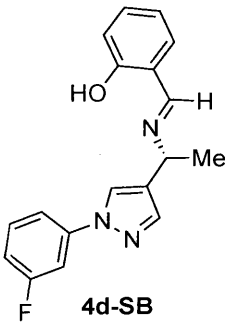
(*R*,*E*)-2-(((1-(2-(methylthio)pyrimidin-5-yl)ethyl)imino)methyl)phenol (4c-SB): yellow oil. **^{1}H NMR** (400 MHz, C_6D_6) δ 13.03 (s, 1H), 8.16 (s, 2H), 7.60 (s, 1H), 7.12 – 7.02 (m, 2H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.69 (ddd, *J* = 8.1, 6.5, 2.0 Hz, 1H), 3.52 (q, *J* = 6.7 Hz, 1H), 2.36 (s, 3H), 0.94 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 172.5, 164.7, 161.9, 155.6, 133.1, 131.9,

131.5, 119.0, 118.8, 117.7, 64.1, 23.7, 14.0. **IR** (neat, cm^{-1}) 2972, 2926, 2862, 1626, 1580, 1395, 1275, 775. **HRMS** (m/z, ESI) Calcd. for $[C_{14}H_{15}N_3OS+H]^+$ 274.1009, found 274.1008. **Specific rotation** $[\alpha]_D^{23}$ = -126.09 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 7.1 min, t_m = 6.4 min) indicated 98% ee.



4d

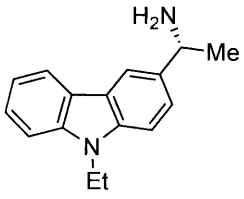
(*R*)-1-(1-(3-fluorophenyl)-1*H*-pyrazol-4-yl)ethan-1-amine (4d): Prepared following General Procedure **A** with 1-(3-fluorophenyl)-4-vinyl-1*H*-pyrazolecarbazole (188 mg, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.1 mg, 50 μmol, 5 mol%), and (*S*)-DTBM-SEGPHOS (65.0 mg, 55 μmol, 5.5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography with silica gel (10% 1.5 M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained as a colorless oil. (1st run: 143 mg, 70%; 2nd run: 150 mg, 73%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.65 (s, 1H), 7.47 – 7.26 (m, 3H), 6.94 (tdd, *J* = 8.2, 2.5, 1.3 Hz, 1H), 4.17 (q, *J* = 6.5 Hz, 1H), 1.70 (s, 2H), 1.43 (d, *J* = 6.5 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (d, *J* = 246.5 Hz), 141.7 (d, *J* = 10.3 Hz), 139.6, 131.1, 130.8 (d, *J* = 9.2 Hz), 123.8, 114.1 (d, *J* = 2.9 Hz), 113.0 (d, *J* = 21.3 Hz), 106.6 (d, *J* = 26.0 Hz), 43.0, 25.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110. **IR** (neat, cm^{-1}). 2966 , 1613, 1601, 1568, 1498, 1461, 1394, 1257, 1182, 1151, 969, 864, 776, 679. **HRMS** (m/z, ESI) Calcd. for $[C_{11}H_{12}FN_3+H]^+$ 206.1094, found 206.1082. **Specific rotation** $[\alpha]_D^{24}$ = 1.10 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by the corresponding Schiff base product (**4d-SB**) with salicylaldehyde.



4d-SB

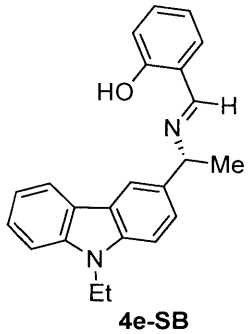
(*R*,*E*)-2-(((1-(1-(3-fluorophenyl)-1*H*-pyrazol-4-yl)ethyl)imino)methyl)phenol (4d-SB): yellow oil. **^{1}H NMR** (500 MHz, C_6D_6) δ 13.61 (s, 1H), 7.87 (s, 1H), 7.49 (s, 1H), 7.37 (dt, *J* = 10.2, 2.3 Hz, 1H), 7.25 (t, *J* = 0.8 Hz, 1H), 7.13 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.07 (ddd, *J* = 8.3, 7.1, 1.7 Hz, 1H), 6.93 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.77 (td, *J* = 8.2, 6.2 Hz, 1H), 6.71 (td, *J* = 7.3, 1.3 Hz, 1H), 6.58 (tdd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 4.03 (q, *J* = 6.7 Hz, 1H), 1.27 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 164.1, 163.6 (d, *J* = 245.6 Hz), 162.0, 141.9 (d, *J* = 10.1 Hz), 139.8, 132.9, 131.8, 130.8 (d, *J* = 9.4 Hz), 127.2, 124.0, 119.2, 118.8, 117.6, 114.1 (d, *J* = 3.6 Hz), 112.8 (d, *J* = 21.7 Hz), 106.5 (d, *J* = 26.7 Hz), 60.0, 23.8. **^{19}F NMR** (471 MHz, C_6D_6) δ -111. **IR** (neat, cm^{-1}).2972, 2922, 2859, 1628, 1613, 1601, 1497, 1460, 1394, 1278, 1257, 1182, 1151, 1034,

969, 864, 756, 680. **HRMS** (m/z, ESI) Calcd. for $[C_{33}H_{35}N_3O+H]^+$ 490.2858, found 490.2857. **Specific rotation** $[\alpha]_D^{24}$ = -87.41 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OJ-H column, see spectra for details, t_M = 8.5 min, t_m = 9.3 min) indicated 97% ee.



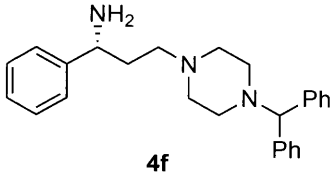
4e

(*R*)-1-(9-ethyl-9*H*-carbazol-3-yl)ethan-1-amine (4e): Prepared following General Procedure **A** with 9-ethyl-3-vinyl-9H-carbazole (221 mg, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.1 mg, 50 μmol, 5 mol%), and (*S*)-DTBM-SEGPHOS (65.0 mg, 55 μmol, 5.5 mol%), the reaction mixture was quenched after 18 h. After workup and purification by flash column chromatography with neutral alumina (0–5% 2M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained as a thick pale-yellow oil. (1st run: 198 mg, 83%; 2nd run: 183 mg, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.05 (m, 2H), 7.46 (td, *J* = 7.6, 6.8, 1.5 Hz, 2H), 7.39 (dd, *J* = 10.9, 8.1 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 4.42 – 4.29 (m, 3H), 1.83 (s, 2H), 1.51 (d, *J* = 6.5 Hz, 3H), 1.43 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 139.3, 138.4, 125.7, 124.0, 123.0, 123.0, 120.5, 118.8, 117.4, 108.6, 108.5, 51.7, 37.7, 26.3, 14.0. **IR** (neat, cm^{-1}) 3049, 2971, 2930, 1600, 1469, 1345, 1331, 1230, 887, 807, 745, 724. **HRMS** (m/z, ESI) Calcd. for $[C_{16}H_{18}N_2+H]^+$ 239.1543, found 239.1541. **Specific rotation** $[\alpha]_D^{23}$ = 32.89 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by the corresponding Schiff base product (**4e-SB**) with salicylaldehyde.



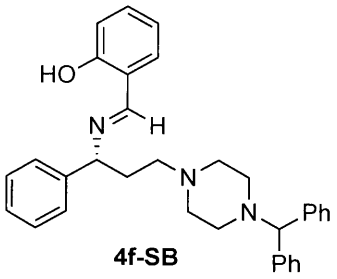
4e-SB

(*R*,*E*)-2-(((1-(9-ethyl-9*H*-carbazol-3-yl)ethyl)imino)methyl)phenol (4e-SB): yellow oil. **^{1}H NMR** (400 MHz, C_6D_6) δ 14.02 (s, 1H), 8.11 – 8.01 (m, 2H), 7.98 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.07 (dd, *J* = 7.8, 4.0 Hz, 2H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 4.39 (q, *J* = 6.7 Hz, 1H), 3.70 (q, *J* = 7.2 Hz, 2H), 1.55 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 163.6, 162.2, 140.7, 139.7, 134.9, 132.5, 131.7, 126.0, 124.6, 123.6, 123.5, 120.9, 119.6, 119.3, 118.8, 118.6, 117.6, 109.1, 108.9, 69.0, 37.4, 25.5, 13.6. **IR** (neat, cm^{-1}) 3049, 2971, 2930, 1625, 1602, 1489, 1470, 1330, 1276, 1231, 1150, 746, 732. **HRMS** (m/z, ESI) Calcd. for $[C_{23}H_{22}N_2O+H]^+$ 343.1805, found 343.1799. **Specific rotation** $[\alpha]_D^{23}$ = -175.46 (*c* = 1.0, $CHCl_3$). **SFC analysis** (AD-H column, see spectra for details, t_M = 8.8 min, t_m = 8.4 min) indicated 98% ee.



4f

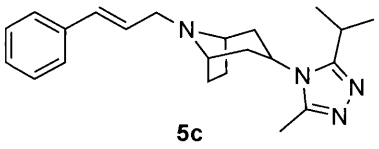
(*R*)-3-(4-benzhydrylpiperazin-1-yl)-1-phenylpropan-1-amine (4f): An oven-dried screw-cap reaction tube (20 mm × 125 mm, Fisherbrand, part # 1495937A) was charged with cinnarizine (369 mg, 1.0 mmol, 1.0 equiv), $Cu(OAc)_2$ (9.08 mg, 50 μmol, 5 mol%) and (*S*)-DTBM-SEGPHOS (64.9 mg, 55.0 μmol, 5.5 mol%). An oven-dried magnetic stir bar (10 mm × 5 mm, egg-shaped) was then added and the reaction tube was capped with a Teflon/silicone septum screw cap (National, part # B7995-18; Kimble Chase, part # 73804-15425). The septum was punctured with a needle attached to a Schlenk line and the reaction tube was evacuated and backfilled with either argon or nitrogen (this process was repeated a total of three times). Cyclohexane (1.0 mL) and DMMS (0.4 mL, 3.2 mmol, 3.2 equiv) were added sequentially using a syringe and the reaction mixture was allowed to stir at rt for 20 min. Using a syringe pump, 1,2-benzisoxozale (30 μL) was added at rt (10 μL/min). Another 120 μL 1,2 benzisoxazole was added at a rate of 30 μL/h. After 18 h, 4 mL $NH_2OH{\cdot}HCl$ in MeOH (0.5 M) was added to the crude reaction mixture (*Caution: gas evolution observed*) and this mixture allowed to stir for around 30 min. The methanol was removed under reduced pressure and the concentrated residue was redissolved in CH_2Cl_2 20 mL) and sat aq. $NaHCO_3$ (10 mL). Using a separatory funnel, the organic phase was removed and the aqueous phase was extracted with DCM for three times. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash column chromatography with silica gel (15% 1.5M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained as a white solid. (1st run: 332 mg, 86%; 2nd run: 315 mg, 82%). **m.p.** 88–92°C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.2, 1.5 Hz, 4H), 7.30 – 7.25 (m, 4H), 7.24 – 7.16 (m, 5H), 7.16 – 7.09 (m, 2H), 4.17 (s, 1H), 3.94 (s, 1H), 2.94 – 2.04 (m, 9H), 1.95 – 1.46 (m, 4H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9, 128.6, 128.6, 128.0, 127.1, 127.0, 126.4, 76.4, 56.1, 55.3, 53.7, 52.1, 36.4. **IR** (neat, cm^{-1}) 3058, 3024, 2943, 2807, 2769, 1597, 1490, 1451, 1306, 1282, 1148, 1134, 1076, 1007, 853, 757, 745, 701. **EA** Calcd. for $C_{26}H_{31}N_3$: C, 81.00; H, 8.10. Found: C, 80.61; H. 8.23. **Specific rotation** $[\alpha]_D^{24}$ = 2.01 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by the corresponding Schiff base product (**4f-SB**) with salicylaldehyde.



4f-SB

(R,E)-2-(((3-(4-benzhydrylpiperazin-1-yl)-1-phenylpropyl)imino)-methyl)phenol(4f-SB): yellow solid. **m.p.** 68–72 °C. **^{1}H NMR** (500 MHz, C_6D_6) δ 13.84 (s, 1H), 8.01 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 4H), 7.28 (d, *J* = 7.1 Hz, 2H), 7.16 – 7.11 (m, 7H), 7.10 – 6.99 (m, 4H), 6.87 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.66 (t, *J* = 7.4 Hz, 1H), 4.29 (t, *J* = 7.0 Hz, 1H), 4.21 (s, 1H), 2.67 – 2.20 (m, 6H), 2.21 – 2.02 (m, 4H), 1.86 (tdd, *J* = 7.3, 5.9, 2.4 Hz, 2H). **^{13}C NMR** (126 MHz, C_6D_6) δ 165.0, 162.1, 143.8, 143.4, 143.4, 132.6, 131.8, 128.9, 128.8, 128.4, 128.3, 127.4, 127.2, 127.2, 119.4, 118.7, 117.6, 76.8, 71.5, 54.6, 53.5, 52.5, 35.9 (two peaks missing due to overlap). **IR** (neat, cm^{-1}) 3060, 3025, 2947, 2808, 1628, 1492, 1451, 1278, 1150, 1138, 1008, 847, 755, 699. **HRMS** (m/z, ESI) Calcd. for $C_{33}H_{35}N_3O$ $[M+H]^+$ 490.2857, found 490.2857. **Specific rotation** $[\alpha]_D^{22}$ = -17.12 (*c* = 1.0, $CHCl_3$) **SFC analysis** (AD-H column, see spectra for details, t_M = 10.8 min, t_m = 13.0 min) indicated 98% ee.

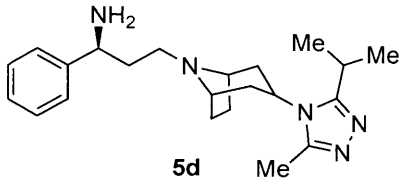
Experimental Procedures and Characterization Data for the 3-Step-Synthesis of Maraviroc



5c

(1*R*,5*S*)-8-cinnamyl-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (5c):An oven-dried round-bottom flask containing a magnetic stir-bar was charged with (1R,5S)-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (1.00 g, 4.27 mmol, 1.0 equiv), cinnamaldehyde (1.13 g, 8.53 mmol, 2.0 equiv) and anhydrous DCM (20 mL). The reaction flask was then purged with Ar for 10 min, at which $NaBH(OAc)_3$ (2.26 g, 10.7 mmol, 2.5 equiv) and AcOH (256 mg, 4.27 mmol, 1.0 equiv) were added. The reaction was stirred at rt until complete consumption of the starting material (22 h, as determined by TLC analysis). After workup and purification by flash column chromatography with silica gel (5% 1.5M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained a white solid. **Yield**: 1.39 g, 93% M.p.:126-132 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.29 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.30 (tt, *J* = 12.3, 6.0 Hz, 1H), 3.45 (s, 2zH), 3.19 (dd, *J* = 6.4, 1.5 Hz, 2H), 3.03 (p, *J* = 6.8 Hz, 1H), 2.56 (s, 3H), 2.26 (td, *J* = 12.7, 3.2 Hz, 2H), 2.13 (dt, *J* = 7.2, 3.3 Hz, 2H), 1.66 (d, *J* = 8.4 Hz, 4H), 1.40 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 150.9, 137.0, 132.1, 128.8, 128.1, 127.7, 126.4, 58.9, 55.0, 47.6, 37.1, 26.6, 26.0, 21.9, 13.3. **IR** (neat, cm^{-1}) 2929, 2847, 1772, 1742, 1449, 1419, 1223,

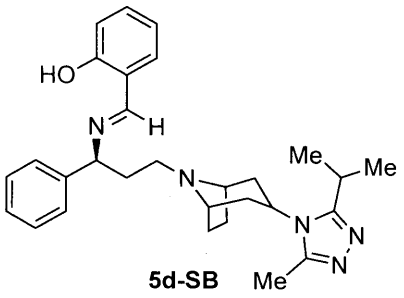
1165, 1097, 1031, 991, 967, 745, 693. **HRMS** (m/z, ESI) Calcd. for $[C_{22}H_{30}N_4+H]^+$ 351.2549, found 351.2539.



5d

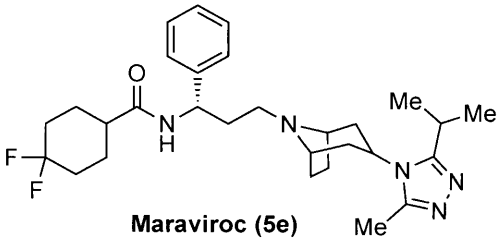
(1S)-3-((1R,5S)-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropan-1-amine (5b): An oven-dried screw-cap reaction tube (20 mm × 125 mm, Fisherbrand, part # 1495937A) was charged with $Cu(OAc)_2$ (4.54 mg, 25 μmol, 5 mol%) and (*R*)-DTBM-SEGPHOS (32.4 mg, 27.5 μmol, 5.5 mol%), **5c** (176 mg, 0.5 mmol, 1.0 equiv). An oven-dried magnetic stir bar (10 mm × 5 mm, egg-shaped) was then added and the reaction tube was capped with a Teflon/silicone septum screw cap (National, part # B7995-18; Kimble Chase, part # 73804-15425). The septum was punctured with a needle attached to a Schlenk line and the reaction tube was evacuated and backfilled with either argon or nitrogen (this process was repeated a total of three times). Cyclohexane (0.5 mL) and DMMS (0.2 mL, 1.6 mmol, 3.2 equiv) were added sequentially using a syringe and the reaction mixture was allowed to stir at rt for 20 min. Using a syringe pump, 1,2-benzisoxazole (15 μL) was added at rt (5 μL/min). Another 60 μL 1,2 benzisoxazole was added at a rate of 20 μL/h. After 5 h, 2 mL $NH_2OH{\cdot}HCl$ in MeOH (0.5 M) was added to the crude reaction mixture (*Caution: gas evolution observed*). The methanol was removed under reduced pressure and the concentrated residue was redissolved in CH_2Cl_2 (20 mL) and sat aq. $NaHCO_3$ (10 mL). Using a separatory funnel, the organic phase was removed and the aqueous phase was extracted with DCM for three times. The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash column chromatography with silica (20% 1.5 M NH_3 in MeOH in CH_2Cl_2) the title compound was obtained as a white foam. (1st run: 131 mg, 71%; 2nd run: 136 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 4.3 Hz, 4H), 7.18 (h, *J* = 4.0 Hz, 1H), 4.20 (tt, *J* = 12.2, 5.9 Hz, 1H), 4.02 (t, *J* = 6.7 Hz, 1H), 3.32 (d, *J* = 15.9 Hz, 2H), 2.92 (p, *J* = 6.8 Hz, 1H), 2.39 (s, 3H), 2.36 (t, *J* = 7.0 Hz, 2H), 2.12 (tdt, *J* = 10.4, 7.2, 3.6 Hz, 4H), 1.98 (dt, *J* = 7.6, 4.0 Hz, 2H), 1.79 (dp, *J* = 20.2, 6.8 Hz, 2H), 1.61 – 1.45 (m, 4H), 1.30 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.1, 150.7, 146.4, 128.6, 127.1, 126.3, 58.9, 59.0, 55.1, 49.3, 47.4, 38.1, 36.1, 26.6, 26.5, 25.8, 21.7, 13.1. **IR** (neat, cm^{-1}) 2957, 2930, 2868, 1516, 1453, 1418, 1345, 1216, 1097, 1030, 749, 701, 663 . **HRMS** (m/z, ESI) Calcd. for $[C_{22}H_{33}N_5+H]^+$ 368.2814, found 368.2786.

Specific rotation $[\alpha]_D^{24}$ = 4.12 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by the corresponding Schiff base product (**5d-SB**) with salicylaldehyde.



5d-SB

2-((*E*)-(((1*S*)-3-((1*R*,5*S*)-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropyl)imino)methyl)phenol (5d-SB): yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.80 (s, 1H), 8.09 (s, 1H), 7.31 (d, *J* = 6.8 Hz, 2H), 7.21 – 7.16 (m, 3H), 7.16 – 7.12 (m, 2H), 7.12 – 7.03 (m, 2H), 6.96 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.70 (td, *J* = 7.3, 1.3 Hz, 1H), 4.40 – 4.26 (m, 1H), 3.87 (tt, *J* = 12.1, 5.9 Hz, 1H), 2.99 – 2.72 (m, 3H), 2.29 (s, 3H), 2.12 (td, *J* = 7.1, 6.1, 3.1 Hz, 2H), 2.01 – 1.80 (m, 4H), 1.58 (td, *J* = 6.5, 6.1, 3.4 Hz, 2H), 1.33 (dd, *J* = 6.8, 1.8 Hz, 6H), 1.08 (d, *J* = 9.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.0, 162.1, 143.5, 132.9, 131.8, 129.1, 127.7, 127.2, 119.3, 118.9, 117.6, 71.9, 65.9, 59.2, 58.5, 48.3, 47.0, 38.0, 36.1, 36.0, 26.8, 26.5, 26.3, 22.0, 15.6, 13.1. **IR** (neat, cm^{-1}) 2959, 2934, 2877, 1627, 1581, 1514, 1492, 1453, 1418, 1345, 1279, 1211, 1120, 1030, 755, 701. **HRMS** (m/z, ESI) Calcd. for $[C_{29}H_{37}N_5O+H]^+$ 472.3076, found 472.3065. **Specific rotation** $[\alpha]_D^{24}$ = 20.76 (*c* = 1.0, $CHCl_3$). **SFC analysis** (OD-H column, see spectra for details, t_M = 10.1 min, t_m = 11.0 min) indicated 94% ee.

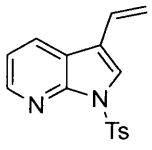


Maraviroc (5e)

Maraviroc (5e): An oven-dried round-bottom flask containing a magnetic stir-bar was charged with 4,4-difluorocyclohexane-1-carboxylic acid (1.0 equiv), EDCI (2.0 equiv), HOBt (2.0 equiv), 4Å molecular sieves (120 mg), and CH_2Cl_2 (1 mL). The mixture was cooled to 0 °C in an ice/water bath, then under a positive pressure of N_2, DIPEA (69.1 mg, 0.6 mmol, 5.0 eq.) was added and the reaction mixture allowed to stir for 15 min. A solution of **5b** (44.1 mg, 0.120 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was then added dropwise. The mixture was then removed from the ice/water bath and allowed to stir at rt until complete consumption of the starting material (as determined by TLC analysis). Upon completion, the reaction mixture was filtered through celite. The filtrate was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. After purification by flash column chromatography (2% 1.5M NH_3 in MeOH in CH_2Cl_2), the title compound was obtained as a white solid. **Yield**: 54 mg, 87%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.29 – 7.20 (m, 3H), 6.73 (s, 1H), 5.10 (q, *J* = 7.1 Hz, 1H),

4.28 (dt, J = 12.5, 6.3 Hz, 1H), 3.39 (d, J = 10.8 Hz, 2H), 2.97 (hept, J = 6.8 Hz, 1H), 2.48 (s, 3H), 2.44 (dt, J = 10.9, 4.3 Hz, 2H), 2.29 – 1.53 (m, 19H), 1.36 (dd, J = 6.8, 2.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5, 159.2, 150.7, 142.0, 128.9, 127.6, 126.5, 125.6 – 119.4 (m), 59.1, 58.3, 52.1, 47.6 (d, J_{CF} = 68.2 Hz), 42.9, 35.3 (d, J_{CF} = 14.7 Hz), 34.7, 33.31 – 32.50 (m), 26.8 (d, J_{CF} = 4.4 Hz), 26.1 (dd, J_{CF} = 10.3, 3.3 Hz), 26.0, 21.8, 13.3. **IR** (neat, cm^{-1}) 2959, 2930, 1652, 1514, 1449, 1372, 1217, 1108, 1030, 964, 751, 701, 664. **Specific rotation** $[\alpha]_D^{24}$ = -26.03 (c = 1.0, $CHCl_3$).Spectral data were in accordance with those in literature.[4]

Experimental Procedures and Characterization Data for Previously Uncharacterized Starting Materials



1-tosyl-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridine: An oven-dried round-bottom flask containing a magnetic stir-bar was charged with methyltriphenylphosphonium bromide (2.97 g, 8.32 mmol, 1.1 equiv) and anhydrous THF (20 mL). The reaction flask was sealed with a rubber septum then purged with Ar for 10 min using a Schlenk line. After cooling to 0 °C in an ice/water bath, the septum was removed and *t*-BuOK (933 mg, 8.32 mmol, 1.1 equiv) was added in one portion. The septum was then quickly placed back and the solution was allowed to stir for 10 min, during which it turned to a bright yellow color. Using a syringe, a solution of 1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbaldehyde (2.27 g, 7.56 mmol, 1.0 equiv) in anhydrous THF (5 mL) was added dropwise. The reaction was stirred at rt until complete consumption of the starting material (1 h, as determined by TLC analysis). After workup and purification by flash column chromatography with silica gel (5% EtOAc in hexanes) the title compound was obtained a white solid. **Yield**: 1.94 g, 86% **m.p.** 117–119 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (dd, J = 4.8, 1.6 Hz, 1H), 8.17 – 8.02 (m, 3H), 7.74 (s, 1H), 7.28 (d, J = 7.9, 6.0 Hz, 2H), 7.21 (dd, J = 7.9, 4.8 Hz, 1H), 6.73 (dd, J = 17.9, 11.4 Hz, 1H), 5.76 (d, J = 17.7 Hz, 1H), 5.36 (d, J = 11.7 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.8, 145.4, 145.3, 135.5, 129.8, 129.1, 128.2, 127.8, 124.4, 121.3, 119.1, 117.7, 115.4, 21.8. **IR** (neat, cm^{-1}) 1593, 1395, 1376, 1293, 1092, 770, 664, 588, 561. **HRMS** (m/z, ESI) Calcd. for $[C_{16}H_{14}N_2O_2S+H]^+$ 299.0849, found 299.0848.

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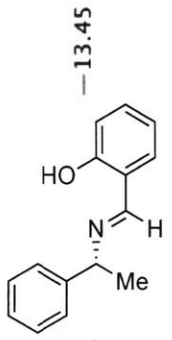
3.6 ^{1}H, ^{13}C, and ^{19}F NMR Spectra



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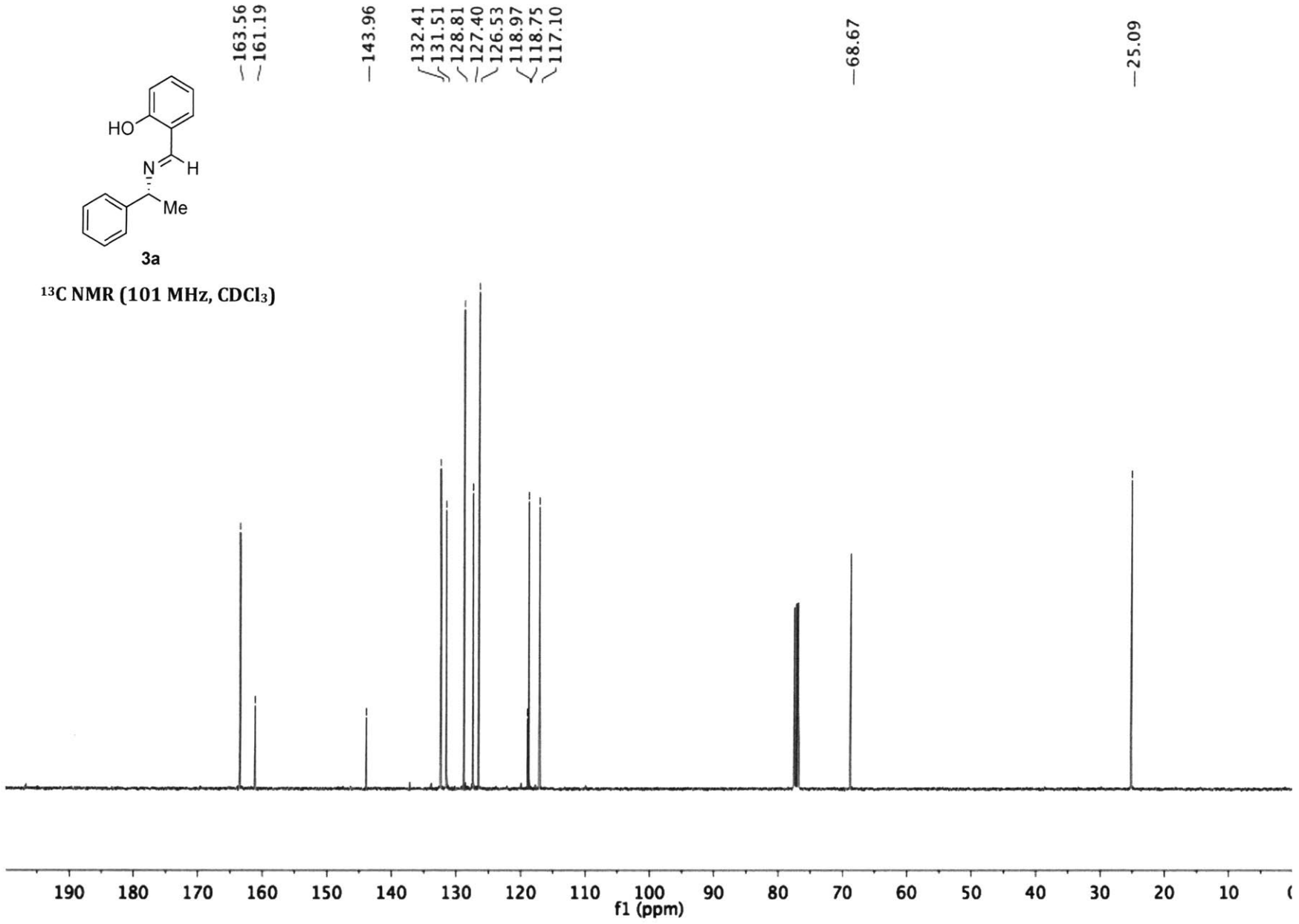
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161.19
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132.41
131.51
128.81
127.40
126.53
118.97
118.75
117.10
68.67
25.09
HO
N
H
Me
3a
13C NMR (101 MHz, CDCl3)
190
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170
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130
120
110
100
90
80
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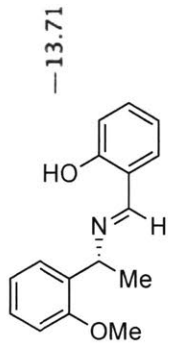
60
50
40
30
20
10
f1 (ppm)



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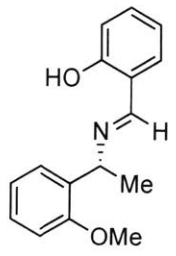

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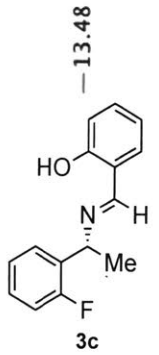

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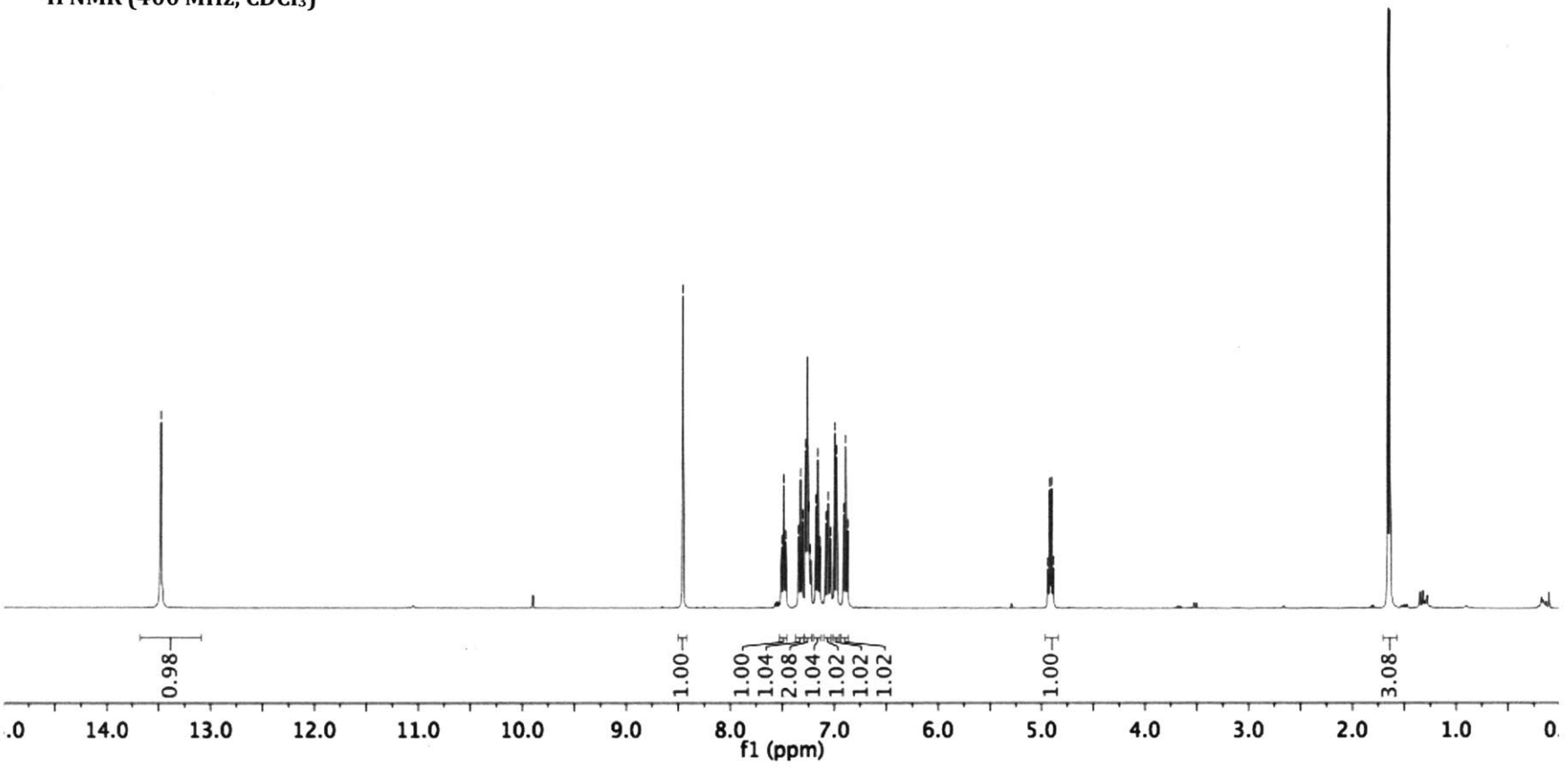

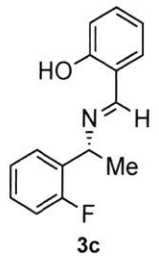

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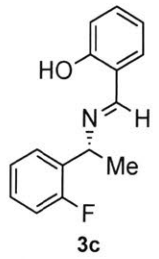
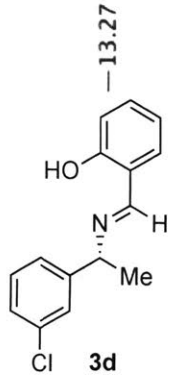


