# TRANSITION METAL CATALYZED REACTIONS OF

# PYRIDINIUM AND IMINIUM IONS

by

Jennie Liao

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry and Biochemistry

Winter 2019

# TRANSITION METAL CATALYZED REACTIONS OF

# PYRIDINIUM AND IMINIUM IONS

by

Jennie Liao

Approved: _____
Brian J. Bahnson, Ph.D.
Chair of the Department of Chemistry and Biochemistry

Approved: _____
John Pelesko, Ph.D.
Interim Dean of the College of Arts and Sciences

Approved: _____
Douglas Doren, Ph.D.
Interim Vice Provost for Graduate and Professional Education

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Mary P. Watson, Ph.D.
Professor in charge of dissertation

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Donald A. Watson, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Klaus H. Theopold, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Christopher J. Kloxin, Ph.D.
Member of dissertation committee

## ACKNOWLEDGMENTS

Grad school has been one of the most memorable times of my life. Here I have had the pleasure of meeting some of the most interesting and extraordinary people in the world. I would not be who I am today without the help and support from everyone who has been a part of this journey. Thank you all from the bottom of my heart!

To my advisor Mary: You are one of the most inspiring people I have ever met. Thank you for all your support and guidance throughout this journey. I may have made some regrettable decisions in my life, but the decision to join your lab is one I will never regret. Thank you for taking me under your wing and for making me a better chemist and a better person. You have taught me so much both on and off the bench. It has truly been an honor to work with you over the past four years. Thank you so much for your encouragement and for believing that I can achieve so much more. You have opened up a world I never thought was possible. I will never forget all that you have done for me. I am sure I will never find anyone like you: a boss, a colleague, and more importantly a friend!

To my committee members, Professor Donald Watson, Professor Klaus Theopold, and Professor Christopher Kloxin: Thank you for your guidance and support throughout my PhD career. You have molded me into a better chemist and prepared me to tackle any problem the real world has to offer. Words cannot express my gratitude for all that you have done.

To my collaborators at Pfizer, Michelle Garnsey, Brian Boscoe, and Joseph Tucker: It has truly been a wonderful and eye-opening experience working with you.

Thank you for all your wonderful suggestions and for sparking my interest in the pharmaceutical industry.

To the wonderful members of the MPW group: You have all been indispensable in my graduate school career. I am so grateful to have been able to call you my friends. You make coming into lab every day all the more enjoyable. Thank you for putting up with me and accepting me into your lives. It has been a pleasure working with you over the past four years. I have learned so much from you and I hope you have done the same. A special thanks to my colleagues Javon, Weiye, Jianyu, Megan, Kristen, and Shane. Thank you for all the wonderful times both in and out of the lab. You have made my mundane life so much more exciting and entertaining. I will forever cherish these memories. I will miss you all!

To all the friends I've made along the way: Thank you for being a part of this journey. From strangers to comrades, you have been there every step of the way. To Klare, Sina, Will, Max, and Tianyu – you have made this road less lonely and your support has led me to the finish line. Thank you for never allowing me to give up and for encouraging me to continue fighting this uphill battle. This is not the end of our adventures, but the start of many new ones.

To my loving family, Mom, Dad, Connie, and Vinson: Thank you for your unwavering love and support throughout this journey. It has always been great to have someone believe in you more than you believe in yourself. Thank you for accepting my flaws and for never giving up on me. You have always encouraged me to follow my dreams and have always been there when I needed you. I am so fortunate to have you in my life. I hope I have made you proud. I love you all so much!

**TABLE OF CONTENTS**

# LIST OF TABLES

# LIST OF SCHEMES

xiii

# ABSTRACT

This dissertation focuses primarily on the development of novel methods for the transition metal-catalyzed cross-couplings of alkyl amine derivatives via carbon-nitrogen (C–N) bond activation. Chapters 1–4 focus on the use of Katritzky pyridinium salts, which can easily be obtained in a single step from primary amines. These redox-active amine derivatives can then serve as non-traditional electrophiles in a variety of nickel-catalyzed cross-coupling reactions. This work allows one to consider alkyl amines as substrates in cross-couplings for the first time and may have applications in late-stage derivatization of pharmaceutical targets. Chapter 5 focuses on the development of a copper-catalyzed enantioselective alkynylation of iminium ions to afford α-tetrasubstituted amines, an important motif in a variety of biologically active molecules.

Chapter 1 describes a nickel-catalyzed Suzuki–Miyaura cross-coupling of alkyl pyridinium salts with arylboronic acids. The combination of air- and moisture-stable $Ni(OAc)_2 \cdot 4H_2O$ and redox non-innocent bathophenanthroline (BPhen) ligand was found to promote the desired cross-coupling. Both primary and secondary alkyl groups participated smoothly under the optimized reaction conditions with excellent functional group tolerance. Excitingly, we have demonstrated the amenability of this method to pharmaceutical intermediates and amino acid derivatives. Notably, this is the first example of a metal-catalyzed cross-coupling of an amine derivative bearing *unactivated* alkyl groups. Preliminary mechanistic experiments suggest the

intermediacy of alkyl radical species, and the reaction is proposed to proceed via a Ni$^{I/III}$ catalytic cycle.

Chapter 2 describes a nickel-catalyzed Suzuki–Miyaura cross-coupling of benzylic pyridinium salts with arylboronic acids. This method enables the synthesis of diarylmethanes, a pharmaceutically relevant motif, from widely abundant benzylic amines. The use of a benzylic pyridinium intermediate allows for the incorporation of heteroaryl substitution, an important facet which is largely overlooked in other cross-couplings to deliver diarylmethanes. Metal-ligand complex PhenNi(OAc)$_2$·4H$_2$O was synthesized to enable facile reaction set-up and a wide solvent tolerance was demonstrated to facilitate the use of this chemistry in synthesis. A one-pot procedure was also developed for the direct conversion of a primary amine into the desired diarylmethane. This work was performed in collaboration with Michelle Garnsey, Brian Boscoe, and Joseph Tucker at Pfizer, Inc.

Chapter 3 describes a nickel-catalyzed Suzuki–Miyaura cross-coupling of benzylic pyridinium salts with vinylboronic acids and esters. This method allows for the rapid construction of 1,3-disubstituted allylic motifs. This chemistry is tolerant of heteroaryl substitution and can employ either the vinylboronic acid or pinacol ester as the coupling partner. Notably, this approach allows for control of the regioselectivity of the alkene.

Chapter 4 describes a nickel-catalyzed reductive cross-electrophile coupling of alkyl pyridinium salts with aryl bromides. This reaction leverages the wide availability of alkyl amines and aryl halides to deliver highly valuable alkylarenes. The optimized reaction conditions employ a catalyst system comprised of NiCl$_2$·DME and 4,4'-diOMeBipy in conjunction with manganese as a stoichiometric reductant. Primary,

secondary, and benzylic pyridinium salts are all amenable to this chemistry. Importantly, this method is tolerant of acidic protons and epimerizable stereocenters. We have shown the applicability of this chemistry to amino acid derivatives, pharmaceuticals, and pharmaceutical intermediates. Preliminary mechanistic experiments suggest that a radical-chain bimetallic pathway may be operative. This work was performed in collaboration with Michelle Garnsey, Brian Boscoe, and Joseph Tucker at Pfizer, Inc.

Chapter 5 describes my efforts towards a copper-catalyzed enantioselective alkynylation of iminium ions to form α-diaryl tetrasubstitued amines. The use of cyclic imines containing a removable tether allow for downstream cleavage to reveal enantioenriched acyclic amine products. Preliminary efforts on cyclic *N*-sulfonyl ketimine substrates have lead to good yields and modest ee's. Futher optimization of this reaction is ongoing. Additionally, unique conditions have been identified that can achieve kinetic resolution of a related benzisoxazoles.

**Chapter 1**

**SUZUKI–MIYAURA CROSS-COUPLING OF ALKYL PYRIDINIUM SALTS
WITH ARYLBORONIC ACIDS**

## 1.1 Introduction

Alkyl primary amines are prevalent amongst a wide range of natural and synthetic biologically active molecules, as well as building blocks of various complexities (Scheme 1.1).[1] The amino ($NH_2$) group possesses many attractive features such as ease of installation, straightforward purification, and the ability to be carried through multi- step syntheses in protected form. The advantages of alkylamines have been well recognized in the synthesis of many nitrogen containing compounds. In contrast, alkylamines have yet to be broadly utilized as alkylating agents in metal-catalyzed cross-coupling reactions. This would allow for rapid construction of new carbon-carbon bonds from inexpensive, widely available primary amine precursors. This would also enable the use of the amine ($NH_2$) moiety as a synthetic handle for structure-activity relationship (SAR) studies, along with late-stage functionalization of complex bioactive molecules.

Scheme 1.1    Examples of natural or synthetic bioactive alkyl primary amines



**1-1**
Tamiflu® (Roche)
*antiviral*

**1-2**
Januvia® (Merck)
*antidiabetic*

**1-3**
lysine
*amino acid*
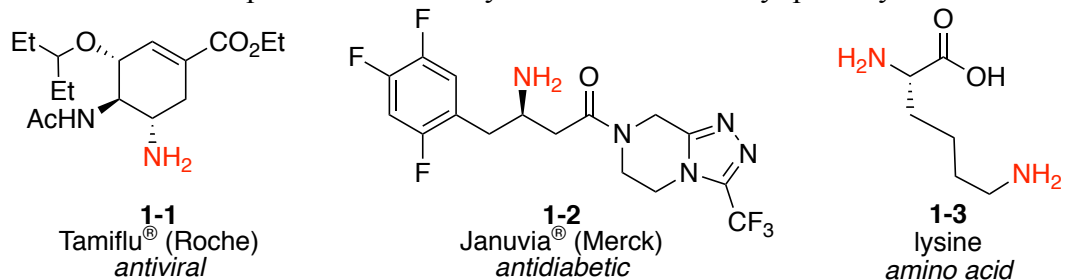
Cross-couplings have been achieved via cleavage of various $C_{sp2}$−N bonds, including those of aniline,[2, 3] enamine,[4] and amide derivatives.[5-9] In contrast, methods to harness $C_{sp3}$–N bonds have been limited to electronically activated benzylic (**1-4**),[10-14] allylic (**1-5**),[15] or α-keto amine derivatives (**1-6**),[16, 17] as well as strain-activated aziridines (**1-7**)[18-20] (Scheme 1.2). Recognizing the potential of unactivated $C_{sp3}$–N bonds, we set out to develop methodologies that would allow for the use of alkylamine derivatives as non-traditional electrophiles in nickel-catalyzed cross-couplings via C–N bond activation. Prior to our work, there were no examples of utilizing an alkylamine derivative bearing *unactivated* alkyl groups in transition metal-catalyzed cross-coupling reactions.

Scheme 1.2    $C_{sp3}$–N electrophiles used in transition metal-catalyzed cross-couplings



**1-4**
Watson
Tian
Rhee

**1-5**
Tian

**1-6**
Wang

**1-7**
Doyle
Jamison
Michael

*electronically activated*                          *strain activated*
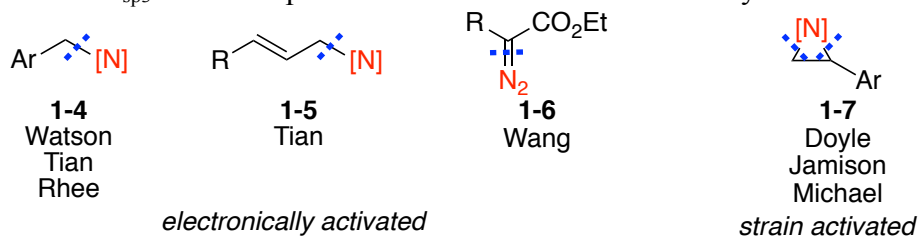
Historically, the use of alkyl $C_{sp3}$ coupling partners (both electrophilic and nucleophilic) have proven challenging. Potential issues include slow oxidative

addition or transmetallation as well as slow reductive elimination. Additionally, the alkylmetallic intermediates are prone to decomposition pathways such as β-hydride elimination and protodemetallation. Nonetheless, intense efforts have identified a variety of reagents suitable for the installation of alkyl groups lacking electronic or strain activation (Scheme 1.3). Conditions have been developed for metal-catalyzed cross-couplings of alkyl halides, pseudohalides, redox-active esters, and organometallic nucleophiles. Moreover, dual photoredox/nickel catalysis has enabled the use of oxalates, carboxylic acids, 1,4-dihydropyridines, organoboronates, and organosilicates. Seminal reports in this area are detailed below.

Scheme 1.3     Reagents for installing unactivated alkyl groups via cross-couplings



| **1-8** | **1-9** | **1-10** | **1-11** | **1-12** | **1-13** |
|---|---|---|---|---|---|
| *halides* | *sulfonates, oxalates* | *carboxylic acids* | *redox-active esters* | *dihydropyridines* | *organometallics* $M = BF_3K$, $Si(O_2R)_2HNR_3$, $SnR_3$, $MgX$, $ZnX$ |
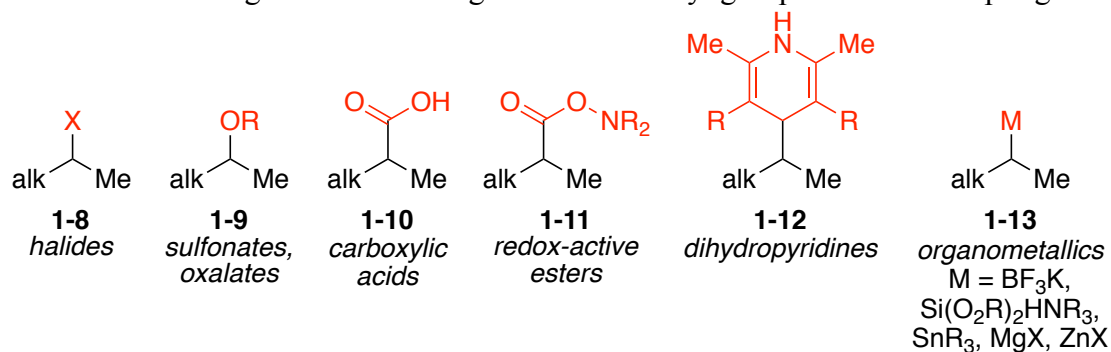
In 2003, Fu reported his seminal publication on the nickel-catalyzed Negishi cross-coupling of unactivated alkyl bromides and iodides (**1-14**) (Scheme 1.4).[21] Notably, this was the first example of a nickel- or palladium-catalyzed cross-coupling of unactivated, β-hydrogen-containing, secondary alkyl halides. Mechanistic studies have revealed that alkyl halides can undergo single-electron transfer (SET) oxidative addition to generate the corresponding alkyl radicals.[22] This finding set the stage for a number of subsequent accounts expanding upon this chemistry for the construction of

new C–C and C–X bonds.[23-26] In fact, alkyl halides remain an active area of research for the installation of alkyl groups via metal-catalyzed cross-coupling reactions.

Scheme 1.4    Fu's Negishi cross-coupling of alkyl halides
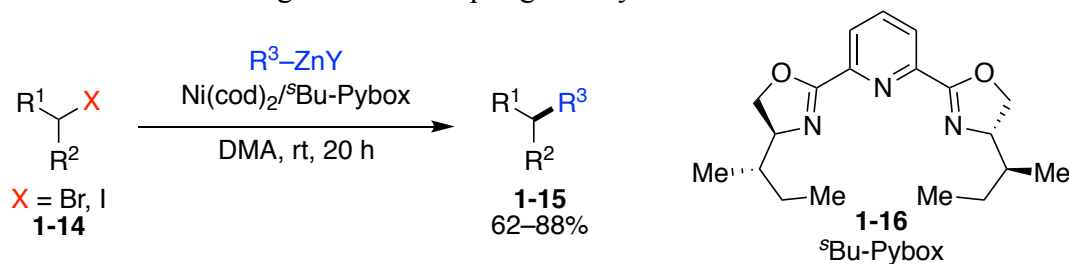


Within the last decade, interest has expanded towards the identification of other readily available alkylating agents such as alcohols and carboxylic acids. The MacMillan group has demonstrated that by combining photoredox and nickel catalysis, cross-coupling of alkyl oxalates (**1-18**) and aryl halides can be achieved (Scheme 1.5).[27] In this case, **1-18** is formed from the corresponding alcohol (**1-17**) and oxalyl chloride, and used without further purification. The iridium photocatalyst is used to generate carbon-centered radical **1-19** via successive loss of two equivalents of $CO_2$. This alkyl radical can then intercept the nickel cycle to deliver cross-coupled product **1-20**. This method highlights the feasibility of alcohols to serve as latent $C_{sp3}$– nucleophiles.

**Scheme 1.5    MacMillan's metallaphotoredox cross-coupling of alkyl oxalates**
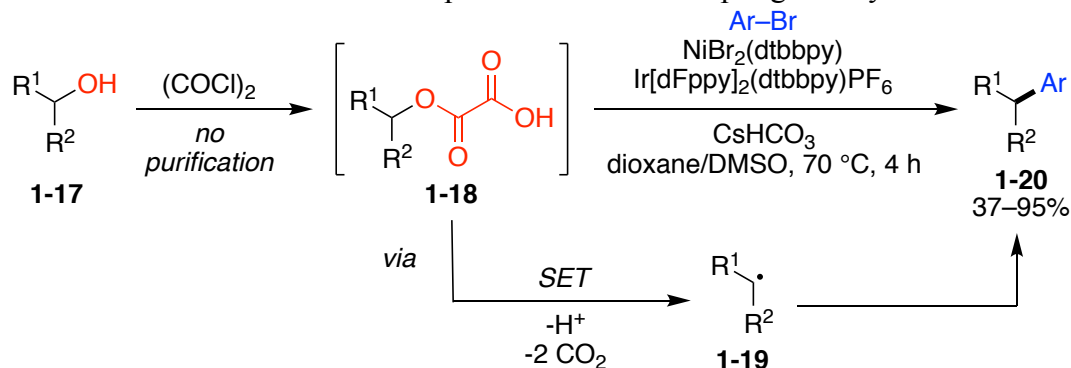


Similarly, carboxylic acids can also serve as alkyl nucleophiles. The Doyle and MacMillan groups have shown that α-amino carboxylic acids (**1-21**) can undergo cross-couplings with aryl halides by merging photoredox and nickel catalysis (Scheme 1.6).[28] Again, the iridium photocatalyst is used to generate the α-amino radical via loss of $CO_2$. This can then engage in the nickel cycle with an aryl halide to give arylated product **1-22**. Additionally, the Molander group has demonstrated a variety of dual photoredox/nickel-catalyzed cross-couplings using alkyl trifluoroborate salts, silicates, and dihydropyridines.[29-31]

**Scheme 1.6    Doyle and MacMillan's decarboxylative metallaphotoredox cross-coupling of α-amino carboxylic acids**
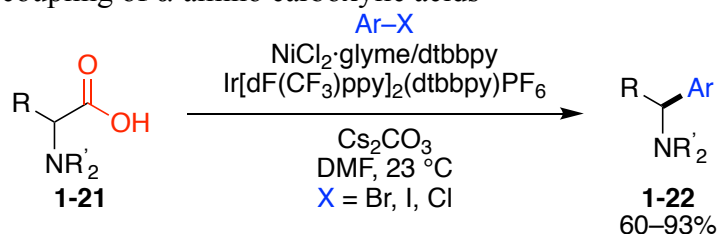
The umpolung approach utilizing carboxylic acids as alkyl electrophiles has also been investigated. Alkyl carboxylic acids can be converted into the corresponding *N*-hydroxyphthalimide esters (**1-23**). These redox-active esters have been demonstrated to participate in a number of cross-coupling reactions. For example, in his seminal publication, Baran has shown that these substrates can undergo Negishi cross-couplings to form arylated products **1-26** (Scheme 1.7A).[32] The proposed mechanism for this transformation involves a $Ni^{I/III}$ catalytic cycle. Radical anion **1-24** is generated via single electron-transfer from a $Ni^{I}$ species into the redox-active ester. Fragmentation of **1-24** leads to extrusion of $CO_2$ and loss of the phthalimide anion, forming alkyl radical **1-25**. Additionally, Weix has demonstrated that these redox-active esters (**1-27**) can participate in a reductive cross-electrophile coupling with aryl iodides using Zn as a stoichiometric reductant (Scheme 1.7B).[33] However, unlike Baran's chemistry, a radical-chain bimetallic pathway is proposed. Since then, a number of different cross-couplings utilizing redox-active esters have been reported.[34-36]

Scheme 1.7    Nickel-catalyzed cross-couplings of redox-active esters

A.  Baran's Negishi cross-coupling
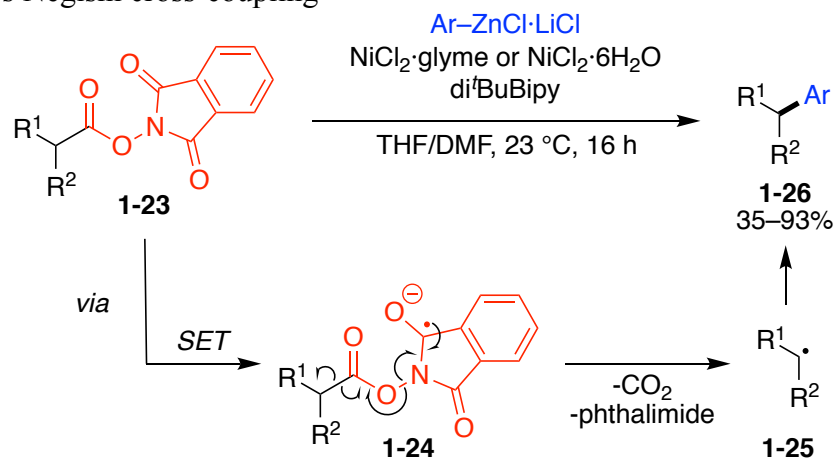
B. Weix's reductive cross-coupling with aryl iodides
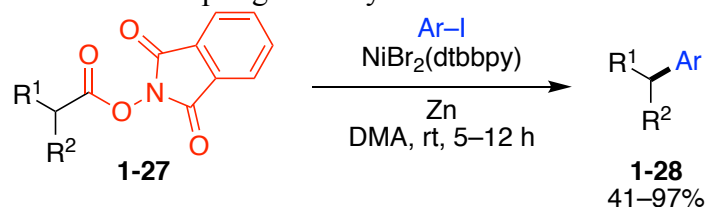


Alkyl amines are inexpensive, widely available feedstock chemicals. The cross-coupling of an alkyl amine derivative would offer an exciting complementary approach for installing unactivated alkyl groups. Towards this end, we identified Katritzky pyridinium salts (**1-31**) as potential electrophiles for nickel-catalyzed cross-couplings (Scheme 1.8).[37] This unique approach hinges on the redox-active nature of these pyridinium salts and their ability to serve as alkyl radical precursors via $C_{sp3}$–N bond cleavage. Historically, these salts have primarily been employed in a variety of two-electron nucleophilic substitution reactions.[38] Herein, we disclose the first example of a metal-catalyzed cross-coupling of an amine derivative bearing *unactivated* alkyl groups.

Scheme 1.8    Proposed cross-coupling of alkyl amine derived pyridinium salts



7
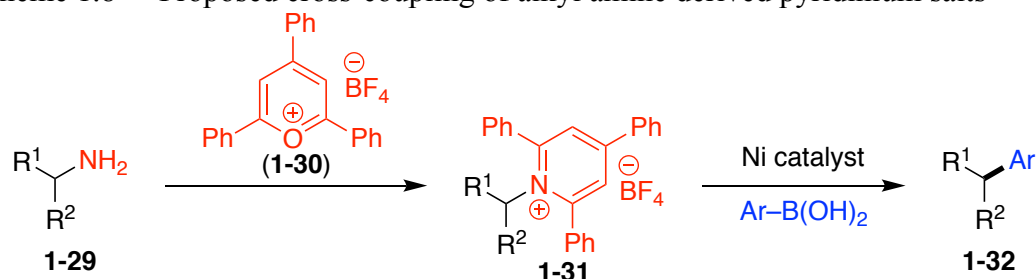
## 1.2 Results and Discussion

### 1.2.1 Synthesis of Katritzky Pyridinium Salts

The Katritzky pyridinium salts (**1-31**) can be prepared in a single step via condensation of an alkyl primary amine (**1-29**) with commercially available 2,4,6-triphenylpyrylium tetrafluoroborate (**1-30**). Excitingly, this method is chemoselective for primary amines and allows for the incorporation of other nitrogen containing functionalities within the organic framework. Moreover, these salts often require no chromatography as they precipitate upon trituration with ether to afford **1-31** as an air- and moisture-stable solid. A variety of alkyl pyridinium salts can be prepared via this method (Scheme 1.9). Notably, both primary and secondary alkyl groups can be incorporated, as well as protected secondary (**1-36**) and tertiary (**1-37** & **1-38**) amines.

Scheme 1.9    Selected examples of alkyl pyridinium salts formed
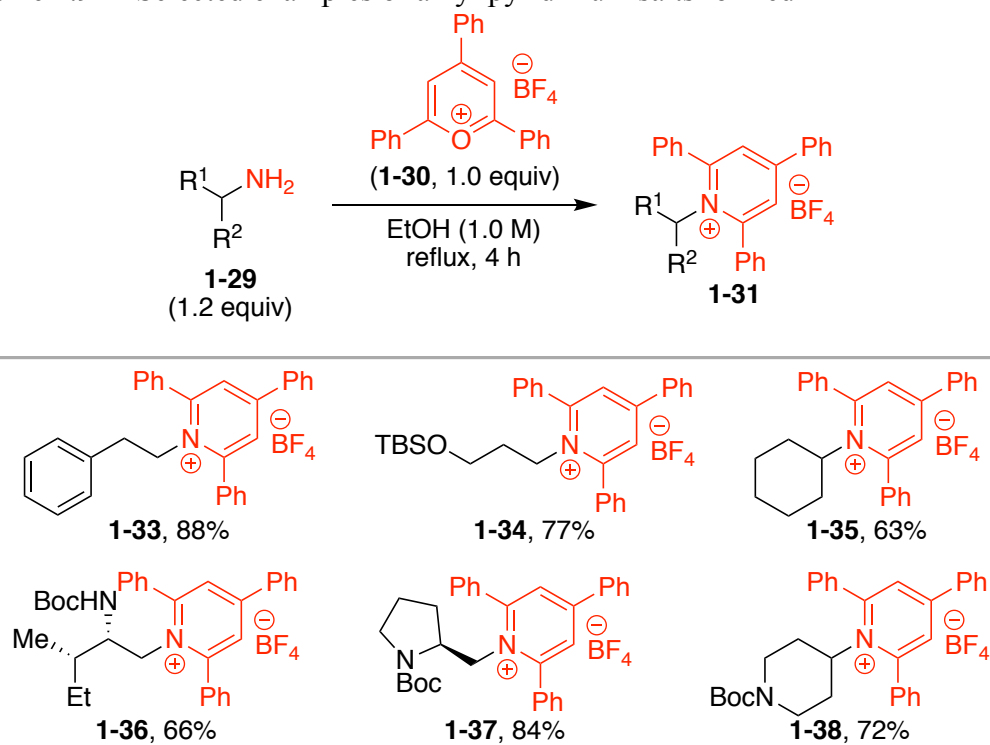
### 1.2.2 Reaction Optimization

My colleague Corey Basch chose pyridinium salt **1-39** for the preliminary investigation of the Suzuki–Miyaura cross-coupling with bench-stable arylboronic acids. Optimization began with the first-generation conditions our group had previously identified for the activation of benzylic trimethylammonium salts.[11] Disappointingly, the formation of only a trace amount of **1-40** was observed (Table 1.1, entry 1). A brief ligand screen revealed that redox non-innocent phenanthroline-based ligands, specifically bathophenanthroline (BPhen, **1-41**), were the most effective in promoting the desired cross-coupling (entry 2). Switching to an alkoxide base as well as from a $Ni^0$ source to a $Ni^{II}$ salt further improved the yield (entries 3 & 4). By pre-mixing the nickel and ligand separately from the rest of the reagents, further improvement was observed (entry 5). Finally, the addition of ethanol was found to increase the yield of the reaction substantially (entry 6). We hypothesize that this additive likely improves the solubility of the base and/or boronic acid.

Table 1.1      Reaction optimization of the Suzuki–Miyaura cross-coupling of alkyl pyridinium salts with arylboronic acids[a]
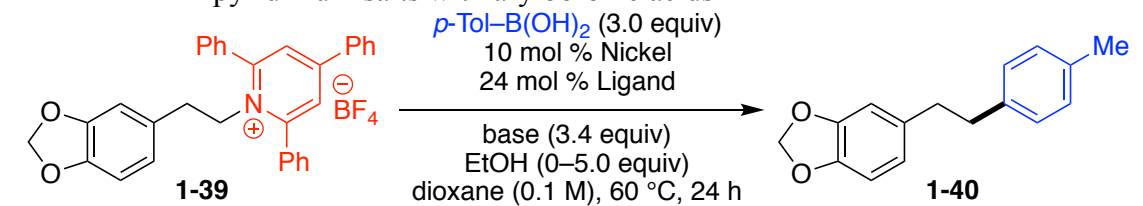


| Entry | Ni Source | Ligand | Base | Additive | Yield (%)[b] |
|-------|-----------|--------|------|----------|--------------|
| 1 | Ni(cod)$_2$ | PPh$_2$Cy | K$_3$PO$_4$ | none | 6 |
| 2 | Ni(cod)$_2$ | BPhen | K$_3$PO$_4$ | none | 21 |
| 3 | Ni(cod)$_2$ | BPhen | KO$^t$Bu | none | 24 |

| | | | | | |
|---|---|---|---|---|---|
| 4 | Ni(OAc)$_2$·4H$_2$O | BPhen | KO$^t$Bu | none | 39 |
| 5$^c$ | Ni(OAc)$_2$·4H$_2$O | BPhen | KO$^t$Bu | none | 52 |
| 6$^c$ | Ni(OAc)$_2$·4H$_2$O | BPhen | KO$^t$Bu | EtOH$^d$ | 81 |

[a]Conditions: pyridinium salt **1-39** (0.10 mmol), *p*-Tol–B(OH)$_2$ (3.0 equiv), [Ni] (10 mol %), ligand (24 mol %), base (3.4 equiv), dioxane (0.1 M), 60 °C, 24 h, unless noted otherwise. [b]Determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]Two mixtures (Vial 1: [Ni], Ligand, dioxane. Vial 2: pyridinium salt **1-39**, *p*-Tol–B(OH)$_2$, Base, EtOH, dioxane.) were stirred for 1 h before combining. [d]EtOH (5.0 equiv) added.



**1-41**
BPhen
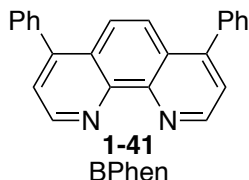
### 1.2.3  Reaction Scope

With optimized conditions in hand, I, along with Jianyu Xu and Jacob Piane, joined the project to demonstrate the scope of this transformation (Scheme 1.10). We were very delighted to find that a number of primary and secondary (cyclic and acyclic) alkyl groups participated smoothly under these reaction conditions. The model reaction afforded **1-40** in 75% isolated yield on a 1.0-mmol scale. We have also shown that the reaction is somewhat tolerant of moisture, as a similar yield was observed in the absence of oven-dried glassware for the formation of cross-coupled product **1-42**. However, a significant drop in yield (31%) was observed when minimal precaution was taken to exclude air or moisture (solvents and glassware were not dried and the reaction was set up under air).

**Scheme 1.10** Scope of non-pyridyl boronic acid[a]



Reaction conditions: Ar–B(OH)₂ (3.0 equiv), 10 mol % Ni(OAc)₂·4H₂O, 24 mol % BPhen, KO$^t$Bu (3.4 equiv), EtOH (5.0 equiv), dioxane (0.1 M), 60 °C, 24 h; converting **1-31** to **1-32**.

**1-40**, 75%

**1-42**, 74%
w/o dry galssware: 66%[b,c]
minimal precaution: 31%[b,d]

**1-43**, 52%

**1-44**, 78%

**1-45**, 70%

**1-46**, 73%

**1-47**, 58%

**1-48**, 66%[b]

**1-49**, 48%

**1-50**, 69%

**1-51**, 81%

**1-52**, 65%[b]
*from proline*

**1-53**, 52%[b]
single diastereomer
*from isoleucine*

**1-54**, 60%, 29% ee[b,e]
25%, 81% ee[b,f]
*from lysine*

11

**1-55**, 71%                    **1-56**, 62%
*from Mosapride intermediate*

---
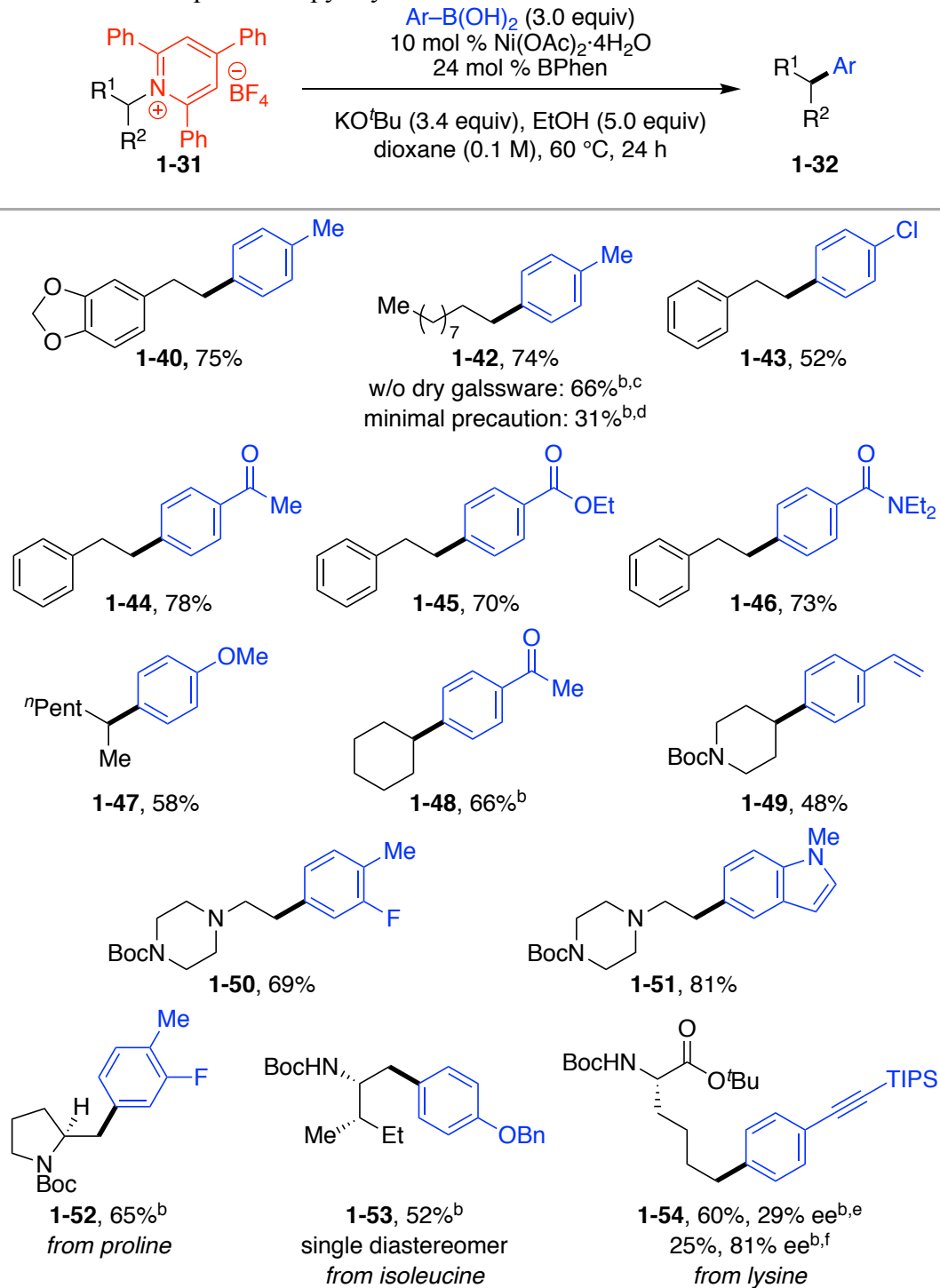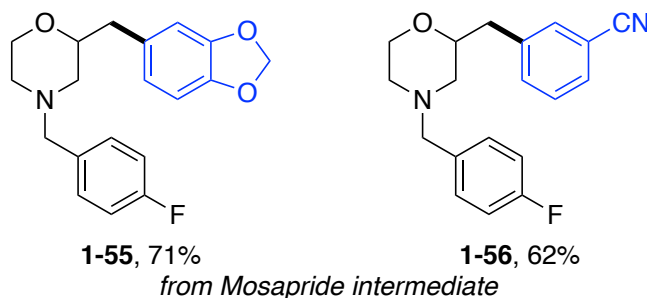
[a]Conditions: pyridinium salt **1-31** (1.0 mmol), Ni(OAc)$_2$·4H$_2$O (10 mol %), BPhen (24 mol %), ArB(OH)$_2$ (3.0 equiv), KO$^t$Bu (3.4 equiv), EtOH (5 equiv), dioxane (0.1 M), 60 °C, 24 h. Average isolated yields (±6%) from duplicate experiments. [b]Single experiment. [c]Glassware not oven-dried before use. [d]Minimal precautions to protect from air and moisture. [e]0.5-mmol scale. [f]0.05-mmol scale. $p$-(CF$_3$)C$_6$H$_4$OH (2 equiv) added. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Many functional groups on the alkyl coupling partner were well tolerated, including ethers, silyl ethers, acetals, and esters. In addition, tertiary and Boc-protected amines as well as heterocycles, such as piperidines, piperazines, and morpholine, can be used. We have also coupled substrates derived from amino acids. Products **1-52** and **1-53** are derived from proline and isoleucine, respectively. Notably, **1-53** is formed as a single diastereomer, indicating that non-acidic stereocenters are preserved under these conditions. Cross-coupling of the amino side chain of *N*-Boc lysine also proceeded in good yield, albeit with poor conservation of enantiomeric excess (*ee*) (**1-54**). However, a much higher *ee*, but lower yield, was observed with the use of an acidic additive (i.e., $p$-(CF$_3$)C$_6$H$_4$OH), suggesting conditions can be identified to solve this problem. Moreover, we have demonstrated the synthetic utility

of this chemistry for late-stage functionalization of intermediates in the synthesis of bioactive molecules. For example, products **1-55** and **1-56** are derived from an amine intermediate in the synthesis of Mosapride, a treatment for gastrointestinal disorders.[39]

Broad scope was also achieved with the arylboronic acid. Various functionalities were tolerated, including aryl chlorides (**1-43**) and fluorides (**1-50**, **1-52**), methyl ketones (**1-44**, **1-48**), esters (**1-45**), amides (**1-46**), ethers (**1-47**, **1-52**), alkenes (**1-49**), silyl-protected alkynes (**1-54**), acetals (**1-55**), and nitriles (**1-56**). Given the prevalence of heterocycles in bioactive molecules, we prioritized the incorporation of heteroarylboronic acids in the cross-coupling. *N*-Methylindole was easily installed (**1-51**). Pyridyl boronic acids can also be used under slightly modified conditions. By utilizing a lower ligand loading (12 mol %) and more dilute conditions (0.025 M), a variety of heteroarenes can be incorporated (Scheme 1.11). Both 3- and 4-pyridyl groups work, including those with fluoride (**1-57**, **1-60**, **1-61**, & **1-65**), ether (**1-58** & **1-63**), and morpholino (**1-64**) substituents. Notably, 2-fluoropyridines are primed for elaboration via $S_N Ar$ chemistry. Unsubstituted pyridyl (**1-59**) and quinoline (**1-62**) were also successful. Moreover, product **1-65** is derived from an amine intermediate used in the synthesis of Lipitor® (Pfizer, Inc.), an anti-cholesterol drug.[40]

Scheme 1.11   Scope of pyridyl boronic acid[a]





**1-57**, 81%

**1-58**, 74%

**1-59**, 53%

**1-60**, 66%

**1-61**, 71%

**1-62**, 59%

**1-63**, 66%

**1-64**, 62%[b]

**1-65**, 46%[b]
*from Lipitor® intermediate*
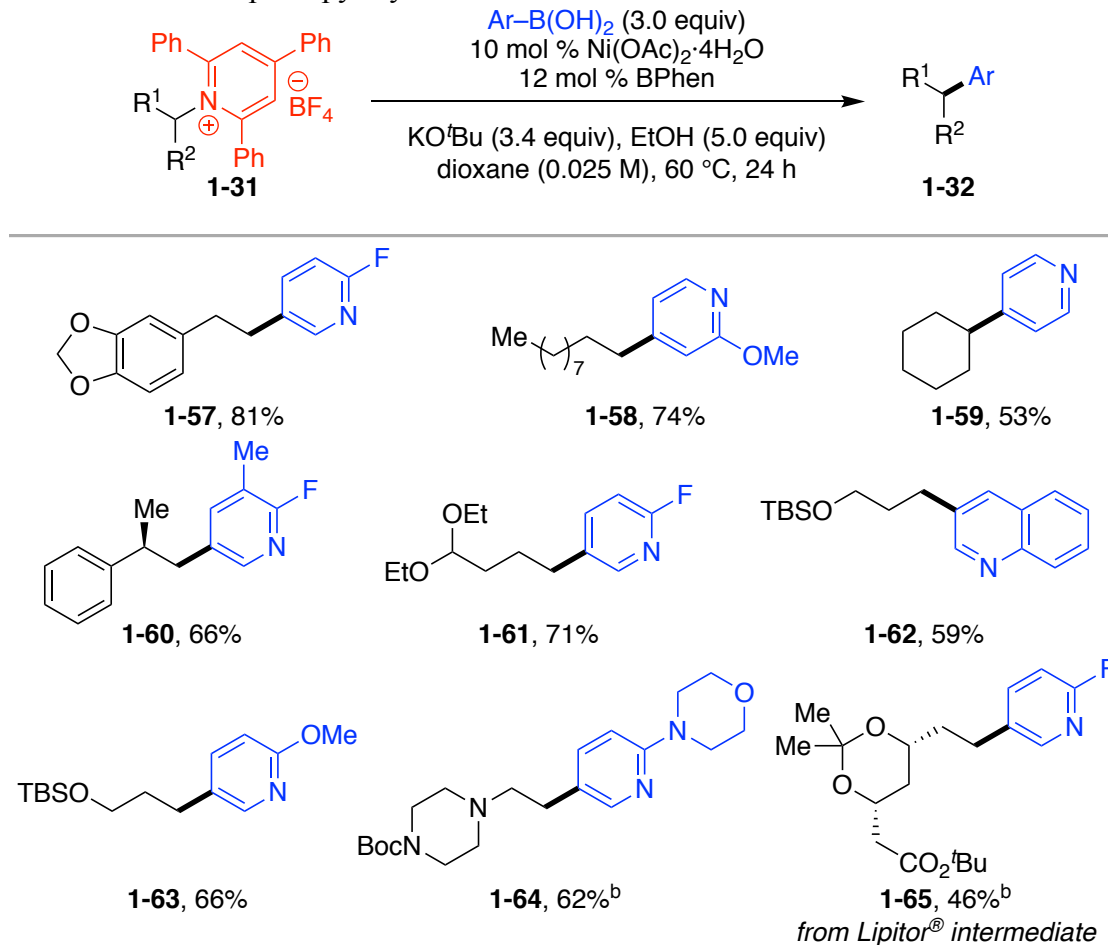
[a]Conditions: pyridinium salt **1-31** (1.0 mmol), Ni(OAc)$_2$·4H$_2$O (10 mol %), BPhen (12 mol %), ArB(OH)$_2$ (3.0 equiv), KO$^t$Bu (3.4 equiv), EtOH (5 equiv), dioxane (0.025 M), 60 °C, 24 h. Average isolated yields (±6%) from duplicate experiments. [b]Single experiment.

## 1.2.4   Mechanistic Studies

We reckoned that the cross-coupling could proceed via a Ni$^{I/III}$ or Ni$^{0/II}$ catalytic cycle. A Ni$^{0/II}$ mechanism would involve two-electron oxidative addition

($S_N1$ or $S_N2$), whereas a $Ni^{I/III}$ cycle would proceed via single-electron transfer (SET) from a $Ni^I$ intermediate to the pyridinium salt. Although, pyridinium salts have been precedented to participate in $S_N2$ chemistry,[41] Katritzky has also shown that these salts can act as single-electron acceptors. For instance, they have been used in the C-alkylation of nitronate anions (Scheme 1.12).[42] Pyridinium salts have also shown to be effective photosensitizers[43] and sources of nitrogen-centered radicals.[44]

Scheme 1.12    Katritzky's alkylation of nitronate anions with alkyl pyridinium salts
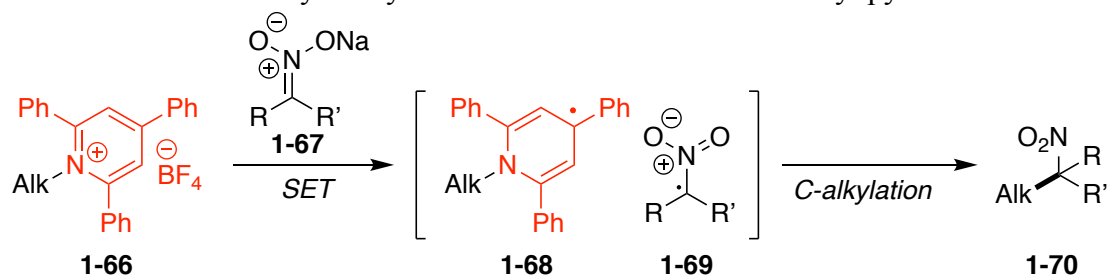


The superiority of bipyridyl ligands, which are often employed in $Ni^{I/III}$ catalysis, and the fact that $Ni^{II}$ precursors outcompete $Ni^0$ pre-catalysts further allude to a SET mechanism (See Table 1.1, entries 3 & 4). This mechanism would lead to the formation of an alkyl radical intermediate. With that in mind, I performed several mechanistic experiments to probe the intermediacy of this alkyl radical species. Given the rapid interconversion of alkyl radicals, we proposed that erosion of stereochemical information through the course of the reaction would be observed. In fact, cross-coupling of pyridinium salt **1-71**, which was prepared from enantiopure (*S*)-2-aminooctane, led to the formation of racemic arylated product **1-72** in 54% yield (Scheme 1.13A). Moreover, cross-coupling of radical-clock cyclopropane **1-73** resulted in ring-opened product **1-74** (Scheme 1.13B). The addition of TEMPO shut

down the cross-coupling reaction and provided only TEMPO-trapped adduct **1-76** in 20% yield (Scheme 1.13C). These results are in support of an alkyl radical intermediate.

Scheme 1.13   Mechanistic support for radical intermediate

A.  Racemization



**1-71**
*from (S)-2-aminooctane*
*(>99% ee)*

Ar–B(OH)$_2$ (3.0 equiv)
10 mol % Ni(OAc)$_2$·4H$_2$O
24 mol % BPhen

KO$^t$Bu (3.4 equiv), EtOH (5 equiv)
dioxane (0.1 M), 60 °C, 24 h

**1-72**
54% (NMR)
racemic

B.  Cyclopropyl ring-opening



**1-73**

*p*-Tol–B(OH)$_2$ (3.0 equiv)
10 mol % Ni(OAc)$_2$·4H$_2$O
24 mol % BPhen

KO$^t$Bu (3.4 equiv), EtOH (5 equiv)
dioxane (0.1 M), 60 °C, 24 h

**1-74**
33% (NMR)

C.  TEMPO trap



**1-33**

*p*-Tol–B(OH)$_2$ (3.0 equiv)
10 mol % Ni(OAc)$_2$·4H$_2$O
24 mol % BPhen

KO$^t$Bu (3.4 equiv), EtOH (5 equiv)
TEMPO (2.0 equiv)
dioxane (0.1 M), 60 °C, 24 h

**1-76**
20% (NMR)
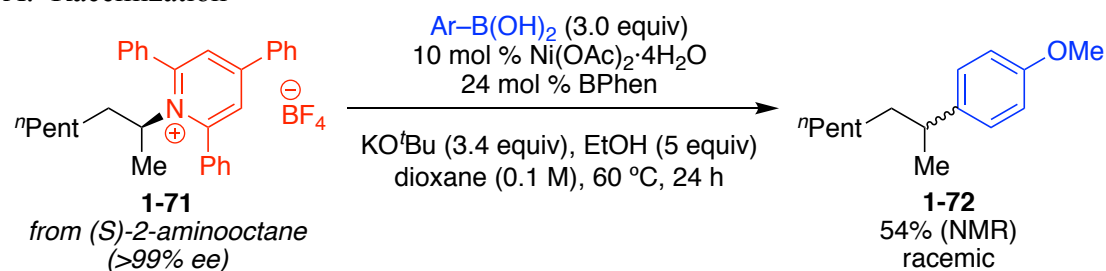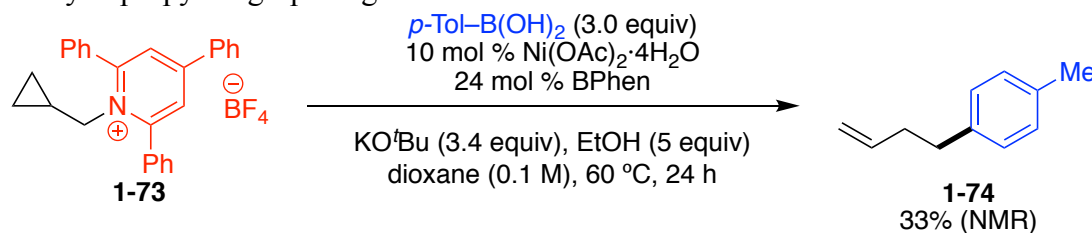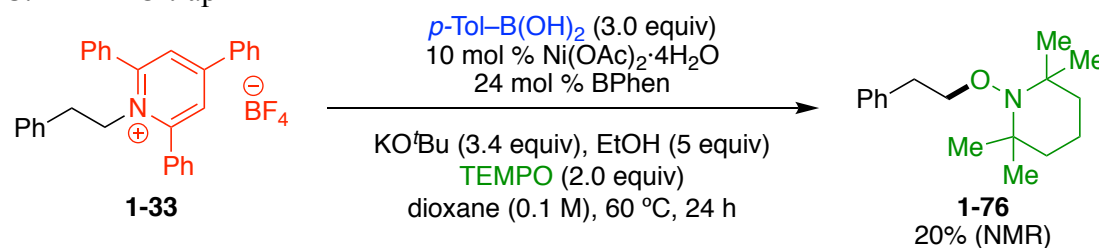
In light of this data, we have proposed the following Ni$^{I/III}$ catalytic cycle (Scheme 1.14). In this scheme, I have assigned redox events only to the nickel center for simplicity, but certainly the BPhen ligand may also be undergoing redox events. Ni$^I$ species **A** undergoes transmetallation with the activated boronate to generate aryl-Ni$^I$ species **B**. Single-electron transfer (SET) from **B** into the pyridinium ring leads to

the formation of radical species **C**. This then induces homolytic C–N bond cleavage to generate alkyl radical **D** as well as 2,4,6-triphenylpyridine as byproduct. Alkyl radical **D** can then recombine with Ni$^{II}$-arene **E** via a radical-rebound pathway to generate Ni$^{III}$ species **F**. This intermediate is then prone to reductive elimination to deliver the desired cross-coupled product and regenerate active catalyst **A**. This monometallic "transmetallation-first" type mechanism is analogous to that proposed by Vicic for Fu's Negishi cross-coupling of alkyl halides.[22] We are cognizant that alternative pathways are possible such as a radical chain bimetallic SET oxidative addition[45] and cannot distinguish these possibilities with the current data. Future efforts in the group are focused on elucidating the elementary steps of this catalytic process.

Scheme 1.14   Proposed catalytic cycle
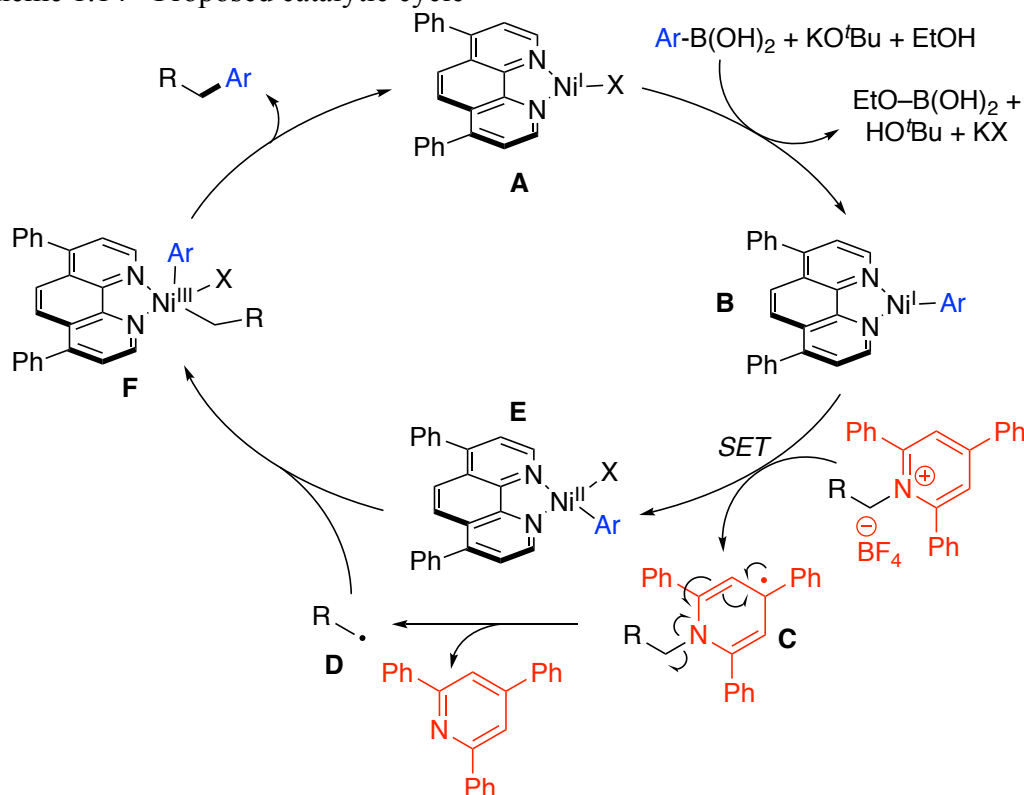
## 1.3   Conclusion

In summary, we have developed a nickel-catalyzed cross coupling of alkyl pyridinium salts with arylboronic acids. We have demonstrated broad substrate scope in both coupling partners, particularly with the incorporation of nitrogen containing functionalities. We have also shown the amenability of this method to a number of amino acid derivatives and drug intermediates. These examples highlight the potential of the amine ($NH_2$) moiety to serve as a handle for elaboration and late-stage functionalization, especially within the context of drug discovery efforts. Moreover, this method allows inexpensive primary amine precursors to be converted into complex, high value compounds. Notably, this is the first example of a metal-catalyzed cross-coupling of an amine derivative bearing unactivated alkyl groups. This work was published in the *Journal of the American Chemical Society*.[46]

## 1.4   Experimental

### 1.4.1   General Information

Reactions were performed in oven-dried Schlenk flasks or in oven-dried round-bottomed flasks unless otherwise noted. Round-bottomed flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of $N_2$. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Silica gel chromatography was performed on silica gel 60 (40-63 μm, 60Å) unless otherwise noted. Commercial reagents, including 2,4,6-triphenylpyrylium tetrafluoroborate and the primary and secondary alkyl amines (or corresponding

hydrochloride salts), were purchased from Sigma Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, AK Scientific, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: anhydrous ethanol was degassed by sparging with $N_2$ for 20-30 minutes prior to use in the cross-coupling reactions; dioxane was dried by passing through drying columns, then degassed by sparging with $N_2$.[47] In some instances oven-dried potassium carbonate was added to $CDCl_3$ to remove trace acid. Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra, fluorine nuclear magnetic resonance spectra (^{19}F NMR), and silicon nuclear magnetic resonance spectra (^{29}Si NMR) were recorded on both 400 MHz and 600 MHz spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3 = \delta$ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3 = \delta$ 77.16). Chemical shifts for fluorine were externally referenced to $CFCl_3$ in $CDCl_3$ ($CFCl_3 = \delta$ 0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, h = heptet), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using FTIR spectrophotometers with material loaded onto a KBr plate. The mass spectral data was obtained at the University of Delaware mass spectrometry facility. Optical rotations were measured using a 2.5 mL cell with a 0.1 dm path length. Melting points were taken on a Thomas-Hoover Uni-Melt Capillary Melting Point Apparatus.

### 1.4.2 Suzuki–Miyaura Cross-Coupling of Alkyl Pyridinium Salts

### 1.4.2.1 General Procedure A: Cross-Coupling with Non-Pyridyl Aryl Boronic Acids

$$
\begin{array}{c}
\text{Ar–B(OH)}_2 \\
\text{Ni(OAc)}_2\text{·4H}_2\text{O (10 mol\%)} \\
\text{BPhen (24 mol\%)} \\
\hline
\text{KO}t\text{-Bu, EtOH} \\
\text{dioxane, 60 °C, 24 h}
\end{array}
$$
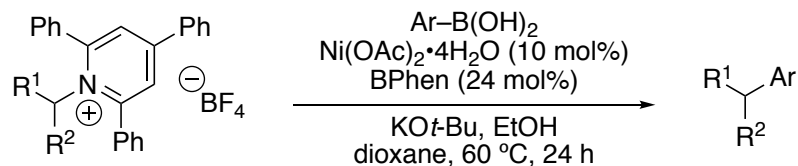
To an oven-dried, 25-mL pear-shaped flask, was added $Ni(OAc)_2 \cdot 4H_2O$ (25 mg, 0.10 mmol, 10 mol %) and bathophenanthroline (BPhen, 80 mg, 0.24 mmol, 24 mol %). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with $N_2$ (x 3). To an oven-dried, 50-mL Schlenk flask was added the alkyl pyridinium salt (1.0 mmol, 1.0 equiv), arylboronic acid (3.0 equiv, 3.0 mmol), and KO$t$-Bu (382 mg, 3.4 mmol, 3.4 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with $N_2$ (x 3). To the pear-shaped flask containing $Ni(OAc)_2 \cdot 4H_2O$ and BPhen was added dioxane (sparged, anhydrous; 2.5 mL). To the Schlenk flask containing the pyridinium salt, boronic acid, and KO$t$-Bu was added dioxane (sparged, anhydrous; 2.5 mL), followed by EtOH (sparged, anhydrous; 0.29 mL, 5.0 mmol, 5.0 equiv). After vigorously stirring of the resulting mixtures for 1 h at room temperature, the heterogeneous mixture containing the catalyst was transferred via cannula to the mixture containing the pyridinium salt and activated boronate complex. The pear-shaped flask was rinsed multiple times with dioxane (totaling 5 mL; each rinse was transferred via cannula to the reaction mixture) to bring the total volume of dioxane in the reaction flask to 10 mL (0.1 M). The resulting reaction mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature. EtOAc (10 mL) was added. The mixture was stirred for 2–5 min, and then filtered through a small plug of silica gel. The filter cake was washed

with EtOAc (4 x 20 mL), and the resulting solution was concentrated. The cross-coupled product was then purified via silica gel chromatography.
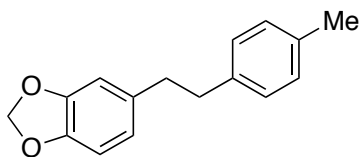


**5-(4-Methylphenethyl)benzo[*d*][1,3]dioxole (1-40).** Prepared via General Procedure A using pyridinium salt **1-39**. The crude mixture was purified by silica gel chromatography (step gradient: 1→5→10→20% toluene/hexanes) to give **1-40** (run 1: 183 mg, 76%; run 2: 177 mg, 74%) as a white solid (mp 81–82 ℃): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.12-7.03 (m, 4H), 6.72 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.5 Hz, 1H), 6.62 (dd, J = 7.9, 1.5 Hz, 1H), 5.92 (s, 2H), 2.87 – 2.78 (m, 4H), 2.32 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 147.6, 145.8, 138.7, 135.9, 135.5, 129.2, 128.4, 121.3, 109.1, 108.2, 100.9, 37.9, 37.9, 21.2; FTIR (neat) 2940, 1490, 1246, 1038, 927, 815, 741 cm$^{-1}$; HRMS (ESI+) calculated for C$_{16}$H$_{17}$O$_2$: 241.1223, found 241.1222.
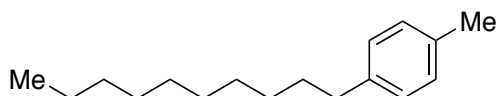


**1-Decyl-4-methylbenzene (1-42).** Prepared via General Procedure A using pyridinium salt **1-77**. The crude mixture was purified by silica gel chromatography (100% pentane) to give **1-42** (run 1: 172 mg, 74%) as a clear oil (Note: This product is slightly volatile. Care should be used when drying under high vacuum.): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.14 – 7.02 (m, 4H), 2.59 – 2.52 (m, 2H), 2.32 (s, 3H), 1.63 – 1.54 (m, 2H), 1.45 – 1.07 (m, 14H), 0.92 – 0.83 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$)

δ 140.0, 135.1, 129.0, 128.4, 35.7, 32.1, 31.8, 29.79, 29.76, 29.7, 29.5, 22.9, 21.2, 14.3. The spectral data matches that of the literature.[48]

*Reaction without Oven-dried Glassware*

Product **1-42** also prepared via General Procedure A, except that the Schlenk flask, pear- shaped flask, stir bars, and cannula were not oven-dried prior to use. The crude mixture was purified by silica gel chromatography (100% pentane) to give **1-42** (154 mg, 66%).

*Reaction with "Minimal Precaution" Set-up*

Product **1-42** was also prepared via a procedure similar to General Procedure A, except that minimal precautions were taken to protect the reaction from air and moisture. No precautions were taken to either dry or degass dioxane and EtOH. Neither the round-bottomed flask nor the pear-shaped flask were oven-dried prior to use. The volume of dioxane was measured with a graduated cylinder and added directly into each flask, open to air. Transfer of the catalyst mixture was performed with a non-oven-dried pipet directly from the pear-shaped flask into the round-bottomed flask. The reaction was set-up under air (no $N_2$).

To a round-bottomed flask equipped with a stir bar was added *p*-TolB(OH)$_2$ (408 mg, 3.0 mmol, 3.0 equiv), pyridinium salt **1-77** (536 mg, 1.0 mmol, 1.0 equiv), and KO*t*-Bu (382 mg, 3.4 mmol, 3.4 equiv). The flask was capped with a septum. To a pear-shaped flask equipped with a stir bar was added Ni(OAc)$_2$·4H$_2$O (25 mg, 0.10 equiv, 0.10 mmol) and BPhen (80 mg, 0.24 mmol, 0.24 equiv), followed by dioxane (2.5 mL). Dioxane (2.5 mL) was added to the round- bottomed flask containing the boronic acid, pyridinium salt, and KO*t*-Bu, followed by EtOH (0.29 mL, 5.0 mmol, 5 equiv) via syringe. The septum was replaced, and the pear-shaped flask was also fitted

with a septum. After stirring both mixtures vigorously for 1 h, both septa were removed, and the catalyst mixture was transferred via pipet to the flask containing the "activated-boronate" mixture. Additional dioxane (5 mL total) was used to rinse the pear-shaped flask in order to ensure complete transfer of the catalyst mixture, thus bringing the total volume of dioxane in the reaction to 10 mL (0.1 M). The reaction flask was fitted with a septum, which was then wrapped in parafilm and secured with a copper wire. The reaction mixture was stirred at 60 °C for 24 h. After cooling to room temperature, EtOAc (10 mL) was added, and the mixture was filtered through a short plug of silica gel. The filter cake was rinsed with EtOAc (4 x 20 mL), and the resulting filtrate solution was concentrated. The residue was purified by silica gel chromatography (100% pentane) to afford **1-42** (73 mg, 31%) as a clear oil.
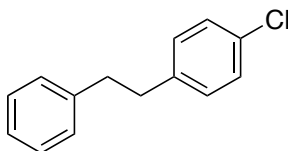


**1-Chloro-4-phenethylbenzene (1-43).** Prepared via General Procedure A using pyridinium salt **1-33**. The crude mixture was purified by silica gel chromatography (100% pentanes) to give **1-43** (run 1: 109 mg, 50%; run 2: 114 mg, 53%) as a white solid: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.30 – 7.26 (m, 2H), 7.25 – 7.22 (m, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 7.11 – 7.05 (m, 2H), 2.89 (s, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 141.4, 140.3, 131.8, 130.0, 128.6, 128.54, 128.52, 126.2, 37.9, 37.3. The spectral data matches that of the literature.[49]

23
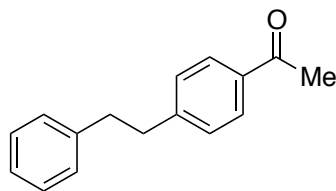
**1-(4-Phenethylphenyl)ethanone (1-44).** Prepared via General Procedure A using pyridinium salt **1-33**. The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes) to give **1-44** (run 1: 175 mg, 78%; run 2: 172 mg 77%) as a white solid: ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.90 – 7.85 (m, 2H), 7.30 – 7.26 (m, 2H), 7.26 – 7.23 (m, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 3.01 – 2.96 (m, 2H), 2.96 – 2.91 (m, 2H), 2.59 (s, 3H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 197.9, 147.6, 141.2, 135.4, 128.9, 128.7, 128.58, 128.55, 126.3, 38.0, 37.6, 26.7. The spectral data matches that of the literature.[50]
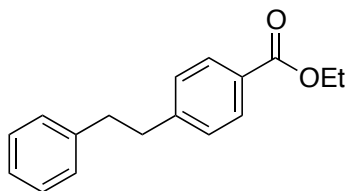


**Ethyl 4-phenethylbenzoate (1-45).** Prepared via General Procedure A using pyridinium salt **1-33**. The crude mixture was purified by silica gel chromatography (50% toluene/hexanes) to give **1-45** (run 1: 178 mg, 70%; run 2: 176 mg, 69%) as an off-white solid: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 – 7.92 (m, 2H), 7.30 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 7.15 (d, $J$ = 7.15 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.00 – 2.96 (m, 2H), 2.95 – 2.91 (m, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.8, 147.2, 141.3, 129.8, 128.63, 128.58, 128.5, 128.4, 126.2, 61.0, 38.0, 37.6, 14.5. The spectral data matches that of the literature.[51]
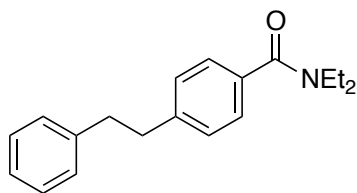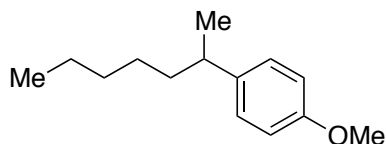
**N,N-Diethyl-4-phenethylbenzamide (1-46).** Prepared via General Procedure A using pyridinium salt **1-33**. The crude mixture was purified by silica gel chromatography (50% EtOAc/hexanes) to give **1-46** (run 1: 211 mg, 75%; run 2: 200 mg, 71%) as a yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.32 – 7.26 (m, 4H), 7.23 – 7.14 (m, 5H), 3.62 – 3.41 (m, br, 2H), 3.37 – 3.16 (m, br, 2H), 2.97 – 2.88 (m, 4H), 1.34 – 1.18 (m, br, 3H), 1.18 – 1.02 (m, br. 3H); $^{13}$C NMR (101 MHz, CDCl3) δ 171.5, 143.0, 141.6, 135.0, 128.59, 128.58, 128.5, 126.5, 126.1, 43.4, 39.4, 37.87, 37.85, 14.4, 13.0; FTIR (neat) 2972, 1630, 1426, 1287, 1095, 700 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{24}$NO: 282.1852, found 282.1852.



**1-(Heptan-2-yl)-4-methoxybenzene (1-47).** Prepared via General Procedure A using pyridinium salt **1-78**. The crude mixture was purified by silica gel chromatography (step gradient: 0→2→5% toluene/hexanes) to give **1-47** (run 1: 119 mg, 58%; run 2: 118 mg, 57%) as a colorless oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.14 – 7.04 (m, 2H), 6.89 – 6.78 (m, 2H), 3.79 (s, 3H), 2.63 (h, $J$ = 7.1 Hz, 1H), 1.56 – 1.48 (m, 2H), 1.31 – 1.12 (m, 9H), 0.90 – 0.81 (m, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.8, 140.3, 127.9, 113.8, 55.4, 39.2, 38.7, 32.1, 27.5, 22.75, 22.67, 14.2; FTIR (neat) 2956, 2926, 1513, 1247, 828 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{23}$O: 207.1743, found 207.1741.
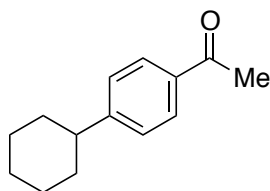
**1-(4-Cyclohexylphenyl)ethanone (1-48).** Prepared via General Procedure A using pyridinium salt **1-35**. The crude mixture was purified by silica gel chromatography (step gradient: 50→75% toluene/hexanes) to give **1-48** (run 1: 134 mg, 66%) as a pale yellow solid: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.94 – 7.83 (m, 2H), 7.33 – 7.27 (m, 2H), 2.63 – 2.49 (m, 4H), 1.93 – 1.80 (m, 4H), 1.80 – 1.73 (m, 1H), 1.48 – 1.35 (m, 4H), 1.31 – 1.23 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 198.0, 153.9, 135.2, 128.7, 127.2, 44.8, 34.3, 26.9, 26.7, 26.2. The spectral data matches that of the literature.[52]



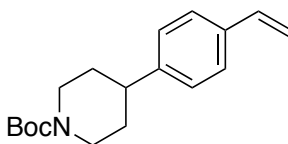**_tert_-Butyl 4-(4-vinylphenyl)piperidine-1-carboxylate (1-49).** Prepared via General Procedure A using pyridinium salt **1-38**. The crude mixture was purified by silica gel chromatography (3% EtOAc/hexanes) to give **1-49** (run 1:  148 mg, 51%; run 2: 130 mg, 45%) as a clear oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.38 – 7.33 (m, 2H), 7.19 – 7.14 (m, 2H), 6.69 (dd, $J$ = 17.6, 10.9 Hz, 1H), 5.72 (dd, $J$ = 17.6, 0.9 Hz, 1H), 5.21 (dd, $J$ = 10.9, 0.8 Hz, 1H), 4.42 – 4.08 (m, br, 2H), 2.88 – 2.70 (m, 2H), 2.63 (tt, $J$ = 12.1, 3.5 Hz, 1H), 1.85 – 1.76 (m, br, 2H), 1.67 – 1.55 (m, 2H), 1.48 (s, 9H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 155.0, 145.7, 136.6, 135.9, 127.1, 126.5, 113.5, 79.6, 44.5 (br), 42.6, 33.3, 28.6; FTIR (neat) 2933, 1693, 1424, 1170, 840 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{18}$H$_{26}$NO$_2$: 288.1958, found 288.1956.
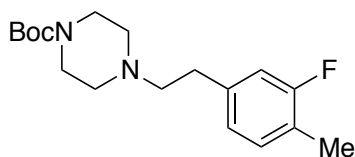
**_tert_-Butyl      4-(3-fluoro-4-methylphenethyl)piperazine-1-carboxylate      (1-50).**
Prepared via General Procedure A using pyridinium salt **1-79**. The crude mixture was
purified by silica gel chromatography (step gradient: 0→10→20→40%
EtOAc/hexanes) to give **1-50** (run 1:  214 mg, 66%; run 2:  228 mg, 71%) as a yellow
semi-solid; $^1$H NMR (600 MHz, CDCl$_3$) δ 7.07 (t, $J$ = 8.0 Hz, 1H), 6.89 – 6.81 (m,
2H), 3.50 – 3.41 (m, 4H), 2.79 – 2.72 (m, 2H), 2.61 – 2.55 (m, 2H), 2.50 – 2.40 (m, br,
4H), 2.23 (s, 3H), 1.46 (s, 9H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 161.4 (d, $J_{C-F}$ = 244.6
Hz), 154.9, 139.9 (d, $J_{C-F}$ = 9.1 Hz), 131.4 (d, $J_{C-F}$ = 6.0 Hz), 124.1 (d, $J_{C-F}$ = 3.0 Hz),
122.5 (d, $J_{C-F}$ = 16.6 Hz), 115.3 (d, $J_{C-F}$ = 22.7 Hz), 79.8, 60.3, 53.1, 43.3 (br), 33.0,
28.6, 14.3; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −118.0; FTIR (neat) 2930, 2809, 1698,
1422, 1249, 1173, 1123, 1004; HRMS (ESI+) [M+H]$^+$ calculated for C$_{18}$H$_{28}$FN$_2$O$_2$:
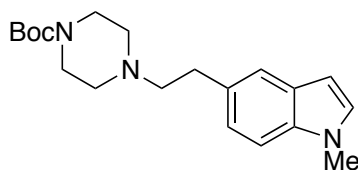323.2129, found 323.2128.



**_tert_-Butyl    4-(2-(1-methyl-1_H_-indol-5-yl)ethyl)piperazine-1-carboxylate    (1-51).**
Prepared via General Procedure A using pyridinium salt **1-79**. The crude mixture was
purified by silica gel chromatography (step gradient: 30→70% EtOAc/hexanes) to
give **1-51** (run 1:  272 mg, 79%; run 2:  282 mg, 82%) as a light orange/yellow solid
(mp 80–83 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.46 – 7.41 (m, 1H), 7.26 – 7.23 (m,
1H), 7.10 – 7.05 (m, 1H), 7.03 (d, $J$ = 3.1 Hz, 1H), 6.43 – 6.39 (m, 1H), 3.77 (m, br,

27

3H), 3.59 – 3.41 (m, br, 4H), 2.91 (m, br, 2H), 2.66 (m, br, 2H), 2.50 (s, 4H), 1.47 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.9, 135.6, 130.9, 129.2, 128.8, 122.7, 120.5, 109.2, 100.5, 79.7, 61.6, 53.2, 43.7, 33.7, 33.0, 28.6; FTIR (neat) 2929, 2808, 1694, 1422, 1247, 1171, 1002, 718 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{20}$H$_{30}$N$_3$O$_2$: 344.2333, found 344.2331.



**(S)-*tert*-Butyl 2-(3-fluoro-4-methylbenzyl)pyrrolidine-1-carboxylate (1-52).** Prepared via General Procedure A using pyridinium salt **1-37**. The crude mixture was purified by silica gel chromatography (5% Et$_2$O/toluene) to give **1-52** (189 mg, 65%) as a yellow oil (mixture of rotamers): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.13 – 7.02 (m, br, 1H), 6.92 – 6.76 (m, br, 2H), 4.05 – 3.85 (m, br, 1H), 3.45 – 3.18 (m, br, 2H), 3.16 – 2.95 (m, br, 1H), 2.59 – 2.41 (m, br, 1H), 2.23 (s, br, 3H), 1.84 – 1.64 (m, br, 4H), 1.57 – 1.44 (s, br, 9H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 161.3 (d, $J_{C-F}$ = 245.1 Hz), 154.6, 138.9 (d, $J_{C-F}$ = 7.4 Hz), 131.4 (d, $J_{C-F}$ = 4.9 Hz, major), 131.2 (d, $J_{C-F}$ = 4.4 Hz, minor), 125.0 (minor), 124.8 (major), 122.6 (d, $J_{C-F}$ = 17.6 Hz, minor), 122.4 (d, $J_{C-F}$ = 16.4 Hz, major), 116.1 (d, $J_{C-F}$ = 20.3 Hz, minor), 115.8 (d, $J_{C-F}$ = 22.2 Hz, major), 79.5 (major), 79.2 (minor), 58.9 (major), 58.6 (minor), 47.0 (minor), 46.4 (major), 40.2 (major), 39.1 (minor), 29.8 (major), 29.1 (minor), 28.7, 23.6 (minor), 22.8 (major), 14.33, 14.31; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −118.0 (major), −118.4 (minor); FTIR (neat) 2973, 2875, 1694, 1394, 1172, 1114, 771 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{17}$H$_{25}$FNO$_2$: 294.1864, found 294.1862.

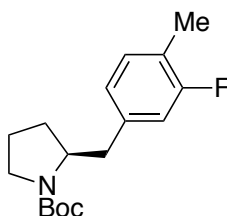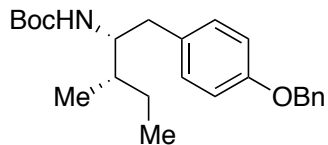**tert-butyl ((2R,3S)-1-(4-(benzyloxy)phenyl)-3-methylpentan-2-yl)carbamate (1-53).** Prepared via General Procedure A using pyridinium salt **1-36**. The crude mixture was purified by silica gel chromatography (gradient: 1→2% EtOAc/toluene) to give **1-53** (201 mg, 52%) as an off-white solid (mp 121–123 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.44 – 7.40 (m, 2H), 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 1 H), 7.12 – 7.05 (m, 2H), 6.92-6.86 (m, 2H), 5.03 (s, 2H), 4.36 – 4.24 (m, 1H), 3.80 – 3.68 (m, br, 1H), 2.79 – 2.73 (m, 1H), 2.57 – 2.53 (m, 1H), 1.55-1.47 (m, 2H), 1.35 (s, br, 9H), 1.15 – 1.05 (m, br, 1H), 0.97-0.86 (m, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.4, 155.7, 137.3, 131.3, 130.3, 128.7, 128.0, 127.6, 114.8, 79.0, 70.1, 56.1, 37.7, 37.0, 28.5, 24.8, 15.8, 11.9; FTIR (neat) 3384, 2962, 1684, 1518, 1240, 744 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{24}$H$_{34}$NO$_3$: 384.2533, found 384.2526.
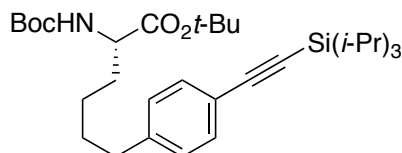


**(S)-tert-Butyl 2-((tert-butoxycarbonyl)amino)-6-(4-((triisopropylsilyl)ethynyl)phenyl)hexanoate (1-54).** Prepared via General Procedure A using pyridinium salt **1-80** and (4-((triisopropylsilyl)ethynyl)phenyl)boronic acid[53] with the following exceptions: the reaction was run on a 0.5 mmol scale and pyridinium salt **1-80** was pre-stirred with Ni(OAc)$_2$·4H$_2$O and BPhen instead of with the boronic acid, KOt-Bu, and EtOH The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes) to give **1-54** (165 mg, 60%) as a clear oil. The enantiomeric excess was determined to be 29%

by chiral HPLC analysis (CHIRALPAK IA, 1.0 mL/min, 2% *i*-PrOH/hexanes, $\lambda$=254 nm); $t_R$(major) = 14.52 min, $t_R$(minor) = 9.78 min. $[\alpha]_D^{26}$ = +40.1° (c 1.6, CHCl$_3$): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 4.98 (d, *J* = 7.8 Hz, 1H), 4.23 – 4.07 (m, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.81 – 1.72 (m, 1H), 1.68 – 1.57 (m, 3H), 1.44 (s, 9H), 1.43 (s, 9H), 1.40 – 1.35 (m, 1H), 1.35 – 1.29 (m, 1H), 1.12 (s, 21H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 172.1, 155.5, 142.9, 132.2, 128.4, 121.1, 107.4, 89.8, 81.9, 79.7, 54.0, 35.7, 33.0, 30.9, 28.5, 28.1, 24.7, 18.8, 11.5; $^{29}$Si NMR (119 MHz, CDCl$_3$) δ –2.0; FTIR (neat) 3358, 2942, 2865, 2155, 1717, 1504, 1367, 1155, 677 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{32}$H$_{54}$NO$_4$Si: 544.3817, found 544.3811.

The arylation of pyridinium salt **1-80** was also performed in the presence of 4-(trifluoromethyl)phenol. In a N$_2$-atmosphere glovebox: Ni(OAc)$_2$·4H$_2$O (1.2 mg, 0.005 mmol, 10 mol %), BPhen (4.0 mg, 0.0012 mmol, 24 mol %), 4-(trifluoromethyl)phenol (16 mg, 0.1 mmol, 2.0 equiv), and pyridinium salt **1-80** (34 mg, 0.05 mmol, 1.0 equiv) were added to an oven-dried 1-dram vial. To a separate oven-dried 1-dram vial was added KO*t*-Bu (19 mg, 0.17 mmol, 3.4 equiv) and (4-((triisopropylsilyl)ethynyl)phenyl)boronic acid (45 mg, 0.15 mmol, 3.0 equiv). Dioxane (125 μL) was added to each vial. Each vial was then equipped with a micro stir bar, capped with a pierceable Teflon-coated cap, and removed from the glovebox. To the vial containing the boronic acid and KO*t*-Bu was added EtOH (15 μL) via a N$_2$-purged syringe. Both mixtures were stirred for 1 h at rt. After pre-stirring was complete, the catalyst mixture containing the pyridinium salt and 4-(trifluoromethyl)phenol was transferred to the "activated- boronate" mixture via a N$_2$-purged syringe. Dioxane (250 μL total) was used to insure complete transfer of the

catalyst mixture and bring the total concentration of the reaction to 0.1 M. The resulting reaction mixture was heated to 60 ºC and stirred vigorously for 24 h. Upon completion, the mixture was diluted with EtOAc (approx. 1.5 mL) and filtered through a short plug of silica gel. The filter cake was washed with EtOAc (5 x 1.5 mL) and the resulting solution was concentrated. The yield of the crude product was determined to be 25% and was obtained by integration by $^1$H-NMR with 1,3,5-trimethoxybenzene as an internal standard. A small sample of the product was purified via preparatory thin-layer chromatography (5% EtOAc/hexanes) and the enantiomeric excess was determined to be 81% by chiral HPLC analysis (CHIRALPAK IA, 1.0 mL/min, 2% *i*-PrOH/hexanes, λ=254 nm); $t_R$(major) = 14.57 min, $t_R$(minor) = 9.84 min.
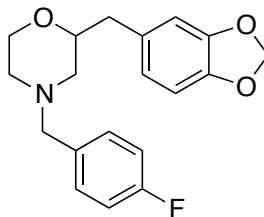


**2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(4-fluorobenzyl)morpholine (1-55).** Prepared via General Procedure A using pyridinium salt **1-81**. After the silica gel filtration, the crude mixture was dissolved in Et$_2$O (20 mL) and washed with HCl (1 N, 4 x 25 mL). The combined aqueous layers were extracted with Et$_2$O (4 x 50 mL, these organic layers were discarded), basified to pH ≥ 12 with NaOH (4 N), and then extracted with Et$_2$O (4 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated. The residue was then purified by silica gel chromatography (step gradient: 10→20% EtOAc/hexanes) to give **1-55** (run 1: 224 mg, 68%; run 2: 240 mg, 73%) as a yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.28 – 7.23 (m, 2H, *overlaps with CHCl$_3$*), 7.04 – 6.94 (m, 2H), 6.76 – 6.67 (m, 2H), 6.65 – 6.60 (m, 1H), 5.92 (s, 2H),

3.87 – 3.81 (m, 1H), 3.74 – 3.66 (m, 1H), 3.64 – 3.57 (m, 1H), 3.52 – 3.46 (m, 1H),

3.41 – 3.34 (m, 1H), 2.78 – 2.67 (m, 2H), 2.62 – 2.55 (m, 2H), 2.16 – 2.08 (m, 1H),

1.96 – 1.87 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.2 (d, $J_{C-F}$ = 245.1 Hz), 147.6,

146.1, 133.6, 131.9, 130.7 (d, $J_{C-F}$ = 7.7 Hz), 122.2, 115.2 (d, $J_{C-F}$ = 21.3 Hz), 109.8,

108.2, 100.9, 76.7, 66.9, 62.6, 58.4, 52.8, 40.0; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –115.8;

FTIR (neat) 2859, 2804, 1604, 1508, 1247, 1114, 1040, 810 cm$^{-1}$; HRMS (ESI+)

[M+H]$^+$ calculated for C$_{19}$H$_{21}$FNO$_3$: 330.1500, found 330.1491.
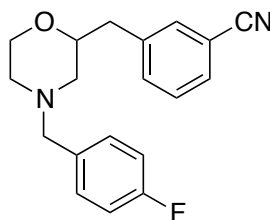


**3-((4-(4-Fluorobenzyl)morpholin-2-yl)methyl)benzonitrile (1-56).** Prepared via

General Procedure A using pyridinium salt **1-81**. After the silica gel filtration, the

crude mixture was dissolved in Et$_2$O (20 mL) and washed with HCl (1 N, 4 x 25 mL).

The combined aqueous layers were extracted with Et$_2$O (4 x 50 mL, these organic

layers were discarded), basified to pH ≥ 12 with NaOH (4 N), and then extracted with

Et$_2$O (4 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, and

concentrated. The residue was then purified by silica gel chromatography (20%

EtOAc/hexanes) to give **1-56** (run 1: 201 mg, 65%; run 2: 180 mg, 58%) as a yellow

oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.51 – 7.50 (m, 2H), 7.44 – 7.43 (m, 1H), 7.39 –

7.36 (m, 1H), 7.28 – 7.25 (m, 2H, *overlaps with CHCl$_3$*), 7.02– 6.99 (m, 2H), 3.82 –

3.84 (m, 1H), 3.72 (m, 1H), 3.61 – 3.57 (m, 1H), 3.48-3.41 (m, 2H), 2.82 – 2.79 (m,

1H), 2.72 – 2.69 (m, 2H), 2.63 – 2.61 (m, 1H), 2.16 – 2.12 (m, 1H), 1.94 – 1.90 (m,

1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.2 (d, $J_{C-F}$ = 245.4 Hz), 139.9, 134.0, 133.4,

133.0, 130.7 (d, $J_{C-F}$ = 7.6 Hz), 130.2, 129.1, 119.1, 115.3 (d, $J_{C-F}$ = 21.1 Hz), 112.4, 75.9, 66.9, 62.5, 58.2, 52.9, 39.7; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −115.6; FTIR (neat) 2933, 2807, 2229, 1508, 1221, 1114, 693 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{20}$FN$_2$O: 311.1554, found 311.1551.

### 1.4.2.2 General Procedure B: Cross-Coupling with Pyridyl Boronic Acids
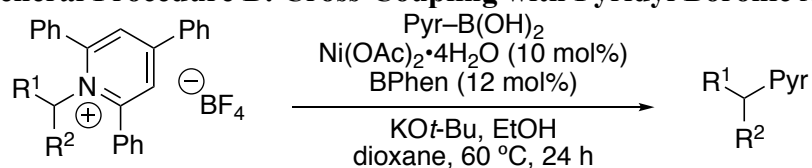


To an oven-dried, 25-mL pear-shaped flask was added Ni(OAc)$_2$·4H$_2$O (25 mg, 0.10 mmol, 10 mol %), bathophenanthroline (BPhen, 40 mg, 0.12 mmol, 12 mol %), and the alkyl pyridinium salt (1.0 mmol, 1.0 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). To an oven-dried, 100-mL Schlenk flask was added the arylboronic acid (3.0 equiv, 3.0 mmol) and KO$t$-Bu (382 mg, 3.4 mmol, 3.4 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). To the pear-shaped flask containing Ni(OAc)$_2$·4H$_2$O and BPhen was added dioxane (sparged, anhydrous; 10 mL). To the Schlenk flask containing the boronic acid and KO$t$-Bu was added dioxane (sparged, anhydrous; 10 mL), followed by EtOH (sparged, anhydrous; 0.29 mL, 5.0 mmol, 5.0 equiv). After vigorously stirring the resulting mixtures for 2 h at room temperature, the mixture (heterogeneous in some cases) of catalyst and pyridinium salt was transferred via large-gauge cannula to the mixture containing the activated boronate complex. The pear-shaped flask was rinsed multiple times with dioxane (totaling 20 mL; each rinse was transferred via cannula to the reaction

mixture) to bring the total volume of dioxane in the reaction to 40 mL (0.025 M). The resulting reaction mixture was stirred at 60 ºC for 24 h. The mixture was allowed to cool to room temperature. EtOAc (10 mL) was added. The mixture was stirred 2–5 min, and then filtered through a small plug of silica gel. The filter cake was washed with EtOAc (4 x 20 mL), and the resulting solution was concentrated. The cross-coupled product was then purified via silica gel chromatography.
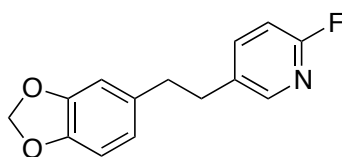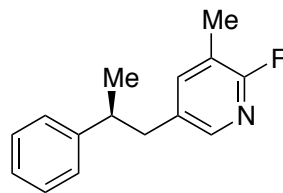


**5-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-2-fluoropyridine (1-57).** Prepared via General Procedure B using pyridinium salt **1-39**. The crude mixture was purified by silica gel chromatography (4% EtOAc/hexanes) to give **1-57** (run 1:  201 mg, 82%; run 2: 193 mg, 79%) as a yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.98 – 7.92 (m, 1H), 7.50 (td, $J$ = 8.1, 2.6 Hz, 1H), 6.82 (dd, $J$ = 8.3, 2.9 Hz, 1H), 6.71 (d, $J$ = 7.9 Hz, 1H), 6.62 (d, $J$ = 1.7 Hz, 1H), 6.54 (dd, $J$ = 7.8, 1.7 Hz, 1H), 5.93 (s, 2H), 2.90 – 2.85 (m, 2H), 2.85 – 2.80 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.4 (d, $J_{C-F}$ = 238.0 Hz), 147.8, 147.3 (d, $J_{C-F}$ = 14.3 Hz), 146.0, 141.3 (d, $J_{C-F}$ = 7.7 Hz), 134.324, 134.319 (d, $J_{C-F}$ = 4.4 Hz), 121.5, 109.1 (d, $J_{C-F}$ = 37.5 Hz), 109.0, 108.3, 101.0, 37.4, 34.2; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −71.9; FTIR (neat) 2925, 1596, 1486, 1246, 1040, 932, 811 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{13}$FNO$_2$: 246.0925, found 246.0925.
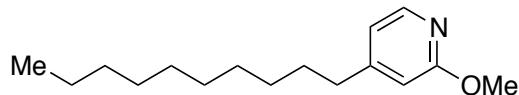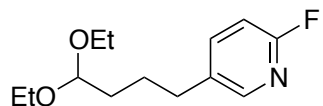
**4-Decyl-2-methoxypyridine (1-58).** Prepared via General Procedure B using pyridinium salt **1-77**. The crude mixture was purified by silica gel chromatography (step gradient: 100% toluene→2% EtOAc/hexanes) to give **1-58** (run 1: 195 mg, 78%; run 2: 175 mg, 70%) as a yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.03 (d, $J$ = 5.3 Hz, 1H), 6.72 – 6.67 (m, 1H), 6.58 – 6.51 (m, 1H), 3.92 (s, 3H), 2.59 – 2.49 (m, 2H), 1.62 – 1.56 (m, 2H), z1.35 – 1.19 (m, 14H), 0.88 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 164.7, 154.8, 146.6, 117.7, 110.4, 53.4, 35.3, 32.0, 30.3, 29.74, 29.68, 29.6, 29.5, 29.3, 22.8, 14.2; FTIR (neat) 2926, 1613, 1398, 1157, 1044, 820; HRMS (ESI+) [M+H]$^+$ calculated for C$_{16}$H$_{27}$NO: 250.2165, found 250.2157.
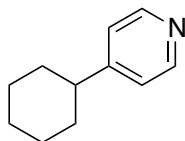


**4-Cyclohexylpyridine (1-59).** Prepared via General Procedure B using pyridinium salt **1-35**. The crude mixture was purified by silica gel chromatography (50% EtOAc/hexanes) to give **1-59** (run 1: 81 mg, 50%; run 2: 91 mg, 56%) as an orange oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.49 – 8.47 (m, 2H), 7.13 – 7.11 (m, 2H), 2.53 – 2.45 (m, 1H), 1.91 – 1.67 (m, 5H), 1.46 – 1.19 (m, 5H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.7, 149.9, 122.5, 43.9, 33.6, 26.7, 26.1. The spectral data matches that of the literature.[54]
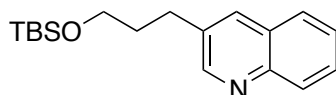
**(*S*)-2-Fluoro-3-methyl-5-(2-phenylpropyl)pyridine (1-60).** Prepared via General Procedure B using pyridinium salt **1-82**. The crude mixture was purified by silica gel chromatography (gradient: 10→20→30→50→70% toluene/hexanes→100% toluene) to give **1-60** (run 1: 151 mg, 66%; run 2: 152 mg, 66%) as a dark orange oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (s, br, 1H), 7.32 – 7.26 (m, 2H), 7.24 – 7.15 (m, 2H), 7.15 – 7.07 (m, 2H), 2.94 (h, *J* = 7.0 Hz, 1H), 2.87 – 2.72 (m, 2H), 2.22 – 2.15 (s, 3H), 1.27 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.1 (d, $J_{C-F}$ = 237.0 Hz), 145.8, 144.8 (d, $J_{C-F}$ = 14.2 Hz), 142.4 (d, $J_{C-F}$ = 5.9 Hz), 133.7 (d, $J_{C-F}$ = 4.6 Hz), 128.6, 127.2, 126.5, 118.8 (d, $J_{C-F}$ = 32.8 Hz), 41.8, 41.1 (d, $J_{C-F}$ = 0.9 Hz), 21.3, 14.6 (d, $J_{C-F}$ = 1.5 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ −76.6; FTIR (neat) 2962, 1591, 1471, 1246, 1143, 700 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{15}$H$_{16}$FN: 230.1340, found 230.1334.



**5-(4,4-Diethoxybutyl)-2-fluoropyridine (1-61).** Prepared via General Procedure B using pyridinium salt **1-83**. The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes) to give **1-61** (run 1: 176 mg, 73%; run 2: 164 mg, 68%) as a yellow oil: ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.02 (s, 1H), 7.59 (td, *J* = 8.1, 2.5 Hz, 1H), 6.84 (dd, *J* = 8.3, 2.9 Hz, 1H), 4.49 (t, *J* = 5.3 Hz, 1H), 3.63 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.48 (dq, *J* = 9.4, 7.1 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.72 – 1.61

(m, 4H), 1.20 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.5 (d, $J_{C\text{-}F}$ = 236.8 Hz), 147.2 (d, $J_{C\text{-}F}$ = 14.3 Hz), 141.1 (d, $J_{C\text{-}F}$ = 7.6 Hz), 135.2 (d, $J_{C\text{-}F}$ = 4.5 Hz), 109.1 (d, $J_{C\text{-}F}$ = 37.4 Hz), 102.8, 61.3, 33.2, 31.94, 31.93, 26.4, 15.5; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −72.3; FTIR (neat) 2975, 2872, 1593, 1485, 1249, 1126, 1065, 831 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{13}$H$_{21}$FNO$_2$: 242.1551, found 242.1548.
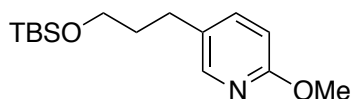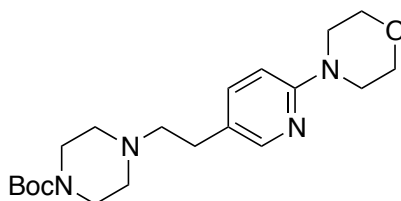


**3-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)quinoline (1-62).** Prepared via General Procedure B using pyridinium salt **1-34**. The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes) to give **1-62** (run 1: 160 mg, 53%; run 2:  195 mg, 65%) as a yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.80 (d, $J$ = 2.2 Hz, 1H), 8.08 (d, $J$ = 8.4 Hz, 1H), 7.94 (s, 1H), 7.76 (d, $J$ = 8.1 Hz, 1H), 7.66 (t, $J$ = 7.2 Hz 1H), 7.52 (t, $J$ = 7.5 Hz, 1H), 3.68 (t, $J$ = 6.1 Hz, 2H), 2.92 – 2.87 (m, 2H), 1.96 – 1.90 (m, 2H), 0.92 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 152.2, 146.9, 135.0, 134.5, 129.3, 128.7, 128.3, 127.4, 126.7, 62.0, 34.1, 29.6, 26.1, 18.5, −5.1; FTIR (neat) 2929, 2857, 1471, 1255, 1102, 836 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{18}$H$_{28}$NOSi: 302.1935, found 302.1934.
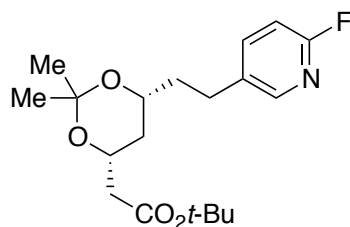


**5-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methoxypyridine (1-63).** Prepared via General Procedure B using pyridinium salt **1-34**. The crude mixture was purified by silica gel chromatography (gradient: 50→75% toluene/hexanes→100% toluene→5% EtOAc/toluene) to give **1-63** (run 1: 196 mg, 70%; run 2: 176 mg, 62%) as a yellow

oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, $J$ = 2.1 Hz, 1H), 7.41 (dd, $J$ = 8.5, 2.5 Hz, 1H), 6.67 (d, $J$ = 8.4 Hz, 1H), 3.91 (s, 3H), 3.62 (t, $J$ = 6.2 Hz, 1H), 2.63 – 2.55 (m, 2H), 1.83 – 1.73 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.7, 146.2, 139.2, 130.1, 110.5, 62.1, 53.4, 34.5, 28.3, 26.1, 18.5, −5.1; FTIR (neat) 2929, 2857, 1608, 1493, 1256, 1102, 835 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{15}$H$_{27}$NO$_2$Si: 282.1884, found 282.1874.



**_tert_-Butyl 4-(2-(6-morpholinopyridin-3-yl)ethyl)piperazine-1-carboxylate (1-64).** Prepared via General Procedure B using pyridinium salt **1-79**. The crude mixture was purified by silica gel chromatography (100% EtOAc) to give **1-64** (233 mg, 62%) as a yellow solid (mp 125–127 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, $J$ = 2.3 Hz, 1H), 7.37 (dd, $J$ = 8.6, 2.4 Hz, 1H), 6.59 (d, $J$ = 8.6 Hz, 1H), 3.91 – 3.75 (m, 4H), 3.58 – 3.32 (m, 8H), 2.73 – 2.64 (m, 2H), 2.58 – 2.51 (m, 2H), 2.50 – 2.35 (m, 4H), 1.46 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.6, 154.9, 147.8, 138.2, 125.3, 107.0, 79.8, 66.9, 60.4, 53.1, 46.0, 43.7 (br), 29.8, 28.6; FTIR (neat) 2971, 2860, 1694, 1499, 1265, 1126, 810 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{20}$H$_{33}$N$_4$O$_3$: 377.2547, found 377.2544.

**tert-Butyl 2-((4R,6R)-6-(2-(6-fluoropyridin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1-65).** Prepared via General Procedure B using pyridinium salt **1-84**. The crude mixture was purified by silica gel chromatography (5% EtOAc/hexanes) to give **1-65** (161 mg, 46%) as a dark pink oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 – 8.01 (m, 1H), 7.59 (td, $J$ = 8.1, 2.6 Hz, 1H), 6.85 (dd, $J$ = 8.4, 2.9 Hz, 1H), 4.21 (dtd, $J$ = 11.6, 6.6, 2.4 Hz, 1H), 3.83 – 3.72 (m, 1H), 2.79 – 2.61 (m, 2H), 2.43 (dd, $J$ = 15.2, 6.9 Hz, 1H), 2.29 (dd, $J$ = 15.2, 6.2 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.73 – 1.61 (m, 1H), 1.53 (dt, $J$ = 12.7, 2.5 Hz, 1H), 1.43 (s, 9H), 1.41 (s, 3H), 1.38 (s, 3H), 1.27 – 1.17 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.4, 162.4 (d, $J_{C-F}$ = 237.8 Hz), 147.2 (d, $J_{C-F}$ = 14.2 Hz), 141.3 (d, $J_{C-F}$ = 7.7 Hz), 134.9 (d, $J_{C-F}$ = 4.5 Hz), 109.2 (d, $J_{C-F}$ = 37.5 Hz), 98.9, 80.8, 67.5, 66.3, 42.8, 37.6, 36.6, 30.2, 28.2, 27.4, 19.9; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −72.2; FTIR (neat) 2981, 2940, 1730, 1484, 1249, 1159, 951, 840 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{29}$FNO$_4$: 354.2075, found 354.2072.

### 1.4.3   Preparation of Pyridinium Salts

#### 1.4.3.1   General Procedure C: Conversion of Amines to Pyridinium Salts
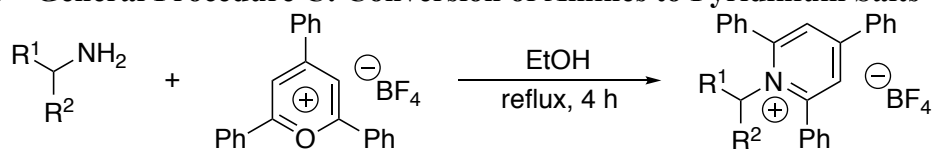
Primary amine (1.2 equiv) was added to a suspension of 2,4,6-triphenylpyrylium tetrafluoroborate (1.0 equiv) and EtOH (1.0 M) in a round-bottomed flask. The flask was fitted with a reflux condenser. The mixture was stirred and heated at reflux in an oil bath at 80–85 ºC for 4 h. The mixture was then allowed to cool to room temperature. If product precipitation occurred during reflux, the solid was filtered, washed with EtOH (3 x 25 mL) and then Et₂O (3 x 25 mL), and dried under high vacuum. If product precipitation did not occur during reflux, the solution was diluted with Et₂O (2–3x volume of EtOH used) and vigorously stirred for 1 h to induce trituration. The resulting solid pyridinium salt was filtered and washed with Et₂O (3 x 25 mL). If the pyridinium salt failed to precipitate at this point, the flask containing the reaction mixture and Et₂O was sealed with parafilm and stored in a –27 °C freezer for 1–3 days (or until precipitation occurred). The cold mixture was quickly filtered and washed with Et₂O (3 x 25 mL) to give the corresponding analytically pure pyridinium salt. If the salt still did not precipitate, it was subjected to silica gel chromatography with acetone/DCM.

The corresponding amine hydrochloride salts can also be used (see synthesis of pyridinium salt **1-82**) using the following modified procedure: Et₃N (1.2 equiv) was added to a mixture of the corresponding alkyl ammonium hydrochloride salt (1.2 equiv) and EtOH (1.0 M). After stirring the mixture for 30 min at room temperature, 2,4,6-triphenylpyrylium tetrafluoroborate (1 equiv) was added. From this point

forward, the same procedure was followed as for alkyl amines described above; however prior to washing the solid product with EtOH and/or Et$_2$O, the mixture was washed with water (3 x 25 mL) to remove Et$_3$N·HCl.
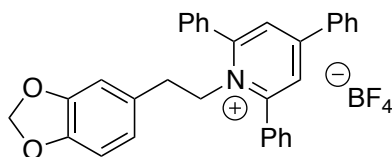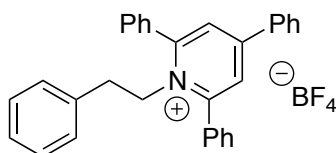


**1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-39).** Prepared via General Procedure C on a 7.5 mmol scale with commercially available 2-(benzo[*d*][1,3]dioxol-5-yl)ethanamine (9.0 mmol) to give **1-39** (3.64 g, 89%) as an off-white solid (mp 234–235 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.91 (s, 2H), 7.83 – 7.77 (m, 6H), 7.68 – 7.62 (m, 6H), 7.59 – 7.55 (m, 1H), 7.55 – 7.51 (m, 2H), 6.48 (d, *J* = 7.9 Hz, 1H), 5.85 (s, 2H), 5.77 – 5.74 (m, 1H), 5.69 – 5.66 (m, 1H), 4.61 – 4.55 (m, 2H), 2.65 – 2.58 (m, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 156.7, 156.3, 148.0, 146.9, 134.2, 132.9, 132.3, 131.4, 129.9, 129.6, 129.3, 128.9, 128.3, 126.9, 121.4, 108.61, 108.57, 101.2, 56.1, 35.7; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −153.27 (minor, $^{11}$BF$_4$), −153.32 (major, $^{10}$BF$_4$); FTIR (neat) 3060, 2903, 1624, 1489, 1053, 699 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{32}$H$_{26}$NO$_4$: 456.1958, found 456.1961.
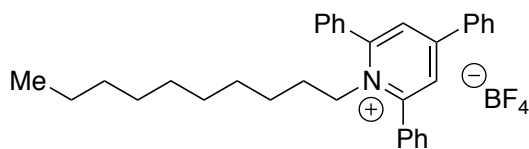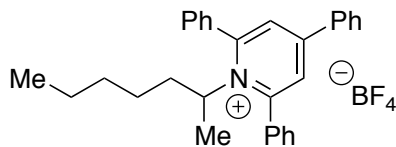


**1-Decyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-77).** Prepared via General Procedure C on a 4.17 mmol scale with commercially available decan-1-amine (5.0 mmol) to give **1-77** (1.56 g, 58%) as a white solid (mp 98–100 ºC): $^1$H

NMR (600 MHz, CDCl$_3$) δ 7.84 (s, 1H), 7.82 – 7.76 (m, 4H), 7.76 – 7.72 (m, 2H), 7.64 – 7.56 (m, 6H), 7.56 – 7.52 (m, 1H), 7.52 – 7.47 (m, 2H), 4.45 – 4.34 (m, 2H), 1.48 – 1.38 (m, 2H), 1.25 (p, $J$ = 7.1 Hz, 2H), 1.20 – 1.08 (m, 4H), 1.05 – 0.97 (m, 2H), 0.95 – 0.81 (m, 5H), 0.79 – 0.69 (m, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 156.6, 155.8, 134.2, 132.9, 132.1, 131.1, 129.8, 129.4, 129.2, 128.2, 126.8, 54.9, 31.9, 29.8, 29.3, 29.2, 29.0, 28.0, 26.1, 22.8, 14.2; $^{19}$F NMR (376 MHz, CDCl$_3$) δ –153.4 (minor, $^{11}$BF$_4$), –153.5 (major, $^{10}$BF$_4$); FTIR (neat) 2926, 1625, 1566, 1056, 704 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{33}$H$_{38}$N: 448.2999, found 448.3004.



**1-Phenethyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-33).** Prepared via General Procedure C on a 10 mmol scale with commercially available 2-phenylethanamine to give **1-33** (4.40 g, 88%) as a white solid (mp >260 ºC): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.92 (s, 2H), 7.89 – 7.73 (m, 6H), 7.73 – 7.48 (m, 9H), 7.15 – 7.09 (m, 1H), 7.09 – 7.03 (m, 2H), 6.32 – 6.26 (m, 2H), 4.69 – 4.62 (m, 2H), 2.73 – 2.66 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.8, 156.2, 135.3, 134.1, 132.8, 132.3, 131.3, 129.9, 129.5, 129.3, 128.9, 128.33, 128.30, 127.4, 126.9, 56.0, 35.8; $^{19}$F NMR (376 MHz, CDCl$_3$) δ –153.26 (minor, $^{11}$BF$_4$), –153.32 (major, $^{10}$BF$_4$); FTIR (neat) 3068, 1624, 1494, 1055, 699 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{31}$H$_{26}$N: 412.2060, found 412.2048.
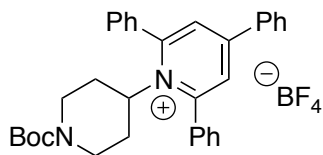
**1-(Heptan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-78).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available heptan-2-amine to give **1-78** (1.21 g, 49%) as a pale yellow solid (mp 157–158 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 87.99 – 7.44 (m, 17H), 4.96 – 4.84 (m, 1H), 1.84 – 1.70 (m, 1H), 1.49 – 1.36 (m, 4H), 1.20 – 1.08 (m, 2H), 1.07 – 0.93 (m, 3H), 0.89 – 0.73 (m, 4H); $^{13}$C NMR (151 MHz, acetone-d$_6$) δ 158.7, 155.3, 135.1, 134.4, 133.3, 131.9, 130.6, 130.4, 129.7, 129.4, 128.6, 68.4, 37.2, 31.7, 26.7, 22.8, 22.5, 14.1; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −153.3 (minor, $^{11}$BF$_4$), −153.4 (major, $^{10}$BF$_4$); FTIR (neat) 2956, 1621, 1412, 1056, 765 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{30}$H$_{32}$N: 406.2529, found 406.2516.
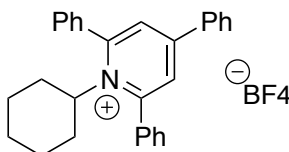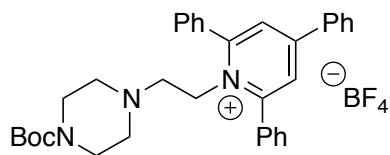


**1-Cyclohexyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-35).** Prepared via General Procedure C on a 10 mmol scale with commercially available cyclohexanamine (12 mmol) to give **1-35** (2.99 g, 63%) as pale yellow solid (mp 181–182 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.83 – 7.76 (m, 2H), 7.76 – 7.69 (m, 6H), 7.64 – 7.54 (m, 6H), 7.54 – 7.48 (m, 1H), 7.48 – 7.42 (m, 2H), 4.61 (tt, $J$ = 12.2, 2.9 Hz, 1H), 2.12 (m, 2H), 1.64 – 1.40 (m, 4H), 1.34 (d, J = 13.3 Hz, 1H), 0.74 (m, 2H), 0.61 (tt, $J$ = 13.1, 3.5 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.1, 155.1, 134.2, 134.1, 131.9, 130.9, 129.7, 129.4, 128.9, 128.4, 128.2, 72.0, 33.7, 26.6, 24.7; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −152.36 (minor, $^{11}$BF$_4$), −153.41 (major, $^{10}$BF$_4$); FTIR (neat) 3061,

2934, 1621, 1055, 705 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{29}$H$_{28}$N: 390.2216, found 390.2199.



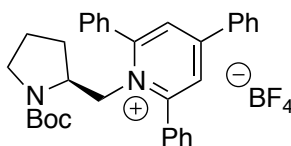**1-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-38).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available *tert*-butyl 4-aminopiperidine-1-carboxylate to give **1-38** (2.08 g, 72%) as an off-white solid (mp 165–166 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.86 – 7.69 (m, 6H), 7.67 (d, $J$ = 7.2 Hz, 2H), 7.64 – 7.52 (m, 6H), 7.52 – 7.46 (m, 1H), 7.46 – 7.36 (m, 2H), 4.82 – 4.69 (m, 1H), 4.04 – 3.75 (m, 2H), 2.27 – 1.95 (m, 4H), 1.74 – 1.51 (m, 2H), 1.30 (s, 9H)$^;$ $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.2, 155.5, 154.3, 134.0, 133.8, 132.1, 131.2, 129.7, 129.4, 129.1, 128.4, 128.3, 80.2, 70.0, 44.3 (br), 32.8 (br), 28.3; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –153.07 (minor, $^{11}$BF$_4$), –153.13 (major, $^{10}$BF$_4$); FTIR (neat) 2977, 1692, 1621, 1057, 706 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{33}$H$_{35}$N$_2$O$_2$: 491.2693, found 491.2686.



**1-(2-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-79).** Prepared via General Procedure C on a 1.67 mmol scale with commercially available *tert*-butyl 4-(2-aminoethyl)piperazine-1-carboxylate to give **1-79** (0.82 g, 81%) as an off-white solid (mp 133–135 ºC): $^1$H NMR (600 MHz,

CDCl$_3$) δ 7.88 – 7.75 (m, 6H), 7.74 – 7.69 (m, 2H), 7.65 – 7.56 (m, 6H), 7.55 – 7.50 (m, 1H), 7.50 – 7.44 (m, 2H), 4.66 – 4.57 (m, 2H), 3.13 – 3.00 (m, 4H), 2.41 – 2.31 (m, 2H), 1.82 – 1.73 (m, br, 4H), 1.39 (s, 9H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.0, 156.1, 154.6, 134.1, 133.0, 132.3, 131.3, 129.8, 129.51, 129.46, 128.3, 126.8, 79.9, 56.4, 52.4, 51.8, 43.2 (br), 28.5; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −152.96 (minor, $^{11}$BF$_4$), −153.01 (major, $^{10}$BF$_4$): FTIR (neat) 2976, 1690, 1623, 1169, 1056, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{34}$H$_{38}$N$_3$O$_2$: 520.2959, found 520.2950.



**(S)-1-((1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-37).** Prepared via General Procedure C on a 4.17 mmol scale with commercially available (S)-tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate to give **1-37** (2.08 g, 84%) as a white solid (mp 180–181 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.31 – 7.84 (m, br, 3H), 7.80 (s, 2H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.70 – 7.38 (m, 10H), 4.89 – 4.74 (m, 1H), 4.71 – 4.55 (m, 1H), 3.98 – 3.83 (m, 1H), 2.91 (td, *J* = 10.7, 6.5 Hz, 1H), 2.66 (t, *J* = 9.3 Hz, 1H), 1.58 – 1.43 (m, 2H), 1.32 (s, 9H), 1.28 – 1.22 (m, 1H), 0.88 – 0.74 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 158.0 (br), 155.6, 155.4, 134.3, 133.5, 132.1, 131.0, 130.4, 129.8, 129.4, 128.0, 126.3, 80.1, 57.5, 55.1, 47.3, 28.5, 28.4, 23.4; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −153.08 (minor, $^{11}$BF$_4$), −153.13 (major, $^{10}$BF$_4$); FTIR (neat) 2975, 1687, 1622, 1383, 1058, 704 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{33}$H$_{35}$N$_2$O$_2$: 491.2693, found 491.2672.
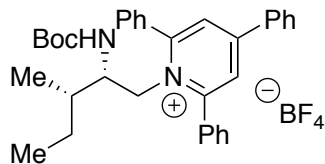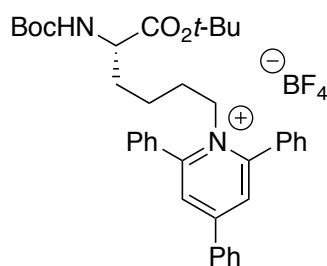
**1-((2*S*,3*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-methylpentyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-36).** Prepared via General Procedure C; however a 1:1 ratio of 2,4,6-triphenylpyrylium tetrafluoroborate (1.9 mmol) to *tert*-butyl ((2*S*,3*S*)-1-amino-3-methylpentan-2-yl)carbamate **1-86** (see synthesis below) was used. After stirring for the 4 h period, the reaction mixture was concentrated. The crude residue was purified via column chromatography (5% acetone/$CH_2Cl_2$) to give pyridinium salt (**1-36**) (0.74 g, 66%) as a pale yellow solid (mp 107–109 ºC): $^1$H NMR (600 MHz, $CDCl_3$) δ 8.42 – 8.12 (m, 2H), 7.96 – 7.50 (m, 15H), 4.98 (dd, *J* = 14.6, 3.4 Hz, 1H), 4.59 (dd, *J* = 14.6, 11.7 Hz, 1H), 3.91 (d, *J* = 10.1 Hz, 1H), 3.61 – 3.54 (m, 1H), 1.31 (s, 9H), 1.09 – 1.01 (m, 1H), 0.85 – 0.72 (m, 2H), 0.49 (t, *J* = 7.4 Hz, 3H), 0.31 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (151 MHz, $CDCl_3$) δ 158.3, 155.9, 155.1, 134.2, 133.5, 132.3, 131.2, 130.4, 129.9, 129.4, 128.0, 126.5, 80.3, 56.4, 53.6, 37.1, 28.5, 25.2, 14.2, 10.6; $^{19}$F NMR (565 MHz, $CDCl_3$) δ −153.0 (minor, $^{11}BF_4$), −153.1 (major, $^{10}BF_4$); FTIR (neat) 3442, 3357, 2968, 1707, 1621, 1057, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for $C_{34}H_{39}N_2O_2$: 507.3006, found 507.2995.
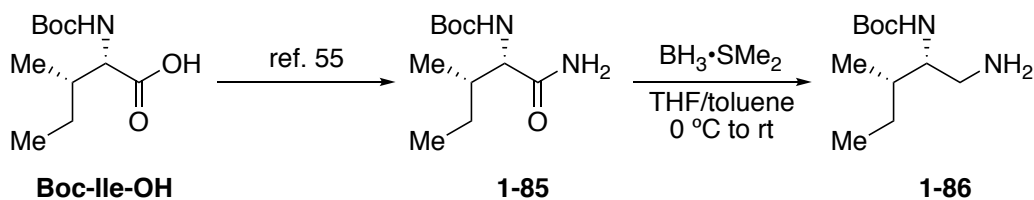


***tert*-Butyl ((2*S*,3*S*)-1-amino-3-methyl-1-oxopentan-2-yl)carbamate (1-85).**

Prepared according to the literature procedure.[55]

**tert-Butyl ((2S,3S)-1-amino-3-methylpentan-2-yl)carbamate (1-86).** Prepared according to a procedure adapted from the literature[56] (note: these reduction conditions are *unoptimized* for Boc-Ile-NH$_2$ **1-85**): In a round-bottomed flask, a solution of amide **1-85** (1.5 g, 6.5 mmol, 1.0 equiv) in THF (21.7 mL, 0.30 M) was cooled to 0 °C. BH$_3$·SMe$_2$ (2.0 M in toluene, 32.6 mL, 65.1 mmol, 10.0 equiv) was added portionwise (approx. 6-7 mL/min). After the addition was complete, the solution was stirred for 5 min at 0 °C, allowed to warm room temperature, and stirred for 24 h. The solution was then concentrated, and MeOH (36 mL, 5.6 mL/mmol) was slowly added (CAUTION: add slowly to prevent violent evolution of gas!). The solution was stirred briefly and then concentrated. This dilution/concentration protocol was repeated two more times. The resulting residue was then dissolved in Et$_2$O (50 mL) and extracted with HCl (1 N, 4 x 50 mL). The combined aqueous layers were washed with Et$_2$O (4 x 50 mL) and then basified with KOH (4 N) to pH≥12. The basic aqueous layer was then extracted with Et$_2$O (4 x 100 mL). The combined organic layers were washed with sat. NaCl (100 mL), dried (MgSO$_4$), filtered through a cotton plug, and concentrated to afford amine **1-86** (0.464 g, 33%) as a white solid which was used without further purification.



**(S)-1-(6-(tert-Butoxy)-5-((tert-butoxycarbonyl)amino)-6-oxohexyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-80).** Prepared via General Procedure C

on a 4.91 mmol scale with Boc-Lys-O$^t$Bu.[57] Attempts to triturate the product failed; the crude residue was purified via column chromatography (5→20% acetone/CH$_2$Cl$_2$) to give pyridinium salt **1-80** as a tan solid (mp 96–100 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.91 (s, 2H), 7.85 – 7.77 (m, 6H), 7.67 – 7.61 (m, 6H), 7.61 – 7.57 (m, 1H), 7.57 – 7.53 (m, 2H), 4.84 (d, br, *J* = 7.7 Hz, 1H), 4.49 – 4.38 (m, 2H), 3.90 – 3.78 (m, 1H), 1.55 – 1.46 (m, 2H), 1.42 (s, 9H), 1.40 (s, 9H), 1.33 – 1.26 (m, 1H), 1.11 – 1.03 (m, 1H), 0.94 – 0.76 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 171.3, 156.6, 156.0, 155.4, 134.2, 132.8, 132.2, 131.2, 129.8, 129.5, 129.2, 128.3, 126.9, 82.2, 79.9, 54.5, 53.5, 31.8, 29.5, 28.4, 28.1, 22.1; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −153.3 (minor, $^{11}$BF$_4$), −153.4 (major, $^{10}$BF$_4$); FTIR (neat) 3374, 2978, 1711, 1624, 1155, 1057, 704 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{38}$H$_{45}$N$_2$O$_4$: 593.3374, found 593.3366.
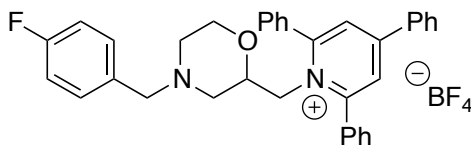


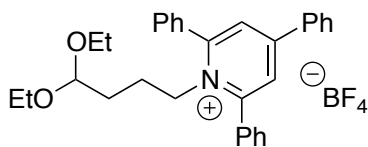**1-((4-(4-Fluorobenzyl)morpholin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-81).** Prepared via General Procedure C (refluxed for 22 h) on a 5 mmol scale with commercially available (4-(4-fluorobenzyl)morpholin-2-yl)methanamine (6.0 mmol) to give **1-81** (2.67 g, 89%) as a tan solid (mp 170–172 ºC): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.89 (s, 2H), 7.87 – 7.67 (m, 6H), 7.64 – 7.51 (m, 9H), 7.09 – 7.03 (m, 2H), 6.98 – 6.91 (m, 2H), 4.73 (dd, *J* = 14.9, 4.1 Hz, 1H), 4.55 (dd, *J* = 14.9, 9.7 Hz, 1H), 3.67 – 3.58 (m, 1H), 3.33 – 3.16 (m, 4H), 2.47 – 2.39 (m, 1H), 2.13 – 2.04 (m, 1H), 1.89 (td, *J* = 11.4, 3.3 Hz, 1H), 1.33 – 1.24 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.2 (d, *J*$_{C-F}$ = 245.7 Hz), 157.8, 155.7, 134.0, 133.2, 132.6, 132.4, 131.1, 130.7 (d, *J*$_{C-F}$ = 7.9 Hz), 129.9, 129.6, 129.3, 128.2, 126.3, 115.2

(d, $J_{C-F}$ = 21.4 Hz), 72.5, 66.6, 61.9, 56.3, 55.6, 52.2; ^{19}F NMR (376 MHz, CDCl$_3$) δ −115.3, −153.2 (minor, [11]BF$_4$), −153.3 (major, [10]BF$_4$); FTIR (neat) 3065, 2815, 1622, 1058, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{35}$H$_{32}$FN$_2$O: 515.2493, found 515.2486.
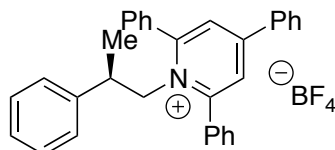


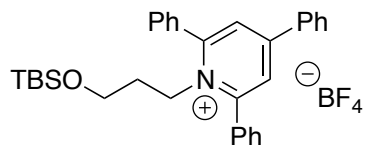**(R)-2,4,6-Triphenyl-1-(2-phenylpropyl)pyridin-1-ium tetrafluoroborate (1-82).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available (R)-2-phenylpropan-1-aminium chloride to give **1-82** (2.27 g, 88%) as a white solid (mp 206–207 ºC): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.44 − 7.30 (m, 17H), 7.23 − 7.16 (m, 1H), 7.08 (t, J = 7.5 Hz, 2H), 6.49 − 6.37 (m, 2H), 5.03 (dd, J = 14.3, 5.5 Hz, 1H), 4.81 (dd, J = 14.3, 9.4 Hz, 1H), 2.80 − 2.63 (m, 1H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.6, 155.8, 140.4, 133.8, 133.2, 132.5, 131.2, 129.9, 129.65, 129.59, 129.1, 128.2, 127.7, 126.9, 126.6, 61.3, 39.8, 17.9; ^{19}F NMR (565 MHz, CDCl$_3$) δ −153.1 (minor, [11]BF$_4$), −153.2 (major, [10]BF$_4$); FTIR (neat) 3062, 1620, 1562, 1057, 702 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{32}$H$_{28}$N: 426.2216, found 426.2220.



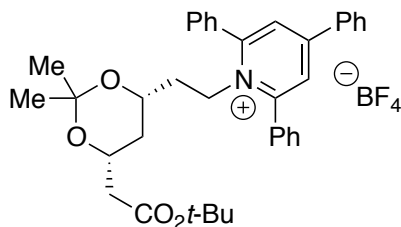**1-(4,4-Diethoxybutyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-83).** Prepared via General Procedure C on a 4.0 mmol scale with commercially available 4,4-diethoxybutan-1-amine (4.8 mmol) to give **1-83** (1.86 g, 86%) as a fluffy white

solid (mp 139–140 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.87 (s, 2H), 7.83 – 7.78 (m, 4H), 7.78 – 7.74 (m, 2H), 7.63 – 7.58 (m, 6H), 7.58 – 7.54 (m, 1H), 7.54 – 7.48 (m, 2H), 4.49 – 4.42 (m, 2H), 4.01 (t, $J$ = 5.2 Hz, 1H), 3.36 (dq, $J$ = 9.0, 7.0 Hz, 2H), 3.18 (dq, $J$ = 9.1, 7.0 Hz, 2H), 1.60 – 1.52 (m, 2H), 1.10 – 0.98 (m, 8H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.5, 155.8, 134.0, 132.8, 132.1, 131.0, 129.7, 129.3, 129.0, 128.1, 126.8, 101.5, 61.6, 54.7, 30.5, 25.1, 15.2; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −153.4 (minor, $^{11}$BF$_4$), −153.5 (major, $^{10}$BF$_4$); FTIR (neat) 2975, 2880, 1624, 1566, 1056, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{31}$H$_{34}$NO$_2$: 452.2584, found 452.2589.



**1-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-34).** Prepared via General Procedure C on a 1.67 mmol scale with 3-((*tert*-butyldimethylsilyl)oxy)propan-1-amine[58] (2.0 mmol) to give **1-34** (0.73 g, 77%) as a white solid (mp 170–171 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.89 (s, 2H), 7.84 – 7.75 (m, 6H), 7.65 – 7.58 (m, 6H), 7.58 – 7.49 (m, 3H), 4.58 – 4.52 (m, 2H), 3.13 (t, $J$ = 5.6 Hz, 2H), 1.74 – 1.65 (m, 2H), 0.67 (s, 9H), −0.21 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.7, 156.0, 134.3, 133.0, 132.1, 131.2, 129.8, 129.5, 129.1, 128.3, 127.1, 60.1, 53.4, 32.8, 25.9, 18.2, −5.5; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −153.4 (minor, $^{11}$BF$_4$), −153.5 (major, $^{10}$BF$_4$); FTIR (neat) 2954, 2855, 1622, 1054, 837, 771, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{32}$H$_{38}$NO$_4$: 480.2717, found 480.2716.
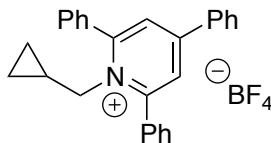
**1-(2-((4R,6R)-6-(2-(*tert*-Butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-84).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available *tert*-Butyl 2-((4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (6.0 mmol) to give **1-84** (1.44 g, 44%) as a white solid (mp 128–130 ºC): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.90 (s, 2H), 7.87 – 7.72 (m, 6H), 7.70 – 7.60 (m, 6H), 7.60 – 7.56 (m, 1H), 7.56 – 7.50 (m, 2H), 4.71 – 4.63 (m, 1H), 4.55 – 4.47 (m, 1H), 4.02 – 3.96 (m, 1H), 3.33 – 3.27 (m, 1H), 2.26 (dd, $J$ = 15.3, 7.2 Hz, 1H), 2.14 (dd, $J$ = 15.3, 5.9 Hz, 1H), 1.65 – 1.54 (m, 2H), 1.42 (s, 9H), 1.16 (s, 3H), 1.13 (dt, $J$ = 12.6, 2.2 Hz, 1H), 1.03 (s, 3H), 0.72 (q, $J$ = 11.7 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.1, 156.9, 156.0, 134.2, 132.9, 132.2, 131.2, 129.8, 129.5, 129.2, 128.2, 126.9, 98.6, 80.9, 66.1, 65.7, 51.9, 42.4, 35.9, 35.4, 29.9, 28.2, 19.6; $^{19}$F NMR (376 MHz, CDCl$_3$) δ –153.3 (minor, $^{11}$BF$_4$), –153.4 (major, $^{10}$BF$_4$); FTIR (neat) 2990, 1726, 1624, 1160, 1057, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{37}$H$_{42}$NO$_4$: 564.3108, found 564.3099.
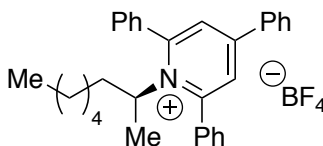


**(*S*)-1-(Octan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-71).** Prepared via General Procedure C; however a 1:1 ratio of 2,4,6-triphenylpyrylium tetrafluoroborate (5.0 mmol) to commercially available (*S*)-octan-2-amine was used.

After refluxing overnight with stirring, the reaction mixture was concentrated. The crude residue was purified via silica gel chromatography (10% acetone/CH$_2$Cl$_2$) to give **1-71** (1.55 g, 61%) as an orange solid (mp 67–69 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.93 – 7.38 (m, 17H), 4.94 – 4.82 (m, 1H), 1.82 – 1.71 (m, 1H), 1.48 – 1.32 (m, 4H), 1.21 – 1.11 (m, 2H), 1.11 – 0.91 (m, 5H), 0.88 – 0.72 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.2 (br), 155.1, 134.0, 133.9, 132.0, 131.0, 129.7, 129.3 (br), 128.9 (br), 128.8 (br), 128.4, 67.1, 36.9, 31.5, 28.5, 26.6, 22.5, 21.7, 14.1; 19F NMR (376 MHz, CDCl$_3$) δ −153.25 (minor, $^{11}$BF$_4$), −153.31 (major, $^{10}$BF$_4$); FTIR (neat) 2927, 2857, 1621, 1564, 1055, 765, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]+ calculated for C$_{31}$H$_{34}$N: 420.2686, found 420.2685.



**1-(cyclopropylmethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (1-73).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available cyclopropylmethanamine (6.0 mmol) to give **1-73** (1.64 g, 71%) as a white solid (mp 178-180 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.86 (s, 2H), 7.84 – 7.78 (m, 4H), 7.78 – 7.71 (m, 2H), 7.66 – 7.56 (m, 6H), 7.56 – 7.45 (m, 3H), 4.51 (d, $J$ = 6.8 Hz, 2H), 0.72 – 0.61 (m, 1H), 0.34 – 0.20 (m, 2H), −0.38 (q, $J$ = 5.1 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.0, 155.7, 133.9, 133.3, 132.3, 131.2, 129.9, 129.54, 129.46, 128.2, 126.8, 59.2, 10.8, 5.1; $^{19}$F NMR (376 MHz, CDCl$_3$) δ −153.2 (minor, $^{11}$BF$_4$), −153.3 (major, $^{10}$BF$_4$); FTIR (neat) 3064, 1621, 1566, 1057, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{27}$H$_{24}$N: 362.1903, found 362.1898.

### 1.4.4    Mechanistic Experiments

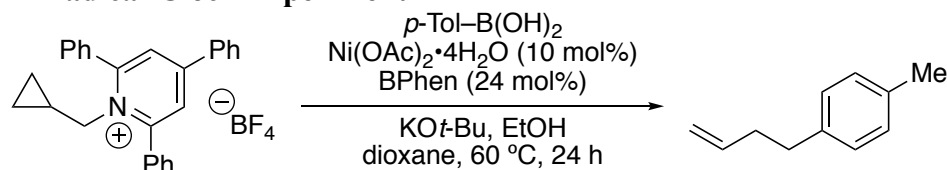#### 1.4.4.1    Test for Stereospecificity
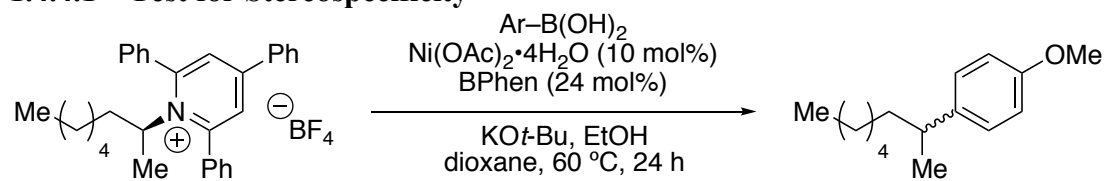


In a $N_2$-filled glovebox: To an oven-dried 1-dram vial was added Ni(OAc)$_2$·4H$_2$O (2.5 mg, 0.01 mmol, 10 mol %) and BPhen (8.0 mg, 0.024 mmol, 24 mol %). To a separate oven-dried 1-dram vial was added KO$t$-Bu (38 mg, 0.17 mmol, 3.4 equiv), 4-methoxyphenylboronic acid (46 mg, 0.30 mmol, 3.0 equiv), and pyridinium salt **1-71** (51 mg, 0.10 mmol, 1.0 equiv). Dioxane (250 μL) was added to each vial. Each vial was then equipped with a micro stir bar, capped with a pierceable Teflon-coated cap, and removed from the glovebox. To the vial containing the boronic acid, KO$t$-Bu, and pyridinium salt **1-71**, was added EtOH (29 μL) via a $N_2$-purged syringe. Both mixtures were stirred for 1 h at rt. The catalyst mixture was then transferred to the "activated-boronate" and pyridinium salt mixture via a $N_2$-purged syringe. Dioxane (500 μL total) was used to ensure complete transfer of the catalyst mixture and bring the total concentration of the reaction to 0.1 M. The resulting reaction mixture was stirred vigorously at 60 °C for 24 h. The mixture was diluted with Et$_2$O (approx. 1.5 mL) and filtered through a short plug of silica gel. The filter cake was washed with Et$_2$O (5 x 1.5 mL), and the resulting solution was concentrated. The yield of the crude product **1-72** was determined to be 54% by ^{1}H-NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. A small sample of the product was purified via preparatory thin-layer chromatography (10% toluene/hexanes), and the enantiomeric excess was determined to be 0% by chiral HPLC analysis

(CHIRALPAK IF, 0.2 mL/min, 100% hexanes, λ=254 nm); $t_R$ (enantiomer A) = 31.32 min, $t_R$ (enantiomer B) = 32.85 min.

### 1.4.4.2 Radical-Clock Experiment



In a $N_2$-filled glovebox: To an oven-dried 1-dram vial was added $Ni(OAc)_2 \cdot 4H_2O$ (2.5 mg, 0.01 mmol, 10 mol %) and BPhen (8.0 mg, 0.024 mmol, 24 mol %). To a separate oven-dried 1-dram vial was added KO$t$-Bu (38 mg, 0.17 mmol, 3.4 equiv), 4-methylphenylboronic acid (41 mg, 0.30 mmol, 3.0 equiv) and pyridinium salt **1-73** (45 mg, 0.10 mmol, 1.0 equiv). Dioxane (250 μL) was added to each vial. Each vial was then equipped with a micro stir bar, capped with a pierceable Teflon-coated cap, and removed from the glovebox. To the vial containing the boronic acid, KO$t$-Bu, and pyridinium salt **1-73**, was added EtOH (29 μL) via a $N_2$-purged syringe. Both mixtures were stirred for 1 h at rt. The catalyst mixture was then transferred to the "activated-boronate" and pyridinium salt mixture via a $N_2$-purged syringe. Dioxane (500 μL total) was used to insure complete transfer of the catalyst mixture and bring the total concentration of the reaction to 0.1 M. The resulting reaction mixture was stirred vigorously at 60 ºC for 24 h. The mixture was then diluted with $Et_2O$ (approx. 1.5 mL) and filtered through a short plug of silica gel. The filter cake was washed with $Et_2O$ (5 x 1.5 mL), and the resulting solution was concentrated. The yield of the crude ring-opened product **1-74** was determined to be 33% by ^{1}H-NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.

### 1.4.4.3 Radical Trap Experiment
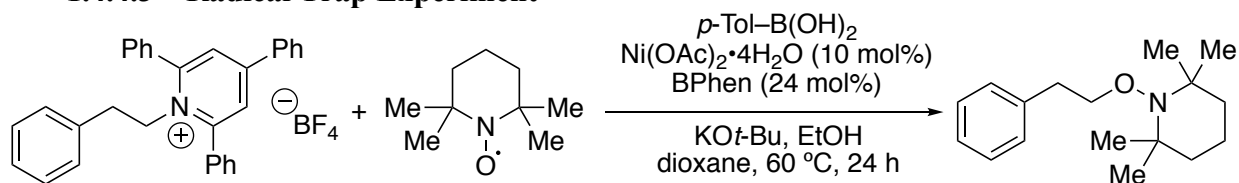


In a $N_2$-filled glovebox: To an oven-dried 1-dram vial was added Ni(OAc)$_2$·4H$_2$O (2.5 mg, 0.01 mmol, 10 mol %) and BPhen (8.0 mg, 0.024 mmol, 24 mol %). To a separate oven-dried 1-dram vial was added KOt-Bu (38 mg, 0.17 mmol, 3.4 equiv), 4-methylphenylboronic acid (41 mg, 0.30 mmol, 3.0 equiv), 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO; 31 mg, 0.20 mmol, 2.0 equiv), and pyridinium salt **1-33** (50 mg, 0.10 mmol, 1.0 equiv). Dioxane (250 μL) was added to each vial. Each vial was then equipped with a micro stir bar, capped with a pierceable Teflon-coated cap, and removed from the glovebox. To the vial containing the boronic acid, KOt-Bu, TEMPO, and pyridinium salt **1-33**, was added EtOH (30 μL) via a $N_2$-purged syringe. Both mixtures were stirred for 1 h at rt. After pre-stirring was complete, the catalyst mixture was transferred to the "activated-boronate" and TEMPO/pyridinium salt mixture via a $N_2$-purged syringe. Dioxane (500 μL total) was used to ensure complete transfer of the catalyst mixture and bring the total concentration of the reaction to 0.1 M. The resulting reaction mixture was heated to 60 ºC and stirred vigorously for 24 h. The mixture was diluted with Et$_2$O (approx. 1.5 mL) and filtered through a short plug of silica gel. The filter cake was washed with Et$_2$O (5 x 1.5 mL), and the resulting solution was concentrated. 1,3,5-trimethoxybenzene (7.2 mg, 0.043 mmol, 0.43 equiv) was added as an internal standard. The yield of known TEMPO adduct **1-76**[59] was determined to be 20% by analysis of the $^1$H-NMR spectrum of the crude reaction mixture. No cross-coupled product was observed.

# REFERENCES

1.      Ruiz-Castillo, P.; Buchwald, S. L., *Chemical Reviews* **2016,** *116*, 12564-12649.

2.      Blakey, S. B.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2003,** *125*, 6046-6047.

3.      Tobisu, M.; Nakamura, K.; Chatani, N., *J. Am. Chem. Soc.* **2014,** *136*, 5587-5590.

4.      Buszek, K. R.; Brown, N., *Org. Lett.* **2007,** *9*, 707-710.

5.      Hie, L.; Baker, E. L.; Anthony, S. M.; Desrosiers, J.-N.; Senanayake, C.; Garg, N. K., *Angewandte Chemie International Edition* **2016,** *55*, 15129-15132.

6.      Meng, G.; Szostak, M., *Org. Lett.* **2016,** *18*, 796-799.

7.      Shi, S.; Meng, G.; Szostak, M., *Angewandte Chemie International Edition* **2016,** *55*, 6959-6963.

8.      Simmons, B. J.; Weires, N. A.; Dander, J. E.; Garg, N. K., *ACS Catalysis* **2016,** *6*, 3176-3179.

9.      Weires, N. A.; Baker, E. L.; Garg, N. K., *Nature Chemistry* **2015,** *8*, 75.

10.     Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P., *J. Am. Chem. Soc.* **2013,** *135*, 280-285.

11.     Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P., *Tetrahedron* **2014,** *70*, 4257-4263.

12.     Basch, C. H.; Cobb, K. M.; Watson, M. P., *Org. Lett.* **2016,** *18*, 136-139.

13.     Li, M.-B.; Tang, X.-L.; Tian, S.-K., *Adv. Synth. Catal.* **2011,** *353*, 1980-1984.

14.     Yoon, S.; Hong, M. C.; Rhee, H., *The Journal of Organic Chemistry* **2014,** *79*, 4206-4211.

15.     Li, M.-B.; Wang, Y.; Tian, S.-K., *Angewandte Chemie International Edition* **2012,** *51*, 2968-2971.

16.     Peng, C.; Wang, Y.; Wang, J., *J. Am. Chem. Soc.* **2008,** *130*, 1566-1567.

17.     Wu, G.; Deng, Y.; Wu, C.; Zhang, Y.; Wang, J., *Angewandte Chemie International Edition* **2014,** *53*, 10510-10514.

18.     Huang, C.-Y.; Doyle, A. G., *J. Am. Chem. Soc.* **2012,** *134*, 9541-9544.

19.     Jensen, K. L.; Standley, E. A.; Jamison, T. F., *J. Am. Chem. Soc.* **2014,** *136*, 11145-11152.

20.     Duda, M. L.; Michael, F. E., *J. Am. Chem. Soc.* **2013,** *135*, 18347-18349.

21.     Zhou, J.; Fu, G. C., *J. Am. Chem. Soc.* **2003,** *125*, 14726-14727.

22.     Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A., *J. Am. Chem. Soc.* **2006,** *128*, 13175-13183.

23.     González-Bobes, F.; Fu, G. C., *J. Am. Chem. Soc.* **2006,** *128*, 5360-5361.

24.     Saito, B.; Fu, G. C., *J. Am. Chem. Soc.* **2007,** *129*, 9602-9603.

25.     Dudnik, A. S.; Fu, G. C., *J. Am. Chem. Soc.* **2012,** *134*, 10693-10697.

26.     Zultanski, S. L.; Fu, G. C., *J. Am. Chem. Soc.* **2013,** *135*, 624-627.

27.     Zhang, X.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2016,** *138*, 13862-13865.

28.     Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C., *Science* **2014,** *345*, 437.

29.     Tellis, J. C.; Primer, D. N.; Molander, G. A., *Science* **2014,** *345*, 433.

30.     Jouffroy, M.; Primer, D. N.; Molander, G. A., *J. Am. Chem. Soc.* **2016,** *138*, 475-478.

31.     Gutiérrez-Bonet, Á.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A., *ACS Catalysis* **2016,** *6*, 8004-8008.

32.     Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S., *J. Am. Chem. Soc.* **2016,** *138*, 2174-2177.

33.     Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J., *J. Am. Chem. Soc.* **2016,** *138*, 5016-5019.

34.     Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S., *Science* **2016,** *352*, 801.

35.     Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S., *J. Am. Chem. Soc.* **2016,** *138*, 11132-11135.

36.     Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S., *Angewandte Chemie International Edition* **2016,** *55*, 9676-9679.

37.     Bapat, J. B.; Blade, R. J.; Boulton, A. J.; Epsztajn, J.; Katritzky, A. R.; Lewis, J.; Molina-Buendia, P.; Nie, P.-L.; Ramsden, C. A., *Tetrahedron Letters* **1976,** *17*, 2691-2694.

38.     Katritzky, A. R.; Marson, C. M., *Angewandte Chemie International Edition in English* **1984,** *23*, 420-429.

39.     Kato, S.; Morie, T.; Yoshida, N., *CHEMICAL & PHARMACEUTICAL BULLETIN* **1995,** *43*, 699-702.

40.     Roth, B. D., US4681893A, 1987/07/21/, 1987.

41.     Said, S. A.; Fiksdahl, A., *Tetrahedron: Asymmetry* **2001,** *12*, 1947-1951.

42.     Katritzky, A. R.; De Ville, G.; Patel, R. C., *Tetrahedron* **1981,** *37*, 25-30.

43.     Álvaro, M.; Formentín, P.; García, H.; Palomares, E.; Sabater, M. J., *The Journal of Organic Chemistry* **2002,** *67*, 5184-5189.

44.     Greulich, T. W.; Daniliuc, C. G.; Studer, A., *Org. Lett.* **2015,** *17*, 254-257.

45.     Biswas, S.; Weix, D. J., *J. Am. Chem. Soc.* **2013,** *135*, 16192-16197.

46.     Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P., *J. Am. Chem. Soc.* **2017,** *139*, 5313-5316.

47.     Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996,** *15*, 1518-1520.

48.     Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M., *Org. Lett.* **2012,** *14*, 1066-1069.

49.     Jin, L.; Zhao, Y.; Zhu, L.; Zhang, H.; Lei, A., *Adv. Synth. Catal.* **2009,** *351*, 630-634.

50.     St. Denis, J. D.; Scully, C. C. G.; Lee, C. F.; Yudin, A. K., *Org. Lett.* **2014,** *16*, 1338-1341.

51.     Krasovskiy, A.; Duplais, C.; Lipshutz, B. H., *J. Am. Chem. Soc.* **2009,** *131*, 15592-15593.

52.     Patel, N. R.; Molander, G. A., *The Journal of Organic Chemistry* **2016,** *81*, 7271-7275.

53.     Godt, A.; Ünsal, Ö.; Roos, M., *The Journal of Organic Chemistry* **2000,** *65*, 2837-2842.

54.     Molander, G. A.; Argintaru, O. A.; Aron, I.; Dreher, S. D., *Org. Lett.* **2010,** *12*, 5783-5785.

55.     Toumi, M.; Couty, F.; Evano, G., *The Journal of Organic Chemistry* **2008,** *73*, 1270-1281.

56.     Bagley, M. C.; Dwyer, J. E.; Molina, M. D. B.; Rand, A. W.; Rand, H. L.; Tomkinson, N. C. O., *Organic & Biomolecular Chemistry* **2015,** *13*, 6814-6824.

57.     Fekner, T.; Li, X.; Lee, M. M.; Chan, M. K., *Angewandte Chemie International Edition* **2009,** *48*, 1633-1635.

58.     Padwa, A.; Rashatasakhon, P.; Ozdemir, A. D.; Willis, J., *The Journal of Organic Chemistry* **2005,** *70*, 519-528.

59.     Thuy-Boun, P. S.; Villa, G.; Dang, D.; Richardson, P.; Su, S.; Yu, J.-Q., *J. Am. Chem. Soc.* **2013,** *135*, 17508-17513.

**Chapter 2**

**SUZUKI–MIYAURA CROSS-COUPLING OF BENZYLIC PYRIDINIUM SALTS WITH ARYLBORONIC ACIDS**

Work described here has already been published (Liao, J.; Guan, W.; Boscoe, B. P.; Tucker, J. W.; Garnsey, M. R.; Watson, M. P. *Org. Lett.*, **2018**, *20* (10), 3030–3033). It is reprinted in this chapter with permission of *Organic Letters* (Copyright © 2018, American Chemical Society). This work was performed in collaboration with Michelle Garnsey, Brian Boscoe, and Joseph Tucker at Pfizer, Inc.

## 2.1 Introduction

Diarylmethanes are an important motif in a number of medicinally relevant molecules including anti-bacterial, anti-HIV, and antitumor agents (Scheme 2.1).[1-4] In particular, heteroaryl substitution is commonly found in these bioactive molecules but largely overlooked in conventional methods to furnish these targets. In fact, our collaborator at Pfizer, Dr. Michelle Garnsey, has identified diarylmethanes such as **2-3** as subtype-selective positive allosteric modulators (PAMs) of the muscarinic $M_1$ receptor.[5, 6] With the growing abundance of diarylmethanes as bioactive molecules, we recognized the importance of developing methods to enable the rapid synthesis of these motifs from readily available precursors. As discussed in Chapter 1, we were attracted to amines as starting materials because of their wide availability and ease of synthesis.

Scheme 2.1    Examples of medicinally relevant diarylmethanes



**2-1**
Trimethoprim
(GlaxoSmithKline)
*antibacterial*

**2-2**
Elvitegravir
(Gilead Sciences)
*HIV treatment*

**2-3**
PF-06827443
(Pfizer)
*M₁PAM*
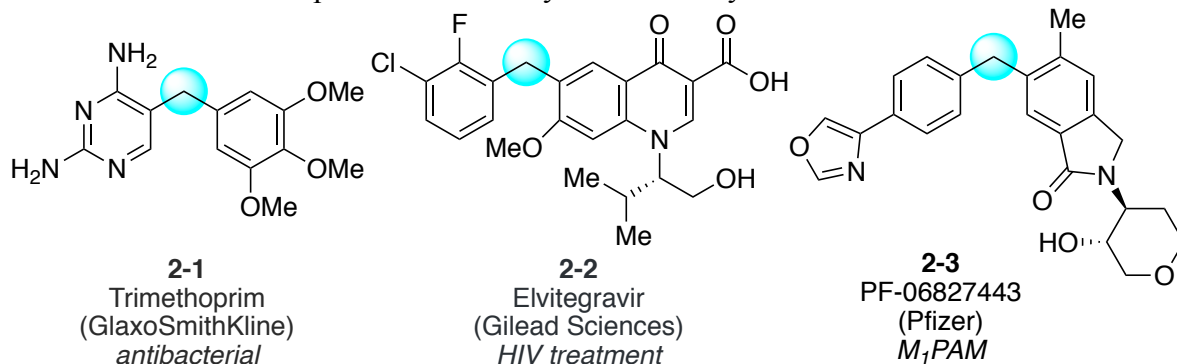
Traditionally, the diarylmethane motif can be synthesized via transition-metal catalyzed cross-couplings of a benzylic electrophile with an aryl nucleophile. One of the most common approaches focuses on the use of benzylic halides. In particular, Suzuki–Miyaura cross-couplings are the method of choice. For example, the Molander group has shown the palladium-catalyzed coupling of potassium aryltrifluoroborates with benzylic halides (**2-4**) to form diarylmethanes (**2-5**) (Scheme 2.2A).[7] Similarly, Tudge et al. at Merck have demonstrated the use of palladium catalyst **2-7** to affect cross-coupling of benzylic chlorides (**2-6**) with (hetero)arylboronic acids for the preparation of highly-functionalized nitrogen-bearing diarylmethanes (**2-8**) (Scheme 2.2B).[8] Other organometallic nucleophiles such as aryl Grignard reagents (Scheme 2.2C)[9] and diaryl zinc reagents (Scheme 2.2D)[10] have also been shown to cross-couple with benzylic halides to access this motif. Alternatively, a reductive approach cross-coupling benzyl chlorides (**2-14**) with aryl chlorides and fluorides using nickel catalyst **2-15** has been demonstrated by the Sun group (Scheme 2.2E).[11]

## Scheme 2.2 Metal-catalyzed arylations of benzylic halides

### A. Aryltrifluoroborates (Molander)

$Ar^2$—$BF_3K$

$Ar^1$⌒$X$ $\xrightarrow[\substack{Cs_2CO_3, \text{ THF or CPME} \\ \text{reflux, 12–24 h}}]{PdCl_2(dppf) \cdot CH_2Cl_2}$ $Ar^1$⌒$Ar^2$

$X = Cl, Br$
**2-4**

**2-5**
67–91%

### B. Boronic acids (Tudge)

$Ar^2$—$B(OH)_2$
**2-7**

$^{(het)}Ar$⌒$Cl$ $\xrightarrow[\substack{K_3PO_4 \\ THF/H_2O, 35 \,°C, 20 \text{ h}}]{}$ $^{(het)}Ar$⌒$Ar^2$

**2-6**

**2-8**
24–97%



**2-7**
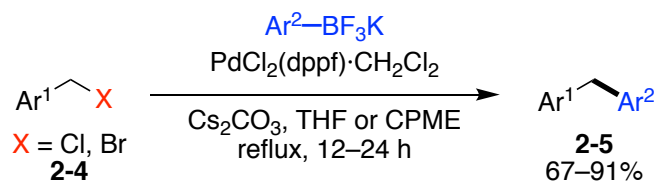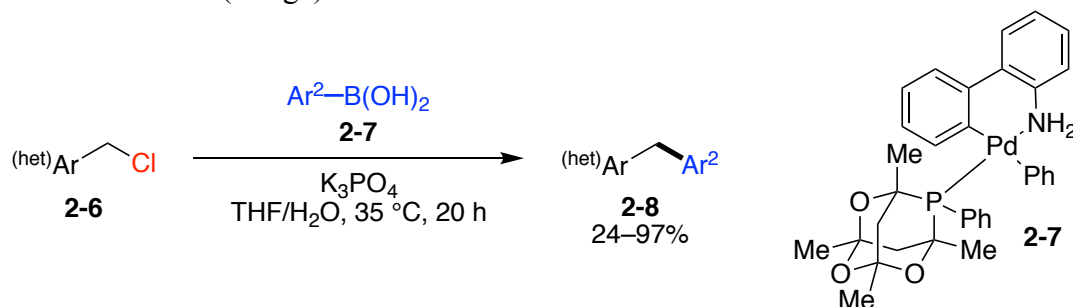
### C. Aryl Grignard reagents (Kozak)

$Ar^2$—$MgBr$
**2-10**

$Ar^1$⌒$X$ $\xrightarrow[\substack{Cs_2CO_3, \text{ THF or CPME} \\ \text{reflux, 12–24 h}}]{}$ $Ar^1$⌒$Ar^2$

$X = Cl, Br$
**2-9**

**2-11**
67–91%



**2-10**
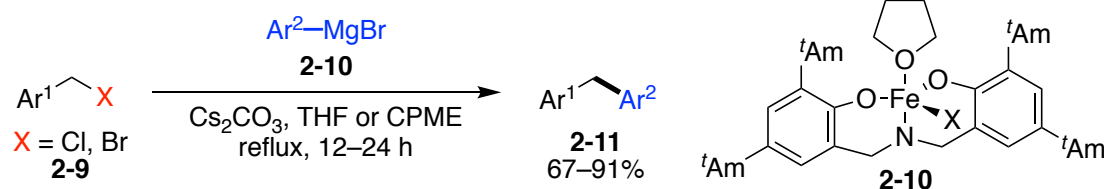
### D. Diaryl zinc reagents (Ingleson)

$Ar^2$—$Zn$—$Ar^2$

$Ar^1$⌒$X$ $\xrightarrow[\substack{C_6D_6 \\ rt–60 \,°C}]{}$ $Ar^1$⌒$Ar^2$

$X = Cl, Br$
**2-12**

**2-13**
82–99%
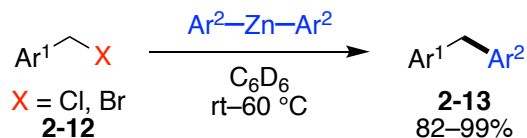
### E. Reductive aryl chlorides/fluorides (Sun)

$Ar^2$—$X$
Ni(PPh$_3$)(NHC)Br$_2$ (**2-15**)

$Ar^1$⌒$Cl$ $\xrightarrow[\substack{Mg \\ THF, 25 \,°C, 1h \\ X = Cl, F}]{}$ $Ar^1$⌒$Ar^2$

**2-14**

**2-16**
44–98%



**2-15**
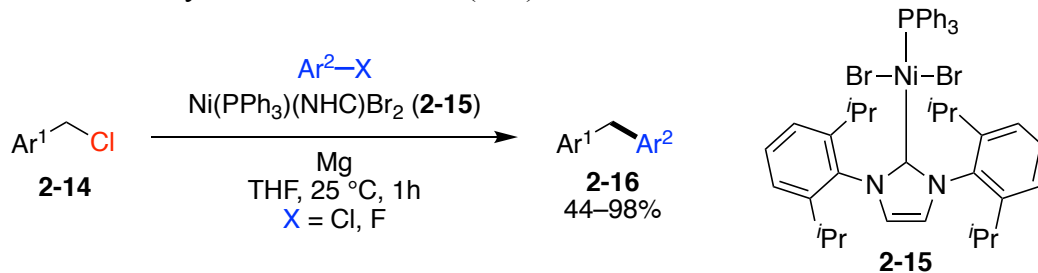
Benzylic alcohols can also serve as common precursors in the synthesis of diarylmethanes. The Shi group has demonstrated the direct arylation of benzyl alcohols (2-17) with Grignard reagents via nickel-catalyzed C–O bond activation (Scheme 2.3A).[12] In addition, a number of benzyl alcohol derivatives have been utilized as electrophiles in metal-catalyzed arylation reactions. The Tobisu and Chatani group have shown that benzyl methyl ethers (2-19) can be cross-coupled with arylboronic esters under nickel-catalysis to form diarylmethanes (2-20) (Scheme 2.3B).[13] Similarly, Stewart and Maligres et al. at Merck have demonstrated an approach to di(hetero)arylmethanes (2-22) via a Suzuki cross-coupling of heterobenzylic acetates (2-21) with heteroarylboronic acids under nickel-catalyzed conditions (Scheme 2.3C).[14] Kuwano has shown that benzylic carbonates (2-23) can undergo analogous Suzuki cross-couplings under palladium catalysis (Scheme 2.3D).[15, 16] McLaughlin has also published on the Suzuki arylation of benzylic phosphates (2-25) (Scheme 2.3E).[17, 18] Additionally, our group and others have identified benzylic alcohol derivatives as electrophiles in a variety of stereospecific transformations.[19-25]

Scheme 2.3    Metal-catalyzed arylations of benzyl alcohols and their derivatives

A.  Benzyl alcohols (Shi)

$Ar^2$—MgX
MeMgBr
$NiCl_2(PCy_3)_2/PCy_3$

$Ar^1$—OH
**2-17**

$^nBuOH/PhMe$, 60 °C, 24 h

$Ar^1$—$Ar^2$
**2-18**
48–93%
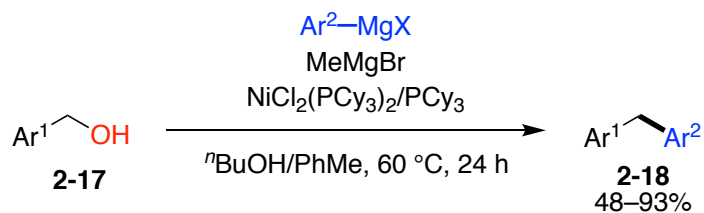
B.  Benzylic ethers (Tobisu and Chatani)

$Ar^2$—$B(OR)_2$
$Ni(COD)_2/ICy$

$Ar^1$—OMe
**2-19**

$NaO^tBu$, CsF
PhMe, 120 °C, 12 h

$Ar^1$—$Ar^2$
**2-20**
34–99%
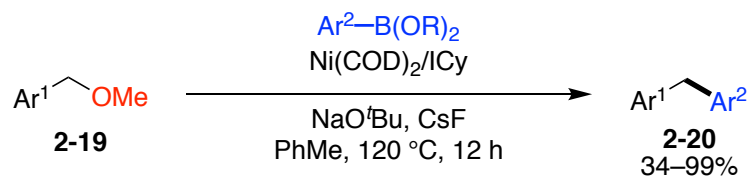
C.  Benzylic acetates (Stewart and Maligres)

$Ar^2$—$B(OH)_2$
$Pd(OAc)_2/RuPhos$

$^{(het)}Ar^1$—OAc
**2-21**

$K_2CO_3$
$^iPrOH/H_2O$, 80 °C, 16 h

$^{(het)}Ar^1$—$Ar^2$
**2-22**
52–91%
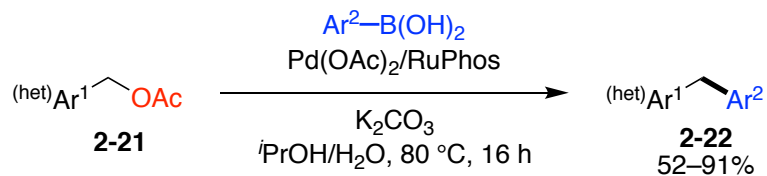
D. Benzylic carbonates (Kuwano)

$Ar^2$—$B(OH)_2$
$[Pd(\eta_3\text{-}C_3H_5)Cl]_2/DPPpent$

$Ar^1$—O—C(=O)—OMe
**2-23**

$K_2CO_3$
DMF, 80 °C

$Ar^1$—$Ar^2$
**2-24**
78–99%
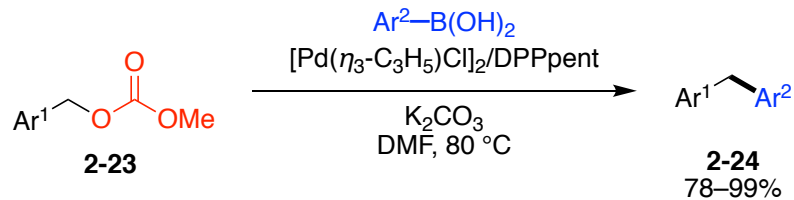
E.  Benzylic phosphates (McLaughlin)

$Ar^2$—$B(OH)_2$
$Pd(OAc)_2/PPh_3$

$Ar^1$—O—P(=O)(OEt)—OEt
**2-25**

$K_3PO_4$
PhMe, 90 °C, 16 h

$Ar^1$—$Ar^2$
**2-26**
67–98%
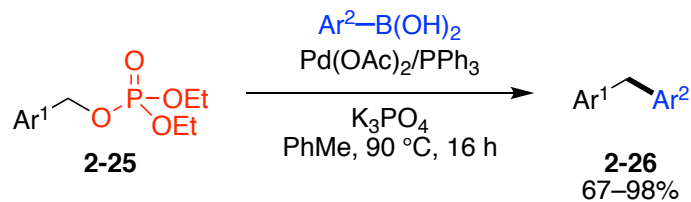
The umpolung approach using metal-based benzylic nucleophiles has also been explored for the construction of diarylmethanes. For example, the Tobisu and Chatani group have shown that benzylic Grignard reagents (**2-27**) can react with anisoles under nickel-catalyzed conditions to form diarylmethanes (**2-28**) via C–O bond cleavage (Scheme 2.4A).[26] The Knochel group has demonstrated that benzylic aluminum organometallic reagents (**2-30**) can be formed from insertion of aluminum powder into the benzylic C–X bond of benzylic chlorides (**2-29**). These can then undergo palladium-catalyzed cross-couplings with various electrophiles such as arylhalides to deliver diarylmethanes (**2-31**) (Scheme 2.4B).[27] Knochel has also shown that TMPZnCl·LiCl (TMP= 2,2,6,6-tetramethylpiperidyl) can afford directed zincation of methyl-substituted *N*-heterocycles (**2-32**) to generate **2-33**. These nucleophiles can then participate in Negishi cross-couplings to afford diarylmethane **2-34** (Scheme 2.4C).[28] Moreover, benzylic boronates have also been employed as nucleophiles, although mostly in the context of stereospecific cross-couplings. For example, the Crudden group has demonstrated palladium-catalyzed cross-coupling of chiral secondary boronic esters (**2-35**) with aryl halides to form enantioenriched 1,1-diarylethanes (**2-36**) (Scheme 2.4D).[29]

Scheme 2.4    Arylations of benzylic organometallic nucleophiles

A.  Benzylic Grignard reagents (Tobisu and Chatani)

$$Ar^1\text{—}MgX \xrightarrow[\text{PhMe, rt, 18 h}]{\substack{Ar\text{—}OMe \\ Ni(OAc)_2/ICy \cdot HCl}} Ar^1\text{—}Ar^2$$

**2-27**                                    **2-28**
                                         60–98%
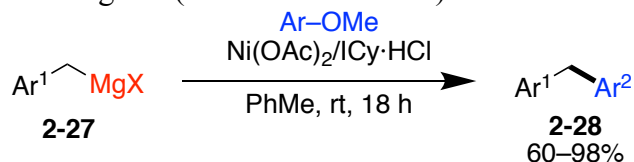
B.  Benzylic aluminum sesquichlorides (Knochel)

$$Ar^1\text{—}Cl \xrightarrow[\text{THF, 20 °C}]{\substack{Al \\ InCl_3}} \left(Ar^1\right)_{2-n}Al(Cl)_{n+1} \xrightarrow[\text{THF/NMP, 50 °C, 2 h}]{\substack{Ar^2\text{—}X \\ Zn(OAc)_2 \\ PEPPSI}} Ar^1\text{—}Ar^2$$

**2-29**                        n = 0, 1                          **2-31**
                               **2-30**                          71–98%
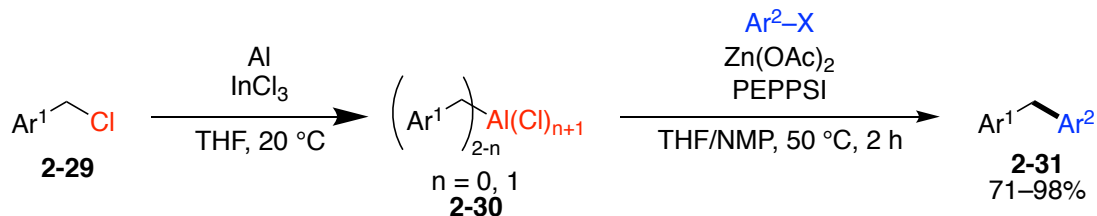
C.  Benzylic zincates (Knochel)



X = N, CH                       **2-33**                          **2-34**
   **2-32**                                                       66–98%
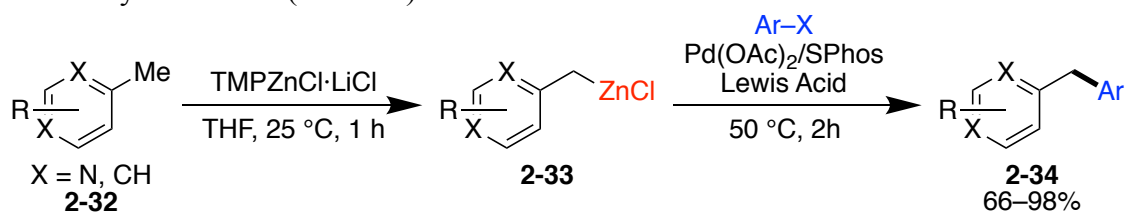
D. Stereospecific cross-coupling of secondary benzylic boronic esters (Crudden)



**2-35**                                    **2-36**
                                         48–86%
                                         > 90% es
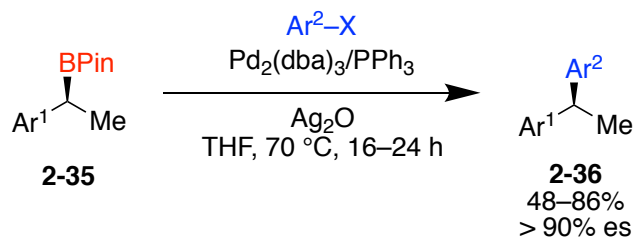
In contrast to benzylic halides and alcohol derivatives, benzylic amine derivatives have only sparingly been investigated as electrophiles for the construction of diarylmethanes. Our group has demonstrated that benzylic trimethylammonium salts (**2-37**) can participate in nickel-catalyzed Suzuki cross-couplings with arylboronic acids to deliver diarylmethanes (**2-38**) (Scheme 2.5A).[30, 31] More recently,

Zhao has reported an analogous cross-coupling using palladium.[32] The benzylic C–N bond can also be activated via conversion to the corresponding benzylic sulfonimides. The Tian group has investigated the copper(I)-catalyzed arylation of **2-39** with Grignard reagents (Scheme 2.5B).[33] In addition, the Rhee group has shown that benzylic sulfonimides (**2-41**) can be coupled with arylboronic acids under palladium catalysis (Scheme 2.5C).[34] Notably, however, conversion of benzylic primary amines to ammonium salts or sulfonimides requires two steps and can limit the inclusion of basic heteroatoms elsewhere in the substrate. These constraints restrict the utility of these cross-couplings, particularly in the context of drug discovery which often requires basic heteroatoms in the final structure.

