Development of Deactivation-Resistant Catalysts for Pd-Catalyzed C–N Cross-Coupling Reactions

by

Elaine C. Reichert

A.B. Chemistry and Physics
Harvard College, 2018

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy in Chemistry

at the

Massachusetts Institute of Technology

June 2023

Authored by: Elaine C. Reichert
Department of Chemistry
May 12, 2023

Certified by: Stephen Leffler Buchwald
Camille Dreyfus Professor of Chemistry
Thesis Supervisor

Accepted by: Adam P. Willard
Associate Professor of Chemistry
Graduate Officer

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

Professor Rick Lane Danheiser_____
Thesis Committee Chair
Arthur C. Cope Professor of Chemistry

Professor Stephen Leffler Buchwald_____
Thesis Supervisor
Camille Dreyfus Professor of Chemistry

Professor Alison Wendlandt_____
Thesis Committee Member
Cecil and Ida Green Career Development Assistant Professor of Chemistry

Development of Deactivation-Resistant Catalysts for
Pd-Catalyzed C–N Cross-Coupling Reactions

by

Elaine C. Reichert

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Chemistry

Abstract

Chapter 1: Introduction to Pd-Catalyzed C–N Cross-Coupling: Rational Biarylphosphine Ligand Design Enhances the Reactivity of Difficult Substrates

Transition-metal-catalyzed C−N cross-coupling reactions are an important class of transformations with applications in a variety of fields, and Pd-based catalysts are among the most effective for these reactions. However, certain classes of compounds, including very bulky substrates as well as those containing coordinating functional groups, can be very difficult to couple. The choice of the supporting ligand on Pd plays an important role in the efficiency of a given reaction, since the ligand is necessary to facilitate the productive coupling reaction and hinder the formation of off-cycle Pd species. Correspondingly, the Buchwald lab has enabled challenging transformations by rationally designing new biarylphosphine ligands.

Chapter 2: Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability

A new dialkylbiaryl monophosphine ligand, GPhos, that supports a palladium catalyst capable of promoting carbon–nitrogen cross-coupling reactions between a variety of primary amines and aryl halides, was developed; in many cases, these reactions can be carried out at room temperature. The reaction development was guided by the idea that the productivity of catalysts employing BrettPhos-like ligands is limited by their lack of stability at room temperature. Specifically, it was hypothesized that primary amine and *N*-heteroaromatic substrates can displace the phosphine ligand, leading to the formation of catalytically dormant palladium complexes that reactivate only upon heating. This notion was supported by the synthesis and kinetic study of a putative off-cycle Pd complex. Consideration of this off-cycle species, together with the identification of substrate classes that are not effectively coupled at room temperature using previous catalysts, led to the design of a new dialkylbiaryl monophosphine ligand. An O*t*-Bu substituent was added ortho to the dialkylphosphino group of the ligand framework to improve the stability of the most active catalyst conformer. To offset the increased size of this substituent, we also removed the para *i*-Pr group of the non-phosphorus-containing ring, which allowed the catalyst to accommodate binding of even very large α-tertiary primary amine nucleophiles. In comparison to previous catalysts, the GPhos-supported catalyst exhibits better reactivity both under ambient conditions and at elevated temperatures. Its use allows for the coupling of a range of amine nucleophiles, including (1)

unhindered, (2) five-membered-ring *N*-heterocycle-containing, and (3) α-tertiary primary amines, each of which previously required a different catalyst to achieve optimal results.

Chapter 3: Pd-Catalyzed Amination of Base-Sensitive Five-Membered Heteroaryl Halides with Aliphatic Amines

A versatile and functional-group-tolerant method was developed for the Pd-catalyzed C–N cross-coupling of five-membered heteroaryl halides with primary and secondary amines, an important but underexplored transformation. Coupling reactions of challenging, pharmaceutically relevant heteroarenes, such as 2-*H*-1,3-azoles, are reported in good-to-excellent yields. High-yielding coupling reactions of a wide set of five-membered heteroaryl halides with sterically demanding α-branched cyclic amines and acyclic secondary amines are reported for the first time. The key to the broad applicability of this method is the synergistic combination of (1) the moderate-strength base NaOTMS, which limits base-mediated decomposition of sensitive five-membered heteroarenes that ultimately leads to catalyst deactivation, and (2) the use of a GPhos-supported Pd catalyst, which effectively resists heteroarene-induced catalyst deactivation while promoting efficient coupling, even for challenging and sterically demanding amines. Cross-coupling reactions between a wide variety of five-membered heteroaryl halides and amines are demonstrated, including eight examples involving densely functionalized medicinal chemistry building blocks.

Thesis Supervisor: Stephen Leffler Buchwald
Title: Camille Dreyfus Professor of Chemistry

Acknowledgements

I am fortunate to have had a genuinely enjoyable graduate school experience, which can be attributed in large part to my incredibly supportive, knowledgeable, and entertaining advisor, Prof. Stephen L. Buchwald. Steve's mentorship style strikes the perfect balance between allowing me the freedom to pursue projects of my own choosing, while providing me with necessary guidance on how to maximize the impact of my work.

To my thesis committee chair, Prof. Rick L. Danheiser, thank you for your thoughtful career advice, and for setting an excellent example of how to be a caring, thorough, and organized instructor for the undergraduates in 5.12. To my third committee member, Prof. Alison E. Wendlandt, thank you for your invaluable mechanistic insight, and for letting me tag along on your group outings.

During my time in graduate school, I was lucky to work with a truly amazing group of mentors, collaborators, and friends. Dr. Scott D. McCann, my first mentor in the Buchwald lab, was simply the best mentor any first-year graduate student could hope for. Scott is a rare breed: so hardworking, so organized, and yet so humble. I credit Scott's mentorship with setting me on a path toward independence as a researcher. Additionally, I benefited greatly from the mentorship of Dr. Alexander W. Schuppe, whom I had the pleasure of working next to for three years. Alex uses his encyclopedic knowledge of synthetic techniques for good, always willing to take time from his own work to help others.

To Dr. Kaibo Feng, my collaborator of three years and alumina chromatography expert, thank you for teaching me the art of "spin." To Dr. Aaron C. Sather and Dr. Pedro Luis Arrechea, Buchwald lab alumni whom I was fortunate to get to know through our collaborations, thank you for your insistence on operational practicality (Aaron) and precise language (Pedro). To Dr. Dennis A. Kutateladze ("Mr. Mechanism"), thank you for the many, many mechanistic discussions. Thank you to Dr. Albert Cabré, Dr. Joseph M. Dennis, Dr. Heemal H. Dhanjee, Dr. Yuyang Dong, Dr. Megan E. Greaves, Dr. Seoung-Tae Kim, James Levi Knippel, Dr. Veronika Kottisch, Dr. James A. Law, Dr. Richard Y. Liu, Dr. Mahesh M. Parsutkar, Jacob Rodriguez, Dr. Simon L. Rössler, Dr. Michael J. Strauss, and many others in the Buchwald lab for helpful discussions. To Gino E. Occhialini, Hayden M. Carder, and Merjema Purak, thank you for your support and friendship.

I would also like to sincerely thank my mentors prior to graduate school, who encouraged my interest in chemistry research: my high school chemistry teacher, Mr. Kenneth Greathouse; Dr. Charles Y. Lin and Prof. James E. Bradner; Dr. Hongkang Zhang and Prof. Adam E. Cohen; Dr. Andreas Greb and Prof. Steven V. Ley; and Dr. Katrina M. Mennie and Prof. Eric N. Jacobsen. You inspire me to pay your generosity forward.

Finally, to my parents and sister, thank you for your love and support. And to Aditya, my collaborator in life: thank you for everything.

Preface

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

Chapter 2: Adapted with permission from McCann, S. D.[†]; Reichert, E. C.[†]; Arrechea, P. L.; Buchwald, S. L. Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability. *J. Am. Chem. Soc.* **2020**, *142*, 15027–15037. Copyright 2020 American Chemical Society. https://doi.org/10.1021/jacs.0c06139

Chapter 3: Adapted with permission from Reichert, E. C.[†]; Feng, K.[†]; Sather, A. C.; Buchwald, S. L. Pd-Catalyzed Amination of Base-Sensitive Five-Membered Heteroaryl Halides with Aliphatic Amines. *J. Am. Chem. Soc.* **2023**, *145*, 3323–3329. Copyright 2023 American Chemical Society. https://doi.org/10.1021/jacs.2c13520

[†] Denotes equal contribution from the authors.

The reader should note that the reference numbers and numerical designation of title compounds are unique to each chapter. That is, for each new chapter, the numbering restarts and proceeds sequentially until the end of the chapter.

Respective Contributions

Chapter 1: This introduction was written by the author.

Chapter 2: This work was done in equal collaboration with Dr. Scott D. McCann and the author. Initial experiments were performed by Dr. McCann; the optimization, substrate scope, and mechanistic studies were performed by Dr. McCann and the author. The conceptualization of this project was informed by Dr. Pedro Luis Arrechea.

Chapter 3: This work was done in equal collaboration with Dr. Kaibo Feng and the author. Initial experiments were performed by the author; the optimization and substrate scope were performed by Dr. Feng and the author. Dr. Aaron C. Sather performed high-throughput experimentation.

Table of Contents

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 1

Introduction to Pd-Catalyzed C–N Cross-Coupling: Rational Biarylphosphine Ligand Design Enhances the Reactivity of Difficult Substrates

1.1 Introduction

Since their development in the mid-20th century, transition-metal-catalyzed cross-coupling reactions have risen to prominence as some of the most-utilized transformations in the synthesis of complex organic molecules.[1] In particular, palladium (Pd)-catalyzed aryl amination reactions are frequently used to synthesize pharmaceutical candidates,[1] agrochemicals,[2] and organic materials[3] (Figure 1A). Pd-catalyzed C–N cross-coupling reactions typically proceed through the mechanism illustrated in Figure 1B.[4] The catalytic cycle begins with a Pd(0) species supported by one or more ligands, collectively represented as L, which are necessary to facilitate the reaction. The Pd oxidatively adds into the carbon–halogen bond of the aryl halide (ArX), generating a Pd(II) species. The amine nucleophile then binds to the Pd(II) and is deprotonated by the base. Finally, the C–N coupled product is reductively eliminated, regenerating Pd(0).

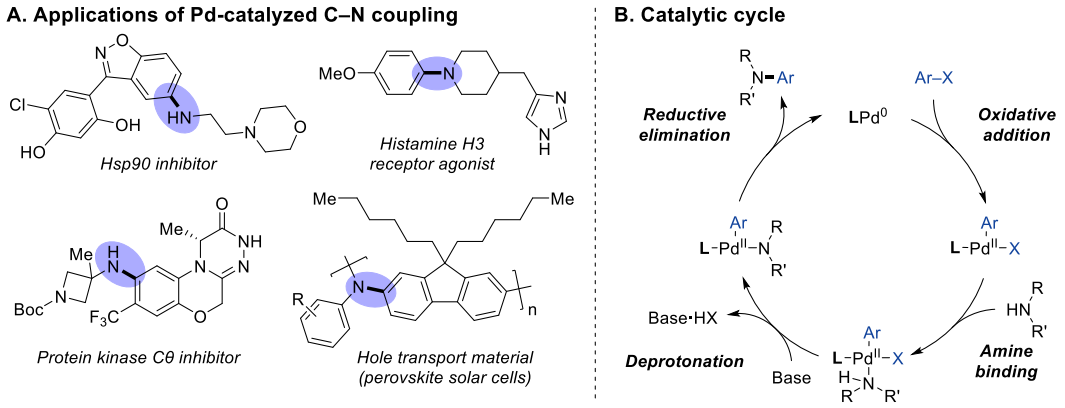


Figure 1. (A) Applications of Pd-catalyzed C–N coupling reactions (Refs. 1b, 3b). (B) Typical catalytic cycle for Pd-catalyzed C–N coupling reactions.

1.2 Discussion

The identity of the supporting ligand on Pd plays an important role in the efficiency of a given cross-coupling reaction, since the ligand is necessary to facilitate the productive reaction and hinder the formation of off-cycle Pd species. For this reason, a significant body of research in the field of Pd-catalyzed C–N cross-coupling reactions has focused on ligand development. The Buchwald lab has contributed to this area through the development of the biarylphosphine ligands, a family of ligands based on the same modular ligand scaffold[4] (Figure 2A). Biarylphosphine ligands are capable of promoting not only efficient C–N coupling, but also C–C,[5] C–O,[6] C–S,[7] and C–F[8] cross-coupling, depending on a given ligand's particular steric and electronic structure.

Several of the biarylphosphine ligands developed by the Buchwald lab for C–N coupling were rationally designed to specifically promote faster elementary steps in the productive catalytic cycle (Figure 2B). For example, the turnover-limiting span for the PhCPhos-promoted coupling of aryl chlorides with α-tertiary primary amines was found to include both oxidative addition and reductive elimination.[9] To improve the performance of this reaction, a more electron-rich (faster oxidative addition) and bulky (faster reductive elimination) *tert*-butyl (*t*-Bu) group replaced one of the phenyl (Ph) groups on phosphorus, resulting in the rationally designed ligand (*t*-Bu)PhCPhos. In another example, the yields of coupling reactions involving α-branched secondary amines were limited by undesired β-hydride elimination (which competes with reductive

elimination) when PhCPhos was used as the ligand.[10] The yields of these reactions was improved with the development of the JackiePhos/CPhos hybrid ligand: the Ph groups on phosphorus were replaced with electron-deficient 3,5-bis(trifluoromethyl)phenyl groups, which increased the rate of reductive elimination relative to β-hydride elimination.

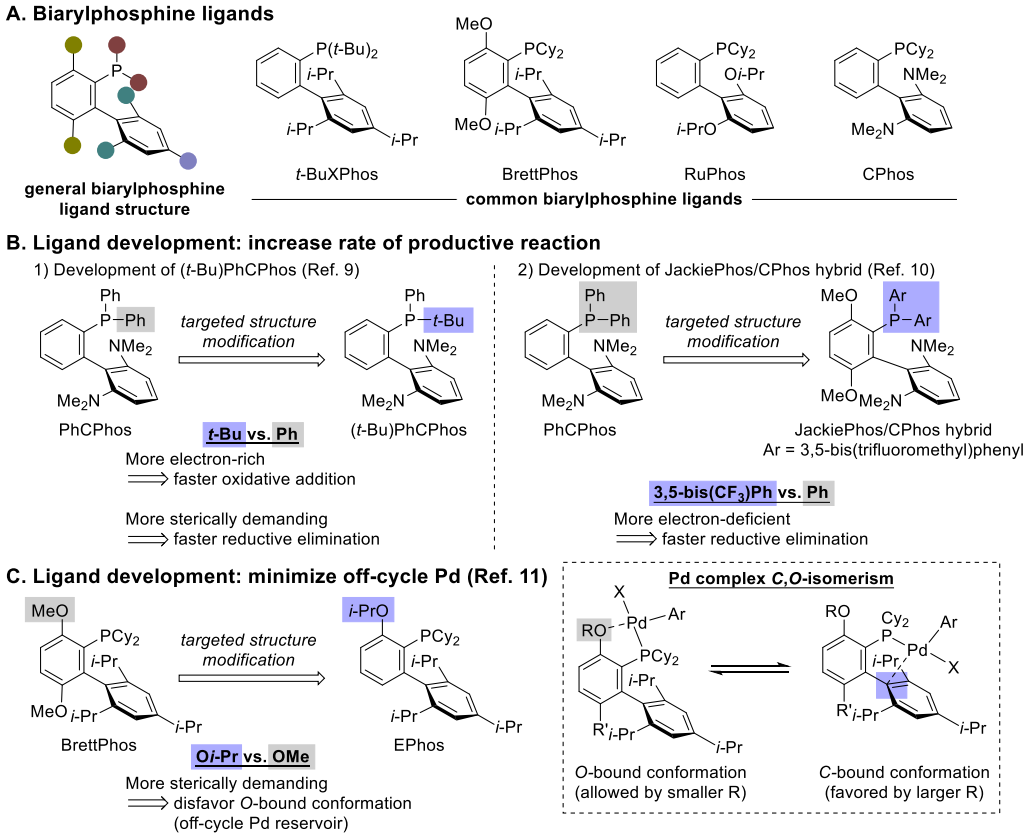


Figure 2. (A) Examples of biarylphosphine ligands. (B) Previous biarylphosphine ligand development efforts motivated by increasing the rate of the productive C–N coupling. (C) Previous biarylphosphine ligand development effort motivated by the avoidance of off-cycle Pd species.

Complementary to the rational design approach that attempts to increase the rate of the productive coupling reaction, the development of EPhos (from BrettPhos) for the coupling of 2-aminooxazoles was motivated by the avoidance of an off-cycle species[11] (Figure 2C). The O*i*-Pr substituent in EPhos (vs. OMe in BrettPhos) was designed to favor the *C*-bound conformation of the ligated Pd complex, since the *O*-bound conformation exhibits slower reductive elimination and can thus behave as an off-cycle Pd reservoir.

While the reaction conditions and scope of aryl amination methodology have greatly improved in recent years, due in large part to ligand development efforts, C–N coupling remains limited by several unsolved challenges. The high failure rate of catalytic aryl amination reactions involving densely functionalized substrates, such as pharmaceutical precursors, presents a significant challenge for industrial practitioners[12] (Figure 3A). While this challenge can be addressed using stoichiometric Pd in small-scale discovery contexts,[12] the development of efficient, catalytic reaction conditions is necessary to couple complex substrates on larger scales. Substrates that contain coordinating *N*-heterocycles are particularly difficult to couple, since these substrates can coordinate to Pd and deactivate the catalyst.[13] The difficulty of C–N coupling in the presence of

coordinating *N*-heterocycles (Figure 3B) really limits the utility of aryl amination methods in the pharmaceutical industry, since approximately 20% of FDA-approved drugs contain coordinating, aromatic *N*-heterocycles.[14] Five-membered heteroaryl halides are especially challenging: in addition to their coordinating nature, the small, electron-rich heteroarenes exhibit slow reductive elimination.[15,16] Other challenging substrate classes include electron-deficient amine nucleophiles[17] as well as hindered substrates, including ortho-substituted aryl halides and anilines,[18] α-tertiary primary amines,[9] and α-branched secondary amines.[10]

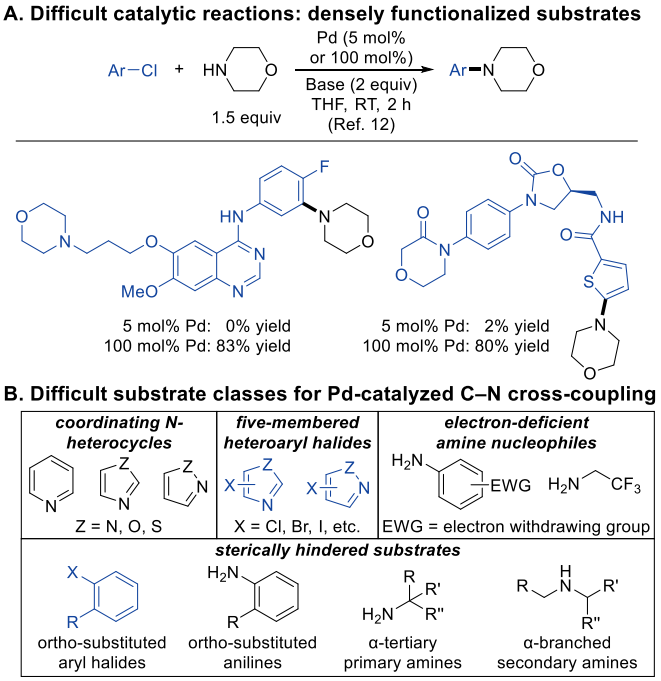


Figure 3. (A) Examples of densely functionalized substrates that are not amenable to Pd-catalyzed C–N coupling under catalytic conditions, but which provide high yields of the C–N coupled product when stoichiometric Pd is used. (B) Difficult substrate classes for Pd-catalyzed C–N cross-coupling reactions.

Another longstanding challenge in the field of Pd-catalyzed C–N coupling is that most broad-scope protocols require heating of the reaction mixture above room temperature, further limiting the scope of this transformation to substrates that do not decompose or undergo undesired side reactions at higher temperatures. For example, because the rates of nucleophilic aromatic substitution (S_NAr) reactions increase with temperature, these processes may become competitive with the desired C–N coupling reaction as the reaction mixture is heated.[9]

1.3 Conclusion

Because the identity of the supporting ligand on Pd can have a tremendous impact on the success of a reaction, the development of new ligands could enable these challenging transformations. This thesis describes the development of a new ligand, GPhos (Figure 4A), that supports a deactivation-resistant Pd catalyst capable of promoting C–N cross-coupling reactions between a wide variety of challenging (hetero)aryl halides with primary and secondary amines. GPhos was designed to not only promote difficult elementary steps of the productive coupling reaction, but also to avoid

the formation of off-cycle Pd species that lead to catalyst deactivation. Chapter 2 describes the development of the GPhos-supported catalyst and explores how the deactivation-resistant nature of this catalyst enables the coupling of a broad scope of substrates at room temperature.[19] Chapter 3 describes a synergistic relationship between the GPhos-supported catalyst and the moderate-strength base NaOTMS to promote efficient coupling between five-membered heteroaryl halides and secondary amines, a substrate combination for which no general method was previously reported[20] (Figure 4B). In both Chapters 2 and 3, mechanistic studies informed an understanding of how these two deactivation-resistant, GPhos-supported catalyst systems facilitate challenging coupling reactions.

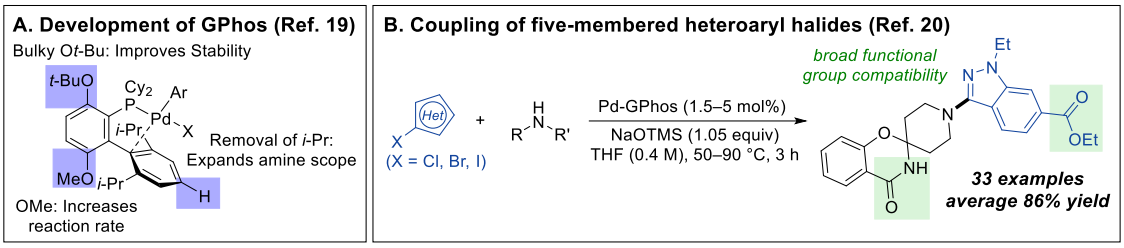


Figure 4. (A) Development of the GPhos ligand for the coupling of primary amines at room temperature. (B) Coupling of five-membered heteroaryl halides with primary and secondary amines promoted by the Pd-GPhos/NaOTMS system.

1.4 References

1. (a) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451–3479. (b) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.
2. Torborg, C.; Beller, M. Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries. *Adv. Synth. Catal.* **2009**, *351*, 3027−3043.
3. (a) Liao, Y.; Wang, H.; Zhu, M.; Thomas, A. Efficient Supercapacitor Energy Storage Using Conjugated Microporous Polymer Networks Synthesized from Buchwald–Hartwig Coupling. *Adv. Mater.* **2018**, *30*, 1705710. (b) Astridge, D. D.; Hoffman, J. B.; Zhang, F.; Park. S. Y.; Zhu, K.; Sellinger, A. Polymer Hole Transport Materials for Perovskite Solar Cells via Buchwald–Hartwig Amination. *ACS Appl. Polym. Mater.* **2021**, *3*, 5578–5587.
4. (a) Surry, D. S.; Buchwald, S. L. Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide. *Chem. Sci.* **2011**, *2*, 27–50. (b) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. Biaryl monophosphine ligands in palladium-catalyzed C–N coupling: An updated User's guide. *Tetrahedron* **2019**, *75*, 4199–4211.
5. (a) Milne, J. E.; Buchwald, S. L. An Extremely Active Catalyst for the Negishi Cross-Coupling Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032. (b) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki−Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.
6. (a) Zhang, H.; Ruiz-Castillo, P.; Buchwald, S. L. Palladium-Catalyzed C–O Cross-Coupling of Primary Alcohols. *Org. Lett.* **2018**, *20*, 1580–1583. (b) Zhang, H.; Ruiz-Castillo, P.; Schuppe, A. W.; Buchwald, S. L. Improved Process for the Palladium-Catalyzed C–O Cross-Coupling of Secondary Alcohols. *Org. Lett.* **2020**, *22*, 5369–5374.

7. Xu, J.; Liu, R. Y.; Yeung, C. S.; Buchwald, S. L. Monophosphine Ligands Promote Pd-Catalyzed C−S Cross-Coupling Reactions at Room Temperature with Soluble Bases. *ACS Catal.* **2019**, *9*, 6461–6466.
8. Sather, A. C.; Buchwald, S. L. The Evolution of Pd^{0}/Pd^{II}-Catalyzed Aromatic Fluorination. *Acc. Chem. Res.* **2016**, *49*, 2146–2157.
9. Ruiz-Castillo, P.; Blackmond, D. G.; Buchwald, S. L. Rational Ligand Design for the Arylation of Hindered Primary Amines Guided by Reaction Progress Kinetic Analysis. *J. Am. Chem. Soc.* **2015**, *137*, 3085–3092.
10. Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. Design of New Ligands for the Palladium-Catalyzed Arylation of α-Branched Secondary Amines. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259–8262.
11. Olsen, E. P. K.; Arrechea, P. L.; Buchwald, S. L. Mechanistic Insight Leads to a Ligand Which Facilitates the Pd-Catalyzed Formation of 2-(Hetero)Arylaminooxazoles and 4-(Hetero)Arylaminothiazoles. *Angew. Chem., Int. Ed.* **2017**, *56*, 10569.
12. Uehling, M. R.; King, R. P.; Krska, S. W.; Cernak, T.; Buchwald, S. L. Pharmaceutical diversification via palladium oxidative addition complexes. *Science* **2019**, *363*, 405–408.
13. For implication/observation of phosphine displacement by heterocycles, see: (a) Paul, F.; Patt, J.; Hartwig, J. F. Structural Characterization and Simple Synthesis of $\{Pd[P(o\text{-}Tol)_3]_2\}$. Spectroscopic Study and Structural Characterization of the Dimeric Palladium(II) Complexes Obtained by Oxidative Addition of Aryl Bromides and Their Reactivity with Amines. *Organometallics* **1995**, *14*, 3030–3039. (b) Wagaw, S.; Buchwald, S. L. The Synthesis of Aminopyridines: A Method Employing Palladium-Catalyzed Carbon–Nitrogen Bond Formation. *J. Org. Chem.* **1996**, *61*, 7240–7241.
14. Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.
15. Arrechea, P. L.; Buchwald, S. L. Biaryl Phosphine Based Pd(II) Amido Complexes: The Effect of Ligand Structure on Reductive Elimination. *J. Am. Chem. Soc.* **2016**, *138*, 12486–12493.
16. (a) Hooper, M. W.; Hartwig, J. F. Understanding the Coupling of Heteroaromatic Substrates: Synthesis, Structures, and Reductive Eliminations of Heteroarylpalladium Amido Complexes. *Organometallics* **2003**, *22*, 3394–3403. (b) Sather, A. C.; Martinot, T. A. Data-Rich Experimentation Enables Palladium-Catalyzed Couplings of Piperidines and Five-Membered (Hetero)aromatic Electrophiles. *Org. Process Res. Dev.* **2019**, *23*, 1725–1739.
17. Pompeo, M.; Farmer, J. L.; Froese, R. D. J.; Organ, M. G. Room-Temperature Amination of Deactivated Aniline and Aryl Halide Partners with Carbonate Base Using a Pd-PEPPSI-$IPent^{Cl}$- *o*-Picoline Catalyst. *Angew. Chem., Int. Ed.* **2014**, *53*, 3223–3226.
18. Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. Pd-Catalyzed Aryl Amination Mediated by Well Defined, N-Heterocyclic Carbene (NHC)–Pd Precatalysts, PEPPSI. *Chem. Eur. J.* **2008**, *14*, 2443–2452.
19. McCann, S. D.; Reichert, E. C.; Arrechea, P. L.; Buchwald, S. L. Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability. *J. Am. Chem. Soc.* **2020**, *142*, 15027–15037.
20. Reichert, E. C.; Feng, K.; Sather, A. C.; Buchwald, S. L. Pd-Catalyzed Amination of Base-Sensitive Five-Membered Heteroaryl Halides with Aliphatic Amines. *J. Am. Chem. Soc.* **2023**, *145*, 3323–3329.

Chapter 2

Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability

2.1 Introduction

The coupling of aryl (pseudo)halide electrophiles with amines to form carbon–nitrogen (C–N) bonds is an important transformation with applications in a variety of fields. In particular, transition-metal-catalyzed aryl amination reactions are one of the most used reaction classes in the synthesis of pharmaceutical candidates.[1,2] Palladium-based catalysts are among the most effective for catalytic aryl amination reactions.[3] We have a longstanding interest in the development of new ligands for palladium-catalyzed C–N bond-forming reactions.[4,5] Specifically, our group has created a variety of dialkylbiaryl monophosphine ligands to support Pd catalysts that are highly active for the coupling of many classes of aryl electrophiles with a broad range of amine nucleophiles.

The mechanism by which palladium catalyzes C–N cross-coupling reactions is well documented (Figure 1A).[5,6] The elementary steps of these reactions, including oxidative addition (Figure 1B),[7] amine binding (Figure 1C),[8] and reductive elimination (Figure 1D),[9,10] occur at or near ambient temperature using Pd complexes ligated by dialkylbiaryl monophosphines. However, most currently used synthetic protocols that exhibit a broad substrate scope are carried out above room temperature. Many early reports of Pd-catalyzed aryl amination reactions included examples of reactions run at room temperature, but the substrate scopes of these protocols were generally limited and included very few primary aliphatic amine nucleophiles.[5c–e,11–13] By increasing the reaction temperature and developing new ligands, our group has been able to improve both the catalyst reactivity and stability.[4,14–16]

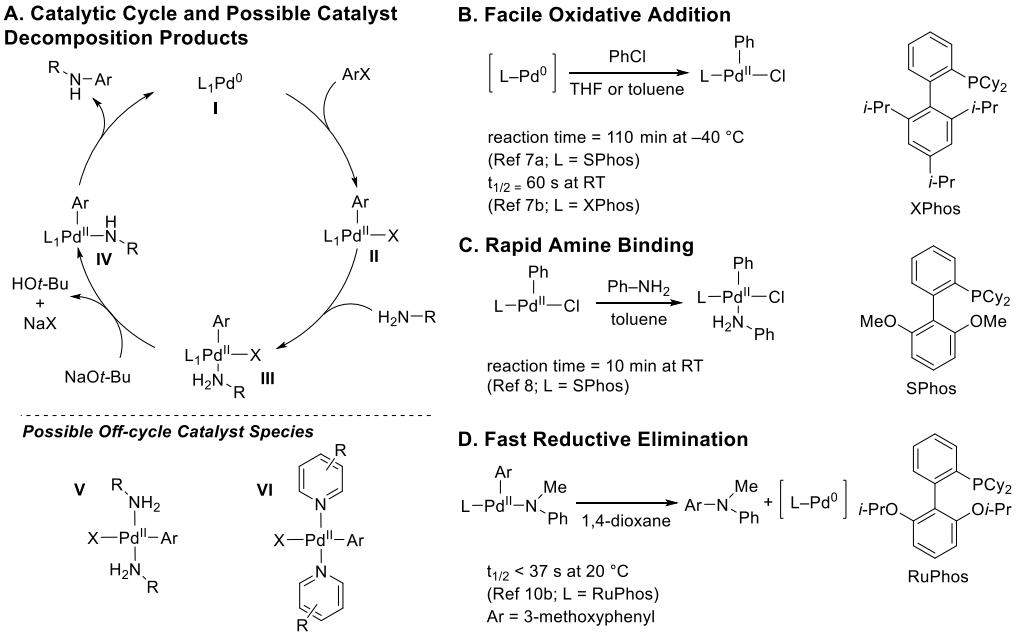


Figure 1. Mechanistic hypothesis and previous studies of elementary steps.

The vast majority of aryl amination reactions that proceed at room temperature use alkoxide bases,[11–13] so we chose to employ NaO*t*-Bu during our reaction development. Based on previous results from our group indicating that amines can displace dialkylbiaryl monophosphine supporting ligands,[17] we anticipated that a key challenge to facilitating a broader scope of C–N coupling reactions at room temperature would be avoiding the production of off-cycle aryl–Pd

species such as **V**[18] and **VI**[19] that form through the reaction of on-cycle Pd complexes with excess primary amine or *N*-heterocycle-containing substrates, respectively (Figure 1A). The formation of both types of Pd complexes (i.e., **V** and **VI**) likely has a negative impact on productive catalytic turnover,[20–22] and minimizing their production could enable more effective catalysis, particularly at room temperature.

Herein, mechanistic studies and ligand design informed the development of a practically useful catalyst that promotes C–N cross-coupling reactions involving a variety of aryl (pseudo)halides and primary amine nucleophiles. The GPhos-supported catalyst can operate at room temperature in many cases, which allows for a greater tolerance of base-sensitive substrates relative to previous catalyst systems that operate above room temperature, while retaining the desirable qualities of those systems, such as low catalyst loadings and fast reaction kinetics.[23] The catalyst can accommodate sterically hindered aryl halides and amines, which were not successfully coupled by our group's recently developed Pd catalyst system that employs an amine base.[15d,15e] In addition to displaying improved stability and reactivity at room temperature, the GPhos-supported catalyst system shows high activity when heated, enabling the coupling of substrates that do not work well at room temperature. Altogether, the precatalyst based on GPhos can perform the function of catalysts based on three different ligand families: BrettPhos (unhindered primary amines),[14b,c] PhCPhos and (*t*-Bu)PhCPhos (α-tertiary amines),[15a] and EPhos (aryl halides or amines containing five-membered-ring *N*-heterocycles).[15c]

2.2 Results and Discussion

2.2.1 Development of New Catalysts for Room Temperature Aryl Amination Reactions

Initial testing of catalytic reactions indicated that coupling reactions of ortho-substituted aryl bromide electrophiles with primary amines were especially challenging for catalysts based on BrettPhos (**L1**) and EPhos (**L2**) at room temperature.[24,25] As noted in the Introduction, we hypothesized that catalyst deactivation is a key factor in the lack of general success for Pd-catalyzed C–N coupling reactions carried out at room temperature. An alternative explanation is that the catalyst is stable, but rate of the productive C–N coupling reaction is slow at room temperature. To differentiate between these two possibilities, reaction calorimetry was used to monitor the progress of the reaction of 2-bromo-1,4-dimethylbenzene and *n*-propylamine (Figure 2A). Catalysts based on BrettPhos (**L1**) and EPhos (**L2**) are among the most active catalysts that our group has developed for the arylation of primary amines, so the oxidative addition complex (OAC) precatalysts bearing these ligands (**OA1**, **OA2**) were tested initially.[26] In both cases, these catalysts produced small amounts of the C–N coupled product (<10%), but the catalyst activity decreased within the first 10–30 min of the reaction. Additionally, after 1 h of reaction time, free BrettPhos or EPhos was the only detectable phosphorus-containing species in the ^{31}P NMR spectrum (Figure 2B). These results are in agreement with the hypothesis that sequestration of the palladium as a non-phosphine-ligated complex is a cause of catalyst deactivation and the resulting low yields for the reactions carried out at room temperature using **OA1** and **OA2**. However, because the **OA1**- and **OA2**-derived catalysts showed activity in the first few minutes of the reactions at room temperature, we anticipated that high yields of the C–N coupled product could be achieved with a catalyst that was more stable toward deactivation under these conditions.

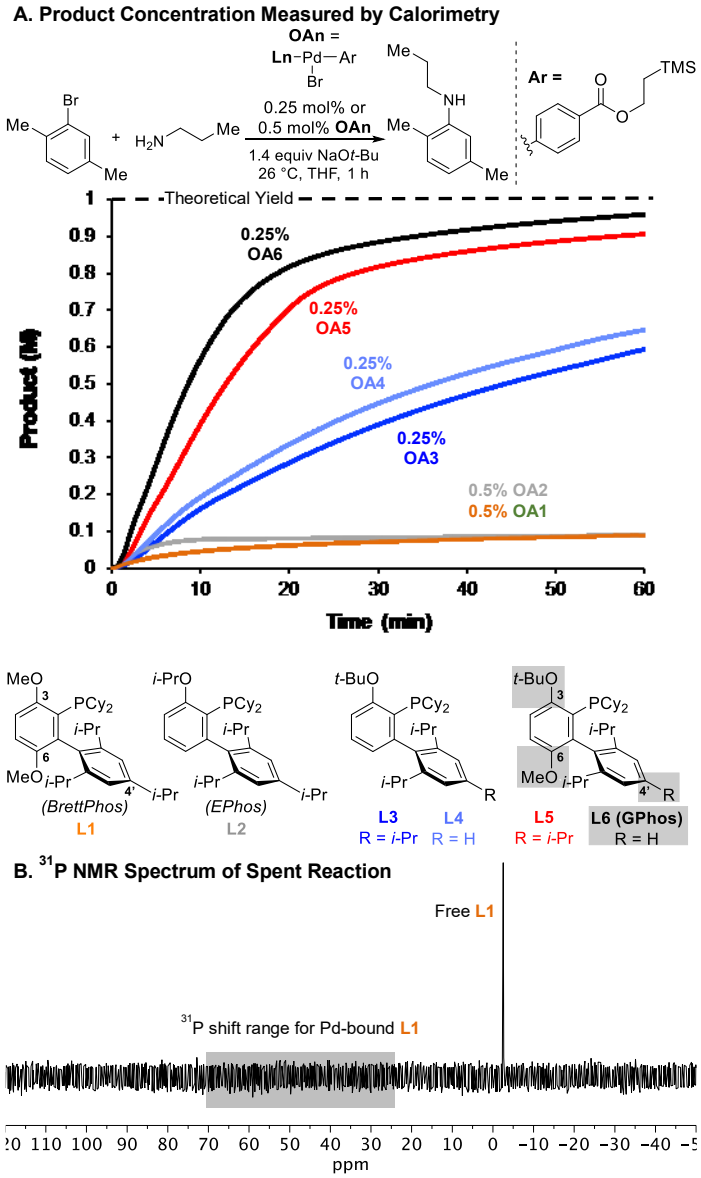


Figure 2. (A) Comparison of reaction time courses as measured by reaction calorimetry for the reaction shown with catalysts **OA1**–**OA6** (Ar = 4-(2-(trimethylsilyl)ethyl benzoate)). (B) ^{31}P NMR spectrum of the reaction employing **OA1** as the precatalyst after 1 h. Reaction conditions: 1.0 mmol 2-bromo-1,4-dimethylbenzene, 1.4 mmol *n*-propylamine, 1.4 mmol NaO*t*-Bu, 0.1 mmol *n*-dodecane (internal standard), 2.5 or 5.0 μmol **OAn** in THF (1.0 M [2-bromo-1,4-dimethylbenzene]) maintained at 26.0 °C in OmniCal calorimeter. Note: **OA1** refers to precatalyst with **L1**, **OA2** to that with **L2**, etc. Reaction GC conversions for each catalyst: **OA1** = 9%, **OA2** = 9%, **OA3** = 60%, **OA4** = 65%, **OA5** = 90%, **OA6** = 96%.

A key difference between EPhos and BrettPhos is the O*i*-Pr substituent at the 3-position in EPhos (vs. OMe in BrettPhos), which was designed to greatly favor the *C*-bound conformation of the OAC (Figure 3A).[15c] Because the *O*-bound isomer exhibits slower reductive elimination[10a] and can thus behave as an off-cycle Pd reservoir,[15c] we hypothesized that adding a larger substituent at the 3-position of the ligand framework could impart additional stability onto the resulting catalyst

by further favoring the *C*-bound isomer relative to the *O*-bound isomer. In accord with this hypothesis, changing the C3-substituent from O*i*-Pr (**OA2**) to O*t*-Bu (**OA3**, **OA4**) significantly decreased the rate of catalyst deactivation relative to the productive reaction rate, although the reaction still failed to reach full conversion within 1 h (Figure 2A). When the 6-OMe group that is present in BrettPhos, but not EPhos, was added to the ligand framework containing the O*t*-Bu substituent (**OA5**, **OA6**), the amination process was fast enough relative to catalyst deactivation to nearly reach completion within 1 h. The progression from **OA1** and **OA2** to the most active catalyst, **OA6**, shows the benefit of improving the ratio of the rate of productive reaction to that of catalyst deactivation. Consideration of catalyst stability is less often an explicit focus of aryl amination catalyst development efforts, but it appears to be an important metric in C–N cross-coupling reactions.

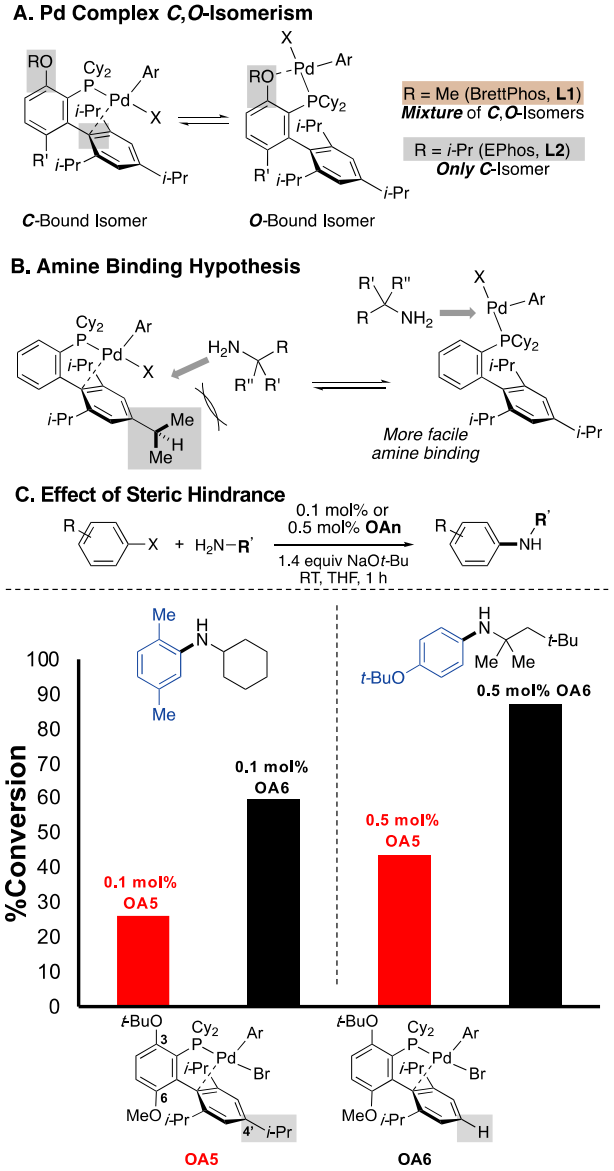


Figure 3. (A) *C*,*O*-isomerism observed in some dialkylbiaryl monophosphine-based OACs. A bulkier R group decreases the relative population of the *O*-bound isomer. (B) Amine binding mode previously proposed for XPhos-supported OAC.[27] (C) Comparison of the performance of precatalysts (**OA5**, **OA6**; Ar = 4-(2-(trimethylsilyl)ethyl benzoate)) for the coupling of α-branched

primary amines. Reaction conditions: 0.4 mmol 2-bromo-1,4-dimethylbenzene or 1-(*tert*-butoxy)-4-chlorobenzene, 0.56 mmol cyclohexylamine or *tert*-octylamine, 0.56 mmol NaO*t*-Bu, 0.04 mmol *n*-dodecane (internal standard), 0.4 or 2.0 μmol **OAn** in 0.2 mL THF at RT.

We next sought to examine each catalyst's reactivity with different aryl halides and amines, with a particular emphasis on bulkier α-branched primary amines. It has previously been suggested that amine binding and/or deprotonation may occur when the Pd is positioned away from the sterically hindered triisopropyl aryl fragment of the ligand (Figure 3B).[27] Such an amine binding mechanism is unlikely with catalysts supported by ligands **L2**–**L6**, which force their corresponding OACs (**OA2**–**OA6**) into the *C*-bound conformation. However, we hypothesized that the catalyst's activity might be increased in coupling reactions involving more hindered α-branched amines if the 4'-*i*-Pr group were removed to reduce the steric hindrance associated with the transition states for amine binding and/or deprotonation. This modification proved critical for enabling the coupling of some α-branched primary amines. For example, **OA6** is significantly more effective than **OA5** for coupling reactions involving cyclohexylamine or *tert*-octyl amine nucleophiles (Figure 3C). Overall, employing **OA6** provided the best combination of catalyst stability and substrate scope of the catalysts tested,[28] likely because it merges the most important features of ligands used in previous catalytic systems (Figure 4): a large substituent ortho to the dialkylphosphino group (cf. EPhos) to stabilize the catalyst, an electron-donating methoxy group in the 6-position (cf. BrettPhos) to improve the reaction rate, and a hydrogen as the 4'-substituent (cf. PhCPhos, (*t*-Bu)PhCPhos) to enable the binding of sterically demanding amine nucleophiles.

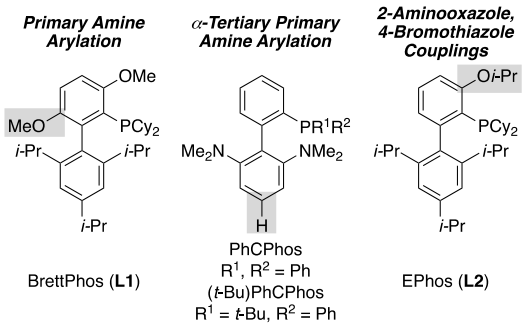


Figure 4. Common dialkylbiaryl monophosphine ligands used to support Pd catalysts for the arylation of different types of primary amine nucleophiles. Key ligand features are highlighted.

2.2.2 Assessment of C–N Coupling Catalysis at Higher Temperatures

Although catalysts based on BrettPhos (**L1**) often do not produce C–N coupled product in high yield at room temperature, they are effective catalysts at higher temperatures.[14b,c] To reconcile the difference in catalyst performance between reactions carried out at room temperature and those that are heated, several mechanistic experiments were performed using **L1**-based catalysts. The studies were initiated by collecting reaction time course data for a model amination reaction similar to the one used for the ligand development described above (cf. Figure 2). Two identical series of reactions were allowed to proceed for 1 h at room temperature, during which time they each produced approximately 20% yield of coupled product (Figure 5). Subsequently, one series of reactions was allowed to continue at room temperature for up to 24 hours. During this extended reaction period, minimal additional product was formed, consistent with the result shown in Figure 2A. The other series of reactions was heated to 90 °C after the first hour of reaction time at room

temperature. In this case, a quantitative yield of product was formed after ~7 h (~6 h at 90 °C). These results, taken together with the results in Figure 2, indicate that C–N coupling promoted by the **L1**-supported OAC can occur readily at room temperature, but when the L–Pd complex deactivates and only free **L1** is observed in solution (Figure 2B), the reaction mixture must be heated to facilitate productive C–N coupling. The need for heating after dissociation of the phosphine ligand suggests that the re-entry of off-cycle species (e.g., **V**/**VI**, Figure 1A) is an elementary step that necessitates higher reaction temperature in many catalytic protocols.

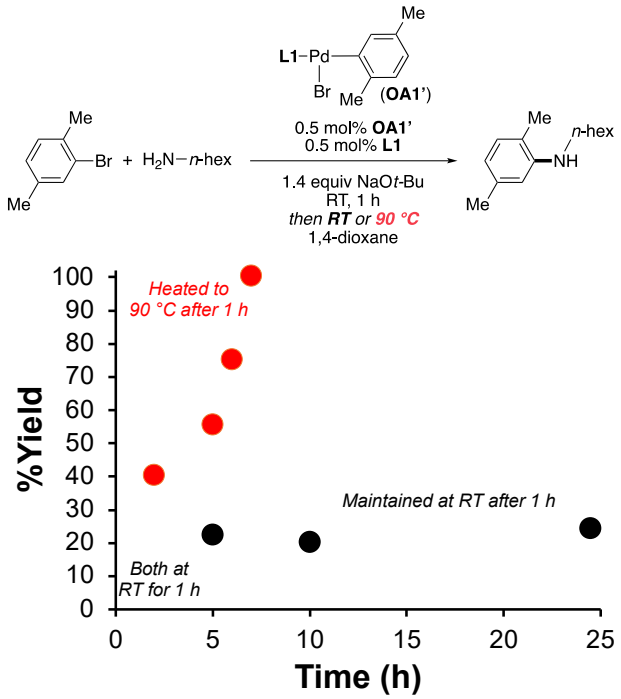


Figure 5. Assessment of unheated and heated **OA1'**-catalyzed aryl amination. Reaction conditions: 0.5 mmol 2-bromo-1,4-dimethylbenzene, 0.7 mmol *n*-hexylamine, 0.7 mmol NaO*t*-Bu, 0.05 mmol *n*-dodecane (internal standard), 2.5 µmol **OA1',** 2.5 µmol **L1** in 0.5 mL 1,4-dioxane at RT (1 h time point) followed by RT (black points) or 90 °C (red points). Calibrated GC yields.

To probe whether putative off-cycle Pd complexes similar to **V** (Figure 1A), formed via displacement of the supporting ligand, can serve as competent catalyst precursors, complex **A** (Figure 6) was prepared.[29] When the reaction mixture containing the model coupling partners was heated to 90 °C in the presence of 0.5 mol% **A** as the Pd source and 1.0 mol% **L1** (to match the amount of catalyst and ligand used in Figure 5), a high yield of product was observed after 24 hours (Figure 6). When our new ligand, **L6**, was used in place of **L1** (in combination with **A**), the reaction was complete within 1 h at 90 °C. This result indicates that **L6** promotes a higher population of active catalyst (cf. **I**–**IV**, Figure 1A) relative to **A** (cf. **V**, Figure 1A) than **L1**, and/or the population of Pd that enters the productive cycle is significantly more active when supported by **L6** than with **L1**. At room temperature, the **L6**-based catalyst showed the highest ratio for the rate of the productive reaction relative to the rate of catalyst deactivation. We suspect that the same structural features of **L6** that led to this high ratio at room temperature are also responsible for the higher reactivity of the **L6**-based catalyst relative to the **L1**-based catalyst observed at 90 °C using **A** as the catalyst precursor. Reactions with **A** and **L1** (or **L6**) that were performed at room

temperature did not yield any desired product. The notion that non-phosphine-ligated off-cycle Pd species, such as **A**, may recombine with free ligand to form on-cycle catalysts when heated is consistent with the beneficial effect of added equivalents of dialkylbiaryl monophosphine ligand in many Pd-catalyzed C–N cross-coupling reactions.[4]

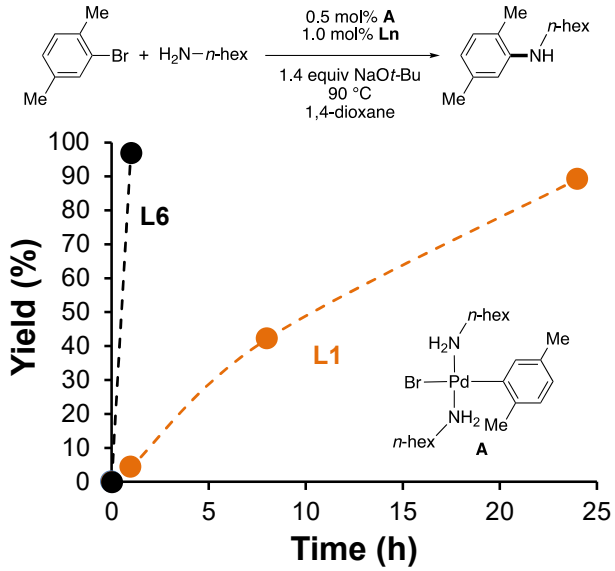


Figure 6. Reaction time course using **A** as a precatalyst. Reaction conditions: 0.5 mmol 2-bromo-1,4-dimethylbenzene, 0.7 mmol *n*-hexylamine, 0.7 mmol NaO*t*-Bu, 0.05 mmol *n*-dodecane (internal standard), 2.5 µmol **A**, 5.0 µmol **L1** or **L6** in 0.5 mL 1,4-dioxane at 90 °C. Calibrated GC yields. Dashed lines are intended to guide the eye and do not reflect a kinetic fit.

Only a small amount of free **L1** was observed when excess *n*-hexylamine was stirred with **OA1'** at room temperature for 1 h, suggesting that displacement of **L1** occurs from an intermediate other than an OAC (cf. **II**/**III**, Figure 1A). This contrasts with previous studies in which it was observed that the addition of excess primary amine to P(*o*-tol)$_3$- or P*t*-Bu$_3$-ligated Pd OACs (cf. **II**, Figure 1A) resulted in the formation of phosphine-free compounds analogous to **A**.[18] Additionally, Hartwig observed a similar bis(amine) Ni complex when a (BINAP)Ni(Ar)Cl species was treated with an excess of primary amine.[30] Although **A** catalyzed C–N bond formation in the presence of **L1** when heated (Figure 6), related bis(amine)Pd(Ar)Br and bis(amine)Ni(Ar)Cl complexes do not always catalyze aryl amination reactions. For example, the combination of P(*o*-tol)$_3$ and bis(amine)Pd(Ar)Br complexes did not form an active catalyst.[18a] Further, the aforementioned Ni-based bis(amine) complex could not promote stoichiometric C–N coupling when heated in the presence of BINAP supporting ligand.[30] These collective observations suggest that complexes such as **A** are relevant in many primary amine arylation reactions, and the facility with which they re-enter the productive catalytic cycle depends on both the metal (e.g., Pd or Ni) and the supporting ligand.

2.2.3 Scope of Room Temperature C–N Coupling Reactions using OA6 as the Precatalyst

The use of precatalyst **OA6**[31,32] enabled the room temperature coupling of aryl (pseudo)halides with a variety of primary aliphatic amine and aniline coupling partners with low catalyst loadings and short reaction times (typically 1 h; Figure 7).[24] Ortho-substituted aryl chlorides (**3k**, **3p**) and

aryl bromides (**3a**, **3l**) were coupled efficiently, even though these are difficult classes of electrophiles for catalysts ligated with BrettPhos (**L1**) and EPhos (**L2**) when the reactions are run at room temperature. An unhindered aryl iodide (**3b**) was coupled in high yield, which is noteworthy because aryl iodide electrophiles often show reduced reaction rates relative to aryl bromides.[33] Finally, an unhindered aryl triflate was readily coupled with an aniline (**3c**). In some cases, heat release was noted in the first several minutes of the reactions,[24,25] but in only one instance was the reaction negatively affected by this exotherm: on 1.0 mmol scale, a decreased product yield was observed for **3c** when the reaction vial was not submerged in a room temperature water bath, a modification that was not needed when the coupling was carried out on 0.2 mmol scale.[34]

Aryl halides or amines containing a free primary alcohol (**3d**, **3t**),[35] secondary amine (**3n**, **3r**), or amide (**3c**, **3o**) functional group gave high yields, and several *N*-heterocycle-containing aryl halides and amines are featured as substrates. Despite the high reactivity of the **OA6** catalyst, several chemoselective reactions were achieved. For example, methyl 4-bromobenzoate was selectively coupled in the presence of an aryl chloride (**3e**). Additionally, 4-aminopiperidine was coupled predominantly at the primary amino group (**3n**). For the reaction of aryl bromide **1e**, NaOMe was used as the base to avoid competitive transesterification.[36] Reduction of the aryl halide to the arene was not observed,[37] although a small amount of aryl methyl ether was observed when the crude reaction mixture was analyzed using ^{1}H NMR (~5%).

Procedures using **OA6** were able to efficiently couple sterically hindered primary amines under room temperature conditions, an advantage of this method relative to our group's previous work using soluble amine bases, which could not accommodate α-tertiary amines or ortho-substituted anilines.[15d] For example, the reaction of 2-chloropyrazine and *tert*-octylamine occurred under much milder conditions than those formerly required (**3f**).[15a,38] In addition to hindered aliphatic amines, ortho-substituted anilines (**3g**, **3h**, **3i**) could be coupled in high yield, though in the cases of an extremely hindered aniline (**3h**) or a hindered electron-deficient aniline (**3i**), a longer reaction time was required (24 h). Electron-deficient anilines (**3e**, **3i**, **3j**, **3k**, **3o**, **3p**, **3t**) were efficiently converted to product under the coupling conditions, including fluorinated anilines (**3i**, **3j**), which have been described as challenging nucleophiles in Pd-catalyzed coupling reactions.[39] Some of the electron-deficient anilines (**3i**, **3o**, **3p**) performed best when NaOPh was used in place of NaO*t*-Bu as the base, perhaps because these anilines are sufficiently acidic to be deprotonated prior to binding to the Pd catalyst (cf. **III**, Figure 1A) or because of their instability in the presence of strong base. (**OA6** is also compatible with carbonate bases. See Figure 18.) Several potentially base-sensitive functional groups were also accommodated,[40] including an *N*-trifluoroethylaniline (**3l**),[41] nitrile (**3p**), and several substrates containing acidic C–H bonds (**3m**, **3n**, **3o**).

In several cases, we compared our conditions to those used for similar or identical coupling reactions that were previously reported. For example, reactions involving fluorinated anilines **3i** and **3j** were formed using less catalyst (6–15-fold) and, in the case of **3j**, shorter reaction time (1 h vs. 24 h) while still operating at room temperature,[39] even though the anilines we employed are either more electron-deficient or more sterically hindered than those in the previous study. Compound **3p** was previously prepared by our group using a BrettPhos-based catalyst.[14c] Under our new conditions, we were able to simultaneously reduce the amount of catalyst (by 3-fold), temperature (RT vs. 110 °C), and reaction time (1 h vs. 14 h), highlighting the improved reactivity of **OA6**. Finally, the room temperature conditions allowed for the use of NaO*t*-Bu to prepare **3l**. Previously published conditions heated the reaction mixture to 100 °C in the presence of a weaker base, KOPh, necessitating longer reaction times (6 h), but our room temperature conditions using

NaO*t*-Bu resulted in full conversion to product within 1 h, while maintaining a catalyst loading similar to that employed in the previous report.[41]

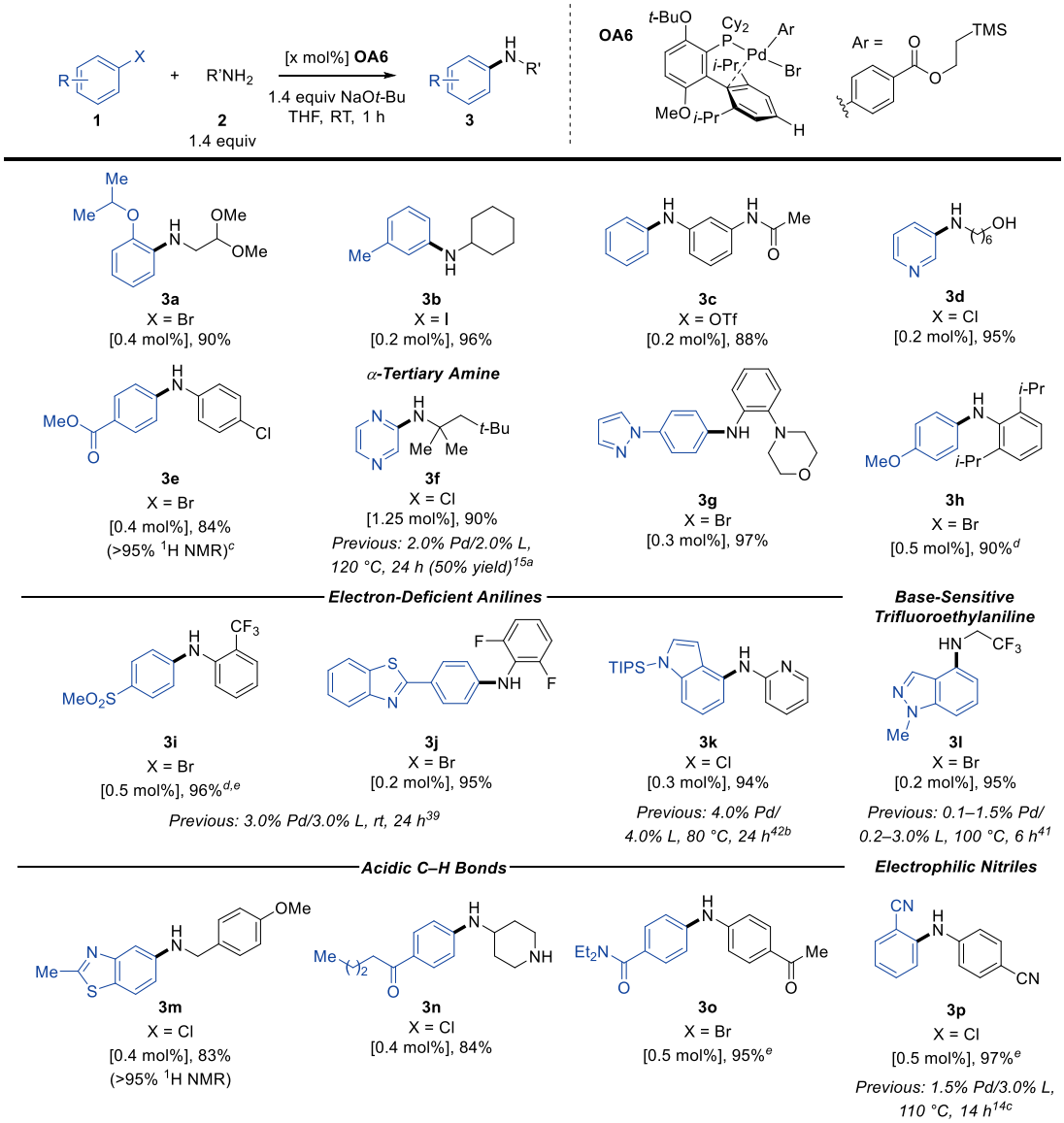


Figure 7. Substrate scope of the room temperature aryl amination protocol.[a,b] Legend: (a) isolated yields are reported as the average of two runs. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] **OA6**, THF (0.5 mL), RT, 1 h; (b) previous conditions refer to previously published conditions for the same or similar coupling reactions, with Pd = Pd loading, L = total ligand loading; (c) 1.4 equiv NaOMe, 45 min reaction time; (d) 24 h; (e) 1.4 equiv NaOPh. See Figure 18 for additional examples of coupling reactions performed at room temperature.

In some instances, poisoning or slowing of reactions has been observed with *N*-heterocycle-containing aryl halide or amine substrates. For example, 2-aminopyridine can function as a ligand for Pd(II). Still, **3k** was formed efficiently at room temperature in 1 h, even though similar coupling processes previously required heating (80–100 °C) with more catalyst (1.7–13-fold) for longer reaction times (24–30 h).[42] Finally, **3f** had been previously prepared using our PhCPhos-based

catalyst.[15a] Now we are able to use a shorter reaction time (1 h vs. 24 h) at a lower temperature (RT vs. 120 °C), while still using less catalyst. The faster rate of C–N bond formation (i.e., shorter reaction time) and lower temperature avoid the formation of the ArO*t*-Bu side product, which was competitively produced under the previous reaction conditions, resulting in a lower yield than that observed here (90% vs. 50%). It is possible that such a significant improvement is observed for this reaction because the large O*t*-Bu group on the ligand "protects" the catalyst from degradation by the pyrazine, while the removal of the *i*-Pr group in the ligand's 4'-position still allows for binding of the sterically demanding *tert*-octylamine nucleophile.

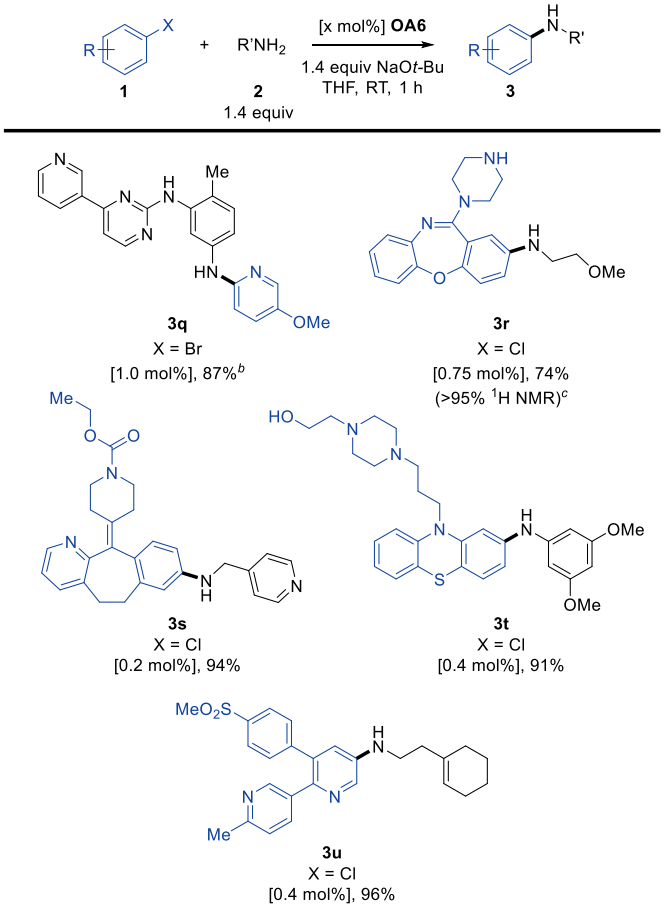


Figure 8. Scope of the room temperature aryl amination of drug-like substrates.[a] Legend: (a) isolated yields are reported as the average of two runs. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] **OA6**, THF (0.5 mL), RT, 1 h; (b) 1.2 mmol aryl halide, 1.0 mmol amine; (c) reaction conditions: aryl halide (0.5 mmol), amine (0.7 mmol), NaO*t*-Bu (0.7 mmol), 0.75 mol% **OA6**, THF (0.25 mL), RT, 1 h.

We next examined **OA6** in the reactions of more complex substrates under our room temperature conditions (Figure 8). C–N cross-coupling reactions involving pharmaceutical derivatives possessing multiple functional groups have been shown to exhibit a high failure rate.[43] The **OA6**-based catalyst system enabled the coupling of several high-complexity molecules while generally allowing for low catalyst loadings and short reaction times. These included the arylation of a pyridine- and pyrimidine-containing aniline (**2q**), which is a fragment of the anti-Leukemia drug Gleevec, to form **3q**. Additionally, several aryl halide-containing pharmaceuticals bearing multiple functional groups, such as amoxapine (**1r**), loratadine (**1s**), perphenazine (**1t**), and

etoricoxib (**1u**), were efficiently transformed to the C–N coupled product.

2.2.4 Scope of C–N Coupling Reactions using OA6 Catalyst with Heating

As noted in the Introduction, most broad-scope protocols for Pd-catalyzed aryl amination are carried out above room temperature. We endeavored to compare the effectiveness of **OA6** to that of previous catalysts under such conditions, and to examine whether reactions that were unsuccessful at room temperature using **OA6** would work with heating. (Heating reactions above the boiling point of the solvent may not be appropriate for reactions run on larger scales.) First, we examined several coupling reactions that were successful at room temperature, and that did not contain functional groups that would be problematic at 90 °C, to probe the general performance of the **OA6** catalyst when heated (Figure 9). Although these exact products (**3a**, **3d**, **3k**, **3o**) have not been previously prepared using catalysts supported by dialkylbiaryl monophosphine ligands, the amount of **OA6** used for these reactions is at or below the levels previously reported by our group for the simplest coupling reactions involving primary aliphatic amines.[14b,c]

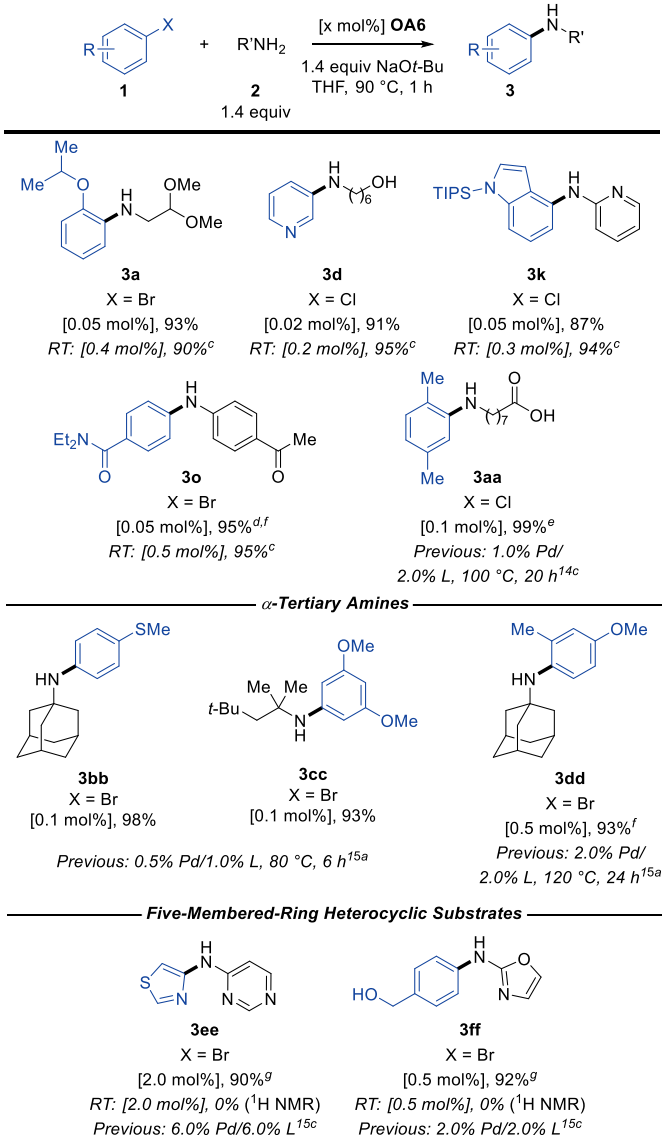
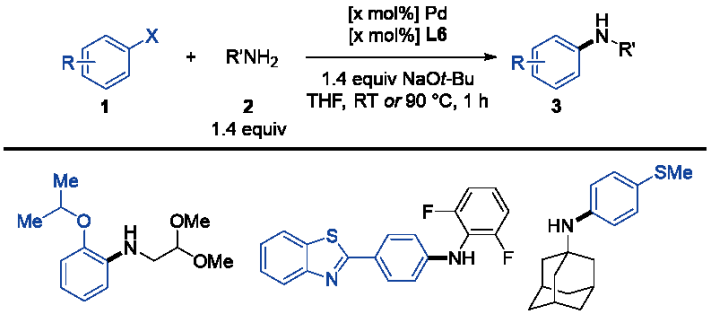


Figure 9. Scope of the aryl amination with heating.[a,b] Legend: (a) isolated yields are reported as

the average of two runs. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] **OA6**, THF (0.5 mL), 90 °C, 1 h; (b) previous conditions refer to previously published conditions for the same or similar coupling reactions, with Pd = Pd loading, L = total ligand loading; (c) RT results from Figure 7; (d) 1.4 equiv NaOPh; (e) 2.4 mmol NaO*t*-Bu, 2.5 mL THF; (f) 75 °C; (g) reaction conditions: aryl halide (1.0 mmol), amine (1.2 mmol), NaOPh (1.2 mmol), [x mol%] **OA6**, 2-MeTHF (4 mL), 100 °C, 3 h.

In addition to the coupling reactions repeated from Figure 7, we evaluated reactions that were previously reported by our group with other ligands. For example, under the conditions employed for **3aa**, the amount of catalyst (decreased 10-fold) and reaction time (1 h vs. 20 h) were both substantially improved relative to those with a BrettPhos-based catalyst.[14c] Additionally, **OA6** performed much better than PhCPhos- or (*t*-Bu)PhCPhos-based catalysts for coupling reactions involving α-tertiary primary amines,[15a] consistent with our observation at room temperature (cf. Figure 7, **3f**). Compounds **3bb**, **3cc**, and **3dd** were prepared using **OA6** with less catalyst (4–5-fold) and shorter reaction times (1 h vs. 6–24 h) than the previous report.[15a]

Certain reactions involving five-membered-ring *N*-heterocyclic substrates were not effective at room temperature. For example, **3ee** and **3ff** gave no yield at room temperature. (See Figure 18 for additional problematic coupling reactions.) Despite these difficulties under room temperature conditions, at higher temperatures the GPhos-based **OA6** precatalyst enabled the coupling reactions that formed **3ee** and **3ff** with less catalyst (3–4-fold) than our group's previously reported EPhos (**L2**)-based catalyst, under otherwise identical conditions.[15c,44] Additionally, imidazole-containing amines gave low product yields at room temperature, which could be improved in some cases upon using heated reaction conditions. Although these coupling reactions are quite different than the model reaction in Figure 2, we suspect that the improved reactivity of **OA6** relative to the EPhos-based catalyst for these reactions is due to the improved stability of the catalyst toward deactivation by *N*-heterocyclic substrates.



Pd source	3a [0.4 mol%] Pd RT	3j [0.2 mol%] Pd RT	3bb [0.1 mol%] Pd 90 °C
OA6[b]	90%	95%	98%
[Pd(cinnamyl)Cl]$_2$	47%	>95%	>95%
Pd$_2$dba$_3$	-	0%	88%
Pd(OAc)$_2$[c]	-	0%	32%
Pd(OAc)$_2$[d]	-	55%	85%

Figure 10. A comparison of reactions employing **OA6** and other, commonly employed, Pd

sources.[a] Legend: (a) yields determined by ^{1}H NMR. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] Pd, [x mol%] **L6** (Pd:**L6** = 1:1), THF (0.5 mL), RT *or* 90 °C, 1 h; (b) results from Figure 7 (**3a**, **3j**) and Figure 9 (**3bb**); (c) reaction conditions: aryl halide (0.4 mmol), amine (0.56 mmol), NaO*t*-Bu (0.56 mmol), [x mol%] $Pd(OAc)_2$, [2x mol%] **L6** (Pd:**L6** = 1:2), THF (0.2 mL), RT *or* 90 °C, 1 h; (d) Pd:**L6** = 1:2. Using water preactivation protocol.[45]

Finally, we investigated the use of several common alternative Pd sources (with free **L6**) as catalyst precursors, to compare their performance to **OA6** (Figure 10). Of these, only $[Pd(cinnamyl)Cl]_2$/**L6** formed an active catalyst at room temperature (**3a**, **3j**). This combination performed as well as **OA6** for the reaction of 2,6-difluoroaniline to provide **3j**, but gave a lower yield for the coupling of an ortho-substituted bromoarene with a primary aliphatic amine (**3a**). Using Pd_2dba_3/**L6** at room temperature resulted in no yield of **3j**. The $Pd(OAc)_2$/**L6** catalyst system required heating in the presence of water to form an active catalyst,[45] which could then catalyze the formation of **3j** at room temperature, albeit with a lower yield than reactions with **OA6** or $[Pd(cinnamyl)Cl]_2$/**L6**. At 90 °C, all of the Pd sources tested were capable of producing significant amounts of **3bb**, though the $Pd(OAc)_2$-based catalyst system performed significantly better with the water activation protocol.[45] While in some cases the reaction yields using these alternative Pd sources were comparable to those obtained using **OA6**, none equaled the overall effectiveness of **OA6** as a precatalyst. From the perspective of convenience, the use of a one-component precatalyst (containing both ligand and Pd) has advantages on small scale. For larger scale reactions, a variety of Pd precursors can be used with **L6**.

2.3 Conclusion

Guided by a combination of mechanistic analysis and ligand design, we developed a new dialkylbiaryl monophosphine ligand, GPhos (**L6**), that supports a palladium catalyst capable of promoting highly efficient coupling between a variety of aryl halide and primary amine coupling partners. The **OA6** catalyst system derived from GPhos enabled room temperature C–N coupling reactions with substantially more complex substrates than had previously been reported, with high levels of efficiency, both in terms of catalyst required and reaction time. Certain coupling reactions involving five-membered-ring *N*-heterocycle-containing substrates required heating, but when heated these reactions proceeded in excellent yield. Overall, the new catalyst system promotes the coupling of a wider range of amines than our group's previously described biarylphosphine-supported systems with equal or greater efficiency. We identified and synthesized a bis(amine)Pd–aryl complex (**A**), a putative off-cycle catalyst species.[29] This complex was not capable of entering the catalytic cycle at room temperature but was found to be a competent catalyst precursor at 90 °C, which is a temperature typical of many Pd-catalyzed C–N coupling protocols. When heated with **A** as the Pd source, the GPhos-based catalyst exhibited a much faster reaction rate than the corresponding BrettPhos-based catalyst. We believe the greater efficiency of the new catalyst at room temperature compared to previously developed dialkylbiaryl monophosphine-based catalysts arises because the new catalyst exhibits an improved ratio of the rate of productive on-cycle catalytic steps relative to that of detrimental catalyst deactivation. At elevated temperatures, the increased reactivity arises from a combination of this improved ratio with accessible activation of off-cycle species back into the productive cycle.

2.4 Experimental Procedures and Characterization Data

1. General Information

General Reagent and Materials Information

Unless otherwise noted, all reactions were set up inside of a chemical fume hood and run under a nitrogen or argon atmosphere. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Sigma-Aldrich and stored in J.T. Baker CYCLE-TAINER® delivery kegs. After transferring into CYCLE-TAINER® delivery kegs, the solvents were purged with argon for 2 h prior to the first use. THF and CH_2Cl_2 were further purified by successive filtration through neutral alumina and CuO columns under argon pressure. Anhydrous 1,4-dioxane was purchased from Sigma-Aldrich and stored in a nitrogen-filled glovebox over activated molecular sieves prior to use. Anhydrous 2-methyltetrahydrofuran (2-MeTHF) was purchased from Sigma-Aldrich and stored in a nitrogen-filled glovebox, and portions were removed from the glovebox in an oven-dried reaction tube (Fisherbrand, 16 x 125 mm, product no. 1495935A) sealed with a screw cap (Thermo Fisher Scientific, catalog no. B7995-18) fitted with a Teflon-lined septum (Thermo Fisher Scientific, catalog no. C47995-15) and used within 1 h of removal from the glovebox. Solvents used for extractions, crystallizations, and column chromatography were purchased from Sigma-Aldrich as ACS grade, expect for hexanes, which was HPLC grade. Water for reverse-phase chromatography was obtained via filtration of deionized water through a MilliporeSigma^{TM} Milli-Q^{TM}Ultrapure Water System. Sodium *tert*-butoxide (NaO*t*-Bu) and sodium phenoxide (NaOPh) were purchased from commercial suppliers and stored in a nitrogen-filled glovebox and portions were removed from the glovebox in a sealed scintillation vial (DKW Life Sciences, catalog no. 03-340-4C), stored in a desiccator, and used within 3 d of removal from the glovebox. Following each use of material from the scintillation vial outside the glovebox, a stream of argon was passed over the contents and the scintillation vial was re-capped and stored in a desiccator. All preparative C–N bond-forming reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques. Screening of reaction conditions and mechanistic experiments were carried out with the aid of a nitrogen-filled glovebox. Aryl chloride **1k** was donated by Dr. Esben P. K. Olsen and was prepared as previously reported.[15c] All other aryl halides and amines were purchased from commercial suppliers and used as received unless otherwise noted. Alkyllithium reagents were titrated within one month prior to use.[46] (COD)Pd($CH_2TMS)_2$ was prepared as previously described.[47] Dicyclohexylchlorophosphine was a gift from Nippon Chemical, and was distilled prior to use and stored in a Schlenk flask under argon. EPhos (**L2**) was donated by Dr. Esben P. K. Olsen and was prepared as previously described.[15c] 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl (BrettPhos–I) and BrettPhos (**L1**) were gifts from MilliporeSigma. 2-(trimethylsilyl)ethyl 4-bromobenzoate,[31a] 2-bromo-1,3-diisopropylbenzene,[48] and μ-OMs dimer[49] were prepared as previously reported. Organic compounds were purified by flash chromatography using Silicycle SiliaFlashP60 (230–400 mesh) silica gel either manually or using a CombiFlash NextGen 300 automated chromatography system. Selected compounds were purified on a Biotage KP-C18-HS Snap Cartridge (30 or 60 g) using a MeCN/H_2O (water contained 0.1% trifluoroacetic acid) solvent gradient on a CombiFlash NextGen 300 automated chromatography system.

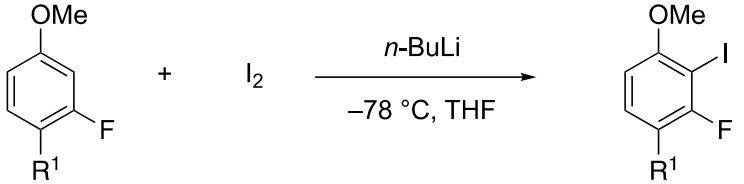
General Analytical Information

$CDCl_3$, CD_3OD, and d_6-DMSO were purchased from Cambridge Isotope Labs, and $CDCl_3$ was dried over activated molecular sieves (4 Å) overnight prior to its first use. NMR spectra were

collected on Bruker Avance III HD 400 or 500 MHz spectrometer. ^{1}H ($CDCl_3$: δ 7.26; CD_3OD: δ 3.31) and ^{13}C NMR shifts ($CDCl_3$: δ 77.16; CD_3OD: δ 49.00; d_6-DMSO: δ 39.52) were referenced to residual solvent peaks.[50] The following abbreviations were used to characterize multiplicities: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, m = multiplet. ^{13}C, ^{19}F, and ^{31}P NMR spectra were obtained with ^{1}H decoupling. ^{19}F spectra were externally referenced using a sealed capillary of 1-fluoronaphthalene (−124.0 ppm) in $CDCl_3$, ^{31}P NMR spectra were externally referenced using a sealed capillary of aqueous 85% H_3PO_4 (0.00 ppm). Gas chromatography (GC) analyses were performed on an Agilent 7890A gas chromatograph with an FID detector using a J&W DB-1 column (10 m, 0.1 mm I.D.). LC/MS was recorded on an Agilent 6120 Quadrupole LC/MS. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA, USA. High-resolution mass spectra were recorded on a JEOL AccuTOF LC-Plus 46 DART system and on an Agilent Technologies 6545 Q-TOF LC/MS system. IR spectra were recorded on a Nicolet iS5 spectrometer equipped with an iD5 diamond laminate ATR accessory from Thermo Fisher Scientific. IR spectra were acquired from neat samples. Melting points were obtained using a Stanford Research Systems EZ-Melt melting point apparatus.

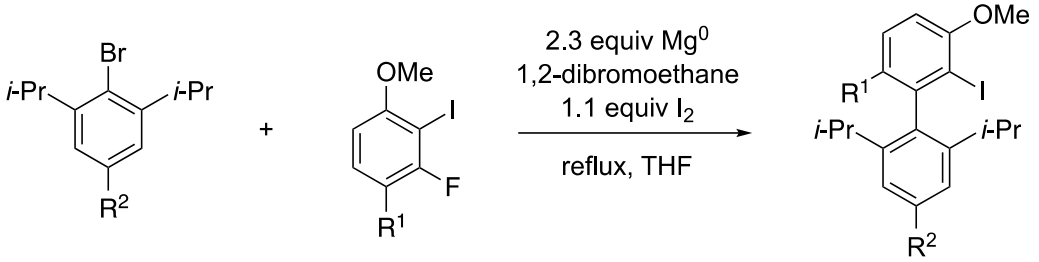
2. Catalyst Synthesis

General Procedure A for Synthesis of Ligands

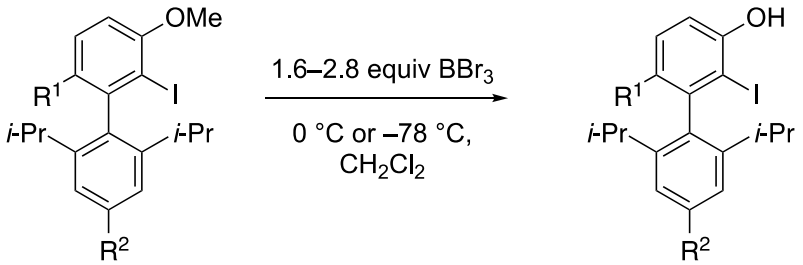


Step 1. A flame-dried round-bottom flask (Flask A), equipped with a Teflon-coated magnetic stir bar, was sealed with a rubber septum. The septum was pierced with a needle attached to a Schlenk line using a rubber hose, and the flask was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Liquid fluoroanisole (25.6 mmol, 1.00 equiv) was added via syringe to Flask A. Anhydrous THF was added via syringe, and the flask was cooled to −78 °C using a dry ice/acetone bath. Then, freshly titrated *n*-BuLi (30.0 mmol, 1.17 equiv) was added via syringe in a dropwise fashion over 10 min. The resulting mixture was then stirred at −78 °C for 1 h, during which time a separate 200 mL round-bottom flask (Flask B) was flame-dried. After Flask B had cooled to room temperature, iodine (30.0 mmol, 7.60 g, 1.17 equiv) was added to it. Flask B was sealed with a rubber septum, the septum was pierced with a needle attached to a Schlenk line using a rubber hose, and Flask B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF (50 mL) was added to Flask B via syringe. Flask B was cooled to −78 °C using a dry ice/acetone bath. After the contents of Flask A had stirred for 1 h, the contents of Flask B were transferred via cannulation into Flask A over approximately 10 min (note: it is important to perform this cannulation slowly to maintain selectivity for the desired product) until the solution maintained a persistent pale purple color (the entire iodine solution was not always used). At this time, Flask A was opened to the air, and a saturated aqueous solution of $Na_2S_2O_3$ was added. Flask A was removed from the dry ice/acetone bath and was allowed to warm to room temperature. The resulting mixture was transferred to a separatory funnel. Then, the organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (1 x 100 mL). The combined organic

layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator to afford a red liquid. The crude material was either used in the next step without purification using a purity estimated by GC analysis or chromatographed and used as a pure, colorless liquid.

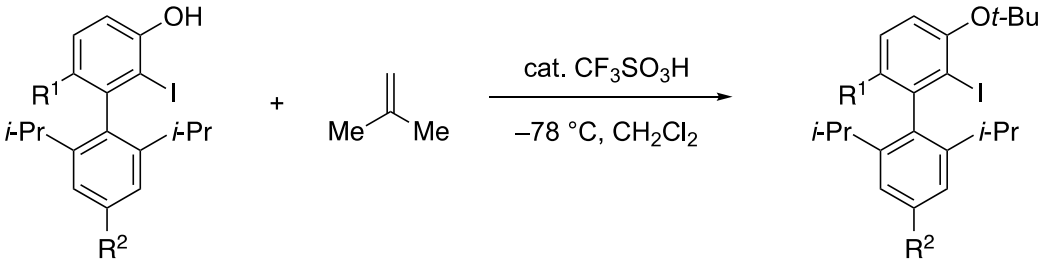


Step 2. An oven-dried 100 mL two-neck round-bottom flask (Flask A), equipped with a Teflon-coated magnetic stir bar, was charged with magnesium (2.30 equiv, 20% powder, 80% turnings). One opening of Flask A was fitted with a reflux condenser that was sealed with a rubber septum, which was pierced with a needle connected to a Schlenk line using a rubber hose, and the second opening was sealed with a rubber septum. The system was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Flask A via syringe, and the flask was placed into a pre-heated oil bath (bath temperature = 70 °C). Liquid bromoarene (1.00 equiv) was added via syringe, followed by the dropwise addition of 1,2-dibromoethane via syringe (if needed). The contents of the resulting mixture were monitored by GC analysis until the bromoarene was completely consumed. Neat fluoroiodoanisole (1.04 equiv) from the previous step was added to Flask A slowly via syringe, and the progress of the reaction was monitored by GC analysis until the iodoarene was completely consumed. The reaction mixture in Flask A was then allowed to cool to room temperature. At this point, a separate 50 mL round-bottom flask (Flask B) was flame-dried. After Flask B had cooled to room temperature, iodine (1.00–1.10 equiv) was added to it. Flask B was sealed with a rubber septum, the septum was pierced with a needle attached to a Schlenk line using a rubber hose, and Flask B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Flask B via syringe. The contents of Flask B were added via syringe to Flask A until the solution in Flask A maintained a persistent pale purple color (the entire iodine solution was not always used). At this time, Flask A was opened to the air and its contents were transferred to a separatory funnel. Saturated aqueous $Na_2S_2O_3$, brine, and EtOAc were also added to the separatory funnel, and the organic and aqueous layers were separated. The separated organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure with the aid of a rotary evaporator. The crude mixture was triturated with MeOH, and the resulting solid was collected by vacuum filtration and used in the next step without further purification.

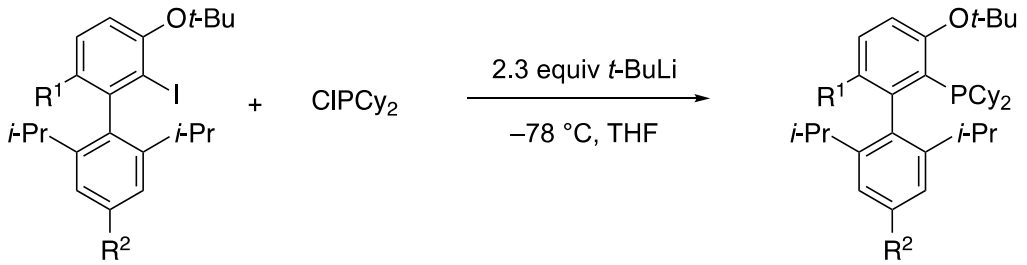


Step 3. A flame-dried round-bottom flask was equipped with a Teflon-coated magnetic stir bar, charged with biaryl iodide (1.00 equiv), and sealed with a rubber septum. The septum was pierced

with a needle attached to a Schlenk line using a rubber hose, and the flask was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous CH_2Cl_2 was added via syringe, and the flask was cooled to 0 °C using an ice/water bath, or to −78 °C using a dry ice/acetone bath. Neat BBr_3 (1.60–2.80 equiv) was added in a dropwise fashion via syringe. The flask was removed from the cold bath and stirring was continued for 1 h while the reaction mixture was allowed to warm to room temperature. The reaction flask was then opened to the air, and CH_2Cl_2 (from a wash bottle, neither dried nor degassed) was *cautiously* added to the reaction flask. MeOH (from a wash bottle, neither dried nor degassed) was *very cautiously* added to the reaction flask until fuming stopped (*Caution: Add MeOH very slowly; this addition is very exothermic*). The resulting solution was then cautiously treated with saturated aqueous $NaHCO_3$. The resulting mixture was transferred to a separatory funnel. The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure with the aid of a rotary evaporator. The crude material was used in the next step without further purification.



Step 4. A flame-dried round-bottom flask (Flask A), equipped with a Teflon-coated magnetic stir bar, was charged with biarylphenol (1.00 equiv), and sealed with a rubber septum. The septum was pierced with a needle attached to a Schlenk line using a rubber hose, and the flask was then evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous CH_2Cl_2 was added via syringe, and the flask was cooled to −78 °C using a dry ice/acetone bath. An oven-dried round-bottom flask sealed with a rubber septum, or reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) (Flask B) was pierced with a needle attached to a Schlenk line using a rubber hose, and a balloon attached to a needle was inserted into the septum. Flask B and the attached balloon were evacuated, and the flask was cooled to −78 °C. A needle attached to a cylinder of isobutylene using a rubber hose was then used to pierce the septum of Flask B, and isobutylene (~30.0 equiv) was then condensed into Flask B. The contents of Flask B were quickly transferred via cannula into Flask A. The septum of Flask A was removed, and neat trifluoromethanesulfonic acid (TfOH) was added in a dropwise fashion using a glass pipette, and then the flask was re-sealed with the septum. The reaction progress was monitored by TLC until the phenol was completely consumed, and additional TfOH or isobutylene were added if needed. After the phenol was completely consumed, triethylamine was added via syringe. The flask was removed from the cold bath and allowed to warm to room temperature with a needle piercing the septum to allow for venting of the isobutylene gas that evolved during warming. The crude product mixture was concentrated under reduced pressure with the aid of a rotary evaporator. Column chromatography (SiO_2) was performed using two column volumes of hexane followed by hexane:EtOAc (5:1 v/v) as the eluent. All of the fractions containing the desired product were combined and concentrated under reduced pressure with the aid of a rotary evaporator.

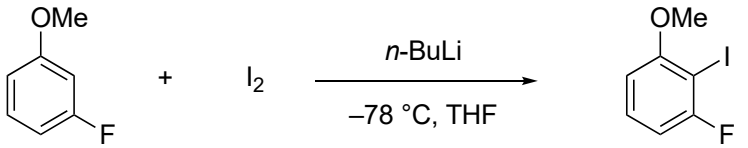


Ln

Step 5. An oven-dried round-bottom flask or reaction tube (Fisherbrand, 20 x 125 mm, product no. 1495937C) containing a Teflon-coated magnetic stir bar was charged with the biaryl iodide generated in *Step 4* (1.00 equiv). In cases using a round-bottom flask, the flask was seal with a rubber septum. In cases using a reaction tube, the tube was sealed with a screw cap (Kimble, supplier no. 73804-18400) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. B7995-18). The septum of the reaction apparatus was pierced with a needle attached to a Schlenk line using a rubber hose. A needle attached to a balloon was also inserted through the septum. The balloon and flask were evacuated and backfilled with argon (the evacuation/backfill process was repeated a total of three times; note: after this process, the balloon was inflated with argon). Anhydrous THF was added via syringe and the reaction flask was cooled to −78 °C using a dry ice/acetone bath. *t*-BuLi (2.3 equiv, 1.7 M in pentane) was added in a dropwise fashion to the solution via syringe, and the reaction mixture was stirred at −78 °C for 1 h, during which time the reaction mixture became heterogenous and bright yellow in color. Chlorodicyclohexylphosphine (1.15 equiv) was added in a dropwise fashion to the solution via syringe, during which time the reaction mixture turned orange in color. The cold bath was removed, and the flask was allowed to warm to room temperature. The solution was stirred for a total of 3 h while warming, during which time it again turned yellow in color. The crude reaction mixture was then opened to the air, diluted with EtOAc and transferred to a separatory funnel. The organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator to yield a white solid. The crude solid was dissolved in a minimal amount of boiling MeOH or EtOAc in a round-bottom flask that was loosely capped with a polyethylene stopper (Kimble Part no. 774240-0024), using an oil bath to heat the mixture. After all of the solid had dissolved, the mixture was allowed to cool to room temperature. When EtOAc was used to dissolve the crude reaction mixture, MeOH was layered onto the EtOAc solution as it was allowed to cool to room temperature. The flask was sealed under air with the polyethylene stopper, and the solution was then stored at −25 °C overnight, which furnished small white crystals that were isolated using vacuum filtration.

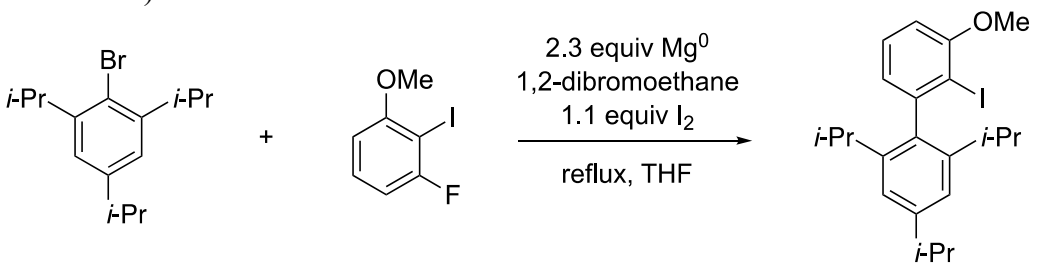
Synthesis of L3

General Procedure A was followed, with the following specifications:

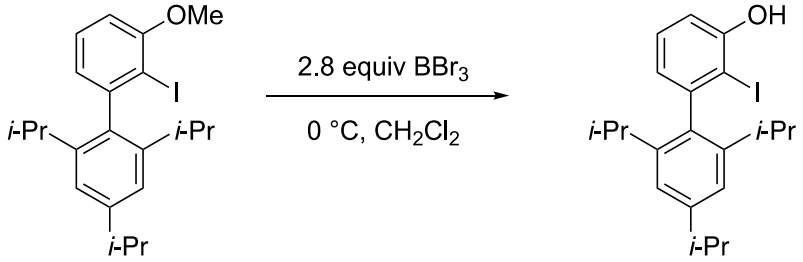


Step 1. Step 1 of General procedure A was followed using 1-fluoro-3-methoxybenzene (25.6

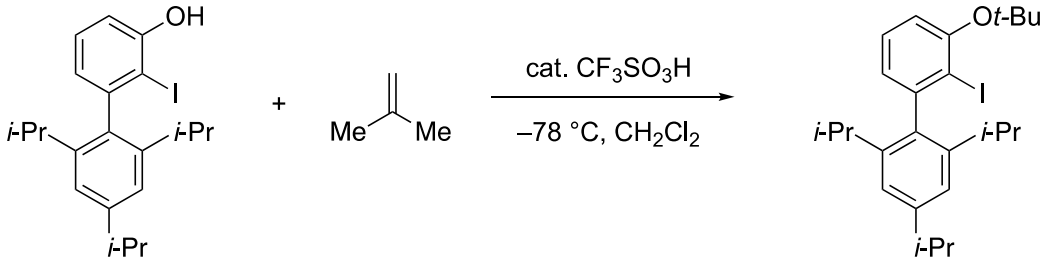
mmol, 3.23 g, 1.00 equiv), anhydrous THF (85 mL), *n*-BuLi (30.0 mmol, 14.9 mL, 1.17 equiv, 2.0 M in hexane), and a 500 mL round-bottom flask (Flask A). The reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (100 mL). The crude material was either used in the next step without purification using the purity estimated by GC analysis (~90% purity as estimated by GC analysis) or chromatographed and used as a pure, colorless liquid (chromatography conditions: SiO_2, 100% hexane).



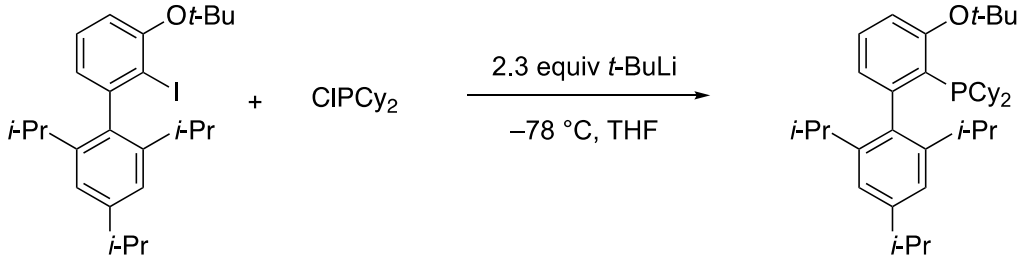
Step 2. Step 2 of General procedure A was followed using magnesium (23.3 mmol, 565 mg, 2.30 equiv, 20% powder, 80% turnings), THF (19 mL), 2-bromo-1,3,5-triisopropylbenzene (10.1 mmol, 2.86 g, 1.00 equiv), and 1,2-dibromoethane (60 µL). When 2-bromo-1,3,5-triisopropylbenzene was completely consumed, chromatographed 1-fluoro-2-iodo-3-methoxybenzene (10.5 mmol, 2.65 g, 1.04 equiv) from the previous step was added to Flask A. A solution of iodine (10.1 mmol, 2.57 g, 1.00 equiv) in anhydrous THF (10 mL) was prepared in Flask B. The product mixture was transferred to a separatory funnel, along with saturated aqueous $Na_2S_2O_3$ (50 mL), brine (25 mL), and EtOAc (50 mL). The organic and aqueous layers were separated, and the organic layer was washed with brine (25 mL). The crude mixture was triturated with MeOH to afford a yellow solid (2.42 g, 55%), which was used in the next step without further purification.



Step 3. Step 3 of General procedure A was followed using 2-iodo-2',4',6'-triisopropyl-3-methoxy-1,1'-biphenyl (7.82 mmol, 3.41 g, 1.00 equiv), CH_2Cl_2 (50 mL), BBr_3 (21.9 mmol, 2.1 mL, 2.8 equiv), and a 250 mL round-bottom flask cooled to 0 °C using an ice/water bath. Prior to the workup, the reaction flask was re-cooled to 0 °C using an ice/water bath, opened to the air, and CH_2Cl_2 (25 mL) and MeOH (10 mL) were *very cautiously* added. The resulting solution was allowed to warm to room temperature and was then cautiously treated with saturated aqueous $NaHCO_3$ (100 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The product was obtained as an off-white solid, which was >95% pure as judged by ^1H NMR (3.32 g, 100%).



Step 4. Step 4 of General procedure A was followed using 2-iodo-2',4',6'-triisopropyl-[1,1'-biphenyl]-3-ol (7.82 mmol, 3.30 g, 1.00 equiv) and CH_2Cl_2 (58 mL) in a 300 mL round-bottom flask (Flask A), isobutylene (~23 mL, ~117 mmol, ~30.0 equiv) in a 50 mL round-bottom flask (Flask B), and TfOH (40 drops). In this case, additional TfOH (10 drops) was added after 1.5 h, and additional isobutylene (10 mL) was added after 7.5 h. The reaction was quenched with triethylamine (100 drops). The product was obtained as a white solid (3.50 g, 94%).



L3

Step 5. Step 5 of General procedure A was followed using 3-(*tert*-butoxy)-2-iodo-2',4',6'-diisopropyl-1,1'-biphenyl (0.50 g, 1.05 mmol, 1.00 equiv), THF (2.5 mL), *t*-BuLi (1.4 mL, 2.4 mmol, 2.3 equiv, 1.7 M in pentane), and chlorodicyclohexylphosphine (1.2 mmol, 0.27 mL, 1.15 equiv) in an oven-dried reaction tube. The workup was performed with EtOAc (5 mL), and the washes were performed with saturated aqueous NH_4Cl (2 x 15 mL). The crystallization was performed using MeOH (80 mL). Yield: 0.265 g, 46%. Overall yield = 20% based on 2,4,6-triisopropylbromobenzene.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, *J* = 7.9 Hz, 1H), 6.95 (m, 3H), 6.62 (dd, *J* = 7.5, 3.6 Hz, 1H), 2.92 (sept, *J* = 7.0 Hz, 1H), 2.50 (sept, *J* = 6.6 Hz, 2H), 2.34 (dtt, *J* = 12.1, 8.2, 3.2 Hz, 2H), 1.84 – 1.59 (m, 8H), 1.65 (s, 9H), 1.53 – 1.46 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.21 (d, *J* = 6.8 Hz, 6H), 1.34 – 1.05 (m, 7H), 1.01 – 0.89 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.2, 151.8, 151.4, 147.0, 145.6, 138.1, 138.0, 128.4, 125.0, 124.8, 123.9, 123.8, 120.5, 112.5, 78.0, 37.5, 37.4, 34.0, 33.7, 33.4, 30.5, 30.4, 30.3, 29.3, 28.2, 28.1, 27.9, 27.8, 26.7, 26.2, 24.1, 23.4.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −4.7

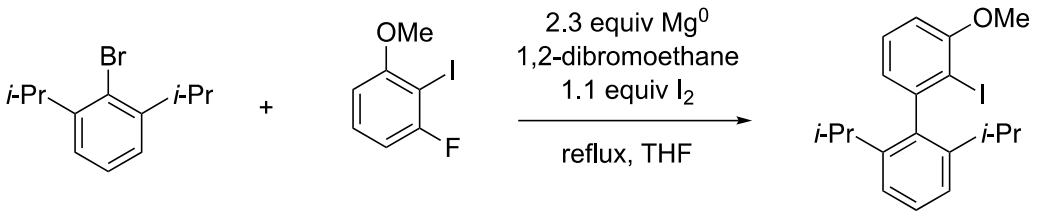
Elemental Analysis calc. for $C_{37}H_{57}OP$: C, 80.97; H, 10.47. Found: C, 80.69; H, 10.55.

IR (Diamond-ATR, neat, cm^{-1}): 2961, 2922, 2848, 1168, 955, 794.

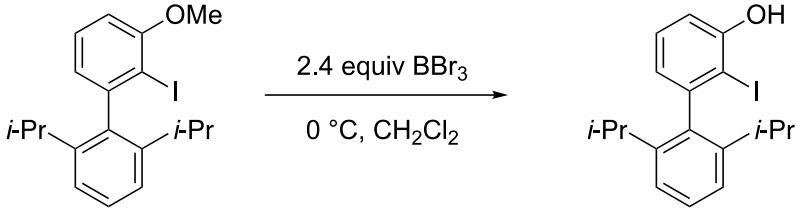
Melting Point: 198 °C

Synthesis of L4

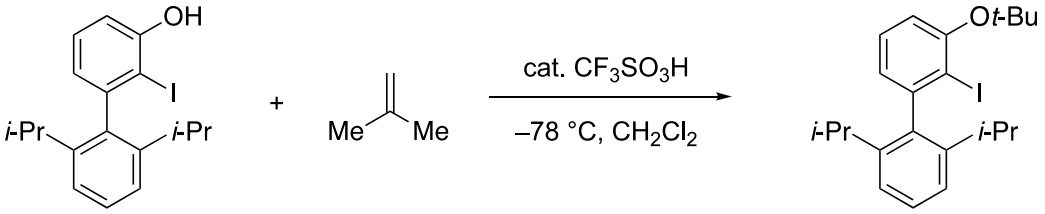
General Procedure A was followed, with the following specifications:



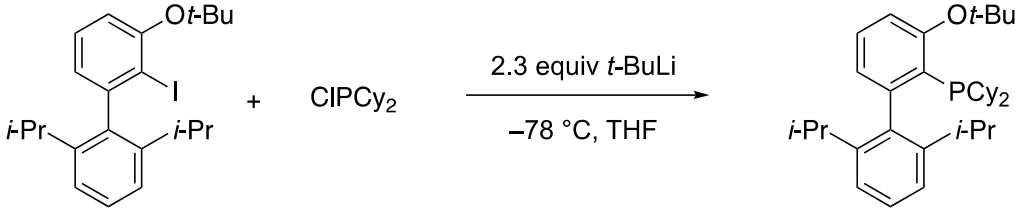
Step 2. Step 2 of General procedure A was followed using magnesium (28.6 mmol, 696 mg, 2.30 equiv, 20% powder, 80% turnings), THF (24 mL), 2-bromo-1,3-diisopropylbenzene (12.4 mmol, 3.00 g, 1.00 equiv),[48] and 1,2-dibromoethane (50 µL). When 2-bromo-1,3-diisopropylbenzene was completely consumed, crude 1-fluoro-2-iodo-3-methoxybenzene (12.9 mmol, 3.6 g, 1.04 equiv) from the previous step was added to Flask A. A solution of iodine (12.4 mmol, 3.16 g, 1.10 equiv) in anhydrous THF (12 mL) was prepared in Flask B. The product mixture was transferred to a separatory funnel, along with saturated aqueous $Na_2S_2O_3$ (50 mL), brine (25 mL), and EtOAc (50 mL). The organic and aqueous layers were separated, and the organic layer was washed with brine (25 mL). The crude mixture was triturated with MeOH to afford an off-white powder (2.48 g, 51%), which was used in the next step without further purification.



Step 3. Step 3 of General procedure A was followed using 2-iodo-2',6'-diisopropyl-3-methoxy-1,1'-biphenyl (3.81 mmol, 1.50 g, 1.00 equiv), CH_2Cl_2 (22 mL), BBr_3 (6.1 mmol, 0.6 mL, 1.6 equiv), and a 250 mL round-bottom flask cooled to −78 °C using a dry ice/acetone bath. The flask was removed from the cold bath and stirring was continued for 30 min while the reaction mixture was allowed to warm to room temperature. The reaction flask was then opened to the air, CH_2Cl_2 (25 mL) and MeOH (10 mL) were *very cautiously* added, and the resulting solution was then cautiously treated with saturated aqueous $NaHCO_3$ (50 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). An off-white solid was obtained, and ^{1}H NMR analysis indicated that the mixture contained ~33 mol % remaining starting material (2-iodo-2',6'-diisopropyl-3-methoxy-1,1'-biphenyl). The off-white solid was thus re-subjected to Step 3 of General procedure A. A 250 mL round-bottom flask was charged with the off-white solid. Anhydrous CH_2Cl_2 (22 mL) was added, and the flask was cooled to 0 °C using an ice/water bath, at which point neat BBr_3 (9.2 mmol, 0.9 mL, 2.4 equiv) was added. The flask was removed from the cold bath and stirring was continued for 1.5 h while the reaction mixture was allowed to warm to room temperature. The reaction flask was then opened to the air, CH_2Cl_2 (25 mL) and MeOH (10 mL) were *very cautiously* added, and the resulting solution was then cautiously treated with saturated aqueous $NaHCO_3$ (50 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The product was obtained as a white solid, which was >95% pure as judged by ^{1}H NMR (1.42 g, 98%).



Step 4. Step 4 of General procedure A was followed using 2-iodo-2',6'-diisopropyl-[1,1'-biphenyl]-3-ol (3.74 mmol, 1.42 g, 1.00 equiv) and CH_2Cl_2 (28 mL) in a 300 mL round-bottom flask (Flask A), isobutylene (~11 mL, ~56 mmol, ~30.0 equiv) in an oven-dried reaction tube (Flask B), and TfOH (10 drops). In this case, additional TfOH (10 drops) was added after 1.5 h. The reaction was quenched with triethylamine (15 drops). In this case, the crude product was obtained as a viscous off-white oil (1.55 g, 91%).



L4

Step 5. Step 5 of General procedure A was followed using 3-(*tert*-butoxy)-2-iodo-2',6'-diisopropyl-1,1'-biphenyl (1.25 g, 2.86 mmol, 1.00 equiv), THF (6.5 mL), *t*-BuLi (3.9 mL, 6.6 mmol, 2.3 equiv, 1.7 M in pentane), and chlorodicyclohexylphosphine (3.3 mmol, 0.73 mL, 1.15 equiv) in a 50 mL round-bottom flask. In this case, the biaryl iodide was transferred into the 50 mL round bottom flask by sealing the scintillation vial (DKW Life Sciences, catalog no. 03-340-4C) containing the biaryl iodide with a rubber septum, piercing the septum with a needle attached to a Schlenk line using a rubber hose, and evacuating and backfilling with nitrogen (the evacuation/backfill process was repeated a total of three times). THF (5 mL) was then added to the scintillation vial via syringe, and the resulting solution was transferred into the 50 mL flask via syringe. To rinse the remaining biaryl iodide from the scintillation vial, THF (1.5 mL) was added via syringe, and the resulting solution was transferred into the 50 mL flask via syringe. After this, General Procedure A was followed as described in General Procedure A. The workup was performed with EtOAc (15 mL), and sequential washes were performed with water (15 mL) and saturated aqueous NH_4Cl (15 mL). The combined aqueous layers were then extracted with EtOAc (20 mL). The resulting organic layer was washed sequentially with water (15 mL) and saturated aqueous NH_4Cl (15 mL). This second organic fraction was combined with the first organic layer and the workup was continued as described in General Procedure A. The crystallization was performed using EtOAc (20 mL) that was layered with MeOH (20 mL). Yield: 0.811 g, 56%. Overall yield = 20% based on 2-bromo-1,3-diisopropylbenzene.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.7 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 7.5, 3.5 Hz, 1H), 2.52 (sept, *J* = 6.7 Hz, 2H), 2.33 (dtt, *J* = 11.7, 7.9, 3.2 Hz, 2H), 1.82 – 1.60 (m, 7H), 1.65 (s, 9H), 1.53 – 1.46 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.30 – 1.04 (m, 8H), 0.97 (d, *J* = 6.7 Hz, 6H), 0.93 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 159.3, 159.3, 151.3, 150.9, 146.2, 146.2, 140.6, 140.6, 128.5, 127.8, 124.9, 124.6, 123.5, 123.4, 122.4, 112.7, 78.0, 37.6, 37.4, 33.7, 33.4, 30.5, 30.38, 30.27,

29.3, 28.2, 28.1, 27.9, 27.7, 26.7, 26.2, 23.2.

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ −4.7.

Elemental Analysis calc. for $C_{34}H_{51}OP$: C, 80.59; H, 10.14. Found: C, 80.84; H, 10.32.

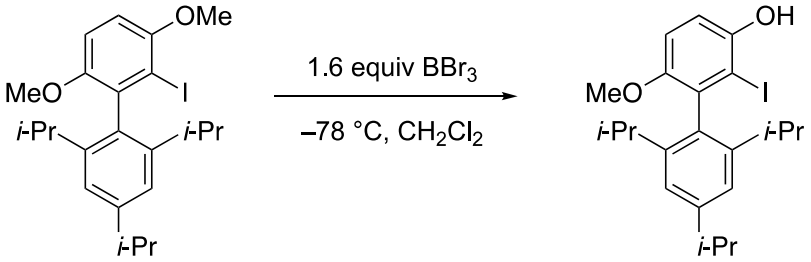
IR (Diamond-ATR, neat, cm^{-1}): 2959, 2918, 2846, 1166, 785, 753.

Melting Point: 236 °C

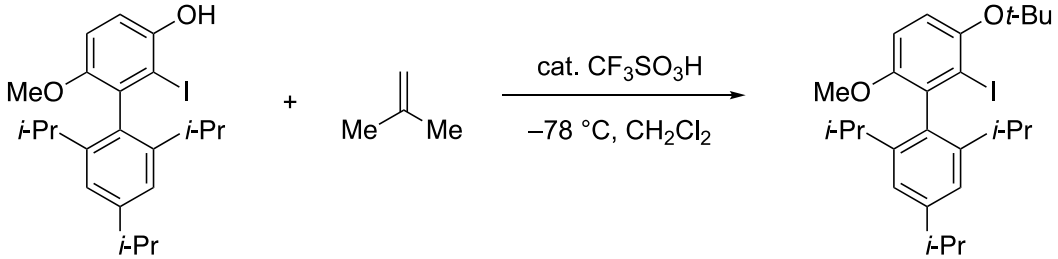
Synthesis of L5

General Procedure A was followed, with the following specifications:

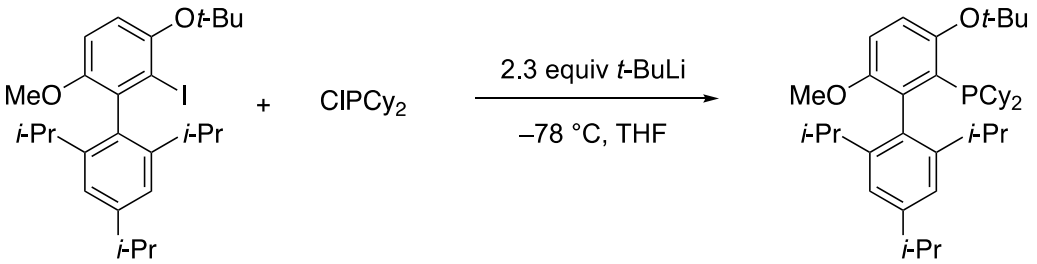
2-iodo-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl (BrettPhos–I) was obtained from MilliporeSigma as a gift.



Step 3. Step 3 of General procedure A was followed using 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl (1.07 mmol, 0.50 g, 1.00 equiv), CH_2Cl_2 (8 mL), BBr_3 (1.72 mmol, 0.165 mL, 1.60 equiv), and a 100 mL round-bottom flask cooled to −78 °C using a dry ice/acetone bath. After the reaction mixture was opened to the air, CH_2Cl_2 (10 mL) and MeOH (5 mL) were *very cautiously* added, and the resulting solution was then cautiously treated with saturated aqueous $NaHCO_3$ (20 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The product was obtained as a white solid, which was >95% pure as judged by ^{1}H NMR (0.476 g, 98%).



Step 4. Step 4 of General procedure A was followed using 2-iodo-2',4',6'-triisopropyl-6-methoxy-[1,1'-biphenyl]-3-ol (1.01 mmol, 0.457 g, 1.00 equiv) and CH_2Cl_2 (8 mL) in a 50 mL round-bottom flask (Flask A), isobutylene (~3 mL, ~15 mmol, ~30.0 equiv) in an oven-dried reaction tube (Flask B), and TfOH (4 drops). The reaction was quenched with triethylamine (10 drops). The product was obtained as a white solid (0.494 g, 96%).



L5

Step 5. Step 5 of General procedure A was followed using 3-(*tert*-butoxy)-2-iodo-2',4',6'-triisopropyl-6-methoxy-1,1'-biphenyl (0.885 mmol, 0.450 g, 1.00 equiv), THF (2.2 mL), *t*-BuLi (2.04 mmol, 1.2 mL, 2.3 equiv, 1.7 M in pentane), and chlorodicyclohexylphosphine (1.02 mmol, 0.225 mL, 1.15 equiv) in a flame-dried 25 mL round-bottom flask. The workup was performed with EtOAc (5 mL), and the washes were performed with saturated aqueous NH_4Cl (2 x 5 mL). The crystallization was performed using EtOAc (3.5 mL) that was layered with MeOH (15 mL). Yield: 0.295 g, 58%. Overall yield = 54% based on 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 2H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 9.0 Hz, 1H), 3.53 (s, 3H), 2.93 (sept, *J* = 6.8 Hz, 1H), 2.46 (sept, *J* = 6.8 Hz, 2H), 2.32 (qt, *J* = 9.7, 7.4, 3.2 Hz, 2H), 1.78 (m, 7H), 1.62 (s, 9H), 1.49 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.37 – 1.06 (m, 9H), 1.00 – 0.85 (m, 2H), 0.92 (d, *J* = 6.7 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.8, 152.8, 151.4, 151.3, 146.8, 146.1, 146.0, 140.1, 139.7, 133.0, 132.9, 127.3, 127. 0, 120.2, 112.1, 110.2, 110.2, 77.3, 54.6, 37.8, 37.6, 33.8, 33.7, 33.4, 30.4, 30.4, 30.3, 29.2, 28.2, 28.1, 27.9, 27.8, 26.7, 26.6, 25.3, 24.1, 23.9.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −4.0.

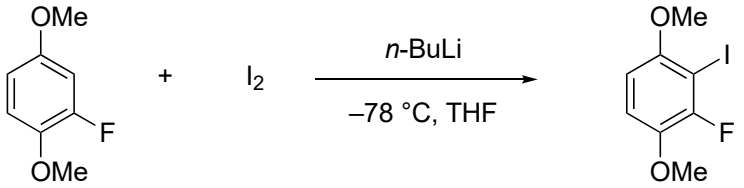
Elemental Analysis calc. for $C_{38}H_{59}O_2P$: C, 78.85; H, 10.27. Found: C, 79.04; H, 10.42.

IR (Diamond-ATR, neat, cm^{-1}): 2957, 2920, 1252, 1170, 1050, 803.

Melting Point: 203 °C

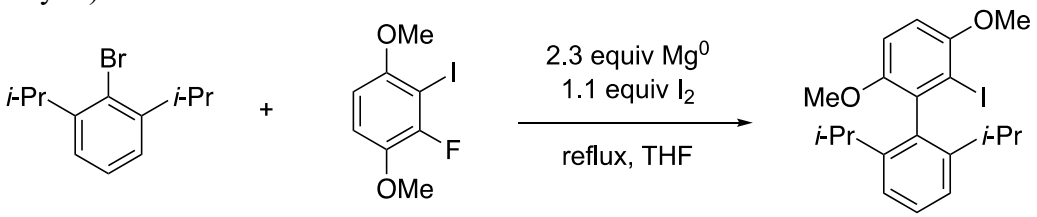
Synthesis of L6 (GPhos)

General Procedure A was followed, with the following specifications:

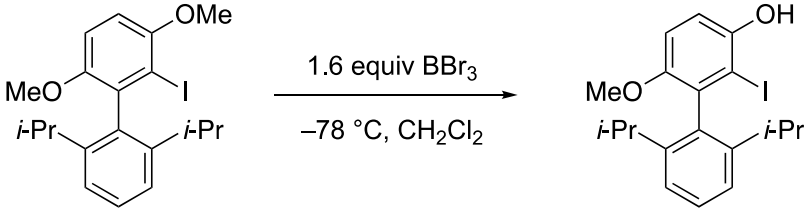


Step 1. Step 1 of General procedure A was followed using 2-fluoro-1,4-dimethoxybenzene (25.6 mmol, 4.00 g, 1.00 equiv), THF (80 mL), *n*-BuLi (30.0 mmol, 13.6 mL, 1.17 equiv, 2.2 M in cyclohexane), and a 250 mL round-bottom flask (Flask A). The reaction was quenched by pouring

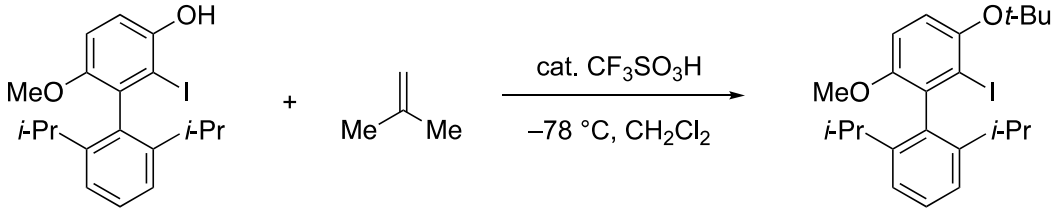
the reaction mixture into a saturated aqueous solution of $Na_2S_2O_3$ (250 mL) in a 500 mL Erlenmeyer flask. The combined layers were then transferred into a separatory funnel and the procedure was continued as described in General Procedure A. The crude material was used in the next step without purification using the purity estimated by GC analysis (~70% purity as estimated by GC analysis).



Step 2. Step 2 of General procedure A was followed using magnesium (35.5 mmol, 863 mg, 2.30 equiv, 20% powder, 80% turnings), THF (30 mL) and 2-bromo-1,3-diisopropylbenzene (15.4 mmol, 4.00 g, 1.00 equiv).[48] 1,2-Dibromoethane was not added. When 2-bromo-1,3-diisopropylbenzene was completely consumed, crude 2-fluoro-3-iodo-1,4-dimethoxybenzene (16.1 mmol, 6.86 g, 1.04 equiv) from the previous step was added to Flask A. A solution of iodine (17.0 mmol, 4.31 g, 1.10 equiv) in anhydrous THF (17 mL) was prepared in Flask B. The product mixture was transferred to a separatory funnel, along with saturated aqueous $Na_2S_2O_3$ (100 mL), brine (25 mL), and EtOAc (50 mL). The organic and aqueous layers were separated, and the organic layer was extracted with EtOAc (1 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure with the aid of a rotary evaporator. The crude mixture was triturated with MeOH to afford an off-white powder (4.12 g, 63%), which was used in the next step without further purification.

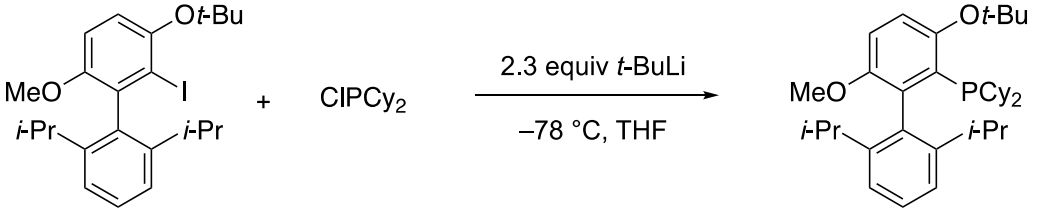


Step 3. Step 3 of General procedure A was followed using 2-iodo-2',6'-diisopropyl-3,6-dimethoxy-1,1'-biphenyl (5.89 mmol, 2.50 g, 1.00 equiv), CH_2Cl_2 (38 mL), BBr_3 (9.4 mmol, 0.91 mL, 1.6 equiv), and a 250 mL round-bottom flask cooled to −78 °C using a dry ice/acetone bath. After the reaction mixture was opened to the air, CH_2Cl_2 (30 mL) and MeOH (10 mL) were *very cautiously* added, and the resulting solution was then cautiously treated with saturated aqueous $NaHCO_3$ (75 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The product was obtained as a brown solid, which was >95% pure as judged by ^{1}H NMR (2.24 g, 93%).



Step 4. Step 4 of General procedure A was followed using 2-iodo-2',6'-diisopropyl-6-methoxy-[1,1'-biphenyl]-3-ol (7.55 mmol, 3.10 g, 1.00 equiv) and CH_2Cl_2 (57 mL) in a 500 mL round-bottom flask (Flask A), isobutylene (~22 mL, ~113 mmol, ~30.0 equiv) in a 25 mL round-bottom flask (Flask B), and TfOH (30 drops). The reaction was quenched with triethylamine (40 drops).

The product was obtained as a white solid (3.22 g, 91%).



L6

Step 5. Step 5 of General procedure A was followed using 3-(*tert*-butoxy)-2-iodo-2',6'-diisopropyl-6-methoxy-1,1'-biphenyl (2.50 g, 5.36 mmol, 1.00 equiv), THF (12 mL), *t*-BuLi (7.30 mL, 12.3 mmol, 2.30 equiv, 1.7 M in pentane), and chlorodicyclohexylphosphine (6.16 mmol, 1.36 mL, 1.15 equiv) in a flame-dried 100 mL round-bottom flask. The workup was performed with EtOAc (20 mL), and the washes were performed with saturated aqueous NH_4Cl (2 x 20 mL). The crystallization was performed using EtOAc (16 mL) that was layered with MeOH (45 mL). Yield: 1.57 g, 55%. Overall yield = 18% based on 2-bromo-1,3-diisopropylbenzene.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 3.55 (s, 3H), 2.49 (sept, *J* = 6.7 Hz, 2H), 2.31 (tdt, *J* = 12.4, 6.6, 3.1 Hz, 2H), 1.79 – 1.64 (m, 7H), 1.62 (s, 9H), 1.52 – 1.44 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 6H), 1.31 – 1.13 (m, 9H), 1.02 – 0.86 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.0, 152.9, 151.1, 151.0, 146.8, 146.7, 139.5, 139.2, 135.9, 135.8, 127.9, 127.1, 126.8, 122.2, 112.3, 110.3, 77.4, 54.6, 37.9, 37.7, 33.7, 33.4, 30.4, 30.3, 29.2, 28.2, 28.1, 27.9, 27.7, 26.6, 25.3, 23.8.

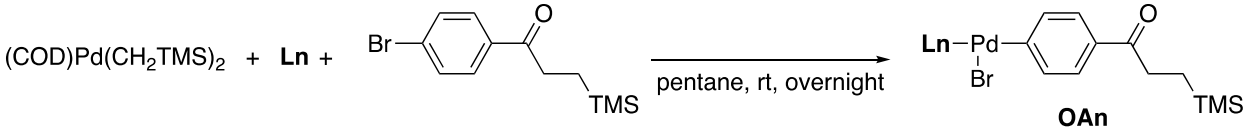
^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ −4.0.

Elemental Analysis calc. for $C_{35}H_{53}O_2P$: C, 78.32; H, 9.95. Found: C, 78.39; H, 10.12.

IR (Diamond-ATR, neat, cm^{-1}): 2923, 1581, 1427, 1255, 1171, 1041, 952, 753.

Melting Point: 240 °C

General Procedure B for Synthesis of Oxidative Addition Complexes (OACs)

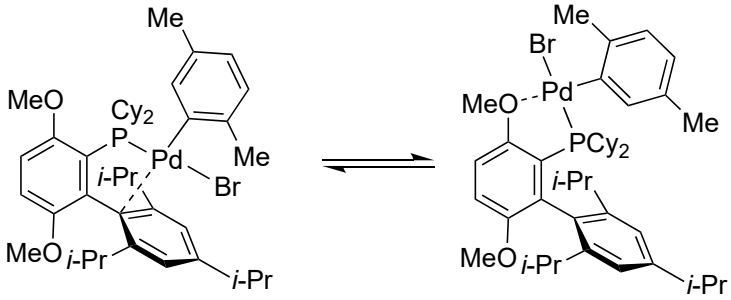


OAn

An oven-dried reaction tube (Fisherbrand, 20 × 150 mm, catalog no. 1495937C) or round-bottom flask containing a Teflon-coated magnetic stir bar was charged with phosphine ligand (1 equiv) and aryl halide (1.5–2 equiv).[31a] The tube was sealed with a screw cap (Kimble Chase Open Top S/T Closure, catalog no. 73804-18400) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. B7995-18), or if using a round-bottom flask, the flask was sealed with a rubber septum. The septum was pierced with a needle attached to a Schlenk line using a rubber hose, and the tube or flask was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Pentane was added via syringe until the ligand completely dissolved (the amount differed based on the ligand identity and reaction scale). The cap or septum was removed

and (COD)Pd($CH_2TMS)_2$ (1 equiv) was added quickly. The cap or septum was immediately replaced, and the reaction mixture was stirred for 16 h at room temperature. Over this time, a precipitate formed. The precipitate was collected using vacuum filtration, and the resulting filter cake was washed with additional pentane to afford a pale yellow or white solid. The resulting solid was dried under high vacuum for ≥2 h.

Synthesis of OA1'



General procedure B was followed using BrettPhos (**L1**) (50 mg, 0.093 mmol), 1-bromo-2,4-dimethylbenzene (34 mg, 0.190 mmol, 2.0 equiv), (COD)Pd($CH_2TMS)_2$ (36 mg, 0.093 mmol), ~5 mL pentane. The filter cake was washed with additional pentane (3 x 10 mL). Pale yellow powder. Yield: 55 mg, 71%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (s), 7.13 – 6.92 (m), 6.87 (dd, *J* = 8.9, 2.7 Hz), 6.79 (d, *J* = 8.9 Hz), 6.68 (s), 6.61 – 6.48 (m), 4.31 (s), 3.82 (s), 3.58 (s), 3.34 (s), 3.20 – 3.00 (m), 2.92 (p, *J* = 7.1 Hz), 2.53 (s), 2.17 (s), 2.13 (s), 1.77 (m), 1.58 (t, *J* = 6.6 Hz), 1.40 (d, *J* = 6.9 Hz), 1.37 (d, *J* = 6.9 Hz), 1.33 – 0.95 (m), 0.89 (d, *J* = 6.6 Hz), 0.83 (d, *J* = 6.7 Hz), 0.66 (d, *J* = 6.6 Hz).

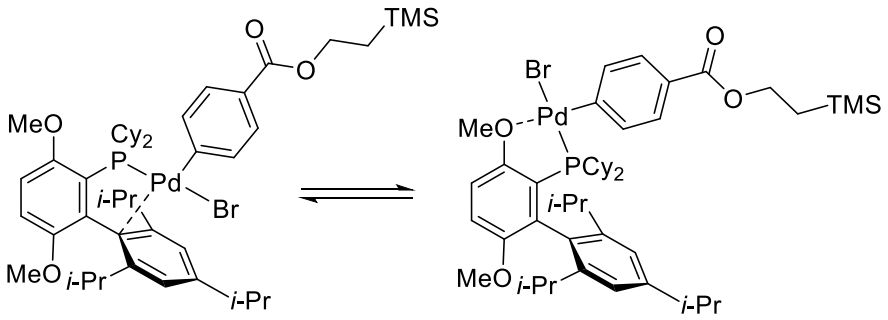
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.3, 154.8, 153.0, 152.2, 152.1, 150.5, 149.0, 146.9, 146.7, 141.1, 138.7, 138.5, 137.6, 136.0, 135.9, 133.5, 128.3, 127.1, 125.5, 125.2, 124.4, 124.33, 124.22, 124.0, 122.3, 120.6, 117.9, 112.9, 112.7, 110.7, 61.2, 55.0, 54.8, 54.5, 34.8, 34.7, 34.5, 34.5, 34.4, 33.2, 31. 5, 31.2, 30.8, 30.6, 29.7, 29.6, 28.9, 28.5, 28.5, 28.0, 27.9, 27.8, 27.4, 27.2, 26.7, 26.5, 26.2, 26.0, 25.6, 25.2, 24.9, 24.8, 24.7, 24.2, 24.1, 23.8, 22.6, 21.3, 21.2.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 43.1, 34.5.

HRMS (ESI) calc. $C_{43}H_{62}O_2PPd^+$ $[M–Br]^+$: 747.3517. Found: 747.3522.

IR (Diamond-ATR, neat, cm^{-1}): 2919, 2851, 1578, 1459, 1258, 1007, 820.

Synthesis of OA1



General procedure B was followed using BrettPhos (**L1**) (210 mg, 0.391 mmol), 2-(trimethylsilyl)ethyl 4-bromobenzoate (177 mg, 0.587 mmol, 1.5 equiv), (COD)Pd($CH_2TMS)_2$ (152 mg, 0.391 mmol), ~15 mL pentane. The filter cake was washed with additional pentane (3 x 10 mL). Pale yellow powder. Yield: 211 mg, 57%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.45 (m, 3H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.09 (s, 2H), 7.01 (m, 2H), 6.88 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.82 (d, *J* = 8.9 Hz, 1H), 4.41 – 4.29 (s + t, *J* = 8.9 Hz, 3H), 3.82 (s, 3H), 3.59 (s, 1H), 3.35 (s, 3H), 3.09 (p, *J* = 7.0 Hz, 1H), 2.92 (p, *J* = 6.9 Hz, 1H), 2.77 (q, *J* = 11.7 Hz, 2H), 2.49 (p, *J* = 6.7 Hz, 2H), 2.32 (p, *J* = 6.7 Hz, 1H), 1.86 (s, 2H), 1.79 – 1.63 (m, 14H), 1.60 (d, *J* = 6.7 Hz, 6H), 1.43 (s, 2H), 1.37 (d, *J* = 6.9 Hz, 6H), 1.25 (d + d, *J* = 6.8, 12H), 1.22 – 1.07 (m, 6H), 1.06 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.81 (d, *J* = 6.6 Hz, 6H), 0.62 (m, 1H), 0.05 (s, 9H).

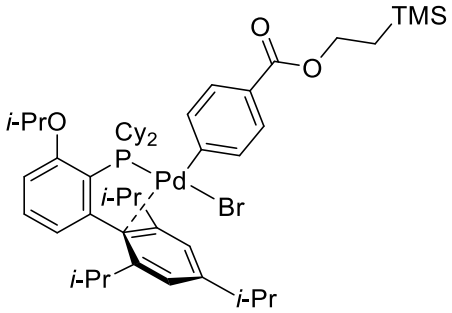
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.0, 167.8, 157.5, 154.1, 152.1, 149.2, 146.8, 138.1, 137.8, 137.7, 133.6, 130.3, 126.9, 126.8, 125.6, 125.4, 124.7, 121.5, 113.4, 113.3, 111.3, 111.0, 62.6, 62.6, 62.3, 55.0, 54.8, 54.5, 36.5, 36.3, 35.4, 35.2, 34.5, 34.4, 31.6, 31.0, 30.9, 29.5, 29.4, 28.0, 27.8, 27.8, 26.8, 26.7, 26.5, 26.4, 26.2, 25.6, 25.5, 25.4, 24.9, 24.6, 24.1, 23.5, 17.5, −1.3.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 46.3, 36.9

HRMS (ESI) calc. $C_{47}H_{70}O_4PPdSi^+$ $[M–Br]^+$: 863.3810. Found: 863.3819.

IR (Diamond-ATR, neat, cm^{-1}): 2931, 1707, 1574, 1258, 1009, 754.

Synthesis of OA2



General procedure B was followed using EPhos (**L2**) (70 mg, 0.13 mmol), 2-(trimethylsilyl)ethyl 4-bromobenzoate (79 mg, 0.26 mmol, 2.0 equiv), (COD)Pd($CH_2TMS)_2$ (51 mg, 0.13 mmol), ~5 mL pentane. The filter cake was washed with additional pentane (3 x 10 mL). Pale yellow powder. Yield: 91 mg, 74%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.10 (s, 2H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.26 (d, *J* = 7.6 Hz, 1H), 4.77 (p, *J* = 6.1 Hz, 1H), 4.34 (t, *J* = 8.3 Hz, 2H), 3.09 (p, *J* = 7.0 Hz, 1H), 2.91 (q, *J* = 12.0 Hz, 2H), 2.54 (p, *J* = 6.8 Hz, 2H), 1.87 (s, 2H), 1.77 (s, 4H), 1.66 (s, 8H), 1.61 (d, *J* = 6.7 Hz, 6H), 1.45 (d, *J* = 5.9 Hz, 6H), 1.38 (d, *J* = 6.9 Hz, 6H), 1.17 (s, 5H), 1.08 (t, *J* = 8.2 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.81 (d, *J* = 11.8 Hz, 2H), 0.05 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.0, 159.9, 157.1, 150.6, 150.2, 150.0, 147.4, 137.8, 137.8,

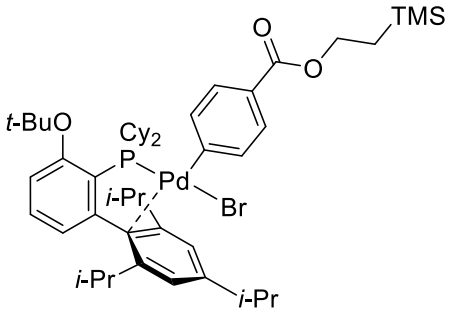
131.8, 126.9, 126.4, 126.3, 125.5, 125.0, 123.0, 121.9, 121.7, 110.4, 70.2, 62.6, 35.2, 34.9, 34.4, 31.7, 29.6, 29.1, 28.0, 27.8, 27.7, 27.6, 26.2, 25.7, 24.9, 22.0, 17.5, −1.3.