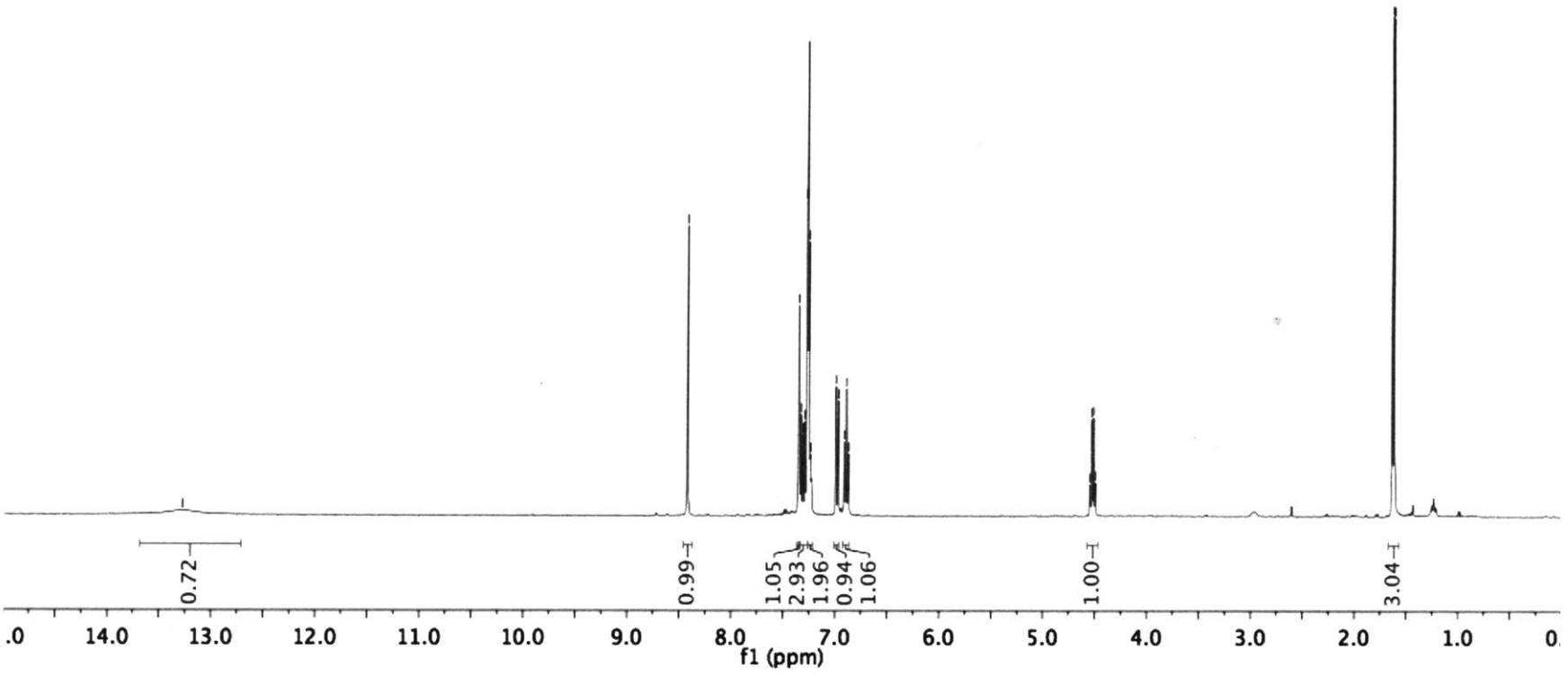
3c

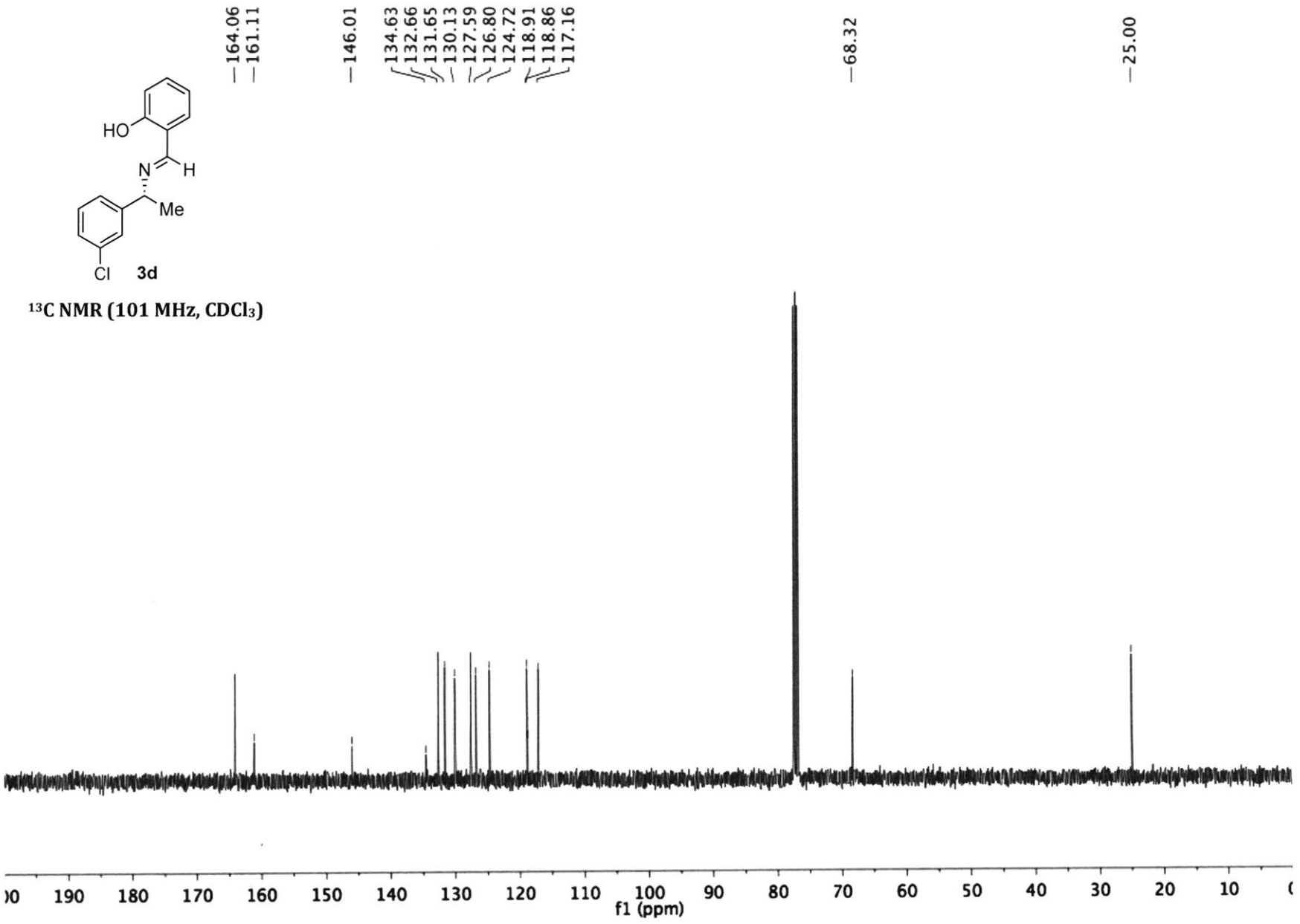
^{19}F NMR (376 MHz, $CDCl_3$)



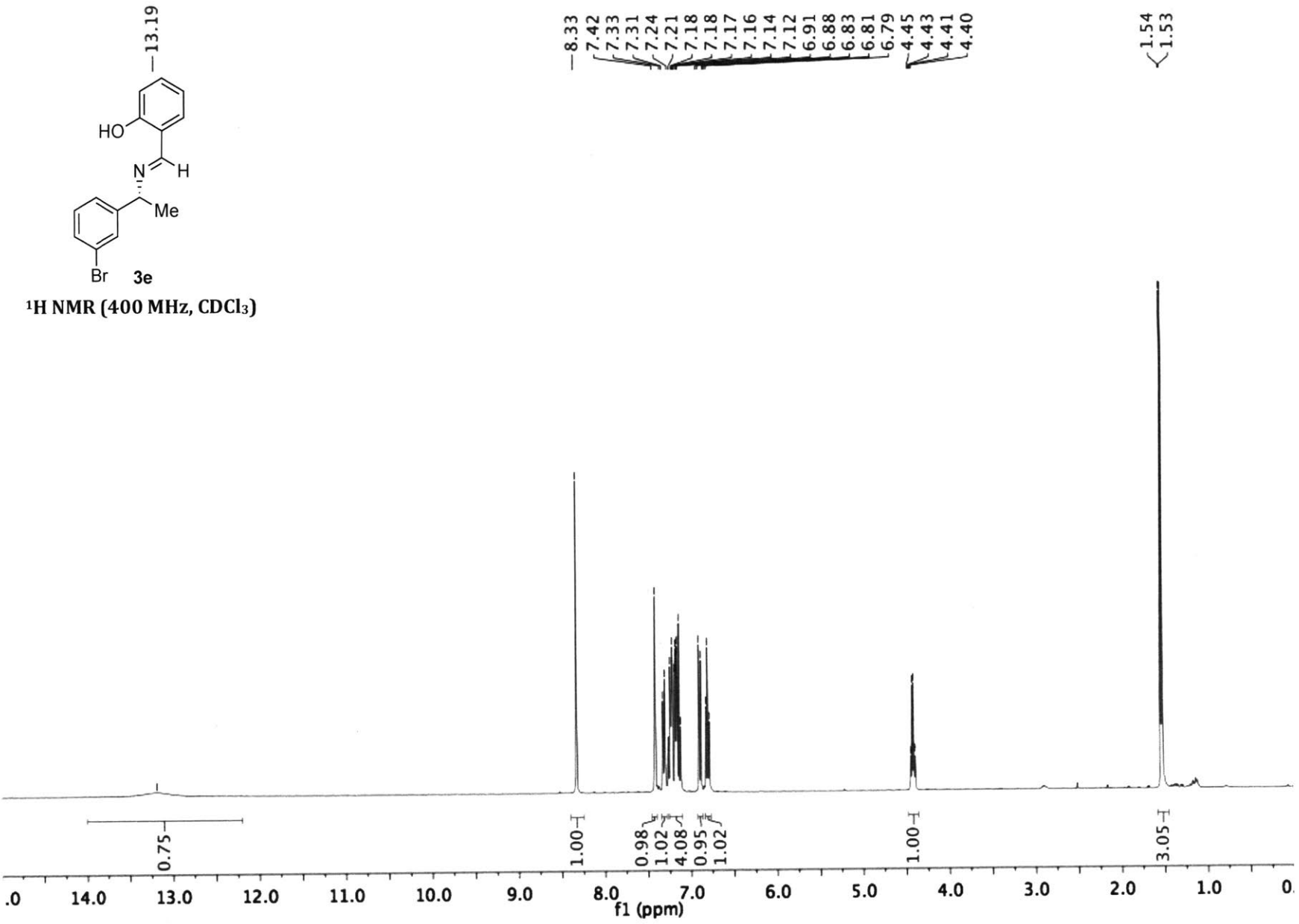
3d

^{1}H NMR (400 MHz, $CDCl_3$)

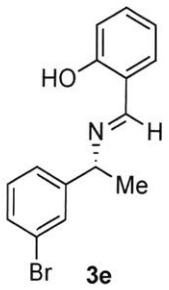




^{13}C NMR (101 MHz, $CDCl_3$)

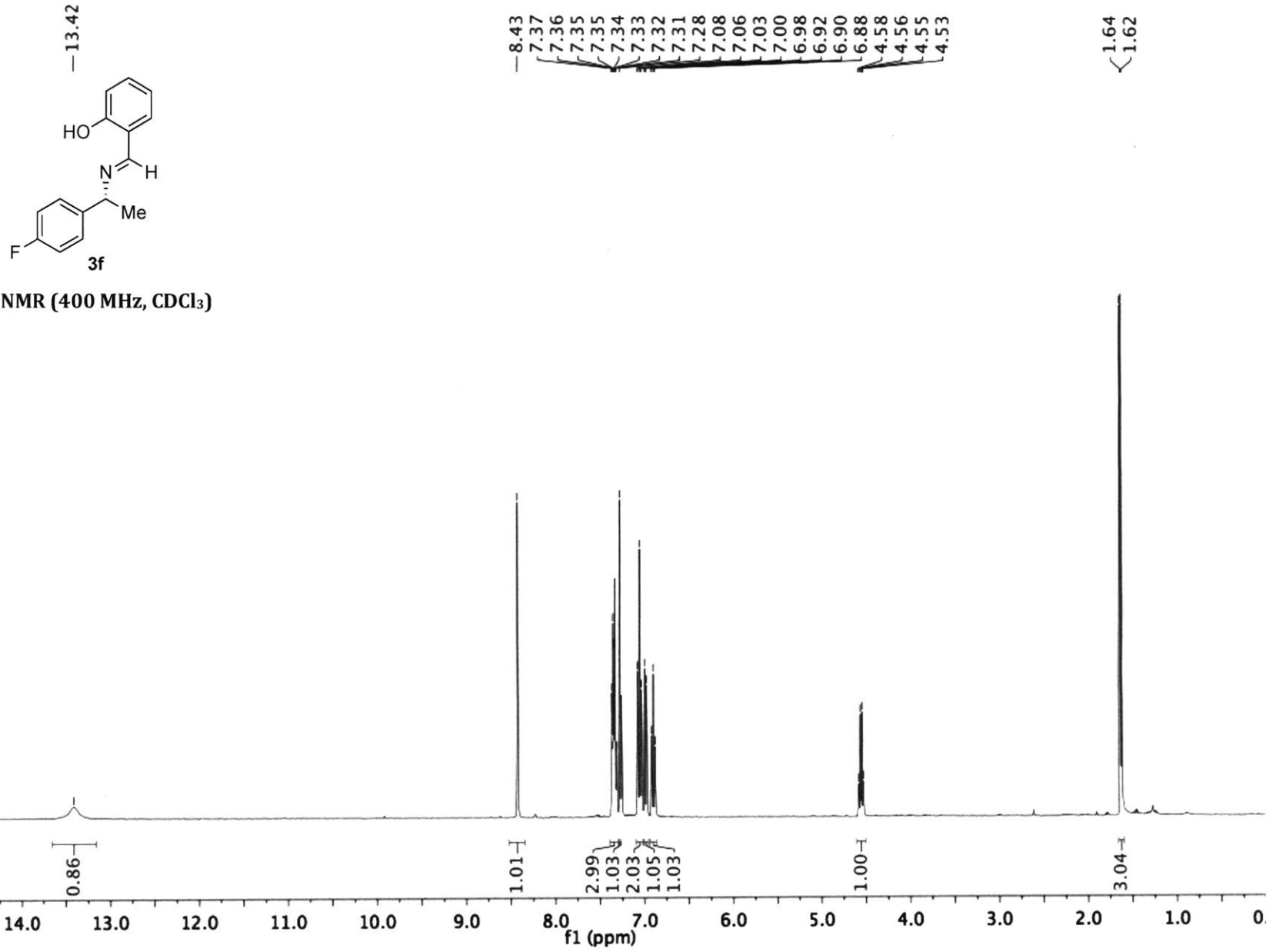


^{1}H NMR (400 MHz, $CDCl_3$)

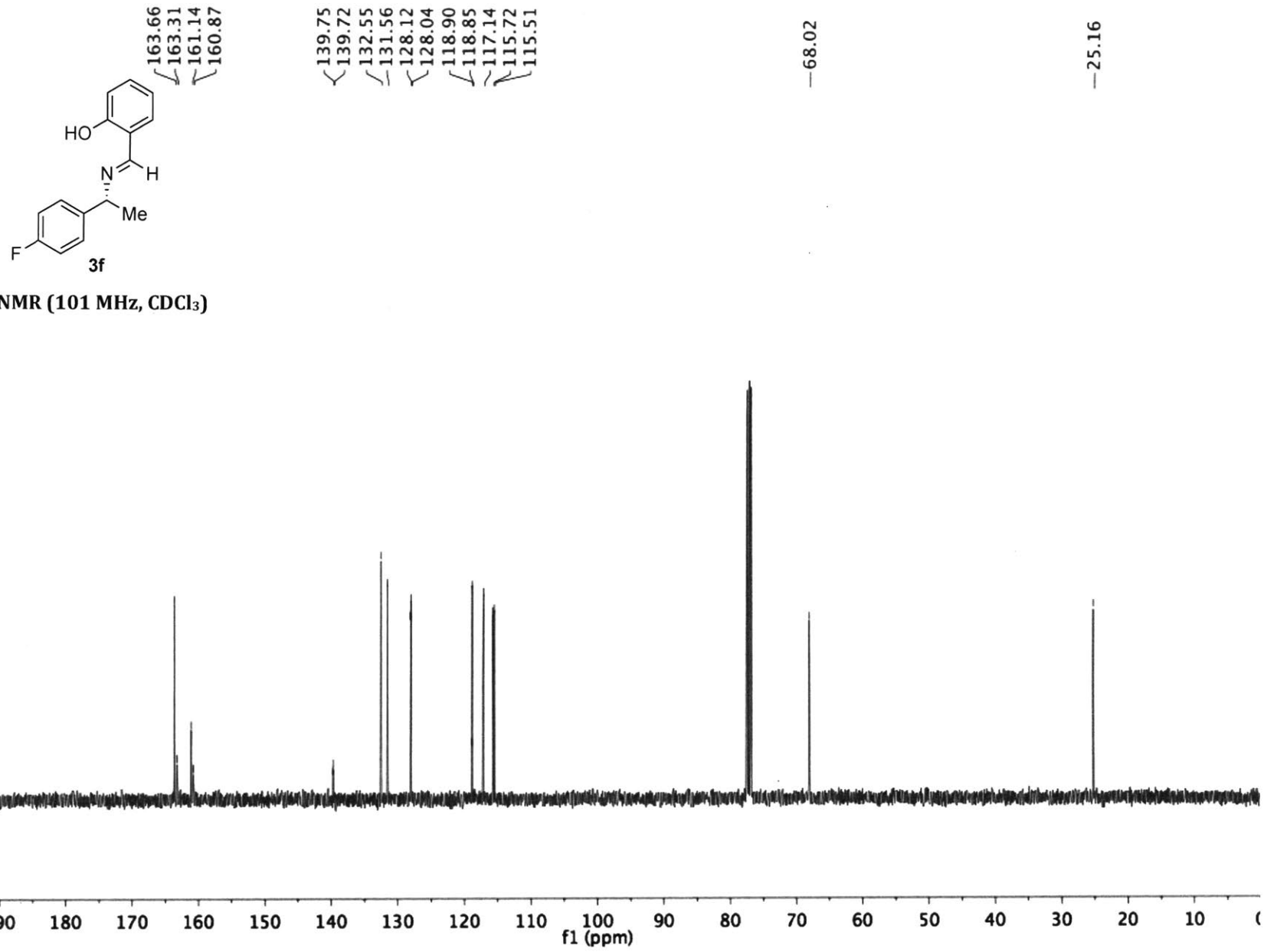


3e

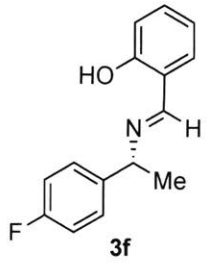
^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)

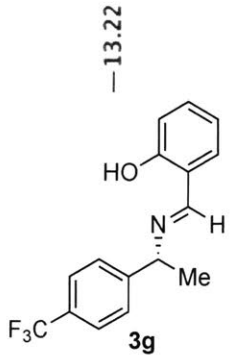


^{13}C NMR (101 MHz, $CDCl_3$)



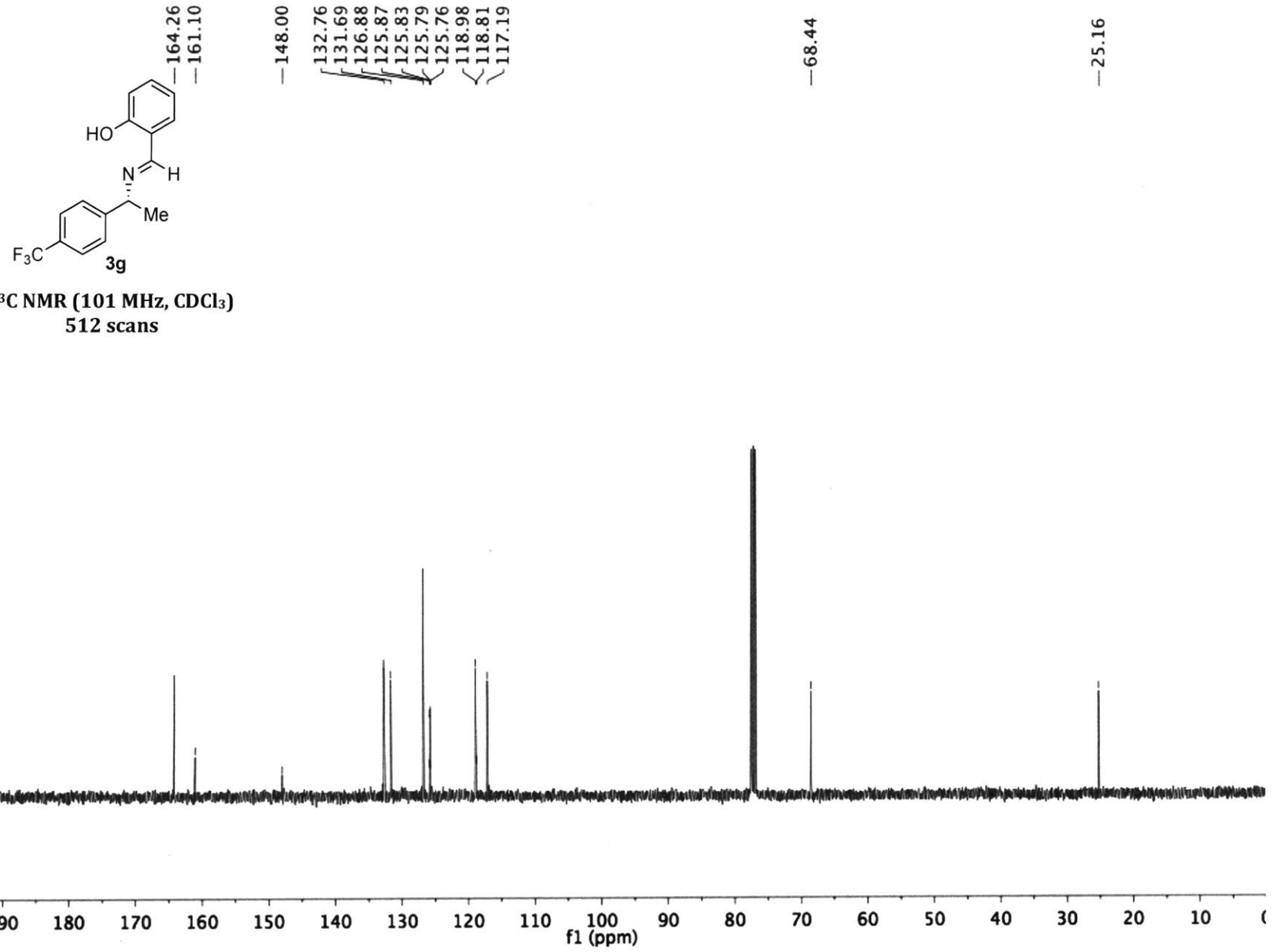
3f

^{19}F NMR (376 MHz, $CDCl_3$)

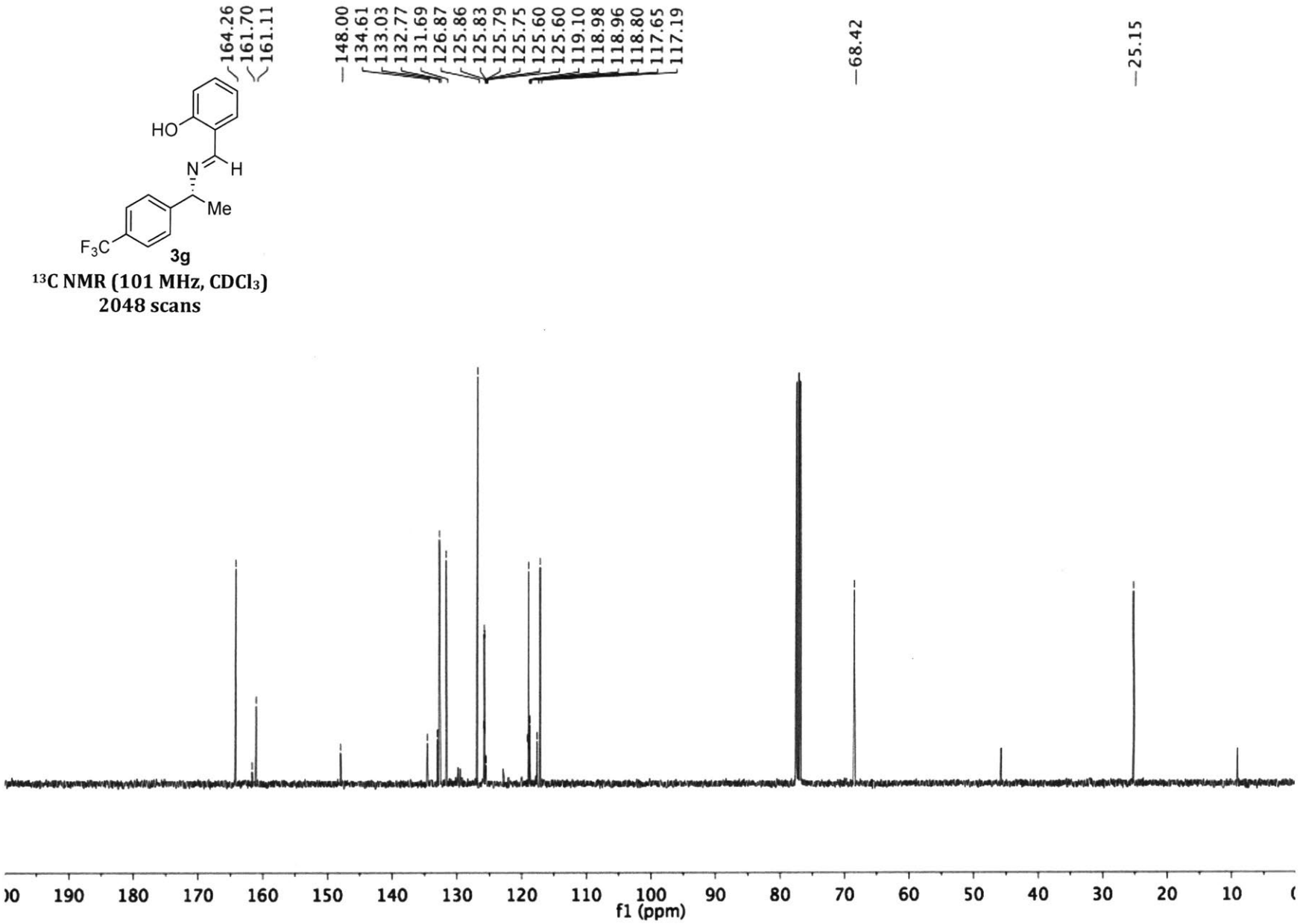


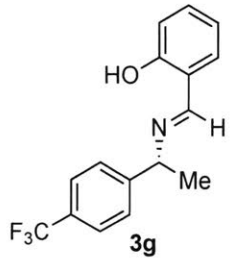
3g

^{1}H NMR (400 MHz, $CDCl_3$)



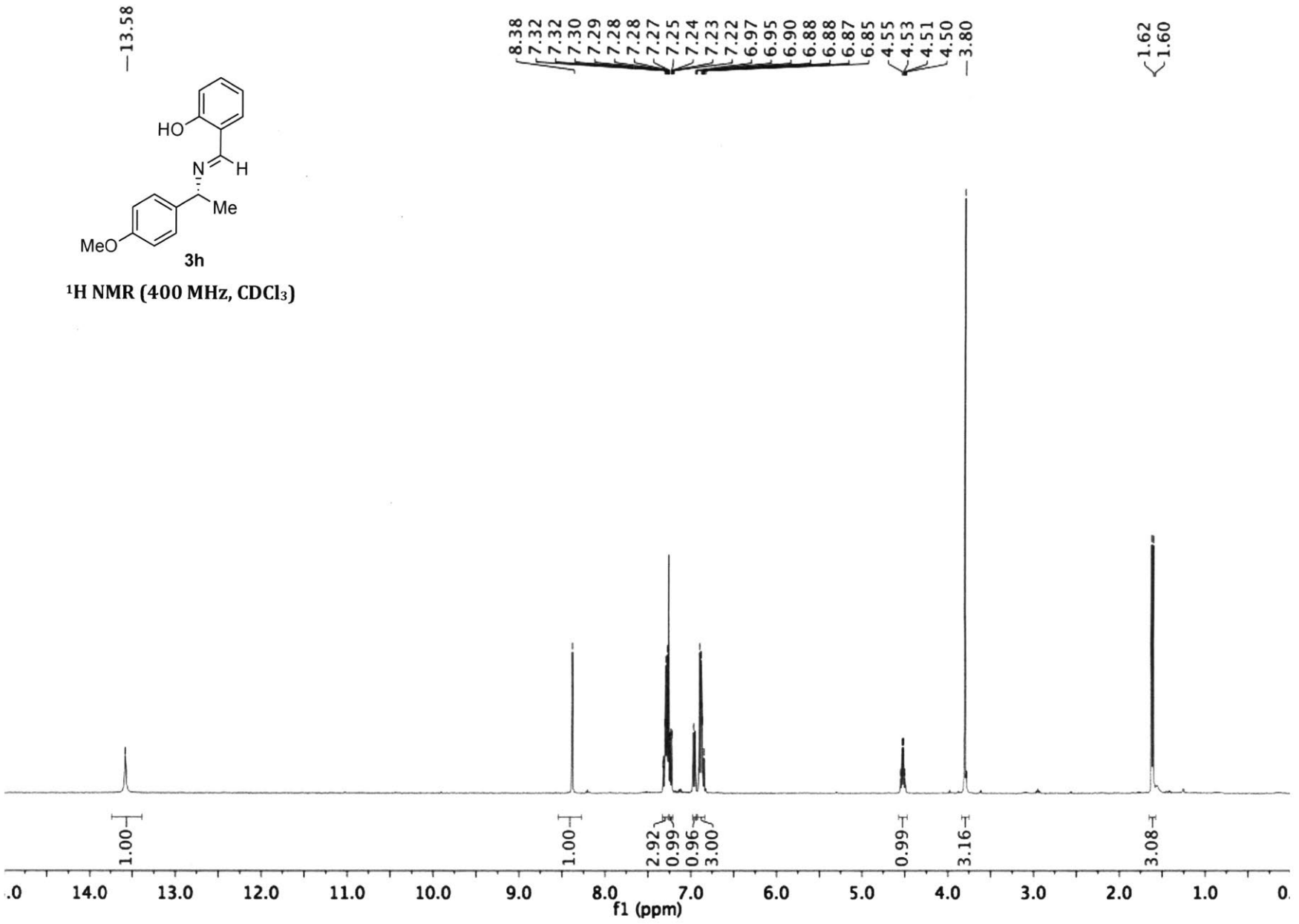
^{13}C NMR (101 MHz, $CDCl_3$)
512 scans


164.26
161.70
161.11
148.00
134.61
133.03
132.77
131.69
126.87
125.86
125.83
125.79
125.75
125.60
125.60
119.10
118.98
118.96
118.80
117.65
117.19
68.42
25.15
HO
N
H
Me
F3C
3g
13C NMR (101 MHz, CDCl3)
2048 scans
f1 (ppm)

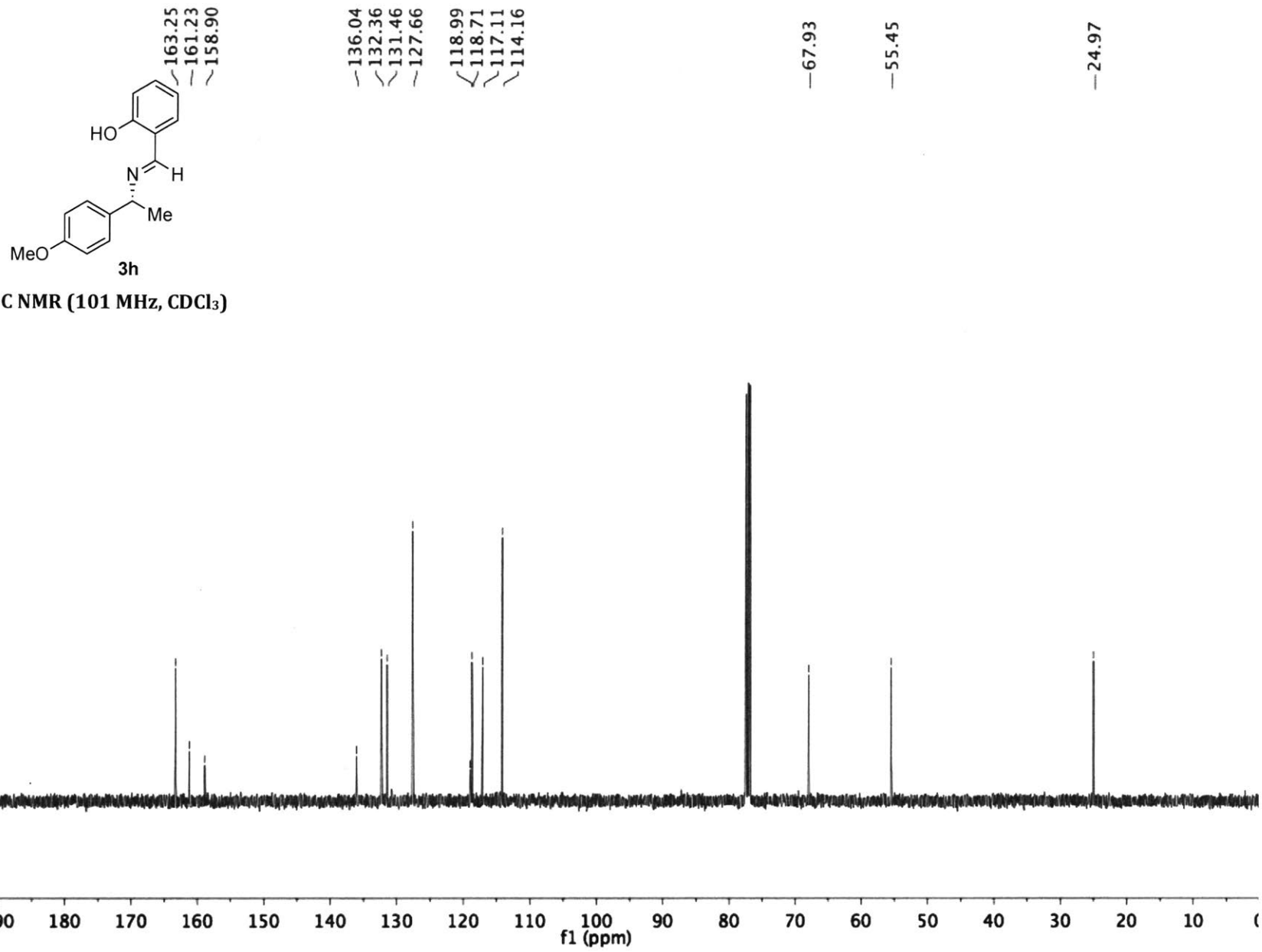


3g

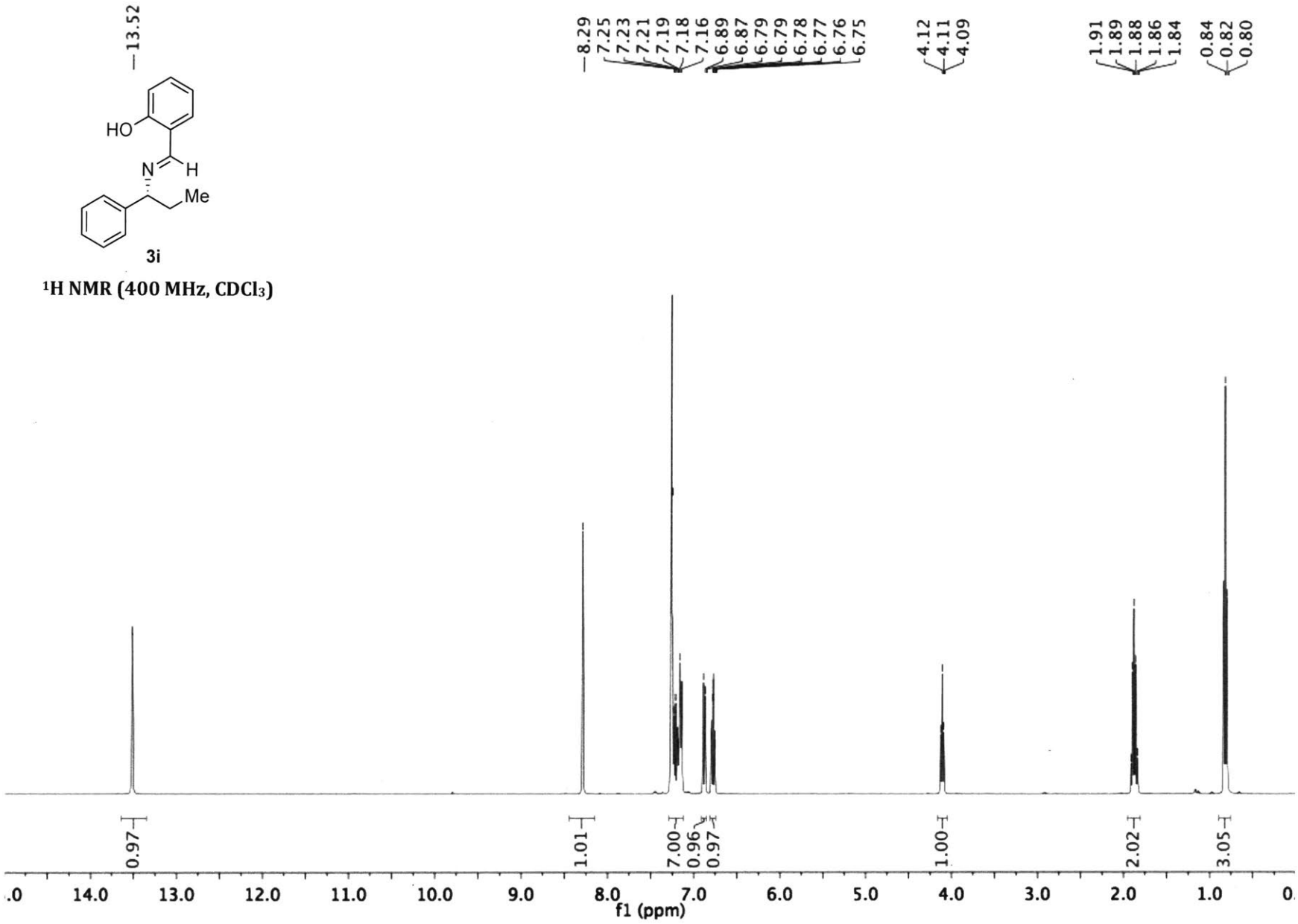
^{19}F NMR (376 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)

