The Nickel-Catalyzed Mizoroki–Heck Reaction: High Regioselectivity in Olefin Migratory Insertion and Photoredox-Enabled Indoline Formation

by

Sarah Z. Tasker

B.Sc. Chemistry, with Honors
Calvin College, 2010

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

September 2015

Signature of Author _____
Department of Chemistry
July 7, 2015

Certified by _____
Timothy F. Jamison
Professor of Chemistry
Thesis Supervisor

Accepted by _____
Robert W. Field
Chair, Department Committee on Graduate Students

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

Professor Rick L. Danheiser _____
Thesis Chair

Professor Timothy F. Jamison _____
Thesis Supervisor

Professor Timothy M. Swager _____

For my family

The Nickel-Catalyzed Mizoroki–Heck Reaction: High Regioselectivity in Olefin Migratory Insertion and Photoredox-Enabled Indoline Formation

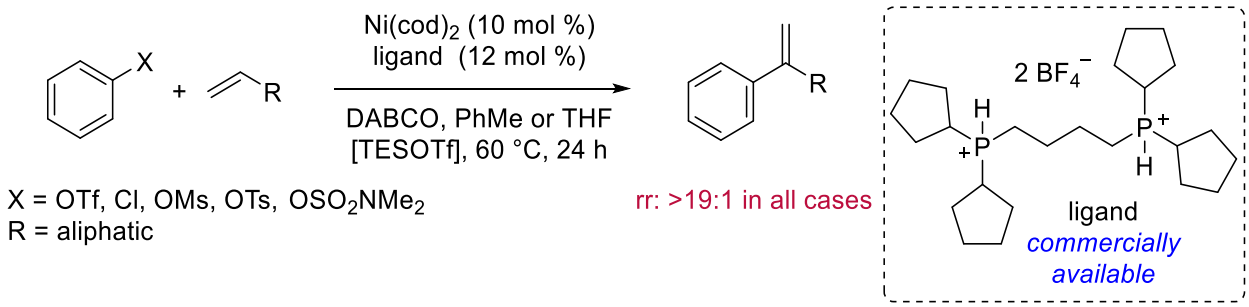
by

Sarah Z. Tasker

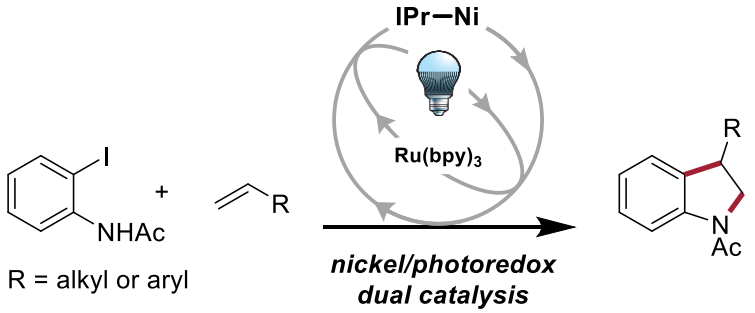
Submitted to the Department of Chemistry on July 7, 2015

in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Organic Chemistry

ABSTRACT



Achieving high selectivity in the Heck reaction of electronically unbiased alkenes has been a longstanding challenge. Using a nickel-catalyzed cationic Heck reaction, we were able to achieve excellent selectivity for branched products (≥19:1 in all cases) over a wide range of aryl electrophiles and aliphatic olefins. A bidentate ligand with a suitable bite angle and steric profile was key to obtaining high branched/linear selectivity, while the appropriate base suppressed alkene isomerization of the product. Though aryl triflates are traditionally used to access the cationic Heck pathway, we have shown that by using triethylsilyl trifluoromethanesulfonate we can effect a counterion exchange of the catalytic nickel complex such that cheaper and more stable aryl chlorides, mesylates, tosylates, and sulfamates can be used to yield the same branched products with high selectivity.



Nickel/photoredox catalysis is used to synthesize indolines in one step from iodoacetanilides and alkenes. Very high regioselectivity for 3-substituted indoline products is obtained for both aliphatic and styrenyl olefins. Mechanistic investigations indicate that oxidation to Ni(III) is necessary to perform the difficult C–N bond-forming reductive elimination, producing a Ni(I) complex which in turn is reduced to Ni(0). This process serves to further demonstrate the utility of photoredox catalysts as controlled single electron transfer agents in multi-oxidation state nickel catalysis.

Thesis Supervisor: Timothy F. Jamison

Title: Professor of Chemistry

Portions of this thesis have been published in the following articles co-written by the author and have been reprinted and/or adapted with permission from their respective publishers.

Nickel-Catalyzed Mizoroki–Heck Reaction of Aryl Sulfonates and Chlorides with Electronically Unbiased Terminal Olefins: High Selectivity for Branched Products.

Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1858–1861. DOI: 10.1002/anie.201308391. Copyright © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

A.C.G. performed initial ligand screening experiments. S.Z.T. optimized the reaction conditions, and carried out screening, scope and mechanistic experiments.

Recent Advances in Homogeneous Nickel Catalysis

Tasker, S. Z.†; Standley, E. A.†; Jamison, T. F. *Nature* **2014**, *509*, 299–309. DOI: 10.1038/nature13274. Copyright © 2014 Nature Publishing Group.

S.Z.T. and E.A.S. worked together to outline and write the content, and T.F.J. helped edit the manuscript, references and figures.

Highly Regioselective Indoline Synthesis under Nickel/Photoredox Dual Catalysis

Tasker, S. Z.; Jamison, T. F. *J. Am. Chem. Soc.* **2015**, [Online early access]. Published Online: July 21, 2015. DOI: 10.1021/jacs.5b05597. Copyright © 2014 American Chemical Society.

All synthetic work was carried out by S.Z.T. Peter Müller (Director, Diffraction Facility of MIT Department of Chemistry) carried out the single-crystal X-ray diffraction experiments.

†These authors contributed equally to this work.

Acknowledgments

My time at MIT has been an amazing time of both scientific and personal growth. Although some parts have been challenging, I would not have made any other decision than to pursue my Ph.D. in this department. Of course, I could never have gotten so far without the help and support of an incredible number of people, whom I would like to briefly thank here.

My early interest in science was fostered by my parents, who encouraged me to run around outside, read voraciously and pursue my interests. My teachers at Westview Elementary and Roosevelt Junior High in Zanesville, Ohio, though the school district was of modest means, fought to challenge me, allowing me to skip ahead in math, paying for summer camps, and sending me to an amazing Talented and Gifted program once a week. There, we played Oregon Trail, created and filmed plays about the Civil War, learned how to use a card catalog, and made up languages.

Perhaps the most important experiences that set me on the path that I'm on today occurred during my time at Calvin College. I entered as a biology major, and took Organic Chemistry as my very first class to "get it out of the way". However, I immediately loved the elegance and challenge of organic synthesis and learning about the fundamentals of reaction mechanisms. I am so thankful that my two professors in organic chemistry, Prof. Carolyn Anderson and Prof. Chad Tatko saw my interest and (strongly) encouraged me to change majors and come do research in their labs during the school year and summer. Carolyn in particular has become an incredible mentor, and taught me innumerable things: proper reaction techniques, methodology design, career planning, leadership, and much more. I also credit any skills in scientific writing and presenting that I may have to her and to my other professors at Calvin. Both Chad and Carolyn also gave me the opportunity to travel to national meetings to give posters on my research and hear talks from prominent chemists. I also want to thank all my chemistry professors at Calvin for giving me a well-rounded foundation in all disciplines of chemistry.

When choosing graduate schools, I was drawn to MIT for its strong academic department and sense of community among the graduate students I met. I could not have made a better choice than to come here and to choose Prof. Tim Jamison as my advisor. Tim has been incredibly supportive, open, and thoughtful in both chemistry and other aspects of graduate school. I have learned so much from his example and ideas, while he has also trusted me with the space and freedom to develop my own ideas and ownership of my chemistry. I appreciate the focus Tim places on the development of all aspects of successful chemists, from setting team synthesis challenges, to painstakingly going over job talks of group members slide-by-slide, to setting up mentoring relationships in the lab.

My coworkers in the Jamison lab have also been exemplary through all the years that I have worked alongside them. Everyone is always willing to drop what they're doing to help out in any way they can. In particular, I would like to thank Dr. Alicia Gutierrez and Dr. Matt Beaver for being amazing mentors and friends during my early graduate career, helping with everything from Schlenk line techniques, to reaction troubleshooting, to career advice. My two fellow fifth years, (now Dr.) Eric Standley and (soon to be Dr.) Toma Halkina have been sources of both fun and commiseration throughout the years. I have also enjoyed collaborating with Eric on three review articles on nickel chemistry that I think will be an important legacy, and he has even put up with my grammatical nitpicking with remarkable patience! I would also like to thank the rest of "Team Nickel" for helpful discussions and interesting ideas: Dr. Jeff Byers, Dr. Kim Jensen, and Dennis Nielsen. I feel fortunate to leave my current projects in the capable hands of Jessica Weber. Many other group members have spent time in the Jamison lab during my time here, and I unfortunately do not have room (or my readers the patience) to thank all of them, but I would also like to call out Dr. Kurt Armbrust for his knowledge and dedication to leading the lab, and to Dr. Matt Katcher for help reading drafts and refining my scientific ideas.

Outside of the Jamison lab, I also am grateful to many others in the department. First of all, Prof. Rick Danheiser has been a conscientious and invested Thesis Chair, with whom I have had many helpful discussions. He and Dr. Beth Vogel Taylor both gave me the opportunity to improve my teaching skills by assisting in graduate and undergraduate organic chemistry classes above and beyond the typical teaching requirements. There are also several technical aspects of my thesis work with which I had assistance. Dr. Peter Müller obtained and interpreted the two crystal structures and Li Li and Eric obtained the HRMS values that appear herein. I would also like to thank the Surendranath lab, and Megan Jackson and Anna Wuttig in particular, for teaching me how to do cyclic voltammetry experiments, and answering all of my naïve questions. Finally, I would like to thank Prof. Brad Pentelute and his lab for our nascent collaboration, which unfortunately I was not able to include here.

Another important part of my graduate experience has been with the ChemREFS student group. I have learned so much about leadership, student advocacy, and the inner workings of academia. For all that we were able to accomplish (with hopefully more to come!), I would like to thank Tim, Prof. Troy Van Voorhis, Jennifer Weisman, Prof. Sylvia Ceyer, Libby Mahaffy, and Carl Brozek.

Finally, I could not have completed this degree without the extensive support from both family and friends. Thanks to Jolene, Alexandra, and Clare for Sunday "liberal arts" dinners and British miniseries, and to Hannah and Elise for hours of phone calls and for moving to amazing places around the world where I can visit them. My family has also been so supportive: Mom, Dad, Rachel, Hannah, Aunt Jan, Uncle Herm, Grandpa, and Nana, thanks!

Table of Contents

Abbreviations

Ac	acetyl
Ar	aryl
ATR	attenuated total reflectance
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthalene
Bn	benzyl
Boc	*t*-butyloxycarbonyl
bpy	2,2’-bipyridine
bpz	bipyrazyl
br	branched
Bu	butyl
CAM	ceric ammonium molybdate
CBz	carboxybenzyl
CCDC	Cambridge Crystallographic Data Centre
CFL	compact fluorescent lightbulb
cod	1,5-cyclooctadiene
Cp	cyclopentyldienyl
CV	cyclic voltammetry
Cy	cyclohexyl
DABCO	diazabicyclo[2.2.2]octane
dap	2,9-bis(para-anisyl)-1,10-phenanthroline
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dcypb	1,4-bis(dicyclohexylphosphino)butane
dcypp	1,3-bis(dicyclohexylphosphino)propane
Dec	decyl
dF(CF_3)ppy	2-(2,4-difluorophenyl)-5-trifluoromethylpyridyl
dippf	1,1’-bis(diisopropylphosphino)ferrocene
dippp	1,3-bis(diisoproylhexylphosphino)propane
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
dnpf	1,1’-bis(1-dinaphthylphosphino)ferrocene
dppf	1,1’-bis(diphenylphosphino)ferrocene
dtbbpy	4,4’-di-*tert*-butyl-2,2’bipyridine
E°	standard reduction potential
$E_{1/2}$	half-cell reduction potential

E_p	peak wave reduction potential
$E_{p/2}$	potential at peak wave half height
equiv	equivalent
Et	ethyl
EWG	electron withdrawing group
F	Faraday constant
Fc	ferrocene
FT	Fourier transform
GC	gas chromatography
GC/MS	gas chromatography/mass spectrometry
Hex	hexyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
i-Pr-PyBOX	2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine
IR	infrared (spectroscopy)
KHMDS	potassium bis(trimethylsilyl)amide
LED	light-emitting diode
ln	linear
Me	methyl
MHz	megahertz
nd	not determined
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance (spectroscopy)
NMP	*N*-methyl-2-pyrrolidone
NOE	nuclear Overhauser effect
OAc	acetate
OMs	methanesulfonate
OTf	trifluoromethanesulfonate
OTs	4-methylphenylsulfonate
Ph	phenyl
PhMe	toluene
PhOTf	phenyl trifluoromethanesulfonate
Piv	pivaloyl/trimethylacetyl
ppy	2-phenylpyridine
Pr	propyl
rr	regioisomeric ratio
rt	room temperature
SCE	standard calomel electrode
SET	single electron transfer
SIPr	1,3-bis(2,6-diisopropylphenyl)imidazolidene
TBAT	tetrabutylammonium difluorotriphenylsilicate

TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin-layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Tol	methylphenyl
Ts	tosyl/4-(methyl)phenylsulfonyl

Preface:
The Role of Nickel in Catalysis

To the uninitiated, nickel might seem like just the impoverished younger sibling of palladium in the field of transition metal catalysis. After all, the use of palladium-catalyzed cross-coupling has skyrocketed over the past half-century: it was honored with the 2010 Nobel Prize in Chemistry, and it is ubiquitous in applications that range from complex natural product synthesis to drug discovery to manufacturing. Nickel lies just above palladium in the periodic table, and as a group 10 metal, it can readily perform many of the same elementary reactions as palladium or platinum. Because of these commonalities, nickel is often viewed solely as a low-cost replacement catalyst for cross-coupling reactions. However, this common misconception is clearly refuted by the numerous and diverse nickel catalyzed reactions reported in the literature. Indeed, homogeneous nickel catalysis is currently experiencing a period of intensified interest, and the intrinsic properties of nickel have enabled its use as an effective catalyst for many intriguing, valuable and difficult transformations.

Historically, the use of nickel in organometallic reactions pre-dates many other examples of transition metal catalysis.[1] Nickel was isolated in 1751; its name is derived from the German *Kupfernickel*, the name given to a nickel ore originally believed by miners to contain copper, but which did not yield copper on extraction (hence use of Nickel, a mischievous demon). In the 1890s, Mond observed one of the unusual reactivity patterns of nickel: elemental nickel and CO reacted at room temperature to form $Ni(CO)_4$, an extremely toxic, low-boiling liquid, which could be used to purify the metal. Shortly thereafter, Sabatier performed the first hydrogenation of ethylene using nickel, for which he was awarded the 1912 Nobel Prize in Chemistry. But undoubtedly, one of the most prominent and prolific early contributors to organonickel chemistry was Wilke.[1a] Wilke made seminal contributions to the structure and reactivity of nickel

[1] a) Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185–206. b) Tamaru, Y., Ed. *Modern Organonickel Chemistry*. Wiley-VCH: Weinheim, 2005.

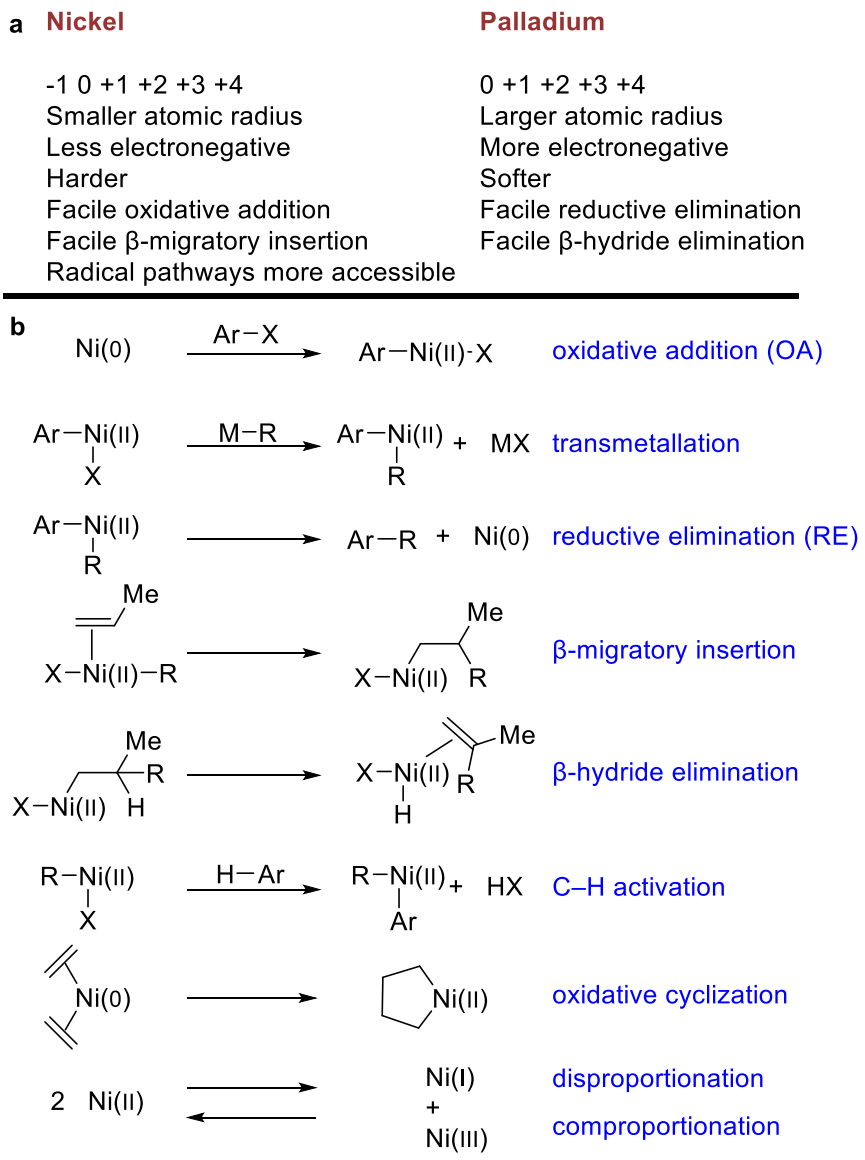
complexes, including the synthesis of $Ni(cod)_2$ (a ubiquitous source of complexed zero-valent nickel), and investigation of olefin oligomerization reactions. Beginning in the 1970s, nickel found extensive use both for cross-coupling and reactions of alkenes and alkynes, such as nucleophilic allylation, oligomerization, cycloisomerization and reductive coupling. Many excellent books and reviews of organonickel chemistry in general,[1b,2] as well as of specific transformations (for example, reductive coupling[3] and cross-coupling[4]), already exist.

Before discussing our work investigating the nickel-catalyzed Heck reaction, a survey of nickel's characteristic modes of reactivity, particularly in regard to some of the elementary steps of transition metal catalysis is needed (Figure 1). Nickel is a relatively electropositive late transition metal. Therefore, oxidative addition,[5] which results in loss of electron density around nickel, tends to occur quite readily (though, conversely, reductive elimination is correspondingly more difficult).[6] This facile oxidative addition allows for the use of cross-coupling electrophiles that would be considerably less reactive under palladium catalysis, such as phenol derivatives,[7] aromatic nitriles[8] or even aryl fluorides.[9] Nickel also has a number of readily available oxidation states commonly invoked in catalysis. The majority of palladium-catalyzed reactions are based on a Pd(0)/Pd(II) catalytic cycle, and most often proceed through polar (that is, non-radical) mechanisms. Likewise, Ni(0)/Ni(II) catalytic cycles are widespread, but the easy accessibility of Ni(I) and Ni(III) oxidation states allows different modes of reactivity and radical mechanisms.

---

[2] Ananikov, V. P. *ACS Catal.* **2015**, *5*, 1964–1971.
[3] a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. b) Standley, E. A.; Tasker, S. Z.; Jensen, K. L.; Jamison, T. F. *Acc. Chem. Res.* **2015**, *48*, 1503–1514.
[4] Diederich, F.; Stang, P. J., Ed. *Metal-Catalyzed Cross-Coupling Reactions.* Wiley-VCH: Weinheim, 1998.
[5] Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319–6332.
[6] Lanni, E. L.; McNeil, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 16573–16579.
[7] a) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728–1759. b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416. c) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29–39.
[8] Garcia, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547–9555.
[9] Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 19505–19511.

Figure 1. Survey of the characteristic modes of nickel reactivity.



As a result, many transformations are based on Ni(I)/Ni(III), Ni(0)/Ni(II)/Ni(I), or even cycles in which nickel remains in the Ni(I) state for the entire catalytic cycle.[10] Many nickel complexes have long been known as privileged catalysts for reactions of alkenes and alkynes, such as oligomerization[11] or reductive coupling. Nickel readily donates d-electrons to π-acceptors, so

[10] Cornella, J.; Gómez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997–2009.
[11] O'Connor, C. T.; Kojima, M. *Catal. Today* **1990**, *6*, 329–349.

olefin bonding is generally strong.[12] β-Hydride elimination tends to be slower with nickel relative to palladium; specifically, the energy barrier to Ni–C bond rotation prior to β-hydride elimination is often significantly higher for nickel than comparable palladium species.[13] Finally, there are a few more obvious differences between nickel and its group 10 counterparts. Practically speaking, the cost of nickel in its elemental form is roughly 2,000 times lower than palladium and 10,000 times lower than platinum on a mole-for-mole basis, though the price of commonly used nickel sources for catalysis can be less favorable. As a first-row transition metal, nickel has a small atomic radius, and Ni–ligand bond lengths are often relatively short.[14]

Many of these features of nickel chemistry, from facile oxidative addition to relatively inert bonds to ready access to multiple oxidation states, have been crucial in the work described herein. It has been my pleasure to contribute to the development of new methodologies in this exciting field.

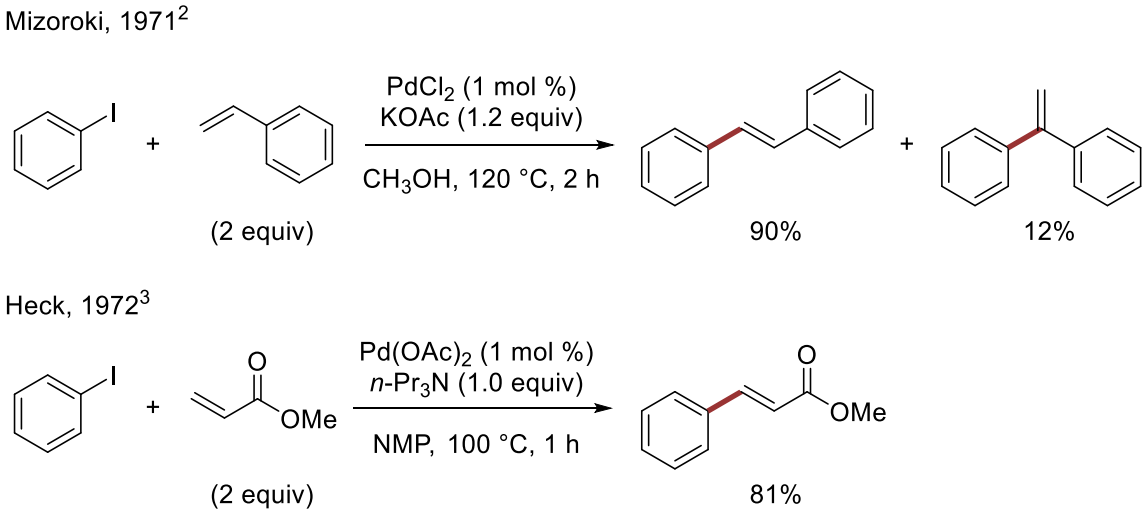
[12] Massera, C.; Frenking, G. *Organometallics* **2003**, *22*, 2758–2765.
[13] Lin, B.-L.; Liu, L.; Fu, Y.; Luo, S.-W.; Chen, Q.; Guo, Q.-X. *Organometallics* **2004**, *23*, 2114–2123.
[14] Cordero, B.; Gómez, V.; Platero-Prats, A. E.; Revés, M.; Echeverría, J.; Cremades, E.; Barragán, F.; Alvarez, S. *Dalton Trans.* **2008**, 2832–2838.

Chapter 1.
Nickel-Catalyzed Branch-Selective Mizoroki–Heck Reactions

Introduction

The Mizoroki–Heck reaction is a powerful way to make more substituted alkenes from aryl electrophiles and less substituted alkenes.[1] It was developed simultaneously in the early 1970s in the laboratories of Tsutomu Mizoroki[2] and Richard Heck (Scheme 1).[3] These first examples demonstrate several general features of the classical (or Type 1)[4] Mizoroki–Heck reaction: the use of aryl iodides (or activated aryl bromides) to react with alkenes containing an electron-withdrawing or resonance-stabilizing group, catalysis by any form of Pd(0) present in the reaction mixture without additional ancillary ligands, use of high temperatures and polar coordinating solvents, and production of *trans*-alkene products resulting from arene insertion at the terminal position of the alkene.

Scheme 1. The Mizoroki–Heck reaction: initial reports



[1] Some excellent reviews include: a) Oestreich, M., Ed. *The Mizoroki–Heck Reaction*. Wiley: Chichester, 2009. b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379–2411. c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. d) Beletskaya, I. P.; Cheprakov, A. V. Modern Heck Reactions. In *New Trends in Cross-Coupling: Theory and Applications;* Colacot, T., Ed.; Royal Society of Chemistry, 2014; pp 355–478.
[2] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
[3] Heck, R. F.; Nolley, Jr., J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.
[4] Beletskaya, I. P.; Cheprakov, A. V. Focus on Catalyst Development and Ligand Design. In *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009; p 55.

Building upon these initial reports, many additional advances in the Mizoroki–Heck reaction, often shortened to simply "the Heck reaction", have been accomplished. For example, electron-rich, sterically hindered monodentate phosphines have allowed the Heck reaction of aryl chlorides,[5] bidentate chiral phosphines have successfully accomplished asymmetric Heck reactions,[6] and use of external oxidants has allowed arene C–H activation or oxidative Heck reactions.[7] The latter is more properly called the Fujiwara–Moritani reaction, first reported in 1967,[8] but it proceeds through a similar mechanism. Although the vast majority of Heck reactions use palladium as a catalyst, nickel catalysts have also been reported to carry out Heck reactions in a few cases.[9] However, despite the advantages of using nickel in catalysis, it seems to be underutilized in the Heck reaction compared to the more prevalent use of nickel in other cross-coupling reactions. The importance of the Mizoroki–Heck reaction was recognized with a portion of the 2010 Nobel Prize for palladium catalyzed carbon–carbon bond formation.[10]

[5] Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.
[6] Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533–1552.
[7] Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115.
[8] Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119–1122.
[9] a) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. *J. Organomet. Chem.* **1986**, *301*, C62–C64. b) Iyer, S.; Ramesh, C.; Ramani, A. *Tetrahedron Lett.* **1997**, *38*, 8533–8536. c) Iyer, S.; Thakur, V. V. *J. Mol. Catal. A: Chem.* **2000**, *157*, 275–278. d) Inamoto, K.; Kuroda, J.-i.; Danjo, T.; Sakamoto, T. *Synlett* **2005**, 1624–1626. e) Ma, S.; Wang, H.; Gao, K.; Zhao, F. *J. Mol. Catal. A: Chem.* **2006**, *248*, 17–20. f) Inamoto, K.; Kuroda, J.-i.; Hiroya, K.; Noda, Y.; Watanabe, M.; Sakamoto, T. *Organometallics* **2006**, *25*, 3095–3098. g) Lin, P.-S.; Jenganmohan, M.; Cheng, C.-H. *Chem. Asian J.* **2007**, *2*, 1409–1416. h) Ehle, A. R.; Zhou, Q.; Watson, M. P. *Org. Lett.* **2012**, *14*, 1202–1205. i) Motswainyana, W. M.; Onani, M. O.; Ojwach, S. O.; Omondi, B. *Inorg. Chim. Acta* **2012**, *391*, 93–97. j) Paulose, T. A. P.; Wu, S.-C.; Olson, J. A.; Chau, T.; Theaker, N.; Hassler, M.; Quail, J. W.; Foley, S. R. *Dalton Trans.* **2012**, *41*, 251–260. k) Gøgsig, T. M.; Kleimark, J.; Nilsson Lill, S. O.; Korsager, S.; Lindhardt, A. T.; Norrby, P.-O.; Skrydstrup, T. *J. Am. Chem. Soc.* **2012**, *134*, 443–452. l) McAtee, J. R; Martin, S. E. S.; Cinderella, A. P.; Reid, W. B.; Johnson, K. A.; Watson, D. A. *Tetrahedron* **2014**, *70*, 4250–4256. m) Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825–7828.
[10] Richard F. Heck - Nobel Lecture: Palladium Reactions for Organic Syntheses. *Nobelprize.org.* Nobel Media AB 2014. Web. 16 Jun 2015. <http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/heck-lecture.html>

Mechanism of the Mizoroki–Heck reaction.

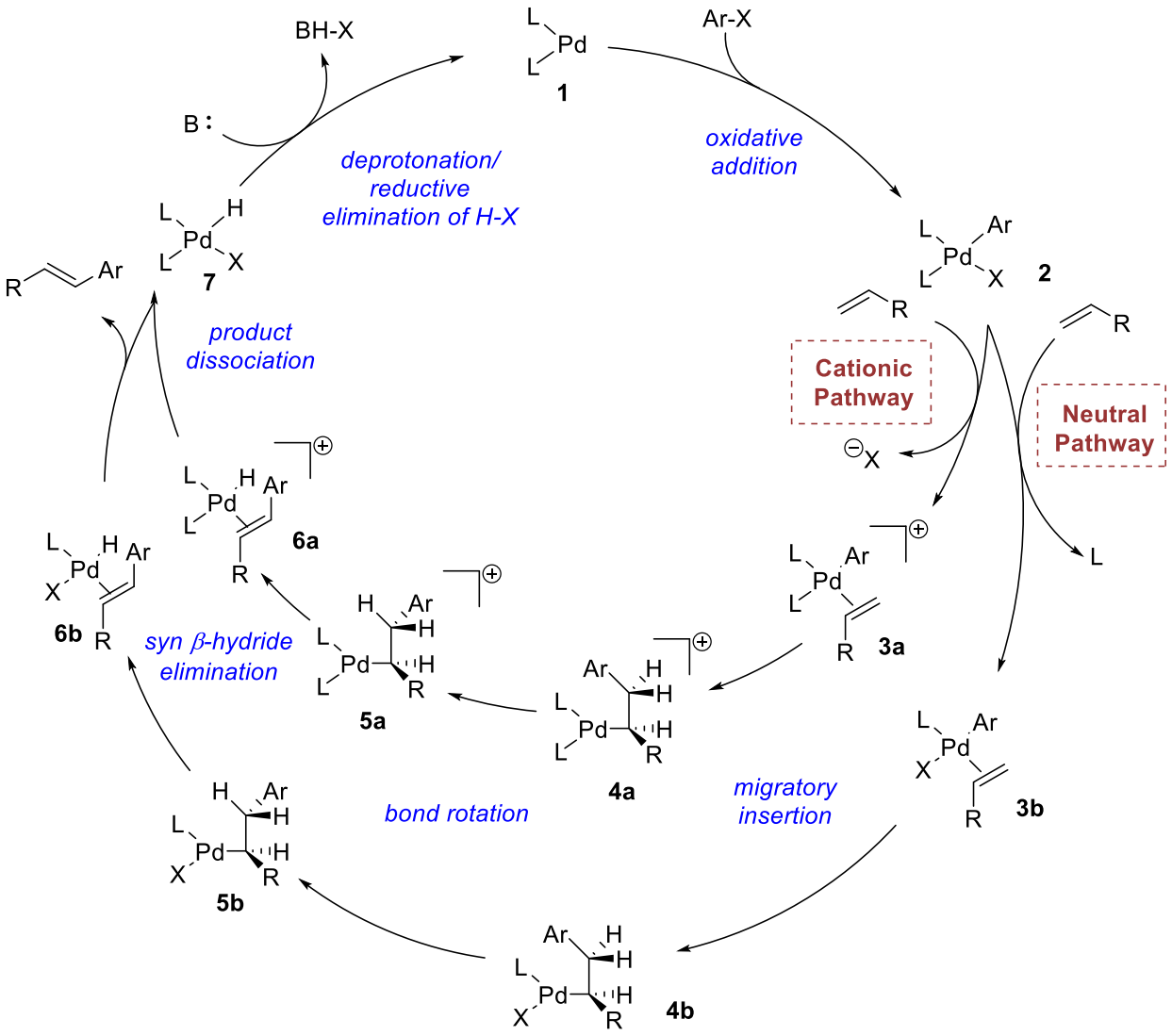
The mechanism of the Mizoroki–Heck reaction can be complex and unpredictable,[1c] and elucidating the precise ligand sphere and catalyst activation pathways can be difficult.[11] The outline of the generally accepted mechanism is shown in Scheme 2.[12] Oxidative addition of a (typically) Pd(0) active catalyst (**1**) to an aryl halide or pseudohalide produces a Pd(II) complex (**2**). Here, it is helpful to divide the Heck reaction into two general manifolds: neutral and cationic (sometimes called nonpolar and polar,[1c] respectively).[13] The former involves the dissociation of an L-type ligand such as phosphine or solvent molecule in order to accommodate the association of the alkene to form **3b**, while the latter involves replacement of an X-type (i.e., anionic) ligand with an alkene to form **3a**. The replacement of an anionic ligand with an olefin produces a formally cationic Pd(II) complex (**3a**), but differences in reactivity in the cationic and neutral reaction pathways (*vide infra*) probably more accurately result from differences in metal coordination sphere (L-type vs. X-type ligands), rather than electronic differences, or the Pd(II) species being "more electrophilic".[1c,14]

Regardless, of the manifold, after olefin coordination, migratory insertion furnishes the new C–C bond and Pd(II) species **4a** or **4b**. Bond rotation is necessary to place a β-hydrogen in a *syn*-orientation to the Pd (**5a**, **5b**), which then undergoes β-hydride elimination to yield the product. Steric interactions between the aryl group and substituent of the alkene, in **5a** or **5b**, generally favor production of (*E*)-alkenes. Finally, the Pd(0) complex (**1**) is re-formed by a

[11] Jutand, A. Mechanisms of the Mizoroki–Heck Reaction. In *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009; pp 1–50.
[12] Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44.
[13] Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.
[14] For example, $(Ph_3P)PdPh^+$ reacts with styrene more slowly than $(Ph_3P)PdPhOAc$: Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605–5614.

formal base-assisted reductive elimination of H–X.[12,15] The Pd–H species **7** can alternatively re-insert into the product double bond to isomerize the resulting alkene in a chain-walking process. When alkenes with pendant alcohols are used, aldehydes can be formed selectively after a chain-walking isomerization process, since the formation of the C=O bond acts as a thermodynamic sink.[16]

Scheme 2. Cationic and neutral mechanisms for the Mizoroki–Heck reaction.



[15] Ziegler Jr, C. B; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941–2946.
[16] Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629–6632.

Possible mechanistic differences between nickel- and palladium-catalyzed Heck reactions have been studied by density-functional theory calculations.[17] Liu, Guo, and coworkers found that oxidative addition and migratory insertion occurred with lower energy barriers for nickel phosphine complexes than for analogous palladium species. However, β-hydride elimination and reductive elimination of H–Cl was much slower for nickel. These general correlations were the same for both neutral and cationic reaction pathways.

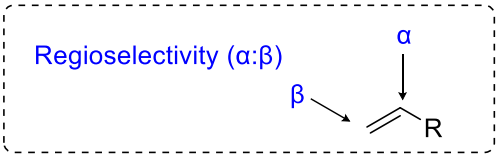
Alkene Regioselectivity in the Mizoroki–Heck Reaction

One of the questions at the heart of the Heck reaction is the regioselectivity of the migratory insertion, leading to the formation of different product alkenes. Often, these alkene regioisomers cannot be separated by conventional means, so achieving high levels of regioselectivity is key in establishing a synthetically useful method. As demonstrated in the initial reports by Mizoroki[2] and Heck,[3] electron-poor alkenes are highly biased for arene migratory insertion at the terminal position of the olefin. However, under standard Heck conditions, poor regioselectivity is observed for alkenes lacking a strong electronic bias.[1c] Substrates can be designed which can dictate regioselectivity, for example by using tethered alkenes to undergo an intramolecular Heck reaction governed by Baldwin's rules,[18,19] or by using an alkene containing a neighboring chelating group.[20]

[17] Lin, B.-L.; Liu, L.; Fu, Y.; Luo, S.-W.; Chen, Q.; Guo, Q.-X. *Organometallics* **2004**, *23*, 2114–2123.
[18] Link, J. T. The Intramolecular Heck Reaction. In *Organic Reactions, Vol. 60*; Overman, L. E., Ed.; Wiley-VCH: Hoboken, 2002; pp 157–561.
[19] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
[20] Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783–792.

On the other hand, a more general solution, at least for several alkene classes, was developed in the mid-1990s by Cabri[21] and others.[22] They discovered that performing the Heck reaction under conditions that favored dissociation of the anionic counterion ligand prior to oxidative addition (the cationic or polar pathway) resulted in the reversal in selectivity for migratory insertion in many cases (Scheme 3). In particular, electon-rich alkenes gave excellent selectivity for arene insertion at the internal position (α) of the alkene to give branched

Scheme 3. Alkene regioselectivity in the Heck reaction under neutral and cationic conditions.



Pathway:	Neutral	Cationic
CO_2Me	0:100	0:100
Ph	0:100	40:60
OH	0:100	100:0
Me	20:80	80:20
OAc	mixture	95:5
O*n*-Bu	mixture	100:0
O, N	40:60	100:0

[21] a) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5796–5800. b) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2–7.

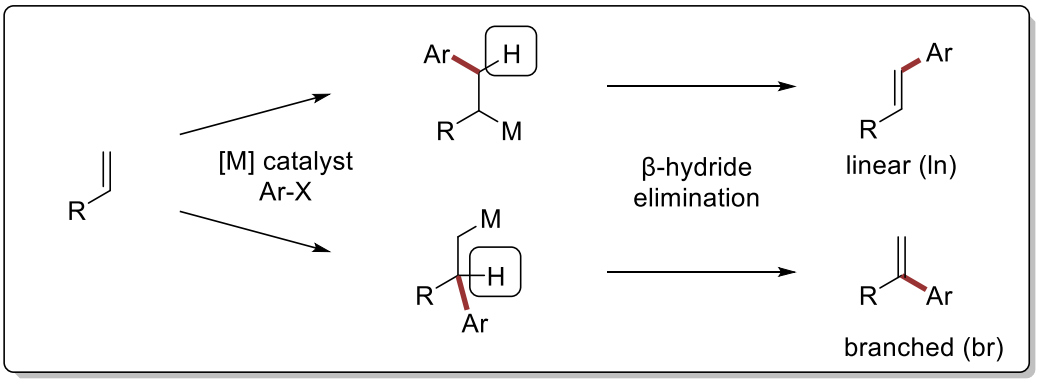
[22] a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417–1419. b) Ruan, J.; Xiao, J. *Acc. Chem. Res.* **2011**, *44*, 614–626. c) Daves Jr., G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433–1445.

(i.e., 1,1-disubstituted) alkene products. The cationic Heck pathway can be accessed by a number of different reaction conditions which act to either discourage the dissociation of an L-type ligand or favor the dissociation of an X-type ligand. Perhaps the most common way to access the cationic Heck pathway is to use aryl triflates as electrophiles, rather than aryl bromides or iodides, since the triflate counterion is highly labile.[21a,23] Bidentate phosphine ligands have also been used to favor phosphine coordination.[24] Alternatively, silver[25] or thallium[26] salts can be used as halide scavengers, and ionic liquids can encourage formation of ionic complexes.[22b,27]

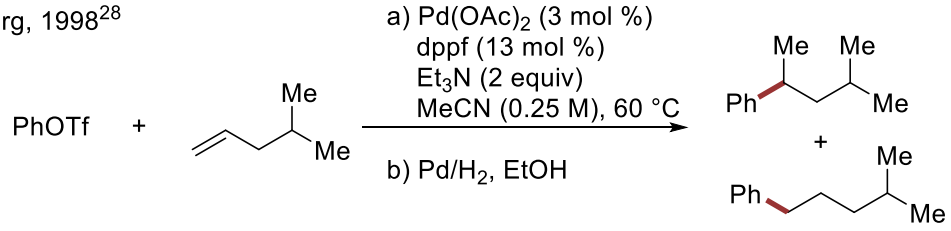
While straightforward access to the cationic Heck manifold provides excellent regioselectivity for electron-rich alkenes to form branched Heck products, electronically unbiased alkenes still provide only moderate levels of regioselectivity for either branched or linear products. For example, when Hallberg and coworkers reacted 4-methyl-1-pentene with phenyl trifluoromethanesulfonate (PhOTf), they observed four alkene products, which became two alkane products after hydrogenation in a 6:1 ratio corresponding to α:β insertion selectivity (Scheme 4a).[28] Since separation of alkene isomers is often not possible, the search for developing a general method for branched-selective Heck reaction of aliphatic olefins has been of interest to researchers and will be the focus of this chapter.

[23] a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417–1419. b) Dekker, G. P. C. M.; Elsevier, C. J.; Vrieze, K.; van Leeuwen, P. W. N. M. *Organometallics* **1992**, *11*, 1598–1603.
[24] a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654–3655. b) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558–3563.
[25] Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896–3900.
[26] Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858–7862.
[27] Hyder, Z.; Mo, J.; Xiao, J. *Adv. Synth. Catal.* **2006**, *348*, 1699–1704.
[28] Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 5076–5079.

Scheme 4: Branch-selective Heck reactions of aliphatic terminal olefins.

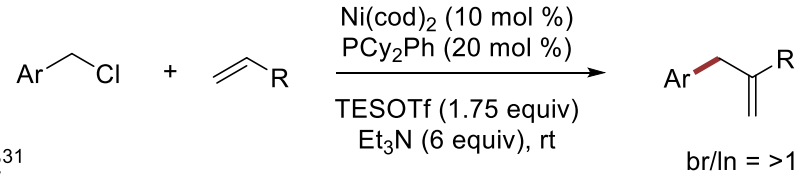


a) Hallberg, 1998[28]



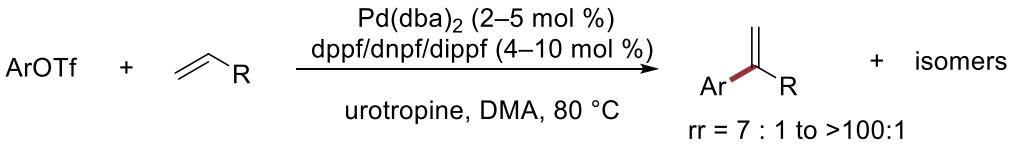
br/ln = 6:1

b) Jamison, 2011[30]



br/ln = >19:1

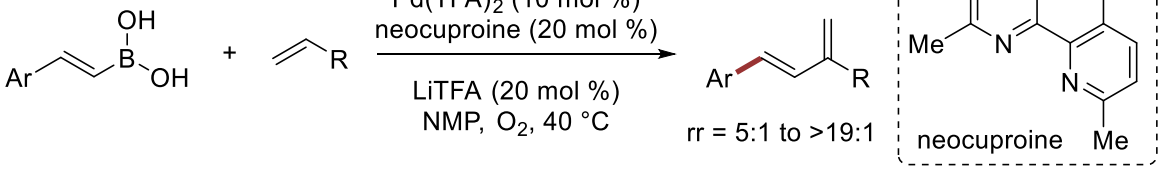
c) Zhou, 2012[31]



rr = 7 : 1 to >100:1

ortho-substituted ArOTf typically needed for rr >19:1

d) Stahl, 2012[32]



rr = 5:1 to >19:1

for all: R = aliphatic

Building on our success in using a nickel-catalyzed allylic substitution reaction to add an η^3-allyl group selectively to the internal position of aliphatic terminal olefins,[29] our laboratories reported a highly branch-selective nickel-catalyzed Heck reaction of benzyl chlorides with ethylene and aliphatic terminal alkenes in 2011 (Scheme 4b).[30] Access to the cationic Heck pathway was essential for both reactivity and selectivity, so triethylsilyl trifluoromethanesulfonate (TESOTf) was used as a counterion exchange agent from the coordinating chloride to the dissociative triflate.

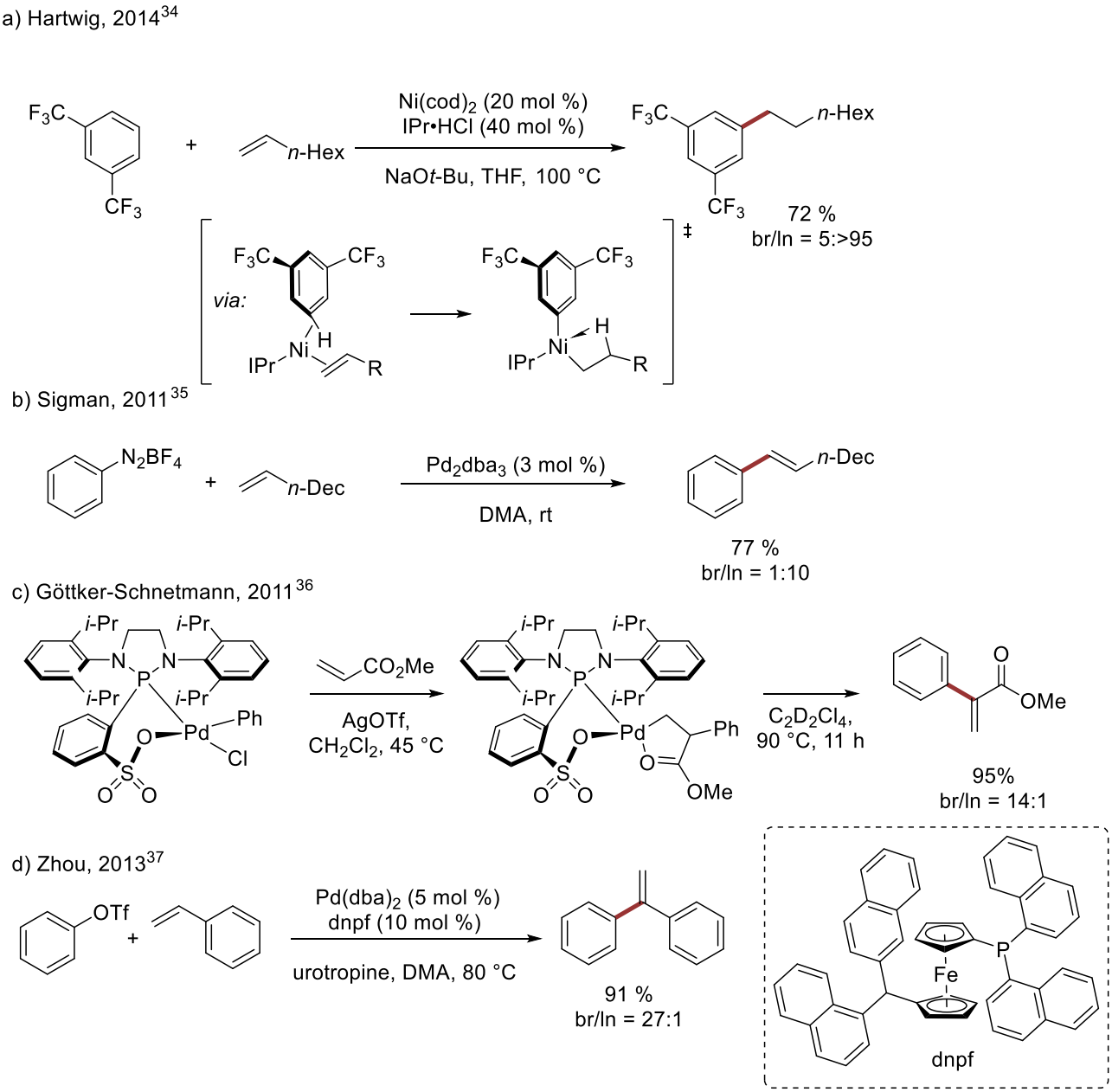
As the work described in this chapter to expand the substrate scope from benzyl chlorides to aryl electrophiles was underway, there were two new reports of highly branch-selective Heck reactions. First, Zhou and coworkers reported using sterically demanding bidentate ferrocenyl ligands in combination with the amine base urotropine to achieve good to excellent selectivities for arene addition to the internal position of aliphatic olefins (Scheme 4c).[31] The best selectivities were observed for *ortho*-substituted arene electrophiles. Stahl and coworkers then reported a de-borylative oxidative Heck reaction of vinyl boronic acids with aliphatic olefins using a phenanthroline-type ligand, neocuproine, to achieve moderate to excellent selectivities for branched diene products (Scheme 4d).[32] The source of the high levels of regioselectivity in these reactions appears to be mainly due to steric interactions between the ligand and olefin, although electronic factors can also have an effect in cationic Heck reactions.[33]

---

[29] a) Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 6880–6881. b) Matsubara, R.; Jamison, T. F. *Chem. Asian J.* **2011**, *6*, 1860–1875.
[30] a) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020–19023. b) Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585–1592.
[31] Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5915–5919.
[32] Zheng, C.; Wang, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2012**, *134*, 16496–16499.
[33] a) Kawataka, F.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 654–660. b) von Schenck, H.; Åkermark, B.; Svensson, M. *J. Am. Chem. Soc.* **2003**, *125*, 3503–3508.

Several other unusual regioselective Heck reactions are noteworthy (Scheme 5). Although not strictly a Heck reaction, in a related hydroarylation reaction catalyzed by nickel and the N-heterocyclic carbene (NHC) ligand IPr, excellent selectivity for linear alkane products

Scheme 5. Other Heck-type reactions displaying interesting regioselective additions.



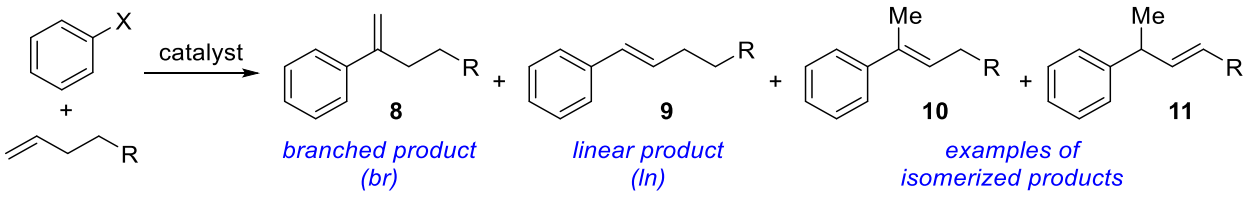
was obtained (Scheme 5a).[34] However, the mechanism involves hydroarylation to selectively produce the primary Ni–C bond followed by arene reductive elimination to give linear products, so a similar sense of migratory insertion regioselectivity is followed. In contrast, the Heck–Matsuda reaction of arene diazonium salts with aliphatic olefins appears to produce only linear products with good selectivity (Scheme 5b).[35] Finally, there are a few recent reports that use highly designed sterically hindered ligands to effect branch-selective (i.e., arene addition at the α-postion) Heck reactions of electron-poor alkenes, overturning the strong inherent substrate preference. Göttker-Schnetmann and coworkers demonstrated a reversal in selectivity for perhaps the most challenging alkene class: acrylates (Scheme 5c).[36] A highly designed diazaphospholidine sulfonato Pd(II) species gave good yields of selective α-insertion to methyl acrylate in a reaction stoichiometric in palladium. Zhou and coworkers also followed up on their previous reports of aliphatic Heck reaction to show that under the same reaction conditions, styrenes selectively produced branched products (Scheme 5d).[37]

[34] Bair, J. S.; Schramm, Y.; Sergeev, A. G.; Clot, E.; Eisenstein, O.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 13098–13101.
[35] Werner, E. W.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 9692–9695.
[36] Wucher, P.; Caporaso, L.; Roesle, P.; Ragone, F.; Cavallo, L.; Mecking, S.; Göttker-Schnetmann, I. *Proc. Natl. Acad. Sci.* **2011**, *108*, 8955–8959.
[37] Zou, Y.; Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Chem.—Eur. J.* **2013**, *19*, 3504–3511.

Preliminary Results

Given our success in developming the nickel-catalyzed Heck reaction of benzyl chloride electrophiles and electronically unbiased terminal alkenes (Scheme 4b),[30] we set out to expand the reaction scope to encompass aryl electrophiles. Our goal was to accomplish this transformation with an excellent level of regioselectivity (defined here as >19:1, or >95:5) for the desired branched alkenes since separation of alkene isomers is generally not possible by the use of column chromatography. There are several possible alkene regioisomers that we (and others) observe throughout this process (Scheme 6). It is necessary both to increase the selectivity for the migratory insertion reaction (resulting in a higher br/ln or **8**/**9** ratio) but also to avoid alkene isomerization by Ni–H reinsertion to the product producing isomerized products (e.g., **10**, **11**). To address the both features, we will report both a br/ln ratio reflecting the migratory insertion selectivity as well as an overall regioisomeric ratio (rr) for the desired branched product compared to the sum of *all* alkene regioisomers produced including linear products and isomerization products, reflecting overall synthetic utility.

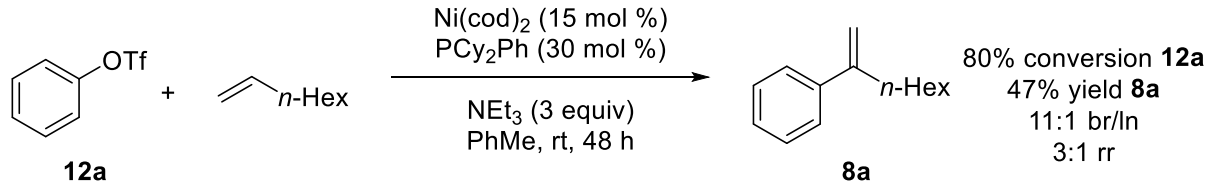
Scheme 6. Products formed in the Heck reaction of aliphatic olefins.



Since we believed access to the cationic Heck pathway to be critical for the success of the reaction, we decided to begin our investigations using phenyl trifluoromethanesulfonate (PhOTf, **12a**) as an electrophile, so as to render a counterion exchange unnecessary. When we tested conditions similar to those reported for benzyl chlorides ($Ni(cod)_2$, PCy_2Ph, Et_3N, toluene) using

PhOTf and 1-octene, we were excited to observe some of the desired product **8a**, albeit in modest yield (Scheme 7). The br/ln selectivity was promising, but the overall rr of the reaction was quite poor. There was also a significant discrepancy in conversion of PhOTf and yield of Heck products. This mass balance loss was determined to arise from reduction of PhOTf to benzene. Alicia Gutierrez, a former postdoctoral researcher in our lab, had performed some preliminary investigations into other ligand types for this reaction, and had determined that Buchwald-type biaryl phosphines, bipyridyl-type ligands, diimine ligands, and ferrocenyl phosphine ligands did not provide substantial amounts of the desired Heck products.

Scheme 7. Heck reaction of aryl electrophiles using PCy_2Ph.[a]

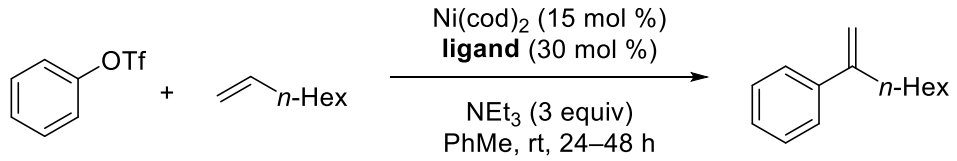


12a **8a**

[a] Conversion, yield, and alkene isomer ratios (as in Scheme 6) determined by GC using dodecane as an internal standard.

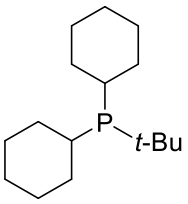
Therefore, we set out to identify whether steric or electronic changes to PCy_2Ph would improve yield, mass balance recovery, or regioisomeric ratios. First, we investigated whether altering alkyl to aryl groups or vice versa would have a significant effect (Scheme 8). Unfortunately, nearly universally poor br/ln ratios were observed when PCy_2Ph was not used, nor was reduction of PhOTf suppressed. Additionally, steric hindrance (e.g., in the case of P(*t*-Bu)$_2$Ph) resulted in the formation of large amounts of isomerized product **10a**, suggesting a long-lived Ni–H species.

Scheme 8. Evaluation of monodentate phosphine ligands.[a]

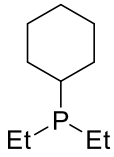


12a **8a**

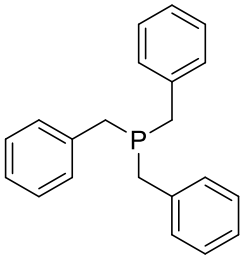
Trialkyl Phophines:



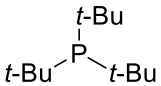
15% conv **12a**
4% yield **8a**
br/ln = 1.5



26% conv **12a**
9% yield **8a**
br/ln = 3.5

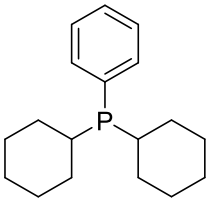


29% conv **12a**
8% yield **8a**
br/ln = 68.9

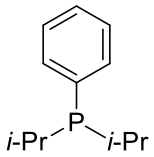


11% conv **12a**
2% yield **8a**
br/ln =0.2

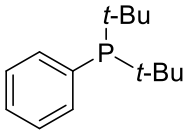
Dialkyl Aryl Phophines:



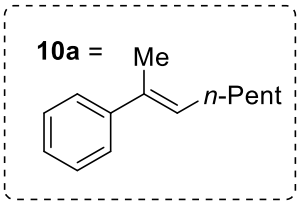
80% conv **12a**
47% yield **8a**
br/ln = 11.4



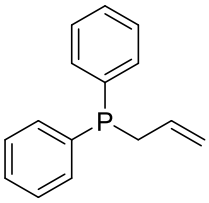
71% conv **12a**
41% yield **8a**
br/ln = 13.1



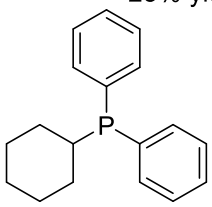
49% conv **12a**
4% yield **8a**
br/ln = 0.4
25% yield **10a**



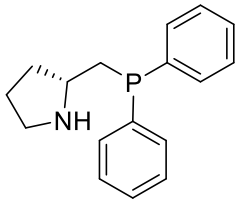
Alkyl Diaryl Phophines:



12% conv **12a**
1% yield **8a**
br/ln = —

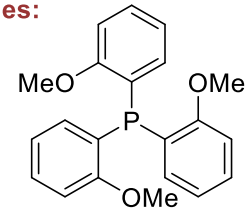


38% conv **12a**
16% yield **8a**
br/ln = 6.3

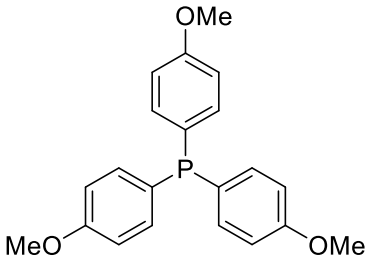


18% conv **12a**
4% yield **8a**
br/ln = 3.1

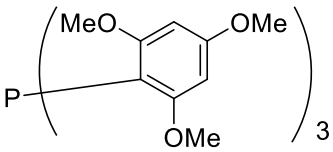
Triaryl Phosphines:



21% conv **12a**
9% yield **8a**
br/ln = 3.6



33% conv **12a**
12% yield **8a**
br/ln = 5.7

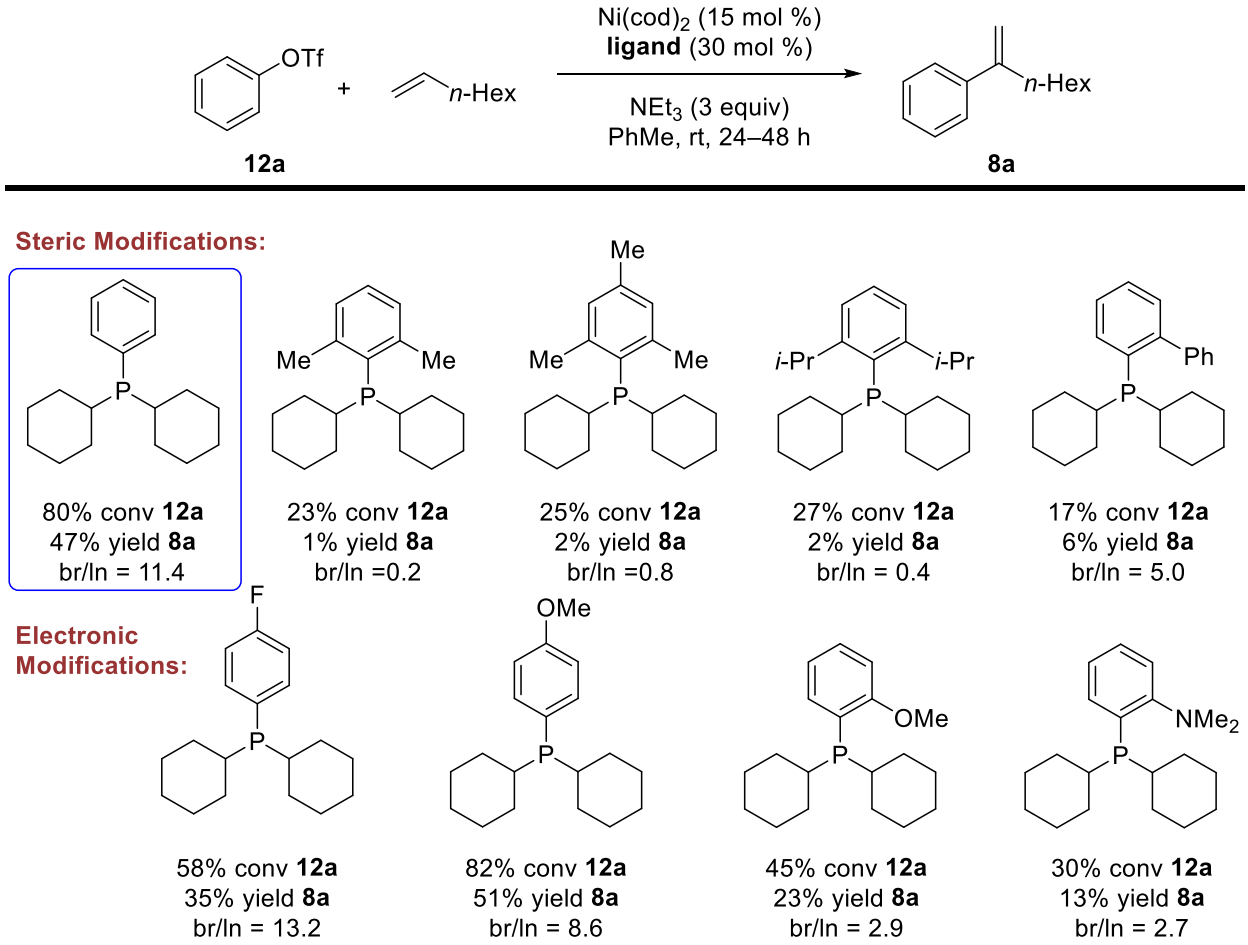


7% conv **12a**
16% yield **8a**
br/ln = 2.0

[a] Conversions, yields, and alkene isomer ratios (as in Scheme 6) determined by GC.

Given that dialkylaryl phosphines were most promising, we investigated steric and electronic modifications to PCy_2Ph (Scheme 9). However, this again proved unfruitful. The addition of alkyl or aryl groups *ortho* to the phosphine on the aromatic ring completely suppressed reactivity, while electronic modification also showed little variation in outcome.

Scheme 9. Steric and electronic modifications to PCy_2Ph.

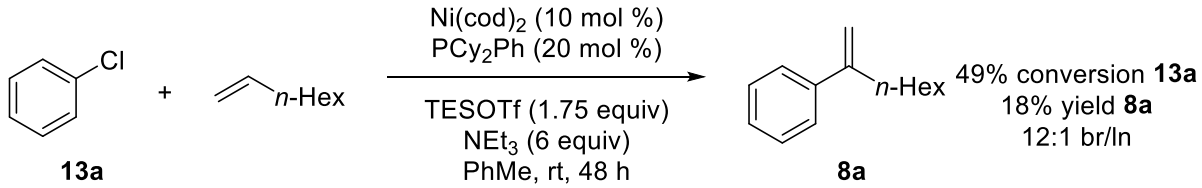


[a] Conversions, yields, and alkene isomer ratios (as in Scheme 6) determined by GC using dodecane as an internal standard.

When these reaction conditions were tested with aryl chlorides in the presence of the counterion exchange reagent TESOTf, the results again proved unsatisfactory (Scheme 10).

Low yields of **8a** were observed, although the same br/ln ratio was produced as with aryl triflates, suggesting that access to the same cationic nickel intermediate was occurring, but that the catalyst was not as active. Optimization of the reaction by evaluating different counterion exchange reagents such as $NaClO_4$, NaOTf, or AgOTf or different solvents did not provide improved yields of **8a**.

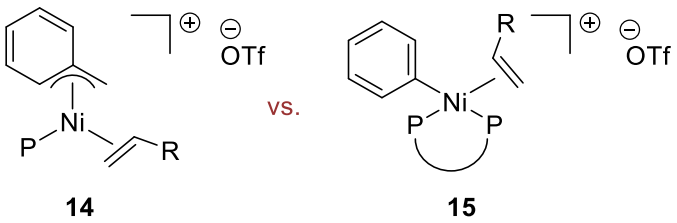
Scheme 10. Reaction of aryl chlorides.[a]



[a] Conversion, yield, and alkene isomer ratios (as in Scheme 6) determined by GC using dodecane as an internal standard.

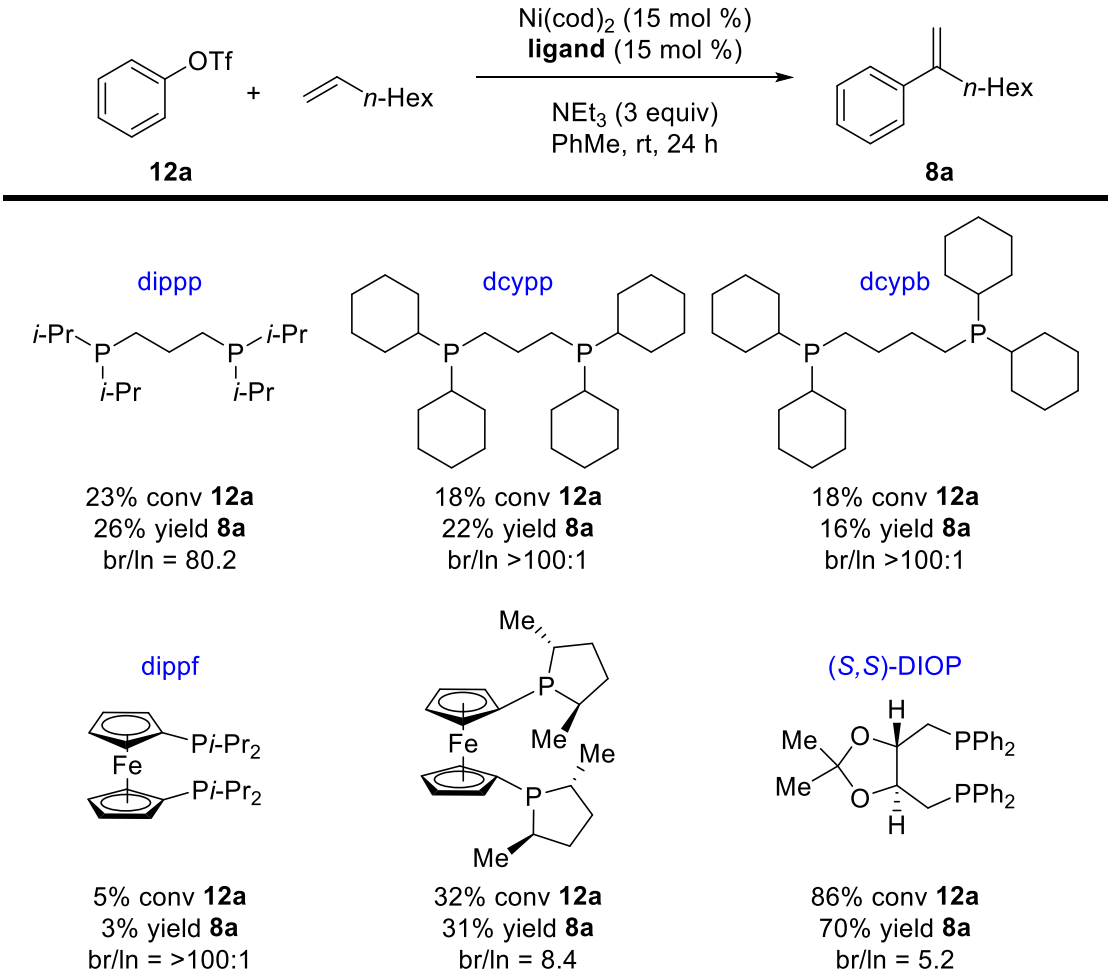
The above results indicate that although changing from benzyl to aryl electrophiles seems a straightforward extension at first, significant differences exist between the two reaction mechanisms. Specifically, we considered the key migratory insertion step of the cationic nickel species (Figure 1). When benzyl electrophiles are used, the cationic nickel species likely adopts an η^3-benzyl conformation, meaning that only one phosphine ligand would be present (**14**). In contrast, Ni–aryl complex **15** cannot access such a binding mode, and therefore two

Figure 1. Key intermediates for benzyl and aryl electrophiles in the cationic Heck mechanism.



phosphines are likely ligated to the nickel species throughout the course of the reaction. This feature, along with the necessity of a *cis*-conformation of the aryl and alkenyl ligands for migratory insertion to occur,[38] suggests the use of bidentate phosphine ligands. The results of a preliminary investigation of bidentate phosphine ligands is shown in Scheme 11. Gratifyingly, although yields of **8a** were low, there was no longer significant aryl triflate reduction and br/ln ratios were excellent, especially when bulky cyclohexyl or isopropyl groups were present.

Scheme 11. Initial investigations of bidentate phosphine ligands.[a]



[a] Conversions, yields, and alkene isomer ratios (as in Scheme 6) determined by GC using dodecane as an internal standard.

[38] Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079–2090.

For bidentate phosphine ligands, a ligand natural bite angle of ~100–110°, corresponding to a three- or four-methylene tether length between the two phosphine atoms proved ideal.[39] This number is suggestive, since the phosphine angle in the transition state of a Pt–H migratory insertion reaction increases from 95° in the ground state to 100° in the transition state,[38,40] although other studies have shown that the migratory insertion of ethylene for Pd(II) complexes is much less sensitive to ligand bite angle than the analogous carbonylation reaction.[41] Alternatively, the larger bite angle could increase the rate of catalyst regeneration by reductive elimination.[42]

Bidentate ligands were also more stable at elevated temperatures. While reactions with PCy_2Ph formed a visible black precipitate at temperatures above 35 °C, presumably of Ni(0), and negligible amounts of Heck products, bidentate ligands of the type shown in Scheme 11 were stable to approximately 60 °C, and produced higher yields at these temperatures. The ligand 1,4-bis(dicyclohexylphosphino)butane, or dcypb, was particularly promising, and after reaction optimization and increase in the amount of Et_3N present, produced good yields and br/ln selectivity of the desired Heck product **8a** (Scheme 12a). Two challenges still remained: the overall regioisomeric ratio of the product mixture was only 9:1, and aryl chlorides remained recalcitrant substrates, even with the addition of TESOTf (Scheme 12b).

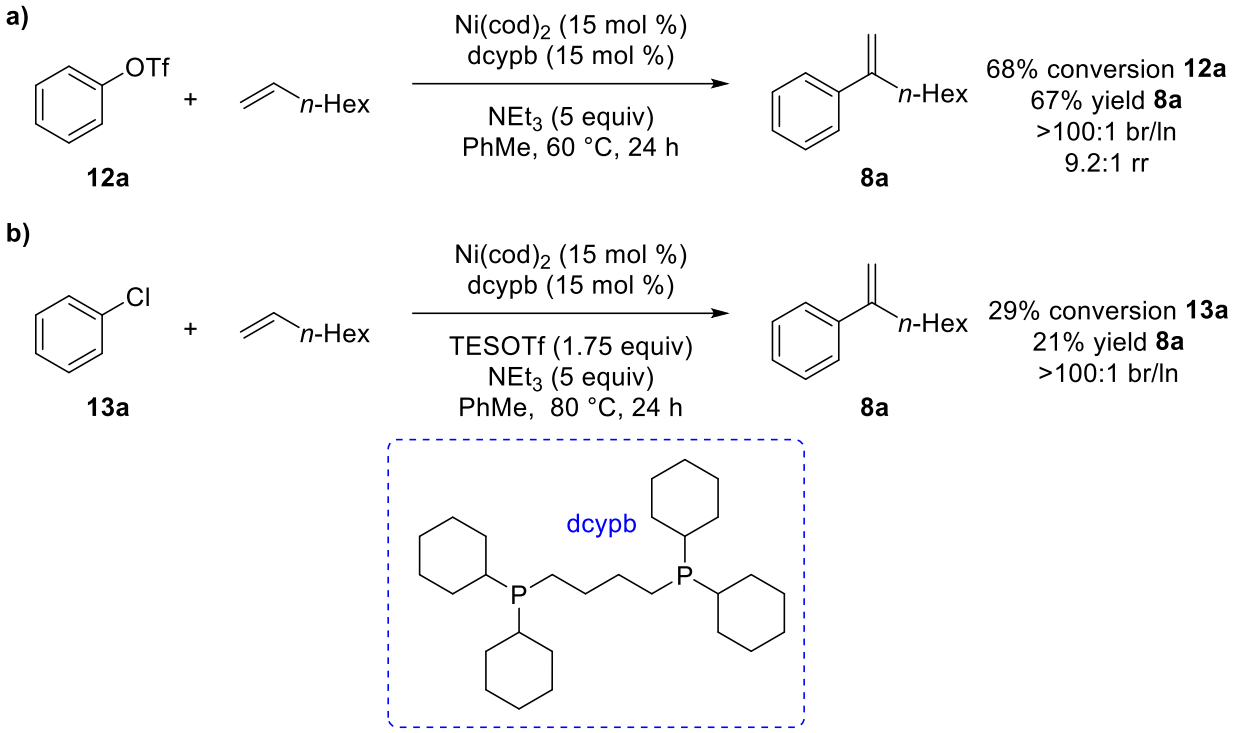
[39] a) Casey, C. P.; Whiteker, G. T. *Israel J. Chem.* **1990**, *30*, 299–304. b) van Leeuwen, P. W. N.; Kamer, P. C. J.; Reek, J. N. H. *Pure Appl. Chem.* **1999**, *71*, 1443–1452. c) Kamer, P. C. J.; van Leeuwen, P. W. N.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904.

[40] The dependence of br/ln selectivity on bite angle is also reminiscent of the ideal bite angle of 112–120° such that the ligand occupies the equatorial positions of the trigonal bipyramidal rhodium catalyst for hydroformylation reactions in order to achieve excellent linear selectivity: Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089.

[41] Ledford, J.; Shultz, C. S.; Gates, D. P.; White, P. S.; DeSimone, J. M.; Brookhart, M. *Organometallics* **2001**, *20*, 5266–5276.

[42] Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249–259.

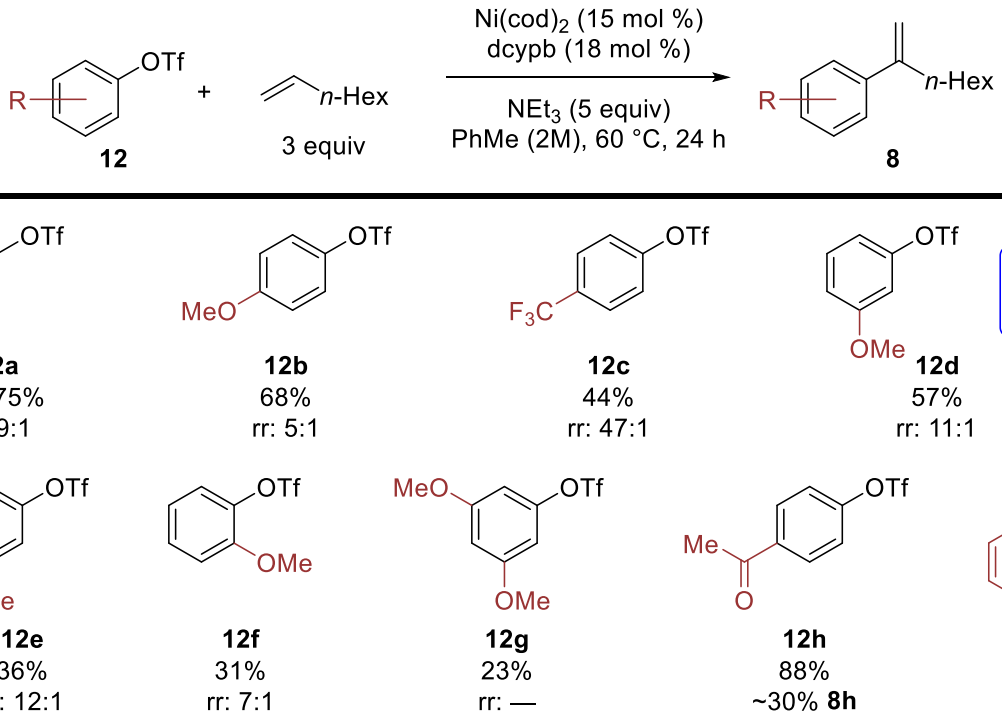
Scheme 12. Optimized conditions for the Heck reaction using dcypb.[a]



[a] Conversions, yields, and alkene isomer ratios (as in Scheme 6) determined by GC using dodecane as an internal standard.

When a range of aryl triflates were tested under the optimized reaction conditions, similar results were obtained (Scheme 13). Although the br/ln ratio was >100:1 in all cases tested, conversions and yields remained relatively modest. Even more importantly, the overall regioisomeric ratios remained below 19:1, except in the case of **12c** containing the electron withdrawing *para*-CF_3 group.

Scheme 13. Scope of aryl triflate coupling partners with dcypb.[a]

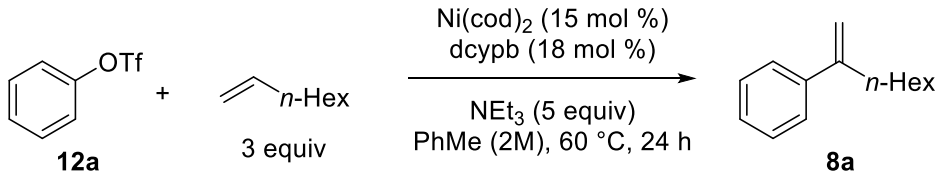


[a] Conversions of **12** (roughly corresponding to yields of **8**) and regioisomeric ratios (as in Scheme 6) determined by GC using dodecane as an internal standard, br/ln ratios for all products >100:1.

Mechanistic Studies

Since unsatisfactory yields and regioisomeric ratios were obtained even after reaction optimization, we set out to study the mechanism of the reaction in hopes of determining what was causing the loss in catalyst activity. First, a series of control experiments were performed (Table 1). As expected, omission of 1-octene produced quantitative oxidative addition to **12a** but no production of **8a** (entry 2), while omission of the base allowed product formation but no catalyst turnover (entry 3). The reaction did not proceed in the absence of nickel (entry 4), but the background reaction in the absence of phosphine ligand did produce considerable yields of Heck products, albeit in a low 1.2:1 br/ln ratio (entry 5).

Table 1. Control reactions.[a]



12a **8a**

Entry	Changes to Reaction Conditions	Conversion **12a** (%)	Yield **8a** (%)
1	—	75	73
2	no 1-octene	15	0
3	no Et_3N	13	15
4	no $Ni(cod)_2$	0	0
5	no dcypb	59	20 (1.2:1 br/ln)
6	PhOTf (3 equiv), 1-octene (1 equiv)	—	69
7	10 μL H_2O	35	25
8	reverse order of addition	68	65

[a] Conversions, yields, and alkene isomer ratios (as in Scheme 6) determined by GC using dodecane as an internal standard.

Alteration of the limiting reagent (entry 6) or the order of addition (entry 8) afforded the product in the same overall yield, while the presence of added H_2O retarded reaction rates, but did not inhibit the catalytic cycle entirely (entry 7).

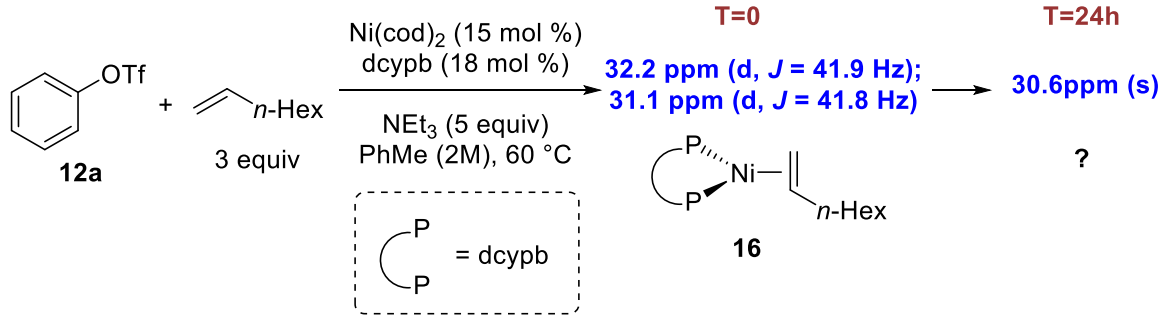
Next, the reaction was studied using ^{31}P NMR to identify any intermediate species present over the course of the reaction.[43] We found that under standard conditions, as the reaction progressed, a signal corresponding to the 1-octene bound Ni(0)/dcypb complex **16** (32.2 ppm, d; 31.1 ppm, d, Table 2b entry 3) disappeared, to be replaced with a new signal (30.6 ppm, s) (Table 2a). To determine the identity of the latter, we attempted to prepare a number of candidate Ni complexes in situ (Table 2b). This signal was determined not to arise from the COD-bound complex **17** (30.4, 29.7 ppm, entry 2), oxidative addition complex **18** (12.7, 12.6 ppm, entry 4), or product-bound complex **19** (32.1 ppm, d; 29.4 ppm, d; entry 5). However, when the reaction was carried out with stoichiometric amounts of nickel in the absence of Et_3N, rapid formation of the same signal was observed (30.9 ppm, entry 6). A reasonable hypothesis for the complex formed in this case would be the Ni–H complex **20**, meaning that this could be the final resting state of the catalyst.

It is also possible that **20** would undergo reductive elimination with dcypb to form phosphonium salt **21**. When $Ni(cod)_2$, dcypb, and TfOH were mixed, a singlet at 29.7 ppm was observed. This signal could in theory arise from either **20** or **21**. In an attempt to remove that ambiguity, dcypb was treated directly with TfOH, resulting in a singlet at 28.0 ppm, presumably arising from phosphonium salt **21**. This last signal is 3 ppm more upfield than the unknown species arising in the catalytic reaction mixture, but perhaps should not be totally ruled out. Also, the large excess of Et_3N typically present under the reaction conditions should relatively readily

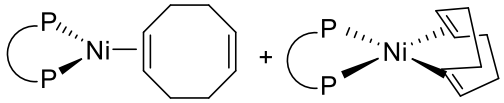
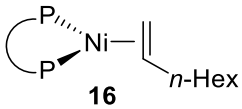
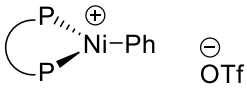
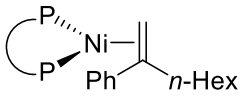
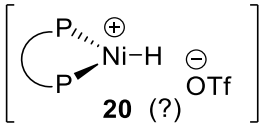
[43] See Figures 4 and 5 for spectra and further experimental details.

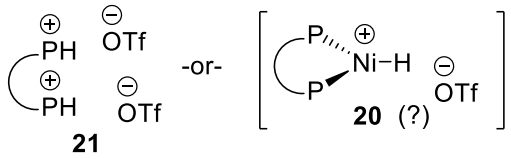
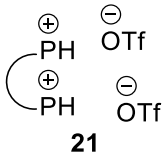
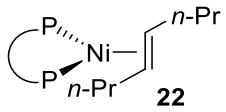
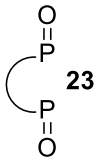
Table 2. ^{31}P NMR studies.[a]

a) *kinetic timecourse: ^{31}P NMR analysis:*



b) *preparation of phosphorous-containing species possibly formed under reaction conditions:*

Entry	Preparation Conditions[b]	Proposed Complex Formed	^{31}P NMR Signals (ppm)
1	dcypb		–5.6
2	Ni(cod)$_2$, dcypb	 **17** + **17'**	30.4 (major); 29.7 (minor)
3	Ni(cod)$_2$, dcypb, 1-octene	 **16**	32.2 (d, *J* = 41.9 Hz); 31.1 (d, *J* = 41.9 Hz)
4	Ni(cod)$_2$, dcypb, PhOTf	 **18**	12.6, 12.7
5	Ni(cod)$_2$, dcypb, **8a**	 **19**	32.1 (d, *J* = 41.3 Hz); 29.4 (d, *J* = 41.4 Hz)
6	Ni(cod)$_2$, dcypb, 1-octene, PhOTf	 **20** (?)	**30.9**

7	$Ni(cod)_2$, dcypb, TfOH[c]	 **21** -or- **20** (?)	**29.7**
8	dcypb, TfOH[c]	 **21**	**28.0**
9	$Ni(cod)_2$, dcypb, *trans*-4-octene	 **22**	multiple: 48.4,48.0, **30.7**, 29.8
10	dcypb, H_2O_2[c]	 **23**	53.3[d]

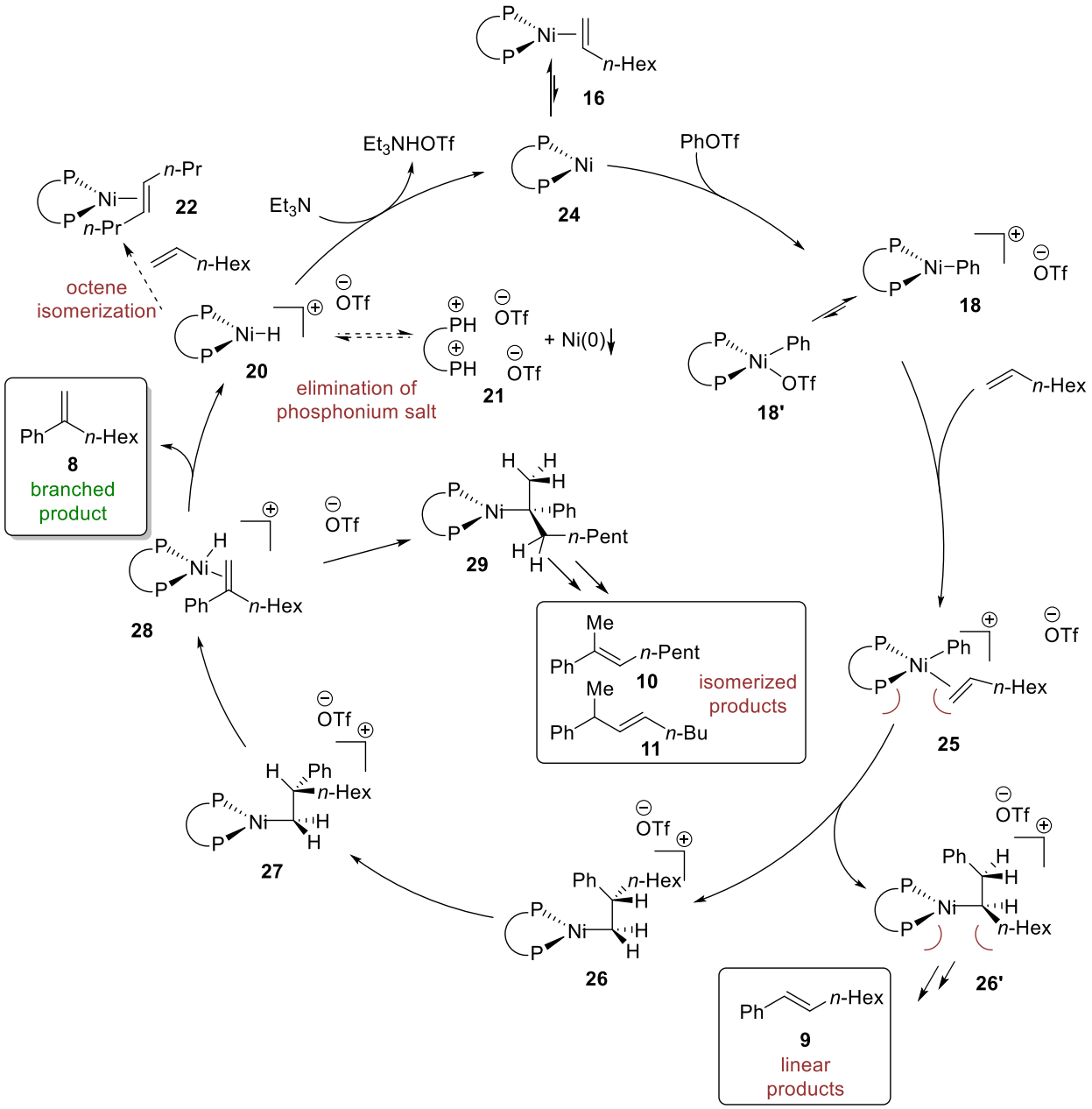
[a] ^{31}P NMR signals (121 MHz) shown for complexes in toluene referenced externally to H_3PO_4 (0 ppm). [b] components present in equimolar ratios unless otherwise noted. [c] reagent used in excess. [d] complex not soluble in toluene, spectrum taken in $CDCl_3$

deprotonate the phosphonium salt unless the resultant unligated Ni(0) precipitated or was unable to re-enter the catalytic cycle. The only other species investigated that resulted in a ^{31}P NMR signal close to 30.6 ppm was the addition of *trans*-4-octene to Ni/dcypb. In fact, isomerization of 1-octene is observed under the reaction conditions, presumably by insertion of Ni–H species **20** to 1-octene followed by chain walking and β-hydride elimination. However, the resulting spectrum was complex, with the peak at 30.7 ppm being only one of several.

Regardless of whether the catalytic reaction results in a resting state of **20**, **21**, or **22**, the dramatic slowing of reaction rates after 18 h, resulting in poor conversion of PhOTf and low yields of Heck products generally points to long-lived Ni–H species **20** as being particularly problematic. The proposed mechanism for this transformation, including possible catalyst decomposition pathways is shown in Scheme 14. After alkene dissociation from initial catalyst

resting state **16**, oxidative addition furnishes **18'** which is in equilibrium with the triflate dissociated **18**, thereby accessing the cationic Heck reaction manifold. The origin of br/ln selectivity likely arises from the steric interactions between the bulky cyclohexyl groups of the ligand with the alkyl chain of 1-octene in the transition state from **25** to either **26** or **26'**.

Scheme 14. Proposed mechanism.



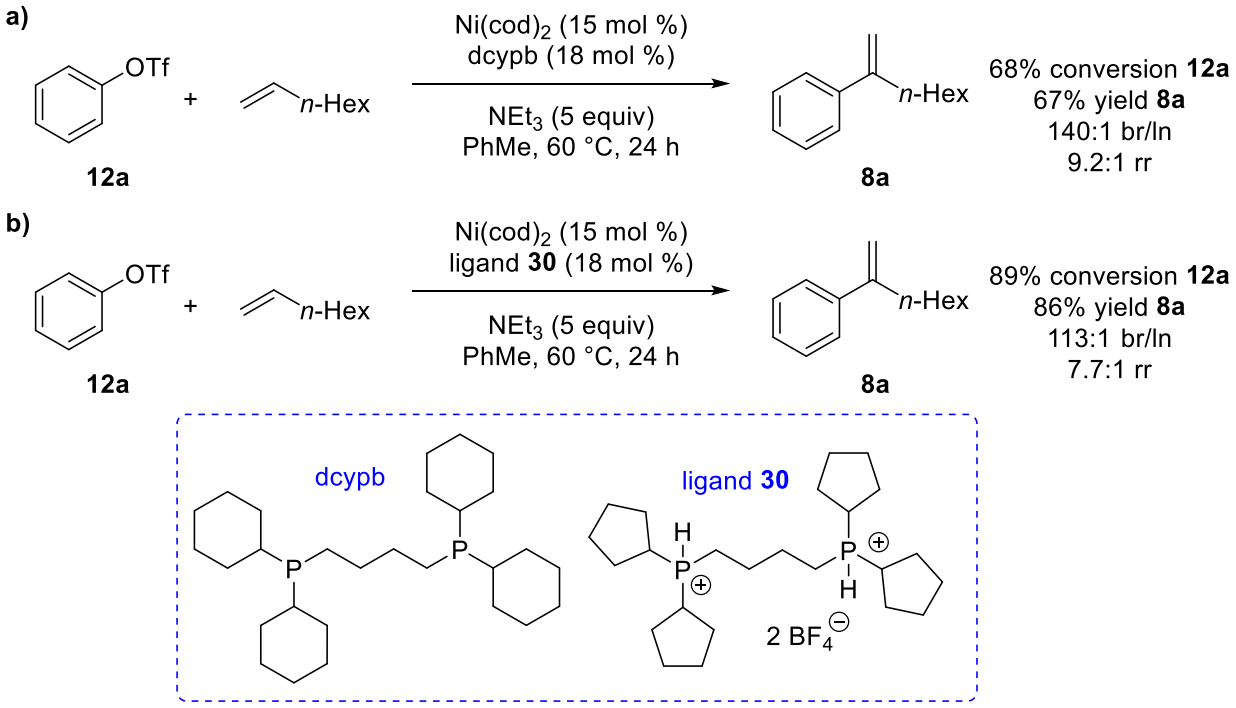
Finally, bond rotation and β-hydride elimination furnishes branched product **8**. The catalyst regenerating formal reductive elimination of HOTf from the resulting Ni–H species **20** appears from our ^{31}P NMR studies to be problematic. From this intermediate, several undesired pathways can be accessed: isomerization of products leading to the observed poor overall regioselectivities (ratio **8**:**10**, **11**, etc.), isomerization of 1-octene, or elimination to phosphonium salt **21** with possible deposition of un-ligated nickel.

Therefore, improvement of the reductive catalyst regeneration was likely necessary to improve yields and regioselectivity of the desired Heck products.

Reaction Optimization

As we attempted to optimize the reaction further, we discovered that the overall yield of the reaction could be improved by decreasing the steric demand of the phosphine ligand to contain cyclopentyl groups, as in ligand **30** (Scheme 15). The br/ln selectivity did decrease slightly, consistent with the decreased steric demand of intermediate **25**, but remained >100:1. The use of the commercially available, air-stable HBF_4 salt did not appear to affect the reaction, since the corresponding HBF_4 salt of dcypb performed identically to the free phosphine in the reaction. However, disappointingly, the overall regioisomeric ratio did not improve and remained below the levels needed for excellent synthetic utility.

Scheme 15. Use of cylopentylphosphino ligand **30**.[a]



To tackle the high amounts of product alkene isomerization, we would need to increase the rate of catalyst turnover (*vide supra*). Perhaps the most straightforward way to increase the

rate of base-assisted formal reductive elimination of HOTf would be to change the identity of the base in the reaction. Such optimization had been attempted with dcypb, with Et_3N consistently providing the best results.

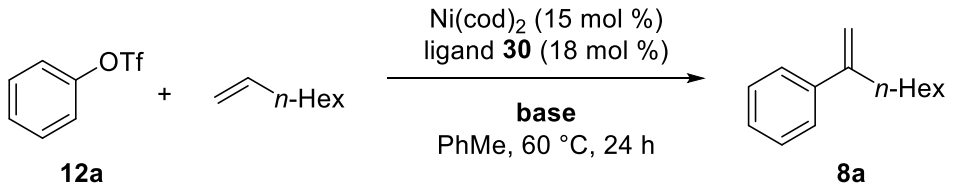
However, we returned to this question with the improved ligand **30** in hand. The results are shown in Table 3. Amine bases appeared to be optimal, and immediately the azabicyclo[2.2.2]octane bases DABCO and quinuclidine (Figure 2) provided an increase in overall yield, and more importantly gave overall regioisomeric ratios of 32:1 and 38:1, respectively (entries 5, 6). The fact that these two bases performed identically, despite their pK_a differences, suggests that the key factor is one of steric hindrance: the restriction of the bicyclooctane framework gives these bases a significantly smaller steric profile than Et_3N (entry 1). This trend is corroborated with other amine bases. For example, morpholine, with its ring structure provides higher regioselectivity than Et_3N (17:1, entry 3), while *i*-Pr_2EtN, with its larger alkyl substituents provides a lower regioselectivity (4.8:1, entry 8). When previously examining bases with dcypb, we had inadvertently overlooked that DABCO also provides excellent regioselectivities, since the yield was significantly lower than with Et_3N (entry 19). On the other hand, inorganic bases uniformly provided insignificant yields of Heck products (entries 13–16), while strong bases such as KO*t*-Bu or KHMDS resulted in complete consumption of PhOTf, but no Heck products (entries 17, 18).

Figure 2. The azabicyclo[2.2.2]octane bases DABCO and quinuclidine.

DABCO
pK_a: 8.82, 2.97

quinuclidine
pK_a: 11.0

Table 3. Evaluation of bases.[a]



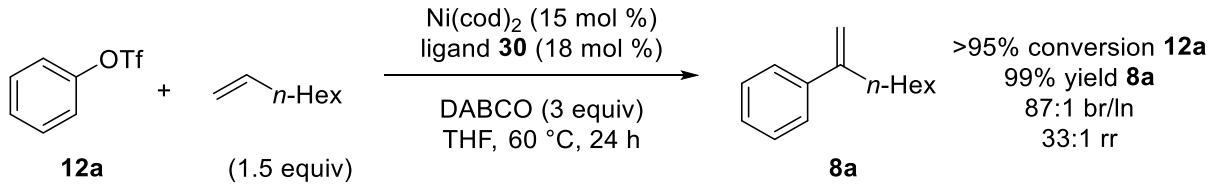
12a **8a**

Entry	Base	(equiv)	Conversion **12a** (%)	Yield **8a** (%)	br/ln	rr
1	Et_3N	5.0	89	86	>100:1	7.5:1
2	$NMeCy_2$	5.0	84	75	75:1	4.3:1
3	morpholine	5.0	46	39	43:1	17:1
4	Et_2NH	5.0	73	67	73:1	24:1
5	**DABCO**	**3.0**	**99**	**100**	**>100:1**	**32:1**
6	**quinuclidine**	**3.0**	**99**	**100**	**>100:1**	**38:1**
7	*n*-Bu_3N	5.0	39	39	64:1	3.0:1
8	Hünig's base (*i*-Pr_2EtN)	5.0	22	21	90:1	4.8:1
9	DBU	5.0	23	–[b]	–	–
10	urotropine	3.0	10	11	61:1	11:1
11	proton sponge	3.0	13	16	12:1	7.6:1
12	Bu_4NOAc	3.0	73	0	–	–
13	$NaHCO_3$	3.0	7	2	–	–
14	K_2CO_3	3.0	7	1	–	–
15	K_3PO_4	3.0	5	2	–	–
16[c]	Cs_2CO_3	3.0	16	0	–	–
17[c]	KO*t*-Bu	5.0	99	0	–	–
18[c]	KHMDS	3.0	99	0	–	–
19[c]	DABCO	3.0	52	43	84:1	34:1

[a] Conversions and yields determined by GC with dodecane as internal standard [b] product overlapped with base in chromatogram [c] with dcypb instead of ligand **30**

With the problem of product isomerization solved, we optimized reaction conditions with $Ni(cod)_2$ and ligand **30** to those shown in Scheme 16. The catalyst loading could be dropped to 10 mol %, and the amount of 1-octene used could be halved, to 1.5 equivalents, with no loss in yield. Use of THF rather than toluene afforded a slightly lower br/ln selectivity but a higher overall regioselectivity.

Scheme 16. Optimized conditions for the Heck reaction of aryl triflates.[a]



12a **8a**

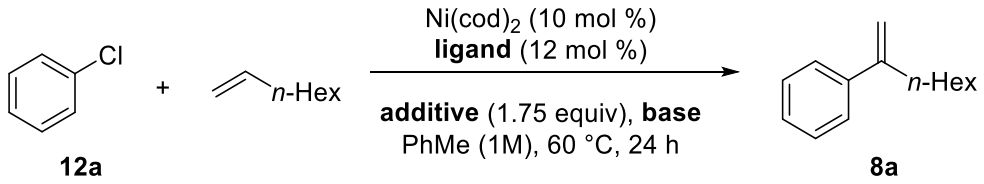
[a] Conversions, yields, and alkene isomer ratios (as in Scheme 6) determined by GC using dodecane as an internal standard.

Reaction of Other Aryl Electrophiles

One of the advantages of using nickel in catalysis is its facile oxidative addition to a wide variety of aryl–heteroatom bonds.[44] First, we decided to revisit the use of aryl chlorides, despite the failure to achieve adequate yields using dcypb and Et_3N (Scheme 12b; Table 4, entry 1). Gratifyingly the use of DABCO in combination with ligand **30** produced good yields of the desired Heck products from chlorobenzene in good br/ln selectivity and overall rr (entry 3). No product was seen in the absence of TESOTf, again reinforcing the necessity of entry to the cationic Heck manifold for successful reaction (entry 2). Use of Et_3N rather than DABCO, even with ligand **30**, afforded yields only slightly higher than the catalyst loading (entry 4). Other

[44] a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature*, **2014**, *509*, 299–309. b) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319–6332.

Table 4. Evaluation of counterion exchange reagents for chlorobenzene.[a]



12a **8a**

Entry	Additive	Ligand	Base	Conversion **12a** (%)	Yield **8a** (%)	br/ln	rr
1	TESOTf	dcypb	Et_3N	29	21	>100:1	0.3:1
2	none	**30**	DABCO	12	2	—	—
3	TESOTf	**30**	DABCO	61	64	59:1	18:1
4	TESOTf	**30**	Et_3N	22	20	>100:1	1.2:1
5	NaOTf	**30**	DABCO	11	0	—	—
6	TMSOTf	**30**	DABCO	14	4	—	—
7[b]	TESOTf	**30**	DABCO	82	87	63:1	36:1

[a] Conversions, yields and alkene isomer ratios (as in Scheme 6) determined by GC with dodecane as internal standard [b] Optimized conditions: $Ni(cod)_2$ (10 mol %), **30** (12 mol %), DABCO (5 equiv), TESOTf (2 equiv), PhMe (0.5 M), 60 °C, 24 h

activators such as NaOTf (entry 5) or TMSOTf (entry 6) were also unsuccessful in performing the counterion exchange, the latter likely because of its instability at elevated temperatures. Finally, after a short optimization of the reaction conditions to include additional DABCO and more dilute conditions, excellent yields and selectivities of Heck product **8a** were observed (entry 7). The necessary use of DABCO for efficient counterion exchange suggests that perhaps, rather than a direct counterion exchange from TESOTf, that the silylated ammonium triflate salt of DABCO (with its reduced steric profile or electronic differences compared to Et_3N) is involved in the counterion exchange step.

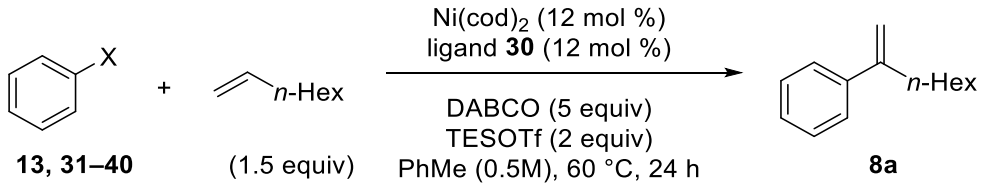
The success in using TESOTf to access the cationic Heck mechanistic pathway beginning from more coordinating Ni–Cl intermediates prompted us to investigate the use of other classes of aryl electrophiles. Specifically, there has recently been great interest in the ability of nickel to oxidatively add to relatively inert C(sp^2)–O bonds for cross-coupling reactions.[45] The first reaction of this sort was reported by Snieckus and coworkers: a Kumada cross-coupling of aryl carbamates.[46] More recently, aryl acetates[47] and pivalates[48] and even aryl methyl ethers[49] and aryl alkoxides[50] have been shown to be good electrophiles for nickel-catalyzed cross-coupling reactions, and the oxidative addition of aryl carbamates and sulfamates has been studied mechanistically.[51]

Therefore, a variety of different electrophiles were tested using counterion exchange reagent TESOTf, in hopes of intercepting a common cationic Heck pathway to produce **8a** in good yields and selectivities (Table 5). We were excited to see that, indeed, TESOTf effected a counterion exchange and improved yields for mesylates (entry 2), tosylates (entry 3), and sulfamates (entry 4) in addition to chlorides. Moreover, the product yields obtained in the absence of TESOTf are correlated with the stability of the counterion (pK_a TsOH < MsOH < NH_2SO_3H). This suggests that the only reaction pathway available under these conditions is the cationic Heck pathway (i.e., migratory insertion only occurs upon dissociation of the counterion). Unfortunately, other aryl halides could not be successfully coupled (entries 5–7). A significant

[45] Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416.
[46] Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066–4068.
[47] Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468–14470.
[48] Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422–14423.
[49] a) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428–2432. b) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866–4869.
[50] a) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4566–4570. b) Yu, D.-G.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7097–7100.
[51] Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352–6363.

distinction is often seen in nickel catalysis between the reactivity of aryl chlorides and triflates, which typically undergo a polar, concerted oxidative addition, and the reactivity of aryl bromides and iodides, which typically undergo a radical oxidative addition.[44b] Less reactive aryl acetates, carbonates, or ethers also did not yield Heck products (entries 8–11).

Table 5. Evaluation of other electrophiles with TESOTf.[a]



13, 31–40 (1.5 equiv) **8a**

Entry	X	Yield **8a** (%)	Yield **8a** without TESOTf (%)	br/ln
1	Cl(**13**)	87	1	63:1
2	OMs(**31**)	81	25	60:1
3	OTs(**32**)	75	33	39:1
4	OSO_2NMe_2(**33**)	65	8	59:1
5	Br(**34**)	4	0	—
6	I(**35**)	2	0	—
7	F(**36**)	0	—	—
8	OAc(**37**)	1	—	—
9	OCO_2t-Bu(**38**)	0	—	—
10	OMe(**39**)	0	—	—
11	$OCOCF_3$(**40**)	4	—	—

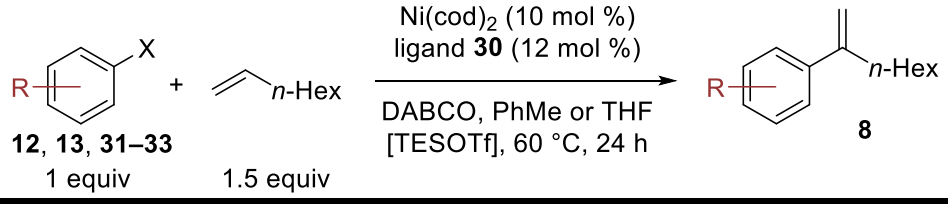
[a] Yields determined by GC using dodecane as an internal standard.

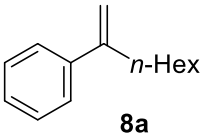
Reaction Scope

With these optimized conditions in hand for both aryl triflates and aryl chlorides, mesylates, tosylates, and sulfamates, we set out to explore the scope of both the arene and alkene coupling partners. First, a range of substituted aryl electrophiles were subjected to the reaction conditions (Scheme 17). A variety of substituents were tolerated, from electron-rich (**8b**) to electron-poor (**8c**, **8j**), with electron-poor substrates providing slightly slower reaction rates, but excellent regioselectivities. Very electron-rich products were prone to isomerization upon purification. Therefore, regioselectivities are reported before and after purification for **8b** and **8w**.