Scheme 2.5    Metal-catalyzed arylations of benzylic amine derivatives

A.  Watson's cross-coupling of benzylic ammonium salts with arylboronic acids



$Ar^2–B(OH)_2$
$Ni(cod)_2/PPh_2Cy$

$Ar^1$⌒$NMe_3OTf$

CsF or $K_3PO_4$
dioxane, 40 °C, 24 h

**2-37**

$Ar^1$⌒$Ar^2$

**2-38**
49%–quant.
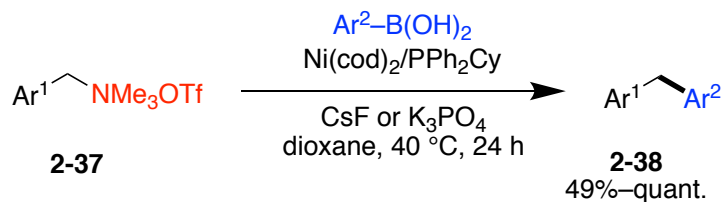
B.  Tian's cross-coupling of benzylic sulfonimides with aryl Grignards

$Ar^2–MgX$
CuI

$Ar^1$⌒$NTs_2$

THF, 70 °C, 2 h

**2-39**

$Ar^1$⌒$Ar^2$

**2-40**
65–93%
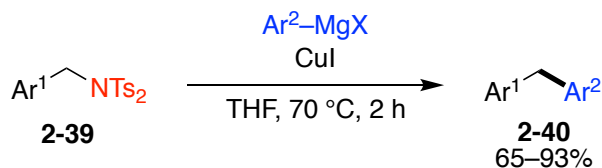
C.  Rhee's cross-coupling of benzylic sulfonimides with arylboronic acids

$Ar^2–B(OH)_2$
$Pd(MeCN)_4(BF_4)_2/DPEPhos$

$Ar^1$⌒$NTs_2$

$K_2CO_3$, DMF, 60 °C

**2-41**

$Ar^1$⌒$Ar^2$

**2-42**
71–99%
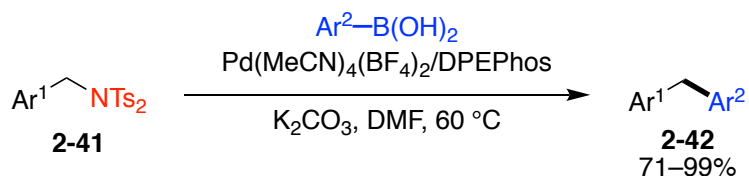
We believe that the lack of methods to harness benzylic amines in cross-couplings is a missed opportunity in the toolbox of reactions for drug discovery. Benzylic amines are generally inexpensive and widely available. They can be easily synthesized[35-39] and can often be purified without chromatography. As a case study for their availability versus more common substrates for cross-couplings, our collaborator Dr. Michelle Garnsey queried the internal Pfizer chemical store in mid-2018. She found that 5,208 benzylic primary amines are present in the internal chemical store, in contrast to only 1,843 benzylic chlorides and 1,020 benzylic bromides. Moreover, we recognized that benzylic halides can serve as genotoxic impurities (GTIs), and benzylic amines would be superior in that regard. Additionally, a benzylic amine can easily be brought through a multi-step synthesis in protected form, providing opportunities for late-stage functionalization.

In Chapter 1, I discussed our development of nickel-catalyzed cross-couplings of Katritzky pyridinium salts bearing unactivated alkyl groups with arylboronic acids. Initial studies suggested that these reactions likely proceed via an alkyl radical formed via single-electron transfer (SET) from a $Ni^I$ intermediate to the pyridinium ring, initiating C−N bond fragmentation.[40] Based on this mechanistic hypothesis, cross-coupling of a benzylic pyridinium salt (**2-45**) should also be feasible, given that a stabilized benzylic radical will be formed in this key step. Thus, we envisioned that benzylic amines could be converted to diarylmethanes in a 2-step process. First, benzylic amine **2-43** could be converted into the corresponding benzylic pyridinium salt **2-45**. Pyridinium salt **2-45** can then participate in nickel-catalyzed Suzuki–Miyaura cross-coupling with arylboronic acids to deliver diarylmethane **2-46** (Scheme 2.6). In particular, I focused on developing this method to enable access to

diarylmethanes with heteroaryl substitution, as these motifs are prevalent in pharmaceuticals and largely overlooked in other cross-couplings to deliver diarylmethanes. Because pyridinium formation is chemoselective for primary amines, other nitrogen containing functionalities such as secondary or tertiary amines as well as other heterocycles can be tolerated using this unique mode of activation.

Scheme 2.6    Proposed cross-coupling of benzylic amine derived pyridinium salts
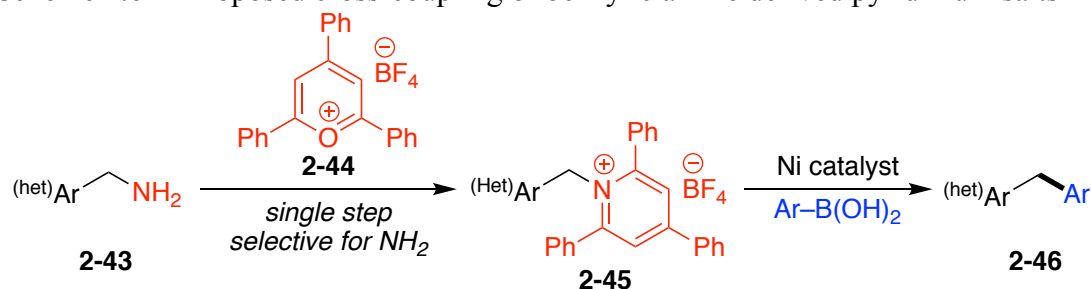


## 2.2    Results and Discussion

### 2.2.1    Synthesis of Benzylic Pyridinium Salts

The benzylic pyridinium salts were prepared following the procedure previously used for the synthesis of alkyl pyridinium salts.[40] The benzylic amine precursors were obtained commercially or via reduction of the corresponding benzonitriles. Treatment of the benzylic amine (**2-43**) with commercially available 2,4,6-triphenylpyrylium tetrafluoroborate (**2-44**) in ethanol afforded the electron-poor benzylic pyridinium salts in excellent yields with no chromatography upon precipitation with ether (Scheme 2.7). A variety of heteroaromatic substrates can be incorporated via this method including pyridines (**2-47**, **2-48**, **2-49**), quinoline (**2-50**), pyrimidine (**2-51**), and pyrazine (**2-52**).

**Scheme 2.7    Selected examples of electron-poor benzylic pyridinium salts formed**



**2-47**, 90%          **2-48**, 94%          **2-49**, 70%

**2-50**, 87%          **2-51**, 85%          **2-52**, 79%
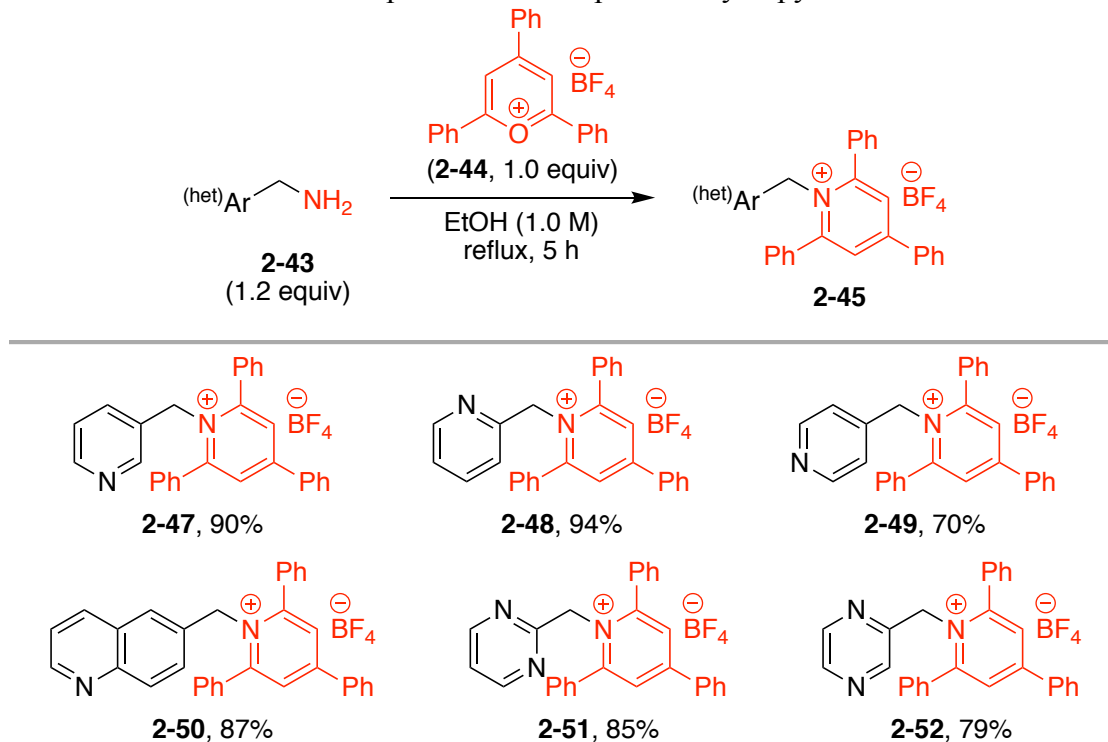
However, utilization of more electron-rich benzylic amine substrates, such as **2-53**, resulted in low desired product yield (**2-54**, 26%). Formation of the undesired benzylic ether byproduct (**2-55**) was observed, likely arising from a nucleophilic substitution reaction of ethanol to cleave the labile C–N bond of the desired pyridinium salt under these elevated temperatures (Scheme 2.8, top). Triphenylpyridine (**2-56**) is also formed as result of this reaction. In an effort to suppress the formation of benzylic ether byproduct **2-55**, the reaction was performed using a non-nucleophilic solvent (CH$_2$Cl$_2$) under much milder conditions (Scheme 2.8, bottom). Excitingly, the desired pyridinium salt was obtained in a much higher yield (71%). It has been shown that the use of acetic acid can help to accelerate the rate of pyridinium ring closure.[41] Moreover, silica gel chromatography can be avoided with

the use of an aqueous work-up, and the target pyridinium salts can then be precipitated with ether.

Scheme 2.8    Synthesis of electron-rich benzylic pyridinium salts
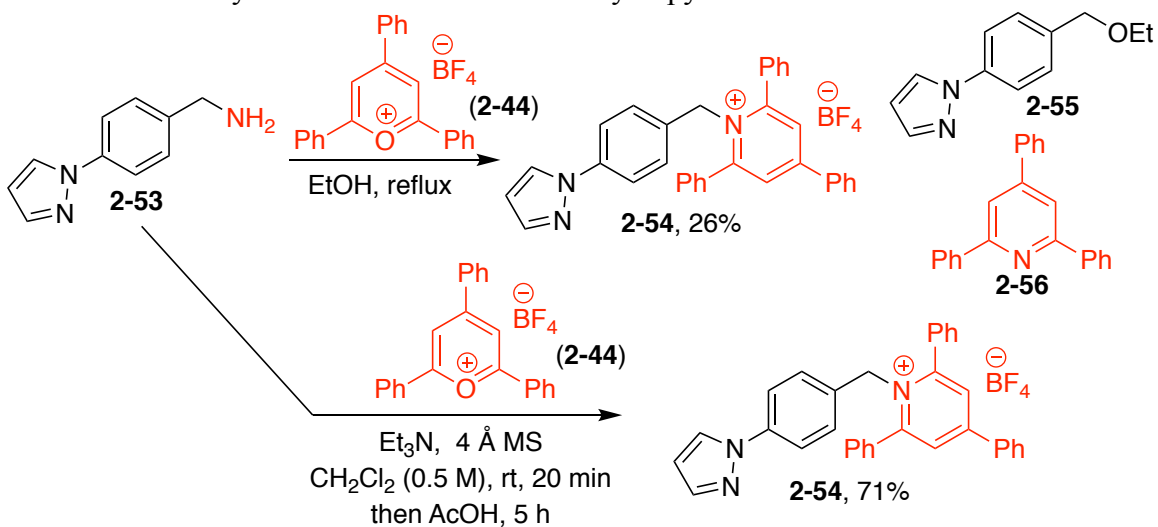


With this procedure, a number of electron-rich benzylic amines (**2-57**) were converted into the corresponding benzylic pyridinium salts (**2-58**) in good to excellent yields, often without the need for chromatographic purifications (Scheme 2.9). Interestingly, secondary benzylic pyridinium salt **2-59** can be formed via this method. Note that a deactivating electron-poor aryl substituent is required for pyridinium formation from secondary benzylic amines; the pyridinium salt of α-methylbenzylamine could not be isolated. I hypothesize that the desired pyridinium salt is relatively unstable and rapidly hydrolyzes to form the corresponding benzylic alcohol. Electron-rich 5-membered heterocycles pendent off the phenyl ring (**2-60**, **2-61**, **2-62**) as well as directly bound to the benzylic carbon (**2-63**, **2-64**) worked well under these conditions.

Scheme 2.9    Selected examples of electron-rich benzylic pyridinium salts formed



**2-59**, 93%    **2-60**, 65%    **2-61**, 78%

**2-62**, quant.    **2-63**, 86%    **2-64**, 44%
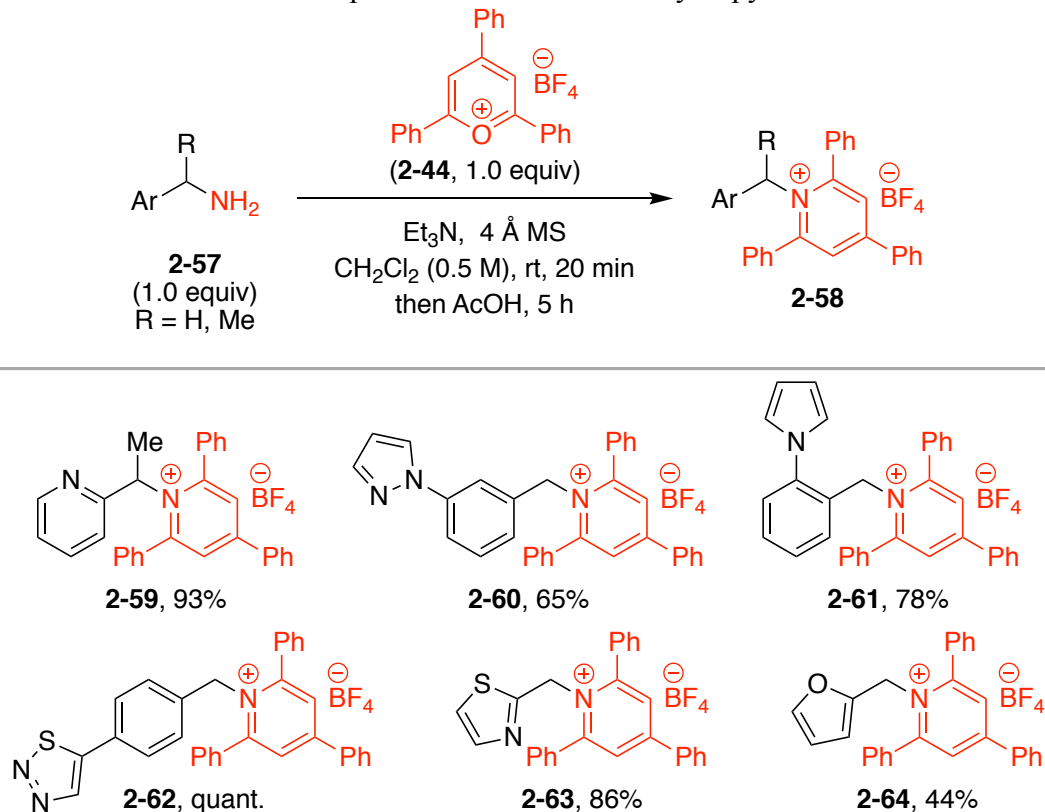
## 2.2.2   Reaction Optimization

My optimization began with examining the conditions previously identified for the Suzuki–Miyaura cross-coupling of alkyl pyridinium salts. I chose pyridinium salt **2-47** for the model reaction. Excitingly, the desired product (**2-65**) was afforded in 66% yield under these conditions (Table 2.1, entry 1). Switching ligands from the exotic bathophenanthroline (BPhen) to the much simpler and cheaper phenanthroline (Phen) provided a comparable yield (entry 2). On the basis of commercial availability and cost, I decided to continue optimizing with phenanthroline as ligand. I hypothesized that the use of a harsh alkoxide base may lead to the formation of the

undesired ylide,[42] especially given the increased acidity of the benzylic proton. Indeed, switching to a milder phosphate base led to a dramatic increase in yield (entry 3).

Table 2.1    Reaction optimization of the Suzuki–Miyaura cross-coupling of benzylic pyridinium salts with arylboronic acids[a]
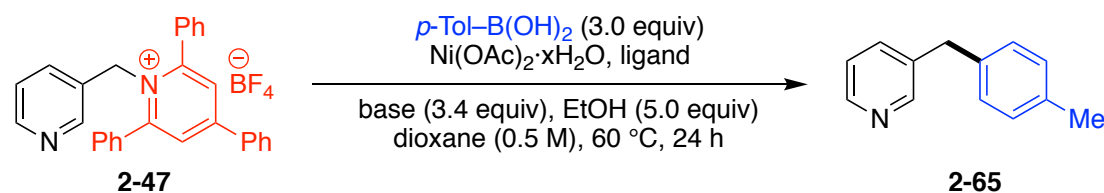


| Entry | Catalyst (mol %) | Base | Yield (%)[b] |
|-------|------------------|------|--------------|
| 1[c] | Ni(OAc)$_2$·4H$_2$O (10)/ BPhen (24) | KO$^t$Bu | 66 |
| 2[c] | Ni(OAc)$_2$·4H$_2$O (10)/ Phen (12) | KO$^t$Bu | 59 |
| 3[c] | Ni(OAc)$_2$·4H$_2$O (10)/ Phen (12) | K$_3$PO$_4$ | 90 |
| 4 | Ni(OAc)$_2$·4H$_2$O (10)/ Phen (12) | K$_3$PO$_4$ | 75 |
| 5 | PhenNi(OAc)$_2$·xH$_2$O (10) | K$_3$PO$_4$ | 93 |
| 6[d] | PhenNi(OAc)$_2$·xH$_2$O (5) | K$_3$PO$_4$ | 93 |
| 7[d,e] | PhenNi(OAc)$_2$·xH$_2$O (5) | K$_3$PO$_4$ | 98 |

[a]Conditions: pyridinium salt **2-47** (0.10 mmol), p-Tol–B(OH)$_2$ (3.0 equiv), [Ni], ligand, base (3.4 equiv), EtOH (5.0 equiv), dioxane (0.1 M), 60 °C, 24 h, unless noted otherwise. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]Two mixtures (Vial 1: [Ni], Ligand, dioxane. Vial 2: pyridinium salt **2-47**, p-Tol–B(OH)$_2$, Base, EtOH, dioxane.) were stirred for 1 h before combining. [d]5 h. [e]0.5 M.

Unfortunately, one of the mechanical issues associated with this reaction was the need to pre-stir Ni(OAc)$_2$·4H$_2$O and Phen for 1 h before combing with the other reagents. In the absence of this protocol, wherein the reaction was set up in a single pot, the desired product **2-65** was obtained in only 75% yield (entry 4). I theorized that pre-ligation of the nickel-ligand complex may be critical, so I decided to synthesize the single-component catalyst **2-66** (Scheme 2.10). This catalyst can easily be made in multi-gram quantities as an air- and moisture-stable solid. Gratifyingly, the utilization of **2-66** enabled the reaction to be set up under a one-pot procedure and eliminated the need for a prestir (Table 2.1, entry 5). With this operationally simplified set-up, much better reproducibility was also observed. Furthermore, this improvement allowed for lower catalyst loadings and shortened reaction times (entry 6). Finally, by increasing the overall concentration of the reaction to 0.5 M, the yield of **2-65** was increased to 98% (entry 7).

Scheme 2.10   Preparation of metal-ligand complex PhenNi(OAc)$_2$·xH$_2$O **2-66**
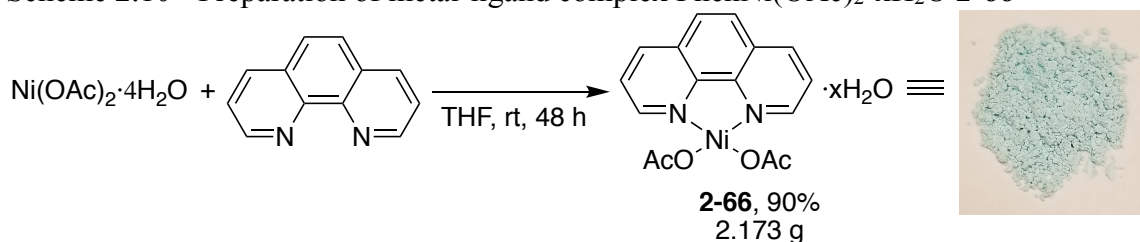


## 2.2.3   Reaction Scope

With optimized conditions in hand, my colleague Weiye Guan and I investigated the scope of this transformation. A wide range of benzylic pyridinium salts successfully underwent the desired cross-coupling reaction (Scheme 2.11). Model

product **2-65** was isolated in 94% yield on a 1.0-mmol scale. I have also demonstrated that the two-component catalyst system is viable using 10 mol % Ni and 12 mol % Phen, and can be used when preparation of the single-component nickel-ligand complex is less convenient. To test the sensitivity of the reaction, it was performed without oven-dried glassware and without precautions against air or moisture. In both cases, good yields were still obtained, highlighting the robustness of the reaction. Other electron-poor heteroaryl pyridinium salts were well-tolerated, including 2-, 3-, and 4-pyridine (**2-74**, **2-65**, **2-75**), quinoline (**2-76**), pyrimidine (**2-77**), and pyrazine (**2-78**). Various electron-rich heteroaryls were also tolerated, including imidazole (**2-80**), pyrazole (**2-81**, **2-82**), pyrrole (**2-83**, **2-84**), thiadiazole (**2-85**), oxazole (**2-86**), and thiazole (**2-87**, **2-88**). Furan-derived pyridinium salts were competent as well, providing **2-89** in 34% yield, along with undesired ethyl ether byproduct. By eliminating EtOH, the yield improved to 47%. When solubility of the pyridinium salt or boronic acid was low, 3:1 dioxane/DMSO was used as solvent.

Scheme 2.11　Reaction scope of Suzuki arylation of benzylic pyridinium salts[a]



75

**2-72**, 93%[g]

**2-73**, 67%[b,d,g]

**2-74**, 92%

**2-75**, 76%

**2-76**, 96%

**2-77**, 88%

**2-78**, 87%

**2-79**, 23%[b,h]
w/o EtOH: 28%[b,h,i]
45%[j]

**2-80**, 80%[g]

**2-81**, 84%

**2-82**, 74%

**2-83**, 44%

**2-84**, 86%

**2-85**, 63%[d]

**2-86**, 90%

**2-87**, 86%

**2-88**, 95%

**2-89**, 34%
w/o EtOH: 47%[i]
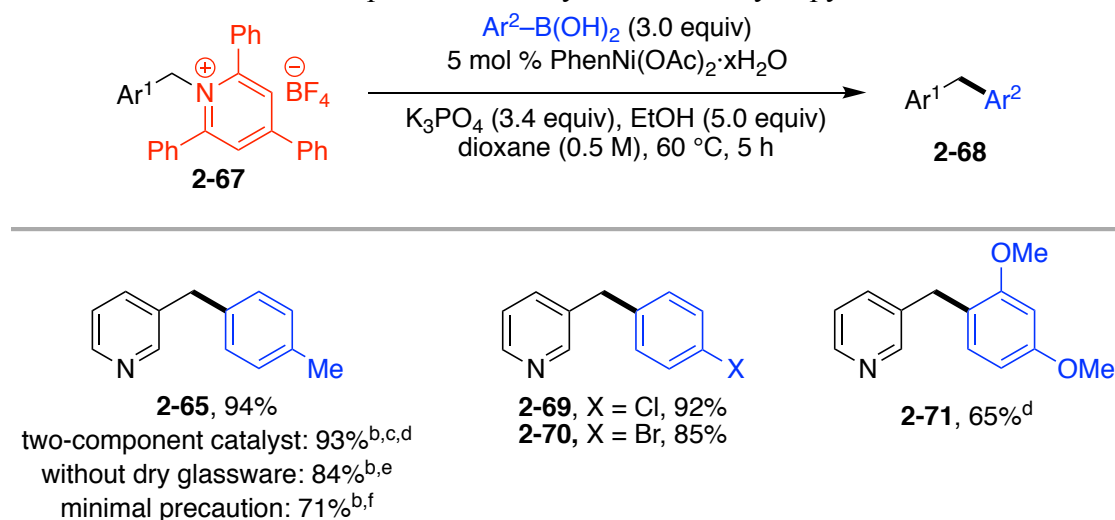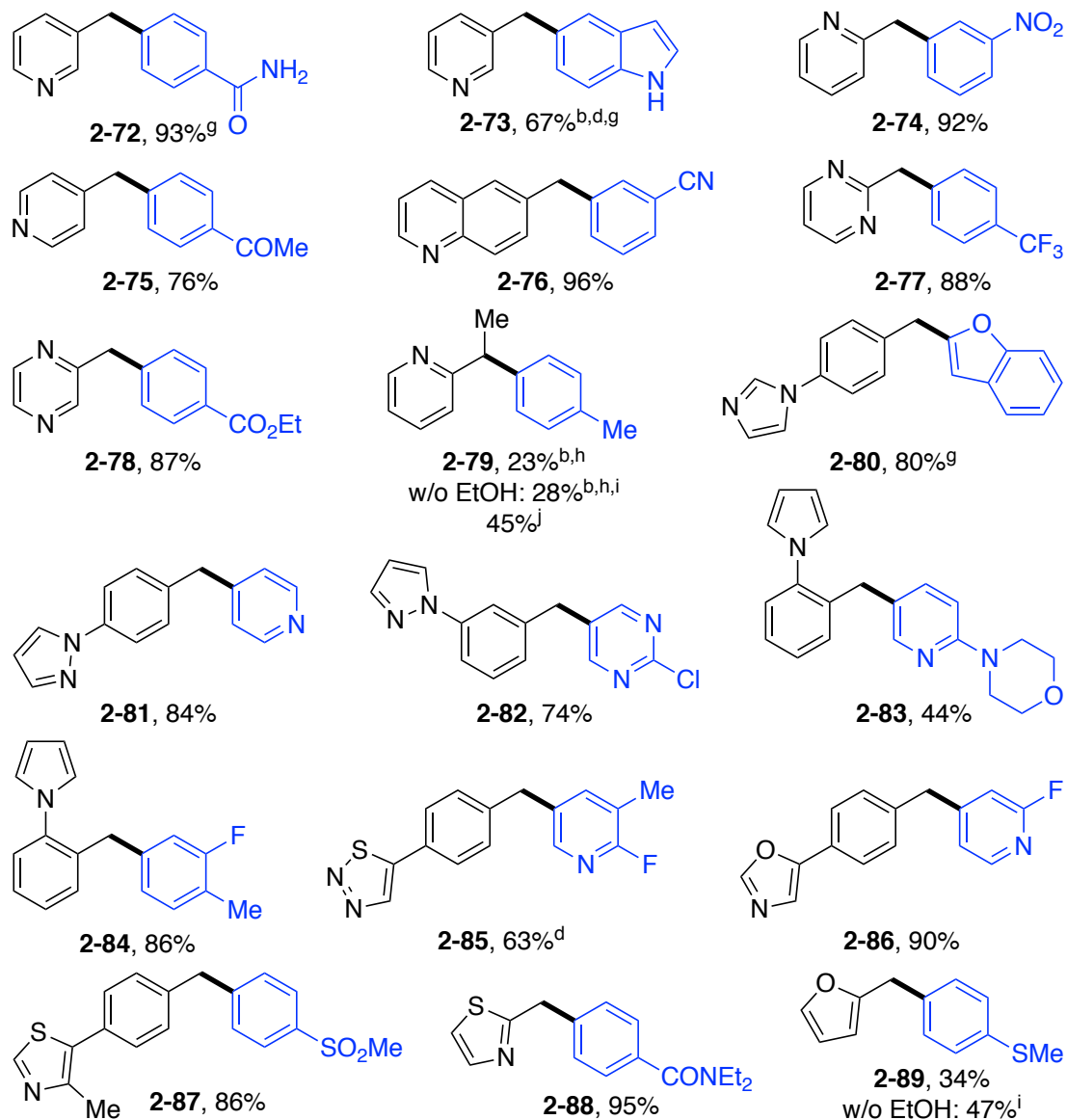
[a]Conditions: pyridinium salt **2-67** (1.0 mmol), PhenNi(OAc)$_2$·xH$_2$O (5 mol %), ArB(OH)$_2$ (3.0 equiv), K$_3$PO$_4$ (3.4 equiv), EtOH (5 equiv), dioxane (0.5 M), 60 °C, 5 h. Average isolated yields (±5%) from duplicate experiments. [b]Single experiment. [c]10 mol % Ni(OAc)$_2$·4H$_2$O, 12 mol % Phen. [d]24 h. [e]Glassware was not oven-dried. [f]Minimal precautions to protect from air and moisture. [g]3:1 dioxane:DMSO. [h]0.1 mmol scale. Yield determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [i]EtOH omitted. [j]Conditions: pyridinium salt **2-59** (1.0 mmol),

Ni(OAc)$_2$·4H$_2$O (10 mol %), 4,4′-di$^t$BuBipy (12 mol %), $p$-Tol–B(OH)$_2$ (3.0 equiv), K$_3$PO$_4$ (3.4 equiv), dioxane (0.1 M), 60 °C, 24 h.

Secondary benzylic pyridinium salts were also examined. However, diarylethane **2-79** was formed in only 23% yield. Omission of EtOH only slightly increased the yield. A brief screen of ligands revealed that the use of 4,4′-di$^t$BuBipy increased the yield to 45%. Triphenylpyridine was only formed in ~60% in this reaction, suggesting that C−N bond cleavage was sluggish.

For the aryl boronic acid, broad tolerance for functional groups and heteroaryls was observed, including aryl chlorides (**2-69**, **2-74**), fluorides (**2-85**, **2-86**) and even bromides (**2-70**), ethers (**2-71**, **2-83**), amides (**2-72**, **2-88**), nitroarenes (**2-74**), ketones (**2-75**), nitriles (**2-76**), trifluoromethyls (**2-77**), esters (**2-78**), tertiary amines (**2-83**), sulfones (**2-87**), and thioethers (**2-89**). Both electron-rich and electron-poor heteroaryls can be used, including unprotected indole (**2-73**), benzofuran (**2-80**), pyridine (**2-81**, **2-83**, **2-85**, **2-86**), and pyrazine (**2-82**). Notably, many of these pyridines are poised for further elaboration via S$_N$Ar chemistry. Moreover, aryl groups containing acidic protons can be used without the need for any excess base (**2-72**, **2-73**).

Cognizant that poor solubility can be limiting for some substrates, I tested the tolerance of this reaction to a variety of solvents (Table 2.2). Excitingly, a wide range of solvents can be used. Etheral solvents provided excellent yields of **2-65** (entries 1–3). Lower yields were observed when very polar solvents such as DMSO or DMF were used (entries 7 & 8), but these yields were still of high synthetic utility. In fact, the reaction can be run in neat ethanol to afford **2-65** in 77% isolated yield (entry 9). Notably, however, this can only be used for pyridinium salts with electron-poor heteroaryls, which do not undergo substitution with EtOH. These results highlight the

feasibility of finding a solvent mixture that would be compatible with any given substrate.

Table 2.2       Wide solvent tolerance[a]
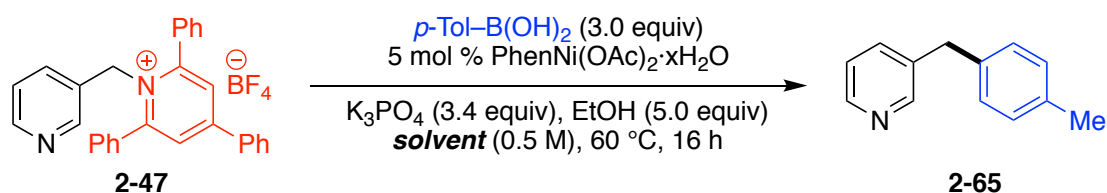


| Entry | Solvent | Yield (%)[b] |
|:-----:|:-------:|:------------:|
| 1 | 2-Me-THF | 96 |
| 2 | CPME | 96 |
| 3 | $Et_2O$ | 90 |
| 4 | PhMe | 94 |
| 5 | MeCN | 91 |
| 6 | $CH_2Cl_2$ | 83 |
| 7 | DMSO | 62 |
| 8 | DMF | 61 |
| 9[c] | EtOH | 77[d] |

[a]Conditions: pyridinium salt **2-47** (0.10 mmol), $PhenNi(OAc)_2 \cdot xH_2O$ (5 mol %), $ArB(OH)_2$ (3.0 equiv), $K_3PO_4$ (3.4 equiv), EtOH (5 equiv), solvent (0.5 M), 60 °C, 16 h. [b]Determined by $^1H$ NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]24 h. [d]Isolated yield.

The robustness of the cross-coupling reaction as well as tolerance for various solvents presented the opportunity to combine the pyridinium formation and cross-coupling in a one-pot operation. By forming the pyridinium salt *in-situ*, cross-coupled product **2-65** can be obtained directly from benzylic amine **2-90** (Scheme 2.12). The addition of 4 Å molecular sieves proved critical in this transformation. In the absence of sieves, **2-65** was obtained in only 19% yield. I believe that the desiccant may aid in pyridinium formation by preventing undesired hydrolysis of intermediate **2-91**, as well as by eliminating water that may be problematic in the cross-coupling. Notably, this is not a two-step, one-pot procedure; all reagents were added simultaneously at the beginning of the reaction. We believe that this approach can enable rapid screening to access a variety of diarylmethanes.

Scheme 2.12   One-pot transformation
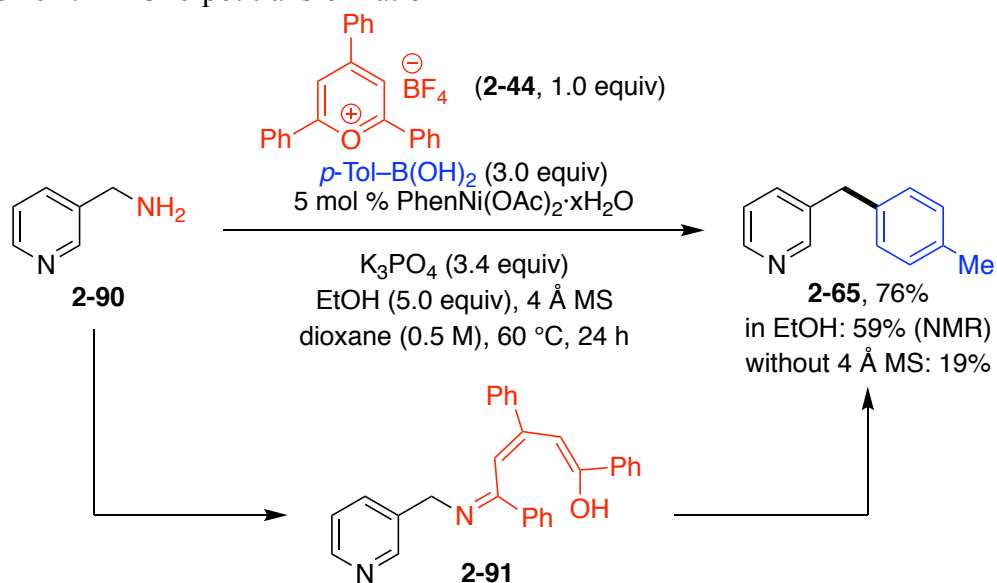
### 2.2.4 Mechanistic Studies

We theorize that this reaction proceeds via a $Ni^{I/III}$ catalytic cycle, analogous to that of the Suzuki–Miyaura cross-coupling of alkyl pyridinium salts (Chapter 1). The identity of the ligand, redox non-innocent phenanthroline, suggests that the oxidative addition likely proceeds through a single-electron transfer (SET) pathway. Although further experiments are needed to confirm the active nickel species, a radical trapping experiment supports the intermediacy of a benzylic radical.[43] When TEMPO was added to the cross-coupling of pyridinium **2-48**, known TEMPO adduct **2-92** was produced in 32% yield (Scheme 2.13). No desired cross-coupled product was observed.

Scheme 2.13  Radical trapping experiment
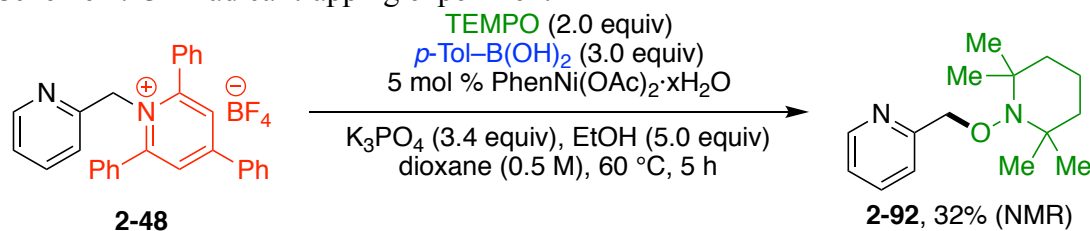


We believe that the following $Ni^{I/III}$ catalytic cycle may be operative (Scheme 2.14). This mechanism is analogous to that of Fu's Negishi cross-coupling of alkyl halides.[44] $Ni^{I}$ species **A** can undergo transmetallation with the activated aryl boronate to generate $Ni^{I}$-arene species **B**. This species can then perform single-electron transfer into the benzylic pyridinium salt to generate **C**, which fragments to give stabilized benzylic radical **D**. This radical can then recombine with $Ni^{II}$ species **E** to afford $Ni^{III}$ species **F**. Reductive elimination from **F** delivers the diarylmethane product and regenerates the active $Ni^{I}$ catalyst **A**. Another possible mechanism is a radical-chain

bimetallic pathway, which has been observed in Weix's reductive cross-electrophile couplings.[45] With our current data, we cannot rule out this possibility.

Scheme 2.14 Proposed catalytic cycle for cross-coupling of benzylic pyridinium salts
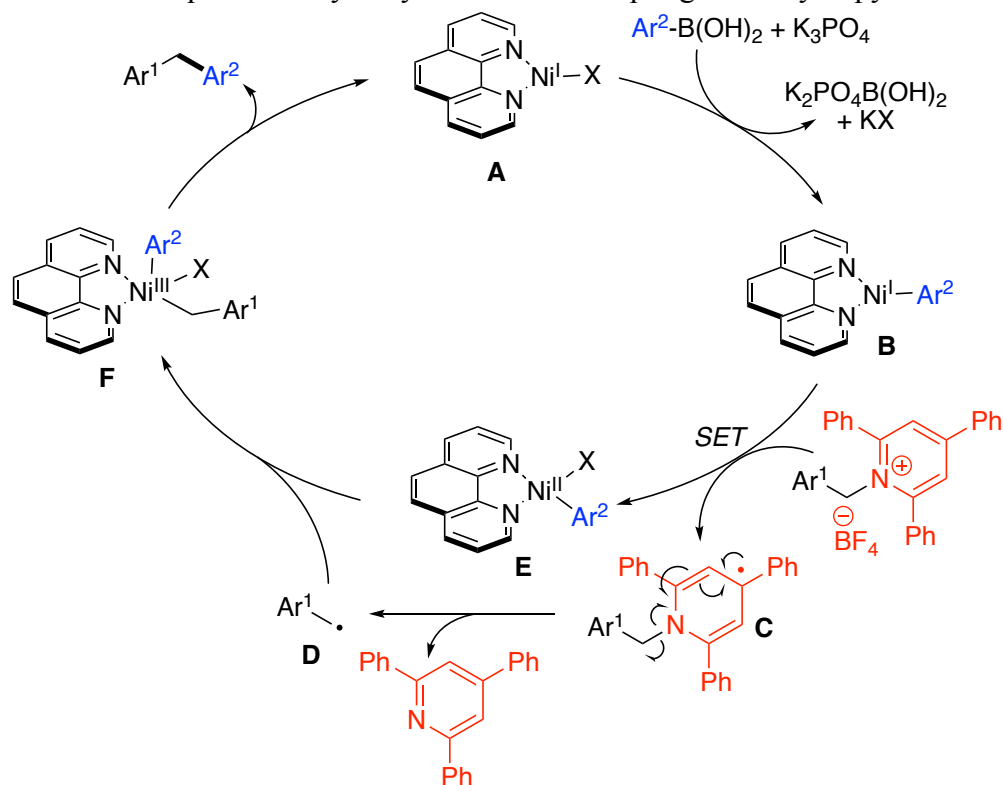


## 2.3 Conclusion

In summary, I have developed a nickel-catalyzed Suzuki−Miyaura cross-coupling of benzylic pyridinium salts with aryl boronic acids. This reaction enables efficient conversion of widely available benzylic amines to diarylmethanes, a prevalent motif in pharmaceuticals and other bioactive molecules. Notably, the use of a pyridinium salt enables broad scope of heteroaromatic substituents, including those that would not be amenable to activation via a trimethylammonium triflate. Broad

solvent tolerance was also demonstrated, providing viable alternatives when solubility becomes problematic. Finally, for benzylic pyridinium salts with electron-poor aryl groups, a one-pot procedure was developed to facilitate the use of this chemistry in synthesis. This work was published in *Organic Letters* and highlighted in *Synfacts*.[46, 47]

## 2.4 Experimental

### 2.4.1 General Information

Reactions were performed in oven-dried Schlenk flasks or in oven-dried round-bottomed flasks unless otherwise noted. Round-bottomed flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of $N_2$. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Silica gel chromatography was performed on silica gel 60 (40-63 μm, 60Å) unless otherwise noted. Commercial reagents were purchased from Sigma Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, AK Scientific, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: anhydrous ethanol and DMSO were degassed by sparging with $N_2$ for 20–30 minutes prior to use in the cross-coupling reactions; THF and $CH_2Cl_2$ were dried by passing through drying columns; dioxane was dried by passing through drying columns, then degassed by sparging with $N_2$.[48] Powdered, activated 4Å molecular sieves were prepared by heating sieves to ~200°C under high vacuum overnight and then crushing to achieve a fine powder. In some instances oven-dried potassium carbonate was added to $CDCl_3$ to remove trace acid. Proton nuclear magnetic resonance ($^1$H NMR) spectra, carbon

nuclear magnetic resonance ($^{13}$C NMR) spectra, and fluorine nuclear magnetic resonance spectra ($^{19}$F NMR) were recorded on both 400 MHz and 600 MHz spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl$_3$ = δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl$_3$ = δ 77.16). Chemical shifts for fluorine were externally referenced to CFCl$_3$ in CDCl$_3$ (CFCl$_3$ = δ 0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, h = heptet), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using FTIR spectrophotometers with material loaded onto a KBr plate. The mass spectral data were obtained at the University of Delaware mass spectrometry facility. Melting points were taken on a Thomas-Hoover Uni-Melt Capillary Melting Point Apparatus.

## 2.4.2   Preparation of PhenNi(OAc)$_2$·xH$_2$O (2-66)
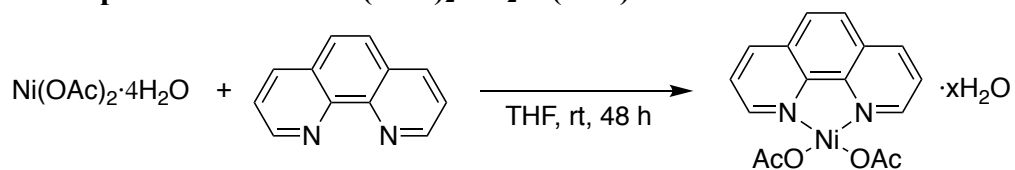


The following was adapted from a literature procedure.[49] To an oven-dried, 100-mL round-bottomed flask was added Ni(OAc)$_2$·4H$_2$O (1.49 g, 6.0 mmol, 1.0 equiv) and phenanthroline (1.08 g, 6.0 mmol, 1.0 equiv). The flask was fitted with a septum, and THF (35 mL) was added. The reaction mixture was stirred at room temperature for 48 h. The resulting pale blue suspension was filtered. The solid was

washed with $Et_2O$ (3 x 20 mL) and dried under high vacuum. The solid was used as is without further purification: $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 47.32 – 41.84 (m, 8H), 22.88 (s, 3H), 18.03 (s, 3H); HRMS (LIFDI) [M]$^+$ calculated for $C_{16}H_{14}N_2O_4Ni$: 356.0307, found 356.0290.

### 2.4.3 Cross-Coupling of Pyridinium Salts to Give Diarylmethanes

### 2.4.3.1 General Procedure A: Cross-Coupling of Pyridinium Salts with Boronic Acids
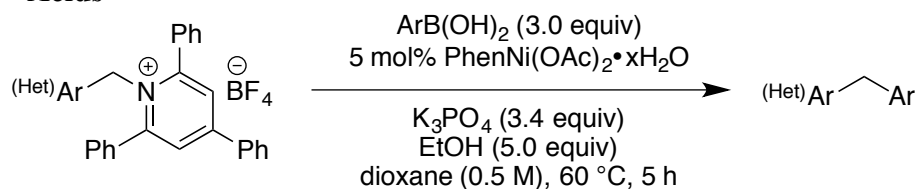


To an oven-dried, 25-mL Schlenk flask was added PhenNi(OAc)$_2$·xH$_2$O (20 mg, 0.050 mmol, 5 mol %), pyridinium salt (1.0 mmol, 1.0 equiv), arylboronic acid (3.0 mmol, 3.0 equiv), and K$_3$PO$_4$ (722 mg, 3.4 mmol, 3.4 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). Dioxane (2.0 mL) was added, followed by EtOH (0.29 mL, 5.0 mmol, 5.0 equiv). The flask was sealed and resulting mixture was stirred at 60 °C for 5 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with CH$_2$Cl$_2$ (4 x 25 mL), and the filtrate was concentrated. The cross-coupled product was then purified via silica gel chromatography.
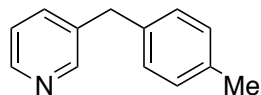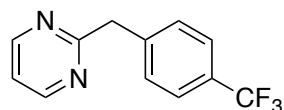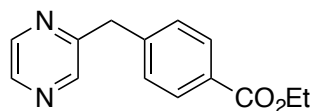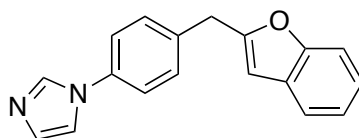
**3-(4-Methylbenzyl)pyridine (2-65).** Prepared via General Procedure A using pyridinium salt **2-47**. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-65** (run 1: 170 mg, 93%; run 2: 172 mg, 94%) as pale yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.50 (s, 1H), 8.47 – 8.43 (m, 1H), 7.48 – 7.43 (m, 1H), 7.21 – 7.16 (m, 1H), 7.11 (d, $J$ = 7.9 Hz, 2H), 7.07 (d, $J$ = 8.0 Hz, 2H), 3.94 (s, 2H), 2.32 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 150.2, 147.6, 136.8, 136.7, 136.2, 136.0, 129.4, 128.7, 123.4, 38.7, 21.0. The spectral data matches that reported in the literature.[50]

*Reaction without Oven-dried Glassware*

Product **2-65** also prepared via General Procedure A, except that the Schlenk flask and stir bar were not oven-dried prior to use. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-65** (155 mg, 84%).

*Reaction with "Minimal Precaution" Set-up*

Product **2-65** was also prepared via a procedure similar to General Procedure A, except that minimal precautions were taken to protect the reaction from air and moisture. Dioxane (ACS grade) and EtOH (absolute) were used as received; they were not dried or degassed. The round-bottomed flask and stir bar were not oven-dried prior to use. Reagents were added directly into the flask, open to air. The reaction was set up under air (no N$_2$).

To a 25-mL round-bottomed flask equipped with a stir bar was added PhenNi(OAc)$_2$·xH$_2$O (20 mg, 0.050 mmol, 5 mol %), pyridinium salt **2-47** (486 mg, 1.0 mmol, 1.0 equiv), *p*-tolylboronic acid (408 mg, 3.0 mmol, 3.0 equiv), and K$_3$PO$_4$ (722 mg, 3.4 mmol, 3.4 equiv). Dioxane (2.0 mL) was added, followed by EtOH (0.29

mL, 5.0 mmol, 5.0 equiv). The flask was fitted with a rubber septum and sealed with parafilm (no $N_2$ inlet). The resulting mixture was stirred at 60 °C for 5 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with $CH_2Cl_2$ (4 x 25 mL), and the filtrate was concentrated. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-65** (131 mg, 71%).

*Reaction with Ethanol as Solvent*

Product **2-65** was also prepared via a procedure similar to General Procedure A, except that EtOH was used as the solvent. To an oven-dried, 25-mL Schlenk flask, was added PhenNi(OAc)$_2$·xH$_2$O (20 mg, 0.050 mmol, 5 mol %), pyridinium salt **2-47** (486 mg, 1.0 mmol, 1.0 equiv), *p*-tolylboronic acid (408 mg, 3.0 equiv, 3.0 mmol), and $K_3PO_4$ (722 mg, 3.4 mmol, 3.4 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with $N_2$ (x 3). EtOH (2.0 mL) was added. The resulting mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with $CH_2Cl_2$ (4 x 25 mL), and the filtrate was concentrated. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-65** (141 mg, 77%).

*Reaction with Two-component Catalyst*

Product **2-65** was also prepared using a two-component catalyst system. To an oven-dried, 25-mL pear-shaped flask, was added Ni(OAc)$_2$·4H$_2$O (25 mg, 0.10 mmol, 10 mol %) and phenanthroline (22 mg, 0.12 mmol, 12 mol %). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with $N_2$ (x 3). To an oven-dried, 25-mL Schlenk flask was added pyridinium salt **2-47** (486 mg,

1.0 mmol, 1.0 equiv), *p*-tolylboronic acid (408 mg, 3.0 equiv, 3.0 mmol), and $K_3PO_4$ (722 mg, 3.4 mmol, 3.4 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with $N_2$ (x 3). To the pear-shaped flask containing $Ni(OAc)_2 \cdot 4H_2O$ and Phen was added dioxane (sparged, anhydrous; 2.5 mL). To the Schlenk flask containing the pyridinium salt, boronic acid, and $K_3PO_4$ was added dioxane (sparged, anhydrous; 2.5 mL), followed by EtOH (sparged, anhydrous; 0.29 mL, 5.0 mmol, 5.0 equiv). After vigorously stirring of the resulting mixtures for 1 h at room temperature, the heterogeneous mixture containing the catalyst was transferred via cannula to the mixture containing the pyridinium salt and activated boronate complex. The pear-shaped flask was rinsed multiple times with dioxane (totaling 5 mL; each rinse was transferred via cannula to the reaction mixture) to bring the total volume of dioxane in the reaction flask to 10 mL (0.1 M). The resulting reaction mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with $CH_2Cl_2$ (4 x 25 mL), and the resulting solution was concentrated. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-65** (171 mg, 93%).
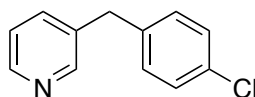


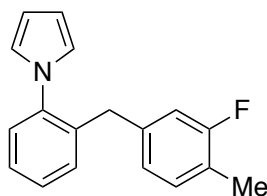**3-(4-Chlorobenzyl)pyridine (2-69).** Prepared via General Procedure A using pyridinium salt **2-47**. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-69** (run 1: 182 mg, 90%; run 2: 190 mg, 93%) as a clear oil: ^{1}H NMR (600 MHz, CDCl₃) δ 8.53 – 8.48 (m, 2H), 7.49 – 7.43 (m, 1H), 7.32 – 7.27 (m, 2H), 7.26 – 7.21 (m, 1H), 7.15 – 7.11 (m, 2H), 3.97 (s, 2H); ^{13}C NMR (151

MHz, CDCl$_3$) δ 150.2, 147.9, 138.3, 136.2, 135.9, 132.4, 130.2, 128.8, 123.5, 38.4. The spectral data matches that reported in the literature.[51]
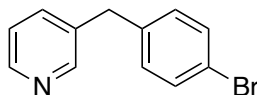


**3-(4-Bromobenzyl)pyridine (2-70).** Prepared via General Procedure A using pyridinium salt **2-47**. The crude mixture was purified by silica gel chromatography (60% ether/hexanes) to give **2-70** (run 1: 222 mg, 89%; run 2: 199 mg, 80%) as a pale yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.50 – 8.45 (m, 2H), 7.46 – 7.40 (m, 3H), 7.23 – 7.18 (m, 1H), 7.07 – 7.02 (m, 2H), 3.93 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 150.1, 147.9, 138.8, 136.2, 135.8, 131.8, 130.6, 123.5, 120.4, 38.5. The spectral data matches that reported in the literature.[52]
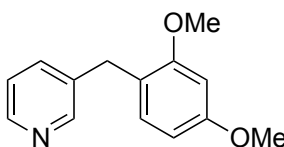


**3-(2,4-Dimethoxybenzyl)pyridine (2-71).** Prepared via General Procedure A using pyridinium salt **2-47**, except that the reaction mixture was heated for 24 h. The crude mixture was purified by silica gel chromatography (30% ethyl acetate/hexanes) to give **2-71** (run 1: 168 mg, 68%; run 2: 154 mg, 62%) as pale yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.53 – 8.47 (m, 1H), 8.44 – 8.37 (m, 1H), 7.50 – 7.42 (m, 1H), 7.20 – 7.12 (m, 1H), 7.03 – 6.96 (m, 1H), 6.48 – 6.38 (m, 2H), 3.87 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.8, 158.2, 150.3, 147.2, 136.9, 136.1, 130.5, 123.2, 120.9, 104.1, 98.7, 55.4, 55.3, 32.8; FTIR (neat) 2936, 2835, 1612, 1507, 1209, 1035, 713 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{16}$NO$_2$: 230.1181, found 230.1178.
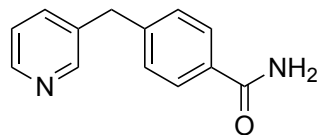
**4-(Pyridin-3-ylmethyl)benzamide (2-72).** Prepared via General Procedure A using pyridinium salt **2-47**, except that a 3:1 mixture of dioxane (1.5 mL) and DMSO (0.5 mL) was used as the solvent. The crude mixture was purified by silica gel chromatography (5–10 MeOH/CH$_2$Cl$_2$) to give **2-72** (run 1: 186 mg, 88%; run 2: 208 mg, 98%) as an off-white solid (mp 152–154 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.53 – 8.46 (m, 2H), 7.78 – 7.73 (m, 2H), 7.48 – 7.42 (m, 1H), 7.28 – 7.25 (m, 2H, *overlaps with CHCl$_3$*), 7.25 – 7.19 (m, 1H), 6.01 (s, br, 1H), 5.57 (s, br, 1H), 4.03 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 168.8, 150.2, 148.0, 144.2, 136.3, 135.6, 131.6, 129.1, 127.8, 123.5, 38.9; FTIR (neat) 3393, 3172, 1652, 1616, 1416, 1394, 1030, 712 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{13}$H$_{13}$N$_2$O: 213.1022, found 213.1019.
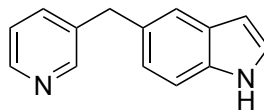


**5-(Pyridin-3-ylmethyl)-1*H*-indole (2-73).** Prepared via General Procedure A using pyridinium salt **2-47**, except that a 3:1 mixture of dioxane (1.5 mL) and DMSO (0.5 mL) was used as the solvent and the reaction mixture was heated for 24 h. The crude mixture was purified by silica gel chromatography (50% ethyl acetate/hexanes) to give **2-73** (140 mg, 67%) as an off-white solid: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.57 – 8.53 (m, 1H), 8.46 – 8.42 (m, 1H), 8.18 (s, br, 1H), 7.52 – 7.47 (m, 1H), 7.47 – 7.43 (m, 1H), 7.35 – 7.30 (m, 1H), 7.22 – 7.19 (m, 1H), 7.19 – 7.15 (m, 1H), 7.04 – 6.99 (m, 1H), 6.52 – 6.48 (m, 1H), 4.08 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 150.2, 147.4, 137.6, 136.3, 134.6, 131.3, 128.2, 124.6, 123.3, 123.3, 120.6, 111.2, 102.5, 39.2. The spectral data matches that reported in the literature.[14]
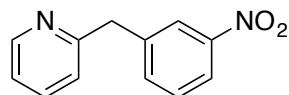
**2-(3-Nitrobenzyl)pyridine (2-74).** Prepared via General Procedure A using pyridinium salt **2-48**. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-74** (run 1: 196 mg, 91%; run 2: 200 mg, 93%) as an orange oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.59 – 8.55 (m, 1H), 8.13 (s, 1H), 8.11 – 8.06 (m, 1H), 7.66 – 7.59 (m, 2H), 7.50 – 7.45 (m, 1H), 7.19 – 7.14 (m, 2H), 4.25 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.2, 149.8, 148.4, 141.5, 136.9, 135.3, 129.4, 123.9, 123.2, 121.8, 121.6, 44.1. The spectral data matches that reported in the literature.[53]
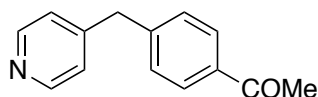


**1-(4-(Pyridin-4-ylmethyl)phenyl)ethan-1-one (2-75).** Prepared via General Procedure A using pyridinium salt **2-49**. The crude mixture was purified by silica gel chromatography (50% ethyl acetate/hexanes) to give **2-75** (run 1: 163 mg, 77%; run 2: 159 mg, 75%) as a yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.52 (d, $J$ = 5.9 Hz, 2H), 7.91 (d, $J$ = 8.2 Hz, 2H), 7.27 (d, $J$ = 8.2 Hz, 2H), 7.09 (d, $J$ = 5.9 Hz, 2H), 4.02 (s, 2H), 2.59 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 197.6, 150.1, 148.8, 144.4, 135.8, 129.2, 128.8, 124.2, 41.2, 26.6; FTIR (neat) 3029, 2921, 1681, 1597, 1414, 1268, 609 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{14}$NO: 212.1075, found 212.1071.
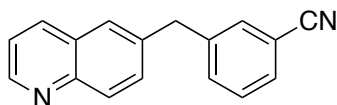


**3-(Quinolin-6-ylmethyl)benzonitrile (2-76).** Prepared via General Procedure A using pyridinium salt **2-50**. The crude mixture was purified by silica gel chromatography

(50–80% ether/hexanes) to give **2-76** (run 1: 231 mg, 94%; run 2: 238 mg, 98%) as a pale yellow solid (mp 79–81 °C): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.93 – 8.87 (m, 1H), 8.14 – 8.02 (m, 2H), 7.61 – 7.56 (m, 1H), 7.56 – 7.45 (m, 4H), 7.45 – 7.38 (m, 2H), 4.20 (s, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 150.3, 147.3, 141.9, 137.8, 135.7, 133.5, 132.5, 130.8, 130.3, 130.1, 129.4, 128.4, 127.1, 121.5, 118.8, 112.7, 41.4; FTIR (neat) 3032, 2920, 2229, 1594, 1501, 838, 688 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{17}$H$_{13}$N$_2$: 245.1079, found 245.1074.



**2-(4-(Trifluoromethyl)benzyl)pyrimidine (2-77).** Prepared via General Procedure A using pyridinium salt **2-51**. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-77** (run 1: 212 mg, 89%; run 2: 208 mg, 87%) as a yellow oil: ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.69 (d, J = 4.9 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 4.9 Hz, 1H), 4.35 (s, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 169.2, 157.5, 142.2 (q, $J_{C\text{-}F}$ = 1.5 Hz), 129.5, 128.9 (q, $J_{C\text{-}F}$ = 32.4 Hz), 125.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 271.9 Hz), 119.0, 45.8; ^{19}F NMR (565 MHz, CDCl$_3$) δ −62.49; FTIR (neat) 3043, 2929, 1563, 1418, 1327, 1067, 633 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{12}$H$_{10}$F$_3$N$_2$: 239.0796, found 239.0791.



**Ethyl 4-(pyrazin-2-ylmethyl)benzoate (2-78).** Prepared via General Procedure A using pyridinium salt **2-52**. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-78** (run 1: 210 mg, 87%; run 2: 209

mg, 86%) as an orange solid (mp 62–65 °C): $^{1}$H NMR (600 MHz, CDCl$_3$) δ 8.53 – 8.49 (m, 1H), 8.49 – 8.46 (m, 1H), 8.45 – 8.41 (m, 1H), 7.99 (d, $J$ = 8.2 Hz, 2H), 7.34 (d, $J$ = 8.2 Hz, 2H), 4.36 (q, $J$ = 7.1 Hz, 2H), 4.22 (s, 2H), 1.37 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 166.3, 155.7, 144.7, 144.2, 143.2, 142.7, 130.0, 129.2, 129.0, 60.9, 41.9, 14.3; FTIR (neat) 2981, 2924, 1713, 1276, 1100, 1019, 758 cm$^{-1}$; HRMS (ESI+) [M+H]$^{+}$ calculated for C$_{14}$H$_{15}$N$_2$O$_2$: 243.1134, found 243.1129.



**1-(4-(Benzofuran-2-ylmethyl)phenyl)-1H-imidazole (2-80).** Prepared via General Procedure A using pyridinium salt **2-93**, except that a 3:1 mixture of dioxane (1.5 mL) and DMSO (0.5 mL) was used as the solvent. The crude mixture was purified by silica gel chromatography (70% ethyl acetate/hexanes) to give **2-80** (run 1: 216 mg, 79%; run 2: 221 mg, 81%) as a pale yellow solid (mp 76–78 °C): $^{1}$H NMR (600 MHz, CDCl$_3$) δ 7.88 – 7.84 (m, 1H), 7.54 – 7.50 (m, 1H), 7.47 – 7.42 (m, 3H), 7.41 – 7.35 (m, 2H), 7.30 – 7.29 (m, 1H), 7.27 – 7.20 (m, 3H), 6.49 – 6.45 (m, 1H), 4.19 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 156.8, 155.0, 136.8, 136.2, 135.6, 130.5, 130.3, 128.6, 123.7, 122.7, 121.8, 120.5, 118.3, 111.0, 103.7, 34.5; FTIR (neat) 3111, 1522, 1303, 1252, 1056, 752 cm$^{-1}$; HRMS (ESI+) [M+H]$^{+}$ calculated for C$_{18}$H$_{15}$N$_2$O: 275.1184, found 275.1180.
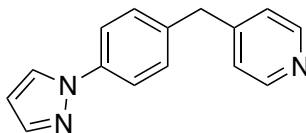
**4-(4-(1H-Pyrazol-1-yl)benzyl)pyridine (2-81).** Prepared via General Procedure A using pyridinium salt **2-54**. The crude mixture was purified by silica gel chromatography (50% ethyl acetate/hexanes) to give **2-81** (run 1: 189 mg, 80%; run 2: 205 mg, 87%) as a tan solid (mp 51–53 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.52 (d, *J* = 6.0 Hz, 2H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 1.5 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H, *overlaps with CHCl$_3$*), 7.11 (d, *J* = 6.0 Hz, 2H), 6.46 (dd, *J* = 2.0, 1.5 Hz, 1H), 4.00 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 150.0, 149.6, 141.1, 139.0, 137.1, 130.0, 126.7, 124.1, 119.5, 107.6, 40.6; FTIR (neat) 3026, 2921, 1599, 1524, 1394, 936, 785 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{15}$H$_{14}$N$_3$: 236.1188, found 236.1183.
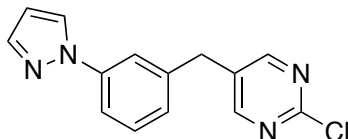


**5-(3-(1H-Pyrazol-1-yl)benzyl)-2-chloropyrimidine (2-82).** Prepared via General Procedure A using pyridinium salt **2-60**. The crude mixture was purified by silica gel chromatography (25–50% ether/hexanes) to give **2-82** (run 1: 188 mg, 70%; run 2: 208 mg, 77%) as an orange solid (mp 71–73 °C: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.49 (s, 2H), 7.93 – 7.89 (m, 1H), 7.73 – 7.70 (m, 1H), 7.64 – 7.60 (m, 1H), 7.57 – 7.52 (m, 1H), 7.45 – 7.39 (m, 1H), 7.09 – 7.05 (m, 1H), 6.49 – 6.45 (m, 1H), 4.02 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.8, 159.6, 141.3, 140.8, 139.4, 132.4, 130.2, 126.7, 126.6, 119.7, 117.6, 107.9, 35.7; FTIR (neat) 2922, 1548, 1393, 1153, 1044, 753; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{12}$ClN$_4$: 271.0750, found 271.0745.
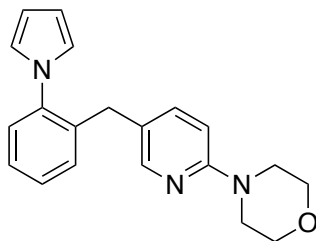
**4-(5-(2-(1H-Pyrrol-1-yl)benzyl)pyridin-2-yl)morpholine (2-83).** Prepared via General Procedure A using pyridinium salt **2-61**. The crude mixture was purified by silica gel chromatography (20% ethyl acetate/hexanes) to give **2-83** (run 1: 135 mg, 42%; run 2: 141 mg, 44%) as a white solid (mp 119–121 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, $J$ = 2.1 Hz, 1H), 7.35 – 7.19 (m, 4H, *overlaps with CHCl$_3$*), 7.08 (dd, $J$ = 8.7, 2.5 Hz, 1H), 6.74 (t, $J$ = 2.1 Hz, 2H), 6.53 (d, $J$ = 8.7 Hz, 1H), 6.31 (t, $J$ = 2.1 Hz, 2H), 3.85 – 3.77 (m, 4H), 3.73 (s, 2H), 3.47 – 3.40 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.3, 147.8, 140.3, 138.1, 136.9, 130.6, 128.0, 127.3, 127.1, 125.5, 122.3, 109.0, 106.8, 66.8, 45.8, 33.3; FTIR (neat) 2959, 2852, 1606, 1493, 1244, 1120, 494, 729 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{20}$H$_{22}$N$_3$O: 320.1763, found 320.1749.



**1-(2-(3-Fluoro-4-methylbenzyl)phenyl)-1H-pyrrole (2-84).** Prepared via General Procedure A using pyridinium salt **2-61**. The crude mixture was purified by silica gel chromatography (25% toluene/hexanes) to give **2-84** (run 1: 220 mg, 83%; run 2: 236 mg, 89%) as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.27 (m, 3H), 7.26 – 7.21 (m, 1H), 7.07 – 6.98 (m, 1H), 6.72 (t, $J$ = 2.1 Hz, 2H), 6.70 – 6.58 (m, 2H), 6.29 (t, $J$ = 2.1 Hz, 2H), 3.81 (s, 2H), 2.21 (d, $J_{H\text{-}F}$ = 1.8 Hz, 3H); $^{13}$C NMR (101 MHz,

CDCl$_3$) δ 161.2 (d, $J_{C-F}$ = 244.4 Hz), 140.4, 140.0 (d, $J_{C-F}$ = 7.2 Hz), 136.5, 131.2 (d, $J_{C-F}$ = 5.6 Hz), 130.9, 128.0, 127.3 (d, $J_{C-F}$ = 6.7 Hz), 124.1 (d, $J_{C-F}$ = 3.2 Hz), 122.5, 122.31, 122.28, 115.2 (d, $J_{C-F}$ = 22.3 Hz), 108.9, 36.3 (d, $J_{C-F}$ = 1.7 Hz), 14.2 (d, $J_{C-F}$ = 3.4 Hz); $^{19}$F NMR (565 MHz, CDCl$_3$) δ −117.88; FTIR (neat) 3030, 2927, 2860, 1503, 1328, 1113, 728 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{18}$H$_{17}$FN: 266.1345, found 266.1341.
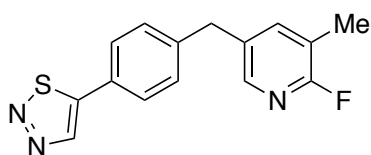


**5-(4-((6-Fluoro-5-methylpyridin-3-yl)methyl)phenyl)-1,2,3-thiadiazole      (2-85).**
Prepared via General Procedure A using pyridinium salt **2-62**, except that the reaction mixture was heated for 24 h. The crude mixture was purified by silica gel chromatography (30–50% ether/hexanes) to give **2-85** (run 1: 172 mg, 60%; run 2: 188 mg, 66%) as a yellow solid (mp 141–143 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.62 (s, 1H), 8.00 (d, $J$ = 8.2 Hz, 2H), 7.93 (s, 1H), 7.42 – 7.36 (m, 1H), 7.32 (d, $J$ = 8.2 Hz, 2H), 4.00 (s, 2H), 2.24 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.5, 161.2 (d$_{C-F}$, $J$ = 237.3 Hz), 144.4 (d, $J_{C-F}$ = 14.3 Hz), 142.0 (d, $J_{C-F}$ = 6.0 Hz), 141.3, 133.7 (d, $J_{C-F}$ = 4.7 Hz), 129.7, 129.6, 129.3, 127.8, 119.5 (d, $J_{C-F}$ = 32.8 Hz), 37.8, 14.5 (d, $J_{C-F}$ = 1.2 Hz); $^{19}$F NMR (565 MHz, CDCl$_3$) δ −75.62; FTIR (neat) 3091, 2923, 2851, 1590, 1464, 1244, 804, 544 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{15}$H$_{13}$FN$_3$S: 286.0814, found 286.0810.
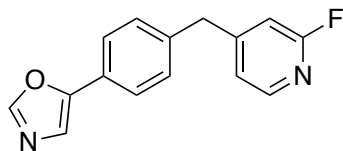
**5-(4-((2-Fluoropyridin-4-yl)methyl)phenyl)oxazole (2-86).** Prepared via General Procedure A using pyridinium salt **2-94**. The crude mixture was purified by silica gel chromatography (30% ethyl acetate/hexanes) to give **2-86** (run 1: 231 mg, 91%; run 2: 224 mg, 88%) as a pale yellow solid (mp 68–71 °C): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 – 8.12 (m, 1H), 7.94 (s, 1H), 7.69 – 7.62 (m, 2H), 7.37 (s, 1H), 7.27 (d, $J$ = 8.3 Hz, 2H), 7.06 – 6.99 (m, 1H), 6.79 – 6.73 (m, 1H), 4.05 (s, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.2 (d, $J_{C-F}$ = 238.9 Hz), 155.5 (d, $J_{C-F}$ = 7.7 Hz), 151.2, 150.5, 147.7 (d, $J_{C-F}$ = 15.3 Hz), 138.6, 129.7, 126.6, 124.9, 121.9 (d, $J_{C-F}$ = 4.0 Hz), 121.6, 109.6 (d, $J_{C-F}$ = 37.2 Hz), 40.8 (d, $J_{C-F}$ = 3.0 Hz); ^{19}F NMR (376 MHz, CDCl$_3$) δ –68.31 ; FTIR (neat) 3124, 1611, 1410, 941, 819, 640 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{15}$H$_{12}$FN$_2$O: 255.0934, found 255.0930.
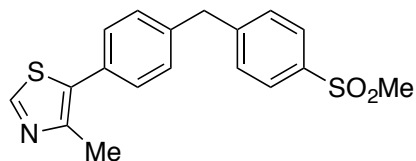


**4-Methyl-5-(4-(4-(methylsulfonyl)benzyl)phenyl)thiazole (2-87).** Prepared via General Procedure A using pyridinium salt **2-95**. The crude mixture was purified by silica gel chromatography (50% ethyl acetate/hexanes) to give **2-87** (run 1: 296 mg, 86%; run 2: 280 mg, 81%) as a pale yellow solid (mp 123–125 °C): ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.67 (s, 1H), 7.91 – 7.86 (m, 2H), 7.44 – 7.37 (m, 4H), 7.26 – 7.21 (m, 2H), 4.11 (s, 2H), 3.05 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 150.2, 148.6, 147.1, 139.2, 138.7, 131.5, 130.5, 129.8, 129.7, 129.3, 127.8, 44.6, 41.5, 16.1;

FTIR (neat) 2922, 1408, 1304, 1149, 759, 533 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{18}$H$_{18}$NO$_2$S$_2$: 344.0779, found 344.0775.
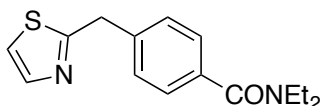


**N,N-Diethyl-4-(thiazol-2-ylmethyl)benzamide (2-88).** Prepared via General Procedure A using pyridinium salt **2-63**. The crude mixture was purified by silica gel chromatography (50–80% ethyl acetate/hexanes) to give **2-88** (run 1: 264 mg, 96%; run 2: 259 mg, 94%) as a dark orange oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.71 (d, $J$ = 3.3 Hz, 1H), 7.36 – 7.31 (m, 4H), 7.22 (d, $J$ = 3.3 Hz, 1H), 4.36 (s, 2H), 3.66 – 3.39 (m, br, 2H), 3.39 – 3.09 (m, br, 2H), 1.35 – 1.17 (m, br, 3H), 1.17 – 0.95 (m, br, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.0, 169.5, 142.6, 138.9, 136.0, 129.0, 126.9, 119.2, 43.3, 39.3 (2C), 14.3, 12.9; FTIR (neat) 3077, 2972, 2933, 1627, 1427, 1427, 1288, 1095 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{15}$H$_{19}$N$_2$OS: 275.1218, found 275.1212.
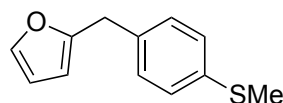


**2-(4-(Methylthio)benzyl)furan (2-89).** Prepared via General Procedure A using pyridinium salt **2-64**. The crude mixture was purified by silica gel chromatography (10–20% toluene/hexanes) to give **2-89** (run 1: 69 mg, 34%; run 2: 70 mg, 34%) as an orange oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.34 – 7.30 (m, 1H), 7.24 – 7.19 (m, 2H), 7.18 – 7.13 (m, 2H), 6.31 – 6.27 (m, 1H), 6.02 – 5.98 (m, 1H), 3.93 (s, 2H), 2.47 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 154.4, 141.5, 136.3, 135.2, 129.2, 127.1, 110.2,

106.2, 34.0, 16.2; FTIR (neat) 3115, 3021, 2919, 1494, 1009, 799, 732 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for $C_{12}H_{13}OS$: 205.0687, found 205.0677.

*Reaction of Pyridinium Salt **2-64** without Ethanol*

Product **2-89** also prepared via General Procedure A, except that no EtOH was added to the reaction mixture. The crude mixture was purified by silica gel chromatography (10–20% toluene/hexanes) to give **2-89** (95 mg, 47%).

### 2.4.3.2   One-pot Cross-Coupling of Benzylamine with Boronic Acid
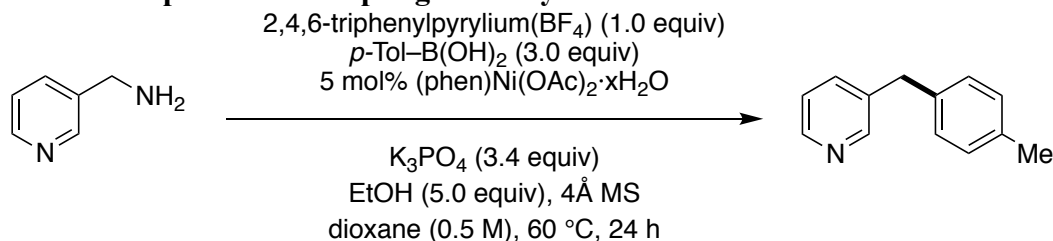


Product **2-65** was formed via a procedure adapted from General Procedure A, except that the pyridinium salt was formed in situ. To an oven-dried, 25-mL Schlenk flask was added PhenNi(OAc)$_2$·xH$_2$O (20 mg, 0.050 mmol, 5 mol %), *p*-tolylboronic acid (408 mg, 3.0 equiv, 3.0 mmol), K$_3$PO$_4$ (722 mg, 3.4 mmol, 3.4 equiv), 2,4,6-triphenylpyrillium tetrafluoroborate (396 mg, 1.0 mmol, 1.0 equiv), and powered, activated 4Å molecular sieves (500 mg, 500 mg/mmol). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). Commercially available 3-(aminomethyl)pyridine (**2-90**) (sparged; 0.10 mL, 1.0 mmol, 1.0 equiv) was added, followed by dioxane (sparged, anhydrous; 2.0 mL) and EtOH (sparged, anhydrous; 0.29 mL, 5.0 mmol, 5.0 equiv). The resulting mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with CH$_2$Cl$_2$ (4

x 25 mL), and the filtrate was concentrated. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **2-65** (140 mg, 76%).

### 2.4.3.3  Cross-Coupling of Secondary Benzylic Pyridinium Salt with Boronic Acid



$p$TolB(OH)$_2$ (3.0 equiv)
10 mol% Ni(OAc)$_2$·4H$_2$O
12 mol% 4,4'-di$^t$BuBipy

K$_3$PO$_4$ (3.4 equiv)
dioxane (0.1 M), 60 °C, 24 h
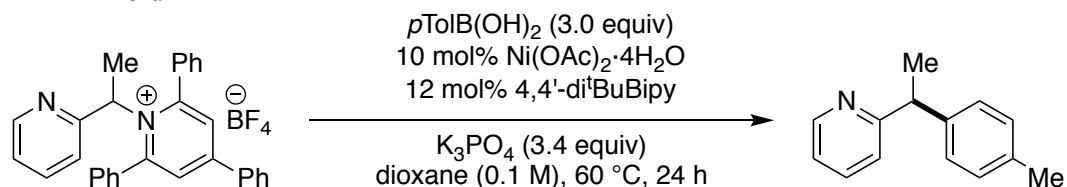
**2-(1-($p$-Tolyl)ethyl)pyridine (2-79).** To an oven-dried, 25-mL pear-shaped flask, was added Ni(OAc)$_2$·4H$_2$O (25 mg, 0.10 mmol, 10 mol %) and 4,4'-di$^t$BuBipy (32 mg, 0.012 mmol, 12 mol %). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). To an oven-dried, 25-mL Schlenk flask was added pyridinium salt **2-59** (500 mg, 1.0 mmol, 1.0 equiv), $p$-tolylboronic acid (408 mg, 3.0 equiv, 3.0 mmol), and K$_3$PO$_4$ (722 mg, 3.4 mmol, 3.4 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). To the pear-shaped flask containing Ni(OAc)$_2$·4H$_2$O and 4,4'-di$^t$BuBipy was added dioxane (sparged, anhydrous; 2.5 mL). To the Schlenk flask containing the pyridinium salt, boronic acid, and K$_3$PO$_4$ was added dioxane (sparged, anhydrous; 2.5 mL). After vigorously stirring of the resulting mixtures for 1 h at room temperature, the heterogeneous mixture containing the catalyst was transferred via cannula to the mixture containing the pyridinium salt and activated boronate complex. The pear-shaped flask was rinsed multiple times with dioxane (totaling 5 mL; each rinse was transferred via cannula to the reaction mixture) to bring the total volume of dioxane in the reaction flask to 10 mL (0.1 M). The flask

was sealed off and resulting mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with CH$_2$Cl$_2$ (4 x 25 mL), and the filtrate was concentrated. The cross-coupled product was then purified via silica gel chromatography (25% ether/hexanes) to give **2-79** (run 1: 92 mg, 47%; run 2: 85 mg, 43%): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.58 – 8.53 (m, 1H), 7.58 – 7.52 (m, 1H), 7.21 – 7.17 (m, 2H), 7.13 – 7.09 (m, 3H), 7.09 – 7.06 (m, 1H), 4.26 (q, $J$ = 7.2 Hz, 1H), 2.31 (s, 3H), 1.69 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 165.3, 149.1, 142.1, 136.3, 135.8, 129.2, 127.5, 122.0, 121.1, 47.0, 21.0, 20.8; FTIR (neat) 3048, 3006, 2968, 2927, 2871, 1588, 1432, 748, 549 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{16}$N: 198.1277, found 198.1272.

### 2.4.4   Preparation of Pyridinium Salts

#### 2.4.4.1   General Procedure B: Conversion of Electron-poor (Hetero)Arylamines to Pyridinium Salts
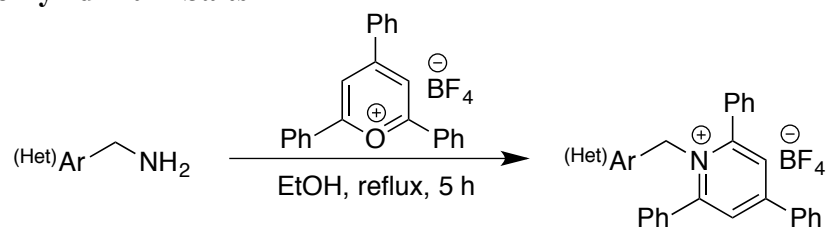


The following reaction was run open to air without oven-dried flasks. To a 25-mL, round-bottomed flask was added 2,4,6-triphenylpyrillium tetrafluoroborate (1.98 g, 5.0 mmol, 1.0 equiv) followed by EtOH (5 mL). Amine (6.0 mmol, 1.2 equiv) was added to the resulting suspension. The flask was fitted with a reflux condenser and heated in an oil bath at 80–85 °C for 5 h. The mixture was then allowed to cool to

room temperature. If product precipitation occurred during reflux or upon cooling, the solid was filtered, washed with EtOH (3 x 25 mL) and then Et$_2$O (3 x 25 mL), and dried under vacuum. If product precipitation did not occur, the solution was diluted with Et$_2$O (15 mL) and vigorously stirred for 1 h to induce precipitation. The resulting solid pyridinium salt was filtered and washed with Et$_2$O (3 x 25 mL). If the pyridinium salt failed to precipitate at this point, the flask containing the reaction mixture and Et$_2$O was sealed with parafilm and stored in a –27 °C freezer for 1–3 days (or until precipitation occurred). The cold mixture was quickly filtered and washed with Et$_2$O (3 x 25 mL) to give the corresponding analytically pure pyridinium salt. If the salt still did not precipitate, it was subjected to silica gel chromatography with acetone/CH$_2$Cl$_2$.
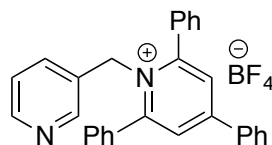


**2,4,6-Triphenyl-1-(pyridin-3-ylmethyl)pyridin-1-ium tetrafluoroborate (2-47).** Prepared via General Procedure B on a 10 mmol scale with commercially available 3-(aminomethyl)pyridine to give **2-47** (4.37 g, 90%) as a white solid (mp 174–176 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.42 – 8.37 (m, 1H), 7.97 (s, 2H), 7.83 – 7.78 (m, 2H), 7.75 – 7.71 (m, 1H), 7.70 – 7.66 (m, 4H), 7.63 – 7.58 (m, 1H), 7.57 – 7.48 (m, 8H), 7.07 – 7.01 (m, 1H), 6.88 – 6.82 (m, 1H), 5.84 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.5, 156.9, 149.6, 147.4, 134.5, 133.7, 132.6, 132.5, 131.3, 130.0, 129.9, 129.5, 129.1, 128.2, 126.8, 123.6, 56.0; $^{19}$F NMR (376 MHz, CDCl$_3$) δ –152.63 (minor, $^{11}$BF$_4$), –152.68 (major, $^{10}$BF$_4$); FTIR (neat) 3063, 1622, 1599, 1057, 703 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{29}$H$_{23}$N$_2$: 399.1856, found 399.1855.
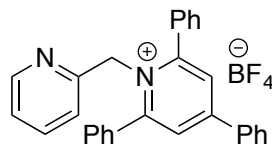
**2,4,6-Triphenyl-1-(pyridin-2-ylmethyl)pyridin-1-ium tetrafluoroborate (2-48).**
Prepared via General Procedure B on a 5.0 mmol scale with commercially available 2-(aminomethyl)pyridine to give **2-48** (2.28 g, 94%) as a white solid (mp 170–173 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.46 – 8.42 (m, 1H), 7.94 (s, 2H), 7.85 – 7.80 (m, 2H), 7.66 – 7.52 (m, 7H), 7.49 – 7.42 (m, 2H), 7.42 – 7.34 (m, 5H), 7.16 – 7.11 (m, 1H), 6.52 (d, $J$ = 7.8 Hz, 1H), 5.78 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.5, 155.9, 153.3, 149.2, 136.7, 134.1, 133.0, 132.1, 130.7, 129.7, 128.88, 128.85, 128.1, 126.1, 123.0, 121.8, 59.0; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –153.30 (minor, $^{11}$BF$_4$), –153.35 (major, $^{10}$BF$_4$); FTIR (neat) 3061, 1622, 1598, 1056, 764, 701 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{29}$H$_{23}$N$_2$: 399.1856, found 399.1859.
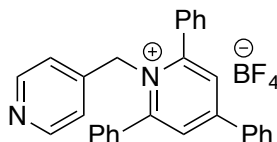


**2,4,6-Triphenyl-1-(pyridin-4-ylmethyl)pyridin-1-ium tetrafluoroborate (2-49).**
Prepared via General Procedure B on a 5.0 mmol scale with commercially available 4-(aminomethyl)pyridine to give **2-49** (1.70 g, 70%) as an orange solid (mp 168–172 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.40 – 8.36 (m, 2H), 8.00 (s, 2H), 7.85 – 7.80 (m, 2H), 7.67 – 7.59 (m, 5H), 7.58 – 7.50 (m, 4H), 7.50 – 7.44 (m, 4H), 6.52 – 6.47 (m, 2H), 5.79 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.6, 157.0, 150.2, 143.0, 133.6, 132.7, 132.3, 131.3, 129.9, 129.4, 129.0, 128.2, 126.7, 120.9, 57.0; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –152.85 (minor, $^{11}$BF$_4$), –152.90 (major, $^{10}$BF$_4$); FTIR (neat) 3061,

1622, 1560, 1055, 702 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{29}$H$_{23}$N$_2$: 399.1856, found 399.1860.
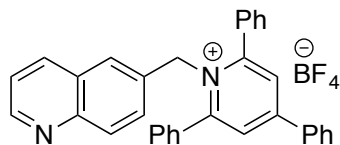


**2,4,6-Triphenyl-1-(quinolin-6-ylmethyl)pyridin-1-ium tetrafluoroborate (2-50).** Prepared via General Procedure B on a 5.0 mmol scale with commercially available 6-aminomethylquinoline to give **2-50** (2.32 g, 87%) as a white solid (mp 207–210 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 8.90 – 8.84 (m, 1H), 8.04 – 7.93 (m, 3H), 7.87 – 7.77 (m, 3H), 7.69 – 7.62 (m, 4H), 7.60 – 7.46 (m, 5H), 7.44 – 7.33 (m, 5H), 6.99 – 6.94 (m, 1H), 6.86 – 6.78 (m, 1H), 5.95 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.5, 156.7, 151.3, 147.4, 136.2, 133.7, 132.7, 132.5, 132.0, 131.1, 130.3, 129.8, 129.3, 129.1, 128.2, 127.8, 126.8, 126.7, 126.3, 122.1, 58.1; $^{19}$F NMR (376 MHz, CDCl$_3$) δ – 152.50 (minor, $^{11}$BF$_4$), –152.55 (major, $^{10}$BF$_4$); FTIR (neat) 3062, 1622, 1564, 1057, 702 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{33}$H$_{25}$N$_2$: 449.2012, found 449.2018.
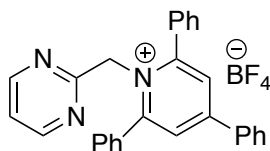


**2,4,6-Triphenyl-1-(pyrimidin-2-ylmethyl)pyridin-1-ium tetrafluoroborate (2-51).** Prepared via General Procedure B on a 5.0 mmol scale with commercially available 2-aminomethylpyrimidine hydrochloride to give **2-51** (2.06 g, 85%) as an orange solid (mp 110–118 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.52 (d, *J* = 4.9 Hz, 2H), 7.95 (s, 2H), 7.84 – 7.79 (m, 2H), 7.70 – 7.50 (m, 6H), 7.48 – 7.31 (m, 7H), 7.22 (t, *J* = 4.9

Hz, 1H), 5.79 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.4, 157.3, 156.5, 134.1, 132.7, 132.2, 130.9, 129.7, 129.0, 128.7, 128.2, 126.3, 120.3, 120.2, 59.5; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −153.43 (minor, $^{11}$BF$_4$), −153.48 (major, $^{10}$BF$_4$); FTIR (neat) 3061, 1622, 1599, 1055, 702 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{28}$H$_{22}$N$_3$: 400.1808, found 400.1812.
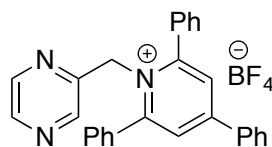


**2,4,6-Triphenyl-1-(pyrazin-2-ylmethyl)pyridin-1-ium tetrafluoroborate (2-52).** Prepared via General Procedure B on a 5.0 mmol scale with commercially available 2-aminomethylpyrazine. The crude residue was purified via silica gel chromatography (10% acetone/dichloromethane) to give **2-52** (1.93 g, 79%) as an orange solid (mp 95–99 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.44 – 8.40 (m, 2H), 7.97 (s, 2H), 7.86 – 7.81 (m, 2H), 7.76 – 7.72 (m, 1H), 7.65 – 7.53 (m, 7H), 7.53 – 7.47 (m, 2H), 7.47 – 7.41 (m, 4H), 5.87 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.5, 156.4, 149.4, 144.1, 143.7, 143.5, 133.9, 132.7, 132.4, 131.2, 129.8, 129.1, 128.8, 128.1, 126.1, 56.8; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −152.94 (minor, $^{11}$BF$_4$), −152.99 (major, $^{10}$BF$_4$); FTIR (neat) 3063, 1624, 1569, 1418, 1057, 702 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{28}$H$_{22}$N$_3$: 400.1808, found 400.1811.

### 2.4.4.2  General Procedure C: Conversion of Electron-rich (Hetero)Arylamines to Pyridinium Salts
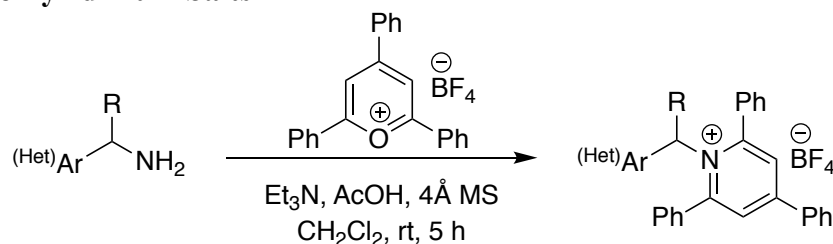


To a 50-mL round-bottomed flask was added 2,4,6-triphenylpyrillium tetrafluoroborate (1.98 g, 5.0 mmol, 1.0 equiv), amine (5.0 mmol, 1.0 equiv), and powered, activated 4Å molecular sieves (2.5 g, 0.5 g/mmol). The flask was fitted with a rubber septum. To the flask was added $CH_2Cl_2$ (anhydrous; 10 mL) followed by $Et_3N$ (0.70 mL, 5.0 mmol, 1.0 equiv). The reaction mixture was stirred for 20 min at room temperature. To the flask was added AcOH (0.57 mL, 10.0 mmol, 2.0 equiv), and the resultant mixture was stirred for 5 h at room temperature. The mixture was filtered through a small pad of Celite, and the filter cake was washed with $CH_2Cl_2$ (4 x 15 mL). The resulting solution was washed with water (2 x 30 mL) and brine (1 x 30 mL) The organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was suspended in $Et_2O$ (25 mL) and vigorously stirred for 1 h to induce precipitation. The resulting solid pyridinium salt was filtered and washed with $Et_2O$ (3 x 25 mL). If the solid contained impurities, it was subjected to silica gel chromatography with acetone/$CH_2Cl_2$.
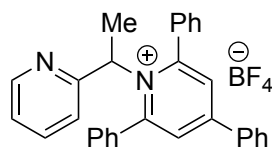


**2,4,6-Triphenyl-1-(1-(pyridin-2-yl)ethyl)pyridin-1-ium  tetrafluoroborate  (2-59).**

Prepared via General Procedure C on a 5.0 mmol scale with commercially available 1-

(pyridin-2-yl)ethan-1-amine to give **2-59** (2.31 g, 93%) as an orange solid (mp 119–123 °C): $^{1}$H NMR (600 MHz, CDCl$_3$) δ 8.57 – 8.52 (m, 1H), 7.91 – 7.84 (m, 4H), 7.83 – 7.78 (m, 2H), 7.56 – 7.40 (m, 9H), 7.29 – 7.15 (m, 4H), 6.69 (d, $J$ = 8.0 Hz, 1H), 6.22 (q, $J$ = 7.2 Hz, 1H), 1.85 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.3, 157.2, 155.7, 149.3, 137.2, 134.2, 133.6, 131.9, 130.5, 129.6, 128.7, 128.5, 128.3, 127.9, 123.3, 120.5, 66.8, 18.4; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –153.26 (minor, $^{11}$BF$_4$), –153.31 (major, $^{10}$BF$_4$); FTIR (neat) 3061, 1621, 1564, 1055, 762, 699 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^{+}$ calculated for C$_{30}$H$_{25}$N$_2$: 413.2012, found 413.2019.
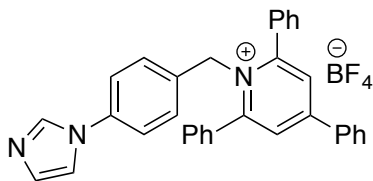


**1-(4-(1H-Imidazol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium    tetrafluoroborate (2-93).** Prepared via General Procedure C on a 6.7 mmol scale with (4-(1*H*-imidazol-1-yl)phenyl)methanamine.[54] The crude residue was purified via silica gel chromatography (30% acetone/CH$_2$Cl$_2$) to give **2-93** (1.69 g, 55%) as a yellow solid (mp 109–114 °C): $^{1}$H NMR (600 MHz, CDCl$_3$) δ 8.01 (s, 2H), 7.89 – 7.83 (m, 2H), 7.82 – 7.78 (m, 1H), 7.73 – 7.66 (m, 4H), 7.65 – 7.50 (m, 9H), 7.24 – 7.15 (m, 4H), 6.68 – 6.62 (m, 2H), 5.87 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.5, 156.7, 137.1, 135.2, 133.7, 133.2, 132.7, 132.6, 131.2, 130.8, 129.9, 129.4, 129.1, 128.2, 128.1, 126.8, 121.3, 117.8, 57.6; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –152.40 (minor, $^{11}$BF$_4$), –152.45 (major, $^{10}$BF$_4$); FTIR (neat) 3062, 1621, 1524, 1058, 701 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^{+}$ calculated for C$_{33}$H$_{26}$N$_3$: 464.2121, found 464.2118.
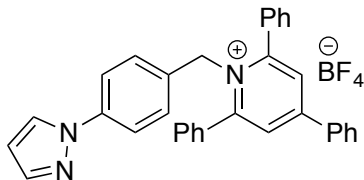
**1-(4-(1H-Pyrazol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (2-54).** Prepared via General Procedure C on a 4.8 mmol scale with [4-(1H-pyrazol-1-yl)phenyl]methylamine.[55] The crude residue was purified via silica gel chromatography (10% acetone/CH$_2$Cl$_2$) to give **2-54** (1.87 g, 71%) as a yellow solid (mp 111–115 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.97 (s, 2H), 7.86 – 7.84 (m, 1H), 7.84 – 7.80 (m, 2H), 7.70 – 7.64 (m, 5H), 7.60 – 7.46 (m, 11H), 6.57 (d, $J$ = 8.3 Hz, 2H), 6.48 – 6.41 (m, 1H), 5.80 (s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.6, 156.6, 141.4, 139.9, 133.8, 132.7, 132.5, 132.0, 131.1, 129.8, 129.3, 129.1, 128.2, 127.5, 126.7, 126.7, 119.1, 108.1, 57.7; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −152.83 (minor, $^{11}$BF$_4$), −152.89 (major, $^{10}$BF$_4$); FTIR (neat) 3061, 1621, 1526, 1395, 1057, 701 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{33}$H$_{26}$N$_3$: 464.2121, found 464.2125.
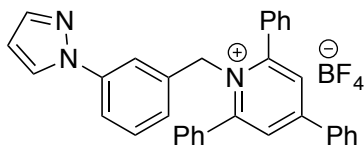


**1-(3-(1H-Pyrazol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (2-60).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available [3-(1H-pyrazol-1-yl)phenyl]methylamine. The crude residue was purified via silica gel chromatography (10% acetone/CH$_2$Cl$_2$) to give **2-60** (1.80 g, 65%) as a tan solid (mp 109–114 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.96 (s, 2H), 7.83 – 7.78 (m, 2H), 7.77 – 7.73 (m, 1H), 7.71 – 7.62 (m, 5H), 7.60 – 7.44 (m, 10H), 7.19 (t, $J$ = 7.9 Hz, 1H), 6.92 – 6.88 (m, 1H), 6.45 – 6.41 (m, 1H), 6.39 (d, $J$ = 7.7 Hz, 1H), 5.82

(s, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.6, 156.5, 141.4, 140.4, 135.5, 133.7, 132.7, 132.5, 131.1, 130.0, 129.8, 129.3, 129.1, 128.2, 126.7, 126.6, 124.0, 118.5, 117.0, 108.1, 57.9; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −152.75 (minor, $^{11}$BF$_4$), −152.80 (major, $^{10}$BF$_4$); FTIR (neat) 3064, 1621, 1057, 765, 701 cm$^{-1}$; HRMS (ESI+) [M−BF$_4$]$^+$ calculated for C$_{33}$H$_{26}$N$_3$: 464.2121, found 464.2129.
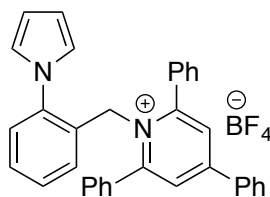


**1-(2-(1H-Pyrrol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (2-61).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available [2-(1H-pyrrol-1-yl)phenyl]methylamine to give **2-61** (2.16 g 78%) as a tan solid (mp 183–188 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.86 (s, 2H), 7.82 − 7.77 (m, 2H), 7.60 − 7.55 (m, 5H), 7.54 − 7.50 (m, 4H), 7.47 − 7.41 (m, 4H), 7.30 − 7.24 (m, 2H, *overlaps with CHCl$_3$*), 6.99 − 6.95 (m, 1H), 6.79 − 6.74 (m, 1H), 6.14 (t, *J* = 2.1 Hz, 2H), 5.97 (t, *J* = 2.1 Hz, 2H), 5.64 (s, 2H); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) δ 157.6, 156.3, 138.9, 133.7, 133.0, 132.6, 131.1, 130.2, 129.7, 129.3, 129.11, 129.09, 128.7, 128.2, 128.1, 127.0, 126.7, 121.8, 109.5, 55.8; $^{19}$F NMR (565 MHz, CDCl$_3$) δ − 153.04 (minor, $^{11}$BF$_4$), −153.09 (major, $^{10}$BF$_4$); FTIR (neat) 3063, 1620, 1503, 1056, 701 cm$^{-1}$; HRMS (ESI+) [M−BF$_4$]$^+$ calculated for C$_{34}$H$_{27}$N$_2$: 463.2169, found 463.2176.
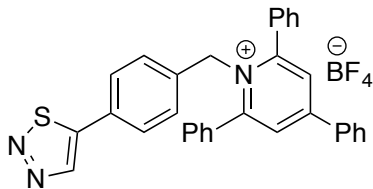
**1-(4-(1,2,3-Thiadiazol-5-yl)benzyl)-2,4,6-triphenylpyridin-1-ium**

**tetrafluoroborate (2-62).** Prepared via General Procedure C on a 4.4 mmol scale with commercially available 4-(1,2,3-thiadiazol-5-yl)benzylamine to give **2-62** (2.53 g, quant.) as a yellow solid (mp 119–122 °C): ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.68 (s, 1H), 7.98 (s, 2H), 7.85 − 7.80 (m, 4H), 7.74 − 7.70 (m, 3H), 7.63 − 7.42 (m, 10H), 6.63 (d, $J$ = 8.1 Hz, 2H), 5.86 (s, 2H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 161.6, 157.6, 156.6, 135.1, 133.7, 132.7, 132.5, 131.1, 130.89, 130.85, 129.8, 129.3, 129.1, 128.2, 127.7, 127.0, 126.7, 58.1; ^{19}F NMR (565 MHz, CDCl$_3$) δ −152.81 (minor, [11]BF$_4$), − 152.86 (major, [10]BF$_4$); FTIR (neat) 3062, 1621, 1560, 1057, 701 cm^{-1}; HRMS (ESI+) [M–BF$_4$][+] calculated for C$_{32}$H$_{24}$N$_3$S: 482.1685, found 482.1693.
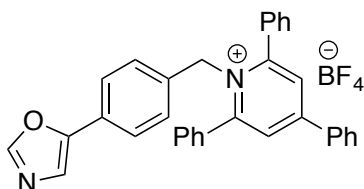


**1-(4-(Oxazol-5-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (2-94).** Prepared via General Procedure C on a 2.8 mmol scale with [4-(1,3-oxazol-5-yl)phenyl]methanamine.[56] The crude residue was purified via silica gel chromatography (10% acetone/CH$_2$Cl$_2$) to give **2-94** (0.680 g, 44%) as a yellow solid (mp 118–123 °C): ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.98 (s, 2H), 7.89 (s, 1H), 7.86 − 7.82 (m, 2H), 7.69 − 7.66 (m, 3H), 7.63 − 7.45 (m, 10H), 7.42 − 7.38 (m, 2H), 7.31 (s, 1H), 6.58 − 6.54 (m, 2H), 5.81 (s, 2H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 157.6, 156.6,

150.7, 150.4, 134.5, 133.8, 132.7, 132.5, 131.1, 129.8, 129.3, 129.1, 128.2, 127.7, 126.9, 126.7, 124.6, 122.3, 57.9; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −153.01 (minor, $^{11}$BF$_4$), −153.07 (major, $^{10}$BF$_4$); FTIR (neat) 3063, 1622, 1559, 1056, 701 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{33}$H$_{25}$N$_2$O: 465.1961, found 465.1963.
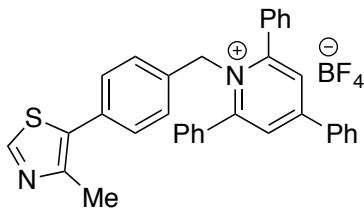


**1-(4-(4-Methylthiazol-5-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (2-95).** Prepared via General Procedure C on a 1.8 mmol scale with [4-(4-methyl-1,3-thiazol-5-yl)phenyl]methanamine.[57] The crude residue was purified via silica gel chromatography (10% acetone/CH$_2$Cl$_2$) to give **2-95** (0.482 g, 46%) as a yellow solid (mp 89–108 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.66 (s, 1H), 7.94 (s, 2H), 7.82 – 7.78 (m, 2H), 7.69 – 7.66 (m, 3H), 7.59 – 7.45 (m, 10H), 7.19 – 7.14 (m, 2H), 6.56 – 6.52 (m, 2H), 5.82 (s, 2H), 2.44 (s, 3H); $^{13}$C NMR (151 MHz, (CD$_3$)$_2$CO) δ 158.2, 156.9, 151.5, 149.5, 134.7, 134.4, 133.9, 133.2, 132.60, 132.58, 131.7, 130.4, 130.0, 129.9, 129.8, 129.3, 127.7, 127.4, 58.9, 16.0; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −152.84 (minor, $^{11}$BF$_4$), −152.89 (major, $^{10}$BF$_4$); FTIR (neat) 3062, 1621, 1560, 1057, 701 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{34}$H$_{27}$N$_2$S: 495.1889, found 495.1890.
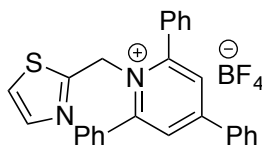


**2,4,6-Triphenyl-1-(thiazol-2-ylmethyl)pyridin-1-ium tetrafluoroborate (2-63).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available 2-

(aminomethyl)thiazole to give **2-63** (2.12 g, 86%) as a tan solid (mp 209–215 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.95 (s, 2H), 7.84 – 7.79 (m, 2H), 7.71 – 7.64 (m, 4H), 7.61 – 7.42 (m, 10H), 7.23 (d, $J$ = 3.2 Hz, 1H), 5.93 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.1, 157.3, 156.4, 142.4, 133.9, 132.6, 132.4, 131.0, 129.8, 129.0, 128.9, 128.2, 126.2, 121.2, 55.5; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –153.23 (minor, $^{11}$BF$_4$), –153.29 (major, $^{10}$BF$_4$); FTIR (neat) 3060, 1621, 1055, 767, 701 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{27}$H$_{21}$N$_2$S: 405.1420, found 405.1423.
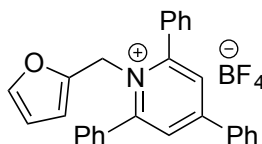


**1-(Furan-2-ylmethyl)-2,4,6-triphenylpyridin-1-ium    tetrafluoroborate    (2-64).** Prepared via General Procedure C on a 5.0 mmol scale with commercially available 2-aminomethylfuran to give **2-64** (1.05 g, 44%) as a tan solid (mp 109–111 °C, decomp): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.91 (s, 2H), 7.81 – 7.77 (m, 2H), 7.75 – 7.70 (m, 4H), 7.59 – 7.51 (m, 9H), 7.23 (s, 1H), 6.11 – 6.07 (m, 1H), 5.71 (s, 2H), 5.37 – 5.33 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 157.4, 156.3, 145.7, 143.1, 133.8, 132.7, 132.3, 131.0, 129.8, 129.2, 129.1, 128.1, 126.5, 110.9, 110.2, 51.9; $^{19}$F NMR (565 MHz, CDCl$_3$) δ –152.98 (minor, $^{11}$BF$_4$), –153.03 (major, $^{10}$BF$_4$); FTIR (neat) 3063, 1621, 1056, 736, 701 cm$^{-1}$; HRMS (ESI+) [M–BF$_4$]$^+$ calculated for C$_{28}$H$_{22}$NO: 388.1696, found 388.1682.

## 2.4.5 Mechanistic Experiment

### 2.4.5.1 Radical Trap Experiment
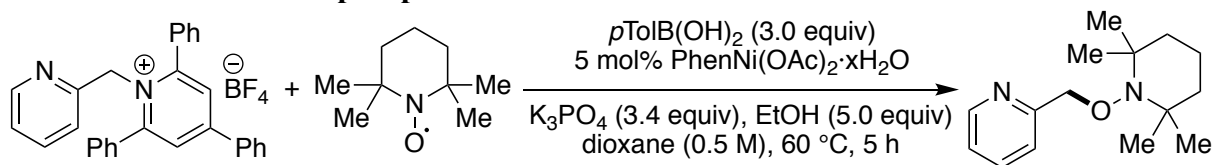


In a $N_2$-filled glovebox, PhenNi(OAc)$_2$·xH$_2$O (2.0 mg, 0.005 mmol, 5 mol %), 2,2,6,6-tetramethylpiperidine-$N$-oxyl (TEMPO; 31 mg, 0.20 mmol, 2.0 equiv), pyridinium salt **2-48** (49 mg, 0.1 mmol, 1.0 equiv), $p$-tolylboronic acid (41 mg, 0.3 mmol, 3.0 equiv), and K$_3$PO$_4$ (722 mg, 3.4 mmol, 3.4 equiv) were added to an oven-dried 1-dram vial. Dioxane (200 μL) was added to the vial. The vial was then equipped with a stir bar, capped with a pierceable Teflon-coated cap, and removed from the glovebox. To the vial was added EtOH (29 μL) via a $N_2$-purged syringe. The resulting mixture was stirred vigorously at 60 °C for 5 h. The mixture was then diluted with EtOAc (1.5 mL) and filtered through a short plug of silica gel. The filter cake was washed with EtOAc (10 mL), and the filtrate was concentrated. 1,3,5-Trimethoxybenzene (internal standard) and CDCl$_3$ were added. The yield of known TEMPO adduct **2-92**[58] was determined to be 32% by analysis of the $^1$H-NMR spectrum of the crude reaction mixture. No cross-coupled product was observed.

# REFERENCES

1.      Brogden, R. N.; Carmine, A. A.; Heel, R. C.; Speight, T. M.; Avery, G. S., *Drugs* **1982,** *23*, 405-430.

2.      Shimura, K.; Kodama, E.; Sakagami, Y.; Matsuzaki, Y.; Watanabe, W.; Yamataka, K.; Watanabe, Y.; Ohata, Y.; Doi, S.; Sato, M.; Kano, M.; Ikeda, S.; Matsuoka, M., *Journal of Virology* **2008,** *82*, 764.

3.      de Wit, R.; Kaye, S. B.; Roberts, J. T.; Stoter, G.; Scott, J.; Verweij, J., *British Journal Of Cancer* **1993,** *67*, 388.

4.      Iyer, R.; Wehrmann, L.; Golden, R. L.; Naraparaju, K.; Croucher, J. L.; MacFarland, S. P.; Guan, P.; Kolla, V.; Wei, G.; Cam, N.; Li, G.; Hornby, Z.; Brodeur, G. M., *Cancer Letters* **2016,** *372*, 179-186.

5.      Davoren, J. E.; Garnsey, M.; Pettersen, B.; Brodney, M. A.; Edgerton, J. R.; Fortin, J.-P.; Grimwood, S.; Harris, A. R.; Jenkinson, S.; Kenakin, T.; Lazzaro, J. T.; Lee, C.-W.; Lotarski, S. M.; Nottebaum, L.; O'Neil, S. V.; Popiolek, M.; Ramsey, S.; Steyn, S. J.; Thorn, C. A.; Zhang, L.; Webb, D., *Journal of Medicinal Chemistry* **2017,** *60*, 6649-6663.

6.      Davoren, J. E.; Lee, C.-W.; Garnsey, M.; Brodney, M. A.; Cordes, J.; Dlugolenski, K.; Edgerton, J. R.; Harris, A. R.; Helal, C. J.; Jenkinson, S.; Kauffman, G. W.; Kenakin, T. P.; Lazzaro, J. T.; Lotarski, S. M.; Mao, Y.; Nason, D. M.; Northcott, C.; Nottebaum, L.; O'Neil, S. V.; Pettersen, B.; Popiolek, M.; Reinhart, V.; Salomon-Ferrer, R.; Steyn, S. J.; Webb, D.; Zhang, L.; Grimwood, S., *Journal of Medicinal Chemistry* **2016,** *59*, 6313-6328.

7.      Molander, G. A.; Elia, M. D., *The Journal of Organic Chemistry* **2006,** *71*, 9198-9202.

8.      Schmink, J. R.; Tudge, M. T., *Tetrahedron Letters* **2013,** *54*, 15-20.

9.      Chard, E. F.; Dawe, L. N.; Kozak, C. M., *Journal of Organometallic Chemistry* **2013,** *737*, 32-39.

10.     Dunsford, J. J.; Clark, E. R.; Ingleson, M. J., *Angewandte Chemie International Edition* **2015,** *54*, 5688-5692.

11.     Zhang, J.; Lu, G.; Xu, J.; Sun, H.; Shen, Q., *Org. Lett.* **2016,** *18*, 2860-2863.

12.     Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J., *J. Am. Chem. Soc.* **2012,** *134*, 14638-14641.

13.     Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N., *Org. Lett.* **2014,** *16*, 5572-5575.

14.     Stewart, G. W.; Maligres, P. E.; Baxter, C. A.; Junker, E. M.; Krska, S. W.; Scott, J. P., *Tetrahedron* **2016,** *72*, 3701-3706.

15.     Kuwano, R.; Yokogi, M., *Org. Lett.* **2005,** *7*, 945-947.

16.     Kuwano, R.; Yokogi, M., *Chemical Communications* **2005**, 5899-5901.

17.     McLaughlin, M., *Org. Lett.* **2005,** *7*, 4875-4878.

18.     Kofink, C. C.; Knochel, P., *Org. Lett.* **2006,** *8*, 4121-4124.

19.     Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P., *J. Am. Chem. Soc.* **2013,** *135*, 3307-3310.

20.     Zhou, Q.; Cobb, K. M.; Tan, T.; Watson, M. P., *J. Am. Chem. Soc.* **2016,** *138*, 12057-12060.

21.     Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R., *J. Am. Chem. Soc.* **2011,** *133*, 389-391.

22.     Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R., *Angewandte Chemie International Edition* **2012,** *51*, 7790-7793.

23.     Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R., *J. Am. Chem. Soc.* **2013,** *135*, 3303-3306.

24.     Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R., *J. Am. Chem. Soc.* **2013,** *135*, 9083-9090.

25.     Li, C.; Zhang, Y.; Sun, Q.; Gu, T.; Peng, H.; Tang, W., *J. Am. Chem. Soc.* **2016,** *138*, 10774-10777.

26. Tobisu, M.; Takahira, T.; Chatani, N., *Org. Lett.* **2015,** *17*, 4352-4355.

27. Blümke, T. D.; Groll, K.; Karaghiosoff, K.; Knochel, P., *Org. Lett.* **2011,** *13*, 6440-6443.

28. Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P., *Angewandte Chemie International Edition* **2011,** *50*, 7686-7690.

29. Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M., *J. Am. Chem. Soc.* **2009,** *131*, 5024-5025.

30. Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P., *J. Am. Chem. Soc.* **2013,** *135*, 280-285.

31. Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P., *Tetrahedron* **2014,** *70*, 4257-4263.

32. Wang, T.; Yang, S.; Xu, S.; Han, C.; Guo, G.; Zhao, J., *RSC Advances* **2017,** *7*, 15805-15808.

33. Li, M.-B.; Tang, X.-L.; Tian, S.-K., *Adv. Synth. Catal.* **2011,** *353*, 1980-1984.

34. Yoon, S.; Hong, M. C.; Rhee, H., *The Journal of Organic Chemistry* **2014,** *79*, 4206-4211.

35. Nystrom, R. F.; Brown, W. G., *J. Am. Chem. Soc.* **1948,** *70*, 3738-3740.

36. Cha, J. S.; Brown, H. C., *The Journal of Organic Chemistry* **1993,** *58*, 3974-3979.

37. Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M., *Org. Lett.* **2002,** *4*, 2055-2058.

38. Bartoli, G.; Di Antonio, G.; Giovannini, R.; Giuli, S.; Lanari, S.; Paoletti, M.; Marcantoni, E., *The Journal of Organic Chemistry* **2008,** *73*, 1919-1924.

39. Laval, S.; Dayoub, W.; Pehlivan, L.; Métay, E.; Favre-Réguillon, A.; Delbrayelle, D.; Mignani, G.; Lemaire, M., *Tetrahedron Letters* **2011,** *52*, 4072-4075.

40. Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P., *J. Am. Chem. Soc.* **2017,** *139*, 5313-5316.

41. Katritzky, A. R.; Manzo, R. H., *Journal of the Chemical Society, Perkin Transactions 2* **1981**, 571-575.

42.      Katritzky, A. R.; Rubio, O.; Aurrecoechea, J. M.; Patel, R. C., *Journal of the Chemical Society, Perkin Transactions 1* **1984**, 941-945.

43.      Marquet, J.; Moreno-Mañas, M.; Pacheco, P.; Prat, M.; Katritzky, A. R.; Brycki, B., *Tetrahedron* **1990,** *46*, 5333-5346.

44.      Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A., *J. Am. Chem. Soc.* **2006,** *128*, 13175-13183.

45.      Biswas, S.; Weix, D. J., *J. Am. Chem. Soc.* **2013,** *135*, 16192-16197.

46.      Liao, J.; Guan, W.; Boscoe, B. P.; Tucker, J. W.; Tomlin, J. W.; Garnsey, M. R.; Watson, M. P., *Org. Lett.* **2018,** *20*, 3030-3033.

47.      Knochel, P.; Lutter, F. H., *Synfacts* **2018,** *14*, 0858.

48.      Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996,** *15*, 1518-1520.

49.      Ye, B.-H.; Chen, X.-M.; Xue, G.-Q.; Ji, L.-N., *Journal of the Chemical Society, Dalton Transactions* **1998**, 2827-2832.

50.      Chen, X.; Zhou, L.; Li, Y.; Xie, T.; Zhou, S., *The Journal of Organic Chemistry* **2014,** *79*, 230-239.

51.      Otohiko, T.; Shuji, K.; Toshio, N.; Junji, T., *Bulletin of the Chemical Society of Japan* **1987,** *60*, 1497-1504.

52.      Tran, D. N.; Battilocchio, C.; Lou, S.-B.; Hawkins, J. M.; Ley, S. V., *Chemical Science* **2015,** *6*, 1120-1125.

53.      De Houwer, J.; Abbaspour Tehrani, K.; Maes, B. U. W., *Angewandte Chemie International Edition* **2012,** *51*, 2745-2748.

54.      Zhang, X., CN105254613 (A), 2016/01/20/, 2016.

55.      Lewis, J. G.; Jacobs, J. W.; Reich, N.; Leadbetter, M. R.; Bell, N.; Chang, H.-T.; Chen, T.; Navre, M.; Charmot, D.; Carreras, C.; Labonte, E., US2015164876 (A1), 2015/06/18/, 2015.

56.     Crews, C.; Buckley, D.; Ciulli, A.; Jorgensen, W.; Gareiss, P.; Molle, I.; Gustafson, J.; Tae, H.-S.; Michel, J.; Hoyer, D.; Roth, A.; Harling, J.; Smith, I. E.; Miah, A.; Campos, S.; Le, J., WO2013106643 (A2), 2013/07/18/, 2013.

57.     Buckley, D. L.; Gustafson, J. L.; Van Molle, I.; Roth, A. G.; Tae, H. S.; Gareiss, P. C.; Jorgensen, W. L.; Ciulli, A.; Crews, C. M., *Angewandte Chemie International Edition* **2012,** *51*, 11463-11467.

58.     Badsara, S. S.; Liu, Y.-C.; Hsieh, P.-A.; Zeng, J.-W.; Lu, S.-Y.; Liu, Y.-W.; Lee, C.-F., *Chemical Communications* **2014,** *50*, 11374-11377.

**Chapter 3**

**SUZUKI–MIYAURA CROSS-COUPLING OF BENZYLIC PYRIDINIUM
SALTS WITH VINYLBORONIC ACIDS**

## 3.1   Introduction

1,3-Disubstituted allylic molecules have proven to be versatile intermediates in the synthesis of complex organic molecules.[1-4] They can be elaborated via the functionalization of the alkene or reactive benzylic position (Scheme 3.1). Excitingly, these molecules can participate in a number of oxidation and reduction reactions as well as addition reactions. Moreover, 1,3-diaryl allylic molecules themselves can possess promising biological activity.[5-8] Building on our success in cross-coupling benzylic pyridinium salts, we believed that an analogous approach would open a new avenue for the synthesis of these valuable molecules.

Scheme 3.1    Synthetic versatility of 1,3-disubstituted allylic molecules
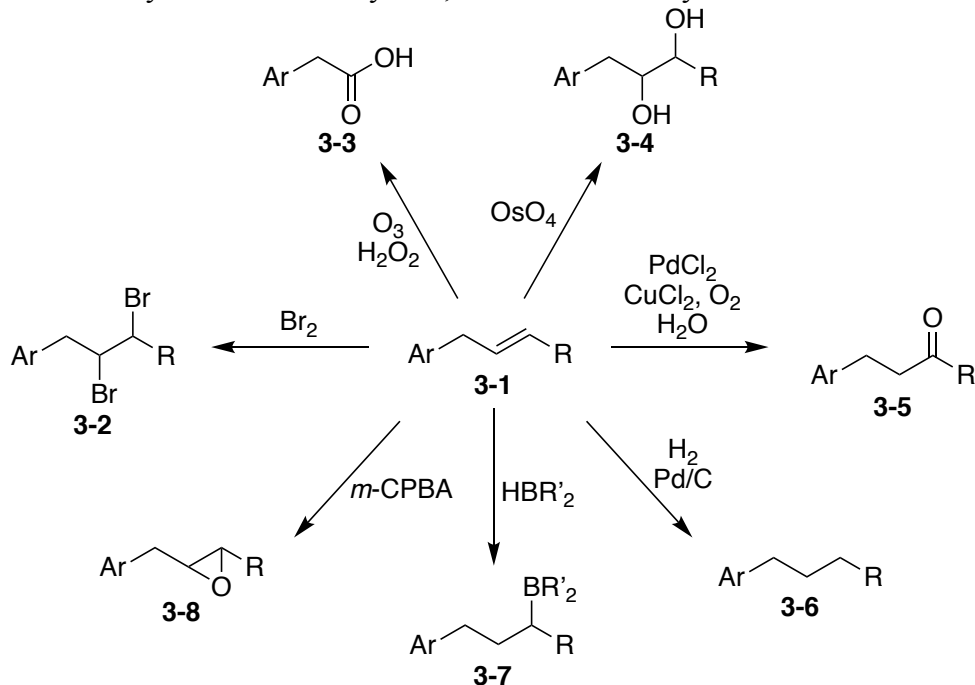


The importance of this motif has encouraged the development of efficient methods to access these targets (**3-9**), with transition metal-catalyzed cross-couplings being a predominant approach. A common strategy employs the cross-coupling of an allylic electrophile with an aryl nucleophile (Scheme 3.2, left). However, controlling regioselectivity and stereoselectivity of the alkene geometry can be challenging. An alternative disconnection relies on the cross-coupling of a benzylic electrophile with a vinyl nucleophile (Scheme 3.2, right). This approach mitigates many of the problematic isomerization issues.

Scheme 3.2    Strategies for the synthesis of 1,3-diaryl allylic compounds
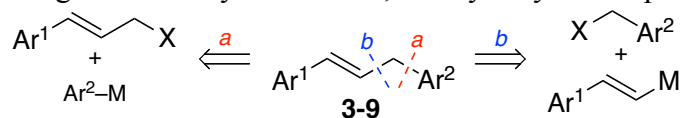
The former approach leverages the wide availability of allylic electrophiles (Scheme 3.3). Towards this end, allylic alcohols[9-15], carbonates,[16, 17] phosphates,[18] ethers,[19] and esters[20-23] have been utilized as electrophiles in this type of chemistry. Additionally, allylic halides[24-26] and amine derivatives[27, 28] have also been demonstrated to be competent electrophiles. The ability to be cross-coupled with various organometallic aryl nucleophiles (e.g., Ar–BX$_2$, Ar–MgX) allows for rapid diversifications of these precursors. However, many of these reactions proceed via a π-allyl intermediate, which can lead to the formation of undesired regioisomers.

Scheme 3.3     Cross-couplings of allylic electrophiles



**3-10**
*alcohols, carbonates, phosphates, ethers, esters*

**3-11**
*halides*

**3-12**
*amines*
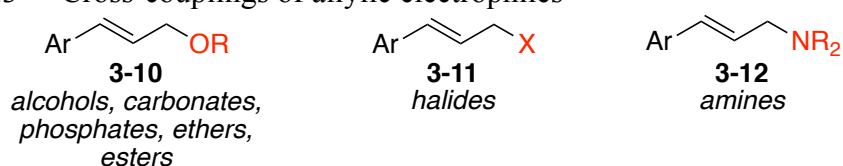
The latter approach utilizes benzylic electrophiles in conjunction with a vinyl nucleophile (Scheme 3.4). Benzylic alcohol derivatives (carbonates, carboxylates, esters)[29, 30] and halides[31-35] are frequently employed. In addition, the umpolung approach of cross-coupling a benzylic nucleophile with a vinyl electrophile[36-38] as well as reductive cross-electrophile couplings of benzylic and vinyl halides[39-42] have also been reported. In contrast, examples of cross-couplings of benzylic amine derivatives with vinyl nucleophiles are much more limited. In one of these examples, our group has shown that benzylic trimethylammonium salts (**3-16**) can participate in Suzuki–Miyaura cross-couplings with vinylboronic acids.[43-46]

Scheme 3.4    Cross-couplings of benzylic substrates

Ar⌒OR                Ar⌒X          Ar⌒M               Ar⌒NMe₃OTf
**3-13**              **3-14**      **3-15**           **3-16**
*carbonates,*         *halides*     *organometallics*  *ammonium salts*
*carboxylates, esters*              *M = MgX, ZnX*
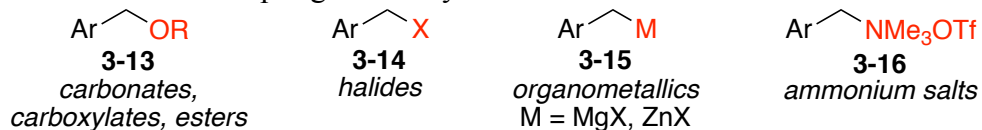
While these methods are highly efficient in the formation of 1,3-disubstituted allylic products, heteroaryl substitution is largely neglected. Given the importance of heteroaromatics in bioactive molecules as well as the abundance of benzylic amines, we envisioned that the cross-coupling of benzylic pyridinium salt **3-19** with vinyl boronic acids would afford vinylated product **3-20** bearing a useful alkene handle (Scheme 3.5). More importantly, this would allow for the incorporation of heteroaryl fragments from readily available benzylic amine precursors **3-17**.

Scheme 3.5    Proposed vinylation of benzylic pyridinium salts
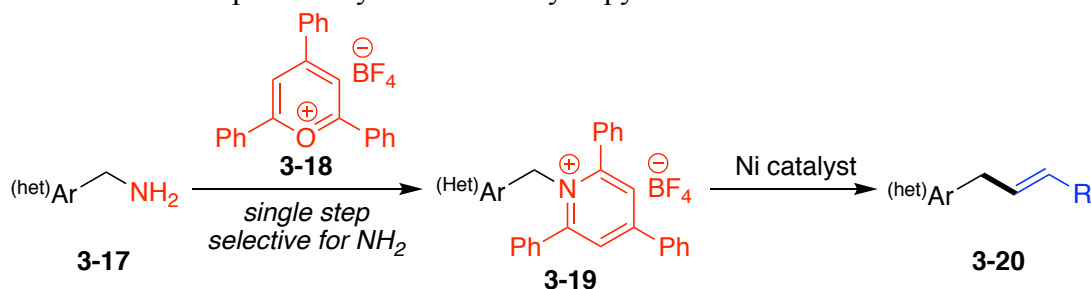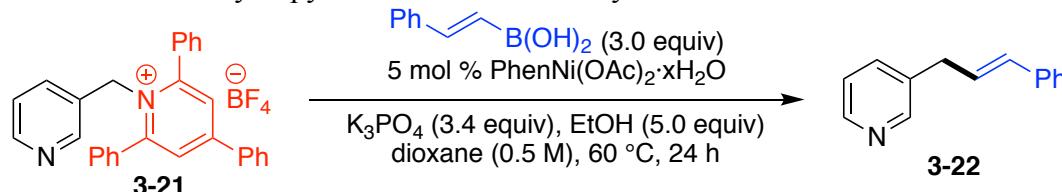


## 3.2    Results and Discussion

Given our success with nickel-catalyzed Suzuki–Miyaura arylation of benzylic pyridinium salts (Chapter 2), we wanted to extend these conditions to incorporate other nucleophiles such as vinylboronic acids. Gratifyingly, the desired vinylated product **3-22** was produced in 76% yield under the previously optimized conditions (Table 3.1, entry 1). Surprisingly, in the absence of nickel catalyst, the formation of **3-**

**22** was also observed, albeit in slightly diminished yield (entry 2). Moreover, in an effort to improve the utility of this reaction, we found that only two equivalents of boronic acid were needed (entry 3). In this case, omission of nickel catalyst led to a greatly reduced yield (entry 4). The pinacol boronic ester could also be used, requiring only 2.5 equivalents of base (entry 5). The ability to cross-couple either a boronic acid or a boronic ester broadens the pool of commercially available reagents that can be used.

Table 3.1    Reaction optimization of the Suzuki–Miyaura cross-coupling of benzylic pyridinium salts with vinylboronic acids[a]



| Entry | Modification from original conditions | Yield (%)[b] |
|:-----:|:-------------------------------------:|:-----------:|
| 1 | none | 76 |
| 2 | no PhenNi(OAc)$_2$·xH$_2$O | 62 |
| 3 | boronic acid (2 equiv) | 74 |
| 4 | no PhenNi(OAc)$_2$·xH$_2$O, boronic acid (2 equiv) | 46 |
| 5 | boronic acid pinacol ester (2.0 equiv), K$_3$PO$_4$ (2.5 equiv) | 74 |

[a]Conditions: pyridinium salt **3-22** (0.10 mmol), PhenNi(OAc)$_2$·xH$_2$O (5 mol %), boronic acid (3.0 equiv), K$_3$PO$_4$ (3.4 equiv), EtOH (5 equiv), dioxane (0.5 M), 60 °C, 24 h. [b]Determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

We were intrigued by the transition-metal-free results and wanted to probe this possibility further. In using only two equivalents of boronic acid, the nickel-catalyzed reaction, produced vinylated product **3-22** in 74% yield, while the metal-free reaction gave only 46% yield (Table 3.1, entries 3 & 4). Similarly, the metal-free conditions proved less effective for other substrates (Scheme 3.6). Phenyl-substituted product **3-25** and imidazole **3-26** were formed in only 23% and 33% yield, respectively, under these conditions. In all cases, a considerable drop in yield was observed when switching to the metal-free conditions. These results demonstrate that a metal-free reaction is feasible but not as efficient as the nickel-catalyzed pathway. There are a few reports of metal-free vinylation reactions.[47-49] We believe that a similar pathway is operational in our case, whereby nucleophilic attack (likely $S_N2$) of a vinyl boronate to the benzylic pyridinium ion leads to the formation of desired product. However, in the presence of the nickel catalyst, a $Ni^{I/III}$ (or $Ni^{0/II}$) catalytic cycle may also be at play. We are also cognizant of the possibility that nickel may act as a Lewis acid. Because higher yields are observed with all three substrates, we proceeded to investigate the scope of the reaction in the presence of the nickel catalyst. Notably, these conditions are also the less expensive choice. For a 1.0-mmol scale reaction, the cost of 5 mol % $Ni(OAc)_2 \cdot 4H_2O$ and 5 mol % Phen (approximately $0.20 from Sigma-Aldrich) is less than an extra equivalent of phenylvinylboronic acid (approximately $2.00) or pinacol ester (approximately $10.40).

Scheme 3.6    Comparison of reactions with and without the nickel catalyst[a]



3-25
with [Ni]: 59%
without [Ni]: 23%

3-26
with [Ni]: 53%
without [Ni]: 33%
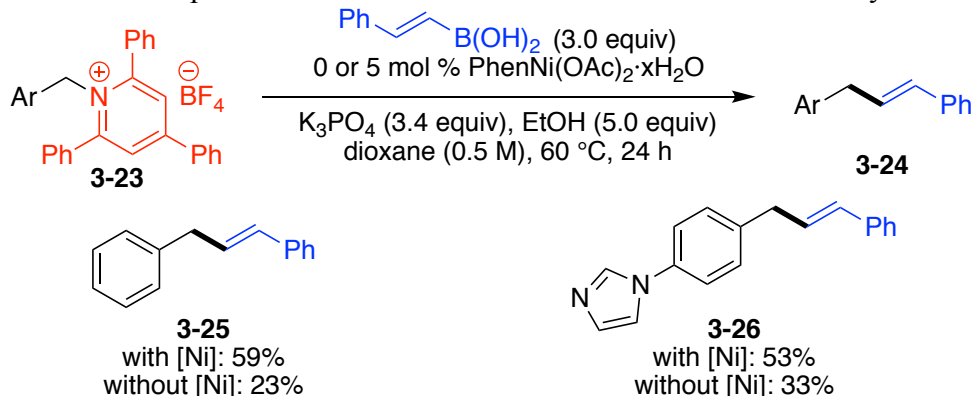
[a]Conditions: Salt **3-23** (0.1 mmol), PhenNi(OAc)$_2$·xH$_2$O (0 or 5 mol %), boronic acid (2.0 equiv), K$_3$PO$_4$ (3.4 equiv), EtOH (5 equiv), dioxane (0.5 M), 60 °C, 24 h. Yields determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

With optimized conditions in hand, my colleague Weiye Guan and I demonstrated the broad scope of this transformation. In particular, we prioritized substrates with heteroaryl substituents. We were delighted to find that a variety of benzylic pyridinium salts cross-coupled effectively (Scheme 3.7). Model product **3-22** was obtained in 80% and 70% yield using the corresponding vinylboronic acid or pinacol boronic ester, respectively. Throughout our scope studies, we used either the boronic acid or ester, depending on which was commercially available. If both were available, the less expensive reagent was used. Electron-poor benzylic coupling partners such as 2-, 3-, and 4-pyridine (**3-22**, **3-26**, **3-27**, **4-28**), quinoline (**3-29**), and pyrimidine (**3-30**) were well tolerated. Substrates containing electron-rich heterocycles such as imidazole (**3-31**), oxazole (**3-32**), pyrazole (**3-33**), thiadiazole (**3-34**), pyrrole (**3-35**), and thiazole (**3-46**) also cross-coupled effectively. Notably, no isomerization of

the alkene double bond was observed except in the case of pyrimidine **3-34**, which gave a 1.3:1 ratio of alkene isomers.

Scheme 3.7    Reaction scope of vinylation reaction[a]

°C, 24 h, unless noted otherwise. Isolated yields. [b]Pinacol boronate ester (2.0 equiv), K$_3$PO$_4$ (2.5 equiv). [c]Alkene isomers readily separated via silica gel chromatography and isolated in 45% and 36% yield.


A wide range of vinyl groups can also be installed via this method. Both electron-rich (**3-29**) and electron-poor (**3-30**) phenyl substitution is well tolerated. Heteroaryls such as thiophene (**3-26**) can also be used. Additionally, aliphatic alkenes can be formed, including cyclic trisubstituted alkene **3-27**, benzyl-substituted alkene **3-31**, and *tert*-butyl-substituted alkene **3-36**, as well as electron-poor α,β-unsaturated ester **3-28**. In addition to the heteroaryl tolerance, multiple functional groups are compatible, including esters (**3-28**), ethers (**3-29**, **3-32**), trifluoromethyl (**3-30**), fluoride (**3-33**, **3-34**), and chloride (**3-35**). Unfortunately, more bulky vinyl groups, such as (3-methyl-2-buten-2-yl)boronic ester, 2-methylprop-1-enylboronic ester, or 1-phenylvinylboronic ester, resulted in less than 30% yield. Simple vinylboronic ester also resulted in a low yield (17% by ^{1}H NMR analysis).

Given the similarity in conditions between the arylation (Chapter 2) and vinylation reactions, we believe that this cross-coupling may proceed via an analogous Ni$^{I/III}$ catalytic cycle involving a stabilized benzylic radical intermediate (See Scheme 2.14). The nickel free pathway may also be in operation and contribute to the observed product formation via a nucleophilic substitution event.


## 3.3   Conclusion

In summary, we have developed conditions for the Suzuki–Miyaura cross-coupling of benzylic pyridinium salts with vinyl boronic acids and esters. This method

allows for efficient access to valuable 1,3-disubstituted allylic molecules. This reaction is amenable to heteroaryl substitution on both coupling partners, as well as a wide range of functional groups. This work was published in *Synthesis* as part of the Special Topic: *Modern Coupling Approaches and their Strategic Applications in Synthesis*.[50]

## 3.4 Experimental

### 3.4.1 General Information

Reactions were performed in oven-dried Schlenk flasks or in oven-dried round-bottomed flasks unless otherwise noted. Round-bottomed flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of $N_2$. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Silica gel chromatography was performed on silica gel 60 (40-63 μm, 60Å) unless otherwise noted. Commercial reagents were purchased from Sigma Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, AK Scientific, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: anhydrous ethanol was degassed by sparging with $N_2$ for 20–30 minutes prior to use in the cross-coupling reactions; dioxane was dried by passing through drying columns, then degassed by sparging with $N_2$.[51] In some instances oven-dried potassium carbonate was added to $CDCl_3$ to remove trace acid. Proton nuclear magnetic resonance ($^1$H NMR) spectra, carbon nuclear magnetic resonance ($^{13}$C NMR) spectra, and fluorine nuclear magnetic resonance spectra ($^{19}$F NMR) were recorded on both 400 MHz and 600 MHz spectrometers. Chemical shifts for protons are reported in parts per million

downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl$_3$ = δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl$_3$ = δ 77.16). Chemical shifts for fluorine were externally referenced to CFCl$_3$ in CDCl$_3$ (CFCl$_3$ = δ 0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, h = heptet), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using FTIR spectrophotometers with material loaded onto a KBr plate. The mass spectral data were obtained at the University of Delaware mass spectrometry facility. Melting points were taken on a Thomas-Hoover Uni-Melt Capillary Melting Point Apparatus.

### 3.4.2 Cross-Coupling of Pyridinium Salts

### 3.4.2.1 General Procedure A: Cross-Coupling of Pyridinium Salts with Boronic Acids
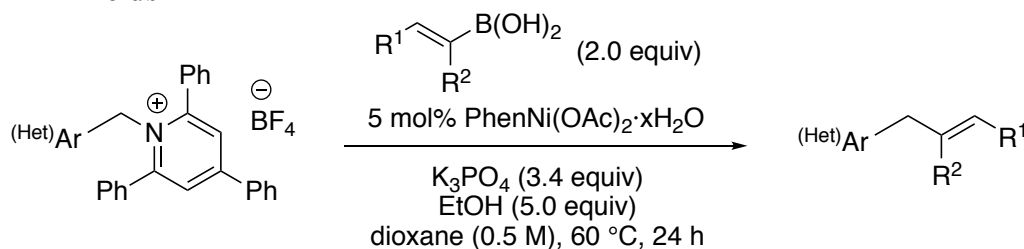


To an oven-dried, 25-mL Schlenk flask equipped with a stir bar was added PhenNi(OAc)$_2$·xH$_2$O (20 mg, 0.050 mmol, 5 mol %), pyridinium salt (1.0 mmol, 1.0 equiv), vinylboronic acid (2.0 equiv, 2.0 mmol), and K$_3$PO$_4$ (722 mg, 3.4 mmol, 3.4 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). Dioxane (2.0 mL) was added, followed by EtOH

(0.29 mL, 5.0 mmol, 5.0 equiv). The flask was sealed off and resulting mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with $CH_2Cl_2$ (4 x 25 mL), and the filtrate was concentrated. The cross-coupled product was then purified via silica gel chromatography.

### 3.4.2.2 General Procedure B: Cross-Coupling of Pyridinium Salts with Boronic Acid Pinacol Ester

$$\text{(Het)Ar–CH}_2\text{–N}^{+}\text{(2,4,6-triphenylpyridinium)} \; BF_4^{-} \xrightarrow[\substack{K_3PO_4 \text{ (2.5 equiv)} \\ \text{EtOH (5.0 equiv)} \\ \text{dioxane (0.5 M), 60 °C, 24 h}}]{\substack{R\text{-}CH=CH\text{-Bpin (2.0 equiv)} \\ 5 \text{ mol\% PhenNi(OAc)}_2\cdot xH_2O}} \text{(Het)Ar–CH}_2\text{–CH=CH–R}$$
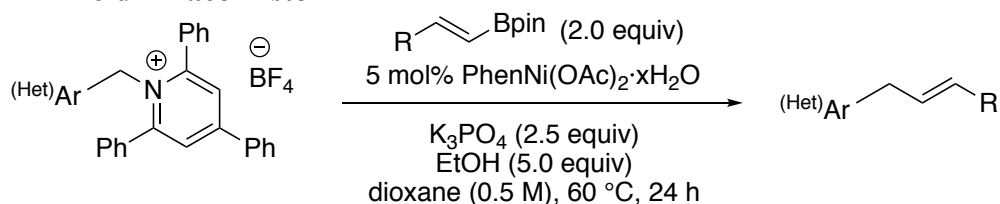
To an oven-dried, 10-mL round bottom flask equipped with a stir bar was added PhenNi(OAc)$_2$·xH$_2$O (20 mg, 0.050 mmol, 5 mol %), pyridinium salt (1.0 mmol, 1.0 equiv), vinylboronic acid pinacol ester (2.0 equiv, 2.0 mmol), and K$_3$PO$_4$ (531 mg, 2.5 mmol, 2.5 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then purged with a nitrogen line for 20 minutes. Dioxane (2.0 mL) was added, followed by EtOH (0.29 mL, 5.0 mmol, 5.0 equiv). The flask was sealed off and resulting mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with $CH_2Cl_2$ (4 x 25 mL), and the filtrate was concentrated. The cross-coupled product was then purified via silica gel chromatography.
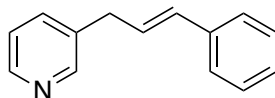
**3-Cinnamylpyridine (3-22).** Prepared via General Procedure A using 2,4,6-Triphenyl-1-(pyridin-3-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (50% ether/hexanes) to give **3-22** (156 mg, 80%) as a pale yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.54 – 8.46 (m, 2H), 7.58 – 7.53 (m, 1H), 7.37 – 7.33 (m, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 2H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.32 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.56 (d, *J* = 5.4 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 150.3, 147.9, 137.2, 136.3, 135.6, 132.1, 128.7, 127.9, 127.6, 126.3, 123.5, 36.6. The spectral data matches that reported in the literature.[52]

Product **3-22** was also prepared via General Procedure B. The crude mixture was purified by silica gel chromatography to give **3-22** (135 mg, 70%).
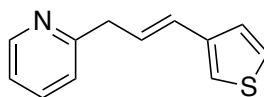


**(*E*)-2-(3-(Thiophen-3-yl)allyl)pyridine (3-26).** Prepared via General Procedure B using 2,4,6-Triphenyl-1-(pyridin-2-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (50% ethyl acetate/hexanes) to give **3-26** (146 mg, 72%) as an orange oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.58 – 8.53 (m, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.26 – 7.18 (m, 3H), 7.16 – 7.08 (m, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.70 (dd, *J* = 7.1, 1.4 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 160.4, 149.6, 140.1, 136.7, 127.6, 126.3, 126.0, 125.2, 123.0, 121.5, 121.4, 42.1; FTIR (neat) 3078, 3007, 2923, 1590, 1472, 1434, 965, 766 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{12}$H$_{12}$NS: 202.0690, found 202.0687.
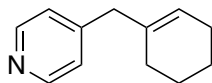
**4-(Cyclohex-1-en-1-ylmethyl)pyridine (3-27).** Prepared via General Procedure A using 2,4,6-Triphenyl-1-(pyridin-4-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 20→100% EtOAc/hexanes) to give **3-27** (88 mg, 51%) as yellow oil: $^{1}$H NMR (600 MHz, CDCl$_3$) δ 8.51 – 8.46 (m, 2H), 7.12 – 7.08 (m, 2H), 5.53 – 5.48 (m, 1H), 3.22 (s, 2H), 2.06 – 2.00 (m, 2H), 1.86 – 1.80 (m, 2H), 1.63 – 1.51 (m, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 149.8, 149.7, 135.6, 124.6, 124.4, 44.1, 28.2, 25.5, 23.0, 22.4; FTIR (neat) 3024, 2926, 2834, 1599, 1559, 1414 cm$^{-1}$; HRMS (ESI+) [M+H]$^{+}$ calculated for C$_{12}$H$_{16}$N: 174.1283, found 174.1277.
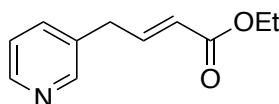


**Ethyl (*E*)-4-(pyridin-3-yl)but-2-enoate (2-28).** Prepared via General Procedure B using 2,4,6-Triphenyl-1-(pyridin-3-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 50→75% EtOAc/hexanes) to give **3-28** (117 mg, 61%) as pale yellow oil: $^{1}$H NMR (400 MHz, CDCl$_3$) δ 8.61 – 8.55 (m, 1H), 8.50 – 8.43 (m, 1H), 7.74 – 7.66 (m, 1H), 7.26 – 7.21 (m, 1H), 6.48 (d, $J$ = 16.0 Hz, 1H), 6.38 (dt, $J$ = 16.0, 6.8 Hz, 1H), 4.18 (q, $J$ = 7.1 Hz, 2H), 3.27 (dd, $J$ = 6.9, 1.2 Hz, 2H), 1.29 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 171.3, 148.8, 148.4, 132.8, 132.6, 130.0, 124.5, 123.6, 61.1, 38.6, 14.4; FTIR (neat) 3030, 2982, 2937, 1734, 1160, 1025, 970, 709 cm$^{-1}$; HRMS (ESI+) [M+H]$^{+}$ calculated for C$_{11}$H$_{14}$NO$_2$: 192.1025, found 192.1020.
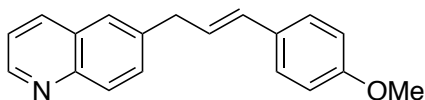
**(*E*)-6-(3-(4-Methoxyphenyl)allyl)quinoline (3-29).** Prepared via General Procedure A using 2,4,6-Triphenyl-1-(quinolin-6-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 5→50% EtOAc/hexanes) to give **3-29** (197 mg, 72%) as yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.88 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.13 – 8.08 (m, 1H), 8.08 – 8.03 (m, 1H), 7.67 – 7.60 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 – 7.29 (m, 2H), 6.87 – 6.83 (m, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.29 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.80 (s, 3H), 3.72 (d, *J* = 6.9 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.2, 150.0, 147.5, 139.1, 135.8, 131.3, 131.3, 130.3, 129.7, 128.6, 127.5, 126.6, 126.4, 121.3, 114.2, 55.5, 39.4; FTIR (neat) 3030, 2956, 2834, 1606, 1511, 1247, 1175, 968, 835 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{18}$NO: 276.1388, found 276.1384.
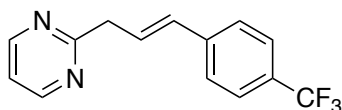


**(*E*)-2-(3-(4-(Trifluoromethyl)phenyl)allyl)pyrimidine (3-30a).** Prepared via General Procedure A using 2,4,6-Triphenyl-1-(pyrimidin-2-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 8→70% EtOAc/hexanes) to give **3-30a** (119 mg, 45%) as yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.71 (d, *J* = 4.9 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.17 (t, *J* = 4.9 Hz, 1H), 6.72 – 6.58 (m, 2H), 3.94 (d, *J* = 6.7 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 169.4, 157.5, 140.9, 131.2, 129.2 (q, *J* = 32.3 Hz), 129.1, 126.6, 125.6 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.7 Hz), 119.0, 43.4; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −62.48; FTIR (neat) 3041, 1563, 1422, 1327, 1164, 1122,

1068 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{12}$F$_3$N$_2$: 265.0953, found 265.0950.
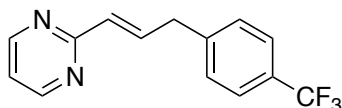


(*E*)-2-(3-(4-(Trifluoromethyl)phenyl)prop-1-en-1-yl)pyrimidine (3-30b). Prepared via General Procedure A using 2,4,6-Triphenyl-1-(pyrimidin-2-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 8→70% EtOAc/hexanes) to give 3-30b (94 mg, 36%) as yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 8.66 (d, *J* = 4.9 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.32 − 7.26 (m, 1H), 7.09 (t, *J* = 4.8 Hz, 1H), 6.61 − 6.55 (m, 1H), 3.69 (d, *J* = 6.6 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 164.4, 157.0, 143.0, 138.8, 131.3, 129.2, 128.9 (q, *J* = 32.1 Hz), 125.5 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 118.7, 38.7; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −62.43; FTIR (neat) 3037, 2918, 1557, 1421, 1332, 1161, 1105 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{12}$F$_3$N$_2$: 265.0953, found 265.0951.
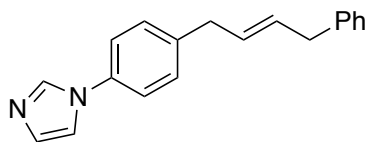


(*E*)-1-(4-(4-Phenylbut-2-en-1-yl)phenyl)-1*H*-imidazole (3-31). Prepared via General Procedure A using 1-(4-(1H-Imidazol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 20→100% EtOAc/hexanes) to give 3-31 (172 mg, 63%) as yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.85 − 7.81 (m, 1H), 7.34 − 7.27 (m, 6H), 7.26 − 7.25 (m,

1H), 7.24 − 7.17 (m, 4H), 5.76 − 5.62 (m, 2H), 3.44 − 3.37 (m, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 140.6, 140.4, 135.8, 135.7, 131.4, 130.5, 130.0, 129.8, 128.7, 128.6, 126.2, 121.8, 118.5, 39.1, 38.5; FTIR (neat) 3026, 2899, 1521, 1492, 1303, 1057, 965 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{19}$N$_2$: 275.1548, found 275.1543.
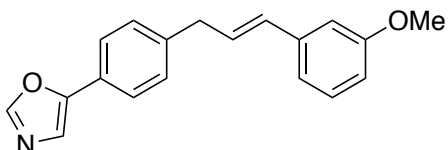


**(*E*)-5-(4-(3-(3-Methoxyphenyl)allyl)phenyl)oxazole (3-32).** Prepared via General Procedure B using 1-(4-(Oxazol-5-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 10→50% EtOAc/hexanes) to give **3-32** (220 mg, 76%) as yellow solid (mp 60–63 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.90 (s, 1H), 7.63 − 7.58 (m, 2H), 7.34 − 7.29 (m, 3H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.99 − 6.94 (m, 1H), 6.92 − 6.88 (m, 1H), 6.80 − 6.75 (m, 1H), 6.48 − 6.41 (m, 1H), 6.35 (dt, *J* = 15.7, 6.8 Hz, 1H), 3.81 (s, 3H), 3.58 (d, *J* = 7.2 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 160.0, 151.7, 150.4, 141.0, 138.9, 131.6, 129.7, 129.4, 129.0, 126.0, 124.8, 121.3, 119.0, 113.1, 111.6, 55.4, 39.2; FTIR (neat) 3027, 2937, 2833, 1598, 1579, 1490, 1267, 1043, 941 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{18}$NO$_2$: 292.1338, found 292.1331.
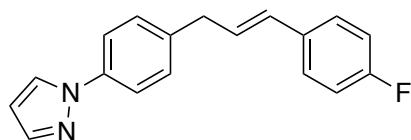


**(*E*)-1-(4-(3-(4-Fluorophenyl)allyl)phenyl)-1*H*-pyrazole (3-33).** Prepared via General Procedure A using 1-(4-(1H-Pyrazol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step

gradient: 5→20% ether/hexanes) to give **3-33** (241 mg, 87%) as light yellow solid (mp 80–83 °C): $^1$H NMR (600 MHz,CDCl$_3$) δ 7.90 (d, $J$ = 2.4 Hz, 1H), 7.72 (d, $J$ = 1.7 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.35 – 7.29 (m, 4H), 7.02 – 6.96 (m, 2H), 6.48 – 6.39 (m, 2H), 6.28 (dt, $J$ = 15.8, 6.8 Hz, 1H), 3.57 (dd, $J$ = 6.8, 1.4 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.3 (d, $J_{C-F}$ = 246.1 Hz), 141.1, 138.8, 138.5, 133.6 (d, $J_{C-F}$ = 3.4 Hz), 130.4, 129.8, 128.7 (d, $J_{C-F}$ = 2.2 Hz), 127.7 (d, $J_{C-F}$ = 8.0 Hz), 126.8, 119.6, 115.6 (d, $J$ = 21.2Hz), 107.6, 38.8; $^{19}$F NMR (565 MHz, CDCl$_3$) δ −115.13; FTIR (neat) 3037, 2922, 1524, 1507, 1394, 1225, 936, 838, 748 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{18}$H$_{16}$FN$_2$: 279.1298, found 279.1292.
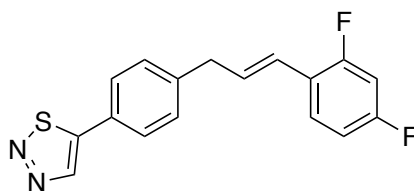


**(*E*)-5-(4-(3-(2,4-Difluorophenyl)allyl)phenyl)-1,2,3-thiadiazole (3-34).** Prepared via General Procedure B using 1-(4-(1,2,3-Thiadiazol-5-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 1→10% ether/hexanes) to give **3-34** (163 mg, 52%) as yellow solid (mp 117–120 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.62 (s, 1H), 8.03 – 7.98 (m, 2H), 7.43 – 7.37 (m, 3H), 6.85 – 6.75 (m, 2H), 6.62 – 6.55 (m, 1H), 6.39 (dt, $J$ = 15.9, 6.9 Hz, 1H), 3.63 (d, $J$ = 6.3 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.88, 162.30 (dd, $J$ = 196.6, 11.9 Hz), 159.81 (dd, $J$ = 199.2, 11.9 Hz), 141.42, 131.01 (dd, $J$ = 4.7, 2.3 Hz), 129.76, 129.60, 129.07, 128.10 (dd, $J$ = 9.5, 5.5 Hz), 127.73, 123.16 (dd, $J$ = 3.0, 1.4 Hz), 121.52 (dd, $J$ = 12.5, 4.0 Hz), 111.51 (dd, $J$ = 21.3, 3.7 Hz), 104.10 (t, $J$ = 25.7 Hz), 39.60; $^{19}$F NMR (565 MHz,CDCl$_3$) δ −111.66 (d, $J_{F-F}$ = 7.1 Hz), −114.30 (d,

$J_{F-F}$ = 7.1 Hz); FTIR (neat) 3094, 2931, 1589, 1503, 1427, 1223, 970, 846, 809 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{17}$H$_{13}$F$_2$N$_2$S: 315.0768, found 315.0759.
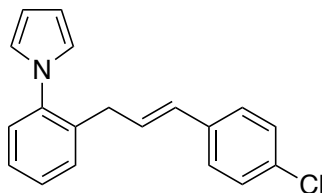


**(*E*)-1-(2-(3-(4-Chlorophenyl)allyl)phenyl)-1*H*-pyrrole (3-35).** Prepared via General Procedure B using 1-(2-(1H-Pyrrol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 1→10% toluene/hexanes) to give **3-35** (220 mg, 75%) as colorless oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.38 − 7.28 (m, 4H), 7.25 − 7.19 (m, 4H), 6.82 − 6.78 (m, 2H), 6.34 − 6.30 (m, 2H), 6.21 (d, *J* = 15.9 Hz, 1H), 6.14 (dt, *J* = 15.8, 6.4 Hz, 1H), 3.40 (d, *J* = 6.4 Hz, 2H); $^{13}$C NMR (151 MHz,CDCl$_3$) δ 140.6, 136.1, 136.0, 132.9, 130.6, 130.4, 129.3, 128.8, 128.1, 127.5, 127.4, 127.3, 122.5, 109.1, 34.8; FTIR (neat) 3028, 1502, 1491, 1327, 1093, 764, 727 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{17}$ClN: 294.1050, found 294.1041.
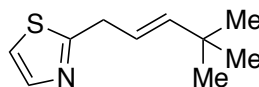


**(*E*)-2-(4,4-Dimethylpent-2-en-1-yl)thiazole (3-36).** Prepared via General Procedure A using 2,4,6-Triphenyl-1-(thiazol-2-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 2→20% EtOAc/hexanes) to give **3-36** (91 mg, 50%) as light yellow oil: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.69 (d, *J* = 3.3 Hz, 1H), 7.20 (d, *J* = 3.3 Hz, 1H), 5.75 − 5.69 (m, 1H), 5.58 (dt, *J* = 15.5, 6.9 Hz, 1H), 3.71 (dd, *J* = 6.9, 1.3 Hz, 2H), 1.04 (s, 9H); $^{13}$C NMR (151

MHz, CDCl$_3$) δ 171.4, 145.9, 142.6, 120.5, 118.6, 36.9, 33.3, 29.6; FTIR (neat) 3081, 2959, 2902, 2866, 1501, 1363, 973, 720 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{10}$H$_{16}$NS: 182.1003, found 182.0998.

# REFERENCES

1.      Yang, Z.; Tang, P.; Gauuan, J. F.; Molino, B. F., *The Journal of Organic Chemistry* **2009,** *74*, 9546-9549.

2.      Yadav, J. S.; Rajendar, G.; Rao, R. S.; Pabbaraja, S., *The Journal of Organic Chemistry* **2013,** *78*, 8524-8530.

3.      Butt, N. A.; Zhang, W., *Chemical Society Reviews* **2015,** *44*, 7929-7967.

4.      Yuan, Q.; Yao, K.; Liu, D.; Zhang, W., *Chemical Communications* **2015,** *51*, 11834-11836.

5.      Breault, G. A.; Oldfield, J.; Tucker, H.; Warner, P., US5811459A, 1998/09/22/, 1998.

6.      Jacques, V.; Rusche, J. R.; Peet, N. P.; Singh, J., WO2012118782A1, 2012/09/07/, 2012.

7.      Lubisch, W.; Moller, A.; Treiber, H.-J., US6103720A, 2000/08/15/, 2000.

8.      Tempone, A. G.; Pompeu da Silva, A. C. M.; Brandt, C. A.; Martinez, F. S.; Treiger Borborema, S. E.; Barata da Silveira, M. A.; de Andrade, H. F., *Antimicrobial Agents and Chemotherapy* **2005,** *49*, 1076.

9.      Kabalka, G. W.; Dong, G.; Venkataiah, B., *Org. Lett.* **2003,** *5*, 893-895.

10.     Kayaki, Y.; Koda, T.; Ikariya, T., *European Journal of Organic Chemistry* **2004,** *2004*, 4989-4993.

11.     Manabe, K.; Nakada, K.; Aoyama, N.; Kobayashi, S., *Adv. Synth. Catal.* **2005,** *347*, 1499-1503.

12.     Tabélé, C.; Curti, C.; Primas, N.; Kabri, Y.; Remusat, V.; Vanelle, P., *Synthesis* **2015,** *47*, 3339-3346.

13.     Tsukamoto, H.; Sato, M.; Kondo, Y., *Chemical Communications* **2004**, 1200-1201.

14.    Tsukamoto, H.; Uchiyama, T.; Suzuki, T.; Kondo, Y., *Organic & Biomolecular Chemistry* **2008,** *6*, 3005-3013.

15.    Zhang, Y.; Yin, S.-C.; Lu, J.-M., *Tetrahedron* **2015,** *71*, 544-549.

16.    Lee, Y.; Shabbir, S.; Lee, S.; Ahn, H.; Rhee, H., *Green Chemistry* **2015,** *17*, 3579-3583.

17.    Xu, J.; Zhai, X.; Wu, X.; Zhang, Y. J., *Tetrahedron* **2015,** *71*, 1712-1717.

18.    Maslak, V.; Tokic-Vujosevic, Z.; Saicic, R. N., *Tetrahedron Letters* **2009,** *50*, 1858-1860.

19.    Mino, T.; Kogure, T.; Abe, T.; Koizumi, T.; Fujita, T.; Sakamoto, M., *European Journal of Organic Chemistry* **2013,** *2013*, 1501-1505.