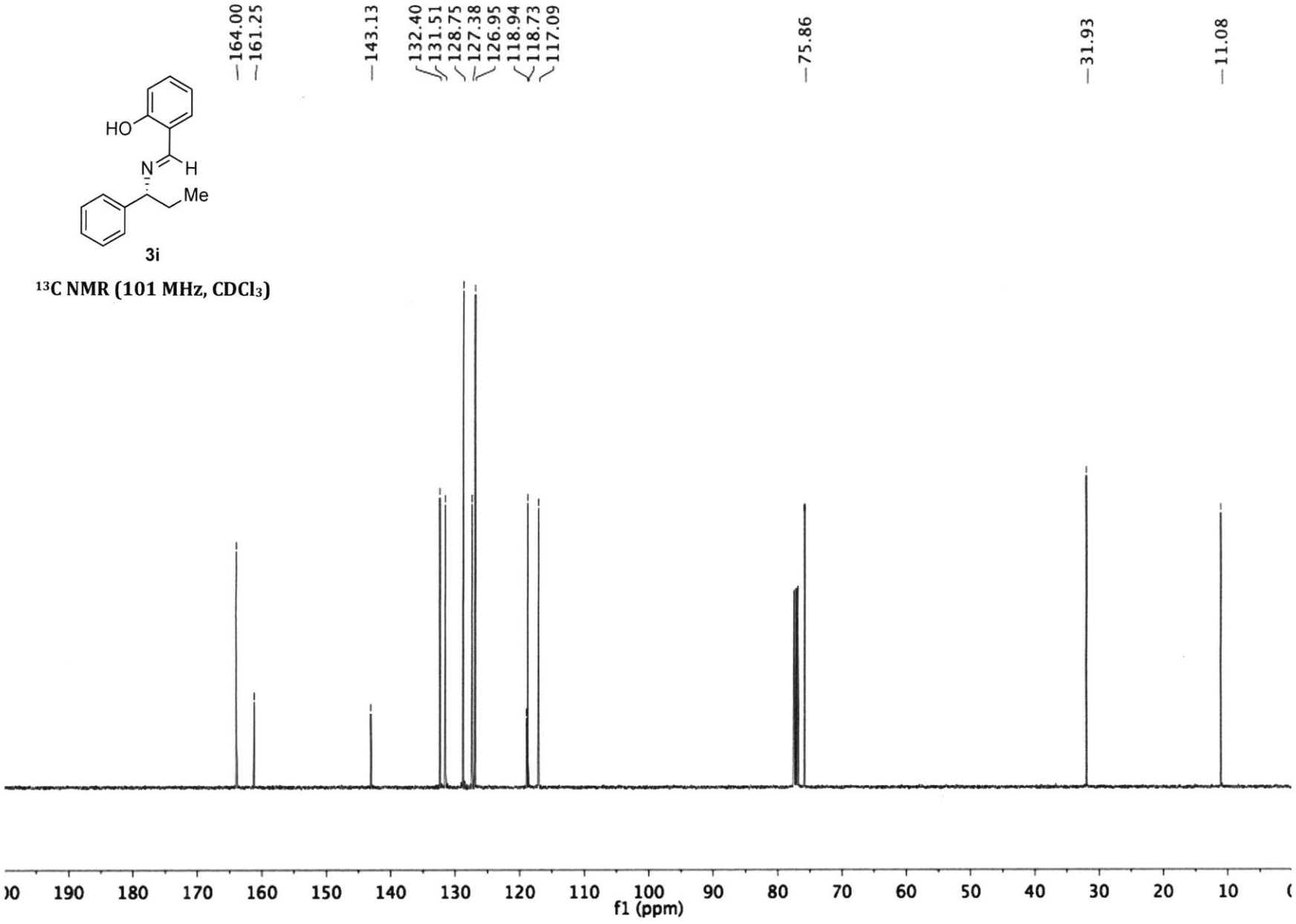


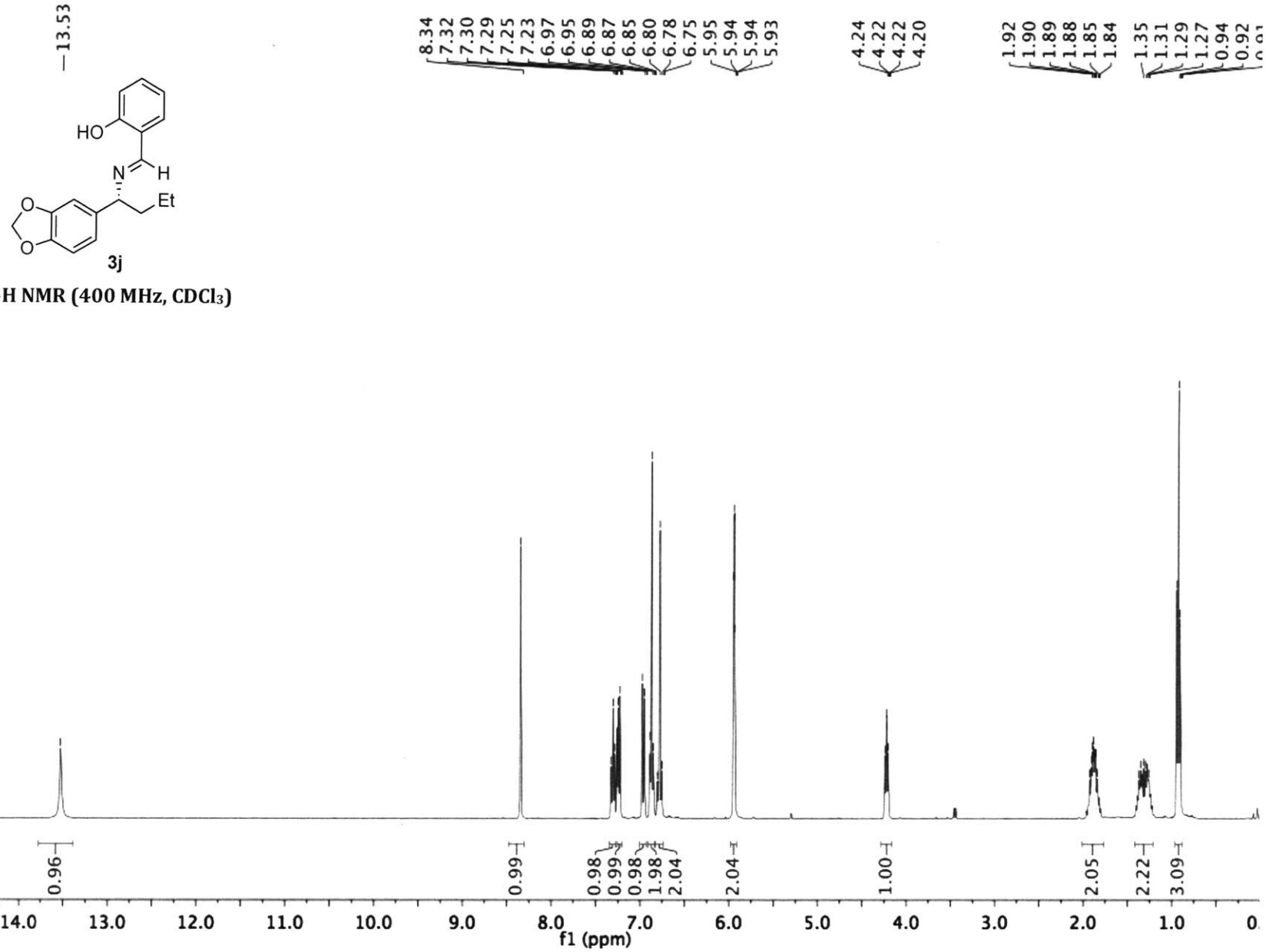
^{13}C NMR (101 MHz, $CDCl_3$)



3i

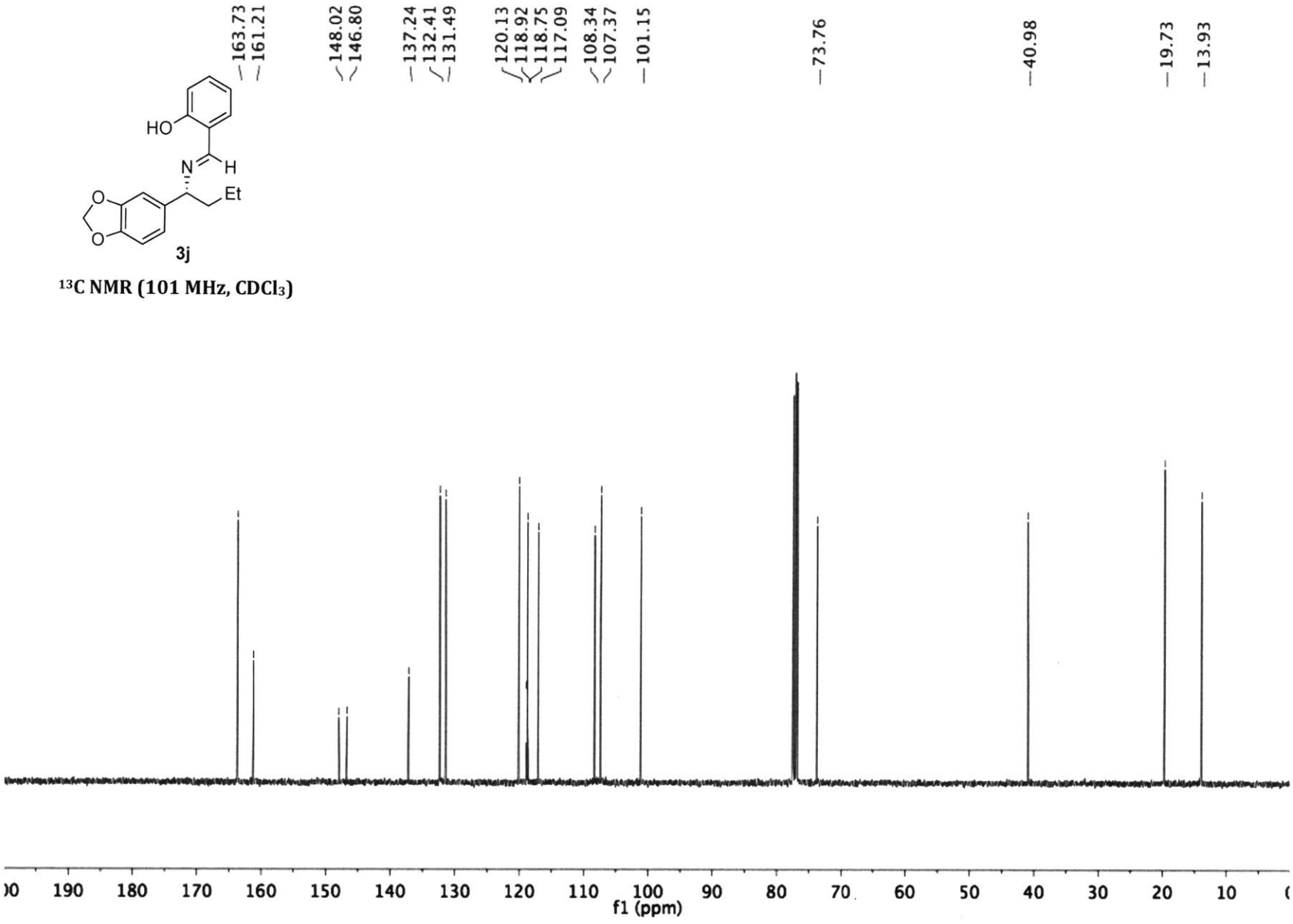
^{1}H NMR (400 MHz, $CDCl_3$)


164.00
161.25
143.13
132.40
131.51
128.75
127.38
126.95
118.94
118.73
117.09
75.86
31.93
11.08
HO
N
H
Me
3i
13C NMR (101 MHz, CDCl3)
f1 (ppm)

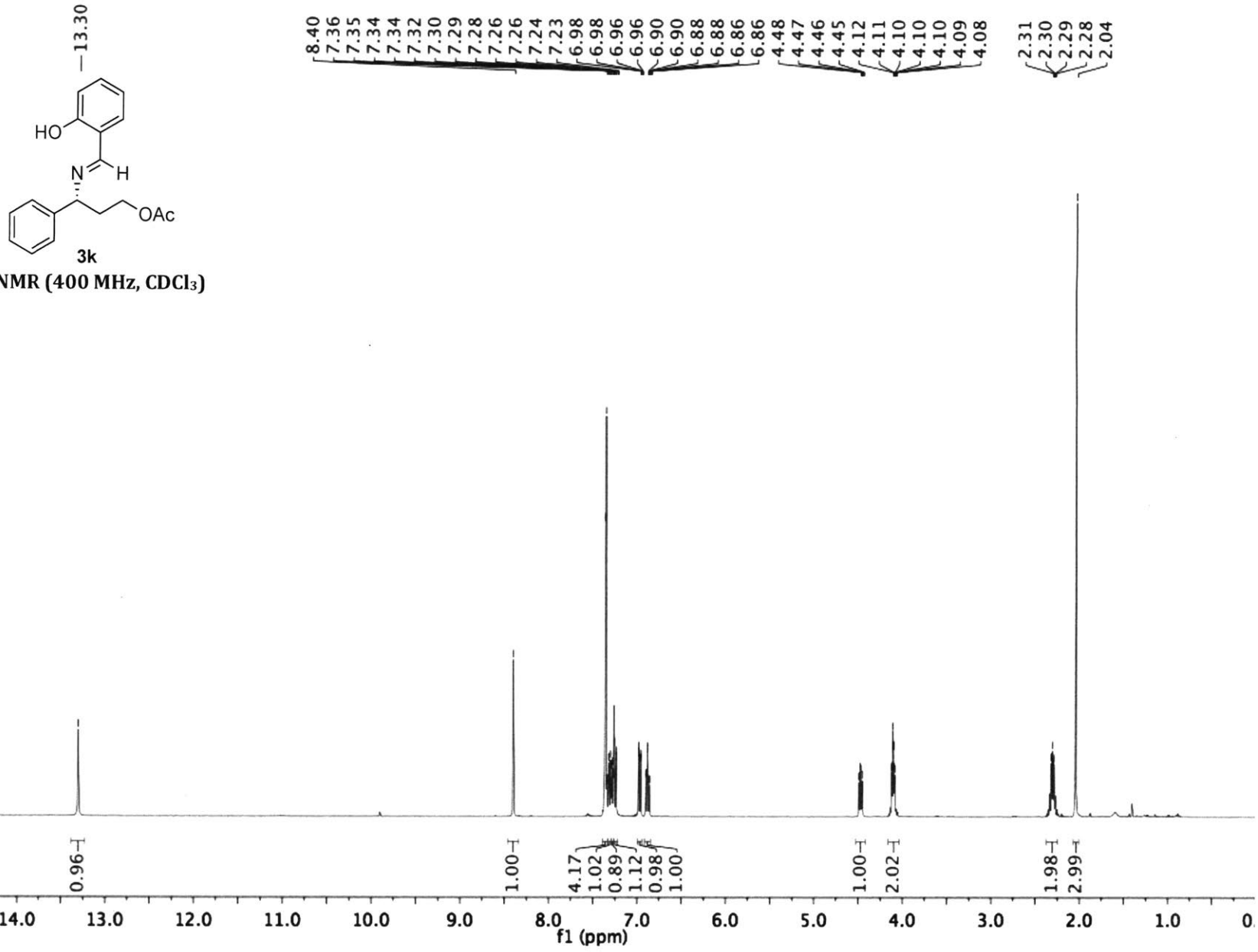


3j

^{1}H NMR (400 MHz, $CDCl_3$)

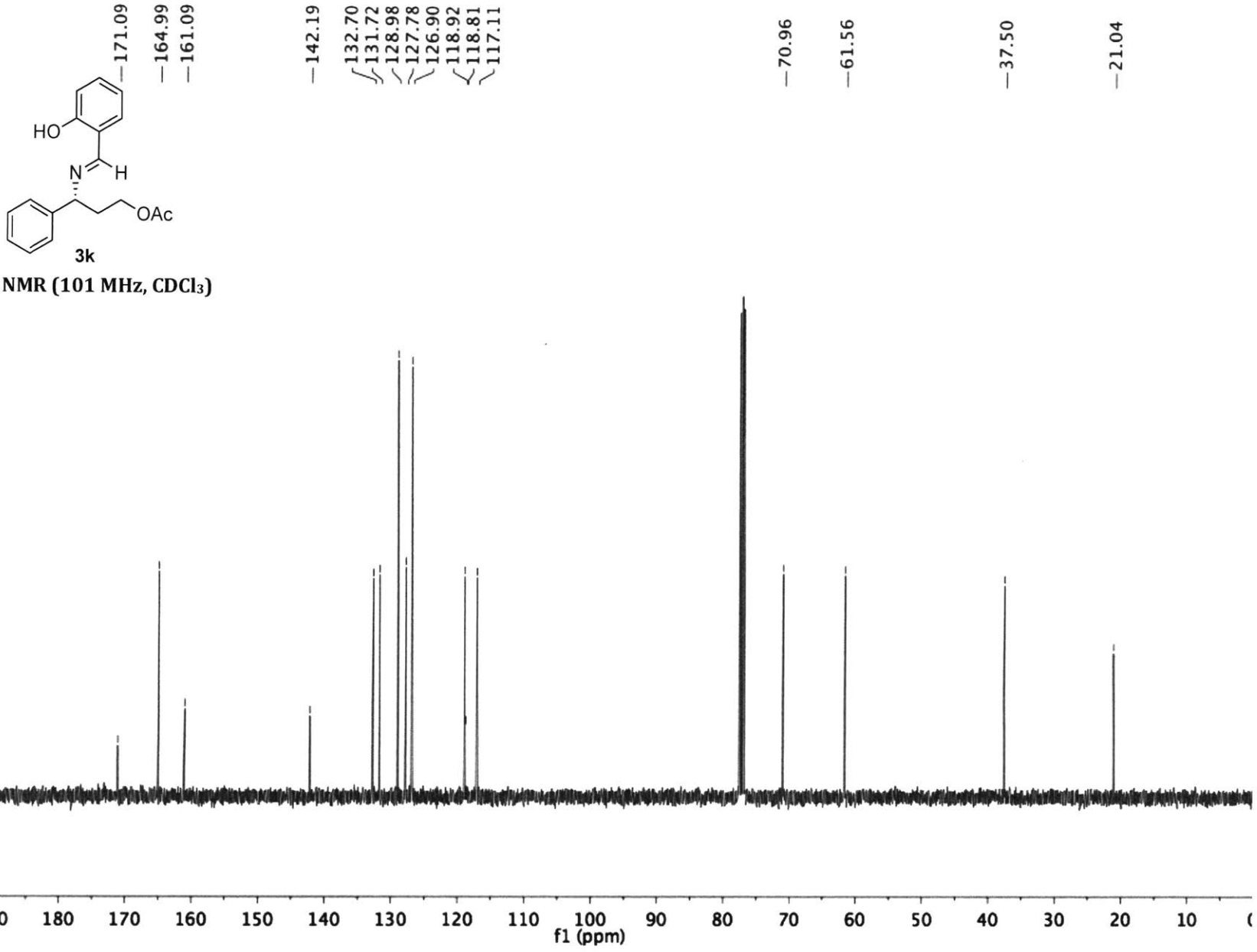


^{13}C NMR (101 MHz, $CDCl_3$)

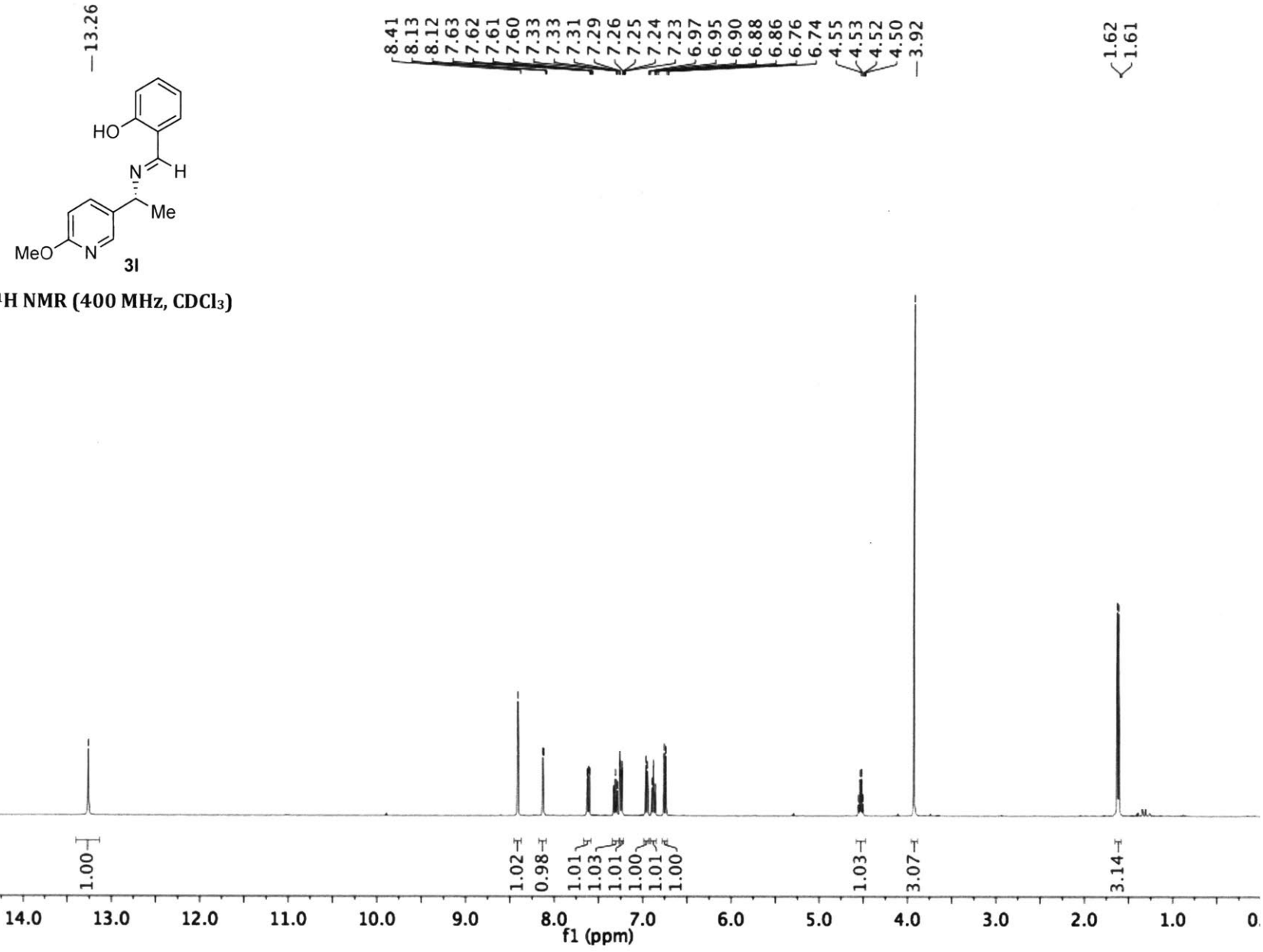


3k

^{1}H NMR (400 MHz, $CDCl_3$)

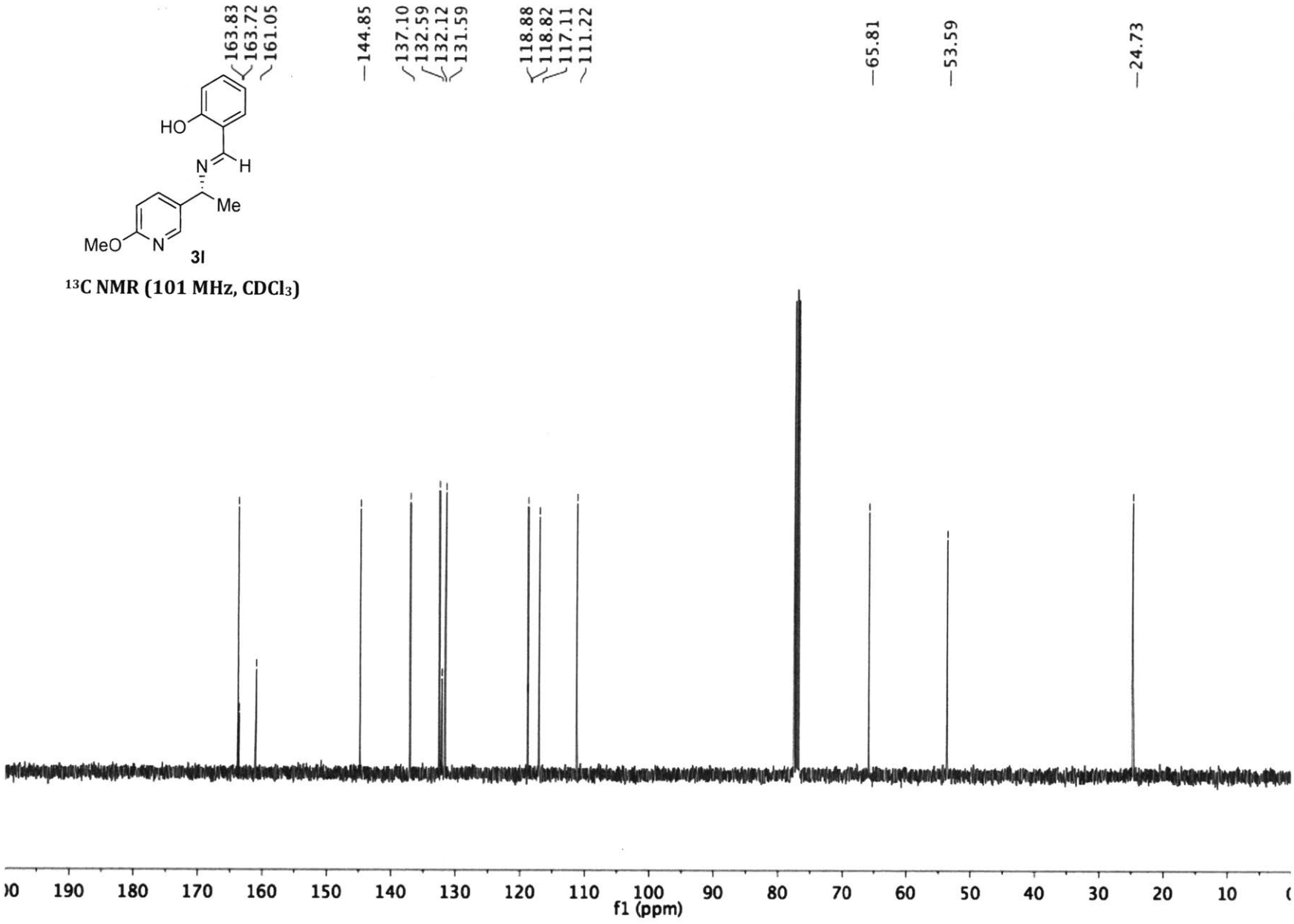


^{13}C NMR (101 MHz, $CDCl_3$)



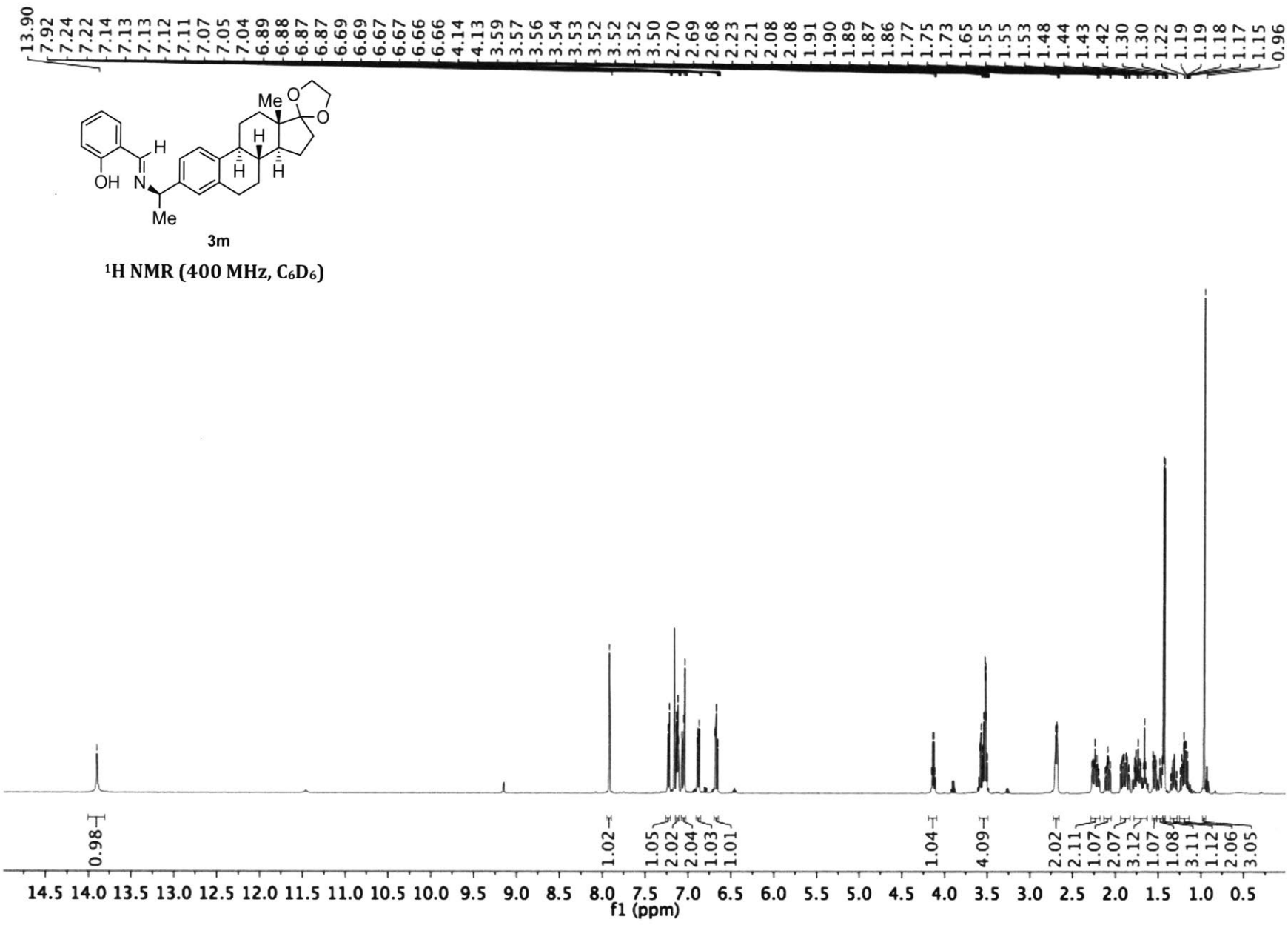
3l

^{1}H NMR (400 MHz, $CDCl_3$)



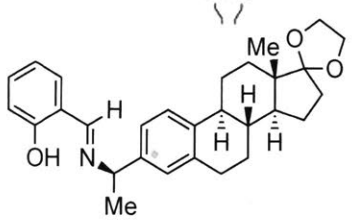
3l

^{13}C NMR (101 MHz, $CDCl_3$)



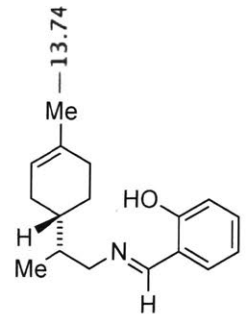
3m

^{1}H NMR (400 MHz, C_6D_6)



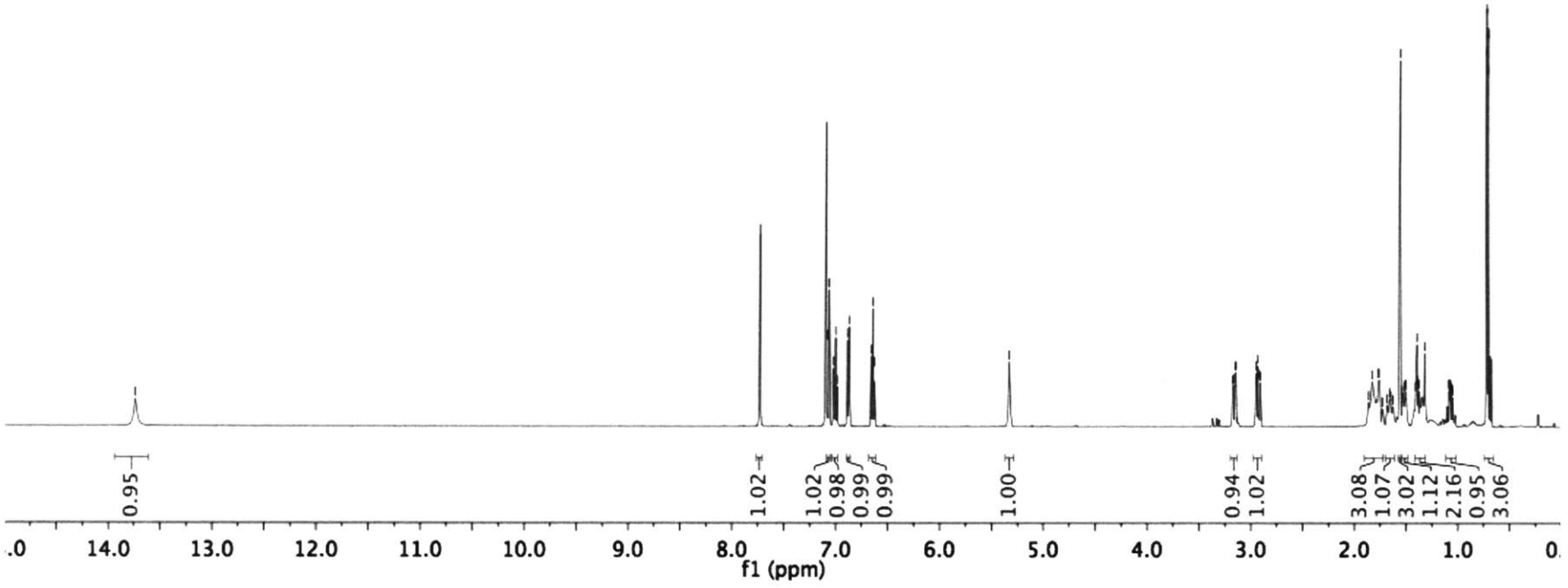
3m

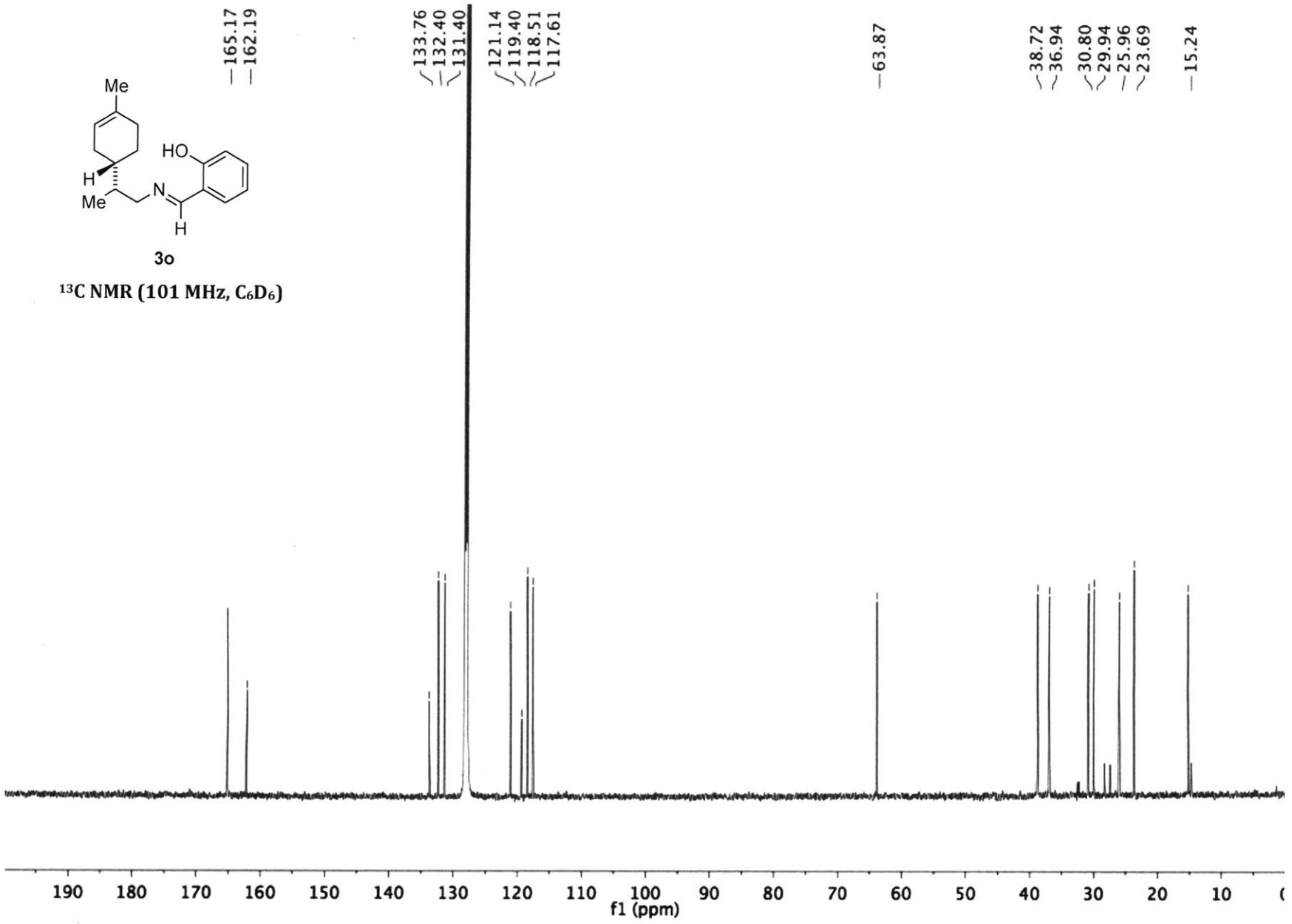
^{13}C NMR (101 MHz, C_6D_6)



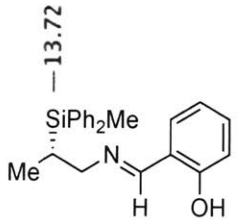
3o

^{1}H NMR (400 MHz, C_6D_6)