Gratifyingly, reactions involving counterion exchange with TESOTf to access the cationic intermediate worked only slightly less efficiently than simply beginning with the aryl triflate. In some cases, extended reaction times (48 h) provided superior yields (**8c, 8j, 8n**), and for non-triflate counterions, TIPSOTf rather than TESOTf proved to be more stable for extended reaction times at the necessary temperatures (**8c**, **8j**). Substitution at the *para*- and *meta*-positions, for the most part, was also well tolerated. *Ortho*-substitution resulted in lower yield and a slightly reduced rr (**8l**), making this method complementary to the related work by Zhou and coworkers, which produced higher levels of regioselectivity for arenes with *ortho*-substitution.[31]

Scheme 17. Aryl electrophile scope.[a]





8a

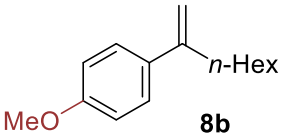
X = OTf: 99% rr: 33:1 br/ln: 87:1

X = Cl: 81% rr: 36:1 br/ln: 62:1

X = OMs: 91% rr: 30:1 br/ln: 60:1

X = OTs: 72% rr: 20:1 br/ln: 37:1

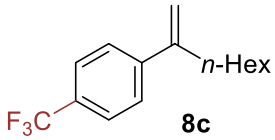
X = OSO_2NMe_2: 61% rr: 20:1 br/ln: 59:1



8b

X = OTf: 96% rr: 9.3:1 [25:1][b] br/ln: 86:1

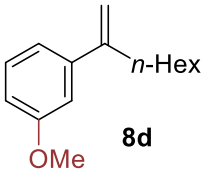
X = Cl:[c] 64% rr: 23:1 br/ln: 84:1



8c

X = OTf:[d] 71% rr: 31:1 br/ln: 115:1

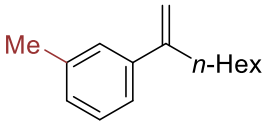
X = Cl:[e] 57% rr: 21:1 br/ln: 164:1



8d

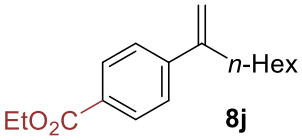
X = OTf: 84% rr: 25:1 br/ln: 75:1

X = OMs: 59% rr: 34:1 br/ln: 112:1



8e

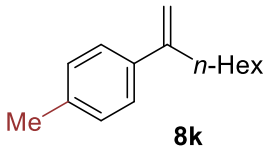
X = OTf: 73% rr: 20:1 br/ln: 63:1



8j

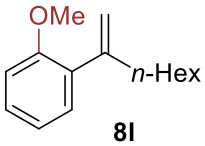
X = OTf:[c] 73% rr: 39:1 br/ln: 83:1

X = OMs:[e] 54% rr: 57:1 br/ln: 107:1



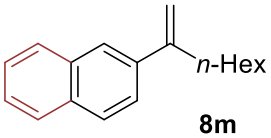
8k

X = OTf:[c] 71% rr: 22:1 br/ln: 60:1



8l

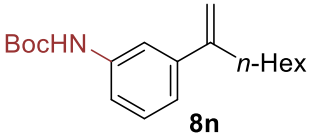
X = OTf: 57% rr: 19:1 br/ln: 38:1



8m

X = OTf: 97% rr: 25:1 br/ln: 57:1

X = OTs: 90% rr: 24:1 br/ln: 45:1



8n

X = OTf:[c] 56% rr: 33:1 br/ln: 58:1

[a] All yields isolated. rr = ratio of **8** to all other isomers, mainly olefin isomerization (as in Scheme 6, GC). br/ln = ratio of **8** to linear product **9** (GC). Reaction conditions: for X = OTf: $Ni(cod)_2$ (10 mol %), ligand **30** (12 mol %), DABCO (3 equiv), THF (1 M), 60 °C, 24 h. For X = Cl, OMs, OTs: $Ni(cod)_2$ (10 mol %), ligand **30** (12 mol %), DABCO (5 equiv), TESOTf (2 equiv), PhMe (0.5 M), 60 °C, 24 h. [b] rr before purification. [c] 48 h. [d] $Ni(cod)_2$ (15 mol %), ligand **30** (18 mol %), 1-octene (3 equiv), 48 h. [e] TIPSOTf (2 equiv), 48 h.

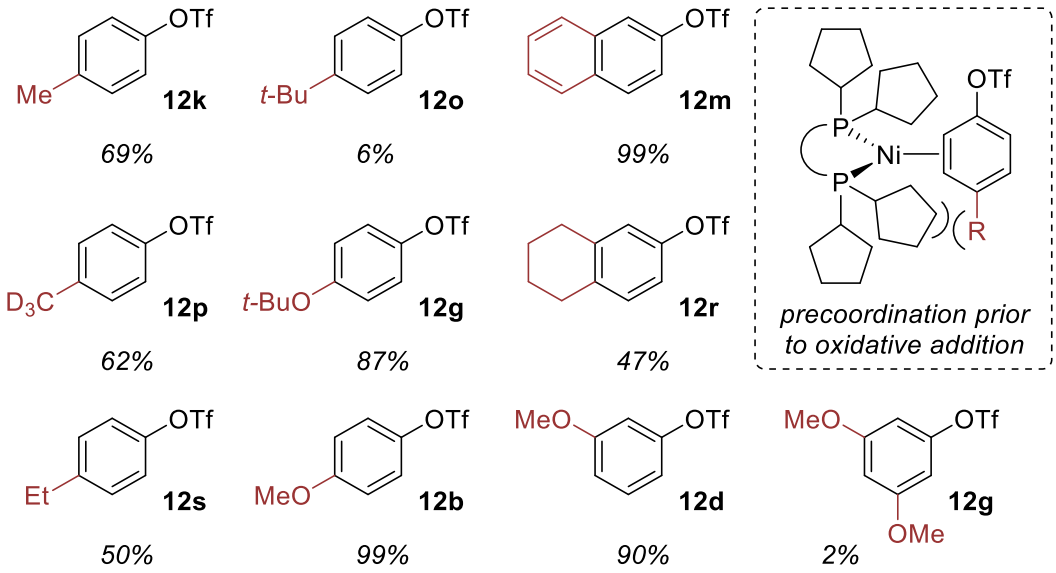
Although electrophile scope was broad, we found that substrates with *para*-alkyl groups such as **12k** suffered from reduced yields and required longer reaction times. This puzzling observation does not seem to stem from the presence of benzylic C–H bonds, since *para*-*t*-BuPhOTf (**12o**) resulted in almost no conversion, suggesting a steric phenomenon. Nakamura and co-workers have proposed an explanation for just such an effect: the rate-limiting pre-coordination of the least hindered portion of the arene, forming a π-complex prior to oxidative addition, for Ni-catalyzed cross-coupling reactions.[52] Bryan and McNeil have also studied this effect in the context of Ni-catalyzed chain-growth polymerizations and found coordination and preferential "intramolecular" oxidative addition to be particularly favored for electron-rich bidentate phosphine ligands similar to **30**.[53] This effect has also been observed in other nickel complexes and reactions.[54]

We sought to explore this mechanistic feature further by preparing a variety of *para*-substituted aryl triflates and subjecting them to the reaction conditions (Scheme 18). Overall, the results are consistent with steric crowding of the ligand cyclopentyl groups and the group in the *para*-position. Substrates with groups in the *meta*-position (e.g., **12d**, **12e**) can coordinate on the

[52] Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 15258–15259.
[53] Bryan, Z. J.; McNeil, A. J. *Chem. Sci.* **2013**, *4*, 1620–1624.
[54] a) Ateşin, T. A.; Li, T.; Lachaize, S.; García, J. J.; Jones, W. D. *Organometallics* **2008**, *27*, 3811–3817. b) Bach, I.; Pörschke, K.-R.; Goddard, R.; Kopiske, C.; Krüger, C.; Rufińska, A.; Seevogel, K. *Organometallics* **1996**, *15*, 4959–4966. c) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624–627.

less sterically hindered side of the arene, and react more quickly than those with *para*-substituents (as also observed by Nakamura). However, when two *meta*-substituents (**12g**) are introduced, the substrate can no longer coordinate well, and the reaction does not proceed.

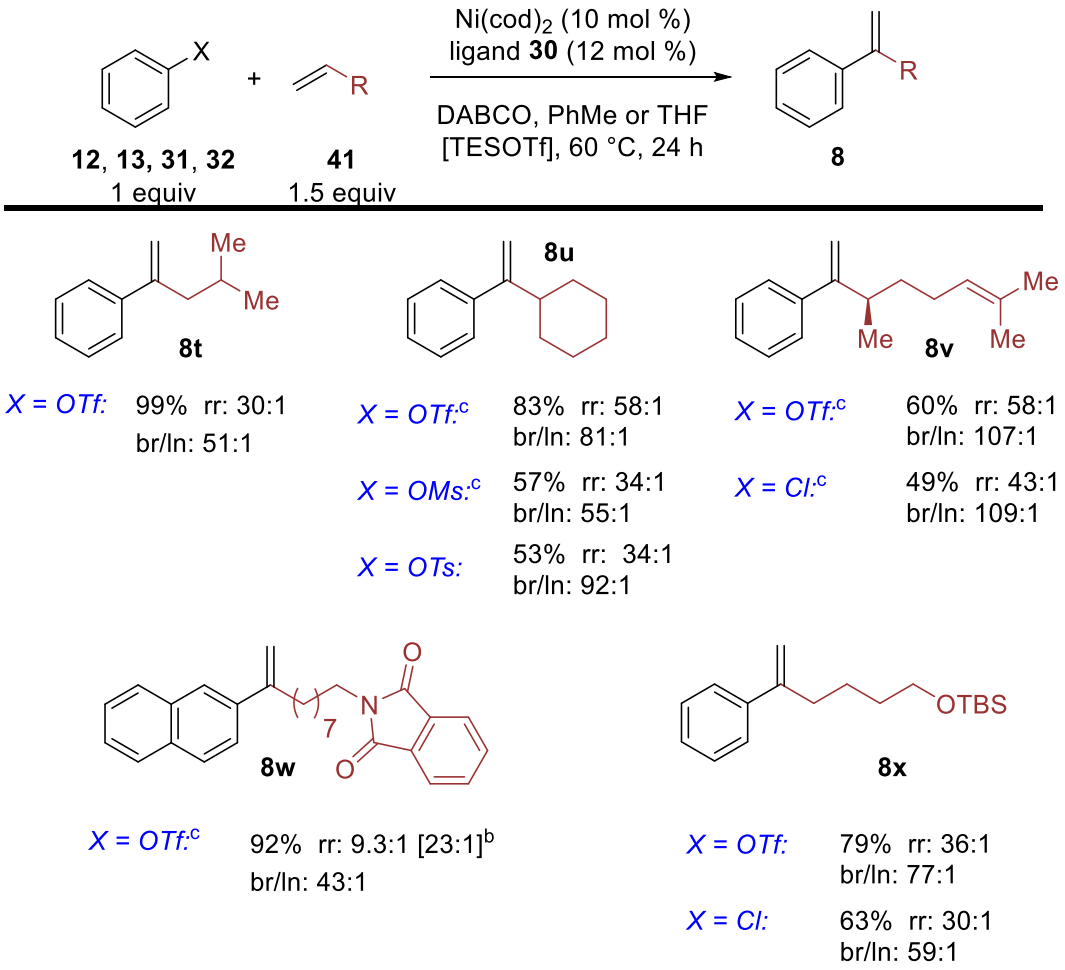
Scheme 18. Investigation of steric substitution effects.[a]



[a] GC conversion of triflate under standard conditions (24 h).

A range of aliphatic alkenes also successfully underwent the desired transformation (Scheme 19), again using triflates or chlorides/sulfonates with TESOTf. The presence of increased steric bulk at the allylic position was well tolerated, although extended reaction times were needed (**8u**). Protected alcohol and amine functional groups were compatible (**8w**, **8x**), though the presence of acidic protons (free alcohols, ketones with enolizable protons, etc.) in the alkene led to complete inhibition of the reaction. The transformation was selective for terminal olefins in the presence of more substituted alkenes, and a complete transfer of chirality from the starting alkene to the product was observed (**8v**).

Scheme 19. Scope of alkene coupling partner.[a]

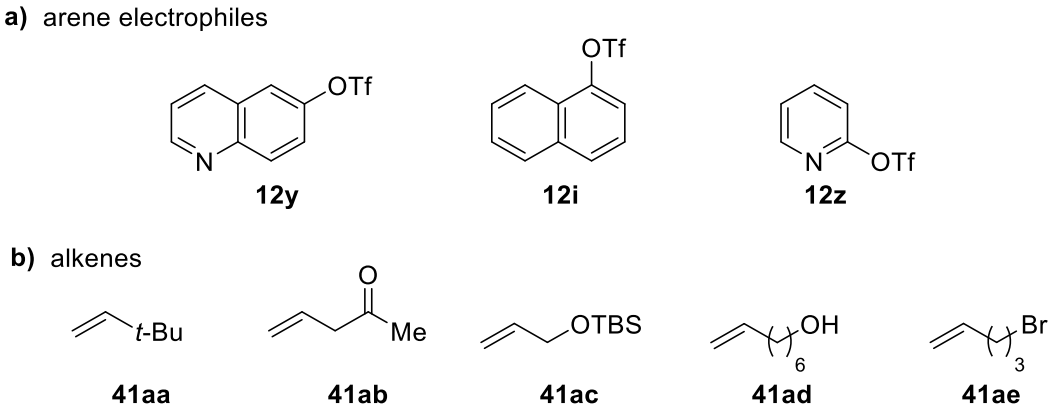


[a] All yields isolated. rr = ratio of **8** to all other isomers, mainly olefin isomerization (as in Scheme 6, GC). br/ln = ratio of **8** to linear product **9** (GC). Reaction conditions: for X = OTf: $Ni(cod)_2$ (10 mol %), ligand **30** (12 mol %), DABCO (3 equiv), THF (1 M), 60 °C, 24 h. For X = Cl, OMs, OTs: $Ni(cod)_2$ (10 mol %), ligand **30** (12 mol %), DABCO (5 equiv), TESOTf (2 equiv), PhMe (0.5 M), 60 °C, 24 h. [b] rr before purification. [c] 48 h.

Of course, there were also some limitations to this method (Figure 3). Heterocyclic substrates **12y** and **12z** afforded no product, likely due to coordination of the nitrogen to the nickel catalyst. Very sterically hindered alkenes such as **41aa** were not successfully coupled.

Any substrate containing an acidic proton such as an alcohol (**41ad**) or even a ketone with α-hydrogens (**41ab**) also produced no Heck products nor did primary alkyl bromides (**41ae**).

Figure 3. Substrates that did not provide desired Heck products.[a]

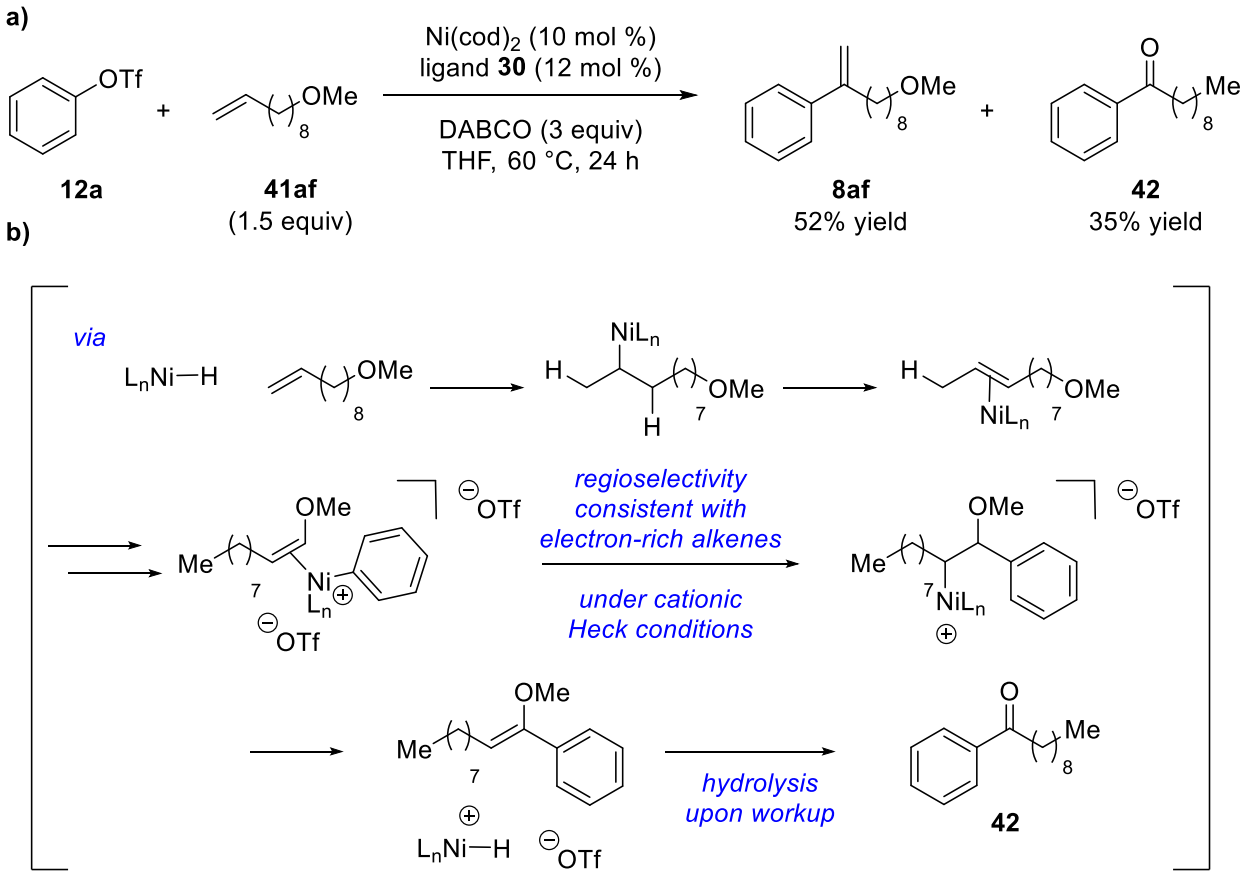


[a] <10% yield desired Heck product observed by GC and GC/MS.

Tandem Isomerization/Heck Reaction

During our studies of the scope of the reaction, we observed an unexpected byproduct of the Heck reaction of alkene **41af** containing a methyl ether (Scheme 20a). In addition to the branched Heck product (**8af**), we obtained a significant amount of the aryl ketone **42**. This product likely arises from isomerization of the alkene starting material by a Ni–H species, followed by a Heck reaction of the enol ether with the expected sense of regioselectivity for electron-rich alkenes (Scheme 20b).[9k]

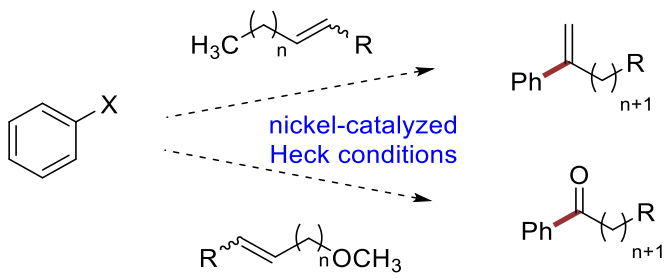
Scheme 20. Observation of ketone product.



The isomerization of the alkene over eight positions prompted us to consider whether we could use a reversible and rapid Ni–H catalyzed chain-walking isomerization reaction in tandem

with a Heck reaction to selectively trap either a terminal alkene to form the 1,1-disubstituted alkene product or a terminal methyl enol ether to form a ketone product (Scheme 21). This process could potentially generate selective molecular complexity to mixtures of internal *cis*- or *trans*-alkenes. In some ways, this reaction could be considered the reverse of many Heck/isomerization reactions beginning with terminal olefins containing a pendant alcohol, and ending with isomerization of the final alkene to form the thermodynamic sink of an aldehyde or ketone.[16,55] A similar strategy has also been recently reported for tandem Ru-catalyzed[56] olefin isomerization/W-catalyzed olefin metathesis.[57]

Scheme 21. Proposed tandem isomerization/Heck reaction.

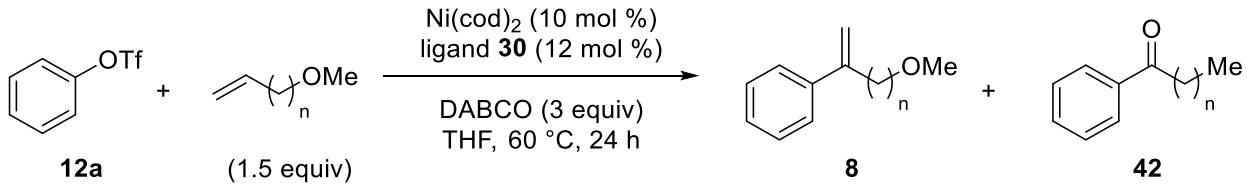


We first investigated whether the ratio of ketone and 1,1-disubstituted alkene products was dependent on alkene chain length (Table 6). The methyl ether of allyl alcohol (n = 1) did not produce any Heck products, nor did we observe significant oxidative addition to PhOTf, suggesting a stable chelate was forming between the alkene, ether, and Ni/**30** (entry 1). However, when the chain length was increased, we did observe a correlation between alkene chain length and product distribution, with fewer methylene units resulting in more ketone

[55] a) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science*, **2012**, *338*, 1455–1458. b) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340–344. c) Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 3462–3465.
[56] Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. *J. Am. Chem. Soc.* **2007**, *129*, 9592–9593.
[57] Dobereiner, G. E.; Erdogan, G.; Larsen, C. R.; Grotjahn, D. B.; Schrock, R. R. *ACS Catal.* **2014**, *4*, 3069–3076.

product **42**, consistent with a fast reversible alkene isomerization followed by a competitive Heck reaction (entry 2, 3).

Table 6. Dependence of isomerization upon alkyl chain length.[a]



12a (1.5 equiv) **8** **42**

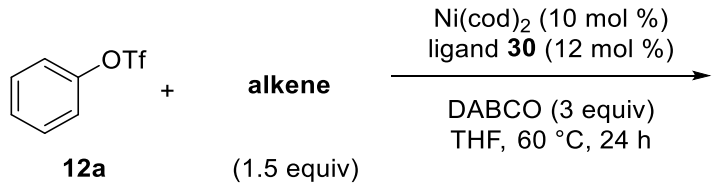
Entry	n	Conversion **12a** (%)	**8** : **42**
1	1	2	—
2	4	44	1 : 1.4
3	8	83	1.5 : 1

[a] Conversions and yields determined by GC with dodecane as internal standard.

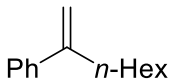
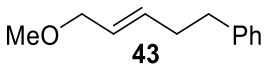
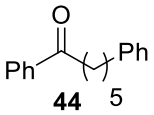
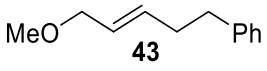
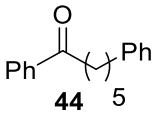
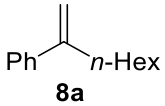
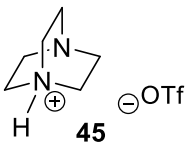
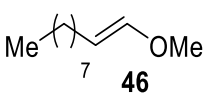
To begin studying whether or not this pathway would be feasible in cases where only one product would be possible, we tested 2-octene under our standard Heck conditions (Table 7, entry 1). However, although oxidative addition to PhOTf (**12a**) was observed, no Heck products were formed. Since accessing a Ni–H species might necessitate the completion of one turn of the Heck catalytic cycle, we added a small amount of 1-octene to the reaction mixture, but only saw Heck product corresponding to the amount of 1-octene added (entry 2). Another species found after the reaction is complete would be DABCO salt **45**, but this did not cause increased formation of Heck products either (entry 6). We observed the same results with both *cis*- and *trans*-4-octene (entry 3). Moving to the possible formation of ketone products, we also tested **43** under the same reaction conditions, and did observe trace amounts of ketone product **44** (entries 4, 5). However, after extensive reaction optimization, including ligands, bases, and additives

that had previously been shown to increase product alkene isomerization, we were not able to obtain more significant amounts of this product in this case or in the case of 2-octene.

Table 7. Evaluating tandem isomerization/Heck reactions.[a]



12a

Entry	Alkene	Additive	Conversion **12a** (%)	Yield Product (%)
1	2-octene	—	10	0
2	2-octene	1-octene (15 mol %)	25	 **8a** 16% yield
3	4-octene (*cis* or *trans*)	—	12	0
4	 **43**	—	21	 **44** 5 3% yield
5	 **43**	1-octene (15 mol %)	26	 **44** 5 2% yield  **8a** 8% yield
6	2-octene	 **45**	14	trace
7	 **46**	—	—	no Heck or ketone product

[a] Conversions and yields determined by GC with dodecane as internal standard.

Finally, most surprisingly, the proposed intermediate **46** in the isomerization shown in Scheme 20b was independently synthesized but did not result in Heck or ketone products (entry 7). To explain this, we propose that the energy barrier for the Ni/**30** complex to coordinate to any internal alkene is prohibitively high, but that in the chain-walking process, nickel remains coordinated to the same alkene, and is able to perform the migratory insertion at the electronically favored electron-rich enol ether. This hypothesis is corroborated by the fact that the only disubstituted alkenes which produced any migratory insertion product are cyclopentene and dihydrofuran, in which the alkene is both strained and has a sterically small profile. Therefore, the proposed reactions in Scheme 21 are likely not feasible, at least not under similar conditions to those developed for the branch-selective Heck reaction.

Conclusions

In summary, we have developed a Ni-catalyzed Mizoroki–Heck coupling of aryl triflates, chlorides, and other sulfonates with electronically unbiased alkenes in good yields. This reaction displays excellent branched/linear selectivity for the coupled product, with overall regioselectivities of desired to all other isomers that are ≥19:1 in all cases. This universally highly branched-selective Heck reaction also leverages the intrinsic properties of nickel to allow for the use of cheap, stable, and synthetically practical chlorides and sulfonates as coupling partners. Though the cost of $Ni(cod)_2$ is not insignificant, we hope to continue to develop alternative catalysts or pre-catalysts from inexpensive nickel sources.[58] These developments continue to show the promise of the Ni-catalyzed Heck reaction as a viable, highly selective alternative to its Pd-catalyzed counterpart.

[58] An air stable Ni(aryl)Cl precatalyst of ligand **30** was synthesized, but purification proved exceptionally challenging. Impure samples of the precatalyst were evaluated, but yields were significantly lower than with $Ni(cod)_2$/**30**: a) Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585–1592. Subsequently, a (TMEDA)Ni(*o*-tolyl)Cl precatalyst was simultaneously reported by Doyle and coworkers and Monfette and Magano, in which the TMEDA ligand can be replaced by phosphines or other ligands. Monfette and Magano specifically demonstrated that this precatalyst was equally as effective as $Ni(cod)_2$ in carrying out the Heck reaction of chlorobenzene and 1-octene under the conditions reported in this chapter: b) Shields, J. D.; Gray, E. E.; Doyle, A. G. *Org. Lett.* **2015**, *17*, 2166–2169. c) Magano, J.; Monfette, S. *ACS Catal.* **2015**, *5*, 3120–3123.

Experimental Section

Materials and Methods

All reactions were performed under an inert atmosphere of nitrogen with exclusion of moisture from reagents and glassware unless otherwise noted. All Ni-catalyzed coupling reactions were carried out in a glovebox (MBraun Unilab) filled with dry nitrogen. Heating was carried out using a Chemglass dryblock stir plate within the glovebox. $Ni(cod)_2$ and ligand **30** were purchased from Strem Chemicals (Newburyport, MA) and stored in the glovebox. $Ni(cod)_2$ was stored at –20 °C, and it is crucial that it is a bright yellow color. Samples that appeared yellow-grey gave reduced yields. Toluene, THF, diethyl ether, and dichloromethane were degassed by sparging with nitrogen and dried by passage through a column of activated alumna on an SG Water solvent purification system. Aryl triflates, chlorides, and sulfonates were either purchased from commercial vendors and sparged with nitrogen before use, or prepared using standard procedures[59] then sparged with nitrogen and dried over 3 Å MS. 1-octene, vinylcyclohexane, (–)-β-citronellene, saffrole, and allyl benzene were distilled from Na prior to use. Other alkenes were used as purchased after sparging with nitrogen. Triethylsilyl trifluoromethanesulfonate (TESOTf) was distilled from CaH_2 under reduced pressure prior to use to give best yields. Alternatively, TESOTf can be used directly from the manufacturer though some reduction in yield was obtained, particularly if the solution was a dark brown rather than colorless (indicating purity). All other reagents (including DABCO) were used as received. Commercially available chemicals were purchased from either Sigma-Aldrich Chemical Company (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Acros Organics (Pittsburgh, PA), or TCI America (Portland, OR). Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated Science silica gel

[59] (a) Triflates and mesylates: Kleimark, J.; Hedström, A.; Larsson, P.-F.; Johansson, C.; Norrby, P.-O. *ChemCatChem*, **2009**, *1*, 152–161. (b) 2-Napthyl tosylate: Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848–13849. (c) Sulfamate: Quasdorf, K. W.; Andoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352–6363.

(EM 60-F254) plates. Visualization was accomplished with UV light (254 nm) and exposure to either ceric ammonium molybdate (CAM), anisaldehyde, or $KMnO_4$ solution followed by heating. Column chromatography was carried out on a Biotage Isolera flash chromatography system using SNAP KP-Sil or HP-Sil columns (silica gel, average particle size 50 μm and 25 μm respectively).

^{1}H NMR Spectra were obtained on either a Bruker 400 MHz, Bruker 600 MHz, or Varian Inova 500 MHz NMR instrument; ^{13}C spectra were recorded on a Bruker 400 MHz (at 100 MHz) NMR instrument. Chemical shifts (^{1}H and ^{13}C) are reported in parts per million and referenced to the residual solvent peak (for $CDCl_3$, δ = 7.27 ppm, 77.0ppm respectively). The following designations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad), app (apparent). IR spectra were obtained on an Agilent Cary 630 FT-IR spectrometer equipped with an ATR accessory. High-resolution mass spectrometry data were acquired by the Department of Chemistry Instrumentation Facility, Massachusetts Institute of Technology on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR Mass Spectrometer. Gas chromatography (GC) was performed on an Agilent 5870 GC (HP-5 column) with a flame ionization detector. GC/MS was performed on an Agilent 5870 GC (HP-5ms column) with an Agilent 5975C MSD. Dodecane (99+%, Alfa Aesar) was used as an internal standard for quantification.

Ni-Catalyzed Heck Reactions

General Procedures

A) For aryl triflates: In a glovebox, ligand **30** (0.06 mmol, 0.12 equiv) and $Ni(cod)_2$ (0.05 mmol, 0.10 equiv) were weighed into an 8mL vial. THF (1 M), DABCO (1.5 mmol, 3.0 equiv), and alkene (0.75 mmol, 1.5 equiv) were added with stirring. The aryl triflate (0.5 mmol, 1.0 equiv) was then added, the vial was capped, and the reaction mixture was heated to 60 °C for 24 h. When completed, the reaction mixture was removed from the glovebox and 3.0 mL of benzene was added.

B) For aryl chlorides, mesylates, tosylates, and sulfamates: In a glovebox, ligand **30** (0.06 mmol, 0.12 equiv) and $Ni(cod)_2$ (0.05 mmol, 0.10 equiv) were weighed into an 8mL vial. Half the toluene (0.5 M in total), DABCO (2.5 mmol, 5.0 equiv), and alkene (0.75 mmol, 1.5 equiv), and were added with stirring. The aryl chloride, mesylate, tosylate or sulfamate (0.5 mmol, 1.0 equiv) was then added, and the sides of the vial were rinsed with the remaining toluene. Triethylsilyl trifluoromethanesulfonate (TESOTf, 1.0 mmol, 2.0 equiv) was then added, the vial was capped, and the reaction mixture was heated to 60 °C for 24 h. When completed, the reaction mixture was removed from the glovebox and 400 µL of dry methanol was added to quench the remaining TESOTf and TESCl and allowed to stir at room temperature (capped) for 20 min. If this step is not carried out, water from the SiO_2 will form the disilyl ether, TES_2O, which, for non-polar substrates can be nearly impossible to separate via column chromatography.

The silyl ether TESOMe is volatile and can be removed under reduced pressure. After the methanol quench, 3.0 mL of benzene was added.

Both A) and B): For reactions analyzed by gas chromatography (GC), the crude mixture was passed through a plug of SiO_2, using a small amount of CH_2Cl_2 to solubilize any precipitate, and eluting with diethyl ether. An external standard (dodecane, 70.2 µL, 1.0 equiv) was then added, the sample was diluted to 50 mL in a volumetric flask and submitted to GC analysis. The desired branched product area was then compared to both the linear product area (br/ln) and to the sum of all isomers, including linear, of the product (rr). The identity of the peak corresponding to the linear product isomer was confirmed by reaction of the substrates with $Ni(cod)_2$ in the absence of ligand **30**, giving a roughly 1:1 mixture of branched/linear products. Mechanistically, there are two sources of regioisomers: br/ln selectivity is determined in the migratory insertion step, while overall rr can be degraded later in the catalytic cycle by reinsertion of a Ni–H species to the product and subsequent isomerization. As expected, the major isomerized product is the trisubstituted (*E*)-styrene derivative (**10**, Scheme 6). When very bulky monodentate phosphines are used, this is the major product. GC conditions: 50 °C for 2 min, ramp 20 °C/min to 250 °C, hold at 250 °C for 10 min.

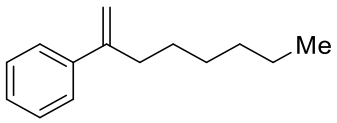
For isolated yields, 15 µL was removed from the mixture diluted in benzene and added to a small amount of hexanes to precipitate out any nickel species. This sample was filtered with a syringe filter into a GC vial, diluted in Et_2O, and measured by GC to determine rr pre-purification. The remaining reaction mixture was passed through a short plug of SiO_2 and then purified via column

chromatography. A small amount of the final mixture was then used to prepare another GC sample to determine rr and br/ln post purification.

A Note on Purification

Some substrates, particularly the electron-rich alkenes such as **8b** and **8u** are prone to acid-catalyzed isomerization. This seems to be especially the case if the crude reaction mixture is loaded directly upon a silica column and eluted with hexanes. Running the reaction through a silica plug, eluting with benzene, tends to mitigate most of the isomerization, though not in every case. Therefore, an rr of the reaction mixture pre-purification as noted above was always obtained via GC analysis. Finally, most column chromatography was performed on Et_3N-pretreated columns to avoid any further isomerization on sensitive substrates. When pre-packed silica gel Biotage columns were used for purification, and pretreatment with Et_3N is noted below, columns were flushed with 5-8 column volumes (CV) of a mixture of 2% Et_3N in Hexanes, then equilibrated with pure hexanes for 8 CV in order to purify non-polar products well. Refer to specific substrates below for details of purification.

Characterization of Products



Oct-1-en-2-ylbenzene (8a):

From PhOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and phenyl trifluoromethanesulfonate (81 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. Complete conversion was obtained, so simple filtration through a silica plug with benzene as the eluent afforded 93.3 mg (99%) **8a** as a colorless oil (rr pre-purification: 38.3:1, rr post-purification: 32.9:1, br/ln 87:1 determind by GC analysis).

From PhCl: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and chlorobenzene (50.9 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 μL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 μL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a

silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 76.6 mg (81%) of **8a** as a colorless oil (rr pre-purification: 27.7:1, rr post purification: 35.7:1, br/ln: 62:1 determined by GC analysis).

From PhOMs: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 µL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 µL, 0.75 mmol, 1.5 equiv), and phenyl methanesulfonate (88.0 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 µL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 µL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 µL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 87.6 mg (91%) of **8a** as a colorless oil (rr pre-purification: 30.0:1, rr post purification: 30.4:1, br/ln: 59:1 determined by GC analysis).

From PhOTs: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 µL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 µL, 0.75 mmol, 1.5 equiv), and phenyl *p*-toluenesulfonate (121.3 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 µL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 µL, 1.0 mmol, 2.0 equiv) was

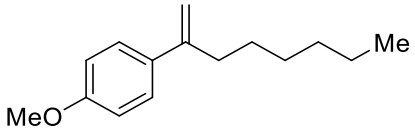
added, and the reaction was stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 66.5 mg (72%) of **8a** as a colorless oil (rr pre-purification:17.4:1, rr post purification: 19.6:1, br/ln: 37:1 determined by GC analysis).

From $PhOSO_2NMe_2$: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and $PhOSO_2NMe_2$ (82.3 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 μL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 μL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 57.4 mg (61%) of **8a** as a colorless oil (rr pre-purification: 20.1:1, rr post purification: 19.6:1, br/ln: 59:1 determined by GC analysis).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.37–7.30 (m, 2H), 7.29–7.24 (m, 1H), 5.27 (app d, *J* = 1.5 Hz, 1H), 5.06 (app d, *J* = 1.4 Hz, 1H), 2.50 (t, *J* = 7.6, 2H), 1.48–1.42 (m, 2H), 1.36–1.23 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.8, 141.5, 128.2, 127.2, 126.1, 112.0, 35.4, 31.7, 29.1, 28.3, 22.7, 14.1.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[60]



1-methoxy-4-(oct-1-en-2-yl)benzene (8b):

From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 4-methoxyphenyl trifluoromethanesulfonate (90.5 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, 100% hexanes) afforded 104.3 mg

[60] Blatter, K.; Schlüter, A.-D. *Synthesis*, **1989**, 356–359.

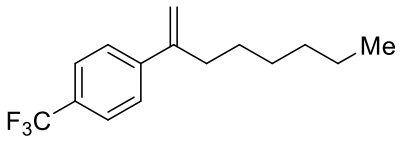
(96%) **8b** as a colorless oil (rr pre-purification: 25.2:1, rr post-purification: 9.3:1, br/ln 86:1 determined by GC analysis).

From ArCl: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 µL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 µL, 0.75 mmol, 1.5 equiv), and 4-methoxy chlorobenzene (61.2 µL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 µL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 µL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 µL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 69.6 mg (64%) of **8b** as a colorless oil (rr pre-purification: 26.1:1, rr post purification: 22.7:1, br/ln: 84:1 determined by GC analysis).

^1H NMR (600 MHz, $CDCl_3$) δ 7.38–7.35 (m, 2H), 6.89–6.85 (m, 2H), 5.20 (d, *J* = 1.6 Hz, 1H), 4.97 (d, *J* = 1.4 Hz, 1H), 3.82 (s, 3H), 2.47 (td, *J* = 7.6, 1.2 Hz, 2H), 1.49–1.40 (m, 2H), 1.35–1.25 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 158.9, 148.0, 133.9, 127.1, 113.6, 110.4, 55.2, 35.4, 31.7, 29.0, 28.3, 22.6, 14.1

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[61]



1-(Oct-1-en-2-yl)-4-(trifluoromethyl)benzene (8c):

From ArOTf: Following the general procedure **A**, ligand **30** (51.3 mg, 0.09 mmol, 0.18 equiv), $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (236 μL, 1.5 mmol, 3.0 equiv), and 4-trifluoromethylphenyl trifluoromethanesulfonate (96.0 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil pretreated with Et_3N, 100% hexanes) afforded 91.0 mg (71%) **8c** as a colorless oil (rr pre-purification: 22.6:1, rr post-purification: 31.3:1, br/ln 115:1 determined by GC analysis).

From ArCl: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (236 μL, 1.5 mmol, 3.0 equiv), and 4-trifluoromethyl chlorobenzene (66.7 μL,

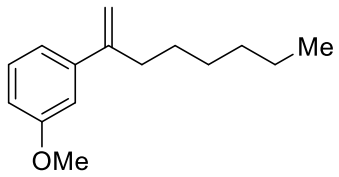
[61] Shirakawa, F.; Imazaki, Y.; Hayashi, T. *Chem. Lett.* **2008**, *37*, 654–655.

0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 µL) was used to rinse down the sides of the vial, and triisopropylsilyl trifluoromethanesulfonate (269 µL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 µL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 85.5g (57%) of **8c** as a colorless oil (rr pre-purification: 19.0:1, rr post purification: 20.7:1, br/ln: 164:1 determined by GC analysis). Note: The yield was adjusted to take into account a small amount of TIPSOMe (the result of the methanol quench) remaining inseparable from the product. Although the use of TIPSOTf allows for longer reaction times, the formation of non-volatile TIPSOMe rather than the volatile TESOMe after quenching with MeOH can make purification difficult in the case of very non-polar products.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 5.32 (app s, 1H), 5.16 (d, *J* = 1.4 Hz, 1H), 2.51 (td, *J* = 7.5, 1.2 Hz, 2H), 1.46–1.41 (m, 2H), 1.35–1.21 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.7, 145.1 (q, *J* = 1.3 Hz), 129.2 (q, *J* = 32.4 Hz), 126.4, 125.2 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 113.9, 35.2, 31.6, 28.9, 28.1, 22.6, 14.0.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[61]



1-Methoxy-3-(oct-1-en-2-yl)benzene (8d):

From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (199 μL, 1.27 mmol, 2.5 equiv), and 3-methoxy trifluoromethanesulfonate (89.5 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil pretreated with Et_3N, 100% hexanes to 99% hexanes/1% ethyl acetate) afforded 91.2 mg (84%) **8d** as a colorless oil (rr pre-purification: 35.3:1, rr post-purification: 24.6:1, br/ln 75:1 determined by GC analysis).

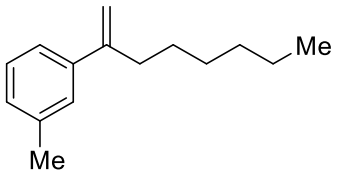
From ArOMs: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 3-methoxyphenyl methanesulfonate (77.9 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 μL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 μL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL)

was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil pretreated with Et_3N, 100% hexanes to 98% hexanes/2% ethyl acetate) afforded 64.9 mg (59%) **8d** as a colorless oil (rr pre-purification: 37.1:1, rr post-purification: 34.1:1, br/ln 112:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8.0 Hz, 1H), 7.01 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.95 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.83 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 5.06 (d, *J* = 1.5 Hz, 1H), 3.84 (s, 3H), 2.48 (td, *J* = 7.6, 1.2 Hz, 2H), 1.45 (quin, *J* = 7.3 Hz, 2H), 1.35–1.25 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 148.7, 143.1, 129.1, 118.7, 112.4, 112.14, 112.10, 55.2, 35.4, 31.7, 29.0, 28.2, 22.6, 14.1.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[61]



1-Methyl-3-(oct-1-en-2-yl)benzene (8e):

From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol,

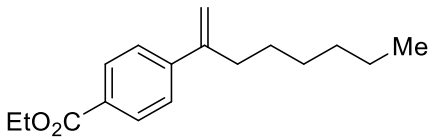
3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 3-methylphenyl trifluoromethanesulfonate (90.5 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, pretreated with Et_3N, 100%) afforded 73.7 mg (73%) **8e** as a colorless oil (rr pre-purification: 25.5:1, rr post-purification: 20.0:1, br/ln 63:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25–7.20 (m, 3H), 7.10–7.08 (m, 1H), 5.25 (d, *J* = 1.6 Hz, 1H), 5.04 (d, *J* = 1.5 Hz, 1H), 2.49 (td, *J* = 7.6, 1.2 Hz, 2H), 2.37 (s, 3H), 1.45 (quin, *J* = 7.3 Hz, 2H), 1.36–1.26 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.9, 141.5, 137.7, 128.1, 128.0, 126.9, 123.2, 111.8, 35.4, 31.7, 29.0, 28.3, 22.6, 21.5, 14.1.

IR (ATR, cm^{-1}) 3028, 2927, 2858, 2360, 2338, 1602, 1582, 1488, 1459, 1426, 1216, 1144, 892, 790, 722.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{22}$, 203.1794; found, 203.1794.



Ethyl 4-(oct-1-en-2-yl)benzoate (8j):

From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 4-CO_2Et phenyl trifluoromethanesulfonate (108.1 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil pretreated with Et_3N, 0-4% ethyl acetate/hexanes) afforded 95.1 mg (73%) **8j** as a colorless oil (rr pre-purification: 46.8:1, rr post-purification: 38.8:1, br/ln 83:1 determined by GC analysis).

From ArOMs: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 4-CO_2Et phenyl methanesulfonate (123.1 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 μL) was used to rinse down the sides of the vial, and triisopropylsilyl trifluoromethanesulfonate (269 μL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 72 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene

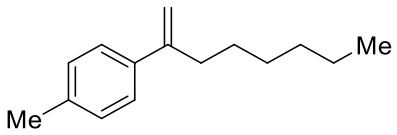
(3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, pretreated with Et_3N, 0-4% ethyl acetate/hexanes) afforded 80.6 mg of a 7.4:1 inseparable mixture of the desired product/4-CO_2EtPhOTIPS (54% adjusted yield) of **8j** as a colorless oil (rr pre-purification: 57.1:1, rr post purification: 57.1:1, br/ln: 107:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04–7.97 (m, 2H), 7.49–7.43 (m, 2H), 5.35 (d, *J* = 1.3 Hz, 1H), 5.15 (q, *J* = 1.4 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.51 (td, *J* = 7.6, 1.2 Hz, 2H), 1.46–1.41 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.34–1.25 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 148.0, 146.0, 129.5, 129.2, 126.0, 113.8, 60.8, 35.2, 31.6, 28.9, 28.1, 22.6, 14.3, 14.0.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[62]

[62] Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5915–5919.



1-Methyl-4-(oct-1-en-2-yl)benzene (8k):

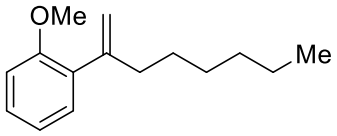
From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 2 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 4-methylphenyl trifluoromethanesulfonate (89.5 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil pretreated with Et_3N, 100% hexanes) afforded 71.6 mg (71%) **8k** as a colorless oil (rr pre-purification: 20.3:1, rr post-purification: 22.0:1, br/ln 60:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.24 (d, *J* = 1.6 Hz, 1H), 5.01 (d, *J* = 1.5 Hz, 1H), 2.48 (td, *J* = 7.6, 1.3 Hz, 2H), 2.36 (s, 3H), 1.44 (quin, *J* = 7.4 Hz, 2H), 1.35–1.25 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.6, 138.5, 136.9, 128.9, 126.0, 111.2, 35.4, 31.7, 29.1, 28.3, 22.6, 21.1, 14.1.

IR (ATR, cm^{-1}) 3082, 3025, 2926, 2857, 1625, 1566, 1513, 1457, 1377, 1299, 1186, 1120, 1040, 1019, 890, 823, 733.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{22}$, 203.1794; found, 203.1787.



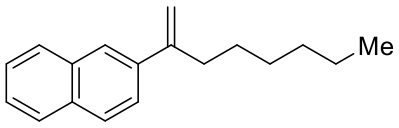
1-Methoxy-2-(oct-1-en-2-yl)benzene (8l):

From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 2-methoxyphenyl trifluoromethanesulfonate (91.5 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, 100% [2% Et_3N in hexanes] to 5% ethyl acetate/95%[2% Et_3N in hexanes]) afforded 62.7 mg (57%) **8l** as a colorless oil (rr pre-purification: 17.9:1, rr post-purification: 19.0:1, br/ln 38:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.23 (m, 1H), 7.13 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.92 (td, *J* = 7.4, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.13 (dt, *J* = 2.4, 1.4 Hz, 1H), 5.00 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 3H), 2.47 (t, *J* = 7.6 Hz, 2H), 1.37–1.21 (m, 8H), 0.86 (t, *J* = 7.0 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.5, 149.4, 132.4, 130.1, 128.2, 120.4, 113.8, 110.6, 55.4, 36.4, 31.7, 29.0, 28.1, 22.6, 14.1.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[61]



2-(Oct-1-en-2-yl)naphthalene (8m):

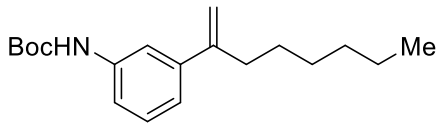
From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 2-naphthyl trifluoromethanesulfonate (136.4 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. Complete conversion was obtained, so simple filtration through a silica plug with benzene as the eluent afforded 114.0 mg (97%) **8m** as a colorless oil (rr pre-purification: 17.2:1, rr post-purification: 24.2:1, br/ln 57:1 determined by GC analysis).

From ArOTs: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 2-naphthyl *p*-toluenesulfonate (150.8 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 μL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 μL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 108.8 mg (72%) of **8m** as a colorless oil (rr pre-purification: 26.1:1, rr post purification: 23.7:1, br/ln: 45:1 determined by GC analysis).

^1H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 4H), 7.61 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.51–7.44 (m, 2H), 5.43 (d, *J* = 1.5 Hz, 1H), 5.18 (d, *J* = 1.4 Hz, 1H), 2.64 (td, *J* = 7.5, 1.2 Hz, 2H), 1.53 (quin, *J* = 7.1 Hz, 2H), 1.42–1.28 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 148.6, 138.7, 133.4, 132.7, 128.1, 127.7, 127.5, 126.0, 125.7, 124.7, 124.6, 112.6, 35.4, 31.7, 29.1, 28.3, 22.6, 14.1.

The ^1H and ^{13}C NMR spectra are in agreement with those reported in the literature.[60,62]



***tert*-Butyl (3-(oct-1-en-2-yl)phenyl)carbamate (8n):**

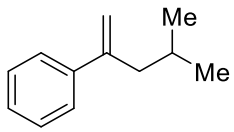
From ArOTf: Following the general procedure **A**, Ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 1-octene (118 μL, 0.75 mmol, 1.5 equiv), and 3-NHBoc-trifluoromethanesulfonate (171.1 mg, 0.50 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. Complete conversion was obtained, so simple filtration through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, 4–16% ethyl acetate/hexanes) afforded 77.0 mg (83%) of **8n** as a colorless oil (rr pre-purification: 9.0:1, rr post purification: 32.5:1, br/ln: 58:1 determined by GC analysis).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 1H), 7.34–7.29 (m, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.08 (dt, *J* = 7.6, 1.4 Hz, 1H), 6.54 (s, 1H), 5.25 (d, *J* = 1.5 Hz, 1H), 5.05 (dd, *J* = 1.4, 1.4 Hz, 1H), 2.47 (td, *J* = 7.5, 1.2 Hz, 2H), 1.54 (s, 9H), 1.49–1.39 (m, 2H), 1.37–1.22 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.7, 148.5, 142.5, 138.3, 128.8, 120.9, 117.4, 116.4, 112.3, 80.4, 35.3, 31.6, 29.0, 28.3, 28.2, 22.6, 14.1.

IR (ATR, cm^{-1}) 2929, 2858, 1700, 1606, 1585, 1526, 1489, 1432, 1392, 1367, 1310, 1280, 1233, 1155, 1054, 907, 891, 791, 729.

HRMS (*m/z*) $[M + Na]^+$ calcd for $C_{19}H_{29}NO_2$, 326.2091; found, 326.2103



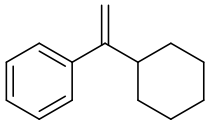
(4-Methylpent-1-en-2-yl)benzene (8t):

From PhOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 4-methyl-1-pentene (94.9 μL, 0.75 mmol, 1.5 equiv), and phenyl trifluoromethanesulfonate (81 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. Complete conversion was obtained, so simple filtration through a silica plug with benzene as the eluent afforded 79.8 mg (99%) **8t** as a colorless oil (rr pre-purification: 31.8:1, rr post-purification: 29.9:1, br/ln 51:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.33 (app dd, *J* = 8.4, 6.8 Hz, 2H), 7.29–7.25 (m, 1H), 5.27 (d, *J* = 1.8 Hz, 1H), 5.04 (d, *J* = 1.5 Hz, 1H), 2.40 (dd, *J* = 7.3, 1.1 Hz, 2H), 1.67 (app septet, *J* = 6.8 Hz, 1H), 0.88 (d, *J* = 6.6 Hz, 6H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.8, 141.5, 128.2, 127.2, 126.3, 113.4, 45.1, 26.4, 22.4.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[63]



(1-Cyclohexylvinyl)benzene (8u):

From PhOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), vinylcyclohexane (103 μL, 0.75 mmol, 1.5 equiv), and phenyl trifluoromethanesulfonate (81 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, 100% hexanes) afforded 77.0 mg (83%) of **8u** as a colorless oil (rr pre-purification: 46.1:1, rr post purification: 57.9:1, br/ln: 81:1 determined by GC analysis).

[63] Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364–9370.

From PhOMs: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), vinylcyclohexane (103 μL, 0.75 mmol, 1.5 equiv), and phenyl methanesulfonate (86.4 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 μL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 μL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 52.9 mg (57%) of **8u** as a colorless oil (rr pre-purification: 28.4:1, rr post purification: 33.9:1, br/ln: 55:1 determined by GC analysis).

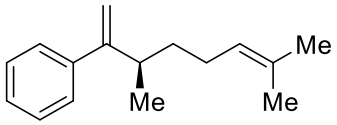
From PhOTs: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 μL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), vinylcyclohexane (103 μL, 0.75 mmol, 1.5 equiv), and phenyl *p*-toluenesulfonate (123.5 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 μL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 μL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 μL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL)

was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 49.0 mg (53%) of **8u** as a colorless oil (rr pre-purification: 37.8:1, rr post purification: 33.9:1, br/ln: 92:1 determined by GC analysis).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 4H), 7.30–7.26 (m, 1H), 5.16 (d, *J* = 1.4 Hz, 1H), 5.03 (app t, *J* = 1.3 Hz, 1H), 2.45 (t, *J* = 11.5 Hz, 1H), 1.92–1.78 (m, 4H), 1.77–1.72 (m, 1H), 1.41–1.14 (m, 5H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.0, 143.0, 128.1, 127.0, 126.6, 110.3, 42.6, 32.7, 26.8, 26.4.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[64]



(*R*)-(3,7-Dimethylocta-1,6-dien-2-yl)benzene (8v):

From PhOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), (–)-β-citronellene (136 μL, 0.75 mmol, 1.5 equiv), and phenyl

[64] Hansen, A. L.; Ebran, J.-P.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464–6472.

trifluoromethanesulfonate (81 µL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, 100% hexanes) afforded 64.0 mg (60%) of **8v** as a colorless oil (rr pre-purification: 51.2:1, rr post purification: 57.8:1, br/ln: 107:1 determined by GC analysis).

From PhCl: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 µL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), (–)-β-citronellene (136 µL, 0.75 mmol, 1.5 equiv), and chlorobenzene (50.9 µL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 µL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 µL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 48 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 µL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 10g HP-sil, pretreated with Et_3N, 100% hexanes) afforded 49.5 mg (49%) of **8v** as a colorless oil (rr pre-purification: 32.5:1, rr post purification: 43.0:1, br/ln: 109:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.31 (m, 4H), 7.29–7.25 (m, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 5.09 (ddt, *J* = 8.6, 5.7, 1.5 Hz, 1H), 5.05 (t, *J* = 1.3 Hz, 1H), 2.70 (sextet, *J* = 6.9 Hz, 1H), 2.01 (br s, 2H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.57 (s, 3H) 1.59–1.54 (m, 1H), 1.40–1.29 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.7, 143.0, 131.4, 128.1, 127.0, 126.7, 124.6, 111.0, 37.5, 36.1, 25.8, 25.7, 20.1, 17.6.

IR (ATR, cm^{-1}) 2964, 2923, 2856, 1625, 1574, 1492, 1451, 1375, 895, 776, 698.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{22}$, 215.1794; found, 215.1799.

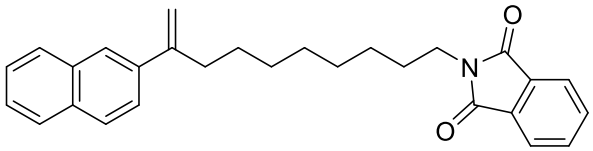
$[\alpha]^{22}_D = -0.107$ (*c* = 0.088, $CHCl_3$)

Conservation of Chirality: Enantiomers were separated by GC Varian Capillary Column CP-Chirasil-Dex CB, 25 m/0.25 mm/0.25 μm. Method: hold 2 min at 50 °C; increase 5 °C/min to 180 °C; hold 15 min at 180 °C

(–)-β-citronellene: 3.59:1 (R)/(S)

Product **8v**: 3.48:1 (R)/(S)

Therefore, there is **97% conservation of chirality** from starting alkene to product



2-(9-(Naphthalen-2-yl)dec-9-en-1-yl)isoindoline-1,3-dione (8w):

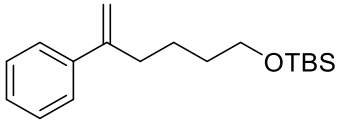
From ArOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 2-(dec-9-en-1-yl)isoindoline-1,3-dione (207 μL, 0.75 mmol, 1.5 equiv), and 2-naphthyl trifluoromethanesulfonate (138.0 mg, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 1-10% ethyl acetate with [2% Et_3N in hexanes] as an eluent) afforded 188.5 mg (92%) **8w** as a white solid (rr pre-purification 23.2:1, rr post-purification: 9.3:1, br/ln 43:1 determined by GC analysis). Note: Because of the high molecular weight of the product, the following GC method was used: 50 °C for 2 min, 20 °C/min to 320 °C, hold at 320 °C for 25 min.

^1H NMR (600 MHz, $CDCl_3$) δ 7.86–7.79 (m, 6H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.58 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.46 (tt, *J* = 8.0, 6.6 Hz, 2H), 5.41 (app s, 1H), 5.15 (app s, 1H), 3.67 (t, *J* = 7.3 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 1.66 (quin, *J* = 7.5 Hz, 2H), 1.49 (quin, *J* = 7.4 Hz, 2H), 1.39–1.25 (m, 8H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.4, 148.5, 138.6, 133.8, 133.4, 132.7, 132.1, 128.1, 127.7, 127.5, 126.0, 125.6, 124.7, 124.6, 123.1, 112.6, 38.0, 35.3, 29.22, 29.19, 29.1, 28.5, 28.2, 26.8.

IR (ATR, cm^{-1}) 3057, 2925, 2853, 1771, 1706, 1617, 1506, 1465, 1432, 1393, 1365, 1058, 1015, 888, 858, 819, 751, 717.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{28}H_{29}NO_2$, 412.2271; found, 412.2286.



***tert*-Butyldimethyl((5-phenylhex-5-en-1-yl)oxy)silane (8x):**

From PhOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 1 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), the TBS-protected alkenol (199 μL, 0.75 mmol, 1.5 equiv), and phenyl trifluoromethanesulfonate (81 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, pretreated with Et_3N, 100% hexanes then subsequent resubjection of mixed fractions to same column to separate product from remaining

alkene) afforded 114.8 mg (79%) of **8x** as a colorless oil (rr pre-purification 31.2:1, rr post purification: 35.6:1, br/ln: 77:1 determined by GC analysis).

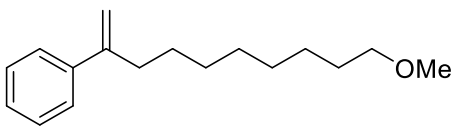
From PhCl: Following the general procedure **B**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), Toluene (500 µL), DABCO (280 mg, 2.5 mmol, 5.0 equiv), the TBS-protected alkenol (199 µL, 0.75 mmol, 1.5 equiv), and chlorobenzene (50.9 µL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial. Toluene (500 µL) was used to rinse down the sides of the vial, and triethylsilyl trifluoromethanesulfonate (226 µL, 1.0 mmol, 2.0 equiv) was added, and the reaction was stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox. Dry methanol (400 µL) was added to quench, and the reaction was stirred for 20 min at room temperature (capped). Benzene (3 mL) was then added, and an aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, pretreated with Et_3N, 100% hexanes then subsequent resubjection of mixed fractions to same column to separate product from remaining alkene) afforded 91.6 mg (63%) of **8x** as a colorless oil (rr pre-purification: 25.7:1, rr post purification: 29.8:1, br/ln: 59:1 determined by GC analysis).

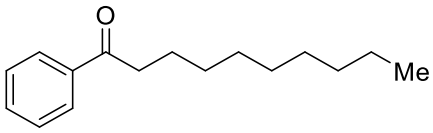
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.40 (m, 2H), 7.33 (ddd, *J* = 7.7, 6.8, 1.1 Hz, 2H), 7.28–7.25 (m, 1H), 5.28 (d, *J* = 1.5 Hz, 1H), 5.07 (app q, *J* = 1.4 Hz, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 2.53 (td, *J* = 7.4, 1.3 Hz, 2H), 1.60–1.46 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.5, 141.3, 128.2, 127.2, 126.1, 112.2, 63.0, 35.1, 32.4, 26.0, 24.4, 18.3, –5.3.

IR (ATR, cm^{-1}) 2929, 2857, 2359, 1627, 1495, 1495, 1472, 1388, 1361, 1253, 1098, 1006, 975, 893, 833, 773, 701, 661.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{18}H_{30}SiO$, 291.2139; found, 291.2137.





(10-Methoxydec-1-en-2-yl)benzene (8af), Nonyl phenyl ketone (42):

From PhOTf: Following the general procedure **A**, ligand **30** (34.2 mg, 0.06 mmol, 0.12 equiv), $Ni(cod)_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), THF (500 μL, 2 M), DABCO (168 mg, 1.5 mmol, 3.0 equiv), 10-methoxydec-1-ene (156 μL, 0.75 mmol, 1.5 equiv), and phenyl trifluoromethanesulfonate (81 μL, 0.5 mmol, 1.0 equiv) were added to an 8 mL vial and stirred at 60 °C for 24 h in a nitrogen-filled glovebox. When the reaction was done, it was removed from the glovebox and 3.0 mL benzene was added. An aliquot was taken for GC analysis as described above. The mixture was passed through a silica plug with benzene as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, pretreated with Et_3N, 100% hexanes then subsequent resubjection of mixed fractions to same column to separate close running products)

afforded 63.5 mg (52%) of **8af** as a colorless oil (rr pre-purification 19.3:1, rr post purification: 25.7:1, br/ln: 51:1 determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.33 (app t, *J* = 7.6 Hz, 2H), 7.28–7.26 (m, 1H), 5.26 (d, *J* = 1.5 Hz, 1H), 5.05 (app q, *J* = 1.4 Hz, 1H), 3.36 (t, *J* = 6.7 Hz, 2H), 3.34 (s, 3H), 2.50 (t, *J* = 7.6 Hz, 2H), 1.59–1.52 (m, 2H), 1.48–1.40 (m, 2H), 1.33–1.26 (m, 8H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.7, 141.4, 128.2, 127.2, 126.1, 112.0, 72.9, 58.5, 35.3, 29.6, 29.41, 29.35, 29.2, 28.2, 26.1.

IR (ATR, cm^{-1}) 2925, 2855, 1627, 1494, 1458, 1386, 1196, 1118, 1028, 892, 777, 702.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{26}O$, 247.2056; found, 247.2064.

Also isolated was ketone **42** as a colorless oil (41.0 mg, 35%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99–7.95 (m, 2H), 7.59–7.54 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.74 (app p, *J* = 7.4 Hz, 2H), 1.41–1.22 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H).

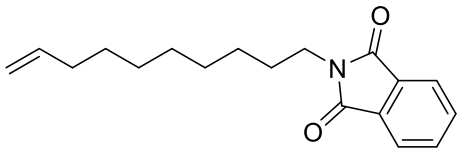
^{13}C NMR (151 MHz, $CDCl_3$) δ 200.6, 137.1, 132.9, 128.6, 128.1, 38.7, 31.9, 29.51, 29.48, 29.41, 29.3, 24.4, 22.7, 14.1.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[65]

[65] Lin, R.; Chen, F.; Jiao, N. *Org. Lett.* **2012**, *14*, 4158–4161.

Synthesis of Substrates and Authentic Product Samples

Non-Commercially Available Alkenes:



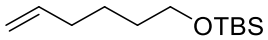
2-(Dec-9-en-1-yl)isoindoline-1,3-dione (41w):[66] To a suspension of 9-decen-1-ol (1.4 mL, 7.85 mmol, 1.0 equiv), phthalimide (1.15 g, 7.85 mmol, 1.0 equiv) and triphenlyphosphine (2.06 g, 7.85 mmol, 1.0 equiv) in THF (24 mL, 0.33 M) at 0 °C was added dropwise diisopropyl azodicarboxylate (DIAD) (1.55 mL, 7.85 mmol, 1.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred overnight. 100 mL Et_2O was added and the slurry was filtered to remove triphenylphosphine oxide. The filtrate was concentrated. Column chromatography (Biotage 50 g HP-sil, 1–18% ethyl acetate/hexanes) afforded 1.60 g (71%) of **41w** as a clear oil. The product was transferred to a vial, sparged with N_2 for 20 min, and dried over 3Å mol sieves overnight before using in the Heck reaction.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.80 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 4.99 (ddt, *J* = 17.2, 1.8, 1.7 Hz, 1H), 4.92 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H), 3.68 (t, *J* = 7.3 Hz, 2H), 2.06–2.00 (m, 2H), 1.67 (app quin, *J* = 7.3 Hz, 2H), 1.38–1.25 (m, 10H).

[66] Procedure adopted from: Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2000**, *56*, 8433–8441.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.4, 139.1, 133.7, 132.1, 123.1, 114.1, 38.0, 33.7, 29.3, 29.1, 29.0, 28.8, 28.5, 26.8.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[67]



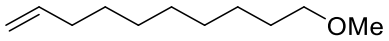
tert-Butyl(hex-5-en-1-yloxy)dimethylsilane (41x): To a solution of 5-hexen-1-ol (2.70 mL, 22.5 mmol, 1.0 equiv) in DMF (22.5 mL, 1 M) was added imidazole (4.59 g, 67.4 mmol, 3.0 equiv) followed by *tert*-butyldimethylsilyl chloride (4.41 g, 29.2 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of 20 mL saturated aq. NH_4Cl. Et_2O (80 mL) and H_2O (70 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (2x70 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (Biotage 100 g HP-Sil, 0–6% ethyl acetate/hexanes) afforded 3.38 g (70%) of **41x** as a clear oil. The product was transferred to a vial, sparged with N_2 for 20 min, and dried over 3Å mol sieves overnight before using in the Heck reaction.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.01 (ddt, *J* = 17.1, 2.2, 1.6 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.4, 1.3 Hz, 1H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.07 (tdt, *J* = 7.9, 6.7, 1.4 Hz, 2H), 1.60–1.49 (m, 2H), 1.48–1.39 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H).

[67] Makado, G.; Morimoto, T.; Sugimoto, Y.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K. *Adv. Synth. Catal.* **2010**, *352*, 299–304.

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.9, 114.3, 63.1, 33.5, 32.3, 26.0, 25.3, 18.4, –5.28.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[68]



10-Methoxydec-1-ene (**41af**):[69] A solution of NaH (960 mg, 40.0 mmol, 2.0 equiv) in THF (20 mL, 1 M) was cooled to 0 °C and 9-decen-1-ol (3.56 mL, 20.0 mmol, 1.0 equiv) was added slowly. After stirring for 15 min, methyl iodide (3.60 mL, 58.0 mmol, 2.9 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched by the addition of 20 mL saturated aq. NH4Cl and stirred for 10 min. Et_2O (60 mL) and H_2O (60 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (2x70 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (Biotage 50 g HP-sil, 1–10% ethyl acetate/hexanes) afforded 3.01 g (88%) of the desired methyl ether **41af** as a clear oil. The product was transferred to a vial, sparged with N_2 for 20 min, and dried over 3Å mol sieves overnight before using in the Heck reaction.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.03–4.96 (m, 1H), 4.93

[68] Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320–328.
[69] Feng, J.-P.; Shi, Z.-F.; Li, Y.; Zhang, J.-T.; Qi, X.-L.; Chen, J.; Cao, X.-P. *J. Org. Chem.* **2008**, *73*, 6873–6876.

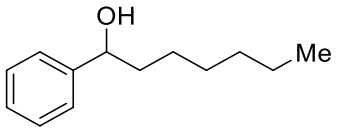
(ddt, J = 10.2, 2.2, 1.3 Hz, 1H), 3.37 (t, J = 6.7 Hz, 2H), 3.34 (d, J = 0.6 Hz, 3H), 2.08–2.00 (m, 2H), 1.62–1.53 (m, 2H), 1.41–1.26 (m, 10H).

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.2, 114.1, 72.9, 58.5, 33.8, 29.7, 29.44, 29.42, 29.1, 28.9, 26.1.

IR (ATR, cm^{-1}) 2979, 2925, 2855, 1641, 1457, 1387, 1195, 119, 992, 908.

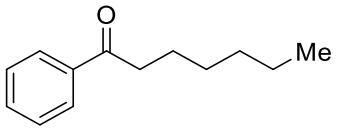
HRMS (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{22}O$, 171.1743; found, 171.1739.

Independent Synthesis of Isomerically Pure Branched Product 8a:

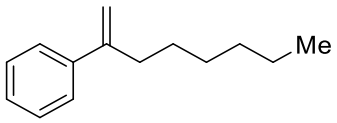


1-Phenylheptan-1-ol (47): To a solution of 1-heptanal (1.27 mL, 9.12 mmol, 1.0 equiv) in Et_2O (29.4 mL) at 0 °C under nitrogen was added a solution of phenyl lithium (1.8 M in *n*-butyl ether, 7.60 mL, 13.7 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 4.5 h. Saturated aq. NH_4Cl (9 mL) was added and stirred for 15 min. Additional Et_2O (50 mL) and H_2O (50 mL)

were added, and the layers were separated. The aqueous layer was extracted with Et_2O (2x70 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (Biotage 50 g HP-Sil, 1–10% ethyl acetate/hexanes) afforded 1.32 g (75%) of desired alcohol **47** as a clear oil.



1-Phenylheptan-1-one (48): To a solution of **47** (1.32g, 6.87 mmol, 1.0 equiv) in CH_2Cl_2 (6.90 mL) was added 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (109 mg, 0.69 mmol, 0.1 equiv) followed by (diacetoxyiodo)benzene (2.44 g, 7.56 mmol, 1.1 equiv). The reaction was stirred at room temperature for 20 h, after which was added saturated aq. $Na_2S_2O_3$ (5 mL) and allowed to stir an additional 15 min. Additional CH_2Cl_2 (50 mL) and H_2O (50 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x70 mL), and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (Biotage 50 g HP-sil, 1–10% ethyl acetate/hexanes) afforded 1.31 g (quant) of desired ketone **48** as a clear oil.



Oct-1-en-2-ylbenzene (8a): To a solution of methyltriphenylphosphonium bromide (2.45 g, 6.87 mmol, 1.0 equiv) in Et_2O (21.5 mL) under nitrogen at room temperature was added *n*-butyl

lithium (1.6 M in hexanes, 4.3 mL, 6.87 mmol, 1.0 equiv). The bright orange reaction mixture was stirred at room temperature for 40 min. **48**, which had been azeotroped from benzene to remove H_2O was then added slowly, rinsing with an additional amount of Et_2O (4 mL), and stirred at room temperature for 21 h. The reaction mixture was then poured into H_2O (70 mL), and extracted with Et_2O (2x50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Column chromatography (25 g HP-Sil Biotage column, 100% hexanes) afforded 931 mg (72%) of the desired alkene **8a** as a clear oil. Characterization details listed above.

^{31}P NMR Experiments

Timecourse of the Catalytic Reaction (Figure 4):

In an airtight J-Young NMR tube, $Ni(cod)_2$ (5.2 mg, 0.020 mmol, 0.30 equiv), dcypb (10.0 mg, 0.022 mmol, 0.35 equiv), 1-octene (58.4 μL, 0.37 mmol, 6.0 equiv), Et_3N (86 μL, 0.62 mmol, 10 equiv), and PhOTf (20 μL, 0.063 mmol, 1.0 equiv) were dissolved in toluene (0.6 mL, 0.10 M). ^{31}P NMR spectrum was obtained, using H_3PO_4 as an external standard (Figure 4a), and heated to 60 °C. Obtained ^{31}P NMR spectrum at T = 3, 6, 24 h (Figure 4b, c, d, respectively).

Preparation of Possible Reaction Intermediates (Figure 5):

In all cases, reagents were weighed into an NMR tube and dissolved in ~0.7 mL toluene in the glovebox before a ^{31}P NMR spectrum was immediately obtained (unless otherwise noted), using H_3PO_4 as an external standard.

(a) dcypb (10.0 mg, 0.022 mmol)

(b) dcypb (10.0 mg, 0.022 mmol), $Ni(cod)_2$ (5.2 mg, 0.020 mmol)

(c) (b) + 1-octene (58.4 μL, 0.37 mmol)

(d) (c) + Et_3N (86 μL, 0.62 mmol)

(e) dcypb (10.0 mg, 0.022 mmol), $Ni(cod)_2$ (5.2 mg, 0.020 mmol), Et_3N (86 μL, 0.62 mmol)

(f) (e) + PhOTf (20 μL, 0.063 mmol)

(g) dcypb (10.0 mg, 0.022 mmol), $Ni(cod)_2$ (5.2 mg, 0.020 mmol), **8a** (20 μL)

(h) dcypb (10.0 mg, 0.022 mmol), $Ni(cod)_2$ (5.2 mg, 0.020 mmol), 1-octene (58.4 μL, 0.37 mmol), PhOTf (20 μL, 0.063 mmol), 60 °C, 1 h

(i) dcypb (10.0 mg, 0.022 mmol), $Ni(cod)_2$ (5.2 mg, 0.020 mmol), TfOH (20 μL, 0.23 mmol)

(j) dcypb (10.0 mg, 0.022 mmol), TfOH (20 μL, 0.23 mmol)

(k) dcypb (10.0 mg, 0.022 mmol), $Ni(cod)_2$ (5.2 mg, 0.020 mmol), *trans*-4-octene (58.4 μL, 0.37 mmol)

(l) dcypb (10.0 mg, 0.022 mmol), H_2O_2 (30 wt % in H_2O, 5 drops). Formed white precipitate not soluble in toluene, so NMR obtained in $CDCl_3$.

Figure 4. Timecourse of the catalytic reaction by ^{31}P NMR.

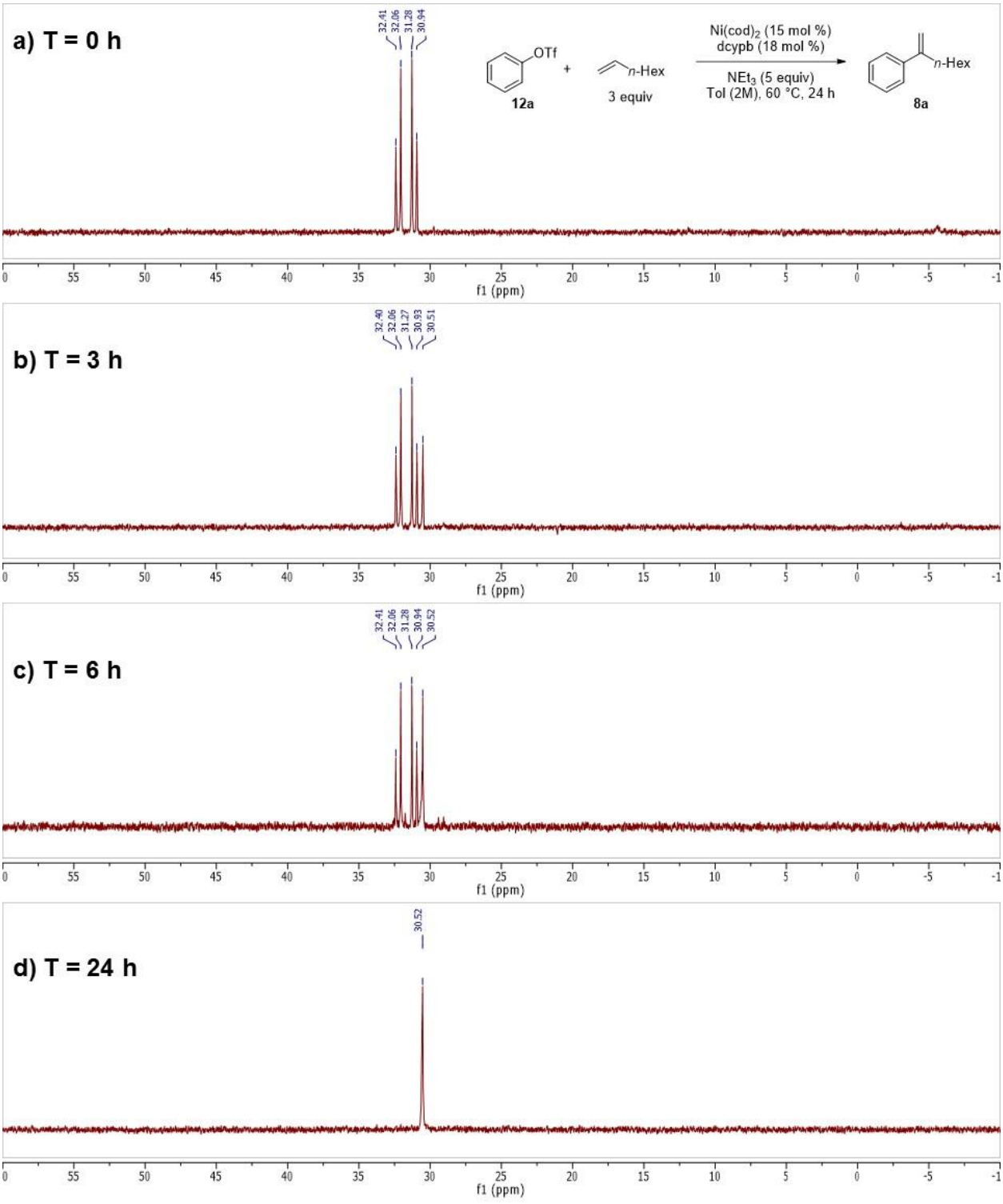
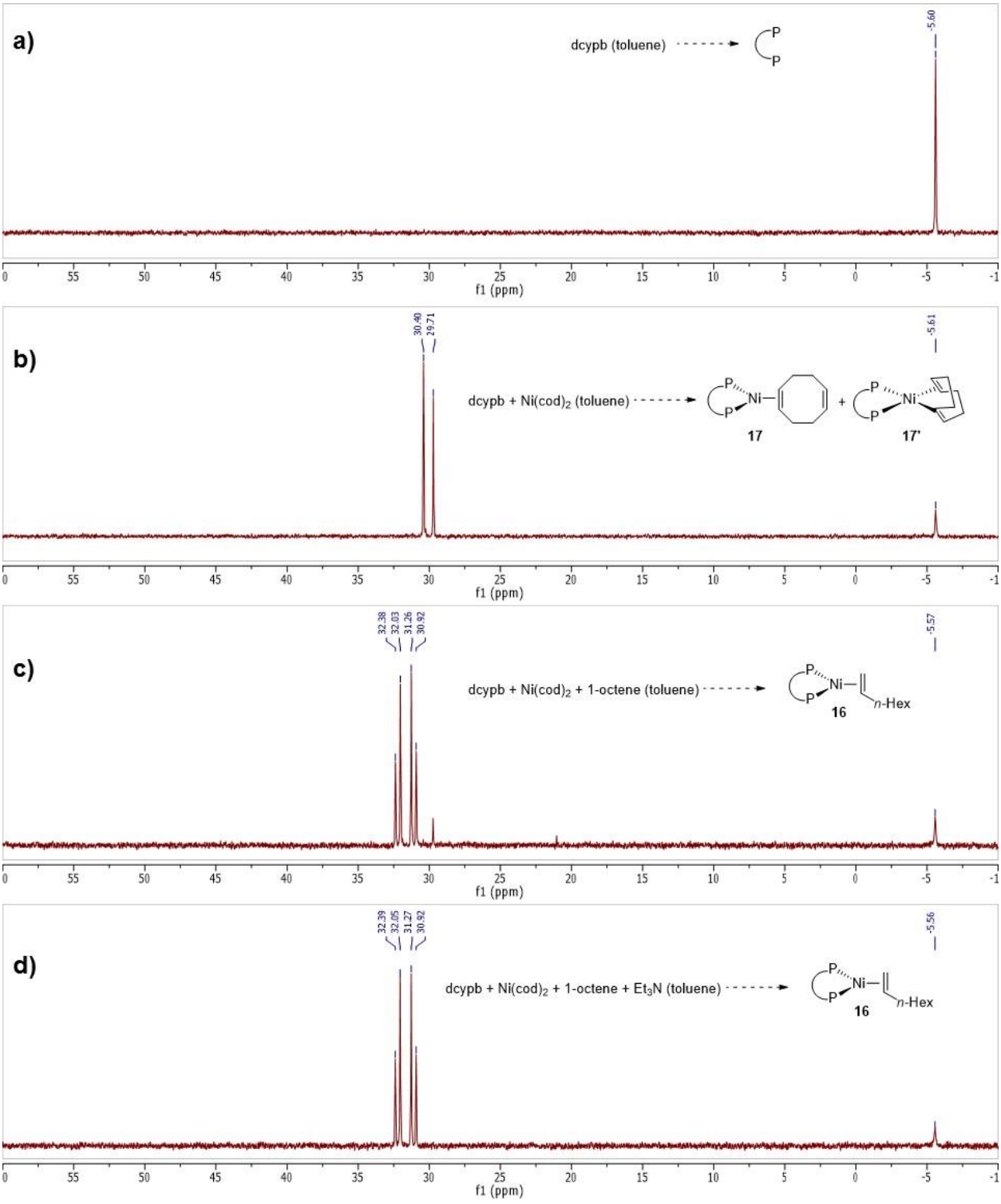
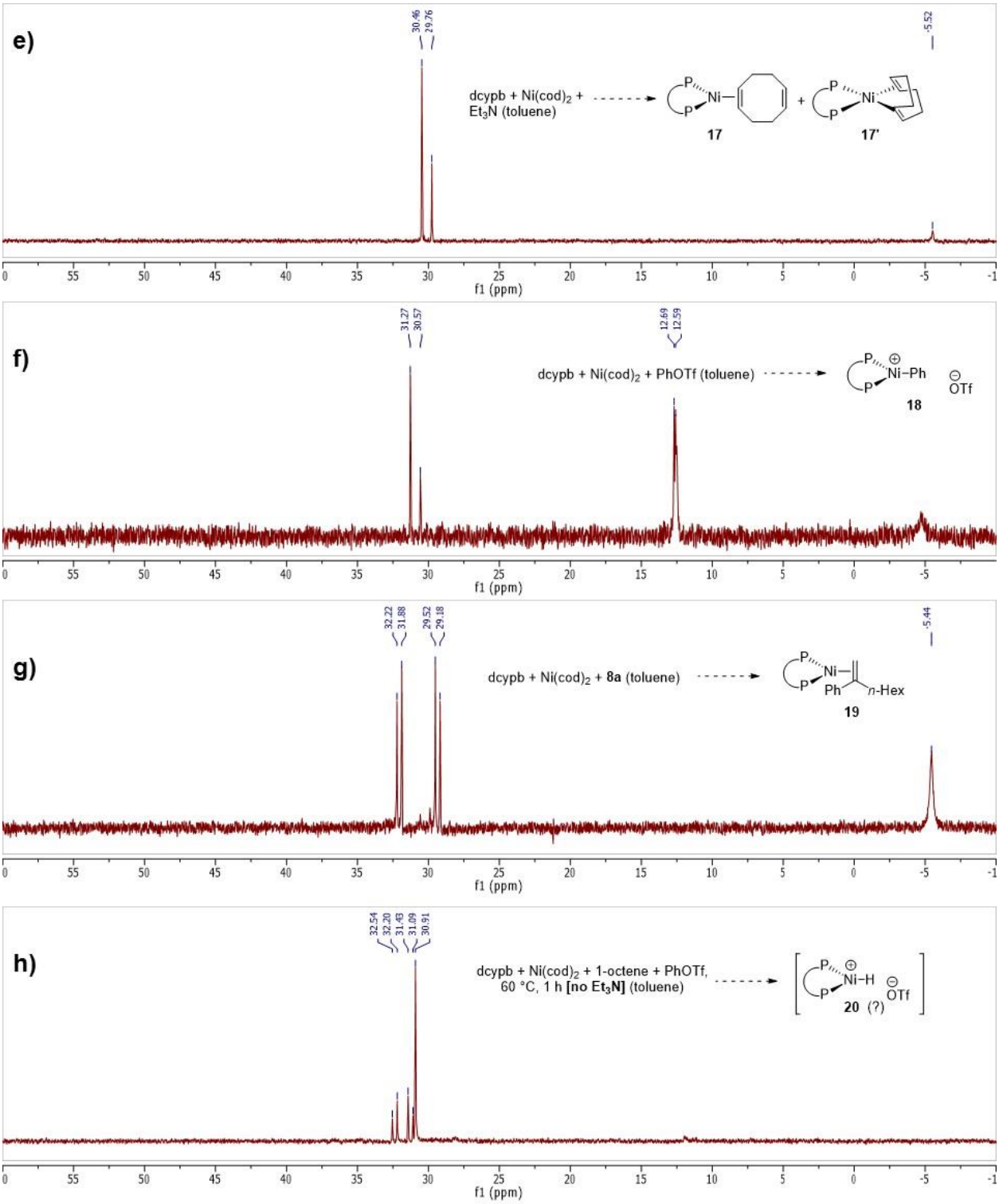
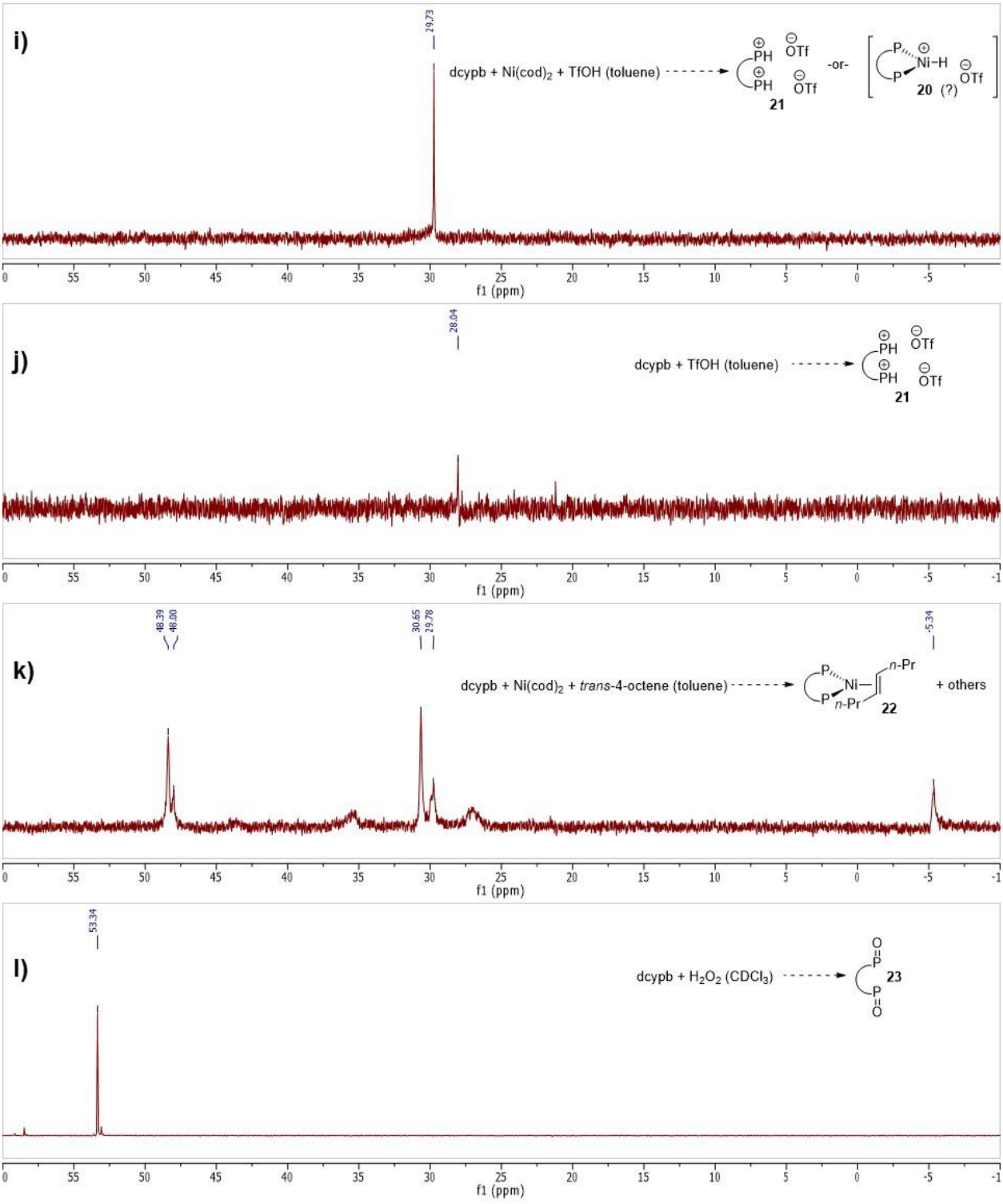


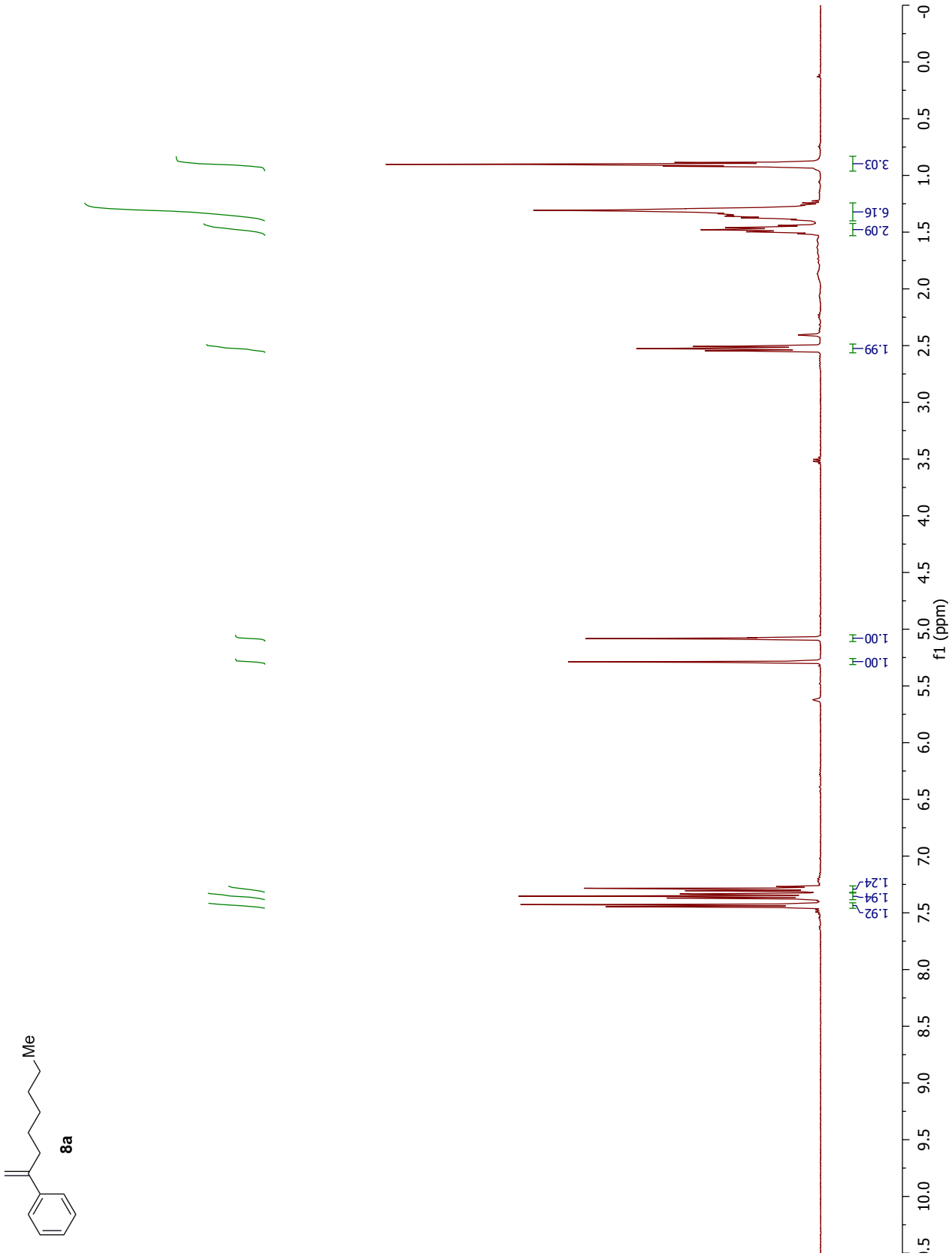
Figure 5. Preparation of possible reaction intermediates.

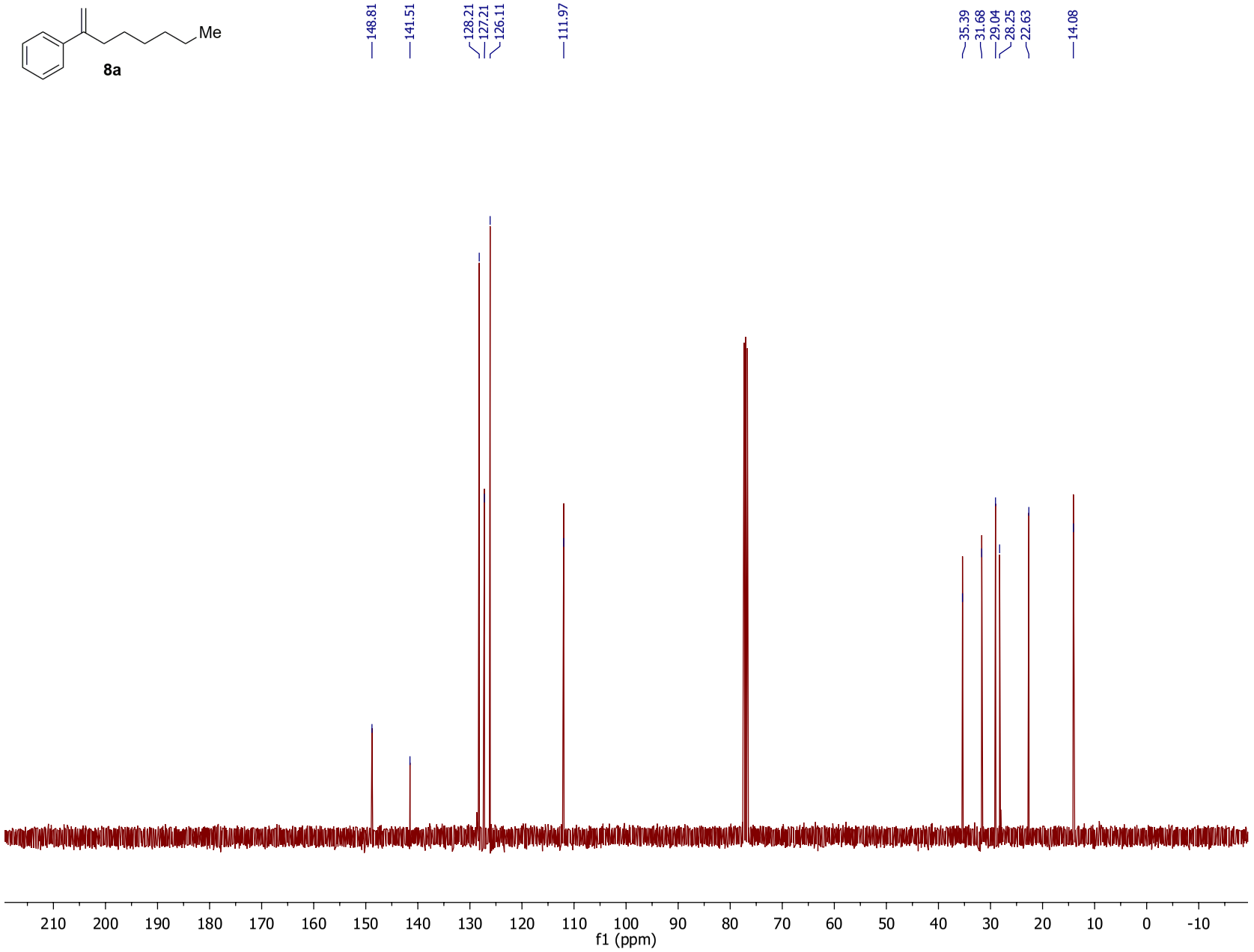


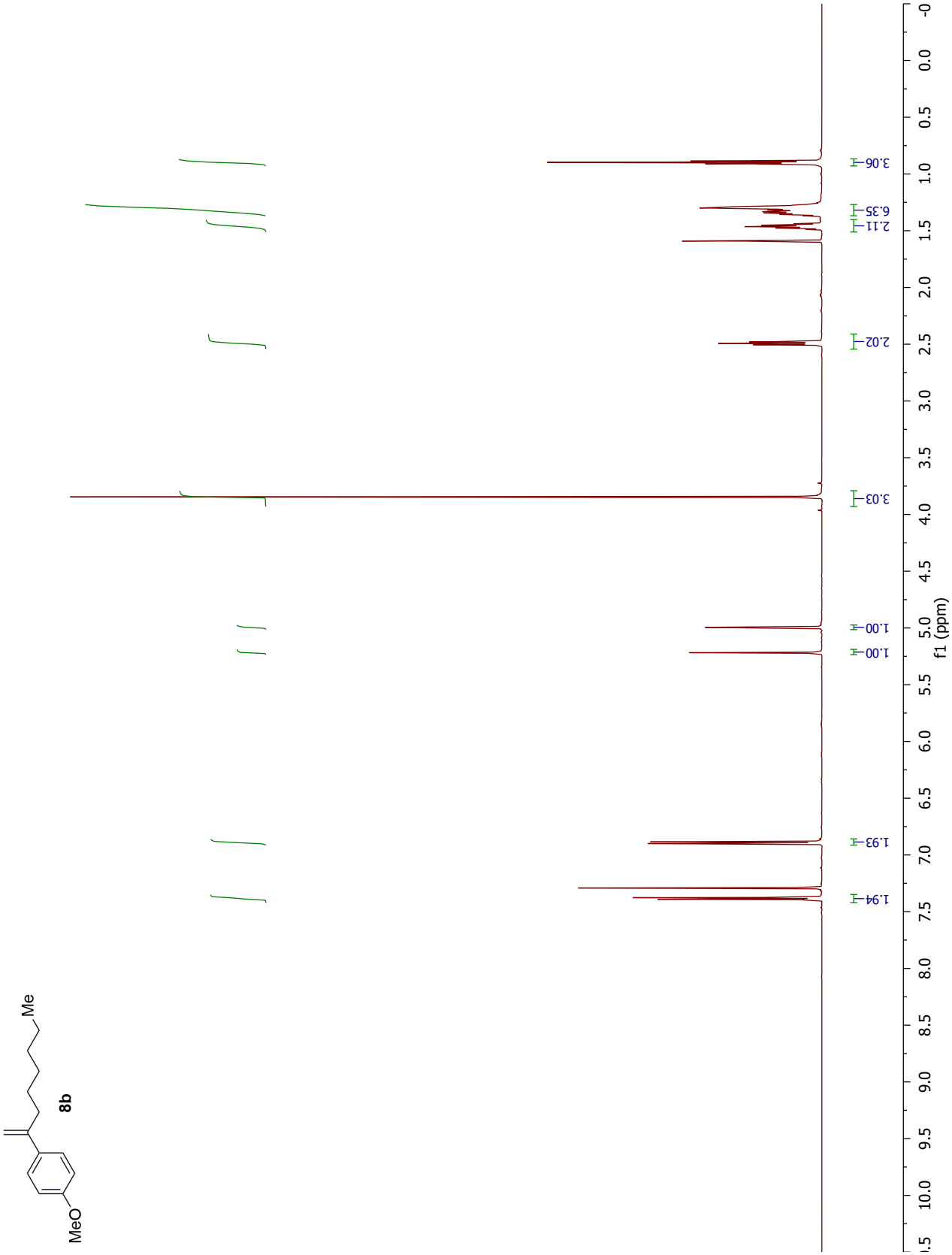

e)
30.46
29.76
-5.52
dcypb + Ni(cod)2 +
Et3N (toluene)
17
17'
f1 (ppm)
f)
31.27
30.57
12.69
12.59
dcypb + Ni(cod)2 + PhOTf (toluene)
18
OTf
f1 (ppm)
g)
32.22
31.88
29.52
29.18
-5.44
dcypb + Ni(cod)2 + 8a (toluene)
Ph
n-Hex
19
f1 (ppm)
h)
32.54
32.20
31.43
31.09
30.91
dcypb + Ni(cod)2 + 1-octene + PhOTf,
60 °C, 1 h [no Et3N] (toluene)
20 (?)
OTf
f1 (ppm)

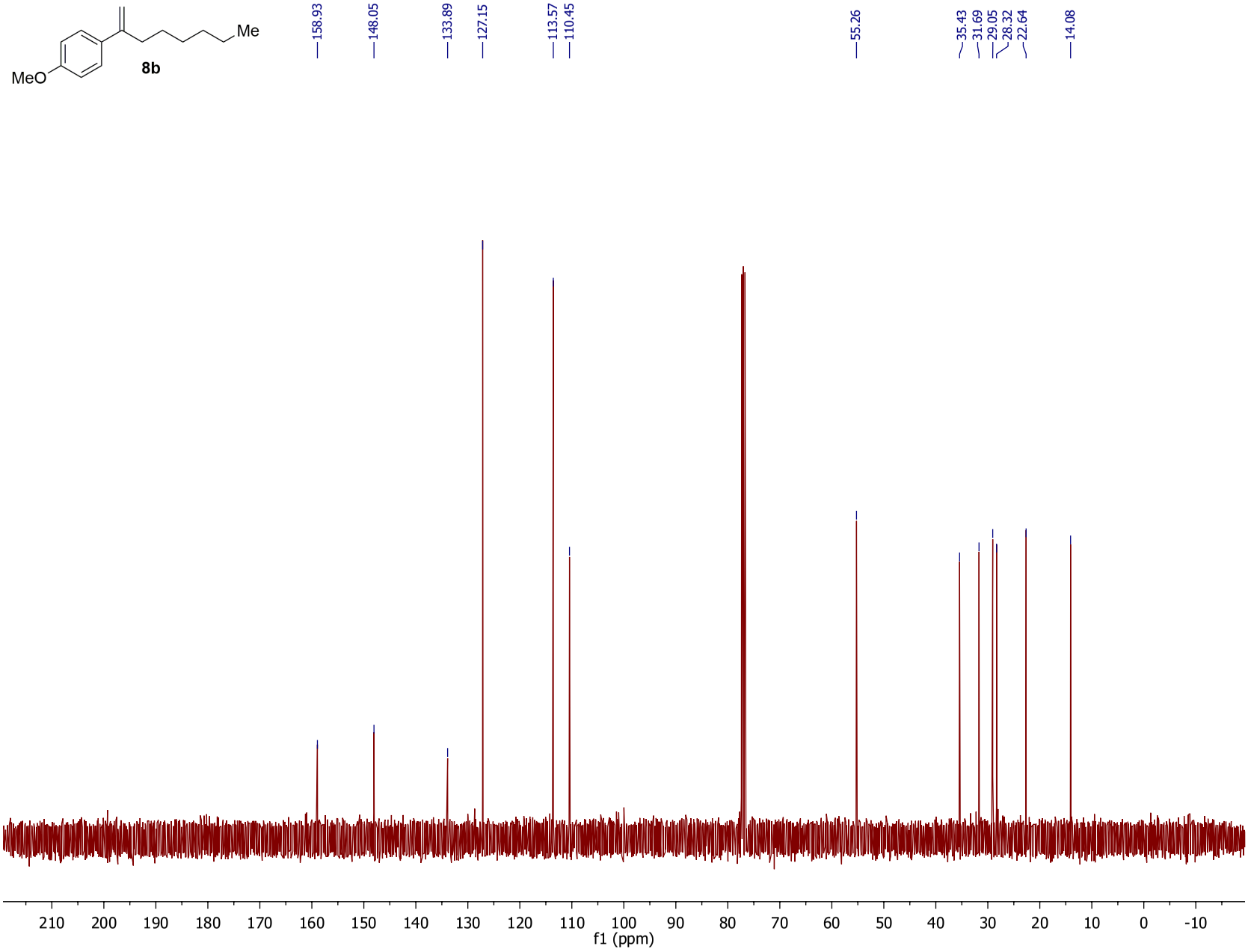

i)
29.73
dcypb + Ni(cod)2 + TfOH (toluene)
21
-or-
20 (?)
f1 (ppm)
j)
28.04
dcypb + TfOH (toluene)
21
f1 (ppm)
k)
48.39
48.00
30.65
29.78
-5.34
dcypb + Ni(cod)2 + trans-4-octene (toluene)
22
+ others
f1 (ppm)
l)
53.34
dcypb + H2O2 (CDCl3)
23
f1 (ppm)

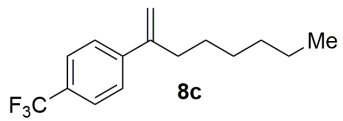
^{1}H and ^{13}C NMR Spectra


Me
8a
3.03
6.16
2.09
1.99
1.00
1.00
1.24
1.94
1.92
f1 (ppm)

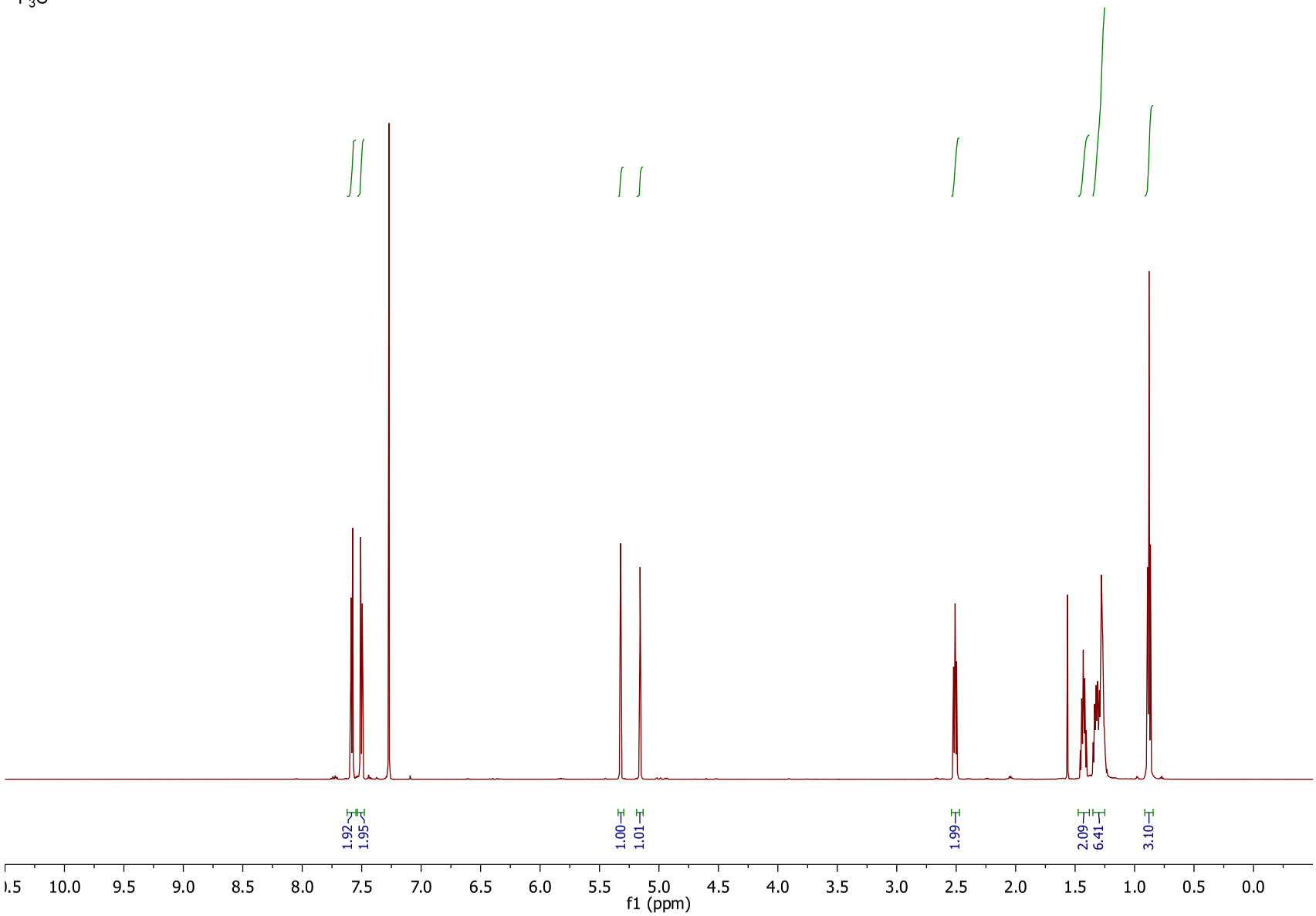

Me
8a
148.81
141.51
128.21
127.21
126.11
111.97
35.39
31.68
29.04
28.25
22.63
14.08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

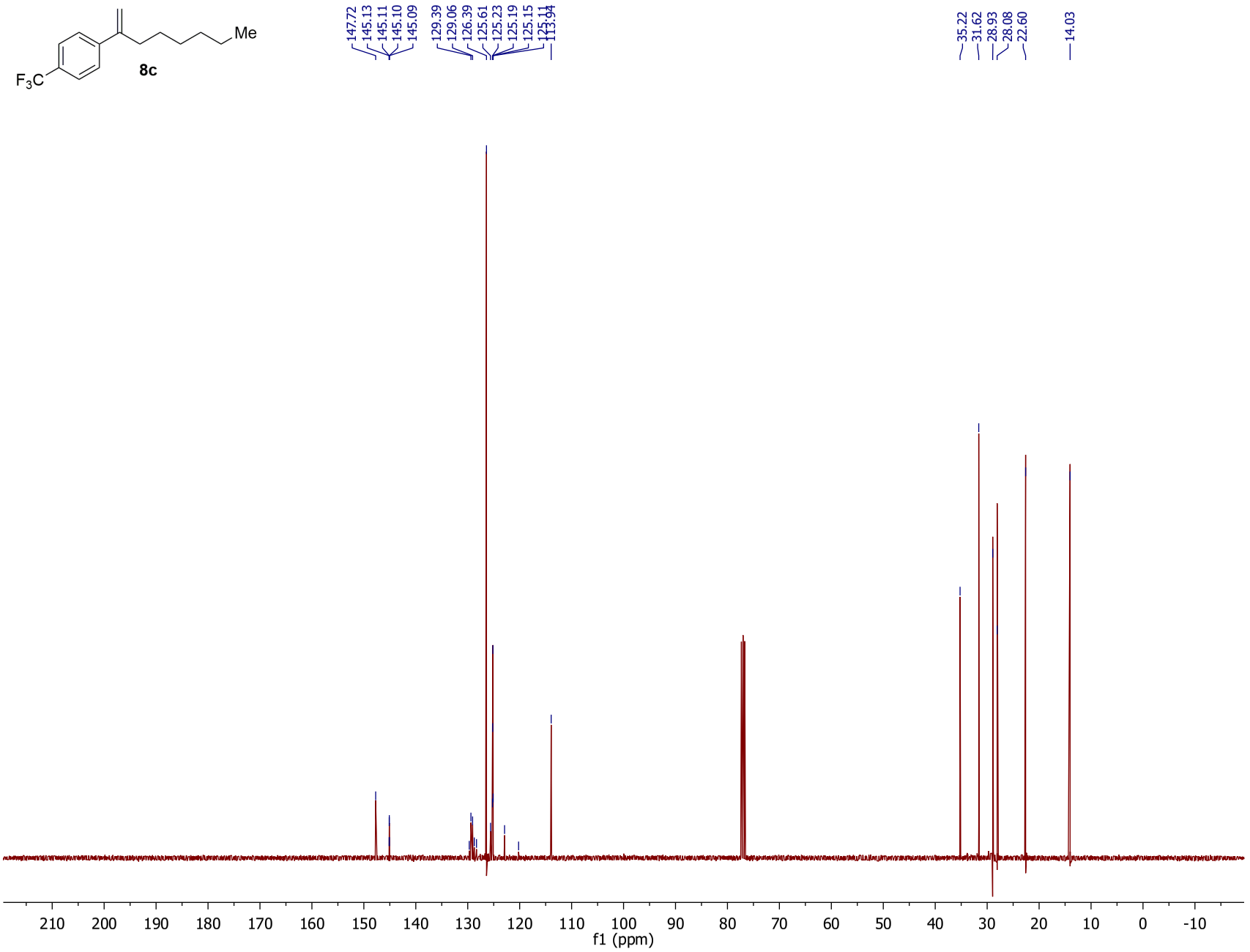

Me
8b
MeO
3.06
6.35
2.11
2.02
3.03
1.00
1.00
1.93
1.94
f1 (ppm)