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 37.4.

HRMS (ESI) calc. $C_{48}H_{72}O_3PPdSi^+$ $[M–Br]^+$: 861.4018. Found: 861.4018.

IR (Diamond-ATR, neat, cm^{-1}): 2930, 1713, 1573, 1261, 1100, 1009, 836, 754.

Synthesis of OA3



General procedure B was followed using **L3** (71 mg, 0.13 mmol), 2-(trimethylsilyl)ethyl 4-bromobenzoate (77 mg, 0.26 mmol, 2.0 equiv), $(COD)Pd(CH_2TMS)_2$ (50 mg, 0.13 mmol), ~6 mL pentane. The filter cake was washed with additional pentane (3 x 5 mL). Pale yellow powder. Yield: 101 mg, 82%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.0 Hz, 2H), 7.23 (m, 3H), 7.09 (s, 2H), 7.04 (d, J = 8.5 Hz, 1H), 6.22 (d, J = 7.4 Hz, 1H), 4.34 (t, J = 8.2 Hz, 2H), 3.09 (sept, J = 6.9 Hz, 1H), 2.95 (q, J = 11.9 Hz, 2H), 2.53 (sept, J = 6.7 Hz, 2H), 1.85 – 1.73 (m, 6H), 1.72 – 1.60 (m, 6H), 1.66 (s, 9H), 1.62 (d, J = 6.9 Hz, 6H), 1.38 (d, J = 6.9 Hz, 6H), 1.17 (s, 6H), 1.08 (t, J = 8.3 Hz, 2H), 0.91 (d + m, J = 6.7 Hz, 8H), 0.05 (s, 9H).

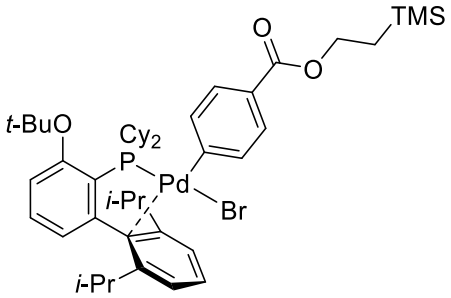
$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 168.0, 159.0, 157.1, 150.6, 150.0, 146.8, 138.3, 138.2, 131.1, 126.7, 126.1, 126.0, 125.5, 125.0, 123.3, 123.0, 114.0, 80.4, 62.6, 35.8, 35.5, 34.4, 31.7, 29.6, 29.4, 29.17, 27.8, 27.7, 27.6, 26.1, 25.7, 25.0, 24.9, 17.5, -1.3.

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 37.1.

HRMS (ESI) calc. $C_{49}H_{74}O_3PPdSi^+$ $[M–Br]^+$: 875.4174. Found: 875.4177.

IR (Diamond-ATR, neat, cm^{-1}): 2929, 1707, 1573, 1260, 1160, 837, 797, 754.

Synthesis of OA4



General procedure B was followed using **L4** (76 mg, 0.15 mmol), 2-(trimethylsilyl)ethyl 4-bromobenzoate (90 mg, 0.30 mmol, 2.0 equiv), (COD)Pd($CH_2TMS)_2$ (58 mg, 0.15 mmol), ~8 mL pentane. The filter cake was washed with additional pentane (5 x 10 mL). Pale yellow powder. Yield: 106 mg, 78%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (t, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.21 (m, 5H), 7.13 – 7.06 (m, 1H), 6.27 (dd, *J* = 7.6, 2.4 Hz, 1H), 4.36 (t, *J* = 8.2 Hz, 2H), 3.00 (q, *J* = 12.3 Hz, 2H), 2.56 (sept, *J* = 6.7 Hz, 2H), 1.93 – 1.63 (m, 8H), 1.69 (s, 9H), 1.63 (d, *J* = 6.7 Hz, 6H), 1.39 – 1.14 (m, 10H), 1.10 (t, *J* = 8.3 Hz, 2H), 0.99 – 0.82 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.08 (s, 9H).

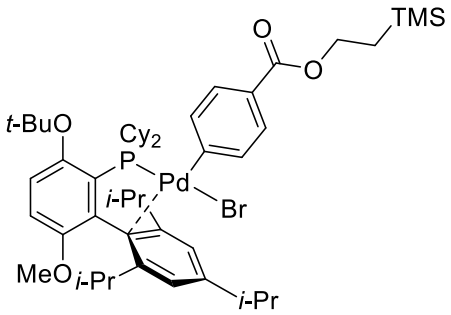
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.9, 159.2, 159.1, 150.6, 149.6, 149.4, 145.3, 145.3, 138.3, 138.2, 134.1, 131.3, 126.9, 126.6, 125.9, 125.8, 122.9, 122.6, 114.3, 114.3, 80.6, 62.7, 35.8, 35.6, 31.6, 29.6, 29.4, 29.2, 29.2, 27.8, 27.7, 27.7, 27.6, 26.1, 25.7, 24.9, 22.5, 17.5, 14.2, −1.3.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 37.5.

HRMS (ESI) calc. $C_{46}H_{68}O_3PPdSi^+$ $[M–Br]^+$: 833.3705. Found: 833.3711.

IR (Diamond-ATR, neat, cm^{-1}): 2918, 1700, 1573, 1274, 1258, 1163, 1009, 838, 756.

Synthesis of OA5



General procedure B was followed using **L5** (52 mg, 0.085 mmol), 2-(trimethylsilyl)ethyl 4-bromobenzoate (51 mg, 0.17 mmol, 2.0 equiv), (COD)Pd($CH_2TMS)_2$ (33 mg, 0.085 mmol), ~4 mL pentane. The filter cake was washed with additional pentane (7 x 3 mL). Pale yellow powder. Yield: 39 mg, 46%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 6.5 Hz, 2H), 7.10 – 7.02 (m, 3H), 6.73 (d, *J* = 9.1 Hz, 1H), 4.40 – 4.28 (m, 2H), 3.33 (s, 3H), 3.08 (sept, *J* = 6.7 Hz, 1H), 3.01

– 2.87 (m, 2H), 2.50 (sept, J = 6.8 Hz, 2H), 1.86 – 1.64 (m, 12H), 1.63 (s, 9H), 1.61 (d, J = 6.9 Hz, 6H), 1.37 (d, J = 6.9 Hz, 6H), 1.17 (d, J = 7.6 Hz, 6H), 1.11 – 1.04 (m, 2H), 0.95 (m, 2H), 0.82 (d, J = 6.6 Hz, 6H), 0.05 (s, 9H).

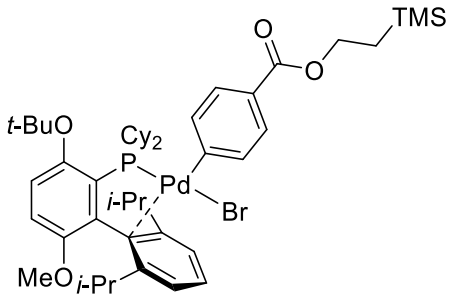
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.1, 157.5, 152.3, 151.8, 151.8, 151.2, 151.1, 147.5, 138.7, 138.6, 138.6, 138.5, 126.8, 126.5, 126.3, 125.3, 124.7, 124.4, 116.5, 116.4, 115.4, 115.4, 112.6, 79.6, 62.6, 54.5, 36.3, 36.0, 34.5, 31.5, 31.5, 29.7, 29.4, 29.3, 29.3, 27.8, 27.8, 27.7, 27.7, 26.1, 25.7, 25.0, 24.7, 17.5, −1.3.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 36.8.

HRMS (ESI) calc. $C_{50}H_{76}O_4PPdSi^+$ $[M–Br]^+$: 905.4280. Found: 905.4285.

IR (neat, cm^{-1}): 2932, 1710, 1574, 1261, 1161, 838, 825, 756.

Synthesis of OA6



General procedure B was followed using **L6** (280 mg, 0.52 mmol), 2-(trimethylsilyl)ethyl 4-bromobenzoate (314 mg, 1.04 mmol, 2.0 equiv), (COD)Pd($CH_2TMS)_2$ (203 mg, 0.52 mmol), ~28 mL pentane. The filter cake was washed with additional pentane (3 x 40 mL). Pale yellow powder. Yield: 414 mg, 84%.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (t, J = 7.7 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.26 – 7.21 (m, 4H), 7.09 (dd, J = 9.1, 3.1 Hz, 1H), 6.78 (d, J = 9.1 Hz, 1H), 4.33 (t, J = 8.3 Hz, 2H), 3.38 (s, 3H), 3.05 – 2.92 (m, 2H), 2.51 (sept, J = 6.9 Hz, 2H), 1.93 – 1.60 (m, 12H), 1.64 (s, 9H), 1.60 (d, J = 6.7 Hz, 6H), 1.39 – 1.10 (m, 1H), 1.17 (d, J = 8.2 Hz, 6H), 1.08 (t, J = 8.3 Hz, 2H), 1.01 – 0.91 (m, 2H), 0.84 (d, J = 6.6 Hz, 6H), 0.05 (s, 9H).

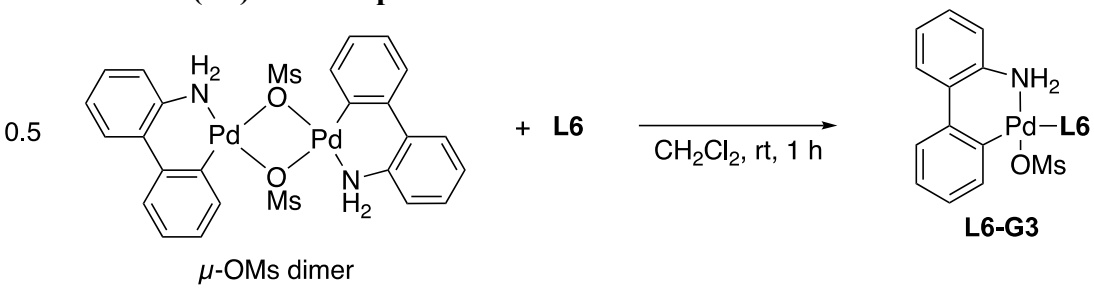
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.8, 152.0, 151.8, 151.8, 150.9, 150.7, 145.5, 138.4, 138.4, 137.9, 137.6, 134.1, 132.4, 131.9, 126.6, 126.2, 126.0, 125.7, 125.5, 120.2, 120.2, 115.6, 115.5, 112.8, 79.6, 62.5, 54.5, 36.3, 36.0, 31.3, 29.5, 29.3, 29.2, 27.7, 27.6, 27.6, 27.5, 25.9, 25.5, 24.6, 17.4, -1.40.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 36.9.

HRMS (ESI) calc. $C_{47}H_{70}O_4PPdSi^+$ $[M–Br]^+$: 863.3810. Found: 863.3818.

IR (Diamond-ATR, neat, cm^{-1}): 2929, 1708, 1575, 1262, 1159, 1011, 835, 753.

Synthesis of GPhos (L6)-G3 Complex



A modified literature procedure was followed, and the μ-OMs starting material was prepared as previously reported.[49] μ-OMs dimer (53.7 mg, 0.073 mmol, 0.5 equiv) and **L6** (78.0 mg, 0.145 mmol, 1.0 equiv) were added to an oven-dried reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) equipped with a Teflon-coated magnetic stir bar. The tube was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) fitted with a Teflon-coated septum (Fisherbrand, C4015-60). The septum was pierced with a needle attached to a Schlenk line using a rubber hose, and the tube was evacuated and backfilled with nitrogen (this process was repeated a total of three times). CH_2Cl_2 (2 mL) was added via syringe, and the dark turbid mixture was stirred until it became homogeneous (~1 h). The reaction mixture was transferred into a 20 mL scintillation vial (DKW Life Sciences, catalog no. 03-340-4C) and concentrated with the aid of a rotary evaporator. Pentane (~15 mL) was added to the resulting dark brown solid and the mixture was agitated with the aid of a sonicator until a fine brown powder formed (~60 min). The brown powder was collected via vacuum filtration and washed with pentane (3 x 20 mL) to give a dark brown powder. Yield: 73 mg, 55%.

^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (m, 1H), 7.72 (dd, J = 7.9, 3.5 Hz, 1H), 7.43 (dd, J = 7.7, 1.3 Hz, 1H), 7.33 (dd, J = 7.4, 1.5 Hz, 1H), 7.21 – 6.98 (m, 8H), 6.84 (d, J = 9.1 Hz, 1H), 5.37 – 5.30 (m, 1H), 3.42 (s, 3H), 2.91 (s, 1H), 2.85 – 2.73 (m, 2H), 2.29 (d, J = 11.6 Hz, 1H), 2.00 – 1.84 (m, 6H), 1.81 (d, J = 6.8 Hz, 4H), 1.60 (s, 9H), 1.40 (q, J = 10.6 Hz, 4H), 1.27 (m, 2H), 1.05 (d, J = 6.6 Hz, 3H), 1.02 – 0.91 (m, 2H), 0.87 – 0.75 (m, 2H), 0.64 (t, J = 7.0 Hz, 6H), 0.41 – 0.27 (m, 1H).

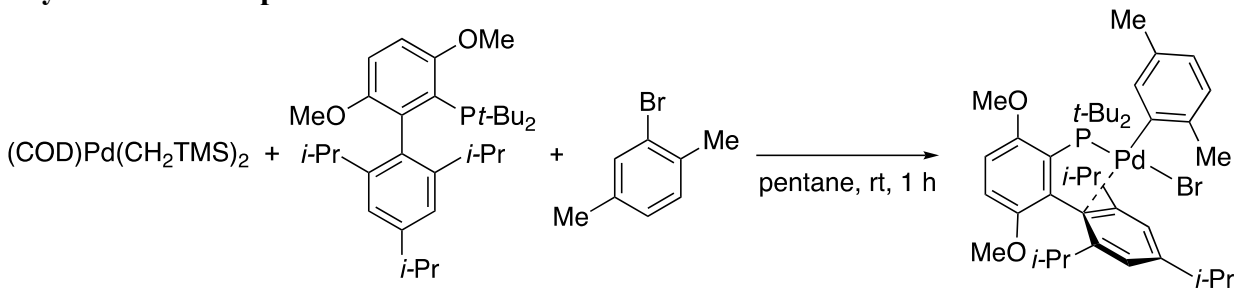
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.0, 153.1, 151.9, 150.9, 141.4, 140.1, 139.9, 136.9, 136.0, 135.7, 134.3, 128.4, 127.9, 126.9, 126.8, 126.6, 126.0, 125.4, 121.8, 120.6, 116.4, 113.9, 80.2, 54.7, 39.5, 34.9, 34.7, 34.5, 34.3, 32.8, 30.6, 29.6, 29.2, 28.9, 27.9, 27.8, 27.7, 27.2, 27.1, 26.9, 26.1, 26.0, 25.9, 24.6, 24.0.

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 42.9.

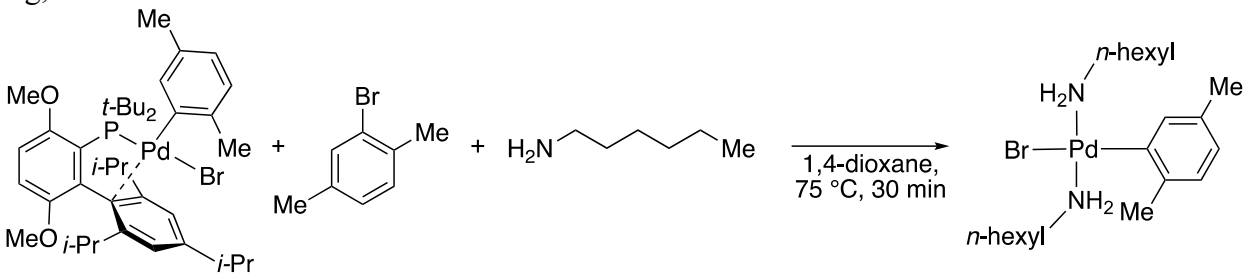
HRMS (ESI) calc. $C_{47}H_{63}NO_2PPd^+$ $[M–OMs]^+$: 810.3626. Found: 810.3630.

IR (Diamond-ATR, neat, cm^{-1}): 2966, 2929, 1230, 1163, 1035, 763, 736.

3. Synthesis of Compound A



An oven-dried reaction tube (Fisherbrand, 20 x 125 mm, product no. 1495937C) containing a Teflon-coated magnetic stir bar was charged with *t*-BuBrettPhos (200 mg, 0.413 mmol, 1 equiv). The flask was sealed with a screw-top cap (Kimble, supplier no. 73804 18400) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. B7995-18). The septum was pierced with a needle attached to a Schlenk line using a rubber hose, and the tube was evacuated and backfilled with nitrogen (this process was repeated a total of three times). 2-Bromo-1,4-dimethylbenzene (153 mg, 114 µL, 0.825 mmol, 2 equiv) was added via syringe, followed by the addition of 9 mL of pentane via syringe. After the ligand dissolved, the septum was removed and $(COD)Pd(CH_2TMS)_2$ (162 mg, 0.413 mmol, 1 equiv) was added quickly. The tube was immediately resealed, the nitrogen inlet needle was removed, and the mixture was stirred overnight, during which time a precipitate formed. The tube was opened to the air, and the precipitate was collected using vacuum filtration, and the filter cake was washed with additional pentane (3 x 10 mL) to afford a yellow solid. The solid was dried under high vacuum for 2 h. 194 mg, 60%.



A flame-dried 250 mL round-bottom flask was equipped with a Teflon-coated magnetic stir bar, charged with the above oxidative addition complex (150 mg, 0.193 mmol, 1 equiv), sealed with a rubber septum, and pierced with a needle attached to a Schlenk line using a rubber hose. The sealed flask was evacuated and backfilled with nitrogen (this process was repeated a total of three times). Anhydrous 1,4-dioxane (15 mL), 2-bromo-1,4-dimethylbenzene (89 mg, 67 µL, 0.69 mmol, 2.5 equiv), and *n*-hexylamine (2.0 g, 1.5 mL, 19.3 mmol, 100 equiv) were added sequentially via syringe. The solution was stirred in a pre-heated oil bath (bath temperature = 75 °C) for 30 min. The solution turned from deep red to golden yellow within 5 min of stirring. The flask was removed from the oil bath and allowed to cool to room temperature. Then, the mixture was filtered through a pad of celite, which was washed with additional anhydrous 1,4-dioxane (5 mL). The filtrate was concentrated under reduced pressure with the aid of a rotary evaporator, and the resulting solid was dried further under high vacuum overnight. The resulting solid was suspended in pentane (10 mL), agitated with the aid of a sonicator for 20 min, and then collected via vacuum filtration. The filter cake was washed with additional pentane (3 x 10 mL). The solid was dried under high vacuum overnight. This process yielded an off-white powder (63 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 7.4 Hz, 1H), 2.77 – 2.61 (m, 8H), 2.50 (q, *J* = 8.9 Hz, 2H), 2.39 (p, *J* = 9.2, 7.6 Hz, 2H), 2.24 (s, 3H), 1.49 (p, *J* = 7.3 Hz, 4H), 1.30 – 1.12 (m, 13H), 0.85 (t, *J* = 6.9 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 150.5, 137.8, 134.7, 134.1, 128.2, 124.9, 45.9, 32.3, 31.3, 26.1, 23.8, 22.5, 20.9, 14.0.

^{31}P{^{1}H} NMR no signal.

Elemental Analysis calc. for $C_{20}H_{39}BrN_2Pd$: C, 48.64; H, 7.96. Found: C, 48.36; H, 7.89.

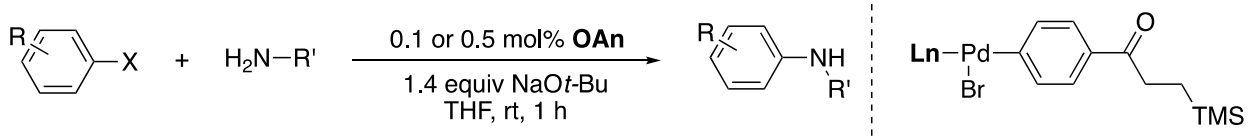
IR (Diamond-ATR, neat, cm^{-1}):3273, 3191, 3130, 2951, 2919, 2855, 1467, 796.

Melting Point: 94–95 °C.

4. Additional Screening of Coupling Reactions

General Procedure C for Assessment of the Generality of OA1–OA6 Precatalysts for Room Temperature Coupling Reactions

To examine the generality of catalysts supported by each newly synthesized ligand, we tested nine different coupling reactions involving a variety of aryl halides and amines. These reactions were set up in a nitrogen-filled glovebox. Into an oven-dried 1-dram vial (Kimble, part no. 60910L-1) containing a Teflon-coated magnetic stir bar, the following reagents were dispensed (listed in order of addition; liquid reagents were added via micropipette to the desired mass): NaO*t*-Bu (54 mg, 1.4 equiv, 0.56 mmol), aryl halide (1 equiv, 0.40 mmol), amine (1.4 equiv, 0.56 mmol). After the addition of these reagents, 0.1 mL THF was added via syringe. The vial was sealed with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60), and the reaction mixture was stirred for 5 min. The palladium precatalyst complex (12 μmol) and *n*-dodecane (41 mg, 0.24 mmol, 0.1 equiv/reaction) were weighed into an oven-dried 1-dram vial (Kimble, part no. 60910L-1), and THF (0.6 mL) was added via syringe (Solution A). Then, Solution B was prepared in a separate oven-dried 1-dram vial: 54.6 mg of *n*-dodecane was weighed into the vial and 0.2 mL of Solution A was added, followed by 0.8 mL of THF. After stirring for 5 min, the reaction vials were opened, and 0.1 mL of either Solution A (0.5 mol% reactions) or Solution B (0.1 mol% reactions) was added to each reaction vial. The reaction vials were re-sealed. The sealed vials were removed from the glovebox, and the reaction mixtures were stirred at room temperature for 1 h in a fume hood. The reaction vials were then opened to the air and the reaction was quenched by the addition of 3 mL EtOAc. An aliquot of the diluted solution was passed through a silica plug (~2 cm) in a Pasteur pipette using EtOAc as an eluent. The filtered reaction mixture was dispensed into a GC vial (Thermo Fisher Scientific, catalog no. C4011-5), diluted (~50:50) with EtOAc, capped (VWR, catalog no. 46610-720) and analyzed by GC analysis. Conversions were determined using calibration relative to the *n*-dodecane internal standard.



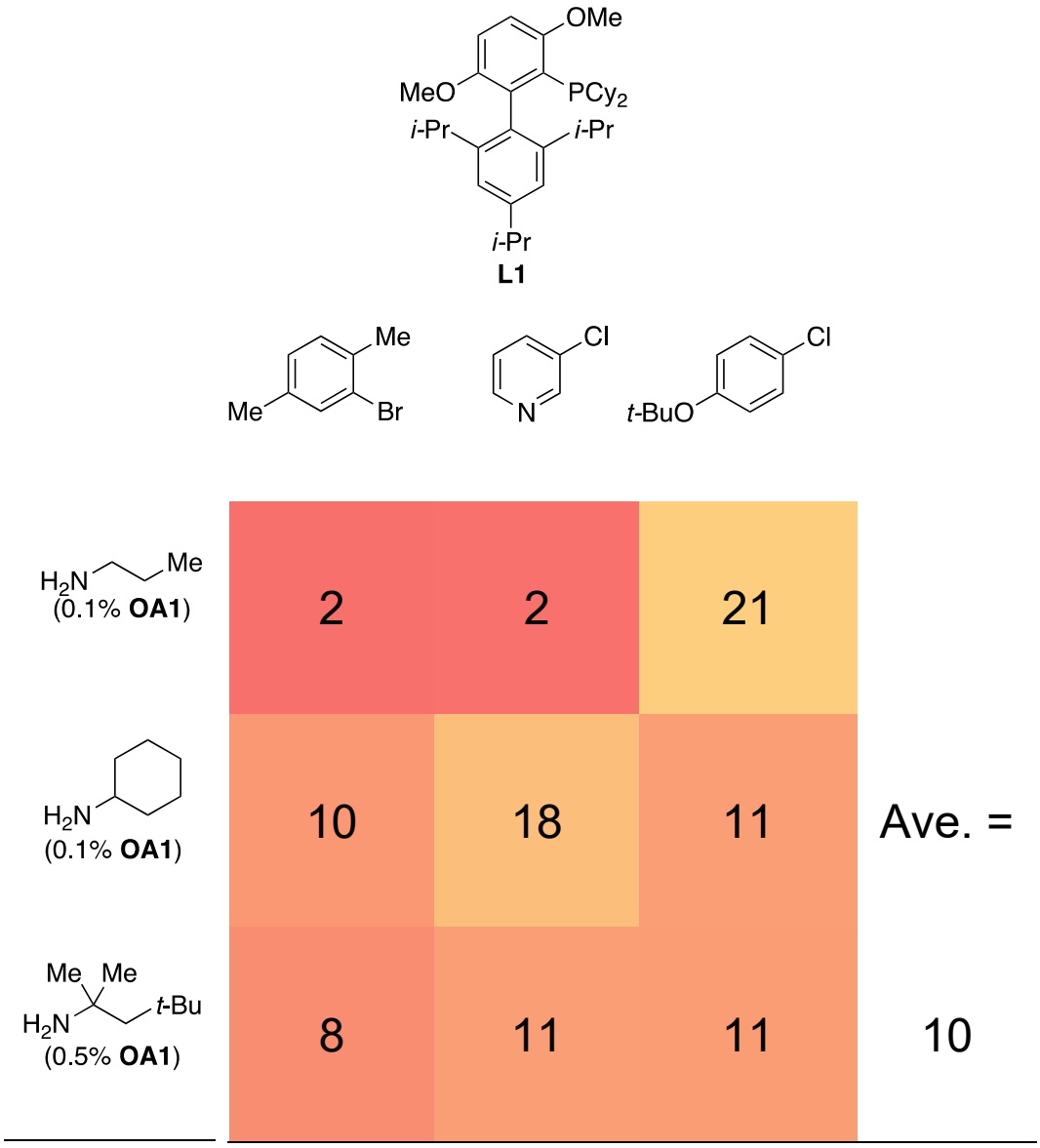


Figure 11. Calibrated GC conversions (%) of aryl halide reflecting the catalyst performance of **OA1** using different aryl halide and amine coupling partners.

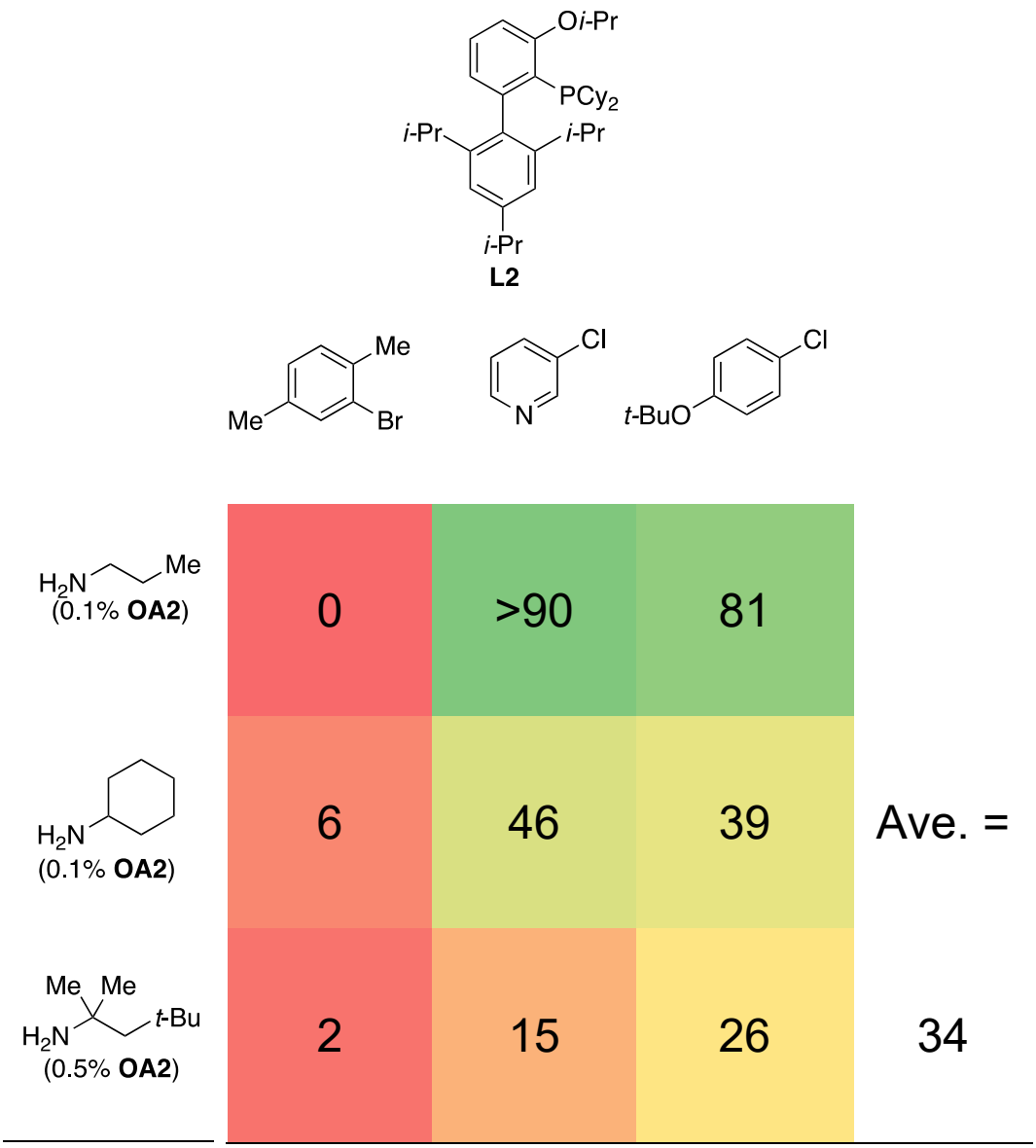


Figure 12. Calibrated GC conversions (%) of aryl halide reflecting the catalyst performance of **OA2** using different aryl halide and amine coupling partners.

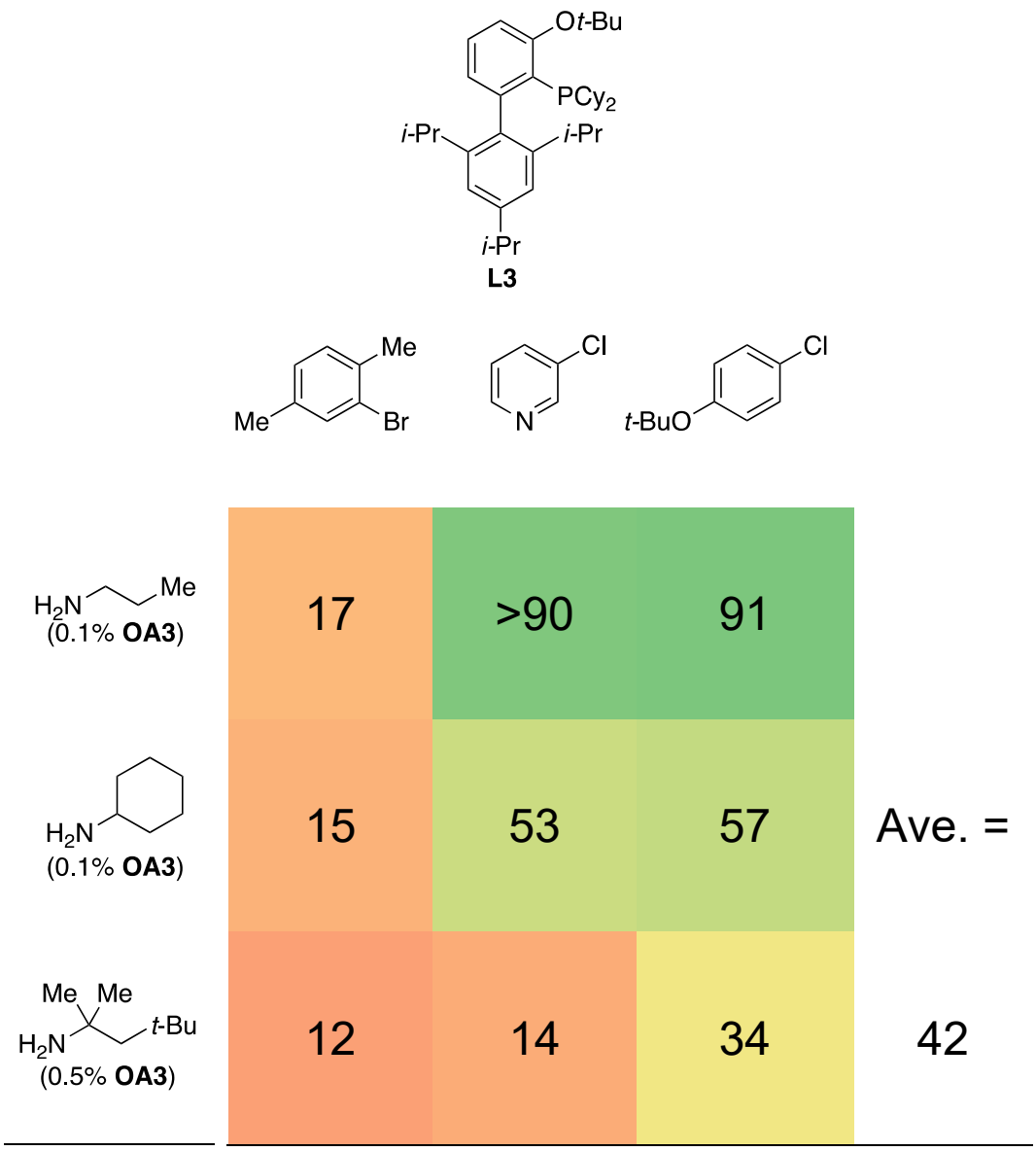


Figure 13. Calibrated GC conversions (%) of aryl halide reflecting the catalyst performance of **OA3** using different aryl halide and amine coupling partners.

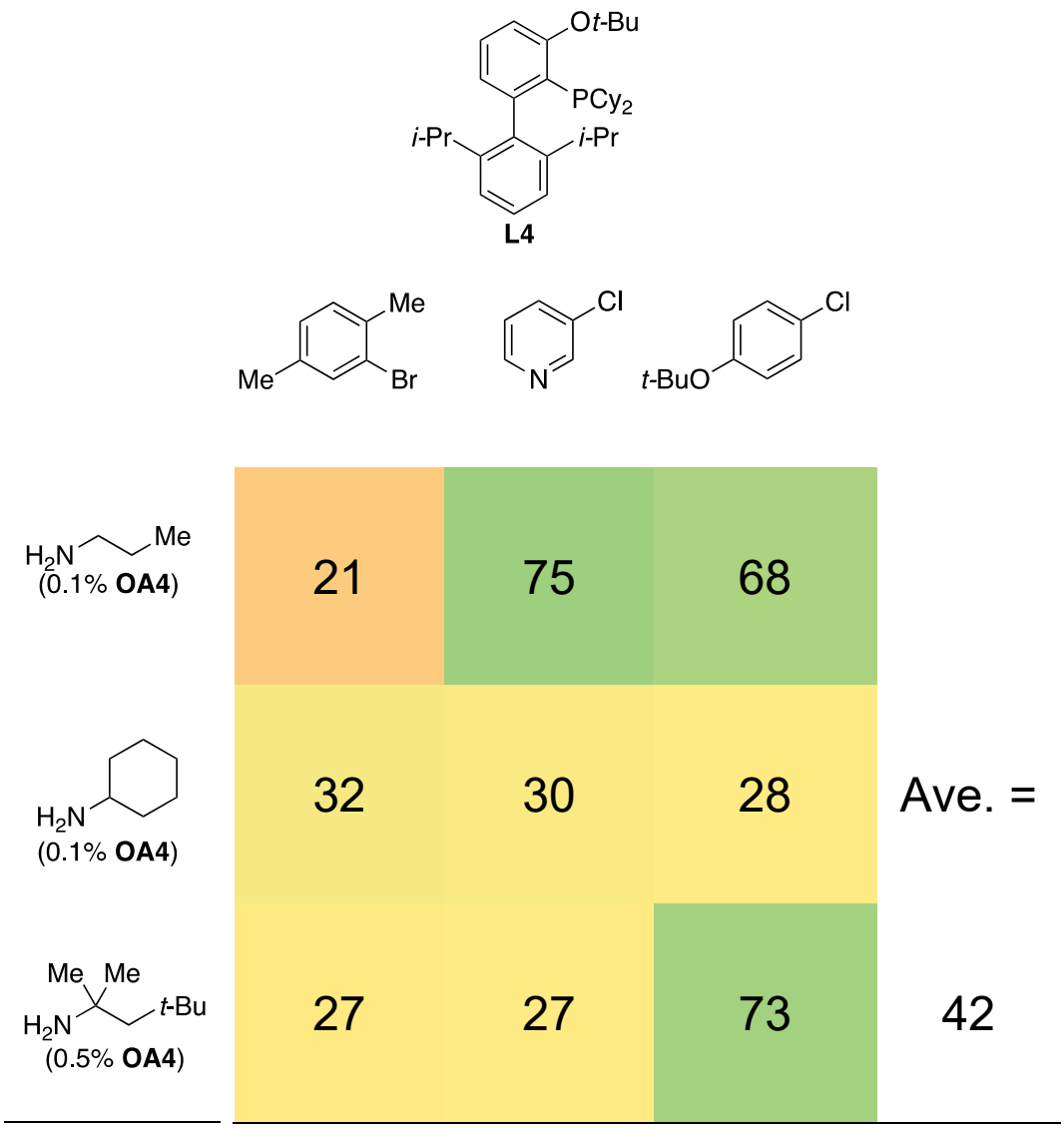


Figure 14. Calibrated GC conversions (%) of aryl halide reflecting the catalyst performance of **OA4** using different aryl halide and amine coupling partners.

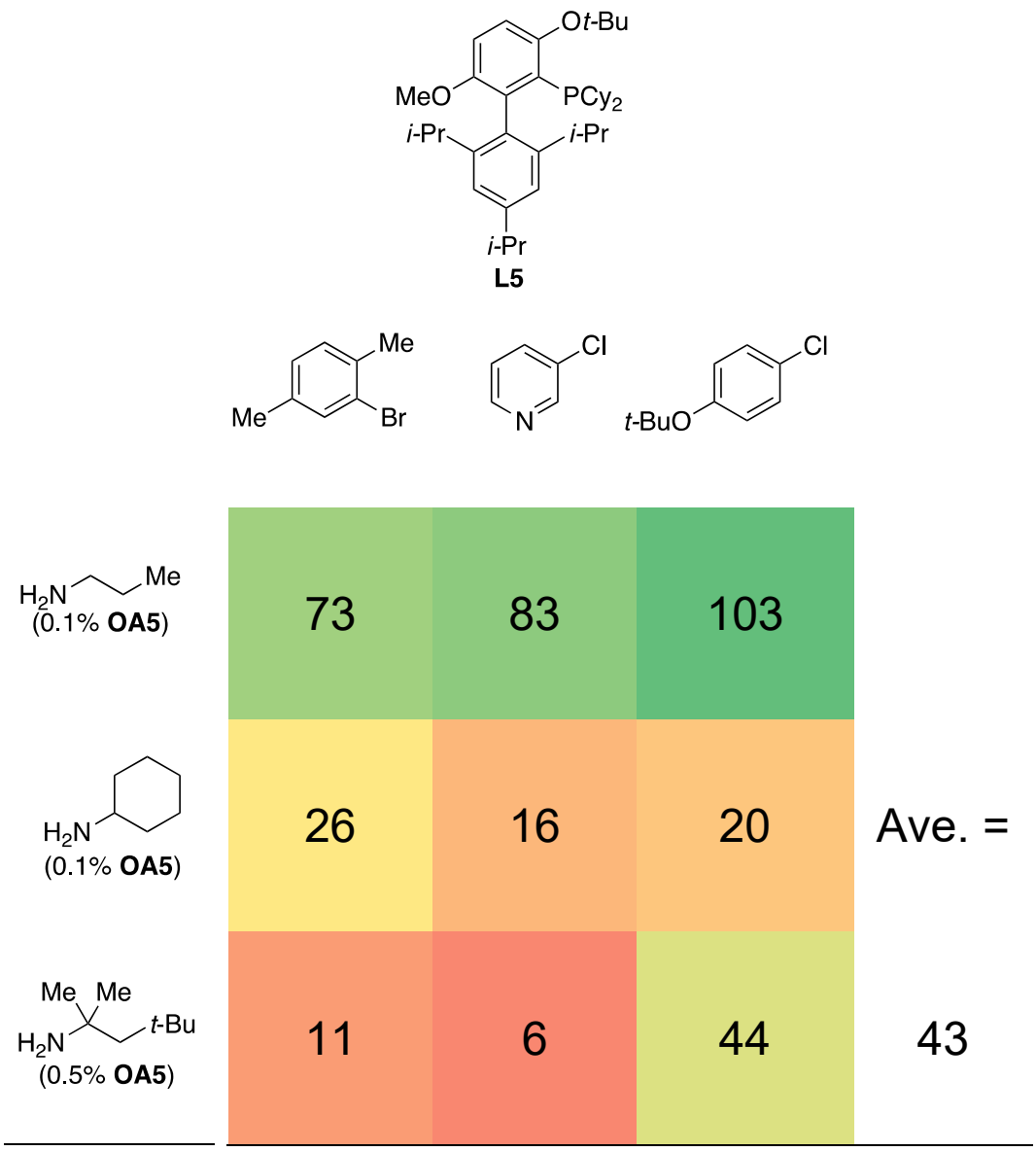


Figure 15. Calibrated GC conversions (%) of aryl halide reflecting the catalyst performance of **OA5** using different aryl halide and amine coupling partners.

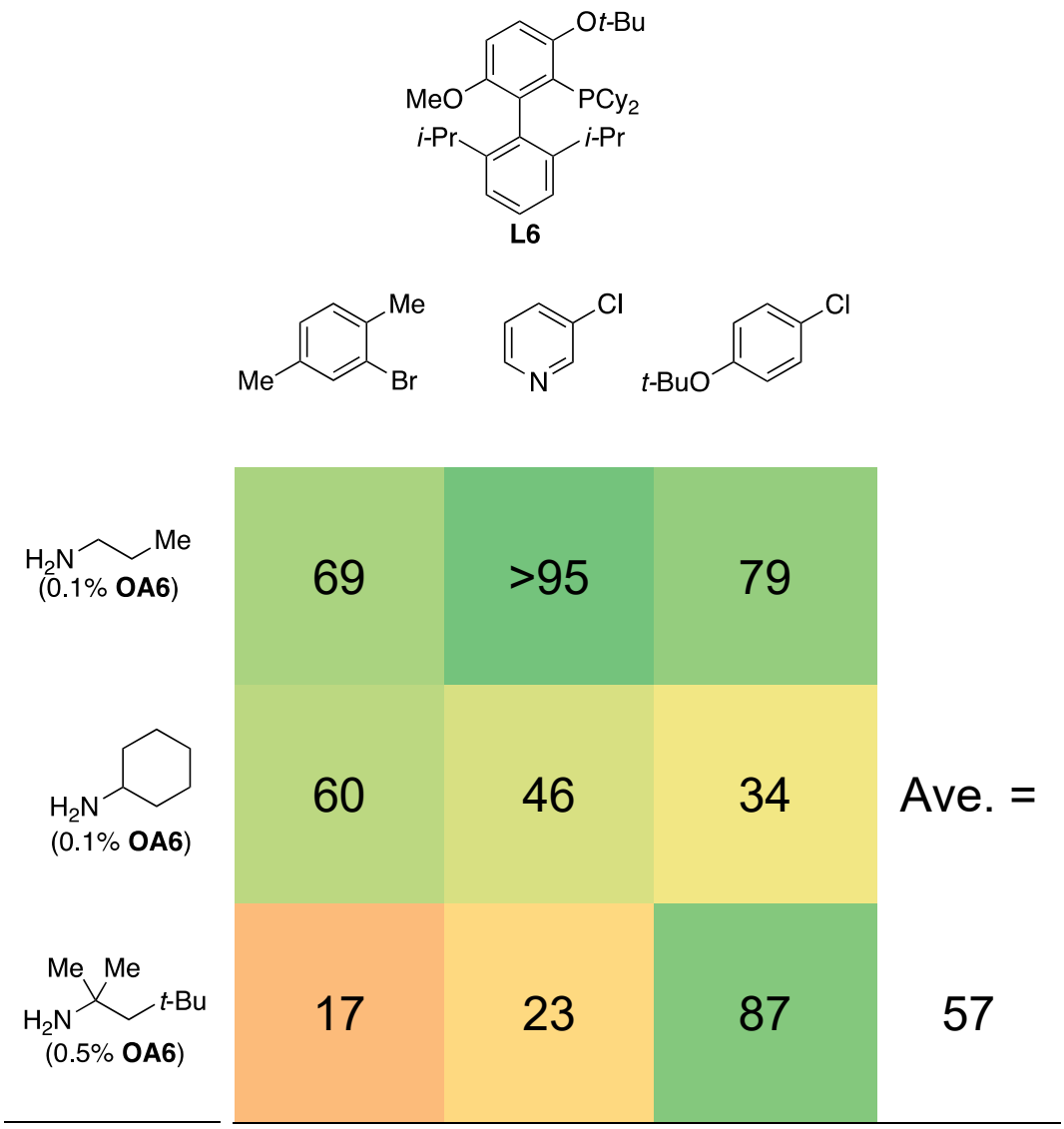
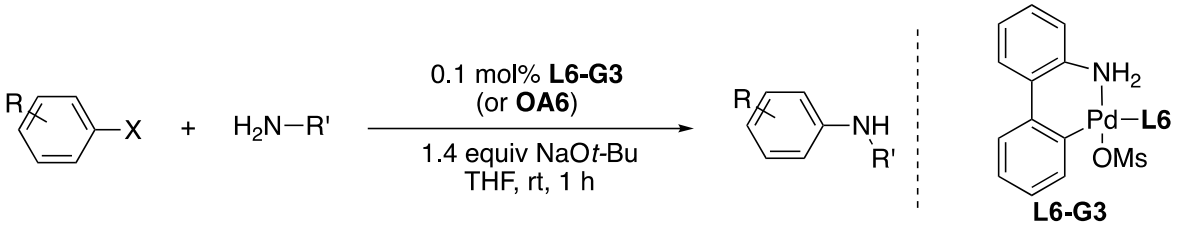
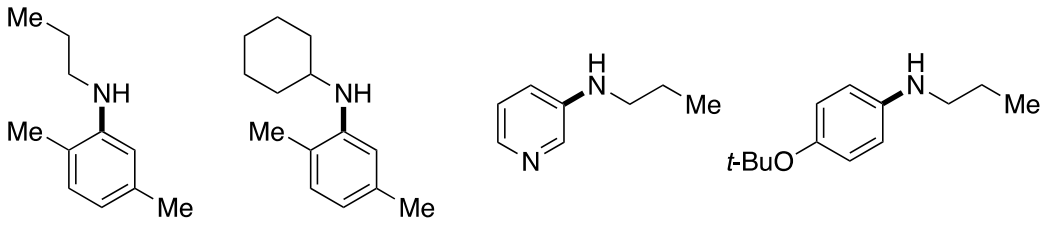


Figure 16. Calibrated GC conversions (%) of aryl halide reflecting the catalyst performance of **OA6** using different aryl halide and amine coupling partners.

Comparison of GPhos Oxidative Addition Complex and G3 Precatalysts





L6-G3: 56%[a] **OA6**: 76%[a]

L6-G3: 65%[a] **OA6**: 73%[a]

L6-G3: 84%[a] **OA6**: 100%[a]

L6-G3: 74%[a] **OA6**: 85%[a]

Figure 17. Comparison of **OA6** and **L6-G3** as catalyst precursors. Legend: (a) reflects the uncalibrated GC conversion (%) of the aryl halide starting material, as judged by dividing the area of the product by the sum of the area of the product and the area of the starting material. Reactions were set up as described in General Procedure C.

Additional Coupling Reactions Not Shown in Figure 7

Additional coupling reactions were tested using **OA6** as the catalyst. These reactions were set up in a nitrogen-filled glovebox. Into an oven-dried reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) containing a Teflon-coated magnetic stir bar, the following reagents were dispensed (listed in order of addition; liquid reagents were added via micropipette to the desired mass): base (1.4 equiv), aryl halide (1 equiv), amine (1.4 equiv). The palladium precatalyst complex (0.2 mol%, 1.0 mol%, or 2.0 mol%) was weighed into an oven-dried 1-dram vial (Kimble, part no. 60910L-1), and THF (0.5 mL/mmol ArX) was added via syringe to make a precatalyst stock solution. 0.5 mL/mmol of the precatalyst stock solution was added to each reaction tube via syringe. The reaction tubes were sealed with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60). The sealed tubes were removed from the glovebox and stirred at room temperature for 1 h in a fume hood. The reactions were then opened to the air and quenched by the addition of 3 mL EtOAc. An internal standard (trimethoxybenzene) was added, and the reaction mixture was filtered through either celite or silica gel. The filtrate was concentrated with the aid of a rotary evaporator. The concentrated reaction mixture was dissolved in $CDCl_3$ (in some cases 1,2-dichloroethane or 1,1,2,2-tetrachloroethane were used as internal standards, and they were added at this point) and analyzed using ^1H NMR (d1 = 10 s). In some cases, GC/MS or LC/MS analyses were used to aid (or in place of ^1H NMR) the analysis of the reaction outcome.

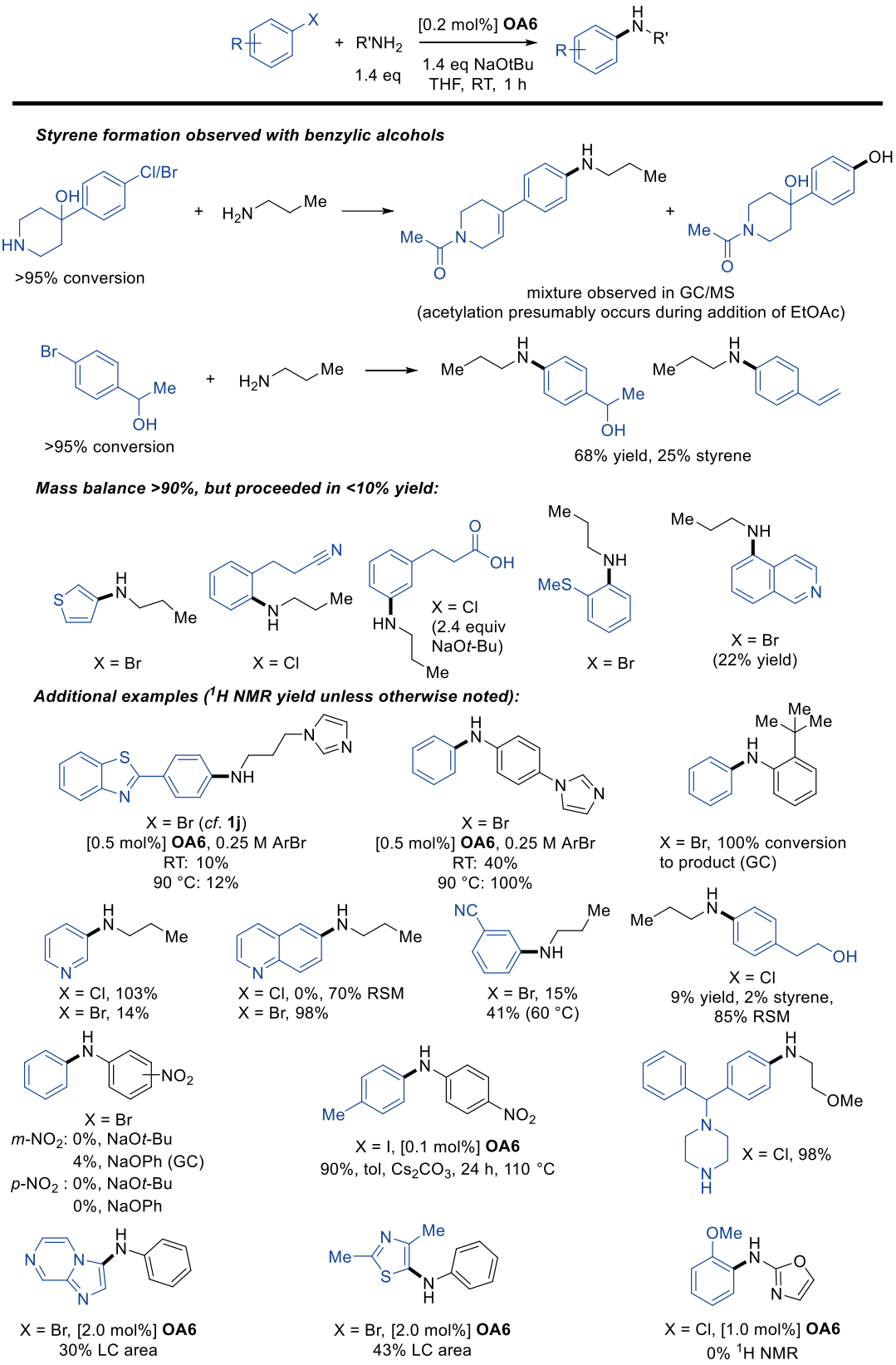


Figure 18. Additional examples of coupling reactions performed at room temperature.

5. Mechanistic Experiments

Calculation of Half-Life for L–Pd(Ar)(N(Me)Ph) in Scheme 1D

As described in reference 10a, for a C–N cross-coupling reaction in which the amido complex (**IV**; Scheme 1A) is the resting state and reductive elimination the rate-determining step, the rate constant for reductive elimination can be obtained using the following formula:

$$k_{RDS} = k_{RE} = \frac{1}{[Pd]\tau_{RXN}}$$

where [Pd] is the ratio of catalyst relative to the limiting reagent and τ_{RXN} is the time for the reaction to go to completion. For a reaction in which reductive elimination is not the rate-determining step, the following inequality applies:

$$k_{RE} > \frac{1}{[Pd]\tau_{RXN}}$$

The cross-coupling of *N*-methylaniline with 3-bromoanisole catalyzed by a RuPhos-based palladium catalyst was performed at 20 °C, as shown in Figure 19. Since this reaction *did not* exhibit kinetics consistent with reductive elimination as a rate determining step, the above inequality applies.

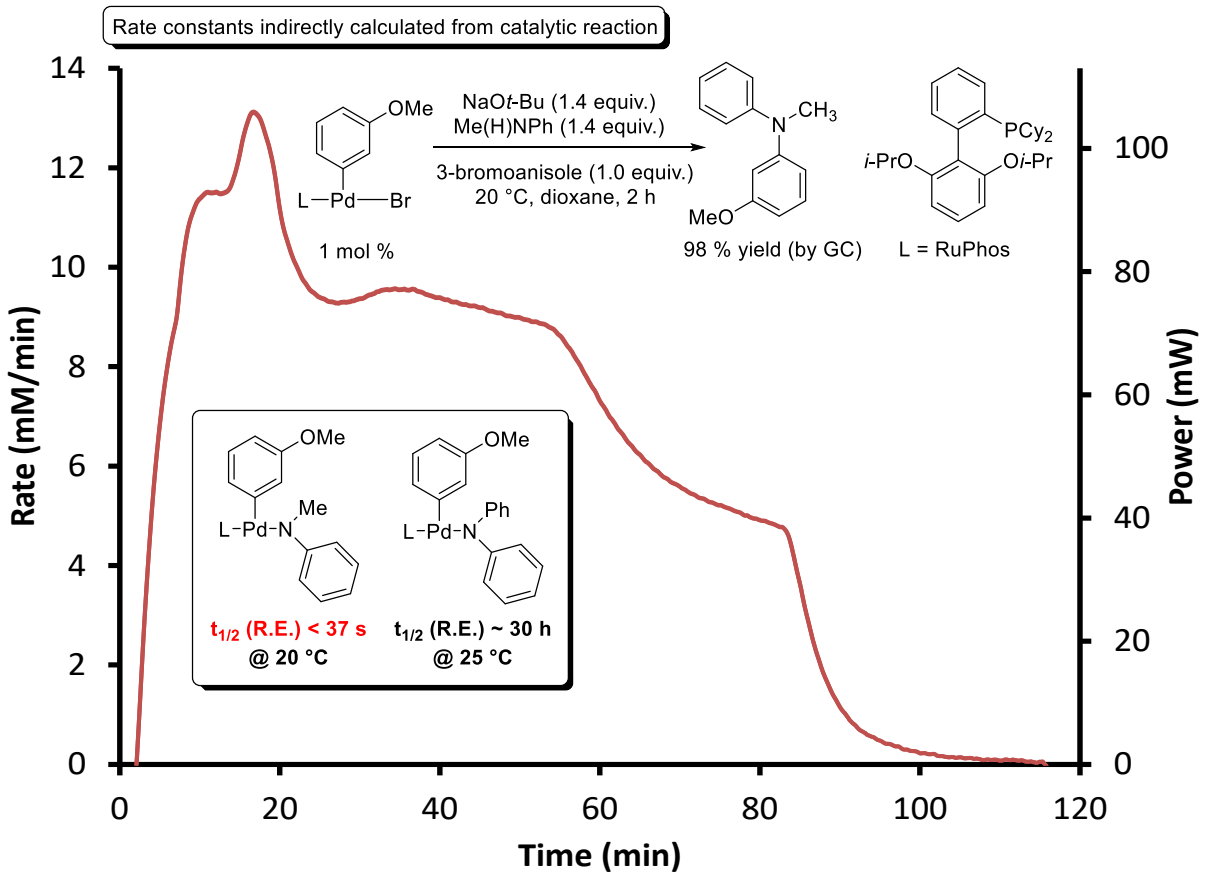
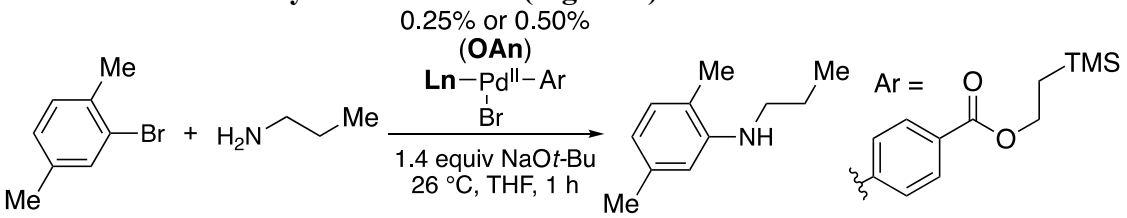


Figure 19. Calorimetry experiment for the cross-coupling of *N*-methylaniline with 3-bromoanisole mediated by a RuPhos-based oxidative addition complex. Data are from reference 17. For comparison, the estimated rate constant of analogous diphenylamido complex is taken from reference 10a. This graph is not dynamically corrected.

Given the experiment above, the rate constant for reductive elimination is >1.1 (min^{-1}) at 20 °C (assuming a first-order rate constant for reductive elimination). It should be noted that the identity of the amine has a strong influence on the propensity of the complex to undergo reductive elimination. Typically, the more nucleophilic the amine, the faster the reductive elimination of the corresponding amido complex.

Procedure for Calorimetry Measurements (Figure 2)



The reactions were run in pairs (i.e., substrate stock solution was used for two reactions employing different catalysts that were run in parallel). In a nitrogen-filled glovebox, 416 mg 1-bromo-2,4-dimethylbenzene, 186 mg *n*-propylamine, 38 mg *n*-dodecane, and 1.2 mL THF (added via syringe) were mixed in an oven-dried 1-dram vial (Kimble, part no. 60910L-1) to prepare a stock solution (Solution A). Two different 16 mL oven-dried reaction vials (Kimble, part no. 60942A-16) containing Teflon-coated magnetic stir bars were each charged with NaO*t*-Bu (1.4 mmol, 135 mg, 1.4 equiv). Solution A (0.8 mL) was added via syringe to each of the two 16 mL reaction vials, and the vials were sealed with a screw cap (Kimble, supplier no. 73804-18400) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. B7995-18). THF (0.8 mL) was added via syringe to a third 16 mL reaction vial containing a Teflon-coated magnetic stir bar, for use as a reference sample. This vial was also sealed with a screw cap equipped with a Teflon septum. All materials were removed from the nitrogen-filled glovebox at this point. The vials containing Solution A were placed into an OmniCal Insight Parallel Reaction Calorimeter and the vial containing only THF was placed into the reference channel. Two circulating baths (Anova A-25 Refrigerated and Heating Circulator) using silicone oil as the thermal fluid were used to control the temperature of the heating blocks at 26.0 °C. The reaction solutions were allowed to thermally equilibrate for at least 60 min. Approximately 15 min before injection, the palladium precatalyst complexes (4 or 8 μmol; 1.6x the amount required for one reaction) were weighed into two separate oven-dried 1-dram vials (Kimble, part no. 60910L-1), Vial A1 and Vial A2, and subsequently sealed with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60). Sealed vials A1 and A2 were each pierced with a needle connected to a Schlenk line using a rubber hose. Vials A1 and A2 were evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). THF (0.32 mL; 1.6x the volume required for one reaction) was added via syringe to each of Vials A1 and A2. After at least 60 min of thermal equilibration, the solution in Vial A1 (0.2 mL) was injected via syringe into one of the 16 mL vials loaded with 0.8 mL Solution A, and at the same time, the solution in Vial A2 (0.2 mL) was injected via syringe into the other 16 mL vial loaded with Solution A. THF (0.2 mL) was injected via syringe into the 16 mL vial containing 0.8 mL THF (the reference vial) as quickly as possible following the injection of the catalyst solutions into their respective vials (all three injections were performed using disposable plastic syringes (Fisher, catalog no. 14-817-25) with 4-inch disposable needles (Fisher, catalog no. 14-817-102)). The reactions were allowed to proceed for 60 min. The reaction vials were then opened to the air and a portion of the solution was quickly transferred into an NMR tube via pipette (only for reactions employing **OA1** and **OA2**). The NMR tube was quickly capped, and the reaction

solution was assessed using ^{31}P NMR. A portion of the remaining reaction solution was filtered through a silica plug (~2 cm) in a Pasteur pipette using EtOAc as an eluent. Product yield and conversion of starting material were assessed using GC analysis.
The output of these experiments is heat flow versus time data. A tau correction was then applied to the raw data due to the delay between heat release and detection.

The heat flow was then converted to reaction rate (M/min):

$$\text{Rate} = \frac{q}{\Delta H_{rxn} * V}$$

Where q is the heat flow (kJ/min; converted from mW given from the instrument), ΔH_{rxn} is the heat of reaction (kJ/mol), and V is the volume of the reaction (L). The heat of the reaction was found to be 215 kJ/mol on average.

The fractional conversion (c_{frac}) as a function of time is given by taking the ratio of the integrated heat output and the total heat output of that reaction and multiplying it by the conversion (c_{GC}) measured by GC. The reactions were stopped at 1 h:

$$c_{frac} = \frac{\int_0^t q\, dt'}{\int_0^{1\,h} q\, dt'} * c_{GC}$$

Finally, the concentration of 1-bromo-2,4-dimethylbenzene [ArX] and [product] were calculated using the fractional conversion:

$$[ArX] = \left(1 - c_{frac}\right)[ArX]_o$$

$$[Product] = [ArX]_o - [ArX]$$

To confirm that calorimetry is a reliable method to investigate the kinetics of this reaction, the reaction with 0.25 mol% **OA6** was monitored with GC analysis. Four identical reactions were set up according to the above procedure, and one reaction was opened to air after 5 min, 10 min, 20 min, and 1 h. The Product vs. Time plot (Figure 20) shows a reasonable correlation between the calorimeter output and the conversion obtained from GC analysis.

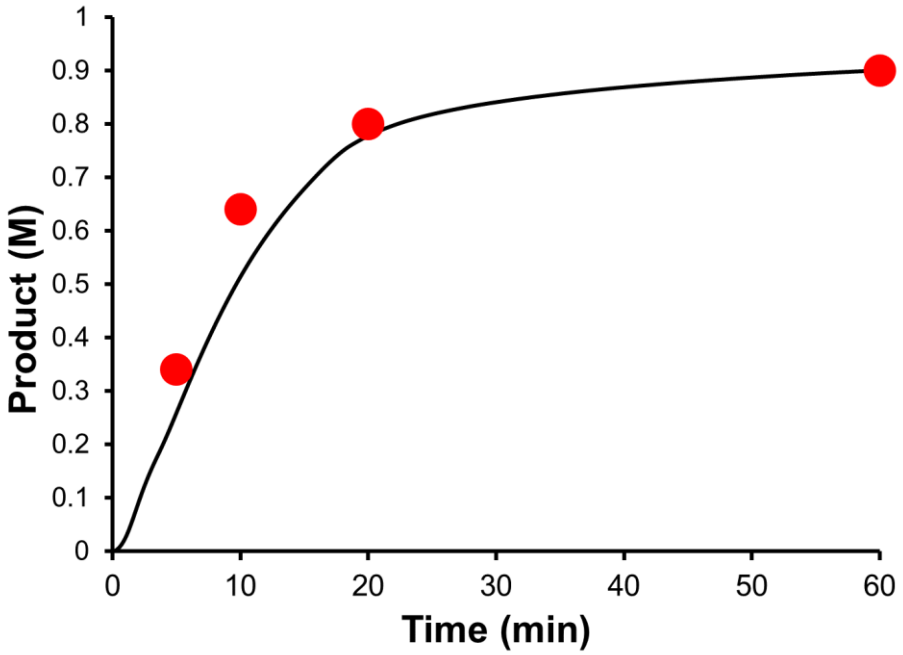


Figure 20. Product versus time for reaction with **OA6**, monitored by calorimetry (black) and GC analysis (red). Reaction conditions: 1.0 mmol 1-bromo-2,4-dimethylbenzene, 1.4 mmol *n*-propylamine, 1.4 mmol NaO*t*-Bu, 0.1 mmol *n*-dodecane (internal standard), 2.5 µmol **OA6** in THF (1.0 M [1-bromo-2,4-dimethylbenzene]) heated to 26.0 °C in OmniCal calorimeter.

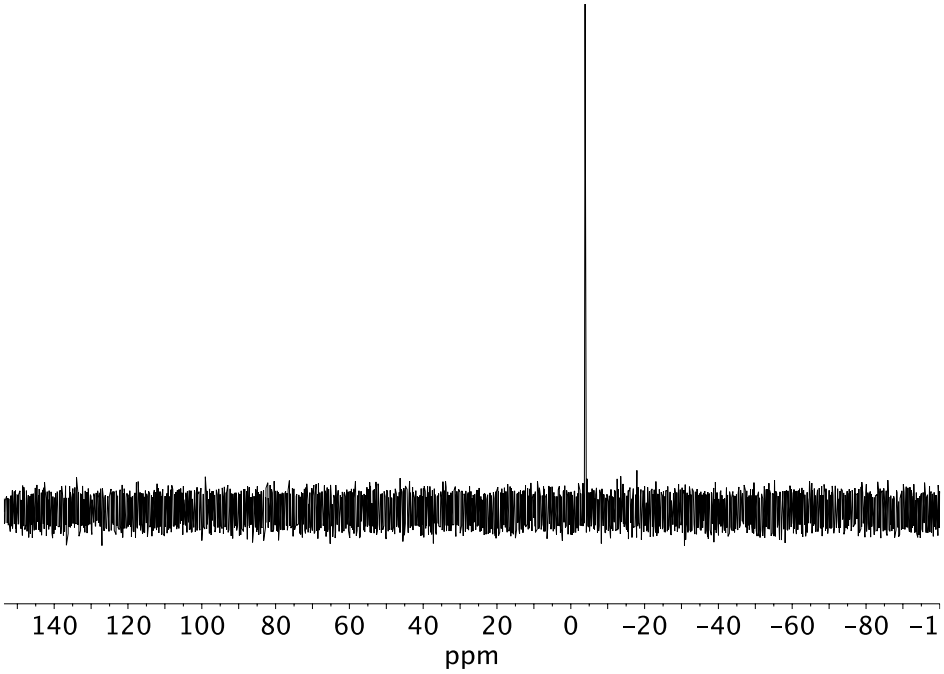


Figure 21. ^{31}P NMR spectrum of the reaction employing **OA2** as the precatalyst in Figure 2. Reaction Conditions: 1.0 mmol 1-bromo-2,4-dimethylbenzene, 1.4 mmol *n*-propylamine, 1.4 mmol NaO*t*-Bu, 0.1 mmol *n*-dodecane (GC internal standard), 5 µmol **OA1** in THF (1.0 M [1-bromo-2,4-dimethylbenzene]) heated to 26.0 °C in OmniCal Insight Parallel Reaction Calorimeter.

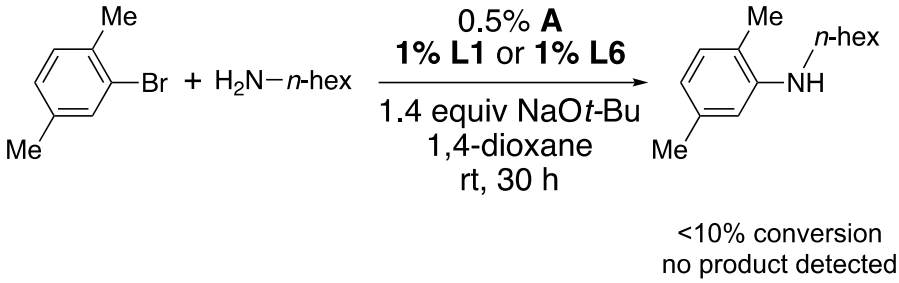
Experiments Comparing L1-Based C–N Coupling Catalysis at Room Temperature or 90 °C
These reactions were set up in a nitrogen-filled glovebox. A stock solution (Solution A) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1): 648 mg 1-bromo-2,4-dimethylbenzene, 456 mg *n*-hexylamine, 60 mg *n*-dodecane, and 1.05 mL 1,4-dioxane (added via syringe). This stock solution was used for all of the reactions. A catalyst solution (Solution B) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1) containing 14.5 mg **OA1'**, 9.4 mg BrettPhos, 0.7 mL 1,4-dioxane (added via syringe), and 40 mg *n*-hexylamine (*n*-hexylamine was added last). The vial containing Solution B was sealed with a screw cap (Thermo Fisher Scientific catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60) and agitated until it became homogeneous. NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 equiv) was weighed into an oven-dried reaction tube (Fisherbrand, 16 x 125 mm, product no. 1495935A) containing a Teflon-coated magnetic stir bar. A total of six reaction tubes were prepared in this fashion. Solution A (320 μL) was added via syringe to each of the six reaction tubes (0.5 mmol ArBr), followed by Solution B (0.1 mL) via syringe (Note: it is important to ensure that all of Solution B is added directly to Solution A; i.e., with no Solution B on the tube walls). The reaction tubes were sealed with a screw cap (Thermo Fisher Scientific, catalog no. B7995-18) fitted with a Teflon-lined septum (Thermo Fisher Scientific, catalog no. C47995-15), and all materials were removed from the glovebox. All of the reaction mixtures were stirred at room temperature for 1 h. After 1 h, one tube was opened to the air and diluted with EtOAc (~3 mL). An aliquot of the mixture (~0.2 mL) was filtered through a silica plug (~2 cm) in a Pasteur pipette, and the conversion was determined by GC analysis. The remaining tubes were further sealed by wrapping Parafilm around the interface of the tube and the screw cap. A subset of the remaining tubes was maintained at room temperature and allowed to stir for the amount of time indicated in Figure 5. A different subset of the tubes was placed into a pre-heated oil bath (bath temperature = 90 °C) and allowed to stir for the amount of time indicated in Figure 5. After the indicated time, the tube was removed from the oil bath and allowed to cool to room temperature (if heated). The reaction mixture was then opened to the air and diluted with EtOAc (~3 mL). An aliquot of the mixture (~0.2 mL) was filtered through a silica plug (~2 cm) in a Pasteur pipette, and the conversion was determined by GC analysis. The results for these experiments are shown in Figure 5. The time points at 2 h, 5 h, 6 h, and 7 h at 90 °C were performed in triplicate and are reported as the average yield of the three trials (red data points, Figure 5).

Experimental Procedure for C–N Coupling Reactions using A/L1 or A/L6 Catalysts at 90 °C

These reactions were set up in a nitrogen-filled glovebox. A stock solution (Solution A) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1): 648 mg 1-bromo-2,4-dimethylbenzene, 496 mg *n*-hexylamine, 60 mg *n*-dodecane, and 1.05 mL 1,4-dioxane (added via syringe), which was used for all of the reactions. A catalyst solution (Solution B1) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1) containing 4.9 mg **A**, 10.7 mg BrettPhos (**L1**), and 0.4 mL 1,4-dioxane (added via syringe), and another catalyst solution (Solution B2) was prepared in a separate oven-dried 1-dram vial containing 4.9 mg **A**, 10.7 mg GPhos (**L6**), and 0.4 mL 1,4-dioxane (added via syringe). NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 equiv) was weighed into an oven-dried reaction tube (Fisherbrand, 16 x 125 mm, product no. 1495935A) containing a Teflon-coated magnetic stir bar. A total of six reaction tubes were prepared in this fashion. Solution A (320 μL) was added via syringe to each of the six tubes (0.5 mmol ArBr). Solution B1 (0.1 mL) was added via syringe to three reaction tubes, and Solution B2 was added via syringe to the other

three reaction tubes. The reaction tubes were each sealed with a screw cap (Thermo Fisher Scientific, catalog no. B7995-18) fitted with a Teflon-lined septum (Thermo Fisher Scientific, catalog no. C47995-15), and all materials were removed from the glovebox. Parafilm was wrapped around the interface of the tube and the screw cap, and the tubes were placed into a pre-heated oil bath (bath temperature = 90 °C). The three tubes containing the **A**/BrettPhos catalyst were heated for 1 h, 8 h, and 22 h. The three tubes containing the **A**/GPhos catalyst were heated for 1 h. After the given amount of time, each tube was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then opened to the air and diluted with EtOAc (~3 mL). An aliquot of the mixture (~0.2 mL) was filtered through a silica plug (~2 cm) in a Pasteur pipette, and the conversion was determined by GC analysis. The results for these experiments are shown in Figure 6.

Experimental Procedure for C–N Coupling Reactions using A/L1 or A/L6 Catalysts at Room Temperature



These reactions were set up in a nitrogen-filled glovebox. A stock solution (Solution A) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1): 555 mg 1-bromo-2,4-dimethylbenzene, 408 mg *n*-hexylamine, 51 mg *n*-dodecane, and 0.90 mL 1,4-dioxane (added via syringe), which was used for all of the reactions. A catalyst solution (Solution B1) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1) containing 2.5 mg **A**, 5.4 mg BrettPhos, and 0.2 mL 1,4-dioxane (added via syringe), and another catalyst solution (Solution B2) was prepared in a separate oven-dried 1-dram vial containing 2.5 mg **A**, 5.4 mg **L6**, and 0.2 mL 1,4-dioxane (added via syringe). NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 equiv) was weighed into an oven-dried reaction tube (Fisherbrand, 16 x 125 mm, product no. 1495935A) containing a Teflon-coated magnetic stir bar. A total of two reaction tubes were prepared in this fashion. Solution A (320 µL) was added via syringe to each of the two tubes (0.5 mmol ArBr). Solution B1 (0.1 mL) was added via syringe to one tube, and Solution B2 (0.1 mL) was added via syringe to the other tube. The reaction tubes were each sealed with a screw cap (Thermo Fisher Scientific, catalog no. B7995-18) fitted with a Teflon-lined septum (Thermo Fisher Scientific, catalog no. C47995-15), and all materials were removed from the glovebox. Both tubes were stirred for 30 h. After this time, the reaction mixture was opened to the air and diluted with EtOAc (~3 mL). An aliquot of the mixture (~0.2 mL) was filtered through a silica plug (~2 cm) in a Pasteur pipette, and the conversion was determined by GC analysis.

Experimental Procedure for C–N Coupling Reactions using A/L6 Catalysts Activated at 90 °C and Allowed to React at Room Temperature

To investigate whether the **A**/**L6** catalyst system could be activated at 90 °C and then undergo turnover at room temperature, the following experiments were conducted:

These reactions were set up in a nitrogen-filled glovebox. A stock solution (Solution A) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1): 648 mg 1-bromo-2,4-dimethylbenzene, 35 mg (0.1 equiv reactions) or 177 mg (0.5 equiv reactions) *n*-hexylamine, 60 mg *n*-dodecane, and 1.05 mL 1,4-dioxane (added via syringe). This stock solution was used for all of the reactions. A catalyst solution (Solution B) was prepared in an oven-dried 1-dram vial (Kimble, part no. 60910L-1) containing 8.6 mg **A**, 18.8 mg GPhos (**L6**), and 0.7 mL 1,4-dioxane (added via syringe). NaO*t*-Bu (67 mg, 0.7 mmol, 1.4 equiv) was weighed into an oven-dried reaction tube (Fisherbrand, 16 x 125 mm, product no. 1495935A) containing a Teflon-coated magnetic stir bar. A total of six reaction tubes were prepared in this fashion. Solution A (234 µL (0.1 equiv reactions) or 263 µL (0.5 equiv reactions)) was added via syringe to each of the six tubes (0.5 mmol ArBr). Solution B (0.1 mL) was added via syringe to each reaction tube. The reaction tubes were each sealed with a screw cap (Thermo Fisher Scientific, catalog no. B7995-18) fitted with a Teflon-lined septum (Thermo Fisher Scientific, catalog no. C47995-15), and all materials were removed from the glovebox. Parafilm was wrapped around the interface of the tube and the screw cap, and the tubes were placed into a pre-heated oil bath (bath temperature = 90 °C), and they were heated for 1 h. The tubes were then removed from the oil bath and allowed to cool to room temperature. At this time, a subset of the tubes was opened to the air and diluted with EtOAc (~3 mL). An aliquot of the mixture (~0.2 mL) was removed, filtered through a silica plug (~2 cm) in a Pasteur pipette, and the conversion was determined by GC analysis. To the remaining tubes, *n*-hexylamine (86 µL (1.3 equiv; for reactions with 0.1 equiv *n*-hexylamine initially) or 59 µL (0.9 equiv; for reactions with 0.5 equiv *n*-hexylamine initially)) was added via syringe, and these tubes were allowed to stir at room temperature for an additional 1 h, 6 h, or 24 h. After the given amount of time, each tube was opened to the air and diluted with EtOAc (~3 mL). An aliquot of the mixture (~0.2 mL) was filtered through a silica plug (~2 cm) in a Pasteur pipette, and the conversion was determined by GC analysis. The results for these experiments are shown in Figure 22.

The activated catalyst was able to generate some product at room temperature (10–20%), but far less than would be expected if all the Pd were active (cf. Figure 2A: At 26 °C, 0.25 mol% **OA6** allowed a similar coupling reaction to almost reach completion within 1 h). This indicates that when **A**/**L6** is heated at 90 °C, only a small fraction of the Pd is active at any given time.

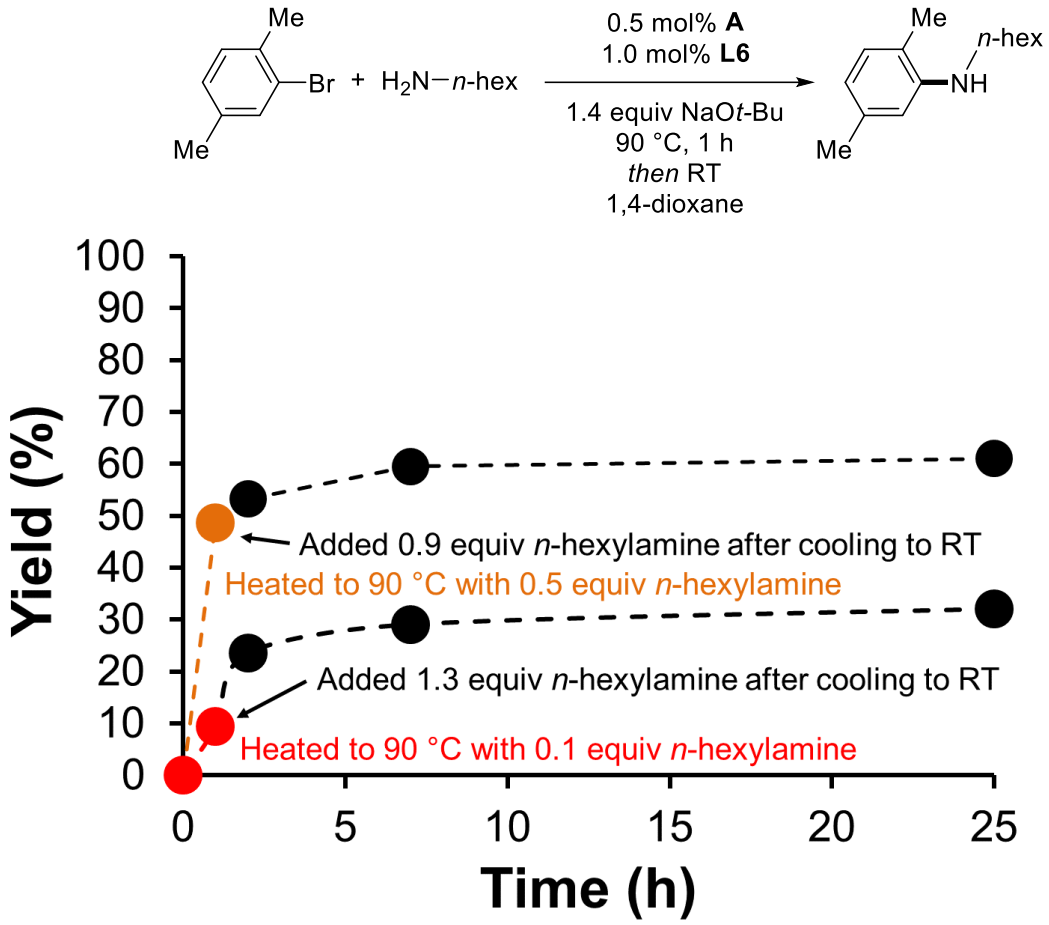


Figure 22. Reaction time course using **A** as a precatalyst. **A**/**L6** were "activated" at 90 °C for 1 h as described above, followed by continued reaction at room temperature. Reaction conditions: 0.5 mmol 2-bromo-1,4-dimethylbenzene, 0.7 mmol *n*-hexylamine (total amine added), 0.7 mmol NaO*t*-Bu, 0.05 mmol *n*-dodecane (internal standard), 2.5 µmol **A**, 5.0 µmol **L6** in 0.5 mL 1,4-dioxane at 90 °C. Calibrated GC yields. Dashed lines are intended to guide the eye and do not reflect a kinetic fit.

Experiments Probing the Elementary Step During Which the Ligand Displacement Occurs

Experiments were performed to assess whether ligand displacement occurs when the oxidative addition complex is mixed only with the amine or only with the base. In these experiments, it was found that most of the ligand remained bound to the Pd center when an oxidative addition complex was mixed with either a primary amine (Figure 23) or base (Figure 24). Because of these results, we conclude that the phosphine ligand is displaced when the palladium catalyst is in the Pd^0 oxidation state.

These reactions were set up in a nitrogen-filled glovebox. **OA1'** (6.2 mg, 5 µmol, 0.005 equiv) was weighed into an oven-dried 1-dram vial (Kimble, part no. 60910L-1) under ambient atmosphere and then transferred into the nitrogen-filled glovebox. Either *n*-hexylamine (142 mg, 184 µL, 1.4 mmol, 1.4 equiv) (Tube A) or NaO*t*-Bu (135 mg, 1.4 mmol, 1.4 equiv) (Tube B) was

weighed into an oven-dried reaction tube (FisherBrand, 13 x 100 mm, catalog no. 1495935C) containing a Teflon-coated magnetic stir bar. THF (1.5 mL) was added via syringe to the vial containing **OA1'**. After dissolution, 0.5 mL of the **OA1'** solution was added to each of Tube A and Tube B via syringe. Tubes A and B were each sealed with a screw cap (Thermo Fisher Scientific catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60). The sealed tubes were removed from the glovebox and stirred at room temperature for 1 h in a fume hood. The reaction tubes were then opened to the air and pipetted into an oven-dried NMR tube (the NMR tube was allowed to cool to just above room temperature prior to transferring). The NMR tubes were capped, and the reaction outcome was assessed using ^{31}P NMR spectroscopy. In the case of Tube A, the contents of the tube were aged in the NMR tube for 9 h total prior to data collection.

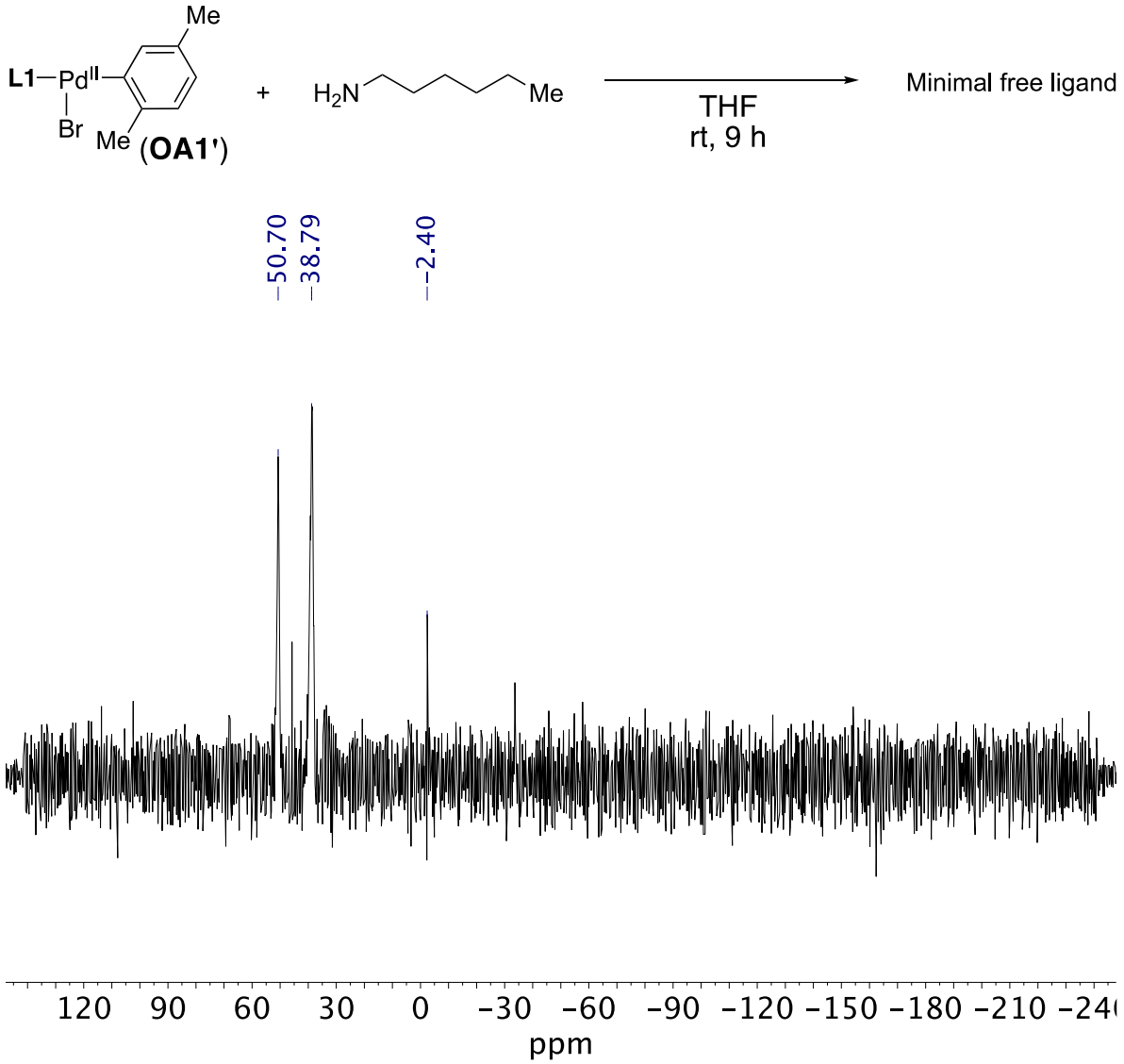


Figure 23. ^{31}P NMR spectrum for the reaction of **OA1'** with *n*-hexylamine. 1024 scans were collected. Free **L1** is attributed to the signal at −2.4 ppm, while the signals at 38.8 ppm and 50.7 ppm are attributed to Pd–**L1** complexes.

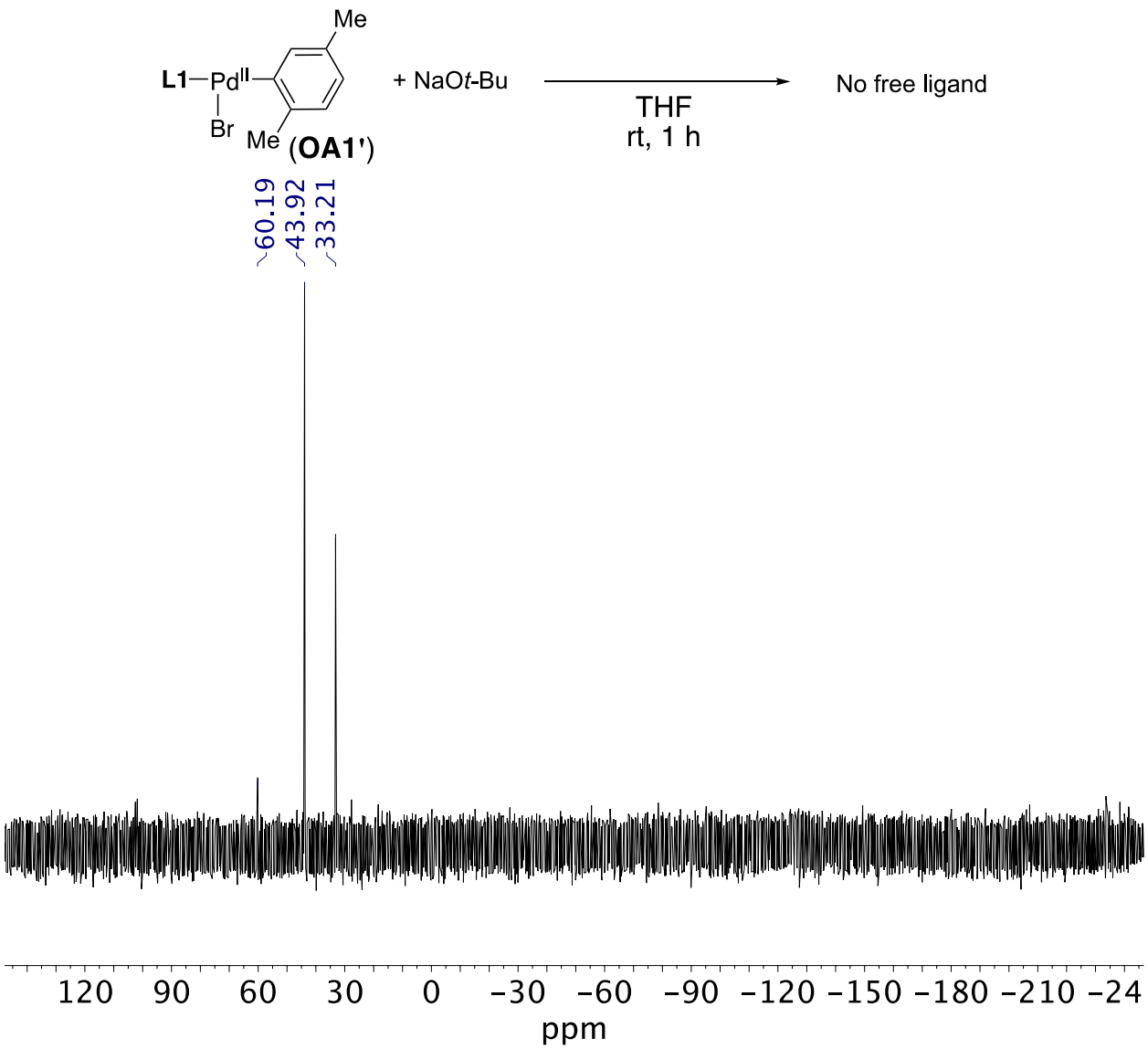


Figure 24. ^{31}P NMR spectrum for the reaction of **OA1'** with NaO*t*-Bu. 128 scans were collected. The signals at 33.2 ppm, 43.9 ppm, and 60.2 ppm are attributed to **L1**–Pd complexes.

Calorimetry Data: Reaction Rate versus Time

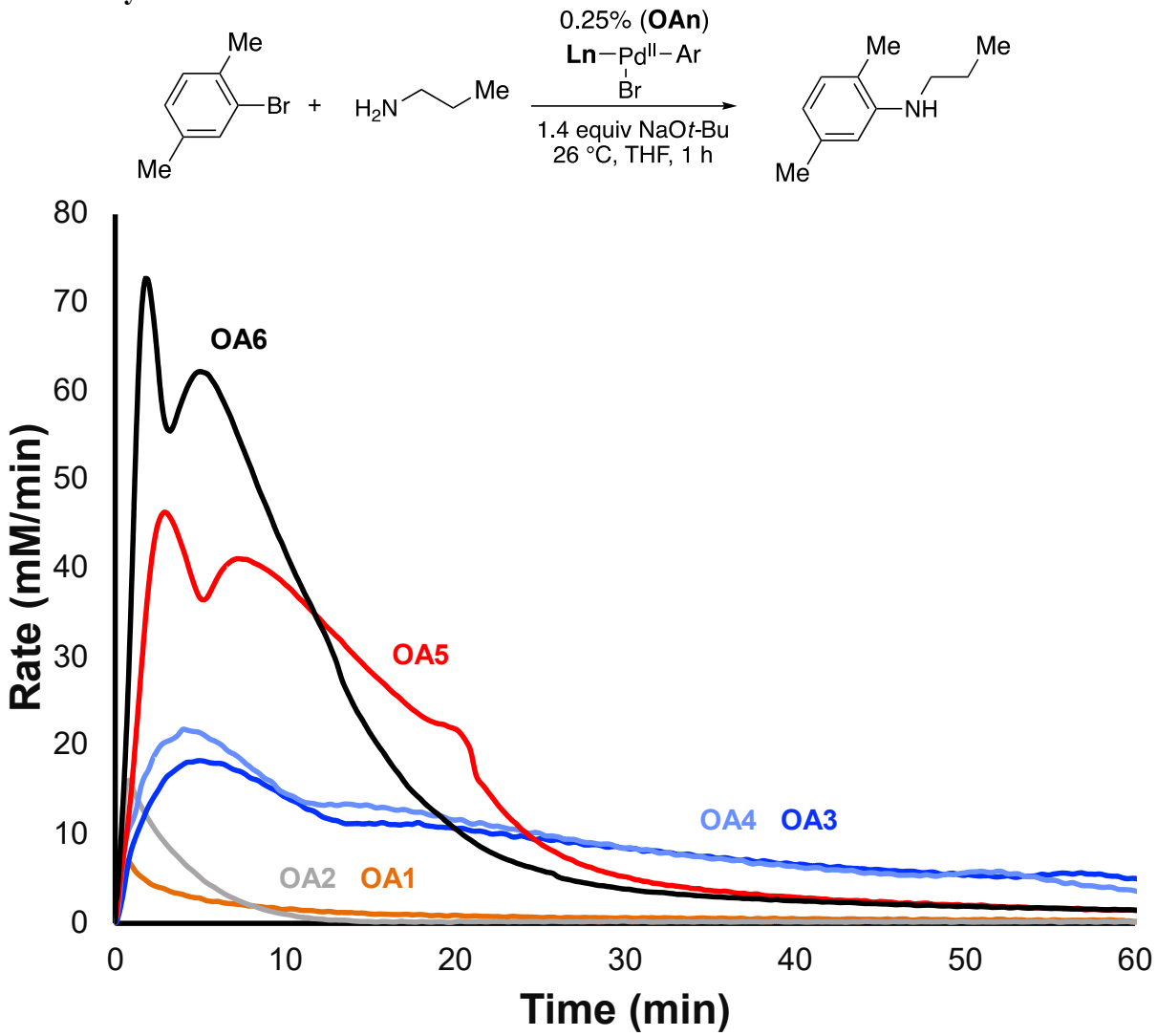


Figure 25. Rate versus time graphs for **OA1**–**OA6**. Reaction Conditions: 1.0 mmol 1-bromo-2,4-dimethylbenzene, 1.4 mmol *n*-propylamine, 1.4 mmol NaO*t*-Bu, 0.1 mmol *n*-dodecane (internal standard), 2.5 or 5 µmol **OAn** in THF (1.0 M [1-bromo-2,4-dimethylbenzene]) heated to 26.0 °C in OmniCal calorimeter.

Calorimetry Data: Power versus Time

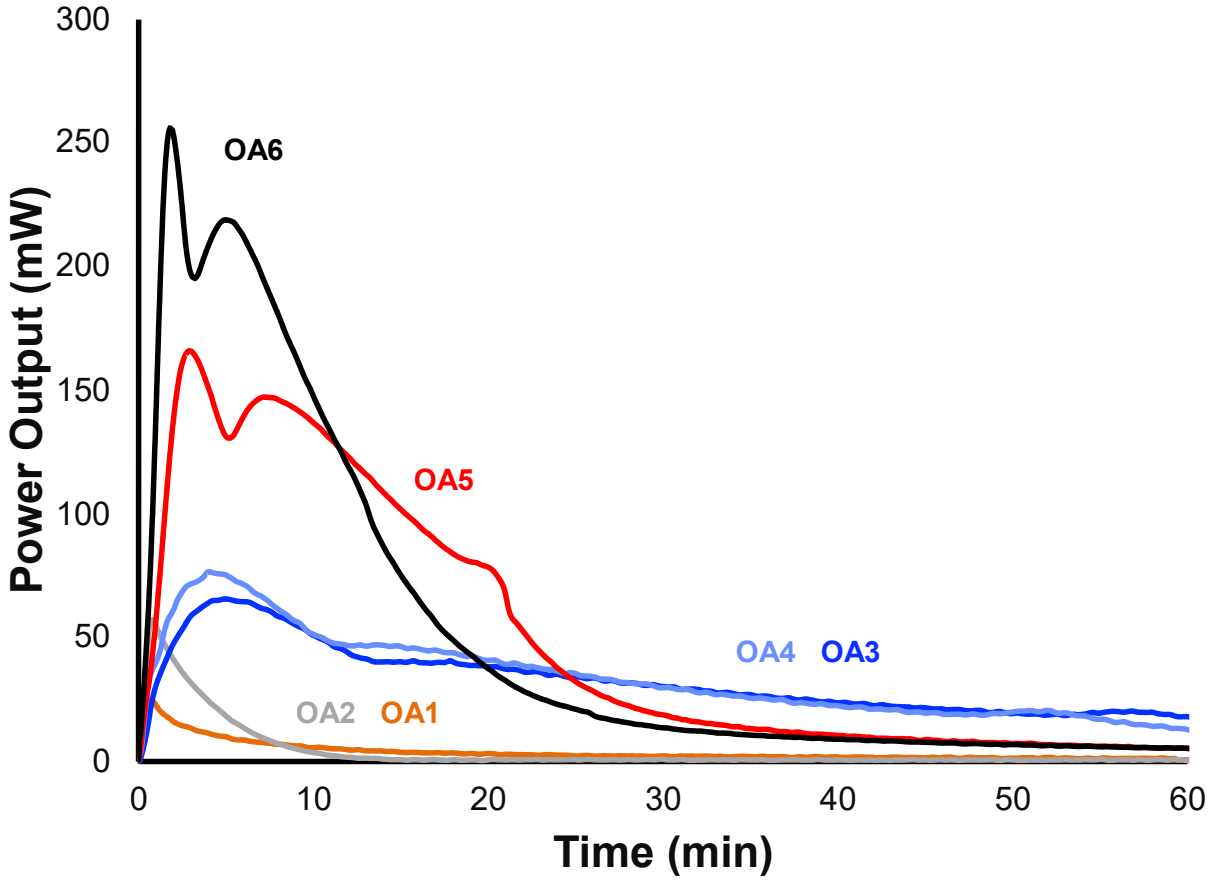


Figure 26. Power versus time graphs for **OA1**–**OA6**. Reaction Conditions: 1.0 mmol 1-bromo-2,4-dimethylbenzene, 1.4 mmol *n*-propylamine, 1.4 mmol NaO*t*-Bu, 0.1 mmol *n*-dodecane (internal standard), 2.5 or 5 µmol **OAn** in THF (1.0 M [1-bromo-2,4-dimethylbenzene]) heated to 26.0 °C in OmniCal calorimeter.

6. Procedures for Preparative Aryl Amination Reactions in Figures 7, 8 and 9.

General procedure D for the coupling of aryl halides with amines at ambient temperature

An oven-dried 1-dram vial (Vial A) (Kimble, part no. 60910L-1) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with base (1.40 mmol, 1.40 equiv), aryl halide, if solid (1.00 mmol, 1.00 equiv), and amine, if solid (1.00–1.40 mmol, 1.00–1.40 equiv). The vial was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The vial was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Aryl halide, if liquid (1.00–1.20 mmol, 1.00–1.20 equiv), was added via syringe, followed by the addition of amine, if liquid (1.40 mmol, 1.40 equiv), via syringe. Anhydrous THF (0.25 mL) was added via syringe, and the reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. If necessary, the reaction mixture was agitated with the aid of a sonicator or vortexer to achieve a homogeneous or homogeneously suspended mixture. A solution of **OA6** (0.008 M–0.050 M, 0.2–1.25 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B). **OA6** was added to the oven-dried Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66)

equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired precatalyst concentration (0.008 M–0.050 M, 0.2–1.25 mol%). **OA6** solution (0.25 mL) from Vial B was transferred to Vial A via syringe. The reaction mixture in Vial A was stirred at room temperature for 1 h, after which it was opened to the air and the contents were rinsed into a separatory funnel using water (3 mL) and EtOAc (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). If necessary, brine (10 mL) was added to help separate the phases. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. For cases in which a CombiFlash NextGen 300 automated chromatography system was used to purify the product, the cartridge size (grams of stationary phase) is given in parentheses.

General procedure E for the coupling of aryl halides with amines at ambient temperature
An oven-dried 1-dram vial (Vial A) (Kimble, part no. 60910L-1) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with base (1.02–1.40 mmol, 1.02–1.40 equiv), aryl halide, if solid (1.00 mmol, 1.00 equiv), and amine, if solid (1.05–1.40 mmol, 1.05–1.40 equiv). The vial was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The vial was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Aryl halide, if liquid (1.00 mmol, 1.00 equiv), was added via syringe, followed by the addition of amine, if liquid (1.40 mmol, 1.40 equiv), via syringe. A solution of **OA6** (0.008 M–0.016 M, 0.2–0.4 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B). **OA6** was added to the oven-dried Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired precatalyst concentration (0.008 M–0.016 M, 0.2–0.4 mol%). **OA6** solution (0.50 mL) from Vial B was transferred to Vial A via syringe. The reaction mixture in Vial A was stirred at room temperature for 45 min or 1 h, after which it was opened to the air and the contents were rinsed into a separatory funnel using water (3 mL) and EtOAc (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). If necessary, brine (10 mL) was added to help separate the phases. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography.

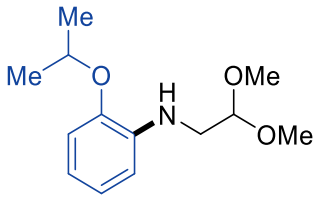
General procedure F for the coupling of aryl halides with amines with heating
Note: Heating reactions above the boiling point of the solvent may not be appropriate for reactions run on larger scales. An oven-dried 8 mL reaction tube (Tube A) (Fisherbrand, 13 x 100 mm, product no. 1495935C) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with base (1.40 mmol, 1.40 equiv), aryl halide, if solid (1.00 mmol, 1.00 equiv), and amine, if solid (1.40 mmol, 1.40 equiv). The tube was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The tube was evacuated and backfilled with nitrogen (the

evacuation/backfill process was repeated a total of three times). Aryl halide, if liquid (1.00 mmol, 1.00 equiv), was added via syringe, followed by the addition of amine, if liquid (1.40 mmol, 1.40 equiv), via syringe. Anhydrous THF (0.25 mL) was added via syringe, and the reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. If necessary, the reaction mixture was agitated with the aid of a sonicator or vortexer to achieve a homogeneous or homogeneously suspended mixture. A solution of **OA6** (0.0008 M–0.020 M, 0.02–0.5 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B) (Kimble, part no. 60910L-1). **OA6** was added to Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired precatalyst concentration (0.0008 M–0.020 M, 0.02–0.5 mol%). **OA6** solution (0.25 mL) from Vial B was transferred to Tube A via syringe. Tube A was then immediately transferred to a pre-heated oil bath (bath temperature = 75 °C or 90 °C). The reaction mixture was stirred at 75 °C or 90 °C for 1 h, after which it was removed from the oil bath and allowed to cool to room temperature. The mixture was then was opened to the air and the contents were rinsed into a separatory funnel using water (3 mL) and EtOAc (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10–50 mL). If necessary, brine (10 mL) was added to help separate the phases. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. For cases in which a CombiFlash NextGen 300 automated chromatography system was used to purify the product the cartridge size (grams of stationary phase) is given in parentheses.

General procedure G for the coupling of aryl halides with amines with heating

Note: Heating reactions above the boiling point of the solvent may not be appropriate for reactions run on larger scales. An oven-dried 16 mL reaction tube (Tube A) (Fisherbrand, 20 x 125 mm, product no. 1495937C) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with aryl halide, if solid (1.00 mmol, 1.00 equiv), solid amine (1.20 mmol), and **OA6** (0.5–2.0 mol%). Tube A was sealed with a screw cap (Kimble, supplier no. 73804-18400) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. B7995-18) and was pierced with a needle connected to a Schlenk line using a rubber hose. Tube A was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). A solution of NaO*t*-Bu (0.3 M, 1.20 equiv) and PhOH (0.325 M, 1.30 equiv) in 2-MeTHF was prepared in a separate oven-dried 8 mL reaction tube (Tube B) (Fisherbrand, 13 x 100 mm, product no. 1495935C) equipped with an oven-dried Teflon-coated magnetic stir bar. NaO*t*-Bu and PhOH were added to Tube B, and Tube B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Tube B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous 2-MeTHF was added to Tube B via syringe, and the mixture was allowed to stir at room temperature until homogeneous. Aryl halide, if liquid (1.00 mmol, 1.00 equiv), was added to Tube A via syringe, followed quickly by the solution from Tube B (4.0 mL), also added via syringe. Tube A was then immediately transferred to a pre-heated oil bath (bath temperature = 100 °C). The reaction mixture was stirred at 100 °C for 3 h, after which it was removed from the oil bath and allowed to cool to room temperature. Tube A was then opened to the air. The crude reaction mixture was filtered through

a small plug of silica, eluting with MeOH (~2 plug volumes), concentrated onto silica gel with the aid of a rotary evaporator, and purified by column chromatography using a CombiFlash NextGen 300 automated chromatography system.



3a

***N*-(2,2-dimethoxyethyl)-2-isopropoxyaniline (3a)**

Product **3a** was prepared according to General Procedure D using 1-bromo-2-isopropoxybenzene (215 mg, 161 µL, 1.00 mmol), aminoacetaldehyde dimethyl acetal (147 mg, 153 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.4 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 5:1 hexane/EtOAc. Yield: Run 1 = 218 mg, 93%; Run 2 = 210 mg, 88%. Average Yield = 90%. Colorless oil.

Product **3a** was also prepared according to General Procedure F at 90 °C using 1-bromo-2-isopropoxybenzene (215 mg, 161 µL, 1.00 mmol), aminoacetaldehyde dimethyl acetal (147 mg, 153 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.05 mol% **OA6** as catalyst. Chromatography conditions: SiO_2 (50 g cartridge), 20:1 hexane/EtOAc to 5:1 hexane/EtOAc. Yield: Run 1 = 231 mg, 97%; Run 2 = 214 mg, 90%. Average Yield = 93%. Colorless oil.

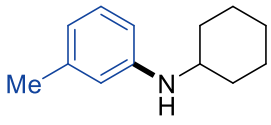
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (td, *J* = 7.6, 1.4 Hz, 1H), 6.81 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.67 (t, *J* = 7.5 Hz, 2H), 4.61 (t, *J* = 5.6 Hz, 1H), 4.58 – 4.36 (sept + br. s, *J* = 6.1, 2H), 3.43 (s, 6H), 3.29 (d, *J* = 5.6 Hz, 2H), 1.37 (d, *J* = 6.1 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.2, 139.1, 121.4, 116.8, 113.1, 110.5, 102.8, 70.9, 53.9, 45.5, 22.4.

Elemental Analysis calc. for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.85. Found: C, 65.49; H, 9.02.

IR (Diamond-ATR, neat, cm^{-1}): 3419, 2976, 2931, 1509, 1245, 1121, 1067, 733.

Product **3a** was also prepared using $[Pd(cinnamyl)Cl]_2$/**L6** (0.4 mol% Pd) as the catalyst precursor. General Procedure D was followed using 1-bromo-2-isopropoxybenzene (215 mg, 161 µL, 1.00 mmol), aminoacetaldehyde dimethyl acetal (147 mg, 153 µL, 1.40 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol). A solution of $[Pd(cinnamyl)Cl]_2$ (0.008 M, 0.2 mol%) and **L6** (0.016 M, 0.4 mol%) was prepared in Vial B and allowed to stir until homogeneous. Yield determined by ^{1}H NMR: 47%.



3b

***N*-cyclohexyl-3-methylaniline (3b)**

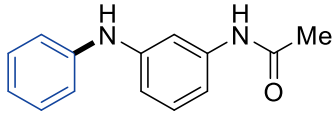
Product **3b**[51] was prepared according to General Procedure D using 3-iodotoluene (218 mg, 128 µL, 1.00 mmol), cyclohexylamine (139 mg, 160 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.2 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 10:1 hexane/EtOAc. Yield: Run 1 = 185 mg, 98%; Run 2 = 180 mg, 95%. Average Yield = 96%. Colorless oil (this oil was volatile and time under high vacuum was minimized to avoid product evaporation).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (t, *J* = 7.7 Hz, 1H), 6.51 (d, *J* = 7.4 Hz, 1H), 6.42 (m, 2H), 3.48 (bs, 1H), 3.27 (tt, *J* = 10.2, 3.8 Hz, 1H), 2.29 (s, 3H), 2.07 (dd, *J* = 12.9, 3.9 Hz, 2H), 1.78 (dt, *J* = 13.4, 4.0 Hz, 2H), 1.67 (dt, *J* = 12.8, 4.0 Hz, 1H), 1.39 (qt, *J* = 13.1, 3.5 Hz, 2H), 1.26 (tt, *J* = 12.1, 3.4 Hz, 1H), 1.21 – 1.11 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.5, 139.1, 129.2, 117.9, 114.0, 110.4, 51.7, 33.6, 26.1, 25.1, 21.7.

Elemental Analysis calc. for $C_{13}H_{19}N$: C, 82.48; H, 10.12. Found: C, 82.27; H, 10.24.

IR (Diamond-ATR, neat, cm^{-1}): 3397, 3041, 2925, 2851, 1602, 764, 691.



3c

***N*-(3-(phenylamino)phenyl)acetamide (3c)**

Product **3c**[52] was prepared according to the following procedure. An oven-dried 1-dram vial (Vial A) (Kimble, part no. 60910L-1) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with NaO*t*-Bu (135 mg, 1.40 mmol, 1.40 equiv) and 3′-aminoacetanilide (210 mg, 1.40 mmol, 1.40 equiv). The vial was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The vial was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF (0.25 mL) was added via syringe, and the reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. If necessary, the reaction mixture was agitated with the aid of a sonicator or vortexer to achieve a homogeneous or homogeneously suspended mixture. A solution of **OA6** and phenyl triflate was prepared in a separate oven-dried 1-dram vial (Vial B). The solution prepared consisted of 1.6x the reagents needed for a single reaction. **OA6** (3.0 mg) was added to Vial B, and the vial was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF (0.40 mL) was added to Vial B via syringe, followed by phenyl triflate (0.26 mL) via syringe. 0.41 mL of the solution from Vial B was transferred to Vial A via syringe. The reaction mixture in Vial A was stirred in a room temperature water bath for 1 h, after which it was opened to the air and the contents were rinsed into a separatory funnel using water (3 mL) and EtOAc (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). If necessary, brine (10 mL) was added to help separate the phases. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. Chromatography conditions: SiO_2, 1:4 hexane/EtOAc. Yield. Run 1 = 206 mg, 91%; Run 2 = 194 mg, 86%. Average Yield = 88%. White

solid.

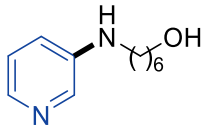
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.35 (d, *J* = 2.2 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.94 (t, *J* = 7.6 Hz, 2H), 6.82 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.76 (s, 1H), 2.13 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.6, 144.2, 142.7, 139.1, 129.8, 129.4, 121.5, 118.6, 113.1, 112.1, 109.0, 24.7.

Elemental Analysis calc. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24. Found: C, 74.17; H, 6.21.

IR (Diamond-ATR, neat, cm^{-1}): 3387, 3315, 2917, 1666, 1598, 1530, 1498, 1267, 730, 684.

Melting Point: 130–132 °C



3d

6-(pyridin-3-ylamino)hexan-1-ol (3d)

Product **3d**[53] was prepared according to General Procedure E using 3-chloropyridine (114 mg, 95 µL, 1.00 mmol), 6-amino-1-hexanol (164 mg, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.2 mol% **OA6** as catalyst. The reaction mixture was allowed to stir for 1 h. Chromatography conditions: SiO_2, 4:1 CH_2Cl_2/MeOH. Yield: Run 1 = 183 mg, 94%; Run 2 = 185 mg, 95%. Average Yield = 95%. Tan solid.

Product **3d** was also prepared according to General Procedure F using 3-chloropyridine (114 mg, 95 µL, 1.00 mmol), 6-amino-1-hexanol (164 mg, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.02 mol% **OA6** as catalyst. For this coupling reaction, the entire reaction volume was added as the catalyst stock solution (cf. General Procedure E). Chromatography conditions: SiO_2, 4:1 CH_2Cl_2/MeOH. Yield: Run 1 = 174 mg, 90%; Run 2 = 178 mg, 92%. Average Yield = 91%. Tan solid.

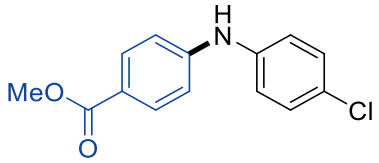
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 2.9 Hz, 1H), 7.93 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.07 (dd, *J* = 8.3, 4.6 Hz, 1H), 6.85 (ddd, *J* = 8.3, 2.9, 1.4 Hz, 1H), 3.66 (t, *J* = 6.5 Hz, 3H), 3.12 (td, *J* = 7.2, 3.3 Hz, 2H), 1.61 (qt, *J* = 9.4, 5.7 Hz, 5H), 1.43 (p, *J* = 3.3 Hz, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.5, 138.4, 135.8, 123.9, 118.5, 62.6, 43.5, 32.8, 29.4, 27.0, 25.7.

Elemental Analysis calc. for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34. Found: C, 67.91; H, 9.36.

IR (Diamond-ATR, neat, cm^{-1}): 3285, 2919, 2853, 1581, 1071, 787, 701.

Melting Point: 58 °C



3e

Methyl 4-((4-chlorophenyl)amino)benzoate (3e)

Product **3e**[54] was prepared according to General Procedure E using methyl 4-bromobenzoate (215 mg, 1.00 mmol), 4-chloroaniline (134 mg, 1.05 mmol), NaOMe (55.1 mg, 1.02 mmol), and 0.4 mol% **OA6** as catalyst. The reaction mixture was allowed to stir for 45 min. Chromatography conditions: SiO_2. Silica gel loaded with 11:3 hexane/CH_2Cl_2, elute with 1.2 column volumes hexane, followed by 3.6 column volumes 11:2:1 hexane/CH_2Cl_2/acetone, then 1.5 column volumes 9:2:1 hexane/CH_2Cl_2/acetone. Yield: Run 1 = 229 mg, 88%; Run 2 = 212 mg, 81%. Average Yield = 84%. White solid.

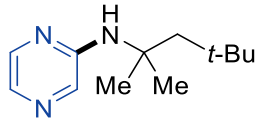
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.7 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.02 (s, 1H), 3.90 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.0, 147.7, 139.7, 131.7, 129.7, 128.0, 121.8, 121.7, 114.9, 51.9.

Elemental Analysis calc. for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62. Found: C, 64.28; H, 4.66.

IR (Diamond-ATR, neat, cm^{-1}): 3329, 1688, 1490, 1281, 1170, 819, 768.

Melting Point: 147–149 °C



3f

***N*-(2,4,4-trimethylpentan-2-yl)pyrazin-2-amine (3f)**

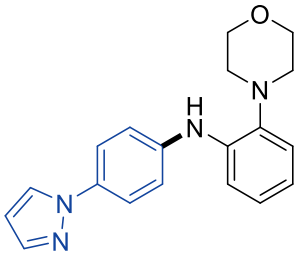
Product **3f**[15a] was prepared according to General Procedure D using 2-chloropyrazine (115 mg, 89 µL, 1.00 mmol), *tert*-octyl amine (181 mg, 225 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 1.25 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 5% MeOH/CH_2Cl_2. Yield: Run 1 = 196 mg, 94%; Run 2 = 179 mg, 86%. Average Yield = 90%. Yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.70 (d, *J* = 2.8 Hz, 1H), 4.47 (s, 1H), 1.85 (s, 2H), 1.49 (s, 6H), 0.99 (s, 9H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 154.7, 141.8, 133.5, 131.9, 55.4, 51.4, 32.0, 31.7, 29.9.

IR (Diamond-ATR, neat, cm^{-1}): 3283, 2948, 1596, 1519, 1000, 819

Melting Point: 83 °C (lit: 82–84 °C)[15a]



3g

***N*-(4-(1*H*-pyrazol-1-yl)phenyl)-2-morpholinoaniline (3g)**

Product **3g** was prepared according to General Procedure D using 1-(4-bromophenyl)-1*H*-pyrazole (223 mg, 1.00 mmol), 2-morpholinoaniline (250 mg, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.3 mol% **OA6** as catalyst. Because the excess 2-morpholinoaniline co-eluted with the desired product on silica, the product mixture was subjected to acylation conditions. Under these conditions, the remaining 2-morpholinoaniline was acylated, and the desired product did not react. After the workup describe in General Procedure D, the reaction mixture was concentrated under reduced pressure with the aid of a rotary evaporator into a 20 mL scintillation vial (DKW Life Sciences, catalog no. 03-340-4C), which was then equipped with a Teflon-coated magnetic stir bar. No precautions were taken to exclude moisture or air. Anhydrous CH_2Cl_2 (5 mL) was added to the vial via syringe, followed by the addition of acetic anhydride (82 mg, 76 µL, 0.800 mmol) and triethylamine (81 mg, 112 µL, 0.800 mmol), each via syringe. This mixture was stirred under ambient conditions for 25 min. Saturated aqueous NH_4Cl (5 mL) was added and the mixture was transferred to a separatory funnel. The reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. ^{1}H NMR analysis of this mixture indicated that all of the remaining 2-morpholinoaniline had been acylated. The mixture of the product and the acylated excess 2-morpholinoanline was separated using column chromatography. Chromatography conditions: SiO_2, 1:1 hexane/EtOAc. Yield: Run 1 = 311 mg, 97%; Run 2 = 307 mg, 96%. Average Yield = 97%. Pink solid.

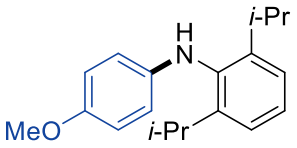
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.13 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.07 (td, *J* = 7.7, 1.5 Hz, 1H), 6.92 (td, *J* = 7.6, 1.4 Hz, 1H), 6.65 (s, 1H), 6.45 (t, *J* = 2.1 Hz, 1H), 3.94 – 3.82 (m, 4H), 2.98 – 2.91 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 141.5, 141.0, 140.7, 138.0, 134.4, 126.7, 125.0, 120.9, 120.7, 120.4, 119.1, 114.9, 107.3, 67.8, 52.1.

Elemental Analysis calc. for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29. Found: C, 71.23; H, 6.47.

IR (Diamond-ATR, neat, cm^{-1}): 3315, 2932, 2867, 2817, 1523, 1508, 1115, 749, 739.

Melting Point: 138–140 °C



3h

2,6-diisopropyl-*N*-(4-methoxyphenyl)aniline (3h)

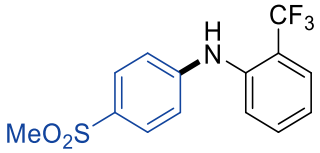
Product **3h**[55] was prepared according to General Procedure D using 4-bromoanisole (187 mg, 1.00 mmol), 90% technical grade 2,6-diisopropylaniline (276 mg, 290 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.5 mol% **OA6** as catalyst for 24 h. Chromatography conditions: SiO_2 using 30:1 pentane/Et_2O to dissolve the crude mixture, then 30:1 pentane/Et_2O for two column volumes, followed by 25:1 pentane/Et_2O for four column volumes. Yield: Run 1 = 255 mg, 90%; Run 2 = 253 mg, 89%. Average Yield = 90%. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.25 (m, 1H), 7.24 – 7.20 (m, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.46 (d, J = 8.4 Hz, 2H), 4.98 (bs, 1H), 3.75 (s, 3H), 3.21 (sept, J = 6.9 Hz, 2H), 1.16 (d, J = 6.9 Hz, 12H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.3, 147.2, 142.4, 136.2, 126.9, 123.9, 114.8, 114.4, 55.8, 28.3, 24.0.

Elemental Analysis calc. for $C_{19}H_{25}NO$: C, 80.52; H, 8.89. Found: C, 80.70; H, 9.05.

IR (Diamond-ATR, neat, cm^{-1}): 3391, 2959, 1506, 1230, 819, 774.



3i

***N*-(4-(methylsulfonyl)phenyl)-2-(trifluoromethyl)aniline (3i)**

Product **3i** was prepared according to General Procedure D using 4-bromophenyl methyl sulfone (235 mg, 1.00 mmol), 2-trifluoromethylaniline (226 mg, 176 µL, 1.40 mmol), NaOPh (163 mg, 1.40 mmol), and 0.5 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 1:1 hexane/EtOAc. Yield: Run 1 = 303 mg, 96%; Run 2 = 301 mg, 95%. Average Yield = 96%. Off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 7.9 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.31 (s, 1H), 3.05 (s, 3H).

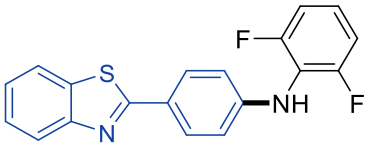
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.4, 138.8, 133.1, 131.6, 129.5, 127.4 (q, $^3J_{CF}$ = 5.3 Hz), 124.2 (q, $^1J_{CF}$ = 273.0 Hz), 124.0, 123.2, 122.4 (q, $^2J_{CF}$ = 29.5 Hz) 116.0, 45.0.

^{19}F{^{1}H} (376 MHz, $CDCl_3$): −62.0.

Elemental Analysis calc. for $C_{14}H_{12}F_3NO_2S$: C, 53.33; H, 3.84. Found: C, 53.57; H, 3.71.

IR (Diamond-ATR, neat, cm^{-1}): 3372, 3035, 1584, 1512, 1279, 1109, 762

Melting Point: 133–135 °C



3j

***N*-(4-(benzo[d]thiazol-2-yl)phenyl)-2,6-difluoroaniline (3j)**

Product **3j** was prepared according to General Procedure D using 2-(4-bromophenyl)benzo[d]thiazole (290 mg, 1.00 mmol), 2,6-difluoroaniline (181 mg, 151 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.2 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 2:1 hexane/EtOAc. Yield: Run 1 = 318 mg, 94%; Run 2 = 326 mg, 96%. Average Yield = 95%. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 8.7 Hz, 2H), 7.86 (d, J = 7.9 Hz, 1H), 7.46 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 7.34 (td, J = 7.6, 7.2, 1.2 Hz, 1H), 7.16 – 7.06 (m, 1H), 7.05 – 6.95 (m, 2H), 6.85 (dt, J = 8.7, 1.4 Hz, 2H), 5.73 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.2, 157.2 (dd, $^{1,3}J_{CF}$ = 248.4, 5.3 Hz), 154.4, 146.3, 134.9, 128.9, 126.3, 126.0, 124.8, 124.7 (t, $^3J_{CF}$ = 9.6 Hz), 122.8, 121.6, 118.1 (t, $^2J_{CF}$ = 15.4 Hz), 115.4, 112.2 (dd, $^{2,4}J_{CF}$ = 17.3, 5.7 Hz).

^{19}F{^{1}H} (376 MHz, $CDCl_3$): −120.0.

Elemental Analysis calc. for $C_{19}H_{12}F_2N_2S$: C, 67.44; H, 3.57. Found: C, 67.32; H, 3.51.

IR (Diamond-ATR, neat, cm^{-1}): 3291, 1602, 1474, 1004, 753, 728, 699.

Melting Point: 164–166 °C

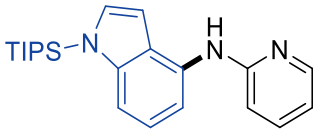
Product **3j** was also prepared using [Pd(cinnamyl)Cl]$_2$/**L6** (0.2 mol% Pd) as the catalyst precursor. General Procedure D was followed using 2-(4 bromophenyl)benzo[d]thiazole (290 mg, 1.00 mmol), 2,6-difluoroaniline (181 mg, 151 µL, 1.40 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol). A solution of [Pd(cinnamyl)Cl]$_2$ (0.004 M, 0.1 mol%) and **L6** (0.008 M, 0.2 mol%) was prepared in Vial B and allowed to stir until homogeneous. Yield determined by ^{1}H NMR: >95%.

Product **3j** was also prepared using Pd_2dba_3/**L6** (0.2 mol% Pd) as the catalyst precursor. General Procedure D was followed using 2-(4 bromophenyl)benzo[d]thiazole (290 mg, 1.00 mmol), 2,6-difluoroaniline (181 mg, 151 µL, 1.40 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol). A solution of Pd_2dba_3 (0.004 M, 0.1 mol%) and **L6** (0.008 M, 0.2 mol%) was prepared in Vial B. Yield determined by ^{1}H NMR: 0%.

Product **3j** was also prepared using $Pd(OAc)_2$/**L6** (0.2 mol% Pd) as the catalyst precursor. General Procedure C was followed using 2-(4 bromophenyl)benzo[d]thiazole (116 mg, 0.40 mmol), 2,6-difluoroaniline (72 mg, 0.56 mmol), and NaO*t*-Bu (54 mg, 0.56 mmol) in an oven-dried 1-dram vial (Kimble, part no. 60910L-1) (Vial A). A solution of $Pd(OAc)_2$ (0.004 M, 0.2 mol%) and **L6** (0.008 M, 0.4 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B). $Pd(OAc)_2$/**L6** solution (0.20 mL) from Vial B was transferred to Vial A via syringe. Yield determined by ^{1}H

NMR: 0%.

Product **3j** was also prepared using pre-activated[45] $Pd(OAc)_2$/**L6** (0.2 mol% Pd) as the catalyst precursor. General Procedure D was followed using 2-(4 bromophenyl)benzo[d]thiazole (290 mg, 1.00 mmol), 2,6-difluoroaniline (181 mg, 151 µL, 1.40 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol). The $Pd(OAc)_2$ was activated using the following procedure: A solution of $Pd(OAc)_2$ (0.008 M, 0.2 mol%) and **L6** (0.016 M, 0.4 mol%) was prepared in an oven-dried 8 mL reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) (Vial B). $Pd(OAc)_2$ and **L6** were added to the oven-dried Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired Pd concentration (0.008 M, 0.2 mol%). Deionized water (0.1 mol%) was then added to Vial B via syringe. Vial B was transferred to a pre-heated oil bath (bath temperature = 90 °C) and allowed to stir for 2 min, during which the solution became deep red. Vial B was then removed from the oil bath and allowed to cool to room temperature. Yield determined by ^{1}H NMR: 55%.



3k

***N*-(pyridin-2-yl)-1-(triisopropylsilyl)-1*H*-indol-4-amine (3k)**

Product **3k** was prepared according to General Procedure D using 4-chloro-1-(triisopropylsilyl)-1*H*-indole (308 mg, 1.00 mmol), 2-aminopyridine (132 mg, 110 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.4 mol% **OA6** as catalyst. The crude reaction mixture was loaded onto the column using $CHCl_3$ due to limited solubility in other common solvents. Chromatography conditions: SiO_2, 4:1:1 hexane/acetone/CH_2Cl_2. Yield: Run 1 = 341 mg, 93%; Run 2 = 348 mg, 95%. Average Yield = 94%. White solid.

Product **3k** was also prepared according to General Procedure F at 90 °C using 4-chloro-1-(triisopropylsilyl)-1*H*-indole (308 mg, 1.00 mmol), 2-aminopyridine (132 mg, 110 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.05 mol% **OA6** as catalyst. Column loaded with $CHCl_3$ due to limited solubility in other commons solvents. Chromatography conditions: SiO_2, 4:1:1 hexane/acetone/CH_2Cl_2. Yield: Run 1 = 324 mg, 89%; Run 2 = 314 mg, 86%. Average Yield = 87%. White solid.

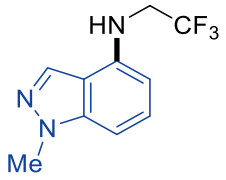
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (ddd, *J* = 5.0, 1.9, 0.9 Hz, 1H), 7.46 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1H), 7.29 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.94 (dt, *J* = 8.5, 1.0 Hz, 1H), 6.78 (s, 1H), 6.71 (ddd, *J* = 7.1, 5.0, 0.9 Hz, 1H), 6.60 (dd, *J* = 3.3, 1.0 Hz, 1H), 1.70 (sept, *J* = 7.5 Hz, 3H), 1.16 (d, *J* = 7.5 Hz, 18H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.8, 148.5, 142.1, 137.6, 132.6, 130.7, 125.5, 121.9, 114.6, 111.4, 110.0, 108.2, 101.9, 18.2, 12.9.

Elemental Analysis calc. for $C_{22}H_{31}N_3Si$: C, 72.28; H, 8.55. Found: C, 72.01; H, 8.61.

IR (Diamond-ATR, neat, cm^{-1}): 2947, 2864, 1437, 1154, 771, 747, 637.

Melting Point: 172 °C



3l

1-methyl-*N*-(2,2,2-trifluoroethyl)-1*H*-indazol-4-amine (3l)

Product **3l** was prepared according to General Procedure D using 4-bromo-1-methyl-1*H*-indazole (211 mg, 1.00 mmol), trifluoroethylamine (139 mg, 110 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.2 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 5% MeOH/CH_2Cl_2. Yield: Run 1 = 218 mg, 95%; Run 2 = 217 mg, 95%. Average Yield = 95%. Brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.26 (dd, J = 8.4, 7.6 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 7.5 Hz, 1H), 4.51 (bs, 1H), 4.03 (s, 3H), 3.94 (q, J = 8.9 Hz, 2H).

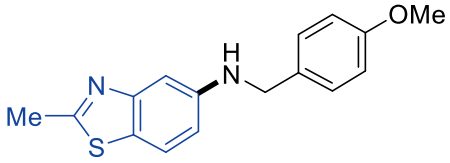
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 141.3, 140.0, 129.2, 127.9, 125.1 (q, $^1J_{CF}$ = 279.8 Hz), 114.6, 99.9, 99.6, 45.8 (q, $^2J_{CF}$ = 34.0 Hz), 35.8.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ −72.6.

Elemental Analysis calc. for $C_{10}H_{10}F_3N_3$: C, 52.40; H, 4.40. Found: C, 52.70; H, 4.44.

IR (Diamond-ATR, neat, cm^{-1}): 3319, 1591, 1255, 1143, 1115, 770.

Melting Point: 107–108 °C



3m

***N*-(4-methoxybenzyl)-2-methylbenzo[d]thiazol-5-amine (3m)**

Product **3m** was prepared according to General Procedure D using 5-chloro-2-methylbenzothiazole (184 mg, 1.00 mmol), 4-methoxybenzylamine (192 mg, 183 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.4 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 2:1 hexane/EtOAc. Yield: Run 1 = 239 mg, 84%; Run 2 = 232 mg, 82%. Average Yield = 83%. Off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.72 (dd, J = 8.6, 2.3 Hz, 1H), 4.31 (d, J = 4.4 Hz, 2H), 4.12 (bs, 1H), 3.80 (s, 3H), 2.77 (s, 3H).

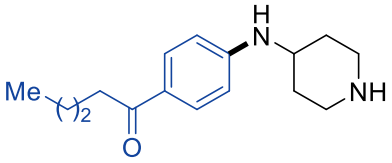
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.6, 159.0, 155.2, 147.4, 131.2, 129.0, 124.4, 121.6, 114.2,

113.6, 104.5, 55.4, 48.2, 20.2.

Elemental Analysis calc. for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67. Found: C, 67.54; H, 5.66.

IR (Diamond-ATR, neat, cm^{-1}): 3335, 2900, 1612, 1507, 1238, 1176, 1166, 811, 786.

Melting Point: 86–88 °C



3n

1-(4-(piperidin-4-ylamino)phenyl)pentan-1-one (3n)

Product **3n** was prepared according to General Procedure D using 4'-chlorovalerophenone (197 mg, 1.00 mmol), 4-aminopiperidine (140 mg, 148 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.4 mol% **OA6** as catalyst. Chromatography conditions: C18 (60 g) 10% MeCN/H_2O (water contained 0.1% trifluoroacetic acid) to 100% MeCN. The product-containing fractions were transferred into a separatory funnel, washed with saturated aqueous $NaHCO_3$ (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (100 mL, 3 x 50 mL) until the aqueous layer contained no UV-active material as judged by TLC. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated using the aid of a rotary evaporator. Yield: Run 1 = 221 mg, 85%; Run 2 = 213 mg, 82%. Average Yield = 84%. Yellow solid. The isolated product was found to be contaminated with trifluoroacetic acid (~2 wt% as determined using ^{19}F NMR) from the reverse-phase chromatographic solvent mixture.

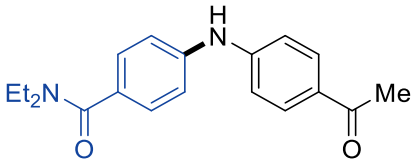
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 4.09 (d, *J* = 7.9 Hz, 1H), 3.45 (dddd, *J* = 14.5, 10.4, 8.0, 4.0 Hz, 1H), 3.14 (dt, *J* = 12.8, 3.8 Hz, 2H), 2.89 – 2.80 (m, 2H), 2.74 (ddd, *J* = 12.5, 11.2, 2.6 Hz, 2H), 2.12 – 2.02 (m, 2H), 1.78 (s, 1H), 1.69 (p, *J* = 7.5 Hz, 2H), 1.47 – 1.29 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 198.9, 150.9, 130.8, 126.5, 111.8, 50.1, 45.5, 37.8, 33.8, 27.3, 22.8, 14.1.

HRMS (DART) calc. $C_{16}H_{25}N_2O^+$ $[M+H]^+$: 261.1961. Found: 261.1971.

IR (Diamond-ATR, neat, cm^{-1}): 3419, 2976, 2931, 1589, 1245, 1067, 733.

Melting Point: 120–121°C



3o

4-((4-acetylphenyl)amino)-*N*,*N*-diethylbenzamide (3o)

Product **3o** was prepared according to General Procedure D using 4-bromo-*N*,*N*-diethylbenzamide

(256 mg, 1.00 mmol), 4'-aminoacetophenone (139 mg, 110 µL, 1.40 mmol), NaOPh (163 mg, 1.40 mmol), and 0.5 mol% **OA6** as catalyst. This reaction was run for 24 h. Chromatography conditions: SiO_2, 1:3 hexane/EtOAc. Yield: Run 1 = 297 mg, 96%; Run 2 = 293 mg, 94%. Average Yield = 95%. White solid.

Product **3o** was also prepared according to General Procedure F at 75 °C using 4-bromo-*N*,*N*-diethylbenzamide (256 mg, 1.00 mmol), 4'-aminoacetophenone (139 mg, 110 µL, 1.40 mmol), NaOPh (163 mg, 1.40 mmol), and 0.05 mol% **OA6** as catalyst. This reaction was run for 24 h. Chromatography conditions: SiO_2, 1:3 hexane/EtOAc. Yield: Run 1 = 306 mg, 98%; Run 2 = 298 mg, 96%. Average Yield = 97%. White solid.

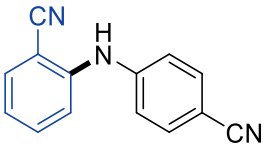
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.45 (bs, 4H), 2.54 (s, 3H), 1.20 (bs, 6H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 40º C): δ 196.5, 171.3, 147.8, 142.4, 131.2, 130.6, 129.7, 128.1, 119.3, 115.4, 43.3, 40.2, 26.2, 13.7.