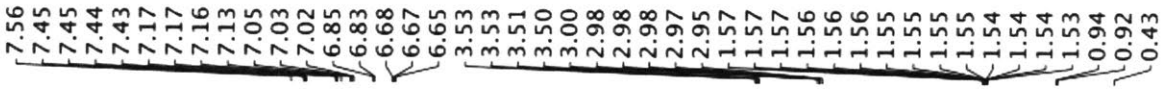


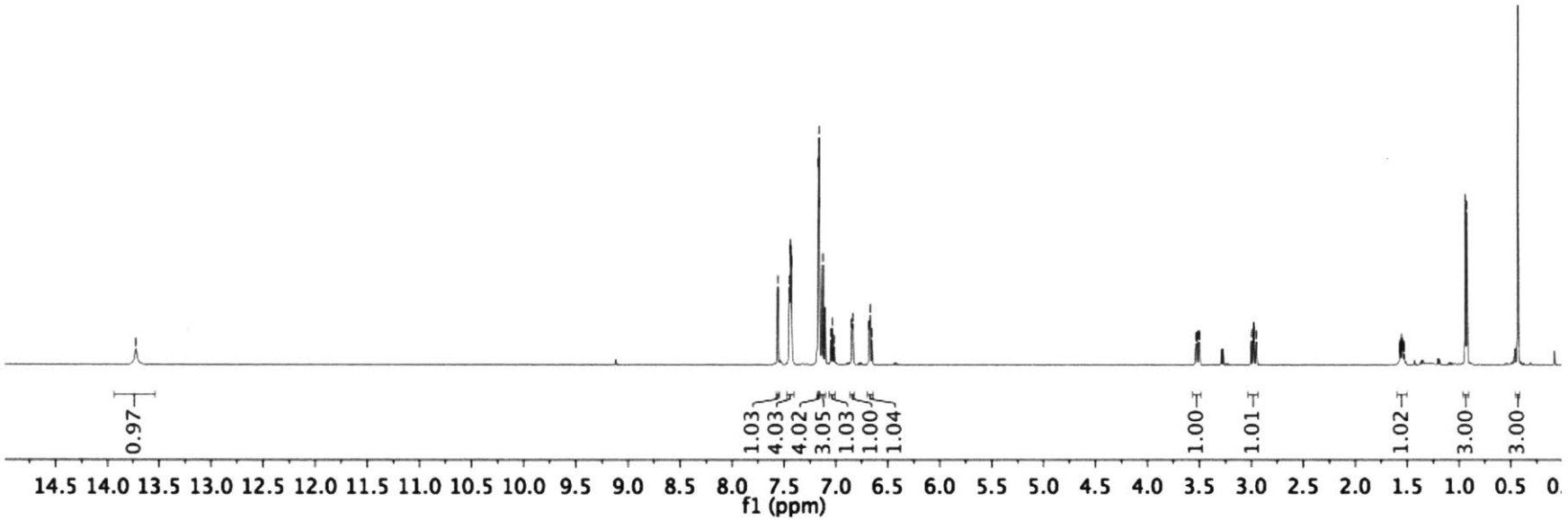
^{13}C NMR (101 MHz, C_6D_6)

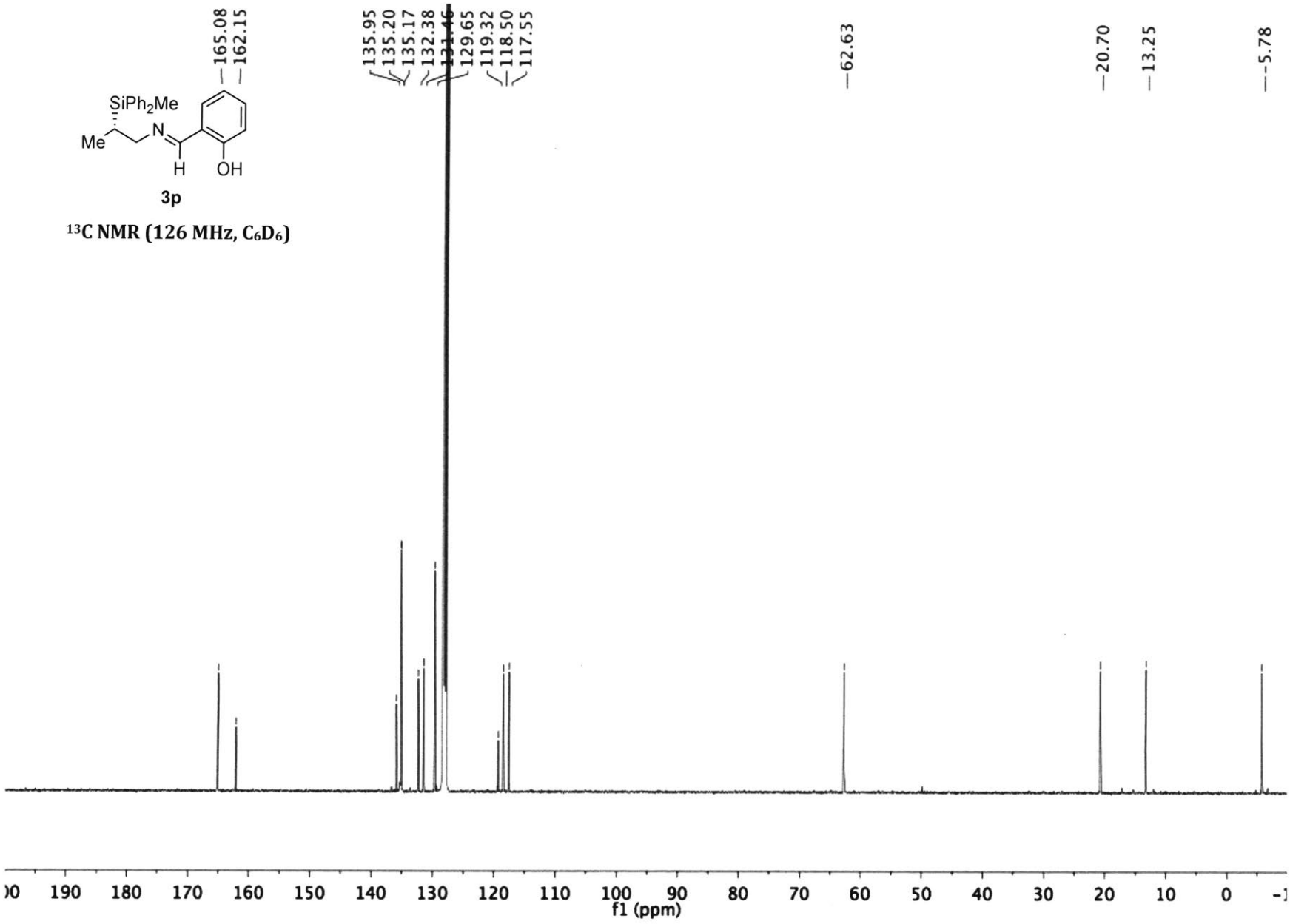


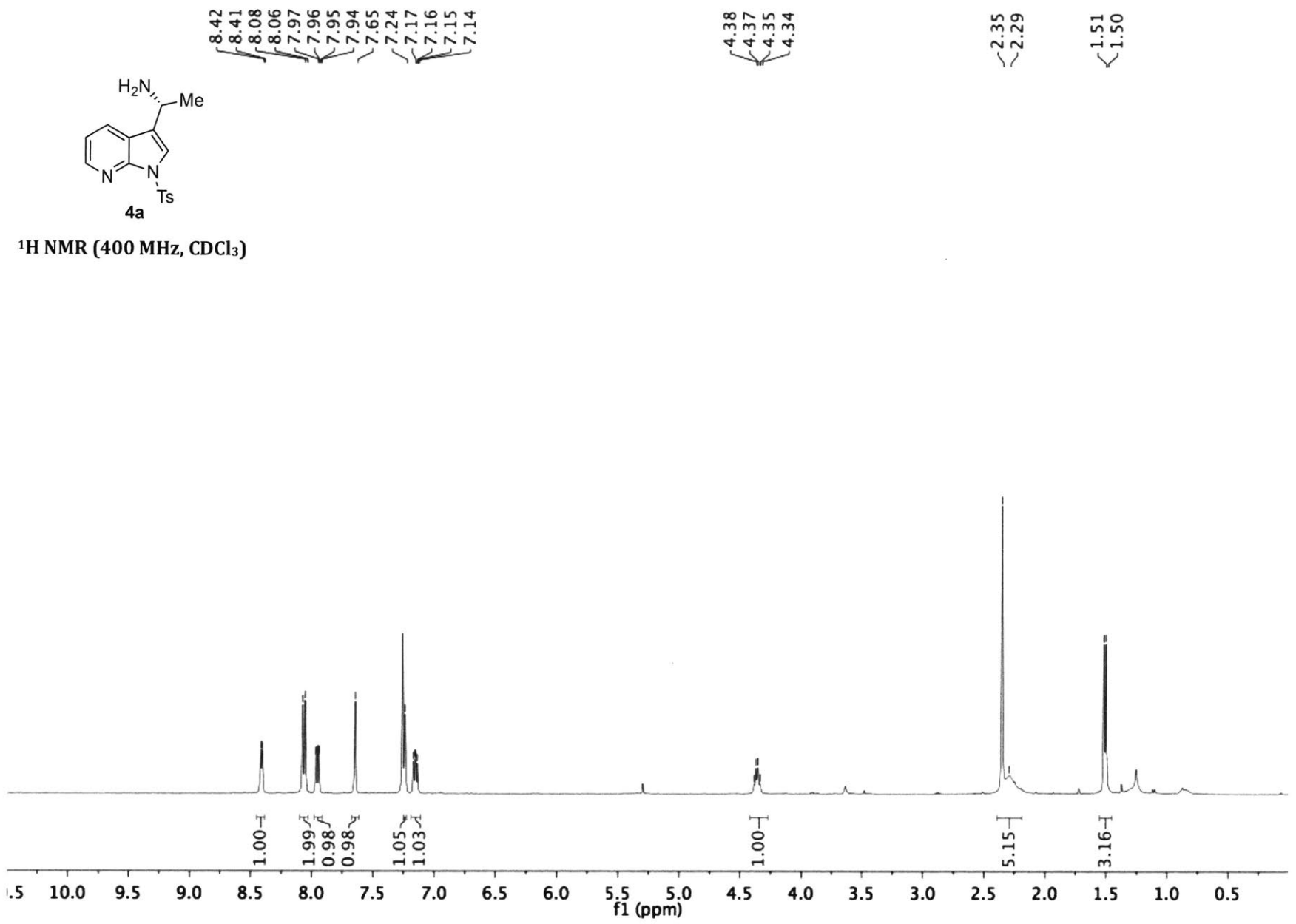
3p

^{1}H NMR (500 MHz, C_6D_6)

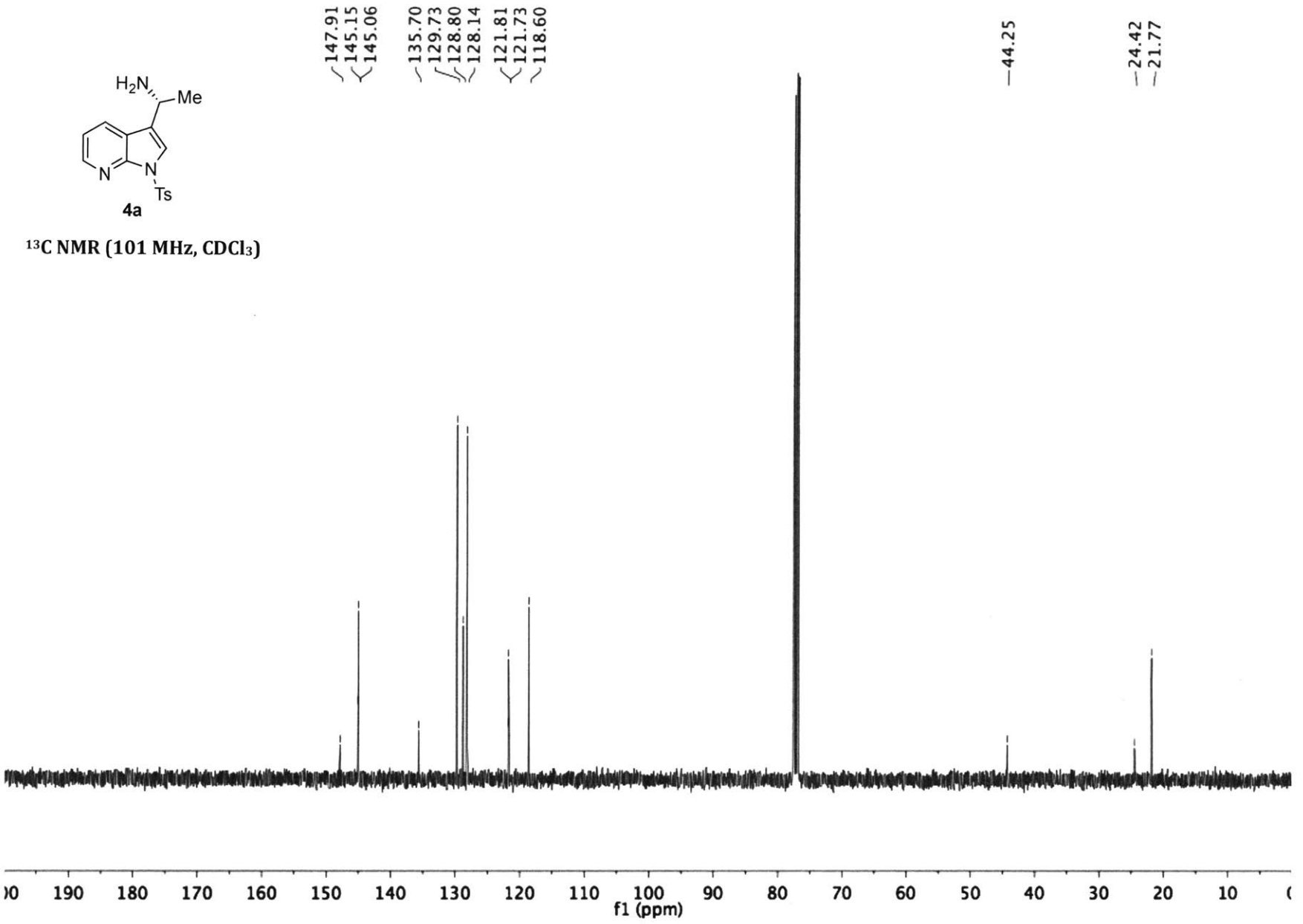


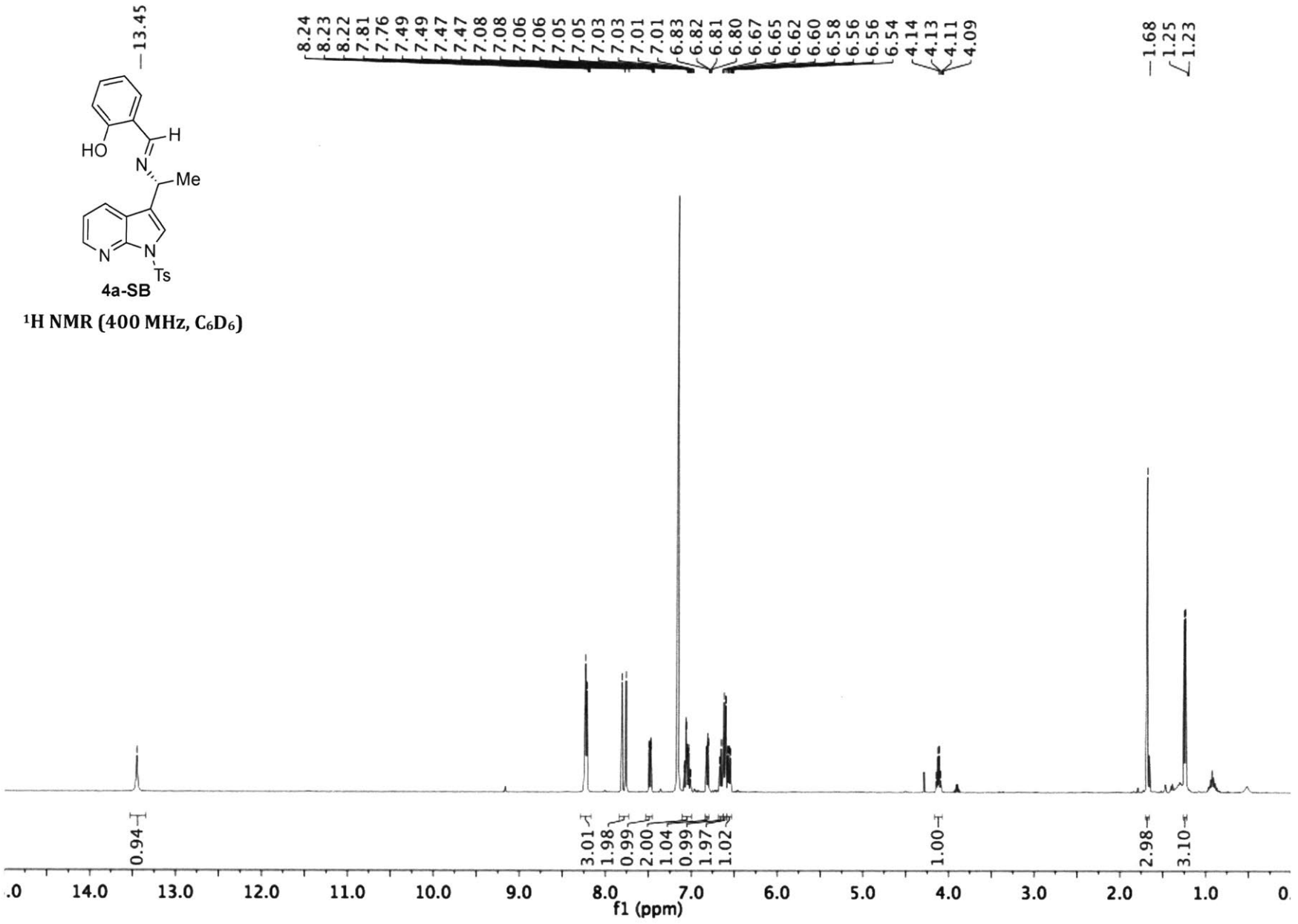



SiPh2Me
Me
N
H
OH
3p
13C NMR (126 MHz, C6D6)
165.08
162.15
135.95
135.20
135.17
132.38
131.46
129.65
119.32
118.50
117.55
62.63
20.70
13.25
-5.78
f1 (ppm)



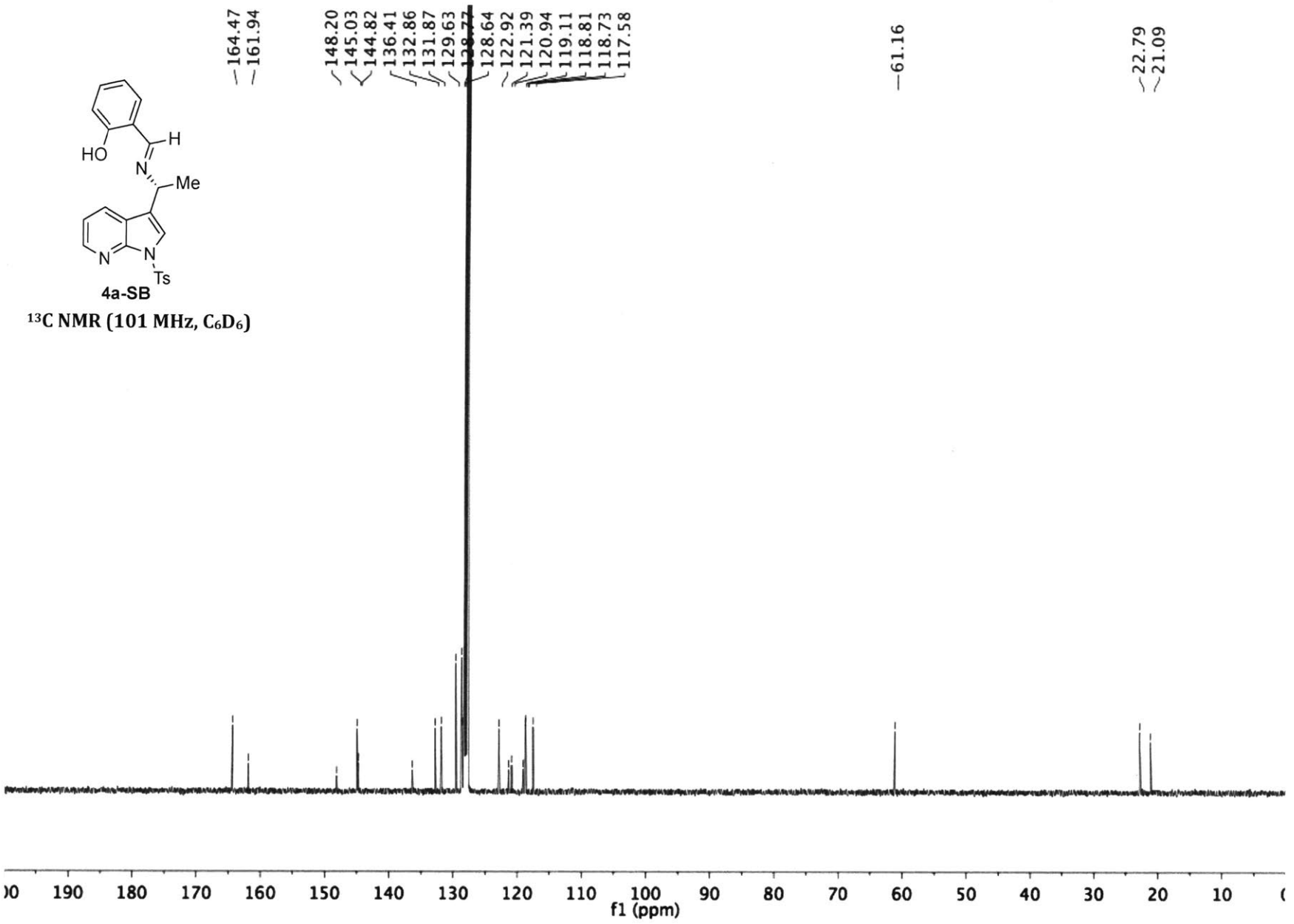
^{1}H NMR (400 MHz, $CDCl_3$)

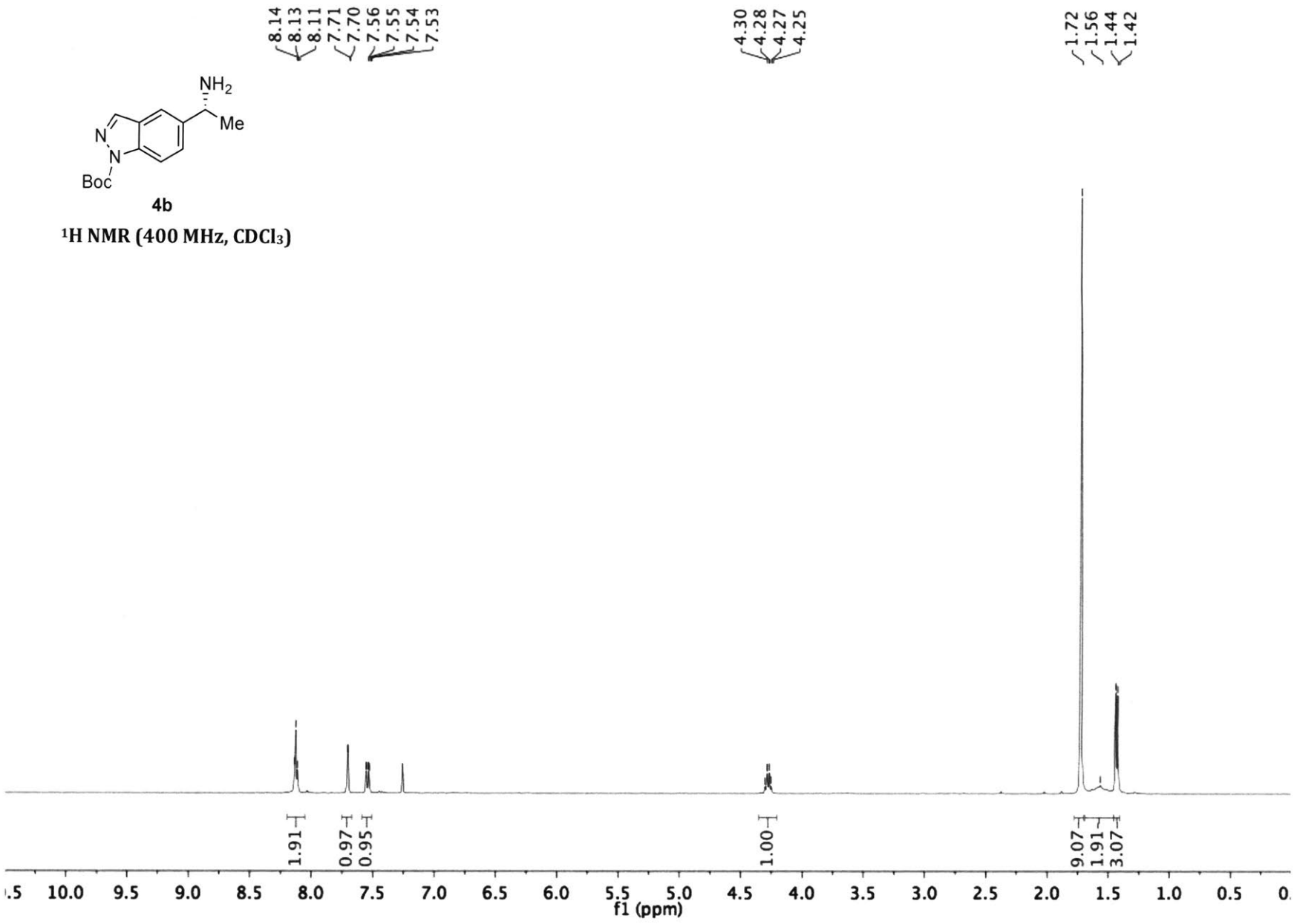

147.91
145.15
145.06
135.70
129.73
128.80
128.14
121.81
121.73
118.60
44.25
24.42
21.77
H2N
Me
N
N
Ts
4a
13C NMR (101 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



4a-SB

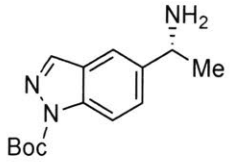
^{1}H NMR (400 MHz, C_6D_6)


164.47
161.94
148.20
145.03
144.82
136.41
132.86
131.87
129.63
128.64
122.92
121.39
120.94
119.11
118.81
118.73
117.58
61.16
22.79
21.09
HO
H
N
Me
N
N
Ts
4a-SB
13C NMR (101 MHz, C6D6)
f1 (ppm)



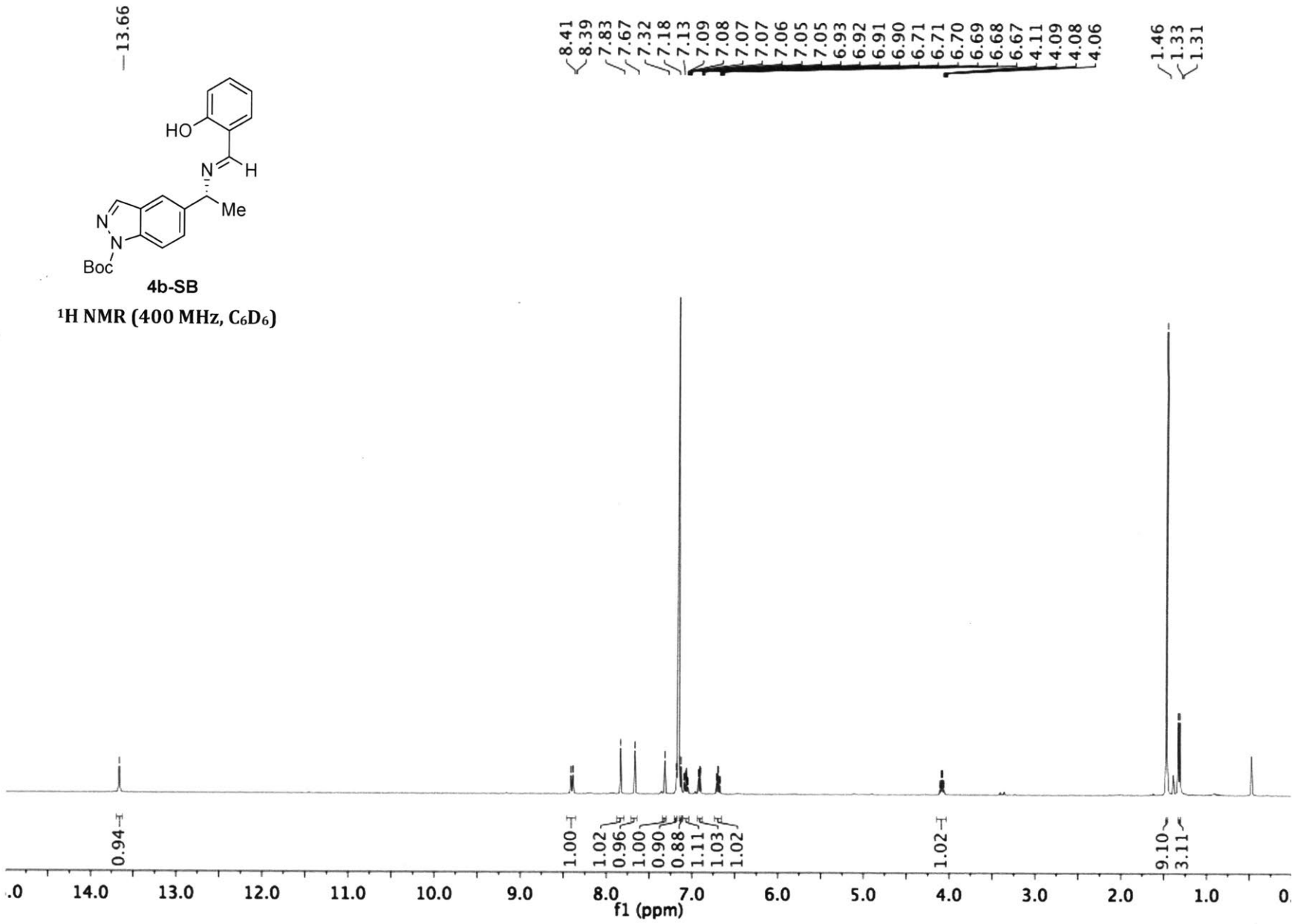
4b

^{1}H NMR (400 MHz, $CDCl_3$)



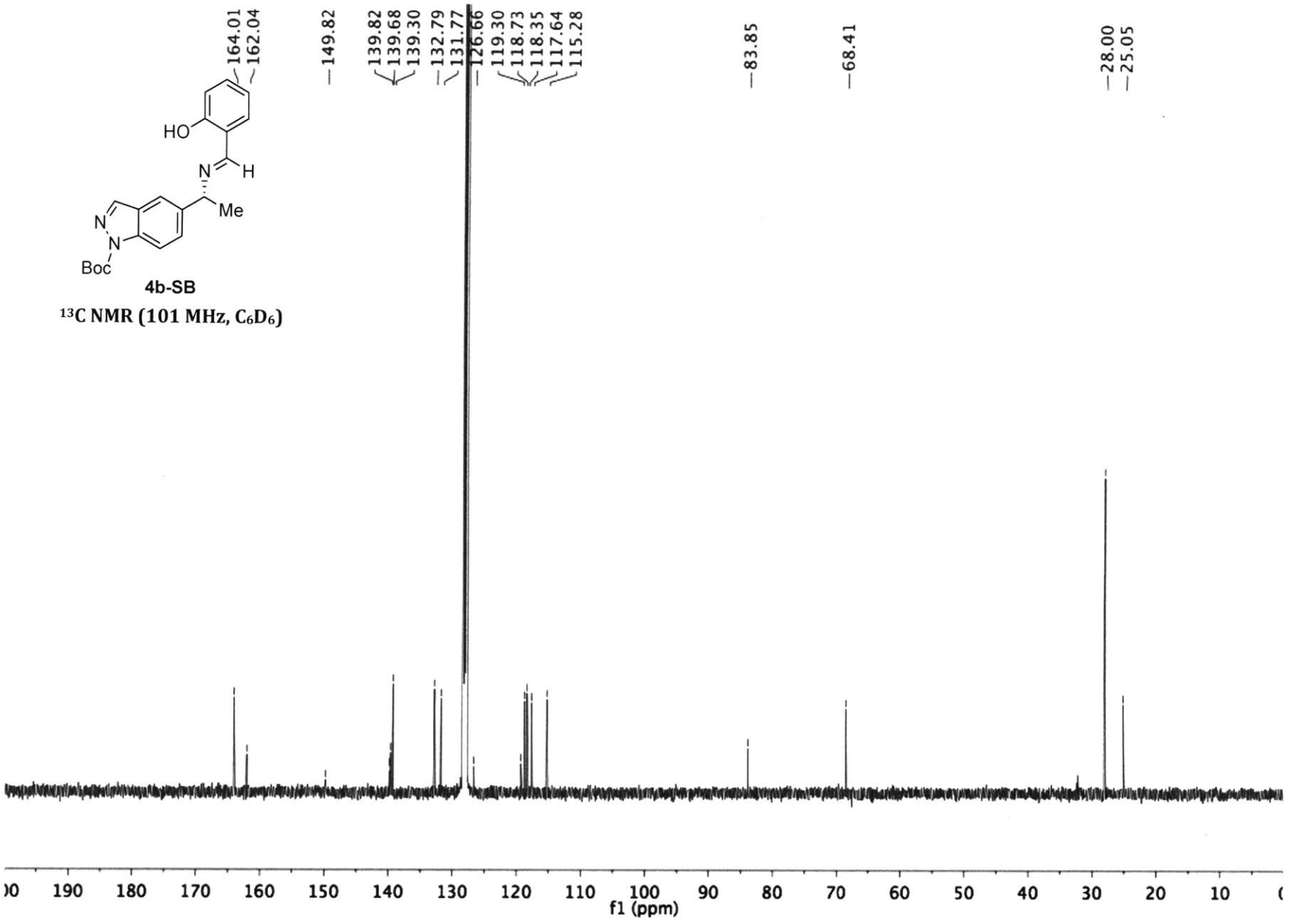
4b

^{13}C NMR (101 MHz, $CDCl_3$)



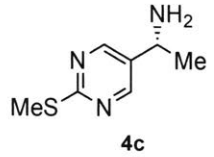
4b-SB

^{1}H NMR (400 MHz, C_6D_6)



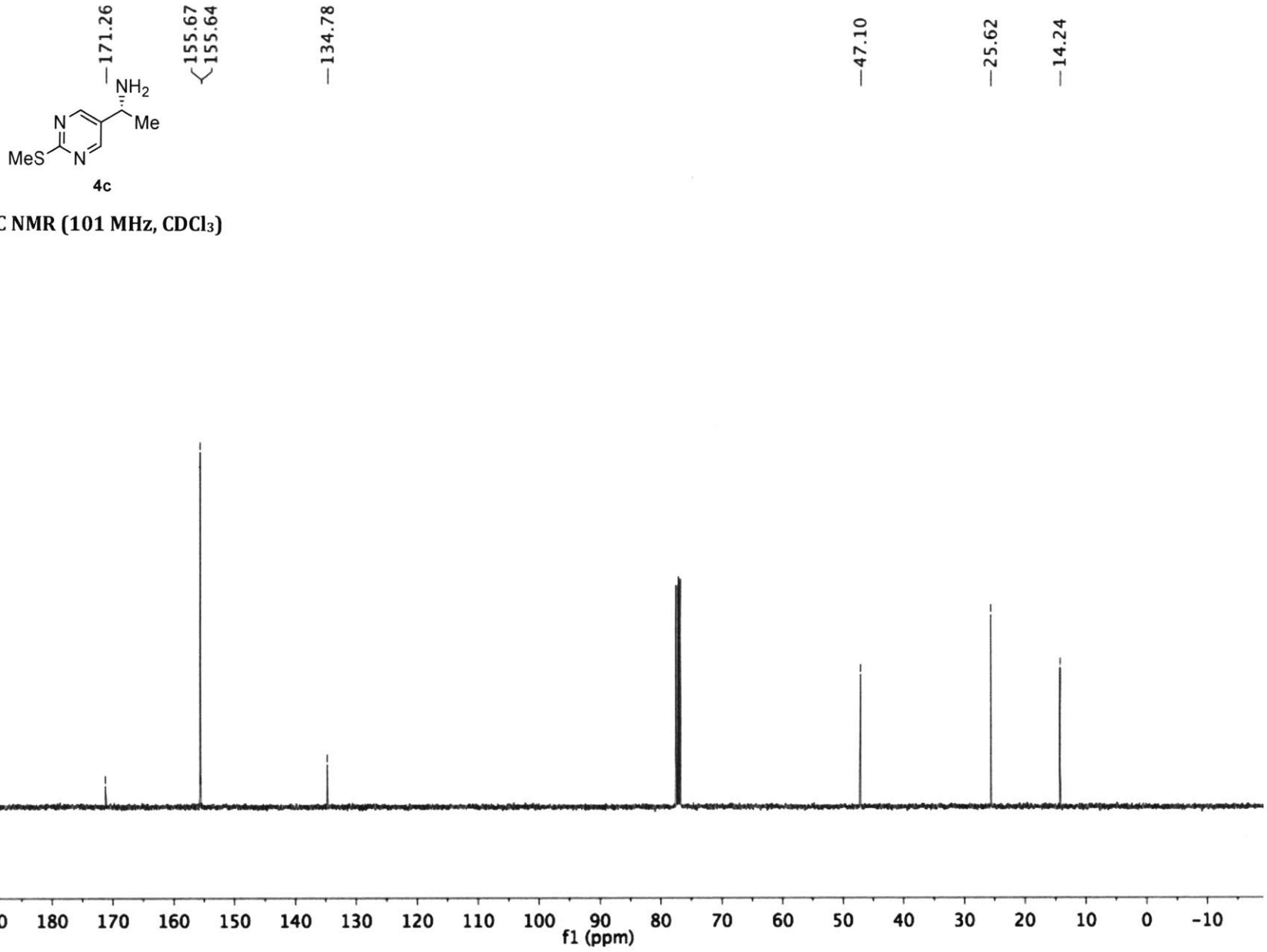
4b-SB

^{13}C NMR (101 MHz, C_6D_6)