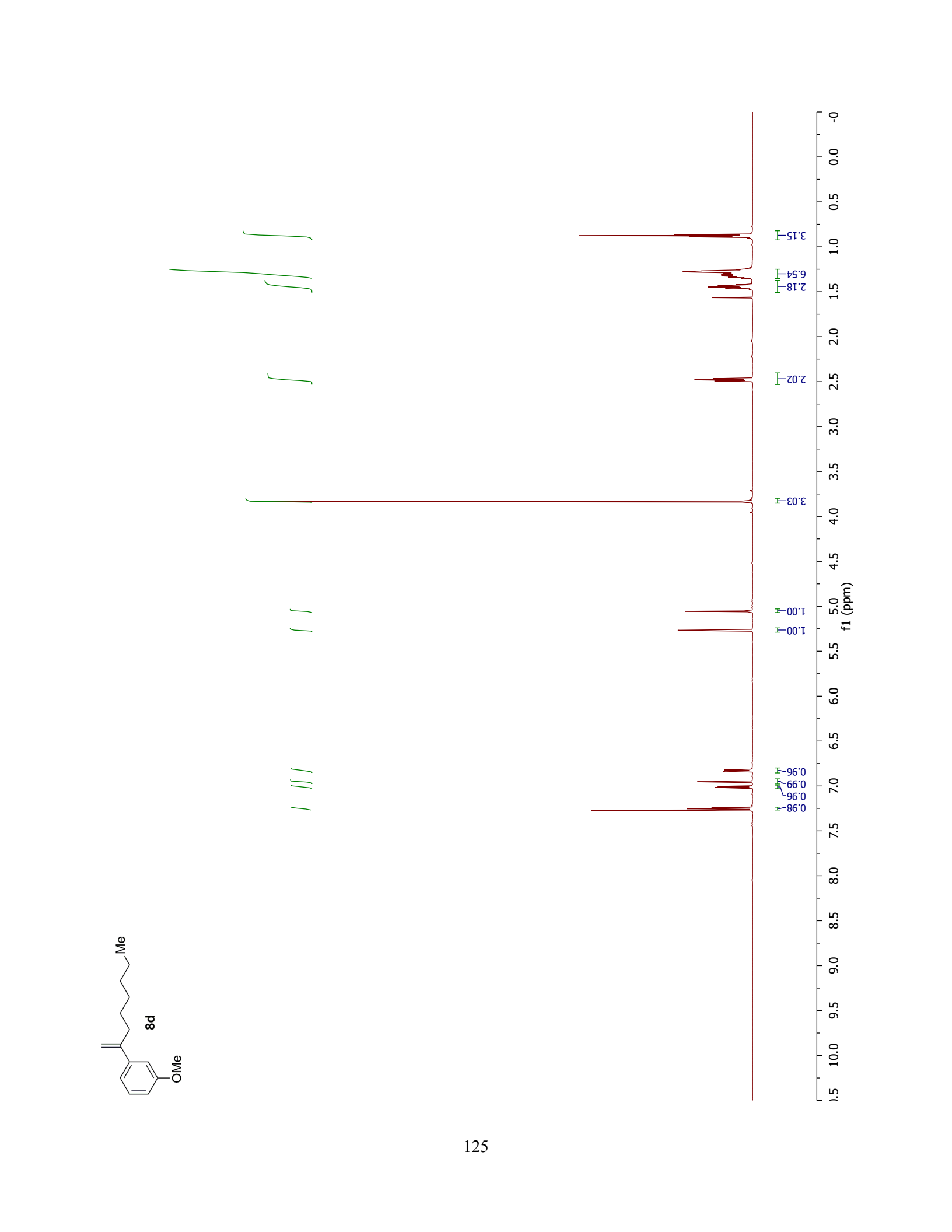

Me
MeO
8b
158.93
148.05
133.89
127.15
113.57
110.45
55.26
35.43
31.69
29.05
28.32
22.64
14.08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

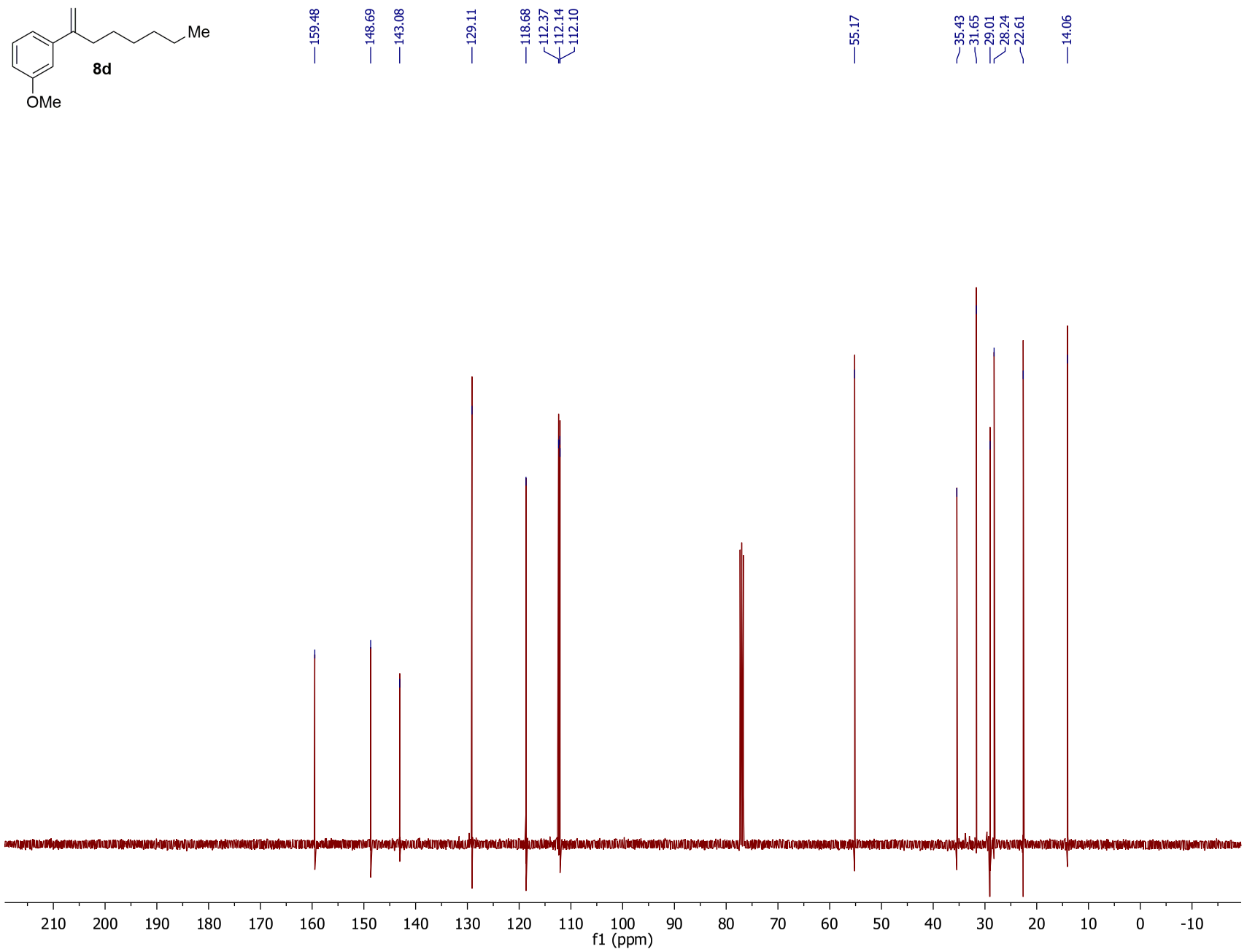

Me
F3C

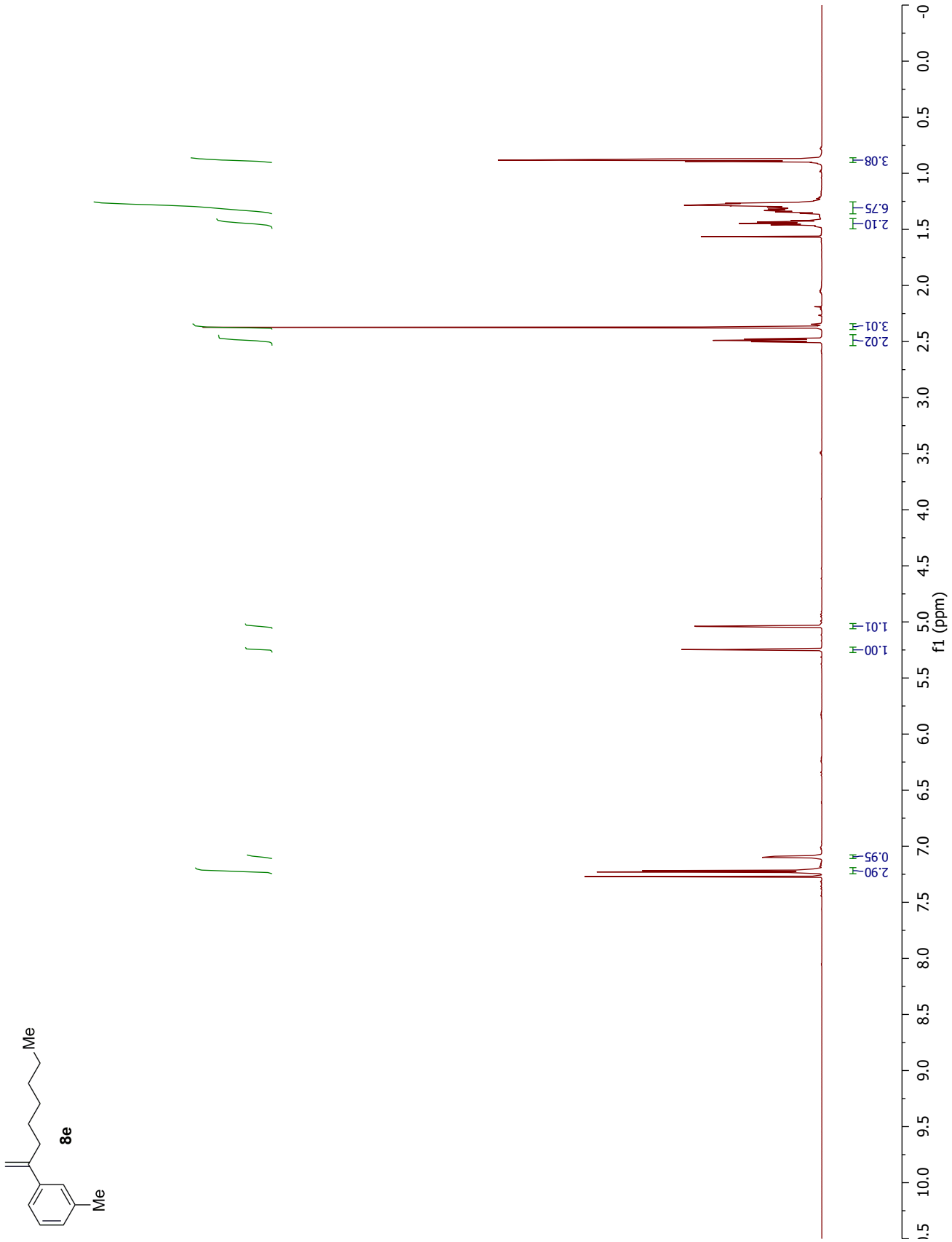
8c

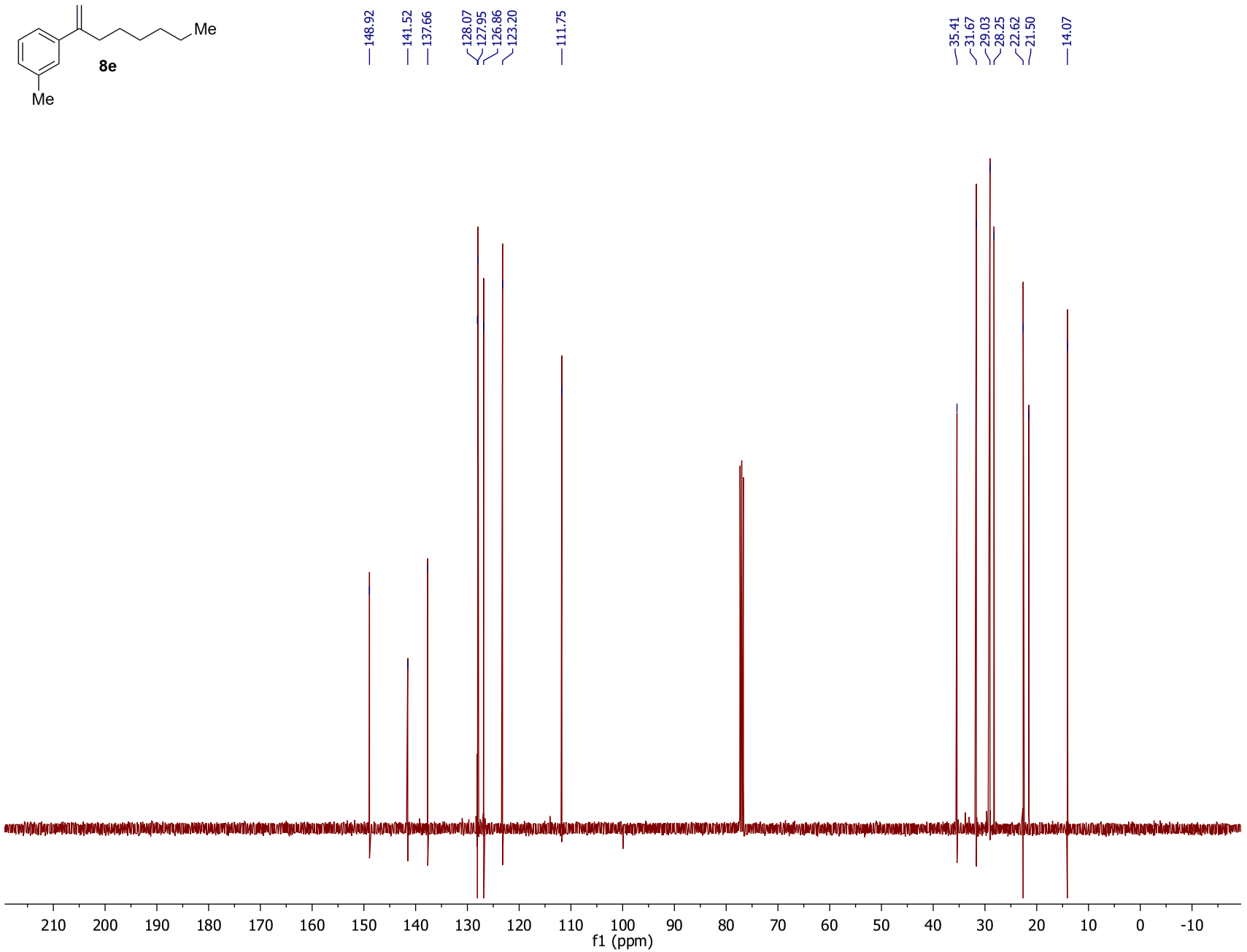

1.92
1.95
1.00
1.01
1.99
2.09
6.41
3.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

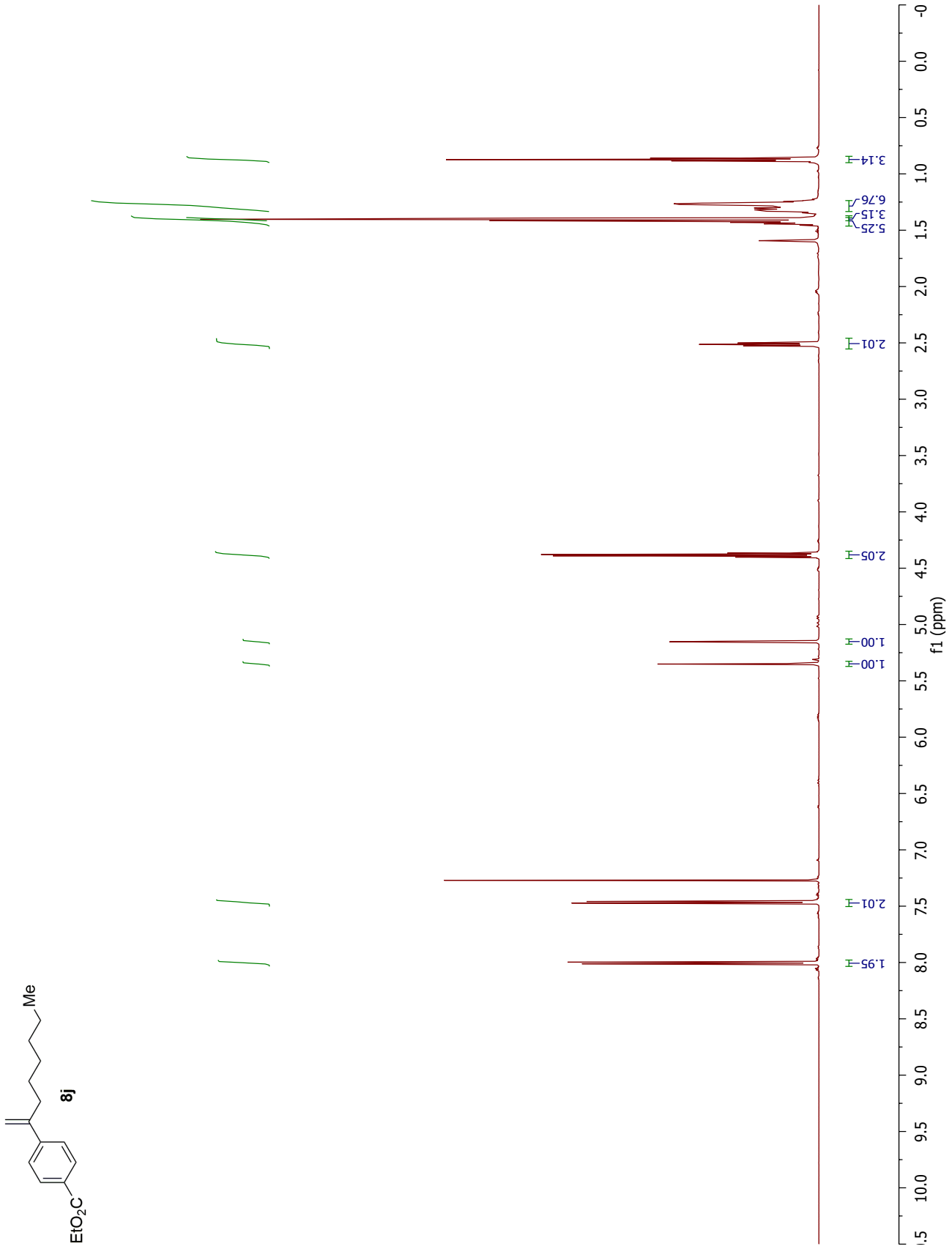

Me
F3C
8c
147.72
145.13
145.11
145.10
145.09
129.39
129.06
126.39
125.61
125.23
125.19
125.15
125.11
113.94
35.22
31.62
28.93
28.08
22.60
14.03
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

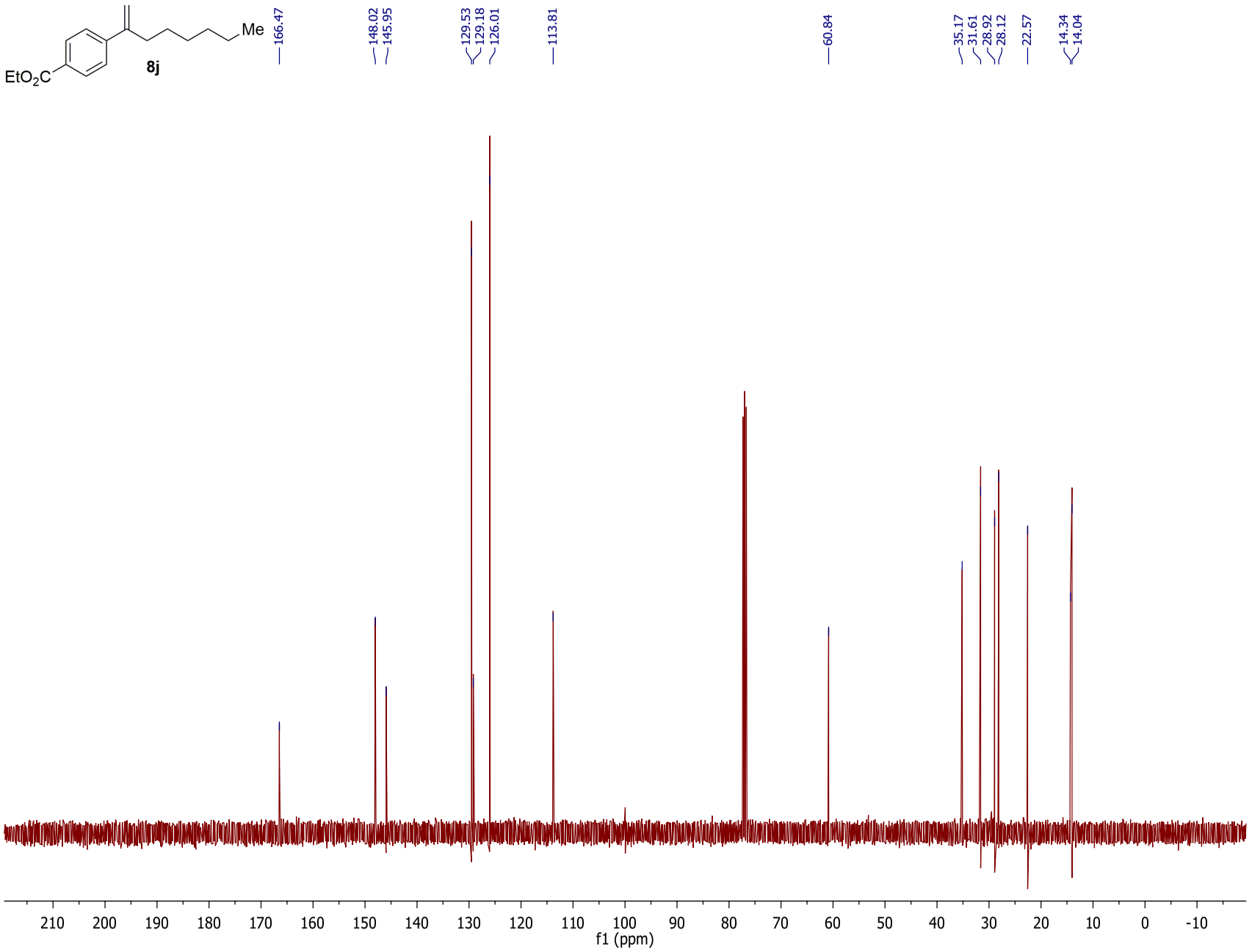

Me
8d
OMe
3.15
6.54
2.18
2.02
3.03
1.00
1.00
0.96
0.99
0.96
0.98
f1 (ppm)

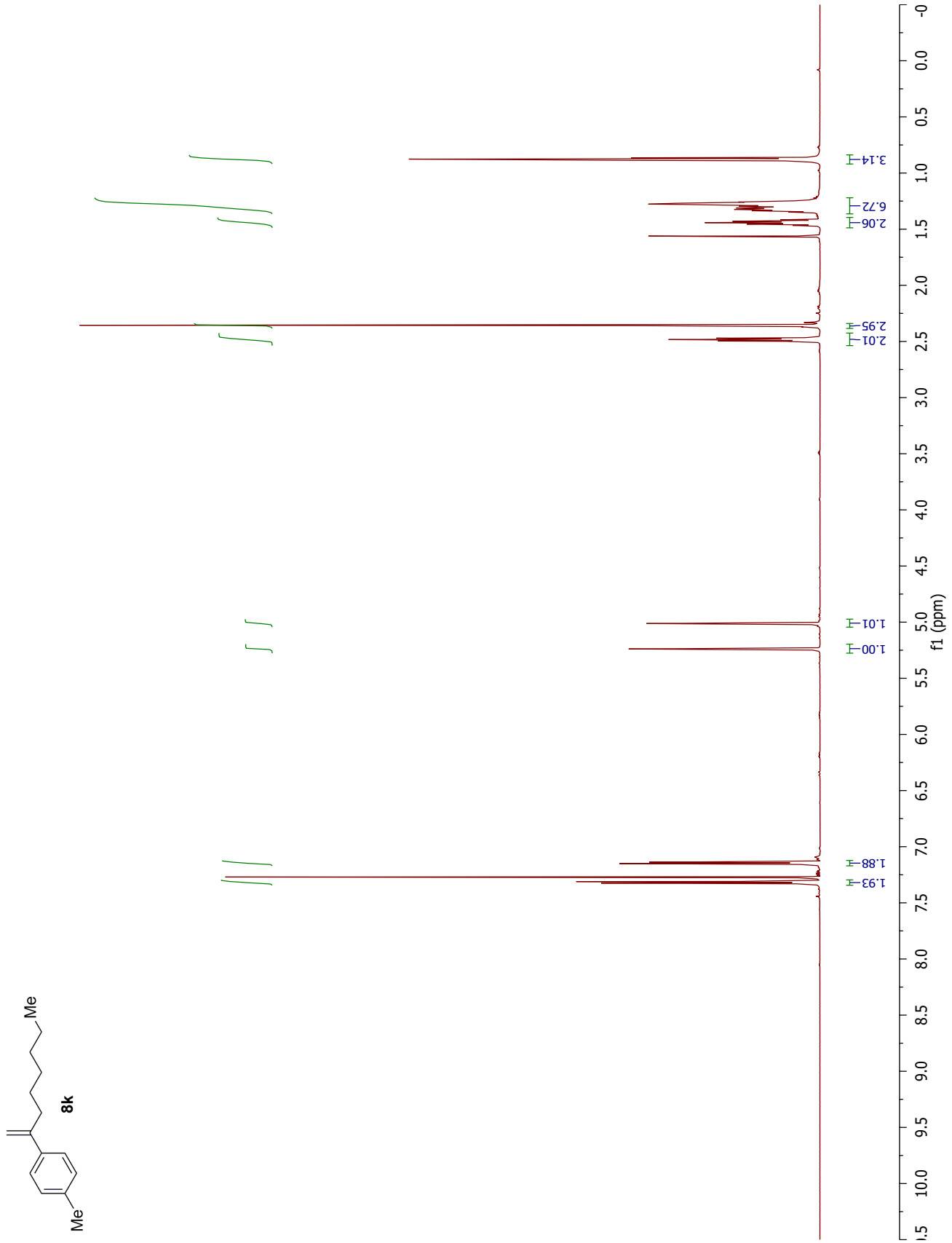

Me
8d
OMe
159.48
148.69
143.08
129.11
118.68
112.37
112.14
112.10
55.17
35.43
31.65
29.01
28.24
22.61
14.06
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

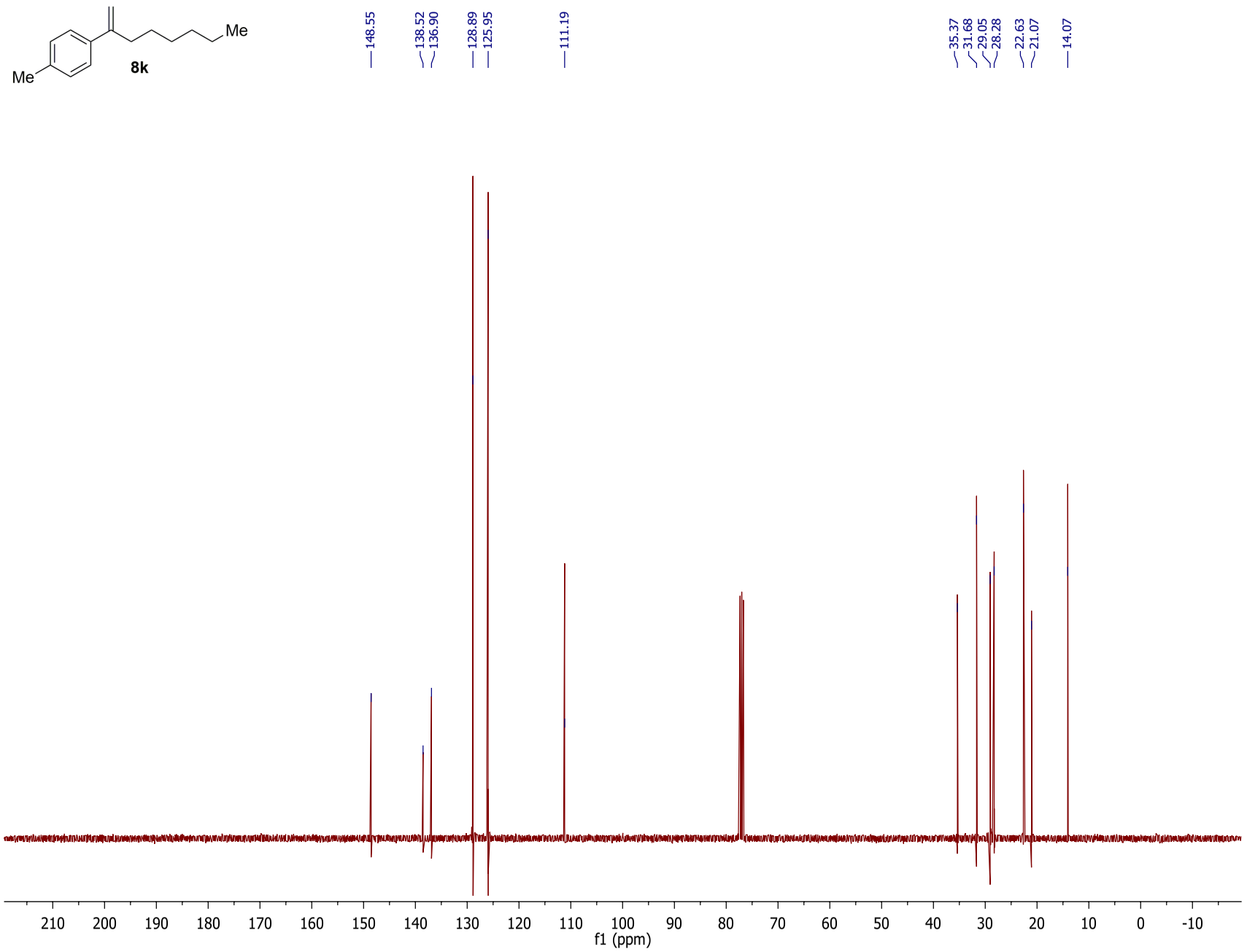

Me
8e
Me
3.08
6.75
2.10
3.01
2.02
1.01
1.00
0.95
2.90
f1 (ppm)

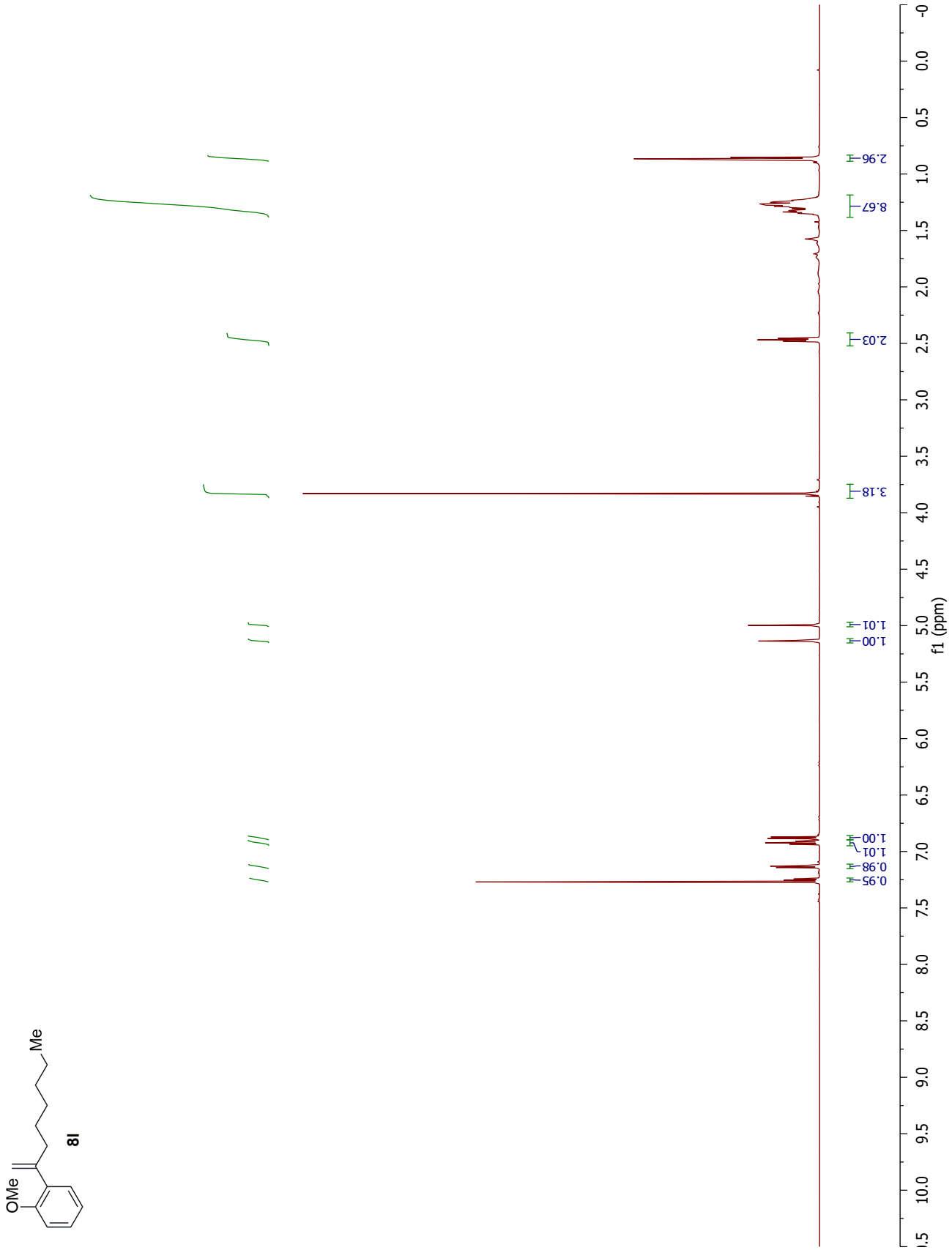

Me
8e
Me
148.92
141.52
137.66
128.07
127.95
126.86
123.20
111.75
35.41
31.67
29.03
28.25
22.62
21.50
14.07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

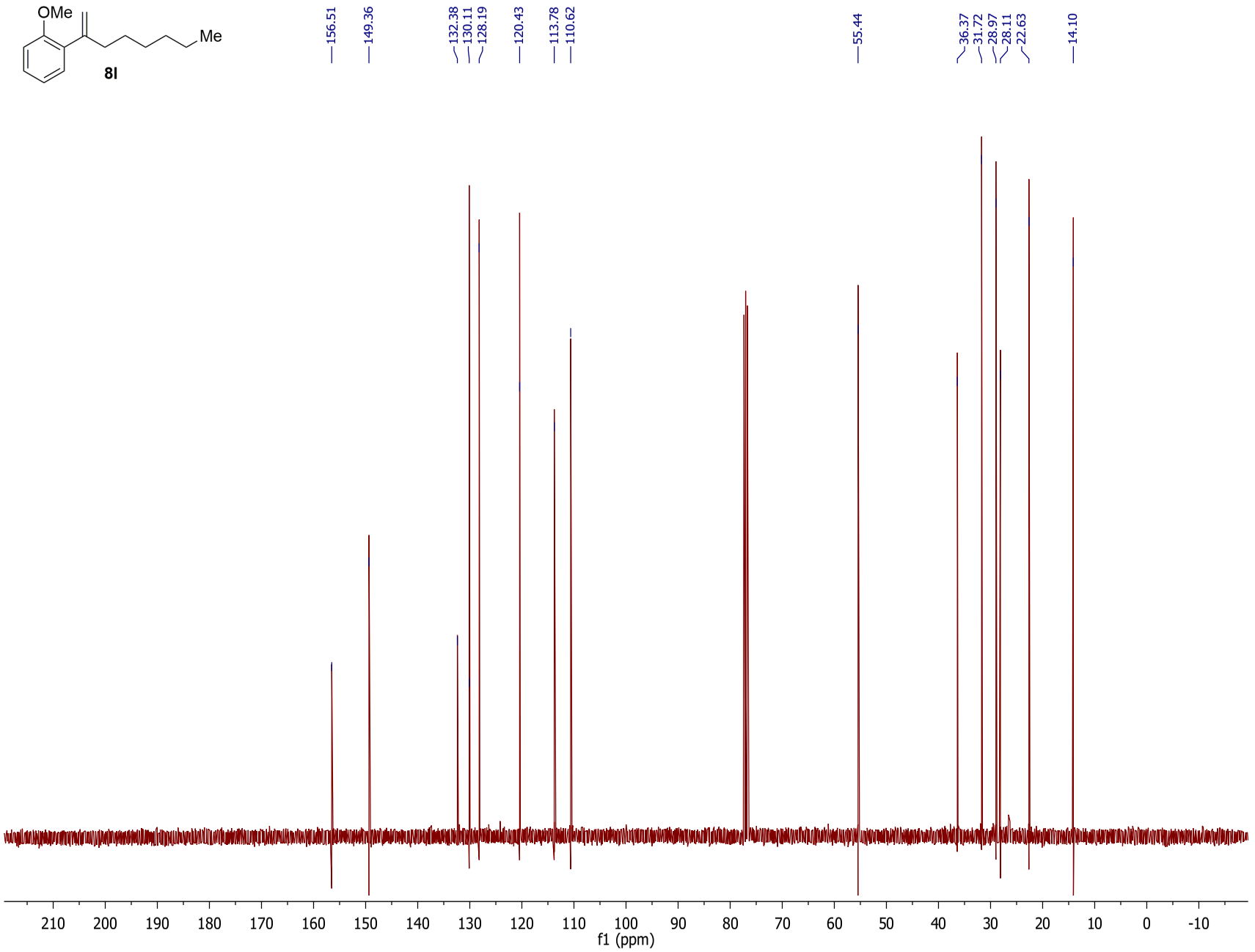

Me
8j
EtO2C
3.14
6.76
3.15
5.25
2.01
2.05
1.00
1.00
2.01
1.95
f1 (ppm)

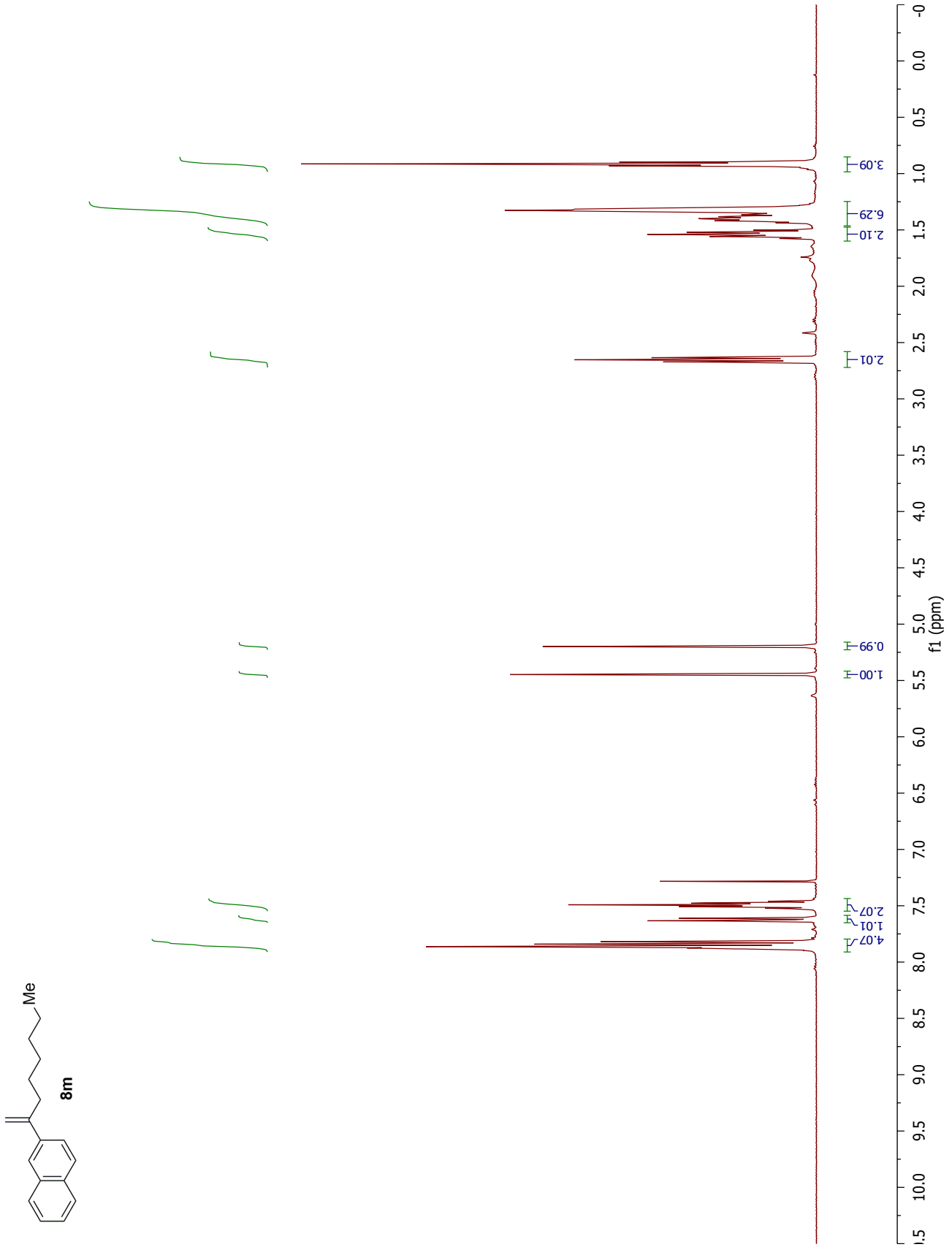

Me
EtO2C
8j
166.47
148.02
145.95
129.53
129.18
126.01
113.81
60.84
35.17
31.61
28.92
28.12
22.57
14.34
14.04
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

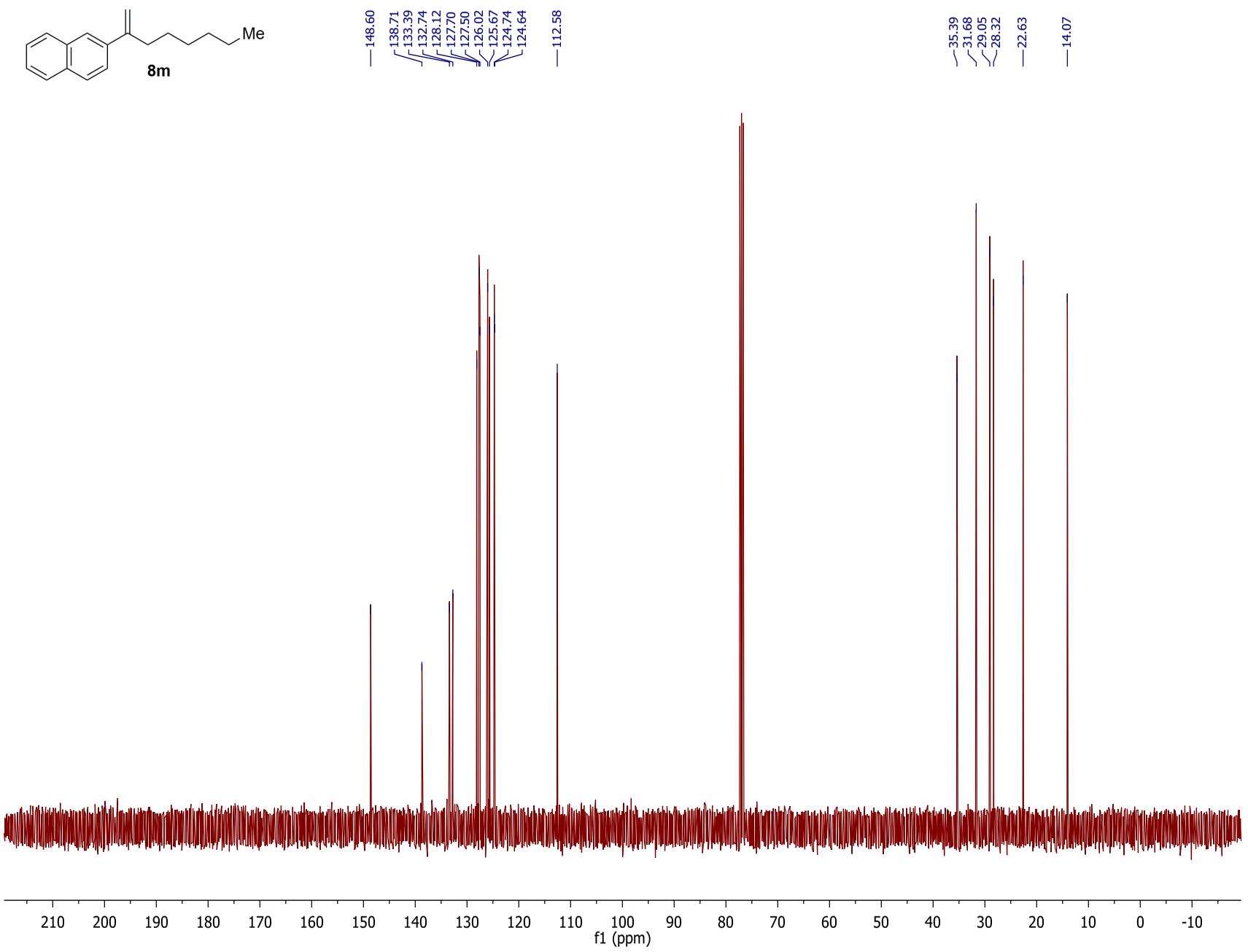

Me
8k
Me
3.14
6.72
2.06
2.95
2.01
1.01
1.00
1.88
1.93
f1 (ppm)

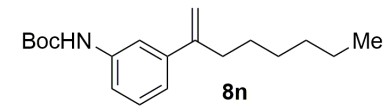

Me
Me
8k
148.55
138.52
136.90
128.89
125.95
111.19
35.37
31.68
29.05
28.28
22.63
21.07
14.07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
OMe
8l
2.96
8.67
2.03
3.18
1.01
1.00
1.00
1.01
0.98
0.95
f1 (ppm)

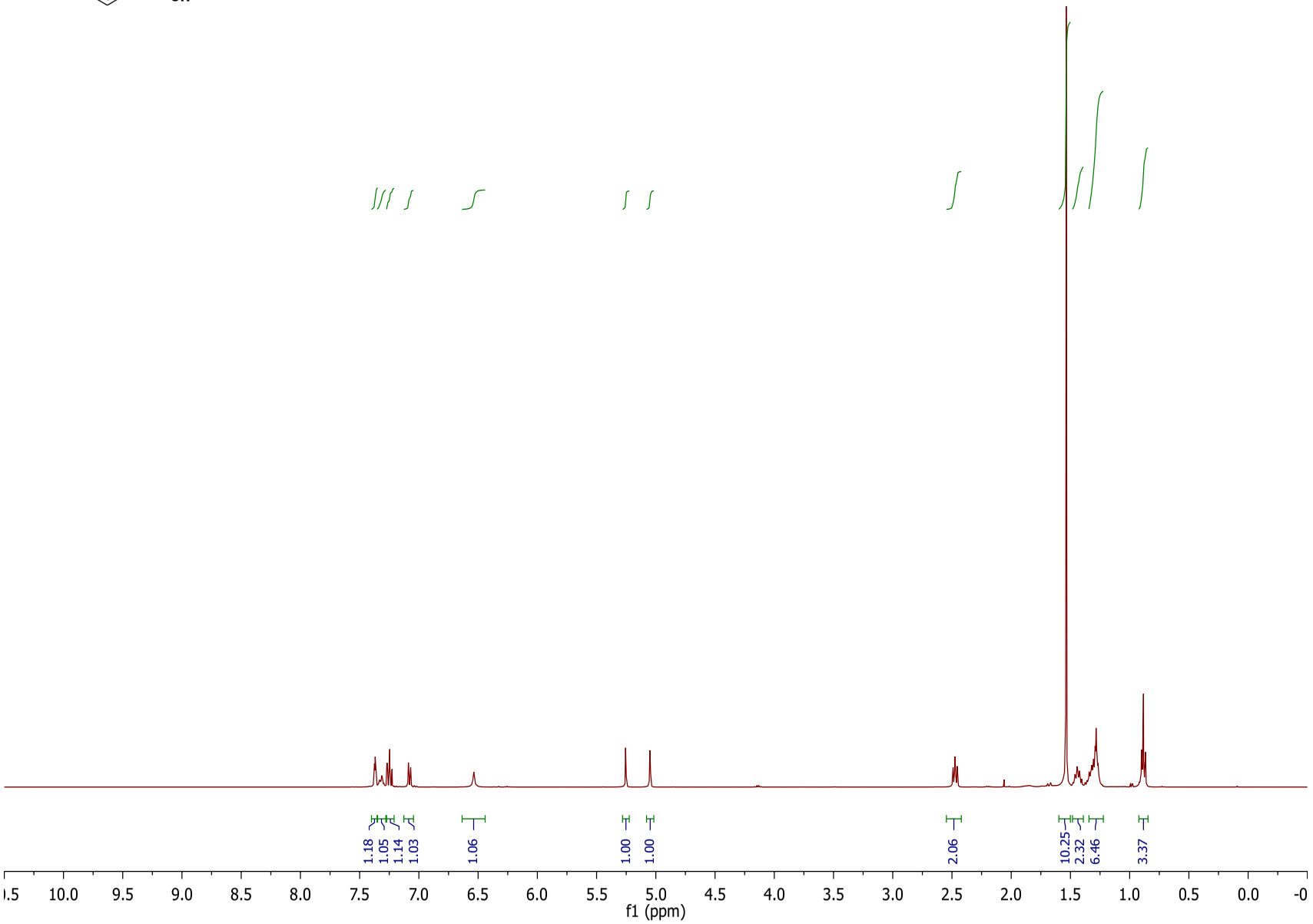

OMe
Me
8l
156.51
149.36
132.38
130.11
128.19
120.43
113.78
110.62
55.44
36.37
31.72
28.97
28.11
22.63
14.10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

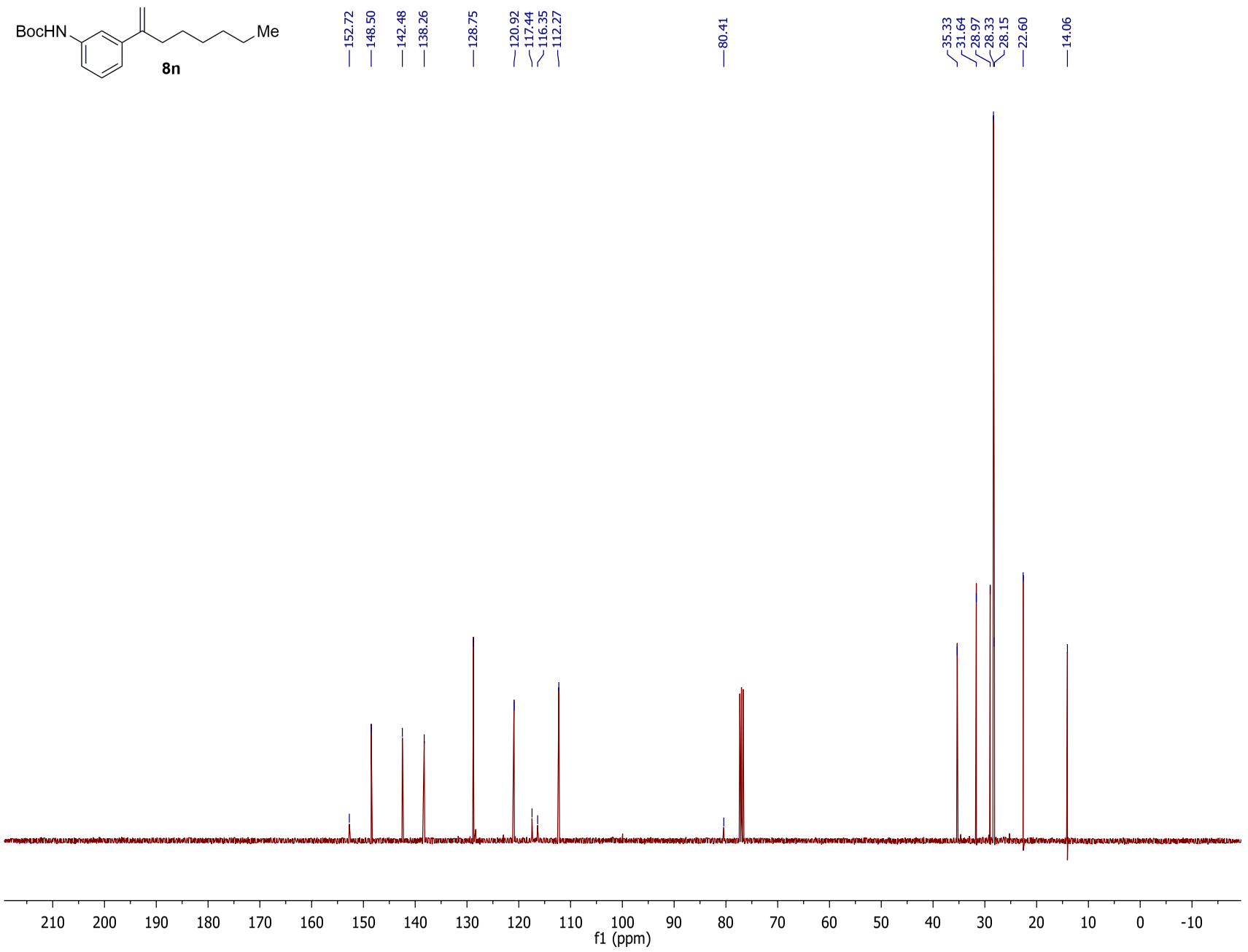

Me
8m
3.09
6.29
2.10
2.01
0.99
1.00
2.07
1.01
4.07
f1 (ppm)

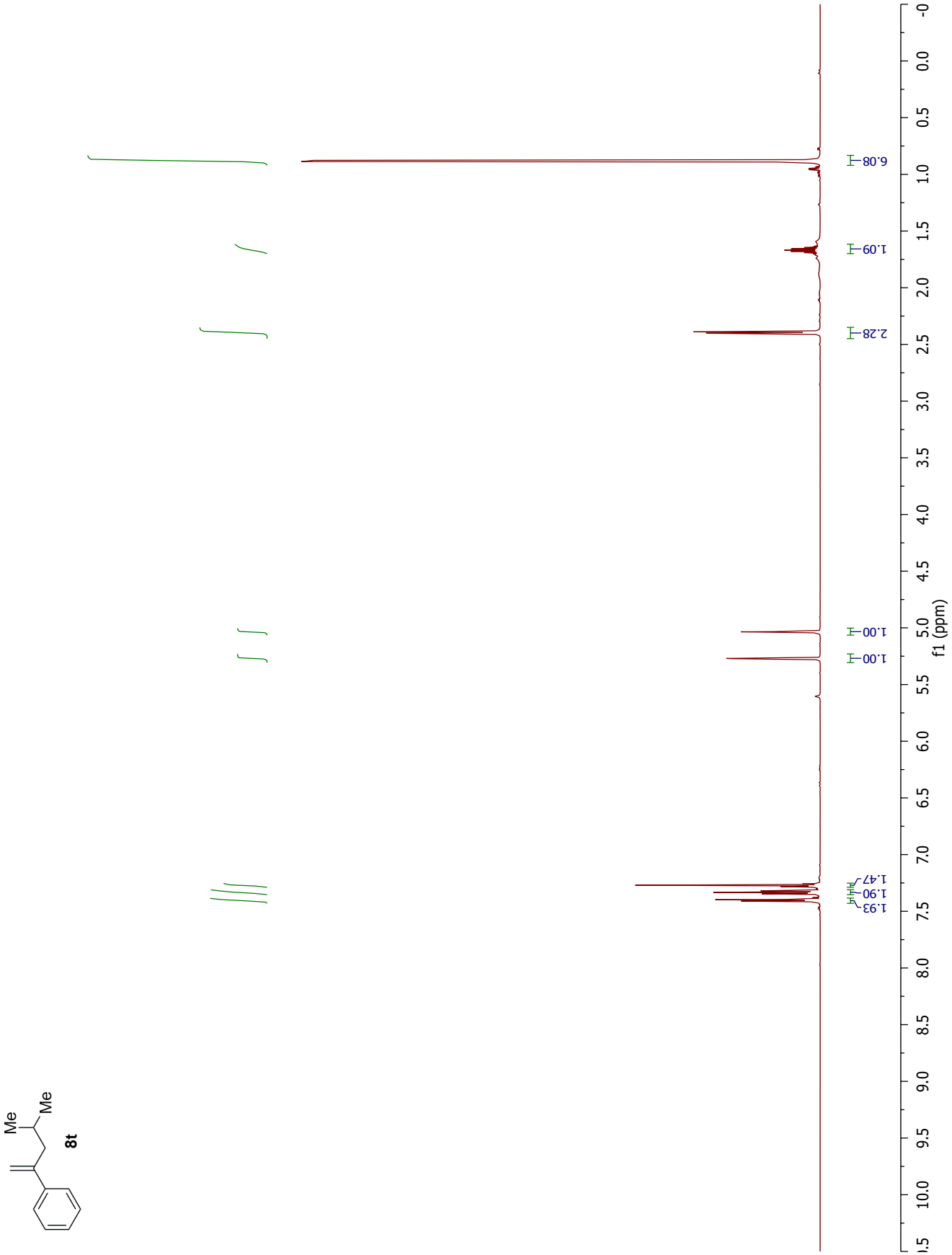

Me
8m
148.60
138.71
133.39
132.74
128.12
127.70
127.50
126.02
125.67
124.74
124.64
112.58
35.39
31.68
29.05
28.32
22.63
14.07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


BocHN
Me

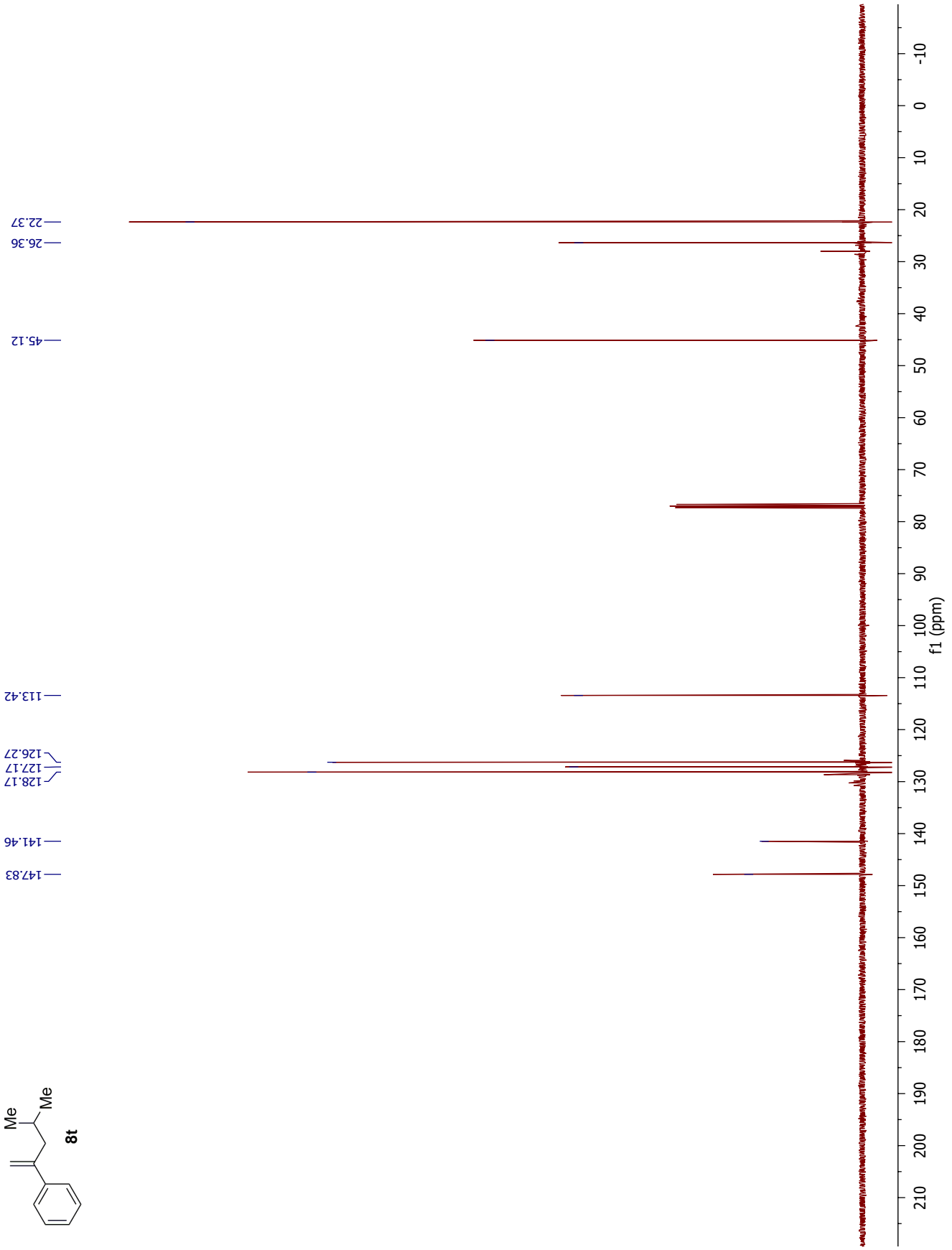
8n

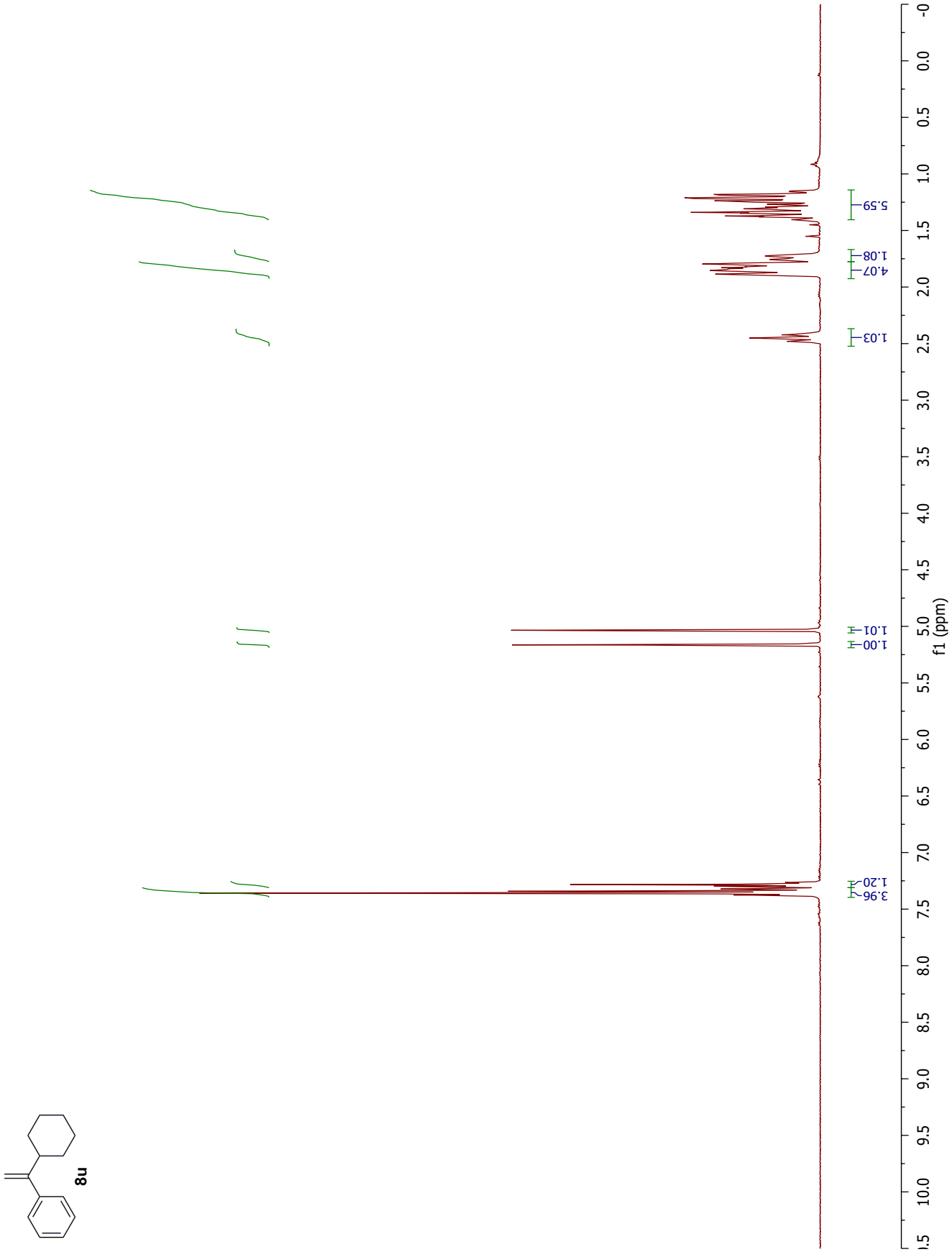

1.18
1.05
1.14
1.03
1.06
1.00
1.00
2.06
10.25
2.32
6.46
3.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

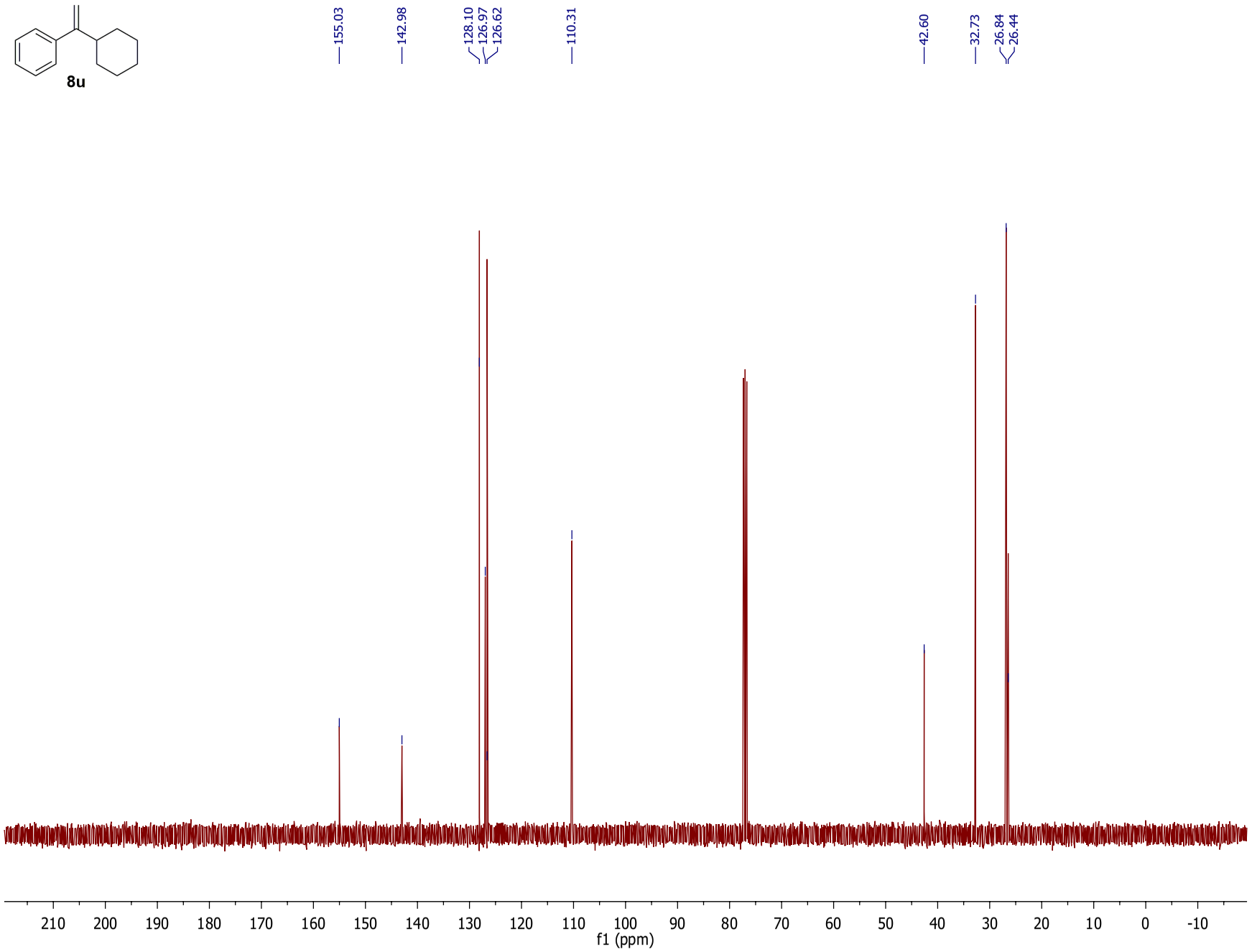

BocHN
Me
8n
152.72
148.50
142.48
138.26
128.75
120.92
117.44
116.35
112.27
80.41
35.33
31.64
28.97
28.33
28.15
22.60
14.06
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

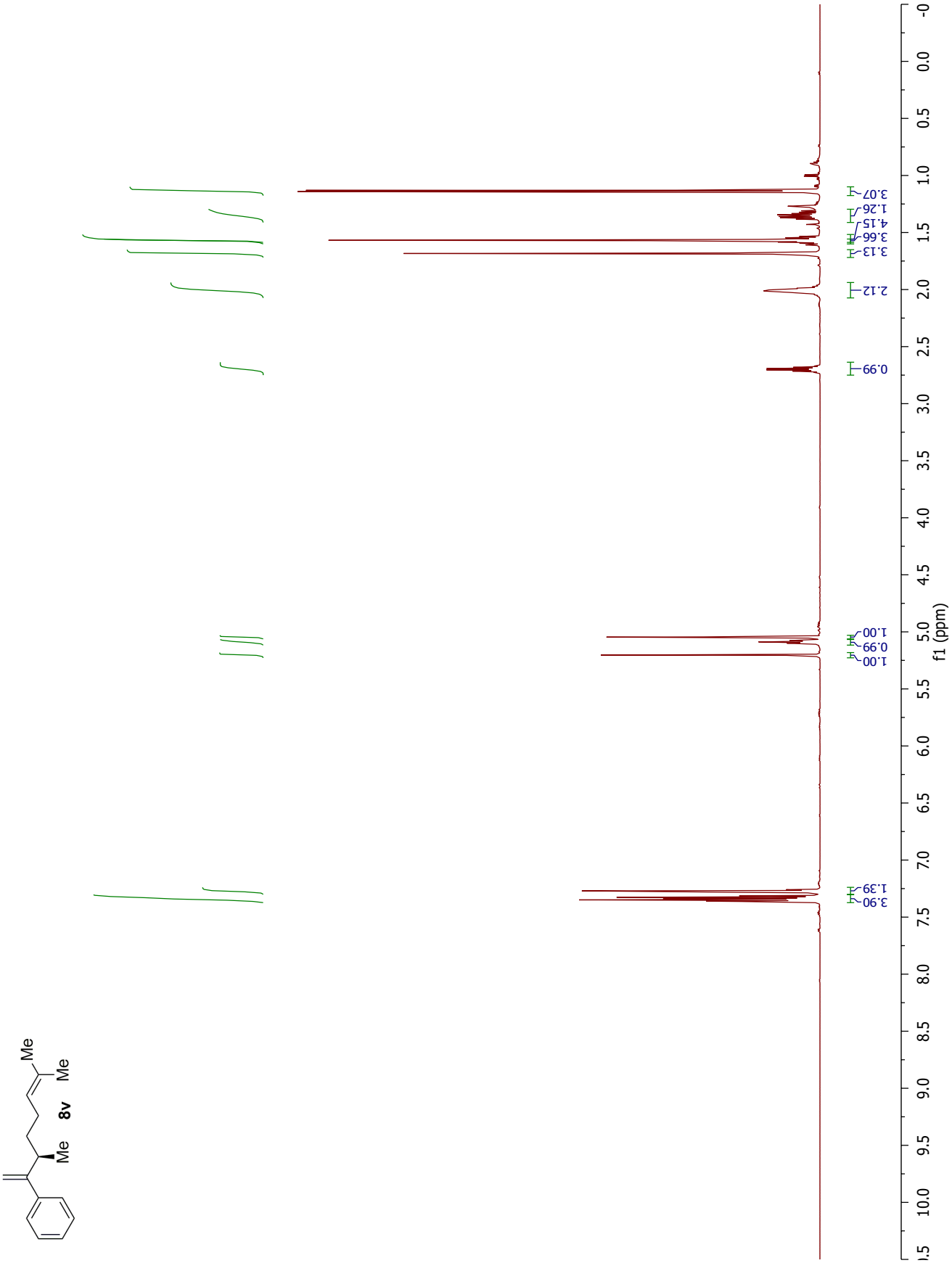


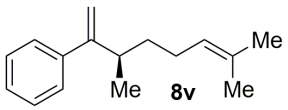
8t


22.37
26.36
45.12
113.42
126.27
127.17
128.17
141.46
147.83
f1 (ppm)
Me
Me
8t

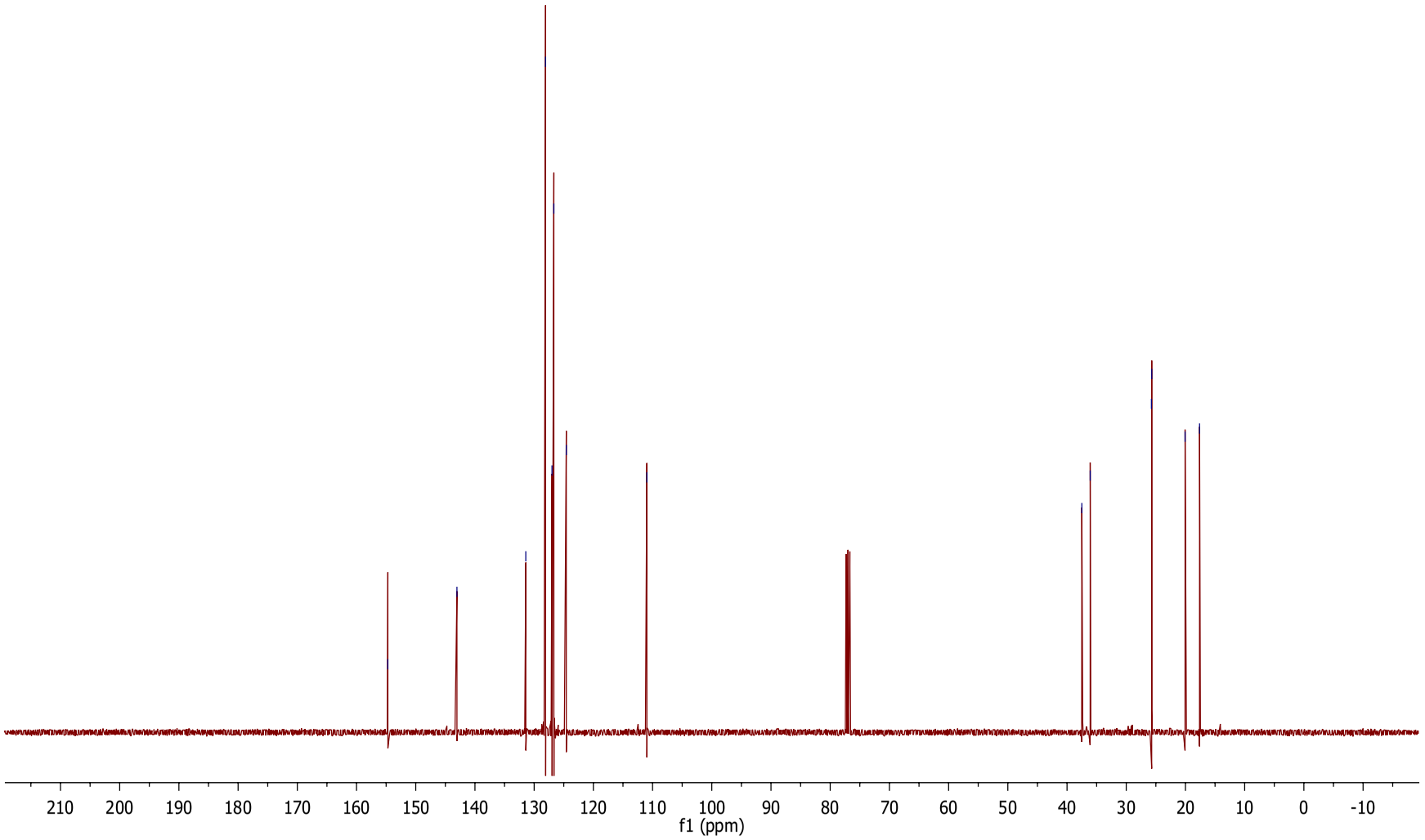

8u
5.59
1.08
4.07
1.03
1.00
1.01
1.20
3.96
f1 (ppm)

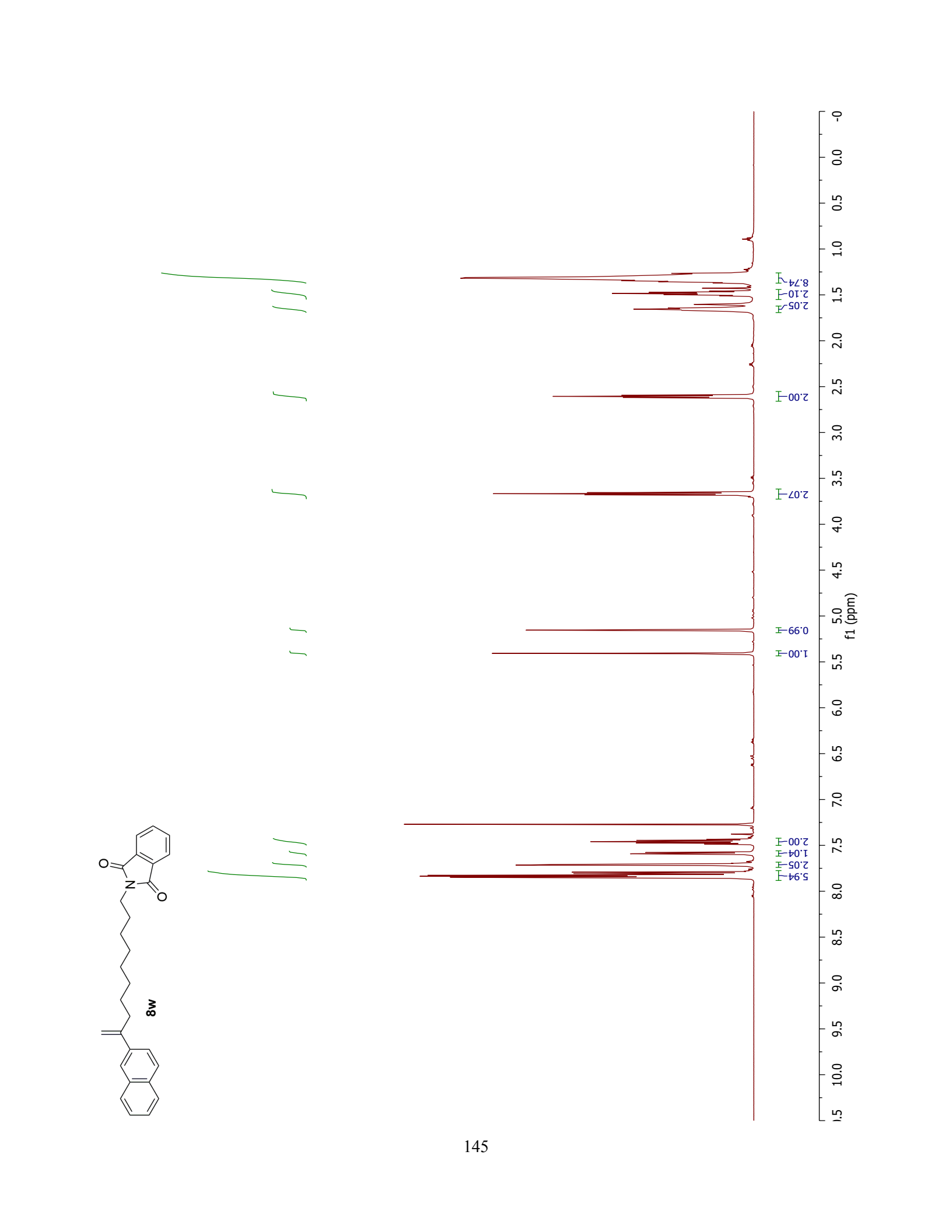

8u
155.03
142.98
128.10
126.97
126.62
110.31
42.60
32.73
26.84
26.44
f1 (ppm)

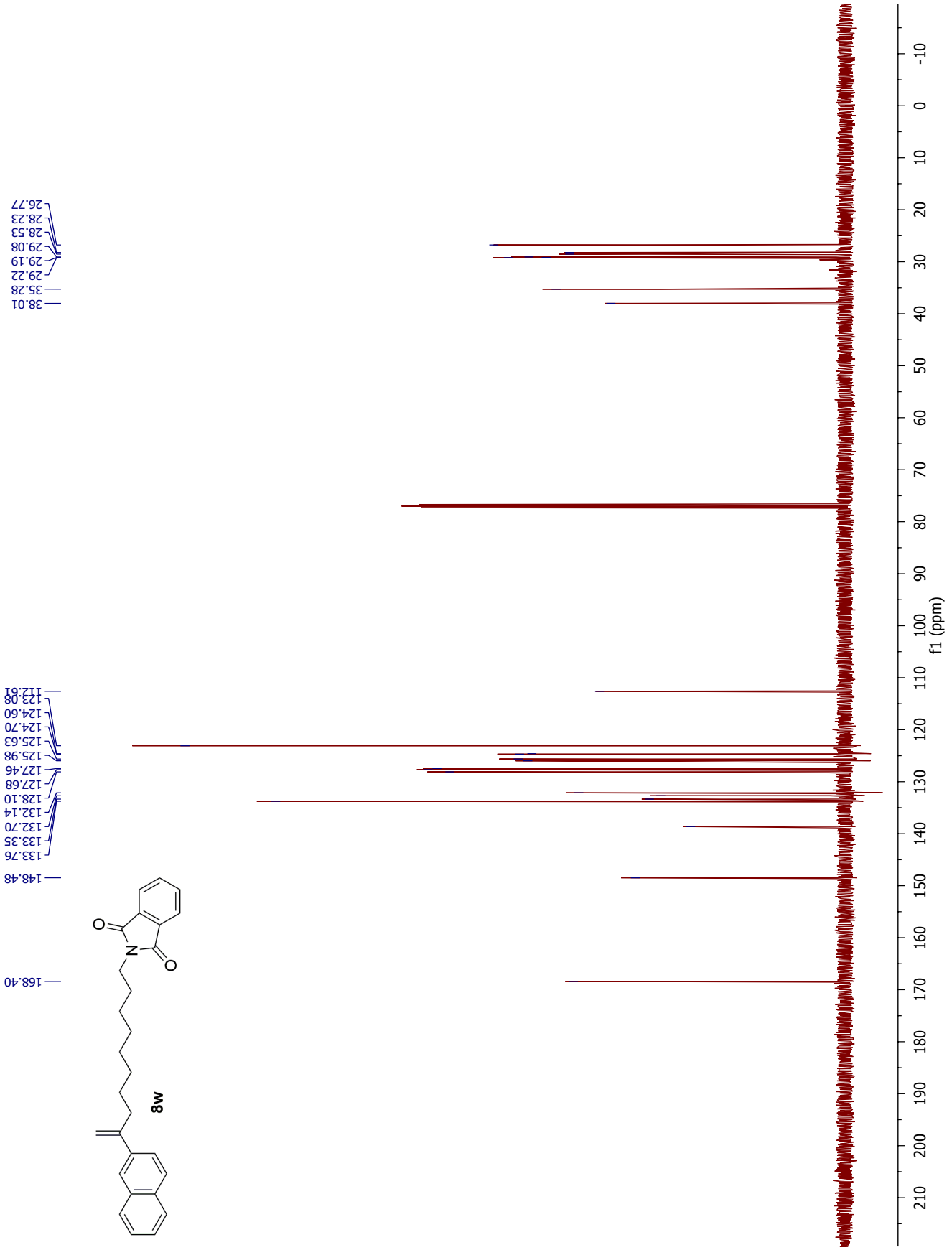

Me
Me
8v
Me
3.07
1.26
4.15
3.66
3.13
2.12
0.99
1.00
0.99
1.00
1.39
3.90
f1 (ppm)

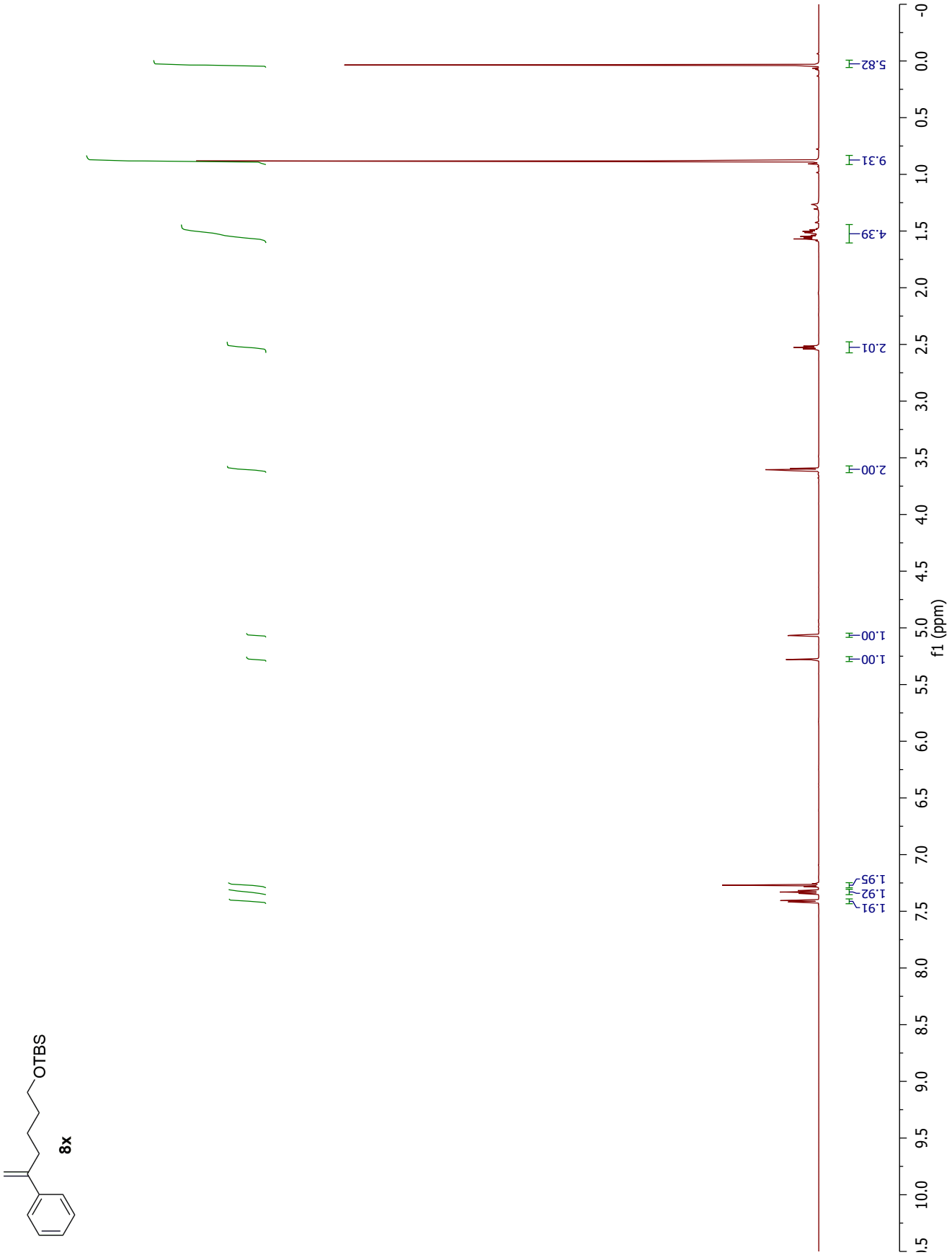


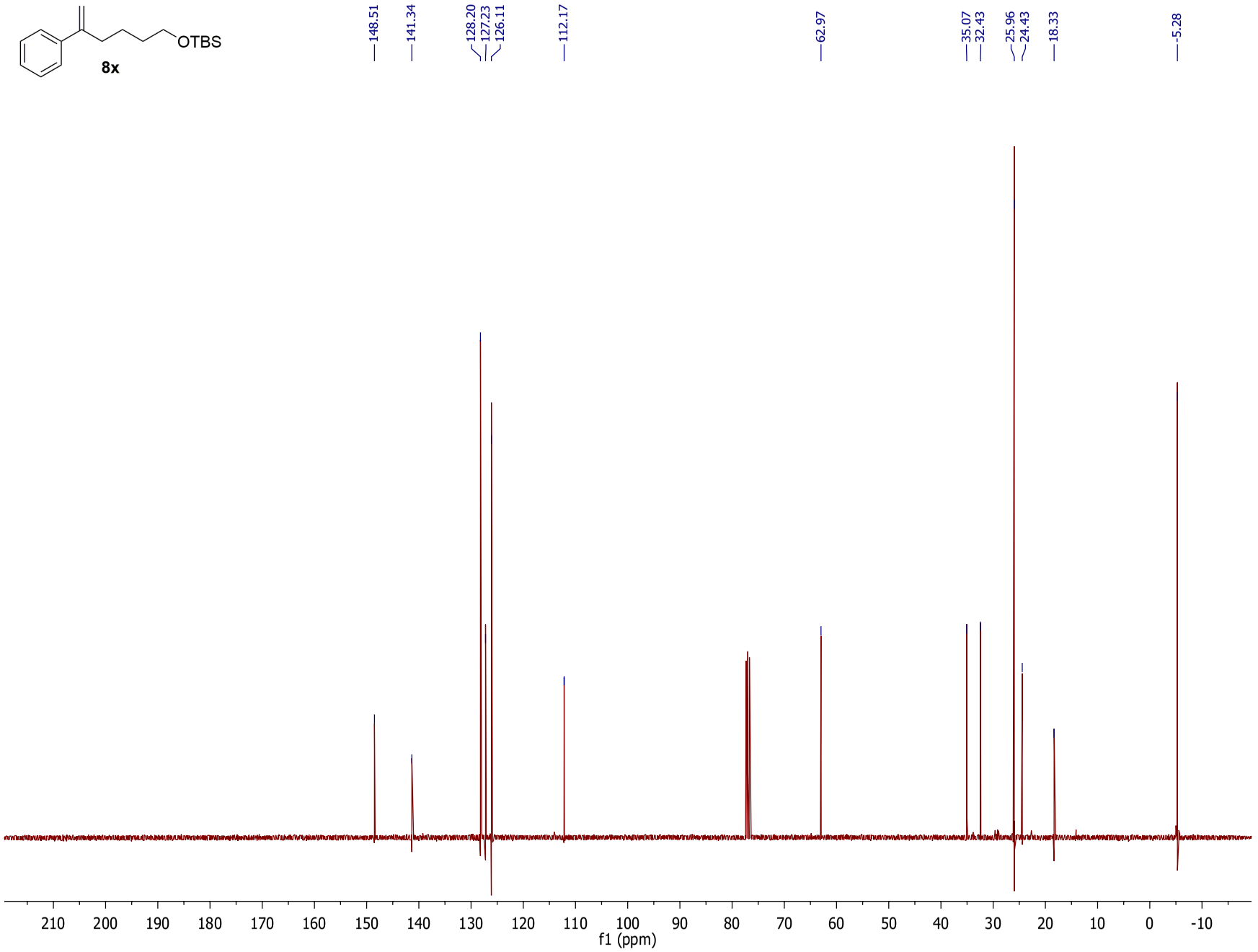
154.71
143.04
131.41
128.07
126.99
126.67
124.57
110.97
37.50
36.09
25.75
25.70
20.06
17.62

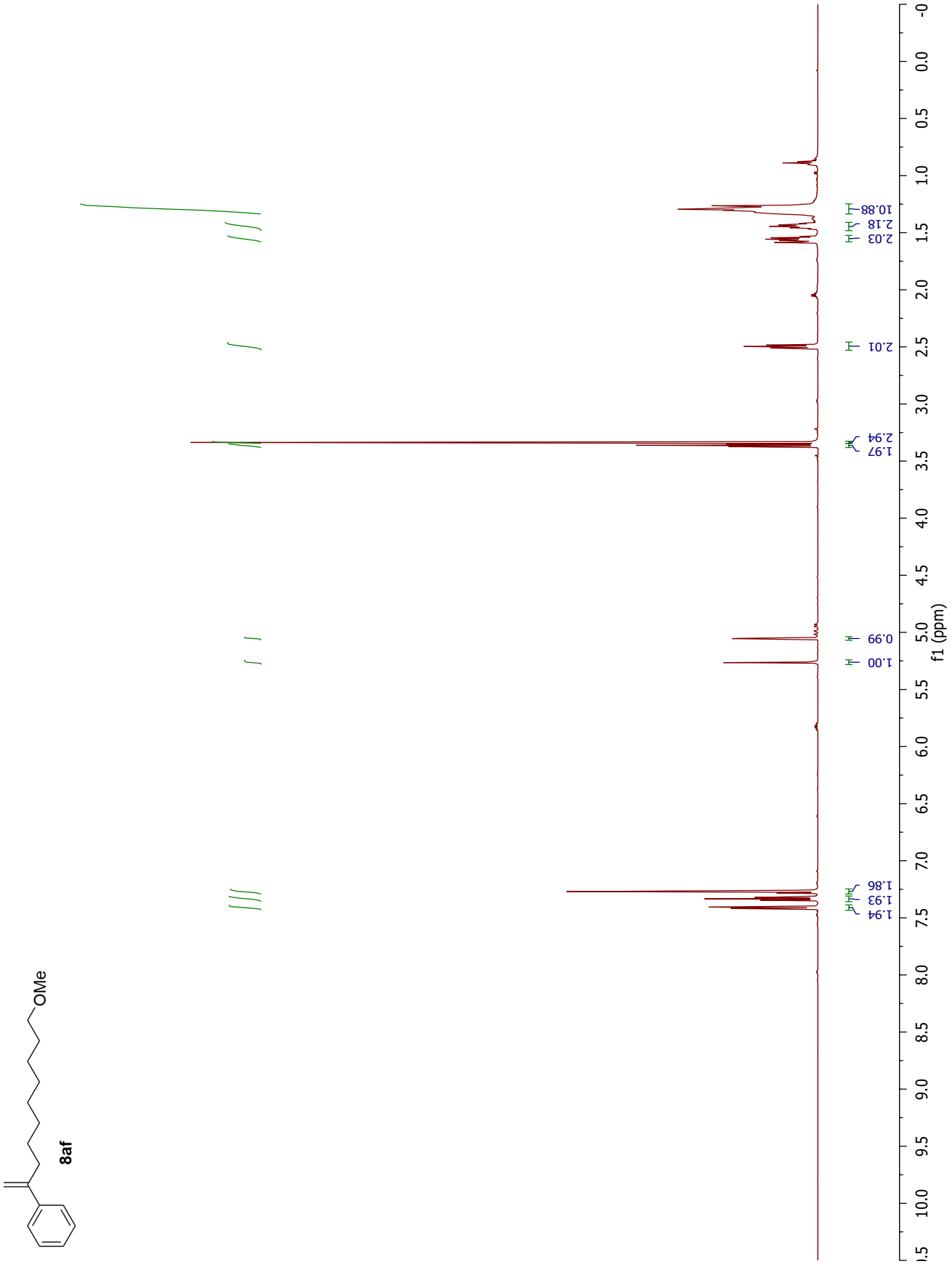


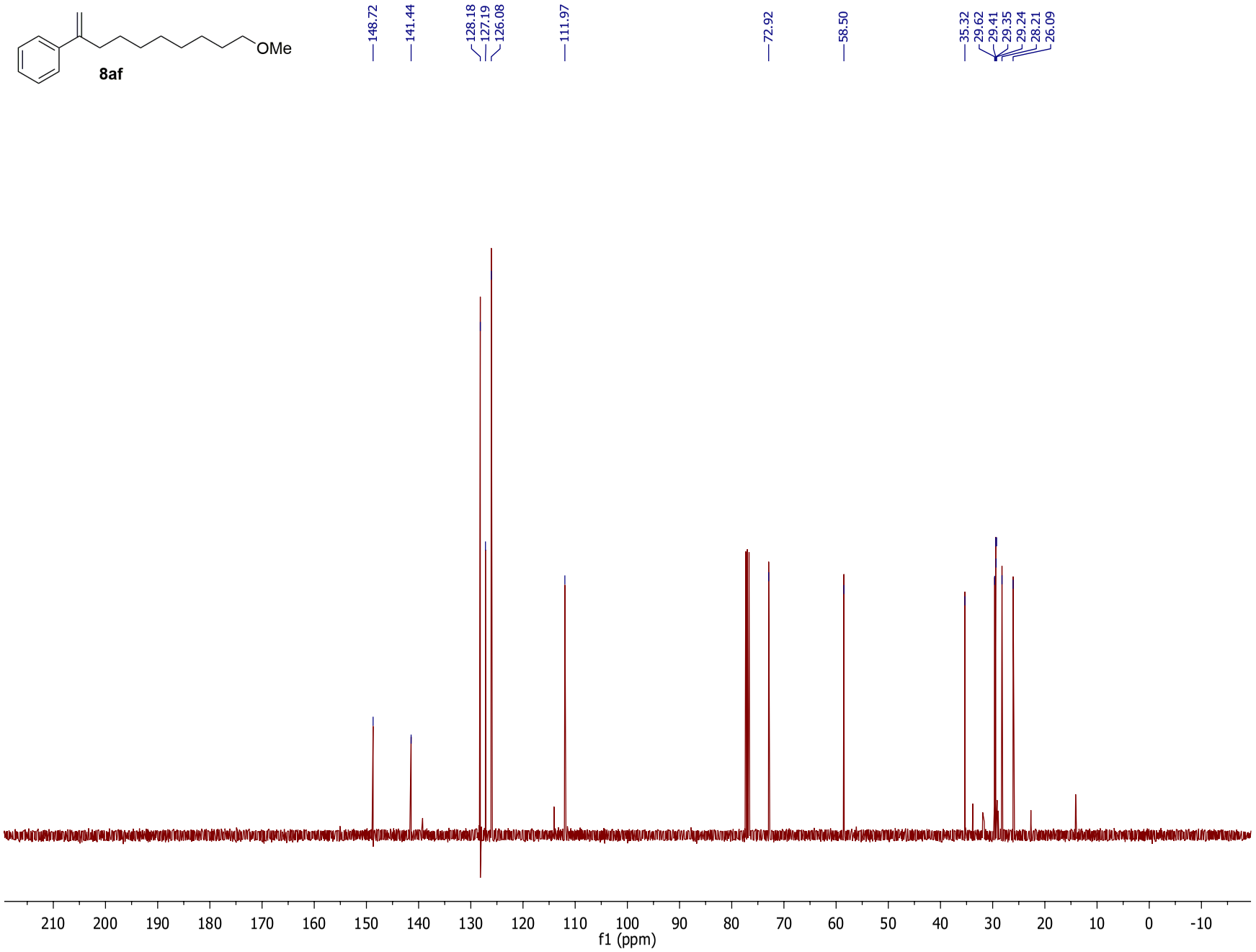

8w
8.74
2.10
2.05
2.00
2.07
0.99
1.00
2.00
1.04
2.05
5.94
f1 (ppm)

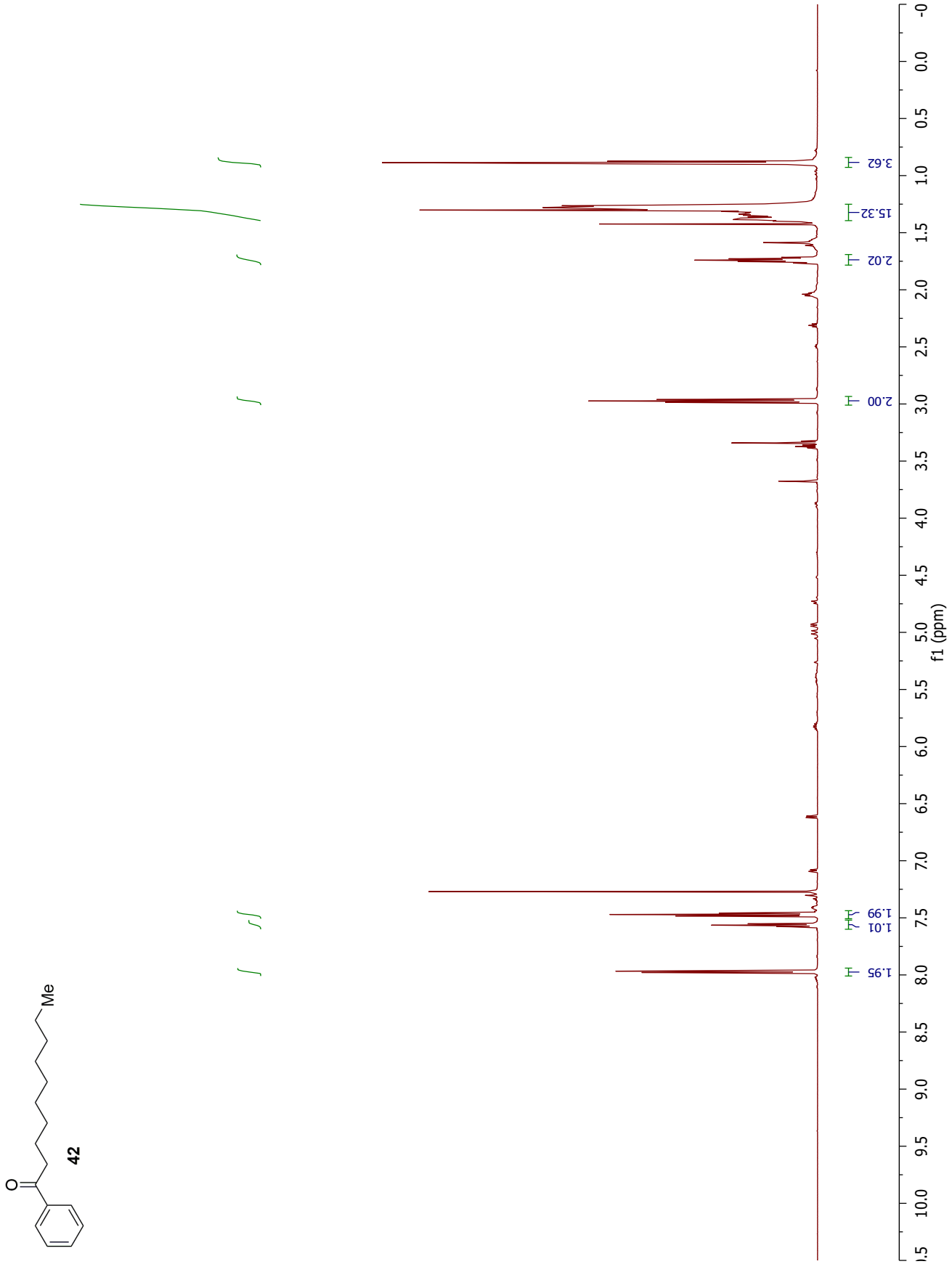

168.40
148.48
133.76
133.35
132.70
132.14
128.10
127.68
127.46
125.98
125.63
124.70
124.60
123.08
112.61
38.01
35.28
29.22
29.19
29.08
28.53
28.23
26.77
8w
f1 (ppm)

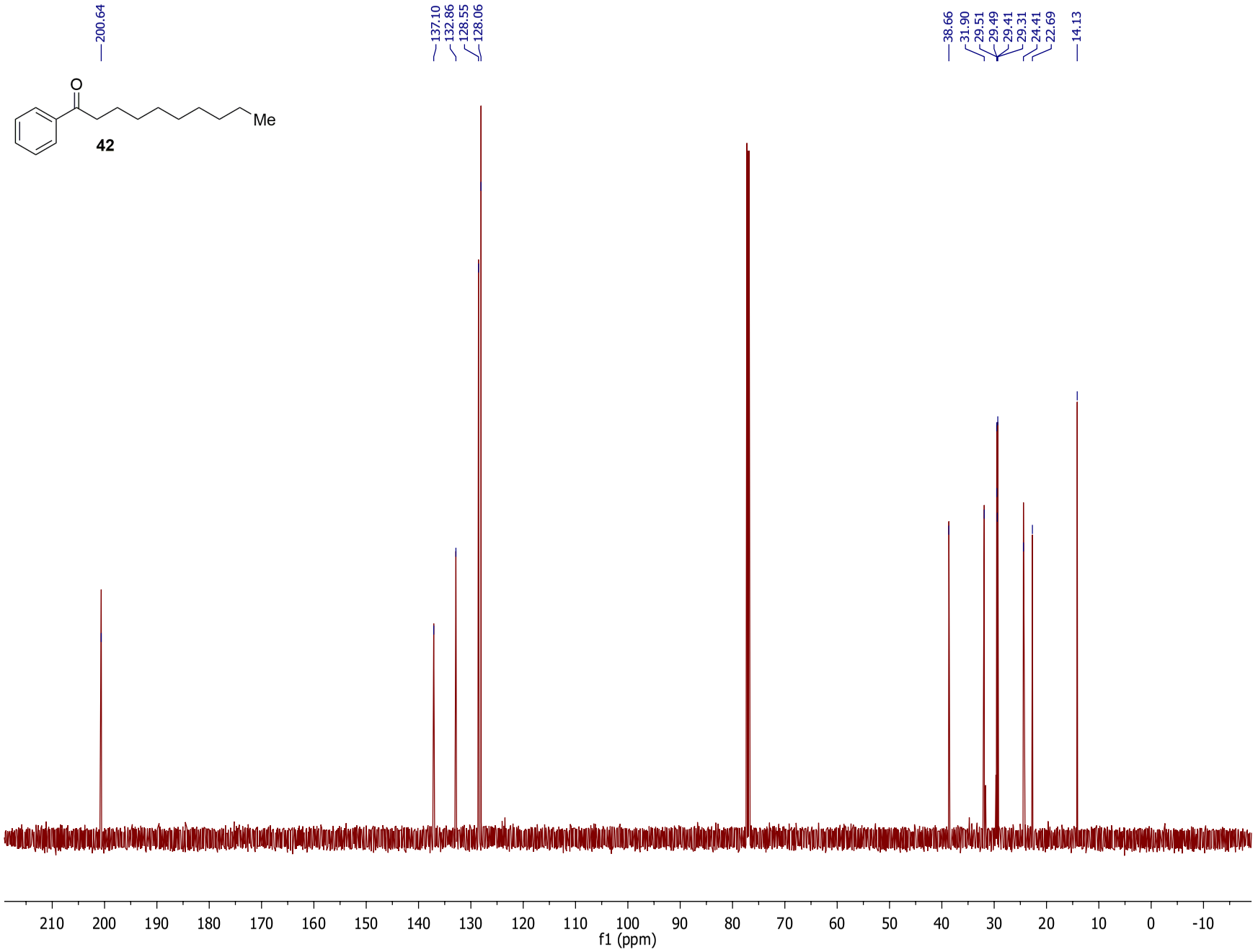

OTBS
8x
5.82
9.31
4.39
2.01
2.00
1.00
1.00
1.95
1.92
1.91
f1 (ppm)