Elemental Analysis calc. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14. Found: C, 73.37; H, 7.15.

IR (Diamond-ATR, neat, cm^{-1}): 3274, 2973, 1661, 1587, 1273, 1177.

Melting Point: 170–172 °C



3p

2-((4-cyanophenyl)amino)benzonitrile (3p)

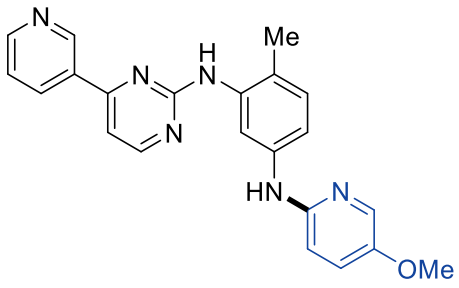
Product **3p**[14c] was prepared according to General Procedure D using 2-chlorobenzonitrile (138 mg, 1.00 mmol), 4-aminobenzonitrile (164 mg, 1.40 mmol), NaOPh (163 mg, 1.40 mmol), and 0.5 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 2:1 hexane/EtOAc. Yield: Run 1 = 218 mg, 99%; Run 2 = 208 mg, 95%. Average Yield = 97%. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.55 (m, 3H), 7.52 (ddd, *J* = 8.8, 7.3, 1.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.07 (td, *J* = 7.6, 1.1 Hz, 1H), 6.62 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.3, 144.2, 134.2, 134.0, 133.7, 122.6, 119.2, 118.1, 118.0, 117.0, 105.1, 102.6

IR (Diamond-ATR, neat, cm^{-1}): 3325, 2218, 2213, 1520, 1323, 1292, 767, 755.

Melting Point: 156–157 °C (lit: 155 °C)[14c]



3q

***N1*-(5-methoxypyridin-2-yl)-4-methyl-*N3*-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (3q)**

Product **3q** was prepared according to General Procedure D using 2-bromo-5-methoxypyridine (226 mg, 1.20 mmol, 1.20 equiv), 6-methyl-N1-(4-(pyridin-3-yl)pyrimidin-2-yl)benzene-1,3-diamine (277 mg, 1.00 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 1.0 mol% **OA6** as catalyst. The crude product mixture was extracted with 3 x 50 mL EtOAc. Chromatography conditions: C18 (60 g) 10% MeCN/H_2O (water contained 0.1% trifluoroacetic acid) to 100% MeCN. The product-containing fractions were transferred into a separatory funnel, washed with saturated aqueous $NaHCO_3$ (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL) until the aqueous layer contained no UV-active material as judged by TLC. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated using the aid of a rotary evaporator. Yield: Run 1 = 340 mg, 88%; Run 2 = 330 mg, 86%. Average Yield = 87%. Tan solid.

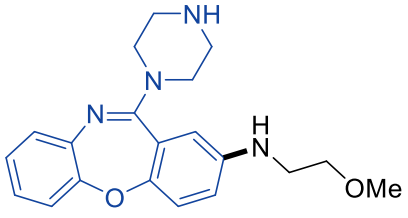
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (d, *J* = 2.3 Hz, 1H), 8.69 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.49 (d, *J* = 5.1 Hz, 1H), 8.31 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 7.86 (d, *J* = 3.0 Hz, 1H), 7.34 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.09 (s, 1H), 7.03 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.99 – 6.87 (m, 2H), 6.68 (s, 1H), 3.76 (s, 3H), 2.32 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.8, 160.8, 159.2, 151.6, 151.5, 150.6, 150.0, 148.6, 139.9, 138.1, 134.7, 133.4, 132.9, 131.1, 125.4, 123.8, 121.9, 114.8, 112.5, 109.7, 108.5, 56.3, 17.6.

HRMS (DART) calc. $C_{22}H_{21}N_6O^+$ $[M+H]^+$: 385.1771. Found: 385.1770.

IR (Diamond-ATR, neat, cm^{-1}): 3275, 3181, 3093, 3005, 2915, 1495, 1451, 1248, 707.

Melting Point: 161–163 °C



3r

N-(2-methoxyethyl)-11-(piperazin-1-yl)dibenzo[b,f][1,4]oxazepin-2-amine (3r)

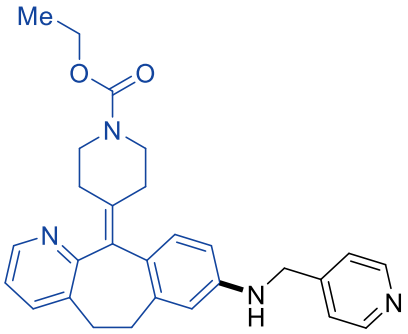
An oven-dried 1-dram vial (Vial A) (Kimble, part no. 60910L-1) equipped with an oven-dried Teflon-coated magnetic stir bar was brought into a nitrogen-filled glovebox and charged with NaO*t*-Bu (68 mg, 0.70 mmol, 1.40 equiv) and amoxapine (157 mg, 0.50 mmol, 1.00 equiv) that was stored in the nitrogen-filled glovebox. The vial was sealed with a screw cap (Fisherbrand, 13-

425, C4015-66) equipped with a Teflon septum (Fisherbrand, 13-425, C4015-60) and was removed from the glovebox. 2-methoxyethan-1-amine (53 mg, 61 µL, 0.70 mmol, 1.40 equiv) was added via syringe. Anhydrous THF (0.125 mL) was added via syringe, and the reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. If necessary, the reaction mixture was agitated with the aid of a sonicator or vortexer to achieve a homogeneous or homogeneously suspended mixture. A solution of **OA6** (0.03 M, 0.75 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B). **OA6** was added to the oven-dried Vial B, the vial was capped, and evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired precatalyst concentration (0.030 M, 0.75 mol%). **OA6** solution (0.125 mL) from Vial B was transferred to Vial A via syringe. The reaction mixture in Vial A was stirred at room temperature for 1 h, was opened to the air and the contents were rinsed into a separatory funnel using water (15 mL) and EtOAc (50 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by using column chromatography. Chromatography conditions: C18 (50 g) 10% MeCN/H_2O (water contained 0.1% trifluoroacetic acid) to 100% MeCN. The product-containing fractions were transferred into a separatory funnel, washed with saturated aqueous Na_2CO_3 (50 mL) and brine (25 mL), and the aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL) until the organic layer contained no UV-active material as judged by TLC. The combined organic layers were sequentially washed with saturated aqueous Na_2CO_3 (2 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL). The organic layers were then dried over $MgSO_4$, filtered, and concentrated using the aid of a rotary evaporator. Yield. Run 1 = 131 mg, 74% (Yield determined by ^{1}H NMR = 97%); Run 2 = 132 mg, 73% (Yield determined by ^{1}H NMR = 94%). Average Yield = 73%. Off-white solid. The isolated product was found to be contaminated with trifluoroacetic acid (0.2 wt% as determined using ^{19}F NMR) from the reverse-phase chromatographic solvent mixture.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 – 7.00 (m, 4H), 6.94 (td, *J* = 7.6, 1.8 Hz, 1H), 6.67 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.54 (d, *J* = 2.9 Hz, 1H), 3.97 (t, *J* = 5.8 Hz, 1H), 3.57 (t, *J* = 5.2 Hz, 2H), 3.53 (s, 4H), 3.37 (s, 3H), 3.20 (q, *J* = 4.8 Hz, 2H), 2.98 (s, 4H), 2.09 (s, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.0, 153.2, 152.9, 145.4, 140.8, 127.0, 125.3, 124.1, 123.9, 121.8, 120.0, 117.6, 112.3, 70.92, 58.9, 48.8, 46.2, 44.1.

HRMS (DART) calc. $C_{20}H_{25}N_4O_2^+$ $[M+H]^+$: 353.1972. Found: 353.1971.
IR (Diamond-ATR, neat, cm^{-1}): 3272, 2913, 1563, 1187, 1017, 778.
Melting Point: 209–211 °C



3s

Ethyl 4-(8-((pyridin-4-ylmethyl)amino)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (3s)

Product **3s** was prepared according to General Procedure D using loratadine (383 mg, 1.00 mmol), 4-aminomethylpyridine (151 mg, 142 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.2 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, one column volume CH_2Cl_2, followed by three column volumes of 10% MeOH/CH_2Cl_2. Yield: Run 1 = 409 mg, 90%; Run 2 = 446 mg, 98%. Average Yield = 94%. Yellow solid.

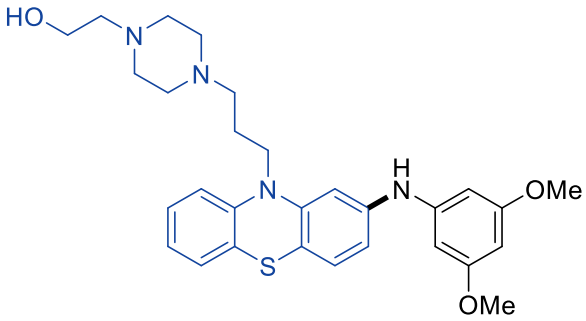
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 – 8.47 (m, 2H), 8.35 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.40 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.04 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.43 – 6.30 (m, 2H), 4.31 (s, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 3.30 (tt, *J* = 12.4, 5.2 Hz, 2H), 3.08 (dddd, *J* = 16.7, 13.1, 9.4, 3.9 Hz, 2H), 2.87 – 2.60 (m, 2H), 2.41 (dtt, *J* = 14.4, 9.0, 4.7 Hz, 3H), 2.25 (dt, *J* = 14.3, 4.5 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 158.7, 155.6, 150.0, 149.0, 146.9, 146.5, 138.6, 137.0, 135.9, 135.1, 133.8, 130.7, 128.8, 122.1, 122.0, 113.2, 110.7, 61.3, 47.1, 45.0, 44.9, 32.4, 31.6, 30.7, 30.6, 14.8.

HRMS (DART) calc. $C_{28}H_{31}N_4O_2^+$ $[M+H]^+$: 455.2442. Found: 455.2441.

IR (Diamond-ATR, neat, cm^{-1}): 3337, 2979, 2906, 1684, 1436, 1227, 1111, 994.

Melting Point: 94–96 °C



3t

2-(4-(3-(2-((3,5-dimethoxyphenyl)amino)-10*H*-phenothiazin-10-yl)propyl)piperazin-1-yl)ethan-1-ol (3t)

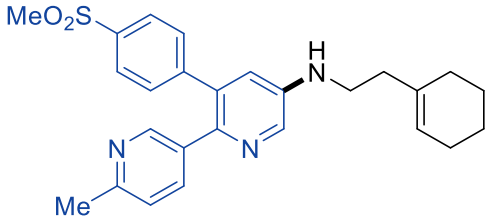
Product **3t** was prepared according to General Procedure D using perphenazine (406 mg, 1.00 mmol), 3,5-dimethoxyaniline (214 mg, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.4 mol% **OA6** as catalyst. Chromatography conditions: C18 (30 g) 10% MeCN/H_2O (water contained 0.1% trifluoroacetic acid) to 100% MeCN. The product-containing fractions were transferred into a separatory funnel, washed with saturated aqueous $NaHCO_3$ (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL) until the aqueous layer contained no UV-active material as judged by TLC. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated using the aid of a rotary evaporator. Yield: Run 1 = 477 mg, 92%; Run 2 = 461 mg, 89%. Average Yield = 91%. Tan solid. The isolated product was found to be contaminated with trifluoroacetic acid (0.7 wt% as determined using ^{19}F NMR) from the reverse-phase chromatographic solvent mixture.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 – 7.10 (m, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.93 – 6.86 (t + d, *J* = 7.5 Hz + 8.4 Hz, 2H), 6.69 – 6.64 (dd + s, *J* = 2.2 Hz, 2H), 6.18 (d, *J* = 2.2 Hz, 2H), 6.06 (t, *J* = 2.2 Hz, 1H), 5.64 (s, 1H), 3.86 (t, *J* = 6.9 Hz, 2H), 3.75 (s, 6H), 3.59 (t, *J* = 5.4 Hz, 2H), 2.65 – 2.31 (m, 12H), 1.96 (p, *J* = 7.0 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.8, 146.5, 145.4, 145.2, 142.4, 128.0, 127.5, 127.2, 125.7, 122.6, 117.0, 115.7, 113.6, 107.2, 95.9, 93.1, 59.3, 57.7, 55.7, 55.4, 53.3, 52.9, 45.5, 24.5.

HRMS (DART) calc. $C_{29}H_{37}N_4O_3S^+$ $[M+H]^+$: 521.2581. Found: 521.2574.

IR (Diamond-ATR, neat, cm^{-1}): 2937, 2812, 1580, 1456, 1200, 1148, 747.



3u

***N*-(2-(cyclohex-1-en-1-yl)ethyl)-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-5-amine (3u)**

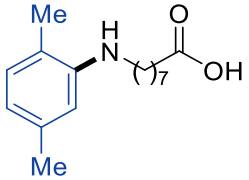
Product **3u** was prepared according to General Procedure D using etoricoxib (359 mg, 1.00 mmol), 2-(1-cyclohexenyl)ethylamine (175 mg, 195 µL, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.4 mol% **OA6** as catalyst. Chromatography conditions: SiO_2, 5% MeOH/CH_2Cl_2. Yield: Run 1 = 434 mg, 97%; Run 2 = 427 mg, 95%. Average Yield = 96%. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.3 Hz, 1H), 8.15 (d, *J* = 2.7 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.51 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 2.8 Hz, 1H), 5.55 (s, 1H), 3.98 (t, *J* = 5.3 Hz, 1H), 3.23 (q, *J* = 6.4 Hz, 2H), 3.07 (s, 3H), 2.49 (s, 3H), 2.31 (t, *J* = 6.8 Hz, 2H), 2.06 – 1.90 (m, 4H), 1.68 – 1.49 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.9, 149.9, 146.2, 143.6, 142.6, 139.5, 137.2, 136.0, 134.7, 134.4, 132.6, 130.6, 127.7, 124.4, 122.7, 120.3, 44.7, 41.0, 37.5, 27.9, 25.4, 24.2, 22.9, 22.4.

Elemental Analysis calc. for $C_{26}H_{29}N_3O_2S$: C, 69.77; H, 6.53. Found: C, 69.50; H, 6.54.

IR (Diamond-ATR, neat, cm^{-1}): 3379, 2919, 1589, 1308, 1147, 775.



3aa

8-((2,5-dimethylphenyl)amino)octanoic acid (3aa)

Product **3aa**[14c] was prepared according to General Procedure F at 90 °C using 2-chloro-1,4-dimethylbenzene (141 mg, 134 µL, 1.00 mmol), 8-aminooctanoic acid (223 mg, 1.40 mmol),

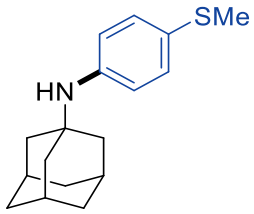
NaO*t*-Bu (231 mg, 2.40 mmol), and 0.1 mol% **OA6** as catalyst. This reaction was performed with 2.5 mL THF. In place of the workup method given in General Procedure F, the following workup procedure was followed: After the reaction mixture was allowed to cool to room temperature, the reaction mixture was opened to the air and the contents were rinsed into a separatory funnel using CH_2Cl_2 (5 mL), H_2O (3 mL), and 1 M HCl (aq) (2 mL), followed by brine (5 mL). The organic and aqueous layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. Chromatography conditions: SiO_2 96:3:1 DCM/MeOH/AcOH. Yield: Run 1 = 259 mg, 98%; Run 2 = 262 mg, 99%. Average Yield = 99%. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (bs, 2H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 6.45 (s, 1H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 2.10 (s, 3H), 1.74 – 1.61(m, 4H), 1.53 – 1.34 (m, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 180.2, 146.3, 136.9, 130.0, 118.9, 117.5, 110.8, 44.1, 34.1, 29.7, 29.2, 29.1, 27.2, 24.7, 21.7, 17.2.

IR (Diamond-ATR, neat, cm^{-1}): 2930, 2856, 1703, 1524, 1423, 790.

Melting Point: 76–77 °C (lit: 77–78 °C)[14c]



3bb

***N*-(4-(methylthio)phenyl)adamantan-1-amine (3bb)**

Product **3bb**[15a] was prepared according to General Procedure F at 90 °C using 4-bromothioanisole (203 mg, 1.00 mmol), 1-adamantylamine (212 mg, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.1 mol% **OA6** as catalyst. Immediately following the addition of precatalyst solution, and preceding submersion in the oil bath, the reaction mixture was agitated with the aid of a vortexer until homogeneous. Chromatography conditions: SiO_2, 10:1 hexane/EtOAc. Yield: Run 1 = 269 mg, 98%; Run 2 = 267 mg, 98%. Average Yield = 98%. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.30 (s, 1H), 2.42 (s, 3H), 2.11 (s, 3H), 1.86 (d, *J* = 2.9 Hz, 6H), 1.76 – 1.57 (m, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.7, 130.2, 126.5, 119.7, 52.4, 43.5, 36.6, 29.8, 18.6.

IR (Diamond-ATR, neat, cm^{-1}): 3375, 2897, 2846, 1591, 1498, 813, 806.

Melting Point: 70–71 °C (lit: 70 °C)[15a]

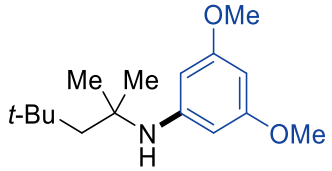
Product **3bb** was also prepared using $[Pd(cinnamyl)Cl]_2$/**L6** (0.1 mol% Pd) as the catalyst precursor. General Procedure F at 90 °C was followed using 4-bromothioanisole (203 mg, 1.00

mmol), 1-adamantylamine (212 mg, 1.40 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol). A solution of [Pd(cinnamyl)Cl]$_2$ (0.002 M, 0.05 mol%) and **L6** (0.004 M, 0.1 mol%) was prepared in Vial B and allowed to stir until homogeneous. Immediately following the addition of precatalyst solution, and preceding submersion in the oil bath, the reaction mixture was agitated with the aid of a vortexer until homogeneous. Yield determined by ^{1}H NMR: >95%.

Product **3bb** was also prepared using Pd$_2$dba$_3$/**L6** (0.1 mol% Pd) as the catalyst precursor. General Procedure F at 90 °C was followed using 4-bromothioanisole (203 mg, 1.00 mmol), 1-adamantylamine (212 mg, 1.40 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol). A solution of Pd$_2$dba$_3$ (0.002 M, 0.05 mol%) and **L6** (0.004 M, 0.1 mol%) was prepared in Vial B. Immediately following the addition of precatalyst solution, and preceding submersion in the oil bath, the reaction mixture was agitated with the aid of a vortexer until homogeneous. Yield determined by ^{1}H NMR: 88%.

Product **3bb** was also prepared using Pd(OAc)$_2$/**L6** (0.1 mol% Pd) as the catalyst precursor. General Procedure C was followed using 4-bromothioanisole (81 mg, 0.40 mmol), 1-adamantylamine (85 mg, 0.56 mmol), and NaO*t*-Bu (54 mg, 0.56 mmol) in an oven-dried 8 mL reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) (Vial A). Anhydrous THF (0.1 mL) was added to Vial A via syringe. A solution of Pd(OAc)$_2$ (0.004 M, 0.1 mol%) and **L6** (0.008 M, 0.2 mol%) was prepared in an oven-dried 1-dram vial (Vial B). Pd(OAc)$_2$/**L6** solution (0.10 mL) from Vial B was transferred to Vial A via syringe. Vial A was transferred to a pre-heated oil bath (bath temperature = 90 °C) and stirred at 90 °C for 1 h. Yield determined by ^{1}H NMR: 32%.

Product **3bb** was also prepared using pre-activated[45] Pd(OAc)$_2$/**L6** (0.1 mol% Pd) as the catalyst precursor. . General Procedure F at 90 °C was followed using 4-bromothioanisole (203 mg, 1.00 mmol), 1-adamantylamine (212 mg, 1.40 mmol), and NaO*t*-Bu (135 mg, 1.40 mmol). Anhydrous THF (0.375 mL) was added via syringe. The Pd(OAc)$_2$ was activated using the following procedure: A solution of Pd(OAc)$_2$ (0.008 M, 0.1 mol%) and **L6** (0.016 M, 0.2 mol%) was prepared in an oven-dried 8 mL reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) (Vial B). Pd(OAc)$_2$ and **L6** were added to the oven-dried Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired Pd concentration (0.008 M, 0.2 mol%). Deionized water (0.1 mol%) was then added to Vial B via syringe. Vial B was transferred to a pre-heated oil bath (bath temperature = 90 °C) and allowed to stir for 2 min, during which the solution became deep red. Vial B was then removed from the oil bath and allowed to cool to room temperature. Activated Pd(OAc)$_2$/**L6** solution from Vial B (0.125 mL) was added to Vial A via syringe. Yield determined by ^{1}H NMR: 85%.



3cc

3,5-dimethoxy-*N*-(2,4,4-trimethylpentan-2-yl)aniline (3cc)

Product **3cc**[15a] was prepared according to General Procedure F at 90 °C using 1-bromo-3,5-dimethoxybenzene (217 mg, 1.00 mmol), *tert*-octyl amine (181 mg, 225 µL, 1.40 mmol), NaO*t*-

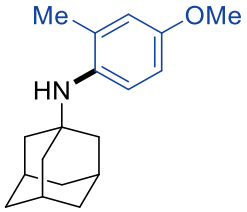
Bu (135 mg, 1.40 mmol), and 0.1 mol% **OA6** as catalyst. Chromatography conditions: SiO_2 (50 g), 100% hexane to 5:1 hexane/EtOAc. Yield: Run 1 = 246 mg, 93%; Run 2 = 247 mg, 93%. Average Yield = 93%. Off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (m, 3H), 3.75 (s, 6H), 3.61 (s, 1H), 1.70 (s, 2H), 1.40 (s, 6H), 1.03 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.4, 148.8, 94.9, 89.4, 55.3, 55.2, 53.0, 31.9, 31.8, 30.7.

IR (Diamond-ATR, neat, cm^{-1}): 3421, 2961, 2934, 1613, 1202, 1170, 1152, 815.

Melting Point: 55–56 °C (lit: 54 °C)[15a]



3dd

***N*-(4-methoxy-2-methylphenyl)adamantan-1-amine (3dd)**

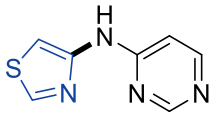
Product **3dd**[15a] was prepared according to General Procedure F at 75 °C using 4-bromo-3-methylanisole (201 mg, 141 µL, 1.00 mmol), 1-adamantylamine (212 mg, 1.40 mmol), NaO*t*-Bu (135 mg, 1.40 mmol), and 0.5 mol% **OA6** as catalyst. Immediately following the addition of precatalyst solution, and preceding submersion in the oil bath, the reaction mixture was agitated with the aid of a vortexer until homogeneous. Chromatography conditions: SiO_2 (50 g), 100% hexane to 95% hexane/EtOAc. Yield: Run 1 = 258 mg, 95%; Run 2 = 247 mg, 91%. Average Yield = 93%. White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 3.0 Hz, 1H), 6.65 (dd, J = 8.7, 3.1 Hz, 1H), 3.75 (s, 3H), 2.98 (s, 1H), 2.20 (s, 3H), 2.09 (bs, 3H), 1.83 (d, J = 3.0 Hz, 6H), 1.65 (m, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.7, 137.5, 129.6, 122.6, 116.3, 111.3, 55.6, 53.2, 44.1, 36.6, 30.0, 29.9, 19.0.

IR (Diamond-ATR, neat, cm^{-1}): 3347, 2885, 1497, 1215, 1050, 792, 721.

Melting Point: 61–62 °C (lit: 60 °C)[15a]



3ee

***N*-(pyrimidine-4-yl)thiazol-4-amine (3ee)**

Product **3ee**[15c] was prepared according to General Procedure G using 4-bromothiazole (164 mg, 89 µL, 1.00 mmol), 4-aminopyrimidine (114 mg, 1.20 mmol), and 2.0 mol% **OA6** as catalyst. Chromatography conditions: SiO_2 (50 g), CH_2Cl_2/MeOH (2% to 10%). Yield: Run 1 = 155 mg,

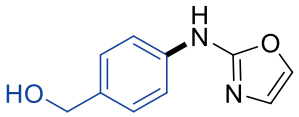
87%; Run 2 = 166 mg, 93%. Average Yield = 90%. White solid.

^{1}H NMR (400 MHz, CD_3OD): δ 8.81 (d, *J* = 2.3 Hz, 1H), 8.67 (s, 1H), 8.24 (d, *J* = 6.1 Hz, 1H), 7.79 (d, *J* = 2.2 Hz, 1H), 6.95 (dd, *J* = 6.1, 1.3 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, d_6-DMSO): δ 158.5, 158.0, 155.1, 152.0, 149.4, 107.4, 99.0.

IR (Diamond-ATR, neat, cm^{-1}): 3257, 3153, 3033, 1505, 968, 824, 709.

Melting Point: 184–185 °C (lit: 183–184 °C)[15c]



3ff

***N*-(4-hydroxymethylphenyl)oxazol-2-amine (3ff)**

Product **3ff**[15c] was prepared according to General Procedure G using 4-bromobenzylalcohol (187 mg, 1.00 mmol), 2-aminooxazole (101 mg, 1.20 mmol), and 0.5 mol% **OA6** as catalyst. Chromatography conditions: SiO_2 (50 g), hexane/EtOAc (30% to 100%). Yield: Run 1 = 174 mg, 91%; Run 2 = 177 mg, 93%. Average Yield = 92%. Off-white solid.

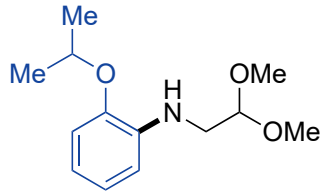
^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 1.1 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 1.1 Hz, 1H), 4.54 (s, 2H).

^{13}C{^{1}H} NMR (101 MHz, CD_3OD): δ 159.3, 140.0, 136.1, 133.6, 129.1, 127.0, 118.2, 65.0.

IR (Diamond-ATR, neat, cm^{-1}): 3350, 2924, 2869, 1664, 1146, 1124, 999, 798

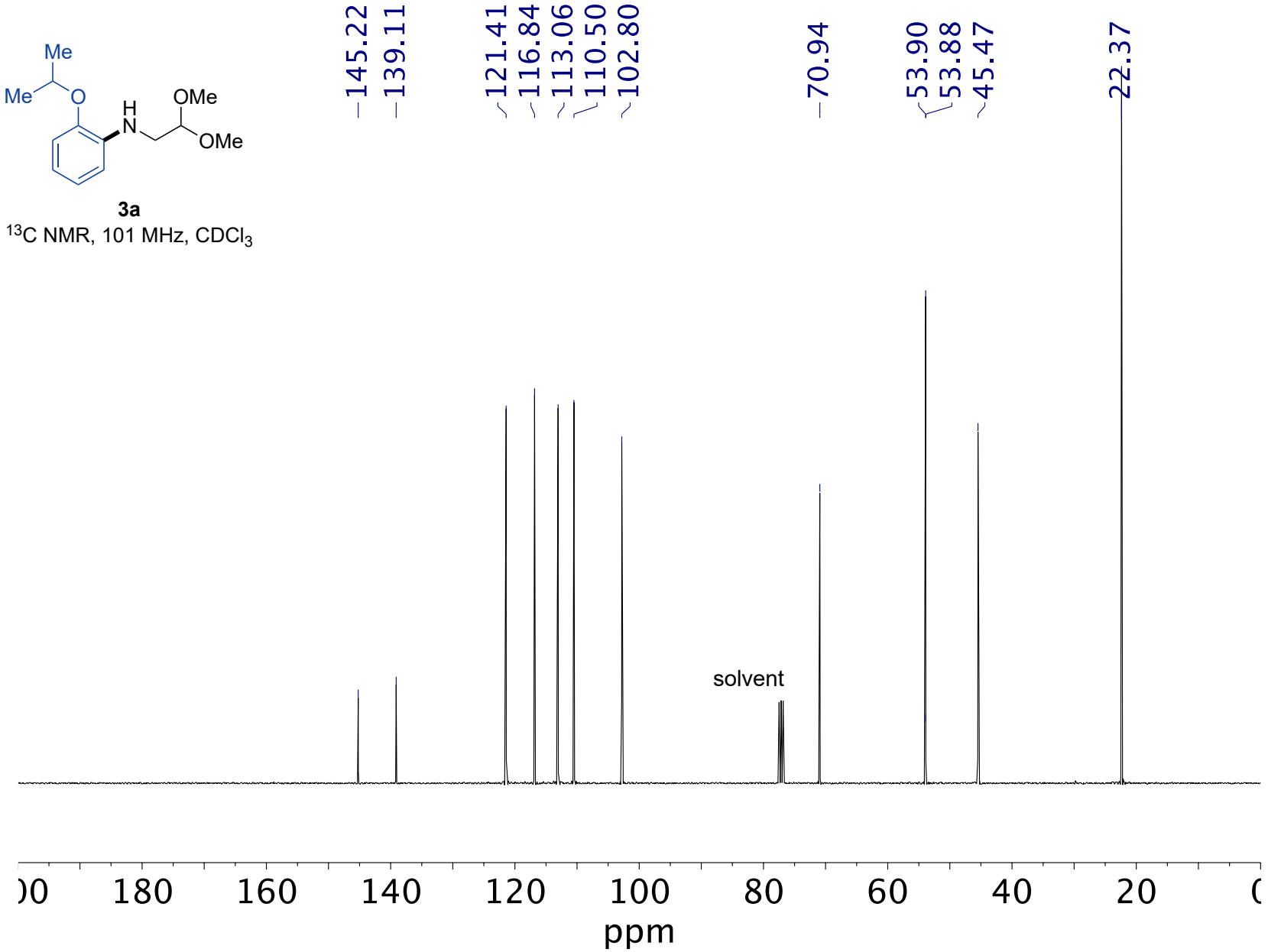
Melting Point: 147–148 °C (lit: 145–146 °C)[15c]

7. NMR Spectra of C–N Coupling Products, Ligands, and Complexes



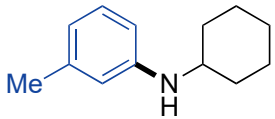
3a

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



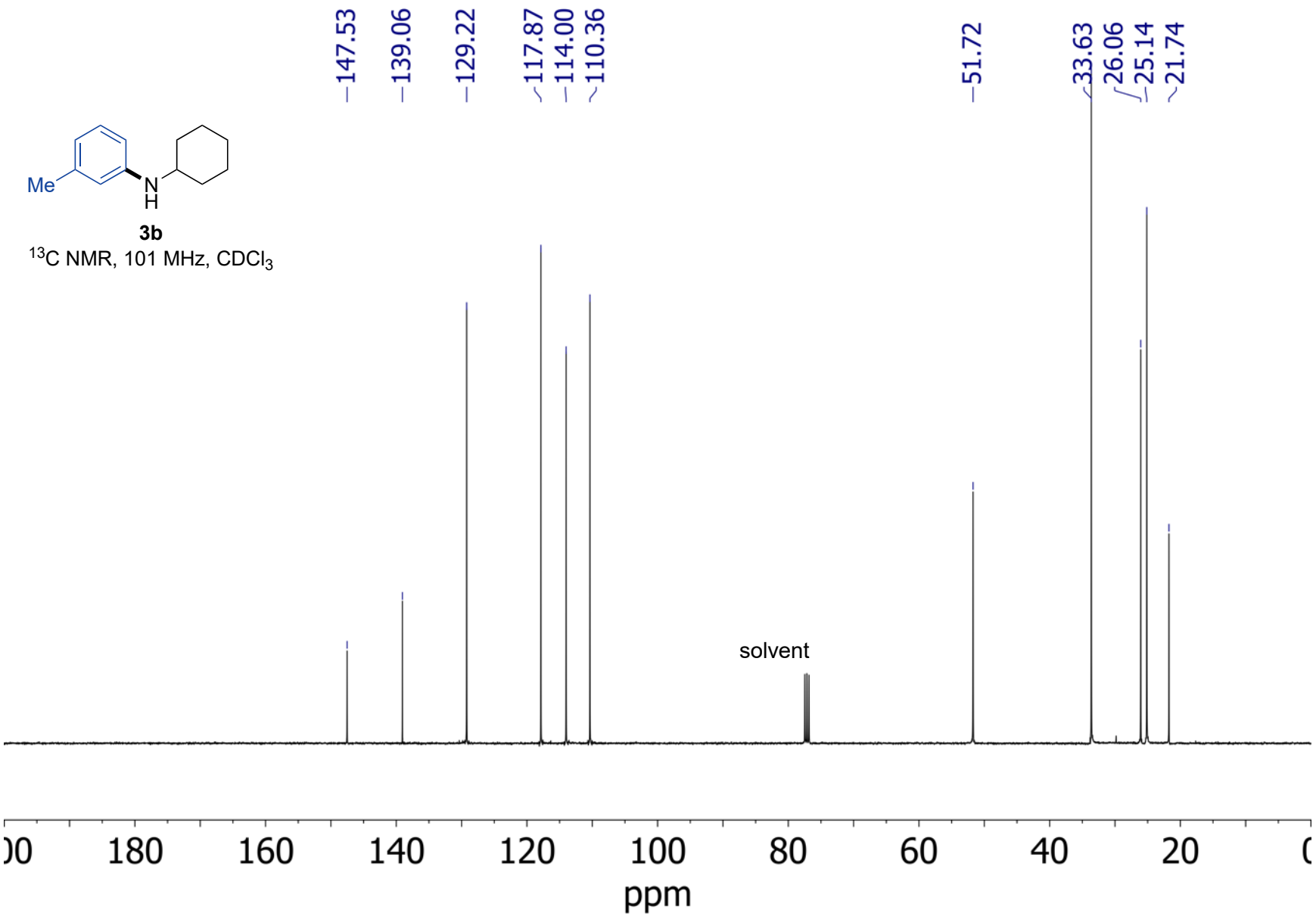
3a

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



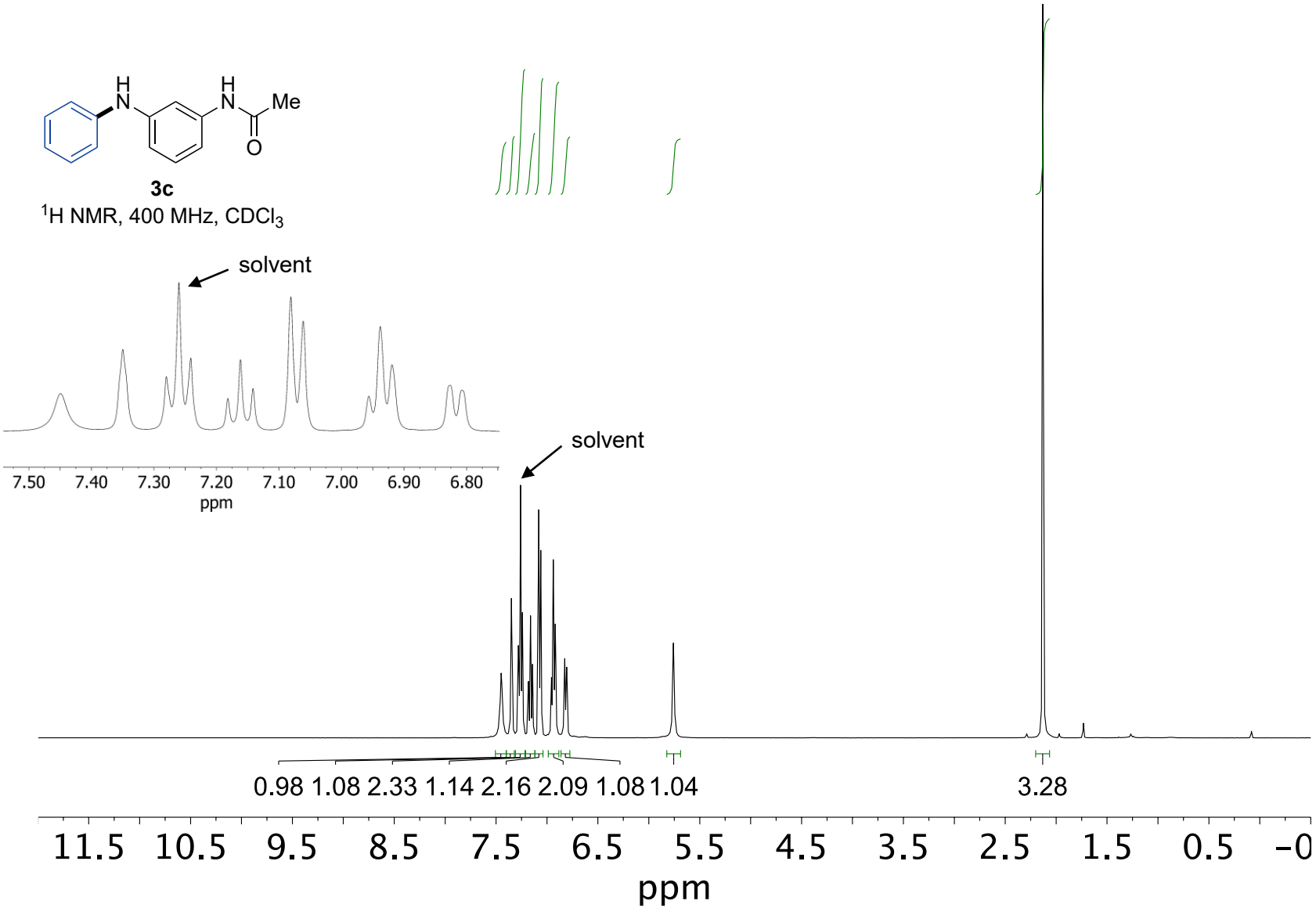
3b

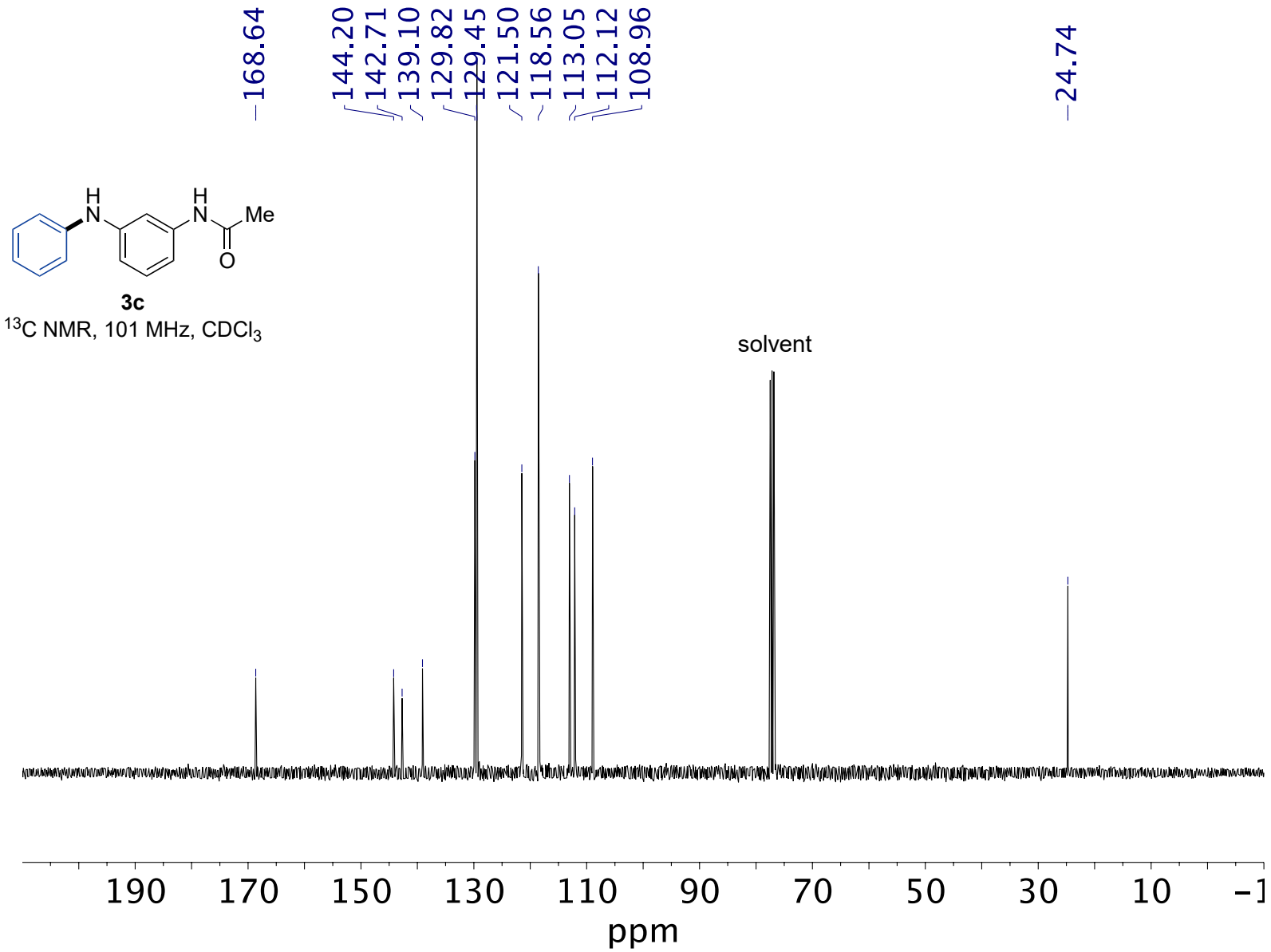
^{1}H NMR, 500 MHz, $CDCl_3$

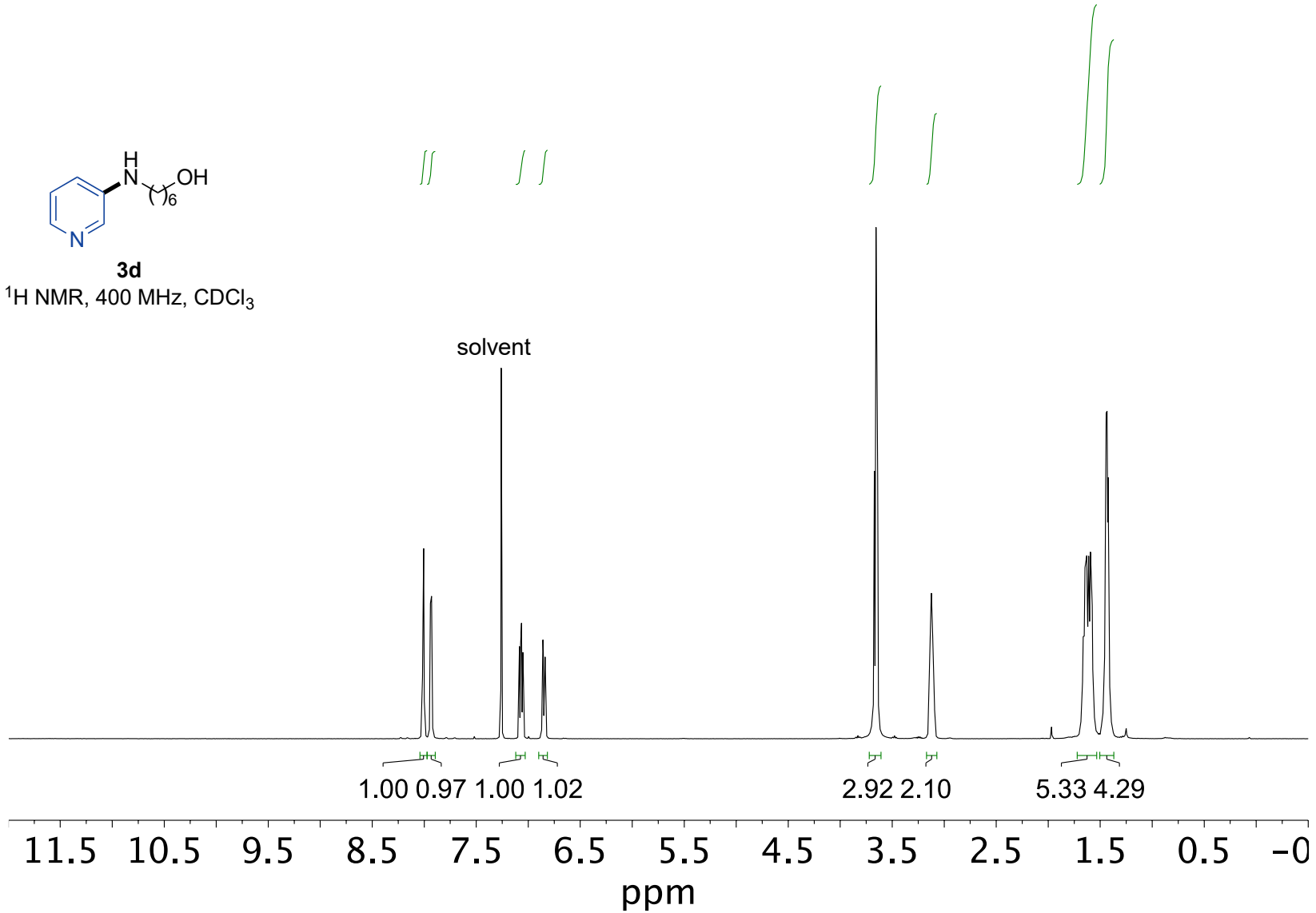


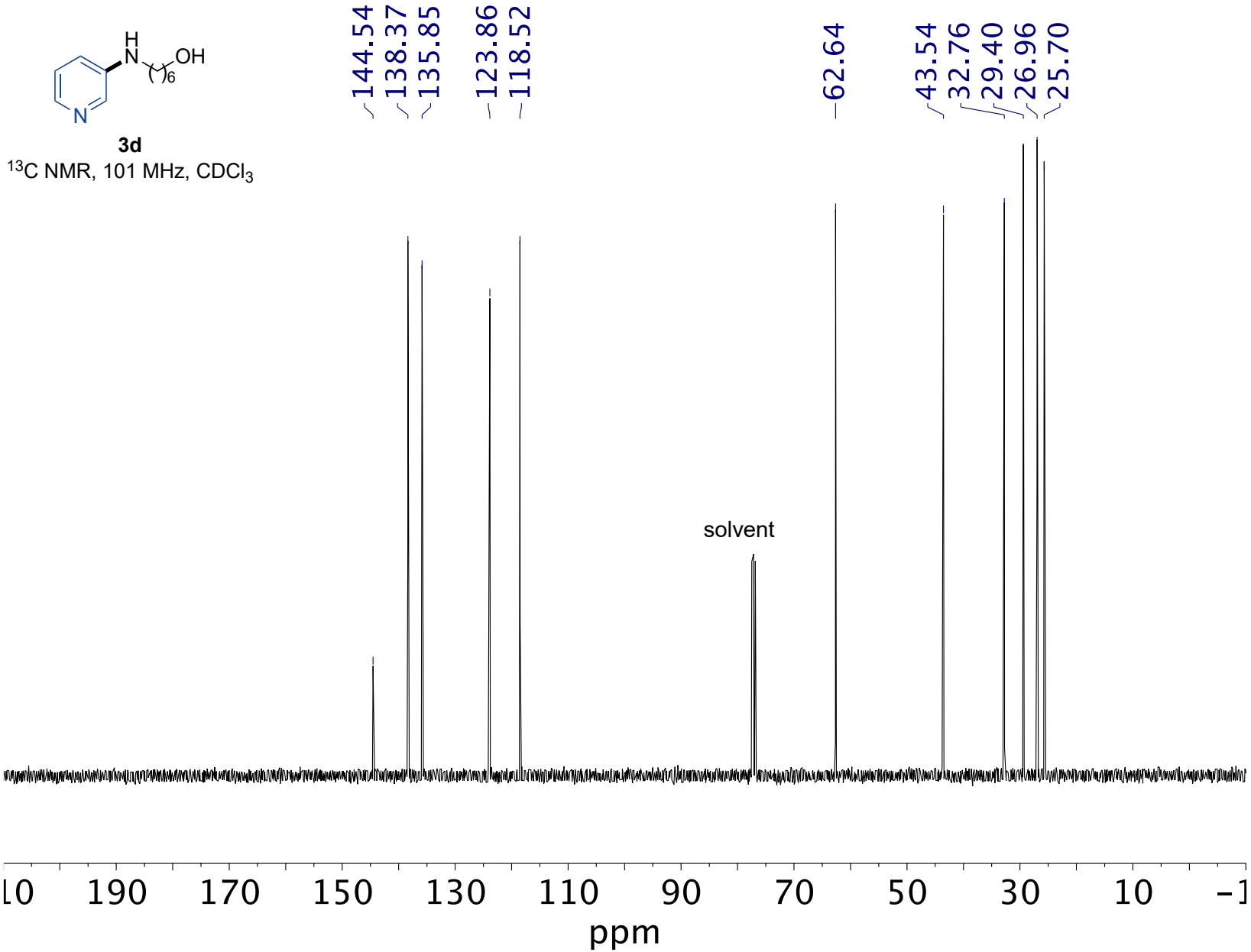
3b

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


H
N
H
N
Me
O
3c
1H NMR, 400 MHz, CDCl3
solvent
7.50 7.40 7.30 7.20 7.10 7.00 6.90 6.80
ppm
solvent
0.98 1.08 2.33 1.14 2.16 2.09 1.08 1.04
3.28
11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm

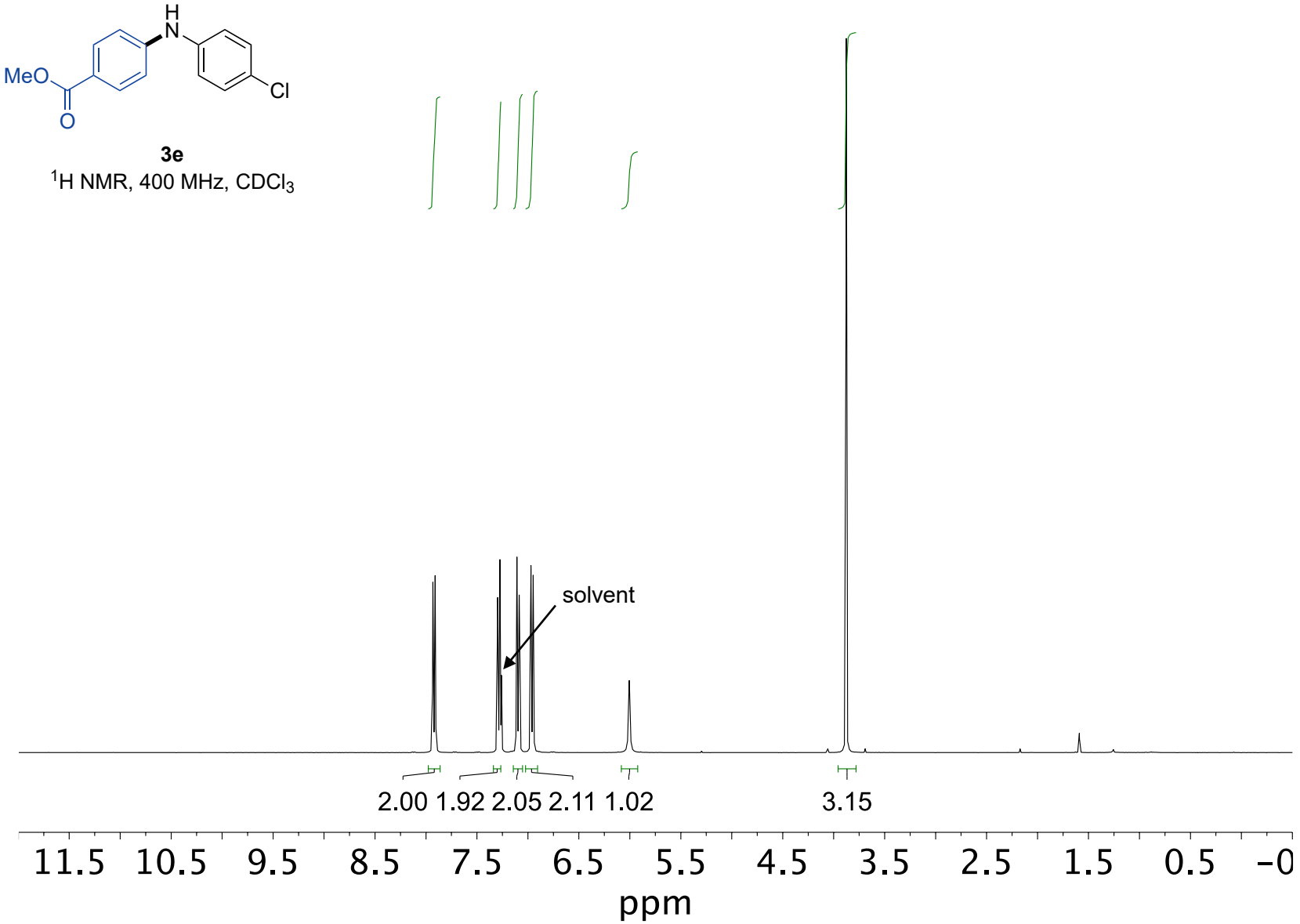

168.64
144.20
142.71
139.10
129.82
129.45
121.50
118.56
113.05
112.12
108.96
24.74
H
N
H
N
Me
O
3c
13C NMR, 101 MHz, CDCl3
solvent
190
170
150
130
110
90
70
50
30
10
-1
ppm

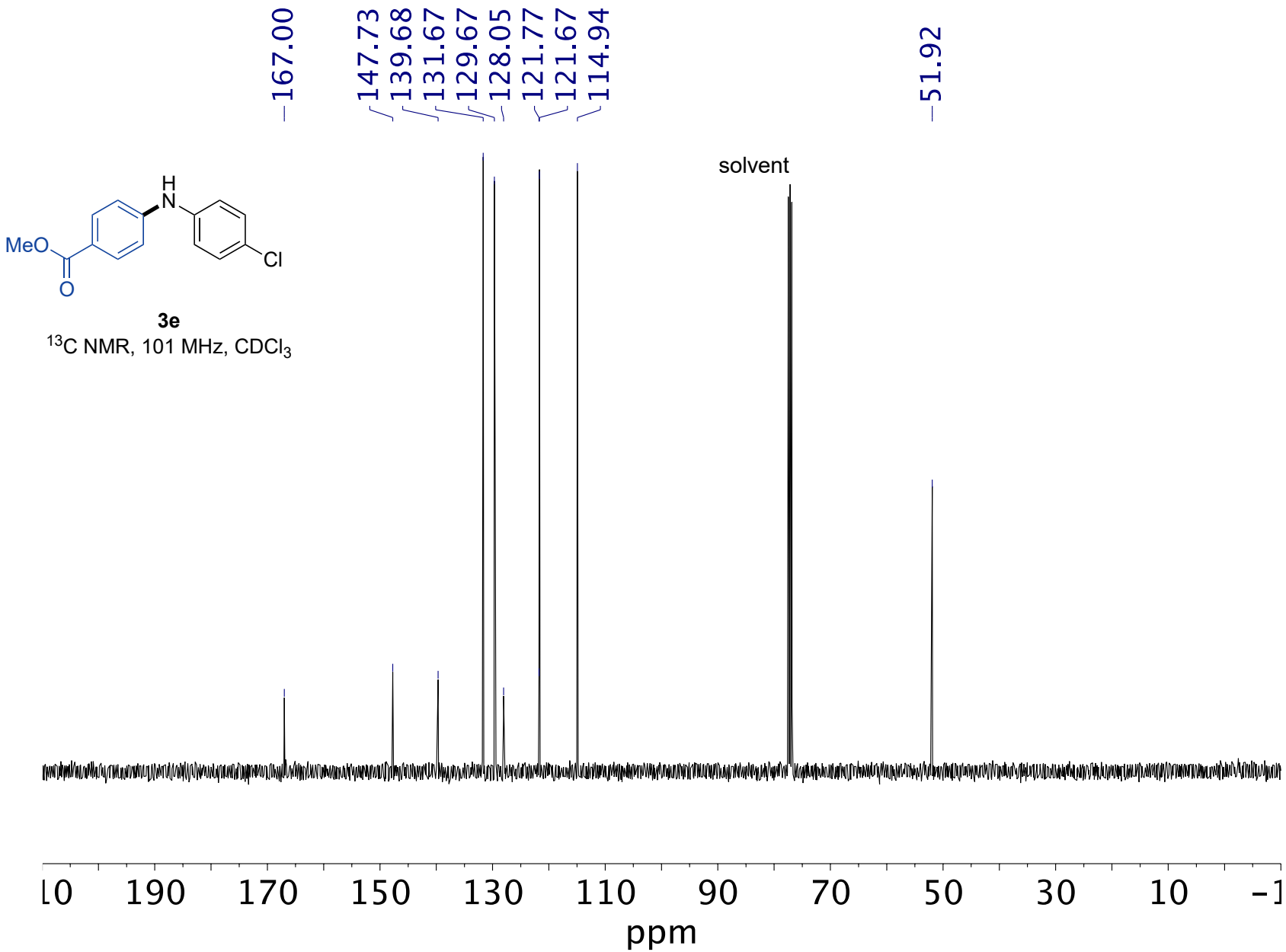

H
N
OH
6
N
3d
1H NMR, 400 MHz, CDCl3
solvent
1.00 0.97 1.00 1.02
2.92 2.10
5.33 4.29
11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm

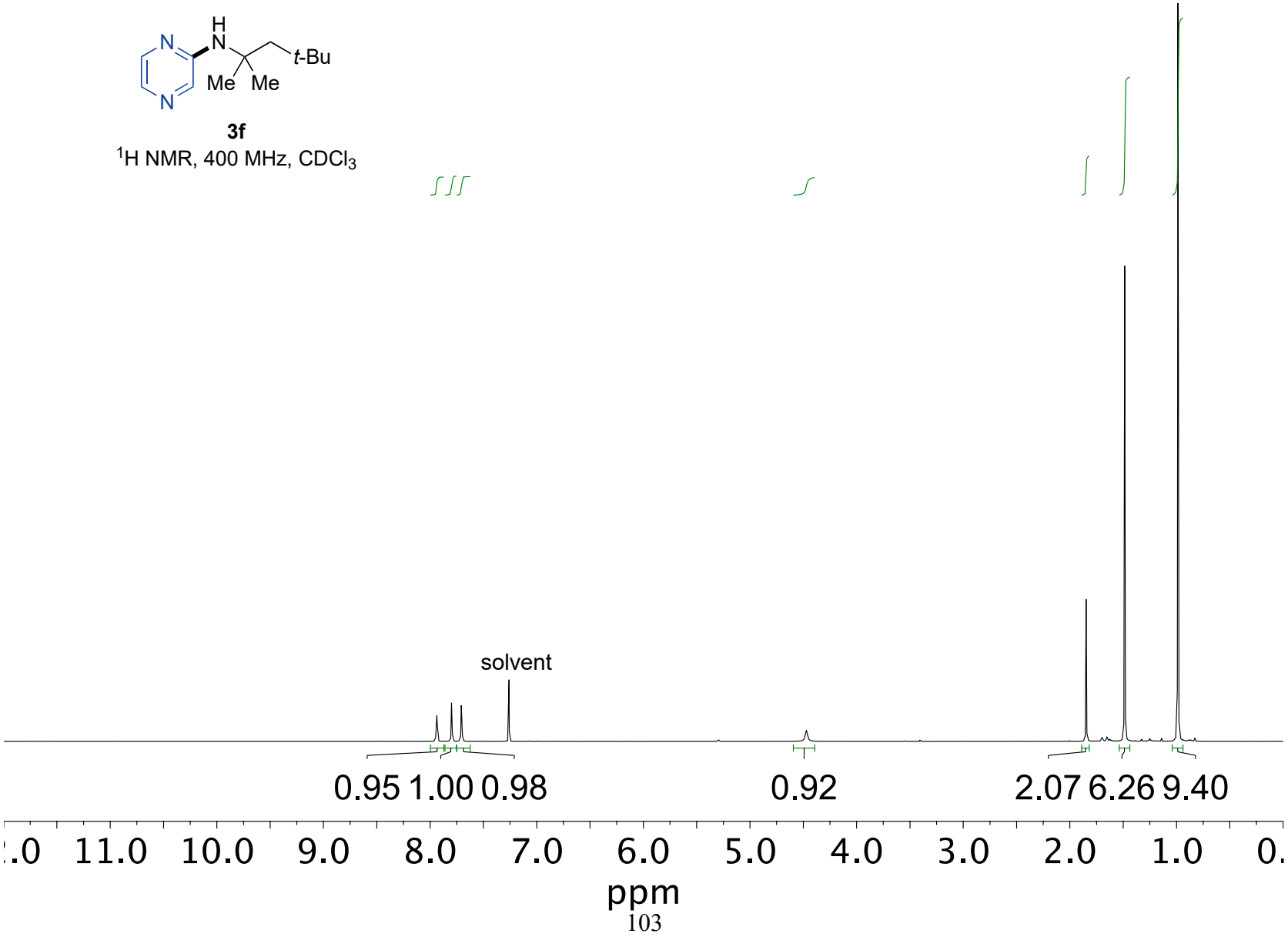


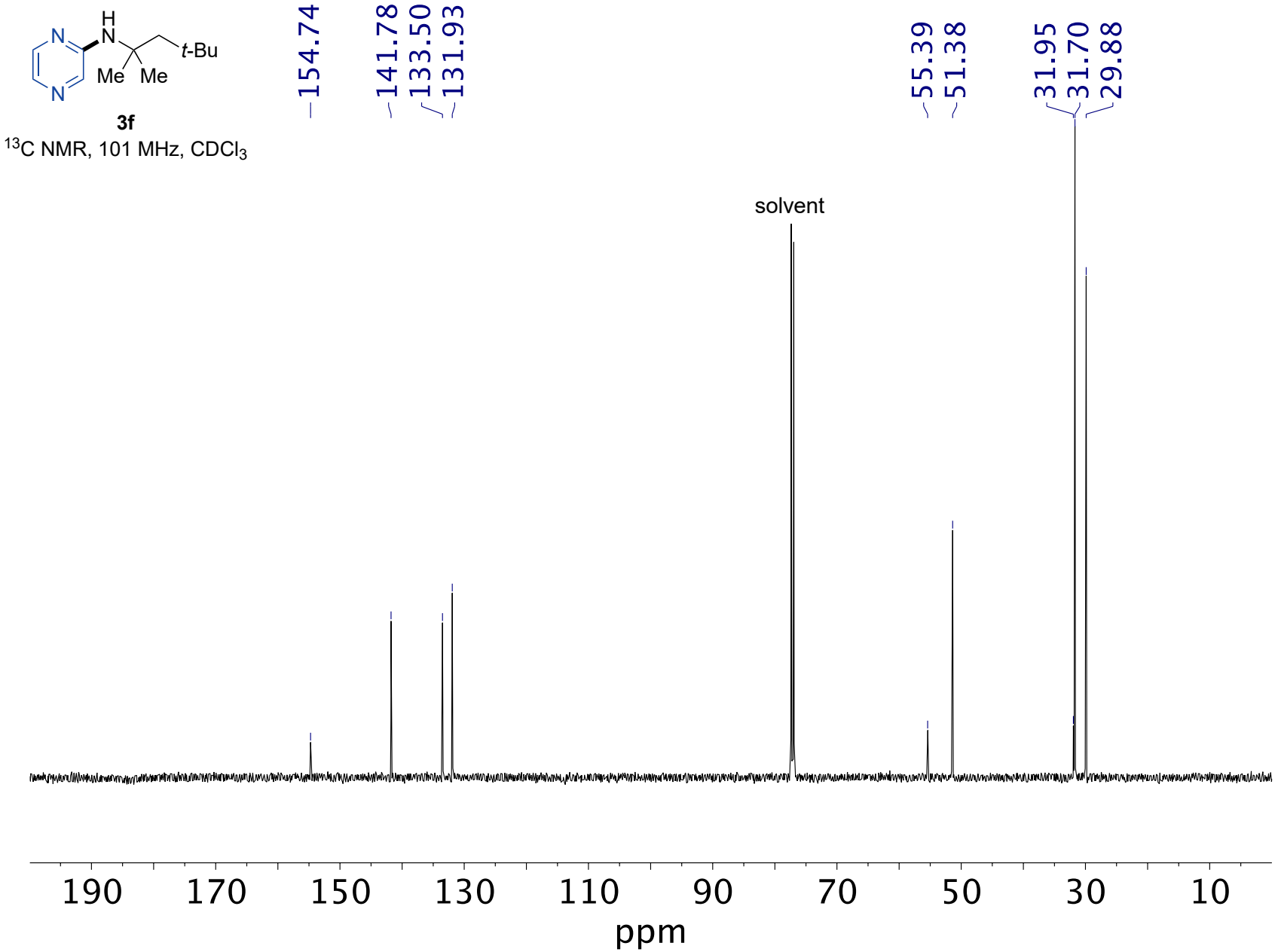
3d

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


MeO
O
H
N
Cl
3e
1H NMR, 400 MHz, CDCl3
solvent
2.00 1.92 2.05 2.11 1.02
3.15
11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm

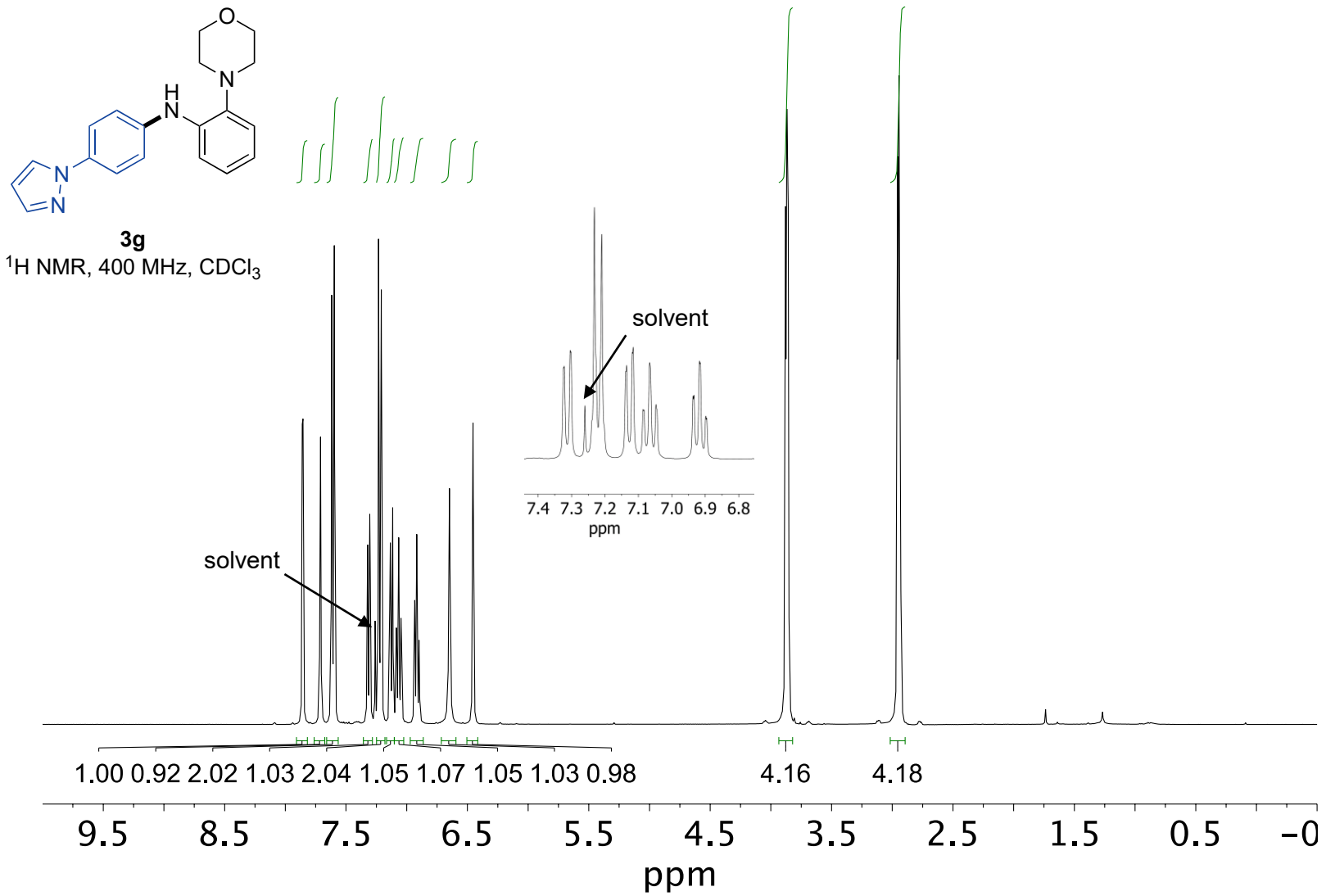

167.00
147.73
139.68
131.67
129.67
128.05
121.77
121.67
114.94
51.92
solvent
MeO
O
H
N
Cl
3e
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm

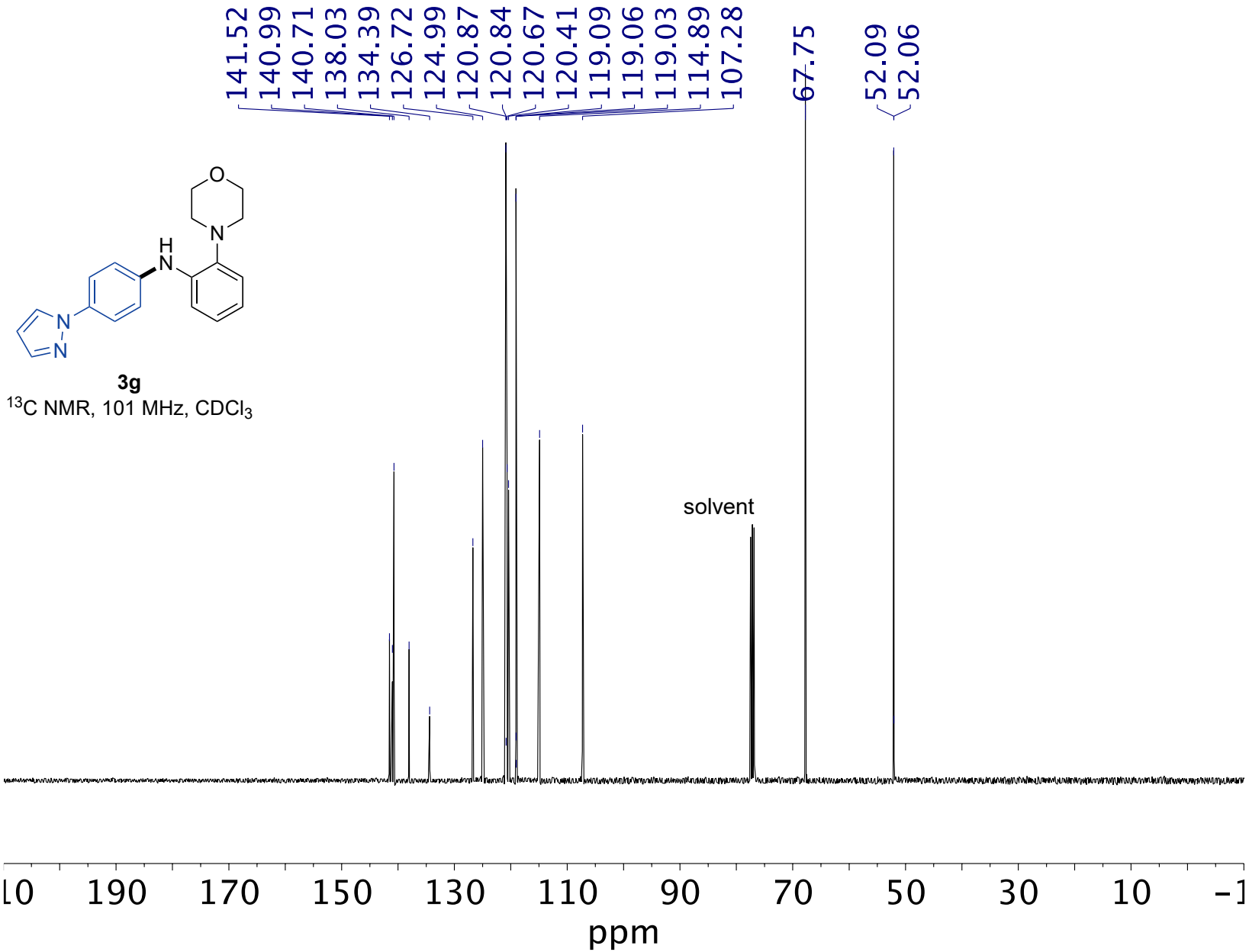

N
H
N
t-Bu
Me
Me
N
3f
1H NMR, 400 MHz, CDCl3
solvent
0.95 1.00 0.98
0.92
2.07 6.26 9.40
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm



3f

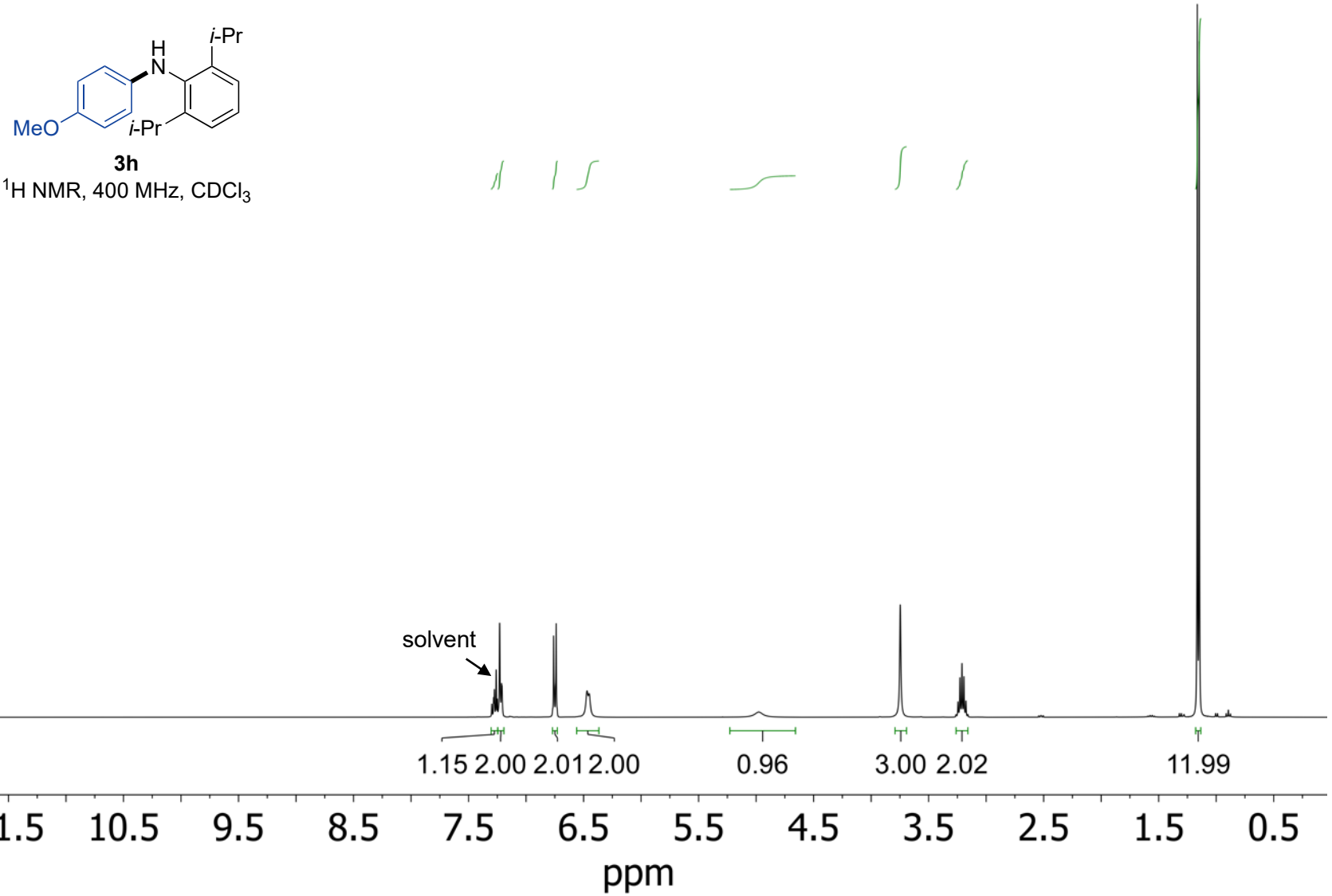
^{13}C NMR, 101 MHz, $CDCl_3$

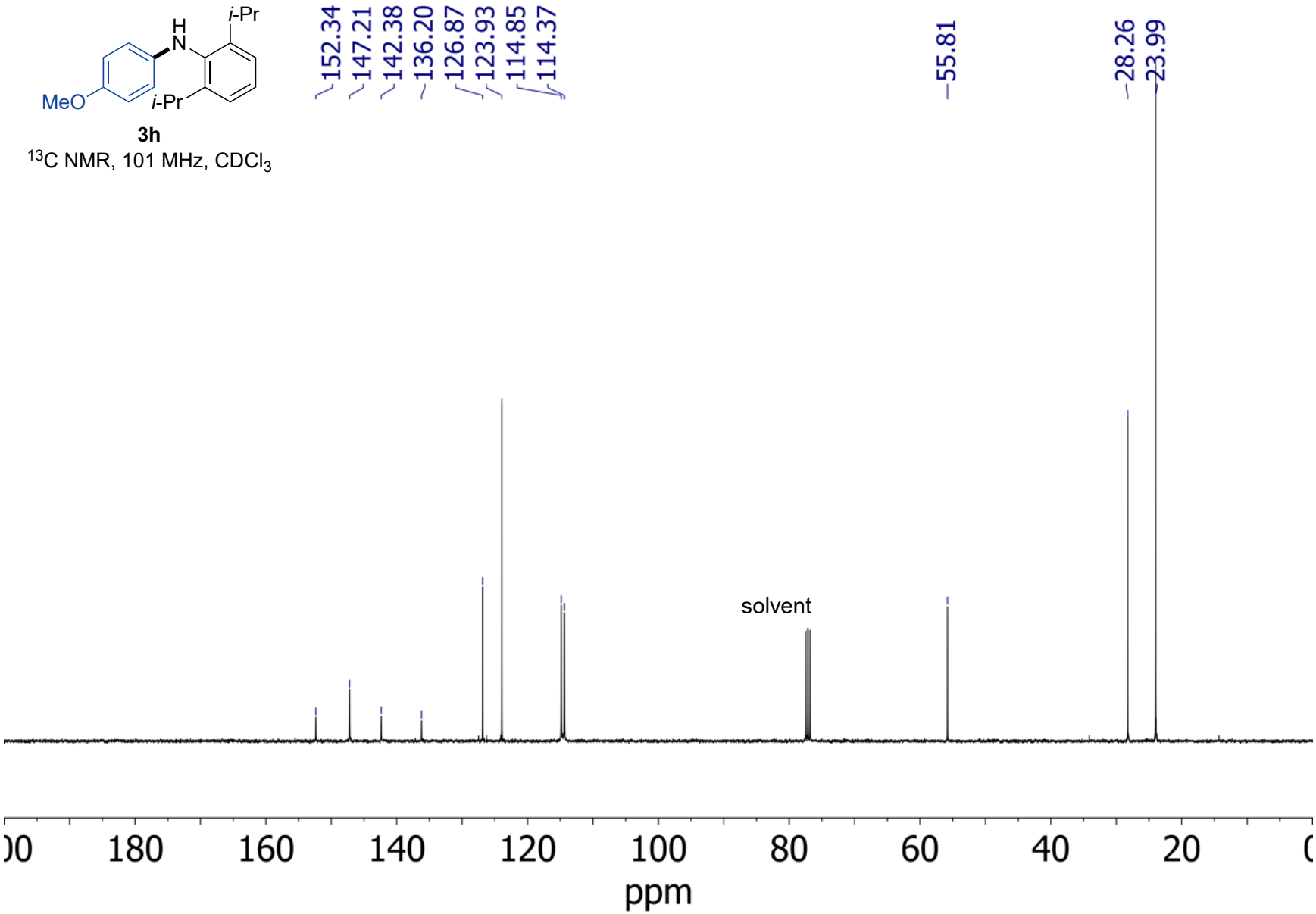

O
N
H
N
N
N
3g
1H NMR, 400 MHz, CDCl3
solvent
7.4 7.3 7.2 7.1 7.0 6.9 6.8
ppm
solvent
1.00 0.92 2.02 1.03 2.04 1.05 1.07 1.05 1.03 0.98
4.16
4.18
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm



3g

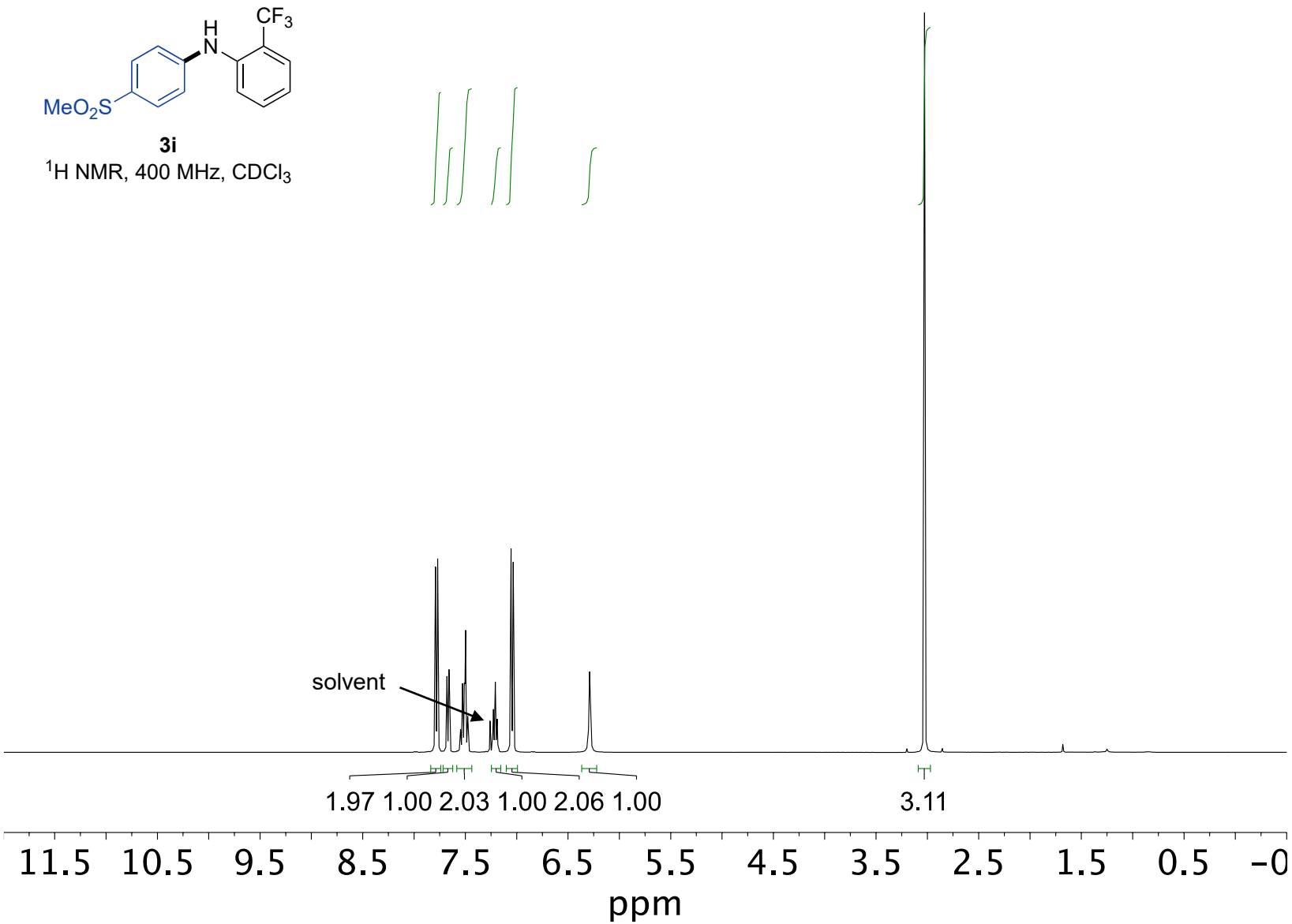
^{13}C NMR, 101 MHz, $CDCl_3$

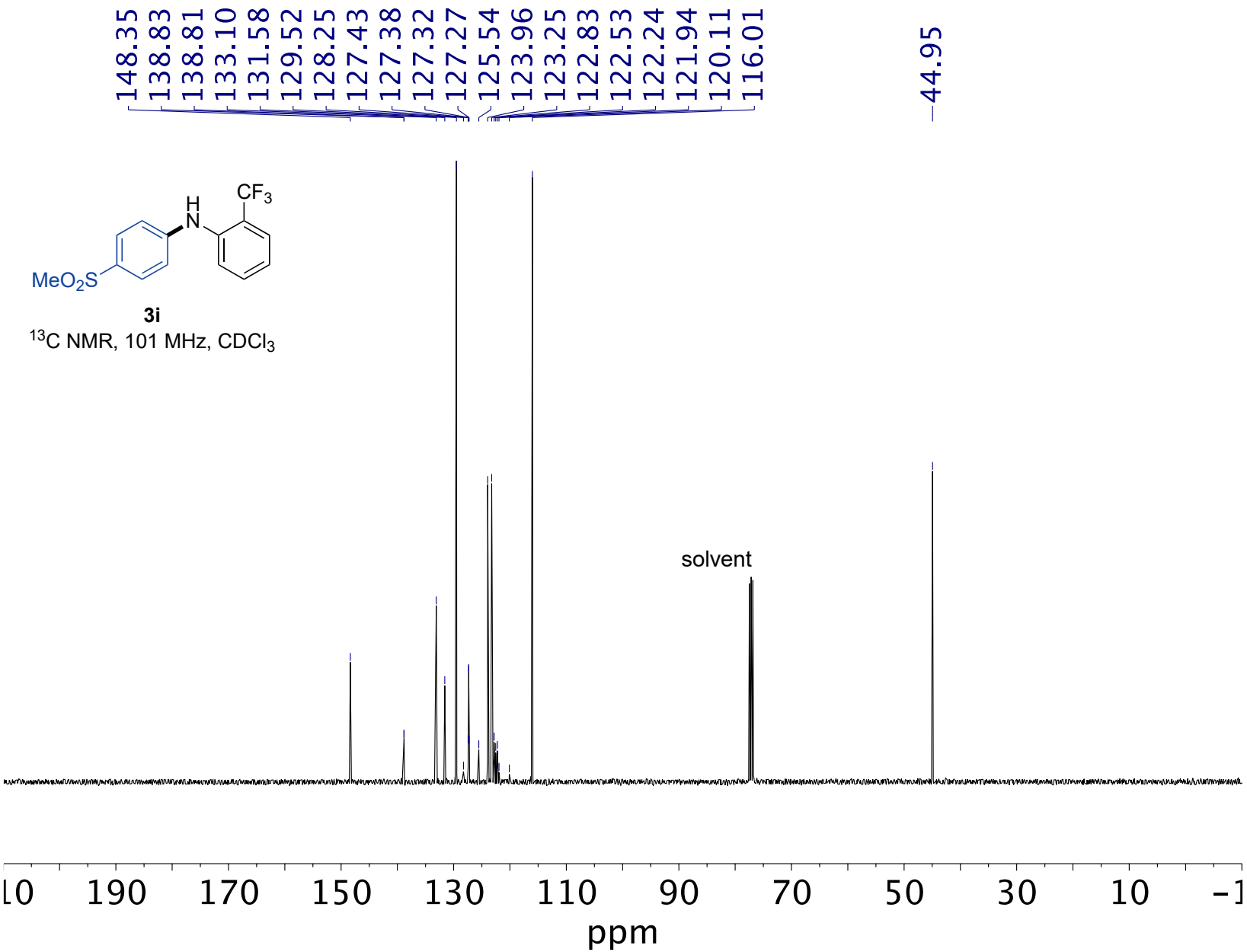

i-Pr
H
N
MeO
i-Pr
3h
1H NMR, 400 MHz, CDCl3
solvent
1.15 2.00 2.01 2.00
0.96
3.00 2.02
11.99
11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5
ppm

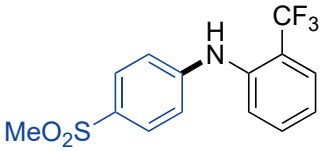


3h

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

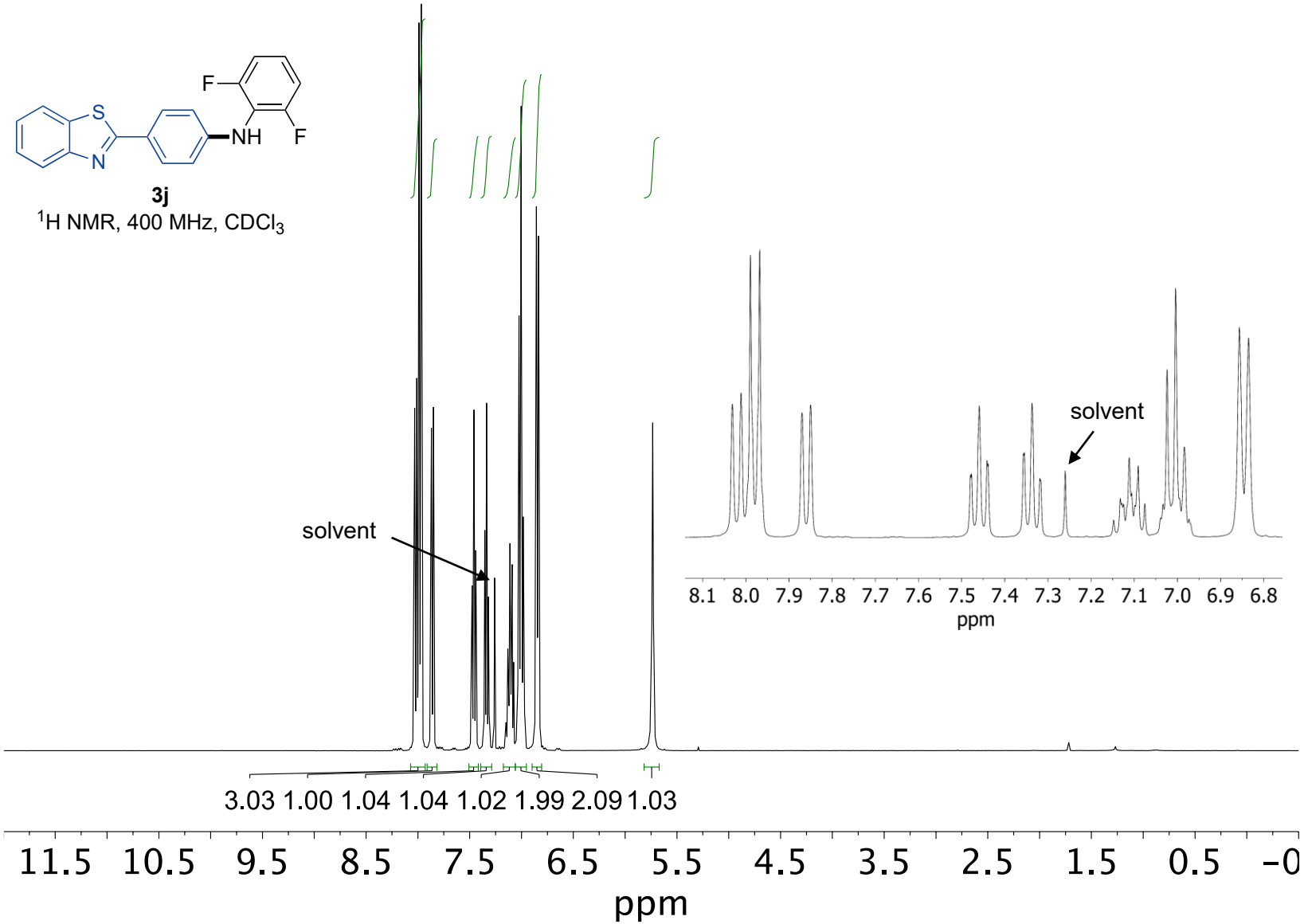

CF3
H
N
MeO2S
3i
1H NMR, 400 MHz, CDCl3
solvent
1.97 1.00 2.03 1.00 2.06 1.00
3.11
11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm

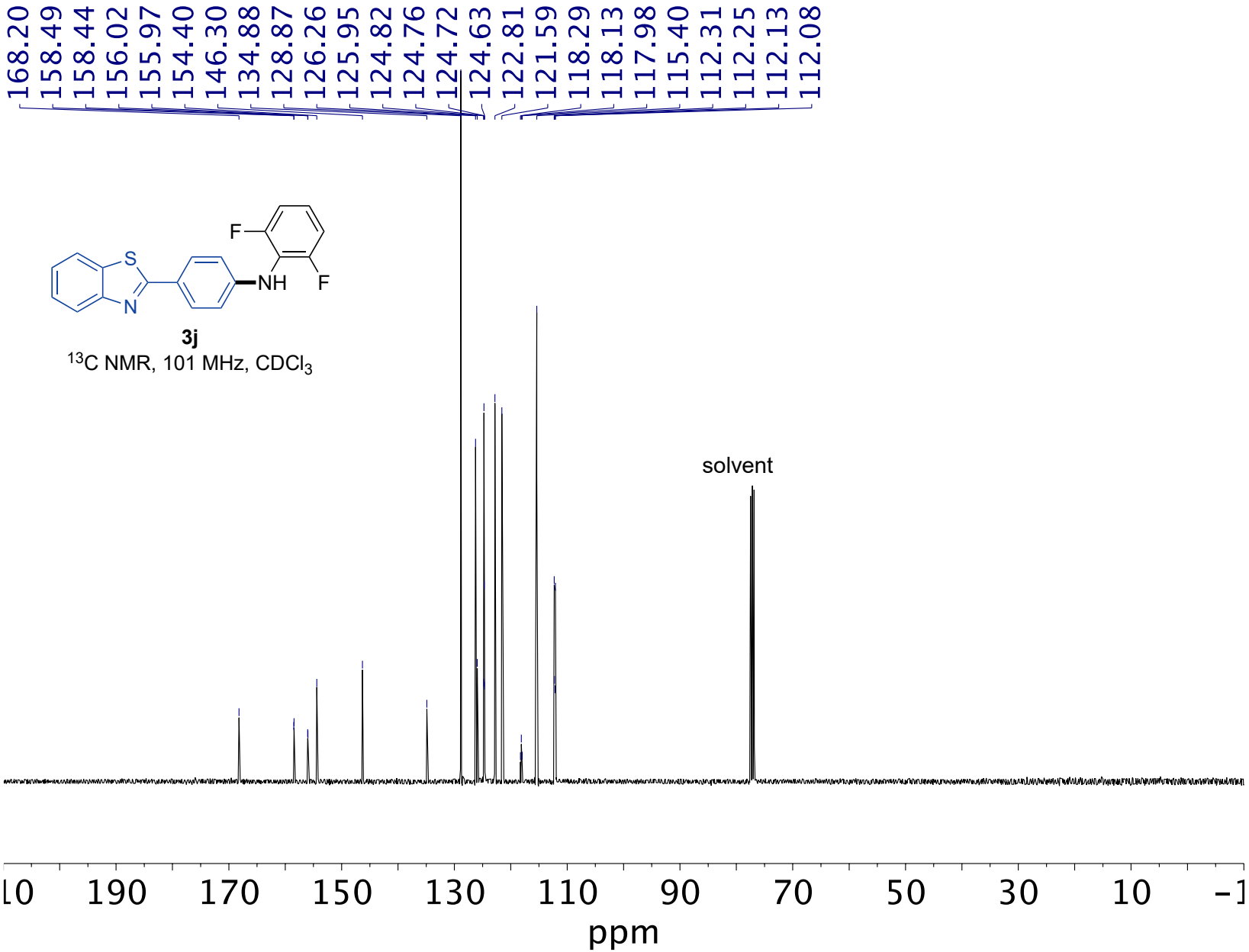

148.35
138.83
138.81
133.10
131.58
129.52
128.25
127.43
127.38
127.32
127.27
125.54
123.96
123.25
122.83
122.53
122.24
121.94
120.11
116.01
44.95
CF3
H
N
MeO2S
3i
13C NMR, 101 MHz, CDCl3
solvent
190
170
150
130
110
90
70
50
30
10
ppm



3i

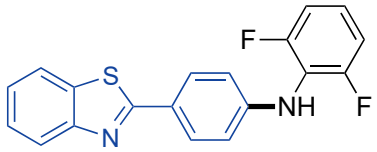
^{19}F NMR, 376 MHz, $CDCl_3$


F
S
NH
F
N
3j
1H NMR, 400 MHz, CDCl3
solvent
solvent
8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
ppm
3.03 1.00 1.04 1.04 1.02 1.99 2.09 1.03
11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm



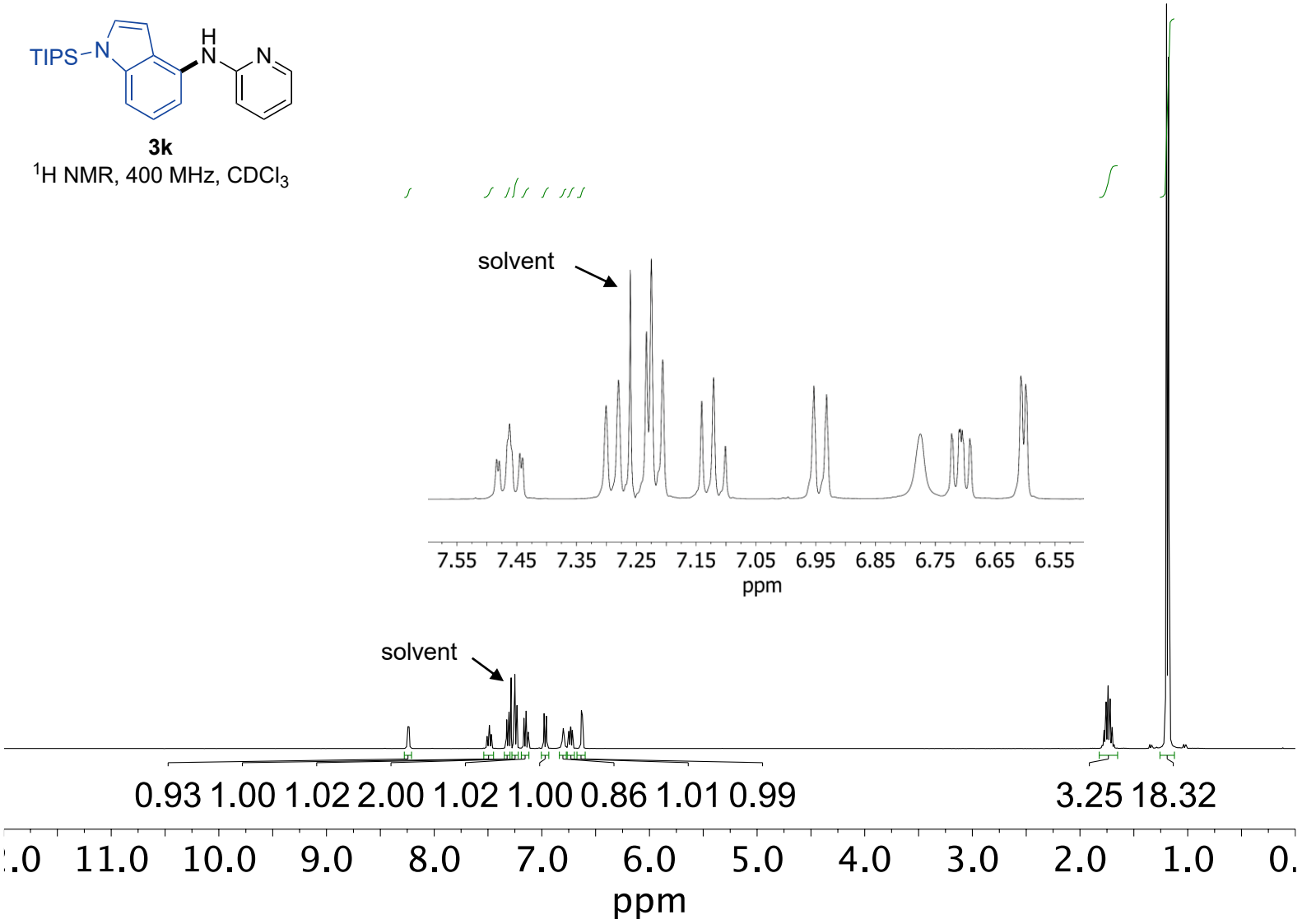
3j

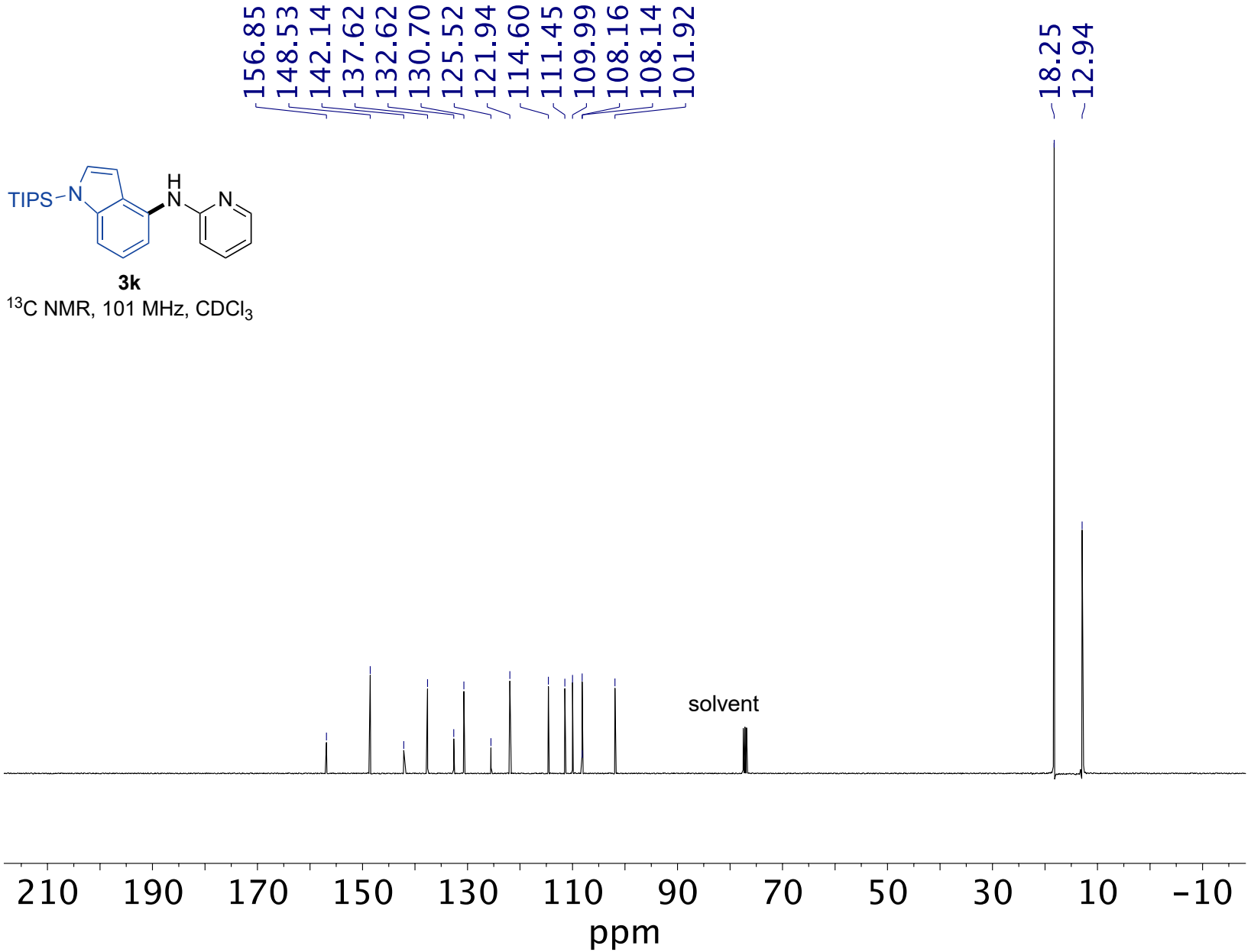
^{13}C NMR, 101 MHz, $CDCl_3$



3j

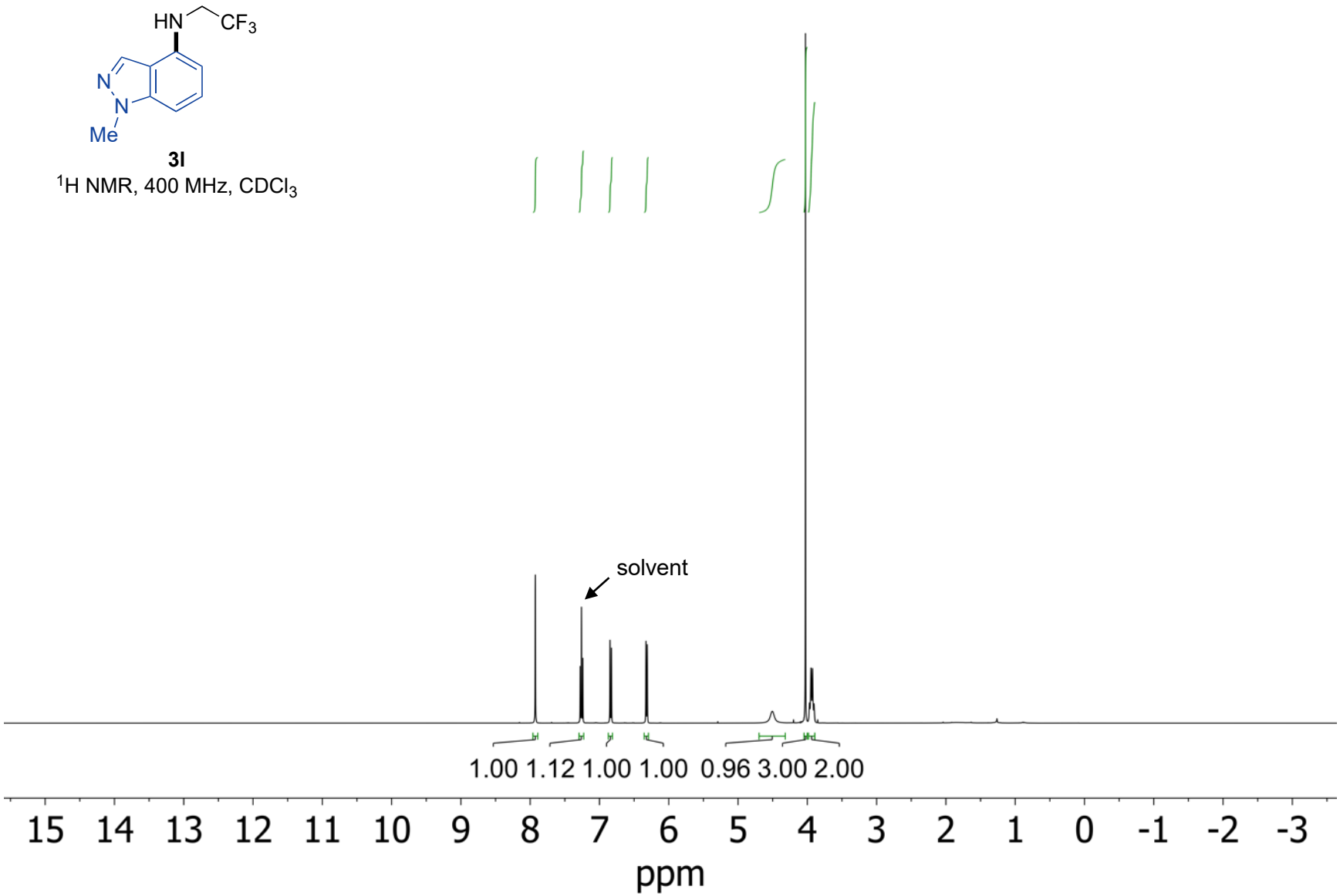
^{19}F NMR, 376 MHz, $CDCl_3$

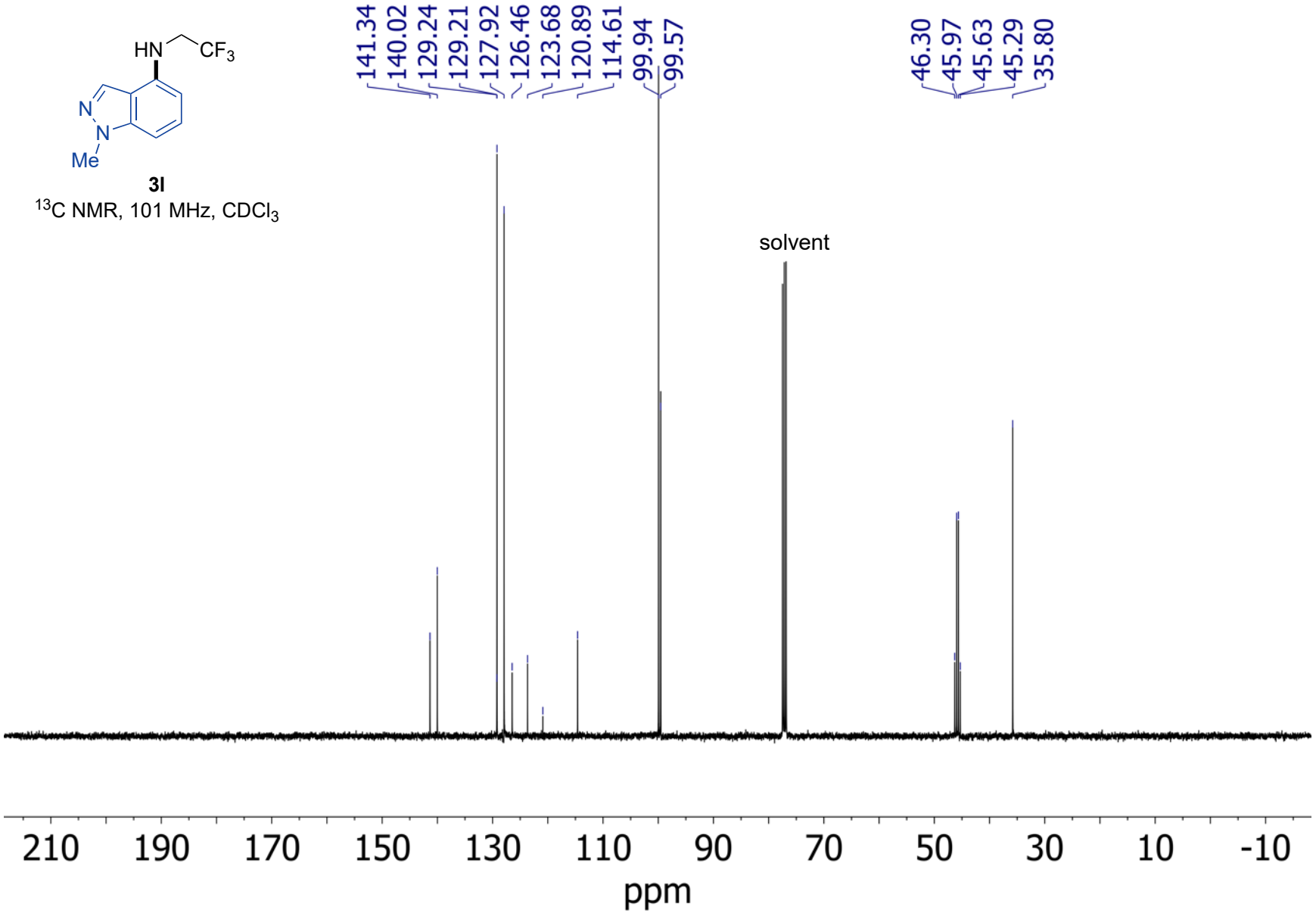

TIPS
N
H
N
N
3k
1H NMR, 400 MHz, CDCl3
solvent
7.55 7.45 7.35 7.25 7.15 7.05 6.95 6.85 6.75 6.65 6.55
ppm
solvent
0.93 1.00 1.02 2.00 1.02 1.00 0.86 1.01 0.99
3.25 18.32
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm

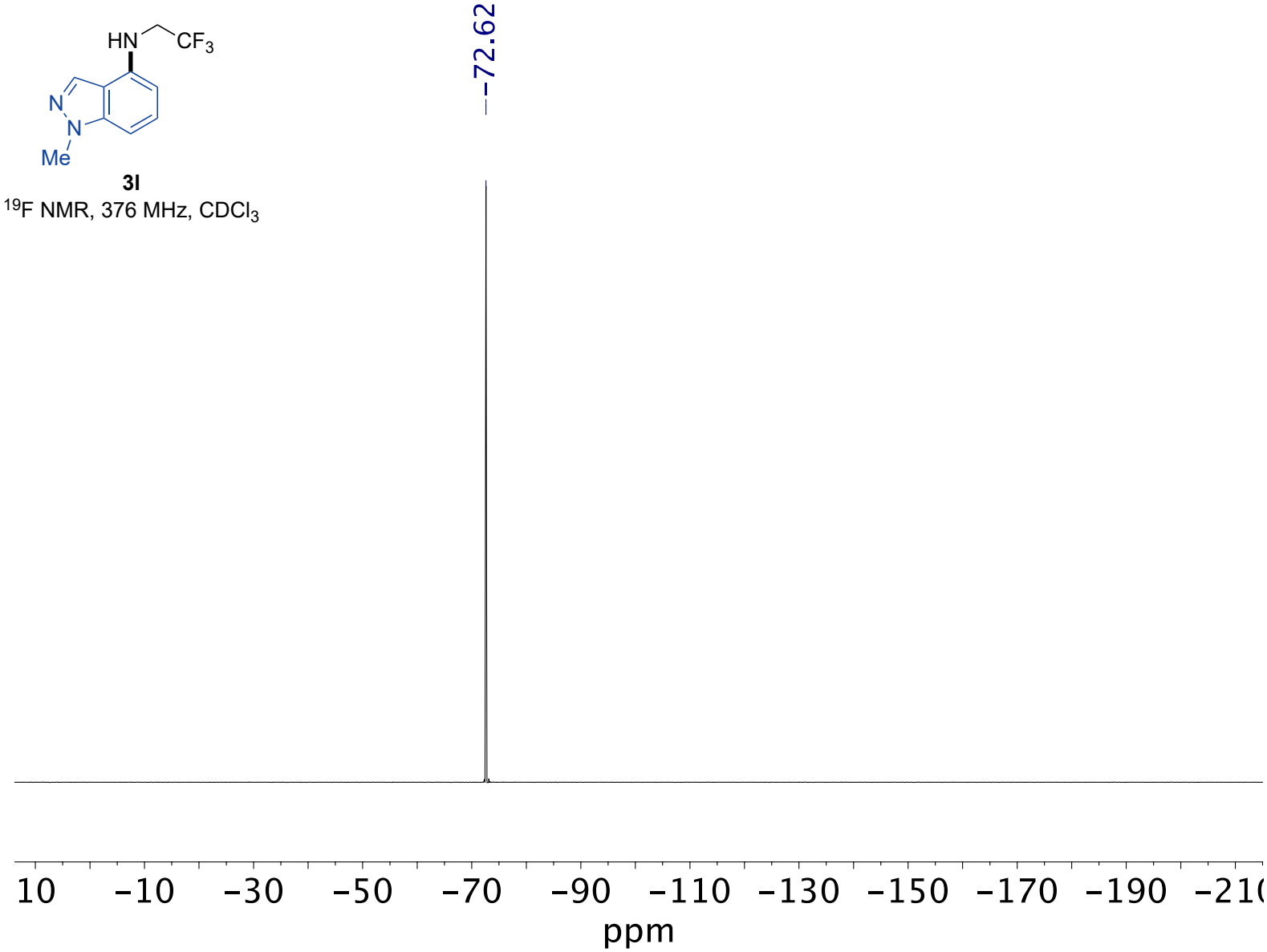


3k

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

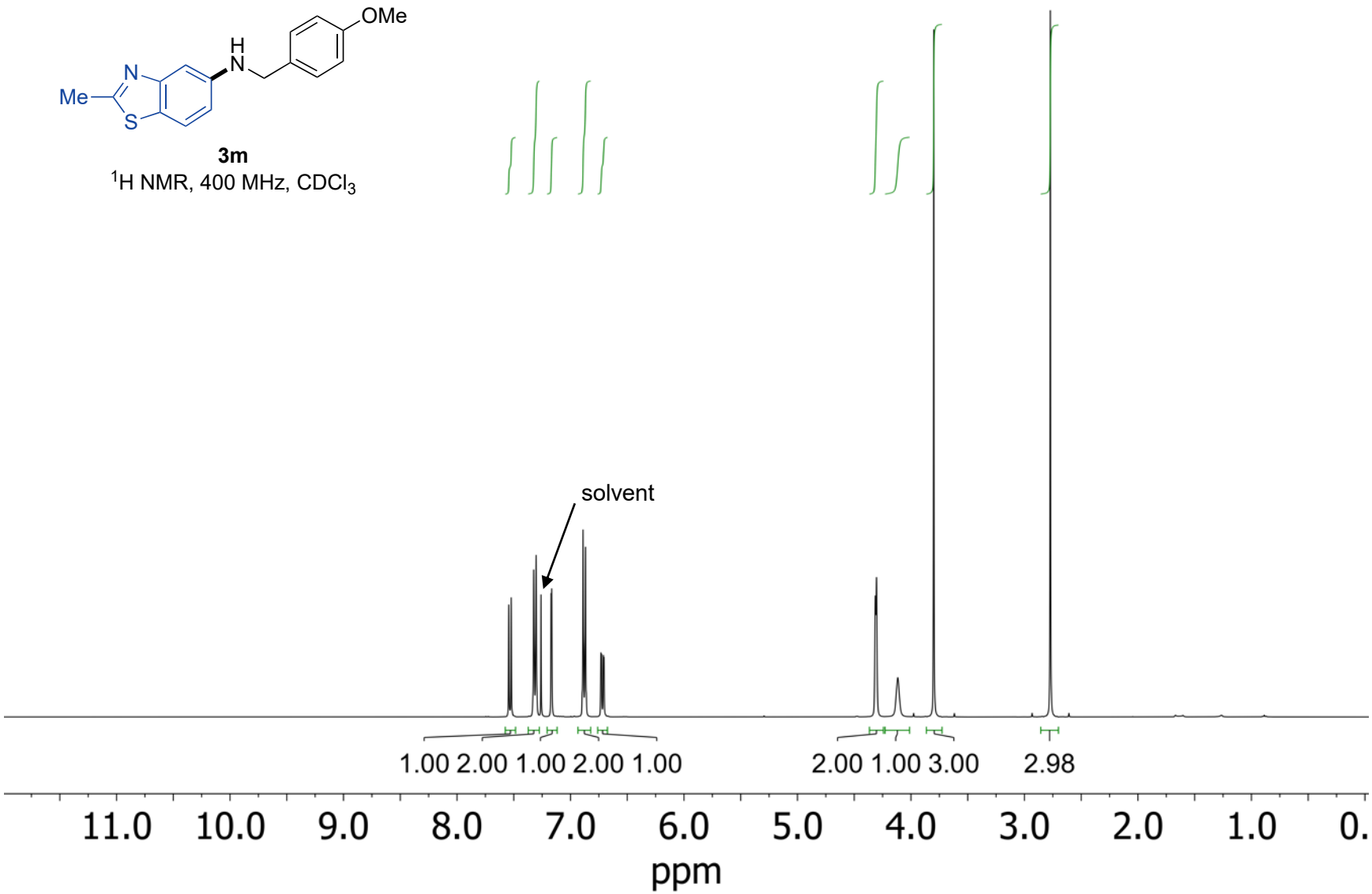

HN
CF3
N
N
Me
3l
1H NMR, 400 MHz, CDCl3
solvent
1.00 1.12 1.00 1.00 0.96 3.00 2.00
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
ppm

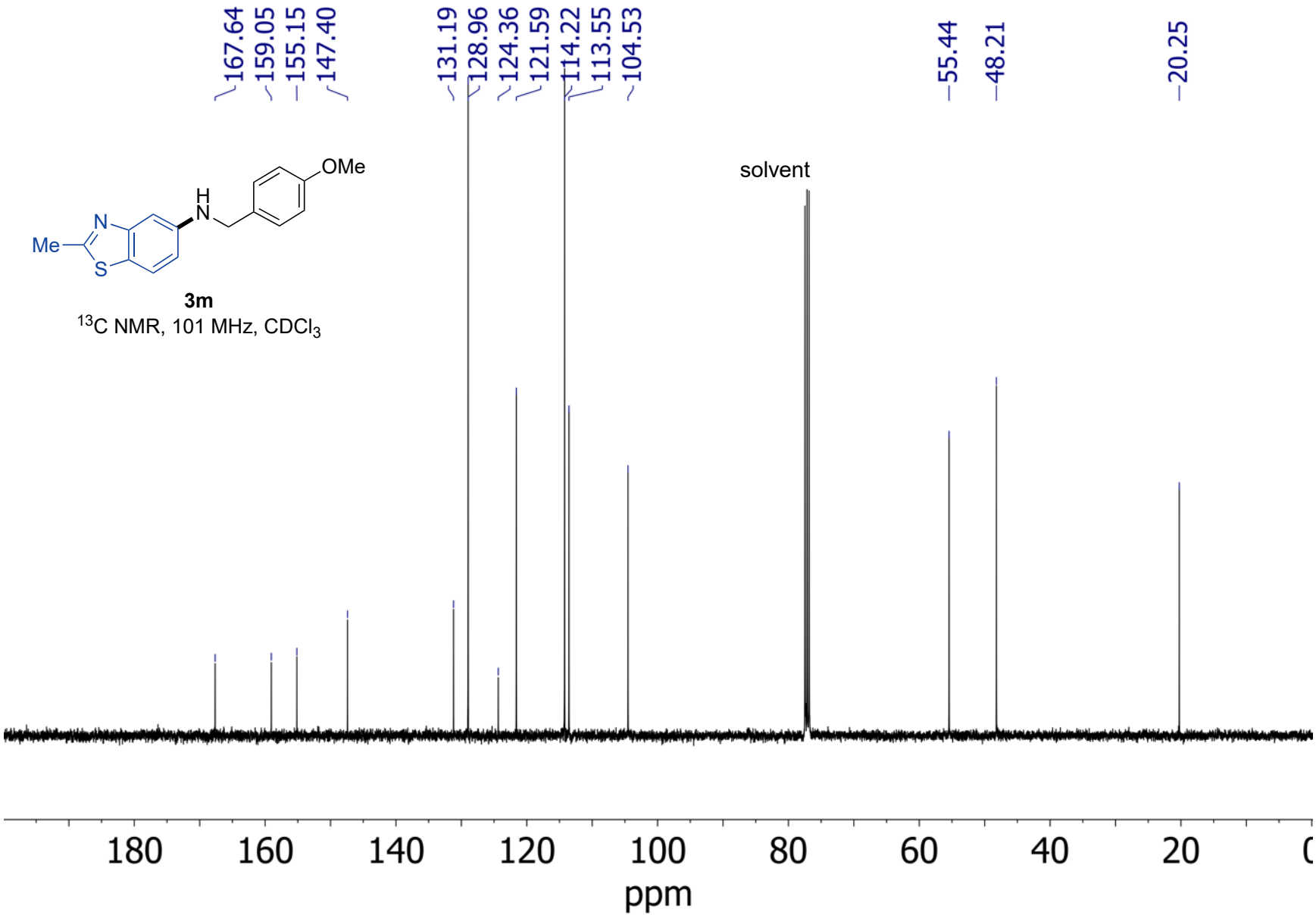

HN
CF3
N
N
Me
3l
13C NMR, 101 MHz, CDCl3
141.34
140.02
129.24
129.21
127.92
126.46
123.68
120.89
114.61
99.94
99.57
46.30
45.97
45.63
45.29
35.80
solvent
210
190
170
150
130
110
90
70
50
30
10
-10
ppm



3l

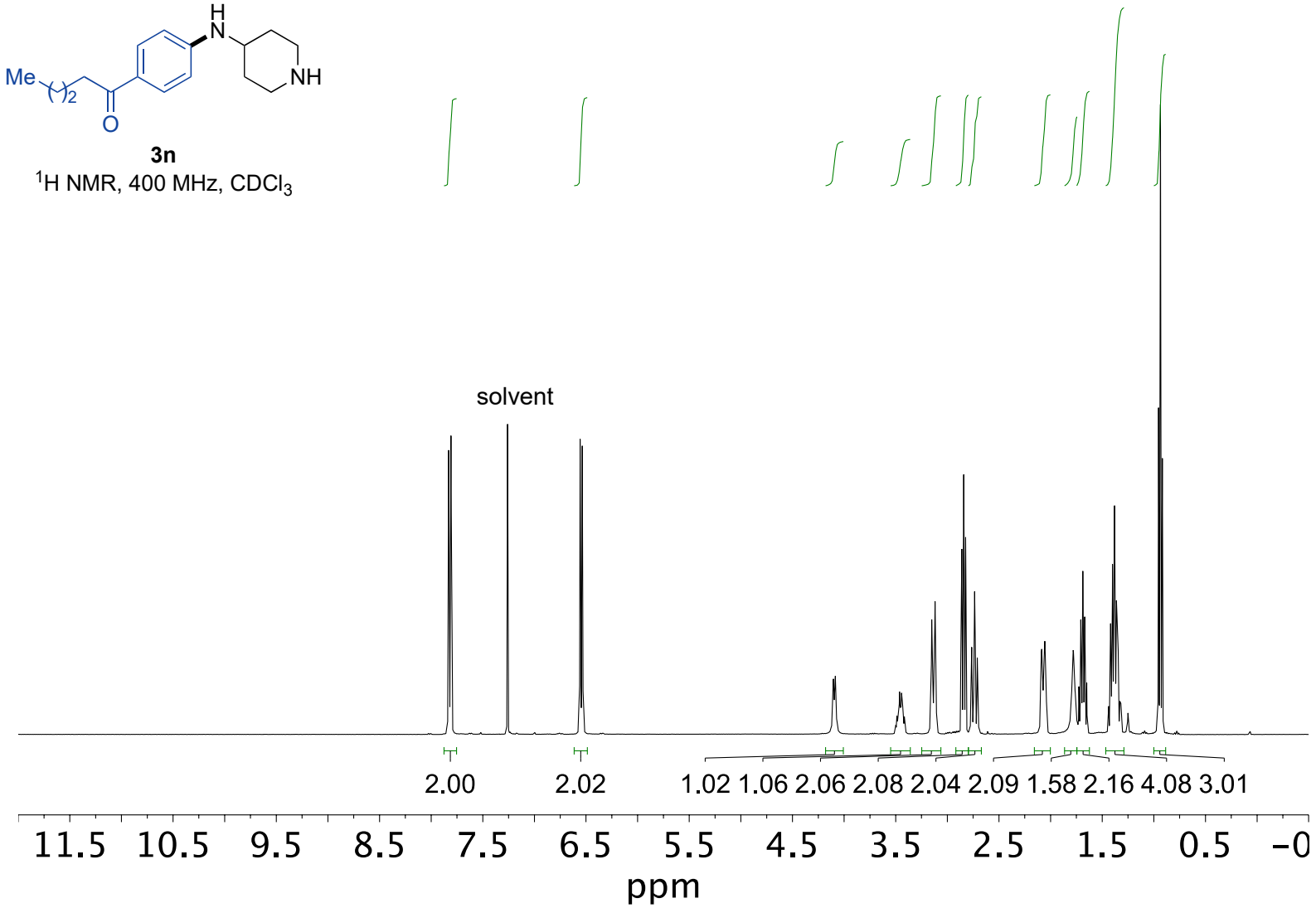
^{19}F NMR, 376 MHz, $CDCl_3$

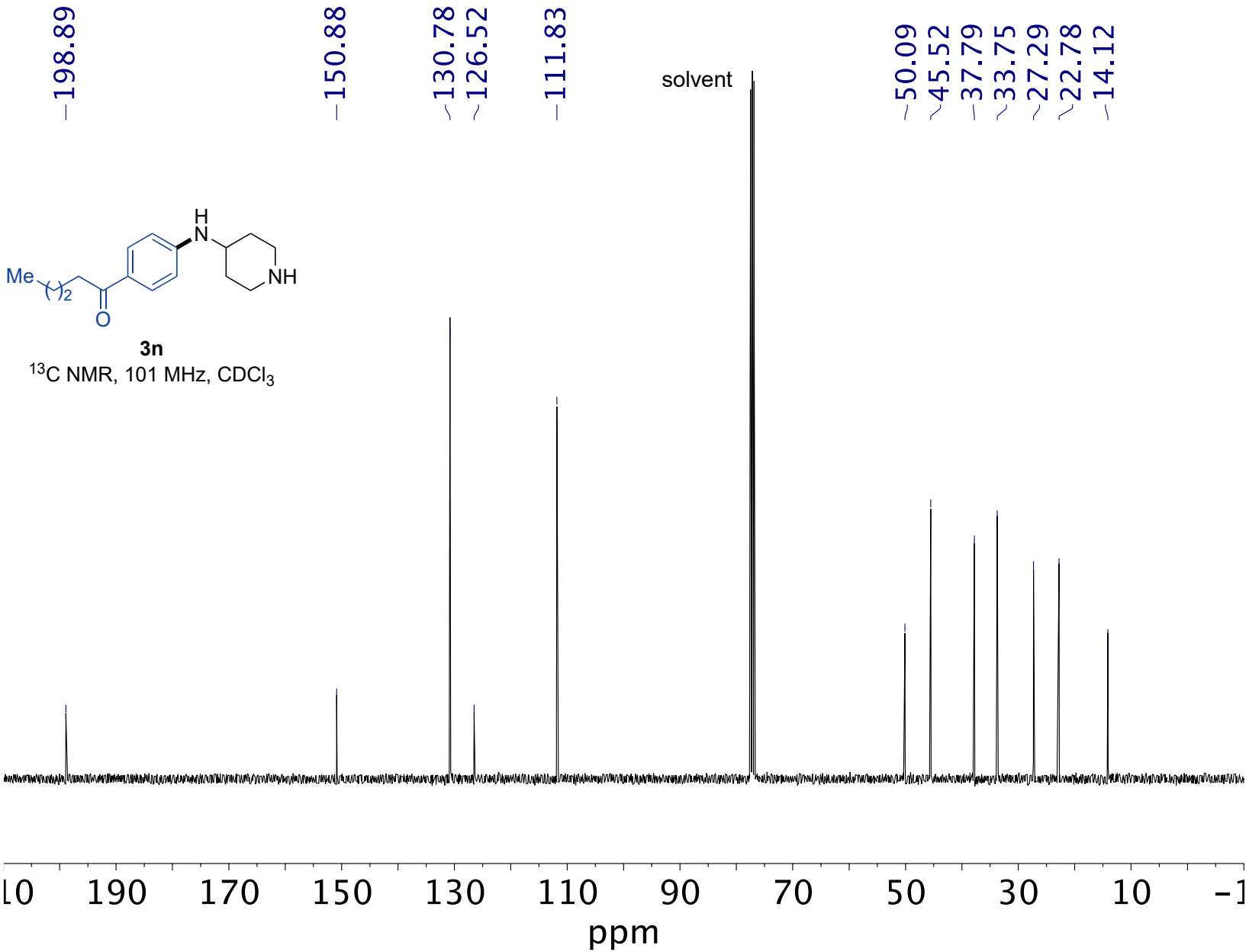

OMe
H
N
N
Me
S
3m
1H NMR, 400 MHz, CDCl3
solvent
1.00 2.00 1.00 2.00 1.00
2.00 1.00 3.00
2.98
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.
ppm

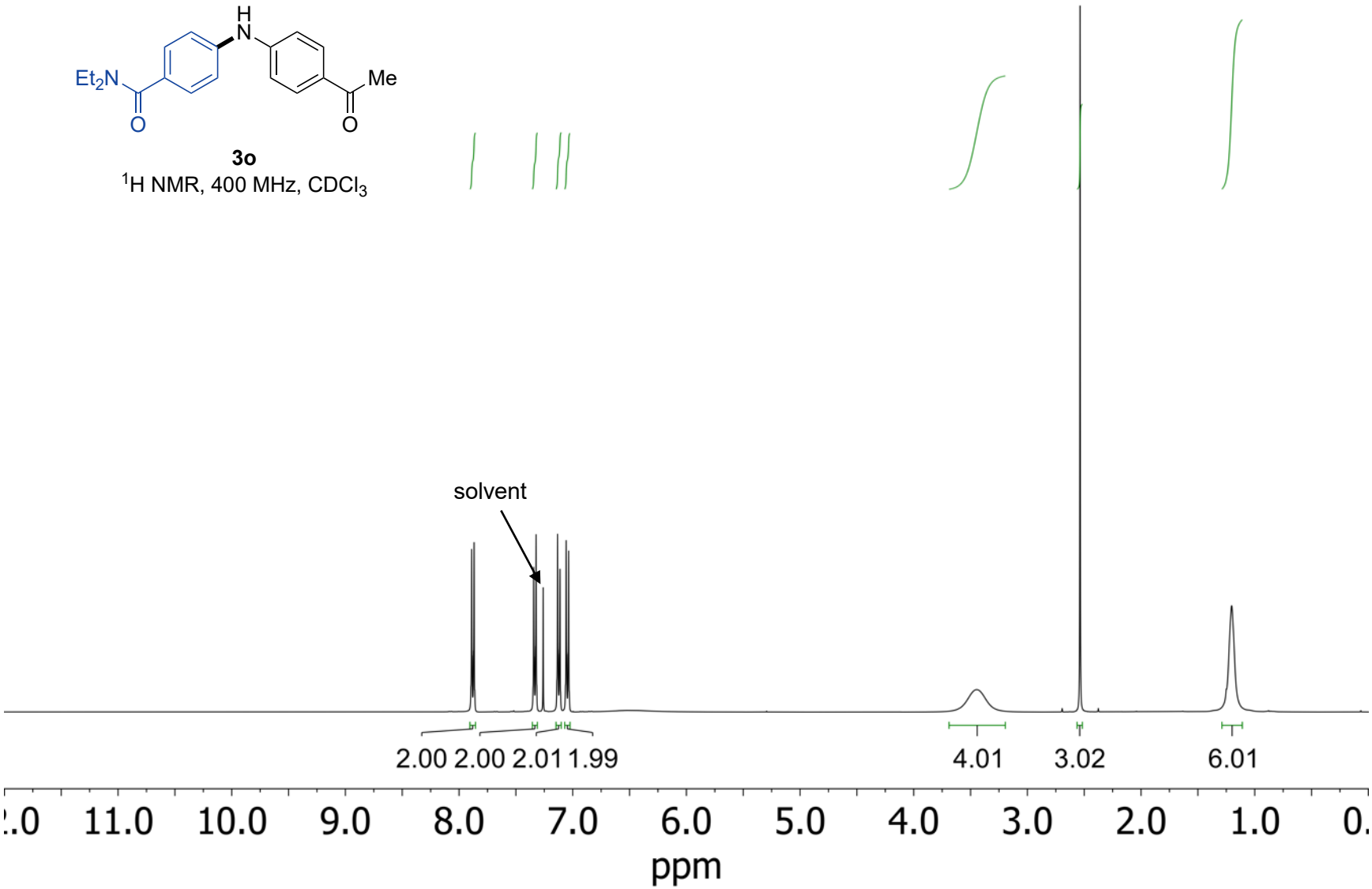


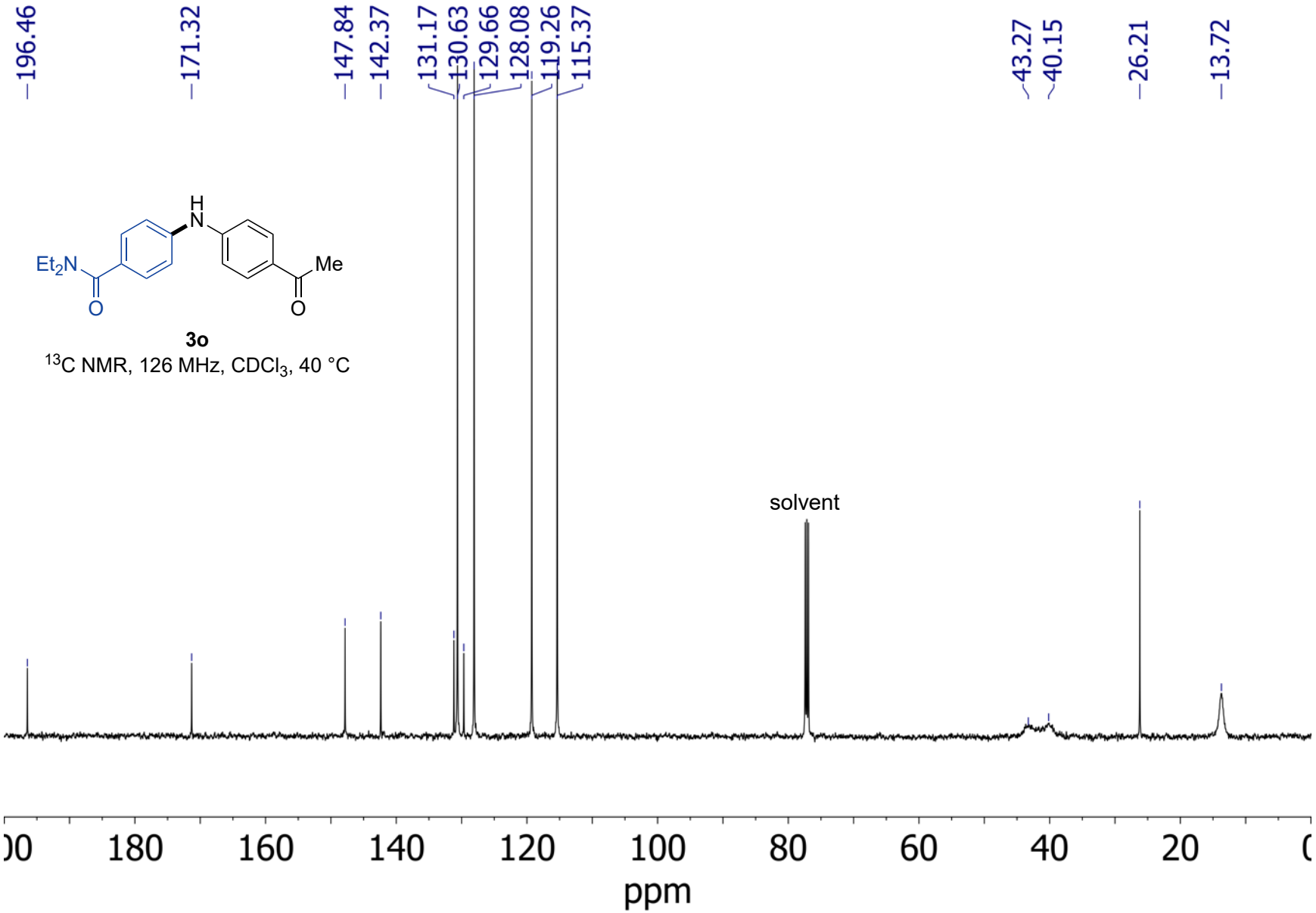
3m

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


Me
H
N
NH
O
3n
1H NMR, 400 MHz, CDCl3
solvent
2.00
2.02
1.02 1.06 2.06 2.08 2.04 2.09 1.58 2.16 4.08 3.01
11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm

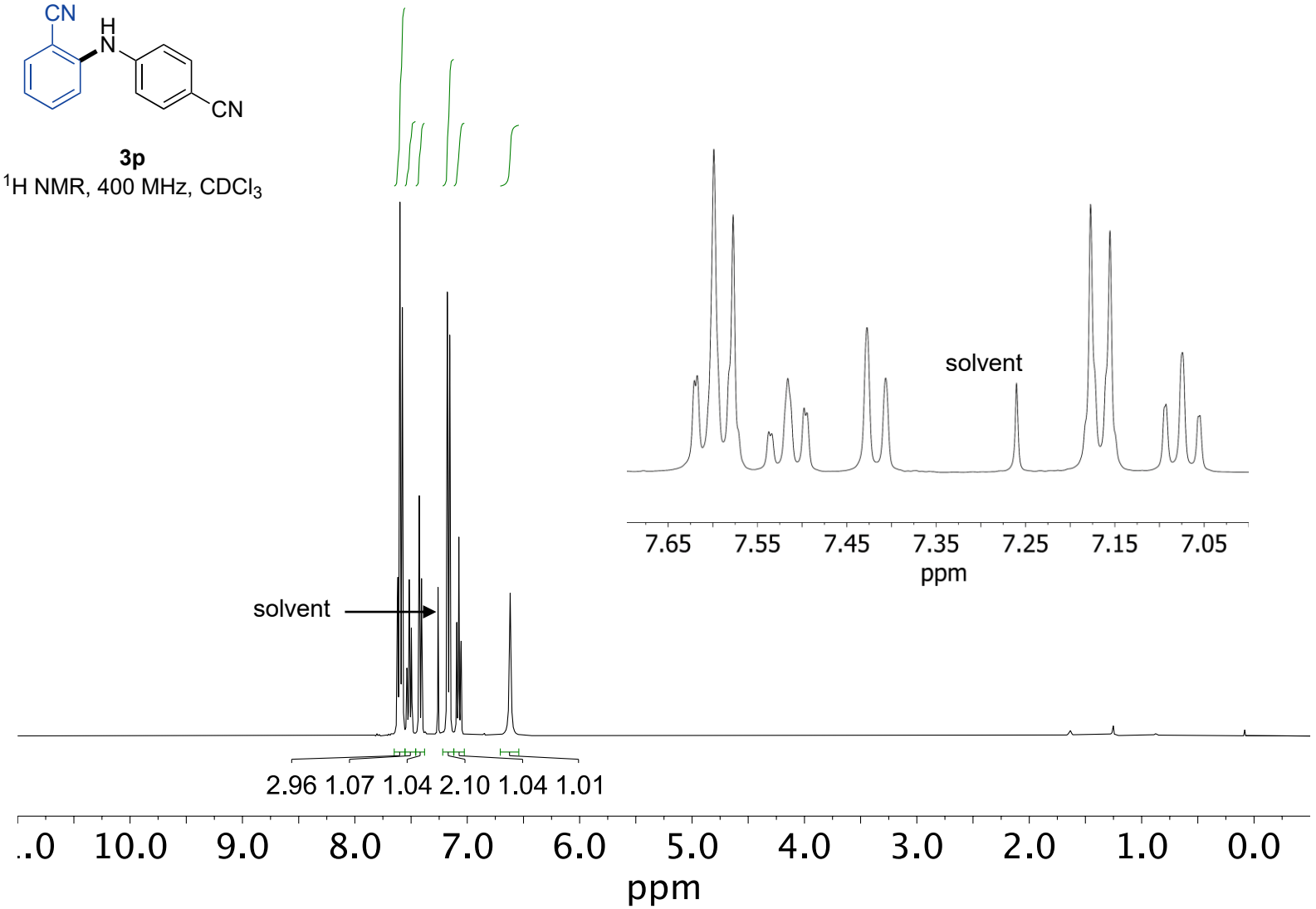

198.89
150.88
130.78
126.52
111.83
solvent
50.09
45.52
37.79
33.75
27.29
22.78
14.12
Me
O
H
N
NH
3n
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm

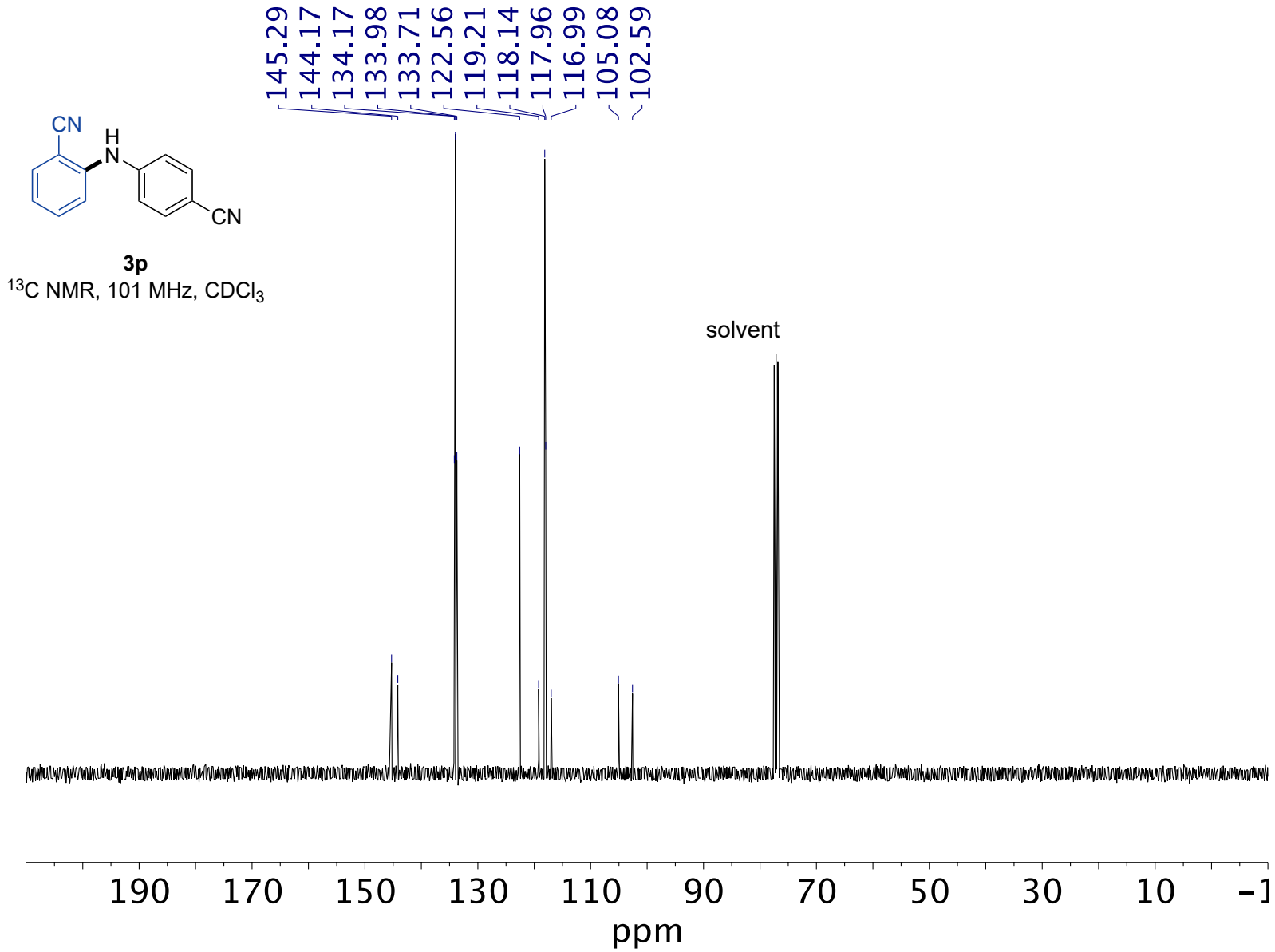

Et2N
O
H
N
O
Me
3o
1H NMR, 400 MHz, CDCl3
solvent
2.00 2.00 2.01 1.99
4.01
3.02
6.01
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

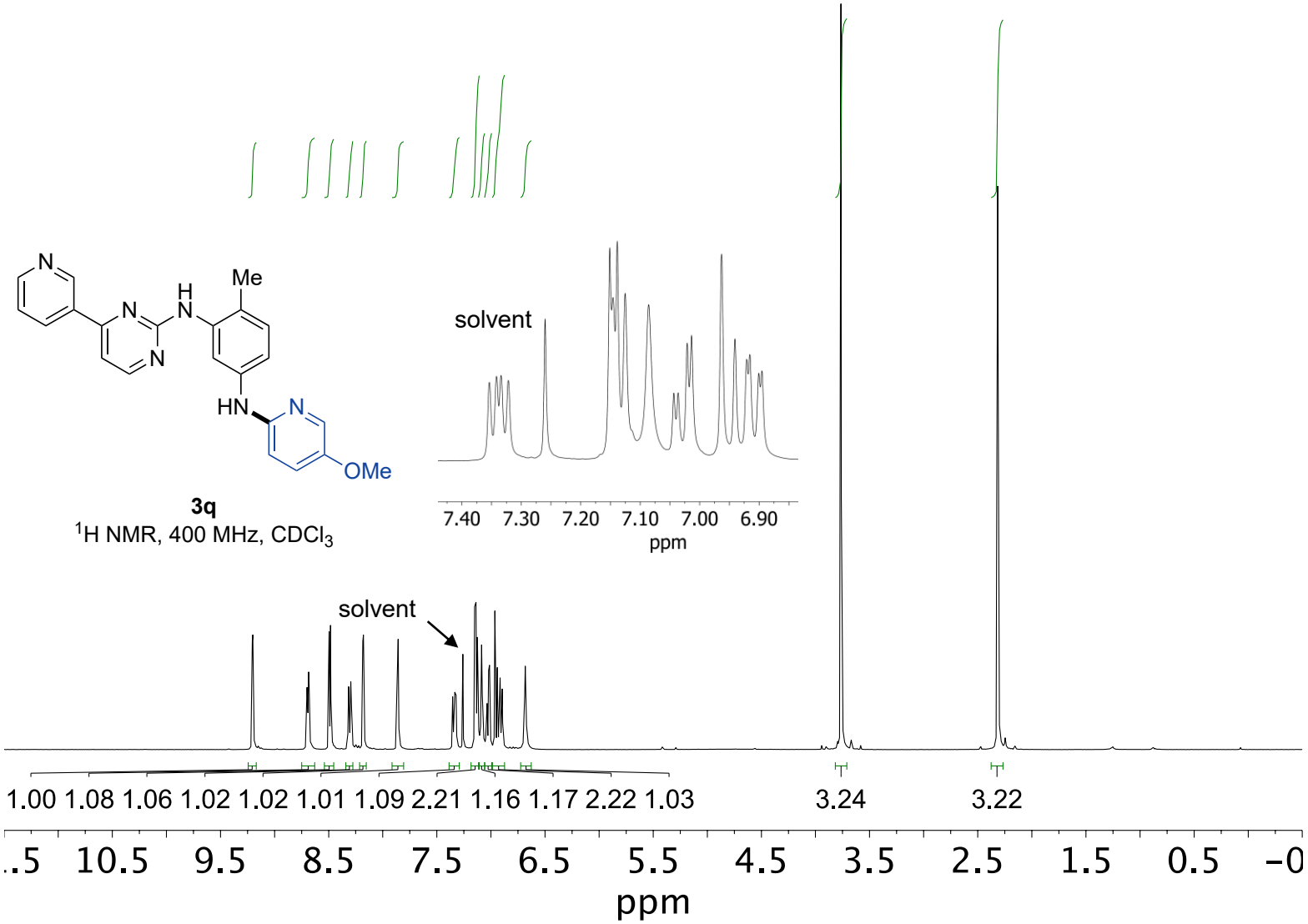


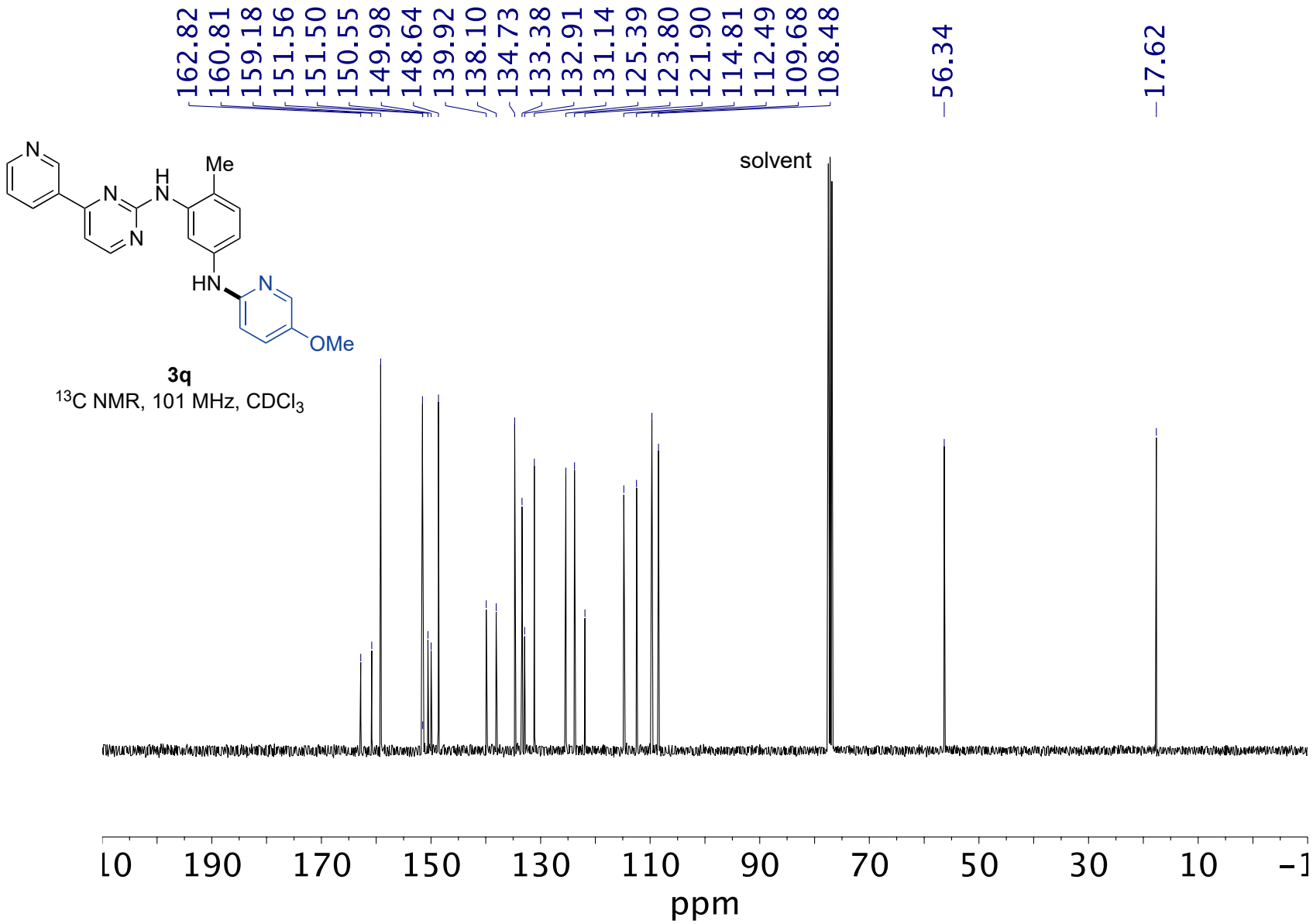
3o

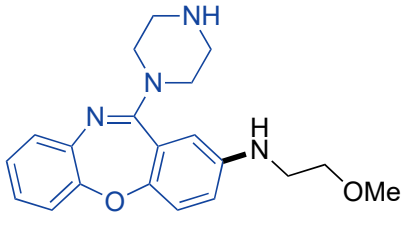
^{13}C NMR, 126 MHz, $CDCl_3$, 40 °C


CN
H
N
CN
3p
1H NMR, 400 MHz, CDCl3
solvent
solvent
7.65
7.55
7.45
7.35
7.25
7.15
7.05
ppm
2.96 1.07 1.04 2.10 1.04 1.01
.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm


145.29
144.17
134.17
133.98
133.71
122.56
119.21
118.14
117.96
116.99
105.08
102.59
CN
H
N
CN
3p
13C NMR, 101 MHz, CDCl3
solvent
190
170
150
130
110
90
70
50
30
10
-1
ppm

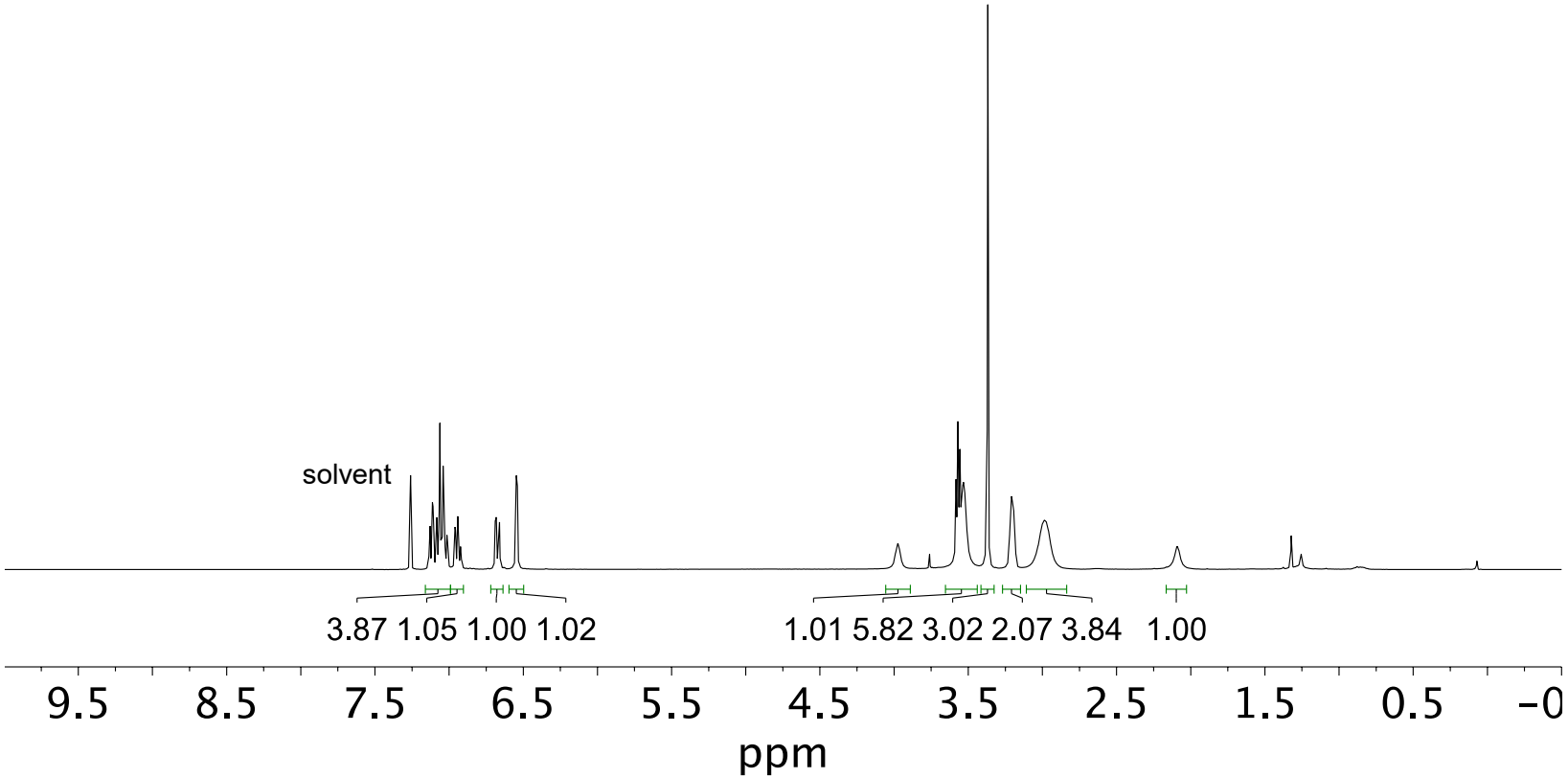

N
N
N
H
N
Me
HN
N
OMe
3q
^{1}H NMR, 400 MHz, $CDCl_3$
solvent
7.40 7.30 7.20 7.10 7.00 6.90
ppm
solvent
1.00 1.08 1.06 1.02 1.02 1.01 1.09 2.21 1.16 1.17 2.22 1.03
3.24
3.22
..5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm

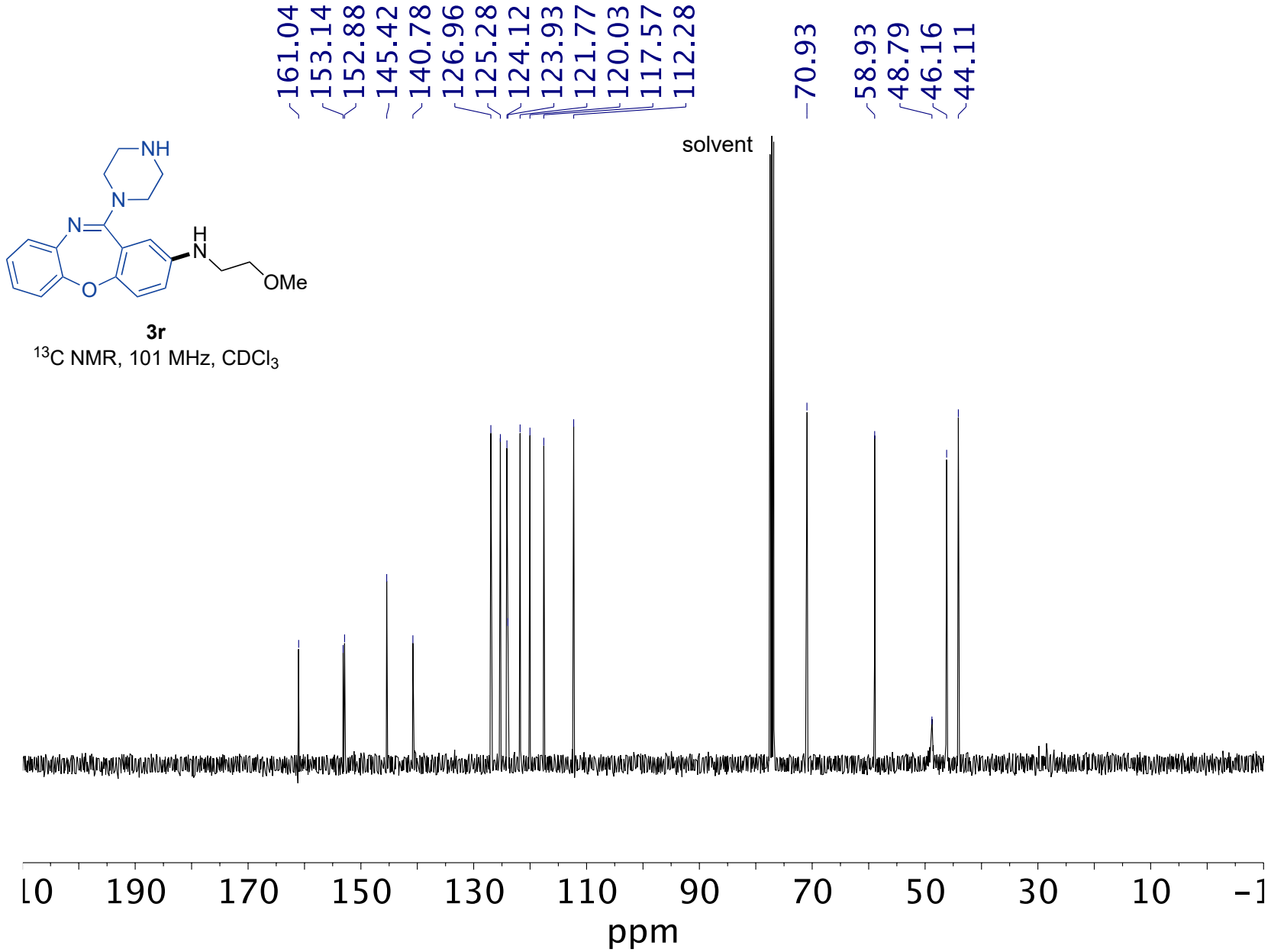

162.82
160.81
159.18
151.56
151.50
150.55
149.98
148.64
139.92
138.10
134.73
133.38
132.91
131.14
125.39
123.80
121.90
114.81
112.49
109.68
108.48
56.34
17.62
solvent
Me
OMe
3q
13C NMR, 101 MHz, CDCl3
ppm

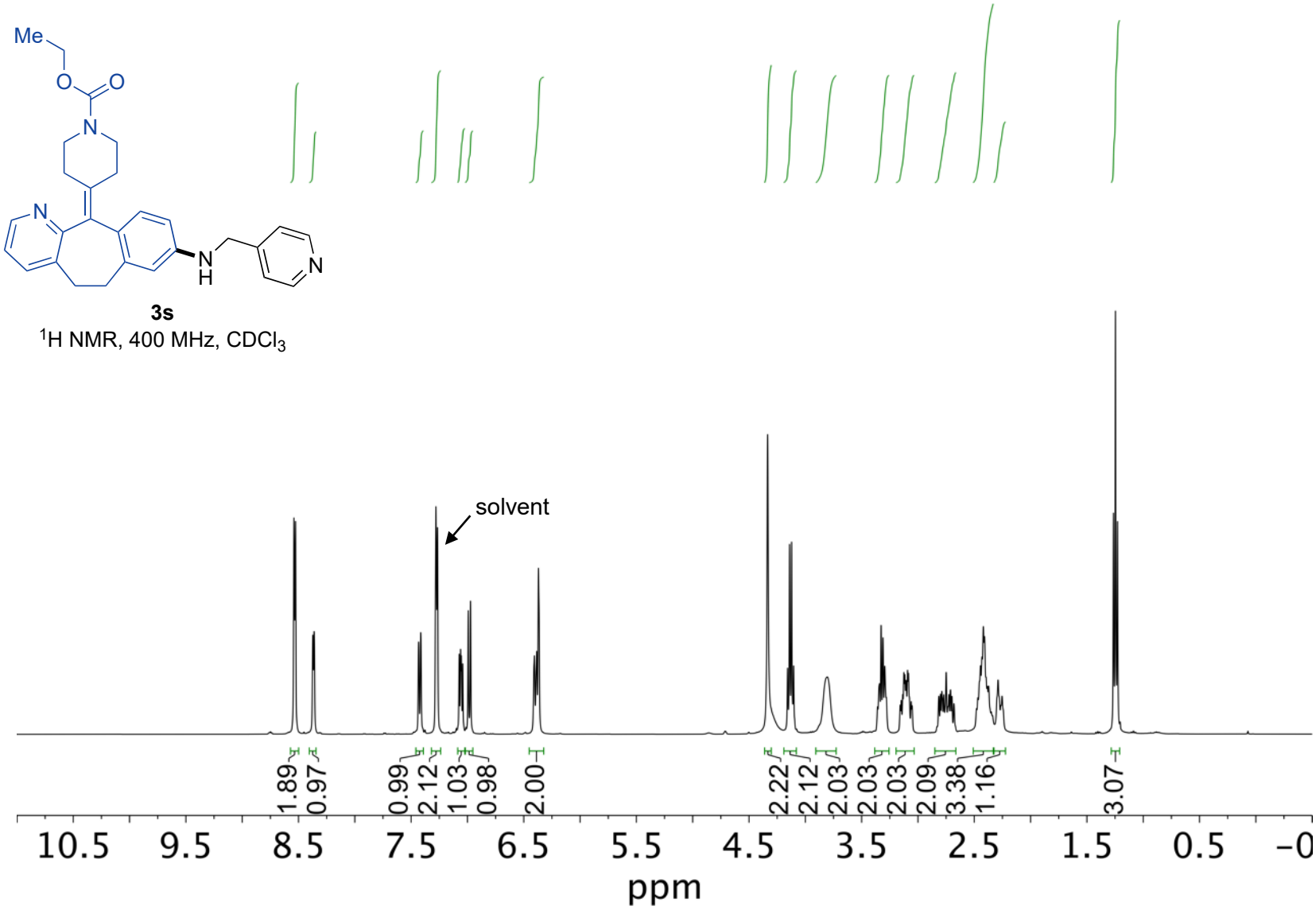


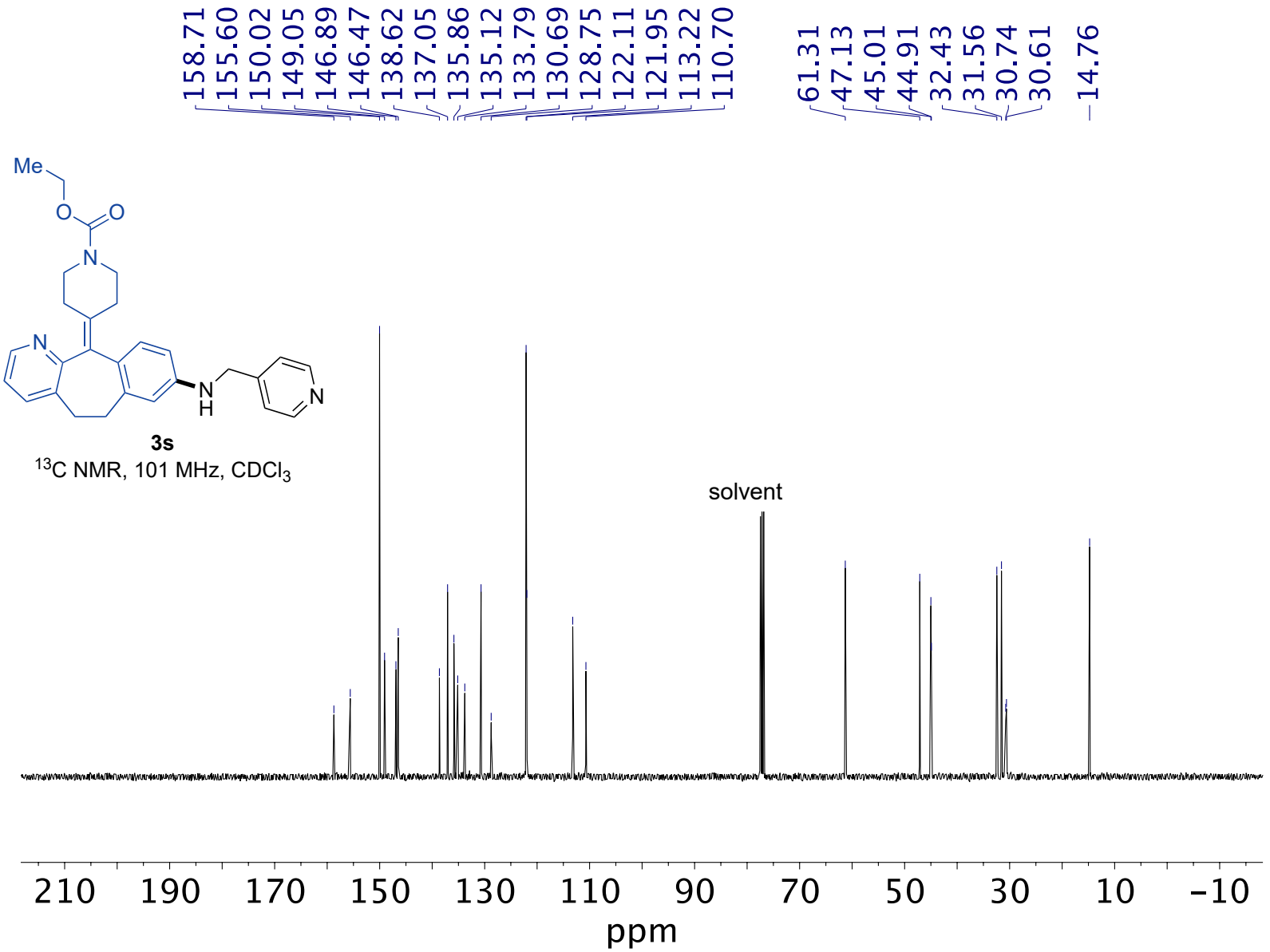
3r

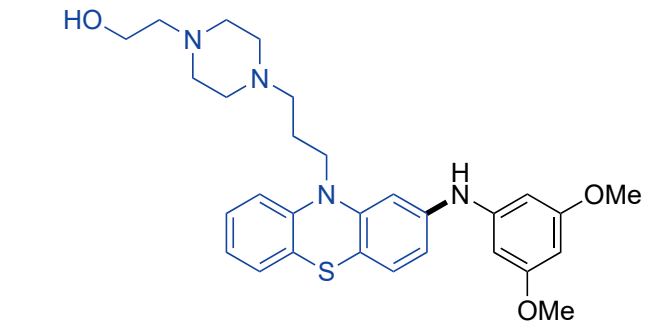
^{1}H NMR, 400 MHz, $CDCl_3$




161.04
153.14
152.88
145.42
140.78
126.96
125.28
124.12
123.93
121.77
120.03
117.57
112.28
70.93
58.93
48.79
46.16
44.11
solvent
NH
N
N
H
N
O
OMe
3r
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm

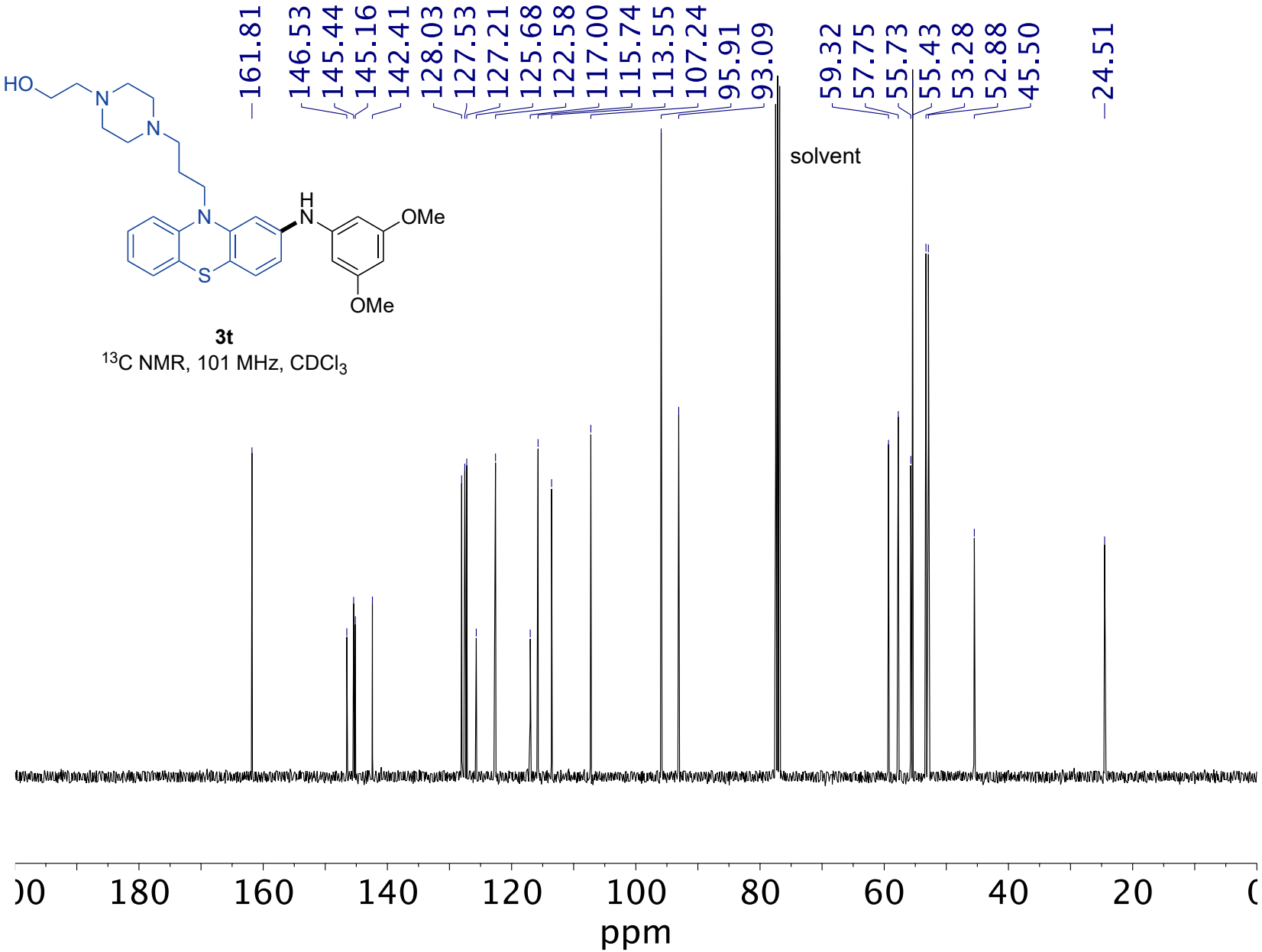

Me
O
O
N
N
N
H
N
3s
1H NMR, 400 MHz, CDCl3
solvent
1.89
0.97
0.99
2.12
1.03
0.98
2.00
2.22
2.12
2.03
2.03
2.03
2.09
3.38
1.16
3.07
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0
ppm

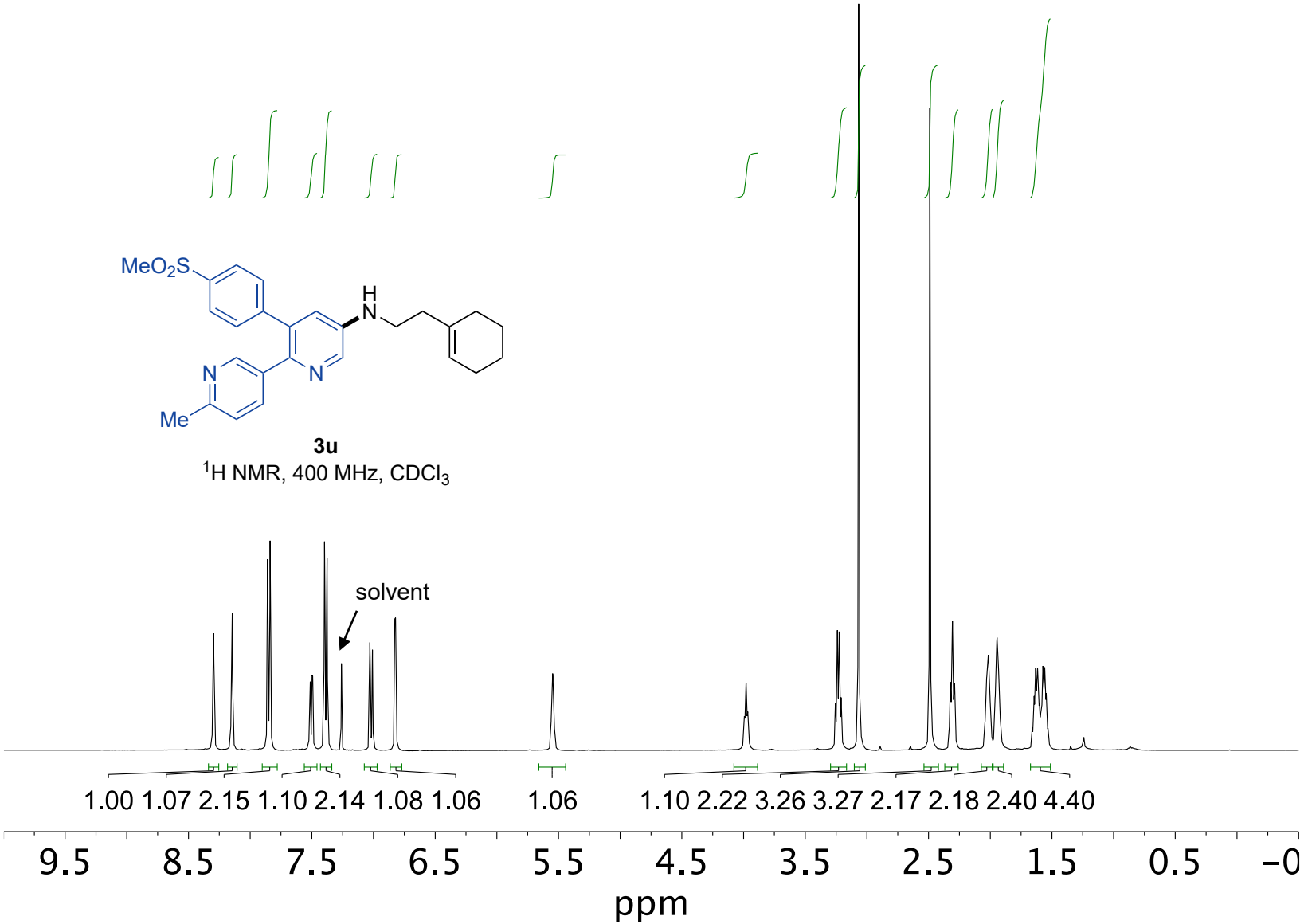

158.71
155.60
150.02
149.05
146.89
146.47
138.62
137.05
135.86
135.12
133.79
130.69
128.75
122.11
121.95
113.22
110.70
61.31
47.13
45.01
44.91
32.43
31.56
30.74
30.61
14.76
Me
O
O
N
N
N
H
N
3s
13C NMR, 101 MHz, CDCl3
solvent
210
190
170
150
130
110
90
70
50
30
10
-10
ppm

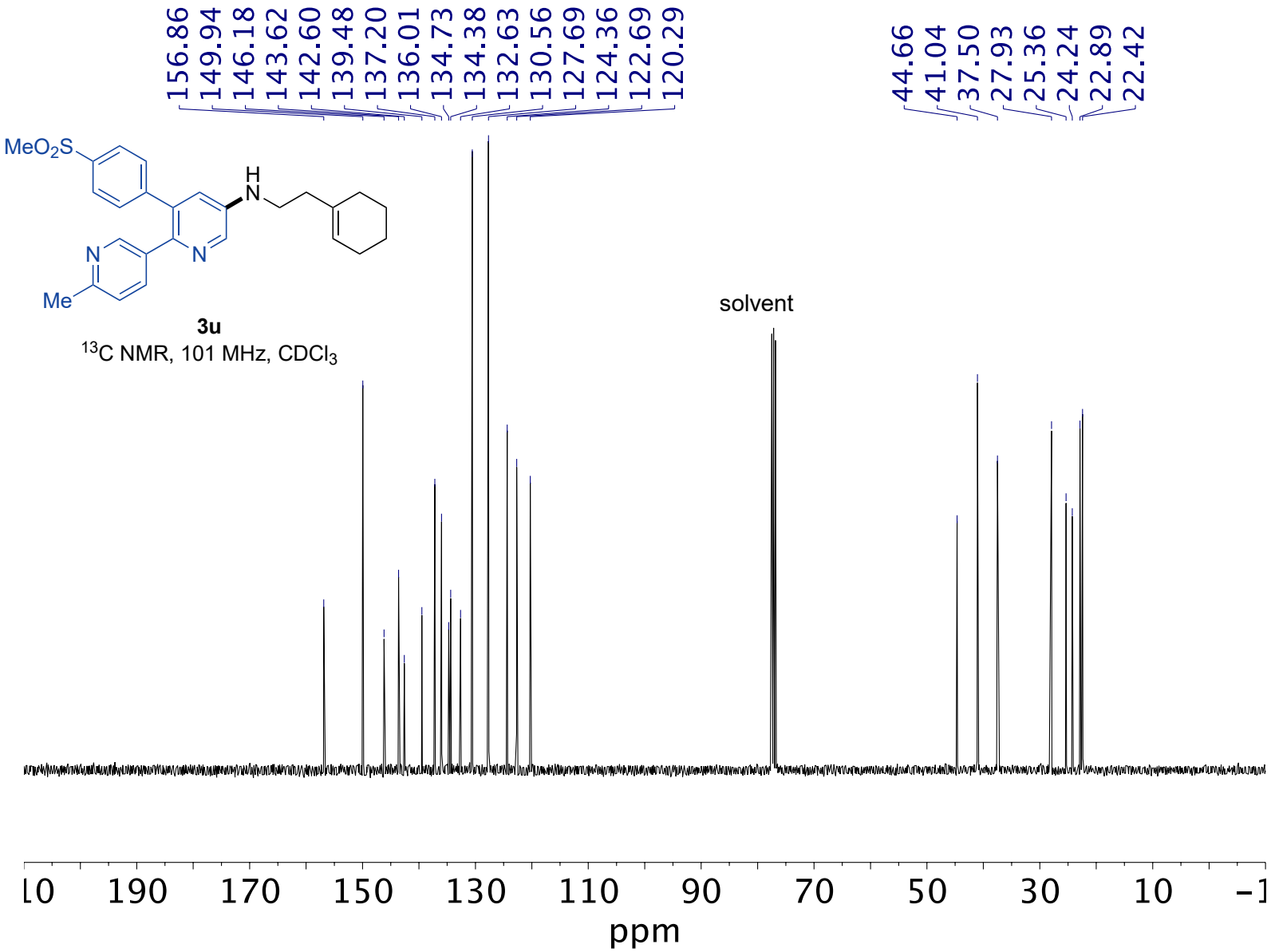


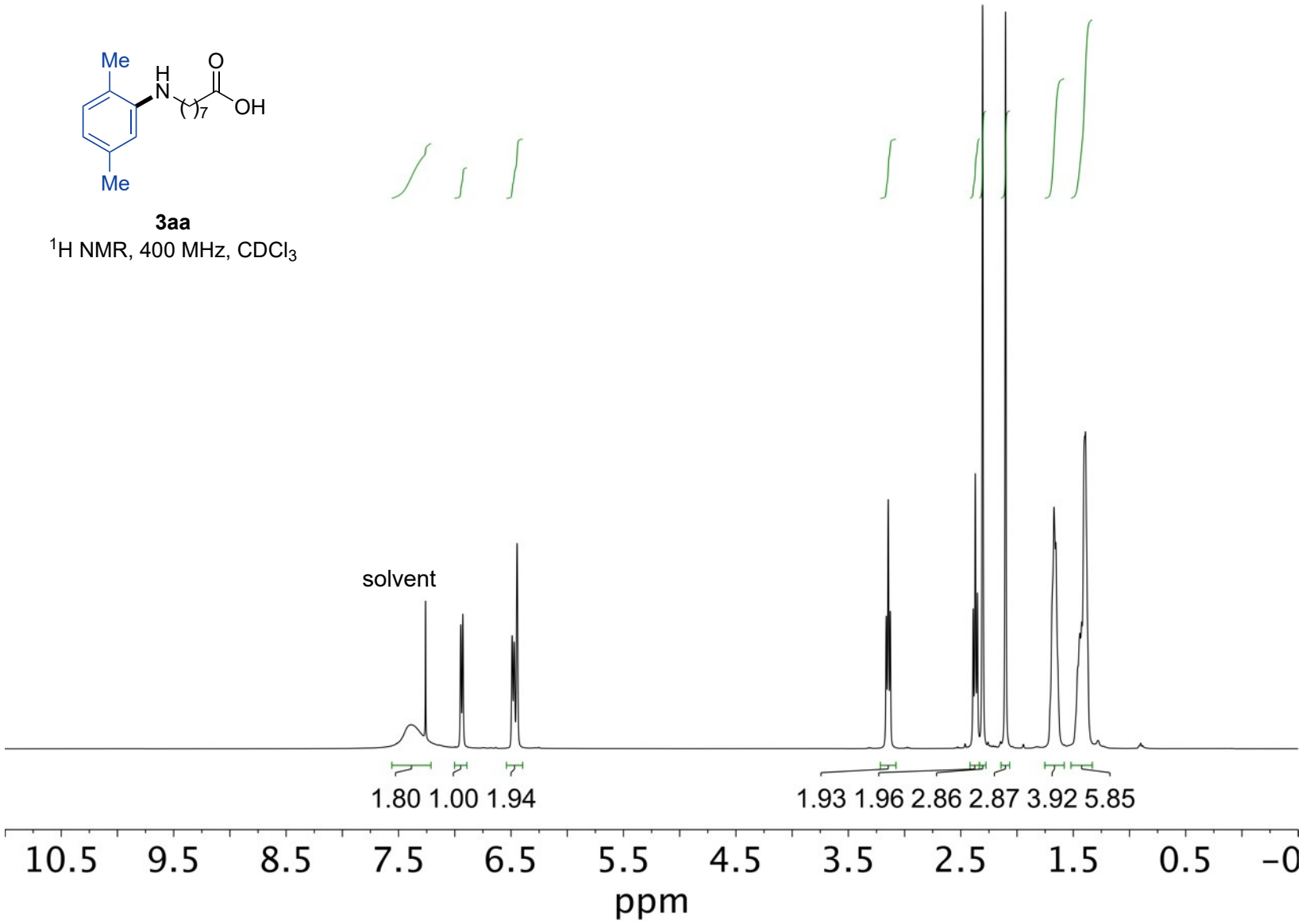
3t

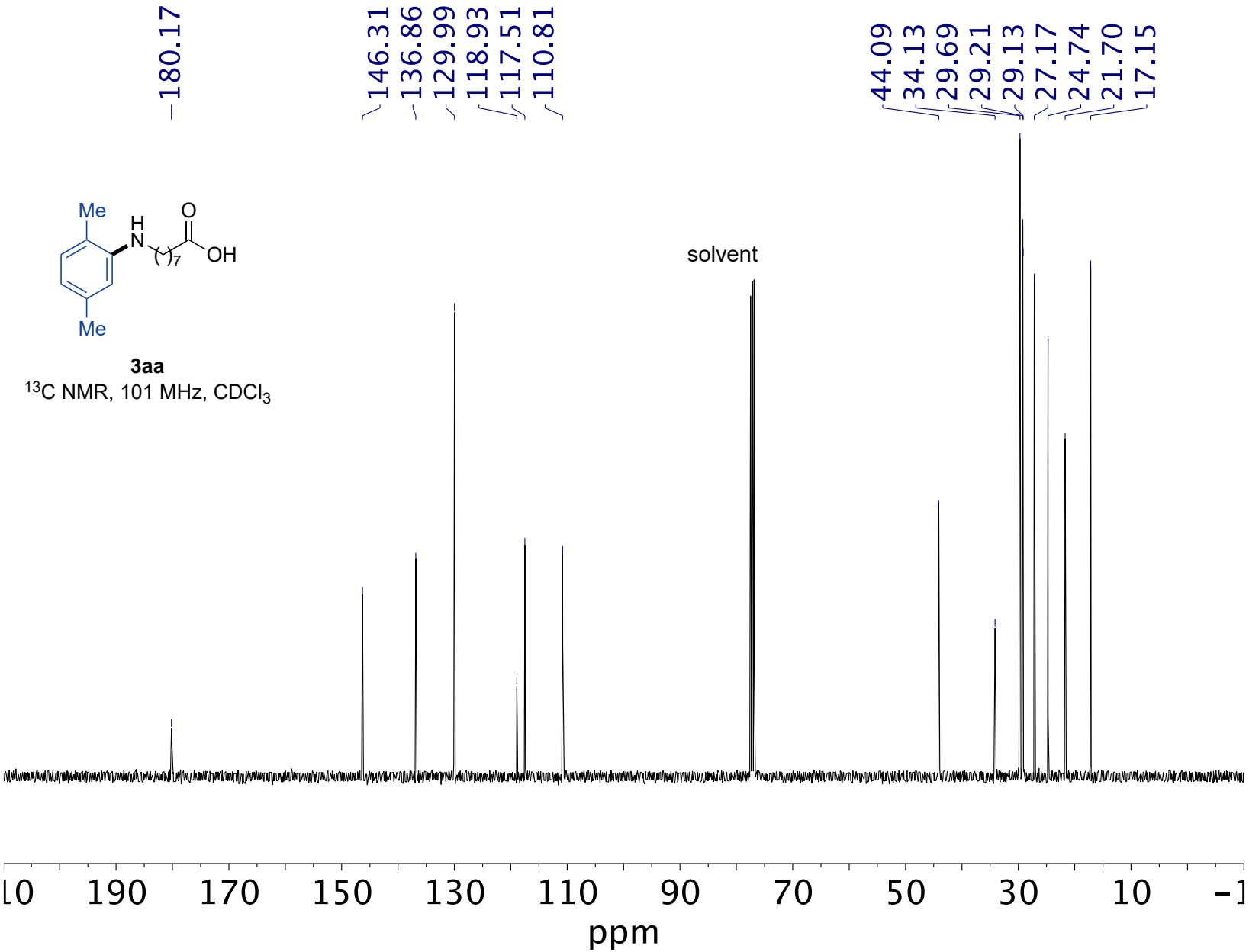
^{1}H NMR, 500 MHz, $CDCl_3$

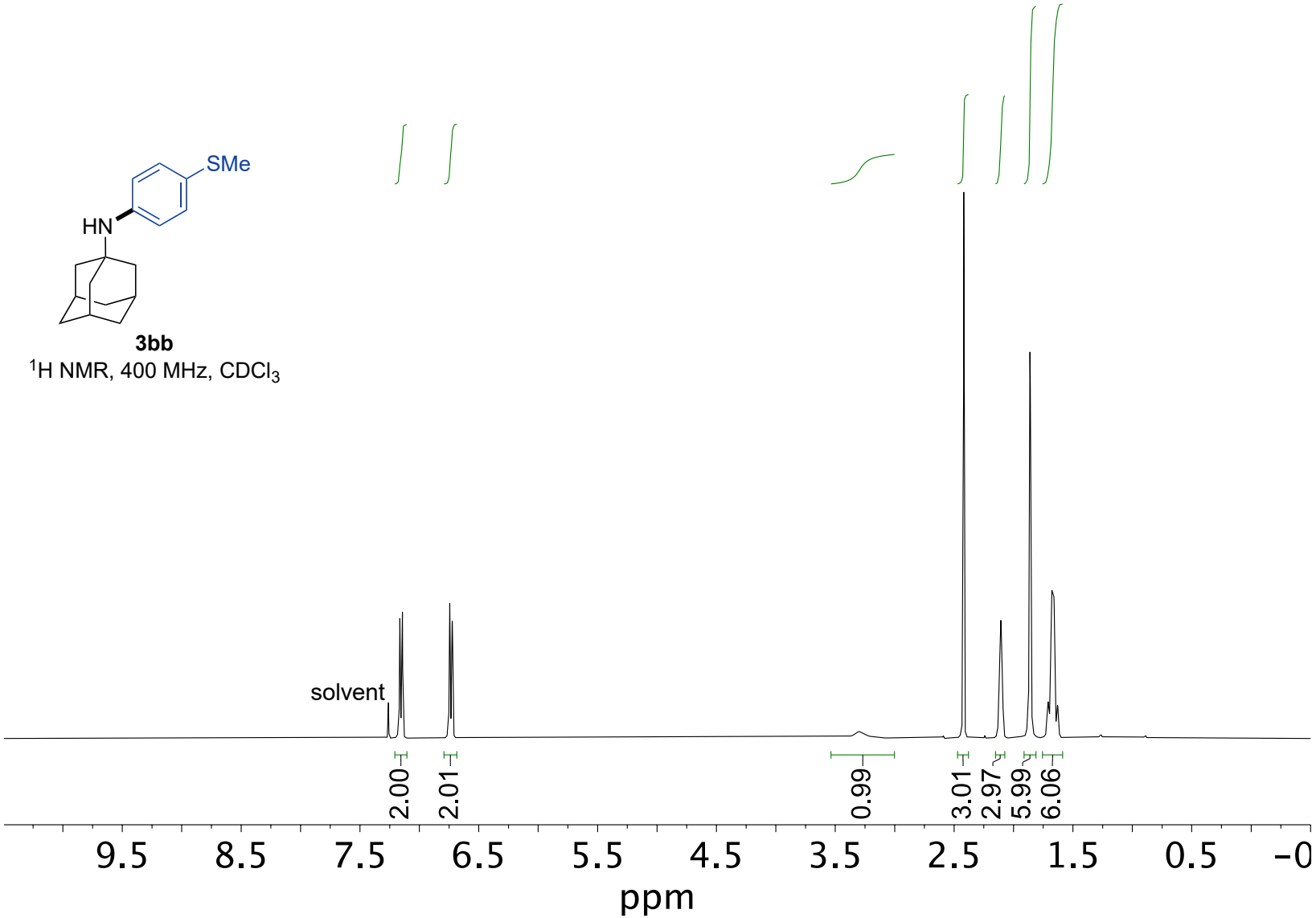

161.81
146.53
145.44
145.16
142.41
128.03
127.53
127.21
125.68
122.58
117.00
115.74
113.55
107.24
95.91
93.09
59.32
57.75
55.73
55.43
53.28
52.88
45.50
24.51
solvent
HO
N
N
N
H
N
OMe
OMe
S
3t
13C NMR, 101 MHz, CDCl3
ppm

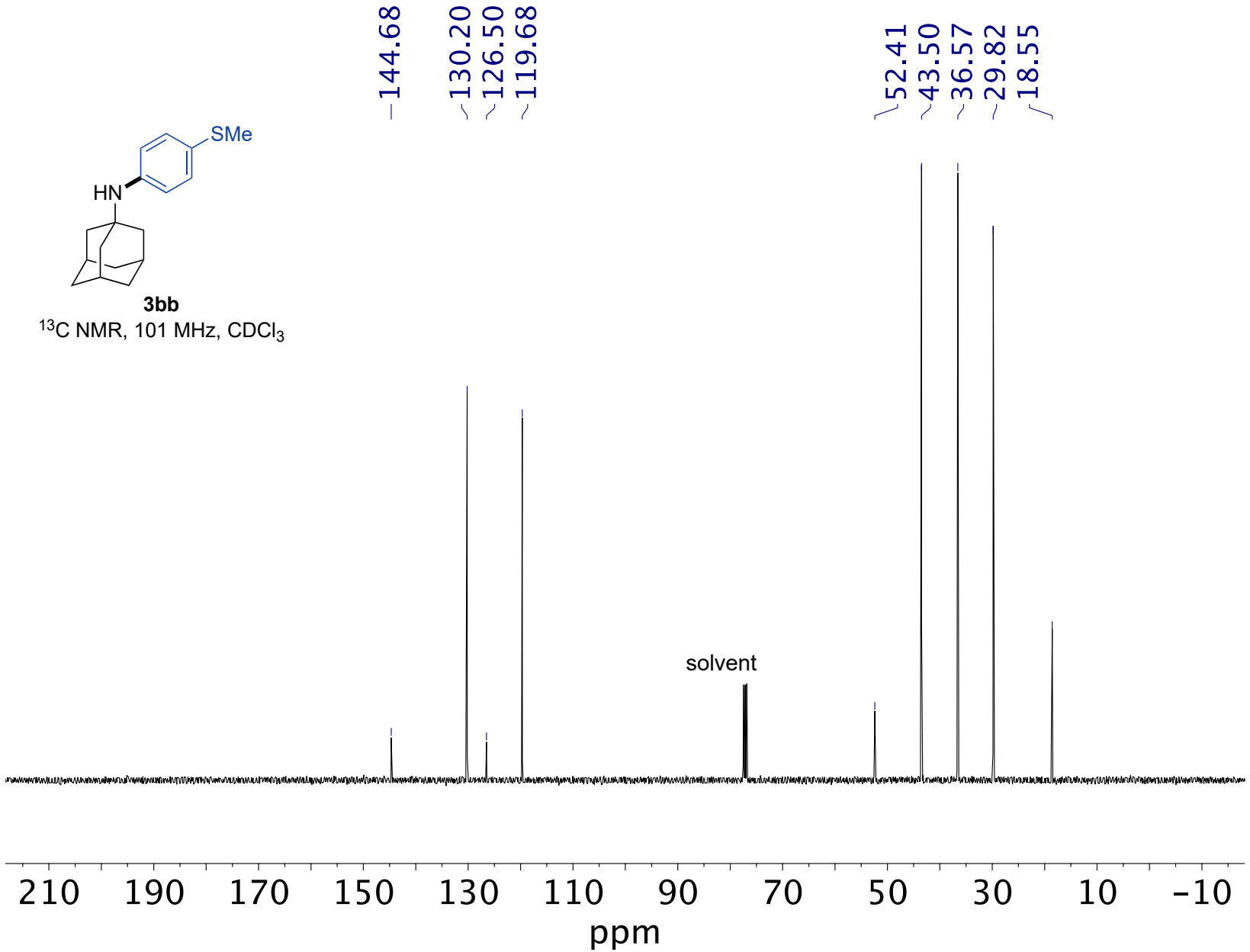

MeO2S
H
N
N
N
Me
3u
1H NMR, 400 MHz, CDCl3
solvent
1.00 1.07 2.15 1.10 2.14 1.08 1.06
1.06
1.10 2.22 3.26 3.27 2.17 2.18 2.40 4.40
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
ppm

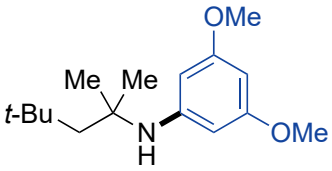

156.86
149.94
146.18
143.62
142.60
139.48
137.20
136.01
134.73
134.38
132.63
130.56
127.69
124.36
122.69
120.29
44.66
41.04
37.50
27.93
25.36
24.24
22.89
22.42
MeO2S
H
N
N
N
Me
3u
13C NMR, 101 MHz, CDCl3
solvent
ppm


Me
H
N
O
OH
7
Me
3aa
1H NMR, 400 MHz, CDCl3
solvent
1.80 1.00 1.94
1.93 1.96 2.86 2.87 3.92 5.85
10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0
ppm


180.17
146.31
136.86
129.99
118.93
117.51
110.81
44.09
34.13
29.69
29.21
29.13
27.17
24.74
21.70
17.15
solvent
Me
H
N
O
OH
7
Me
3aa
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm

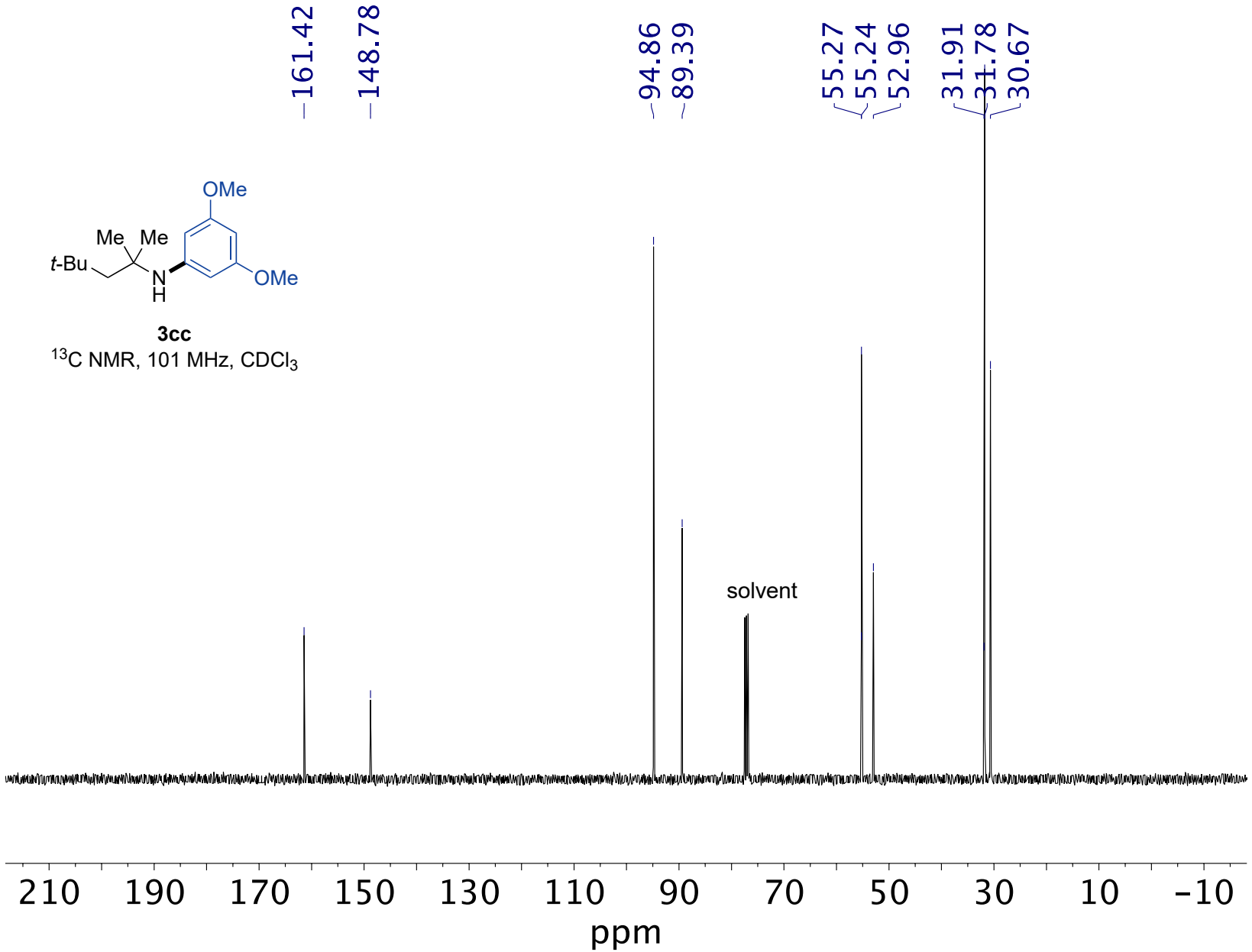

SMe
HN
3bb
1H NMR, 400 MHz, CDCl3
solvent
2.00
2.01
0.99
3.01
2.97
5.99
6.06
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0
ppm

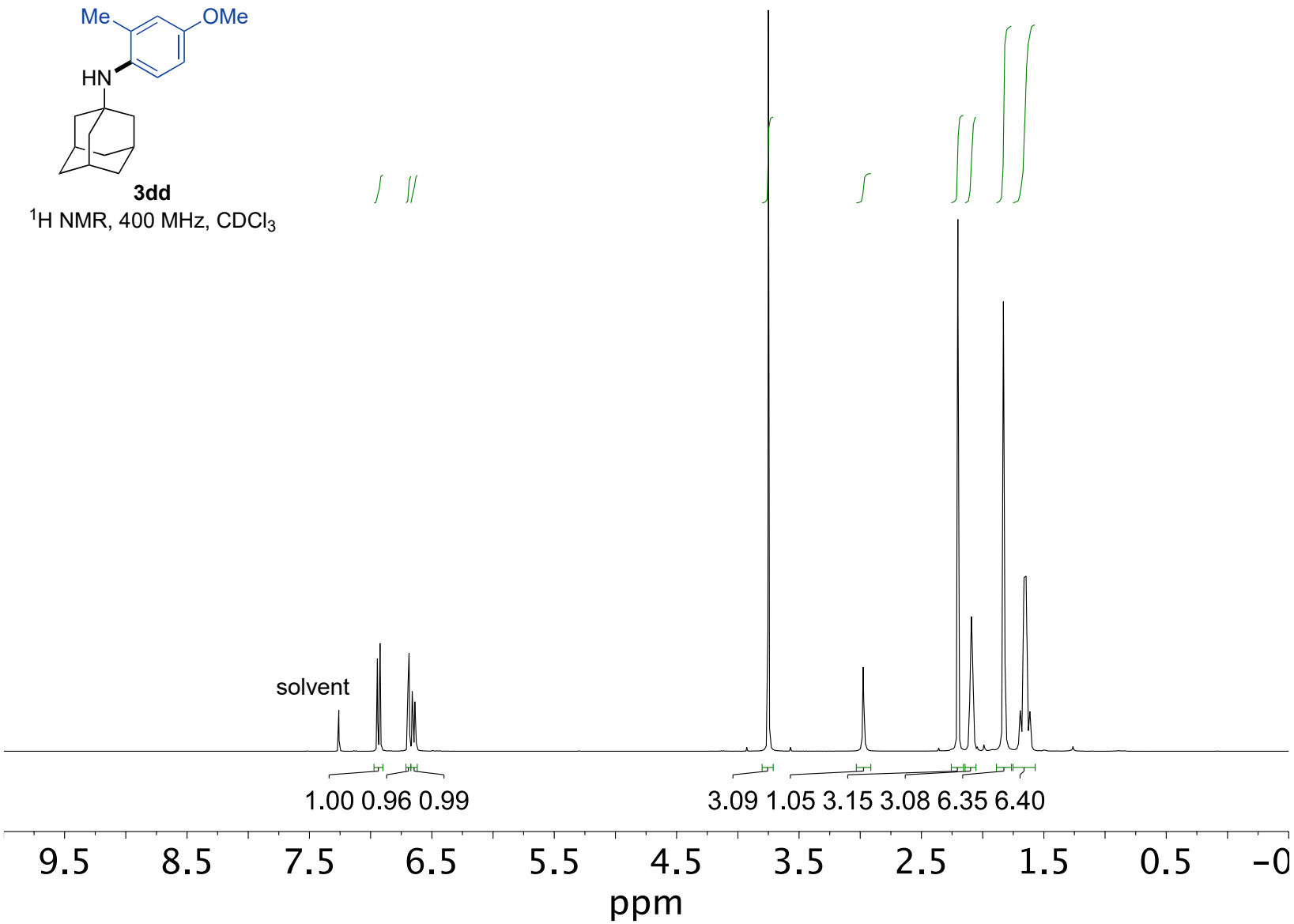

144.68
130.20
126.50
119.68
52.41
43.50
36.57
29.82
18.55
SMe
HN
3bb
13C NMR, 101 MHz, CDCl3
solvent
210
190
170
150
130
110
90
70
50
30
10
-10
ppm



3cc

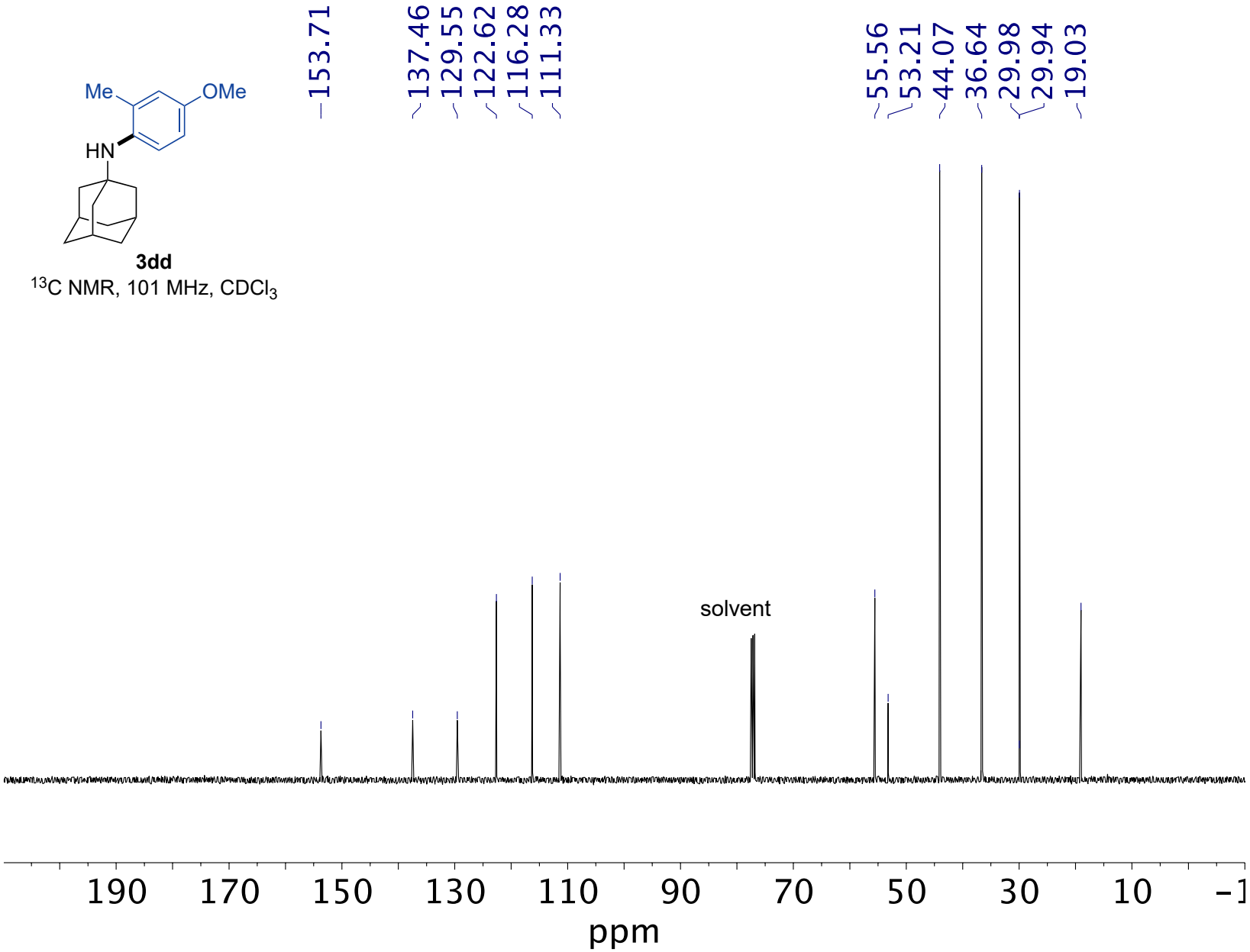
^{1}H NMR, 400 MHz, $CDCl_3$


161.42
148.78
94.86
89.39
55.27
55.24
52.96
31.91
31.78
30.67
OMe
Me
Me
t-Bu
N
H
OMe
3cc
13C NMR, 101 MHz, CDCl3
solvent
210
190
170
150
130
110
90
70
50
30
10
-10
ppm



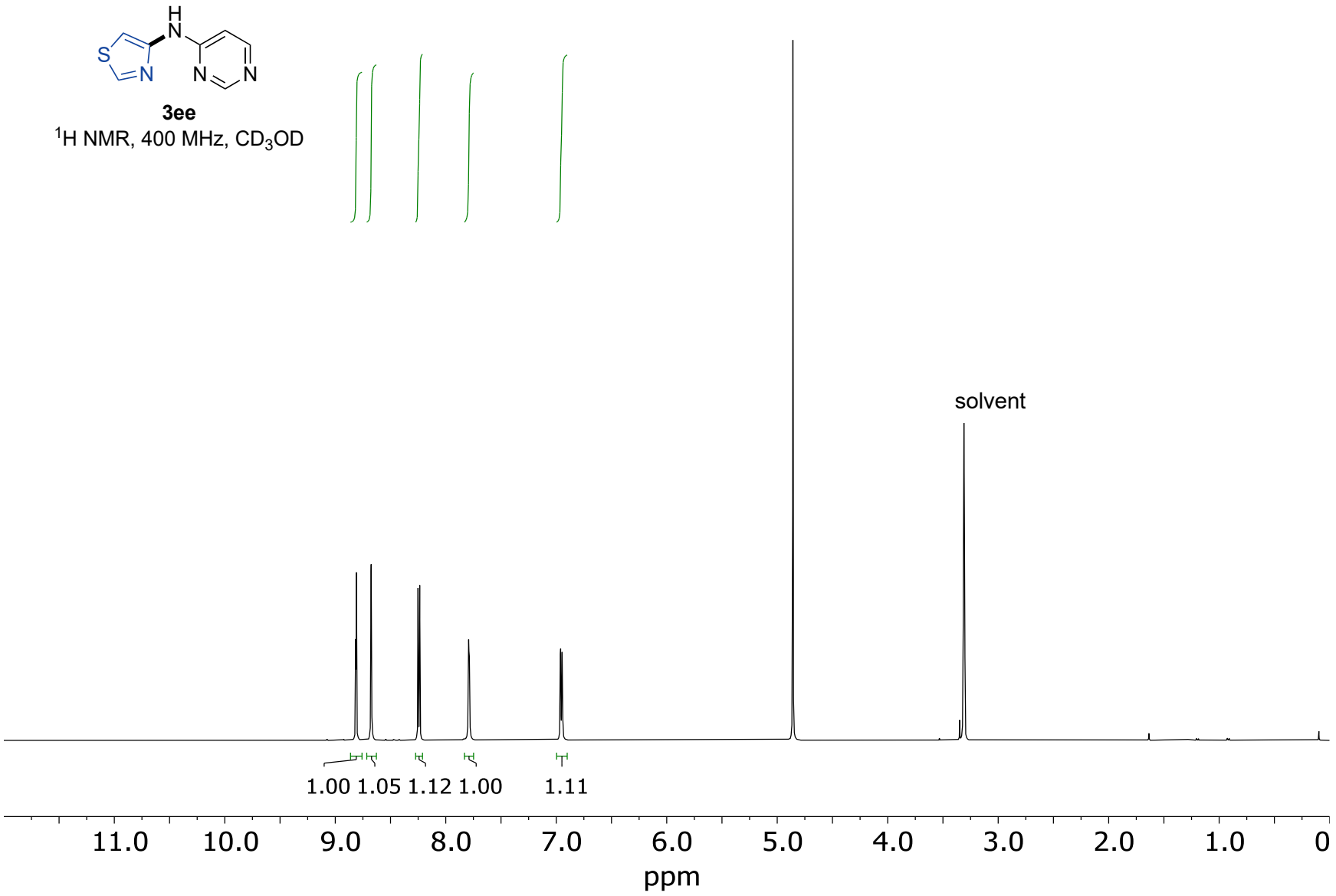
3dd

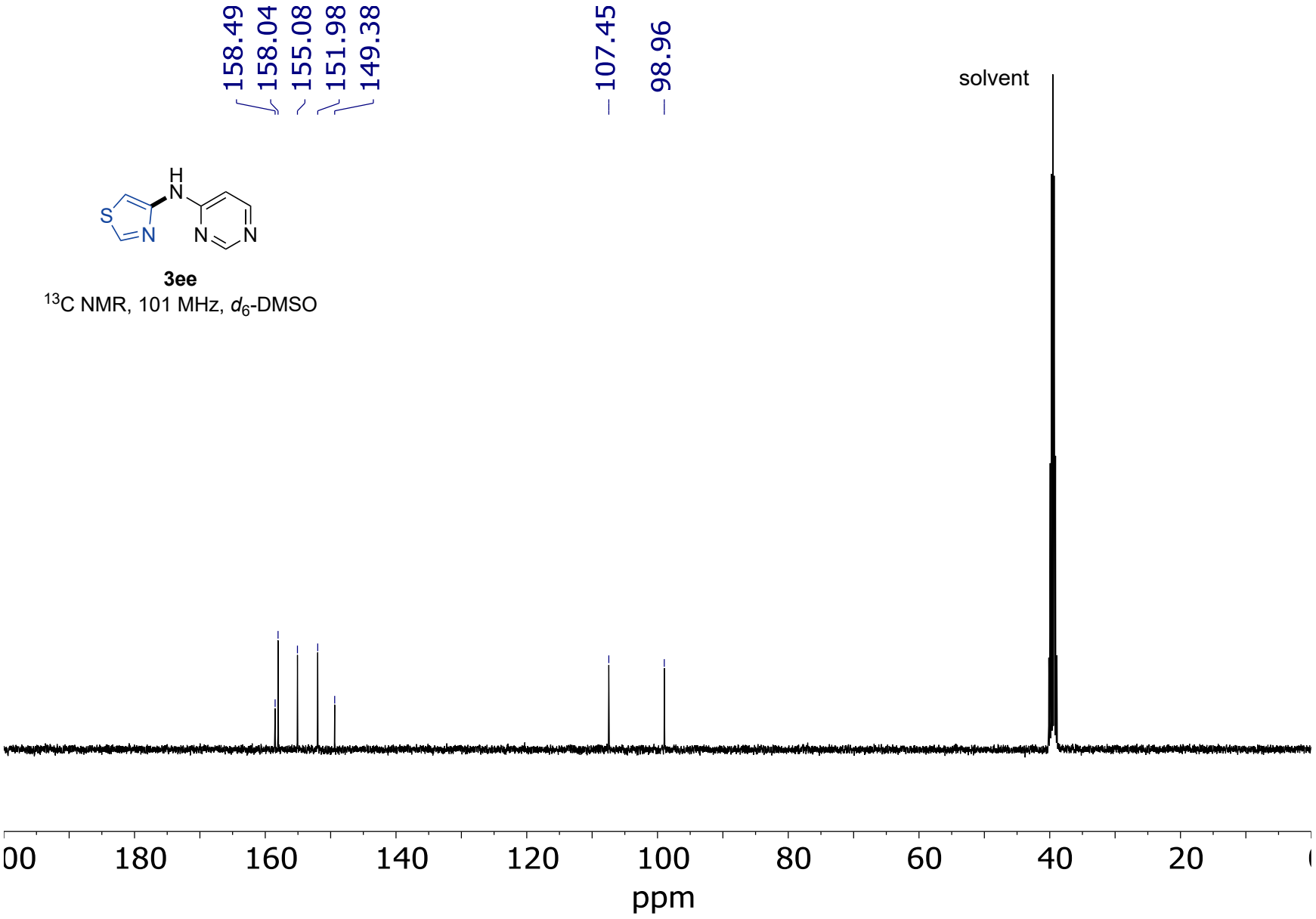
^{1}H NMR, 400 MHz, $CDCl_3$

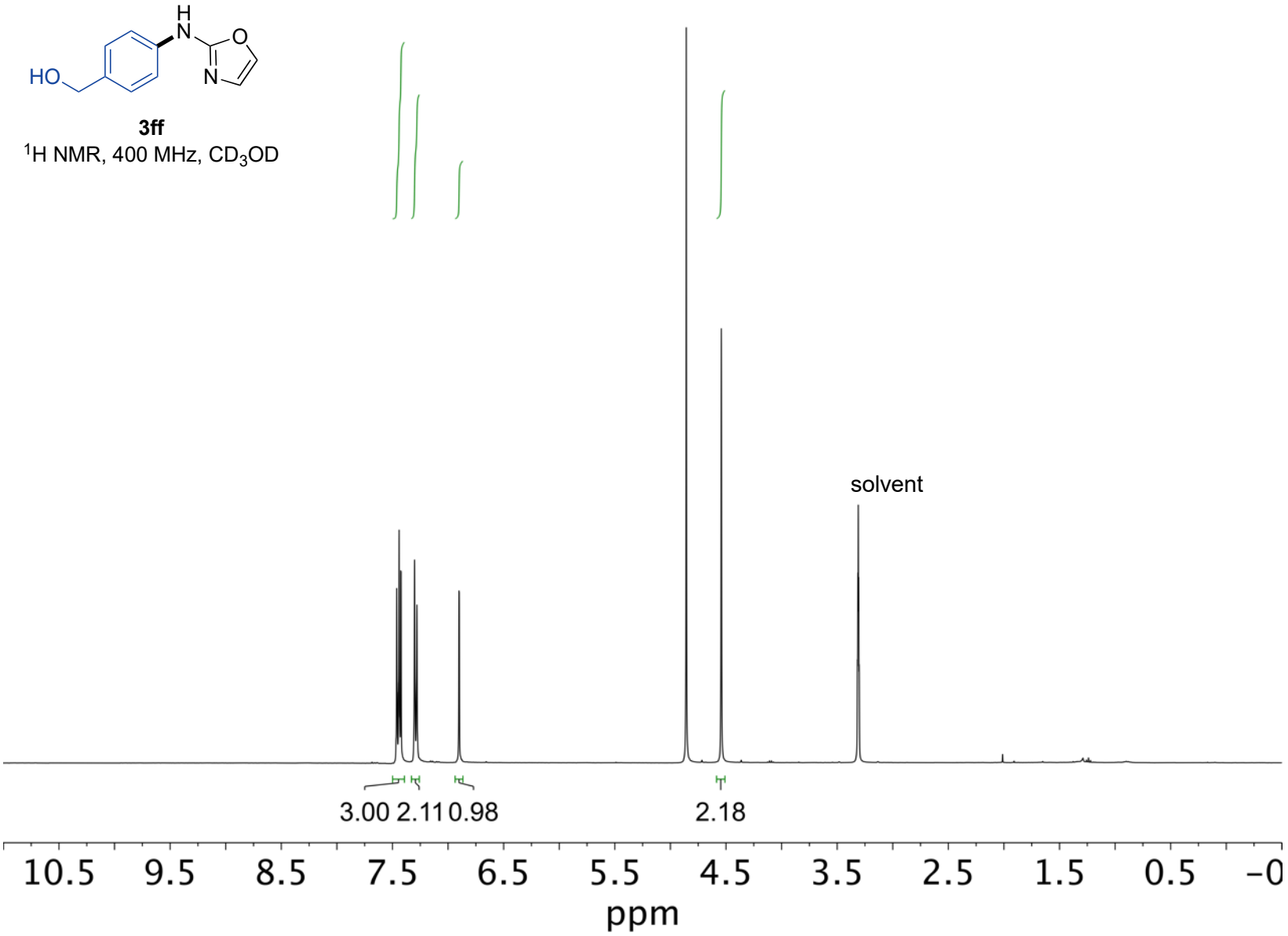


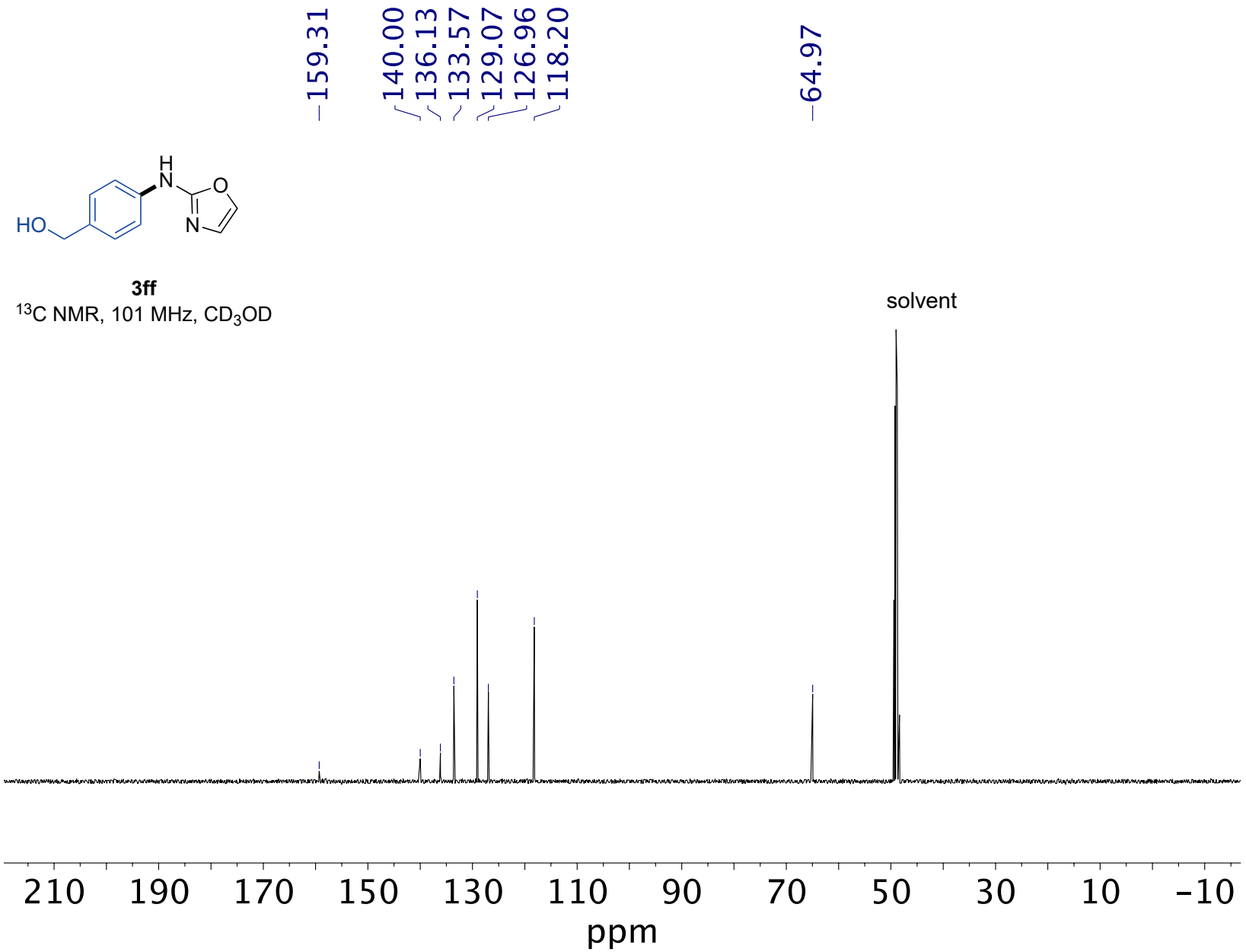
3dd

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


H
N
S
N
N
N
3ee
1H NMR, 400 MHz, CD3OD
solvent
1.00 1.05 1.12 1.00 1.11
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
ppm

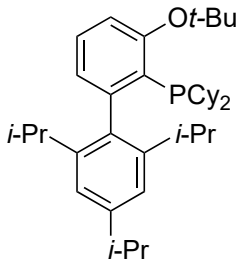

158.49
158.04
155.08
151.98
149.38
107.45
98.96
solvent
H
N
S
N
N
N
3ee
^{13}C NMR, 101 MHz, d_6-DMSO
00
180
160
140
120
100
80
60
40
20
ppm


HO
H
N
O
N
3ff
1H NMR, 400 MHz, CD3OD
solvent
3.00 2.11 0.98
2.18
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0
ppm



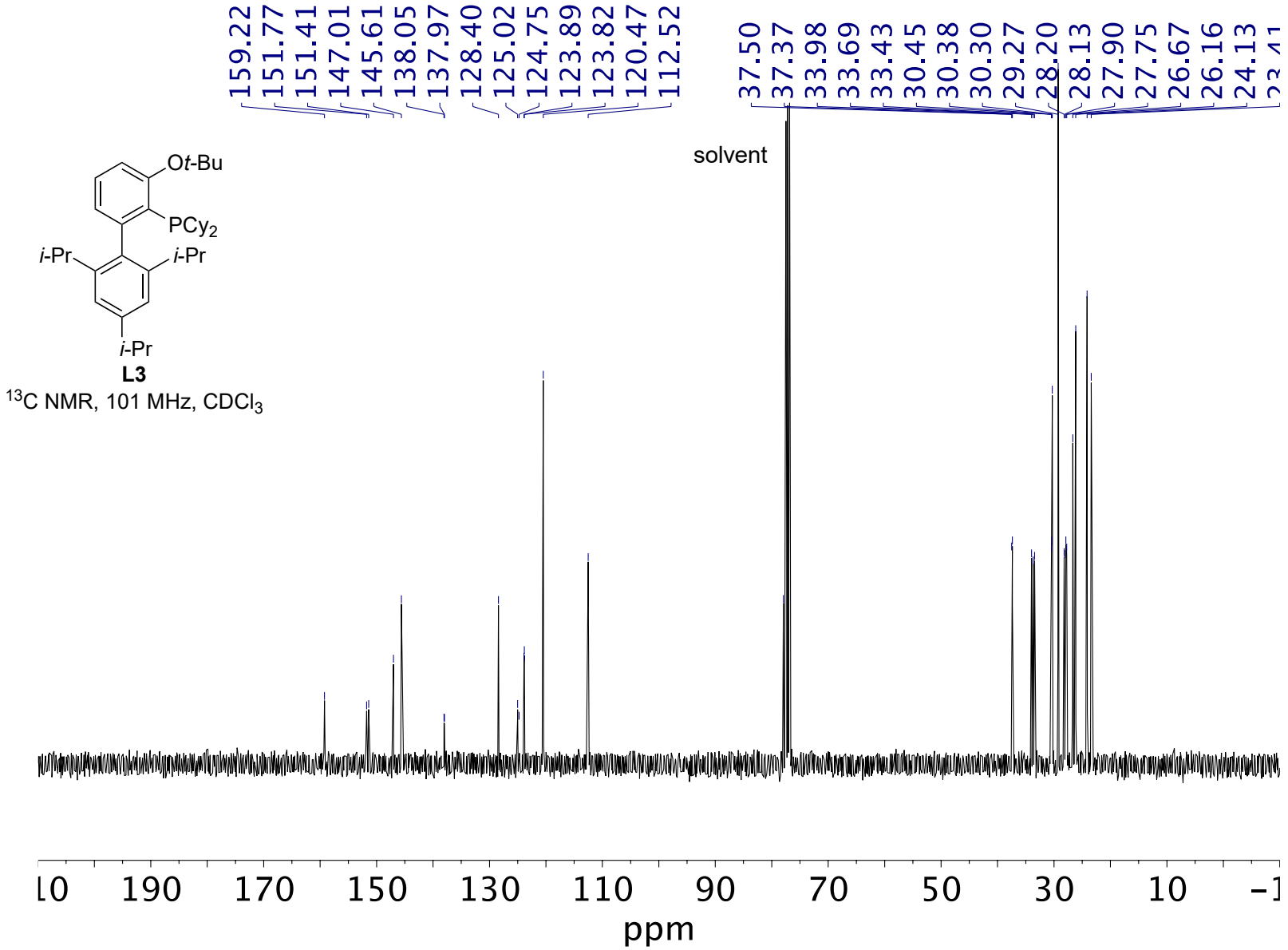
3ff

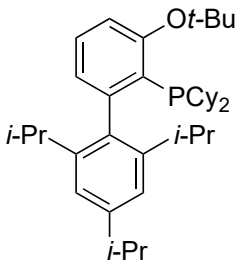
^{13}C NMR, 101 MHz, CD_3OD



L3

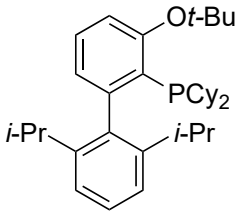
^{1}H NMR, 400 MHz, $CDCl_3$


159.22
151.77
151.41
147.01
145.61
138.05
137.97
128.40
125.02
124.75
123.89
123.82
120.47
112.52
37.50
37.37
33.98
33.69
33.43
30.45
30.38
30.30
29.27
28.20
28.13
27.90
27.75
26.67
26.16
24.13
solvent
Ot-Bu
PCy2
i-Pr
i-Pr
i-Pr
L3
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm



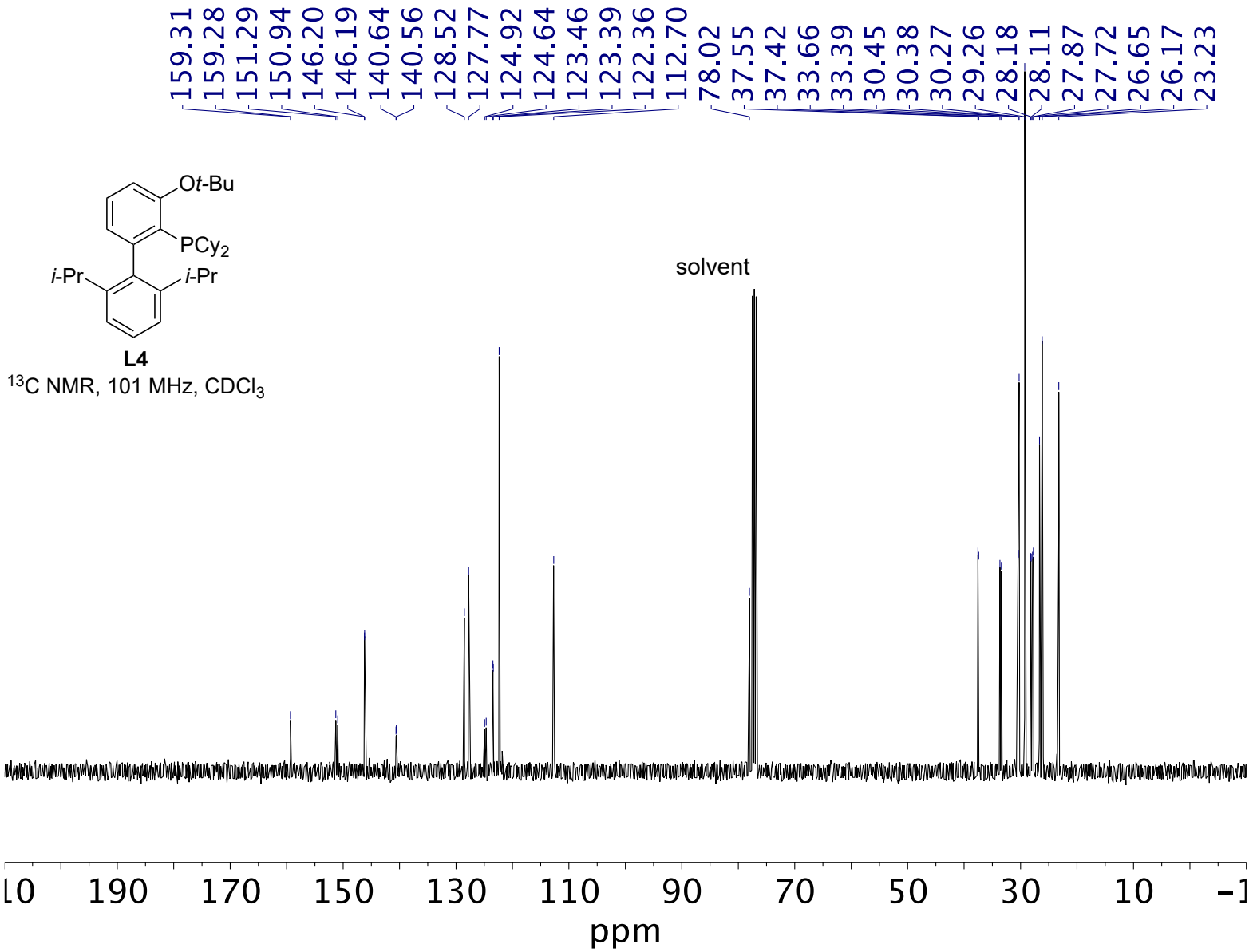
L3

^{31}P NMR, 162 MHz, $CDCl_3$



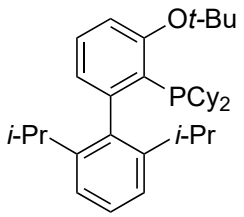
L4

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



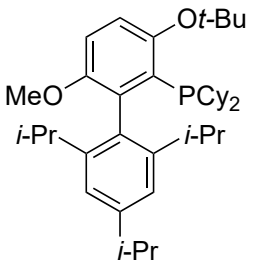
L4

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



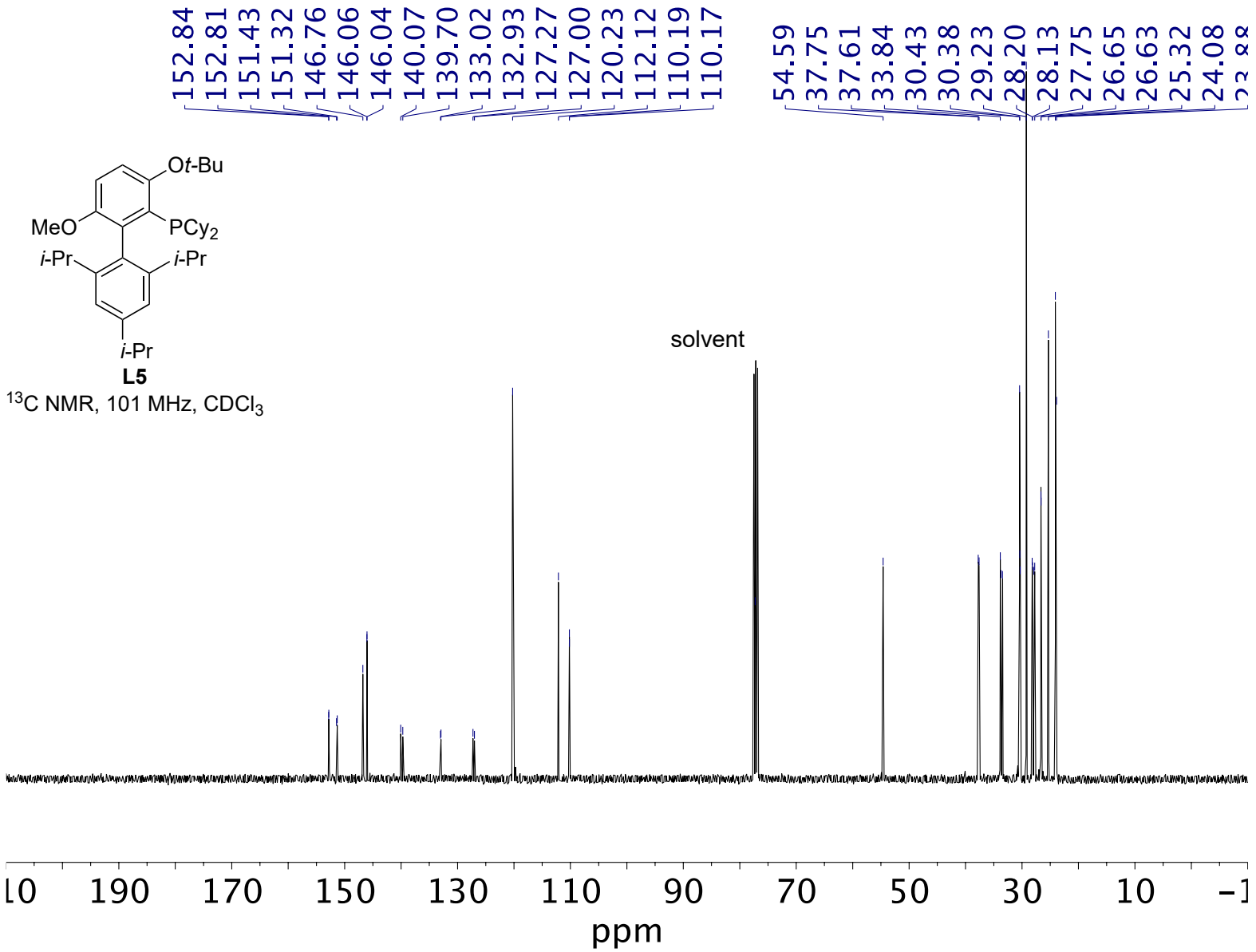
L4

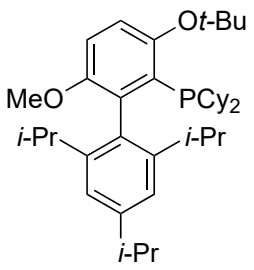
^{31}P NMR, 162 MHz, $CDCl_3$



L5

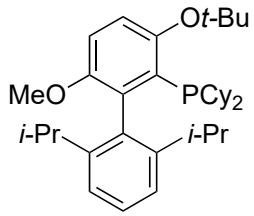
^{1}H NMR, 400 MHz, $CDCl_3$


152.84
152.81
151.43
151.32
146.76
146.06
146.04
140.07
139.70
133.02
132.93
127.27
127.00
120.23
112.12
110.19
110.17
54.59
37.75
37.61
33.84
30.43
30.38
29.23
28.20
28.13
27.75
26.65
26.63
25.32
24.08
Ot-Bu
MeO
PCy2
i-Pr
i-Pr
i-Pr
L5
13C NMR, 101 MHz, CDCl3
solvent
190
170
150
130
110
90
70
50
30
10
ppm

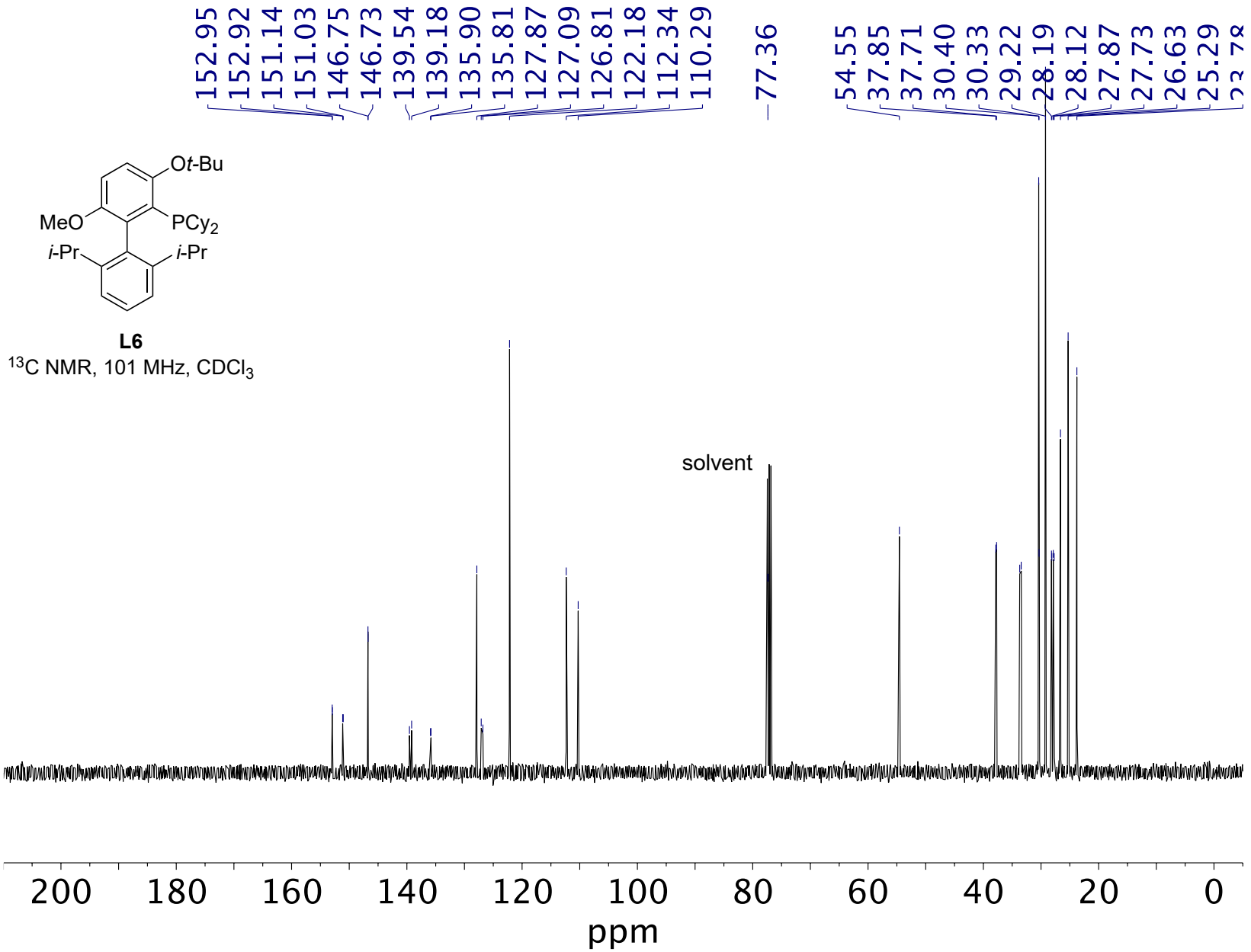


L5

^{31}P NMR, 162 MHz, $CDCl_3$

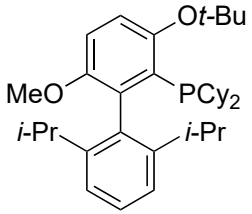


L6
^{1}H NMR, 400 MHz, $CDCl_3$



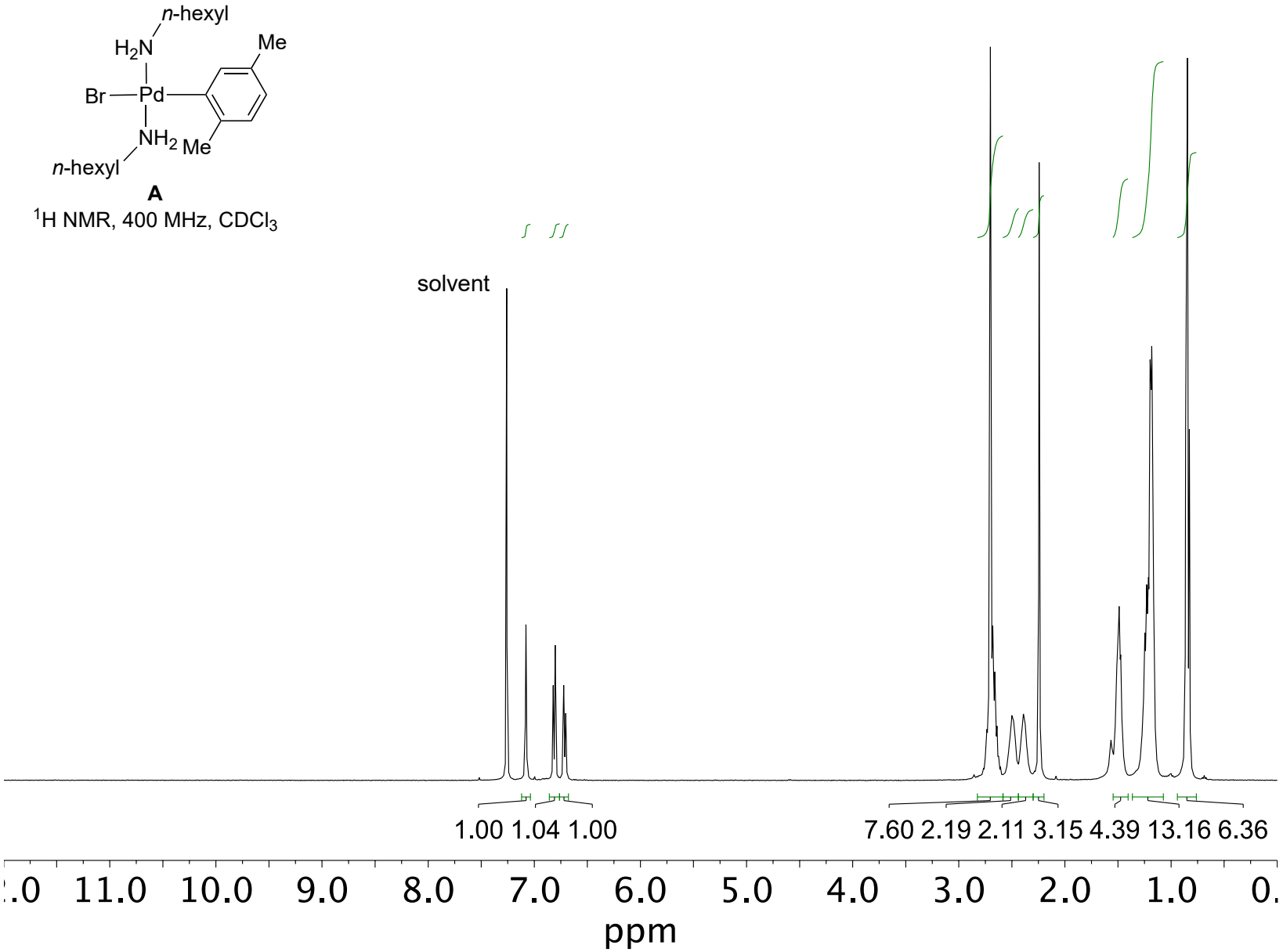
L6

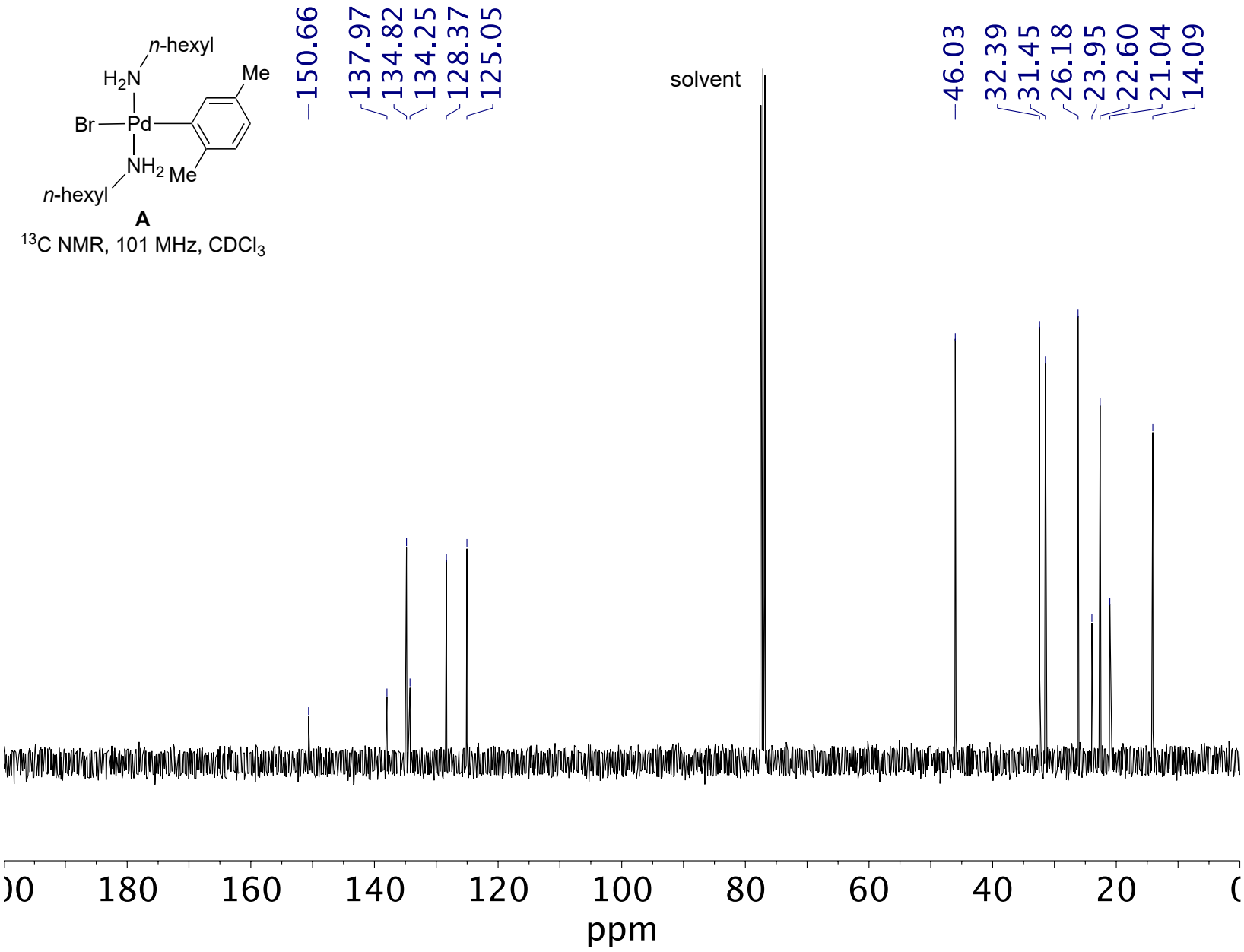
^{13}C NMR, 101 MHz, $CDCl_3$

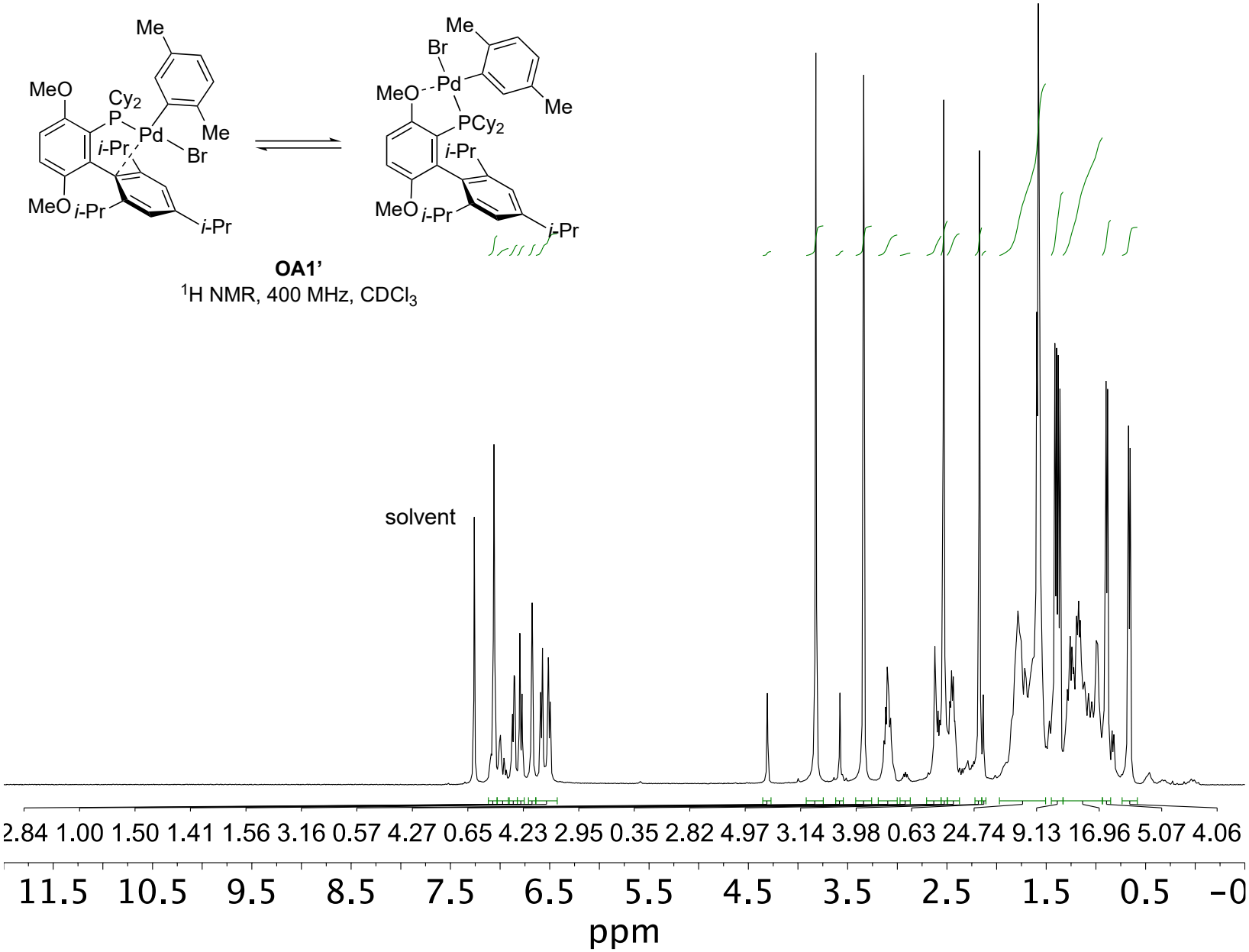


L6

^{31}P NMR, 162 MHz, $CDCl_3$

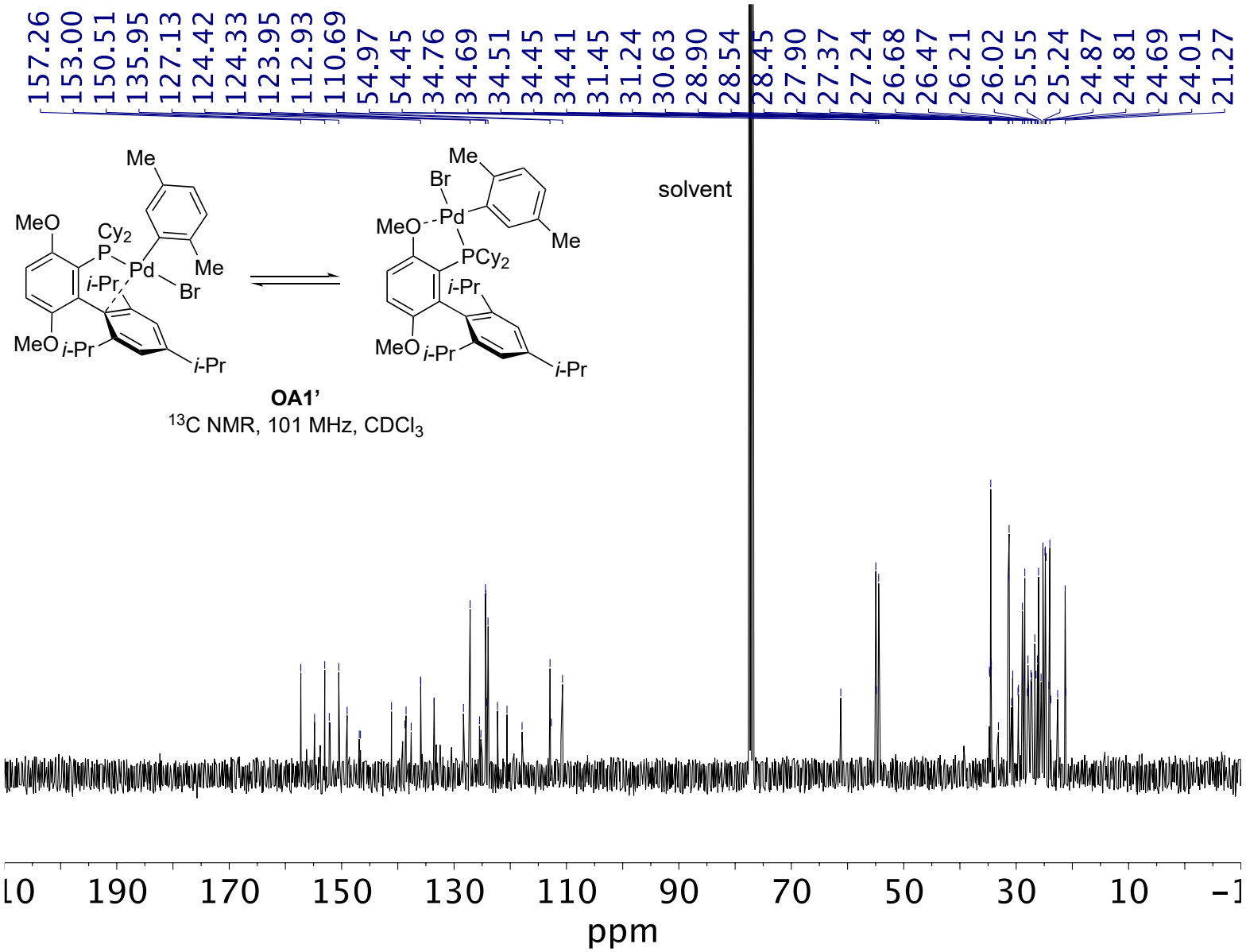

n-hexyl
H2N
Me
Br
Pd
NH2
Me
n-hexyl
A
1H NMR, 400 MHz, CDCl3
solvent
1.00 1.04 1.00
7.60 2.19 2.11 3.15 4.39 13.16 6.36
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm

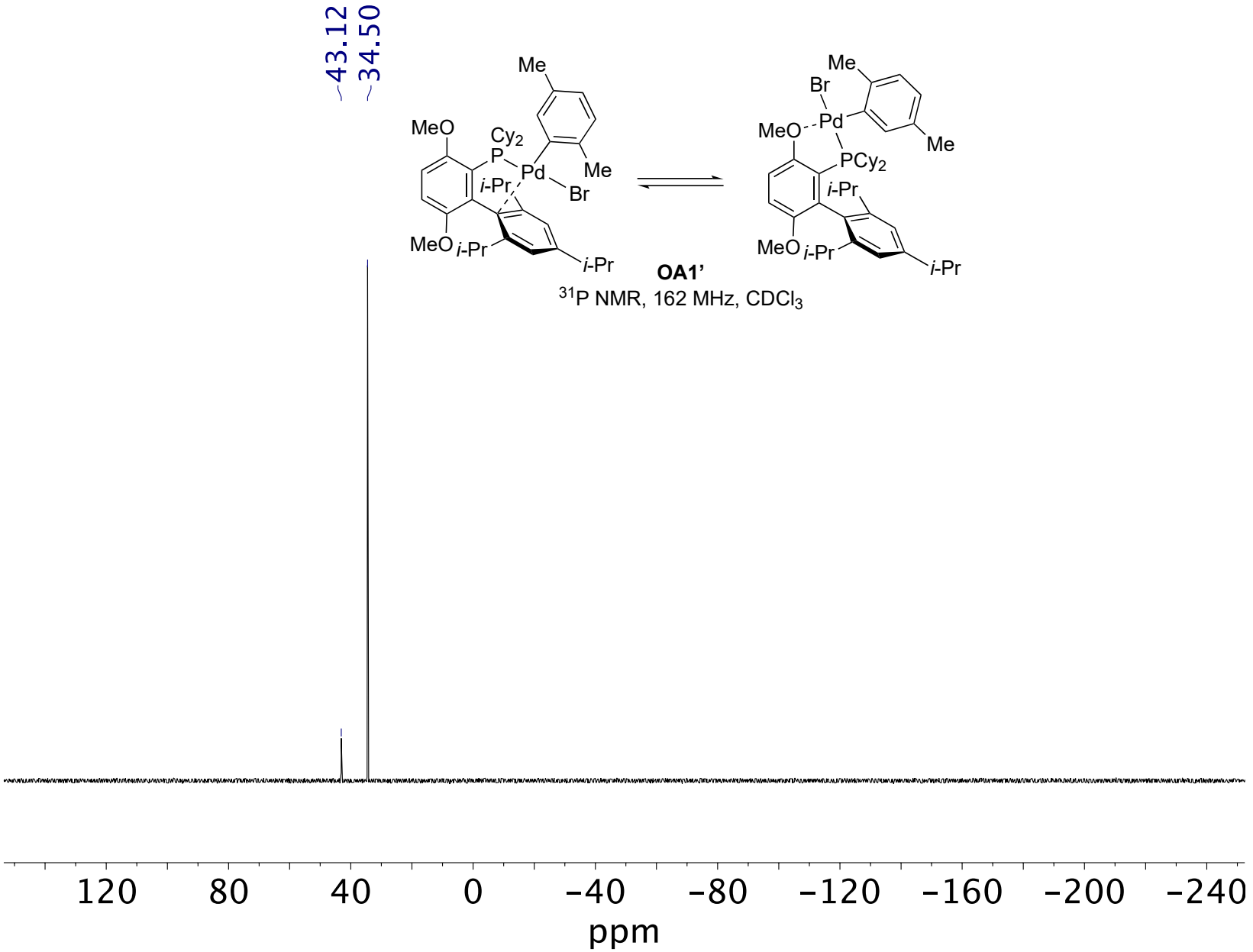

n-hexyl
H2N
Me
Br
Pd
NH2
Me
n-hexyl
A
13C NMR, 101 MHz, CDCl3
150.66
137.97
134.82
134.25
128.37
125.05
solvent
46.03
32.39
31.45
26.18
23.95
22.60
21.04
14.09
180
160
140
120
100
80
60
40
20
ppm



OA1'

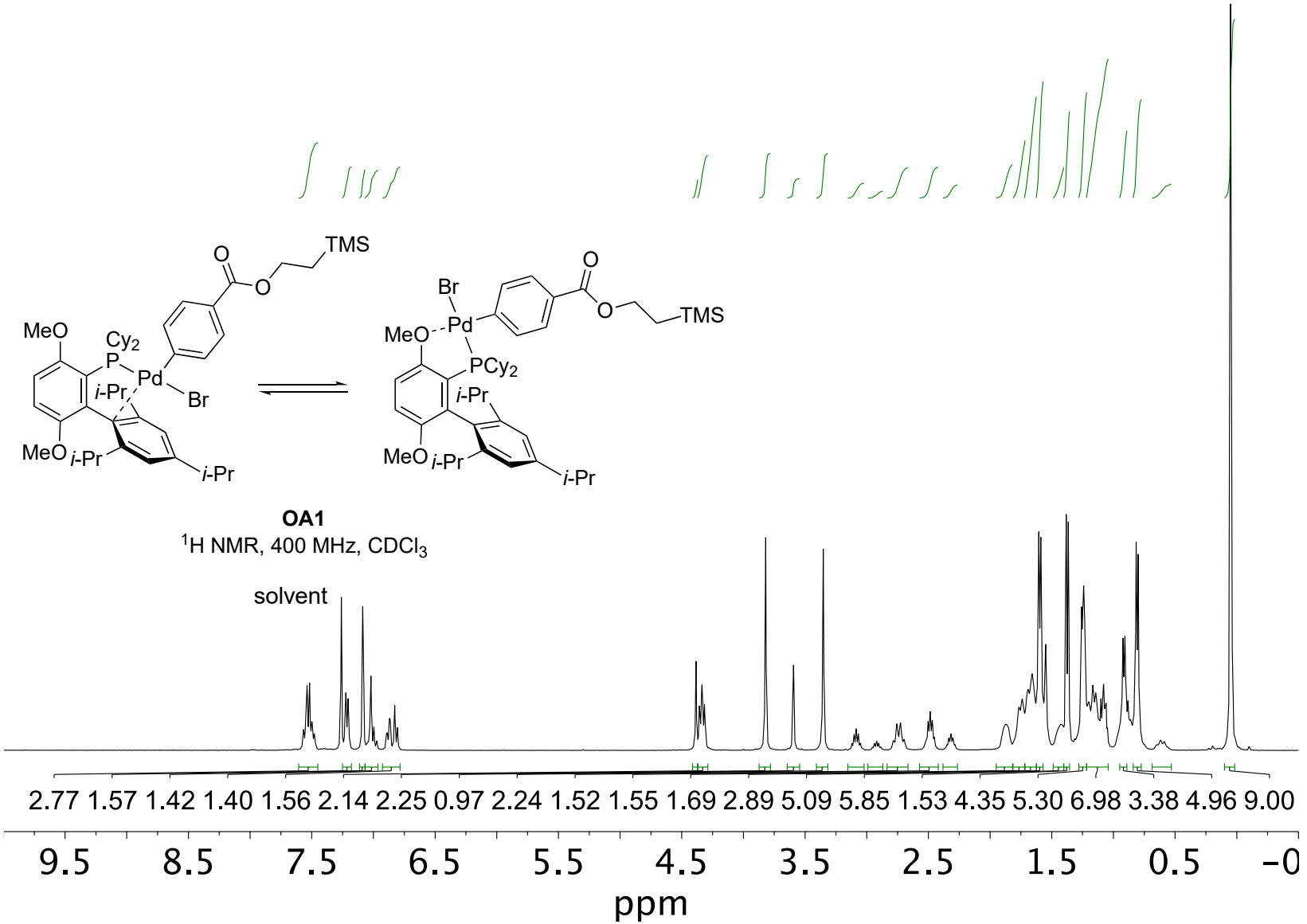
^{1}H NMR, 400 MHz, $CDCl_3$

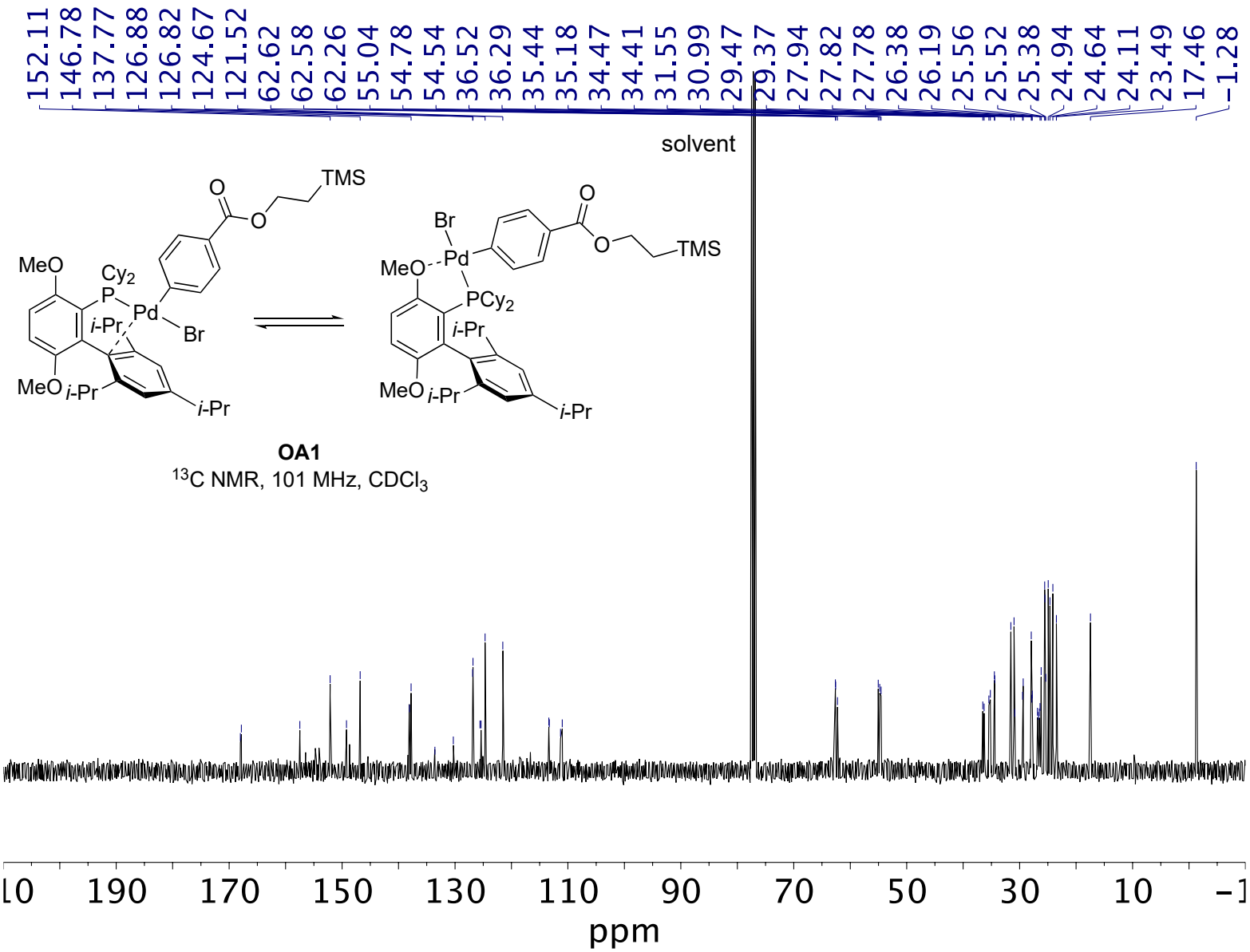

157.26
153.00
150.51
135.95
127.13
124.42
124.33
123.95
112.93
110.69
54.97
54.45
34.76
34.69
34.51
34.45
34.41
31.45
31.24
30.63
28.90
28.54
28.45
27.90
27.37
27.24
26.68
26.47
26.21
26.02
25.55
25.24
24.87
24.81
24.69
24.01
21.27
solvent
Me
MeO
Cy2
P
Pd
Me
Br
i-Pr
MeO
i-Pr
i-Pr
Me
Br
MeO
Pd
Me
PCy2
i-Pr
MeO
i-Pr
i-Pr
OA1'
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm

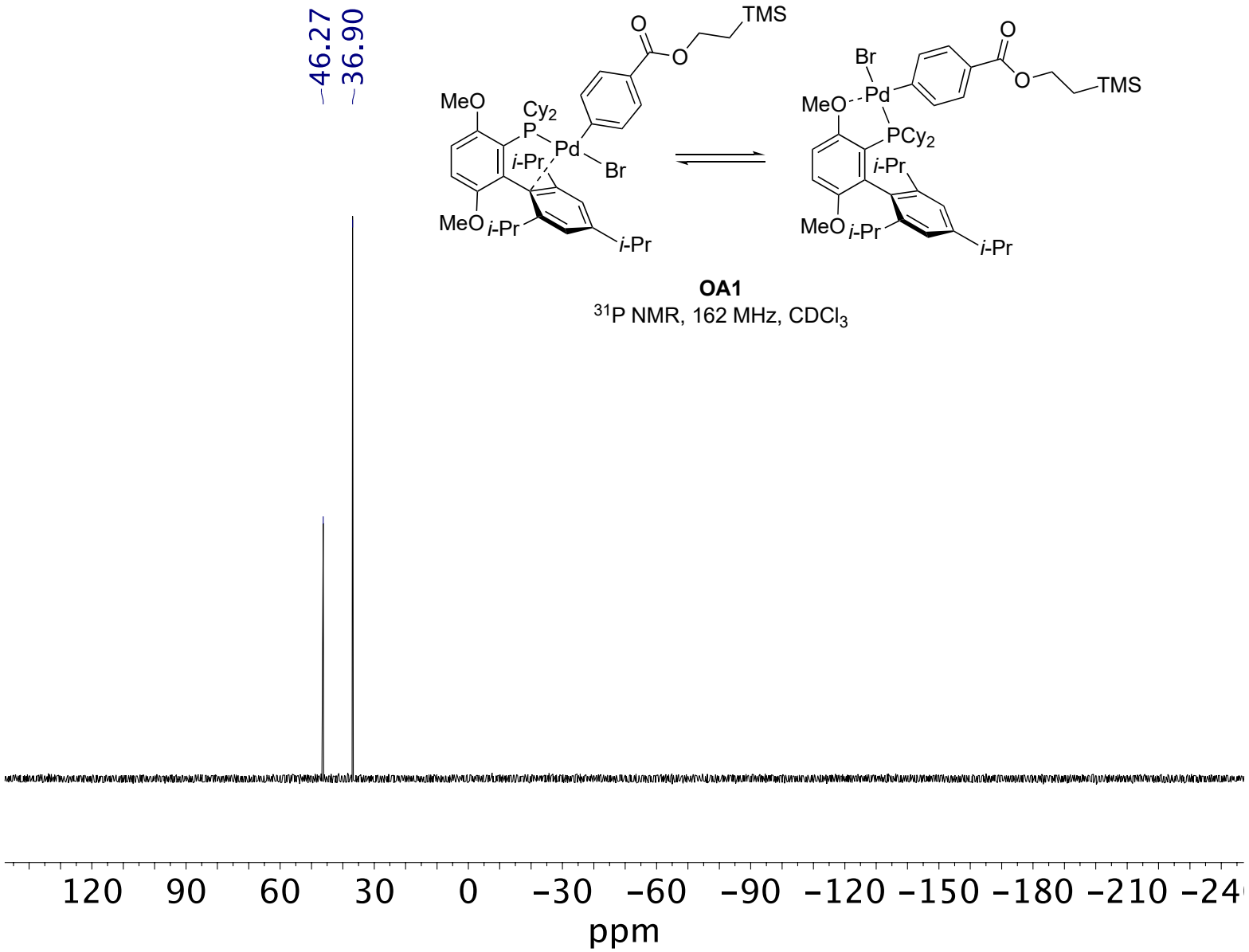


OA1'

^{31}P NMR, 162 MHz, $CDCl_3$

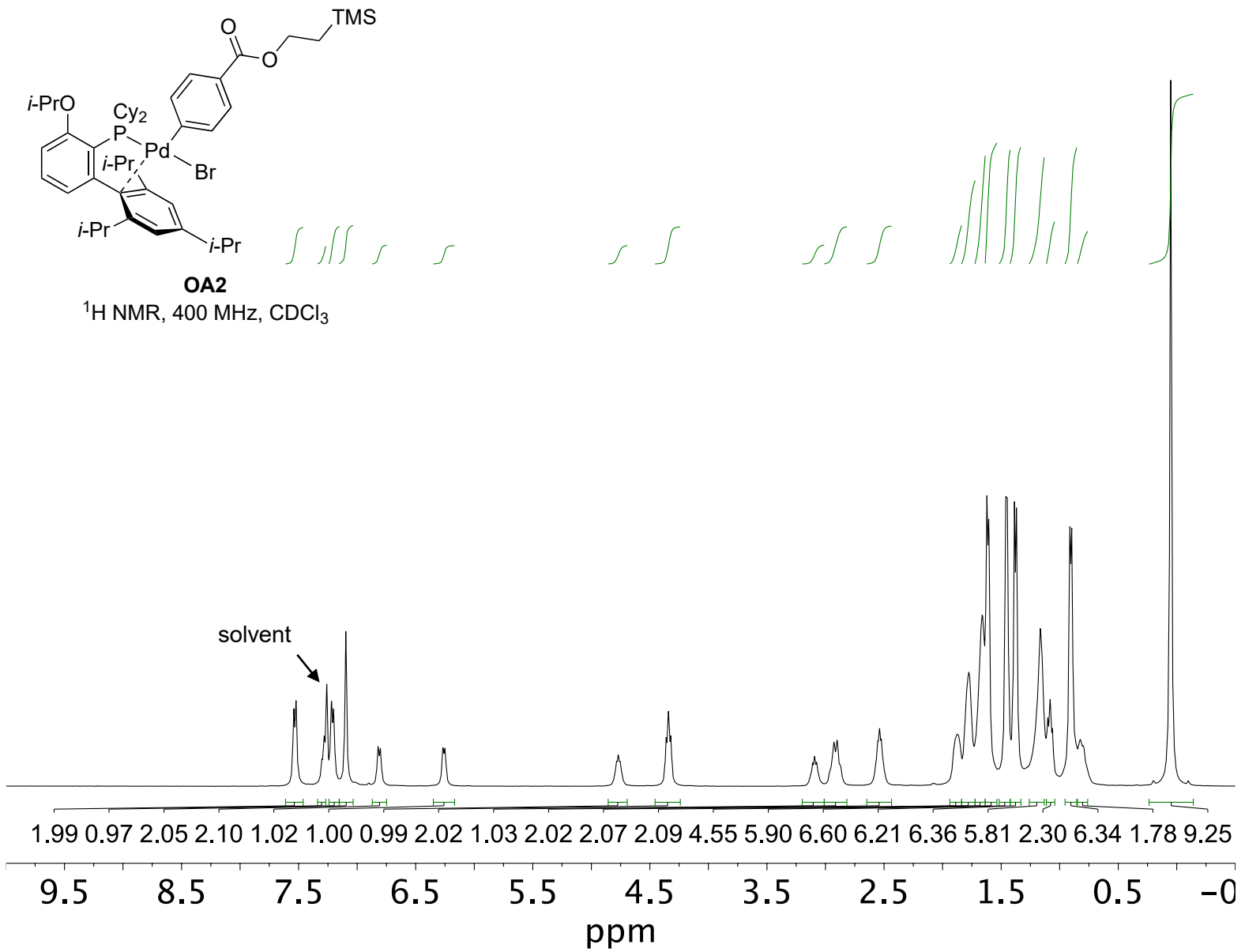

TMS
O
O
MeO
Cy2
P
Pd
Br
i-Pr
MeO
i-Pr
i-Pr
Br
Pd
MeO
PCy2
i-Pr
MeO
i-Pr
i-Pr
O
O
TMS
OA1
1H NMR, 400 MHz, CDCl3
solvent
2.77 1.57 1.42 1.40 1.56 2.14 2.25 0.97 2.24 1.52 1.55 1.69 2.89 5.09 5.85 1.53 4.35 5.30 6.98 3.38 4.96 9.00
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0
ppm


152.11
146.78
137.77
126.88
126.82
124.67
121.52
62.62
62.58
62.26
55.04
54.78
54.54
36.52
36.29
35.44
35.18
34.47
34.41
31.55
30.99
29.47
29.37
27.94
27.82
27.78
26.38
26.19
25.56
25.52
25.38
24.94
24.64
24.11
23.49
17.46
-1.28
solvent
TMS
O
O
MeO
Cy2
P
Pd
Br
i-Pr
MeO
i-Pr
i-Pr
Br
Pd
O
O
TMS
MeO
PCy2
i-Pr
MeO
i-Pr
i-Pr
OA1
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm



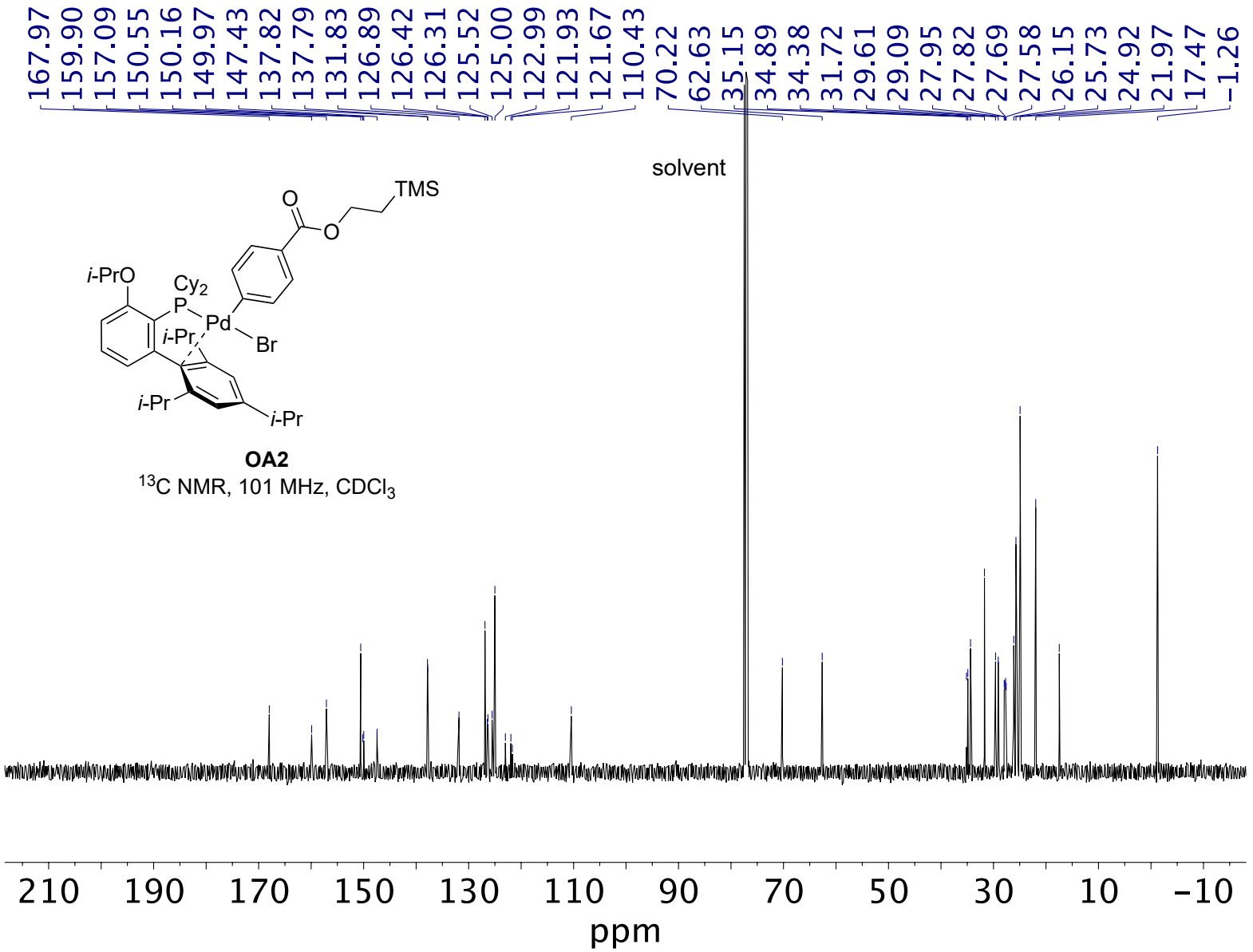
OA1

^{31}P NMR, 162 MHz, $CDCl_3$



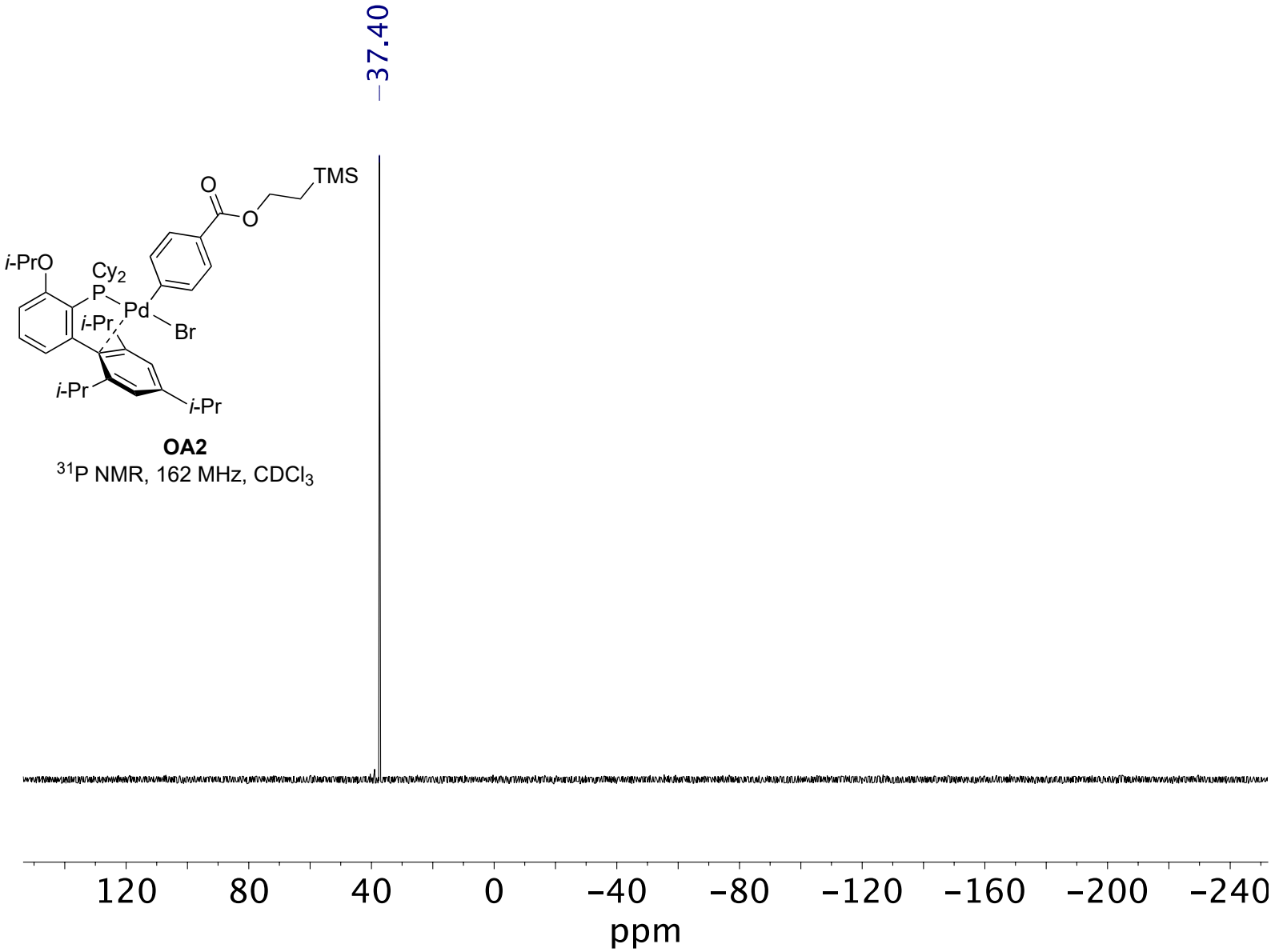
OA2

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



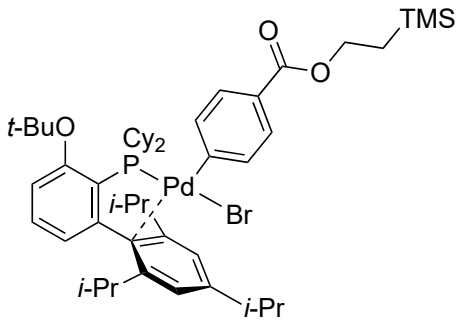
OA2

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



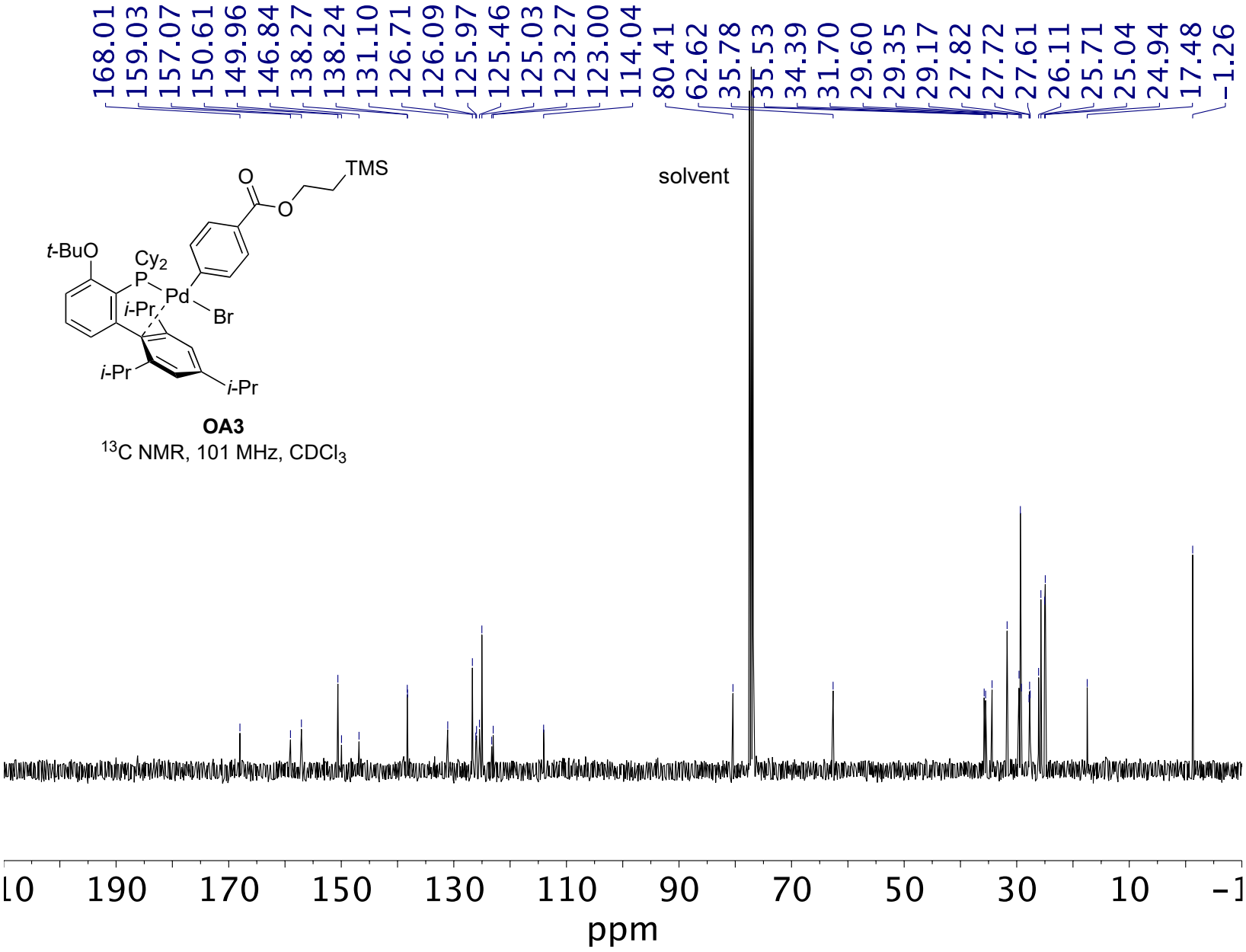
OA2

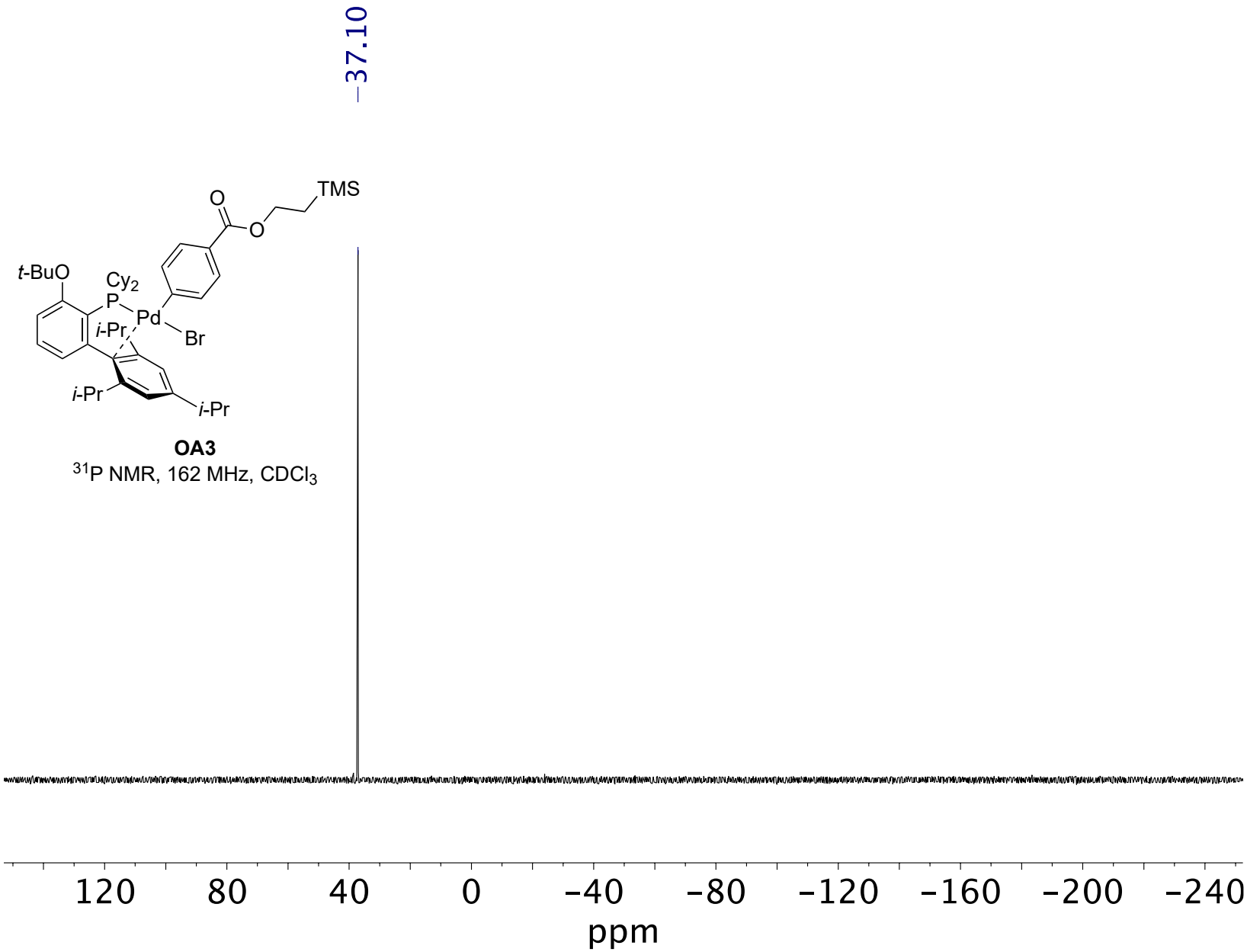
^{31}P NMR, 162 MHz, $CDCl_3$



OA3

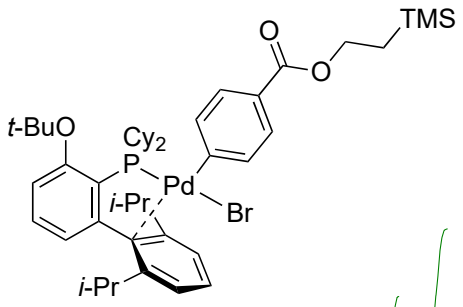
^{1}H NMR, 400 MHz, $CDCl_3$


168.01
159.03
157.07
150.61
149.96
146.84
138.27
138.24
131.10
126.71
126.09
125.97
125.46
125.03
123.27
123.00
114.04
80.41
62.62
35.78
35.53
34.39
31.70
29.60
29.35
29.17
27.82
27.72
27.61
26.11
25.71
25.04
24.94
17.48
-1.26
solvent
TMS
O
O
t-BuO
Cy2
P
Pd
i-Pr
Br
i-Pr
i-Pr
OA3
13C NMR, 101 MHz, CDCl3
190
170
150
130
110
90
70
50
30
10
ppm



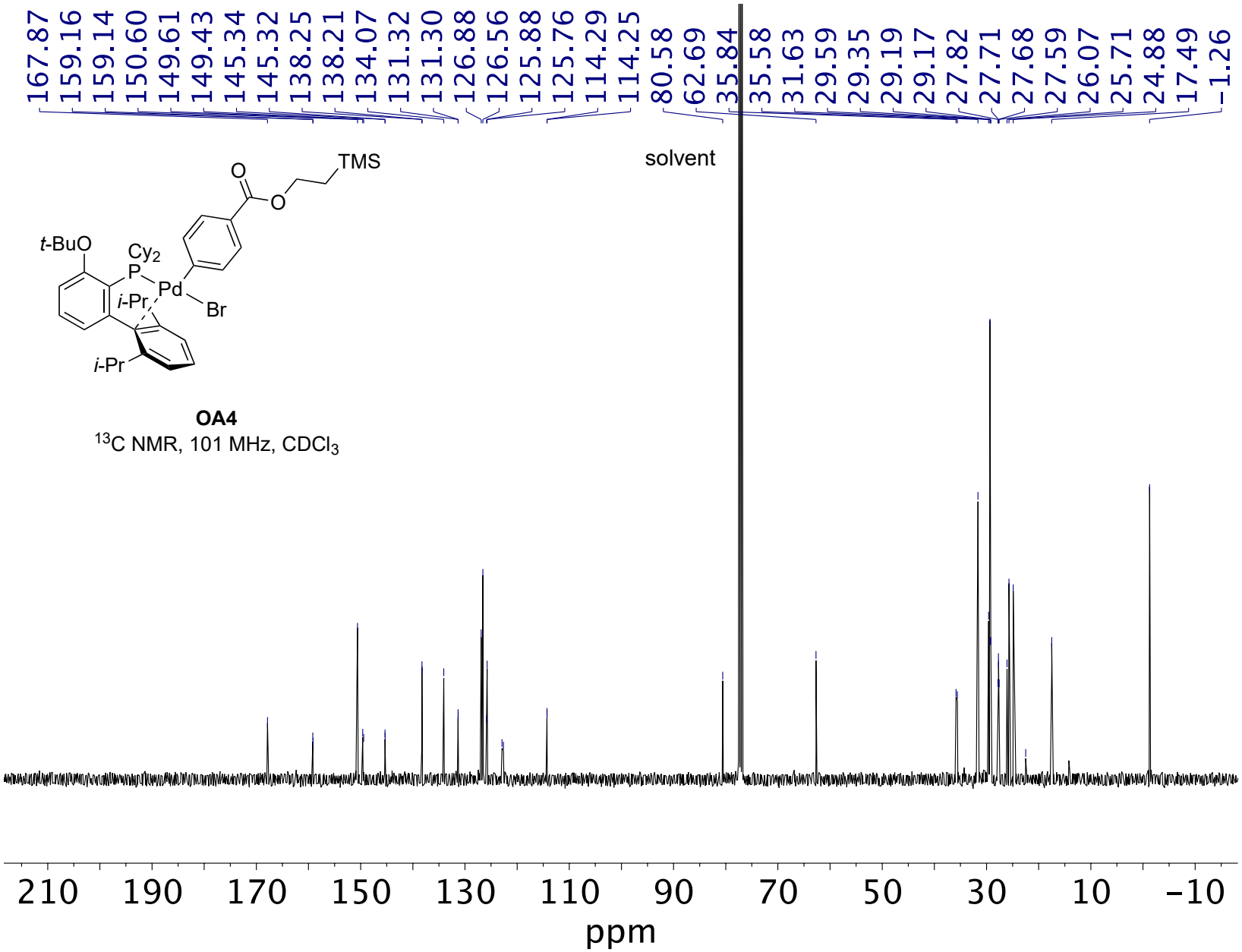
OA3

^{31}P NMR, 162 MHz, $CDCl_3$



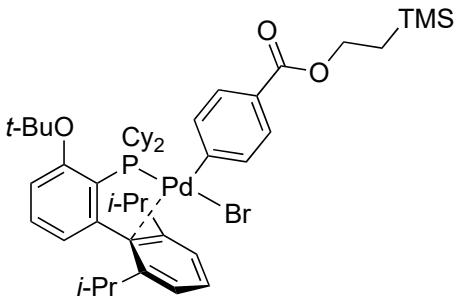
OA4

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



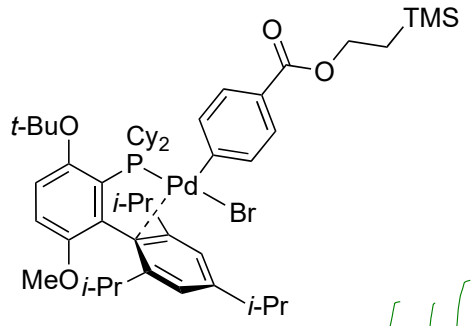
OA4

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



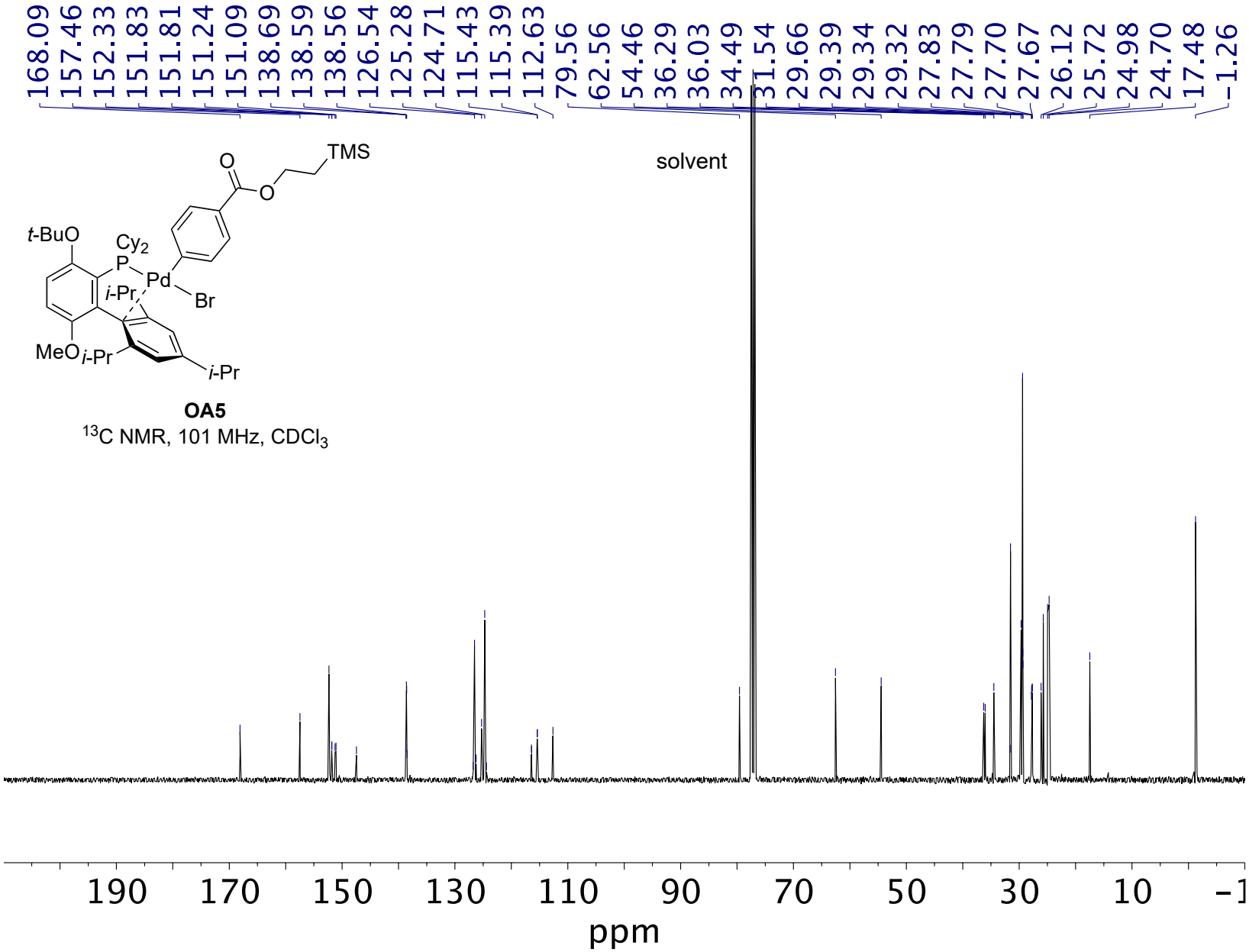
OA4

^{31}P NMR, 162 MHz, $CDCl_3$



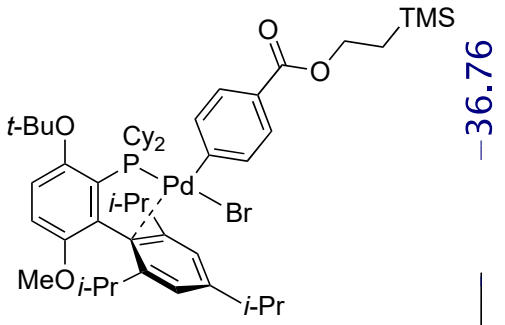
OA5

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



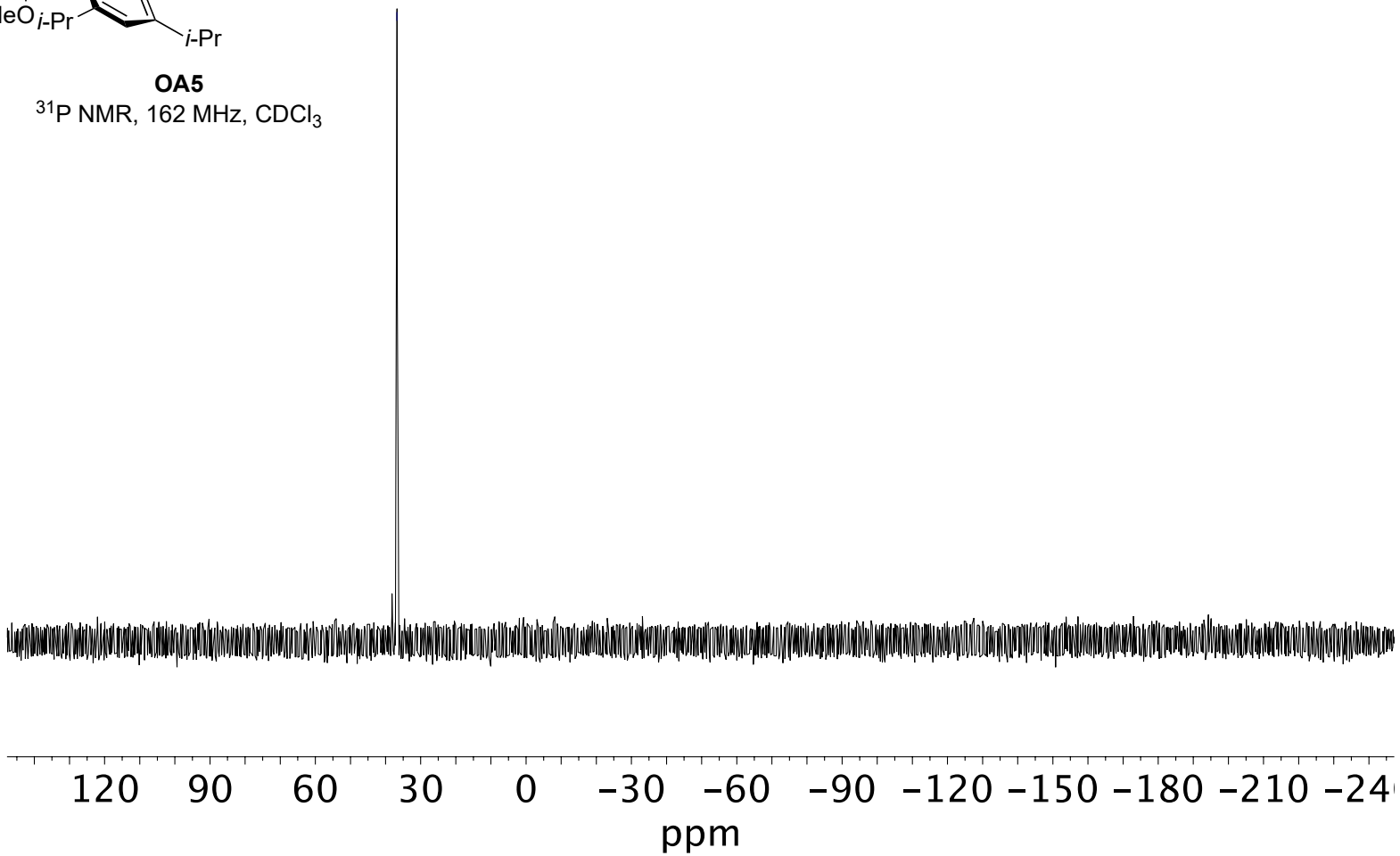
OA5

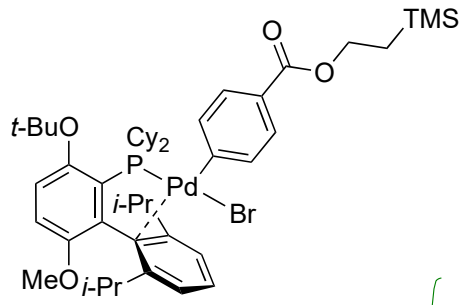
^{13}C NMR, 101 MHz, $CDCl_3$



OA5

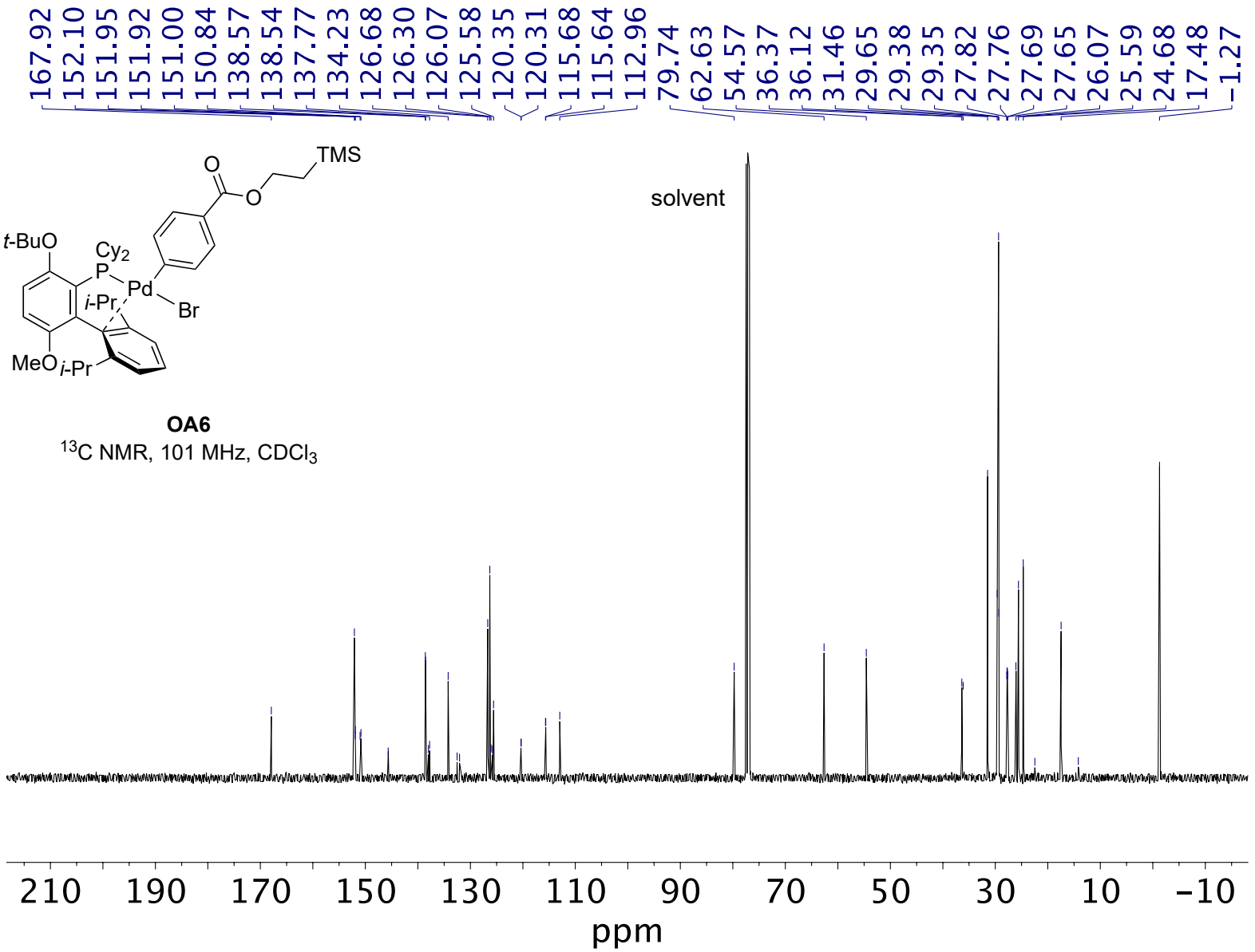
^{31}P NMR, 162 MHz, $CDCl_3$





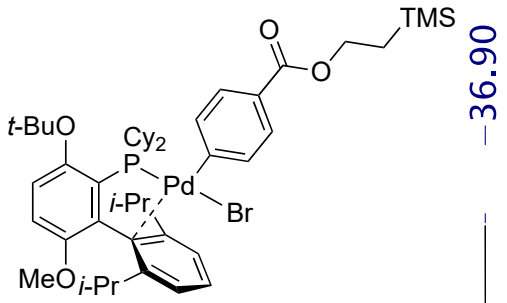
OA6

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



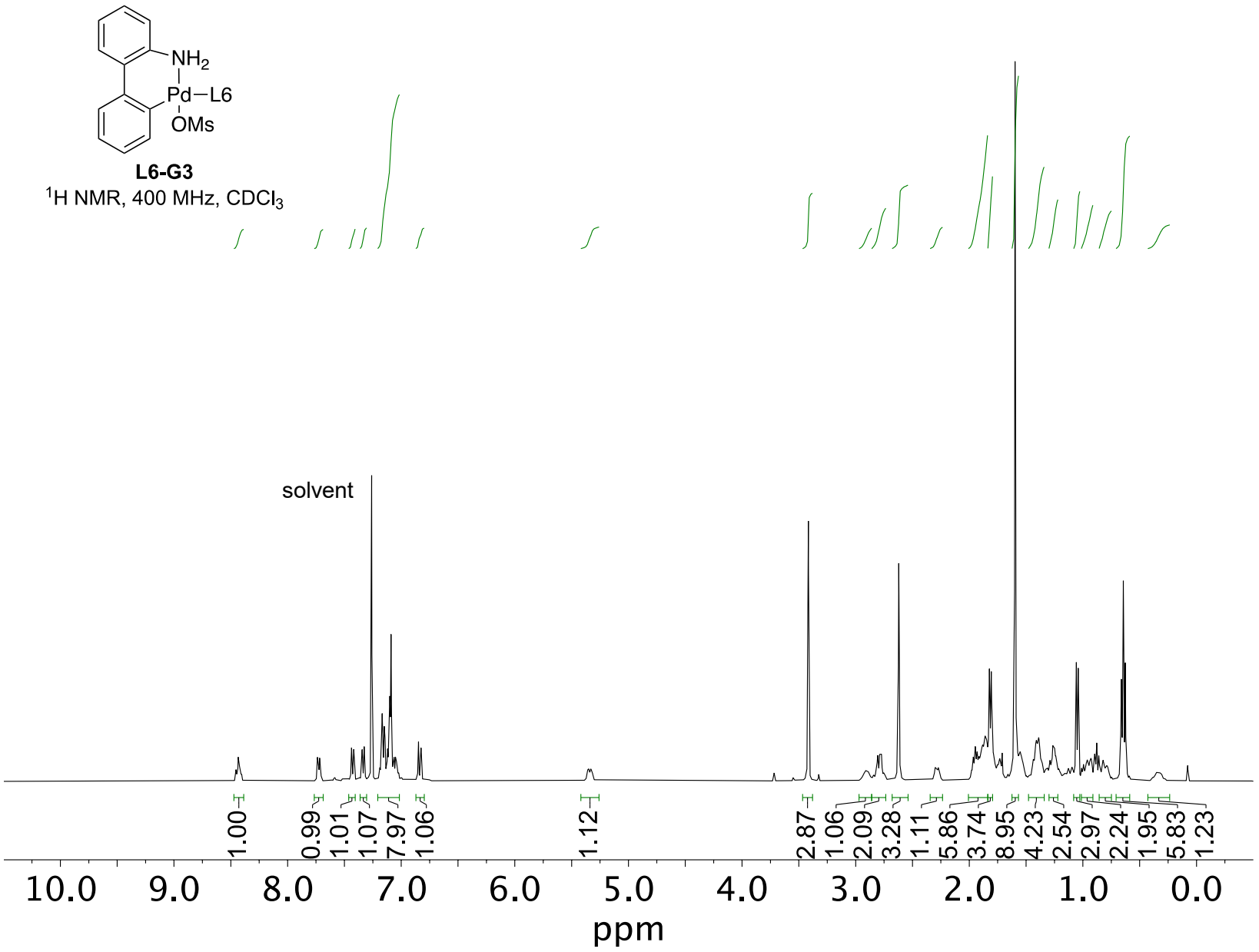
OA6

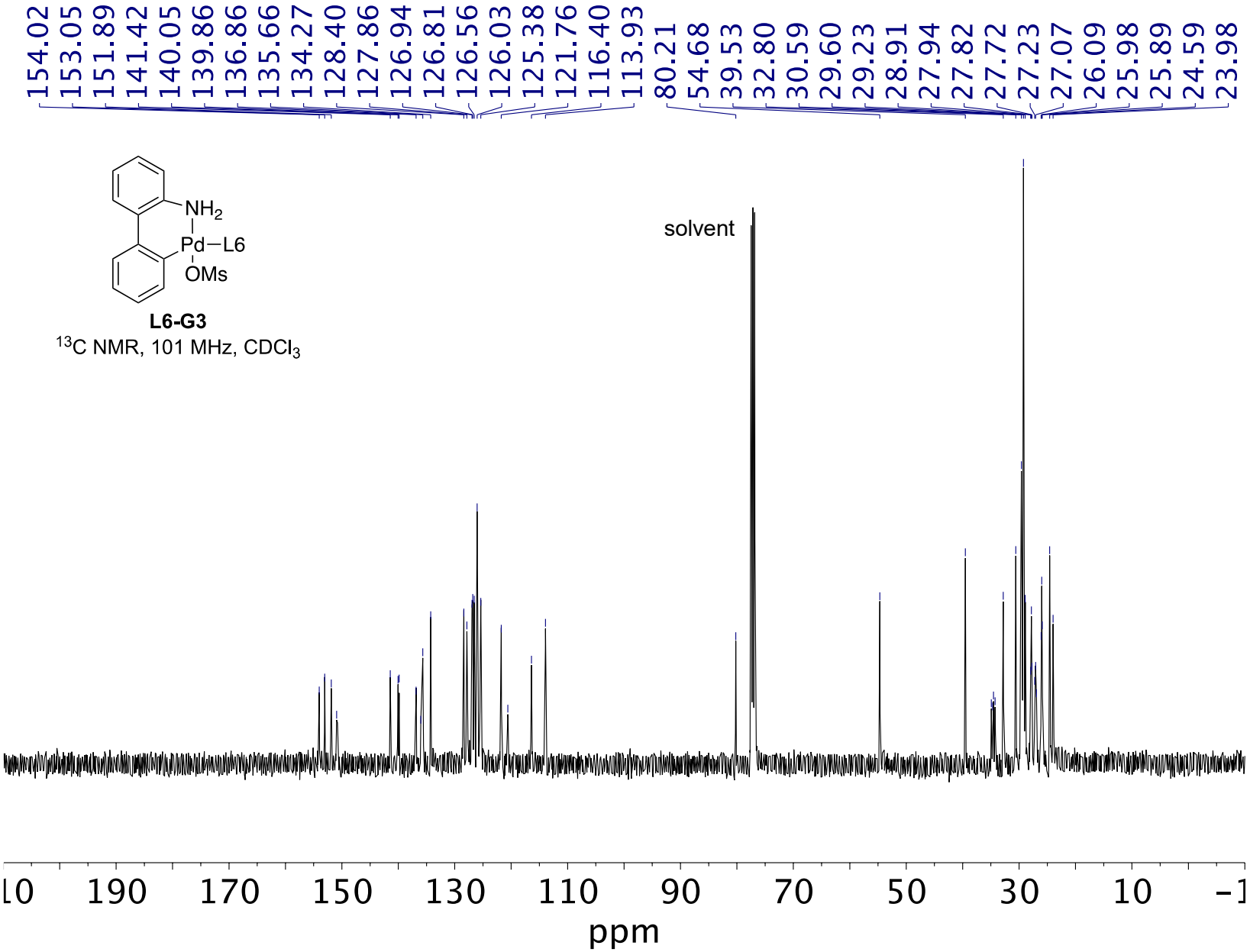
^{13}C NMR, 101 MHz, $CDCl_3$

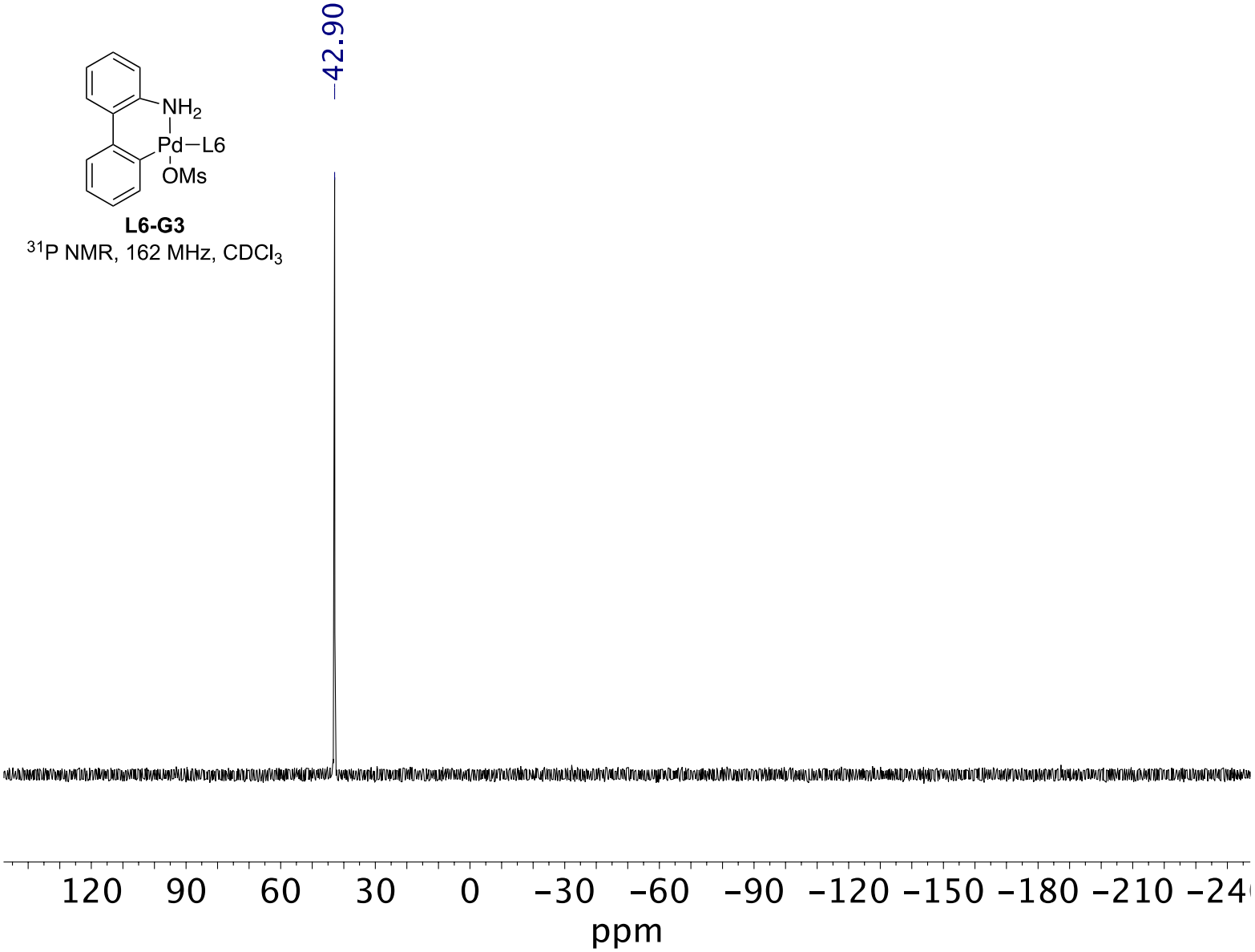


OA6

^{31}P NMR, 162 MHz, $CDCl_3$


NH2
Pd—L6
OMs
L6-G3
1H NMR, 400 MHz, CDCl3
solvent
1.00
0.99
1.01
1.07
7.97
1.06
1.12
2.87
1.06
2.09
3.28
1.11
5.86
3.74
8.95
4.23
2.54
2.97
2.24
1.95
5.83
1.23
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm


154.02
153.05
151.89
141.42
140.05
139.86
136.86
135.66
134.27
128.40
127.86
126.94
126.81
126.56
126.03
125.38
121.76
116.40
113.93
80.21
54.68
39.53
32.80
30.59
29.60
29.23
28.91
27.94
27.82
27.72
27.23
27.07
26.09
25.98
25.89
24.59
23.98
NH2
Pd—L6
OMs
L6-G3
13C NMR, 101 MHz, CDCl3
solvent
190
170
150
130
110
90
70
50
30
10
ppm


NH2
Pd—L6
OMs
L6-G3
31P NMR, 162 MHz, CDCl3
-42.90
120
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
ppm

2.5 References

1. (a) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451–3479. (b) Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists' Bread and Butter. *J. Med. Chem.* **2016**, *59*, 4385–4402. (c) Brown, D. G.; Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443–4458.
2. Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.
3. For recent examples of Cu- and Ni-catalyzed C–N cross coupling reactions, see: (a) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. Aryl amination using ligand-free Ni(II) salts and photoredox catalysis. *Science* **2016**, *353*, 279–283. (b) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. Selected Copper-Based Reactions for C–N, C–O, C–S, and C–C Bond Formation. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136-16179. (c) Lavoie, C. M.; Stradiotto, M. Bisphosphines: A Prominent Ancillary Ligand Class for Application in Nickel-Catalyzed C−N Cross-Coupling. *ACS Catal.* **2018**, *8*, 7228–7250. (d) Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; deGruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, H. S.; Neurock, M.; Minteer, S. D.; Baran, P. S. Electrochemically Driven, Ni-Catalyzed Aryl Amination: Scope, Mechanism, and Applications. *J. Am. Chem. Soc.* **2019**, *141*, 6392–6402. (e) Kudisch, M.; Lim, C.-H.; Thordarson, P.; Miyake, G. M. Energy Transfer to Ni-Amine Complexes in Dual Catalytic, Light-Driven C−N Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 19479–19486.
4. (a) Surry, D. S.; Buchwald, S. L. Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide. *Chem. Sci.* **2011**, *2*, 27–50. (b) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. Biaryl monophosphine ligands in palladium-catalyzed C–N coupling: An updated User's guide. *Tetrahedron* **2019**, *75*, 4199–4211.
5. For Pd catalysts developed by others for C–N coupling, see: (a) Ehrentraut, A.; Zapf, A.; Beller, M. A new improved catalyst for the palladium-catalyzed amination of aryl chlorides. *J. Mol. Catal. A: Chem.* **2002**, *181–182*, 515–523. (b) Singer, R. A.; Doré, M.; Sieser, J. E.; Berliner, M. A. Development of nonproprietary phosphine ligands for the Pd-catalyzed amination reaction. *Tetrahedron Lett.* **2006**, *47*, 3727–3731. (c) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (d) Fortman, G. C.; Nolan, S. P. *N*-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. *Chem. Soc. Rev.* **2011**, *40*, 5151–5169. (e) Froese, R. D. J.; Lombardi, C.; Pompeo, M.; Rucker, R. P.; Organ, M. G. Designing Pd−N-Heterocyclic Carbene Complexes for High Reactivity and Selectivity for Cross-Coupling Applications. *Acc. Chem. Res.* **2017**, *50*, 2244–2253. (f) Crawford, S. M.; Wheaton, C. A.; Mishra, V.; Stradiotto, M. Probing the effect of donor-fragment substitution in Mor-DalPhos on palladium-catalyzed C–N and C–C cross-coupling reactivity. *Can. J. Chem.* **2018**, *96*, 578–586.
6. (a) Hartwig, J. F. Carbon–Heteroatom Bond-Forming Reductive Eliminations of Amines, Ethers, and Sulfides. *Acc. Chem. Res.* **1998**, *31*, 852–860. (b) Hartwig, J. F. Transition Metal

Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067. (c) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. Reevaluation of the Mechanism of the Amination of Aryl Halides Catalyzed by BINAP-Ligated Palladium Complexes. *J. Am. Chem. Soc.* **2006**, *128*, 3584–3591.

7. (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. A New Class of Easily Activated Palladium Precatalysts for Facile C–N Cross-Coupling Reactions and the Low Temperature Oxidative Addition of Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687. (b) Wagschal, S.; Perego, L. A.; Simon, A.; Franco-Espejo, A.; Tocqueville, C.; Albaneze-Walker, J.; Jutand, A.; Grimaud, L. Formation of XPhos-Ligated Palladium(0) Complexes and Reactivity in Oxidative Additions. *Chem.–Eur. J.* **2019**, *25*, 6980–6987. Note: the half-reaction time of oxidative addition was measured starting from $Pd^0(XPhos)_2$, so the rate of oxidative addition is limited in part by ligand dissociation.
8. Biscoe, M. R.; Barder, T. E.; Buchwald, S. L. Electronic Effects on the Selectivity of Pd-Catalyzed C–N Bond-Forming Reactions Using Biarylphosphine Ligands: The Competitive Roles of Amine Binding and Acidity. *Angew. Chem., Int. Ed.* **2007**, *46*, 7232–7235.
9. Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. Reductive Elimination of d^8-Organotransition Metal Complexes. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857–1867.
10. (a) Arrechea, P. L.; Buchwald, S. L. Biaryl Phosphine Based Pd(II) Amido Complexes: The Effect of Ligand Structure on Reductive Elimination. *J. Am. Chem. Soc.* **2016**, *138*, 12486–12493. Note: Ph_2NH is an especially challenging nucleophile for reductive elimination, which is why isolation of the L–Pd(aryl)amido was possible. All other amine nucleophiles undergo reductive elimination sufficiently rapidly that isolation is not possible at room temperature. (b) The half-life was calculated from data in reference 17. See Figure 19 for details.
11. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions: Room-Temperature Suzuki Couplings and Amination of Unactivated Aryl Chlorides. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723. (b) Wolfe, J. P.; Buchwald, S. L. A Highly Active Catalyst for the Room-Temperature Amination and Suzuki Coupling of Aryl Chlorides. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. Simple, Efficient Catalyst System for the Palladium-Catalyzed Amination of Aryl Chlorides, Bromides, and Triflates. *J. Org. Chem.* **2000**, *65*, 1158–1174.
12. For selected examples of early room-temperature Pd-catalyzed C–N coupling reactions by others, see: (a) Hamann, B. C.; Hartwig, J. F. Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. Room-Temperature Palladium-Catalyzed Amination of Aryl Bromides and Chlorides and Extended Scope of Aromatic C–N Bond Formation with a Commercial Ligand. *J. Org. Chem.* **1999**, *64*, 5575–5580. (c) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. Unparalleled Rates for the Activation of Aryl Chlorides and Bromides: Coupling with Amines and Boronic Acids in Minutes at Room Temperature. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746–4748.
13. For more recent examples of room-temperature aryl amination protocols, see: (a) Moss, T. A.; Addie, M. S.; Nowak, T.; Waring, M. J. Room-Temperature Palladium-Catalyzed Coupling of

Heteroaryl Amines with Aryl or Heteroaryl Bromides. *Synlett* **2012**, *23*, 285–289. (b) Lavoie, C. M.; MacQueen, P. M.; Rotta-Loria, N. L.; Sawatzky, R. S.; Borzenko, A.; Chisholm, A. J.; Hargreaves, B. K. V.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. Challenging nickel-catalysed amine arylations enabled by tailored ancillary ligand design. *Nat. Commun.* **2016**, *7*, 11073. (c) Weber, P.; Scherpf, T.; Rodstein, I.; Lichte, D.; Scharf, L. T.; Goossen, L. J.; Gessner, V. H. A Highly Active Ylide-Functionalized Phosphine for Palladium-Catalyzed Aminations of Aryl Chlorides. *Angew. Chem., Int. Ed.* **2019**, *58*, 3203–3207. (d) Scharf, L. T.; Rodstein, I.; Schmidt, M.; Scherpf, T.; Gessner, V. H. Unraveling the High Activity of Ylide-Functionalized Phosphines in Palladium-Catalyzed Amination Reactions: A Comparative Study with ^{Cy}JohnPhos and P*t*Bu$_3$. *ACS Catal.* **2020**, *10*, 999–1009. (e) Tappen, J.; Rodstein, I.; McGuire, K.; Grossjohann, A.; Löffler, J.; Scherpf, T.; Gessner, V. H. Palladium Complexes based on Ylide-Functionalized Phosphines (YPhos): Broadly Applicable High-Performance Precatalysts for the Amination of Aryl Halides at Room Temperature. *Chem.–Eur. J.* **2020**, *26*, 4281–4288.

14. (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-Catalyzed C–N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655. (b) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554. (c) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. Palladium-catalyzed coupling of functionalized primary and secondary amines with aryl and heteroaryl halides: two ligands suffice in most cases. *Chem. Sci.* **2011**, *2*, 57–68.
15. For recently developed ligands and reaction conditions from our group for aryl amination reactions, see: (a) Ruiz-Castillo, P.; Blackmond, D. G.; Buchwald, S. L. Rational Ligand Design for the Arylation of Hindered Primary Amines Guided by Reaction Progress Kinetic Analysis. *J. Am. Chem. Soc.* **2015**, *137*, 3085–3092. (b) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. Design of New Ligands for the Palladium-Catalyzed Arylation of α-Branched Secondary Amines. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259–8262. (c) Olsen, E. P. K.; Arrechea, P. L.; Buchwald, S. L. Mechanistic Insight Leads to a Ligand Which Facilitates the Pd-Catalyzed Formation of 2-(Hetero)Arylaminooxazoles and 4-(Hetero)Arylaminothiazoles. *Angew. Chem., Int. Ed.* **2017**, *56*, 10569. (d) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. Breaking the Base Barrier: An Electron-Deficient Palladium Catalyst Enables the Use of a Common Soluble Base in C−N Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 4721–4725. (e) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. Pd-Catalyzed C–N Coupling Reactions Facilitated by Organic Bases: Mechanistic Investigation Leads to Enhanced Reactivity in the Arylation of Weakly Binding Amines. *ACS Catal.* **2019**, *9*, 3822–3830.
16. (a) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. Insights into the Origin of High Activity and Stability of Catalysts Derived from Bulky, Electron-Rich Monophosphinobiaryl Ligands in the Pd-Catalyzed C–N Bond Formation. *J. Am. Chem. Soc.* **2003**, *125*, 13978–13980. (b) Strieter, E. R.; Buchwald, S. L. Evidence for the Formation and Structure of Palladacycles during Pd-Catalyzed C–N Bond Formation with Catalysts Derived from Bulky Monophosphinobiaryl Ligands. *Angew. Chem., Int. Ed.* **2006**, *45*, 925–928.

17. Arrechea, P. L. Mechanistic studies on palladium-catalyzed C–N cross-coupling reaction. Ph.D. Thesis, Massachusetts Institute of Technology, September 2016.
18. (a) Widenhoefer, R. A.; Buchwald, S. L. Formation of Palladium Bis(amine) Complexes from Reaction of Amine with Palladium Tris(*o*-tolyl)phosphine Mono(amine) Complexes. *Organometallics* **1996**, *15*, 3534–3542. (b) Zhong, H. A.; Widenhoefer, R. A. Kinetics and Mechanism of the Formation of Palladium Bis(benzylamine) Complexes from Reaction of Benzylamine with Palladium Tri-*o*-tolylphosphine Mono(amine) Complexes. *Inorg. Chem.* **1997**, *36*, 2610–2616. (c) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. Highly Reactive, General, and Long-Lived Catalysts for Coupling of Heteroaryl and Aryl Chlorides with Primary Nitrogen Nucleophiles. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371–1375.
19. For implication/observation of phosphine displacement by heterocycles, see: (a) Paul, F.; Patt, J.; Hartwig, J. F. Structural Characterization and Simple Synthesis of {Pd[P(*o*-Tol)$_3$]$_2$}. Spectroscopic Study and Structural Characterization of the Dimeric Palladium(II) Complexes Obtained by Oxidative Addition of Aryl Bromides and Their Reactivity with Amines. *Organometallics* **1995**, *14*, 3030–3039. (b) Wagaw, S.; Buchwald, S. L. The Synthesis of Aminopyridines: A Method Employing Palladium-Catalyzed Carbon–Nitrogen Bond Formation. *J. Org. Chem.* **1996**, *61*, 7240–7241.
20. For a discussion of the importance of catalyst deactivation in cross-coupling reactions, see: Balcells, D.; Nova, A. Designing Pd and Ni Catalysts for Cross-Coupling Reactions by Minimizing Off-Cycle Species. *ACS Catal.* **2018**, *8*, 3499–3515.
21. For examples of studies in which nucleophilic functional groups or coupling partners were found to degrade the Pd catalyst in other cross-coupling reactions, see: (a) Alvaro, E.; Hartwig, J. F. Resting State and Elementary Steps of the Coupling of Aryl Halides with Thiols Catalyzed by Alkylbisphosphine Complexes of Palladium. *J. Am. Chem. Soc.* **2009**, *131*, 7858–7868. (b) Ushkov, A. V.; Grushin, V. V. Rational Catalysis Design on the Basis of Mechanistic Understanding: Highly Efficient Pd-Catalyzed Cyanation of Aryl Bromides with NaCN in Recyclable Solvents. *J. Am. Chem. Soc.* **2011**, *133*, 10999–11005. (c) Düfert, M. A.; Billingsley, K. L.; Buchwald, S. L. Suzuki-Miyaura Cross-Coupling of Unprotected, Nitrogen-Rich Heterocycles: Substrate Scope and Mechanistic Investigation. *J. Am. Chem. Soc.* **2013**, *135*, 12877–12885. (d) Böck, K.; Feil, J. E.; Karaghiosoff, K.; Koszinowski, K. Catalyst Activation, Deactivation, and Degradation in Palladium-Mediated Negishi Cross-Coupling Reactions. *Chem.–Eur. J.* **2015**, *21*, 5548–5560. (e) Chernyshev, V. M.; Khazipov, O. V.; Shevchenko, M. A.; Chernenko, A. Y.; Astakhov, A. V.; Eremin, D. B.; Pasyukov, D. V.; Kashin, A. S.; Ananikov, V. P. Revealing the unusual role of bases in activation/ deactivation of catalytic systems: O–NHC coupling in M/NHC catalysis. *Chem. Sci.* **2018**, *9*, 5564–5577. (f) Eckert, P.; Organ, M. G. A Path to More Sustainable Catalysis: The Critical Role of LiBr in Avoiding Catalyst Death and its Impact on Cross-Coupling. *Chem.–Eur. J.* **2020**, *26*, 4861–4865.
22. For examples of examination of catalyst deactivation in other C–N cross-coupling reactions employing biaryl-type ligands, see: (a) Allgeier, A. M.; Shaw, B. J.; Hwang, T.-L.; Milne, J. E.; Tedrow, J. S.; Wilde, C. N. Characterization of Two Stable Degradants of Palladium ^{t}BuXPhos Catalyst and a Unique Dearomatization Reaction. *Organometallics* **2012**, *31*, 519–522. (b) Strotman, N. A.; Soumeillant, M. C.; Zhu, K.; Markwalter, C. E.; Wei, C. S.; Hsiao, Y.; Eastgate, M. D. Effects of Multiple Catalyst Deactivation Pathways and Continuous Ligand

Recycling on the Kinetics of Pd-Catalyzed C−N Coupling Reactions. *J. Org. Chem.* **2019**, *84*, 4653–4660.
23. The cost of reactor time and labor associated with carrying out chemical reactions is of particular importance in process chemistry applications. For example, see: Zhang, T. Y. Process Chemistry: The Science, Business, Logic, and Logistics. *Chem. Rev.* **2006**, *106*, 2583–2595.
24. The reactions performed in the OmniCal calorimeter were maintained at 26.0 °C using an external cooling bath. All other reactions were run under ambient conditions unless otherwise noted (i.e., no heating or cooling bath unless otherwise noted). In many cases, heat evolution was noted upon initiation of the cross-coupling reactions. This phenomenon was previously noted in another C–N cross-coupling protocol that was nominally carried out at room temperature, and likely plays a role in other aryl amination reactions that are effective without heating. See reference 13b.
25. Yang, Q.; Babij, N. R.; Good, S. Potential Safety Hazards Associated with Pd-Catalyzed Cross-Coupling Reactions. *Org. Process Res. Dev.* **2019**, *23*, 2608–2626.
26. (a) The OAC precatalyst was chosen for the mechanistic studies because an analogous OAC is an on-cycle species, which removes the possibility of slow catalyst activation leading to failed reactions at room temperature (seen for sources such as $Pd(OAc)_2$), and it also minimizes the potential for the kinetics of activation to be convoluted with the kinetics of the catalytic cycle (i.e., all of the catalyst is active immediately). (b) The aryl group (Ar = 4-(2-(trimethylsilyl)ethyl benzoate)) on the OAC precatalysts was chosen so that, if necessary, the Ar–NHR byproduct of catalyst activation could be transformed to the carboxylate (upon addition of TBAF) and separated from the desired product by an aqueous wash. See reference 31a.
27. Barder, T. E.; Buchwald, S. L. Insights into Amine Binding to Biaryl Phosphine Palladium Oxidative Addition Complexes and Reductive Elimination from Biaryl Phosphine Arylpalladium Amido Complexes via Density Functional Theory. *J. Am. Chem. Soc.* **2007**, *129*, 12003–12010.
28. Precatalyst **OA6** enabled the broadest scope of coupling reactions, but **OA2**–**OA5** are effective catalysts for a subset of the coupling reactions tested (see Figures 11–16).
29. It is possible that **A** is not the final catalyst deactivation product but is rather an intermediate in the catalyst deactivation pathway, particularly because Pd/amine complexes are known to form dimeric μ-amido species under basic conditions. See reference 6c and: Driver, M. S.; Hartwig, J. F. Energetics and Mechanism of Alkylamine N–H Bond Cleavage by Palladium Hydroxides: N–H Activation by Unusual Acid-Base Chemistry. *Organometallics* **1997**, *16*, 5706–5715.
30. Ge, S.; Green, R. A.; Hartwig, J. F. Controlling First-Row Catalysts: Amination of Aryl and Heteroaryl Chlorides and Bromides with Primary Aliphatic Amines Catalyzed by a BINAP-Ligated Single-Component Ni(0) Complex. *J. Am. Chem. Soc.* **2014**, *136*, 1617–1627.
31. For use of oxidative addition complexes as precatalysts in C–N, C–C, C–F, and C–S cross-coupling reactions, see: (a) Ingoglia, B. T.; Buchwald, S. L. Oxidative Addition Complexes as Precatalysts for Cross-Coupling Reactions Requiring Extremely Bulky Biarylphosphine Ligands. *Org. Lett.* **2017**, *19*, 2853–2856. (b) Chen, L.; Francis, H.; Carrow, B. P. An "On-Cycle" Precatalyst Enables Room-Temperature Polyfluoroarylation Using Sensitive Boronic Acids. *ACS Catal.* **2018**, *8*, 2989–2994. (c) Xu, J.; Liu, R. Y.; Yeung, C. S.; Buchwald, S. L.

Monophosphine Ligands Promote Pd-Catalyzed C−S Cross-Coupling Reactions at Room Temperature with Soluble Bases. *ACS Catal.* **2019**, *9*, 6461–6466.
32. The G3 precatalyst based on **L6** performed slightly worse than the corresponding oxidative addition complex. See Figure 17 for details.
33. Fors, B. P.; Davis, N. R.; Buchwald, S. L. An Efficient Process for Pd-Catalyzed C–N Cross-Coupling Reactions of Aryl Iodides: Insight Into Controlling Factors. *J. Am. Chem. Soc.* **2009**, *131*, 5766–5768.
34. NaO*t*-Bu is known to cleave triflates at elevated temperatures. Hartwig was able to minimize triflate cleavage at high temperature with slow addition of the aryl triflate. (a) Louie, J.; Driver. M. S.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Triflates and Importance of Triflate Addition Rate. *J. Org. Chem.* **1997**, *62*, 1268–1273. (b) Wolfe, J. P.; Buchwald, S. L. Palladium-Catalyzed Amination of Aryl Triflates. *J. Org. Chem.* **1997**, *62*, 1264–1267.
35. Substrates containing secondary or tertiary benzylic alcohols underwent competitive dehydration reactions to form the corresponding styrene derivatives. See Figure 18.
36. Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repič, O.; Blacklock, T. J. *β*-Hydrogen-Containing Sodium Alkoxides as Suitable Bases in Palladium-Catalyzed Aminations of Aryl Halides. *J. Org. Chem.* **2000**, *65*, 2612–2614.
37. Zask, A.; Helquist, P. Palladium hydrides in organic synthesis. Reduction of aryl halides by sodium methoxide catalyzed by tetrakis(triphenylphosphine)palladium. *J. Org. Chem.* **1978**, *43*, 1619–1620.
38. For a recent nickel catalyst capable of performing the arylation of α-tertiary amines, see: Tassone, J. P.; England, E. V.; MacQueen, P. M.; Ferguson, M. J.; Stradiotto, M. PhPAd-DalPhos: Ligand-Enabled, Nickel-Catalyzed Cross-Coupling of (Hetero)aryl Electrophiles with Bulky Primary Alkylamines. *Angew. Chem., Int. Ed*. **2019**, *58*, 2485–2489.
39. Pompeo, M.; Farmer, J. L.; Froese, R. D. J.; Organ, M. G. Room-Temperature Amination of Deactivated Aniline and Aryl Halide Partners with Carbonate Base Using a Pd-PEPPSI-IPent^{Cl}- *o*-Picoline Catalyst. *Angew. Chem., Int. Ed.* **2014**, *53*, 3223–3226.
40. For an example of NaO*t*-Bu reacting with a base-sensitive substrate at elevated temperature, see: Sperry, J. B.; Wiglesworth, K. E. P.; Edmonds, I.; Fiore, P.; Boyles, D. C.; Damon, D. B.; Dorow, R. L.; Chekler, E. L. P.; Langille, J.; Coe, J. W. Kiloscale Buchwald−Hartwig Amination: Optimized Coupling of Base-Sensitive 6-Bromoisoquinoline-1-carbonitrile with (*S*)-3-Amino-2-methylpropan-1-ol. *Org. Process Res. Dev.* **2014**, *18*, 1752–1758.
41. Brusoe, A. T.; Hartwig, J. F. Palladium-Catalyzed Arylation of Fluoroalkylamines. *J. Am. Chem. Soc.* **2015**, *137*, 8460–8468.
42. (a) Sheng, Q.; Ogata, T.; Hartwig, J. F. Highly Reactive, General and Long-Lived Catalysts for Palladium-Catalyzed Amination of Heteroaryl and Aryl Chlorides, Bromides, and Iodides: Scope and Structure–Activity Relationships. *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596. (b) Khadra, A.; Mayer, S.; Organ, M. G. Pd-PEPPSI-IPent^{Cl}: A Useful Catalyst for the Coupling of 2-Aminopyridine Derivatives. *Chem.–Eur. J.* **2017**, *23*, 3206–3212.
43. (a) Kutchukian, P. S.; Dropinski, J. F.; Dykstra, K. D.; Li, B.; DiRocco, D. A.; Streckfuss, E. C.; Campeau, L.-C.; Cernak, T.; Vachal, P.; Daavies, I. W.; Krska, S. W.; Dreher, S. D. Chemistry informer libraries: a chemoinformatics enabled approach to evaluate and advance synthetic methods. *Chem. Sci.* **2016**, *7*, 2604–2613. (b) Lin, S.; Dikler, S.; Blincoe, W. D.; Ferguson, R. D.; Sheridan, R. P.; Peng, Z.; Conway, D. V.; Zawatzky, K.; Wang, H.; Cernak,

T.; Davies, I. W.; DiRocco, D. A.; Sheng, H.; Welch, C. J.; Dreher, S. D. Mapping the dark space of chemical reactions with extended nanomole synthesis and MALDI-TOF MS. *Science* **2018**, *361*, eaar6236. (c) Uehling, M. R.; King, R. P.; Krska, S. W.; Cernak, T.; Buchwald, S. L. Pharmaceutical diversification via palladium oxidative addition complexes. *Science* **2019**, *363*, 405–408.

44. For a recent nickel catalyst capable of performing the arylation of 2-aminooxazole and 2-aminothiazole, see: Clark, J. S. K.; Ferguson, M. J.; McDonald, R.; Stradiotto, M. PAd2-DalPhos Enables the Nickel-Catalyzed C-N Cross-Coupling of Primary Heteroarylamines and (Hetero)aryl Chlorides. *Angew. Chem., Int. Ed.* **2019**, *58*, 6391–6395.
45. Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. Water-Mediated Catalyst Preactivation: An Efficient Protocol for C−N Cross-Coupling Reactions. *Org. Lett.* **2008**, *10*, 3505–3508.
46. Kofron, W. G.; Baclawski, L. M. A Convenient Method for Estimation of Alkyllithium Concentrations. *J. Org. Chem.* **1976**, *41*, 1879.
47. Pan, Y.; Young, G. B. Syntheses and spectroscopic characteristics of dialkylpalladium(II)complexes; PdR_2(cod) as precursors for derivatives with N- or P-donor ligands. *J. Organomet. Chem.* **1999**, *577*, 257.
48. Wallasch, M. W.; Weismann, D.; Riehn, C.; Ambrus, S.; Walmershäuser, G.; Lagutschenkov, A.; Niedner-Schatteburg, G.; Sitzmann, H. Reactive Sigma-Aryliron Complexes or Iron-Promoted Coupling of Two Phenyl Anions to One Bis(cyclohexadienylidene) Ligand: Synthesis, Structure, Mass Spectrometry, and DFT Calculations. *Organometallics* **2010**, *29*, 806.
49. Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and preparation of new palladium precatalysts for C–C and C–N cross-coupling reactions. *Chem. Sci.* **2013**, *4,* 916.
50. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176.
51. Huang, P.; Wang, Y.-W.; Yu, H.-F.; Lu, J.-M. N-Heterocyclic Carbene−Palladium(II)−4,5-Dihydrooxazole Complexes: Synthesis and Catalytic Activity toward Amination of Aryl Chlorides. *Organometallics* **2014**, *33*, 1587.
52. Liu, Z.; Larock, R. C. Facile *N*-Arylation of Amines and Sulfonamides and *O*-Arylation of Phenols and Arenecarboxylic Acids. *J. Org. Chem.* **2006**, *71*, 3198.
53. Deng, Q.; Zhang, Y.; Zhu, H.; Tu, T. Robust Acenaphthoimidazolylidene Palladacycles: Highly Efficient Catalysts for the Amination of N-Heteroaryl Chlorides. *Chem. Asian J.* **2017**, *12*, 2364.
54. Adeniji, A. O.; Twenter, B. M.; Byrns, M. C.; Jin, Y.; Chen, M.; Winkler, J. D.; Penning, T. M. Development of Potent and Selective Inhibitors of Aldo−Keto Reductase 1C3 (Type 5 17*β*-Hydroxysteroid Dehydrogenase) Based on *N*-Phenyl-Aminobenzoates and Their Structure−Activity Relationships. *J. Med. Chem.* **2012**, *55*, 2311.
55. Hill, L. L.; Crowell, J. L.; Tutwiler, S. L.; Massie, N. L.; Hines, C. C.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H.; Grasa, G. A.; Seechurn, C. C. C. J.; Li, H.; Colacot, J.; Chou, J.; Wiltermann, C. J. Synthesis and X-ray Structure Determination of Highly Active Pd(II), Pd(I), and Pd(0) Complexes of Di(*tert*-butyl)neopentylphosphine (DTBNpP) in the Arylation of Amines and Ketones. *J. Org. Chem.* **2010**, *75*, 6477.

Chapter 3

Pd-Catalyzed Amination of Base-Sensitive Five-Membered Heteroaryl Halides with Aliphatic Amines

3.1 Introduction

Five-membered heteroarenes and aliphatic amines are among the most prevalent substructures in pharmaceuticals,[1] agrochemicals,[2] and natural products.[3] While Pd-catalyzed C–N cross-coupling reactions are among the most frequently used transformations in medicinal chemistry,[4] very few methods have been reported for the coupling of five-membered heteroaryl halides. Notably, multi-heteroatom five-membered heteroarenes and aliphatic secondary amines account for a large fraction of the heterocycles found in pharmaceuticals and bioactive molecules,[1] but examples of coupling reactions between them are particularly rare.[5,6]

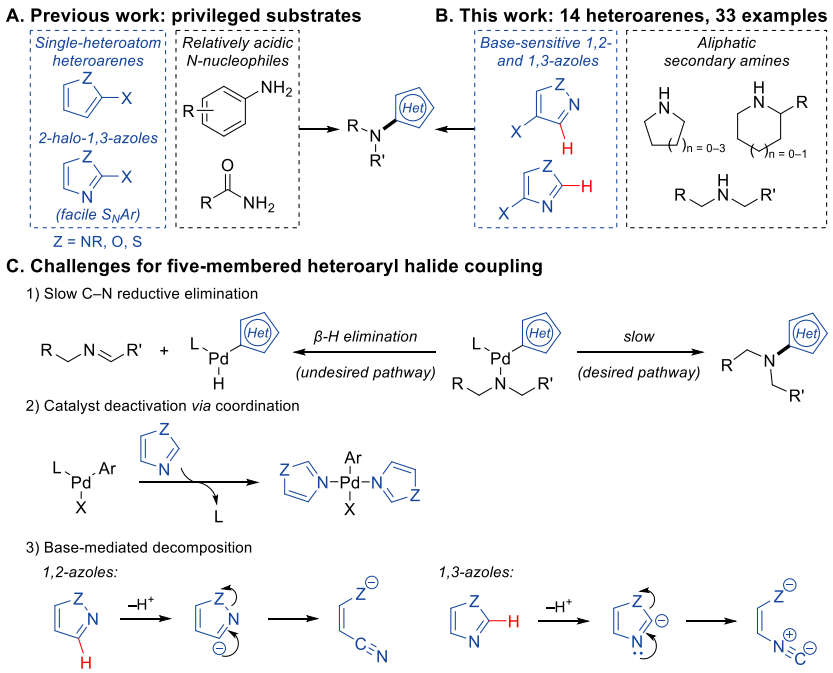


Figure 1. Limitations and challenges of Pd-catalyzed C–N coupling of five-membered heteroaryl halides.

Reported methods for coupling five-membered heteroaryl halides with secondary amines are largely limited to small classes of privileged substrates (Figure 1A). The heteroarenes investigated, with few exceptions,[6] are generally restricted to either arenes that contain a single heteroatom (e.g., thiophene, indole)[7] or activated 2-halo-1,3-azoles,[7a,8] the latter of which readily undergo S_NAr reactions in the absence of Pd.[8a–b,9] The scope of the amine coupling partner is similarly constrained. Several examples of relatively acidic primary nitrogen nucleophiles, such as anilines[10,11] and amides,[12] have been reported using weak bases, yet comparatively few studies have demonstrated coupling reactions of simple aliphatic amines,[5,6] especially α-branched[1a,13] or acyclic[4a] secondary amines. A general strategy that enables coupling between a wide range of five-membered heteroarenes and secondary amines remains highly desirable (Figure 1B).

Numerous challenges have hampered the development of a general method for the C–N coupling of five-membered heteroaryl halides (Figure 1C). Relative to six-membered arenes, the smaller, more electron-rich five-membered heteroarenes increase the difficulty of C–N reductive elimination,[14] in some cases rendering this process rate-limiting.[6a,15] Consequently, unproductive β-hydride elimination of the amine can become competitive, resulting in lower yields of the desired

C–N coupled products. (β-hydride elimination is a common side reaction in coupling reactions involving sterically demanding secondary amines.[13a]) Additionally, small, electron-rich five-membered heteroarenes frequently coordinate to Pd, promoting catalyst deactivation *via* displacement of the supporting phosphine ligand.[10,16] Secondary amine coupling partners often exacerbate this problem by requiring the use of smaller ligands,[17] which increase the susceptibility of the Pd center to heteroarene coordination and subsequent deactivation. Finally, many five-membered heteroarenes, including 3-H-1,2-[6a,18] and 2-H-1,3-azoles,[19] are unstable in the presence of the strong bases necessary for coupling aliphatic amines. Base-mediated decomposition of these heteroarenes results in the formation of unhindered anionic fragments that could act as potent catalyst deactivators, even when only a small fraction of the heteroarene has decomposed.

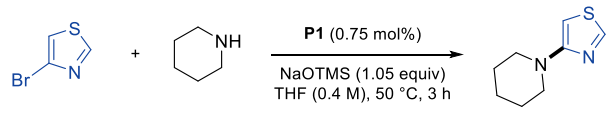
3.2 Results and Discussion

Recently, we reported a GPhos-supported Pd catalyst **P1** for the efficient C–N coupling of six-membered (hetero)aryl halides with primary aliphatic amines and anilines.[10] (An active GPhos-supported catalyst can be generated using alternative Pd sources, including the GPhos G4 precatalyst. See the Experimental section for results using Pd sources other than **P1**.) We envisioned that the previously reported ability of **P1** to resist catalyst deactivation arising from substrate coordination to the metal center[20] would make it a promising candidate to facilitate the amination of strongly coordinating five-membered heteroaryl halides. In our report describing **P1**, 4-bromothiazole was efficiently coupled with an electron-deficient aniline using NaOPh as the base,[10] an observation that prompted us to explore the ability of **P1** to couple five-membered heteroaryl halides with more challenging aliphatic secondary amines.

Although weak bases such as NaOPh[10,11] ($pK_aH=10$)[21] and Cs_2CO_3[12] ($pK_aH=10$)[22] were previously demonstrated to facilitate the coupling of relatively acidic aniline and amide nucleophiles with base-sensitive five-membered heteroaryl halides, we observed low reactivity when employing either base to couple 4-bromothiazole (**1a**) with piperidine (**2a**) (Figure 2, entries 2, 3). NaO*t*-Bu, a much stronger base ($pK_aH=19$),[21] is one of the most commonly used bases for C−N coupling reactions, particularly those involving aliphatic amines.[23] Its use, however, led to a low yield and poor mass balance for the model reaction (entry 4), presumably due to decomposition of **1a** *via* deprotonation at the 2-position and subsequent ring-opening (Figure 1C).[6a,18,19] Based on these observations, we hypothesized that a base with an intermediate strength between NaOPh and NaO*t*-Bu could prevent heteroarene decomposition while still facilitating productive amination. Consistent with this hypothesis, replacing one CH_3 group on NaO*t*-Bu with the more electron-withdrawing CF_3 resulted in a milder base ($pK_aH=13$)[24] that led to a substantially increased yield of **3a** and improved mass balance (entry 5). Following an examination of atypical bases for C–N cross-coupling with similar pK_aH values, we determined that a commercially available base, NaOTMS ($pK_aH=11$),[21] was optimal (entry 1). Despite the low pK_aH of NaOTMS relative to NaO*t*-Bu, a diminished yield was observed when an excess of NaOTMS (2.0 equiv vs. 1.05 equiv) was used (Figure 2, entry 6). While silanolate bases have rarely been utilized in C−N cross-coupling reactions,[25,26] our results suggest their wider adoption could increase yields for substrates bearing base-sensitive functional groups.

Conventionally, increasing the reaction concentration and/or temperature improves the yields of Pd-catalyzed C−N coupling reactions;[23] yet, in the case of the model reaction, a lower concentration (0.4 M) (Figure 2, entries 1 vs. 7) and a moderate temperature (50 °C) (entries 1 vs. 8, 9) were found to be optimal. To understand the basis of these trends, the decomposition of **1a**

was measured under various reaction conditions (Figure 3A). As expected, treatment of **1a** with NaO*t*-Bu under the standard reaction conditions resulted in significant decomposition, with only 59% of **1a** remaining after 3 hours (entry 2), compared to 93% after exposure to NaOTMS under the same conditions (entry 1). However, at a higher concentration (2 M, entry 3) or temperature (100 °C, entry 4), **1a** exhibited meaningful decomposition even in the presence of NaOTMS. This relationship between the base-mediated decomposition of **1a** and lower reaction yields is consistent with the hypothesis that substrate decomposition contributes to catalyst deactivation.



Entry	Deviation from optimal conditions	Conversion (%)	Yield (%)
1	None	100	99
2	Base = NaOPh	22	4
3	Base = Cs_2CO_3 (100 °C)	29	10
4	Base = NaO*t*-Bu	54	12
5	Base = $NaOC(CH_3)_2CF_3$	75	70
6	2.0 equiv NaOTMS	64	65
7	2.0 M in THF	54	25
8	Room temperature	50	33
9	100 °C	61	43
10	Precatalyst = **P2**	19	0

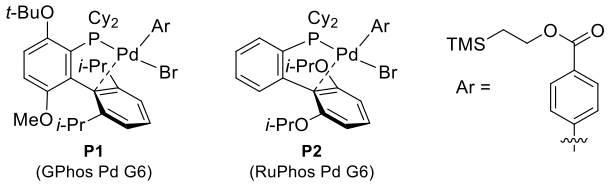


Figure 2. Reaction conditions: 4-bromothiazole (**1a**, 0.2 mmol), piperidine (**2a**, 0.24 mmol), NaOTMS (0.21 mmol), **P1** (0.75 mol%), THF (0.5 mL), 50 °C, 3 h. Yields were determined by ^{1}H NMR spectroscopy of the crude product mixtures, using 1,3,5-trimethoxybenzene as the internal standard.

We hypothesized that the unique ability of the Pd-GPhos/NaOTMS catalytic system to couple base-sensitive five-membered heteroaryl halides with aliphatic secondary amines originates from a complementary relationship between the base and catalyst. Compared to stronger bases, NaOTMS leads to slower decomposition of base-sensitive heteroarenes, hampering the formation of negatively charged ring-opened degradation products that could deactivate the catalyst. However, NaOTMS cannot fully prevent catalyst deactivation arising from coordination of the Lewis-basic heteroarenes themselves. Even though **P1** was originally designed for the coupling of primary amines,[10] the bulky GPhos ligand[27] resists heteroarene coordination, leading **P1** to significantly outperform RuPhos-based **P2**,[17] a catalyst that conventionally has been optimal for the coupling of secondary amines (Figure 2, entry 10). Conversely, GPhos shields the Pd center from heteroarene coordination, but the GPhos-based catalyst could still be deactivated by negatively charged, strongly coordinating heteroarene decomposition products. Therefore, sufficient resistance to these two heteroarene-induced deactivation pathways necessitates employing Pd-GPhos and NaOTMS together. This reaction design hypothesis is demonstrated in Figure 3B, in which the inhibitory effects of heteroarene additives on the cross-coupling between bromobenzene (**1b**) and morpholine (**2b**) were examined. Both GPhos- and RuPhos-based[17] catalysts promote coupling of **1b** with **2b** in good yields using either NaO*t*-Bu or NaOTMS as the

base. However, this model cross-coupling reaction is significantly inhibited by several of the most pharmaceutically relevant[1] heteroarene additives,[28] unless the Pd-GPhos/NaOTMS reaction conditions are employed. When either **P1** or NaOTMS is not employed, non-Lewis-basic additives (**4a**–**4c**) have little to no inhibitory effect, while basic-nitrogen-containing additives (**4d**–**4g**) result in near-complete catalyst inhibition. In contrast, when the optimal Pd-GPhos/NaOTMS conditions are utilized, reactivity is virtually unaffected by the presence of nearly all heteroarene additives. Indeed, extended optimization of the reaction conditions for a variety of five-membered heteroaryl halides revealed that the Pd-GPhos/NaOTMS catalytic system resulted in the highest yield for all heteroarenes examined.

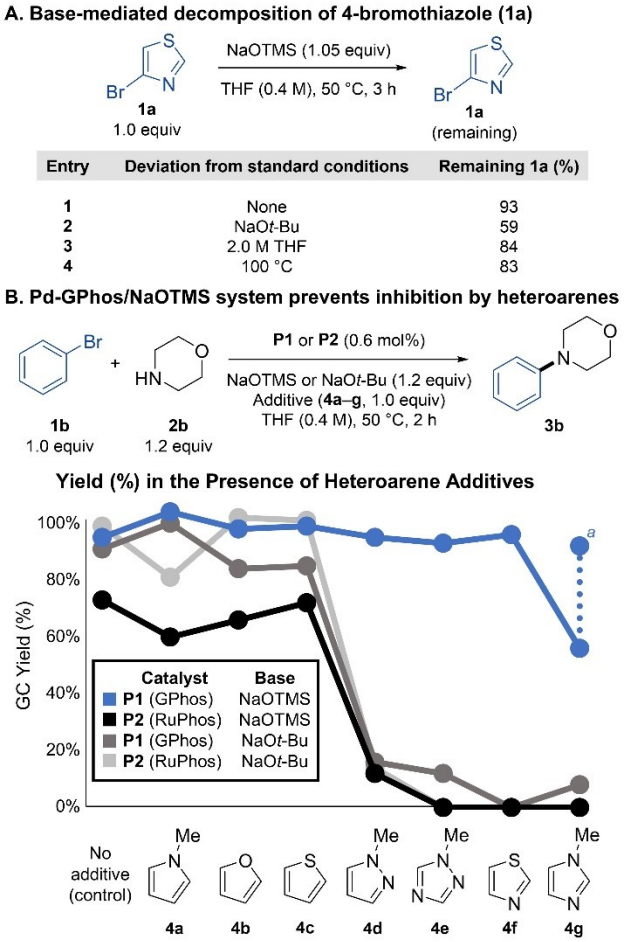


Figure 3. (A) Reaction conditions: 4-bromothiazole (**1a**, 0.2 mmol), NaOTMS (0.21 mmol), THF (0.5 mL), 50 °C, 3 h. Remaining **1a** was determined by ^{1}H NMR spectroscopy of the crude product mixtures, using 1,3,5-trimethoxybenzene as the internal standard. (B) Reaction conditions: bromobenzene (**1b**, 0.2 mmol), morpholine (**2b**, 0.24 mmol), base (0.24 mmol), **P1** or **P2** (0.6 mol%), THF (0.5 mL), 50 °C, 2 h. Legend: (a) **P1** (1.2 mol%). Yields were determined by gas chromatography (GC) of the crude product mixtures, using *n*-dodecane as the internal standard.

GPhos-supported catalyst **P1** and NaOTMS enabled the cross-coupling of a wide range of pharmaceutically relevant[1] five-membered heteroaryl halides and secondary amines in good-to-excellent yields, including challenging substrates for which few previously reported examples exist (Figure 4). Structurally diverse five-membered heteroarenes, halogenated at various

positions, were coupled effectively, and base-sensitive 3-H pyrazoles[6a] (**1p**–**r**) and 2-H-1,3-azoles[19] (**1c**, **1g**, **1k**–**m**) were well-tolerated. The coupling product **3k**, which contains multiple highly coordinating nitrogen atoms, was formed in excellent yield on a gram scale. While this report emphasizes the coupling of readily accessible heteroaryl bromides,[29] the Pd-GPhos/NaOTMS system can also couple heteroaryl chlorides (**1g**, **1x**) and iodides (**1l**, **1r**).[30] Ortho-substituted aryl halides (**1j**, **1q**, **1s**–**u**, **1w**) were coupled successfully despite their steric hindrance. The coupling of heteroaryl bromide **1f** was achieved with complete chemoselectivity, despite the presence of an aryl chloride on amine **2f**.

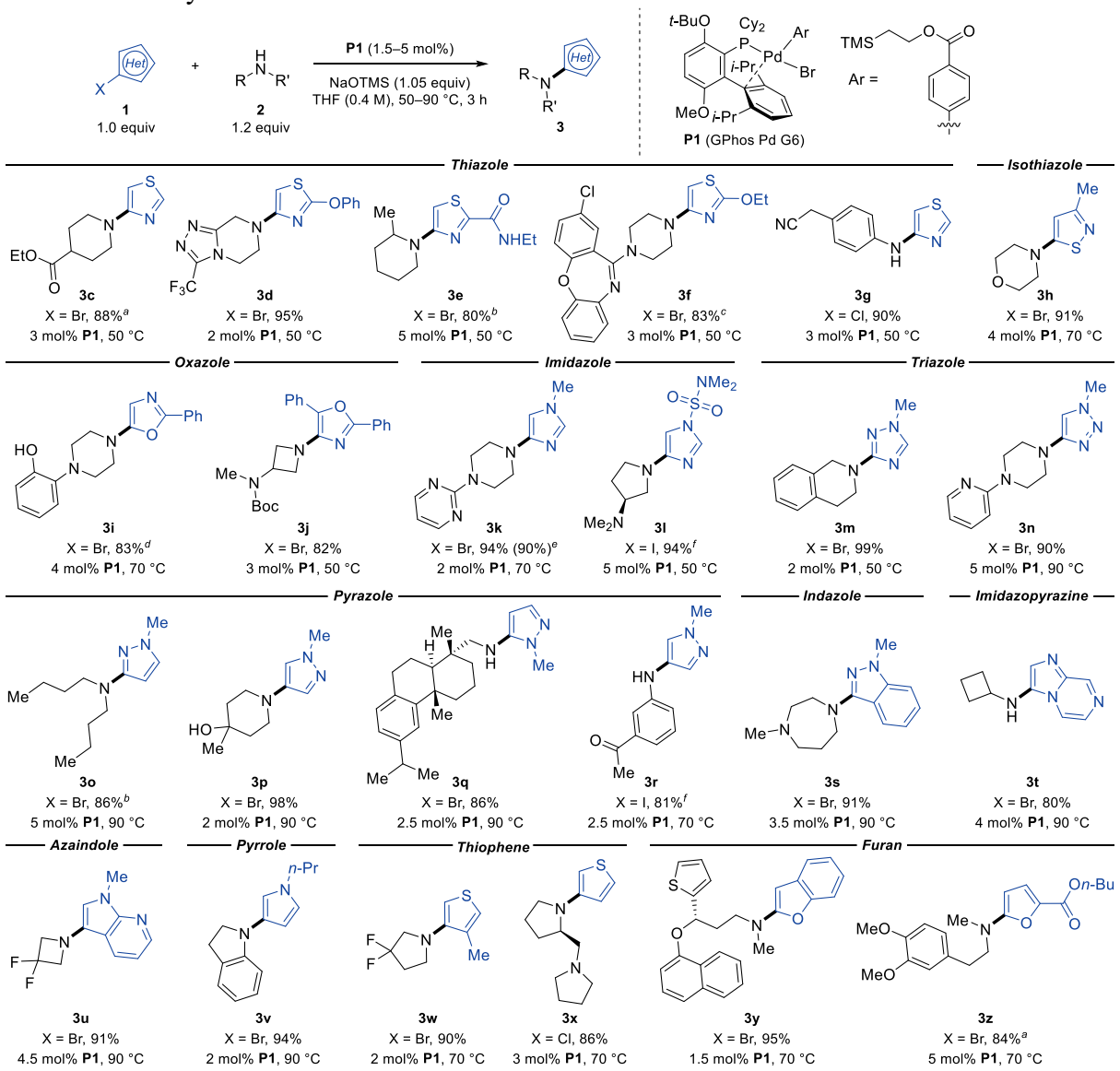


Figure 4. Isolated yields reported as the average of two runs. Reaction conditions: aryl halide (**1**, 0.5 mmol), amine (**2**, 0.6 mmol), NaOTMS (0.525 mmol), **P1** (1.5–5 mol%), THF (1.25 mL), 50–90 °C, 3 h. Legend: (a) slow addition of NaOTMS over 1 h using a syringe pump; (b) **2** (5.0 equiv); (c) **2** (1.1 equiv); (d) NaOTMS (2.25 equiv); (e) 5.0 mmol scale; (f) 1,4-dioxane (1.25 mL). See Figures 6 and 7 for additional examples of successful and unsuccessful coupling reactions.

Cyclic aliphatic amines are among the most prevalent nitrogen heterocycles in FDA-approved drugs.[1] Cyclic amines of varying size and nucleophilicity, including four- (**2j**, **2u**), five- (**2l**, **2v**–**x**), six- (**2c**–**f**, **2h**–**i**, **2k**, **2m**–**n**, **2p**), and seven-membered rings (**2s**) were readily coupled in good-to-excellent yields, including high-complexity drug molecules and fragments such as the antidepressant amoxapine (**2f**) and a fragment of the anti-diabetic sitagliptin (**2d**). Excellent reactivity was observed for highly hindered α-branched cyclic amines such as 2-substituted pyrrolidines (**2v**, **2x**) and 2-methylpiperidine (**2e**).[1a] These examples are among the first high-yielding coupling reactions of α-branched cyclic amines with five-membered heteroaryl halides.[6a] Acyclic secondary amines (**2o**, **2y**–**z**), another important substrate class for which efficient coupling with five-membered heteroaryl halides is rarely reported, were coupled effectively using the Pd-GPhos/NaOTMS system, including the antidepressant duloxetine (**2y**). Primary amines, including both aliphatic primary amines (**2q**, **2t**) and anilines (**2g**, **2r**), were successfully coupled under the same conditions.

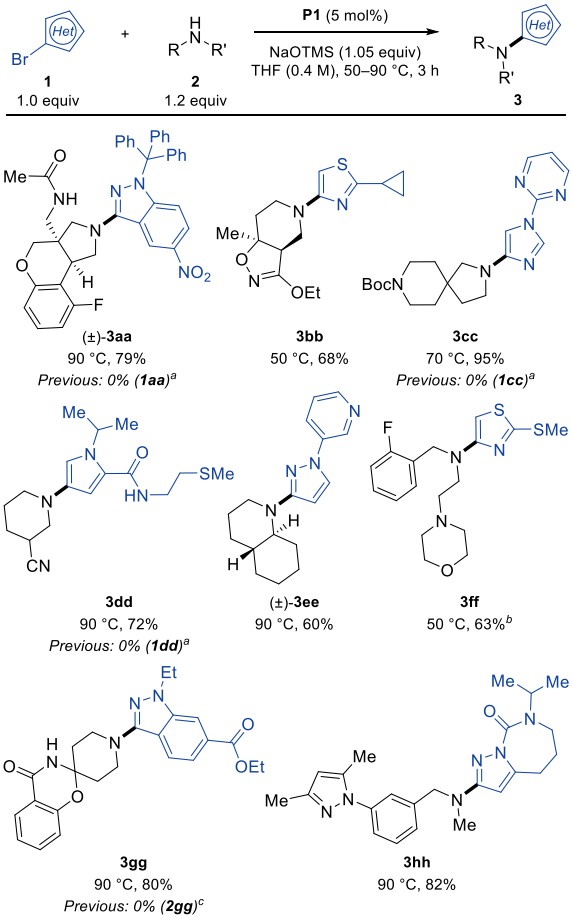


Figure 5. Isolated yields reported as the average of two runs. Reaction conditions: aryl halide (**1**, 0.5 mmol), amine (**2**, 0.6 mmol), NaOTMS (0.525 mmol), **P1** (5 mol%), THF (1.25 mL), 50–90 °C, 3 h. Legend: (a) coupling was previously attempted between the aryl bromide and 4-phenylpiperidine (reference 6a); (b) **P1** (8 mol%), **2** (2 equiv); (c) coupling was previously attempted between the amine and 4-bromo-1-phenyl-1*H*-pyrazole (reference 6a). See Figure 12 for additional examples of complex substrate combinations.

Acidic functional groups, including an unprotected phenol and alcohol (**2i**, **2p**), an enolizable acetophenone (**2r**), and a secondary amide (**1e**) were well-tolerated. Substrates containing electrophilic functional groups such as nitriles (**2g**) and esters (**2c**, **1z**) were coupled in excellent yields. While NaOTMS is typically not compatible with ethyl esters due to competitive transesterification,[31,32] the Pd-GPhos/NaOTMS system promotes such rapid C−N coupling that transesterification is outcompeted when the NaOTMS is slowly added to the reaction mixture. However, highly sensitive functional groups, such as electrophilic methyl esters and base-sensitive 3-H isoxazoles,[18] were not tolerated, even with slow addition of NaOTMS.[33]

We further established the utility of the Pd-GPhos/NaOTMS system by coupling structurally complex five-membered heteroaryl halides and aliphatic secondary amines selected from the Merck Building Block Collection (Figure 5).[34] Sterically demanding, α-branched cyclic (**2ee**) and acyclic secondary amines (**2ff**, **2hh**) were successfully combined with densely functionalized aryl halides in good yields. Notably, electrophilic groups (alkoxyimidate **2bb**, nitrile **2dd**, ester **1gg**) and acidic secondary amides (**2aa**, **1dd**, **2gg**) were preserved as a result of utilizing NaOTMS. The high activity of the Pd-GPhos/NaOTMS system is further demonstrated by the coupling of several complex heteroaryl halides and amines that were previously unable to be coupled by other methods (**1aa**, **1cc**, **1dd**, **2gg**).[6a]

3.3 Conclusion

In summary, we have developed a general method for the C−N cross-coupling of five-membered heteroaryl halides that accommodates a broad scope of five-membered heteroaryl halides and amines, including several underexplored substrate classes. Together, the moderate-strength base NaOTMS and the deactivation-resistant GPhos-supported catalyst **P1** are especially effective in enabling cross-coupling of densely functionalized drug molecules and complex medicinal chemistry building blocks. In light of the highly successful application of the Pd-GPhos/NaOTMS system to C−N coupling reactions involving a variety of challenging substrates, we anticipate that the system described herein can be more generally extended to enable other previously inaccessible amination reactions, thus expediting the discovery of new pharmaceuticals and agrochemicals.

3.4 Experimental Procedures and Characterization Data

1. General Information

General Reagent and Materials Information

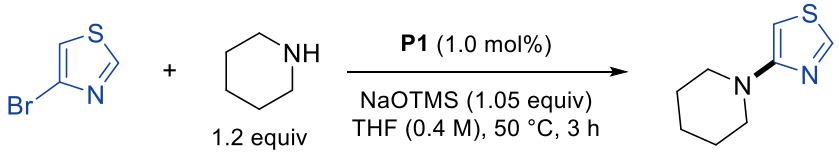
Unless otherwise noted, all reactions were set up inside of a chemical fume hood and run under a nitrogen atmosphere. Tetrahydrofuran (THF) was purchased from Millipore-Sigma and stored in J.T. Baker CYCLE-TAINER® delivery kegs. After transferring into CYCLE-TAINER® delivery kegs, the solvents were purged with argon for 2 h prior to the first use. THF was further purified by successive filtration through neutral alumina and CuO columns under argon pressure. 1,4-Dioxane was purchased from Millipore-Sigma, degassed, and stored in a nitrogen-filled glovebox prior to use. Anhydrous dimethylsulfoxide (DMSO), CCl_4, and dimethylformamide (DMF) were purchased from Millipore-Sigma in SureSeal™ bottles. Acetonitrile (MeCN) was purchased from Millipore-Sigma as HPLC grade. Solvents used for extractions, crystallizations, and column chromatography were purchased from Millipore-Sigma as HPLC grade. Sodium trimethylsilanolate (NaOTMS) was purchased from Millipore-Sigma and stored in a nitrogen-filled glovebox, and portions were removed from the glovebox in a sealed scintillation vial (DKW Life Sciences, catalog no. 03-340-4C) and stored in a desiccator under air (the quality of NaOTMS remained satisfactory during at least two months of storage under air). All preparative C–N bond-forming reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques. Screening of reaction conditions and mechanistic experiments were carried out with the aid of a nitrogen-filled glovebox. Aryl bromide **1j** was prepared by Anton Ni according to a previously reported procedure.[35] All other aryl halides and amines, unless otherwise noted, were purchased from commercial suppliers and used as received. Substrates found in Section 9 (High-throughput experimentation) and Section 10 (Additional examples of complex substrate combinations not shown in Figure 5) were obtained from Merck & Co., Inc.'s internal building block collection and used as received. Analysis of the substrates by LCMS was performed to assess quality prior to use. Catalysts **P1**[10] and **P2**[36] were prepared as previously reported. Unless otherwise noted, liquid reagents dispensed via micropipette were measured by mass. Organic compounds were purified by flash chromatography using Silicycle SiliaFlashP60 (230–400 mesh) silica gel either manually or using a CombiFlash NextGen 300 automated chromatography system. Selected compounds were purified using basic aluminum oxide, Brockmann grade I, or Brockmann grade III (6% H_2O added to Brockmann grade I) prepared from Alfa Aesar aluminum oxide, activated, basic, Brockmann grade I, 58 angstroms, 60 mesh power, S.A. 150 m^2/g, CAS 1344-28-1. Compound **3ee** was purified on a Biotage KP-C18-HS Snap Cartridge (60 g) using a MeCN/H_2O (water contained 0.1% trifluoroacetic acid) solvent gradient on a CombiFlash NextGen 300 automated chromatography system.

General Analytical Information

$CDCl_3$ was purchased from Cambridge Isotope Labs. NMR spectra were collected on a Bruker Avance III HD 400 or 500 MHz spectrometer. ^1H ($CDCl_3$: δ 7.26) and ^{13}C NMR shifts ($CDCl_3$: δ 77.16) were referenced to residual solvent peaks. The following abbreviations were used to characterize multiplicities: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, m = multiplet. Gas chromatography (GC) analyses were performed on an Agilent 7890A gas chromatograph with an FID detector using a J&W DB-1 column (10 m, 0.1 mm I.D.). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA, USA. High-resolution mass spectra were recorded on a JEOL AccuTOF LC-Plus 46 DART system. IR

spectra were recorded on a Nicolet iS5 spectrometer equipped with an iD5 diamond laminate ATR accessory from Thermo Fisher Scientific. IR spectra were acquired from neat samples. Melting points were obtained using a Stanford Research Systems EZ-Melt melting point apparatus. Analysis of the high-throughput experimentation (HTE) experiments was performed with an Agilent 1290 Infinity II UPLC system equipped with an Agilent Infinity lab mass spectrometer. The mobile phase was 0.05% TFA in water and 0.05% TFA in acetonitrile, and a Waters Cortecs C18 2.7 µm 2.1x50 mm column (part no. 186007365) was used for the solid phase. The eluents were monitored from 190 nm to 400 nm, followed by MS detection in API-ES ionization in positive mode.

2. Optimization of the model reaction conditions: 4-bromothiazole + piperidine
Reaction setup (0.5 mmol scale, outside the glovebox)



Procedure	Yield (%)
Procedure 1 (standard)	104[a], 93[b]
Procedure 2 (simplified)	98[a], 89[b]

Legend: (a) yield determined by ^{1}H NMR spectroscopy of the crude product mixture, using 1,1,2,2-tetrachloroethane as the internal standard; (b) isolated yield.

Procedure 1 (standard)
An oven-dried 13 x 100 mm reaction tube (Tube A) (Fisherbrand, product no. 1495935C) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with NaOTMS (59 mg, 0.525 mmol, 1.05 equiv). Tube A was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The tube was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF (0.65 mL) was added via syringe. 4-Bromothiazole (**1a**) (82 mg, 45 µL, 0.50 mmol, 1.00 equiv), was added via syringe, followed by the addition of piperidine (51 mg, 59 µL, 0.60 mmol, 1.20 equiv), via syringe. The reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. A solution of **P1** (GPhos Pd G6) (0.00833 M, 1.0 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B) (Kimble, part no. 60910L-1). Solid **P1** was added to Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired precatalyst concentration (0.00833 M, 1.0 mol%). **P1** solution (0.60 mL) from Vial B was transferred to Tube A via syringe. Tube A was then immediately transferred to a pre-heated oil bath (bath temperature = 50 °C). The reaction mixture was stirred at 50 °C for 3 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air and the contents were filtered through a plug of Celite, and rinsed with EtOAc (3 x 5 mL). The crude material was

purified by column chromatography. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 5% EtOAc/hexane, followed by 4 column volumes 10% EtOAc/hexane. Yield: 78 mg, 93%. Light yellow oil. The NMR spectra matched those reported in the literature.[37]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.1 Hz, 1H), 5.89 (d, *J* = 2.1 Hz, 1H), 3.43 – 3.04 (m, 4H), 1.71 (p, *J* = 5.7 Hz, 4H), 1.64 – 1.53 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.8, 150.9, 89.3, 50.0, 25.5, 24.4.

Elemental Analysis calc. for $C_8H_{12}N_2S$: C, 57.11; H, 7.19. Found: C, 57.01; H, 7.08.

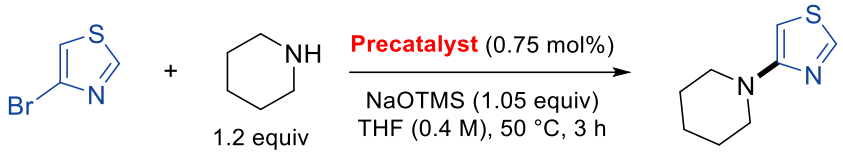
IR (Diamond-ATR, neat, cm^{-1}): 2930, 2850, 2806, 1611, 1513, 1219, 1131, 966, 881, 801.

Procedure 2 (simplified)
A 13 x 100 mm reaction tube (Fisherbrand, product no. 1495935C) equipped with a Teflon-coated magnetic stir bar was charged with **P1** (4.7 mg, 5.0 μmol, 0.01 equiv), followed by NaOTMS (59 mg, 0.525 mmol, 1.05 equiv). (Neither the reaction tube nor the magnetic stir bar was oven-dried prior to use.) The reaction tube was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The tube was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). 4-Bromothiazole (**1a**) (82 mg, 45 μL, 0.50 mmol, 1.00 equiv), was added via syringe, followed by the addition of piperidine (51 mg, 59 μL, 0.60 mmol, 1.20 equiv), via syringe. Anhydrous THF (1.25 mL) was added via syringe. The reaction tube was then immediately transferred to a pre-heated oil bath (bath temperature = 50 °C). The reaction mixture was stirred at 50 °C for 3 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air and the contents were filtered through a plug of Celite, and rinsed with EtOAc (3 x 5 mL). The crude material was purified by column chromatography. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 5% EtOAc/hexane, followed by 4 column volumes 10% EtOAc/hexane. Yield: 75 mg, 89%. Light yellow oil.

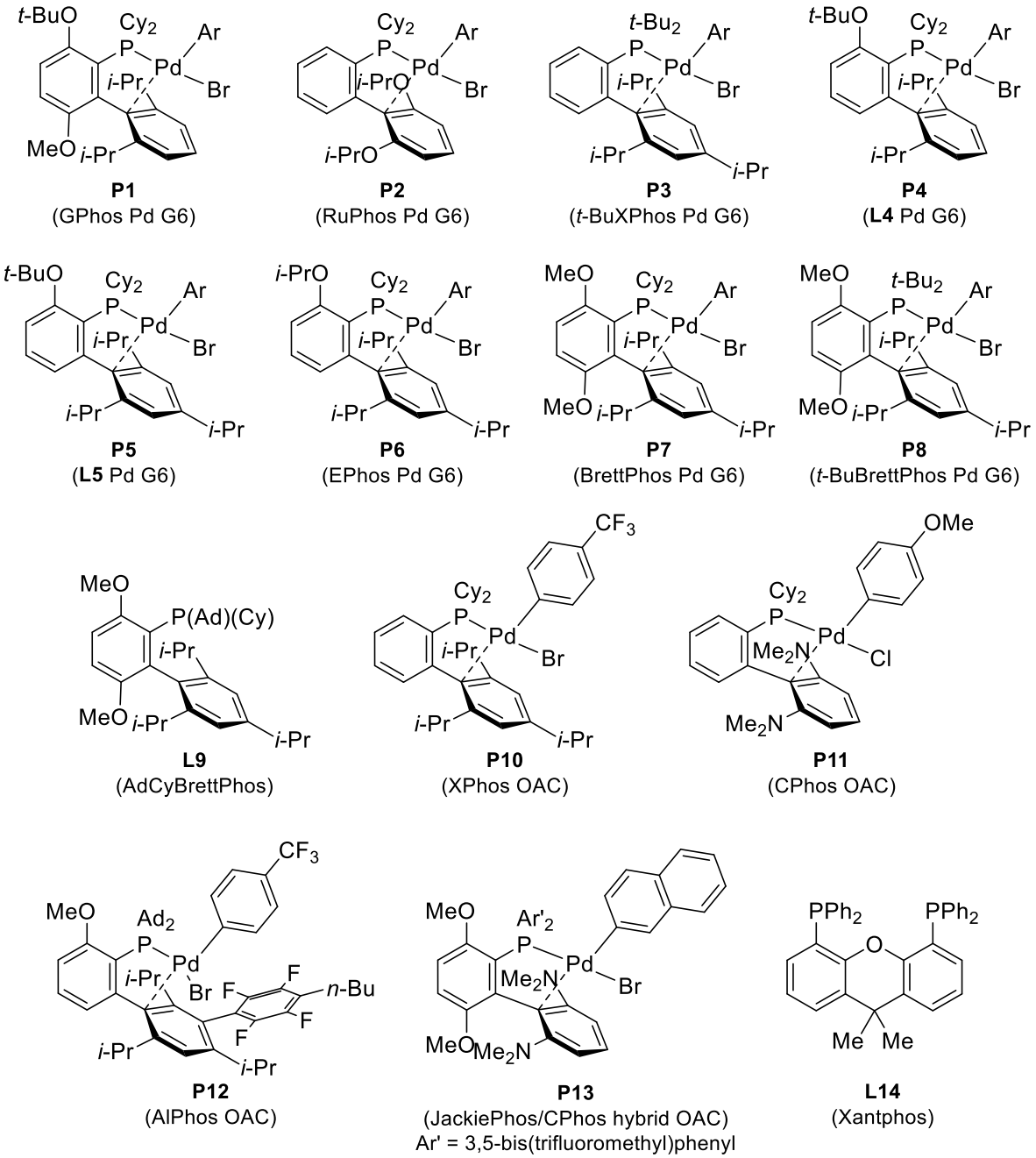
General Procedure A for small-scale optimization of the model reaction
Inside a N_2-filled glovebox, each oven-dried 13 x 100 mm reaction tube (Fisherbrand, part no. 1495935C) was equipped with an oven-dried magnetic stir bar and charged with NaOTMS (24 mg, 0.21 mmol, 1.05 equiv). A substrate solution was prepared: 4-bromothiazole (**1a**) (per reaction: 33 mg, 18 μL, 0.2 mmol, 1.0 equiv), piperidine (**2a**) (per reaction: 20 mg, 24 μL, 0.24 mmol, 1.2 equiv), and anhydrous THF (per reaction: 0.25 mL) were added to an oven-dried 1 dram vial (Kimble, part no. 60910L-1) (Solution A). Liquid reagents **1a** and **2a** were added via micropipette; anhydrous THF was added via syringe. Solution A (0.29 mL) was added via syringe to the reaction tube, and the reaction mixture was allowed to stir until homogeneous (~1 min). A solution of **P1** (0.75 mol%) in anhydrous THF (0.006 M) was prepared in a separate oven-dried 1 dram vial (Solution B). Solution B (0.25 mL) was added via syringe to the reaction tube. The reaction tube was capped with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60), removed from the glovebox, and placed in a pre-heated oil bath (bath temperature = 50 °C), where it was allowed to stir at 50 °C for 3 h. The reaction vessel was removed from the oil bath and allowed to cool to

room temperature. The reaction tube was opened to the air, and EtOAc (~1 mL) was added. A solution of internal standard (trimethoxybenzene in EtOAc) was added via syringe. The product mixture was passed through a plug of Celite, rinsing with EtOAc (2 x 1 mL). The filtrate was concentrated under reduced pressure with the aid of a rotary evaporator, then analyzed by ^{1}H NMR in $CDCl_3$ to assess the yield relative to the trimethoxybenzene standard.

Ligand

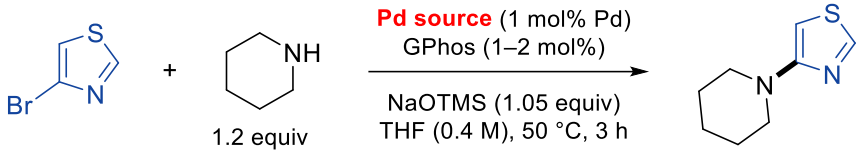


Precatalyst	**Yield (%)**
P1 (GPhos Pd G6)	91
P2 (RuPhos Pd G6)	0
P3 (*t*-BuXPhos Pd G6)	58
P4 (**L4** Pd G6)	55
P5 (**L5** Pd G6)	54
P6 (EPhos Pd G6)	53
P7 (BrettPhos Pd G6)	16
P8 (*t*-BuBrettPhos Pd G6)	16
P9 (AdCyBrettPhos Pd G3)	1
P10 (XPhos OAC)	1
P11 (CPhos OAC)	1
P12 (AlPhos OAC)	2
P13 (JackiePhos/CPhos hybrid OAC)	0
P14 (Xantphos Pd G3)	0

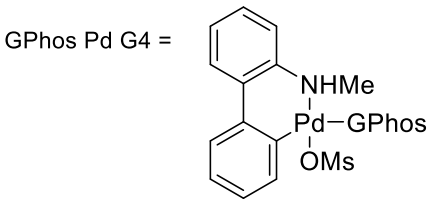


General Procedure A was followed except for the modifications noted: Each precatalyst (0.75 mol%) was weighed directly into each 13 x 100 mm reaction tube prior to the addition of NaOTMS; no Solution B was prepared. Solution A was prepared with 0.50 mL THF per reaction.

Pd source



Pd source	GPhos (if applicable)	Yield (%)
P1 (1 mol%)	(included with Pd source)	99
GPhos Pd G4 (1 mol%)	(included with Pd source)	98
$[Pd(cinnamyl)Cl]_2$ (0.5 mol%)	1 mol%	36, 99[a]
Pd_2dba_3 (0.5 mol%)	1 mol%	44
$Pd(OAc)_2$ (1 mol%)	2 mol%	13, 31[b]



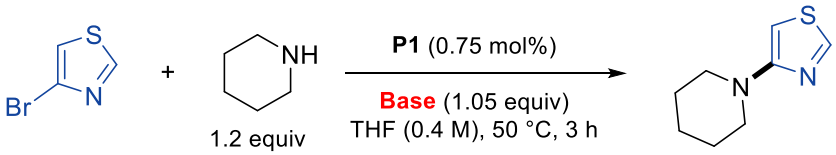
General Procedure A was followed except for the modifications noted: Each Pd source (1 mol% Pd) and the indicated amount of GPhos, if applicable, were weighed directly into each 13 x 100 mm reaction tube prior to the addition of NaOTMS; no Solution B was prepared. Solution A was prepared with 0.50 mL THF per reaction.

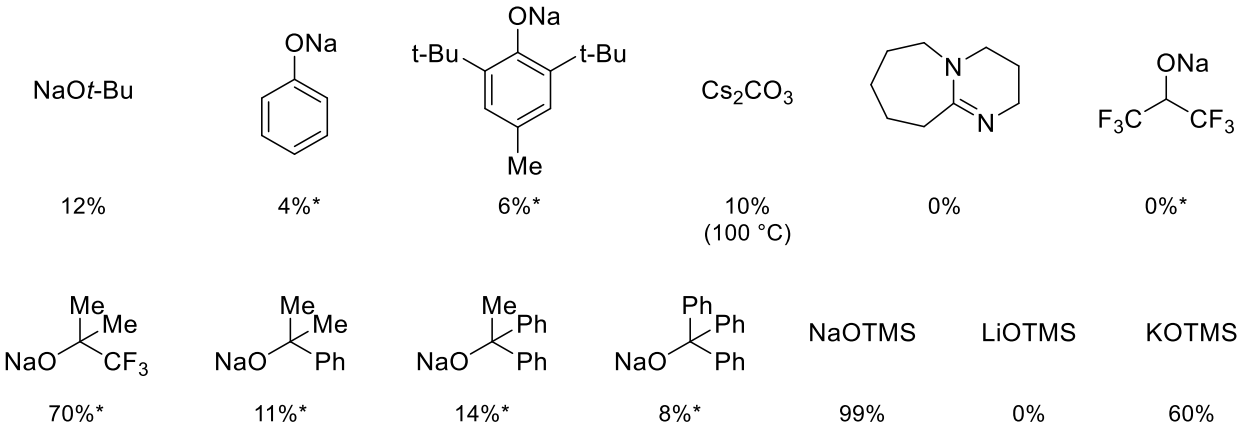
Additional modifications:

(a) Solution A was prepared with 0.25 mL THF per reaction. Solution B was prepared with $[Pd(cinnamyl)Cl]_2$ (0.5 mol%) and GPhos (1 mol%) in THF (per reaction: 0.25 mL) and was allowed to stir until homogeneous.

(b) Solution A was prepared with 0.25 mL THF per reaction. Solution B was prepared by pre-activating $Pd(OAc)_2$ (1 mol%) in the presence of GPhos (2 mol%) and H_2O (5 mol%) in THF (per reaction: 0.25 mL), using the water-mediated pre-activation protocol.[38]

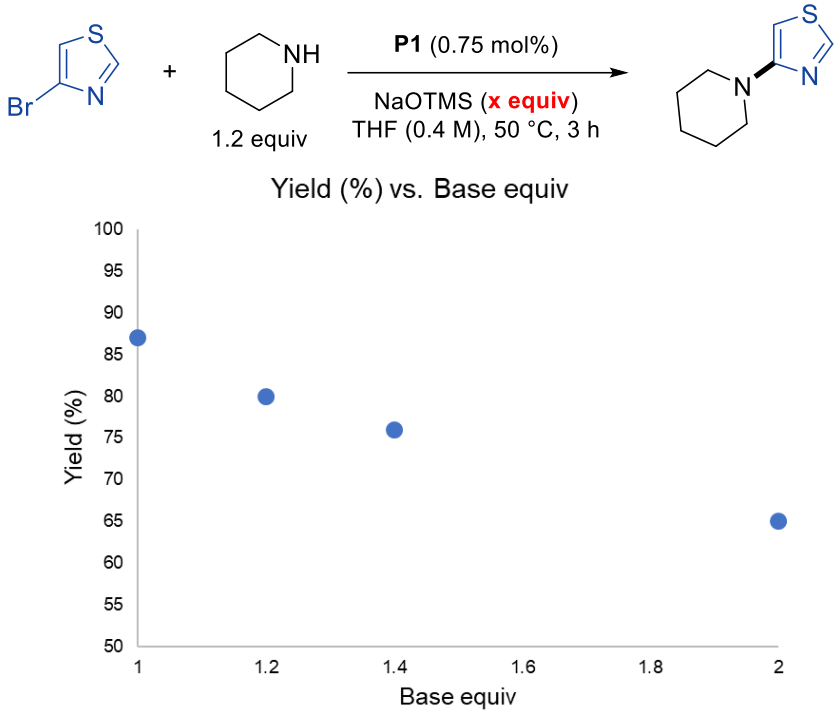
Base





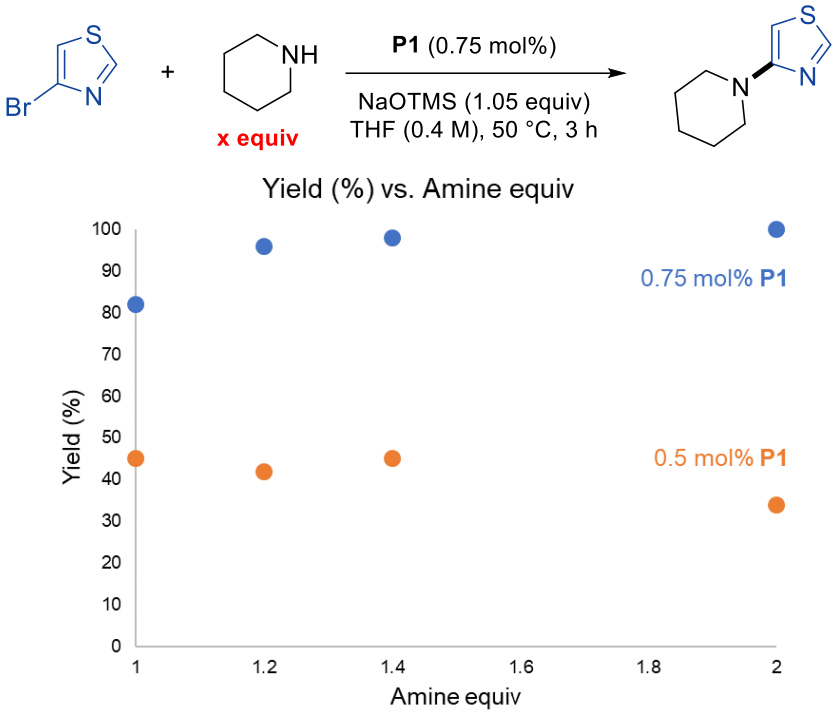
General Procedure A was followed except for the modifications noted: The indicated base (0.21 mmol, 1.05 equiv) was added. Bases indicated with an asterisk (*) were formed in situ from the corresponding alcohol and NaO*t*-Bu; in these cases, solid NaO*t*-Bu (20 mg, 0.21 mmol, 1.05 equiv), the solid or liquid alcohol (0.22 mmol, 1.10 equiv), then Solution A were added in subsequent order to the reaction tube.

Base equivalents



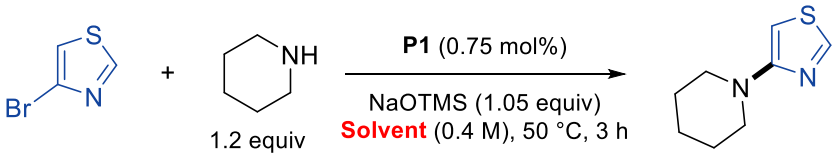
General Procedure A was followed except for the modifications noted: The indicated amount of NaOTMS (x equiv) was added to each reaction tube.

Amine equivalents



General Procedure A was followed except for the modifications noted: Instead of Solution A, separate solutions were prepared with 4-bromothiazole (**1a**) (Solution A1) and piperidine (**2a**) (Solution A2). A solution of **1a** (164 mg, 1.0 mmol, 5.0 equiv) in anhydrous THF (0.50 mL) was prepared in an oven-dried 1 dram vial (Solution A1). A solution of **2a** (136 mg, 1.6 mmol, 8.0 equiv) in anhydrous THF (0.60 mL) was prepared in a separate oven-dried 1 dram vial (Solution A2). Solution A1 (0.12 mL), Solution A2 (0.095x mL, x = amine equiv), and anhydrous THF (0.19–0.95x mL, x = amine equiv) were added via syringe to each reaction tube, and the reaction mixtures were allowed to stir until homogeneous (~1 min). The experiment was also repeated with 0.5 mol% **P1** (Solution B: 0.004 M **P1** in THF).

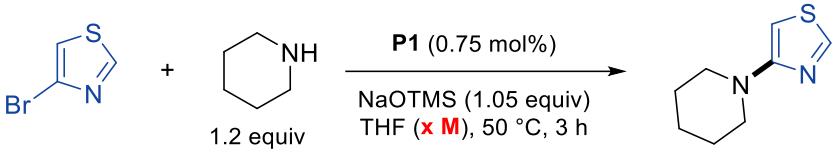
Solvent

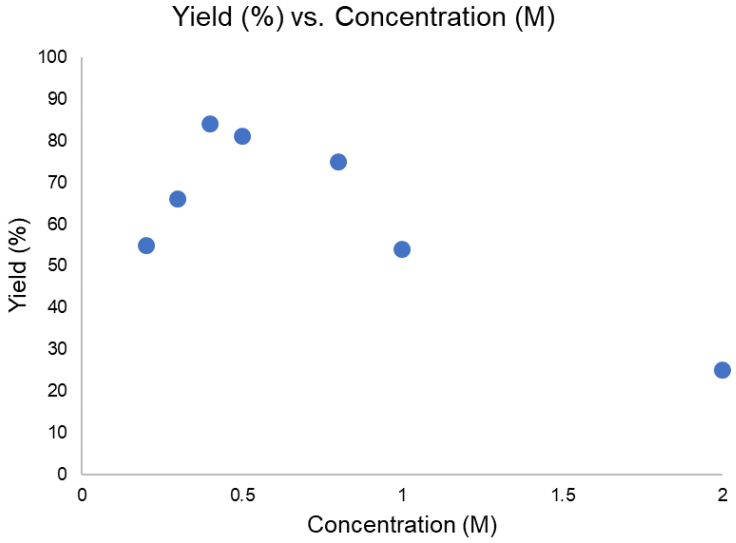


Solvent	Yield (%)
THF	96
1,4-Dioxane	37
Tetrahydropyran	23
2-methyl THF	14
Cyclopentyl methyl ether (CPME)	0
Methyl *tert*-butyl ether (MTBE)	0
Toluene	0
Tert-butanol	4
Dimethylformamide (DMF)	26

General Procedure A was followed except for the modifications noted: Solution A was not prepared; instead, solvent, 4-bromothiazole (**1a**), and piperidine (**2a**) were added directly to the reaction tube (in that order). A separate Solution B was prepared for each solvent.

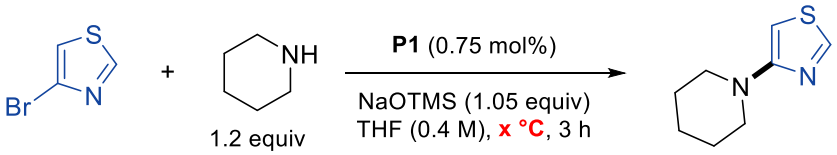
Concentration

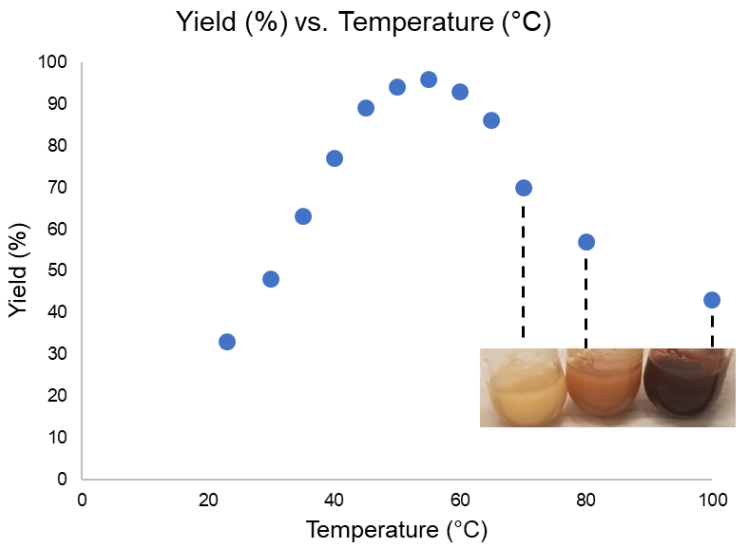




General Procedure A was followed except for the modifications noted: Solution A was prepared with 4-bromothiazole (**1a**) (295 mg, 1.8 mmol, 9.0 equiv), piperidine (**2a**) (184 mg, 2.16 mmol, 10.8 equiv), and THF (0.45 mL). Solution B: 0.03 M **P1** in THF. Solution A (0.09 mL) was added to each reaction tube, followed by THF (0.2/x–0.1 mL, x = molar reaction concentration), followed by Solution B (0.05 mL).