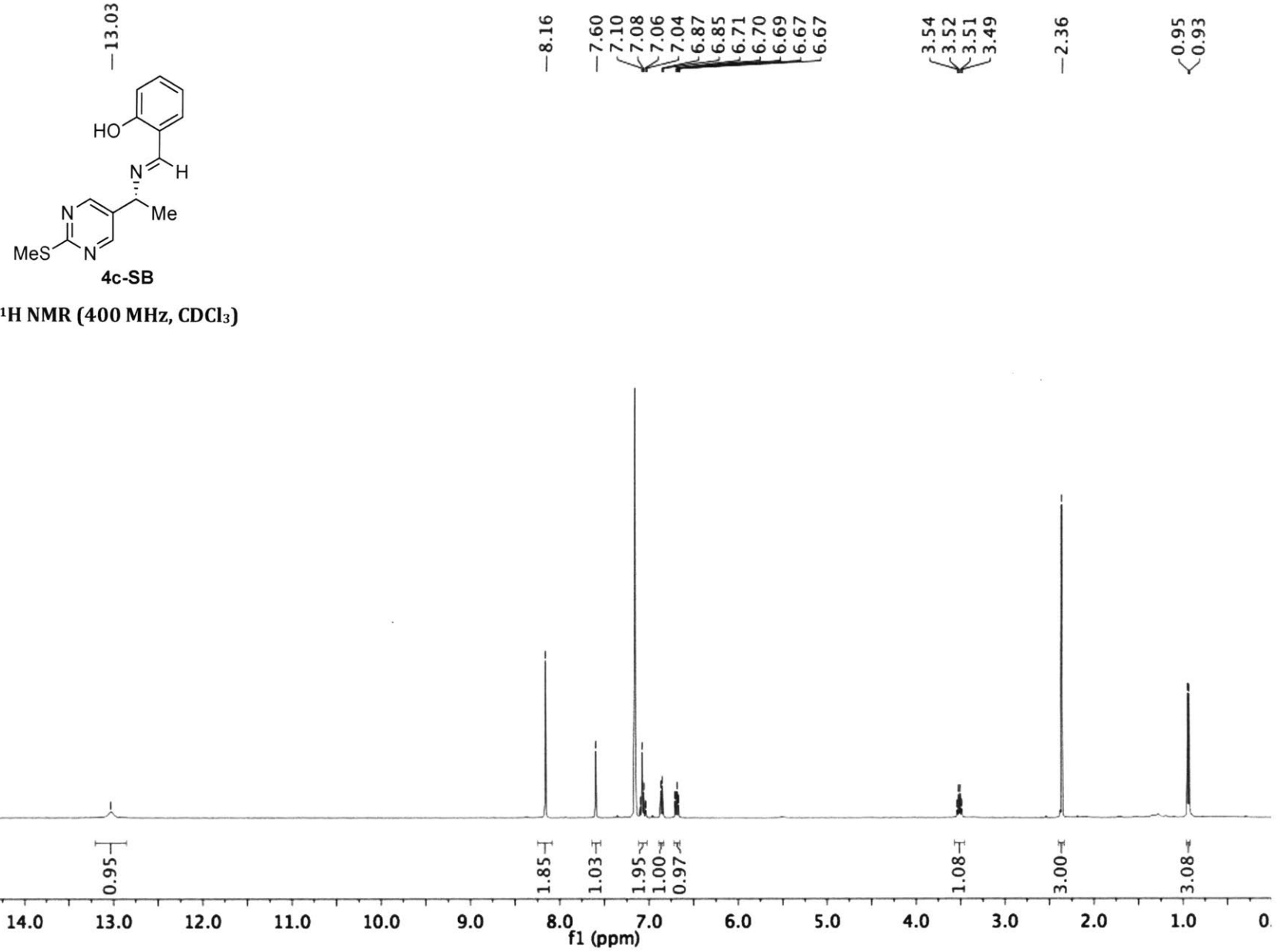


4c

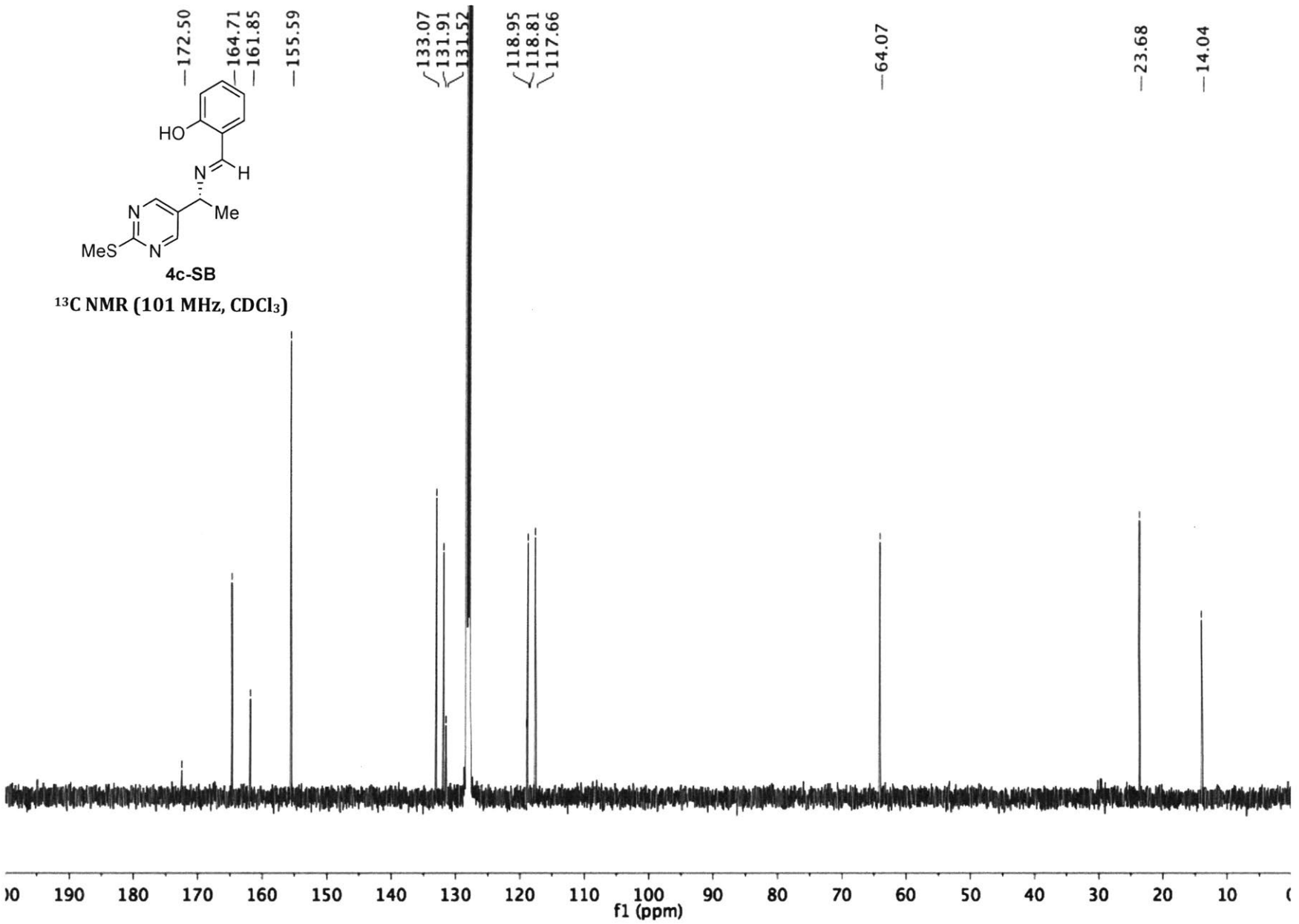
^{1}H NMR (400 MHz, $CDCl_3$)

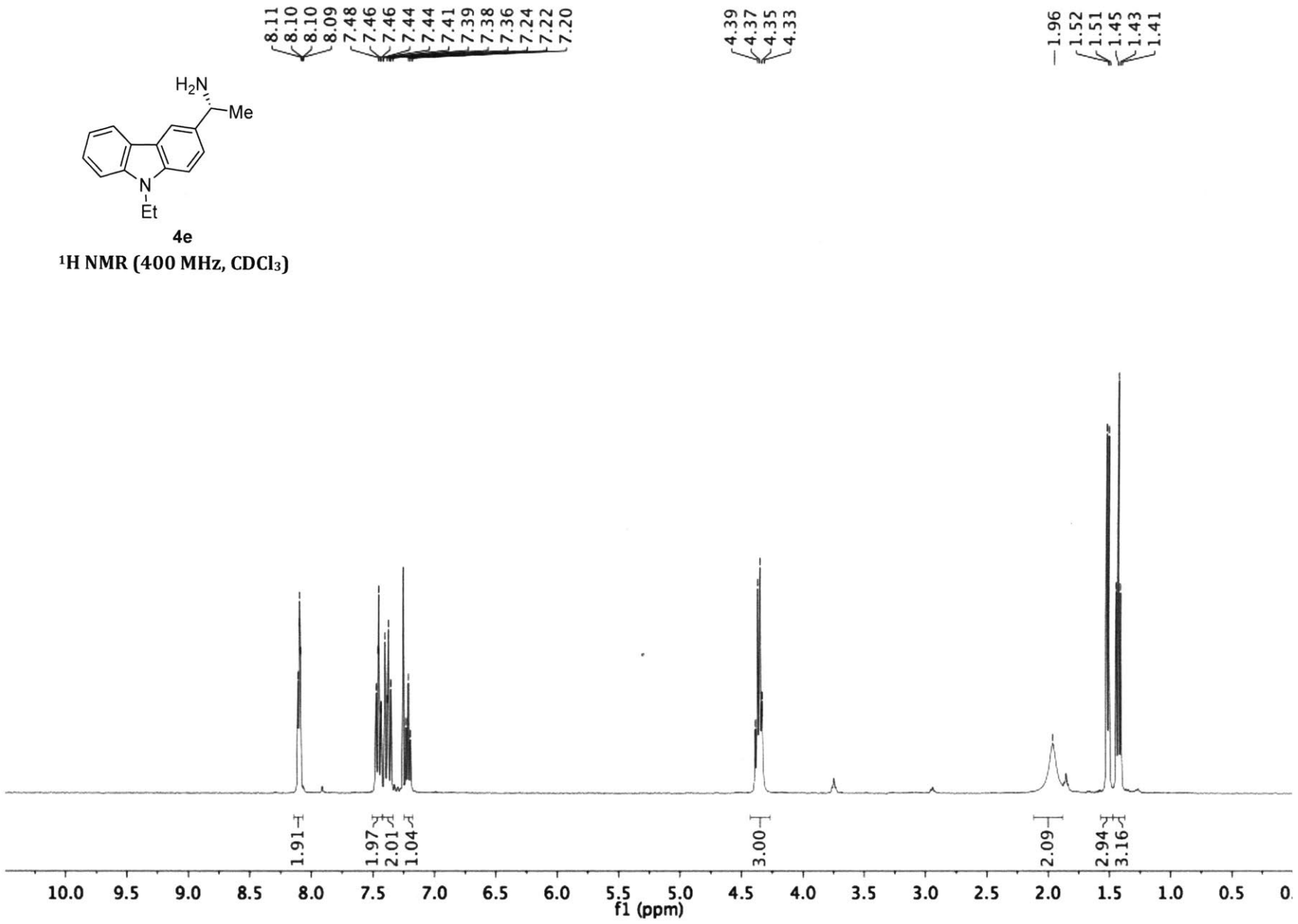


^{13}C NMR (101 MHz, $CDCl_3$)



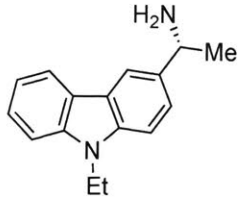
^{1}H NMR (400 MHz, $CDCl_3$)


172.50
164.71
161.85
155.59
133.07
131.91
131.52
118.95
118.81
117.66
64.07
23.68
14.04
HO
N
H
N
Me
MeS
N
4c-SB
13C NMR (101 MHz, CDCl3)
f1 (ppm)



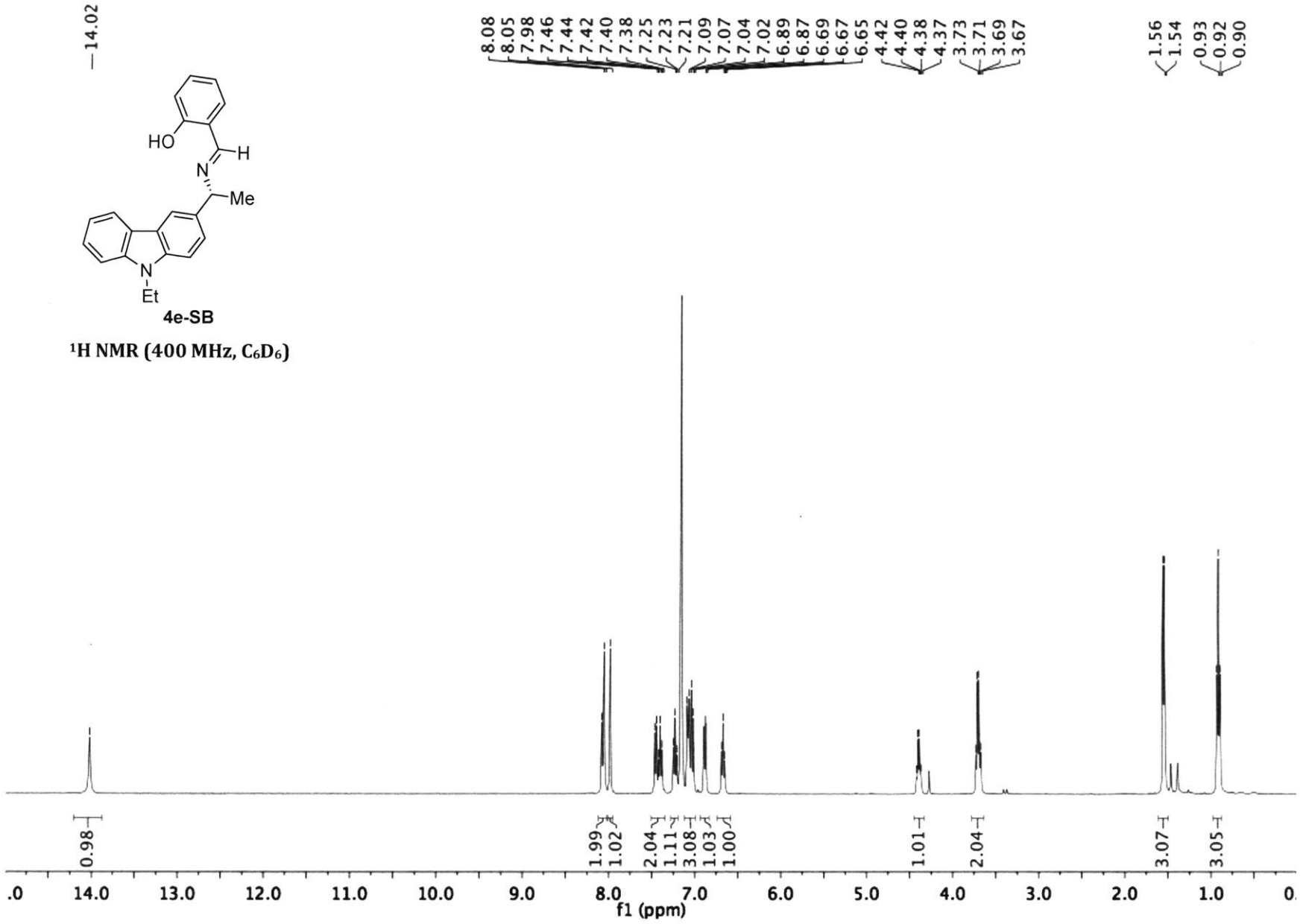
4e

^{1}H NMR (400 MHz, $CDCl_3$)



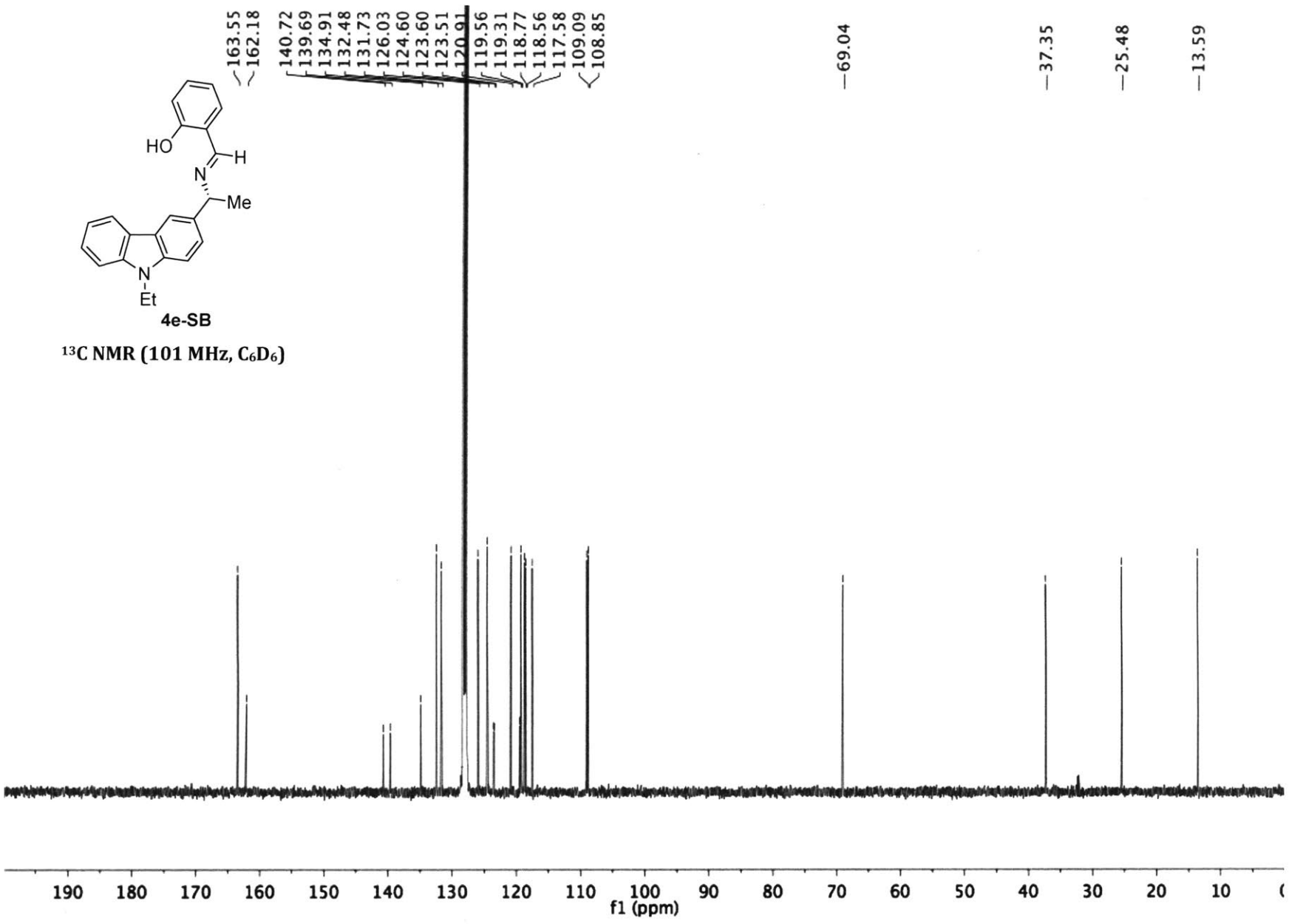
4e

^{13}C NMR (101 MHz, $CDCl_3$)

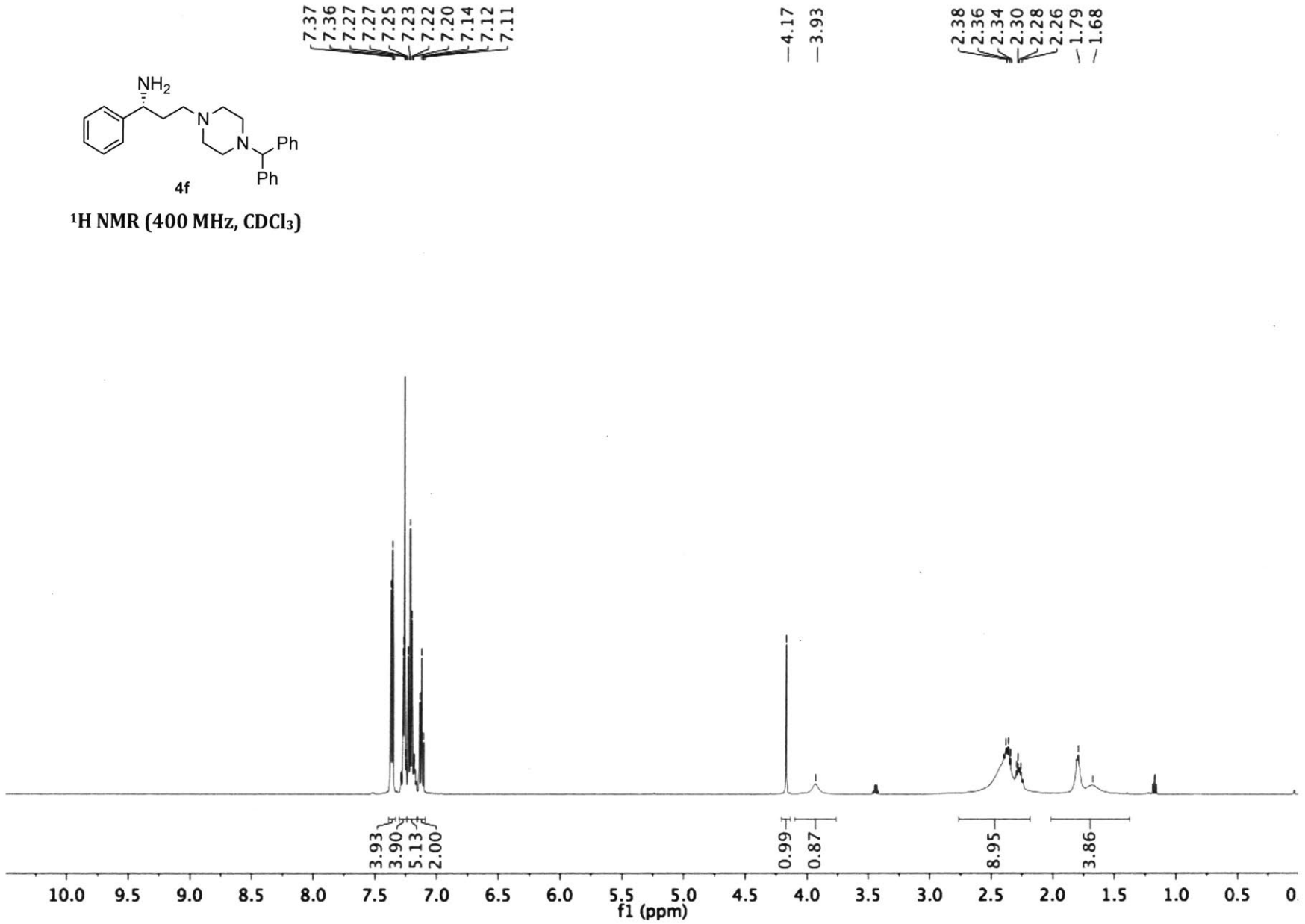


4e-SB

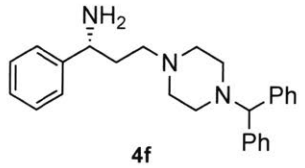
^{1}H NMR (400 MHz, C_6D_6)



^{13}C NMR (101 MHz, C_6D_6)

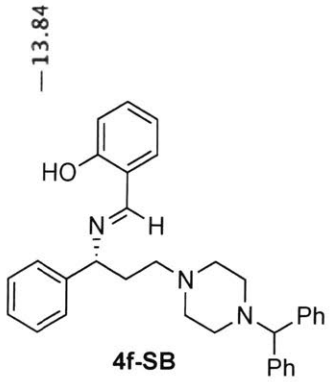


^{1}H NMR (400 MHz, $CDCl_3$)

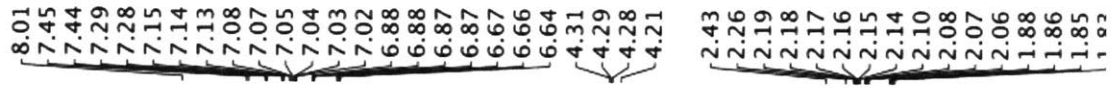


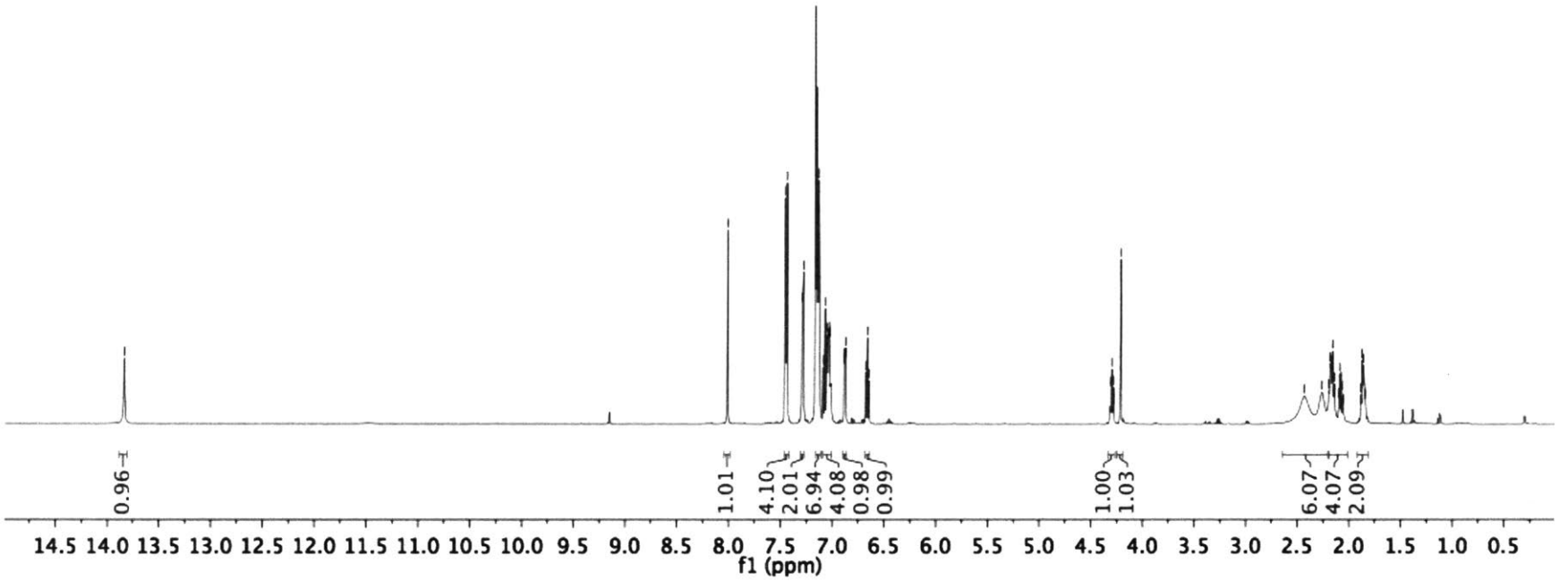
4f

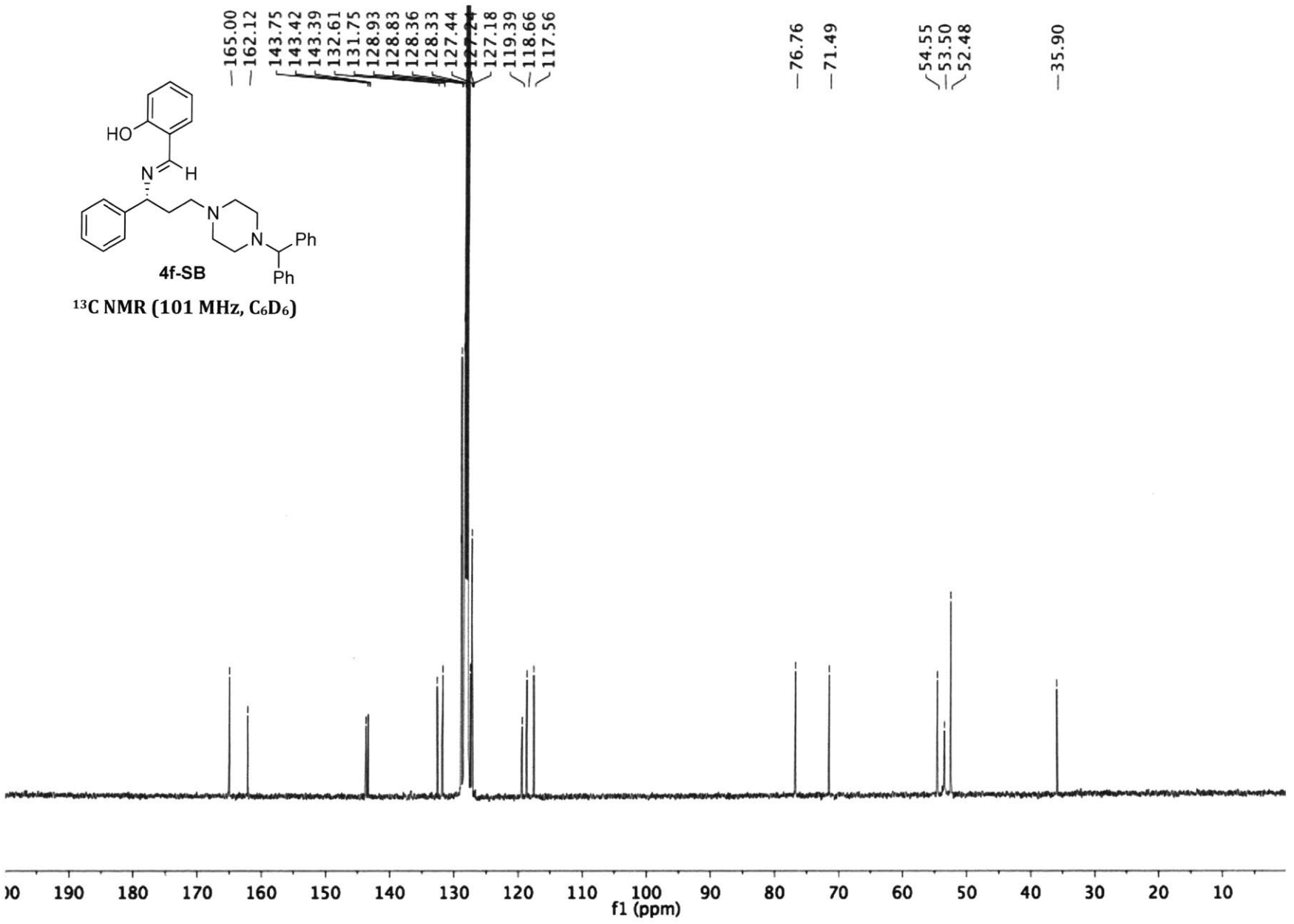
^{13}C NMR (101 MHz, $CDCl_3$)



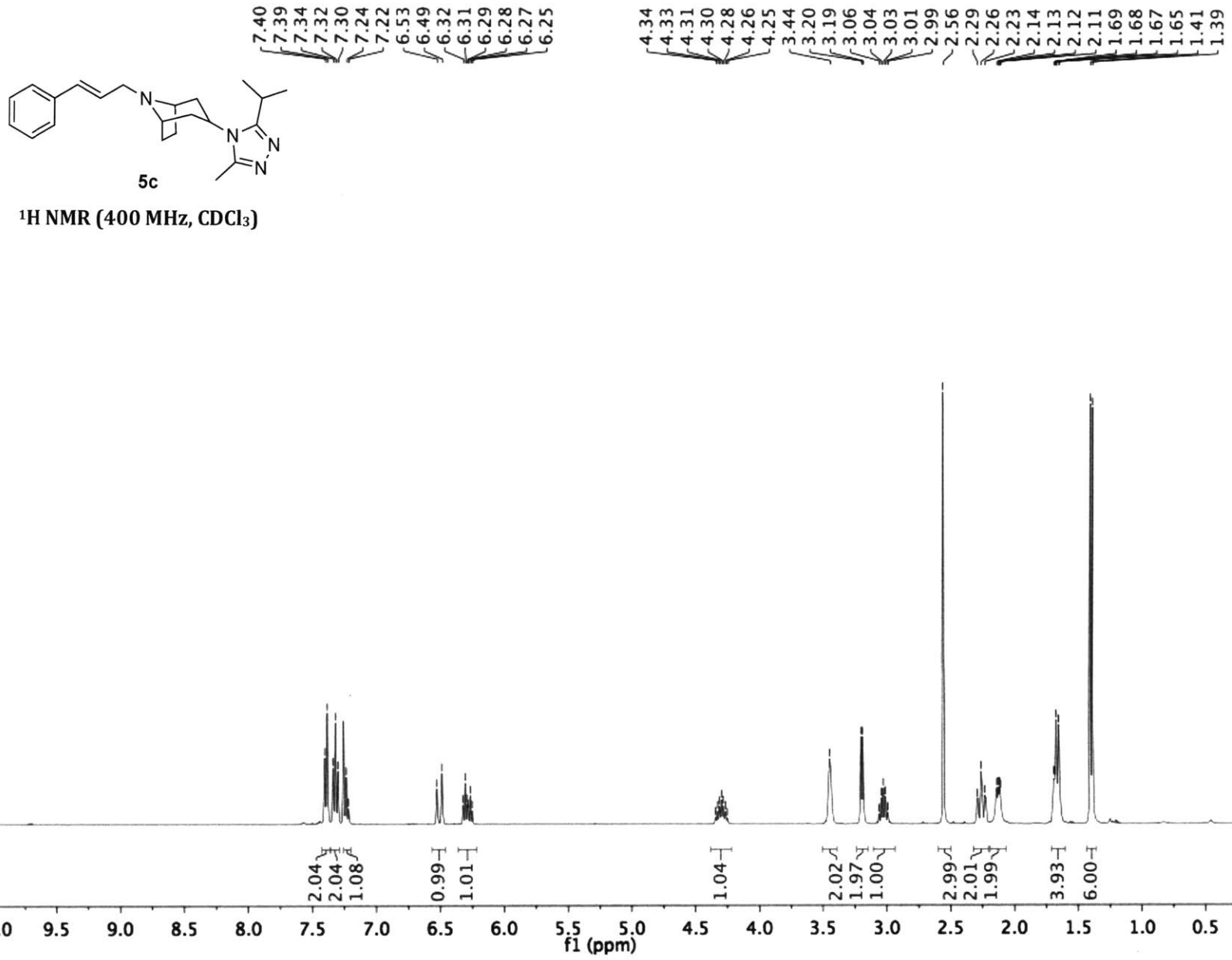
^{1}H NMR (400 MHz, C_6D_6)



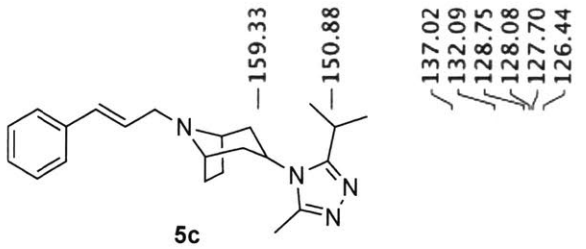




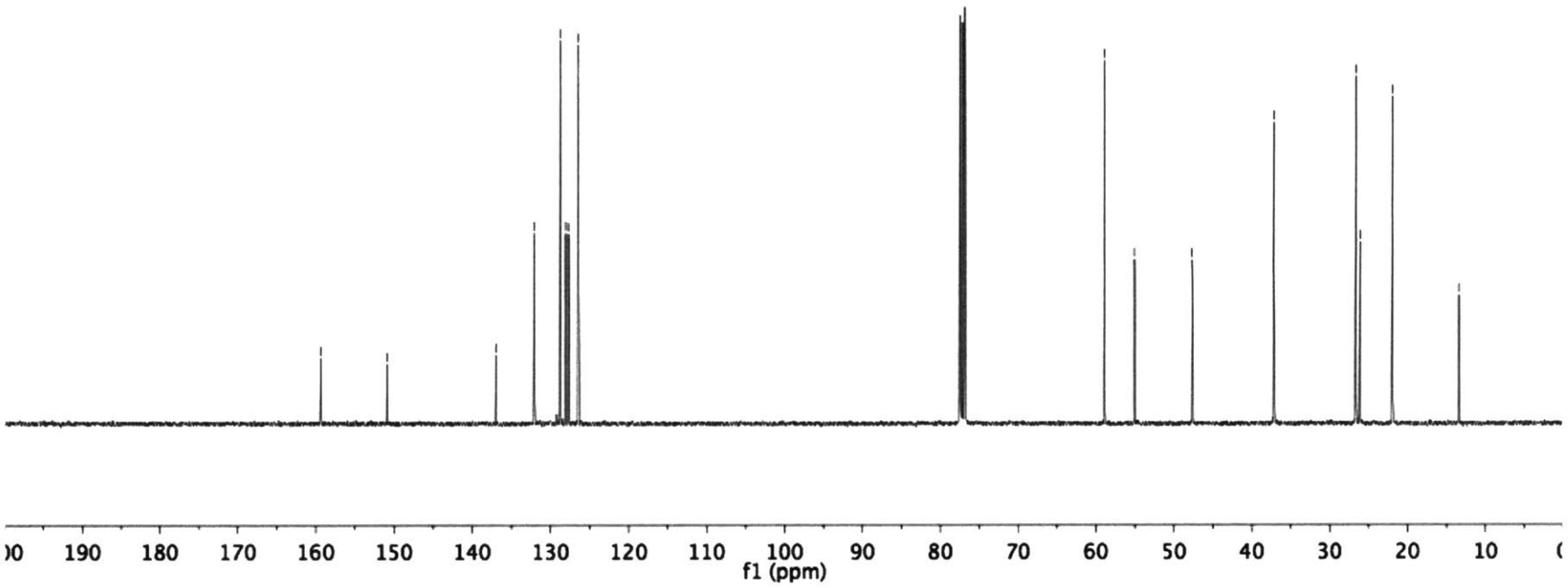
^{13}C NMR (101 MHz, C_6D_6)