20.    Bouyssi, D.; Gerusz, V.; Balme, G., *European Journal of Organic Chemistry* **2002,** *2002*, 2445-2448.

21.    Hamasaka, G.; Sakurai, F.; Uozumi, Y., *Tetrahedron* **2015,** *71*, 6437-6441.

22.    Hamasaka, G.; Sakurai, F.; Uozumi, Y., *Chemical Communications* **2015,** *51*, 3886-3888.

23.    Poláčková, V.; Toma, Š.; Oliver Kappe, C., *Tetrahedron* **2007,** *63*, 8742-8745.

24.    Moreno-Manas, M.; Pajuelo, F.; Pleixats, R., *The Journal of Organic Chemistry* **1995,** *60*, 2396-2397.

25.    Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P., *Org. Lett.* **2005,** *7*, 1829-1832.

26.    Nájera, C.; Gil-Moltó, J.; Karlström, S., *Adv. Synth. Catal.* **2004,** *346*, 1798-1811.

27.    Li, M.-B.; Wang, Y.; Tian, S.-K., *Angewandte Chemie International Edition* **2012,** *51*, 2968-2971.

28.    Li, M.-B.; Tang, X.-L.; Tian, S.-K., *Adv. Synth. Catal.* **2011,** *353*, 1980-1984.

29.    Narahashi, H.; Shimizu, I.; Yamamoto, A., *Journal of Organometallic Chemistry* **2008,** *693*, 283-296.

30.    Kuwano, R.; Yokogi, M., *Org. Lett.* **2005,** *7*, 945-947.

31.     Fernandez Reina, D.; Ruffoni, A.; Al-Faiyz, Y. S. S.; Douglas, J. J.; Sheikh, N. S.; Leonori, D., *ACS Catalysis* **2017,** *7*, 4126-4130.

32.     Alacid, E.; Nájera, C., *The Journal of Organic Chemistry* **2009,** *74*, 2321-2327.

33.     Anselmi, E.; Abarbri, M.; Duchêne, A.; Langle-Lamandé, S.; Thibonnet, J., *Synthesis* **2012,** *44*, 2023-2040.

34.     Frye, E. C.; O' Connor, C. J.; Twigg, D. G.; Elbert, B.; Laraia, L.; Hulcoop, D. G.; Venkitaraman, A. R.; Spring, D. R., *Chemistry – A European Journal* **2012,** *18*, 8774-8779.

35.     Ronson, T. O.; Carney, J. R.; Whitwood, A. C.; Taylor, R. J. K.; Fairlamb, I. J. S., *Chemical Communications* **2015,** *51*, 3466-3469.

36.     Frlan, R.; Sova, M.; Gobec, S.; Stavber, G.; Časar, Z., *The Journal of Organic Chemistry* **2015,** *80*, 7803-7809.

37.     Sova, M.; Frlan, R.; Gobec, S.; Stavber, G.; Časar, Z., *Applied Organometallic Chemistry* **2015,** *29*, 528-535.

38.     Baba, Y.; Toshimitsu, A.; Matsubara, S., *Synlett* **2008,** *2008*, 2061-2063.

39.     Cai, Y.; Benischke, A. D.; Knochel, P.; Gosmini, C., *Chemistry – A European Journal* **2016,** *23*, 250-253.

40.     Johnson, K. A.; Biswas, S.; Weix, D. J., *Chemistry – A European Journal* **2016,** *22*, 7399-7402.

41.     Cherney, A. H.; Reisman, S. E., *J. Am. Chem. Soc.* **2014,** *136*, 14365-14368.

42.     Krasovskaya, V.; Krasovskiy, A.; Bhattacharjya, A.; Lipshutz, B. H., *Chemical Communications* **2011,** *47*, 5717-5719.

43.     Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P., *J. Am. Chem. Soc.* **2013,** *135*, 280-285.

44.     Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P., *Tetrahedron* **2014,** *70*, 4257-4263.

45.     Basch, C. H.; Cobb, K. M.; Watson, M. P., *Org. Lett.* **2016,** *18*, 136-139.

46.     Wang, T.; Yang, S.; Xu, S.; Han, C.; Guo, G.; Zhao, J., *RSC Advances* **2017,** *7*, 15805-15808.

47.     Li, C.; Zhang, Y.; Sun, Q.; Gu, T.; Peng, H.; Tang, W., *J. Am. Chem. Soc.* **2016,** *138*, 10774-10777.

48.     Li, G.; Wu, L.; Lv, G.; Liu, H.; Fu, Q.; Zhang, X.; Tang, Z., *Chemical Communications* **2014,** *50*, 6246-6248.

49.     Ueda, M.; Nishimura, K.; Kashima, R.; Ryu, I., *Synlett* **2012,** *23*, 1085-1089.

50.     Guan, W.; Liao, J.; Watson, M. P., *Synthesis* **2018,** *50*, 3231-3237.

51.     Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996,** *15*, 1518-1520.

52.     Ellwart, M.; Knochel, P., *Angewandte Chemie International Edition* **2015,** *54*, 10662-10665.

# Chapter 4

# REDUCTIVE CROSS-ELECTROPHILE COUPLING OF ALKYL
# PYRIDINIUM SALTS WITH ARYL BROMIDES

This work was performed in collaboration with Michelle Garnsey, Brian Boscoe, and Joseph Tucker at Pfizer, Inc.

## 4.1   Introduction

Over the last century, transition-metal catalysis has revolutionized our ability to form new carbon-carbon bonds. Notably, these advancements have enabled the rapid construction of a variety of $C_{sp3}$–$C_{sp2}$ bonds. For example, alkylarene **4-1** can easily be obtained via the cross-coupling of an alkyl halide with an arylboronic acid or arylzinc halide (Scheme 4.1, left).[1] However, the generation of these aryl nucleophiles requires additional synthetic steps and can sometimes limit functional group tolerance and scope. Thus, intense efforts have focused on the identification of novel, inexpensive cross-coupling partners for synthesis. In particular, we were drawn towards aryl halides because of their wide abundance and ease of synthesis. As a case study for their availability versus more common aryl nucleophiles, our collaborator, Dr. Michelle Garnsey, performed a search of Pfizer's internal chemical store. Over 56,000 (hetero)aryl bromides are present in the internal chemical store, in contrast to only 6,200 boronic acids/esters. We have previously developed methods to utilize Katritzky pyridinium salts in nickel-catalyzed cross-coupling reactions as a means to

142

harness ubiquitous alkyl amines as electrophiles via C–N bond activation (Chapters 1–3). We envisioned that the cross-coupling of these two feedstock chemicals (i.e., an alkyl amine derivative with an aryl halide) would allow one to build complexity from inexpensive starting materials and greatly expand the pools of compounds available for such cross-coupling approaches (Scheme 4.1, right).

Scheme 4.1    Synthesis of alkylarenes
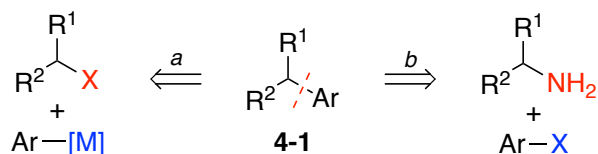


Most conventional approaches to cross-couplings require the use of a preformed organometallic nucleophile (e.g., R–BX$_2$, R–MgX, R–ZnX) in conjunction with an organic electrophile (e.g., R–X) (Scheme 4.2, top).[1] The inherent differences in reactivity between the nucleophile and electrophile allow these reactions to be cross-selective; the nucleophile reacts with the catalyst by transmetallation, and the electrophile reacts by oxidative addition. Nonetheless, the use of nucleophilic carbon reagents presents some shortcomings and challenges. Many organometallic reagents have limited commercial availability and are often synthesized from the corresponding organohalide, which adds steps to a synthetic sequence. Furthermore, some of these reagents have limited air and moisture stability, preventing their widespread use in industry. The intrinsic nucleophilicity of these organometallic reagents can limit the incorporation of electrophilic functional groups; the basic reagents required to facilitate transmetallation poses issues in substrates containing acidic protons. More importantly, these couplings often require a large excess of the organic nucleophile

due to competing side reactions such as protodemetallation, thereby decreasing the overall atom economy of these transformations.

Scheme 4.2    Conventional cross-coupling vs reductive cross electrophile-coupling

Conventional Transition Metal-Catalyzed Cross-Coupling

$$R^1-[M] \quad + \quad R^2-X \quad \xrightarrow{\text{metal catalyst}} \quad R^1-R^2$$

nucleophile          electrophile                     *inherent substrate reactivity*
*transmetallation*   *oxidative addition*             *favors cross-selectivity*

Reductive Cross-Electrophile Coupling

$$R^1-X \quad + \quad R^2-X \quad \xrightarrow[\text{reductant}]{\text{metal catalyst}} \quad R^1-R^2$$

electrophile          electrophile                     *catalyst controls homo-*
*oxidative addition*  *oxidative addition*             *vs cross-selectivity*
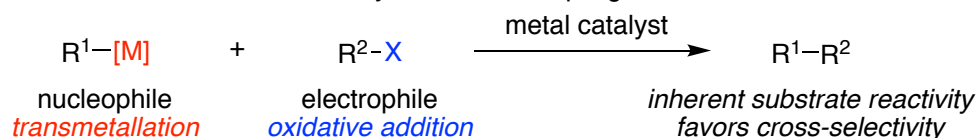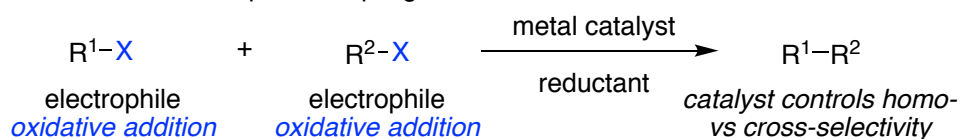
In contrast, a reductive cross-electrophile approach mitigates many of these issues by eliminating the need for preformed organometallic species (Scheme 4.2, bottom).[2] As a result, this area has garnered significant attention over the past decade. These couplings employ the use of commercially abundant organohalides, which are much more stable and easier to handle than their organometallic counterparts. More importantly, greater functional group compatibility can be observed due to the omission of stoichiometric strong bases and nucleophiles. This approach also provides a unique opportunity for synthetic orthogonality to traditional cross-couplings.

However, one of the ongoing challenges associated with cross-electrophile couplings is selectivity. The two coupling partners are both electrophilic in nature and tend to react with a metal catalyst via oxidative addition. This can lead to dimerization of either electrophile, as well as other byproducts such as protodehalogenation and β-hydride elimination. Intense efforts have identified several strategies to afford high

yields and/or cross-selectivity in these types of reductive cross-couplings (Scheme 4.3).[3]

Scheme 4.3    Strategies for obtaining high yields in reductive cross-couplings

A.  Excess of one reagent

$$R^1\text{-}X \ + \ R^2\text{-}X \ \xrightarrow[\text{reductant}]{M_{cat}} \ R^1\text{-}R^2 \ + \ R^2\text{-}R^2$$

R^2-X: *excess*

R^1–R^2: *high yield based on R$^1$–X*

R^2–R^2: *major product*
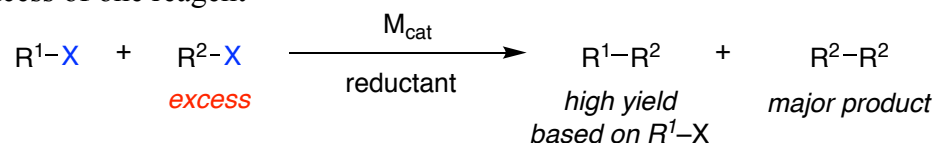
B.  Electronic differentiation of starting materials

$$M_{cat}^0 \ \xrightarrow[\textit{selective O.A.}]{R^1\text{-}X} \ M_{cat}^{II}\!\!\begin{smallmatrix}R^1\\X\end{smallmatrix} \ \xrightarrow[\text{reductant}]{e^-} \ \left[M_{cat}^0\text{-}R^1\right]^{\ominus} \ \xrightarrow{R^2\text{-}X} \ R^1\text{-}R^2$$

R^1–R^2: *major product*
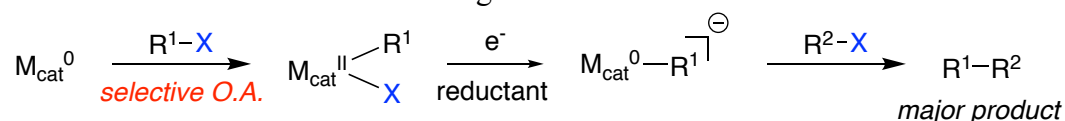
C.  Steric matching of substrate and catalyst

$$R^1\text{-}X \ \xrightarrow[\text{reductant}]{L\text{-}M_{cat}} \ L\text{-}M_{cat}\text{-}R^1 \ \xrightarrow{R^2\text{-}X} \ R^1\text{-}R^2$$

*sterics of ligand or reductant govern selectivty*

R^1–R^2: *major product*

D.  Radical chain process

$$R^1\text{-}X \ + \ R^2\text{-}X \ \xrightarrow[\text{reductant}]{M_{cat}} \ R^1\text{-}R^2$$

R^1-X: *oxidative addition*

R^2-X: *radical precursor*
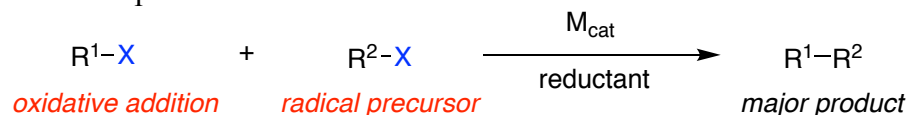
R^1–R^2: *major product*

Employing an excess of one reagent leads to a statistical mixture of products and delivers the cross-coupled product in high yield (Scheme 4.3A). However, this sacrifices a large amount of one starting material, and the major product of this reaction is the dimer of the excess reagent. The second approach relies on the electronic differentiation of two unlike electrophiles through sequential oxidative addition (Scheme 4.3B). The catalytic cycle must have two different active, low-valent species that can each selectively react with one of the starting materials. If the

reactivities of the electrophiles are similar, sterics can be used to differentiate the two species (Scheme 4.3C). Steric matching between substrate and ligand or reductant can afford cross-selectivity. Finally, the native heterolytic versus homolytic reactivity patterns of the starting materials can be exploited to achieve selective cross-coupling (Scheme 4.3D). One electrophile is prone to undergo a two-electron oxidative addition, while the other proceeds through a SET mechanism to generate the corresponding radical intermediate. In this case, the catalyst must be capable of both single- and two-electron processes. We sought to utilize this strategy for our proposed reaction.

In 2010, Weix and coworkers disclosed a seminal report on the nickel-catalyzed reductive cross-coupling of primary and secondary alkyl halides (**4-3**) with aryl halides using manganese as a stoichiometric reductant (Scheme 4.4).[4] In contrast to previously reported couplings of alkyl halides with aryl halides, this reaction does not go through an intermediate organometallic species. Instead, this approach relies on the ability of the aryl halide to undergo a two-electron oxidative addition, while the alkyl halide can serve as a radical precursor. Shortly after, Weix expanded on this initial finding and published more general conditions using zinc as the stoichiometric metal reductant.[5] He demonstrated broad scope with over 40 examples including those containing nucleophilic and electrophilic groups as well as acidic protons. Additionally, vinyl halides were also amenable to this chemistry. More recently, Weix disclosed an analogous reductive cross-coupling of redox-active esters (**4-4**) with aryl iodides (Scheme 4.5).[6]

**Scheme 4.4**   Weix's reductive coupling of alkyl halides with aryl halides
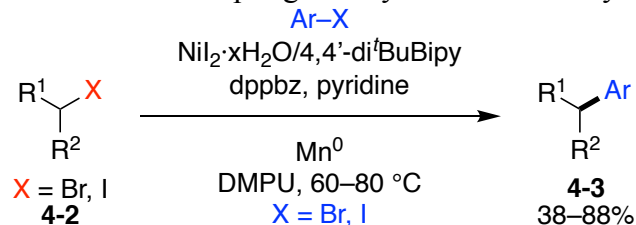


**Scheme 4.5**   Weix's reductive coupling of redox-active esters with aryl iodides
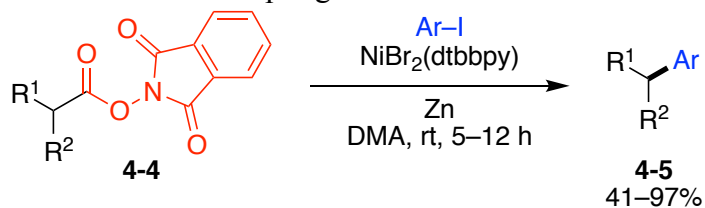


In a subsequent publication, the Weix group performed detailed mechanistic studies to elucidate the mechanism of his reductive cross-electrophile coupling of alkyl halides with aryl halides.[2, 7] He proposed a radical-chain bimetallic pathway (Scheme 4.6). Notably, this is distinct from the traditional radical rebound mechanism in which the radical intermediate recombines with the same nickel complex that formed it. Starting from low-valent $Ni^0$ species **A**, selective two-electron oxidative addition of the aryl halide generates $Ni^{II}$-arene **B**, which appears to be the catalyst resting state. This then reacts with a solvent cage escaped alkyl radical **C** to form diorgano-$Ni^{III}$ species **D**. Reductive elimination of the cross-coupled product produces reactive $Ni^I$ species **E** that can then undergo SET with the alkyl halide to generate the aforementioned alkyl radical **C** and $Ni^{II}$ species **F**. Finally, the cycle can be turned-over via reduction of **F** back to the active $Ni^0$ species **A** with a stoichiometric reductant such as manganese or zinc.

Scheme 4.6    Weix's proposed radical-chain bimetallic pathway
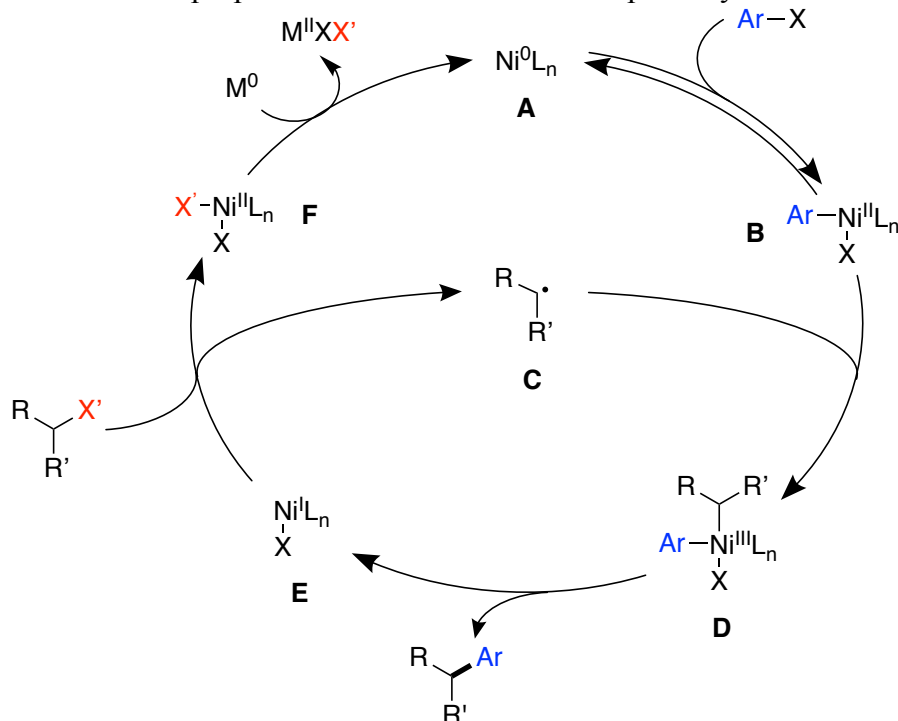


Although Weix focused primarily on primary alkyl halides, he demonstrated limited examples of cross-coupling secondary alkyl halides and only in modest yields (<70%). Gong later improved on this chemistry to affect cross-coupling of secondary alkyl bromides (**4-6**) with aryl bromides (Scheme 4.7).[8] Notably, however, these methods lacked scope in heterocyclic alkyl electrophiles. Towards this end, the Molander group has optimized conditions for the cross-coupling of saturated heterocyclic bromides (**4-8**) with (hetero)aryl bromides (Scheme 4.8).[9] A number of 4-, 5-, and 6-membered *O*- and *N*-heterocyclic alkyl bromides were well tolerated under these conditions. This chemistry was later extended to heterocyclic tosylates as well.[10]

Scheme 4.7    Gong's coupling of secondary alkyl bromides
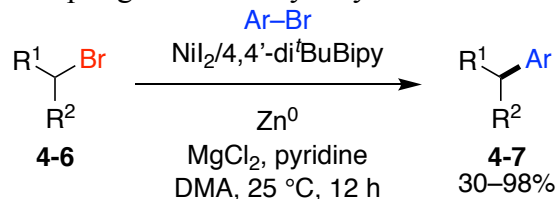


Scheme 4.8    Molander's coupling of heterocyclic alkyl bromides
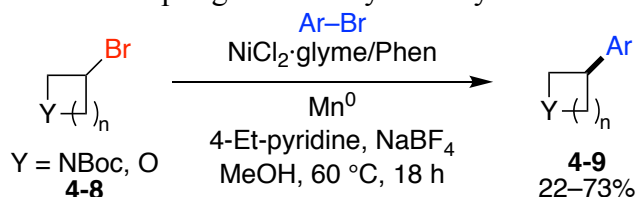


However, despite these advancements, tertiary alkyl halides remained a challenging class of substrates. In 2015, the Gong group disclosed conditions for the reductive cross-coupling of tertiary alkyl bromides (**4-10**) with aryl bromides to afford all-carbon quaternary centers (**4-12**) (Scheme 4.9).[11] Although pyridine-based bidentate and tridentate ligands were ineffective, the use of *N*-heterocyclic carbene precursors (**4-11**) resulted in the desired cross-coupling. Unfortunately, cross-couplings of electron-rich aryl halides were problematic under these original conditions. More recently, Gong modified these conditions to enable the coupling of electron-rich aryl iodides.[12]

Scheme 4.9    Gong's reductive coupling of tertiary alkyl halides
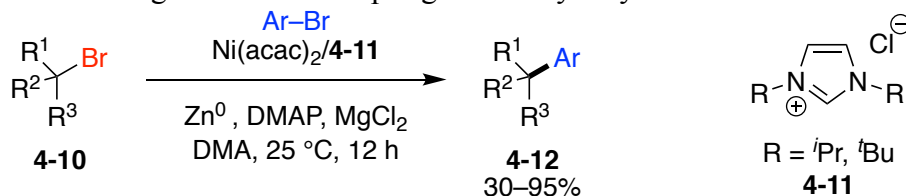
Reductive cross-couplings utilizing a metallaphotoredox approach have also been investigated. Unlike methods that employ a stoichiometric metal reductant, this approach allows for the cross-coupling to occur under much milder conditions by utilizing a photocatalyst. The MacMillan group has demonstrated that under Ni/Ir dual-photoredox conditions, alkyl bromides (**4-13**) can be coupled with aryl bromides at room temperature with blue LED irradiation (Scheme 4.10).[13] This method relies on a photocatalytically generated silyl radical species, which can perform halogen-atom abstraction to generate the nucleophilic carbon-centered radical **4-14**. Notably a variety of heteroarenes can be incorporated as well as two examples of tertiary alkyl groups.

Scheme 4.10   MacMillan's metallaphotoredox reductive coupling
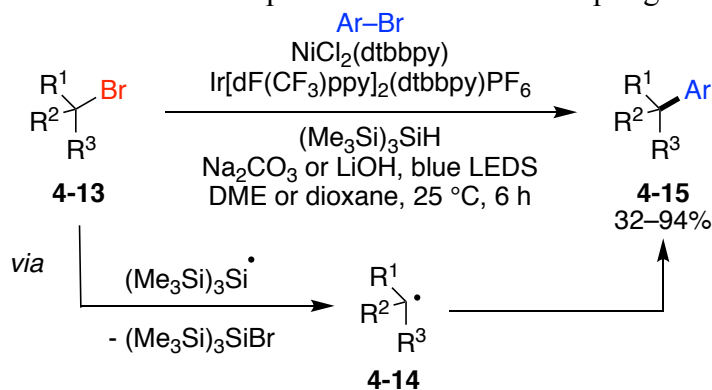


Although nickel-catalyzed reductive cross-couplings have exploded within the past decade, a number of other metals have also been found to effect analogous reactions. For example, the Buchwald group has found that palladium precatalyst **4-17** can promote the cross-coupling of heterocyclic alkyl bromides (**4-16**) with aryl halides and triflates under aqueous Lipshutz-Negishi conditions (Scheme 4.11A).[14] In 2009, Jacobi von Wagelin published the first direct iron-catalyzed cross-coupling of alkyl

bromides (**4-19**) with aryl bromides (Scheme 4.11B).[15] However, the functional group tolerance was much lower than manganese- or zinc-mediated reactions due to the formation of a Grignard reagent *in-situ*. Gosmini reported a cobalt-catalyzed coupling of alkyl bromides (**4-21**) with aryl bromides (Scheme 4.11C).[16] Notably, however, the alkyl electrophile is generally used in excess (1.1–3 equiv).

Scheme 4.11   Metal-catalyzed reductive cross-couplings

A.  Buchwald's palladium-catalyzed coupling
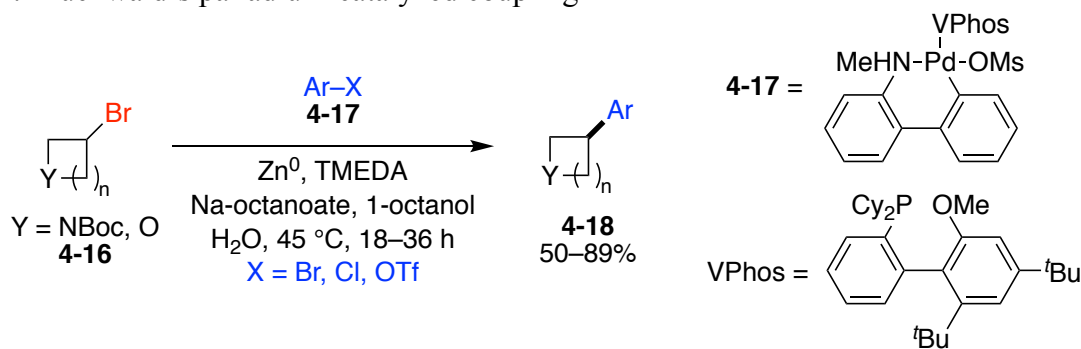


B.  Jacobi von Wagelin's iron-catalyzed coupling
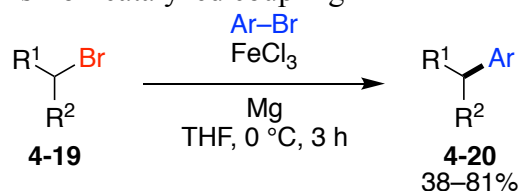


C.  Gosmini's cobalt-catalyzed coupling
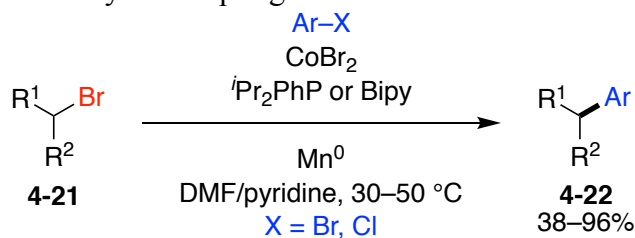
With the advancement of metal-catalyzed reductive cross-couplings, a variety of $C_{sp3}$–$C_{sp2}$ bonds can be forged via these types of approaches. However, examples of cross-selective couplings of two unactivated alkyl electrophiles to form new $C_{sp3}$–$C_{sp3}$ bonds have been much more limited. In 2011, Gong reported a nickel-catalyzed coupling of two unactivated alkyl halides (primary or secondary) (Scheme 4.12).[17] Notably, a large excess of one alkyl halide (3 equiv) was required to achieve high selectivity and competing dimerization was a major side reaction. Gong later improved upon this chemistry and reported an analogous reaction using $B_2Pin_2$ as the terminal reductant in place of zinc.[18] In this case, only a slight excess (1.5 equiv) of one of the alkyl halides can be used to achieve good yields. This method relies on the steric differentiation of the two alkyl electrophiles (*vide supra*, Scheme 4.3C) to enable selective sequential oxidative addition. More recently, the Fu and Liu groups disclosed the copper-catalyzed coupling of alkyl tosylates and mesylates with alkyl and aryl bromides (Scheme 4.13).[19] Again, this method relies on an excess of the alkyl or aryl bromide (2–3 equiv). There is also one example of coupling *tert*-butyl bromide, albeit in poor yield (25%). To date, a general cross-selective reductive alkyl-alkyl cross-coupling remains an unsolved challenge.

Scheme 4.12   Gong's nickel-catalyzed reductive alkyl-alkyl coupling
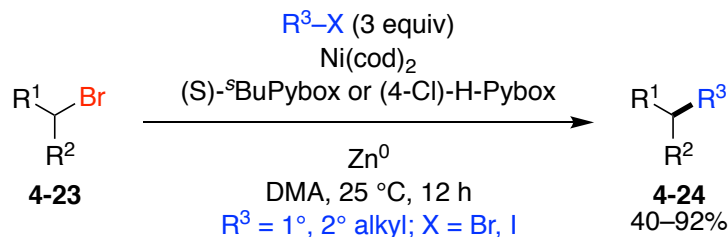
Scheme 4.13   Fu and Liu's cobalt-catalyzed reductive alkyl-alkyl/aryl coupling
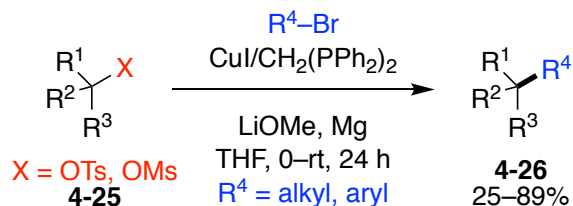


Recognizing the advantages of a reductive cross-electrophile coupling as well as the lack of methods to utilize alkyl amine derivatives in this regard, I set out to develop a reductive coupling of alkyl pyridinium salts with aryl bromides. Unlike the previously discussed Suzuki–Miyaura cross-coupling (Chapter 1), this approach allows for a much broader scope under mild conditions. In particular, I hoped to successfully utilize substrates that were problematic under our basic Suzuki conditions (Scheme 4.14). Substrates such as **4-27** and **4-28** were prone to elimination under the basic conditions. Acidic protons as well as substrates susceptible to base-promoted epimerization events (**4-29)** are now tolerated and existing stereocenters are preserved under the new reductive conditions. More importantly, this approach allows for the use of more widely abundant aryl bromides in place of arylboronic acids and provides a complementary method to our existing chemistries.

Scheme 4.14   Challenging substrates under Suzuki conditions



4-27
β-keto amine derivatives
*Mannich adducts*

4-28
acidic hydrogens
(elimination)

4-29
epimerizable stereocenters

153
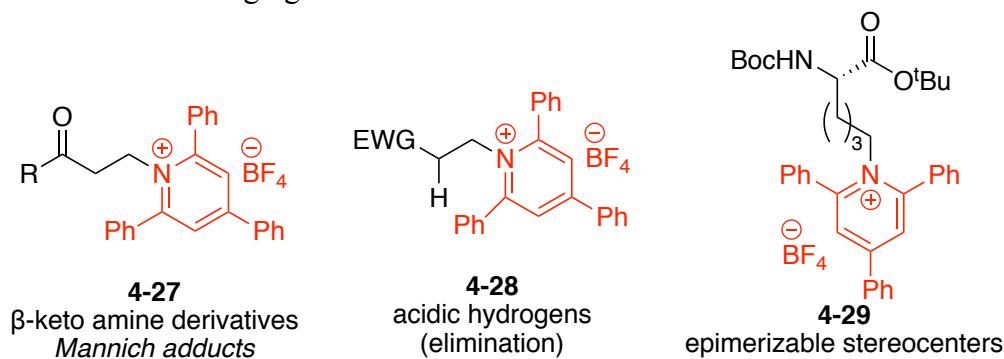
## 4.2  Results and Discussion

### 4.2.1  Reaction Optimization: Primary Alkyl Pyridinium Salts

The optimization of this reductive cross-coupling began by coupling model pyridinium salt **4-30** with 3-bromoquinoline to afford desired arylated product **4-31**. Analogous to the competing dimerization of alkyl halides, one of the major byproducts (**4-32**) results from addition of the alkyl radical into the 4-position of another molecule of unreacted pyridinium salt. My colleague Corey Basch conducted preliminary experiments to demonstrate the feasibility of this reductive approach. Initial screens focused on the identification of a suitable reductant for this transformation. Common metal reductants such as zinc and manganese were tested (Table 4.1, entries 1 & 2). Excitingly, the arylated product **4-31** was observed in 26% yield using manganese. The addition of an additive, such as lithium chloride, was found to increase the yield considerably as well as suppress the formation of **4-32** (entry 3). Switching to *N*-methylpyrrolidone as solvent under slightly more dilute conditions further improved the yield of the reaction (entry 4). Upon investigating a variety of additives, I found that magnesium chloride was superior in giving high yields of **4-31** while suppressing the formation of **4-32** (entry 5). We propose that the magnesium chloride may serve a role in accelerating the rate of reduction of the $Ni^{II}$ intermediates as well as help activate the surface of the metal reductant.[20, 21] Decreasing the amount of metal reductant to two equivalents did not impact yield (entry 6). I screened a variety of ligands and found that the more electron-rich 4,4'-dimethoxy-2,2'-bipyridine ligand was unique in improving this reaction (entry 7). Finally, by employing a slight excess of pyridinium salt **4-30** (1.2 equiv) relative to the aryl bromide (1.0 equiv), **4-31** was observed in 85% isolated yield (entry 8).

154

Table 4.1 Reaction optimization of the reductive cross-electrophile coupling primary alkyl pyridinium salts with aryl bromides[a]



| Entry | $M^0$ | Additive | Ligand | Solvent | Yield (%)[b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | 4-31 | 4-32 | Ar-Ar |
| 1 | $Zn^0$ | none | 4,4'-di$^t$BuBipy | DMA (0.33 M) | 9 | 24 | 5 |
| 2 | $Mn^0$ | none | 4,4'-di$^t$BuBipy | DMA (0.33 M) | 26 | 25 | 4 |
| 3 | $Mn^0$ | LiCl | 4,4'-di$^t$BuBipy | DMA (0.33 M) | 54 | 14 | 4 |
| 4 | $Mn^0$ | LiCl | 4,4'-di$^t$BuBipy | NMP (0.17 M) | 62 | 10 | 10 |
| 5 | $Mn^0$ | MgCl$_2$ | 4,4'-di$^t$BuBipy | NMP (0.17M) | 65 | 8 | 15 |
| 6[c] | $Mn^0$ | MgCl$_2$ | 4,4'-di$^t$BuBipy | NMP (0.17M) | 67 | 6 | 17 |
| 7[c] | $Mn^0$ | MgCl$_2$ | 4,4'-diOMeBipy | NMP (0.17M) | 74 | 7 | 15 |
| 8[c,d] | $Mn^0$ | MgCl$_2$ | 4,4'-diOMeBipy | NMP (0.17 M) | 85[e] | n.d. | n.d. |

[a]Conditions: pyridinium salt **4-30** (0.10 mmol), 3-bromoquinoline (1.1 equiv), [Ni] (10 mol %), ligand (12 mol %), $M^0$ (3.0 equiv), 80 °C, 24 h, unless noted otherwise. [b]Determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]2.0 equiv $M^0$. [d]1.2 equiv **4-30**, 1.0 equiv ArBr. [e]Isolated yield.

### 4.2.2 Reaction Optimization: Secondary Alkyl Pyridinium Salts

With conditions optimized for the primary alkyl system, I wanted to see if the same conditions would be amenable to the corresponding secondary alkyl system. I chose pyridinium salt **4-33** to test for reactivity. Although the desired product (**4-34**) was formed in 19% yield, the unwanted 4-addition byproduct (**4-35**) was observed in 32% yield (Scheme 4.15, top). Notably for every molecule of **4-35** formed, two molecules of starting material **4-33** are consumed, making this a particularly detrimental competing reaction. I decided to run a series of control experiments to probe this competing pathway. In the absence of nickel and ligand, **4-35** was formed in a similar 39% yield (Scheme 4.15, bottom). Therefore, this byproduct can arise from an off-cycle non-nickel-catalyzed pathway at a rate that is competitive with cross-coupling. The major challenge here was to figure out how to use transition metal catalysis to accelerate the rate of productive cross-coupling while suppressing this unwanted off-cycle pathway.

Scheme 4.15   Cross-coupling of secondary alkyl pyridinium salt **4-33**
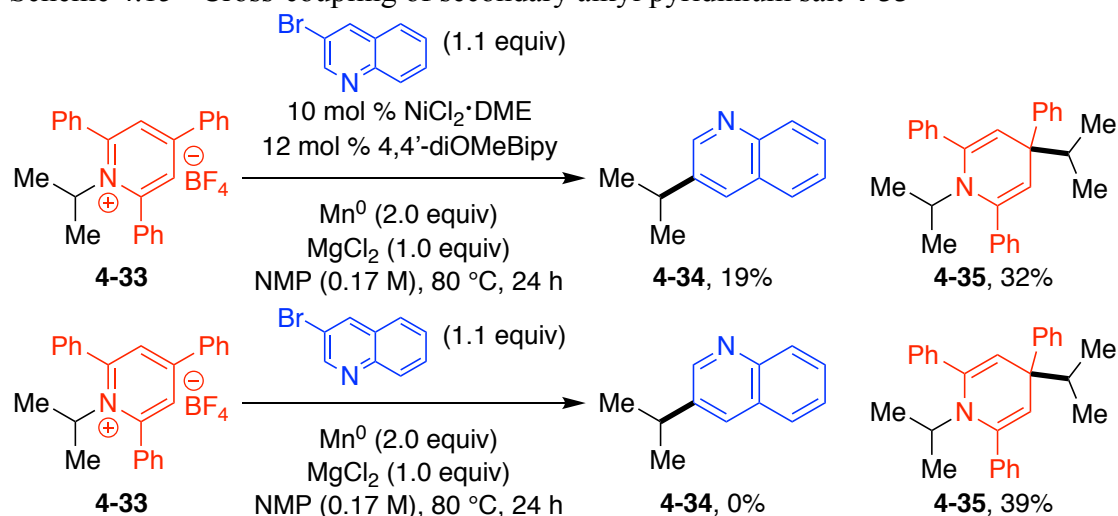


Yields determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

To gain a deeper understanding of the reaction, I took a closer look at one possible mechanism. I proposed a radical-chain bimetallic pathway (Scheme 4.16), analogous to Weix's reductive coupling of alkyl halides with aryl halides (*vide supra*, Scheme 4.6).[7] If the generated alkyl radical intermediate **4-36** proceeds via a productive on-cycle event (Path A), desired cross-coupling is observed. However, if instead it gets trapped by another molecule of unreacted pyridinium **4-37** (Path B), we observe the formation of 4-addition byproduct **4-38**. This is further complicated by the fact that manganese appears to be able to directly reduce the pyridinium to form alkyl radical **4-36**, and in turn lead to the formation of undesired **4-38**.

Scheme 4.16   Proposed radical-chain mechanism for reductive coupling
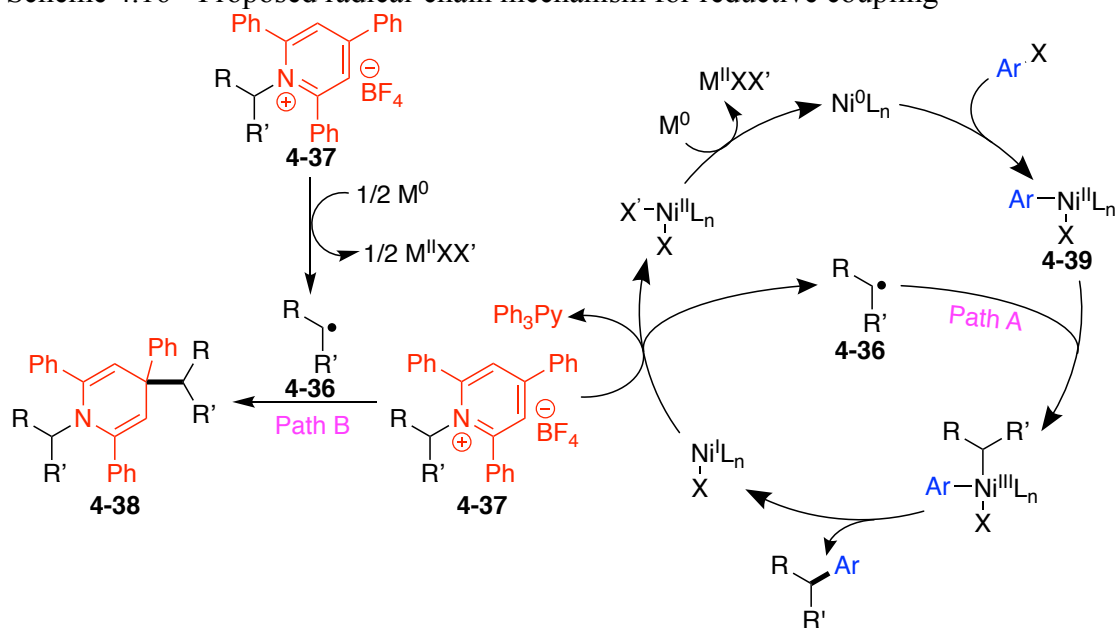


Thus, effectively controlling the reactivity of carbon-centered radical **4-36** is key in controlling the selectivity of this reaction. We need to limit the concentration of pyridinium salt **4-37** relative to radical **4-36** to suppress the competing dimerization

pathway (Path B), while having a relatively high concentration of $Ni^{II}$-arene **4-39** to intercept alkyl radical **4-36** and enable cross-coupling (Path A). I proposed performing a slow-addition of pyridinium salt **4-37**. This procedure would limit the concentration of **4-36** in solution and suppress the formation of unwanted **4-38**. Additionally, this would allow for build-up of Ni species **4-39** to enable rapid capture of alkyl radical **4-36** and feed back into the catalytic cycle.

I was delighted to find that a slow-addition of **4-33** over the course of two hours more than doubled the yield of desired cross-coupled product **4-34** (Table 4.2, entries 1 vs 3). Moreover, the formation of 4-addition **4-35** was greatly suppressed. Notably, however, the amount of biaryl (Ar–Ar) formed increased significantly. This dimer presumably arises from metathesis of the $Ni^{II}$-arene species **4-39** followed by reductive elimination. This tells us that the rate of oxidative addition of the aryl halide into the low valent $Ni^{0}$ species is likely fast. Additionally, the overall mass balance for the alkyl portion of the molecule is quite poor, suggesting that the corresponding rate of radical formation is slower. In order to mitigate these issues, I performed a slow addition of a solution of both the alkyl pyridinium salt as well as the aryl halide. In doing so, the amount of biaryl formation was suppressed and a much better mass balance was observed (entry 4). Finally, good yield of cross-coupled product **4-34** was observed with a slow addition of pyridinium salt **4-33** and 3-bromoquinoline over six hours (entry 7). Excitingly, there is only minimal formation the 4-addition **4-35** and biaryl byproducts under these conditions.

Table 4.2    Reaction optimization of the reductive cross-electrophile coupling secondary alkyl pyridinium salts with aryl bromides[a]



| | **Slow Addition** | | **Yield (%)[b]** | | |
|:---:|:---:|:---:|:---:|:---:|:---:|
| **Entry** | **Reagents** | **Time (h)** | **4-34** | **4-35** | **Ar–Ar** |
| 1 | none | none | 19 | 32 | 12 |
| 2 | **4-33** | 1 | 24 | 28 | 28 |
| 3 | **4-33** | 2 | 50 | 3 | 20 |
| 4 | **4-33** + ArBr | 2 | 50 | 14 | 12 |
| 5 | **4-33** + ArBr | 3 | 68 | 9 | 11 |
| 6 | **4-33** + ArBr | 4 | 76 | 8 | 6 |
| 7 | **4-33** + ArBr | 6 | 84 | 2 | 4 |

[a]Conditions: pyridinium salt **4-33** (0.5 mmol), 3-bromoquinoline (1.1 equiv), NiCl$_2$·DME (10 mol %), 4,4'-dimethoxy-2,2'-bipyridine (12 mol %), Mn$^0$ (2.0 equiv), MgCl$_2$ (1.0 equiv), NMP (0.17 M), 80 °C, 24 h, unless noted otherwise. [b]Determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

### 4.2.3   Reaction Scope

With conditions optimized for both the primary and secondary alkyl systems, I recruited my colleagues Megan Hoerrner and Mike Talley to help explore the scope of

this transformation. Overall, very broad substrate scope was realized (Scheme 4.17). Model product **4-31** was isolated in 85% yield on a 1.0-mmol scale. A variety of primary and secondary (cyclic and acyclic) alkyl groups coupled effectively. Excitingly, substrates containing heterocycles such as piperazine (**4-45**), piperidine (**4-51**), pyrrolidine (**4-56**), and pyridine (**4-50 & 4-52**) were amenable to this chemistry. Additionally, benzylic pyridinium salts were competent coupling partners (**4-52**). I have also demonstrated the cross-coupling of tertiary alkyl substrate **4-53**, albeit in low yield. Importantly, substrates that readily eliminate under the basic Suzuki conditions such as **4-46** and **4-47** proceeded smoothly under these reductive conditions. Additionally, unprotected alcohol **4-48** was well tolerated.

Scheme 4.17   Reaction scope of reductive coupling[a]
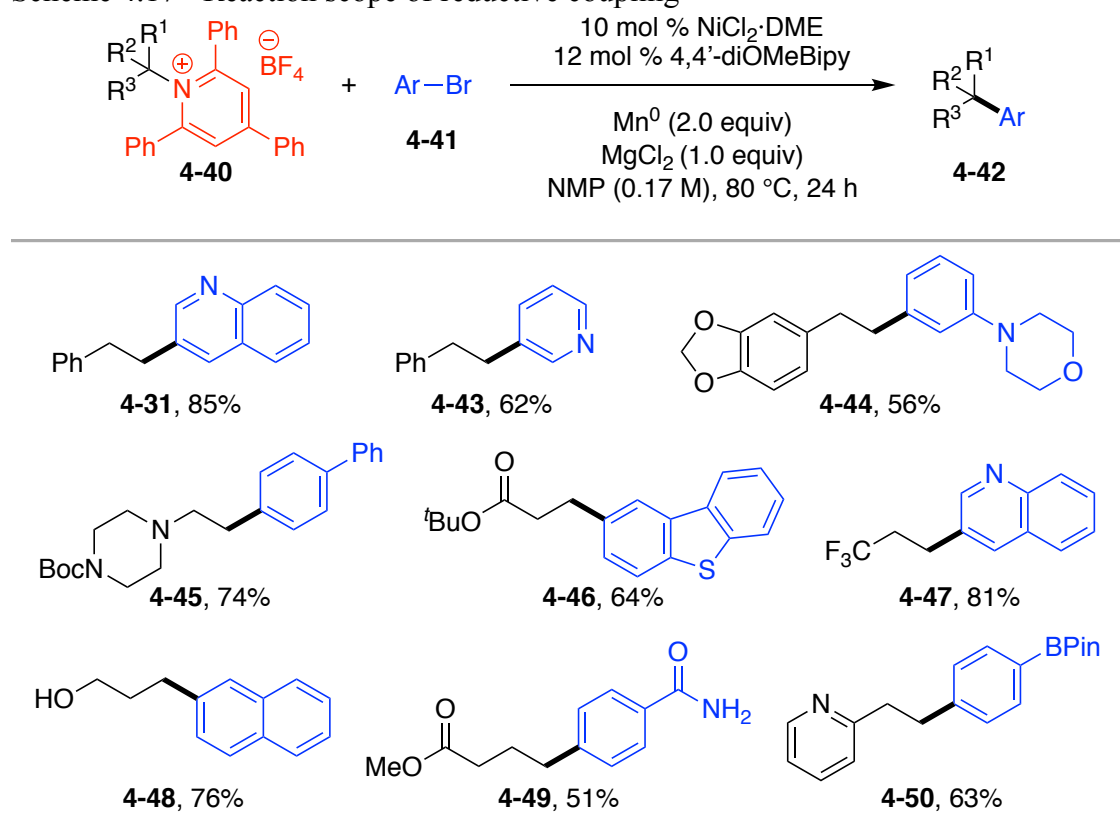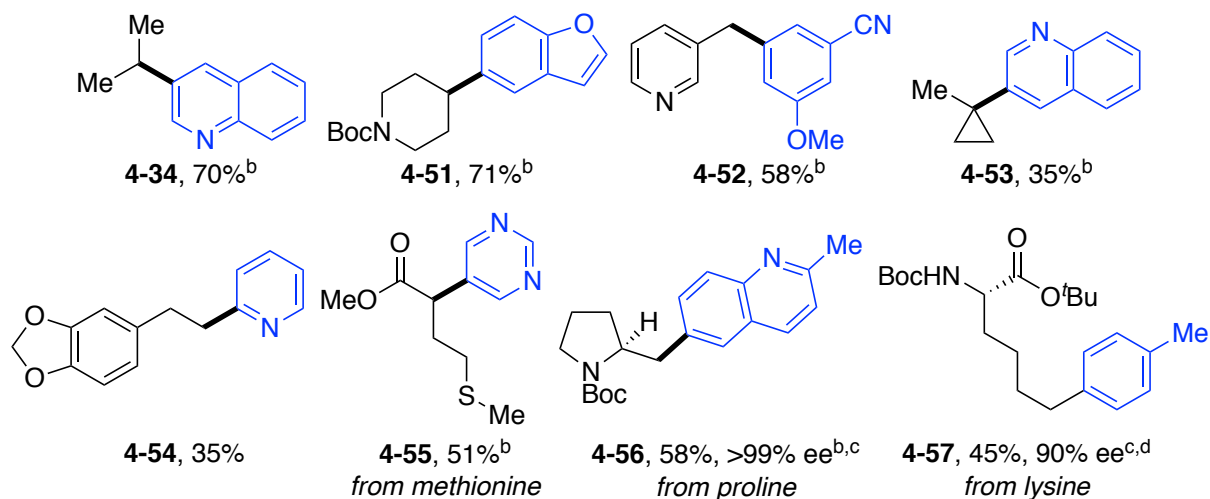


160

**4-34**, 70%[b]     **4-51**, 71%[b]     **4-52**, 58%[b]     **4-53**, 35%[b]

**4-54**, 35%     **4-55**, 51%[b]
*from methionine*     **4-56**, 58%, >99% ee[b,c]
*from proline*     **4-57**, 45%, 90% ee[c,d]
*from lysine*

[a]Conditions: pyridinium salt **4-40** (1.2 mmol), aryl bromide **4-41** (1.0 mmol), NiCl$_2$·DME (10 mol %), 4,4'-dimethoxy-2,2'-bipyridine (12 mol %), Mn$^0$ (2.0 equiv), MgCl$_2$ (1.0 equiv), NMP (0.17 M) 80 °C, 24 h. Average isolated yields (±5%) from duplicate experiments. [b]Pyridinium salt **4-40** (1.0 mmol), aryl bromide **4-41** (1.1 mmol). [c]Enantiomeric excess determined by chiral HPLC analysis. [d]Single experiment. 0.1-mmol scale. Yield determined by $^1$H NMR using 1,3,5-trimethoxybenzene as internal standard.

Substrates derived from amino acids were also competent coupling partners. Cross-coupling of the α-amino group of methionine methyl ester (**4-55**) and a proline derivative (**4-56**) proceeded smoothly. Moreover, cross-coupling of the amino side chain of *N*-Boc lysine produced **4-57** in 45% yield and 90% *ee*. Notably, the parent amine of *N*-Boc lysine *tert*-butyl ester was determined to be 90% *ee*. This example highlights the advantage of this reductive approach for the preservation of enantiomeric excess in substrates containing epimerizable stereocenters. Excitingly, this has implications for biological applications of this chemistry, particularly in the

context of peptide conjugation and the formation of cyclic peptides via cross couplings of the *N*-terminus or lysine side chain.

Broad scope was also observed in the aryl bromide coupling partner. Heteroarenes such as quinoline (**4-31**, **4-47**, **4-34**, **4-53** & **4-56**), 2- and 3-pyridine (**4-43** & **4-54**), pyrimidine (**4-55**), benzofuran (**4-51**), and dibenzothiophene (**4-46**) were well tolerated. Excitingly, unprotected benzamide (**4-49**) participated smoothly under the reaction conditions, demonstrating that functional groups containing acidic protons can be incorporated via this method. Aryl boronic ester (**4-50**) highlights the orthogonality of this approach to standard Suzuki–Miyaura cross-couplings.

Additionally, I wanted to demonstrate the advantage of utilizing an alkyl amine, as well as the utility of this chemistry for late-stage functionalization by cross-coupling substrates derived from pharmaceutical drugs and their intermediates (Scheme 4.18). Product **4-58** derives from an amine intermediate used in the synthesis of Lipitor® (Pfizer, Inc.), an anti-cholesterol drug.[22] Products **4-59** and **4-60** are derived from an amine intermediate in the synthesis of Mosapride, a treatment for gastrointestinal disorders.[23] Notably, **4-60** was formed on a gram scale (1.04 g), highlighting the scalability of this reaction, even with the heterogeneous nature of the metal reductant. Moreover, we recognized that the amine ($NH_2$) moiety is present in a number of bioactive molecules and can be further derivatized via this approach. Amlodipine, a treatment for high blood pressure,[24] cross-coupled effectively under the standard reaction conditions to afford **4-61** in 64% yield. Norephedrine, a common decongestant,[25] afforded **4-62** in synthetically useful yield, albeit in poor diastereomeric ratio (dr). Excitingly, these examples demonstrate the advantage of harnessing the native amine ($NH_2$) moiety of these molecules in cross-couplings.

Scheme 4.18   Cross-coupling of substrates derived from pharmaceutical drugs[a]
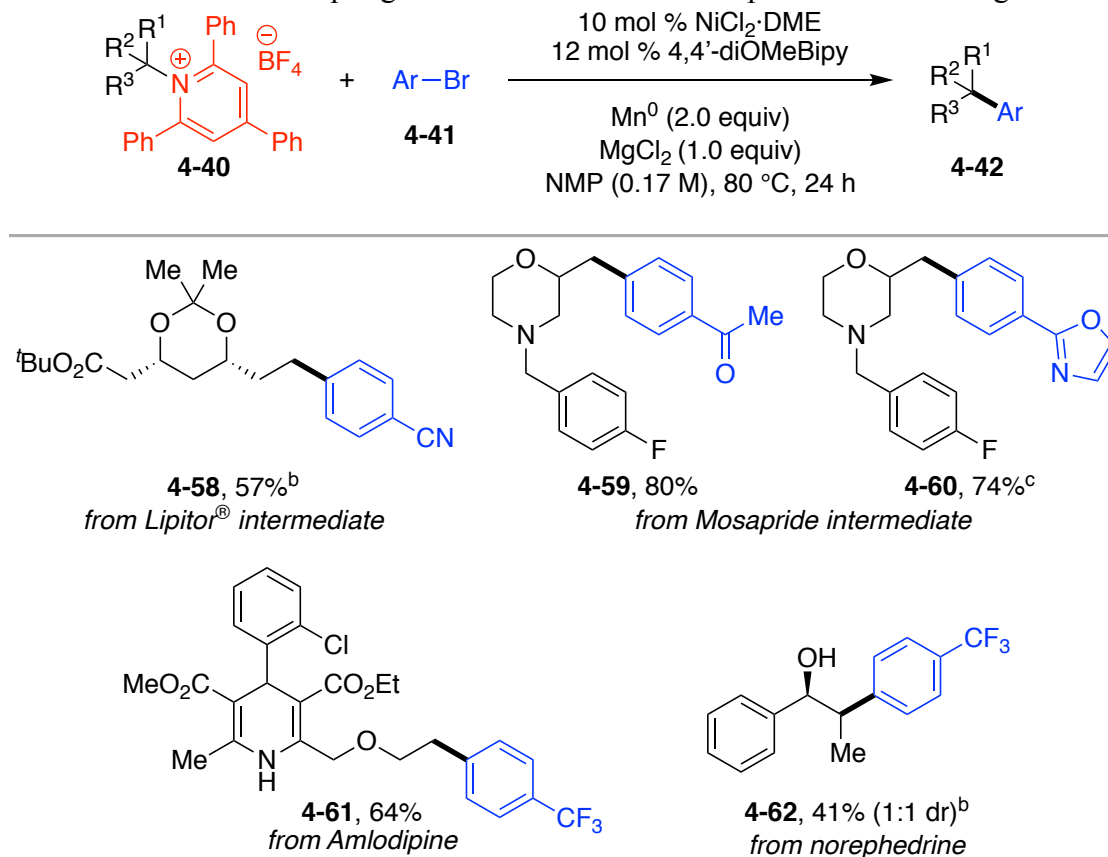




**4-58**, 57%[b]
*from Lipitor® intermediate*

**4-59**, 80%          **4-60**, 74%[c]
*from Mosapride intermediate*

**4-61**, 64%
*from Amlodipine*

**4-62**, 41% (1:1 dr)[b]
*from norephedrine*

[a]Conditions: pyridinium salt **4-40** (1.2 mmol), aryl bromide **4-41** (1.0 mmol), NiCl$_2$·DME (10 mol %), 4,4'-dimethoxy-2,2'-bipyridine (12 mol %), Mn$^0$ (2.0 equiv), MgCl$_2$ (1.0 equiv), NMP (0.17 M) 80 °C, 24 h. Average isolated yields (±5%) from duplicate experiments. [b]Pyridinium salt **4-40** (1.0 mmol), aryl bromide **4-41** (1.1 mmol). [c]Single experiment. 4.0-mmol scale.

## 4.2.4   Mechanism Studies

A series of mechanistic experiments were conducted to elucidate the mechanism of this transformation (Scheme 4.19). In using an organic reductant such as tetra(dimethylamino)ethylene (TDAE) in place of manganese, arylated product 4-

**31** was observed in 24% yield (Scheme 4.19A). This result suggests that an organomanganese species is not an intermediate, because both arylated product **4-31** and catalyst turnover are observed in the absence of manganese. Furthermore, cyclopropyl ring-opening and TEMPO trapping experiments (Scheme 4.19B and C) support the formation of an alkyl radical intermediate from the alkyl pyridinium salt. This is evidence against mechanisms involving sequential two-electron oxidative additions.

Scheme 4.19   Mechanistic experiments
A.  Organic reductant
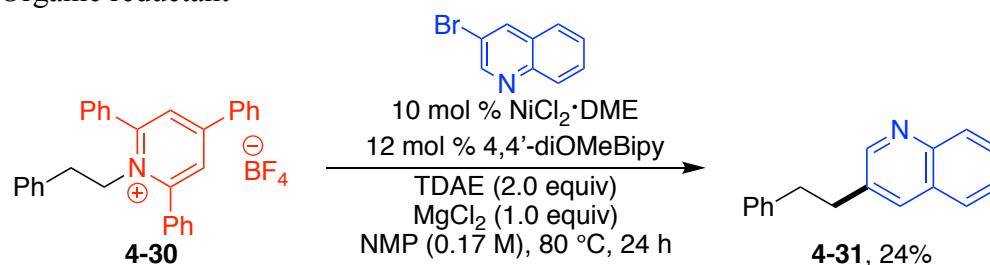


B.  Cyclopropyl ring-opening
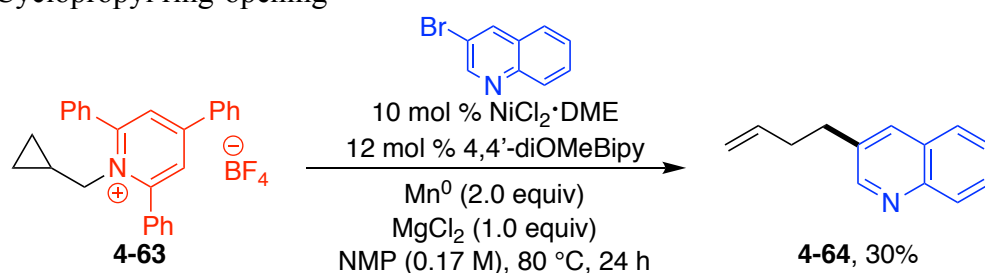


C.  TEMPO trapping
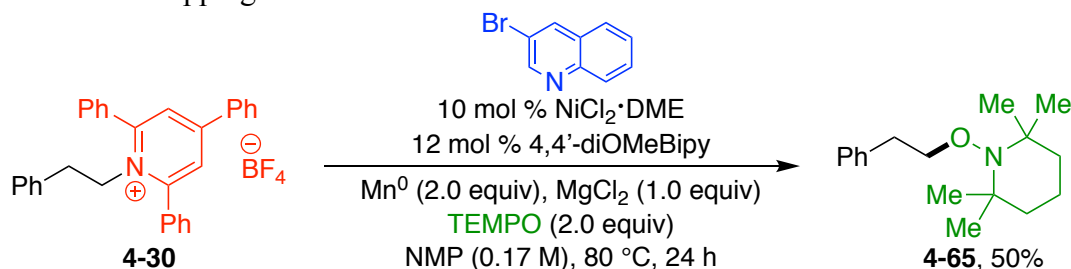


Yields determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

Based on observations made in related cross-couplings of alkyl halides, the two most likely mechanistic pathways involving alkyl radical intermediates are shown in Scheme 4.20. The proposed radical-chain bimetallic pathway (*vide supra*) is shown on the left. The other major competing mechanism invokes a radical rebound pathway (Scheme 4.20, right). In this case, low valent $Ni^0$ species **A** undergoes oxidative addition into the aryl halide to form $Ni^{II}$-arene species **B**. This is followed by a single-electron reduction to generate $Ni^I$-arene **C**. Oxidative addition of the alkyl pyridinium salt via single electron transfer and recombination leads to diorgano-$Ni^{III}$ species **D**, which is primed to undergo reductive elimination forming arylated product and $Ni^I$-X species **E**. Finally, the cycle is turned over via a single-electron reduction of **E** back to $Ni^0$ species **A** by manganese.

Scheme 4.20  Two possible mechanisms for the reductive coupling of alkyl pyridinium salts with aryl bromides
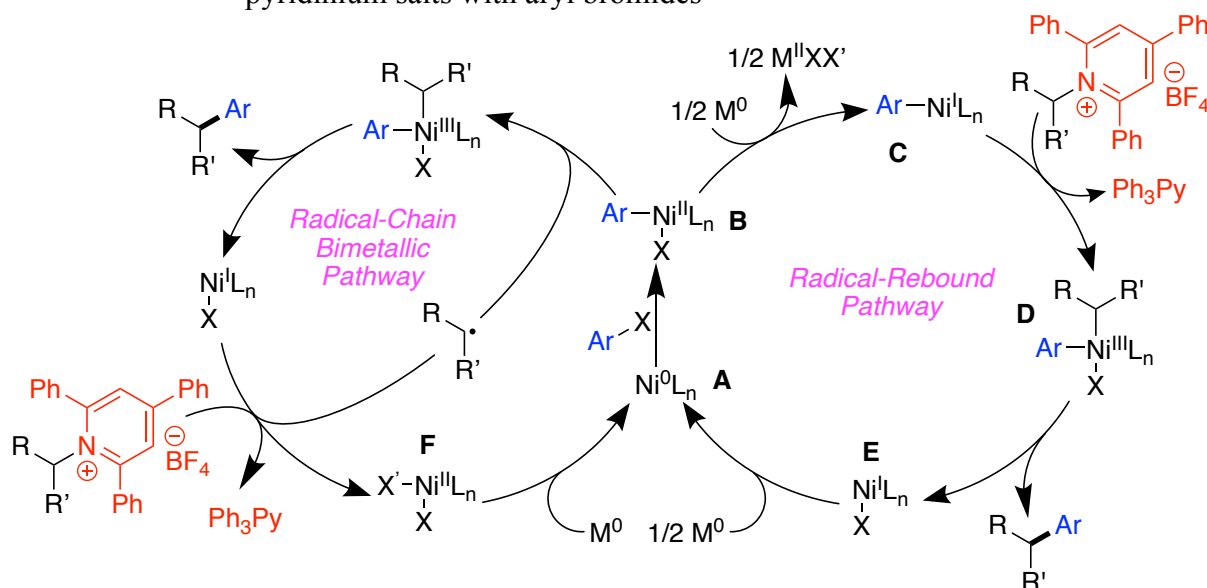


Notably, the role of manganese is unique in each pathway. In the radical-chain bimetallic pathway, manganese is required to reduce $Ni^{II}$ species **F** back to $Ni^0$ species

**A** and turn over the catalytic cycle. However, in the radical-rebound pathway, manganese is involved in both reduction of Ni$^{II}$-arene **B** to Ni$^{I}$-arene **C** as well as reduction of Ni$^{I}$ species **F** back to Ni$^{0}$ species **A**. In this case, manganese is required for catalyst turnover and for one of the elementary steps of the catalytic cycle. A stoichiometric nickel study in the absence of manganese would help differentiate between the two mechanisms. In the case of the former mechanism, the lack of a reductant should have little or no effect on the reaction if it is only required for catalyst turnover. However, in the latter mechanism, the absence of manganese should prevent the desired pathway from proceeding, leading to little or no product formation. In utilizing a stoichiometric amount of Ni$^{0}$, the desired product **4-31** was observed in substantial yield (Scheme 4.21). This is evidence against the radical-rebound pathway. Notably, however, there are other ways to get to Ni$^{I}$-arene species **C** such as comproportionation of **A** and **B**, and therefore we cannot currently rule out this possibility. Moreover, although initiation of this reaction has not been studied in detail, it may involve Mn$^{0}$ or one of the Ni intermediates (on- or off-cycle). Further mechanistic studies are needed to confirm our proposed radical-chain bimetallic pathway.

Scheme 4.21   Stoichiometric Ni$^{0}$ study
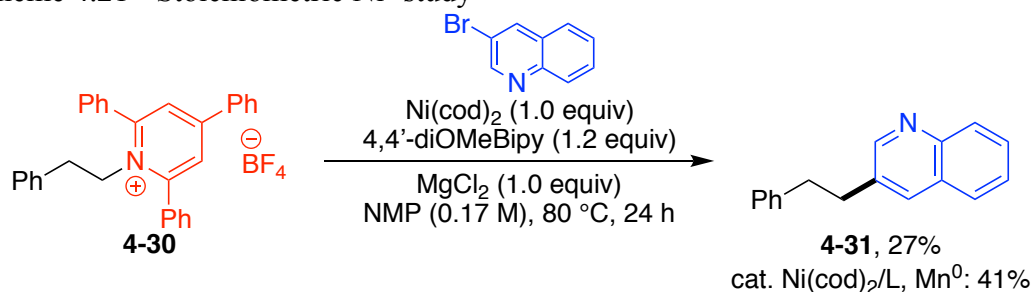


Yield determined by $^{1}$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

## 4.3 Conclusion

In summary, I have developed a reductive cross-electrophile coupling of alkyl pyridinium salts with aryl bromides. This approach leverages the wide availability of alkyl amines and aryl halides for the construction of new carbon-carbon bonds. Additionally, this method demonstrates increased scope compared to the initial Suzuki–Miyaura cross-coupling. Notably, substrates containing acidic protons, eliminatable hydrogens, or epimerizable stereocenters were well tolerated. We have also shown the applicability of this chemistry to amino acid derivatives, pharmaceuticals, and pharmaceutical intermediates. Preliminary mechanistic data supports a radical-chain bimetallic pathway.

## 4.4 Experimental

### 4.4.1 General Information

Reactions were performed in oven-dried Schlenk flasks or in oven-dried round-bottomed flasks unless otherwise noted. Round-bottomed flasks were fitted with rubber septa, and reactions were conducted under a positive pressure of $N_2$. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Silica gel chromatography was performed on silica gel 60 (40-63 μm, 60Å) unless otherwise noted. Commercial reagents were purchased from Sigma Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, AK Scientific, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: anhydrous NMP degassed by sparging with $N_2$ for 20–30 minutes prior to use in the cross-coupling reactions; $CH_2Cl_2$ was dried by passing through drying columns.[26] Powdered, activated 4Å molecular sieves were prepared by heating sieves to ~200°C under high

vacuum overnight and then crushing to achieve a fine powder. In some instances oven-dried potassium carbonate was added to $CDCl_3$ to remove trace acid. Proton nuclear magnetic resonance ($^1H$ NMR) spectra, carbon nuclear magnetic resonance ($^{13}C$ NMR) spectra, and fluorine nuclear magnetic resonance spectra ($^{19}F$ NMR) were recorded on both 400 MHz and 600 MHz spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3 = \delta$ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3 = \delta$ 77.16). Chemical shifts for fluorine were externally referenced to $CFCl_3$ in $CDCl_3$ ($CFCl_3 = \delta$ 0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, hept = heptet), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using FTIR spectrophotometers with material loaded onto a KBr plate. The mass spectral data were obtained at the University of Delaware mass spectrometry facility. Melting points were taken on a Thomas-Hoover Uni-Melt Capillary Melting Point Apparatus.

### 4.4.2 General Optimization Procedure

In a $N_2$-filled glovebox: To an oven-dried 1-dram vial was added nickel salt (0.010 mmol, 10 mol %), ligand (0.012 mmol, 12 mol %), additive (0.1 mmol, 1.0 equiv), reductant (0.3 mmol, 3.0 equiv), and pyridinium salt **4-30**. 3-Bromoquinoline (15 μL, 0.11 mmol, 1.1 equiv) was then added to the vial followed by solvent. The vial was then equipped with a stir bar, capped with a Teflon-coated cap, and removed from the glovebox. The resulting mixture was stirred vigorously at 80 °C for 24 h. The

mixture was then diluted with EtOAc (1.5 mL), filtered through a short plug of silica gel, and the filter cake was washed with EtOAc (10 mL). The filtrate was then washed with brine (2 x 5 mL), dried with MgSO$_4$, and concentrated. 1,3,5-Trimethoxybenzene (internal standard) and CDCl$_3$ were added, and the yield was determined by $^1$H NMR analysis.

### 4.4.3 Reductive Cross-Electrophile Coupling of Alkyl Pyridinium Salts with Aryl Bromides
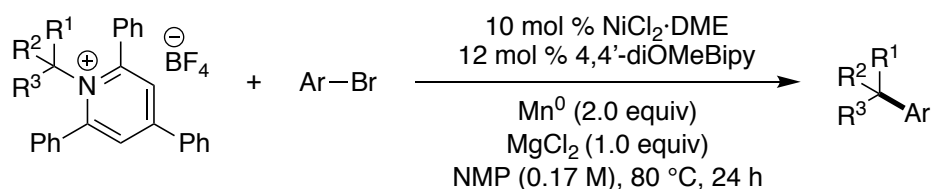


### 4.4.3.1 General Procedure A: Cross-Coupling of Primary Alkyl Pyridinium Salts

To an oven-dried, 25-mL Schlenk flask was added NiCl$_2$·DME (22 mg, 0.10 mmol, 10 mol %), 4,4'-dimethoxy-2,2'-bipyridine (26 mg, 0.12 mmol, 12 mol %), magnesium chloride (95 mg, 1.0 mmol, 1.0 equiv), manganese powder (110 mg, 2.0 mmol, 2.0 equiv), alkyl pyridinium salt (1.2 mmol, 1.2 equiv), and arylbromide (1.0 mmol, 1.0 equiv), if solid. The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). If the arylbromide was a liquid, it was introduced via syringe at this point. *N*-Methyl-2-pyrrolidone (6.0 mL) was added, and the flask was sealed. The resulting mixture was stirred at 80 °C for 24 hours. The mixture was then allowed to cool to room temperature, filtered through a short plug of silica gel, and the filter cake washed with ethyl acetate (4 x 25 mL). The

filtrate was then washed with brine (4 x 25 mL). The combined aqueous layers were back-extracted with ethyl acetate (1 x 25 mL). The combined organic layers were dried with magnesium sulfate and concentrated. The cross-coupled product was then purified via silica gel chromatography.

### 4.4.3.2 General Procedure B: Cross-Coupling of Secondary Alkyl Pyridinium Salts

To an oven-dried, 25-mL Schlenk flask was added NiCl$_2$·DME (22 mg, 0.10 mmol, 10 mol %), 4,4'-dimethoxy-2,2'-bipyridine (26 mg, 0.12 mmol, 12 mol %), magnesium chloride (95 mg, 1.0 mmol, 1.0 equiv), and manganese powder (110 mg, 2.0 mmol, 2.0 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). *N*-Methyl-2-pyrrolidone (4.0 mL) was added, and the resultant mixture was heated to 80 °C. To a separate oven-dried, 10-mL Schlenk flask was added alkyl pyridinium salt (1.0 mmol, 1.0 equiv) and arylbromide (1.1 mmol, 1.1 equiv), if solid. The flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N$_2$ (x 3). If the arylbromide was a liquid, it was introduced via syringe at this point. *N*-Methyl-2-pyrrolidone (2.0 mL) was added and the contents transferred into a 3-mL nitrogen-purged leur-lock syringe. The solution was added at a steady rate into the flask containing the catalyst mixture via syringe pump over a period of six hours. The resulting mixture was stirred at 80 °C for an additional 18 hours (24 hours total). The mixture was then allowed to cool to room temperature, filtered through a short plug of silica gel, and the filter cake washed with ethyl acetate (4 x 25 mL). The filtrate was then washed with brine (4 x 25 mL). The combined aqueous layers were back-extracted with ethyl acetate (1 x 25 mL). The

combined organic layers were dried with magnesium sulfate and concentrated. The cross-coupled product was then purified via silica gel chromatography.
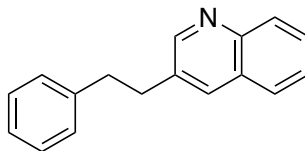


**3-Phenethylquinoline (4-31)**. Prepared via General Procedure A using 1-phenethyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (10–50% ethyl acetate/hexanes) to give **4-31** (run 1: 201 mg, 86%; run 2: 195 mg, 84%) as a pale yellow oil: ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.75 (d, $J$ = 2.2 Hz, 1H), 8.08 (d, $J$ = 8.5 Hz, 1H), 7.88 − 7.85 (m, 1H), 7.77 − 7.72 (m, 1H), 7.69 − 7.63 (m, 1H), 7.55 − 7.49 (m, 1H), 7.29 (t, $J$ = 7.5 Hz, 2H), 7.23 − 7.14 (m, 3H), 3.13 (t, $J$ = 7.8 Hz, 2H), 3.03 (t, $J$ = 7.8 Hz, 2H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 152.0, 146.9, 140.8, 134.4, 134.2, 129.2, 128.7, 128.5, 128.1, 127.3, 126.6, 126.2, 37.5, 35.1. The spectral data matches that reported in the literature.[27]
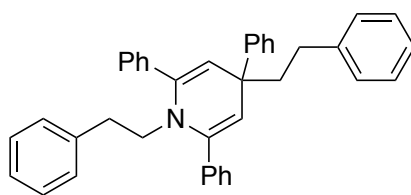


**1,4-Diphenethyl-2,4,6-triphenyl-1,4-dihydropyridine (4-32)**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (s, 6H), 7.44 − 7.35 (m, 8H), 7.25 − 7.11 (m, 6H), 7.04 − 6.95 (m, 3H), 6.51 − 6.44 (m, 2H), 5.18 (s, 2H), 3.29 − 3.20 (m, 2H), 2.72 − 2.63 (m, 2H), 2.37 − 2.28 (m, 2H), 2.20 − 2.11 (m, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 151.4, 143.1, 143.0, 139.1, 138.0, 128.42, 128.39, 128.37, 128.35, 128.3, 128.11, 128.08, 128.00,

126.4, 125.8, 125.6, 125.5, 113.3, 50.0, 46.7, 43.8, 34.7, 32.7; HRMS (ESI+) [M+H]$^+$ calculated for $C_{39}H_{36}N$: 518.2842, found 518.2823.
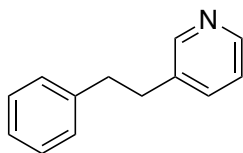


**3-Phenethylpyridine (4-43)**. Prepared via General Procedure A using 1-phenethyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (5–60% ether/hexanes w/ 1% Et$_3$N) to give **4-43** (run 1: 115 mg, 63%; run 2: 110 mg, 60%) as a pale yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.45 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.44 – 8.41 (m, 1H), 7.43 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.23 – 7.13 (m, 4H), 2.93 (s, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 150.2, 147.6, 141.0, 136.9, 136.0, 128.59, 128.57, 126.3, 123.3, 37.6, 35.1. The spectral data matches that reported in the literature.[28]
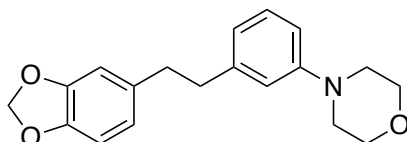


**4-(3-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)phenyl)morpholine (4-44)**. Prepared via General Procedure A using 1-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (5–20% ethyl acetate/hexanes) to give **4-44** (run 1: 164 mg, 53%; run 2: 181 mg, 58%) as an off-white solid (mp 44–46 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 7.20 (t, *J* = 7.8 Hz, 1H), 6.76 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.74 – 6.70 (m, 3H), 6.68 (d, *J* = 1.6 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 3.88 – 3.83 (m, 4H), 3.16 – 3.11 (m, 4H), 2.83 (s, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 151.4, 147.5, 145.6, 142.7,

135.7, 129.1, 121.2, 120.3, 116.1, 113.4, 109.0, 108.1, 100.8, 67.0, 49.5, 38.6, 37.7; FTIR (neat) 2853, 1600, 1489, 1443, 1242, 1121, 928, 696 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for $C_{19}H_{22}NO_3$: 312.1594, found 312.1590.
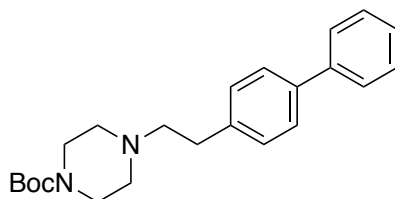


***tert*-Butyl 4-(2-([1,1'-biphenyl]-4-yl)ethyl)piperazine-1-carboxylate (4-45)**. Prepared via General Procedure A using 1-(2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (10–20% ethyl acetate/hexanes) to give **4-45** (run 1: 268 mg, 73%; run 2: 275 mg, 75%) as a white solid (mp 85–89 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 – 7.55 (m, 2H), 7.55 – 7.48 (m, 2H), 7.48 – 7.39 (m, 2H), 7.38 – 7.31 (m, 1H), 7.31 – 7.27 (m, 2H), 3.52 – 3.44 (m, 4H), 2.90 – 2.81 (m, 2H), 2.69 – 2.60 (m, 2H), 2.52 – 2.46 (m, 4H), 1.47 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 154.8, 141.0, 139.2, 139.1, 129.1, 128.8, 127.2, 127.1, 127.0, 79.7, 60.5, 53.0, 33.2, 28.5; FTIR (neat) 2929, 2807, 1695, 1420, 1247, 1171, 1003, 761 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for $C_{23}H_{31}N_2O_2$: 367.2380, found 367.2376.
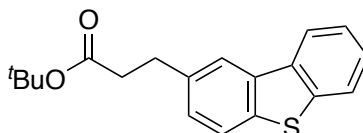


***tert*-Butyl 3-(dibenzo[*b,d*]thiophen-2-yl)propanoate (4-46)**. Prepared via General Procedure A using 1-(3-(*tert*-butoxy)-3-oxopropyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (2–

10% diethyl ether/hexanes) to give **4-46** (run 1: 200 mg, 64%; run 2: 199 mg, 64%) as a white solid (mp 53–55 °C): $^1$H NMR (600 MHz, CDCl$_3$) δ 8.19 – 8.13 (m, 1H), 8.02 (s, 1H), 7.90 – 7.84 (m, 1H), 7.79 (d, $J$ = 8.2 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.37 – 7.32 (m, 1H), 3.12 (t, $J$ = 7.8 Hz, 2H), 2.67 (t, $J$ = 7.8 Hz, 2H), 1.45 (s, 9H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 172.2, 139.8, 137.23, 137.21, 135.8, 135.4, 127.5, 126.6, 124.3, 122.9, 122.7, 121.5, 121.2, 80.5, 37.5, 31.2, 28.1; FTIR (neat) 2976, 2930, 1726, 1366, 1150, 764 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{19}$H$_{21}$O$_2$S: 313.1257, found 313.1245.
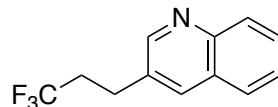


**3-(3,3,3-Trifluoropropyl)quinoline (4-47)**. Prepared via General Procedure A using 2,4,6-triphenyl-1-(3,3,3-trifluoropropyl)pyridin-1-ium tetrafluoroborate.    The crude mixture was purified by silica gel chromatography (10–40% ethyl acetate/hexanes) to give **4-47** (run 1: 188 mg, 84%; run 2: 173 mg, 77%) as a pale yellow solid (mp 54–55 °C): $^1$H NMR (400 MHz, CDCl$_3$) δ 8.80 (d, $J$ = 2.3 Hz, 1H), 8.10 (d, $J$ = 8.5 Hz, 1H), 7.97 (d, $J$ = 1.3 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.75 – 7.66 (m, 1H), 7.60 – 7.51 (m, 1H), 3.14 – 3.05 (m, 2H), 2.60 – 2.43 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.3, 147.2, 134.5, 131.5, 129.3, 129.2, 127.9, 127.4, 127.0, 126.4 (q, $J_{C-F}$ = 276.9 Hz), 35.3 (q, $J_{C-F}$ = 28.8 Hz), 25.7 (q, $J_{C-F}$ = 3.3 Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) δ – 66.43; FTIR (neat) 2955, 1496, 1235, 1143, 1097, 976, 756 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{12}$H$_{11}$F$_3$N: 226.0838, found 266.0838.
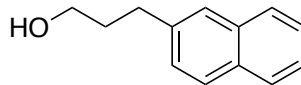
**3-(Naphthalen-2-yl)propan-1-ol (4-48)**. Prepared via General Procedure A using 1-(3-hydroxypropyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (10–40% ethyl acetate/hexanes) to give 4-48 (run 1: 145 mg, 78%; run 2: 137 mg, 74%) as a white solid: $^1$H NMR (600 MHz, CDCl$_3$) δ 7.73 (d, $J$ = 8.0 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.57 (s, 1H), 7.40 – 7.33 (m, 2H), 7.30 – 7.26 (m, 1H), 3.64 (t, $J$ = 6.4 Hz, 2H), 2.84 – 2.78 (m, 2H), 1.96 – 1.88 (m, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 139.30, 133.64, 132.03, 127.97, 127.61, 127.40, 127.27, 126.43, 125.94, 125.18, 62.28, 34.10, 32.22. The spectral data matches that reported in the literature.[29]
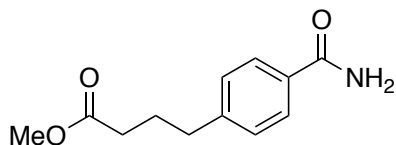


**Methyl 4-(4-carbamoylphenyl)butanoate (4-49)**. Prepared via General Procedure A using 1-(4-methoxy-4-oxobutyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (50–100% ethyl acetate/hexanes) to give **4-49** (run 1: 103 mg, 46%; run 2: 125 mg, 56%) as a light pink solid: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.74 (d, $J$ = 8.2 Hz, 2H), 7.26 (d, $J$ = 8.0 Hz, 2H, *overlaps with CHCl$_3$*), 6.06 (s, br, 1H), 5.69 (s, br, 1H), 3.67 (s, 3H), 2.70 (t, $J$ = 7.6 Hz, 2H), 2.33 (t, $J$ = 7.4 Hz, 2H), 1.97 (p, $J$ = 7.5 Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.7, 169.2, 145.9, 131.1, 128.8, 127.6, 51.6, 35.0, 33.3, 26.2; HRMS (ESI+) [M+H]$^+$ calculated for C$_{12}$H$_{16}$NO$_3$: 222.1125, found 222.1124.
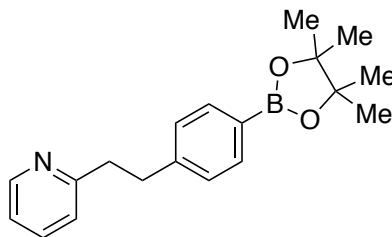
**2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenethyl)pyridine** **(4-50)**.

Prepared via General Procedure A using 2,4,6-triphenyl-1-(2-(pyridin-2-yl)ethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (2–10% ethyl acetate/hexanes) to give **4-50** (run 1: 183 mg, 59%; run 2: 203 mg, 66%) as a white solid: $^{1}$H NMR (400 MHz, CDCl$_3$) δ 8.59 – 8.52 (m, 1H), 7.72 (d, $J$ = 8.0 Hz, 2H), 7.55 (td, $J$ = 7.7, 1.9 Hz, 1H), 7.21 (d, $J$ = 7.9 Hz, 2H), 7.13 – 7.08 (m, 1H), 7.08 – 7.01 (m, 1H), 3.13 – 3.02 (m, 4H), 1.33 (s, 12H); $^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO) δ 161.9, 150.13, 150.11, 146.2, 137.0, 135.6, 128.8, 123.7, 122.0, 84.4, 40.5, 36.5, 25.2; HRMS (ESI+) [M+H]$^{+}$ calculated for C$_{19}$H$_{25}$BNO$_2$: 310.1973, found 310.1972.
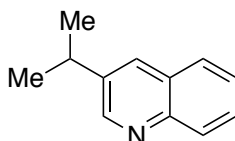


**3-Isopropylquinoline (4-34)**. Prepared via General Procedure B using 1-isopropyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (5–15% ethyl acetate/hexanes) to give **4-34** (run 1: 119 mg, 70%; run 2: 118 mg, 69%) as a yellow oil: $^{1}$H NMR (400 MHz, CDCl$_3$) δ 8.84 (d, $J$ = 2.3 Hz, 1H), 8.07 (d, $J$ = 8.5 Hz, 1H), 7.93 (d, $J$ = 2.2 Hz, 1H), 7.82 – 7.75 (m, 1H), 7.70 – 7.61 (m, 1H), 7.56 – 7.47 (m, 1H), 3.14 (hept, $J$ = 7.0 Hz, 1H), 1.38 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.3, 146.9, 141.1, 131.8, 129.1, 128.5,

128.2, 127.5, 126.5, 31.9, 23.7. The spectral data matches that reported in the literature.[30]
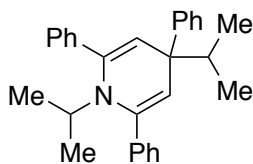


**1,4-Diisopropyl-2,4,6-triphenyl-1,4-dihydropyridine (4-35)**: ^{1}H NMR (400 MHz, CDCl₃) δ 7.67 – 7.60 (m, 4H), 7.50 – 7.43 (m, 2H), 7.42 – 7.29 (m, 8H), 7.20 – 7.12 (m, 1H), 5.29 (s, 2H), 3.30 (hept, $J$ = 6.9 Hz, 1H), 2.01 (hept, $J$ = 6.8 Hz, 1H), 0.78 (d, $J$ = 6.8 Hz, 6H), 0.58 (d, $J$ = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, CDCl₃) δ 151.7, 145.2, 140.9, 128.2, 128.0, 127.9, 127.7, 126.8, 125.1, 115.3, 53.6, 47.0, 39.5, 22.6, 18.4; HRMS (ESI+) [M+H]⁺ calculated for $C_{29}H_{32}N$: 394.2529, found 394.2513.
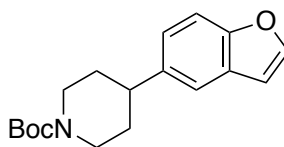


***tert*-Butyl 4-(benzofuran-5-yl)piperidine-1-carboxylate (4-51)**. Prepared via General Procedure B using 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (2–10% ethyl acetate/hexanes) to give **4-51** (run 1: 218 mg, 72%; run 2: 210 mg, 70%) as a white solid: ^{1}H NMR (600 MHz, CDCl₃) δ 7.62 – 7.58 (m, 1H), 7.44 – 7.40 (m, 2H), 7.17 – 7.12 (m, 1H), 6.73 (s, 1H), 4.37 – 4.17 (br m, 2H), 2.92 – 2.77 (m, 2H), 2.74 (tt, $J$ = 12.2, 3.6 Hz, 1H), 1.89 – 1.83 (m, 2H), 1.73 – 1.62 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (151 MHz, CDCl₃) δ 154.9, 153.7, 145.3, 140.5, 127.6, 123.4,

118.7, 111.2, 106.5, 79.4, 44.5 (br), 42.7, 33.8, 28.5. The spectral data matches that reported in the literature.[9]
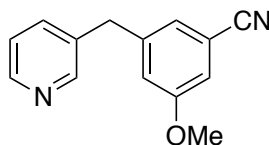


**3-Methoxy-5-(pyridin-3-ylmethyl)benzonitrile (4-52)**. Prepared via General Procedure B using 2,4,6-triphenyl-1-(pyridin-3-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (20–60% ethyl acetate/hexanes) to give **4-52** (run 1: 129 mg, 58%, run 2: 127 mg, 57%) as an off-white solid (mp 74–78 °C): ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.54 – 8.46 (m, 2H), 7.49 – 7.41 (m, 1H), 7.26 – 7.23 (m, 1H), 7.08 – 7.04 (m, 1H), 7.03 – 6.98 (m, 1H), 6.95 – 6.90 (m, 1H), 3.97 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.9, 150.1, 148.3, 142.8, 136.3, 134.8, 124.8, 123.7, 120.0, 118.6, 114.8, 113.4, 55.6, 38.6; FTIR (neat) 3029, 2923, 2841, 2228, 1591, 1292, 1059, 718 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{14}$H$_{13}$N$_2$O: 225.1022, found 255.1021.
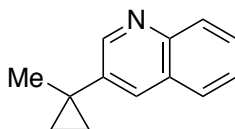


**3-(1-Methylcyclopropyl)quinoline (4-53)**. Prepared via General Procedure B using 1-(1-methylcyclopropyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (5–20% ethyl acetate/hexanes) to give **4-53** (run 1: 61 mg. 33%, run 2: 65 mg, 36%) as a yellow oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.84 (d, $J$ = 2.3 Hz, 1H), 8.06 (d, $J$ = 8.4 Hz, 1H), 7.99 – 7.93 (m, 1H), 7.76 (d, $J$ = 8.1 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.56 – 7.47 (m, 1H), 1.51 (s, 3H),

1.00 (t, $J$ = 5.4 Hz, 2H), 0.87 (t, $J$ = 5.4 Hz, 2H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 151.0, 146.5, 139.6, 132.9, 129.1, 128.5, 127.9, 127.3, 126.6, 25.6, 18.4, 15.0; FTIR (neat) 3076, 3001, 2958, 2925, 2870, 1492, 1016, 750 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{13}$H$_{14}$N: 184.1121; found 184.1116.
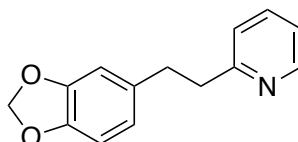


**2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)pyridine (4-54)**. Prepared via General Procedure A using 1-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (5–40% ether/hexanes) to give **4-54** (run 1: 83 mg, 36%; run 2: 77 mg, 34%) as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.57 – 8.54 (m, 1H), 7.56 (td, $J$ = 7.7, 1.9 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.71 (d, $J$ = 7.9 Hz, 1H), 6.69 (d, $J$ = 1.6 Hz, 1H), 6.63 (dd, $J$ = 7.9, 1.7 Hz, 1H), 5.91 (s, 2H), 3.07 – 3.01 (m, 2H), 3.00 – 2.94 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.2, 149.5, 147.6, 145.8, 136.4, 135.5, 123.1, 121.34, 121.31, 109.1, 108.3, 100.9, 40.7, 35.9. The spectral data matches that reported in the literature.[31]
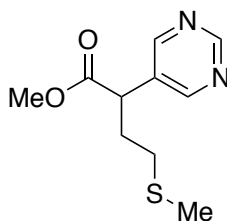


**Methyl 4-(methylthio)-2-(pyrimidin-5-yl)butanoate (4-55)**. Prepared via General Procedure B using 1-(1-methoxy-4-(methylthio)-1-oxobutan-2-yl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified via silica gel

chromatography (5–30% ethyl acetate/hexanes) to give **4-55** (run 1: 113 mg, 50%; run 2: 116 mg, 51%) as a pale yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 9.15 (s, 1H), 8.71 (s, 2H), 3.87 – 3.82 (m, 1H), 3.71 (s, 3H), 2.54 – 2.34 (m, 3H), 2.12 – 2.01 (m, 1H), 2.07 (s, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.6, 158.1, 156.7, 132.1, 52.8, 45.4, 31.9, 31.6, 15.4; FTIR (neat) 2917, 1736, 1561, 1412, 1203, 728 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{10}$H$_{15}$N$_2$O$_2$S: 227.0849, found 227.0851.
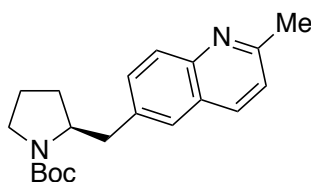


***tert*-Butyl (*S*)-2-((2-methylquinolin-6-yl)methyl)pyrrolidine-1-carboxylate (4-56)**. Prepared via General Procedure B using (*S*)-1-((1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified via silica gel chromatography (10–50% ethyl acetate/hexanes) to give 4-56 (run 1: 191 mg, 59%; run 2: 182 mg, 56%) as a yellow oil (mixture of rotamers): $^1$H NMR (400 MHz, CDCl$_3$) δ 8.03 – 7.92 (m, br, 2H), 7.62 – 7.49 (m, br, 2H), 7.31 – 7.26 (m, br, 1H, *overlaps with CHCl$_3$*), 4.16 – 4.02 (m, br, 1H), 3.44 – 3.15 (m, br, 3H), 2.80 – 2.65 (m, br, 1H), 2.74 (s, br, 3H), 1.81 – 1.70 (m, br, 4H), 1.51 (s, br, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.5 (major), 158.3 (minor), 154.6 (minor), 154.6 (major), 146.6, 136.8 (minor), 135.9 (major), 132.0 (minor), 131.4 (major), 128.5 (major), 128.2 (minor), 127.4, 127.3, 126.5, 122.2 (major), 122.0 (minor), 79.4 (major), 79.2 (minor), 58.7, 46.9 (minor), 46.3 (major), 40.5 (major), 39.5 (minor), 29.8 (major), 29.0 (minor), 28.6, 25.3, 23.5 (minor), 22.7 (major); FTIR (neat) 2972, 2875, 1691, 1395, 1170, 1116, 772 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{20}$H$_{27}$N$_2$O$_2$: 327.2067, found 327.2066. The enantiomeric excess was determined to

be >99% by chiral HPLC analysis (CHIRALPAK IA, 0.2 mL/min, 2% *i*-PrOH/hexanes, $\lambda$=210 nm); $t_R$(major) = 103.75 min, $t_R$(minor) = 111.85 min.
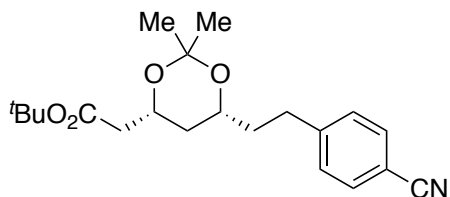


***tert*-Butyl 2-((4*R*,6*R*)-6-(4-cyanophenethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (4-58)**. Prepared via General Procedure B using 1-(2-((4*R*,6*R*)-6-(2-(*tert*-butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified via silica gel chromatography (5–60% ether/hexanes) to give 4-58 (run 1: 191 mg, 53%; run 2: 219 mg, 61%) as a clear oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.23 (dtd, *J* = 11.5, 6.5, 2.5 Hz, 1H), 3.86 – 3.74 (m, 1H), 2.91 – 2.65 (m, 2H), 2.45 (dd, *J* = 15.2, 6.9 Hz, 1H), 2.31 (dd, *J* = 15.2, 6.3 Hz, 1H), 1.90 – 1.76 (m, 1H), 1.78 – 1.64 (m, 1H), 1.56 (dt, *J* = 12.7, 2.4 Hz, 1H), 1.46 (s, 9H), 1.43 (s, 3H), 1.41 (s, 3H), 1.29 – 1.19 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.3, 147.8, 132.2, 129.3, 119.1, 109.7, 98.8, 80.7, 67.5, 66.2, 42.6, 37.3, 36.5, 31.4, 30.1, 28.1, 19.8; FTIR (neat) 2980, 2227, 1729, 1368, 1159, 845 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{21}$H$_{30}$NO$_4$: 360.2169, found 360.2167.
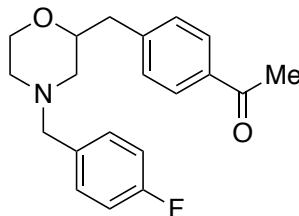
**1-(4-((4-(4-Fluorobenzyl)morpholin-2-yl)methyl)phenyl)ethan-1-one** **(4-59)**.
Prepared via General Procedure A using 1-((4-(4-fluorobenzyl)morpholin-2-yl)methyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (20–75% ethyl acetate/hexanes w/ 1% Et$_3$N) to give **4-59** (run 1: 244 mg, 77%; run 2: 258 mg, 82%) as a pale yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.92 – 7.85 (m, 2H), 7.33 – 7.28 (m, 2H), 7.28 – 7.21 (m, 2H, *overlaps with CHCl$_3$*), 7.04 – 6.94 (m, 2H), 3.88 – 3.80 (m, 1H), 3.80 – 3.71 (m, 1H), 3.59 (td, *J* = 11.3, 2.5 Hz, 1H), 3.51 – 3.35 (m, 2H), 2.86 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.78 – 2.66 (m, 2H), 2.65 – 2.55 (m, 1H), 2.58 (s, 3H), 2.13 (td, *J* = 11.3, 3.3 Hz, 1H), 1.99 – 1.89 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.0, 162.2 (d, *J* = 245.1 Hz), 144.2, 135.52, 133.46 (d, *J* = 3.1 Hz), 130.7 (d, *J* = 8.0 Hz), 129.6, 128.6, 115.2 (d, *J* = 21.2 Hz), 76.2, 67.0, 62.5, 58.4, 52.8, 40.3, 26.8; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -115.59; FTIR (neat) 2935, 2805, 1682, 1268, 842 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{20}$H$_{23}$FNO$_2$: 328.1707, found 328.1703.
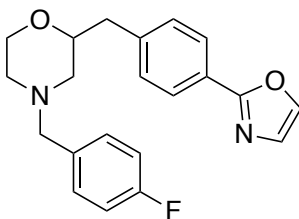


**4-(4-Fluorobenzyl)-2-(4-(oxazol-2-yl)benzyl)morpholine** **(4-60)**. Prepared via General Procedure A using 1-((4-(4-fluorobenzyl)morpholin-2-yl)methyl)-2,4,6-

triphenylpyridin-1-ium tetrafluoroborate on a 4 mmol scale. The crude mixture was purified by silica gel chromatography (10–15% ethyl acetate/hexanes) to give **4-60** (1041 mg, 74%) as a pale yellow oil: ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.96 (d, $J$ = 8.3 Hz, 2H), 7.69 (s, 1H), 7.30 (d, $J$ = 8.1 Hz, 2H), 7.28 – 7.23 (m, 2H, *overlaps with CHCl$_3$*), 7.22 (s, 1H), 6.99 (t, $J$ = 8.7 Hz, 2H), 3.87 – 3.81 (m, 1H), 3.81 – 3.74 (m, 1H), 3.65 – 3.57 (m, 1H), 3.48 (d, $J$ = 13.0 Hz, 1H), 3.39 (d, $J$ = 13.0 Hz, 1H), 2.87 (dd, $J$ = 14.0, 7.4 Hz, 1H), 2.76 – 2.69 (m, 2H), 2.60 (d, $J$ = 11.2 Hz, 1H), 2.17 – 2.10 (m, 1H), 1.95 (t, $J$ = 10.5 Hz, 1H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 162.05 (d, $J$ = 244.9 Hz), 162.04, 140.8, 138.3, 133.4 (d, $J$ = 3.2 Hz), 130.5 (d, $J$ = 7.9 Hz), 129.7, 128.4, 126.4, 125.7, 115.1 (d, $J$ = 21.2 Hz), 76.2, 66.9, 62.4, 58.3, 52.7, 40.1; ^{19}F NMR (565 MHz, CDCl$_3$) δ −115.72; FTIR (neat) 3125, 3040, 2935, 2856, 2805, 1921, 1509, 1221, 1112, 846, 715 cm$^{-1}$; HRMS (ESI+) [M+H]$^+$ calculated for C$_{21}$H$_{22}$FN$_2$O$_2$: 353.1660, found 353.1654.
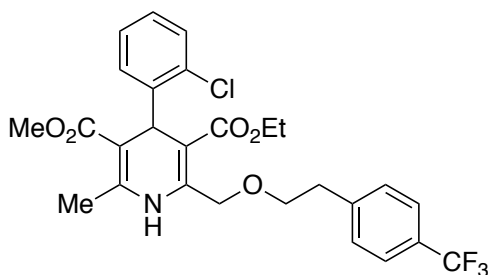


**3-Ethyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-((4-(trifluoromethyl)phenethoxy)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (4-61)**. Prepared via General Procedure A using 1-(2-((4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridin-2-yl)methoxy)ethyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified via silica gel chromatography (5–40% ethyl acetate/hexanes) to give 4-61

(run 1: 326 mg, 61%; run 2: 357 mg, 67%) as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, $J$ = 7.7 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.31 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.22 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.16 – 7.07 (m, 1H), 7.08 – 6.99 (m, 1H), 6.68 (s, 1H), 5.36 (s, 1H), 4.79 – 4.62 (m, 2H), 4.10 – 3.97 (m, 2H), 3.88 – 3.73 (m, 2H), 3.60 (s, 3H), 3.02 (t, $J$ = 6.3 Hz, 2H), 2.08 (s, 3H), 1.17 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.93, 167.14, 145.61, 145.12, 143.64, 142.96, 132.35, 131.46, 129.28, 129.27, 129.04 (q, $J$ = 32.5 Hz), 127.40, 126.82, 125.56 (q, $J$ = 3.7 Hz), 123.71 (q, $J$ = 271.7 Hz), 103.92, 101.43, 71.44, 67.68, 59.84, 50.84, 37.18, 35.95, 19.26, 14.28; $^{19}$F NMR (376 MHz, CDCl$_3$) δ –62.43; HRMS (ESI+) [M+H]$^+$ calculated for C$_{27}$H$_{28}$ClF$_3$NO$_5$: 538.1603, found 538.1590.

# REFERENCES

1. Tasker, S. Z.; Standley, E. A.; Jamison, T. F., *Nature* **2014**, *509*, 299.

2. Weix, D. J., *Accounts of Chemical Research* **2015**, *48*, 1767-1775.

3. Everson, D. A.; Weix, D. J., *The Journal of Organic Chemistry* **2014**, *79*, 4793-4798.

4. Everson, D. A.; Shrestha, R.; Weix, D. J., *J. Am. Chem. Soc.* **2010**, *132*, 920-921.

5. Everson, D. A.; Jones, B. A.; Weix, D. J., *J. Am. Chem. Soc.* **2012**, *134*, 6146-6159.

6. Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J., *J. Am. Chem. Soc.* **2016**, *138*, 5016-5019.

7. Biswas, S.; Weix, D. J., *J. Am. Chem. Soc.* **2013**, *135*, 16192-16197.

8. Wang, S.; Qian, Q.; Gong, H., *Org. Lett.* **2012**, *14*, 3352-3355.

9. Molander, G. A.; Traister, K. M.; O'Neill, B. T., *The Journal of Organic Chemistry* **2014**, *79*, 5771-5780.

10. Molander, G. A.; Traister, K. M.; O'Neill, B. T., *The Journal of Organic Chemistry* **2015**, *80*, 2907-2911.

11. Wang, X.; Wang, S.; Xue, W.; Gong, H., *J. Am. Chem. Soc.* **2015**, *137*, 11562-11565.

12. Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H., *J. Am. Chem. Soc.* **2018**, *140*, 14490-14497.

13. Zhang, P.; Le, C. C.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2016**, *138*, 8084-8087.

14.     Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L., *Angewandte Chemie International Edition* **2015,** *55*, 1849-1853.

15.     Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A., *Angewandte Chemie International Edition* **2008,** *48*, 607-610.

16.     Amatore, M.; Gosmini, C., *Chemistry – A European Journal* **2010,** *16*, 5848-5852.

17.     Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H., *Org. Lett.* **2011,** *13*, 2138-2141.

18.     Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H., *Chemical Science* **2013,** *4*, 4022-4029.

19.     Liu, J.-H.; Yang, C.-T.; Lu, X.-Y.; Zhang, Z.-Q.; Xu, L.; Cui, M.; Lu, X.; Xiao, B.; Fu, Y.; Liu, L., *Chemistry – A European Journal* **2014,** *20*, 15334-15338.

20.     Zhao, C.; Jia, X.; Wang, X.; Gong, H., *J. Am. Chem. Soc.* **2014,** *136*, 17645-17651.

21.     Feng, C.; Cunningham, D. W.; Easter, Q. T.; Blum, S. A., *J. Am. Chem. Soc.* **2016,** *138*, 11156-11159.

22.     Roth, B. D., US4681893A, 1987/07/21/, 1987.

23.     Kato, S.; Morie, T.; Yoshida, N., *CHEMICAL & PHARMACEUTICAL BULLETIN* **1995,** *43*, 699-702.

24.     Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Stubbs, J. K.; Burges, R. A.; Gardiner, D. G.; Blackburn, K. J., *Journal of Medicinal Chemistry* **1986,** *29*, 1696-1702.

25.     Gronborg, H.; Winther, B.; Brofeldt, S.; Borum, P.; Mygind, N., *Rhinology* **1983,** *21*, 3-12.

26.     Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996,** *15*, 1518-1520.

27.     Planellas, M.; Guo, W.; Alonso, F.; Yus, M.; Shafir, A.; Pleixats, R.; Parella, T., *Adv. Synth. Catal.* **2014,** *356*, 179-188.

28.     Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S., *J. Am. Chem. Soc.* **2016,** *138*, 11132-11135.

29.     Wendling, T.; Risto, E.; Krause, T.; Gooßen, L. J., *Chemistry – A European Journal* **2018,** *24*, 6019-6024.

30.     Mierde, H. V.; Voort, P. V. D.; Verpoort, F., *Tetrahedron Letters* **2009,** *50*, 201-203.

31.     Harrowven, D. C.; Sutton, B. J.; Coulton, S., *Organic & Biomolecular Chemistry* **2003,** *1*, 4047-4057.

# Chapter 5

# COPPER-CATALYZED ENANTIOSELECTIVE ALKYNYLATION OF IMINIUM IONS TO FORM α-DIARYL TETRASUBSTITUTED STEREOCENTERS

## 5.1  Introduction

Chirality is present in a wide array of molecules ranging from simple amino acids to complex bioactive molecules. Recognizing the importance of these stereogenic centers, intense efforts have focused on the development of enantioselective methodologies to enable synthesis. In particular, amines bearing an α-diaryl tetrasubstitued stereocenter are found in a number of pharmaceutically relevant molecules (Scheme 5.1).[1-3] Unfortunately, construction of these stereocenters is challenging, and there are a limited number of methods that enable efficient access to these motifs.

Scheme 5.1    Examples of bioactive amines containing an α-diaryl tetrasubstitued stereocenter



**5-1**
BMS-795311
(Bristol-Myers Squibb)
*cholesteryl ester transfer protein inhibitor*

**5-2**
(Pfizer)
*Prostaglandin D synthase inhibitor*

**5-3**
Dizocilpine
(Merck)
*anticonvulsant and anesthetic*
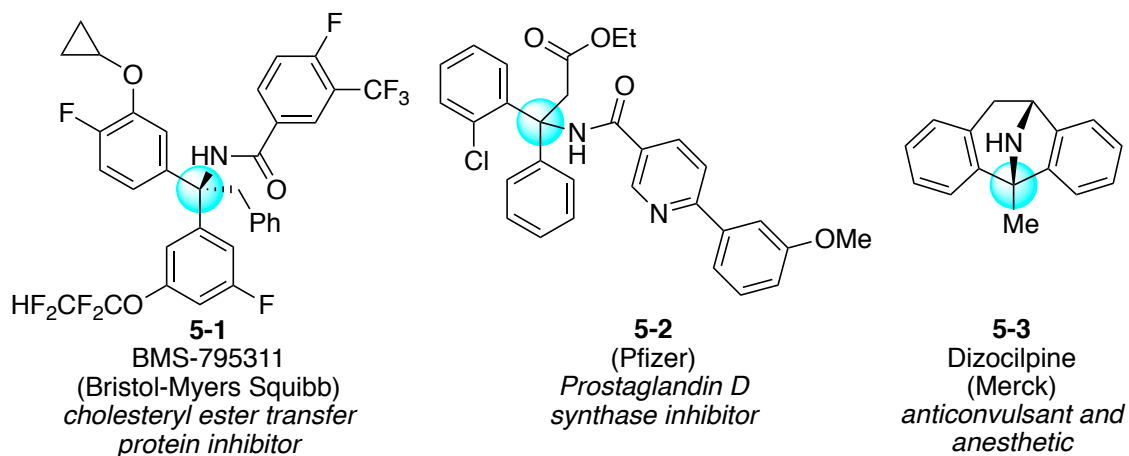
An enantioselective addition of a chiral nucleophile to a prochiral ketimine (**5-4**) would allow access to amines bearing an α-tetrasubstituted stereocenter (**5-5**) (Scheme 5.2, left). Moreover, addition of an alkyne moiety would enable the incorporation of a versatile handle that can be used for further product elaboration (Scheme 5.2, right). For example, product **5-5** can be hydrogenated to form the corresponding alkene or alkane (**5-6**). The alkyne can also participate in click chemistry to form triazole **5-7**. In addition, it can be oxidized to form ketone **5-8**.

Scheme 5.2    Synthetic utility of alkynylated products
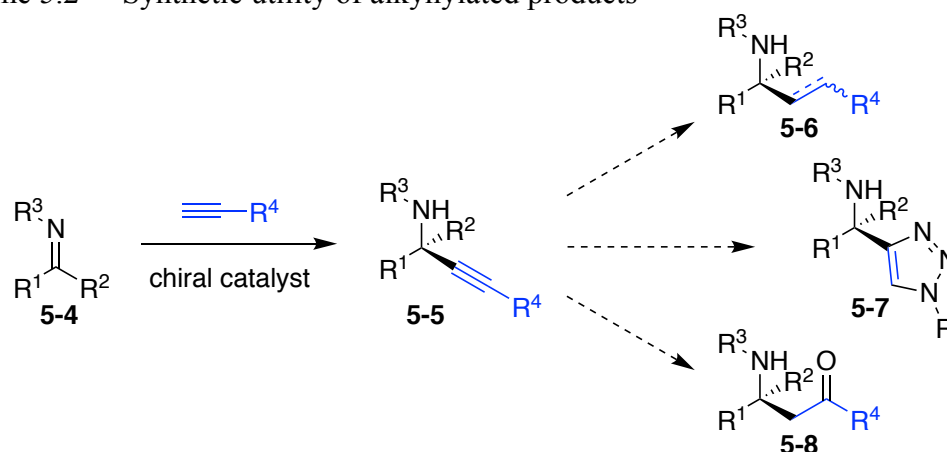


Unfortunately, enantioselective additions to diaryl ketimines remains an on-going challenge. It is very difficult for a chiral catalyst to distinguish between two similar aryl groups, thereby resulting in poor enantioselectivities. Nonetheless, there are limited examples in the literature that demonstrate the feasibility of this approach (Scheme 5.3). In 2010, the Zhang and Gosselin groups disclosed an asymmetric hydrogenation of substituted benzophenone N–H ketimines (**5-9**) using an iridium/phosphoramidite (**5-10**) catalyst system (Scheme 5.3A).[4] Similarly, the Wang group published the enantioselective transfer hydrogenation of *ortho*-hydroxybenzophenone N–H ketimines (**5-12**) using chiral phosphoric acid (**5-13**)

(Scheme 5.3B).[5] In this case, a Hantzsch ester is employed as the hydrogen source. Additionally, the Feng group has demonstrated an asymmetric cyanation of ketimine **5-15** to deliver Strecker products **5-18** (Scheme 5.3C).[6] This reaction employs a catalyst generated from titanium isopropoxide [Ti(O$^i$Pr)$_4$], cinchona alkaloid **5-16**, and achiral biphenol **5-17**. Notably, in every instance *ortho*-substitution on one of the aryl rings is required for good stereoinduction. Chiral auxiliary based approaches have also been used, but again rely on steric differentiation of the two aryl groups to obtain good diastereomeric ratios (dr).[7]

Scheme 5.3    Enantioselective additions to diaryl ketimines

A. Zhang and Gosselin's asymmetric hydrogenation
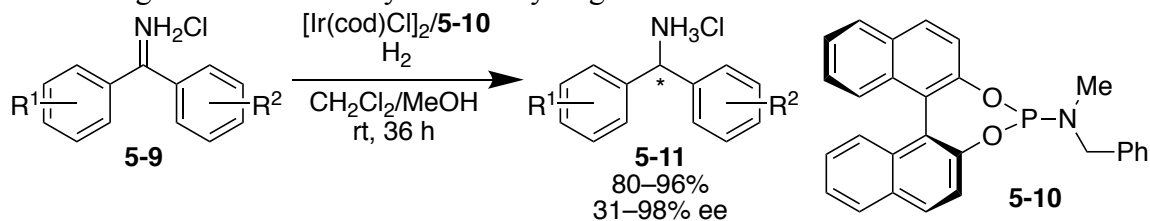


B. Wang's asymmetric transfer hydrogenation
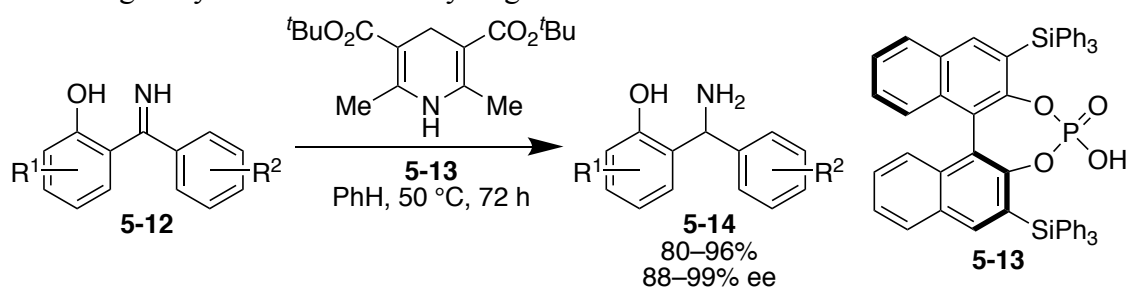


C. Feng's asymmetric cyanation
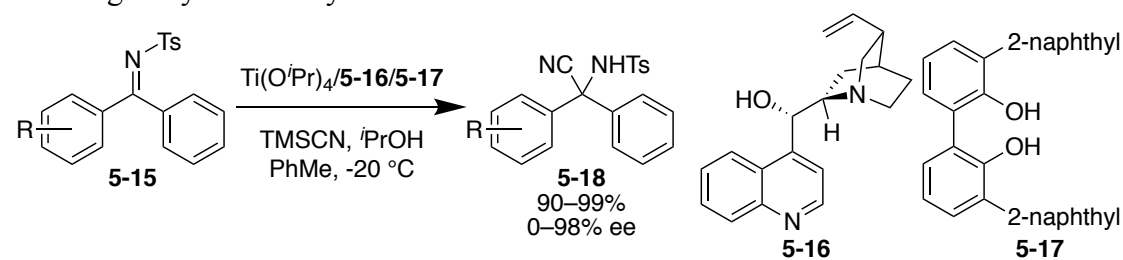
Previously, our group has developed copper-catalyzed enantioselective alkynylations of isochroman acetals and isoquinolines to form these types of α-diaryl tetrasubstituted stereocenters (Scheme 5.4).[8] In the former case, a Lewis acid (BF$_3$·OEt$_2$) is used to ionize the racemic acetal substrate (5-19) to form prochiral oxocarbenium ion intermediate 5-20 (Scheme 5.4A).[9-11] This cation is then susceptible to addition of a chiral ligand-bound copper-acetylide to form alkynylated product 5-21 bearing an α-diaryl tetrasubstitued stereocenter. An analogous reaction can be performed on *N*-acyl iminium ion 5-23, formed from the acylation of ketimine 5-22 with methyl chloroformate (Scheme 5.4B).[12] This delivers isoquinoline products 5-24 bearing a similar tetrasubstitued stereocenter. Notably, in both cases, the substrates are designed so that an alkyl tether can be used to differentiate the faces of the diaryl oxocarbenium or iminium ion, resulting in the formation of *cyclic* products.

Scheme 5.4    Watson's copper-catalyzed enantioselective alkynylations

A. Oxocarbenium ions



B. Iminium ions
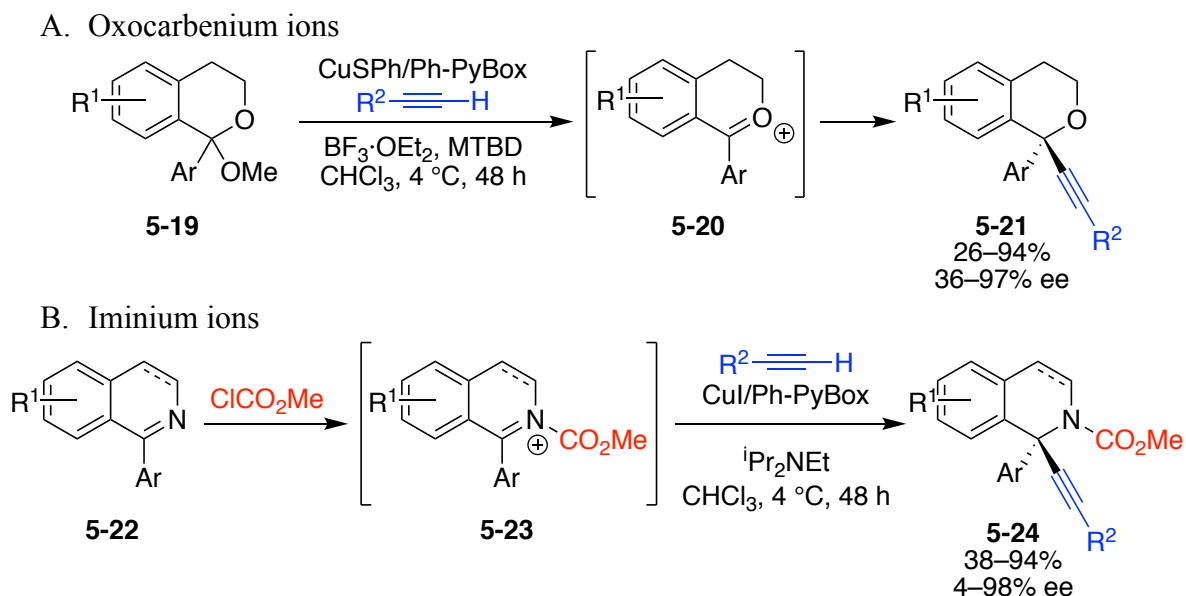
Having developed methods for the enantioselective alkylation of these types of cyclic substrates, we envisioned designing substrates containing a removable tether (**5-25**), which would allow us to access *acyclic* amines bearing an α-diaryl tetrasubstitued stereocenter (**5-28**) (Scheme 5.5). Effectively, the tether would allow for differentiation of the ketimine faces to afford high levels of enantioselectivity in the alkynylated product (**5-27**). The tether can then be cleaved to reveal the desired acyclic product (**5-28**). This approach would circumvent many of the issues associated with the differentiation of two similar aryl groups in acyclic substrates.

Scheme 5.5    Proposed strategy towards enantioselective synthesis of acyclic amines
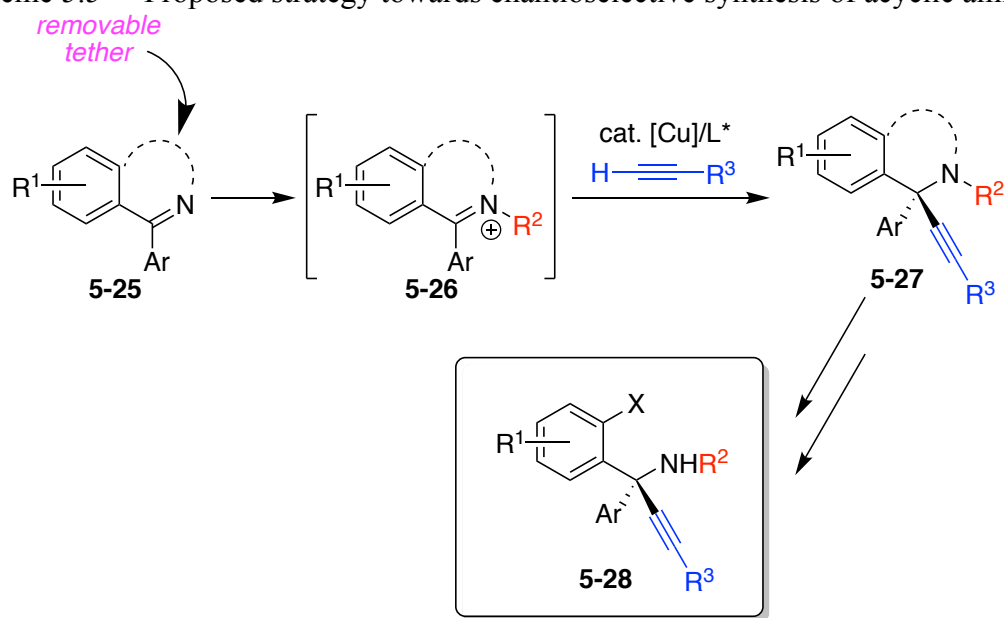


With this intrinsic protecting group anchoring strategy in mind,[13, 14] I designed several substrates that contained a suitable tether (Scheme 5.6). The two aryl groups can be differentiated based on the freedom of rotation exhibited by the pendant aryl ring versus the tethered aryl ring. It is also possible that the π-faces are more

electronically differentiated because of the tether onto nitrogen (lone pair vs alkyl group). Cyclic 5- and 6-membered *N*-sulfonyl ketimines (**5-29** & **5-30**) as well as benzisoxazole (**5-31**) were chosen as model substrates.

Scheme 5.6     Substrates containing a removable tether
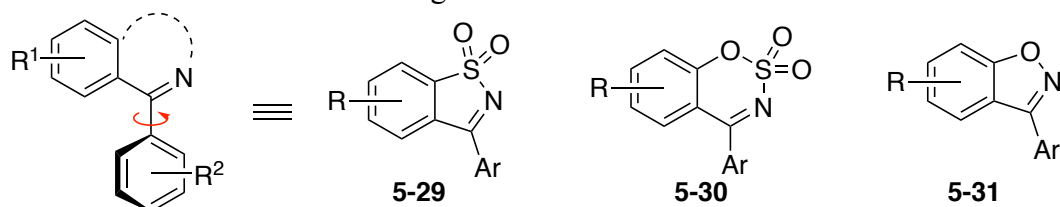


Enantioselective additions of a variety of nucleophiles to cyclic *N*-sulfonyl imines have been reported including arylations,[15-20] vinylations,[21, 22] propargylations,[23] and hydrogenations[24] (Scheme 5.7). More importantly, the sulfonyl group can be cleaved with little or no loss of enantiopurity of the α-stereocenter. Aryl sulfamates and sulfonamides have also been shown to participate in a variety of cross-coupling reactions.[25-29] Excitingly, isoxazolidines, the resultant products from isoxazole **5-31**, have proven to be a privileged scaffold for organic and medicinal chemistry.[30]

Scheme 5.7     Enantioselective additions to cyclic *N*-sulfonyl imines
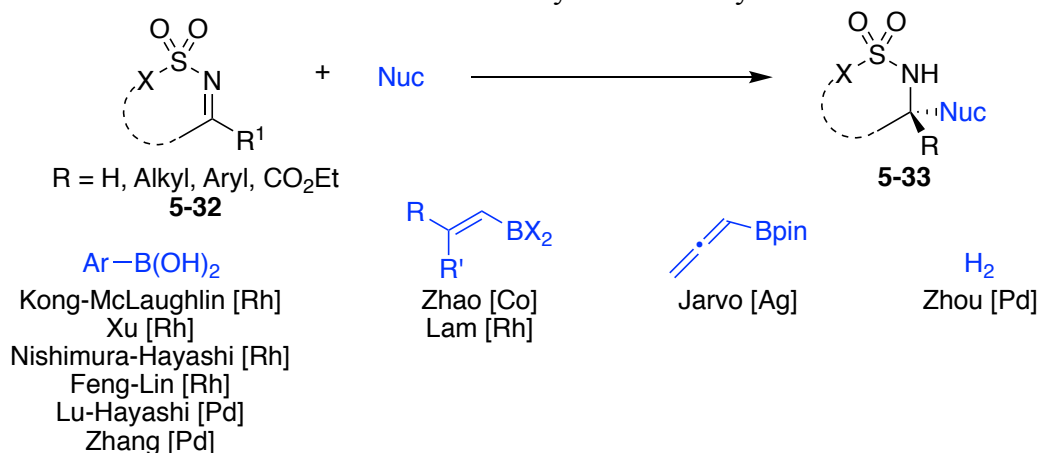
In comparison to these previously established methods, examples of enantioselective *alkynylations* of cyclic *N*-sulfonyl imines are much more limited. The Pedro group has shown that an asymmetric addition of an alkyne to aldimine **5-34** can be achieved using dimethylzinc and a chiral VAPOL ligand (Scheme 5.8A).[31] Additionally, Morimoto and Ohshima have demonstrated that a chiral (Phebox)Rhodium(III) complex (**5-37**) can be used to catalyze the enantioselective alkynylation of α-ketiminoesters (**5-36**) (Scheme 5.8B).[32] However, enantioselective alkynylations of cyclic *N*-sulfonyl ketimines to set α-diaryl tetrasubstitued stereocenters has not yet been achieved. With that in mind, I set out to develop an asymmetric copper-catalyzed alkynylation of cyclic ketimines bearing a removable tether en-route to this challenging class of products.

Scheme 5.8    Enantioselective alkynylations of cyclic *N*-sulfonyl imines

A.  Pedro (aldimine)



**5-34**

**5-35**
54–93%
56–86% ee

(R)-VAPOL
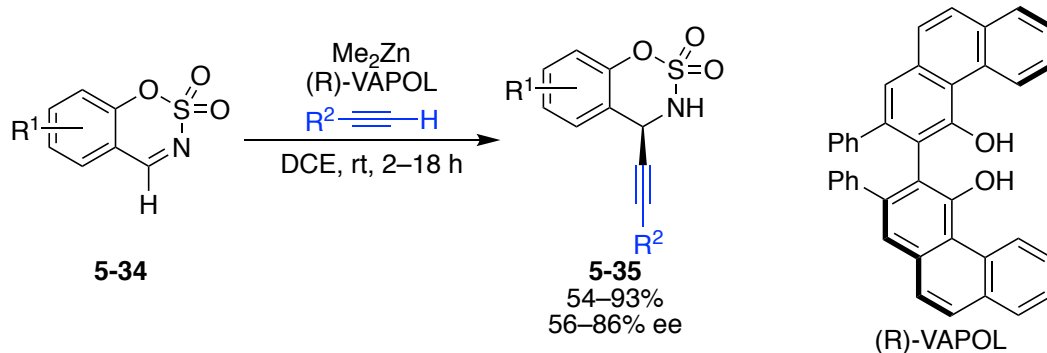
B.  Morimoto and Ohshima (α-ketiminoesters)



**5-36**

**5-38**
90–99%
78–86% ee

**5-37**
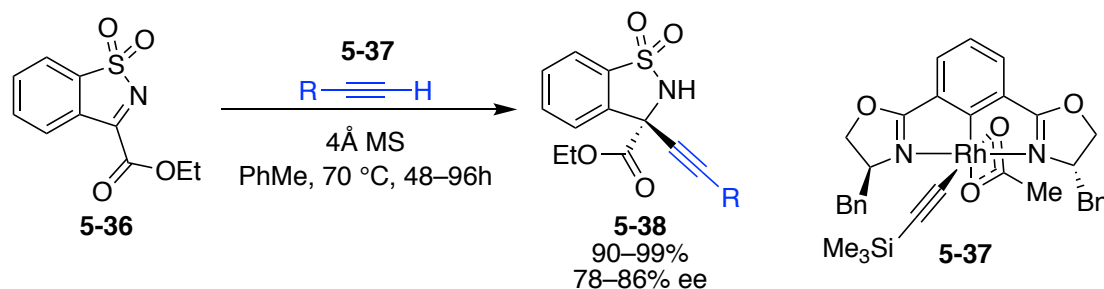
## 5.2 Results and Discussion

Initial screening began with 5- and 6-membered sufonyl ketimines **5-40** and **5-42**. These substrates can be easily synthesized in a single step in excellent yields and in multi-gram quantities (Scheme 5.9). Excitingly, these products can simply be recrystallized and require no column chromatography for isolation. This route also allows for the rapid incorporation of a variety of aryl groups.

Scheme 5.9      Synthesis of cyclic *N*-sulfonyl ketimines **5-40** and **5-42**
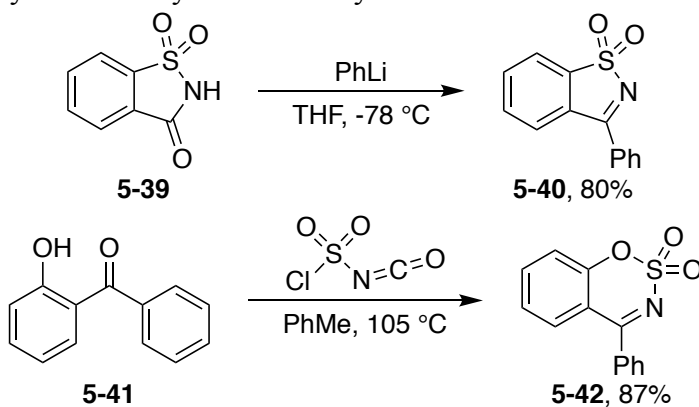


Unfortunately, these substrates were unreactive towards alkynylation under a variety of conditions tried, including activation with a Lewis acid. I hypothesized that formation of the corresponding iminium ion intermediate would increase the electrophilicity of the α-carbon and enhance reactivity. Indeed, when **5-40** was treated with methyl triflate to form methylated iminium ion **5-43**, alkynylated product **5-44** was afforded in 41% yield under standard conditions (Scheme 5.10). Notably, iminium intermediate **5-43** required elevated temperatures to form (70 °C) and was used without purification. Other methylating reagents such as methyl iodide and dimethyl sulfate were ineffective at promoting this transformation.

Scheme 5.10    Methylation and alkynylation of sulfonyl ketimine **5-40**
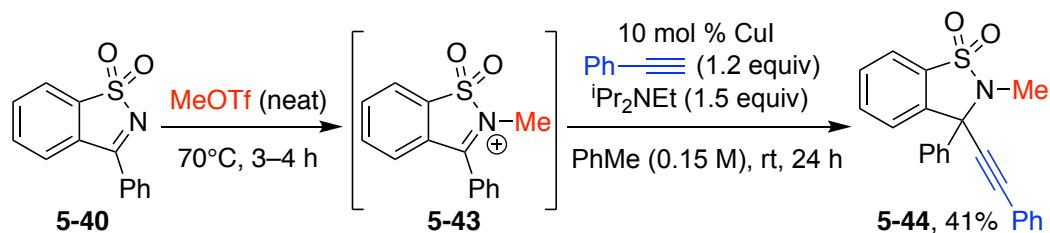


Yield determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

   I then turned my attention towards the identification of a suitable chiral ligand that would impart enantioselectivity in this reaction. Our group has shown that bis(oxazoline) (Box) and pyridine bis(oxazoline) (PyBox) ligands are privileged ligand architectures for copper-catalyzed alkynylations of cyclic iminium and oxocarbenium ions. Preliminary screening efforts identified IndaBox ligand **5-45** as a promising lead. However, upon extensive screening of various parameters such as copper source, base, solvent, temperature, and concentration, alkynylated product **5-44** was only observed in 31% yield and 30% *ee* (Scheme 5.11, top). PHOX ligand **5-46** also demonstrated similar reactivity and selectivity, giving 35% yield and 33% *ee*.

**Scheme 5.11** Enantioselective alkynylations of sulfonyl ketimines **5-40** and **5-42**
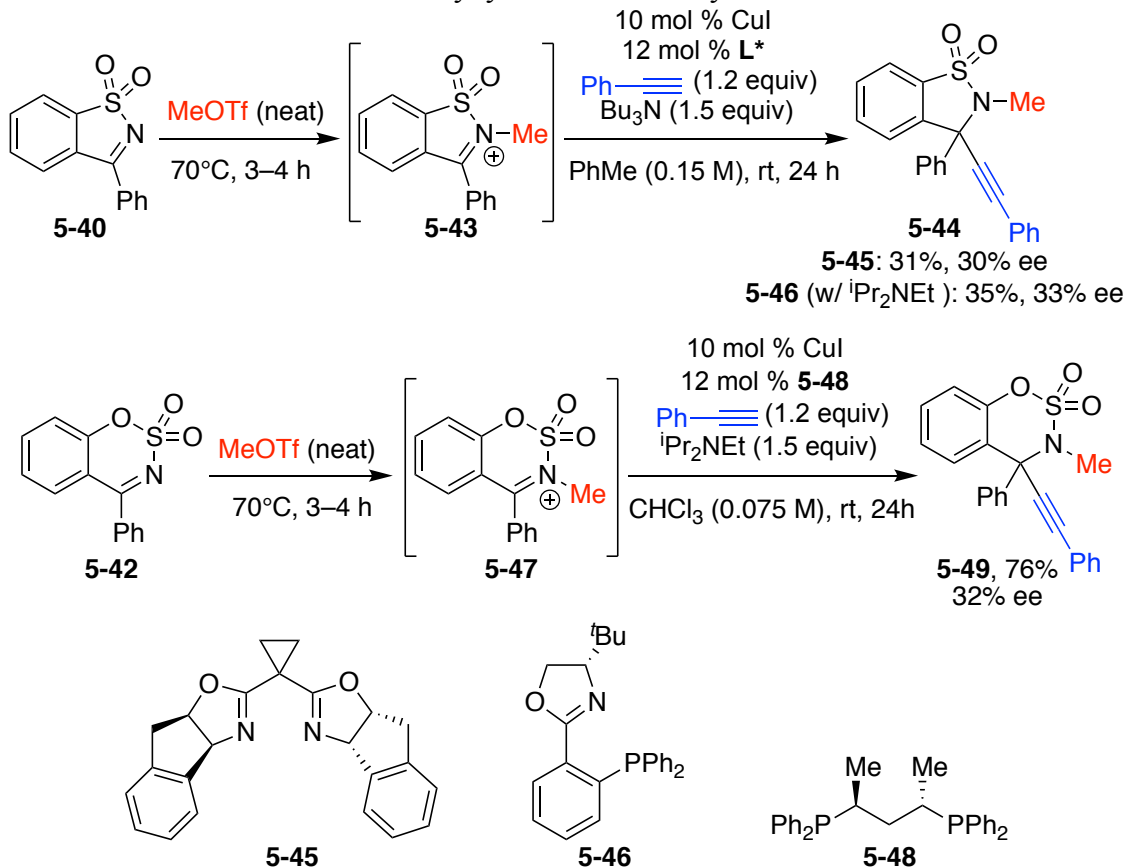


Yields determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. Enantiomeric excesses determined by chiral HPLC analysis

 

Simultaneously, 6-membered sulfonyl ketimine **5-42** was tested under similar conditions. In this case, chiral bidentate phosphine ligand BDPP (**5-48**) was found to afford the highest level of stereoinduction (Scheme 5.11, middle). Intense screening efforts revealed that the use of a halogenated solvent such as CHCl$_3$ under dilute conditions (0.075 M) afforded the desired product **5-49** in 76% yield and 32% *ee*. Further efforts to increase the yields and ee's are on-going in the group.

Meanwhile, I focused my efforts towards the use of benzisoxazole substrate **5-52**, which can be synthesized in two steps from commercial reagents (Scheme 5.12, top). Excitingly, the iminium intermediate is stable and can isolated as the corresponding triflate salt. Upon treatment of benzisoxazole **5-52** with methyl triflate, iminium salt **5-53** precipitates from solution and can be obtained as a white, crystalline solid (Scheme 5.12, bottom).

Scheme 5.12   Synthesis of **5-53**
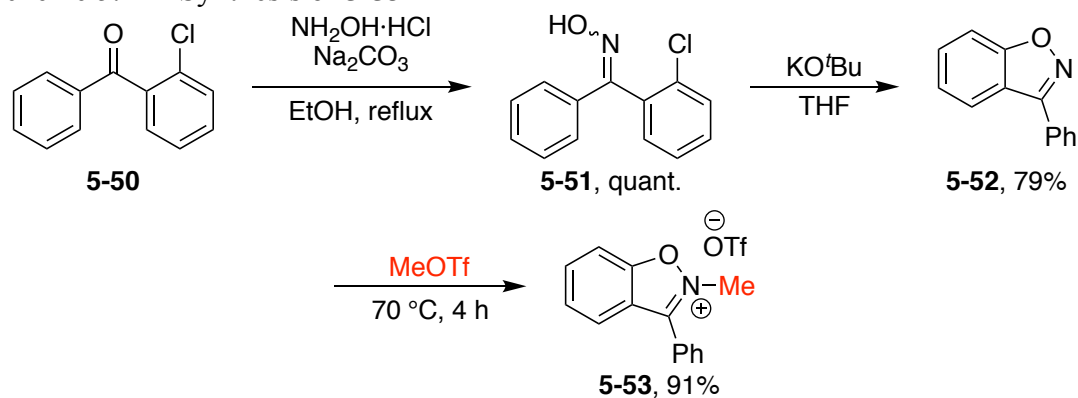


With **5-53** in hand, I decided that this substrate was perfect for high-throughput experimentation (HTE). A representative HTE plate is shown in Scheme 5.13. This set-up enables rapid screening of a variety of parameters in a 96-well format using a minimal amount of starting material (< 5 mg). I tested a number of chiral ligands including diamines, diols, phosphines, phosphoramidites, amino alcohols, and P–N ligands to identify a lead ligand class (See Appendix E for ligand structures).

**Scheme 5.13  Representative HTE plate**
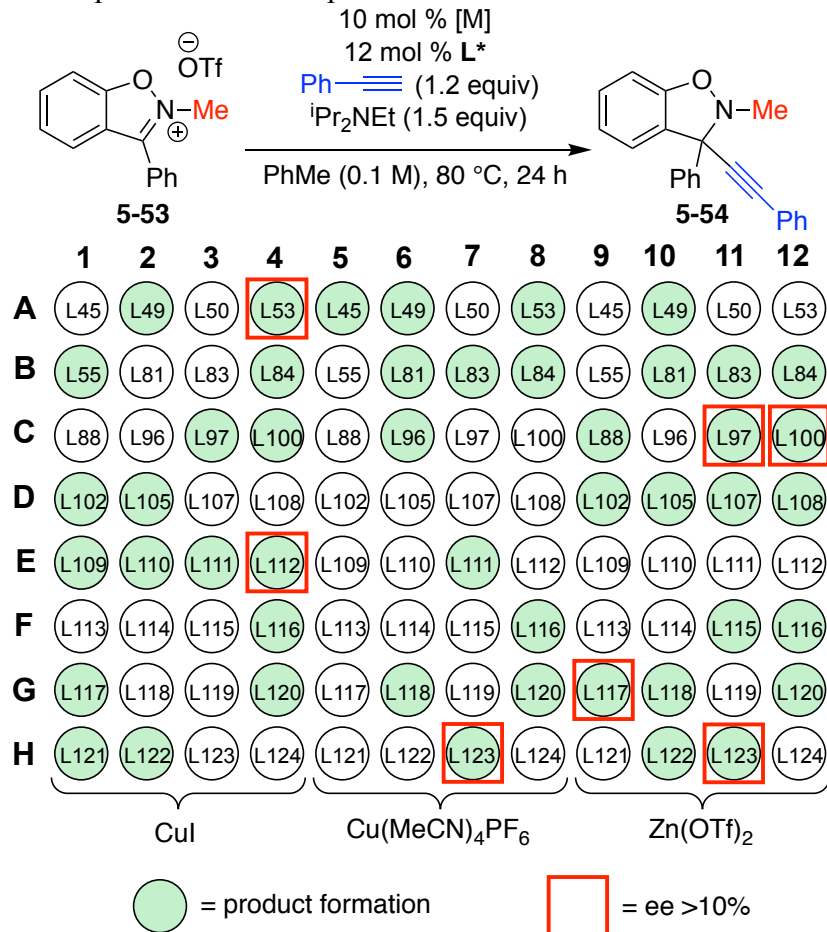


Upon screening a variety of chiral ligands, I identified phosphinooxazolines (PHOX) as a promising ligand class. These ligands are highly tunable and can be easily synthesized (Scheme 5.14).[33, 34] The stereogenic center (R group) on the oxazoline ring can be introduced from a chiral amino alcohol (5-56), which is often derived from an amino acid (5-55). The R' group on the aryl ring can be installed from a substituted 2-bromobenzoyl chloride (5-57). Finally, the diarylphosphino group can be obtained from the corresponding diarylphosphine or diarylphosphine chloride.

Scheme 5.14   Synthesis of PHOX ligands
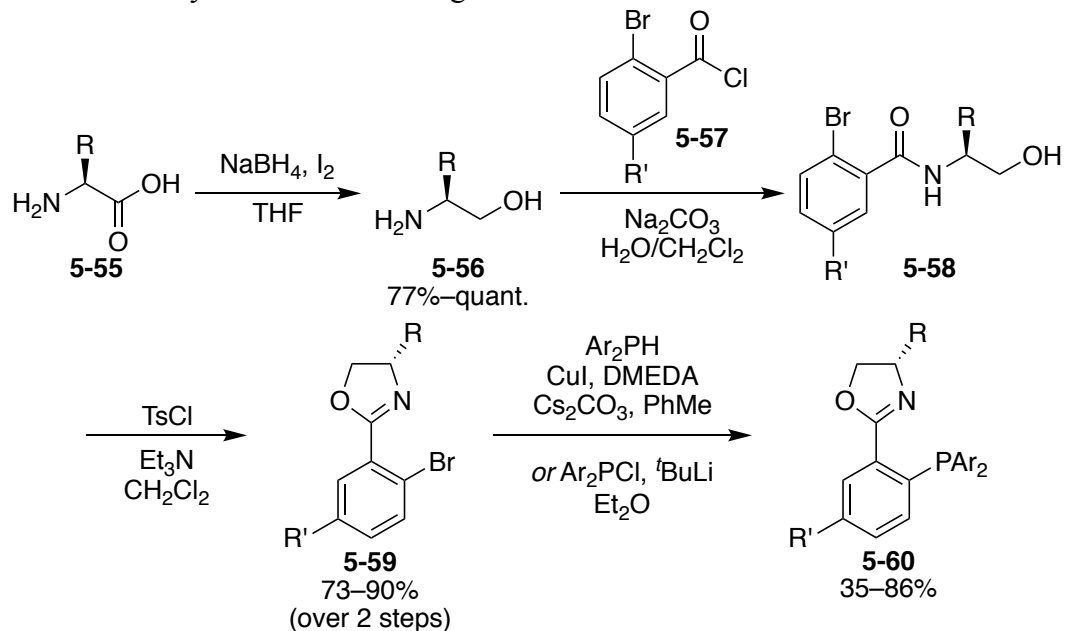


I synthesized a library of PHOX ligands to probe various steric and electronic effects on the reactivity and selectivity of the alkynylation reaction (Scheme 5.15). Upon testing a variety of substituents on the oxazoline ring, I found that a bulky *tert-*butyl group (**5-46**) afforded the best reactivity and selectivity, compared to other groups such as isopropyl (**5-61**) or phenyl (**5-62**). The incorporation of a number of different diarylphosphines revealed that electron-donating groups on the aryl (OMe, **5-65**) increased the *ee* substantially compared to electron-withdrawing groups (CF$_3$, **5-66**). Moreover, an *ortho*-substituent afforded increased yield (*o*-tolyl, **5-67**). However, further steric bulk lead to low *ee* (mesityl, **5-68**). Finally, a bulky, electron-rich *ortho*-substituent (O$^i$Pr, **5-70**) afforded excellent selectivity (97% *ee*). The electronic character of the backbone aryl group was found to also influence selectivity. Again, an electron-donating group resulted in increased levels of enantioselectivity (OMe, **5-71**). In combining these observations, ligand **5-74** afforded the desired product in >99% *ee*, albeit in low yield.

Scheme 5.15   Screening of various PHOX ligands[a]

10 mol % Cu(MeCN)$_4$PF$_6$
12 mol % **L***
Ph —≡ (1.2 equiv)
$^i$Pr$_2$NEt (1.5 equiv)
DCE (0.1 M), 80 °C, 24 h

**5-53** → **5-54**

**5-61**, 6%
10% ee

**5-46**, 24%
47% ee

**5-62**, 2%
0% ee

**5-63**, 9%
20% ee

**5-64**, 47%
-14% ee

**5-65**, 11%
83% ee

**5-66**, 37%
17% ee

**5-67**, 48%
45% ee

**5-68**, 42%
9% ee

**5-69**, 32%
76% ee

**5-70**, 21%
97% ee

**5-71**, 15%
58% ee

**5-72**, 26%
22% ee

**5-73**, 24%
85% ee

**5-74**, 16%
>99% ee

201
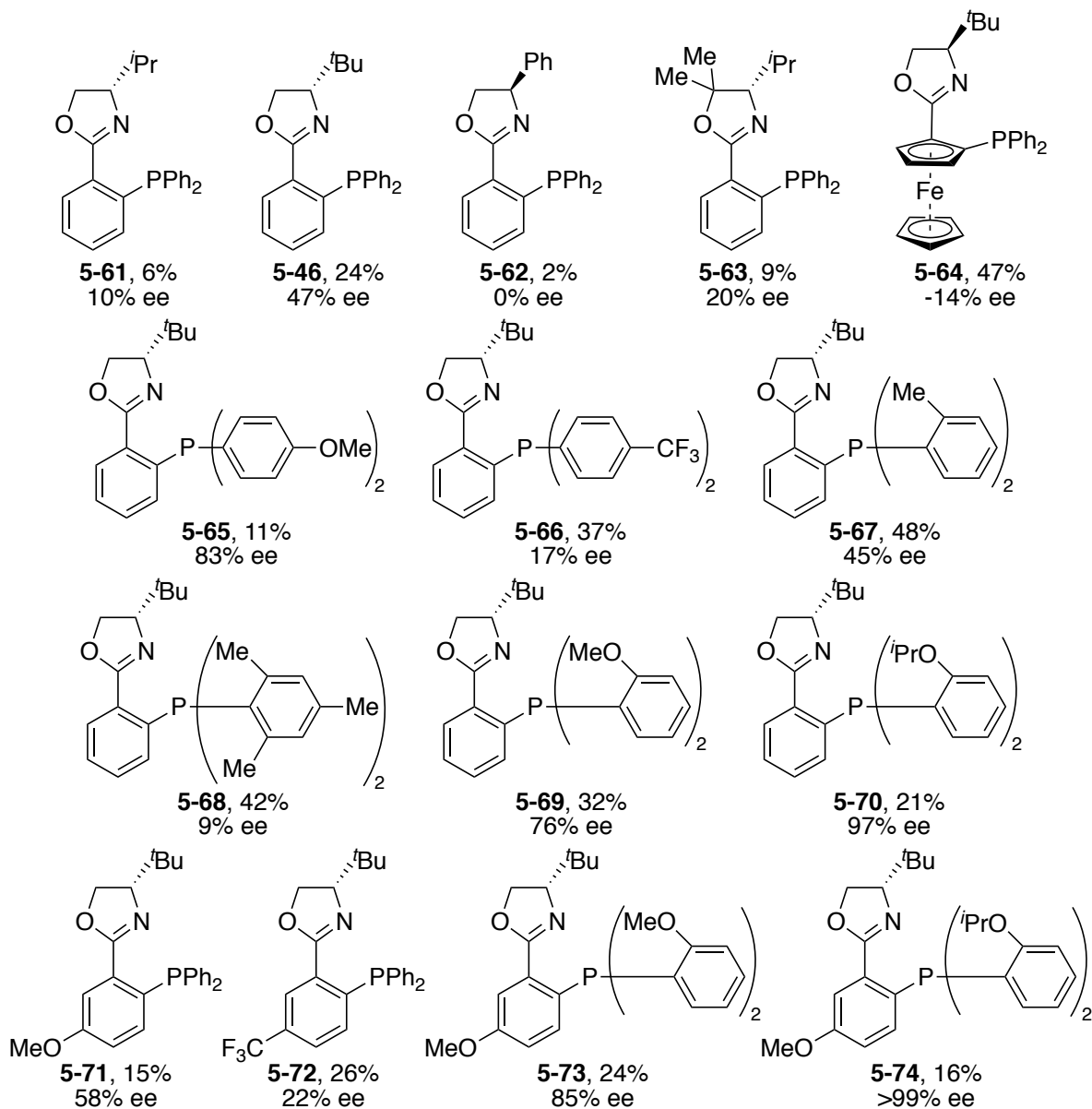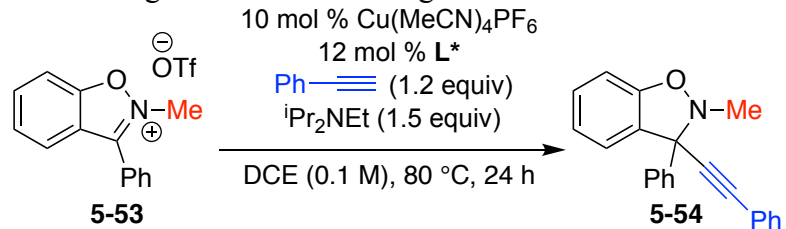
Conditions: **5-53** (0.10 mmol), [Cu] (10 mol %), L* (12 mol %), alkyne (1.2 equiv),
base (1.5 equiv), DCE (0.1 M), 80 °C, 24 h. Yield and enantiomeric excess determined
by chiral SFC analysis using 1,3,5-trimethoxybenzene as internal standard.

Having identified a suitable ligand, I then turned to examine the temperature
dependence of this reaction (Table 5.1). Typically for an enantioselective reaction,
lower reaction temperatures can lead to increased *ee*'s. Unfortunately, the yield may
be lower due to a slower rate of reaction. Surprisingly, at lower reaction temperatures
(70 and 60 °C), the *ee*'s of desired product dropped substantially (entries 2 & 3).
However, an improvement in yield was observed at these lower temperatures. Since
these results are somewhat counterintuitive, I wanted to probe if another reaction
pathway may be operational under these reaction conditions. No reaction was
observed at room temperature (entry 4).

Table 5.1        Temperature dependence of the alkynylation reactionᵃ
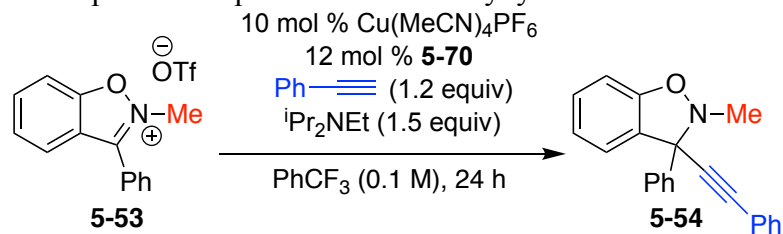


| Entry | Temperature (°C) | Yield (%)ᵇ | ee (%)ᶜ |
|-------|------------------|-----------|---------|
| 1 | 80 | 28 | 97 |
| 2 | 70 | 32 | 57 |
| 3 | 60 | 46 | 27 |

| 4 | rt | <5 | 4 |

With these odd results in hand, I first wanted to test if the alkynylated product **5-54** was stable under the reaction conditions. I subjected racemic product **5-54** (synthesized independently via addition of lithium phenylacetylide to **5-53**) to the standard reaction conditions (Table 5.2, entry 1). Interestingly, product decomposition was observed, and **5-54** was recovered in only 46% yield. Surprisingly, the recovered starting material was determined to be 96% *ee*, a value similar to that observed in the copper-catalyzed reaction. This result suggests a highly efficient kinetic resolution, giving high *ee*'s and yields (50% maximum theoretical yield). This result also implies that there may be a resolution event of alkynylated product **5-54** that is occurring under the alkynylation conditions. Additionally, it is plausible that the copper-catalyzed reaction proceeds to give **5-54** that is racemic or with lower *ee*, and selective decomposition of one enantiomer then leads to highly enantioenriched product.

Table 5.2    Decomposition of alkynylated product **5-54**[a]
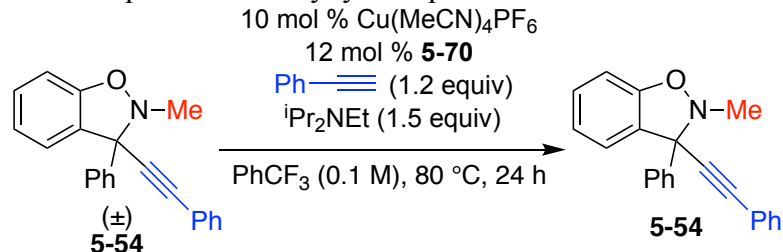


| Entry | Deviation from above | Yield (%)[b] | ee (%)[c] |
|:-----:|:--------------------:|:------------:|:---------:|
| 1 | none | 46 | 96 |
| 2 | no [Cu] | 98 | 0 |
| 3 | no L* | quant. | 0 |
| 4 | no alkyne | <5 | n.d. |
| 5 | no base | <5 | n.d. |

[a]Conditions: **5-54** (0.10 mmol), [Cu] (10 mol %), **5-70** (12 mol %), alkyne (1.2 equiv), base (1.5 equiv), PhCF$_3$ (0.1 M), 80 °C, 24 h. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by chiral HPLC analysis.

To investigate this phenomenon further, I ran a series of control reactions to elucidate what was required for the decomposition event. In the absence of either copper or chiral ligand, no product decomposition was observed (entries 2 & 3). Interestingly, in the absence of alkyne or base, no remaining starting material **5-54** was recovered (entries 4 & 5). These results indicate that all the components of the reaction (copper, ligand, alkyne, and base) are required to promote the kinetic resolution, but also prevent complete decomposition of the alkynylated product.

Future efforts should be focused on identifying the decomposition products of this resolution reaction. Perhaps one enantiomer of alkynylated product **5-54** reacts with the chiral copper catalyst to afford some type of ring-opened or rearranged product. We are extremely interested in probing this possibility further. Unfortunately, we do not yet have a deep mechanistic understanding of this resolution event. With more evidence and mechanistic insight, I believe that this can be turned into a useful method for the kinetic resolution of related substrates.

## 5.3 Conclusion

I have described my efforts towards a copper-catalyzed enantioselective alkynylation of cyclic iminium ions bearing a removable tether, en-route to acyclic amines bearing an α-diaryl tetrasubstitued stereocenter. Promising results have been obtained for both 5- and 6-membered cyclic *N*-sulfonyl ketimine substrates. Interestingly, in the case of the benzisoxazolidine product, there appears to be a kinetic resolution event occurring under the optimized reaction conditions. Further mechanistic insight may lead to the development of this method as a kinetic resolution to deliver highly enantioenriched products.

## 5.4    Experimental

### 5.4.1    Enantioselective Alkynylation of Iminium Ions

#### 5.4.1.1    General Procedure A: Reaction Optimization of *N*-sulfonyl Ketimines

In a $N_2$-filled glovebox: To an oven-dried 1-dram vial was added substrate (0.10 mmol, 1.0 equiv). The vial was then equipped with a micro stir bar, capped with a pierceable Teflon-coated cap, and removed from the glovebox. Methyl triflate (0.11 mmol, 1.1 equiv) was added into the vial via a $N_2$-purged microsyringe. The mixture was heated at 70 ºC for 4 h. To a separate oven-dried 1-dram vial was added [Cu] (0.010 mmol, 10 mol %), ligand (0.012 mmol, 12 mol %), and solvent. The vial was equipped with a micro stir bar, and the resultant solution was stirred for 30 min at rt. Alkyne (0.12 mmol, 1.2 equiv) and base (0.15, 1.5 equiv) were added. The vial was removed from the glovebox, and the copper acetylide mixture was transferred to the substrate vial via a $N_2$-purged syringe. The resulting mixture was stirred vigorously at room temperature for 24 hours. The mixture was then diluted with $Et_2O$ (1.5 mL) and filtered through a short plug of silica gel. The filter cake was washed with $Et_2O$ (10 mL), and the filtrate was concentrated. 1,3,5-Trimethoxybenzene (internal standard) and $CDCl_3$ were added, and the yield was determined by $^1H$ NMR analysis. An analytical sample of the product was prepared via preparatory thin layer chromatography, and the *ee* of this sample was determined by HPLC using a chiral stationary phase.
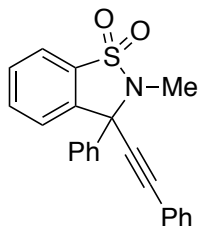
**2-Methyl-3-phenyl-3-(phenylethynyl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (5-44)**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 – 7.83 (m, 1H), 7.72 – 7.64 (m, 2H), 7.60 – 7.47 (m, 4H), 7.44 – 7.30 (m, 6H), 7.24 – 7.18 (m, 1H), 2.83 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 140.9, 138.1, 133.5, 132.9, 132.0, 129.7, 129.2, 129.1, 128.9, 128.4, 127.3, 125.2, 121.5, 121.2, 90.2, 84.0, 66.8, 24.7.
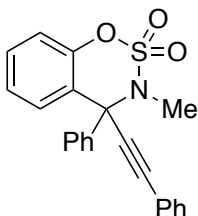


**3-Methyl-4-phenyl-4-(phenylethynyl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (5-49)**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 – 7.73 (m, 2H), 7.62 – 7.57 (m, 2H), 7.48 – 7.35 (m, 6H), 7.34 – 7.27 (m, 1H), 7.16 – 7.08 (m, 3H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 147.5, 140.9, 132.0, 130.3, 129.6, 129.2, 129.0, 128.8, 128.4, 127.6, 127.0, 126.1, 121.7, 118.8, 90.6, 84.4, 68.9, 31.3.

### 5.4.1.2 General Procedure B: Reaction Optimization of Benzisoxazole 5-53

In a N$_2$-filled glovebox: To an oven-dried 1-dram vial was added [Cu] (0.010 mmol, 10 mol %), ligand (0.012 mmol, 12 mol%), and solvent. The vial was equipped with a micro stir bar, and the resultant solution was stirred for 30 min at rt. Alkyne (0.12 mmol, 1.2 equiv), base (0.15, 1.5 equiv), and **5-53** (0.10 mmol, 1.0 equiv) were

added. The vial was removed from the glovebox, and the resulting mixture was stirred vigorously at 80 °C for 24 h. The mixture was then diluted with Et$_2$O (1.5 mL) and filtered through a short plug of silica gel. The filter cake was washed with Et$_2$O (10 mL), and the filtrate was concentrated. 1,3,5-Trimethoxybenzene (internal standard) and CDCl$_3$ were added, and the yield was determined by $^1$H NMR analysis. An analytical sample of the product was prepared via preparatory thin layer chromatography, and the *ee* of this sample was determined by SFC or HPLC using a chiral stationary phase.
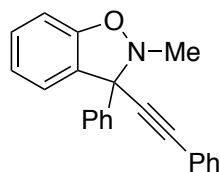


**2-Methyl-3-phenyl-3-(phenylethynyl)-2,3-dihydrobenzo[*d*]isoxazole (5-54)**.
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.70 (d, *J* = 7.5 Hz, 2H), 7.45 − 7.40 (m, 2H), 7.35 − 7.31 (m, 2H), 7.31 − 7.22 (m, 4H), 7.18 − 7.12 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 2.96 (s, 3H).

### 5.4.2  Preparation of Substrates
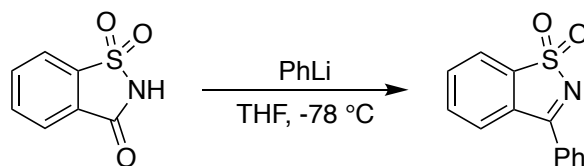


**3-Phenylbenzo[*d*]isothiazole 1,1-dioxide (5-40)**. Prepared according to the literature procedure.[35]
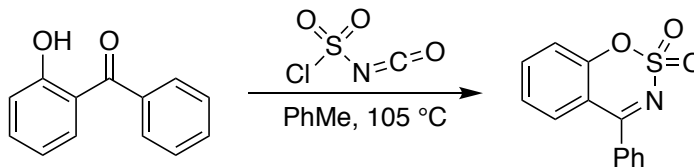
**4-Phenylbenzo[e][1,2,3]oxathiazine 2,2-dioxide (5-42)**. Prepared according to the literature procedure.[36]
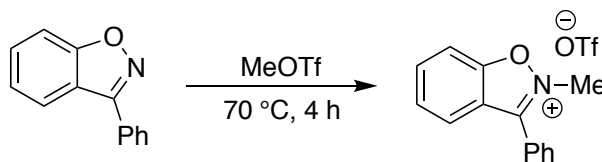


**3-Phenylbenzo[d]isoxazole (5-52)**. Prepared according to the literature prodecure.[37]

**2-Methyl-3-phenylbenzo[d]isoxazol-2-ium trifluoromethanesulfonate (5-53)**. To an oven dried 25 mL round-bottomed flask was added benzisoxazole **5-52** (600 mg, 3.0 mmol, 1.0 equiv) and methyl triflate (0.37 mL, 3.3 mmol, 1.1 equiv). The resulting mixture was heated in an oil bath at 70 °C for 4 h. The mixture was allowed to cool to room temperature, and 2 mL of $CH_2Cl_2$ was added to dissolve the crude material. The solution was diluted with $Et_2O$ and vigorously stirred to induce trituration. The resultant solid was filtered and washed with $Et_2O$ to give **5-53** (1.0 g, 91%) as a white solid: $^1H$ NMR (600 MHz, CDCl$_3$) δ 8.07 (t, $J$ = 7.9 Hz, 1H), 7.99 – 7.92 (m, 3H), 7.86 – 7.79 (m, 2H), 7.77 (t, $J$ = 7.5 Hz, 2H), 7.72 (t, $J$ = 7.7 Hz, 1H), 4.60 (s, 3H); $^{13}C$ NMR (151 MHz, CDCl$_3$) δ 159.9, 156.4, 137.5, 134.1, 130.4, 130.1, 128.3, 124.8, 121.3, 119.7, 110.7, 40.5.