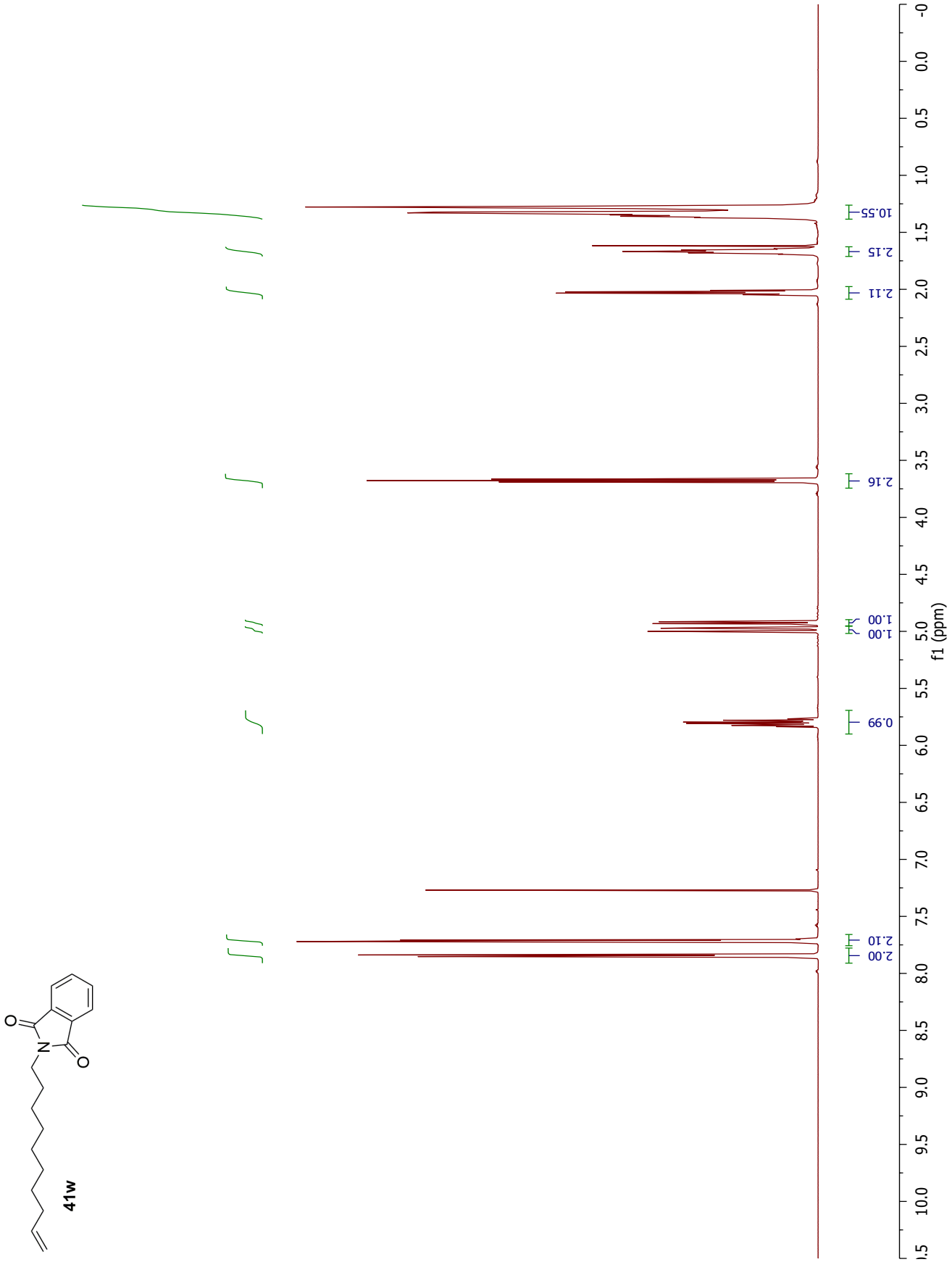

OTBS
8x
148.51
141.34
128.20
127.23
126.11
112.17
62.97
35.07
32.43
25.96
24.43
18.33
-5.28
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

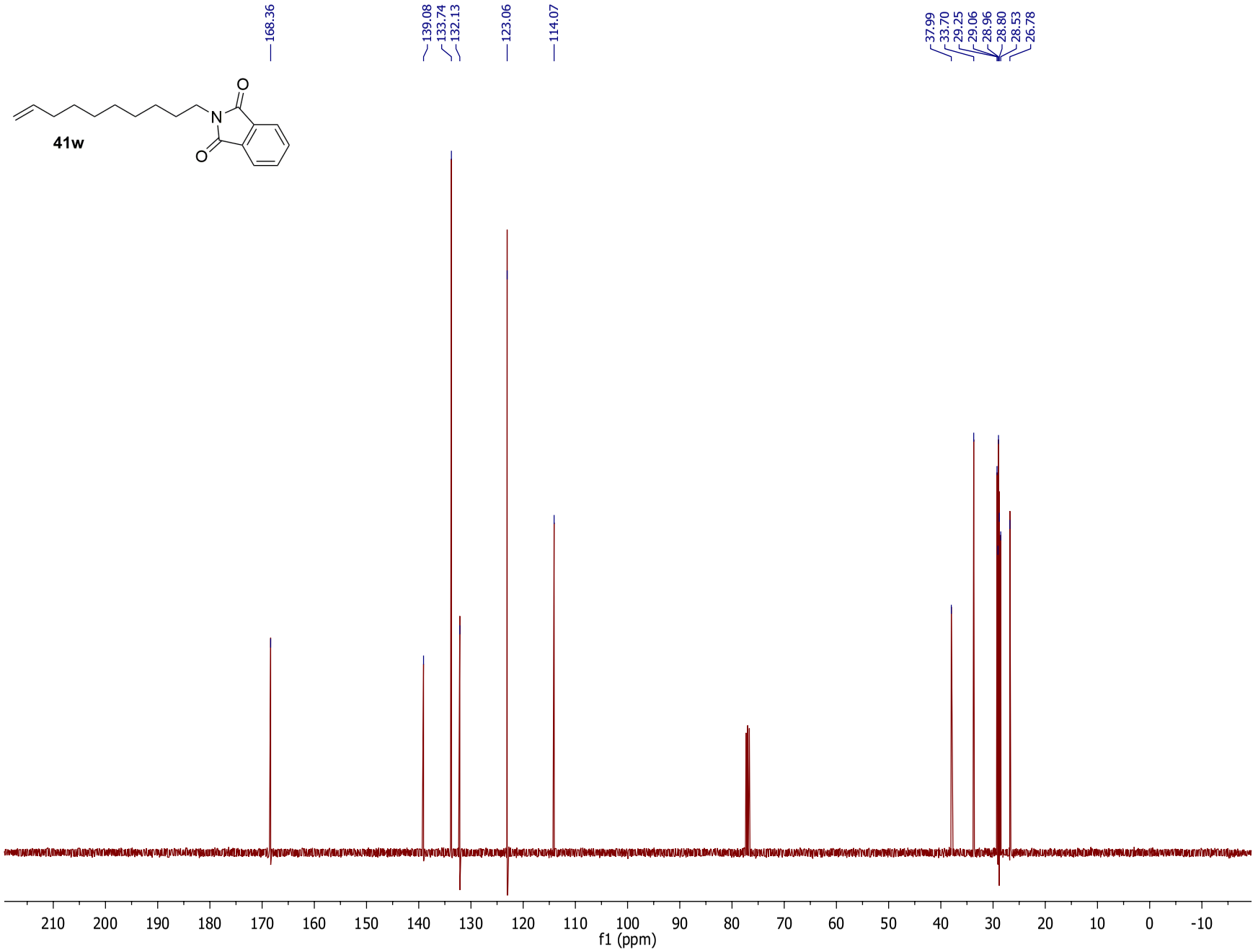

OMe
8af
10.88
2.03
2.18
2.01
1.97
2.94
0.99
1.00
1.94
1.93
1.86
f1 (ppm)

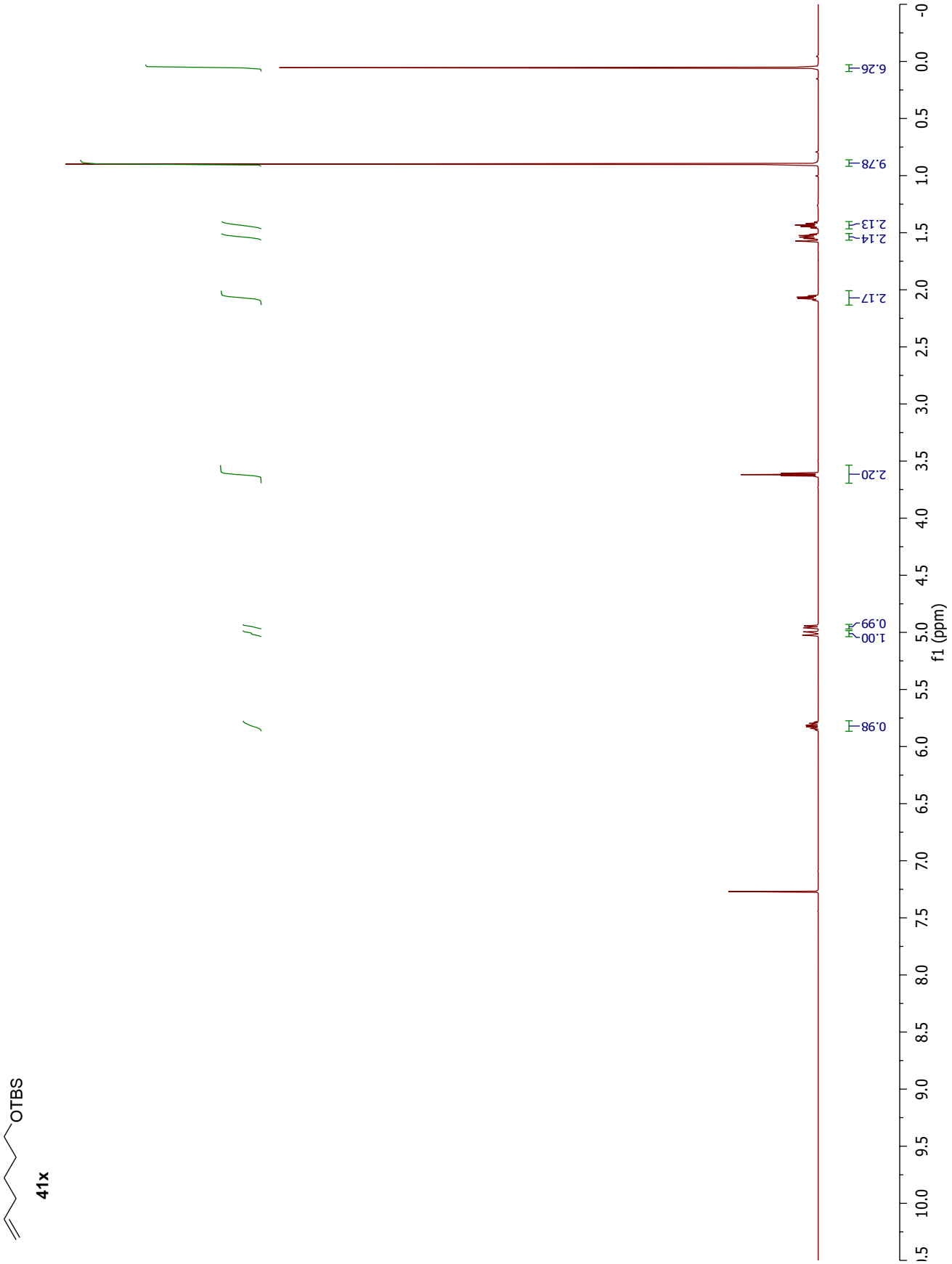

OMe
8af
148.72
141.44
128.18
127.19
126.08
111.97
72.92
58.50
35.32
29.62
29.41
29.35
29.24
28.21
26.09
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

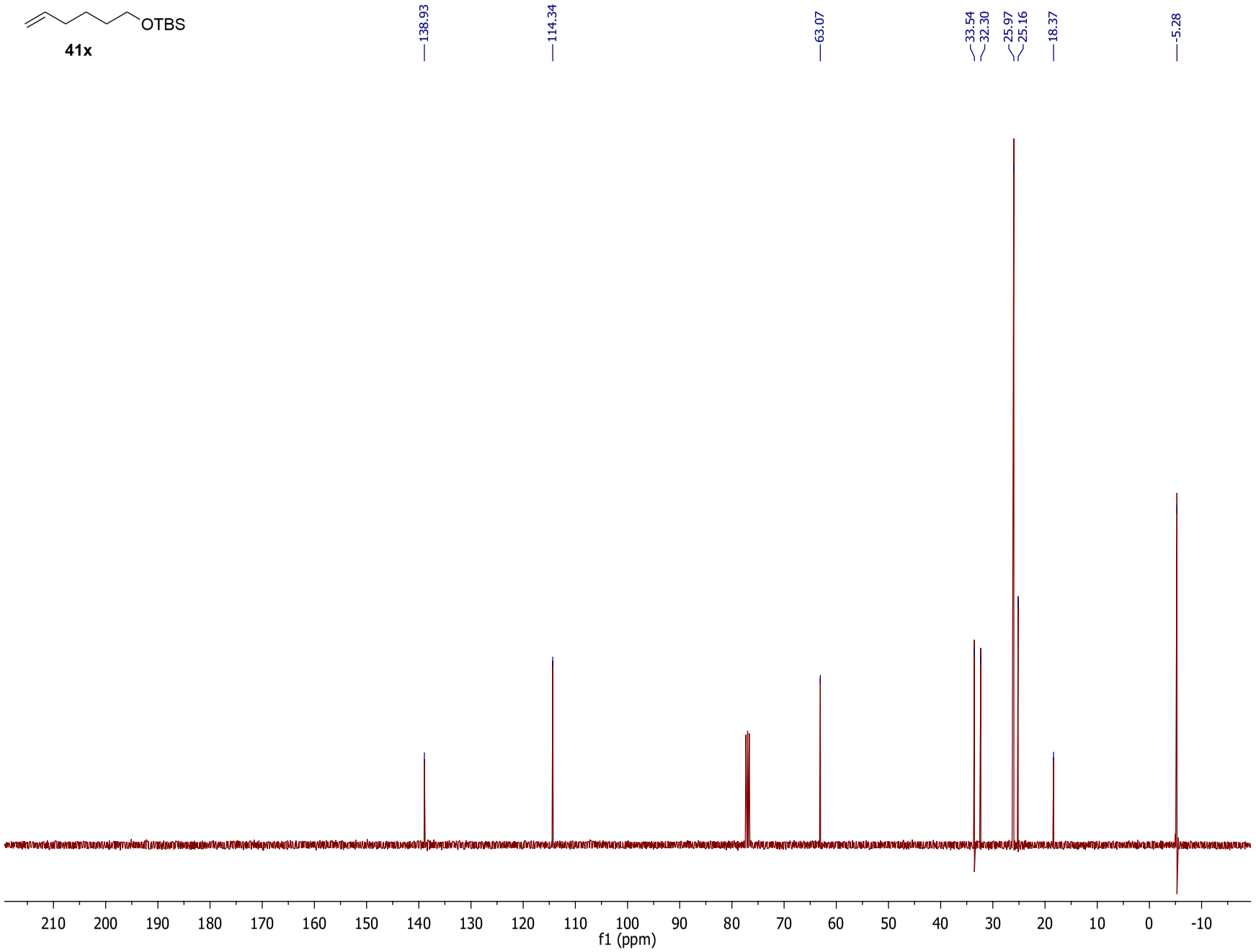

Me
O
42
3.62
15.32
2.02
2.00
1.99
1.01
1.95
f1 (ppm)

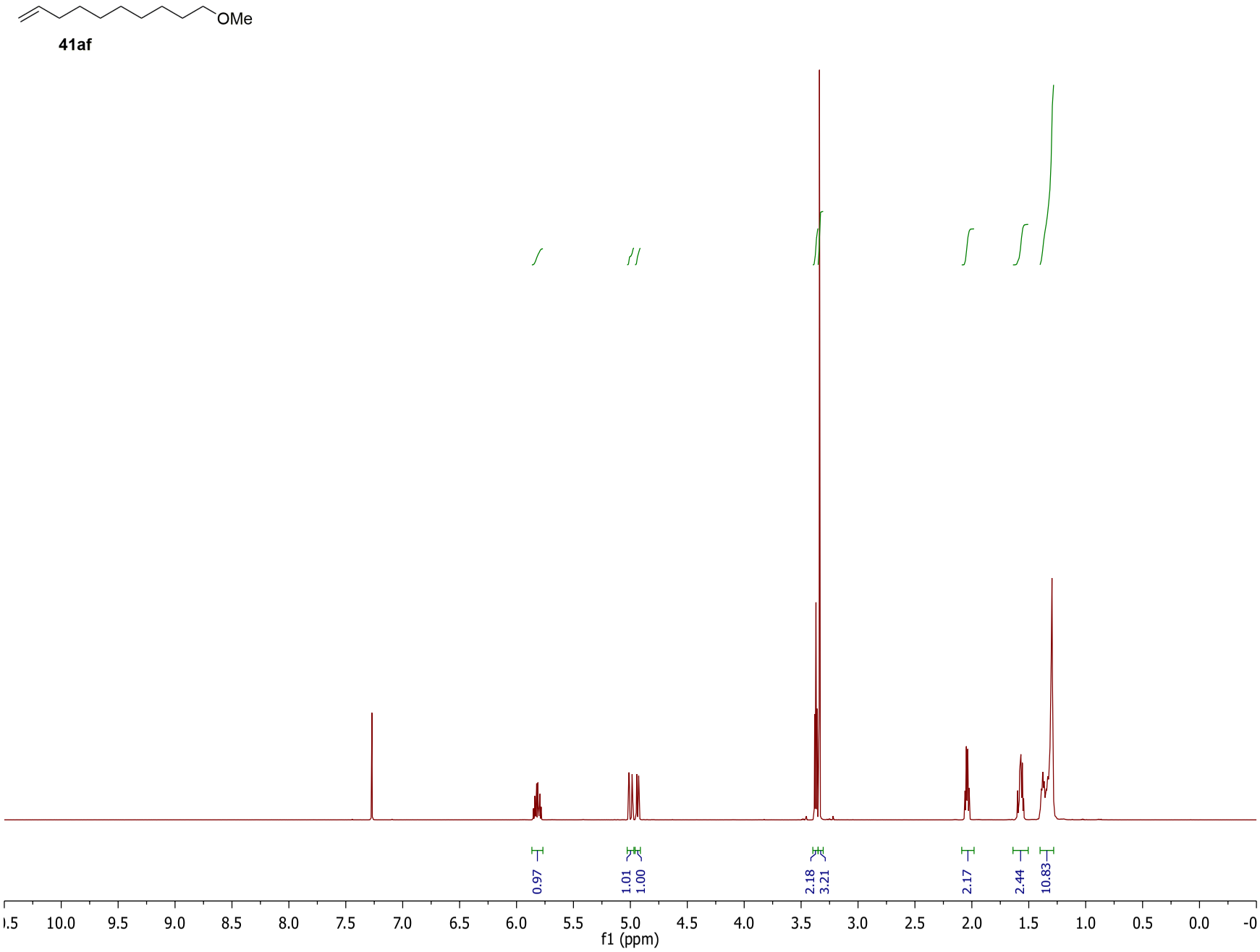

200.64
137.10
132.86
128.55
128.06
38.66
31.90
29.51
29.49
29.41
29.31
24.41
22.69
14.13
O
Me
42
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

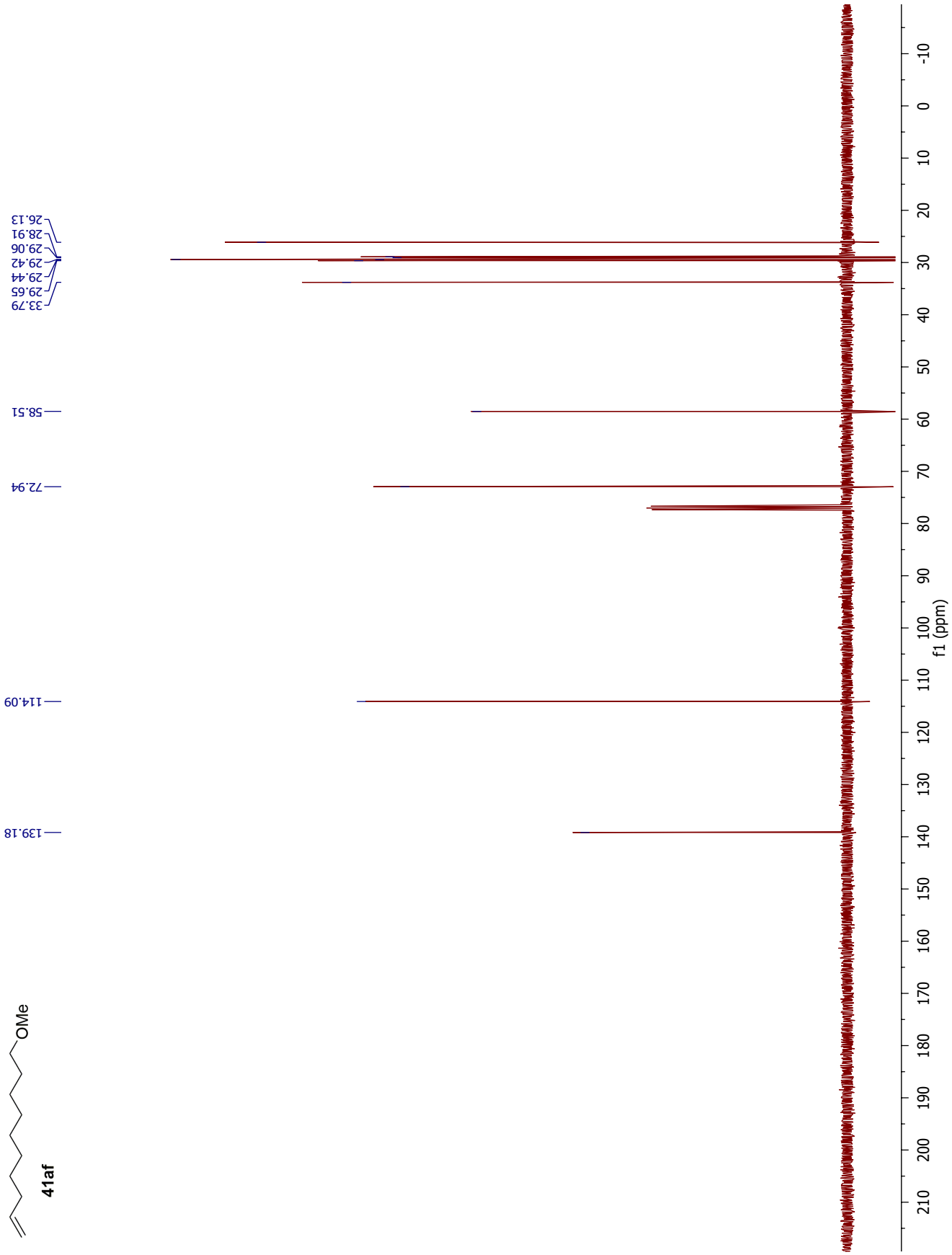

10.55
2.15
2.11
2.16
1.00
1.00
0.99
2.10
2.00
f1 (ppm)
41w


168.36
139.08
133.74
132.13
123.06
114.07
37.99
33.70
29.25
29.06
28.96
28.80
28.53
26.78
41w
O
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OTBS
41x
6.26
9.78
2.13
2.14
2.17
2.20
0.99
1.00
0.98
f1 (ppm)


OTBS
41x
138.93
114.34
63.07
33.54
32.30
25.97
25.16
18.37
-5.28
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OMe
41af
0.97
1.01
1.00
2.18
3.21
2.17
2.44
10.83
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

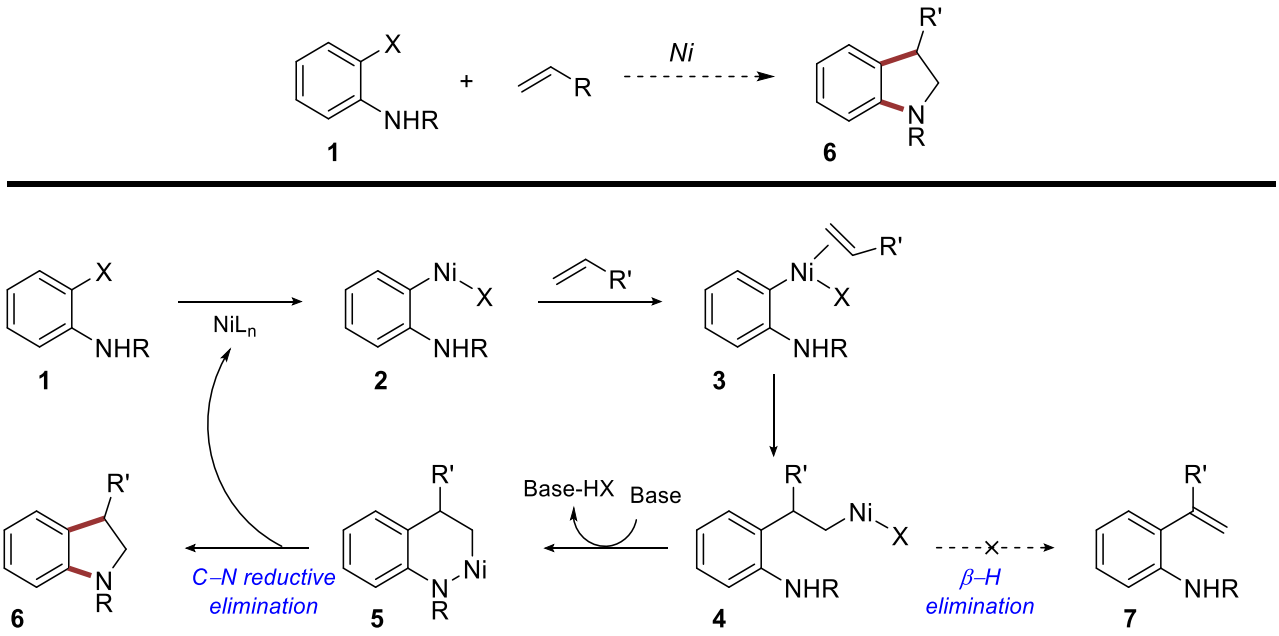

OMe
41af
26.13
28.91
29.06
29.42
29.44
29.65
33.79
58.51
72.94
114.09
139.18
f1 (ppm)

Chapter 2.
Nickel/Photoredox Dual Catalysis and the Synthesis of Indolines

Introduction

After developing the branch-selective Mizoroki–Heck reaction described in Chapter 1, we wondered whether any of the intermediate nickel species accessed over the course of the reaction could be leveraged to accomplish new and interesting chemistry. Specifically, we focused on the migratory insertion complex **4**. If an arene with an adjacent amine functionality were submitted to the reaction conditions, we wondered whether C(sp^3)–N reductive elimination could occur to form indoline products such as **6** (Scheme 1).

Scheme 1. Proposed synthesis of indolines.

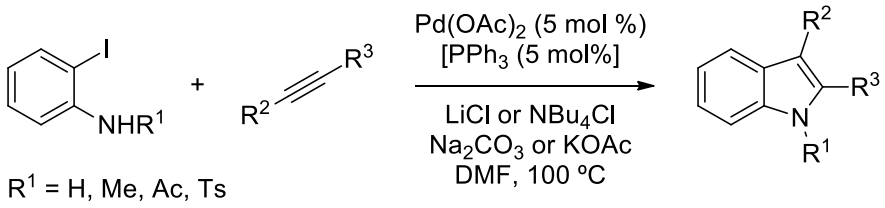


This process is directly analogous to the Larock indole synthesis, which joins similar arene electrophiles and alkynes, typically with a palladium catalyst (Scheme 2).[1] Two main challenges make the process shown in Scheme 1 difficult compared with its alkyne counterpart.

[1] *Original reports*: a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662. *Reviews*: c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.

First, the presence of available *syn* β-hydrogens means that reductive elimination must outcompete β-hydride elimination. Second, reductive elimination must occur from a sp^3-hybridized carbon, which can be particularly challenging (*vide infra*).

Scheme 2. The Larock indole synthesis.



C(sp^3)–N Reductive Elimination from Group 10 Metals

Reductive elimination is a fundamental process in organometallic chemistry and has been well studied for nickel, palladium, and platinum.[2] Carbon–nitrogen and other carbon–heteroatom reductive elimination was first studied and developed into useful reactions rather later than carbon–carbon reductive elimination, although it can be incredibly useful in preparing pharmaceutically active products, natural products, and polymers.[3] The first Pd-catalyzed reaction involving C–N reductive elimination was reported by Migata and coworkers in 1983 in a cross-coupling of aryl bromides with tin amides,[4] but it was not until 1994 that the simultaneous reports from Hartwig[5] and Buchwald[6] further expanded on this chemistry in a synthetically useful sense. This chemistry has been further developed and elaborated into what

[2] Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857–1867.
[3] Hartwig, J. F. *Nature* **2008**, *455*, 314–322.
[4] Kosugi, M.; Kameyama, M.; Migata, T. *Chem. Lett.* **1983**, *12*, 927–928.
[5] Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970.
[6] Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902.

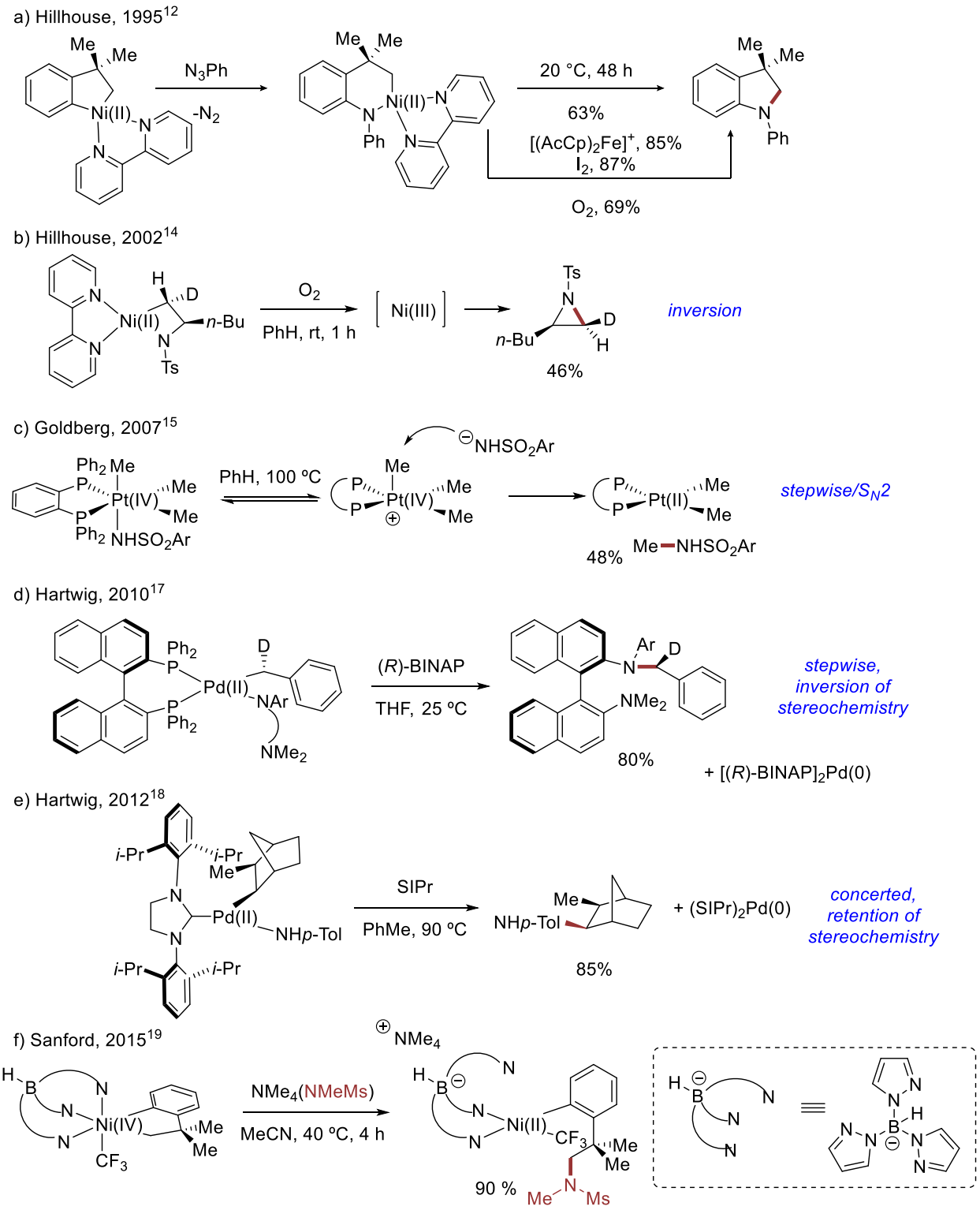
we now know as the Buchwald–Hartwig amination reaction, and typically involves the palladium-catalyzed synthesis of aryl amines from aryl halides and pseudohalides and aryl or alkyl amines.[7] In addition, several Ni-catalyzed Buchwald–Hartwig amination reactions have been reported.[8]

Mechanistically, reductive elimination is generally faster for electron-poor[9] and sterically hindered[10] metal centers, since it involves an overall two electron reduction of the metal and a lower coordination number, potentially relieving steric congestion. More specifically, electronic effects have been well studied in C–N reductive elimination from Pd(II) species.[11] Briefly, these studies by Hartwig and coworkers found that the rate of C(sp^2)–N reductive elimination increased with more nucleophilic/electron-rich amido groups, more electron-poor aryl groups, and electron-poor symmetric ancillary ligands.

While C(sp^2)–N reductive elimination of nickel, palladium, and platinum complexes has been relatively well studied, only a few examples of C(sp^3)–N reductive elimination have been reported (Scheme 3). Hillhouse and coworkers were the first to study C(sp^3)–N reductive elimination from well-defined nickel complexes. They initially demonstrated that with a (bpy)Ni(II) species for which β-hydride elimination was blocked by a *gem*-dimethyl group, C–N reductive elimination proceeded slowly at room temperature, but was greatly accelerated by the

[7] a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860.
[8] See for example: a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058. b) Hie, L.; Ramgren, S. D.; Mesganaw, T.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4182–4185. c) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 2929–2932. d) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220–223.
[9] Low, J. J.; Goddard, W. A. *J. Am. Chem. Soc.* **1986**, *108*, 6115–6128.
[10] Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775–2789.
[11] Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947.

Scheme 3. Well-defined C(sp^3)–N reductive elimination from group 10 metals.



addition of stoichiometric oxidants (Scheme 3a).[12] These oxidants were presumably forming a higher-valent Ni(III) species, increasing the rate of two electron reduction, though the slow reaction in the absence of oxidant could also potentially proceed via a Ni(III) pathway, either by oxidation by a low concentration of external oxidant or by nickel disproportionation. This possibly thermal Ni(II) reductive elimination in the absence of oxidants was also accelerated by the use of phosphine rather than N-type ligands.[13] It was also not clear whether reductive elimination was occurring though by a concerted or stepwise (S_N2) pathway. In order to address the question of mechanism, Hillhouse and coworkers also studied the C–N reductive elimination of diastereomerically pure aziridines (Scheme 3b).[14] A similar (bpy)Ni(II) species can be formed by oxidative addition (a S_N2 process) to an aziridine. Upon reductive elimination, again induced by oxidation to Ni(III), clean inversion of the carbon center was observed, implying an S_N2 or homolysis/ring closing pathway. Such a dissociative S_N2 pathway was also observed in the reductive elimination of high-valent Pt(IV) complexes with sulfonamide ligands (Scheme 3c),[15] while either S_N2 attack or direct concerted reductive elimination depending on reaction conditions was proposed for other Pt(IV) complexes.[16]

The first well-studied C(sp^3)–N reductive elimination from a *low-valent* group 10 metal reported by Hartwig and coworkers also appeared to proceed via an S_N2 pathway.[17] In this case, as well, β-hydride elimination was precluded by use of a benzyl C(sp^3)-component. More electron-rich amido groups and more sterically hindered benzyl groups increased the rate of reductive elimination. The dissociative ionic S_N2 pathway was corroborated by use of a

[12] Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421–4423.
[13] Koo, K.; Hillhouse, G. L. *Organometallics* **1996**, *15*, 2669–2671.
[14] Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890–2891.
[15] Pawlikowski, A. V.; Getty, A. D.; Goldberg, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 10382–10393.
[16] Riveda-Wheelaghan, O.; Roselló-Merino, M.; Díez, J.; Maya, C.; López-Serrano, J.; Conejero, S. *Organometallics* **2014**, *33*, 5944–5947.
[17] Marquard, S. L.; Rosenfeld, D. C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 793–796.

deuterium-labeled benzyl derivative as shown in Scheme 3d. The rate of reductive elimination was also increased by use of a more polar solvent, though addition of external amine did not significantly alter the rate of reaction.

However, a contrasting *concerted* reductive elimination was observed from another low valent Pd(II) species by Hartwig and coworkers.[18] In the benzyl case, although an η^3-intermediate was not directly observed, the ability of benzyl species to transition to such an intermediate might encourage ionic dissociation of the amido ligand and external attack. To avoid this, the diastereomerically pure norbornylpalladium species with a sterically bulky and electron-rich N-heterocyclic carbene (NHC) ligand was synthesized (Scheme 3e). These norbornyl groups are also stable to β-hydride elimination. In this case, the reductive elimination of the amido ligand proceeded with *retention* of configuration with respect to the C(sp^3)-component, suggesting a concerted reductive elimination process.

Finally, returning to nickel complexes, Sanford and coworker recently reported one of the first studies of structure and reactivity of a well-defined Ni(IV) complex, including its ability to form new C(sp^3)–nucleophile bonds (Scheme 3f).[19] Preliminary studies suggest an external S_N2 attack rather than coordination/concerted reductive elimination.

In addition to the above reactions, a number of catalytic reactions have been reported that invoke C(sp^3)–N reductive elimination. These include reactions of low-valent group 10 metals without the addition of an external oxidant (often where β-hydride elimination is disallowed)[20] as

[18] Hanley, P. S.; Marquard, S. L.; Cundari, T. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 15281–15284.
[19] Camasso, N. M.; Sanford, M. S. *Science* **2015**, *347*, 1218–1220.
[20] See for example: a) Catellani, M.; Del Rio, A. *Russ. Chem. Bull.* **1998**, *47*, 928–931. b) Miura, T.; Morimoto, M.; Yamauchi, M.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 5359–5362. c) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8647–8651.

well as those with an external oxidant which presumably proceed via high valent intermediates.[21] In summary, C(sp^3)–N reductive elimination is known in relatively rare cases from both high and low valent nickel, palladium, and platinum. It appears to proceed under a dissociative S_N2 manifold or a concerted manifold depending on the identity of the complex and conditions used.

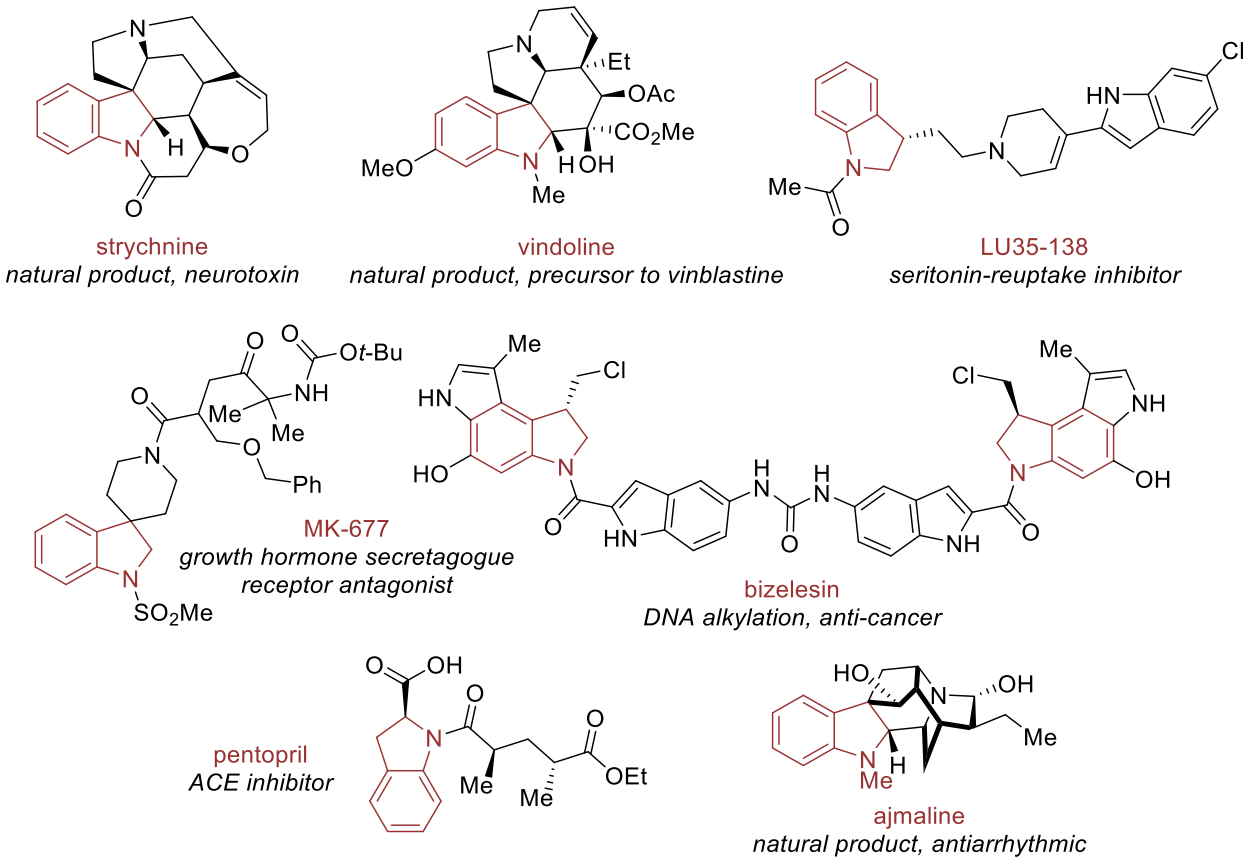
Synthesis of Indolines

Not only would the proposed synthesis of indolines (Scheme 1) using a Larock-type reaction of aminoarene electrophiles and alkenes be mechanistically intriguing, but it would also be a good way to synthesize indolines using an annulation strategy. Indolines, or dihydroindoles, are a common motif in natural products and pharmaceutically active compounds including vindoline,[22] ajmaline,[23] pentopril,[24] and bizelesin[25] among others (Figure 1).[26]

Numerous synthetic routes to this heterocycle exist, but most include multiple steps, generally forming either the C(sp^2)–N bond or the C(sp^2)–C(sp^3) bond first, followed by a cyclization to form the five-membered ring (Scheme 4).[27] Others involve reduction of

[21] See for example: a) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868–2869. b) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892–6895. c) Iglesias, Á.; Álvarez, R.; de Lera, Á. R.; Muñiz, K. *Angew. Chem., Int. Ed*. **2012**, *51*, 2225–2228.
[22] Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058–1059.
[23] Siddiqui, S.; Siddiqui, R. H. *J. Indian Chem. Soc.* **1931**, *8*, 667–680.
[24] Goodman, F. R.; Weiss, G. B.; Hurley, M. E. *Cardiovasc. Drug Rev.* **1985**, *3*, 57–69.
[25] Schwartz, G. H.; Patnaik, A.; Hammond, L. A.; Rizzo, J.; Berg, K.; Von Hoff, D. D.; Rowinsky, E. K. *Ann. Oncol.* **2003**, *14*, 775–782.
[26] a) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455–3482. b) Hertel, P.; Didriksen, M.; Pouzet, B.; Brennum, L. T.; Søby, K. K.; Larsen, A. K.; Christoffersen, C. T.; Ramirez, T.; Marcus, M. M.; Svensson, T. H.; Di Matteo, V.; Esposito, E.; Bang-Andersen, B.; Arnt, J. *Eur. J. Pharmacol.* **2007**, *573*, 148–160. c) Patchett, A. A.; Nargund, R. P.; Tata, J. R.; Chen, M.-H.; Barakat, K. J.; Johnston, D. B. R.; Cheng, K.; Chan, W. W.-S.; Butler, B.; Hickey, G.; Jacks, T.; Schleim, K.; Pong, S.-S.; Chaung, L.-Y. P.; Chen, H. Y.; Frazier, E.; Leung, K. H.; Chiu, S.-H. L.; Smith, R. G. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 7001–7005.
[27] Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975–3984 *and references therein.*

Figure 1. Selected indoline-containing natural products and pharmaceutically active compounds.

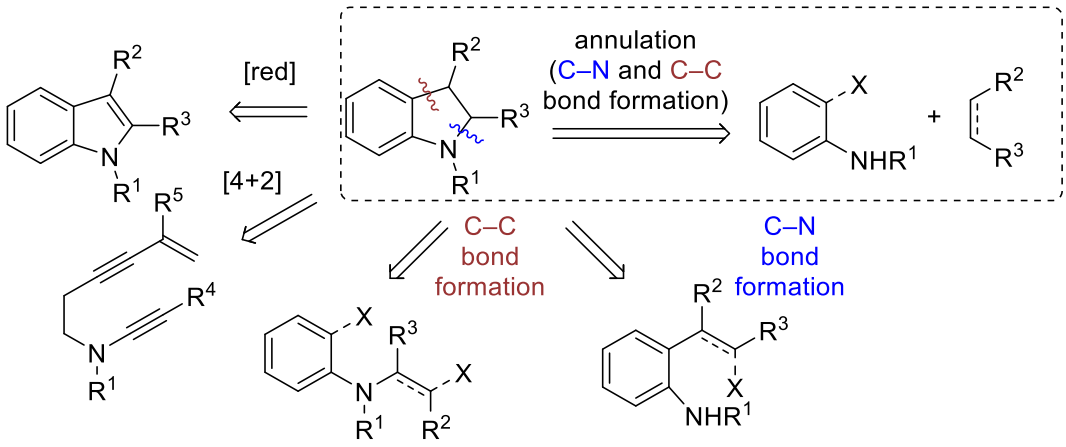


indoles [28] (including enantioselectively [29]), or intramolecular [4+2] cycloadditions to form indolines with substituents on the aromatic ring.[30] Intermolecular annulation strategies are inherently more convergent than these approaches, but applications to indolines remain rare (Scheme 5). Perhaps surprisingly, given the ubiquity of the Larock indole synthesis, a general indoline synthesis of 2-haloaniline derivatives with alkenes has not been reported. Two main challenges are inherent in this approach (as discussed, *vide supra*): C–N bond reductive

[28] Gribble, G. W.; Hoffman, J. H. *Synthesis*, **1977**, 859–860.
[29] a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615. b) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909–8911. c) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661–10664.
[30] Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776–5777.

elimination must outcompete β-hydride elimination to form Heck-type products, and C(sp^3)–N reductive elimination must occur.

Scheme 4. General strategies for indoline synthesis.

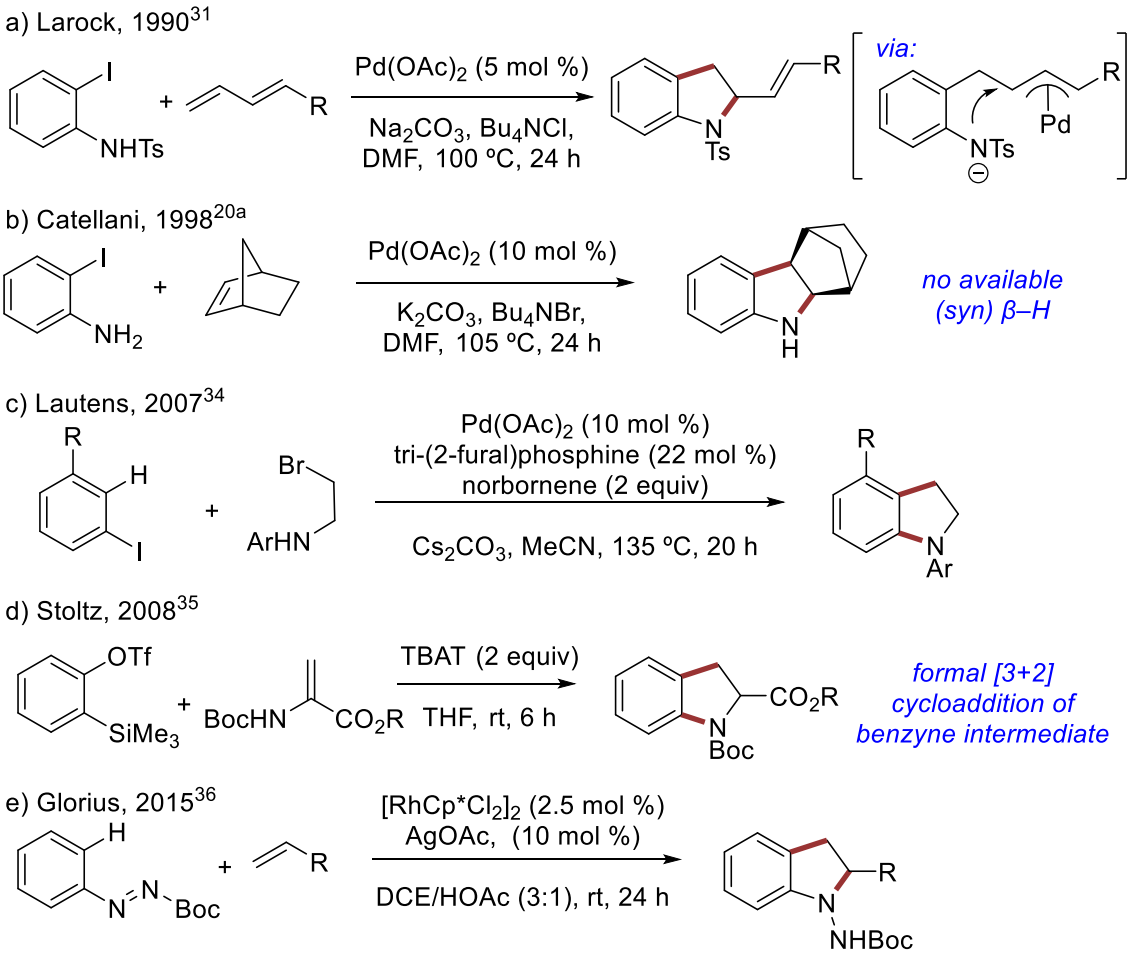


The first indoline synthesis via alkene annulation was reported by Larock and coworkers, who reported indoline formation using 1,3-dienes, which cannot undergo β-H elimination and cause C–N bond formation to presumably proceed via well-studied external nucleophilic attack on a π-allyl intermediate (Scheme 5a).[31] This approach was also recently leveraged in a coupling using 2-vinylnaphthalene, which can also form η^3-intermediates.[32] Another approach involves the use of alkene coupling partners without available β-H atoms, first reported by Catellani and coworker in 1998 (Scheme 5b),[20a] and used by others.[33] Annulation of the five-membered ring of indolines can also be accomplished by foregoing alkenes altogether; for example, Lautens and coworkers reported a palladium-catalyzed C–C/C(sp^2)–N cross coupling of bromoalkylamines (Scheme 5c).[34] Stoltz and coworkers later reported a different approach to form the same bonds

[31] Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447–3450.
[32] Manna, M. K.; Hossian, A.; Jana, R. *Org. Lett.* **2015**, *17*, 672–675.
[33] a) Emrich, D. E.; Larock, R. C. *J. Organomet. Chem.* **2004**, *689*, 3756–3766. b) Thansandote, P.; Hulcoop, D. G.; Langer, M.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 1673–1678.
[34] Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255–5258.

by formal [3+2] cycloaddition (Scheme 5d).[35] Arguably the most general approach thus far was reported by Glorius and coworkers earlier this year which used an internal diazinecarboxylate oxidant and Rh(III)-catalyzed directed C–H functionalization to yield 2-substituted aminoindolines from chiefly electron poor alkenes (Scheme 5e).[36] The 1-amino group can then be removed in good yield in a subsequent step to reveal the NH-indoline.

Scheme 5. Intermolecular annulation strategies for indoline synthesis.



[35] Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559.
[36] Zhao, D.; Vásquez-Céspedes, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 1657–1661.

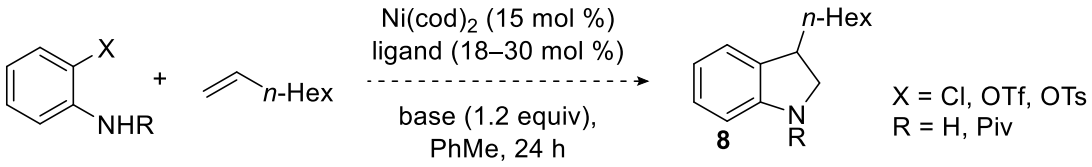
Preliminary Results

Given this relative lack of direct annulation approaches to indoline synthesis, we set out to develop a nickel-catalyzed Larock-type indoline synthesis as outlined in Scheme 1. We began by testing conditions similar to those needed for Heck reactions with a variety of ligands. A few of the conditions tested are shown in Table 1. Generally, conversions were low (at catalyst loading), and several products, including Heck coupling (**9**), reduction (**10**), and homocoupling (**11**), and were observed. However, no desired indoline product was formed. This is perhaps not surprising given the challenging nature of performing the reaction with 1-octene (an aliphatic olefin containing available β-hydrogens as well as no strong electronic bias for regiocontrol of migratory insertion).

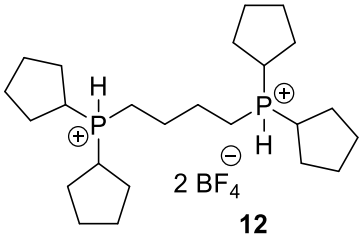
In order to limit the number of possible routes for side product formation, and to mirror an intermediate used by Hillhouse and coworkers (Scheme 3a),[12] we changed the alkene from 1-octene to isobutylene. A similar screen of ligands, bases, and temperatures produced many of the same products, although since Heck-type products were no longer accessible, *t*-butyl arene products were observed resulting from migratory insertion of isobutylene and protonolysis for several phosphine ligands. However, for the first time, we were able to observe desired indoline product formation (**14**) when the NHC ligand IPr was used (Scheme 6). Yields remained under 10% despite attempted optimization of NHC ligand, solvent, base, nickel source, temperature, and other variables. Other 1,1-disubstituted alkenes gave no desired indoline product whatsoever.

Since we did not wish to optimize reaction conditions for the formation of indoline product **14** alone, we returned to reactions of 1-octene to presumably provide a more robust substrate scope. However, we had obtained important information that NHC ligands could be competent for each of the elementary steps of the proposed reaction, including migratory

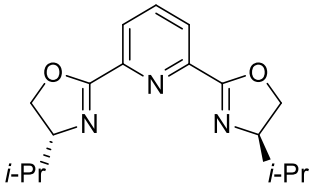
Table 1. Preliminary screening results.[a]



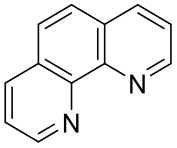
Entry	Ligand	Base	Temperature (°C)	Products Observed
1	**12**	DABCO	60	Heck, **9** reduction, **10**
2	phenanthroline	K_3PO_4	60	homocoupling, **11** reduction, **10**
3	*i*-Pr-PyBOX	DABCO	60	homocoupling, **11**, reduction, **10**
4	PCy_3	K_3PO_4	23	no reaction
5	IPr	LiO*t*-Bu	60	large numbers of products in trace amounts



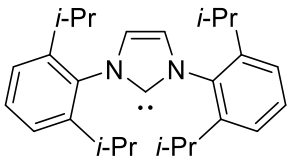
12



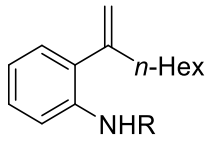
***i*-Pr-PyBOX**



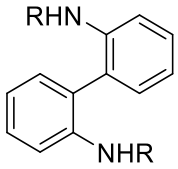
phenanthroline



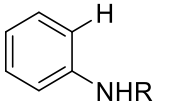
IPr



Heck product
9



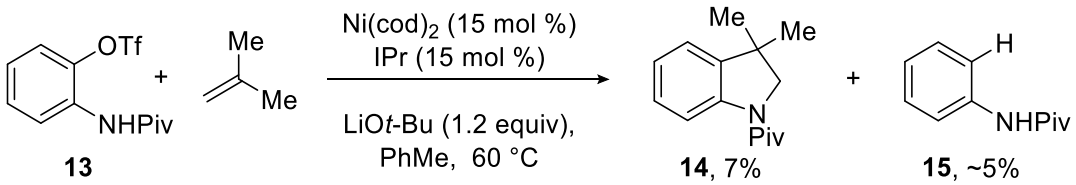
homocoupling
11



reduction
10

[a] Products observed by GC and GC/MS analysis.

Scheme 6. Best results for indoline formation from isobutylene.[a]



13

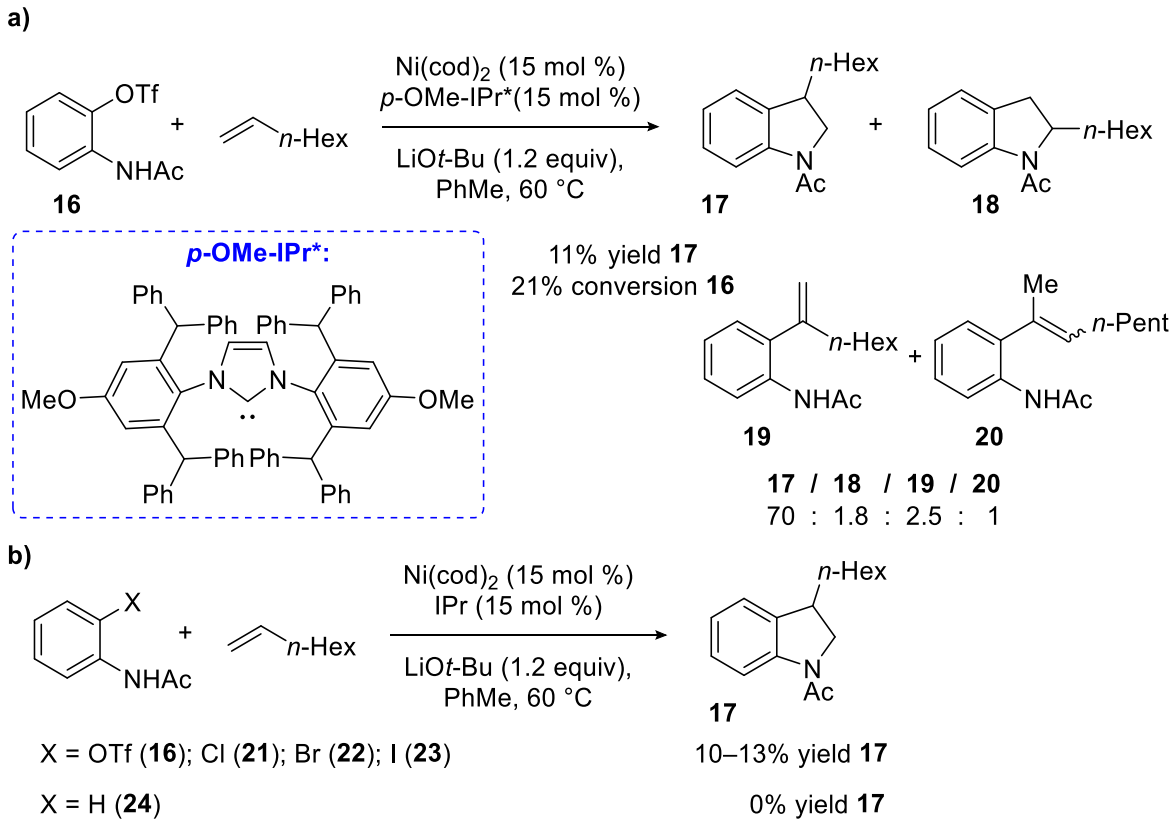
14, 7%

15, ~5%

[a] Yields determined by GC using dodecane as an internal standard

insertion and C(sp^3)–N reductive elimination. In fact, after changing the protecting group to *N*-acetyl (**16**) and using the more sterically demanding *p*-OMe-IPr* NHC ligand[37], we observed clean formation of desired indoline product **17**, albeit in low yield (Scheme 7a). 2-Alkyl indoline (**18**), Heck (**19**), and isomerized Heck (**20**) products were also observed in trace amounts.

Scheme 7. Formation of desired indoline product using NHC ligands.



In fact, with *N*-acetyl arene substrates, IPr could also be used to form desired indoline **17** in similar yields and selectivities (Scheme 7b). Surprisingly, chloro-, bromo-, and iodo-analogues of the arene substrate (**21**–**23**) worked identically well. This suggests that oxidative addition is occurring readily, but that some other step of the catalytic cycle was inhibiting catalyst turnover. The mechanism shown in Scheme 1, which begins with oxidative addition,

[37] Meiries, S.; Speck, K.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2013**, *32*, 330–339.

rather than an initial hydroamination, was likely operative since no conversion of acetanilide (**24**) was observed under the reaction conditions. Again, extensive optimization produced no change in yields. Product inhibition was also ruled out as an issue. Ultimately, we realized that formation of indoline product **17** was only occurring upon exposure of the reaction mixture to air during workup. This fact suggests that, as discussed in the work of Hillhouse and others,[12,13] oxidation to a high-valent nickel species is necessary for reductive elimination to take place. This exposure to an oxidant only occurred as the reaction mixture was quenched, meaning that yields higher than catalyst turnover were likely unobtainable with the current catalytic system.

If oxidation to Ni(III) were a prerequisite for C(sp^3)–N reductive elimination, a Ni(I) species (**25**) would then result (Scheme 8a). Ni(III/I) catalytic cycles are common for cross-coupling of C(sp^3)–hybridized electrophiles and have recently been studied in great detail mechanistically.[38] However, the Ni(I) oxidative addition of aryl electrophiles (**25** to **26**), which would be needed to rejoin the catalytic cycle is less well-known and potentially challenging. Ni(III/I) catalytic cycles are often accessed by comproportionation or disproportionation events,[39] although this was apparently not occurring in our system. Therefore, a variety of oxidants and reductants were tested with the standard reaction conditions with aryl bromide **22** (Table 2). Other agents, such as *p*-fluorostyrene have also been known to help induce reductive elimination from recalcitrant nickel complexes by coordination to a fifth coordination site, and were also tested (Table 2, entry 2).[40] In practice, the reaction remained remarkably intractable to further optimization, producing between 5 and 13% of the desired product independent of conditions used.

[38] a) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. *J. Am. Chem. Soc.* **2013**, *135*, 12004–12012. b) Schley, N. D.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 16588–16593.
[39] Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature*, **2014**, *509*, 299–309.
[40] Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79–85.

Scheme 8. Possible catalytic cycles leading to reaction turnover.

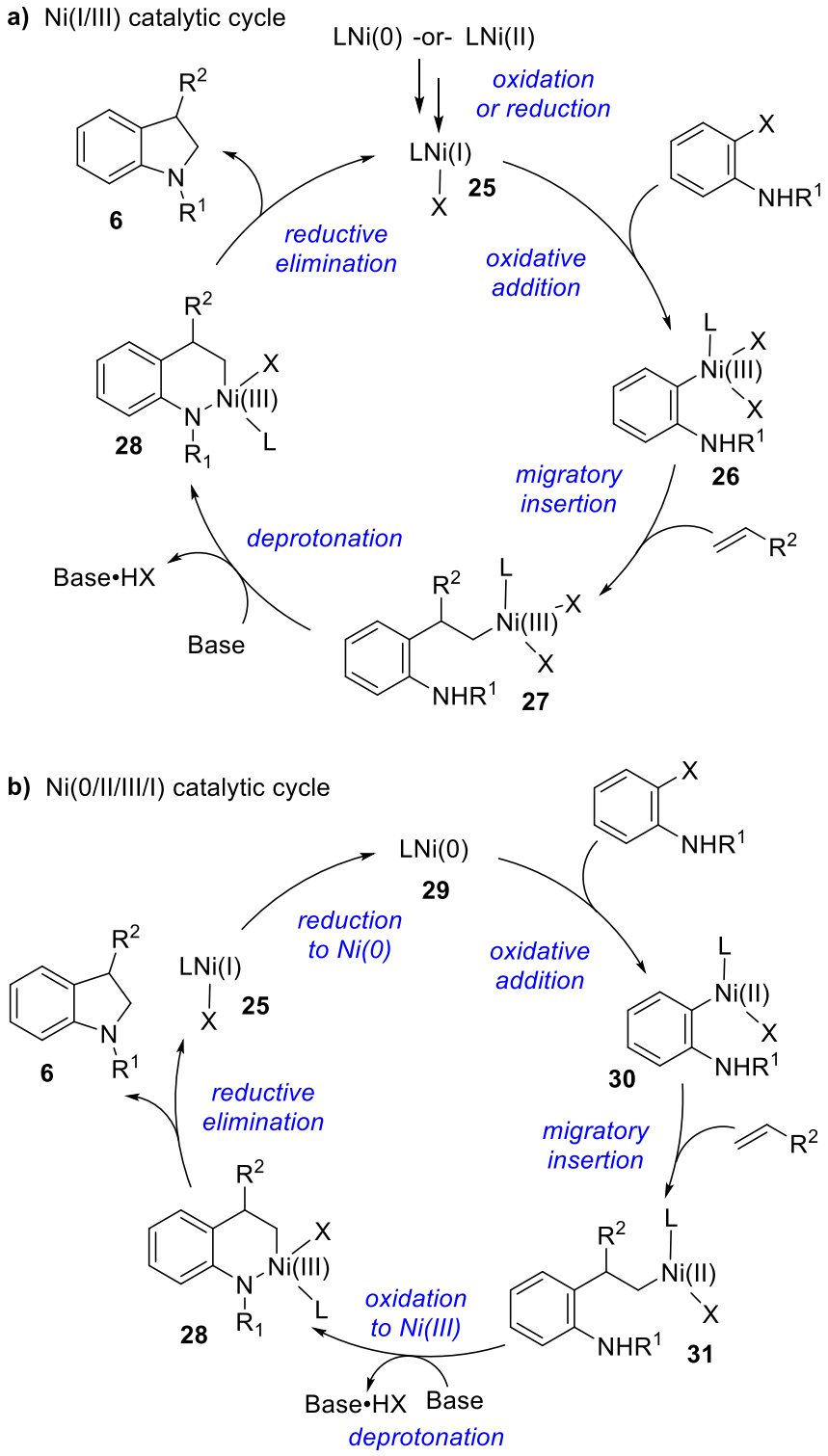
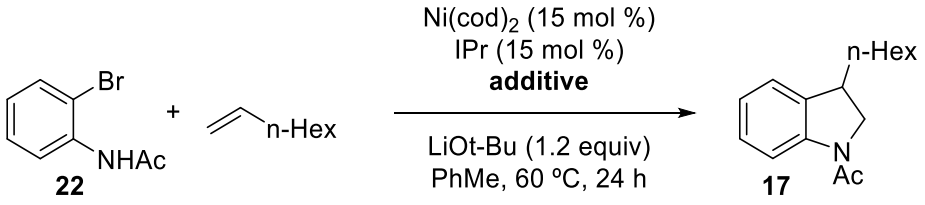


Table 2. Evaluation of additives to increase catalyst turnover.[a]



22 **17**

Entry	Additive	Amount	Conversion **22** (%)	Yield **17** (%)
1	none	–	7	10
2	*p*-fluorostyrene	50 mol %	12	6
3[b]	Zn(0)	200 mol %	79	13
4	ceric ammonium nitrate	50 mol %	22	6
5	sodium formate	50 mol %	48	8
6	$(Me_3Si)_3SiH$	50 mol %	16	6
7	Et_2MeSiH	50 mol %	36	7
8	Hantzsch Ester	50 mol %	30	9
9	TEMPO	50 mol %	20	5
10	SiO_2	50 mol %	29	9
11	Mn(0)	200 mol %	17	9
12	*p*-benzoquinone	50 mol %	27	5
13[b,c]	$Ru(bpy)_3(PF_6)_2$	3 mol %	6	8

[a] Conversions and yields determined by GC with dodecane as internal standard [b] no LiO*t*-Bu [c] *i*-Pr_2EtN (2.0 equiv), MeCN, compact fluorescent light (CFL)

A perhaps more nearly optimal catalytic cycle could be envisioned that would involve both single electron oxidation of Ni(II) species **30** to Ni(III) (**31**) and then single electron reduction of the resulting Ni(I) species **25** to Ni(0) (Scheme 8b). The presence of both a single electron oxidation and reduction in the same catalytic cycle is a scenario perhaps uniquely suited to visible light photoredox catalysis (*vide supra*).[41] However, when attempted under standard conditions (acetonitrile, $Ru(bpy)_3(PF_6)_2$, *i*-Pr_2EtN), no change in product yield was observed (Table 2, entry 13). Despite this initial failure, the catalytic cycle depicted in Scheme 8b is extremely attractive, and we decided it was worth investigating further.

[41] Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363.

Four-Oxidation-State Nickel Catalysis

Among the many advantages of using nickel in the development of new synthetic methods[39] is the availability of various oxidation states for catalysis, including Ni(0/I/II/III) and even the recently reported well-defined Ni(IV) species shown in Scheme 3f.[19] Nickel-catalyzed methods have generally fallen into either those proposed to proceed via a Ni(0/II) pathway (e.g., aryl cross-coupling,[42] reductive coupling[43]) or those proposed to proceed via a Ni(I/III) pathway (e.g., C(sp^3) cross-coupling[38]). However, controlled access to additional oxidation states in a single catalytic cycle of the sort proposed in Scheme 8b are known in a few cases and can lead to novel and interesting chemistry (Scheme 9).

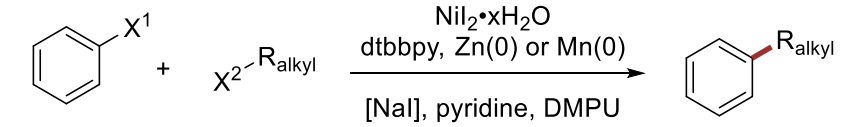
For example, Weix and coworkers recently reported a cross-electrophile coupling of alkyl and aryl halides.[44] Extensive mechanistic investigation suggests the mechanism shown in Scheme 9a, with a concurrent polar Ni(0/II) oxidative addition of an aryl halide and radical chain oxidative addition/reductive elimination of an alkyl electrophile.[45] The latter process proceeds by the trapping of a free carbon-centered aliphatic radical by the Ni(II) oxidative addition complex. Reductive elimination from the Ni(III) complex affords the product and a Ni(I)-halide complex that is competent to generate carbon-centered radicals from the alkyl halide. Reduction of the subsequent Ni(II)-dihalide complex is then accomplished by a stoichiometric manganese or zinc reductant. This work has also been extended to the reductive cross-coupling of acyl

[42] Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19–30.
[43] a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. b) Standley, E. A.; Tasker, S. Z.; Jensen, K. L.; Jamison, T. F. *Acc. Chem. Res.* **2015**, *48*, 1503–1514.
[44] a) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920–921. b) Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159. c) Weix, D. J. *Acc. Chem. Res.* **2015**, *48*, 1767–1775.
[45] Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.

Scheme 9. Nickel-catalyzed transformations involving four nickel oxidation states.

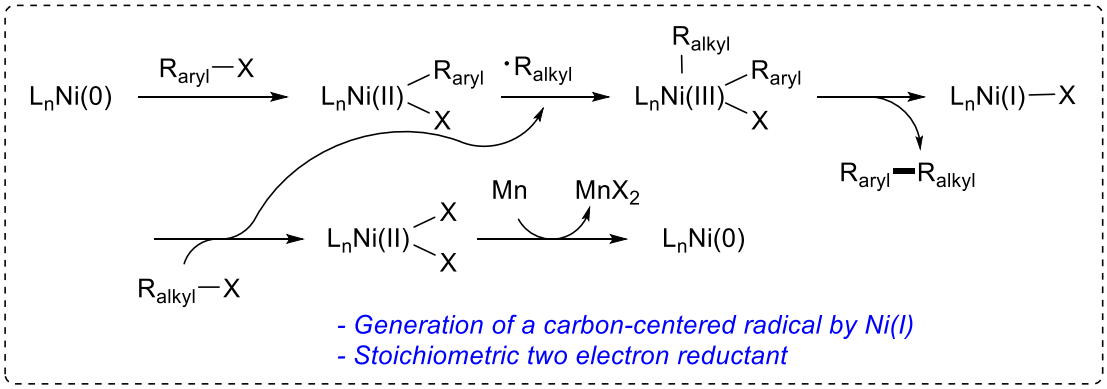
a) Cross Electrophile Coupling

Weix, 2010,[44a] 2013[45]



X^1 = I, Br, Cl

X^2 = I, Br

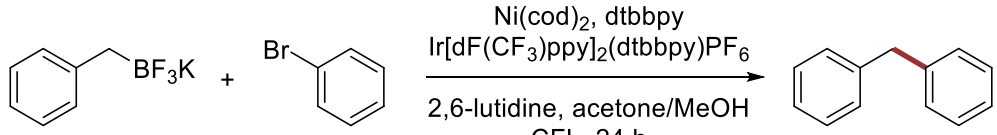


- Generation of a carbon-centered radical by Ni(I)

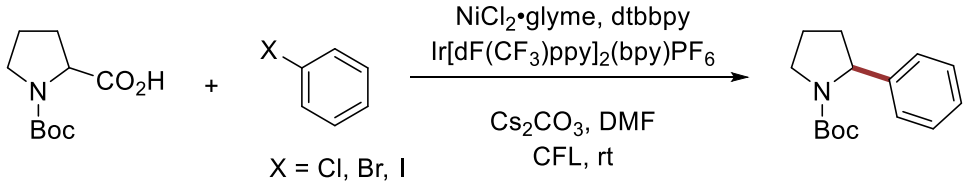
- Stoichiometric two electron reductant

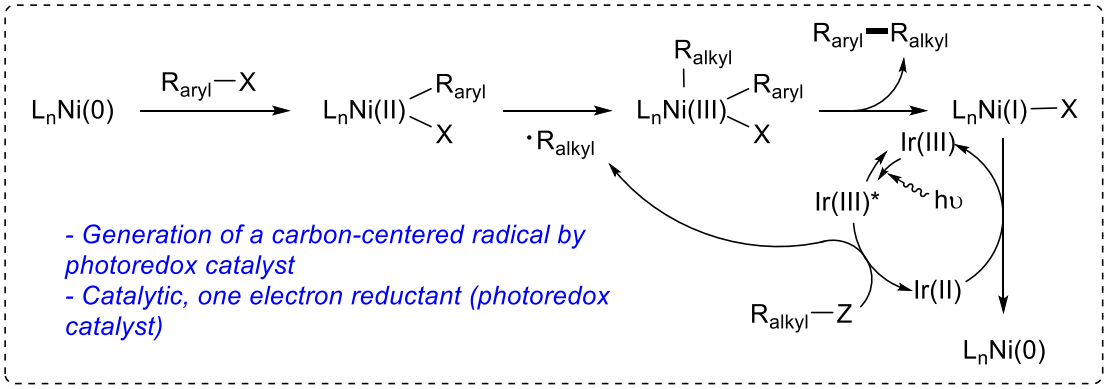
b) Photoredox/Nickel Dual Catalysis

Molander, 2014[48]



MacMillan and Doyle, 2014[49]





- Generation of a carbon-centered radical by photoredox catalyst

- Catalytic, one electron reductant (photoredox catalyst)

halides,[46] likely proceeding via a similar mechanism, and can be carried out enantioselectively in some cases.[47]

The simultaneous recent reports from the research groups of Molander[48] and MacMillan and Doyle[49] opened the door to a different and potentially more versatile way of generating the carbon radicals and reduction steps needed for four-oxidation-state nickel catalysis (Scheme 9b). They describe a nickel-catalyzed aryl–alkyl cross-coupling, using visible light photoredox catalysis[41] to generate alkyl carbon radicals which can be trapped by Ni(II) intermediates.[50] Then, after reductive elimination, the subsequent Ni(I) species is reduced by the same photoredox catalyst to Ni(0) to complete the catalytic cycle. After these initial reports, this field has expanded rapidly, giving access to novel reaction manifolds including C–P bond formation,[51] secondary alkyl boron cross-coupling,[52] and others.[53]

Metal/Photoredox Dual Catalysis

The principles underlying visible light photoredox catalysis have been thoroughly elaborated elsewhere.[41] Suffice it to say that for synthetic organic chemists, the ability to access discrete single electron transfers by irradiation by visible light (a method both easy to use and orthogonal to other reaction methodologies) has been groundbreaking. The oxidizing and

[46] Wotal, A. C.; Weix, D. J. *Org. Lett*. **2012**, *14*, 1476–1479.
[47] Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442–7445. b) Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365–14368.
[48] Tellis, J. C.; Primer, D. N.; Molander, G. A *Science* **2014**, *345*, 433–436.
[49] Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science*, **2014**, *345*, 437–440.
[50] Recent DFT calculations have suggested trapping of a radical by Ni(0/I), oxidative addition of the aryl halide Ni(I/III), followed by reversible radical dissociation/association (Ni(II/III) and reductive elimination Ni(III/I) for the former case: Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896–4899.
[51] Xuan, J.; Zeng, T.-T.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem.—Eur. J.* **2015**, *21*, 4962–4965.
[52] Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195–2198.
[53] a) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624–627. (b) Chu, L.; Lipshultz, J. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929–7933.

reducing power of the photoredox catalyst can also be tuned by alteration of metal and ligand properties, which is helpful for selective reaction development. Moreover, the stability and mild nature of most visible light photoredox catalysts mean that they can relatively easily be combined with other catalytic manifolds, including organocatalysis,[54] Lewis acid catalysis,[55] and metal catalysis.

Since the first report of reaction acceleration of a palladium-catalyzed Sonogashira coupling reaction by $Ru(bpy)_3^{2+}$,[56] metal/photoredox dual catalysis has been reported for palladium-,[57] copper-,[58] gold-,[59] rhodium-,[60] and nickel-[61]catalyzed reactions. To the best of our knowledge, all reported transformations involve the use of a photoredox catalyst either as solely a single electron oxidant *or* reductant of the metal catalyst (similar to the way it is typically used in non-dual catalysis settings to interact with the substrate via oxidative or reductive quenching cycles) or to generate external free radicals which are then trapped by the metal catalyst. In contrast, the catalytic cycle depicted in Scheme 8b would likely involve direct oxidation *and* reduction of the metal catalyst.

---

[54] Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.
[55] a) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605. b) Zhu, S.; Rueping, M. *Chem. Commun.* **2012**, *48*, 11960–11962. c) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392–396.
[56] Osawa, M.; Nagai, H.; Akita, M. *Dalton Trans.* **2007**, 827–829.
[57] Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569.
[58] a) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem.—Eur. J.* **2012**, *18*, 5170–5174. b) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034–9037.
[59] a) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505–5508. b) Shu, X.-z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844–5847.
[60] Fabry, D. C.; Zoller, J.; Raja, S.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10228–10231.
[61] In fact, the first nickel/photoredox reaction was not the Molander or MacMillan/Doyle reports, but the reduction of CO_2 to CO in which the photoredox catalyst was proposed to perform two single electron reductions of a Ni(II) intermediate: Thoi, V. S.; Kornienko, N.; Margarit, C. G.; Yang, P.; Chang, C. J. *J. Am. Chem. Soc.* **2013**, *135*, 14413–14424.

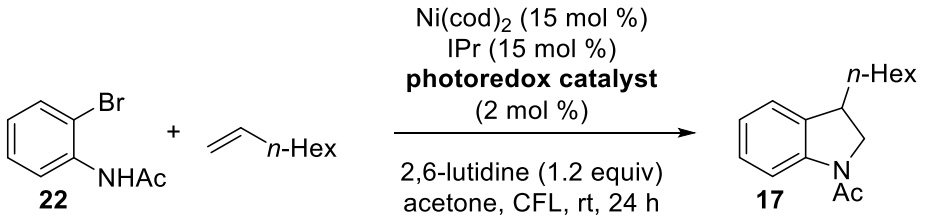
Reaction Optimization

We were inspired to revisit the possibility of using a combined nickel/photoredox catalyst system by the reports of Molander[48] and Doyle and MacMillan.[49] Under conditions similar to those used by Molander (2,6-lutidine, acetone) we observed higher yields upon addition of photocatalyst (Table 3, entry 2) than without (Table 3, entry 1) for the first time. Conditions similar to those of Doyle and Macmillan (Cs_2CO_3, DMF; Table 3, entries 3, 4) or more standard conditions (*i*-Pr_2EtN, MeCN; Table 2, entry 13) did not produce a similar augmentation of yield.

However, yields still remained below the total catalyst loading, even at elevated temperature (entry 5). Control experiments supported the photoredox catalyst absorbing visible light to increase yield (entries 6, 7). Evaluation of solvents (entry 8) and ionic bases (entry 9) did not improve the reaction yields, but tertiary amine bases did (entries 10–13), including for the first time yields in excess of the catalyst loading for Et_3N after extended reaction times (entry 13). During this time, we observed that increased temperatures caused yields to remain approximately the same, but also increased the amount of Heck and isomerized Heck products observed (resulting from β-hydride elimination). Although they give off much less heat than incandescent bulbs, compact fluorescent lightbulbs (CFLs) do increase the air temperature immediately adjacent to them to ~35–40 °C. Placement of a small fan next to the light and reaction vials was highly successful in regulating the temperature to ~23 °C, and thus was used throughout for all room temperature reactions (see Figures 5 and 6 for photos of reaction setup). In this way, high selectivities for desired indoline product **17** over the sum of Heck (**19**) and isomerized Heck (e.g., **20**) products were kept to ~30:1 as analyzed by gas chromatography.

Next, we decided to investigate the use of different photoredox catalysts for indoline

Table 3. Evaluation of reaction conditions with $Ru(bpy)_3(PF_6)_2$.[a]



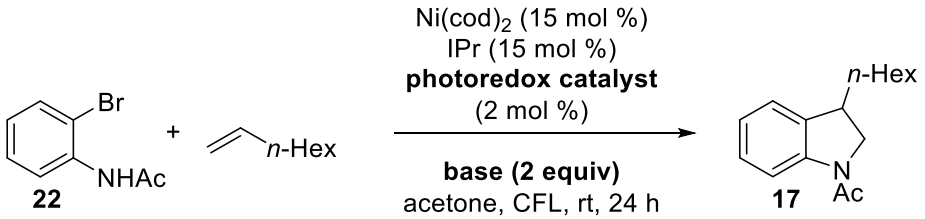
22 17

Entry	Photoredox Catalyst	Changes to Reaction Conditions	Conversion **22** (%)	Yield **17** (%)
1	none	—	12	5
2	$Ru(bpy)_3(PF_6)_2$	—	28	14
3	none	Cs_2CO_3, DMF	14	7
4	$Ru(bpy)_3(PF_6)_2$	Cs_2CO_3, DMF	11	6
5	$Ru(bpy)_3(PF_6)_2$	50 °C	28	13
6	$Ru(bpy)_3(PF_6)_2$	run in dark	13	6
7	none	2,2'-bipyridine (3 mol %)	16	4
8	$Ru(bpy)_3(PF_6)_2$	MeCN, pyridine, CH_2Cl_2, DMF, or EtOAc	2–24	<6
9	$Ru(bpy)_3(PF_6)_2$	Cs_2CO_3, K_3PO_4, LiO*t*-Bu	22–47	<5
10	$Ru(bpy)_3(PF_6)_2$	$NCyMe_2$[b]	n.d.[c]	19
11	$Ru(bpy)_3(PF_6)_2$	*i*-Pr_2EtN[b]	33	25
12	$Ru(bpy)_3(PF_6)_2$	Et_3N[b]	33	22
13	**$Ru(bpy)_3(PF_6)_2$**	**Et_3N,[b] 66 h**	**61**	**33**
14	none	Et_3N[b]	8	10

[a] Conversions and yields determined by GC with dodecane as internal standard. [b] 2 equiv. base. [c] $NCyMe_2$ overlapped with **22** in the chromatogram.

formation (Table 4). A range of commercially available photoredox catalysts were tested, with a wide range of oxidation and reduction half-cell potentials.[41] However, none performed better than $Ru(bpy)_3(PF_6)_2$ ($E_{1/2}^{ox*}/E_{1/2}^{red}$ +0.77/–1.33; entry 2). $Ir(dtbbpy)(ppy)_2(PF_6)$, which is more strongly reducing ($E_{1/2}^{red}$ –1.51), for example, produced large amounts of aryl bromide reduction (entry 13).

Table 4. Optimization of bromides with photoredox catalysts and additives.[a]



22 **17**

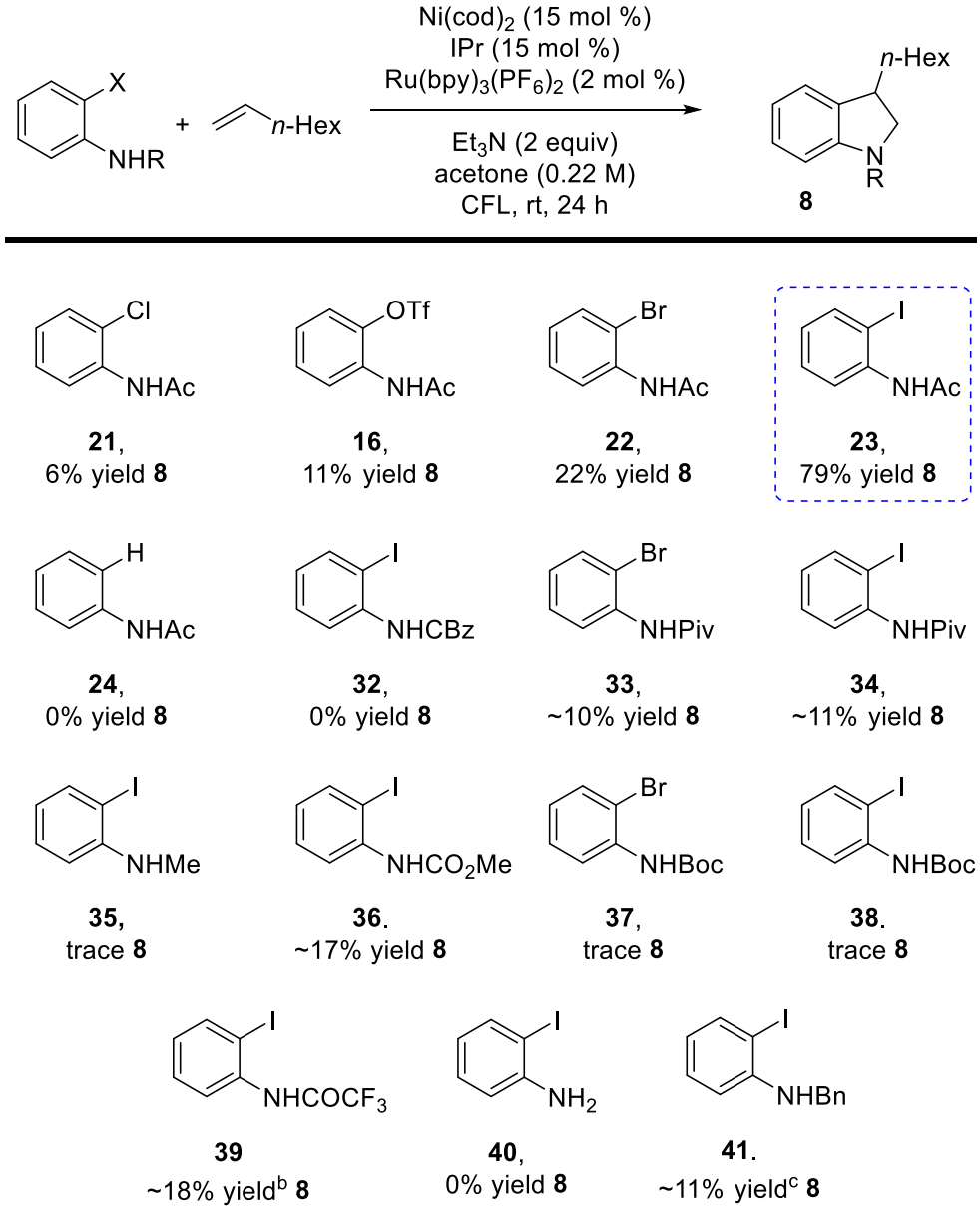
Entry	Photoredox Catalyst	$E_{1/2}^{ox*}/E_{1/2}^{red}$ (V)[b]	Base	Additive	Conversion **22** (%)	Yield **17** (%)
1	none	—	2,6-lutidine	—	12	5
2	$Ru(bpy)_3(PF_6)_2$	+0.77/–1.33	2,6-lutidine	—	28	14
3	$Ir(dtbbpy)(ppy)_2(PF_6)$	+0.66/–1.51	2,6-lutidine	—	13	9
4	9-mesityl-10-methylacridinium ClO_4	+2.06/–0.57	2,6-lutidine	—	13	7
5	$Ir[dF(CF_3)ppy_2](dtbbpy)(PF_6)$	+1.21/–1.37	2,6-lutidine	—	39	11
6	$Cu(dap)_2Cl$	+0.62/–1.43	2,6-lutidine	—	11	7
7	$Ru(bpz)_3\ 2PF_6$	+1.45/–0.80	2,6-lutidine	—	21	9
8	$Ru(bpy)_3(PF_6)_2$	+0.77/–1.33	Et_3N	—	33	22
9[c]	$Ru(bpy)_3(PF_6)_2$	+0.77/–1.33	Et_3N	—	61	33
10	none	—	Et_3N	—	8	10
11	$Ru(bpy)_3(PF_6)_2$	+0.77/–1.33	Et_3N	LiI (30 mol %)	22	15
12	$Ru(bpy)_3(PF_6)_2$	+0.77/–1.33	Et_3N	I_2 (50 mol %)	12	10
13	$Ir(dtbbpy)(ppy)_2(PF_6)$	+0.66/–1.51	Et_3N	–	98[d]	18

[a] Conversions and yields determined by GC with dodecane as internal standard [b] see reference [41] [c] 66 h. [d] large amounts of aryl bromide reduction (i.e., ArBr → ArH)

Since initial optimization of reaction conditions still gave relatively low yields of indoline product from aryl bromide **22**, we decided to survey a range of different electrophiles, varying the halide or pseudohalide group as well as the aniline protecting group (Scheme 10).

Gratifyingly, 2'-iodoacetanilide (**23**) produced a 79% yield of indoline product without any further reaction optimization. Both the halide and aniline protecting group were important for good reaction yields. The exact reason for this is unclear; however, given the delicate balance between the redox potentials and/or pK_a of the amide proton and rates of the desired reaction

Scheme 10. Aryl electrophile substrate optimization.

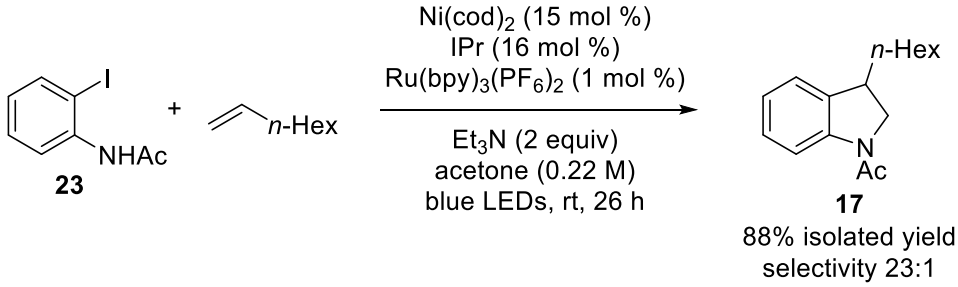


[a] Conversions and yields determined by GC with dodecane as internal standard [b] large amounts of arene homocoupling [c] 30 °C, 48 h.

pathway vs. off cycle reactions, it is possible that these groups tune the electronic properties of key nickel species to encourage productive reaction pathways. The divide between chlorides and triflates producing poor yields and bromides and iodides producing higher yields is possibly of note, since the former generally undergo oxidative addition in a concerted step while the latter generally undergo a two-step radical oxidative addition.[62] However, again it is unclear whether a change in oxidative addition is in fact significant, or whether the halide counterion alters the redox potential of key nickel oxidation states. Steric bulk of the aniline protecting group also seems to have a detrimental effect (e.g., **36** vs. **38**).

After reexamination of the stoichiometry of the reaction components, we settled on the final conditions depicted in Scheme 11. Blue LEDs improved reaction rates, although a CFL could also be used with an additional ~12 h of reaction time to reach full conversion. The amount of photoredox catalyst was also decreased to 1 mol % with no detrimental effect. Reduction in nickel catalyst loading was less successful, with 10 mol % $Ni(cod)_2$ affording slightly lower yields (68%) even after 48 h. Since oxidation/reduction steps are already present under the reaction conditions, NiI_2 was tested as a nickel source, but gave no indoline product. Absence of nickel altogether also produced no product. The optimized conditions produced **17** in 88% isolated yield, with a selectivity for **17** to Heck (**19**) and isomerized Heck (**20**) products of >19:1.

Scheme 11. Optimized conditions for indoline formation.

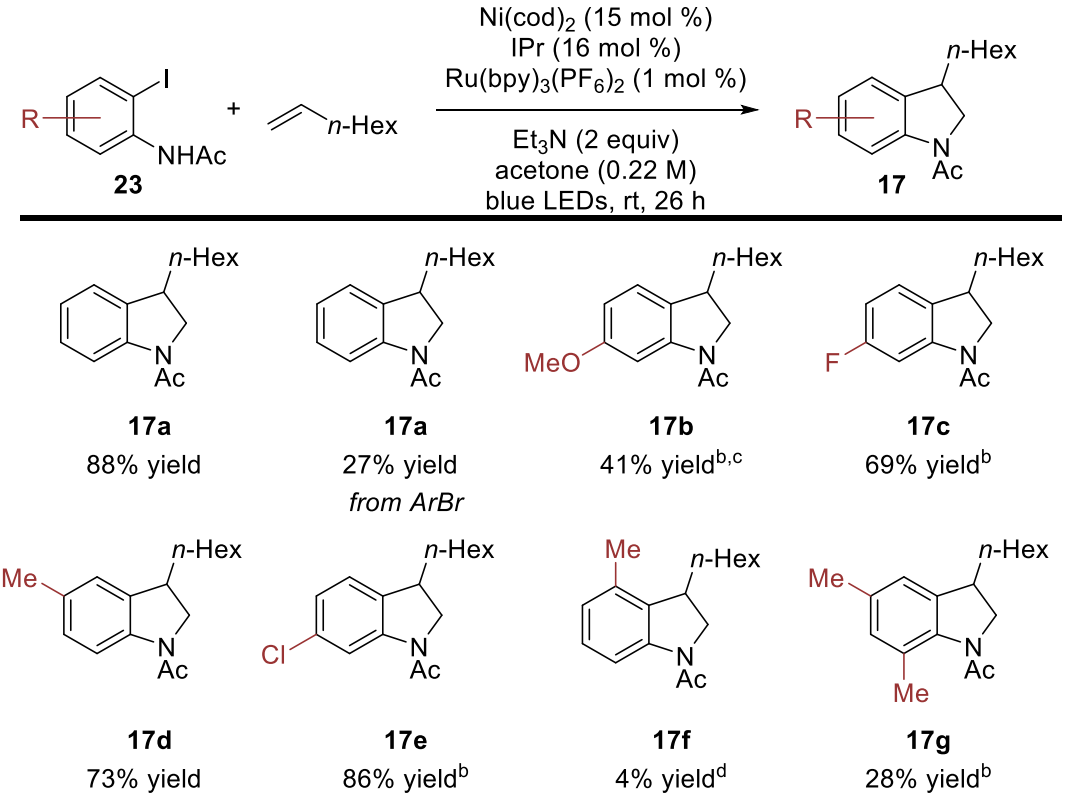


[62] Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319–6332.

Reaction Scope

With these optimized conditions in hand, we explored the scope of this transformation (Scheme 12). Substitution at the 4- or 5-positions of the 2-iodoacetanilide electrophile was well-tolerated with both electron donating (e.g., **23b**) and electron withdrawing (e.g., **23c**) substituents. However, substitution at the 3- or 6- positions of the arene resulted in substantially lower yields (**23f** and **23g**). In several cases, reaction yields were improved by slightly elevated temperatures (35 °C) and longer reaction times, although generally greater amounts of products corresponding

Scheme 12. Scope of aryl electrophile.[a]



[a] All yields are isolated yields unless otherwise noted. Selectivity 3-alkyl indoline products **17** to sum of Heck, isomerized Heck, and 2-substituted indoline >19:1 unless otherwise noted. Reaction conditions: $Ni(cod)_2$ (15 mol %), IPr (16 mol %), $Ru(bpy)_3(PF_6)_2$ (1 mol %), Et_3N (2 equiv), Acetone (0.22 M), blue LEDs, rt, 26 h. [b] $Ru(bpy)_3(PF_6)_2$ (2 mol %), CFL, 35 °C, 48 h. [c] 7:1 selectivity [d] GC yield.

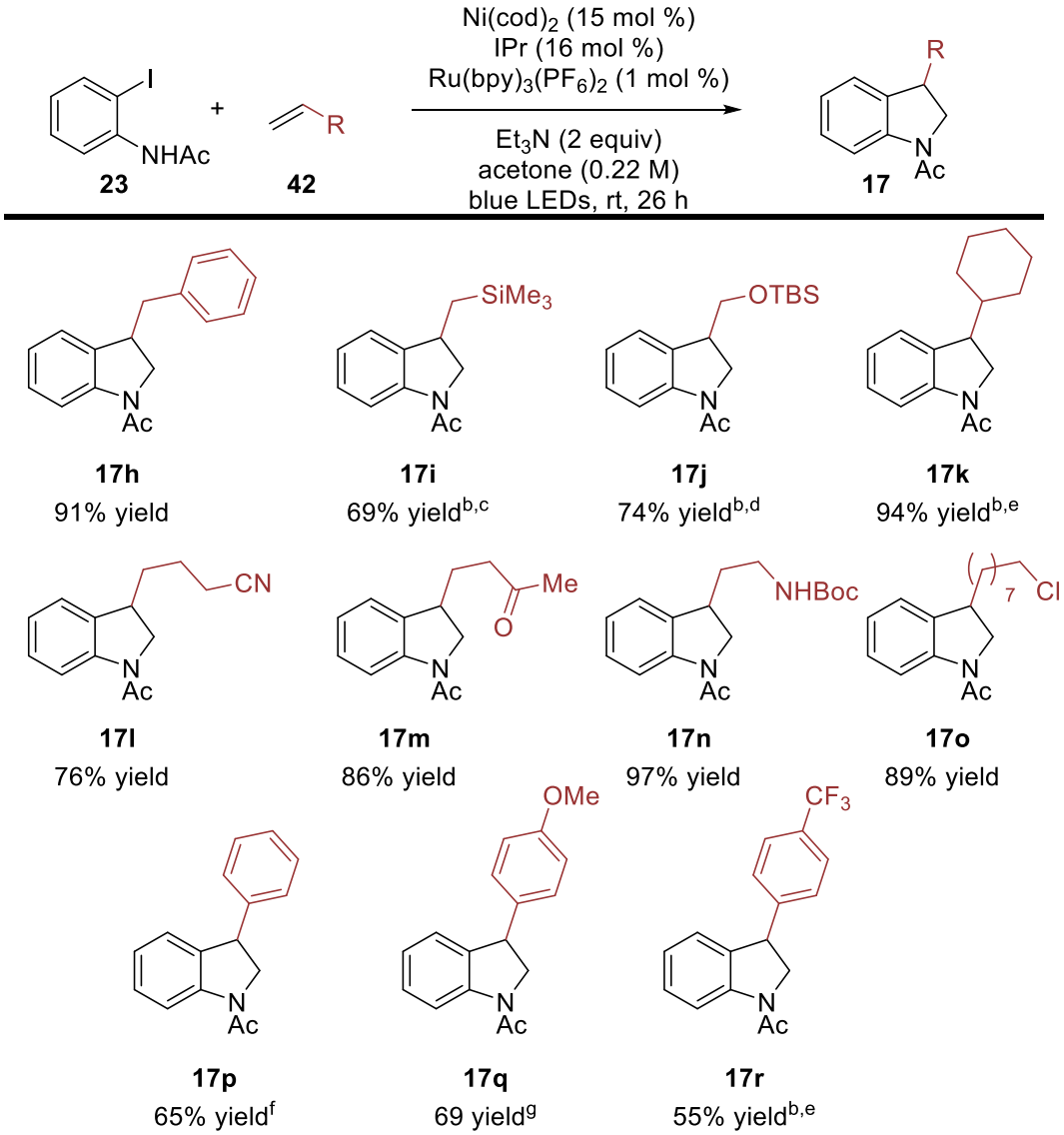
to β-H elimination were observed at higher temperatures. Importantly, selectivities for desired indoline product **17** over the sum of other possible products (inseparable by standard column chromatography) including Heck (**19**), isomerized Heck (e.g., **20**), and possibly 2-alkyl indoline (**18**) (see Scheme 7a) were >19:1 unless otherwise noted.

The substrate scope of alkene coupling partners is significantly broader (Scheme 13). A variety of functional groups are well tolerated in the indoline formation, including trimethylsilyl groups (**17i**), protected alcohols and amines (**17j**, **17n**), ketones (**17m**), and alkyl chlorides (**17o**). Styrene was also a competent coupling partner and gave the same 3-substituted indoline product **17p** as aliphatic alkenes despite the overwhelming preference for arene insertion to the terminal position of such alkenes. For styrenyl substrates, increased amounts of Heck products were observed, but 2-substituted indoline products were not observed by ^{1}H NMR analysis, nor were they observed, even in trace amounts, by gas chromatography. Such a high level of selectivity for arene migratory insertion with this branched sense of regioselectivity is nearly unprecedented. Perhaps the highest selectivity obtained in the literature was by Zhou and coworkers, producing 1,1-diaryl Heck products from styrenes with selectivities of generally ~20–30:1 branched/linear.[63] Styrenes substituted with electron donating and electron withdrawing groups were also competent reaction partners (**17q**, **17r**).

Of course, there were also some limitations in the method in addition to the use of aryl iodides and the acetyl aniline protecting group (Figure 2). Aryl nitriles (**23s**) and nitro groups (**23t**) were not tolerated, presumably due to their well-known reactions with Ni(0)

[63] Zou, Y.; Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Chem.—Eur. J.* **2013**, *19*, 3504–3511.

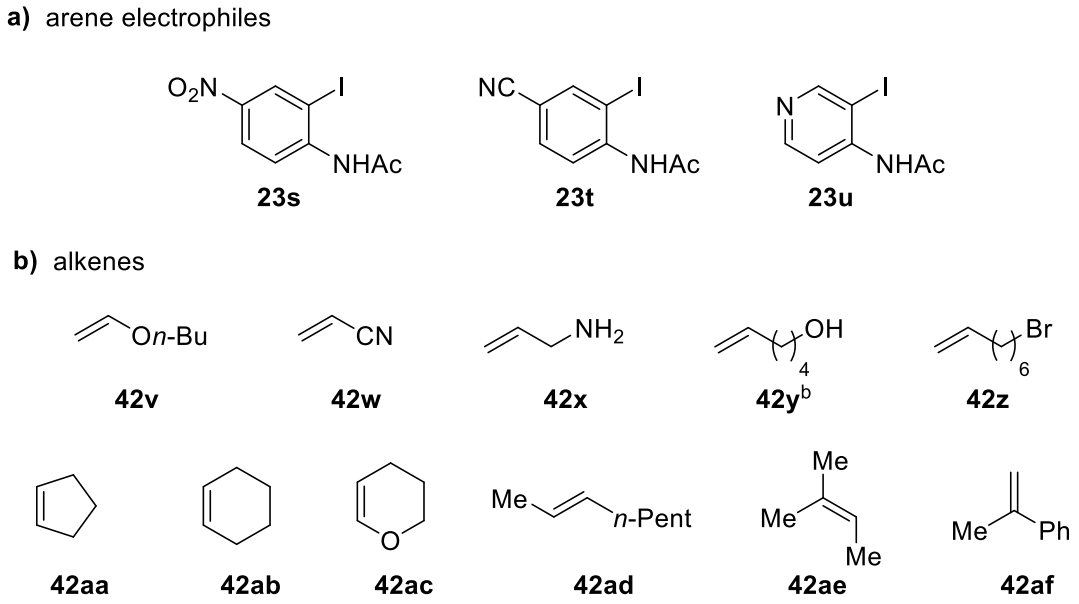
Scheme 13. Scope of alkene coupling partner.[a]



[a] All yields are isolated yields. Selectivity of 3-alkyl indoline products **17** to sum of Heck, isomerized Heck, and 2-substituted indoline >19:1 unless otherwise noted. Reaction conditions: $Ni(cod)_2$ (15 mol %), IPr (16 mol %), $Ru(bpy)_3(PF_6)_2$ (1 mol %), Et_3N (2 equiv), Acetone (0.22 M), blue LEDs, rt, 26 h. [b] $Ru(bpy)_3(PF_6)_2$ (2 mol %), CFL, 35 °C, 48 h. [c] 5:1 selectivity [d] 12:1 selectivity [e] 9:1 selectivity [f] 8:1 selectivity [g] 11:1 selectivity.

catalysts.[64] Heterocyclic substrate **23u** also produced no product, although whether this is due to coordination of the pyridine moiety to the nickel catalyst or electronic perturbation of the catalytic system is unknown. Electron-rich and electron-poor alkenes (**42v** and **42w**) were unreactive, as were alkenes with free amines (**42x**) or hydroxyl (**42y**) groups. Only terminal monosubstituted alkenes were reactive under these conditions; internal (e.g., **42ab**) and 1,1-disubstituted (e.g., **42af**) alkenes gave no desired product, even in the case of slightly strained cyclopentene (**42aa**), which is often a privileged alkene for coordination and migratory insertion.

Figure 2. Substrates that did not provide desired indoline products.[a]



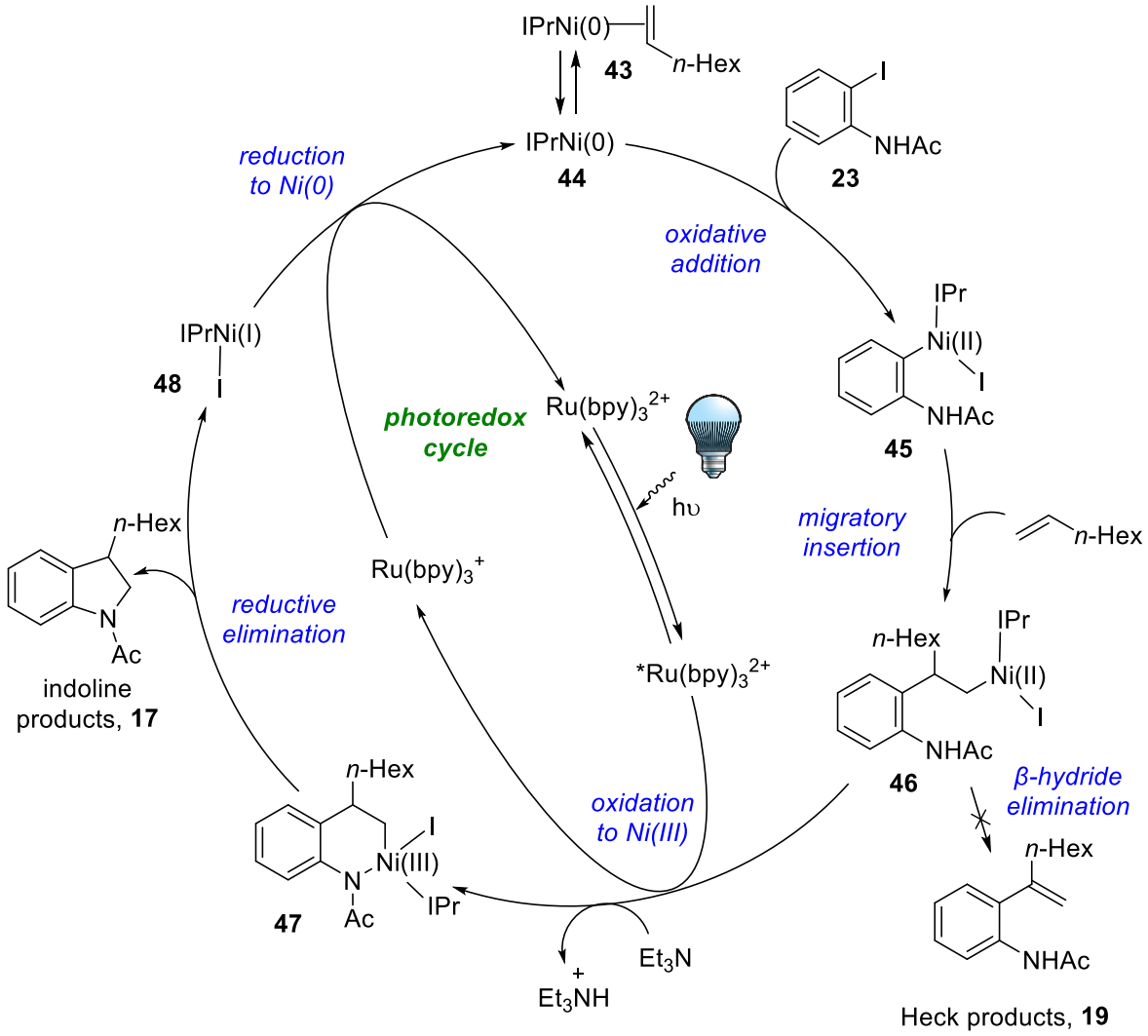
[a] No desired indoline product observed by GC and GC/MS unless otherwise noted. [b] ~20% indoline was observed at complete conversion of **23a**.

[64] a) Berman, R. S.; Kochi, J. K. *Inorg. Chem.* **1980**, *19*, 248–254. b) Garcia, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547–9555.

Mechanistic Investigation

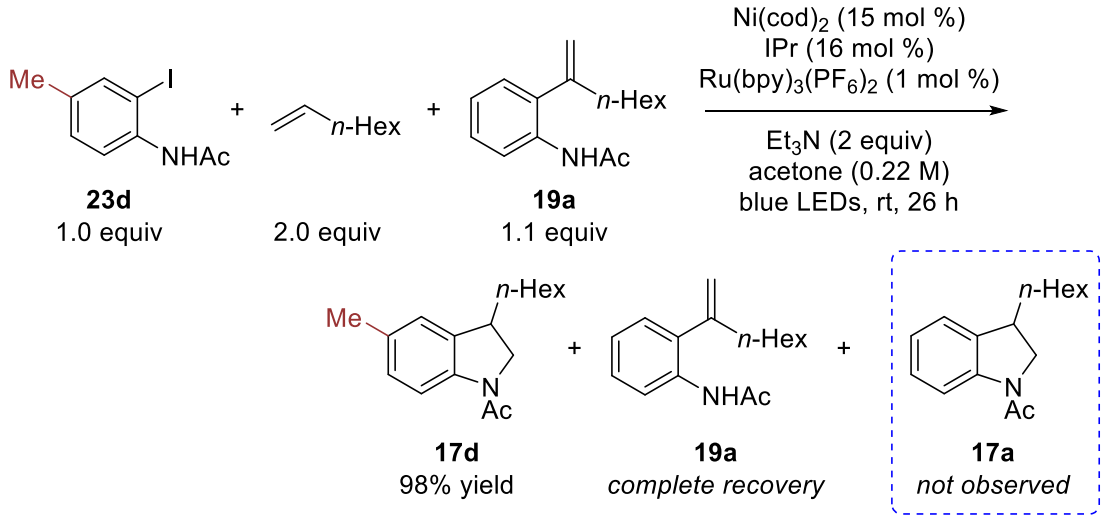
The proposed mechanism for this Larock-type indoline synthesis is shown in Scheme 14. As discussed previously, the key step for C(sp^3)–N reductive elimination to occur is hypothesized to be the oxidation of Ni(II) species **46** to a Ni(III) species (**47**) by the exited state form of the photoredox catalyst, *$Ru(bpy)_3^{2+}$. After reductive elimination, the reduced form of the photoredox catalyst, $Ru(bpy)_3^{+}$, then reduces the resultant Ni(I) species **48** back to a Ni(0) species (**44**) to rejoin the catalytic cycle. If β-hydride elimination from **46** or **47** occurs instead, Heck-type products such as **19** are formed, decreasing the selectivity of the reaction.