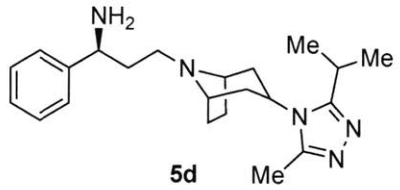


^{1}H NMR (400 MHz, $CDCl_3$)



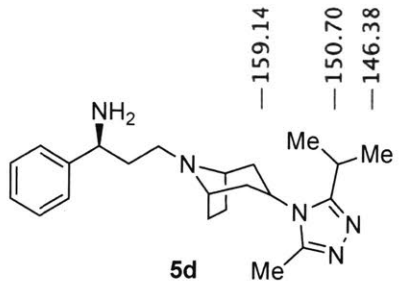
^{13}C NMR (101 MHz, $CDCl_3$)





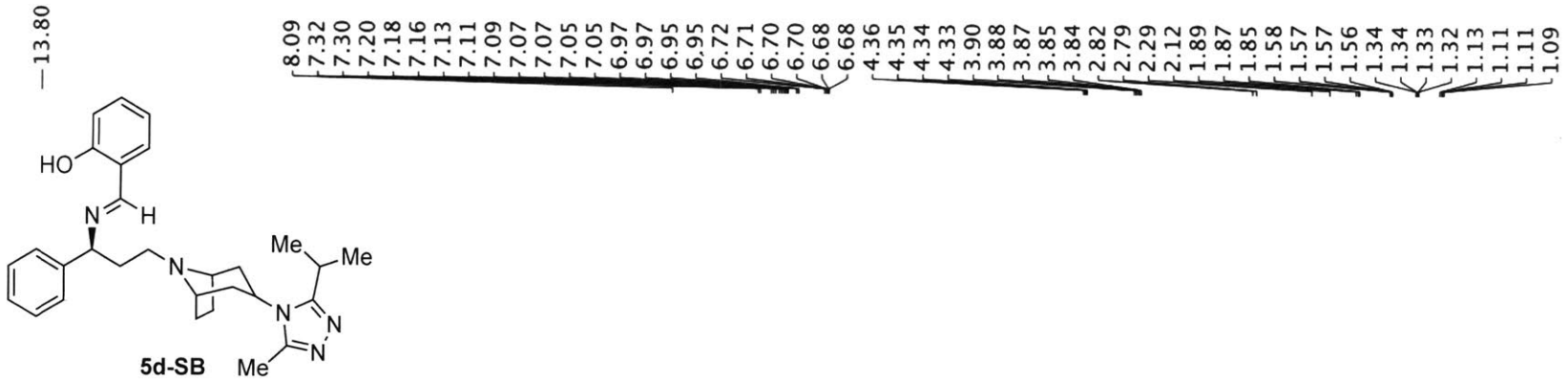
5d

^{1}H NMR (400 MHz, $CDCl_3$)

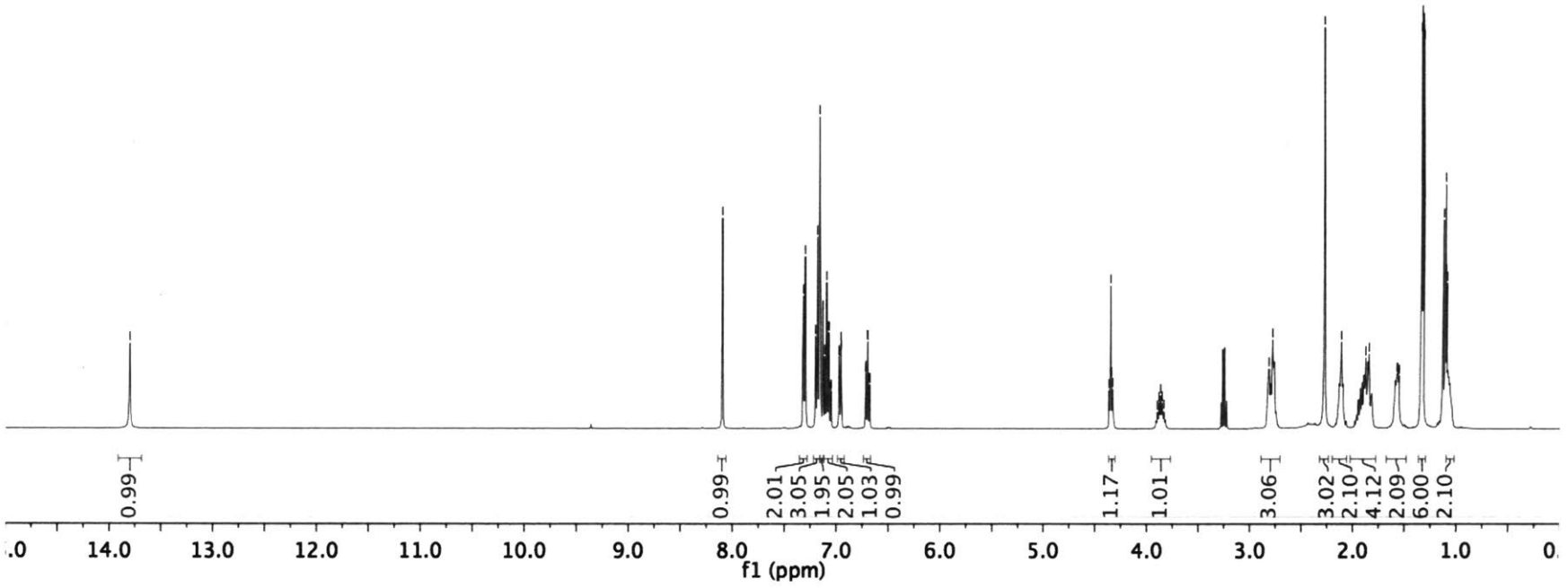


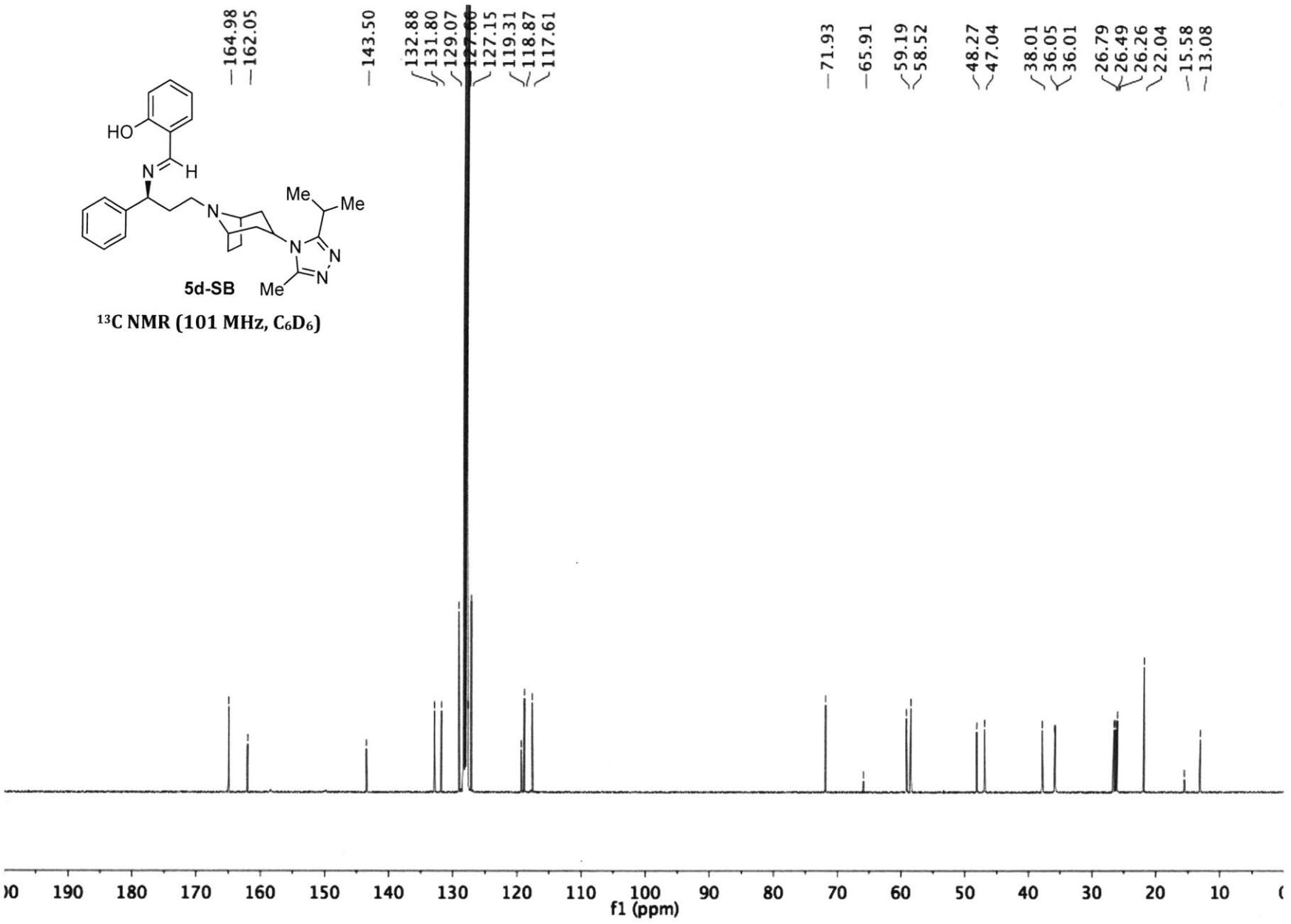
5d

^{13}C NMR (101 MHz, $CDCl_3$)

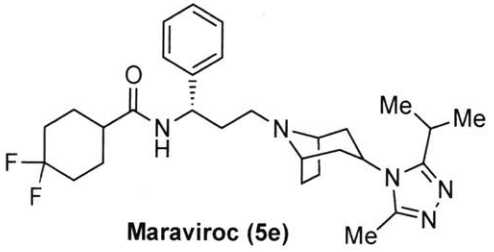


^{1}H NMR (400 MHz, C_6D_6)



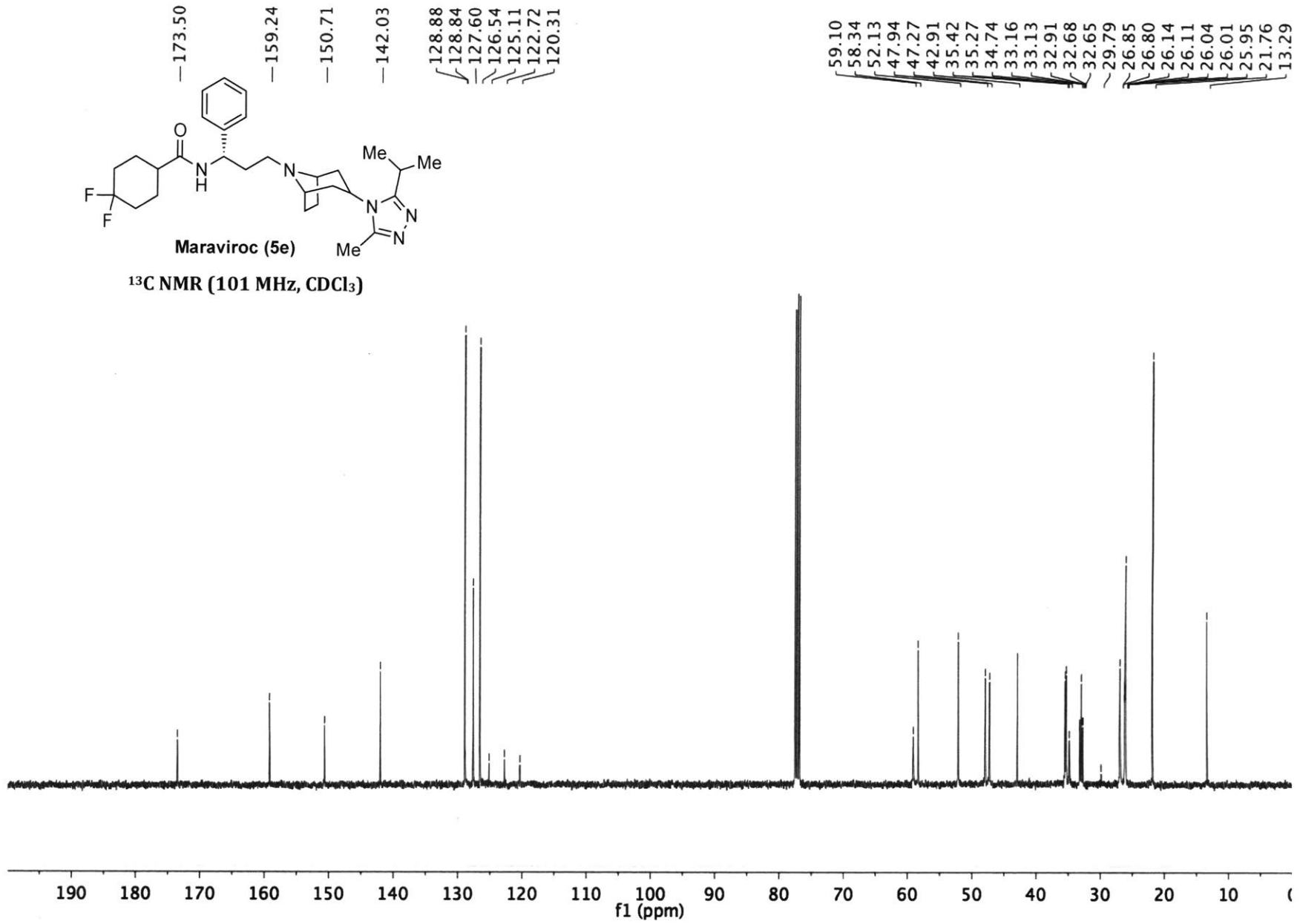


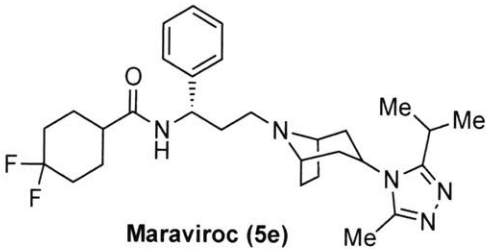
^{13}C NMR (101 MHz, C_6D_6)



Maraviroc (5e)

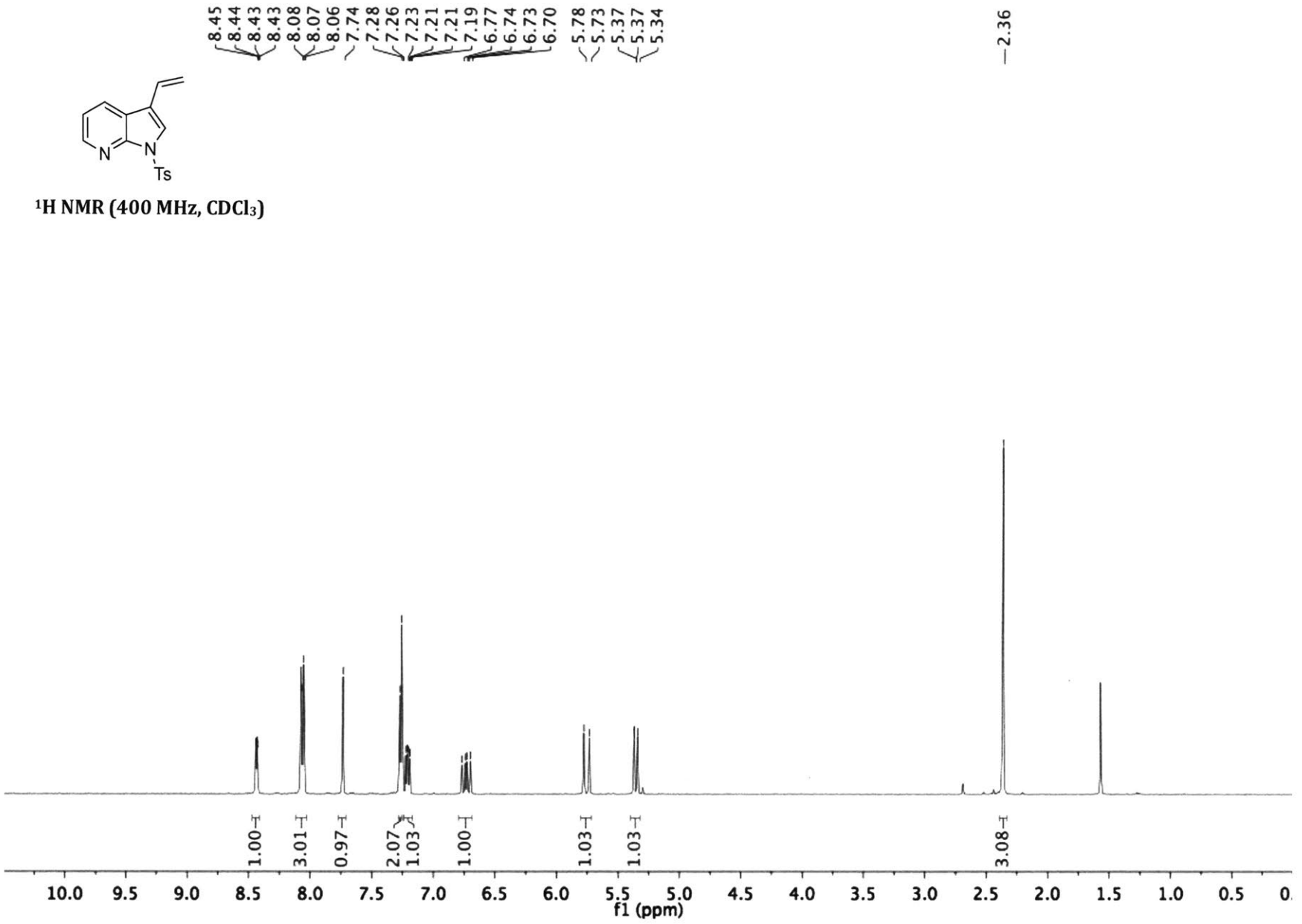
^{1}H NMR (400 MHz, $CDCl_3$)


173.50
159.24
150.71
142.03
128.88
128.84
127.60
126.54
125.11
122.72
120.31
59.10
58.34
52.13
47.94
47.27
42.91
35.42
35.27
34.74
33.16
33.13
32.91
32.68
32.65
29.79
26.85
26.80
26.14
26.11
26.04
26.01
25.95
21.76
13.29
Maraviroc (5e)
^{13}C NMR (101 MHz, CDCl$_3$)
f1 (ppm)

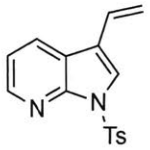


Maraviroc (5e)

^{19}F NMR (376 MHz, $CDCl_3$)

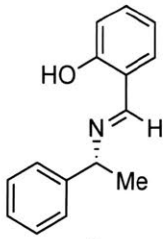


^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

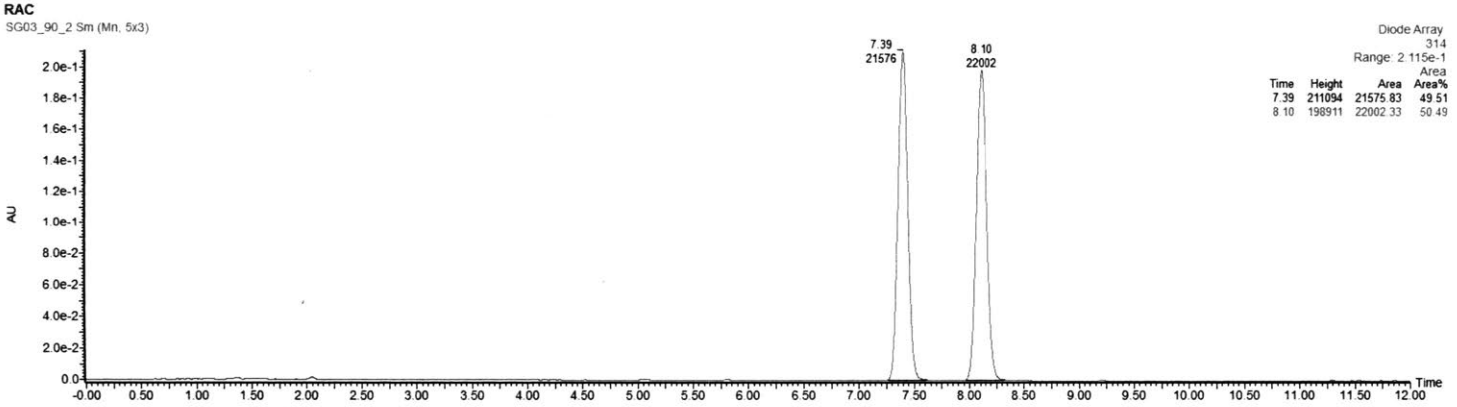
3.7Chiral SFC Spectra



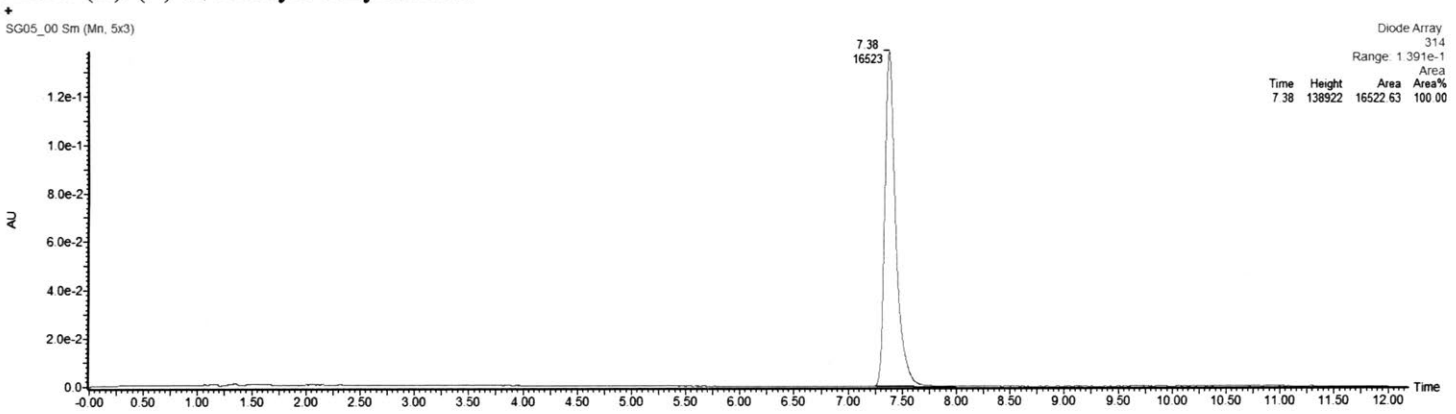
3a

(*R*,*E*)-2-(((1-phenylethyl)imino)methyl)phenol (3a): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 314 nm): t_R(major) = 7.4 min, t_R(minor) = 8.1 min, *97% ee*.

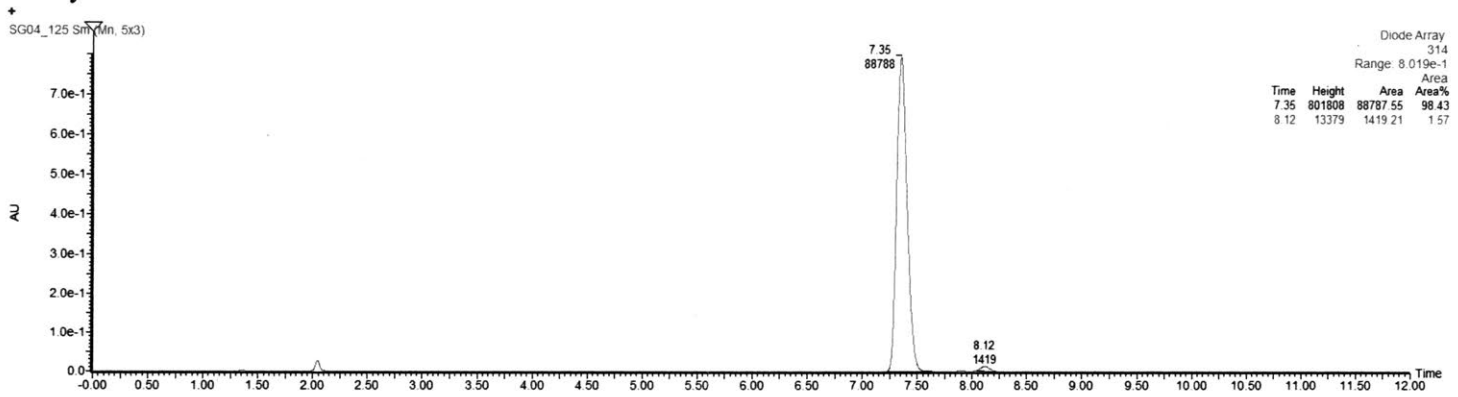
Racemic Product:

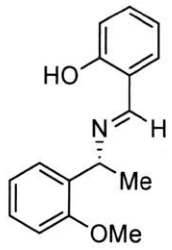


Schiff base from (*R*)-(+)-α-methylbenzylamine:



Enantiomerically Enriched Product:

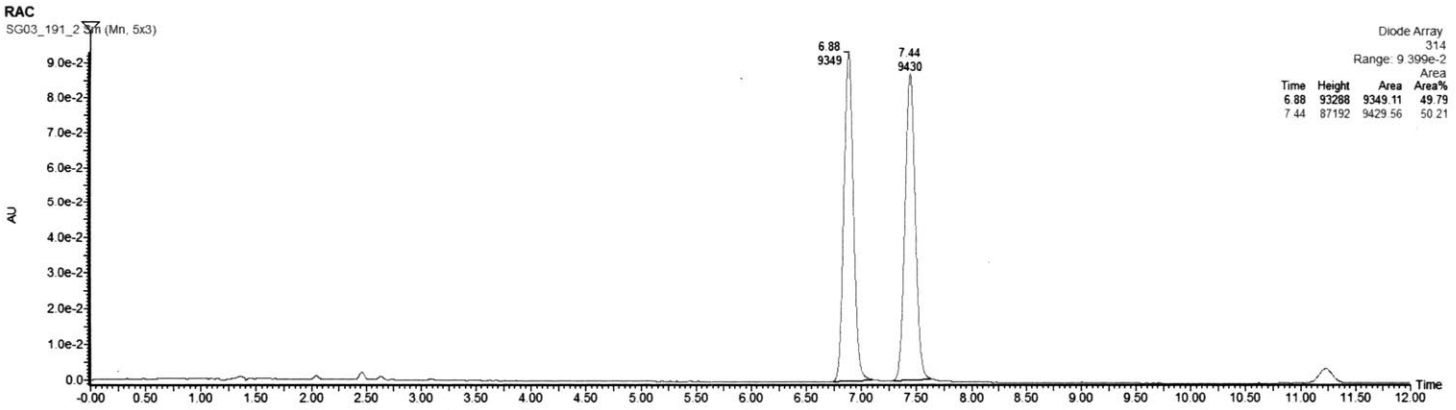




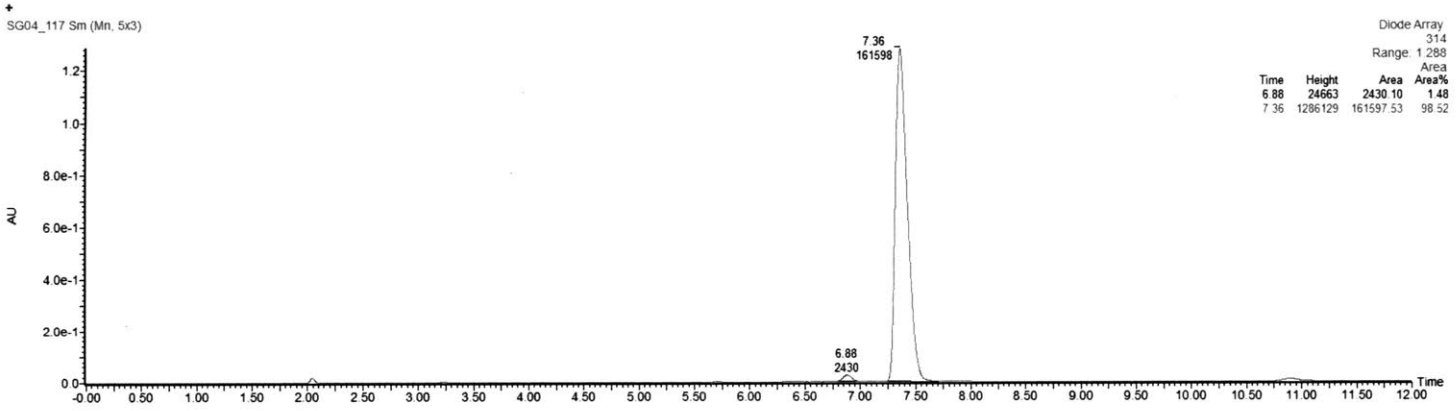
3b

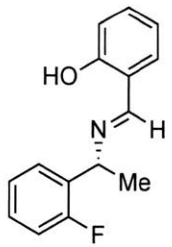
(*R*,*E*)-2-(((1-(2-methoxyphenyl)ethyl)imino)methyl)phenol (3b): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 314 nm): t_R(major) = 7.4 min, t_R(minor) = 6.9 min, *97% ee*.

Racemic Product:



Enantiomerically Enriched Product:

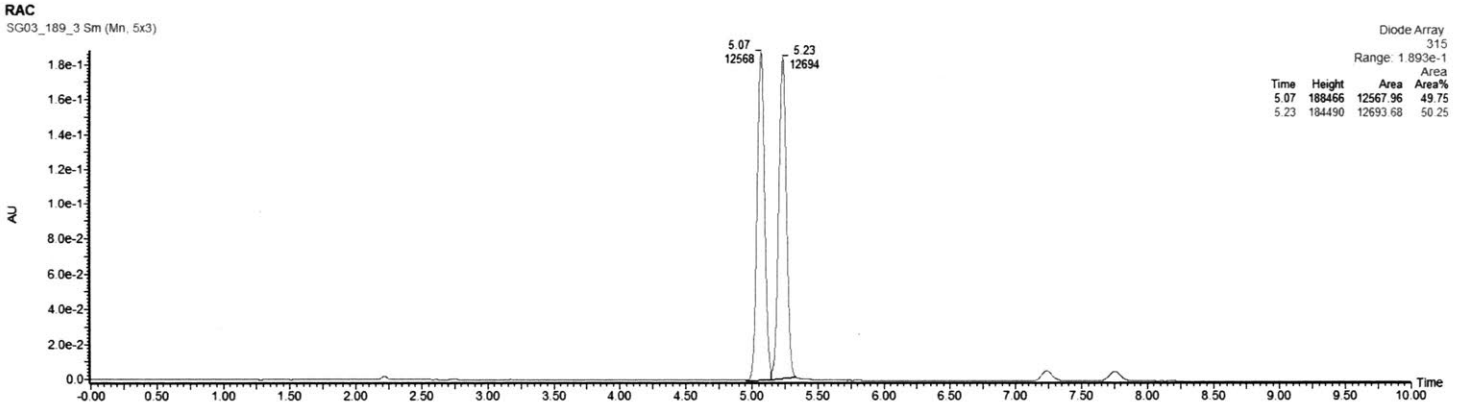




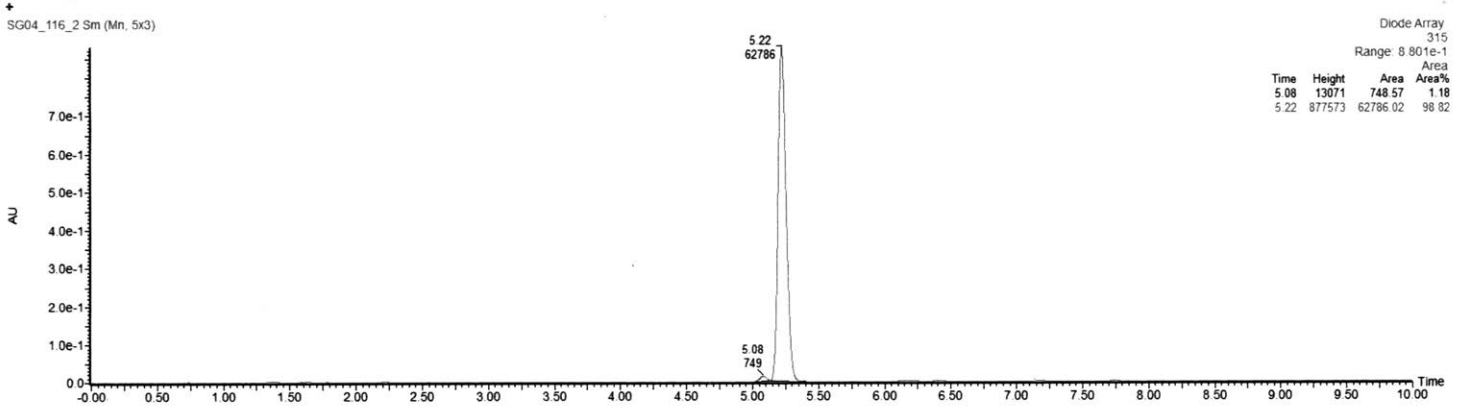
3c

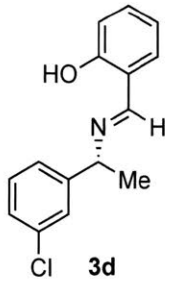
(*R*,*E*)-2-(((1-(2-fluorophenyl)ethyl)imino)methyl)phenol (3c): SFC analysis (OJ-H column, 7 min linear gradient from 1–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 2.5 min hold time, then a 30 s linear gradient from 7–1% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 315 nm): t_R(major) = 5.2 min, t_R(minor) = 5.1 min, *98% ee*.

Racemic Product:



Enantiomerically Enriched Product:

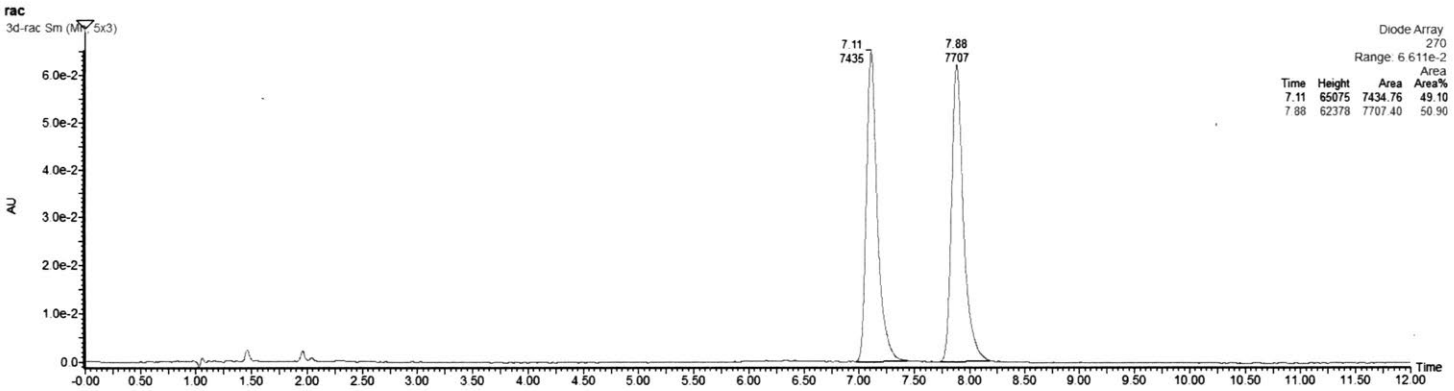




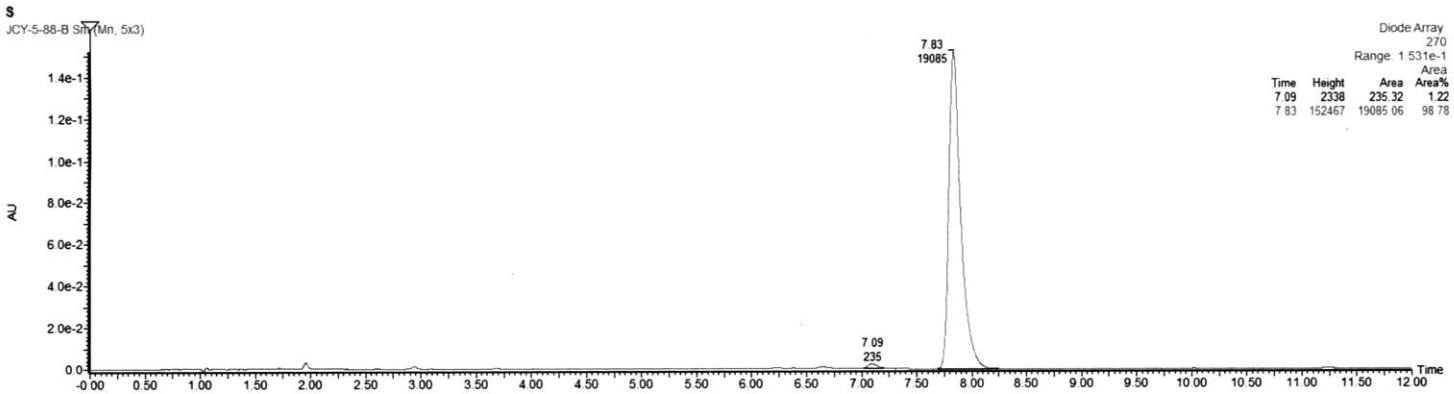
3d

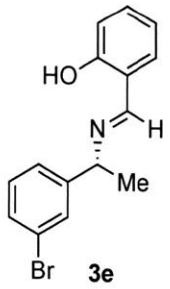
(*R*,*E*)-2-(((1-(3-chlorophenyl)ethyl)imino)methyl)phenol (3d): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 270 nm): t_R(major) = 7.8 min, t_R(minor) = 7.1 min, *98% ee*.