### 5.4.3   Preparation of PHOX Ligands
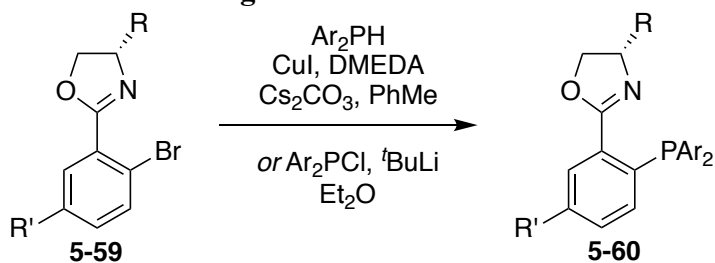


The PHOX ligands can be prepared according to a procedure adapted from the literature using the corresponding diarylphosphine.[33] In a $N_2$-filled glovebox: To an oven-dried 10 mL round-bottomed flask was added CuI (8.4 mg, 0.044 mmol, 12.5 mol%), diarylphosphine (0.67 mmol, 1.88 equiv), DMEDA (33µL, 0.31 mmol, 0.875 equiv), and toluene (1.5 mL). The resulting mixture was stirred at rt for 20 min. Aryl bromide (5-59) (0.35 mmol, 1.0 equiv) and $Cs_2CO_3$ (433 mg, 1.33 mmol, 3.75 equiv) were added along with an additional aliquot of toluene (1.5 mL). The resulting mixture was sealed, removed from the glovebox, and heated in an oil bath at 110 ºC for 2 h. The reaction was then allowed to cool to rt. The crude mixture was filtered, washed with $CH_2Cl_2$, and concentrated. The desired PHOX ligand 5-60 was then purified via silica gel chromatography.

For sterically encumbered diarylphosphino groups, the PHOX ligands can be prepared according to a procedure adapted from the literature using the corresponding diarylphosphine chloride.[34] To an oven-dried 10 mL round-bottomed flask was added aryl bromide (5-59) (0.35 mmol, 1.0 equiv) and anhydrous $Et_2O$ (2.5 mL). The resulting solution was cooled to −78 ºC. *tert*-Butyl lithium (0.43 mmol, 1.2 equiv) was added dropwise at this temperature. The solution was stirred for an additional 1 h at −78 ºC. Diarylphosphine chloride (0.43 mmol, 1.2 equiv) was added. The reaction was warmed to rt and stirred for an additional 1 h. The crude reaction was poured into an aq. $NH_4Cl$ solution and extracted with $Et_2O$ (x 3). The combined organic layers were

dried with magnesium sulfate and concentrated. The desired PHOX ligand **5-60** was then purified via silica gel chromatography.
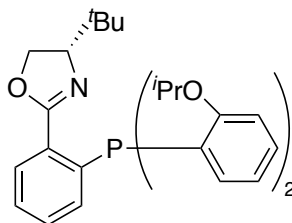


**(S)-2-(2-(Bis(2-isopropoxyphenyl)phosphaneyl)phenyl)-4-(*tert*-butyl)-4,5-dihydrooxazole (5-70)**. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.92 – 7.84 (m, 1H), 7.33 (td, $J$ = 7.6, 1.3 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.09 – 7.02 (m, 1H), 6.86 – 6.73 (m, 6H), 4.53 – 4.38 (m, 2H), 4.17 – 4.01 (m, 2H), 4.00 – 3.90 (m, 1H), 1.10 (dd, $J$ = 13.9, 6.0 Hz, 9H), 0.99 – 0.88 (m, 3H), 0.75 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.5, 159.4, 134.8, 134.4, 129.8, 129.3, 129.3, 129.2, 129.1, 127.6, 120.2, 120.0, 111.3, 70.2, 69.6, 68.4, 33.8, 25.8, 21.9, 21.8, 21.6; $^{31}$P NMR (162 MHz, CDCl$_3$) δ –24.44.

## REFERENCES

1.     Qiao, J. X.; Wang, T. C.; Adam, L. P.; Chen, A. Y. A.; Taylor, D. S.; Yang, R. Z.; Zhuang, S.; Sleph, P. G.; Li, J. P.; Li, D.; Yin, X.; Chang, M.; Chen, X.-Q.; Shen, H.; Li, J.; Smith, D.; Wu, D.-R.; Leith, L.; Harikrishnan, L. S.; Kamau, M. G.; Miller, M. M.; Bilder, D.; Rampulla, R.; Li, Y.-X.; Xu, C.; Lawrence, R. M.; Poss, M. A.; Levesque, P.; Gordon, D. A.; Huang, C. S.; Finlay, H. J.; Wexler, R. R.; Salvati, M. E., *Journal of Medicinal Chemistry* **2015,** *58*, 9010-9026.

2.     Crawforth, J. M.; Glossop, P. A.; Hamper, B. C.; Huang, W.; Mantell, S. J.; Neal, B. E.; Olson, K.; Thorarensen, A.; Turner, S. R., WO2009153721A1, 2009/12/23/, 2009.

3.     Anderson, P.; Christy, M. E.; Evans, B. E., US4399141 (A), 1983/08/16/, 1983.

4.     Hou, G.; Tao, R.; Sun, Y.; Zhang, X.; Gosselin, F., *J. Am. Chem. Soc.* **2010,** *132*, 2124-2125.

5.     Nguyen, T. B.; Wang, Q.; Guéritte, F., *Chemistry – A European Journal* **2011,** *17*, 9576-9580.

6.     Wang, J.; Wang, W.; Li, W.; Hu, X.; Shen, K.; Tan, C.; Liu, X.; Feng, X., *Chemistry – A European Journal* **2009,** *15*, 11642-11659.

7.     Shaw, A. W.; deSolms, S. J., *Tetrahedron Letters* **2001,** *42*, 7173-7176.

8.     Liu, J.; Dasgupta, S.; Watson, M. P., *Beilstein Journal of Organic Chemistry* **2015,** *11*, 2696-2706.

9.     Dasgupta, S.; Rivas, T.; Watson, M. P., *Angewandte Chemie International Edition* **2015,** *54*, 14154-14158.

10.    Maity, P.; Srinivas, H. D.; Watson, M. P., *J. Am. Chem. Soc.* **2011,** *133*, 17142-17145.

11.    Srinivas, H. D.; Maity, P.; Yap, G. P. A.; Watson, M. P., *The Journal of Organic Chemistry* **2015,** *80*, 4003-4016.

12.    Dasgupta, S.; Liu, J.; Shoffler, C. A.; Yap, G. P. A.; Watson, M. P., *Org. Lett.* **2016,** *18*, 6006-6009.

13.    Zhuang, W.; Saaby, S.; Jørgensen, K. A., *Angewandte Chemie International Edition* **2004,** *43*, 4476-4478.

14.    Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jørgensen, K. A., *Chemistry – A European Journal* **2003,** *9*, 6145-6154.

15.    Kong, J.; McLaughlin, M.; Belyk, K.; Mondschein, R., *Org. Lett.* **2015,** *17*, 5520-5523.

16.    Wang, H.; Jiang, T.; Xu, M.-H., *J. Am. Chem. Soc.* **2013,** *135*, 971-974.

17.    Nishimura, T.; Noishiki, A.; Chit Tsui, G.; Hayashi, T., *J. Am. Chem. Soc.* **2012,** *134*, 5056-5059.

18.    Chen, Y.-J.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q., *Org. Lett.* **2014,** *16*, 3400-3403.

19.    Jiang, C.; Lu, Y.; Hayashi, T., *Angewandte Chemie International Edition* **2014,** *53*, 9936-9939.

20.    Yang, G.; Zhang, W., *Angewandte Chemie International Edition* **2013,** *52*, 7540-7544.

21.    Huang, Y.; Huang, R.-Z.; Zhao, Y., *J. Am. Chem. Soc.* **2016,** *138*, 6571-6576.

22.    Luo, Y.; Carnell, A. J.; Lam, H. W., *Angewandte Chemie International Edition* **2012,** *51*, 6762-6766.

23.    Osborne, C. A.; Endean, T. B. D.; Jarvo, E. R., *Org. Lett.* **2015,** *17*, 5340-5343.

24.    Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G., *Org. Lett.* **2008,** *10*, 2071-2074.

25.    Wehn, P. M.; Du Bois, J., *Org. Lett.* **2005,** *7*, 4685-4688.

26.    Milburn, R. R.; Snieckus, V., *Angewandte Chemie International Edition* **2004,** *43*, 888-891.

27.    Macklin, T. K.; Snieckus, V., *Org. Lett.* **2005,** *7*, 2519-2522.

28.     Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K., *Angewandte Chemie International Edition* **2011,** *50*, 2171-2173.

29.     Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K., *J. Am. Chem. Soc.* **2011,** *133*, 6352-6363.

30.     Berthet, M.; Cheviet, T.; Dujardin, G.; Parrot, I.; Martinez, J., *Chemical Reviews* **2016,** *116*, 15235-15283.

31.     De Munck, L.; Monleón, A.; Vila, C.; Muñoz, M. C.; Pedro, J. R., *Organic & Biomolecular Chemistry* **2015,** *13*, 7393-7396.

32.     Morisaki, K.; Sawa, M.; Yonesaki, R.; Morimoto, H.; Mashima, K.; Ohshima, T., *J. Am. Chem. Soc.* **2016,** *138*, 6194-6203.

33.     Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M., *Org. Lett.* **2007,** *9*, 2529-2531.

34.     García-Fortanet, J.; Buchwald, S. L., *Angewandte Chemie International Edition* **2008,** *47*, 8108-8111.

35.     Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P.; Harakal, M. E.; Gosciniak, D. J., *The Journal of Organic Chemistry* **1990,** *55*, 1254-1261.

36.     Kamal, A.; Sattur, P. B., *Synthesis* **1981,** *1981*, 272-273.

37.     Shan, G.; Huang, G.-Y.; Rao, Y.; Zhang, H., *Chinese Chemical Letters* **2015,** *26*, 1236-1240.

**Appendix A**

**SPECTRAL AND CHROMATOGRAPHY DATA FOR CHAPTER 1**

2.323

2.797
2.806
2.814
2.821
2.826
2.828
2.833
2.840
2.848
2.857

5.923
6.614
6.617
6.627
6.630
6.685
6.687
6.715
6.728
7.059
7.073
7.086
7.100

Me
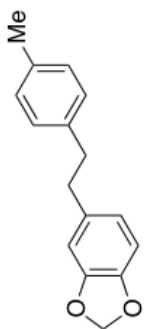
**Compound 1-40**
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

3.06
4.16
2.06
1.00
0.96
0.98
3.97

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5  -1.0
f1 (ppm)

21.169

37.906
37.931

CHCl₃

100.884

108.238
109.070

121.310

128.445
129.159

135.506
135.923
138.706

145.754
147.631

Me
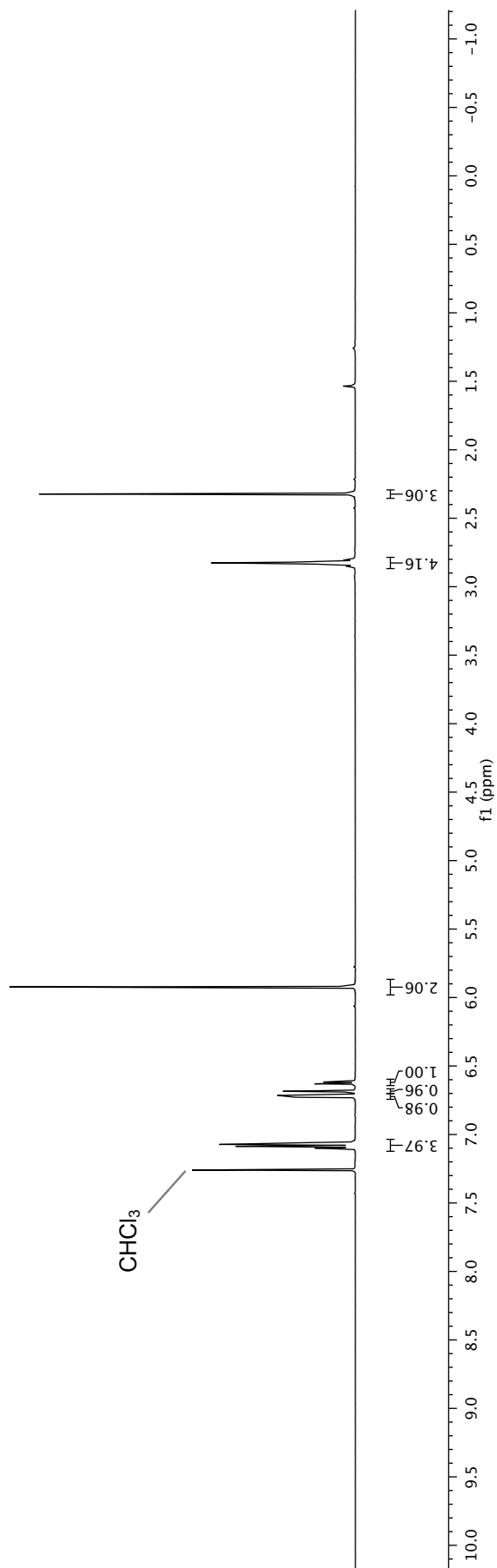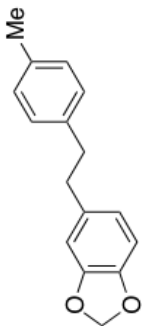
**Compound 1-40**
¹³C NMR (151 MHz, CDCl₃)

217

f1 (ppm)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10
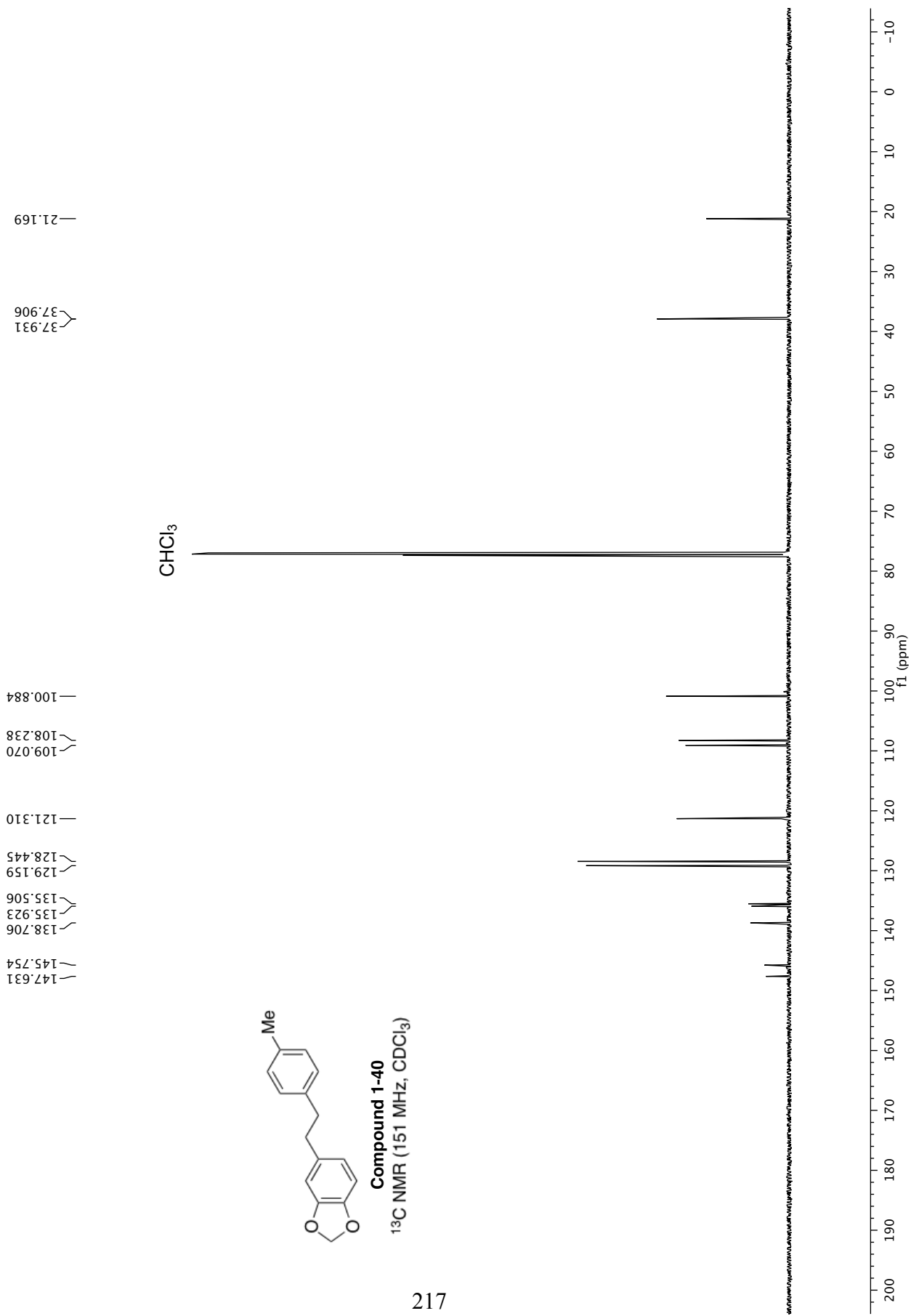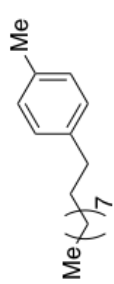
Compound 1-42
1H NMR (400 MHz, CDCl₃)

CHCl₃

218

14.295

21.152
22.851
29.505
29.693
29.763
29.790
31.845
32.063
35.682

CHCl₃

128.406
129.033

135.057

140.023

Me
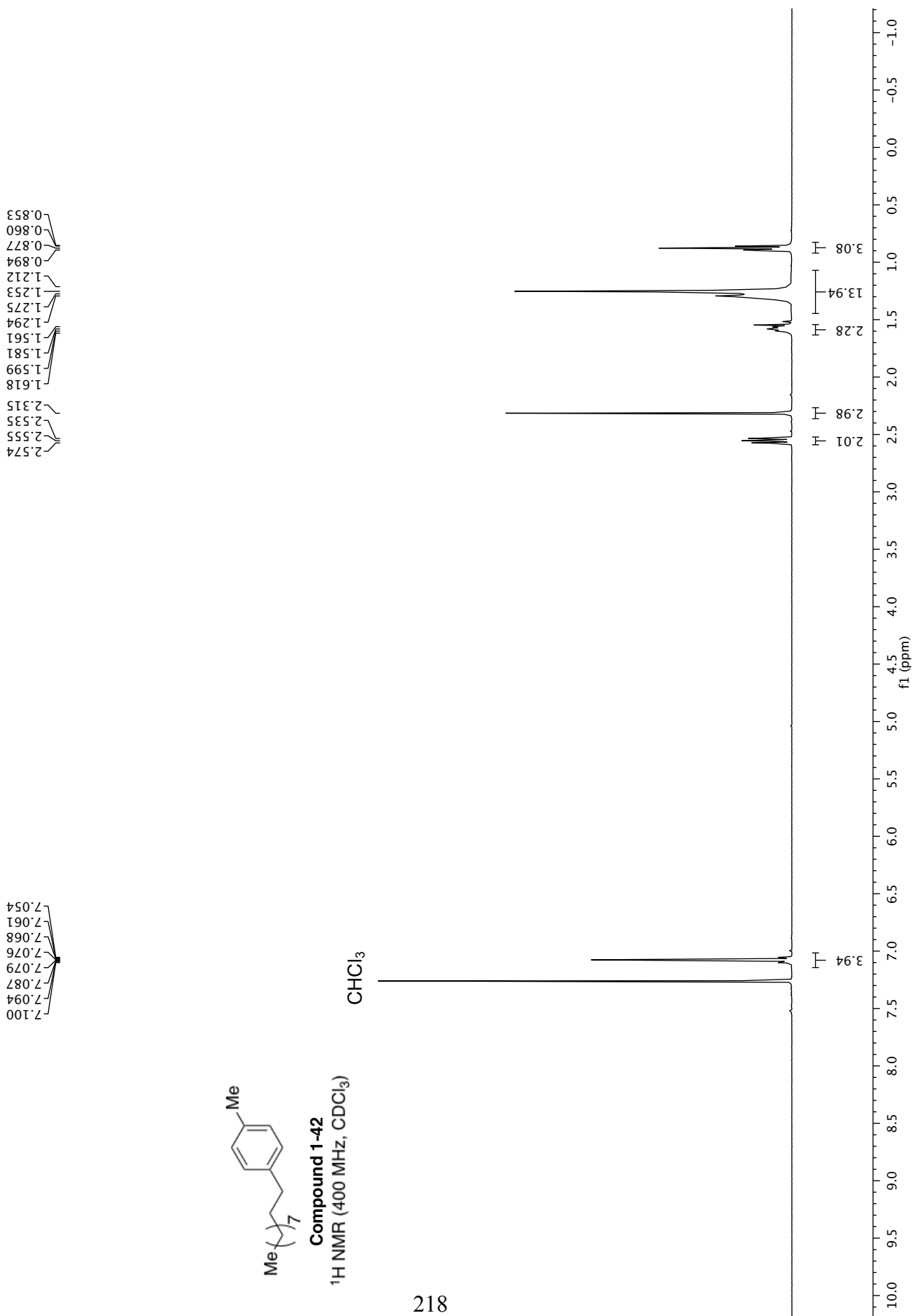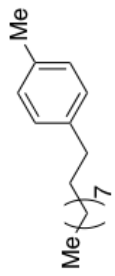
Compound 1-42
¹³C NMR (101 MHz, CDCl₃)
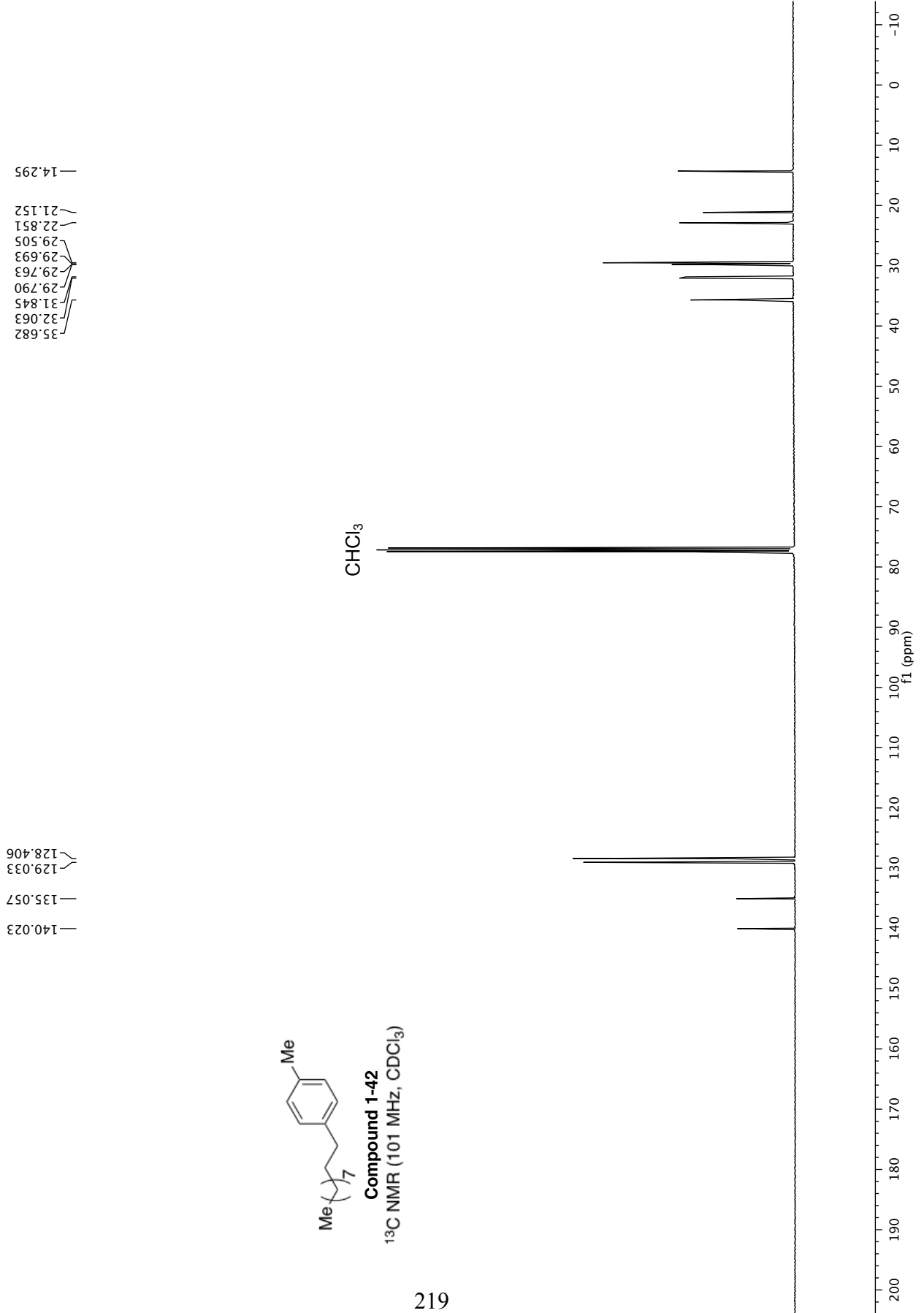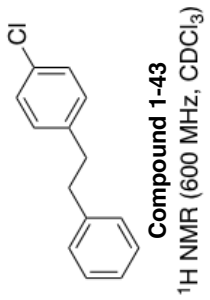
Me—⧸⧹₇

219

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

2.895

7.077
7.091
7.144
7.156
7.187
7.199
7.211
7.223
7.227
7.230
7.238
7.241
7.245
7.266
7.277
7.279
7.291

Cl

**Compound 1-43**
**$^1$H NMR (600 MHz, CDCl$_3$)**

220

CHCl$_3$

2.00
1.95
0.98
1.94
2.05

4.07

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5  -1.0
f1 (ppm)

37.344
37.899

126.184
128.519
128.538
128.608
129.983
131.773

140.254
141.419

CHCl₃

Cl
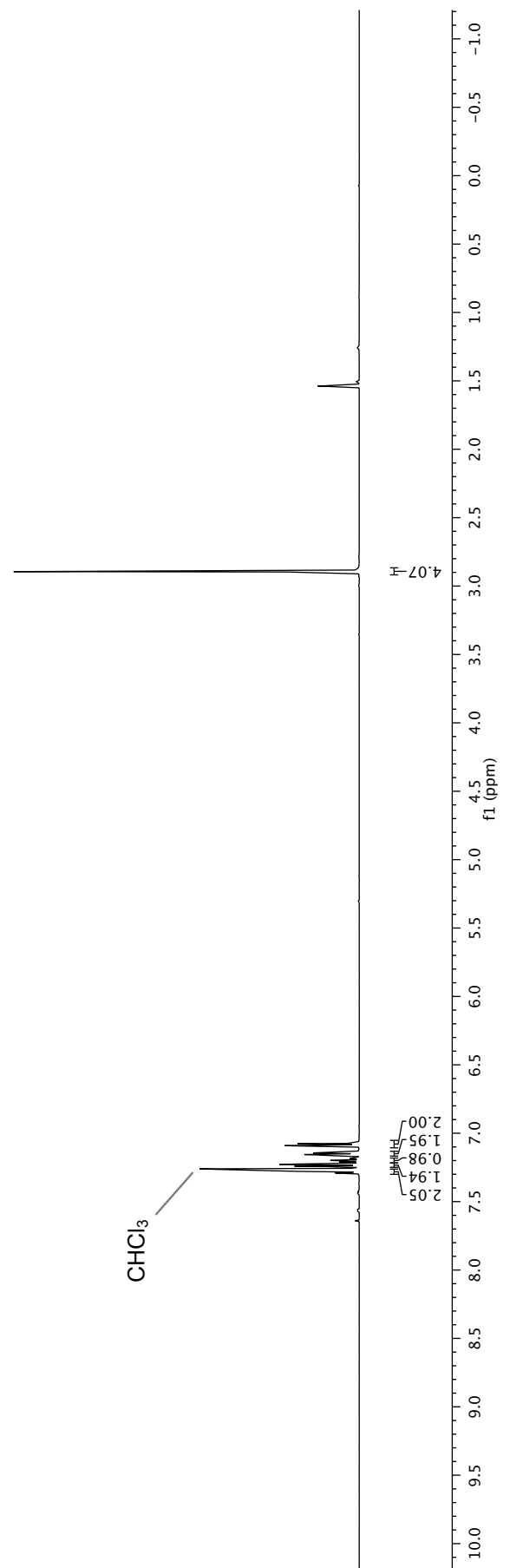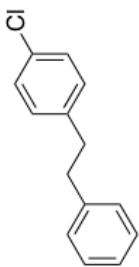
**Compound 1-43**
¹³C NMR (151 MHz, CDCl₃)

221

f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

2.586
2.924
2.928
2.939
2.943
2.974
2.984
2.986
2.999
3.003

7.151
7.163
7.165
7.188
7.190
7.192
7.199
7.202
7.205
7.212
7.214
7.216
7.243
7.257
7.266
7.279
7.289
7.291
7.867
7.870
7.878
7.881

CHCl$_3$

**Compound 1-44**
$^1$H NMR (600 MHz, CDCl$_3$)

3.03

2.07
1.99

1.98
1.00
2.09
1.93

1.99

26.754

37.571
38.003

CHCl₃

126.252
128.551
128.582
128.662
128.863
135.254

141.225

147.620

Me

O
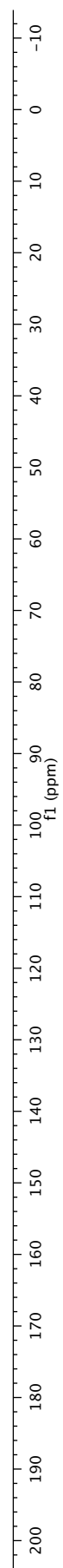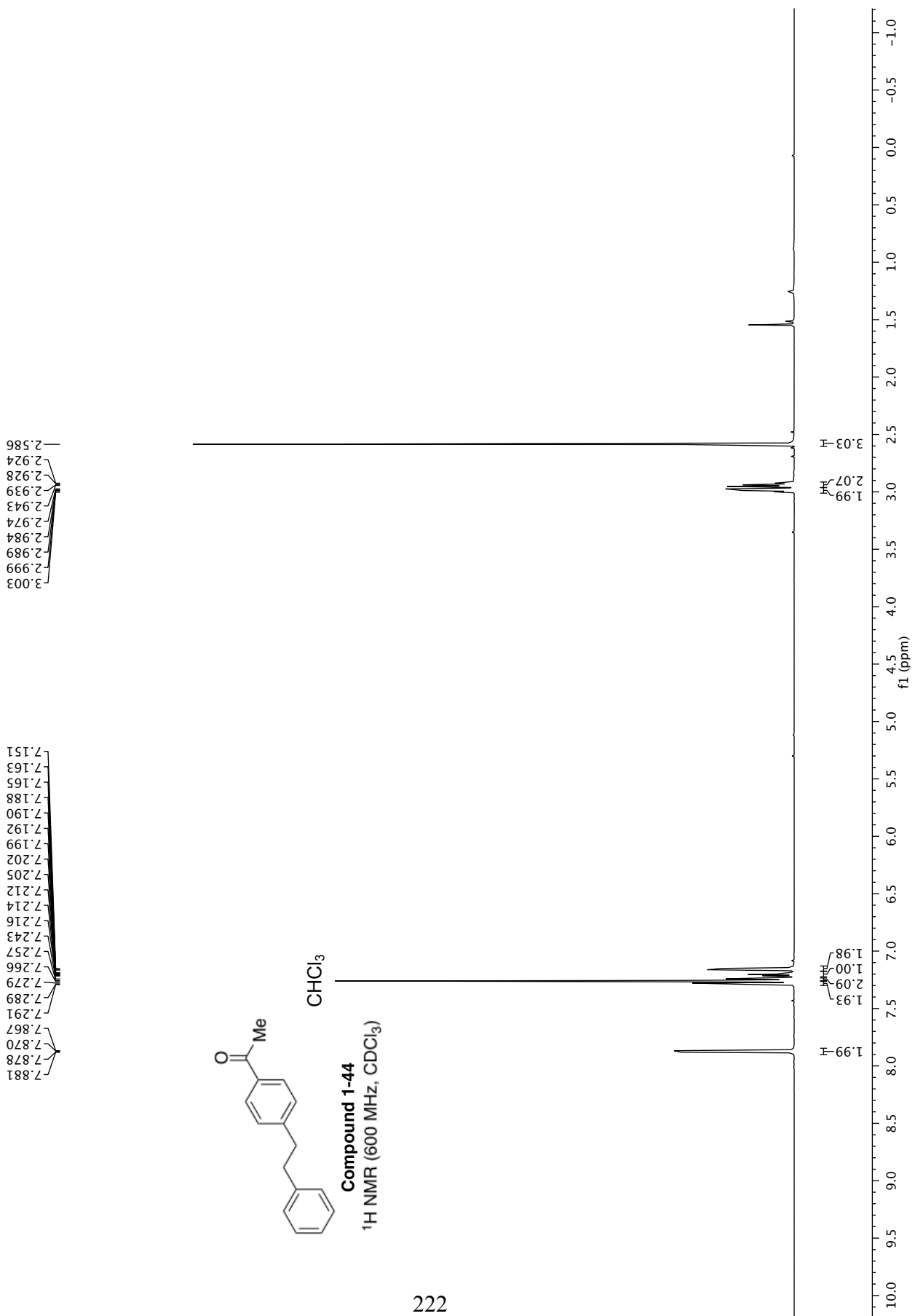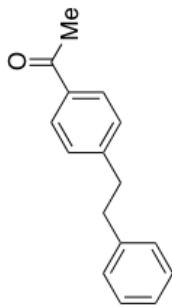
Compound 1-44
¹³C NMR (101 MHz, CDCl₃)

198.087

223

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

1.378
1.390
1.402

2.918
2.922
2.930
2.933
2.938
2.947
2.967
2.976
2.981
2.984
2.991
2.995

4.348
4.360
4.372
4.384

7.147
7.159
7.185
7.198
7.210
7.215
7.228
7.263
7.265
7.275
7.285
7.288
7.944
7.958

CHCl₃
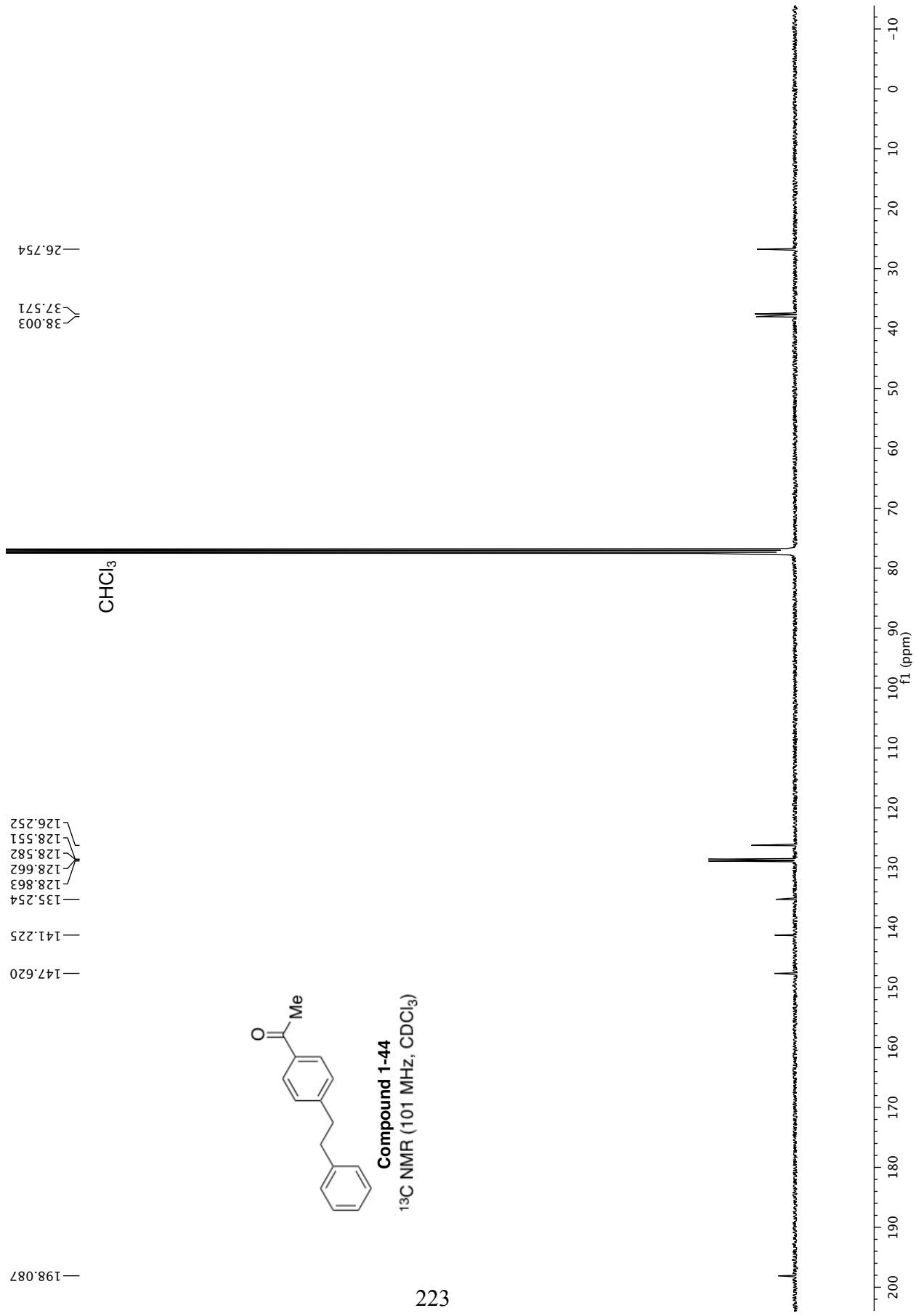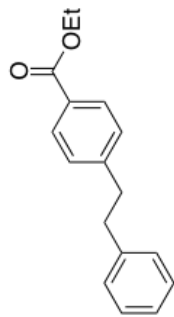
**Compound 1-45**
¹H NMR (600 MHz, CDCl₃)

224

3.04

2.06
1.94

2.00

1.98
2.95
1.97

1.96

f1 (ppm)
10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5  -1.0

14.504

37.634
38.027

60.946

CHCl₃

126.223
128.439
128.539
128.598
128.638
129.791

141.316

147.185

166.819

**Compound 1-45**
¹³C NMR (151 MHz, CDCl₃)

225

f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

1.112
1.238

2.898
2.905
2.915
2.920
2.926
2.930
2.936
2.942
2.951
2.958
3.263

3.541

7.161
7.172
7.175
7.178
7.191
7.196
7.206
7.208
7.263
7.276
7.281
7.284
7.288
7.291
7.294

Compound 1-46
¹H NMR (600 MHz, CDCl₃)

CHCl₃

226

3.14
3.13

3.97

1.98
2.00

4.93
3.93

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  0.0  -0.5  -1.0
f1 (ppm)

13.046
14.398

37.853
37.866
39.380
43.432

CHCl₃

126.134
126.549
128.491
128.579
128.592
135.000

141.560
142.995

171.546

**Compound 1-46**
¹³C NMR (101 MHz, CDCl₃)

227

f1 (ppm)
200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10

0.841
0.847
0.852
0.853
0.863
0.864
1.154
1.159
1.165
1.168
1.181
1.199
1.211
1.237
1.240
1.248
1.255
1.277
1.502
1.512
1.518
1.522
1.528
1.537
1.545

2.598
2.610
2.622
2.633
2.645
2.657

3.794

6.832
6.835
6.847
6.846
7.092
7.096
7.103
7.107

OMe

Me

3

Me
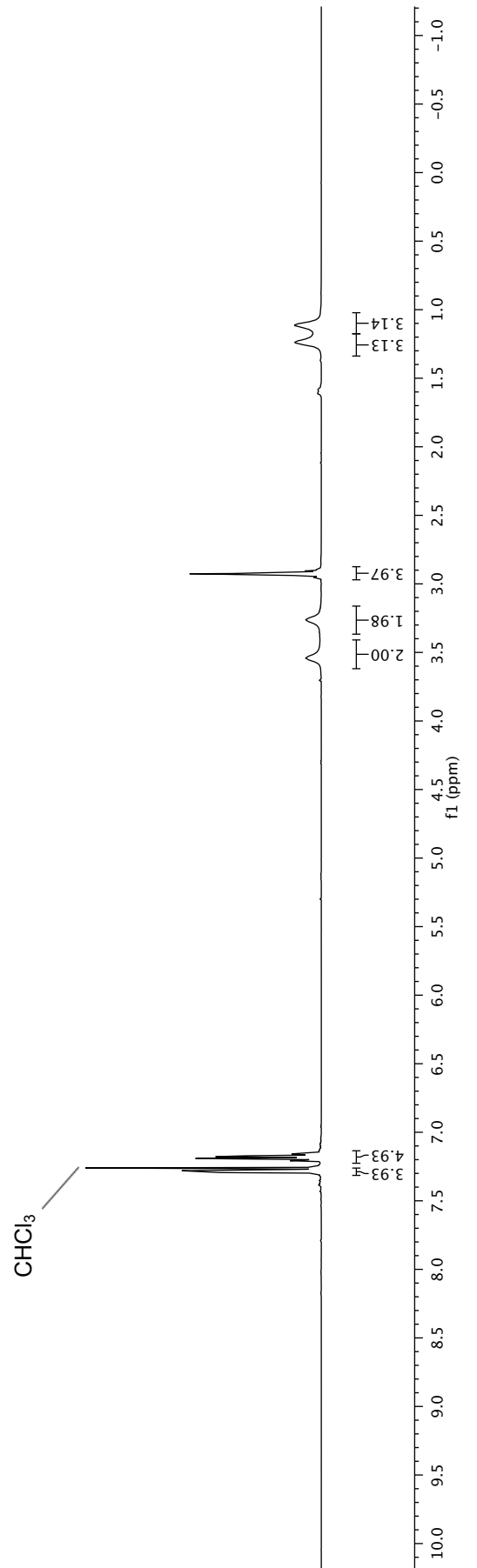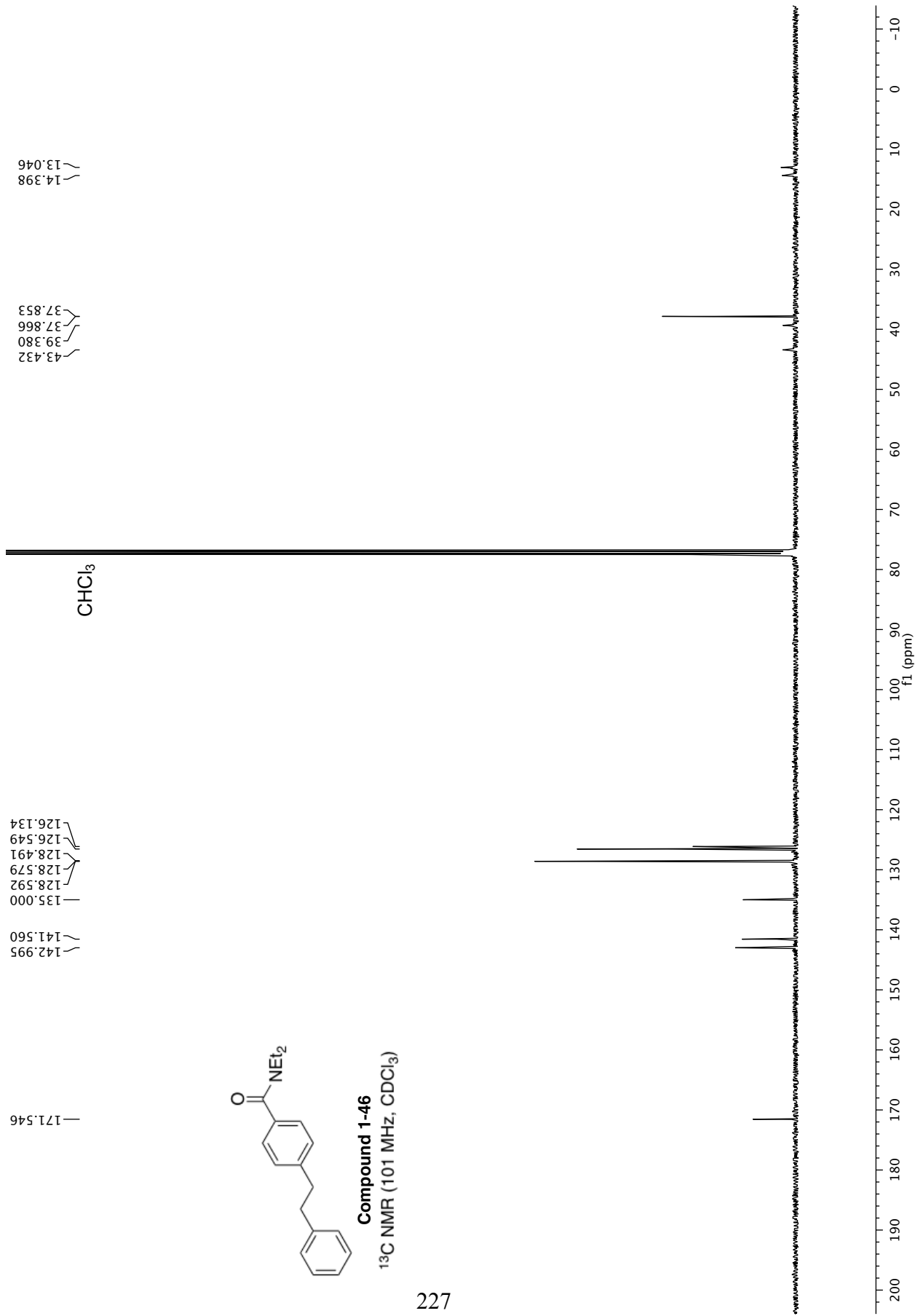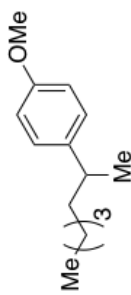
**Compound 1-47**
$^1$H NMR (600 MHz, CDCl$_3$)

228

CHCl$_3$

3.00
9.22
2.08

1.00

2.94

1.88
1.93

f1 (ppm)

14.221

22.749
22.667
27.540
32.118

38.748
39.230

55.380

113.808

127.929

140.296

157.804

CHCl₃

OMe

Me

Me

3
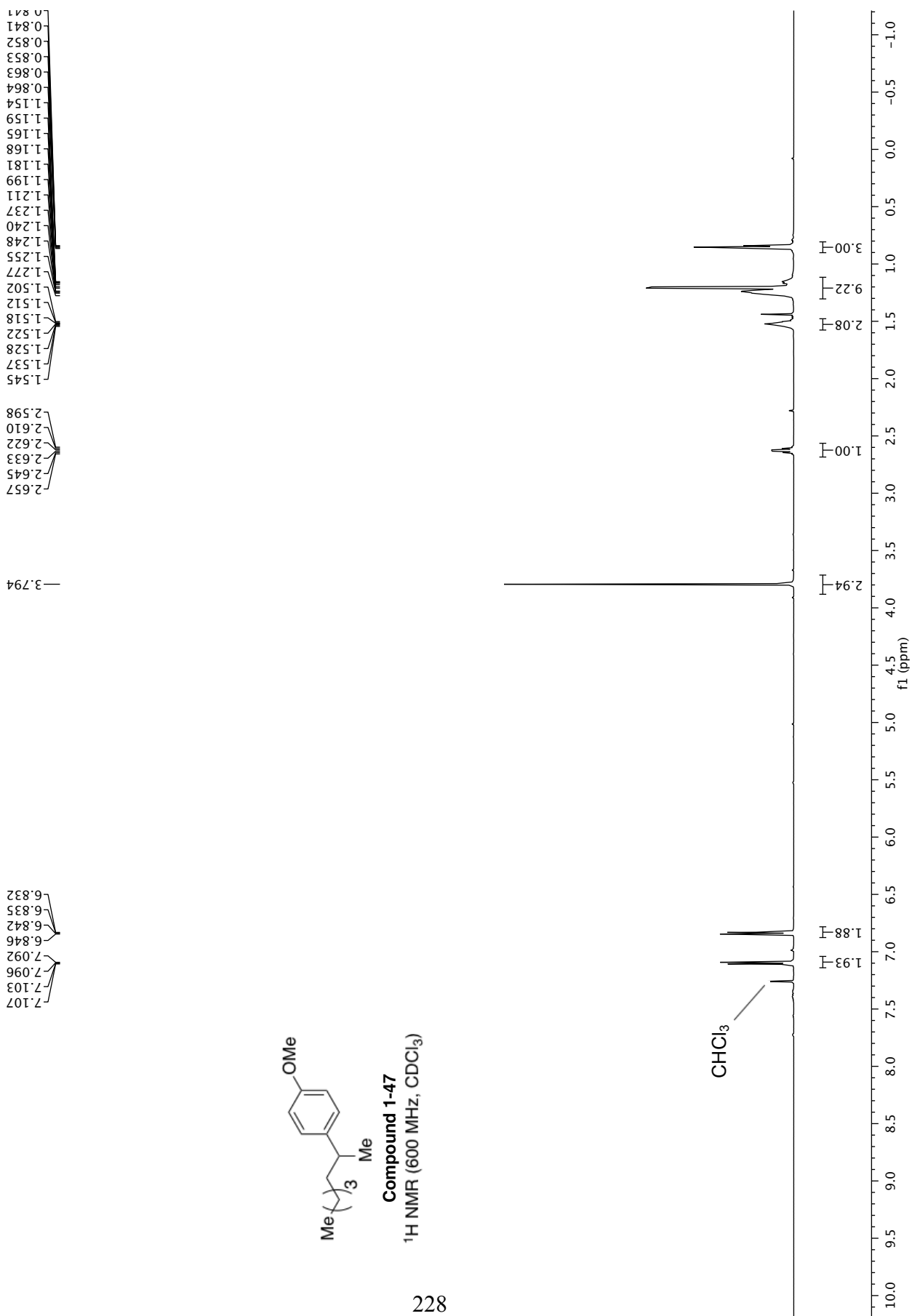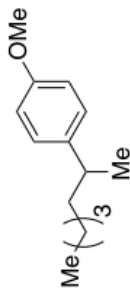
**Compound 1-47**

¹³C NMR (151 MHz, CDCl₃)

229

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1.235
1.240
1.271
1.276
1.282
1.292
1.298
1.303
1.365
1.370
1.374
1.391
1.396
1.412
1.429
1.445
1.450
1.467
1.470
1.756
1.777
1.849
1.854
1.869
1.885
2.543
2.548
2.563
2.568
2.580

7.288
7.302

7.883
7.896
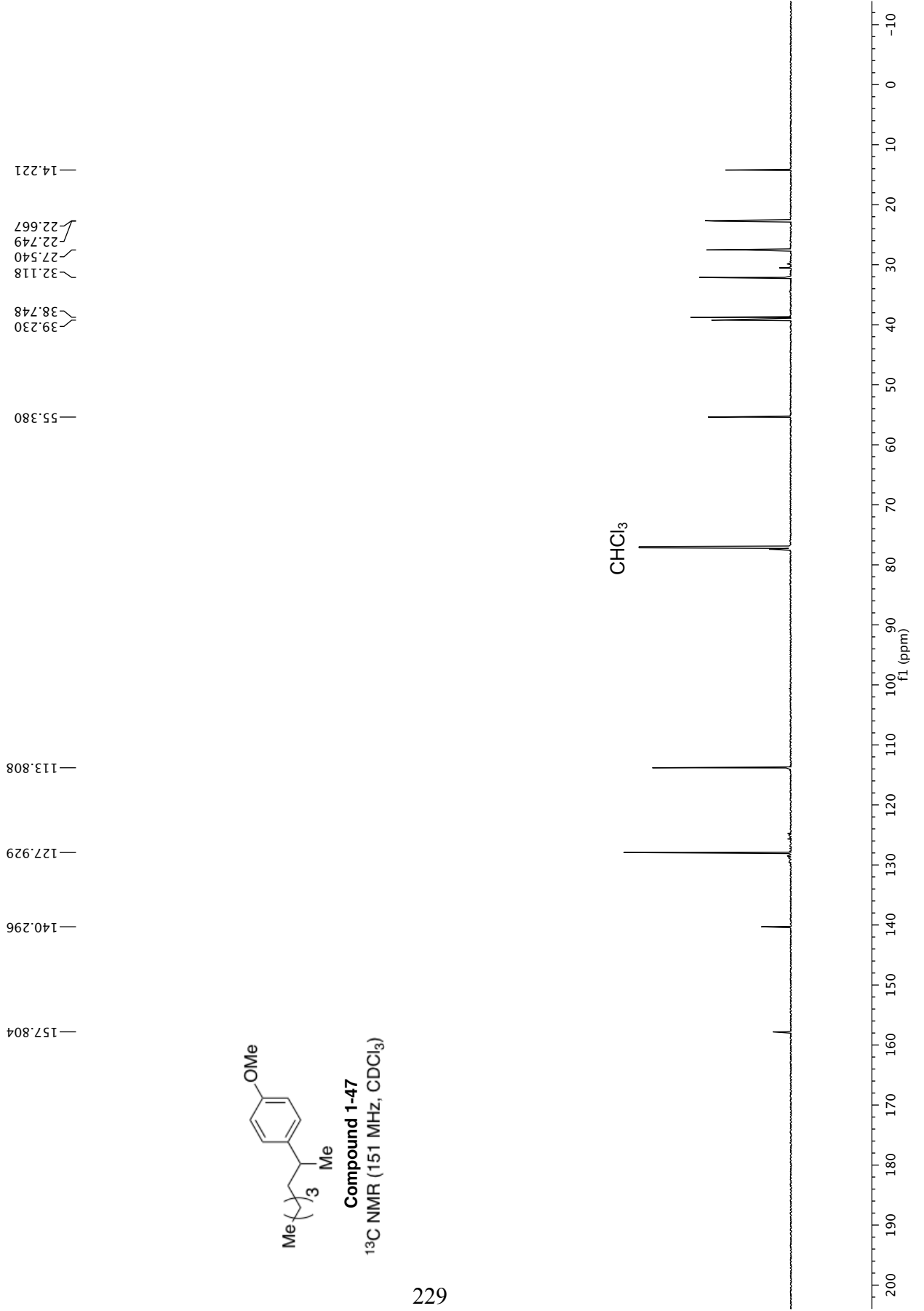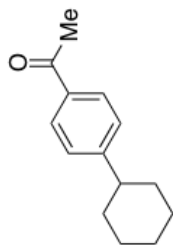
**Compound 1-48**
1H NMR (600 MHz, CDCl₃)

CHCl₃

1.44
4.09
1.09
4.00
3.91
1.94
1.95

-1.0  -0.5  0.0  0.5  1.0  1.5  2.0  2.5  3.0  3.5  4.0  4.5  5.0  5.5  6.0  6.5  7.0  7.5  8.0  8.5  9.0  9.5  10.0
f1 (ppm)

26.190
26.702
26.882

34.268

44.849

CHCl₃

127.188
128.688

135.216

153.911

198.017

Me

O
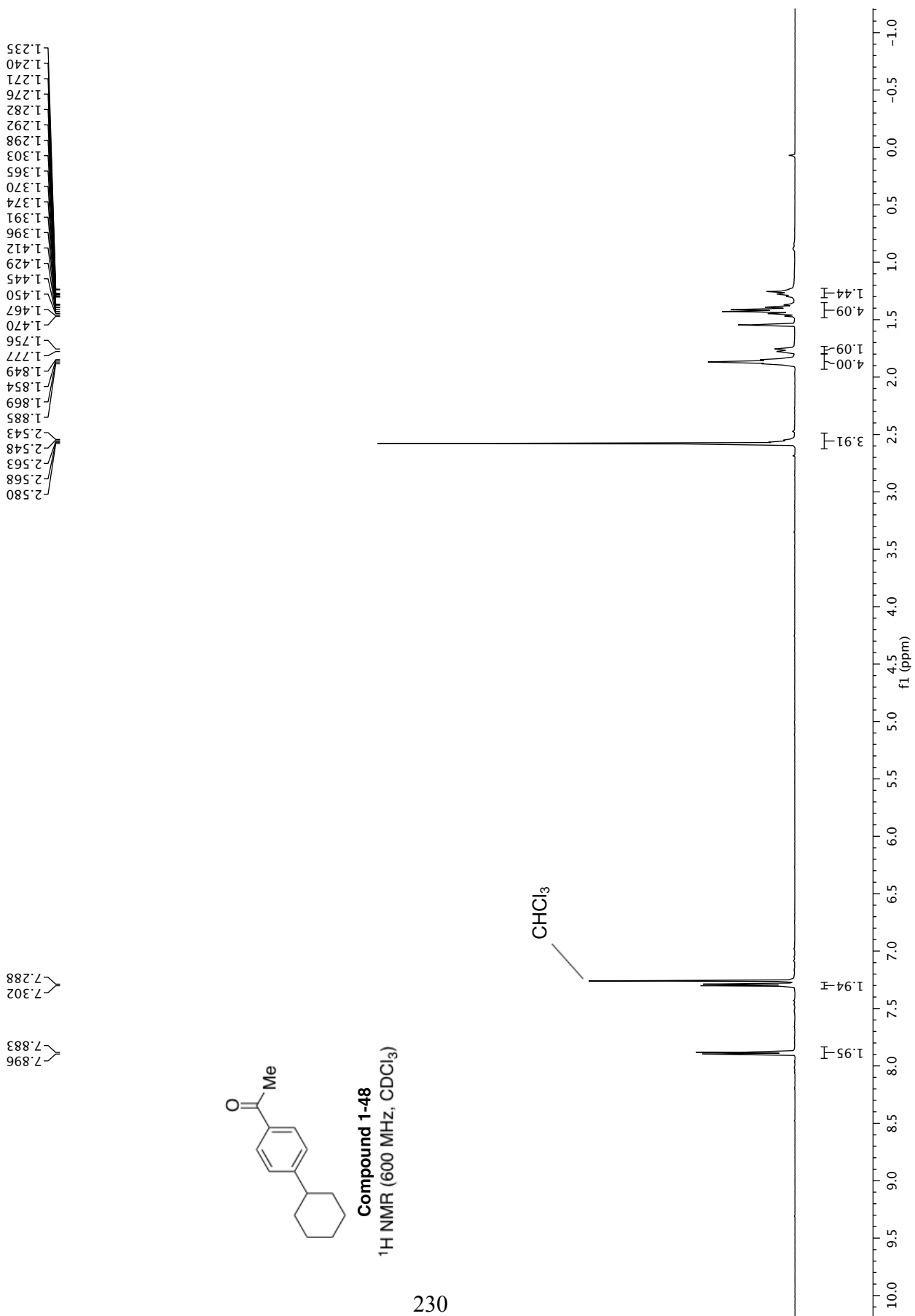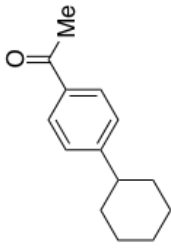
**Compound 1-48**
¹³C NMR (151 MHz, CDCl₃)

231

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10
f1 (ppm)
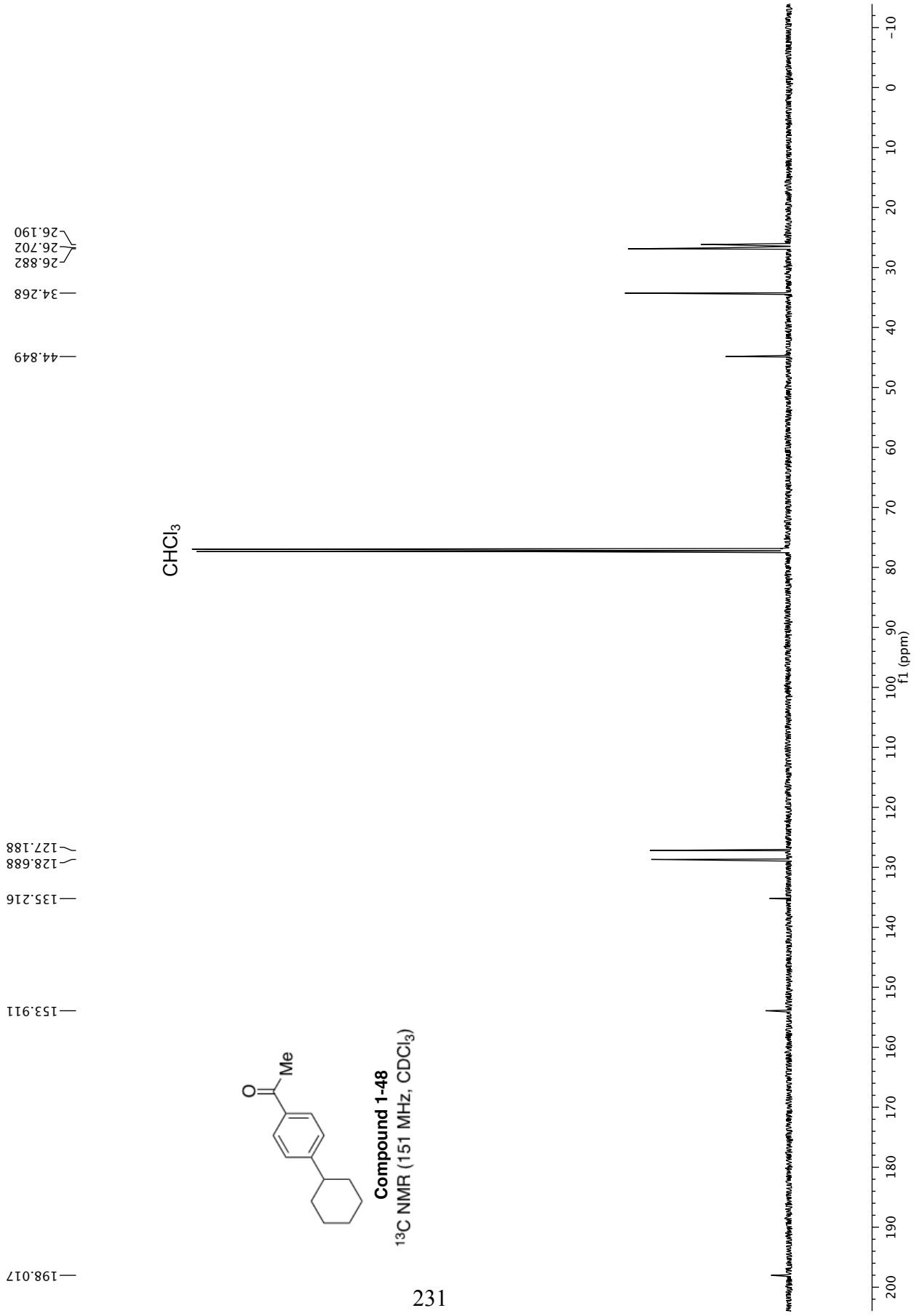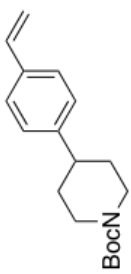
Compound 1-49
¹H NMR (400 MHz, CDCl₃)

CHCl₃

1.484
1.559
1.569
1.591
1.601
1.622
1.635
1.639
1.654
1.664
1.794
1.826
2.595
2.604
2.612
2.625
2.634
2.643
2.655
2.664
2.673
2.771
2.796
2.825
4.243
5.194
5.196
5.221
5.223
5.692
5.694
5.736
5.738
6.658
6.686
6.702
6.730
7.155
7.175
7.349
7.370

8.52
2.28
2.01
1.16
2.18
2.15
1.04
1.05
1.09
2.02
2.00

28.645
33.295
42.626
44.478

CHCl₃

79.584

113.451

126.497
127.082

135.944
136.650

145.651

155.006
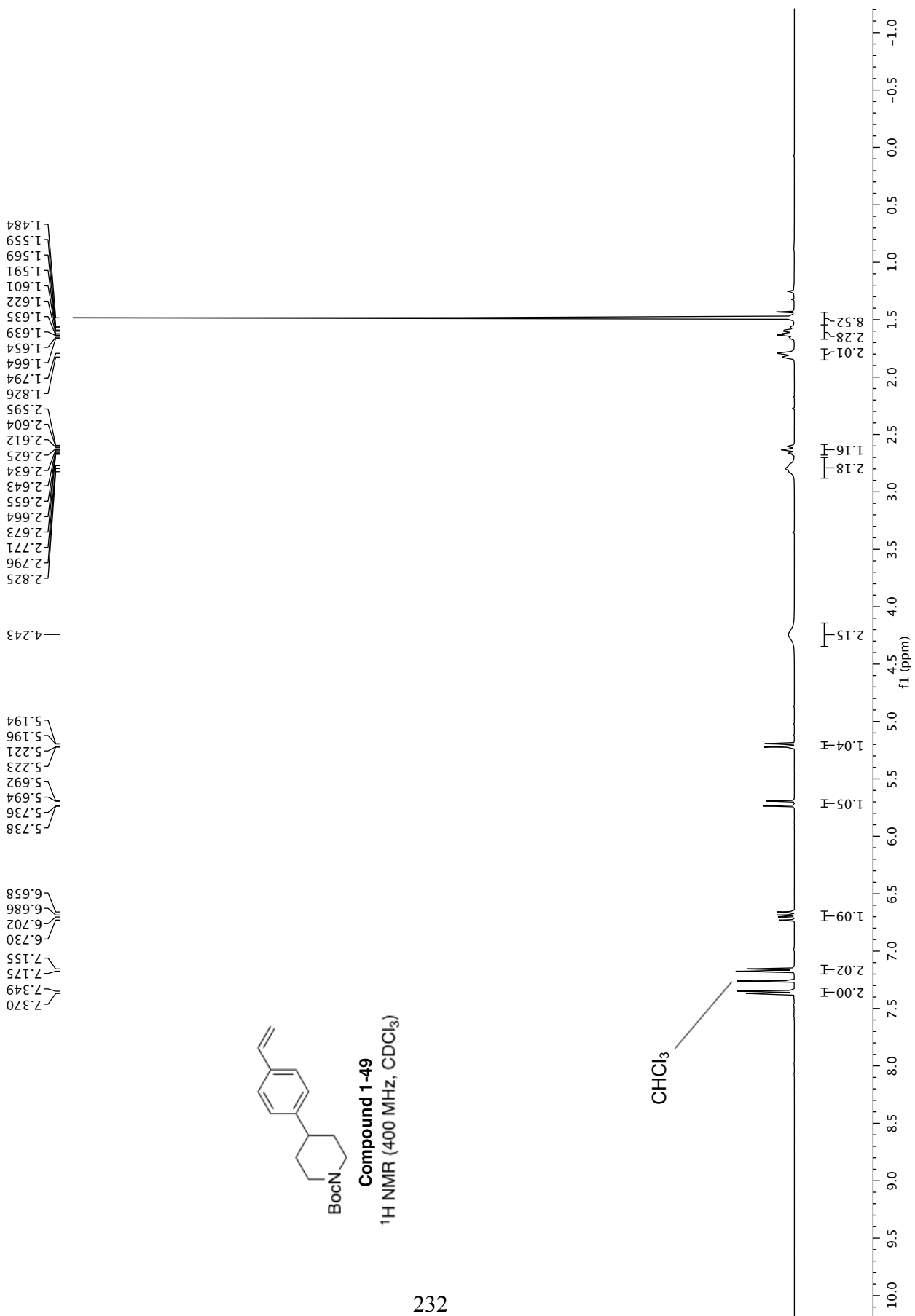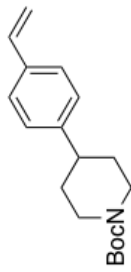
Compound 1-49
¹³C NMR (151 MHz, CDCl₃)

233

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

Compound 1-50
$^1$H NMR (600 MHz, CDCl$_3$)

234

14.294
14.317

28.581

32.998

43.774

53.119

60.293

79.812

CHCl₃

115.191
115.336
122.409
122.523
124.119
124.139
131.381
131.417

139.855
139.907

154.878

160.562
162.181
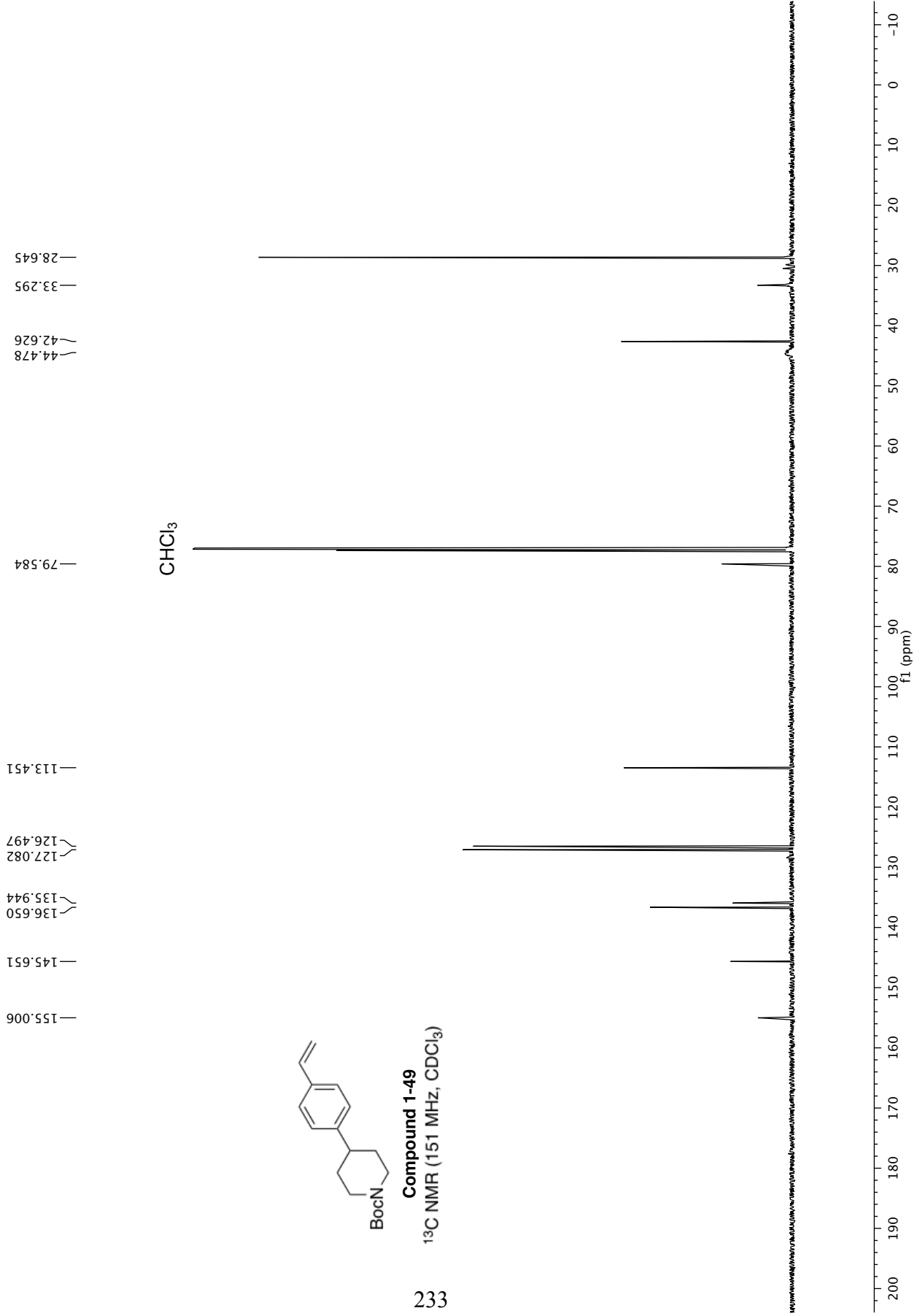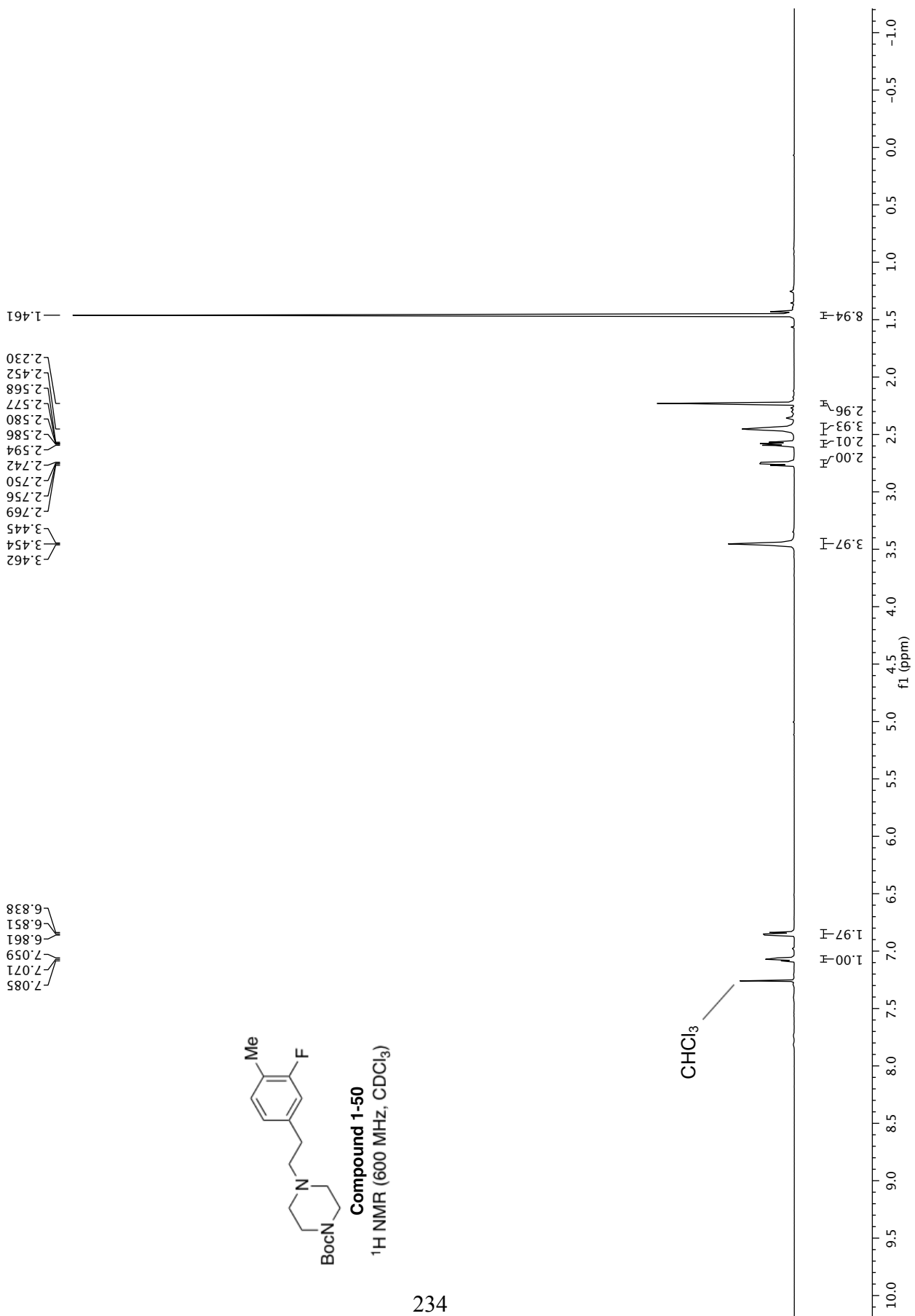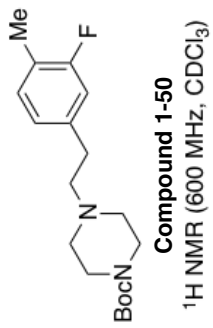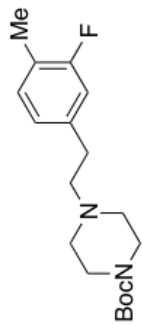
Compound 1-50
¹³C NMR (151 MHz, CDCl₃)

235

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)
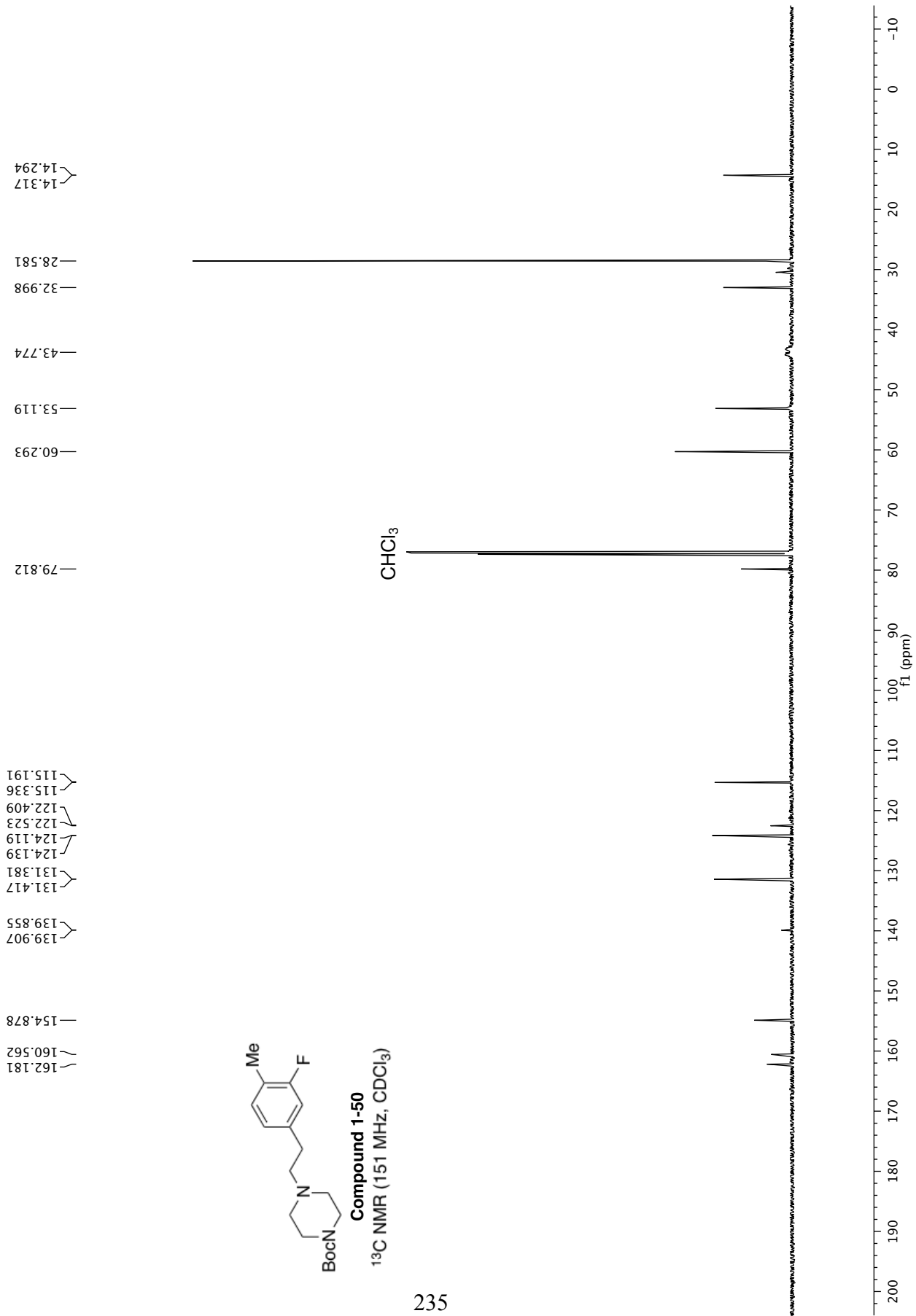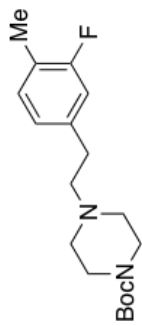
−117.975

Compound 1-50
19F NMR (565 MHz, CDCl$_3$)

236

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

1.466

2.497
2.657
2.911

3.485
3.773

6.411
6.412
6.416
6.418
7.024
7.029
7.061
7.064
7.075
7.078
7.239
7.258
7.439
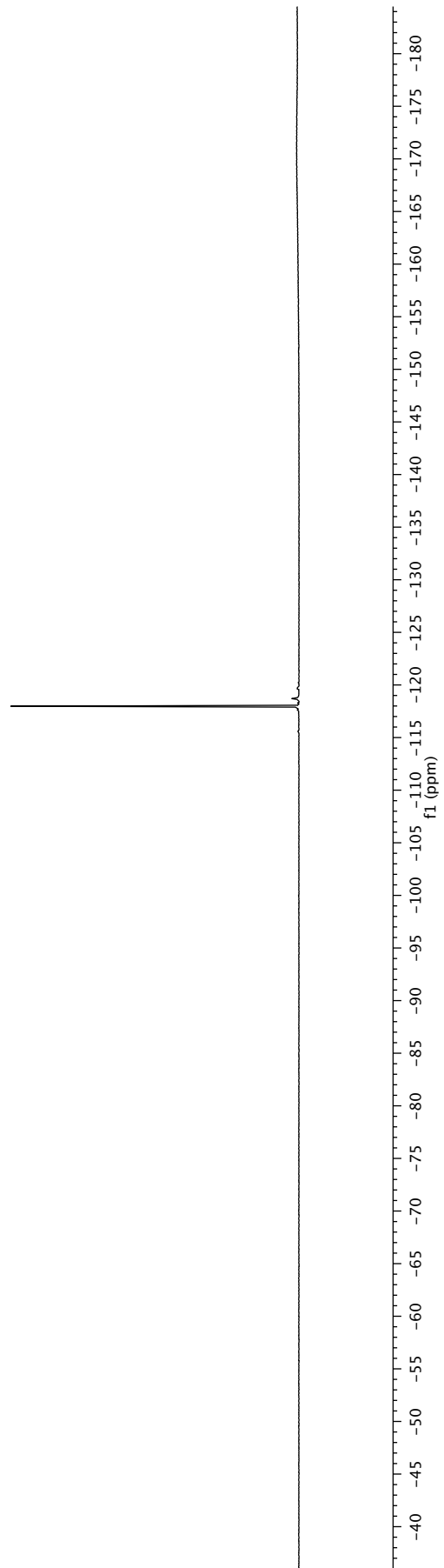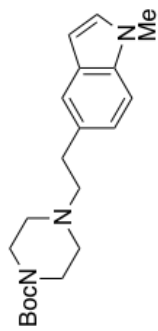
CHCl₃

**Compound 1-51**
¹H NMR (600 MHz, CDCl₃)

237

8.81

4.03
2.06
2.05

4.04
3.05

1.00

0.95
0.97
1.09
0.95

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5  -1.0
f1 (ppm)

28.57
33.00
33.68

43.74

53.17

61.64

CHCl₃

79.71

100.54

109.21

120.47
122.72

128.77
129.18
130.89
135.56

154.88
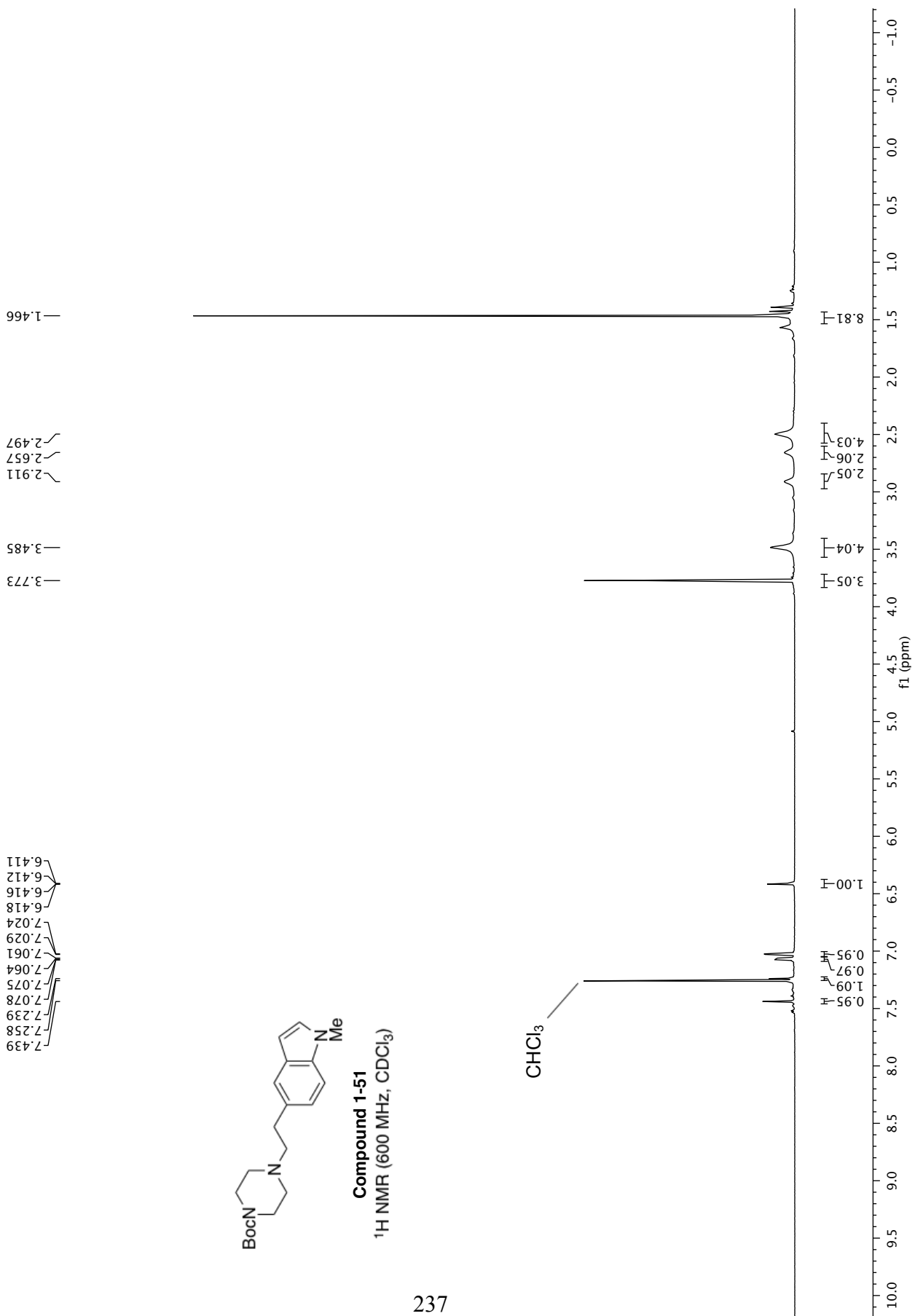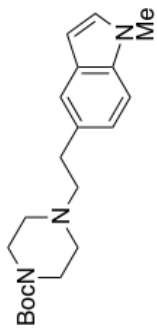
Compound 1-51
¹³C NMR (101 MHz, CDCl₃)

238

200   190   180   170   160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10   0   -10
f1 (ppm)

1.49
1.50
1.67
1.71
1.73
1.74
1.76
1.77
1.78
2.23
2.43
2.46
2.47
2.49
2.51
2.53
2.56
2.57
2.98
3.01
3.02
3.08
3.11
3.12
3.27
3.28
3.35
3.36
3.38
3.69
3.90
4.00

6.79
6.80
6.81
6.83
6.84
6.87
6.89
7.06
7.07
7.10

Me

F

N
Boc
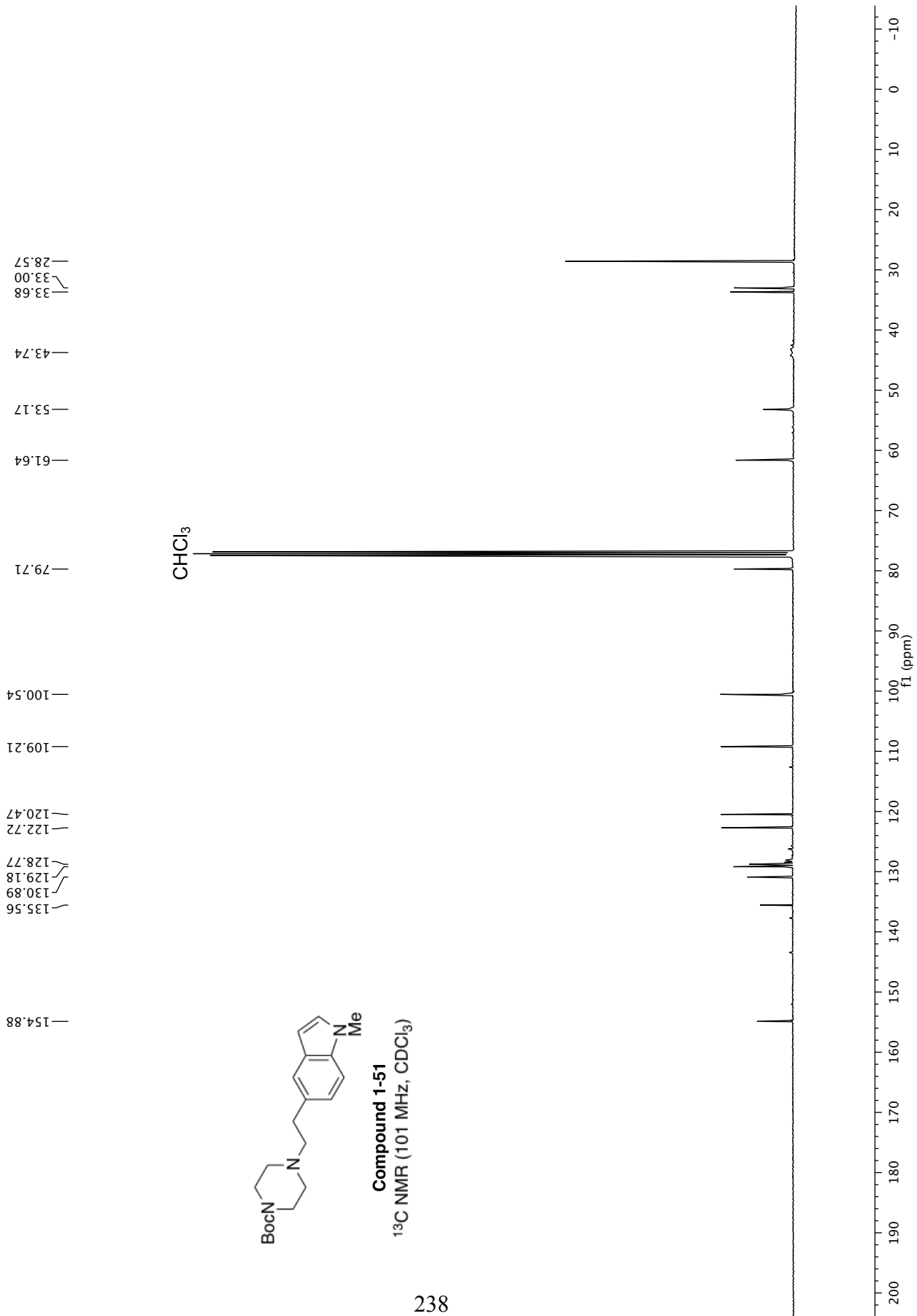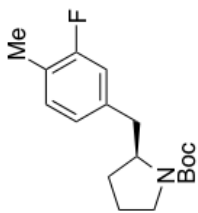
**Compound 1-52**
¹H NMR (600 MHz, CDCl₃)

CHCl₃

8.71
4.17
2.85
1.02
0.97
2.01
1.00

2.08
1.00

f1 (ppm)

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5  -1.0

14.330
14.365

22.784
23.567
28.730
29.015
29.792

39.074
40.142

46.425
46.951

58.618
58.884

CHCl$_3$

79.224
79.502

115.736
115.966
115.994
116.195
122.314
122.467
122.522
122.696
124.824
125.043
131.221
131.265
131.387
131.436
138.895
138.968

154.645

160.099
162.526

Me

F

Boc
N
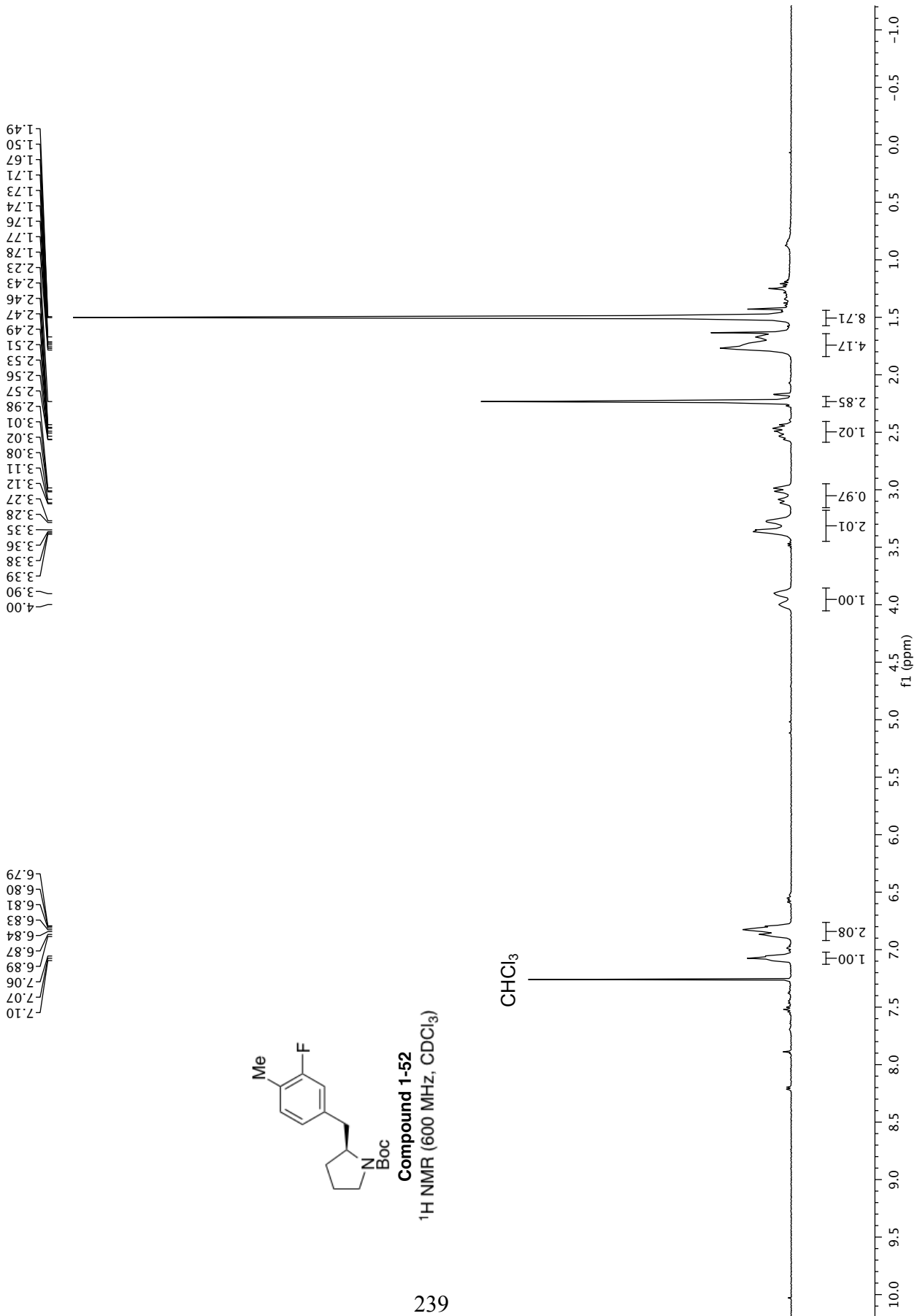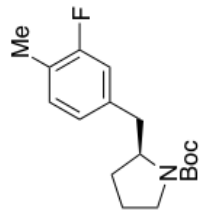
**Compound 1-52**
$^{13}$C NMR (101 MHz, CDCl$_3$)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10
f1 (ppm)

240

−118.39
−117.98

Me

F

N
Boc
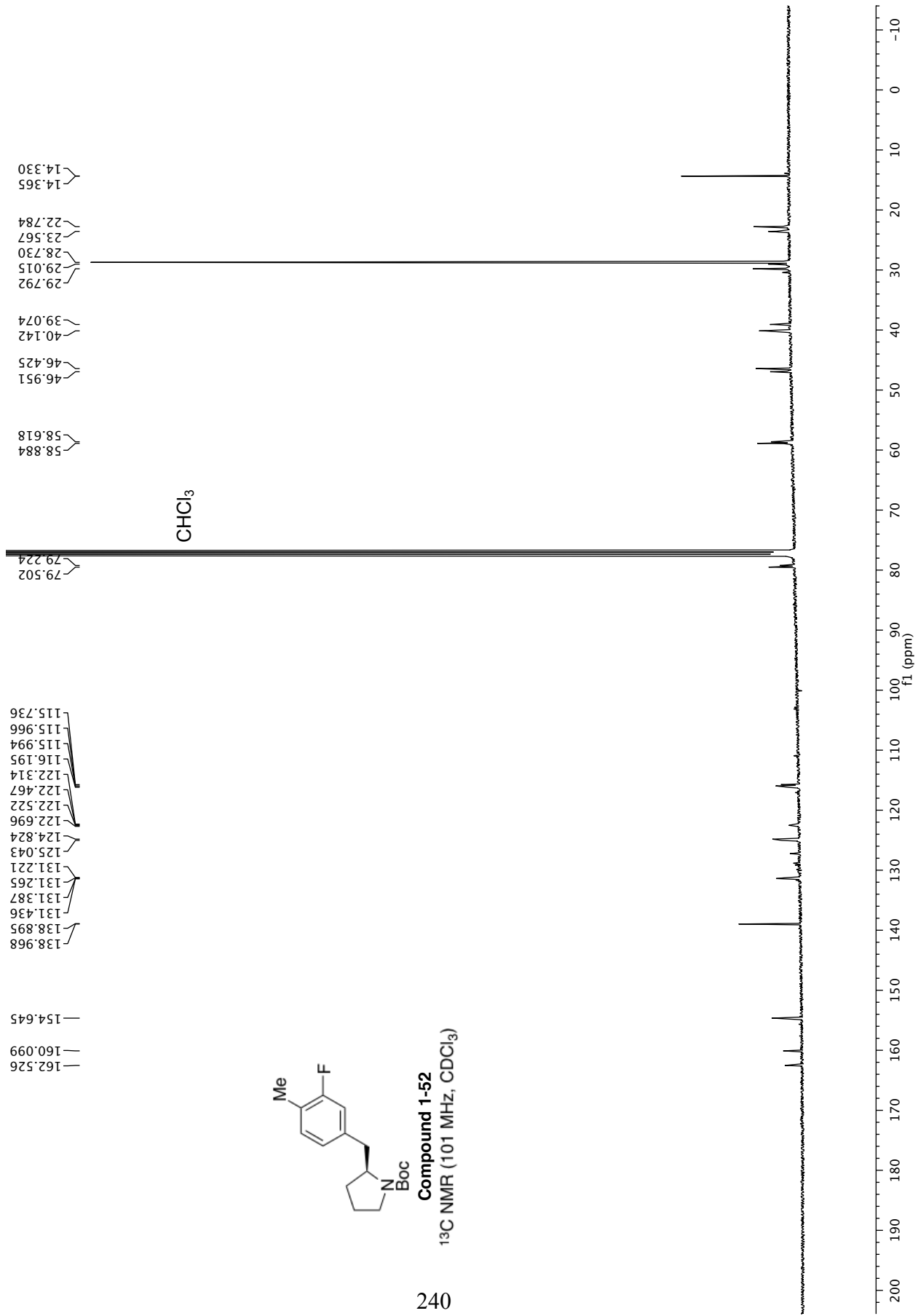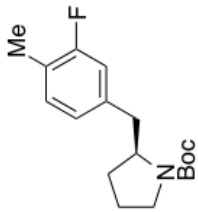
**Compound 1-52**
$^{19}$F NMR (565 MHz, CDCl$_3$)

0.73
1.00
0.04

241

f1 (ppm)

−40 −45 −50 −55 −60 −65 −70 −75 −80 −85 −90 −95 −100 −105 −110 −115 −120 −125 −130 −135 −140 −145 −150 −155 −160 −165 −170 −175 −180

Compound 1-53
1H NMR (600 MHz, CDCl3)

242

11.916
15.783
24.841
28.501
36.970
37.671
56.086
70.127
78.982

CHCl$_3$

114.784
127.592
128.028
128.689
130.305
131.261
137.278
155.710
157.369

Compound 1-53

$^{13}$C NMR (101 MHz, CDCl$_3$)

BocHN

Me

Et

OBn

243
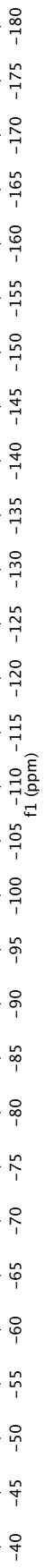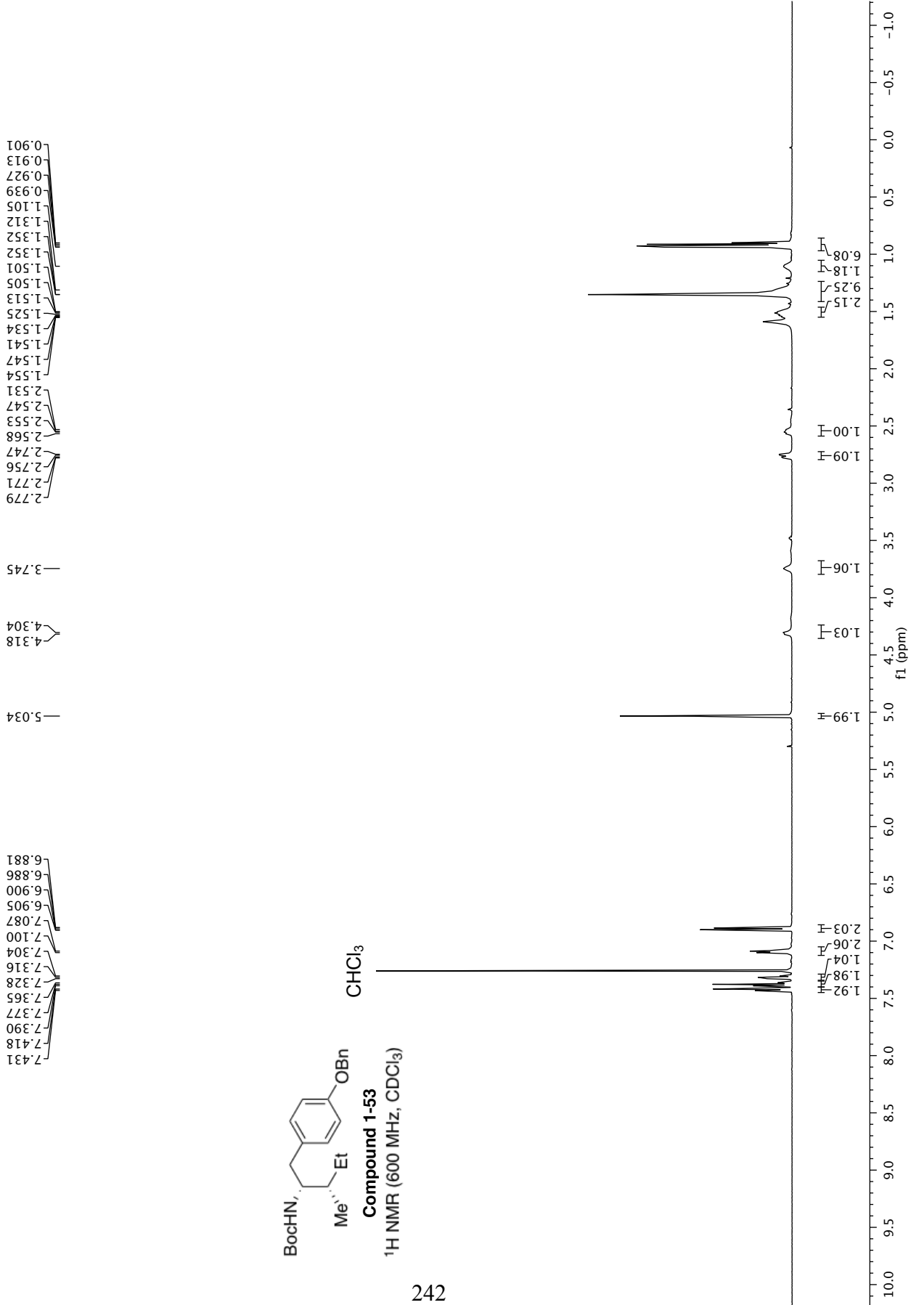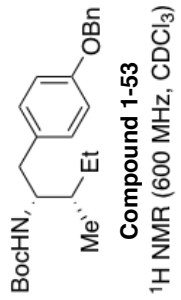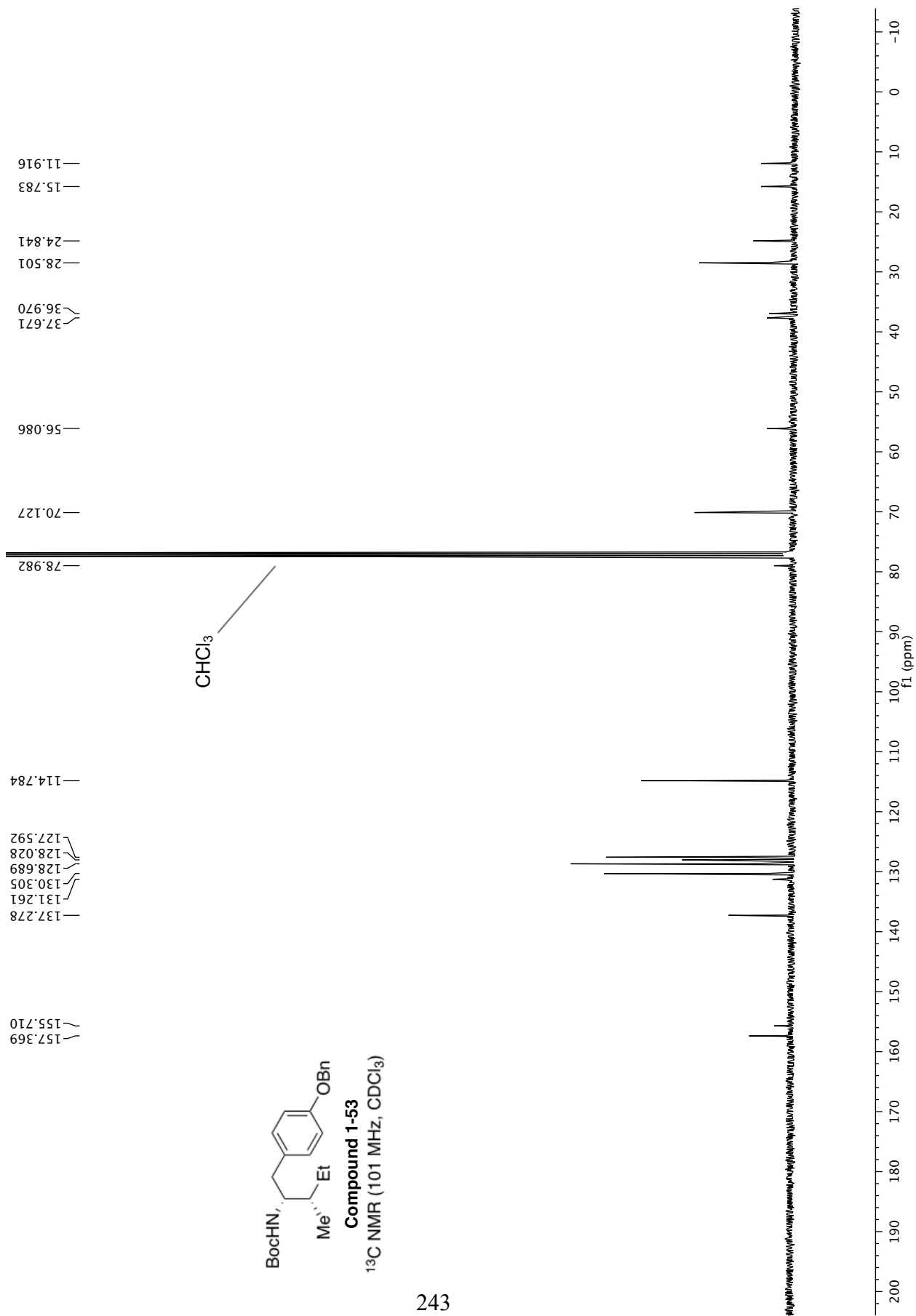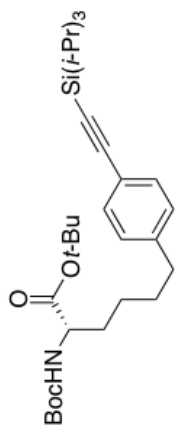
Compound 1-54
¹H NMR (600 MHz, CDCl₃)

CHCl₃

244

1.123
1.310
1.322
1.329
1.338
1.348
1.357
1.364
1.372
1.381
1.390
1.430
1.437
1.569
1.579
1.592
1.604
1.616
1.629
1.639
1.653
1.746
1.754
1.763
1.772
1.794

2.581
2.594
2.606

4.150
4.160

4.974
4.987

7.081
7.094
7.370
7.384

20.74
1.13
1.09
8.78
8.89
2.97
0.98

2.00

0.99

0.97

1.97
1.96

—172.132

—155.469

—142.904

—132.157
—128.417

—121.090

—107.434

—89.794

—81.873
—79.715

CHCl₃

—53.997

—35.723
—32.997
—30.919
—28.495
—28.137
—24.724

—18.826

—11.505

**Compound 1-54**

¹³C NMR (151 MHz, CDCl₃)

f1 (ppm)

245

-1.983

**Compound 1-54**
29Si NMR (119 MHz, CDCl3)

246

50   45   40   35   30   25   20   15   10   5   0   -5   -10   -15   -20   -25   -30   -35   -40   -45   -50
f1 (ppm)

1.898
1.915
1.933
2.093
2.099
2.113
2.119
2.132
2.137
2.569
2.580
2.593
2.602
2.693
2.712
2.727
2.739
2.751
2.763
3.363
3.385
3.475
3.498
3.588
3.606
3.625
3.677
3.689
3.701
3.715
3.728
3.825
3.827
3.829
3.832
3.844
3.846
3.848
3.851

5.922

6.623
6.626
6.636
6.639
6.708
6.710
6.713
6.726
6.978
6.981
6.988
6.992
6.996
7.003
7.007
7.247
7.256
7.270
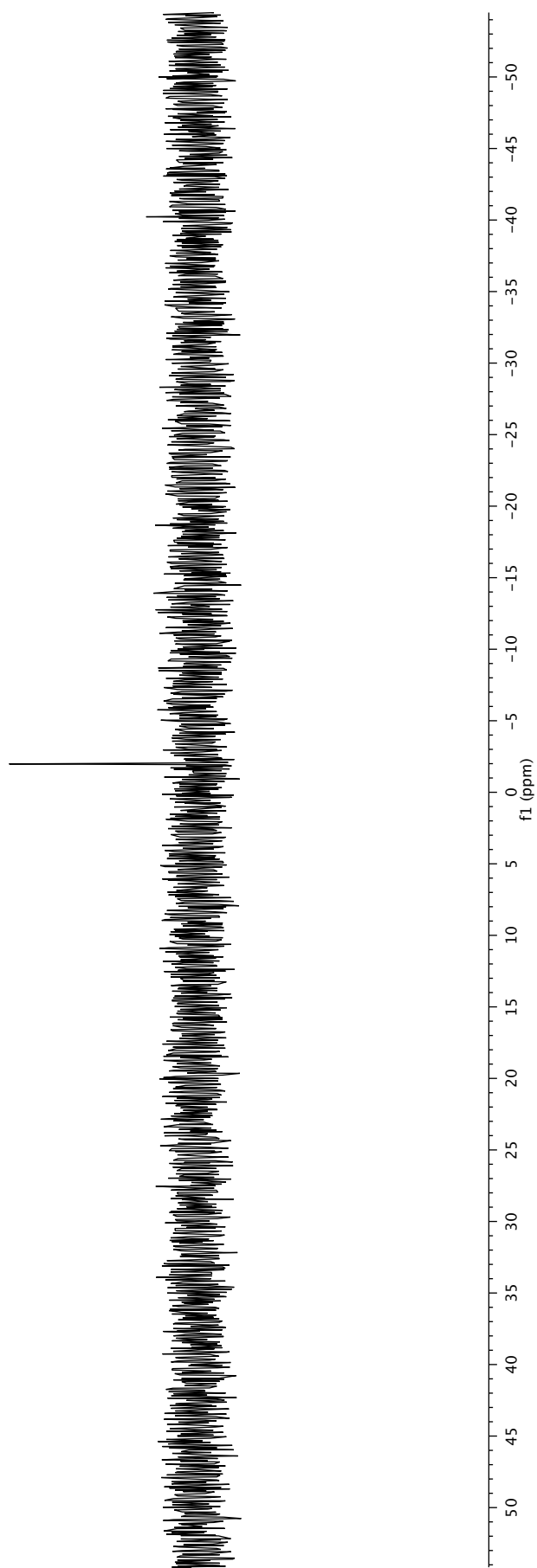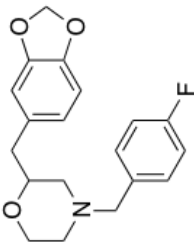
**Compound 1-55**
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

247

1.05
1.01

1.99
2.02

1.03
1.06
1.01
1.06
1.00

1.96

1.00
1.91

1.96
2.42

f1 (ppm)

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5  -1.0

Compound 1-55
$^{13}$C NMR (151 MHz, CDCl$_3$)

40.024

52.830

58.431
62.551
66.947

76.695

CHCl$_3$

100.940

108.230
109.762

115.128
115.269

122.223

130.703
130.754
131.941
133.578

146.129
147.645

161.369
162.992

f1 (ppm)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10

248
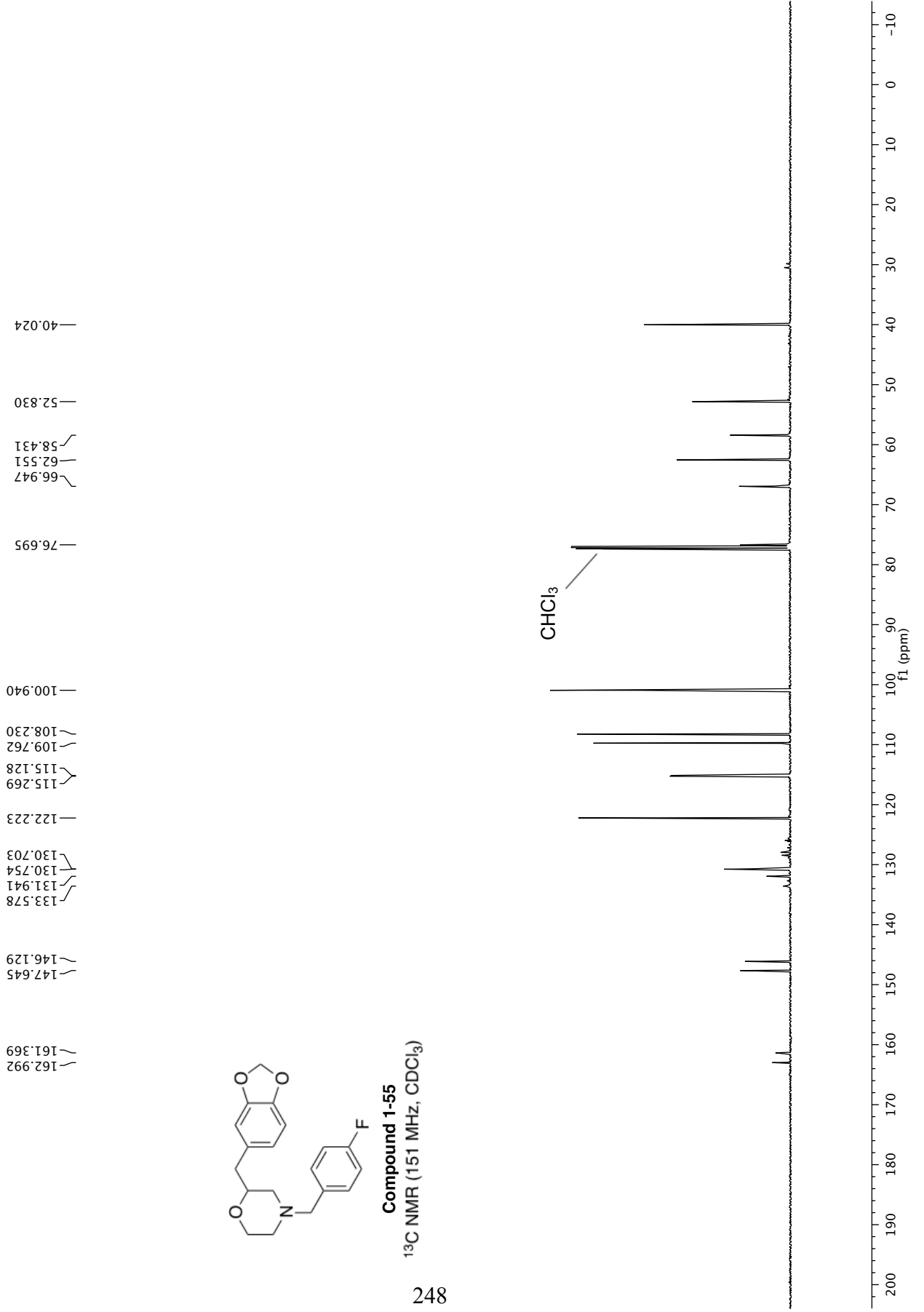
—115.769
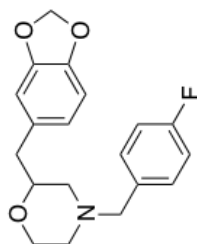
**Compound 1-55**
19F NMR (565 MHz, CDCl3)

249

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)
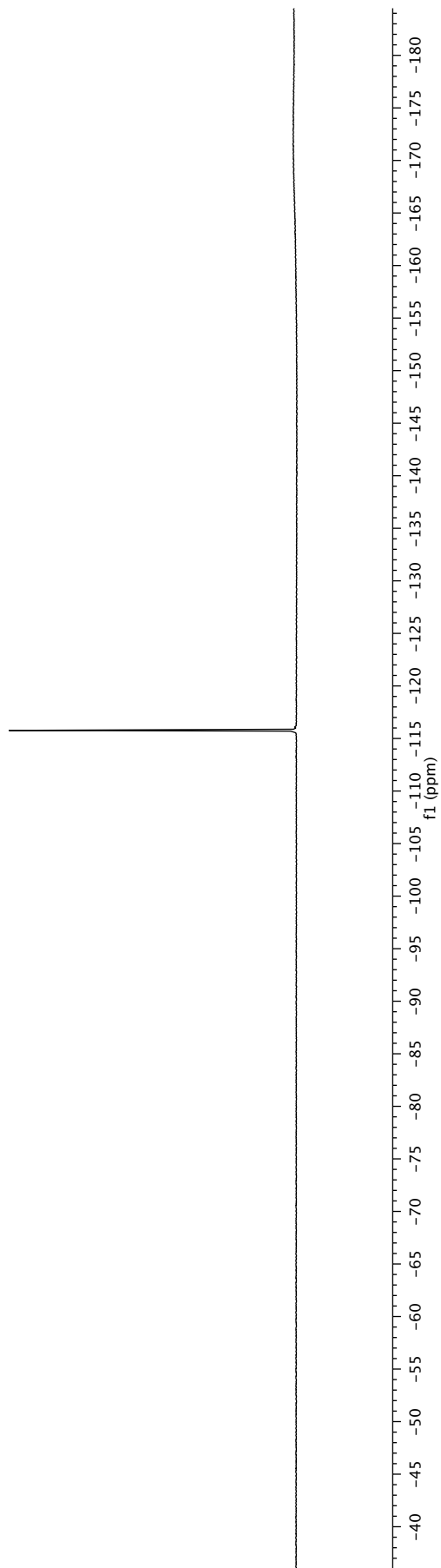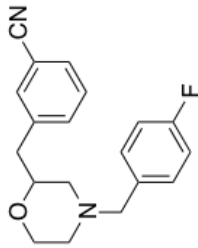
Compound 1-56
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

1.903
1.920
1.938
2.120
2.138
2.157
2.609
2.626
2.685
2.693
2.703
2.709
2.717
2.785
2.799
2.809
2.822
3.412
3.434
3.453
3.476
3.568
3.587
3.605
3.718
3.821
3.823
3.840
3.842

6.988
6.991
7.002
7.013
7.017
7.254
7.260
7.267
7.278
7.362
7.364
7.373
7.375
7.386
7.388
7.426
7.428
7.431
7.439
7.441
7.444
7.497
7.499
7.501
7.511
7.513

250

39.690

52.856

58.223
62.484
66.936

75.901

112.449
115.186
115.326
119.111
129.138
130.219
130.685
130.735
132.973
133.438
133.953

139.904

161.402
163.027

CHCl₃
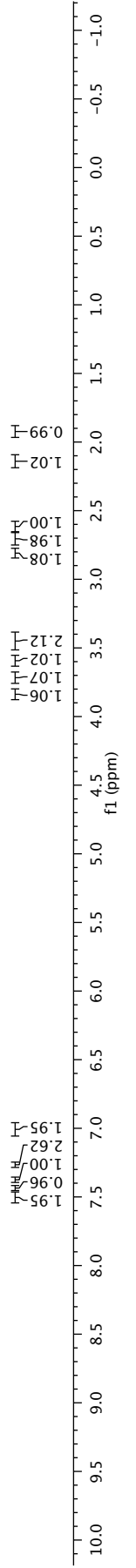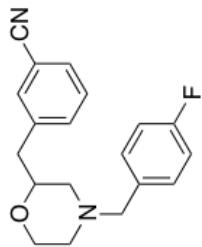
**Compound 1-56**
¹³C NMR (151 MHz, CDCl₃)

f1 (ppm)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10

251
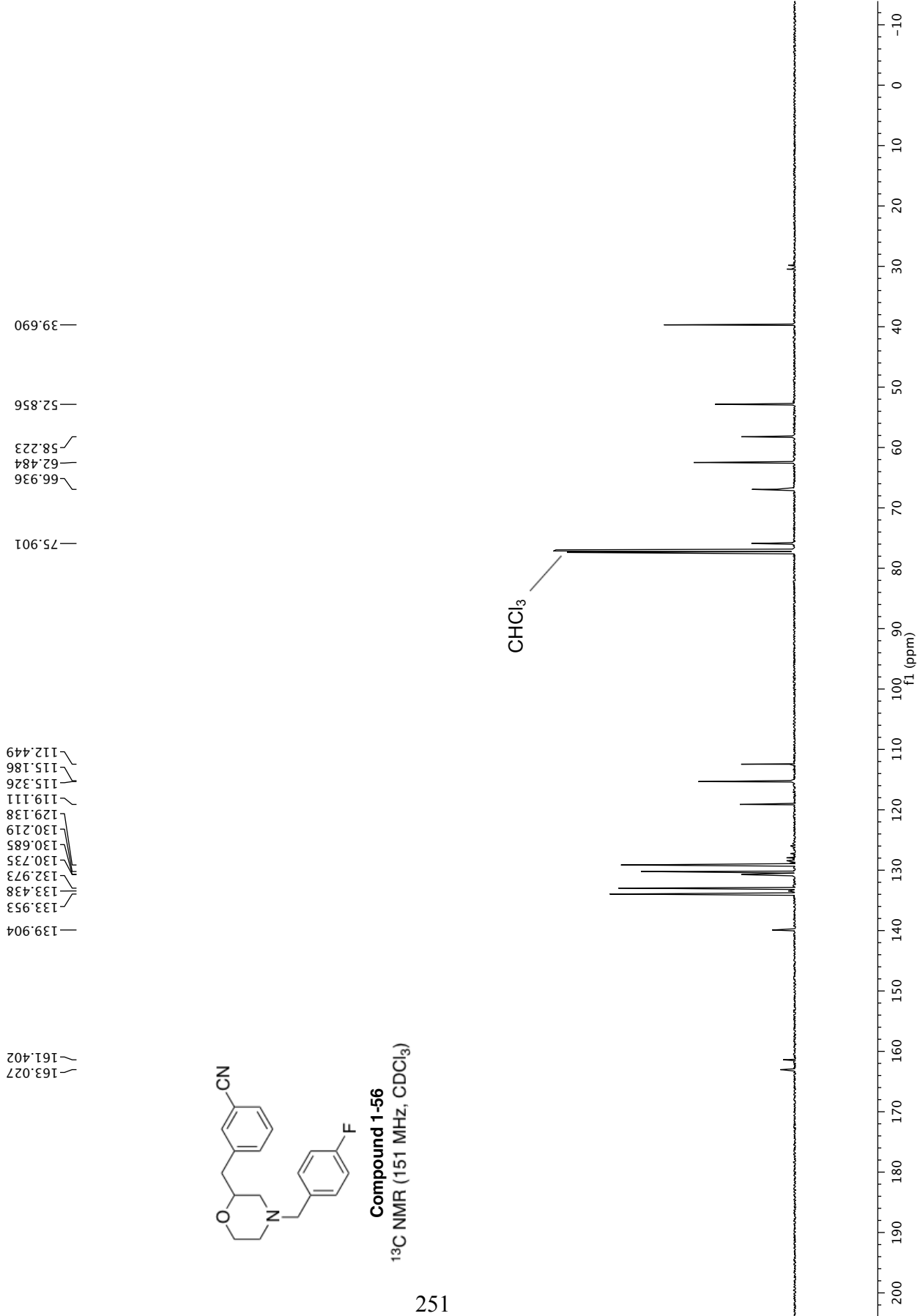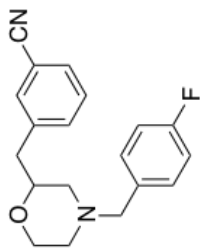
—115.578

**Compound 1-56**
19F NMR (565 MHz, CDCl3)

252



f1 (ppm)

2.806
2.809
2.820
2.823
2.833
2.860
2.873
2.884
2.887

5.929
6.530
6.532
6.543
6.545
6.618
6.621
6.700
6.713
6.814
6.819
6.828
6.832
7.484
7.488
7.497
7.501
7.511
7.515
7.952
7.955

CHCl₃
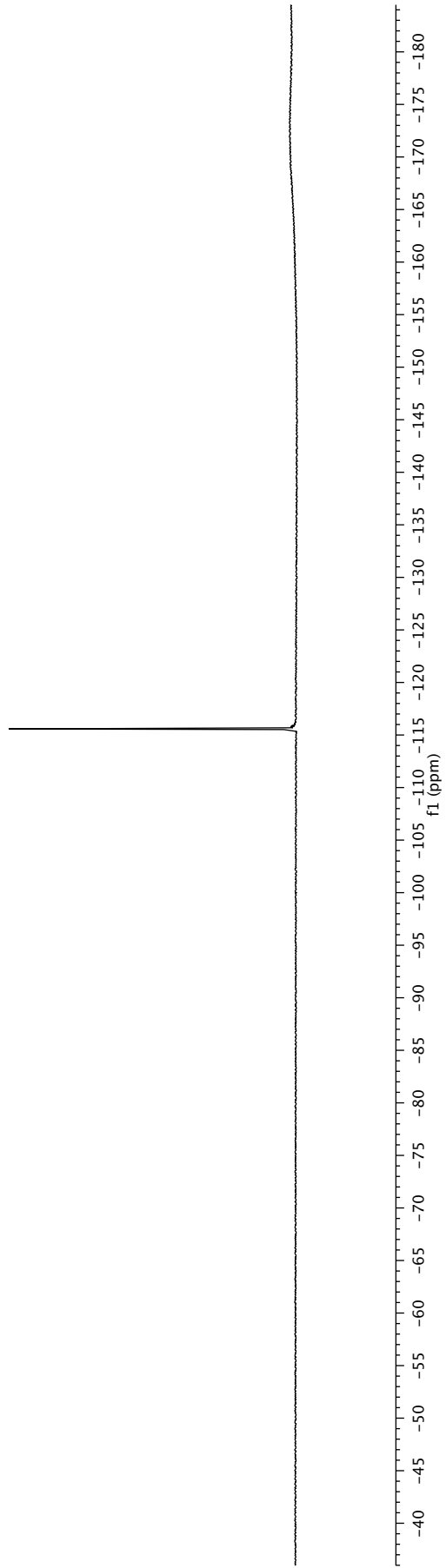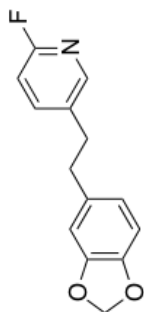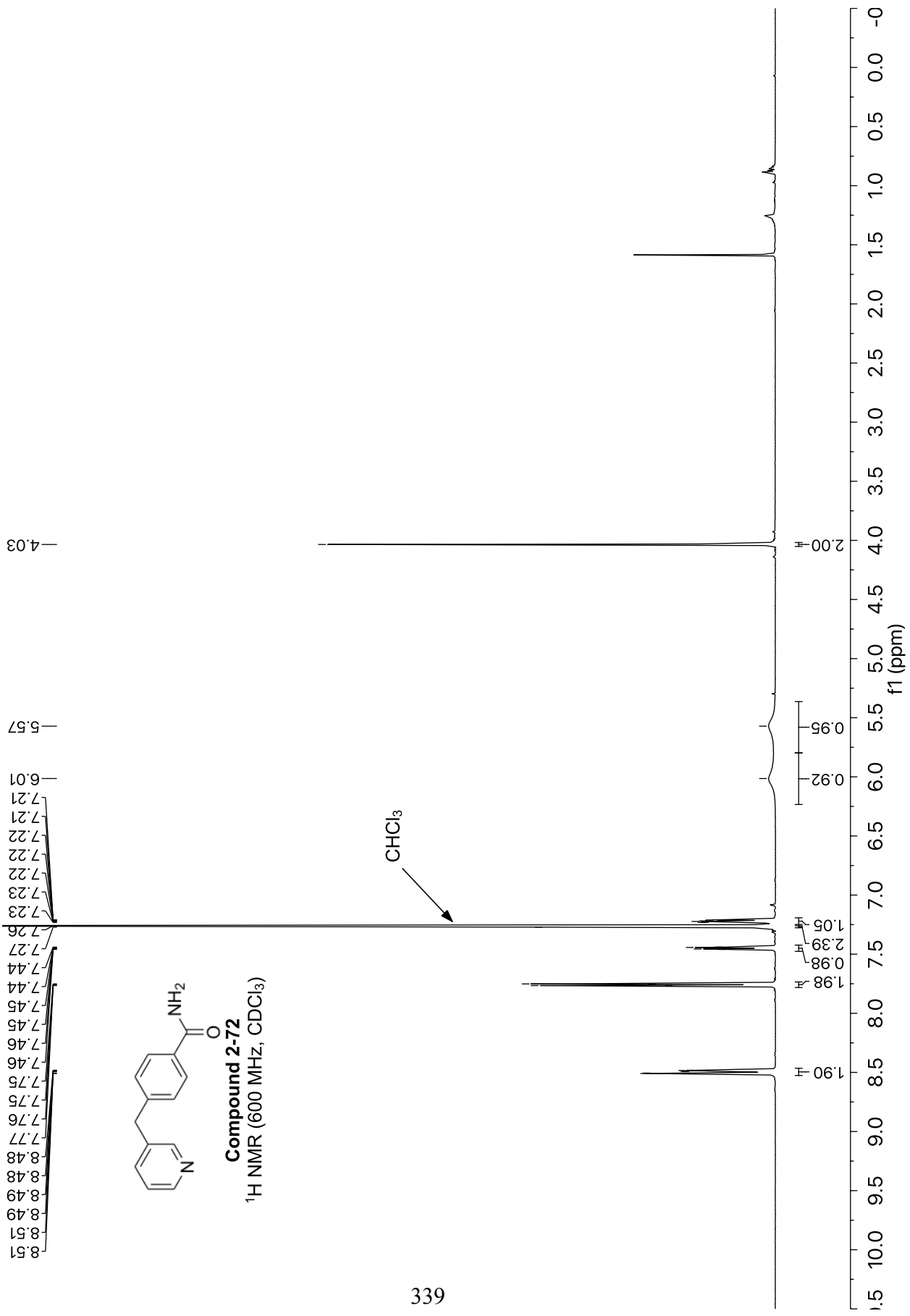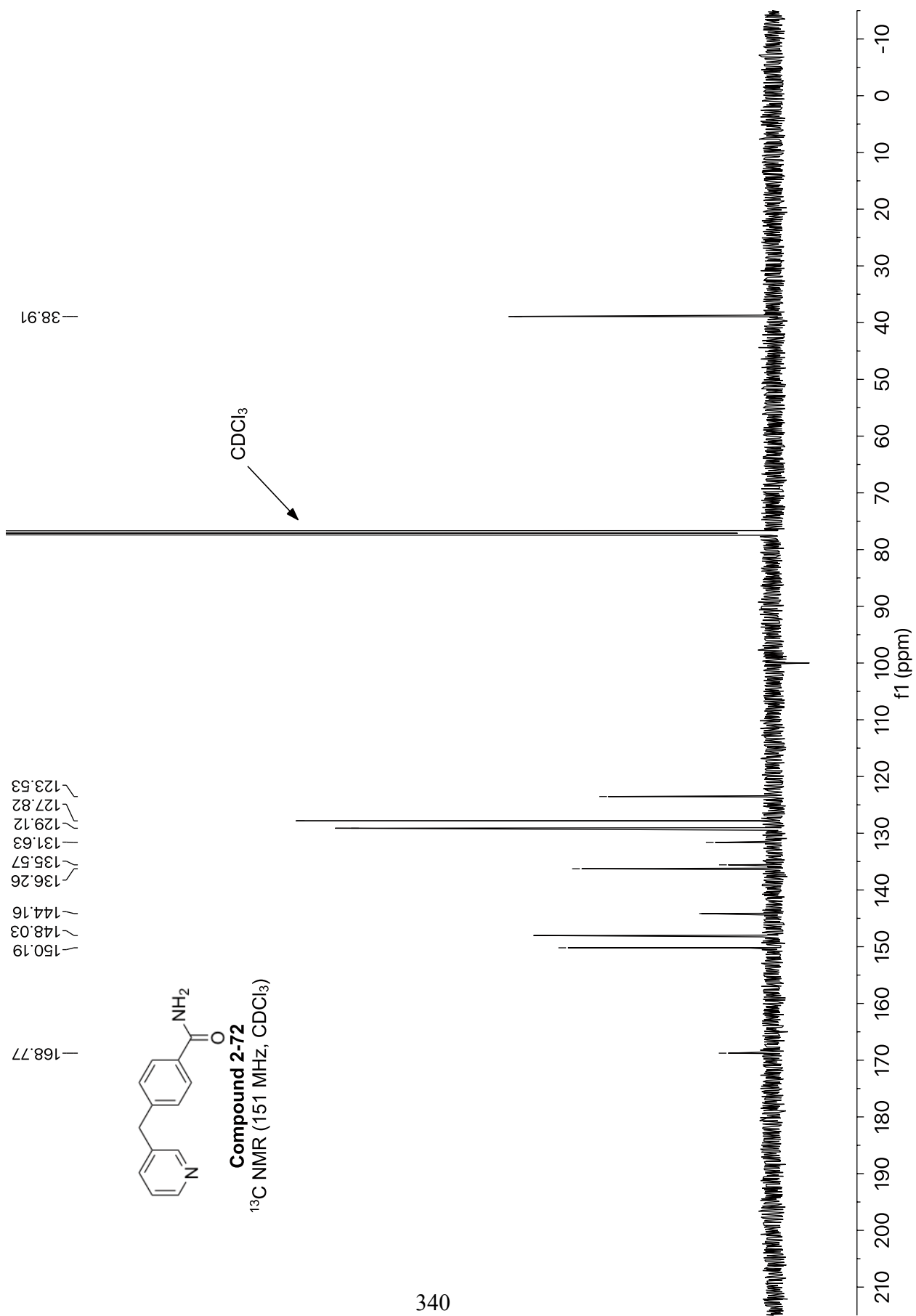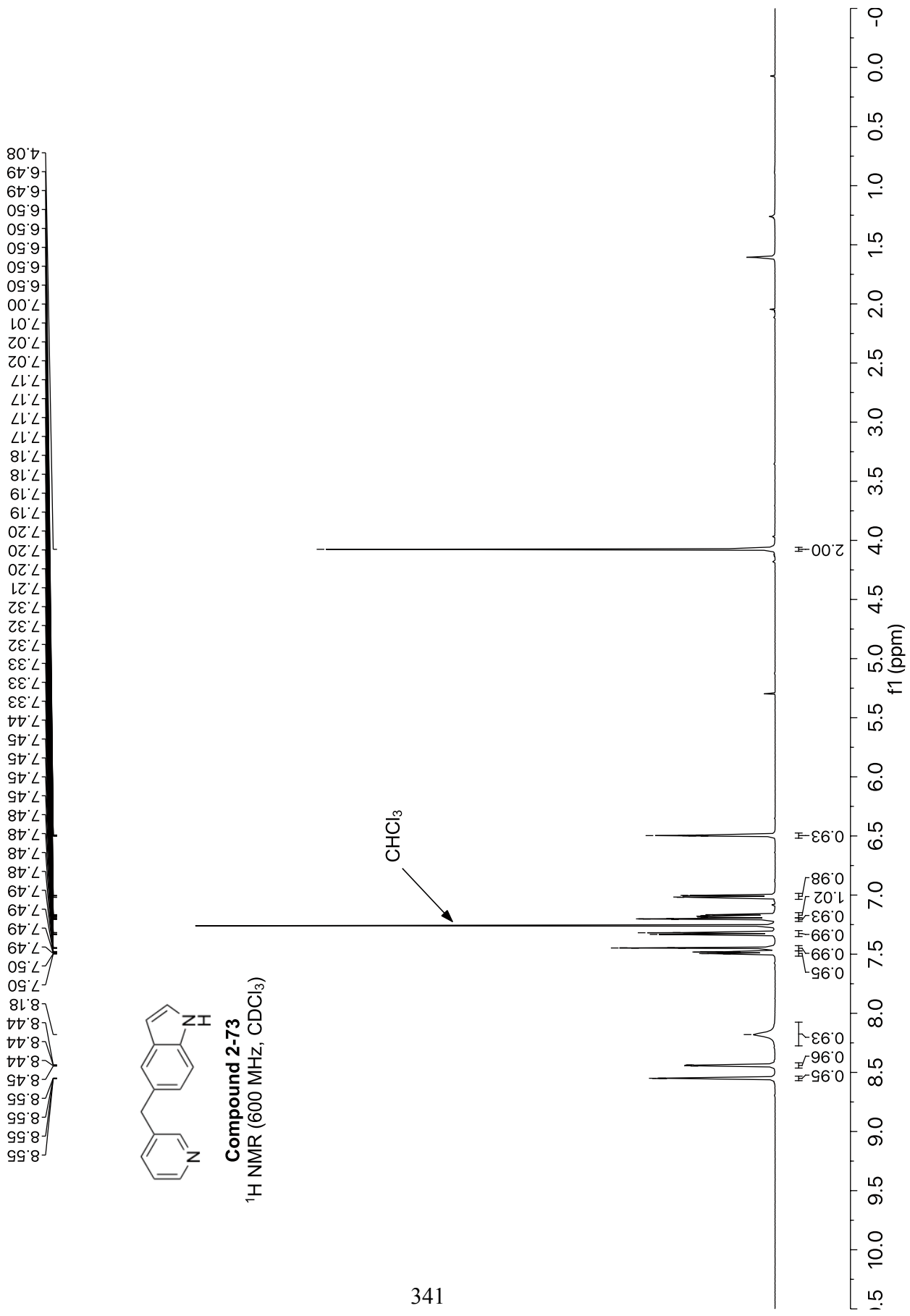
**Compound 1-57**
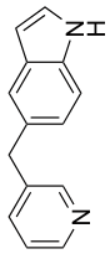¹H NMR (600 MHz, CDCl₃)

f1 (ppm)

2.08
2.07

1.03
0.95
0.99
1.00

1.02

1.00

Compound 1-57
$^{13}$C NMR (101 MHz, CDCl$_3$)

34.240
37.362

CHCl$_3$

101.002
108.349
108.912
108.967
109.283

121.478

134.297
134.324
134.341
141.253
141.329
146.049
147.179
147.321
147.772

161.262
163.618

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10
f1 (ppm)

254
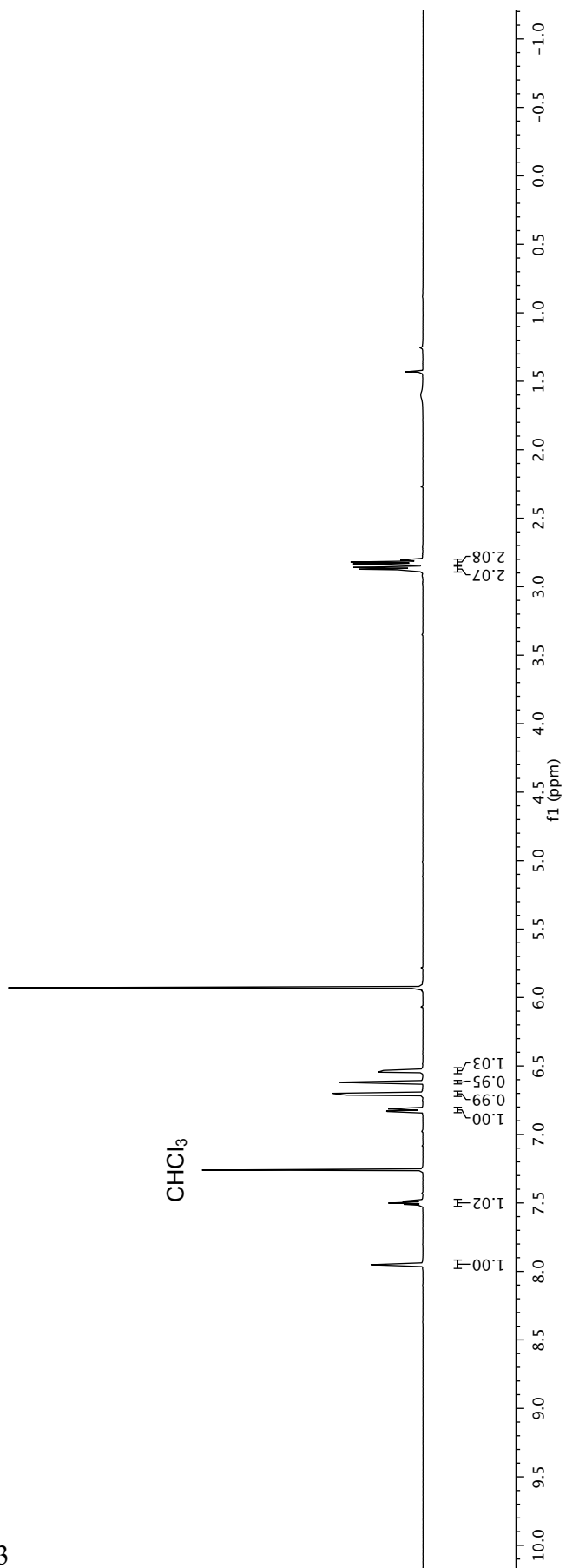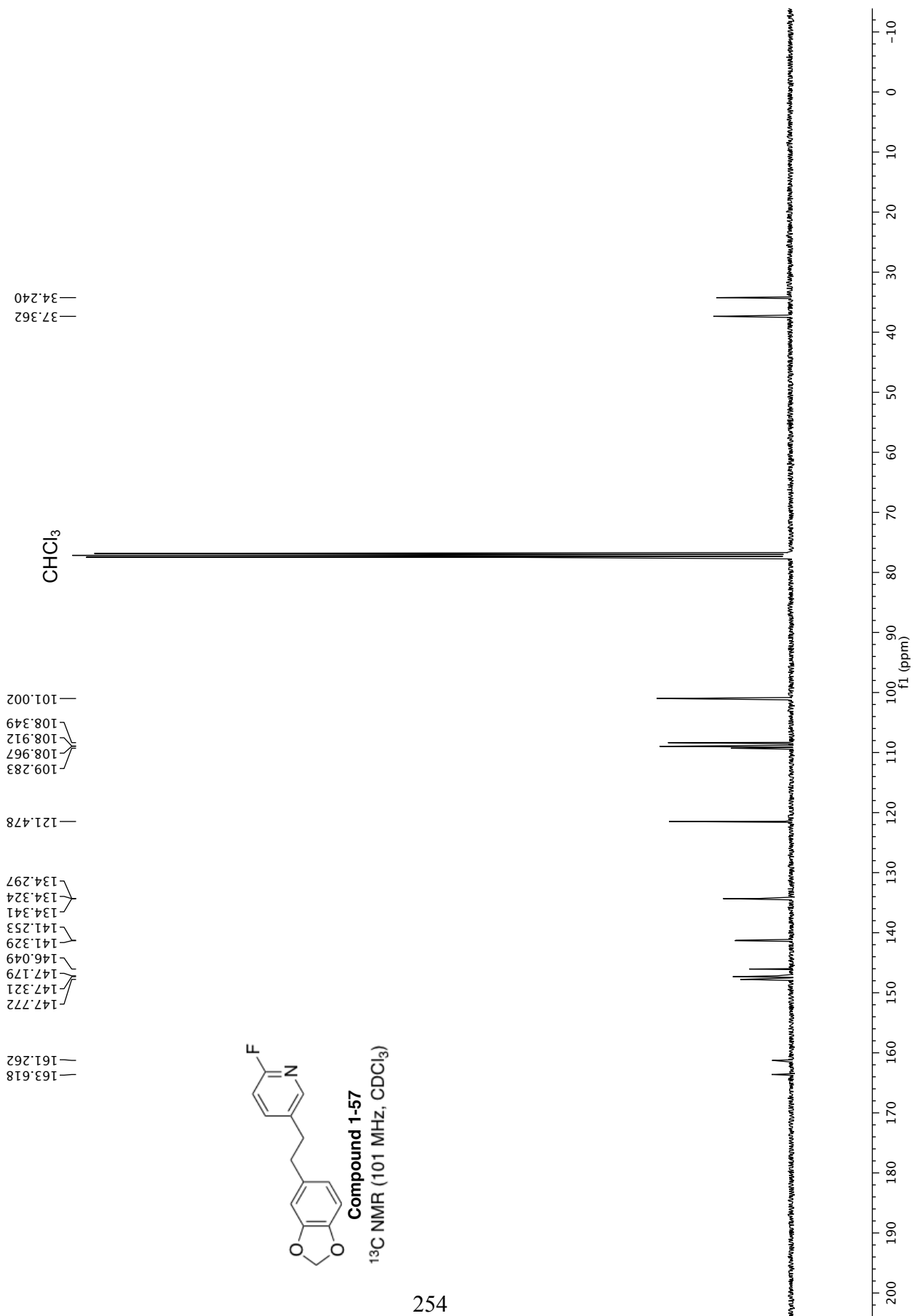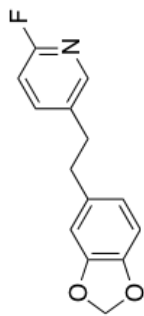
−71.922

**Compound 1-57**

$^{19}$F NMR (376 MHz, CDCl$_3$)

255
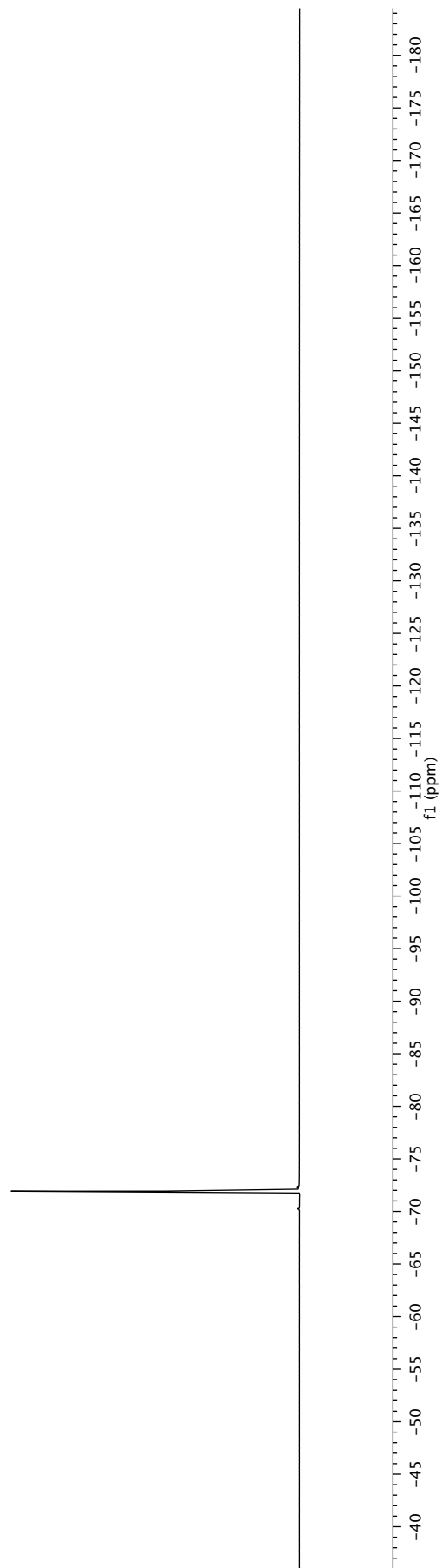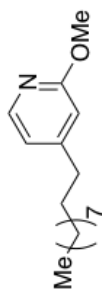
Compound 1-58
1H NMR (600 MHz, CDCl3)

256

0.866
0.878
0.889
1.254
1.270
1.283
1.294
1.303
1.319
1.332
1.569
1.579
1.594
1.606
1.618
2.527
2.540
2.553

3.919

6.550
6.551
6.694
6.696
6.703
6.705

8.031
8.039

CHCl3

3.00
14.05
2.47
1.96
2.94
0.95
0.98
0.95

Compound 1-58
$^{13}$C NMR (151 MHz, CDCl$_3$)

14.242
22.828
29.332
29.460
29.565
29.677
29.739
30.298
32.048
35.305
53.404
110.371
117.721
146.582
154.810
164.668

CHCl$_3$

257

1.189
1.195
1.202
1.207
1.211
1.225
1.234
1.241
1.248
1.258
1.266
1.274
1.283
1.290
1.298
1.304
1.333
1.340
1.348
1.363
1.371
1.378
1.394
1.402
1.411
1.418
1.425
1.449
1.455
1.672
1.735
1.742
1.746
1.749
1.757
1.766
1.773
1.777
1.781
1.784
1.830
1.841
1.848
1.854
1.861
1.870
1.877
1.906
1.912
2.451
2.458
2.467
2.474
2.480
2.488
2.496
2.503
2.510
2.517
2.525
7.109
7.114
7.121
7.125

8.474
8.478
8.485
8.489



Compound 1-59
$^{1}$H NMR (400 MHz, CDCl$_3$)

CHCl$_3$

4.86
4.99
1.00
2.02
1.95

f1 (ppm)

258

26.067
26.661
33.643
43.949

CHCl₃

122.490

149.850
156.678
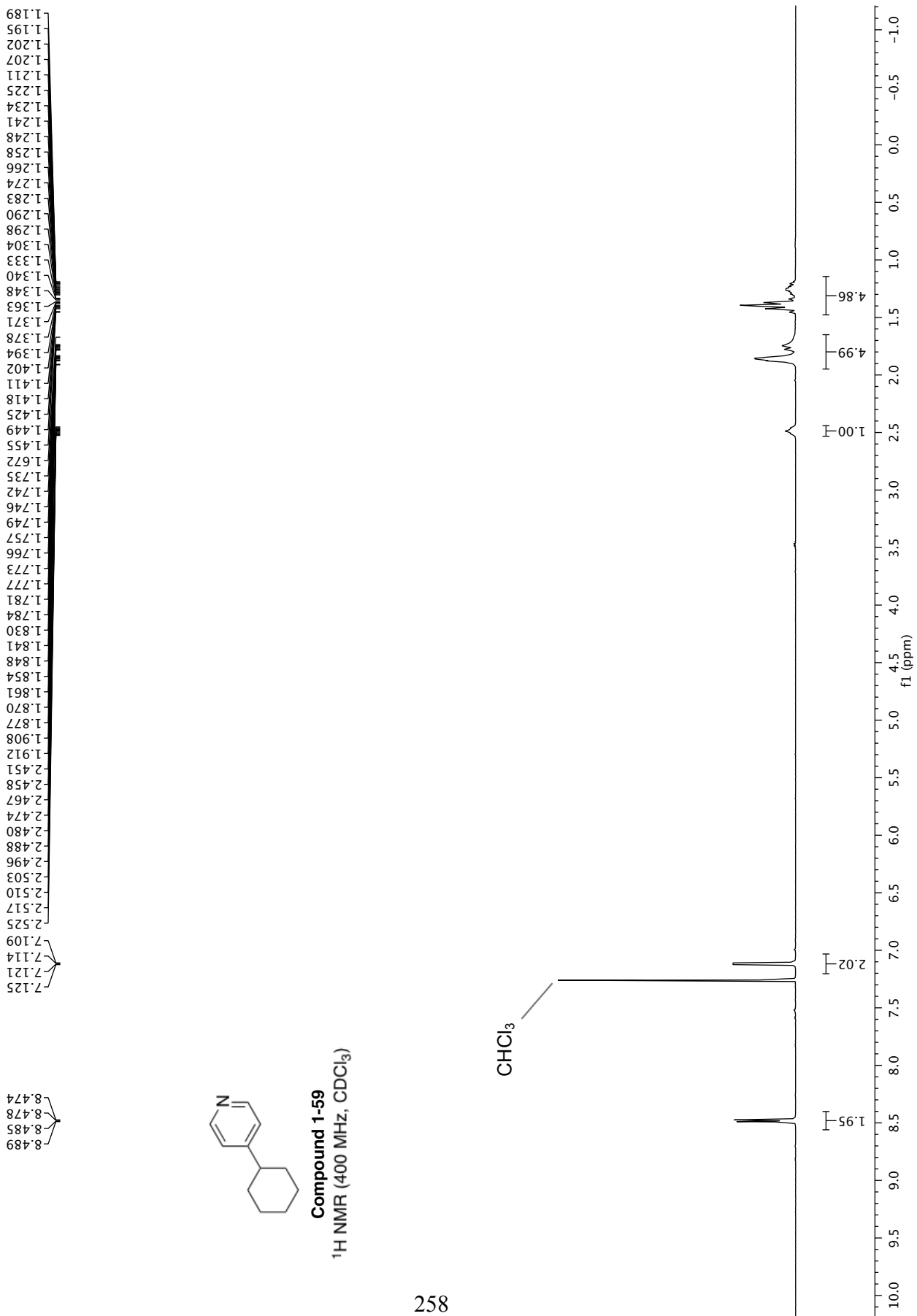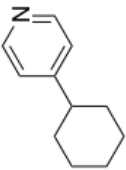
**Compound 1-59**
¹³C NMR (101 MHz, CDCl₃)

259

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10
f1 (ppm)

1.261
1.278

2.190
2.734
2.753
2.768
2.787
2.810
2.827
2.844
2.861
2.900
2.918
2.935
2.953
2.971
2.988

7.110
7.117
7.130
7.134
7.138
7.167
7.171
7.173
7.191
7.196
7.206
7.210
7.213
7.260
7.279
7.293
7.297
7.674
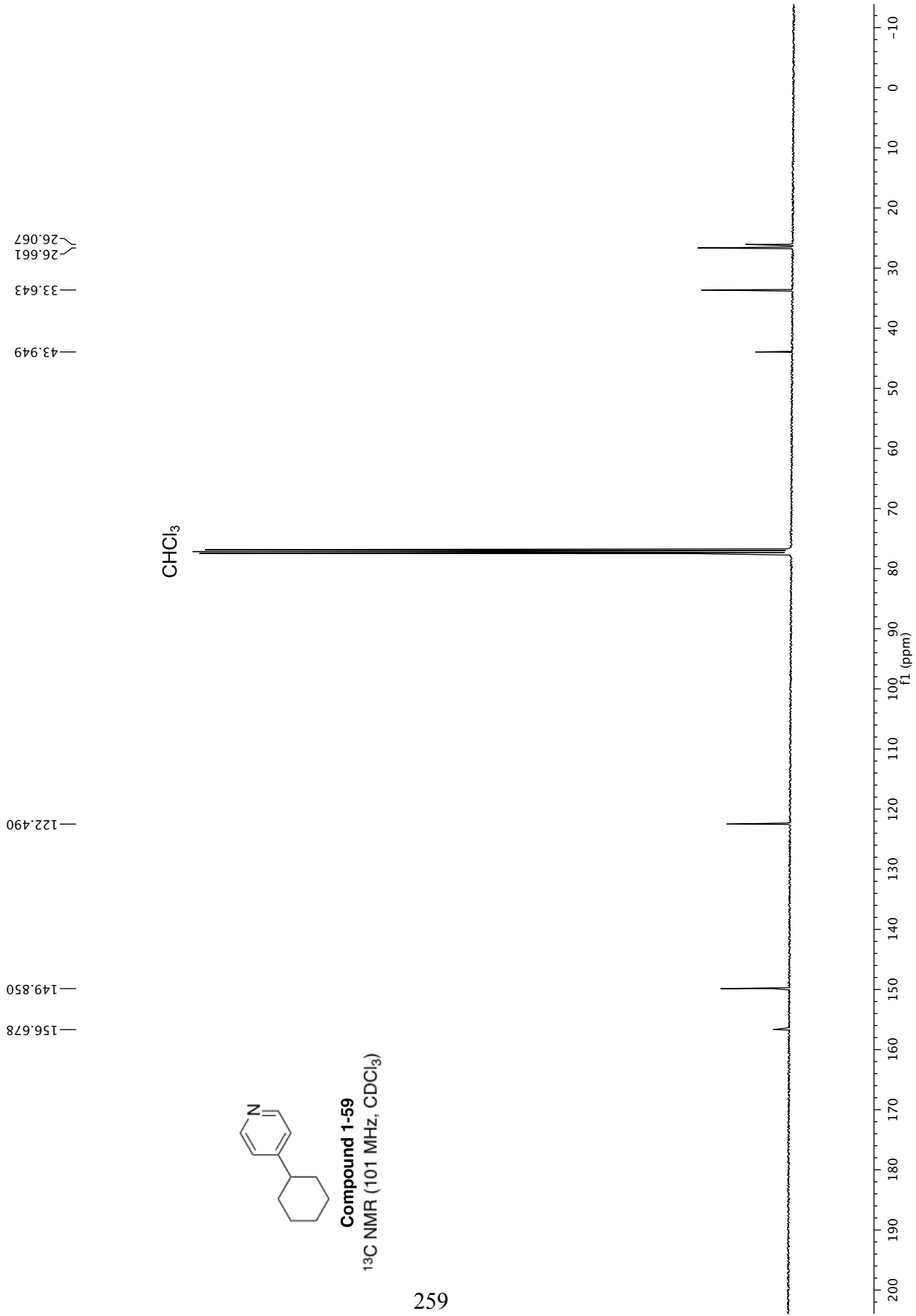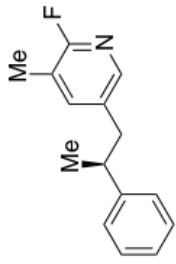
**Compound 1-60**
$^1$H NMR (400 MHz, CDCl$_3$)

CHCl$_3$

3.08
2.90
2.15
1.17
1.91
1.91
1.94
1.00

10.0   9.5   9.0   8.5   8.0   7.5   7.0   6.5   6.0   5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   0.5   0.0   -0.5   -1.0
f1 (ppm)

260

14.546
14.562

21.282

41.056
41.065
41.817

CHCl₃

118.600
118.924

126.513
127.159
128.573
133.642
133.689

142.327
142.385
144.684
144.825
145.826

159.882
162.229
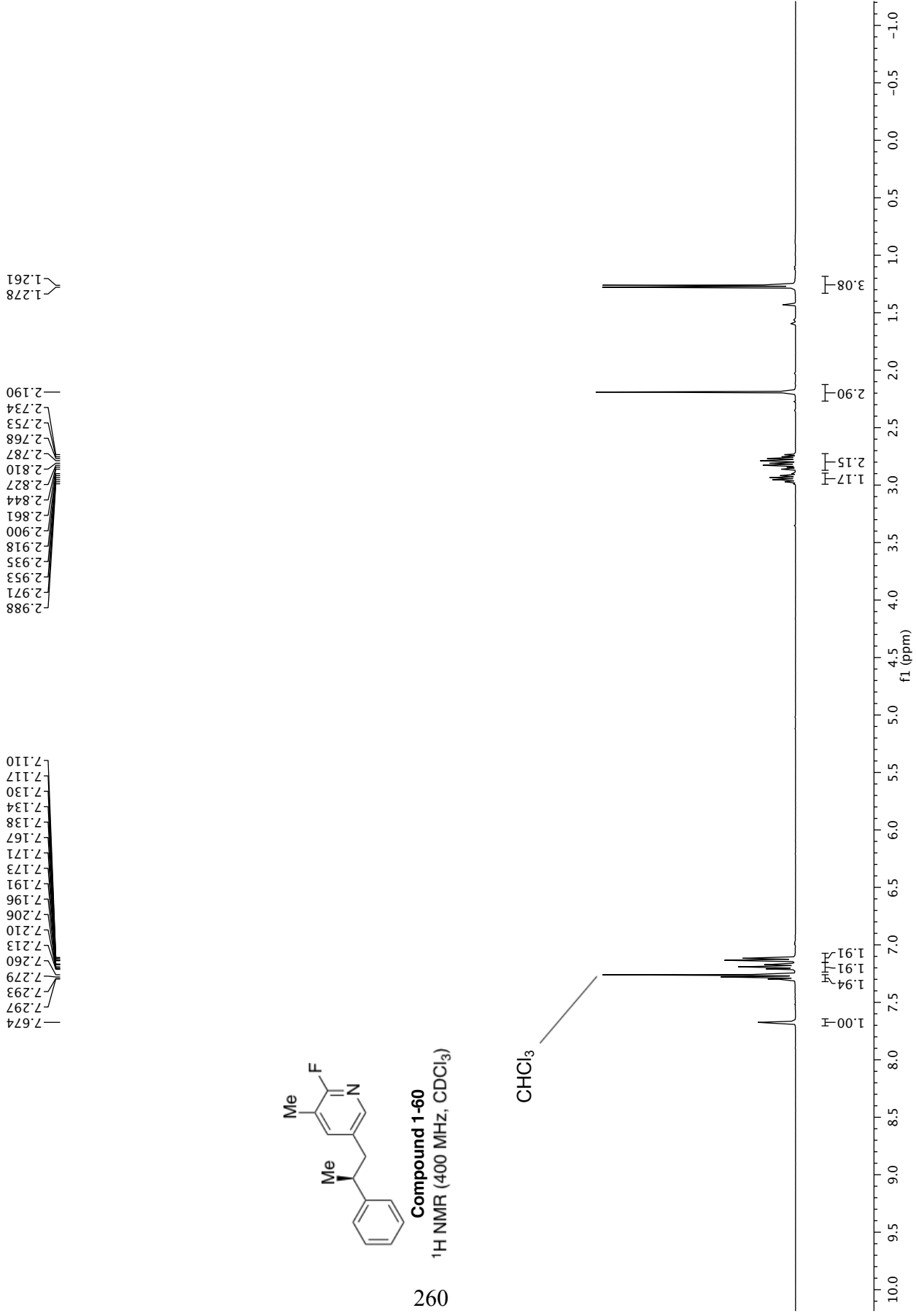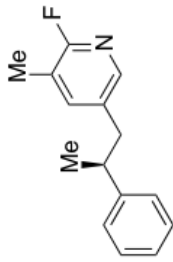
**Compound 1-60**
¹³C NMR (101 MHz, CDCl₃)