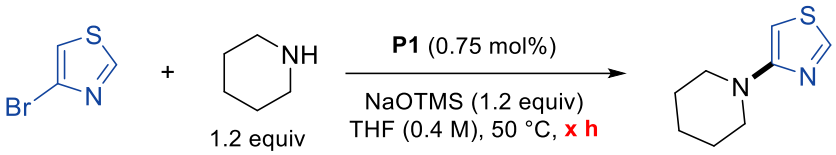
Temperature

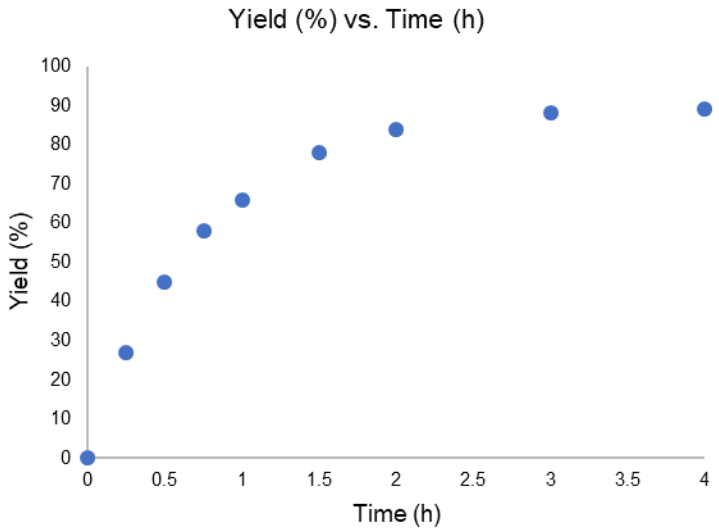




General Procedure A was followed except for the modifications noted: Each heated reaction was placed in an oil bath pre-heated to the indicated temperature (30, 35, 40, 45, 50, 55, 60, 65, 70, 80, or 100 °C). The room temperature reaction was allowed to stir under ambient conditions (the temperature of the room was measured to be 23 °C).

Reaction time





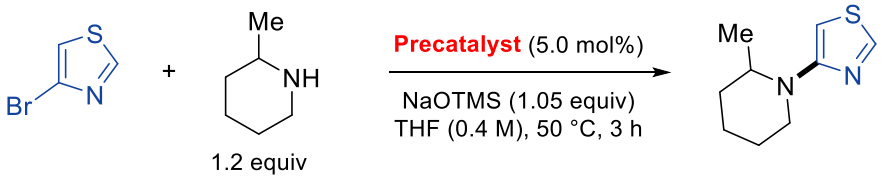
General Procedure A was followed except for the modifications noted: Eight (8) reactions were prepared, and each was removed from the oil bath at the indicated time. NaOTMS (27 mg, 0.24 mmol, 1.2 equiv) was used as the base.

3. Optimization of reaction conditions: 4-bromothiazole + 2-methylpiperidine

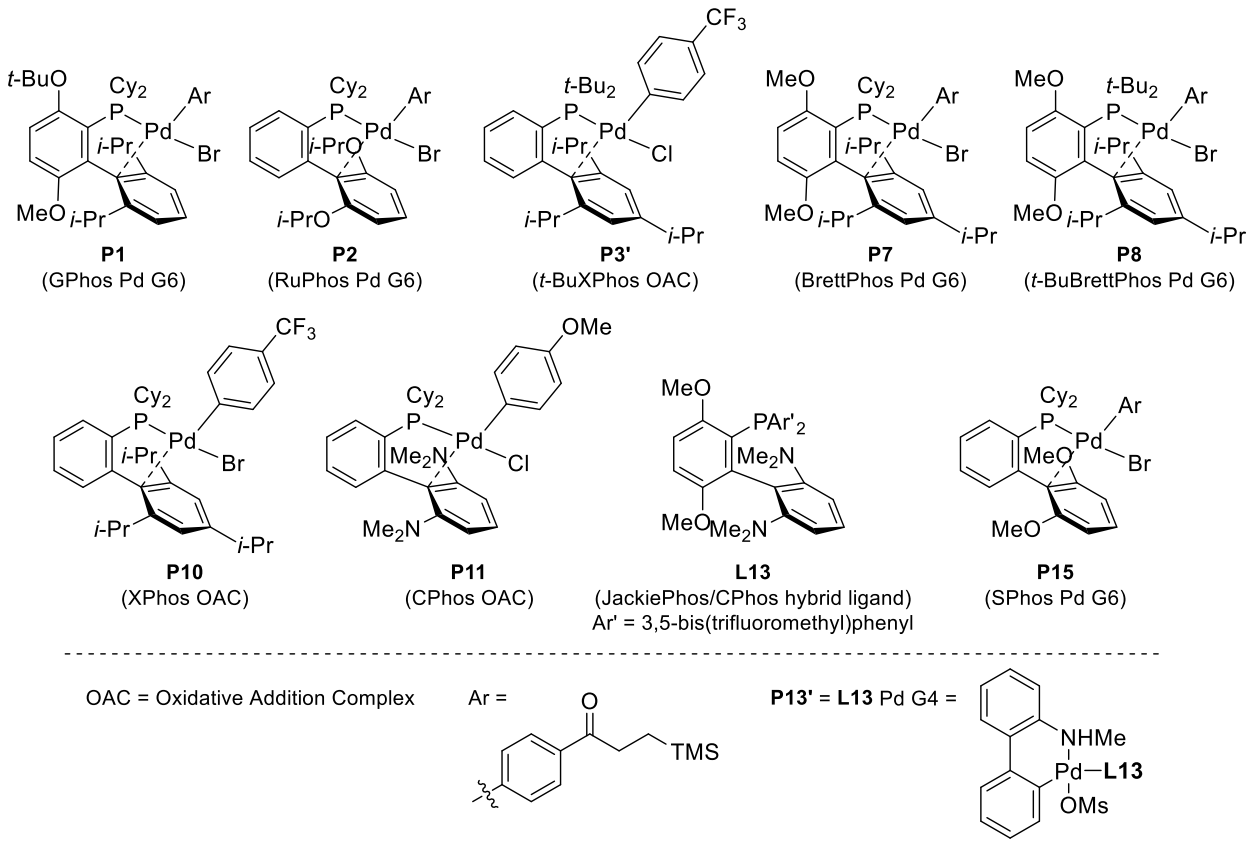
General Procedure B for small-scale optimization with 2-methylpiperidine

Inside a N_2-filled glovebox, each oven-dried 13 x 100 mm reaction tube (Fisherbrand, part no. 1495935C) was equipped with an oven-dried magnetic stir bar and charged with NaOTMS (12 mg, 0.105 mmol, 1.05 equiv). A substrate solution was prepared: 4-bromothiazole (**1a**) (per reaction: 16 mg, 9 µL, 0.1 mmol, 1.0 equiv), 2-methylpiperidine (**2e**) (per reaction: 12 mg, 14 µL, 0.12 mmol, 1.2 equiv), and anhydrous THF (per reaction: 0.125 mL) were added to an oven-dried 1 dram vial (Kimble, part no. 60910L-1) (Solution A). Liquid reagents **1a** and **2e** were added via micropipette; anhydrous THF was added via syringe. Solution A (0.15 mL) was added via syringe to the reaction tube, and the reaction mixture was allowed to stir until homogeneous (~1 min). A solution of **P1** (3–5 mol%) in anhydrous THF (0.024–0.04 M) was prepared in a separate oven-dried 1 dram vial (Solution B). Solution B (0.125 mL) was added via syringe to the reaction tube. The reaction tube was capped with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60), removed from the glovebox, and placed in a pre-heated oil bath (bath temperature = 50 °C), where it was allowed to stir at 50 °C for 3 h. The reaction vessel was removed from the oil bath and allowed to cool to room temperature. The reaction tube was opened to the air, and EtOAc (~1 mL) was added. A solution of internal standard (trimethoxybenzene in EtOAc) was added via syringe. The product mixture was passed through a plug of Celite, and rinsed with EtOAc (2 x 1 mL). The filtrate was concentrated under reduced pressure with the aid of a rotary evaporator, then analyzed by ^1H NMR in $CDCl_3$ to assess the yield relative to the trimethoxybenzene standard.

Ligand

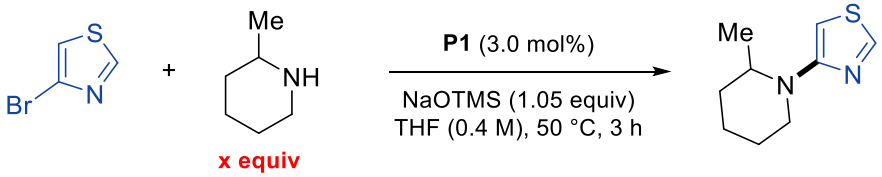


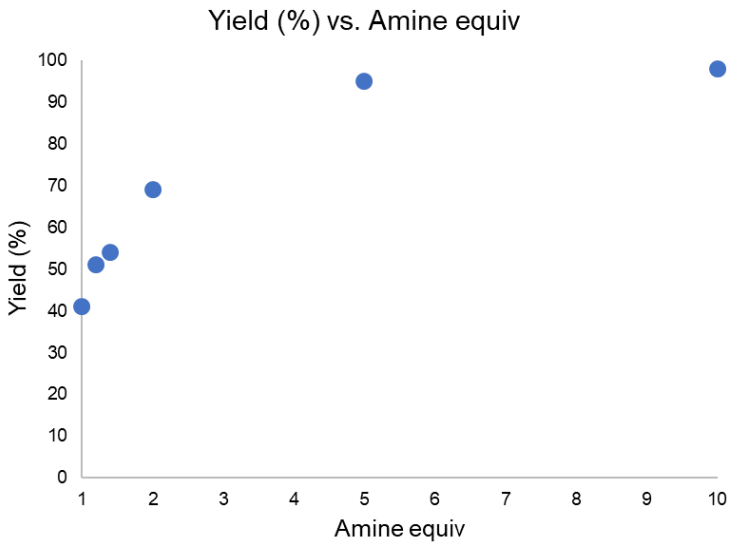
Precatalyst	Yield (%)
P1 (GPhos Pd G6)	67
P2 (RuPhos Pd G6)	0
P3' (*t*-BuXPhos OAC)	39
P7 (BrettPhos Pd G6)	3
P8 (*t*-BuBrettPhos Pd G6)	2
P10 (XPhos OAC)	0
P11 (CPhos OAC)	2
P13' (JackiePhos/CPhos hybrid Pd G4)	0
P15 (SPhos Pd G6)	0



General Procedure B was followed except for the modifications noted: Each precatalyst (5 mol%) was weighed directly into each 13 x 100 mm reaction tube prior to the addition of NaOTMS; no Solution B was prepared. Solution A was prepared with 0.25 mL THF per reaction.

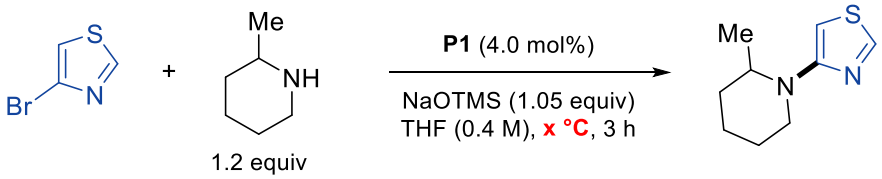
Amine equivalents

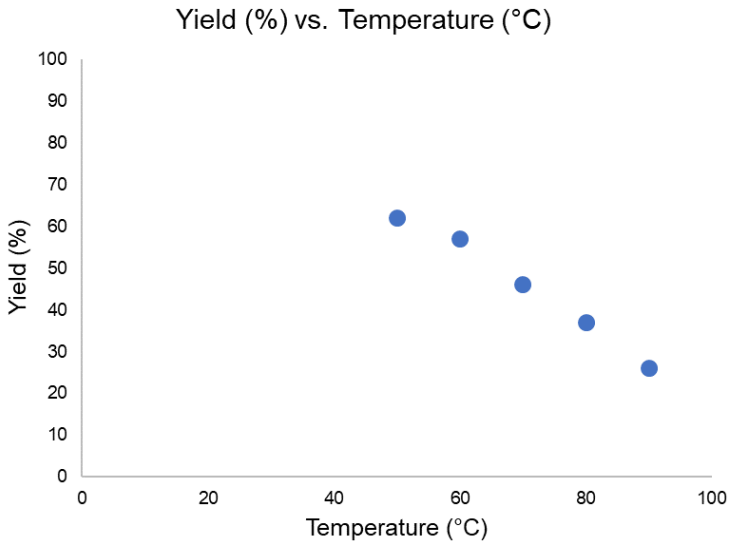




General Procedure B was followed except for the modifications noted: Solution A contained only 4-bromothiazole (**1a**), with no amine: the solution of **1a** (112 mg, 0.68 mmol, 6.8 equiv) in anhydrous THF (0.85 mL) was prepared in an oven-dried 1 dram vial. Solution A (0.135 mL) was added to the reaction tube via syringe. Then, the indicated amount of 2-methylpiperidine (**2e**) (x equiv) was added directly to the reaction tube via micropipette. Solution B was prepared with 3 mol% **P1**.

Temperature



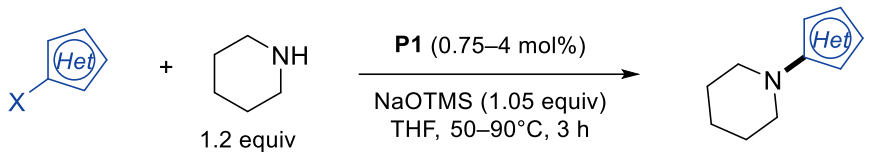


General Procedure B was followed except for the modifications noted: Each heated reaction was placed in an oil bath pre-heated to the indicated temperature (50, 60, 70, 80, or 90 °C).

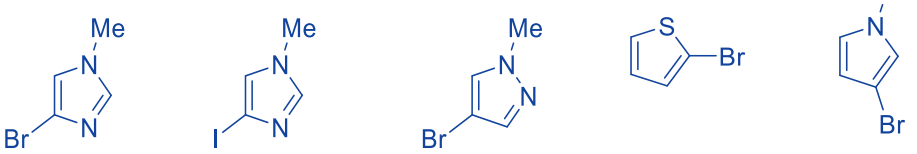
4. Optimization of reaction conditions for additional five-membered heteroaryl halides

Summary of optimization results

All reactions were analyzed by ^{1}H NMR in $CDCl_3$ to assess the yield relative to a trimethoxybenzene standard.

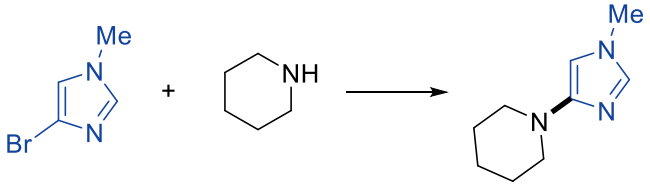


Aryl halide



Precatalyst	**P1** (GPhos)	-	**P1** (GPhos)	-	**P1** (GPhos)
Base	NaOTMS	NaOTMS	NaOTMS	NaOTMS	NaOTMS
Base equiv.	-	-	1.05–1.4	1.05	-
Solvent	THF	1,4-Dioxane	THF	THF	THF
Concentration	0.4–1.0 M	0.4–1.0 M	0.4–1.0 M	≥1.0 M	0.4–1.0 M
Temperature	70–90 °C	50 °C	≥90 °C	70 °C	≥90 °C
Reaction time	-	3 h	3 h (minimal additional product formation between 3–23 h)	3 h	-

4-Bromo-1-methyl-1*H*-imidazole



Precatalyst	**Yield (%)**
P1 (GPhos Pd G6)	53
P2 (RuPhos Pd G6)	0
P3 (*t*-BuXPhos Pd G6)	12
P7 (BrettPhos Pd G6)	2
P8 (*t*-BuBrettPhos Pd G6)	5

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 2 mol% precatalyst, THF (0.4 M), 70 °C, 3 h.

Base	**Yield (%)**

NaOTMS	65 (0% ArH)
NaO*t*-Bu	29 (7% ArH)

ArH = 1-methyl-1*H*-imidazole

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv base, 2 mol% **P1**, THF (0.4 M), 70 °C, 17 h.

Solvent	**Yield (%)**
THF	55
1,4-Dioxane	51

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 2 mol% **P1**, solvent (0.4 M), 70 °C, 3 h.

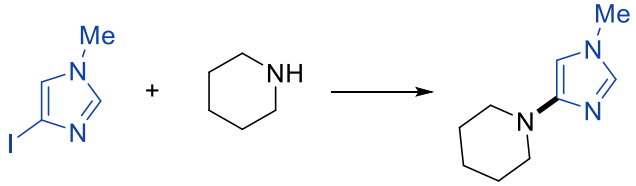
Concentration	**Yield (%)**
0.4 M	58
1.0 M	59

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 2 mol% **P1**, THF, 70 °C, 18 h.

Temperature	**Yield (%)**
50 °C	26
70 °C	45
90 °C	46

Reaction conditions: 1.0 equiv (0.1 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 2 mol% **P1**, THF (0.4 M), 3 h.

4-Iodo-1-methyl-1*H*-imidazole



Base	**Yield (%)**
NaOTMS	14 (0% ArH)
NaO*t*-Bu	11 (8% ArH)

ArH = 1-methyl-1*H*-imidazole

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv base, 2 mol% **P1**, 1,4-dioxane (0.4 M), 70 °C, 17 h.

Solvent	Yield (%)
THF	6
1,4-Dioxane	19

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 2 mol% **P1**, solvent (0.4 M), 70 °C, 3 h.

Concentration	Yield (%)
0.4 M	15
1.0 M	18

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 2 mol% **P1**, 1,4-dioxane, 70 °C, 18 h.

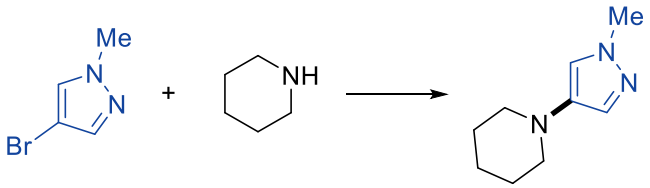
Temperature	Yield (%)
50 °C	24
70 °C	8
90 °C	7

Reaction conditions: 1.0 equiv (0.1 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 2 mol% **P1**, THF (0.4 M), 3 h.

Reaction time	Yield (%)
3 h	9
30 h	10

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, THF (0.4 M), 50 °C.

4-Bromo-1-methyl-1*H*-pyrazole



Precatalyst	Yield (%)
P1 (GPhos Pd G6)	72
P2 (RuPhos Pd G6)	0

P3 (*t*-BuXPhos Pd G6)	11
P7 (BrettPhos Pd G6)	12
P8 (*t*-BuBrettPhos Pd G6)	7

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% precatalyst, THF (0.4 M), 90 °C, 3 h.

Base	**Yield (%)**
NaOTMS	62
NaO*t*-Bu	9

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv base, 0.75 mol% **P1**, THF (0.4 M), 90 °C, 3 h.

Base equivalents	**Yield (%)**
1.05	60
1.2	60
1.4	59
2.0	20

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, NaOTMS, 0.75 mol% **P1**, THF (0.4 M), 90 °C, 3 h.

Solvent	**Yield (%)**
THF	64
1,4-Dioxane	38

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, solvent (0.4 M), 90 °C, 3 h.

Concentration	**Yield (%)**
0.4 M	18
1.0 M	16

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, THF, 50 °C, 3 h.

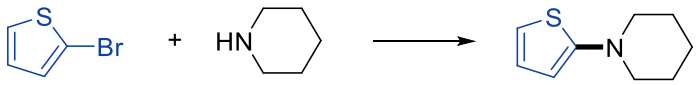
Temperature	**Yield (%)**
50 °C	19
70 °C	39
90 °C	65

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, THF (0.4 M), 3 h.

Reaction time	Yield (%)
3 h	64
7 h	68
23 h	76

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, THF (0.4 M), 90 °C.

2-Bromothiophene



Base	Yield (%)
NaOTMS	42
NaO*t*-Bu	1

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv base, 0.75 mol% **P1**, THF (0.4 M), 70 °C, 3 h.

Base equivalents	Yield (%)
1.05	41
1.2	37
1.4	36
2.0	22

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, NaOTMS, 0.75 mol% **P1**, THF (0.4 M), 70 °C, 3 h.

Solvent	Yield (%)
THF	34
1,4-Dioxane	28

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, solvent (0.4 M), 70 °C, 3 h.

Concentration	Yield (%)
0.4 M	32
1.0 M	41

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, THF, 50 °C, 3 h.

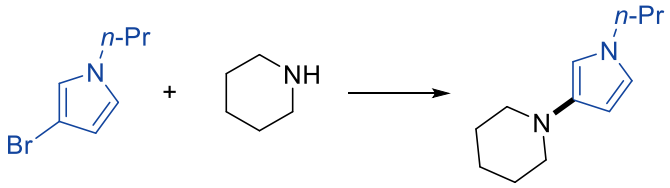
Temperature	Yield (%)
50 °C	36
70 °C	46
90 °C	34

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, THF (0.4 M), 5 h.

Reaction time	Yield (%)
3 h	41
30 h	42

Reaction conditions: 1.0 equiv (0.2 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 0.75 mol% **P1**, THF (1.0 M), 50 °C.

3-Bromo-1-propyl-1*H*-pyrrole



Precatalyst	Yield (%)
P1 (GPhos Pd G6)	79
P2 (RuPhos Pd G6)	3
P3' (*t*-BuXPhos OAC)	21
P11 (CPhos OAC)	23

Reaction conditions: 1.0 equiv (0.1 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 4 mol% precatalyst, THF (0.4 M), 70 °C, 5 h.

Base	Yield (%)
NaOTMS	45
NaO*t*-Bu	14

Reaction conditions: 1.0 equiv (0.1 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv base, 1.5 mol% **P1**, THF (0.4 M), 70 °C, 4 h.

Solvent	Yield (%)

THF	45
1,4-Dioxane	34

Reaction conditions: 1.0 equiv (0.1 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 1.5 mol% **P1**, solvent (0.4 M), 70 °C, 4 h.

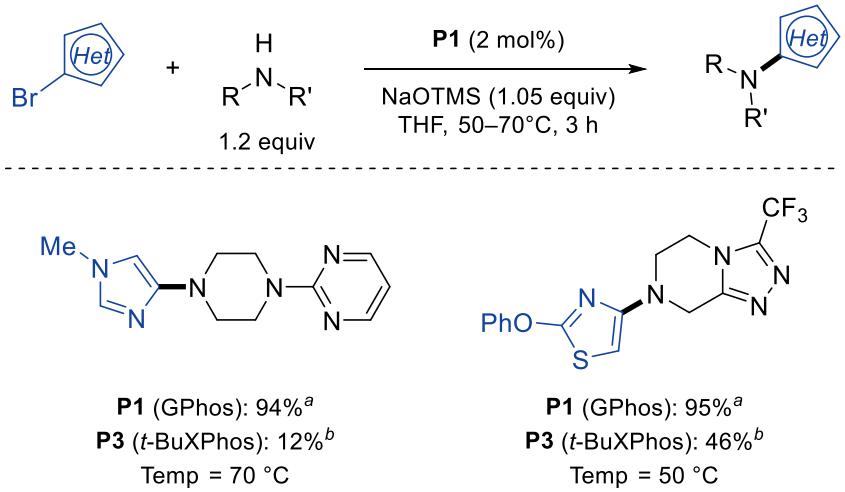
Concentration	**Yield (%)**
0.4 M	45
1.0 M	43

Reaction conditions: 1.0 equiv (0.1 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 1.5 mol% **P1**, THF, 70 °C, 4 h.

Temperature	**Yield (%)**
50 °C	14
70 °C	45
90 °C	60

Reaction conditions: 1.0 equiv (0.1 mmol) aryl halide, 1.2 equiv amine, 1.05 equiv NaOTMS, 1.5 mol% **P1**, THF (0.4 M), 4 h.

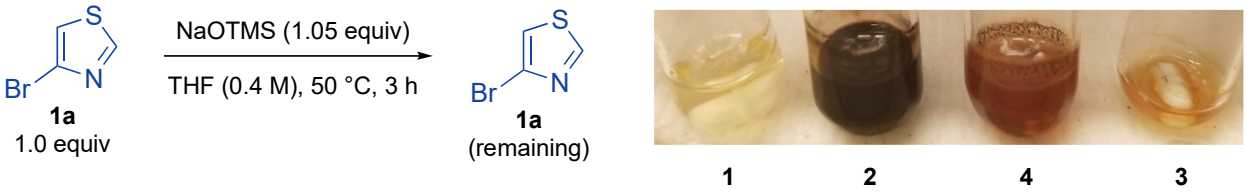
Ligand comparison: GPhos vs. *t*-BuXPhos



Legend: (a) isolated yield (Manuscript, Figure 4); (b) yields determined by ^{1}H NMR spectroscopy of the crude product mixtures, using 1,3,5-trimethoxybenzene as the internal standard.

5. Procedures for mechanistic experiments

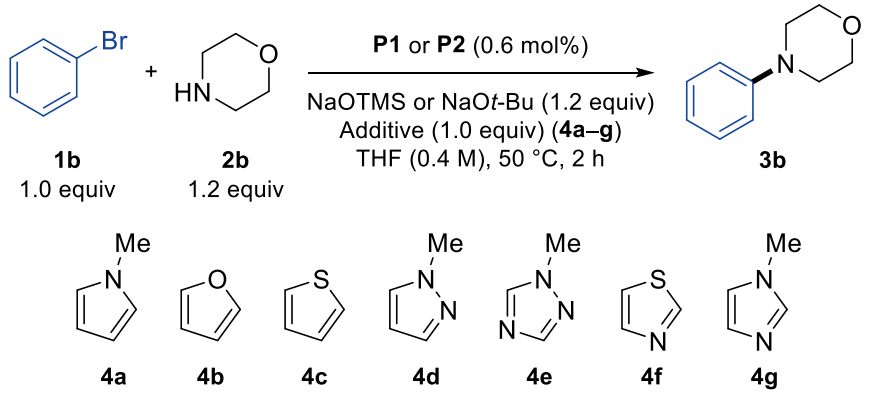
Investigation of base-mediated decomposition of 4-bromothiazole (Figure 3A)



Entry	Deviation from standard conditions	Remaining 1a (%)
1	None	93
2	NaO*t*-Bu	59
3	2.0 M THF	84
4	100 °C	83

These reactions were set up in a nitrogen-filled glovebox. Into an oven-dried reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) containing a Teflon-coated magnetic stir bar, the appropriate solid base was added: NaOTMS (entries 1, 3, 4) (24 mg, 0.21 mmol, 1.05 equiv) or NaO*t*-Bu (entry 2) (20 mg, 0.21 mmol, 1.05 equiv). Anhydrous THF (0.40 mL) was added via syringe to entries 1, 2, and 4, rinsing down the sides of the reaction tube. A stock solution of 4-bromothiazole (**1a**) was prepared in an oven-dried 1 dram vial: 4-bromothiazole (164 mg, 1.0 mmol, 5.0 equiv; per reaction: 33 mg, 0.2 mmol, 1.0 equiv) was added via micropipette, followed by anhydrous THF (0.50 mL; per reaction: 0.10 mL), added via syringe. The 4-bromothiazole stock solution (0.12 mL) was added to entries 1–4 via syringe, directly to the bottom of the reaction tube. The reaction tubes were sealed with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60). The sealed tubes were removed from the glovebox and immediately transferred to a pre-heated oil bath (bath temperature = 50 °C for entries 1–3; bath temperature = 100 °C for entry 4). The reaction mixture was stirred at 50 °C (entries 1–3) or 100 °C (entry 4) for 3 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air, an internal standard (trimethoxybenzene) was added, and the mixture was transferred directly to a scintillation vial via glass pipette. The mixture was concentrated with the aid of a rotary evaporator. The concentrated reaction mixture was dissolved in $CDCl_3$, and the amount of 4-bromothiazole remaining was determined using ^1H NMR analysis (d1 = 10 s).

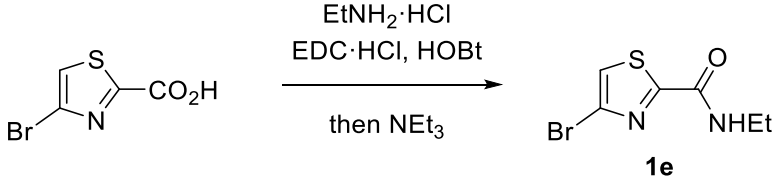
Investigation of C−N coupling inhibition by five-membered heteroarenes (Figure 3B)



These reactions were set up in a nitrogen-filled glovebox. Into an oven-dried reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) containing a Teflon-coated magnetic stir bar, the appropriate solid base was added: NaOTMS (27 mg, 0.24 mmol, 1.2 equiv) or NaO*t*-Bu (23 mg, 0.24 mmol, 1.2 equiv). A stock solution of bromobenzene (**1b**) and morpholine (**2b**) was prepared in an oven-dried 1 dram vial: bromobenzene (per reaction: 31 mg, 0.2 mmol, 1.0 equiv),

followed by morpholine (per reaction: 21 mg, 0.24 mmol, 1.2 equiv), were each added via micropipette, followed by anhydrous THF (0.25 mL per reaction), added via syringe. The bromobenzene/morpholine stock solution (0.29 mL) was added to each reaction via syringe, directly to the bottom of the reaction tube. The heteroarene additive (**4a**–**g**) (0.2 mmol, 1.0 equiv) was added to the reaction tube via micropipette. A stock solution of precatalyst (**P1** or **P2**) was prepared in an oven-dried 1 dram vial: precatalyst (0.6 mol%) was weighed into an oven-dried 1-dram vial (Kimble, part no. 60910L-1) outside of the glovebox, and anhydrous THF (0.125 mL per reaction) was added via syringe inside the glovebox to make the precatalyst stock solution. Precatalyst stock solution (0.25 mL) was added to each reaction tube via syringe, rinsing down the sides of the reaction tube. The reaction tubes were sealed with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60). The sealed tubes were removed from the glovebox and immediately transferred to a pre-heated oil bath (bath temperature = 50 °C). The reaction mixture was stirred at 50 °C for 2 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air, an internal standard (*n*-dodecane) was added, and the product mixture was filtered through a plug of silica. The yield of each reaction was determined using GC analysis (flame ionization detection; calibrated peak area relative to *n*-dodecane internal standard).

6. Procedures for synthesis of aryl halide substrates



1e

4-bromo-*N*-ethylthiazole-2-carboxamide (1e)

A 50 mL round-bottom flask was equipped with a Teflon-coated magnetic stir bar and charged with 4-bromothiazole-2-carboxylic acid (1.04 g, 5.00 mmol, 1.0 equiv), 3-(((ethylimino)methylene)amino)-*N*,*N*-dimethylpropan-1-amine hydrochloride (1.15 g, 6.00 mmol, 1.2 equiv), 1*H*-benzo[d][1,2,3]triazol-1-ol (80 wt%, 253 mg, 1.50 mmol 0.3 equiv), and ethanamine hydrochloride (408 mg, 5.00 mmol, 1.0 equiv). MeCN (7 mL) was added to the flask via syringe, then the flask was capped with a yellow plastic cap (Chemglass CG-3021-01) and the solution was allowed to stir for 5 min. The yellow cap was removed and Et_3N (531 mg, 732 µL, 5.25 mmol, 1.05 equiv) was added via syringe. The flask was re-capped with the yellow cap and the reaction was allowed to stir at room temperature overnight. The yellow cap was removed and water (5 mL) was added to the reaction mixture. The mixture was transferred to a separatory funnel and was extracted with EtOAc (3 x 20 mL), then washed with brine (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 10% EtOAc/hexane, followed by 2.7 column volumes 20% EtOAc/hexane, followed by 2.7 column volumes 40% EtOAc/hexane. Yield: 480 mg, 41%. White powder.

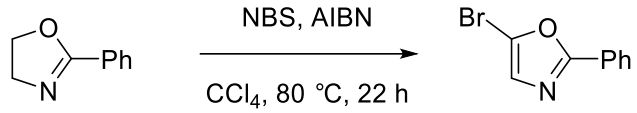
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.16 (br s, 1H), 3.49 (p, J = 7.1 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.4, 158.2, 125.5, 123.0, 34.9, 14.8.

Elemental Analysis calc. for $C_6H_7BrN_2OS$: C, 30.65; H, 3.00. Found: C, 30.78; H, 2.86.

IR (Diamond-ATR, neat, cm^{-1}): 3264, 3115, 2973, 1662, 1652, 1541, 1154, 899, 845, 745, 707.

Melting Point: 69–70 °C



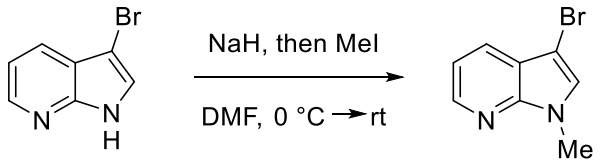
1i

5-bromo-2-phenyloxazole (1i)
A 100 mL round-bottom flask equipped with a Teflon-coated magnetic stir bar was charged with 2-phenyl-4,5-dihydrooxazole (2.21 g, 15.0 mmol, 1.0 equiv), *N*-bromosuccinimide (NBS) (8.01 g, 45.0 mmol, 3.0 equiv), and azobisisobutyronitrile (AIBN) (123 mg, 0.75 mmol, 0.5 mol%). The round-bottom flask was fitted with a reflux condenser that was sealed with a rubber septum, which was pierced with a needle connected to a Schlenk line using a rubber hose. The system was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous CCl_4 (30 mL) was added via syringe, and the reaction mixture was transferred to a pre-heated oil bath (bath temperature = 80 °C). The reaction mixture was heated to reflux at 80 °C for 22 h. At this time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The product mixture was filtered through a pad of Celite (10 mL), eluting with CH_2Cl_2 (50 mL). The filtrate was transferred to a separatory funnel and washed with saturated $Na_2S_2O_3$ (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. Chromatography conditions: SiO_2 (150 mL), 1.3 column volumes hexane, followed by 1.3 column volumes 5% EtOAc/hexane, followed by 1.3 column volumes 10% EtOAc/hexane, followed by 1.3 column volumes 15% EtOAc/hexane, followed by 1.3 column volumes 20% EtOAc/hexane, followed by 1.3 column volumes 25% EtOAc/hexane, followed by 1.3 column volumes 30% EtOAc/hexane. The product-containing fractions were further purified by column chromatography. Chromatography conditions: SiO_2 (50 g CombiFlash cartridge), 2 column volumes hexane, followed by 25 column volumes 0% to 35% EtOAc/hexane. Yield: 499 mg, 15%. Brown solid. The NMR spectra matched those reported in the literature.[39]

^1H NMR (400 MHz, $CDCl_3$) δ 8.05-7.96 (m, 2H), 7.51-7.42 (m, 3H), 7.10 (s, 1H).

IR (Diamond-ATR, neat, cm^{-1}): 3134, 1556, 1517, 1487, 1448, 1116, 952, 831, 773, 706, 682.

Melting Point: 56–59 °C



1u

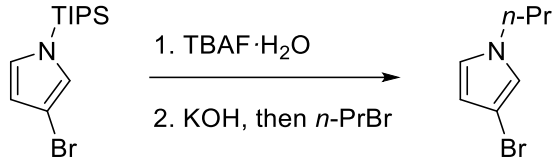
3-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1u)

An oven-dried 25 mL round-bottom flask equipped with an oven-dried Teflon-coated magnetic stir bar was charged with 3-bromo-1*H*-pyrrolo[2,3-b]pyridine (493 mg, 2.50 mmol, 1.0 equiv), and the flask was sealed with a rubber septum. The septum was pierced with a needle attached to a Schlenk line using a rubber hose, and the flask was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous DMF (10 mL) was added via syringe. The flask was cooled to 0 °C in an ice/water bath. Sodium hydride (60 wt%, 160 mg, 4.00 mmol, 1.6 equiv) was added in two equal-sized portions, 15 min apart: the rubber septum was removed from the flask, solid sodium hydride was added quickly, and the flask was re-sealed with the rubber septum. The flask was removed from the ice/water bath and the reaction mixture was allowed to stir at room temperature for 30 min. The flask was then cooled to 0 °C in an ice/water bath, and iodomethane (355 mg, 156 µL, 2.50 mmol, 1.0 equiv) was added dropwise over 1 min via syringe. The flask was removed from the ice/water bath and the reaction mixture was allowed to stir at room temperature for 26 h. At this time the reaction mixture was cooled to 0 °C in an ice/water bath, and water (5 mL) was *carefully* added via syringe. The septum was removed and the mixture was transferred to a separatory funnel and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with water (10 mL) and brine (5 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. Chromatography conditions: SiO_2 (115 mL), 2.1 column volumes 17% EtOAc/hexane, followed by 1.3 column volumes 33% EtOAc/hexane. Yield: 437 mg, 83%. Red oil. The NMR spectra matched those reported in the literature.[40]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.21 (s, 1H), 7.13 (dd, *J* = 7.9, 4.7 Hz, 1H), 3.88 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.9, 144.1, 128.1, 127.6, 120.1, 116.3, 87.8, 31.5.

IR (Diamond-ATR, neat, cm^{-1}): 3051, 2938, 1597, 1565, 1404, 1321, 1296, 945, 764.



1v

3-bromo-1-propyl-1*H*-pyrrole (1v)

A 50 mL round-bottom flask (Flask A) equipped with a Teflon-coated magnetic stir bar was charged with 3-bromo-1-(triisopropylsilyl)-1*H*-pyrrole (907 mg, 791 µL, 3.00 mmol, 1.0 equiv), added via syringe. Flask A was sealed with a rubber septum, the septum was pierced with a needle attached to a Schlenk line using a rubber hose, and the flask was evacuated and backfilled with

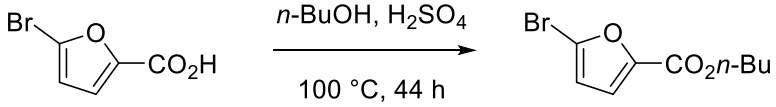
nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF (8 mL) was added via syringe. A separate oven-dried 1-dram vial (Vial B) (Kimble, part no. 60910L-1) was charged with tetrabutylammonium fluoride hydrate (TBAF·H_2O) (880 mg, 3.15 mmol, 1.05 equiv). Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Anhydrous THF (2 mL) was added to Vial B via syringe, and Vial B was shaken slightly to form a homogeneous solution. The solution in Vial B was added to Flask A dropwise via syringe over 5 min. The reaction mixture in Flask A was allowed to stir at room temperature for 2 h, after which time water (10 mL) was added. The mixture was transferred to a separatory funnel and was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO4, filtered, and concentrated with the aid of a rotary evaporator. KOH (505 mg, 9.00 mmol, 3.0 equiv) was added to the crude product mixture in a 50 mL round-bottom flask equipped with a magnetic stir bar, and the flask was sealed with a rubber septum. Anhydrous DMSO (6 mL) was added via syringe. The solution was allowed to stir at room temperature for 25 min. Then, 1-bromopropane (387 mg, 286 µL, 3.15 mmol, 1.05 equiv) was added via syringe. The reaction mixture was allowed to stir at room temperature for 19 h. At this time the rubber septum was removed, and the reaction mixture was transferred to a separatory funnel. Water (10 mL) and EtOAc (10 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were washed with brine (2 x 5 mL), dried over MgSO4, filtered, and concentrated with the aid of a rotary evaporator. The crude material was purified by column chromatography. Chromatography conditions: SiO_2 (50 g CombiFlash cartridge), 2 column volumes hexane, followed by 20 column volumes 0% to 5% EtOAc/hexane. Yield: 336 mg, 60%. Colorless oil. *Note: This compound is not stable under ambient conditions and will decompose over several days to form a brown oil; decomposition can be slowed by storing this compound under nitrogen in the glovebox freezer (−40 °C), in which it is stable for months.*

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65-6.60 (m, 1H), 6.54 (t, *J* = 2.6 Hz, 1H), 6.12 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.78 (t, *J* = 7.1 Hz, 2H), 1.76 (h, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 121.3, 120.2, 110.5, 95.0, 52.0, 24.8, 11.3.

HR-MS (DART+) calc. for $C_7H_{10}BrN$ $[M+H]^+$: 188.00694. Found: 188.00558.

IR (Diamond-ATR, neat, cm^{-1}): 2964, 2932, 2875, 1494, 1295, 1111, 915, 757, 690, 615, 603.



1z

Butyl 5-bromofuran-2-carboxylate (1z)

A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with 5-bromofuran-2-carboxylic acid (955 mg, 5.00 mmol, 1.0 equiv), via syringe; 1-butanol (15 mL), via syringe; and concentrated sulfuric acid (1 mL), via syringe. The round-bottom flask was fitted with a reflux condenser that was sealed with a rubber septum, which was pierced with a needle connected to a Schlenk line using a rubber hose. The system was placed under a positive pressure of nitrogen.

The flask was transferred to a pre-heated oil bath (bath temperature = 100 °C). The reaction mixture was allowed to stir at 100 °C for 44 h. At this time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The resulting mixture was concentrated with the aid of a rotary evaporator, and the crude material was added to a separatory funnel containing ice water (5 mL). Sat. $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added, and the layers were separated. The organic layer was washed with brine (5 mL), dried over MgSO4, filtered, and concentrated with the aid of a rotary evaporator. The crude material was passed through a pad of silica (10 mL), eluting with 25% EtOAc/hexane (50 mL), and the resulting filtrate was concentrated with the aid of a rotary evaporator. Yield: 1.068 g, 87%. Orange oil. The NMR spectra matched those reported in the literature.[41]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 3.5 Hz, 1H), 6.44 (d, *J* = 3.5 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 2H), 1.76 – 1.67 (m, 2H), 1.50 – 1.37 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.9, 146.6, 127.5, 120.0, 114.0, 65.2, 30.8, 19.2, 13.8.

IR (Diamond-ATR, neat, cm^{-1}): 2960, 2874, 1717, 1583, 1464, 1289, 1110, 756.

7. Procedures for preparative C–N coupling reactions in Figures 4 and 5

General Procedure C for the coupling of aryl halides with amines

An oven-dried 13 x 100 mm reaction tube (Tube A) (Fisherbrand, product no. 1495935C) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with NaOTMS (59 mg, 0.525 mmol, 1.05 equiv), aryl halide, if solid (0.50 mmol, 1.00 equiv), and amine, if solid (0.60 mmol, 1.20 equiv). Tube A was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The tube was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF (0.65 mL) was added via syringe. Aryl halide, if liquid (0.50 mmol, 1.00 equiv), was added via syringe, followed by the addition of amine, if liquid (0.60 mmol, 1.20 equiv), via syringe. The reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. A solution of **P1** (0.0167 M–0.0417 M, 2–5 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B) (Kimble, part no. 60910L-1). Solid **P1** was added to Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired precatalyst concentration (0.0167 M–0.0417 M, 2–5 mol%). **P1** solution (0.60 mL) from Vial B was transferred to Tube A via syringe. Tube A was then immediately transferred to a pre-heated oil bath (bath temperature = 50–90 °C). The reaction mixture was stirred at 50–90 °C for 3 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air and the contents were filtered through a plug of Celite, rinsing with EtOAc (3 x 5 mL). The crude material was purified by column chromatography.

General Procedure D for the coupling of aryl halides with amines via slow base addition

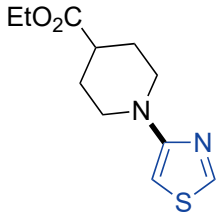
An oven-dried 13 x 100 mm reaction tube (Tube A) (Fisherbrand, product no. 1495935C) equipped with an oven-dried Teflon-coated magnetic stir bar was charged with aryl halide, if solid (0.50 mmol, 1.00 equiv), and amine, if solid (0.60 mmol, 1.20 equiv). Tube A was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The tube was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Aryl halide, if liquid (0.50 mmol, 1.00 equiv), was added via syringe, followed by the addition of amine, if liquid (0.60 mmol, 1.20 equiv), via syringe. A solution of **P1** (0.025 M–0.0417 M, 3–5 mol%) was prepared in a separate oven-dried 1-dram vial (Vial B) (Kimble, part no. 60910L-1). Solid **P1** was added to Vial B, and Vial B was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial B was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial B via syringe to achieve the desired precatalyst concentration (0.025 M–0.0417 M, 3–5 mol%). **P1** solution (0.65 mL) from Vial B was transferred to Tube A via syringe. The reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. Tube A was then immediately transferred to a pre-heated oil bath (bath temperature = 50–90 °C). A solution of NaOTMS (0.875 M) was prepared in another separate oven-dried 1-dram vial (Vial C) (Kimble, part no. 60910L-1). Solid NaOTMS was added to Vial C, and Vial C was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. Vial C was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to Vial C via syringe to achieve the desired base concentration (0.875 M). NaOTMS solution (0.65 mL) from Vial C was transferred into a 1-mL syringe and slowly added via needle to Tube A in oil bath over the course of 1 h with the aid of a syringe pump. The reaction mixture was further stirred at 50–90 °C for 2 h while leaving the syringe needle in Tube A, after which time Tube A was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air and the contents were filtered through a plug of Celite, rinsing with EtOAc (3 x 5 mL). The crude material was purified by column chromatography.

General Procedure E for the coupling of aryl iodides with amines

General Procedure C was followed with the following modification: 1,4-dioxane was used as the solvent, in the same amount as THF (instead of THF).

General Procedure F for the coupling of thiophenyl/furyl halides with amines

General Procedure C was followed with the following modification: these reactions were run with a total volume of 0.50 mL THF, instead of 1.25 mL THF. To achieve this, following the evacuation/backfilling of the reaction tube with nitrogen, 0.25 mL THF was added to the reaction tube (instead of 0.65 mL). The solution of **P1** ranged in concentration from 0.03 M–0.06 M (1.5–3 mol%), and 0.25 mL **P1** solution was added to the reaction tube (instead of 0.60 mL). These reactions were all performed at 70 °C.



3c

Ethyl 1-(thiazol-4-yl)piperidine-4-carboxylate (3c)

Product **3c** was prepared according to General Procedure D at 50 °C using 4-bromothiazole (82 mg, 44.6 µL, 0.50 mmol), ethyl piperidine-4-carboxylate (94 mg, 92.5 µL, 0.60 mmol), and 3.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (70 mL), 1.4 column volumes hexane, followed by 2.9 column volumes 12.5% EtOAc/hexane, followed by 4.3 column volumes 16.7% EtOAc/hexane. Yield: Run 1 = 105 mg, 88%; Run 2 = 105 mg, 88%. Average Yield = 88%. White solid.

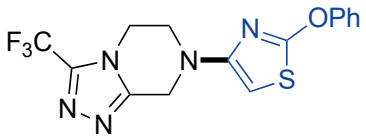
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.86 (dt, *J* = 12.5, 4.0 Hz, 2H), 2.84 (td, *J* = 11.9, 3.0 Hz, 2H), 2.45 (tt, *J* = 11.1, 3.9 Hz, 1H), 2.08-1.97 (m, 2H), 1.94-1.81 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.9, 163.0, 151.1, 89.8, 60.6, 48.6, 41.2, 27.7, 14.4.

Elemental Analysis calc. for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71. Found: C, 55.22; H, 6.82.

IR (Diamond-ATR, neat, cm^{-1}): 3110, 2957, 2823, 1717, 1609, 1520, 1312, 1177, 1042, 883, 817.

Melting Point: 48–49 °C



3d

2-phenoxy-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)thiazole (3d)

Product **3d** was prepared according to General Procedure C at 50 °C using 4-bromo-2-phenoxythiazole (128 mg, 0.50 mmol), 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (115 mg, 0.60 mmol), and 2.0 mol% **P1** as catalyst. Upon completion, the vessel was then opened to the air and the contents were filtered through a plug of Celite, rinsing with CH_2Cl_2 (3 x 2 mL) instead of EtOAc. Chromatography conditions: SiO_2 (70 mL), 3.6 column volumes 40% EtOAc/hexane, followed by 2.9 column volumes 50% EtOAc/hexane, followed by 3.6 column volumes 67% EtOAc/hexane. Yield: Run 1 = 166 mg, 90%; Run 2 = 183 mg, 100%. Average Yield = 95%. Off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.9 Hz, 2H), 7.33-7.24 (m, 3H), 5.54 (s, 1H), 4.58 (s, 2H), 4.22 (t, *J* = 5.5 Hz, 2H), 3.87 (t, *J* = 5.5 Hz, 2H).

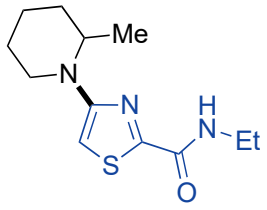
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.9, 155.1, 152.8, 150.9, 143.7 (q, J = 40.6 Hz), 130.1, 126.4, 120.5, 118.5 (q, J = 270.4 Hz), 85.0, 44.84, 44.78, 43.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.03.

Elemental Analysis calc. for $C_{15}H_{12}F_3N_5OS$: C, 49.04; H, 3.29. Found: C, 48.88; H, 3.13.

IR (Diamond-ATR, neat, cm^{-1}): 3129, 3060, 1546, 1489, 1137, 767, 701.

Melting Point: 166–168 °C



3e

***N*-ethyl-4-(2-methylpiperidin-1-yl)thiazole-2-carboxamide (3e)**

Product **3e** was prepared according to General Procedure C at 50 °C using 4-bromo-N-ethylthiazole-2-carboxamide (118 mg, 0.50 mmol), 2-methylpiperidine (248 mg, 294 µL, 2.50 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 10% EtOAc/hexane, followed by 2.7 column volumes 20% EtOAc/hexane, followed by 2.7 column volumes 30% EtOAc/hexane, followed by 2.7 column volumes 40% EtOAc/hexane. Yield: Run 1 = 100 mg, 79%; Run 2 = 102 mg, 81%. Average Yield = 80%. Yellow crystalline solid.

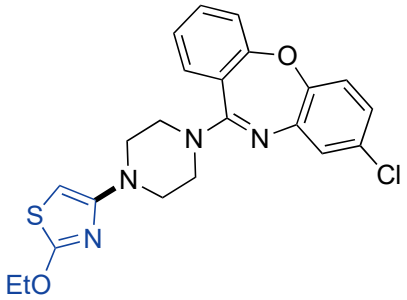
^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (br s, 1H), 6.05 (s, 1H), 4.27 (p, J = 6.5 Hz, 1H), 3.60-3.36 (m, 3H), 2.98 (t, J = 11.7 Hz, 1H), 1.92-1.80 (m, 1H), 1.79-1.71 (m, 1H), 1.69-1.55 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 6.7 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.9, 160.2, 159.7, 95.8, 50.2, 43.2, 34.4, 30.5, 25.5, 18.8, 14.9, 12.8.

HR-MS (DART+) calc. for $C_{12}H_{19}N_3OS$ $[M+H]^+$: 254.13216. Found: 254.13278.

IR (Diamond-ATR, neat, cm^{-1}): 3301, 3096, 2967, 2926, 2859, 2824, 1640, 1531, 1509, 1157, 833, 704.

Melting Point: 66–68 °C



3f

8-chloro-11-(4-(2-ethoxythiazol-4-yl)piperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepane (3f)

Product **3f** was prepared according to General Procedure C at 50 °C using 4-bromo-2-ethoxythiazole (104 mg, 62.9 µL, 0.50 mmol), 2-chloro-11-(piperazin-1-yl)dibenzo[b,f][1,4]oxazepine (173 mg, 0.55 mmol), and 3.0 mol% **P1** as catalyst. *Note: Product is unstable in the crude mixture and should be rapidly isolated.* Chromatography conditions: SiO_2 (75 mL), 4 column volumes 20% EtOAc/hexanes. Yield: Run 1 = 184 mg, 83%; Run 2 = 181 mg, 82%. Average Yield = 83%. Light yellow solid.

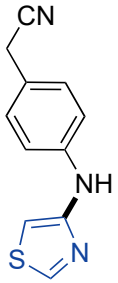
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.35 (d, *J* = 2.6 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.13-7.06 (m, 2H), 7.00 (td, *J* = 7.5, 1.8 Hz, 1H), 5.31 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.65 (br s, 4H), 3.32 (br s, 4H), 1.42 (d, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.1, 159.5, 159.1, 155.3, 152.0, 140.2, 132.8, 130.4, 129.2, 127.2, 126.0, 125.2, 124.8, 122.9, 120.3, 81.9, 67.6, 48.4, 47.1, 14.6.

HR-MS (DART+) calc. for $C_{22}H_{21}ClN_4O_2S$ $[M+H]^+$: 441.11465. Found: 441.11570.

IR (Diamond-ATR, neat, cm^{-1}): 2978, 2849, 1600, 1586, 1538, 1239, 1179, 996, 772.

Melting Point: 77–80 °C



3g

2-(4-(thiazol-4-ylamino)phenyl)acetonitrile (3g)

Product **3g** was prepared according to General Procedure C at 50 °C using 4-chlorothiazole (42 mg, 59.8 µL, 0.50 mmol), 2-(4-aminophenyl)acetonitrile (79 mg, 0.60 mmol), and 3.0 mol% **P1** as catalyst. Because the excess 2-(4-aminophenyl)acetonitrile co-eluted with the desired product on silica, the product mixture was subjected to acylation conditions. Under these conditions, the remaining 2-(4-aminophenyl)acetonitrile was acylated, and the desired product did not react. After the workup described in General Procedure C, the reaction mixture was concentrated under reduced pressure with the aid of a rotary evaporator into a 20 mL scintillation vial (DKW Life

Sciences, catalog no. 03-340-4C), which was then equipped with a Teflon-coated magnetic stir bar. No precautions were taken to exclude moisture or air. Anhydrous CH_2Cl_2 (2.5 mL) was added to the vial via syringe, followed by the addition of acetic anhydride (20 mg, 18.9 µL, 0.20 mmol) and triethylamine (20 mg, 27.9 µL, 0.20 mmol), each via syringe. This mixture was stirred under ambient conditions for 25 min. Saturated aqueous NH_4Cl (5 mL) was then added and the mixture was transferred to a separatory funnel. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated with the aid of a rotary evaporator. ^{1}H NMR analysis of this mixture indicated that all of the remaining 2-(4-aminophenyl)acetonitrile had been acylated. The mixture of the product and the acylated excess 2-(4-aminophenyl)acetonitrile was separated using column chromatography. Chromatography conditions: SiO_2 (70 mL), 5.7 column volumes 25% EtOAc/hexane, followed by 4.3 column volumes 33% EtOAc/hexane. Yield: Run 1 = 97 mg, 90%; Run 2 = 97 mg, 90%. Average Yield = 90%. Light yellow solid.

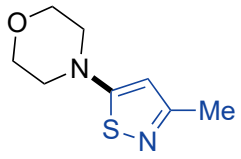
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.76 (br s, 1H), 6.51 (d, *J* = 2.1 Hz, 1H), 3.70 (s, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.7, 151.4, 142.3, 129.2, 122.0, 118.3, 117.0, 92.8, 23.1.

Elemental Analysis calc. for $C_{11}H_9N_3S$: C, 61.37; H, 4.21. Found: C, 61.63; H, 4.21.

IR (Diamond-ATR, neat, cm^{-1}): 3259, 3087, 2246, 1614, 1594, 1544, 1410, 882, 825, 693.

Melting Point: 140–141 °C



3h

4-(3-methylisothiazol-5-yl)morpholine (3h)

Product **3h** was prepared according to General Procedure C at 70 °C using 5-bromo-3-methylisothiazole (89 mg, 0.50 mmol), morpholine (52 mg, 52.5 µL, 0.60 mmol), and 4.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 20% EtOAc/hexane, followed by 2.7 column volumes 30% EtOAc/hexane, followed by 2.7 column volumes 40% EtOAc/hexane, followed by 2.7 column volumes 50% EtOAc/hexane. Yield: Run 1 = 82 mg, 89%; Run 2 = 86 mg, 93%. Average Yield = 91%. Yellow solid.

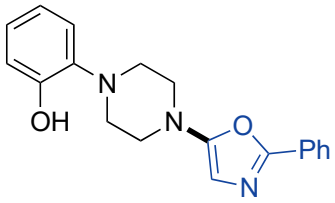
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (s, 1H), 3.87-3.76 (m, 4H), 3.23-3.10 (m, 4H), 2.32 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.7, 167.1, 102.4, 66.0, 50.2, 19.7.

HR-MS (DART+) calc. for $C_8H_{12}N_2OS$ $[M+H]^+$: 185.07431. Found: 185.07400.

IR (Diamond-ATR, neat, cm^{-1}): 2958, 2924, 2867, 1533, 1113, 884, 751.

Melting Point: 42–42 °C



3i

2-(4-(2-phenyloxazol-5-yl)piperazin-1-yl)phenol (3i)

Product **3i** was prepared according to General Procedure C at 70 °C using 5-bromo-2-phenyloxazole (112 mg, 0.50 mmol), 2-(piperazin-1-yl)phenol (107 mg, 0.60 mmol), NaOTMS (126 mg, 1.13 mmol, 2.25 equiv), and 4.0 mol% **P1** as catalyst. Upon completion, the reaction mixture was diluted with EtOAc (5 mL) and quenched with NH_4Cl (5 mL), and the aqueous layer extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered, then condensed. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 10% EtOAc/hexane, followed by 2.7 column volumes 25% EtOAc/hexane, followed by 2.7 column volumes 50% EtOAc/hexane. Yield: Run 1 = 129 mg, 81%; Run 2 = 138 mg, 86%. Average Yield = 83%. Pale yellow solid.

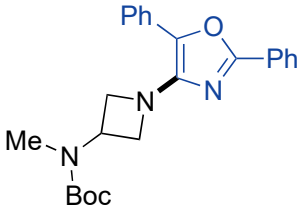
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.52-7.32 (m, 3H), 7.20 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.12 (td, *J* = 7.7, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.90 (td, *J* =7.7, 1.5 Hz, 1H), 3.38 (dd, *J* = 6.0, 3.9 Hz, 4H), 3.06 (dd, *J* = 6.2, 3.7 Hz, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.2, 154.6, 151.5, 138.7, 129.4, 128.8, 127.9, 127.0, 125.4, 121.5, 120.4, 114.6, 104.9, 51.8, 49.0.

HR-MS (DART+) calc. for $C_{19}H_{19}N_3O_2$ $[M+H]^+$: 322.15500. Found: 322.15546.

IR (Diamond-ATR, neat, cm^{-1}): 3320, 3105, 2826, 1594, 1491, 1249, 931, 743, 685.

Melting Point: 138–140 °C



3j

***Tert*-butyl (1-(2,5-diphenyloxazol-4-yl)azetidin-3-yl)(methyl)carbamate (3j)**

Product **3j** was prepared according to General Procedure C at 50 °C using 4-bromo-2,5-diphenyloxazole (150 mg, 0.50 mmol), tert-butyl azetidin-3-yl(methyl)carbamate hydrochloride (134 mg, 0.60 mmol), NaOTMS (126 mg, 1.13 mmol, 2.25 equiv), and 3.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 10% EtOAc/hexane, followed by 2.7 column volumes 20% EtOAc/hexane, followed by 2.7 column volumes 30% EtOAc/hexane. Yield: Run 1 = 170 mg, 84%; Run 2 = 165 mg, 81%. Average Yield = 82%. Yellow solid.

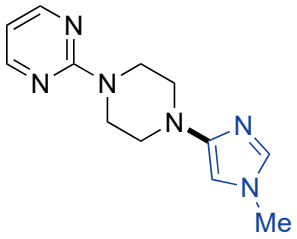
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.61 (d, *J* = 7.1 Hz, 2H), 7.52-7.37 (m, 5H), 7.23 (t, *J* = 7.5 Hz, 1H), 4.19 (t, *J* = 8.1 Hz, 2H), 3.97 (dd, *J* = 8.3, 6.5 Hz, 2H), 2.98 (s, 3H), 1.46 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.7, 155.6, 146.6, 130.2, 129.3, 128.8, 128.7, 127.7, 126.4, 126.3, 124.6, 110.4, 80.2, 57.6, 46.9, 30.0, 28.5.

HR-MS (DART+) calc. for $C_{24}H_{27}N_3O_3$ $[M+H]^+$: 406.21252. Found: 406.21416.

IR (Diamond-ATR, neat, cm^{-1}): 2959, 2864, 1684, 1613, 1485, 1327, 1148, 764, 696, 685.

Melting Point: 88–89 °C



3k

2-(4-(1-methyl-1*H*-imidazol-4-yl)piperazin-1-yl)pyrimidine (3k)

Product **3k** was prepared according to General Procedure C at 70 °C using 4-bromo-1-methyl-1*H*-imidazole (80 mg, 49.9 µL, 0.50 mmol), 2-(piperazin-1-yl)pyrimidine (98 mg, 85.1 µL, 0.60 mmol), and 2.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 2% MeOH/CH_2Cl_2, followed by 2.7 column volumes 5% MeOH/CH_2Cl_2, followed by 4 column volumes 10% MeOH/CH_2Cl_2. Yield: Run 1 = 118 mg, 96%; Run 2 = 111 mg, 91%. Average Yield = 94%. Orange solid.

Gram scale: An oven-dried 100 mL two-neck flask equipped with an oven-dried Teflon-coated magnetic stir bar was charged with NaOTMS (589 mg, 5.25 mmol, 1.05 equiv). The flask was sealed with a rubber septum on the side neck and a reflux condenser. The condenser was sealed with a rubber septum, which was pierced with a needle connected to a Schlenk line using a rubber hose. The apparatus was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF (6.5 mL) was added via syringe by puncturing through the septum on the side neck with a needle. 4-bromo-1-methyl-1*H*-imidazole (805 mg, 499 µL, 5.00 mmol) was added via syringe, followed by the addition of 2-(piperazin-1-yl)pyrimidine (985 mg, 851 µL, 6.00 mmol) via syringe. The reaction mixture was allowed to stir at room temperature for 5 min or until it was homogeneous or homogeneously suspended. A solution of **P1** (0.0167 M, 2 mol%) was prepared in a separate oven-dried 13 x 100 mm reaction tube (Fisherbrand, product no. 1495935C). Solid **P1** was added to the reaction tube, and the tube was sealed with a screw cap (Fisherbrand, 13-425, C4015-66) equipped with a Teflon septum (Fisherbrand, C4015-60) and was pierced with a needle connected to a Schlenk line using a rubber hose. The tube was evacuated and backfilled with nitrogen (the evacuation/backfill process was repeated a total of three times). Anhydrous THF was added to the reaction tube via syringe to achieve the desired precatalyst concentration (0.0167 M, 2 mol%). **P1** solution (6.0 mL) from the

reaction tube was transferred to the two-neck flask via syringe. The reaction apparatus was then immediately transferred to a pre-heated oil bath (bath temperature = 70 °C). The reaction mixture was stirred at 70 °C for 3 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air and the contents were filtered through a plug of Celite, rinsing with EtOAc (3 x 50 mL). The crude material was purified by column chromatography. Chromatography conditions: SiO_2 (150 mL), 2 column volumes 2% MeOH/CH_2Cl_2, followed by 2 column volumes 5% MeOH/CH_2Cl_2, followed by 2 column volumes 10% MeOH/CH_2Cl_2. Yield: Run 1 = 1.113 g, 91%; Run 2 = 1.075 g, 88%. Average Yield = 90%. Orange solid.

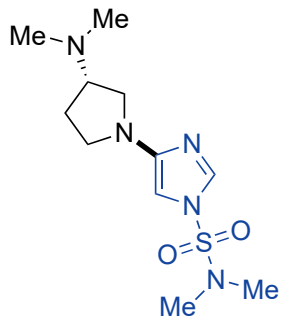
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.9 Hz, 1H), 7.16 (d, *J* = 1.5 Hz, 1H), 6.48 (t, *J* = 4.7 Hz, 1H), 6.14 (d, *J* = 1.6 Hz, 1H), 3.99-3.91 (m, 4H), 3.59 (s, 3H), 3.18-3.10 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.0, 157.8, 152.8, 134.8, 110.1, 101.2, 49.1, 43.4, 33.7.

HR-MS (DART+) calc. for $C_{12}H_{16}N_6$ $[M+H]^+$: 245.15092. Found: 245.15225.

IR (Diamond-ATR, neat, cm^{-1}): 3087, 2995, 2859, 2824, 1706, 1654, 1614, 1582, 1544, 1439, 1358, 1253.

Melting Point: 113–116 °C



3l

(*S*)-4-(3-(dimethylamino)pyrrolidin-1-yl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (3l)
Product **3l** was prepared according to General Procedure E at 50 °C using 4-iodo-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (151 mg, 0.50 mmol), (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine (68 mg, 76.2 µL, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: basic Al_2O_3 Brockmann III (30 mL), 2 column volumes CH_2Cl_2, followed by 2 column volumes 2% MeOH/CH_2Cl_2, followed by 2 column volumes 5% MeOH/CH_2Cl_2. Yield: Run 1 = 130 mg, 89%; Run 2 = 142 mg, 99%. Average Yield = 94%. Orange crystalline solid.

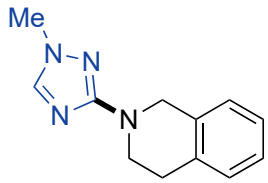
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 1.5 Hz, 1H), 6.22 (d, *J* = 1.6 Hz, 1H), 3.51 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.39 (td, *J* = 9.1, 3.0 Hz, 1H), 3.25 (td, *J* = 9.1, 7.2 Hz, 1H), 3.17 (t, *J* =8.4 Hz, 1H), 3.01-2.89 (m, 1H), 2.86 (s, 6H), 2.35 (s, 6H), 2.20 (dtd, *J* = 14.3, 7.0, 2.9, 1H), 1.98 (dq, *J* = 12.3, 9.0 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.8, 134.8, 93.7, 65.8, 52.8, 48.0, 44.0, 38.4, 29.9.

HR-MS (DART+) calc. for $C_{11}H_{21}N_5O_2S$ $[M+H]^+$: 288.14887. Found: 288.15097.

IR (Diamond-ATR, neat, cm^{-1}): 3132, 2970, 2827, 2781, 1589, 1456, 1383, 1172, 725, 712, 598.

Melting Point: 70–72 °C



3m

2-(1-methyl-1*H*-1,2,4-triazol-3-yl)-1,2,3,4-tetrahydroisoquinoline (3m)

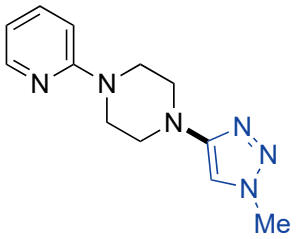
Product **3m** was prepared according to General Procedure C at 50 °C using 3-bromo-1-methyl-1*H*-1,2,4-triazole (81 mg, 0.50 mmol), 1,2,3,4-tetrahydroisoquinoline (80 mg, 75.1 µL, 0.60 mmol), and 2.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 2% MeOH/CH_2Cl_2, followed by 2.7 column volumes 5% MeOH/CH_2Cl_2. Yield: Run 1 = 106 mg, 99%; Run 2 = 107 mg, 100%. Average Yield = 99%. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.22-7.10 (m, 4H), 3.87-3.76 (m, 4H), 4.61 (s, 2H), 3.81-3.73 (m, 5H), 5.86 (t, *J* = 5.9 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.6, 142.8, 134.7, 134.0, 128.9, 126.7, 126.3, 126.1, 48.5, 43.9, 36.1, 28.6.

HR-MS (DART+) calc. for $C_{12}H_{14}N_4$ $[M+H]^+$: 215.12912. Found: 215.12867.

IR (Diamond-ATR, neat, cm^{-1}): 2967, 2924, 1669, 1549, 1495, 938, 752, 725.



3n

1-(1-methyl-1*H*-1,2,3-triazol-4-yl)-4-(pyridin-2-yl)piperazine (3n)

Product **3n** was prepared according to General Procedure C at 90 °C using 4-bromo-1-methyl-1*H*-1,2,3-triazole (81 mg, 0.50 mmol), 1-(pyridin-2-yl)piperazine (98 mg, 91.4 µL, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 50% EtOAc/hexane, followed by 2.7 column volumes 2% MeOH/CH_2Cl_2, followed by 2.7 column volumes 5% MeOH/CH_2Cl_2, followed by 1.3 column volumes 10% MeOH/CH_2Cl_2. Yield: Run 1 = 111 mg, 91%; Run 2 = 110 mg, 89%. Average Yield = 90%. Yellow solid.

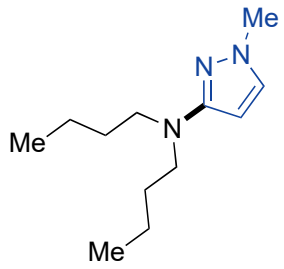
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 5.0, 2.0 Hz, 1H), 7.50 (ddd, *J* = 8.8, 7.1, 2.0 Hz, 1H), 6.89 (s, 1H), 6.71 (t, *J* = 8.6 Hz, 1H), 6.65 (dd, *J* = 7.1, 4.9 Hz, 1H), 4.02 (s, 3H), 3.76-3.65 (m, 4H), 3.31 (dd, *J* = 6.9, 4.1 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.6, 157.7, 148.0, 137.7, 113.8, 108.2, 107.4, 48.9, 44.8, 37.1.

Elemental Analysis calc. for $C_{12}H_{16}N_6$: C, 59.00; H, 6.60. Found: C, 58.74; H, 6.65.

IR (Diamond-ATR, neat, cm^{-1}): 3143, 2996, 2847, 1595, 1563, 1436, 1249, 948, 767.

Melting Point: 163–164 °C



3o

***N*,*N*-dibutyl-1-methyl-1*H*-pyrazol-3-amine (3o)**

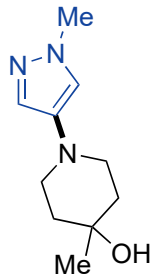
Product **3o** was prepared according to General Procedure C at 90 °C using 3-bromo-1-methyl-1*H*-pyrazole (80 mg, 0.50 mmol), dibutylamine (323 mg, 421 µL, 2.50 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 10% EtOAc/hexane, followed by 5.3 column volumes 25% EtOAc/hexane. Yield: Run 1 = 90 mg, 86%; Run 2 = 89 mg, 85%. Average Yield = 86%. Light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.3 Hz, 1H), 5.47 (d, *J* = 2.3 Hz, 1H), 3.71 (s, 3H), 3.25-3.12 (m, 4H), 1.59-1.47 (m, 4H), 1.33 (h, *J* = 7.4 Hz, 4H), 0.92 (t, *J* = 7.3 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.2, 131.0, 90.1, 49.7, 38.7, 29.8, 20.5, 14.2.

HR-MS (DART+) calc. for $C_{12}H_{23}N_3$ $[M+H]^+$: 210.19647. Found: 210.19534.

IR (Diamond-ATR, neat, cm^{-1}): 2954, 2929, 2860, 1554, 1504, 1374, 720.



3p

4-methyl-1-(1-methyl-1*H*-pyrazol-4-yl)piperidin-4-ol (3p)

Product **3p** was prepared according to General Procedure C at 90 °C using 4-bromo-1-methyl-1*H*-pyrazole (80 mg, 51.7 µL, 0.50 mmol), 4-methylpiperidin-4-ol (69 mg, 0.60 mmol), and 2.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 5% MeOH/CH_2Cl_2, followed by 5.3 column volumes 10% MeOH/CH_2Cl_2. Yield: Run 1 = 95 mg, 97%; Run 2 = 97 mg, 100%. Average Yield = 98%. Light yellow solid.

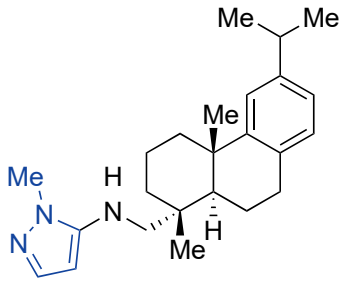
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.93 (s, 1H), 3.81 (s, 3H), 3.47 (br s, 1H), 3.05 – 2.89 (m, 4H), 1.78 (ddd, *J* = 14.7, 10.3, 4.7 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.28 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.6, 128.9, 117.1, 67.7, 48.3, 39.3, 38.2, 29.9.

HR-MS (DART+) calc. for $C_{10}H_{17}N_3O$ $[M+H]^+$: 196.14444. Found: 196.14541.

IR (Diamond-ATR, neat, cm^{-1}): 3215, 3105, 3085, 2958, 2945, 2920, 2856, 1564, 1355, 1155, 993, 972, 876, 689.

Melting Point: 108–110 °C



3q

***N*-(((1*R*,4a*S*,10a*R*)-6-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-1-methyl-1*H*-pyrazol-5-amine (3q)**

Product **3q** was prepared according to General Procedure C at 90 °C using 5-bromo-1-methyl-1*H*-pyrazole (80 mg, 0.50 mmol), ((1*R*,4a*S*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methanamine (171 mg, 0.60 mmol), and 2.5 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 6.7 column volumes 50% EtOAc/hexane. Yield: Run 1 = 158 mg, 86%; Run 2 = 156 mg, 85%. Average Yield = 86%. White solid.

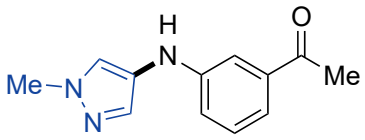
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 1.9 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 5.46 (d, *J* = 2.0 Hz, 1H), 3.60 (s, 3H), 3.15 (t, *J* = 6.8 Hz, 1H), 3.05 (dd, *J* = 12.4, 6.1 Hz, 1H), 2.99-2.72 (m, 4H), 2.33 (dd, *J* = 13.0, 3.3 Hz, 1H), 1.92-1.66 (m, 4H), 1.63 (dd, *J* = 9.9, 4.7 Hz, 1H), 1.56-1.35 (m, 3H), 1.25 (s, 6H), 1.24 (s, 3H), 1.02 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.6, 147.2, 145.8, 138.2, 134.7, 127.0, 124.4, 124.1, 88.0, 57.6, 45.4, 38.5, 37.6, 37.4, 36.2, 34.4, 33.5, 30.3, 25.5, 24.1, 24.1, 19.2, 19.0, 18.8.

HR-MS (DART+) calc. for $C_{24}H_{35}N_3$ $[M+H]^+$: 366.29037. Found: 366.29215.

IR (Diamond-ATR, neat, cm^{-1}): 3271, 2924, 2865, 2362, 1559, 820, 720, 630.

Melting Point: 48–50 °C



3r

1-(3-((1-methyl-1*H*-pyrazol-4-yl)amino)phenyl)ethan-1-one (3r)

Product **3r** was prepared according to General Procedure E at 70 °C using 4-iodo-1-methyl-1*H*-pyrazole (104 mg, 0.50 mmol), 1-(3-aminophenyl)ethan-1-one (81 mg, 0.60 mmol), and 2.5 mol% **P1** as catalyst. Upon completion, the reaction mixture was diluted with EtOAc (5 mL) and quenched with NH_4Cl (5 mL), and the aqueous layer extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered, then condensed. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 25% EtOAc/hexane, followed by 2.7 column volumes 50% EtOAc/hexane, followed by 5.3 column volumes EtOAc. Yield: Run 1 = 88 mg, 82%; Run 2 = 86 mg, 80%. Average Yield = 81%. Red solid.

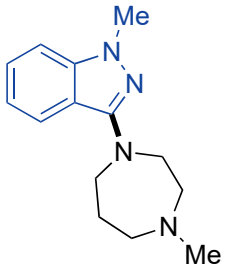
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.38 (s, 1H), 7.37-7.32 (m, 2H), 7.29 (d, J = 8.1 Hz, 1H), 6.97 (ddd, J = 8.0, 2.5, 1.2 Hz, 1H), 5.36 (br s, 1H), 3.93 (s, 3H), 2.58 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.6, 147.4, 138.4, 135.7, 129.5, 125.2, 124.2, 118.9, 118.1, 112.5, 39.5, 26.8.

HR-MS (DART+) calc. for $C_{12}H_{13}N_3O$ $[M+H]^+$: 216.11314. Found: 216.11428.

IR (Diamond-ATR, neat, cm^{-1}): 3372, 3036, 2932, 1671, 1598, 1573, 1360, 887, 772, 686.

Melting Point: 77–77 °C



3s

1-methyl-3-(4-methyl-1,4-diazepan-1-yl)-1*H*-indazole (3s)

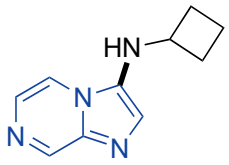
Product **3s** was prepared according to General Procedure C at 90 °C using 3-bromo-1-methyl-1*H*-indazole (106 mg, 0.50 mmol), 1-methyl-1,4-diazepane (68 mg, 74.6 µL, 0.60 mmol), and 3.5 mol% **P1** as catalyst. Chromatography conditions: Al_2O_3 Brockmann III (30 mL), 2 column volumes 15% EtOAc/hexane, followed by 2 column volumes CH_2Cl_2, followed by 2 column volumes 1% MeOH/CH_2Cl_2, followed by 2 column volumes 2% MeOH/CH_2Cl_2, followed by 2 column volumes 3% MeOH/CH_2Cl_2. Yield: Run 1 = 113 mg, 92%; Run 2 = 110 mg, 90%. Average Yield = 91%. Yellow gel.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.1, 6.8, 1.0 Hz, 1H), 7.17 (dt, *J* = 8.6, 1.0 Hz, 1H), 6.93 (ddd, *J* = 8.1, 6.8, 1.0 Hz, 1H), 3.84 (s, 3H), 3.83-3.79 (m, 2H), 3.76 (t, *J* = 6.3 Hz, 2H), 2.87-2.81 (m, 2H), 2.71-2.65 (m, 2H), 2.42 (s, 3H), 2.08 (p, *J* = 5.9 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.4, 142.4, 126.4, 122.2, 117.8, 114.4, 108.7, 59.2, 57.7, 49.71, 49.67, 46.9, 34.9, 28.4.

HR-MS (DART+) calc. for $C_{14}H_{20}N_4$ $[M+H]^+$: 245.17607. Found: 245.17619.

IR (Diamond-ATR, neat, cm^{-1}): 2934, 2843, 2793, 1609, 1541, 1451, 736.



3t

***N*-cyclobutylimidazo[1,2-*a*]pyrazin-3-amine (3t)**

Product **3t** was prepared according to General Procedure C at 90 °C using 3-bromoimidazo[1,2-a]pyrazine (99 mg, 0.50 mmol), cyclobutanamine (43 mg, 51.2 µL, 0.60 mmol), and 4.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (70 mL), 1.4 column volumes CH_2Cl_2, followed by 3.7 column volumes 4% MeOH/CH_2Cl_2, followed by 1.5 column volumes 5% MeOH/CH_2Cl_2, followed by 1.4 column volumes 6% MeOH/CH_2Cl_2, followed by 1.6 column volumes 9% MeOH/CH_2Cl_2. Yield: Run 1 = 75 mg, 80%; Run 2 = 75 mg, 80%. Average Yield = 80%. Yellow solid.

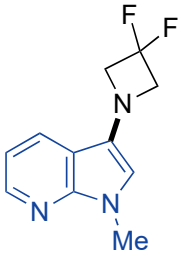
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.80-7.74 (m, 2H), 7.23 (s, 1H), 3.86 (h, *J* = 7.6 Hz, 1H), 3.45 (br d, *J* = 8.1 Hz, 1H), 2.42 (tdt, *J* = 9.9, 7.4, 2.6 Hz, 2H), 2.02-1.87 (m, 2H), 1.87-1.67 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.9, 137.0, 131.2, 128.7, 122.6, 114.7, 51.9, 31.5, 14.9.

HR-MS (DART+) calc. for $C_{10}H_{12}N_4$ $[M+H]^+$: 189.11347. Found: 189.10278.

IR (Diamond-ATR, neat, cm^{-1}): 3188, 2978, 2960, 2933, 1625, 1557, 1493, 1353, 1309, 1166, 1131, 904, 784, 601.

Melting Point: 127–128 °C



3u

3-(3,3-difluoroazetidin-1-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (3u)

Product **3u** was prepared according to General Procedure C at 90 °C using 3-bromo-1-methyl-1*H*-pyrrolo[2,3-b]pyridine (106 mg, 0.50 mmol), 3,3-difluoroazetidine hydrochloride (78 mg, 51.2 µL, 0.60 mmol), NaOTMS (126 mg, 1.13 mmol, 2.25 equiv), and 4.5 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 25% EtOAc/hexane, followed by 5.3 column volumes 50% EtOAc/hexane. Yield: Run 1 = 103 mg, 92%; Run 2 = 100 mg, 90%. Average Yield = 91%. Dense red oil.

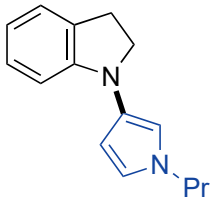
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.97 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.49 (s, 1H), 4.23 (t, *J* = 11.8 Hz, 1H), 3.80 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.6, 143.8, 128.6 (t, *J* = 2.1 Hz), 126.8, 116.8 (t, *J* = 275.3 Hz), 114.4, 113.5, 112.0, 65.7 (t, *J* = 24.0 Hz), 31.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -98.50 (p, *J* = 11.9 Hz).

HR-MS (DART+) calc. for $C_{11}H_{11}F_2N_3$ $[M+H]^+$: 224.09938. Found: 224.09720.

IR (Diamond-ATR, neat, cm^{-1}): 2951, 2361, 1725, 1684, 1596, 1468, 1405, 1348, 1247.



3v

1-(1-propyl-1*H*-pyrrol-3-yl)indoline (3v)

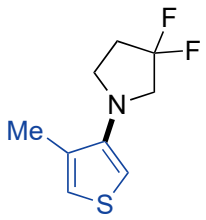
Product **3v** was prepared according to General Procedure C at 90 °C using 3-bromo-1-propyl-1*H*-pyrrole (94 mg, 0.50 mmol), indoline (72 mg, 67.3 µL, 0.60 mmol), and 2.0 mol% **P1** as catalyst. *Note: Product is unstable on silica gel and should be rapidly isolated.* Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes hexane, followed by 2.7 column volumes 2.5% EtOAc/hexane, followed by 2.7 column volumes 5% EtOAc/hexane. Yield: Run 1 = 106 mg, 94%; Run 2 = 106 mg, 94%. Average Yield = 94%. Dense orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 6.58 (br s, 1H), 6.54 (br s, 1H), 6.12 (d, *J* = 2.8 Hz, 1H), 3.84-3.76 (m, 4H), 3.10 (t, *J* = 8.5 Hz, 2H), 1.81 (d, *J* = 7.2 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.6, 130.4, 130.2, 127.4, 124.5, 119.5, 117.4, 108.8, 107.4, 100.4, 53.5, 51.9, 28.4, 24.8, 11.5.

HR-MS (DART+) calc. for $C_{15}H_{18}N_2$ $[M+H]^+$: 227.15428. Found: 227.15562.

IR (Diamond-ATR, neat, cm^{-1}): 2961, 2930, 2872, 1691, 1605, 1566, 1484, 1458, 1379, 739.



3w

3,3-difluoro-1-(4-methylthiophen-3-yl)pyrrolidine (3w)

Product **3w** was prepared according to General Procedure F at 70 °C using 3-bromo-4-methylthiophene (88 mg, 55.9 µL, 0.50 mmol), 3,3-difluoropyrrolidine hydrochloride (86 mg, 0.60 mmol), NaOTMS (126 mg, 1.13 mmol, 2.25 equiv), and 2.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 5% EtOAc/hexane, followed by 2.7 column volumes 10% EtOAc/hexane. Yield: Run 1 = 93 mg, 92%; Run 2 = 90 mg, 89%. Average Yield = 90%. Pale yellow oil.

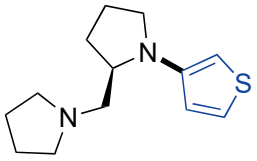
^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (dq, J = 3.4, 1.2 Hz, 1H), 6.28 (d, J = 3.4 Hz, 1H), 3.51 (t, J = 13.4 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H), 2.43 (d, J = 14.2, 7.0 Hz, 2H), 2.23 (s, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.2, 131.6, 129.3 (t, J = 247.8 Hz), 122.4, 104.2, 59.7 (t, J = 30.2 Hz), 50.1 (t, J = 3.6 Hz), 35.5 (t, J = 24.2 Hz), 15.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -94.41 (p, J = 14.1 Hz).

HR-MS (DART+) calc. for $C_9H_{11}F_2NS$ $[M+H]^+$: 204.06530. Found: 204.06428.

IR (Diamond-ATR, neat, cm^{-1}): 2957, 2831, 2360, 1553, 1461, 1333, 1110, 924, 774.



3x

(*R*)-2-(pyrrolidin-1-ylmethyl)-1-(thiophen-3-yl)pyrrolidine (3x)

Product **3x** was prepared according to General Procedure F at 70 °C using 3-chlorothiophene (59 mg, 46.5 µL, 0.50 mmol), (*R*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine (93 mg, 0.60 mmol), and 3.0 mol% **P1** as catalyst. Chromatography conditions: Al_2O_3 Brockmann I (50 mL), 2 column volumes hexane, followed by 2 column volumes 1% EtOAc/hexane, followed by 2 column volumes 2% EtOAc/hexane, followed by 2 column volumes 3% EtOAc/hexane, followed by 2 column volumes

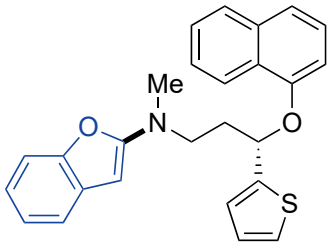
4% EtOAc/hexane. Yield: Run 1 = 107 mg, 91%; Run 2 = 97 mg, 82%. Average Yield = 86%. Dense colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 5.2, 3.1 Hz, 1H), 6.74 (dd, *J* = 5.2, 1.6 Hz, 1H), 5.83 (dd, *J* = 3.3, 1.6 Hz, 1H), 3.66 (tq, *J* = 7.1, 2.4 Hz, 1H), 3.42 (ddd, *J* = 7.9, 5.0, 2.4 Hz, 1H), 3.09 (td, *J* = 9.0, 6.1 Hz, 1H), 2.82-2.61 (m, 2H), 2.60-2.45 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.5, 125.0, 118.5, 93.5, 60.6, 60.0, 55.0, 50.9, 30.3, 23.9, 23.6.

HR-MS (DART+) calc. for $C_{13}H_{20}N_2S$ $[M+H]^+$: 237.14200. Found: 237.14208.

IR (Diamond-ATR, neat, cm^{-1}): 2961, 2872, 2781, 1547, 1423, 1148, 734.



3y

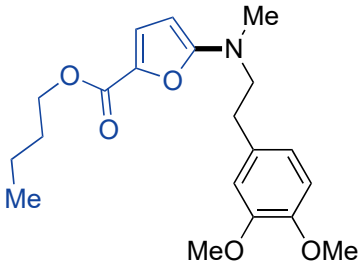
(*S*)-*N*-methyl-*N*-(3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl)benzofuran-2-amine (3y)
Product **3y** was prepared according to General Procedure F at 70 °C using 2-bromobenzofuran (98 mg, 0.50 mmol), (*S*)-*N*-methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine hydrochloride (93 mg, 0.60 mmol), NaOTMS (126 mg, 1.13 mmol, 2.25 equiv), and 1.5 mol% **P1** as catalyst. *Note: Product is unstable in the column and should be rapidly isolated.* Chromatography conditions: Al_2O_3 Brockmann I (30 mL), 3.3 column volumes CH_2Cl_2. Yield: Run 1 = 190 mg, 92%; Run 2 = 201 mg, 97%. Average Yield = 95%. Orange gel.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 6.5 Hz, 1H), 7.58-7.48 (m, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.30-7.19 (m, 3H), 7.13-7.00 (m, 3H), 6.99-6.88 (m, 2H), 6.83 (d, *J* = 7.7 Hz, 1H), 5.76 (dd, *J* = 8.4, 4.6 Hz, 1H), 5.27 (s, 1H), 3.78-3.55 (m, 2H), 2.97 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.9, 153.3, 150.7, 145.0, 134.8, 131.6, 127.7, 126.8, 126.5, 126.2, 125.8, 125.4, 125.0, 124.9, 122.8, 122.2, 120.8, 119.4, 117.4, 109.4, 107.0, 77.0, 74.0, 48.1, 37.2, 37.0.

HR-MS (DART+) calc. for $C_{26}H_{23}NO_2S$ $[M+H]^+$: 414.15223. Found: 414.15268.

IR (Diamond-ATR, neat, cm^{-1}): 3052, 2924, 1604, 1579, 1234, 1093, 770, 739, 699.



3z

Butyl 5-((3,4-dimethoxyphenethyl)(methyl)amino)furan-2-carboxylate (3z)

Product **3z** was prepared according to General Procedure D at 70 °C using butyl 5-bromofuran-2-carboxylate (124 mg, 89.9 µL, 0.50 mmol), 2-(3,4-dimethoxyphenyl)-*N*-methylethan-1-amine (117 mg, 111 µL, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (70 mL), 1.4 column volumes hexane, followed by 2.9 column volumes 2.4% EtOAc/hexane, followed by 2.4 column volumes 5% EtOAc/hexane, followed by 1.6 column volumes 9% EtOAc/hexane, followed by 3.4 column volumes 17% EtOAc/hexane, followed by 1.8 column volumes 20% EtOAc/hexane, followed by 4.3 column volumes 30% EtOAc/hexane. Yield: Run 1 = 153 mg, 85%; Run 2 = 152 mg, 84%. Average Yield = 84%. Off-white solid.

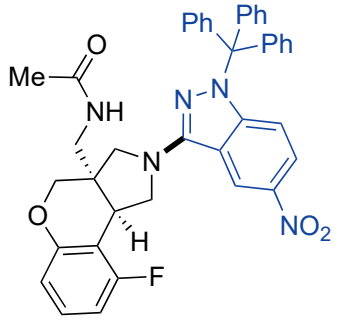
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 3.7 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.76-6.66 (m, 2H), 5.01 (d, *J* = 3.7 Hz, 1H), 4.22 (d, *J* = 6.7 Hz, 2H), 3.86 (dd, *J* = 3.8, 1.1 Hz, 6H), 3.53 (t, *J* = 7.4 Hz, 2H), 2.90 (s, 3H), 2.83 (t, *J* = 7.4 Hz, 2H), 1.69 (p, *J* = 6.9 Hz, 2H), 1.43 (h, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.4, 159.0, 149.1, 147.8, 134.8, 131.6, 123.3, 120.9, 112.1, 111.5, 83.5, 63.8, 56.04, 56.01, 53.1, 36.8, 33.5, 31.1, 19.4, 13.9.

Elemental Analysis calc. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53. Found: C, 66.41; H, 7.46.

IR (Diamond-ATR, neat, cm^{-1}): 2959, 2873, 1691, 1601, 1547, 1514, 1299, 1112, 1019, 714.

Melting Point: 58–58 °C



(±)-**3aa**

***rac*-*N*-(((3a*S*,9b*R*)-9-fluoro-2-(5-nitro-1-trityl-1*H*-indazol-3-yl)-1,2,3,9b-tetrahydrochromeno[3,4-*c*]pyrrol-3a(4*H*)-yl)methyl)acetamide ((±)-3aa)**

Product (±)-**3aa** was prepared according to General Procedure C at 90 °C using 3-bromo-5-nitro-1-trityl-1H-indazole (242 mg, 0.50 mmol), *N*-((9-fluoro-1,2,3,9b-tetrahydrochromeno[3,4-c]pyrrol-3a(4H)-yl)methyl)acetamide (159 mg, 0.60 mmol), and 5.0 mol% **P1** as catalyst.

Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 50% EtOAc/hexane, followed by 2.7 column volumes 75% EtOAc/hexane, followed by 2.7 column volumes EtOAc. Yield: Run 1 = 262 mg, 78%; Run 2 = 269 mg, 81%. Average Yield = 79%. Red solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.2 Hz, 1H), 7.75 (dd, *J* = 9.5, 2.1 Hz, 1H), 7.33-7.24 (m, 9H), 7.24-7.17 (m, 6H), 7.13 (td, *J* = 8.3, 6.6 Hz, 1H), 6.77-6.62 (m, 2H), 6.17 (d, *J* = 9.6 Hz, 1H), 5.77 (t, *J* = 6.5 Hz, 1H), 4.37 (d, *J* = 9.2 Hz, 1H), 4.13 (dd, *J* = 11.6, 1.5 Hz, 1H), 3.94 (d, *J* = 11.6 Hz, 1H), 3.75 (d, *J* = 10.9 Hz, 1H), 3.63-3.52 (m, 2H), 3.52-3.37 (m, 3H), 1.90 (s, 3H).

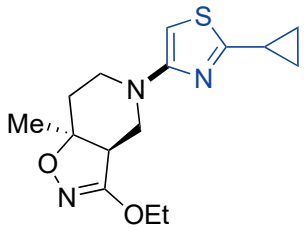
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.7, 162.0 (d, *J* = 245.7 Hz), 154.8 (d, *J* = 6.8 Hz), 150.0, 144.7, 142.5, 140.2, 130.3, 128.5 (d, *J* = 10.5 Hz), 127.73, 127.66, 120.8, 119.7, 115.8, 113.4, 112.8 (d, *J* = 2.8 Hz), 111.4 (d, *J* = 21.0 Hz), 107.9 (d, *J* = 21.3 Hz), 78.8, 67.7, 55.3, 54.6, 43.0, 42.6, 35.8, 23.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.87 (t, *J* = 7.7 Hz).

HR-MS (DART+) calc. for $C_{40}H_{35}N_5O_4F$ $[M+H]^+$: 668.26676. Found: 668.27272.

IR (Diamond-ATR, neat, cm^{-1}): 1654, 1602, 1584, 1553, 1470, 1311, 742, 701.

Melting Point: 245–246 °C



3bb

(3a*R*,7a*S*)-5-(2-cyclopropylthiazol-4-yl)-3-ethoxy-7a-methyl-3a,4,5,6,7,7a-hexahydroisoxazolo[4,5-*c*]pyridine (3bb)

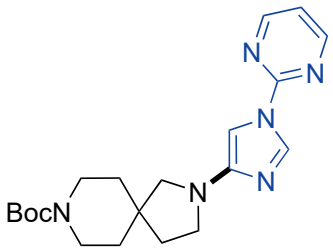
Product **3bb** was prepared according to General Procedure C at 50 °C using 4-bromo-2-cyclopropylthiazole (102 mg, 0.50 mmol), (3a*R*,7a*S*)-3-ethoxy-7a-methyl-3a,4,5,6,7,7a-hexahydroisoxazolo[4,5-c]pyridine (111 mg, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 2.7 column volumes 10% EtOAc/hexane, followed by 2.7 column volumes 20% EtOAc/hexane, followed by 2.7 column volumes 30% EtOAc/hexane. Yield: Run 1 = 103 mg, 67%; Run 2 = 105 mg, 69%. Average Yield = 68%. Orange gel.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 1H), 4.24-4.02 (m, 2H), 3.78 (dd, *J* = 13.1, 4.7 Hz, 1H), 3.47 (ddd, *J* = 12.5, 8.7, 4.3 Hz, 1H), 3.38 (dd, *J* = 13.1, 5.2 Hz, 1H), 3.09 (ddd, *J* = 11.7, 6.7, 4.4 Hz, 1H), 2.94 (t, *J* = 5.0 Hz, 1H), 2.19 (ddd, *J* = 11.7, 6.5, 4.1 Hz, 1H), 2.09 (ddd, *J* = 14.3, 6.8, 4.3 Hz, 1H), 1.87 (ddd, *J* = 14.2, 8.7, 4.4 Hz, 1H), 1.44 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.14-0.93 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.5, 168.4, 160.0, 85.6, 83.6, 65.9, 49.7, 44.5, 44.4, 32.4, 25.5, 14.8, 14.4, 10.8, 10.8.

HR-MS (DART+) calc. for $C_{15}H_{21}N_3O_2S$ $[M+H]^+$: 308.14272. Found: 308.14349.

IR (Diamond-ATR, neat, cm^{-1}): 2972, 2931, 1669, 1616, 1533, 1379, 1338, 1024.



3cc

***tert*-butyl 2-(1-(pyrimidin-2-yl)-1H-imidazol-4-yl)-2,8-diazaspiro[4.5]decane-8-carboxylate (3cc)**

Product **3cc** was prepared according to General Procedure C at 70 °C using 2-(4-bromo-1H-imidazol-1-yl)pyrimidine (113 mg, 0.50 mmol), *tert*-butyl 2,8-diazaspiro[4.5]decane-8-carboxylate (144 mg, 0.60 mmol, pre-mixed with THF as a 0.92 M stock solution, 0.8 mL), and 5.0 mol% **P1** as catalyst. Chromatography conditions: Al_2O_3 Brockmann III (30 mL, packed with 2% MeOH/CH_2Cl_2), 2 column volumes 2% MeOH/CH_2Cl_2, followed by 2 column volumes 8% MeOH/CH_2Cl_2. Yield: Run 1 = 190 mg, 99%; Run 2 = 175 mg, 91%. Average Yield = 95%. Yellow solid.

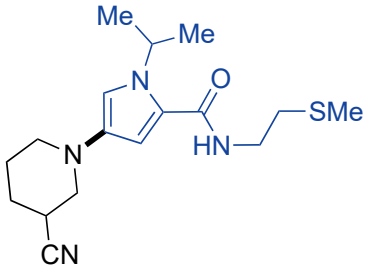
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.8 Hz, 2H), 8.37 (d, J = 1.5 Hz, 1H), 7.10 (t, J = 4.9 Hz, 1H), 6.83 (d, J = 1.5 Hz, 1H), 3.53 (dt, J = 16.0, 5.0 Hz, 2H), 3.36 (t, J = 7.1 Hz, 2H), 3.30 (td, J = 8.4, 4.0 Hz, 2H), 3.22 (s, 3H), 1.85 (t, J = 7.0 Hz, 2H), 1.58 (qdd, J = 13.3, 7.8, 4.1 Hz, 4H), 1.46 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.6, 155.0, 154.9, 151.6, 133.8, 118.0, 92.4, 79.5, 58.8, 47.5, 41.0, 36.8, 35.7, 28.6.

HR-MS (DART+) calc. for $C_{20}H_{29}N_6O_2$ $[M+H]^+$: 385.23465. Found: 385.23591.

IR (Diamond-ATR, neat, cm^{-1}): 2926, 2854, 1683, 1596, 1566, 1443, 1362, 1153.

Melting Point: 140–142 °C



3dd

4-(3-cyanopiperidin-1-yl)-1-isopropyl-N-(2-(methylthio)ethyl)-1H-pyrrole-2-carboxamide (3dd)

Product **3dd** was prepared according to General Procedure C at 90 °C using 4-bromo-1-isopropyl-*N*-(2-(methylthio)ethyl)-1H-pyrrole-2-carboxamide (153 mg, 0.50 mmol), piperidine-3-carbonitrile (66 mg, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (75 mL), 5.3 column volumes 50% EtOAc/hexane. Yield: Run 1 = 123 mg, 74%; Run 2 = 118 mg, 70%. Average Yield = 72%. Light orange solid.

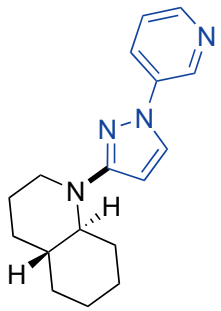
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, *J* = 2.1 Hz, 1H), 6.24 (t, *J* = 5.9 Hz, 1H), 6.16 (d, *J* = 2.1 Hz, 1H), 5.45 (hept, *J* = 6.7 Hz, 1H), 3.56 (q, *J* = 6.2 Hz, 2H), 3.28 (dd, *J* = 11.6, 3.4 Hz, 1H), 3.09-3.01 (m, 1H), 2.97 (dd, *J* = 11.5, 8.4 Hz, 1H), 2.93-2.85 (m, 1H), 2.85-2.77 (m, 1H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.13 (s, 3H), 1.99 (ddd, *J* = 12.8, 6.6, 3.6 Hz, 1H), 1.88 (ddq, *J* = 12.7, 6.2, 3.4 Hz, 1H), 1.82-1.61 (m, 2H), 1.38 (d, *J* = 6.7 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.9, 138.0, 123.9, 121.1, 108.2, 101.3, 53.8, 51.4, 48.2, 37.5, 34.1, 27.65, 27.63, 23.92, 23.90, 23.4, 15.1.

HR-MS (DART+) calc. for $C_{17}H_{27}N_4OS$ $[M+H]^+$: 335.19001. Found: 335.19206.

IR (Diamond-ATR, neat, cm^{-1}): 3336, 2967, 2931, 2816, 2231, 1622, 1569, 1520, 1204.

Melting Point: 109–110 °C



(±)-**3ee**

***rac*-(4a*R*,8a*S*)-1-(1-(pyridin-3-yl)-1*H*-pyrazol-3-yl)decahydroquinoline ((±)-3ee)**

Product (±)-**3ee** was prepared according to General Procedure C at 90 °C using 3-(3-bromo-1H-pyrazol-1-yl)pyridine (112 mg, 0.50 mmol), *trans*-decahydroquinoline (84 mg, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: C18 (60 g) 10% MeCN/H_2O to 30% MeCN/H_2O. The pure product-containing fractions were transferred to a 500 mL round-bottom

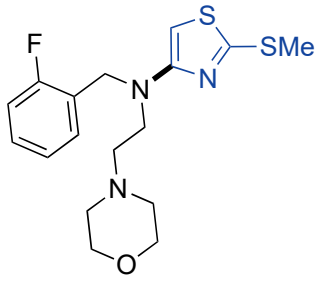
flask, and rinsed with acetone. The acetone and MeCN were evaporated using the aid of a rotary evaporator. Solid K_2CO_3 (~500 mg) was added to the remaining aqueous solution, which was then transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) until the aqueous layer contained no UV-active material as judged by TLC. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated using the aid of a rotary evaporator. Yield: Run 1 = 85 mg, 60%; Run 2 = 86 mg, 61%. Average Yield = 60%. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.6 Hz, 1H), 8.44 (t, *J* = 4.5 Hz, 1H), 8.00 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.82 (d, *J* = 2.6 Hz, 1H), 7.34 (dd, *J* = 8.3, 4.7 Hz, 1H), 6.18 (d, *J* = 2.6 Hz, 1H), 3.38 (dt, *J* = 11.6, 3.8 Hz, 1H), 2.88 (td, *J* = 11.9, 2.7 Hz, 1H), 2.44 (td, *J* = 9.8, 3.8 Hz, 1H), 2.01 (dt, *J* = 9.1, 4.4 Hz, 1H), 1.91-1.77 (m, 1H), 1.76-1.58 (m, 5H), 1.54-1.38 (m, 1H), 1.36-1.20 (m, 3H), 1.21-0.99 (m, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.9, 146.6, 139.7, 136.8, 126.8, 125.6, 123.9, 102.7, 66.0, 55.3, 41.7, 33.3, 32.2, 31.7, 26.2, 25.74, 25.70.

HR-MS (DART+) calc. for $C_{17}H_{23}N_4$ $[M+H]^+$: 283.19172. Found: 283.19308.

IR (Diamond-ATR, neat, cm^{-1}): 2919, 2851, 1585, 1530, 1445, 940, 800, 703.



3ff

***N*-(2-fluorobenzyl)-2-(methylthio)-*N*-(2-morpholinoethyl)thiazol-4-amine (3ff)**

Product **3ff** was prepared according to General Procedure C at 50 °C using 4-bromo-2-(methylthio)thiazole (105 mg, 0.50 mmol), *N*-(2-fluorobenzyl)-2-morpholinoethan-1-amine (238 mg, 1.00 mmol), and 8.0 mol% **P1** as catalyst. Chromatography conditions: Al_2O_3 Brockmann III (30 mL), 2 column volumes hexane, followed by 2 column volumes 5% EtOAc/hexane, followed by 2 column volumes 10% EtOAc/hexane, followed by 4 column volumes 20% EtOAc/hexane. Yield: Run 1 = 108 mg, 59%; Run 2 = 122 mg, 66%. Average Yield = 63%. Orange gel.

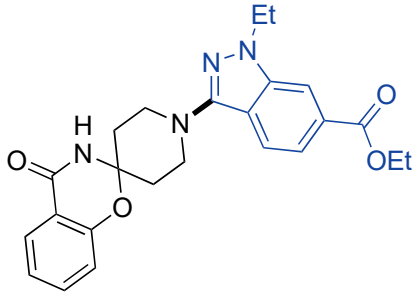
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (td, *J* = 7.8, 1.9 Hz, 1H), 7.25-7.16 (m, 1H), 7.04 (q, *J* = 8.3 Hz, 2H), 5.44 (s, 1H), 4.64 (s, 2H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.56 (t, *J* = 7.1 Hz, 2H), 2.62 (s, 3H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.46 (t, *J* = 4.7 Hz, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.7, 161.0 (d, *J* = 245.1 Hz), 159.6, 129.5 (d, *J* = 4.5 Hz), 128.6 (d, *J* = 8.0 Hz), 125.8 (d, *J* = 14.3 Hz), 124.2 (d, *J* = 3.6 Hz), 115.3 (d, *J* = 21.7 Hz), 84.4, 67.1, 56.5, 54.1, 48.0 (d, *J* = 4.3 Hz), 47.9, 16.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ -118.93 – -119.11 (m).

HR-MS (DART+) calc. for $C_{17}H_{23}N_3OS_2F$ $[M+H]^+$: 368.12611. Found: 368.12911.

IR (Diamond-ATR, neat, cm^{-1}): 2926, 2853, 2805, 1585, 1538, 1486, 1454, 1115, 756.



3gg

Ethyl 1-ethyl-3-(4-oxo-3,4-dihydrospiro[benzo[*e*][1,3]oxazine-2,4'-piperidin]-1'-yl)-1*H*-indazole-6-carboxylate (3gg)

Product **3gg** was prepared according to General Procedure C at 90 °C using ethyl 3-bromo-1-ethyl-1H-indazole-6-carboxylate (149 mg, 0.50 mmol), spiro[benzo[e][1,3]oxazine-2,4'-piperidin]-4(3H)-one (131 mg, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (70 mL), 1.4 column volumes hexane, followed by 4.3 column volumes 25% acetone/hexane, followed by 1.4 column volumes 33% acetone/hexane. Yield: Run 1 = 175 mg, 81%; Run 2 = 174 mg, 80%. Average Yield = 80%. Pale yellow solid.

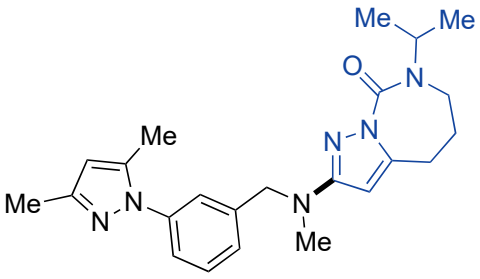
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 8.01 (d, *J* = 3.1 Hz, 1H), 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.45 (td, *J* = 7.7, 1.7 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.76 (dt, *J* = 13.1, 4.2 Hz, 2H), 3.54-3.36 (m, 2H), 2.37 (d, *J* = 12.6 Hz, 2H), 2.17 (ddd, *J* = 14.1, 11.0, 4.3 Hz, 2H), 1.44 (app q, *J* = 7.5 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.0, 163.1, 155.5, 150.9, 140.4, 134.8, 128.4, 128.0, 122.2, 121.0, 119.1, 117.8, 117.7, 117.3, 111.3, 86.4, 61.3, 46.3, 43.5, 35.4, 15.0, 14.5.

HR-MS (DART+) calc. for $C_{24}H_{27}N_4O_4$ $[M+H]^+$: 435.20268. Found: 435.20488.

IR (Diamond-ATR, neat, cm^{-1}): 3178, 3070, 2955, 2848, 1716, 1668, 1612, 1367, 1234, 762, 746.

Melting Point: 171–173 °C



3hh

2-((3-(3,5-dimethyl-1*H*-pyrazol-1-yl)benzyl)(methyl)amino)-7-isopropyl-4,5,6,7-tetrahydro-8*H*-pyrazolo[1,5-*c*][1,3]diazepin-8-one (3hh)

Product **3hh** was prepared according to General Procedure C at 90 °C using 2-bromo-7-isopropyl-4,5,6,7-tetrahydro-8H-pyrazolo[1,5-c][1,3]diazepin-8-one (136 mg, 0.50 mmol), 1-(3-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)-*N*-methylmethanamine (129 mg, 0.60 mmol), and 5.0 mol% **P1** as catalyst. Chromatography conditions: SiO_2 (70 mL), 4.3 column volumes EtOAc, followed by 2.9 column volumes 2% MeOH/EtOAc, followed by 1.4 column volumes 4% MeOH/EtOAc. Yield: Run 1 = 166 mg, 81%; Run 2 = 168 mg, 82%. Average Yield = 82%. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.7 Hz, 1H), 7.33 (s, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 5.97 (s, 1H), 5.41 (s, 1H), 4.92 (s, 2H), 4.83 (hept, *J* = 6.9 Hz, 1H), 4.40 (s, 2H), 3.65-3.57 (m, 2H), 3.01-2.92 (m, 2H), 2.81 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4, 158.4, 149.0, 140.4, 140.1, 139.7, 139.6, 129.1, 126.6, 124.0, 123.4, 107.0, 91.7, 56.3, 55.7, 45.0, 38.0, 37.2, 27.9, 20.3, 13.6, 12.5.

HR-MS (DART+) calc. for $C_{23}H_{31}N_6O$ $[M+H]^+$: 407.25539. Found: 407.25643.

IR (Diamond-ATR, neat, cm^{-1}): 2974, 1635, 1552, 1423, 799, 767.

Melting Point: 159–160 °C

8. Additional examples not shown in Figure 4

Additional coupling reactions were tested using **P1** as the catalyst. These reactions were set up in a nitrogen-filled glovebox. Into an oven-dried reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) containing a Teflon-coated magnetic stir bar, the following solid reagents were dispensed (listed in order of addition): NaOTMS (1.05 equiv), aryl bromide if solid (1.0 equiv), amine if solid (1.2 equiv). Anhydrous THF (1.25 mL/mmol ArBr) was added via syringe, rinsing down the sides of the reaction tube. Then, the following liquid reagents were dispensed (listed in order of addition; liquid reagents were added via micropipette): aryl bromide if liquid (1.0 equiv), amine if liquid (1.2 equiv). **P1** (0.75 mol%) was weighed into an oven-dried 1-dram vial (Kimble, part no. 60910L-1) outside of the glovebox, and anhydrous THF (1.25 mL/mmol ArBr) was added via syringe inside the glovebox to make a **P1** stock solution. **P1** stock solution (1.25 mL/mmol ArBr) was added to each reaction tube via syringe, rinsing down the sides of the reaction tube. The reaction tubes were sealed with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60). The sealed tubes were removed from the glovebox and immediately transferred to a pre-heated oil bath (bath temperature = 50 °C). The reaction mixture was stirred at 50 °C for 3 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air, an internal standard (trimethoxybenzene) was added, and the product mixture was filtered through a plug of Celite, rinsing with EtOAc (3 x 2 mL). The mixture was concentrated with the aid of a rotary evaporator. The concentrated reaction mixture was dissolved in $CDCl_3$, and the yield was determined using ^{1}H NMR analysis (d1 = 10 s). The amount of aryl halide remaining is given in parentheses.

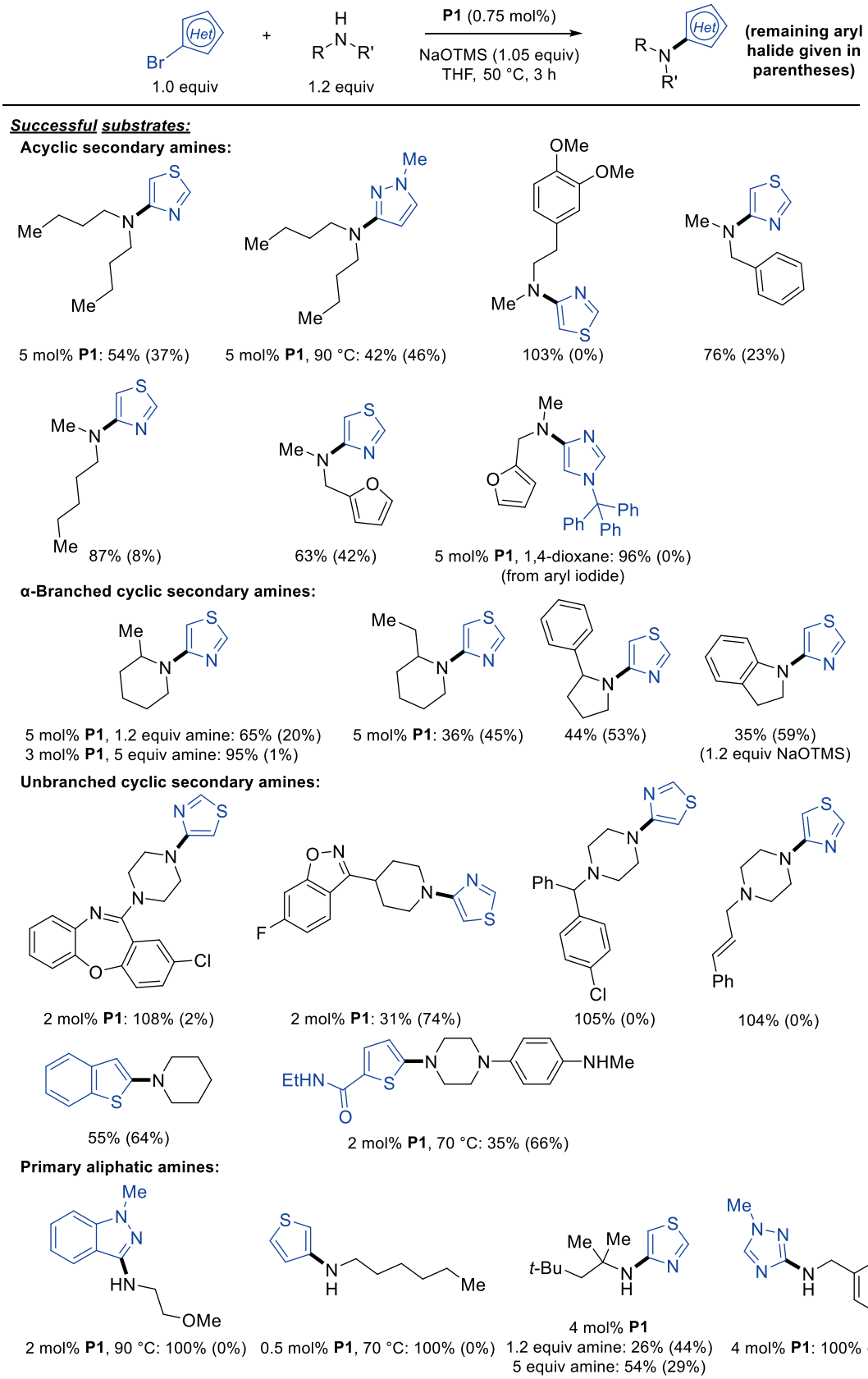


Figure 6. Additional successful coupling reactions not shown in Figure 4.

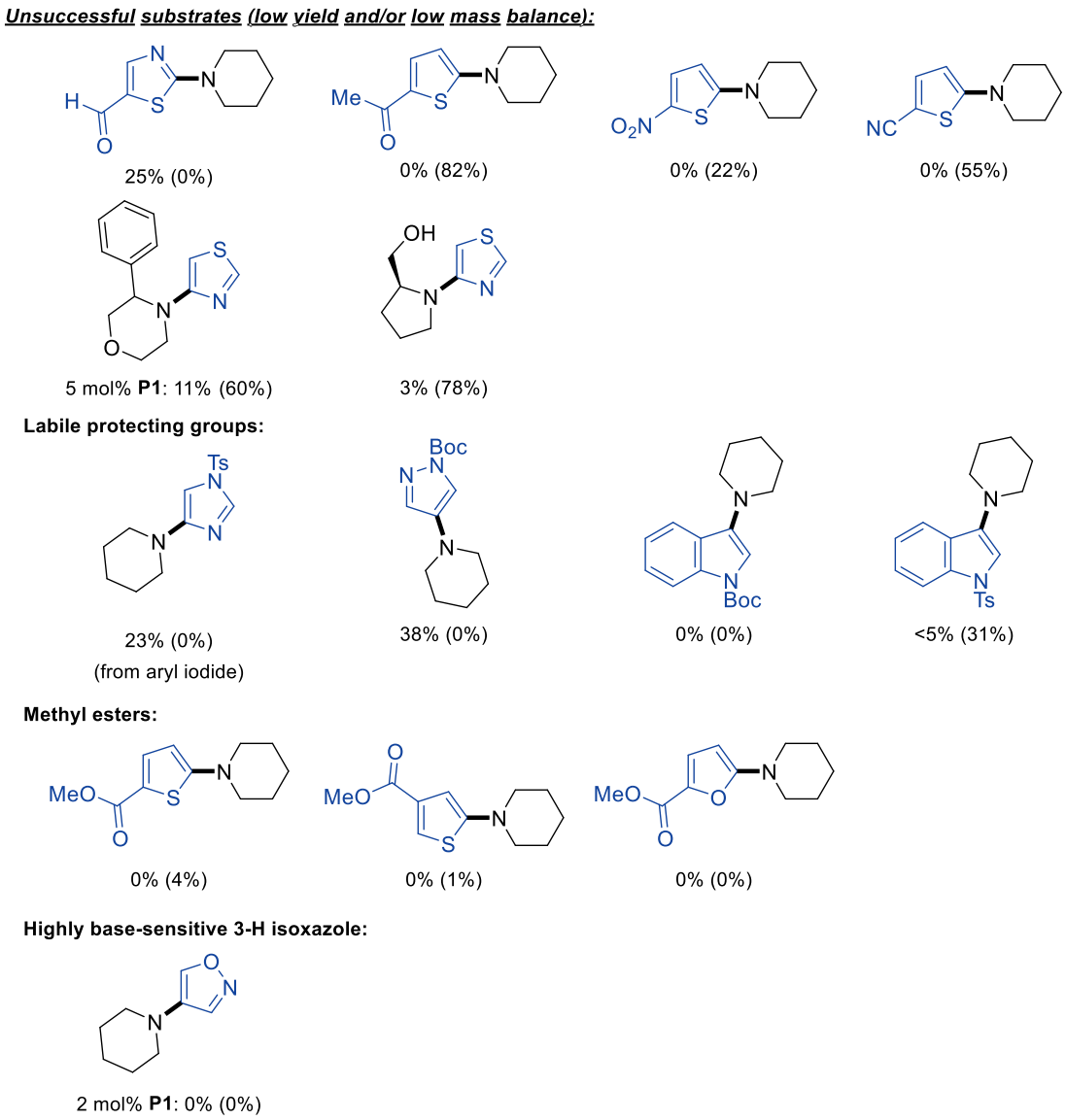


Figure 7. Additional unsuccessful coupling reactions not shown in Figure 4.

9. High-throughput experimentation

Procedures for high-throughput experimentation

Five-membered heteroaryl bromide screen

The 48 aryl halides (0.1 mmol, 1.0 equiv) were plated into 2 mL HPLC vials containing a stir bar (Analytical Sales & Services; catalog no. 13258), and the vials were set in an aluminum parallel reactor block (Analytical Sales & Services; 2 mL; catalog no. 48012). The vials and reactor block were brought into a nitrogen-filled glovebox. All subsequent operations were carried out inside of the glovebox. A catalyst solution was prepared by dissolving **P1** (208 mg, 4 mol%) in anhydrous THF (11 mL). A base solution (1 M) was prepared by dissolving NaOTMS (1.122 g) in anhydrous THF to a final volume of 10 mL using a volumetric flask. To each 2 mL reaction vial was added piperidine (12 µL, 0.12 mmol, 1.2 equiv), NaOTMS solution (105 µL, 1.05 equiv), and **P1** solution (200 µL, 4 mol %), in that order, by volume via a calibrated micropipette. The reaction block was sealed with a PFA film (Analytical Sales & Services; catalog no. 48483), two rubber mats

(Analytical Sales & Services; catalog no. 48482), and aluminum reactor top. The assembly was secured using screws (Analytical Sales & Services; catalog no. VScrew48), which were tightened using a battery-operated electric screwdriver. Once sealed, the reaction assembly was removed from the glovebox and placed onto a tumble stirrer (V & P Scientific, Inc. model no. VP 710 Series) with heating to 90 °C. After 3 h at 90 °C, the reactor block was allowed to cool to room temperature. The block was opened by removing the screws. To each reaction vial, 9:1 MeCN:H_2O (500 µL) and MeOH (500 µL) were added. The reactor block was resealed and agitated to mix/dissolve each reaction mixture. The reaction block was then reopened and a 60 µL sample was removed from each well and diluted to 1 mL using 9:1 MeCN:H_2O. The prepared samples were then analyzed by UPLC/MS.

Secondary aliphatic amine screen

The 48 nucleophiles (0.12 mmol, 1.2 equiv) were plated into 2 mL HPLC vials containing a stir bar (Analytical Sales & Services; catalog no. 13258), and the vials were set in an aluminum parallel reactor block (Analytical Sales & Services; 2 mL; catalog no. 48012). The vials and reactor block were brought into a nitrogen-filled glovebox. All subsequent operations were carried out inside of the glovebox. A catalyst solution was prepared by dissolving **P1** (208 mg, 4 mol%) in anhydrous THF (11 mL). A base solution (1 M) was prepared by dissolving NaOTMS (1.122 g) in anhydrous THF to a final volume of 10 mL using a volumetric flask. To each 2 mL reaction vial was added 4-bromothiazole (8.9 µL, 0.10 mmol, 1.0 equiv), NaOTMS solution (105 µL, 1.05 equiv); and **P1** (200 µL, 4 mol %), in that order, by volume via a calibrated micropipette. The reaction block was sealed with a PFA film (Analytical Sales & Services; catalog no. 48483), two rubber mats (Analytical Sales & Services; catalog no. 48482), and aluminum reactor top. The assembly was secured using screws (Analytical Sales & Services; catalog no. VScrew48), which were tightened using a battery-operated electric screwdriver. Once sealed, the reaction assembly was removed from the glovebox and placed onto a tumble stirrer (V & P Scientific, Inc. model no. VP 710 Series) with heating to 50 °C. After 3 h at 50 °C, the reactor block was allowed to cool to room temperature. The block was opened by removing the screws. To each reaction vial, 9:1 MeCN:H_2O (500 µL) and MeOH (500 µL) were added. The reactor block was resealed and agitated to mix/dissolve each reaction mixture. The reaction block was then reopened and a 60 µL sample was removed from each well and diluted to 1 mL using 9:1 MeCN:H_2O. The prepared samples were then analyzed by UPLC/MS.

Interpretation of results (LCAP)

Definition of LCAP. The results of the high-throughput screen are analyzed by UPLC/MS. Because it is not possible to make a calibration curve for every desired product relative to an internal standard, the degree of success of each reaction is measured by LCAP (Liquid Chromatography Area Percent), defined below as the UV area of the product divided by the sum of the UV areas of everything present in the LC chromatogram.

$$\text{LCAP (Liquid Chromatography Area Percent)} = \frac{\text{Area(Product)}}{\text{Area(Product)} + \text{Area(ArBr)} + \text{Area(Unknown)}}$$

Interpretation of LCAP. A positive LCAP indicates the presence of desired product, while LCAP = 0 indicates the absence of desired product. The magnitude of a positive LCAP cannot be used to predict the yield of a reaction; LCAP = 100 is essentially impossible, due to the presence of UV-active byproducts present in the product mixture (for example, ligand-derived byproducts will always be present in this case). *LCAP values should thus be viewed as binary*: either the reaction generated the desired product, or it did not. For any individual substrate combination of interest, the reaction can be repeated and analyzed by more quantitative techniques, such as ^{1}H NMR.

LCAP > 0 → Successful coupling reaction
LCAP = 0 → Unsuccessful coupling reaction

Examples of the relationship between LCAP and yield. Below are several examples of the relationship between LCAP (as determined in the high-throughput study) and yield (as determined by ^{1}H NMR of separately prepared reactions under the same conditions). In several cases, the ^{1}H NMR yield is significantly higher than the LCAP.

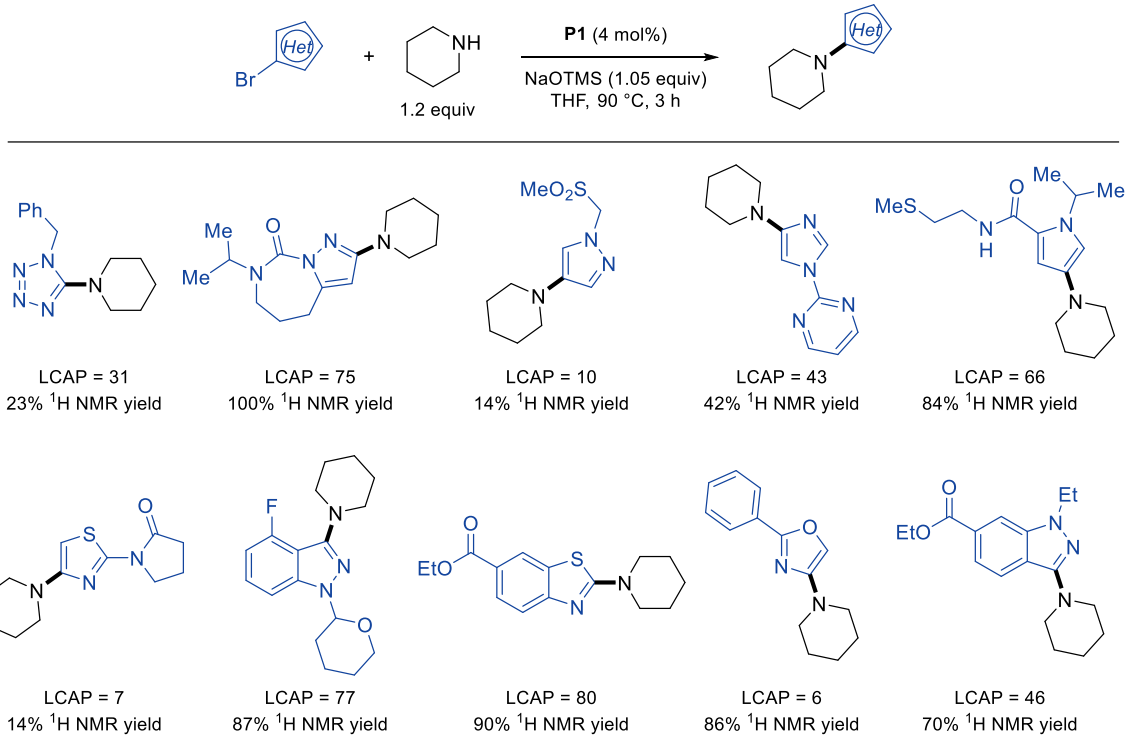


Figure 8. Examples of the relationship between LCAP and yield, with a variety of aryl bromides.

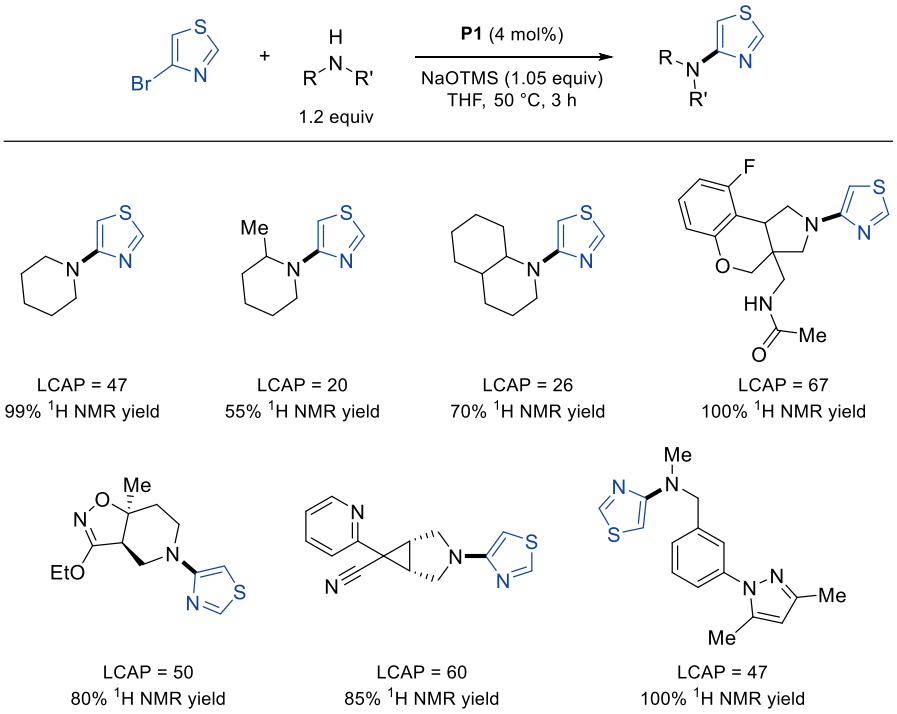
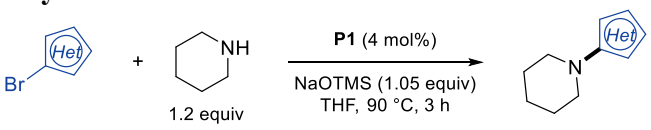


Figure 9. Examples of the relationship between LCAP and yield, with a variety of amines.

Five-membered heteroaryl bromide screen[6a]



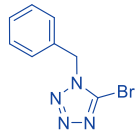
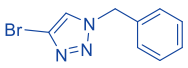
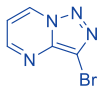
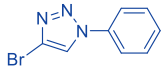
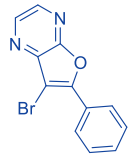
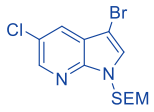
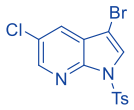
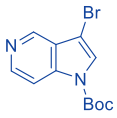
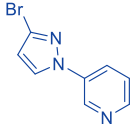
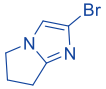
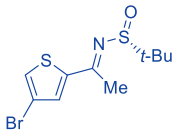
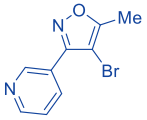
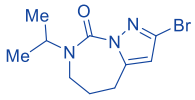
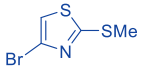
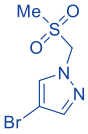
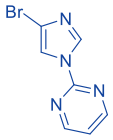
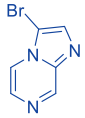
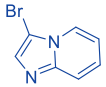
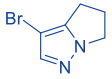
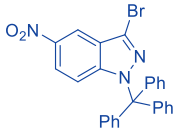
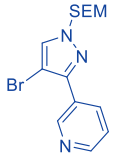
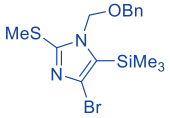
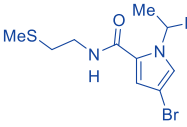
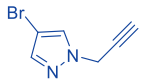
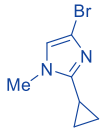
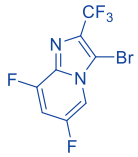
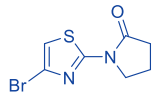
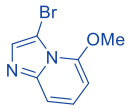
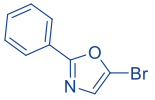
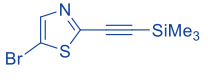
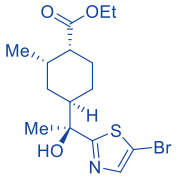
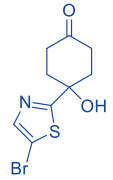
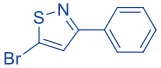
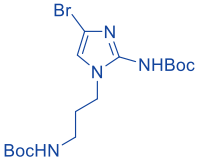
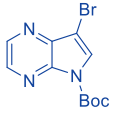
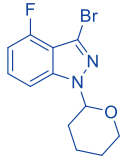
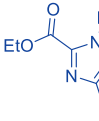
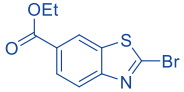
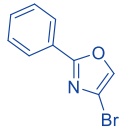
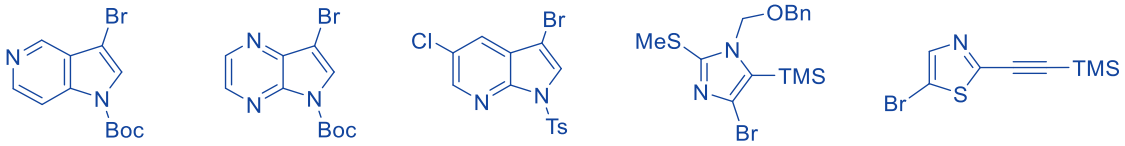
	1	2	3	4	5	6	7	8
A	 LCAP = 31	 LCAP = 85	 LCAP = 0	 LCAP = 86	 LCAP = 15	 LCAP = 41	 LCAP = 0	 LCAP = 0
B	 LCAP = 83	 LCAP = 45	 LCAP = 0	 LCAP = 3	 LCAP = 75	 LCAP = 47	 LCAP = 10 *Previous*[6a] *LCAP = 0*	 LCAP = 43 *Previous*[6a] *LCAP = 0*
C	 LCAP = 30	 LCAP = 45	 LCAP = 41	 LCAP = 44 *Previous*[6a] *LCAP = 0*	 LCAP = 6	 LCAP = 0	 LCAP = 66 *Previous*[6a] *LCAP = 0*	 LCAP = 0 LCAP = 49 (50 °C)
D	 LCAP = 0	 LCAP = 77	 LCAP = 0	 LCAP = 7	 LCAP = 1	 LCAP = 21	 LCAP = 0	 LCAP = 3
E	 LCAP = 0	 LCAP = 57	 LCAP = 0	 LCAP = 0	 LCAP = 77	 LCAP = 0	 LCAP = 80	 LCAP = 6
F	LCAP = 46	LCAP = 0 LCAP = 5 (50 °C)	LCAP = 56	LCAP = 8	LCAP = 4	LCAP = 0	LCAP = 0	LCAP = 51

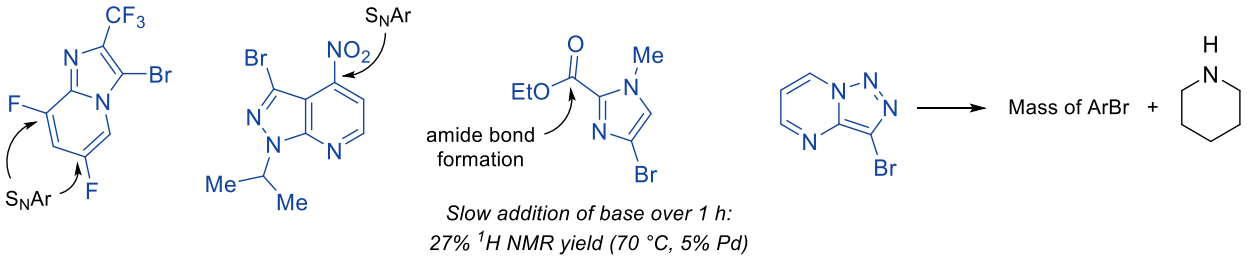
Figure 10. High-throughput screen of five-membered heteroaryl bromide substrates.

Explanations for unsuccessful aryl bromide substrates

1. Labile protecting group

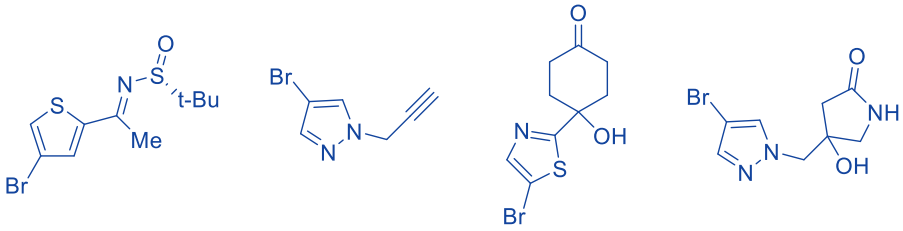


2. Undesired side reaction

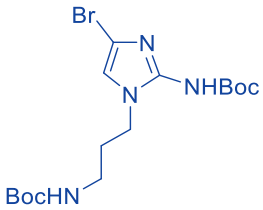


Slow addition of base over 1 h:
27% ^{1}H NMR yield (70 °C, 5% Pd)

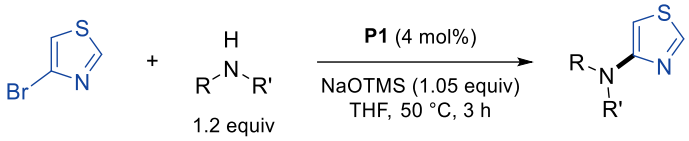
3. Substrate or product decomposition



4. Unreactive aryl bromide substrate



Secondary aliphatic amine screen



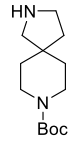
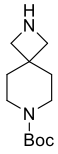
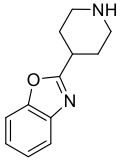
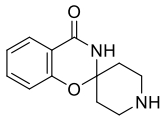
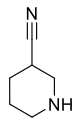
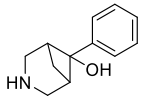
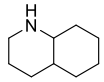
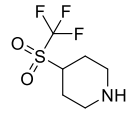
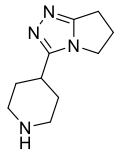
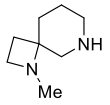
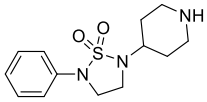
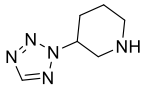
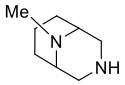
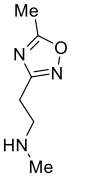
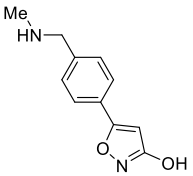
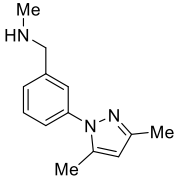
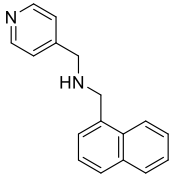
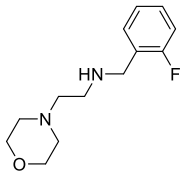
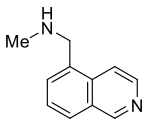
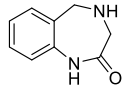
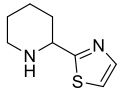
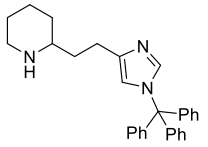
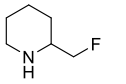
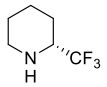
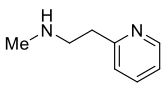
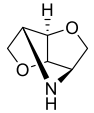
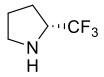
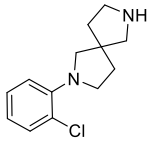
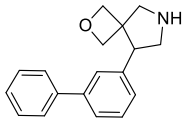
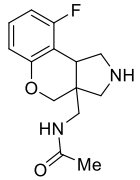
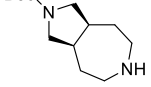
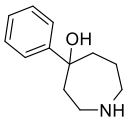
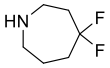
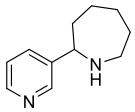
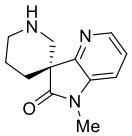
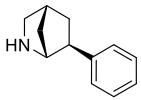
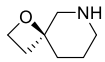
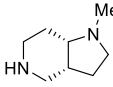
	1	2	3	4	5	6	7	8
A	 LCAP = 0 95% ^{1}H NMR	 LCAP = 18	 LCAP = 52	 LCAP = 42 *Previous [6a] LCAP = 0*	 LCAP = 80	 LCAP = 20	 LCAP = 0	 LCAP = 26
B	 LCAP = 30 *Previous [6a] LCAP = 0*	 LCAP = 29	 LCAP = 33	 LCAP = 42	 LCAP = 22 *Previous [6a] LCAP = 0*	 LCAP = 53	 LCAP = 3	 LCAP = 0
C	 LCAP = 47	 LCAP = 0	 LCAP = 29	 LCAP = 57	 LCAP = 59	 LCAP = 5	 LCAP = 5	 LCAP = 3
D	 LCAP = 0	 LCAP = 72	 LCAP = 17	 LCAP = 25	 LCAP = 13	 LCAP = 23	 LCAP = 67	 LCAP = 3
E	 LCAP = 0	 LCAP = 14	 LCAP = 2	 LCAP = 29	 LCAP = 0	 LCAP = 0	 LCAP = 2	 LCAP = 0
F	LCAP = 5 *Previous [6a] LCAP = 0*	LCAP = 60	LCAP = 50	LCAP = 33	LCAP = 43	LCAP = 62	LCAP = 0	LCAP = 47

Figure 11. High-throughput screen of secondary aliphatic amine substrates.

10. Additional examples of complex substrate combinations not shown in Figure 5

Additional coupling reactions between complex substrates from the Merck Building Block Collection were tested using **P1** as the catalyst. These reactions were set up in a nitrogen-filled glovebox. Into an oven-dried reaction tube (Fisherbrand, 13 x 100 mm, product no. 1495935C) containing a Teflon-coated magnetic stir bar, the following solid reagents were dispensed (listed in order of addition): NaOTMS (12 mg, 0.105 mmol, 1.05 equiv), aryl bromide if solid (0.10 mmol, 1.0 equiv), amine if solid (0.12 mmol, 1.2 equiv). Anhydrous THF (0.125 mL) was added via syringe, rinsing down the sides of the reaction tube. Then, the following liquid reagents were dispensed (listed in order of addition; liquid reagents were added via micropipette): aryl bromide if liquid (0.10 mmol, 1.0 equiv), amine if liquid (0.12 mmol, 1.2 equiv). **P1** (5 mol%) was weighed into an oven-dried 1-dram vial (Kimble, part no. 60910L-1) outside of the glovebox, and anhydrous THF (0.125 mL per reaction) was added via syringe inside the glovebox to make a **P1** stock solution. **P1** stock solution (0.125 mL) was added to each reaction tube via syringe, rinsing down the sides of the reaction tube. The reaction tubes were sealed with a screw cap (Thermo Fisher Scientific, catalog no. C4015-66) equipped with a Teflon septum (Thermo Fisher Scientific, catalog no. C4015-60). The sealed tubes were removed from the glovebox and immediately transferred to a pre-heated oil bath (bath temperature = 50–90 °C). The reaction mixture was stirred at 50–90 °C for 3 h, after which time the reaction vessel was removed from the oil bath and allowed to cool to room temperature. The vessel was then opened to the air, an internal standard (trimethoxybenzene) was added, and the mixture was either (a) filtered through a plug of Celite, rinsing with EtOAc (3 x 2 mL) and CH_2Cl_2 (3 x 2 mL), or (b) transferred directly to a scintillation vial, rinsing with MeOH (3 x 2 mL), depending on the solubility of the desired product. The mixture was concentrated with the aid of a rotary evaporator. The concentrated reaction mixture was dissolved in $CDCl_3$ (or methanol-d_4, if the mixture was insoluble in $CDCl_3$), and the yield was determined using ^1H NMR analysis (d1 = 10 s). In some cases, LC/MS analysis was used to aid the analysis of the reaction outcome. The amount of aryl bromide remaining is given in parentheses.

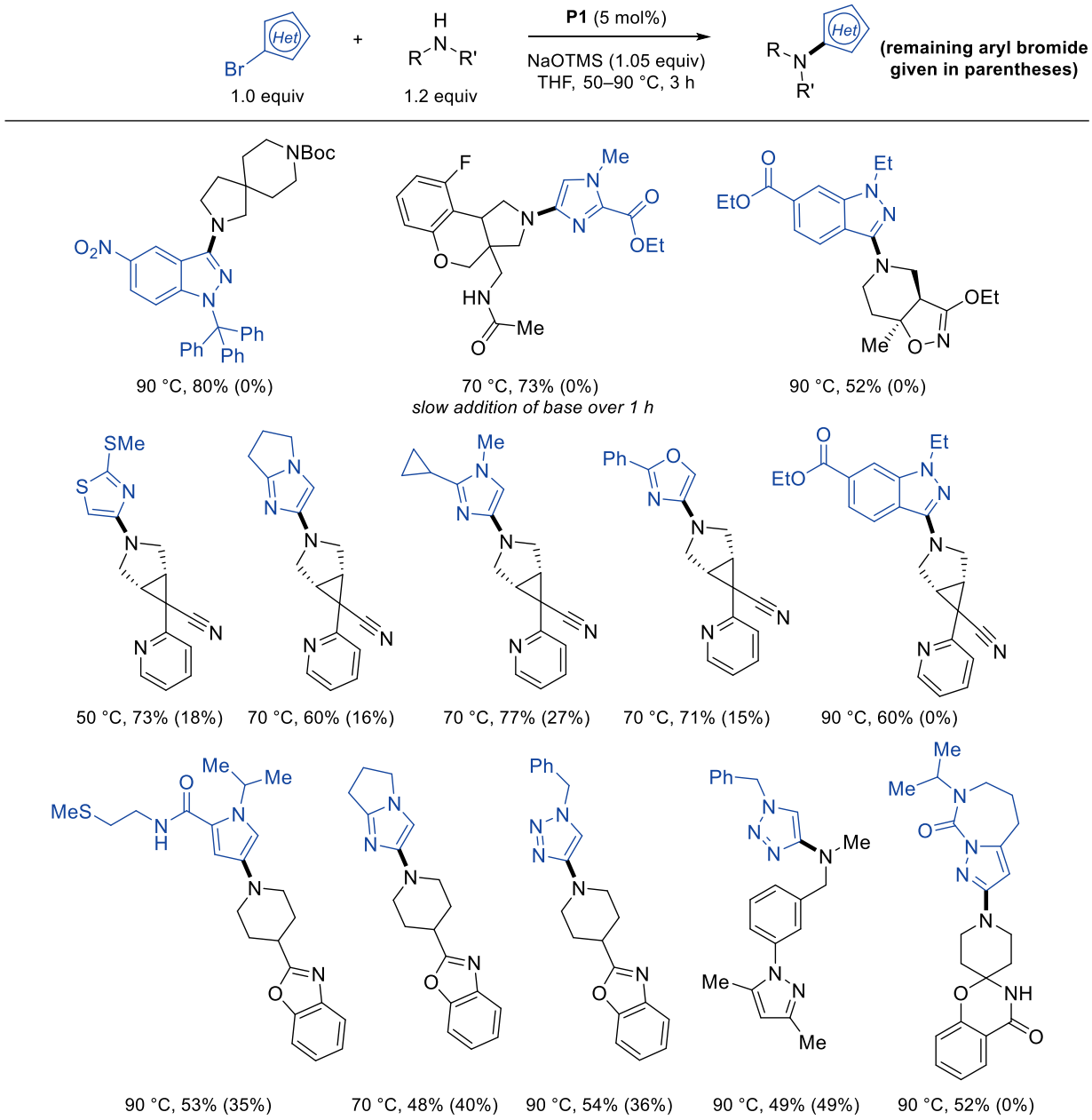
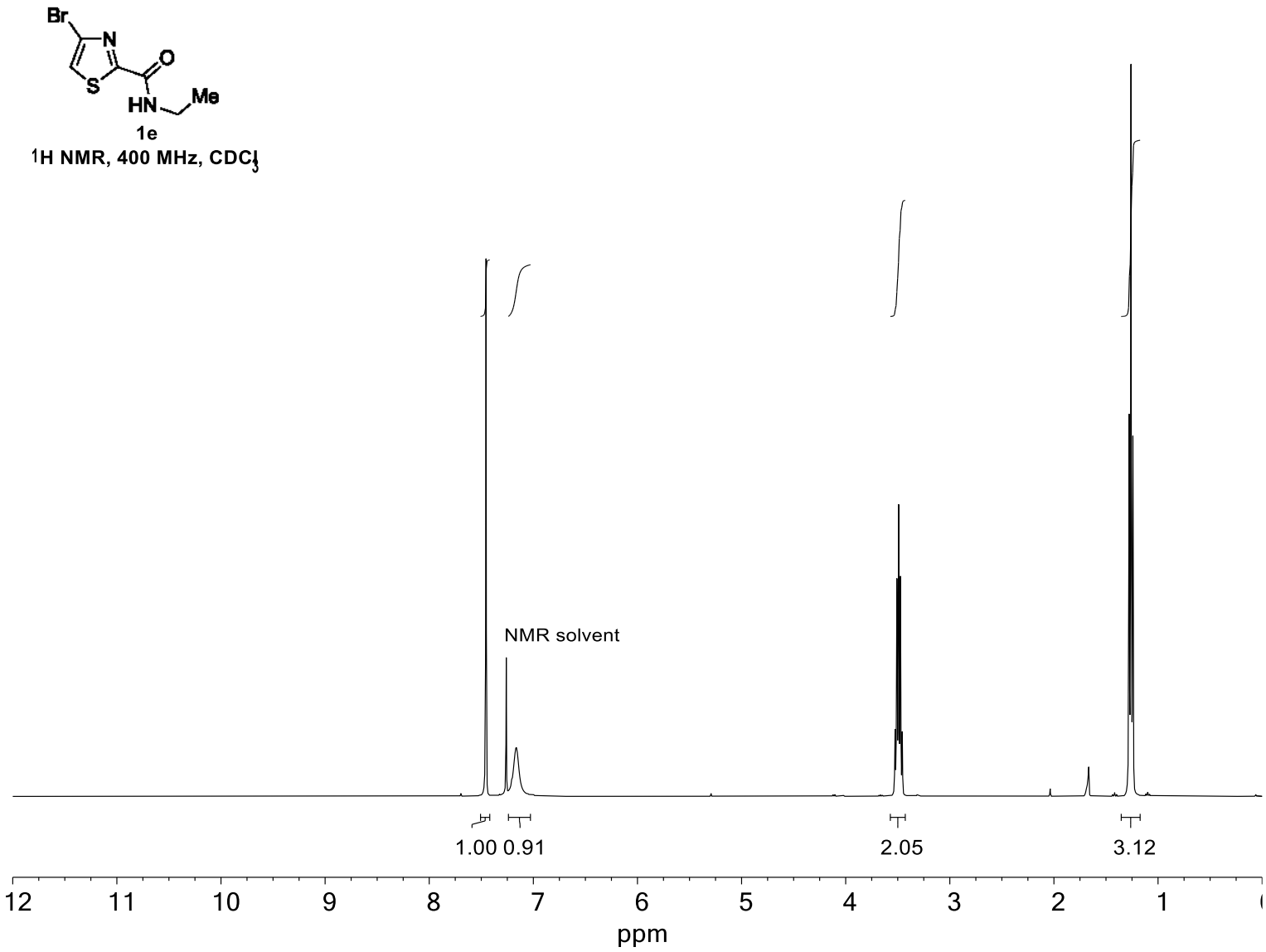
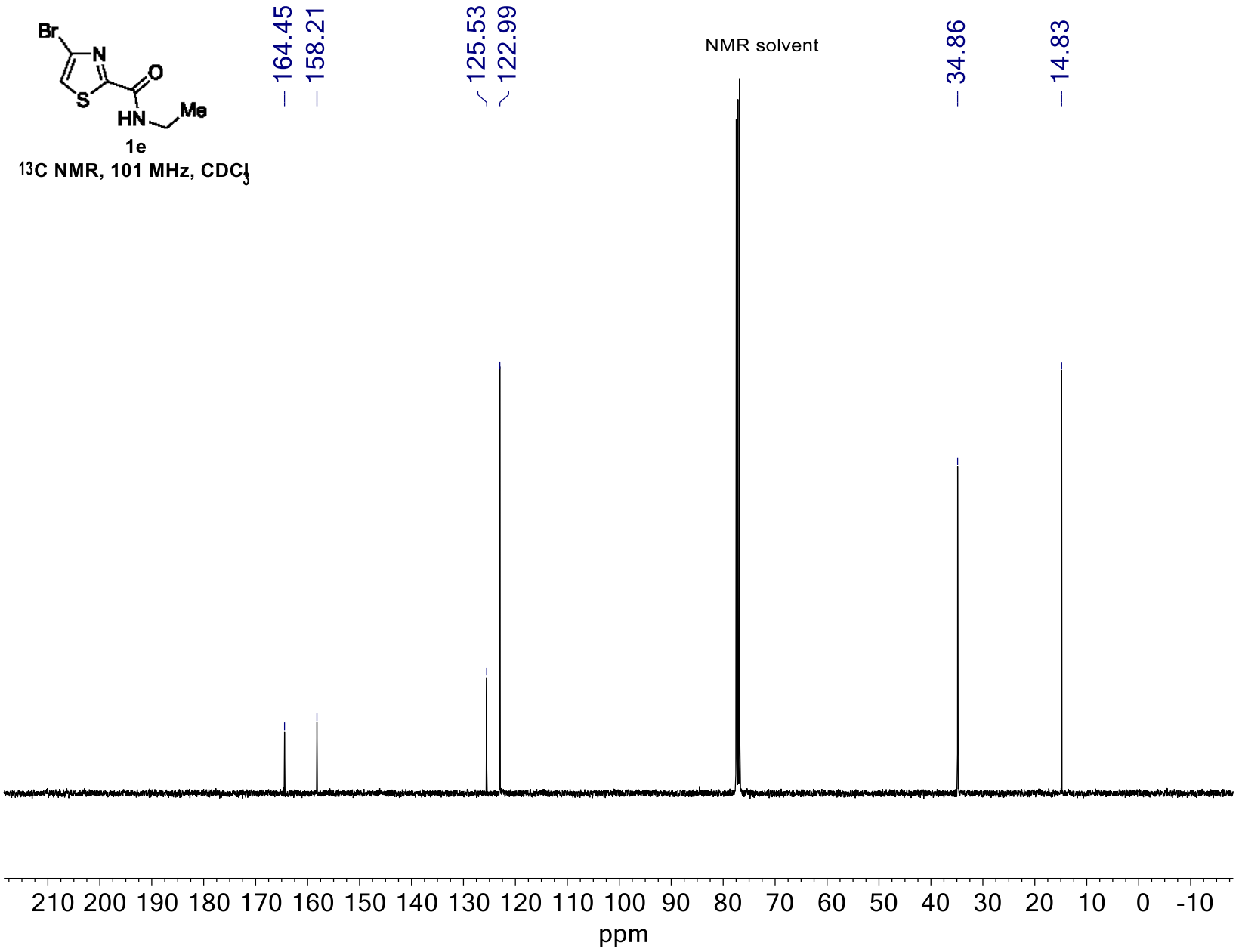
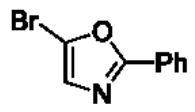


Figure 12. Additional examples of complex substrate combinations not shown in Figure 5.

11. NMR spectra of aryl halide substrates and C–N coupling products

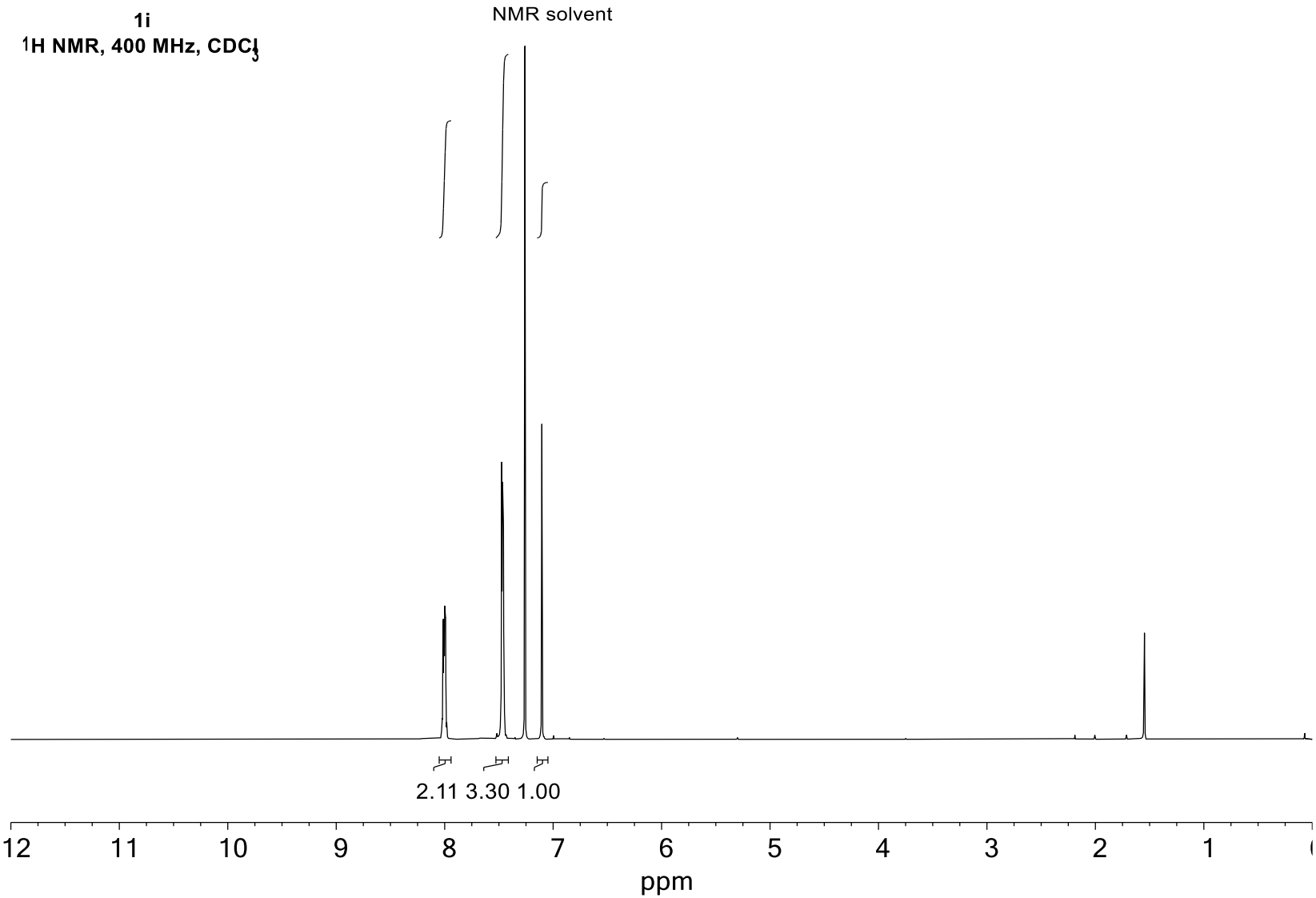


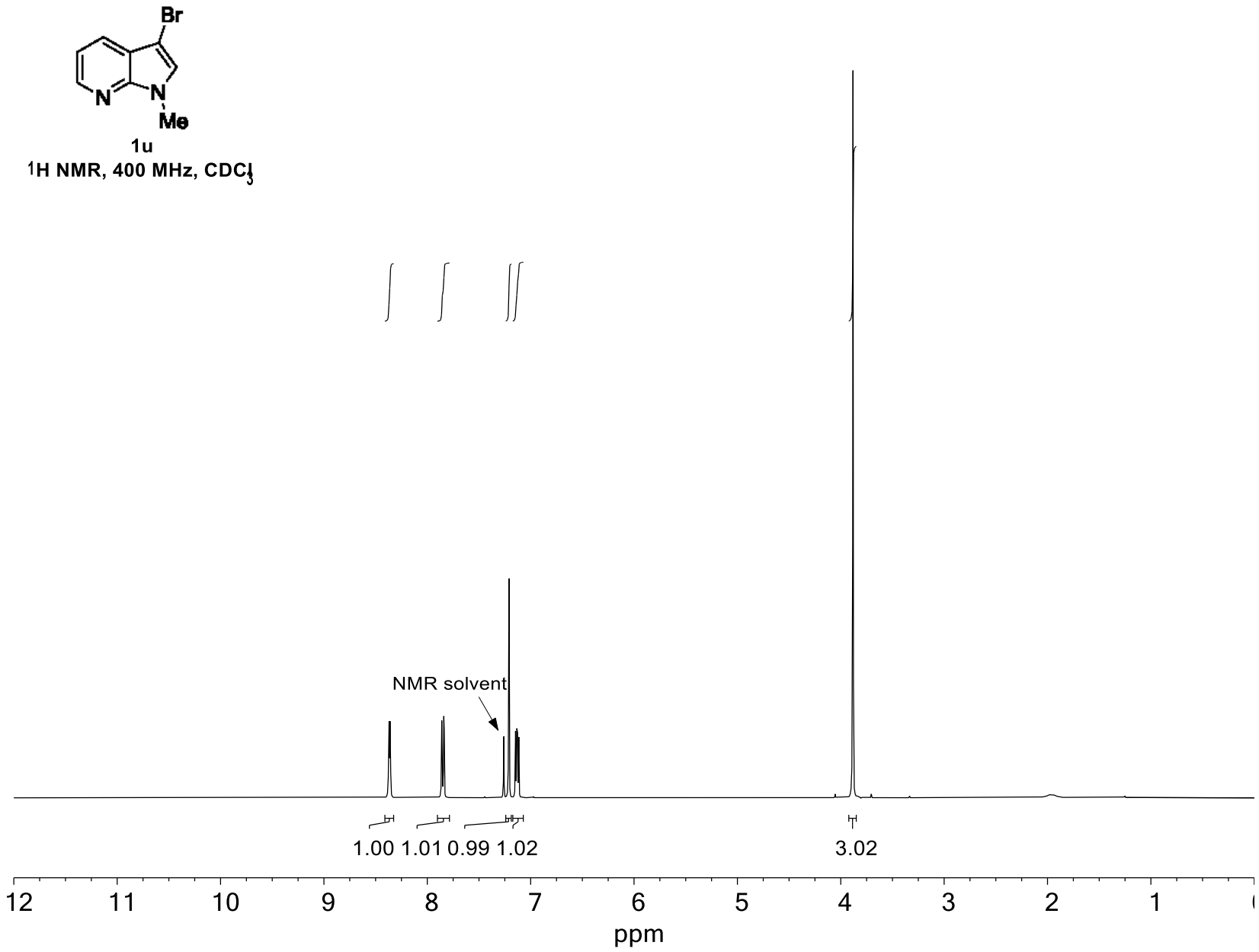

Br
N
O
S
HN
Me
1e
13C NMR, 101 MHz, CDCl3
164.45
158.21
125.53
122.99
NMR solvent
34.86
14.83
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

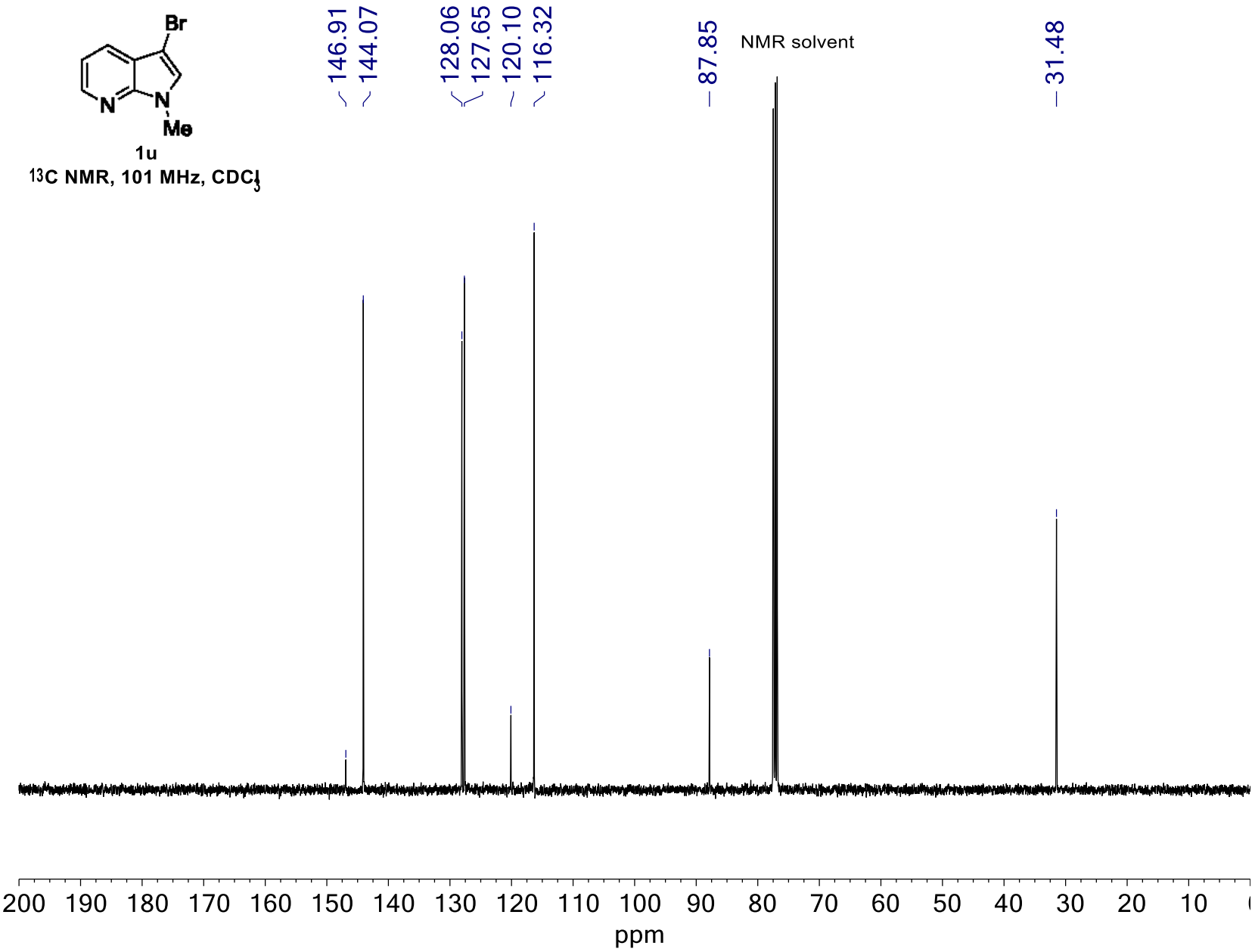


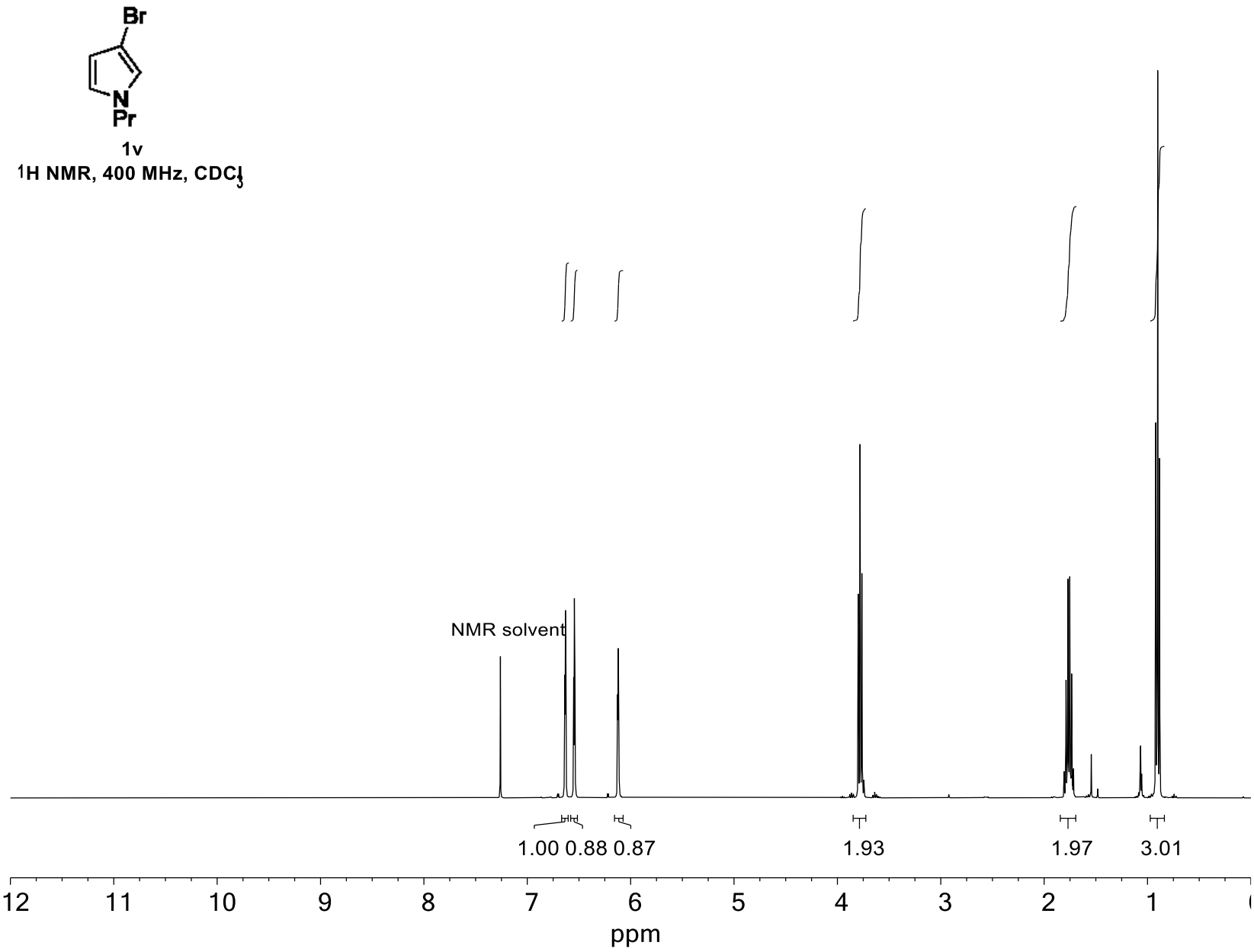
1i

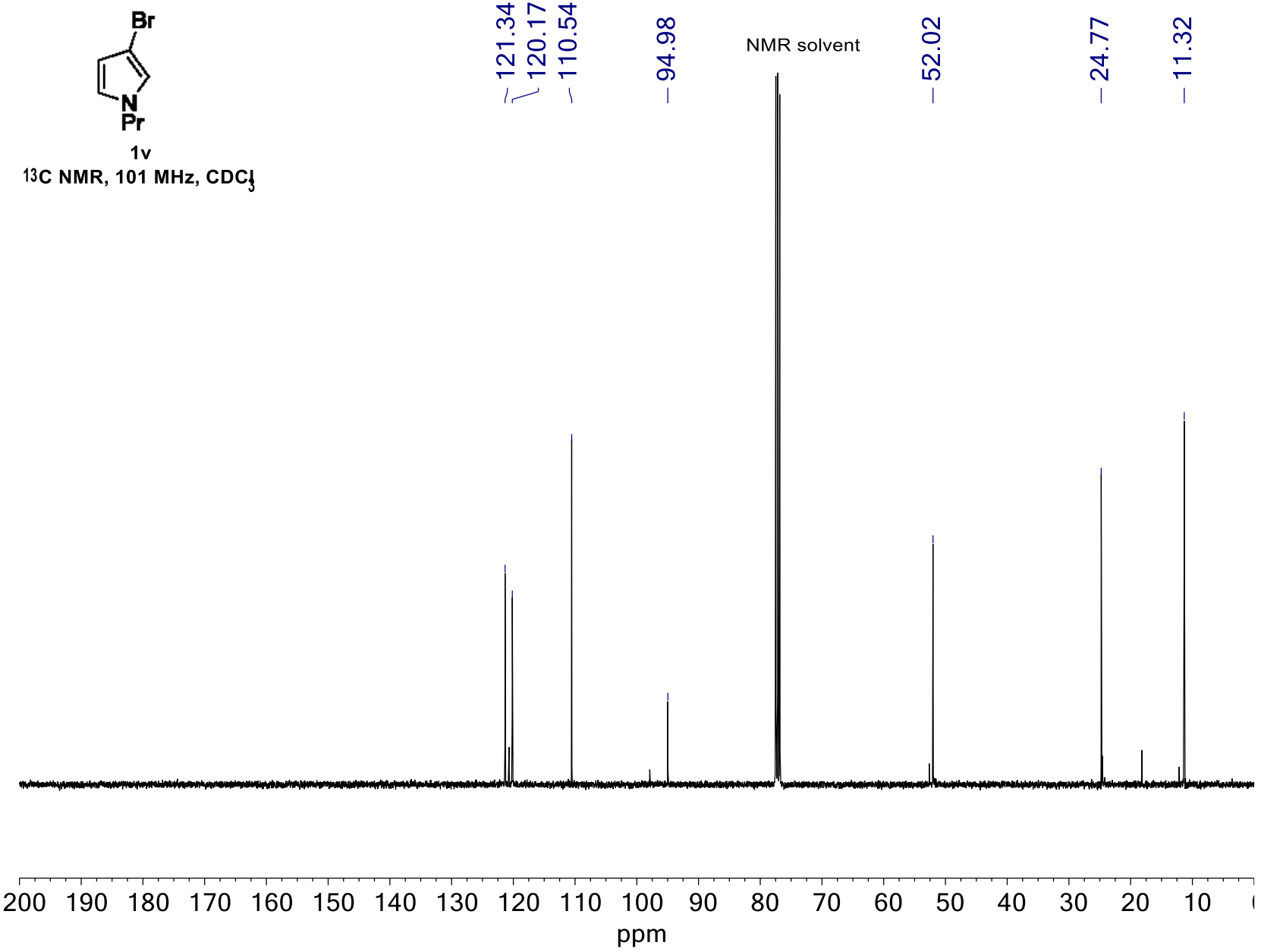
^{1}H NMR, 400 MHz, $CDCl_3$

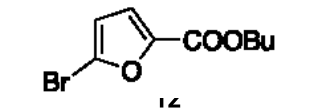



Br
N
N
Me
1u
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00 1.01 0.99 1.02
3.02
12
11
10
9
8
7
6
5
4
3
2
1
ppm


Br
N
N
Me
1u
13C NMR, 101 MHz, CDCl3
146.91
144.07
128.06
127.65
120.10
116.32
87.85
NMR solvent
31.48
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

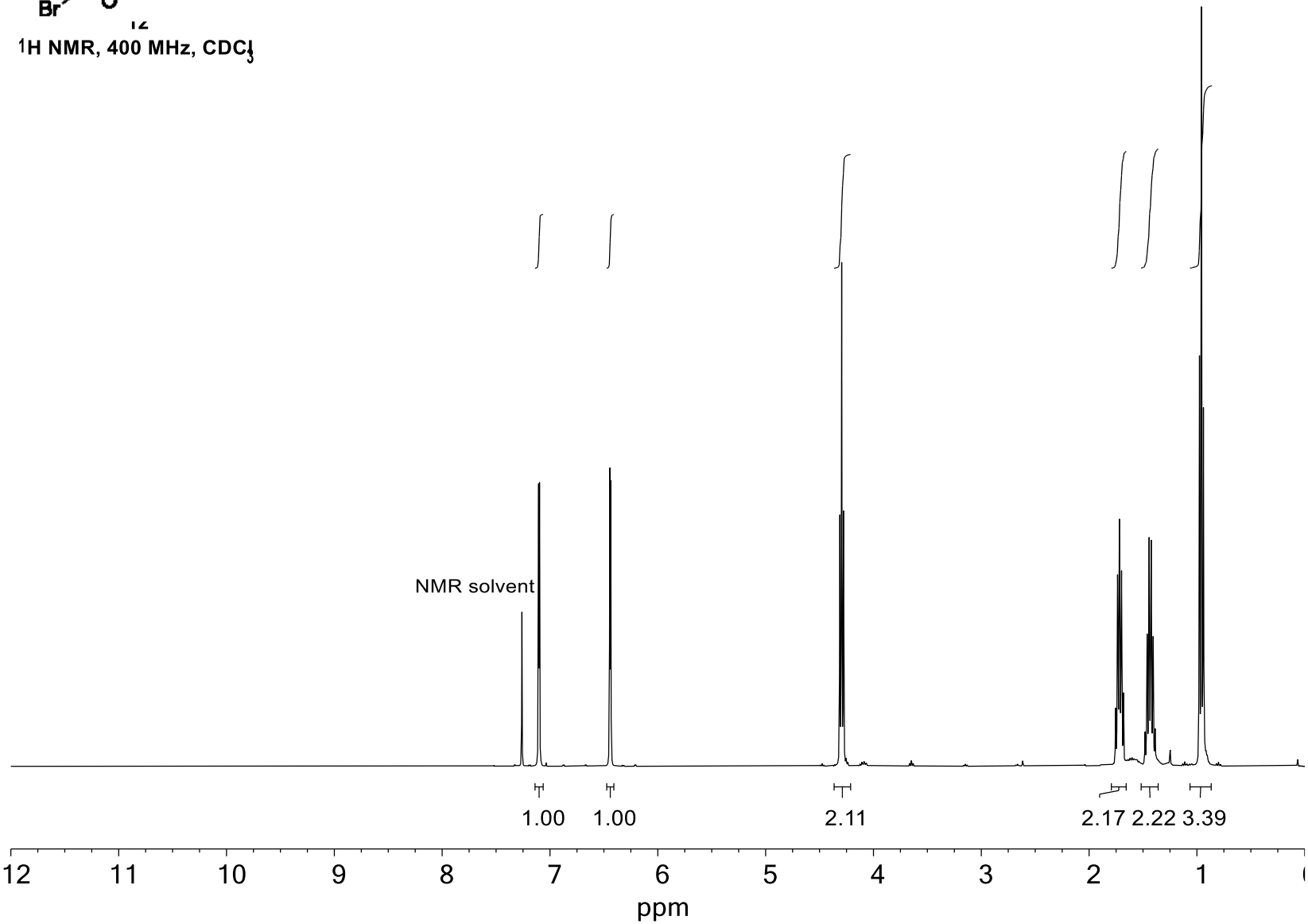

Br
N
Pr
1v
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00 0.88 0.87
1.93
1.97
3.01
12
11
10
9
8
7
6
5
4
3
2
1
ppm

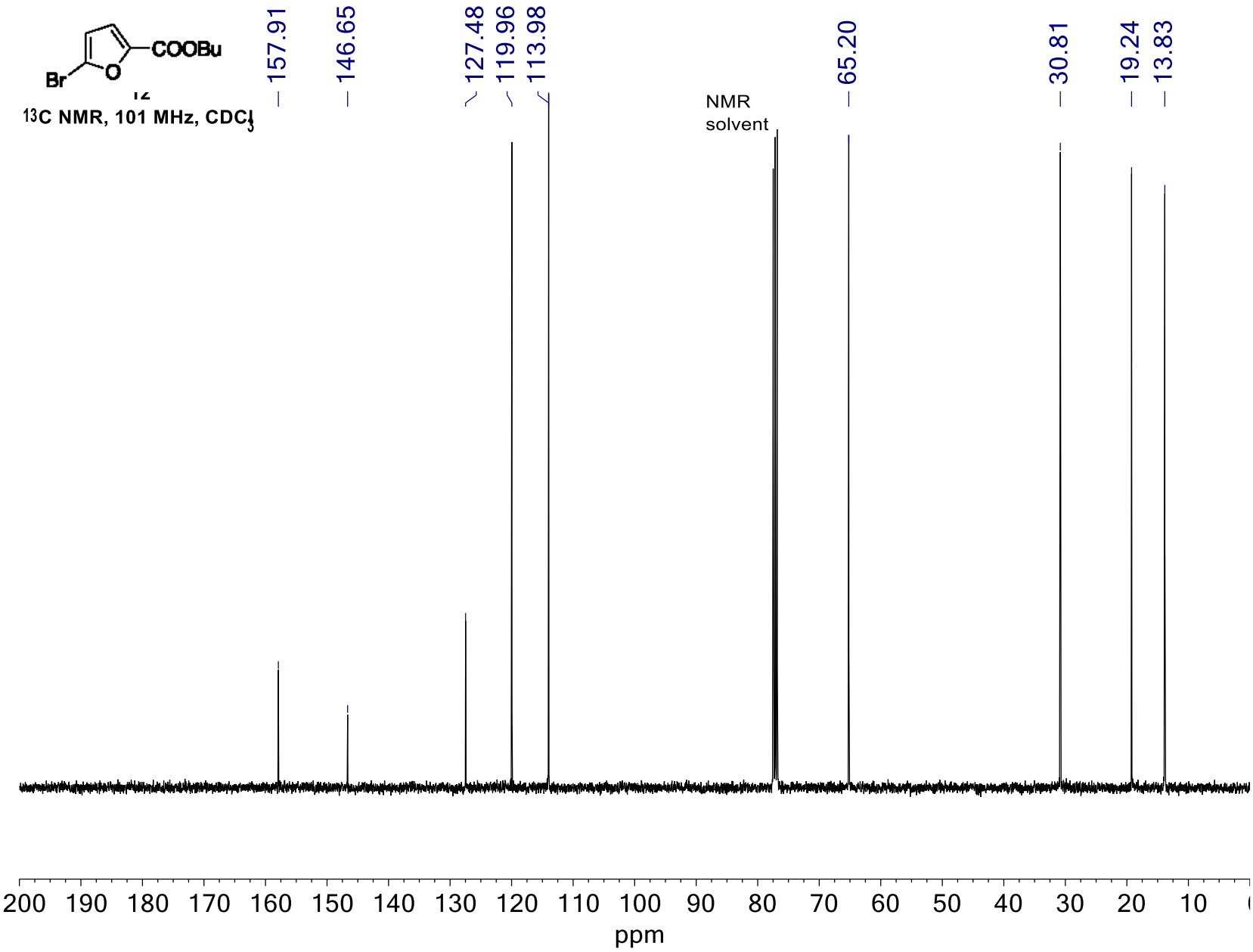

Br
N
Pr
1v
13C NMR, 101 MHz, CDCl3
121.34
120.17
110.54
94.98
NMR solvent
52.02
24.77
11.32
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



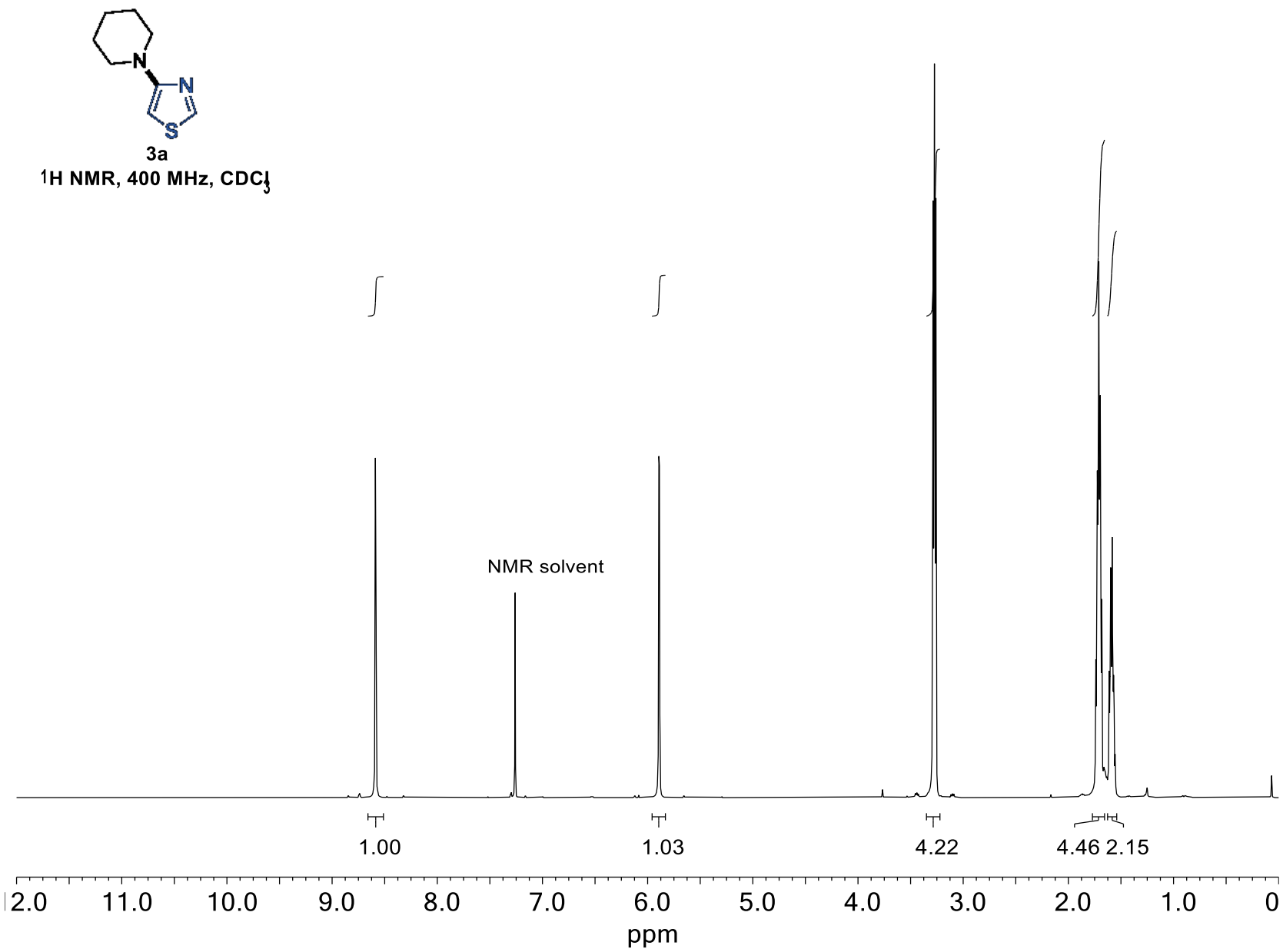
12

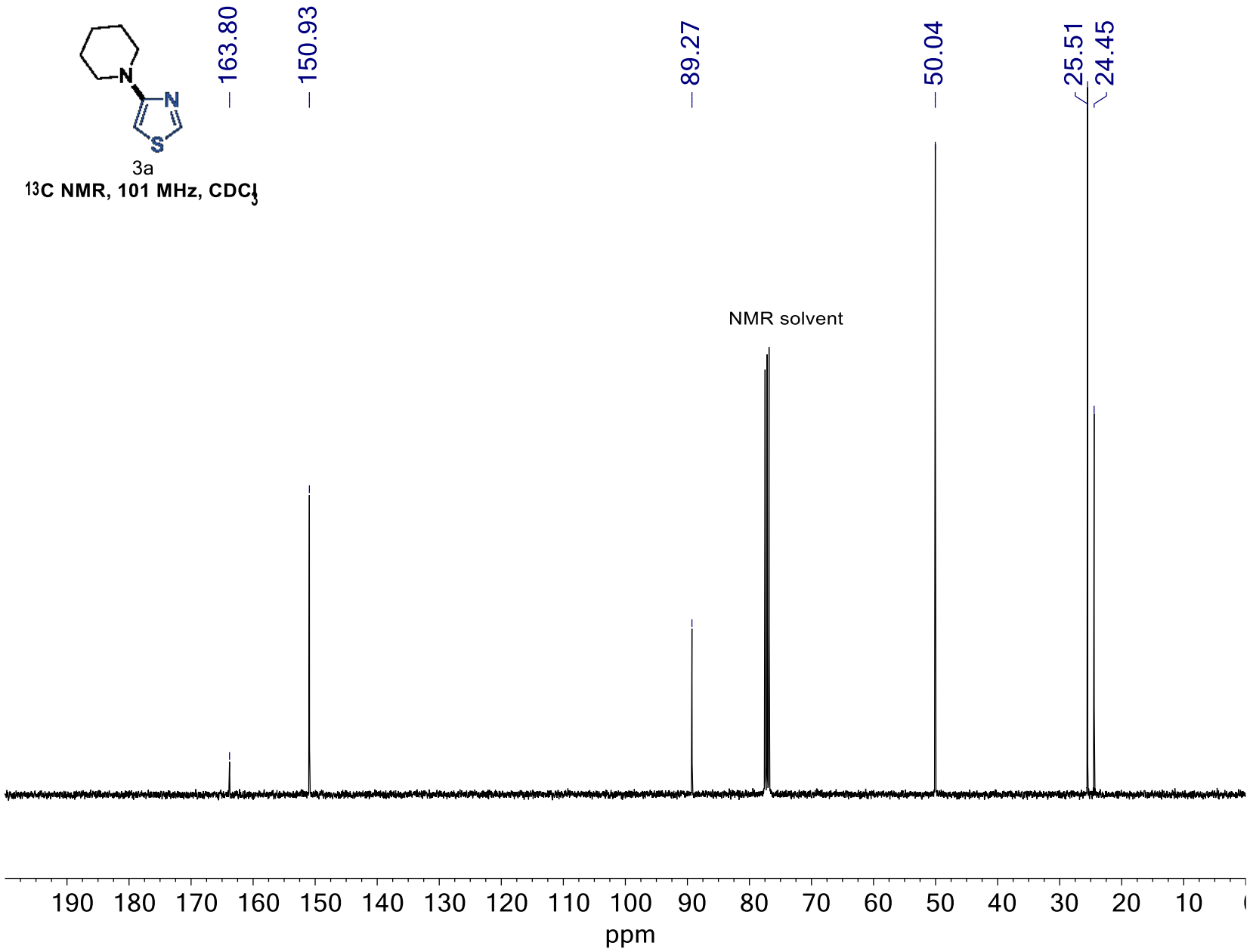
^{1}H NMR, 400 MHz, $CDCl_3$





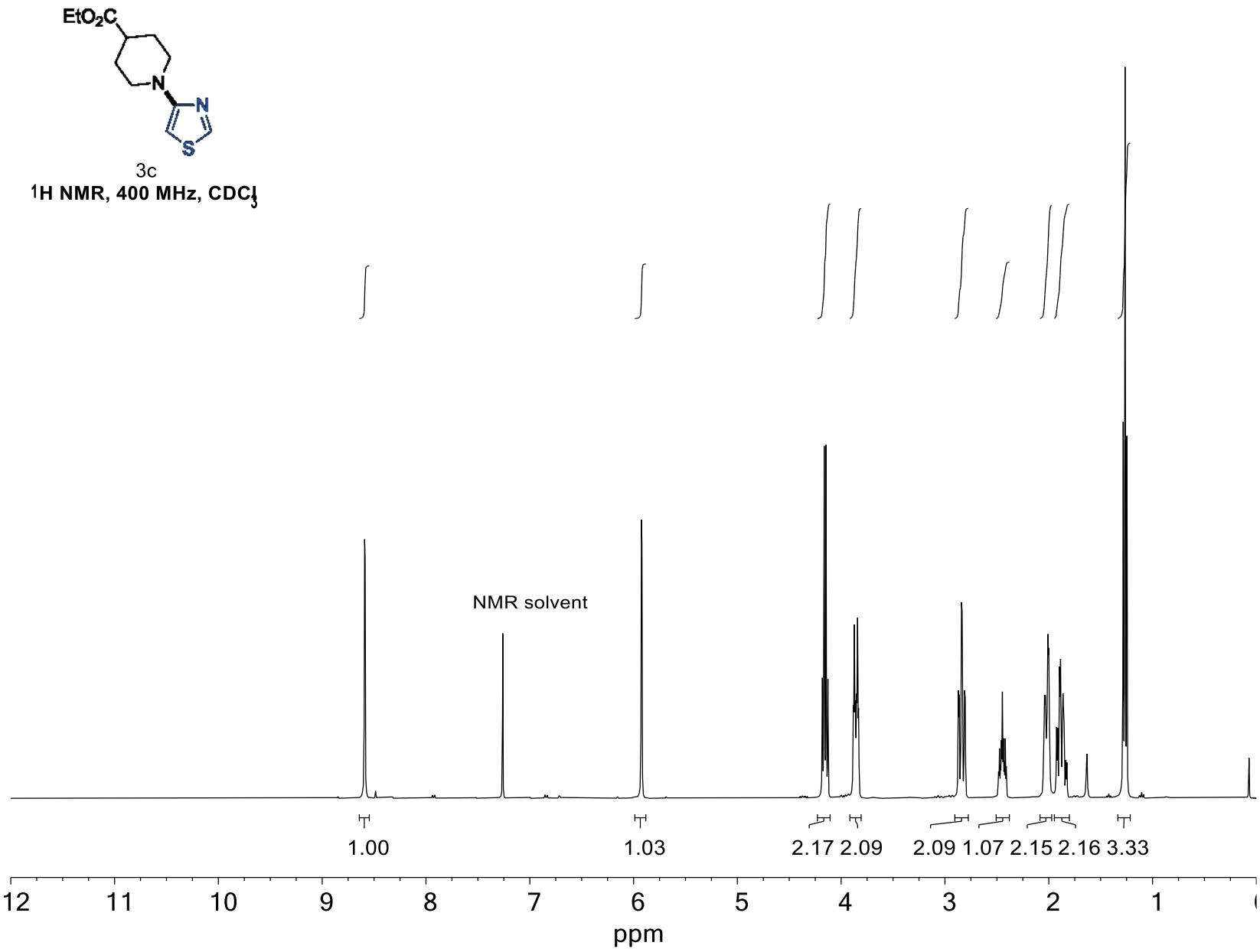
^{13}C NMR, 101 MHz, $CDCl_3$

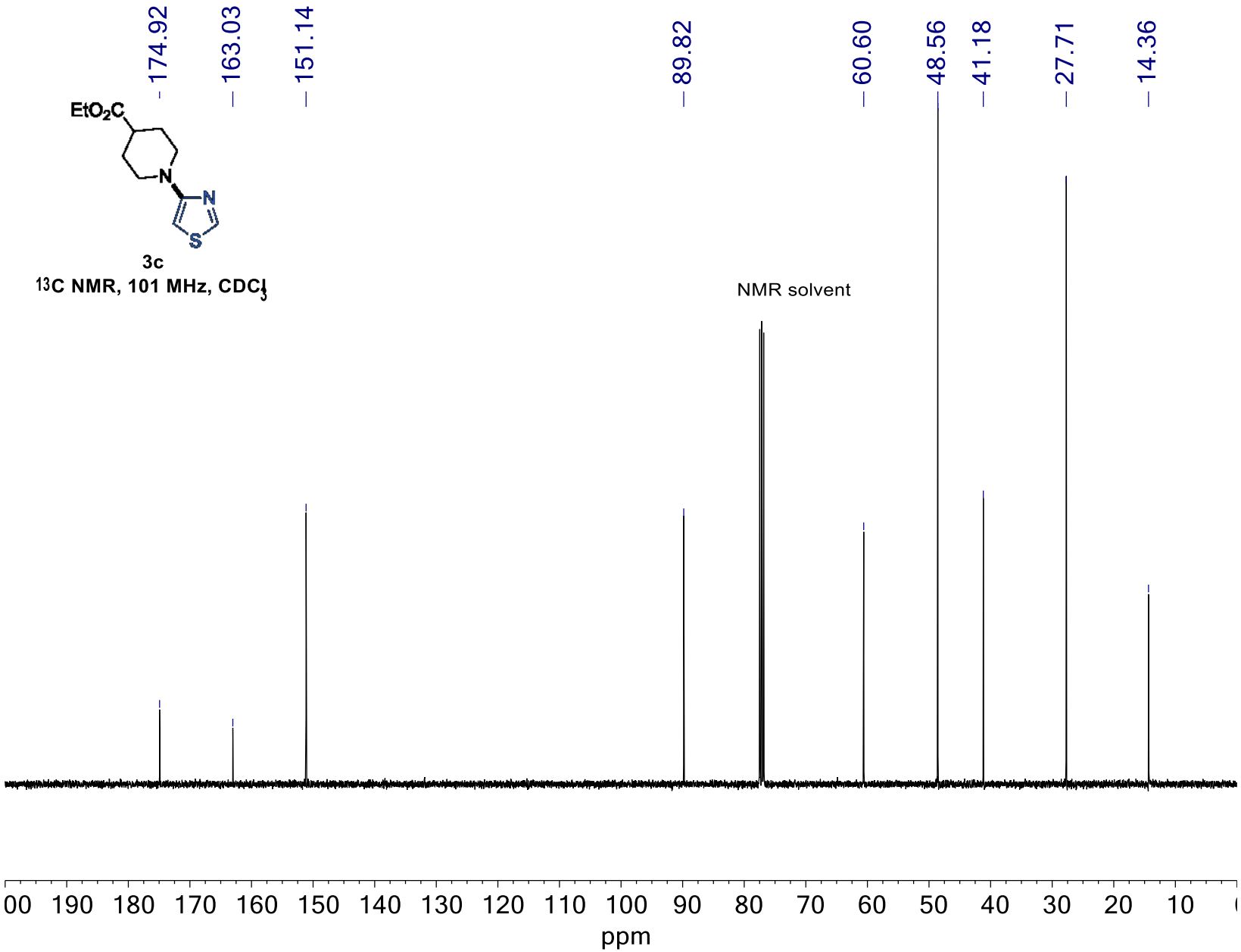

3a
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00
1.03
4.22
4.46 2.15
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

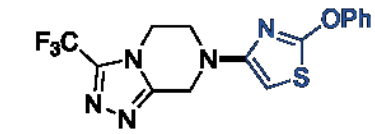


3a

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

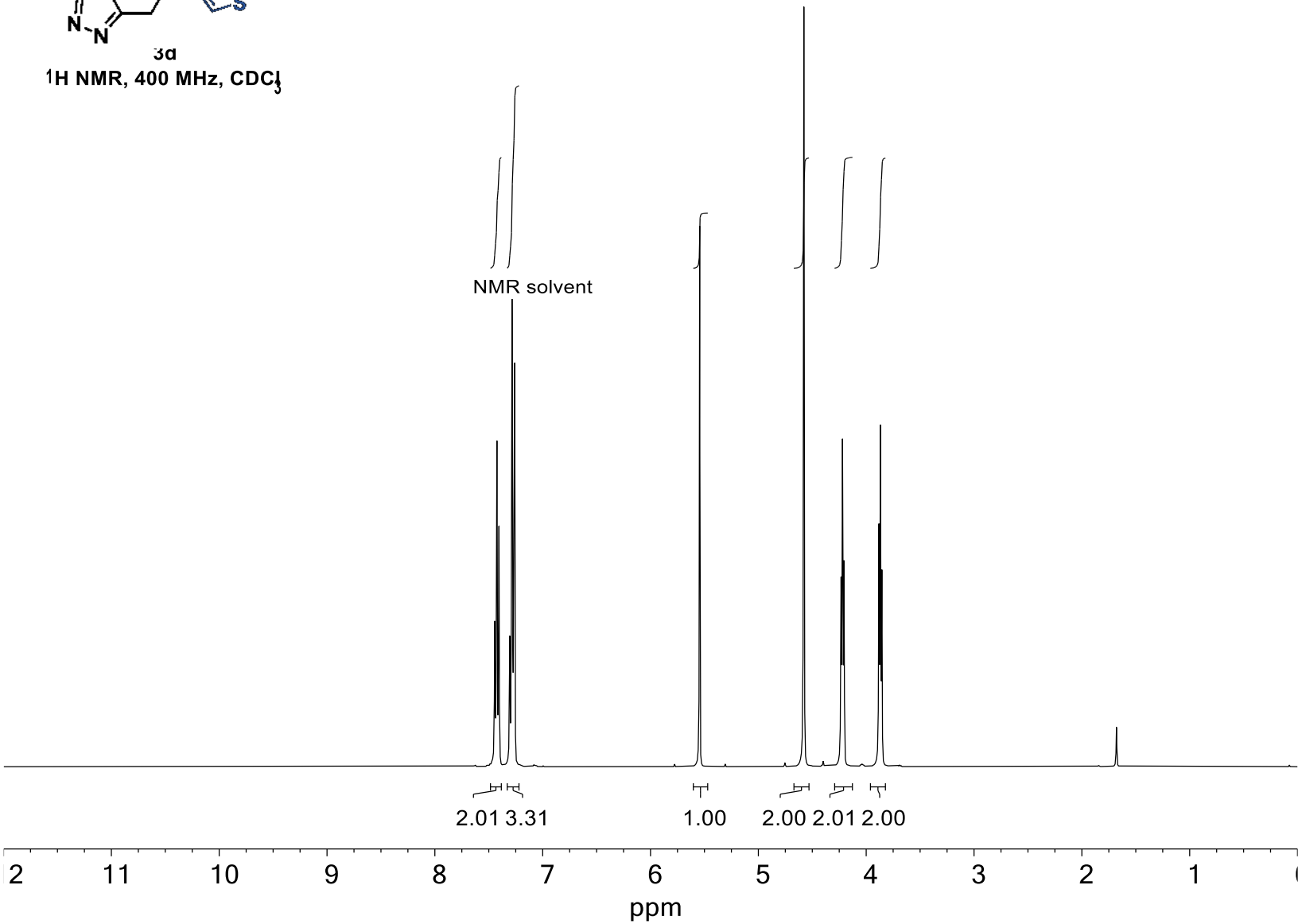

EtO2C
N
N
S
3c
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00
1.03
2.17 2.09
2.09 1.07 2.15 2.16 3.33
12
11
10
9
8
7
6
5
4
3
2
1
ppm

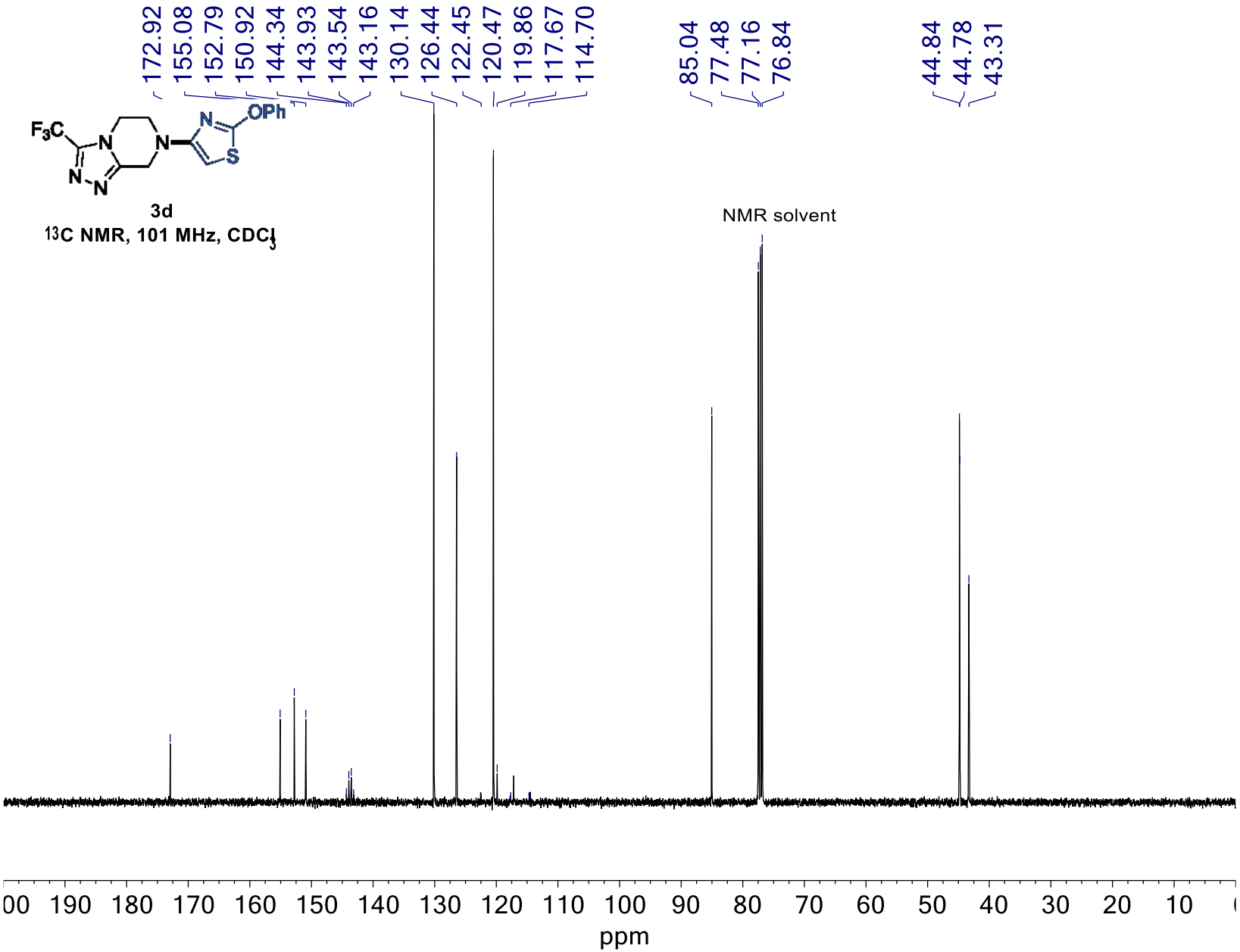

174.92
163.03
151.14
89.82
60.60
48.56
41.18
27.71
14.36
EtO2C
N
N
S
3c
13C NMR, 101 MHz, CDCl3
NMR solvent
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

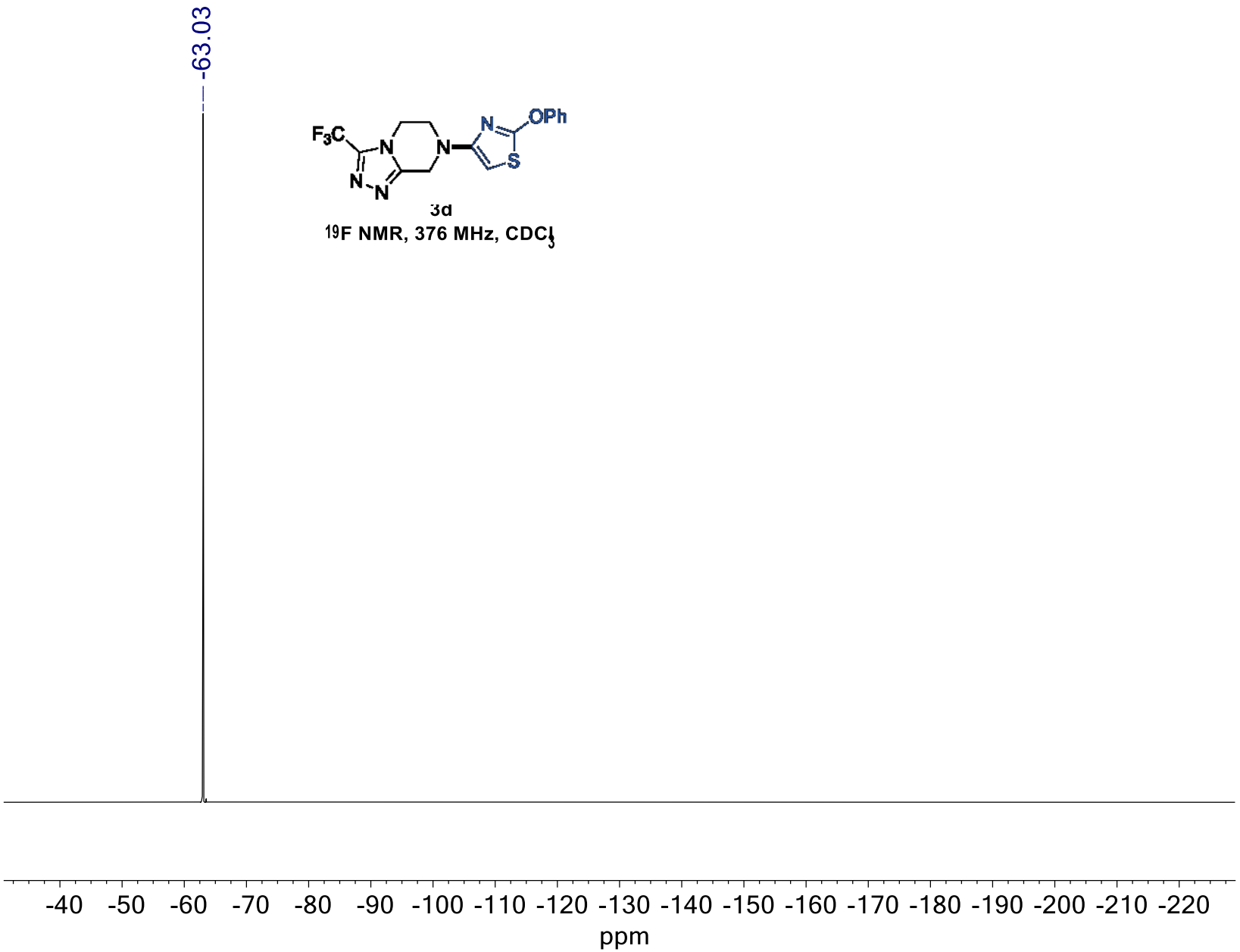


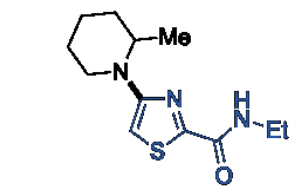
3d

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



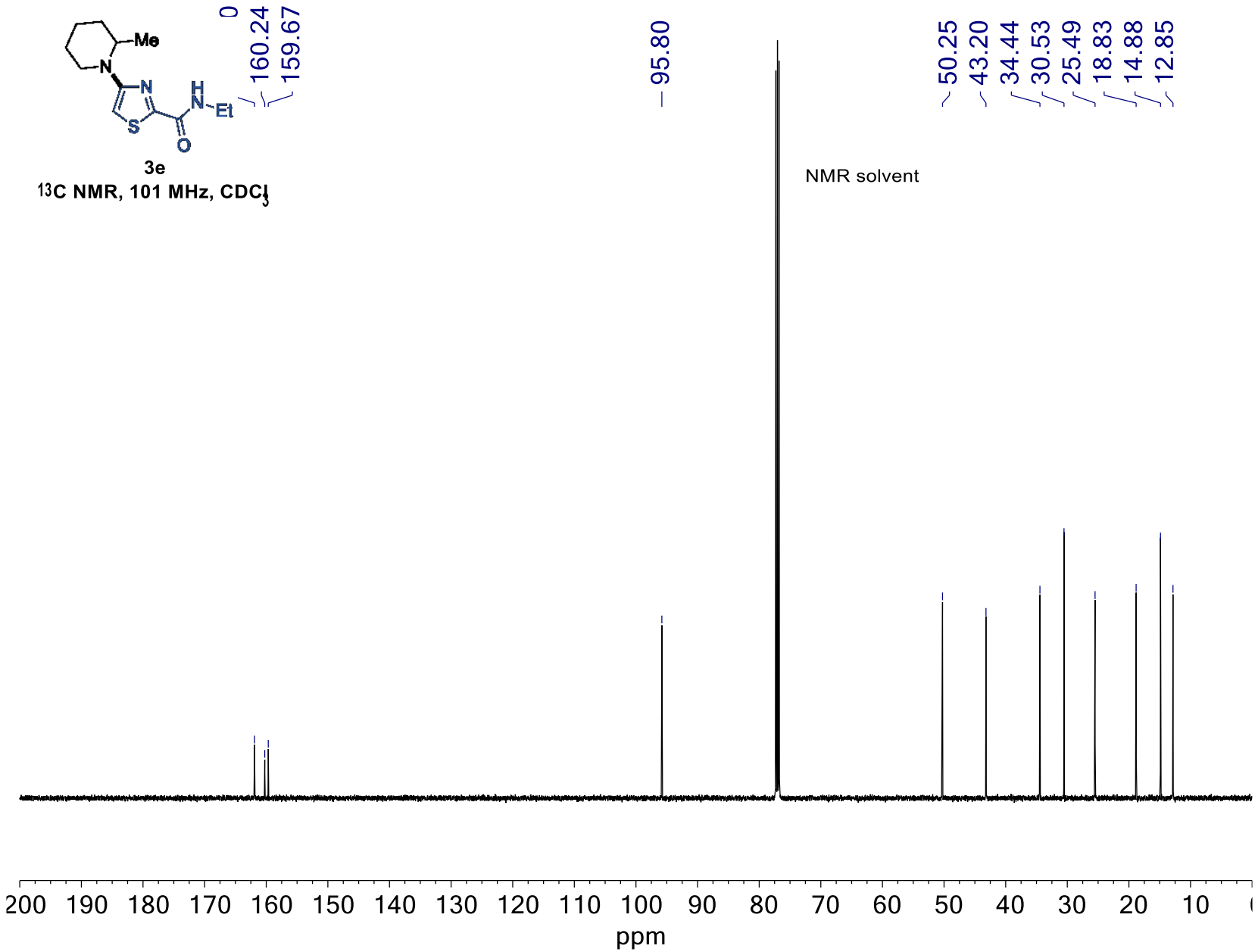

172.92
155.08
152.79
150.92
144.34
143.93
143.54
143.16
130.14
126.44
122.45
120.47
119.86
117.67
114.70
85.04
77.48
77.16
76.84
44.84
44.78
43.31
NMR solvent
F3C
N
N
N
N
S
OPh
3d
13C NMR, 101 MHz, CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

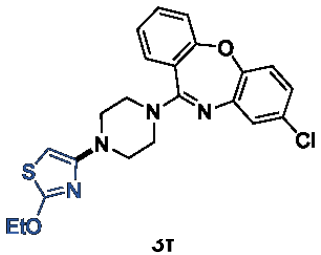

-63.03
F3C
N
N
N
N
S
OPh
3d
19F NMR, 376 MHz, CDCl3
-40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
ppm



3e

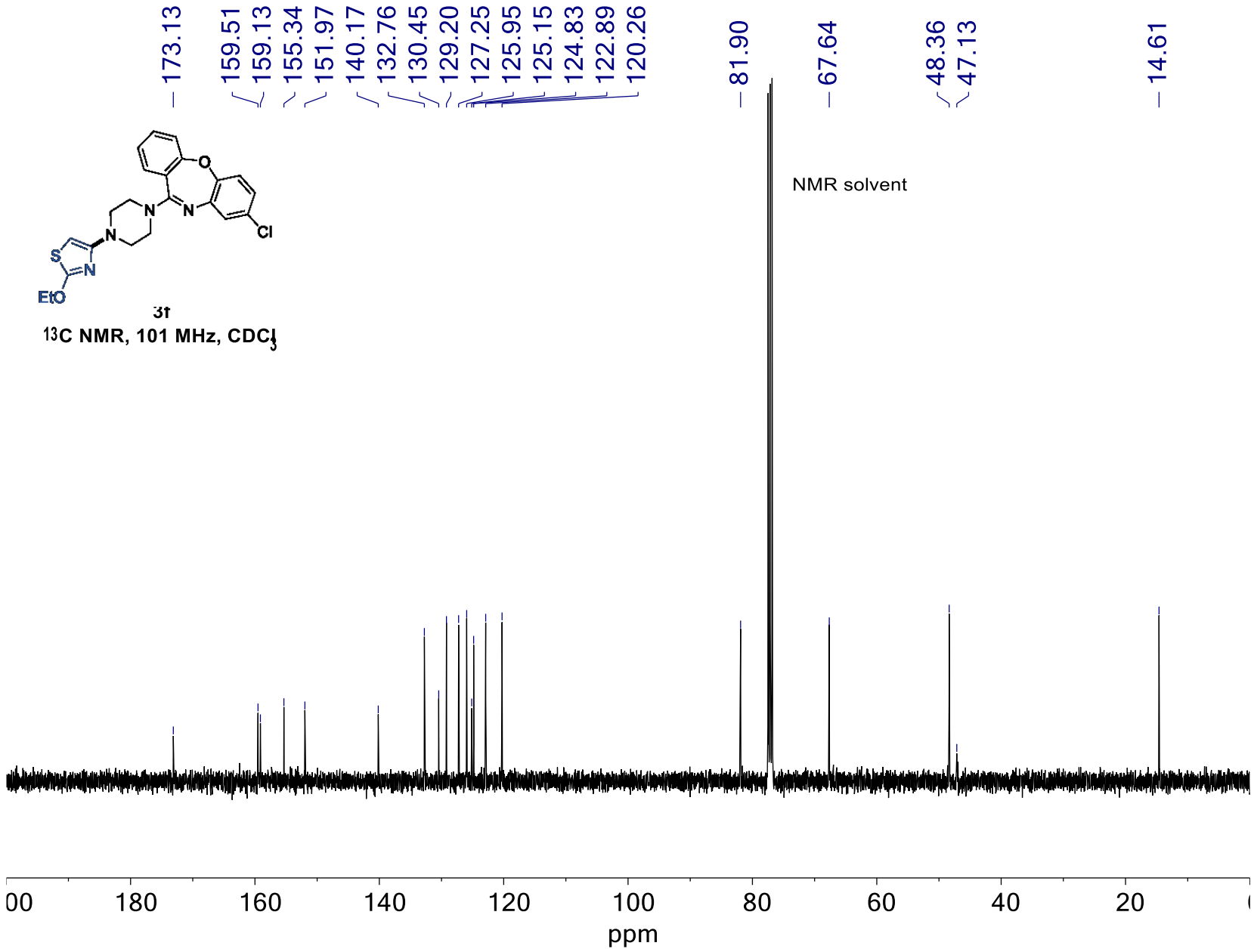
^{1}H NMR, 400 MHz, $CDCl_3$

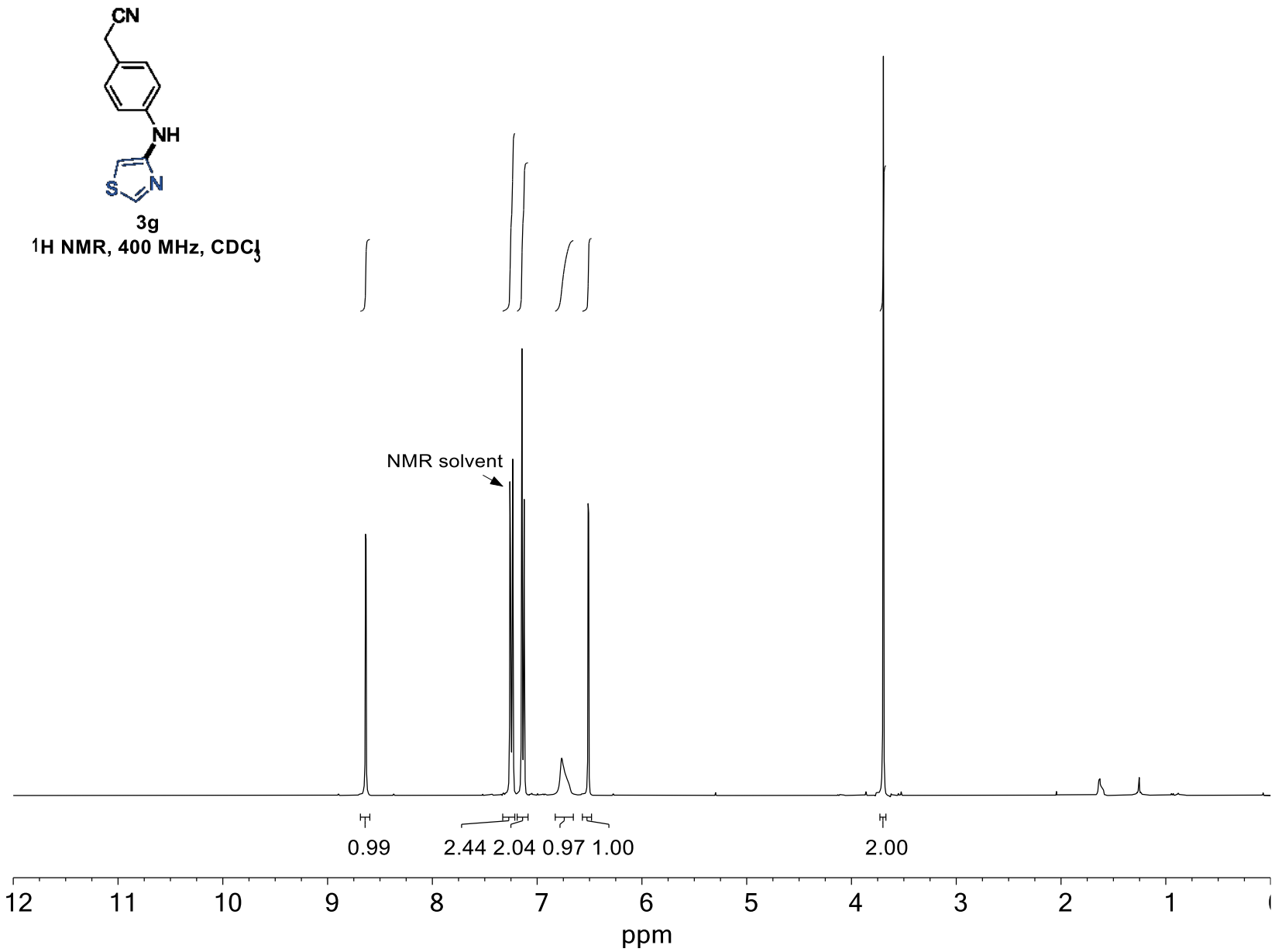

Me
N
N
S
H
N
Et
O
3e
13C NMR, 101 MHz, CDCl3
160.24
159.67
95.80
50.25
43.20
34.44
30.53
25.49
18.83
14.88
12.85
NMR solvent
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

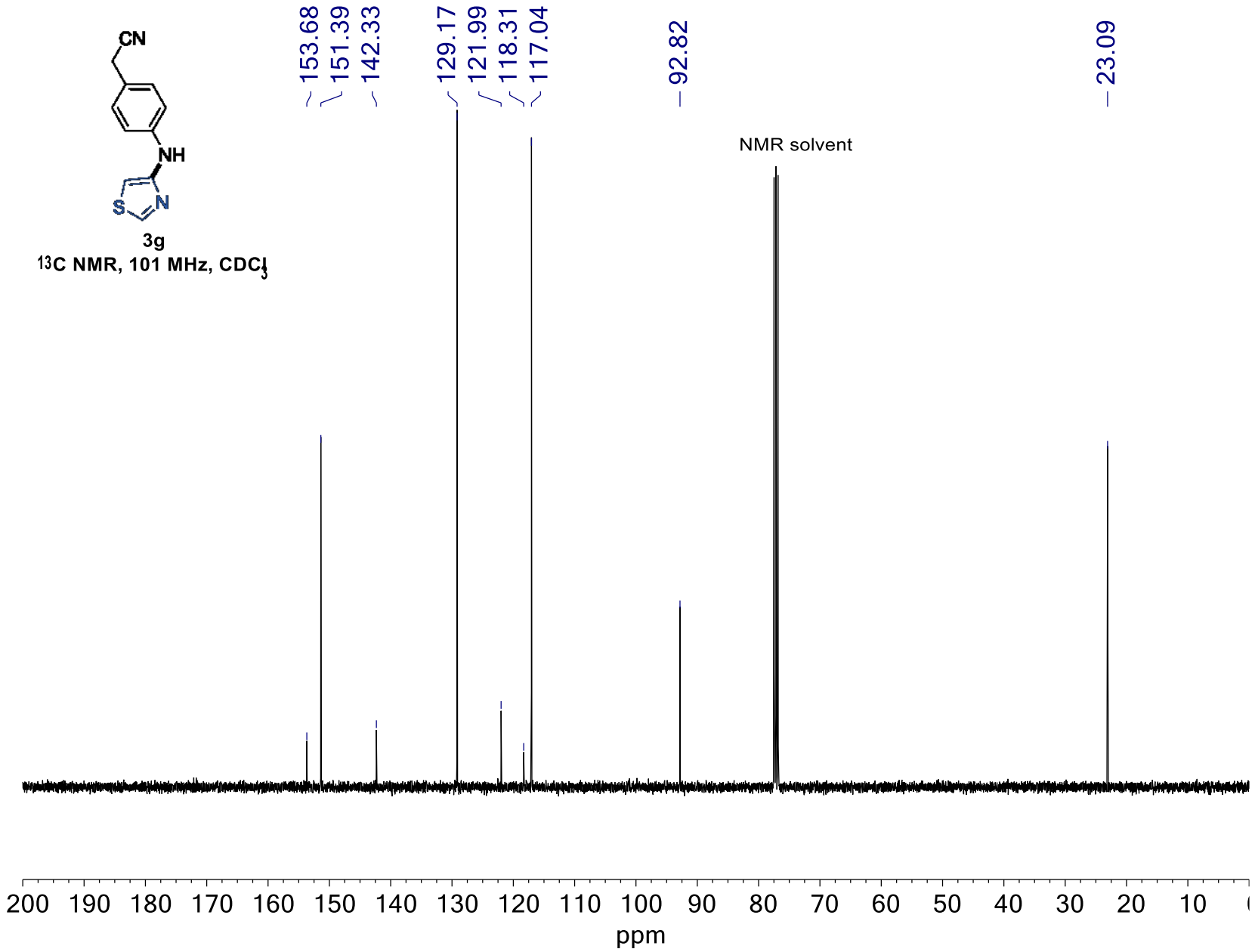


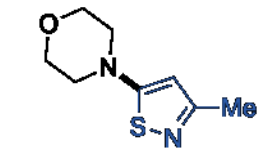
3T

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


173.13
159.51
159.13
155.34
151.97
140.17
132.76
130.45
129.20
127.25
125.95
125.15
124.83
122.89
120.26
81.90
67.64
48.36
47.13
14.61
NMR solvent
EtO
Cl
3t
13C NMR, 101 MHz, CDCl3
00
180
160
140
120
100
80
60
40
20
ppm

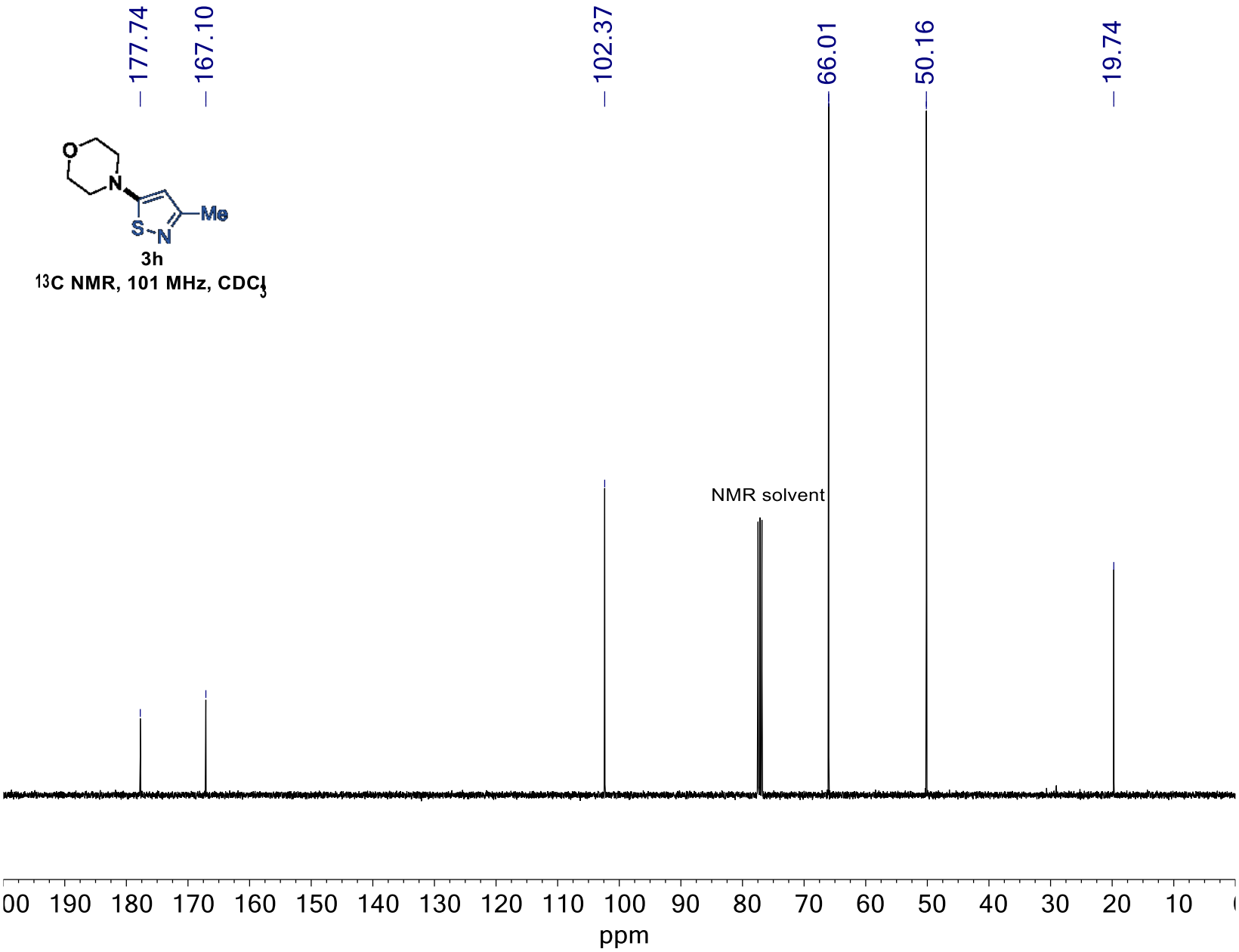

CN
NH
S
N
3g
1H NMR, 400 MHz, CDCl3
NMR solvent
0.99
2.44
2.04
0.97
1.00
2.00
12
11
10
9
8
7
6
5
4
3
2
1
ppm

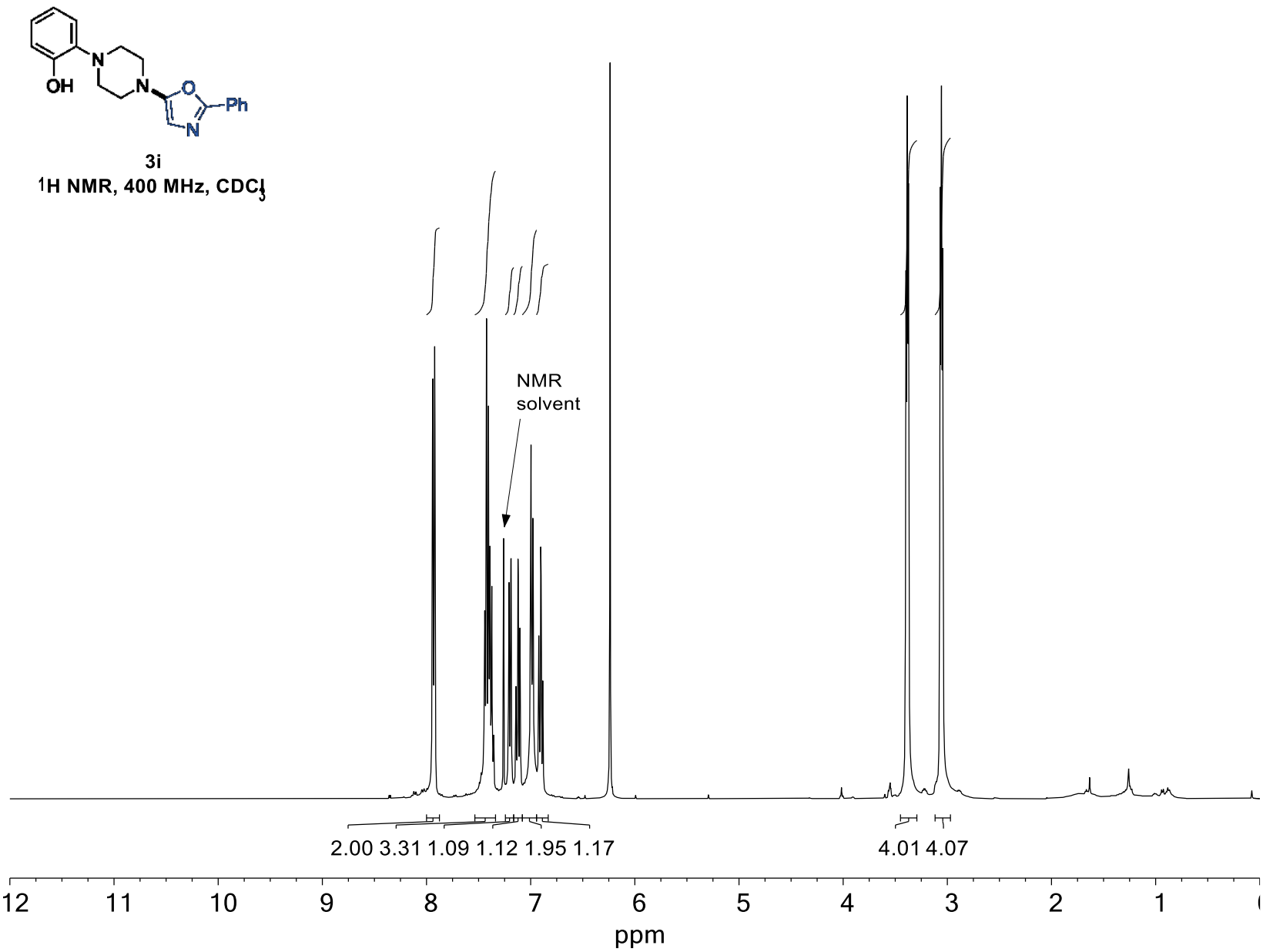

CN
NH
S
N
3g
13C NMR, 101 MHz, CDCl3
153.68
151.39
142.33
129.17
121.99
118.31
117.04
92.82
23.09
NMR solvent
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

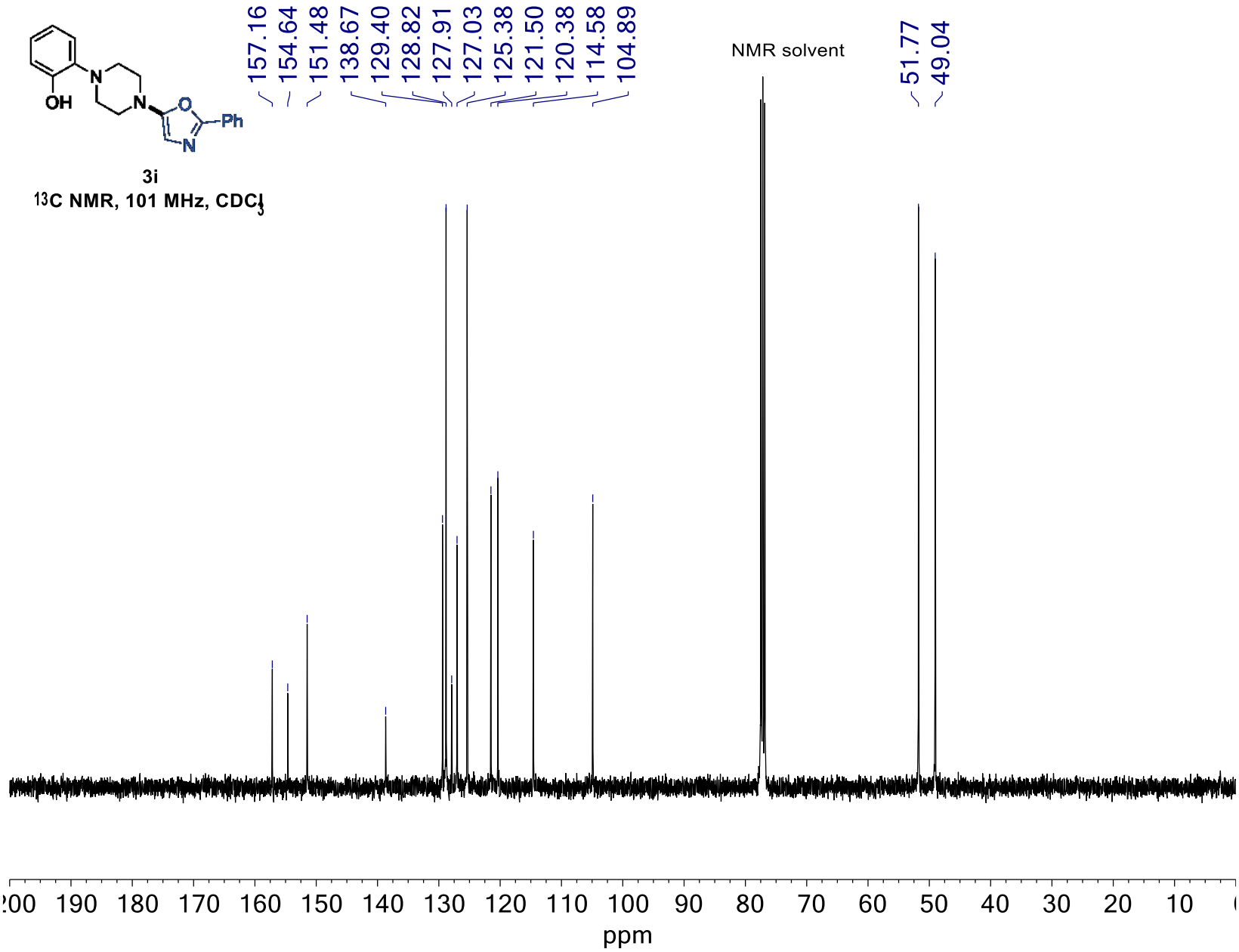


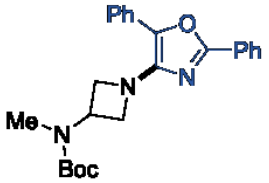
3h

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


177.74
167.10
102.37
66.01
50.16
19.74
O
N
S
N
Me
3h
13C NMR, 101 MHz, CDCl3
NMR solvent
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

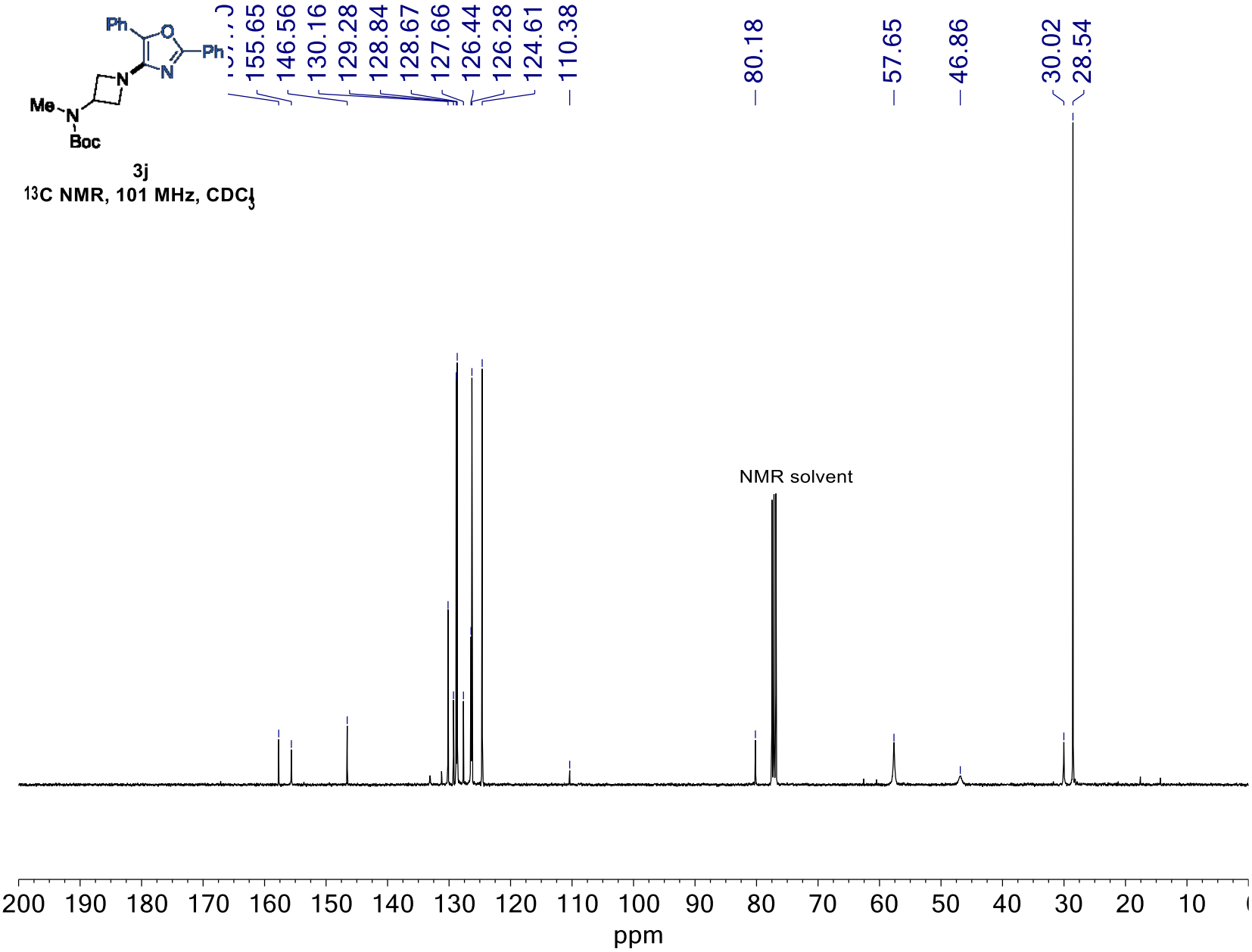

OH
N
N
O
Ph
N
3i
1H NMR, 400 MHz, CDCl3
NMR
solvent
2.00 3.31 1.09 1.12 1.95 1.17
4.01 4.07
12
11
10
9
8
7
6
5
4
3
2
1
ppm


157.16
154.64
151.48
138.67
129.40
128.82
127.91
127.03
125.38
121.50
120.38
114.58
104.89
NMR solvent
51.77
49.04
OH
N
N
O
N
Ph
3i
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
ppm



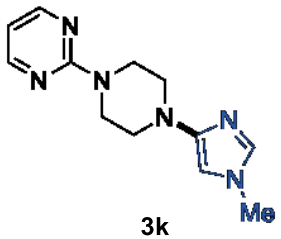
3j

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



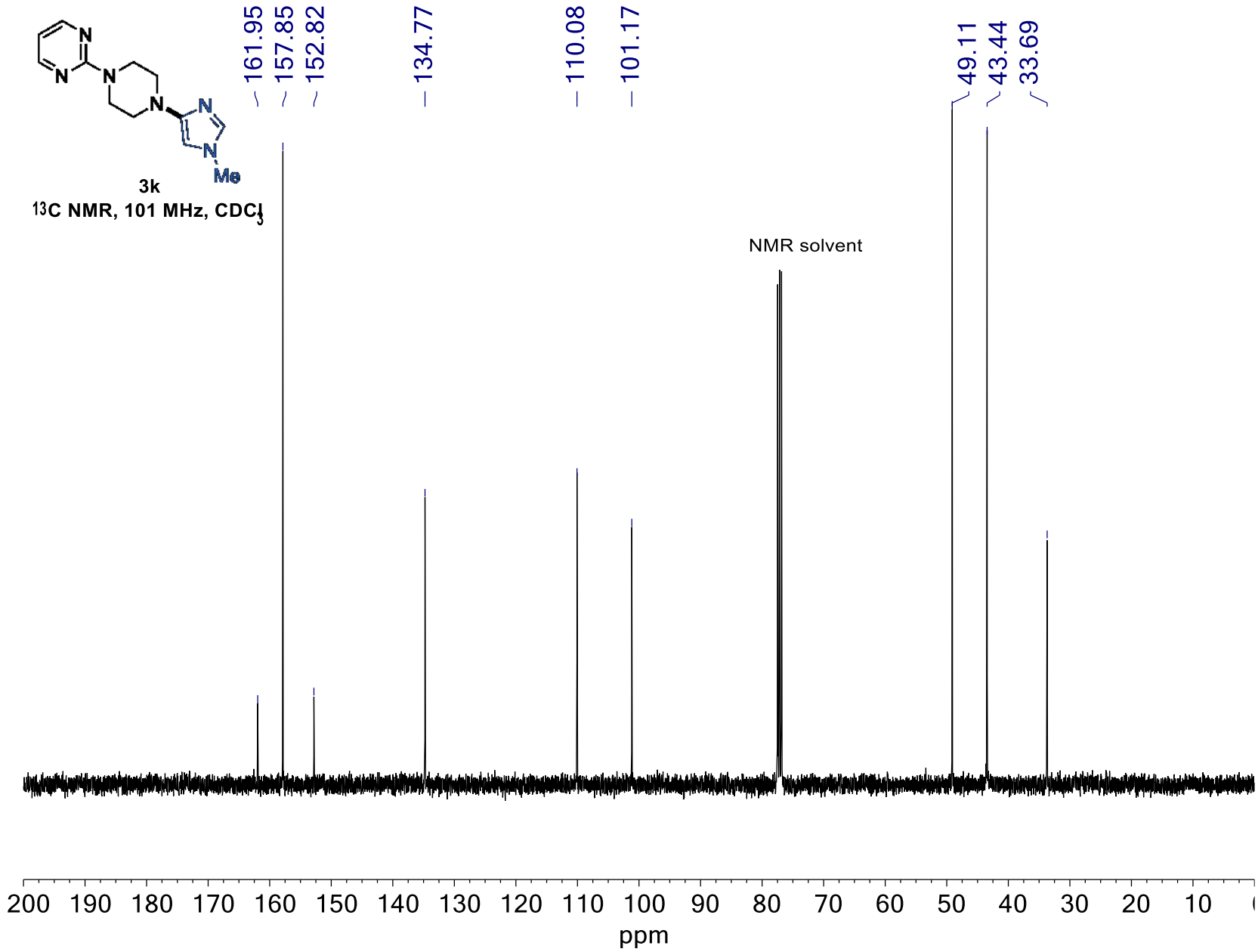
3j

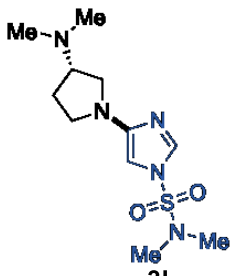
^{13}C NMR, 101 MHz, $CDCl_3$



3k

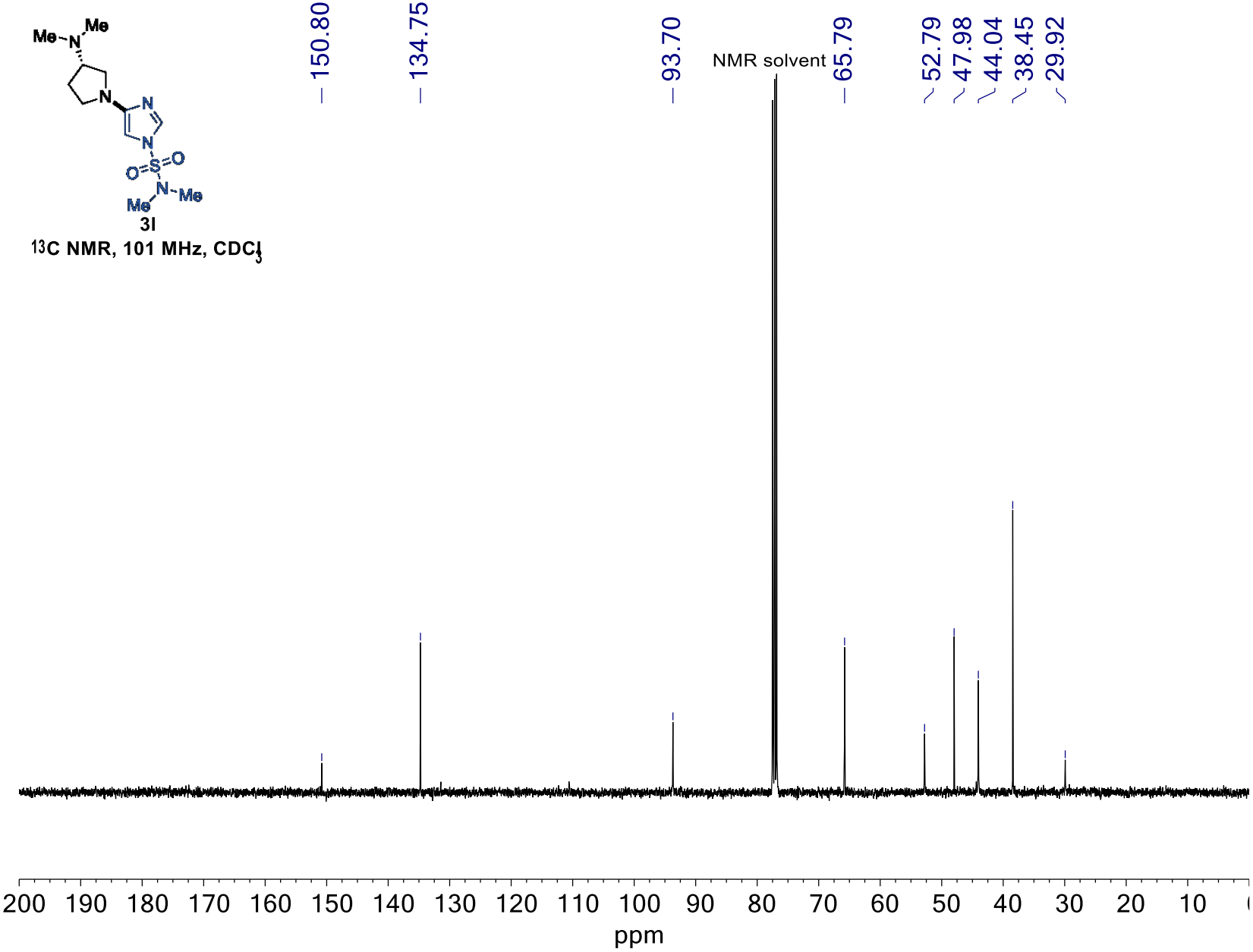
^{1}H NMR, 400 MHz, $CDCl_3$


161.95
157.85
152.82
134.77
110.08
101.17
49.11
43.44
33.69
NMR solvent
3k
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
ppm



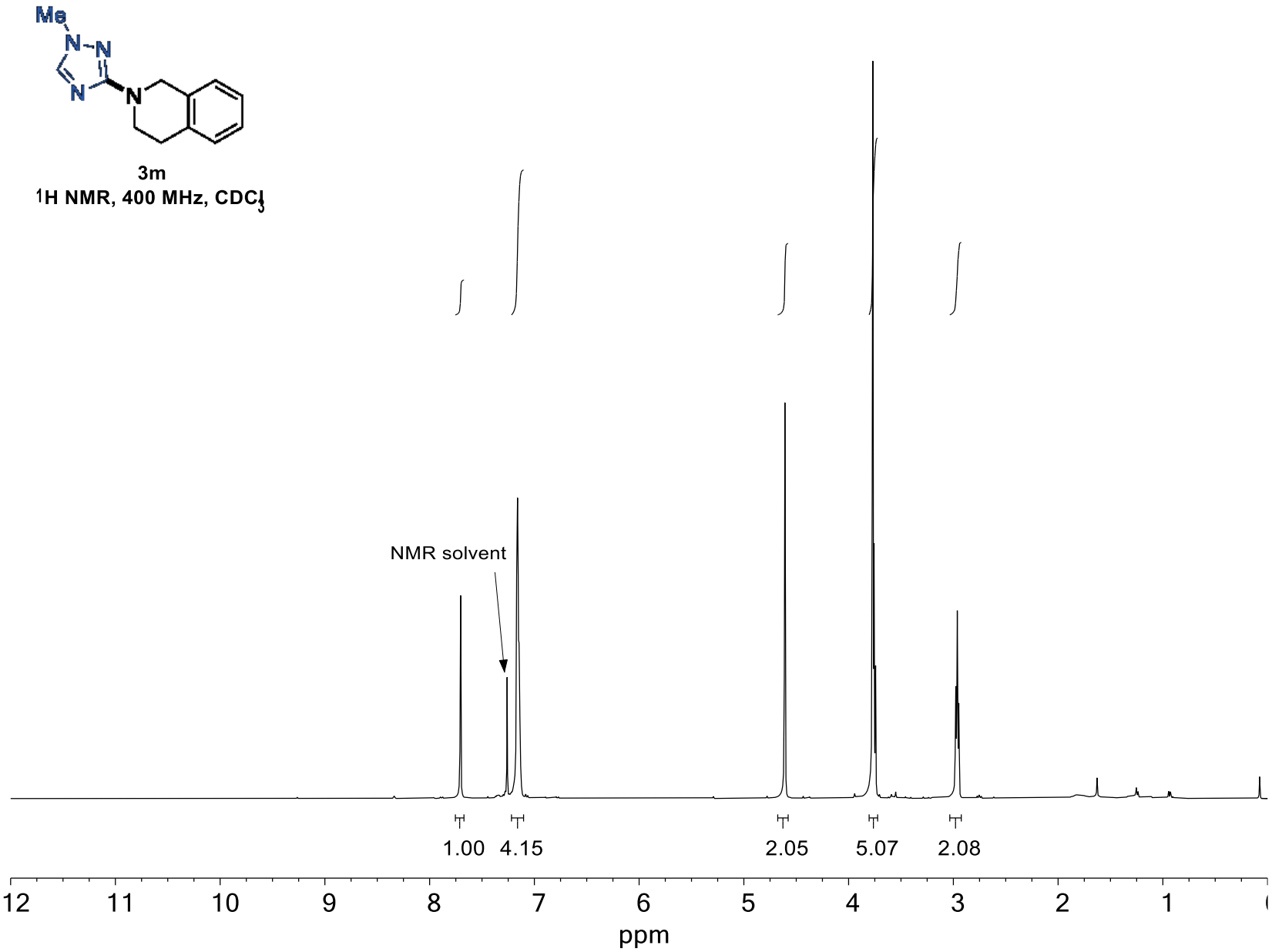
3l

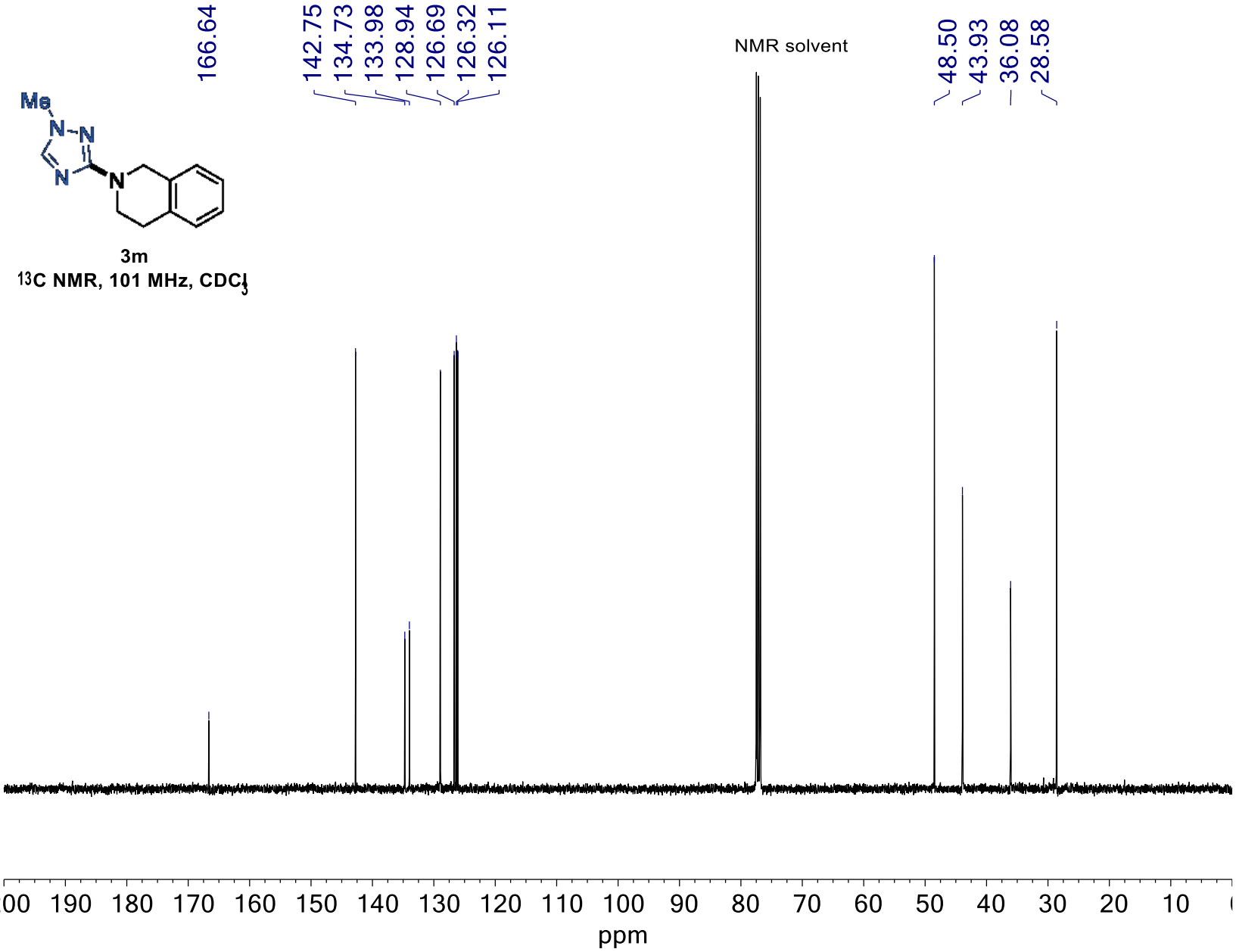
^{1}H NMR, 400 MHz, $CDCl_3$

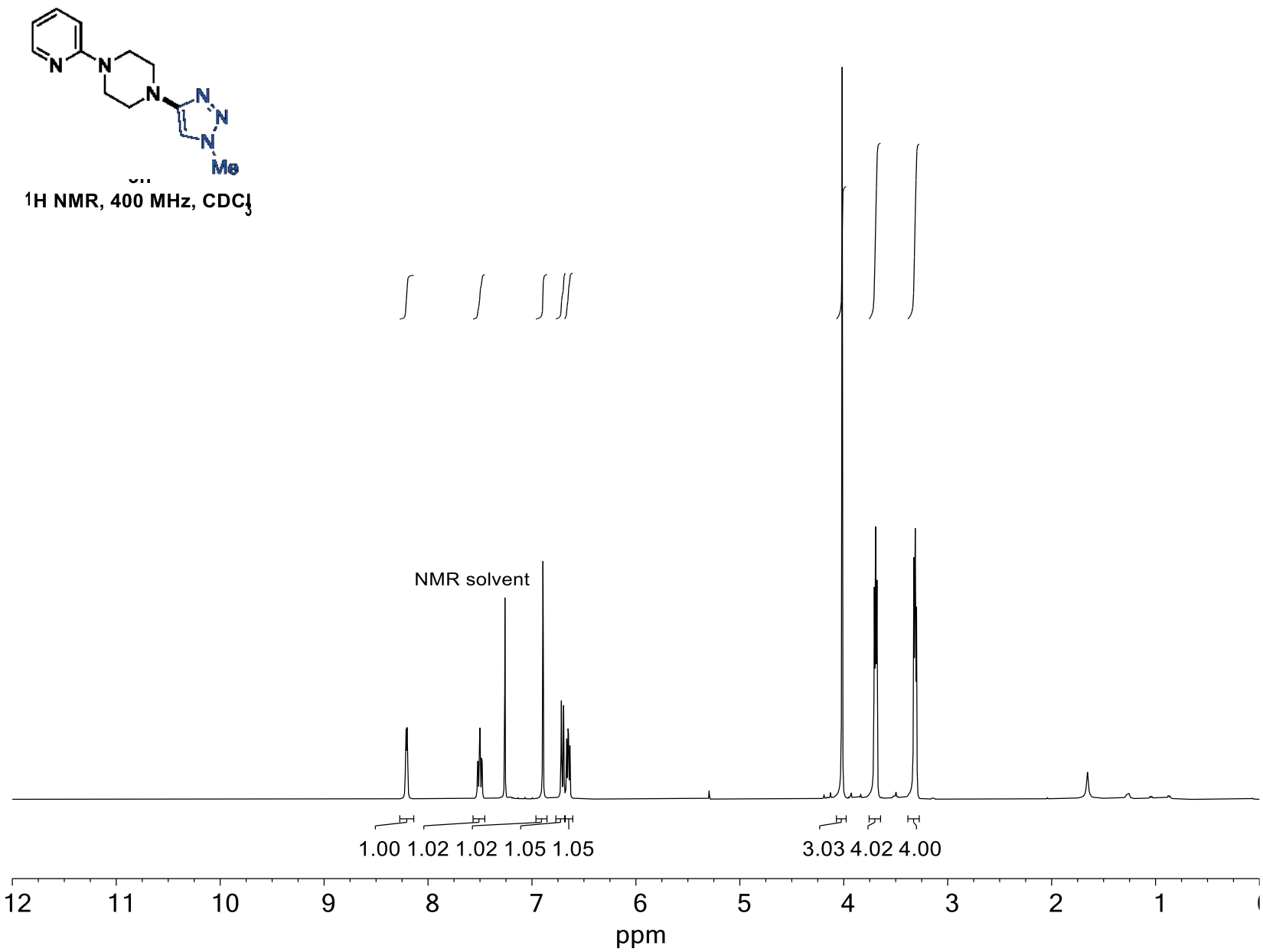


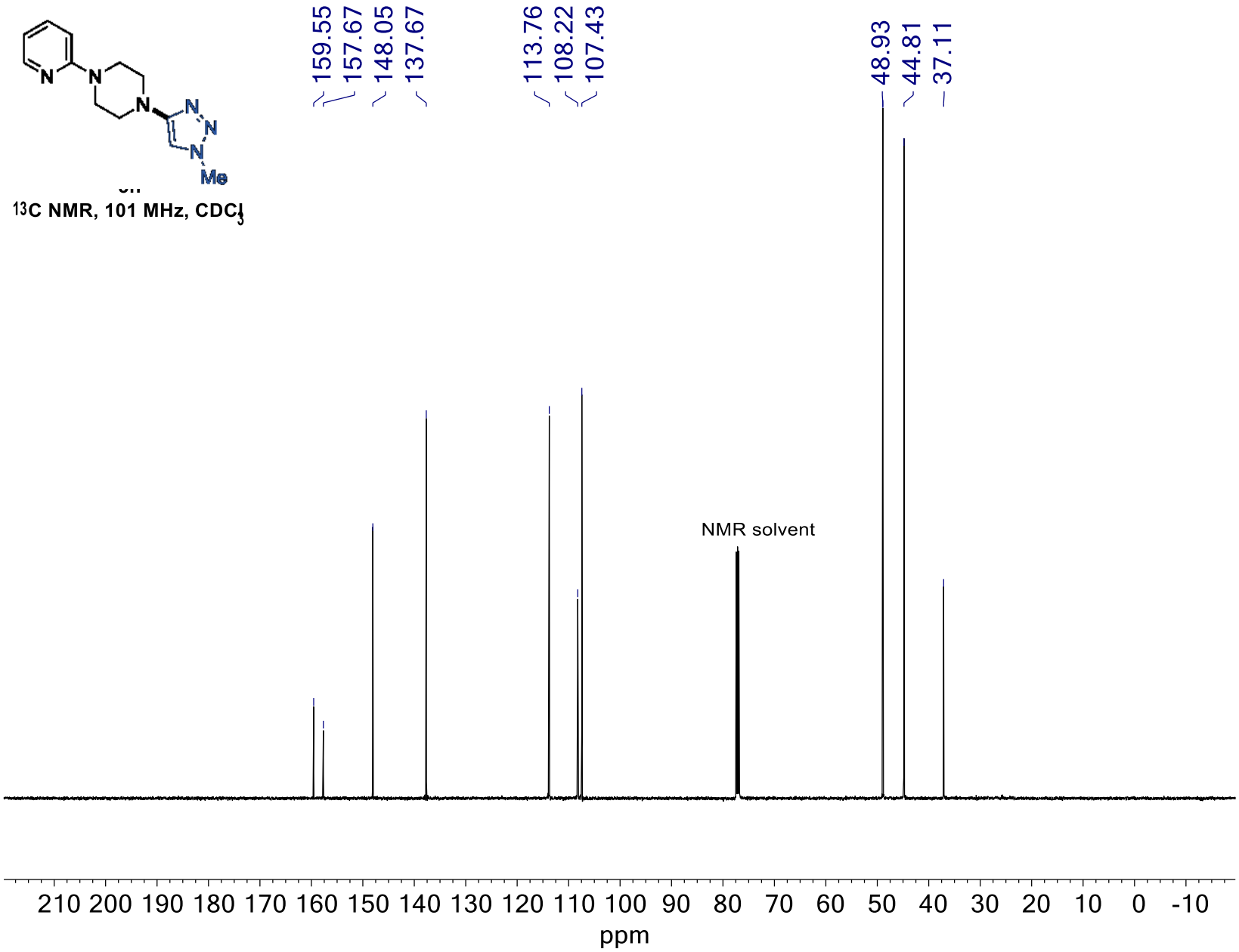
3l

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

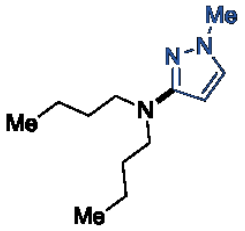

Me
N
N
N
N
3m
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00
4.15
2.05
5.07
2.08
12
11
10
9
8
7
6
5
4
3
2
1
ppm


166.64
142.75
134.73
133.98
128.94
126.69
126.32
126.11
NMR solvent
48.50
43.93
36.08
28.58
Me
N
N
N
N
3m
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
ppm


Me
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00 1.02 1.02 1.05 1.05
3.03 4.02 4.00
12
11
10
9
8
7
6
5
4
3
2
1
ppm

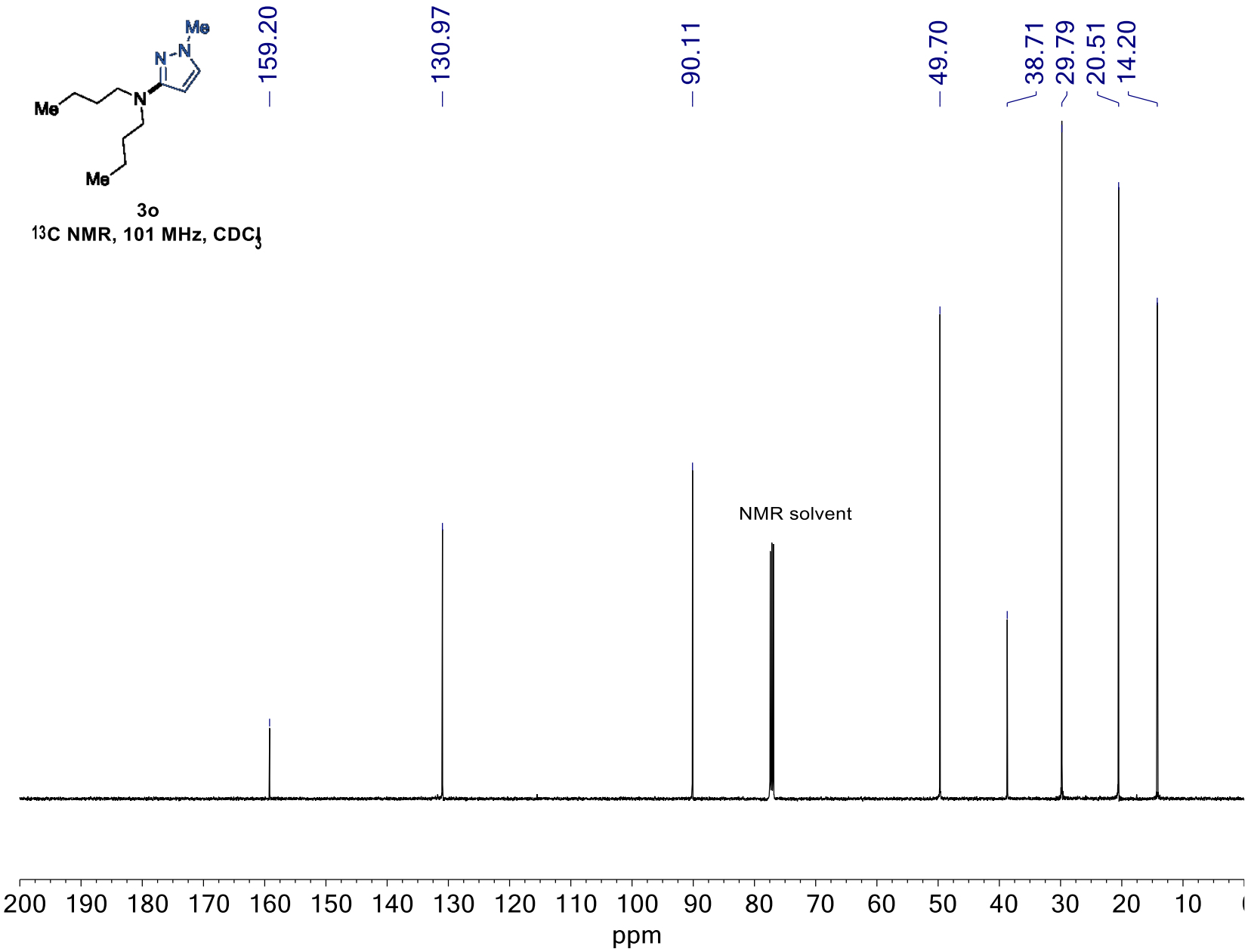


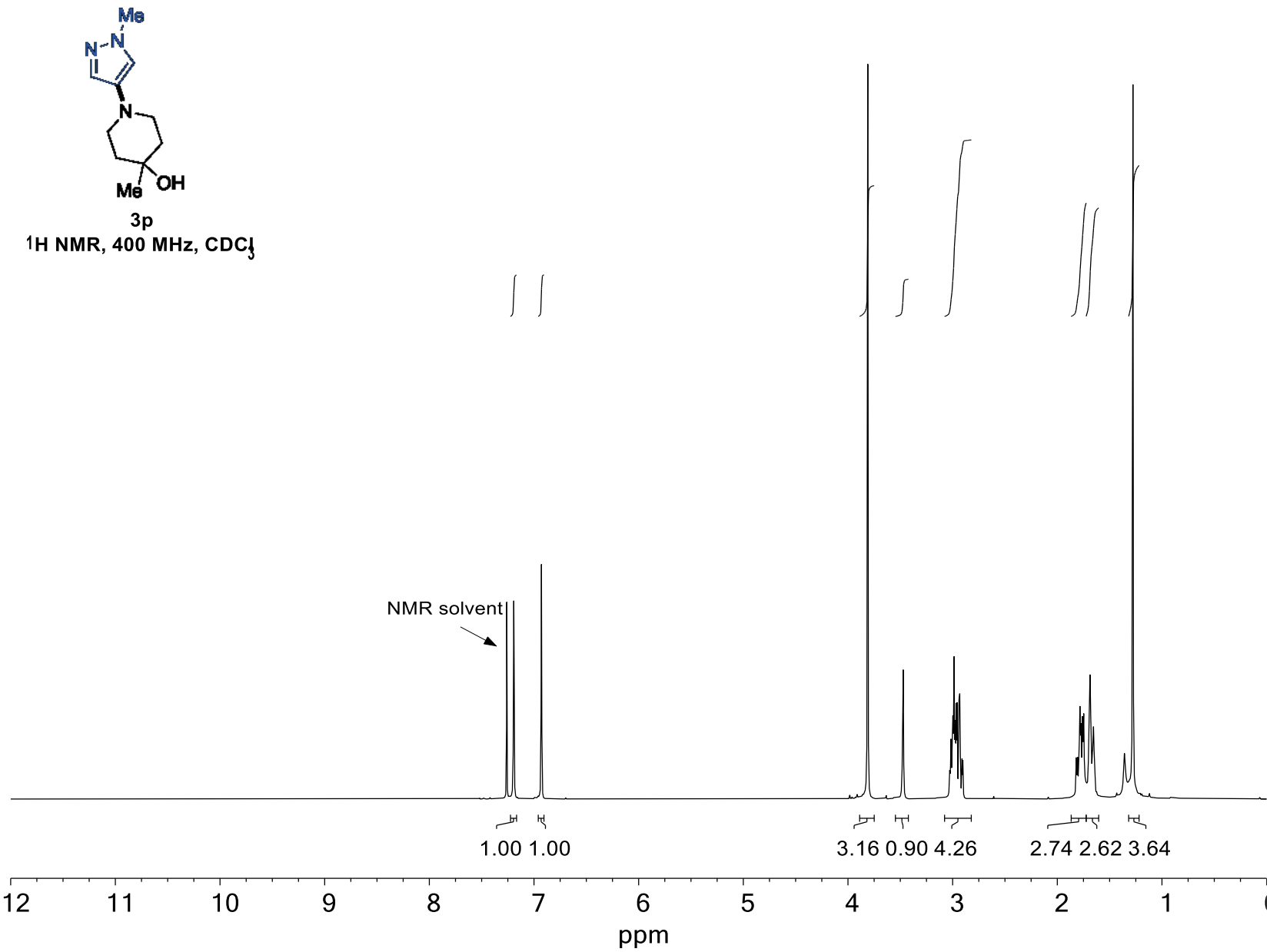
^{13}C NMR, 101 MHz, $CDCl_3$

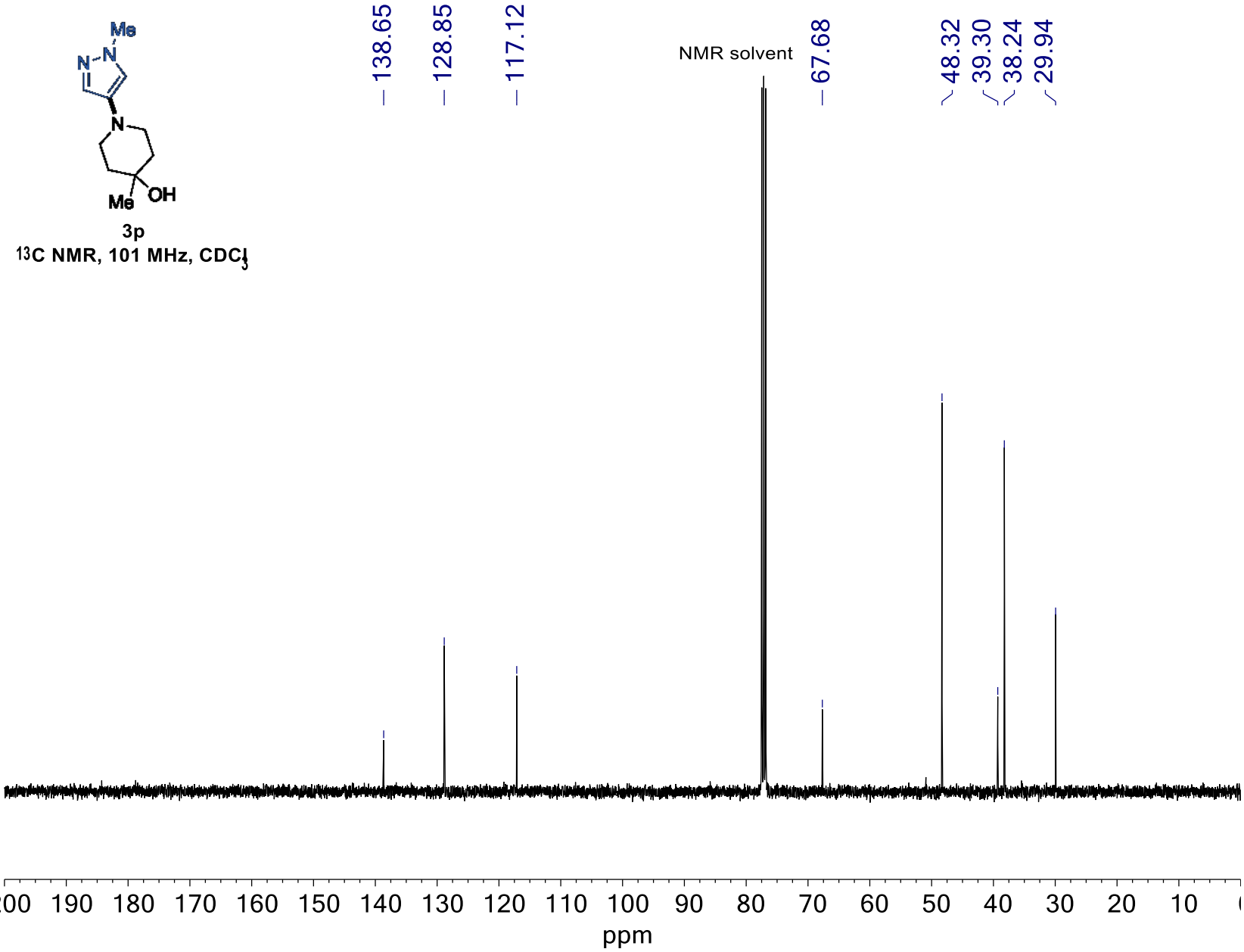


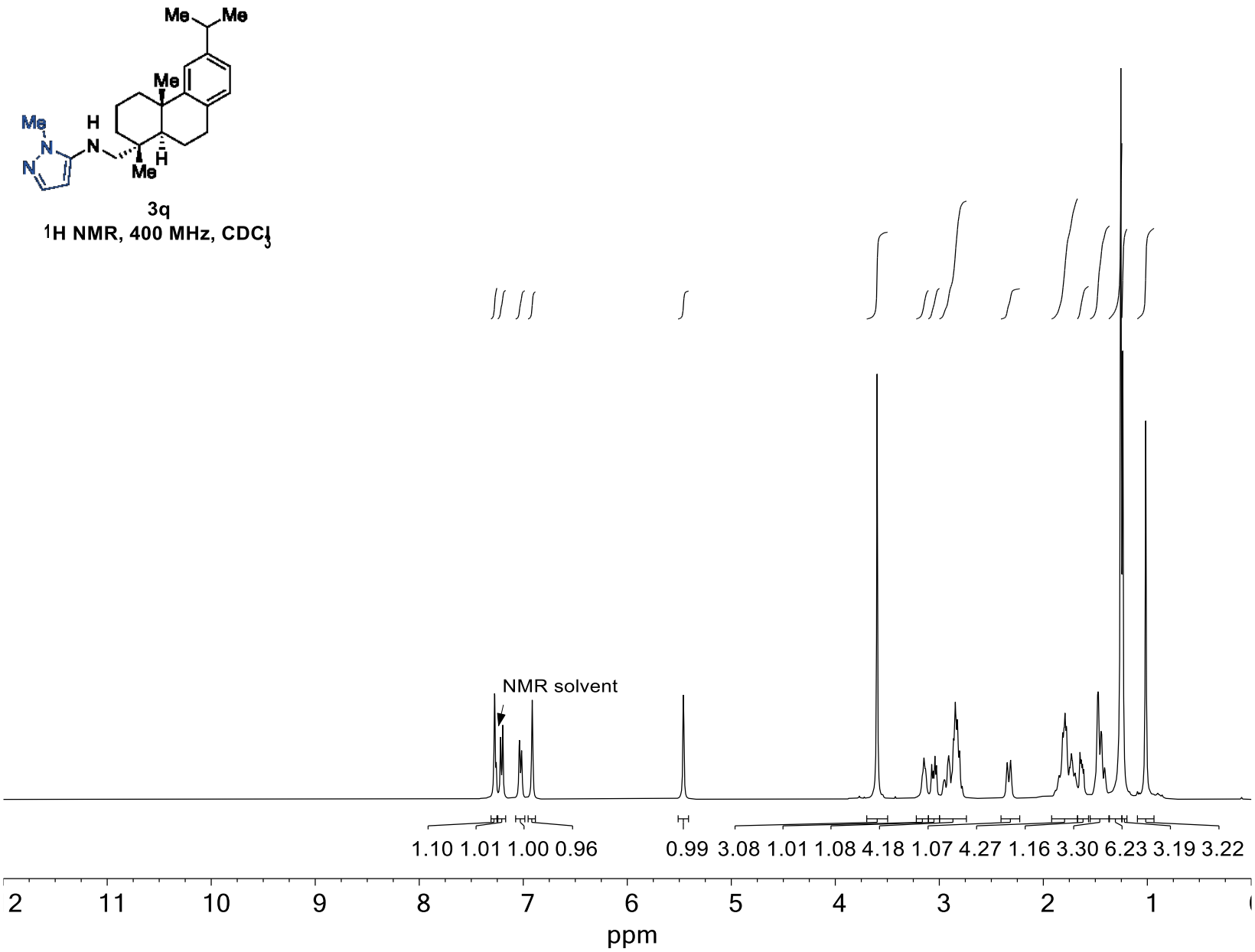
3o

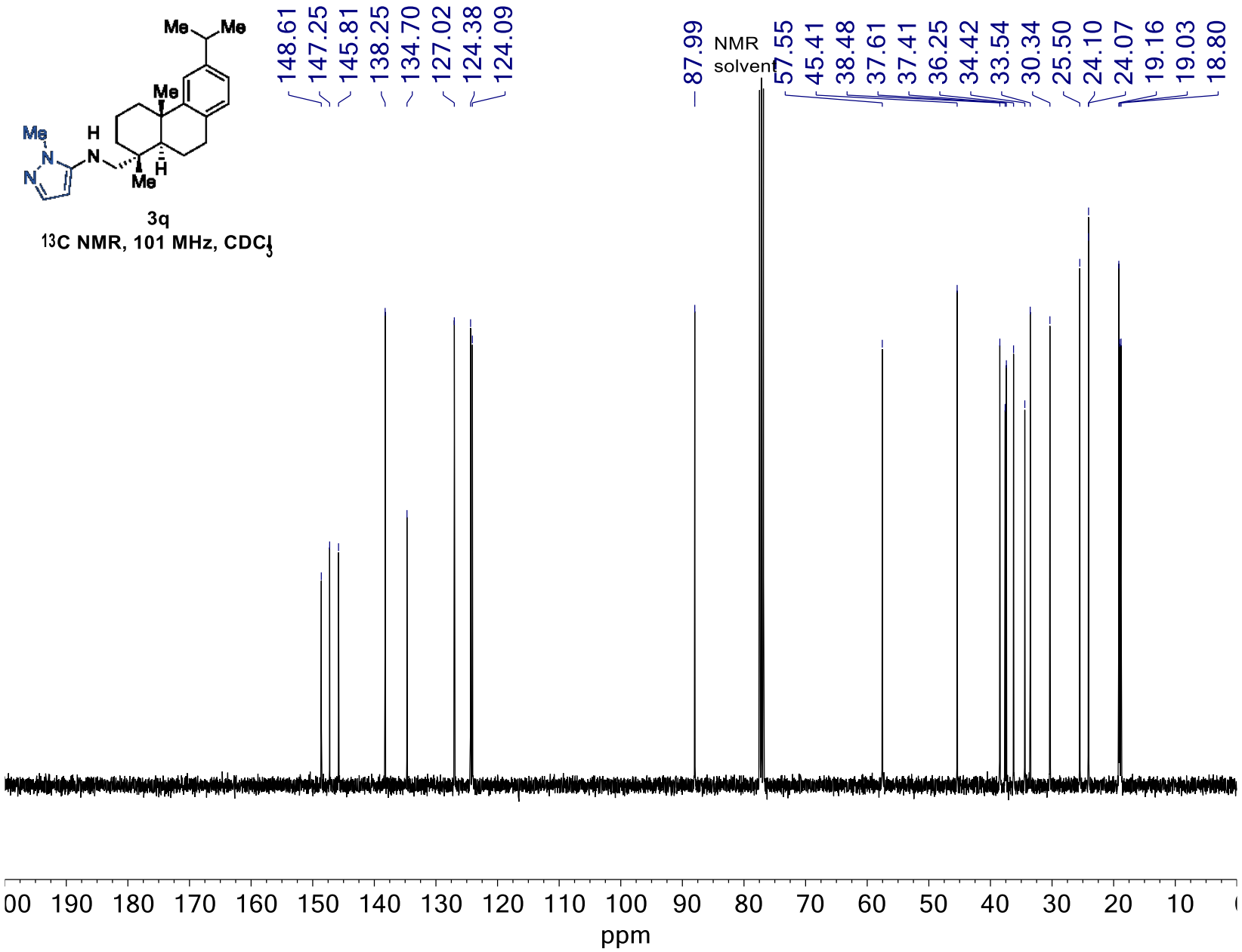
^{1}H NMR, 400 MHz, $CDCl_3$

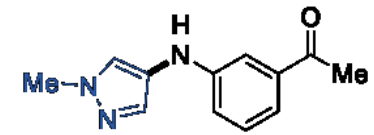

Me
N
N
Me
Me
Me
3o
13C NMR, 101 MHz, CDCl3
159.20
130.97
90.11
49.70
38.71
29.79
20.51
14.20
NMR solvent
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


Me
N
N
N
Me
OH
3p
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00 1.00
3.16 0.90 4.26
2.74 2.62 3.64
12
11
10
9
8
7
6
5
4
3
2
1
ppm


Me
N
N
N
Me
OH
3p
13C NMR, 101 MHz, CDCl3
138.65
128.85
117.12
NMR solvent
67.68
48.32
39.30
38.24
29.94
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

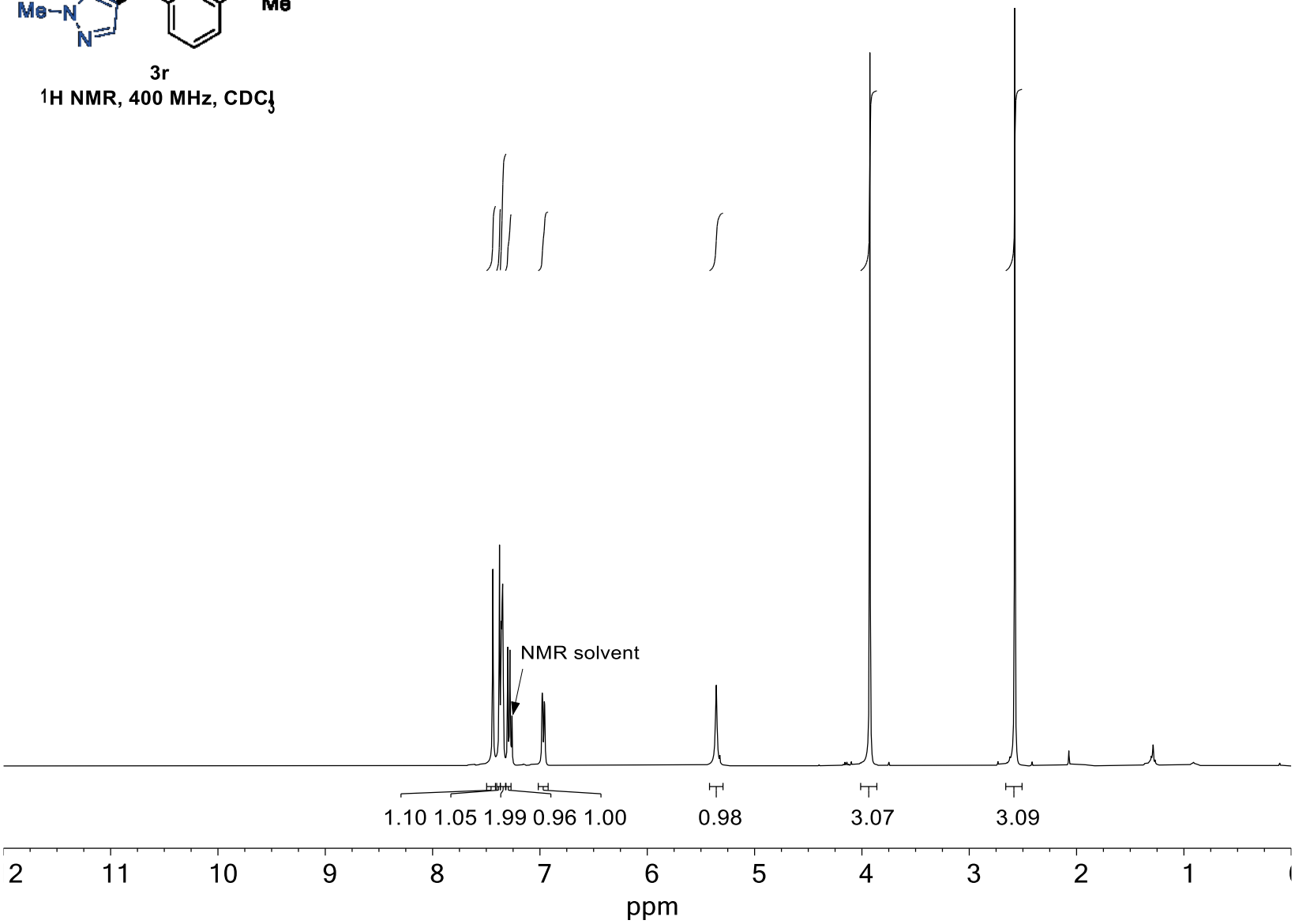

Me
Me
Me
H
N
Me
N
N
H
Me
3q
1H NMR, 400 MHz, CDCl3
NMR solvent
1.10 1.01 1.00 0.96
0.99 3.08 1.01 1.08 4.18 1.07 4.27 1.16 3.30 6.23 3.19 3.22
2
11
10
9
8
7
6
5
4
3
2
1
ppm

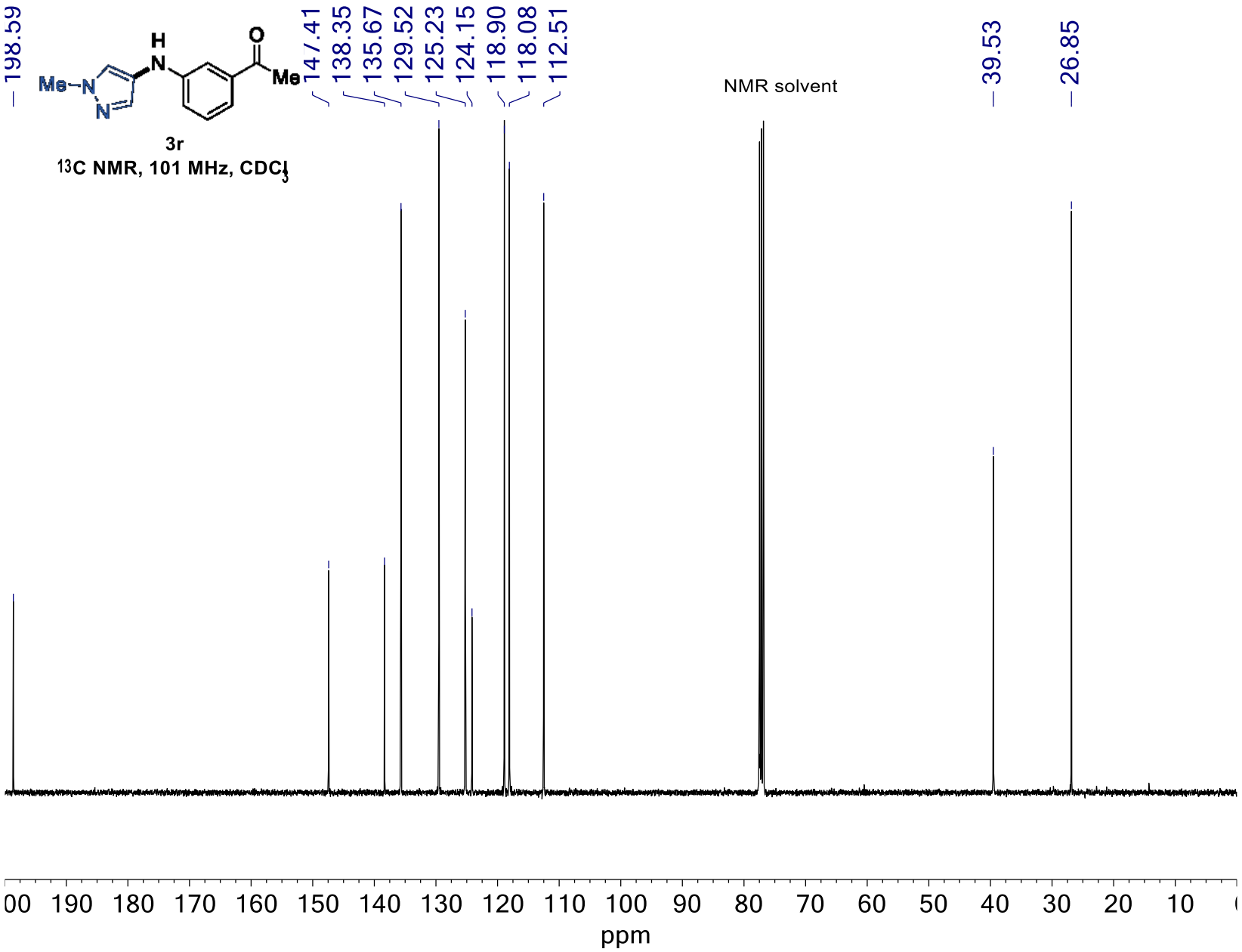

Me
Me
Me
H
N
N
N
Me
H
Me
3q
13C NMR, 101 MHz, CDCl3
148.61
147.25
145.81
138.25
134.70
127.02
124.38
124.09
87.99
NMR
solvent
57.55
45.41
38.48
37.61
37.41
36.25
34.42
33.54
30.34
25.50
24.10
24.07
19.16
19.03
18.80
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

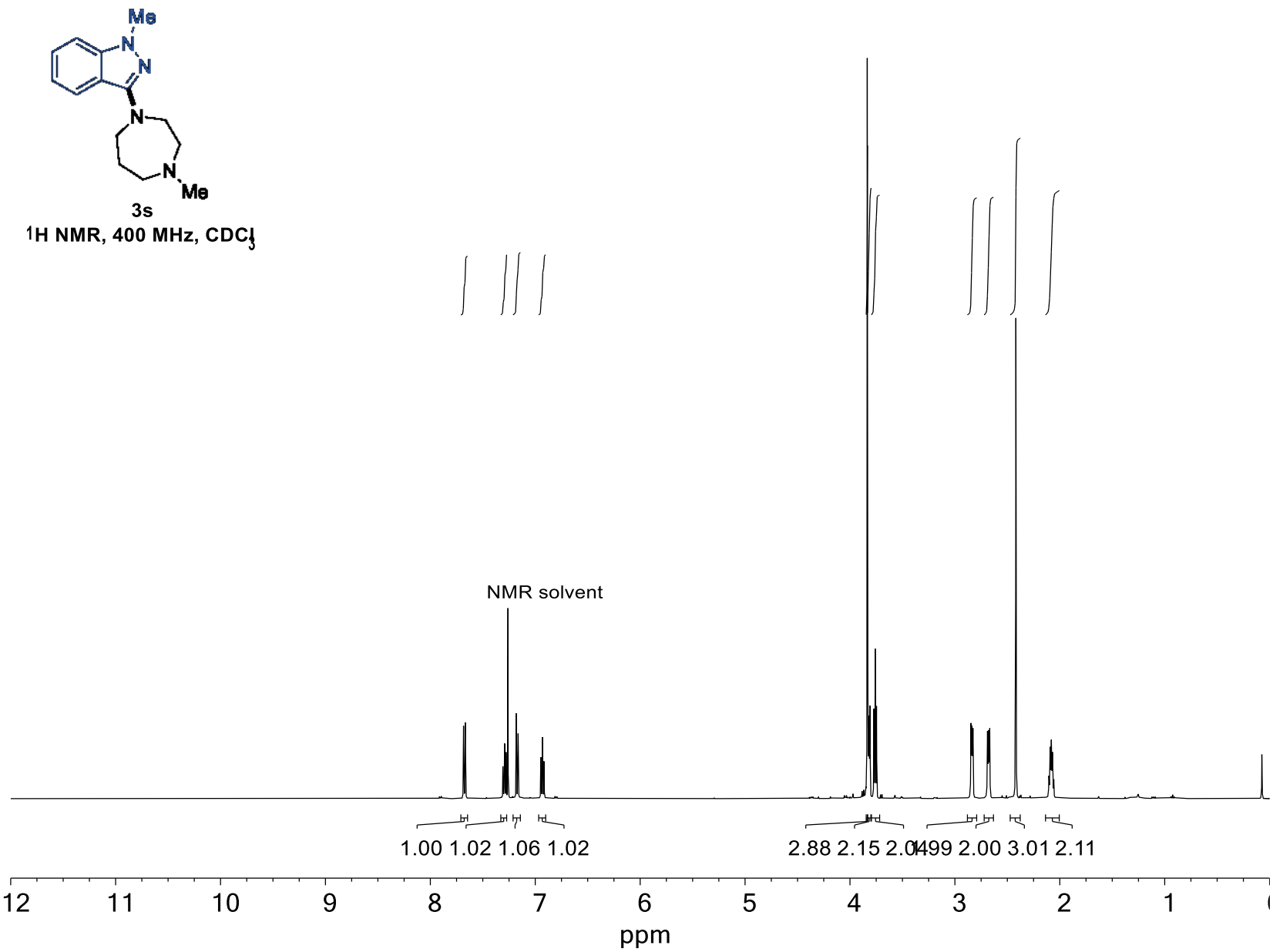


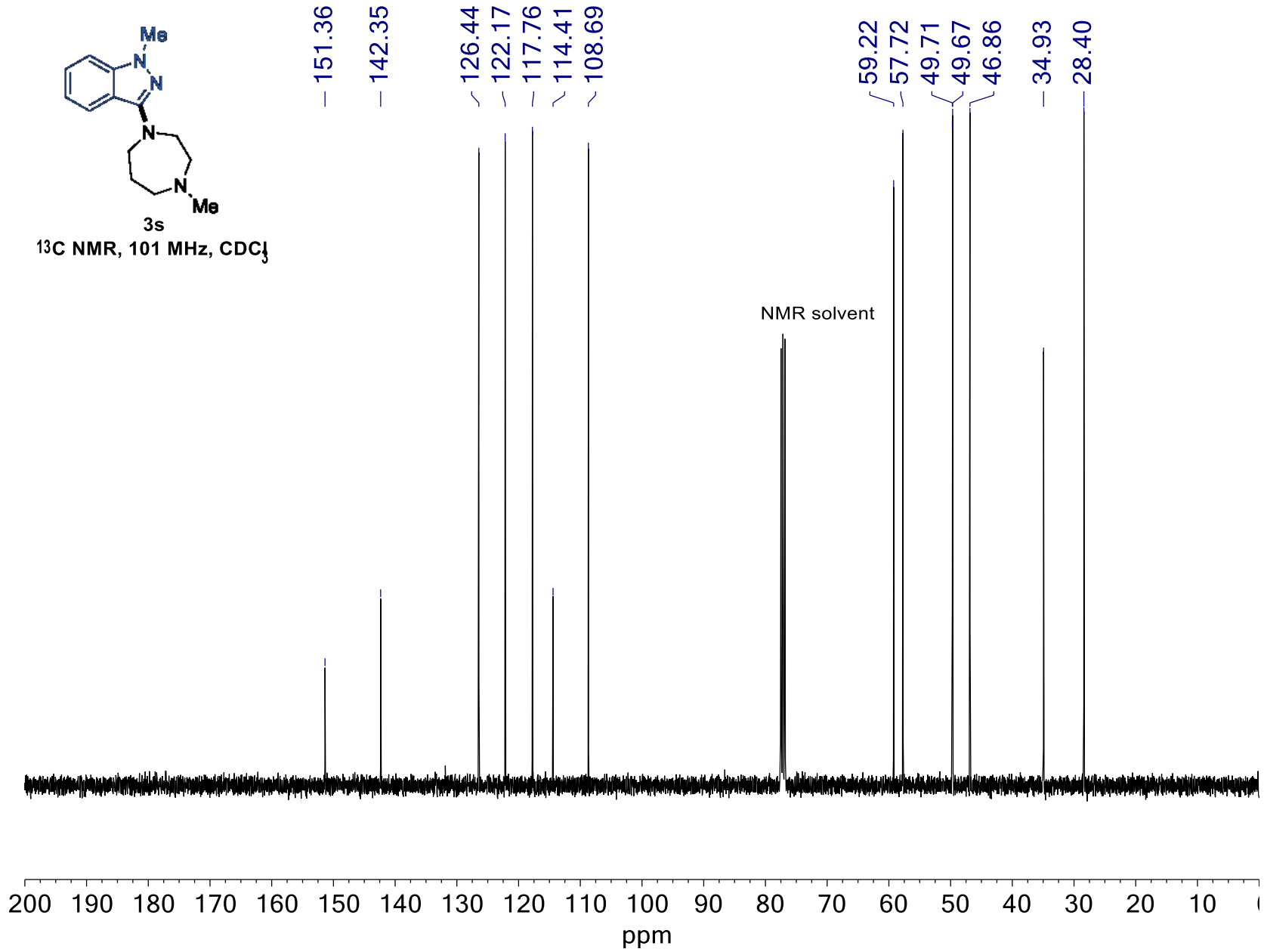
3r

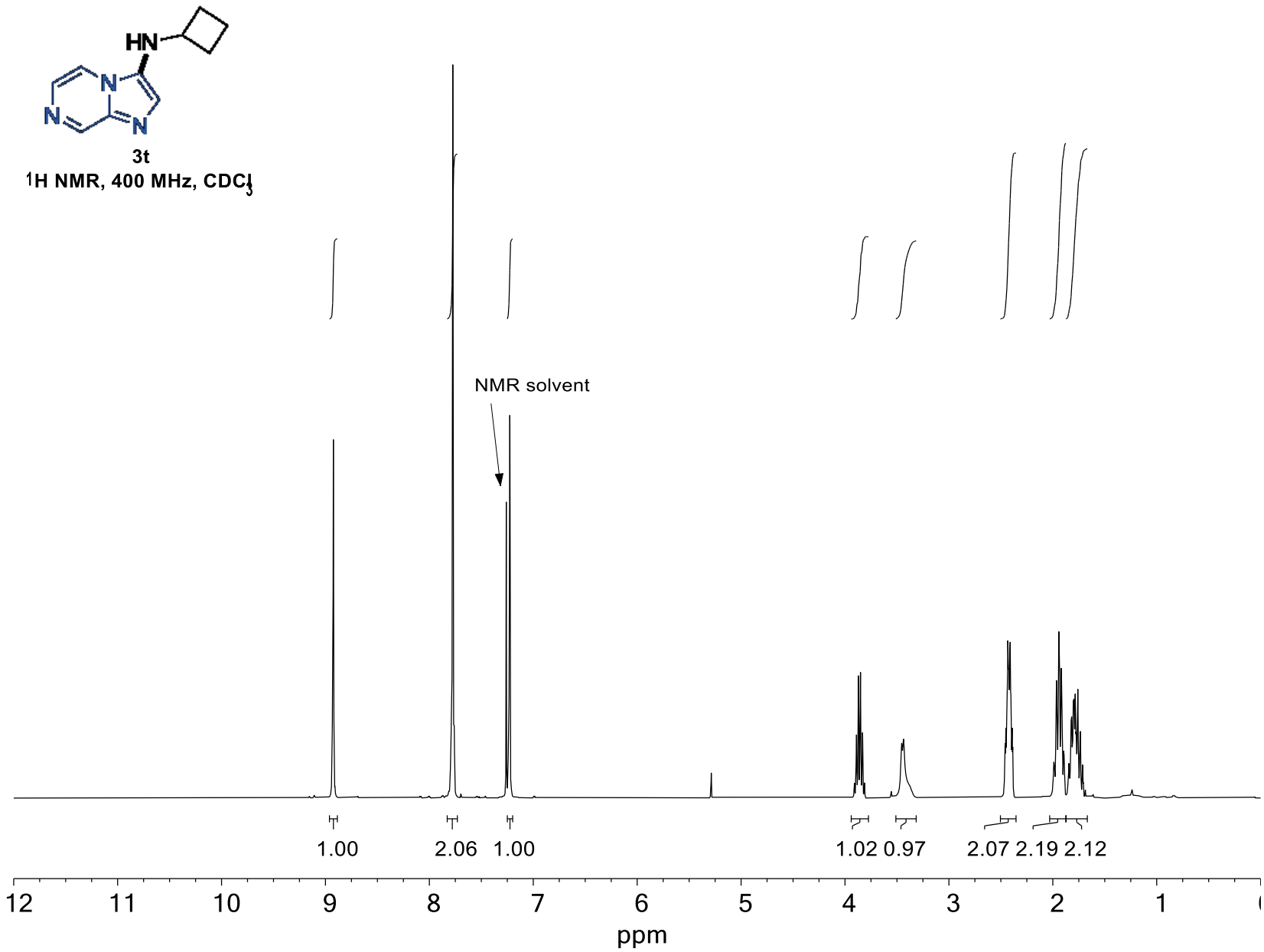
^{1}H NMR, 400 MHz, $CDCl_3$

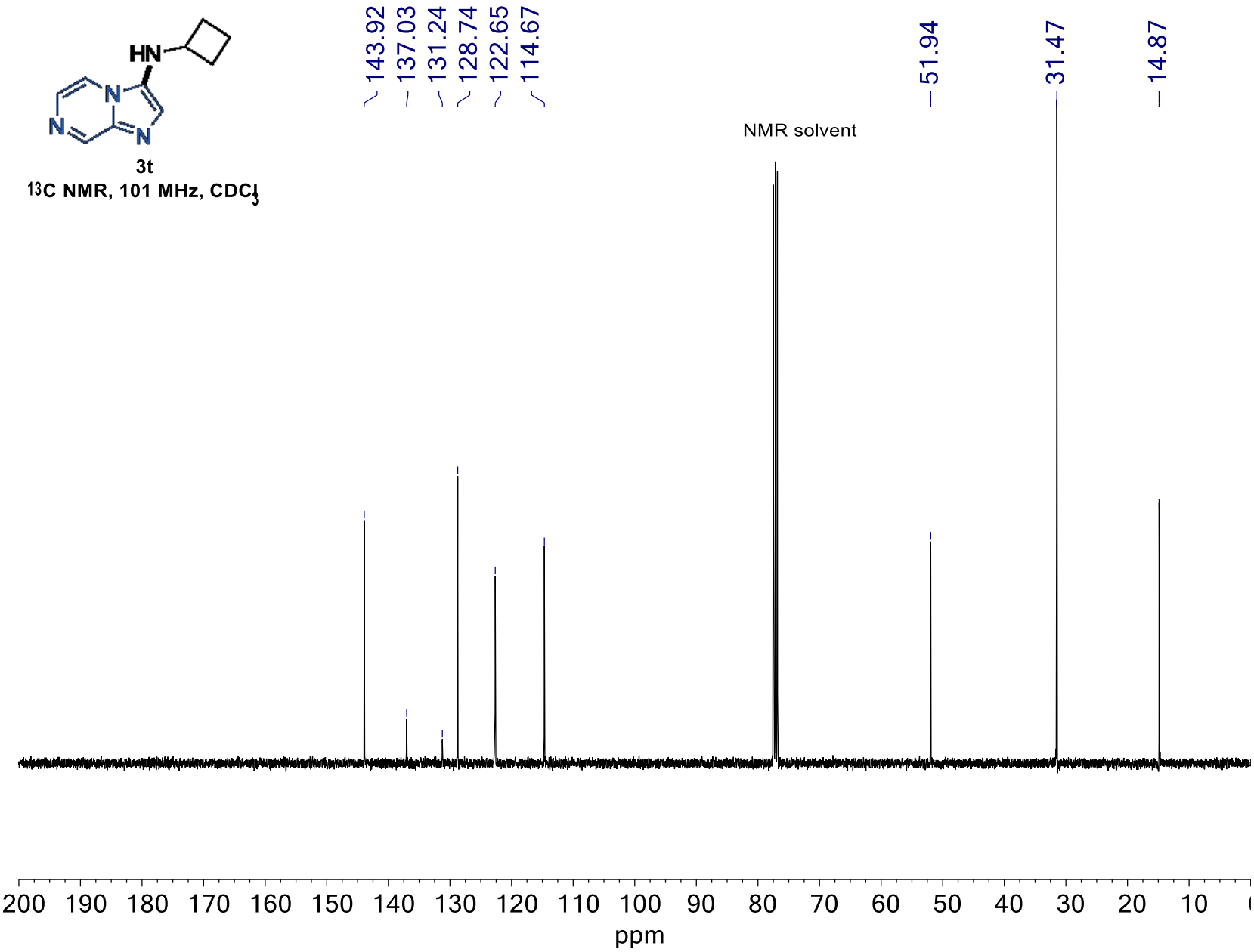


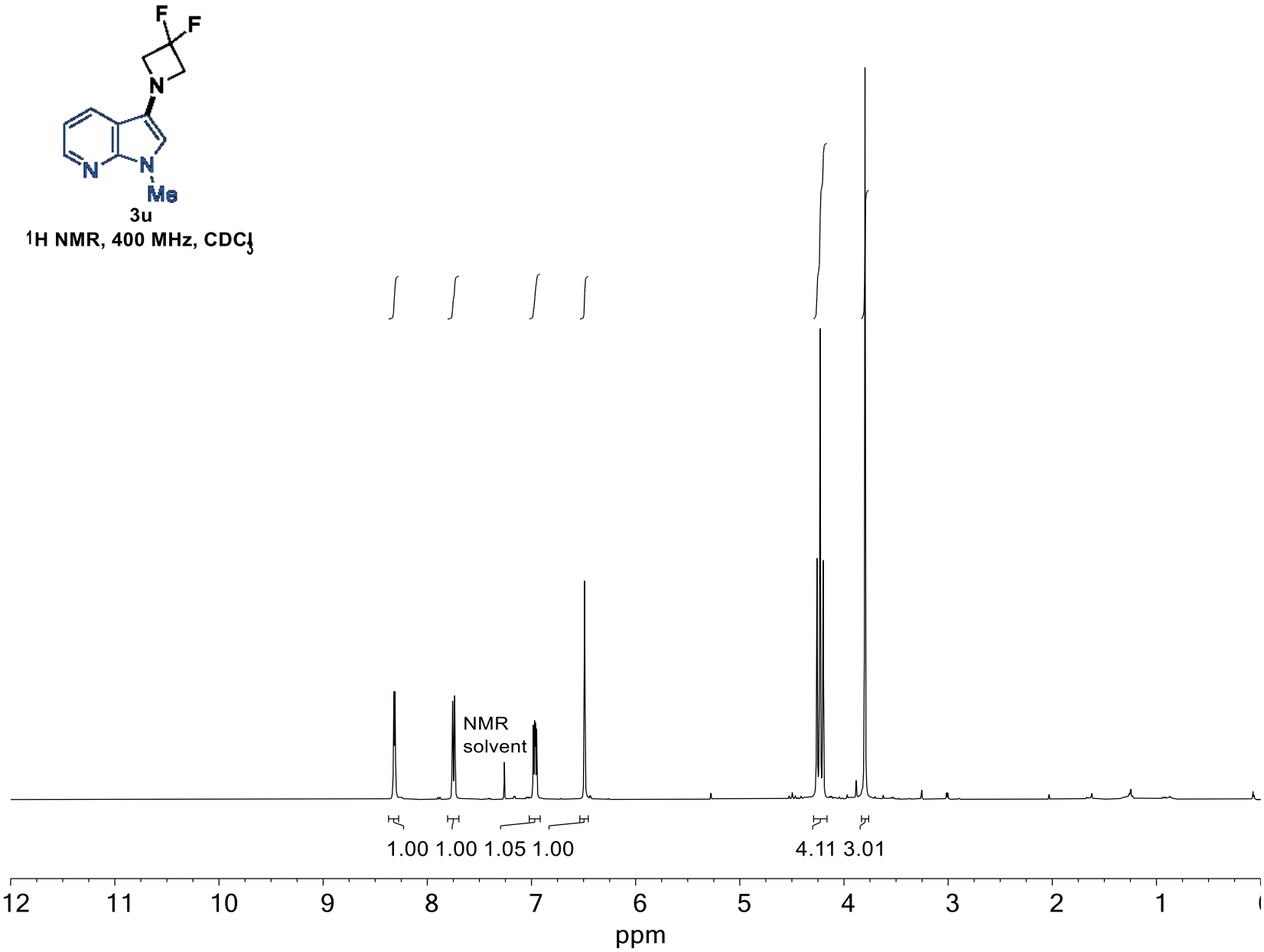

198.59
147.41
138.35
135.67
129.52
125.23
124.15
118.90
118.08
112.51
NMR solvent
39.53
26.85
Me
N
H
N
Me
N
3r
13C NMR, 101 MHz, CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

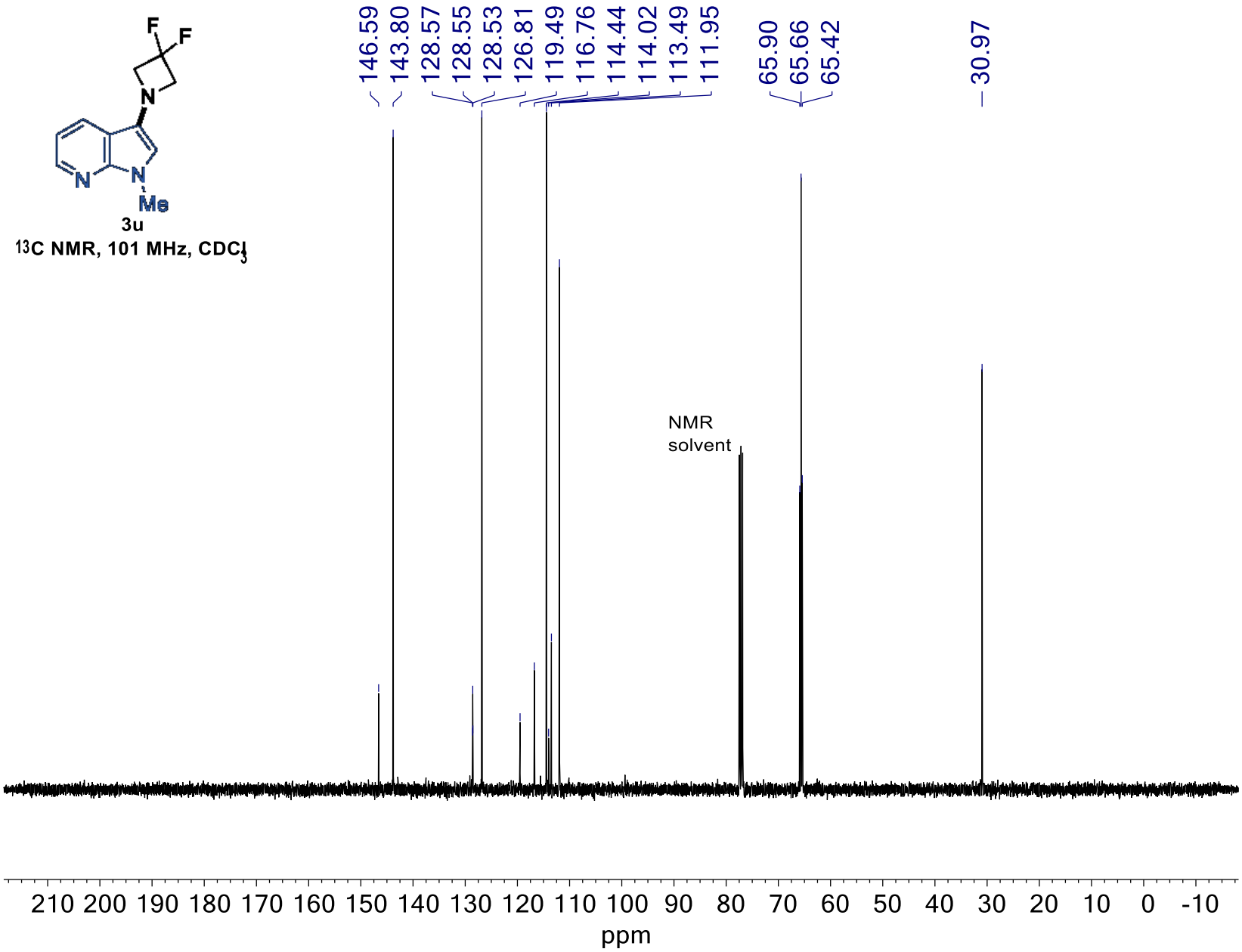

Me
N
N
N
N
Me
3s
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00 1.02 1.06 1.02
2.88 2.15 2.01 4.99 2.00 3.01 2.11
12
11
10
9
8
7
6
5
4
3
2
1
ppm

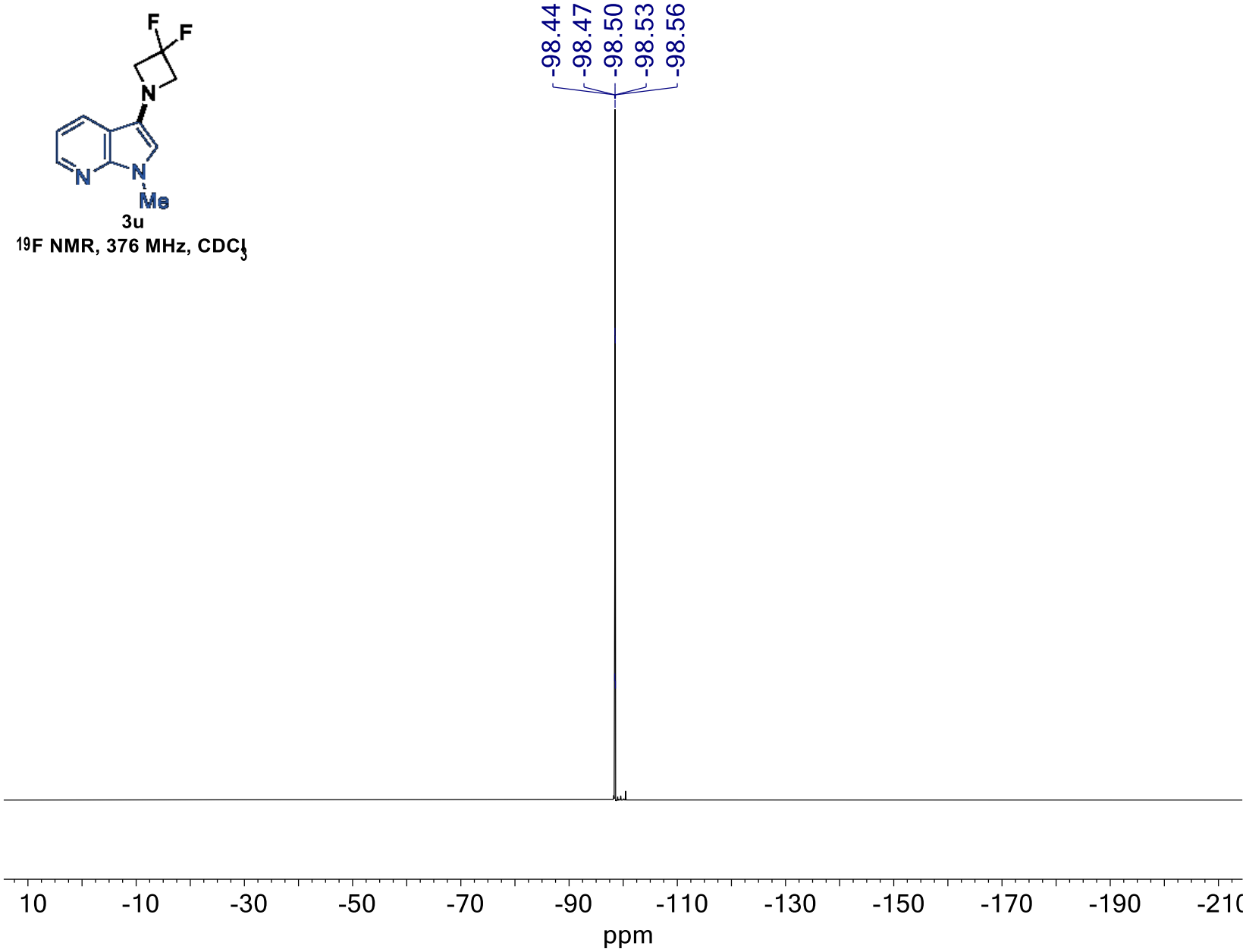

Me
N
N
N
N
Me
3s
13C NMR, 101 MHz, CDCl3
151.36
142.35
126.44
122.17
117.76
114.41
108.69
59.22
57.72
49.71
49.67
46.86
34.93
28.40
NMR solvent
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


HN
N
N
N
3t
1H NMR, 400 MHz, CDCl3
NMR solvent
1.00
2.06
1.00
1.02
0.97
2.07
2.19
2.12
12
11
10
9
8
7
6
5
4
3
2
1
ppm


HN
N
N
N
3t
13C NMR, 101 MHz, CDCl3
143.92
137.03
131.24
128.74
122.65
114.67
51.94
31.47
14.87
NMR solvent
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

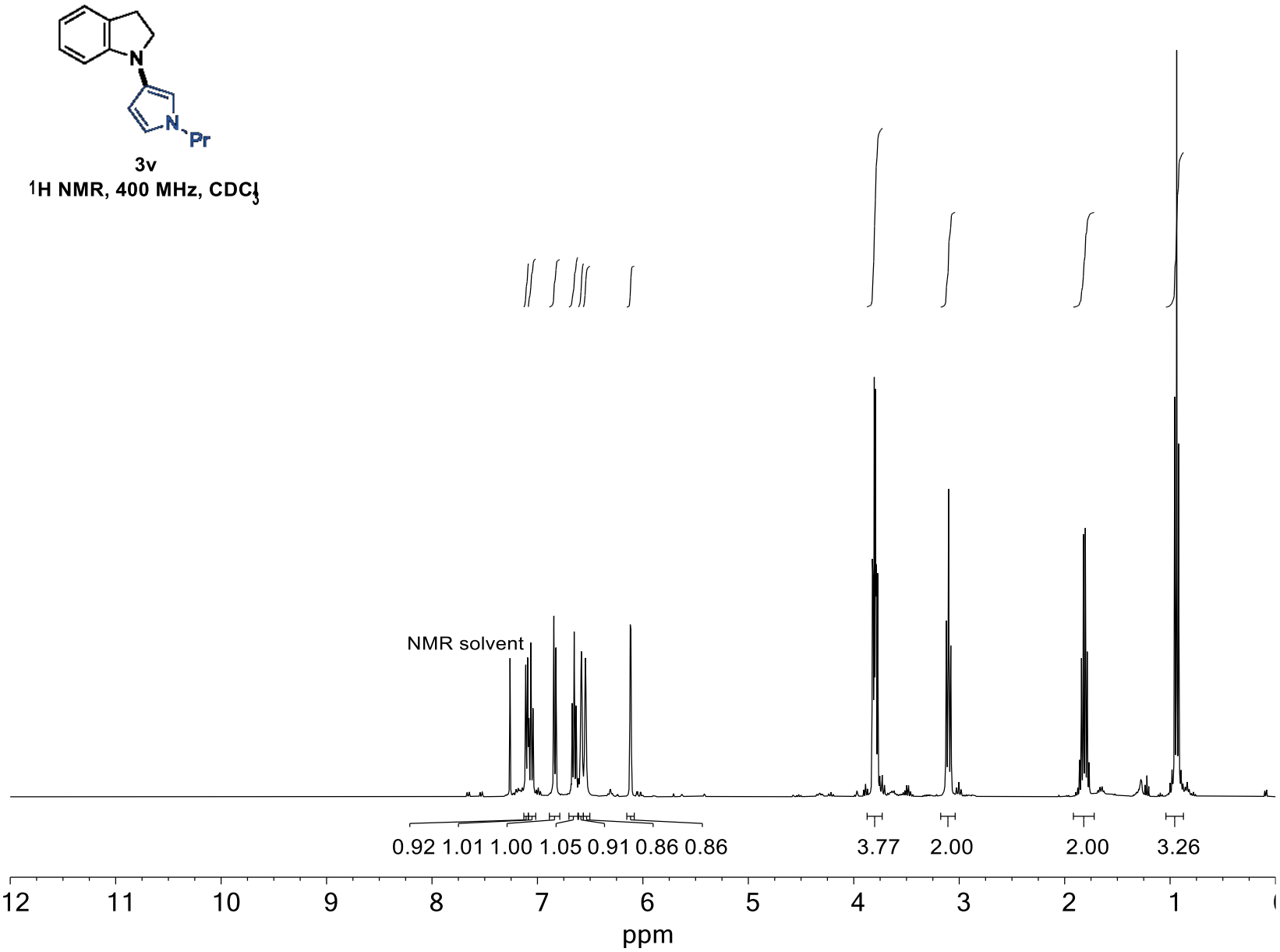

F
F
N
N
N
Me
3u
1H NMR, 400 MHz, CDCl3
NMR
solvent
1.00 1.00 1.05 1.00
4.11 3.01
12
11
10
9
8
7
6
5
4
3
2
1
ppm

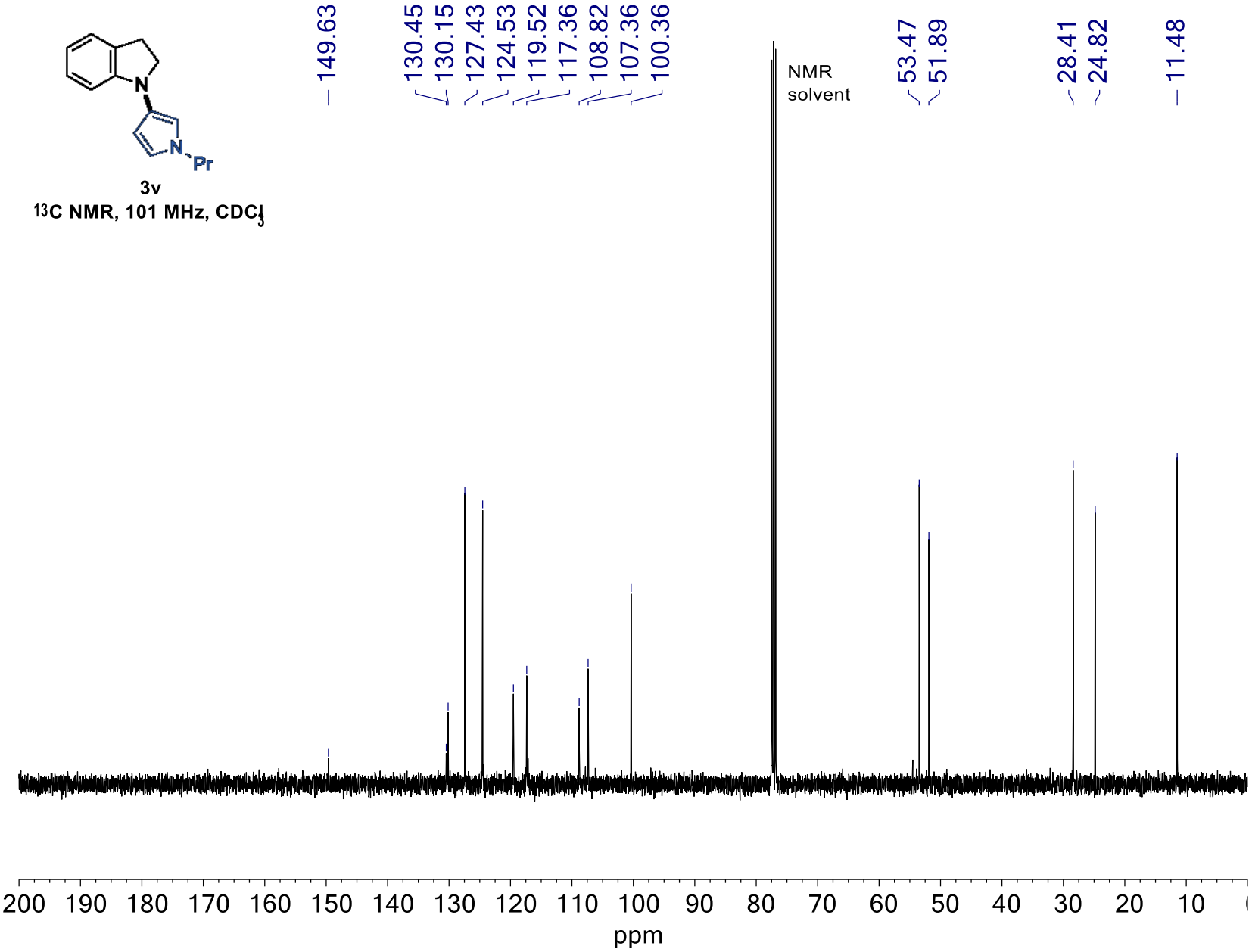

F
F
N
N
N
Me
3u
13C NMR, 101 MHz, CDCl3
146.59
143.80
128.57
128.55
128.53
126.81
119.49
116.76
114.44
114.02
113.49
111.95
65.90
65.66
65.42
30.97
NMR
solvent
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

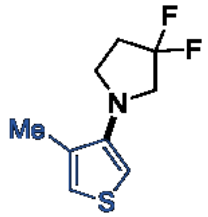


3u

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

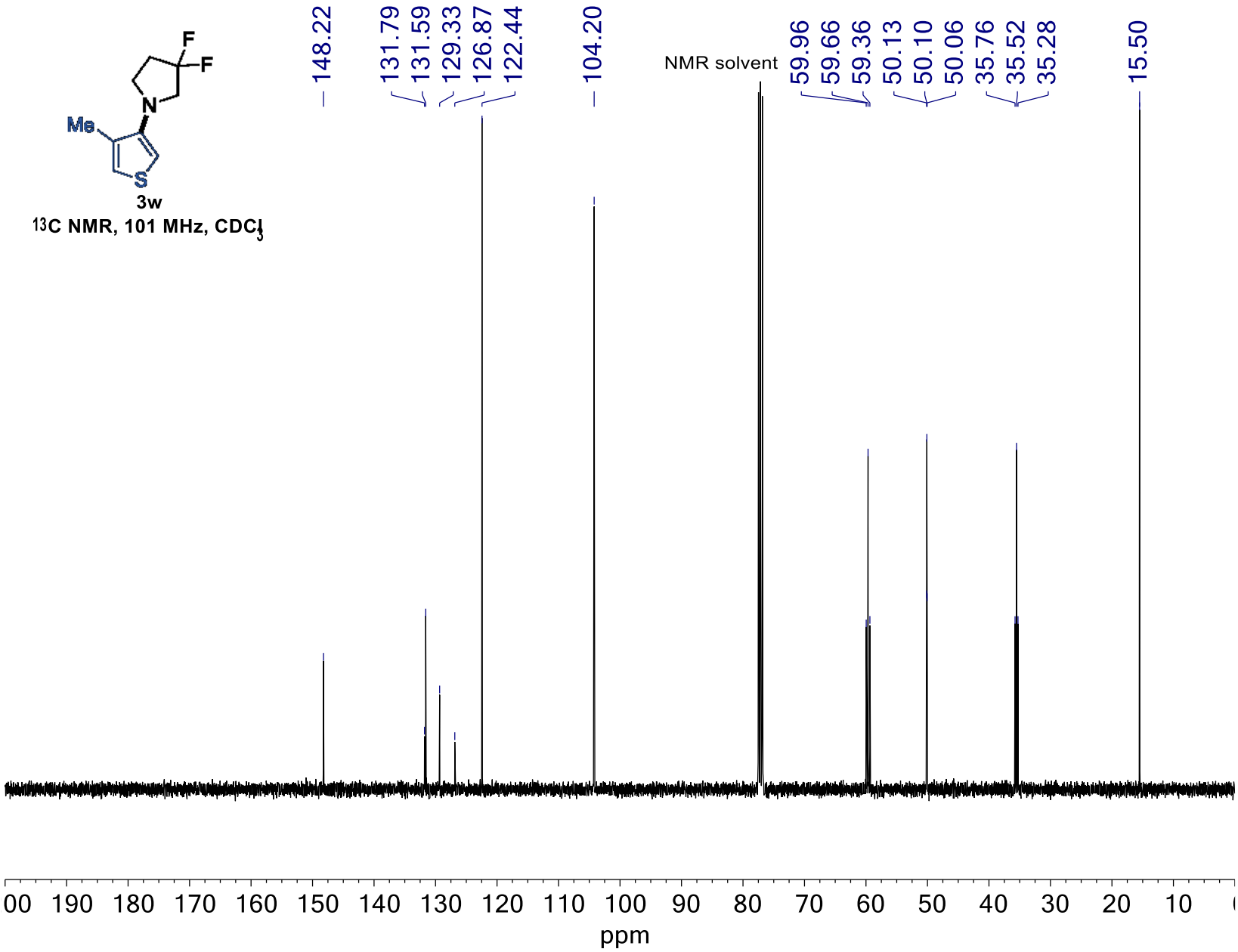

N
N
Pr
3v
1H NMR, 400 MHz, CDCl3
NMR solvent
0.92 1.01 1.00 1.05 0.91 0.86 0.86
3.77
2.00
2.00
3.26
12
11
10
9
8
7
6
5
4
3
2
1
ppm

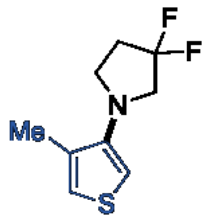

149.63
130.45
130.15
127.43
124.53
119.52
117.36
108.82
107.36
100.36
NMR
solvent
53.47
51.89
28.41
24.82
11.48
N
N
Pr
3v
13C NMR, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



3w

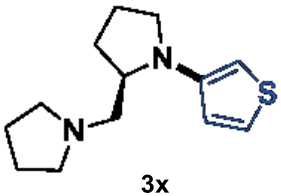
^{1}H NMR, 400 MHz, $CDCl_3$


F
F
N
Me
S
3w
13C NMR, 101 MHz, CDCl3
148.22
131.79
131.59
129.33
126.87
122.44
104.20
NMR solvent
59.96
59.66
59.36
50.13
50.10
50.06
35.76
35.52
35.28
15.50
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



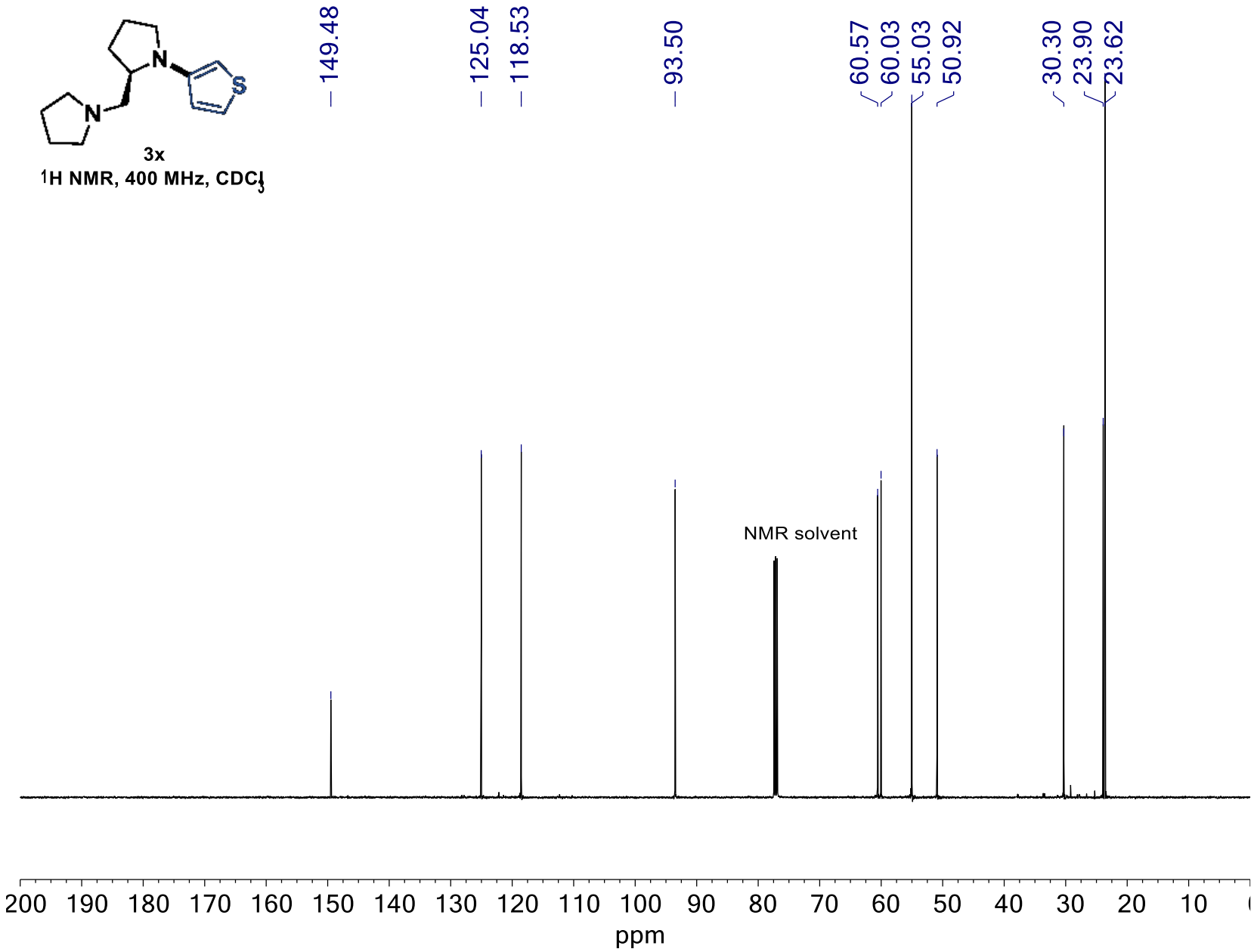
3w

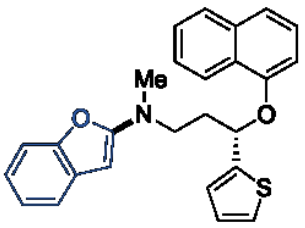
^{19}F NMR, 376 MHz, $CDCl_3$



3x

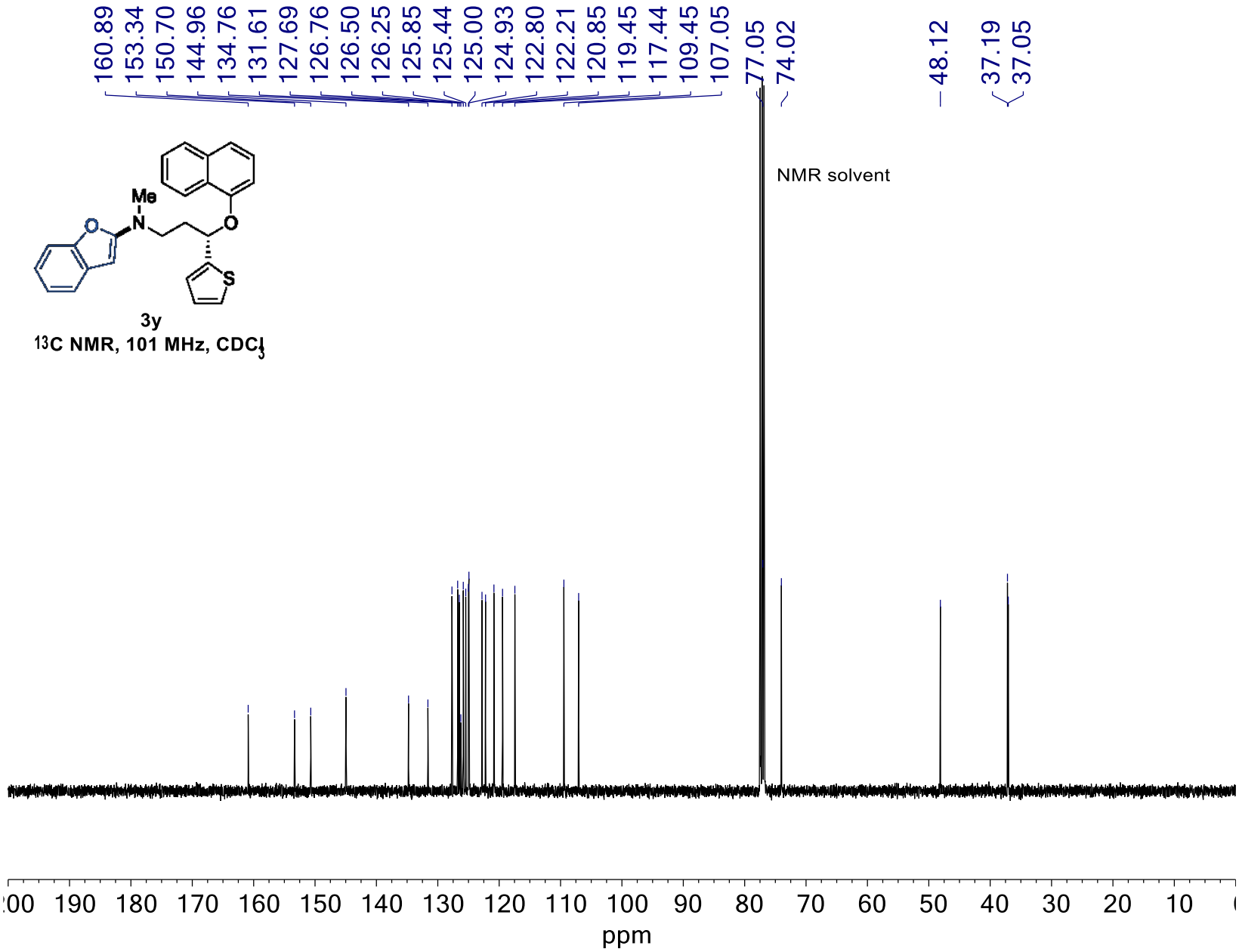
^{1}H NMR, 400 MHz, $CDCl_3$

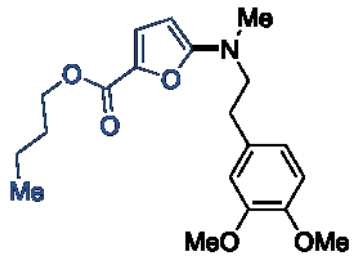

3x
1H NMR, 400 MHz, CDCl3
149.48
125.04
118.53
93.50
60.57
60.03
55.03
50.92
30.30
23.90
23.62
NMR solvent
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



3y

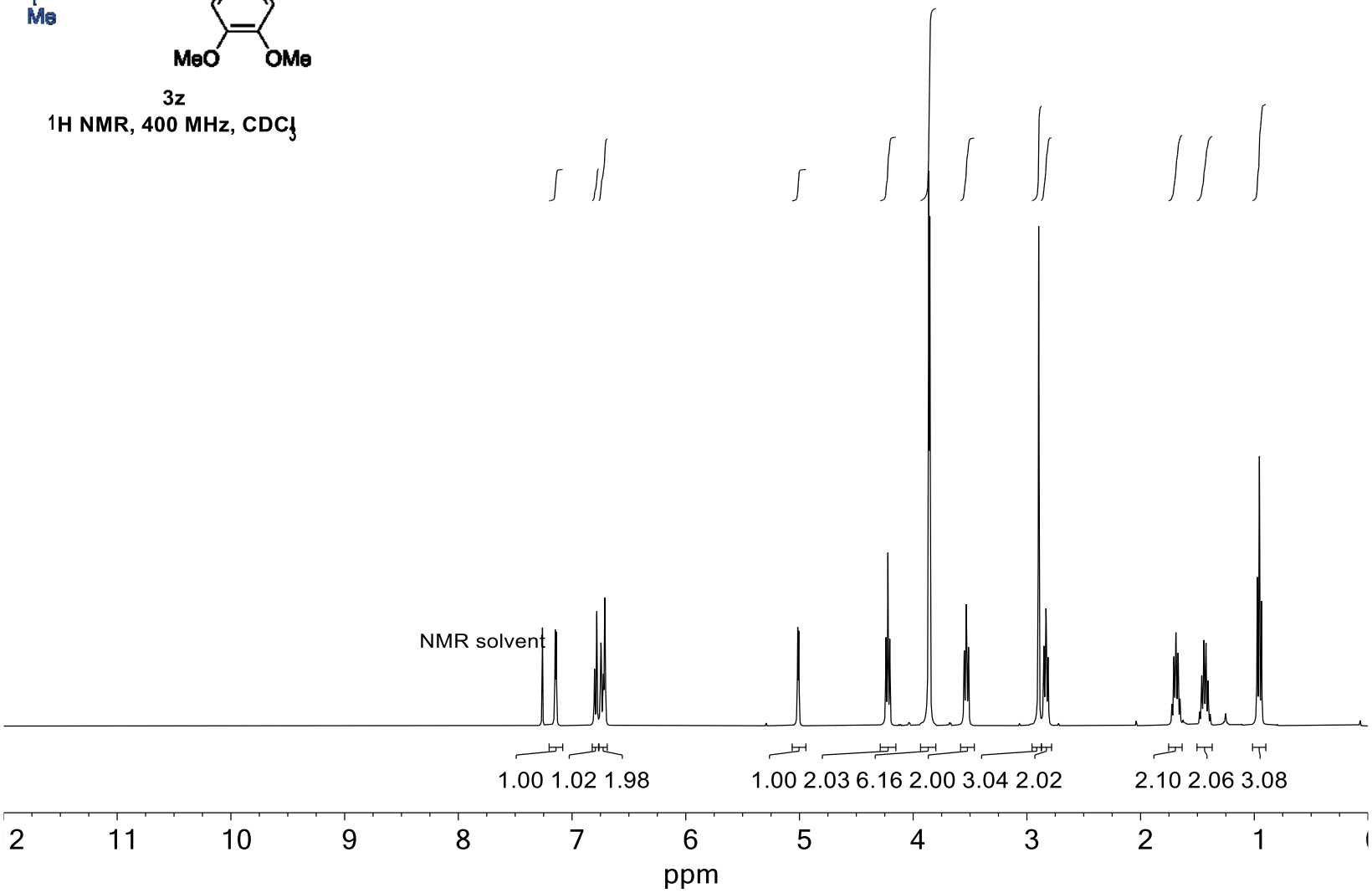
^{1}H NMR, 400 MHz, $CDCl_3$

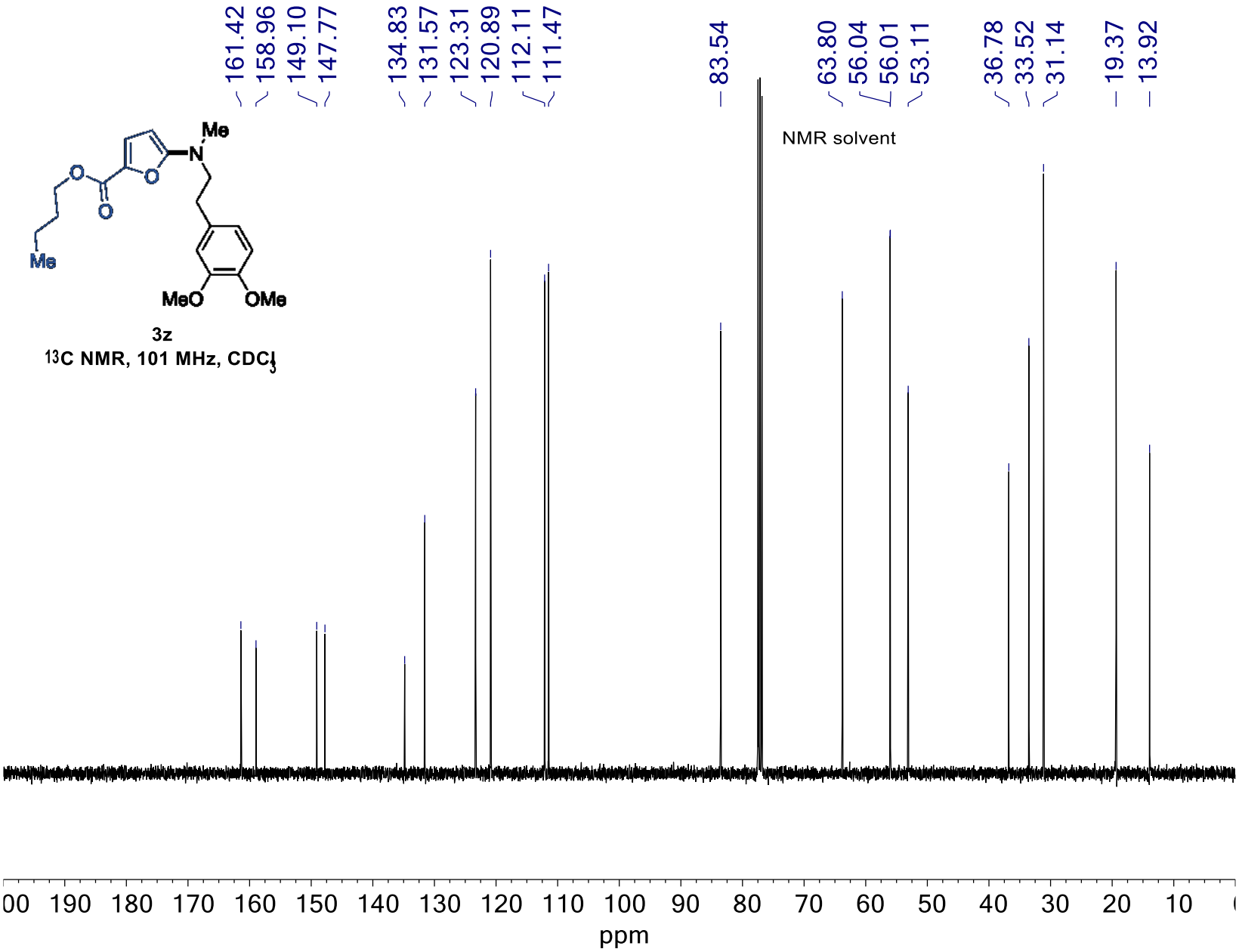

160.89
153.34
150.70
144.96
134.76
131.61
127.69
126.76
126.50
126.25
125.85
125.44
125.00
124.93
122.80
122.21
120.85
119.45
117.44
109.45
107.05
77.05
74.02
48.12
37.19
37.05
NMR solvent
Me
N
O
O
S
3y
13C NMR, 101 MHz, CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

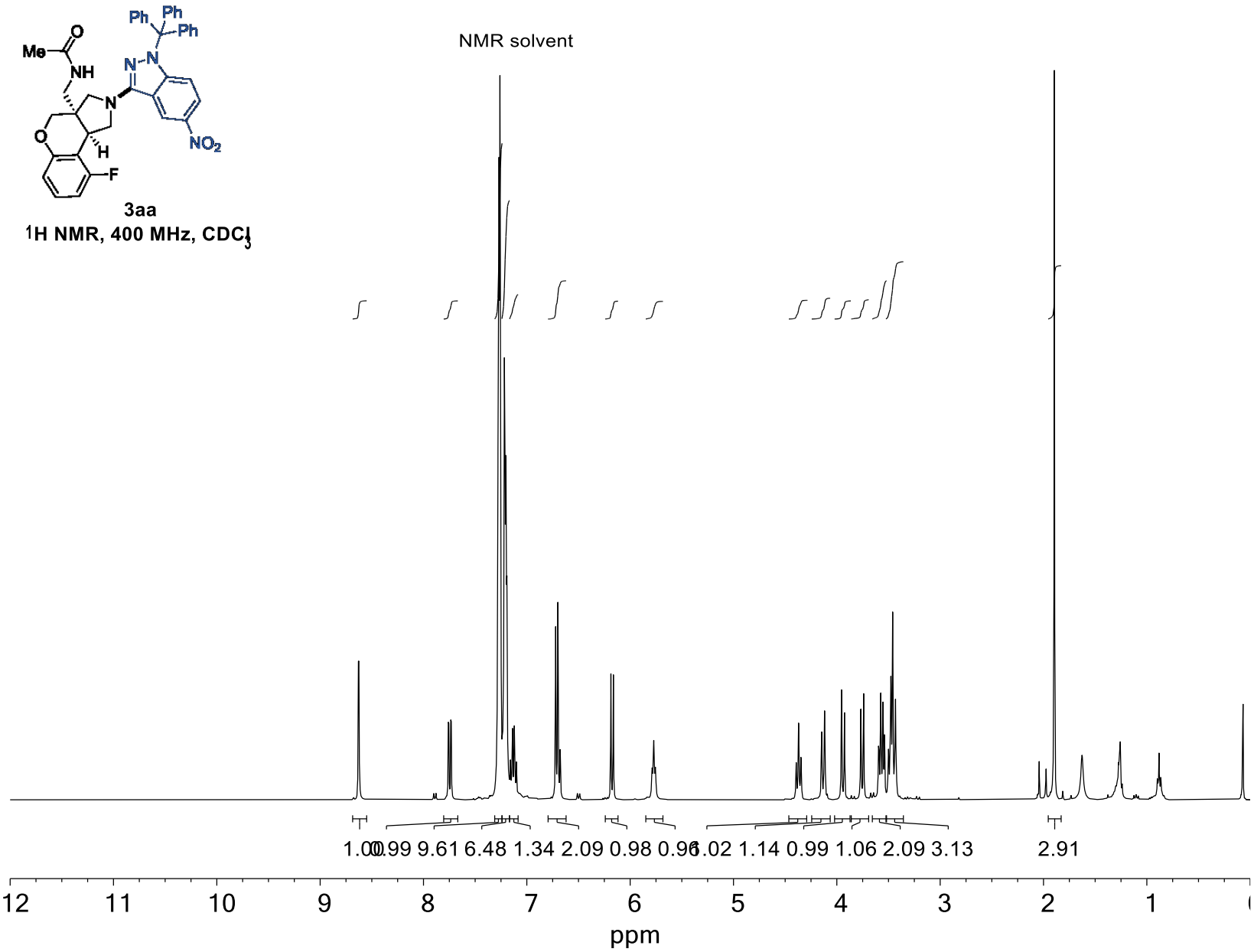


3z

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

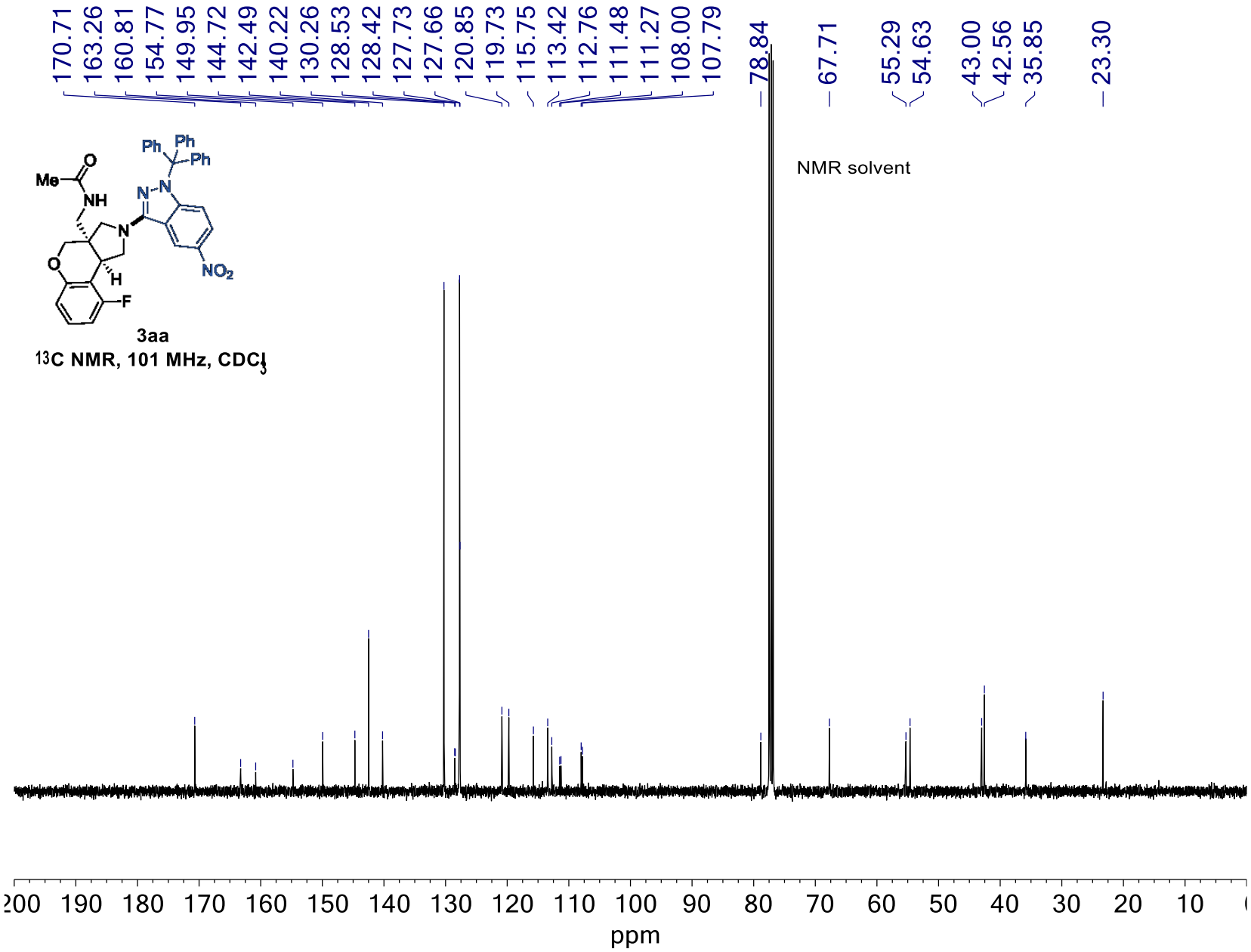


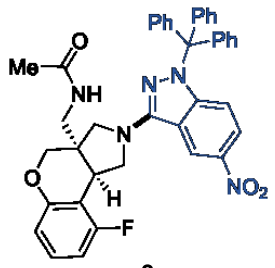

161.42
158.96
149.10
147.77
134.83
131.57
123.31
120.89
112.11
111.47
83.54
63.80
56.04
56.01
53.11
36.78
33.52
31.14
19.37
13.92
NMR solvent
Me
N
O
O
O
Me
MeO
OMe
3z
13C NMR, 101 MHz, CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



3aa

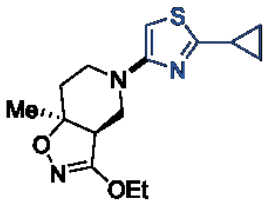
^{1}H NMR, 400 MHz, $CDCl_3$


170.71
163.26
160.81
154.77
149.95
144.72
142.49
140.22
130.26
128.53
128.42
127.73
127.66
120.85
119.73
115.75
113.42
112.76
111.48
111.27
108.00
107.79
78.84
67.71
55.29
54.63
43.00
42.56
35.85
23.30
NMR solvent
Me
O
NH
N
N
Ph
Ph
Ph
O
H
F
NO2
3aa
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
ppm



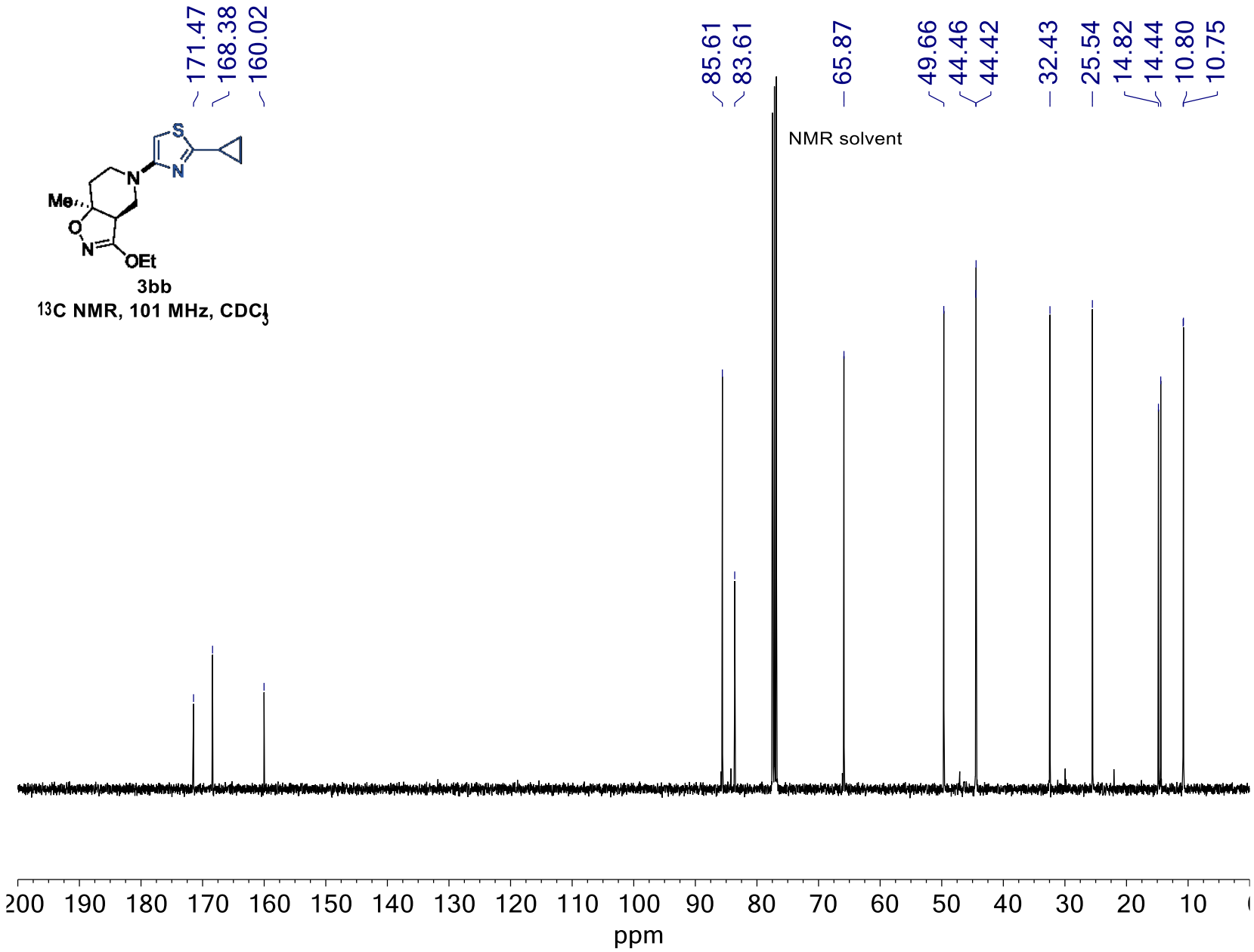
3aa

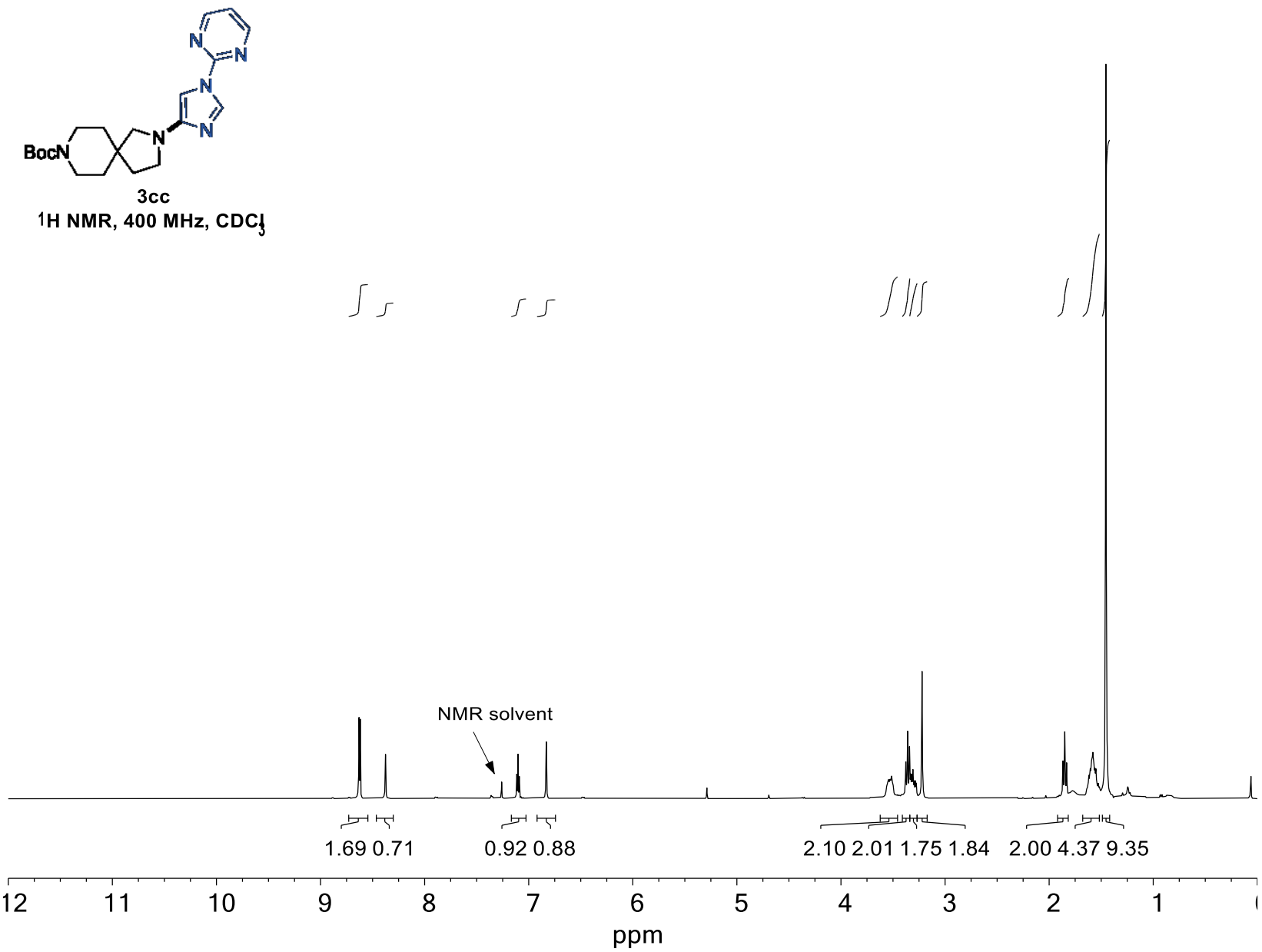
^{19}F NMR, 376 MHz, $CDCl_3$

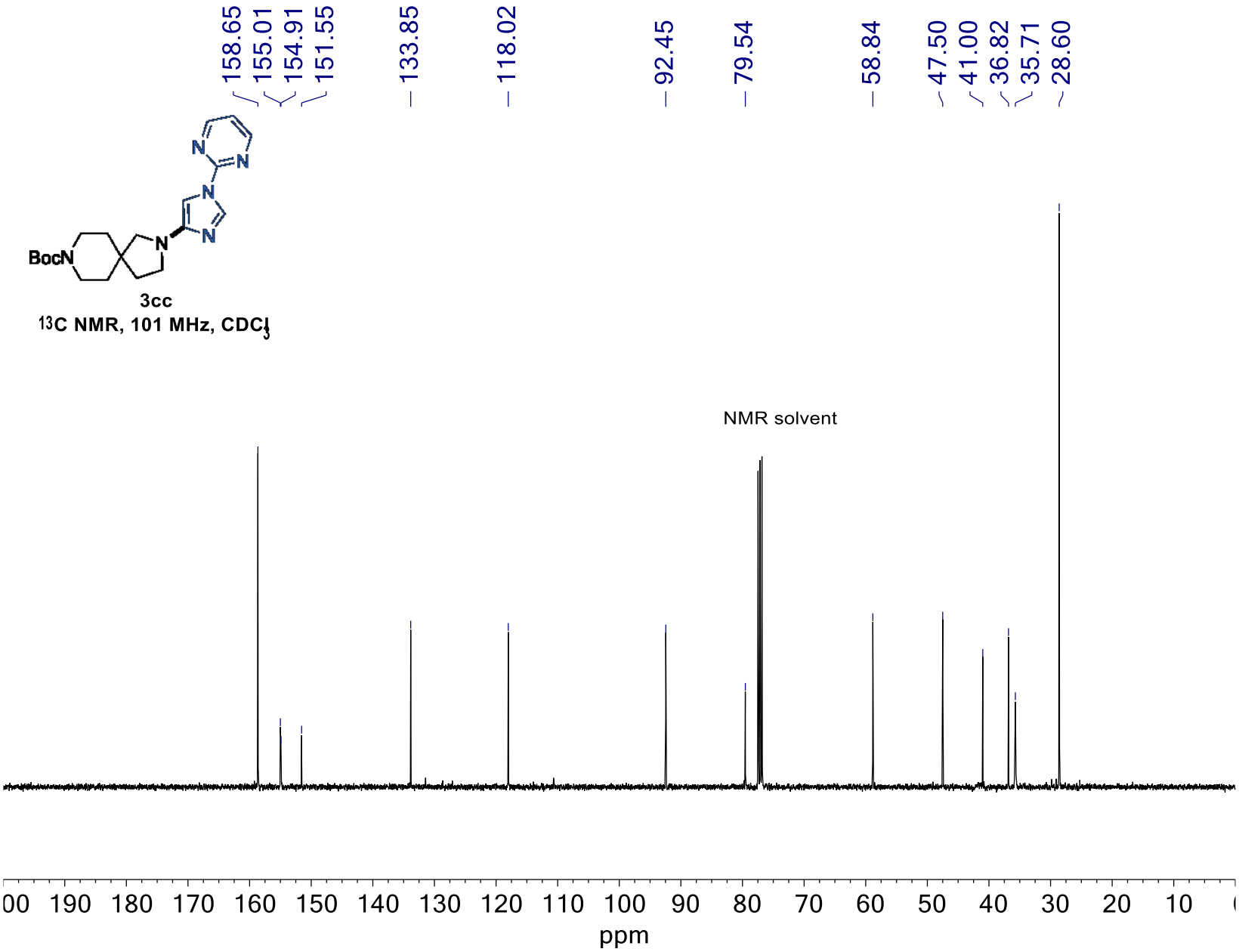


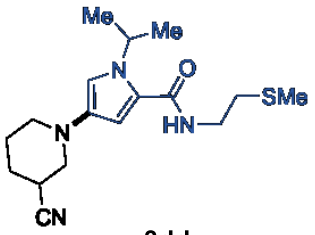
3bb

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


171.47
168.38
160.02
85.61
83.61
65.87
49.66
44.46
44.42
32.43
25.54
14.82
14.44
10.80
10.75
NMR solvent
Me
O
N
OEt
S
N
N
3bb
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
ppm

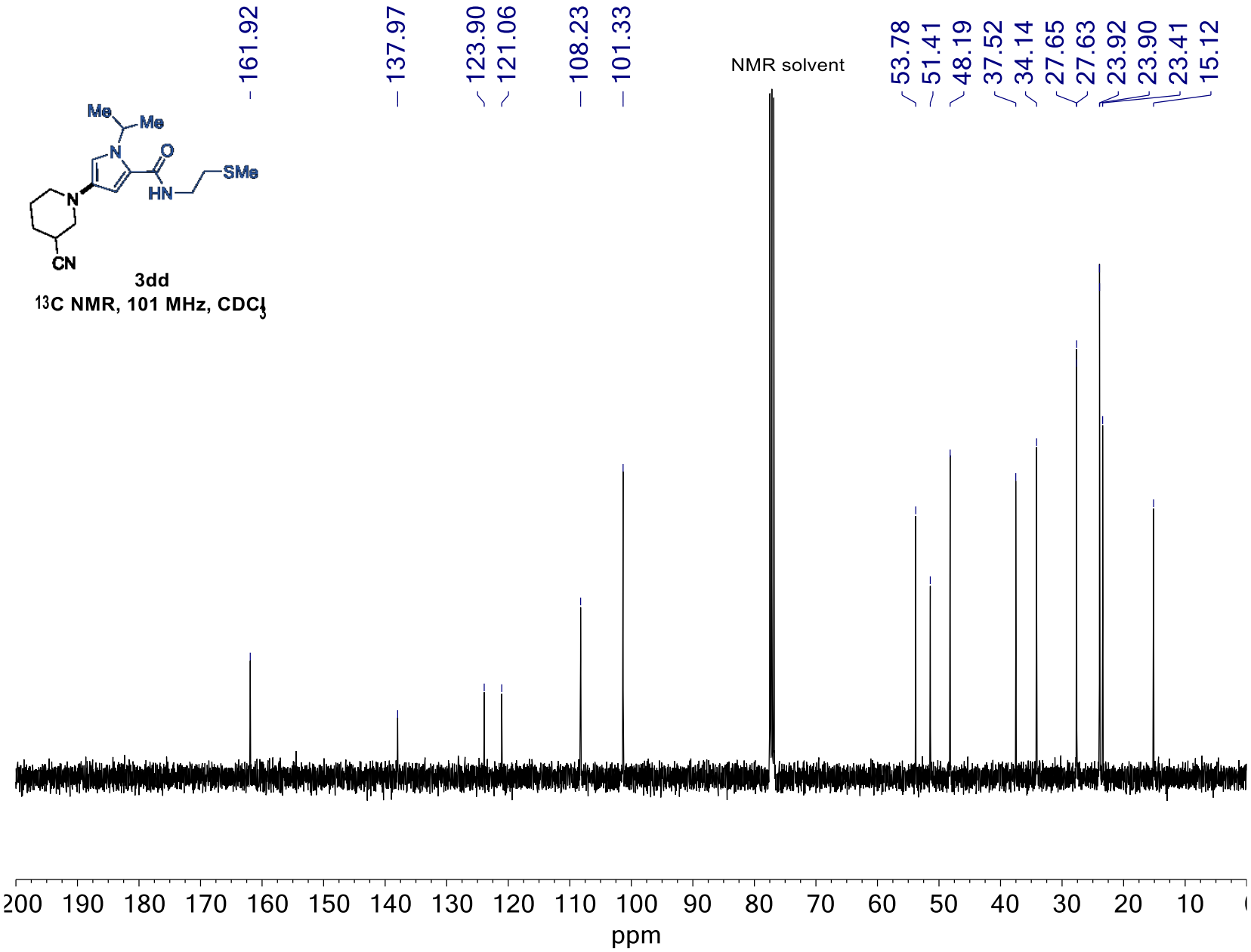

3cc
1H NMR, 400 MHz, CDCl3
NMR solvent
1.69 0.71
0.92 0.88
2.10 2.01 1.75 1.84
2.00 4.37 9.35
12
11
10
9
8
7
6
5
4
3
2
1
ppm

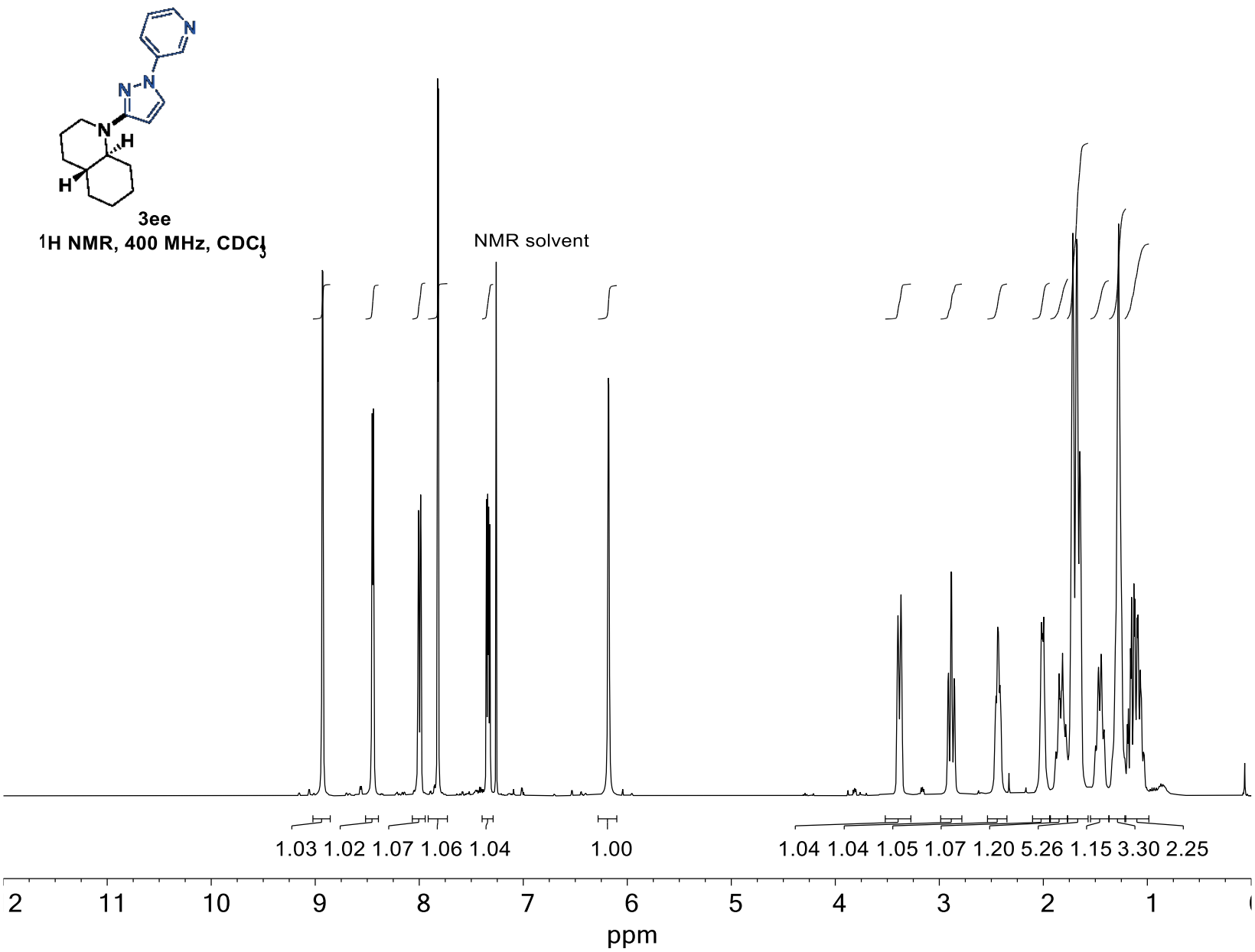

158.65
155.01
154.91
151.55
133.85
118.02
92.45
79.54
58.84
47.50
41.00
36.82
35.71
28.60
BocN
N
N
N
N
3cc
13C NMR, 101 MHz, CDCl3
NMR solvent
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

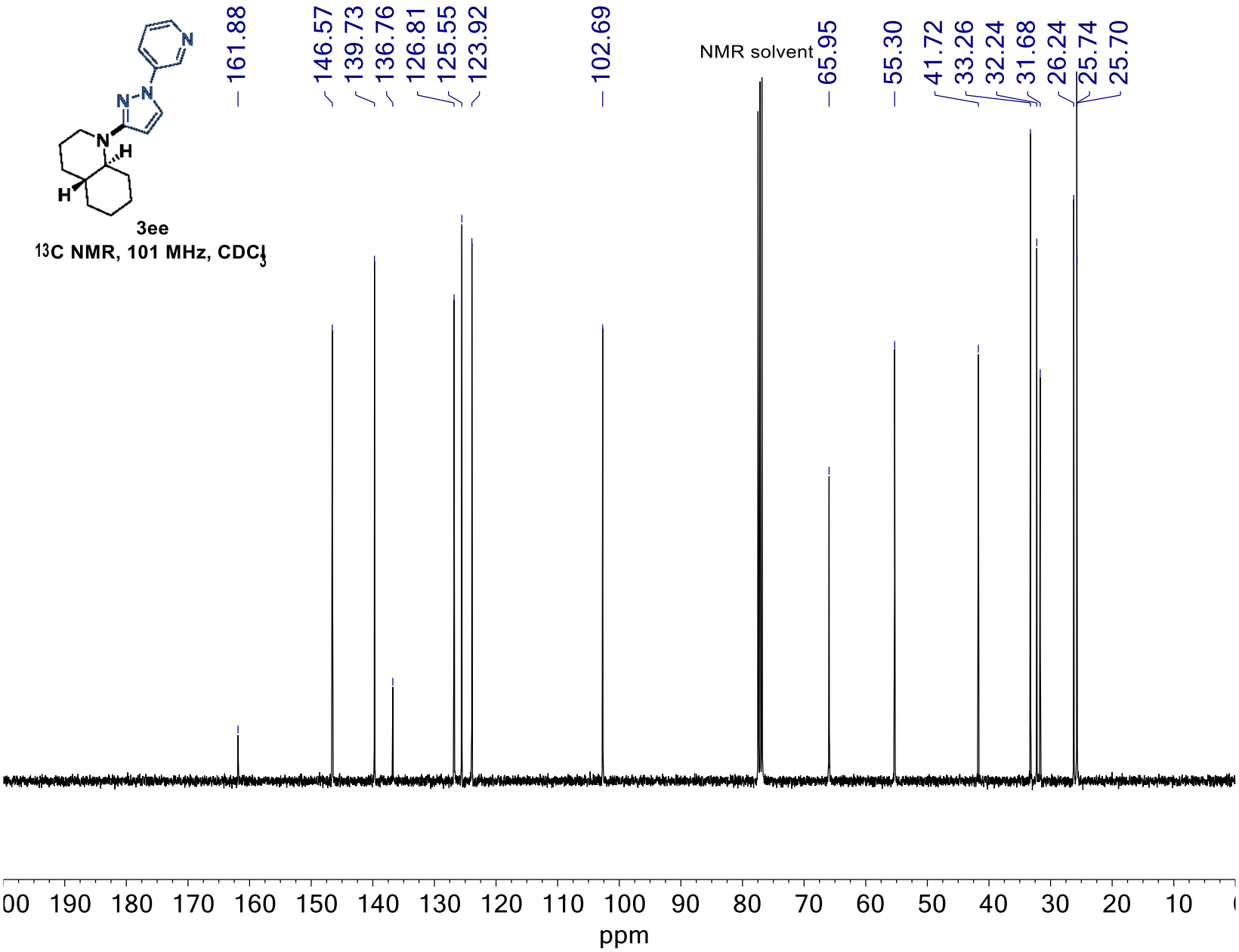


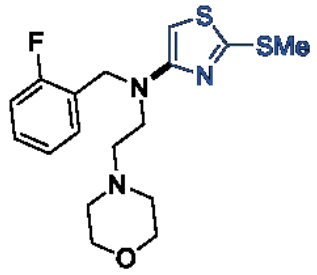
3dd

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


161.92
137.97
123.90
121.06
108.23
101.33
NMR solvent
53.78
51.41
48.19
37.52
34.14
27.65
27.63
23.92
23.90
23.41
15.12
Me
Me
N
O
HN
SMe
N
CN
3dd
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
ppm

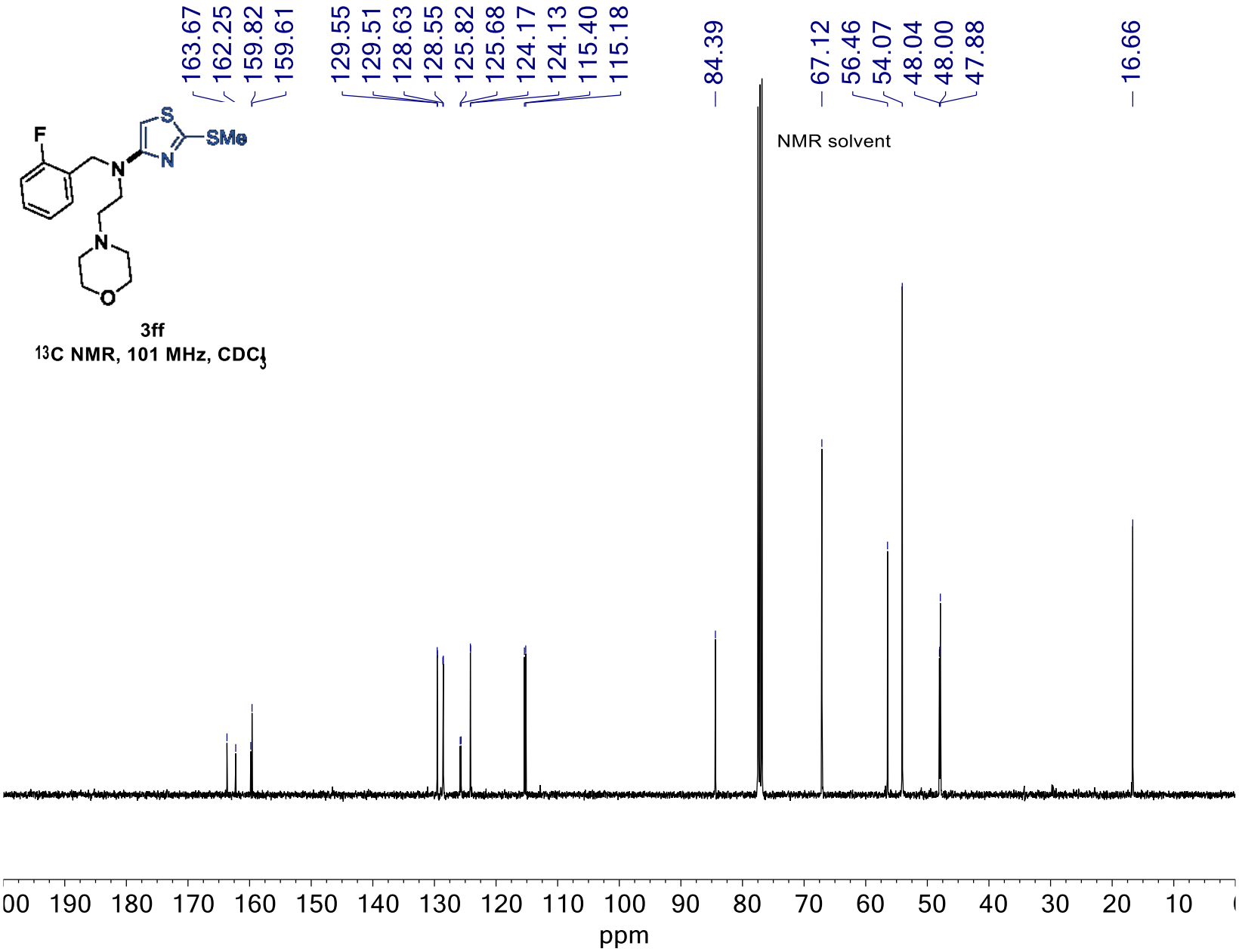

3ee
1H NMR, 400 MHz, CDCl3
NMR solvent
1.03 1.02 1.07 1.06 1.04 1.00 1.04 1.04 1.05 1.07 1.20 5.26 1.15 3.30 2.25
2 11 10 9 8 7 6 5 4 3 2 1
ppm

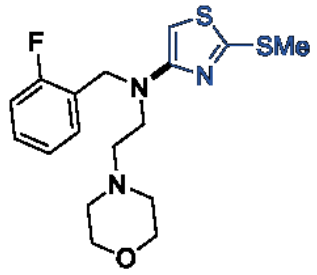

161.88
146.57
139.73
136.76
126.81
125.55
123.92
102.69
NMR solvent
65.95
55.30
41.72
33.26
32.24
31.68
26.24
25.74
25.70
3ee
13C NMR, 101 MHz, CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



3ff

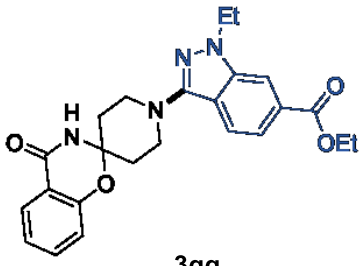
^{1}H NMR, 400 MHz, $CDCl_3$


163.67
162.25
159.82
159.61
129.55
129.51
128.63
128.55
125.82
125.68
124.17
124.13
115.40
115.18
84.39
67.12
56.46
54.07
48.04
48.00
47.88
16.66
NMR solvent
F
S
SMe
N
N
N
O
3ff
13C NMR, 101 MHz, CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



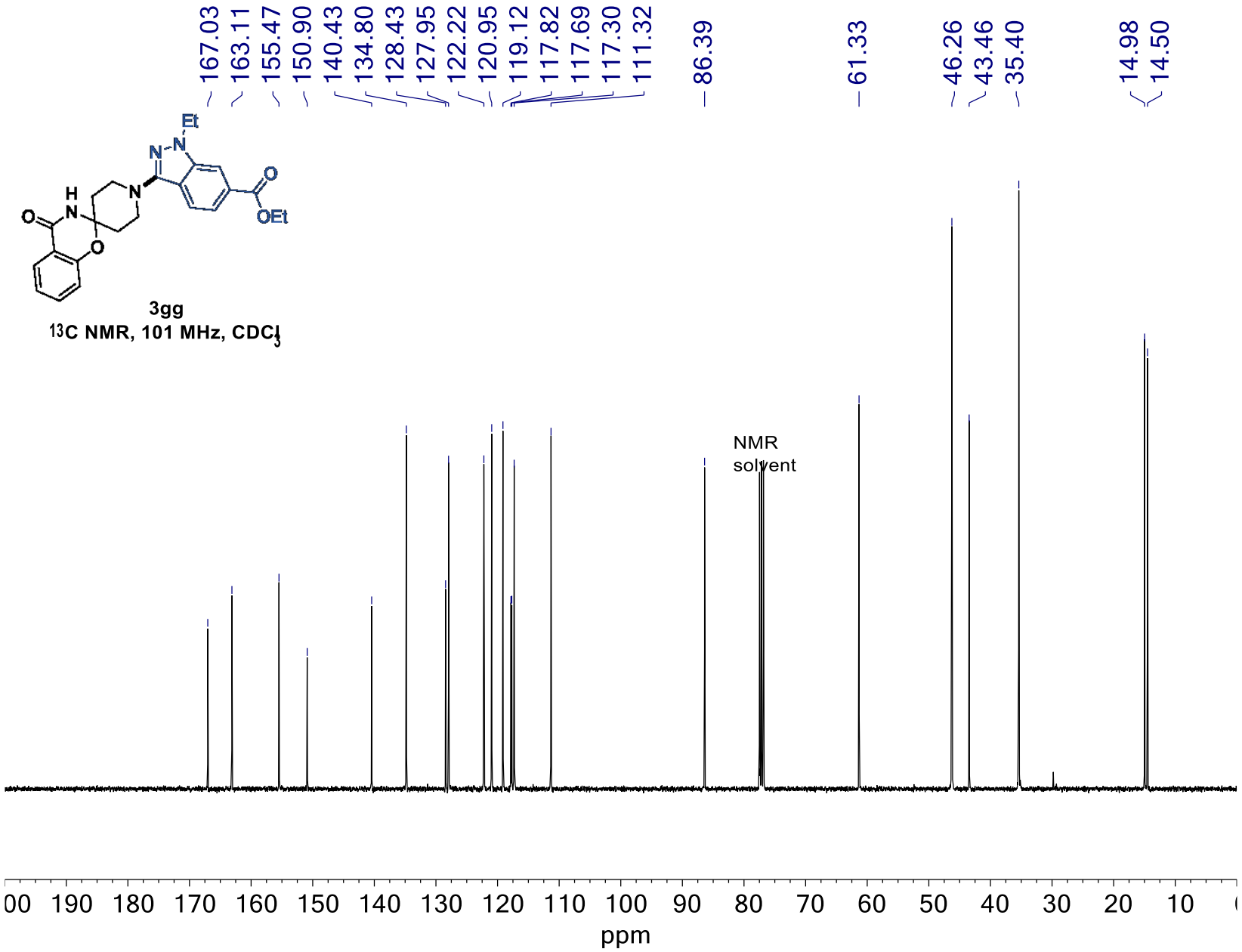
3ff

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



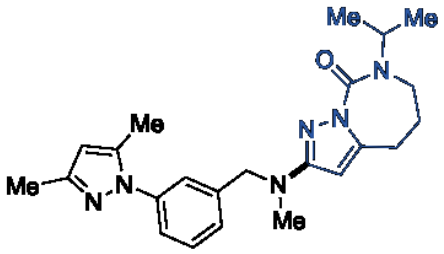
3gg

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



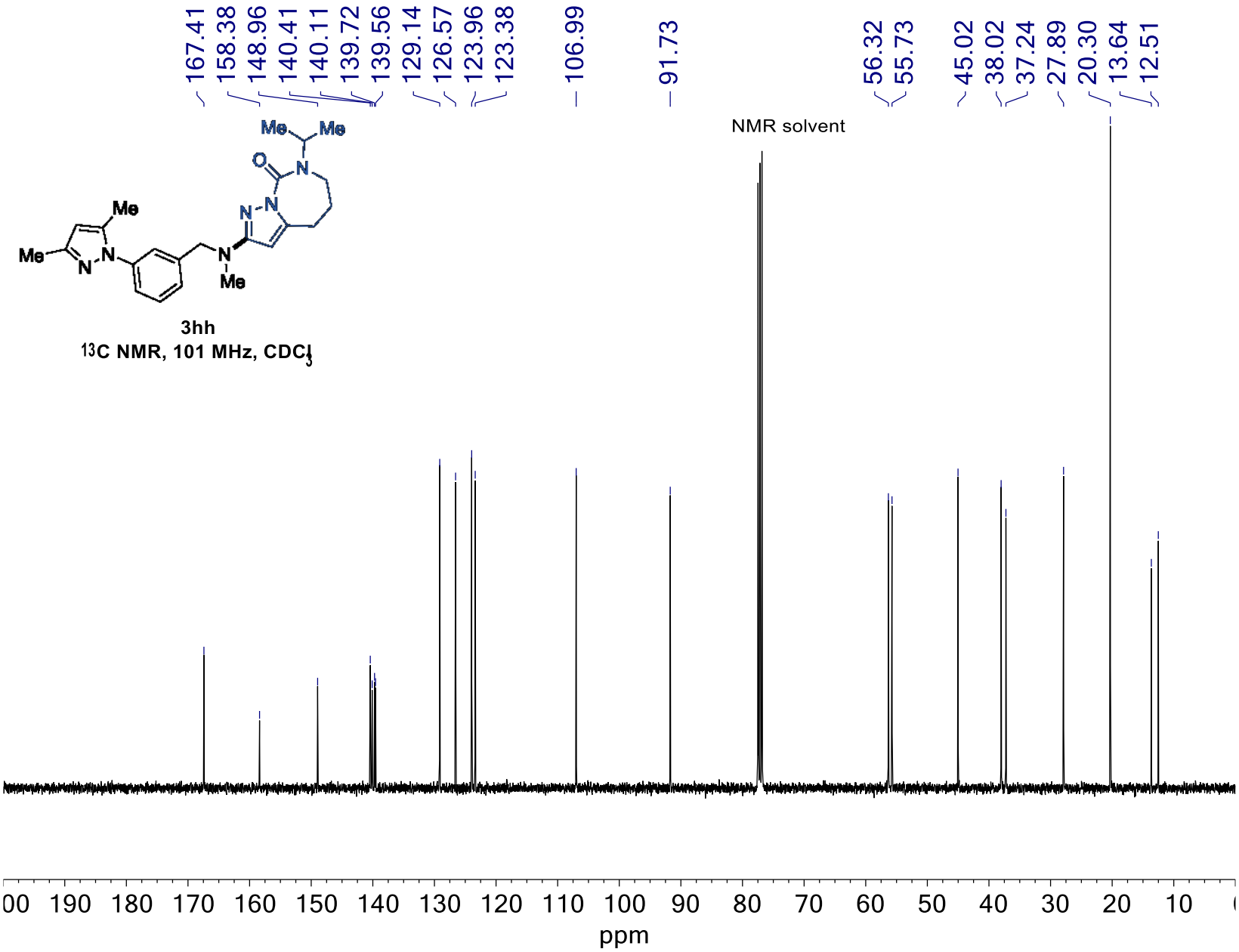
3gg

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



3hh

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


167.41
158.38
148.96
140.41
140.11
139.72
139.56
129.14
126.57
123.96
123.38
106.99
91.73
56.32
55.73
45.02
38.02
37.24
27.89
20.30
13.64
12.51
NMR solvent
Me
Me
Me
Me
O
N
N
N
N
N
Me
3hh
13C NMR, 101 MHz, CDCl3
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

3.5 References

1. (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845–5859.
2. Lamberth, C. Heterocyclic chemistry in crop protection. *Pest Manag. Sci.* **2013**, *69*, 1106–1114.
3. Boto, A.; Alvarez, L.; Miyabe, H.; Miyata, O.; Naito, T.; Mal, D.; Shome, B.; Dinda, B. K.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Kiuru, P.; Yli-Kauhaluoma, J.; Montalban, A. G.; Gruner, K. K.; Knölker, H.-J.; Majumdar, K. R.; Mondal, S.; Knight, D. W.; Xu, Z.; Ye, T.; Kumar, V.; Mahajan, M. P. Common Ring Heterocycles in Natural Product Synthesis. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chat-Topaghyay, S. K., Eds.; Wiley-VCH, 2011, pp 97–533. DOI: 10.1002/9783527634880
4. (a) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451-3479. (b) Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. Big Data from Pharmaceutical Patents: A Computational Analysis of Medicinal Chemists' Bread and Butter. *J. Med. Chem.* **2016**, *59*, 4385–4402. (c) Brown, D. G.; Bostrom, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59*, 4443–4458.
5. For examples of C–N coupling reactions between multi-heteroatom five-membered heteroaryl halides and primary aliphatic amines, see: (a) Su, M.; Hoshiya, N.; Buchwald, S. L. Palladium-Catalyzed Amination of Unprotected Five-Membered Heterocyclic Bromides. *Org. Lett.* **2014**, *16*, 832–835. (b) Akao, Y.; Canan, S.; Cao, Y.; Condroski, K.; Engkvist, O.; Itono, S.; Kaki, R.; Kimura, C.; Kogej, T.; Nagaoka, K.; Naito, A.; Nakai, H.; Pairaudeau, G.; Radu, C.; Roberts, I.; Shimada, M.; Shum, D.; Watanabe, N.; Xie, H.; Yonezawa, S.; Yoshida, O.; Yoshida, R.; Mowbray, C.; Perry, B. Collaborative virtual screening to elaborate an imidazo[1,2-a]pyridine hit series for visceral leishmaniasis. *RSC Med. Chem.* **2021**, *12*, 384–393. (c) Sharif, S.; Rucker, R. P.; Chandrasoma, N.; Mitchell, D.; Rodriguez, M. J.; Froese, R. D. J.; Organ, M. G. Selective Monoarylation of Primary Amines Using the Pd-PEPPSI-IPent^{Cl} Precatalyst. *Angew. Chem. Int. Ed.* **2015**, *54*, 9507–9511.
6. For examples of C–N coupling reactions between multi-heteroatom five-membered heteroaryl halides and secondary aliphatic amines, see: (a) Sather, A. C.; Martinot, T. A. Data-Rich Experimentation Enables Palladium-Catalyzed Couplings of Piperidines and Five-Membered (Hetero)aromatic Electrophiles. *Org. Process Res. Dev.* **2019**, *23*, 1725–1739. (b) Li, D.-H.; Lan, X.-B.; Song, A.-X.; Rahman, M.; Xu, C.; Huang, F.-D.; Szostak, R.; Szostak, M.; Liu, F.-S. Buchwald-Hartwig Amination of Coordinating Heterocycles Enabled by Large-but-Flexible Pd-BIAN-NHC Catalysts. *Chem. Eur. J.* **2022**, *28*, e202103341. (c) Murai, T.; Yamaguchi, K.; Hayano, T.; Maruyama, T.; Kawai, K.; Kawakami, H.; Yashita, A. Synthesis and Photophysical Properties of 5-*N*-Arylamino-4-methylthiazoles Obtained from Direct C–H Arylations and Buchwald–Hartwig Aminations of 4-Methylthiazole. *Organometallics* **2017**, *36*, 2552–2558. (d) Shibata, K.; Yoshida, Ml; Doi, T.; Takahashi, T. Derivatization of a tris-oxazole using Pd-catalyzed coupling reactions of a 5-bromooxazole moiety. *Tetrahedron Lett.* **2010**, *51*, 1674–1677. (e) Spencer, J.; Patel, H.; Amin, J.; Callear, S. K.; Coles, S. J.; Deadman, J. J.; Furman, C.; Mansouri, R.; Chavatte, P.; Millet, R. Microwave-mediated synthesis and

manipulation of a 2-substituted-5-aminooxazole-4-carbonitrile library. *Tetrahedron Lett.* **2012**, *53*, 1656–1659. (f) Usami, Y.; Tatsui, Y.; Yoneyama, H.; Harusawa, S. C4-Alkylamination of C4-Halo-1*H*-1-tritylpyrazoles Using $Pd(dba)_2$ or CuI. *Molecules* **2020**, *25*, 4634. (g) Lohou, E.; Collot, V.; Stiebing, S.; Rault, S. Direct Access to 3-Aminoindazoles by Buchwald-Hartwig C–N Coupling Reaction. *Synthesis* **2011**, *16*, 2651–2663.

7. For examples of C–N coupling reactions between single-heteroatom five-membered heteroaryl halides and secondary amines, see: (a) Charles, M. D.; Schultz, P.; Buchwald, S. L. Efficient Pd-Catalyzed Amination of Heteroaryl Halides. *Org. Lett.* **2005**, *7*, 3965–3968. (b) Lu, Z.; Twieg, R. J. A mild and practical copper catalyzed amination of halothiophenes. *Tetrahedron* **2005**, *61*, 903–918. (c) Plas, A.; Martin, C.; Joubert, N.; Viaud-Massuard, M.-C. Palladium-Catalyzed Amination of *N*-Free 2-Chloro-7-azaindole. *Org. Lett.* **2015**, *17*, 4710–4713. (d) Castellote, I.; Vaquero, J. J.; Alvarez-Builla, J. Palladium-catalysed amination of 2-acyl-1-alkyl-5-bromopyrroles. *Tetrahedron* **2004**, *45*, 769–772.
8. For examples of C–N coupling reactions between 2-halo-1,3-azoles and secondary amines, see: (a) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. Scope and Mechanism of Palladium-Catalyzed Amination of Five-Membered Heterocyclic Halides. *J. Org. Chem.* **2003**, *68*, 2861–2873. (b) Huang, F.-D.; Xu, C.; Lu, D.-D.; Shen, D.-S.; Li, T.; Liu, F.-S. Pd-PEPPSI-IPent^{An} Promoted Deactivated Amination of Aryl Chlorides with Amines under Aerobic Conditions. *J. Org. Chem.* **2018**, *83*, 9144–9155. (c) Toulot, S.; Heinrich, T.; Leroux, F. R. Convenient and Reliable Routes Towards 2-Aminothiazoles: Palladium-Catalyzed *versus* Copper-Catalyzed Aminations of Halothiazoles. *Adv. Synth. Catal.* **2013**, *355*, 3263–3272.
9. For examples of metal-free (S_NAr) aminations of 2-halo-1,3-azoles, see: (a) Kumar, R. U.; Reddy, K. H. V.; Kumar, B. S. P. A.; Satish, G.; Reddy, V. P.; Nageswar, Y. V. D. Metal free amination of 2-chloroazoles in aqueous medium. *Tetrahedron Lett.* **2016**, *57*, 637–640. (b) Fan, G.-G.; Jiang, B.-W.; Sang, W.; Cheng, H.; Zhang, R.; Yu, B.-Y.; Yuan, Y.; Chen, C.; Verpoort, F. Metal-Free Synthesis of Heteroaryl Amines or Their Hydrochlorides via an External-Base-Free and Solvent-Free C–N Coupling Protocol. *J. Org. Chem.* **2021**, *86*, 14627–14639.
10. McCann, S. D.; Reichert, E. C.; Arrechea, P. L.; Buchwald, S. L. Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability. *J. Am. Chem. Soc.* **2020**, *142*, 15027–15037.
11. Olsen, E. P. K.; Arrechea, P. L.; Buchwald, S. L. Mechanistic Insight Leads to a Ligand Which Facilitates the Palladium-Catalyzed Formation of 2-(Hetero)Arylaminooxazoles and 4-(Hetero)Arylaminothiazoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 10569–10572.
12. Su, M.; Buchwald, S. L. A Bulky Biaryl Phosphine Ligand Allows for Palladium-Catalyzed Amidation of Five-Membered Heterocycles as Electrophiles. *Angew. Chem. Int. Ed.* **2012**, *51*, 4710–4713.
13. For examples of C–N coupling reactions between six-membered aryl halides and α-branched secondary amines, see: (a) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. Design of New Ligands for the Palladium-Catalyzed Arylation of α-Branched Secondary Amines. *Angew. Chem. Int. Ed.* **2015**, *54*, 8259–8262. (b) Khadra, A.; Mayer, S.; Mitchell, D.; Rodriguez, M. J.; Organ, M. G. A General Protocol for the Broad-Spectrum Cross-Coupling of Nonactivated Sterically Hindered 1° and 2° Amines. *Organometallics* **2017**, *36*, 3573−3577.

14. Arrechea, P. L.; Buchwald, S. L. Biaryl Phosphine Based Pd(II) Amido Complexes: The Effect of Ligand Structure on Reductive Elimination. *J. Am. Chem. Soc.* **2016**, *138*, 12486–12493.
15. Hooper, M. W.; Hartwig, J. F. Understanding the Coupling of Heteroaromatic Substrates: Synthesis, Structures, and Reductive Eliminations of Heteroarylpalladium Amido Complexes. *Organometallics* **2003**, *22*, 3394–3403.
16. For implication/observation of phosphine displacement by heterocycles, see: (a) Paul, F.; Patt, J.; Hartwig, J. F. Structural Characterization and Simple Synthesis of {Pd[P(*o*-Tol)$_3$]$_2$}. Spectroscopic Study and Structural Characterization of the Dimeric Palladium(II) Complexes Obtained by Oxidative Addition of Aryl Bromides and Their Reactivity with Amines. *Organometallics* **1995**, *14*, 3030−3039. (b) Wagaw, S.; Buchwald, S. L. The Synthesis of Aminopyridines: A Method Employing Palladium-Catalyzed Carbon−Nitrogen Bond Formation. *J. Org. Chem.* **1996**, *61*, 7240−7241.
17. Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. Palladium-catalyzed coupling of functionalized primary and secondary amines with aryl and heteroaryl halides: two ligands suffice in most cases. *Chem. Sci.* **2011**, *2*, 57–68.
18. Casey, M. L.; Kemp, D. S.; Paul, K. G.; Cox, D. D. Physical organic chemistry of benzisoxazoles. I. Mechanism of the base-catalyzed decomposition of benzisoxazoles. *J. Org. Chem.* **2002**, *38*, 2294–2301.
19. Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. Functionalization of pyridines and thiazoles via the halogen-dance reaction, application to the total synthesis of caerulomycin c and WS75624 B. *Strateg. Tactics Org. Synth.* **2005**, *6*, 415–436.
20. Two key design features contribute to the ability of the GPhos-supported catalyst to promote efficient C–N coupling that outcompetes catalyst deactivation: 1) the O*t*-Bu substituent increases the proportion of catalyst that is in the most active conformation, which is also the conformation from which reductive elimination is the fastest, and 2) the absence of a large substituent at the para position of the non-phosphorus-containing ring allows the catalyst to accommodate binding of sterically demanding secondary amine nucleophiles. See reference 10 for additional details about the GPhos ligand design.
21. Tsutomu, K.; Yūzō, S.; Toshihiro, T. An Infrared Spectroscopic Study of Hydrogen Bonding Interaction. Structural Studies of Proton-donating and -accepting Powers. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3716–3722.
22. Ahmad, M.; Masohan, A.; Sawhney, S. S. Alkanolmonoamines as Activators for the Hot Potash Process for CO_2 Capture. *Asian J. Chem.* **2014**, *26*, 975–980.
23. Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.
24. Arrowsmith, C. H.; Kresge, A. J.; Tang, Y. C. The base-catalyzed decomposition of nitramide: mechanism of the second reaction pathway. *J. Am. Chem. Soc.* **1991**, *113*, 179–182.
25. Lipshutz, B. H.; Chung, D. W.; Rich, B. Aminations of Aryl Bromides in Water at Room Temperature. *Adv. Synth. Catal.* **2009**, *351*, 1717–1721.
26. Xu, J.; Kalyani, D.; Struble, T.; Dreher, S.; Krska, S.; Buchwald, S. L.; Jensen, K. F. Roadmap to Pharmaceutically Relevant Reactivity Models Leveraging High-Throughput Experimentation. *ChemRxiv (Catalysis)* September 19, 2022, DOI: 10.26434/chemrxiv-2022-x694w (accessed 2022-11-28).
27. The GPhos-based catalyst is more sterically congested around the Pd center than the RuPhos-based catalyst due to 1) the O*t*-Bu group on the phosphorus-containing ring and 2) the *i*-Pr

groups (vs. O*i*-Pr in RuPhos) on the non-phosphorus-containing ring. See reference 10 for additional details about the GPhos ligand design.
28. The detrimental effects of base-sensitive heteroarene additives on the yields of Pd-catalyzed C−N coupling reactions have been observed using other ligands. See: Collins, K. D.; Glorius, F. A robustness screen for the rapid assessment of chemical reactions. *Nat. Chem.* **2013**, *5*, 597–601.
29. Shermolovich, Y.; Pazenok, S. Synthesis of Halogenated 5- and 6-Membered Sulfur- and Sulfur, Nitrogen-Containing Heterocycles. In *Halogenated Heterocycles: Synthesis, Application and Environment*; Iskra, J., Ed.; Springer, 2012, pp 101–138. DOI: 10.1007/978-3-642-25103-0
30. For the coupling of aryl iodides, the use of 1,4-dioxane instead of THF effectively mitigated problematic inhibition of the productive reaction by the semi-soluble NaI byproduct. See: Fors, B. P.; Davis, N. R.; Buchwald, S. L. An Efficient Process for Pd-Catalyzed C−N Cross-Coupling Reactions of Aryl Iodides: Insight Into Controlling Factors. *J. Am. Chem. Soc.* **2009**, *131*, 5766–5768.
31. Laganis, E. D.; Chenard, B. L. Metal silanolates: organic soluble equivalents for O^{-2}. *Tetrahedron Lett.* **1984**, *25*, 5831–5834.
32. Kassel, V. M.; Hanneman, C. M.; Delaney, C. P.; Denmark, S. E. Heteroaryl–Heteroaryl, Suzuki–Miyaura, Anhydrous Cross-Coupling Reactions Enabled by Trimethyl Borate. *J. Am. Chem. Soc.* **2021**, *143*, 13845–13853.
33. See Figures 6 and 7 for additional examples of successful and unsuccessful coupling reactions.
34. The Merck Building Block Collection is an internal collection of compounds maintained by Merck & Co., Inc. in service of the company's drug development endeavors.
35. Schuppe, A. W.; Borrajo-Calleja, G. M.; Buchwald, S. L. Enantioselective Olefin Hydrocyanation without Cyanide. *J. Am. Chem. Soc*. **2019**, *141*, 18668–18672.
36. King, R. P.; Krska, S. W.; Buchwald, S. L. A Neophyl Palladacycle as an Air- and Thermally Stable Precursor to Oxidative Addition Complexes. *Org. Lett*. **2021**, *23*, 7927–7932.
37. Forlani, L.; Todesco, P. E. Reactivity of halogenothiazoles towards nucleophiles. Kinetics of reactions between 2- and 4-halogenothiazoles and nucleophiles. *J. Chem. Soc., Perkin trans. II* **1978**, *10*, 1016–1019.
38. Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. Water-Mediated Catalyst Preactivation: An Efficient Protocol for C−N Cross-Coupling Reactions. *Org. Lett.* **2008**, *10*, 3505–3508.
39. Solomin, V. V.; Radchenko, D. S.; Slobodyanyuk, E. Y.; Geraschenko, O. V.; Vashchenko, B. V.; Grygorenko, O. O. Widely Exploited, Yet Unreported: Regiocontrolled Synthesis and the Suzuki–Miyaura Reactions of Bromooxazole Building Blocks. *Eur. J. Org. Chem*. **2019**, *2019*, 2884–2898.
40. Tatsugi, J.; Zhiwei, T.; Amano, T.; Izawa, Y. A Facile Synthesis of 1-Alkyl-7-azaisatins. *Heterocycles* **2000**, *53*, 1145–1150.
41. Nishii, U.; Ikeda, M.; Hayashi, Y.; Kawauchi, S.; Miura, M. Triptycenyl Sulfide: A Practical and Active Catalyst for Electrophilic Aromatic Halogenation Using *N*-Halosuccinimides. *J. Am. Chem. Soc*. **2020**, *142*, 1621–1629.