Scheme 14. Proposed mechanism



Keeping this mechanistic proposal in mind, we set out to test the feasibility of several of the proposed steps. First, although we propose a direct migratory insertion of the alkene and reductive elimination, it could be possible that the reaction proceeds via a discrete Heck reaction followed by a hydroamination, which has been shown to afford similar products previously.[65] To test this possibility, we submitted independently synthesized Heck product **19a** to the reaction conditions, including methyl-substrate **23d** with 1-octene (Scheme 15).[66] No formation of product **17a** arising from **19a** was observed, suggesting that it is not a competent intermediate in indoline formation. Nor did it inhibit the reaction, since complete conversion of **23d** to indoline **17d** was accomplished.

Scheme 15. Testing Heck products as competent intermediates.[a]



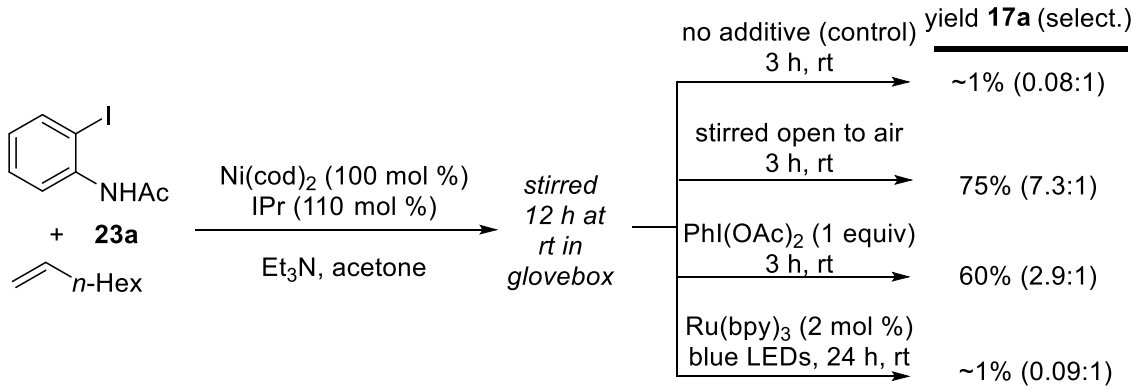
[a] Conversions and yields determined by GC using dodecane as an internal standard.

Next, we sought to investigate whether oxidation to Ni(III) was indeed responsible for product formation (Scheme 16). 2-Iodoacetanilide (**23a**) was submitted to stoichiometric reaction

[65] a) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542–14543. b) Hopkins, B. A.; Wolfe, J. P. *Chem. Sci.* **2014**, *5*, 4840–4844. c) Sharma, U.; Kancherla, R.; Naveen, T.; Agasti, S.; Maiti, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 11895–11899.
[66] Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5915–5919.

conditions without photoredox catalyst for 12 hours. This mixture was then split into portions and exposed to various oxidants, before filtration through alumina under inert atmosphere and GC analysis. When no oxidant was added, very little indoline was observed, and a number of other products were formed in trace amounts. However, when stirred open to air or $PhI(OAc)_2$ was added, significant amounts of product **17a** (75 and 60%, respectively) were observed with good selectivity for the desired indoline product. The addition of catalytic $Ru(bpy)_3(PF_6)_2$ did not produce significant amounts of **17a**, but this result is inconclusive since the large excess of nickel could lead to unselective or unproductive oxidation/reduction and/or to photoredox catalyst death. Given that stoichiometric oxidants do successfully increase the amount of C–N bond formation as expected, a necessary oxidation to Ni(III) prior to product formation is likely.

Scheme 16. Treatment with stoichiometric oxidants.[a]



[a] Conversions and yields determined by GC using dodecane as an internal standard.

Cyclic Voltammetry

Next, we set out to determine whether the photoredox catalyst would indeed be competent to perform both the oxidation and reduction steps. In order to do this, evaluation of

the standard reduction potential (E°) of the electron transfer reaction (always written in the form of $X + e^- \rightarrow X^-$) is necessary. When comparing reduction potentials for a one-electron redox reaction referenced against the same reference electrode, the species with the more positive E° value will oxidize a species with a lower E° value, while the latter species would reduce the former. A standard way of measuring reduction potential values is to use cyclic voltammetry (CV)[67] to measure the half-wave reduction potential, $E_{1/2}$, which is generally an excellent estimate of E°.[68]

In a CV experiment, the potential of a working electrode is continuously swept from an initial voltage to a final voltage and then reversed to return to the initial voltage at the same scan rate. This voltage change produces a current as the analyte of interest is oxidized or reduced, which peaks as the analyte near the electrode is depleted (CV experiments are carried out under diffusion-controlled conditions, without stirring). Upon reversal of the potential, under ideal conditions, the electron transfer between the analyte and electrode is reversed, and an equal and opposite current wave appears. The potential-current response is then plotted to produce a cyclic voltammogram. $E_{1/2}$ can be measured by averaging the peak potentials (E_p) at the cathode and anode: $E_{1/2} = (E_p^c + E_p^a)/2$.

Since $E_{1/2}$ values of $*Ru(bpy)_3^{2+}$ (+0.77V vs. SCE)[69] and $Ru(bpy)_3^+$ (–1.33V vs. SCE)[70] have been reported, $E_{1/2}$ values for IPrNi(II) species (**45**, **46**) oxidation and IPrNi(I) species (**48**) reduction are needed. Fortunately, upon mixing IPr, $Ni(cod)_2$, and aryl iodide **23**, clean

[67] a) Pletcher, D.; Greef, R.; Peat, R.; Peter, L. M.; Robinson, J. *Instrumental Methods in Electrochemistry*, Horwood: Chichester, 2001. b) Scholz, F. (Ed.) *Electroanalytical Methods*, Springer: Berlin, 2002. c) Mabbott, G. A. *J. Chem. Ed.* **1983**, *60*, 697–702. d) Evans, D. H.; O'Connell, K. M.; Petersen, R. A.; Kelly, M. J. *J. Chem. Ed.* **1983**, *60*, 290–293.

[68] Since cyclic voltammetry measurements depend on rates of diffusion, $E_{1/2} = E°$ if the rates of diffusion of oxidized and reduced species are the same: Scholz, F. (Ed.) *Electroanalytical Methods*, Springer: Berlin, 2002. p. 78.

[69] Bock, C. R.; Connor, J. A.; Gutierrez, A. R.; Meyer, T. J.; Whitten, D. G.; Sullivan, B. P.; Nagle, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4815–4824.

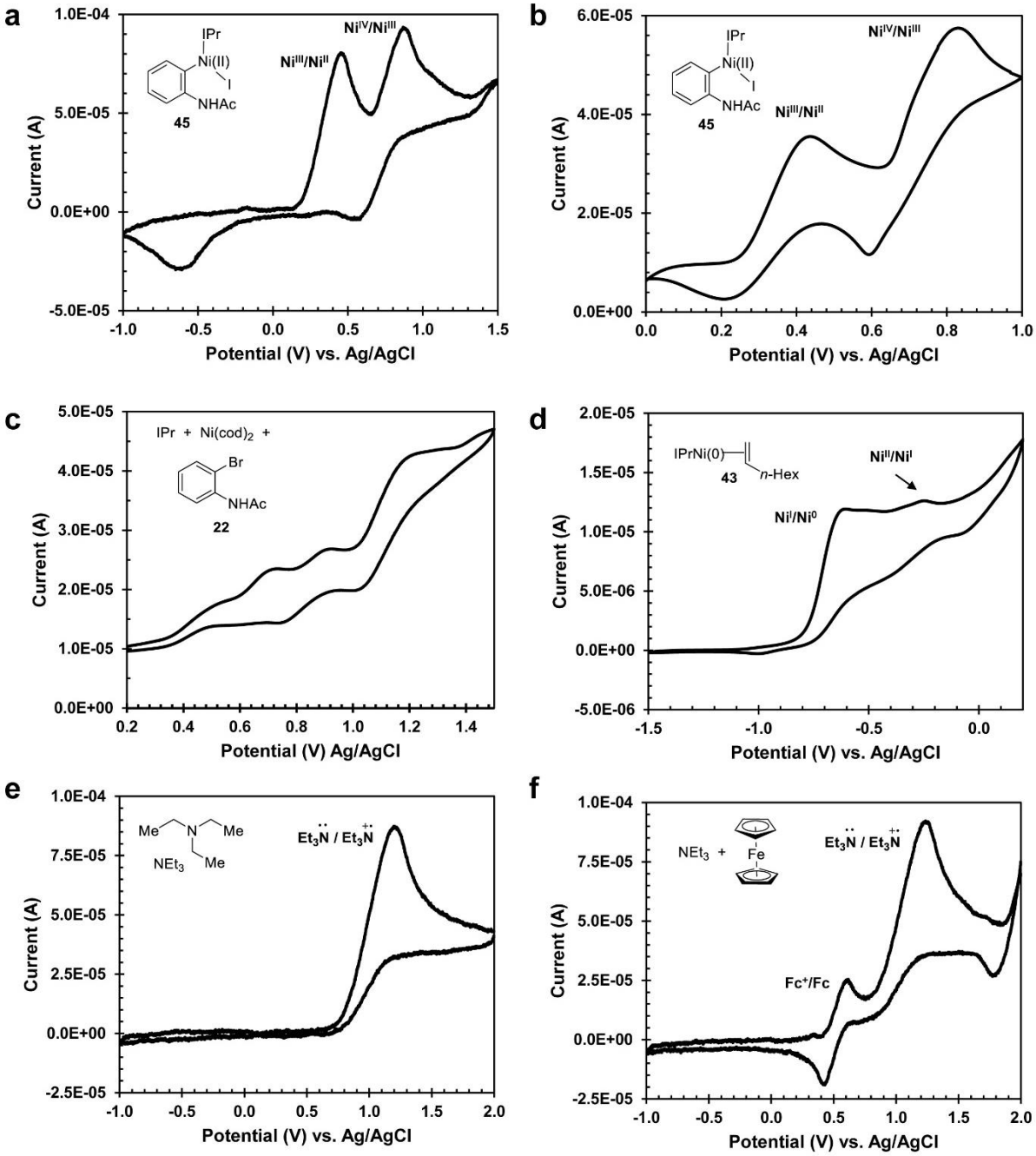
[70] Tokel-Takvoryan, N. E.; Hemingway, R. E.; Bard, A. J. *J. Am. Chem. Soc.* **1973**, *95*, 6582–6589.

conversion was observed using ^{1}H NMR to nickel complex **45**.[71] Similarly, IPr, Ni(cod)$_2$, and 1-octene produced Ni(0) complex **43**. A crystal structure of oxidative addition complex **45'** was also obtained (*vide infra*, Figure 4a). CV studies were then performed on both complexes formed in situ in acetone using a standard three-electrode cell with a glassy carbon working electrode, a Ag/AgCl reference electrode, and a Pt wire counter electrode, all under an inert atmosphere. The resulting cyclic voltammograms are shown in Figure 3.

First, let's examine cyclic voltammograms of Ni(II) oxidative addition complex **45** at two different scan rates: 100mV/s (Figure 3a) and 10 mV/s (Figure 3b). In both cases, two peaks were observed in the region of 0 to 1.0V vs Ag/AgCl, assigned to the Ni(II→III) and Ni(III→IV) transitions as shown. At a 100mV/s scan rate, the Ni(II→III) oxidation was not reversible, but at a lower scan rate, clearly reversible peaks for both transitions were observed. Observation of varying amounts of reversibility at different scan rates is well known,[67a] and although several explanations are possible, this would be consistent with a fast electron transfer and slower and reversible chemical step. $E_{1/2}^{III/II}$ could be easily measured by averaging peak potential values in Figure 3b to be +0.32V vs. Ag/AgCl. Referencing to an external ferrocene couple measured in Figure 3f gave –0.20V vs. Fc/Fc$^+$, or converting to the more standard reference, +0.18 V vs. SCE.[72] Given that the formal reduction potential for *Ru(bpy)$_3^{2+}$ is +0.77V vs. SCE, the proposed oxidation of Ni(II) species **46** in Scheme 14 is reasonable. In fact, using the Nernst equation, $\Delta G = -nFE$, where n is the number of electrons transferred, and F is the Faraday constant, this oxidation is predicted to be favored by 13.6 kcal/mol.

[71] See Experimental Methods for more details.
[72] Pavlishchuk, V. V.; Addison, A. W. *Inorg. Chim. Acta* **2000**, *298*, 97–102.

Figure 3. Cyclic voltammetry studies on proposed intermediates.[a]



[a] Cyclic voltammograms measured using a standard three-electrode cell with a glassy carbon working electrode, a Ag/AgCl reference electrode, and a Pt wire counter electrode, all under an inert atmosphere. CVs of **45** at (**a**) 100 mV/s and (**b**) 10 mV/s. (**c**) CV of 1:1:1 mixture of IPr/Ni(cod)2/**22** at 10 mV/s. (**d**) CV of **43** at 10 mV/s. (**e**) CV of Et_3N at 100 mV/s. (**f**) Internal reference CV of Fc/Fc^+ with Et_3N.

Empirically, aryl bromides such as **22** produce yields of indoline products far below those of aryl iodide substrates such as **23**. One possible explanation could be that the iodide rather than bromide counterion alters the redox potentials of the corresponding nickel species. To further examine this possibility, we wanted to study the analogous bromide oxidative addition complex. However, when equal amounts of IPr, $Ni(cod)_2$, and aryl bromide **22** were combined, a complex mixture of products was observed by ^1H NMR (Figure 9). When the same mixture was studied by CV under the same conditions as above, a large number of peaks were observed (Figure 3c), consistent with the ^1H NMR results. Unfortunately, these results do not conclusively explain the lack of reactivity of aryl bromides in the full catalytic system, although it seems clear that aryl bromides are, for whatever reason, less well behaved.

Next, we examined the cyclic voltammogram of Ni(0) complex **43** (Figure 3d). Unfortunately, under all scan rates tested, completely irreversible behavior was observed, so $E_{1/2}$ could not be directly measured since by definition, a half-wave reduction potential requires a reversible process. To estimate the feasibility of redox reactions taking place, we can use the measurement of E_p, or oxidation peak potential. In this case, the oxidation wave peaks at $E_p^{I/0}$ = –0.60V vs. Ag/AgCl, which is –1.12 V vs. Fc/Fc^+, or –0.74V vs. SCE. However, $E_{1/2}$ likely is significantly more negative than E_p^a, since $E_{1/2}$ lies between E_p^a and E_p^c (latter not observed). $E_{p/2}$, or the voltage at half the current peak height (E_p), may be a closer approximation. In an ideal reversible cyclic voltammogram, $E_{1/2} = E_{p/2} \pm 0.028V/n$ where n is the number of electrons transferred. For an irreversible process, this measurement is not ideal, since the location of E_p will also vary with voltage sweep rate, by about 0.03V per order of magnitude change in sweep rate. Therefore, using this estimation must be used with caution, and a large error should be expected. For complex **43**, $E_{p/2}^{I/0}$ = –0.72V vs. Ag/AgCl, or –1.24V vs. Fc/Fc^+, which is –0.86V

vs. SCE. With either approximation, the proposed reduction step of Ni(I) complex **48** by $Ru(bpy)^+$ (–1.33V vs. SCE) is likely feasible (Scheme 14). Using the Nernst equation with $E_{p/2}$, $\Delta G = -3.9$ kcal/mol.

Finally, the presence of Et_3N or *i*-Pr_2EtN for good reaction yields is curious, since these trialkyl amine bases are often used as reductive quenchers to access $Ru(bpy)_3^+$ in photoredox reaction development.[54,73] Large amounts of triethylamine are present in the reaction mixture compared to both the photoredox catalyst and any oxidizable nickel intermediates. CV studies were performed on triethylamine in acetone (Figure 3e). Consistent with previous reports, the oxidation was irreversible, so $E_{1/2}$ could not be measured.[74] Again, using the voltage of peak half height as an estimation, $E_{p/2}^{red}$= +0.97V vs. Ag/AgCl, or +0.45V vs. Fc/Fc^+ which is approximately +0.83V vs. SCE. This value is slightly *higher* than reduction potential of $*Ru(bpy)_3^{2+}$, but that value was measured in MeCN, rather than acetone, and there is some error involved in converting between reference electrodes,[72] so this value still could indicate that Et_3N will be oxidized.

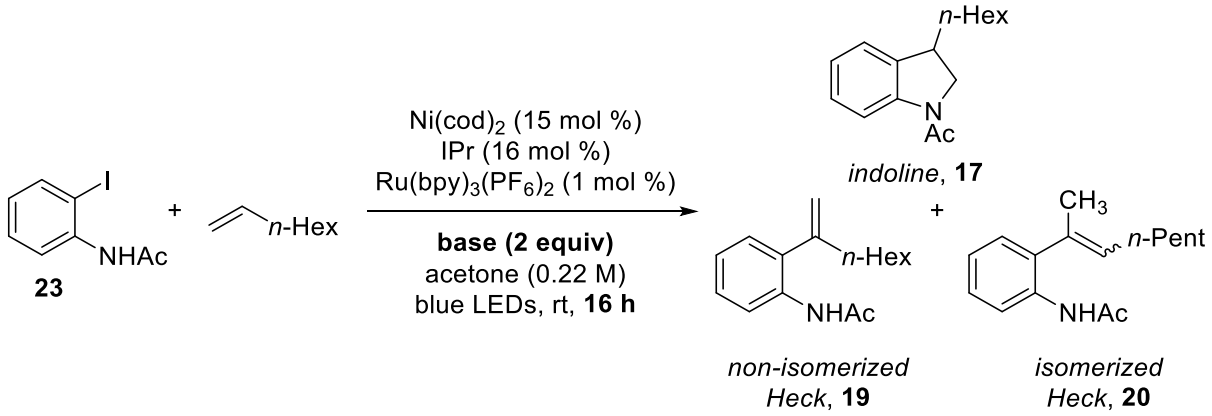
Role of Triethylamine

Further investigations of the role of the base under the optimized reaction conditions (Table 5) demonstrated that the identity, of the base clearly has a strong effect on the overall yield of indoline products obtained, with triethylamine (entry 2) and Hünig's base (entry 6)

[73] First reports: a) DeLaive, P. J.; Lee, J. T.; Sprintschnik, H. W.; Abruna, H.; Meyer, T. J.; Whitten, D. G. *J. Am. Chem. Soc.* **1977**, *99*, 7094–7097. b) DeLaive, P. J.; Sullivan, B. P.; Meyer, T. J.; Whitten, D. G. *J. Am. Chem. Soc.* **1979**, *101*, 4007–4008. c) Kern, J.-M.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1987**, 546–548. d) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757.

[74] Note: The commonly reported "$E_{1/2}$" value for triethylamine of +1.00V[41] is in fact the peak oxidation potential, E_p since the oxidation is irreversible, which likely overestimates this value (corroborated by the fact that triethylamine is in fact oxidized by $*Ru(bpy)_3^{2+}$). See: a) Mann, C. K. *Anal. Chem.* **1964**, *36*, 2424–2426. b) Smith, J. R. L.; Masheder, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 47–51. c) Nelsen, S. F.; Hintz, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 7114–7117.

Table 5. Evaluation of bases.[a]

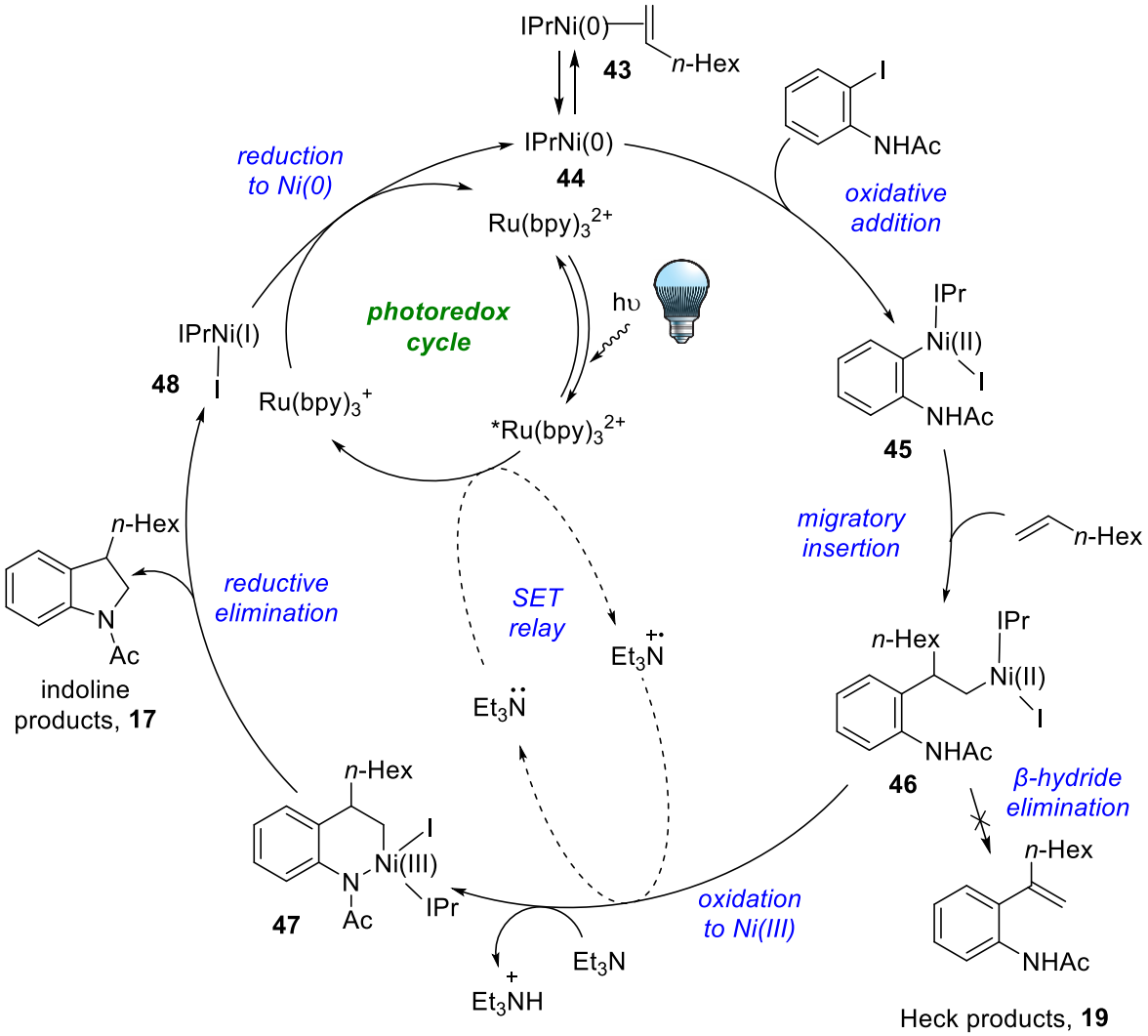


Entry	Base	Conversion **23** (%)	Yield **17** (%)	Ratio **17**/Total Heck (**19** + **20**)	Ratio Isomerized Heck **20**/Non-Isomerized Heck **19**
1	none	25	10	0.5:1	8:1
2	**Et_3N**	**94**	**88**	**35:1**	**7:1**
3	DABCO	90	18	10:1	0:1
4	quinuclidine	74	17	5:1	0:1
5	Et_2NH	46	28	96:1	0:1
6	*i*-Pr_2EtN	83	73	14:1	8:1
7	DBU	29	3	0.4:1	0:1
8	Ph_2MeN	–[b]	11	0.5:1	9:1
9	$PhMe_2N$	23	13	0.7:1	9:1
10	LiO*t*-Bu[c] + Et_3N[d]	56	~1	0.07:1	5:1
11	quinuclidine[c] + Et_3N[d]	95	19	5.7	0:1

[a] Conversions and yields determined by GC with dodecane as internal standard [b] **23** overlapped with base in chromatogram. [c] (1 equiv) [d] (30 mol %)

proving optimal. There does not seem to be a clear correlation between pK_a and indoline yield, since both weaker bases like $PhMe_2N$ (entry 9) and slightly stronger bases like DBU (entry7) apparently produce no reaction turnover. DABCO (entry 3) and quinuclidine (entry 4) also produce little product despite the latter having an essentially identical pK_a value as triethylamine (11[75] vs. 10.75[76]). It is clear from a simple examination of the reaction that deprotonation of the amide must occur at some point, but could the base have another role as well?

Scheme 17. Possible amine single electron relay mechanism.



[75] Hext, N. M.; Hansen, J.; Blake, A. J.; Hibbs, D. E.; Hursthouse, M. B.; Shishkin, O. V.; Mascal, M. *J. Org. Chem.* **1998**, *63*, 6016–6020.
[76] Hall Jr., H. K. *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444.

A speculative possibility draws on the fact mentioned in the previous section that triethylamine is a well-known reductant of the photoredox catalyst excited state, $*Ru(bpy)_3^{2+}$. Perhaps the resulting triethylamine radical cation could be acting as a single electron transfer relay to modulate the oxidizing power of the photoredox catalyst to prevent undesired oxidations of other reaction intermediates (Scheme 17). One piece of evidence to support this possibility is that, while the pK_a of quinuclidine is roughly the same as triethylamine, its oxidation potential is +0.23V higher due to the ring strain of the radical cation, which prefers to adopt a planar configuration.[74b] However, when catalytic amounts of triethylamine were used in combination with other bases, higher yields of indoline products were not obtained (Table 5, entries 10 and 11). Trialkylamine radical cations are also known to decompose rapidly into a variety of other products,[77] although they have also been known to go on to react in productive ways as a hydrogen atom source in photoredox catalysis.[73d] Therefore, whether amine oxidation modulates the oxidizing strength of the photoredox catalyst acting as a SET relay for nickel oxidation, acts to build up the reducing $Ru(bpy)_3^+$, or is irrelevant (with triethylamine acting solely as a base) is unclear

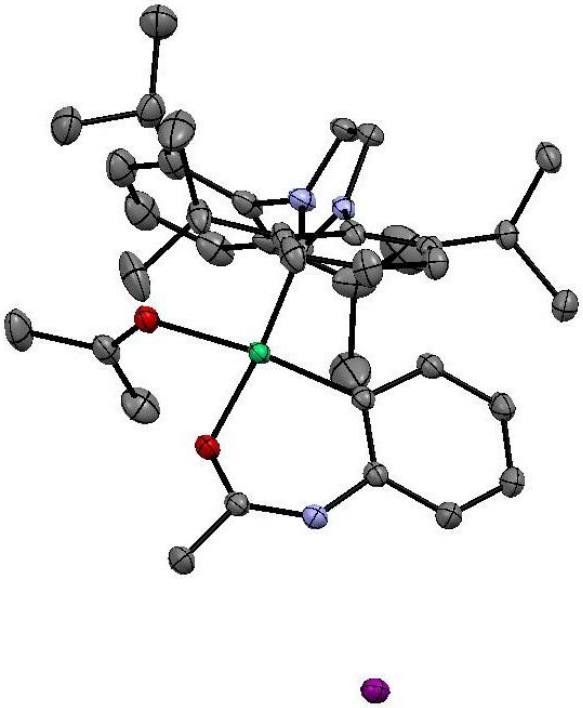
X-ray Crystallography of Reaction Intermediates

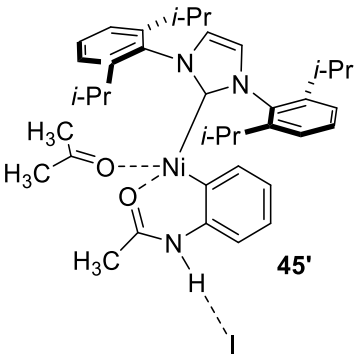
Finally, we also were able to grow crystals suitable for single-crystal X-ray diffraction analysis from solutions containing equimolar amounts of all the reaction components except for the photoredox catalyst in acetone by vapor diffusion. The resulting crystal structures (determined by standard procedures[78]) are shown in Figure 4.[79] When standard aryl iodide

[77] Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem.* **2013**, *9*, 1977–2001.
[78] Müller, P. *Crystallogr. Rev.* **2009**, *15*, 57–83.
[79] CCDC 1403188 and 1403189 contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

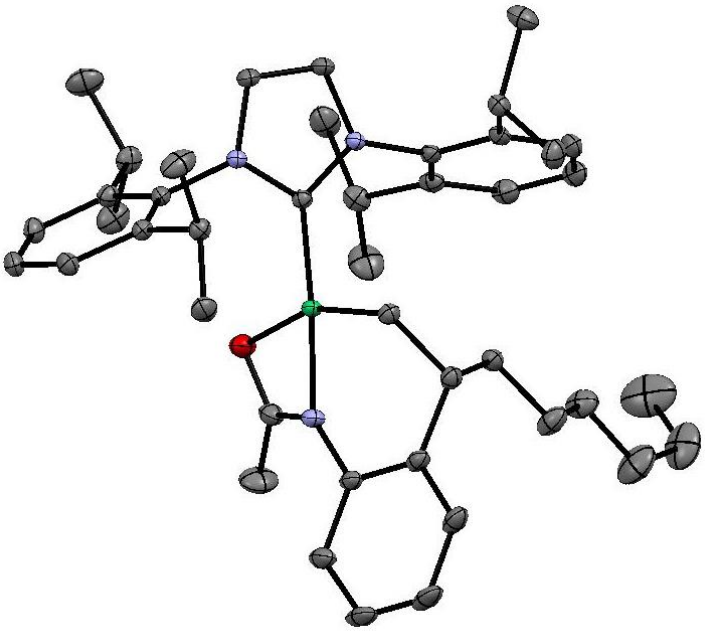
Figure 4. Single-crystal X-ray diffraction characterization of proposed reaction intermediates.

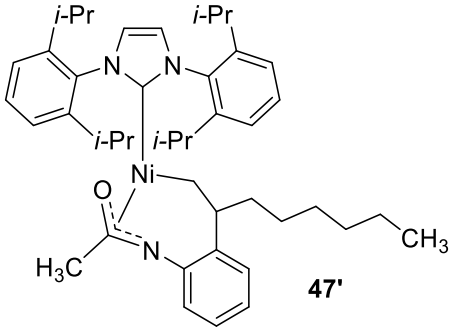
a) Crystal obtained from reaction of aryl iodide **23**[a]





b) Crystal obtained from reaction of aryl bromide **22**[b]





[a] Disorder in IPr ligand and second molecule of acetone removed, and hydrogens omitted for clarity. [b] Disorder in hexyl sidechain removed, and hydrogens omitted for clarity

electrophile **23** was used, the oxidative addition Ni(II) complex **45'** was observed, in which the iodide counterion has dissociated and forms a hydrogen bond with the amide. A molecule of acetone is also included in the coordination sphere. The geometry at nickel is square planar.

In contrast, migratory insertion complex **47'** was crystalized when aryl bromide electrophile **22** was used. Unfortunately, large amounts of this complex were not easily obtainable with which to perform exhaustive mechanistic experiments; however, its presence does suggest it may be an intermediate in the catalytic cycle. Deprotonation of the amide nitrogen has occurred, and nickel has an η^3 bonding relationship with the amide. The geometry at nickel is planar (deviations <5°), with IPr perpendicular to the plane of the substrate. Migratory insertion has occurred with the sense of regioselectivity displayed in the product, and the complex could be primed for reductive elimination to produce the desired product. However, since aryl bromides are not good substrates under the standard reaction conditions, it is difficult to draw absolute conclusions. Perhaps oxidation to Ni(III) *prior* to migratory insertion is necessary for good reaction turnover and suppression of β-hydride elimination to form Heck-type products.

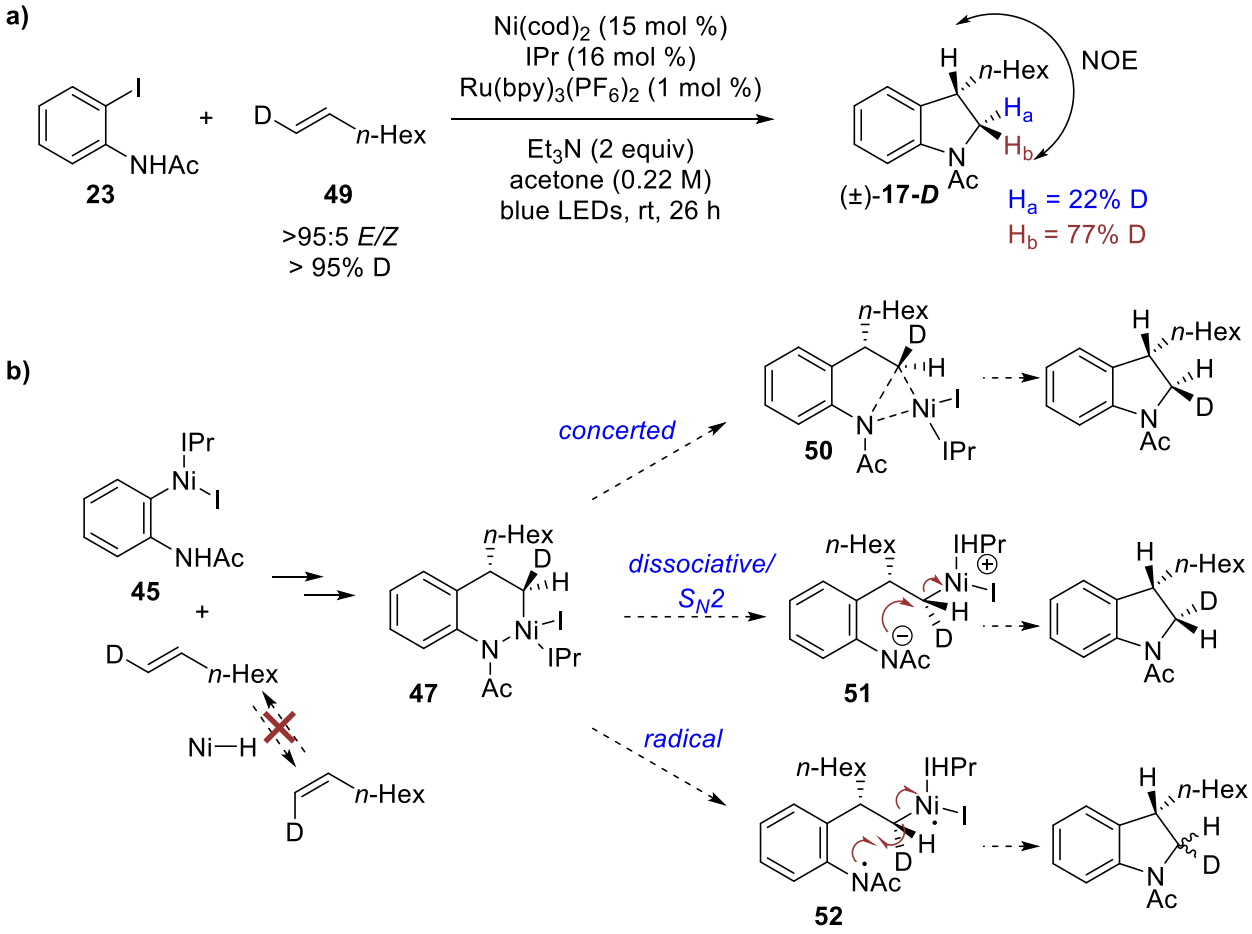
Stereochemistry of Reductive Elimination

As shown in Scheme 3, C(sp^3)–N reductive elimination for group 10 metals has in some cases been shown to proceed through nitrogen dissociation and external S_N2 attack[14,15,17] or through a concerted reductive elimination.[18] Additionally, C(sp^3)–C reductive elimination from Ni(III) is generally believed to proceed via a concerted reductive elimination.[38b,50,80] In order to investigate the stereochemical course of reductive elimination in our reaction, we synthesized

[80] Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799–5817.

trans-1-D-1-octene (**49**) with >95:5 *E*/*Z* ratio and >95% deuterium incorporation.[81] When subjected to the reaction conditions, H_a (H *cis* to the *n*-hexyl sidechain) was enriched in 22% deuterium, while H_b (H *trans* to the *n*-hexyl sidechain) was enriched in 77% deuterium (**17-*D***, Scheme 18a). Given that migratory insertion proceeds from a single face of the alkene, this result could point to any of three possibilities (Scheme 18b). First, isomerization of 1-octene by a Ni–H species could be occurring prior to the Heck reaction. However, when remaining *trans*-1-D-octene was isolated after the reaction was complete, no alkene isomerization or erosion of deuterium labeling was observed, thereby essentially ruling out this possibility. Second, a

Scheme 18. Stereochemical course of reductive elimination.



[81] Lloyd-Jones, G. C.; Robinson, A. J.; Lefort, L.; de Vries, J. G. *Chem.—Eur. J.* **2010**, *16*, 9449–9452.

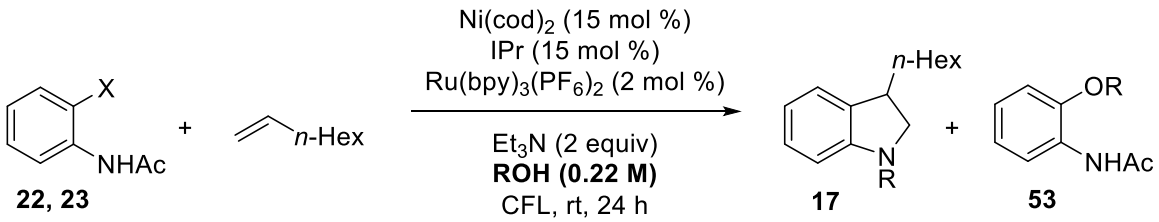
combination of concerted and dissociative/S_N2 reductive elimination pathways could be operative with a relative rate of 3.5:1. Finally, an alternative scenario would involve Ni–C or Ni–N bond homolysis (**52**), followed by radical bond formation and partial loss of stereochemical purity. Unfortunately, without easy access to intermediate **47**, we are unable to directly study this important step, so additional study would be needed to elucidate the mechanism for reductive elimination.

In summation, these mechanistic experiments are generally consistent with the proposed mechanism shown in Scheme 14. While further investigation may be necessary to further elaborate each step, we have demonstrated that the reaction does not proceed via a discrete β-hydride elimination/hydroamination step, nickel oxidation is a prerequisite for product formation, and the photoredox catalyst should be competent to perform single electron oxidation and reduction of key nickel intermediates. We have also characterized two putative intermediates by X-ray crystallography.

Other Observed Reactions

Over the course of the described investigations, two additional examples of photoredox-catalyst-assisted bond formation were also observed. First, during investigations of reaction solvent, we observed C–O bond formation when methanol was used as a solvent (Table 6). Production of **53** was observed even in the presence of 1-octene with aryl bromide **22** under the standard reaction conditions (entry 1), although when a 10:1 acetone/MeOH solvent mixture was used, a 3:1 ratio of indoline/C–O reductive elimination was produced. When aryl iodide **23** was used instead, a 76% yield of **53** was obtained (entry 3), while in the absence of photoredox catalyst, the yield of **53** was below the catalyst loading (entry 4). These reactions are certainly suggestive of a Ni(III)-oxidation induced C–O bond reductive elimination. Additionally, analogously to their work on C–N reductive elimination from high-valent nickel complexes,[12,13] Hillhouse and coworkers have established that the rate of C–O reductive elimination is increased by oxidation to Ni(III), while heating induced β-hydride elimination.[82] Unfortunately, when

Table 6. C–O bond reductive elimination of alcohols.



Entry	X	ROH	Conv **22** or **23** (%)	Yield **17** (%)	Yield **53** (%)
1	Br (**22**)	MeOH	23	0	20
2	Br (**22**)	MeOH[b]	24	11	4
3	I (**23**)	MeOH	86	0	76
4[c]	I (**23**)	MeOH	17	0	11
5	I (**23**)	*i*-PrOH	26	9	not observed

[a] Conversions and yields determined by GC with dodecane as internal standard [b] 10:1 acetone/MeOH. [c] no $Ru(bpy)_3(PF_6)_2$

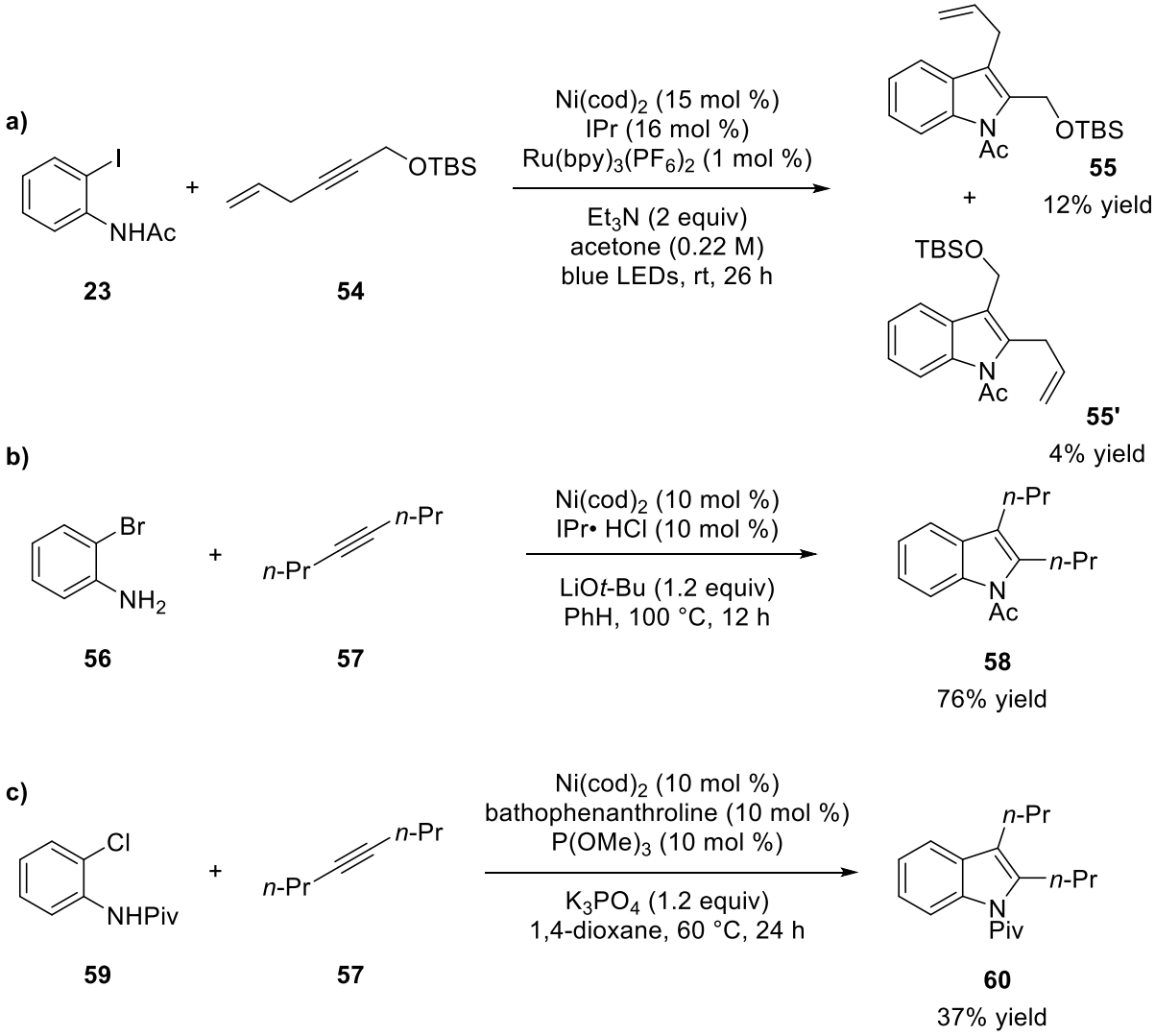
[82] a) Matsunaga, P. T.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075–2077. b) Han, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135–8136.

i-PrOH was used in place of MeOH, no C–O reductive elimination of the secondary alcohol was seen (entry 5).[83] Given the challenges of C–O reductive elimination,[84] along with the high temperatures and alkoxides often used in other cross-coupling methods to produce these bonds,[85] a similar nickel/photoredox dual catalytic system merits further investigation.

Additionally, when enyne **54** was submitted to the reaction conditions, preferential formation of indole product **55** resulting from reaction of the alkyne was observed (Scheme 19a). A nickel-catalyzed Larock indole synthesis has been reported previously, which used IPr as a ligand and LiO*t*-Bu as a base, but high temperatures (100 °C) were needed for product formation (Scheme 19b).[86] We have investigated the Larock indole synthesis of aryl chlorides in our laboratories, but were only able to achieve moderate yields using a Ni/bathophenanthroline catalyst system (Scheme 19c).[87] Perhaps reinvestigation of similar systems with nickel/ photoredox dual catalysis will allow for better yields under milder reaction conditions.

[83] A mild Pd-catalyzed formation of methyl aryl ethers has recently been reported: Cheung, C. W.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 3998–4001.
[84] a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067. b) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576–2587. c) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974–10983.
[85] a) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413–5418. b) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286. c) Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 11592–11598.
[86] Yoshida, Y.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2011**, *40*, 1067–1068.
[87] Winkler, E. Studies on the Nickel-Catalyzed Indole Synthesis via Heteroannulation of 2-Chloroanilines and Alkynes. M.Sc. Dissertation, Eidgenössische Technische Hochschule (ETH), Zürich, 2014.

Scheme 19. Nickel-catalyzed Larock indole synthesis.



Conclusions

In summary, the first general annulation reaction of 2-iodoaniline derivatives and terminal alkenes to form indolines has been developed. Using a nickel/NHC catalytic system, high selectivities for insertion to the terminal position of both aliphatic and styrenyl alkenes is achieved. Moreover, C(sp^3)–N bond formation is achieved by leveraging the various oxidation states available to nickel within the same reaction system using photoredox catalysis as a powerful tool. We envision that using similar dual catalytic systems will enable other reactions for which reductive elimination would otherwise be particularly challenging.

Experimental Section

Materials and Methods

All reactions were performed under an inert atmosphere of nitrogen with exclusion of moisture from reagents and glassware unless otherwise noted. All Ni-catalyzed coupling reactions were carried out in a glovebox (MBraun Unilab) filled with dry nitrogen. $Ni(cod)_2$ and IPr were purchased from Strem Chemicals (Newburyport, MA) and stored in the glovebox. $Ni(cod)_2$ was stored at –20 °C, and it should be a bright yellow color. IPr was used in the free carbene form, rather than a salt. Acetone was distilled from $CaSO_4$ and freeze/pump/thawed to remove oxygen. Essentially identical yields were obtained using a fresh bottle of >99% purity acetone, sparged for 20 minutes with N_2. Et_3N was distilled from Na and freeze/pump/thawed prior to use, although identical yields were obtained using non-distilled commercial Et_3N stored under atmospheric conditions, if it was sparged for 20 minutes with N_2. 1-octene, vinylcyclohexane, styrene, and allyl benzene were distilled from Na prior to use. Other alkenes were used as purchased, unless significant amounts of peroxides had formed, in which case they were passed through a plug of neutral alumina. All alkenes were sparged with nitrogen prior to use. Commercial $Ru(bpy)_3(PF_6)_2$ gave slightly (~5–15%) lower yield than $Ru(bpy)_3(PF_6)_2$ made by treating $Ru(bpy)_3Cl_2$ with NH_4PF_6 in H_2O, rinsed with Et_2O and dried in a vacuum oven. Alternatively, commercial $Ru(bpy)_3(PF_6)_2$ dried in a vacuum oven at 50 °C for 6 h also gave improved yields. All other reagents were used as received. Commercially available chemicals were purchased from either Sigma-Aldrich Chemical Company (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Acros Organics (Pittsburgh, PA), or TCI America (Portland, OR). Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated Science silica gel (EM 60-F254) plates. Visualization was accomplished with UV light (254 nm) and exposure to either ceric ammonium molybdate (CAM), *para*-anisaldehyde, or $KMnO_4$ solution followed by heating.

Column chromatography was carried out on a Biotage Isolera flash chromatography system using SNAP KP-Sil, HP-Sil, or Ultra-Sil columns (silica gel, average particle size 50 µm, 25 µm, and 25 µm spherical respectively).

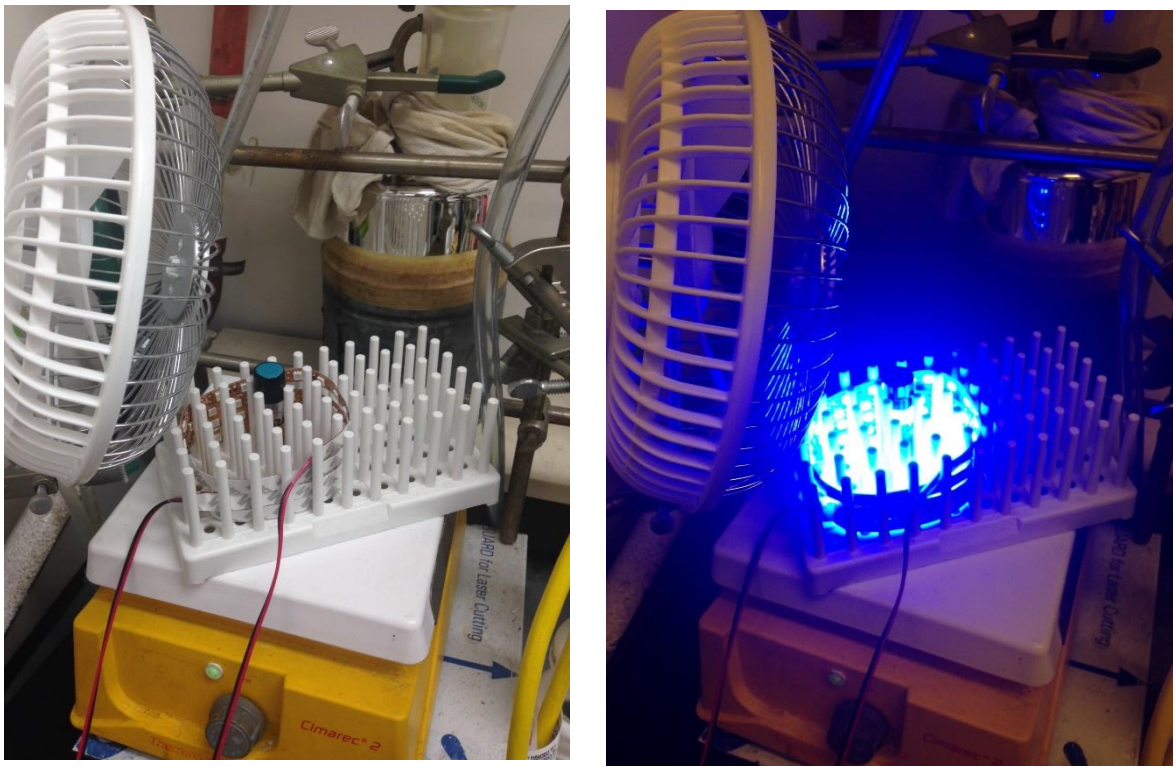
^{1}H NMR Spectra were obtained on either a Bruker 400 MHz, Bruker 600 MHz, or Varian Inova 500 MHz NMR instrument; ^{13}C spectra were recorded on a Bruker 600 MHz (at 151 MHz) NMR instrument. Chemical shifts (^{1}H and ^{13}C) are reported in parts per million and referenced to the residual solvent peak (for $CDCl_3$, δ = 7.27 ppm, 77.0ppm respectively). The following designations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), app (apparent). When rotational isomers are present, the major rotational isomer is reported, as are any clearly differentiated signals arising from the minor rotational isomer. IR spectra were obtained on an Agilent Cary 630 FT-IR spectrometer equipped with an ATR accessory. High-resolution mass spectrometry data were acquired by the Department of Chemistry Instrumentation Facility, Massachusetts Institute of Technology on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR Mass Spectrometer. Gas chromatography (GC) was performed on an Agilent 5870 GC (HP-5 column) with a flame ionization detector. GC/MS was performed on an Agilent 5870 GC (HP-5ms column) with an Agilent 5975C MSD. Dodecane (99+%, Alfa Aesar) was used as an internal standard for quantification.

Nickel/Photoredox-Catalyzed Synthesis of Indolines

General Procedures

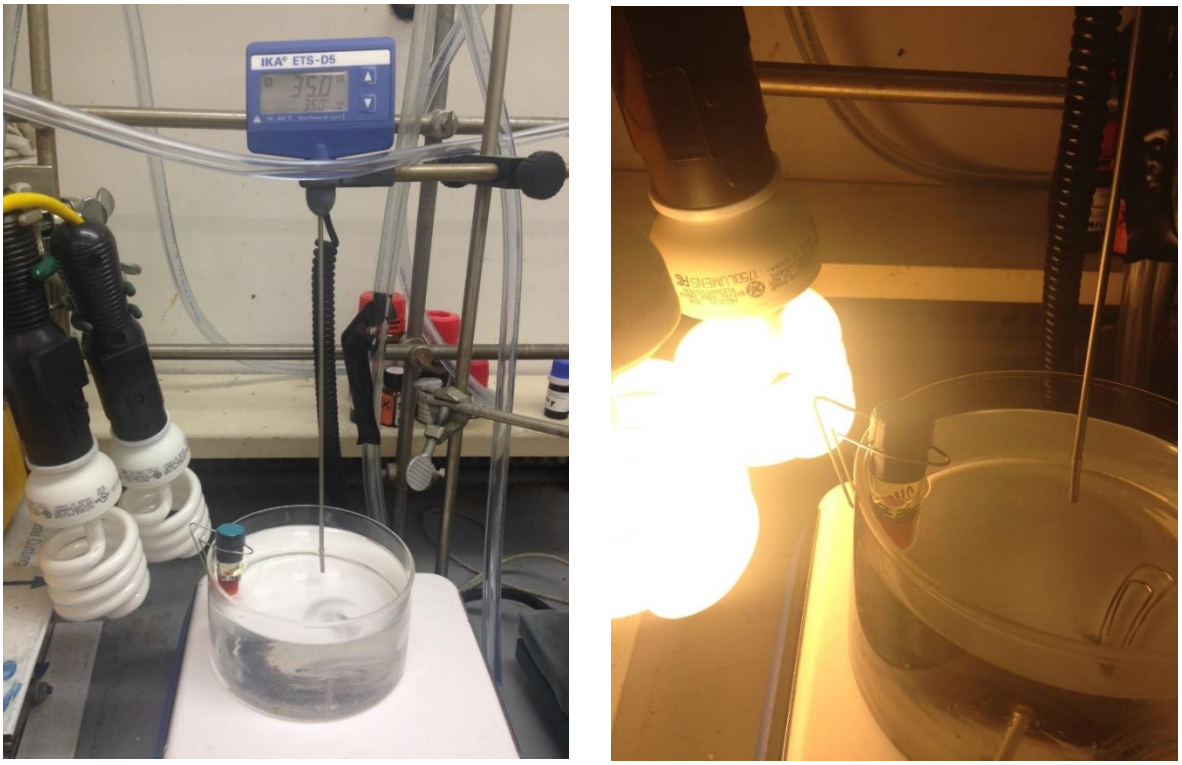
A) Standard Conditions (Room Temperature): In a nitrogen-filled glovebox, $Ni(cod)_2$ (0.075 mmol, 0.15 equiv) and IPr (0.08 mmol, 0.16 equiv) were weighed into a 2 dram (7.4 mL) dry vial. Acetone (0.22 M) was added, solubilizing IPr but not $Ni(cod)_2$, followed by 1-octene (1.0 mmol, 2.0 equiv) to form a homogeneous solution. Et_3N (1.0 mmol, 2.0 equiv), 2'-iodoacetanilide substrate (0.50 mmol 1.0 equiv), and finally $Ru(bpy)_3(PF_6)_2$ (0.005 mmol, 0.01 equiv) were added. The vial cap was then securely fitted and sealed with electrical tape before being removed from the glovebox and placed on a stirplate surrounded by blue LED lights (Figure 5). Maintaining the reaction mixture at room temperature is key for high selectivity, since more β-hydride elimination occurs at higher temperatures. The heat given off by the LEDs can easily be dispersed by directing a small clip-on desk fan at the reaction mixture. [A lamp containing a compact fluorescent lightbulb (CFL) can also be used as a light source, again with a fan to disperse heat generated by the lamp, but additional time is needed for reaction completion (~36–48 h).] The reaction was stirred in this manner for 26 h, before being opened to air, and hexanes and EtOAc were added.

Figure 5. Reaction setup using blue LEDs.



B) Elevated Temperature Conditions (35 °C): In a nitrogen-filled glovebox, $Ni(cod)_2$ (0.075 mmol, 0.15 equiv) and IPr (0.08 mmol, 0.16 equiv)were weighed into a 2 dram (7.4 mL) dry vial. Acetone (0.22 M) was added, solubilizing IPr but not $Ni(cod)_2$, followed by 1-octene (1.0 mmol, 2.0 equiv) to form a homogeneous solution. Et_3N (1.0 mmol, 2.0 equiv), 2'-iodoacetanilide substrate (0.50 mmol 1.0 equiv), and finally $Ru(bpy)_3(PF_6)_2$ (0.01 mmol, 0.02 equiv) were added. The vial cap was then securely fitted and sealed with electrical tape before the vial was removed from the glovebox and clamped to the side of an oil bath at 35 °C adjacent to two CFL lamps (Figure 6). [Unfortunately taping blue LED lights around an oil bath directly heated the oil bath to above 40 °C without any external heating, so could not be used.] The reaction was stirred in this manner for 48 h, before being opened to air, and hexanes and EtOAc were added.

Figure 6. Reaction setup using CFL lamps and oil bath.

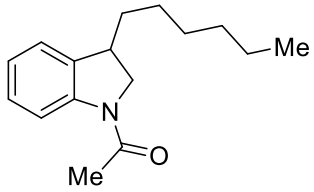


Both A) and B): For reactions analyzed by gas chromatography (GC, reactions run at 0.151 mmol), the crude mixture was passed through a short plug of SiO_2, using a small amount of CH_2Cl_2 to solubilize any precipitate, eluting with EtOAc to a total volume of ~20 mL. Dodecane (35.1 μL, 1.0 equiv) was then added, and a sample was submitted to GC analysis using a method which cleanly separated Heck and indoline products (GC conditions: 50 °C for 2 min, ramp 20 °C/min to 250 °C, hold at 250 °C for 10 min). The desired indoline product area was then compared the sum of all small peaks with similar retention times. For **23a**, the main byproducts were the 1,1-disubstituted Heck product **19**, and the isomerized trisubstituted *E*-styrene derivative **20**. Mechanistically, the former arises from β-hydride elimination followed by reinsertion and isomerization of Ni–H to produce the latter. An authentic sample of the 2-hexyl

indoline product **18** was synthesized, but this product was not observed using IPr and $Ru(bpy)_3(PF_6)_2$.

For isolated yields (reactions run at 0.50 mmol), the reaction mixture was immediately passed through a short plug of SiO_2, using a small amount of CH_2Cl_2 to solubilize any precipitate, eluting with EtOAc to a total volume of ~50 mL. This mixture was then concentrated and purified by column chromatography (see conditions below). If the first step is not performed and the crude reaction mixture concentrated and placed on the column directly, some over-oxidation to indole is observed. A small amount of the purified product was then used to determine ratio of indoline to all other trace products including Heck and isomerized Heck products, as well as possibly 2-substituted indoline products (not observed for **23a** in GC, nor for other products using ^{1}H NMR) using GC using the same method as above. This selectivity ratio is key, since other products are not separable by standard column chromatography.

Characterization of Products



1-(3-hexylindolin-1-yl)ethan-1-one (17a):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-octene (157 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and

$Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 5–40 % EtOAc in hexanes) afforded 108.2 mg (88%) of **17a** as a yellow oil (selectivity ratio of indoline **17a** to [Σ Heck/isomerized Heck/etc.] 22.5:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$): present in a 5:1 ratio of rotational isomers about the amide

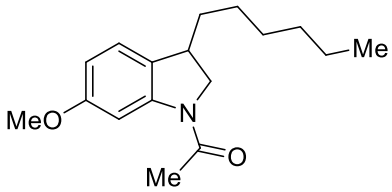
major rotational isomer: δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.15 (app t, *J* = 9.9 Hz, 1H), 3.68 (dd, *J* = 10.2, 6.1 Hz, 1H), 3.39 (tt, *J* = 9.7, 5.4 Hz, 1H), 2.24 (s, 3H), 1.85–1.77 (m, 1H), 1.58–1.52 (m, 1H), 1.43–1.22 (m, 8H), 0.90 (t, *J* = 6.7 Hz, 3H).

minor rotational isomer: δ 4.25 (app t, *J* = 10.6 Hz, 1H), 3.80 (dd, *J* = 12.1, 6.1 Hz, 1H), 3.24 (app p, *J* = 7.1, 6.6 Hz, 1H), 2.44 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 142.6, 135.3, 127.7, 123.8, 123.5, 116.9, 55.2, 40.1, 35.5, 31.8, 29.3, 27.0, 24.3, 22.6, 14.1.

IR (ATR, cm^{-1}) 2925, 2855, 1660, 1598, 1481, 1460, 1398, 1337, 1321, 1273, 1128, 1098, 1022, 921, 752, 730.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{23}NO$, 246.1852; found, 246.1855.



1-(3-hexyl-6-methoxyindolin-1-yl)ethan-1-one (17b):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-octene (157 μL, 1.0 mmol, 2.0 equiv), 2'-iodo-5'-methoxyacetanilide (145.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 7–60 % EtOAc in hexanes) afforded 56.1 mg (41%) of **17b** as a yellow oil (selectivity ratio of indoline **17b** to [Σ Heck/isomerized Heck/etc.] 7.2:1, determined by GC analysis).

^1H NMR (600 MHz, $CDCl_3$) present in ~7:1 ratio of rotational isomers about the amide

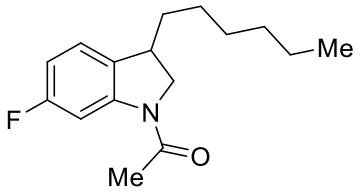
major rotational isomer: δ 7.90 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.59 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.16 (app t, *J* = 9.8 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.32 (tt, *J* = 9.5, 5.4 Hz, 1H), 2.23 (s, 3H), 1.79–1.74 (m, 1H), 1.54–1.48 (m, 1H), 1.41–1.23 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H).

minor rotational isomer: δ 4.26 (app t, *J* = 11.5 Hz, 1H), 3.17 (app br s, 1H), 2.43 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.8, 159.5 143.7, 127.3, 123.9, 109.9, 102.7, 56.0, 55.6, 39.4, 35.8, 31.8, 29.4, 27.0, 24.3, 22.6, 14.1.

IR (ATR, cm^{-1}) 2924, 2855, 1661, 1596, 1489, 1448, 1398, 1357, 1321, 1281, 1203, 1162, 1116, 1032, 856, 812.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{25}NO_2$, 276.1958; found, 276.1952.



1-(6-fluoro-3-hexylindolin-1-yl)ethan-1-one (17c):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-octene (157 μL, 1.0 mmol, 2.0 equiv), 5'-fluoro-2'-iodoacetanilide (139.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 5–40 % EtOAc in hexanes) afforded 90.3 mg (69%) of **17c** as a yellow oil (selectivity ratio of indoline **17c** to [Σ Heck/isomerized Heck/etc.] 20.1:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) present in ~10:1 ratio of rotational isomers about the amide

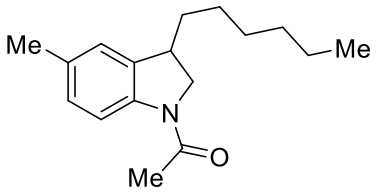
major rotational isomer: δ 7.96 (dd, *J* = 10.6, 2.4 Hz, 1H), 7.07 (dd, *J* = 8.2, 5.6 Hz, 1H), 6.72 (td, *J* = 8.6, 2.3 Hz, 1H), 4.19 (app t, *J* = 9.8 Hz, 1H), 3.71 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.35 (tt, *J* = 9.7, 5.5 Hz, 1H), 2.23 (s, 3H), 1.81–1.75 (m, 1H), 1.56–1.50 (m, 1H), 1.43–1.25 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H).

minor rotational isomer: δ 4.26 (t, *J* = 10.9 Hz, 1H), 3.82 (dd, *J* = 12.4, 6.0 Hz, 1H), 3.20 (app br s, 1H), 2.42 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.9, 162.4 (d, *J* = 242.0 Hz), 143.7 (d, *J* = 12.8 Hz), 130.6 (d, *J* = 2.6 Hz), 124.1 (d, *J* = 9.9 Hz), 109.9 (d, *J* = 22.8 Hz), 105.0 (d, *J* = 29.0 Hz), 55.8, 39.5, 35.6, 31.7, 29.3, 26.9, 24.2, 22.6, 14.1.

IR (ATR, cm^{-1}) 2927, 2856, 1665, 1611, 1484, 1438, 1399, 1358, 1318, 1264, 1176, 1160, 1097, 1030, 958, 866, 813.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{22}FNO$, 264.1758; found, 264.1740.



1-(3-hexyl-5-methylindolin-1-yl)ethan-1-one (17d):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-octene (157 μL, 1.0 mmol, 2.0 equiv), 2'-iodo-4'-methylacetanilide (137.5 mg, 0.50 mmol 1.0 equiv), and

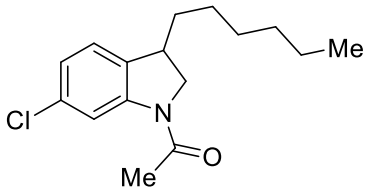
$Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 5–40 % EtOAc in hexanes) afforded 95.1 mg (73%) of **17d** as a pale yellow oil (selectivity ratio of indoline **17d** to [Σ Heck/isomerized Heck/etc.] 19.9:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide
major rotational isomer: δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.01 (m, 2H), 4.14 (app t, *J* = 9.8 Hz, 1H), 3.66 (dd, *J* = 10.2, 6.1 Hz, 1H), 3.35 (tt, *J* = 9.7, 5.4 Hz, 1H), 2.32 (s, 3H), 2.22 (s, 3H), 1.84–1.76 (m, 1H), 1.56–1.50 (m, 1H), 1.42–1.26 (m, 8H), 0.91 (t, *J* = 6.7 Hz, 3H).
minor rotational isomer: δ 4.24 (dd, *J* = 12.1, 9.1 Hz, 1H), 3.78 (dd, *J* = 12.0, 6.2 Hz, 1H), 3.19 (tt, *J* = 9.4, 5.3 Hz, 1H), 2.42 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 140.4, 135.4, 133.1, 128.2, 124.4, 116.6, 55.3, 40.1, 35.5, 31.8, 29.4, 27.0, 24.2, 22.7, 21.1, 14.1.

IR (ATR, cm^{-1}) 2925, 2855, 1656, 1489, 1432, 1394, 1338, 1270, 1138, 1030, 820, 725.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{25}NO$, 260.2009; found, 260.2011.



1-(6-chloro-3-hexylindolin-1-yl)ethan-1-one (17e):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-octene (157 μL, 1.0 mmol, 2.0 equiv), 5'-chloro-2'-iodoacetanilide (148 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 50g Ultra-sil, 5–40 % EtOAc in hexanes) afforded 120.5 mg (86%) of **17e** as a yellow oil (selectivity ratio of indoline **17e** to [Σ Heck/isomerized Heck/etc.] 41:1, determined by GC analysis).

^1H NMR (500 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide.

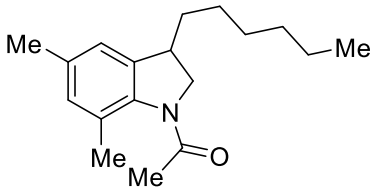
major rotational isomer: δ 8.23 (d, *J* = 1.9 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.17 (app t, *J* = 9.9 Hz, 1H), 3.69 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.35 (tt, *J* = 9.6, 5.3 Hz, 1H), 2.23 (s, 3H), 1.83–1.70 (m, 1H), 1.53 (dtd, *J* = 13.8, 8.9, 5.1 Hz, 1H), 1.42–1.22 (m, 8H), 0.90 (t, *J* = 6.6 Hz, 3H).

minor rotational isomer: δ 4.24 (t, *J* = 10.1 Hz, 1H), 3.81 (dd, *J* = 12.4, 6.2 Hz, 1H), 3.20 (app br s, 1H), 2.43 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.8, 143.6, 133.7, 133.2, 124.4, 123.5, 117.1, 55.5, 39.7, 35.4, 31.7, 29.3, 26.8, 24.2, 22.6, 14.1.

IR (ATR, cm^{-1}) 2926, 2854, 1664, 1595, 1475, 1419, 1394, 1313, 1253, 1133, 1070, 1029, 932, 876, 806, 728.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{22}ClNO$, 280.1463; found, 280.1461.



1-(3-hexyl-5,7-dimethylindolin-1-yl)ethan-1-one (17g):

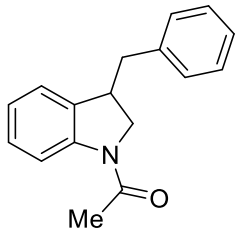
Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-octene (157 μL, 1.0 mmol, 2.0 equiv), 2'-iodo-4',6'-dimethylacetanilide (145 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g Ultra-sil, 5–40 % EtOAc in hexanes) afforded 38.5 mg (28%) of **17g** as a yellow oil (selectivity ratio of indoline **17g** to [Σ Heck/isomerized Heck/etc.] >100:1, determined by GC analysis).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (br s, 1H), 6.84 (br s, 1H), 4.15 (br s, 1H), 3.68 (br s, 1H), 3.13 (app br quin, *J* = 7.0 Hz, 1H), 2.30 (s, 3H), 2.24 (s, 6H), 1.81–1.70 (m, 1H), 1.49–1.24 (m, 9H), 0.90 (t, *J* = 6.8 Hz, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3 (br), 139.0 (br), 138.5 (br), 134.8, 130.5, 128.7 (br), 121.7 (br), 57.3, 41.9 (br), 33.5, 31.7, 29.4, 27.2, 23.8 (br), 22.6, 21.0, 20.5 (br), 14.1.

IR (ATR, cm^{-1}) 2924, 2855, 1666, 1475, 1410, 1375, 1245, 1195, 1151, 1033, 970, 853, 725.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{25}NO$, 274.2165; found, 274.2160.



1-(3-benzylindolin-1-yl)ethan-1-one (17h):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), allylbenzene (132 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc

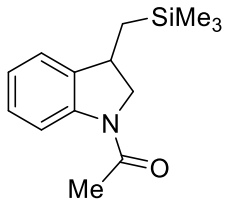
as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 6–48 % EtOAc in hexanes) afforded 114.5 mg (91%) of **17h** as a pale yellow solid (selectivity ratio of indoline **17h** to [Σ Heck/isomerized Heck/etc.] 45.6:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide.
major rotational isomer: δ 8.21 (d, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 4.02 (app t, *J* = 11.6 Hz, 1H), 3.77–3.71 (m, 2H), 3.15 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.80 (dd, *J* = 14.0, 8.8 Hz, 1H), 2.17 (s, 3H).
minor rotational isomer: δ 4.10 (app t, *J* = 10.6 Hz, 1H), 3.58 (app br s, 1H), 3.07 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.38 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.7, 142.7, 138.8, 134.3, 129.0, 128.7, 128.1, 126.7, 124.0, 123.6, 117.1, 54.5, 41.56, 41.54, 24.3.

IR (ATR, cm^{-1}) 3062, 3027, 2922, 2883, 1656, 1597, 1480, 1459, 1398, 1355, 1337, 1280, 1132, 1085, 1030, 750, 701.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{17}NO$, 252.1383; found, 252.1373.



1-(3-((trimethylsilyl)methyl)indolin-1-yl)ethan-1-one (17i):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), allyltrimethylsilane (159 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 5–40% EtOAc in hexanes) afforded 85.0 mg (69%) of **17i** as a white solid (selectivity ratio of indoline **17i** to [Σ Heck/isomerized Heck/etc.] 5:1, determined by GC analysis).

^1H NMR (600 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide.

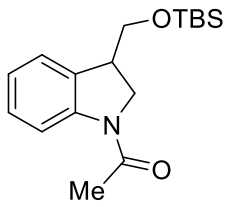
major rotational isomer: δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 4.18 (t, *J* = 9.5 Hz, 1H), 3.56 (dd, *J* = 9.8, 7.1 Hz, 1H), 3.51 (app q, *J* = 10.5 Hz, 1H), 2.23 (s, 3H), 1.22 (dd, *J* = 14.9, 3.3 Hz, 1H), 0.88 (dd, *J* = 14.9, 10.9 Hz, 1H), 0.09 (d, *J* = 1.2 Hz, 9H).

minor rotational isomer: δ 4.40 (t, *J* = 10.6 Hz, 1H), 3.35 (app q, *J* = 8.4 Hz, 1H), 2.44 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 142.0, 137.6, 127.6, 123.7, 123.3, 116.8, 57.1, 36.5, 24.2, 23.4, -0.8.

IR (ATR, cm^{-1}) 3065, 2952, 2883, 2802, 1660, 1597, 1519, 1478, 1457, 1404, 1353, 1319, 1273, 1247, 1222, 1201, 1160, 1131, 1101, 1032, 960, 837, 742, 692.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{21}NOSi$, 248.1465; found, 248.1471.



1-(3-(((tert-butyldimethylsilyl)oxy)methyl)indolin-1-yl)ethan-1-one (17j):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), allyloxy-*tert*-butyldimethylsilane (213 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 5–40% EtOAc in hexanes) afforded 113.5 mg (74%) of **17j** as a pale yellow oil (selectivity ratio of indoline **17j** to [Σ Heck/isomerized Heck/etc.] 12.3:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) present in ~7:1 ratio of rotational isomers about the amide

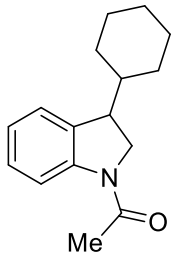
major rotational isomer: δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.02 (tt, *J* = 7.5, 1.0 Hz, 1H), 4.10 (dd, *J* = 10.5, 9.1 Hz, 1H), 3.94 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.82 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.60 (dd, *J* = 9.8, 8.3 Hz, 1H), 3.55 (app tt, *J* = 9.0, 4.8 Hz, 1H), 2.25 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

minor rotational isomer: δ 4.15 (app t, *J* = 10.7 Hz, 1H), 4.03 (dd, *J* = 12.1, 4.5 Hz, 1H), 3.77 (app t, *J* = 8.0 Hz, 1H), 3.66 (app t, *J* = 8.6 Hz, 1H), 3.46–3.38 (m, 1H), 2.44 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.7, 143.2, 131.8, 128.3, 124.3, 123.4, 117.0, 66.0, 52.3, 43.1, 25.8, 24.2, 18.3, –5.3, –5.5.

IR (ATR, cm^{-1}) 2953, 2929, 2886, 2857, 1663, 1599, 1482, 1462, 1400, 1359, 1287, 1252, 1114, 1086, 1006, 833, 776, 752, 670.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{27}NO_2Si$, 306.1884; found, 306.1883.



1-(3-cyclohexylindolin-1-yl)ethan-1-one (17k):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv),

vinylcyclohexane (137 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 5–46 % EtOAc in hexanes) afforded 114.4 mg (94%) of **17k** as a pale yellow solid (selectivity ratio of indoline **17k** to [Σ Heck/isomerized Heck/etc.] 9.1:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide

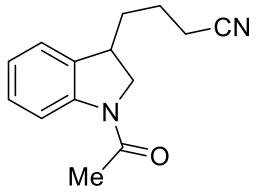
major rotational isomer: δ 8.21 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.01 (t, *J* = 10.1 Hz, 1H), 3.84 (dd, *J* = 10.5, 4.7 Hz, 1H), 3.31 (app dt, *J* = 9.6, 4.7 Hz, 1H), 2.25 (d, *J* = 1.1 Hz, 3H), 1.82–1.62 (m, 5H), 1.44 (d, *J* = 13.4 Hz, 1H), 1.32–1.21 (m, 1H), 1.15 (dddd, *J* = 25.8, 16.2, 9.9, 3.5 Hz, 2H), 1.03 (qdd, *J* = 12.6, 9.5, 3.6 Hz, 2H).

minor rotational isomer: δ 4.12 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.96 (app d, *J* = 11.5 Hz, 1H), 3.16–3.10 (m, 1H), 2.43 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 143.2, 133.5, 127.7, 124.5, 123.4, 116.8, 51.9, 45.6, 42.3, 30.6, 27.9, 26.47, 26.40, 26.3, 24.3.

IR (ATR, cm^{-1}) 2923, 2851, 1660, 1597, 1517, 1481, 1460, 1401, 1356, 1340, 1286, 1223, 1128, 1032, 923, 892, 753.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{21}NO$, 244.1696; found, 244.1700.



4-(1-acetylindolin-3-yl)butanenitrile (17l):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 5-hexenenitrile (114 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 17–100 % EtOAc in hexanes) afforded 86.7 mg (76%) of **17l** as a pale orange solid (selectivity ratio of indoline **17l** to [Σ Heck/isomerized Heck/etc.] 61.5:1, determined by GC analysis).

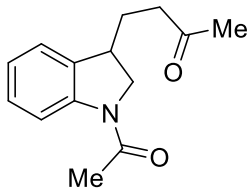
^1H NMR (600 MHz, $CDCl_3$) present in a ~4.5:1 ratio of rotational isomers about the amide major rotational isomer: δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 4.20 (app t, *J* = 9.9 Hz, 1H), 3.70 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.49–3.44 (m, 1H), 2.40 (t, *J* = 6.5 Hz, 2H), 2.24 (s, 3H), 1.99–1.89 (m, 1H), 1.81–1.67 (m, 3H).

minor rotational isomer: δ 4.24 (app t, *J* = 10.6 Hz, 1H), 3.84 (dd, *J* = 12.1, 5.6 Hz, 1H), 3.30 (br s, 1H), 2.45 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 142.7, 133.7, 128.3, 123.78, 123.75, 119.2, 117.1, 54.7, 39.4, 34.3, 24.3, 22.6, 17.4.

IR (ATR, cm^{-1}) 2931, 2875, 2246, 1654, 1596, 1480, 1460, 1400, 1349, 1323, 1274, 1131, 1029, 843, 755.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{16}N_2O$, 229.1335; found, 229.1344.



4-(1-acetylindolin-3-yl)butan-2-one (17m):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), allylacetone (116 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air and concentrated. Column chromatography (Biotage 25g HP-sil, 10–100 % EtOAc in hexanes)

afforded 99.4 mg (86%) of **17m** as an orange oil (selectivity ratio of indoline **17m** to [Σ Heck/isomerized Heck/etc.] 22:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) present in ~4.5:1 ratio of rotational isomers about the amide

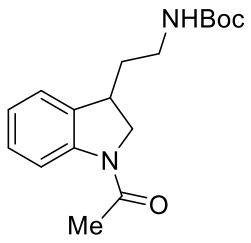
major rotational isomer: δ 8.23 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 4.17 (app t, *J* = 9.9 Hz, 1H), 3.70 (dd, *J* = 10.3, 5.3 Hz, 1H), 3.47 (app tt, *J* = 8.7, 5.4 Hz, 1H), 2.56–2.44 (m, 2H), 2.25 (s, 3H), 2.17 (s, 3H), 2.09 (tdd, *J* = 13.9, 7.7, 3.6 Hz, 1H), 1.92 (dtd, *J* = 14.2, 8.1, 6.2 Hz, 1H).

minor rotational isomer: δ 4.23 (app t, *J* = 10.7 Hz, 1H), 3.82 (dd, *J* = 12.0, 5.9 Hz, 1H), 3.30 (app q, *J* = 5.5, 5.0 Hz, 1H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 207.9, 168.7, 142.7, 134.0, 128.1, 123.9, 123.7, 117.0, 54.8, 40.1, 39.1, 30.1, 28.7, 24.3.

IR (ATR, cm^{-1}) 2922, 1711, 1654, 1597, 1480, 1460, 1399, 1354, 1272, 1161, 1130, 1030, 936, 753.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{17}NO_2$, 232.1332; found, 232.1340.



tert-butyl (2-(1-acetylindolin-3-yl)ethyl)carbamate (17n):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-(Boc-amino)-3-butene (184 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air and concentrated. Column chromatography (Biotage 25g Ultra-sil, 12–100 % EtOAc in hexanes) afforded 147.2 mg (97%) of **17n** as a yellow solid (selectivity ratio of indoline **17n** to [Σ Heck/isomerized Heck/etc.] 28:1, determined by GC analysis).

^1H NMR (500 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide

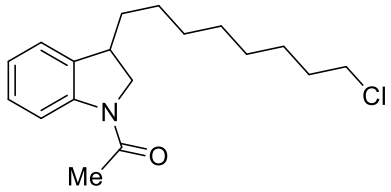
major rotational isomer: δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 4.66 (br s, 1H), 4.21 (app t, *J* = 9.9 Hz, 1H), 3.75 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.45 (tt, *J* = 9.8, 5.2 Hz, 1H), 3.32–3.19 (m, 2H), 2.23 (s, 3H), 2.00 (dtd, *J* = 12.7, 7.7, 4.6 Hz, 1H), 1.79–1.69 (m, 1H), 1.45 (s, 9H).

minor rotational isomer: δ 4.30–4.23 (m, 1H), 3.83 (dd, *J* = 12.2, 5.8 Hz, 1H), 2.44 (s, 3H).

^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 168.7, 156.1, 142.6, 134.4, 128.0, 123.7, 117.0, 79.5, 54.9, 38.3, 37.7, 36.0, 29.4, 28.4, 24.3.

IR (ATR, cm^{-1}) 3322, 2972, 2936, 1694, 1651, 1596, 1517, 1481, 1403, 1364, 1272, 1248, 1165, 1031, 911, 846, 728.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{24}N_2O_3$, 327.1679; found, 327.1699.



1-(3-(8-chlorooctyl)indolin-1-yl)ethan-1-one (17o):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 10-chloro-1-decene (199 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air and concentrated. Column chromatography (Biotage 50g Ultra-sil, 5–40 % EtOAc in hexanes) afforded 137.4 mg (89%) of **17o** as a yellow oil (selectivity ratio of indoline **17o** to [Σ Heck/isomerized Heck/etc.] 20.1:1, determined by GC analysis. A significant amount of primary chloride elimination was observed upon GC injection as identified by GCMS, but since no elimination product was observed in the ^1H NMR, this peak was disregarded).

^1H NMR (500 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide

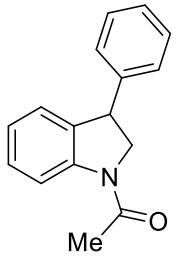
major rotational isomer: δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 4.15 (app t, *J* = 9.8 Hz, 1H), 3.67 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.54 (t, *J* = 6.7 Hz, 2H), 3.39 (tt, *J* = 9.6, 5.4 Hz, 1H), 2.24 (s, 3H), 1.84–1.73 (m, 3H), 1.59–1.49 (m, 1H), 1.48–1.25 (m, 10H).

minor rotational isomer: δ 4.24 (dd, *J* = 12.0, 9.3 Hz, 1H), 3.80 (dd, *J* = 12.0, 6.1 Hz, 1H), 3.24 (tt, *J* = 7.0, 4.2 Hz, 1H), 2.44 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 142.6, 135.2, 127.7, 123.8, 123.6, 116.9, 55.1, 45.2, 40.1, 35.4, 32.6, 29.5, 29.4, 28.8, 26.9, 26.8, 24.3.

IR (ATR, cm^{-1}) 2926, 2854, 1660, 1598, 1481, 1399, 1338, 1271, 1129, 1095, 1023, 935, 753.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{18}H_{26}ClNO$, 308.1776; found, 308.1765.



1-(3-phenylindolin-1-yl)ethan-1-one (17p):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), styrene (115 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air and concentrated. Column chromatography (Biotage 25g HP-sil, 5–45 % EtOAc in hexanes)

afforded 77.1 mg (65%) of **17p** as a yellow oil (selectivity ratio of indoline **17p** to [Σ Heck/isomerized Heck/etc.] 8.2:1, determined by GC analysis).

^{1}H NMR (600 MHz, $CDCl_3$) present in ~6:1 ratio of rotational isomers

major rotational isomer: δ 8.29 (d, *J* = 8.1 Hz, 1H), 7.38–7.30 (m, 2H), 7.32–7.22 (m, 2H), 7.19 (d, *J* = 6.9 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 4.62 (dd, *J* = 10.2, 6.9 Hz, 1H), 4.46 (t, *J* = 10.3 Hz, 1H), 3.95 (dd, *J* = 10.4, 6.8 Hz, 1H), 2.22 (s, 3H).

minor rotational isomer: δ 4.06 (dd, *J* = 12.1, 7.1 Hz, 1H), 2.49 (s, 3H).

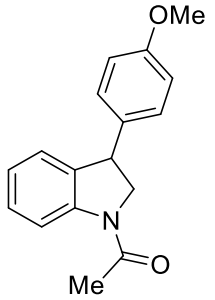
^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 143.1, 143.0, 134.5, 129.0, 128.2, 127.8, 127.3, 125.0, 124.0, 117.0, 58.1, 46.6, 24.3.

IR (ATR, cm^{-1}) 3029, 2881, 1654, 1594, 1517, 1479, 1396, 1353, 1332, 1286, 1266, 1129, 1094, 1017, 978, 922, 869, 750, 699.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{15}NO$, 238.1226; found, 238.1235.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[88]

[88] Ma, L.-J.; Li, X.-X.; Kusuyama, T.; El-Sayed, I. E.-T.; Inokuchi, T. *J. Org. Chem.* **2009**, *74*, 9218–9221.



1-(3-(4-methoxyphenyl)indolin-1-yl)ethan-1-one (17q):

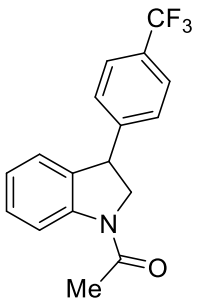
Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 4-vinyl anisole (133 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air and concentrated. Column chromatography (Biotage 25g HP-sil, 8–70 % EtOAc in hexanes) afforded 92.4 mg (69%) of **17q** as a viscous orange oil (selectivity ratio of indoline **17q** to [Σ Heck/isomerized Heck/etc.] 11.4:1, determined by GC analysis).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.1 Hz, 1H), 7.29–7.21 (m, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.59 (dd, *J* = 10.1, 7.0 Hz, 1H), 4.44 (app t, *J* = 10.2 Hz, 1H), 3.91 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.81 (s, 3H), 2.22 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 158.8, 142.9, 135.2, 134.8, 128.9, 128.1, 125.0, 124.0, 116.9, 114.3, 58.3, 55.3, 45.8, 24.3.

IR (ATR, cm^{-1}) 3001, 2932, 2835, 1655, 1596, 1510, 1479, 1396, 1353, 1243, 1177, 1111, 1031, 980, 923, 830, 753.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{17}NO_2$, 268.1332; found, 268.1335.



1-(3-(4-(trifluoromethyl)phenyl)indolin-1-yl)ethan-1-one (17r):

Following general procedure **B**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 4-(trifluoromethyl)styrene (98 μL, 0.66 mmol, 1.3 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 0.01 mmol, 0.02 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed in a 35 °C oil bath next to a compact fluorescent lightbulb. After 48 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 50g HP-sil, 5–40 % EtOAc in hexanes) afforded 84.5 mg (55%) of **17r** as a white solid (selectivity ratio of indoline **17r** to [Σ Heck/isomerized Heck/etc.] 8.5:1, determined by GC analysis).

^1H NMR (500 MHz, $CDCl_3$) present in ~5:1 ratio of rotational isomers about the amide

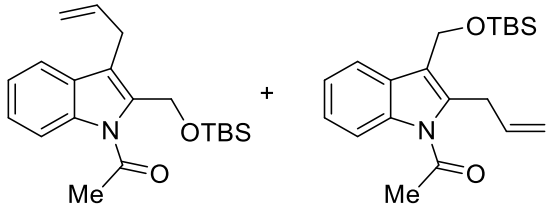
major rotational isomer: δ 8.30 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.34–7.26 (m, 3H), 7.04 (ddd, *J* = 7.3, 6.6, 0.9 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 4.70 (dd, *J* = 10.1, 6.6 Hz, 1H), 4.51 (app t, *J* = 10.3 Hz, 1H), 3.95 (dd, *J* = 10.6, 6.6 Hz, 1H), 2.24 (s, 3H).

minor rotational isomer: δ 4.65–4.55 (m, 2H), 4.07 (dd, *J* = 11.6, 6.3 Hz, 1H), 2.51 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 147.1, 142.3, 133.5, 129.67 (q, *J* = 32.5 Hz), 128.6, 128.2, 125.96, 125.93, 125.0, 124.2, 117.1, 57.7, 46.4, 24.2.

IR (ATR, cm^{-1}) 1660, 1619, 1597, 1481, 1399, 1358, 1322, 1289, 1163, 1110, 1067, 1018, 980, 839, 754, 725.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{14}F_3NO$, 306.1100; found, 306.1089.



1-(3-allyl-2-(((tert-butyldimethylsilyl)oxy)methyl)-1H-indol-1-yl)ethan-1-one (55):

Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), **54** (248 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air and concentrated.

Column chromatography (Biotage 50g HP-sil, benzene) afforded 21.3 mg (12%) of **55** as an yellow oil and 7.2 mg (4%) of **55'** as a yellow oil.

55: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (app dt, *J* = 8.4, 0.9 Hz, 1H), 7.52 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.34 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.27–7.23 (m, 1H), 5.96 (ddt, *J* = 17.1, 10.1, 5.9 Hz, 1H), 5.11–5.04 (m, 2H), 4.96 (s, 2H), 3.52 (dt, *J* = 5.9, 1.8 Hz, 2H), 2.86 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.7, 136.7, 135.7, 134.2, 125.2, 123.0, 119.6, 119.2, 116.1, 115.86, 115.85, 56.0, 28.5, 26.1, 25.8, 18.2, -5.3.

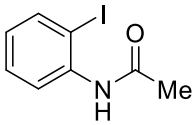
IR (ATR, cm^{-1}) 2954, 2929, 2890, 2857, 1701, 1455, 1366, 1317, 1255, 1134, 1065, 1009, 836, 777, 748.

HRMS (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{29}NO_2Si$, 366.1860; found, 366.1858.

55': ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.82 (m, 1H), 7.69–7.65 (m, 1H), 7.32–7.24 (m, 2H), 6.02 (ddtd, *J* = 17.3, 10.1, 5.5, 0.8 Hz, 1H), 5.07 (dqd, *J* = 10.1, 1.6, 0.7 Hz, 1H), 4.96 (ddt, *J* = 17.9, 2.5, 1.5 Hz, 1H), 4.82 (d, *J* = 0.8 Hz, 2H), 3.87 (dtd, *J* = 5.4, 1.8, 0.7 Hz, 2H), 2.76 (d, *J* = 0.8 Hz, 3H), 0.92 (d, *J* = 0.8 Hz, 9H), 0.12 (d, *J* = 0.8 Hz, 6H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.3, 135.84, 135.75, 135.5, 129.9, 124.0, 122.9, 120.1, 119.5, 116.0, 114.7, 56.0, 30.7, 27.5, 26.0, 18.4, –5.2.

Synthesis of Substrates



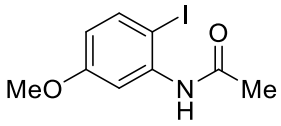
2'-Iodoacetanilide (23a):

In a 25 mL round bottom flask, 2-iodoaniline (2.63 g, 12.0 mmol, 1.0 equiv) was dissolved in EtOAc (12 mL, 1M), acetic anhydride (1.63 mL, 17.2 mmol, 1.4 equiv) was added, and the reaction was stirred at room temperature overnight. Additional EtOAc to fully solubilize reaction mixture was added and the solution was filtered through a plug of SiO_2. Recrystallization from EtOAc/Hexanes yielded 2.52 g (80%) of **23a** as a light tan solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.43 (br s, 1H), 7.35 (ddd, *J* = 8.4, 7.4, 1.5 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 2.25 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.4, 138.8, 138.3, 129.2, 126.3, 122.5, 90.5, 24.8.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[89]



2'-Iodo-5'-methoxyacetanilide (23b):

In a 500 mL round bottom flask, 4-iodo-3-nitroanisole (1.0 g, 3.6 mmol, 1.0 equiv), Zn powder (18.8 g, 290 mmol, 80 equiv), NH_4Cl (3.08 g, 58 mmol, 16 equiv), MeOH (220 mL, 0.016M)

[89] Gimbert, C.; Vallribera, A. *Org. Lett.* **2009**, *11*, 269–271.

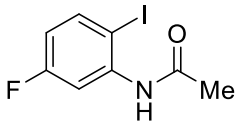
and H_2O (24 mL, 0.15M) were stirred at room temperature overnight. The mixture was diluted with additional water, and extracted twice with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Then, the crude mixture was dissolved in EtOAc (8 mL, 0.45M), acetic anhydride (0.68 mL, 7.2 mmol, 2.0 equiv) was added and the mixture was stirred at room temperature overnight. Column chromatography (Biotage 25g HP-sil, 11–90 % EtOAc in hexanes) afforded 429 mg (41% over two steps) of **23b** as a light tan solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 3.2 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.42 (br s, 1H), 6.49 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.81 (s, 3H), 2.25 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 160.6, 139.0, 138.6, 112.8, 107.2, 77.8, 55.5, 25.0.

IR (ATR, cm^{-1}) 3251, 1658, 1579, 1524, 1468, 1408, 1372, 1312, 1287, 1236, 1201, 1172, 1045, 1022, 972, 844, 815, 699.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_9H_{10}INO_2$, 291.9829; found, 291.9820.



5'-Fluoro-2'-iodoacetanilide (23c):

In a 25 mL round bottom flask, 5-fluoro-2-iodoaniline (1.90 g, 8.0 mmol, 1.0 equiv) was dissolved in EtOAc (8 mL, 1M), acetic anhydride (0.91 mL, 9.6 mmol, 1.2 equiv) was added,

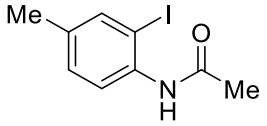
and the reaction mixture was stirred at room temperature overnight. The precipitate was filtered, washing with EtOAc to yield 1.077 g (48%) of **23c** as white filamentous crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 11.2, 2.9 Hz, 1H), 7.71 (dd, *J* = 8.8, 6.0 Hz, 1H), 7.48 (br s, 1H), 6.64 (ddd, *J* = 8.6, 7.6, 3.0 Hz, 1H), 2.26 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 163.2 (d, *J* = 246.4 Hz), 139.5 (d, *J* = 11.7 Hz), 139.1 (d, *J* = 9.0 Hz), 113.0 (d, *J* = 22.5 Hz), 109.3 (d, *J* = 28.5 Hz), 82.0, 24.9.

IR (ATR, cm^{-1}) 3249, 1662, 1593, 1526, 1464, 1438, 1414, 1365, 1283, 1234, 1167, 1108, 1026, 973, 875, 805, 774, 677.

HRMS (*m*/*z*) $[M + H]^+$ calcd for C_8H_7FINO, 279.9629; found, 279.9615.



2'-Iodo-4'-methylacetanilide (23d):

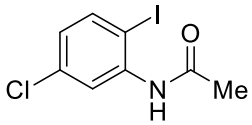
In a 250 mL round bottom flask, 3-iodo-4-nitrotoluene (1.13 mL, 8 mmol, 1.0 equiv), Fe powder (4.48 g, 80 mmol, 10 equiv), NH_4Cl (1.71 g, 32 mmol, 4.0 equiv), MeOH (80 mL, 0.1M) and H_2O (27 mL, 0.3M) were heated to 50 °C for 2 d. The reaction mixture was then diluted with additional water, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Then, the resulting orange solid was

dissolved in EtOAc (16 mL, 0.5M), acetic anhydride (1.6 mL, 16 mmol, 2.0 equiv) was added, and the reaction mixture was stirred at room temperature overnight. Column chromatography (30–70 % EtOAc in hexanes) afforded 1.04 g (47% after two steps) of **23d** as a light brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 1H), 7.61 (s, 1H), 7.33 (br s, 1H), 7.16 (dd, *J* = 8.3, 1.9 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.2, 139.0, 136.1, 135.8, 129.9, 122.3, 90.5, 24.7, 20.4.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[90]



5'-Chloro-2'-iodoacetanilide (23e):

In a 25 mL round bottom flask, 5-chloro-2-iodoaniline (2.02 g, 8.0 mmol, 1.0 equiv) was dissolved in EtOAc (8 mL, 1M), acetic anhydride (1.82 mL, 16 mmol, 2.0 equiv) was added, and the reaction mixture was stirred at room temperature overnight. The precipitate was filtered, washing with EtOAc to yield 1.91 g (81%) of **23e** as a white powder.

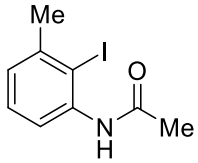
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.43 (br s, 1H), 6.86 (dd, *J* = 8.4, 2.5 Hz, 1H), 2.26 (s, 3H).

[90] Bruch, A.; Fröhlich, R.; Grimme, S.; Studer, A.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 16270–16276.

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.2, 139.18, 139.14, 135.4, 125.9, 121.7, 86.4, 24.9.

IR (ATR, cm^{-1}) 3274, 1656, 1568, 1526, 1452, 1398, 1282, 1225, 1090, 1023, 909, 869, 805, 661.

HRMS (*m*/*z*) $[M + H]^+$ calcd for C_8H_7ClINO, 295.9334; found, 295.9342.



2'-Iodo-3'-methylacetanilide (23f):

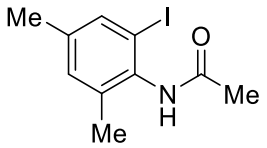
In a 250 mL round bottom flask, 2-iodo-3-nitrotoluene (2.10 g, 8 mmol, 1.0 equiv), Fe powder (4.48 g, 80 mmol, 10 equiv), NH_4Cl (1.71 g, 32 mmol, 4.0 equiv), MeOH (80 mL, 0.1M) and H_2O (27 mL, 0.3M) were heated to 50 °C for 2 d. The reaction mixture was diluted with additional water, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Then, the resulting orange liquid was diluted in EtOAc (13 mL, 0.5M), acetic anhydride (0.94 mL, 9.9 mmol, 1.5 equiv) was added, and the reaction mixture was stirred at room temperature overnight. The precipitate was filtered, washing with EtOAc then hexanes to yield 516 mg (24% over two steps) of **23f** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 1H), 7.59 (br s, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 2.48 (s, 3H), 2.26 (s, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 142.3, 138.4, 128.5, 125.9, 119.7, 98.0, 29.7, 24.9.

IR (ATR, cm^{-1}) 3255, 1659, 1583, 1528, 1460, 1394, 1367, 1291, 1255, 1167, 1013, 789, 712, 670.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_9H_{10}INO$, 275.9880; found, 275.9899.



2'-Iodo-4',6'-dimethylacetanilide (23g):

In a 25 mL round bottom flask, 2-iodo-4,6-dimethylaniline (1.00 g, 4.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (8 mL, 0.5M), acetyl chloride (0.35 mL, 4.8 mmol, 1.2 equiv) and pyridine (0.39 mL, 4.8 mmol, 1.2 equiv) were added, and the reaction mixture was stirred at room temperature overnight. It was then concentrated under reduced pressure and purified by column chromatography (1–10 % MeOH in CH_2Cl_2) to afford 717 mg (61%) of **23g** as a light tan solid.

^{1}H NMR (500 MHz, $CDCl_3$) present in ~4:1 ratio of rotational isomers about the amide

major rotational isomer: δ 7.52 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.03 (s, 1H), 6.84 (s, 1H), 2.27 (s, 6H), 2.23 (s, 3H).

minor rotational isomer δ 7.61 (s, 1H), 7.08 (s, 1H), 6.68 (s, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 1.77 (s, 3H).

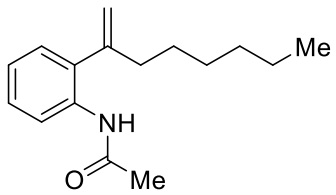
^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) rotational isomers clearly visible

major rotational isomer: δ 168.9, 139.0, 137.8, 137.0, 134.8, 131.7, 99.6, 23.4, 20.47, 19.6.

minor rotational isomer: δ 173.1, 140.3, 137.7, 137.2, 135.6, 132.0, 102.1, 20.7, 20.51, 19.7.

IR (ATR, cm^{-1}) 3226, 3180, 3021, 2920, 1654, 1597, 1559, 1523, 1470, 1437, 1368, 1293, 1265, 1129, 1036, 1011, 971, 858, 788, 703.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_{12}INO$, 290.0036; found, 290.0048.



***N*-(2-(oct-1-en-2-yl)phenyl)acetamide (19a):**

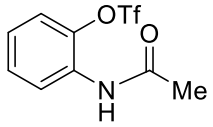
In a 20 mL vial in a nitrogen filled glovebox, mixed $Pd(dba)_2$ (86.5 mg, 0.15 mmol, 0.1 equiv), dppf (100 mg, 0.18 mmol, 0.12 equiv) in DMA (8.8 mL, 0.17 M) for 10 min at room temperature. Then 2-acetamidophenyl trifluoromethanesulfonate **13** (425 mg, 1.5 mmol, 1.0 equiv), 1-octene (470 μL, 3.0 mmol, 2.0 equiv), and urotropine (420 mg, 3.0 mmol, 2.0 equiv) were added. The reaction mixture was heated to 80 °C for 48 h. After cooling, the reaction mixture was passed through a plug of SiO_2, eluting with diethyl ether, and concentrated. Column chromatography (Biotage 25g HP-sil, 5–40 % EtOAc in hexanes) afforded 335 mg (91%) **19a** as a colorless oil (rr **19a** to linear product or isomerized Heck 23.4:1, determined by GC analysis).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 1H), 7.53 (br s, 1H), 7.31–7.23 (m, 1H), 7.11–7.06 (m, 2H), 5.37 (s, 1H), 5.03 (s, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.15 (s, 3H), 1.44–1.34 (m, 2H), 1.34–1.22 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.0 147.6, 134.4, 132.8, 128.0, 127.8, 123.6, 120.7, 115.7, 38.1, 31.6, 29.0, 27.8, 24.8, 22.6, 14.1.

IR (ATR, cm^{-1}) 3279, 2927, 2856, 1664, 1579, 1516, 1445, 1368, 1294, 1041, 1006, 905, 755.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{23}NO$, 246.1852; found, 246.1845.



2-acetamidophenyl trifluoromethanesulfonate (16):

In a 100 mL flask, 2-aminophenol (4.36 g, 40 mmol, 1.0 equiv) was dissolved in EtOAc (40 mL, 1M). Acetic anhydride (4.54 mL, 48 mmol, 1.2 equiv) was added, and the reaction mixture was stirred at room temperature overnight. It was then concentrated under reduced pressure and purified by recrystallization from EtOAc/hexanes to yield 5.39 g (89%) of 2-hydroxyacetanilide.

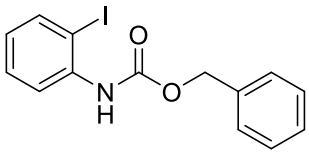
In a 250 mL oven dried flask, 2-hydroxyacetanilide (5.39 g, 35.7 mmol, 1.0 equiv) and pyridine (8.65 mL, 107 mmol, 3.0 equiv) were dissolved in CH_2Cl_2 (150 mL, 0.2 M). Trifluoroacetic anhydride (6.78 mL, 40.3 mmol, 1.13 equiv) was added, and the reaction mixture was stirred at

room temperature overnight. Water and CH_2Cl_2 were added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, then combined organic layers were washed with 1M HCl, water, and brine sequentially, dried over $MgSO_4$, filtered, and concentrated. Column chromatography (20–40% EtOAc in Hexanes) afforded 7.50 g (74%) **16** as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.3 Hz, 1H), 7.42–7.34 (m, 2H), 7.31 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.20 (app t, *J* = 7.5 Hz, 1H), 2.23 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.1, 140.3, 130.2, 128.9, 125.7, 121.5, 118.6 (q, *J* = 321 Hz), 24.0.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[91]



Benzyl (2-iodophenyl)carbamate (32):

In a 2 dram vial, 2-iodoaniline (880 mg, 4.0 mmol, 1.0 equiv) and benzyl chloroformate (0.86 mL, 6.0 mmol, 1.5 equiv) were diluted in 1M aq. NaOH (4 mL, 1M). The reaction mixture was stirred at room temperature for 3 h, then EtOAc and water were added. The layers were

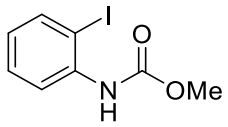
[91] Pisaneschi, F.; Sejberg, J. J. P.; Blain, C.; Ng, W. H.; Aboagye, E. O.; Spivey, A. C. *Synlett* **2011**, 241–244.

separated, and the aqueous layer was extracted twice with EtOAc. Then, the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by filtration through a plug of SiO_2, eluting with 30% EtOAc in Hexanes afforded 1.4 g (98%) of **32** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.77 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.47–7.31 (m, 6H), 7.04 (br s, 1H), 6.82 (ddd, *J* = 7.9, 7.3, 1.6 Hz, 1H), 5.24 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.3, 139.0, 138.4, 135.9, 129.4, 128.7, 128.53, 128.51, 125.3, 120.5, 89.1, 67.4.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[92]



Methyl (2-iodophenyl)carbamate (36):

In a 25 mL flask, 2-iodoaniline (880 mg, 4.0 mmol, 1.0 equiv) was dissolved in pyridine (8 mL, 0.5 mL) at –10 °C then methyl chloroformate (0.49 mL, 6.3 mmol, 1.6 equiv) was added. The reaction mixture was warmed to room temperature overnight, then EtOAc and water were added. The layers were separated, and the aqueous layer was extracted twice with EtOAc. Then, the

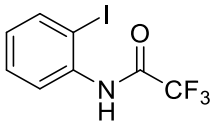
[92] Nieman, J. A.; Ennis, M. D. *J. Org. Chem.* **2001**, *66*, 2175–2177.

combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification by filtration through a plug of SiO_2, eluting with 30% EtOAc in Hexanes afforded 974 mg (88%) of **36** as a light tan solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.7 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.36 (ddd, *J* = 8.4, 7.4, 1.4 Hz, 1H), 6.99 (br s, 1H), 6.87–6.77 (m, 1H), 3.83 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 138.9, 138.4, 129.3, 125.2, 120.5, 89.1, 52.6.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[93]



2,2,2-Trifluoro-*N*-(2-iodophenyl)acetamide (39):

In a 50 mL flask, 2-iodoaniline (2.19 g, 10.0 mmol, 1.0 equiv) and triethylamine (1.53 mL, 11.0 mmol, 1.1 equiv) were dissolved in THF (12 mL, 0.8 M), and the reaction mixture was cooled to –15 °C. Trifluoroacetic anhydride (1.53 mL, 11.0 mmol, 1.1 equiv) was added dropwise and stirred at –15 °C for 30 min. The reaction mixture was then warmed to room temperature overnight, then EtOAc and water were added. The layers were separated, and the aqueous layer

[93] Martínez-Estíbalez, U.; García-Calvo, O.; Ortiz-de-Elguea, V.; Sotomayor, N.; Lete, E. *Eur. J. Org. Chem.* **2013**, 3013–3022.

was extracted twice with EtOAc. Then, the combined organic layers were washed with brine, dried over $NaSO_4$, and concentrated. Purification by filtration through a plug of SiO_2, eluting with 10% EtOAc in Hexanes afforded 2.61 g (83%) of **39** as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 8.22 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.43 (ddd, *J* = 8.5, 7.5, 1.4 Hz, 1H), 6.99 (app td, *J* = 7.7, 1.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.82 (q, *J* = 37.7 Hz), 139.2, 135.7, 129.6, 127.9, 122.2, 115.65 (q, *J* = 289 Hz), 90.4.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[94]

***tert*-Butyl(hex-5-en-2-yn-1-yloxy)dimethylsilane (54):**

In a 20 mL vial, 5-hexyen-2-yn-1-ol (1.24 mL, 12 mmol, 1.0 equiv), *tert*-butyldimethylsilyl chloride (2.4 g, 15.6 mmol, 1.2 equiv), and imidazole (2.45 g, 36 mmol, 3.0 equiv) were dissolved in DMF (12 mL, 1 M) and stirred room temperature overnight. The reaction mixture was filtered through a plug of silica, using EtOAc to elute, and concentrated. Column

[94] Cironi, P.; Tulla-Puche, J.; Barany, G.; Albericio, F.; Álvarez, M. *Org. Lett.* **2004**, *6*, 1405–1408.

chromatography (Biotage 50g HP-sil, 0–6% EtOAc in hexanes) afforded 1.29 g (51%) of **54** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87–5.75 (m, 1H), 5.32 (dddd, *J* = 17.0, 3.5, 1.9, 0.7 Hz, 1H), 5.11 (app dqd, *J* = 10.1, 1.7, 0.6 Hz, 1H), 4.34 (app tt, *J* = 2.3, 0.7 Hz, 2H), 3.00 (app tdt, *J* = 3.9, 2.1, 1.1 Hz, 2H), 0.92 (d, *J* = 0.7 Hz, 9H), 0.13 (d, *J* = 0.6 Hz, 6H).

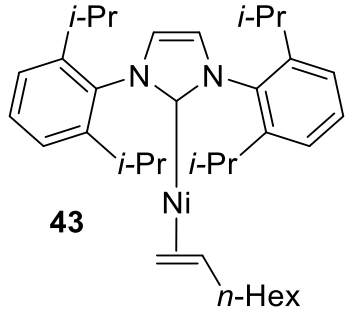
^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 132.4, 116.1, 81.8, 81.0, 51.9, 25.9, 23.1, 18.3, –5.1.

IR (ATR, cm^{-1}) 2957, 2930, 2889, 2858, 1473, 1420, 1370, 1254, 1140, 1079, 916, 835, 776.

HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{22}OSi$, 211.1513; found, 211.1527.

Mechanistic Experiments

A) [1]H NMR Studies



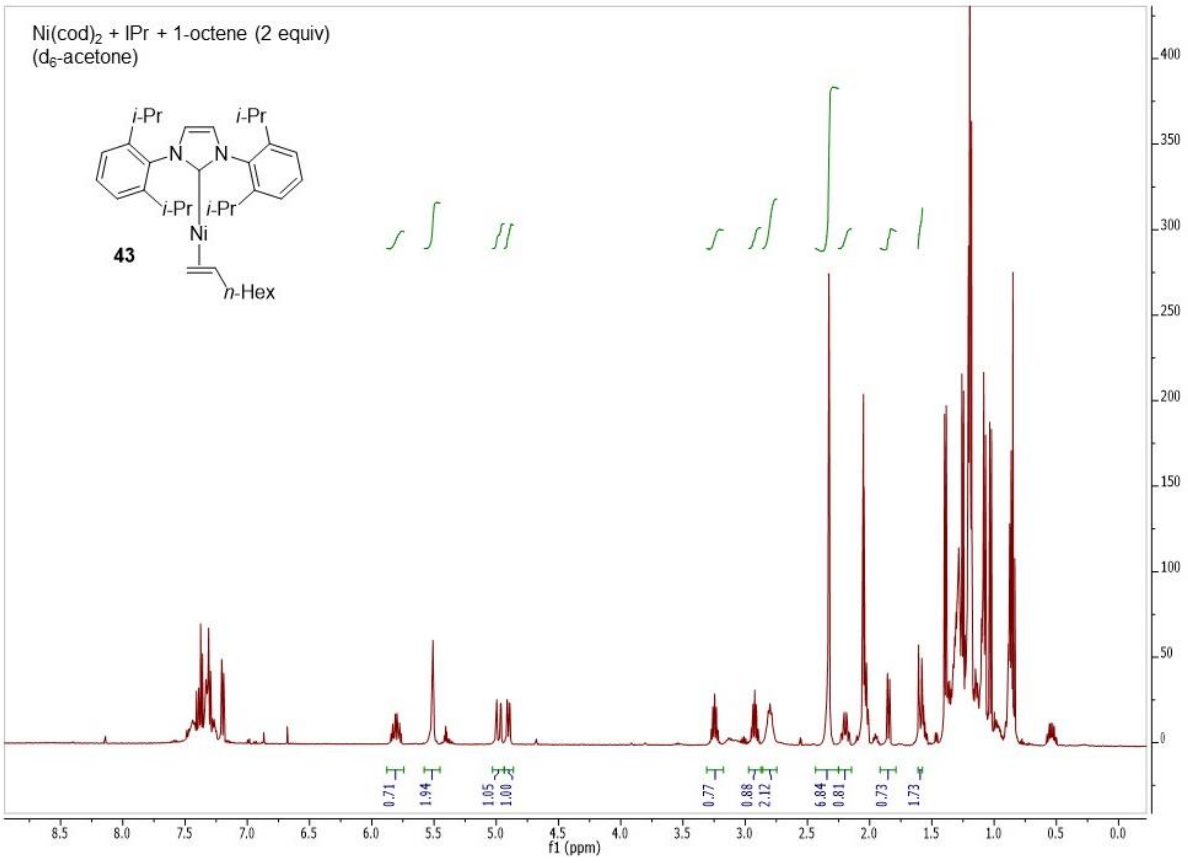
43

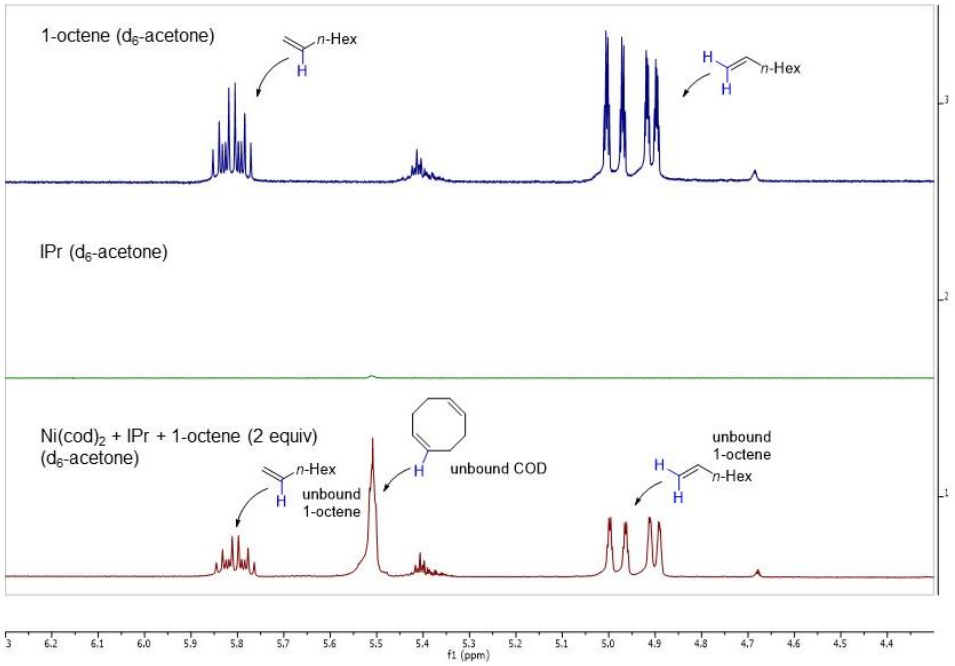
Preparation of 43: $Ni(cod)_2$ (2.1 mg, 0.0076 mmol, 1.0 equiv), IPr (3.0 mg, 0.0077 mmol, 1.0 equiv), 1-octene (2.5 μL, 0.016 mmol, 2.1 equiv), and d_6-acetone (700 μL, 0.01 M) were added to a dry NMR tube in a nitrogen-filled glovebox. The tube was then capped and taped shut, the vial was removed from the glovebox, and put on a nutating mixer for 2 h, until all $Ni(cod)_2$ had gone into solution.

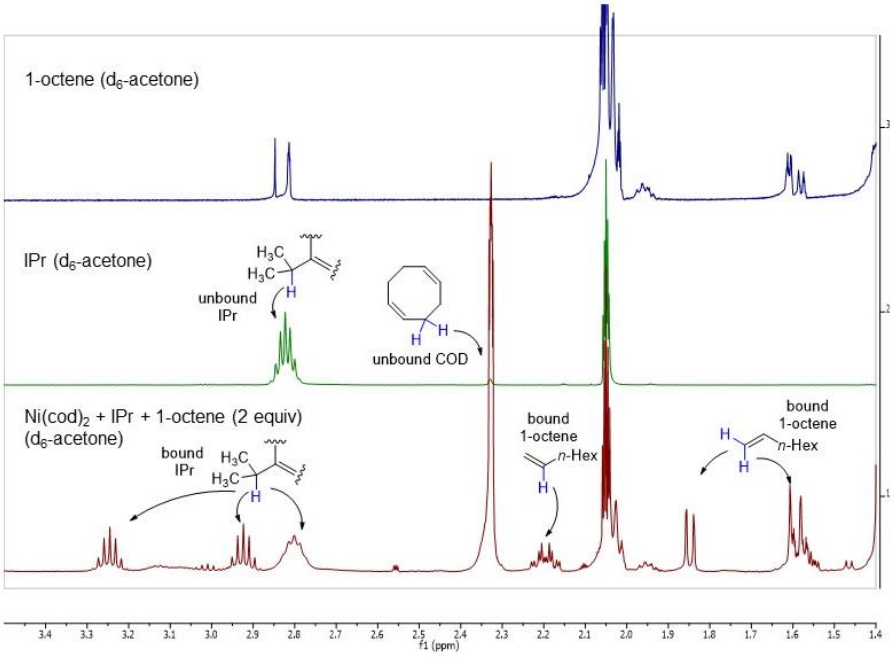
The resulting ^{1}H NMR spectrum (Figure 7) was consistent with the structure **43** with one molecule of 1-octene bound to Ni, and complete displacement of COD as a ligand.

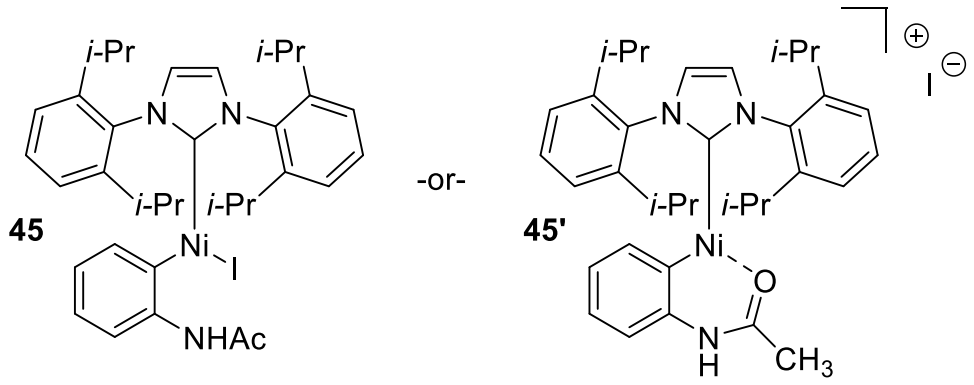
^{1}H NMR (500 MHz, acetone-d_6) δ 7.55–7.23 (m, 7H), 7.20 (dd, *J* = 7.6, 1.5 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.51 (ddd, *J* = 3.5, 2.4, 1.4 Hz, 2H), 4.99 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.91 (ddt, *J* = 10.2, 2.4, 1.2 Hz, 1H), 3.25 (hept, *J* = 7.2 Hz, 1H), 2.93 (hept, *J* = 6.5 Hz, 1H), 2.88–2.75 (m, *J* = 5.9, 5.4 Hz, 2H), 2.35–2.32 (m, 6H), 2.20 (dtd, *J* = 12.4, 9.0, 3.3 Hz, 1H), 1.85 (dd, *J* = 9.1, 1.0 Hz, 1H), 1.63–1.56 (m, 2H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.38–1.10 (m, 38H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.91–0.83 (m, 8H).

Figure 7. ^{1}H NMR spectra of **43**.




1-octene (d_6-acetone)
n-Hex
H
H
n-Hex
IPr (d_6-acetone)
Ni(cod)$_2$ + IPr + 1-octene (2 equiv)
(d_6-acetone)
n-Hex
H
unbound
1-octene
H
unbound COD
unbound
1-octene
H
H
n-Hex
f1 (ppm)


1-octene (d_6-acetone)
IPr (d_6-acetone)
H_3C
H_3C
H
unbound
IPr
H
H
unbound COD
Ni(cod)$_2$ + IPr + 1-octene (2 equiv)
(d_6-acetone)
bound
IPr
H_3C
H_3C
H
bound
1-octene
n-Hex
H
bound
1-octene
H
H
n-Hex
f1 (ppm)

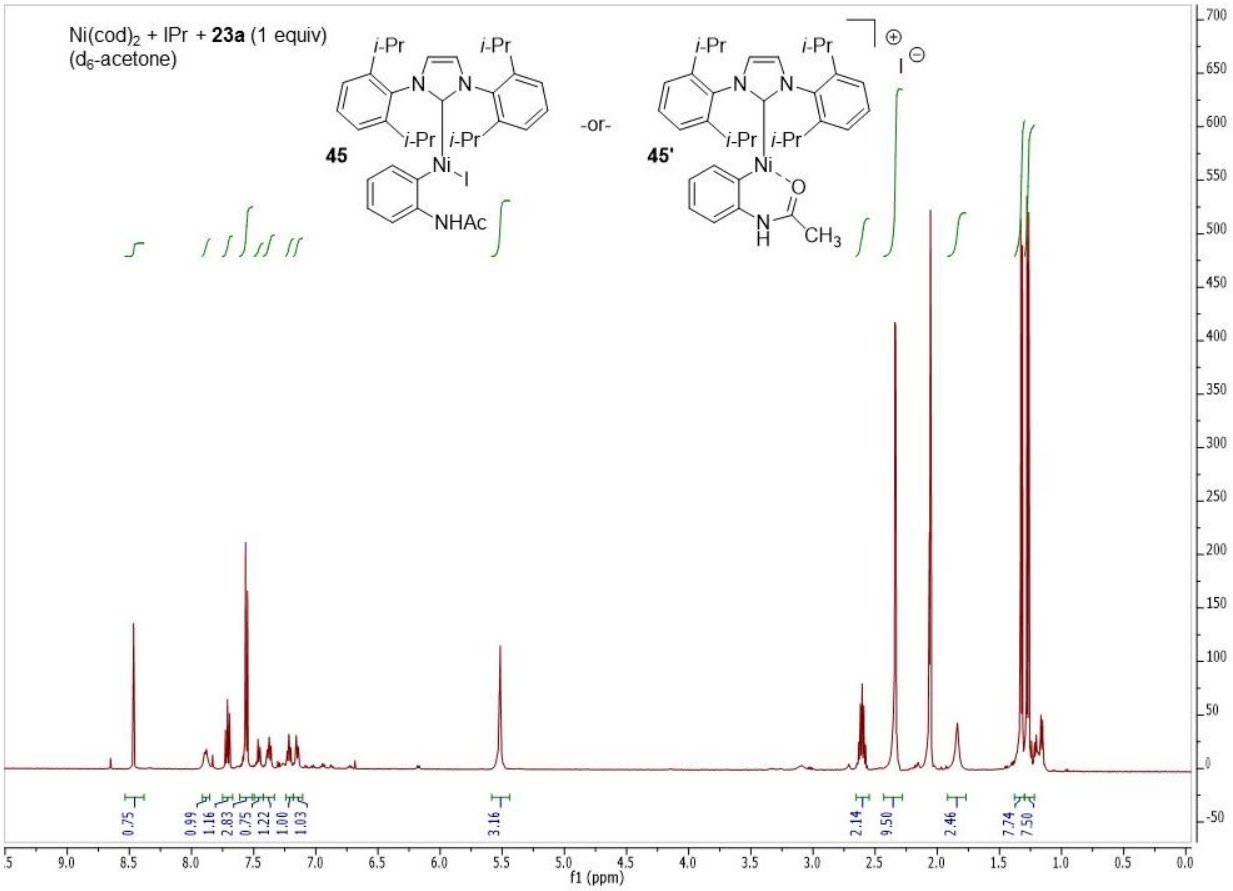


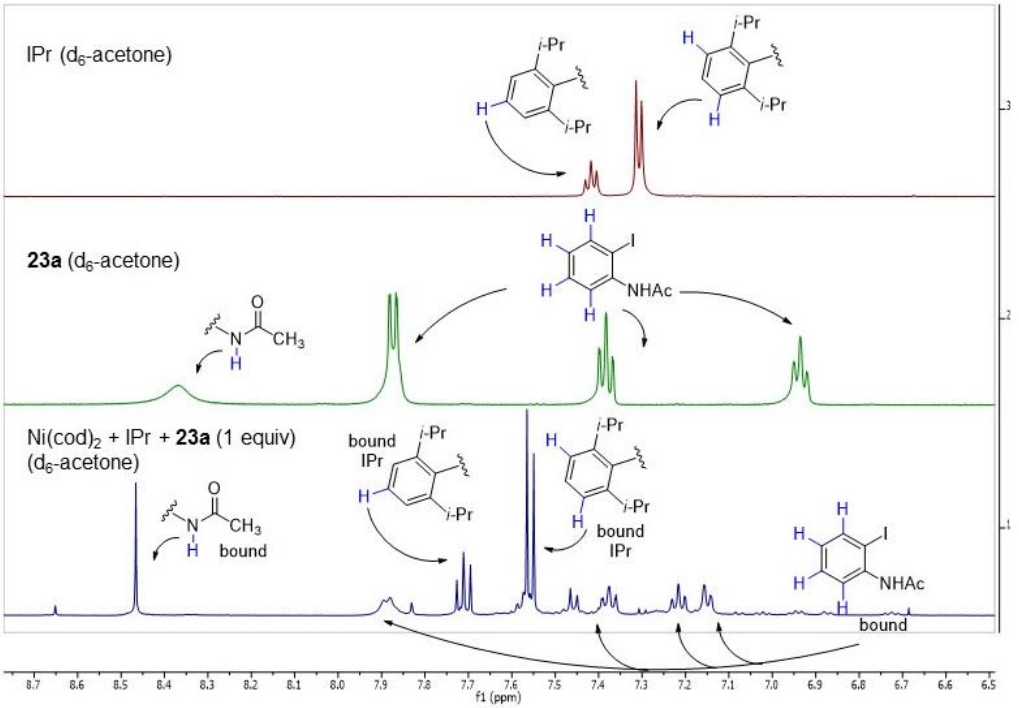
Preparation of 45: $Ni(cod)_2$ (2.1 mg, 0.0076 mmol, 1.0 equiv), IPr (3.0 mg, 0.0077 mmol, 1.0 equiv), **23a** (2.0 mg, 0.0077 mmol, 1.0 equiv), and d_6-acetone (700 μL, 0.01 M) were added to a dry NMR tube in a nitrogen-filled glovebox. The tube was then capped and taped shut, removed from the glovebox, and put on a nutating mixer for 16 h.

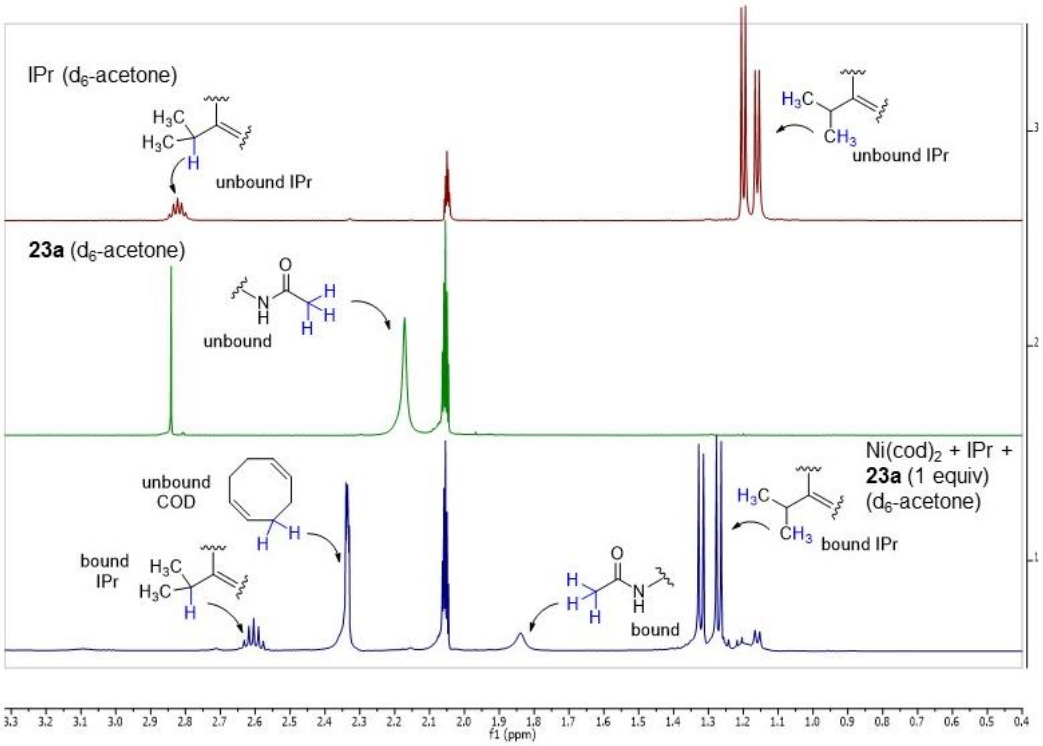
The resulting ^{1}H NMR spectrum (Figure 8) was consistent with the structure **45** or **45'** oxidative addition complex with complete reaction of **23a** as well as crystal structure data of **45'** (Figure 10).

^{1}H NMR (500 MHz, acetone-d_6) δ 8.47 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.71 (ddd, *J* = 8.1, 7.5, 0.5 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.42–7.32 (m, 1H), 7.22 (td, *J* = 7.5, 1.2 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.52 (dddt, *J* = 3.0, 2.4, 1.7, 0.7 Hz, 3H), 2.60 (hept, *J* = 7.1 Hz, 2H), 2.35–2.32 (m, 10H), 1.84 (br s, 2H), 1.32 (d, *J* = 6.8 Hz, 9H), 1.27 (d, *J* = 6.9 Hz, 9H).

Figure 8. ^{1}H NMR data for the formation of **45**.



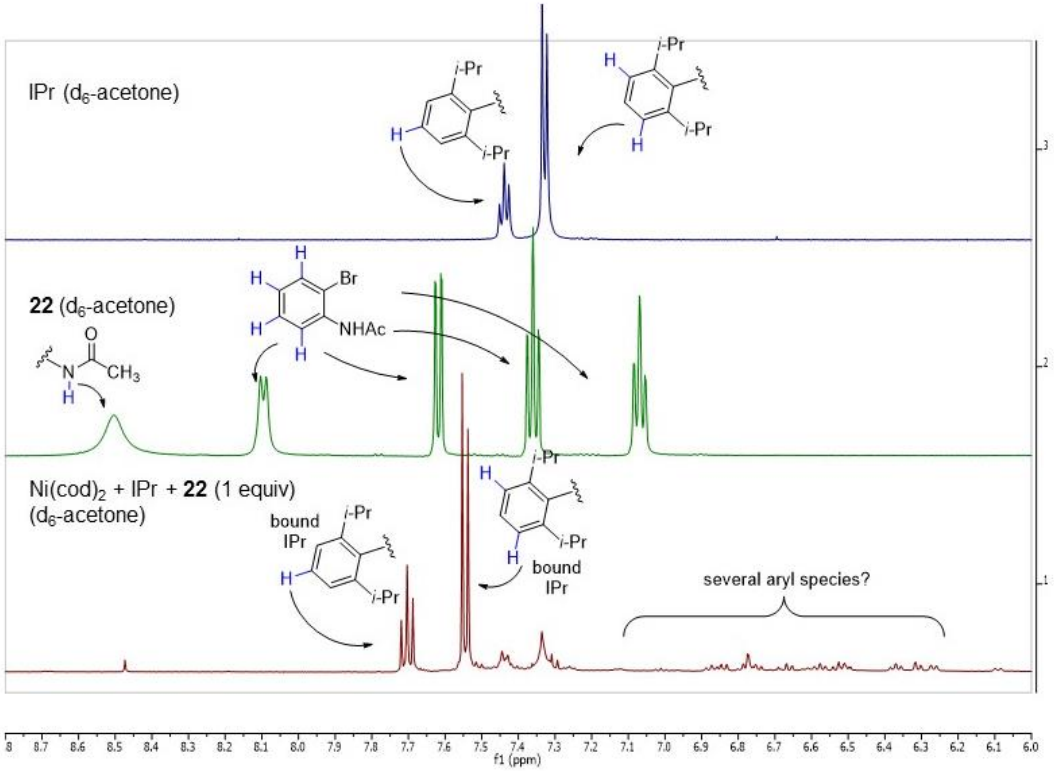

IPr (d6-acetone)
23a (d6-acetone)
Ni(cod)2 + IPr + 23a (1 equiv)
(d6-acetone)
bound
IPr
NHAc
f1 (ppm)


IPr (d6-acetone)
unbound IPr
23a (d6-acetone)
unbound
unbound
COD
bound
IPr
bound
Ni(cod)2 + IPr +
23a (1 equiv)
(d6-acetone)
bound IPr
f1 (ppm)

Oxidative Addition of ArBr (22): $Ni(cod)_2$ (2.1 mg, 0.0076 mmol, 1.0 equiv), IPr (3.0 mg, 0.0077 mmol, 1.0 equiv), **22** (1.6 mg, 0.0077 mmol, 1.0 equiv), and d_6-acetone (700 μL, 0.01 M) were added to a dry NMR tube in a nitrogen-filled glovebox. The tube was then capped and taped shut, removed from the glovebox, and put on a nutating mixer for 16 h.

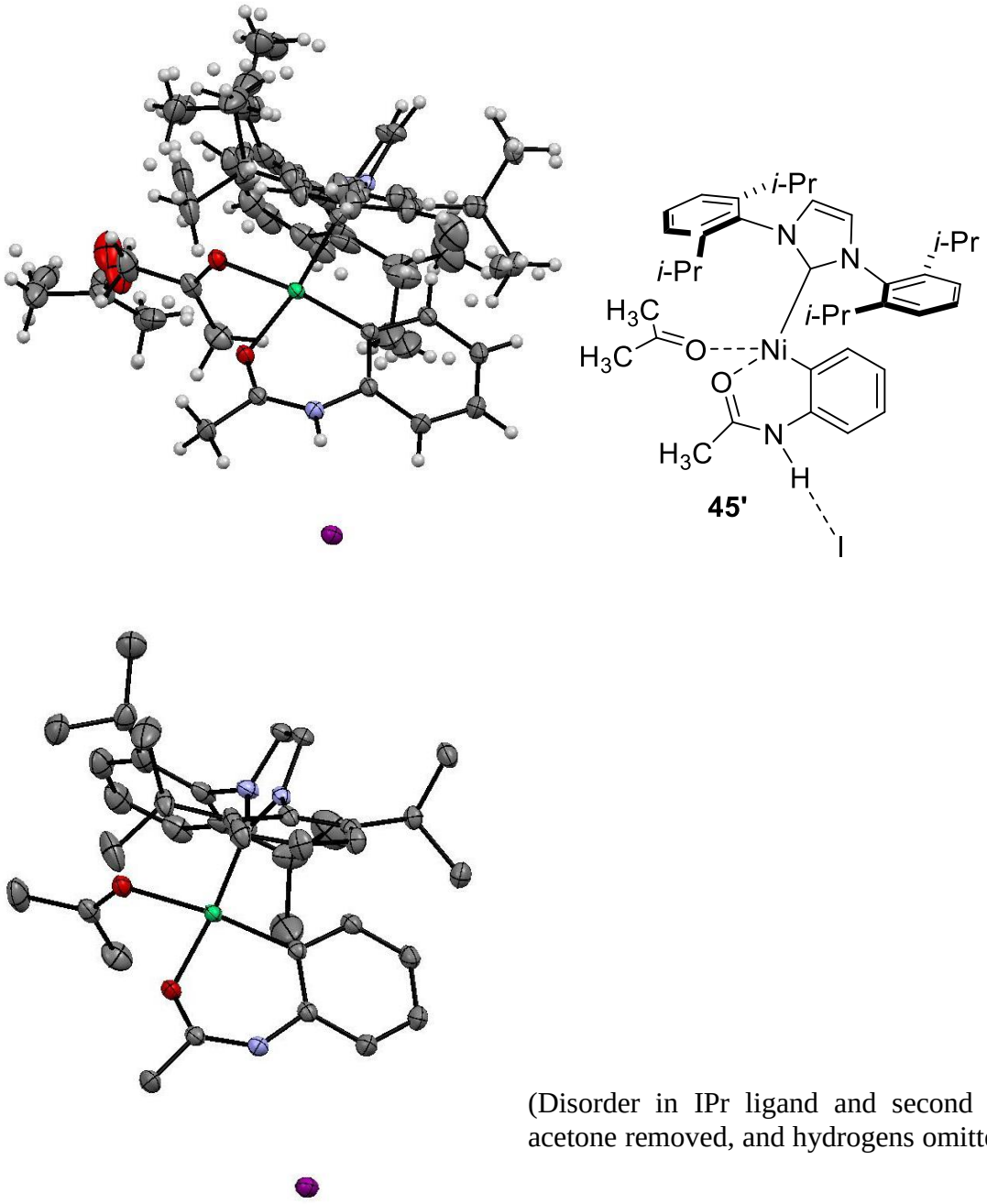
The resulting ^{1}H NMR spectrum (Figure 9), unlike that for the oxidative addition complex of the corresponding ArI (**23a**) (Figure 8) did not show clean formation of one species in solution. Complete consumption of **22** occurred, but a complex series of small signals in the aromatic region resulted. A similar complex spectrum was observed when 1-octene was added. The presence of multiple species in solution is also corroborated by the complex CV spectrum that also results (Figure 9).

Figure 9. ^{1}H NMR data for oxidative addition of ArBr **22**.



B) Crystal Structures

Figure 10. Thermal ellipsoid depiction of oxidative addition complex **45'**.



(Disorder in IPr ligand and second molecule of acetone removed, and hydrogens omitted for clarity)

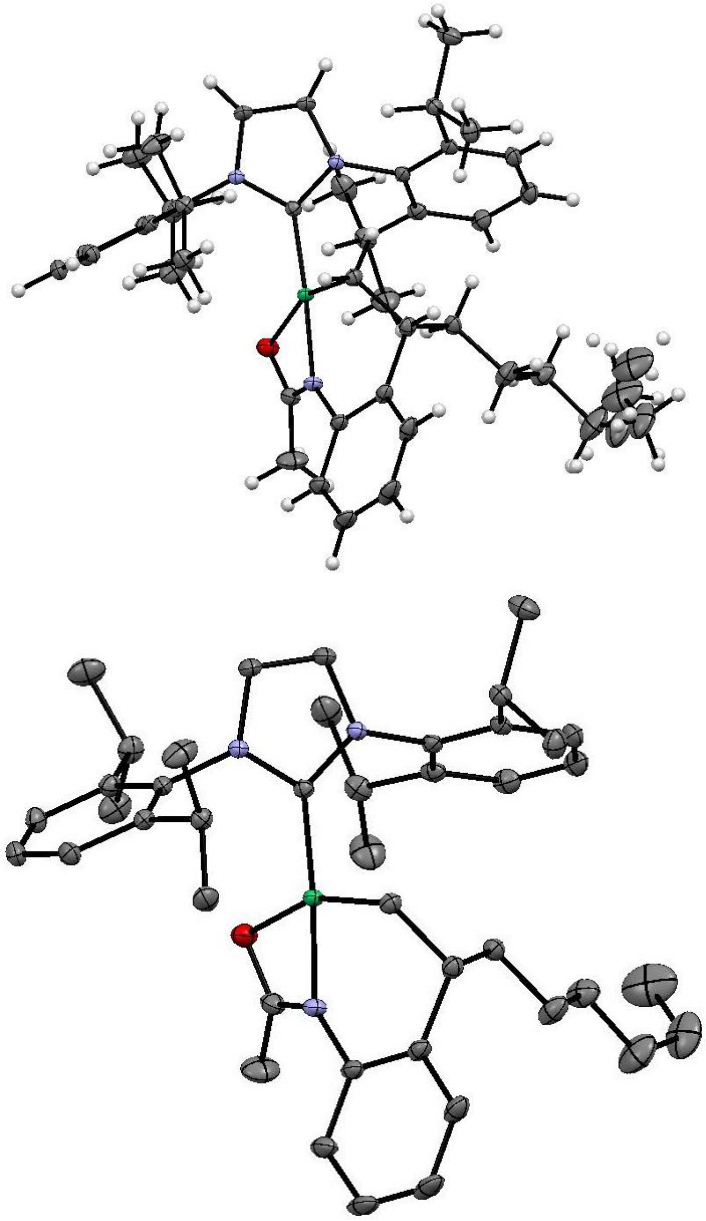
Crystals were grown directly by vapor diffusion with pentane at –20 °C under inert atmosphere from a solution of $Ni(cod)_2$ (25.6 mg, 0.093 mmol, 1.0 equiv), IPr (39.6 mg, 0.10 mmol, 1.1 equiv), 1-octene (34 µL, 0.21 mmol, 2.0 equiv), **23a** (24.2 mg, 0.093 mmol, 1.0 equiv), Et_3N (13 µL, and acetone (1.0 mL).

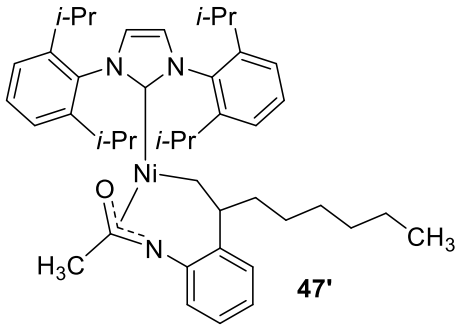
The complete data for this structure are on file with the CCDC under entry 1403188

Table 7. Crystal data and structure refinement for compound **45'**.

Identification code	14042	
Empirical formula	$C_{41}H_{56}INiO_3$	
Formula weight	824.49	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.9159(2) Å	α= 68.5985(9)°.
	b = 13.6522(3) Å	β= 77.8452(10)°.
	c = 13.8179(3) Å	γ = 82.4777(10)°.
Volume	2042.34(7) Å^3	
Z	2	
Density (calculated)	1.341 Mg/m^3	
Absorption coefficient	1.269 mm^{-1}	
F(000)	856	
Crystal size	0.280 x 0.175 x 0.080 mm^3	
Theta range for data collection	1.605 to 29.574°.	
Index ranges	-16<=h<=16, -18<=k<=18, -19<=l<=19	
Reflections collected	99315	
Independent reflections	11448 [R_{int} = 0.0346]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7462 and 0.6859	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11448 / 2133 / 579	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2σ(I)]	R1 = 0.0251, wR2 = 0.0593	
R indices (all data)	R1 = 0.0311, wR2 = 0.0631	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.083 and -0.772 e.Å^{-3}	

Figure 11. Thermal ellipsoid depiction of migratory insertion complex **47'** from aryl bromide **22**.





47'

(Disorder in hexyl sidechain removed, and hydrogens omitted for clarity)

Crystals were grown directly by vapor diffusion with pentane at –20 °C under inert atmosphere from a solution of $Ni(cod)_2$ (25.6 mg, 0.093 mmol, 1.0 equiv), IPr (39.6 mg, 0.10 mmol, 1.1 equiv), 1-octene (34 μL, 0.21 mmol, 2.0 equiv), **22** (20.0 mg, 0.093 mmol, 1.0 equiv), Et_3N (13 μL, and acetone (1.0 mL).

The complete data for this structure are on file with the CCDC under entry 1403189.

Table 8. Crystal data and structure refinement for compound **47'**.

Identification code	X15054	
Empirical formula	C_{43} H_{59} N_3 Ni O	
Formula weight	692.64	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	*a* = 11.6854(8) Å	α= 91.6260(19)°.
	b = 13.0659(9) Å	β= 109.3194(17)°.
	c = 14.9978(10) Å	γ= 114.9560(18)°.
Volume	1921.0(2) $Å^3$	
Z	2	
Density (calculated)	1.197 Mg/m^3	
Absorption coefficient	0.541 mm^{-1}	
F(000)	748	
Crystal size	0.390 x 0.300 x 0.290 mm^3	
Theta range for data collection	1.467 to 30.999°.	
Index ranges	-16<=*h*<=16, -18<=*k*<=18, -21<=*l*<=21	
Reflections collected	79302	
Independent reflections	12233 [R_{int} = 0.0364]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12233 / 85 / 451	
Goodness-of-fit on F^2	1.037	
Final *R* indices [I>2σ(I)]	*R*1 = 0.0327, *wR*2 = 0.0864	
R indices (all data)	*R*1 = 0.0356, *wR*2 = 0.0881	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.764 and -0.740 $e.Å^{-3}$	

C) Cyclic Voltammetry Studies

Experimental Procedures:

Complexes **43** and **45** were prepared and studied in situ as in section A) above.

For **43**, $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 1.0 equiv), IPr (38.9 mg, 0.1 mmol, 1.0 equiv), 1-octene (16 μL, 0.1 mmol, 1.0 equiv), and acetone (20 mL, 0.005 M) were stirred at room temperature in a nitrogen-filled glovebox. After 2 h, NBu_4PF_6 (38.7 mg, 0.1 mmol, 1.0 equiv) was added, and the mixture was transferred to an electrochemical cell (also in a nitrogen-filled glovebox). Cyclic voltammetry was them performed using a three-electrode cell with a 3 mm glassy carbon working electrode, a Ag/AgCl reference electrode, and a Pt wire counter electrode. Scans were taken at 10 mV/s starting from –1.5V to +0.2V in the positive direction. (Note: adjustment of the scan rate did not produce reversible behavior) (Figure 12a).

For **45**, $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 1.0 equiv), IPr (38.9 mg, 0.1 mmol, 1.0 equiv), **23a** (26.1 mg, 0.1 mmol, 1.0 equiv), and acetone (20 mL, 0.005 M) were stirred at room temperature in a nitrogen-filled glovebox. After 16 h, NBu_4PF_6 (38.7 mg, 0.1 mmol, 1.0 equiv) was added, and the mixture was transferred to an electrochemical cell (also in a nitrogen-filled glovebox). Cyclic voltammetry was them performed using a three-electrode cell with a 3 mm glassy carbon working electrode, a Ag/AgCl reference electrode, and a Pt wire counter electrode. Scans were taken at 10 mV/s starting from –1.0V to +1.5V in the positive direction. (Note: at 100 mV/s, the Ni(III/II) oxidation was irreversible, while the lower scan rate of 10mV/s was needed for **45** to demonstrate reversible behavior) (Figure 12b).

We also obtained a cyclic voltammogram of Et_3N in acetone given the possibility of it acting as a single electron oxidation transfer relay between the photocatalyst and the Ni(II) intermediate.

Et_3N (14 μL, 0.1 mmol, 1.0 equiv), NBu_4PF_6 (38.7 mg, 0.1 mmol, 1.0 equiv), and acetone (20 mL, 0.005 M) mixed and the solution was transferred to an electrochemical cell in a nitrogen-filled glovebox. Cyclic voltammetry was them performed using a three-electrode cell with a 3 mm glassy carbon working electrode, a Ag/AgCl reference electrode, and a Pt wire counter electrode. Scans were taken at 100 mV/s starting from –1.0V to +2.0V in the positive direction (Figure 12c).

The spectra were then referenced against Fc/Fc^+. Significant overlap occurred between this redox couple and **43** and **45**, while Et_3N did not have significant overlap, the $E_{1/2}$ of the Fc/Fc^+ couple was measured and referenced internally for Et_3N (Fc/Fc^+ = +0.52V vs. Ag/AgCl, see below) and the spectra of **43** and **45** were referenced to ferrocene externally. These values can then be converted to values vs. the standard calomel electrode (SCE) to compare with the literature values for the relevant oxidation states of $Ru(bpy)_3$ by adding 0.38V.[95]

Since both single electron oxidations of **45** were reversible, $E_{1/2}$ was calculated by the standard method: $E_{1/2} = (E_p – E_c)/2$. [96] The other potentials of interest were irreversible, so $E_{1/2}$ could not be directly measured since by definition, a half cell reduction potential requires a reversible process. Alongside the measurement of E_p, or oxidation peak potential, for purposes of estimation of redox feasibility, I have shown $E_{p/2}$, or the voltage at half the current peak height (E_p). In an ideal reversible cyclic voltammogram, $E_{1/2} = E_{p/2} \pm 0.028V/n$ where n is the number of moles of electrons transferred. For an irreversible process, this measurement is not ideal, since the location of E_p will also vary with voltage sweep rate, by about 0.03V per order of magnitude change in

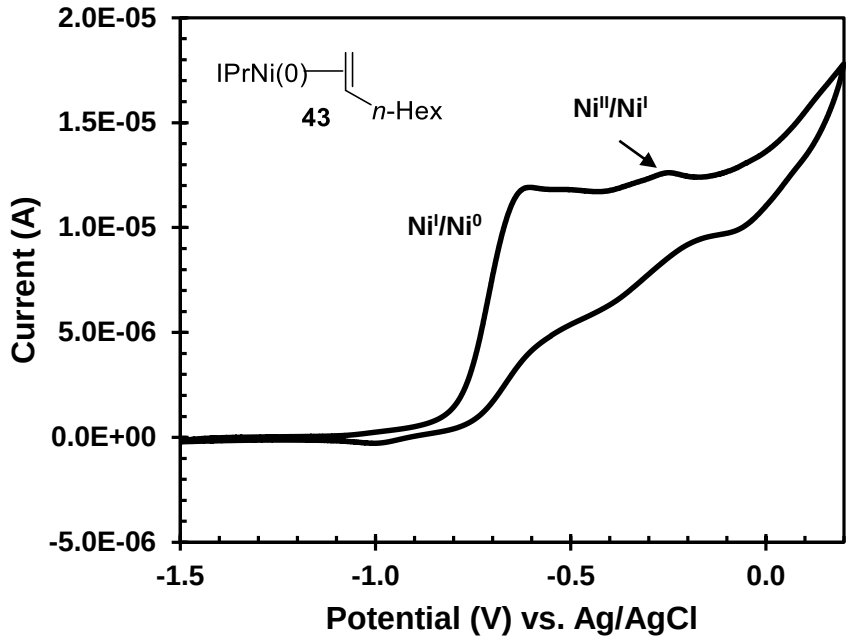
[95] Pavlishchuk, V. V.; Addison, A. W. *Inorg. Chim. Acta* **2000**, *298*, 97–102.
[96] a) Pletcher, D.; Greef, R.; Peat, R.; Peter, L. M.; Robinson, J. *Instrumental Methods in Electrochemistry*, Horwood: Chichester, 2001. b) Scholz, F. (Ed.) *Electroanalytical Methods*, Springer: Berlin, 2002. c) Mabbott, G. A. *J. Chem. Ed.* **1983**, *60*, 697–702. d) Evans, D. H.; O'Connell, K. M.; Petersen, R. A.; Kelly, M. J. *J. Chem. Ed.* **1983**, *60*, 290–293.

sweep rate. Therefore, using this estimation must be used with caution, and a large error should be expected.

Finally, the oxidative addition of aryl bromide **22** was also studied. $Ni(cod)_2$ (27.5 mg, 0.1 mmol, 1.0 equiv), IPr (38.9 mg, 0.1 mmol, 1.0 equiv), **22** (21.4 mg, 0.1 mmol, 1.0 equiv), and acetone (20 mL, 0.005 M) were stirred at room temperature in a nitrogen-filled glovebox. After 16 h, NBu_4PF_6 (38.7 mg, 0.1 mmol, 1.0 equiv) was added, and the mixture was transferred to an electrochemical cell (also in a nitrogen-filled glovebox). Cyclic voltammetry was them performed using a three-electrode cell with a 3 mm glassy carbon working electrode, a Ag/AgCl reference electrode, and a Pt wire counter electrode. Scans were taken at 10 mV/s starting from +0.2V to +1.5V in the positive direction (Figure 12d). Consistent with the ^1H NMR studies (Figure 9), a complex cyclic voltammogram was observed, suggesting the presence of multiple redox-active species in solution.

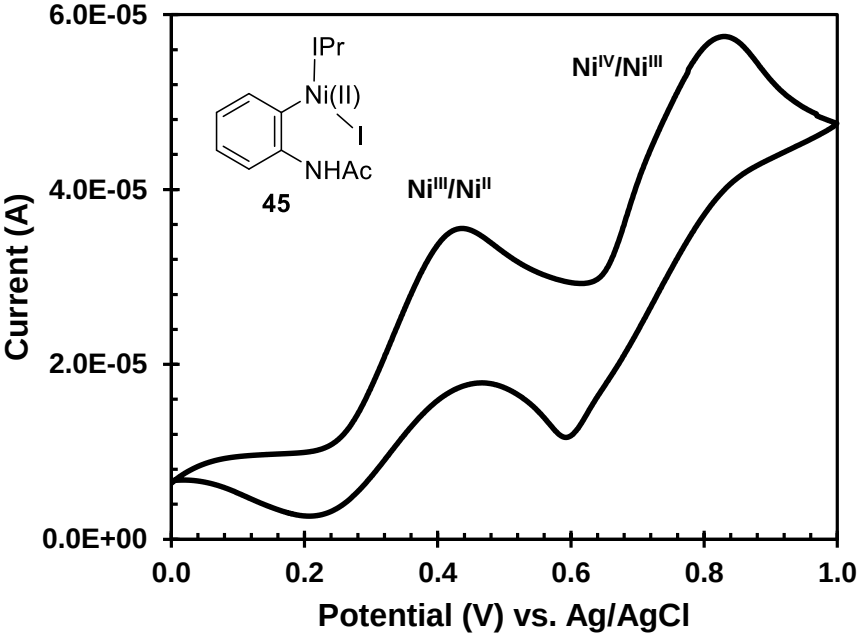
Figure 12. Cyclic voltammograms and calculated reduction potentials.

a)



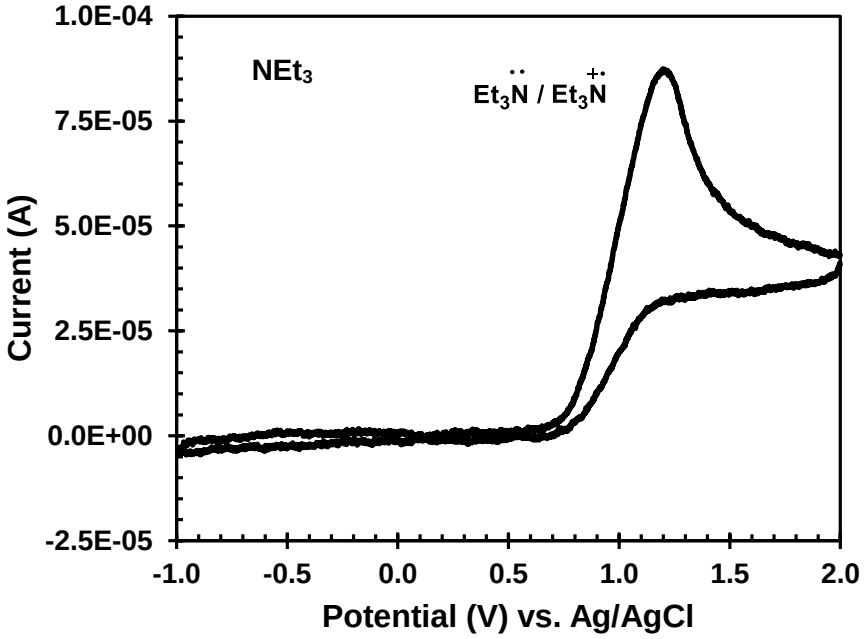
43: $E_p^{I/0}$ = –0.60V vs. Ag/AgCl; –1.12 V vs. Fc/Fc^+; ~ –0.74V vs. SCE
$E_{p/2}^{I/0}$ = –0.72V vs. Ag/AgCl; –1.24V vs. Fc/Fc^+; ~ –0.86V vs. SCE

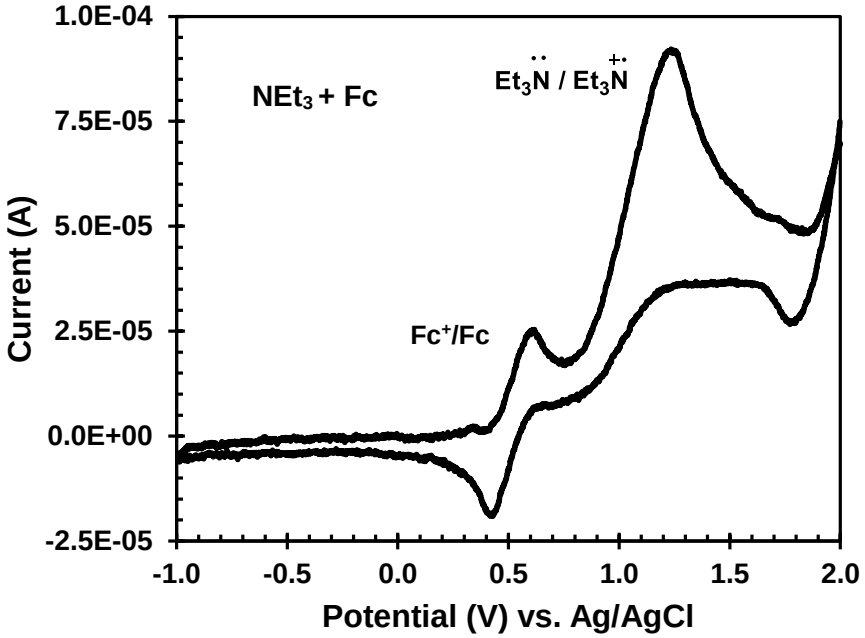
b)



45: $E_{1/2}^{III/II}$ = +0.32V vs. Ag/AgCl; –0.20V vs. Fc/Fc^+; ~ +0.18 V vs. SCE
Additionally, $E_{1/2}^{IV/III}$ = +0.71V vs. Ag/AgCl; +0.19V vs. Fc/Fc^+; ~ +0.57V vs. SCE

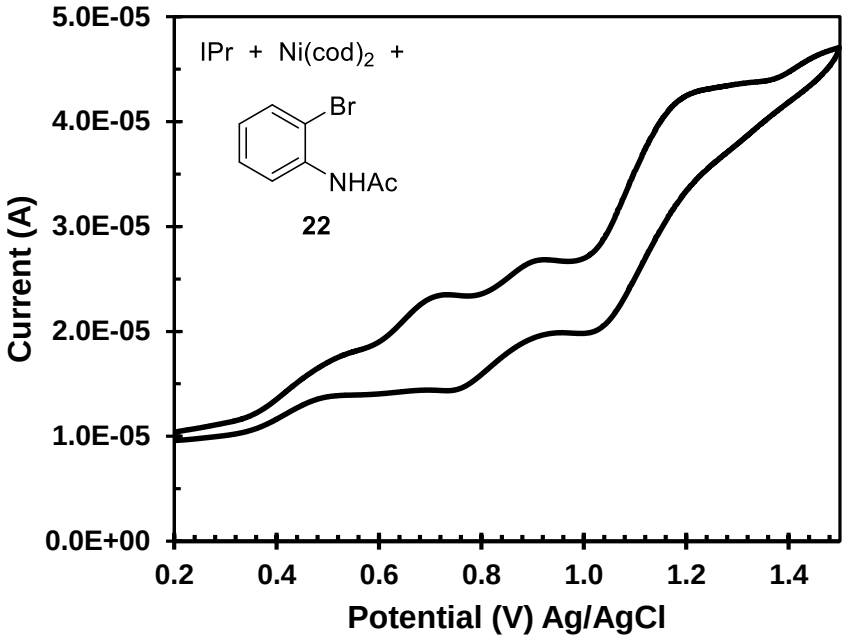
c)





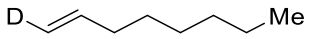
Et3N: E_p^{red} = +1.21V vs. Ag/AgCl; +0.69V vs. Fc/Fc^+; ~ 1.07 V vs. SCE
$E_{p/2}^{red}$= +0.97V vs. Ag/AgCl; +0.45V vs. Fc/Fc^+; ~ +0.83V vs. SCE

d)



[Complex mixture of compounds formed.]

D) Deuterium Labeling Studies



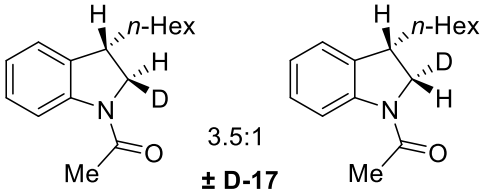
Preparation of (49):[97] In an oven-dried 50 mL flask, Schwartz's reagent (4.82 g, 18.7 mmol, 1.3 equiv) was weighed out in a nitrogen-filled glovebox. The flask was removed from glovebox and cooled to –10 °C before adding CH_2Cl_2 (11 mL, 1.3 M)[98] followed by 1-octyne (2.13 mL, 14.4 mmol, 1.0 equiv). The reaction mixture was stirred at –10 °C for 20 min, warmed to 0 °C for 10 min and rt for 5 min, upon which the reaction mixture turned dark yellow. It was then cooled to 0 °C, D_2O (3 mL, 166 mmol, 12 equiv) was added, stirring vigorously, and the reaction mixture was warmed to rt for 20 min. CH_2Cl_2 and H_2O were added, and the layers separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated carefully under reduced pressure (~150 torr). The resulting mixture was then isolated by Kugelrohr distillation (110 °C, 760 torr), and then again carefully concentrated by rotavap (~110 torr) until all CH_2Cl_2 had been removed (monitoring by ^{1}H NMR), to yield 521 mg (32%) **49** as a clear liquid, D-incorporation ~98:2.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.83 (dtt, *J* = 16.8, 6.7, 1.5 Hz, 1H), 4.99 (dt, *J* = 17.1, 1.6 Hz, 1H), 2.08–2.00 (m, 2H), 1.43–1.35 (m, 2H), 1.35–1.23 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 139.1, 113.8 (t, *J* = 24.0 Hz), 33.8 (t, *J* = 1.7 Hz), 31.8, 28.94, 28.85, 22.6, 14.1.

[97] Lloyd-Jones, G. C.; Robinson, A. J.; Lefort, L.; de Vries, J. G. *Chem.—Eur. J.* **2010**, *16*, 9449–9452.
[98] Care must be taken when using CH_2Cl_2 as a solvent, since Schwartz's reagent is known to exothermically decompose in CH_2Cl_2 after extended contact times (~1 h at rt): Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

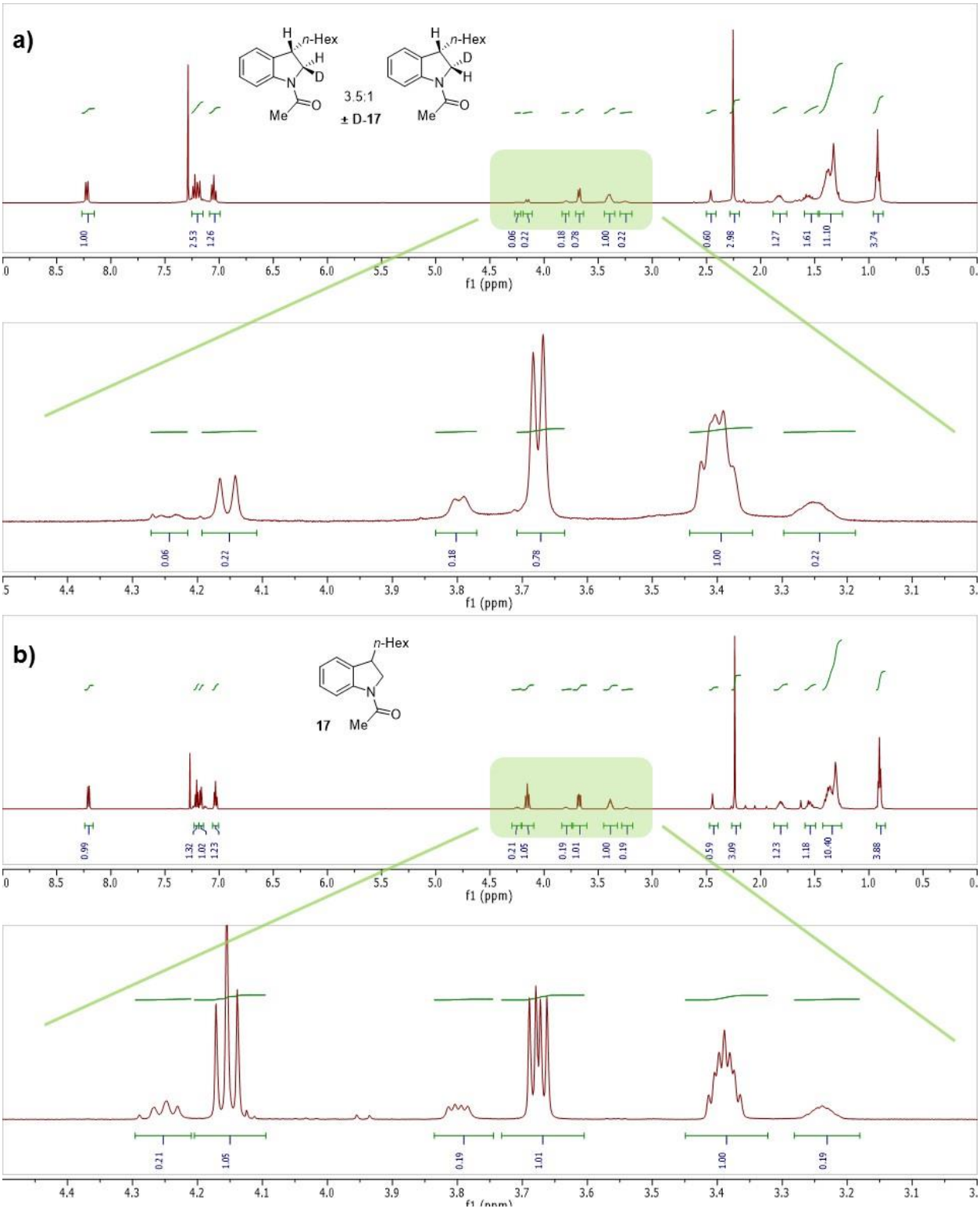
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[99]



1-(3-hexylindolin-1-yl)ethan-1-one (D-17a): Following general procedure **A**, $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), IPr (31.1 mg, 0.08 mmol, 0.16 equiv) acetone (2.3 mL, 0.22 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), *trans*-1-D-1-octene (157 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide (130.5 mg, 0.50 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a short silica plug with EtOAc as the eluent and concentrated. Column chromatography (Biotage 25g HP-sil, 5–40 % EtOAc in hexanes) afforded 107.2 mg (87%) of **D-17a** as a yellow oil (selectivity ratio of indoline **17a** to [Σ Heck/isomerized Heck/etc.] 26.5:1, determined by GC analysis). ^{1}H NMR below (Figure 13). The ratio of D-incorporation *trans* to the *n*-Hexyl group compared to *cis* to the *n*-Hexyl group (positions determined by NOE-DIFF experiment) was 3.5:1.

[99] Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10693.

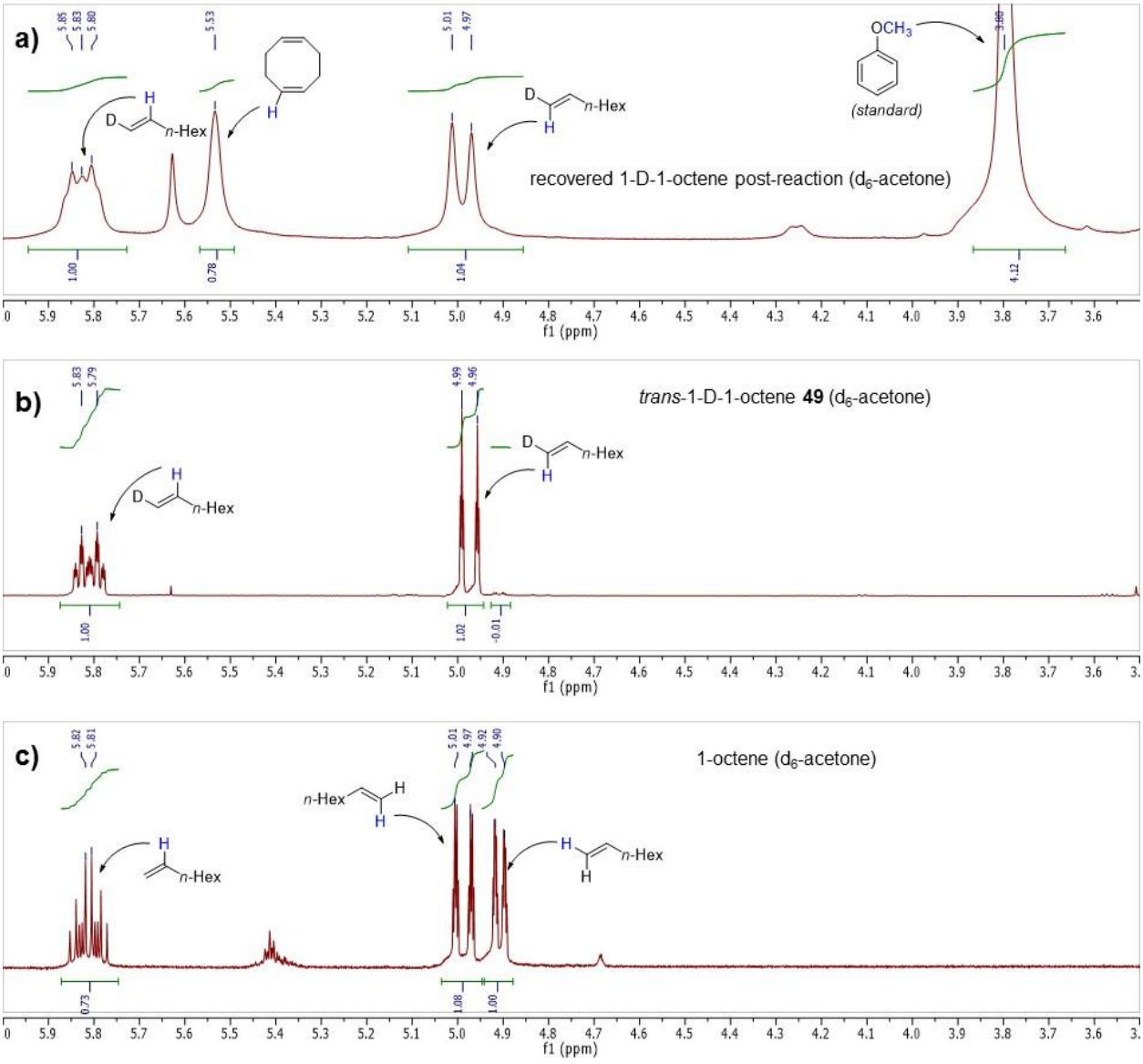
Figure 13. ^{1}H NMR results of deuterium-labeling study compared to non-deuterated **17**.



Observation of Remaining 1-Octene:

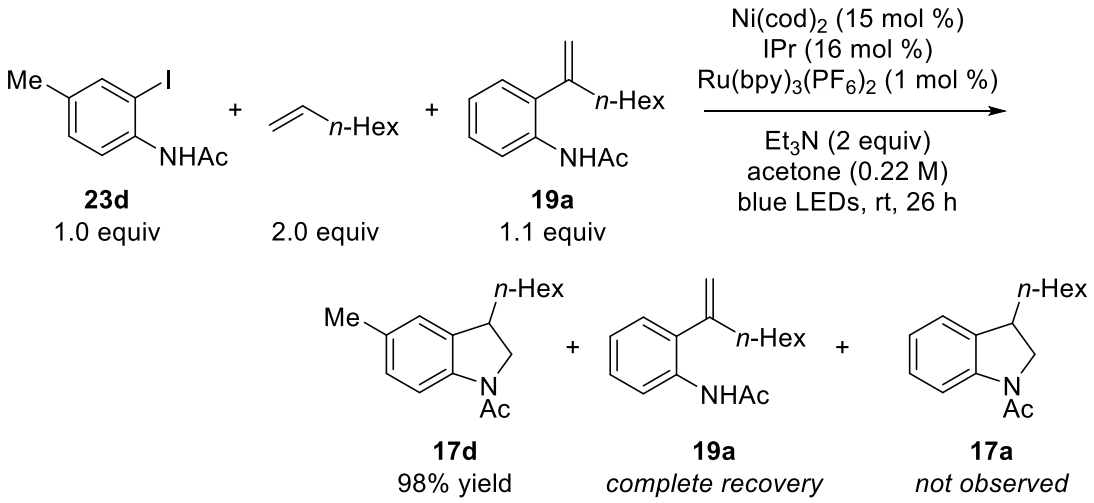
Following general procedure **A**, $Ni(cod)_2$ (6.4 mg, 0.023 mmol, 0.15 equiv), IPr (9.9 mg, 0.025 mmol, 0.16 equiv) d_6-acetone (0.7 mL, 0.22 M), Et_3N (43 μL, 0.31 mmol, 2.0 equiv), *trans*-1-D-1-octene (74 μL, 0.47 mmol, 3.0 equiv), 2'-iodoacetanilide (40 mg, 0.155 mmol 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (1.4 mg, 0.005 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air, pentane was added, and the reaction mixture was filtered through a short silica plug with pentane as the eluent and concentrated carefully under reduced pressure (~180 torr). Anisole (17 μL, 0.155 mmol, 1.0 equiv) was added as standard, and an aliquot was taken and diluted further with d_6-acetone. ^1H NMR below (Figure 14). The remaining alkene (~35% recovery based on 2 equiv alkene remaining after completion of the reaction) did not show any *E*/*Z* isomerization or D-scrambling.

Figure 14. Recovery of 1-octene: ^{1}H NMR.



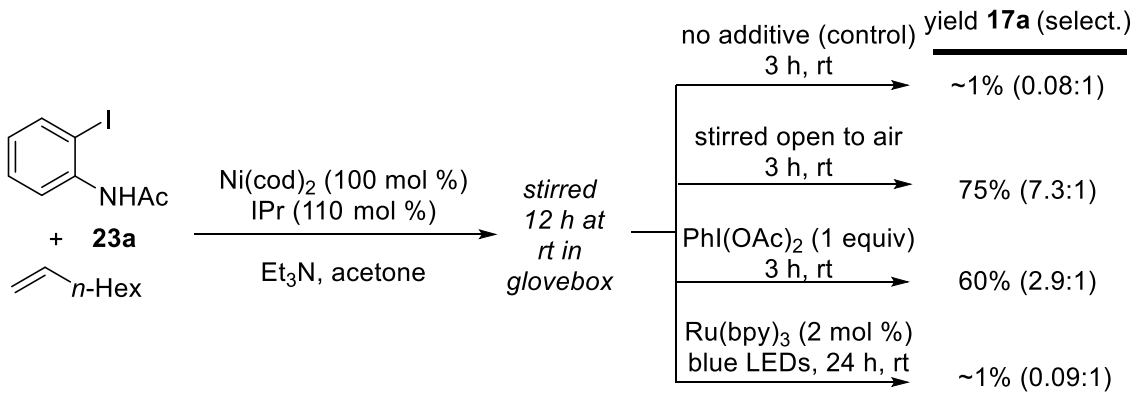
E) Other Mechanistic Studies

Scheme 15. Testing Heck products as competent intermediates



$Ni(cod)_2$ (6.4 mg, 0.023 mmol, 0.15 equiv), IPr (9.9 mg, 0.025 mmol, 0.16 equiv) acetone (0.7 mL, 0.22 M), Et_3N (43 μL, 0.31 mmol, 2.0 equiv), 1-octene (49 μL, 0.31 mmol, 2.0 equiv), 2'-iodo-4'-methylacetanilide **23d** (42.5 mg, 0.15 mmol 1.0 equiv), **19a** (37.7 μL, 0.17 mmol, 1.1 equiv), and $Ru(bpy)_3(PF_6)_2$ (1.4 mg, 0.0016 mmol, 0.01 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 26 h, the reaction was opened to air, EtOAc was added, and the reaction mixture was filtered through a silica plug using ~20 mL EtOAc as the eluent. Dodecane (35 μL, 0.15 mmol, 1.0 equiv) was then added, and the reaction mixture was analyzed by gas chromatography. Calibration curves for 2'-iodo-4'-methylacetanilide **23d**, **19a**, **17d**, and **17a** had been generated using dodecane as an internal standard, and each product had a cleanly differentiated retention time. Using these results, 100% conversion of **23d** and 98% yield of **17d** were observed. Additionally, 111 mol % of **19a** was recovered (complete recovery), and **17a** was not observed at the GC limit of detection.

Scheme 16. Treatment with stoichiometric oxidants.



$Ni(cod)_2$ (137 mg, 0.5 mmol, 1.0 equiv), IPr (194 mg, 0.5 mmol, 1.0 equiv) acetone (4.6 mL, 0.11 M), Et_3N (139 μL, 1.0 mmol, 2.0 equiv), 1-octene (157 μL, 1.0 mmol, 2.0 equiv), 2'-iodoacetanilide **23a** (130.5 mg, 0.50 mmol 1.0 equiv), and dodecane (114 μL, 0.50 mmol, 1.0 equiv) were added to a 2 dram vial in a nitrogen-filled glovebox. The vial cap was then taped shut, and stirred at room temperature for 12 h. Then, the reaction was split into five portions of ~1.04 mL each labeled A–E.

A: Control, no additive. After 3 h, half of the reaction mixture was filtered through a plug of neutral alumina in the glovebox to remove metals, eluting with Et_2O. Analysis by gas chromatography revealed ~1% **17a**, with trace amounts also of approximately four other products, including known Heck products (overall selectivity ratio of indoline **17a** to [Σ Heck/isomerized Heck/etc.]: 0.08). After 24 h, the remainder of the mixture was worked up in the same way to again yield ~1% **17a** and other products in trace amounts.

B: Open to air. The vial was removed from the glovebox, the cap was removed, and it was stirred at room temperature for 3 h. The reaction mixture was then filtered through a plug of

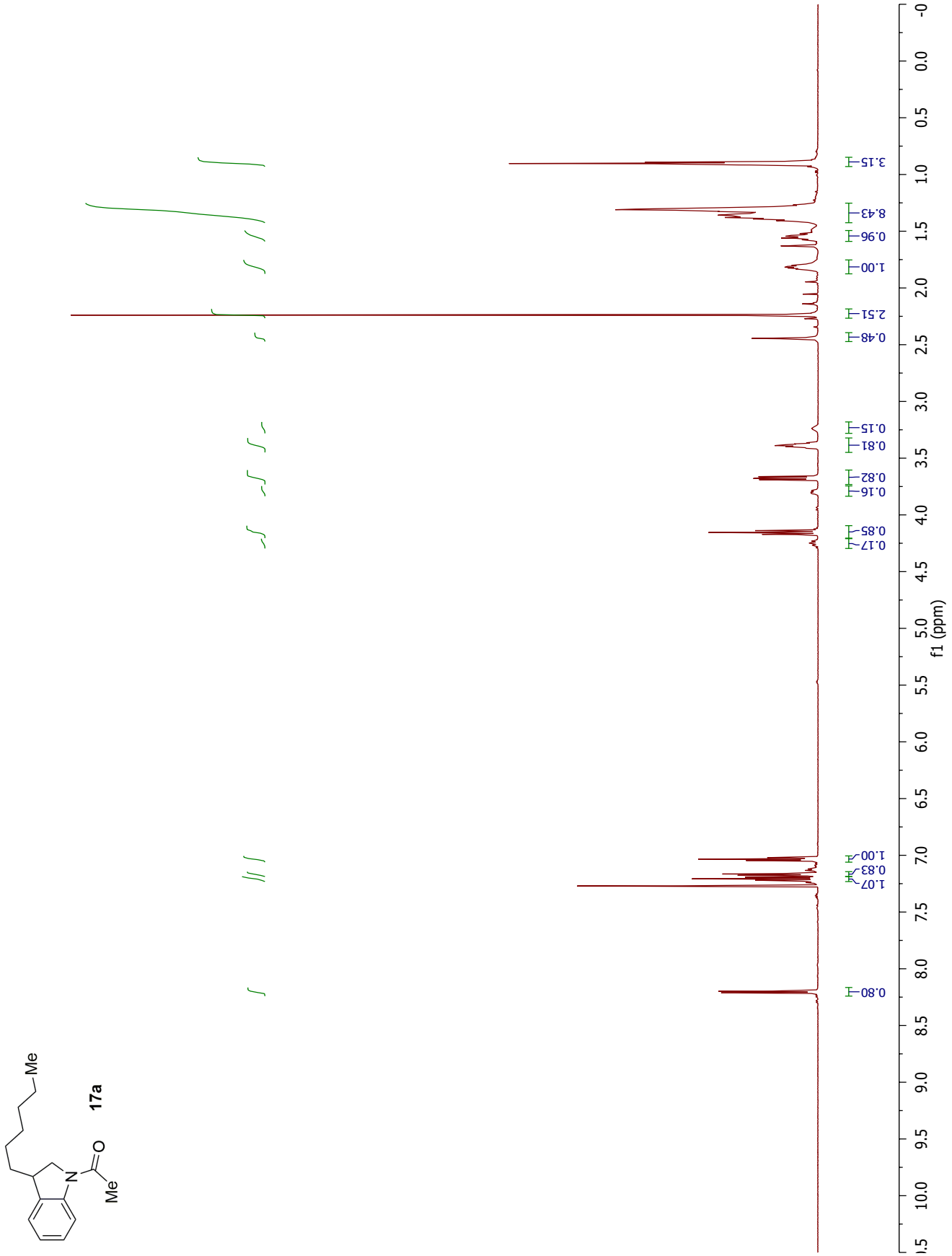
neutral alumina using Et_2O as the eluent and analyzed by gas chromatography to yield 75% **17a** and selectivity ratio of indoline **17a** to [Σ Heck/isomerized Heck/etc.]: 7.3:1.

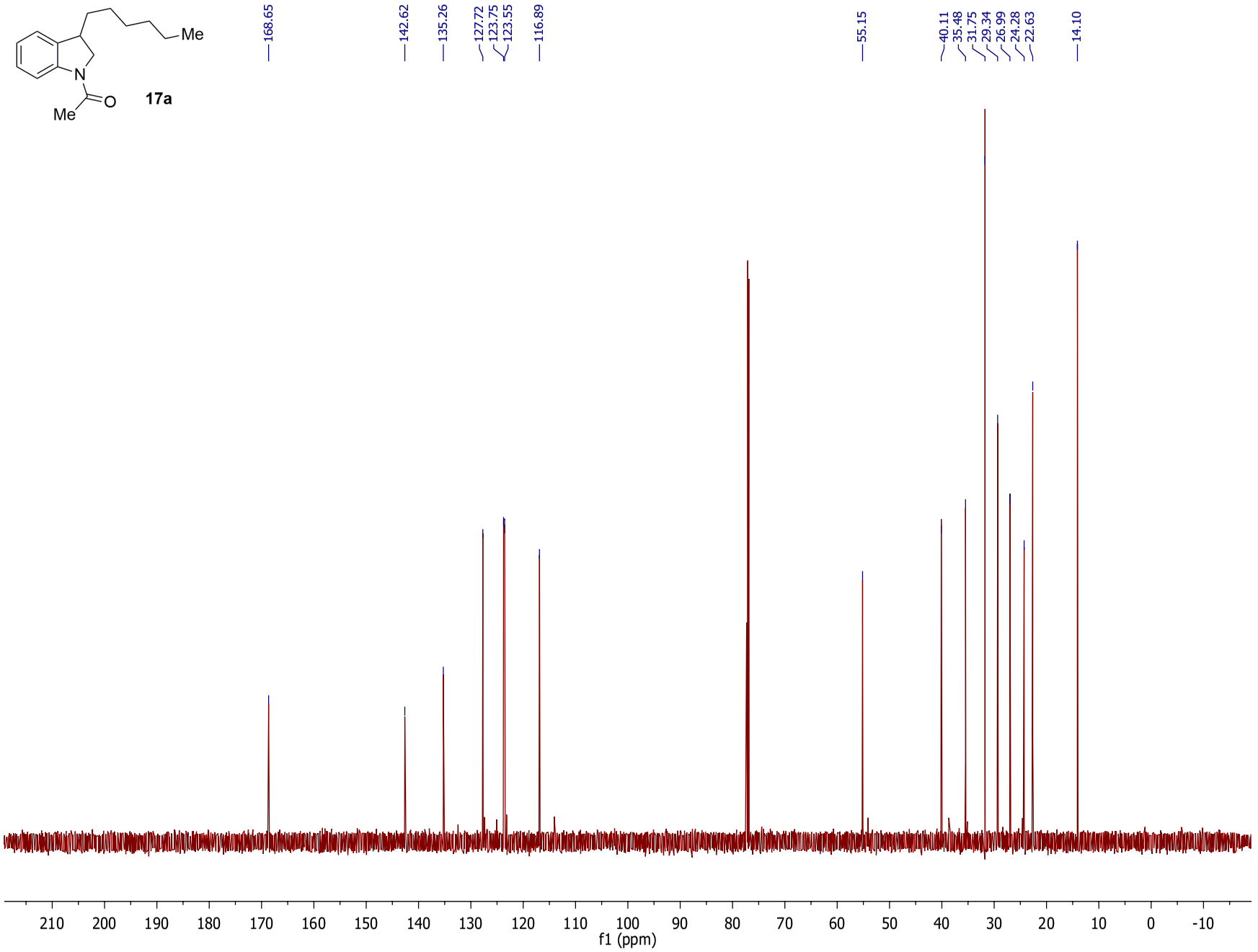
C: $PhI(OAc)_2$. $PhI(OAc)_2$ (39 mg, 0.12 mmol, 1.2 equiv) was added in the glovebox, and the vial was stirred at room temperature. After 3 h, the reaction mixture was filtered through a plug of neutral alumina in the glovebox to remove metals, eluting with Et_2O. Analysis by gas chromatography revealed 60% **17a**, selectivity ratio of indoline **17a** to [Σ Heck/isomerized Heck/etc.] 2.9:1.

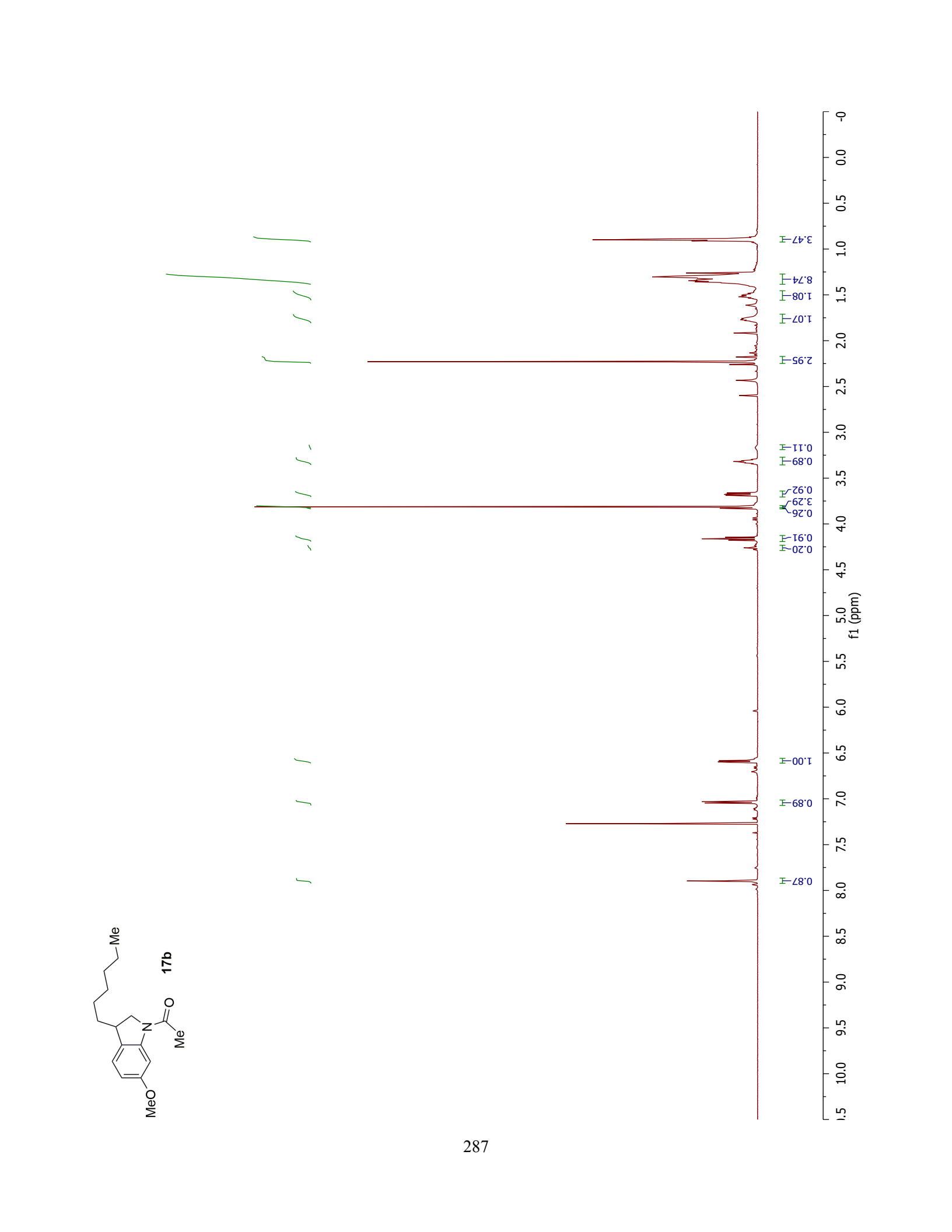
D: $Ru(bpy)_3(PF_6)_2$, blue LEDs: $Ru(bpy)_3(PF_6)_2$ (1.7 mg, 0.0020 mmol, 0.02 equiv) was added in the glovebox. The vial cap was then taped shut, the vial was removed from the glovebox, and it was placed next to blue LED lights cooled by a fan. After 24 h, the reaction vial was again brought inside the glovebox to be worked up under inert atmosphere. The reaction mixture was filtered through a plug of neutral alumina in the glovebox to remove metals, eluting with Et_2O. Analysis by gas chromatography revealed ~1% **17a**, selectivity ratio of indoline **17a** to [Σ Heck/isomerized Heck/etc.] 0.09:1 with a variety of trace products.

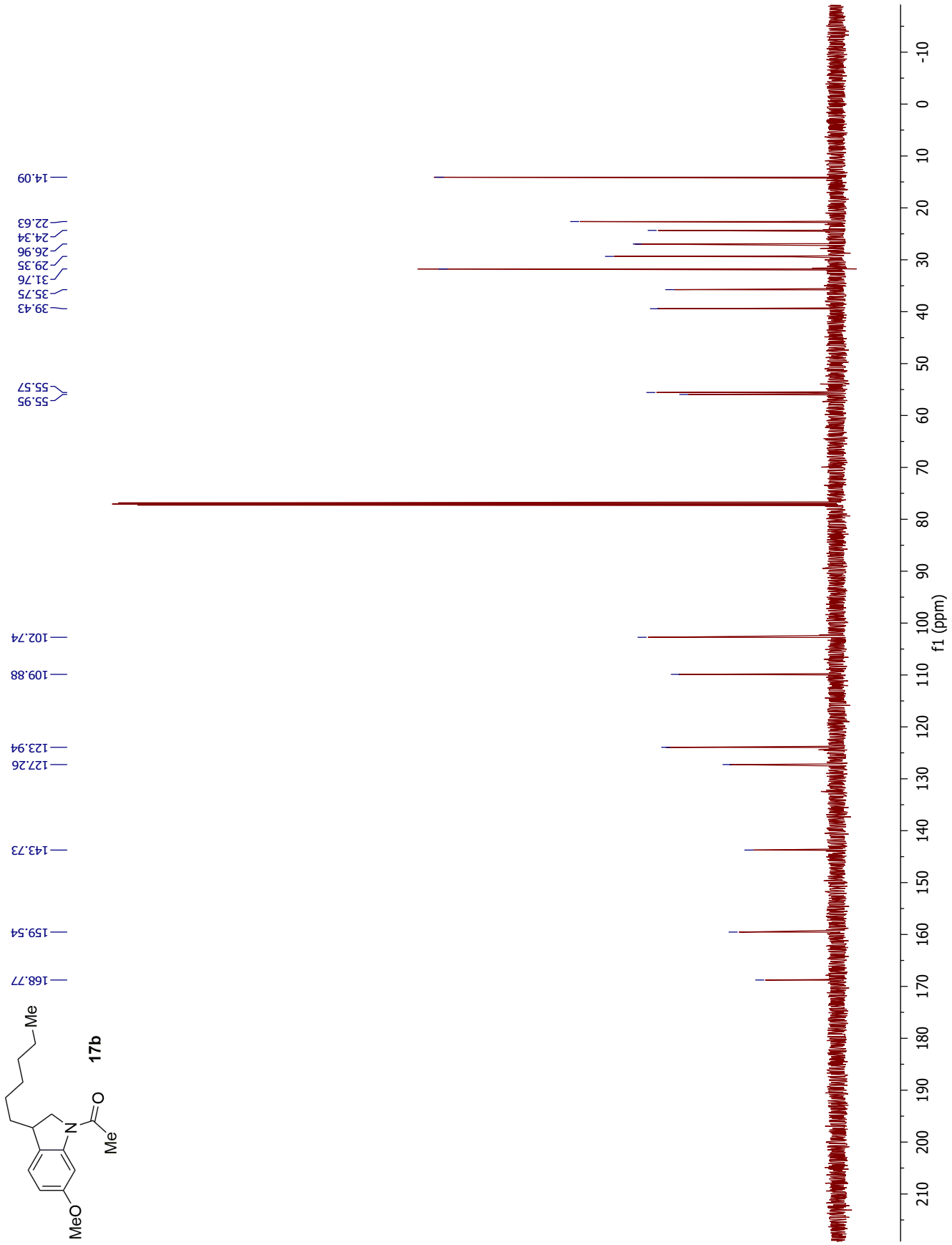
E: $Ru(bpy)_3(PF_6)_2$, dark: $Ru(bpy)_3(PF_6)_2$ (1.7 mg, 0.0020 mmol, 0.02 equiv) was added in the glovebox to a vial tightly wrapped in foil. The vial cap was then taped shut and stirred at room temperature in the glovebox. After 24 h, the reaction mixture was filtered through a plug of neutral alumina in the glovebox to remove metals, eluting with Et_2O. Analysis by gas chromatography revealed ~1% **17a**, selectivity ratio of indoline **17a** to [Σ Heck/isomerized Heck/etc.]: 0.03:1 with a variety of trace products.

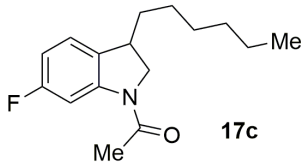
^{1}H and ^{13}C NMR Spectra


Me
17a
O
N
Me
3.15
8.43
0.96
1.00
2.51
0.48
0.15
0.81
0.82
0.16
0.85
0.17
1.00
0.83
1.07
0.80
f1 (ppm)

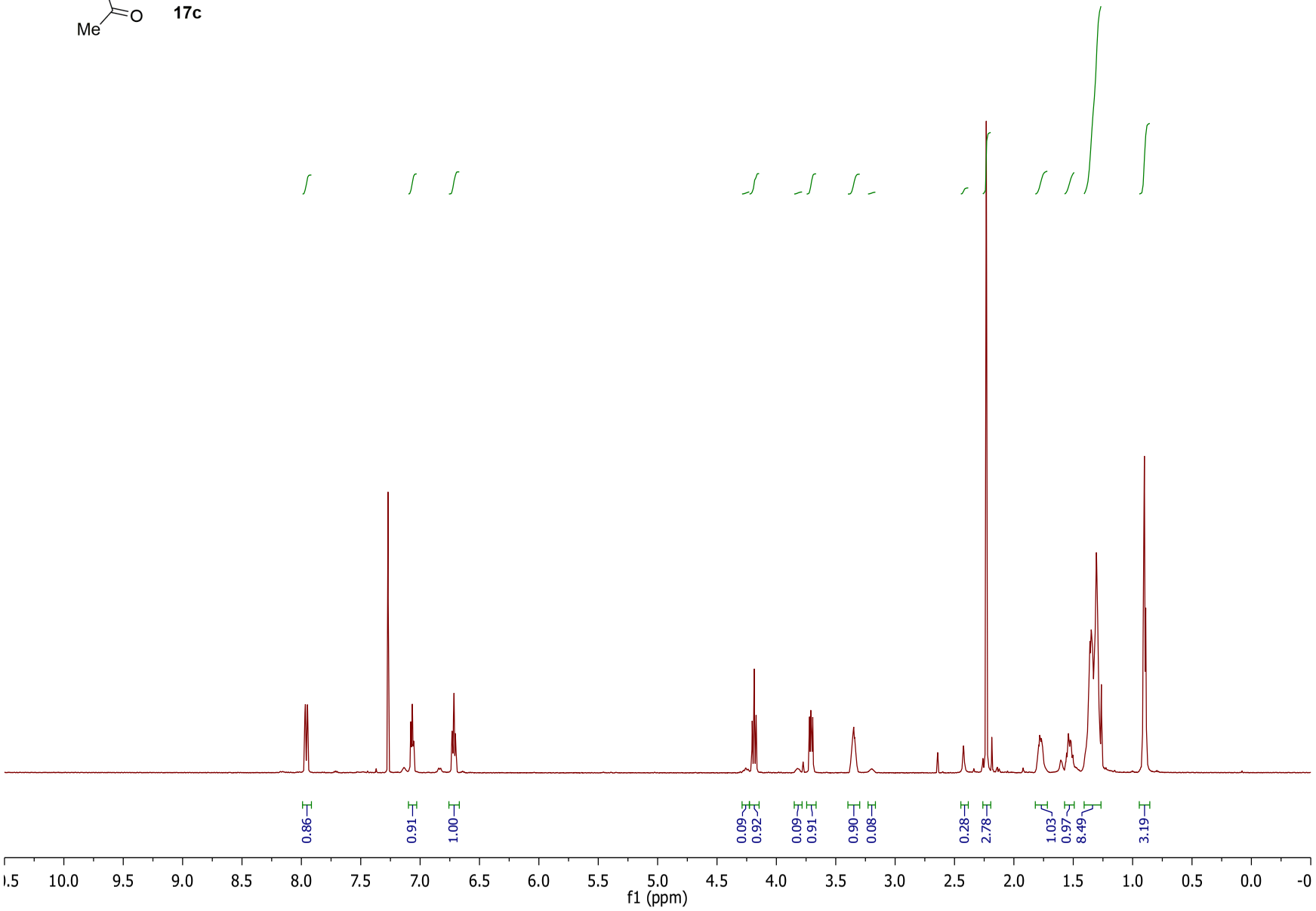

Me
N
O
Me
17a
168.65
142.62
135.26
127.72
123.75
123.55
116.89
55.15
40.11
35.48
31.75
29.34
26.99
24.28
22.63
14.10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

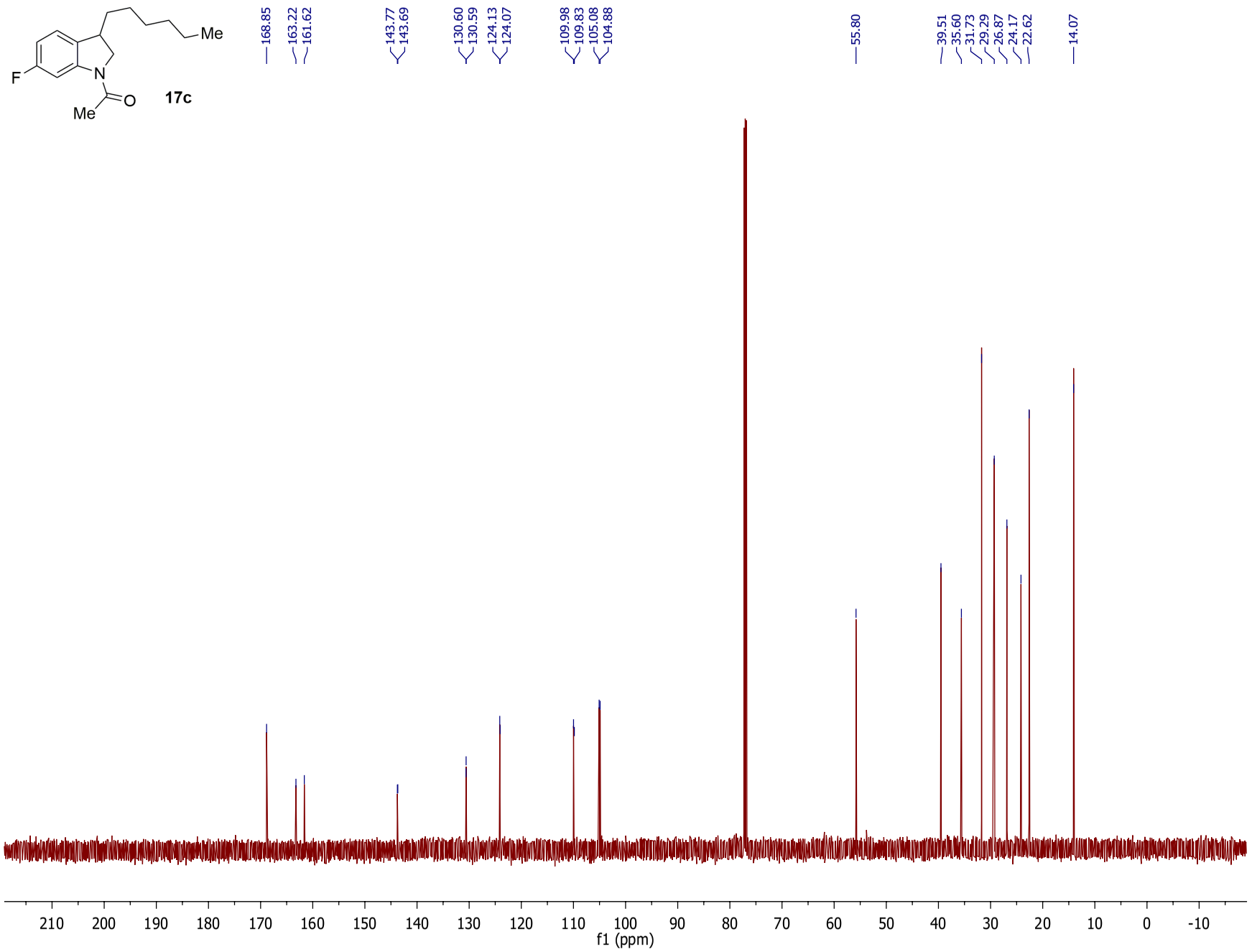

Me
17b
O
N
Me
MeO
3.47
8.74
1.08
1.07
2.95
0.11
0.89
0.92
3.29
0.26
0.91
0.20
1.00
0.89
0.87
f1 (ppm)

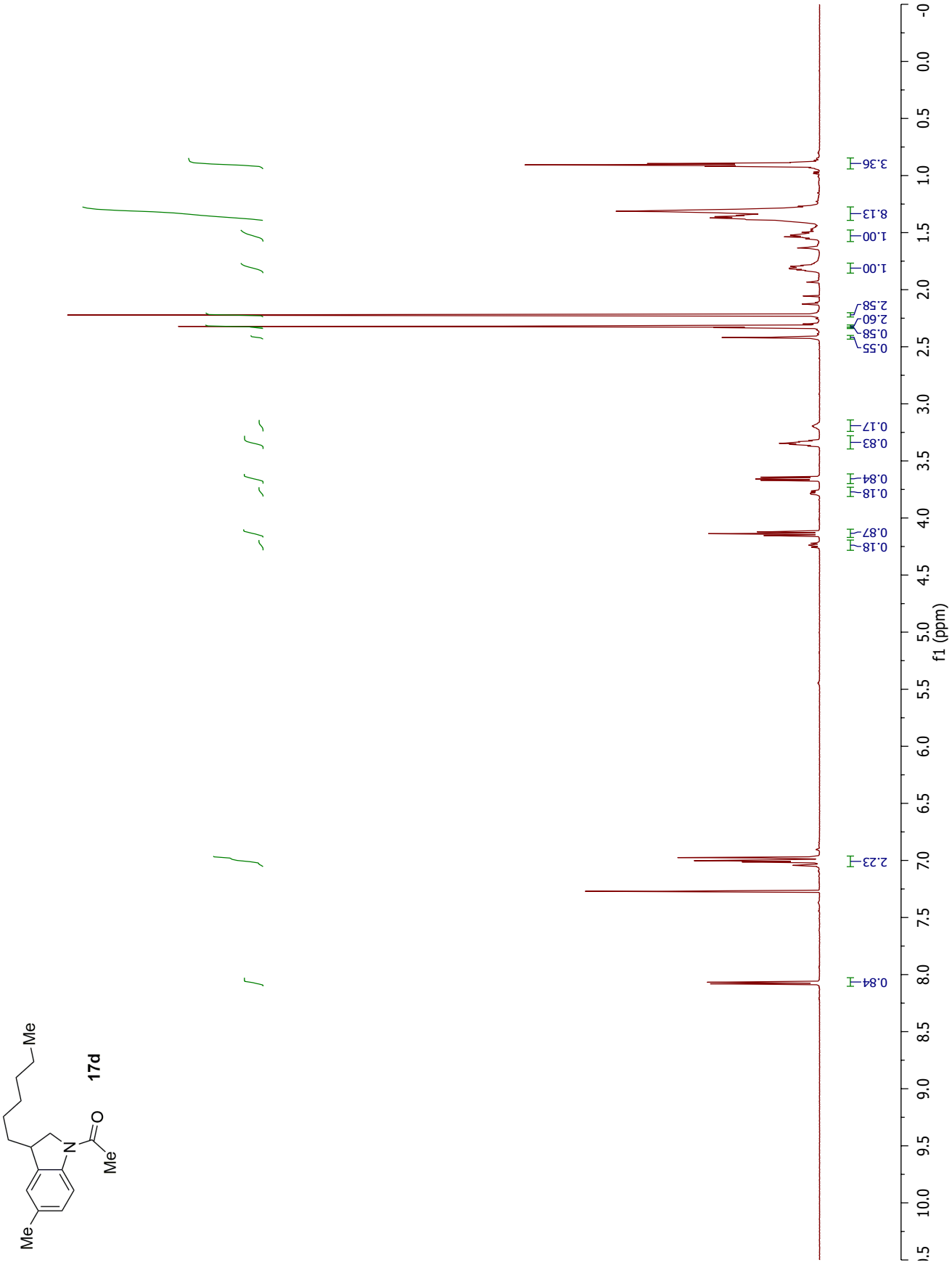

14.09
22.63
24.34
26.96
29.35
31.76
35.75
39.43
55.57
55.95
102.74
109.88
123.94
127.26
143.73
159.54
168.77
f1 (ppm)
17b
Me
O
N
Me
MeO

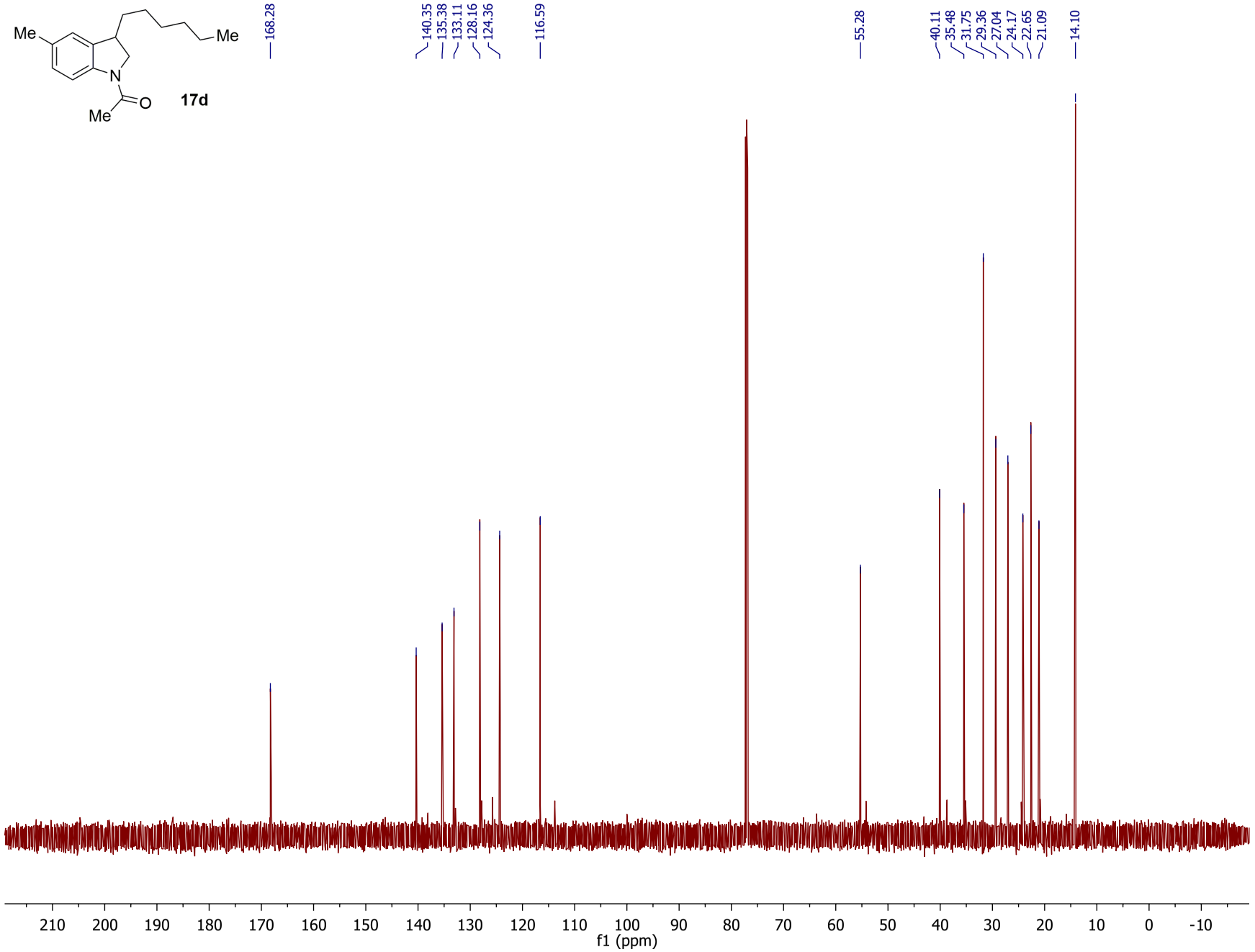

Me
F
N
O
Me

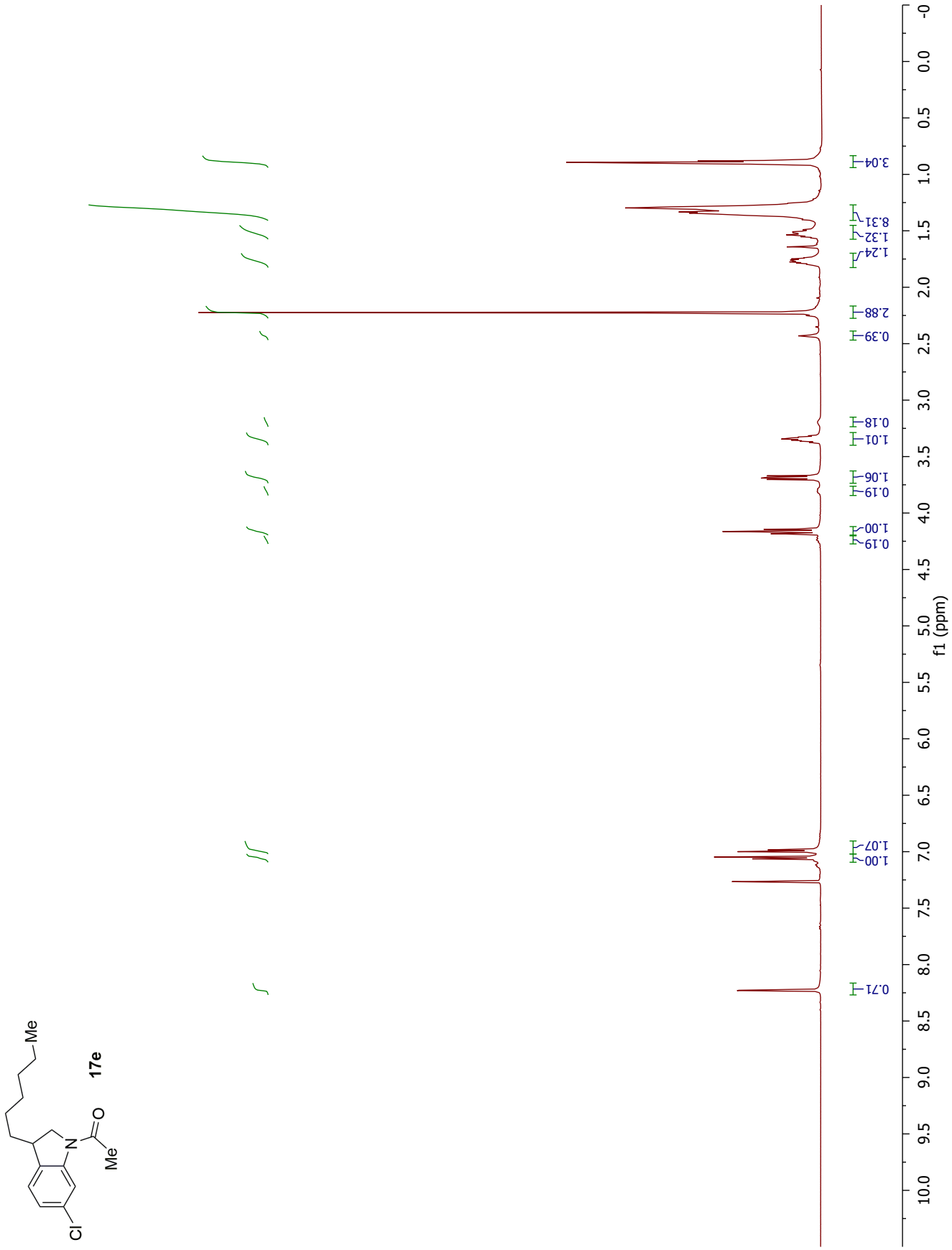
17c

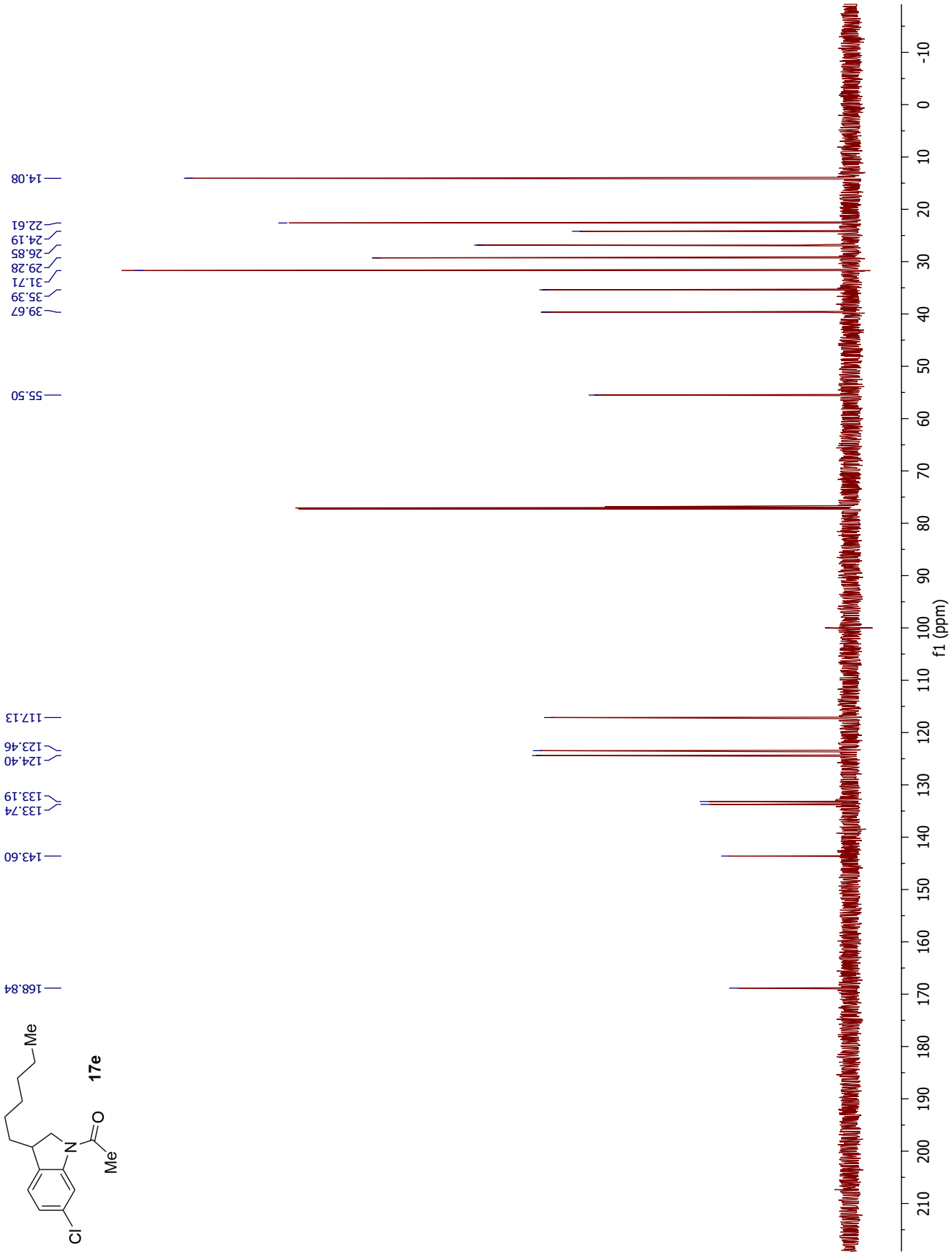

0.86
0.91
1.00
0.09
0.92
0.09
0.91
0.90
0.08
0.28
2.78
1.03
0.97
8.49
3.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

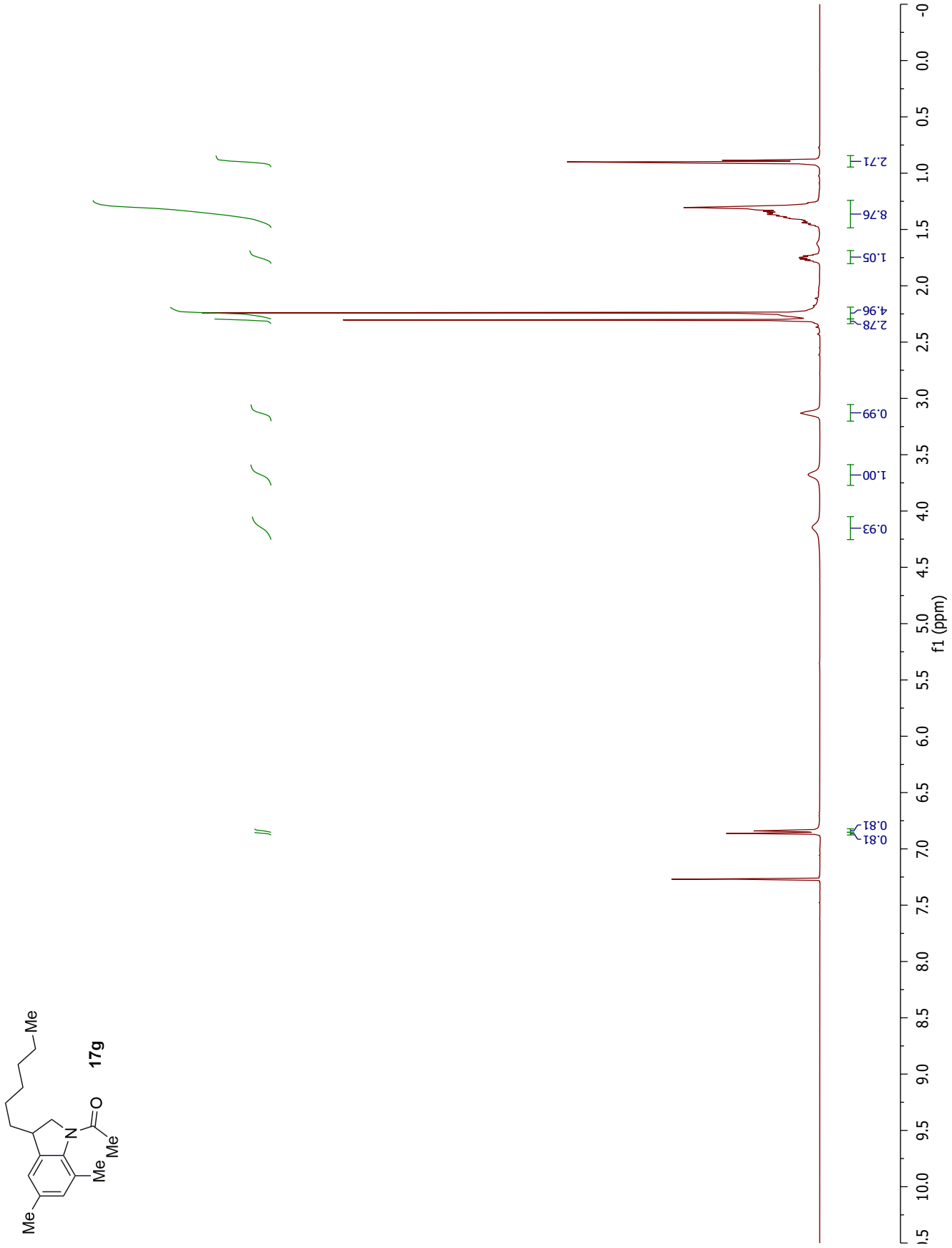

F
N
O
Me
Me
17c
168.85
163.22
161.62
143.77
143.69
130.60
130.59
124.13
124.07
109.98
109.83
105.08
104.88
55.80
39.51
35.60
31.73
29.29
26.87
24.17
22.62
14.07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

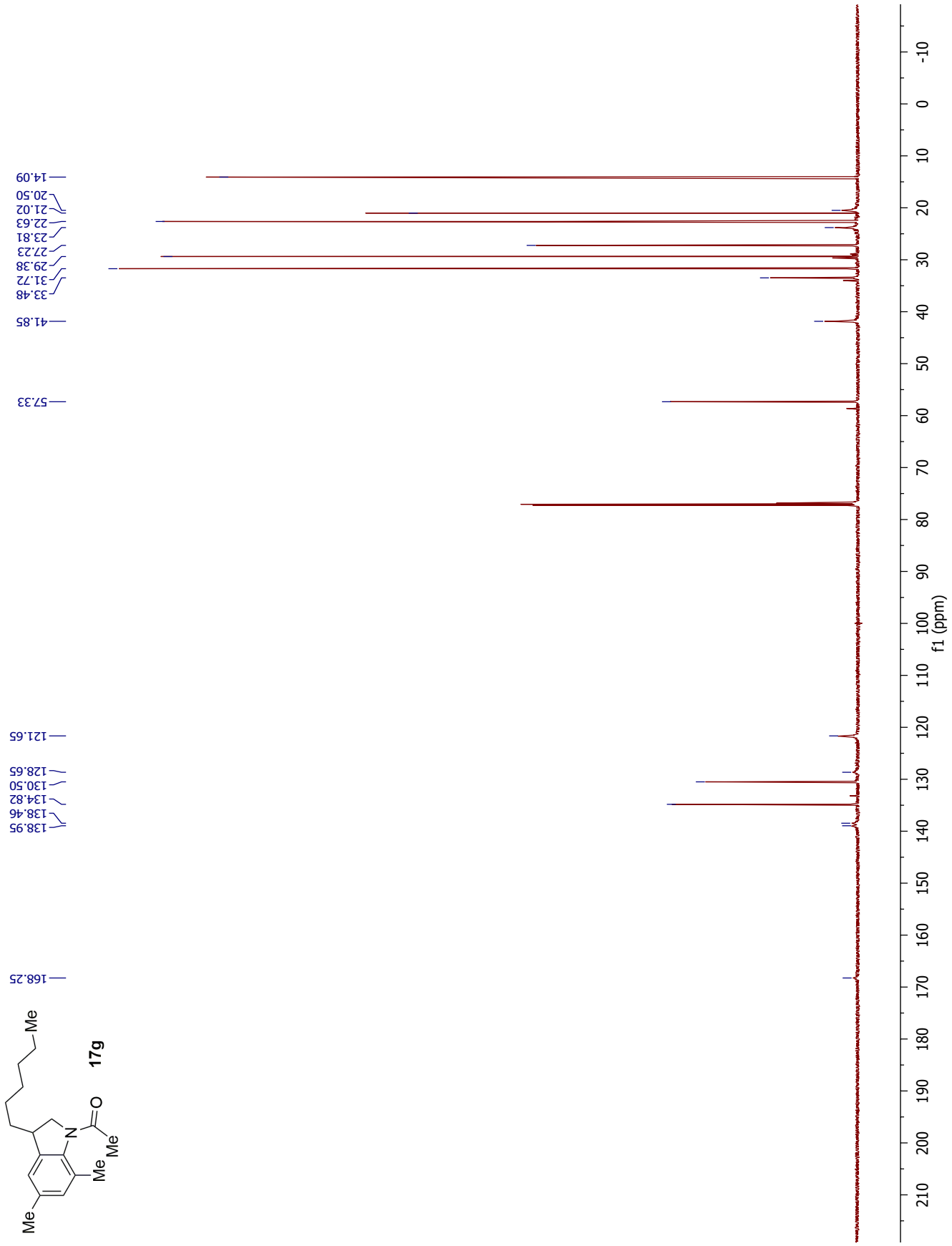

Me
Me
N
O
Me
Me
17d
3.36
8.13
1.00
1.00
2.58
2.60
0.58
0.55
0.17
0.83
0.84
0.18
0.87
0.18
2.23
0.84
f1 (ppm)

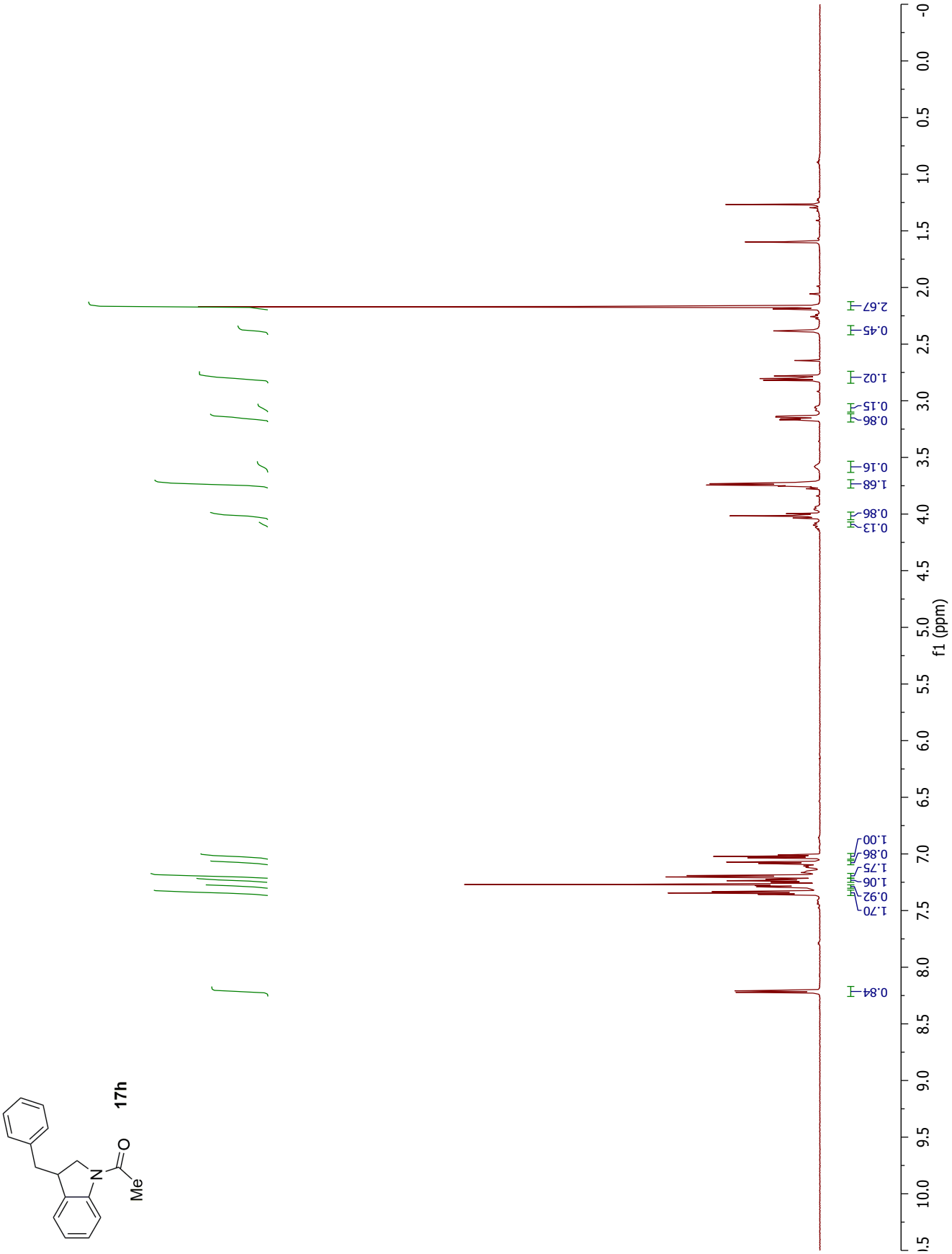

Me
Me
N
O
Me
17d
168.28
140.35
135.38
133.11
128.16
124.36
116.59
55.28
40.11
35.48
31.75
29.36
27.04
24.17
22.65
21.09
14.10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

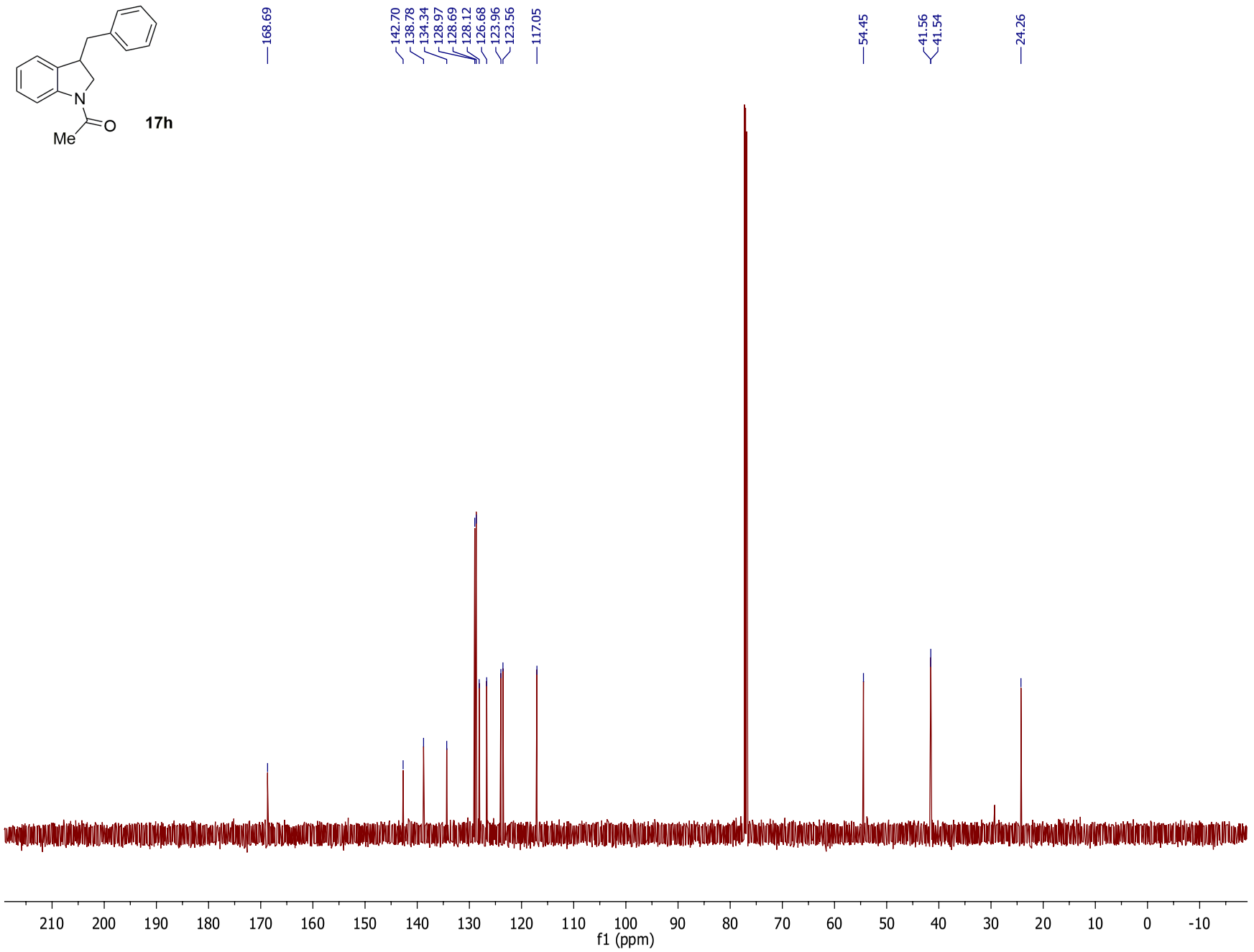

Me
17e
O
N
Me
Cl
3.04
8.31
1.32
1.24
2.88
0.39
0.18
1.01
1.06
0.19
1.00
0.19
1.00
1.07
0.71
f1 (ppm)

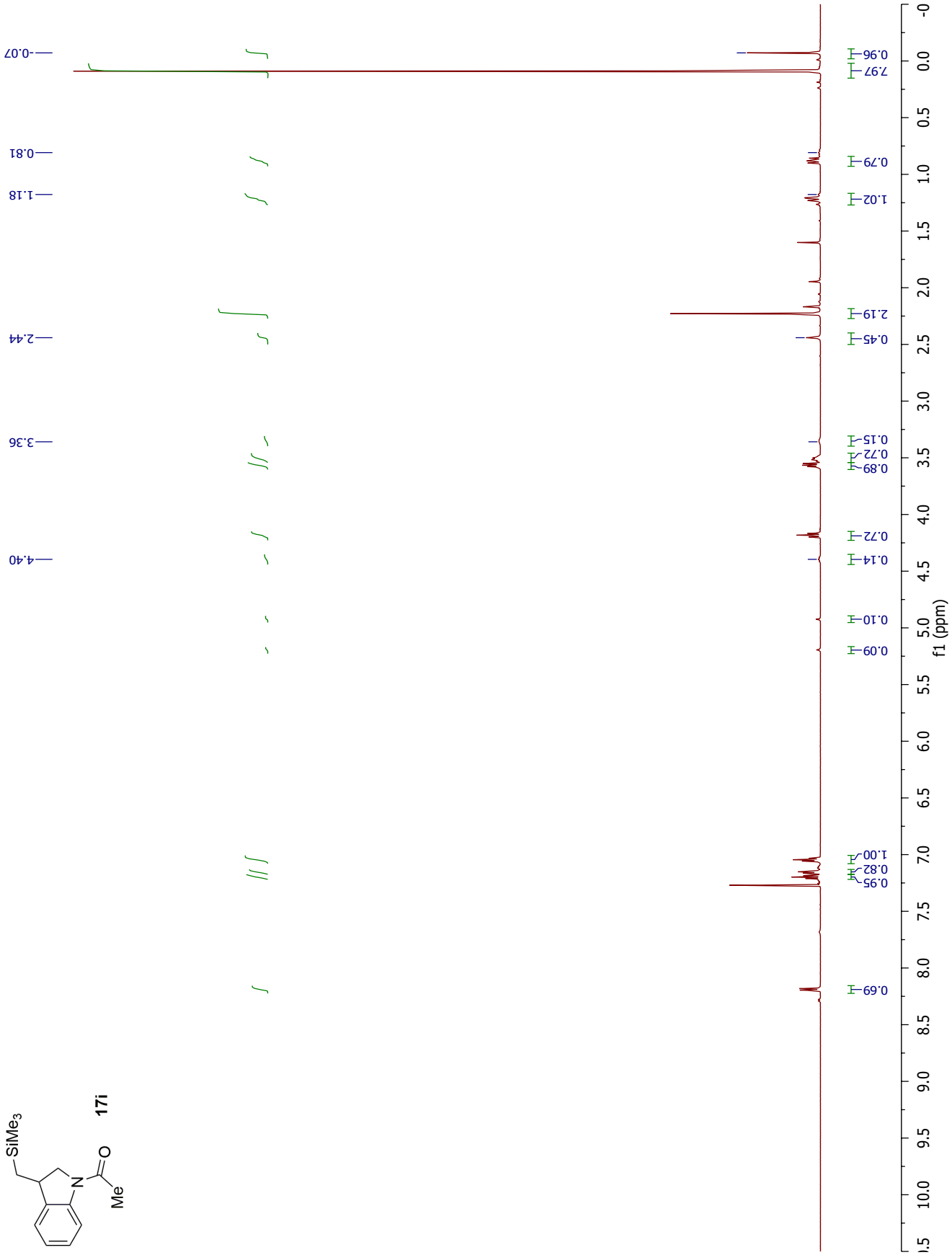

14.08
22.61
24.19
26.85
29.28
31.71
35.39
39.67
55.50
117.13
123.46
124.40
133.19
133.74
143.60
168.84
f1 (ppm)
Me
17e
O
N
Me
Cl

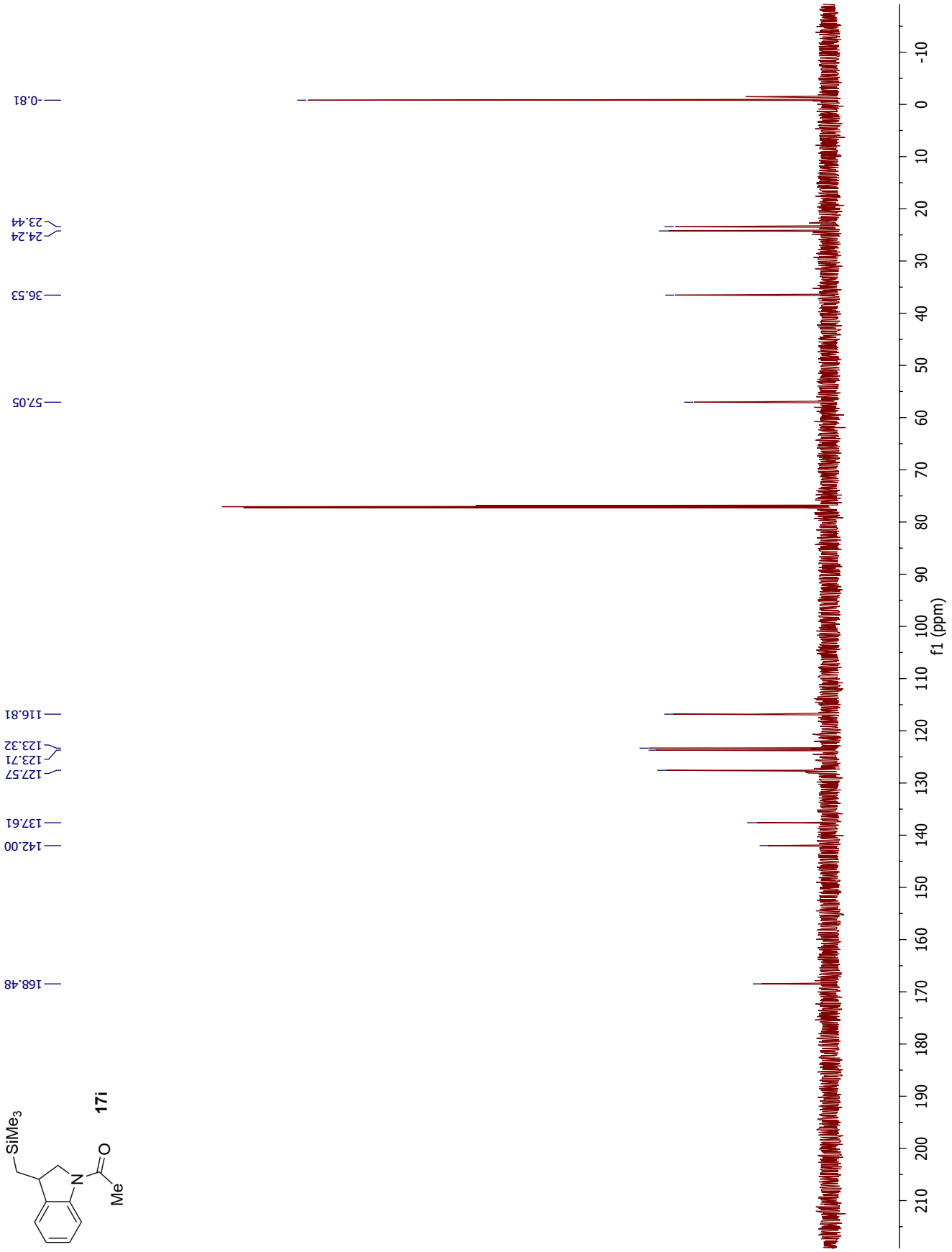

Me
17g
O
N
Me
Me
Me
2.71
8.76
1.05
4.96
2.78
0.99
1.00
0.93
0.81
0.81
f1 (ppm)

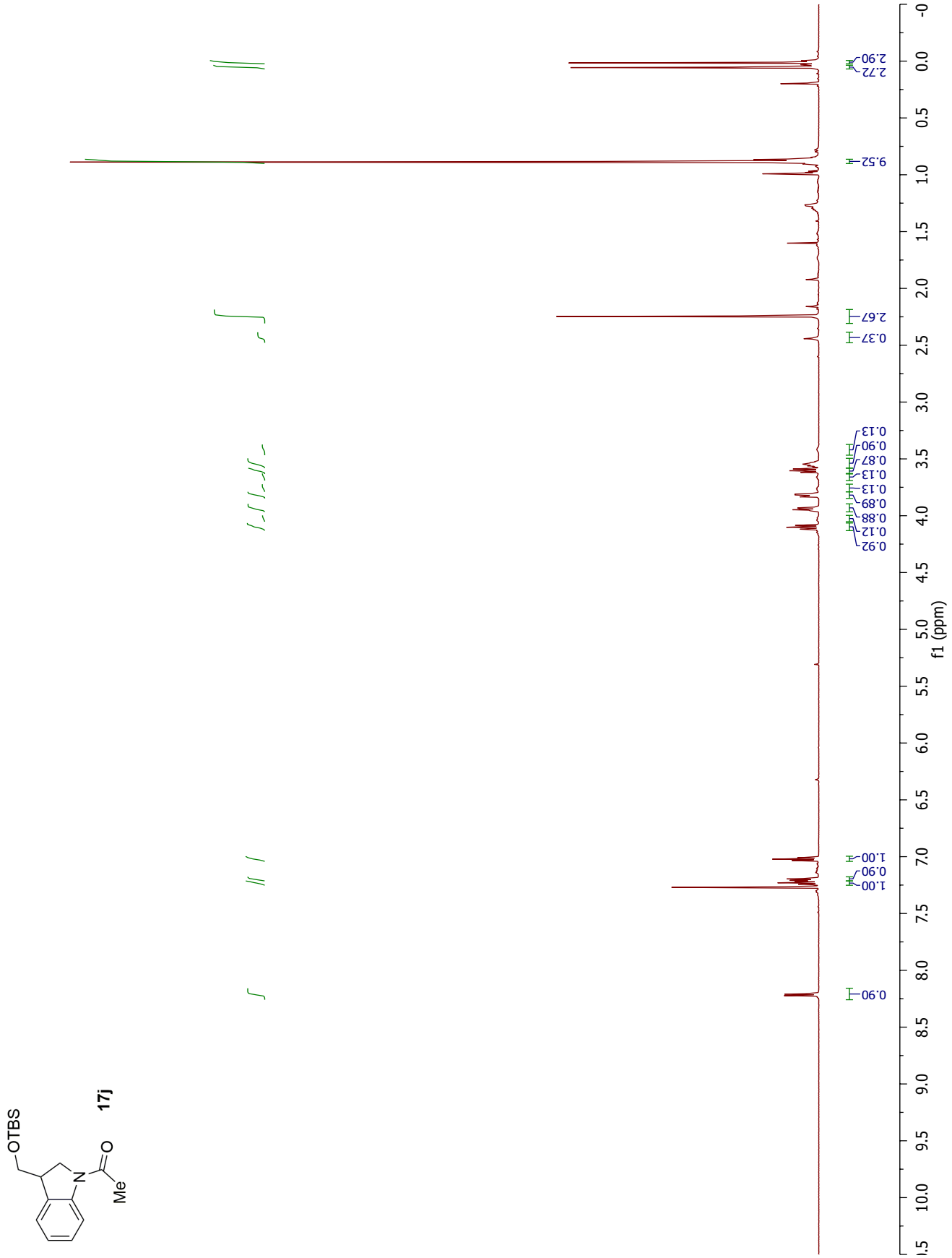

17g
Me
Me
Me
Me
O
N
168.25
138.95
138.46
134.82
130.50
128.65
121.65
57.33
41.85
33.48
31.72
29.38
27.23
23.81
22.63
21.02
20.50
14.09
f1 (ppm)

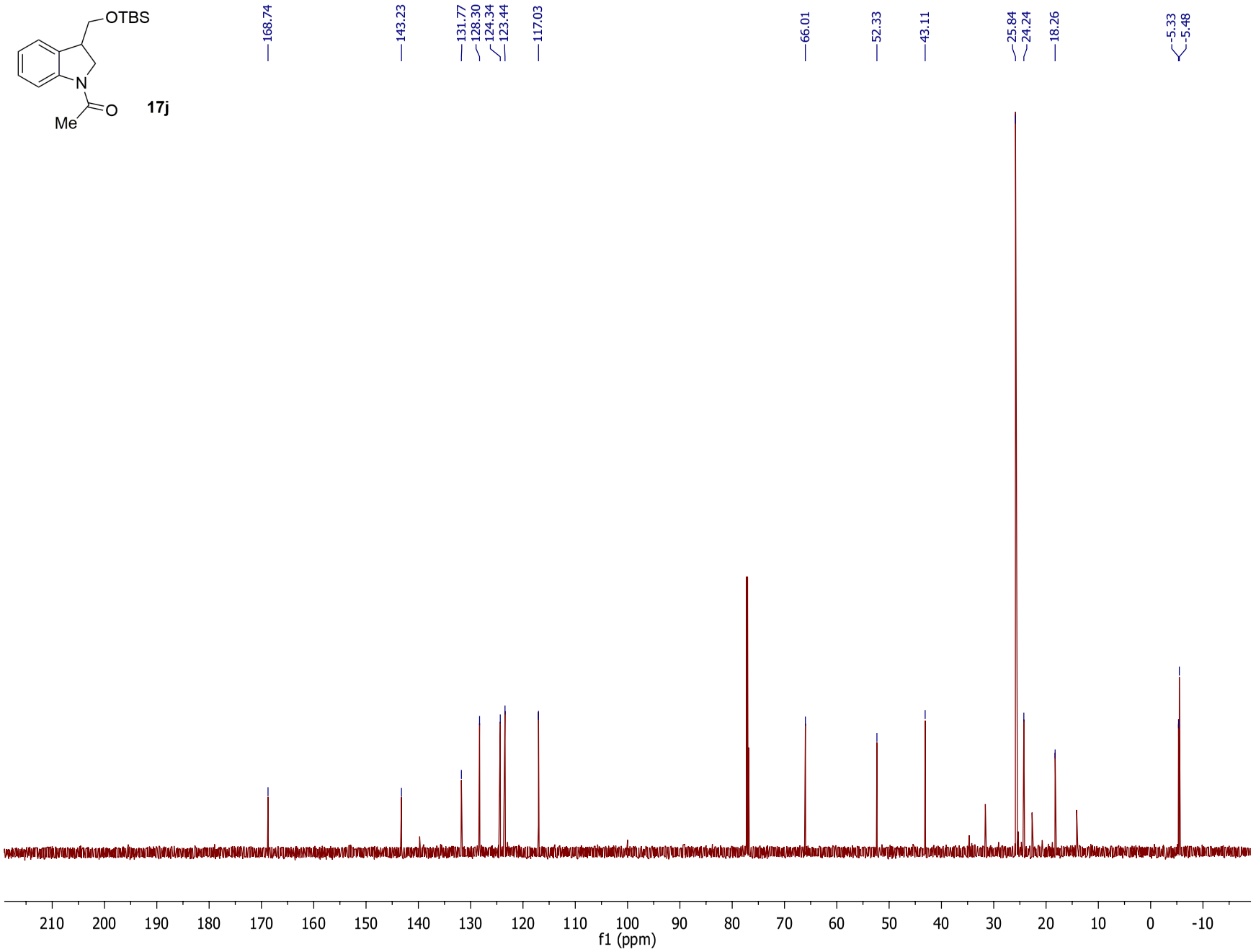

17h
N
O
Me
2.67
0.45
1.02
0.86
0.15
0.16
1.68
0.86
0.13
1.00
0.86
1.75
1.06
0.92
1.70
0.84
f1 (ppm)

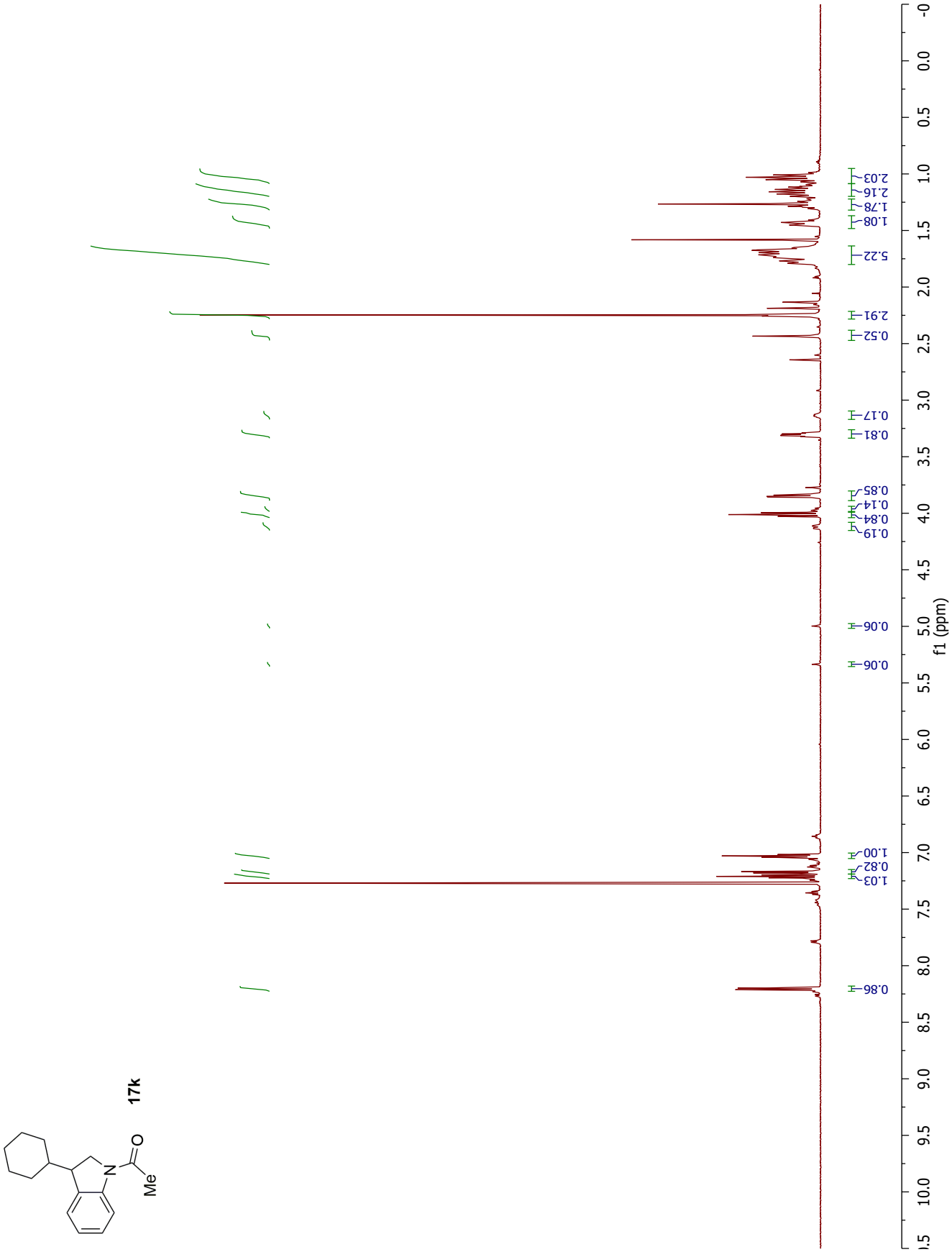

168.69
142.70
138.78
134.34
128.97
128.69
128.12
126.68
123.96
123.56
117.05
54.45
41.56
41.54
24.26
N
O
Me
17h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

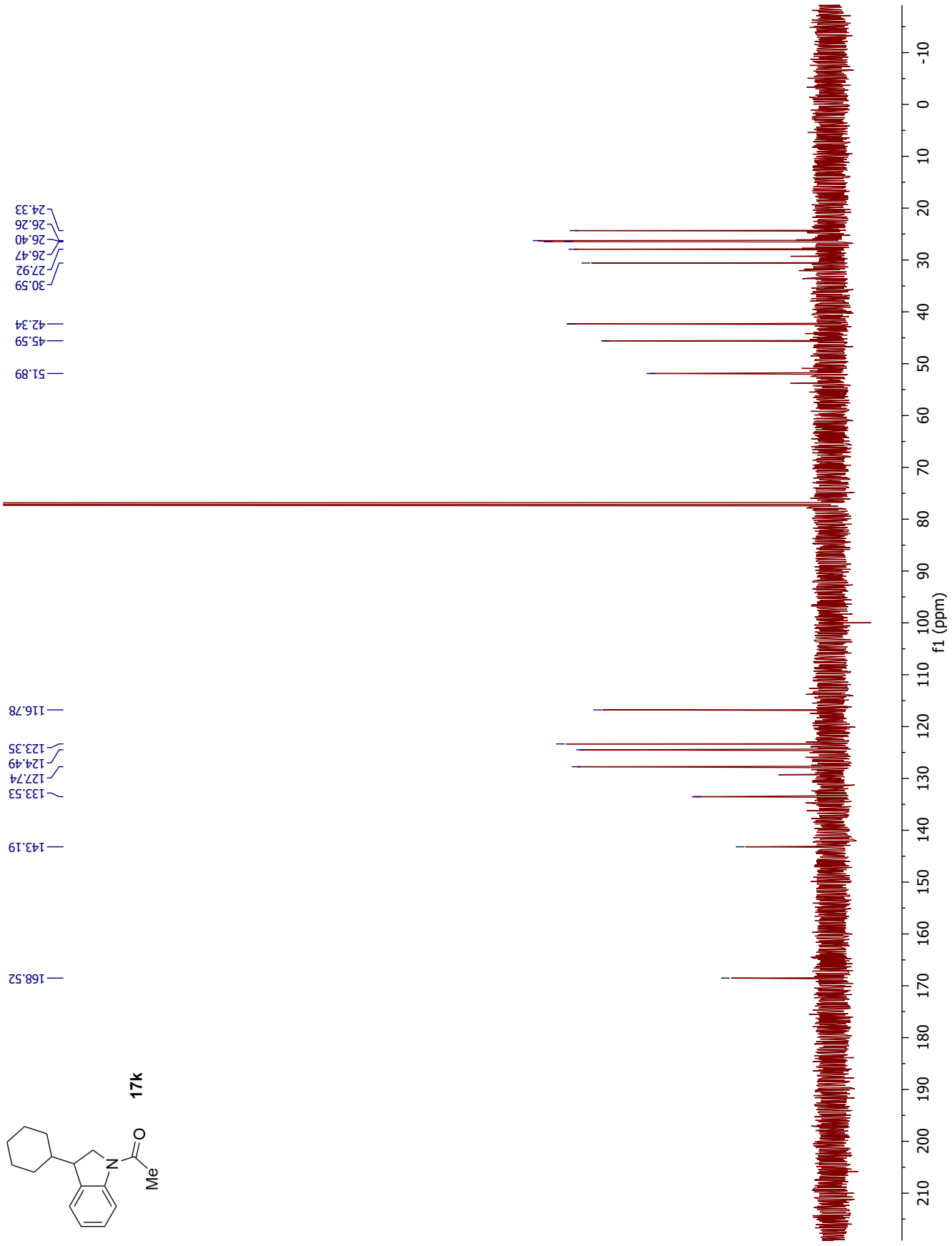

SiMe3
N
O
Me
17i
-0.07
0.81
1.18
2.44
3.36
4.40
0.96
7.97
0.79
1.02
2.19
0.45
0.15
0.72
0.89
0.72
0.14
0.10
0.09
1.00
0.82
0.95
0.69
f1 (ppm)

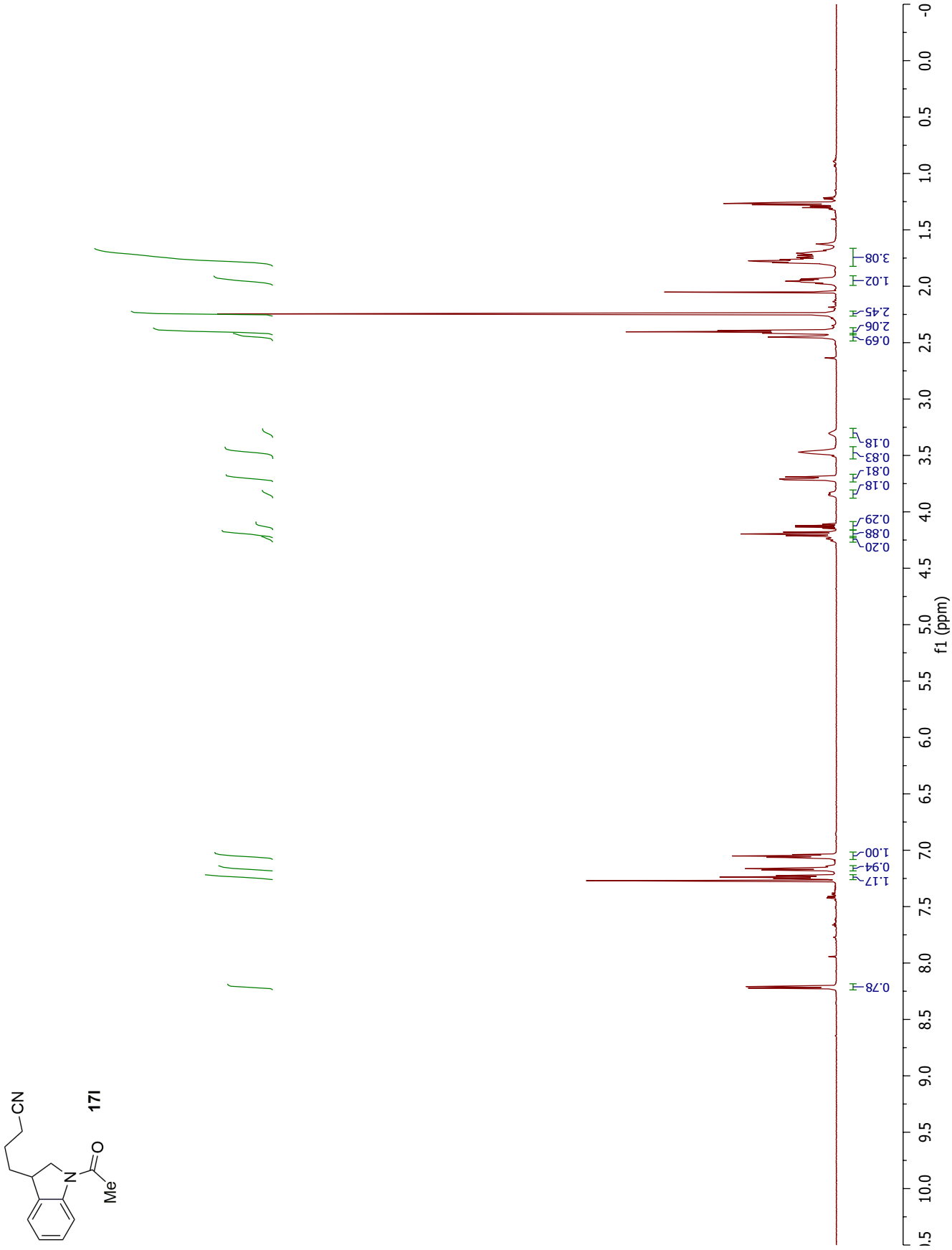

-0.81
23.44
24.24
36.53
57.05
116.81
123.32
123.71
127.57
137.61
142.00
168.48
SiMe3
N
O
Me
17i
f1 (ppm)

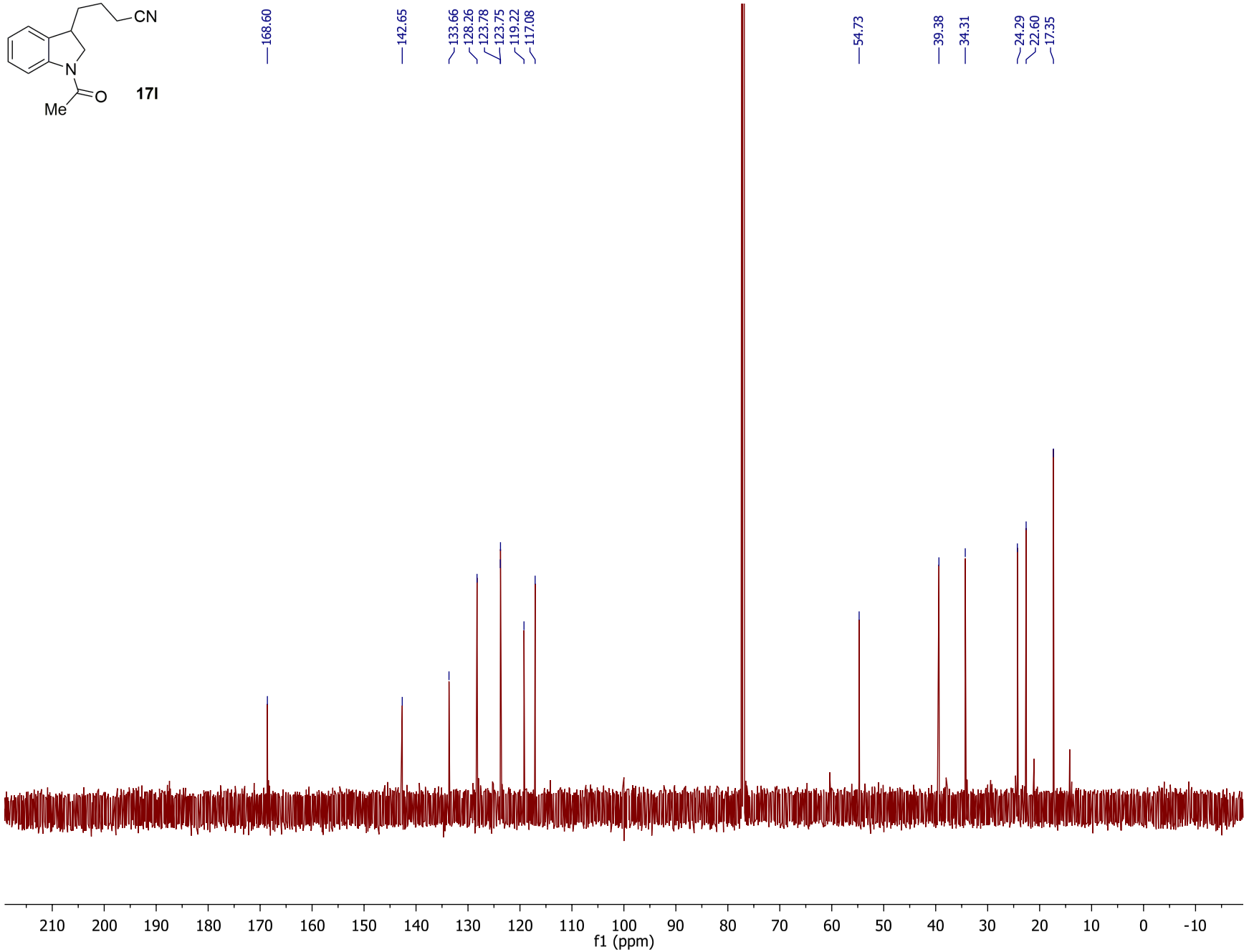

OTBS
N
O
Me
17j
2.90
2.72
9.52
2.67
0.37
0.13
0.90
0.87
0.13
0.13
0.89
0.88
0.12
0.92
1.00
0.90
1.00
0.90
f1 (ppm)

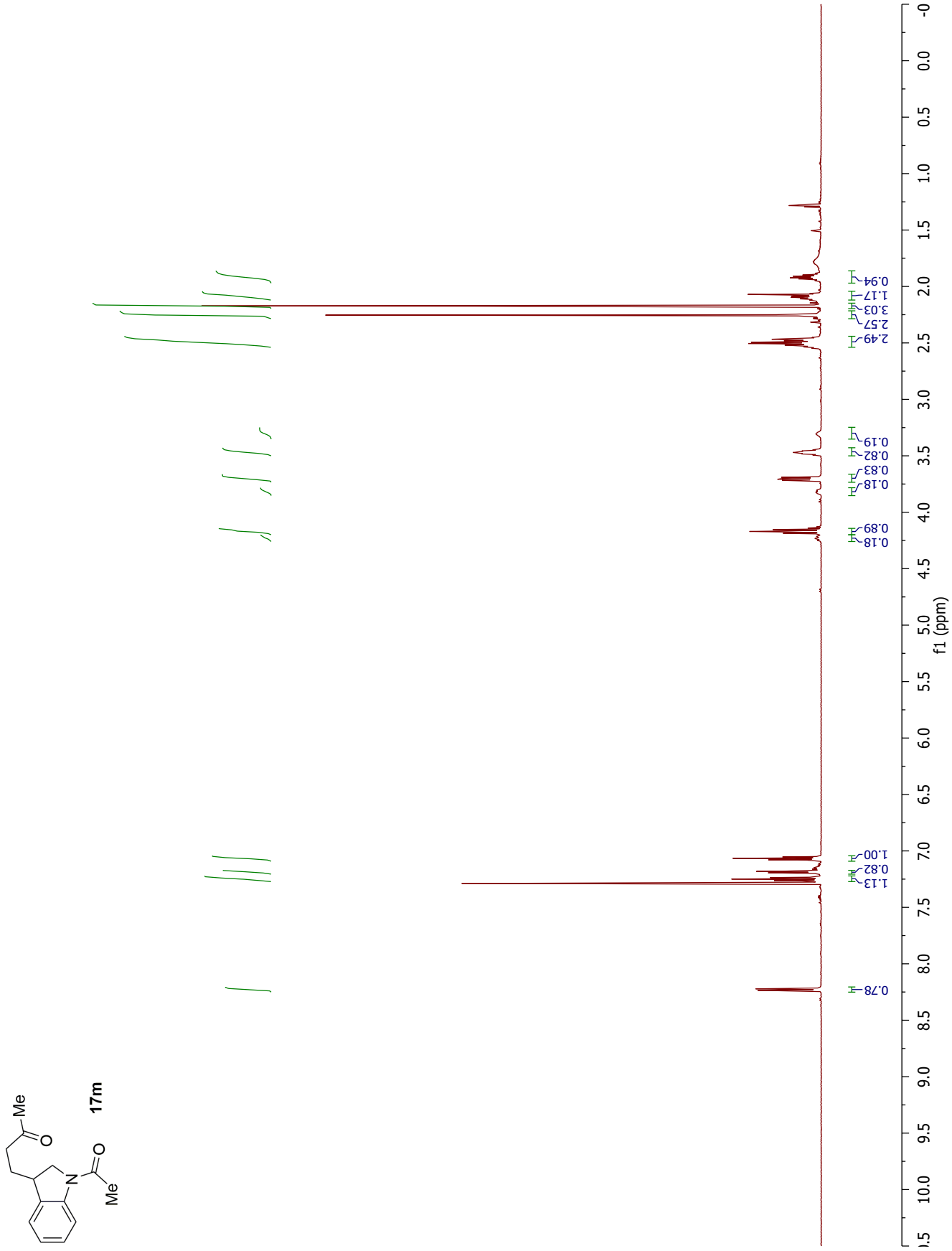

OTBS
N
O
Me
17j
168.74
143.23
131.77
128.30
124.34
123.44
117.03
66.01
52.33
43.11
25.84
24.24
18.26
-5.33
-5.48
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

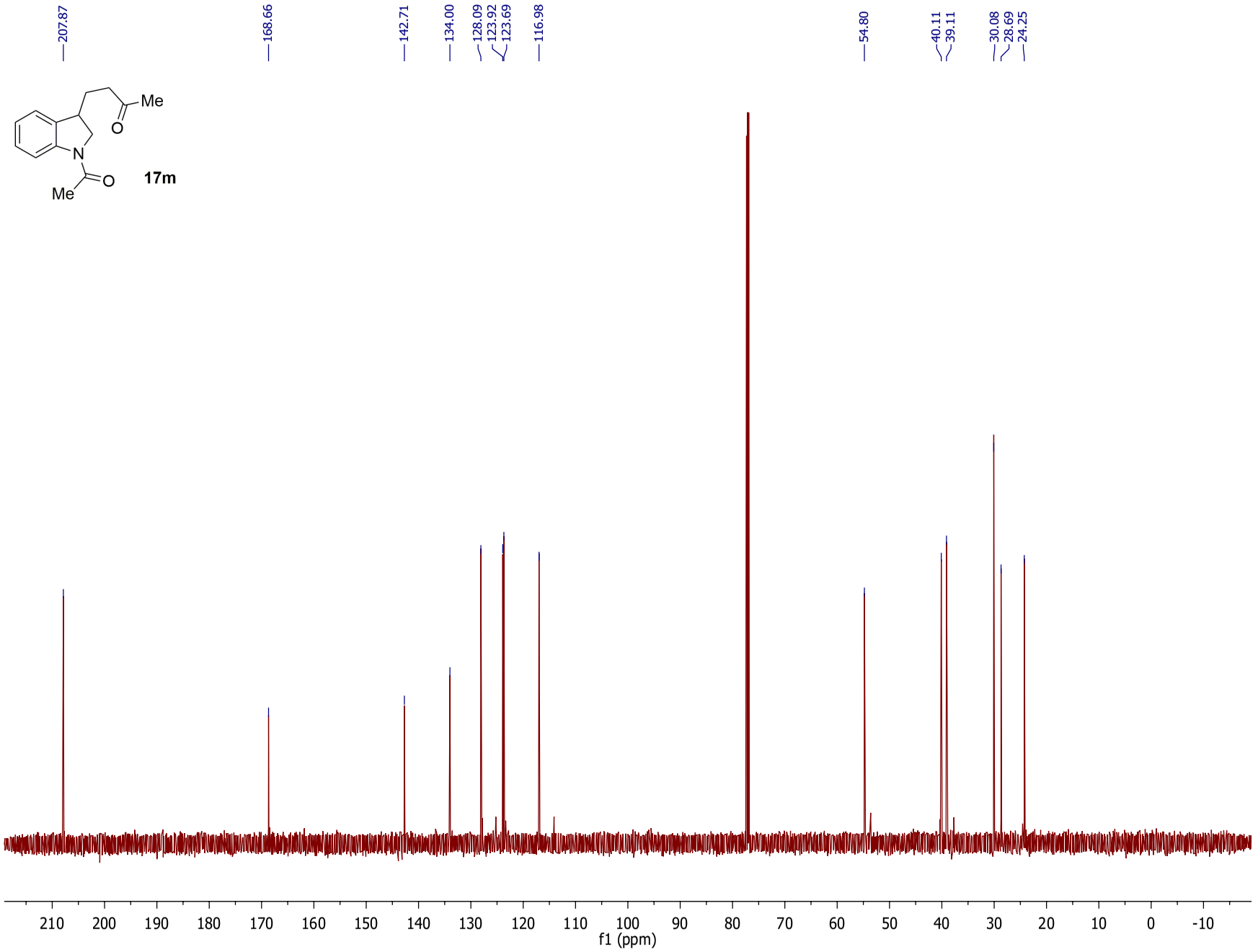

17k
N
O
Me
0.86
1.03
0.82
1.00
0.19
0.84
0.14
0.85
0.06
0.06
0.81
0.17
2.91
0.52
5.22
1.08
1.78
2.16
2.03
f1 (ppm)

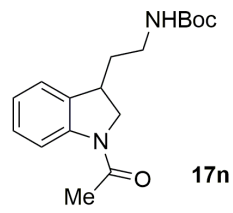

17k
N
O
Me
168.52
143.19
133.53
127.74
124.49
123.35
116.78
51.89
45.59
42.34
30.59
27.92
26.47
26.40
26.26
24.33
f1 (ppm)


CN
N
O
Me
17l
3.08
1.02
2.45
2.06
0.69
0.18
0.83
0.81
0.18
0.29
0.88
0.20
1.17
0.94
1.00
0.78
f1 (ppm)


CN
N
O
Me
17l
168.60
142.65
133.66
128.26
123.78
123.75
119.22
117.08
54.73
39.38
34.31
24.29
22.60
17.35
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

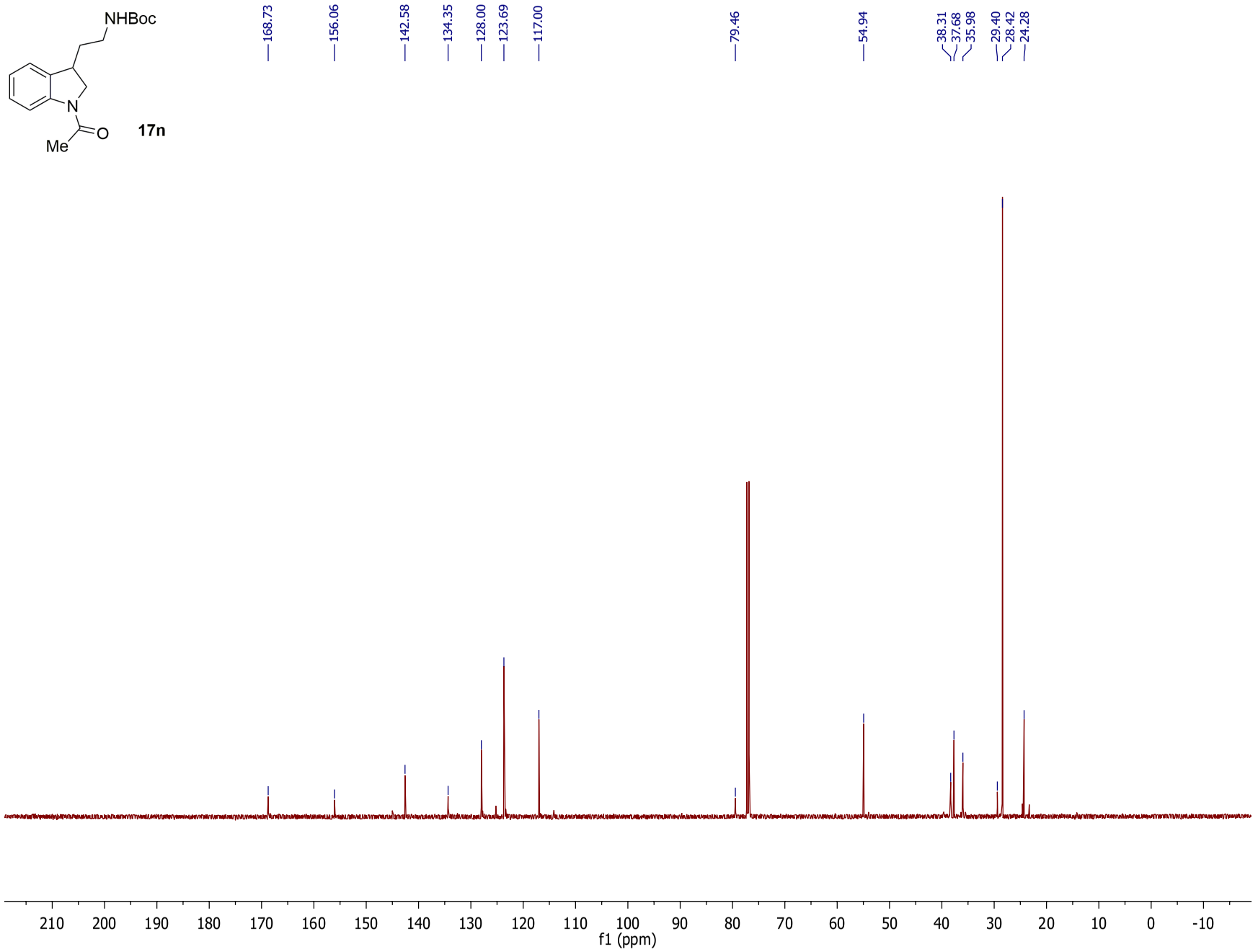

Me
O
O
N
Me
17m
0.78
1.13
0.82
1.00
0.18
0.89
0.18
0.83
0.82
0.19
2.49
2.57
3.03
1.17
0.94
f1 (ppm)

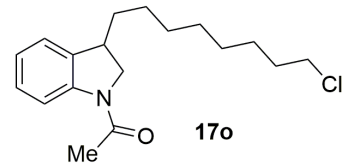

207.87
168.66
142.71
134.00
128.09
123.92
123.69
116.98
54.80
40.11
39.11
30.08
28.69
24.25
Me
O
N
O
Me
17m
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


NHBoc
N
O
Me

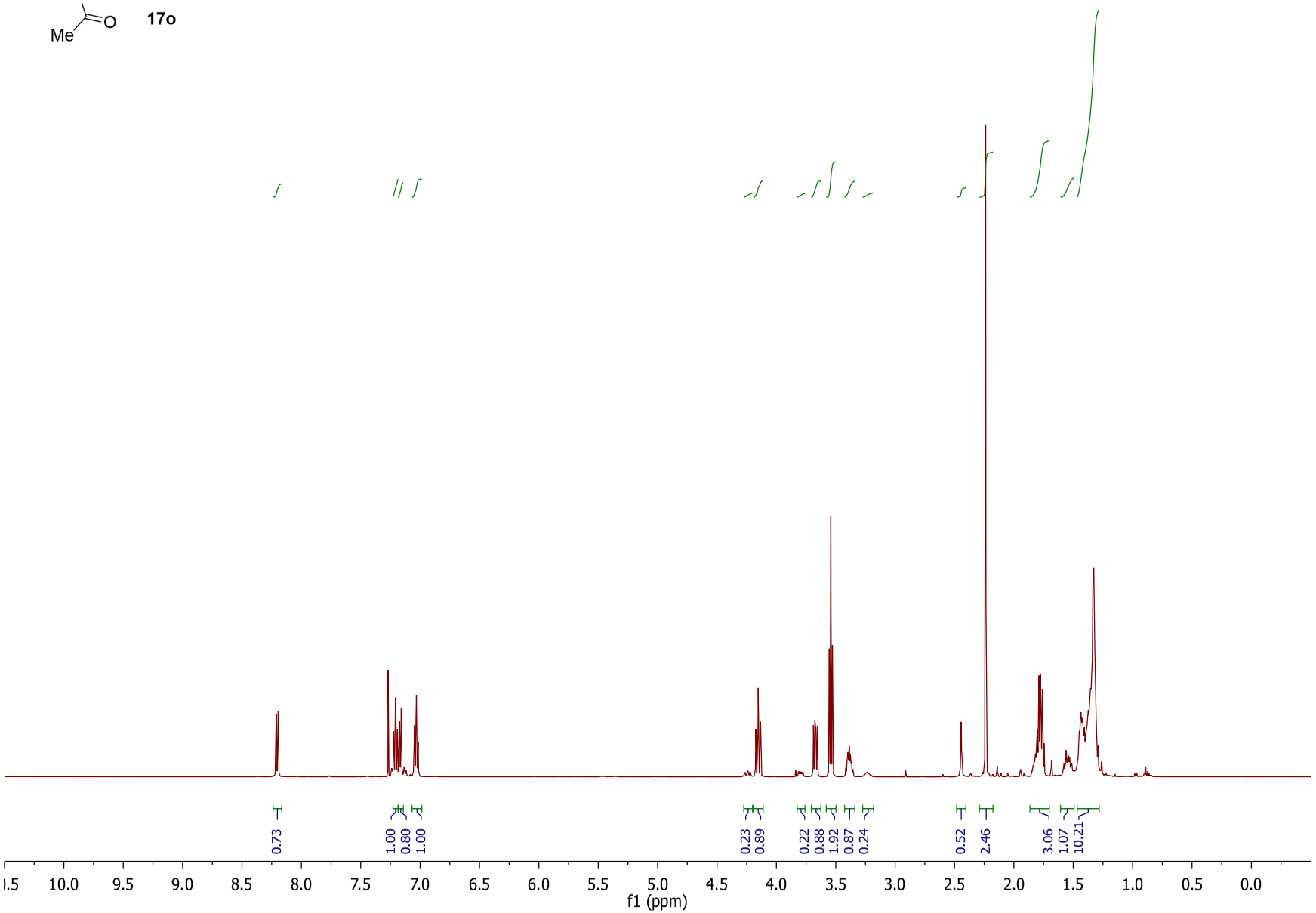
17n

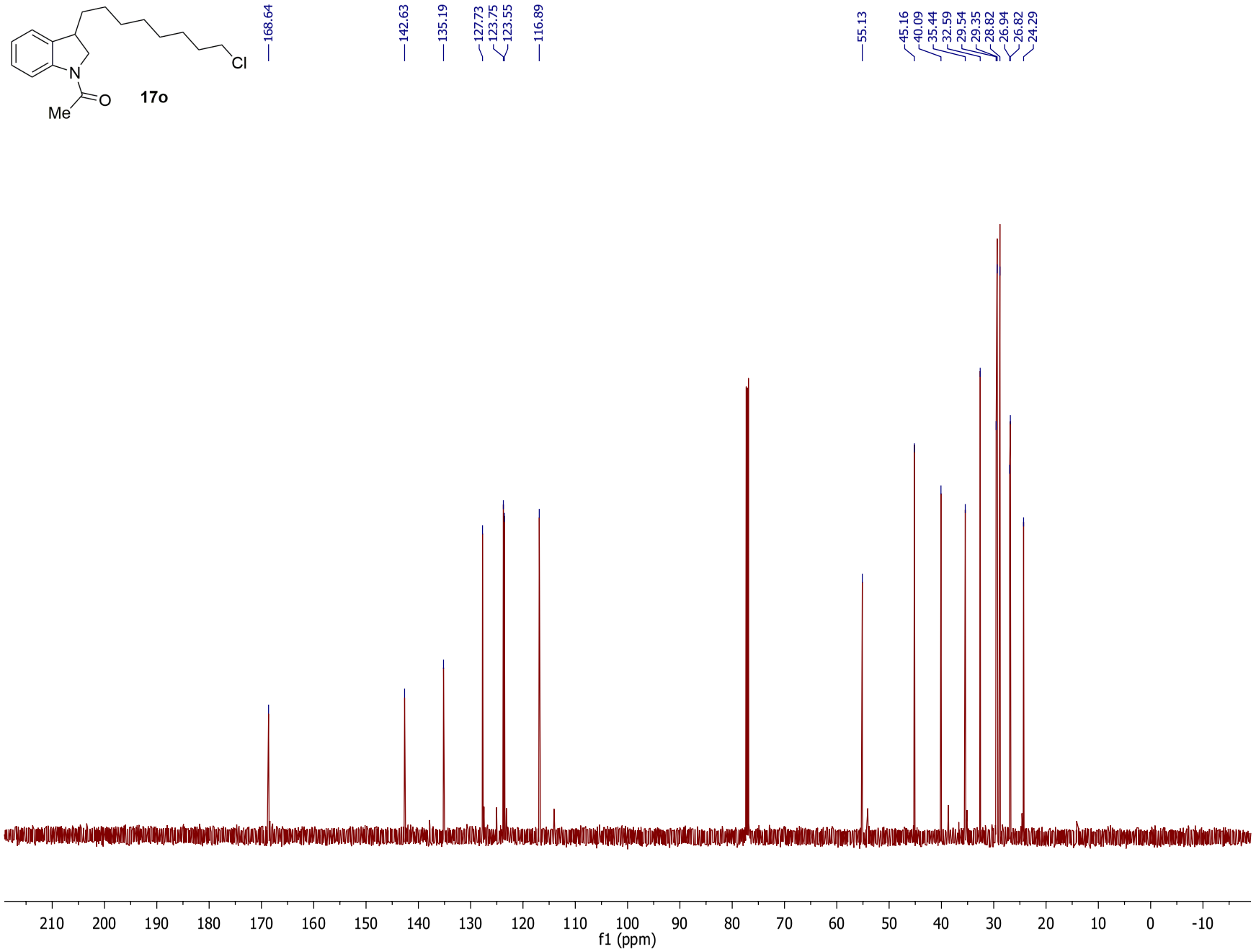
0.80
0.99
0.83
1.00
1.00
1.05
0.23
1.00
0.95
2.44
0.51
2.63
1.25
1.35
9.36
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

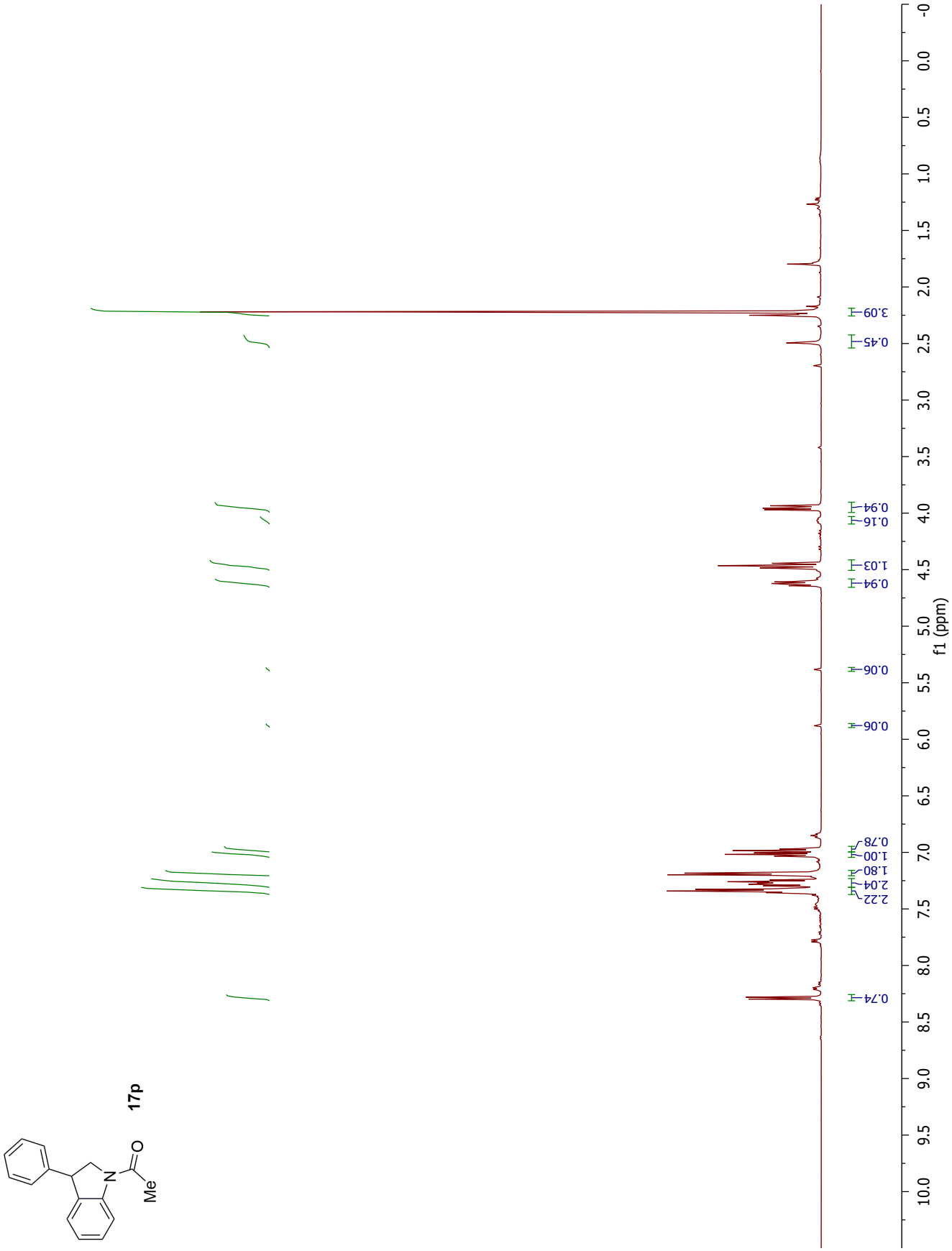

NHBoc
N
O
Me
17n
168.73
156.06
142.58
134.35
128.00
123.69
117.00
79.46
54.94
38.31
37.68
35.98
29.40
28.42
24.28
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

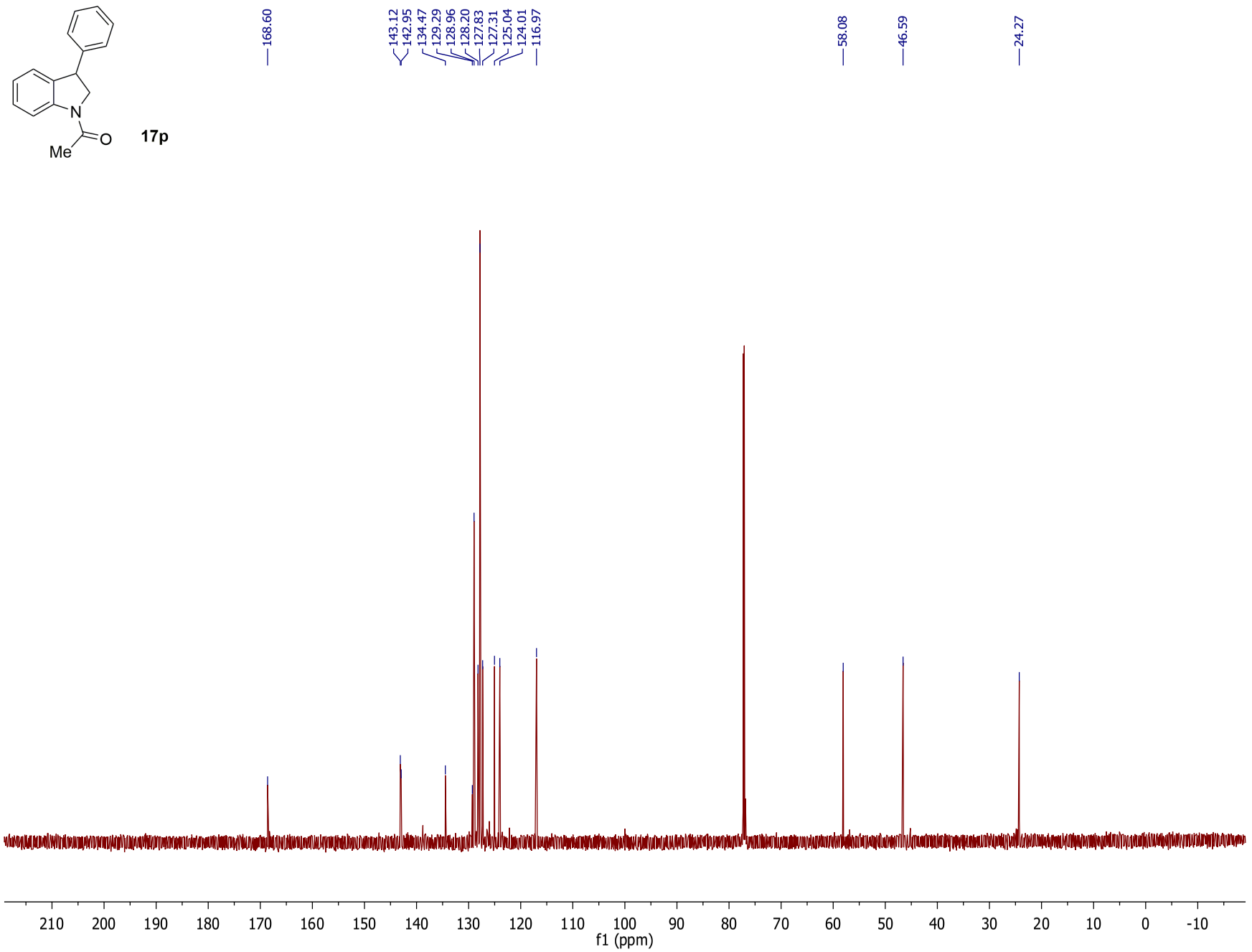

Cl
N
O
Me

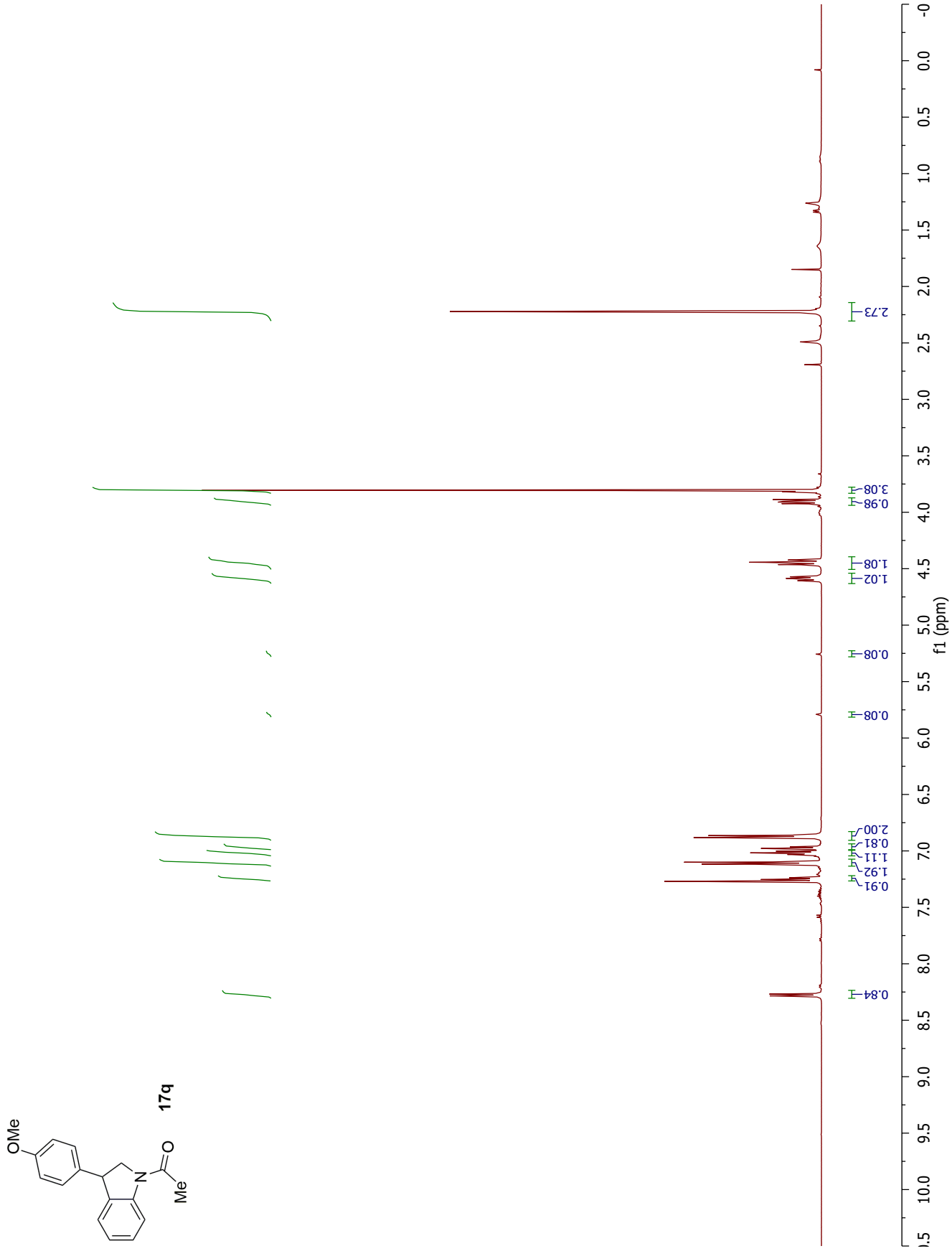
17o

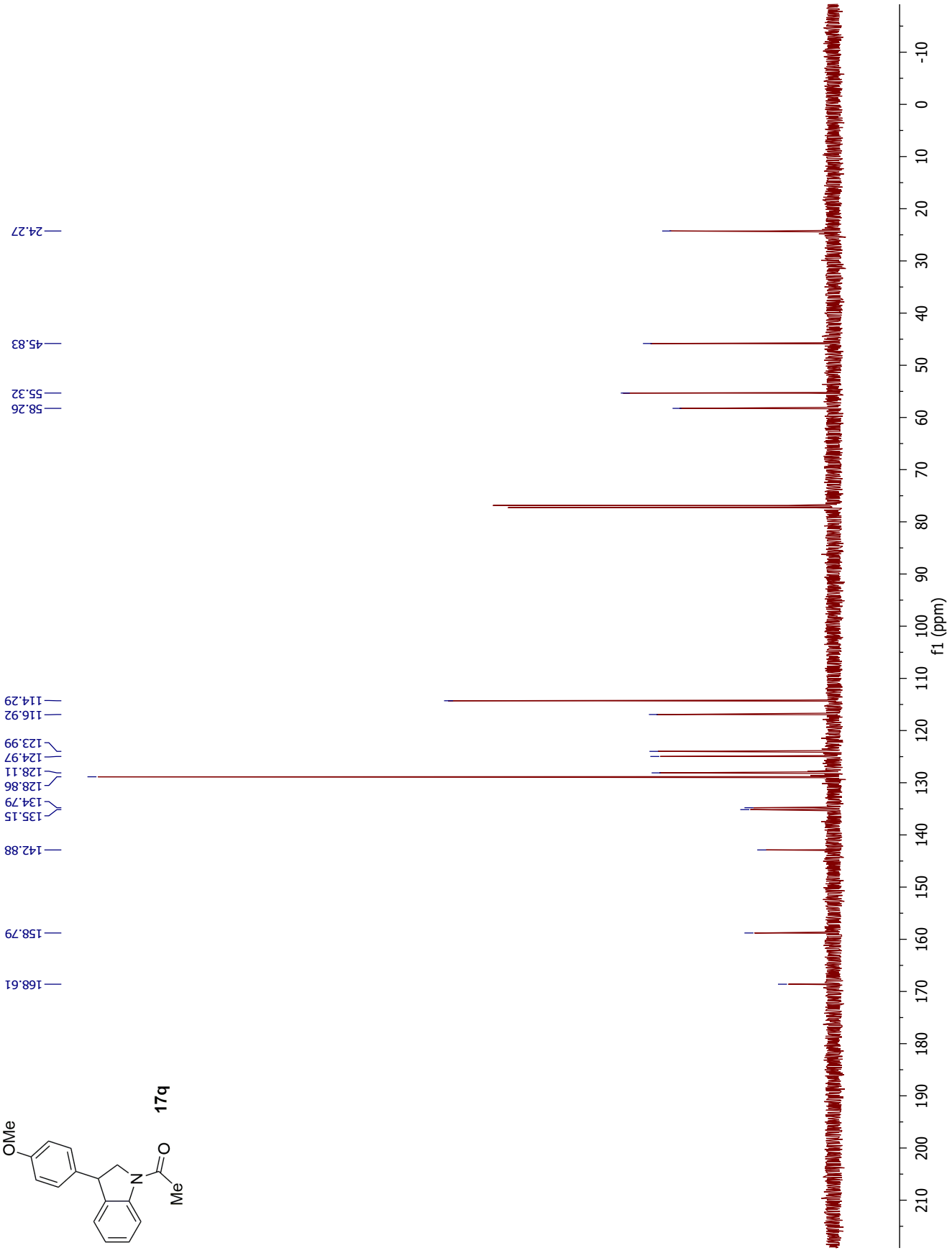

0.73
1.00
0.80
1.00
0.23
0.89
0.22
0.88
1.92
0.87
0.24
0.52
2.46
3.06
1.07
10.21
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

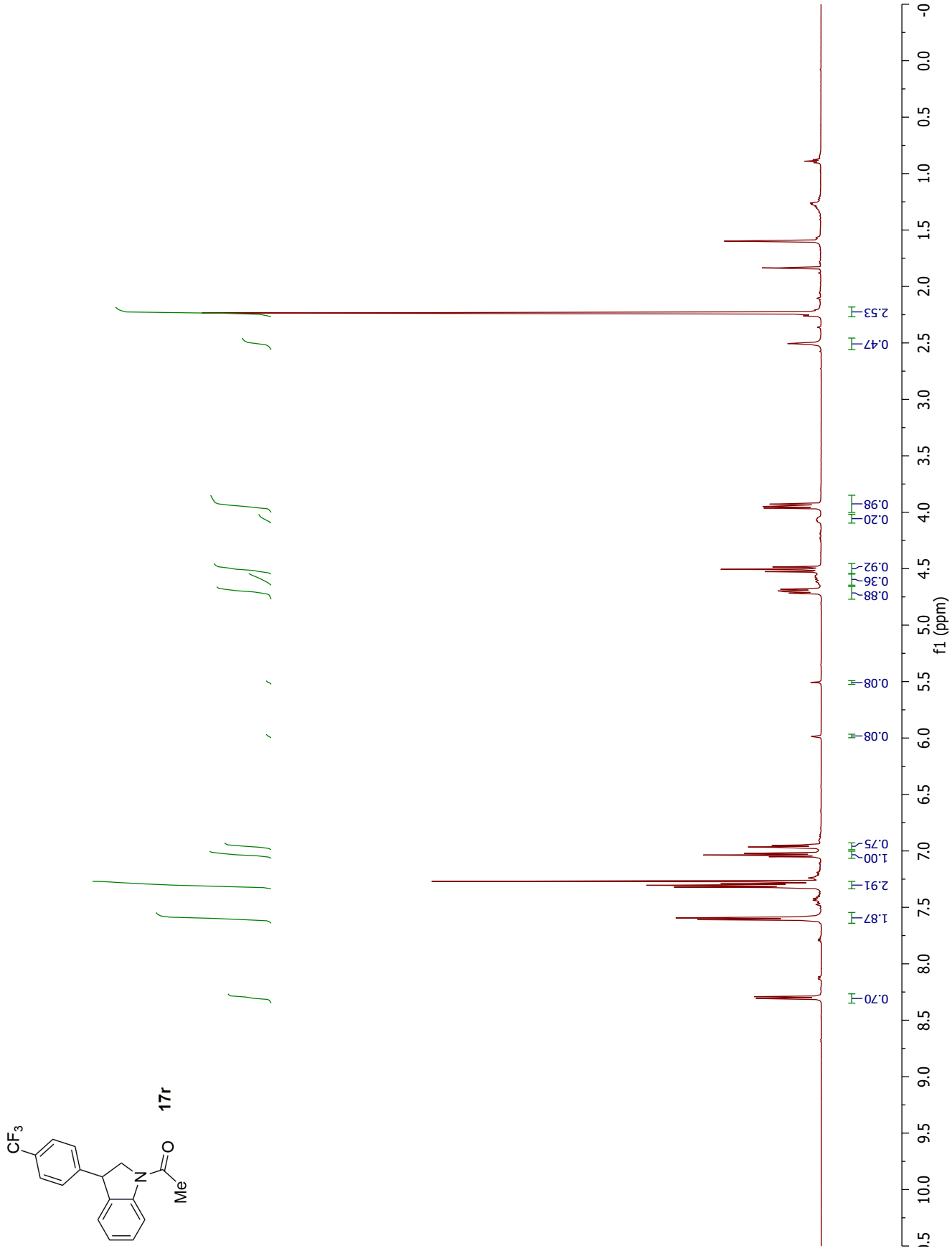

168.64
142.63
135.19
127.73
123.75
123.55
116.89
55.13
45.16
40.09
35.44
32.59
29.54
29.35
28.82
26.94
26.82
24.29
Cl
N
O
Me
17o
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

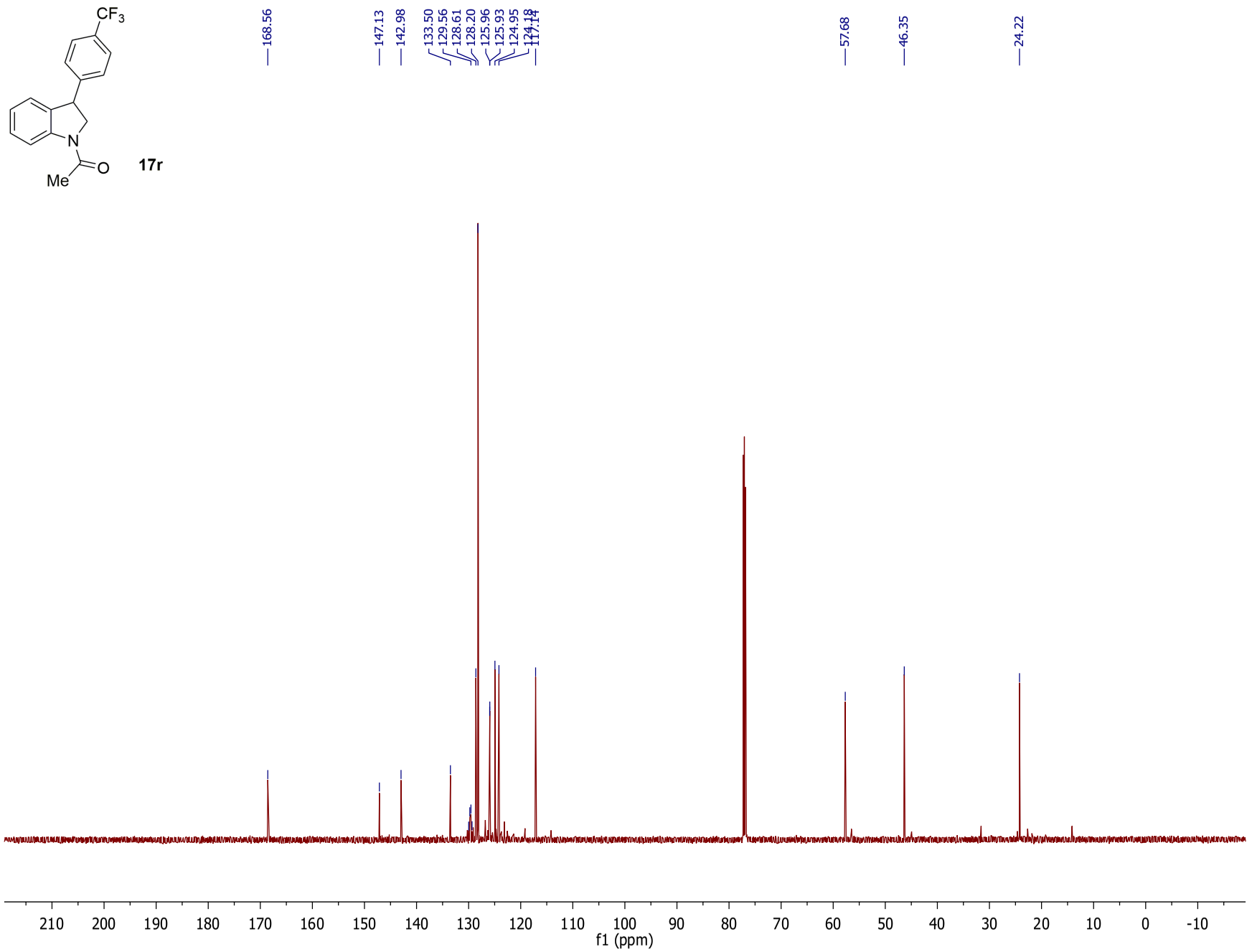

17p
N
O
Me
3.09
0.45
0.94
0.16
1.03
0.94
0.06
0.06
0.78
1.00
1.80
2.04
2.22
0.74
f1 (ppm)

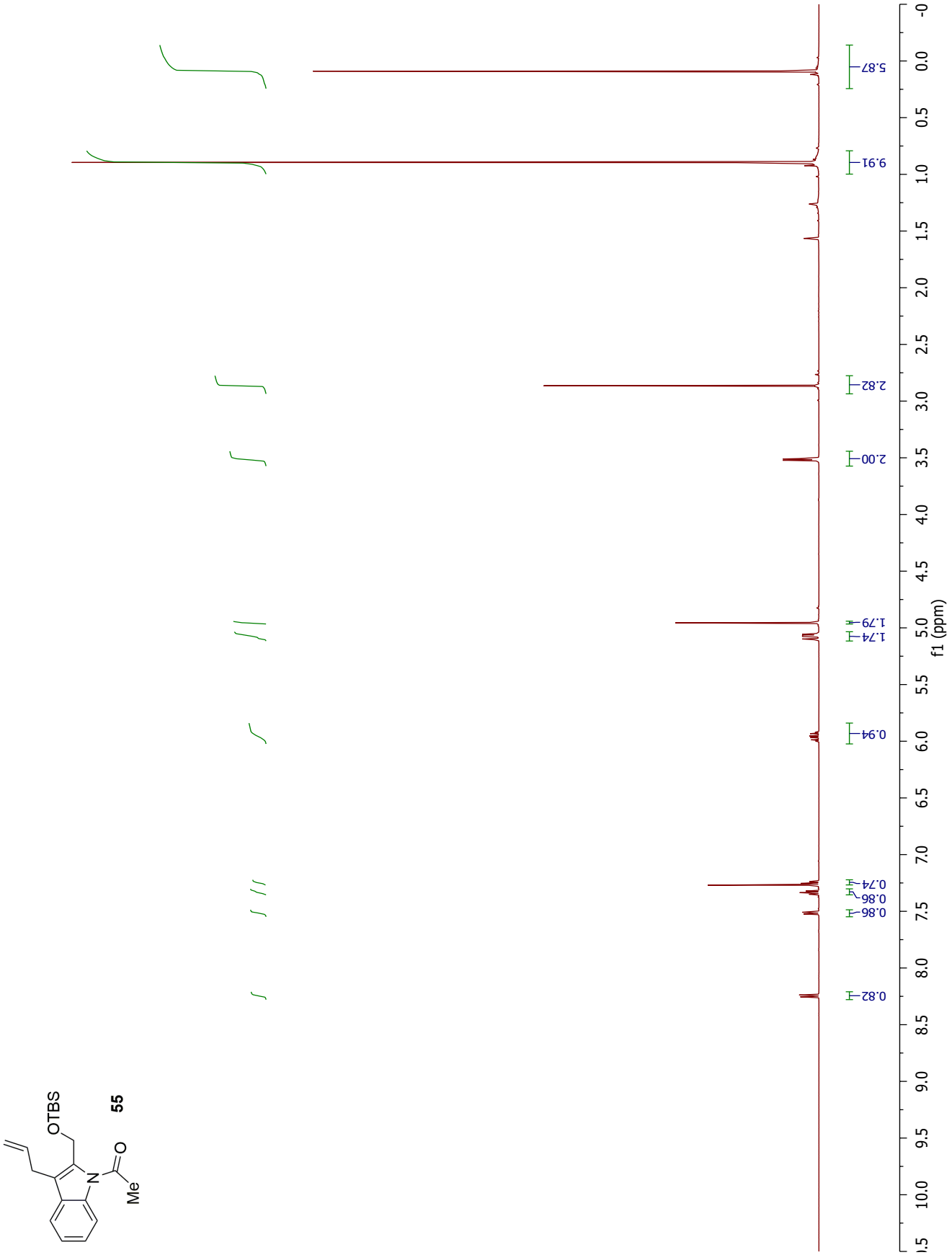

168.60
143.12
142.95
134.47
129.29
128.96
128.20
127.83
127.31
125.04
124.01
116.97
58.08
46.59
24.27
N
O
Me
17p
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

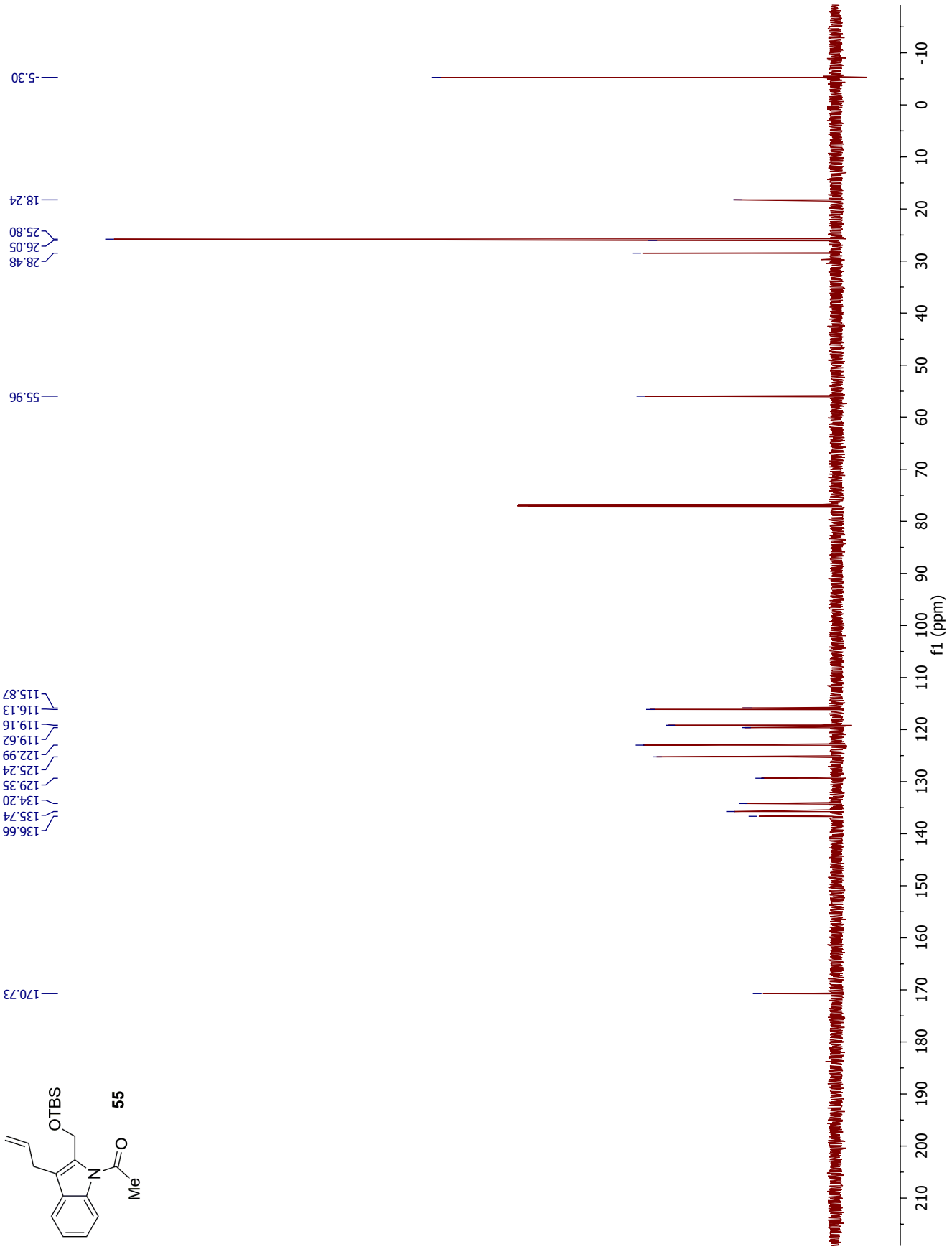

17q
OMe
N
O
Me
2.73
3.08
0.98
1.02
1.08
0.08
0.08
2.00
0.81
1.11
1.92
0.91
0.84
f1 (ppm)

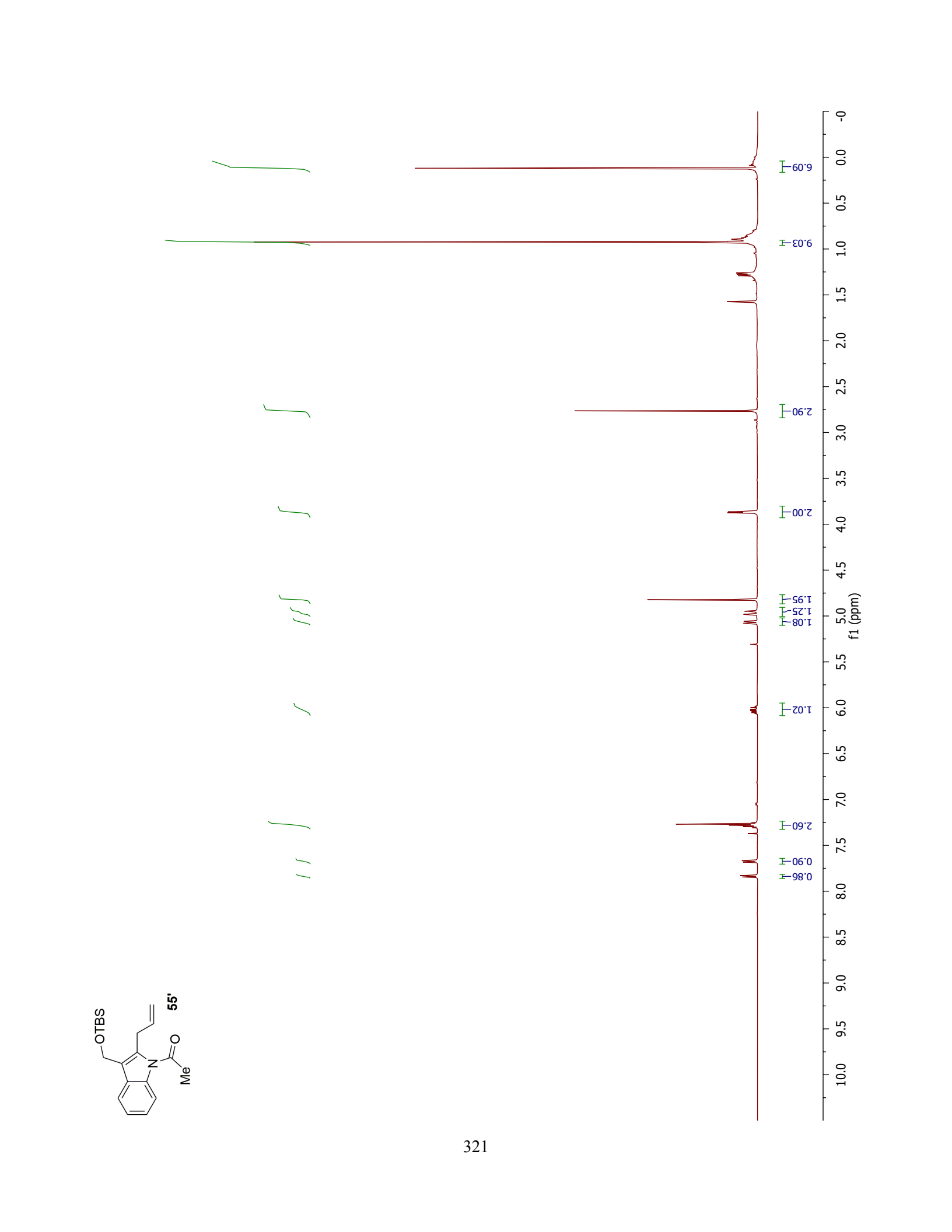

17q
OMe
N
O
Me
168.61
158.79
142.88
135.15
134.79
128.86
128.11
124.97
123.99
116.92
114.29
58.26
55.32
45.83
24.27
f1 (ppm)

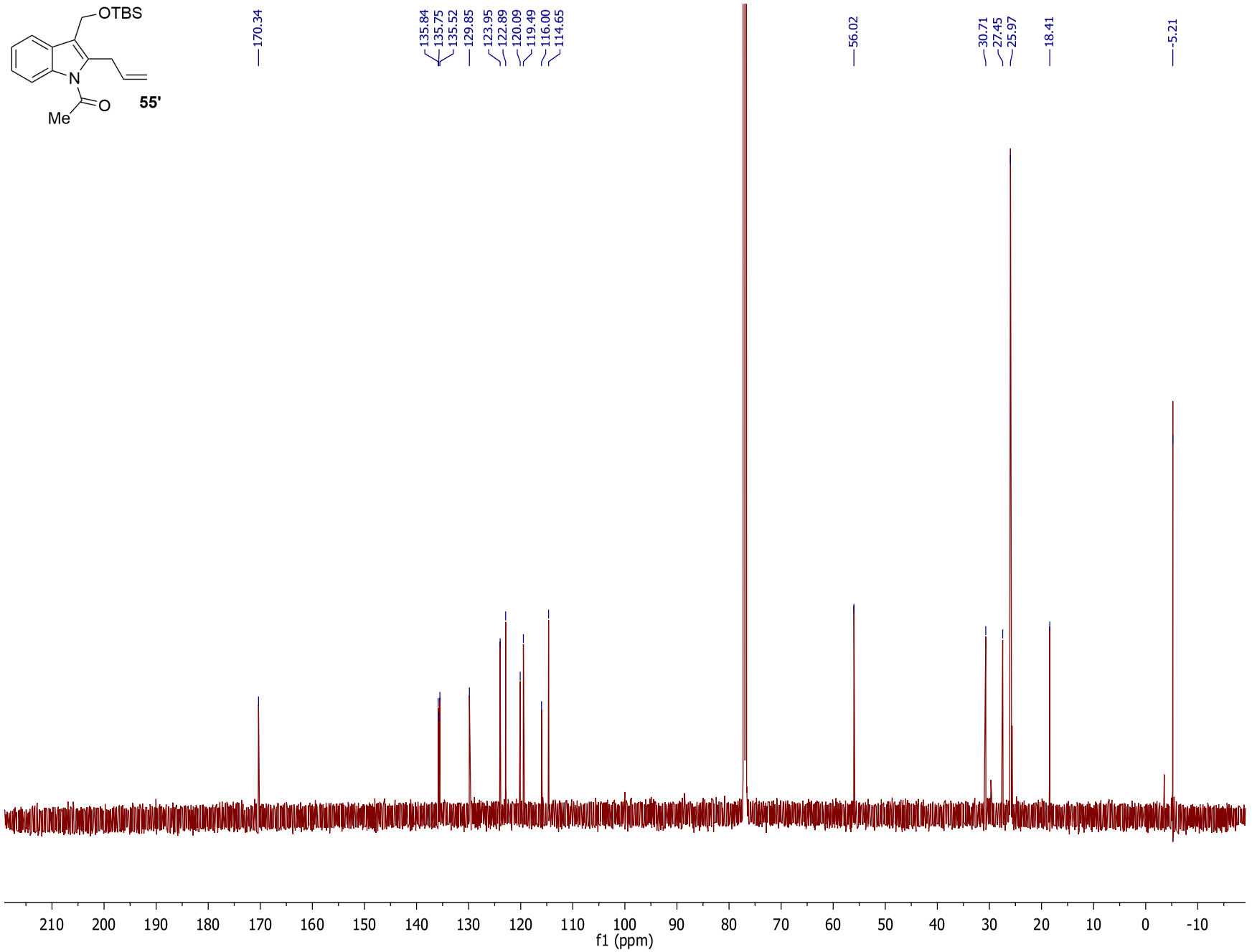

CF3
N
O
Me
17r
2.53
0.47
0.98
0.20
0.92
0.36
0.88
0.08
0.08
0.75
1.00
2.91
1.87
0.70
f1 (ppm)

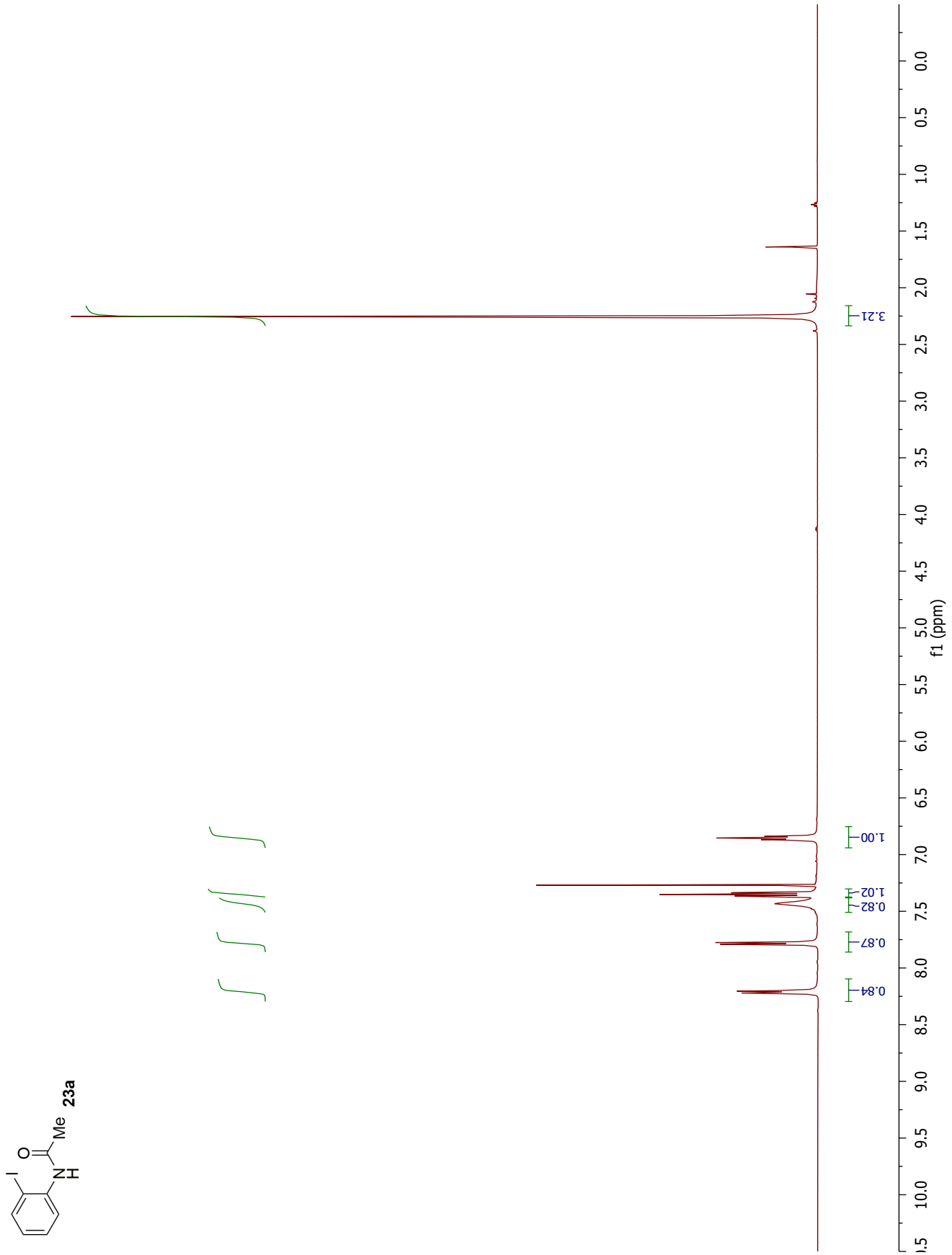

CF3
N
O
Me
17r
168.56
147.13
142.98
133.50
129.56
128.61
128.20
125.96
125.93
124.95
124.18
117.14
57.68
46.35
24.22
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

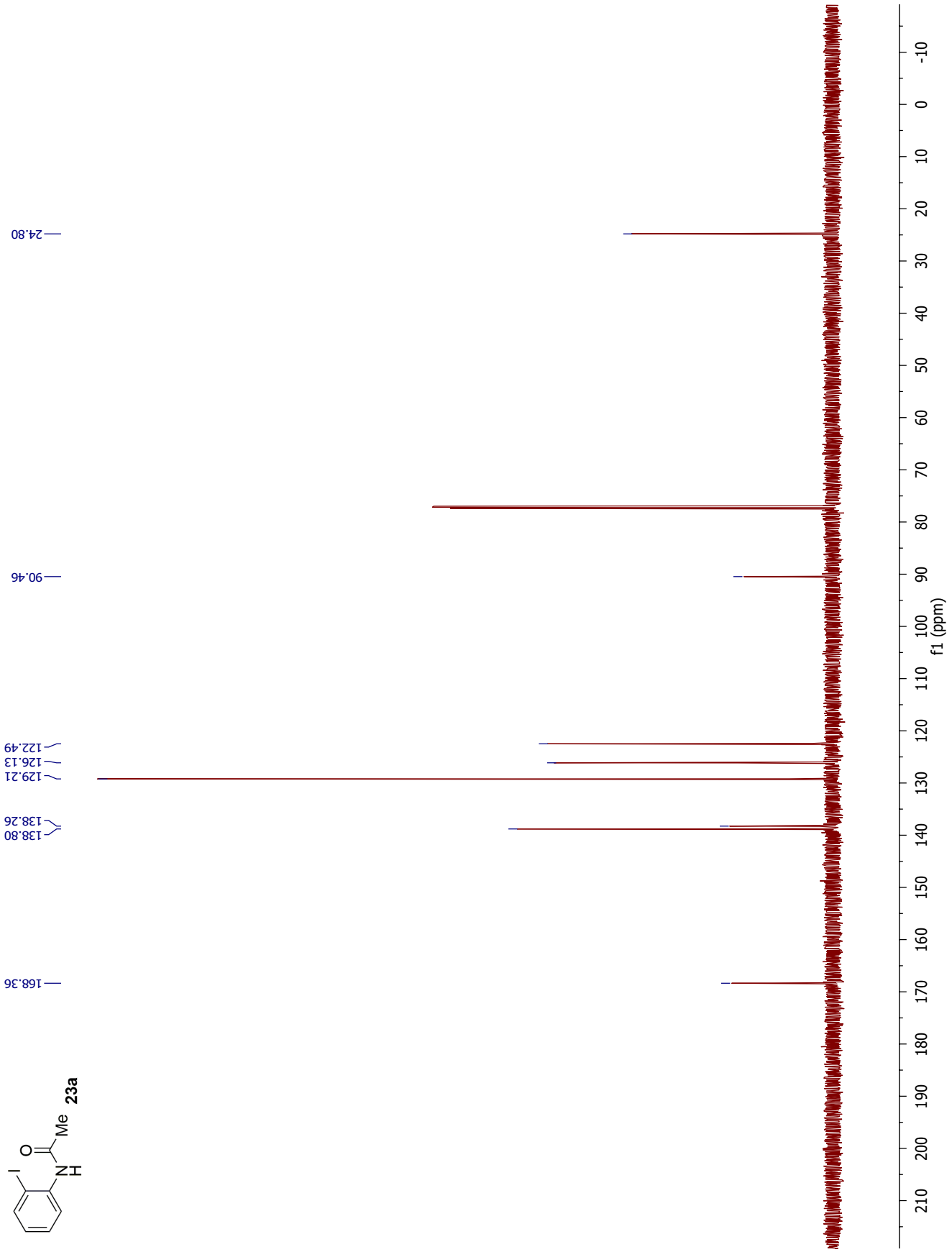

OTBS
55
N
O
Me
5.87
9.91
2.82
2.00
1.79
1.74
0.94
0.74
0.86
0.86
0.82
f1 (ppm)

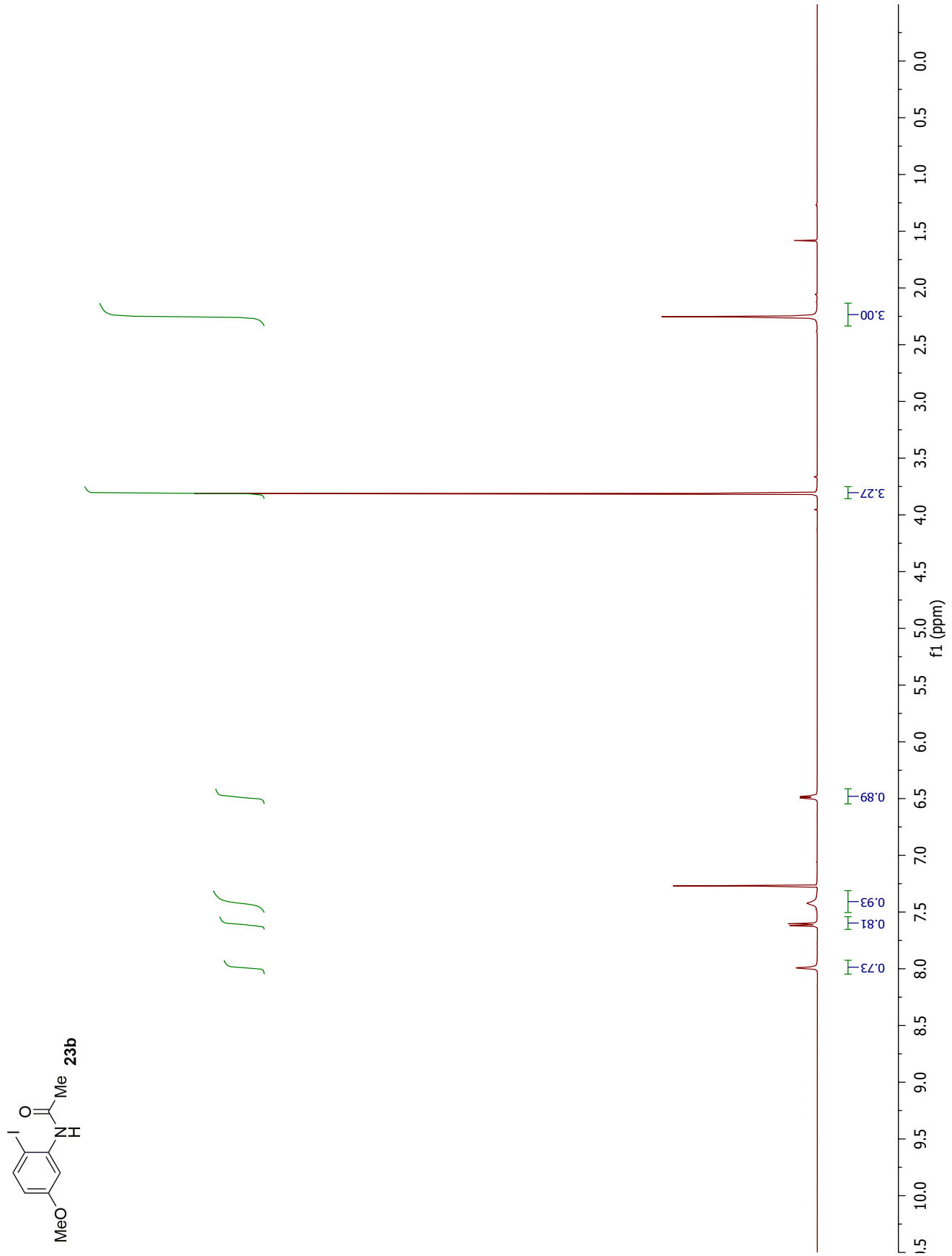

-5.30
18.24
25.80
26.05
28.48
55.96
115.87
116.13
119.16
119.62
122.99
125.24
129.35
134.20
135.74
136.66
170.73
f1 (ppm)
OTBS
55
N
O
Me

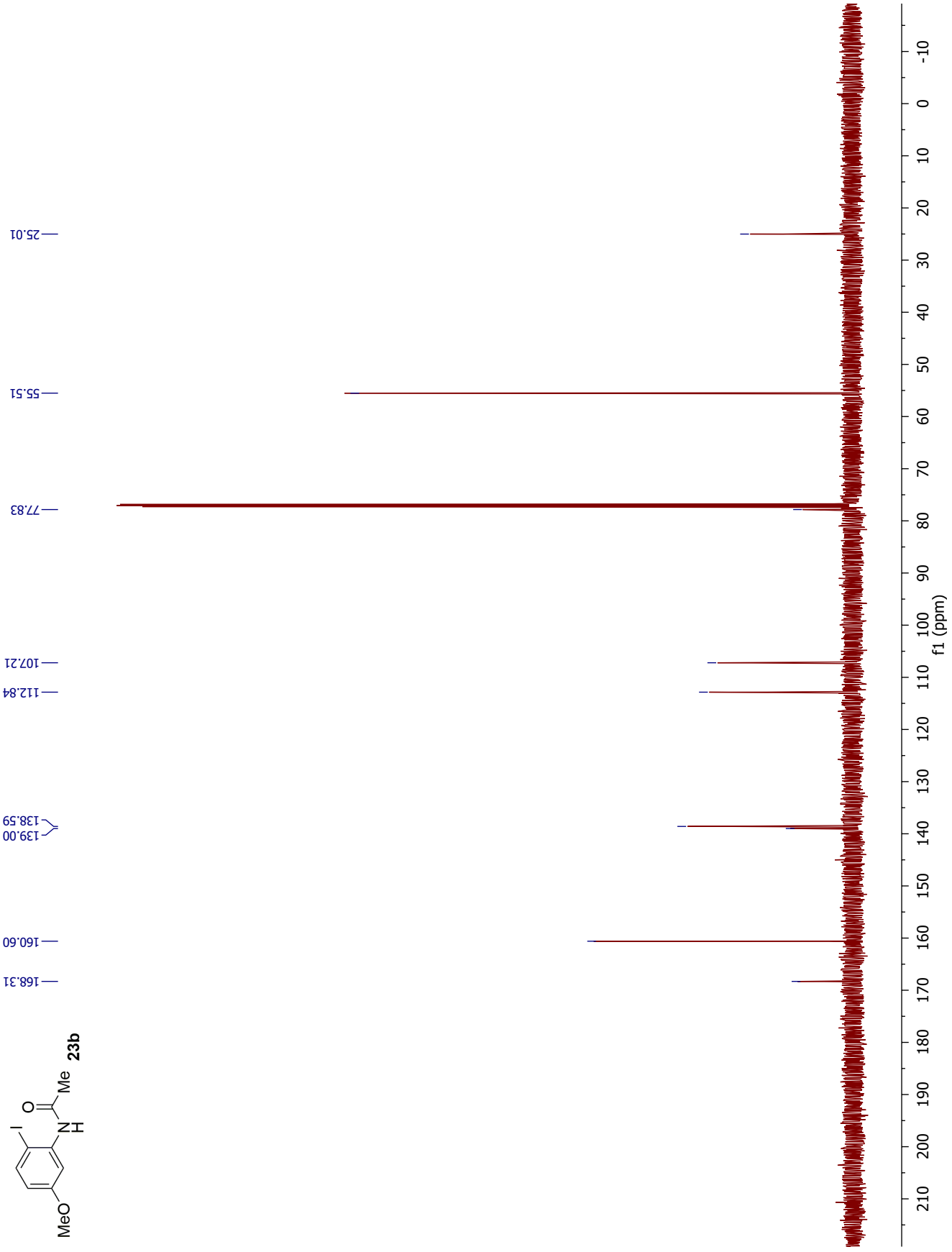

55'
OTBS
N
O
Me
6.09
9.03
2.90
2.00
1.95
1.25
1.08
1.02
2.60
0.90
0.86
f1 (ppm)

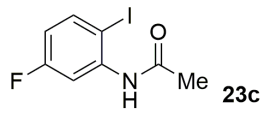

OTBS
N
O
Me
55'
170.34
135.84
135.75
135.52
129.85
123.95
122.89
120.09
119.49
116.00
114.65
56.02
30.71
27.45
25.97
18.41
-5.21
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


23a
3.21
1.00
1.02
0.82
0.87
0.84
f1 (ppm)

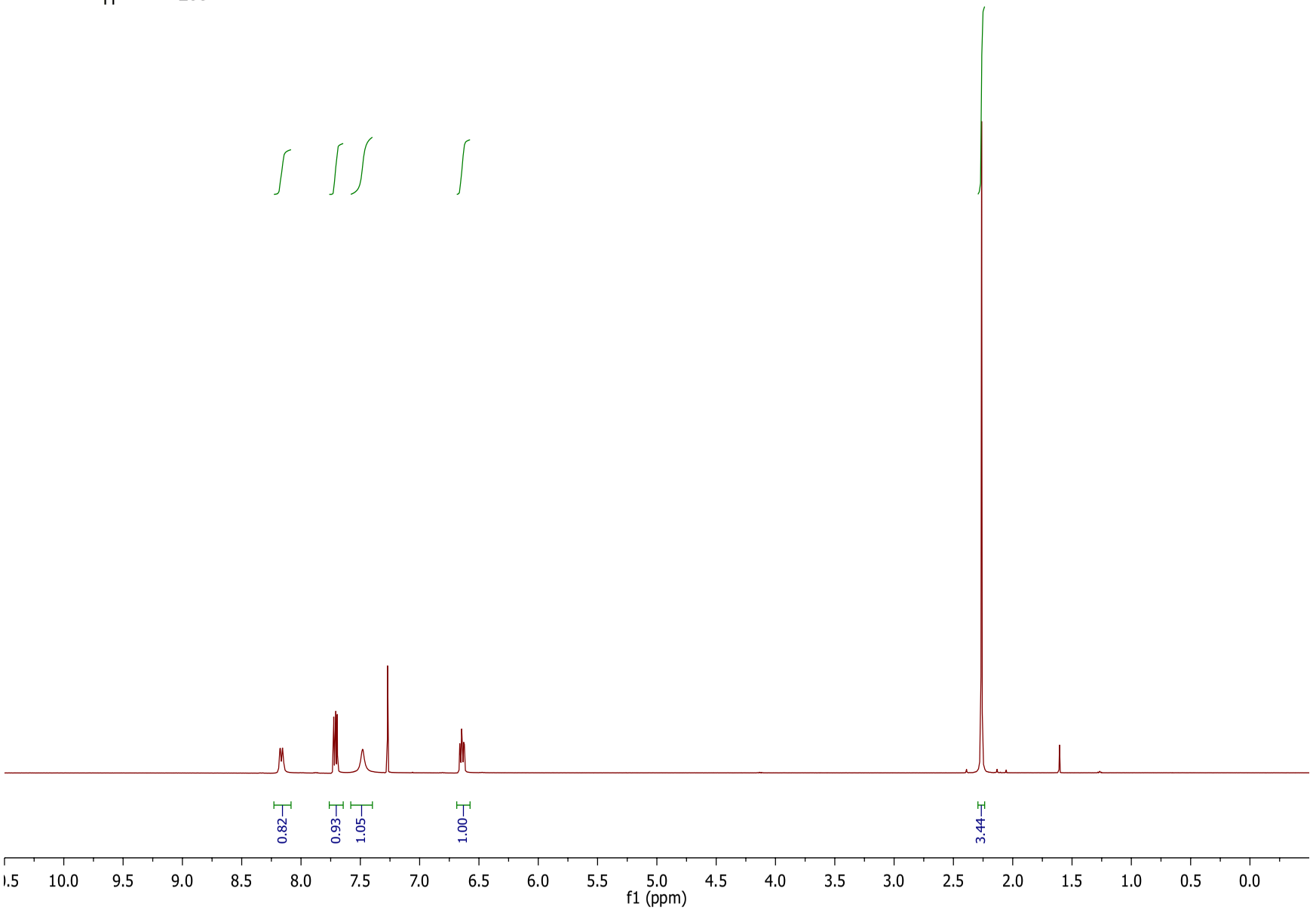

23a
168.36
138.80
138.26
129.21
126.13
122.49
90.46
24.80
f1 (ppm)

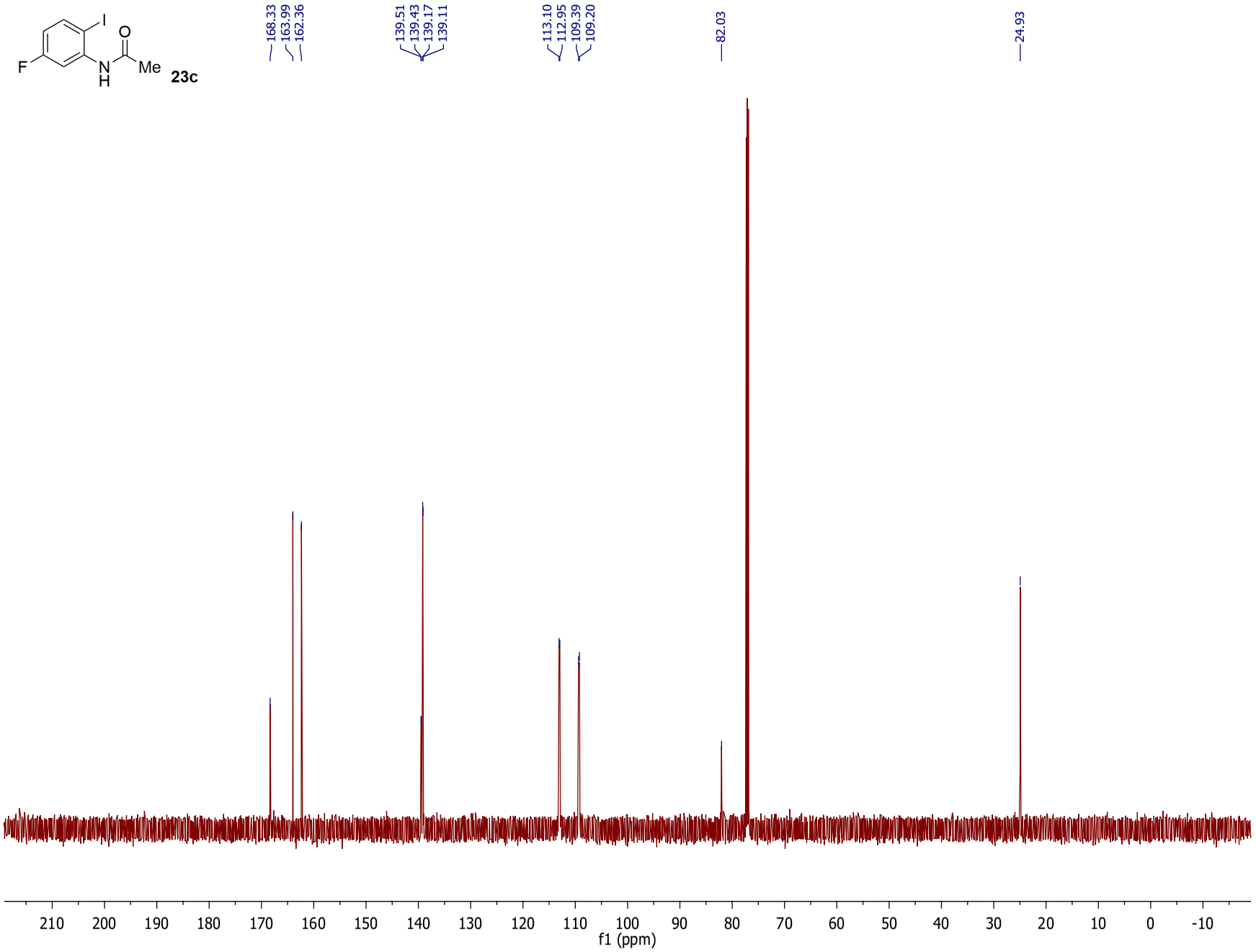

23b
I
O
N
H
Me
MeO
3.00
3.27
0.89
0.93
0.81
0.73
f1 (ppm)

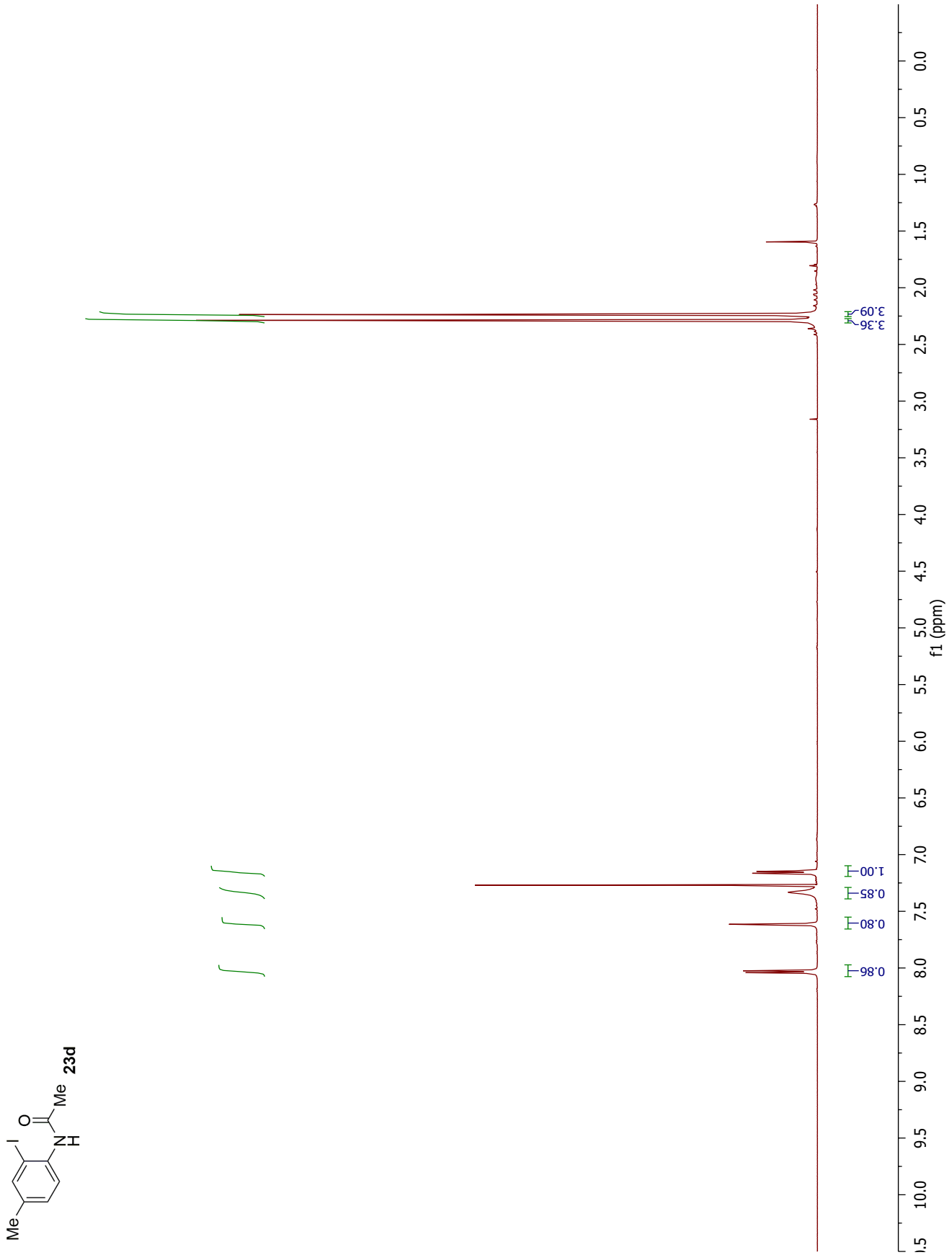

23b
MeO
I
O
Me
N
H
168.31
160.60
139.00
138.59
112.84
107.21
77.83
55.51
25.01
f1 (ppm)

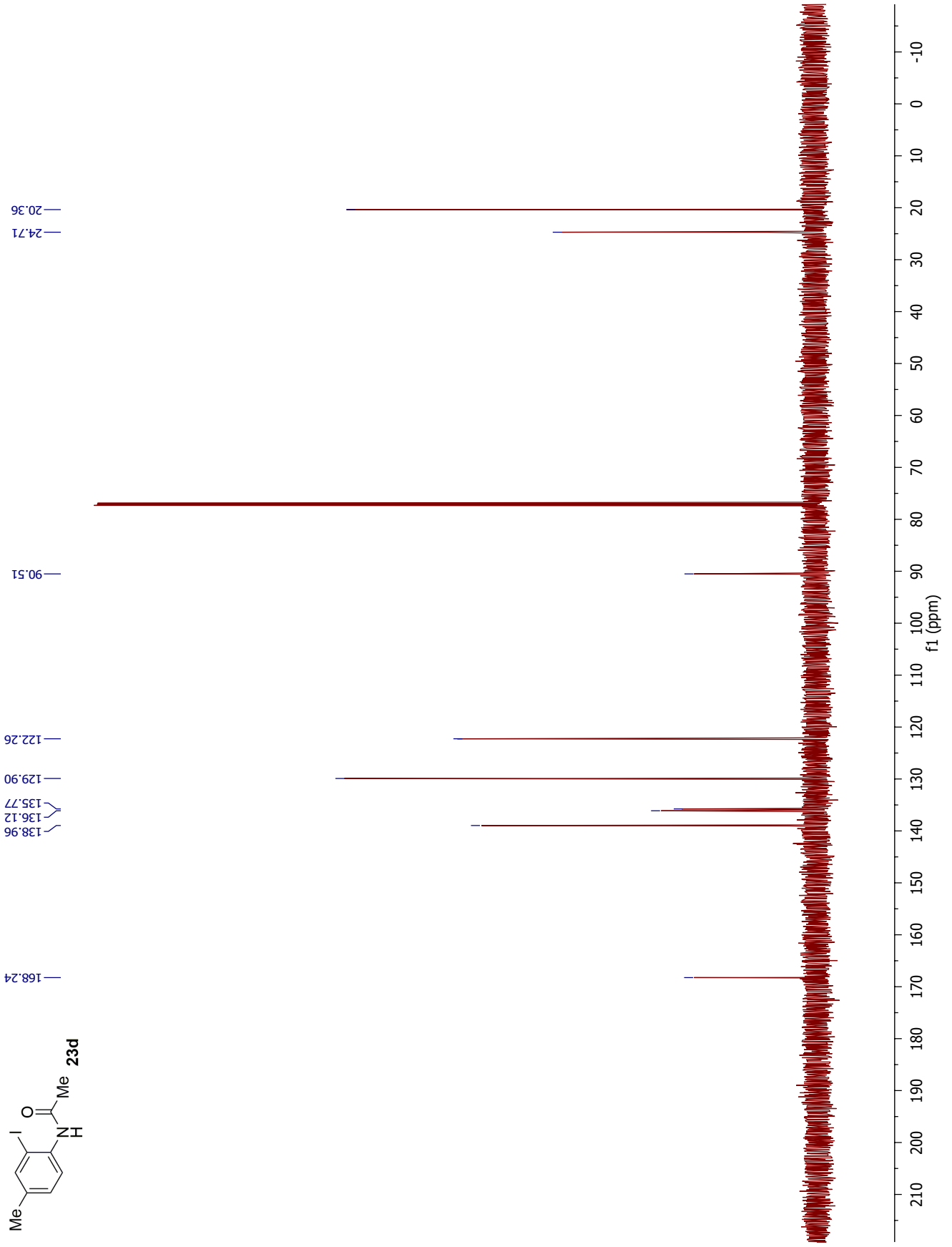

I
O
F
N
H
Me

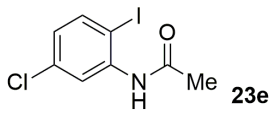
23c


0.82
0.93
1.05
1.00
3.44
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

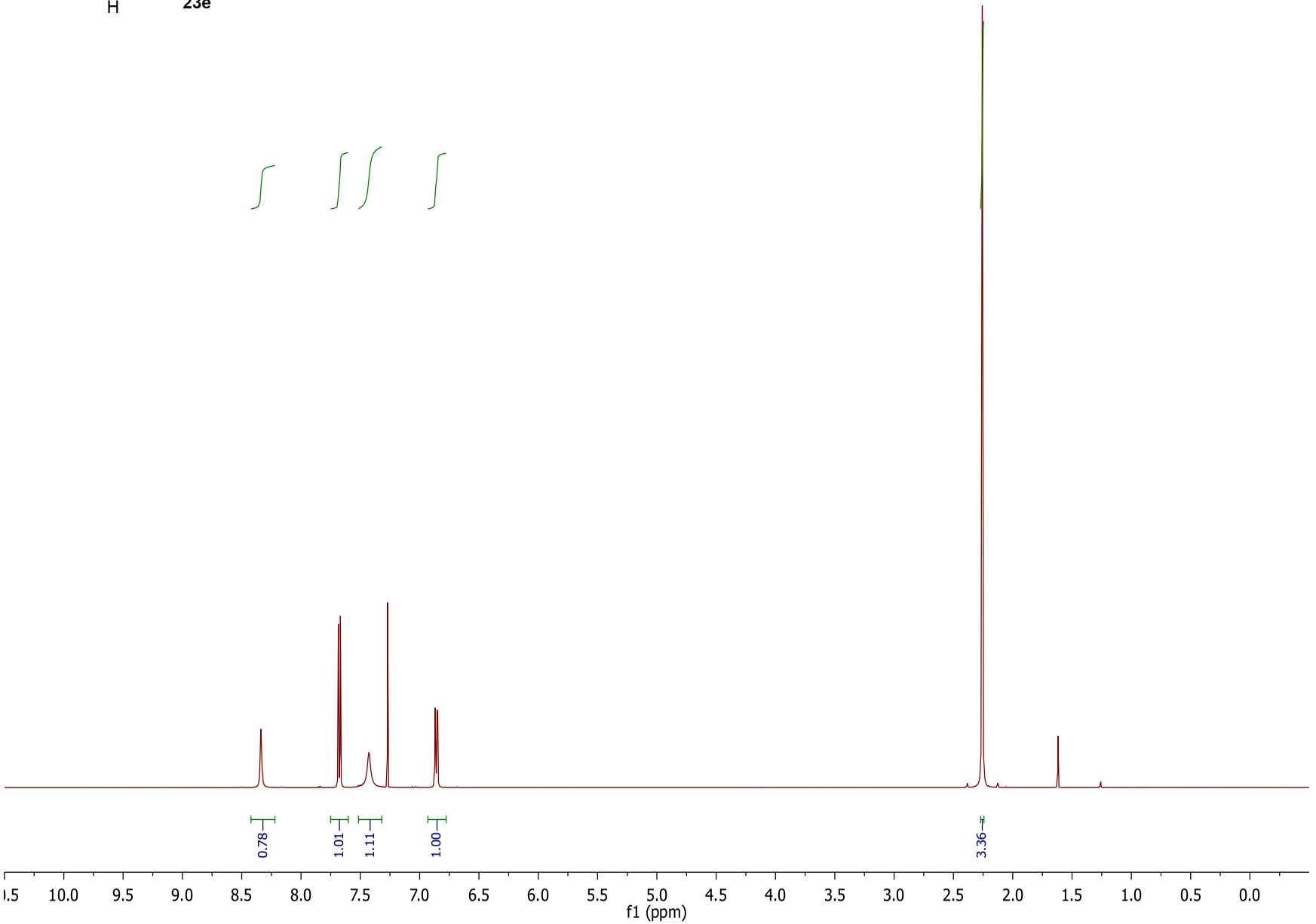

I
O
F
N
H
Me
23c
168.33
163.99
162.36
139.51
139.43
139.17
139.11
113.10
112.95
109.39
109.20
82.03
24.93
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

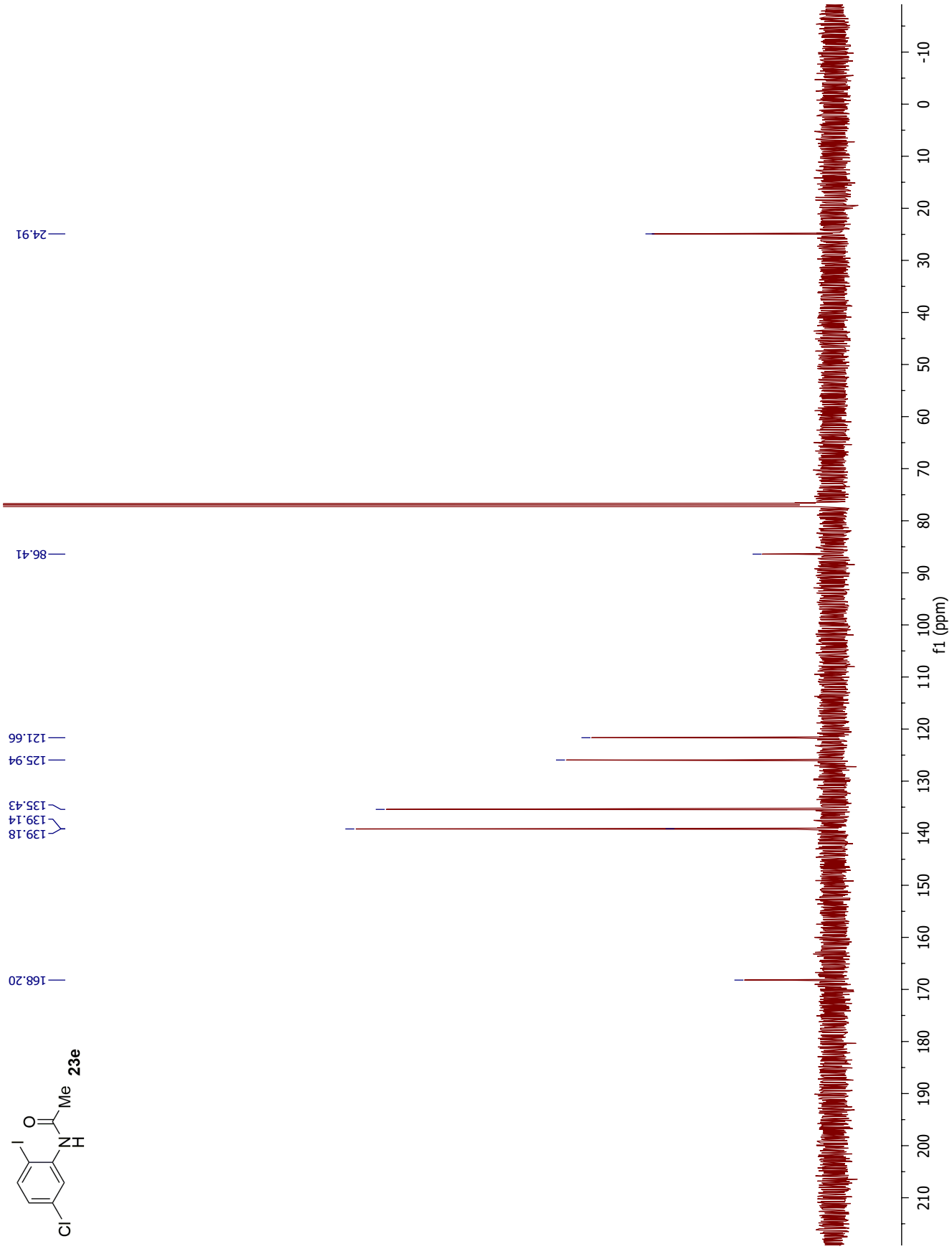

23d
Me
O
N
H
I
Me
3.36
3.09
1.00
0.85
0.80
0.86
f1 (ppm)

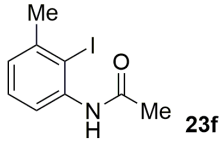

23d
Me
O
N
H
I
Me
168.24
138.96
136.12
135.77
129.90
122.26
90.51
24.71
20.36
f1 (ppm)


I
O
Cl
N
H
Me

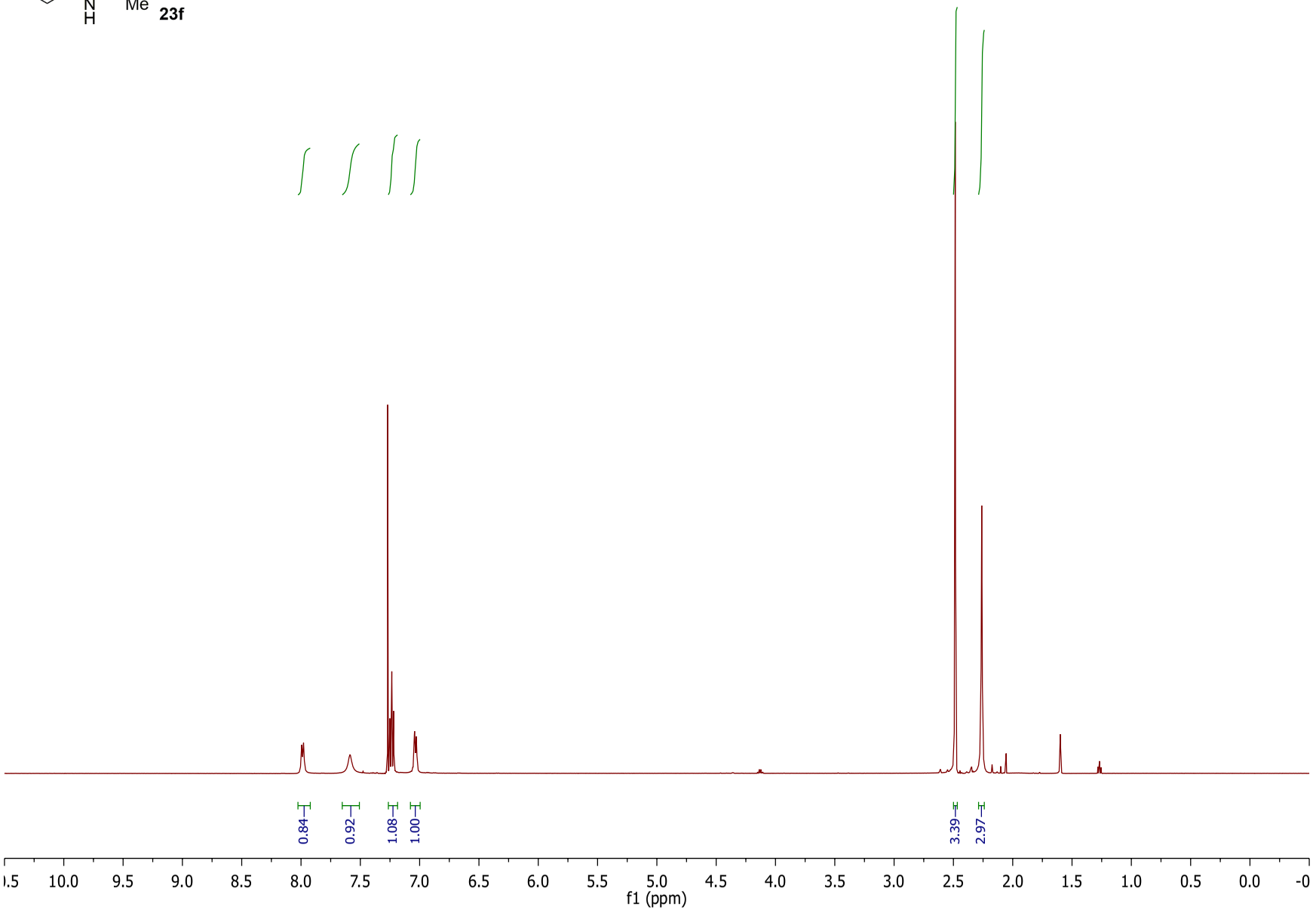
23e

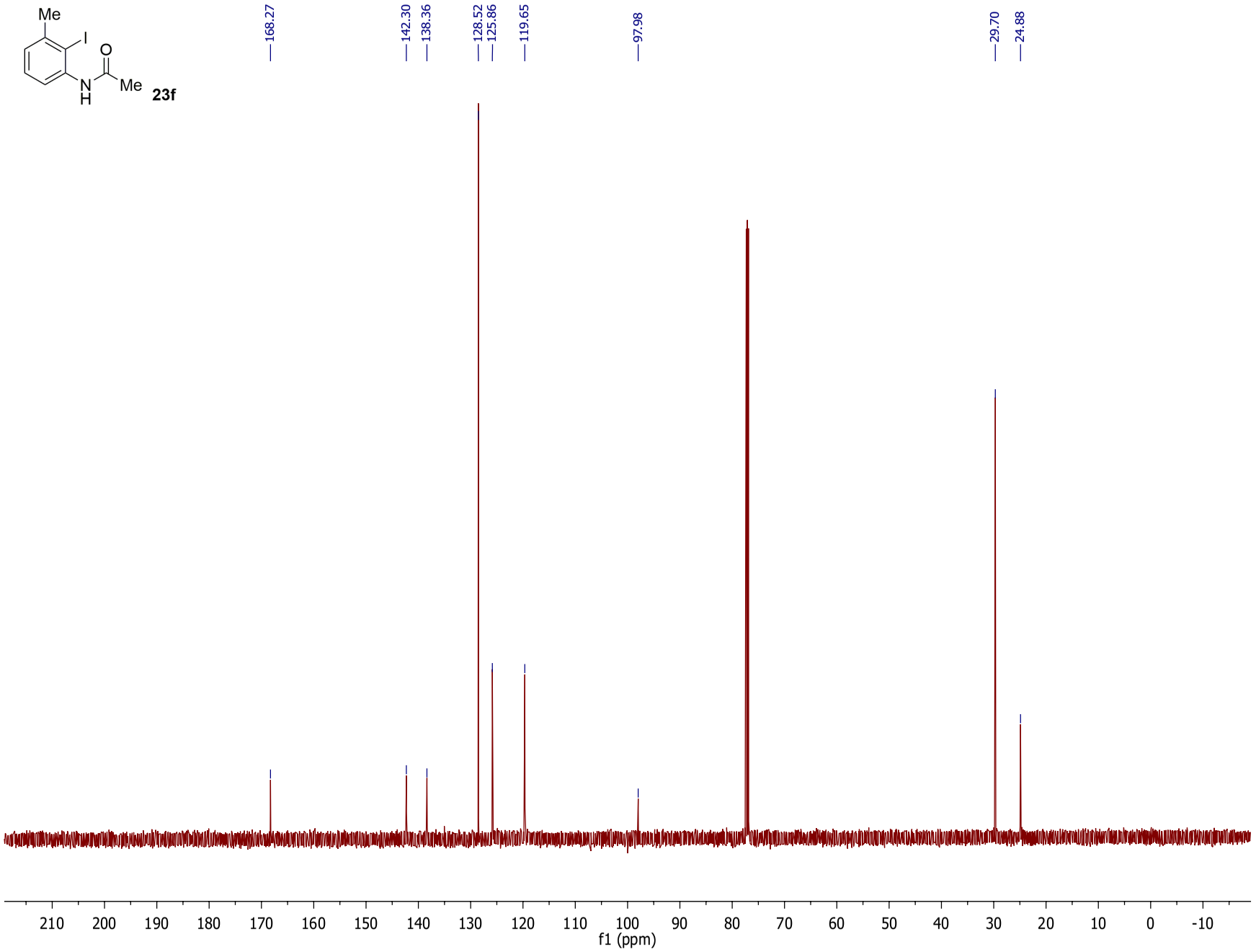

0.78
1.01
1.11
1.00
3.36
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

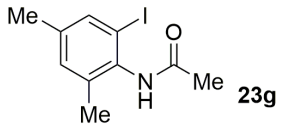

23e
168.20
139.18
139.14
135.43
125.94
121.66
86.41
24.91
f1 (ppm)


Me
I
O
N
H
Me

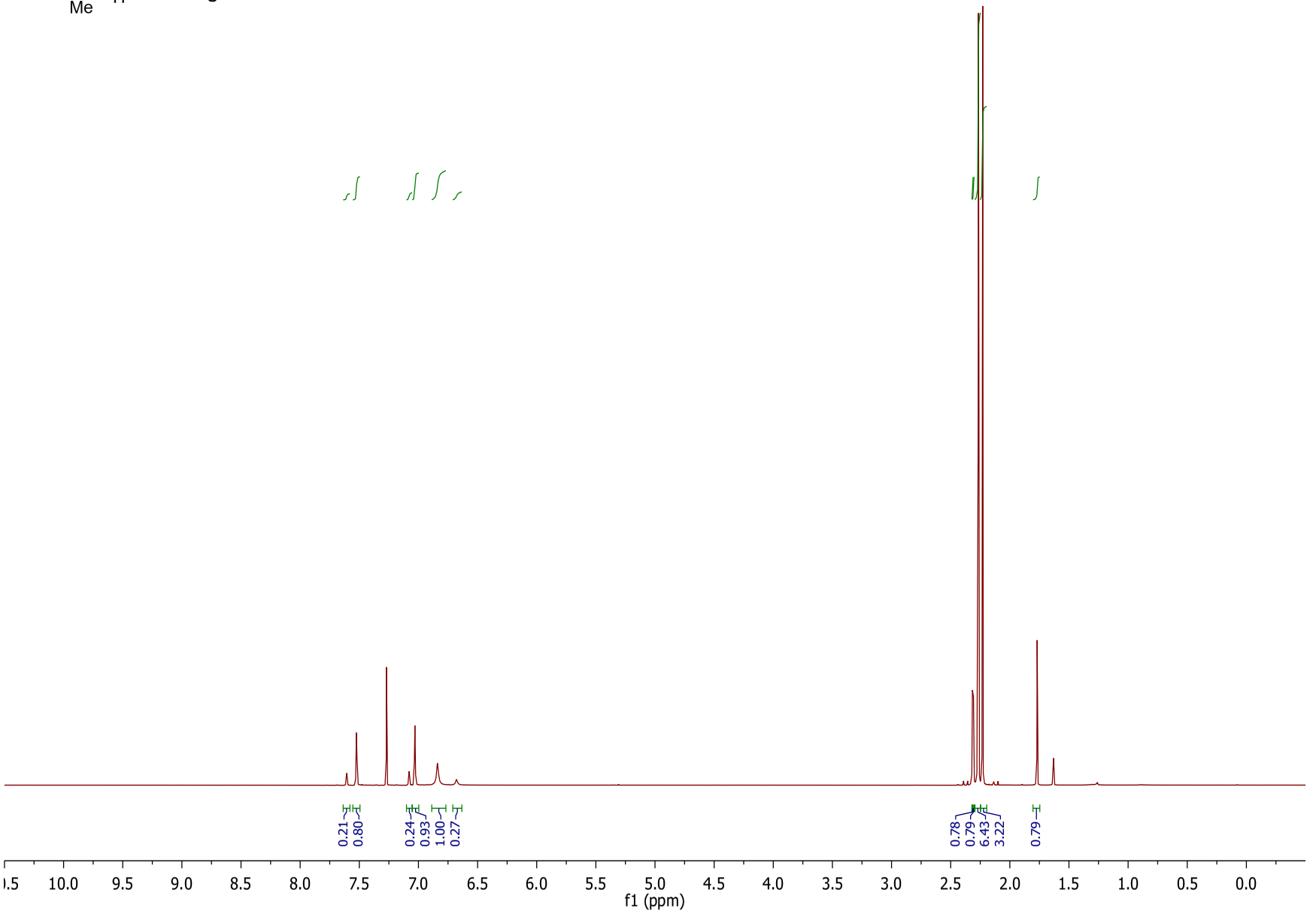
23f

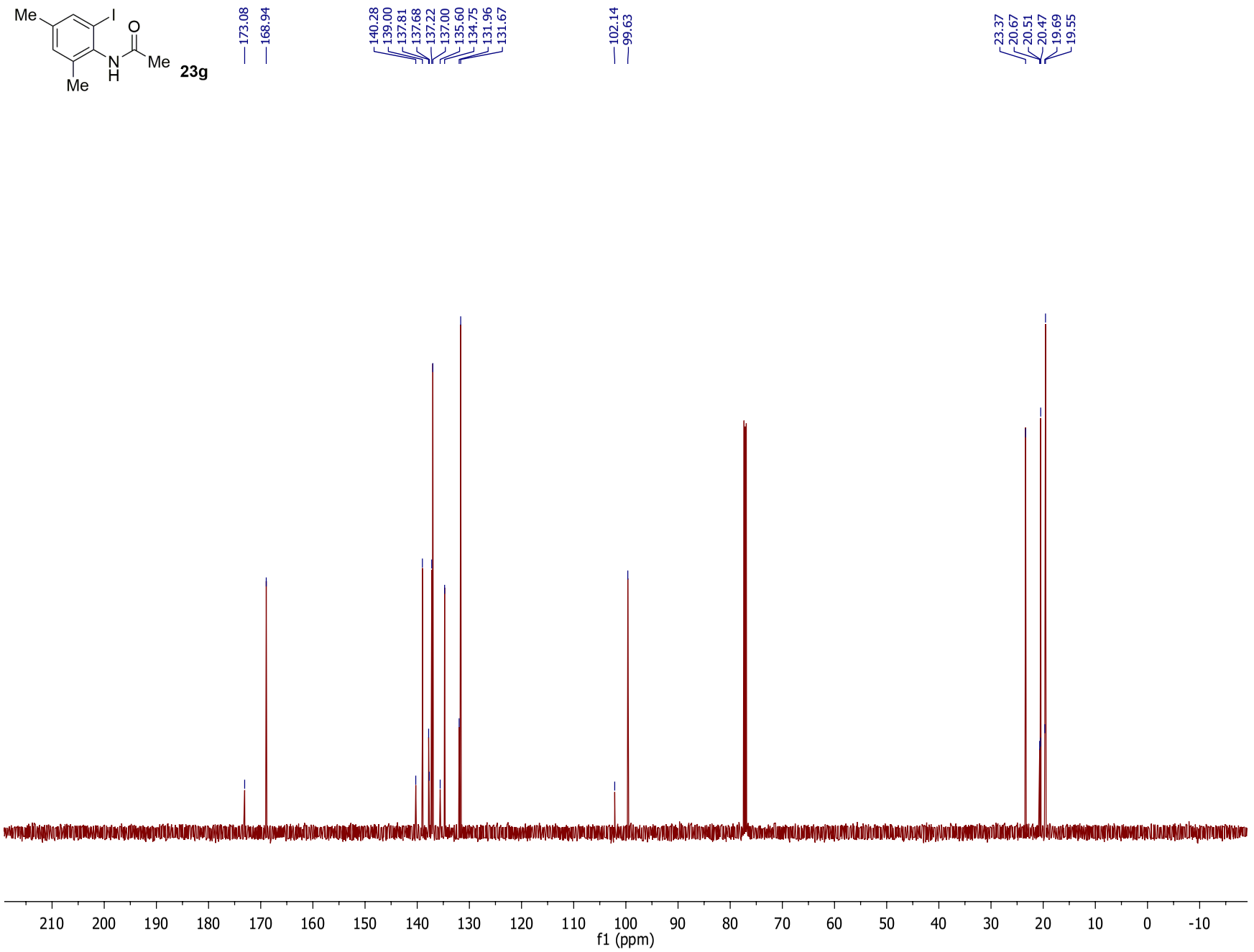

0.84
0.92
1.08
1.00
3.39
2.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

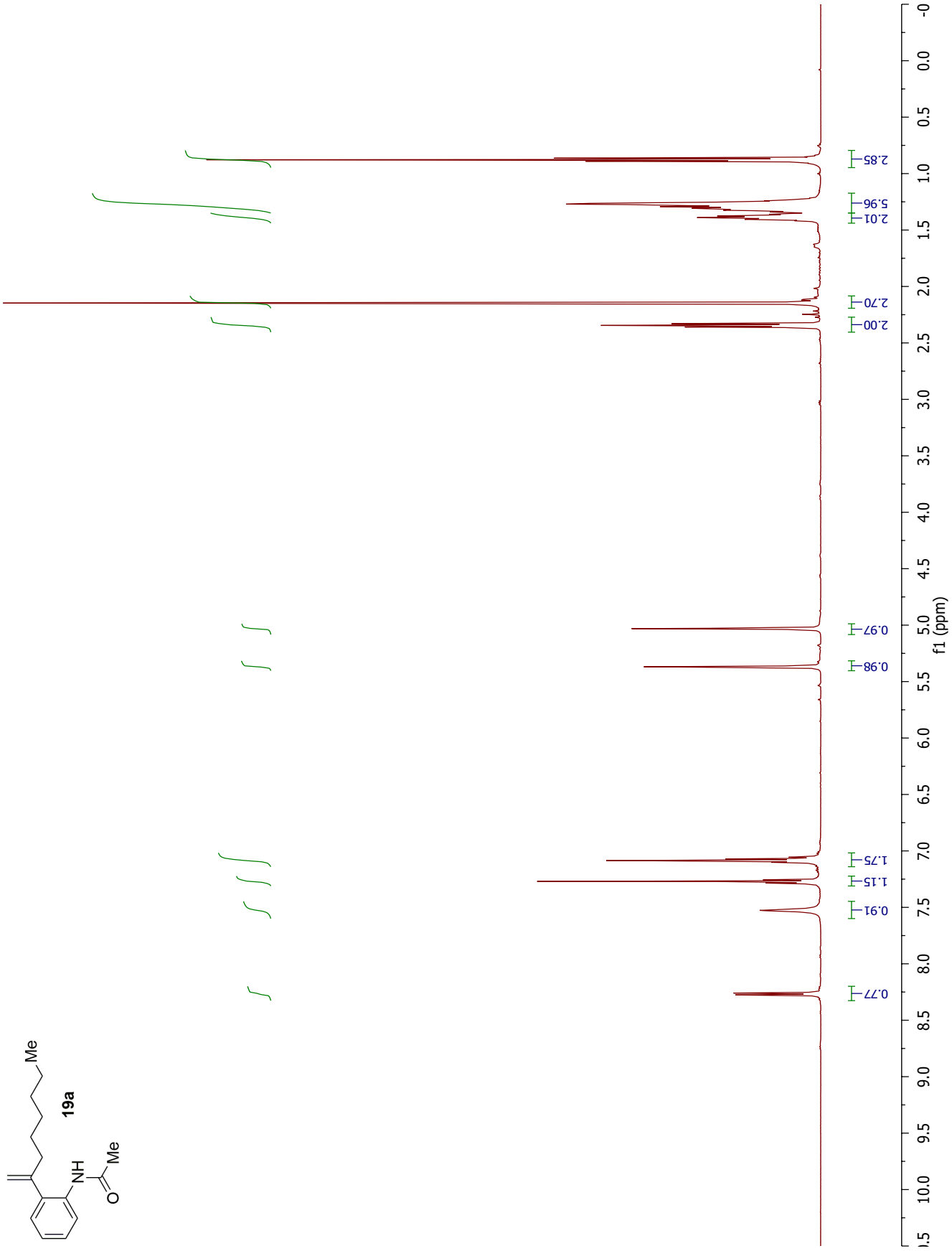

Me
I
O
N
H
Me
23f
168.27
142.30
138.36
128.52
125.86
119.65
97.98
29.70
24.88
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

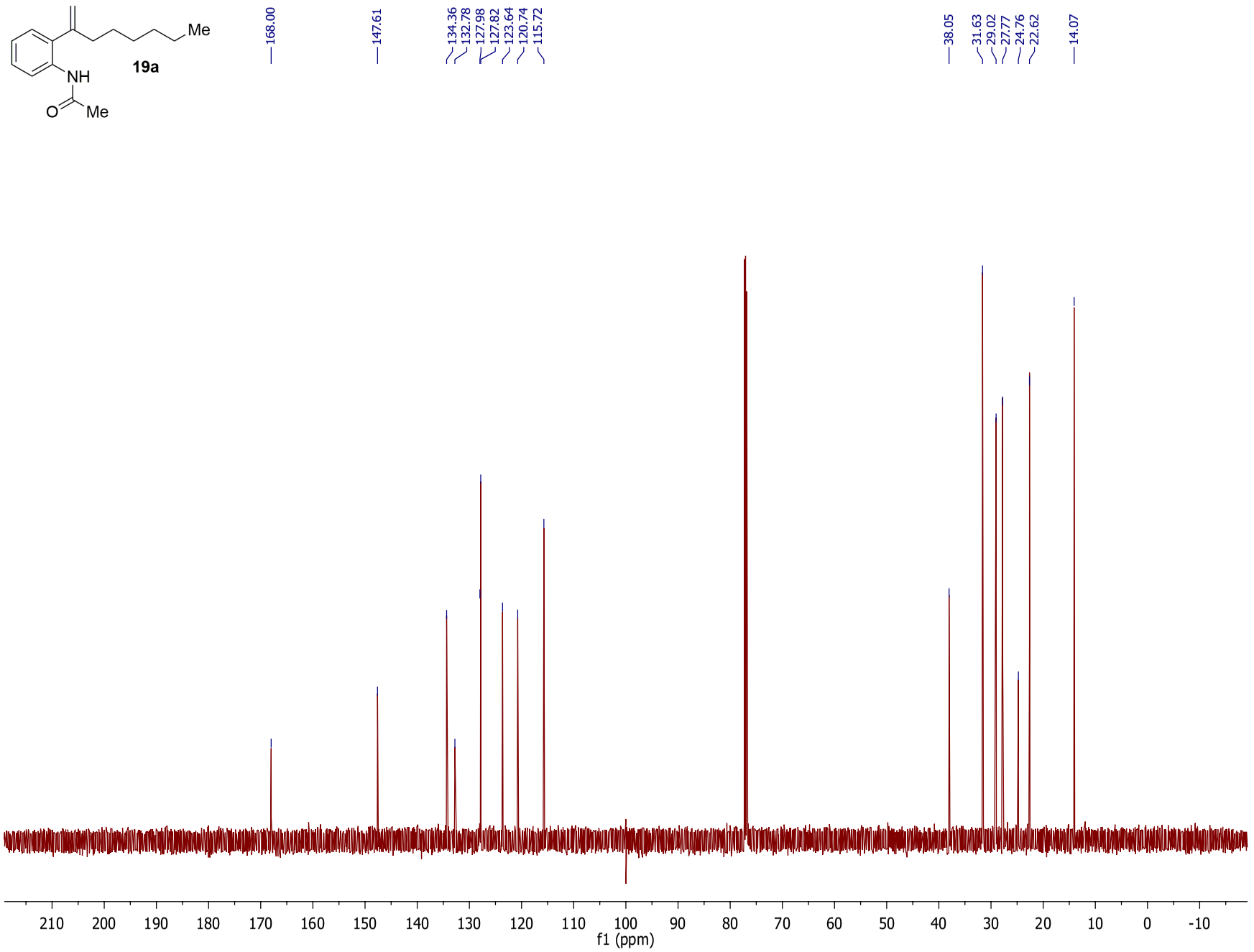


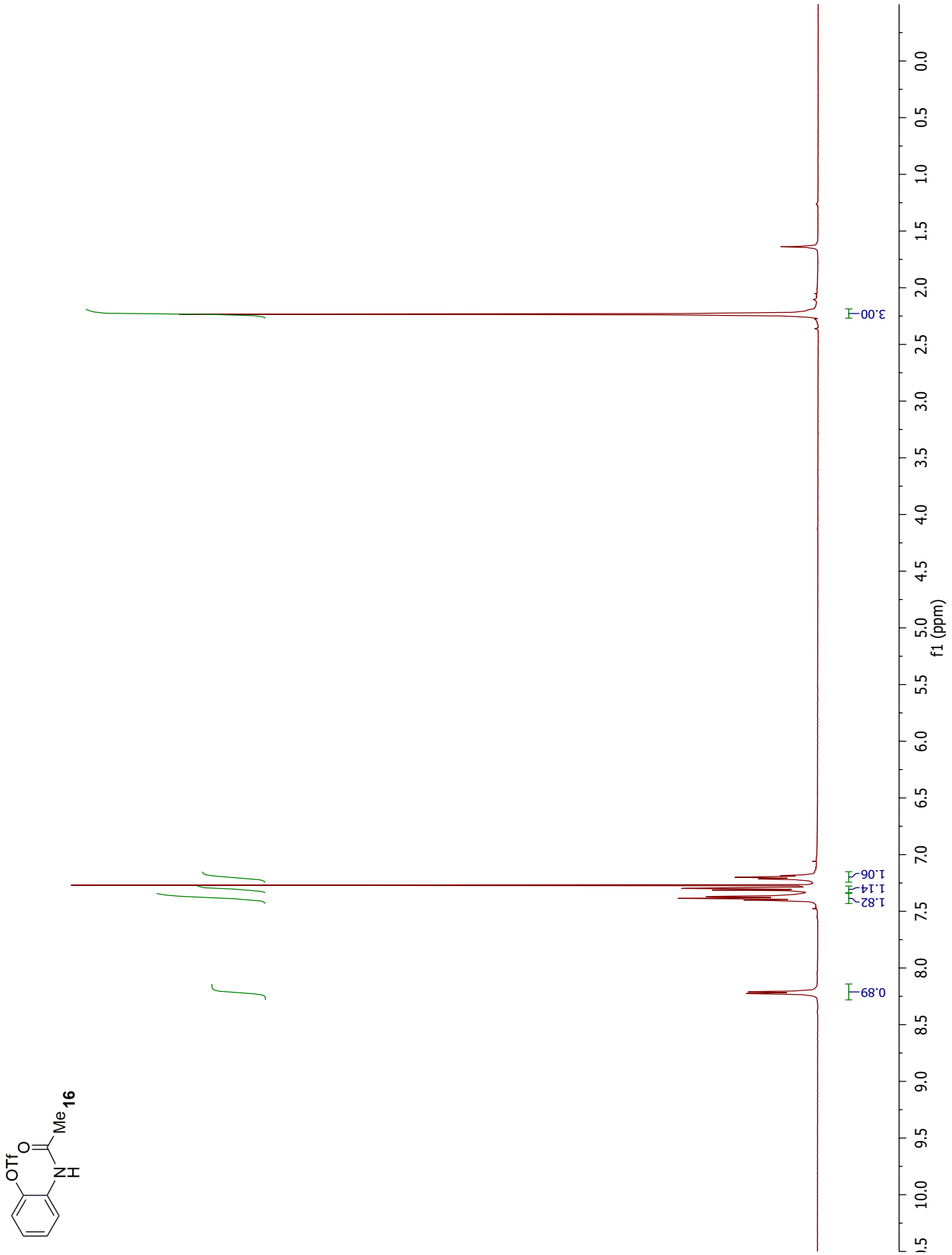
23g

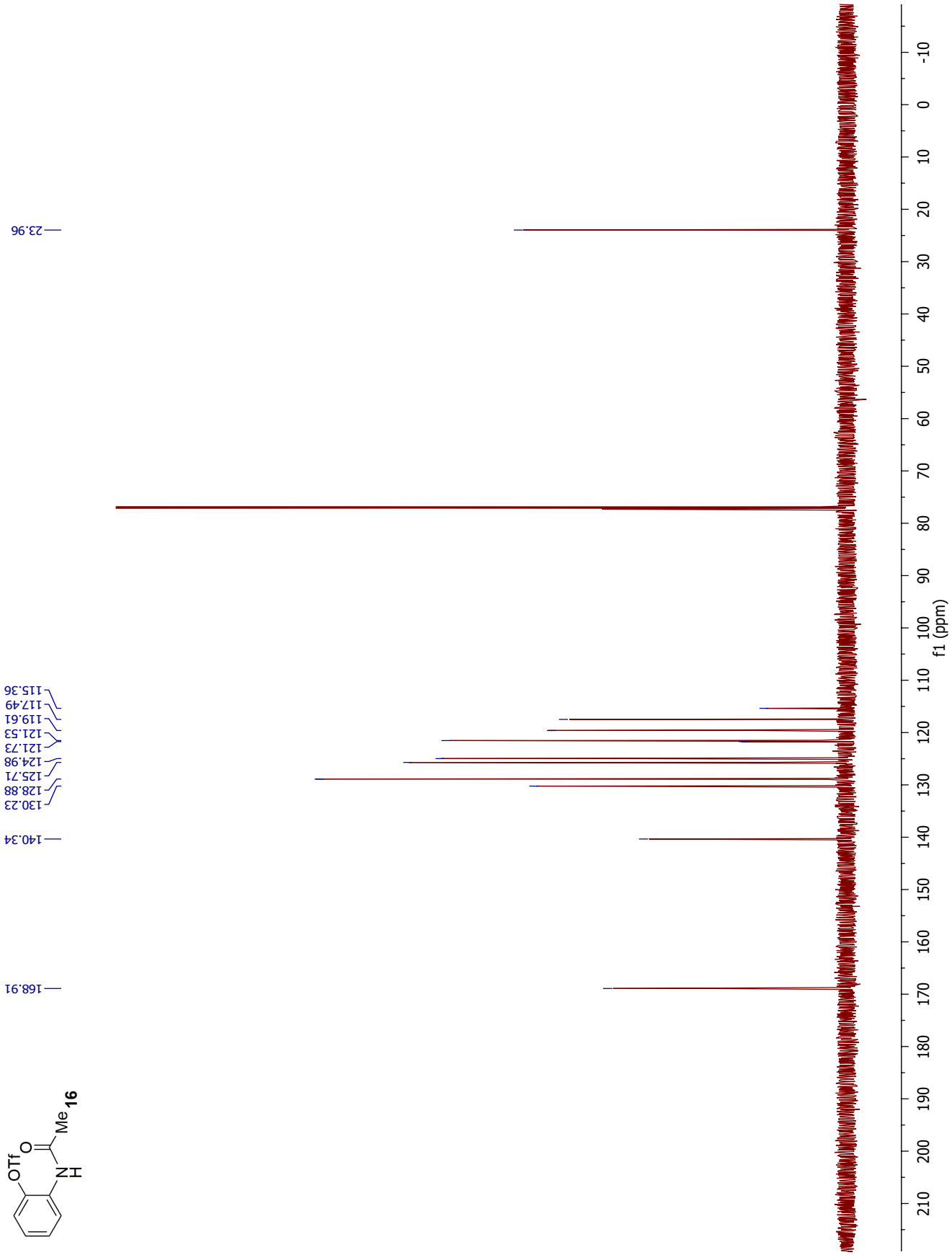


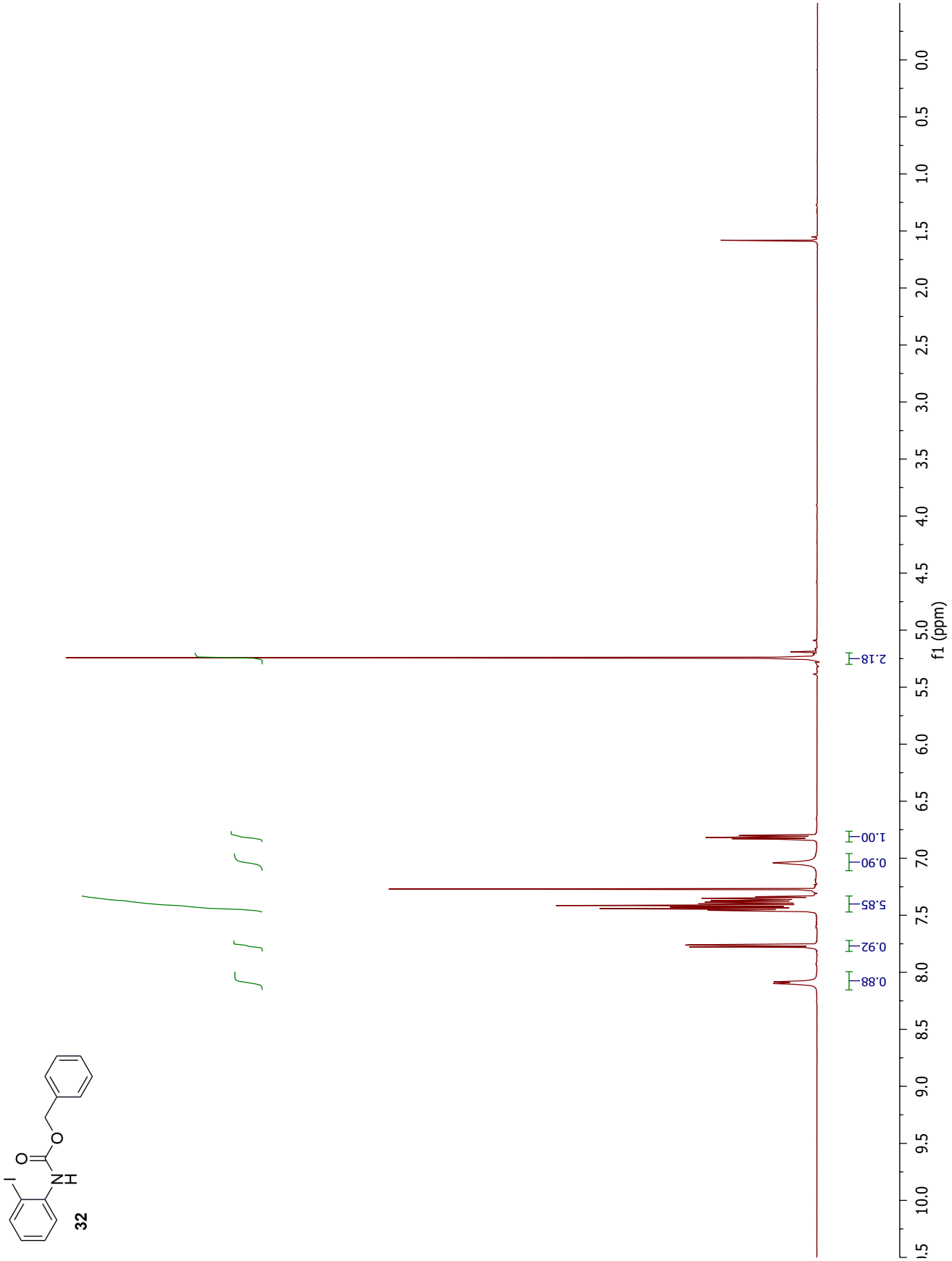

Me
I
O
N
H
Me
Me
23g
173.08
168.94
140.28
139.00
137.81
137.68
137.22
137.00
135.60
134.75
131.96
131.67
102.14
99.63
23.37
20.67
20.51
20.47
19.69
19.55
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

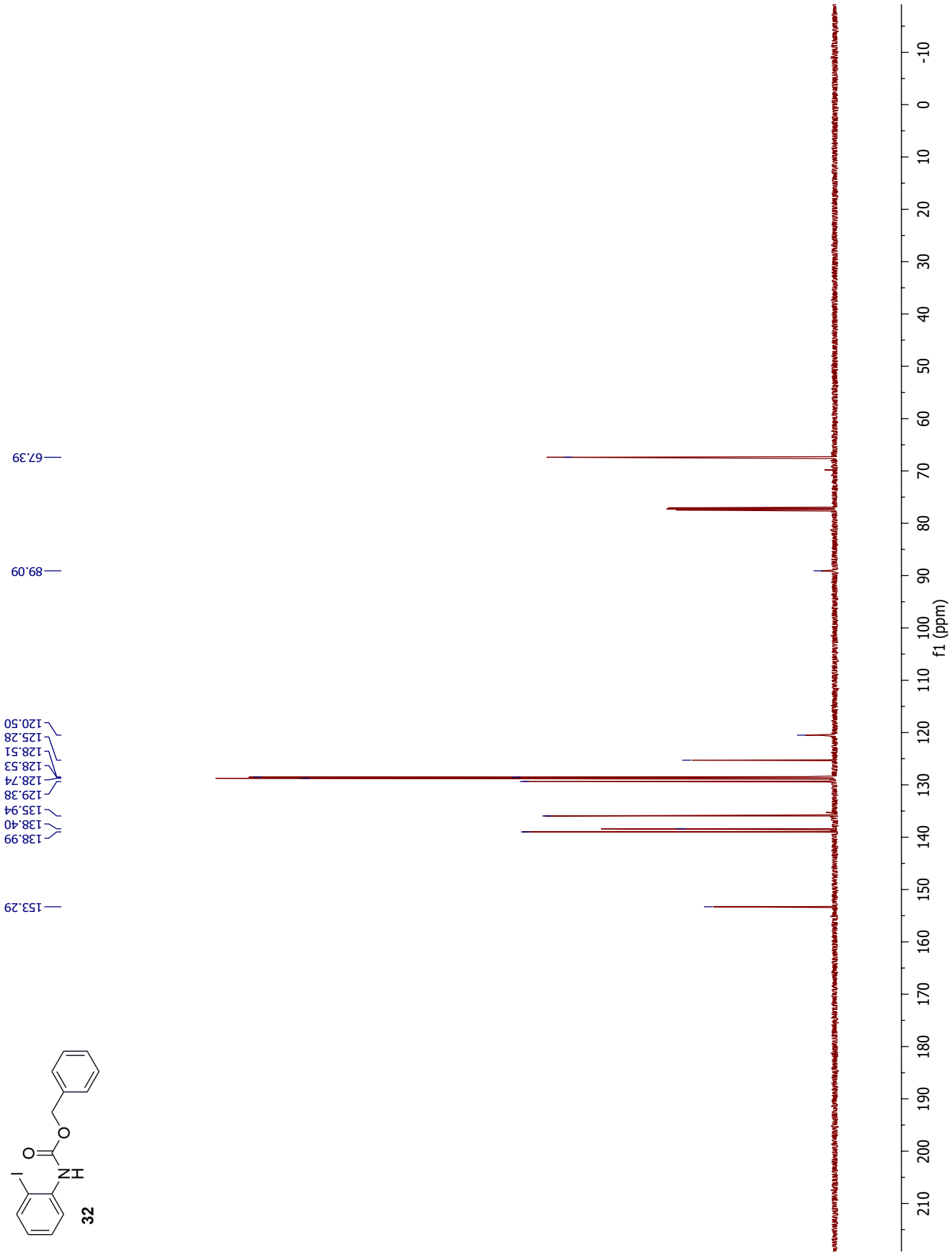

Me
19a
NH
Me
O
2.85
5.96
2.01
2.70
2.00
0.97
0.98
1.75
1.15
0.91
0.77
f1 (ppm)

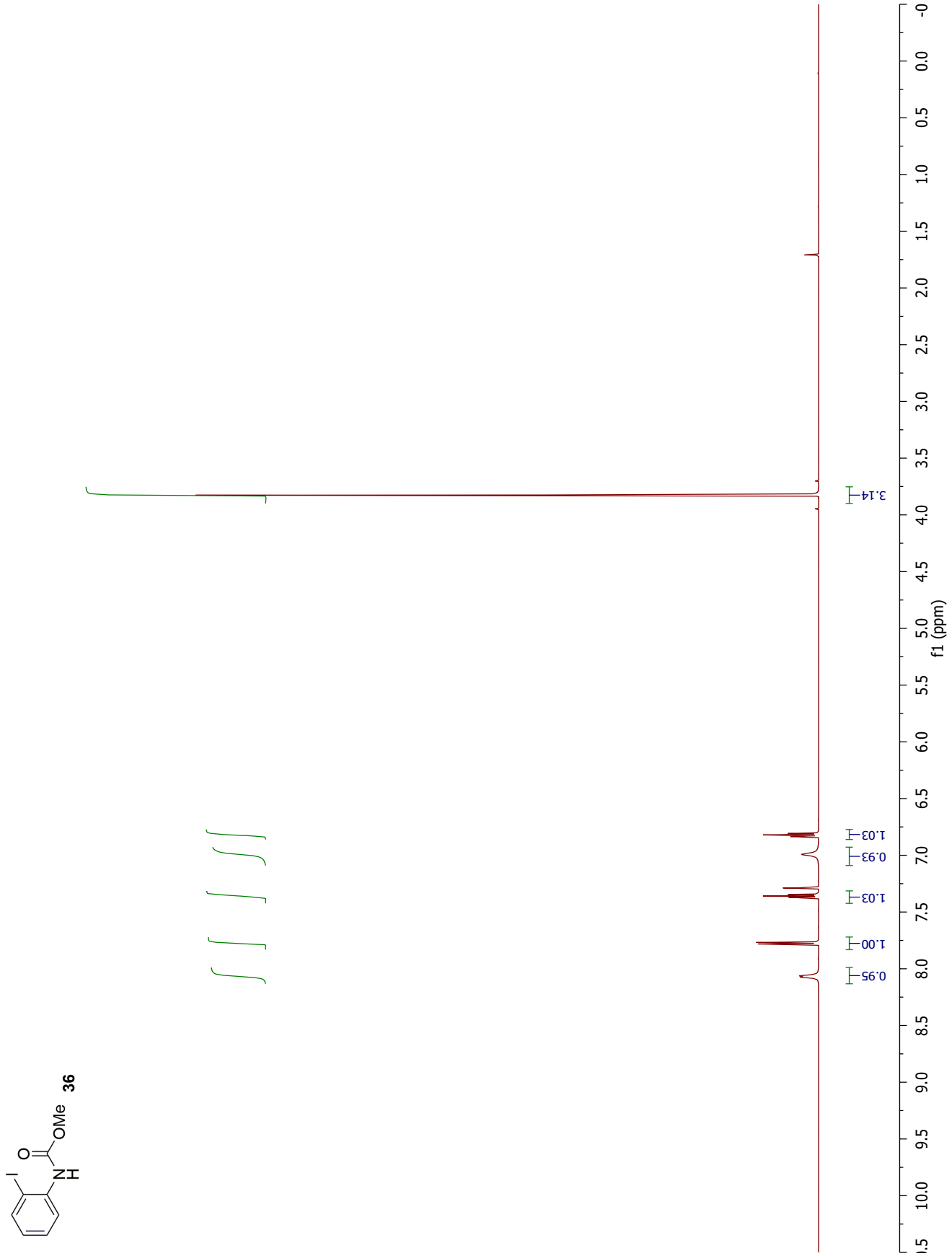

Me
19a
NH
O
Me
168.00
147.61
134.36
132.78
127.98
127.82
123.64
120.74
115.72
38.05
31.63
29.02
27.77
24.76
22.62
14.07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

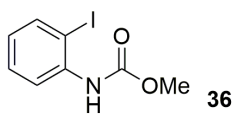

OTf
O
Me
16
N
H
3.00
1.82
1.14
1.06
0.89
f1 (ppm)


23.96
115.36
117.49
119.61
121.53
121.73
124.98
125.71
128.88
130.23
140.34
168.91
OTf
O
N
H
Me
16
f1 (ppm)


I
O
O
NH
32
2.18
1.00
0.90
5.85
0.92
0.88
f1 (ppm)

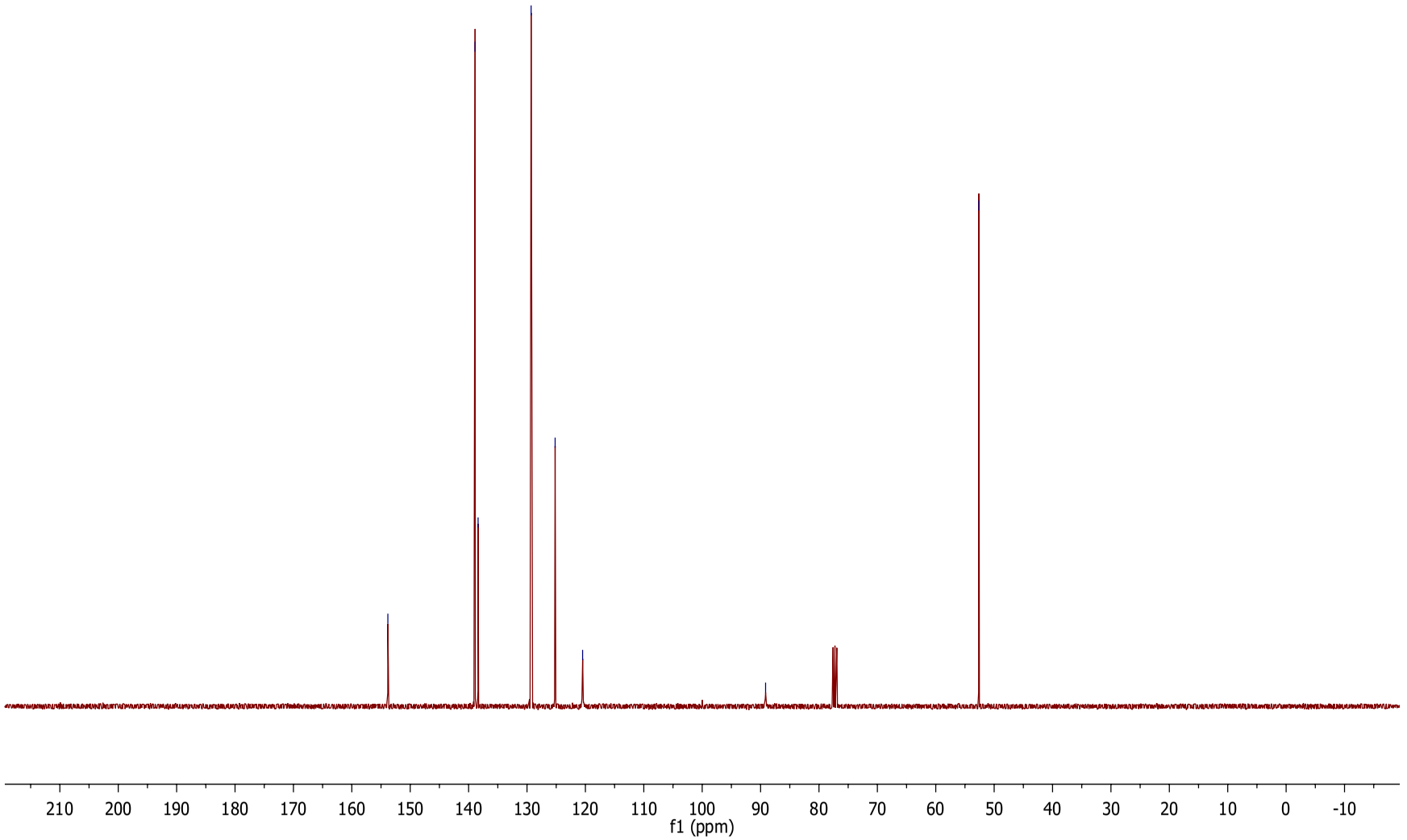

67.39
89.09
120.50
125.28
128.51
128.53
128.74
129.38
135.94
138.40
138.99
153.29
I
O
O
N
H
32
f1 (ppm)

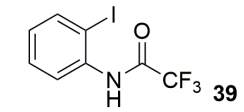

36
3.14
1.03
0.93
1.03
1.00
0.95
f1 (ppm)



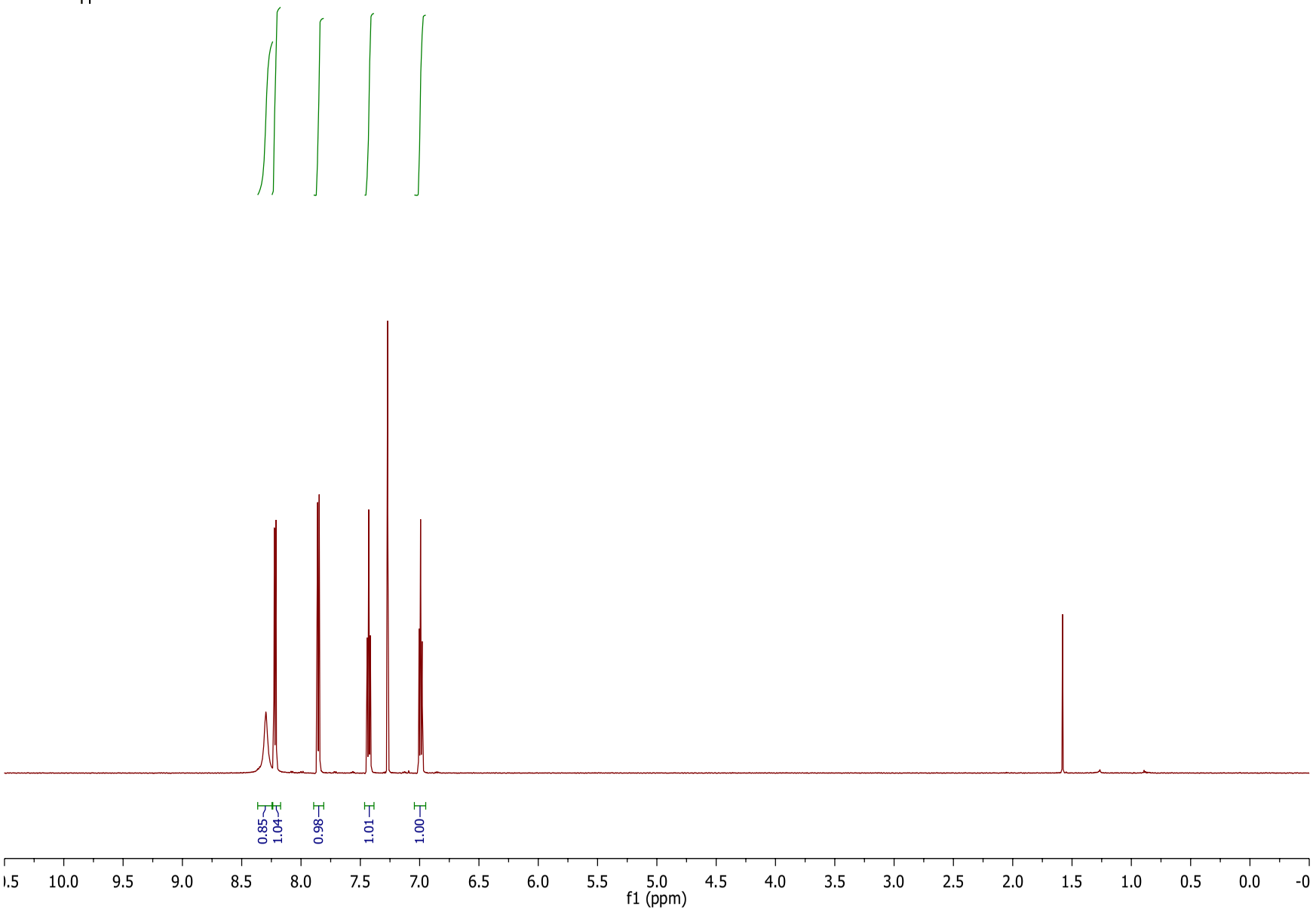
36

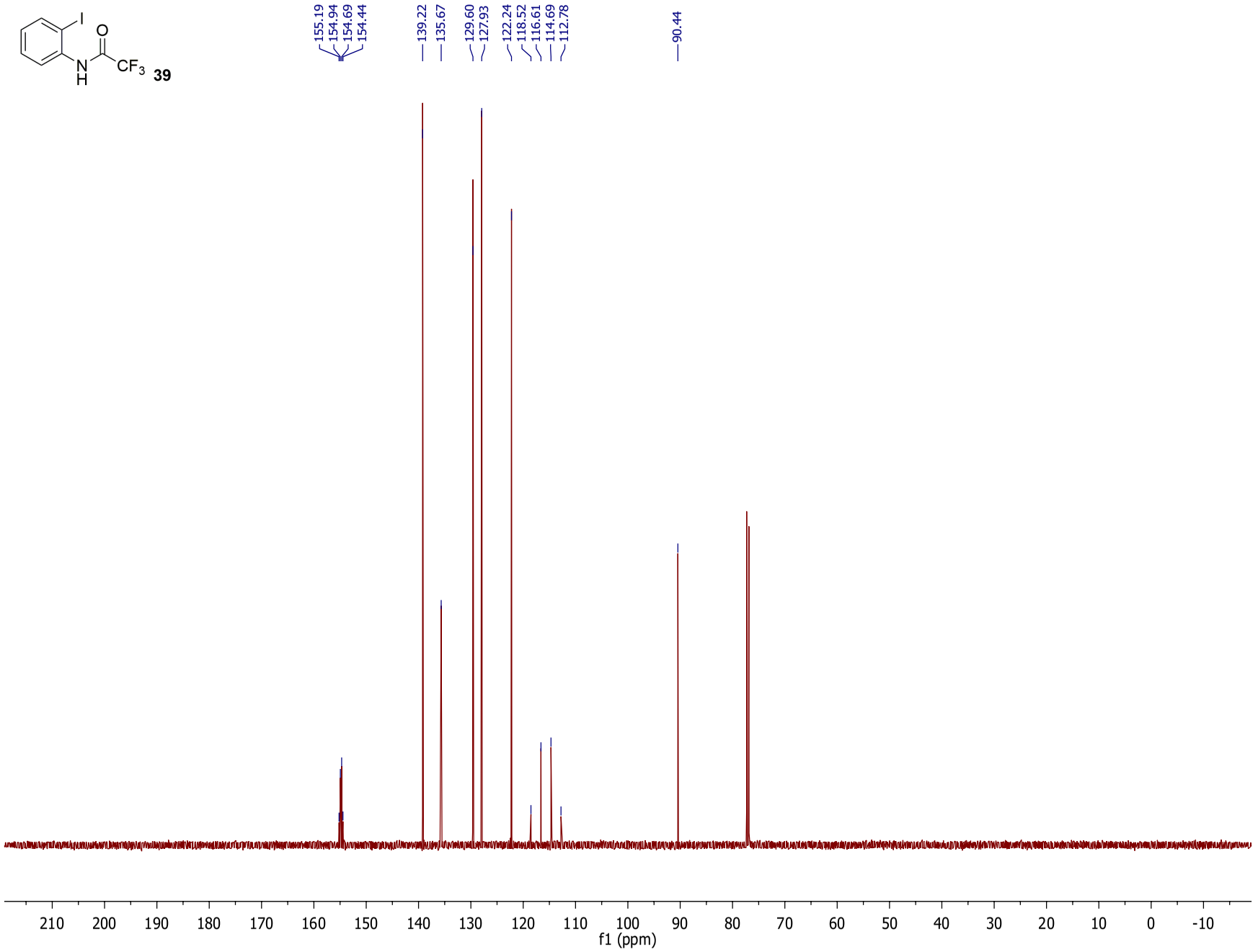
153.83
138.88
138.38
129.30
125.18
120.48
89.14
52.63

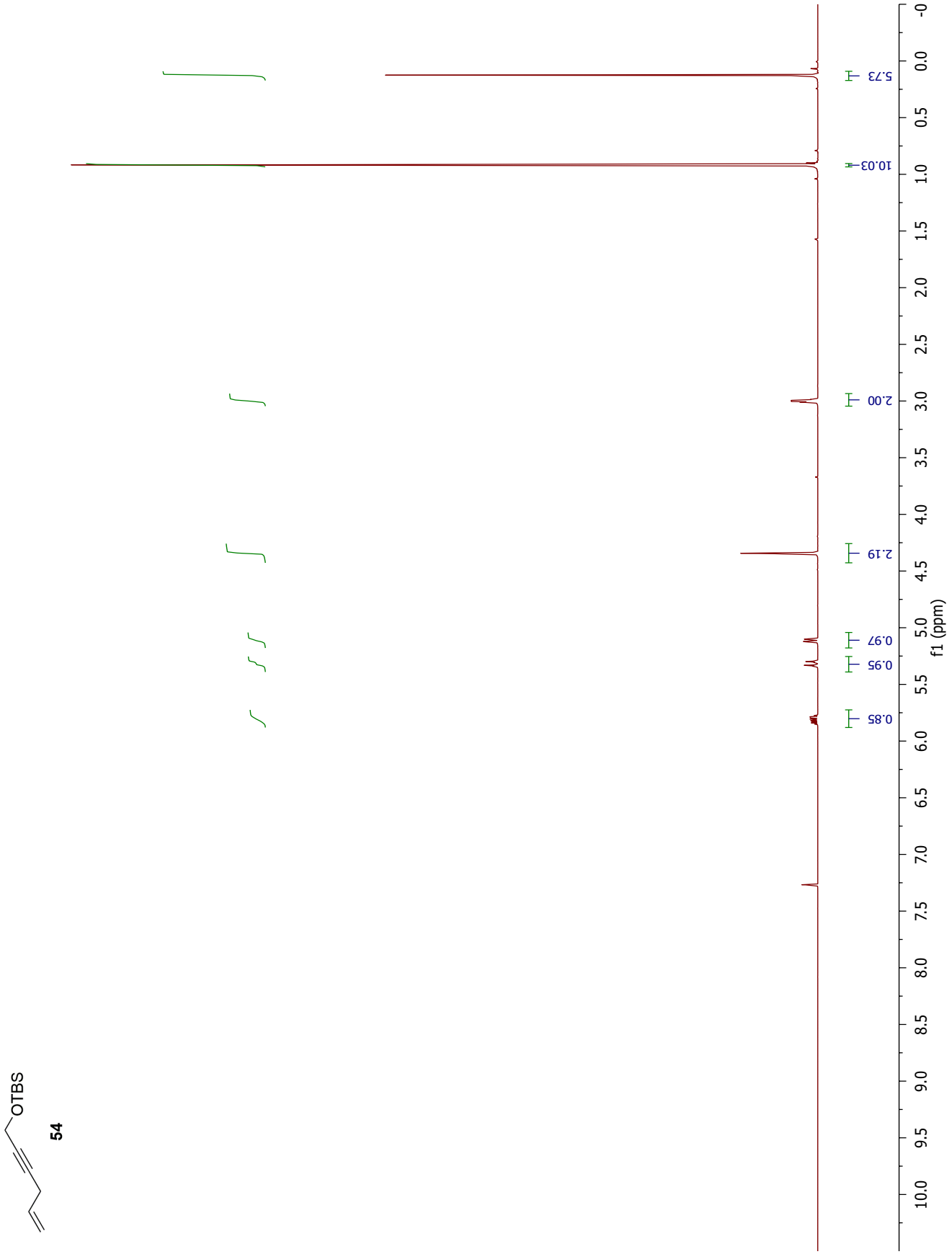


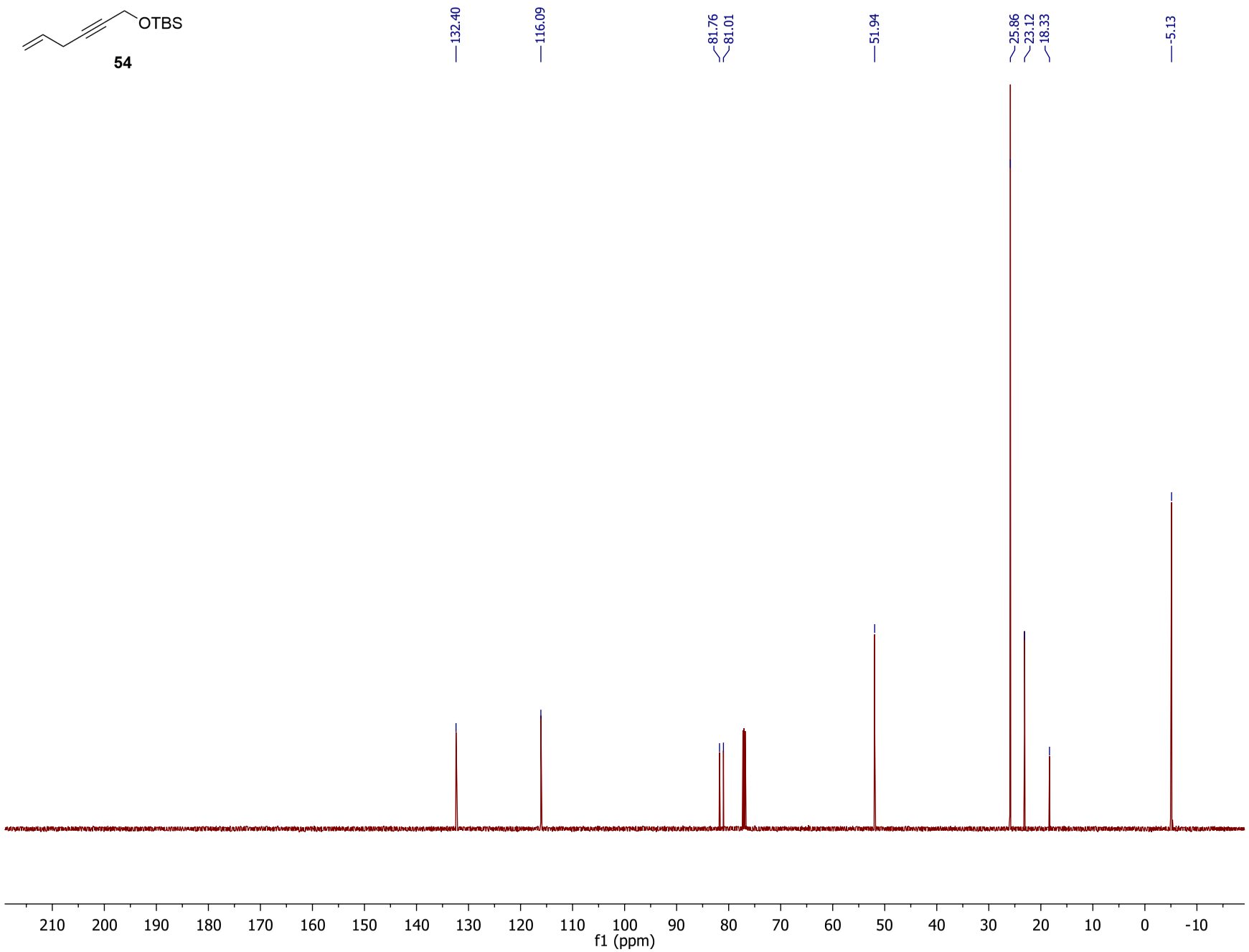

I
O
N
H
CF3

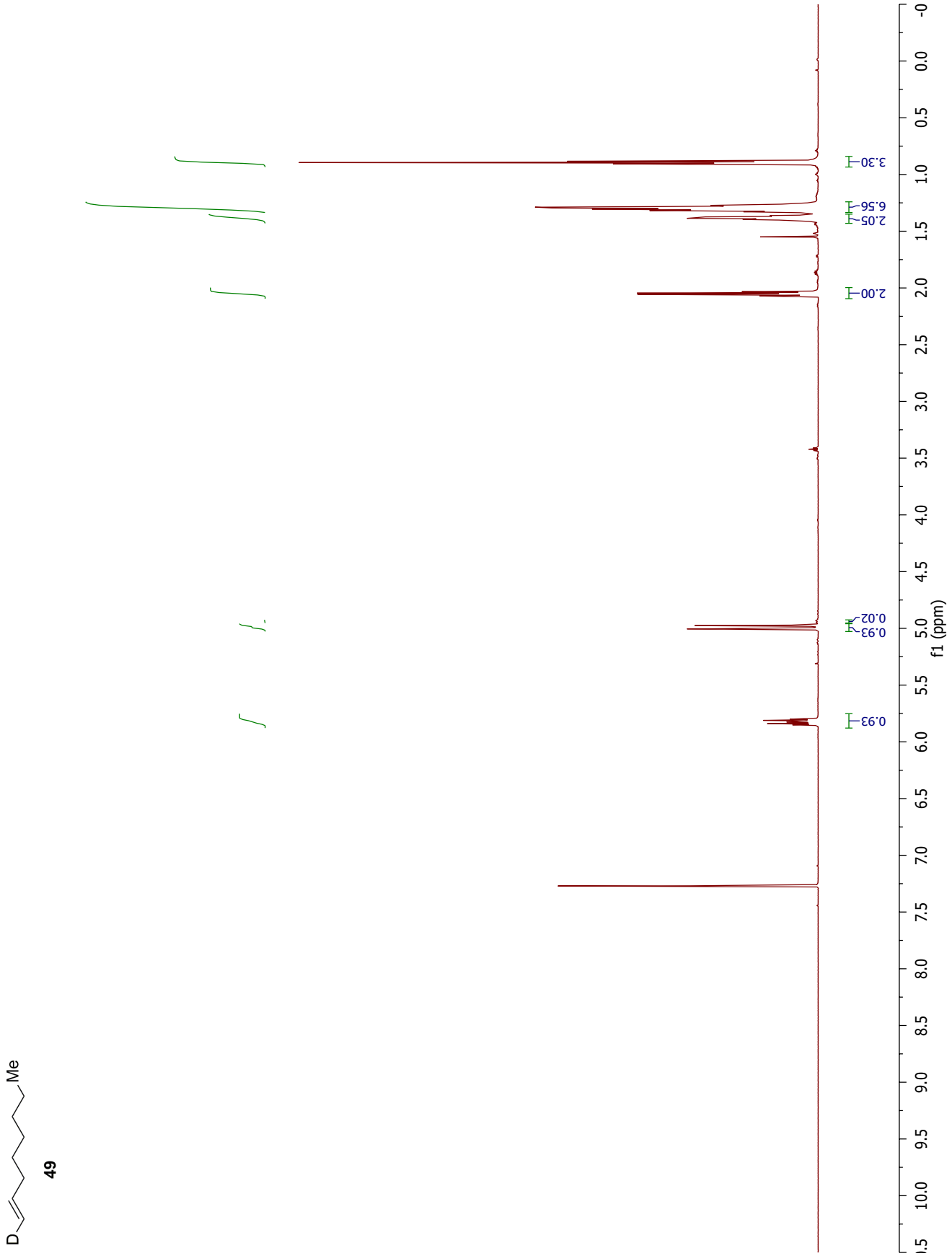
39

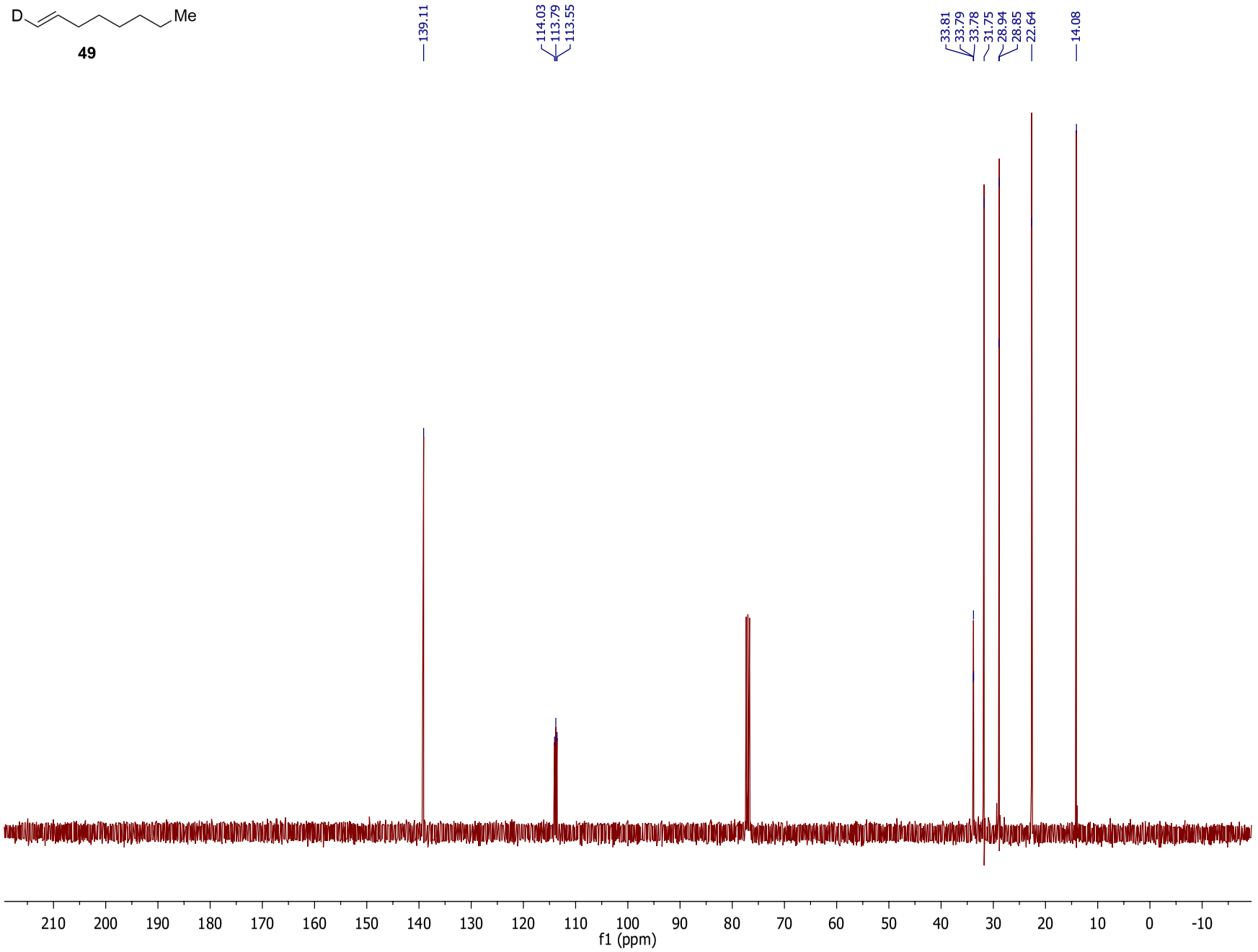

0.85
1.04
0.98
1.01
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


I
O
N
H
CF3
39
155.19
154.94
154.69
154.44
139.22
135.67
129.60
127.93
122.24
118.52
116.61
114.69
112.78
90.44
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OTBS
54
5.73
10.03
2.00
2.19
0.97
0.95
0.85
f1 (ppm)


OTBS
54
132.40
116.09
81.76
81.01
51.94
25.86
23.12
18.33
-5.13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
D
49
3.30
6.56
2.05
2.00
0.93
0.93
0.02
f1 (ppm)


D
Me
49
139.11
114.03
113.79
113.55
33.81
33.79
33.78
31.75
28.94
28.85
22.64
14.08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Curriculum Vitae

Sarah Zinnen Tasker

Home Address
70 Pacific St Apt 556C
Cambridge, MA 02139

sarah.z.tasker@gmail.com

University Address
77 Massachusetts Ave
Bldg 18-205
Cambridge, MA 02139

Education:

Massachusetts Institute of Technology, Cambridge, MA
Doctor of Philosophy in Organic Chemistry, September 2015
Research Advisor: Professor Timothy F. Jamison

Calvin College, Grand Rapids, MI
Bachelor of Science, May 2010
Honors Student; Double major: Chemistry (ACS-certified), Spanish
GPA: 4.00

Grand Rapids Christian High School, Grand Rapids, MI
June 2006
Class Valedictorian, GPA: 4.00

Research Experience:

Graduate Research with Prof. Timothy F. Jamison (January 2011–August 2015)

- Developed a highly selective nickel-catalyzed Heck reaction, and continue to investigate novel reaction methodology in nickel catalysis.
- Explored hydrogen-bonding organocatalysis for the synthesis of challenging seven-membered oxepane rings found in ladder polyether natural products.

Undergraduate Research with Prof. Carolyn Anderson (May 2008–August 2010)

- Designed, implemented, and analyzed experiments in order to determine the mechanism of a rearrangement of 2-alkoxypyridines and optimize conditions for the synthesis of β-iodo *N*-alkenyl 2-pyridones
- Helped mentor and train other students in the lab

Undergraduate Research with Prof. Chad Tatko (May 2007–January 2008)

- Synthesized, purified and characterized a small library of peptides
- Evaluated binding of aromatic substrates to peptides using fluorescence and UV-Vis techniques

Publications:

- Tasker, S. Z.; Jamison, T. F. Larock-type Indoline Synthesis via Nickel and Photoredox Dual Catalysis. *J. Am. Chem. Soc.* **2015**, [Online early access]. DOI: 10.1021/jacs.5b05597.
- Standley, E. A.* Tasker, S. Z.*; Jensen, K. L.; Jamison, T. F. Nickel Catalysis: From Reductive Coupling to the Heck Reaction. *Accounts of Chemical Research*, **2015**, *48*, 1503–1514.
- Tasker, S. Z.*; Standley, E. A.*; Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, *509*, 299–309.
- Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. Nickel-Catalyzed Mizoroki–Heck Reaction of Aryl Sulfonates and Chlorides with Electronically Unbiased Terminal Olefins: High Selectivity for Branched Products. *Angew. Chem., Int. Ed.* **2013**, *53*, 1858–1861.
- Tasker, S. Z.; Bosscher, M. A.; Shandro, C. A.; Lanni, E. L.; Ryu, K. A.; Snapper, G. S.; Utter, J. M.; Ellsworth, B. A.; Anderson, C. E. Preparation of *N*-Alkyl 2-Pyridones *via* a Lithium Iodide Promoted *O*- to *N*-Alkyl Migration: Scope and Mechanism. *J. Org. Chem.* **2012**, *77*, 8220–8230.

- Tasker, S. Z.; Brandsen, B. M.; Ryu, K. A.; Snapper, G. S.; Staples, R. J.; DeKock, R. L.; Anderson, C. E. Synthesis of a New Class of β-Iodo *N*-Alkenyl 2-Pyridones. *Org. Lett.* **2011**, *13*, 6224–6227.

Non-Refereed Contributions:

- Standley, E. A.*; Tasker, S. Z.*; Jamison, T. F. Bis(1,5-cyclooctadiene)nickel(0). e-EROS Encyclopedia of Reagents for Organic Synthesis, John Wiley & Sons, Ltd. **2015**.

Presentations:

- Tasker, S. Z.; Jamison, T. F. Organic Reactions & Processes, Gordon Research Conference, Smithfield, RI, July 13–18, 2014 (Poster).
- Tasker, S. Z.; Jamison, T. F. The Nickel-Catalyzed Heck Reaction: Regiocontrol and Novel Reactivity. Fourth Year Graduate Research Symposium, MIT, May 27, 2014 (Oral).
- Tasker, S. Z.; Jamison, T. F. The Nickel-Catalyzed Heck Reaction: Regiocontrol and Novel Reactivity. Chemistry Student Seminar, MIT, April 25, 2014 (Oral).
- Tasker, S. Z.; Anderson, C. E. Synthesis of a Novel *N*-Alkenyl Pyridone. Van Andel Institute Undergraduate Research Conference, Grand Rapids, MI, October 31, 2009 (Poster).
- Tasker, S. Z.; Anderson, C. E. Synthesis of *N*-Alkyl Pyridones *via* and *O*- to *N*- Alkyl Migration: Mechanistic Studies. Beckman Scholars Symposium, Irvine, CA, July 23–25, 2009 (Poster).
- Tasker, S. Z.; Anderson, C. E. Synthesis of *N*-Alkyl Pyridones *via* and *O*- to *N*- Alkyl Migration: Mechanistic Studies. American Chemical Society National Organic Symposium, Boulder, CO, June 7–11, 2009 (Poster).
- Tasker, S. Z.; Anderson, C. E. Mechanistic Studies of the LiI-Promoted Rearrangement of *O*-Alkyl Pyridines. Van Andel Institute Undergraduate Research Conference, Grand Rapids, MI, November 1, 2008 (Poster).
- Tasker, S. Z.; Meyer, D. B. Desulfurization of Diesel Fuel: A Peptide Approach. 236th American Chemical Society National Meeting, Philadelphia, PA, August 17–21, 2008. CHED-268 (Poster).

Teaching Experience:

Teaching Assistant, CC5.12 (February 2015–May 2015)

- Taught weekly recitation sections for Organic Chemistry I for the Concourse program at MIT, a first-year living community in which students take typical classes in smaller settings and imitating a liberal arts environment
- Graded problem sets

Grader, 5.511 (September 2013–December 2013 and September 2014–December 2014)

- Led review sessions for the graduate-level class Synthetic Organic Chemistry I
- Met with students individually to assist with learning the material

Teaching Certificate Program (February 2013–May 2013)

- Attended biweekly seminars on pedagogy, course design, educational technology, and active learning.

Mentored an Undergraduate Research Assistant (January 2012–January 2013)

- Designed project, trained in laboratory techniques, and gave general guidance to Vince D'Andrea (MIT '14).

Teaching Assistant, 5.12 & 5.13 (September 2010–May 2011)

- Taught weekly recitation sections for Organic Chemistry I and II
- Graded problem sets and exams

Chemistry Tutor (September 2007–May 2010)

- Planned and led group help sessions for organic chemistry students
- Tutored students individually

Teaching Assistant, Organic Chemistry Lab (September 2007–December 2007)

- Answered questions, helped students complete the experiments, and graded lab reports

Selected Honors:

National Science Foundation Graduate Fellowship
MIT Presidential Fellowship
MIT Spot Award for Service to the School of Science
Goldwater Scholar
Beckman Foundation Scholar
National Merit Scholar
Howard Hughes Medical Institute Scholarship
ACS-PolyEd Outstanding Achievement Award in Organic Chemistry
American Chemistry Society Division of Analytical Chemistry Undergraduate Award
Dean's List, all semesters

Activities and Community Service:

Chemistry REFS (Resources for Easing Friction and Stress) (January 2012–July 2015)
MIT Chemistry Outreach (May 2013, May 2014, May 2015)
Chemistry Student Advisory Council (September 2009–May 2010)
Volunteer English as a Second Language Tutor (October 2004–May 2010)