261
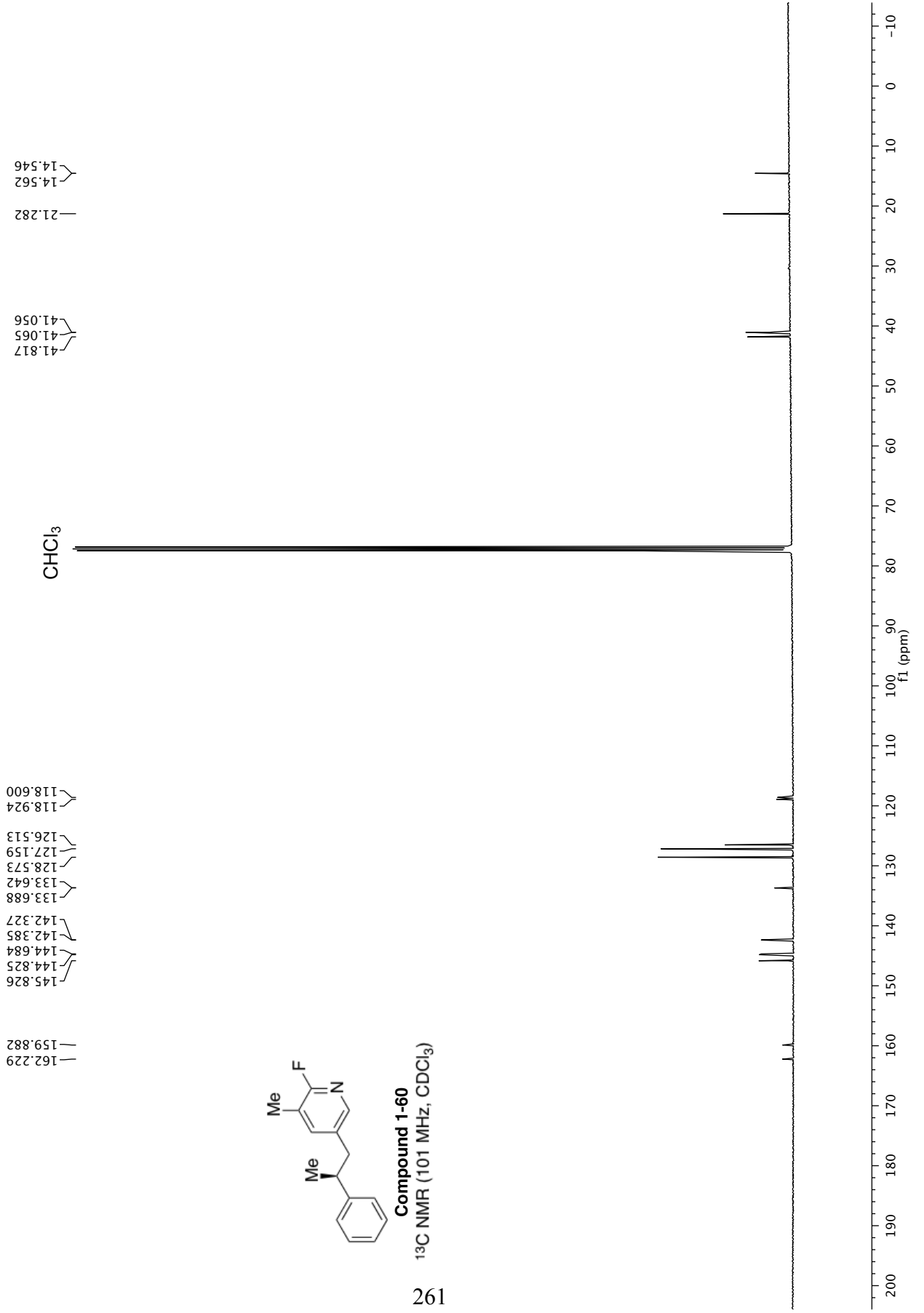
−76.561
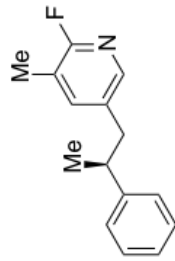
**Compound 1-60**
$^{19}$F NMR (376 MHz, CDCl$_3$)

262

f1 (ppm)

−40  −45  −50  −55  −60  −65  −70  −75  −80  −85  −90  −95  −100  −105  −110  −115  −120  −125  −130  −135  −140  −145  −150  −155  −160  −165  −170  −175  −180

1.180
1.185
1.196
1.208
1.623
1.628
1.636
1.640
1.645
1.650
1.659
1.661
1.666
1.670
1.674
1.678
1.683
1.685
1.688
1.691
1.696
1.700
1.708
1.712
2.615
2.628
2.639
3.450
3.462
3.466
3.474
3.478
3.486
3.489
3.501
3.600
3.611
3.615
3.623
3.627
3.635
3.639
3.651
4.481
4.489
4.498

6.834
6.839
6.848
6.853
7.576
7.580
7.589
7.593
7.603
7.607
8.018

CHCl₃

**Compound 1-61**
¹H NMR (600 MHz, CDCl₃)

263

5.97
4.12
2.04
2.08
2.07
1.05
1.02
1.00
0.97

f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

15.482

26.439
31.932
31.937
33.198

61.339

CHCl₃

102.768

109.017
109.265

135.151
135.181

141.079
141.129

147.114
147.209

161.677
163.245
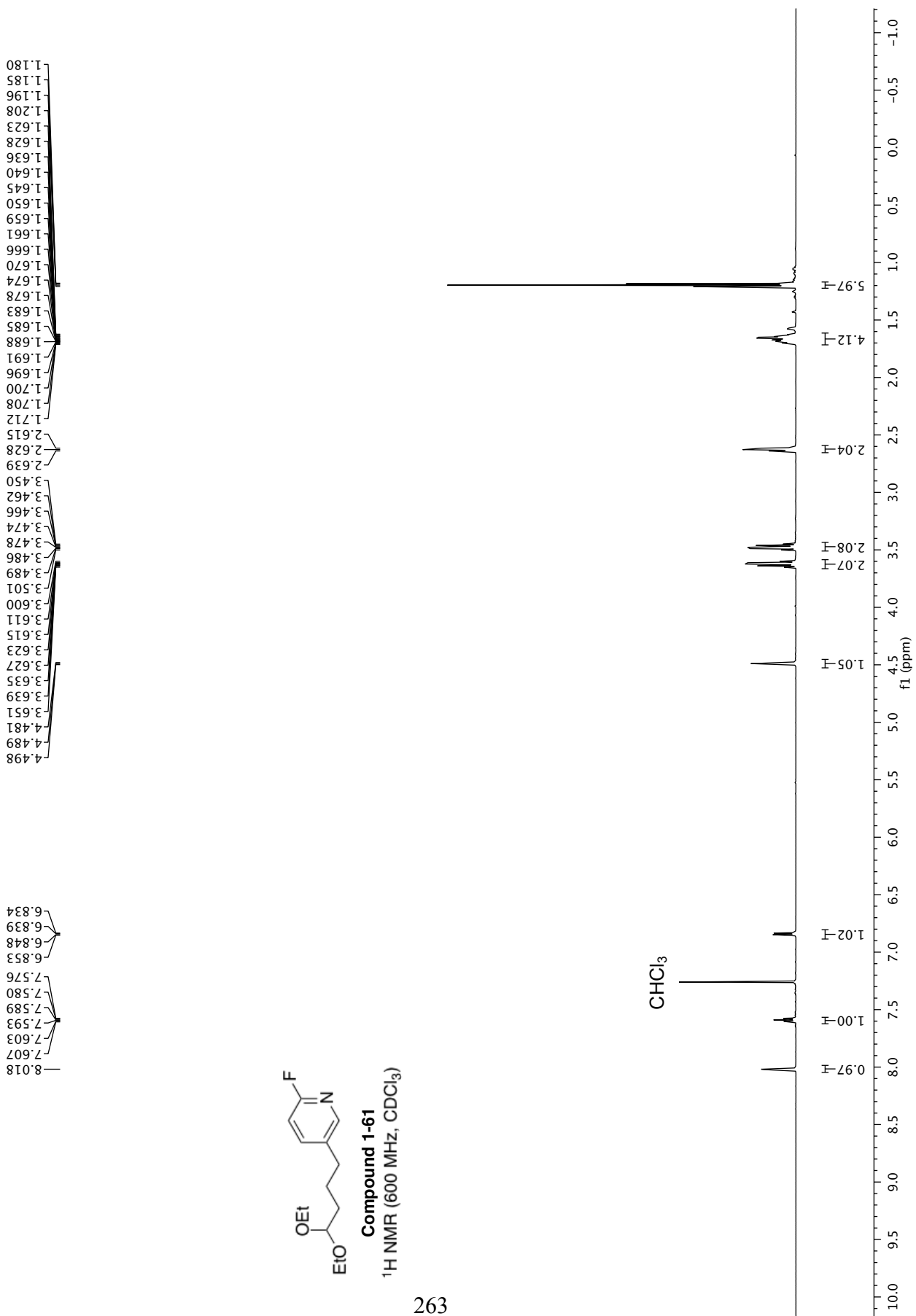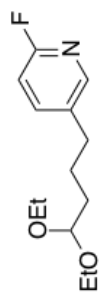
Compound 1-61
¹³C NMR (151 MHz, CDCl₃)

264

f1 (ppm)

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
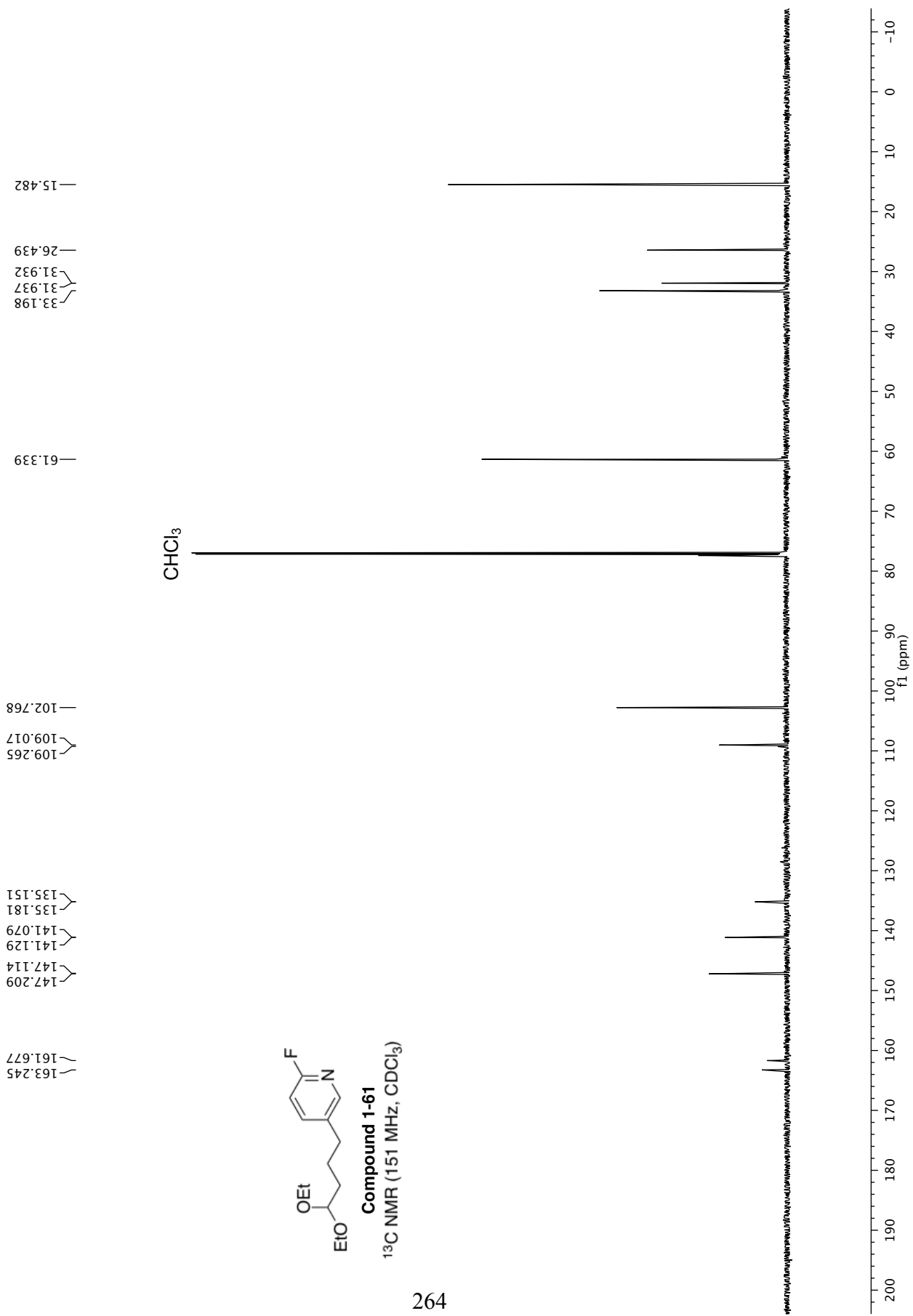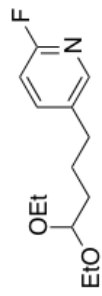
-72.271

**Compound 1-61**

¹⁹F NMR (565 MHz, CDCl₃)

265



f1 (ppm)
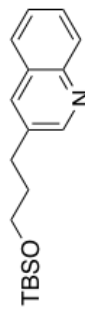
Compound 1-62
$^1$H NMR (600 MHz, CDCl$_3$)

266

-5.133

-18.479

26.110
29.561
34.143

62.009

CHCl₃

126.720
127.429
128.342
128.731
129.261
134.516
134.989

146.880

152.207
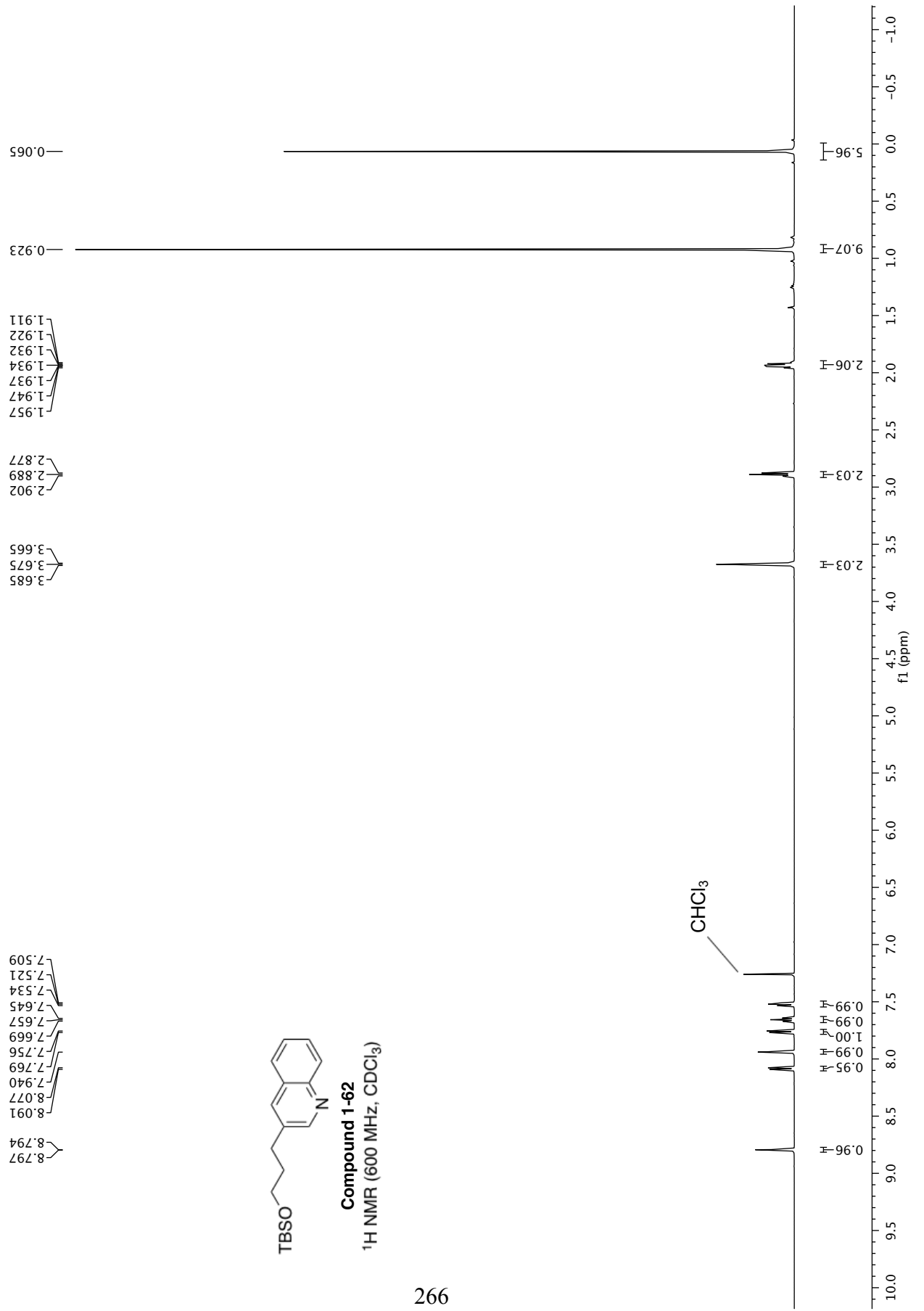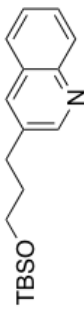
**Compound 1-62**
¹³C NMR (151 MHz, CDCl₃)

TBSO

267

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

0.046

0.900
1.744
1.760
1.762
1.767
1.775
1.778
1.782
1.791
1.794
1.798
1.813

2.578
2.598
2.617

3.600
3.615
3.631
3.909

6.663
6.684

7.397
7.403
7.418
7.424

7.969
7.974

CHCl₃

5.98
8.85
2.09
2.02
2.00
3.00
1.05
1.04
1.00

f1 (ppm)
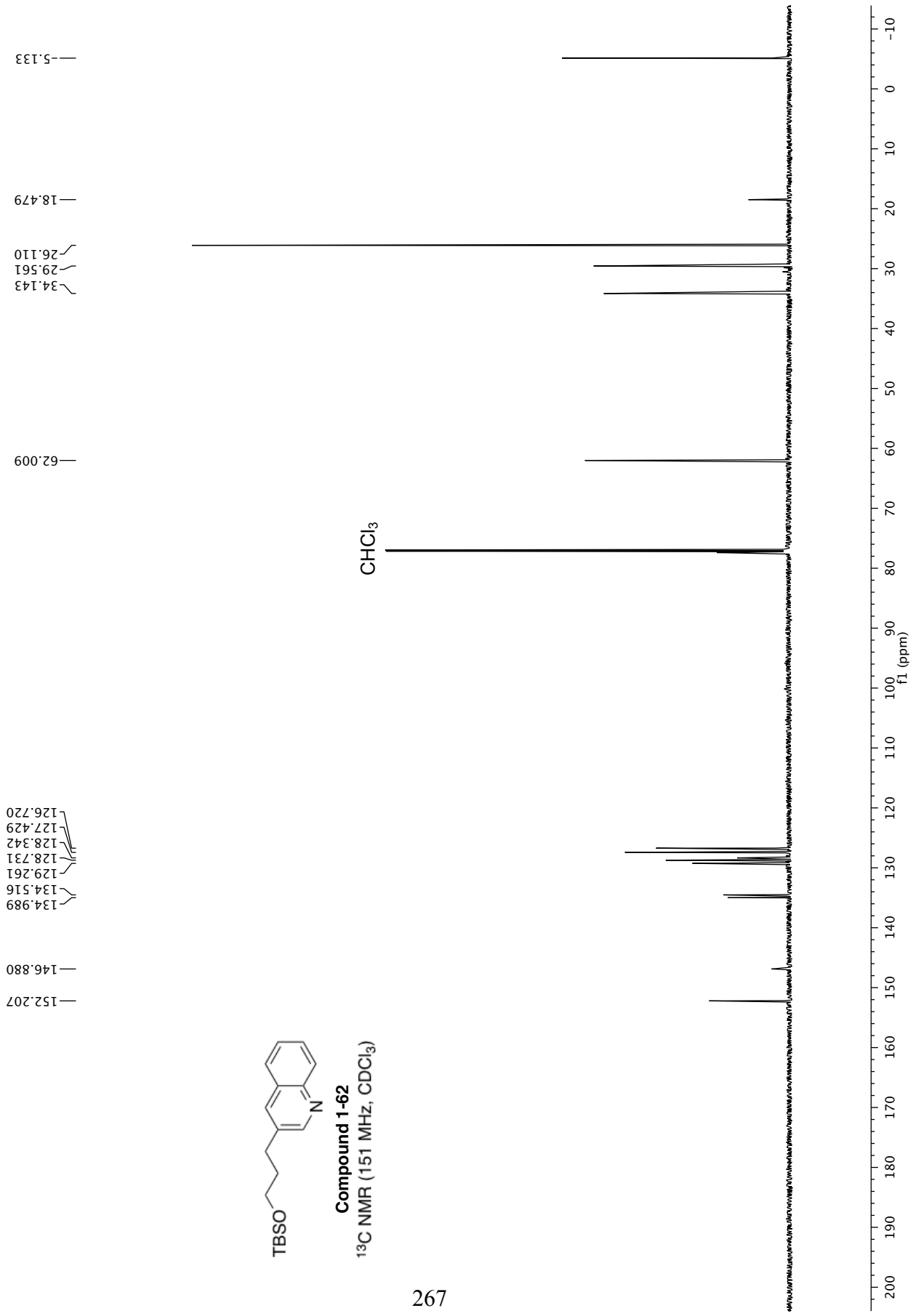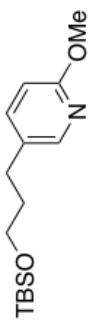
**Compound 1-63**
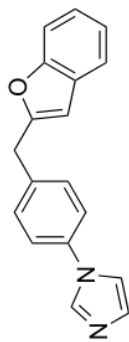¹H NMR (400 MHz, CDCl₃)

TBSO

OMe
N

268
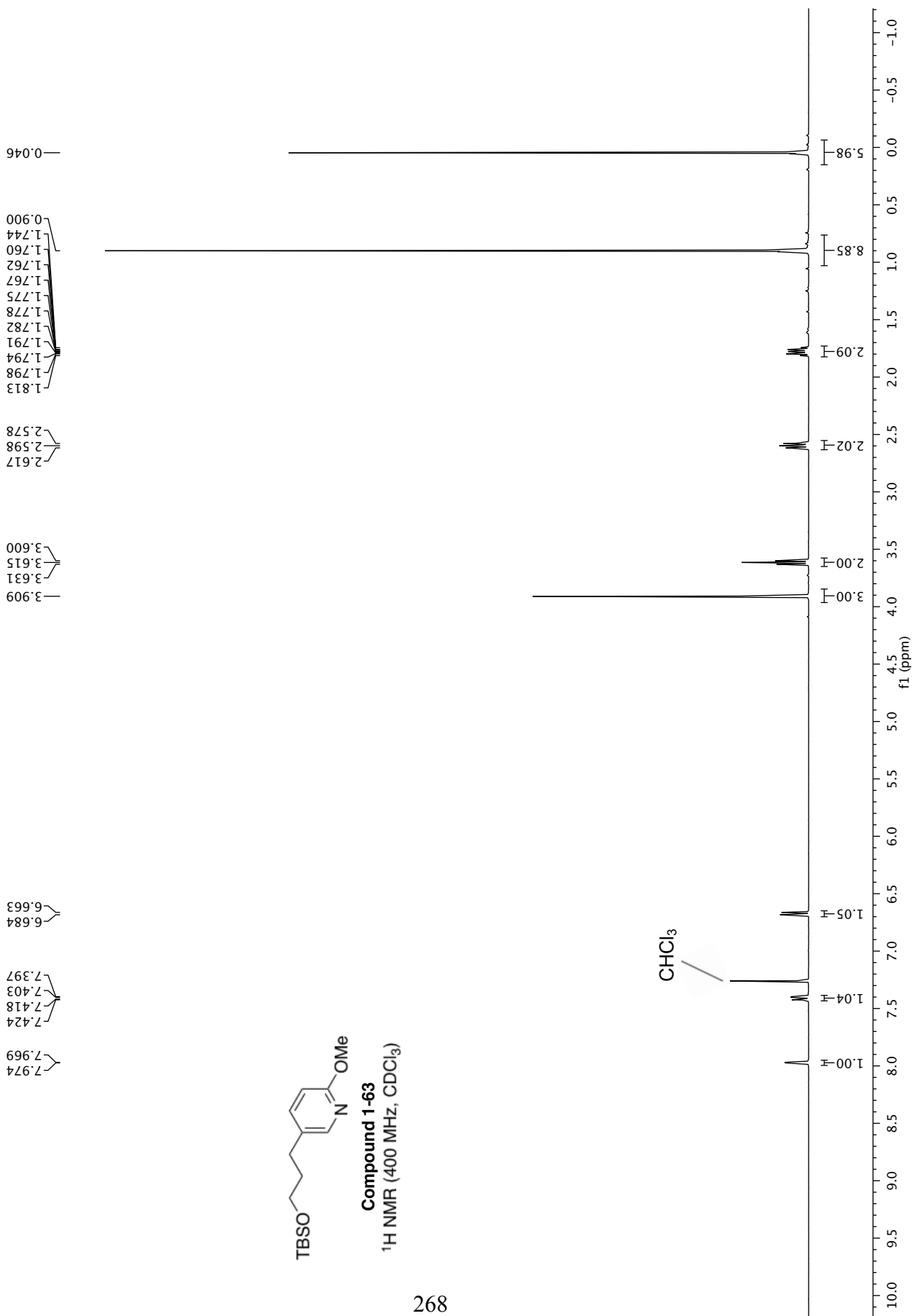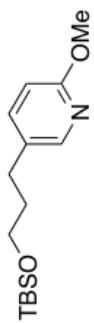
Compound 1-63
13C NMR (101 MHz, CDCl3)

5.139
18.469
26.089
28.346
34.450
53.444
62.094
CHCl3
110.511
130.125
139.161
146.185
162.730

f1 (ppm)
200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10

269

1.458

2.449
2.513
2.530
2.552
2.662
2.684
2.701

3.437
3.449
3.462
3.810
3.823
3.835

6.582
6.603

7.354
7.360
7.376
7.382

8.050
8.056

CHCl₃
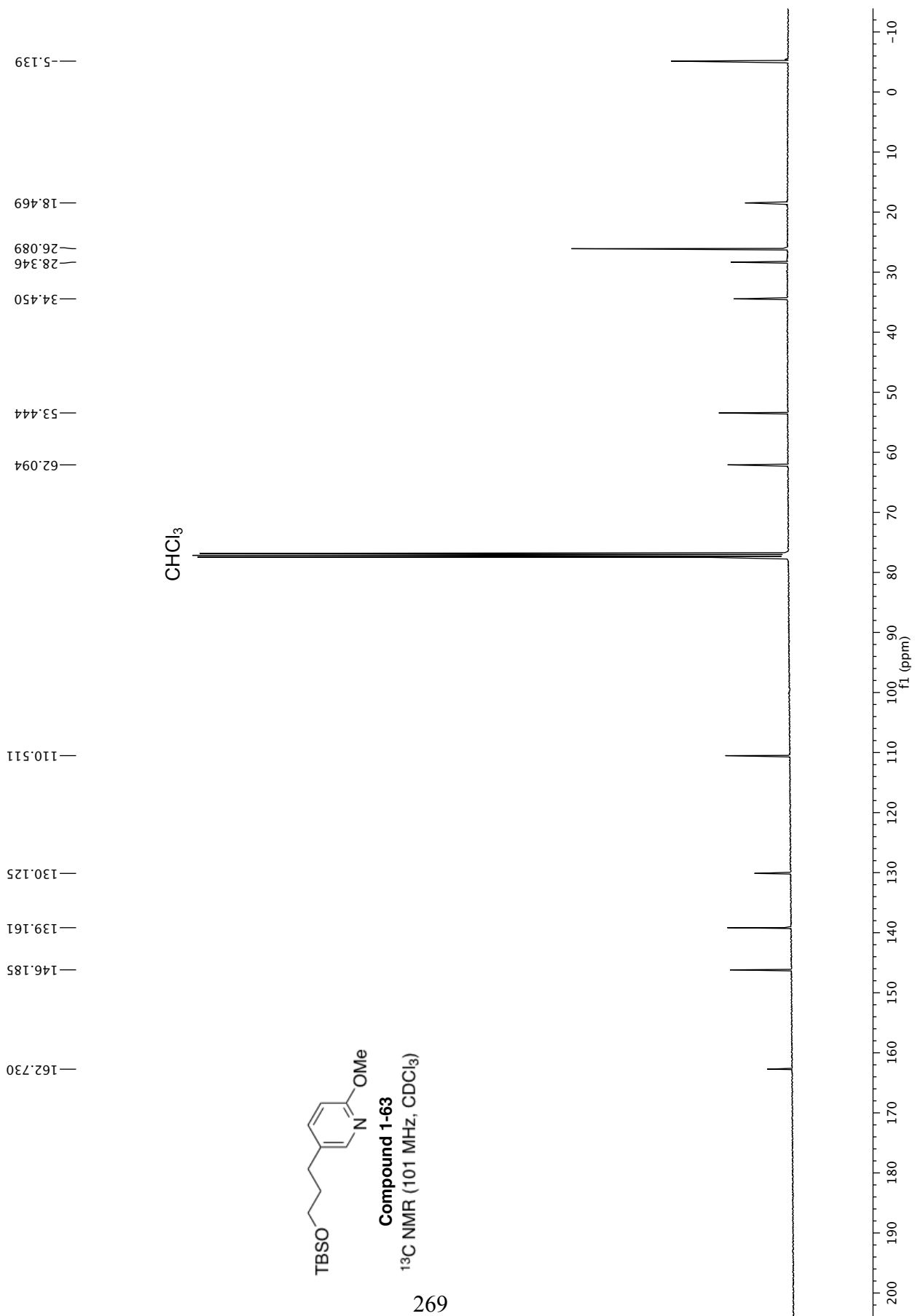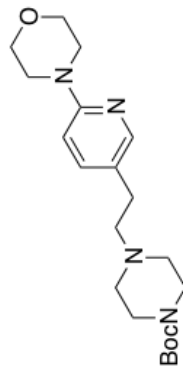
**Compound 1-64**
¹H NMR (400 MHz, CDCl₃)

8.65

3.98
2.05
2.08

8.00

4.12

1.08

1.13

1.01

4.5
f1 (ppm)

270

28.564
29.759

43.657
46.034

53.083

60.426

66.927

CHCl₃

79.814

106.979

125.341

138.174

147.809

154.857
158.620

**Compound 1-64**
¹³C NMR (101 MHz, CDCl₃)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

Compound 1-65
$^1$H NMR (400 MHz, CDCl$_3$)

CHCl$_3$

272

19.868

27.439
28.224
30.237

36.596
37.614

42.756

66.277
67.466

CHCl₃

80.800

98.916

108.984
109.354
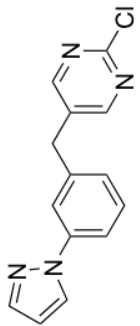
134.854
134.898

141.216
141.292

147.176
147.317

161.215
163.569

170.374

Compound 1-65
¹³C NMR (101 MHz, CDCl₃)

273



200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

−72.197

**Compound 1-65**
¹⁹F NMR (376 MHz, CDCl₃)

274

f1 (ppm)

2.602
2.616
2.629

4.569
4.583
4.596

5.677
5.679
5.750
5.752
5.763
5.765
5.847

6.476
6.489
7.517
7.529
7.542
7.560
7.572
7.584
7.627
7.632
7.642
7.654
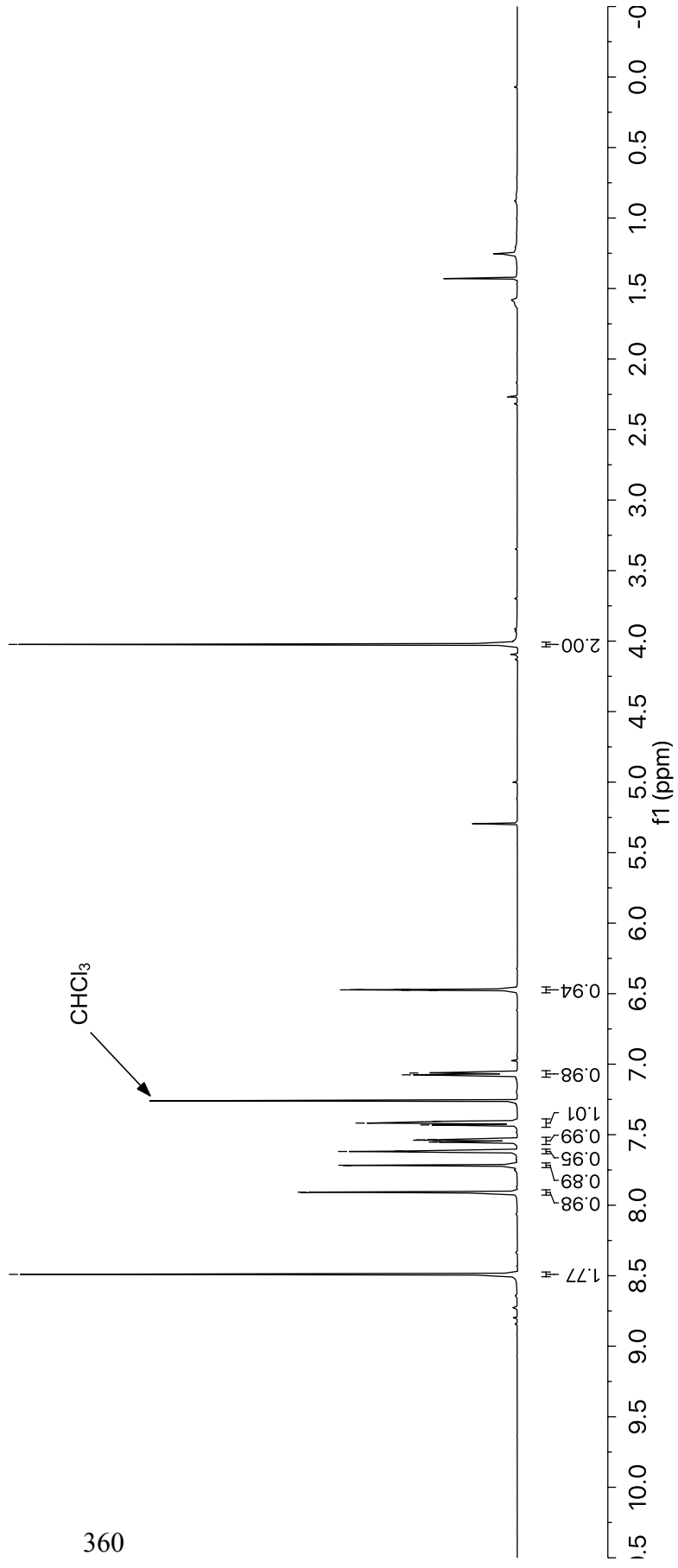7.664
7.677
7.785
7.798
7.803
7.805
7.818
7.914

Ph

⊖ BF₄

Ph

N ⊕ Ph

Ph

O O
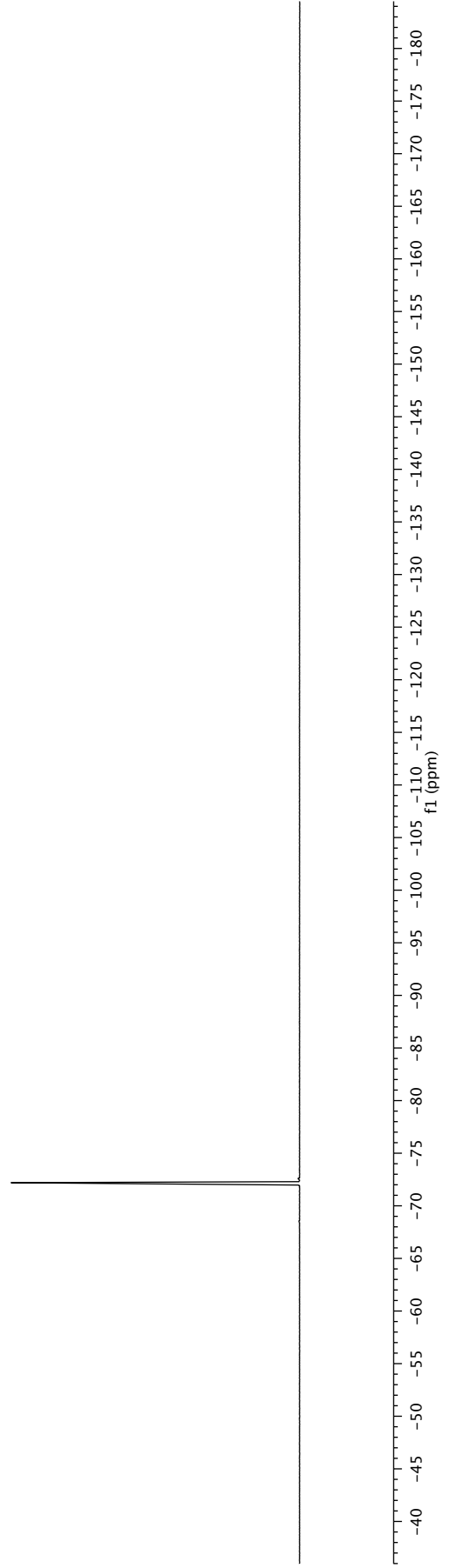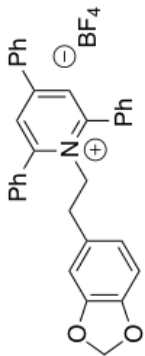
**Compound 1-39**

¹H NMR (600 MHz, CDCl₃)

CHCl₃

2.05

2.06

1.00
1.00
2.02

1.05

2.03
1.07
6.13
6.09
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  0.0  -0.5  -1.0
f1 (ppm)

35.658

56.106

CHCl₃

101.154

108.572
108.613

121.392
126.934
128.320
128.875
129.263
129.555
129.868
131.350
132.285
132.878
134.221
146.924
147.953
156.286
156.704

**Compound 1-39**
¹³C NMR (151 MHz, CDCl₃)

276

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
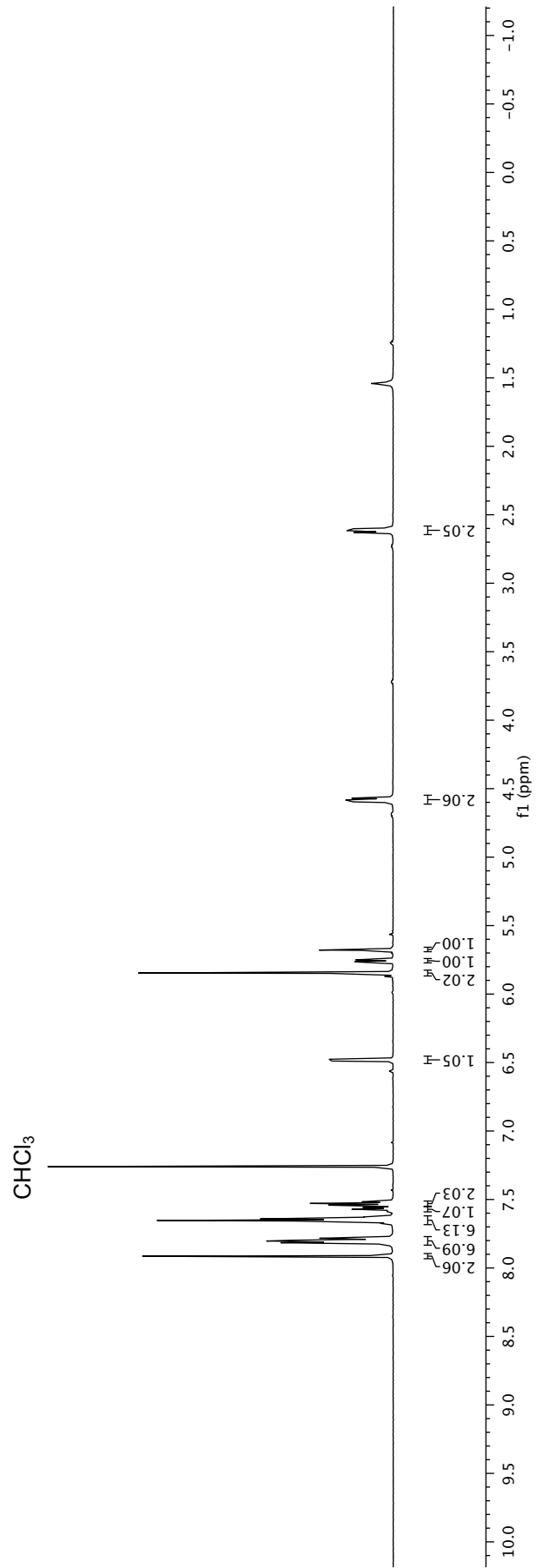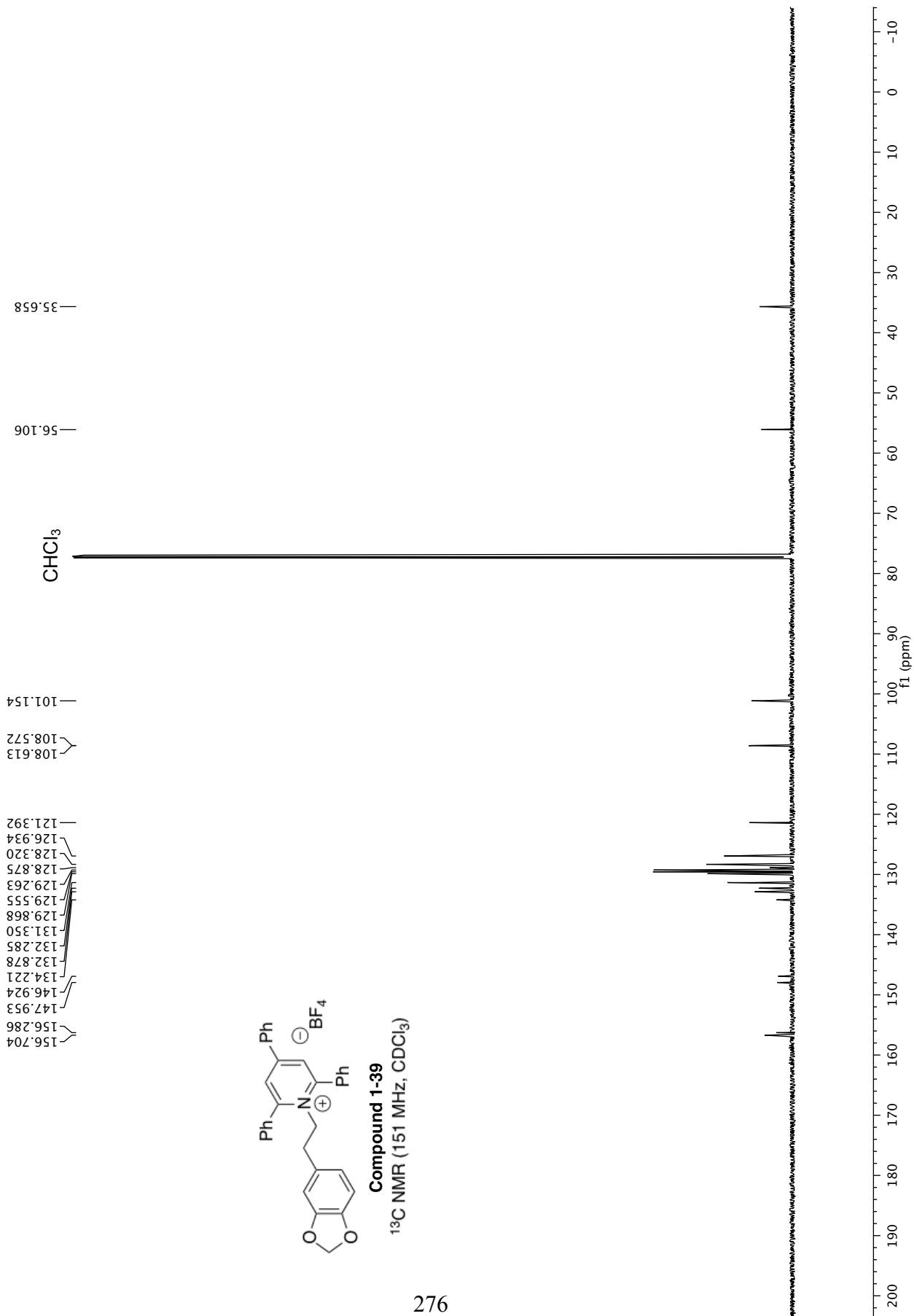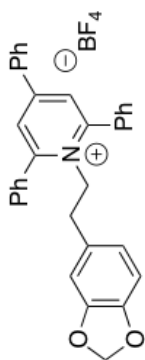
−153.276
−153.329

**Compound 1-39**

$^{19}$F NMR (376 MHz, CDCl$_3$)

277

0.734
0.740
0.746
0.851
0.863
0.876
0.893
0.905
0.918
0.985
0.996
1.009
1.023
1.034
1.088
1.099
1.104
1.111
1.114
1.126
1.137
1.143
1.153
1.158
1.165
1.168
1.175
1.180
1.191
1.222
1.233
1.245
1.257
1.270
1.282
1.400
1.411
1.420
1.425
1.430
1.438
1.449
4.384
4.393
4.398
4.403
4.412

7.484
7.496
7.509
7.532
7.541
7.544
7.548
7.556
7.591
7.596
7.602
7.734
7.737
7.749
7.786
7.790
7.796
7.801
7.845
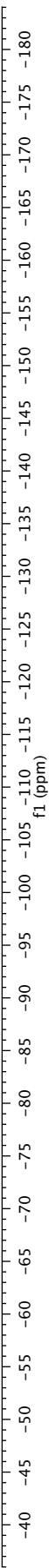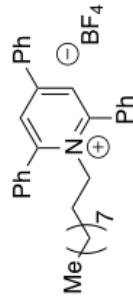
**Compound 1-77**
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

278

14.228

22.759
26.098
28.046
28.987
29.223
29.312
29.761
31.927

54.859

126.826
128.232
129.189
129.395
129.806
131.104
132.149
132.940
134.204

155.807
156.603

CHCl$_3$
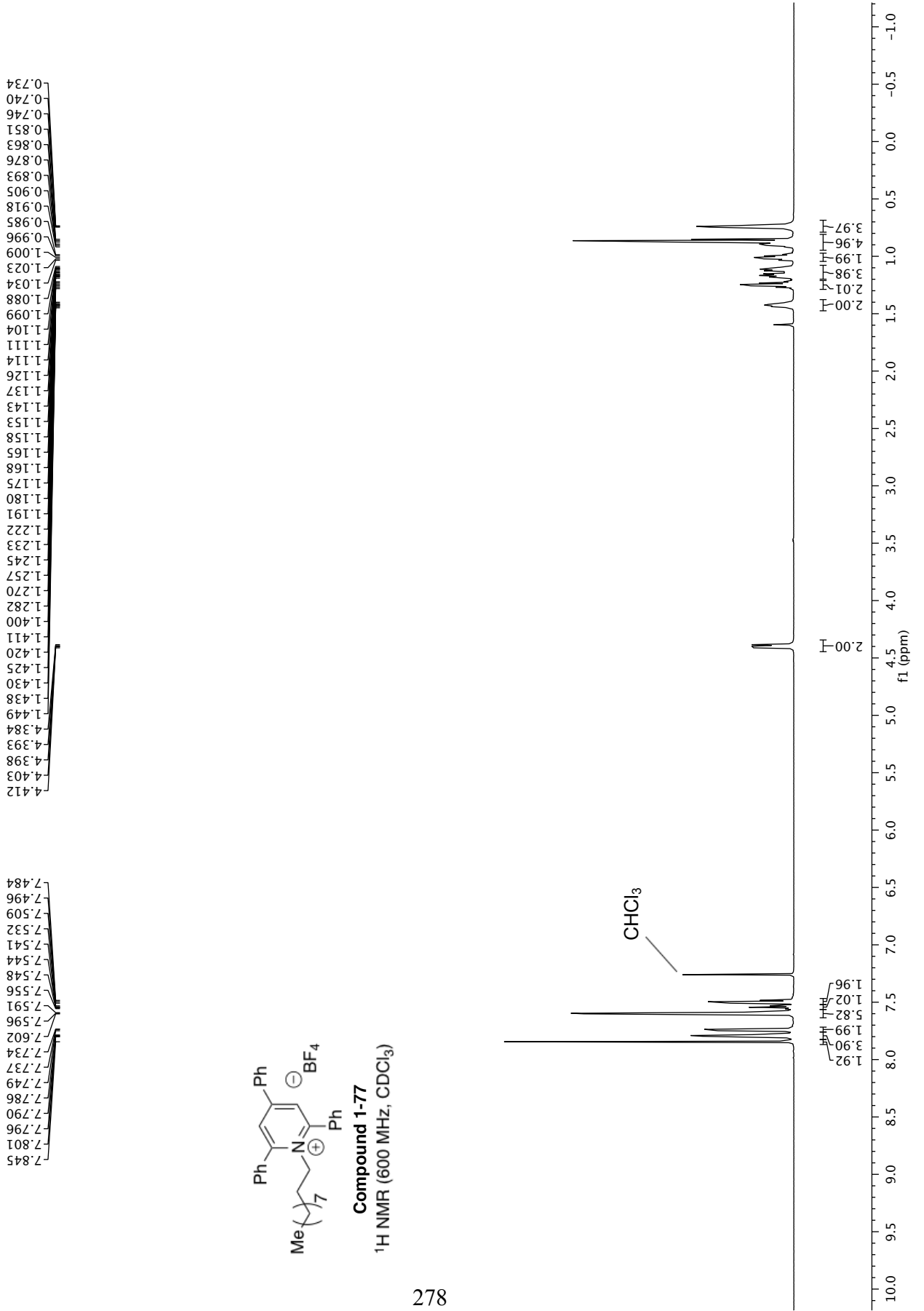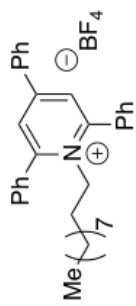
Compound 1-77

$^{13}$C NMR (151 MHz, CDCl$_3$)

279

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

-153.454
-153.401

Ph

Ph

N⁺  Ph

Ph

Me $\left(\!\!\!\!\!\!\right)_{7}$

⊖ BF₄
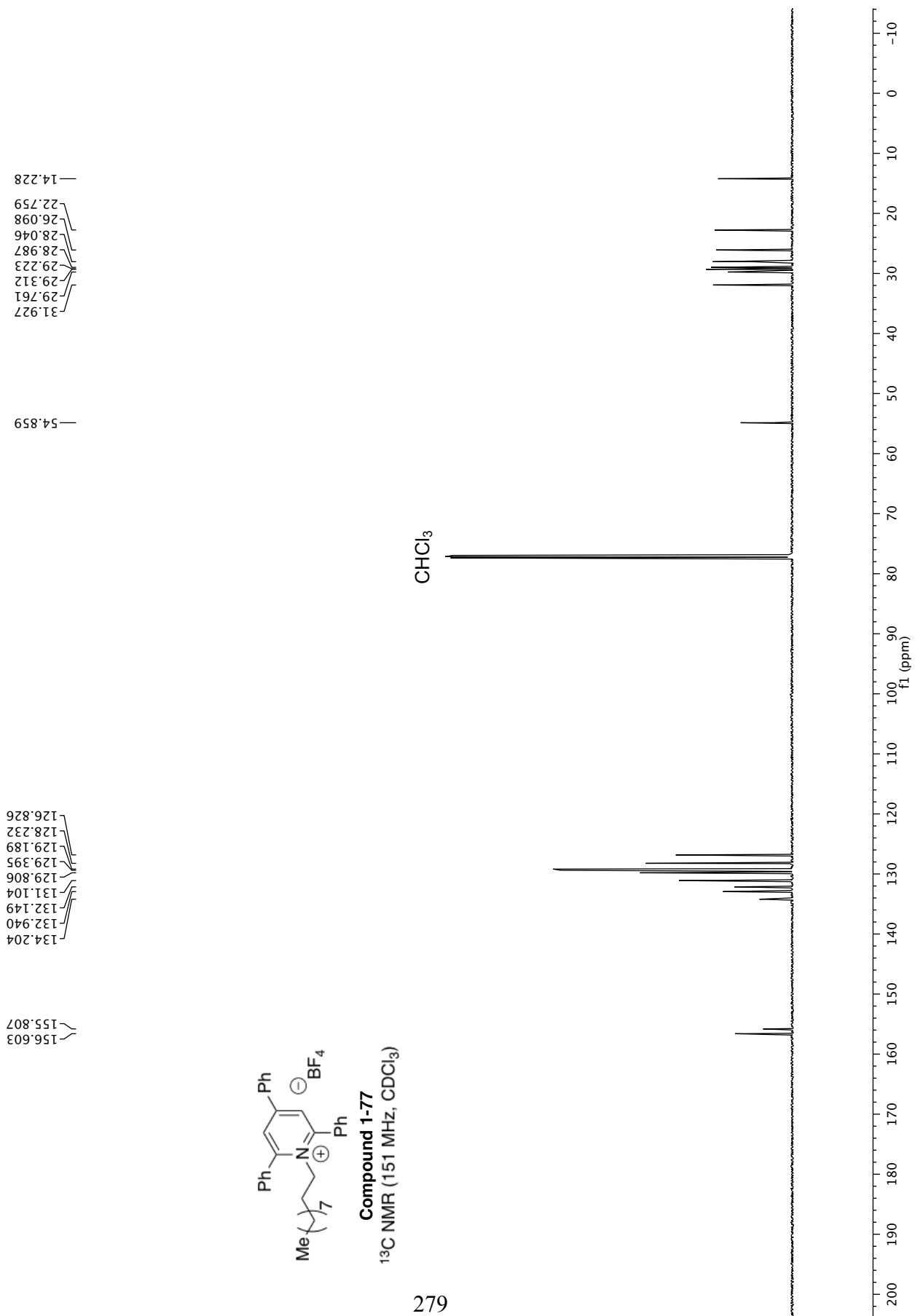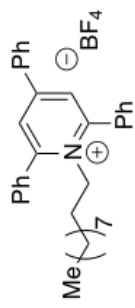
**Compound 1-77**
¹⁹F NMR (376 MHz, CDCl₃)

280
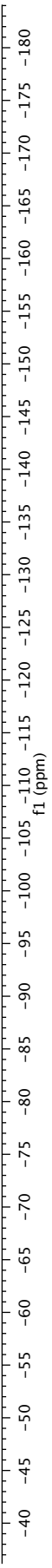
-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

2.672
2.688
2.693
2.698
2.713

4.635
4.650
4.655
4.660
4.676

6.275
6.278
6.296
7.035
7.039
7.053
7.072
7.104
7.116
7.122
7.128
7.140
7.532
7.537
7.547
7.550
7.557
7.561
7.578
7.630
7.640
7.646
7.648
7.658
7.777
7.784
7.788
7.793
7.798
7.801
7.804
7.807
7.916
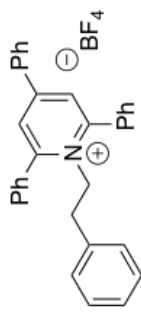
**Compound 1-33**
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

CHCl<sub>3</sub>

2.06
2.06
1.94
2.00
1.22
8.95
5.94
2.00

13C NMR spectrum

35.812

55.985

CHCl₃

126.885
127.447
128.298
128.327
128.944
129.258
129.538
129.862
131.299
132.296
132.848
134.147
135.267

156.179
156.773
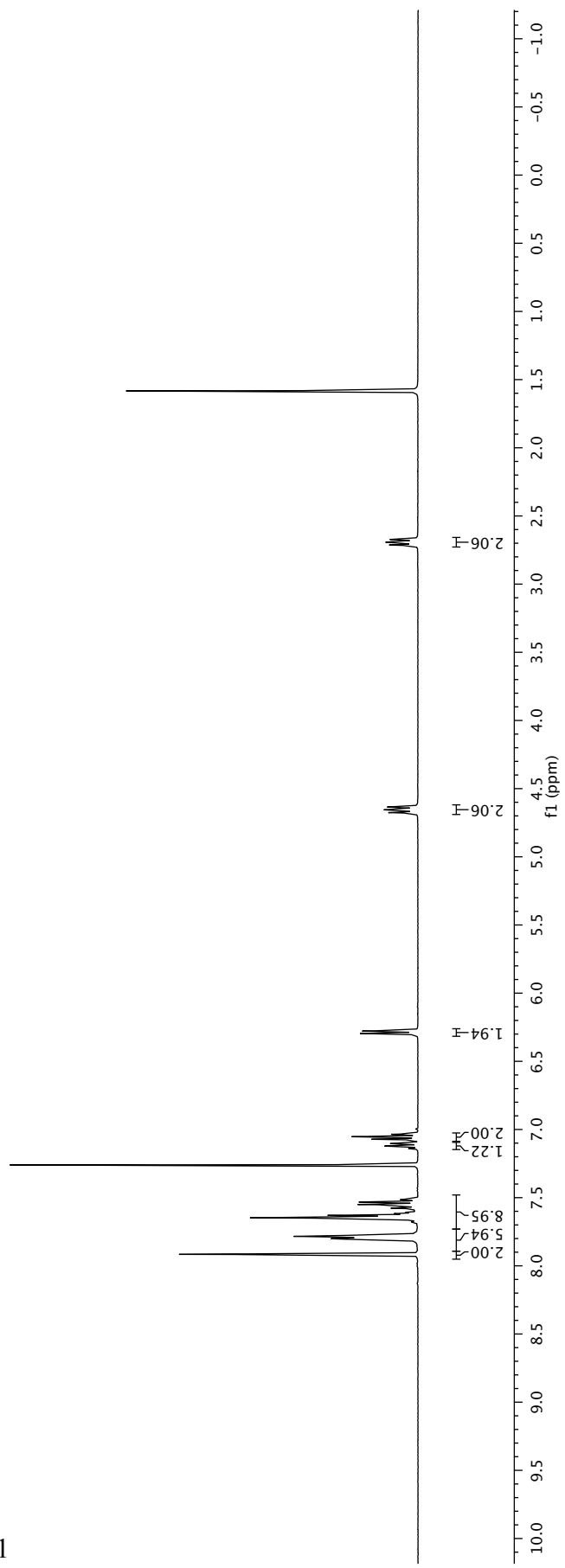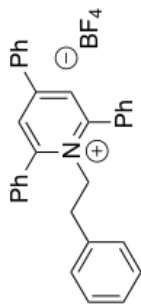
Compound 1-33
¹³C NMR (101 MHz, CDCl₃)

f1 (ppm)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
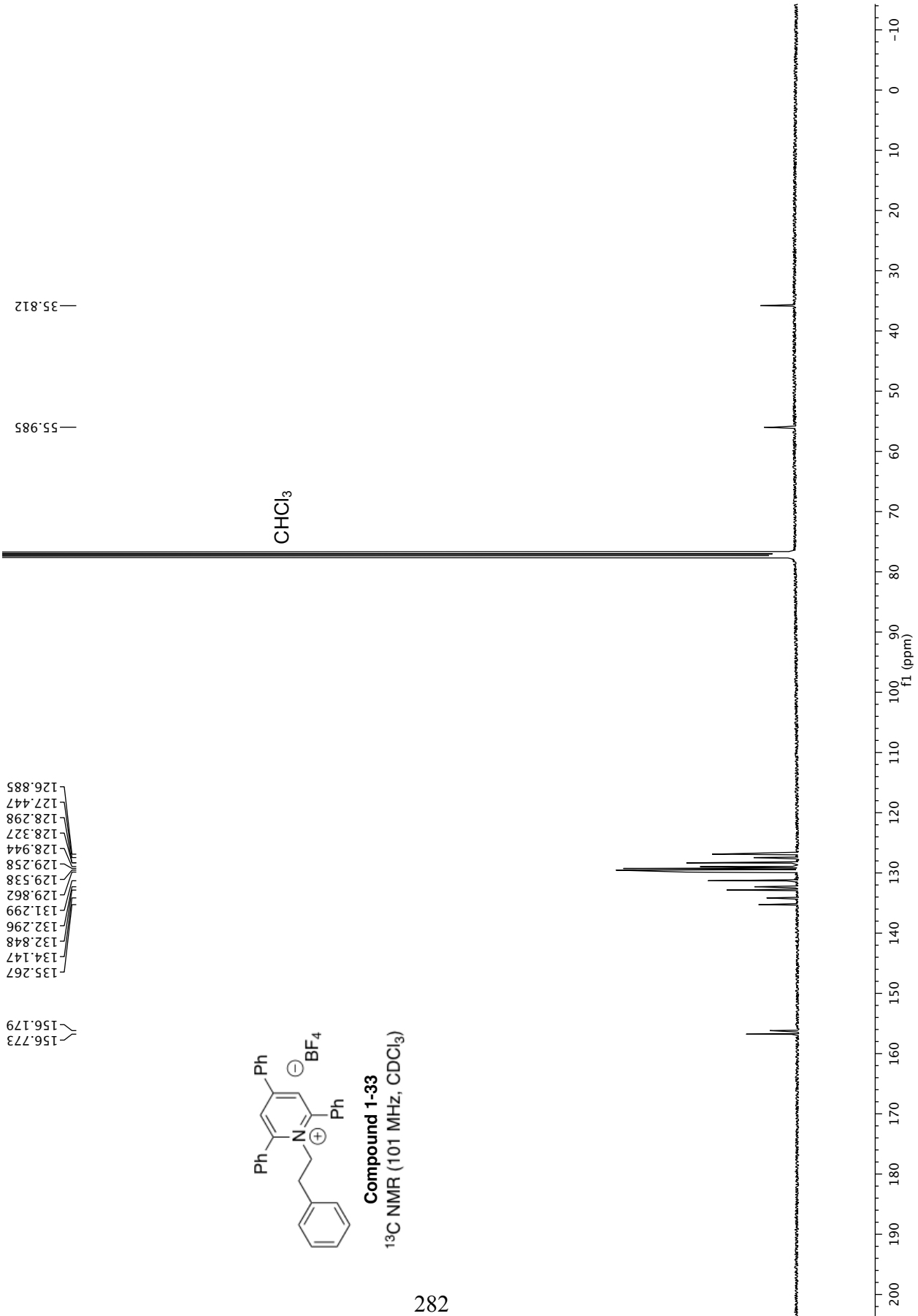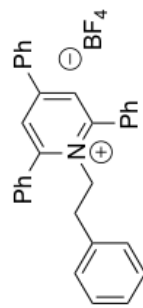
−153.317
−153.264

Compound 1-33
19F NMR (376 MHz, CDCl3)

283

−40 −45 −50 −55 −60 −65 −70 −75 −80 −85 −90 −95 −100 −105 −110 −115 −120 −125 −130 −135 −140 −145 −150 −155 −160 −165 −170 −175 −180
f1 (ppm)

Compound 1-78
¹H NMR (400 MHz, CDCl₃)

CHCl₃

284

14.121

22.536
22.829
26.736
31.688

37.236

C$_3$H$_6$O

68.362

128.607
129.389
129.747
130.369
130.597
131.896
133.299
134.351
135.109

155.317
158.710

Compound 1-78
$^{13}$C NMR (151 MHz, C$_3$D$_6$O)

285

-153.400
-153.348

Ph

Ph          Ph

N⁺   Me   Ph
            BF₄⁻

/3

Me
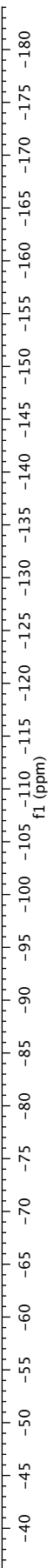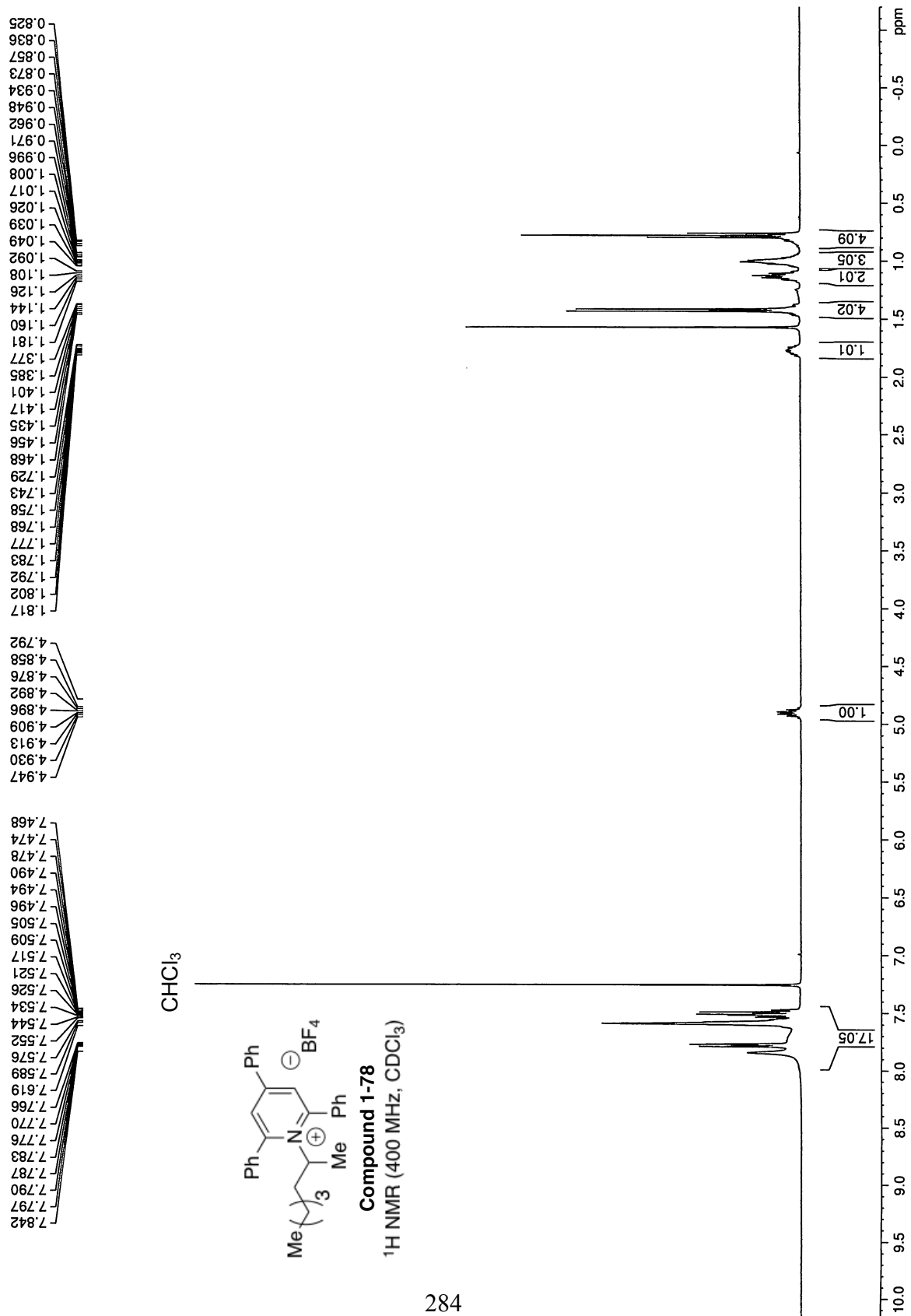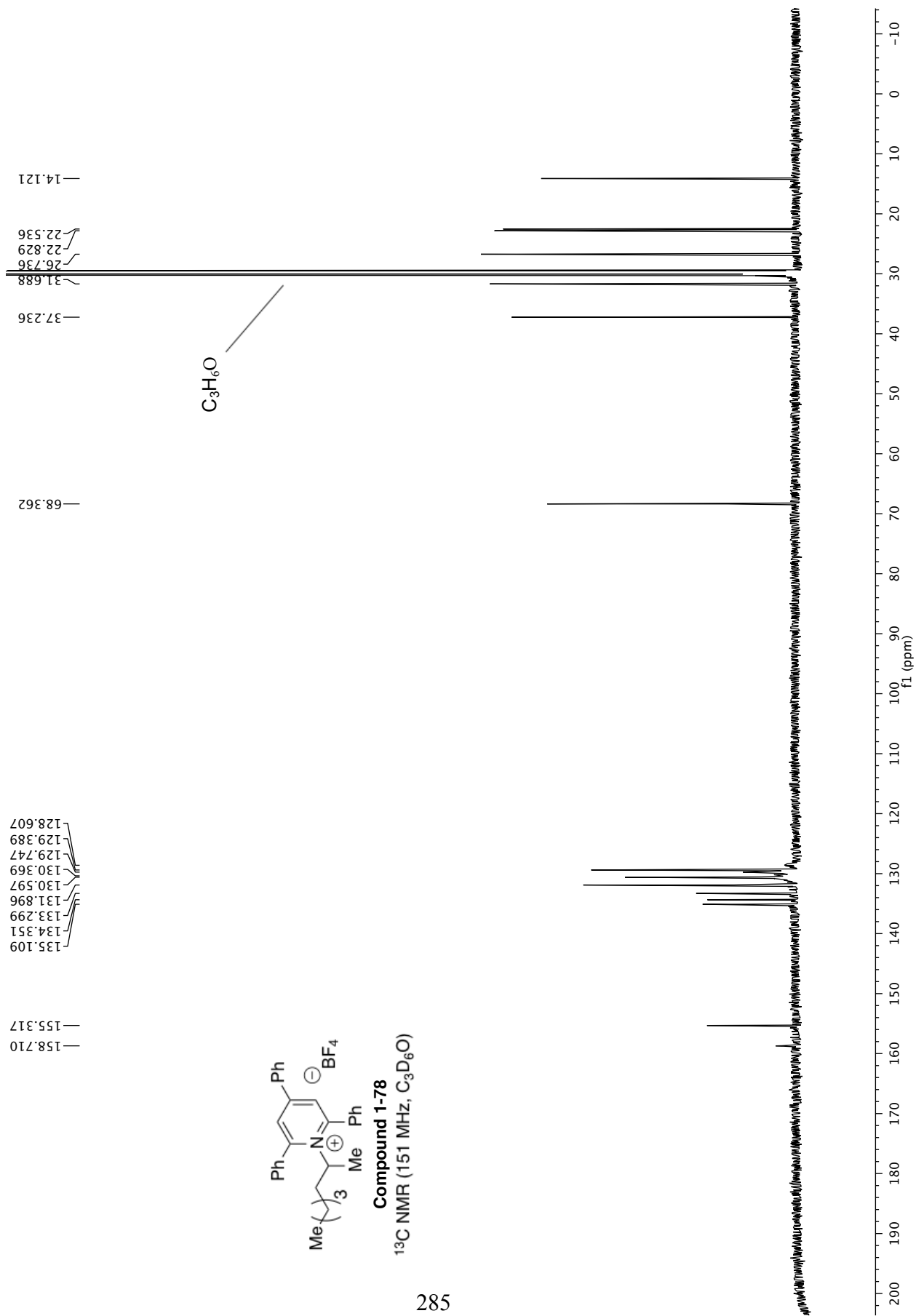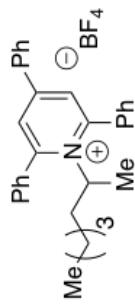
**Compound 1-78**
¹⁹F NMR (565 MHz, CDCl₃)

286

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

0.571
0.581
0.590
0.604
0.613
0.622
0.637
0.645
0.684
0.692
0.700
0.715
0.724
0.732
0.748
0.756
0.764
0.780
0.788
1.320
1.329
1.354
1.422
1.430
1.453
1.461
1.483
1.492
1.513
1.522
1.545
1.553
1.561
1.580
1.588
1.595
2.101
2.131
4.567
4.575
4.582
4.598
4.605
4.613
4.629
4.636
4.643
7.425
7.429
7.433
7.446
7.451
7.456
7.465
7.468
7.470
7.488
7.492
7.495
7.502
7.508
7.517
7.524
7.528
7.543
7.550
7.566
7.583
7.587
7.592
7.597
7.604
7.616
7.618
7.623
7.626
7.714
7.719
7.729
7.734
7.738
7.746
7.783
7.786
7.789

Compound 1-35
¹H NMR (400 MHz, CDCl₃)

CHCl₃

287

24.744
26.604

33.676

72.012
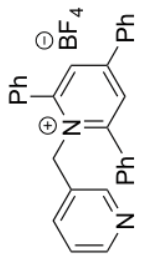
CHCl₃

128.208
128.377
128.888
129.437
129.658
130.931
131.950
134.109
134.154

155.091
157.134
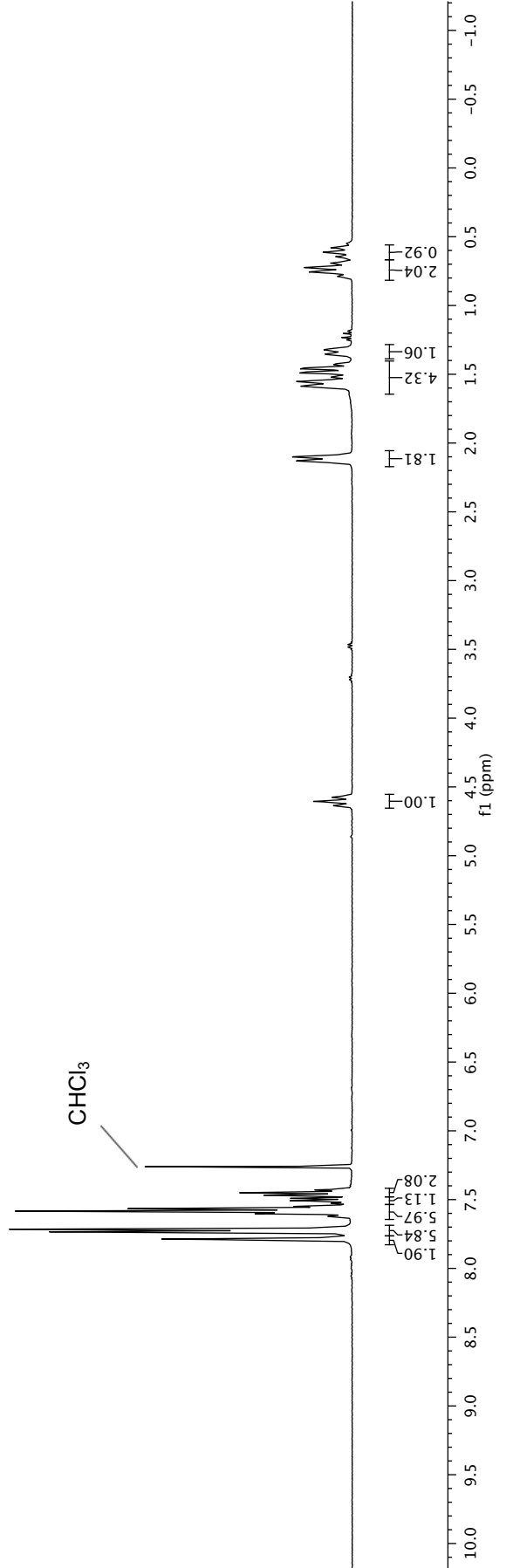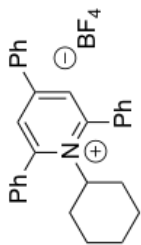
Compound 1-35
¹³C NMR (101 MHz, CDCl₃)

288

-153.411
-153.358

Ph

Ph ⊖BF₄ Ph

N⊕
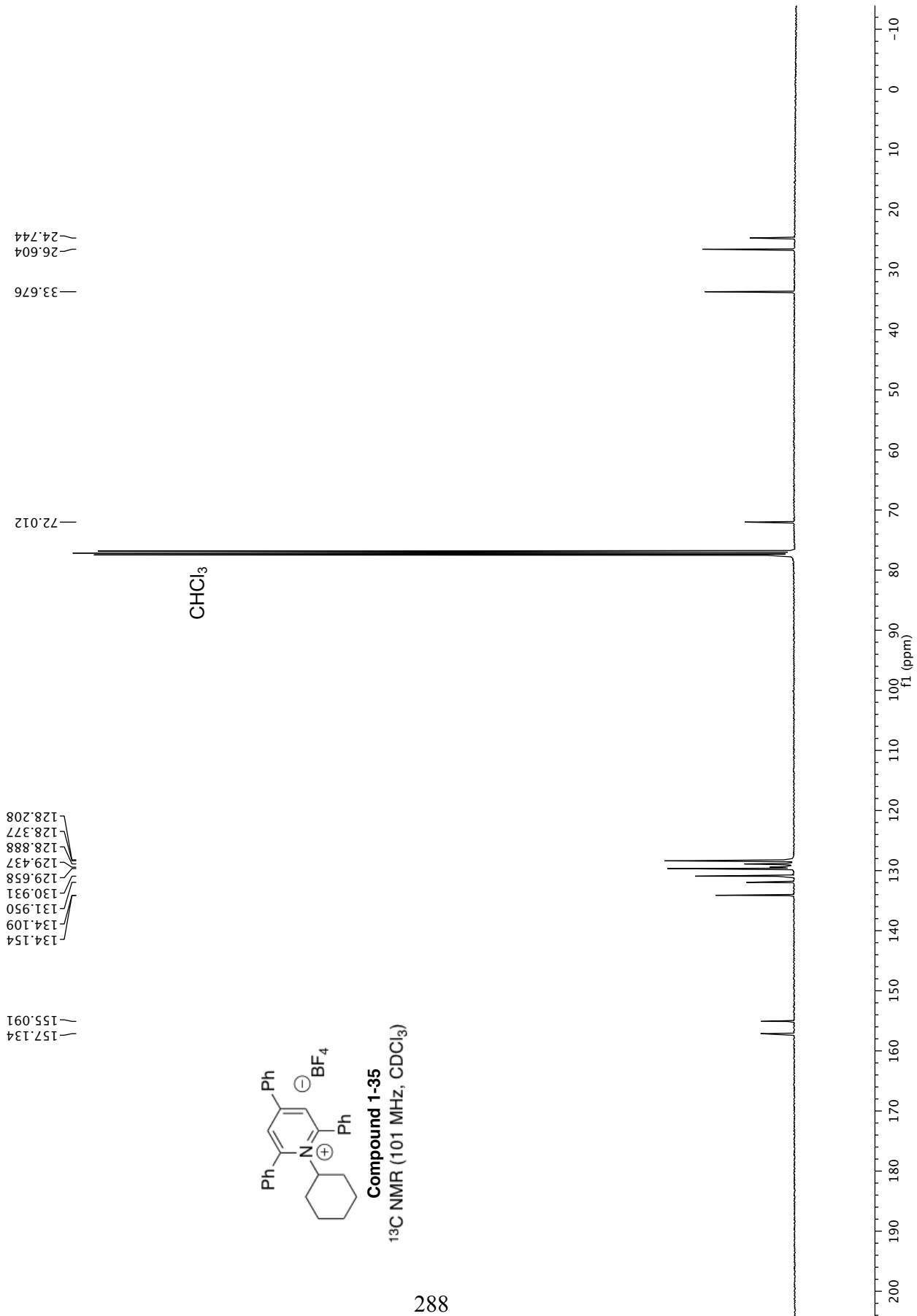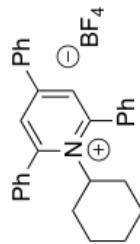
**Compound 1-35**
¹⁹F NMR (376 MHz, CDCl₃)

289

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

Compound 1-38
$^1$H NMR (600 MHz, CDCl$_3$)

290

28.345

32.776

44.259

70.000

80.237

CHCl₃

128.334
128.405
129.111
129.411
129.712
131.88
132.149
133.813
134.004

154.314
155.527
157.228
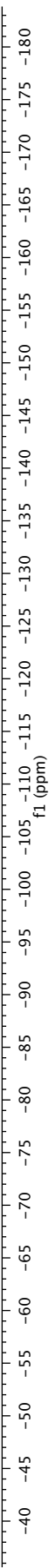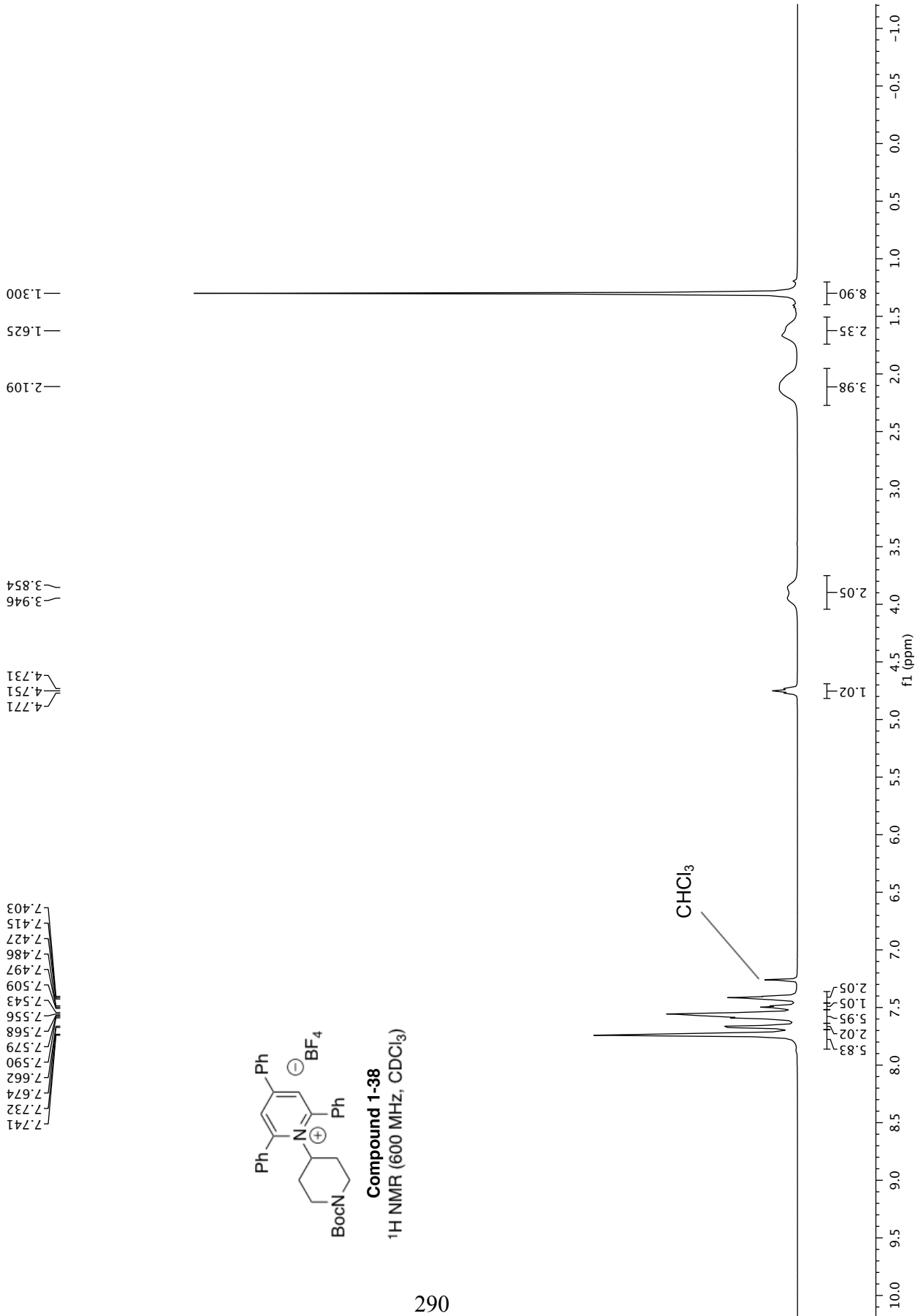
**Compound 1-38**
¹³C NMR (101 MHz, CDCl₃)

291
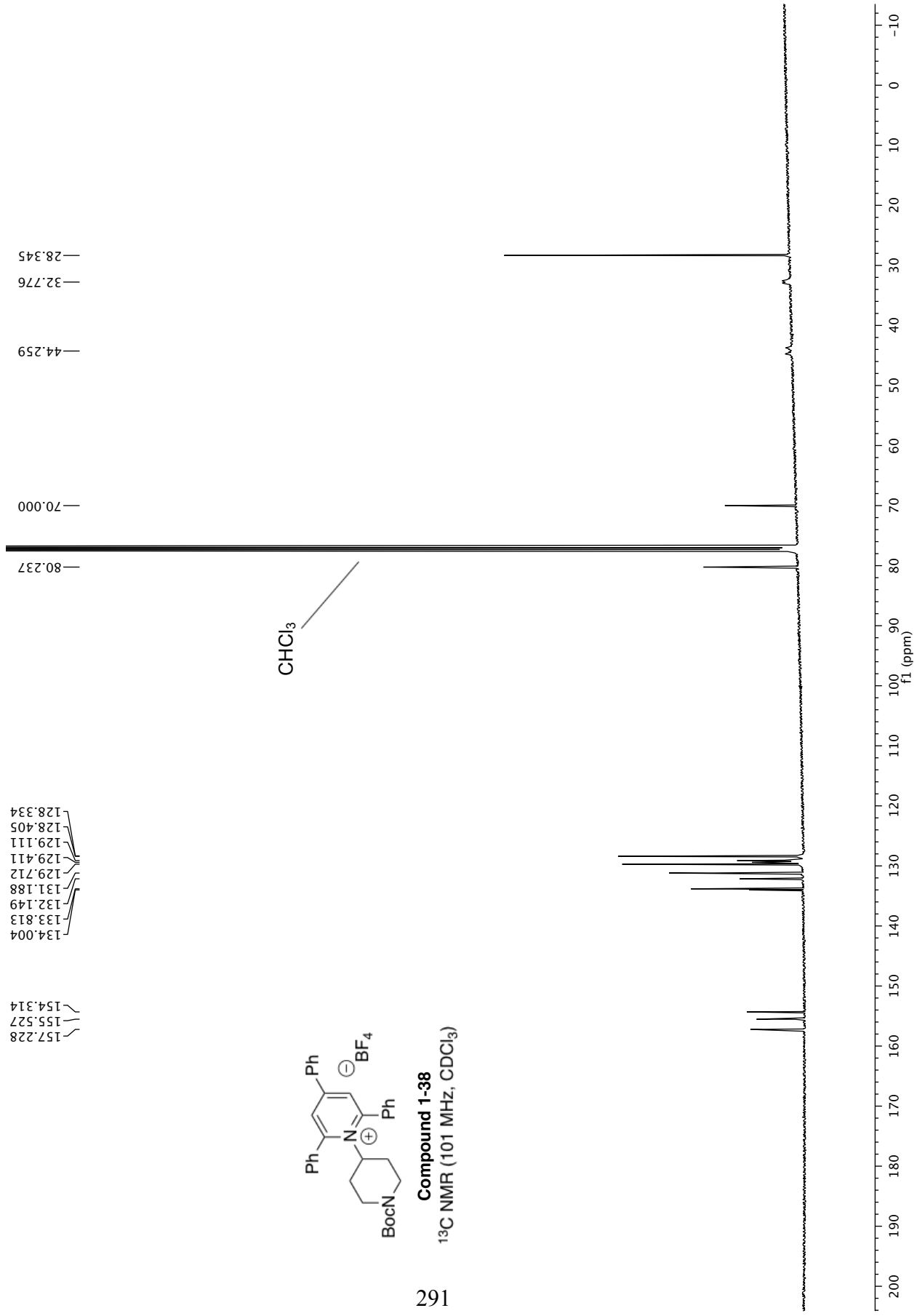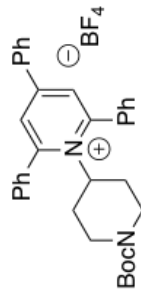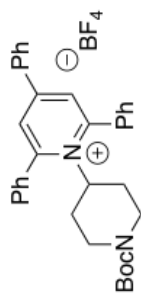
153.128
153.074

Compound 1-38
$^{19}F$ NMR (376 MHz, $CDCl_3$)

292

f1 (ppm)

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
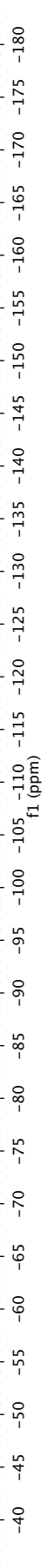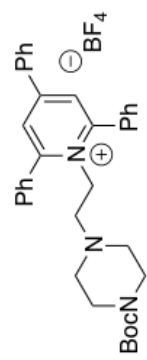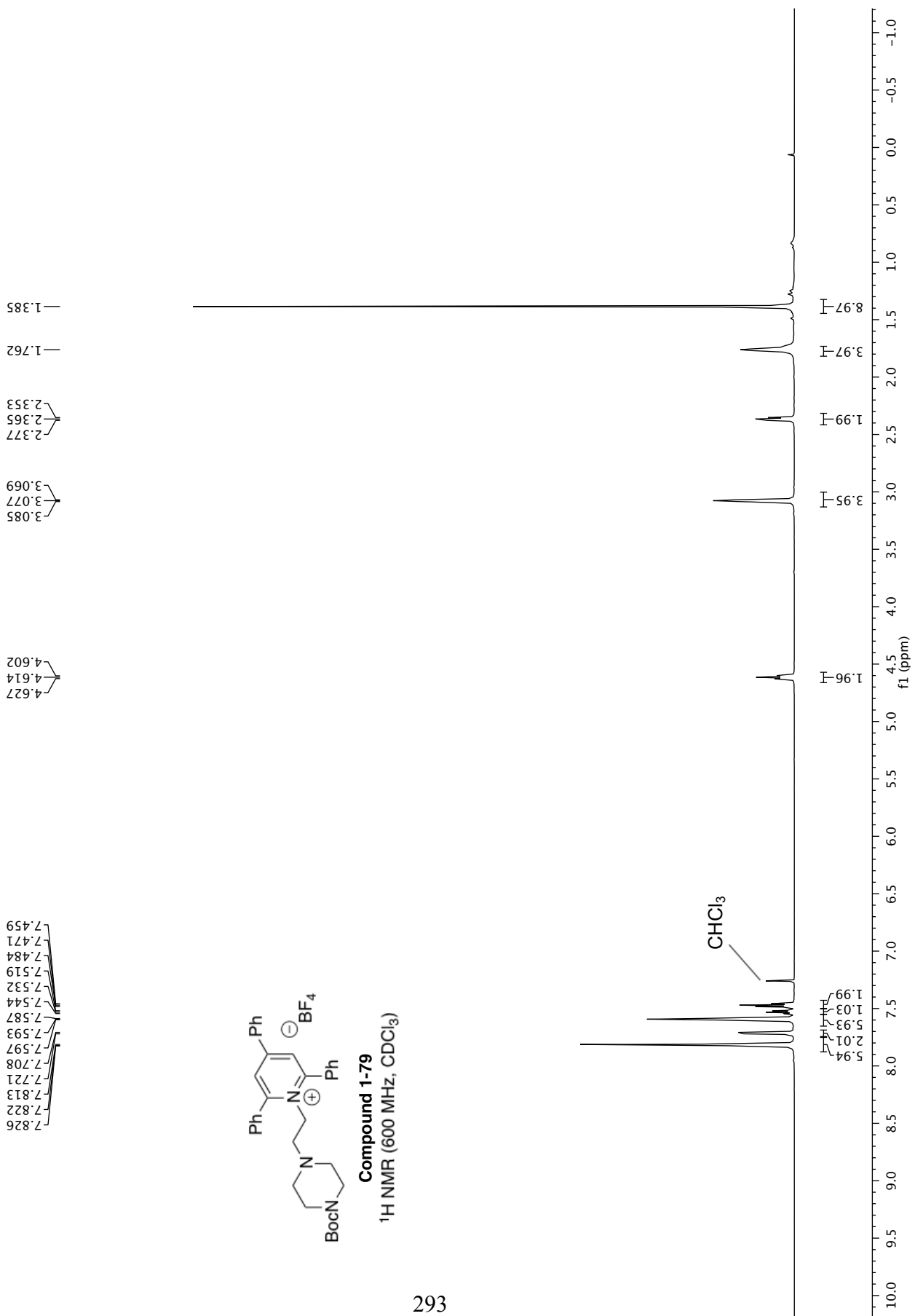
Compound 1-79
$^1$H NMR (600 MHz, CDCl$_3$)

293

28.480

43.191

51.845
52.378
56.438

CHCl₃

79.887

126.789
128.263
129.455
129.505
129.816
131.292
132.265
132.960
134.083

154.569
156.082
156.961
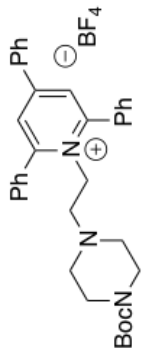
**Compound 1-79**
¹³C NMR (151 MHz, CDCl₃)

294

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10
f1 (ppm)
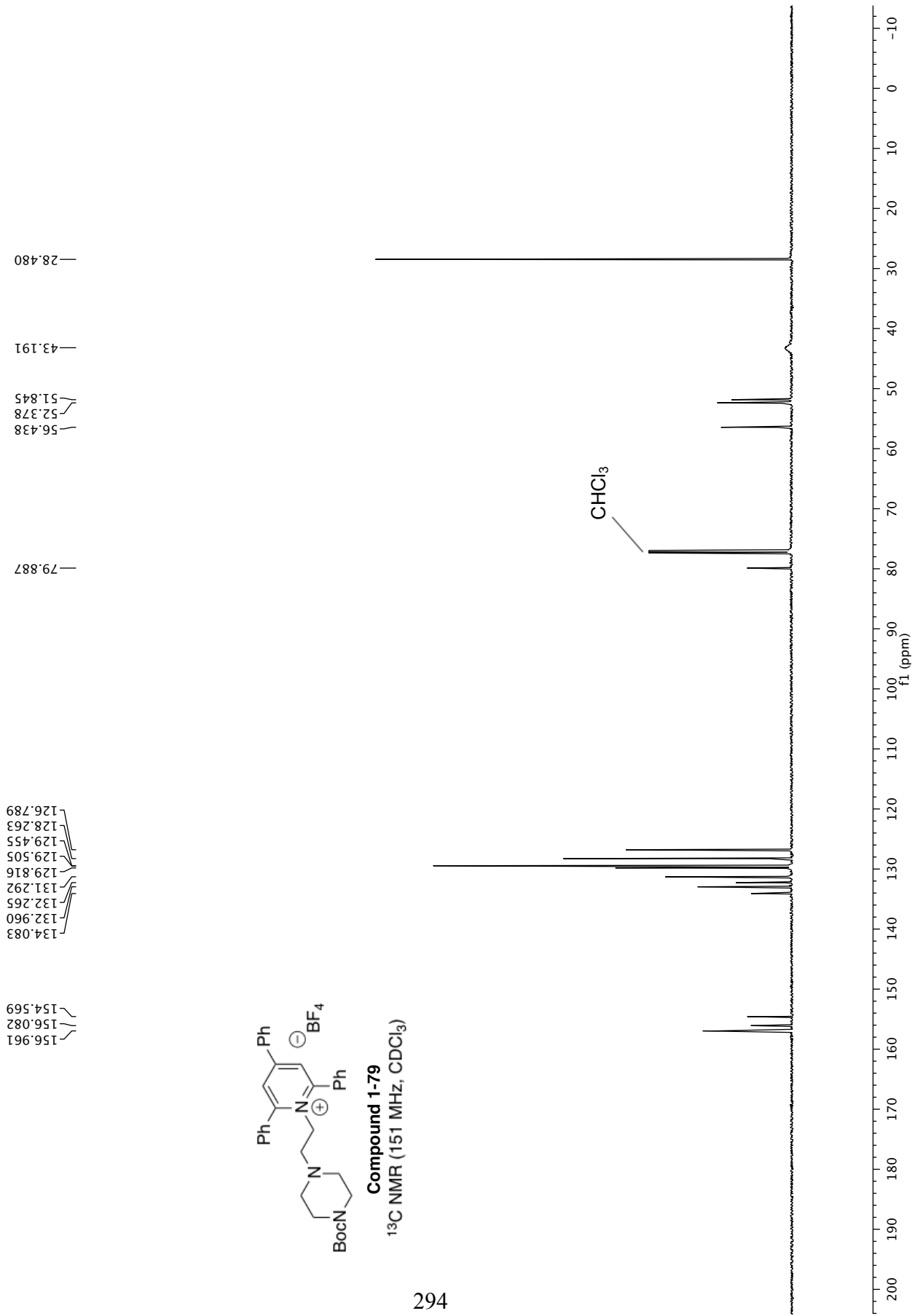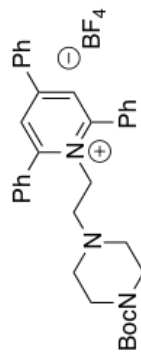
-153.009
-152.956

Compound 1-79
¹⁹F NMR (565 MHz, CDCl₃)

295

0.788
0.803
0.817
0.830
0.842
1.229
1.240
1.248
1.260
1.315
1.466
1.477
1.497
1.509
1.522
1.534
2.649
2.664
2.679
2.885
2.896
2.903
2.914
2.921
2.932
3.896
3.903
3.915
3.928
3.933
4.627
4.651
4.670
4.791
4.796
4.815
4.820

7.513
7.524
7.537
7.550
7.562
7.569
7.581
7.593
7.615
7.627
7.638
7.718
7.731
7.805
7.914
8.046
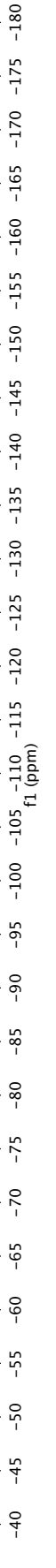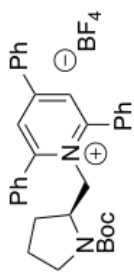
**Compound 1-37**
¹H NMR (600 MHz, CDCl₃)

CHCl₃

0.95
1.31
8.97
1.99
0.93
0.94
1.00
1.00
0.95
9.90
2.07
2.07
2.95

23.440
28.372
28.516

47.302

55.127
57.526

CHCl₃

80.080

126.342
127.954
129.397
129.838
130.403
130.958
132.100
133.505
134.325

155.376
155.597
158.029
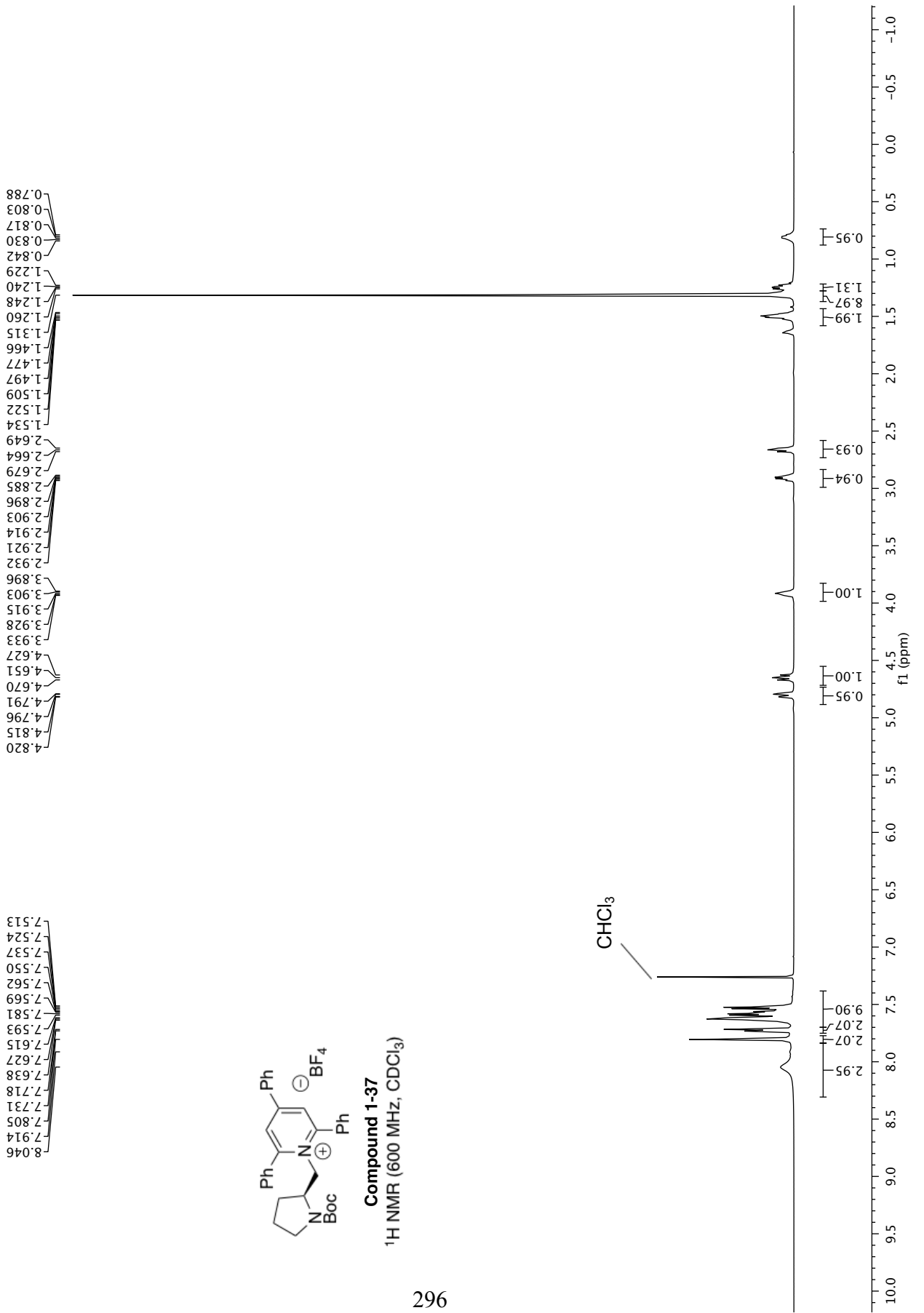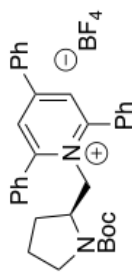
**Compound 1-37**
$^{13}C$ NMR (151 MHz, CDCl₃)

f1 (ppm)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  −10
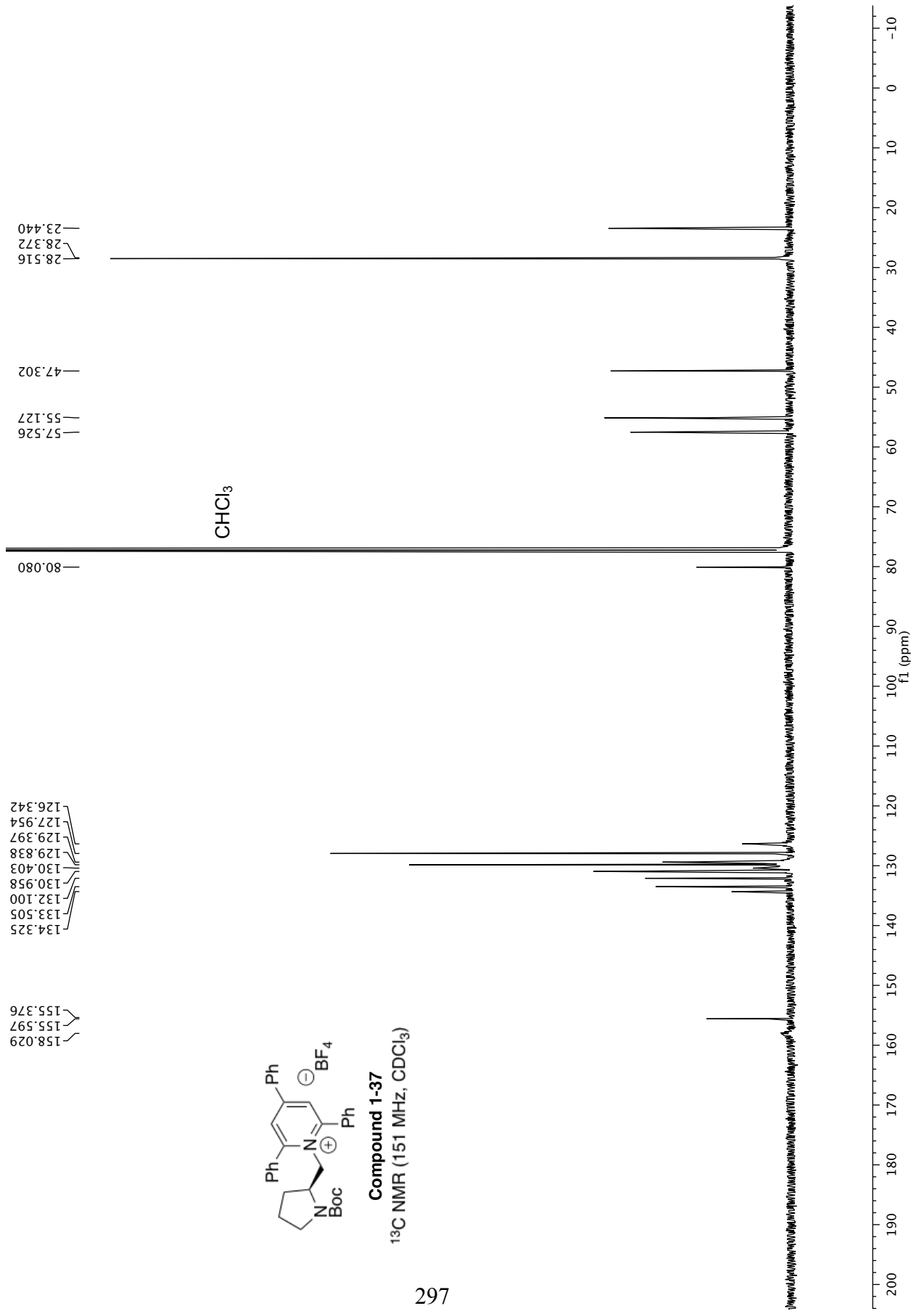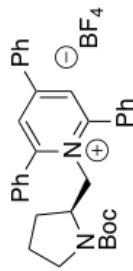
-153.131
-153.078

**Compound 1-37**
¹⁹F NMR (565 MHz, CDCl₃)

298

f1 (ppm)
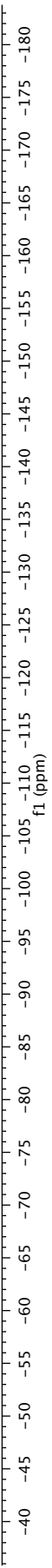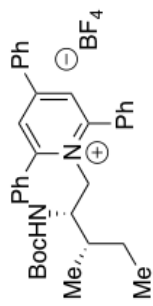
Compound 1-36
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

299

Compound 1-36
¹³C NMR (101 MHz, CDCl₃)

CHCl₃

154.978
155.822
157.915
158.310

125.982
126.829
127.998
128.932
129.275
129.885
130.193
130.412
130.749
131.223
132.259
133.098
133.892
134.125

80.225

56.215
53.485

37.038

28.497
25.191

14.153
10.654

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

300

-153.073
-153.021

Ph

⊖ BF₄

Ph

N⁺

BocHN Ph

Me    Me
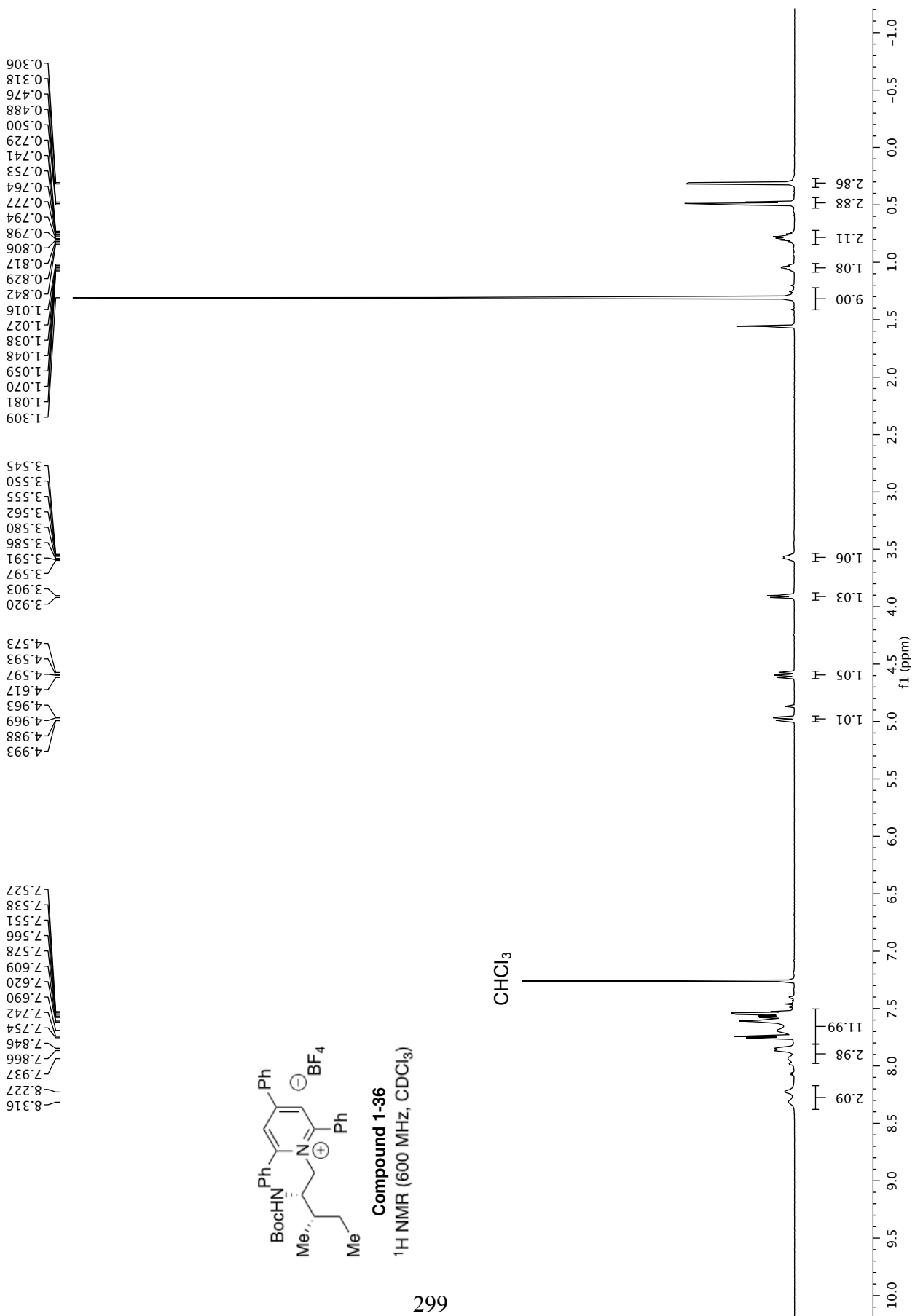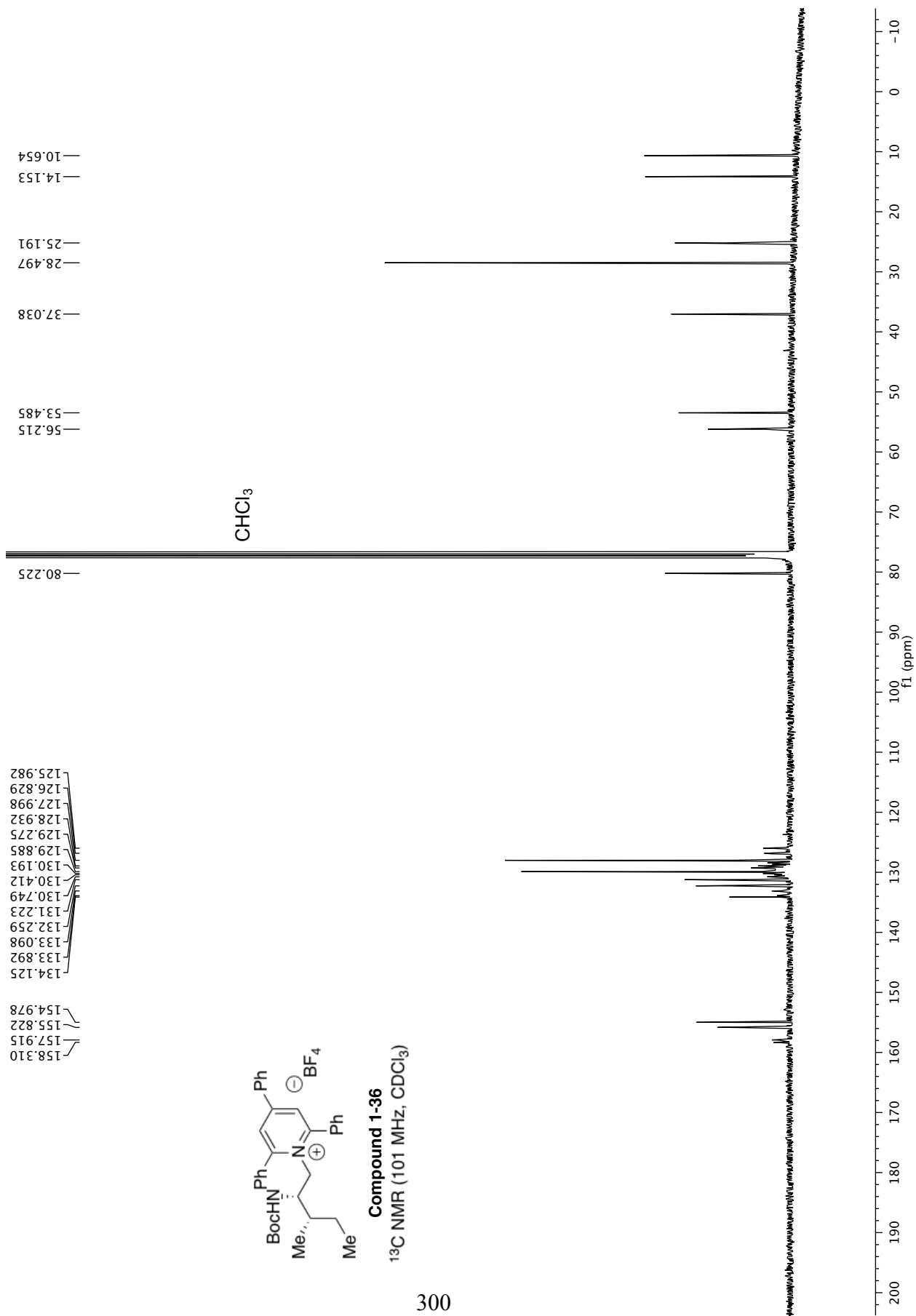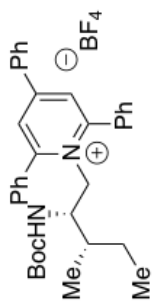
**Compound 1-36**
¹⁹F NMR (565 MHz, CDCl₃)

301

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

Compound 1-80
1H NMR (600 MHz, CDCl₃)

CHCl₃

Peak list (left to right region, top):

0.810
0.880
1.041
1.054
1.063
1.072
1.081
1.094
1.103
1.267
1.279
1.284
1.294
1.306
1.402
1.423
1.483
1.498
1.510
1.523
1.537

3.832
3.845
3.855
3.866
4.427
4.440
4.453
4.834
4.847

7.535
7.546
7.559
7.578
7.586
7.590
7.594
7.602
7.618
7.631
7.634
7.640
7.642
7.648
7.658
7.788
7.790
7.802
7.820
7.823
7.829
7.833
7.906

Integration labels:
2.26
1.12
0.73
1.32
8.81
8.73
2.26
0.99
2.24
1.02
2.09
1.12
6.04
6.07
2.00

Compound 1-80
$^{13}$C NMR (151 MHz, CDCl$_3$)

22.121
28.085
28.449
29.492
31.770
53.482
54.546
79.862
82.236
126.925
128.266
129.184
129.497
129.842
131.231
132.231
132.846
134.187
155.420
156.040
156.648
171.347

CHCl$_3$

303

-153.355
-153.302

**Compound 1-80**
$^{19}$F NMR (376 MHz, CDCl$_3$)
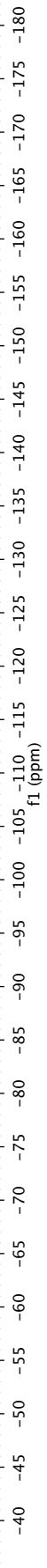
304

1.264
1.288
1.293
1.316
1.860
1.869
1.889
1.897
1.917
1.925
2.076
2.103
2.416
2.422
2.446
2.451
3.189
3.197
3.206
3.213
3.220
3.228
3.245
3.255
3.261
3.278
3.283
3.289
3.311
3.317
3.604
3.611
3.617
3.633
3.640
4.523
4.548
4.561
4.585
4.709
4.719
4.746
4.757

6.923
6.928
6.938
6.944
6.950
6.961
6.966
6.973
7.038
7.046
7.051
7.059
7.066
7.076
7.081
7.519
7.525
7.535
7.541
7.547
7.556
7.560
7.568
7.572
7.578
7.584
7.590
7.601
7.789
7.793
7.799
7.805
7.810
7.813
7.822
7.889

CHCl₃

Compound 1-81
¹H NMR (400 MHz, CDCl₃)

305

52.227
55.642
56.311

61.947

66.604

72.465

CHCl₃

115.178
115.320
126.275
128.195
129.307
129.625
129.891
130.626
130.678
131.087
132.383
132.595
133.193
133.979

155.748
157.758
161.419
163.046

**Compound 1-81**
¹³C NMR (151 MHz, CDCl₃)

306

f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

-153.275
-153.222
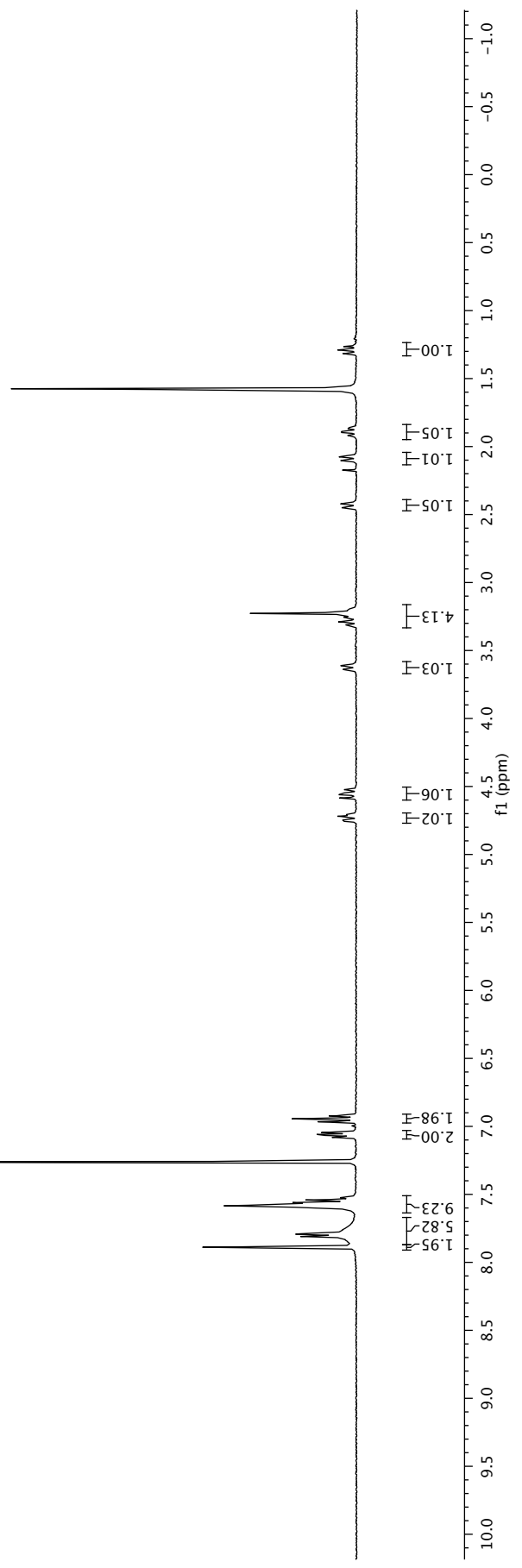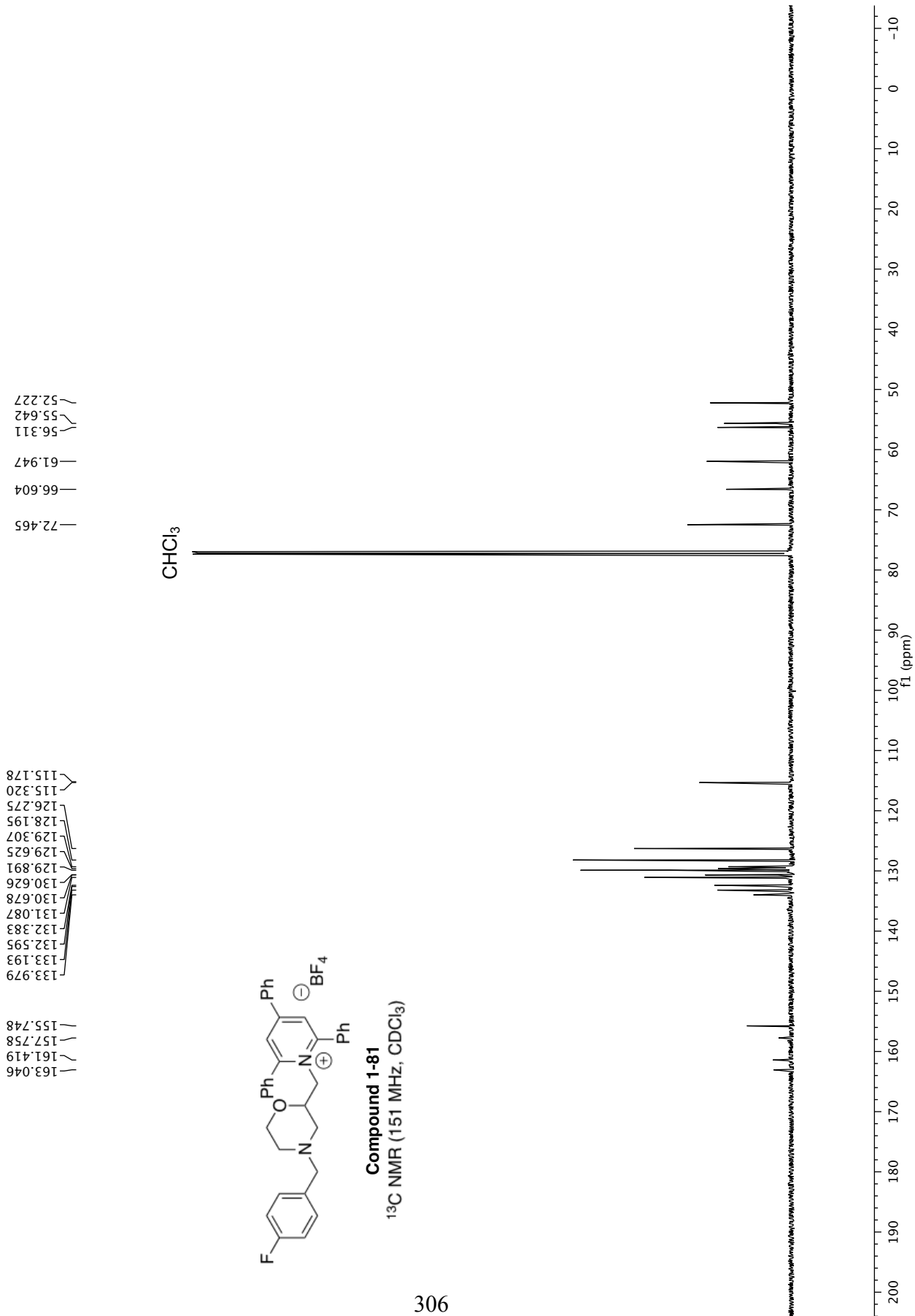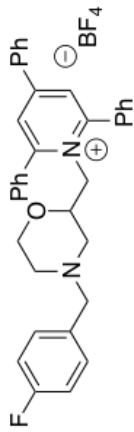
-115.296

Compound 1-81
$^{19}$F NMR (376 MHz, CDCl$_3$)

307

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

**Compound 1-82**
$^1$H NMR (400 MHz, CDCl$_3$)

CHCl$_3$

0.81
0.83

2.66
2.68
2.70
2.70
2.72
2.72
2.74
2.75

4.77
4.80
4.81
4.83
5.00
5.01
5.03
5.04

6.42
6.44
7.06
7.08
7.10
7.17
7.19
7.21
7.52
7.54
7.56
7.57
7.58
7.60
7.77
7.78
7.82
7.97

2.98
1.18
1.06
1.00
2.05
1.90
1.03
16.93

17.921

39.800

61.303

CHCl₃

126.555
126.887
127.697
128.179
129.095
129.587
129.646
129.929
131.226
132.476
133.175
133.847
140.381

155.772
157.587

**Compound 1-82**
¹³C NMR (101 MHz, CDCl₃)

309

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

-153.178
-153.127

Ph

Ph

Ph

N⁺

BF₄⁻

Me

Ph

**Compound 1-82**
¹⁹F NMR (565 MHz, CDCl₃)
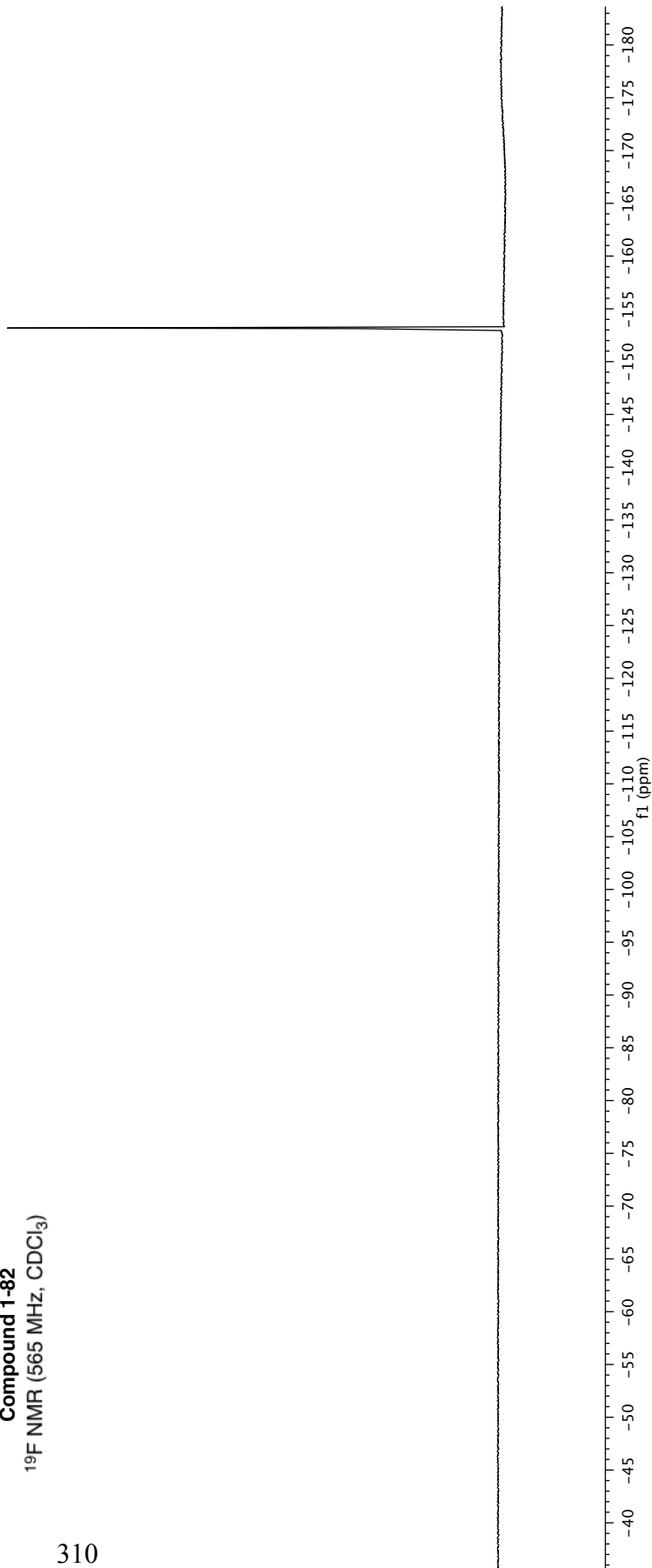
310

-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

7.872
7.809
7.804
7.798
7.794
7.770
7.758
7.756
7.619
7.605
7.600
7.571
7.563
7.558
7.555
7.546
7.528
7.515
7.506
7.503
7.260

4.474
4.460
4.446
4.018
4.009
4.000
3.390
3.378
3.374
3.366
3.363
3.354
3.351
3.339
3.203
3.191
3.187
3.179
3.175
3.167
3.164
3.152

1.570
1.562
1.557
1.555
1.551
1.544
1.539
1.530
1.072
1.061
1.049
1.037
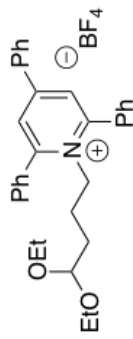
Compound 1-83
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

7.89
2.45
2.02
2.01
1.00
2.00

1.97
1.03
5.80
2.01
3.83
1.93

f1 (ppm)

Compound 1-83
$^{13}$C NMR (101 MHz, CDCl$_3$)

CHCl$_3$

15.351
25.238
30.651
54.837
61.701
101.605
126.910
128.247
129.141
129.437
129.836
131.151
132.213
132.873
134.155
155.927
156.633

312
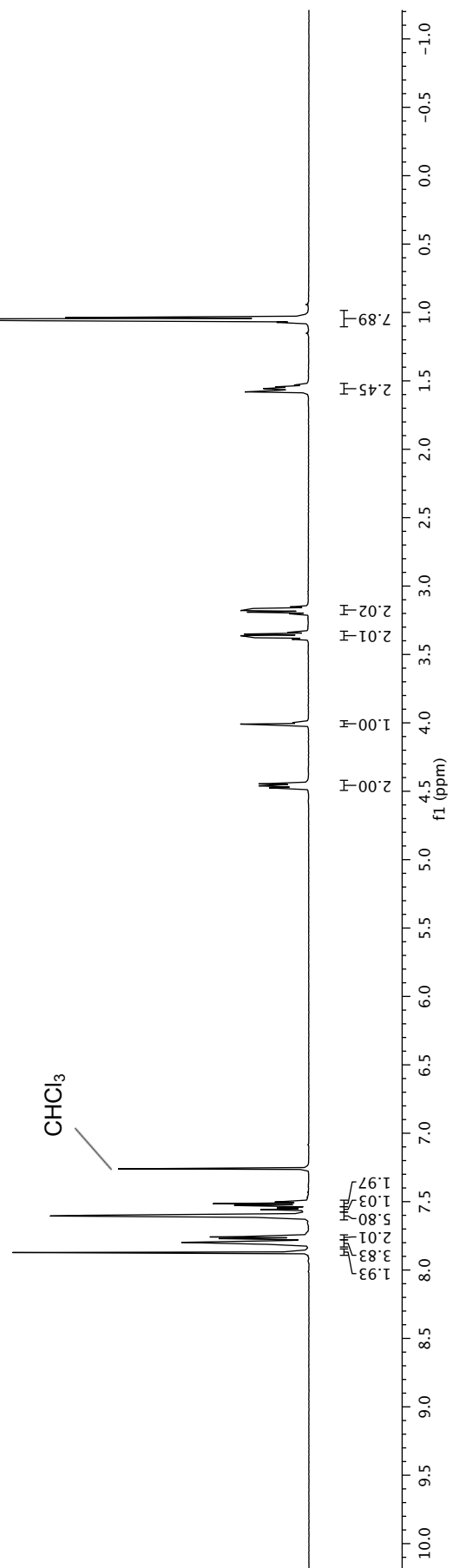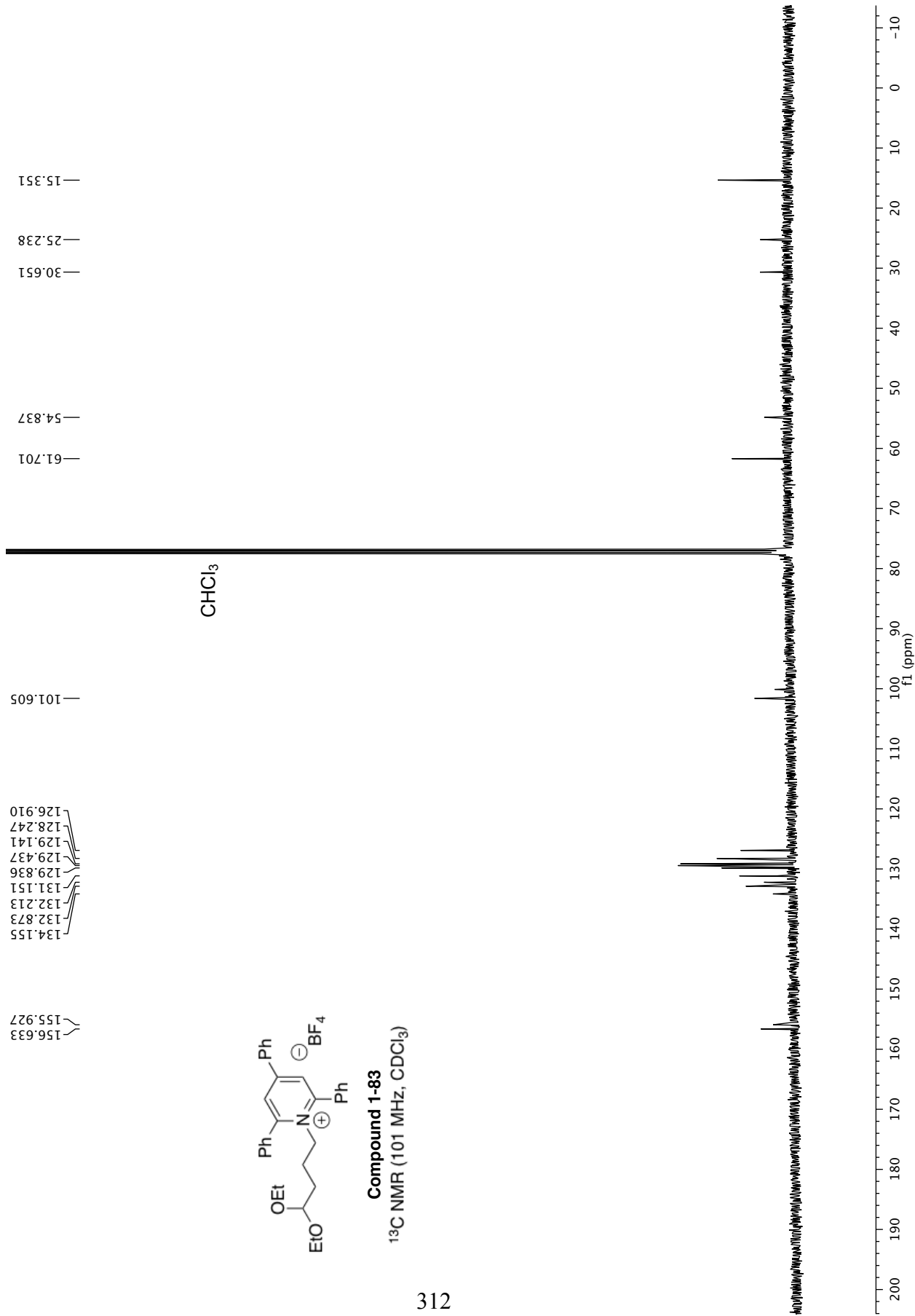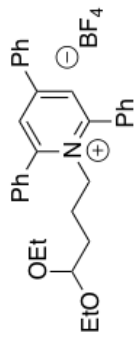
-153.464
-153.411

**Compound 1-83**
¹⁹F NMR (376 MHz, CDCl₃)

313

f1 (ppm)

-0.209

0.669

1.674
1.684
1.693
1.701
1.711
1.720

3.123
3.132
3.142

4.538
4.547
4.552
4.556
4.565

7.260
7.509
7.511
7.523
7.535
7.548
7.556
7.559
7.564
7.572
7.601
7.605
7.611
7.619
7.628
7.777
7.780
7.792
7.795
7.799
7.805
7.811
7.891

CHCl₃

Ph
Ph
Ph
BF₄
N
Ph
TBSO

**Compound 1-34**
¹H NMR (600 MHz, CDCl₃)

314

6.00
8.97
2.09
2.03
2.04
3.13
5.80
5.96
2.02

f1 (ppm)

-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0

-5.504

18.175

25.905

32.799

53.409

60.077

CHCl$_3$

127.107
128.293
129.127
129.489
129.801
131.168
132.124
132.951
134.286

156.032
156.706



**Compound 1-34**
$^{13}$C NMR (101 MHz, CDCl$_3$)

200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

315

-153.425
-153.477

Compound 1-34
$^{19}$F NMR (376 MHz, CDCl$_3$)

316

f1 (ppm)

Compound 1-84
$^1$H NMR (600 MHz, CDCl$_3$)

317

19.585

28.182
29.865
35.378
35.911
42.397

51.863

65.661
66.059

CHCl₃

80.863

98.646

126.927
128.245
129.229
129.482
129.840
131.196
132.199
132.852
134.202

156.025
156.850

170.091

**Compound 1-84**
¹³C NMR (101 MHz, CDCl₃)



318

f1 (ppm)
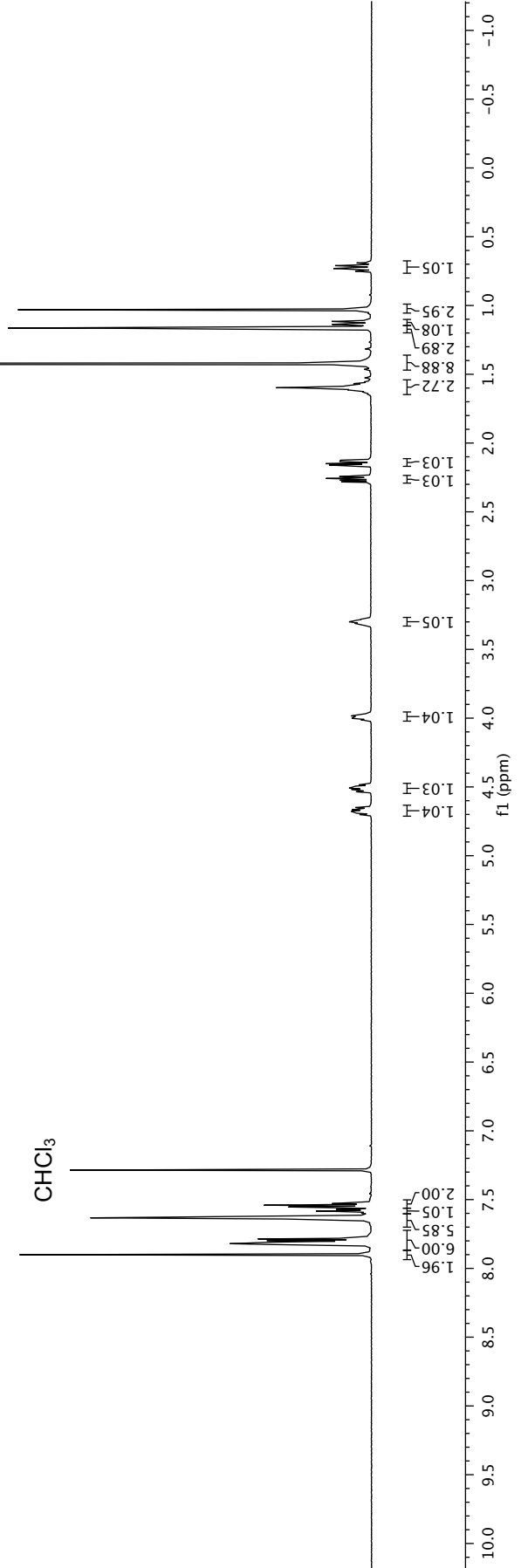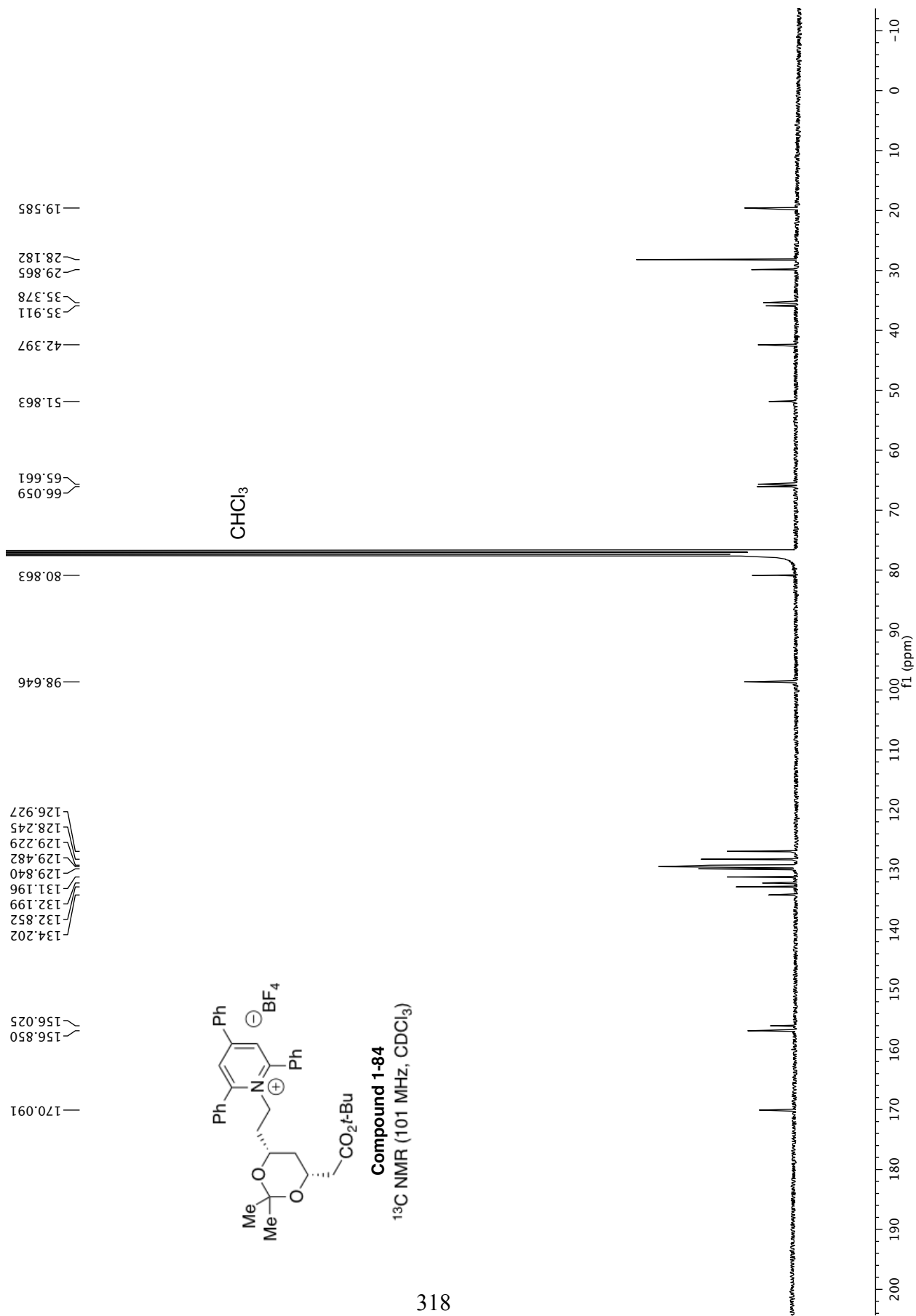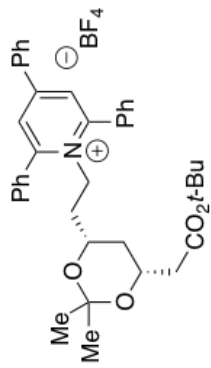
-153.372
-153.319

**Compound 1-84**
$^{19}$F NMR (376 MHz, CDCl$_3$)

319

f1 (ppm)
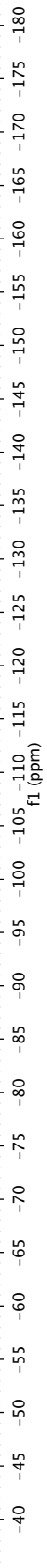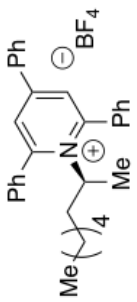
Compound 1-71
$^1$H NMR (400 MHz, CDCl$_3$)

7.422
7.440
7.459
7.487
7.505
7.523
7.560
7.578
7.593
7.609
7.707
7.710
7.728
7.774

0.728
0.759
0.777
0.787
0.805
0.823
0.850
0.909
0.922
0.944
0.957
0.978
0.990
1.005
1.021
1.037
1.052
1.060
1.064
1.072
1.086
1.107
1.119
1.136
1.172
1.186
1.190
1.201
1.366
1.371
1.396
1.413
1.442
1.454
1.709
1.725
1.740
1.749
1.759
1.765
1.772
1.784
1.799
4.835
4.853
4.870
4.889
4.907
4.924

CHCl$_3$

17.00
1.06
1.12
3.97
2.22
5.16
4.17

321

14.07

21.74
22.52
26.65
28.46
31.49

36.86

67.15

CHCl₃

128.36
128.81
128.94
129.34
129.67
130.97
132.04
133.94
133.99

155.15
157.24

Compound 1-71
$^{13}$C NMR (101 MHz, CDCl₃)

f1 (ppm)

-153.31
-153.25

Ph

BF₄⁻

Ph

N⁺

Me   Ph

Me

4
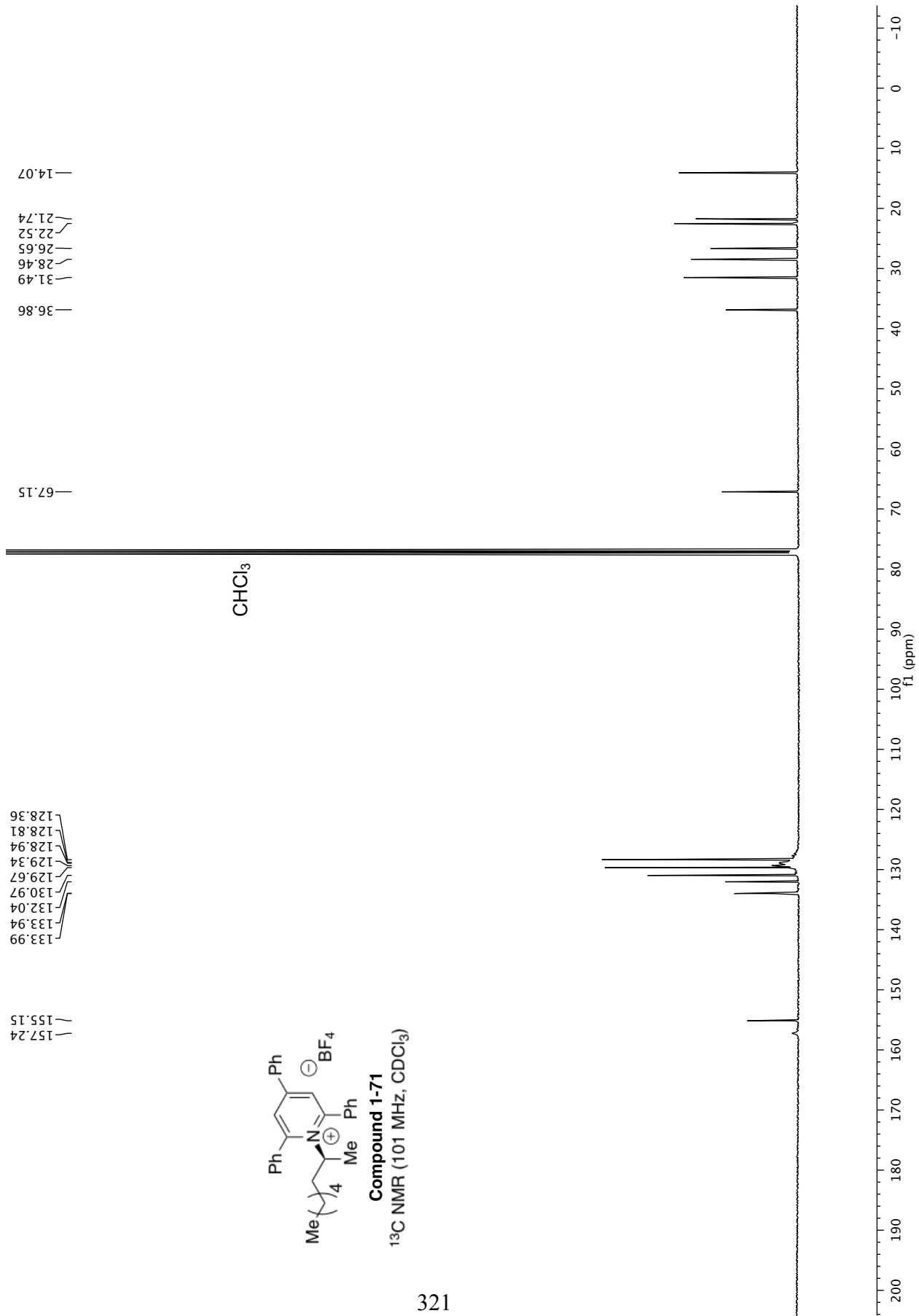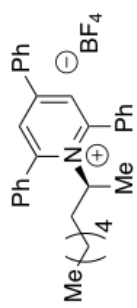
**Compound 1-71**

¹⁹F NMR (376 MHz, CDCl₃)

322

-40  -45  -50  -55  -60  -65  -70  -75  -80  -85  -90  -95  -100  -105  -110  -115  -120  -125  -130  -135  -140  -145  -150  -155  -160  -165  -170  -175  -180
f1 (ppm)

0.399
0.386
0.372
0.359
0.246
0.259
0.261
0.277
0.294
0.612
0.624
0.629
0.641
0.644
0.649
0.653
0.661
0.669
0.673
0.678
0.691
0.693
0.698
0.711

4.505
4.522

7.481
7.485
7.490
7.503
7.521
7.532
7.536
7.539
7.547
7.553
7.580
7.587
7.596
7.738
7.741
7.759
7.808
7.815
7.820
7.824
7.829
7.832
7.856
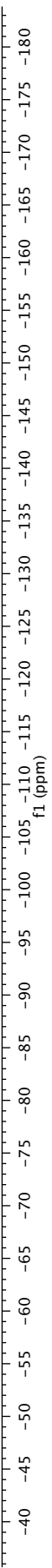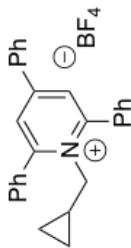
**Compound 1-73**
$^1$H NMR (400 MHz, CDCl$_3$)

CHCl$_3$

2.13
2.16
1.18
1.94
2.94
5.78
1.99
3.77
1.96

f1 (ppm)

323

5.148

10.769

59.221

CHCl₃

126.763
128.185
129.463
129.538
129.851
131.200
132.298
133.317
133.941

155.705
156.951
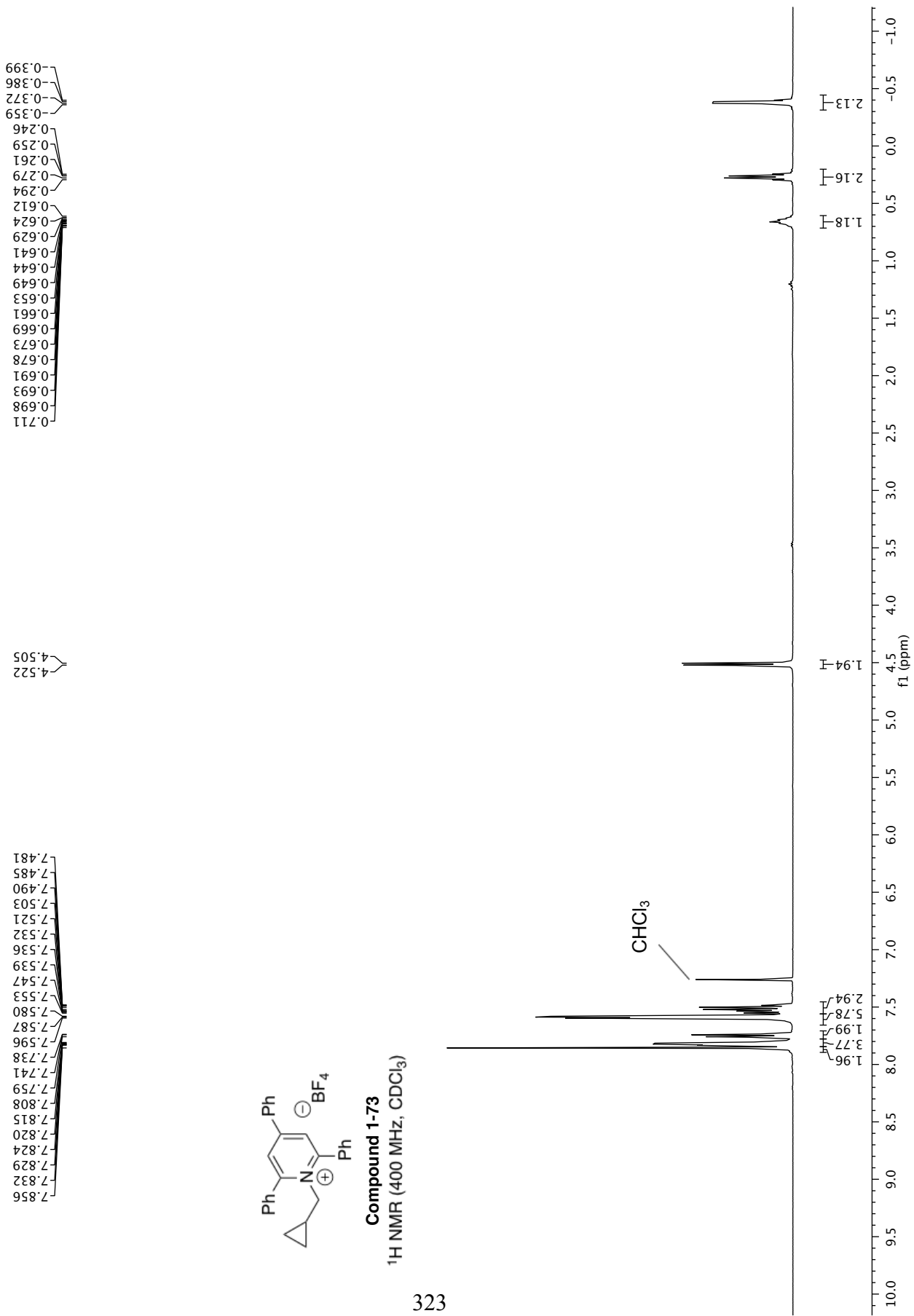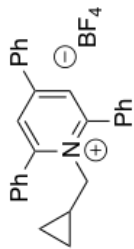
Compound 1-73
¹³C NMR (101 MHz, CDCl₃)

324
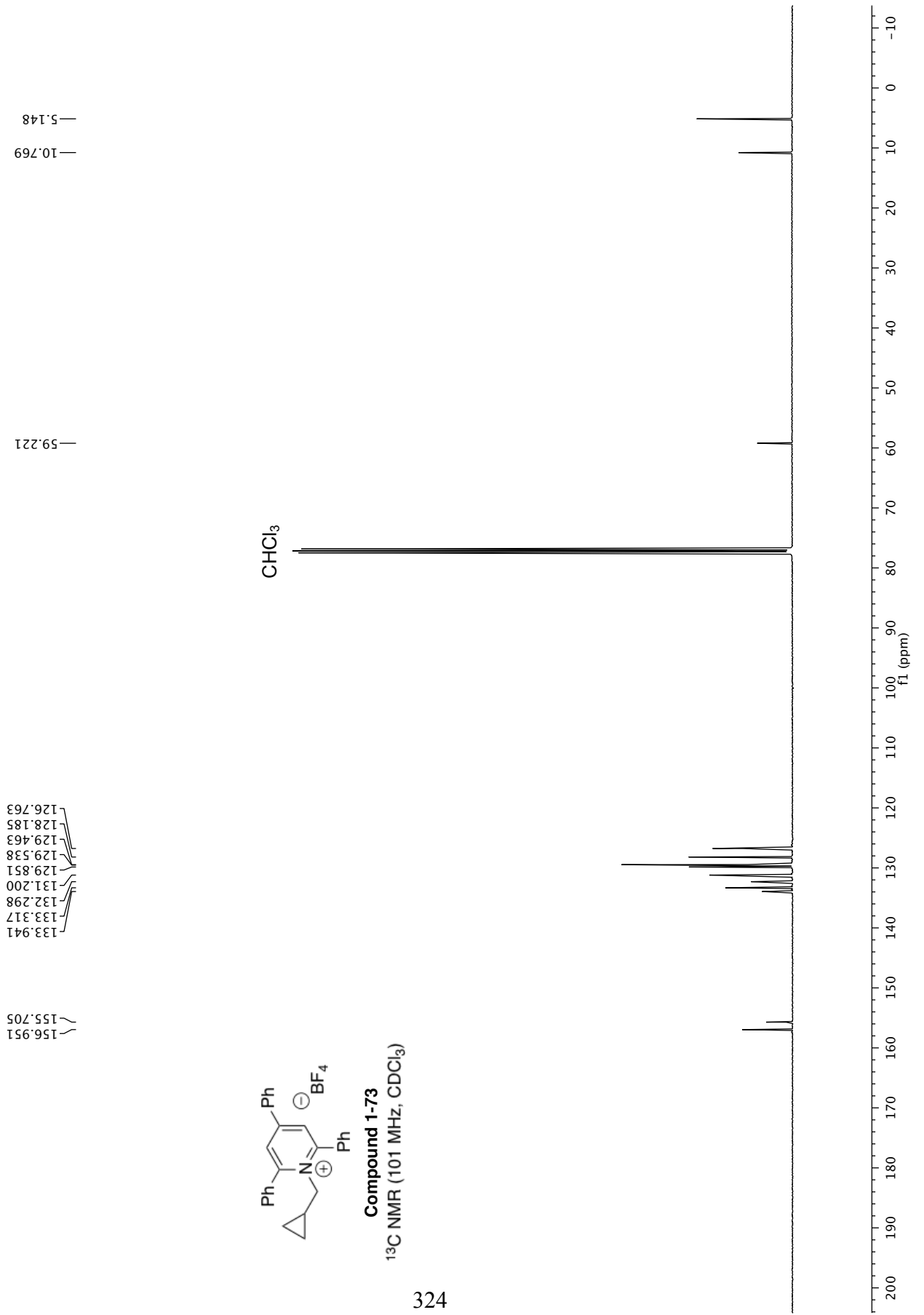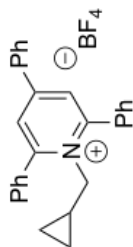
−153.286
−153.232

**Compound 1-73**

$^{19}$F NMR (376 MHz, CDCl$_3$)

325

−40 −45 −50 −55 −60 −65 −70 −75 −80 −85 −90 −95 −100 −105 −110 −115 −120 −125 −130 −135 −140 −145 −150 −155 −160 −165 −170 −175 −180
f1 (ppm)

**Compound 1-54**, racemic (254 nm)
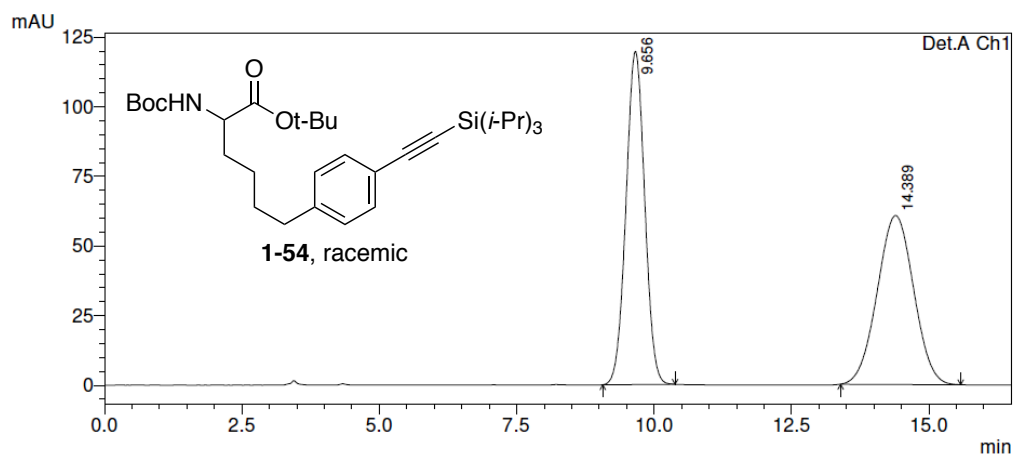


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 9.656 | 2833525 | 119647 | 50.307 | 66.357 |
| 2 | 14.389 | 2798895 | 60660 | 49.693 | 33.643 |
| Total | | 5632419 | 180307 | 100.000 | 100.000 |

**Compound 1-54**, 29% ee (254 nm)
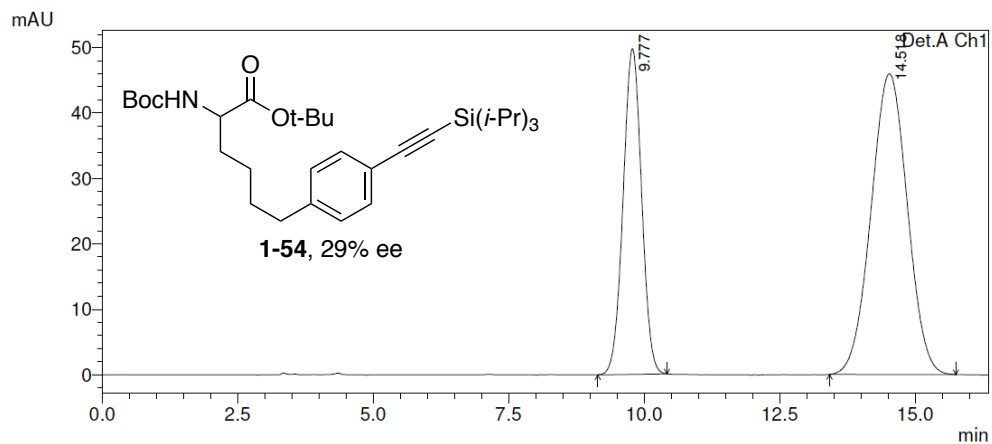


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 9.777 | 1180374 | 49751 | 35.522 | 51.983 |
| 2 | 14.518 | 2142537 | 45955 | 64.478 | 48.017 |
| Total | | 3322911 | 95706 | 100.000 | 100.000 |

**Compound 1-54**, 81% ee (254 nm), reaction with 4-(trifluoromethyl)phenol additive
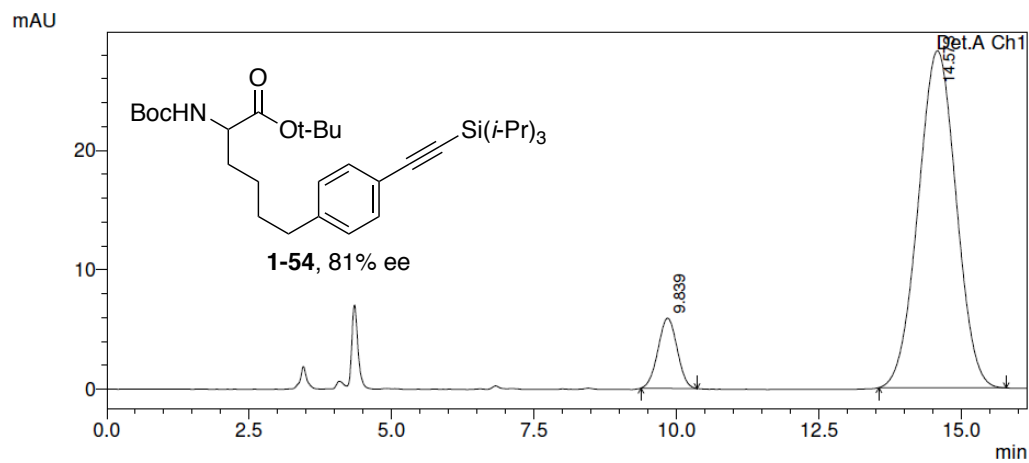


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 9.839 | 137403 | 5876 | 9.510 | 17.224 |
| 2 | 14.573 | 1307395 | 28238 | 90.490 | 82.776 |
| Total | | 1444798 | 34114 | 100.000 | 100.000 |

**Compound 1-72**, racemic (254 nm)
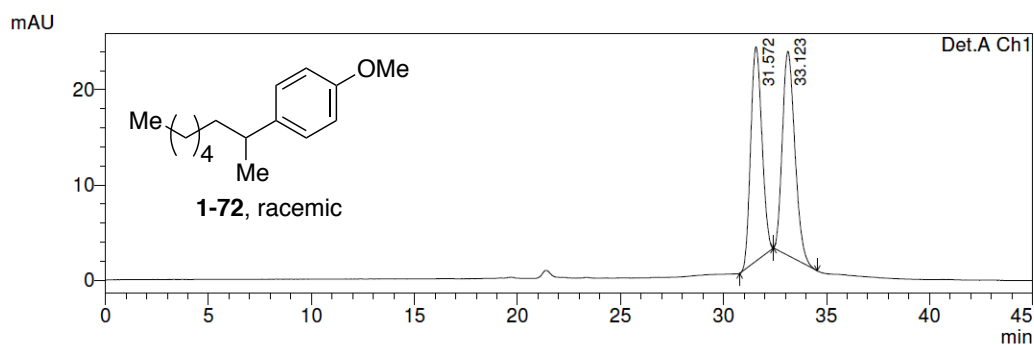


Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 31.572 | 850548 | 22514 | 48.386 | 51.255 |
| 2 | 33.123 | 907290 | 21411 | 51.614 | 48.745 |
| Total | | 1757837 | 43925 | 100.000 | 100.000 |

**Compound 1-72**, 0% ee (254 nm), from cross-coupling reaction
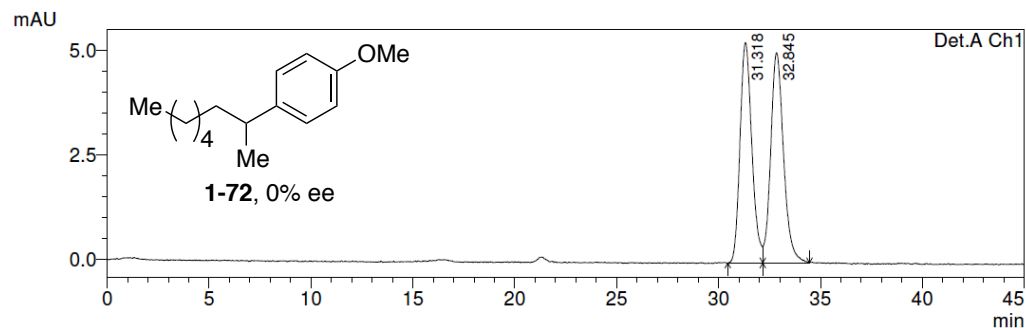


Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 31.318 | 212990 | 5277 | 49.079 | 51.202 |
| 2 | 32.845 | 220984 | 5029 | 50.921 | 48.798 |
| Total | | 433974 | 10306 | 100.000 | 100.000 |

**Appendix B**

**SPECTRAL AND CHROMATOGRAPHY DATA FOR CHAPTER 2**
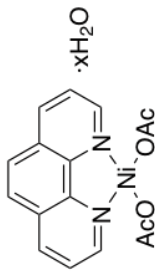
PhenNi(OAc)₂·xH₂O (2-66)
¹H NMR (400 MHz, DMSO-d₆)

DMSO

— 18.03
— 22.88

43.87
44.73
46.29

3.16
3.02

8.00

f1 (ppm)

330

Compound 2-65
$^1$H NMR (600 MHz, CDCl$_3$)

331
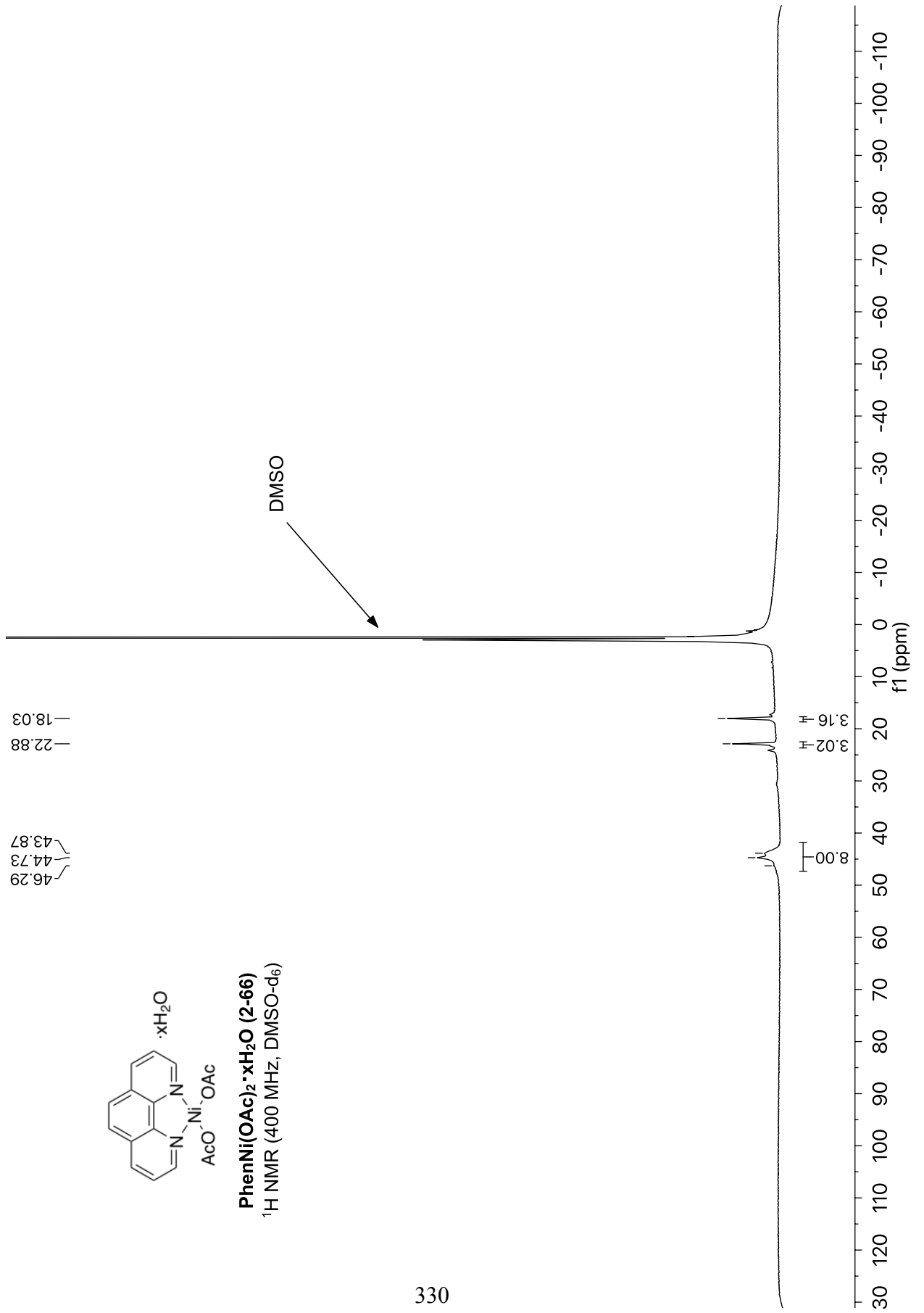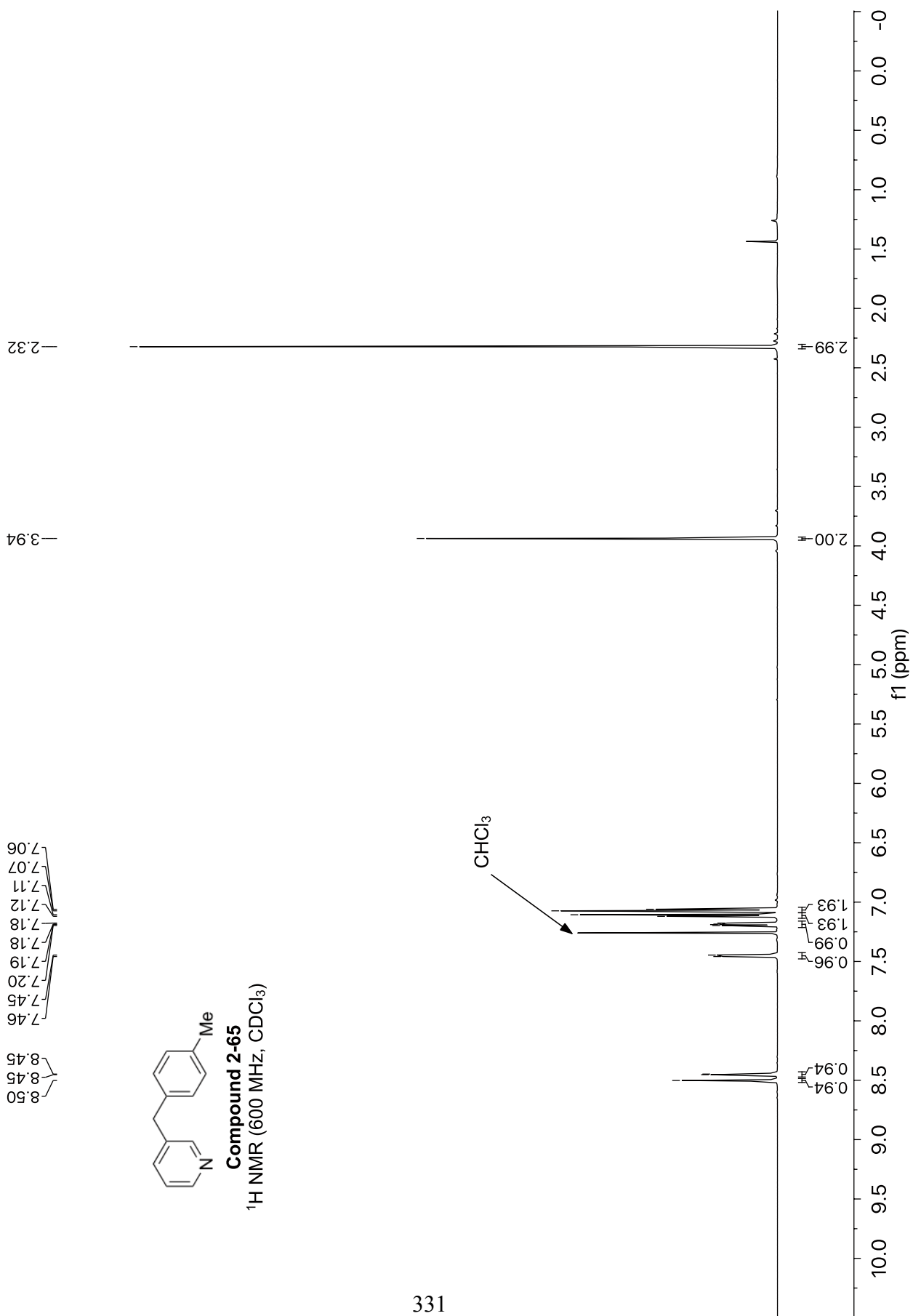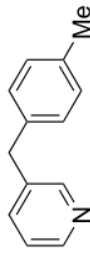
Compound 2-65
$^{13}$C NMR (151 MHz, CDCl$_3$)

21.00

38.65

CDCl$_3$

123.38
128.73
129.36
136.04
136.21
136.73
136.77
147.62
150.19

f1 (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

332

**Compound 2-69**
¹H NMR (600 MHz, CDCl₃)

7.12
7.13
7.13
7.14
7.22
7.23
7.24
7.25
7.29
7.29
7.30
7.30
7.45
7.45
7.46
7.46
7.47
7.47
8.49
8.50
8.50
8.51
8.51
8.52

3.97

CHCl₃

333
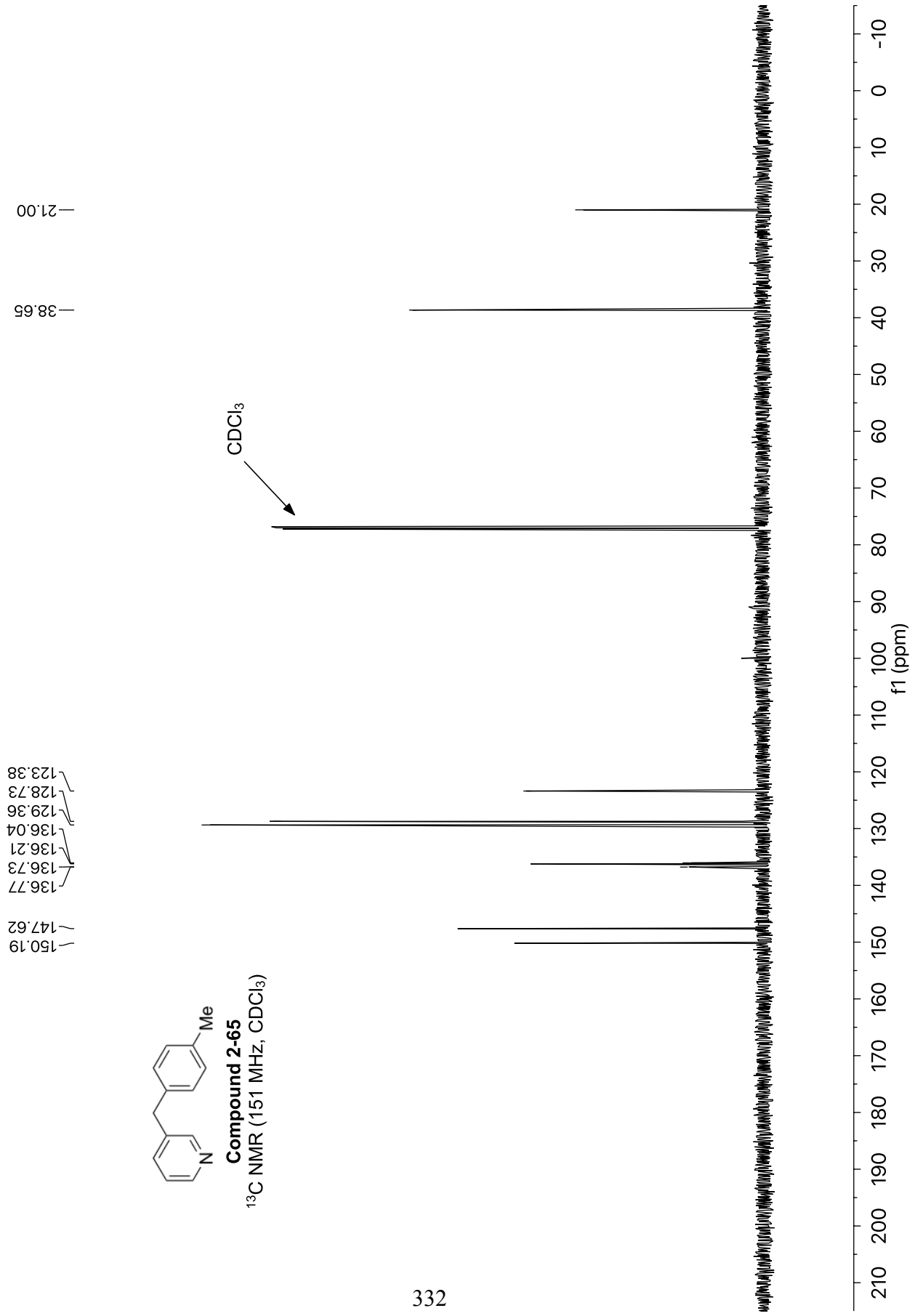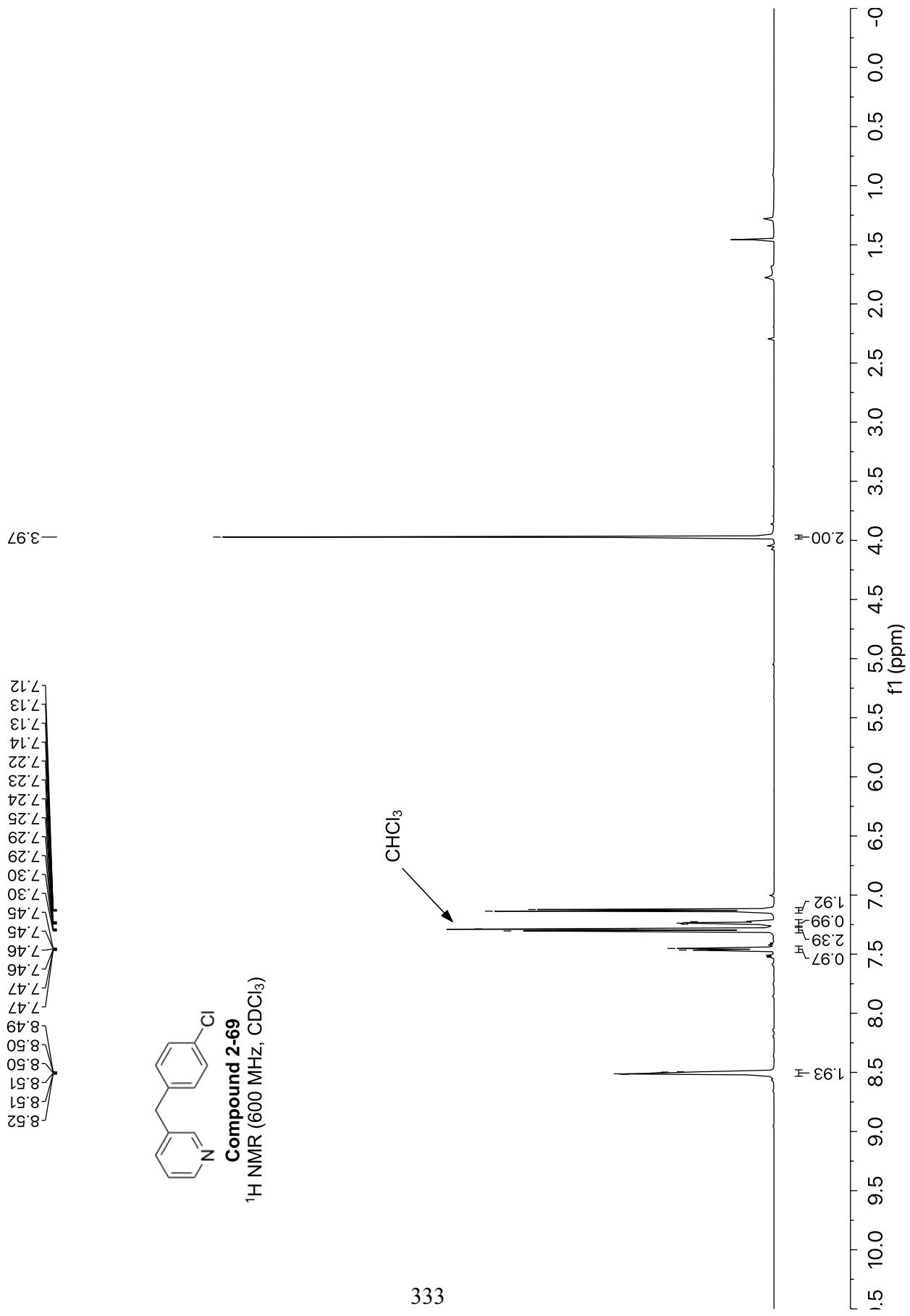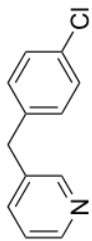
**Compound 2-69**
$^{13}$C NMR (151 MHz, CDCl$_3$)

38.38

123.47
128.82
130.17
132.41
135.91
136.17
138.25

147.93
150.15

CDCl$_3$

f1 (ppm)

334
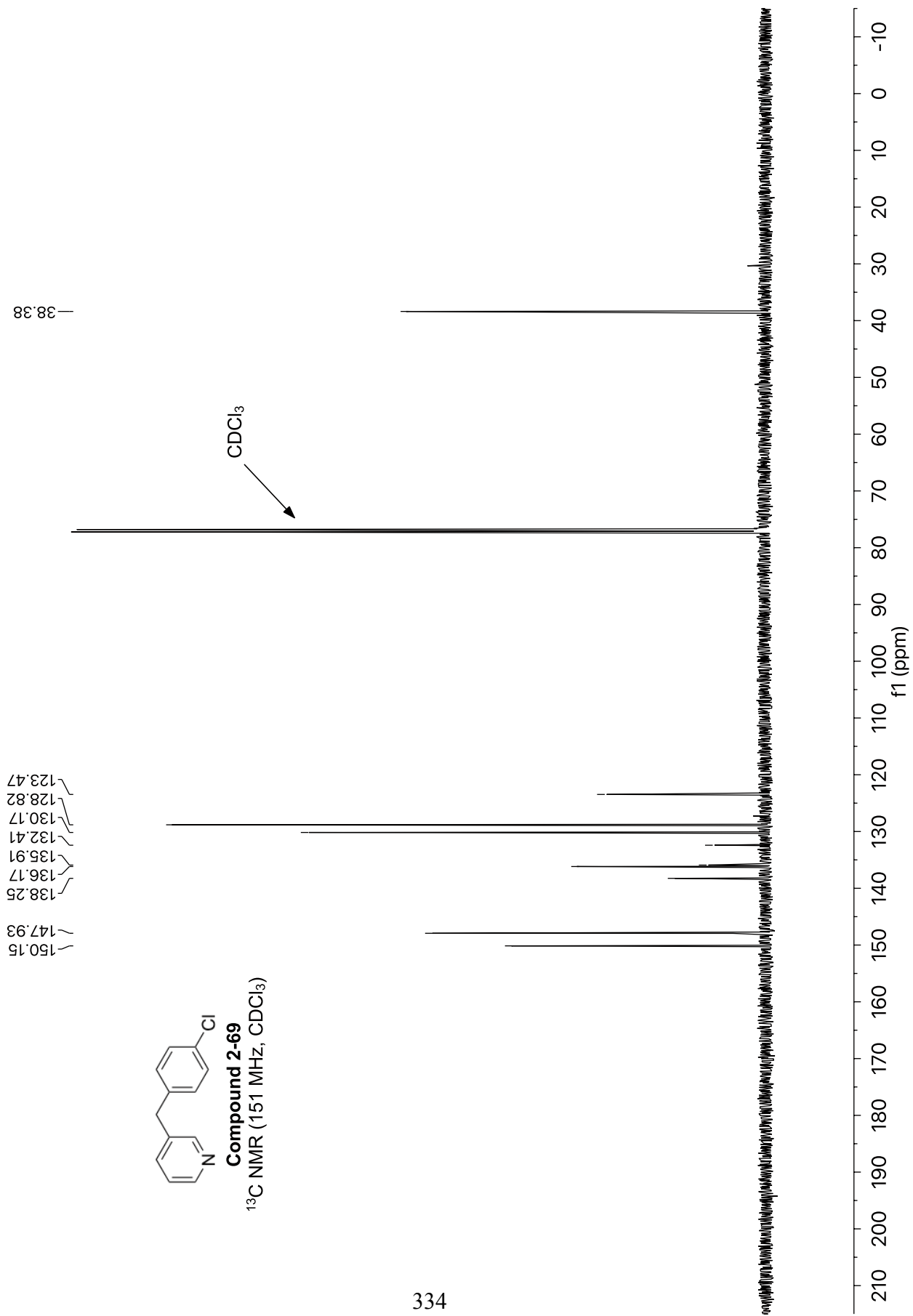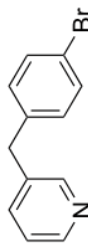
Compound 2-70
¹H NMR (600 MHz, CDCl₃)

335

—38.45

—120.43
—123.47
130.55
131.78
135.81
136.17
138.77
147.93
150.14
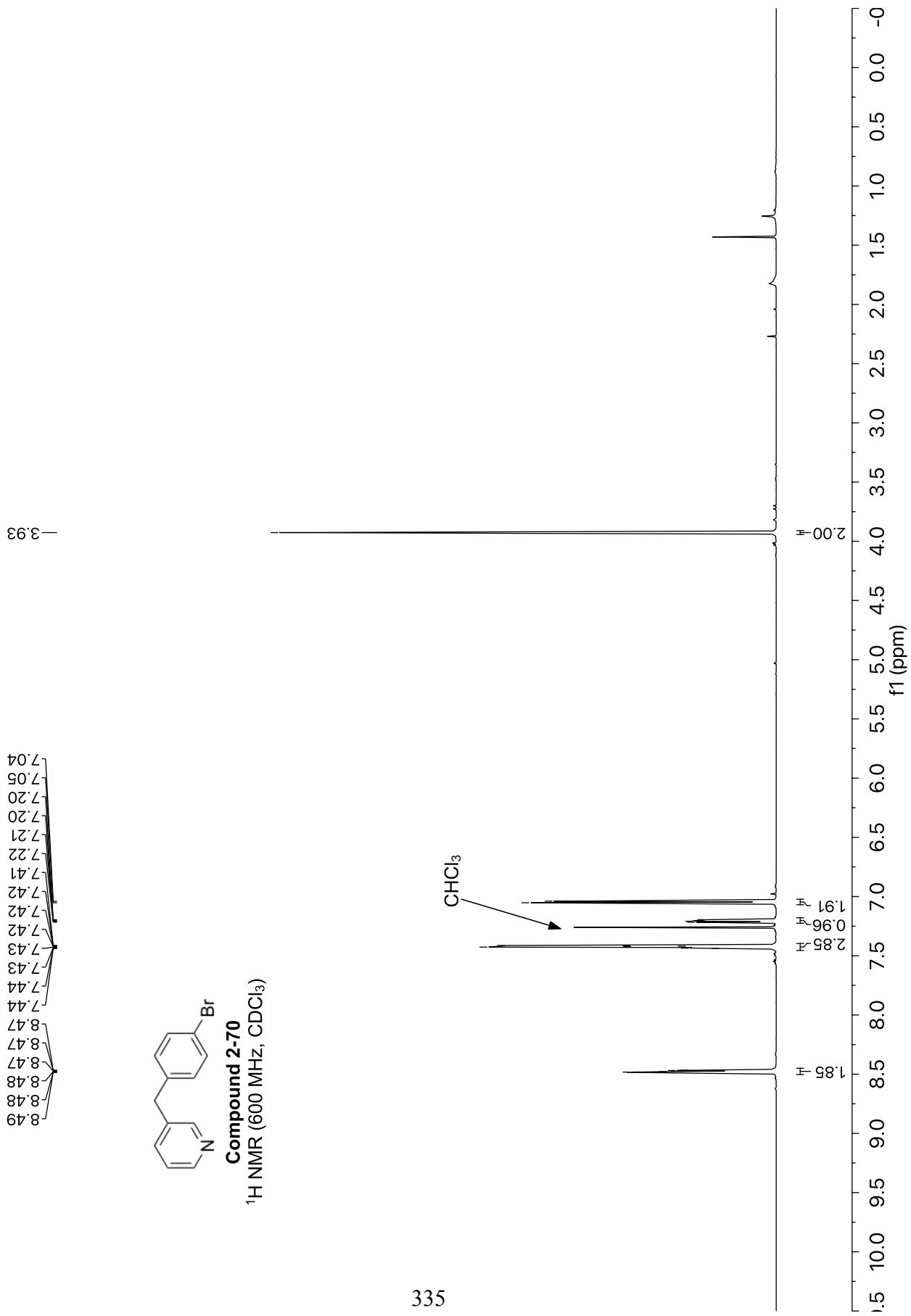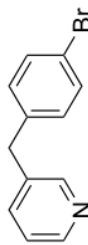
CDCl₃

**Compound 2-70**
¹³C NMR (151 MHz, CDCl₃)

f1 (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

336

3.77
3.79
3.87

6.41
6.41
6.43
6.43
6.45
6.46
6.99
7.01
7.14
7.14
7.15
7.15
7.16
7.16
7.17
7.17
7.45
7.45
7.45
7.46
7.47
7.47
7.47
7.48
8.40
8.40
8.41
8.42
8.49
8.49
8.50
8.50

**Compound 2-71**
¹H NMR (400 MHz, CDCl₃)

CHCl₃

3.14
2.92
2.00

1.99

1.00
0.99
0.99

0.96
0.97

f1 (ppm)

32.83

55.31
55.37

CDCl₃

98.68

104.08

120.88
123.16

130.48
136.05
136.86

147.19
150.29

158.18
159.80
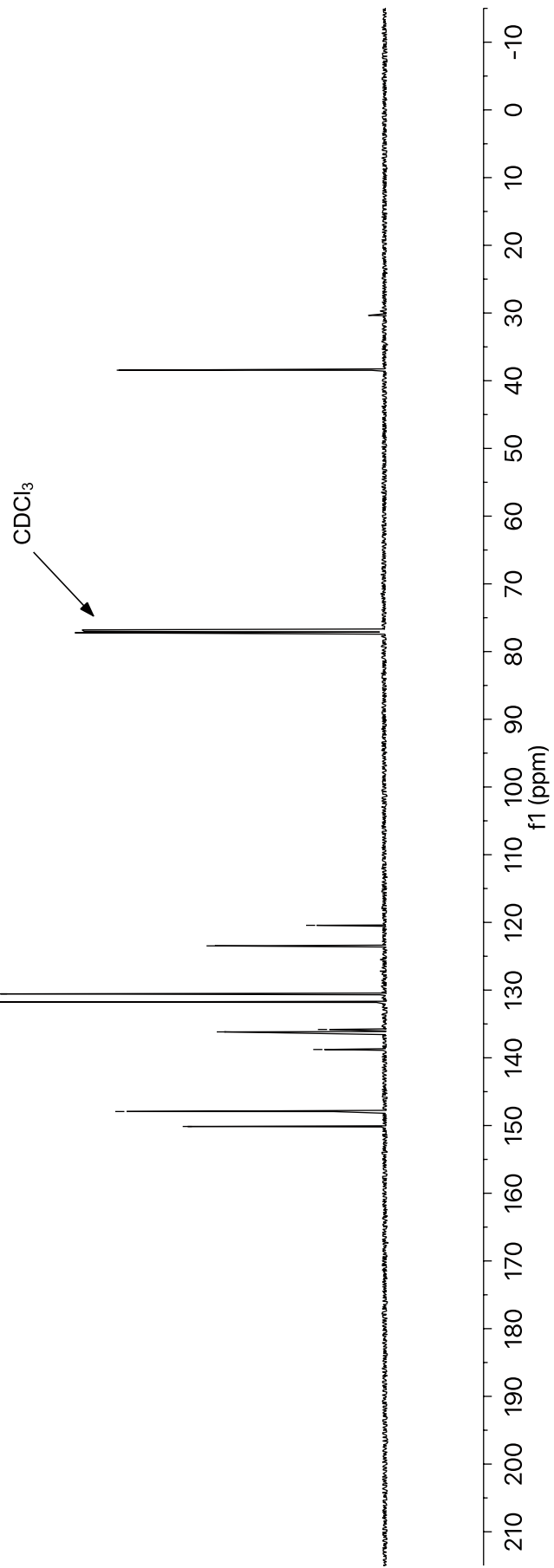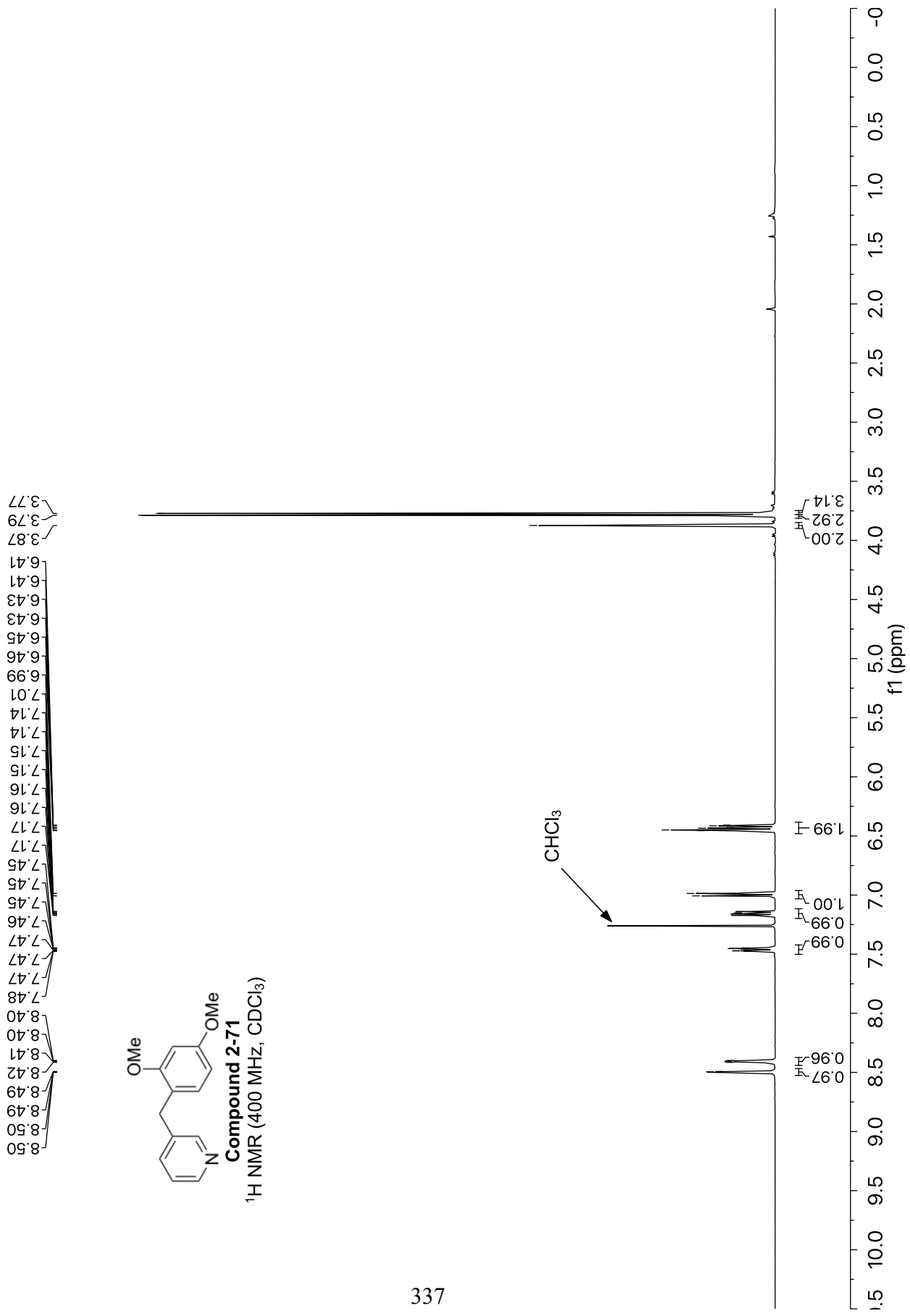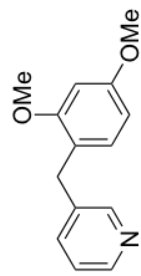
**Compound 2-71**
¹³C NMR (151 MHz, CDCl₃)

Compound 2-72
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

339

Compound 2-72
$^{13}$C NMR (151 MHz, CDCl$_3$)

168.77

150.19
148.03
144.16
136.26
135.57
131.63
129.12
127.82
123.53

CDCl$_3$

38.91

f1 (ppm)

340

**Compound 2-73**
¹H NMR (600 MHz, CDCl₃)

CHCl₃
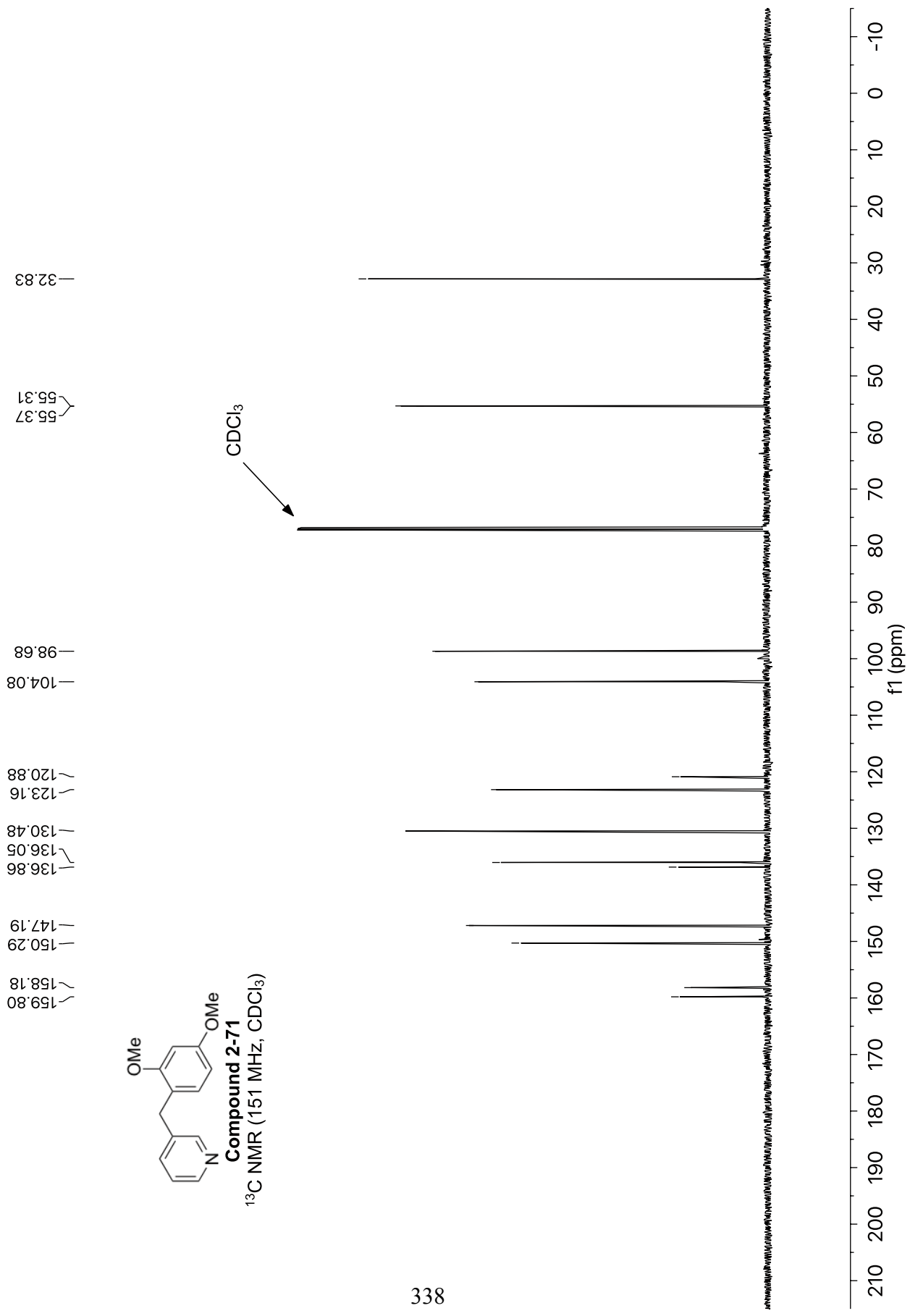
Compound 2-73
13C NMR (151 MHz, CDCl3)

39.17

CDCl3

102.46

111.20
120.64
123.26
123.34
124.60
128.21
131.25
134.61
136.31
137.59
147.42
150.19

342

**Compound 2-74**
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

7.16
7.16
7.16
7.17
7.17
7.18
7.45
7.47
7.48
7.61
7.61
7.62
7.62
7.63
7.63
7.64
7.64
7.65
8.07
8.08
8.08
8.09
8.09
8.13
8.13
8.13
8.56
8.57
8.57
8.58

4.25

343

44.11

CDCl₃

121.59
121.81
123.21
123.92
129.39
135.32
136.85
141.54
148.44
149.80

159.18
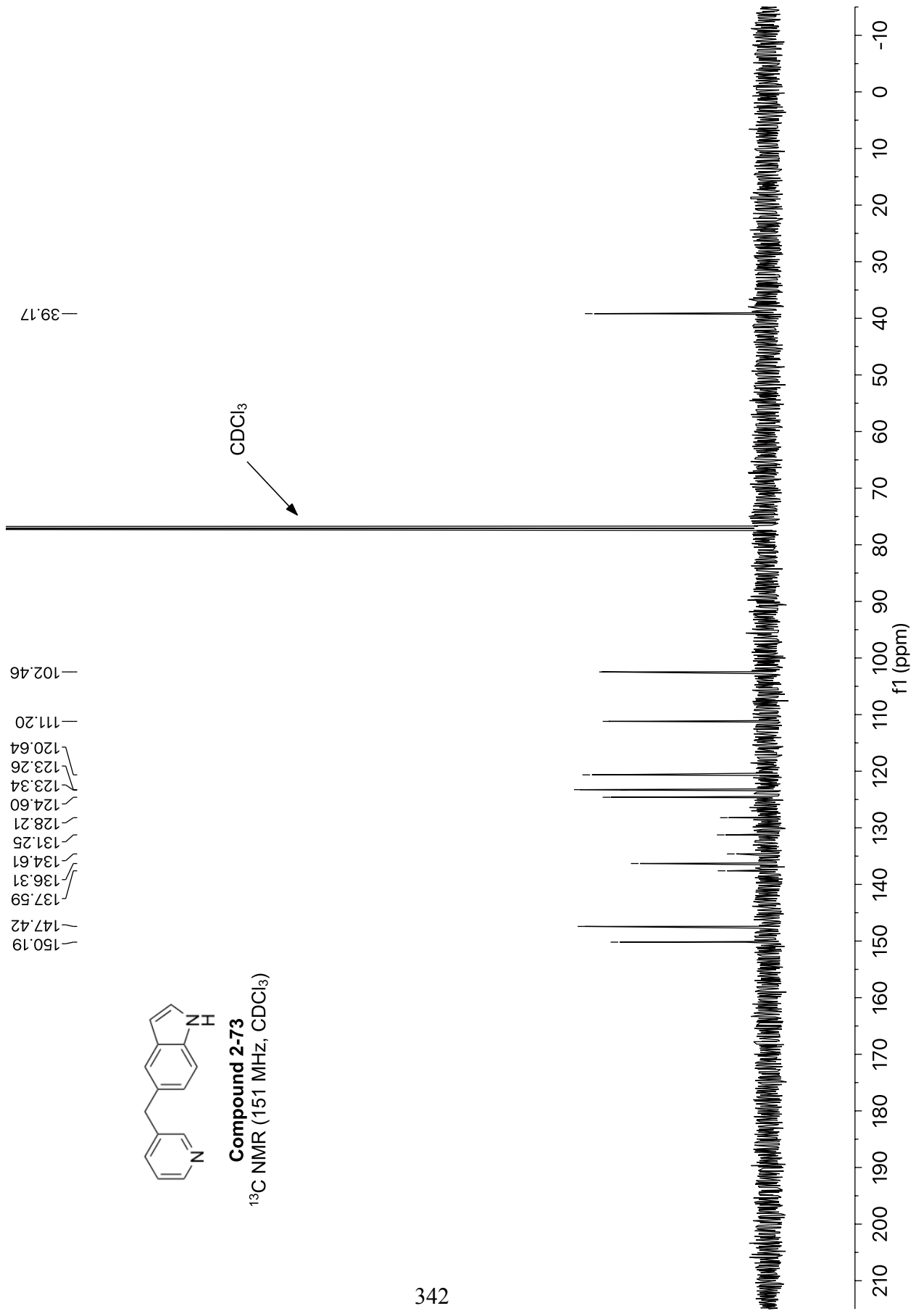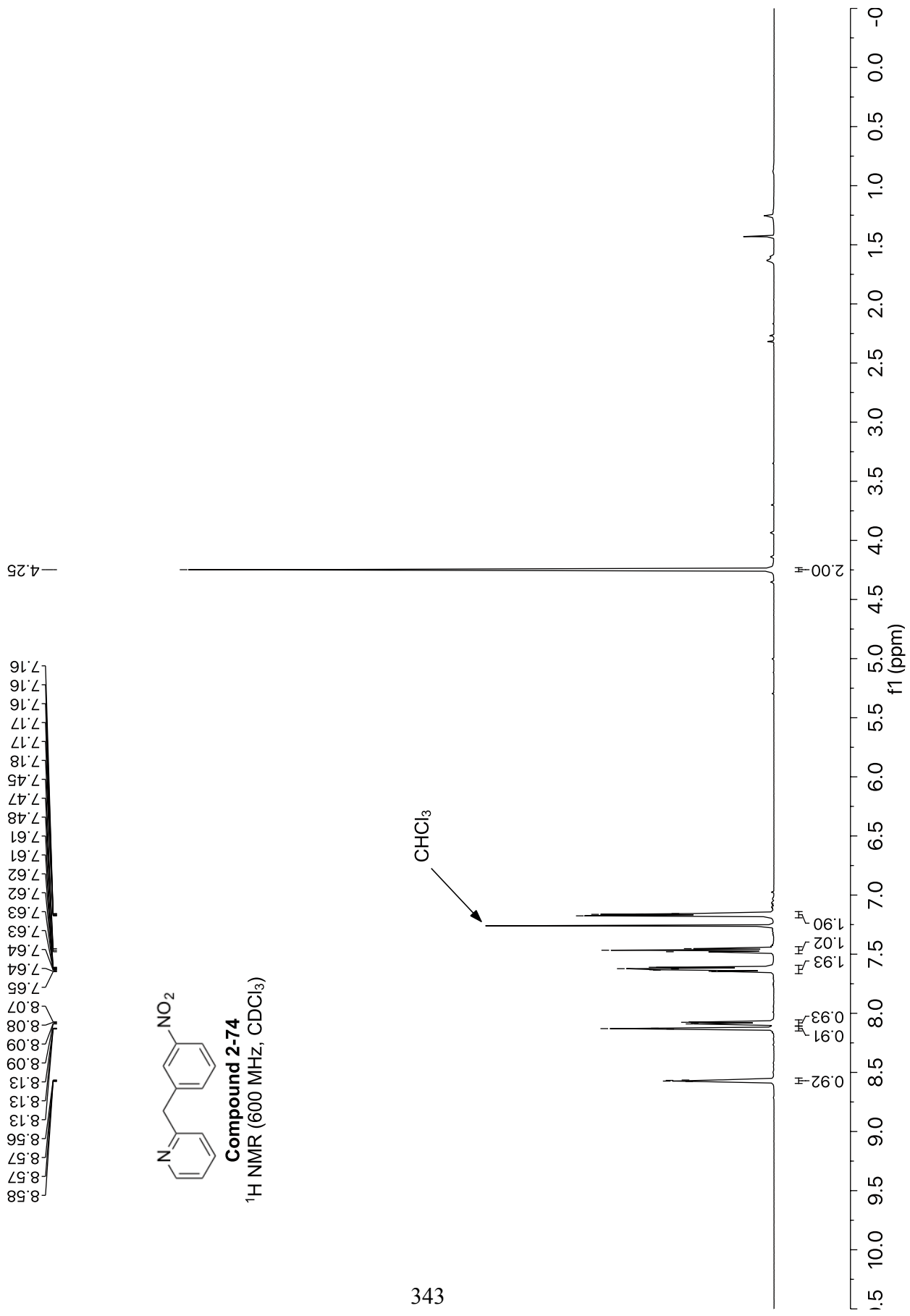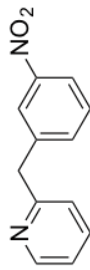
**Compound 2-74**
¹³C NMR (151 MHz, CDCl₃)

344
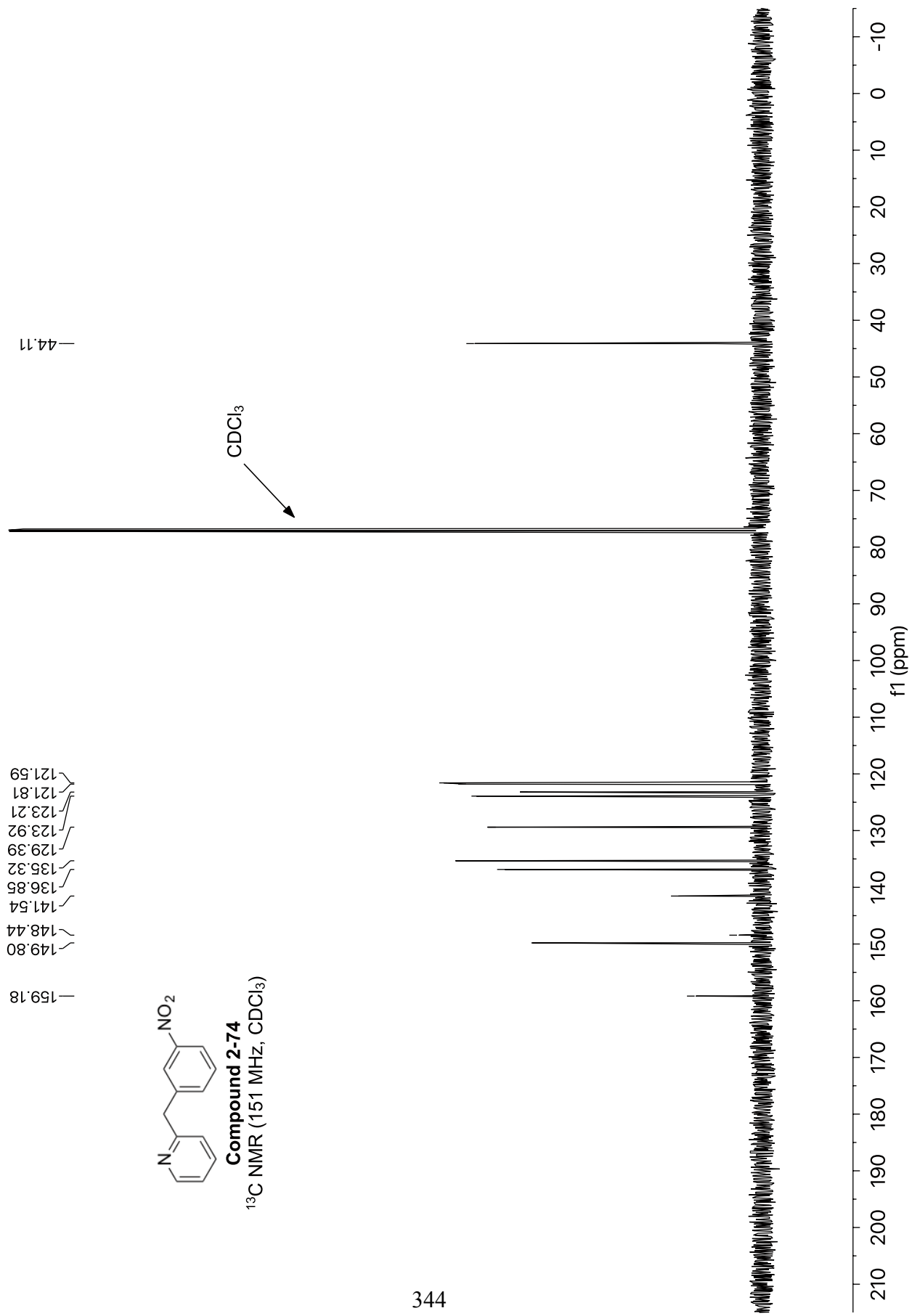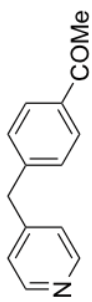
Compound 2-75
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

7.09
7.10
7.26
7.28
7.91
7.92
8.51
8.52

2.59

4.02

2.97

2.00

1.90
2.03

1.96

1.93

345

Compound 2-75
¹³C NMR (151 MHz, CDCl₃)

197.55

150.05
148.84
144.36

135.79
129.24
128.84
124.15

CDCl₃

41.15

26.57

**Compound 2-76**
$^1$H NMR (400 MHz, CDCl$_3$)

4.20

7.39
7.40
7.41
7.42
7.43
7.46
7.46
7.47
7.48
7.48
7.48
7.50
7.51
7.52
7.52
7.53
7.54
7.54
7.55
7.58
7.59
8.05
8.07
8.09
8.10
8.11
8.12
8.12
8.88
8.90
8.90
8.91

CHCl$_3$
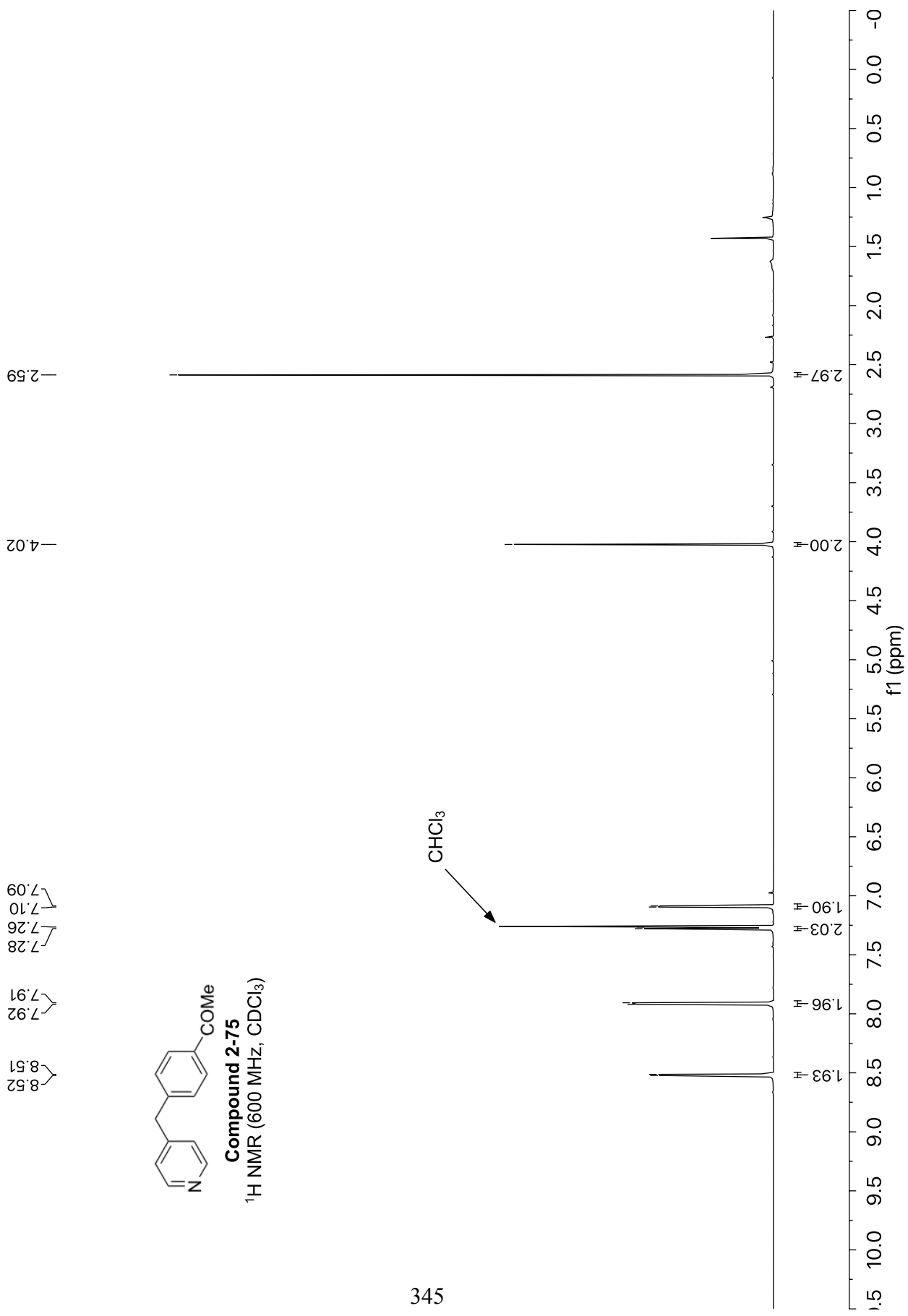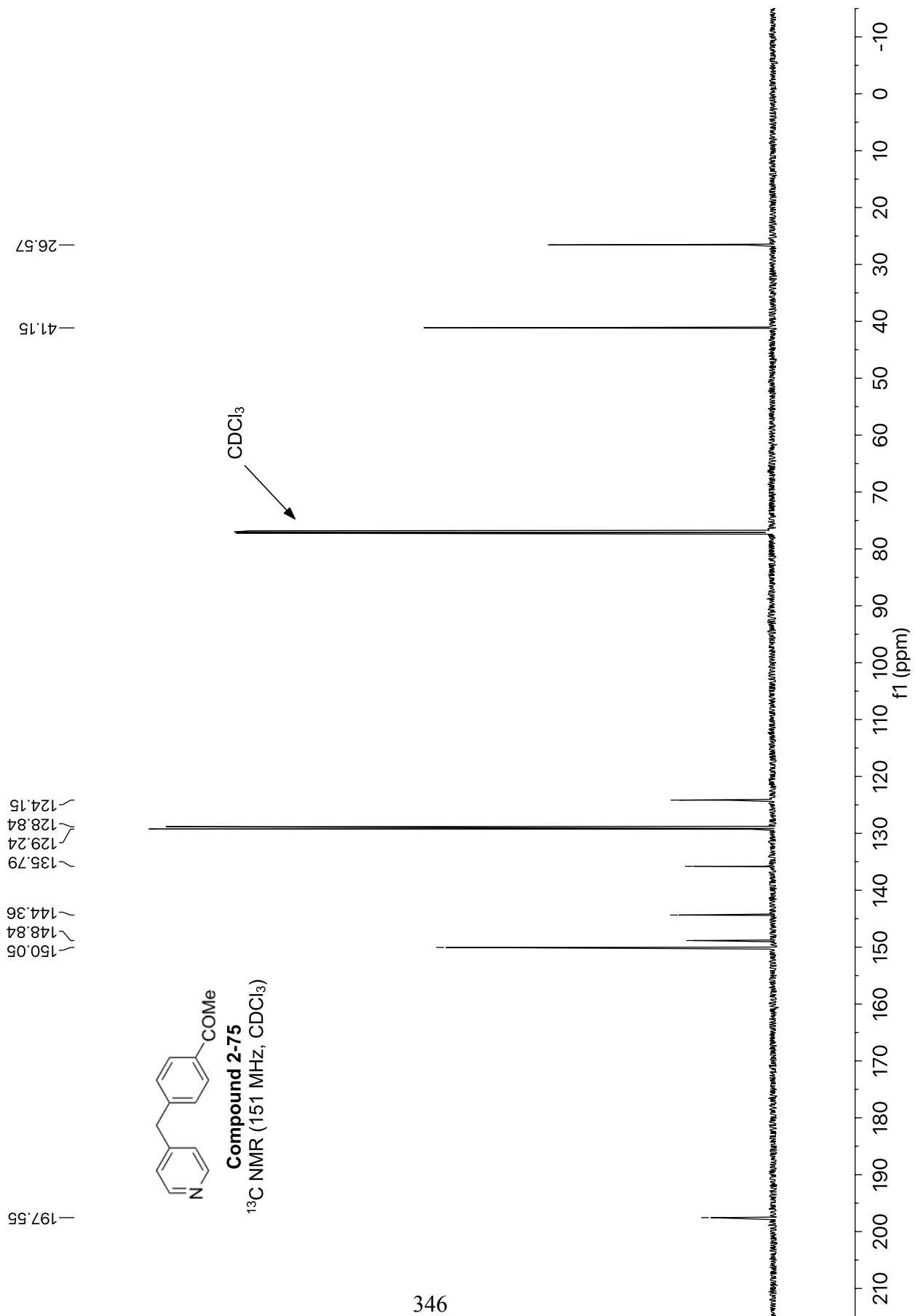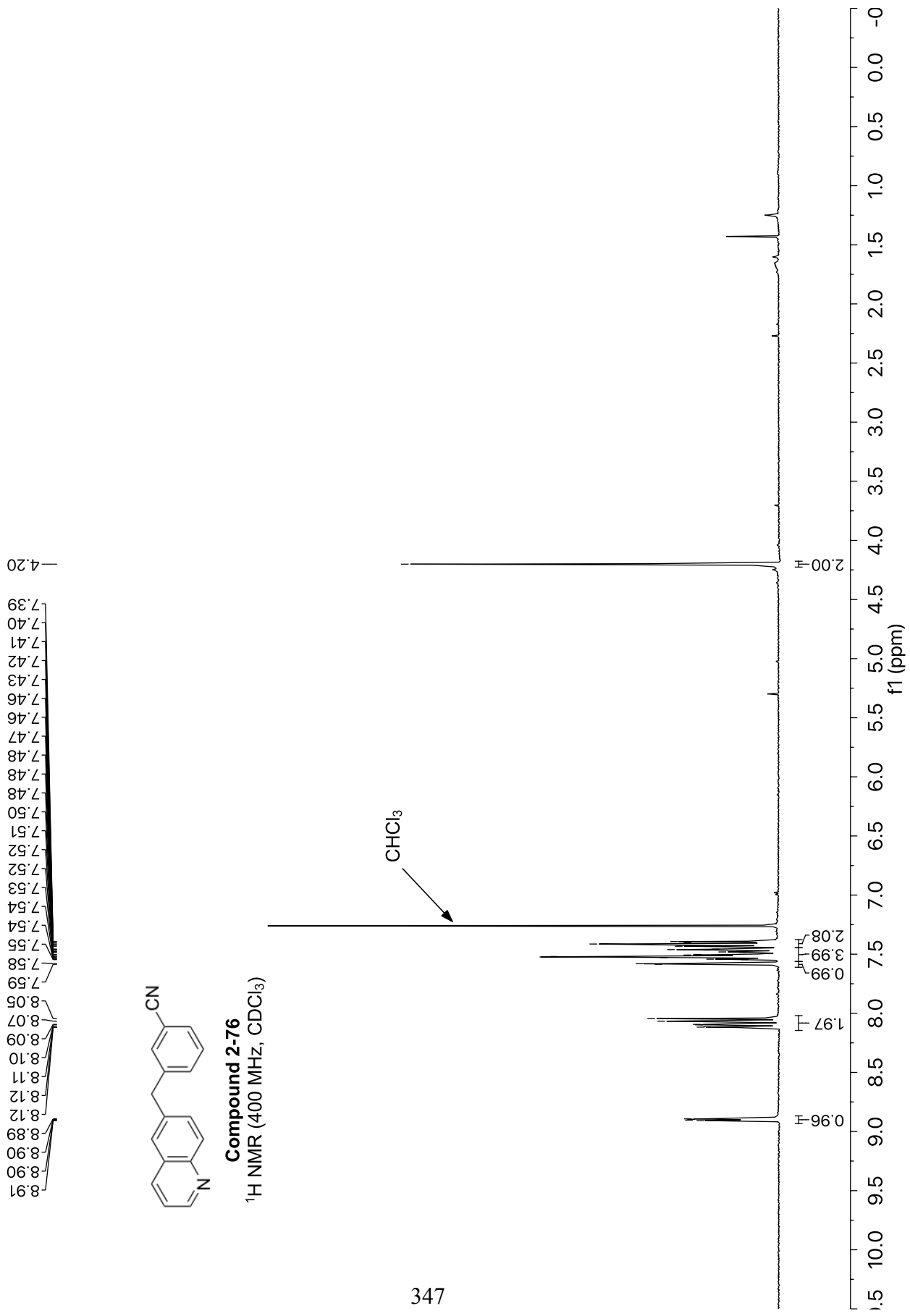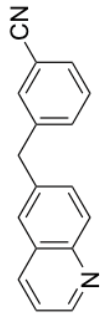
Compound 2-76
13C NMR (101 MHz, CDCl₃)

41.35

CDCl₃

112.70
118.82
121.48
127.10
128.35
129.44
130.06
130.25
130.84
132.48
133.51
135.73
137.82
141.93
147.32
150.34

348
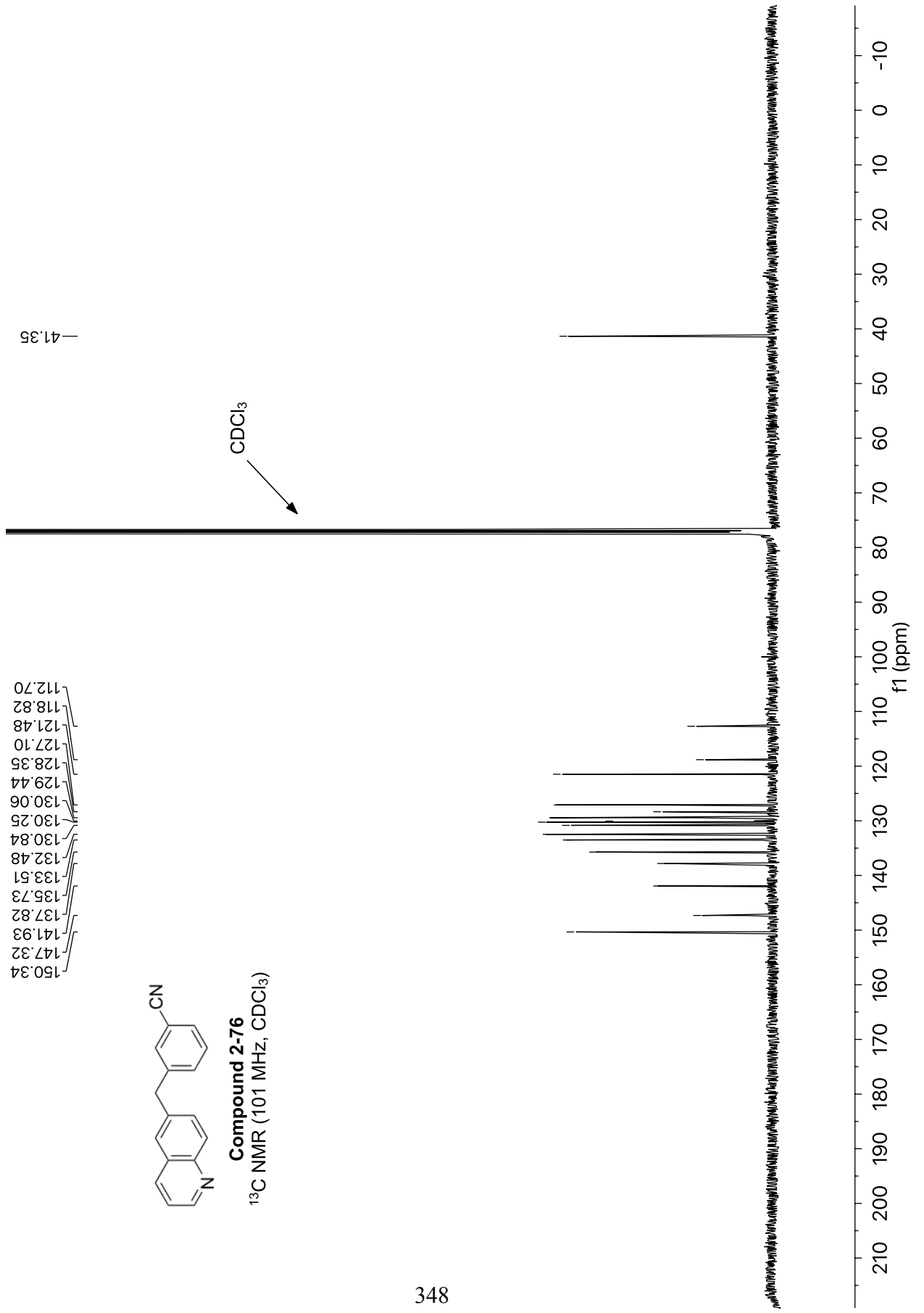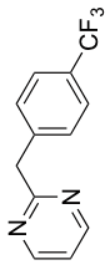
Compound 2-77
$^1$H NMR (600 MHz, CDCl$_3$)

349

45.78

CDCl₃

118.96
120.18
122.88
125.42
125.46
125.49
125.53
125.58
128.29
128.42
128.75
129.07
129.39
129.52
142.13
142.14
142.16
142.17

157.45

169.17
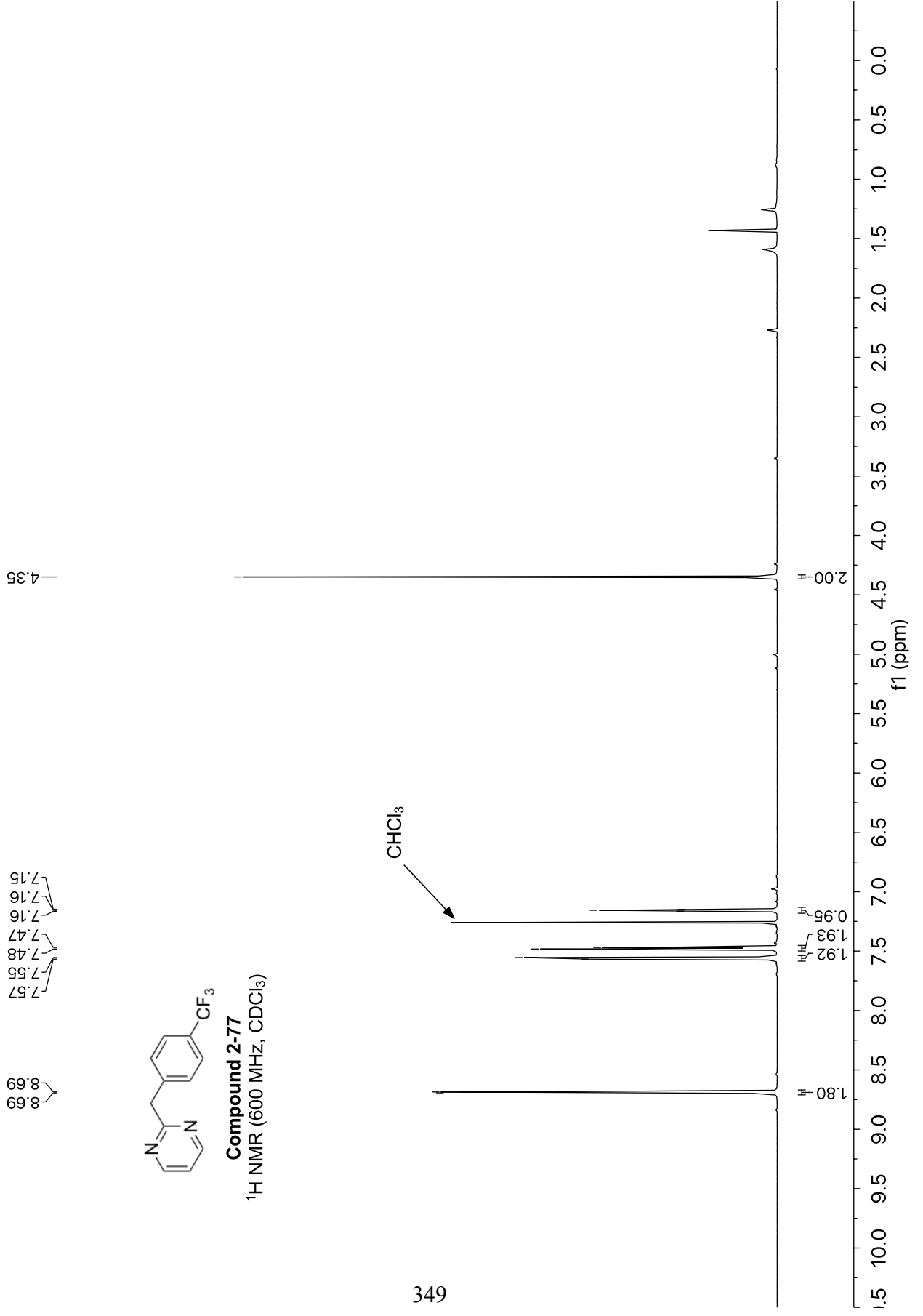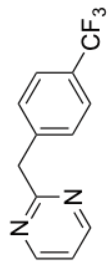
**Compound 2-77**
¹³C NMR (101 MHz, CDCl₃)

CF₃

350
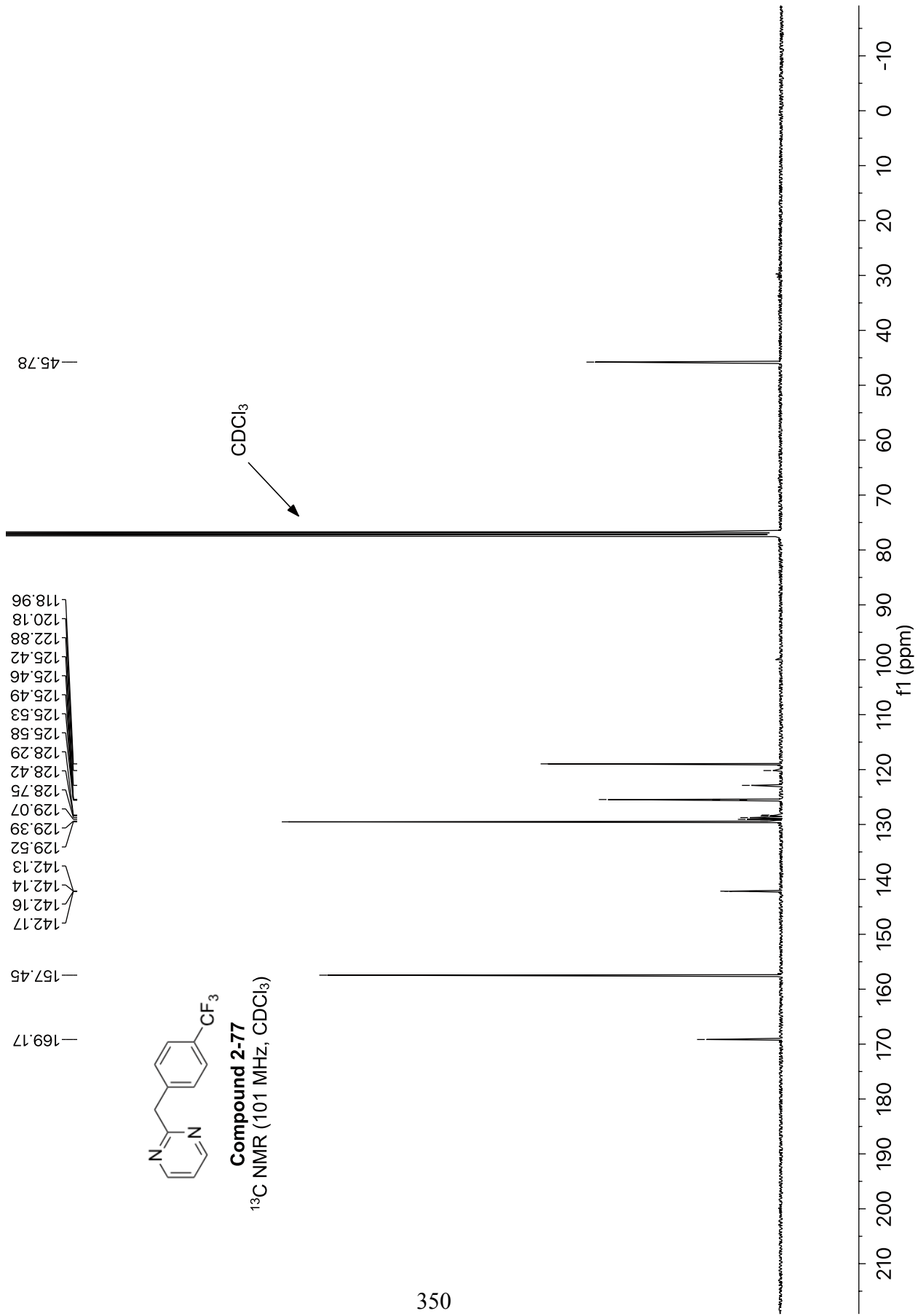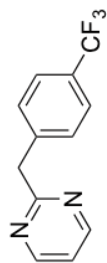
−62.49

**Compound 2-77**
19F NMR (565 MHz, CDCl3)

351

f1 (ppm)

10  0  -10  -20  -30  -40  -50  -60  -70  -80  -90  -100  -110  -120  -130  -140  -150  -160  -170  -180  -190  -200  -210
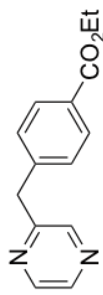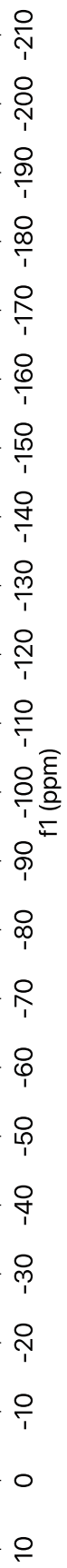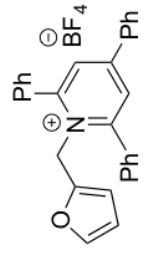
Compound 2-78
$^1$H NMR (600 MHz, CDCl$_3$)

1.36
1.37
1.39

4.22
4.34
4.35
4.36
4.38

7.33
7.34

7.99
8.00
8.43
8.43
8.48
8.51

CHCl$_3$

3.06

2.00
2.05

1.99

1.96

0.95
0.96
0.92

f1 (ppm)

14.33

41.87

60.92

CDCl$_3$

129.02
129.17
130.04

142.71
143.22
144.25
144.73

155.65

166.34

**Compound 2-78**
$^{13}$C NMR (151 MHz, CDCl$_3$)

353

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 2-79
1H NMR (600 MHz, CDCl3)

1.68
1.69

2.31

4.24
4.25
4.27
4.28
7.07
7.07
7.07
7.08
7.08
7.08
7.09
7.09
7.10
7.10
7.10
7.11
7.11
7.12
7.12
7.18
7.19
7.20
7.53
7.54
7.55
7.55
7.56
7.56
8.55
8.55
8.55
8.55
8.56
8.56
8.56
8.56

CHCl3

2.99
2.94
1.00
1.00
2.83
1.93
1.03
0.90
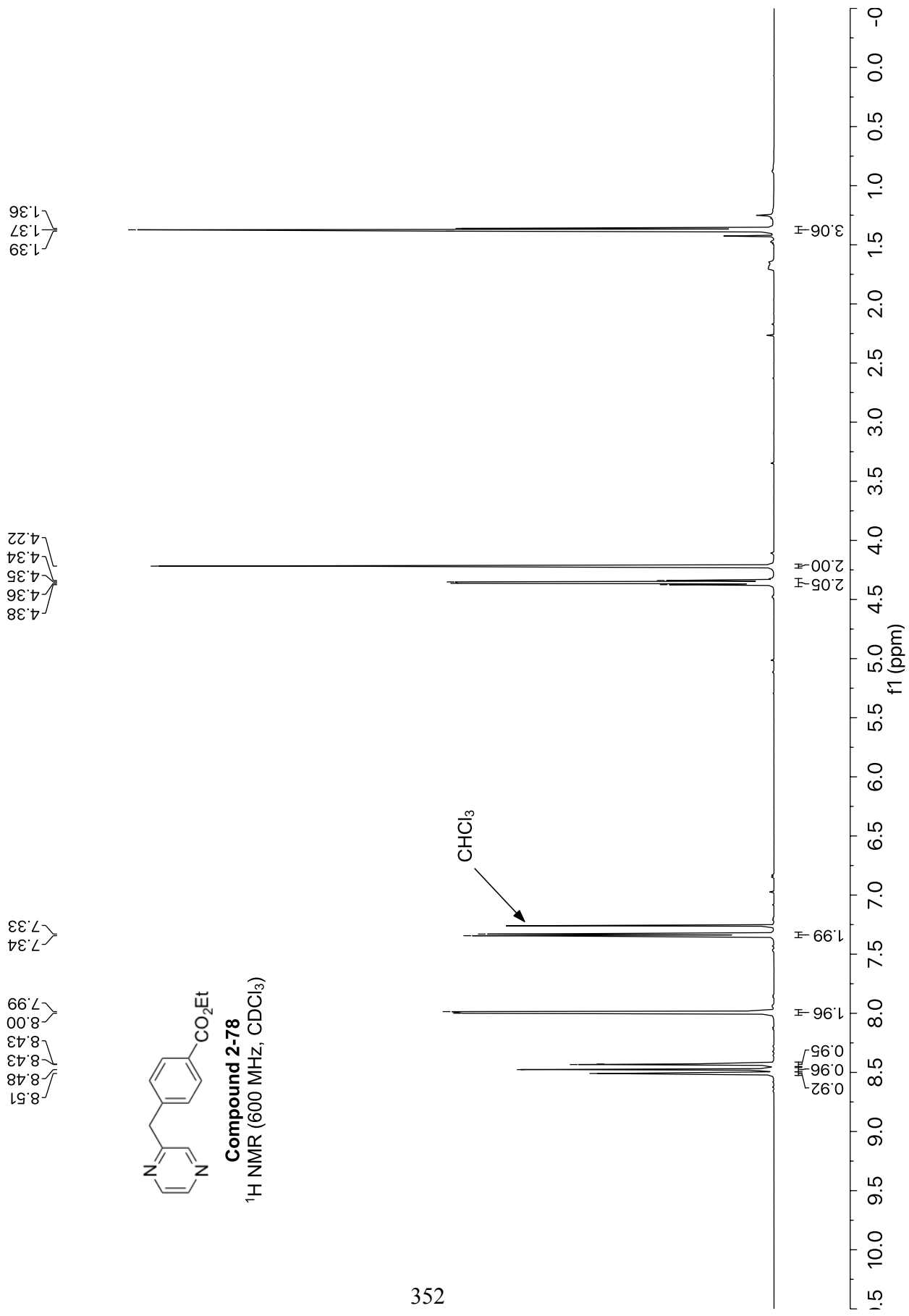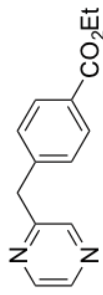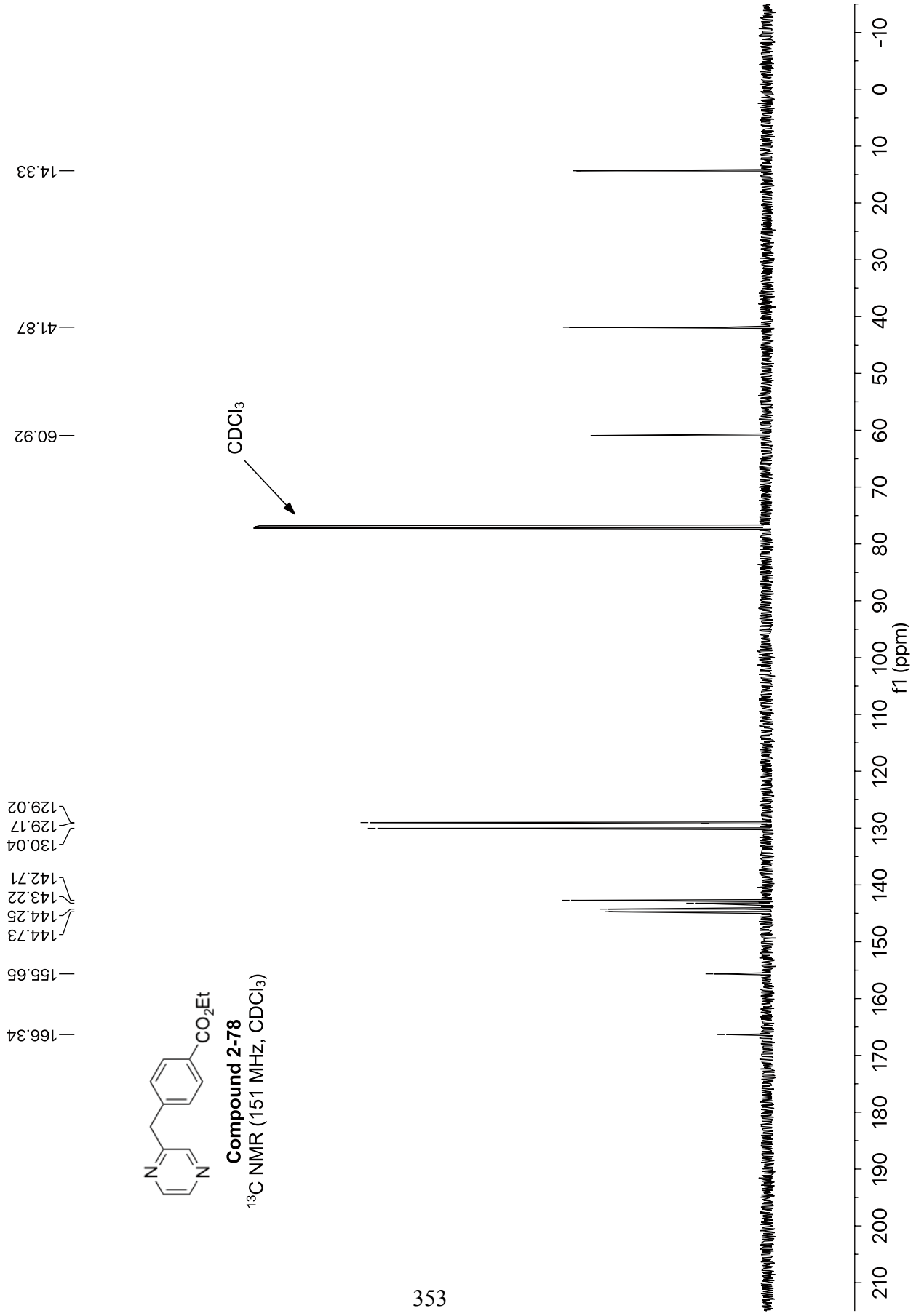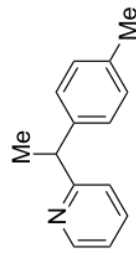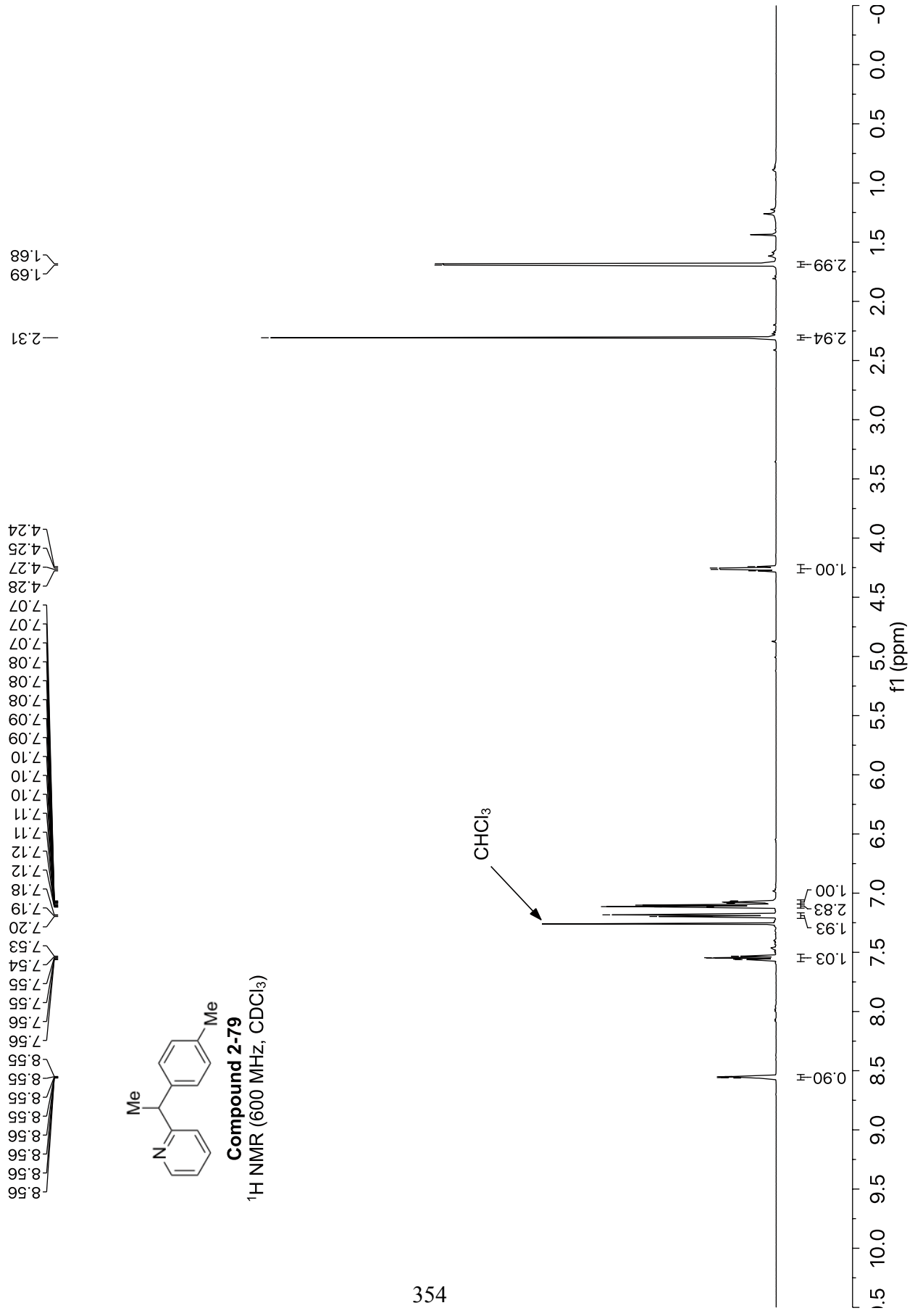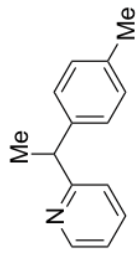
Compound 2-79
$^{13}C$ NMR (151 MHz, $CDCl_3$)

20.79
20.99
47.02
121.09
122.03
127.55
129.15
135.80
136.33
142.15
149.12
165.31

$CDCl_3$

f1 (ppm)

355

**Compound 2-80**
¹H NMR (600 MHz, CDCl₃)

CHCl₃

4.19
6.46
6.47
6.47
6.47
7.21
7.21
7.22
7.22
7.23
7.23
7.23
7.24
7.25
7.25
7.26
7.26
7.27
7.27
7.29
7.29
7.29
7.37
7.37
7.37
7.38
7.38
7.39
7.43
7.43
7.44
7.44
7.45
7.45
7.51
7.51
7.51
7.52
7.52
7.53
7.53
7.53
7.53
7.86
7.86
7.86

2.00
0.91
2.82
1.16
1.99
2.94
1.01
0.95
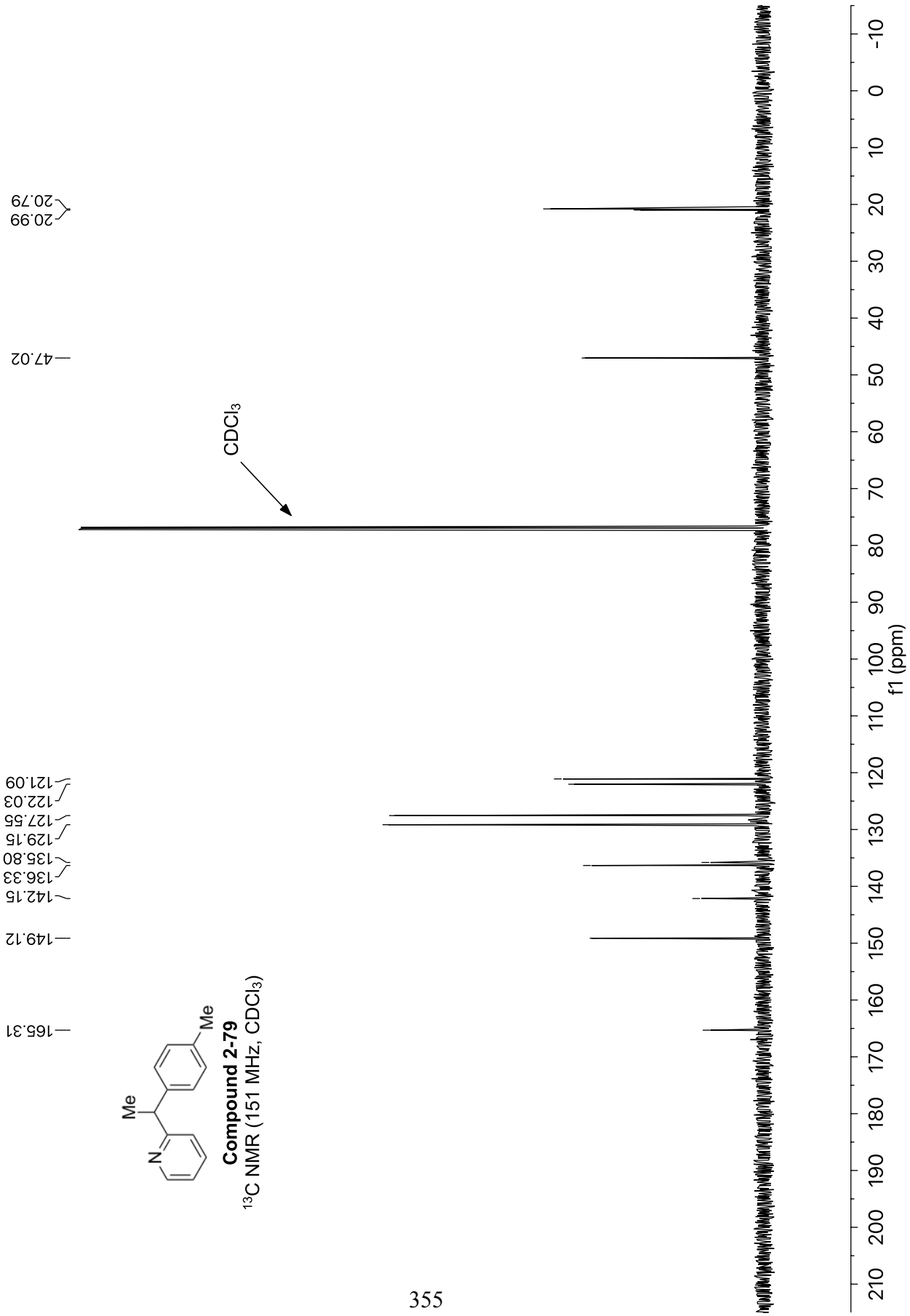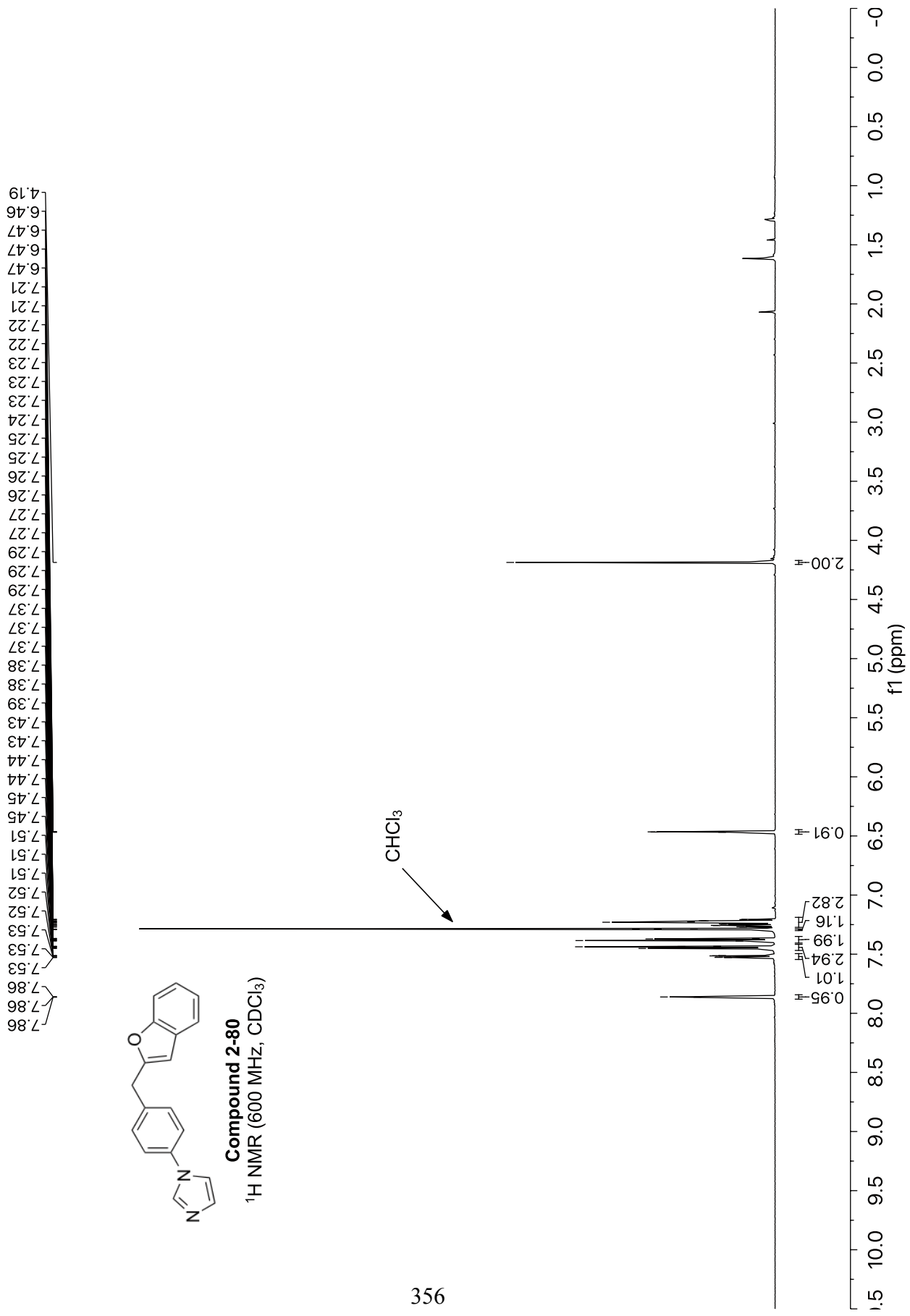
**Compound 2-80**
$^{13}$C NMR (151 MHz, CDCl$_3$)

34.45

CDCl$_3$

103.68
110.95
118.27
120.52
121.75
122.69
123.69
128.63
130.32
130.47
135.63
136.17
136.82

155.03
156.80

f1 (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

357

**Compound 2-81**
¹H NMR (600 MHz, CDCl₃)

6.46
6.46
6.47
7.11
7.12
7.25
7.26
7.27
7.64
7.66
7.72
7.72
7.90
7.90
8.52
8.52

4.00

CHCl₃

2.00

0.95
1.91
2.43
1.98
0.91
0.99
1.79
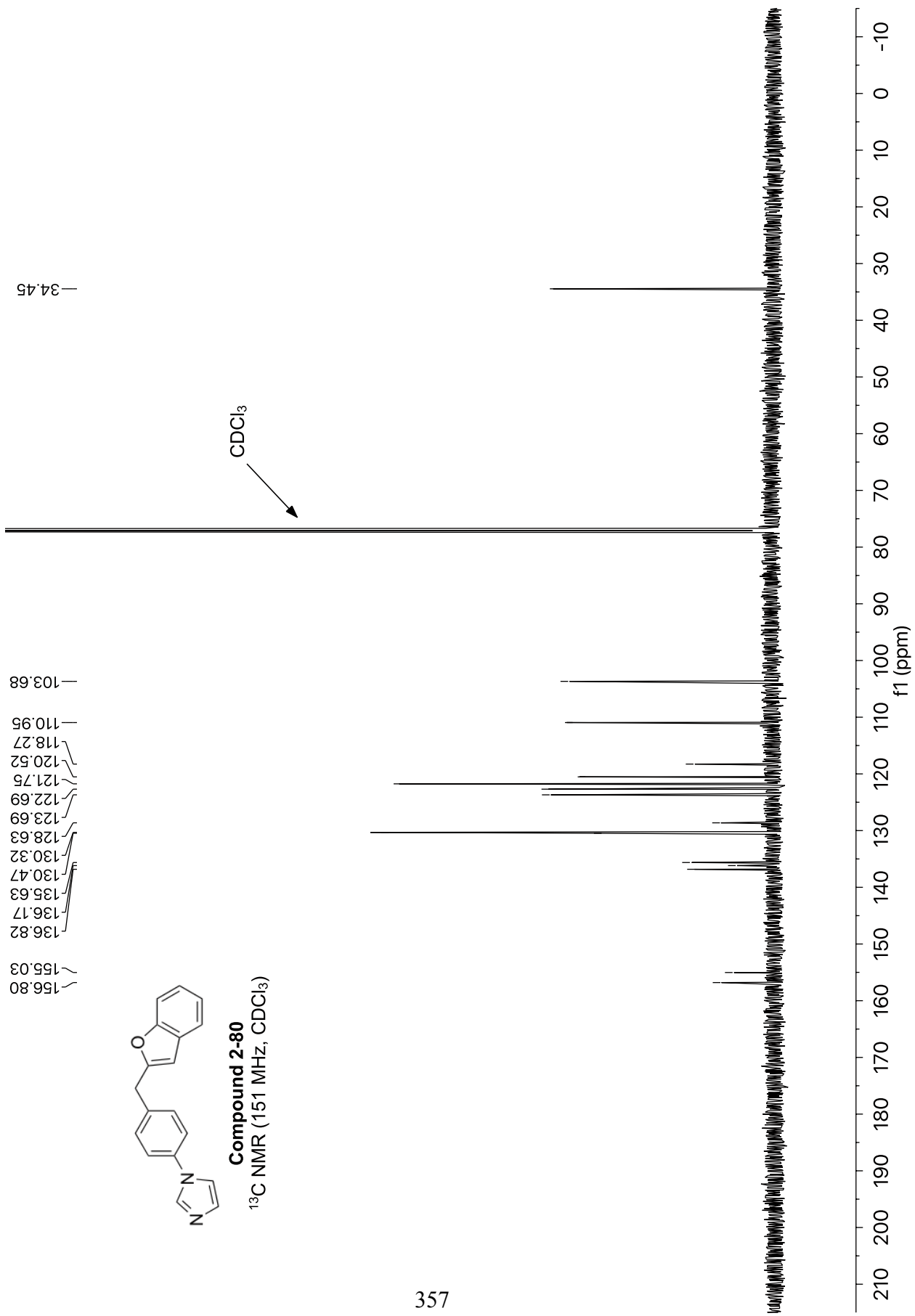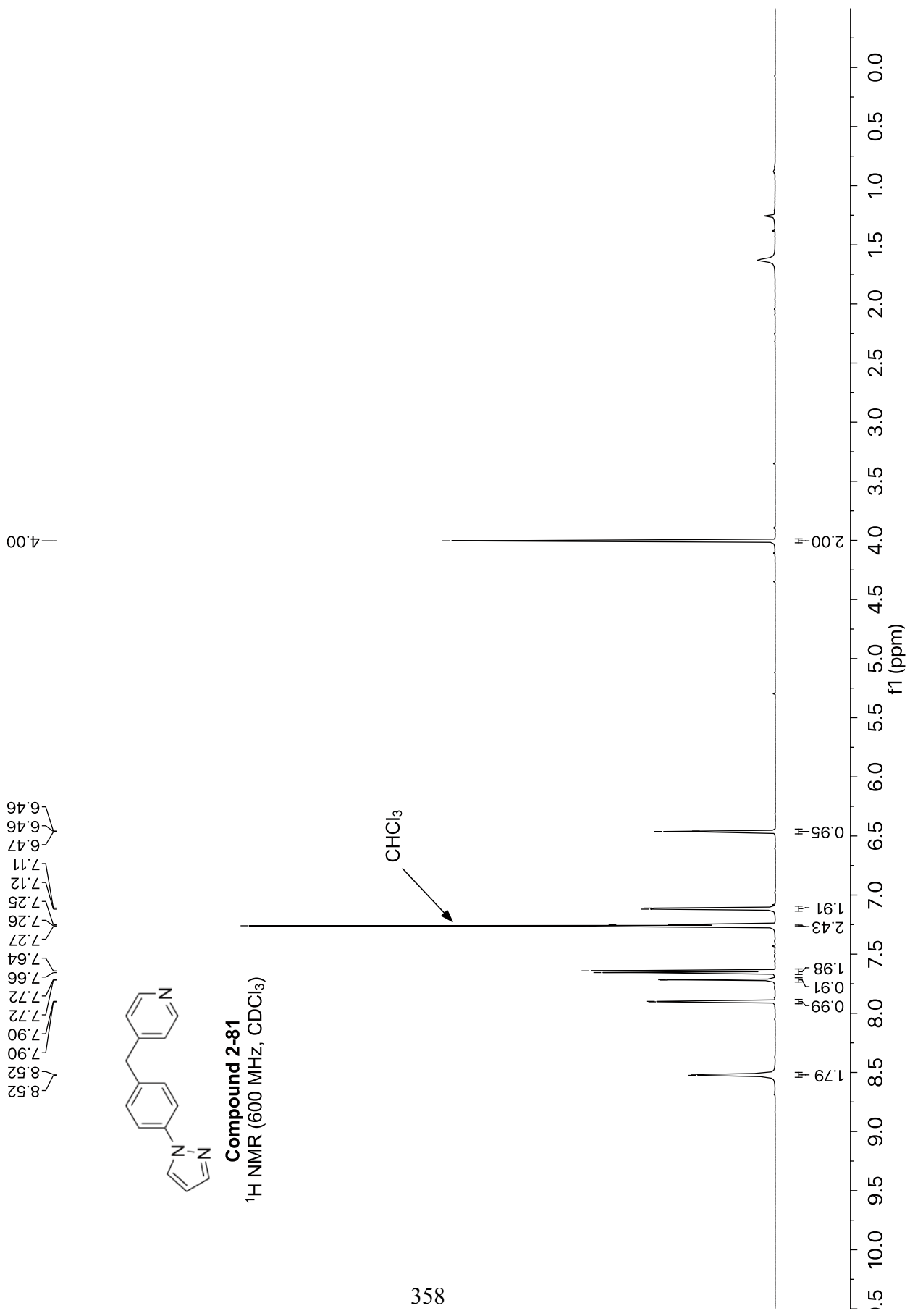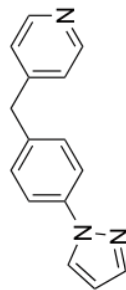
f1 (ppm)

**Compound 2-81**
13C NMR (151 MHz, CDCl₃)

40.62

CDCl₃

107.61

119.54
124.12
126.66
130.04
137.11
138.99
141.08
149.60
149.97

359
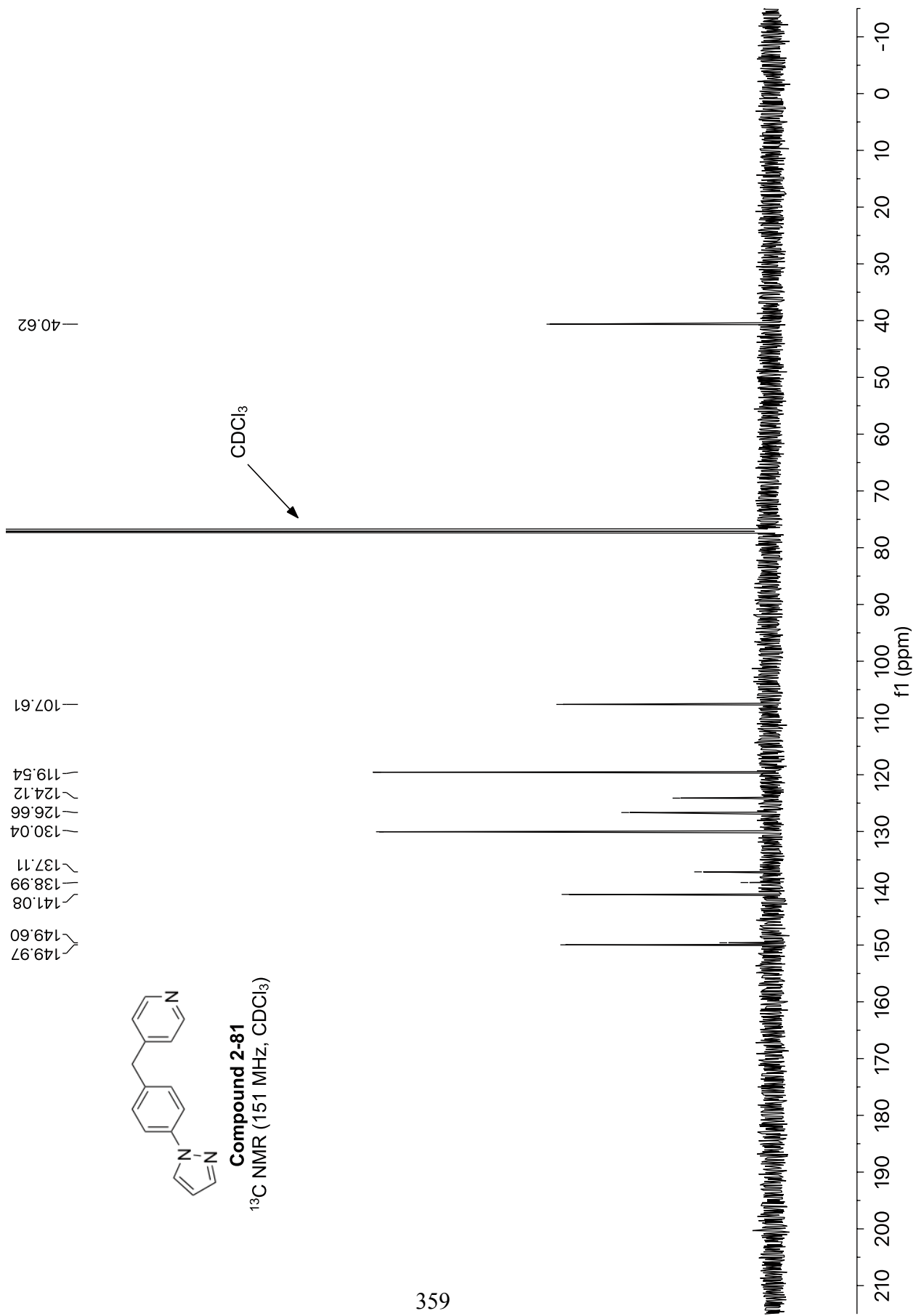
Compound 2-82
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

6.47
6.47
6.47
6.47
6.48
6.48
7.06
7.08
7.40
7.42
7.43
7.53
7.54
7.54
7.55
7.55
7.62
7.62
7.62
7.72
7.72
7.91
7.91
8.49

4.02

2.00
0.94
0.98
1.01
0.99
0.95
0.89
0.98
1.77

360

Compound 2-82
$^{13}$C NMR (151 MHz, CDCl$_3$)

35.66

CDCl$_3$

107.92

117.62
119.73
126.62
126.74
130.15
132.38
139.42
140.79
141.33

159.61
159.79

f1 (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

361

**Compound 2-83**
$^1$H NMR (400 MHz, CDCl$_3$)

CHCl$_3$

362

Compound 2-83
$^{13}$C NMR (101 MHz, CDCl$_3$)

33.30

45.81

CDCl$_3$

66.79

106.83
109.00

122.31
125.51
127.13
127.32
128.01
130.59
136.93
138.08
140.29
147.79

158.34

f1 (ppm)

Compound 2-84
$^1$H NMR (400 MHz, CDCl$_3$)

2.21
2.22

3.81

6.29
6.29
6.30
6.30
6.61
6.61
6.64
6.64
6.66
6.66
6.67
6.68
6.71
6.72
6.72
7.01
7.03
7.05
7.23
7.23
7.24
7.25
7.27
7.28
7.29
7.29
7.29
7.30
7.30
7.30
7.31
7.32
7.33
7.34
7.34

CHCl$_3$

2.98
2.00
1.93
1.94
1.96
1.01
0.95
3.03

364

Compound 2-84
$^{13}$C NMR (101 MHz, CDCl$_3$)

14.19
14.23

36.31
36.32

CDCl$_3$

108.94
115.11
115.34
122.28
122.31
122.45
124.06
124.09
127.24
127.30
127.96
130.87
131.21
131.26
136.52
139.96
140.03
140.41
160.02
162.45

365

−117.88

**Compound 2-84**
19F NMR (565 MHz, CDCl₃)

-210 -200 -190 -180 -170 -160 -150 -140 -130 -120 -110 -100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10
f1 (ppm)

Compound 2-85
$^1$H NMR (600 MHz, CDCl$_3$)

7.31
7.32
7.38
7.38
7.38
7.39
7.40
7.40
7.40
7.40
7.40
7.93
7.99
8.01
8.62

2.24

4.00

CHCl$_3$

367

**Compound 2-85**
$^{13}$C NMR (151 MHz, CDCl$_3$)

14.48
14.49

37.79

CDCl$_3$

119.41
119.63
127.79
129.28
129.58
129.74
133.64
133.67
141.29
141.99
142.03
144.32
144.41

160.44
162.02
162.53

−75.62

**Compound 2-85**
19F NMR (565 MHz, CDCl3)

369
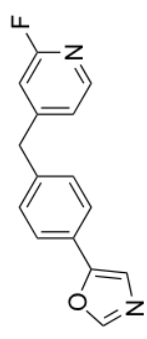
Compound 2-86
$^1$H NMR (400 MHz, CDCl$_3$)

CHCl$_3$

370

Compound 2-86
$^{13}$C NMR (101 MHz, CDCl$_3$)

40.78
40.81

CDCl$_3$

109.36
109.73
121.57
121.84
121.88
124.90
126.59
129.65
138.63
147.57
147.72
150.49
151.15
155.43
155.51
162.97
165.35
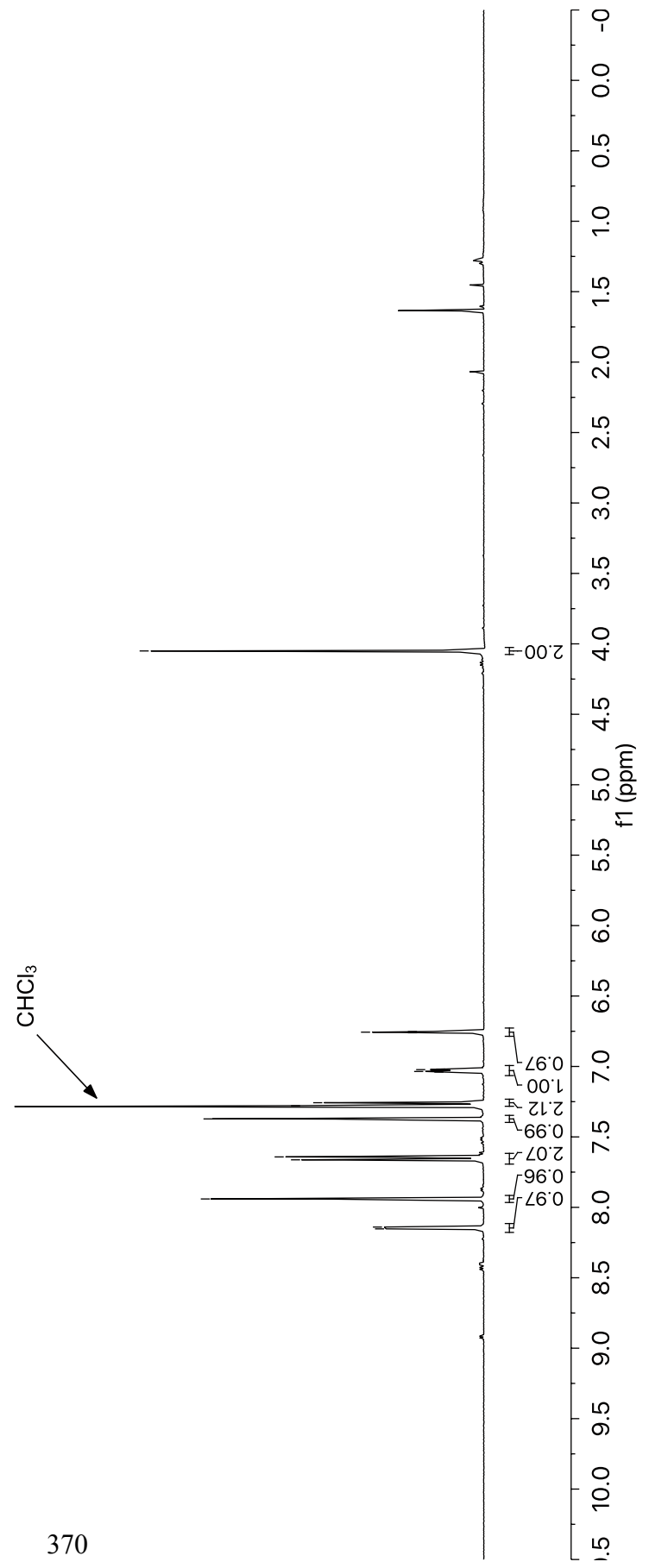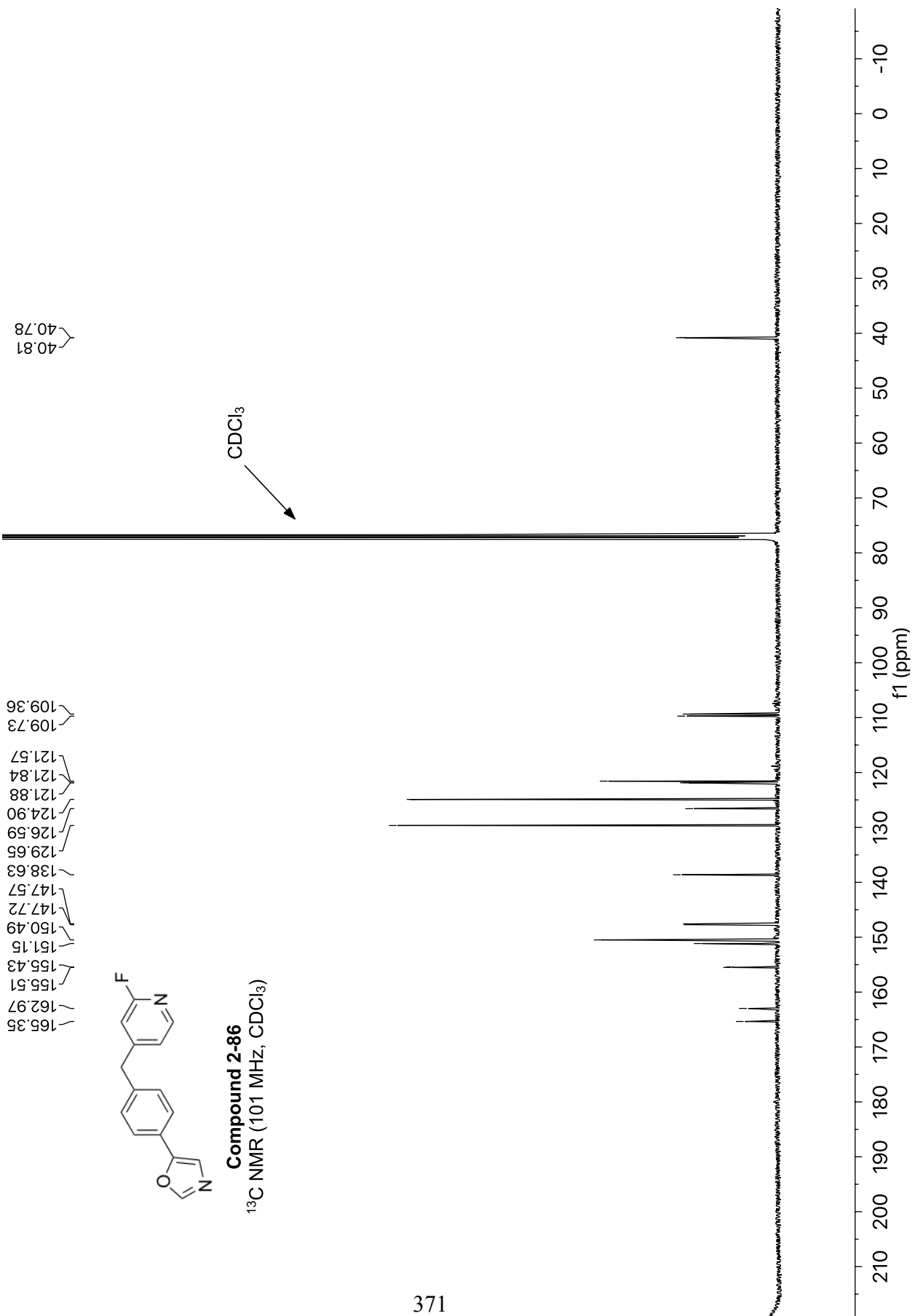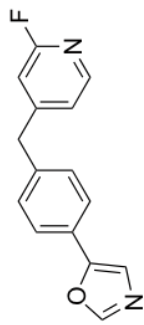
**Compound 2-86**
¹⁹F NMR (565 MHz, CDCl₃)

−68.31



f1 (ppm)

372

Compound 2-87
$^1$H NMR (600 MHz, CDCl$_3$)

2.53

3.05

4.11

7.23
7.23
7.23
7.23
7.24
7.24
7.39
7.39
7.39
7.40
7.40
7.41
7.41
7.41
7.42
7.43
7.88
7.88
7.88
7.89
7.89
7.90
8.67

CHCl$_3$

373
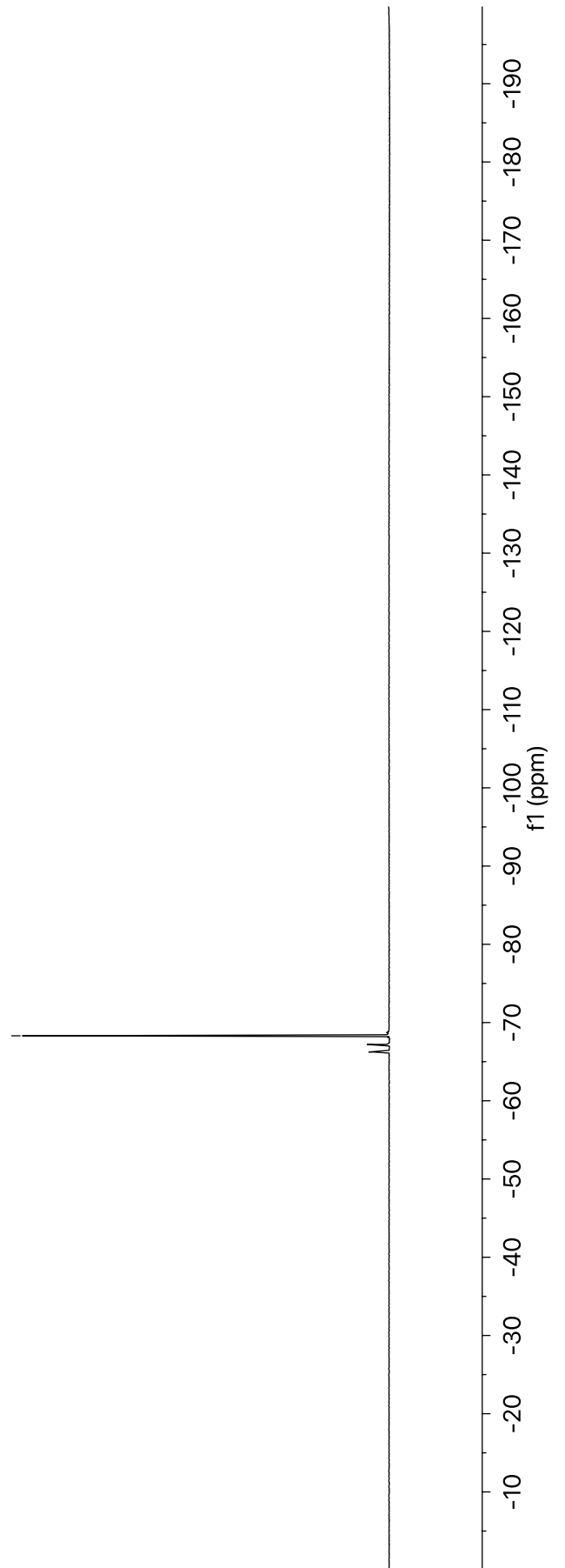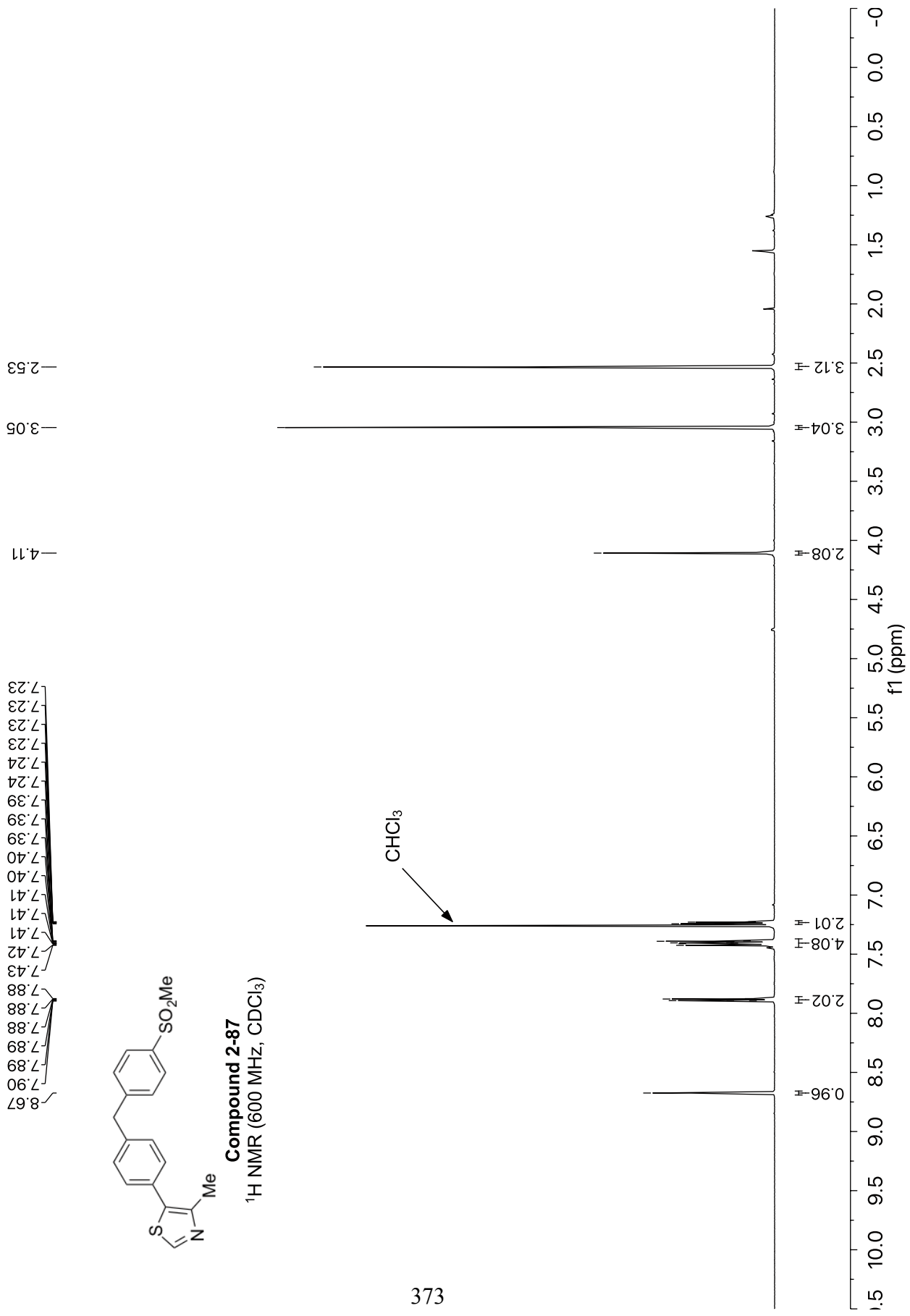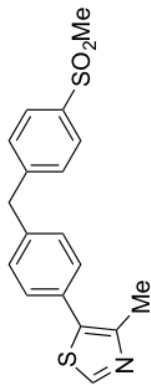
Compound 2-87
13C NMR (151 MHz, CDCl3)

16.13

41.49
44.57

CDCl3

127.75
129.29
129.65
129.84
130.47
131.47
138.67
139.24
147.14
148.56
150.24

374
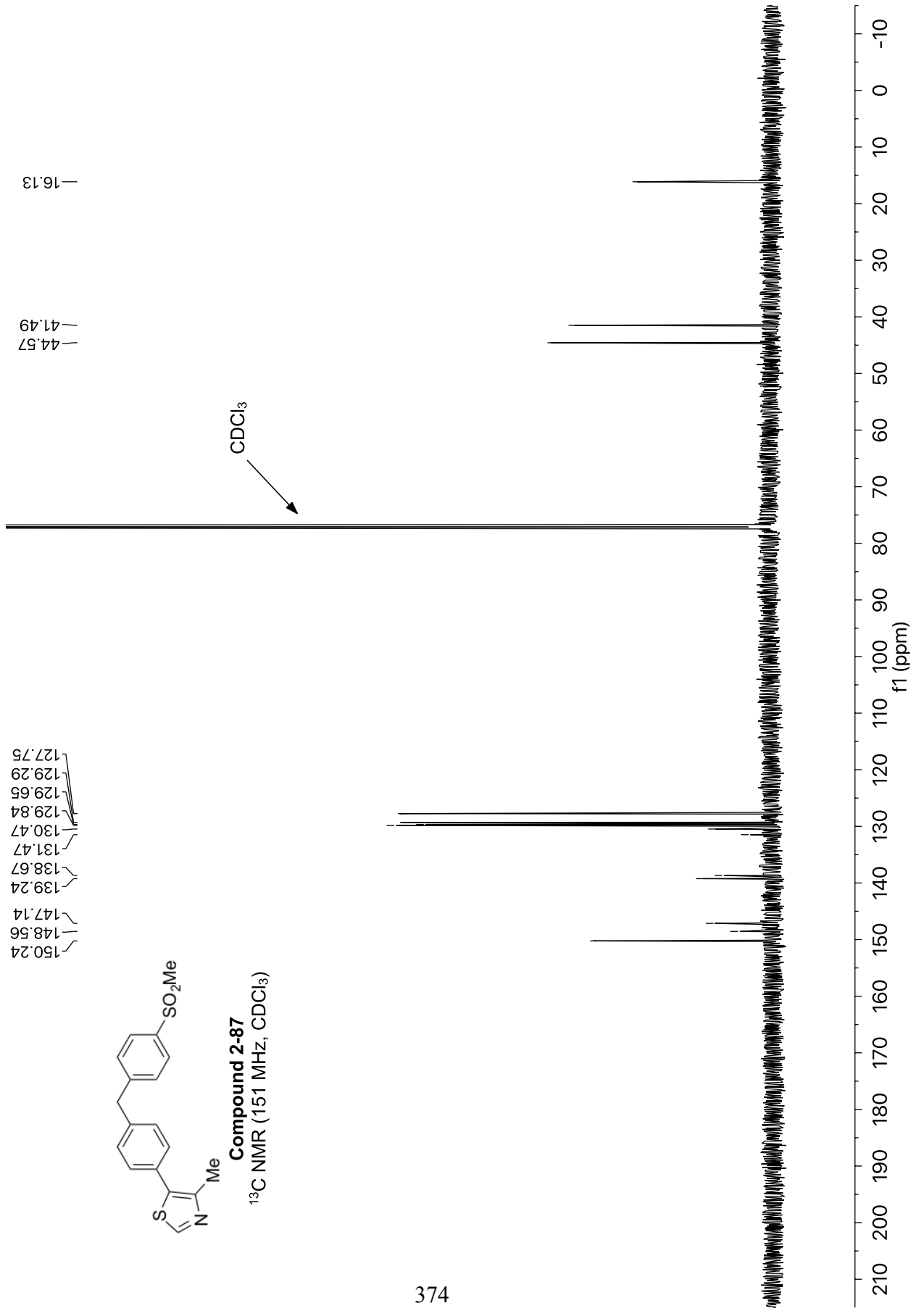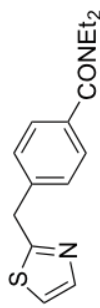
Compound 2-88
$^1$H NMR (400 MHz, CDCl$_3$)

375

13.92
14.27

39.26
43.30

CDCl₃

119.17

126.86
128.99

136.04
138.94
142.59

169.47
170.99
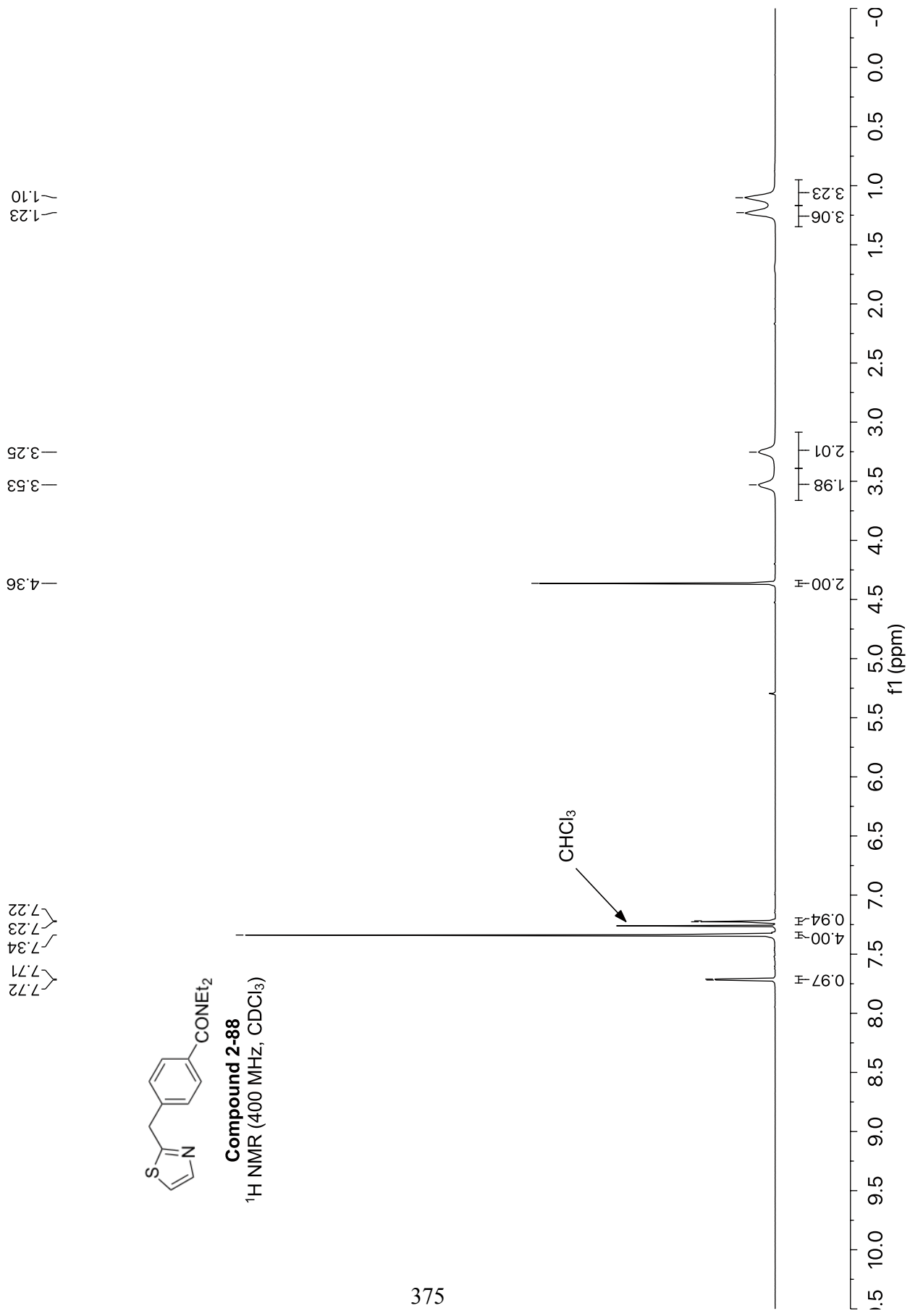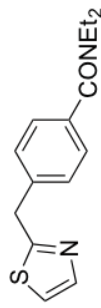
**Compound 2-88**
¹³C NMR (101 MHz, CDCl₃)

210  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)

376

2.47

3.93

6.99
6.99
6.00
6.00
6.00
6.00
6.28
6.29
6.29
6.29
7.15
7.15
7.15
7.16
7.16
7.20
7.21
7.21
7.22
7.22
7.22
7.32
7.32
7.32
7.32

SMe

**Compound 2-89**
¹H NMR (600 MHz, CDCl₃)

CHCl₃

3.13
2.00
0.93
0.94
2.00
1.97
0.90

f1 (ppm)
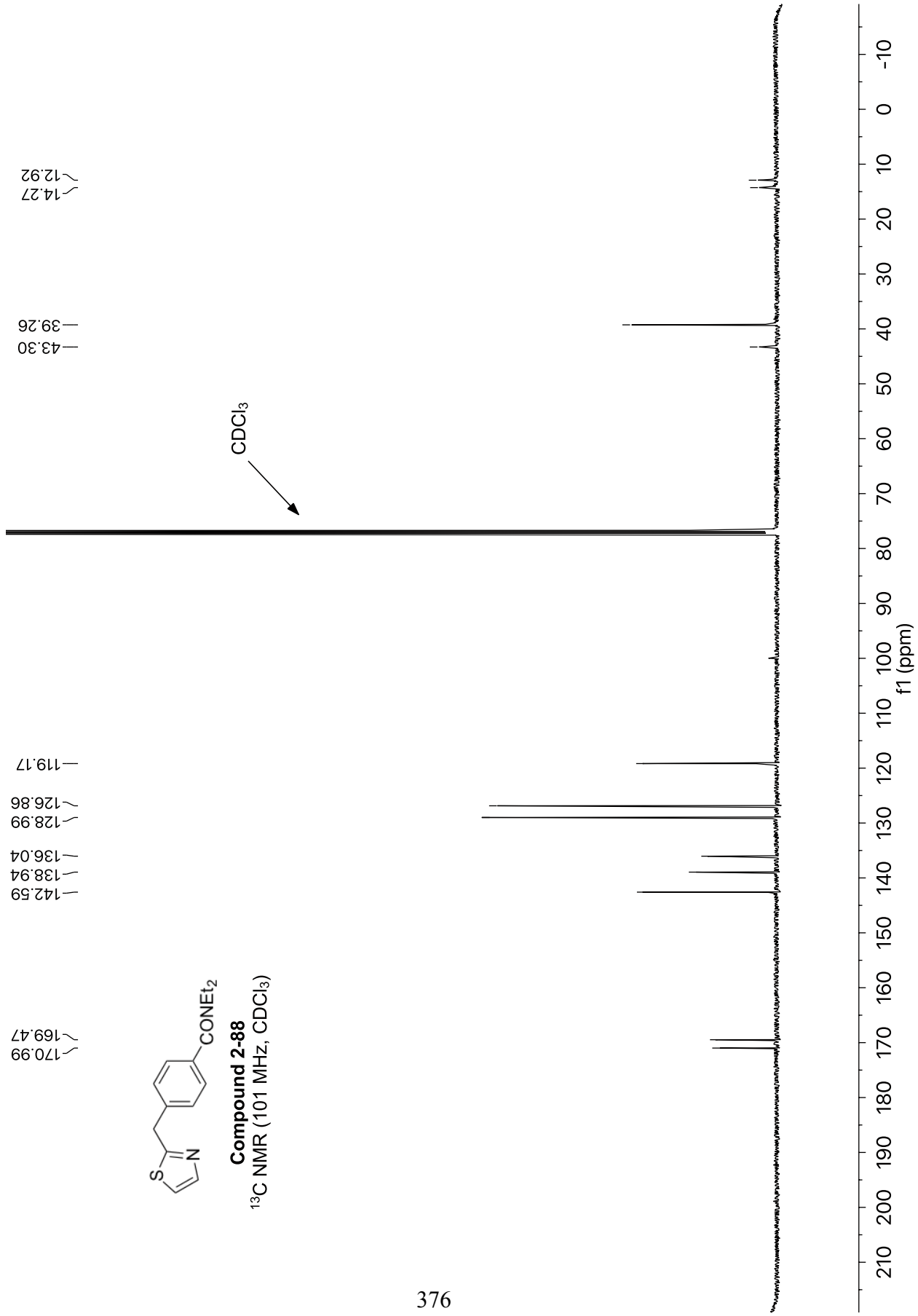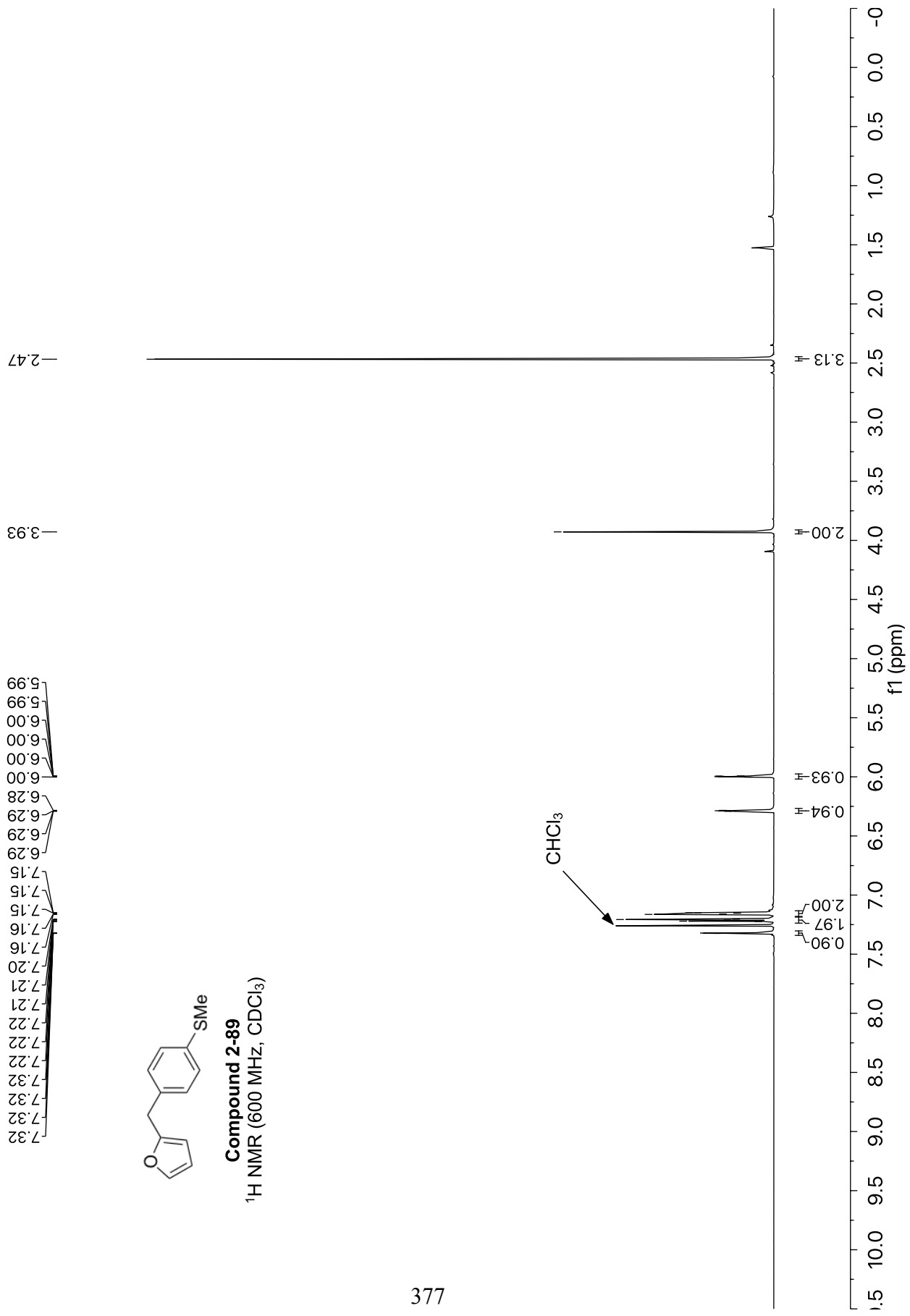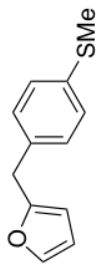
Compound 2-89
$^{13}$C NMR (151 MHz, CDCl$_3$)
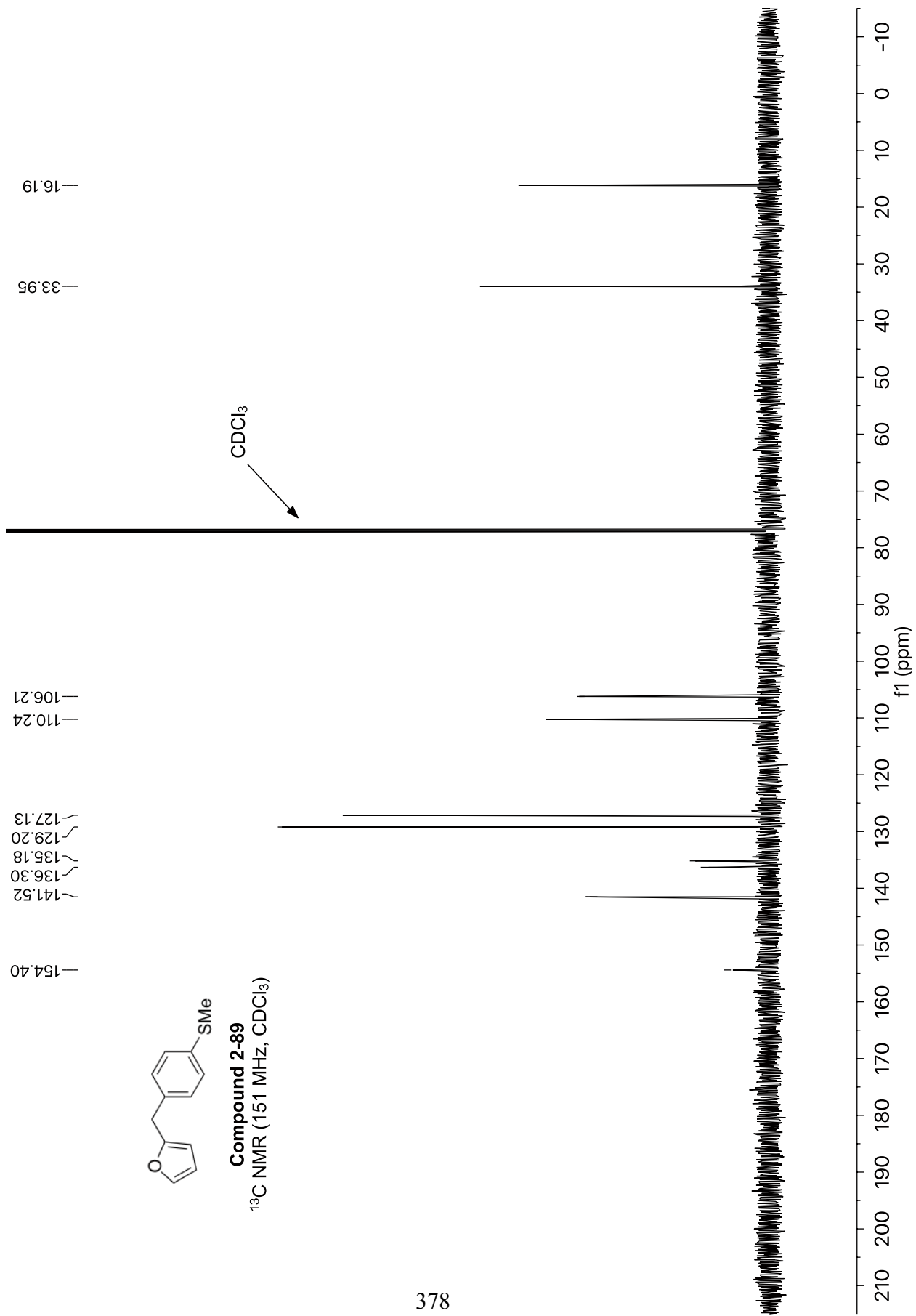
16.19
33.95
106.21
110.24
127.13
129.20
135.18
136.30
141.52
154.40

CDCl$_3$

f1 (ppm)

378

Compound 2-47
$^1$H NMR (600 MHz, CDCl$_3$)

379

55.99

CDCl₃

123.60
126.75
128.19
129.10
129.45
129.87
129.96
131.34
132.54
132.57
133.67
134.46
147.42
149.56

156.85
157.52

**Compound 2-47**
¹³C NMR (151 MHz, CDCl₃)
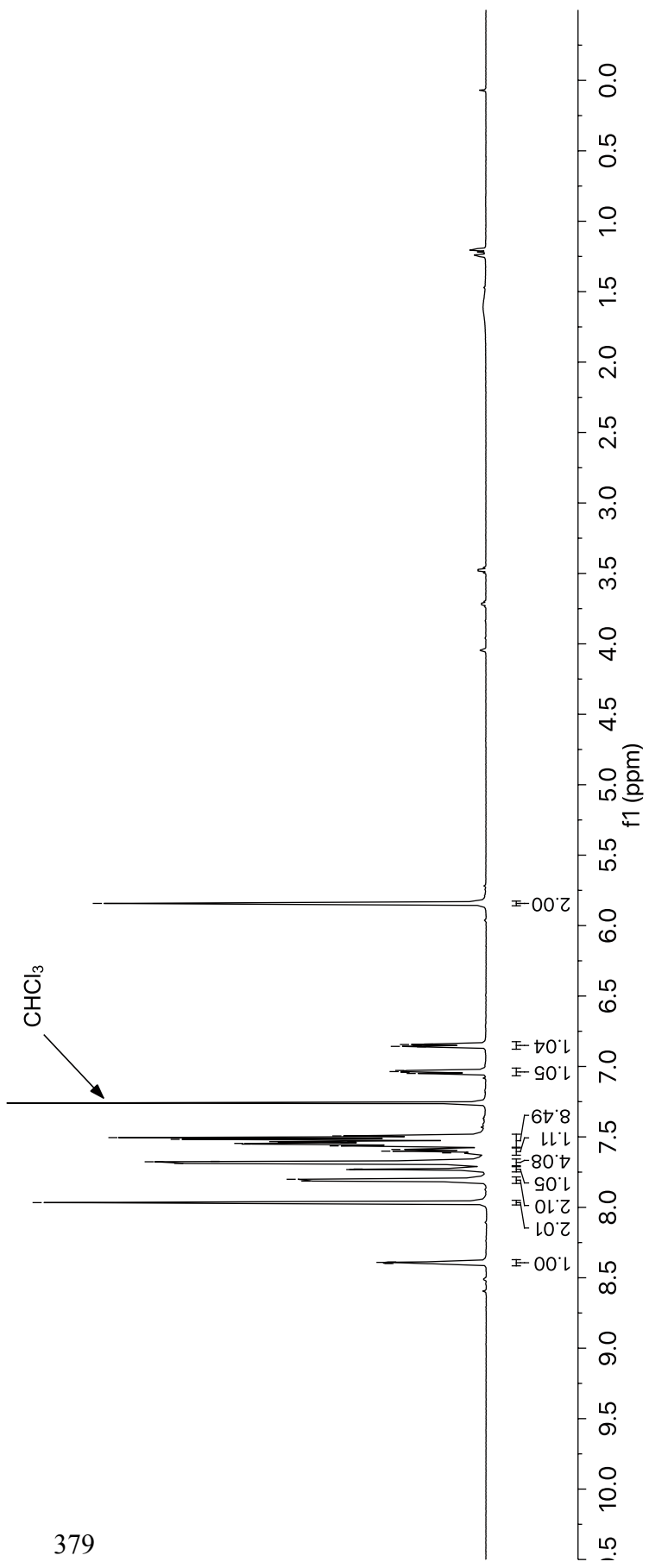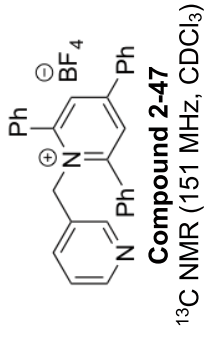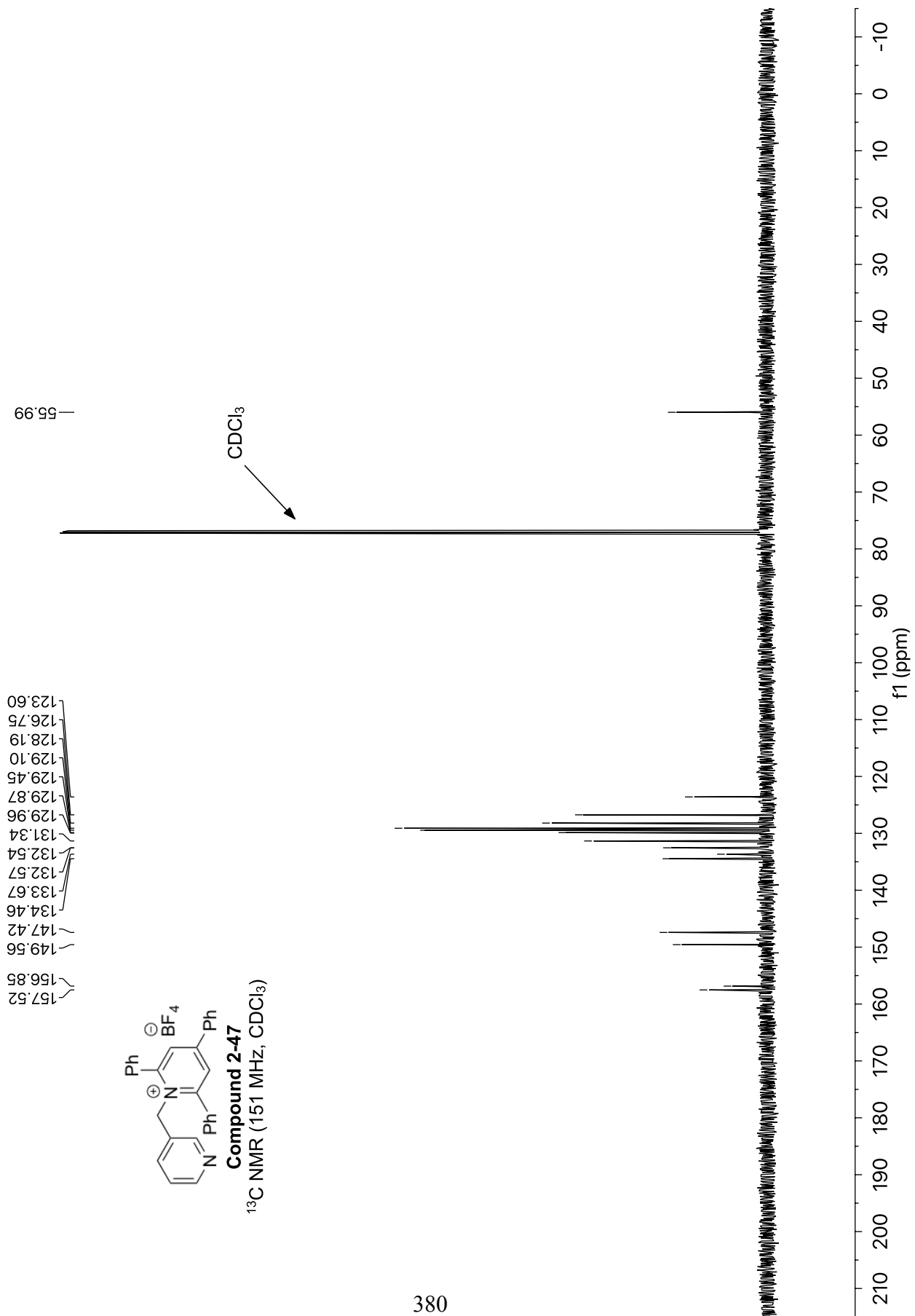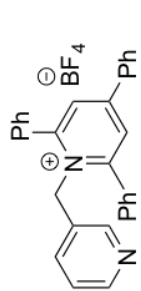
-152.68
-152.63

**Compound 2-47**
$^{19}$F NMR (376 MHz, CDCl$_3$)

-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

Compound 2-48
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

382

121.82
123.01
126.07
128.10
128.85
128.88
129.73
130.74
132.14
132.96
134.11
136.72
149.16
153.35
155.91
157.54

59.03

CDCl₃

Compound 2-48
¹³C NMR (151 MHz, CDCl₃)

-153.35
-153.30

Compound 2-48
$^{19}$F NMR (565 MHz, CDCl$_3$)

384

f1 (ppm)
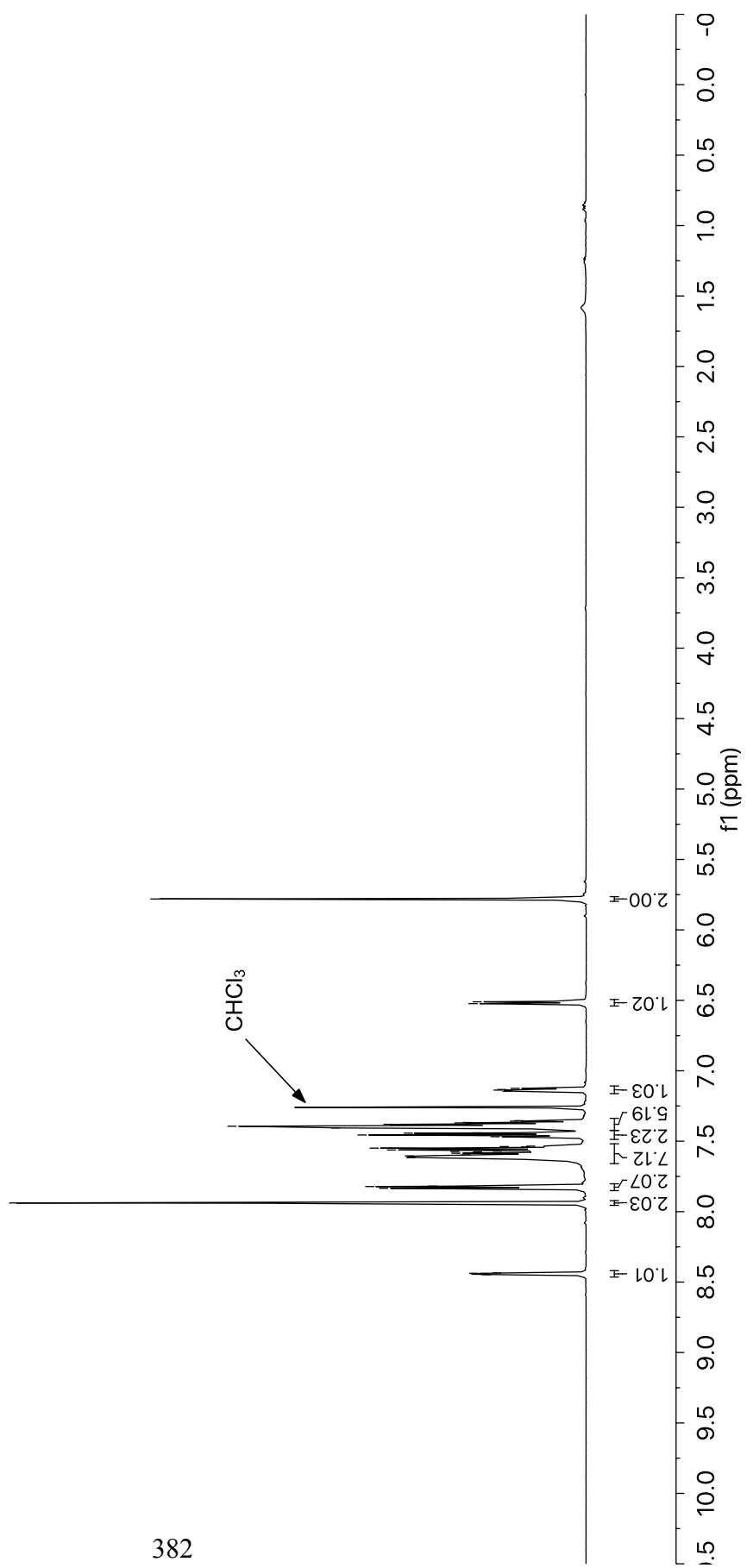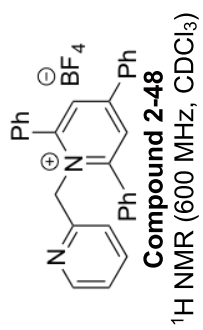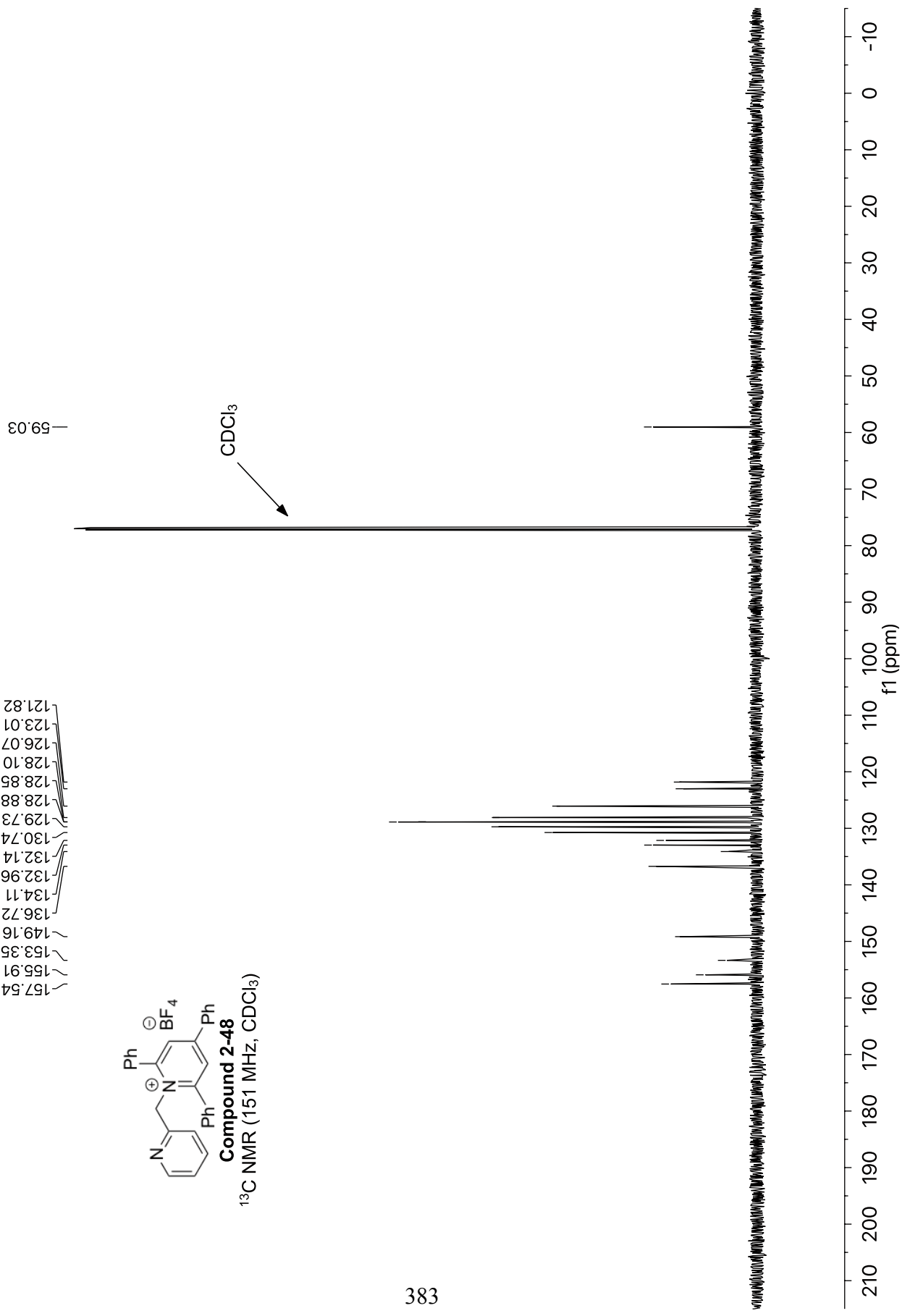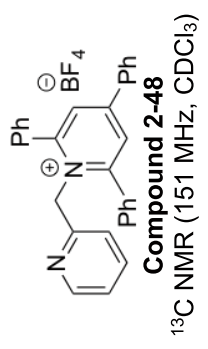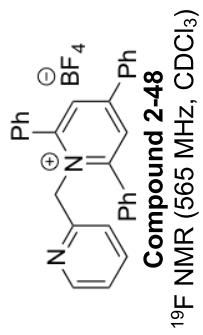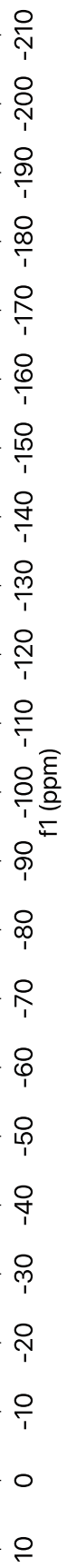
**Compound 2-49**
$^1$H NMR (600 MHz, CDCl$_3$)