Racemic Product:



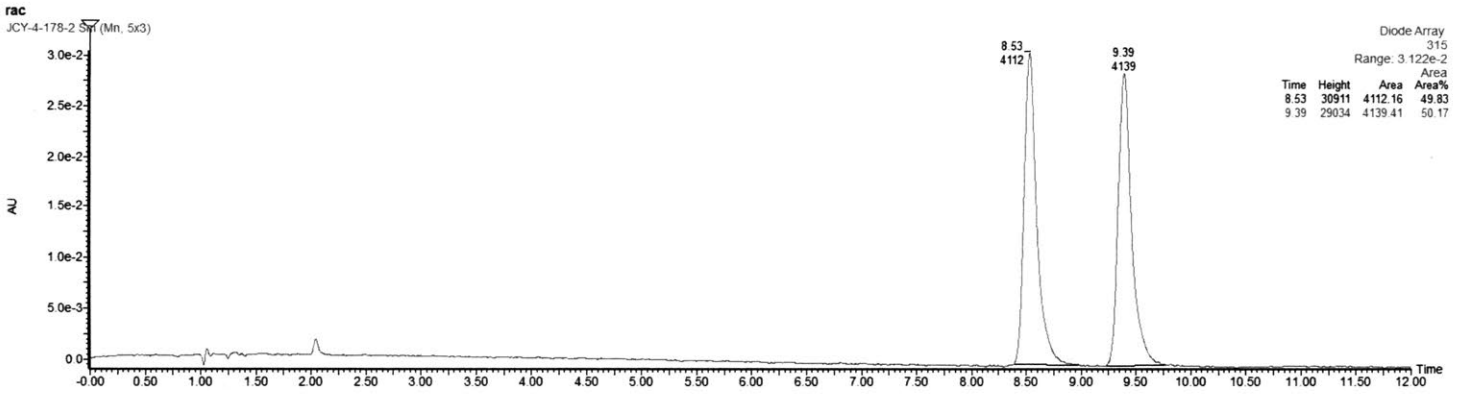
Enantiomerically Enriched Product:



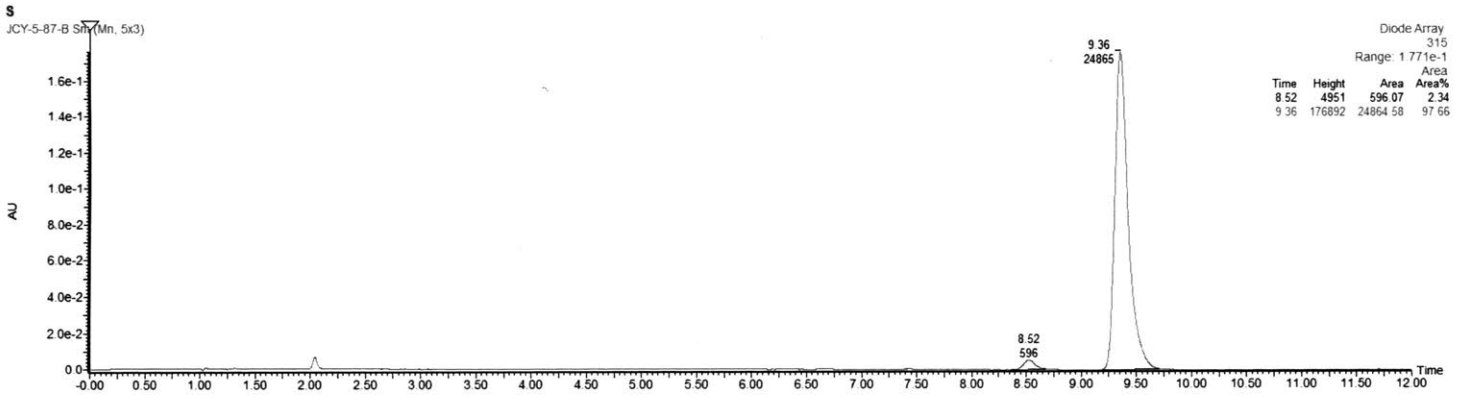


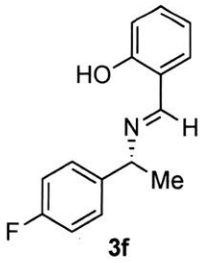
(*R*,*E*)-2-(((1-(3-bromophenyl)ethyl)imino)methyl)phenol (3e): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 315 nm): t_R(major) = 9.3 min, t_R(minor) = 8.4 min, *95% ee*.

Racemic Product:



Enantiomerically Enriched Product:

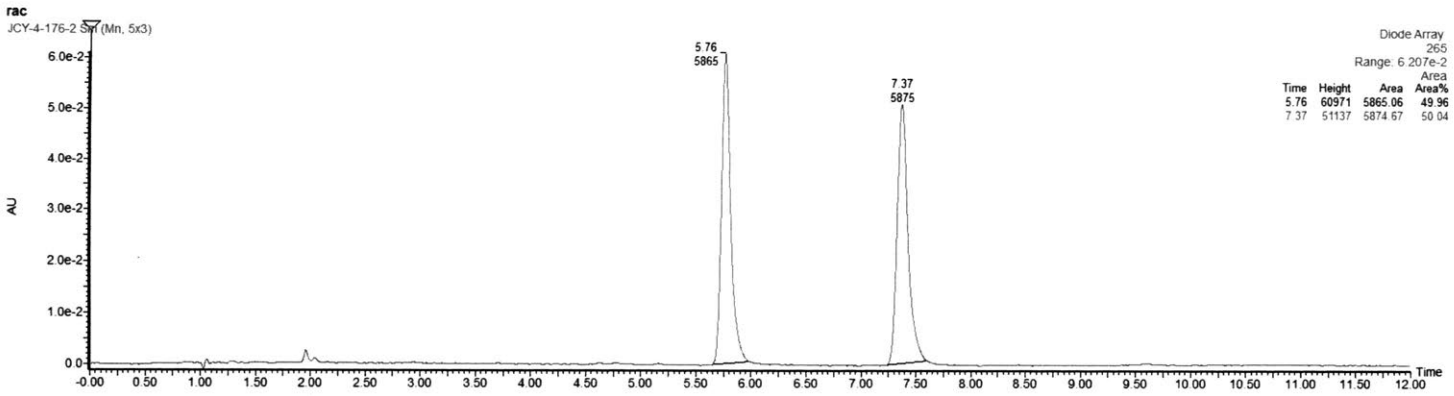




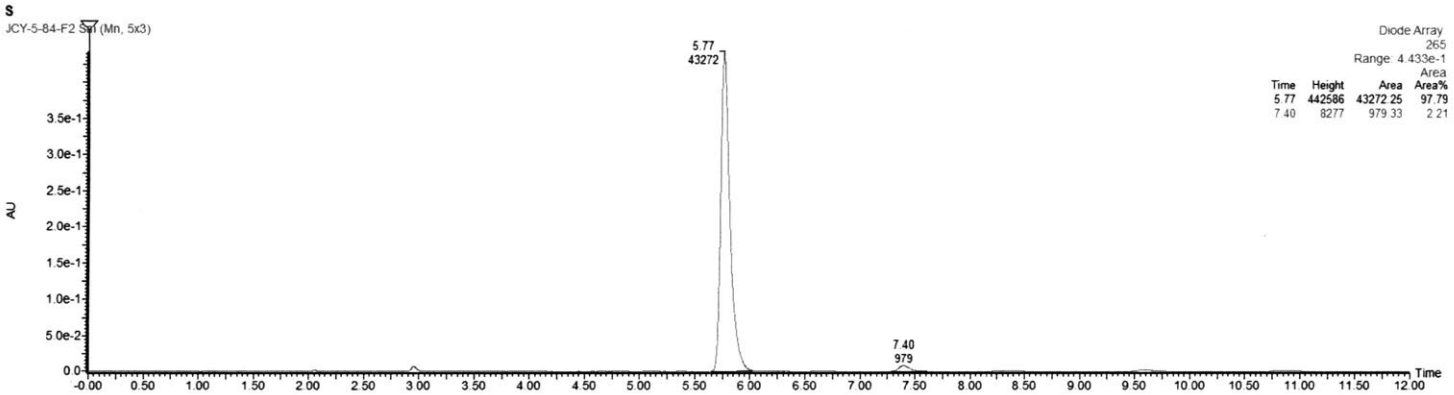
3f

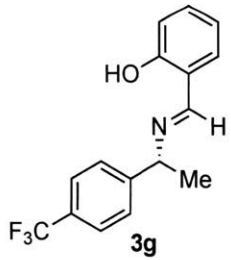
(*R*,*E*)-2-(((1-(4-fluorophenyl)ethyl)imino)methyl)phenol (3f): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 265 nm): t_R(major) = 5.8 min, t_R(minor) = 7.4 min, *96% ee*.

Racemic Product:



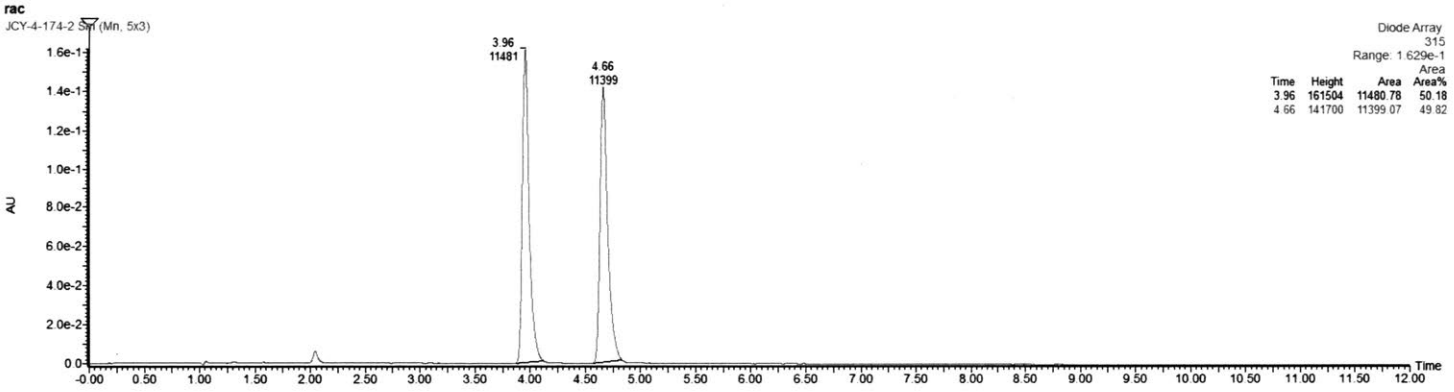
Enantiomerically Enriched Product:



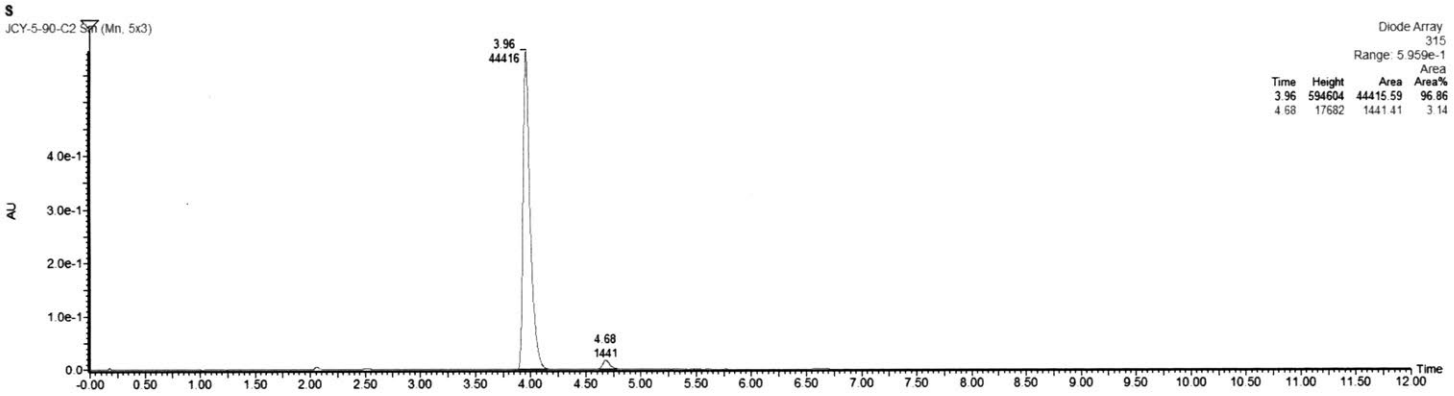


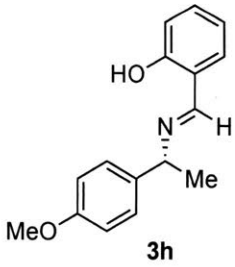
(*R*,*E*)-2-(((1-(4-(trifluoromethyl)phenyl)ethyl)imino)methyl)phenol (3g): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 315 nm): t_R(major) = 3.9 min, t_R(minor) = 4.6 min, *93% ee*.

Racemic Product:



Enantiomerically Enriched Product:

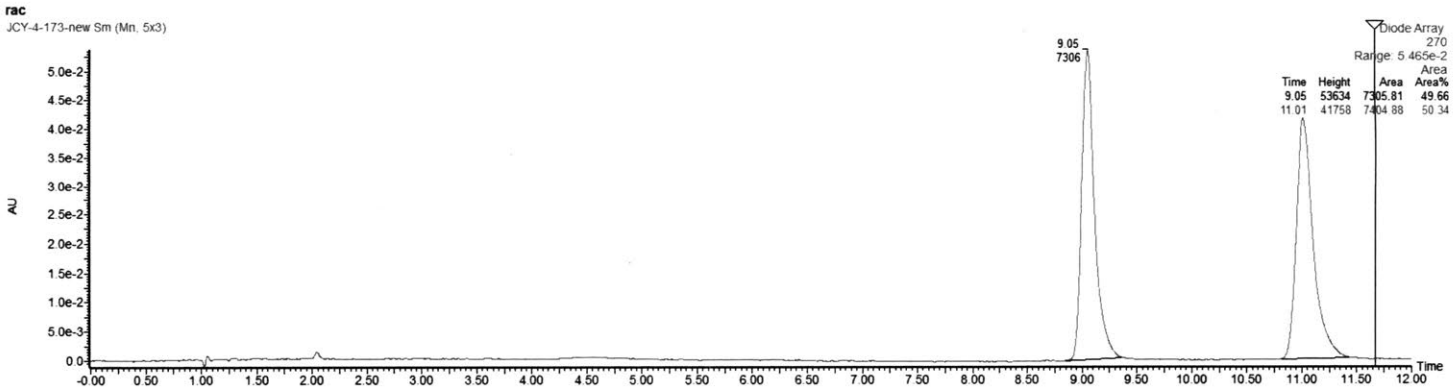




3h

(*R*,*E*)-2-(((1-(4-methoxyphenyl)ethyl)imino)methyl)phenol (3h): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 270 nm): t_R(major) = 8.9 min, t_R(minor) = 10.8 min, *98% ee*.

Racemic Product:



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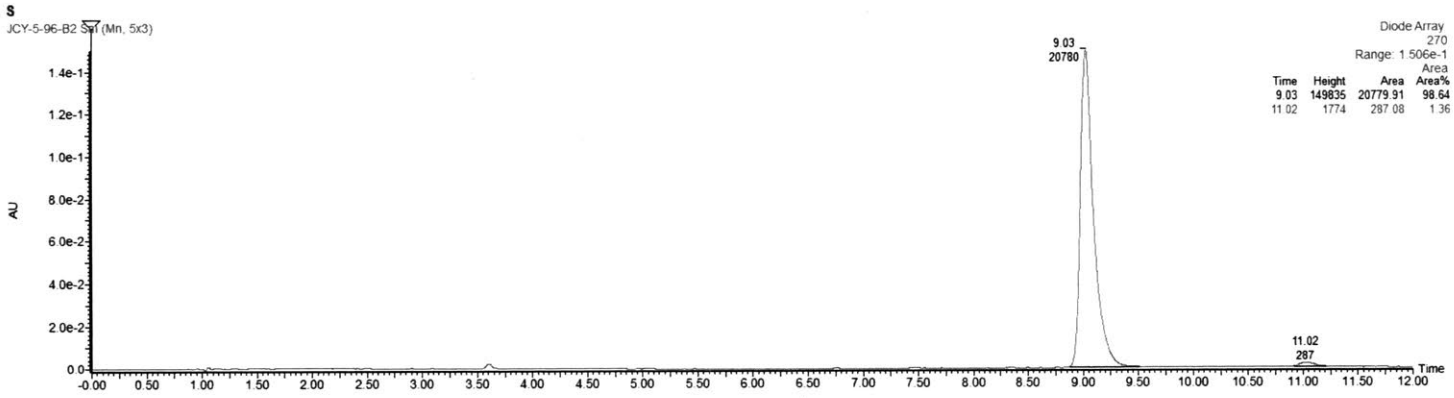
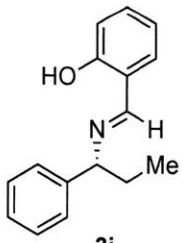
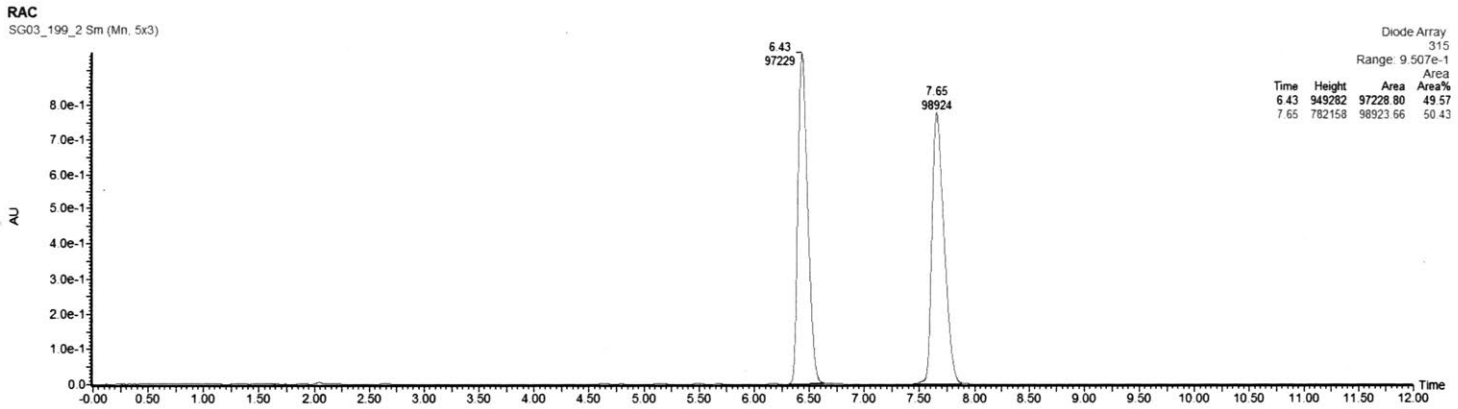




3i

(*R*,*E*)-2-(((1-phenylpropyl)imino)methyl)phenol (3i): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 315 nm): t_R(major) = 6.3 min, t_R(minor) = 7.7 min, *96% ee*.

Racemic Product:



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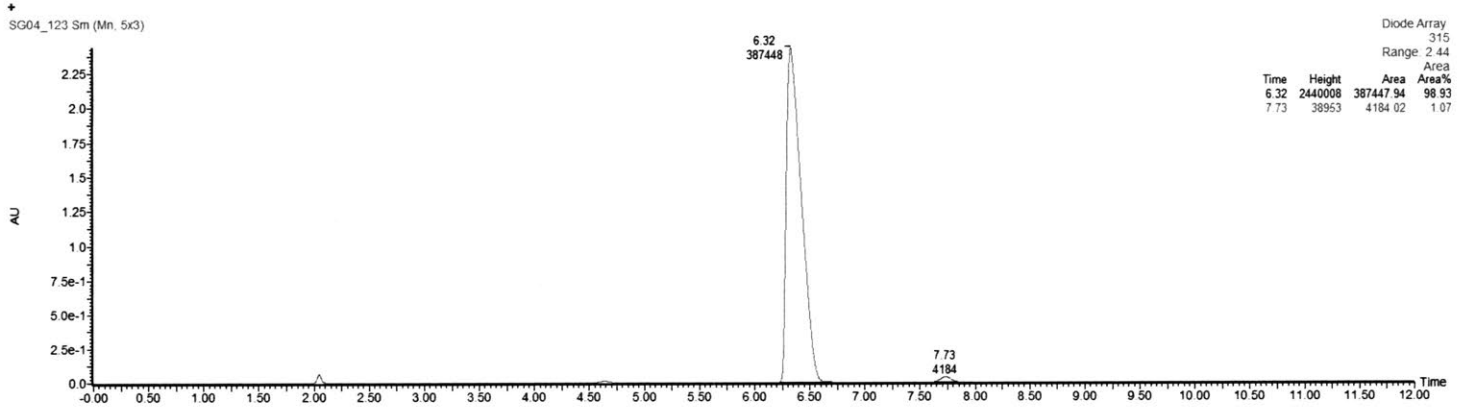
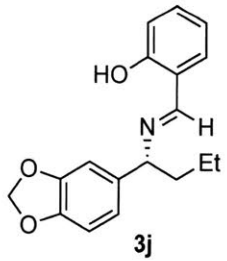
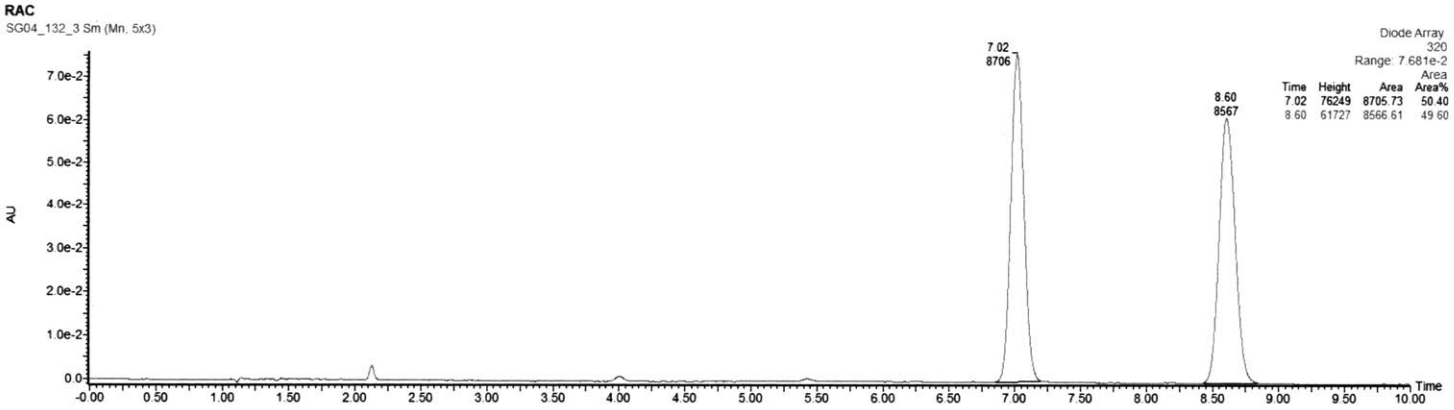




3j

(*R*,*E*)-2-(((1-(benzo[*d*][1,3]dioxol-5-yl)butyl)imino)methyl)phenol (3j): SFC analysis (AD-H column, 8 min linear gradient from 5–10% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 1 min hold time, then a 1 min linear gradient from 10–5% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 320 nm): t_R(major) = 8.5 min, t_R(minor) = 7.0 min, *99% ee*.

Racemic Product:



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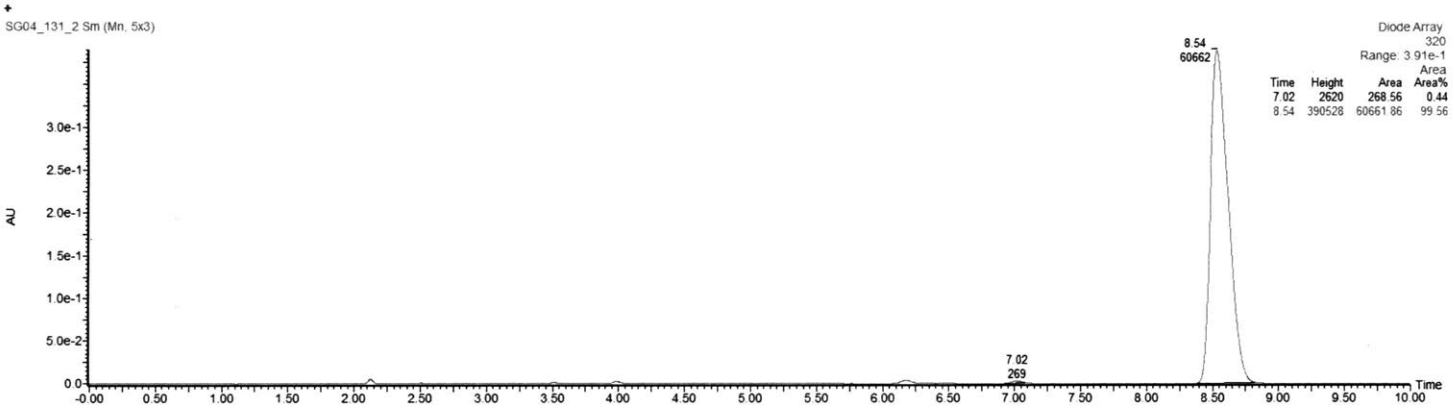
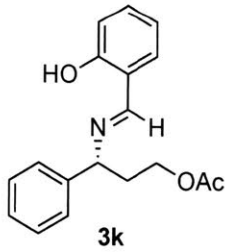
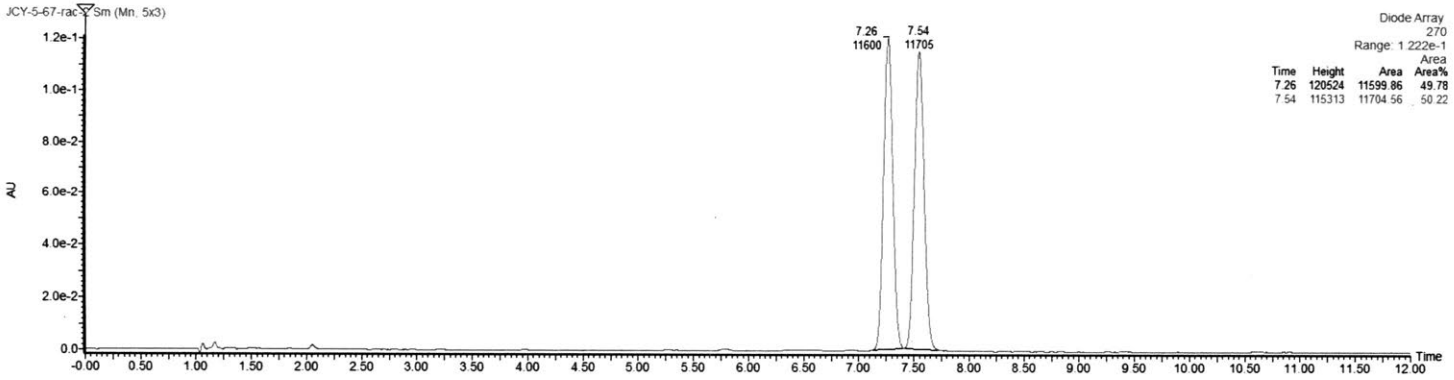




3k

(*R*,*E*)-3-((2-hydroxybenzylidene)amino)-3-phenylpropyl acetate (3k): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 270 nm): t_R(major) = 7.2 min, t_R(minor) = 7.5 min, *98% ee*.

Racemic Product:



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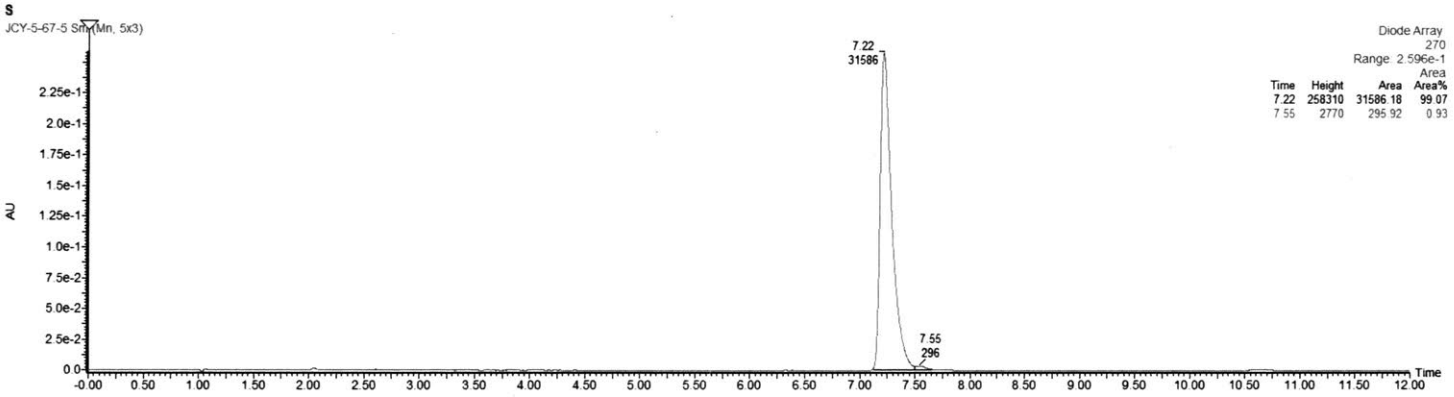
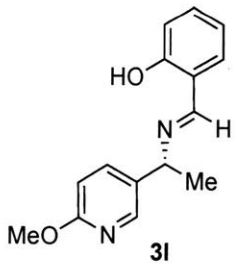
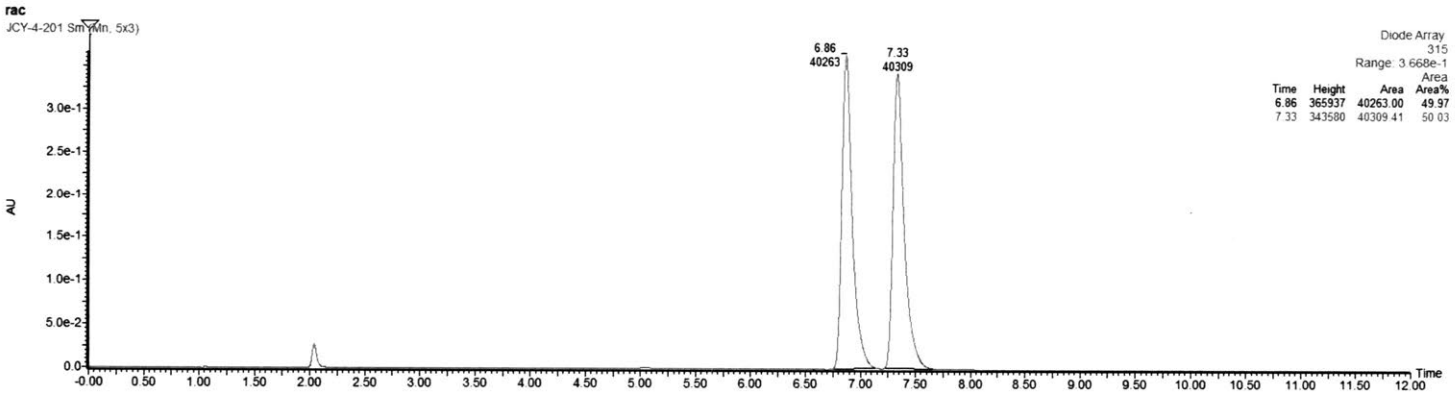




3l

(*R*,*E*)-2-(((1-(6-methoxypyridin-3-yl)ethyl)imino)methyl)phenol (3l): SFC analysis (OJ-H column, 8 min linear gradient from 2–7% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 3.5 min hold time, then a 30 s linear gradient from 7–2% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 315 nm): t_R(major) = 6.8 min, t_R(minor) = 7.3 min, *98% ee*.

Racemic Product:



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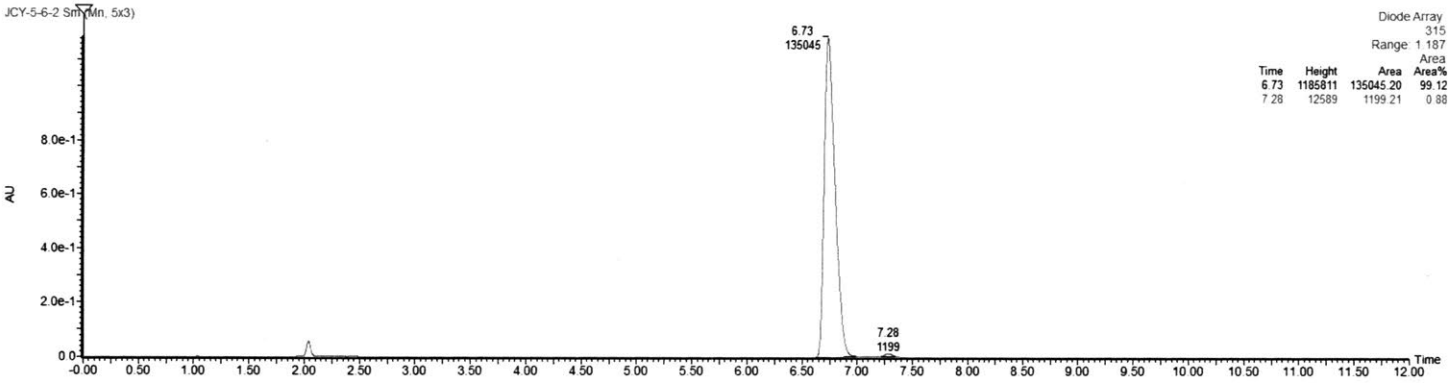
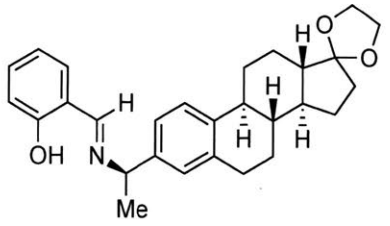
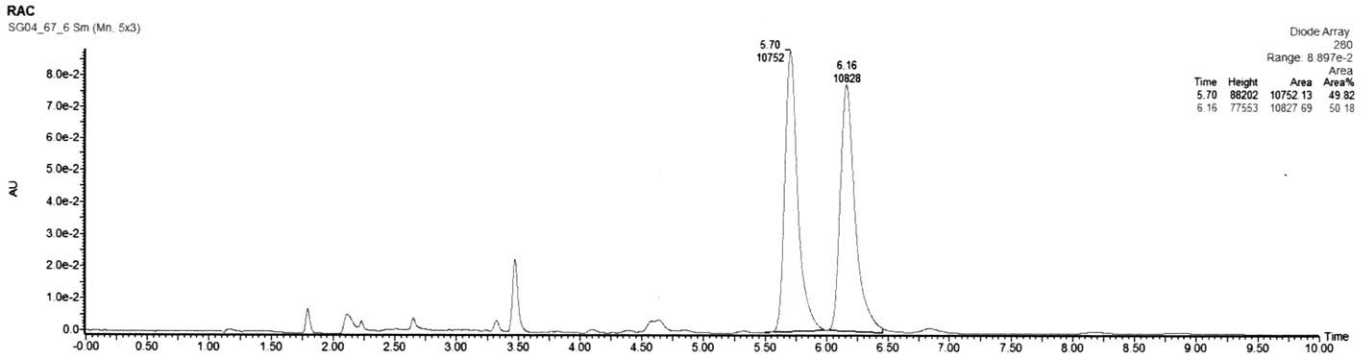




3m

2-((*E*)-(((*R*)-1-((8*S*,9*S*,13*S*,14*S*)-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)ethyl)imino)methyl)phenol (3m): SFC analysis (OJ-H column, 6 min linear gradient from 5–40% MeOH (0.1% diethylamine v/v) in scCO (0.1% diethylamine v/v) in $scCO_2$, followed by a 1 min hold time, then a 15 s linear gradient from 40–5% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 45 s hold time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 280 nm): t_R(major) = 5.7 min, t_R(minor) = 6.2 min, *98% ee*.