385

Compound 2-49
13C NMR (151 MHz, CDCl3)

57.06

120.88
126.68
128.23
129.04
129.39
129.88
131.32
132.25
132.65
133.62
143.01
150.20
156.98
157.61

CDCl3

f1 (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
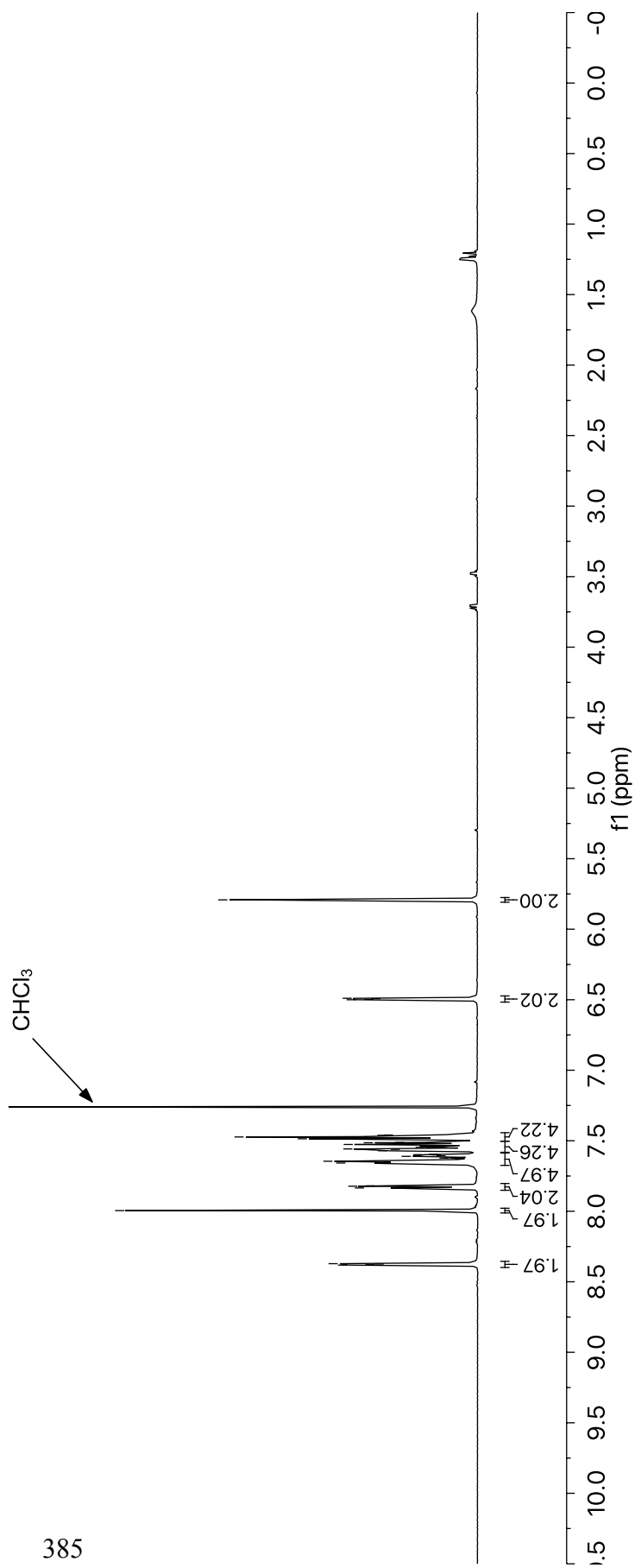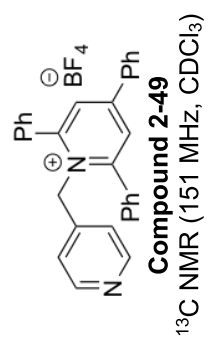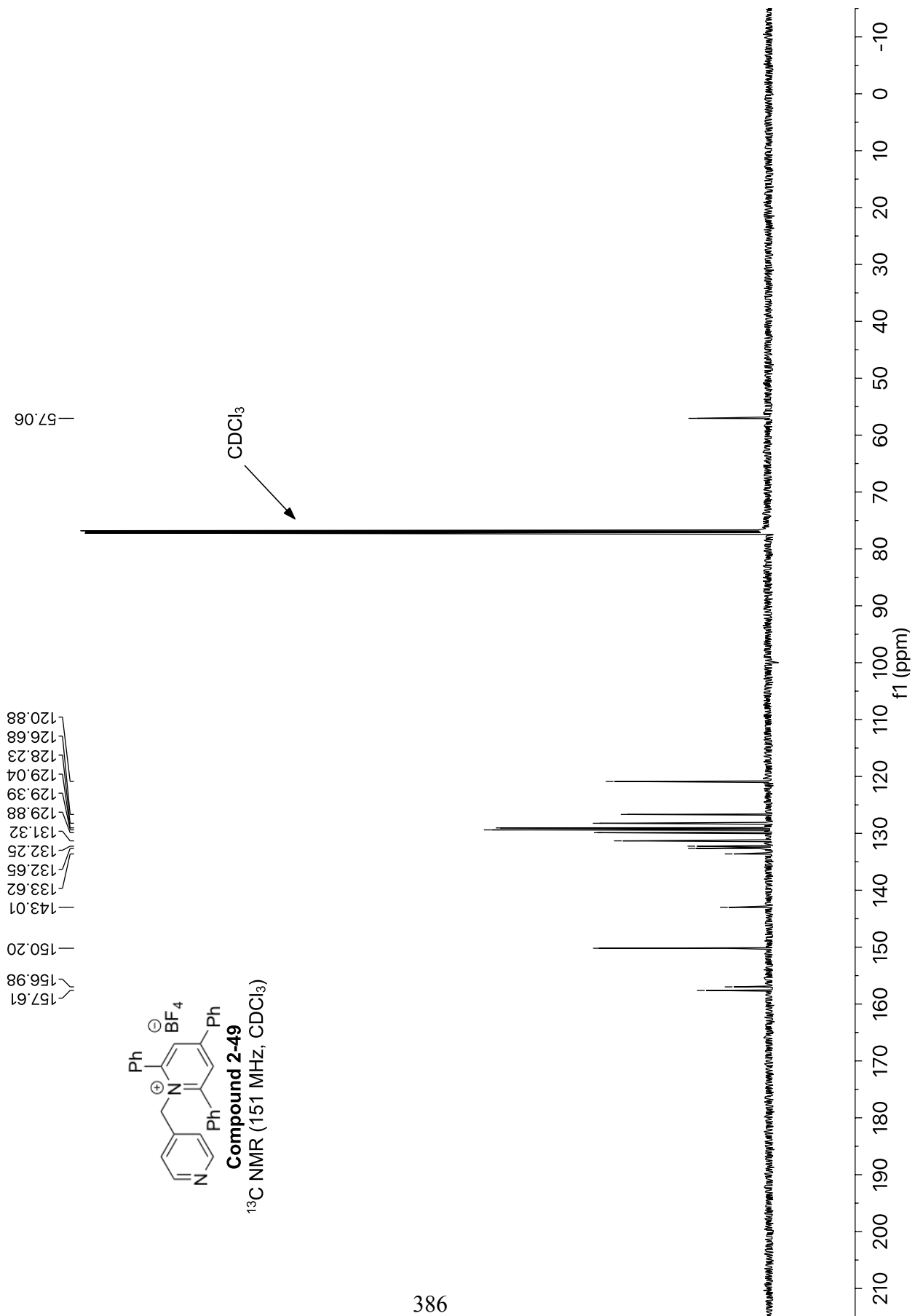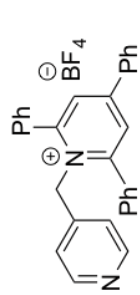
-152.85, -152.90

**Compound 2-49**
19F NMR (565 MHz, CDCl₃)
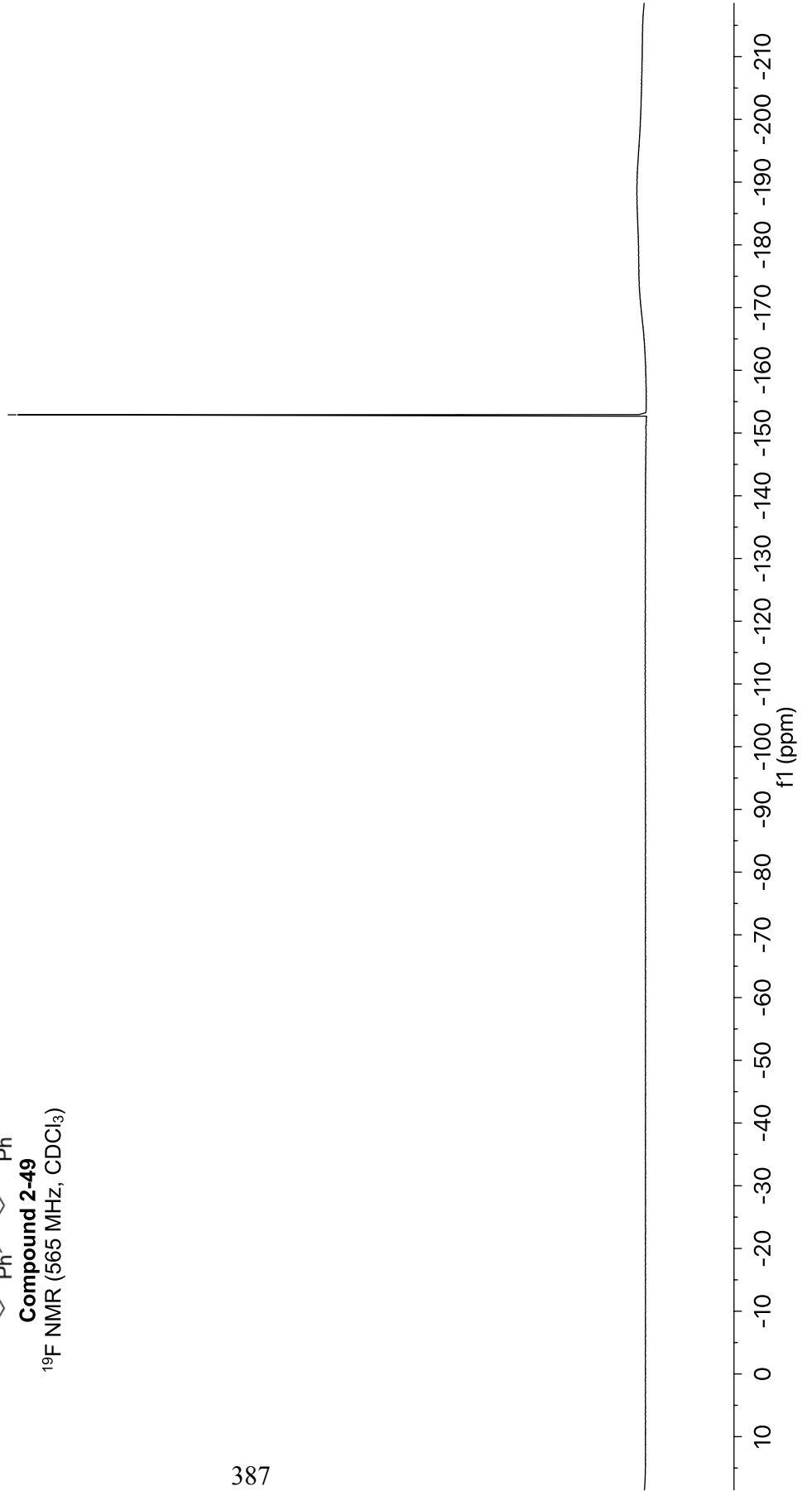
387

6.95
6.80
6.81
6.83
6.83
6.96
6.97
7.36
7.37
7.38
7.39
7.39
7.41
7.41
7.43
7.46
7.46
7.46
7.47
7.48
7.48
7.49
7.50
7.50
7.51
7.52
7.52
7.53
7.54
7.55
7.55
7.56
7.57
7.57
7.58
7.59
7.59
7.59
7.64
7.65
7.67
7.79
7.80
7.80
7.81
7.81
7.82
7.82
7.84
7.96
7.98
7.98
8.00
8.00
8.01
8.86
8.86
8.87
8.88

**Compound 2-50**
$^1$H NMR (400 MHz, CDCl$_3$)

388

CHCl$_3$
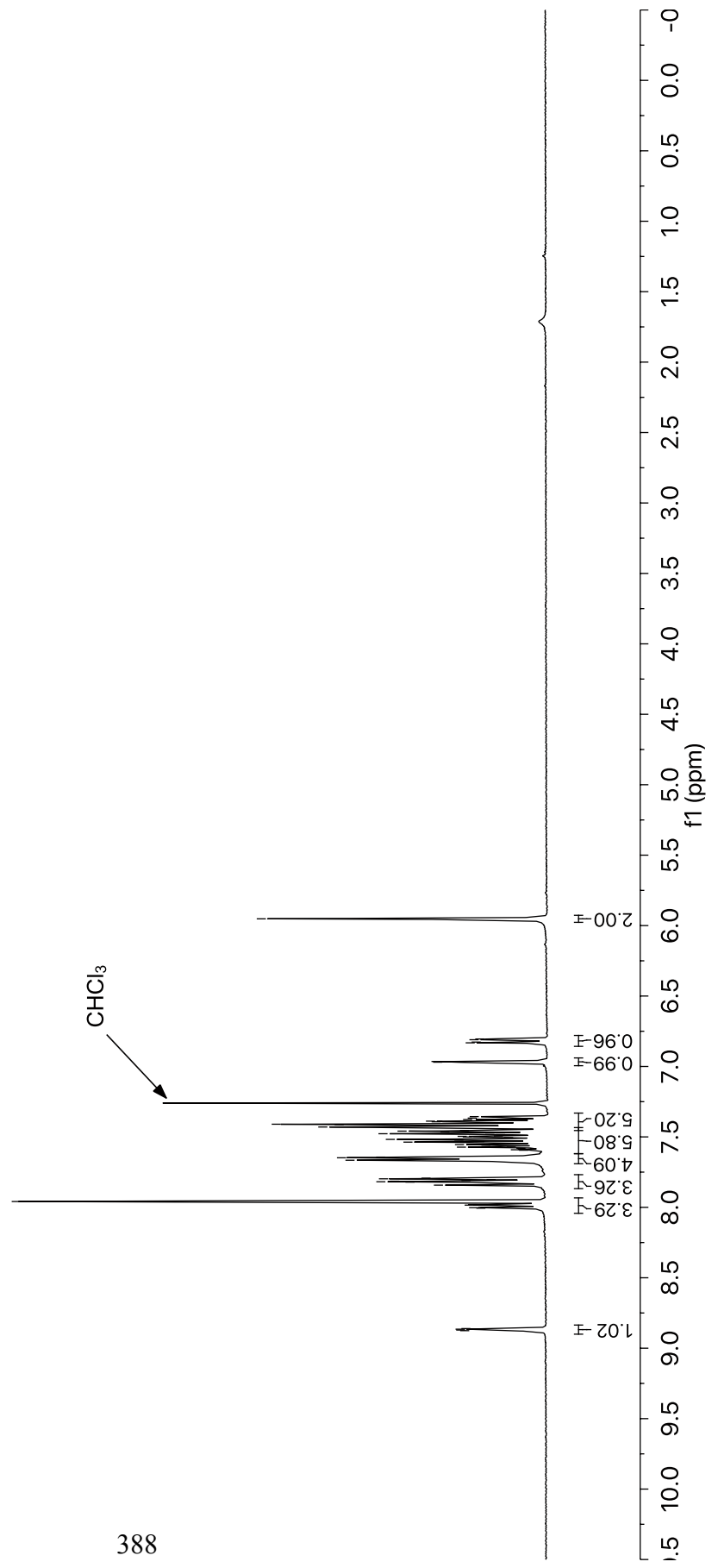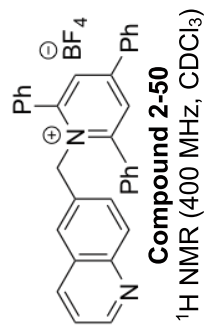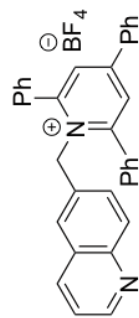
Compound 2-50
$^{13}$C NMR (101 MHz, CDCl$_3$)

58.07

CDCl$_3$

122.06
126.34
126.70
126.78
127.81
128.24
129.08
129.29
129.82
130.29
131.13
131.98
132.49
132.67
133.73
136.24
147.37
151.34
156.65
157.52
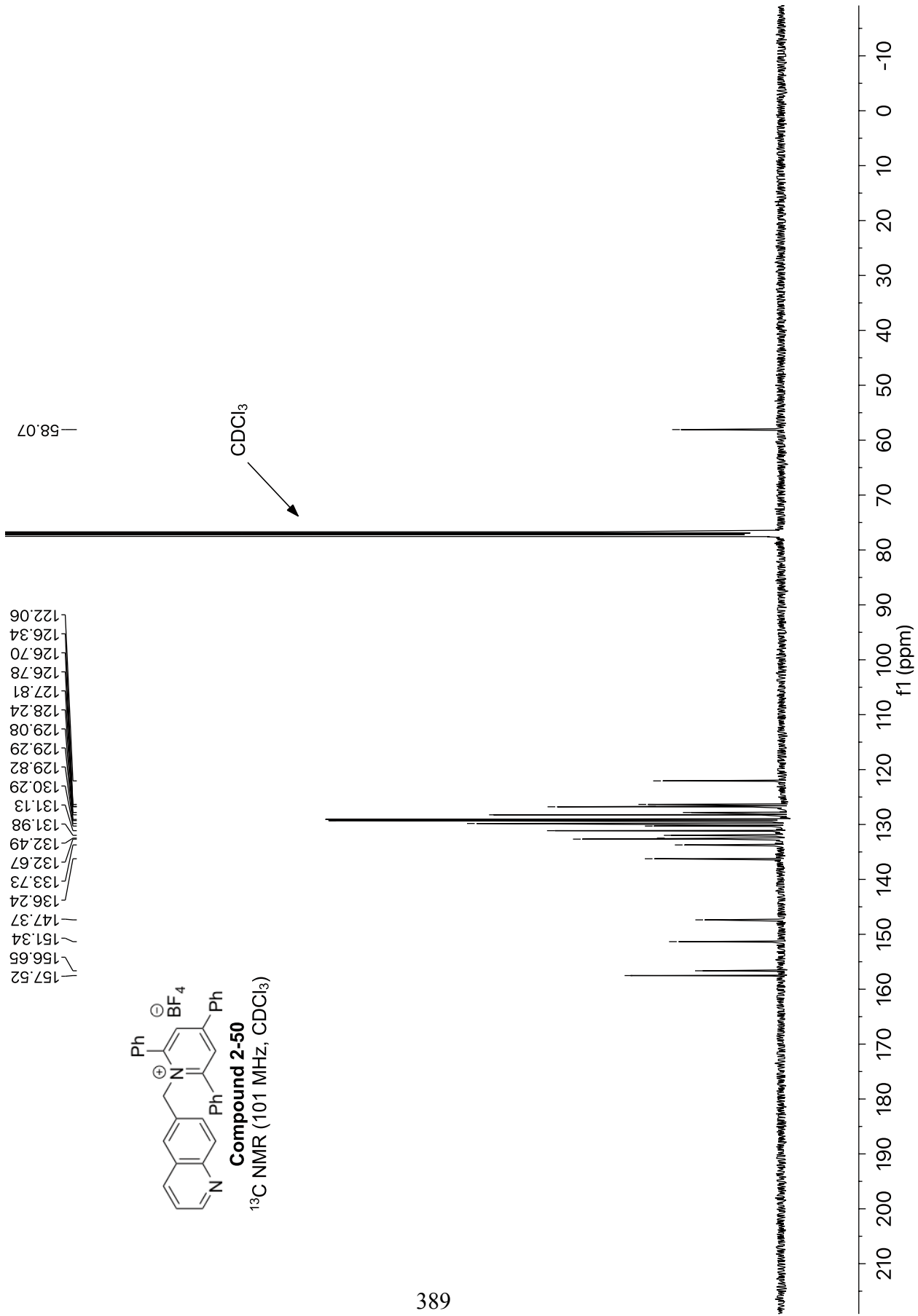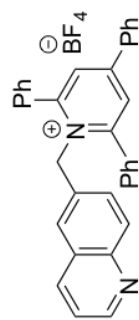
-152.55
-152.50

**Compound 2-50**
$^{19}$F NMR (376 MHz, CDCl$_3$)
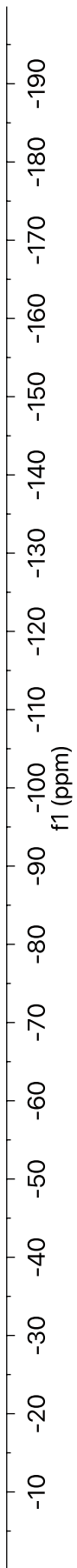
390

f1 (ppm)

-10  -20  -30  -40  -50  -60  -70  -80  -90  -100  -110  -120  -130  -140  -150  -160  -170  -180  -190

**Compound 2-51**
$^1$H NMR (600 MHz, CDCl$_3$)

391

59.50
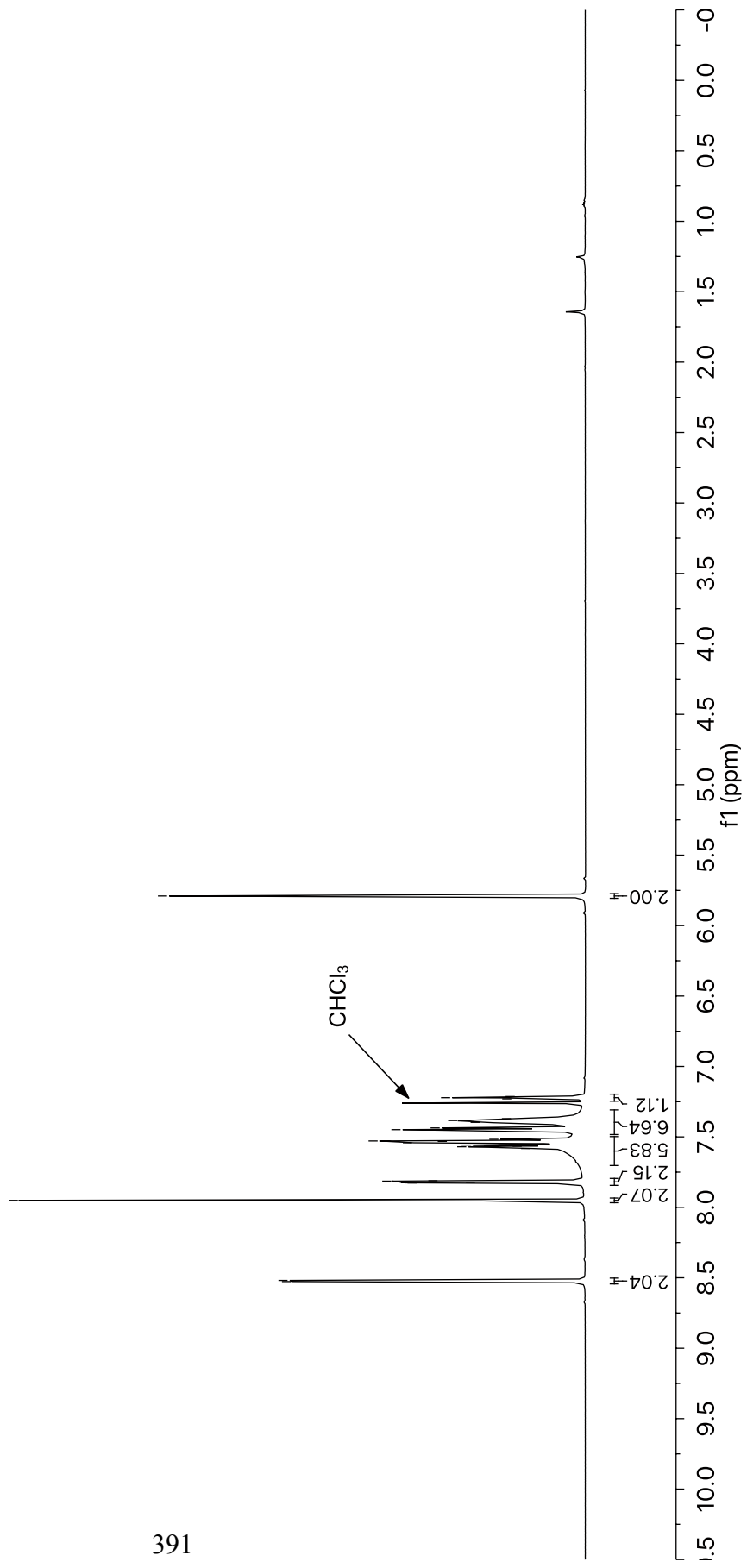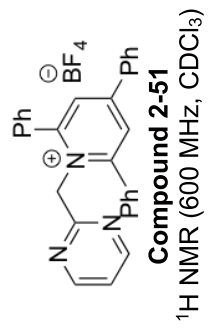
CDCl₃

120.23
120.33
126.28
128.22
128.73
129.03
129.73
130.90
132.20
132.66
134.12

156.50
157.32
157.36
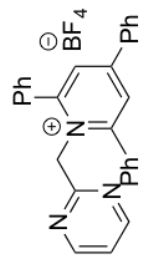
**Compound 2-51**
¹³C NMR (151 MHz, CDCl₃)
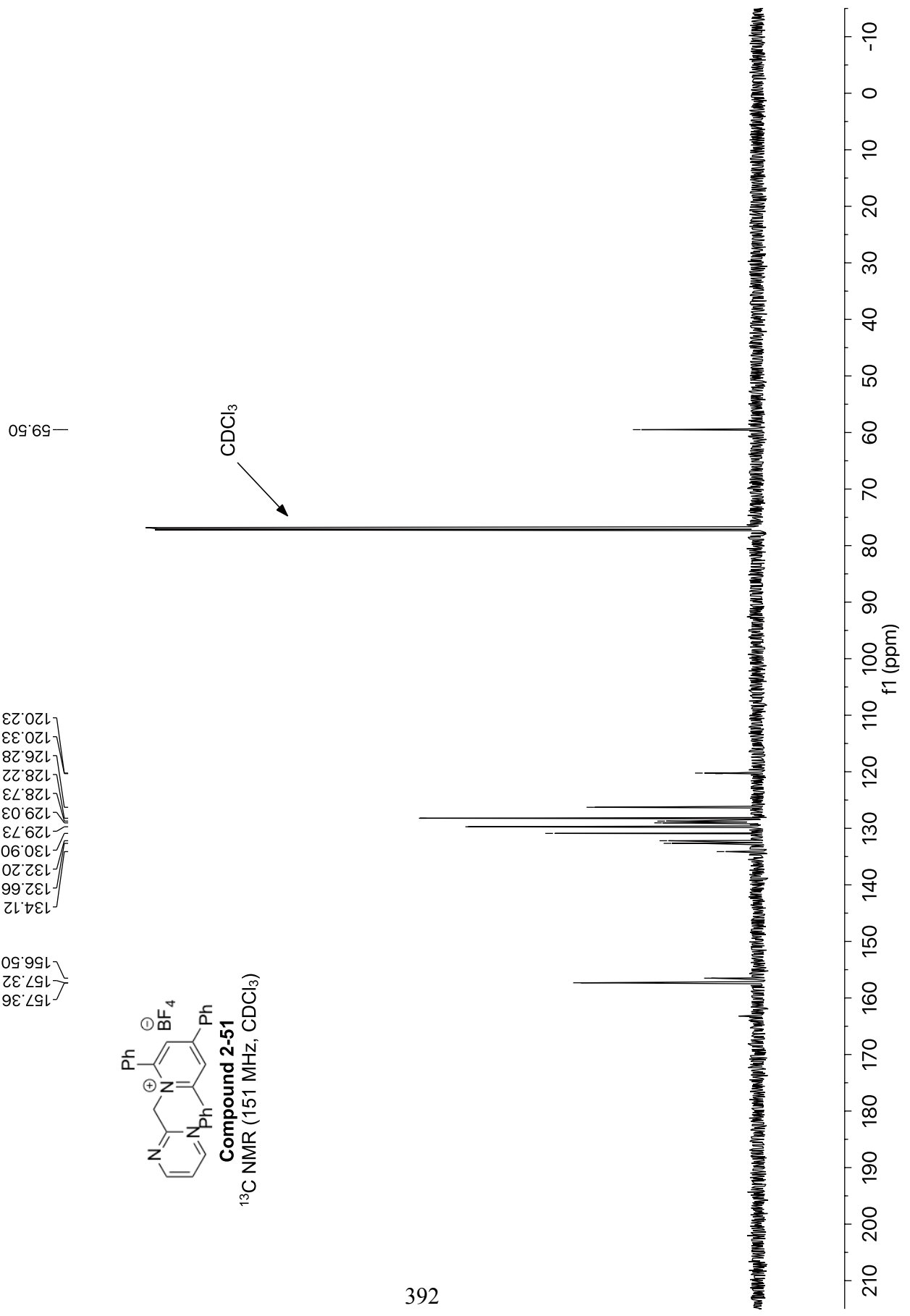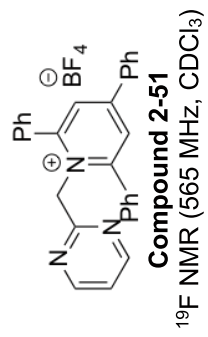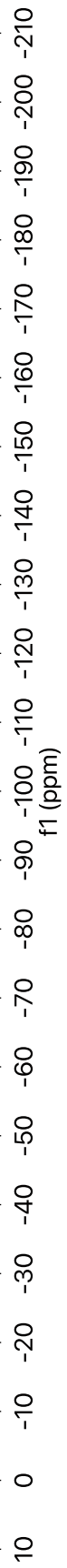
392

-153.48
-153.43

**Compound 2-51**

$^{19}$F NMR (565 MHz, CDCl$_3$)

393

Compound 2-52
$^1$H NMR (600 MHz, CDCl$_3$)

394

56.78

CDCl₃

126.14
128.13
128.83
129.12
129.81
131.17
132.39
132.70
133.87
143.45
143.72
144.06
149.39
156.39
157.54

Compound 2-52
¹³C NMR (151 MHz, CDCl₃)

395

-152.99
-152.94

Compound 2-52
$^{19}F$ NMR (565 MHz, CDCl$_3$)

396

10   0   -10   -20   -30   -40   -50   -60   -70   -80   -90   -100   -110   -120   -130   -140   -150   -160   -170   -180   -190   -200   -210
f1 (ppm)

1.85
1.86

6.20
6.22
6.23
6.24
6.68
6.70
7.23
7.23
7.24
7.25
7.43
7.45
7.46
7.46
7.47
7.47
7.48
7.48
7.49
7.49
7.49
7.50
7.50
7.51
7.52
7.52
7.52
7.53
7.53
7.54
7.55
7.80
7.80
7.81
7.86
7.87
7.89
7.90
8.54
8.54
8.55
8.55
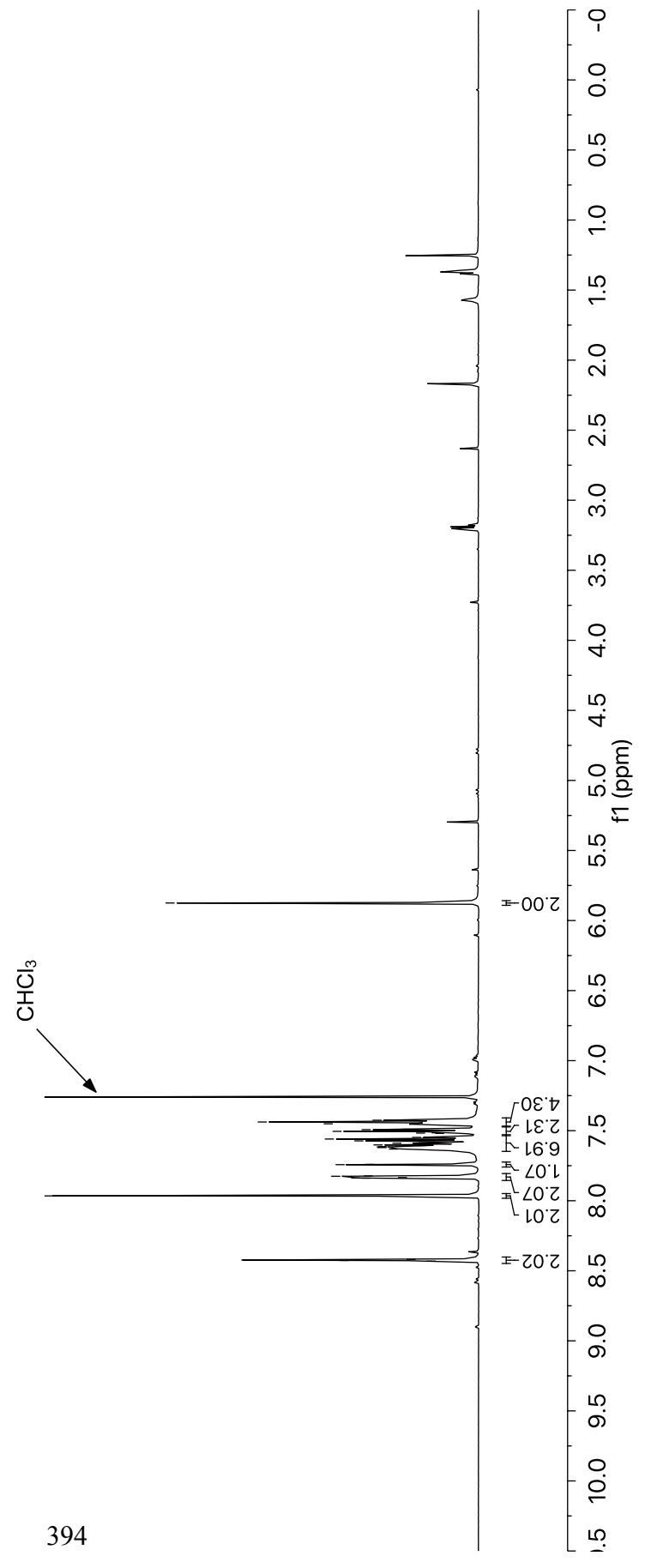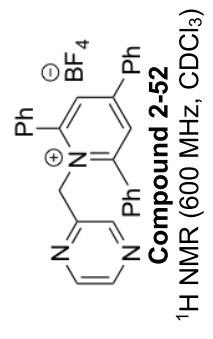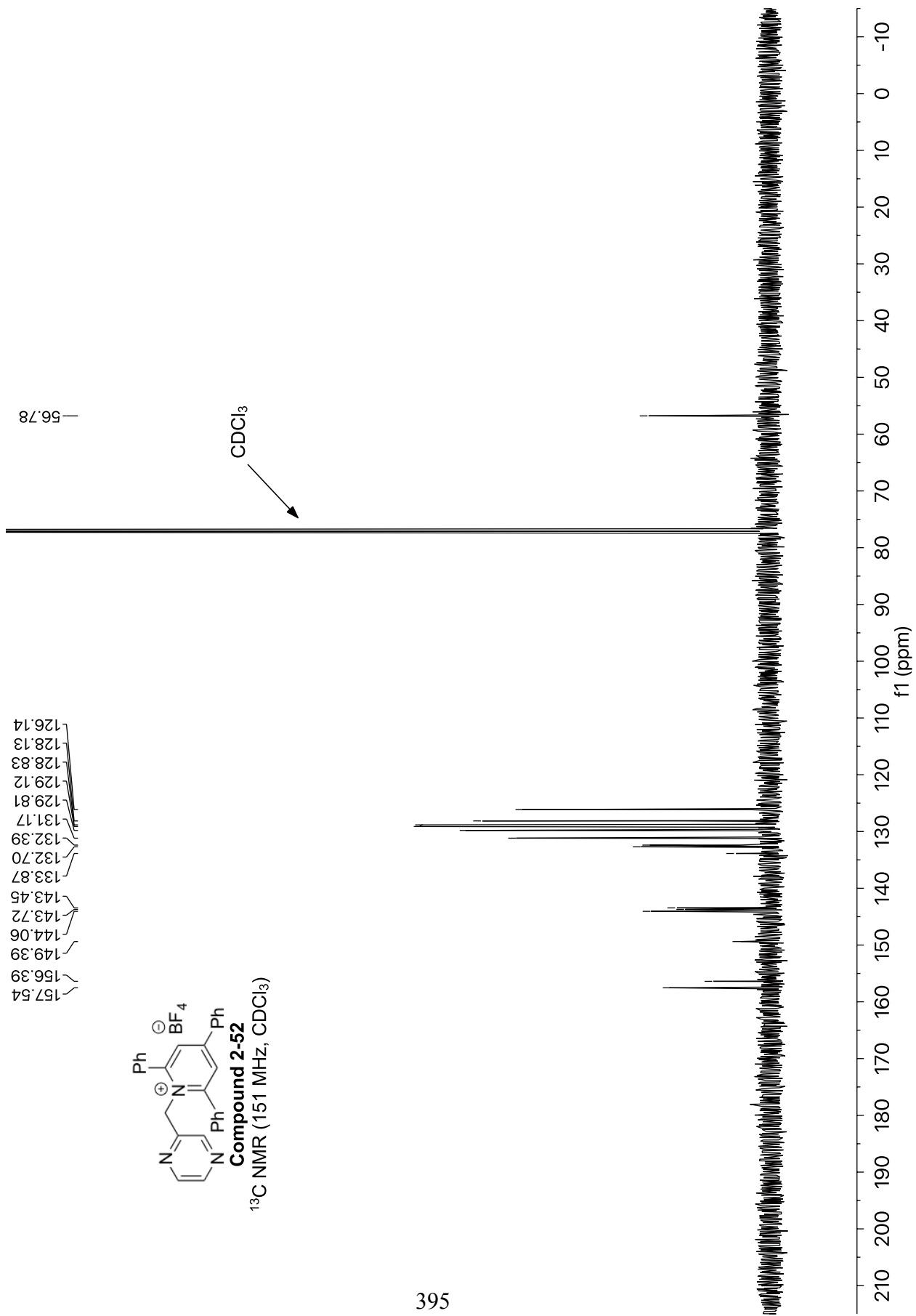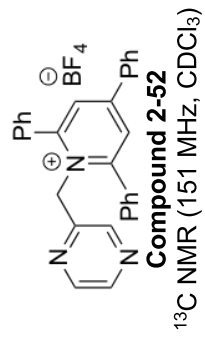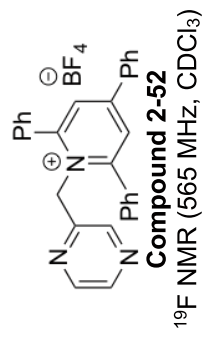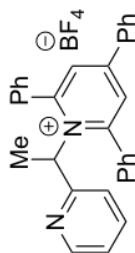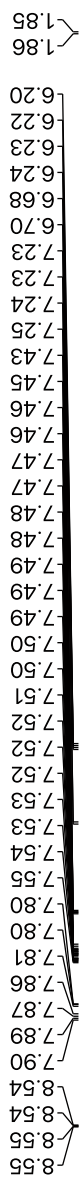
**Compound 2-59**
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

3.03
1.00
1.00
3.79
8.90
2.10
4.07
1.02

397

18.36

66.75

CDCl₃

120.51
123.31
127.90
128.34
128.49
128.71
129.57
130.47
131.90
133.58
134.19
137.23
149.31
155.75
157.15
157.32
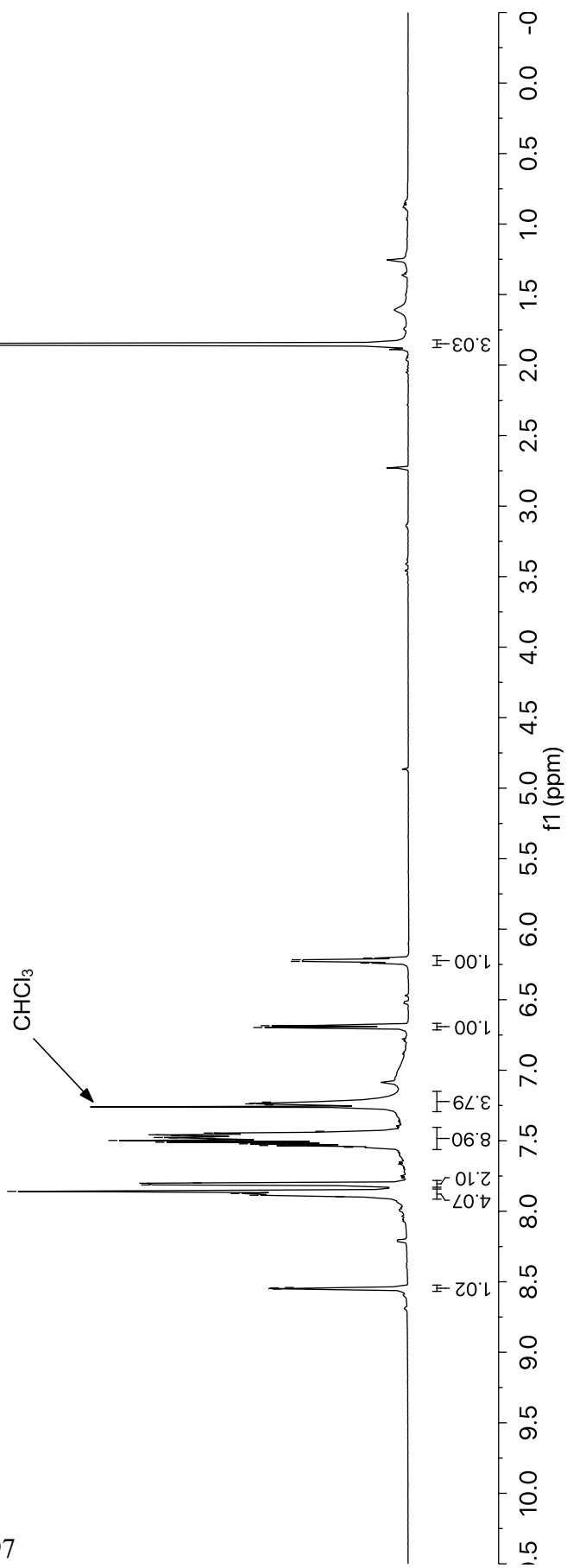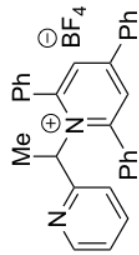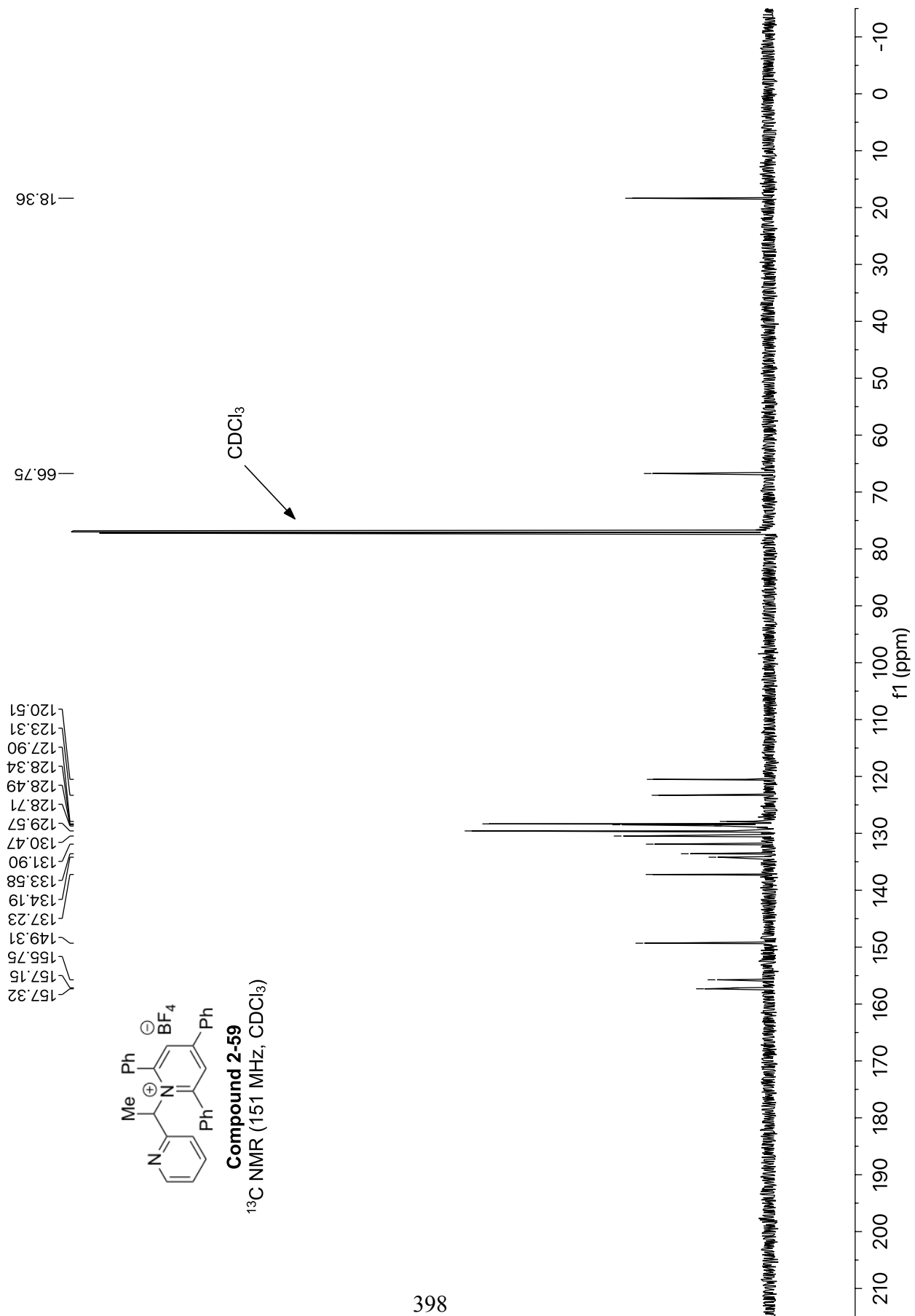
**Compound 2-59**
¹³C NMR (151 MHz, CDCl₃)

398
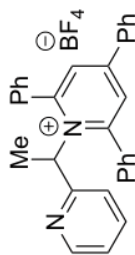
-153.31
-153.26

**Compound 2-59**
$^{19}$F NMR (565 MHz, CDCl$_3$)
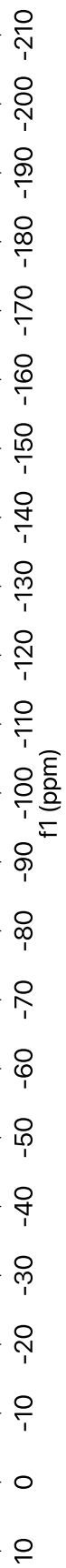
399
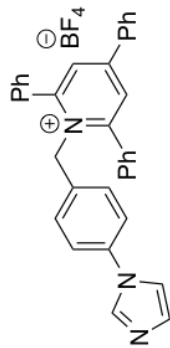
Compound 2-92
¹H NMR (600 MHz, CDCl₃)

400

−57.57

CDCl₃

117.79
121.27
126.76
128.07
128.20
129.10
129.35
129.86
130.81
131.23
132.56
132.65
133.17
133.70
135.24
137.11
156.74
157.55

**Compound 2-92**
¹³C NMR (151 MHz, CDCl₃)
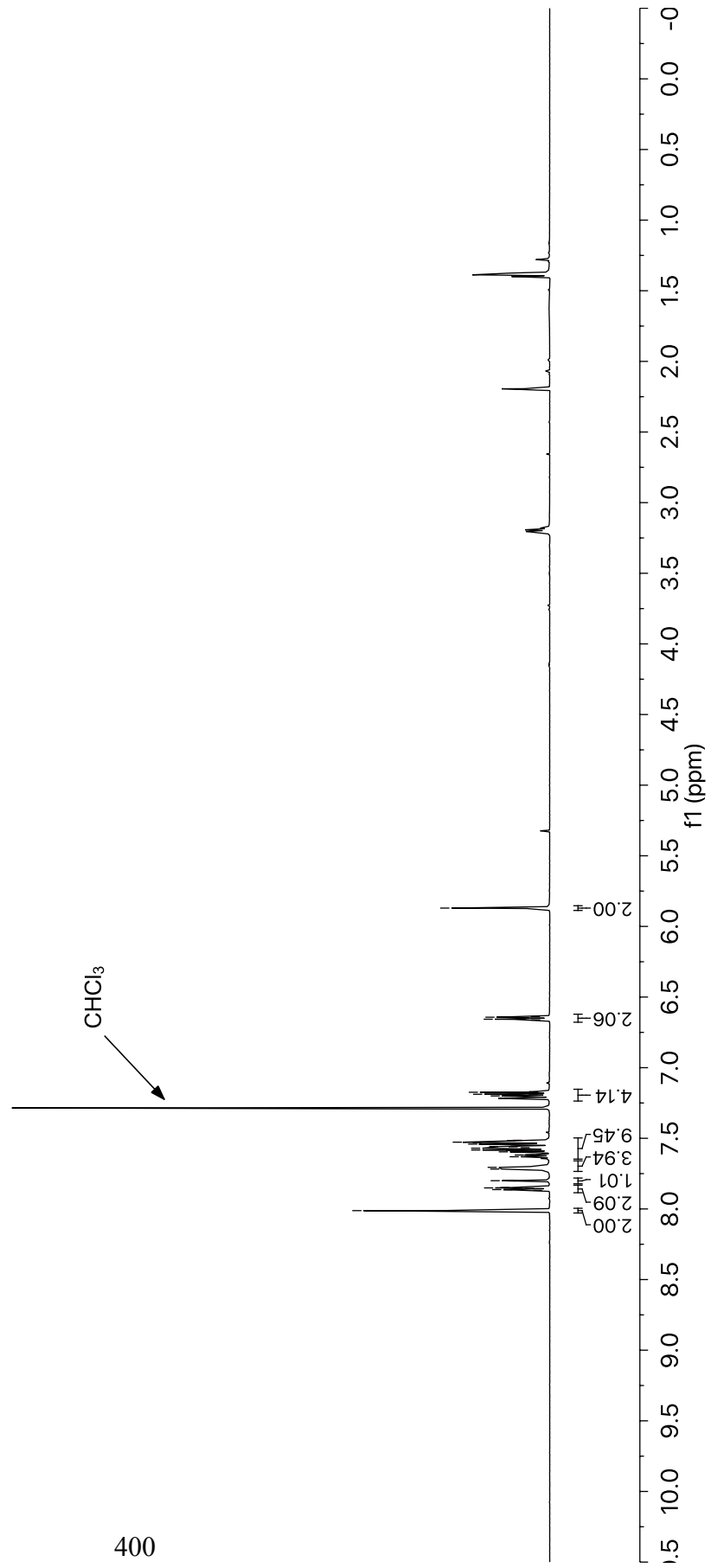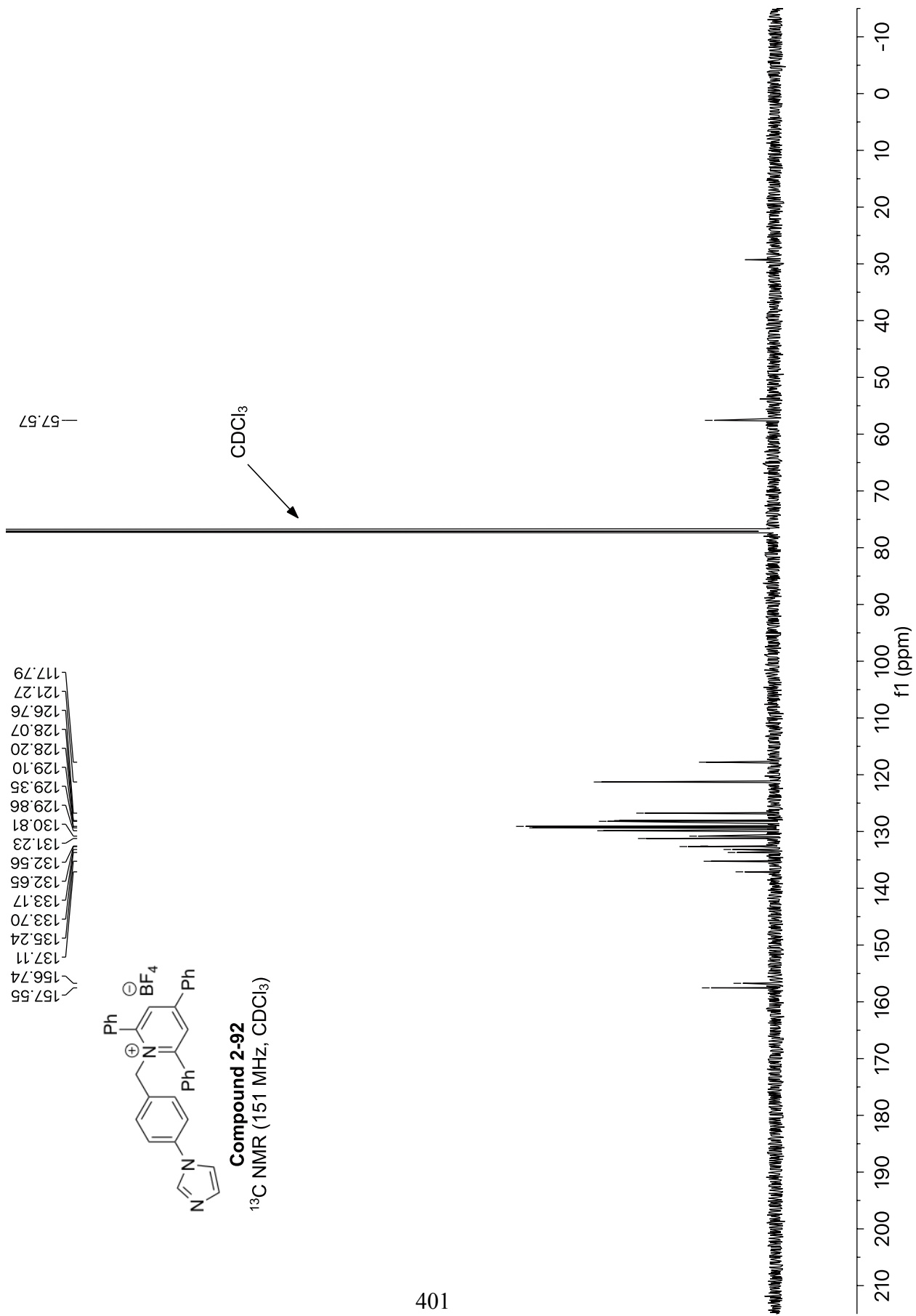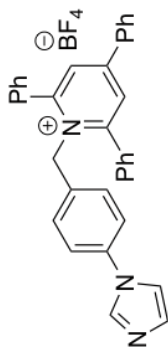
-152.45
-152.40

**Compound 2-92**
$^{19}$F NMR (565 MHz, CDCl$_3$)

Ph

⊕N

Ph

Ph

Ph

⊖BF$_4$

N

N

402

-210 -200 -190 -180 -170 -160 -150 -140 -130 -120 -110 -100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10
f1 (ppm)

5.80

6.45
6.45
6.45
6.56
6.58
7.46
7.47
7.47
7.48
7.48
7.50
7.51
7.52
7.53
7.55
7.55
7.56
7.67
7.69
7.69
7.81
7.81
7.83
7.83
7.85
7.85
7.97
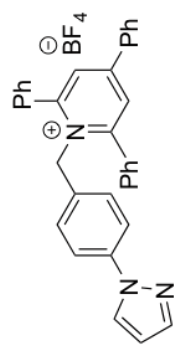
**Compound 2-54**
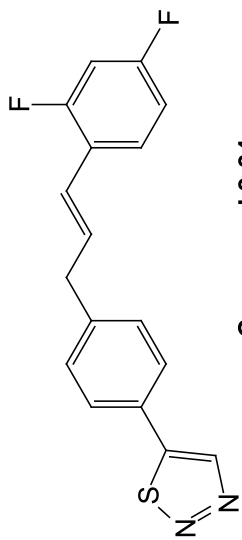¹H NMR (600 MHz, CDCl₃)

CHCl₃

2.00

1.04
2.06

11.40
4.99
2.31
1.06
2.13

403

57.73

CDCl₃

108.14

119.09
126.71
126.73
127.47
128.20
129.09
129.30
129.83
131.14
131.97
132.46
132.67
133.77
139.88
141.45
156.56
157.58

**Compound 2-54**
¹³C NMR (151 MHz, CDCl₃)

404
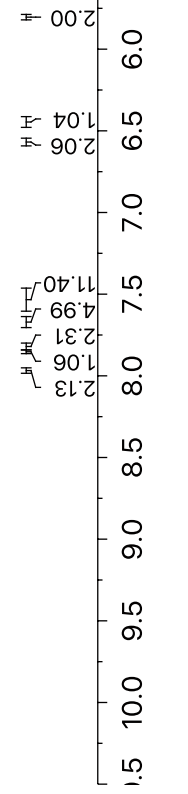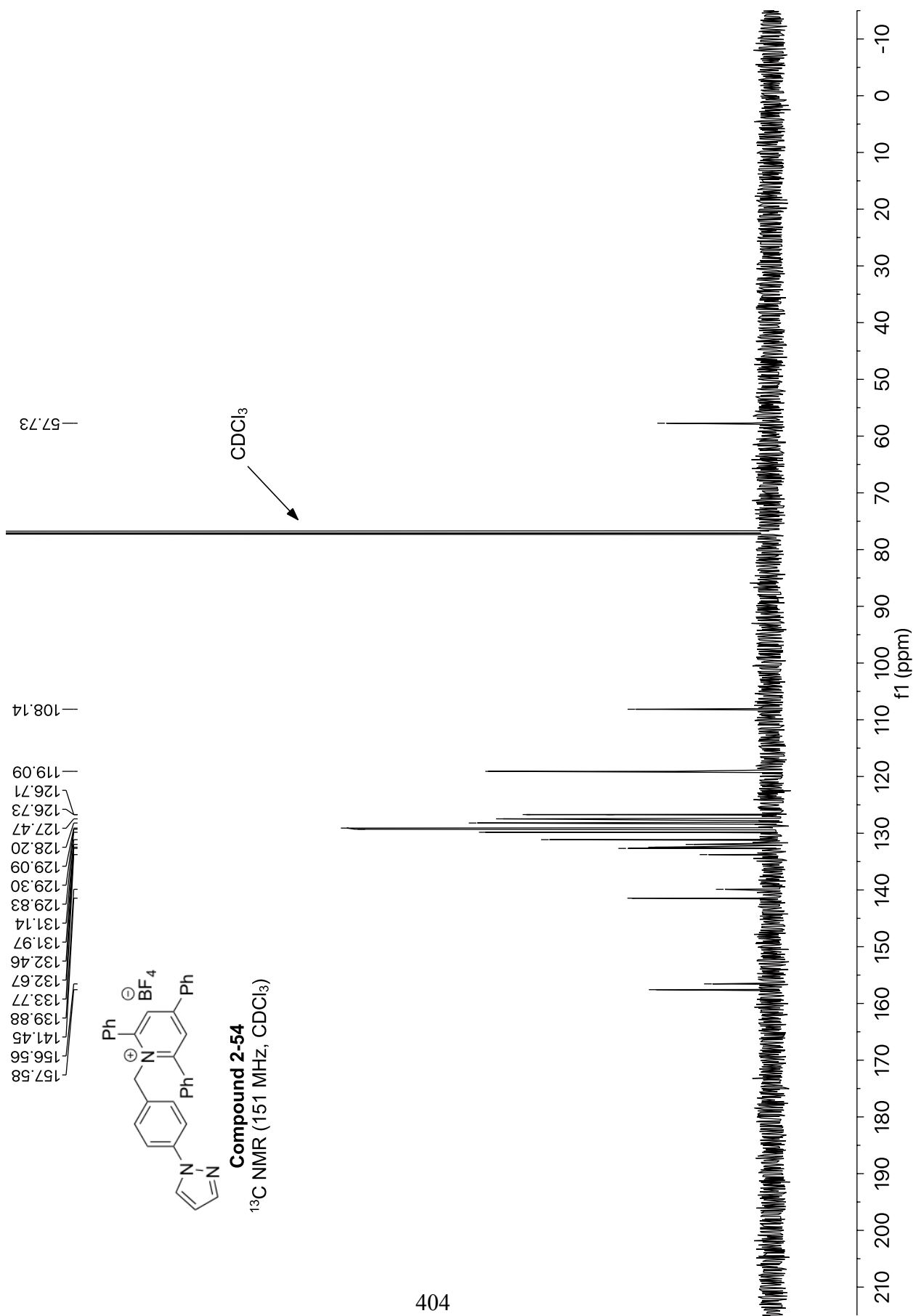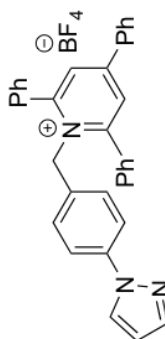
-152.89
-152.83

**Compound 2-54**
$^{19}$F NMR (565 MHz, CDCl$_3$)

f1 (ppm)

7.82
6.38
6.39
6.43
6.43
6.43
6.89
6.90
6.90
7.17
7.19
7.20
7.45
7.45
7.46
7.46
7.48
7.49
7.50
7.50
7.52
7.52
7.52
7.53
7.53
7.54
7.56
7.57
7.57
7.58
7.58
7.58
7.59
7.65
7.66
7.68
7.68
7.69
7.75
7.75
7.80
7.80
7.81
7.81
7.96

Compound 2-60
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

57.91
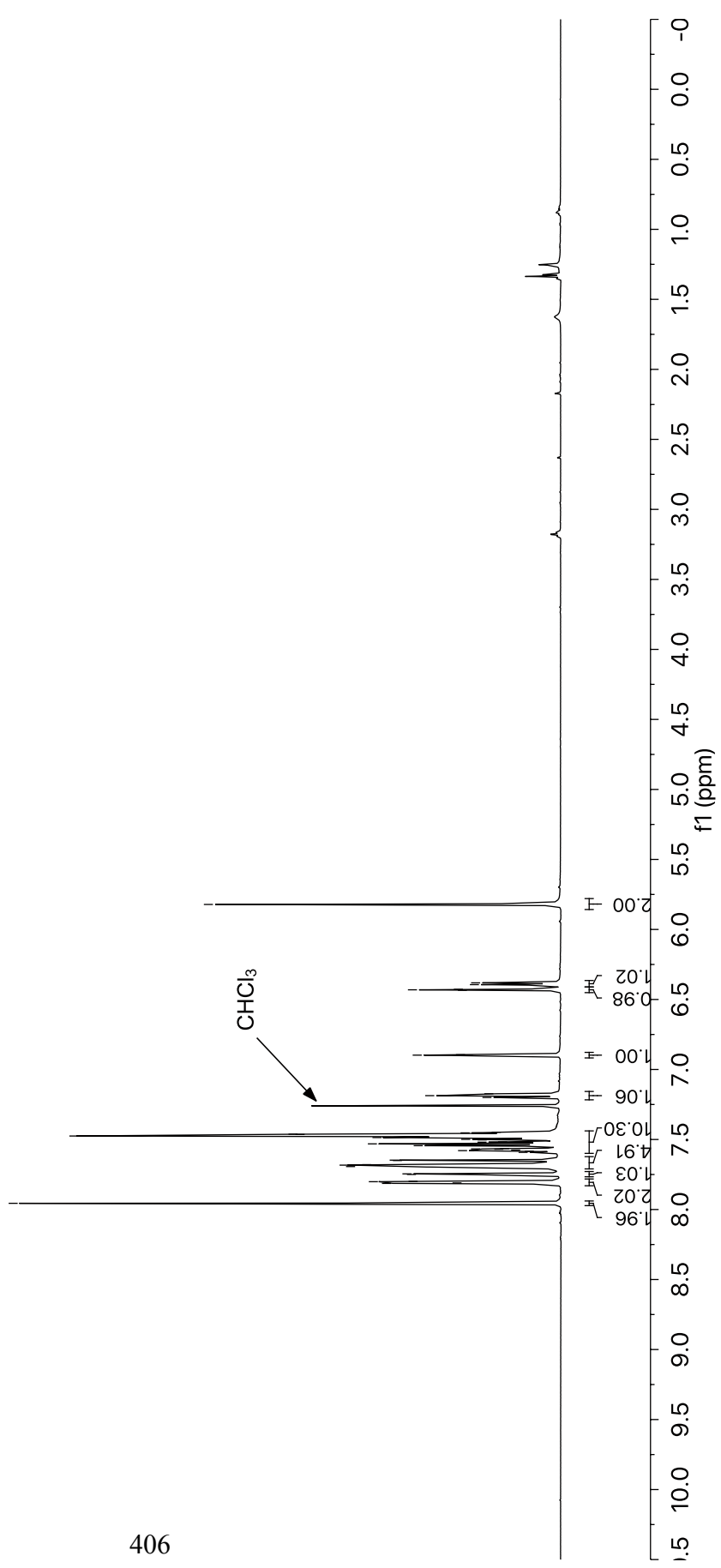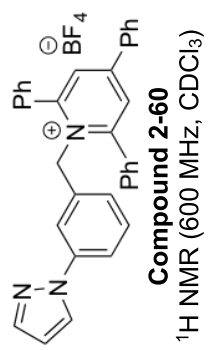
108.13
116.98
118.47
124.04
126.64
126.68
128.21
129.15
129.26
129.81
129.96
131.09
132.46
132.67
133.74
135.54
140.40
141.42
156.54
157.58
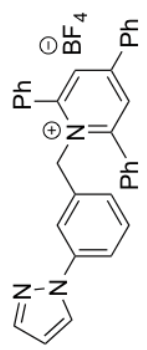
CDCl$_3$

**Compound 2-60**
$^{13}$C NMR (151 MHz, CDCl$_3$)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
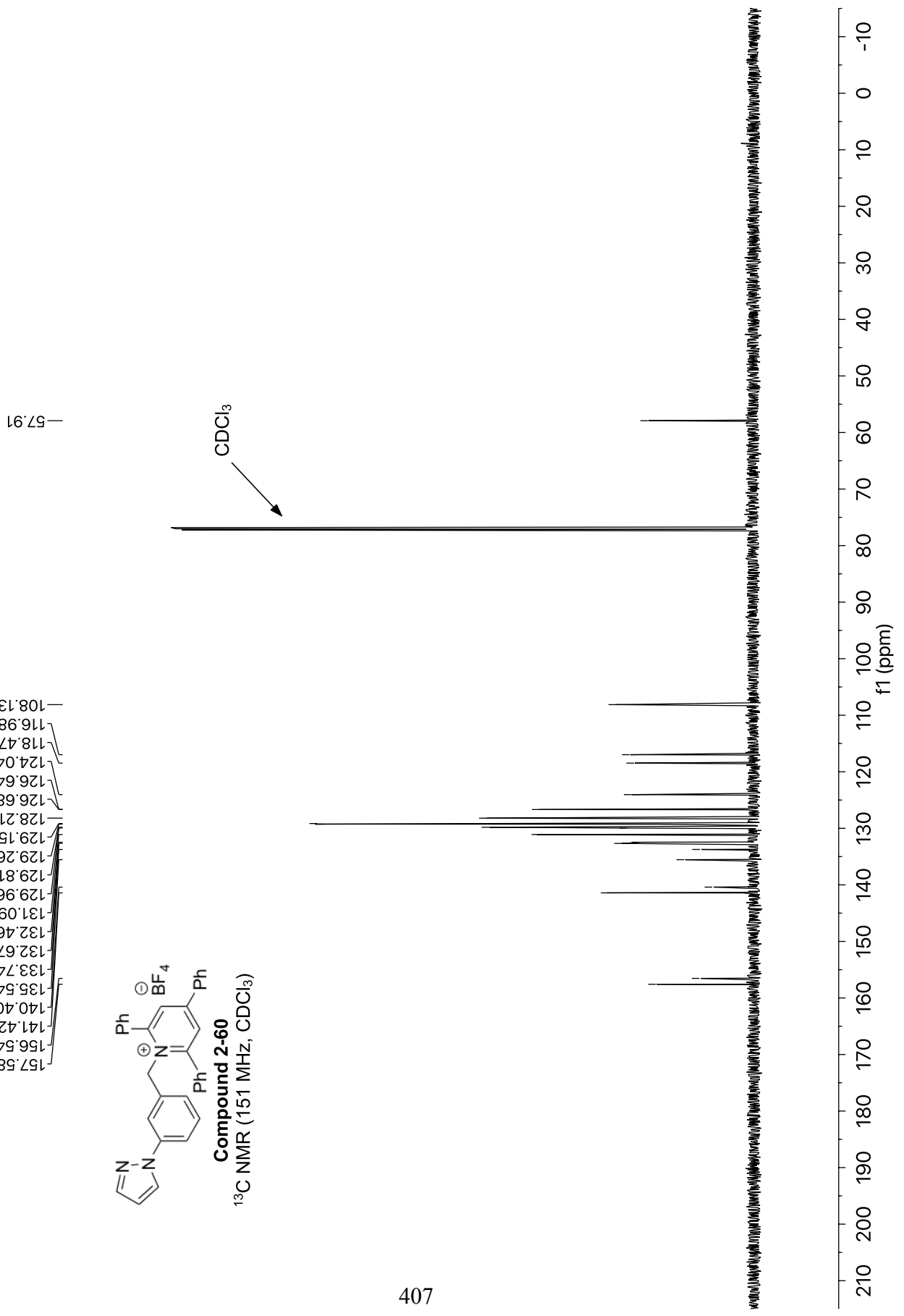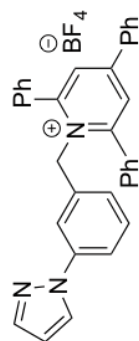
-152.80
-152.75

**Compound 2-60**
<sup>19</sup>F NMR (565 MHz, CDCl₃)

f1 (ppm)

Compound 2-61
$^1$H NMR (600 MHz, CDCl$_3$)

409

$^{13}C$ NMR (101 MHz, (CD$_3$)$_2$CO)

**Compound 2-61**

56.31

110.09
122.38
127.28
127.51
128.64
128.77
129.23
129.64
129.65
129.84
130.29
130.73
131.66
133.17
133.52
134.26
139.42
156.84
158.13

(CD$_3$)$_2$CO

(CD$_3$)$_2$CO

f1 (ppm)

410

-153.09
-153.04

Compound 2-61
19F NMR (565 MHz, CDCl₃)

411

-210 -200 -190 -180 -170 -160 -150 -140 -130 -120 -110 -100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10
f1 (ppm)
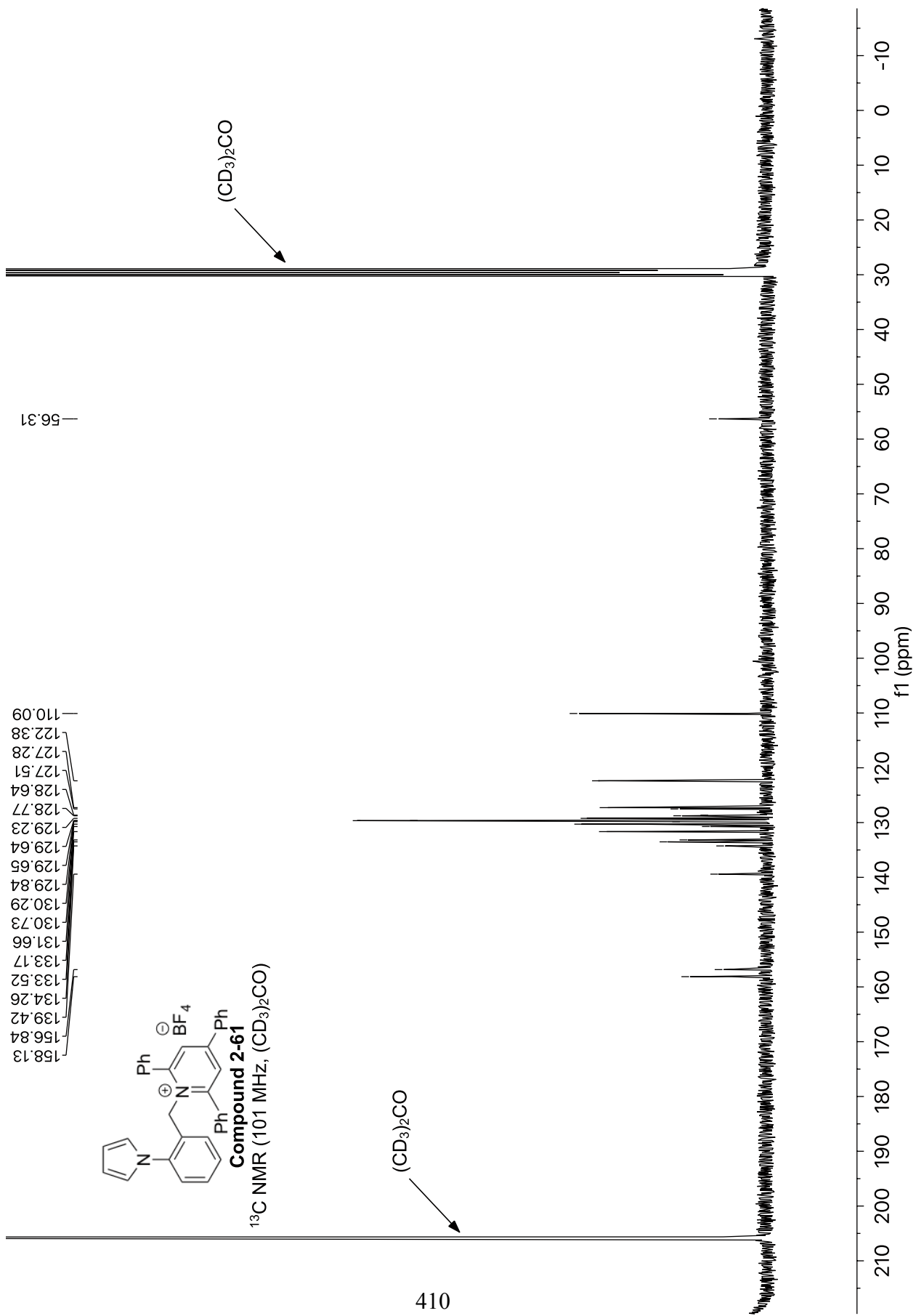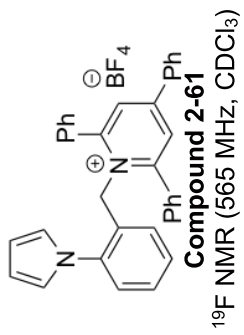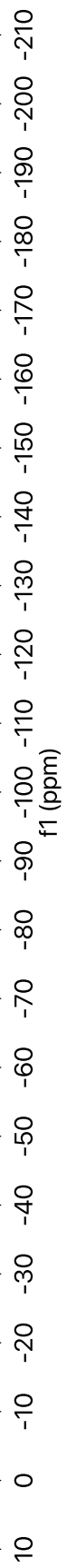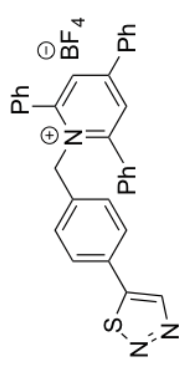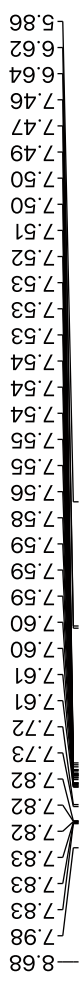
**Compound 2-62**
¹H NMR (600 MHz, CDCl₃)

CHCl₃

5.86
6.62
6.64
7.46
7.47
7.49
7.50
7.50
7.51
7.52
7.53
7.53
7.53
7.54
7.54
7.54
7.55
7.55
7.56
7.58
7.59
7.59
7.59
7.60
7.60
7.61
7.61
7.72
7.73
7.73
7.82
7.82
7.82
7.82
7.83
7.83
7.83
7.98
8.68

58.08

CDCl₃

126.67
127.05
127.72
128.20
129.15
129.28
129.85
130.85
130.89
131.15
132.51
132.67
133.72
135.14
156.56
157.63
161.57
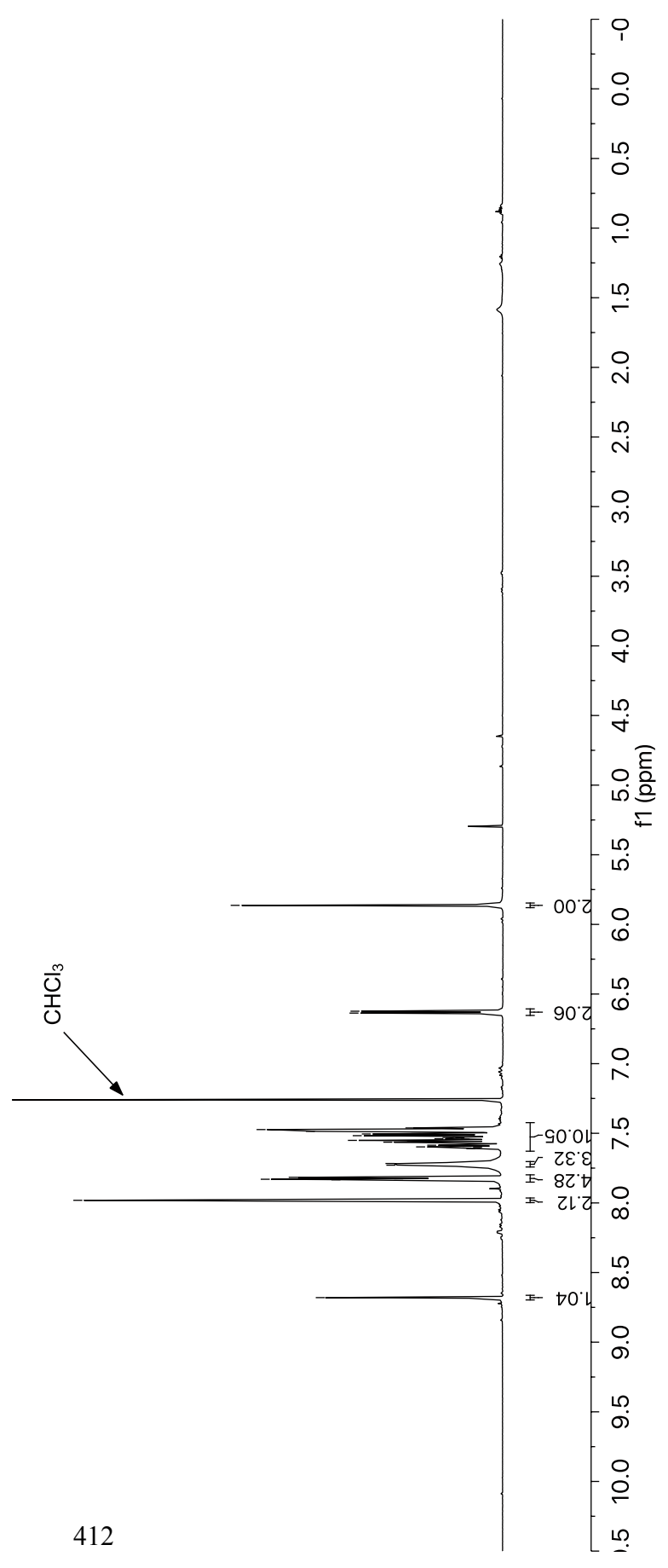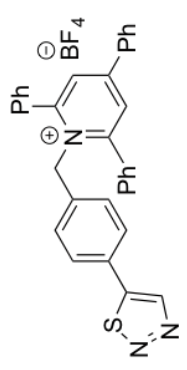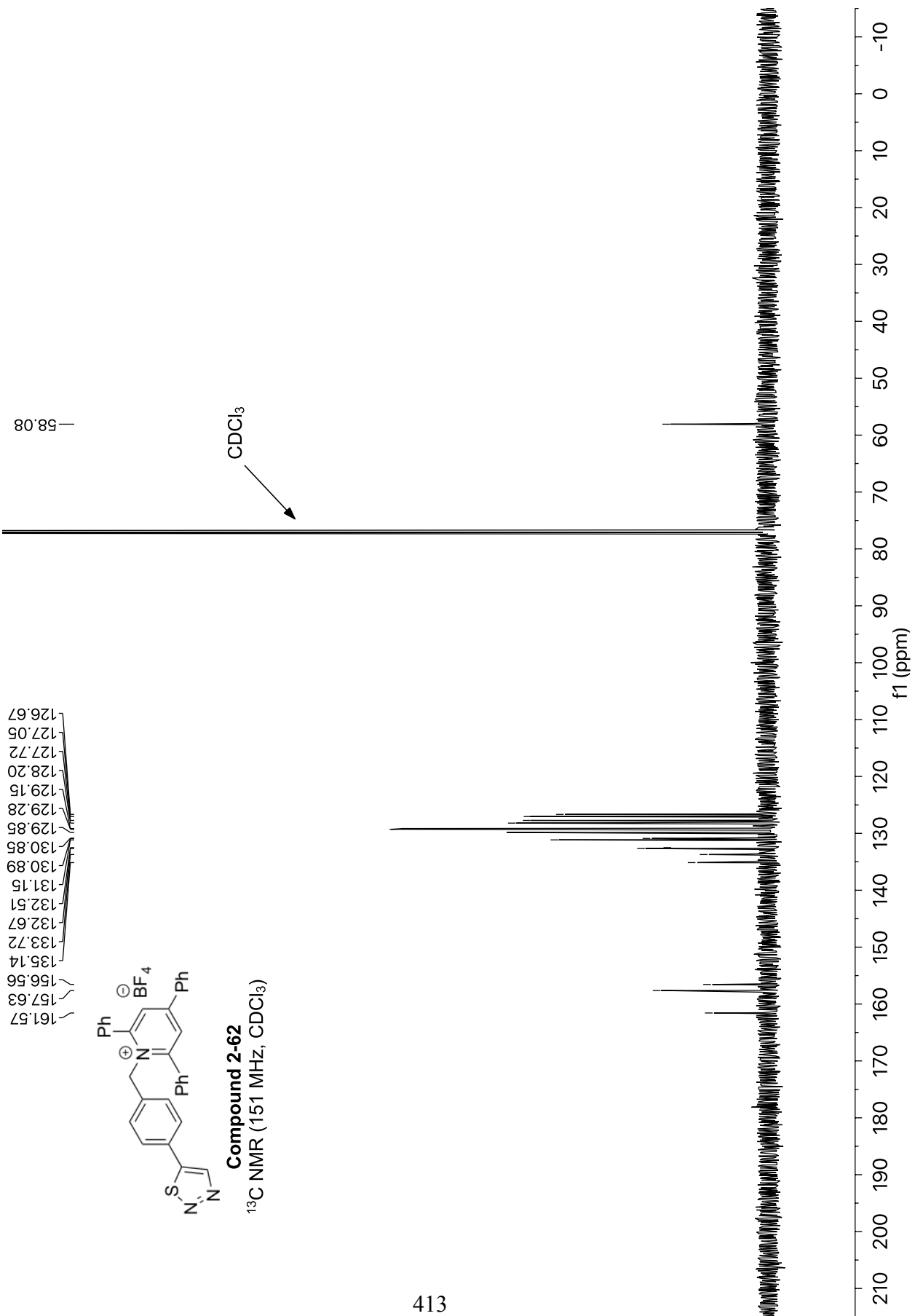
**Compound 2-62**
¹³C NMR (151 MHz, CDCl₃)

413
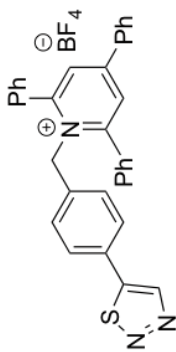
-152.86
-152.81

Compound 2-62
$^{19}$F NMR (565 MHz, CDCl$_3$)

414

Compound 2-93
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

415

57.93

CDCl₃

122.28
124.61
126.68
126.93
127.73
128.18
129.08
129.28
129.84
131.13
132.48
132.66
133.77
134.47
150.41
150.72
156.57
157.61

Ph
Ph
BF₄⁻
⊕
N
Ph
O
N

**Compound 2-93**
¹³C NMR (151 MHz, CDCl₃)



416

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
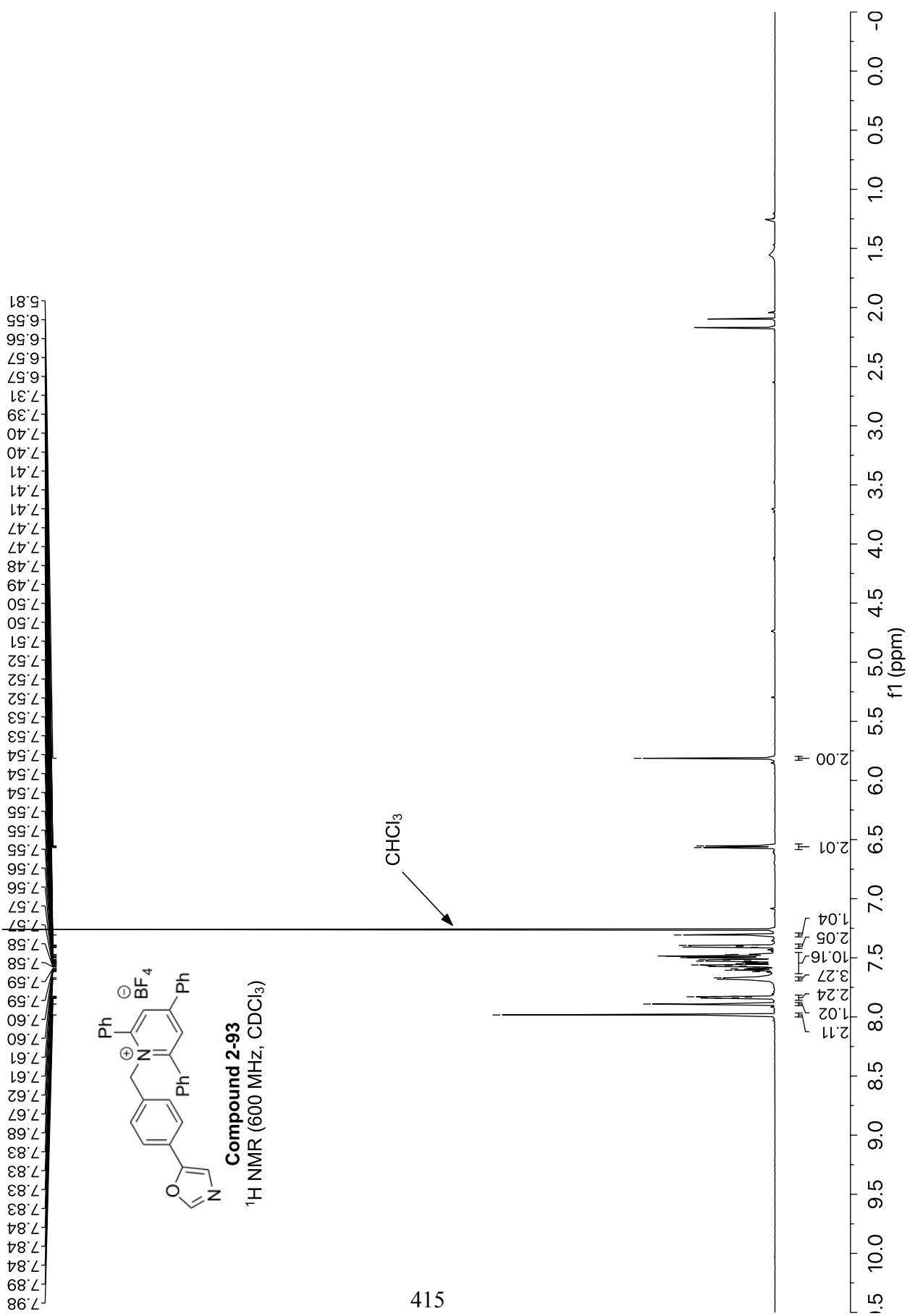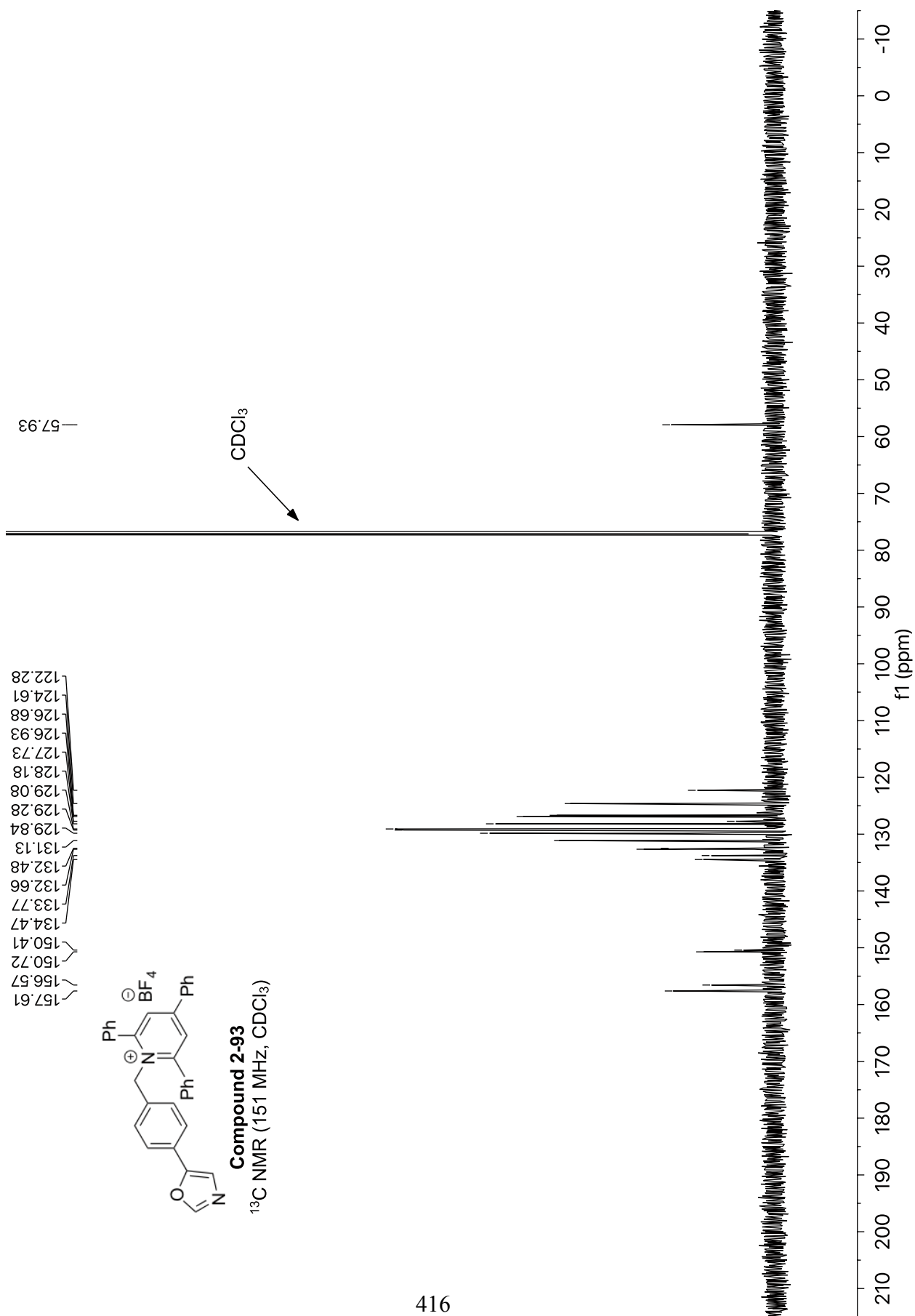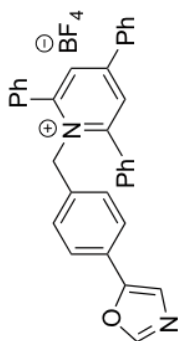
-153.07
-153.01

**Compound 2-93**
19F NMR (565 MHz, CDCl₃)

f1 (ppm)

Compound 2-94
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

418

Compound 2-94
$^{13}$C NMR (151 MHz, (CD$_3$)$_2$CO)

—16.01

—58.86

(CD$_3$)$_2$CO

127.42
127.72
129.31
129.76
129.90
129.98
130.38
131.71
132.58
132.60
133.22
133.93
134.39
134.70
149.50
151.53
156.94
158.18

(CD$_3$)$_2$CO

f1 (ppm)

419
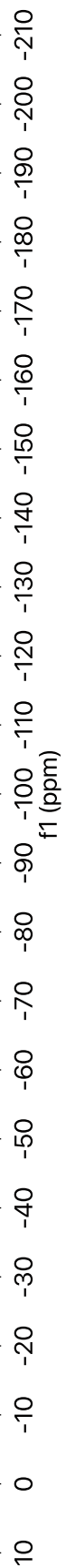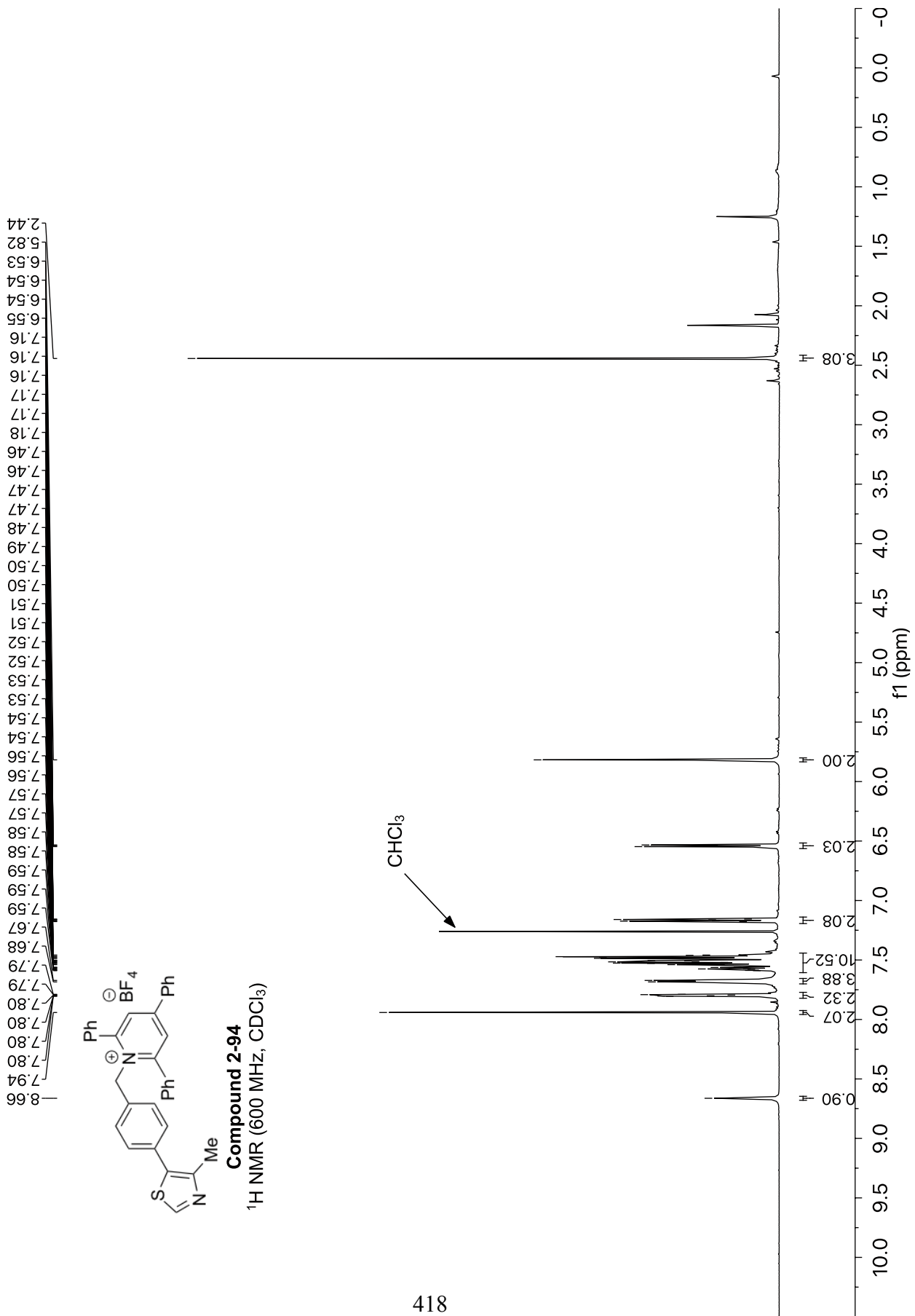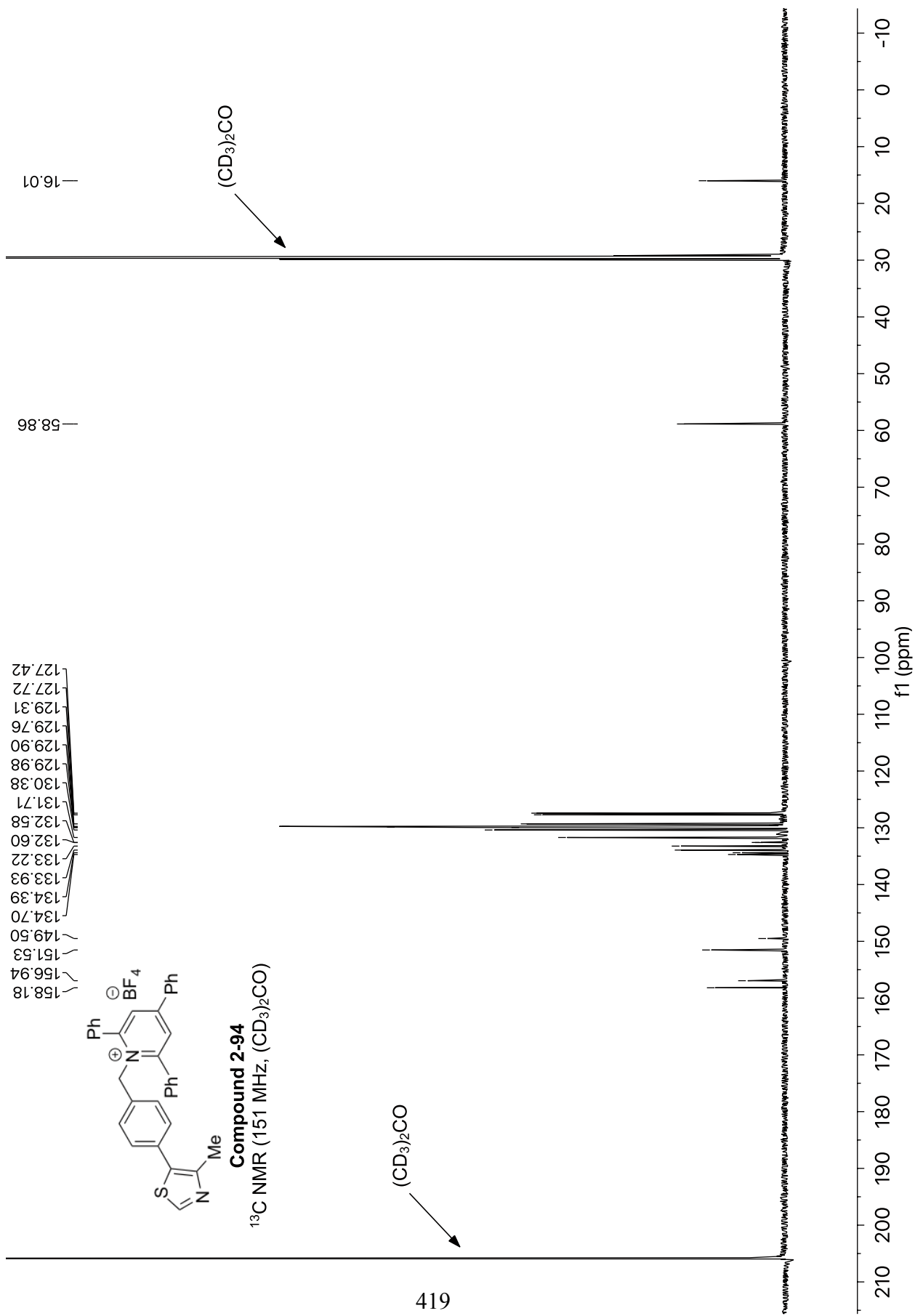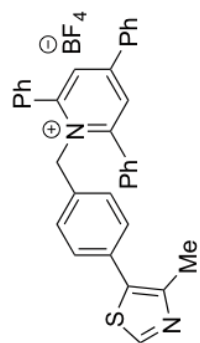
-152.89
-152.84

**Compound 2-94**
$^{19}F$ NMR (565 MHz, CDCl$_3$)

420

f1 (ppm)
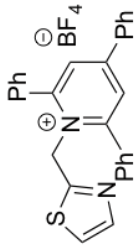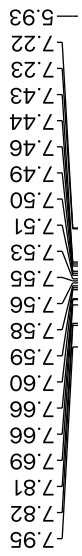
**Compound 2-63**
$^{1}$H NMR (600 MHz, CDCl$_3$)

5.93
7.22
7.23
7.43
7.44
7.46
7.49
7.50
7.51
7.53
7.55
7.56
7.58
7.59
7.60
7.66
7.66
7.69
7.81
7.82
7.95

CHCl$_3$

2.00
1.13
10.44
4.23
2.23
2.10

55.45

CDCl₃

121.18
126.17
128.16
128.87
129.04
129.79
131.00
132.38
132.59
133.86
142.38

156.41
157.33
162.14

**Compound 2-63**
¹³C NMR (101 MHz, CDCl₃)
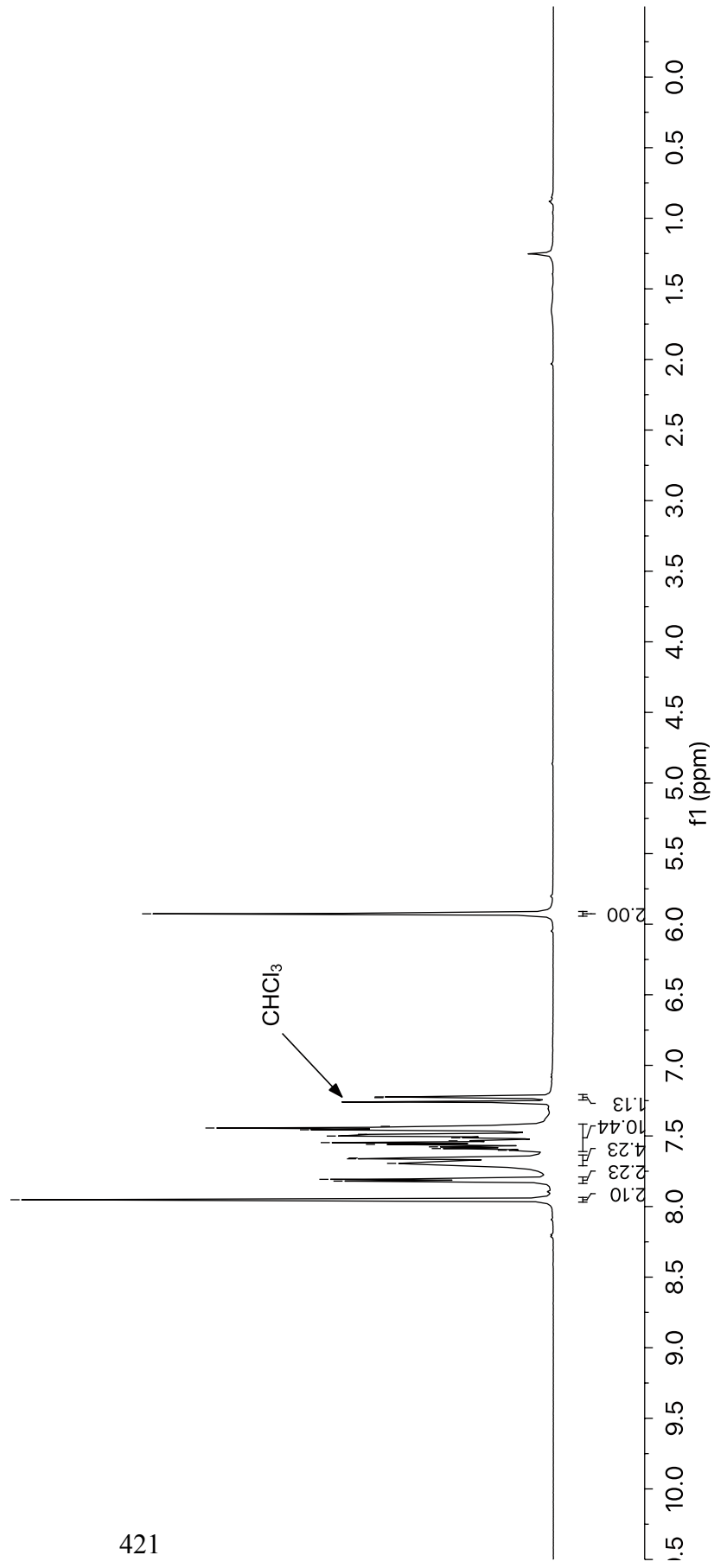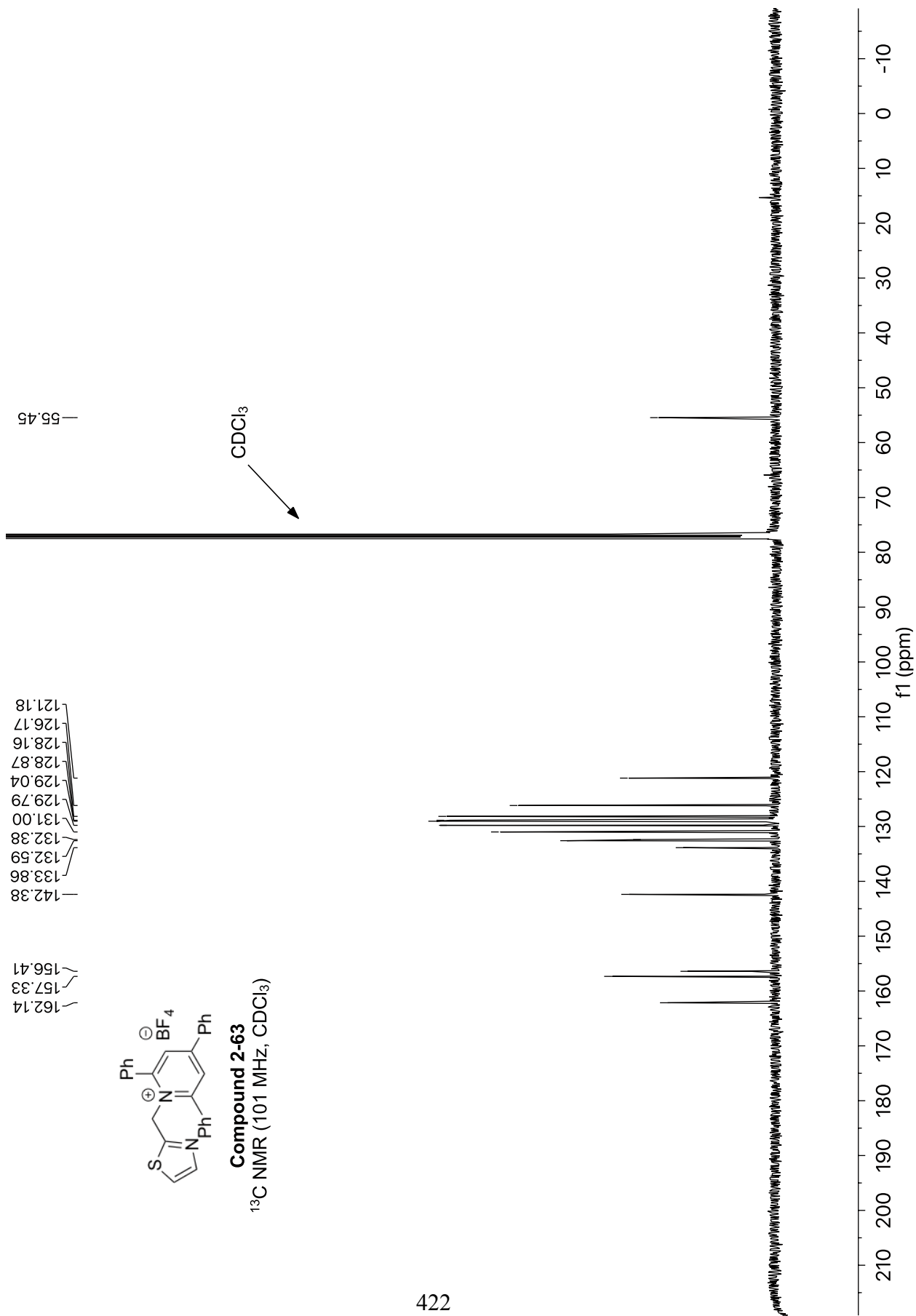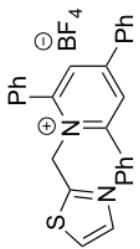
−153.29
−153.23

**Compound 2-63**
$^{19}$F NMR (565 MHz, CDCl$_3$)

f1 (ppm)

423

7.91
7.79
7.78
7.73
7.72
7.59
7.58
7.58
7.57
7.57
7.56
7.55
7.54
7.53
7.53
7.52
7.52
7.23
6.10
6.09
6.09
5.71
5.35
5.34

Ph

Ph

N⁺

BF₄⁻

Ph

Ph

O

**Compound 2-64**
¹H NMR (600 MHz, CDCl₃)
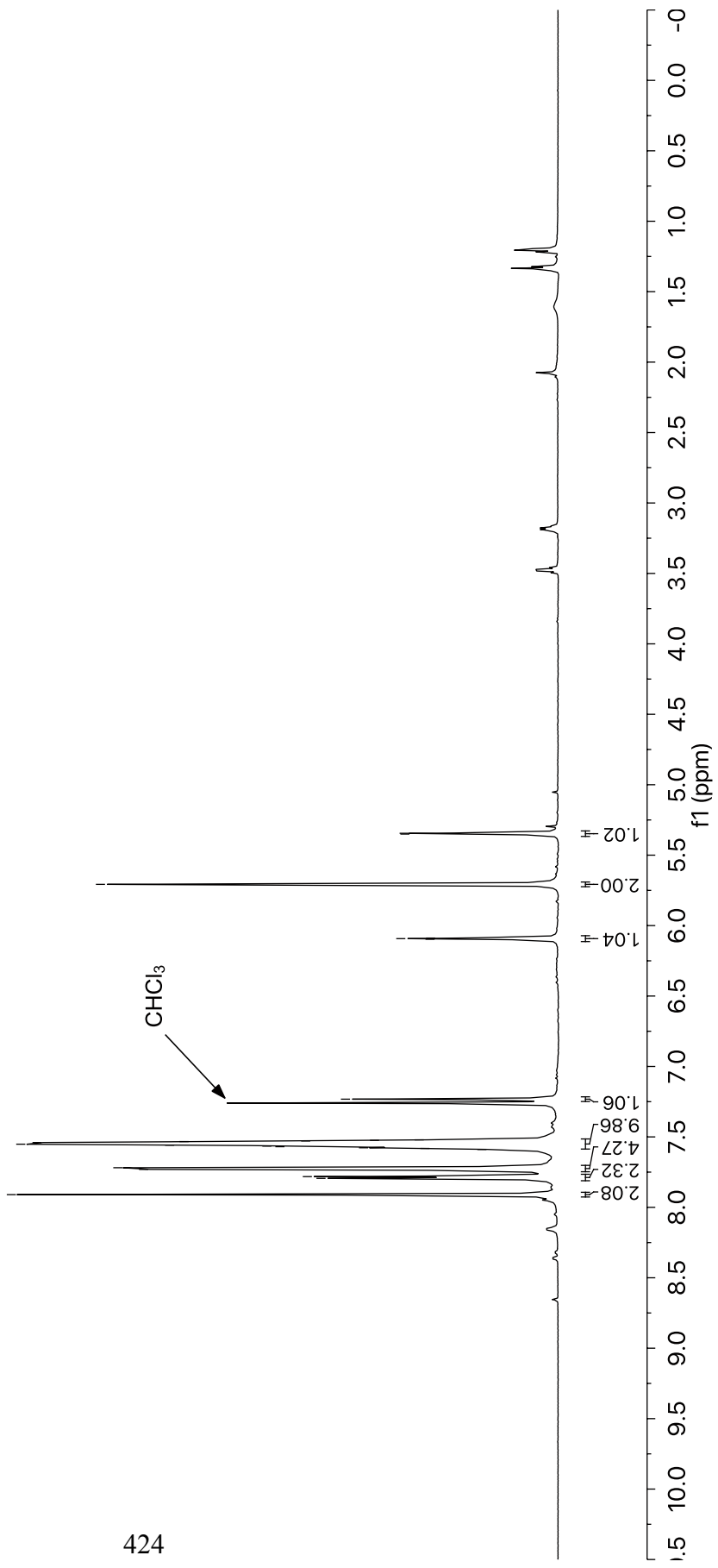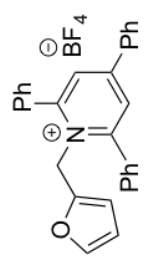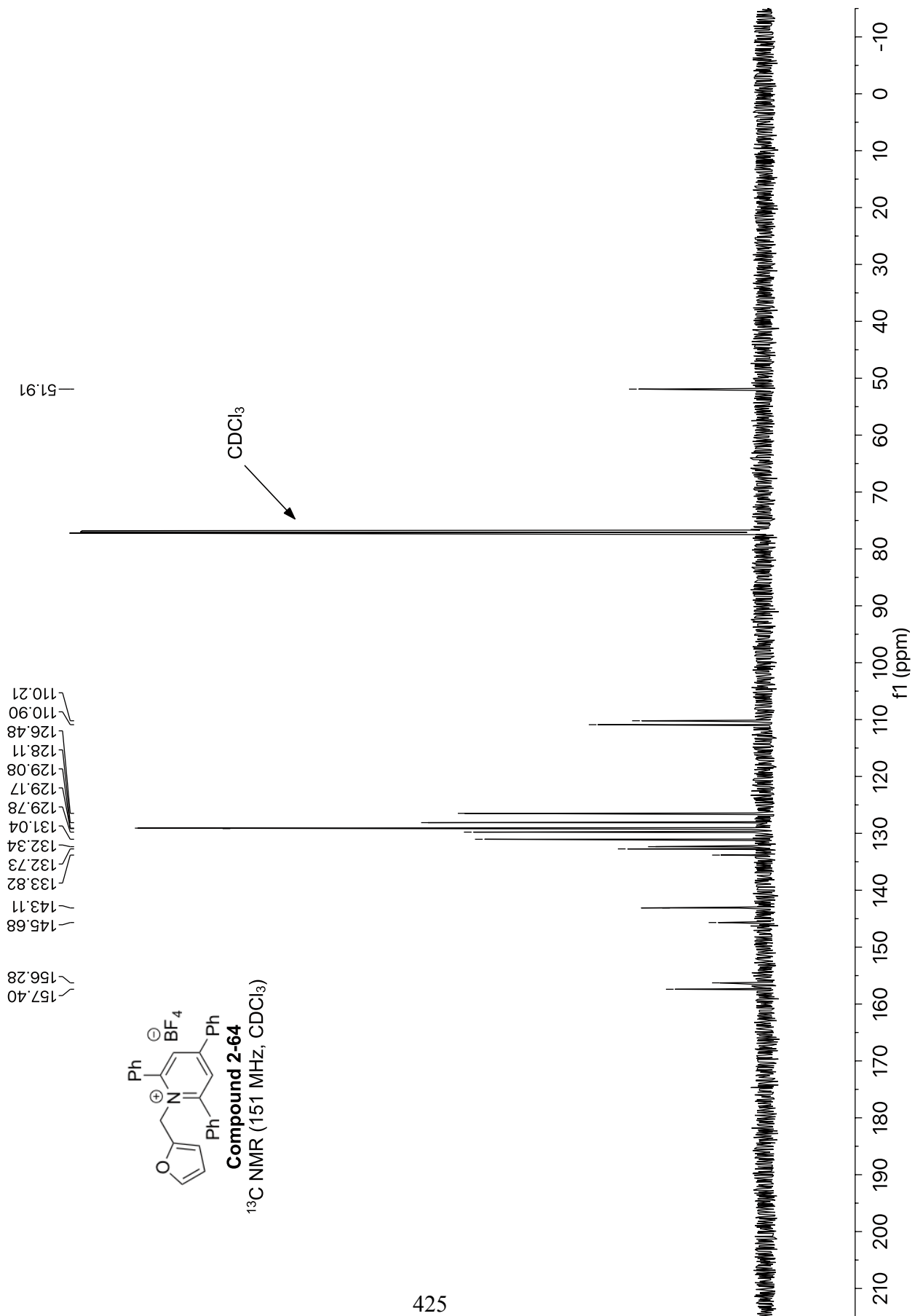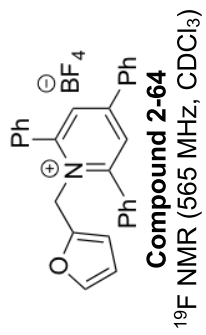
CHCl₃

1.02
2.00
1.04
1.06
9.86
4.27
2.32
2.08

10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  -0.5
f1 (ppm)

424

Compound 2-64
$^{13}$C NMR (151 MHz, CDCl$_3$)

51.91

110.21
110.90
126.48
128.11
129.08
129.17
129.78
131.04
132.34
132.73
133.82
143.11
145.68
156.28
157.40

CDCl$_3$

425

-153.03
-152.98

Compound 2-64
$^{19}$F NMR (565 MHz, CDCl$_3$)

f1 (ppm)

**Appendix C**

**SPECTRAL AND CHROMATOGRAPHY DATA FOR CHAPTER 3**
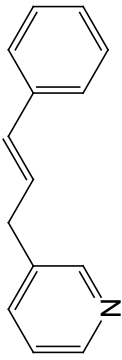
**Compound 3-22**
$^1$H NMR (600 MHz, CDCl$_3$)

428
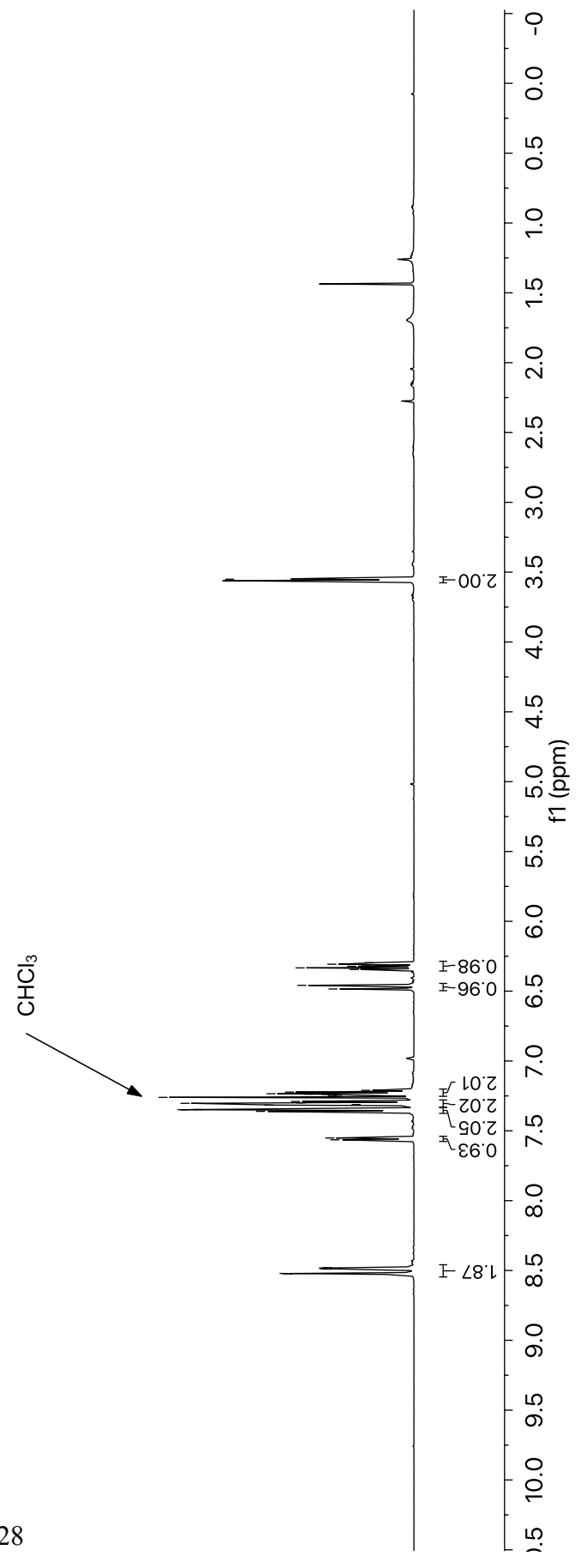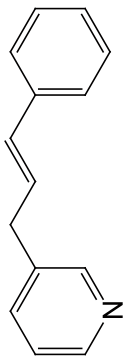
**Compound 3-22**
$^{13}$C NMR (151 MHz, CDCl$_3$)

36.55

123.54
126.31
127.55
127.93
128.71
132.14
135.61
136.26
137.21
147.94
150.28

CDCl$_3$

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

429

3.70
3.70
3.71
3.71
6.28
6.29
6.30
6.30
6.31
6.33
6.53
6.56
7.10
7.10
7.11
7.11
7.12
7.13
7.13
7.13
7.13
7.14
7.14
7.20
7.20
7.20
7.21
7.21
7.21
7.22
7.22
7.22
7.23
7.24
7.24
7.25
7.60
7.60
7.61
7.61
7.62
7.63
8.55
8.55
8.55
8.55
8.56
8.56
8.56
8.56
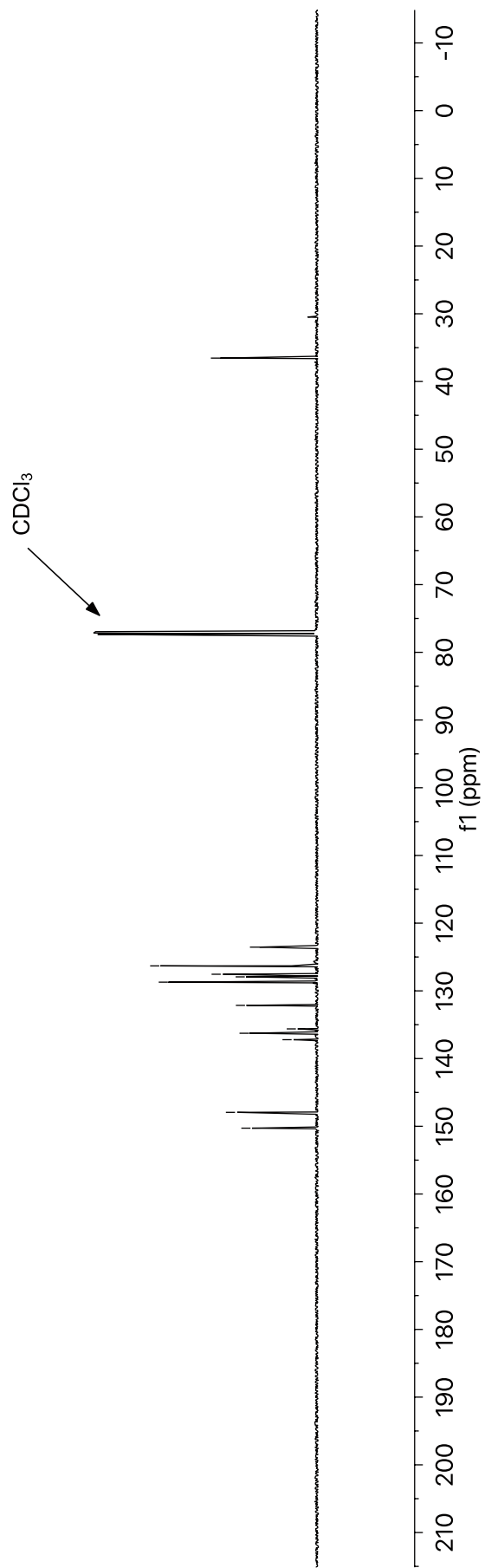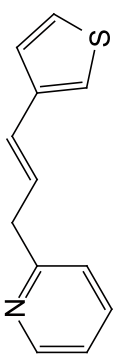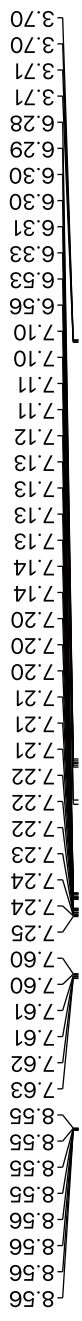
**Compound 3-26**
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

2.01
0.97
0.97
1.87
2.87
0.96
0.91

f1 (ppm)
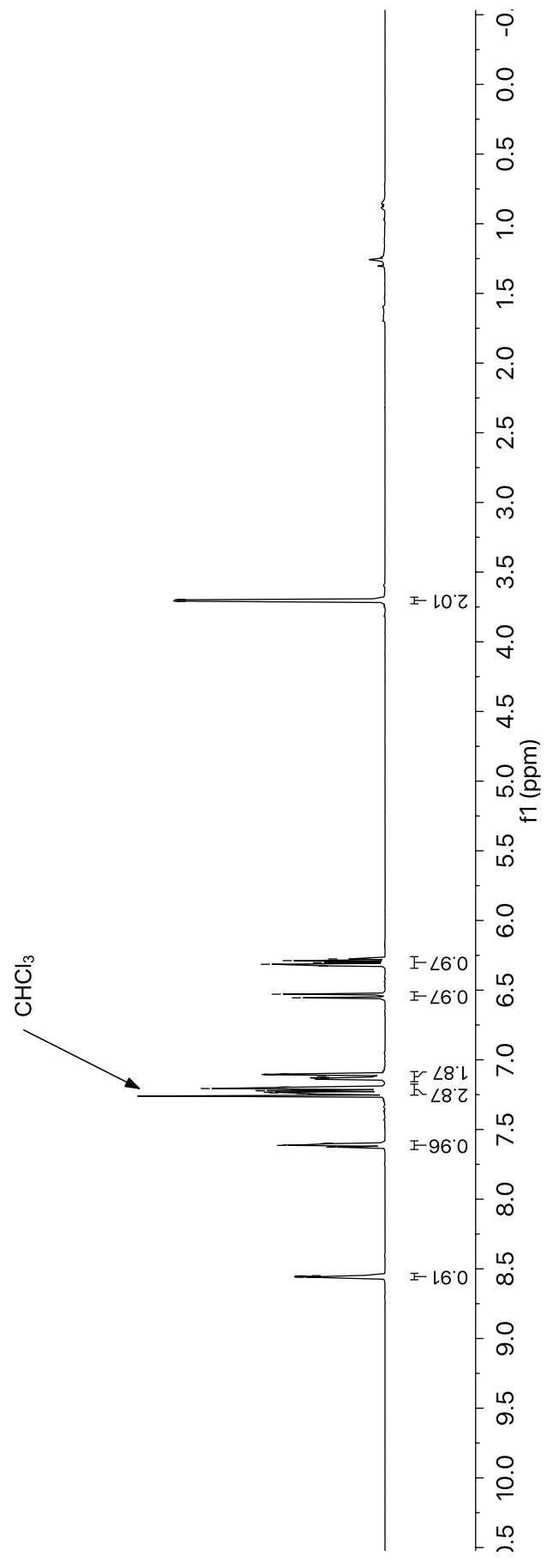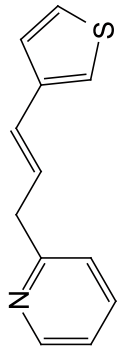
Compound 3-26
$^{13}$C NMR (151 MHz, CDCl$_3$)

160.39
149.61
140.10
136.67
127.55
126.34
125.97
125.17
122.98
121.46
121.44

42.14

CDCl$_3$

f1 (ppm)

431

1.53
1.54
1.54
1.55
1.55
1.55
1.56
1.56
1.56
1.57
1.57
1.57
1.58
1.58
1.59
1.59
1.59
1.60
1.60
1.61
1.61
1.82
1.82
1.83
1.83
1.84
1.84
2.02
2.02
2.02
2.03
2.03
2.03
2.04
2.04
2.04
2.05
3.22
5.49
5.50
5.50
5.50
5.51
5.51
5.51

7.10
7.10
7.10
7.11

8.48
8.48
8.49
8.49

**Compound 3-27**
$^1$H NMR (600 MHz, CDCl$_3$)

CHCl$_3$

4.19
2.02
2.05
1.98
0.96
1.92
1.88

f1 (ppm)

432

22.39
22.96
25.47
28.21

44.13

124.44
124.60

135.55
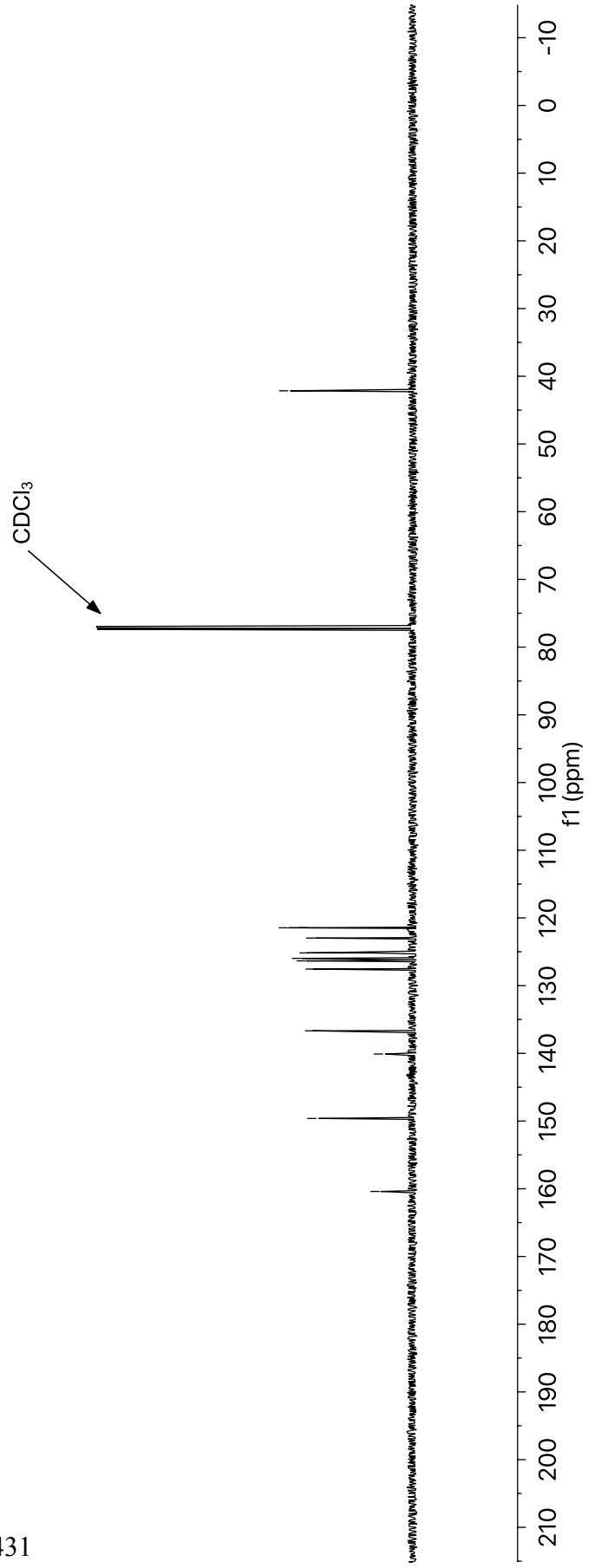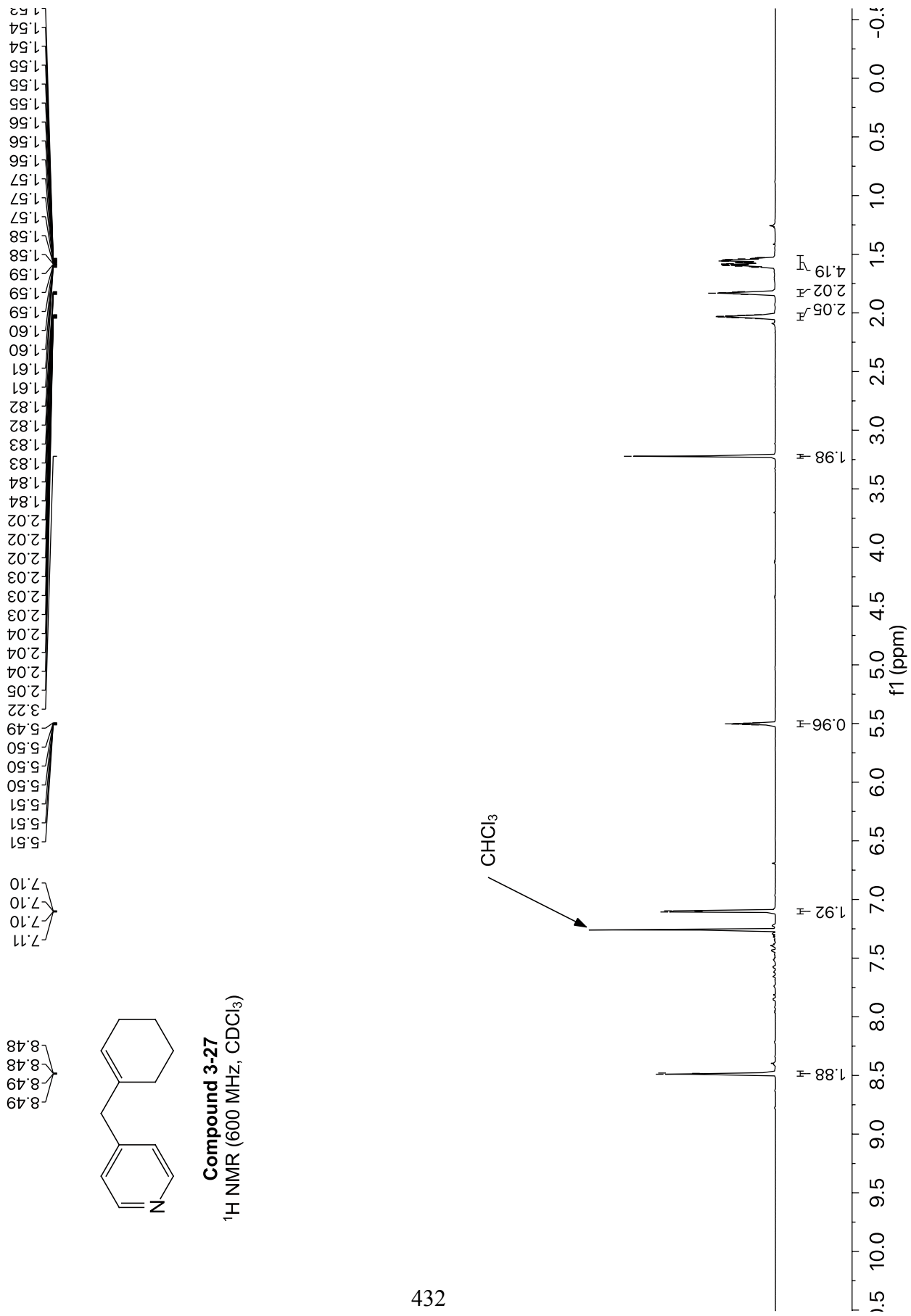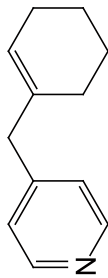
149.67
149.75

CDCl₃

**Compound 3-27**
¹³C NMR (151 MHz, CDCl₃)

f1 (ppm)

433

Compound 3-28
¹H NMR (600 MHz, CDCl₃)
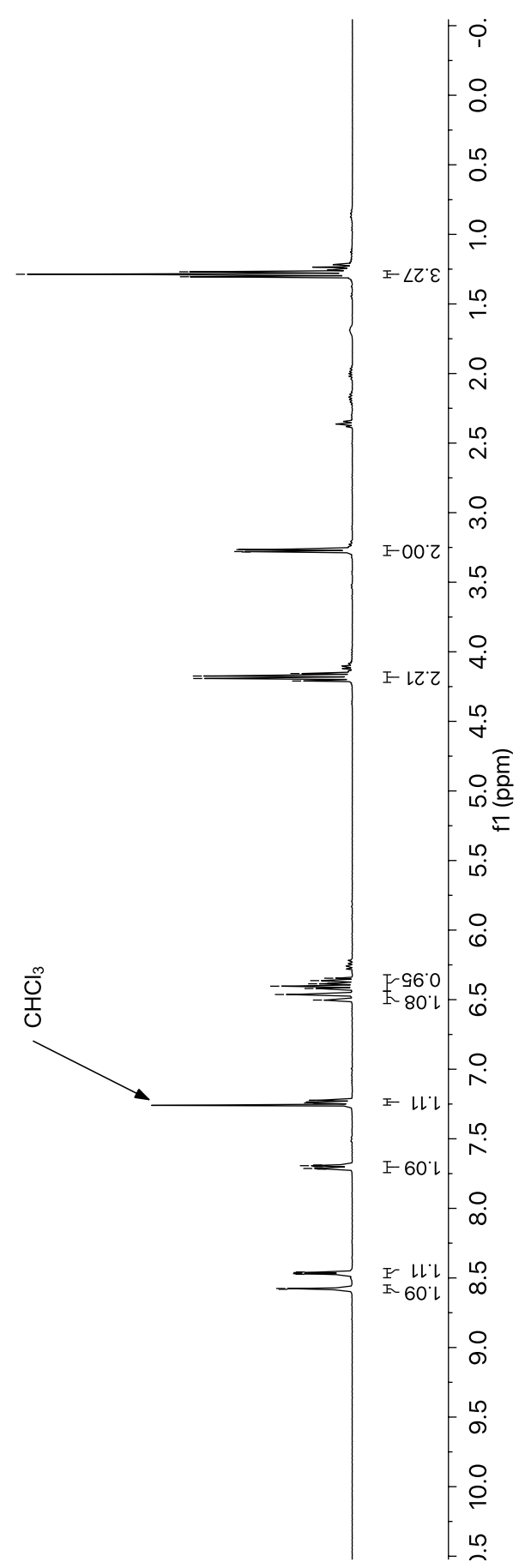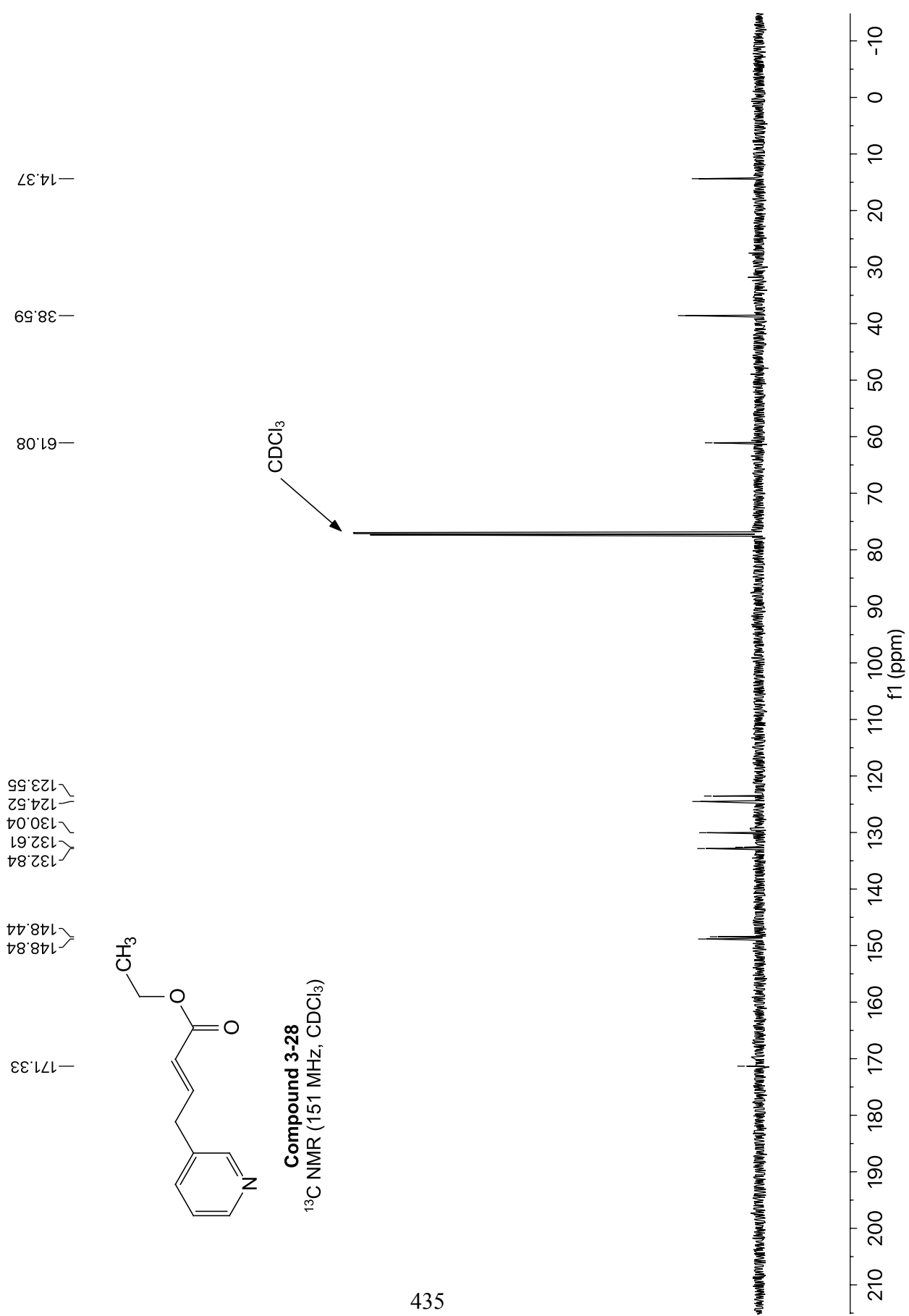
1.27
1.29
1.30

3.26
3.27
3.28
3.28

4.16
4.17
4.19
4.21

6.35
6.36
6.38
6.39
6.40
6.42
6.46
6.50

7.22
7.22
7.23
7.24

7.69
7.69
7.70
7.71
7.71
7.72

8.46
8.46
8.47
8.47
8.58
8.58

CHCl₃

3.27
2.00
2.21
0.95
1.08
1.11
1.09
1.11
1.09

**Compound 3-28**
$^{13}$C NMR (151 MHz, CDCl$_3$)

14.37

38.59

61.08

CDCl$_3$

123.55
124.52
130.04
132.61
132.84

148.44
148.84

171.33

435
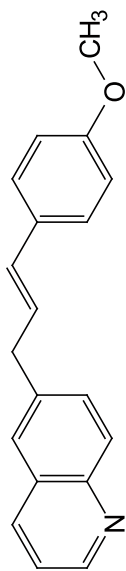
**Compound 3-29**
$^1$H NMR (600 MHz, CDCl$_3$)

436
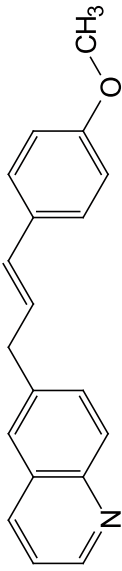
**Compound 3-29**
$^{13}$C NMR (151 MHz, CDCl$_3$)

39.37
55.46

114.15
121.29
126.39
126.57
127.45
128.55
129.65
130.26
131.26
131.31
135.75
139.05
147.49
150.02
159.17

CDCl$_3$

f1 (ppm)

437
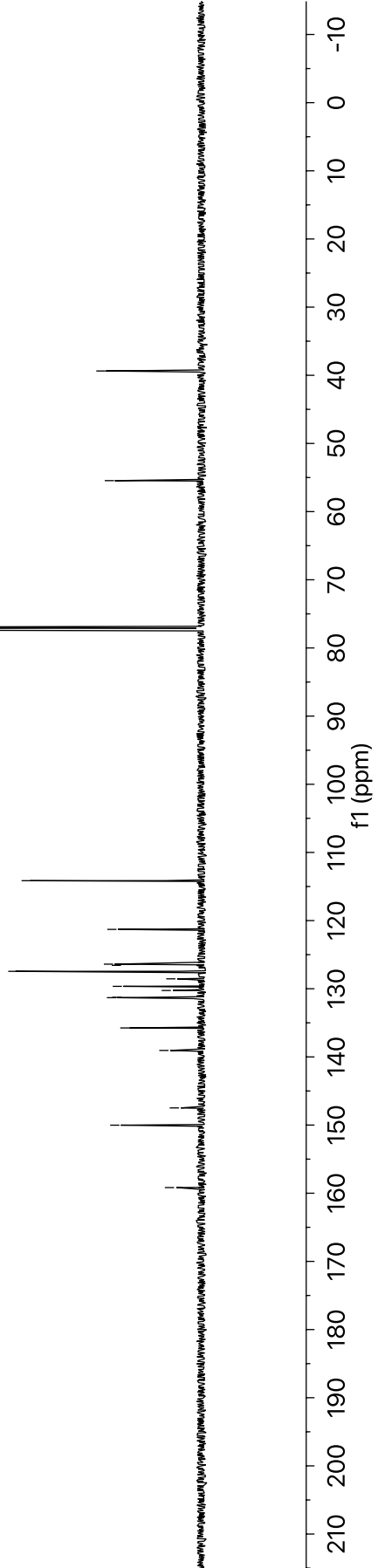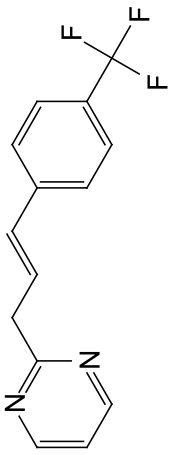
**Compound 3-30a**
¹H NMR (600 MHz, CDCl₃)

3.93
3.95

6.60
6.63
6.65
6.66
6.68
6.69
6.69
6.70
7.16
7.17
7.18
7.47
7.48
7.53
7.54

8.71
8.71

CHCl₃

2.08
2.03
0.98
2.07
2.01
1.86

438

Compound 3-30a
$^{13}$C NMR (151 MHz, CDCl$_3$)

43.38

CDCl$_3$

119.03
121.81
123.49
125.29
125.53
125.56
125.59
125.61
126.57
127.09
128.92
129.08
129.13
129.35
129.56
131.20
140.89
157.52
169.36

439
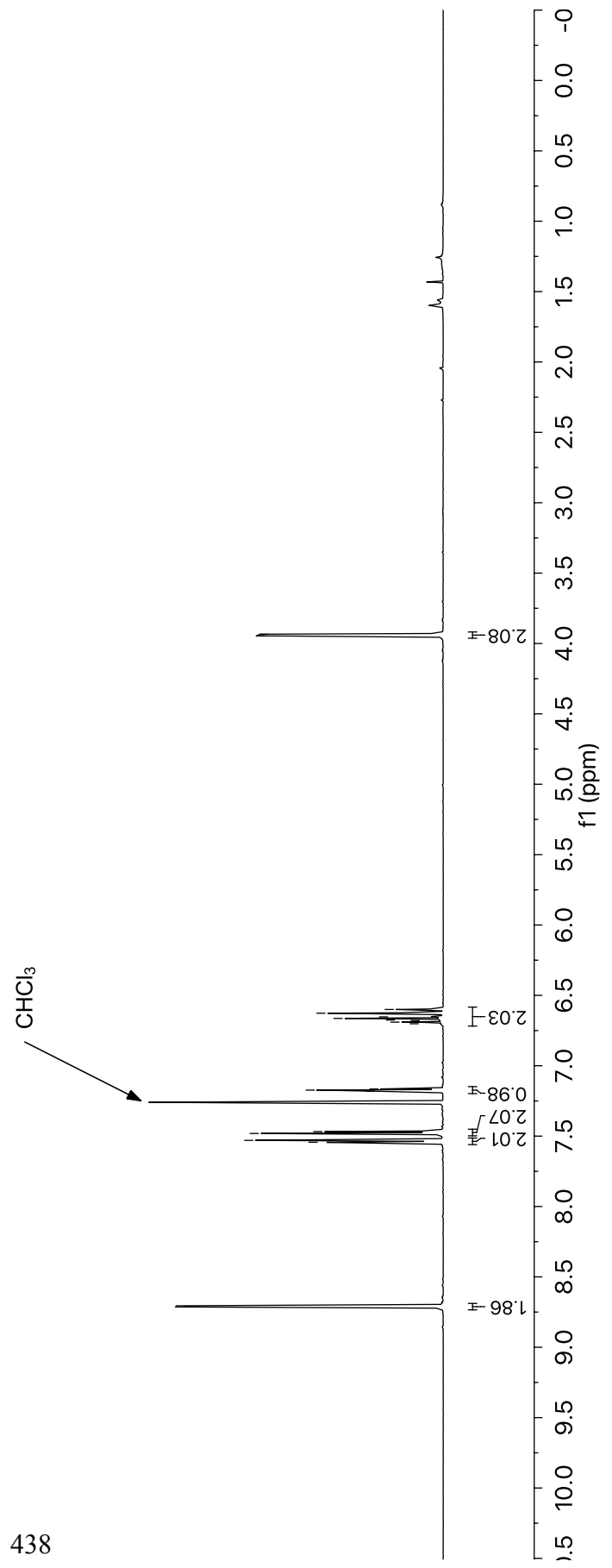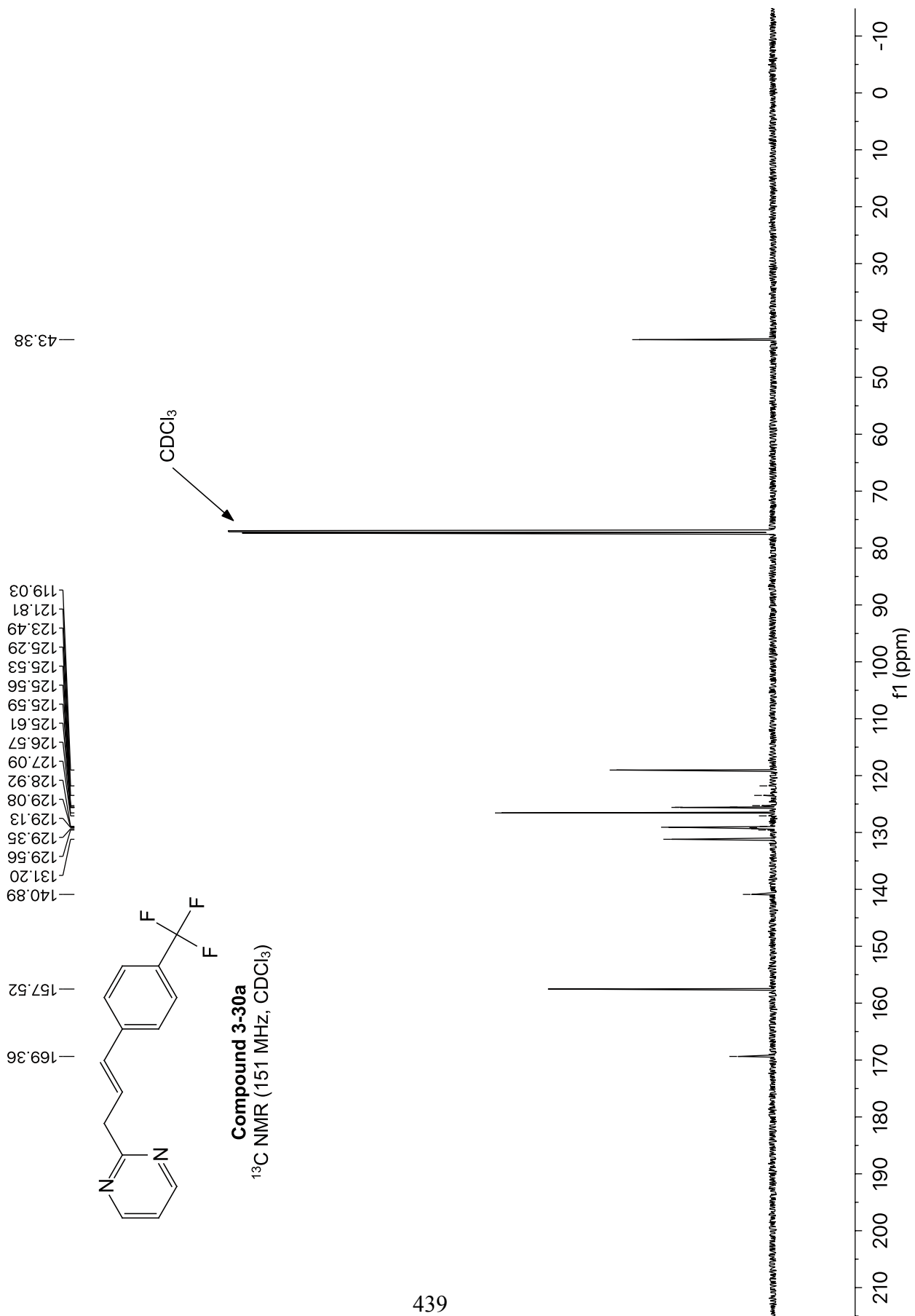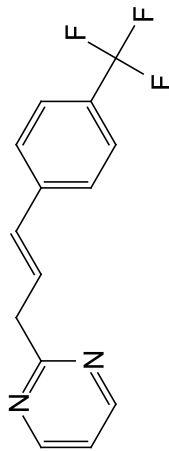
−62.48

**Compound 3-30a**
$^{19}F$ NMR (565 MHz, $CDCl_3$)
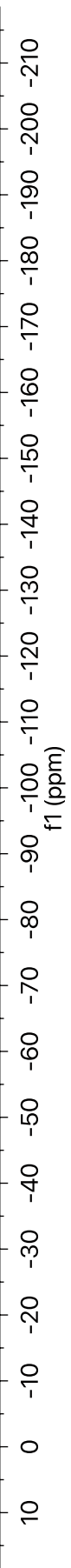
440

f1 (ppm)

10  0  −10  −20  −30  −40  −50  −60  −70  −80  −90  −100  −110  −120  −130  −140  −150  −160  −170  −180  −190  −200  −210
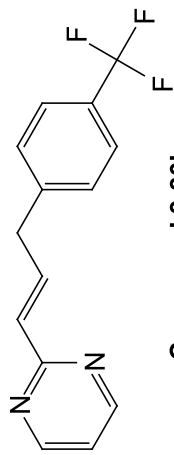
**Compound 3-30b**
¹H NMR (600 MHz, CDCl₃)

3.69
3.70

6.56
6.57
6.57
6.59
6.59
6.59
7.08
7.09
7.09
7.28
7.29
7.29
7.30
7.31
7.37
7.38
7.56
7.58
8.65
8.66

CHCl₃

Compound 3-30b
$^{13}$C NMR (151 MHz, CDCl$_3$)

38.65

CDCl$_3$

118.74
121.55
123.35
125.16
125.50
125.53
125.55
125.58
126.96
128.52
128.74
128.95
129.18
129.22
131.33
138.84
143.03
157.00
164.35
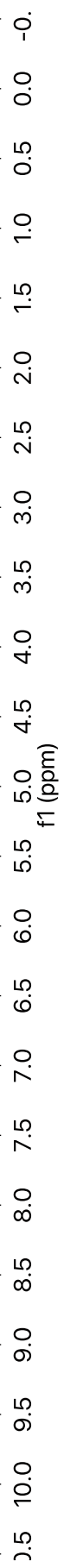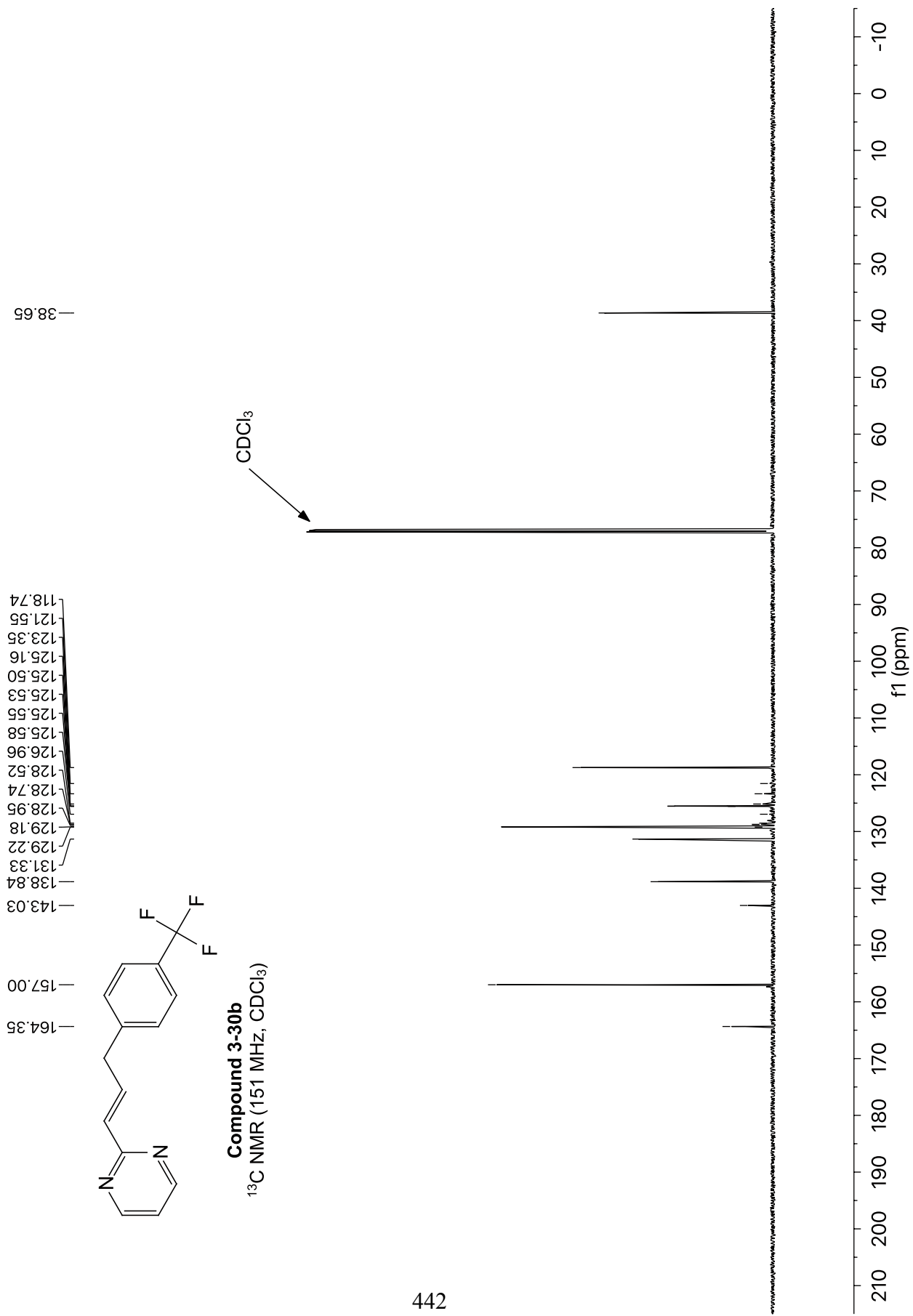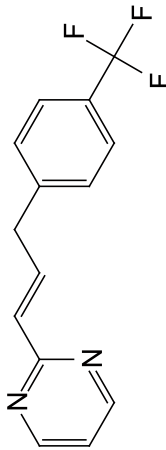
−62.43

**Compound 3-30b**
¹⁹F NMR (565 MHz, CDCl₃)

443

f1 (ppm)
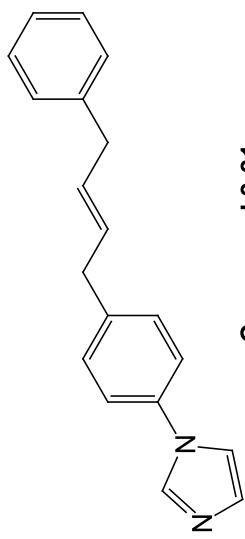
**Compound 3-31**
$^1$H NMR (600 MHz, CDCl$_3$)
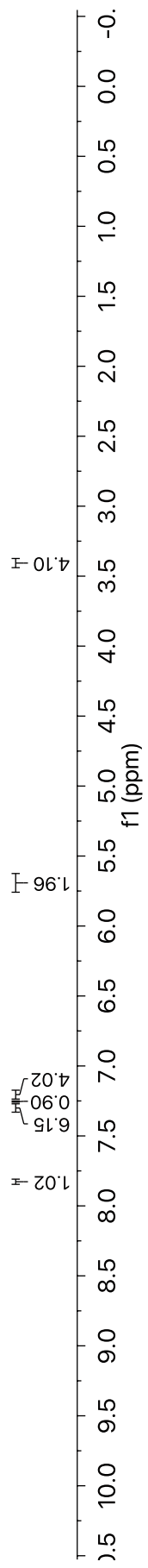
CHCl$_3$

f1 (ppm)

444
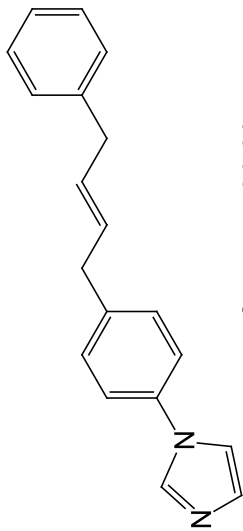
**Compound 3-31**
$^{13}$C NMR (151 MHz, CDCl$_3$)
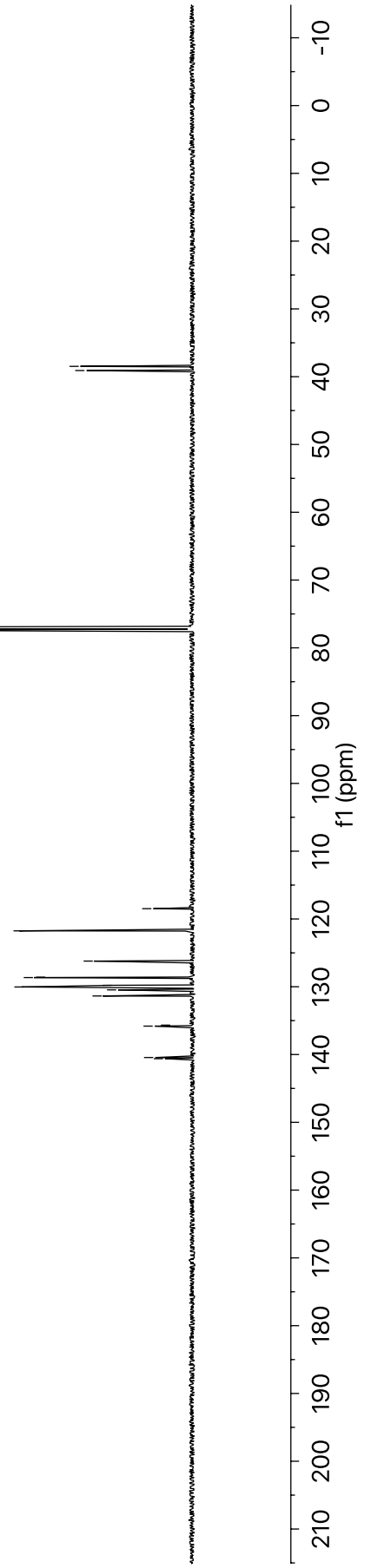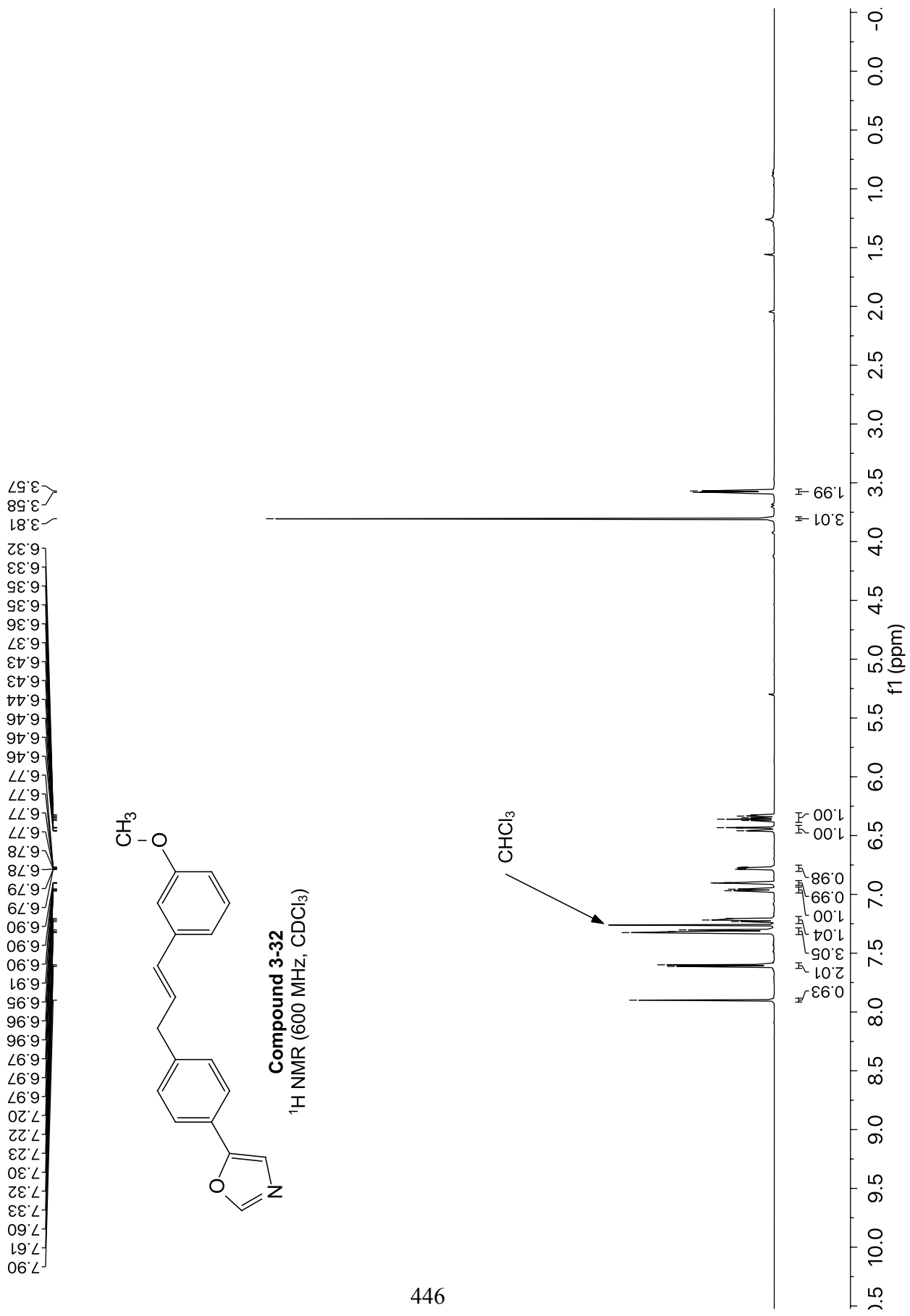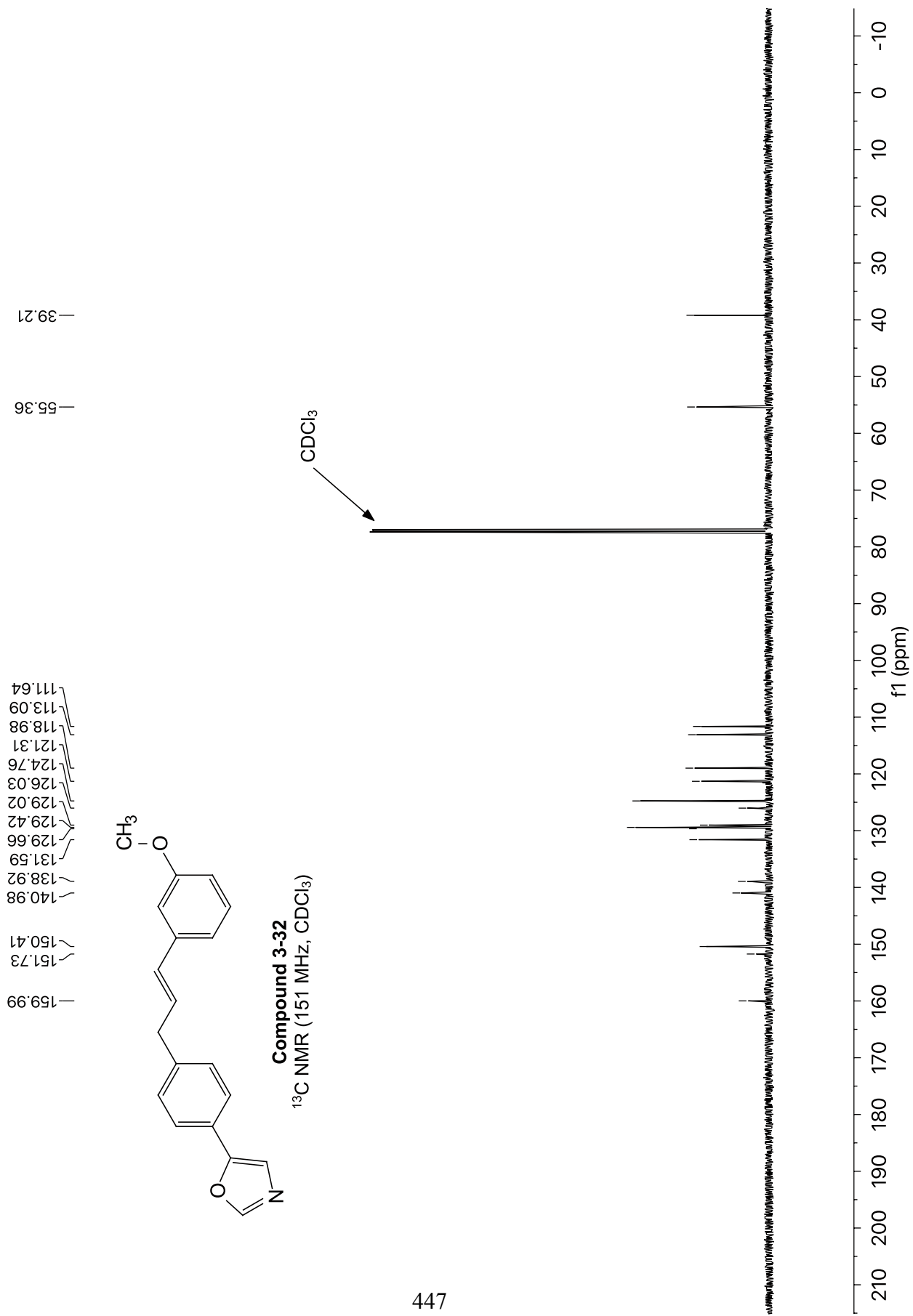
38.48
39.09

118.48
121.75
126.21
128.59
128.65
129.79
130.03
130.46
131.36
135.66
135.81
140.44
140.61

CDCl$_3$

445

**Compound 3-32**
$^1$H NMR (600 MHz, CDCl$_3$)

446

**Compound 3-32**
$^{13}$C NMR (151 MHz, CDCl$_3$)

39.21

55.36

CDCl$_3$

111.64
113.09
118.98
121.31
124.76
126.03
129.02
129.42
129.66
131.59
138.92
140.98

150.41
151.73

159.99
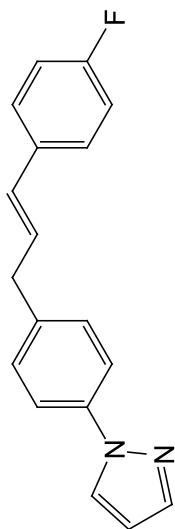
**Compound 3-33**
¹H NMR (600 MHz, CDCl₃)



CHCl₃

f1 (ppm)

448

38.78

CDCl₃

107.60
115.48
115.63
119.56
126.83
127.71
127.77
128.68
128.69
129.77
130.37
133.63
133.65
138.49
138.83
141.08
161.45
163.08

**Compound 3-33**
¹³C NMR (151 MHz, CDCl₃)

f1 (ppm)

210  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10

449
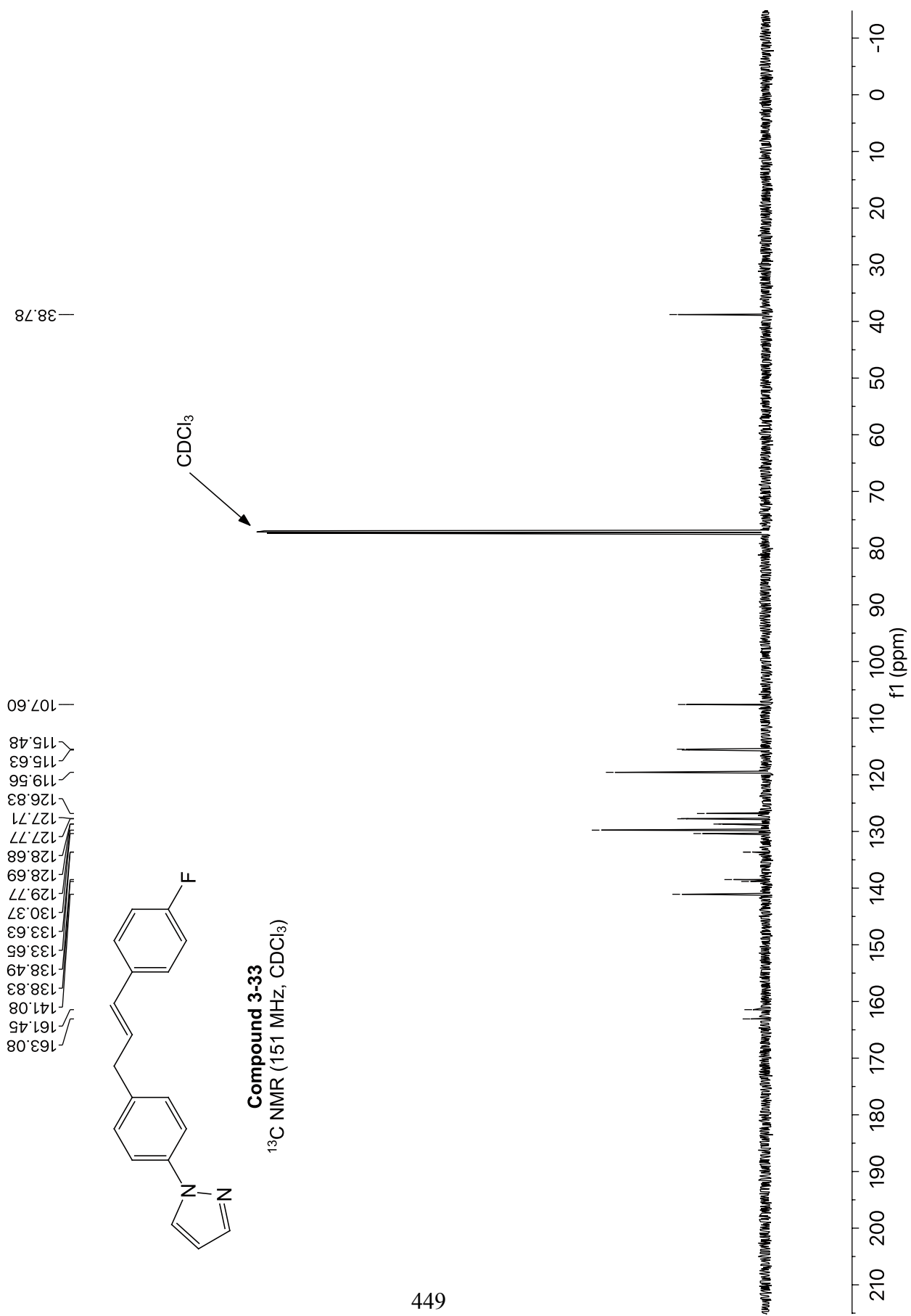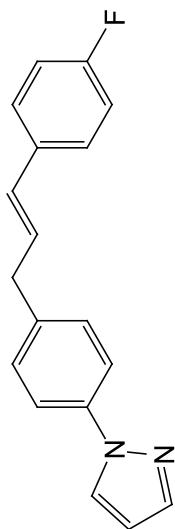
**Compound 3-33**
$^{19}F$ NMR (565 MHz, CDCl$_3$)

−115.13
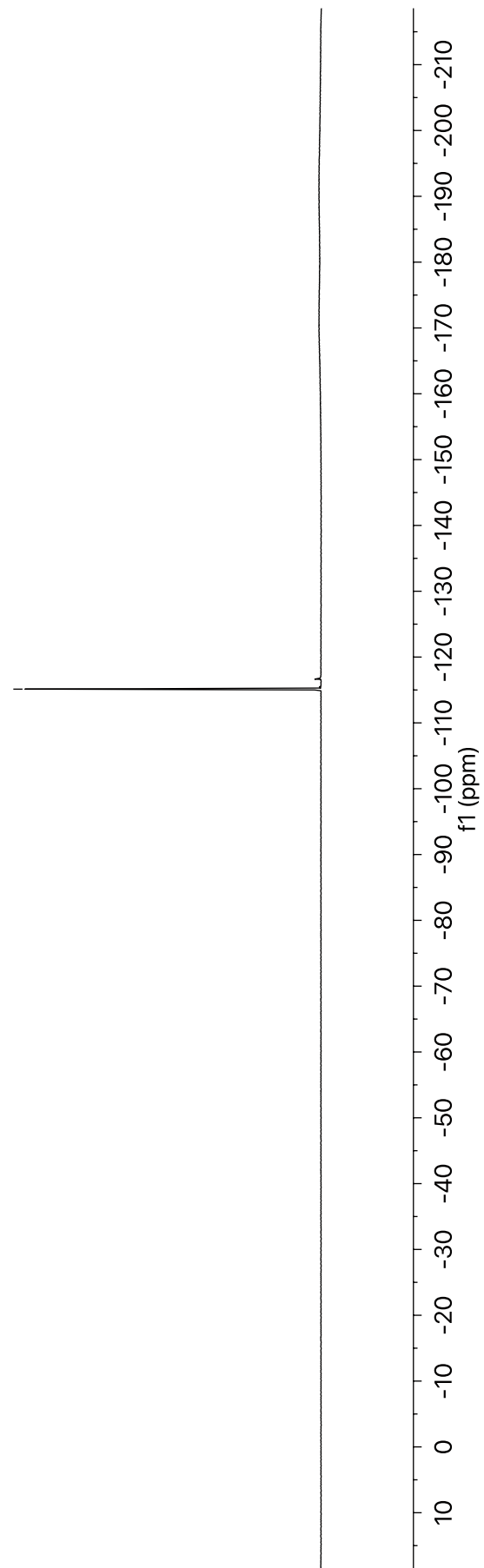
10  0  −10  −20  −30  −40  −50  −60  −70  −80  −90  −100  −110  −120  −130  −140  −150  −160  −170  −180  −190  −200  −210
f1 (ppm)

450
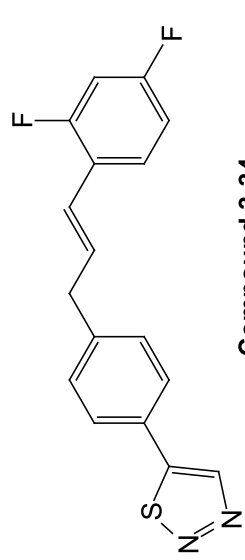
Compound 3-34
$^1$H NMR (600 MHz, CDCl$_3$)

451

**Compound 3-34**
¹³C NMR (151 MHz, CDCl₃)

39.60

103.85
104.10
104.36
111.39
111.42
111.60
111.63
121.44
121.48
121.56
121.60
123.14
123.15
123.17
123.18
127.73
128.03
128.08
128.12
128.17
129.07
129.60
129.76
130.98
131.00
131.02
131.05
141.42

158.77
158.88
160.74
160.86
161.26
161.38
162.88
163.22
163.34

CDCl₃

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

452
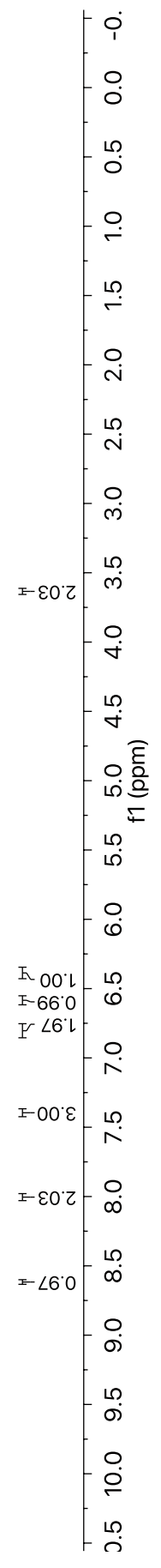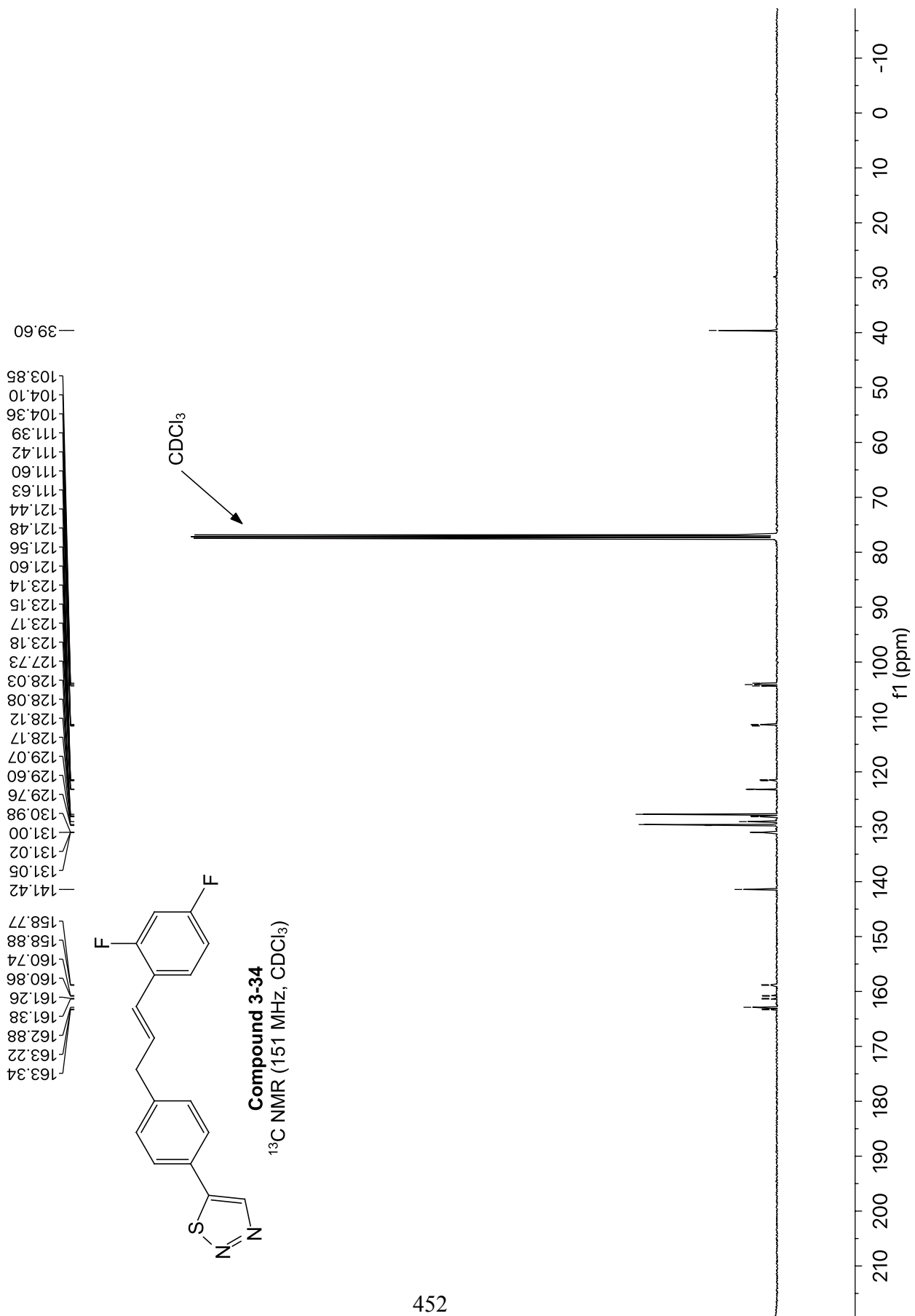
**Compound 3-34**
$^{19}F$ NMR (565 MHz, CDCl$_3$)

-114.30
-114.29
-111.67
-111.65

453
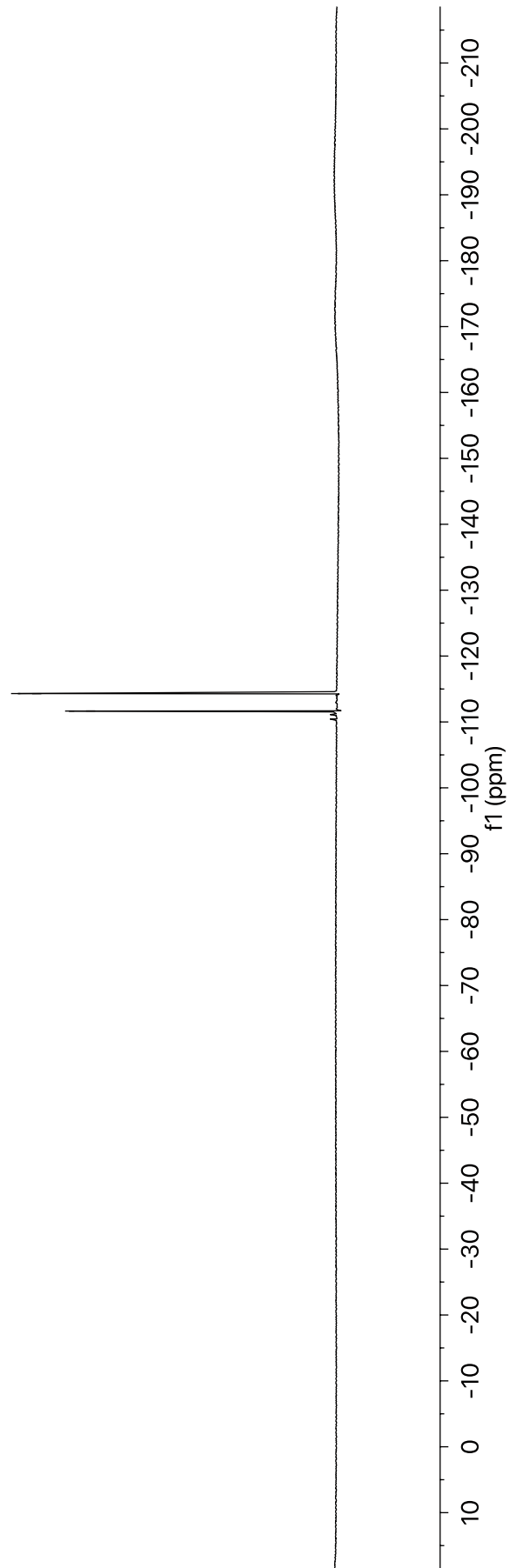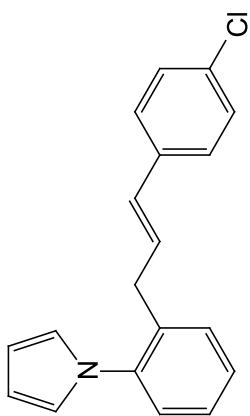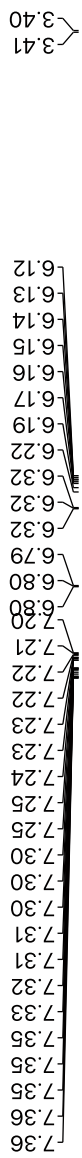
**Compound 3-35**
¹H NMR (600 MHz, CDCl₃)

454
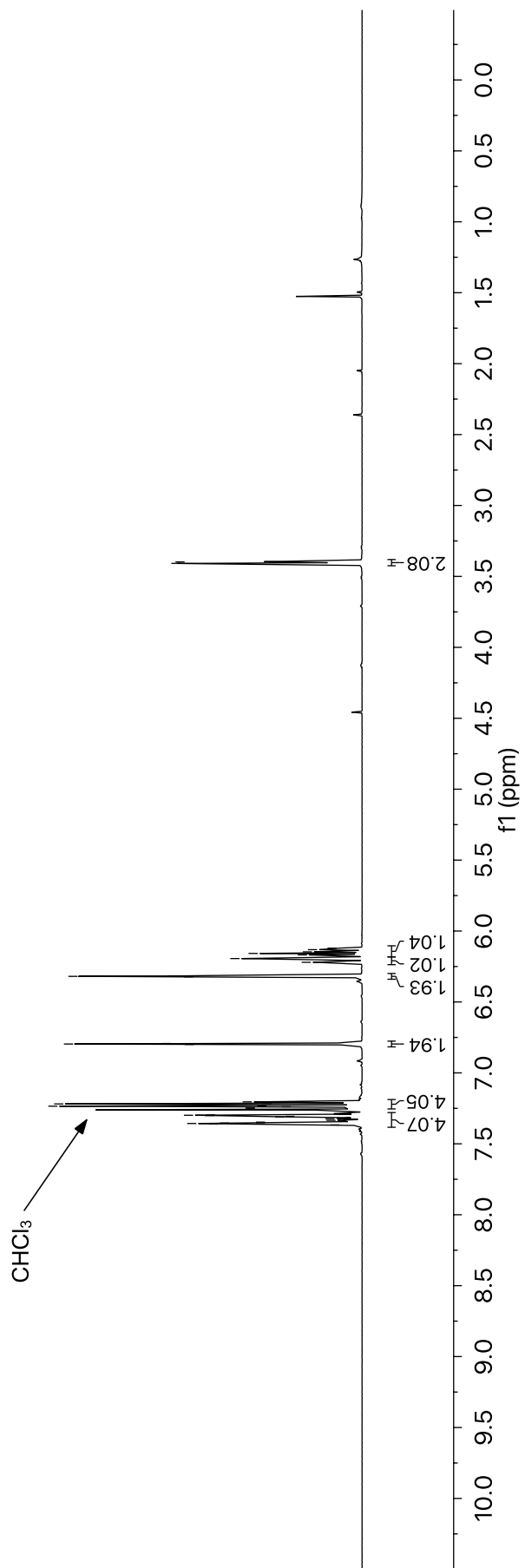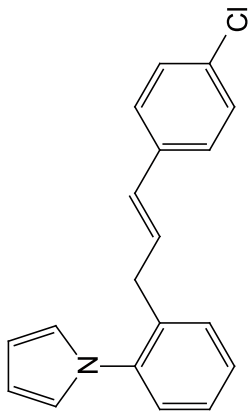
**Compound 3-35**
¹³C NMR (151 MHz, CDCl₃)

34.77

109.07
122.48
127.33
127.41
127.45
128.08
128.75
129.30
130.37
130.61
132.89
136.01
136.05
140.56

CDCl₃

455
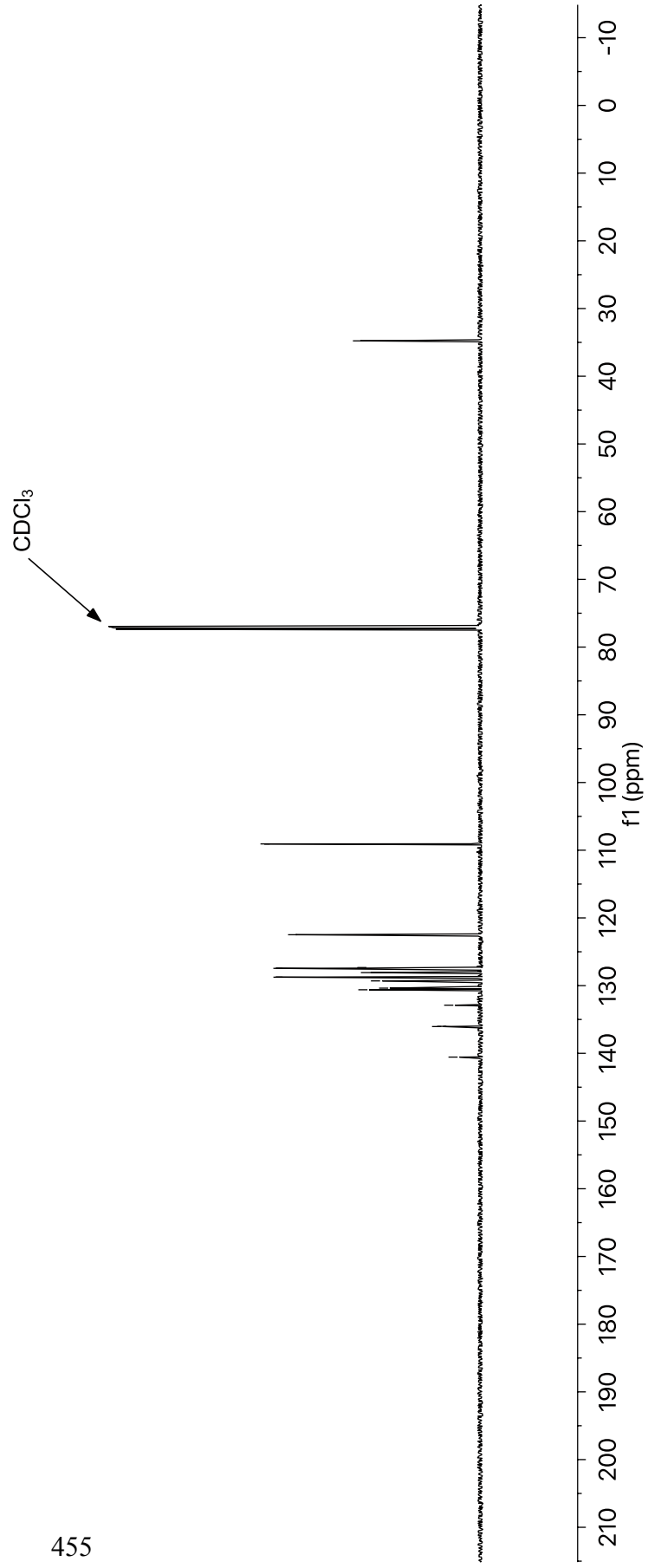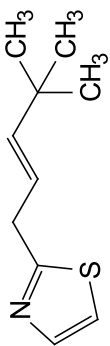
**Compound 3-36**
$^1$H NMR (600 MHz, CDCl$_3$)

456

29.63
33.27
36.86

CDCl₃

118.60
120.45

142.61
145.87

171.36

CH₃
CH₃
CH₃
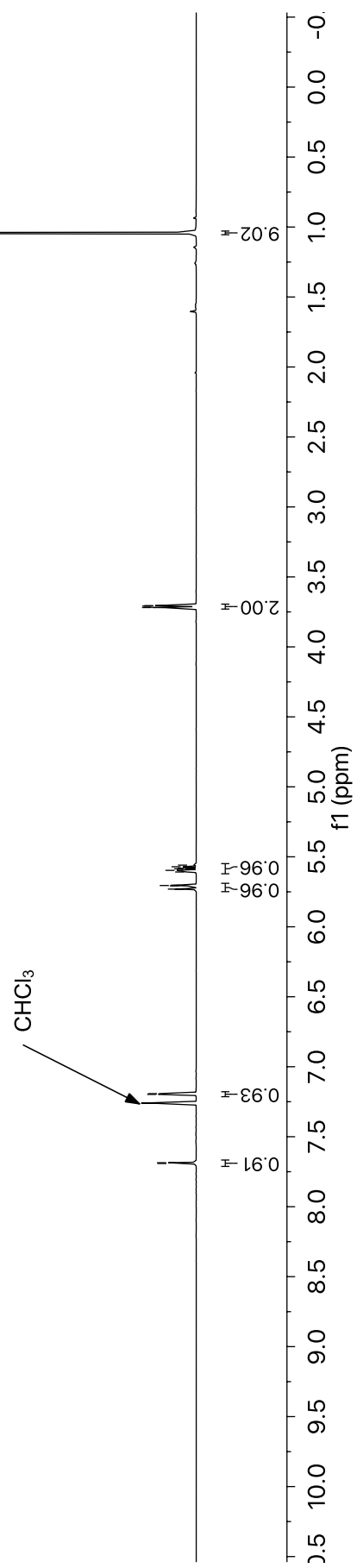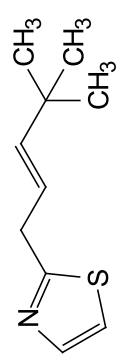
**Compound 3-36**
¹³C NMR (151 MHz, CDCl₃)

457

210  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
f1 (ppm)
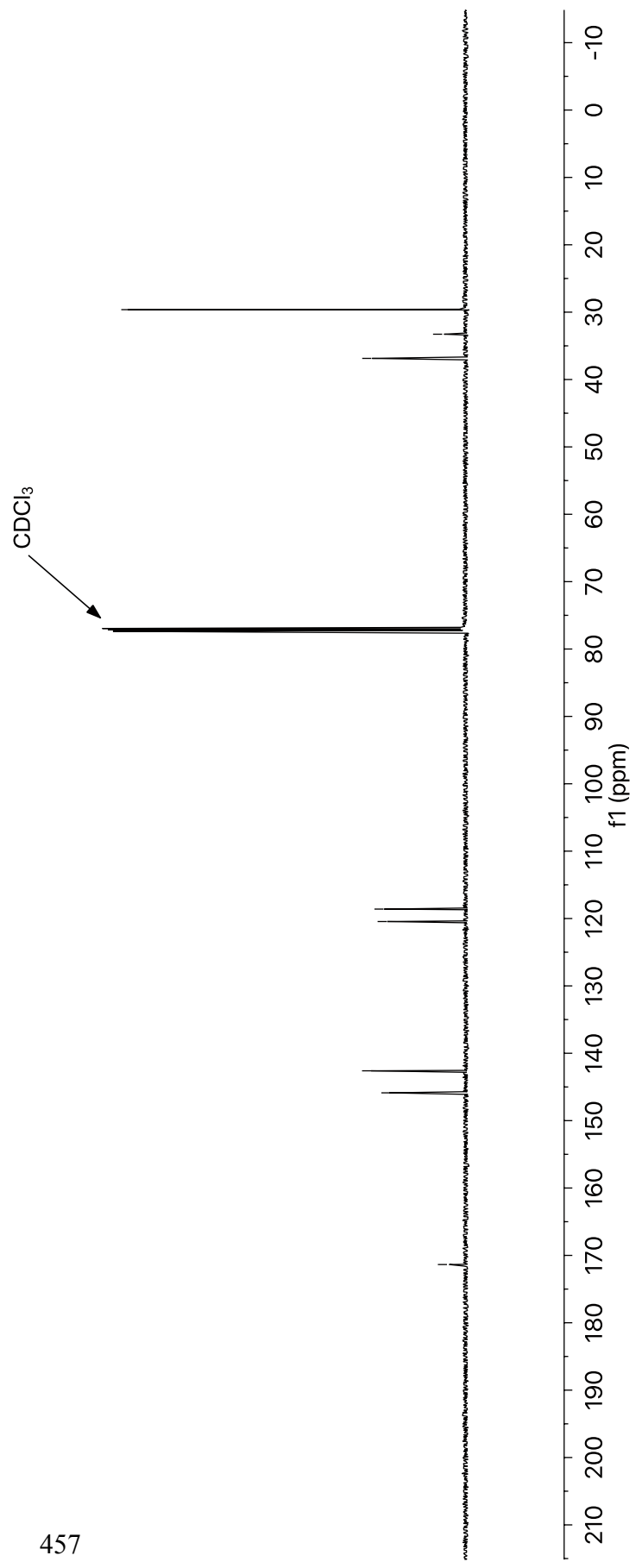
**Appendix D**

**SPECTRAL AND CHROMATOGRAPHY DATA FOR CHAPTER 4**

Compound 4-31
$^1$H NMR (600 MHz, CDCl$_3$)

459
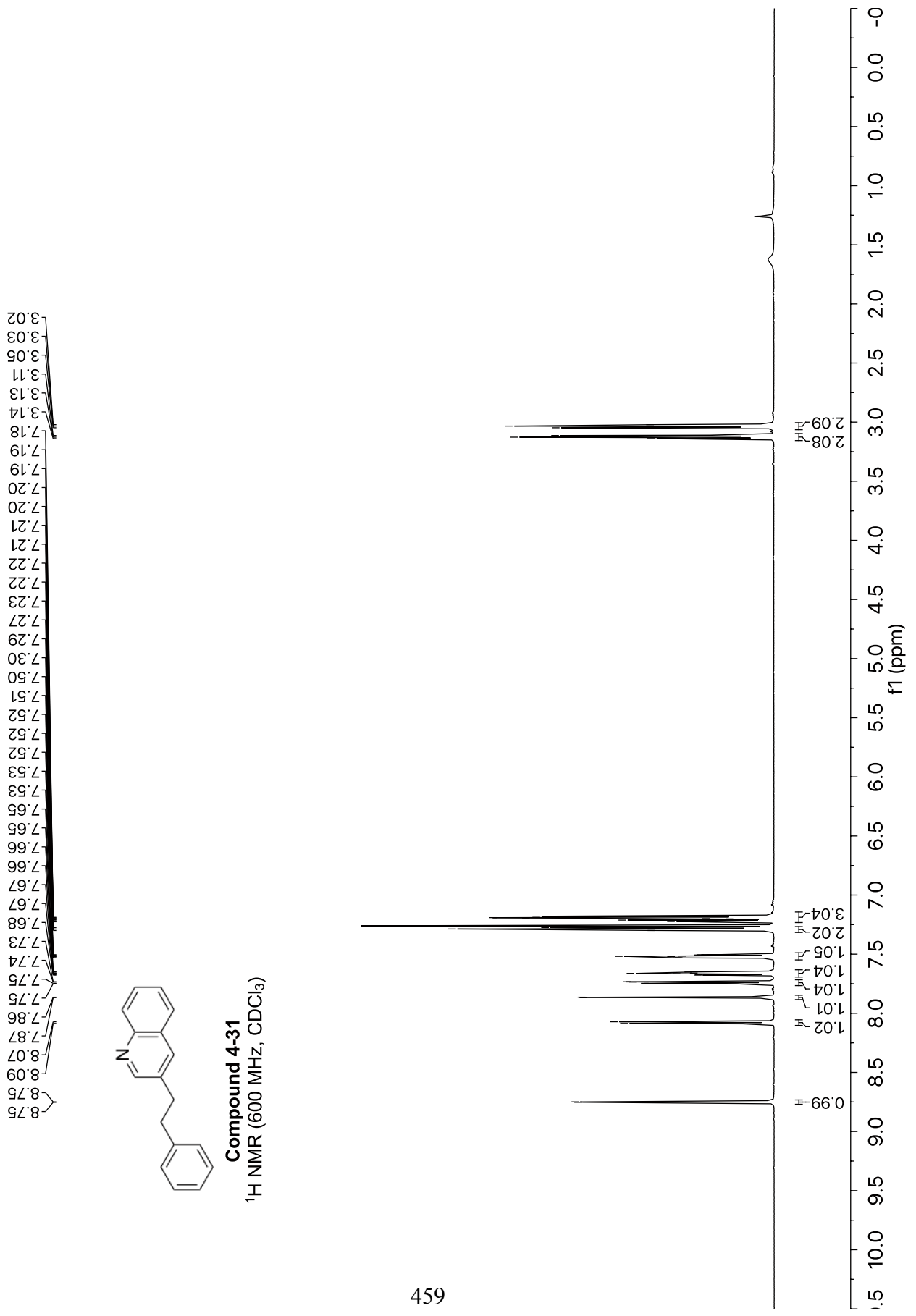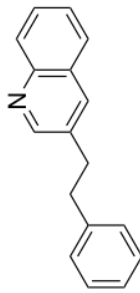
**Compound 4-31**
$^{13}C$ NMR (151 MHz, CDCl$_3$)

35.12
37.46

126.24
126.56
127.35
128.10
128.50
128.65
129.22
134.18
134.39
140.79
146.93
151.99

460
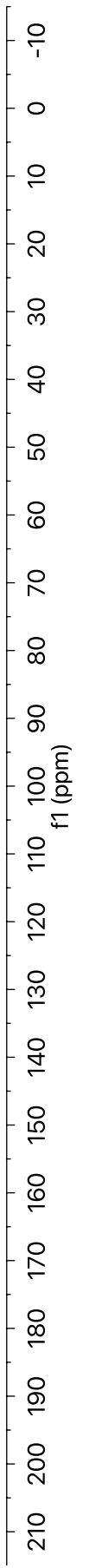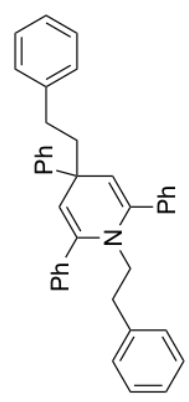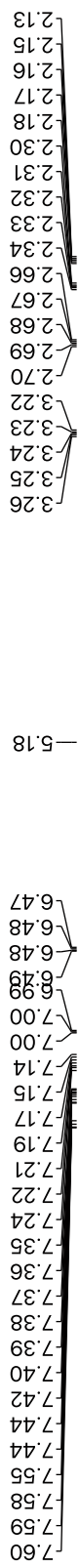
Compound 4-32
$^1$H NMR (400 MHz, CDCl$_3$)

2.13
2.15
2.16
2.17
2.18
2.30
2.31
2.32
2.33
2.34
2.66
2.67
2.68
2.69
2.70
3.22
3.23
3.24
3.25
3.26

5.18

6.47
6.48
6.48
6.49
6.99
7.00
7.00
7.14
7.15
7.17
7.19
7.21
7.22
7.24
7.35
7.36
7.37
7.38
7.39
7.40
7.42
7.44
7.44
7.55
7.58
7.59
7.60

461

32.67
34.72

43.81
46.70
50.03

113.31
125.53
125.60
125.77
126.39
128.00
128.08
128.11
128.28
128.35
128.37
128.39
128.42
138.00
139.15
143.05
143.08
151.36
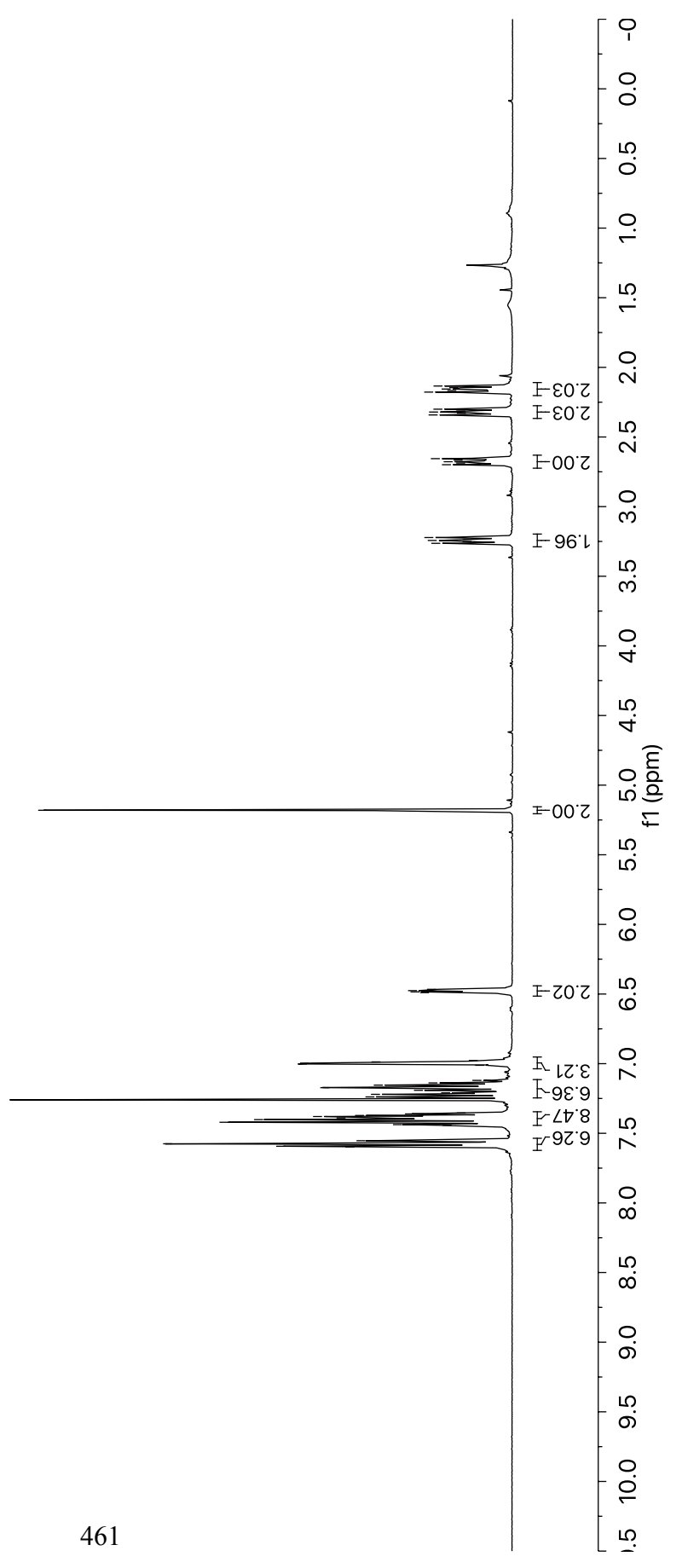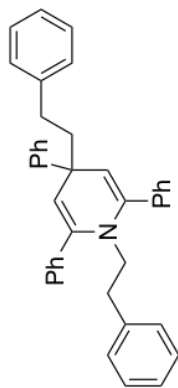
**Compound 4-32**
$^{13}$C NMR (101 MHz, CDCl$_3$)

f1 (ppm)

210  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10

**Compound 4-43**
$^1$H NMR (400 MHz, CDCl$_3$)

463

35.07
37.61

123.33
126.31
128.57
128.59
136.04
136.90
140.94
147.64
150.15
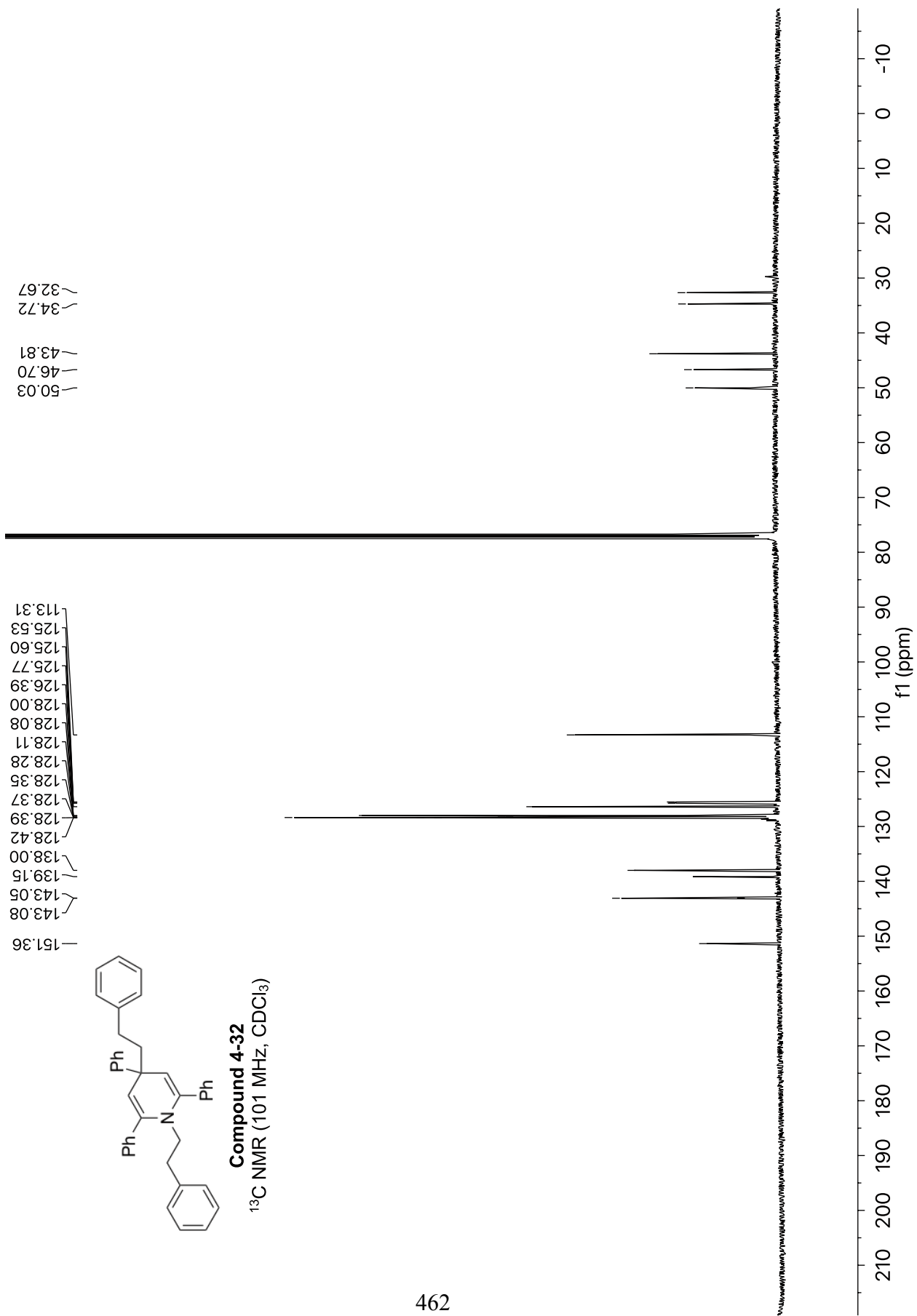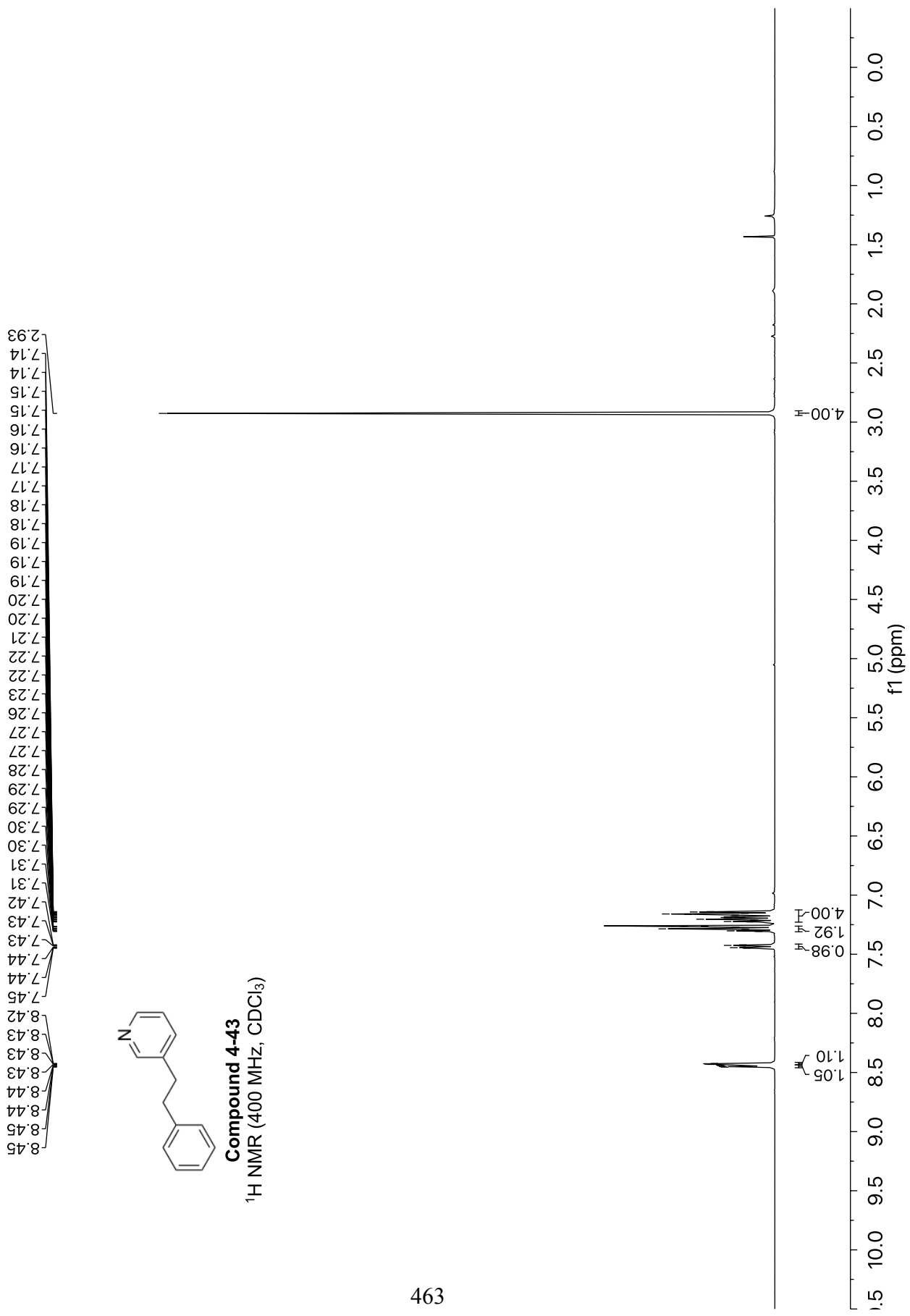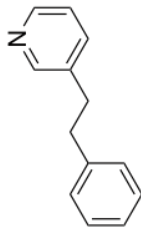
**Compound 4-43**

$^{13}$C NMR (101 MHz, CDCl$_3$)

f1 (ppm)

464

**Compound 4-44**
¹H NMR (600 MHz, CDCl₃)

465

**Compound 4-44**
$^{13}C$ NMR (151 MHz, CDCl$_3$)

37.69
38.59
49.52
66.98
100.75
108.11
108.97
113.41
116.10
120.31
121.18
129.13
135.72
142.69
145.64
147.49
151.38

**Compound 4-45**
¹H NMR (400 MHz, CDCl₃)



7.27
7.27
7.28
7.29
7.31
7.31
7.32
7.33
7.33
7.34
7.35
7.35
7.35
7.41
7.42
7.43
7.43
7.44
7.45
7.51
7.51
7.52
7.53
7.53
7.56
7.57
7.57
7.58
7.58
7.59

1.47
2.48
2.49
2.51
2.63
2.64
2.65
2.66
2.67
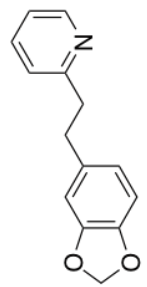2.83
2.85
2.86
2.86
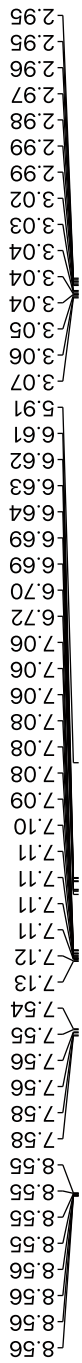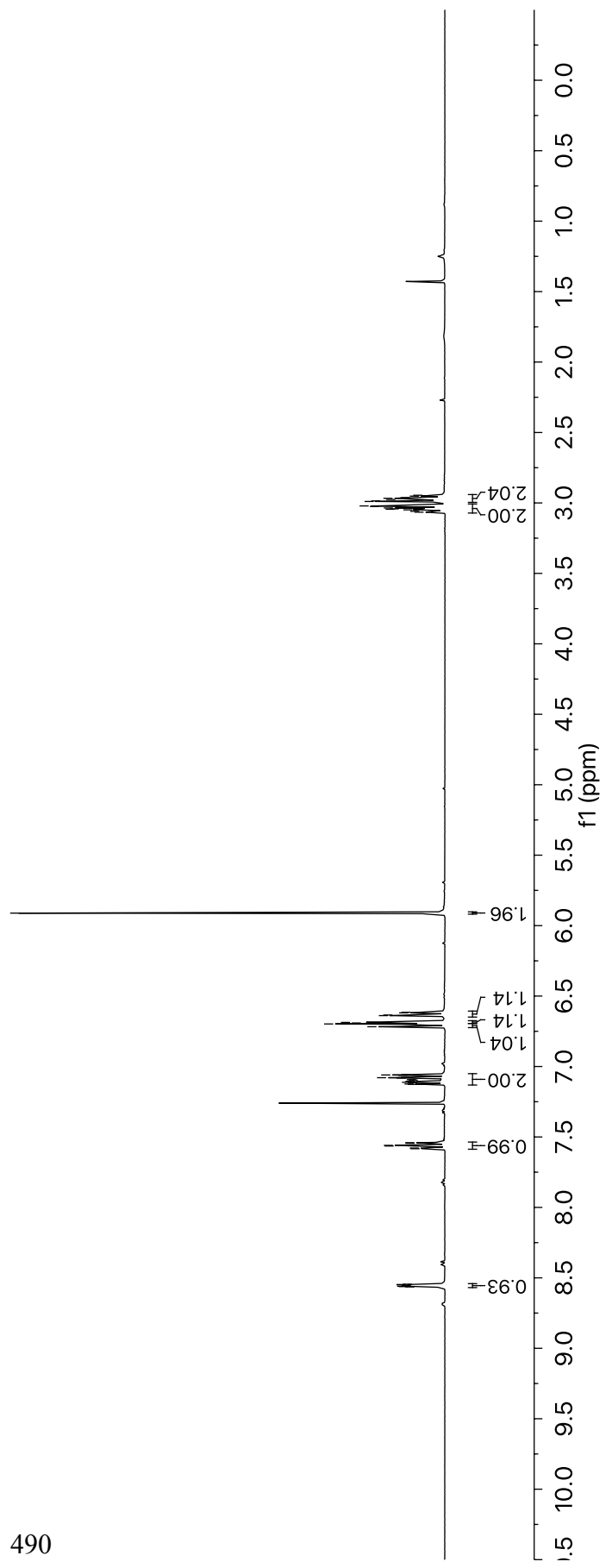2.87
3.47
3.48
3.49

9.37
4.21
2.12
2.01
4.00
2.12
1.13
2.17
2.17
2.19

Compound 4-45
¹³C NMR (101 MHz, CDCl₃)
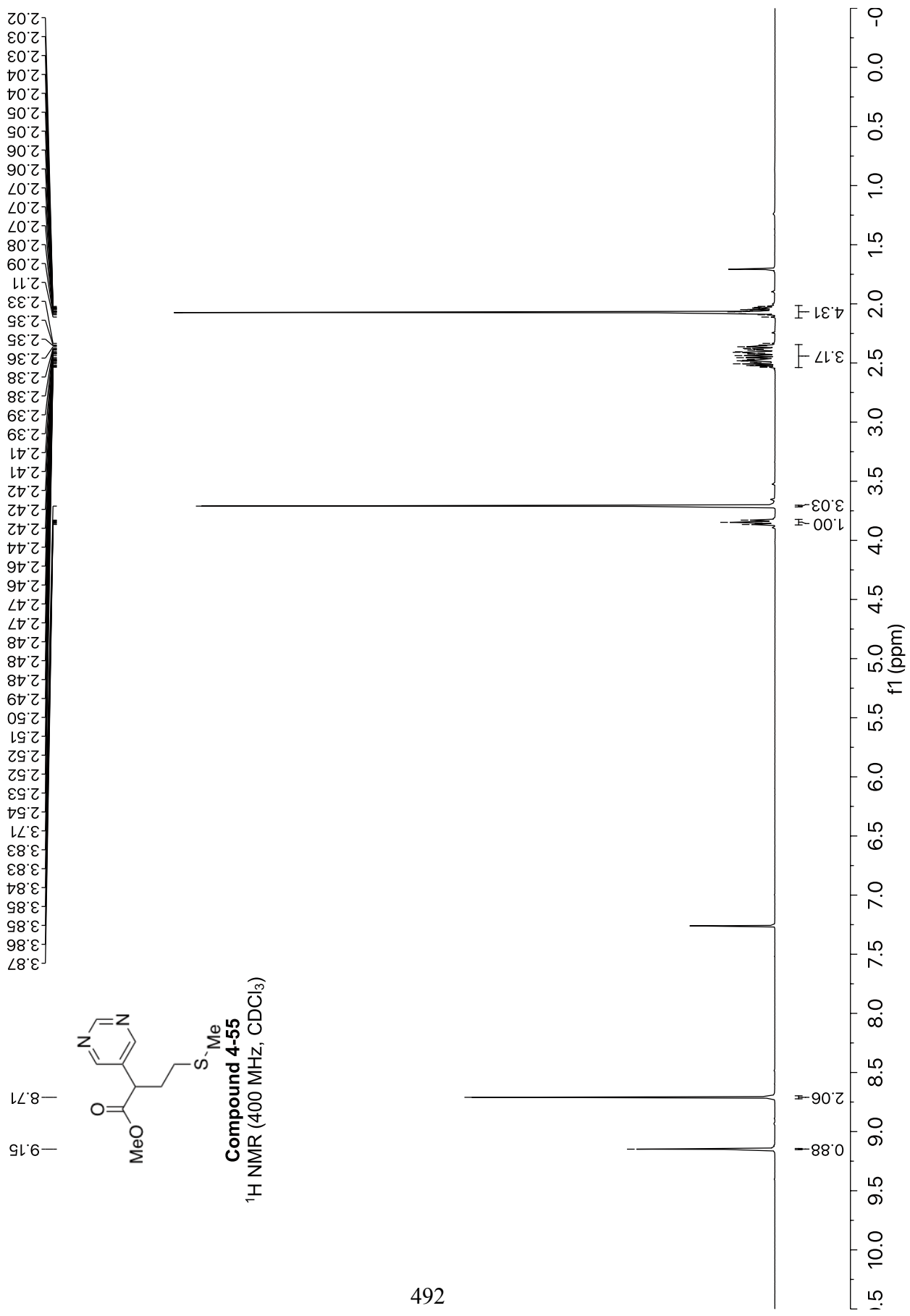
28.46
33.16
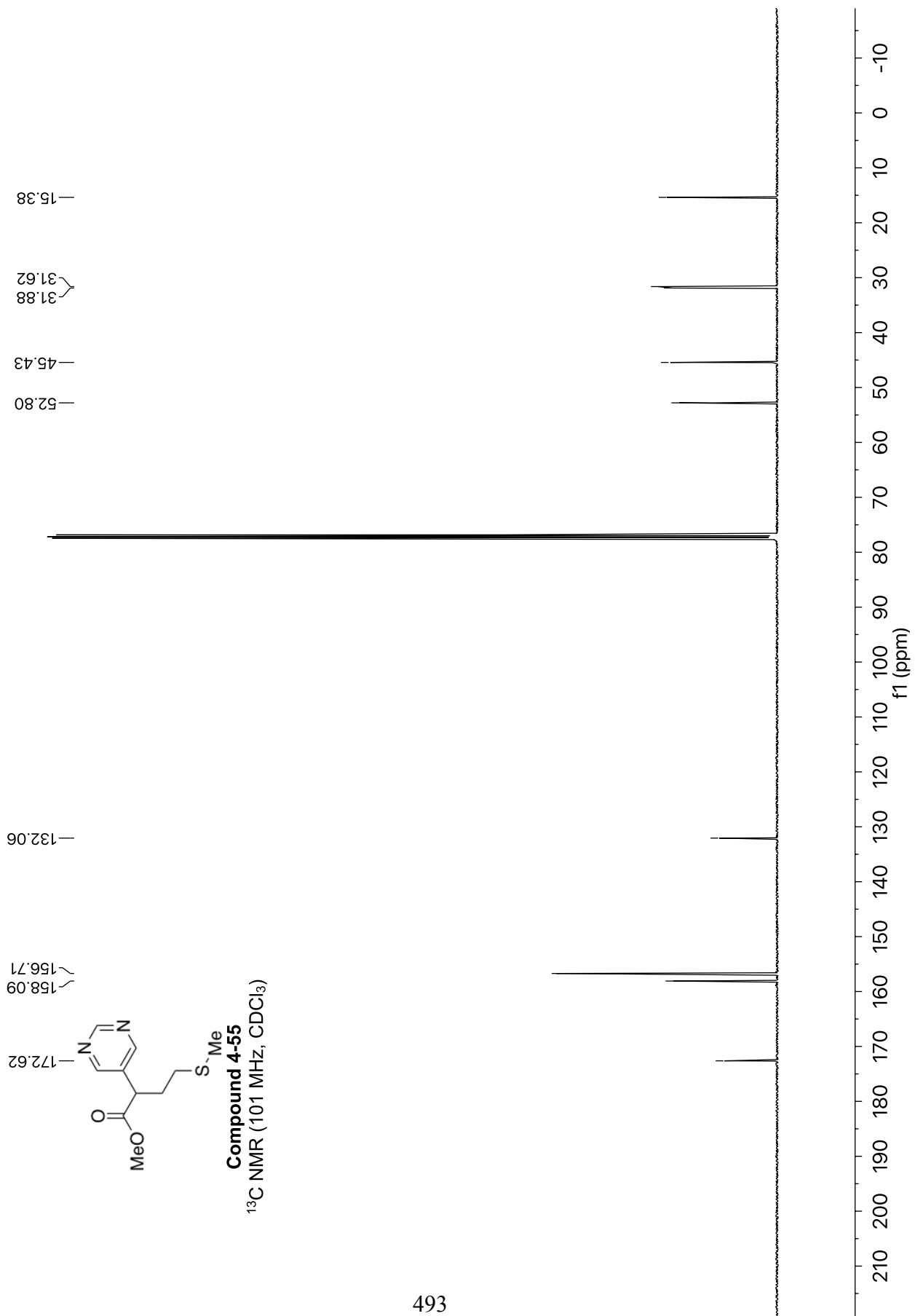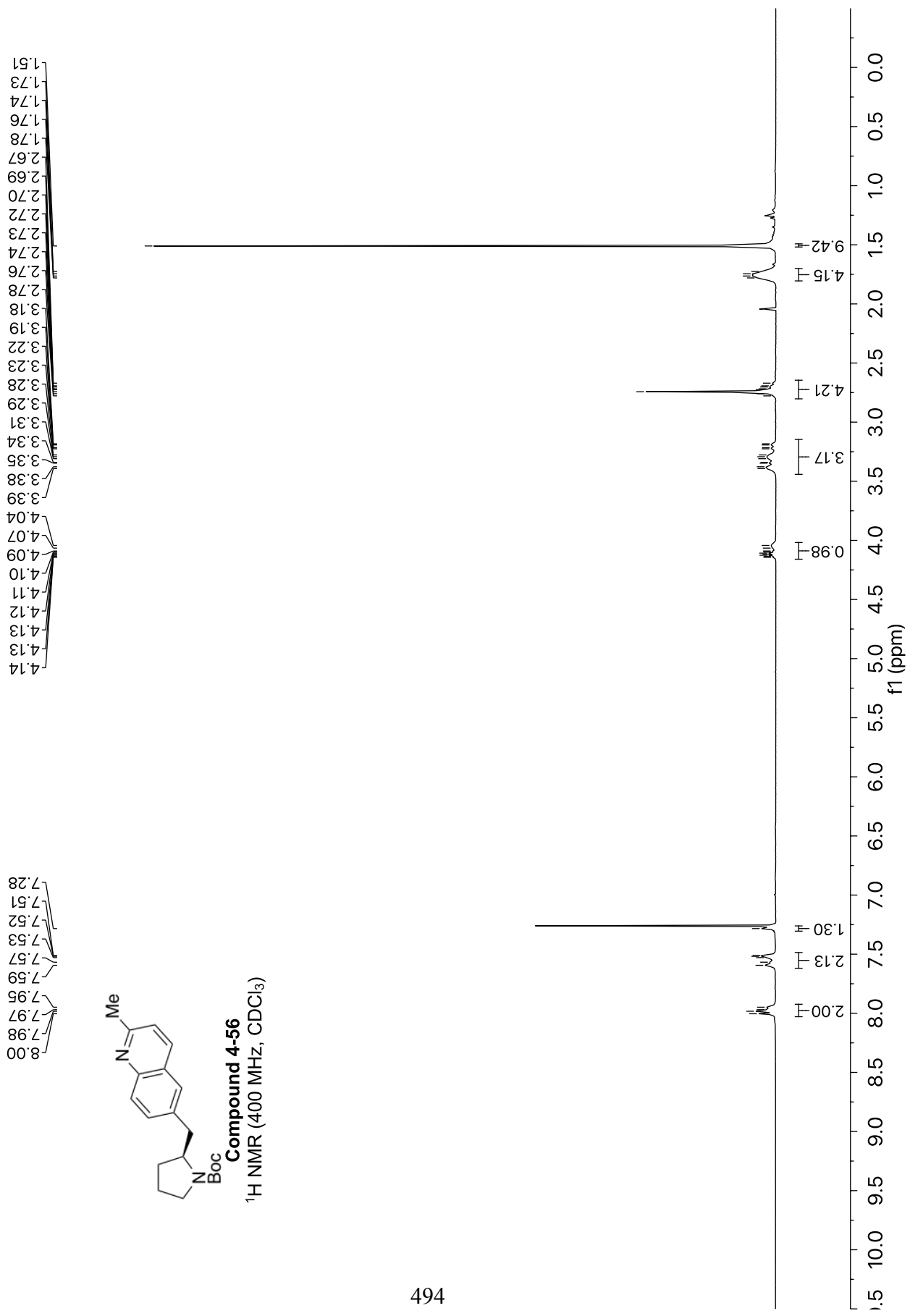53.03
60.48
79.68
127.01
127.12
127.18
128.75
129.13
139.12
139.20
140.96
154.76

Compound 4-46
¹H NMR (600 MHz, CDCl₃)

469

28.12
31.19
37.49

80.49

121.19
121.48
122.67
122.86
124.28
126.62
127.46
135.42
135.76
137.21
137.23
139.83

172.20

**Compound 4-46**
$^{13}$C NMR (151 MHz, CDCl$_3$)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

470

Compound 4-47
$^1$H NMR (400 MHz, CDCl$_3$)

471

25.67
25.70
25.74
25.77
34.83
35.11
35.40
35.68

122.32
125.07
127.01
127.39
127.82
127.92
129.25
129.30
130.57
131.55
134.50
147.19
151.25

**Compound 4-47**
$^{13}$C NMR (101 MHz, CDCl$_3$)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

472
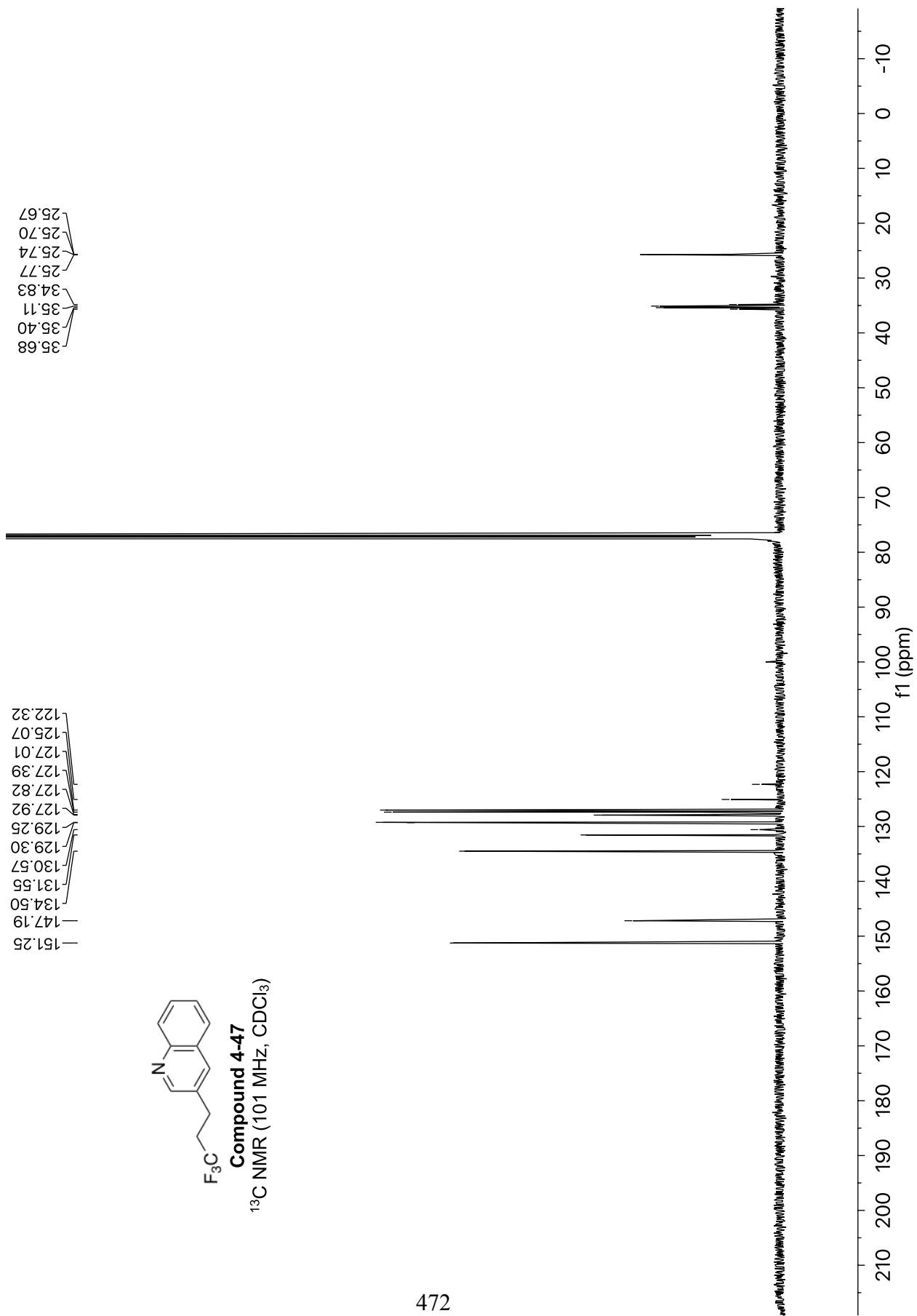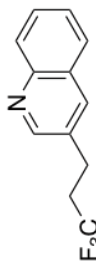
−66.43

**Compound 4-47**
¹⁹F NMR (376 MHz, CDCl₃)

473
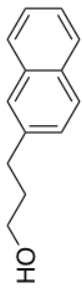
**Compound 4-48**
¹H NMR (600 MHz, CDCl₃)

474
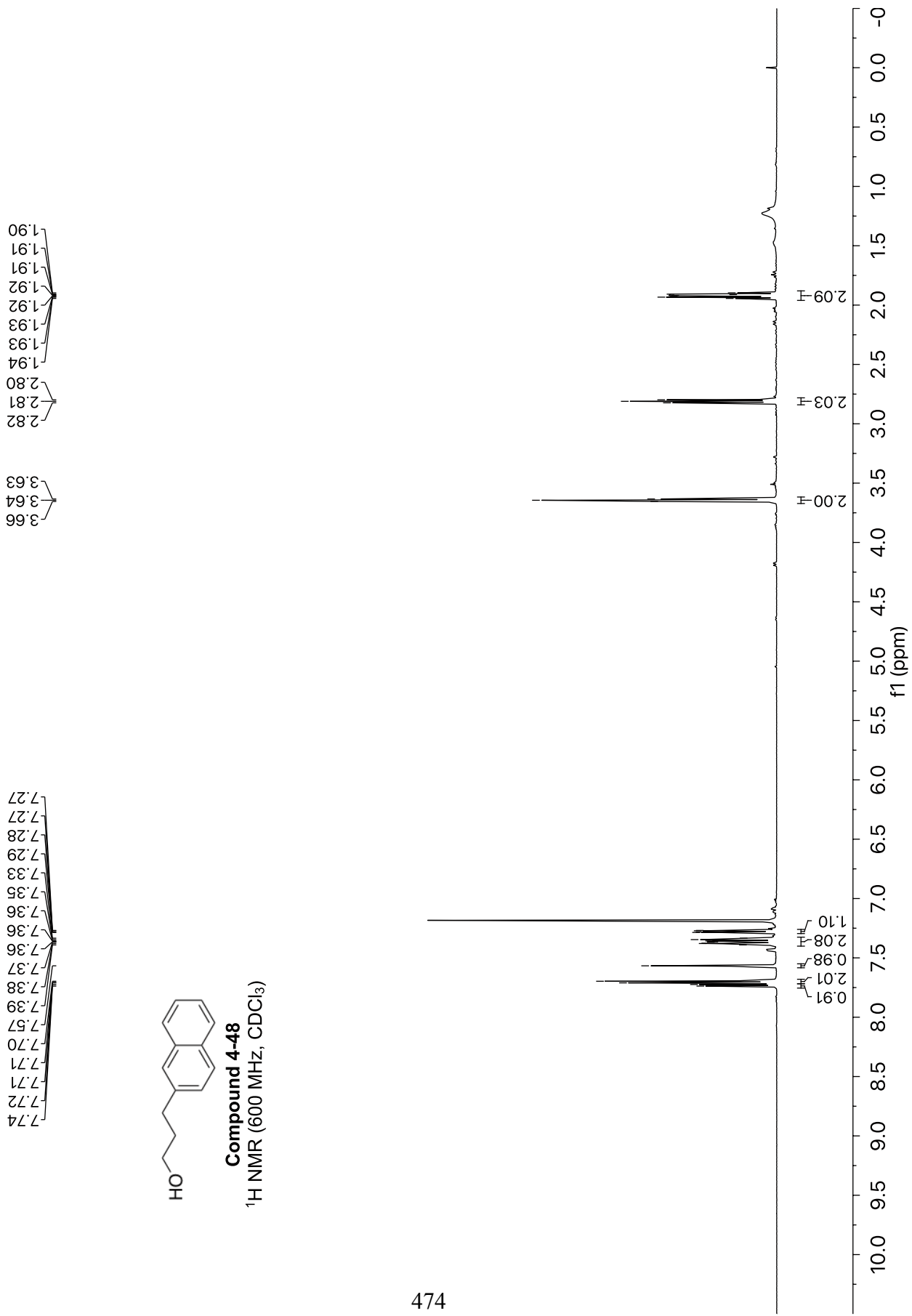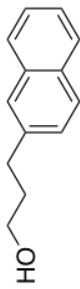
**Compound 4-48**
13C NMR (151 MHz, CDCl3)

32.22
34.10

62.28

125.18
125.94
126.43
127.27
127.40
127.61
127.97
132.03
133.64
139.30

f1 (ppm)

Compound 4-49
$^1$H NMR (400 MHz, CDCl$_3$)

476

26.17
33.25
34.97
51.64
127.55
128.76
131.08
145.91
169.17
173.75

Compound 4-49
$^{13}$C NMR (101 MHz, CDCl$_3$)

f1 (ppm)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

477

Compound 4-50
¹H NMR (400 MHz, CDCl₃)

478

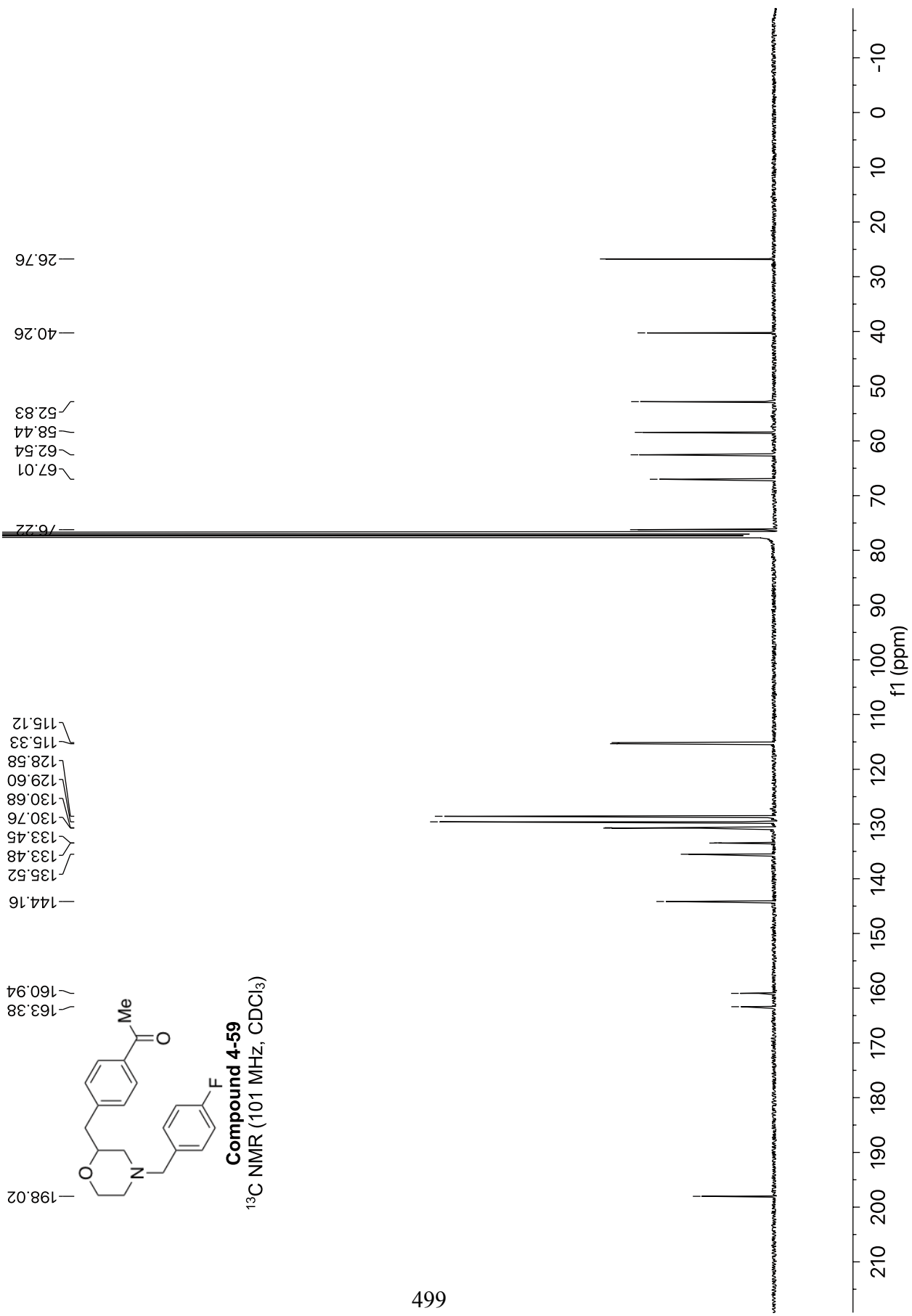**Compound 4-50**

$^{13}$C NMR (101 MHz, (CD$_3$)$_2$CO)

25.25

36.55
40.49

84.38

122.04
123.70
128.80
135.64
137.00

146.24
150.11
150.13

161.95

f1 (ppm)

479

**Compound 4-34**
¹H NMR (400 MHz, CDCl₃)

480

**Compound 4-34**
$^{13}C$ NMR (101 MHz, CDCl$_3$)

23.69

31.87

126.50
127.47
128.23
128.53
129.11
131.78
141.12
146.90
151.28

481

Compound 4-35
$^1$H NMR (400 MHz, CDCl$_3$)

0.57
0.59
0.77
0.79

1.96
1.97
1.99
2.01
2.02
2.04
2.06

3.25
3.27
3.28
3.30
3.32
3.34
3.35

5.29

7.14
7.16
7.18
7.31
7.32
7.33
7.34
7.36
7.38
7.40
7.45
7.47
7.62
7.64

6.20
6.20
1.03
1.00
2.04
1.14
8.41
2.16
4.19

482

18.44
22.56

39.48
47.00
53.59

115.30
125.05
126.83
127.66
127.89
127.96
128.17

140.87
145.25
151.66
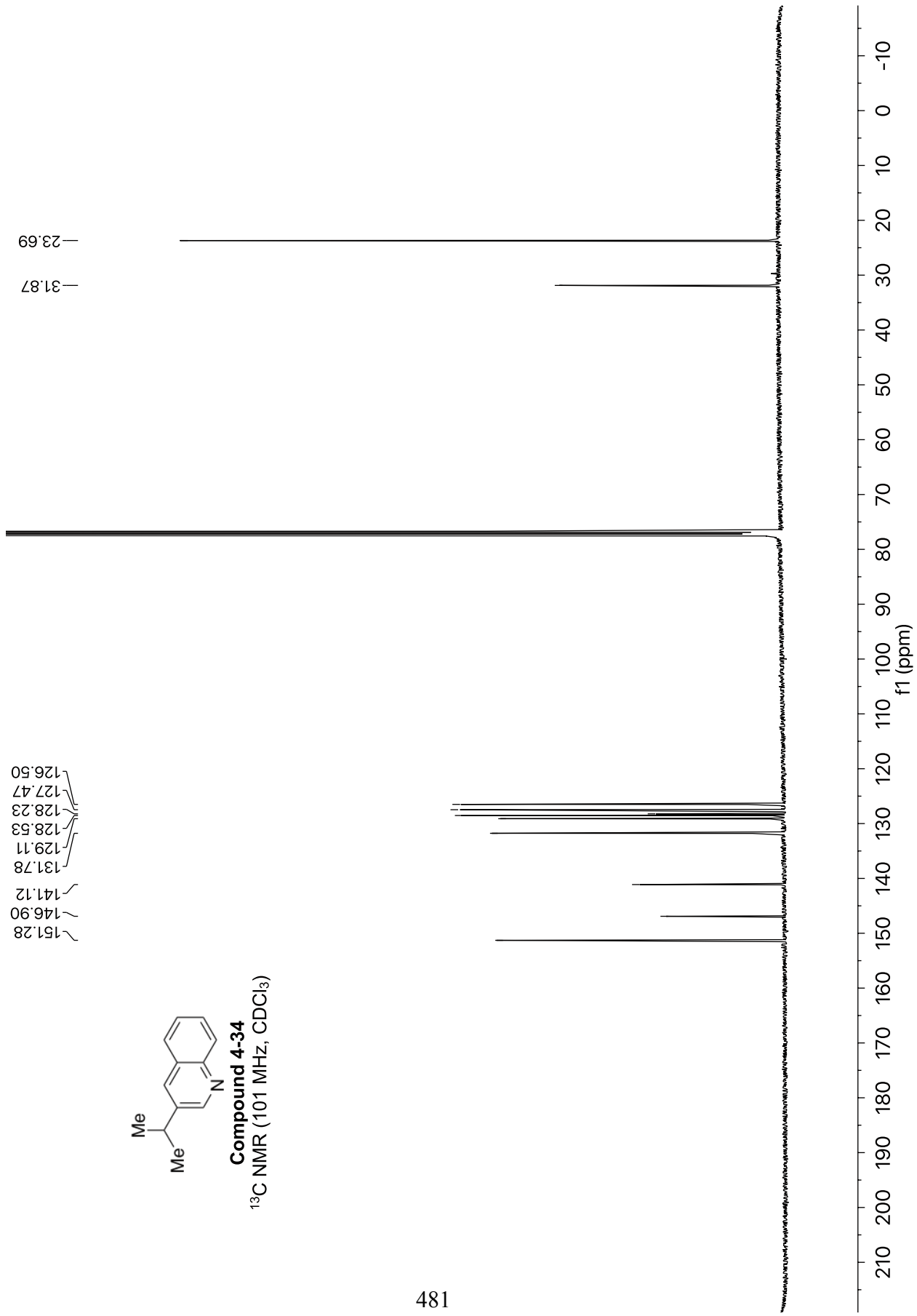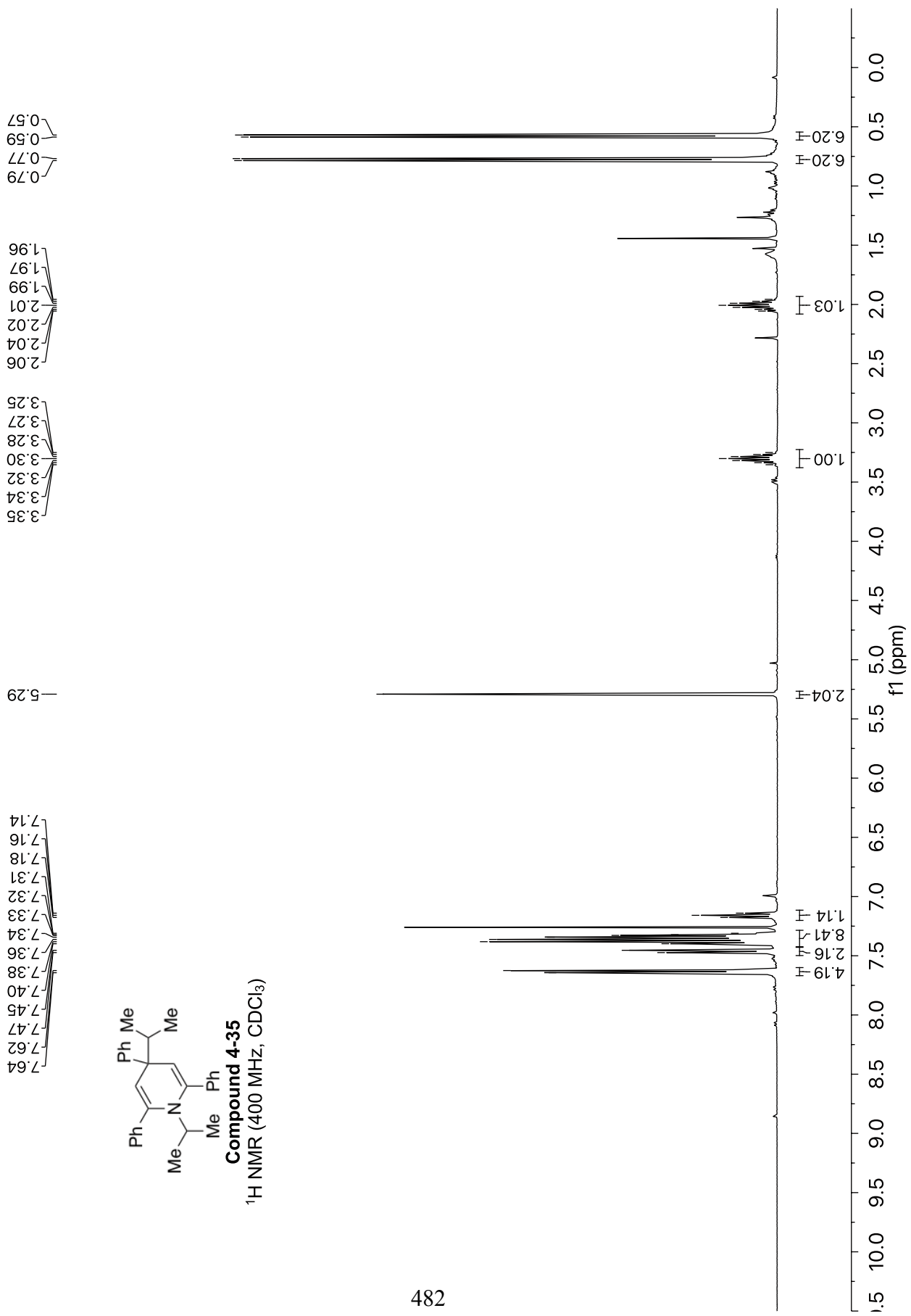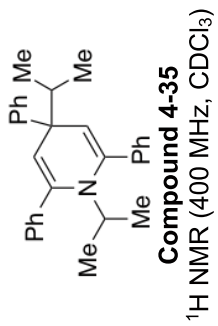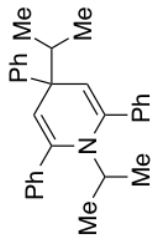
**Compound 4-35**
$^{13}$C NMR (101 MHz, CDCl$_3$)



210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
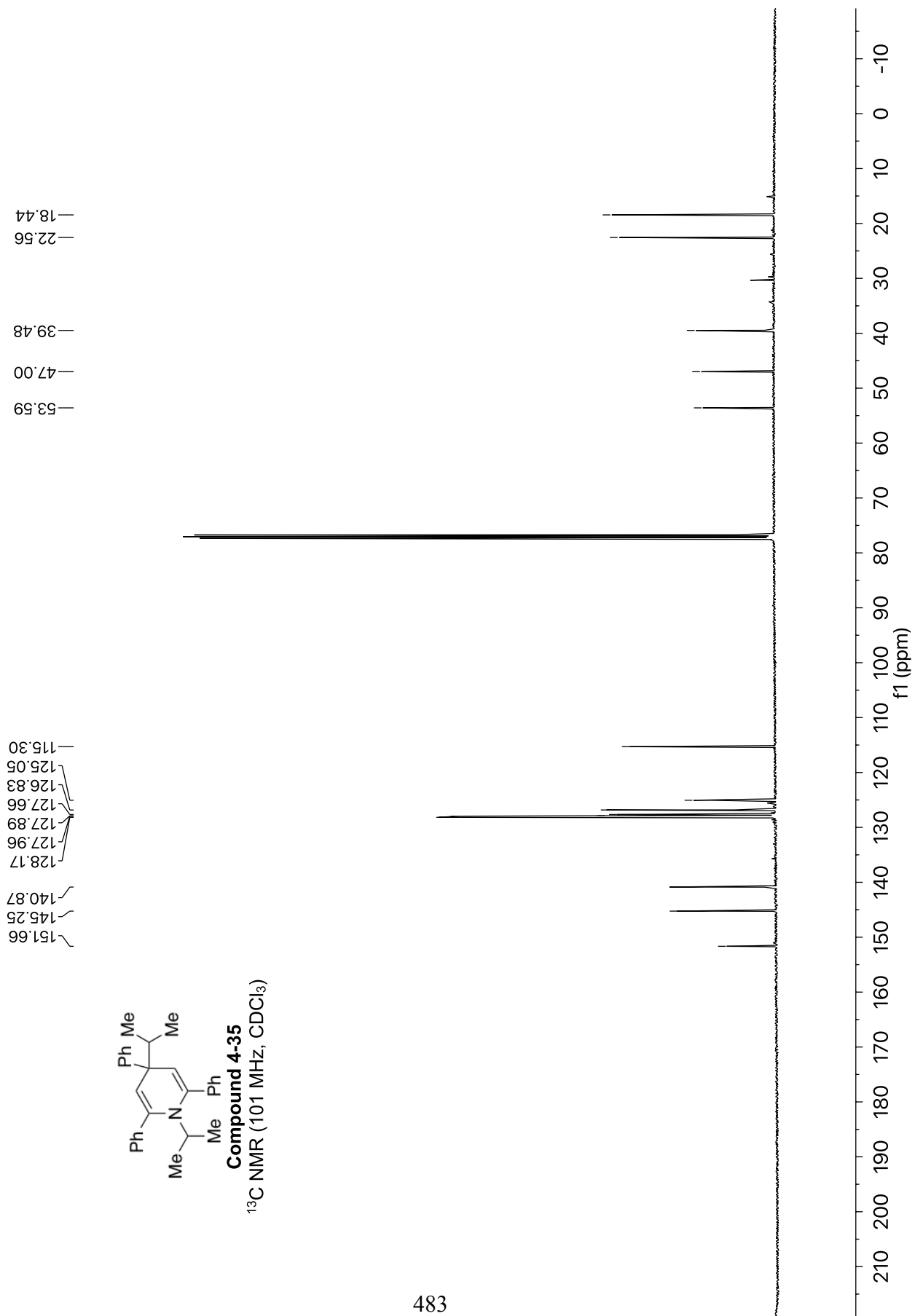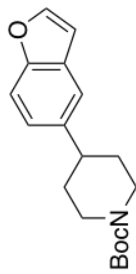
**Compound 4-51**
$^1$H NMR (600 MHz, CDCl$_3$)

1.49
1.64
1.65
1.66
1.66
1.67
1.68
1.70
1.70
1.85
1.87
2.71
2.72
2.72
2.73
2.74
2.75
2.75
2.76
2.77
2.82
4.26
6.73
7.14
7.15
7.42
7.43
7.44
7.60
7.60

9.40
2.18
2.02
1.18
2.07
1.98
1.00
1.04
1.97
1.00

484

28.52
33.80
42.74
44.54
79.43
106.48
111.21
118.75
123.41
127.55
140.51
145.26
153.74
154.90
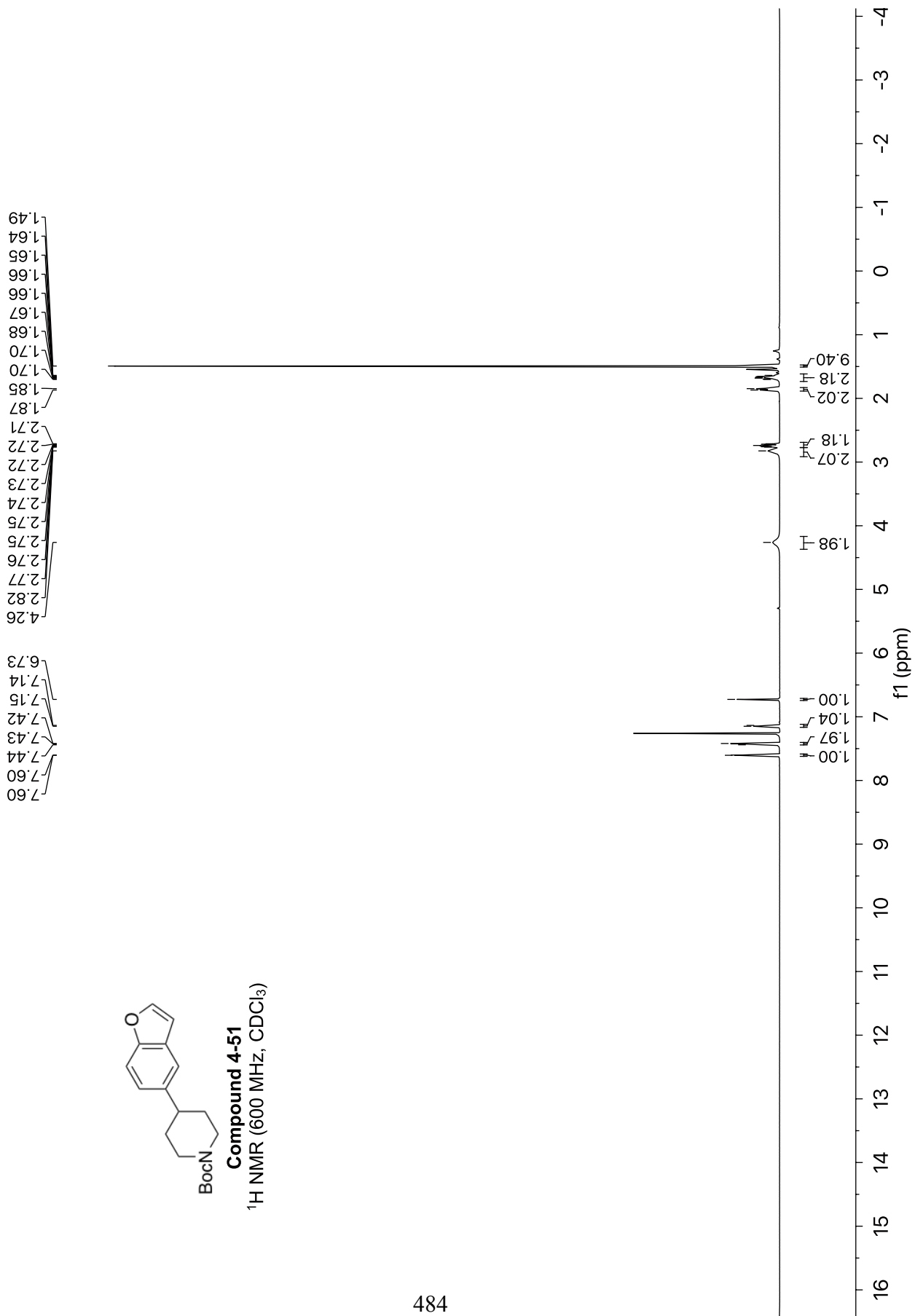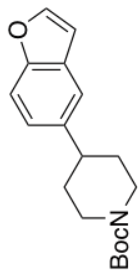
**Compound 4-51**
$^{13}$C NMR (151 MHz, CDCl$_3$)

f1 (ppm)

210  200  190  180  170  160  150  140  130  120  110  100  90  80  70  60  50  40  30  20  10  0  -10
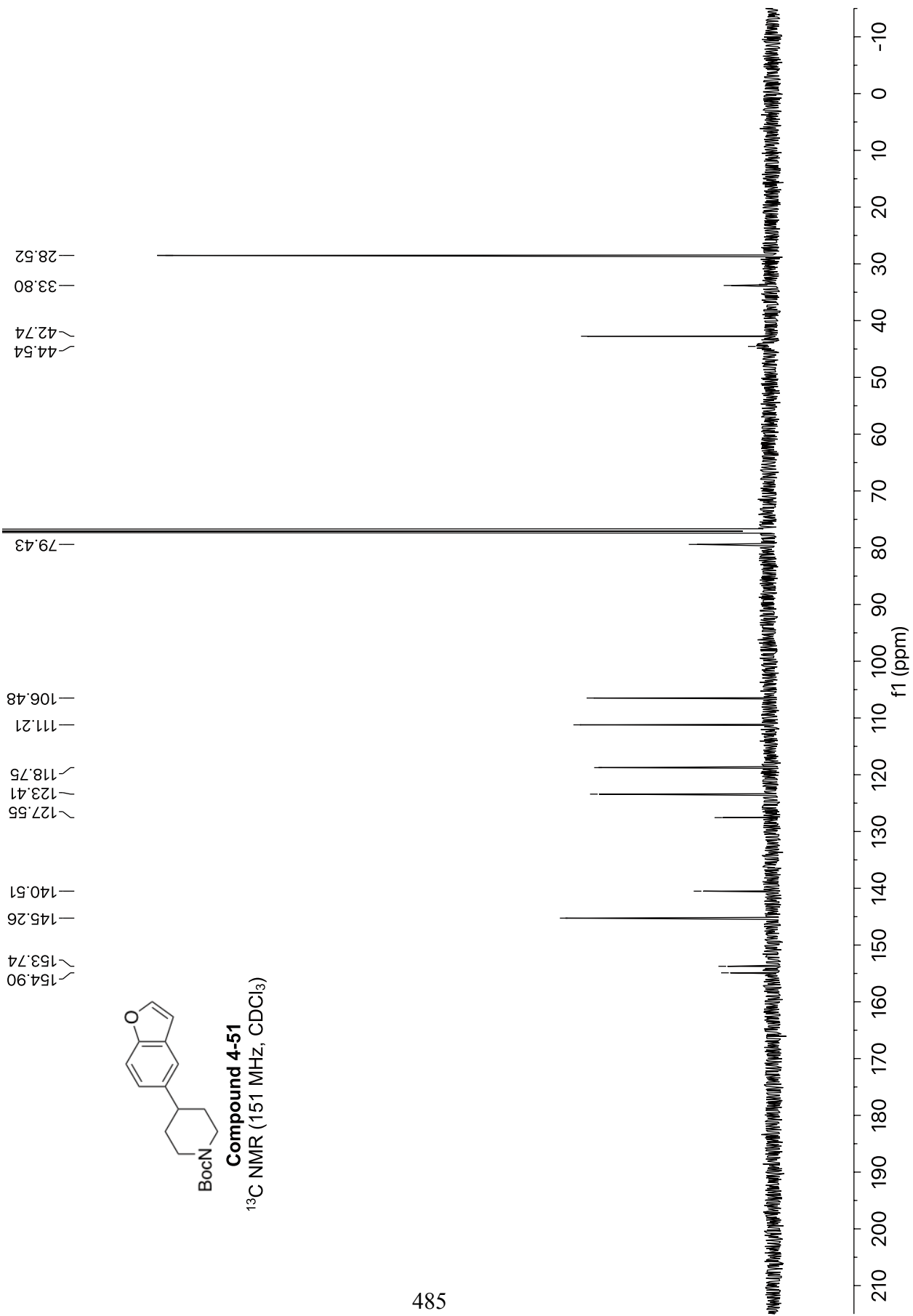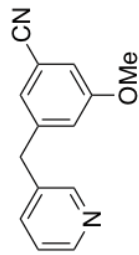
Compound 4-52
¹H NMR (400 MHz, CDCl₃)

8.52
8.51
8.51
8.50
8.49
8.48
7.47
7.46
7.46
7.45
7.44
7.44
7.26
7.25
7.25
7.24
7.23
7.23
7.06
7.06
7.06
7.02
7.01
7.01
6.93
6.93
6.92

3.97
3.80
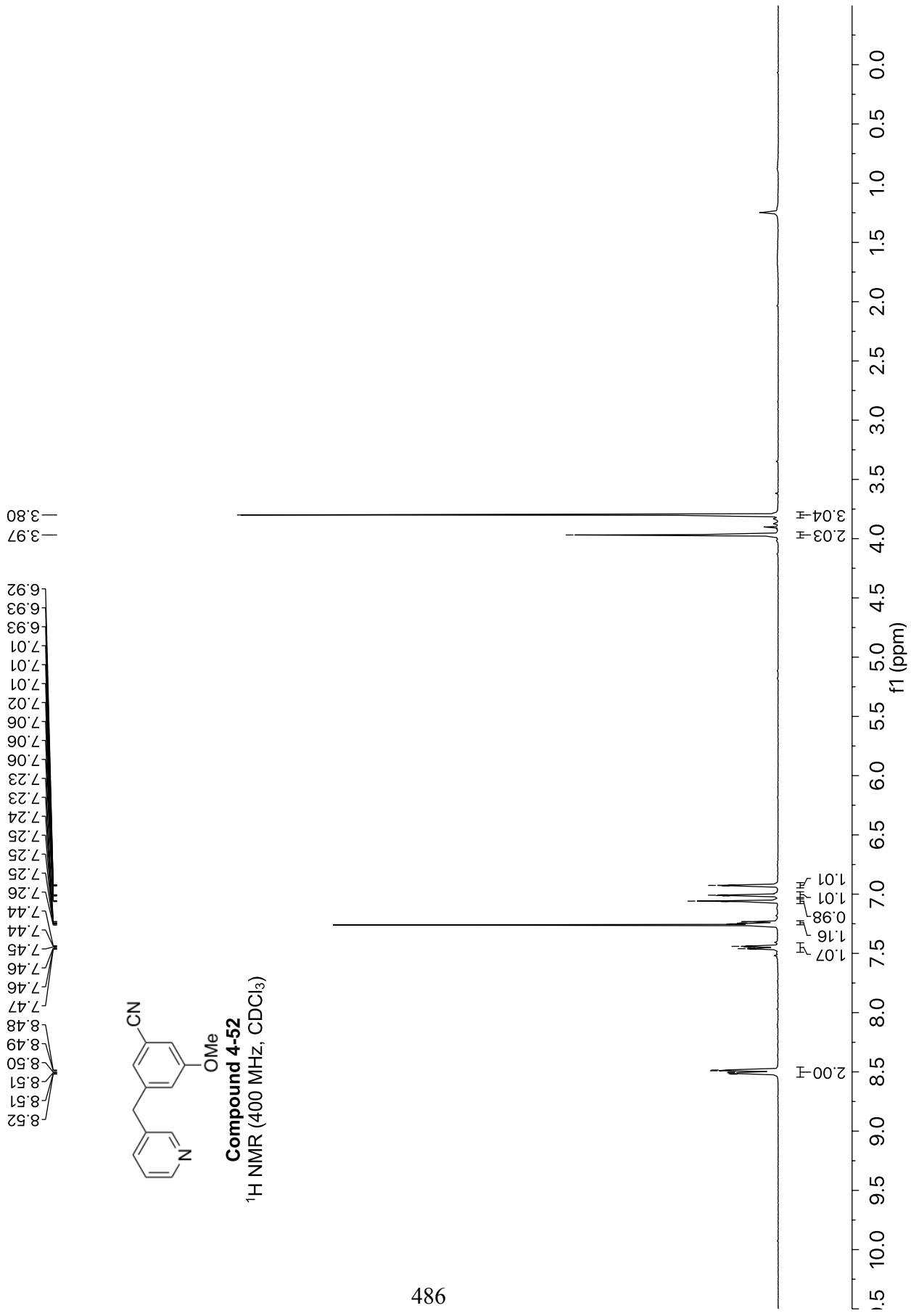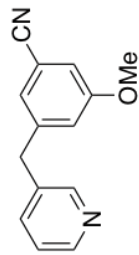
**Compound 4-52**
$^{13}$C NMR (101 MHz, CDCl$_3$)

38.60

55.62

113.44
114.78
118.63
120.04
123.67
124.83

134.84
136.31
142.84
148.30
150.10

159.95
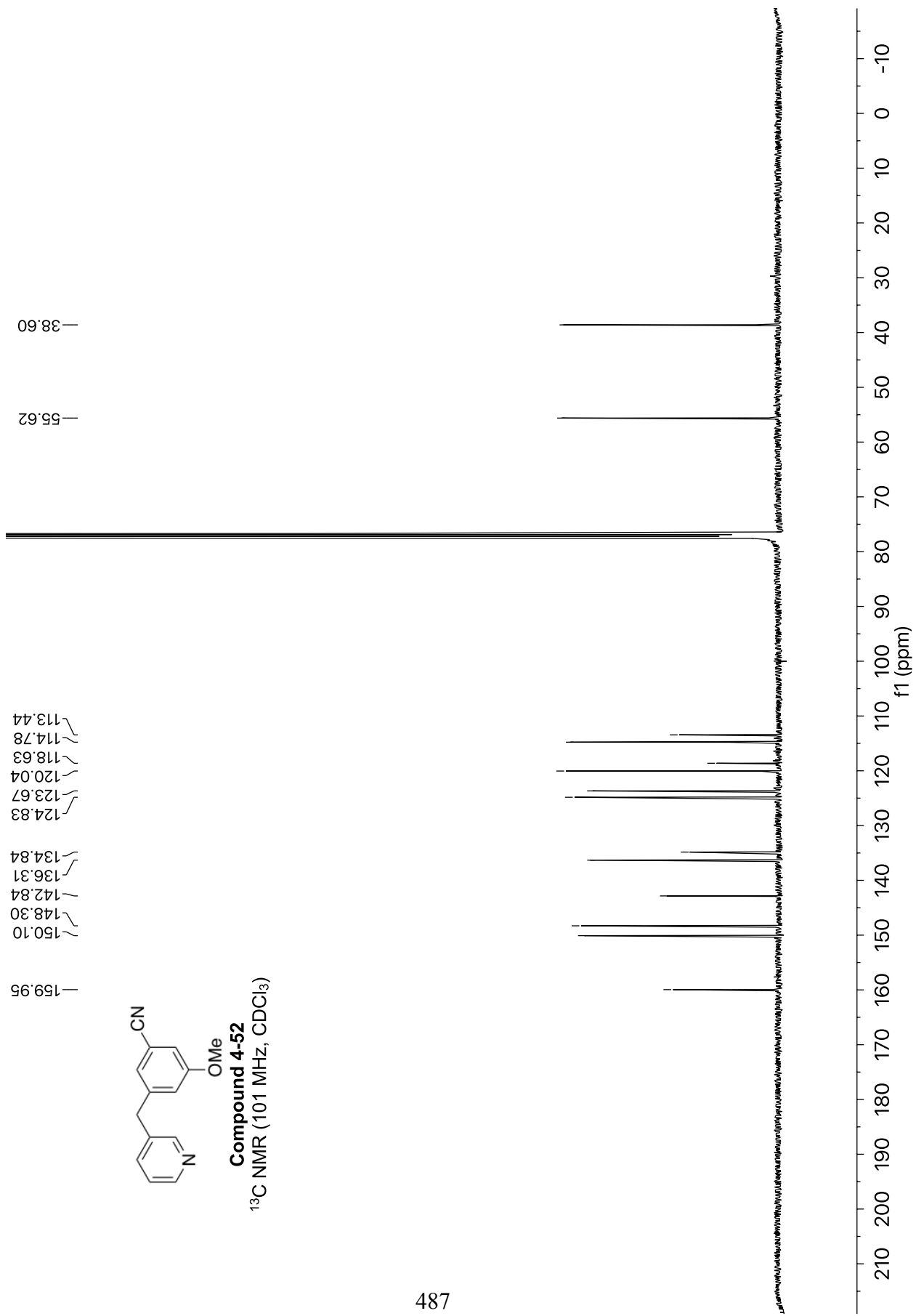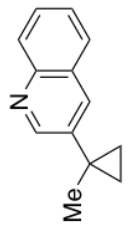
Compound 4-53
$^1$H NMR (400 MHz, CDCl$_3$)

488

15.03
18.40
25.58

126.56
127.35
127.95
128.54
129.09
132.91
139.58
146.55
151.02
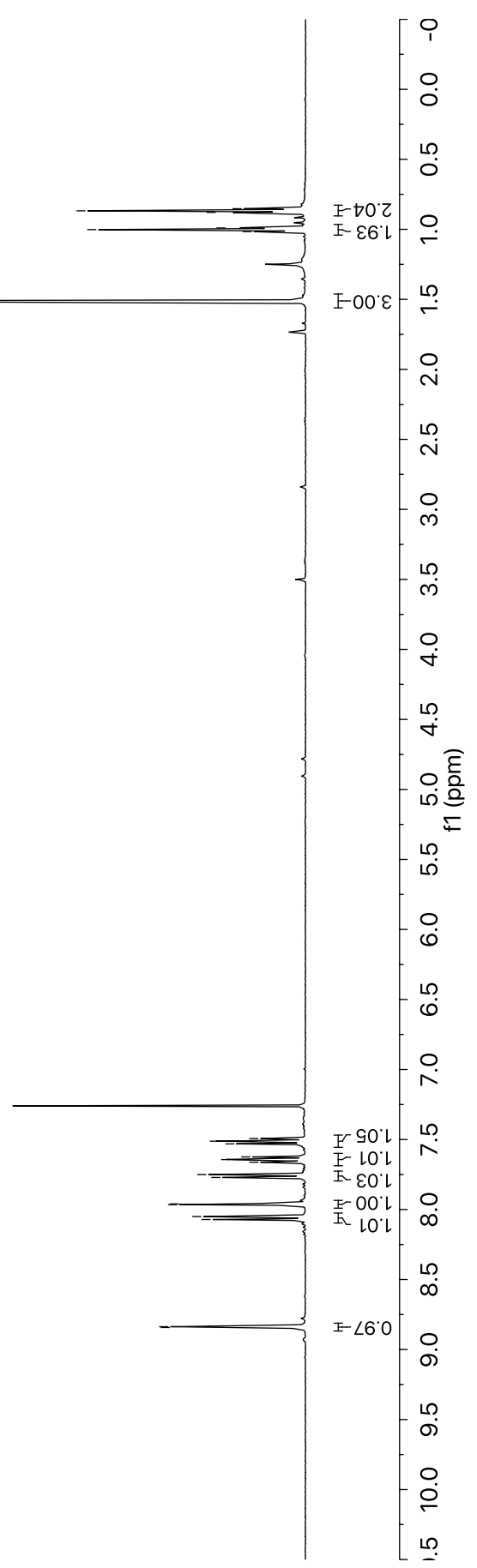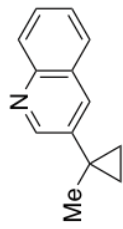
**Compound 4-53**
$^{13}$C NMR (151 MHz, CDCl$_3$)

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Compound 4-54
¹H NMR (400 MHz, CDCl₃)

2.95
2.95
2.96
2.97
2.98
2.99
3.02
3.03
3.04
3.04
3.04
3.05
3.06
3.07
5.91
6.61
6.62
6.63
6.64
6.69
6.69
6.70
6.72
7.06
7.06
7.06
7.08
7.08
7.08
7.09
7.10
7.11
7.11
7.11
7.11
7.12
7.13
7.54
7.55
7.56
7.56
7.58
7.58
8.55
8.55
8.55
8.55
8.56
8.56
8.56
8.56

Compound 4-54
$^{13}$C NMR (101 MHz, CDCl$_3$)

35.88
40.65
100.87
108.26
109.06
121.31
121.34
123.15
135.52
136.41
145.77
147.60
149.47
161.20

f1 (ppm)

491

Compound **4-55**
$^1$H NMR (400 MHz, CDCl$_3$)

492

Compound 4-55
13C NMR (101 MHz, CDCl₃)

15.38

31.62
31.88

45.43

52.80

132.06

156.71
158.09

172.62

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

**Compound 4-56**
¹H NMR (400 MHz, CDCl₃)

Peak labels: 1.51, 1.73, 1.74, 1.76, 1.78, 2.67, 2.69, 2.70, 2.72, 2.73, 2.74, 2.76, 2.78, 3.18, 3.19, 3.22, 3.23, 3.28, 3.29, 3.31, 3.34, 3.35, 3.38, 3.39, 4.04, 4.07, 4.09, 4.10, 4.11, 4.12, 4.13, 4.13, 4.14

Peak labels (aromatic region): 7.28, 7.51, 7.52, 7.53, 7.57, 7.59, 7.95, 7.97, 7.98, 8.00

Integrations: 9.42, 4.15, 4.21, 3.17, 0.98, 1.30, 2.13, 2.00

**Compound 4-56**

$^{13}$C NMR (101 MHz, CDCl$_3$)

22.72
23.51
25.25
28.64
29.03
29.75
39.53
40.54
46.34
46.85
58.71
79.16
79.43
122.05
122.15
126.46
127.28
127.35
128.19
128.54
131.45
132.00
135.92
136.83
146.62
154.56
154.61
158.27
158.46

**Compound 4-58**
$^1$H NMR (400 MHz, CDCl$_3$)

496

Compound 4-58
$^{13}$C NMR (101 MHz, CDCl$_3$)

19.75
28.11
30.12
31.35
36.48
37.28
42.62
66.15
67.47
80.68
98.78
109.69
119.13
129.34
132.16
147.79
170.26

Compound 4-59
$^1$H NMR (400 MHz, CDCl$_3$)

498

Compound 4-59
13C NMR (101 MHz, CDCl3)

26.76
40.26
52.83
58.44
62.54
67.01
76.22
115.12
115.33
128.58
129.60
130.68
130.76
133.45
133.48
135.52
144.16
160.94
163.38
198.02

f1 (ppm)

499

−115.59

**Compound 4-59**
$^{19}$F NMR (376 MHz, CDCl$_3$)

500

-10  -20  -30  -40  -50  -60  -70  -80  -90  -100  -110  -120  -130  -140  -150  -160  -170  -180  -190
f1 (ppm)

Compound 4-60
$^1$H NMR (600 MHz, CDCl$_3$)

501

40.11 —

52.73
58.33
62.43
66.87

76.25 —

115.00
115.14
125.70
126.37
128.36
129.70
130.52
130.57
133.42
133.45
138.35
140.81

161.24
162.04
162.86

**Compound 4-60**
¹³C NMR (151 MHz, CDCl₃)

502
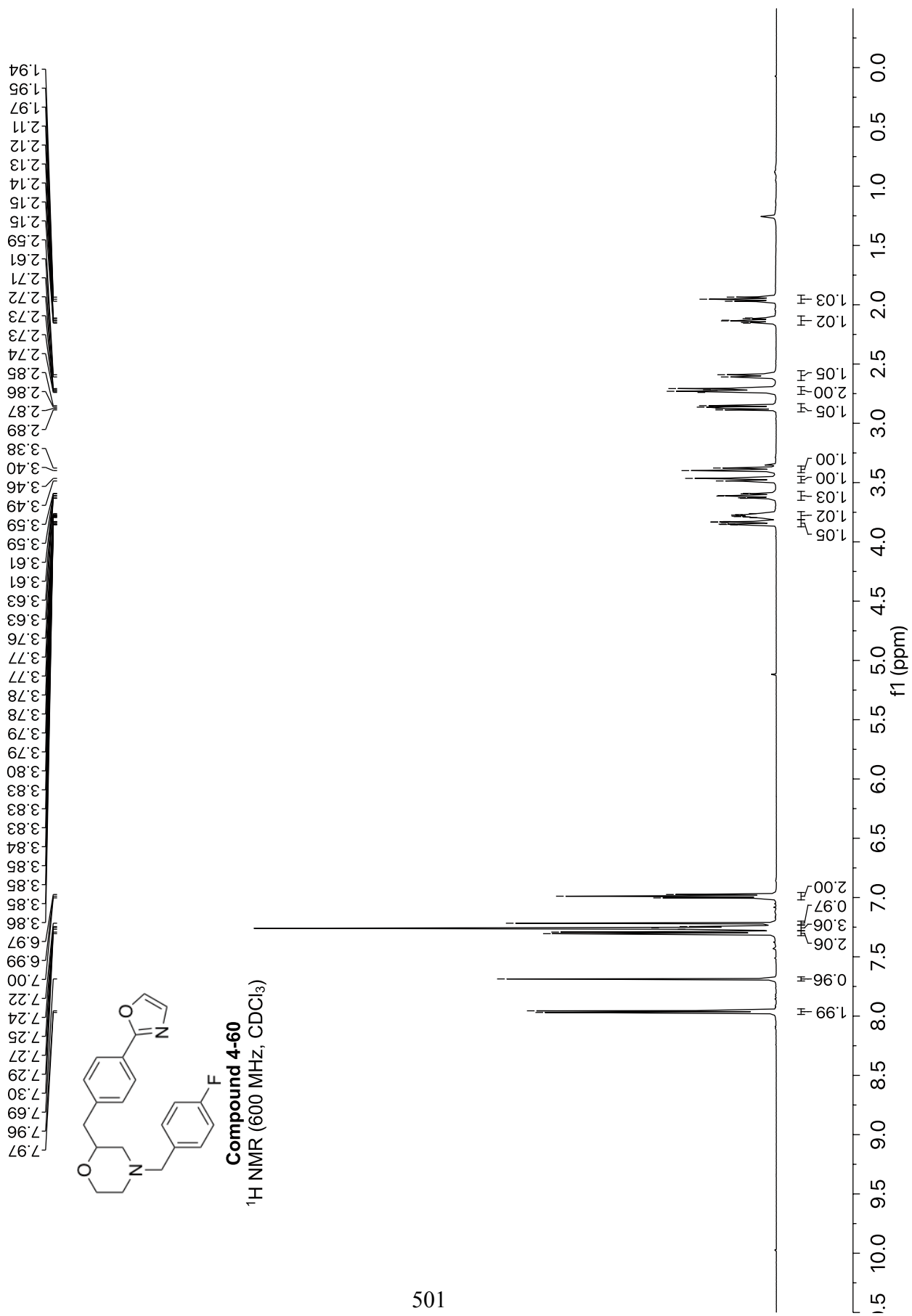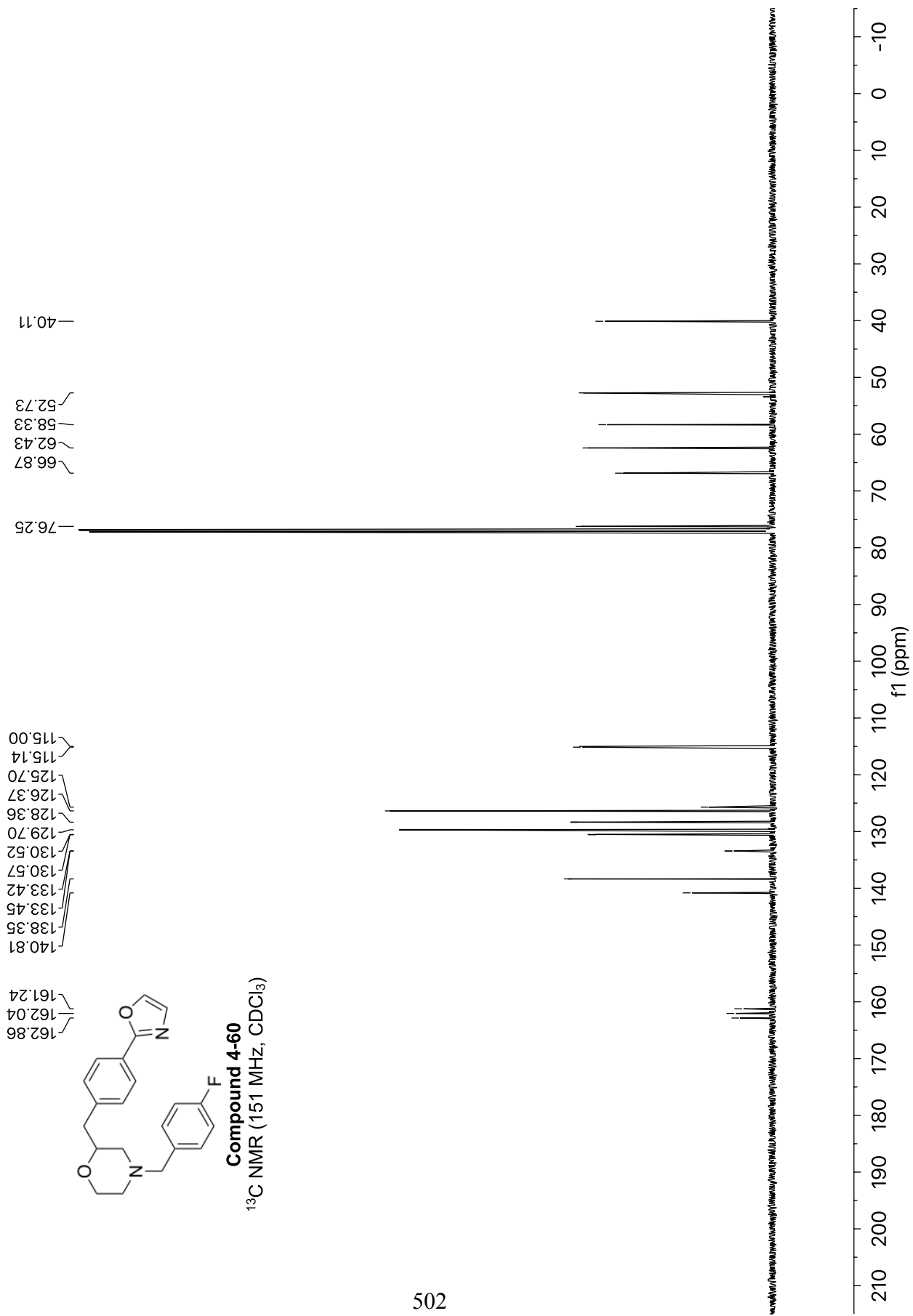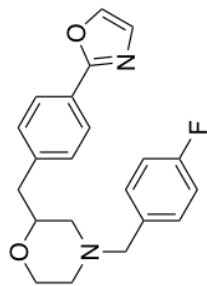
−115.72

**Compound 4-60**
<sup>19</sup>F NMR (565 MHz, CDCl₃)

503

f1 (ppm)

Compound 4-61
$^1$H NMR (400 MHz, CDCl$_3$)

504

14.28
19.26
35.95
37.18
50.84
59.84
67.68
71.44
101.43
103.92
120.11
122.81
125.51
125.51
125.55
125.59
125.62
126.82
127.40
128.22
128.55
128.88
129.20
129.27
129.28
129.52
131.46
132.35
142.96
143.64
145.12
145.61
167.14
167.93

**Compound 4-61**
$^{13}C$ NMR (101 MHz, CDCl$_3$)
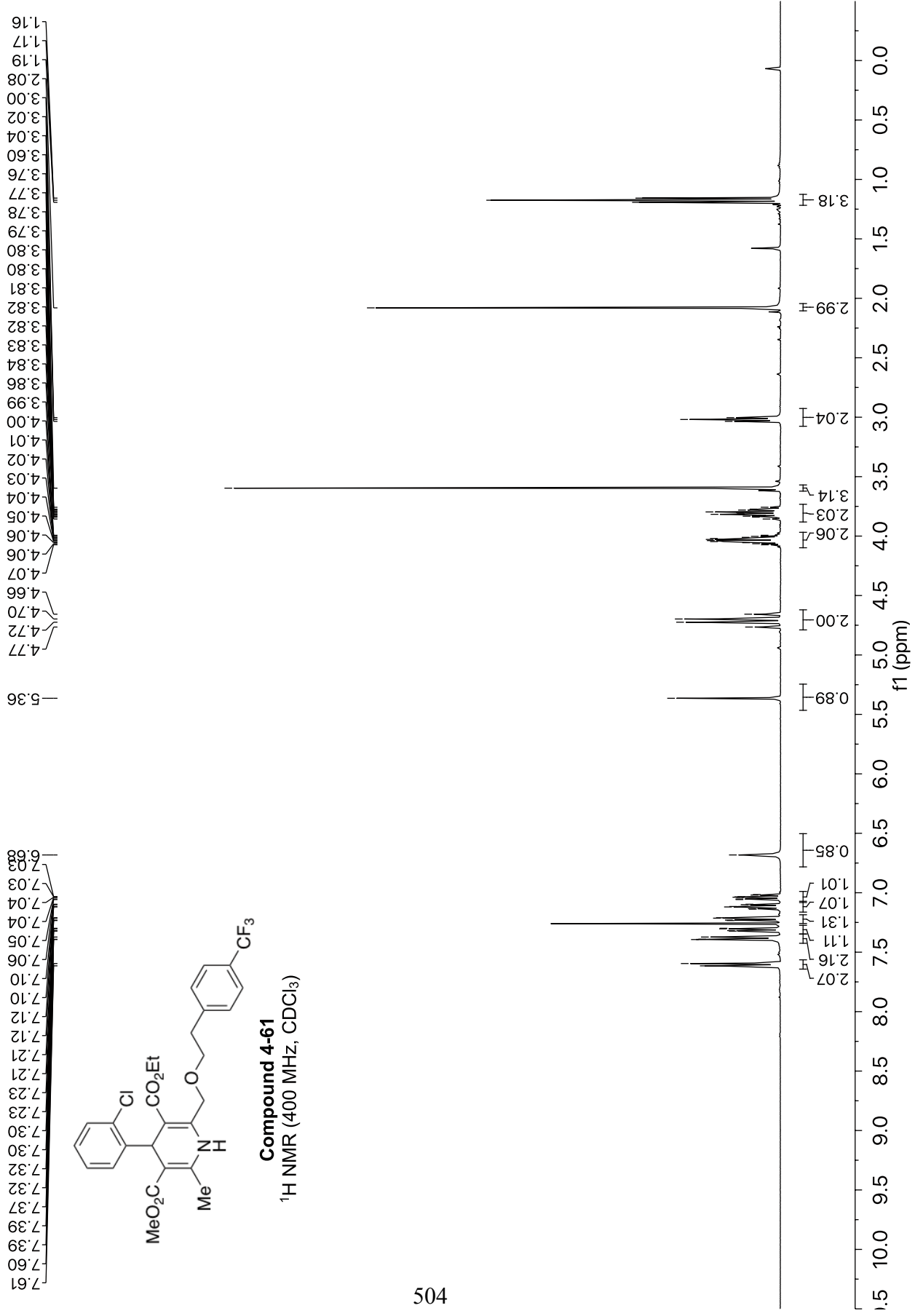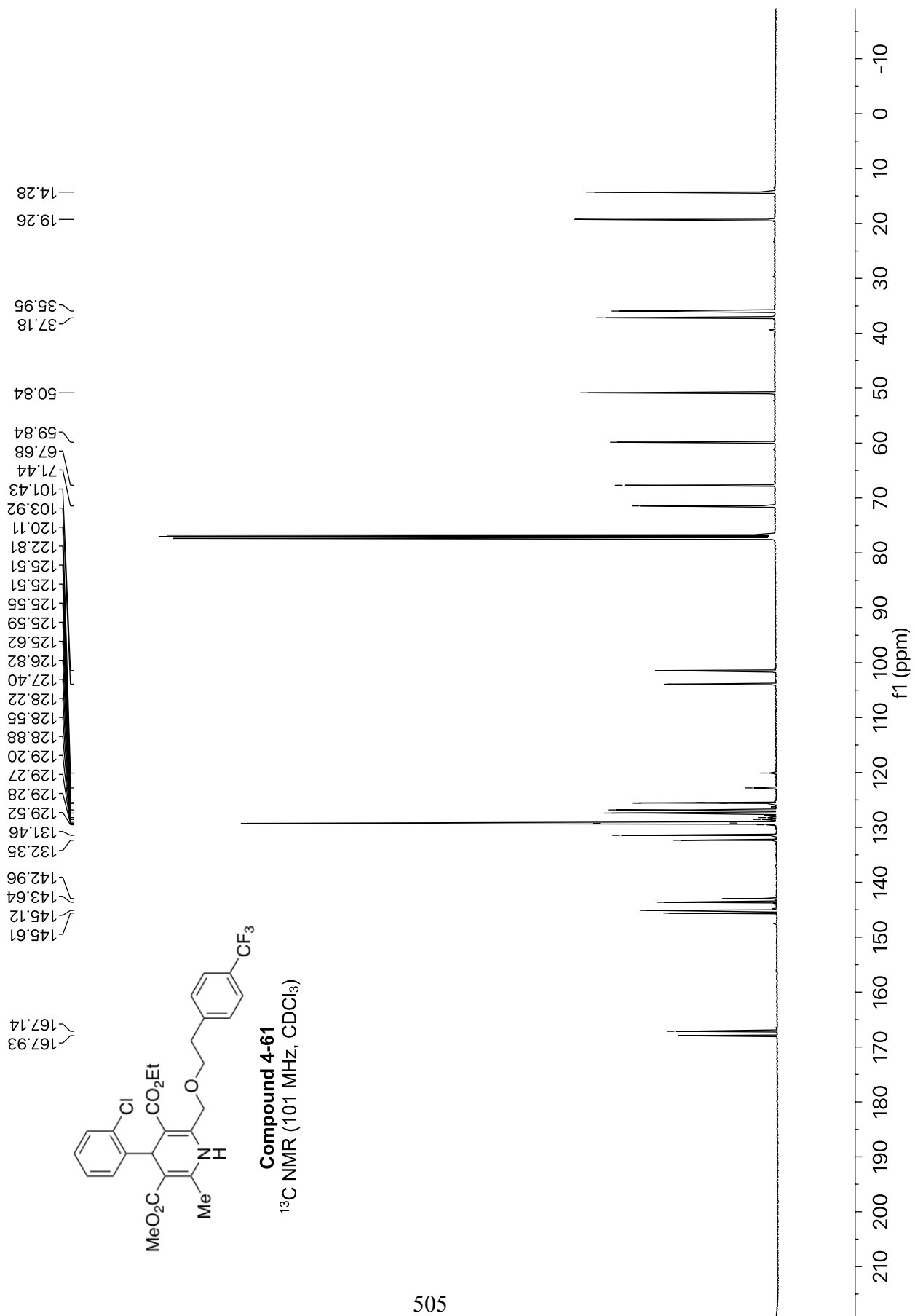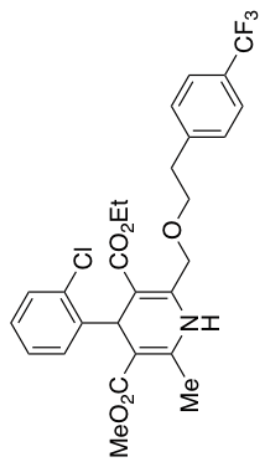
−62.43

**Compound 4-61**
$^{19}$F NMR (376 MHz, CDCl$_3$)

506

-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

**Compound 4-56**, racemic (210 nm)

mAU
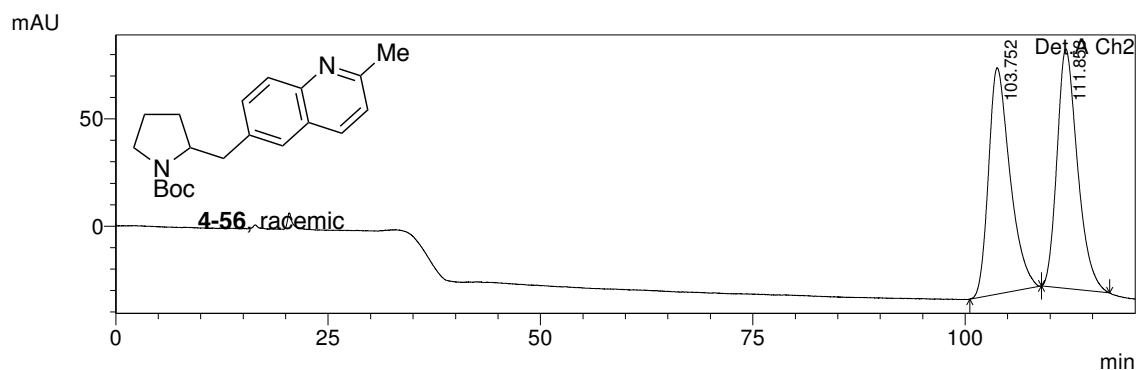


Detector A Ch2 210nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 103.752 | 18566299 | 105683 | 49.739 | 48.610 |
| 2 | 111.853 | 18761296 | 111728 | 50.261 | 51.390 |
| Total | | 37327594 | 217412 | 100.000 | 100.000 |

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 103.769 | 1621878 | 9271 | 50.216 | 48.923 |
| 2 | 111.787 | 1607943 | 9679 | 49.784 | 51.077 |
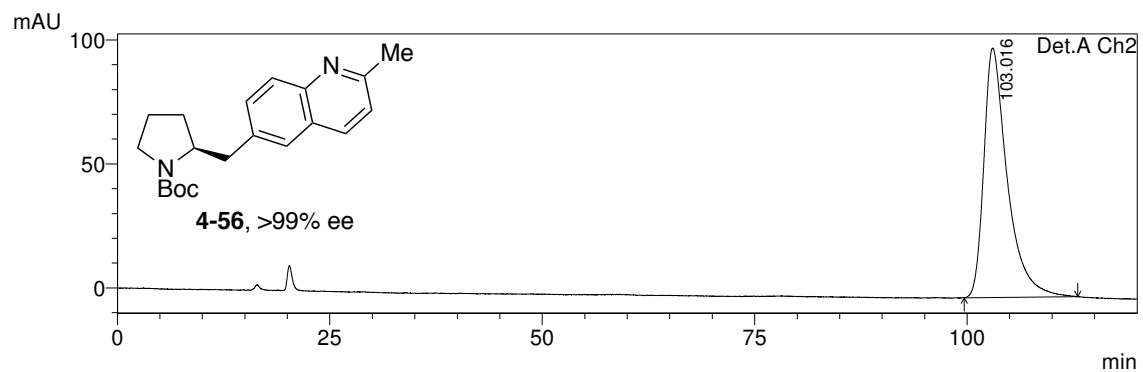
**Compound 4-56**, >99% ee (210 nm)

mAU



Detector A Ch2 210nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 103.016 | 19309963 | 100587 | 100.000 | 100.000 |
| Total | | 19309963 | 100587 | 100.000 | 100.000 |

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 102.903 | 1679541 | 8804 | 100.000 | 100.000 |
| Total | | 1679541 | 8804 | 100.000 | 100.000 |

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 103.016 | 19309963 | 100587 | 100.000 | 100.000 |
| Total | | 19309963 | 100587 | 100.000 | 100.000 |

507

**Appendix E**

**SPECTRAL AND CHROMATOGRAPHY DATA FOR CHAPTER 5**

Chiral ligands used in HTE (Scheme 5.13)

45

49

50

53

55

81

83

84

88

96

97

100

102

105

107

108

109

110

111

112

113

114

115

116

117

118

119

120

121

122

123

124

**Compound 5-44**
$^1$H NMR (400 MHz, CDCl$_3$)

511

Compound 5-44
$^{13}C$ NMR (101 MHz, CDCl$_3$)

31.25

68.87

84.38

90.63

118.75
121.71
126.08
127.03
127.61
128.42
128.82
129.01
129.17
129.64
130.35
132.02
140.90
147.48

Compound 5-49
¹H NMR (400 MHz, CDCl₃)

513

Peak labels (left axis, top to bottom):
2.83
7.19
7.20
7.21
7.22
7.22
7.24
7.31
7.31
7.32
7.33
7.33
7.34
7.35
7.35
7.36
7.36
7.37
7.38
7.38
7.39
7.40
7.40
7.41
7.42
7.43
7.43
7.44
7.49
7.50
7.50
7.51
7.52
7.52
7.53
7.53
7.54
7.55
7.56
7.57
7.58
7.67
7.67
7.68
7.68
7.69
7.70
7.86
7.87
7.88
7.88
7.89
7.90

Integration labels: 3.00, 1.27, 6.17, 4.06, 1.92, 0.88

x-axis: f1 (ppm) — 10.0, 9.5, 9.0, 8.5, 8.0, 7.5, 7.0, 6.5, 6.0, 5.5, 5.0, 4.5, 4.0, 3.5, 3.0, 2.5, 2.0, 1.5, 1.0, 0.5, 0.0

24.73

66.79

83.99

90.18

121.21
121.52
125.18
127.33
128.39
128.88
129.13
129.19
129.70
132.01
132.92
133.53
138.07
140.92

**Compound 5-49**
$^{13}$C NMR (101 MHz, CDCl$_3$)

514

Compound 5-54
$^1$H NMR (600 MHz, CDCl$_3$)

515
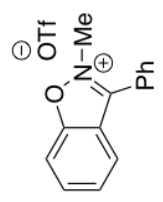
Compound 5-53
$^1$H NMR (600 MHz, CDCl$_3$)

516
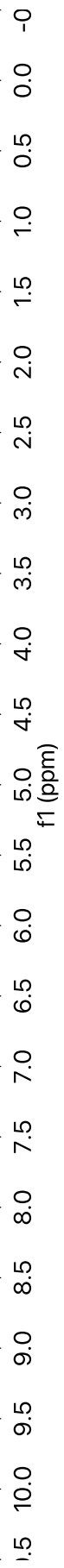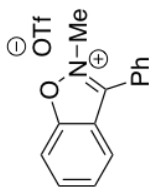
Compound 5-53
$^{13}$C NMR (151 MHz, CDCl$_3$)

40.46

110.68
119.68
121.28
124.81
128.33
130.09
130.38
134.14
137.51

156.41
159.86

Compound 5-70
$^1$H NMR (400 MHz, CDCl$_3$)

518

Compound 5-70
$^{13}$C NMR (101 MHz, CDCl$_3$)

21.57
21.83
21.86
25.83
33.82
68.42
69.63
70.18
111.32
120.02
120.24
127.58
129.10
129.24
129.28
129.30
129.77
134.37
134.78
159.40
159.55
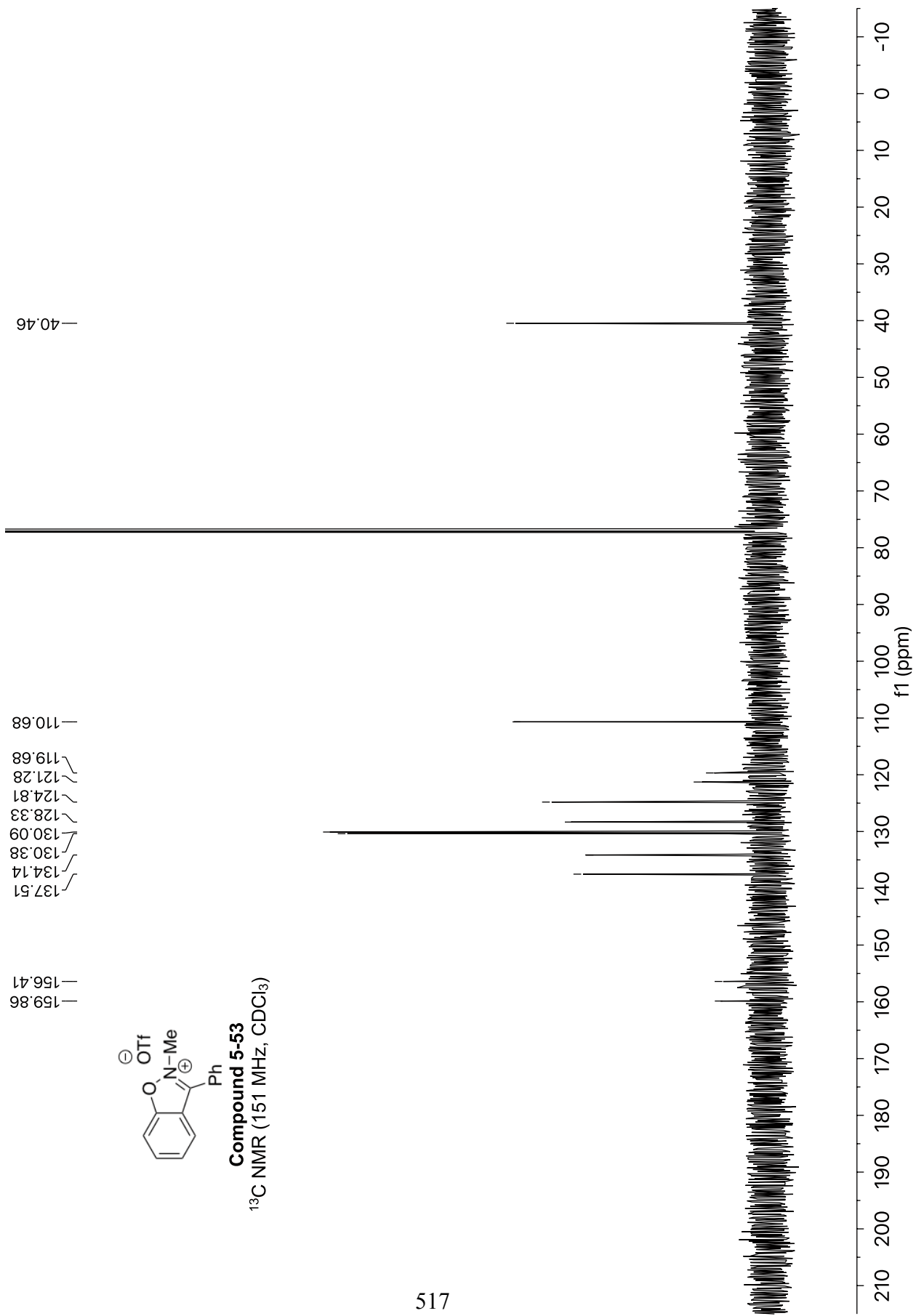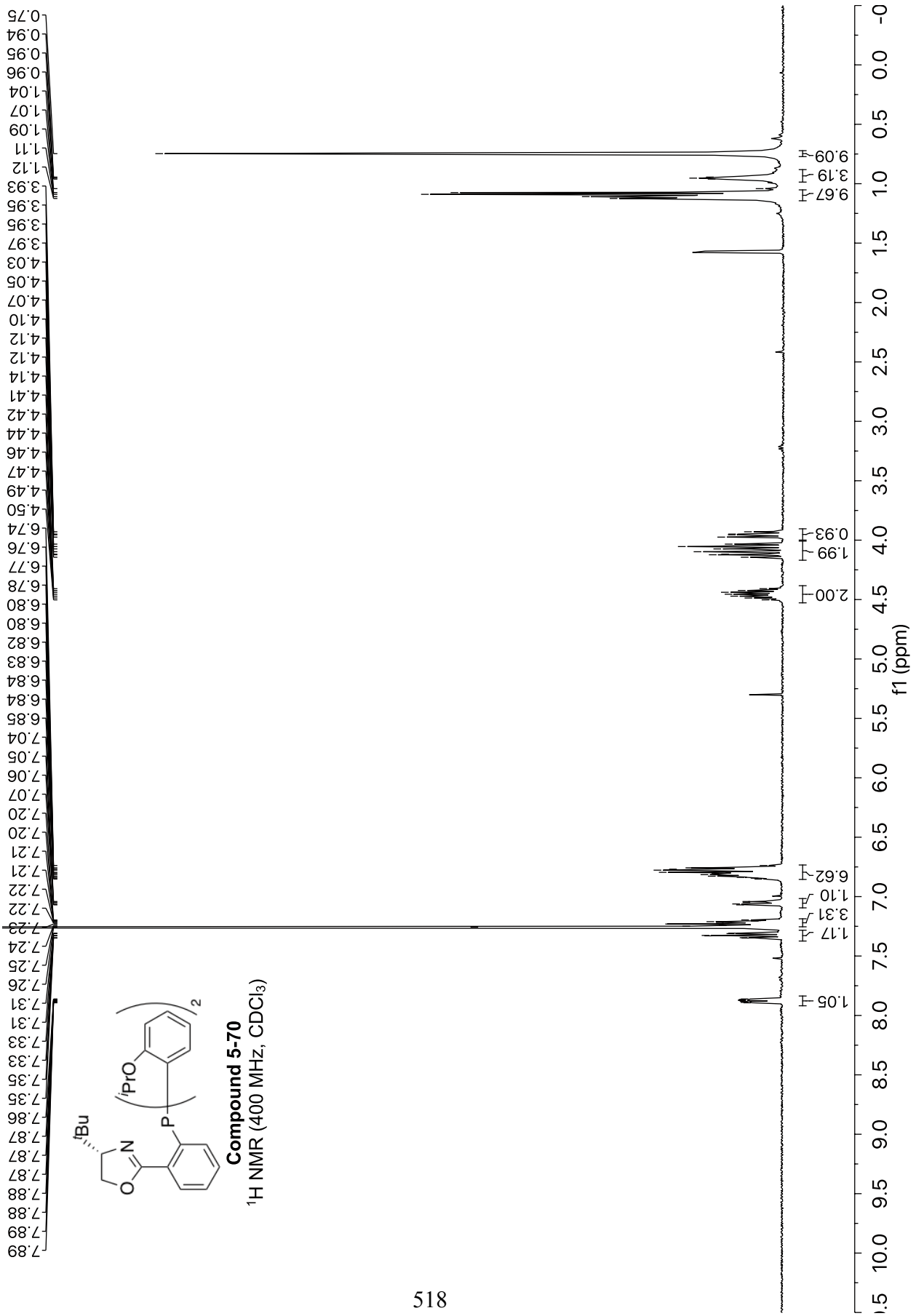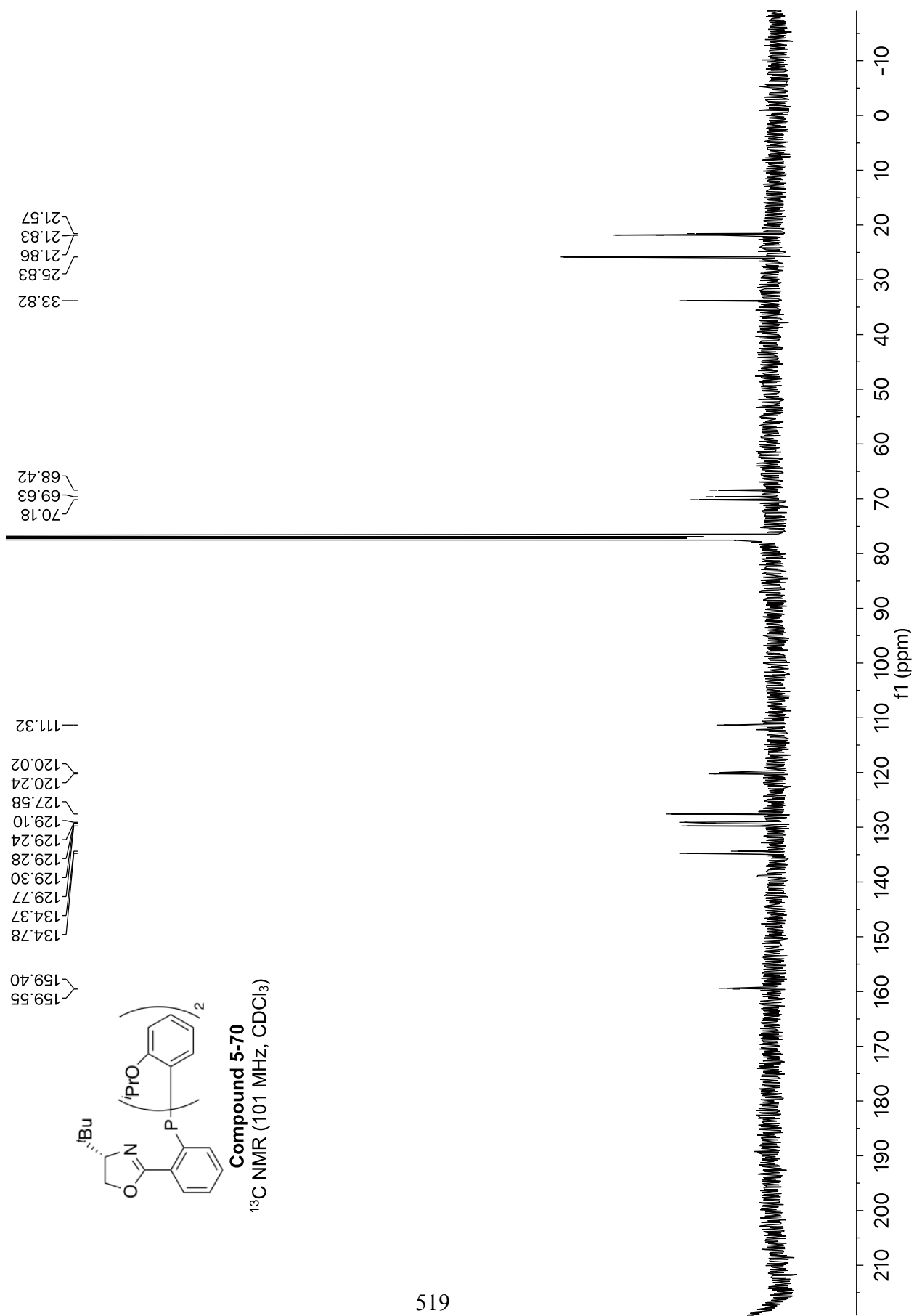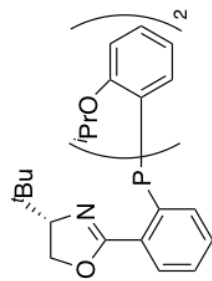
−24.44

**Compound 5-70**
31P NMR (162 MHz, CDCl₃)

520

f1 (ppm)

130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190 -210 -230
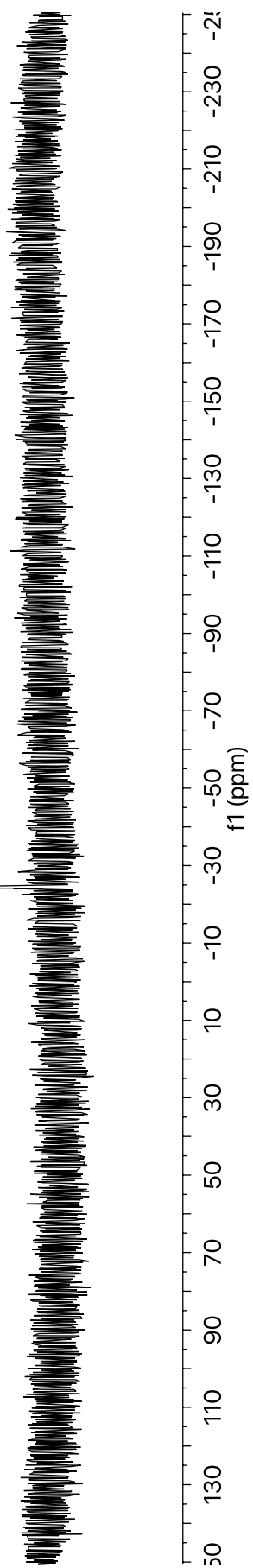
**Appendix F**

**PERMISSION LETTERS**

**PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE**

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

**ACS Publications**
Most Trusted. Most Cited. Most Read.

**Title:** Transforming Benzylic Amines into Diarylmethanes: Cross-Couplings of Benzylic Pyridinium Salts via C–N Bond Activation

**Author:** Jennie Liao, Weiye Guan, Brian P. Boscoe, et al

**Publication:** Organic Letters

**Publisher:** American Chemical Society

**Date:** May 1, 2018

Copyright © 2018, American Chemical Society

### PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

BACK | CLOSE WINDOW

This Agreement between Jennie Liao ("You") and Georg Thieme Verlag KG ("Georg Thieme Verlag KG") consists of your license details and the terms and conditions provided by Georg Thieme Verlag KG and Copyright Clearance Center.

The publisher has provided special terms related to this request that can be found at the end of the Publisher's Terms and Conditions.

| | |
|---|---|
| License Number | 4476470141077 |
| License date | Nov 26, 2018 |
| Licensed Content Publisher | Georg Thieme Verlag KG |
| Licensed Content Publication | Synthesis |
| Licensed Content Title | Vinylation of Benzylic Amines via C–N Bond Functionalization of Benzylic Pyridinium Salts |
| Licensed Content Author | Weiye Guan, Jennie Liao, Mary P. Watson |
| Licensed Content Date | Jan 1, 2018 |
| Licensed Content Volume | 50 |
| Licensed Content Issue | 16 |
| Type of Use | Dissertation/Thesis |
| Requestor type | author of the original Thieme publication |
| Format | print and electronic |
| Portion | full article/document |
| Will you be translating? | no |
| Distribution quantity | 1 |
| Specified additional information | This work will be described in detail in my PhD thesis. |
| Order reference number | |
| Title of your dissertation / thesis | Harnessing Alkyl Amines in Nickel-Catalyzed Cross-Couplings Via C–N Bond Activation |
| Expected completion date | Dec 2018 |
| Estimated size (number of pages) | 400 |
| Requestor Location | Jennie Liao<br>109 King William St<br><br>NEWARK, DE 19711<br>United States<br>Attn: Jennie Liao |

525

negatively on the publisher or any writer of the material), nor may you translate the material into another language.

**Reservation of Rights**
Publisher reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

**License Contingent on Payment**
While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and publisher reserves the right to take any and all action to protect its copyright in the materials.

**Copyright Notice: Disclaimer**
Must include the following copyright and permission notice in connection with any reproduction of the licensed material: "© Georg Thieme Verlag KG."

**Warranties: None**
Publisher makes no representations or warranties with respect to the licensed material and adopts on its own behalf the limitations and disclaimers established by CCC on its behalf in its Billing and Payment terms and conditions for this licensing transaction.

**Indemnity**
You hereby indemnify and agree to hold harmless publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

**No Transfer of License**
This license is personal to you, but may be assigned or transferred by you to a business associate (or to your employer) if you give prompt written notice of the assignment or transfer to the publisher. No such assignment or transfer shall relieve you of the obligation to pay the designated license fee on a timely basis (although payment by the identified assignee can fulfill your obligation).

**No Amendment Except in Writing**
This license may not be amended except in a writing signed by both parties (or, in the case of publisher, by CCC on publisher's behalf).

**Objection to Contrary Terms**

Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

**Jurisdiction:**
This license transaction shall be governed by and construed in accordance with the laws of the Federal Republic of Germany. You hereby agree to submit to the jurisdiction of the federal and state courts located in Berlin, Germany for purposes of resolving any disputes that may arise in connection with this licensing transaction.

**Special Terms:** We grant permission to use this material for the aforesaid publication in printed and electronic form to be stored in the electronic academic repository of the University. The article is to be used in the accepted WORD version without layout. Use of the final PDF version is explicitly excluded. Permission for further rights and for storage in any other repositories is explicitly excluded.
v 1.4

**Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.**