Racemic Product:



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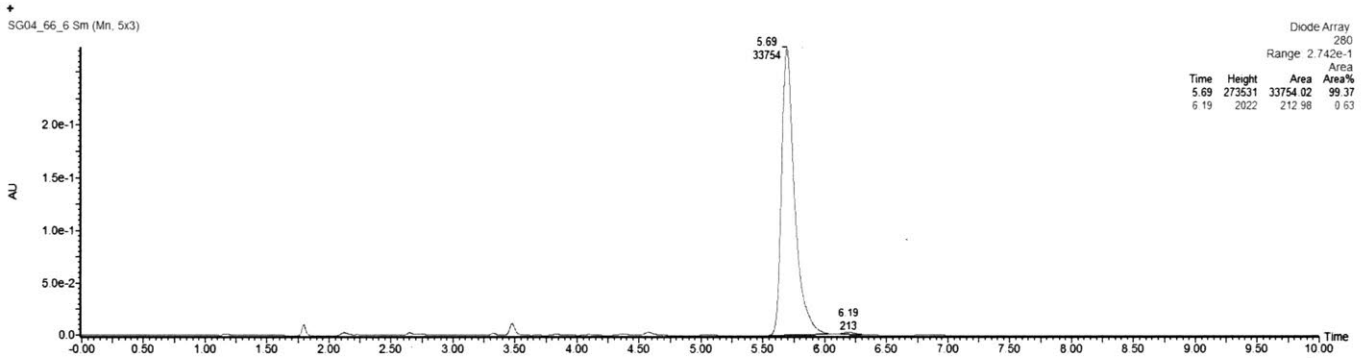
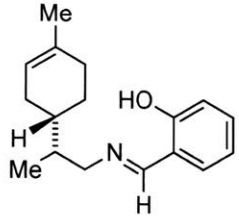
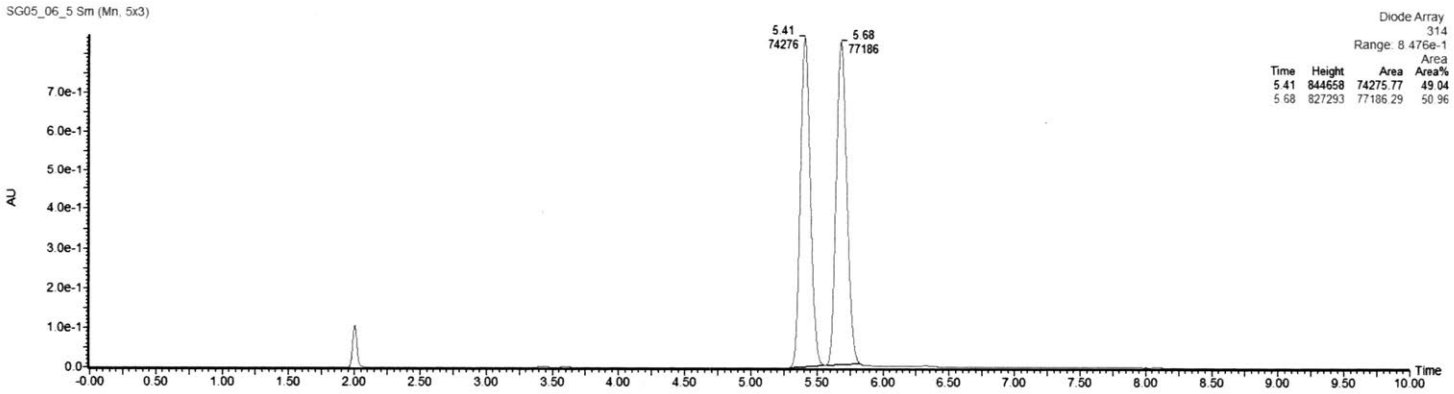




3o

2-((*E*)-(((*S*)-2-((*S*)-4-methylcyclohex-3-en-1-yl)propyl)imino)methyl)phenol (3o): SFC analysis (OD-H column, 8 min linear gradient from 5–10% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 1 min hold time, then a 1 min linear gradient from 10–5% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 314 nm): t_R(major) = 5.7 min, t_R(minor) = 5.4 min, *96:2 d.r.*

Racemic Product:



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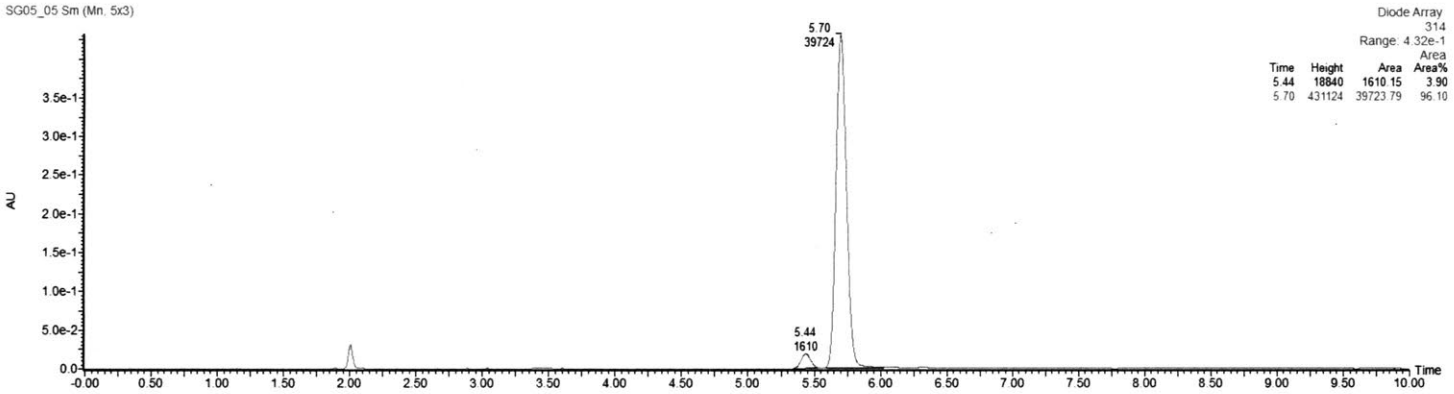
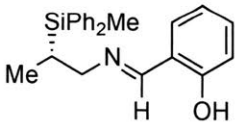
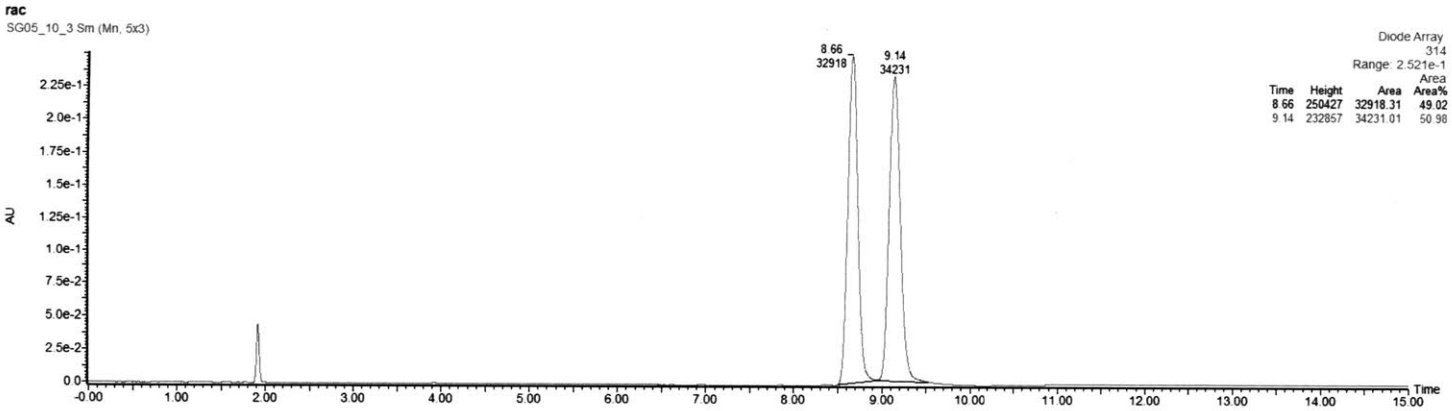




3p

(*S*,*E*)-2-(((2-(methyldiphenylsilyl)propyl)imino)methyl)phenol (3p): SFC analysis (OD-H column, 7 min linear gradient from 5–12% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 2 min hold time, then a 15 s linear gradient from 12–5% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 45 s hold time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 314 nm): t_R(major) = 9.1 min, t_R(minor) = 8.7 min, *98% ee*.

Racemic Product:



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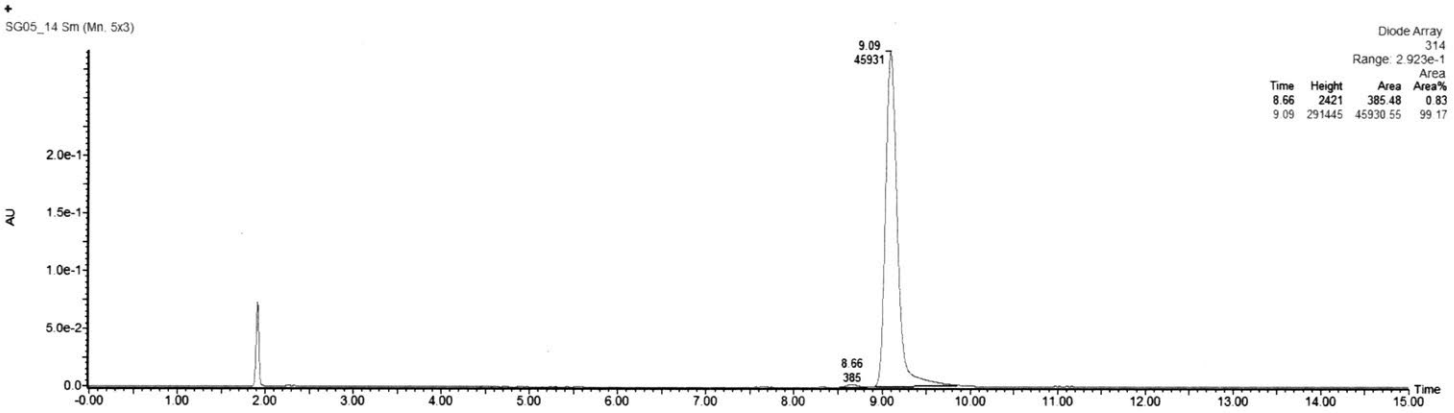
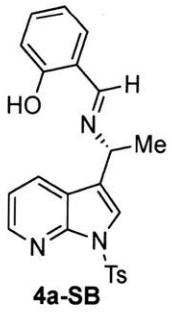
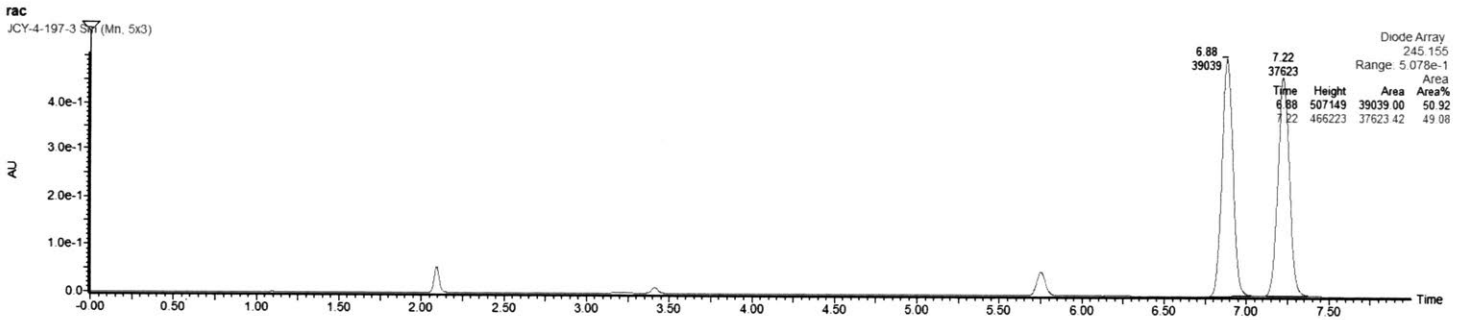




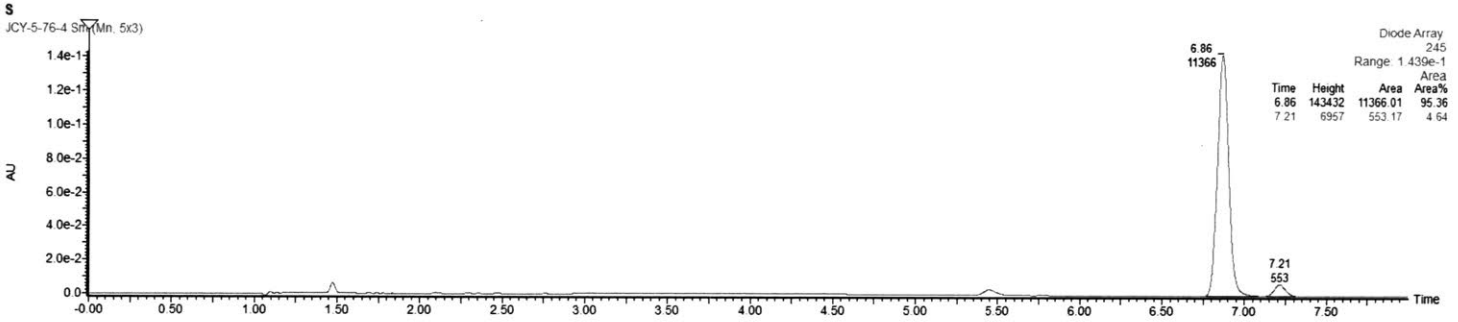
4a-SB

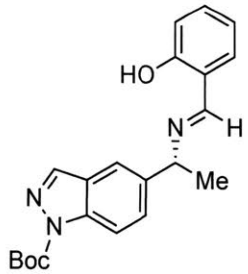
(*R*,*E*)-2-(((1-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl)imino)methyl)phenol (4a-SB): SFC analysis (AD-H column, 6 min linear gradient from 5–40% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 1 min hold time, then a 15 s linear gradient from 40–5% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 45 s hold time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 254 nm): t_R(major) = 6.9 min, t_R(minor) = 7.2 min, *91% ee*.

Racemic Product:



Enantiomerically Enriched Product:

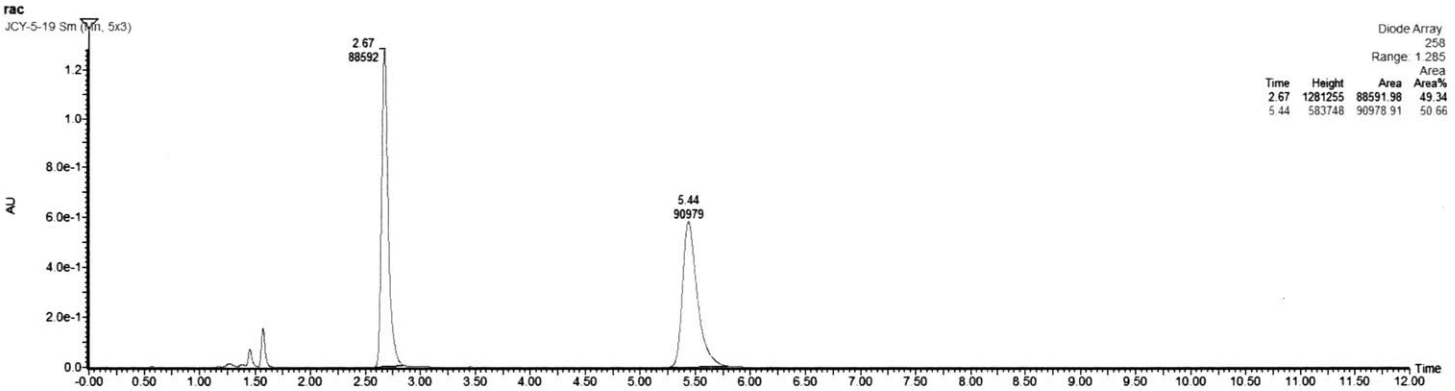




4b-SB

***tert*-butyl (*R*,*E*)-5-(1-((2-hydroxybenzylidene)amino)ethyl)-1*H*-indazole-1-carboxylate (4b-SB)**: SFC analysis (OJ-H column, 30% MeOH (0.1% diethylamine v/v) in $scCO_2$ 12 min hold time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 258 nm): t_R(major) = 2.7 min, t_R(minor) = 5.4 min, *96% ee*.

Racemic Product:



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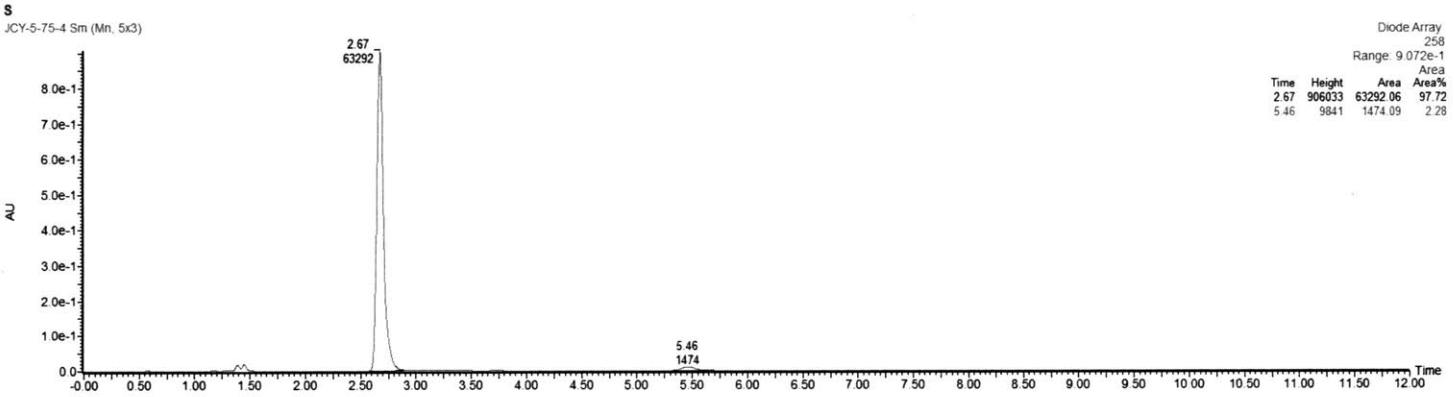
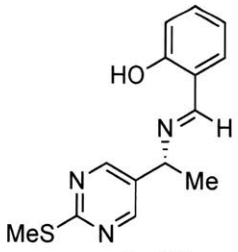
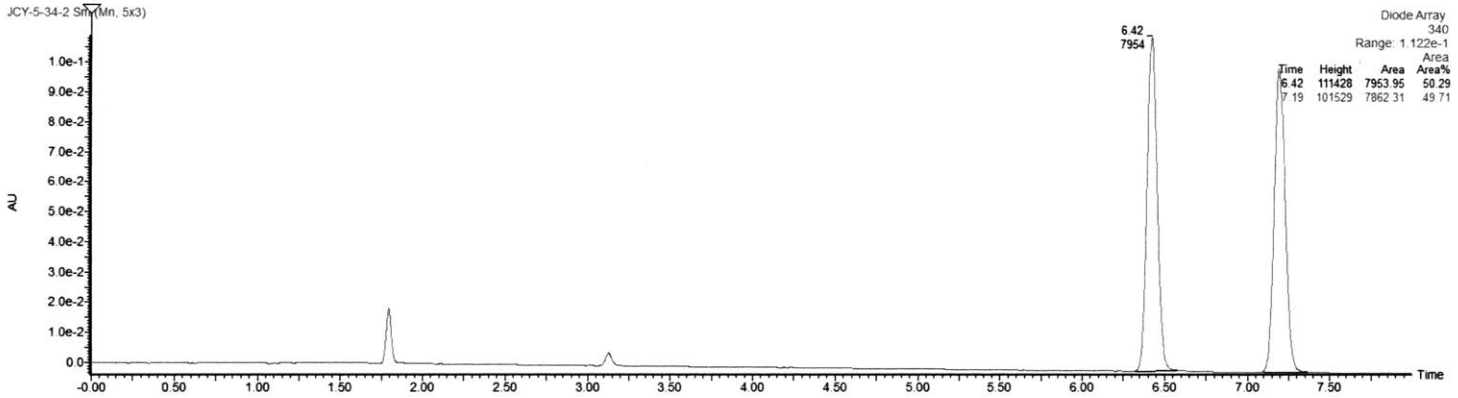




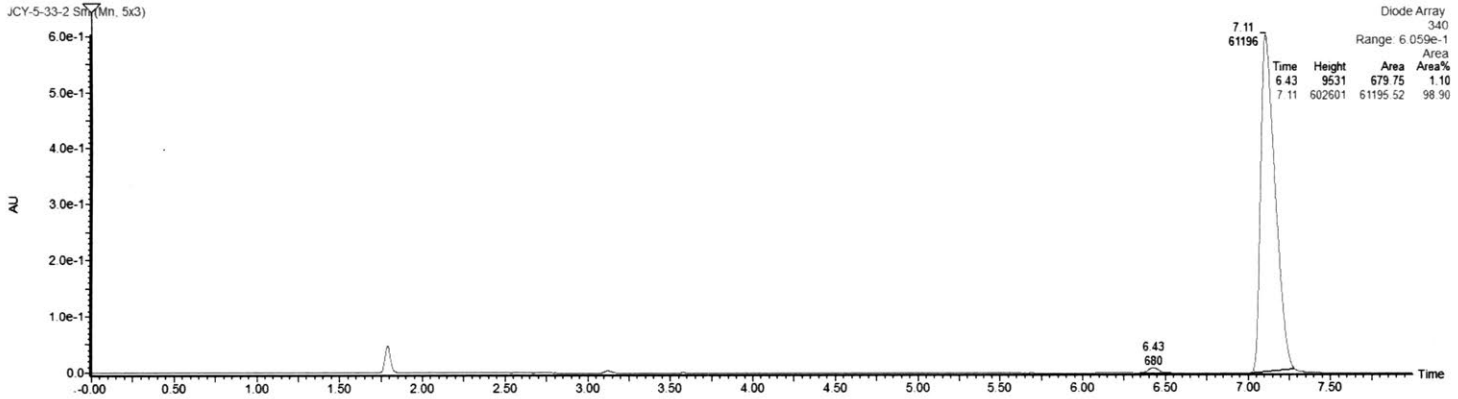
4c-SB

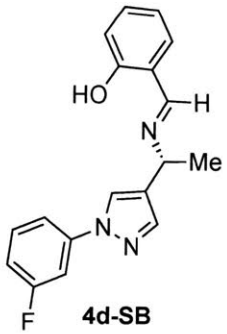
(*R*,*E*)-2-(((1-(2-(methylthio)pyrimidin-5-yl)ethyl)imino)methyl)phenol (4c-SB): SFC analysis (OJ-H column, 6 min linear gradient from 5–25% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 1 min hold time, then a 15 s linear gradient from 25–5% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 45 s hold time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 340 nm): t_R(major) = 7.1 min, t_R(minor) = 6.4 min, *98% ee*.

Racemic Product:



Enantiomerically Enriched Product:

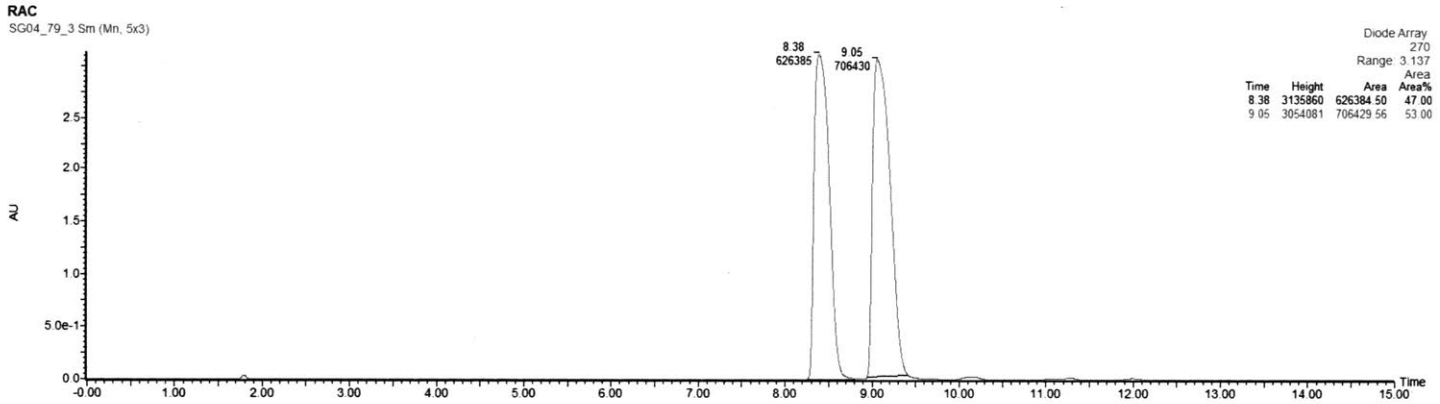




4d-SB

(*R*,*E*)-2-(((1-(1-(3-fluorophenyl)-1*H*-pyrazol-4-yl)ethyl)imino)methyl)phenol (4d-SB): SFC analysis (OJ-H column, 12.5 min linear gradient from 5–20% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 2 min hold time, then a 30 s linear gradient from 20–5% MeOH (0.1% diethylamine v/v) in $scCO_2$, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 270 nm): t_R(major) = 8.5 min, t_R(minor) = 9.3 min, *97% ee*.

Racemic Product:



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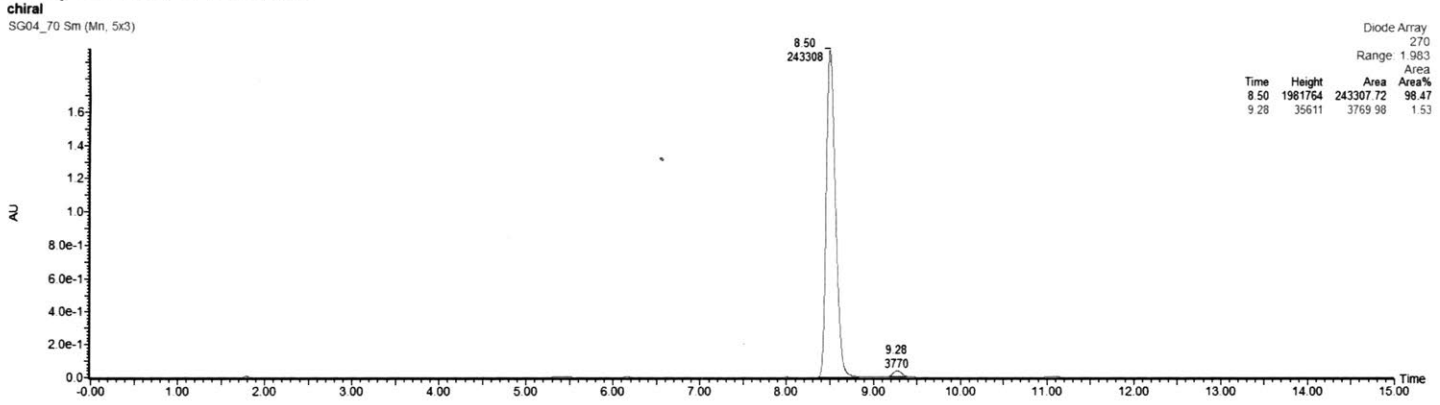
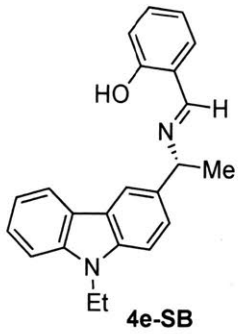
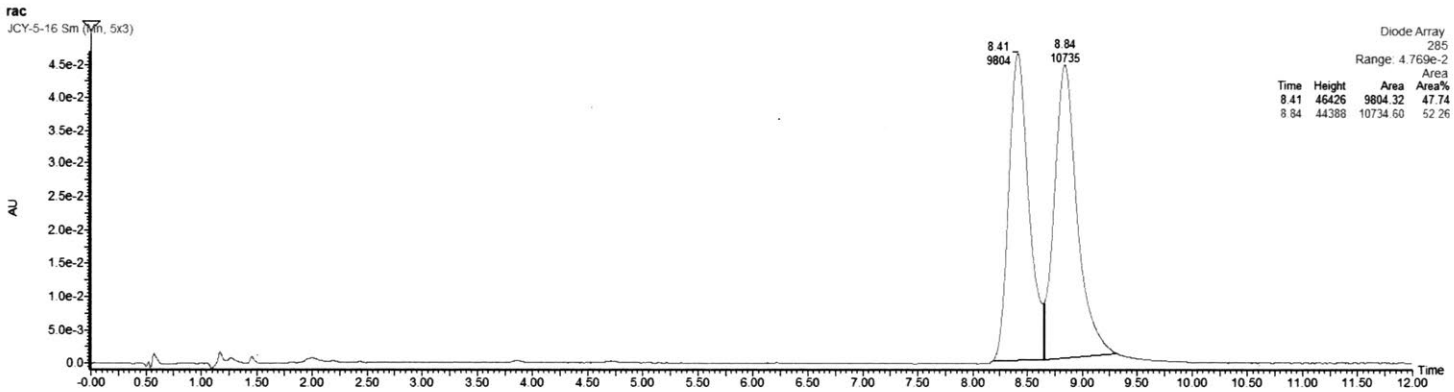




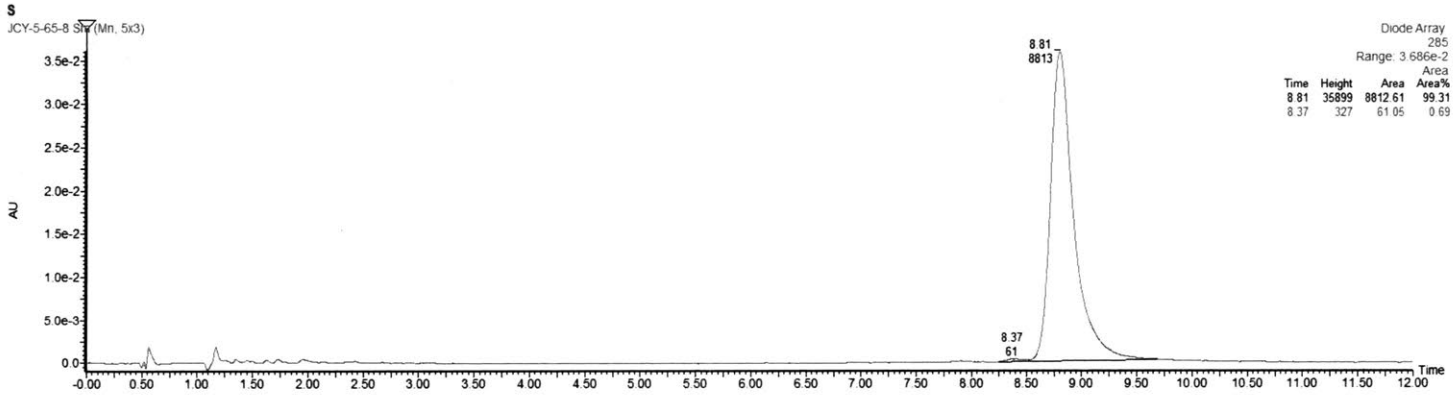
4e-SB

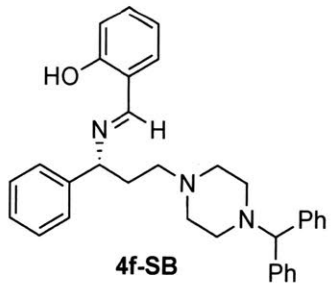
(*R*,*E*)-2-(((1-(9-ethyl-9*H*-carbazol-3-yl)ethyl)imino)methyl)phenol (4e-SB): SFC analysis (OJ-H column, 30% MeOH (0.1% diethylamine v/v) in $scCO_2$ 12 min hold time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 285 nm): t_R(major) = 8.8 min, t_R(minor) = 8.4 min, *98% ee*.

Racemic Product:



Enantiomerically Enriched Product:

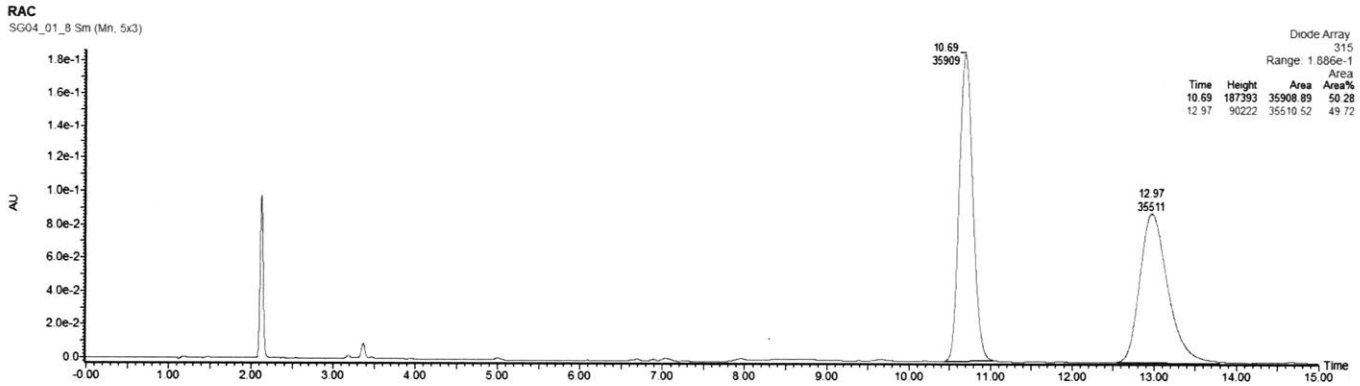




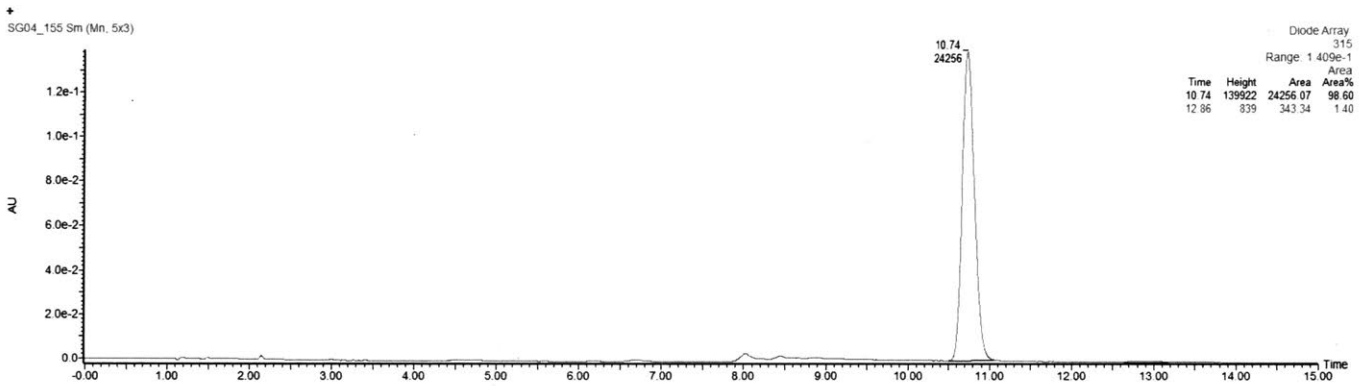
4f-SB

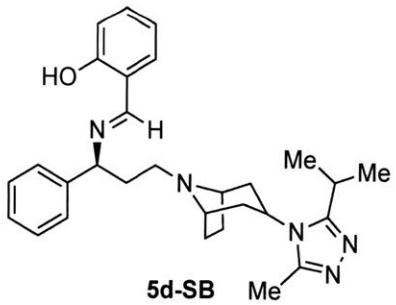
(*R*,*E*)-2-(((3-(4-benzhydrylpiperazin-1-yl)-1-phenylpropyl)imino)methyl)phenol (4f-SB): SFC analysis (AD-H column, 12 min linear gradient from 5–40% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 2 min hold time, then a 30 s linear gradient from 40–5% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 30 s hold time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 315 nm): t_R(major) = 10.8 min, t_R(minor) = 13.0 min, *97% ee*.

Racemic Product:



Enantiomerically Enriched Product:

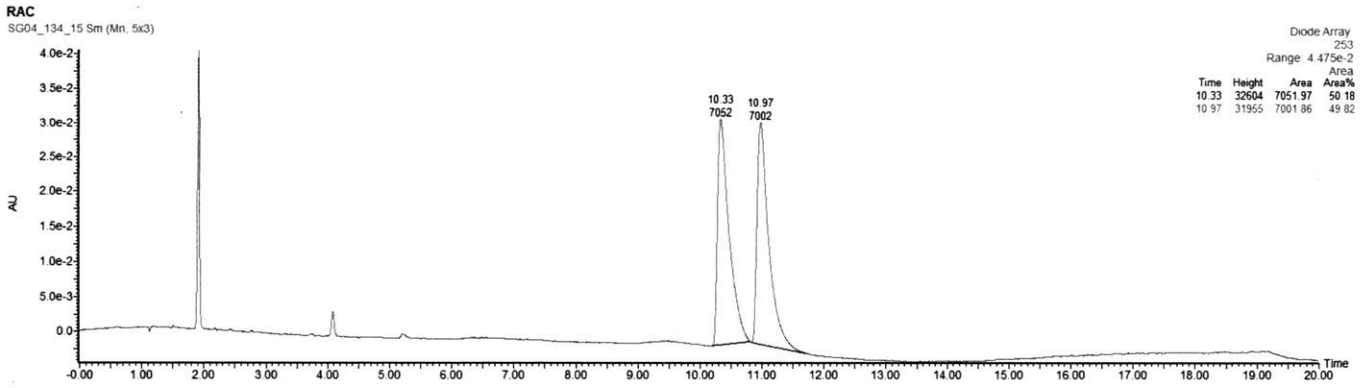




5d-SB

2-((*E*)-(((1*S*)-3-((1*R*,5*S*)-3-(3-isopropyl-5-methyl-4*H*-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropyl)imino)methyl)phenol (5d-SB): SFC analysis (OD-H column, 18 min linear gradient from 5–40% MeOH (0.1% diethylamine v/v) in $scCO_2$ followed by a 1.5 min hold time, then a 30 s linear gradient from 40–5% MeOH (0.1% diethylamine v/v) in $scCO_2$, time, 2.5 mL/min, simultaneous detection from 210–400 nm, quantitation wavelength = 253 nm): t_R(major) = 10.1 min, t_R(minor) = 11.0 min, *97% ee*.

Racemic Product:



Enantiomerically Enriched Product: