Advancements in Nickel-catalyzed Cross-Electrophile Coupling

by

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A dissertation submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

(Chemistry)

at the

UNIVERSITY OF WISCONSIN-MADISON

2019

Date of final oral examination: 7/02/2019

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Dedication

To all those that believed in me even when I didn't believe in myself
and in loving memory of Prof. Burnaby Munson, without whom I would not be where I am today

Biographical Sketch

The author was born on April 24th, 1991 in Manhattan, New York and relocated to Saint Croix, U.S. Virgin Islands. He attended the University of Delaware for his undergraduate studies. While there he conducted research on palladium and nickel-catalyzed silyl-Heck reactions under the supervision of Professor Donald A. Watson from 2011 to 2013. During the summer of 2012 he studied the use of ionic liquids as photosensitizers in dye-sensitized solar cells at Louisiana State University under the supervision of Professor Isiah Warner.

After graduating with a Bachelor's of Science in Chemistry in 2013, he joined the lab of Professor Daniel J. Weix at the University of Rochester. His research focused on the use of vinyl halides in cross-electrophile coupling, the coupling of organochlorides, and macrocyclization. He received a Master's of Science from the University of Rochester in 2015. He was awarded the Sherman Clarke Fellowship from the Department of Chemistry in 2014, and in 2015 he was awarded both the Graduate Research Fellowship from the National Science Foundation and the Gilliam Fellowship from the Howard Hughes Medical Institute. In 2017, he was awarded the Graduate Research Opportunities Worldwide Program award from the National Science Foundation, which allowed him to study the functionalization of alkenes using *gem*-diborylmethane derivatives under the supervision of Professor Yoshiaki Nakao at Kyoto University in Kyoto, Japan.

In 2017, the author relocated with Professor Daniel J. Weix to the University of Wisconsin-Madison. After graduation, he will pursue postdoctoral studies in asymmetric transformations with Professor F. Dean Toste at the University of California, Berkeley.

The following publications were a result of work conducted during doctoral study:

1. Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. "Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides" *J. Am. Chem. Soc.* **2016,** *138* (15), 5016-5019
2. Johnson, K. A.; Biswas, S.; Weix, D. J., "Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides" *Chem. Eur. J.* **2016,** *22* (22), 7399-7402
3. Johnson, K.**;** Weix, D., "When two metal atoms are better than one" *Science* **2019**, *363* (6429), 819.

Acknowledgments

For me, this achievement would not have been possible without the help and guidance of a multitude of people in my life. However large or small, their collective contributions have led to this point and I cannot be more grateful.

First and foremost, I would like to thank my family, especially my mother Claudette, for instilling in me the drive and passion to pursue my dreams and the things that interest me most. Even if they don't completely understand what it is that I do, they believe in my ability to accomplish my goals and be successful.

I would like to acknowledge Prof. Donald A. Watson at the University of Delaware for giving me my first real look into the world of chemistry research, showing me what it is to develop new ideas, and for giving me a taste of what graduate school would look like. I would also like to thank Dr. Sara Martin, now a professor at the College of Wooster, for being an amazing mentor and teaching me how to apply my ideas in the laboratory. Finally, I would like to thank former members of the Watson Lab, Jesse McAtee, Derek Ahneman Peter Gildner, Amber Gietter-Burch, Kirk Shimkin, Scott Shuler, Andrew Cinderella, and Will Reid for providing a nurturing environment for a young chemist in the making and for enabling me to pursue graduate studies. Special thanks to Kirk and Scott for driving 7-hours from Delaware to Rochester, NY in cars full of my stuff in order to take me to graduate school.

I would like to thank Prof. Dan Weix for being an outstanding mentor, courageous leader, great collaborator, and an overall swell guy. He is always ready to have a good conversation, whether it is about chemistry, whiskey, or computers. A man who never takes

himself too seriously, it has been a pleasure working with you for the past six years. Thank you for pushing me beyond my limits, showing me what I am truly capable of, and always believing in me, even when I don't.

I would also like to give thanks to the Weix group, both former and current. The group has always been a collection of eccentric intellectuals, and I am grateful for my time with each of you. I want to particularly acknowledge Dr. Laura Ackerman, who will be starting her independent career with her husband Kyle at Arizona State University. She was the first member of the Weix group that I met and has taught me the most about what it is to be a good chemist, friend, and person. From our times in 443 to brushing elbows at the Gordon Research Conference to your beautiful wedding in Hawaii, you will always be a treasured friend. I also want to thank all of the friends that I have made in graduate school, both at Rochester and at Wisconsin, for making these past six years truly the best of my life.

I would like to thank my committee members, Profs. Shannon Stahl, Tehshik Yoon, and John Berry for great scientific discussion, life and career advice, and for reading this dissertation. I would also like to acknowledge my former committee members at the University of Rochester, Profs. Joseph Dinnocenzo and Michael Neidig, for helping me move forward in graduate schools and for help generating ideas and directions for my research to move forward.

Lastly, I would like to acknowledge the late Prof. Burnaby Munson from the University of Delaware. Prof. Munson taught incoming freshman chemistry majors in a special course designed to expose us to the different career paths that our degrees could

take us. He held a party at his home every semester, and supplied Smartees at every exam he gave. He would track every year of his life by the periodic table and made it to Pb. He is also the person that convinced me to stay in college when I was about to drop out due to underperforming and a general lack of interest. He saw this future about to be wasted and prevented that from happening. Without his intervention, I would not be writing this dissertation, and I am grateful to have had his influence in my life.

Abstract

In this thesis, the extension of cross-electrophile coupling to engage vinyl halides, organic chlorides, and dihalides for cyclization will be described in detail.

Chapter 1 will provide an introduction to cross-electrophile coupling and the current state of the art for these transformations.

Chapter 2 describes the development of improved coupling conditions for the nickel-catalyzed cross-electrophile coupling of vinyl halides with alkyl halides. The application of these conditions to aryl-alkyl coupling, substrate scope and limitations, and preliminary mechanistic insights are also discussed.

Chapter 3 describes studies performed for the coupling of aryl and alkyl chlorides. The effects of a dual ligand system on reaction selectivity, as well as implications of dimethoxyethane and diglyme nickel precatalysts are also conferred.

Chapter 4 provides a survey of macrocyclization methodologies and details the application of cross-electrophile coupling to the synthesis of macrocyclic rings. Efforts towards the total synthesis of (±)-Recifeiolide are also discussed.

Contributors and Funding Sources

This work was supervised by a dissertation committee consisting of Professors Daniel J. Weix (advisor), Shannon Stahl, Tehshik Yoon, and John F. Berry of the Department of Chemistry. The author performed all experimental procedures in this dissertation unless specified below:

Chapter 3:

Initial experiments for Chapter 3 were performed by Seoyoung Kim and Dr. Laura Ackerman (Arizona State University).

Chapter 4:

The reaction in Figure 4.10 was performed by Dr. David George (Bristol Meyers Squibb).

All the work included in this thesis was supported by the University of Rochester, the University of Wisconsin-Madison, the National Institutes of Health, the National Science Foundation Graduate Research Fellowship Program, and the Howard Hughes Medical Institute Gilliam Fellowship.

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List of Symbols and Abbreviations

-	minus, negative or hyphen
α	alpha
β	beta
δ	delta
μ	micro
μL	microliter
μm	micrometer
°	degrees
°C	degrees Celsius
%	percent
^{1}H	proton
^{13}C	carbon-13
^{19}F	fluorine-19
A%	area percent
Ac	acyl
acac	acetylacetonate
ACS	American Chemical Society
Ad	adamantyl
Al	aluminum
aq	aqueous
B	boron
Bn	benzyl
Boc	tert-butoxylcarbonyl
bpy	2,2’-bipyridyl
Bphen	bathophenantrholine, 4,7-Diphenyl-1,10-phenanthroline
Br	bromide
Bu	butyl
Bz	benzoyl

C	carbon or Celsius
cat.	catalytic species
Cbz	benzyloxycarbonyl
$CDCl_3$	chloroform-d
CI	chemical ionization
Cl	chloride
cm	centimeter
CO	carbonyl (C=O)
Co	cobalt
CO_2	carbon dioxide
cod	1,5-cyclooctadiene
Csp	carbon with sp hybridized orbitals
$C(sp^2)$	carbon with sp2 hybridized orbitals
$C(sp^3)$	carbon with sp3 hybridized orbitals
Cu	copper
CuI	copper iodide
Cs_2CO_3	cesium carbonate
Cy	cyclohexyl
D	deuterium
d	doublet
dba	dibenzylideneacetone
d.r.	diastereomer ratio
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
diglyme	bis(2-methoxyethyl) ether
DMA	N,N-dimethylacetamide
DMAP	4-(N,N-dimethylamino)pyridine
DMF	N,N-dimethylformamide
dmbpy	4,4’-dimethoxy-2,2’-bipyridyl
dme	1,2-Dimethoxyethane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone

DMSO	dimethyl sulfoxide
dppBz	1,2-bis(diphenylphosphino)benzene
dtbbpy	4,4’-di-tert-butyl-2,2’-bipyridyl
EDC	(3-dimethylaminopropyl)-N’-ethylcarbodiimide
EDG	electron donating group
equiv	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
Fe	iron
FID	flame ionization detector
FTIR	Fourier transform infrared
g	gram
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
H	hydride, hydrogen or proton
h	hour(s)
H_2O	water
HCl	hydrochloric acid
HRMS	high-resolution mass spectrometry
Hz	hertz
I	iodide
I_2	iodine
inj.	injection or injector
^{i}Pr	isopropyl
IPr	1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
Ir	iridium
J	coupling constant
J_{C-F}	carbon-fluorine coupling constant

K	potassium
kcal	kilocalorie
KF	potassium fluoride
KHMDS	potassium hexamethyldisilazane
KI	potassium iodide
$KMnO_4$	potassium permanganate
L	liter or Ligand
LDA	lithium diisopropyl amide
Li	lithium
LiBr	lithium bromide
lit.	literature
[M]	metal
M	molar (mol/L)
m	meter or milli or multiplet
M+	mass peak from organic cation in GCMS
m/z	mass-to-charge ratio
Me	methyl
MeCN	acetonitrile
mg	milligram
Mg	magnesium
$MgCl_2$	magnesium chloride
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute(s)
mL	milliliter
mm	millimeter
mmol	millimole
Mn	manganese
mol	mole
mp	melting point
Ms	mesyl (methanesulfonyl)

MsCl	methansulfonyl chloride
MS	mass spectrometry or molecular sieves
MW	molecular weight
n	normal isomer
N	nitrogen or normal (H/L)
N_2	nitrogen (gas)
Na	sodium
Na_2SO_4	sodium sulfate
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
$NaHSO_4$	sodium bisulfate
NaI	sodium iodide
NaOH	sodium hydroxide
NaO^tBu	sodium tert-butoxide
Ni	nickel
NHP	N-hydroxyphthalimide
NMP	N-methyl-2-pyrolidinone
NMR	nuclear magnetic resonance
NR	no reaction
Nu	nucleophile
o	ortho
OAc	acetate
OMs	mesylate
OR	alkoxy
OTf	triflate
OTs	tosylate
P	phosphorus
PC	phthalocyanine
p	para
Pd	palladium
Ph	phenyl

PhCN	benzonitrile
phen	1,10-phenanthroline
PPh_3	triphenylphosphine
ppm	parts per million
psi	pounds per square inch
PTFE	polytetrafluoroethylene
py	pyridine
q	quartet
R	organic substructure
R’	organic substructure
R’’	organic substructure
R-[M]	organometallic
R-X	organic halide
Rf	retention factor
Rh	rhodium
rpm	revolutions per minute
rt	room temperature (~25 °C)
s	singlet or sec
S	sulfur
Se	selenium
Si	silicon
SM	starting material
Sn	tin
S_N2	second-order nucleophilic substitution
sp	linear hybridized orbitals with 50% s and 50% p character
sp^2	trigonal planar hybridized orbitals with 33% s and 67% p character
sp^3	tetrahedral hybridized orbitals with 25% s and 75% p character
t tert	(tertiary)
t-Bu	tert-butyl
T	temperature
TBAF	tetrabutylammonium fluoride

TDAE	1,2,2-tetrakis(dimethylamino)ethylene
T.M.	transition metal
Ti	titanium
THF	tetrahydrofuran
tol	toluene
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMS	trimethylsilyl
TMS-Br	trimethylsilyl bromide
TMS-Cl	trimethylsilyl chloride
ttbtpy	4,4′,4″-tri-tert-butyl-2,2′:6′,2″-terpyridine
UV	ultraviolet
vs.	versus
W	watt or tungsten
wt	weight
X	halide or pseudohalide
Y	heteroatom
Zn	zinc

Chapter 1: State of the Art for Nickel-Catalyzed Cross Electrophile Coupling

1.1. Introduction

Transition-metal catalysis has revolutionized the way that we approach the formation of carbon-carbon (C-C) bonds. These methods have allowed for significant advances in the synthesis of advanced drug candidates, complex polymers, and fine chemicals through the development of novel transformations that target difficult bond disconnections. Pioneering work on the palladium-catalyzed coupling of organomagnesium,[1-2] organozinc,[3] organostannane,[4] organoboron[5-6] and organosilane[7-8] reagents with organic electrophiles has been the impetus of many academic research groups (Figure 1.1). Our increased understanding of the mechanisms by which these couplings occur has led to the rational improvement and expansion of these methods.[9]

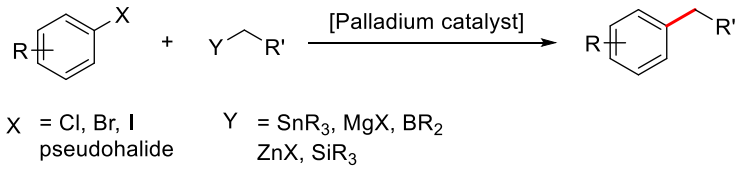


Figure 1.1. Palladium catalyzed cross-coupling.

While there have been noteworthy advances with these methods in the formation of $C(sp^2)$-$C(sp^3)$ bonds, they are still not at the level of $C(sp^2)$-$C(sp^2)$ bond formation. The challenges that still plague these transformations are usually associated with the organometallic reagent. These reagents can limit functional group tolerance, tend to be air and moisture sensitive, and suffer from low commercial availability, requiring additional steps for their synthesis. Methods for the *in-situ* formation of these reagents have been reported,[10-11] however a complimentary approach that would allow for the direct coupling

of two organic electrophiles would circumvent the requirement for a stoichiometric organometallic reagent and allow for an increased substrate pool to be used.

1.2. Transition-Metal Catalyzed Cross-Electrophile Coupling

In 1855, Wurtz reported the dimerization of alkyl halides using sodium metal as both reductant and reaction mediator (Figure 1.2, A).[12] Soon after, Fittig reported the coupling of alkyl iodides with aryl bromides also mediated by sodium metal (Figure 1.2, B).[13] These reports revealed that the coupling of two organohalides is possible, and that selectivity can be garnered through differences in the activation of the electrophiles. Ullman also reported in 1901 the reductive dimerization of aryl halides with stoichiometric copper (Figure 1.2, C).[14]

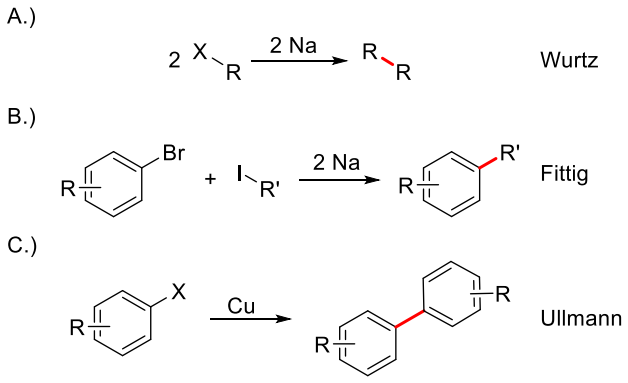


Figure 1.2. Reductive coupling of organohalides.

Decades later the Ullman was rendered catalytic using nickel catalysts. Key to this development was discovering that the nickel catalyst could be turned over by a stoichiometric metal reductant, such as zinc.[15-17] Durandetti and coworkers reported the coupling of aryl halides with α-chloroesters using a nickel catalyst, a bipyridine ligand, and manganese as the reductant (Figure 1.3).[18] While they had previously reported the electrochemical coupling of aryl halides and alkyl halides,[19-20] this was the first report of catalytic $C(sp^2)$-$C(sp^3)$ bond formation from organic electrophiles catalyzed by nickel

using a chemical reductant. However, all these methods were limited to the use of activated alkyl halides.

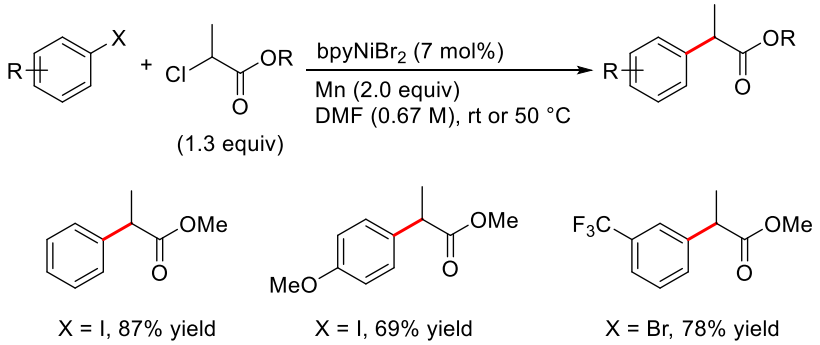


Figure 1.3. Reductive coupling of aryl halides and α-chloroesters.

Our group reported the first general nickel-catalyzed cross-electrophile coupling of aryl iodides and unactivated alkyl iodides (Figure 1.4, A).[21] Two years later we reported the coupling of aryl and vinyl bromides with alkyl bromides (Figure 1.4, B).[22] The key finding in both of these reports is that the ligand used for nickel has significant influence on the selectivity of the reaction for cross-product over dimerization.[23-24] This demonstrates the need for ligands outside of the bipyridine ligand class. This led to the discovery of novel ligand classes for the coupling of difficult aryl and heteroaryl halides via nickel-catalyzed cross-electrophile coupling (Figure 1.4, C).[25-26]

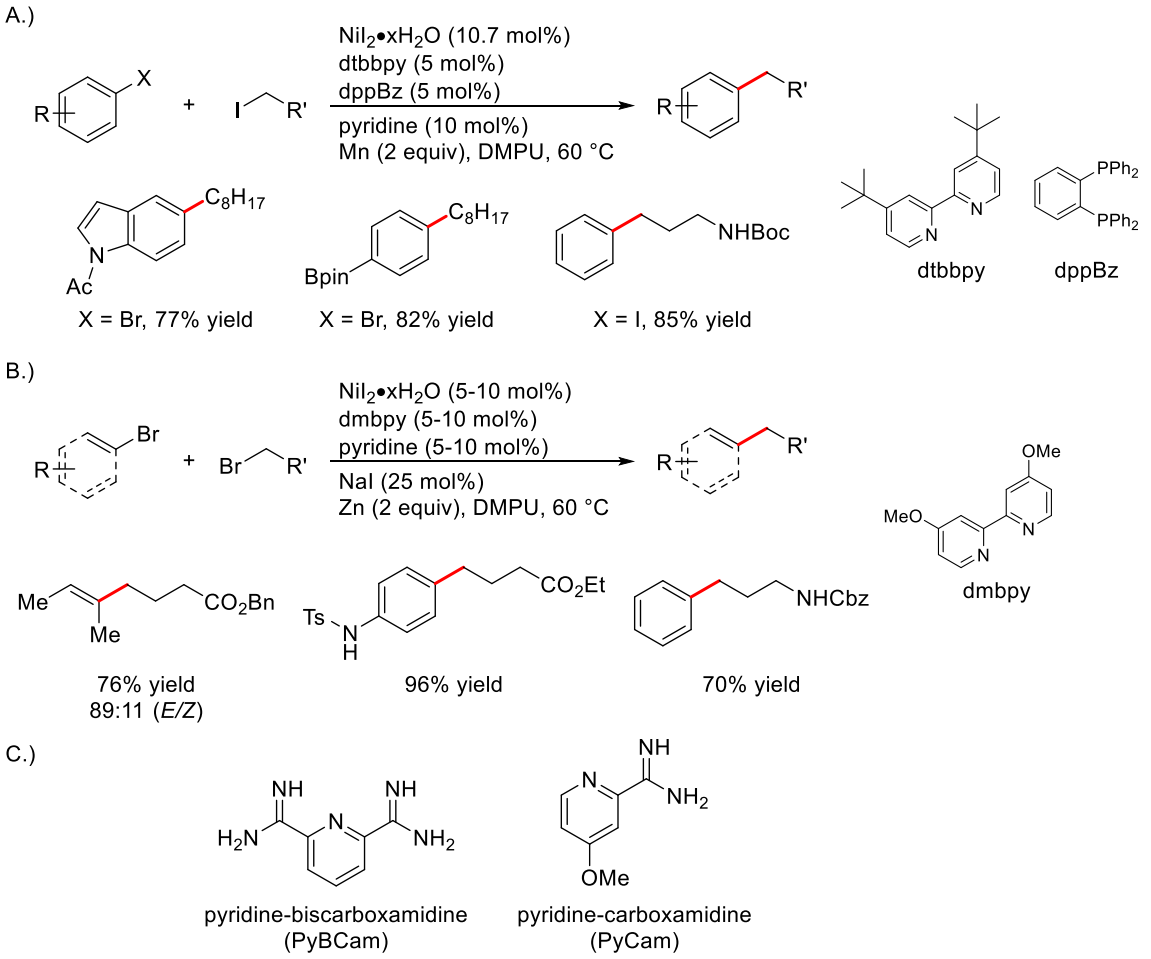


Figure 1.4. Nickel-catalyzed cross-electrophile coupling.

1.3. Mechanistic Insights into Nickel-Catalyzed Cross-Electrophile Coupling

A thorough mechanistic understanding of metal-catalyzed transformations allows for rational improvements and advances to be made. In palladium-catalyzed cross-coupling reactions, selectivity is gained from the preferential interactions of the coupling partners with different oxidation states of palladium. Organic electrophiles prefer to react with low valent palladium via oxidative addition, and the nucleophile then reacts with the higher valent palladium species via transmetallation (Figure 1.5).[27] While this typical transmetallation paradigm holds true for the majority of palladium-catalyzed cross-coupling, there are several instances that deviate from this mechanism. A notable example

is the "back"-transmetallation of Pd onto organozinc reagents to form more functionalized organozinc reagents *in situ*.[28-29]

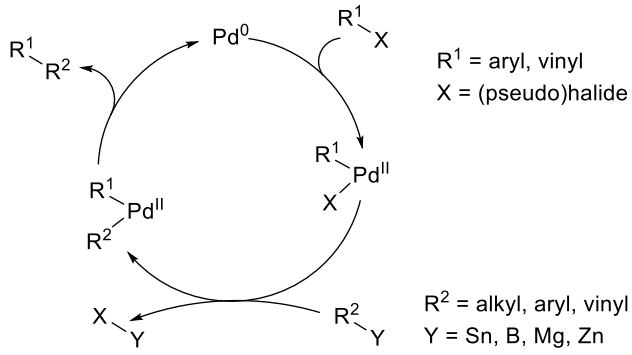


Figure 1.5. General mechanism for palladium-catalyzed cross-coupling reactions.

However, for nickel-catalyzed cross-electrophile coupling, both coupling partners are organic electrophiles that can undergo oxidative addition. Mechanistic studies by our group for the nickel-catalyzed coupling of aryl halides and alkyl halides suggested that (1) oxidative addition of the aryl halide occurs faster than the alkyl halide, (2) the alkyl halide reacts through an alkyl radical, (3) the reaction proceeds through a radical chain mechanism, and (4) an organozinc reagent is not formed in this reaction (Figure 1.6).[30]

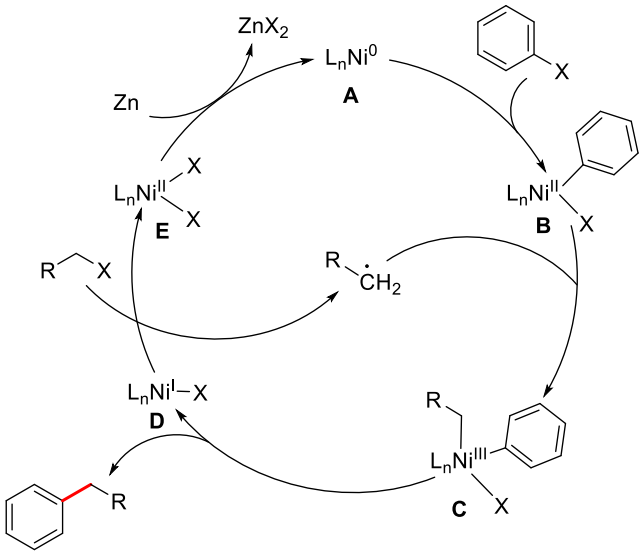


Figure 1.6. Proposed mechanism for nickel-catalyzed cross-electrophile coupling.

$L_nNi(0)$ (**A**) undergoes oxidative addition into the aryl halide bond, followed by capture of an alkyl radical to form a $L_nNi(III)$ species (**C**). This species undergoes reductive elimination to give the desired product and $L_nNi(I)$-X (**D**), which can abstract a halogen atom from the alkyl halide, forming another alkyl radical and $L_nNi(II)X_2$ (**E**), which is then reduced by the stoichiometric reductant. The key finding in these studies is that the Ni(II)Aryl(X) (**B**) species can capture an alkyl radical and then form a C-C bond upon reductive elimination. This species can also initiate the radical chain, and Hegedus suggested this mechanism for the reaction of alkyl halides with Ni(II)allyl species.[31] Our group and others have taken advantage of this mechanistic proposal to develop new reactions.

1.4. Recent Advances in Cross-Electrophile Coupling

As the formation of the alkyl radical is independent of the oxidative addition of the aryl halide, decoupling the alkyl radical formation from nickel allows for this strategy to be extended beyond alkyl halides. Our group has shown that epoxides can be opened with a titanocene co-catalyst to form a secondary radical which is then captured by a Ni(II)aryl(X) species to form product.[32] This reaction can also be rendered enantioselective for pro-chiral epoxides with the use of a chiral titanium co-catalyst (Figure 1.7).[33] The opening of epoxides and aziridines can also be achieved through the use of an iodide co-catalyst to furnish the iodohydrin or β-iodoamine, respectively.[32, 34-35] These intermediates can then participate in the cross-electrophile coupling as previously described.

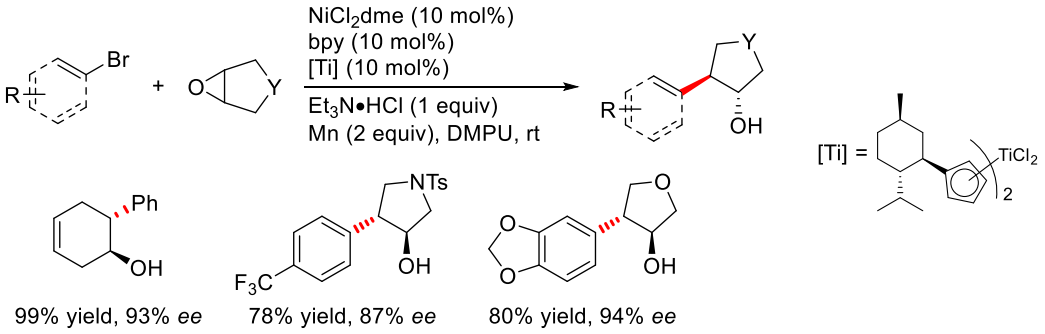


Figure 1.7. Enantioselective arylation of meso-epoxides.

We have also reported the Ni/Co catalyzed coupling of benzyl mesylates with aryl halides (Figure 1.8).[36] Cobalt phthalocyanine (Co(Pc)) is capable of undergoing nucleophilic substitution with benzyl mesylates, after which homolysis of the Co-C bond furnishes the benzyl radical.[37] This radical can then be captured by the nickel (II) aryl species and form product upon reductive elimination. This work was further extended by Komeyama and coworkers to non-activated alkyl tosylates.[38] They were able to achieve this through the use of vitamin B_{12} (cyanocobalamin) as a co-catalyst for the activation of the alkyl tosylate. Molander has also reported the nickel-catalyzed cross-electrophile coupling of unactivated alkyl tosylates with aryl and heteroaryl bromides using KI as a mediator.[39] More recently, Shenvi and coworkers have reported a Ni/Fe catalyzed olefin hydroarylation that proceeds through Markovnikov H atom addition catalyzed by Fe, followed by trapping by a Ni(II) aryl intermediate.[40]

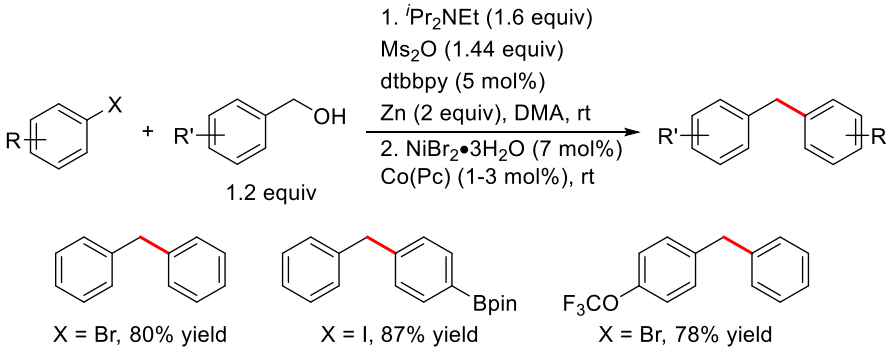


Figure 1.8. Nickel/Cobalt co-catalyzed coupling of aryl halides and benzyl mesylates**.**

Recently, a number of photochemical approaches to generating alkyl radicals have been coupled to the same nickel system. Doyle and MacMillan reported the photochemical oxidation of alkyl carboxylates to generate an alkyl radical via decarboxylation which can be coupled with nickel (Figure 1.9).[41] The photocatalyst, after oxidation, is capable of reducing the nickel catalyst to regenerate the low valent nickel, resulting in a redox-neutral reaction. Fu and MacMillan reported the enantioselective coupling of α-amino acids with aryl halides catalyzed by a chiral nickel catalyst and a photocatalyst.[42] This also undergoes oxidative decarboxylation to give a stabilized alkyl radical. MacMillan has also reported the photochemical generation of alkyl radicals from alkyl bromides using tris(trimethylsilyl)silane, a photocatalyst, and nickel.[43] They hypothesize that a silyl radical species, formed photochemically, is capable of abstracting the halide atom, forming the corresponding alkyl radical.

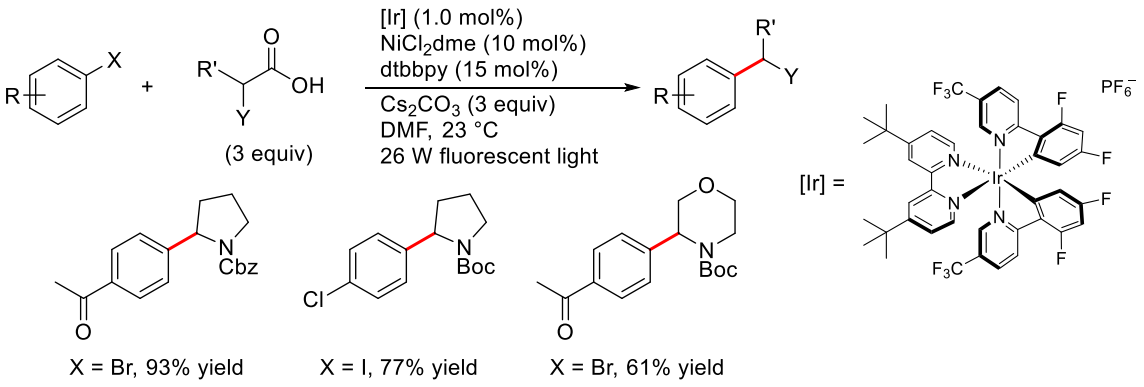


Figure 1.9. Nickel/Photoredox co-catalyzed coupling of aryl halides and carboxylic acids.

While the previous examples utilize a co-catalyst, nickel is capable of forming alkyl radicals from substrates other than alkyl halides. Overman and Okada have shown that alkyl radicals can be formed through photochemical reduction of *N*-hydroxyphthalimide (NHP) esters.[44-45] Our group has shown that NHP esters can be reduced in the absence of a photocatalyst by nickel and zinc (Figure 1.10).[46] These can be readily prepared from carboxylic acids and *N*-hydroxyphthalimide, and undergo reductive decarboxylation to give the alkyl radical. They participate in cross-electrophile coupling with aryl iodides similar to alkyl iodides, and mechanistic experiments suggest that a similar reaction mechanism is operative. This work can be extended to the coupling of alkynyl bromides,[47] and Reisman has reported the enantioselective coupling of NHP esters with vinyl bromides using a chiral nickel catalyst.[48] More recently, Baran and our group have reported the coupling of acyl electrophiles with NHP esters for the synthesis of ketones, with both coupling partners being derived from carboxylic acids (Figure 1.10).[49-50]

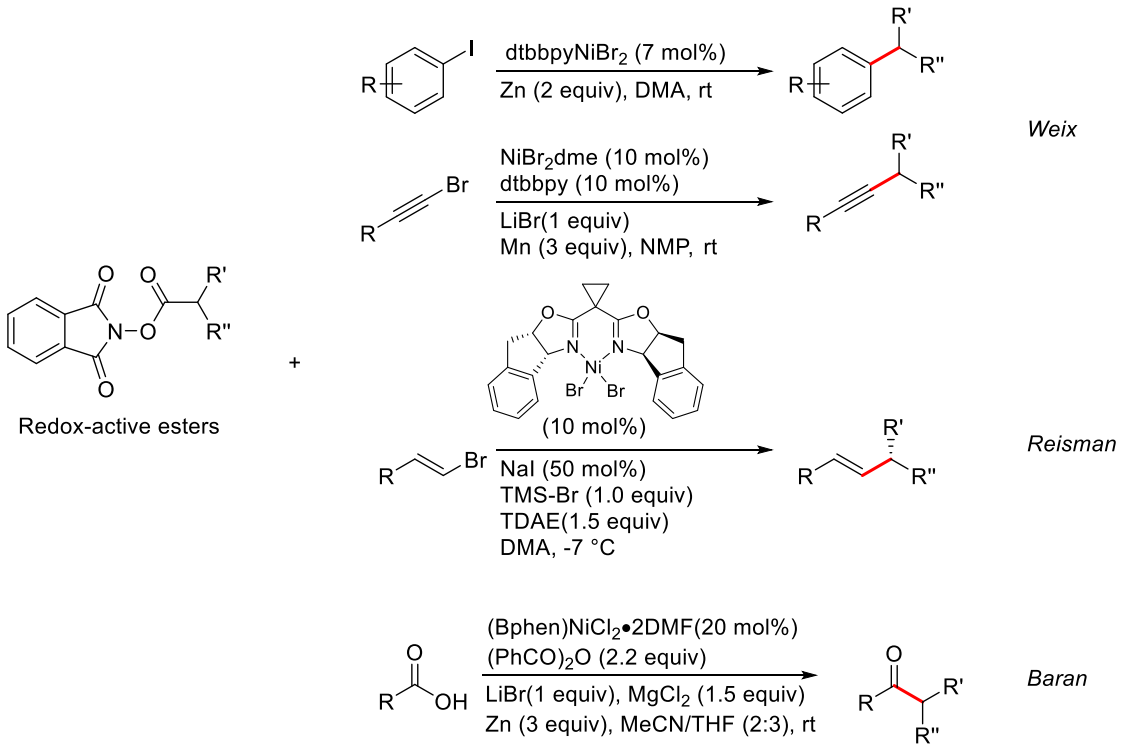
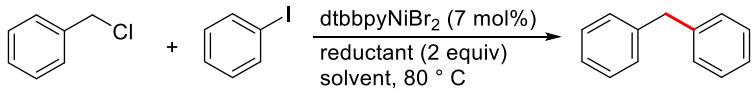


Figure 1.10. Nickel-catalyzed cross-electrophile coupling of redox-active esters with various electrophiles.

The identity of the reductant also plays an important role in nickel catalyzed cross-electrophile coupling. Tetrakis(dimethylamino)ethylene (TDAE) was utilized in our mechanistic studies to show that an organozinc intermediate was not necessary for cross coupling.[30] Our group has found that the use of TDAE as reductant in cross-electrophile couplings allows for the use of non-amide solvents such as acetonitrile and propylene carbonate (Table 1.1).[51] These solvents qualify as "green" solvents and avoid workup and purification issues that are present with amide solvents. Nevado and coworkers reported the difunctionalization of alkenes with aryl and alkyl iodides.[52] Interestingly, the three-component coupling only occurred when TDAE was used as the reductant (Figure 1.10). No product was observed when Zn or Mn were used.

Table 1.1. Effects of TDAE vs. Zn as reductant.



Entry	Solvent	Zinc Yield (%)[a]	TDAE Yield (%)[a]
1	DMA	82	79
2	MeCN	15	88
3	propylene carbonate	58	102
4	diethyl carbonate	19	75
5	isopropyl acetate	53	79
6	2-Me-THF	51	76
7	toluene	4	66
8	2-butanol	64	20

[a]GC yields vs. dodecane as internal standard.

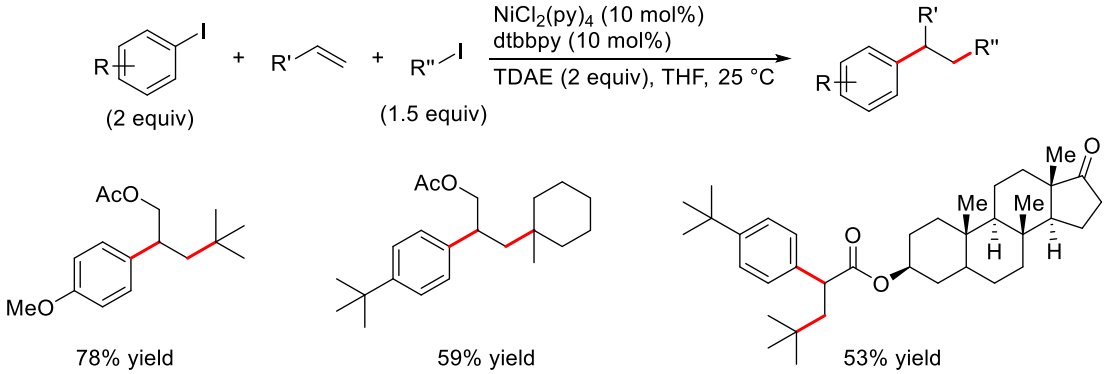


Figure 1.11. Three-component cross-electrophile coupling.

1.5. Outline of Thesis

Our increased mechanistic understanding of the nickel-catalyzed cross-electrophile coupling of aryl and alkyl halides has led to the development of improved reaction conditions, the expansion of the methodology to new substrate classes, and the proliferated interest in cross-electrophile coupling as a complimentary and orthogonal approach to the formation of C-C bonds. This dissertation will describe some of the advances made in cross-electrophile coupling in greater detail. Chapter 2 will discuss the cross-electrophile coupling of unhindered vinyl halides with alkyl halides as well as improved conditions for

aryl-alkyl coupling. Chapter 3 details the extension of cross-electrophile coupling to aryl and alkyl chlorides, which have been previously inert under previous reaction conditions. Chapter 4 applies our newfound mechanistic understanding to the synthesis of macrocycles through intramolecular cross-electrophile coupling.

1.6. References

1. Tamao, K.; Sumitani, K.; Kumada, M., Selective carbon-carbon bond formation by cross-coupling of Grignard reagents with organic halides. Catalysis by nickel-phosphine complexes. *J. Am. Chem. Soc.* **1972,** *94* (12), 4374-4376.
2. Corriu, R. J. P.; Masse, J. P., Activation of Grignard reagents by transition-metal complexes. A new and simple synthesis of trans-stilbenes and polyphenyls. *J. Chem. Soc., Chem. Commun.* **1972,** (3), 144a-144a.
3. Negishi, E., Palladium- or nickel-catalyzed cross coupling. A new selective method for carbon-carbon bond formation. *Acc. Chem. Res.* **1982,** *15* (11), 340-348.
4. Stille, J. K., The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles [New Synthetic Methods (58)]. *Angew. Chem. Int. Ed. Engl.* **1986,** *25* (6), 508-524.
5. Miyaura, N.; Yamada, K.; Suzuki, A., A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett.* **1979,** *20* (36), 3437-3440.
6. Miyaura, N.; Suzuki, A., Stereoselective synthesis of arylated (E)-alkenes by the reaction of alk-1-enylboranes with aryl halides in the presence of palladium catalyst. *J. Chem. Soc., Chem. Commun.* **1979,** (19), 866-867.
7. Denmark, S. E.; Regens, C. S., Palladium-Catalyzed Cross-Coupling Reactions of Organosilanols and Their Salts: Practical Alternatives to Boron- and Tin-Based Methods. *Acc. Chem. Res.* **2008,** *41* (11), 1486-1499.
8. Hatanaka, Y.; Hiyama, T., Cross-coupling of organosilanes with organic halides mediated by a palladium catalyst and tris(diethylamino)sulfonium difluorotrimethylsilicate. *J. Org. Chem.* **1988,** *53* (4), 918-920.
9. Jana, R.; Pathak, T. P.; Sigman, M. S., Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011,** *111* (3), 1417-1492.
10. Krasovskiy, A.; Duplais, C.; Lipshutz, B. H., Stereoselective Negishi-like Couplings Between Alkenyl and Alkyl Halides in Water at Room Temperature. *Org. Lett.* **2010,** *12* (21), 4742-4744.
11. Krasovskiy, A.; Lipshutz, B. H., Ligand Effects on Negishi Couplings of Alkenyl Halides. *Org. Lett.* **2011,** *13* (15), 3818-3821.
12. Wurtz, A., Ueber eine neue Klasse organischer Radicale. *Justus Liebigs Annalen der Chemie* **1855,** *96* (3), 364-375.
13. Tollens, B.; Fittig, R., Ueber die Synthese der Kohlenwasserstoffe der Benzolreihe. *Justus Liebigs Ann. Chem.* **1864,** *131* (3), 303-323.

14. Ullmann, F.; Bielecki, J., Ueber Synthesen in der Biphenylreihe. *Ber. Dtsch. Chem. Ges.* **1901,** *34* (2), 2174-2185.
15. Kende, A. S.; Liebeskind, L. S.; Braitsch, D. M., In situ generation of a solvated zerovalent nickel reagent. Biaryl formation. *Tetrahedron Lett.* **1975,** *16* (39), 3375-3378.
16. Zembayashi, M.; Tamao, K.; Yoshida, J.-i.; Kumada, M., Nickel-phosphine complex-catalyzed homo coupling of aryl halides in the presence of zinc powder. *Tetrahedron Lett.* **1977,** *18* (47), 4089-4091.
17. Colon, I.; Kelsey, D. R., Coupling of aryl chlorides by nickel and reducing metals. *J. Org. Chem.* **1986,** *51* (14), 2627-2637.
18. Durandetti, M.; Gosmini, C.; Périchon, J., Ni-catalyzed activation of α-chloroesters: a simple method for the synthesis of α-arylesters and β-hydroxyesters. *Tetrahedron* **2007,** *63* (5), 1146-1153.
19. Durandetti, M.; Sibille, S.; Nédélec, J.-Y.; Périchon, J., A Novel Method of Arylation of α-Chloroketones. *Synth. Commun.* **1994,** *24* (2), 145-151.
20. Durandetti, M.; Nédélec, J.-Y.; Périchon, J., Nickel-Catalyzed Direct Electrochemical Cross-Coupling between Aryl Halides and Activated Alkyl Halides. *J. Org. Chem.* **1996,** *61* (5), 1748-1755.
21. Everson, D. A.; Shrestha, R.; Weix, D. J., Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010,** *132* (3), 920-921.
22. Everson, D. A.; Jones, B. A.; Weix, D. J., Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012,** *134* (14), 6146-6159.
23. Everson, D. A.; Weix, D. J., Cross-electrophile coupling: principles of reactivity and selectivity. *J. Org. Chem.* **2014,** *79* (11), 4793-4798.
24. Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A., Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem. Eur. J.* **2014,** *20* (23), 6828-6842.
25. Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J., New ligands for nickel catalysis from diverse pharmaceutical heterocycle libraries. *Nat. Chem.* **2016,** *8* (12), 1126-1130.
26. Hansen, E. C.; Li, C.; Yang, S.; Pedro, D.; Weix, D. J., Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling. *J. Org. Chem.* **2017,** *82* (14), 7085-7092.
27. Hartwig, John F., Organotransition Metal Chemistry: From Bonding to Catalysis
28. Jin, L.; Lei, A., Insights into the elementary steps in Negishi coupling through kinetic investigations. *Org. Biomol. Chem.* **2012,** *10* (34), 6817-6825.
29. Li, J.; Jin, L.; Liu, C.; Lei, A., Quantitative kinetic investigation on transmetalation of ArZnX in a Pd-catalysed oxidative coupling. *Chem. Commun.* **2013,** *49* (83), 9615-9617.
30. Biswas, S.; Weix, D. J., Mechanism and selectivity in nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides. *J. Am. Chem. Soc.* **2013,** *135* (43), 16192-16197.
31. Hegedus, L. S.; Miller, L. L., Reaction of .pi.-allylnickel bromide complexes with organic halides. Stereochemistry and mechanism. *J. Am. Chem. Soc.* **1975,** *97* (2), 459-460.

32. Zhao, Y.; Weix, D. J., Nickel-catalyzed regiodivergent opening of epoxides with aryl halides: co-catalysis controls regioselectivity. *J. Am. Chem. Soc.* **2014,** *136* (1), 48-51.
33. Zhao, Y.; Weix, D. J., Enantioselective Cross-Coupling of meso-Epoxides with Aryl Halides. *J. Am. Chem. Soc.* **2015,** *137* (9), 3237-3240.
34. Woods, B. P.; Orlandi, M.; Huang, C.-Y.; Sigman, M. S.; Doyle, A. G., Nickel-Catalyzed Enantioselective Reductive Cross-Coupling of Styrenyl Aziridines. *J. Am. Chem. Soc.* **2017,** *139* (16), 5688-5691.
35. Banerjee, A.; Yamamoto, H., Nickel Catalyzed Regio-, Diastereo-, and Enantioselective Cross-Coupling of 3,4-Epoxyalcohol with Aryl Iodides. *Org. Lett.* **2017,** *19* (16), 4363-4366.
36. Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J., Cobalt co-catalysis for cross-electrophile coupling: diarylmethanes from benzyl mesylates and aryl halides. *Chem. Sci.* **2015,** *6* (2), 1115-1119.
37. Espenson, J. H.; Sellers, T. D., Kinetics and mechanism of alkylchromium formation in the reductive cobalt-carbon bond cleavage of alkylcorrins by chromium(II). *J. Am. Chem. Soc.* **1974,** *96* (1), 94-97.
38. Komeyama, K.; Ohata, R.; Kiguchi, S.; Osaka, I., Highly nucleophilic vitamin B12-assisted nickel-catalysed reductive coupling of aryl halides and non-activated alkyl tosylates. *Chem. Commun.* **2017,** *53* (48), 6401-6404.
39. Molander, G. A.; Traister, K. M.; O'Neill, B. T., Engaging Nonaromatic, Heterocyclic Tosylates in Reductive Cross-Coupling with Aryl and Heteroaryl Bromides. *J. Org. Chem.* **2015,** *80* (5), 2907-2911.
40. Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A., Iron–Nickel Dual-Catalysis: A New Engine for Olefin Functionalization and the Formation of Quaternary Centers. *J. Am. Chem. Soc.* **2018,** *140* (36), 11317-11324.
41. Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C., Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp3-carbons with aryl halides. *Science* **2014,** *345* (6195), 437-440.
42. Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C., Enantioselective Decarboxylative Arylation of α-Amino Acids via the Merger of Photoredox and Nickel Catalysis. *J. Am. Chem. Soc.* **2016,** *138* (6), 1832-1835.
43. Zhang, P.; Le, C. C.; MacMillan, D. W. C., Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2016,** *138* (26), 8084-8087.
44. Pratsch, G.; Lackner, G. L.; Overman, L. E., Constructing Quaternary Carbons from N-(Acyloxy)phthalimide Precursors of Tertiary Radicals Using Visible-Light Photocatalysis. *J. Org. Chem.* **2015,** *80* (12), 6025-6036.
45. Okada, K.; Okamoto, K.; Oda, M., A new and practical method of decarboxylation: photosensitized decarboxylation of N-acyloxyphthalimides via electron-transfer mechanism. *J. Am. Chem. Soc.* **1988,** *110* (26), 8736-8738.
46. Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T.; Kim, S.; Ackerman, L. K. G.; Weix, D. J., Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides. *J. Am. Chem. Soc.* **2016**, *138* (15), 5016-5019

47. Huang, L.; Olivares, A. M.; Weix, D. J., Reductive Decarboxylative Alkynylation of N-Hydroxyphthalimide Esters with Bromoalkynes. *Angew. Chem. Int. Ed.* **2017,** *56* (39), 11901-11905.
48. Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E., Nickel-Catalyzed Enantioselective Cross-Coupling of N-Hydroxyphthalimide Esters with Vinyl Bromides. *Org. Lett.* **2017,** *19* (8), 2150-2153.
49. Ni, S.; Padial, N. M.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M. M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B. B.; Yang, S.; Perry, M. A.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S., A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc.* **2019,** *141* (16), 6726-6739.
50. Wang, J.; Cary, B. P.; Beyer, P.; Gellman, S. H.; Weix, D. J., Ketones from Nickel-Catalyzed Decarboxylative, Non-Symmetric Cross-Electrophile Coupling of Carboxylic Acid Esters. Angew. Chem. Int. Ed. 2019. doi: 10.1002/anie.201906000
51. Anka-Lufford, L. L.; Huihui, K. M. M.; Gower, N. J.; Ackerman, L. K. G.; Weix, D. J., Nickel-Catalyzed Cross-Electrophile Coupling with Organic Reductants in Non-Amide Solvents. *Chem. Eur. J.* **2016,** *22* (33), 11564-11567.
52. García-Domínguez, A.; Li, Z.; Nevado, C., Nickel-Catalyzed Reductive Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2017,** *139* (20), 6835-6838.

Chapter 2: Nickel-Catalyzed Cross-Electrophile Coupling of Vinyl Halides and Alkyl Halides

2.1. Introduction

Olefins are ubiquitous functional groups in synthetic chemistry. In addition to being useful precursors for a plethora of organic transformations and polymer syntheses, they have also found utility in catalysis as ligands,[1] and are ever-present in natural products and pharmaceutical targets. Among the several methods reported for the synthesis of alkenes, only a few address the synthesis of *(Z)*-alkenes. These include the semi-reduction of alkynes, the use of Wittig reagents and other phosphonium ylides, olefin metathesis, and transition-metal catalyzed cross-coupling transformations.[2] While these methods have found wide use in organic chemistry, there exists certain limitations that these methods suffer which will be discussed herein.

2.1.1. Established Methods for the Synthesis of *(Z)*-alkenes

Since its discovery in the early 1950s, the Wittig olefination remains one of the most widely applied methods for the synthesis of alkenes.[3] A phosphonium ylide, generated from deprotonation of an alkyl phosphonium salt, reacts with an aldehyde or ketone to form the desired alkene through a [2+2]/retro [2+2] mechanism (Figure 2.1).[4]

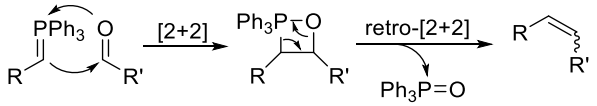


Figure 2.1. Mechanism of Wittig olefination.

This reaction usually furnishes a mixture of isomers, and selectivity for the *(E)*-alkene vs. the *(Z)*-alkene is significantly dependent on the carbonyl compound and the phosphonium ylide used. Additionally, the generation of stoichiometric triphenylphosphineoxide waste can be problematic for purification of the desired product.[5]

Therefore, efforts have been made to make this transformation more general and address these challenges. The most notable advances are the Still-Gennari modification of the Horner-Wadsworth-Emmons (HWE) olefination[6] and more recently the use of tunable *N*-sulfonyl imines in place of aldehydes.[7-8] The Horner-Wadsworth-Emmons olefination is a variant of the Wittig reaction in which the use of a stabilized phosphonate carbanion in place of a phosphonium ylide allows for the selective formation of *(E)*-olefins.[9-10] Still and Gennari found that when the phosphonate ester is substituted with electron-withdrawing groups, the synthesis of *(Z)*-olefins can be achieved under non-coordinating conditions (Figure 2.2, A).[6] Ando has also seen similar results with the use of diarylphosphonoacetates for the formation of *(Z)*-α,β-unsaturated esters.[11-12] Tian and co-workers reported the olefination of semi-stabilized phosphonium ylides with *N*-sulfonyl imines. They observed that they can control the olefin geometry by varying the substituent on the sulfonyl group (Figure 2.2, B).[7]

These methods allow for *(Z)*-alkenes to be synthesized in modest to high yields with excellent selectivity; however, they still require stoichiometric phosphorous reagents which need to be prepared prior to use. Additionally, generation of the ylide usually requires a strong base, which limits functional group compatibility.

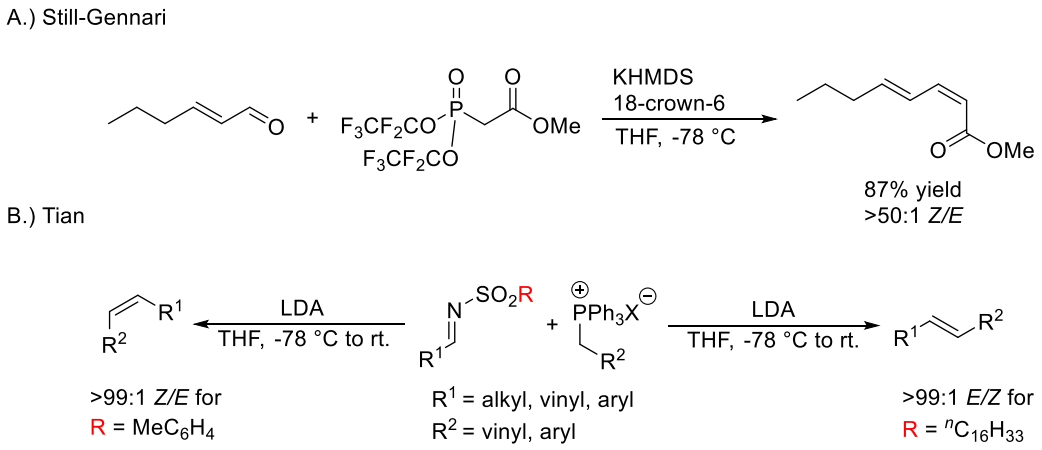


Figure 2.2. Wittig olefination of N-sulfonyl imines.

One of the earliest metal-catalyzed reactions to yield *(Z)*-olefins with excellent selectivity is the partial reduction of alkynes by use of a poisoned catalyst and hydrogen gas.[13-14] The most common catalyst for this type of transformation is Lindlar's catalyst, which consists of palladium deposited on calcium carbonate and treated with lead (II) acetate, which deactivates the catalyst.[15] The catalyst is further deactivated with quinoline, which prevents the alkene from being further reduced. Since addition of the metal hydride occurs on the same face of the alkyne (*syn*), the *(Z)*-alkene is usually observed. Other catalytic methods have explored other heterogenous palladium catalyst,[16-18] homogeneous systems,[19-20] and photochemical reduction.[21] Partial hydrogenation of alkynes has found significant use in the synthesis of polyenes due to its selectivity for the reduction of alkynes over alkenes.[22] However, starting from internal alkynes limits this methodology to the synthesis of 1,2-disubstituted alkenes.

Olefin metathesis is one of the most widely used methods for the synthesis of alkenes in complex systems. A metal alkylidene exchanges olefins to furnish the desired alkene via a [2+2]/retro-[2+2] mechanism (Figure 2.3, A). This reaction allows for a diverse array of alkene products to be generated through a myriad of various reaction types

(ring closing/opening metathesis, cross metathesis, ring opening metathesis polymerization, etc.). For their efforts in elucidation of the reaction mechanism and development of robust catalysts capable of performing these transformations, Chauvin, Grubbs, and Schrock received the Nobel Prize in Chemistry in 2005. In the decade since this achievement, there has been an extensive effort to expand the range of this transformation to afford previously inaccessible products. Recently, Hoveyda and Schrock have reported successes in both the development of catalysts capable of *(Z)*-selective olefin metathesis as well as its application in the total synthesis of a number of natural products (Figure 2.3, B).[23-26] While these advances showcase the utility of olefin metathesis in synthetic chemistry, there still exist limitations to these methods, primarily the synthesis of tri- and tetrasubstituted olefins and the high cost of evaluating these sophisticated catalysts for different substitution patterns of the desired olefin.

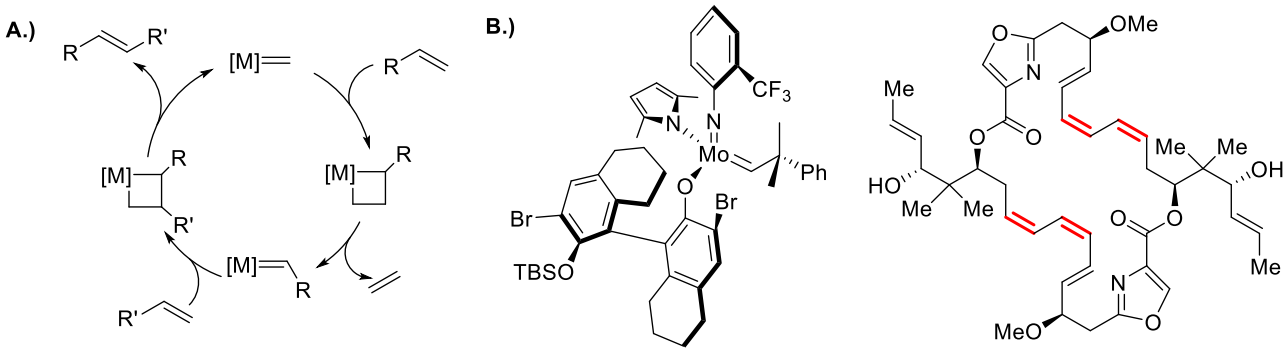


Figure 2.3. A.) General mechanism of olefin metathesis. B.) Molybdenum alkylidene, left, used in the total synthesis of Disorazole C1, right.

2.1.2. Coupling of Vinyl/Alkyl Halides with Organometallic Reagents

The formation of C-C bonds through transition-metal catalyzed cross-coupling reactions has found widespread use in academia and industry.[27-28] The native reactivity of group 10 metals towards organohalides, mainly C(sp^2)-X bonds, and their subsequent reactivity with organometallic reagents has been heavily exploited in organic synthesis.[29]

A palladium (0) center oxidatively adds to the C(sp^2)-X bond to give a palladium (II) complex, which then reacts with the chosen organometallic reagent via transmetallation. Reductive elimination furnishes the desired product and regenerates the metal catalyst (Figure 2.4).

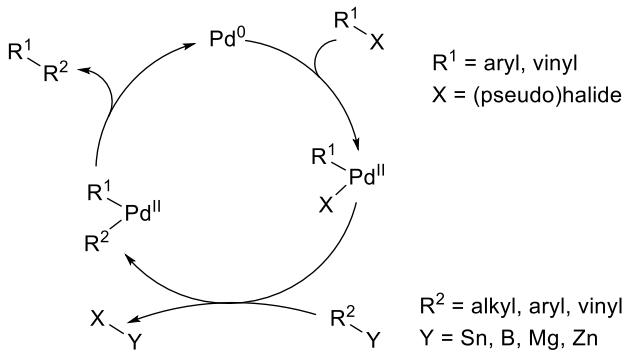


Figure 2.4. General mechanism for palladium catalyzed cross-coupling reactions.

This inherent ability for the metal catalyst to react selectively with the substrates depending on oxidation state enables high cross selectivity in these C-C bond forming reactions. However, the limitations of these methods stem from the organometallic reagent; due to their reactivity, these reagents are often air and moisture sensitive. This restricts their commercial availability and therefore they must be synthesized prior to use. Finally, the nucleophilic, and often basic, organometallic reagent limits the functional group compatibility of the method.[28]

Unlike the aforementioned methods, transition-metal catalyzed cross-coupling reactions with *(Z)*-vinyl halides differ in that the stereochemistry of the olefin is generally retained throughout the reaction rather than produced as a result of the method. This can be advantageous in reaction development as the geometry of the resulting alkene is independent of the method. Lipshutz has reported the stereoretentive Stille,[30] Negishi,[31] Kumada-Corriu,[32] and Suzuki-Miyaura[33] couplings of vinyl halides with the respective

alkyl organometallic reagents. Lipshutz has also disclosed studies into the loss of olefin geometry for these reactions, and has deduced that the ligand on palladium plays a crucial role in the retention of the olefin's stereochemistry (Figure 2.5).[30, 33-34] These findings provide key insights into the loss of stereochemical integrity of vinyl halides and the factors that contribute therein, however only palladium catalyzed transformations were investigated.

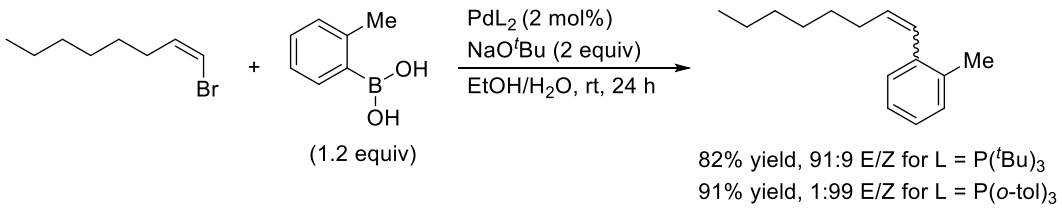


Figure 2.5. Ligand effects on the stereochemical outcome of Suzuki-Miyaura couplings.

2.1.3. Previous Results and Concurrent Work

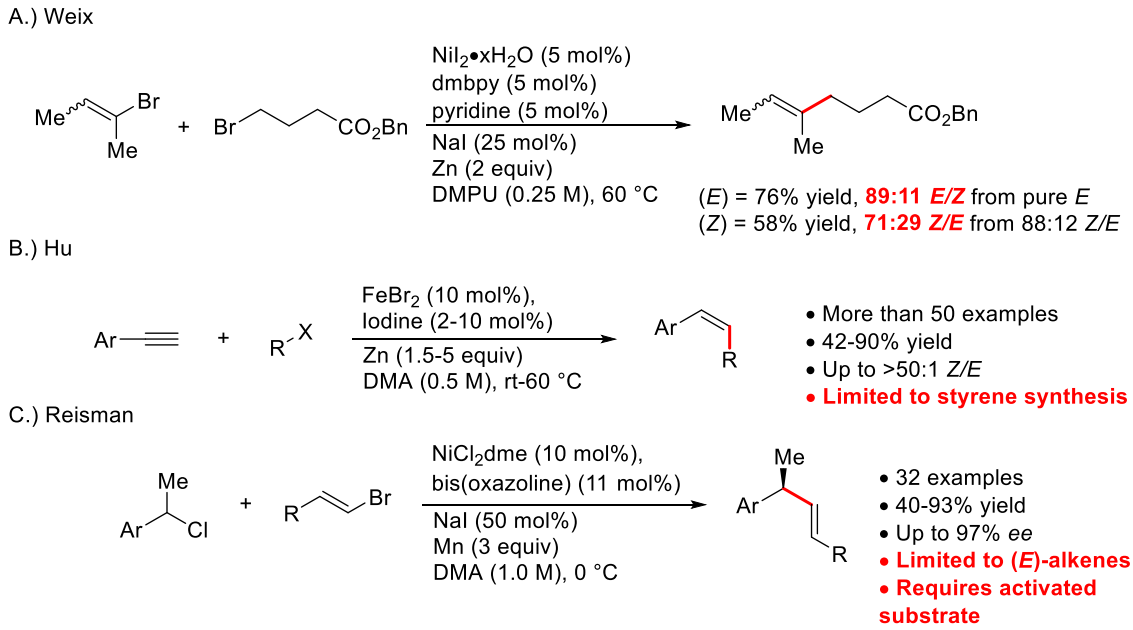


Figure 2.6. Olefin synthesis via reductive cross-electrophile coupling.

The application of reductive coupling to the synthesis of *(Z)*-olefins has seen limited success. Our group reported a few examples of coupling vinyl bromides with alkyl bromides.[35] While satisfactory yields were obtained, some erosion of the olefin geometry

was observed, especially for the *(Z)*-isomer (Figure 2.6, A). Hu has recently reported an iron-catalyzed reductive coupling of alkyl halides with terminal alkynes to form *(Z)*-alkenes (Figure 2.6, B).[36] While this method boasts high functional group tolerance and selectivity, it is limited to terminal arylalkynes. Reisman has disclosed the enantioselective reductive cross-coupling of vinyl bromides with benzyl chlorides (Figure 2.6, C),[37] but this report is limited to *(E)*-vinyl bromides, as the corresponding *(Z)*-vinyl bromides do not react under the reaction conditions. These reports showcase the need for a general set of conditions that are high yielding, stereo-retentive, and compatible with various functional groups. Herein is discussed the nickel-catalyzed cross-electrophile coupling of vinyl halides with alkyl halides.

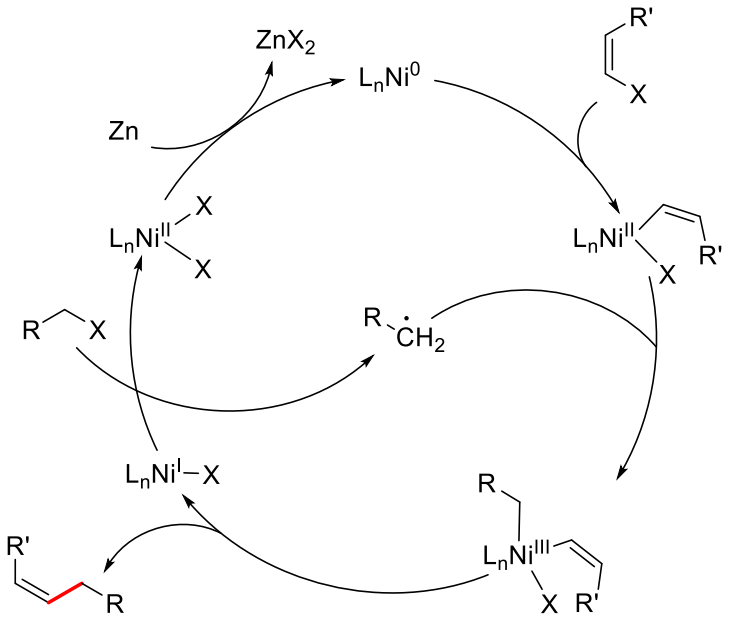


Figure 2.7. Proposed mechanism for cross-electrophile coupling of alkyl and vinyl halides.

2.2. Results

2.2.1. Reaction Optimization

2.2.1.1. Initial Reaction Conditions

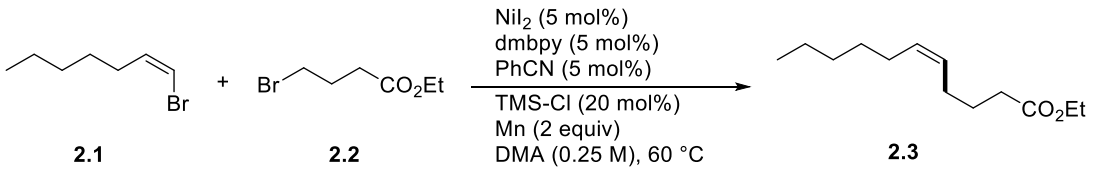
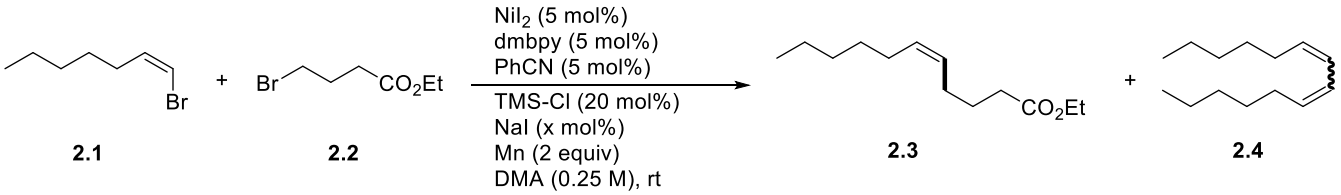


Figure 2.8. Preliminary Reaction Conditions.

We started with conditions similar to those employed for the coupling of aryl bromides with alkyl bromides (Figure 2.8).[35] During our mechanistic studies on the coupling of aryl iodides with alkyl iodides,[38] we found that the use of chlorotrimethylsilane (TMS-Cl) accelerated the rate of reaction without loss of selectivity, presumably by activation of the manganese reductant.[39] We decided this would be beneficial for this investigation. Anhydrous NiI_2 and 4,4'-dimethoxy-2,2'-bipyridine (dmbpy) were utilized as the precatalyst and ligand, and the pyridine additive from previous reports was replaced with benzonitrile as nitrile additives have been shown to stabilize low valent nickel species.[40-41]

2.2.1.2. Salt Additive

Table 2.1. Effect of Sodium Iodide.



Entry	mol% NaI	Time (h)	Yield **2.3** (%)[a]	Yield **2.4** (%)
1[b]	-	2	12	27
2	-	20	15	19
3	25	20	36	14
4	50	20	57	21
5	100	70	53	13

[a]Uncorrected GC yields vs. dodecane as internal standard. [b]Reaction performed at 60 °C.

It was quickly observed that dimerization of the vinyl bromide **2.1** was favored under these reaction conditions, even when the reaction temperature was lowered from 60 °C to room temperature (Table 2.1, 1-2). We hypothesized that while activation of the vinyl halide happened readily, the alkyl halide was not as reactive. Previously, the use of iodide salts was found to turn on selectivity for the cross product in cross-electrophile couplings.[35] While the exact basis of the selectivity enhancement can be debated,[42] one possibility is that the iodide anion displaces the bromide of the alkyl bromide (an in-situ Finkelstein reaction)[43] leading to the more reactive alkyl iodide. We were pleased to find that when we introduced sodium iodide to the reaction the yield of the cross-product increased substantially (Table 2.1, 3-5). Since turnover of the catalyst forms iodide salts from reduction of nickel (II), the iodide can be recycled. Increasing the amount of sodium iodide to 50 mol% did increase the yield, but a stoichiometric amount of the salt lead to increased reaction times, presumably due to unfavorable saturation of the catalyst.

2.2.1.3. Catalyst Concentration

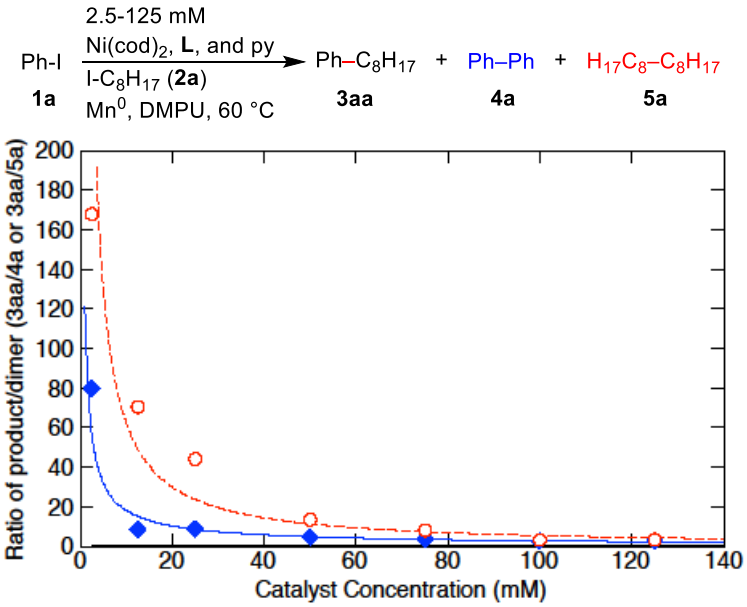
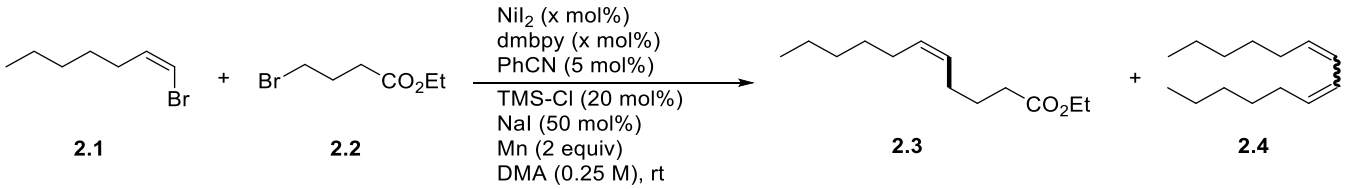


Figure 2.9. Selectivity as a function of catalyst concentration.

Work by Osakada and coworkers suggests that the rate of dimerization of aryl halides using a bipyridine-ligated nickel catalyst is directly dependent on the catalyst concentration, with the rate increasing as the catalyst concentration increases.[44-45] We also observed this trend when interrogating the coupling of aryl and alkyl iodides (Figure 2.9).[39] We hypothesized that this scenario was present in our system and that by lowering the catalyst loading, we could decrease the rate of the undesirable dimer formation and favor product formation.

Table 2.2. Effect of Catalyst Concentration.



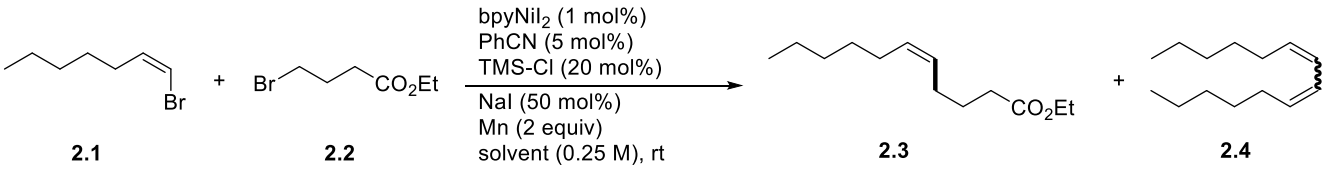
Entry	Catalyst Loading	Yield **2.3** (%)[a]	Yield **2.4** (%)
1	5 mol%	57	15
2	1 mol%	62	10
3[b]	1 mol%	71	7

[a]Uncorrected GC yields vs. dodecane as internal standard. [b]bpyNiI$_2$ used as precatalyst.

When applied, this was the case; lowering the catalyst loading from 5 mol% to 1 mol% gave an increase in yield and decrease in diene formation (Table 2.2, 2). Additionally, changing ligands to simple 2,2'-bipyridine (bpy) led to further improved yield and selectivity (Table 2.2, 3).

2.2.1.4. Solvent Screen

Table 2.3. Effect of Solvent.



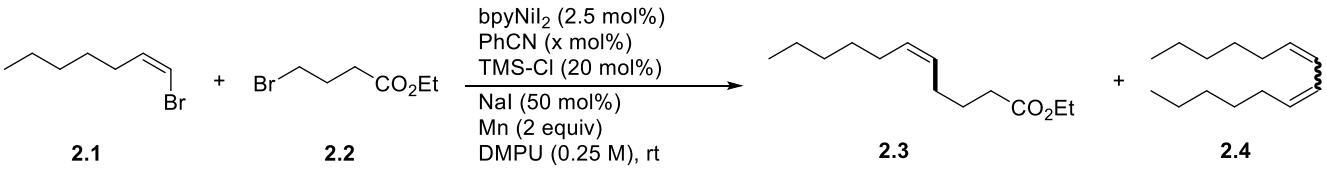
Entry	Solvent	Yield **2.3** (%)[a]	Yield **2.4** (%)
1	DMA	71	7
2	DMF	61	11
3	DMPU	88 (80)[b]	4
4[c]	NMP	28	3
5[c]	THF	3	-
6[c]	MeCN	6	1

[a]Uncorrected GC yields vs. dodecane as internal standard. 16 h. [b]Isolated yield. [c]Starting materials remain.

Reactions conducted in amide solvents were superior, as previously observed, with DMPU giving an 80% isolated yield of the desired product (Table 2.3). We observed very low conversion of starting materials in non-amide solvents.

2.2.2. Evaluation of Substrate Scope

Table 2.4. Effect of Benzonitrile.

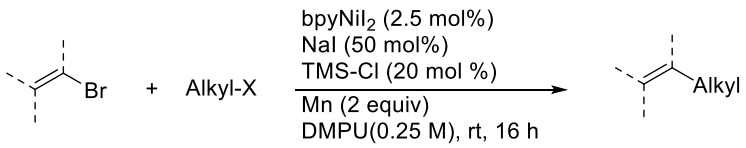


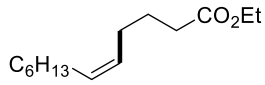
Entry	PhCN Loading	time (h)	Yield **2.3** (%)[a]	Yield **2.4** (%)
1	5 mol%	15	74	13
2	-	3	74	13

[a]Uncorrected GC yields vs. dodecane as internal standard.

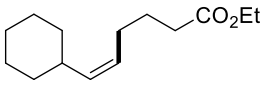
The scope of the reaction was then evaluated. We observed that reactions at 2.5 mol% catalyst consumed all starting materials in reasonable reaction times. Additionally, at this catalyst loading the beneficial effects of benzonitrile was not seen, so we omitted it from the reaction (Table 2.4). Therefore, the substrate scope was examined with these changes made.

Table 2.5. Substrate Scope.

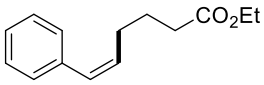




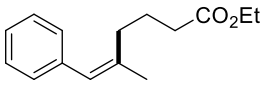
2.3, 67% (86% Z)
80% (93% Z)[a]



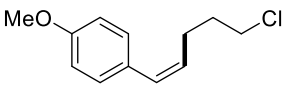
2.5, 69% (89% Z)



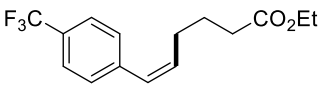
2.6, 80% (98% Z)



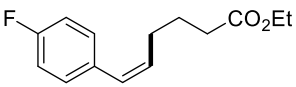
2.7, 73% (96% Z)



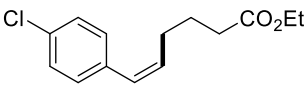
2.8, 79% (95% Z)[b]



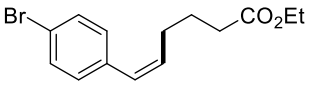
2.9, 59% (94% Z)



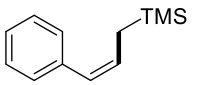
2.10, 74% (99% Z)



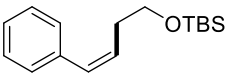
2.11, 63% (98% Z)



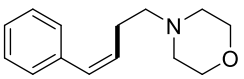
2.12, 45% (90% Z)



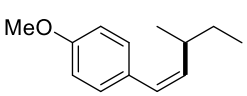
2.13, 64% (98% Z)



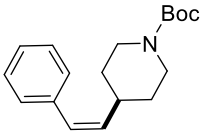
2.14, 70% (97% Z)[c]



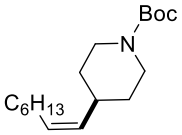
2.15, 72% (>99% Z)



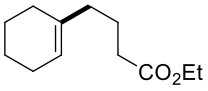
2.16, 71% (95% Z)[b,d]



2.17, 87% (>99% Z)[d]



2.18, 82% (90% Z)[d]



2.19, Vinyl-Br 70%
Vinyl-OTf 73%

Reactions were performed on 2.0 mmol scale with 1:1 ratio of starting materials. Yields are of isolated product mixtures. [a]0.5 mmol scale, 1 mol% bpyNiI$_2$, 5 mol% PhCN. [b]Starting material was 91% *(Z)*. [c]1.5 equivalents of alkyl bromide used. [d]Alkyl iodide used; NaI was omitted.

Primary and secondary alkyl substituted vinyl bromides coupled well under these conditions (Table 2.5, **2.3**, **2.5**). Styrenyl bromides with varying electronic properties, **2.6**-**2.9**, also coupled in good yield, with α-substitution being well tolerated. Various halide substitution on the aryl ring are also well tolerated (**2.10**-**2.12**), allowing for further functionalization of the products (see Chapter 3.3). In the case of vinyl bromide **2.12**, prolonged reaction times led to dimerization of the product along with other defunctionalization of the aryl C-Br bond. This observation suggests that (1) vinyl bromides are more reactive than aryl bromides,[46] and (2) aryl bromides can be functionalized under these reaction conditions. This is discussed further in section 2.2.4.

A variety of alkyl coupling partners were evaluated under these conditions. Allyl silane **2.13** was isolated in 64% yield with good stereoretention. This product can be utilized in further transformations (allylation, oxidation) or protiodesilylated to give net-methylation of the vinyl bromide. An alkyl bromide with a β-silyloxy group also coupled in 70% yield (**2.14**), which is noteworthy as these types of substrates are difficult to couple using other methods due to completing β-silyloxy elimination.[27] A tertiary amine was also well tolerated (**2.15**). When we tried to couple secondary alkyl bromides, we found that selectivity for the product and conversion of the alkyl bromide were both low. We hypothesized that this was due to the slower conversion of the alkyl bromide to the more reactive alkyl iodide, akin to what was observed in the optimization of the reaction (Table 2.1).[43] As expected, the reactivity was recovered when we started with the secondary alkyl iodide, resulting in high yields of the desired products (**2.16**-**2.18**). We found that vinyl triflates also participate in the reaction with the same selectivity of its vinyl bromide counterpart (**2.19**).

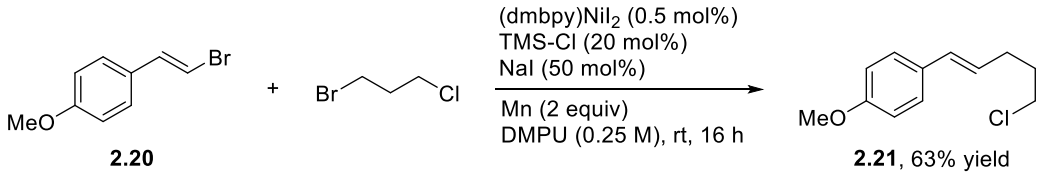
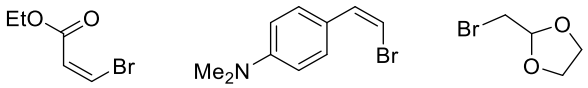


Figure 2.10. Coupling of *(E)*-vinyl halides.

When the optimized conditions were applied to the coupling of *(E)*-vinyl bromides, the yield of the product was low due to competing dimerization of the vinyl bromide. Based on the lessons learned through optimization of the reaction conditions, dimerization could be suppressed by lowering the catalyst concentration; lowering the catalyst loading to 0.5 mol% and using a different ligand provided a satisfactory yield (Figure 2.10).

2.2.3. Unsuccessful Substrates



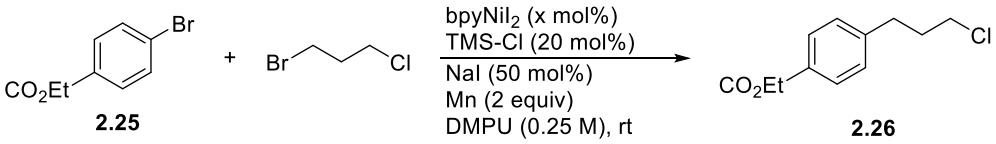
2.22 **2.23** **2.24**

Figure 2.11. Problematic Coupling Partners.

A few of the substrates examined proved problematic for the coupling reaction (Figure 2.11). The vinyl bromide based on ethyl acrylate, **2.22**, gave no observable yield. The fate of the vinyl bromide also could not be discerned; we hypothesize that under these reaction conditions polymerization of the substrate is facile. The electron-rich aryl bromide **2.23** coupled with good selectivity (assay by GC), however we observed both the cross-coupled product and the vinyl bromide were unstable, readily decomposing into unidentified byproducts. Finally, the cyclic acetal **2.24** did not react with the vinyl bromide, similar to the secondary alkyl bromides. We did not attempt in this case to couple the corresponding alkyl iodide but hypothesize that it would couple in good yield.

2.2.4. Improved Aryl/Alkyl Coupling

Table 2.6. Coupling of Aryl and Alkyl Halides.



2.25 **2.26**

Entry	bpyNiI$_2$ (mol%)	time	Yield **2.26** (%)[a]
1	1	18 h	85
2	2.5	14 h	78
3	5	3 h	78
4	10	60 min	84
5[b]	10	20 min	79

[a]Uncorrected GC yields vs. dodecane as internal standard.
[b]Reaction performed at 60 °C.

We were interested in how these new reaction conditions compared to the previous conditions reported for the coupling of aryl halides with alkyl halides. We examined the

coupling of ethyl 4-bromobenzoate **2.25** with 1-bromo-3-chloropropane under the optimized conditions and found that the product **2.26** was furnished in 85% yield (Table 2.6). As aryl bromides are less reactive than the vinyl bromides surveyed in this study, we wondered if the selectivity would be lost at higher catalyst concentrations with aryl bromides due to competing dimerization. Surprisingly, we found that this was not the case as the yield remained consistent between 1-10 mol% catalyst. Additionally, we also observed that as the catalyst concentration increased, the reaction took less time to reach completion, with reactions at 10 mol% nickel loading being complete in 60 minutes. Heating the reaction led to faster conversions with full conversion of starting materials being observed after 20 minutes, consistent with our previous observations.[39] However, at temperatures higher than these or prolonged reaction times the alkyl chloride of the product starts to react. In an effort to demonstrate the utility of this new method, the coupling of ethyl 4-bromobutyrate **2.2** and 4-chlorobromobenzene **2.27** was conducted on a 22 mmol scale using standard equipment. The reaction gave 72% isolated yield of the desired product at only 0.5 mol% catalyst loading, the lowest catalyst loading reported to date for cross-electrophile coupling (Figure 2.12).

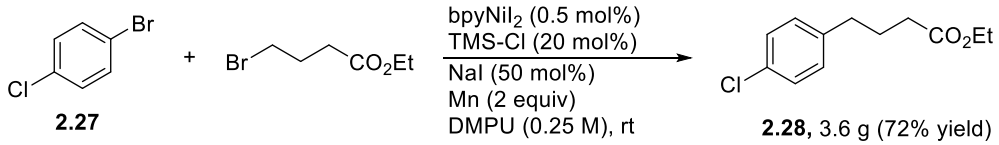


Figure 2.12. Large scale coupling of aryl and alkyl halides.

2.2.5. Studies on Product Isomerization

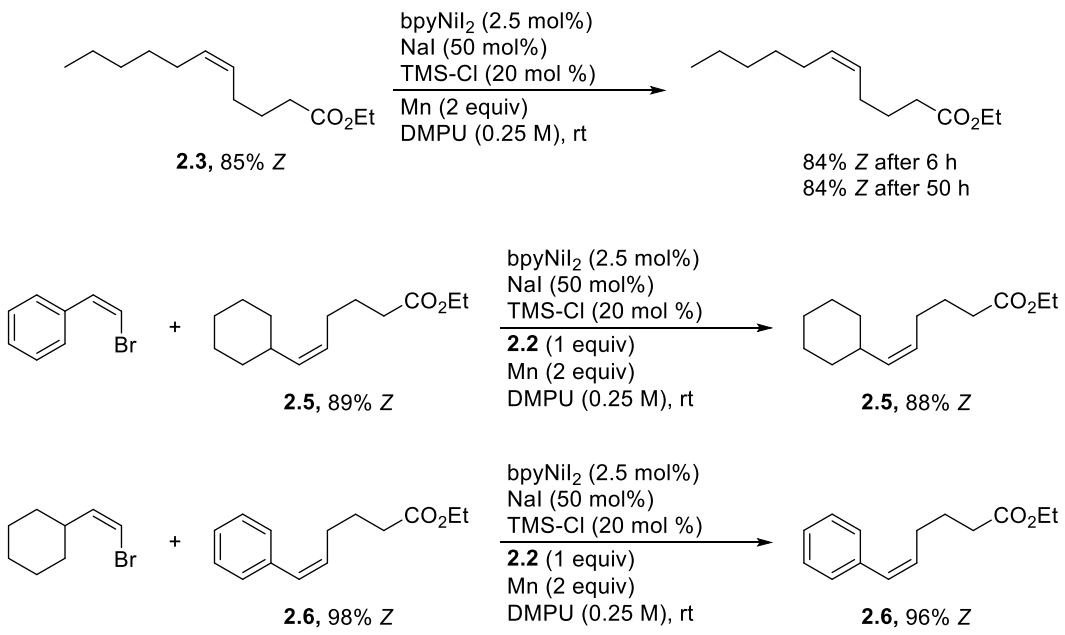


Figure 2.13. Mechanistic studies on isomerization.

For the coupling of vinyl bromides, we observed that a small amount of the *(E)*-alkene even though we started from pure *(Z)*-vinyl bromides. Isomerization of the alkene can occur either prior to, during, or after C-C bond formation. More specifically, the *(E)*-product is derived from either (1) coupling of isomerized *(E)*-vinyl bromide, (2) isomerization of a vinyl-nickel intermediate, or (3) isomerization of the *(Z)*-product to the *(E)*-product. To interrogate this further, the isolated product **2.3** was re-subjected to the reaction conditions. After 50 hours, no significant isomerization was observed. Additionally, to rule out isomerization of the product by an on-cycle nickel intermediate isolated products **2.5** and **2.6** were added in excess to active reactions with coupling partners present. In these reactions, the added alkenes did not isomerize nor did they affect the *Z/E* ratio of the products formed. With these results, we can confidently rule out isomerization of the product as the source of *(E)*-alkene. While isomerization of the *(Z)*-vinyl bromide was not observed by GC analysis, we cannot rule it out as the *(E)*-vinyl

bromide is significantly more reactive (see above) and may not accumulate. Therefore, the mechanism of isomerization remains unknown.

2.3. Conclusion

We have developed an improved method for the coupling of aryl and vinyl halides with alkyl halides. Key to the success of this method was identifying conditions that accelerated turnover of the catalyst, allowing for lower concentration of catalyst to be used. This in turn lead to significant suppression of the dimerization of unhindered vinyl bromides. We were even able to use simple 2,2'-bipyridine as a ligand, where other reports require functionalized and more expensive bipyridine ligands. The method is applicable to both *(E)*- and *(Z)*-vinyl bromides, as well as vinyl triflates, with high yields and stereoretention. When applied to the coupling of aryl bromides, these reaction conditions are comparable to previously reported methods. We have also demonstrated how high catalyst concentrations can allow for very rapid reactions and low catalyst concentrations can be utilized for gram scale synthesis. We reported the lowest catalyst loading (0.5 mol%) for cross-electrophile coupling to date. This method has already been utilized by other groups successfully in the total syntheses of two natural products, (-)-6,7-Dideoxysqualestatin H5 and (-)-Rasfonin.[47-48] It has also become the state of the art for the coupling of aryl and vinyl halides with alkyl halides, leading to a number of reports based on this method.[49-52]

2.4. Experimental

2.4.1. Materials

Anhydrous NiI_2 and sodium iodide were purchased from Strem and used as received. 2, 2'-bypridine nickel (II) iodide ($bpyNiI_2$) and 4, 4'-dimethoxy-2, 2'-bypiridine

nickel (II) iodide (dmbpyNiI_2) were prepared as described below. Trimethylsilyl chloride was purchased from Gelest and used as received. Manganese powder (-325 mesh) was purchased from Alfa Aesar and used as received.

The following substrates were synthesized according to a common literature procedure:[53] *(Z)*-1-bromooct-1-ene, *(Z)*-(2-bromovinyl)cyclohexane, *(Z)*-(2-bromovinyl)benzene, *(Z)*-1-(2-bromovinyl)-4-fluorobenzene, *(Z)*-1-(2-bromovinyl)-4-chlorobenzene, *(Z)*-1-bromo-4-(2-bromovinyl)benzene, *(Z)*-1-(2-bromovinyl)-4-methoxybenzene, *(Z)*-1-(2-bromovinyl)-4-(trifluoromethyl)benzene, *(Z)*-(2-bromoprop-1-en-1-yl)benzene.

(E)-1-(2-bromovinyl)-4-methoxybenzene was synthesized according to a known literature procedure.[54]

1-bromo-3-chloropropane and 1-bromo-4-chlorobenzene was purchased from Aldrich and used as received.

Ethyl-4-bromobutyrate, ethyl-4-bromobenzoate and 2-iodobutane were purchased from Alfa Aesar and used as received.

N-Boc-4-iodopiperidine was purchased from Combi-blocks and used as received.

(Bromomethyl)trimethylsilane was purchased from Gelest and used as received.

(2-bromoethoxy)tert-butyldimethylsilane,[55] 1-bromocyclohex-1-ene,[56] and cyclohex-1-en-1-yl trifluoromethanesulfonate[57] were prepared according to known literature procedures.

4-(2-bromoethyl)morpholine was prepared as described below.

DMPU (1,3-Dimethyltetrahydropyrimidin-2(1H)-one, absolute, over molecular sieves (H2O ≤0.03%), ≥99.0% (GC)) was purchased from Aldrich or AK Scientific and

was used as received (Aldrich) or distilled over CaH_2 (AK Scientific). All other dry solvents were prepared from ACS grade, inhibitor free solvents by passage through activated alumina and molecular sieves in a Vacuum Atmospheres solvent purification system. Water content was routinely measured using Karl-Fisher titration (Metrohm) and was less than 50 ppm in all cases.

2.4.2. General Methods

NMR Spectroscopy.

^{1}H and ^{13}C NMR spectra were acquired on 400 and 500 MHz Bruker NMR instruments. NMR chemical shifts are reported in ppm and referenced to tetramethylsilane at 0.00 ppm (^{1}H) and 0.00 ppm (^{13}C), α, α, α-trifluorotoluene at 0.00 ppm (^{19}F), or the residual solvent peaks for $CDCl_3$ at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C). Coupling constants (*J*) are reported in Hertz. For substrates that existed as rotamers at ambient temperature, the ^{1}H NMR spectrum was obtained at 55 °C.

Gas Chromatography.

Instrument. GC analyses were performed on an Agilent 7890A GC equipped with dual DB-5 columns (20 m × 180 μm × 0.18 μm), dual FID detectors, and using hydrogen as the carrier gas.

Sample preparation. A 50 μL aliquot was removed from the reaction mixture using a gas-tight syringe and quenched with 1.5 mL each of water and diethyl ether, and the resulting mixture was then passed through a 1-inch pipette column of silica. The filtrate is used for GC and GC-MS analysis.

Analysis Method. 1 μL injection of sample, injection temp of 300 °C, 100:1 split ratio, initial inlet pressure was 20.3 psi but varied as the column flow was held constant at

1.8 mL/min for the duration of the run. Initial oven temperature of 50 °C was held for 0.46 min followed by a temperature ramp up to 300 °C at 65 °C/min and finally the temperature was held at 300 °C for 0.69 min. Total run time was ~ 5 min. FID temperature was 325 °C.

GC/MS Analysis

GC/MS analyses were performed on a Shimadzu GCMS-QP2010 equipped with an RTX-XLB column (30 m × 0.25 mm × 0.28 μm) with a quadrupole mass analyzer using helium as the carrier gas. The analysis method used in all cases was 5 μL injection of sample, injection temp of 225 ºC, 25:1 split ratio, initial inlet pressure was 7.8 psi, but varied as the column flow was held constant at 1.0 mL/min for the duration of the run, the interface temperature was held at 250 ºC, and the ion source (EI+, 30 eV) was held at 250 ºC. Initial oven temperature was held at 50 ºC for 3 min with the detector off followed by a temperature ramp, with the detector on, to 280 ºC at 40 ºC/min, and finally the temperature was held at 280 ºC for 3 min. Total run time was 11.75 min.

Low Resolution Mass Spectrometry (LRMS) Analysis

LRMS analyses were performed on a Thermo LTQ Velos LC/MS equipped with an electrospray (ESI) probe operating in positive ion mode (ESI+) with an ion trap mass analyzer. Direct injection analysis was employed in all cases with a sample solution in methanol.

Chromatography

Chromatography was performed on silica gel (EMD, silica gel 60, particle size 0.040-0.063 mm) using standard flash techniques Products were visualized by one of the following methods: UV light, $KMnO_4$ stain or by GC.

Elemental Analysis.

Elemental analyses were performed by CENTC Elemental Analysis Facility at University of Rochester, funded by NSF CHE-0650456.

2.4.3. General Reaction Procedures

General procedure for Nickel-catalyzed cross-coupling reactions

Glovebox procedure: In a nitrogen-filled glovebox, to an oven-dried 1-dram vial containing a teflon-coated stir-bar was sequentially added: nickel catalyst (5.9 mg of bpyNiI_2, 0.0125 mmol), Mn^0 dust (55 mg, 1.00 mmol), sodium iodide (37 mg, 0.25 mmol), DMPU (2 mL), dodecane (if used, 10 µL as internal GC standard), organohalides (0.50 mmol each), and trimethylsilyl chloride (0.10 mmol). The reaction vials were capped with a PTFE-faced silicone septum cap, removed from the glove box, and stirred on the benchtop (1200 rpm) at room temperature.

Benchtop procedure: To a 25 mL round-bottom flask containing a teflon-coated stir-bar was sequentially added: nickel catalyst (23.4 mg of bpyNiI_2, 0.05 mmol), Mn^0 dust (220 mg, 4.00 mmol), sodium iodide (148 mg, 1.00 mmol), solid organohalides (2.00 mmol each). The reaction flask was sealed with a rubber septum and the headspace was purged with argon gas for two minutes. DMPU (8 mL), organohalides (2.00 mmol each), and trimethylsilyl chloride (51 µL, 0.40 mmol) were sequentially added via syringe, then the reaction was stirred on the benchtop (1200 rpm) at room temperature under Ar. Yields on the benchtop were comparable to those obtained with the glovebox procedure.

GC analysis

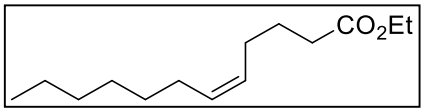
After 16-24 h reaction time, 50 µL aliquots of the reaction mixture were removed with a 250 µL gas-tight syringe and quenched with water (1.5 mL), extracted with ethyl ether (1.5 mL), and filtered through a short silica pad (1.5 cm) in a pipette packed with

glass wool. The filtrate was analyzed by gas chromatography and percent yield was calculated vs. the internal standard (dodecane).

Isolation and purification

After 16-24 h reaction time, the reaction mixture was poured into water (40 mL). This aqueous mixture was then extracted with diethyl ether (3 × 40 mL). The organic layers were combined, washed with 50 mL of brine, and dried over anhydrous $MgSO_4$. After filtration of the organic layer, volatile materials were removed on a rotary evaporator. The crude product was purified by flash chromatography on silica gel to afford the pure product.

2.4.4. Product Characterization

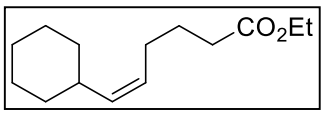


Ethyl-*(Z)*-dodec-5-enoate (2.3) General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-bromooct-1-ene (382 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 67% yield (302 mg).

^{1}**H-NMR** (400 MHz; $CDCl_3$): δ 5.45-5.39 (m, 1H), 5.39-5.32 (m, 1H), 4.17-4.13 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.09 (q, *J* = 7.2 Hz, 2H), 2.03 (q, *J* = 6.7 Hz, 2H), 1.70 (quintet, *J* = 7.4 Hz, 2H), 1.35-1.26 (m, 11H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}**C-NMR** (101 MHz, $CDCl_3$): δ 173.87, 131.27, 128.53, 60.33, 33.92, 31.91, 29.82, 29.13, 27.37, 26.69, 25.08, 22.79, 14.39, 14.23.

GC-MS m/z (% relative intensity, ion): 226.15 (2.12, M^+), 180.20 (15.98, M^+-C_2H_5O), 101.05 (23.95, M^+-C_9H_{17}), 88.05 (100.00, M^+-$C_{10}H_{19}$).



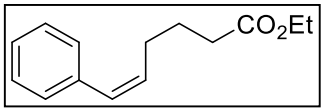
Ethyl-*(Z)*-6-cyclohexylhex-5-enoate (2.5) General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg,

2.0 mmol, 1.0 equiv) and *(Z)*-(2-bromovinyl)cyclohexane (378 mg, 2.0 mmol, 1.0 equiv) at room temperature for 15 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 69% yield (311 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.29-5.20 (m, 2H), 4.17-4.13 (m, 2H), 2.34-2.31 (m, 2H), 2.24 (dt, *J* = 7.8, 3.7 Hz, 1H), 2.10 (q, *J* = 6.9 Hz, 2H), 1.73-1.59 (m, 7H), 1.28 (t, *J* = 7.1 Hz, 5H), 1.19 (dd, *J* = 13.9, 10.8 Hz, 1H), 1.07 (qd, *J* = 12.0, 2.9 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.72, 137.13, 126.56, 60.20, 36.28, 33.75, 33.31, 26.76, 26.03, 25.95, 25.10, 14.25.

GC-MS m/z (% relative intensity, ion): 224.15 (3.29, M^+), 178.20 (20.41, M^+-C_2H_5O), 101.10 (30.22, M^+-C_9H_{15}), 88.05 (34.90, M^+-$C_{10}H_{17}$).

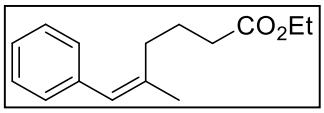


Ethyl-*(Z)*-6-phenylhex-5-enoate (2.6) General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-(2-bromovinyl)benzene (366 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 80% yield (351 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 2H), 7.26-7.23 (m, 1H), 6.48 (d, *J* = 11.7 Hz, 1H), 5.66 (dt, *J* = 11.7, 7.3 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.40 (qd, *J* = 7.4, 1.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.81 (quintet, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.50, 137.48, 131.65, 129.74, 128.71, 128.14, 126.59, 60.26, 33.84, 27.91, 25.14, 14.21.

GC-MS m/z (% relative intensity, ion): 218.15 (14.90, M^+), 173.15 (8.86, M^+-C_2H_5O), 130.15 (100.0, M^+-$C_4H_7O_2$), 117.10 (29.10, M^+-$C_5H_9O_2$).

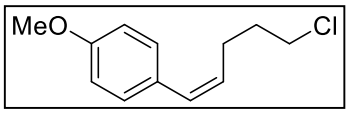


Ethyl-*(Z)*-5-methyl-6-phenylhex-5-enoate (2.7) General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-(2-bromoprop-1-en-1-yl)benzene (394 mg, 2.0 mmol, 1.0 equiv) at room temperature for 15 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 73% yield (341 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 3H), 6.32 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.26 (q, *J* = 7.8 Hz, 4H), 1.88 (s, 3H), 1.85-1.78 (m, 2H), 1.23-1.21 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.47, 138.32, 138.28, 128.56, 128.09, 126.36, 125.98, 60.25, 34.08, 31.78, 23.76, 23.31, 14.22.

GC-MS m/z (% relative intensity, ion): 232.15 (30.47, M^+), 187.15 (8.42, M^+-C_2H_5O), 129.10 (100.0, M^+-$C_5H_9O_2$).

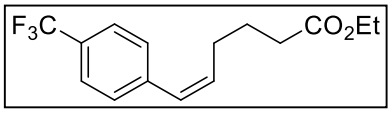


***(Z)*-1-(5-chloropent-1-en-1-yl)-4-methoxybenzene (2.8)** General benchtop procedure was followed with 1-bromo-3-chloropropane (314 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-(2-bromovinyl)-4-methoxybenzene (426 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 79% yield (333 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 11.5 Hz, 1H), 5.55 (dt, *J* = 11.6, 7.2 Hz, 1H), 3.84 (s, 3H), 3.58 (t, *J* = 6.7 Hz, 2H), 2.53-2.48 (m, 2H), 1.99-1.92 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.32, 129.96, 129.89, 129.53, 129.13, 113.61, 55.24, 44.54, 32.84, 25.94.

GC-MS m/z (% relative intensity, ion): 210.10 (33.61, M^+), 147.10 (100.00, M^+-C_2H_4Cl).



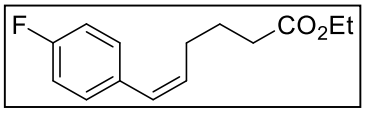
Ethyl-*(Z)*-6-(4-(trifluoromethyl)phenyl)hex-5-enoate (2.9) General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-(2-bromovinyl)-4-(trifluoromethyl)benzene (502 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 59% yield (339 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.47 (d, *J* = 11.6 Hz, 1H), 5.75 (dt, *J* = 11.7, 7.3 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.36-2.30 (m, 4H), 1.79 (quintet, *J* = 7.4 Hz, 2H), 1.23 (dt, *J* = 13.6, 6.7 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.70, 141.41, 134.19, 129.29, 128.97 (q, *J* = 32.1 Hz), 128.95, 124.62 (q, J = 270.4 Hz), 125.47 (q, J = 3.8 Hz), 60.69, 34.07, 28.26, 25.31, 14.56.

^{19}F-NMR (376 MHz, $CDCl_3$): δ 0.37.

GC-MS m/z (% relative intensity, ion): 286.15 (13.17, M^+), 241.05 (13.68, M^+-C_2H_5O), 185.05 (8.84, M^+-$C_5H_9O_2$).



Ethyl-*(Z)*-6-(4-flurophenyl)hex-5-enoate (2.10) General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-(2-bromovinyl)-4-fluorobenzene (402 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 74% yield (347 mg).

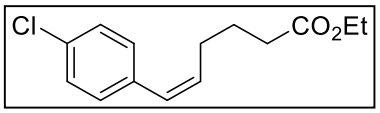
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.21 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.03-6.99 (m, 2H), 6.40 (d,

J = 11.6 Hz, 1H), 5.61 (dt, *J* = 11.6, 7.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.36-2.30 (m, 4H), 1.78 (quintet, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C-NMR (101 MHz; $CDCl_3$): δ 173.1, 161.2 (d, *J* = 246.7 Hz), 133.1, 129.9 (d, J = 8.1 Hz), 128.3, 14.7 (d, J = 21.4 Hz), 59.9, 33.4, 27.4, 24.7, 13.9

^{19}F-NMR (376 MHz, $CDCl_3$): δ -52.89.

GC-MS m/z (% relative intensity, ion): 236.10 (14.67, M^+), 191.10 (9.57, M^+-C_2H_5O), 148.15 (100.0, M^+-$C_4H_7O_2$), 135.10 (33.01, M^+-$C_5H_9O_2$).



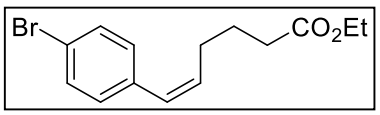
Ethyl-*(Z)*-6-(4-chlorophenyl)hex-5-enoate (2.11)

General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-(2-bromovinyl)-4-chlorobenzene (435 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 63% yield (317 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.39 (d, *J* = 11.6 Hz, 1H), 5.65 (dt, *J* = 11.6, 7.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.35-2.30 (m, 4H), 1.78 (quintet, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.40, 135.87, 132.35, 132.32, 129.99, 128.59, 128.30, 60.30, 33.74, 27.84, 25.00, 14.21.

GC-MS m/z (% relative intensity, ion): 252.10 (14.17, M^+), 207.05 (7.55, M^+-C_2H_5O), 151.05 (10.56, M^+-$C_5H_9O_2$).



Ethyl-*(Z)*-6-(4-bromophenyl)hex-5-enoate (2.12)

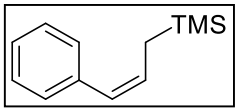
General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-bromo-4-(2-bromovinyl)benzene

(523 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 45% yield (270 mg).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.37 (d, *J* = 11.6 Hz, 1H), 5.66 (dt, *J* = 11.6, 7.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 4H), 1.77 (quintet, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, CDCl3): δ 173.76, 136.71, 132.85, 131.64, 130.72, 129.01, 120.85, 60.70, 34.12, 28.24, 25.37, 14.61.

GC-MS m/z (% relative intensity, ion): 298.05 (8.59, M^++2), 296.05 (8.47, M^+), 251.00 (4.00, M^+-C_2H_5O), 208.00 (28.97, M^+-$C_4H_7O_2$).

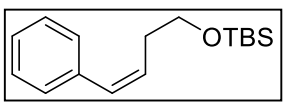


Ethyl-*(Z)*-6-phenylhex-5-enoate (2.13) General benchtop procedure was followed with (bromomethyl)trimethylsilane (334 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-(2-bromovinyl)benzene (366 mg, 2.0 mmol, 1.0 equiv) at room temperature for 15 hours. The product was isolated by flash column chromatography (hexanes) as colorless oil in 64% yield (279 mg)

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.33-7.28 (m, 4H), 7.20-7.17 (m, 1H), 6.33 (d, *J* = 11.7 Hz, 1H), 5.72 (dt, *J* = 11.6, 9.1 Hz, 1H), 1.84 (dd, *J* = 9.1, 1.4 Hz, 2H), 0.04 (d, *J* = 0.6 Hz, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 138.37, 129.18, 128.72, 128.23, 126.92, 126.15, 19.77, -1.45.

GC-MS m/z (% relative intensity, ion): 190.10 (25.83, M^+), 73.05 (100.00, M^+-C_9H_9).



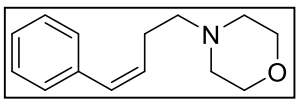
Ethyl-*(Z)*-6-phenylhex-5-enoate (2.14) General benchtop procedure was followed with (2-bromoethoxy)*tert*-butyldimethylsilane (718 mg, 3.0 mmol, 1.5 equiv) and *(Z)*-(2-bromovinyl)benzene (366

mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (hexanes) as colorless oil in 70% yield (365 mg)

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.37-7.32 (m, 4H), 7.27-7.23 (m, 1H), 6.53 (d, J = 11.7 Hz, 1H), 5.73 (dt, J = 11.7, 7.3 Hz, 1H), 3.74 (t, J = 6.7 Hz, 2H), 2.58 (qd, J = 7.0, 1.7 Hz, 2H), 0.92 (s, 9H), 0.08 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 137.93, 130.79, 129.40, 129.12, 128.50, 126.97, 63.28, 32.62, 26.35, 18.77, -4.88.

LRMS (ESI+) *m/z*: 263.3 [$M+H^+$], 285.3 [$M+Na^+$].

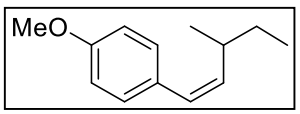


***(Z)*-4-(4-phenylbut-3-en-1-yl)morpholine (2.15)** General benchtop procedure was followed with 4-(2-bromoethyl)morpholine (388 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-(2-bromovinyl)benzene (366 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl acetate/hexane) as a pale yellow oil in 72% yield (311 mg)

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.48 (d, *J* = 11.6 Hz, 1H), 5.67 (dt, *J* = 11.7, 6.8 Hz, 1H), 3.70 (t, *J* = 4.7 Hz, 4H), 2.55-2.43 (m, 8H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 137.83, 130.39, 130.33, 129.04, 128.57, 127.04, 67.35, 59.17, 54.03, 26.36.

LRMS (ESI+) *m/z*: 218.7 [$M+H^+$], 240.3 [$M+Na^+$].



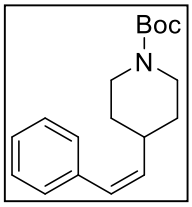
***(Z)*-1-methoxy-4-(3-methylpent-1-en-1-yl)benzene (2.16)** General benchtop procedure was followed with 2-iodobutane (368 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-(2-bromovinyl)-4-methoxybenzene (426 mg, 2.0

mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 70% yield (267 mg)

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.31 (d, *J* = 11.7 Hz, 1H), 5.34 (t, *J* = 11.0 Hz, 1H), 3.80 (s, 3H), 2.69-2.61 (m, 1H), 1.39-1.31 (m, 2H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 158.49, 138.44, 131.03, 130.17, 127.32, 113.94, 55.63, 34.14, 30.80, 21.07, 12.21.

GC-MS m/z (% relative intensity, ion): 190.15 (32.87, M^+), 175.10 (10.71, M^+-CH_3), 161.15 (100.0, M^+-C_2H_5).



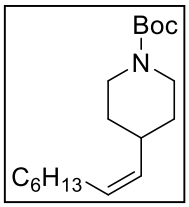
Tert-butyl *(Z)*-4-styrylpiperidine-1-carboxylate (2.17) General benchtop procedure was followed with N-Boc-4-iodopiperidine (622 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-(2-bromovinyl)benzene (366 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl acetate/hexane) as a white crystalline solid in 87% yield (500 mg).

mp 63-66 °C

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.34 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 3H), 6.40 (d, *J* = 11.6 Hz, 1H), 5.46 (dd, *J* = 11.5, 10.1 Hz, 1H), 4.09-4.07 (m, 2H), 2.76-2.70 (m, 2H), 1.67 (dd, *J* = 12.1, 0.7 Hz, 2H), 1.46 (s, 9H), 1.38-1.34 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.24, 137.91, 136.99, 128.89, 128.73, 128.70, 127.13, 79.73, 43.78, 35.48, 32.48, 28.87.

LRMS (ESI+) *m/z*: 310.3 [M+Na^+].

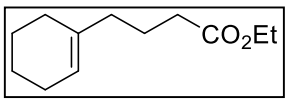


Tert-butyl *(Z)*-4-(oct-1-en-1-yl)piperidine-1-carboxylate (2.18) General benchtop procedure was followed with N-Boc-4-iodopiperidine (622 mg, 2.0 mmol, 1.0 equiv) and *(Z)*-1-bromooct-1-ene (382 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (5% ethyl acetate/hexane) as colorless oil in 82% yield (483 mg)

^{1}H-NMR (500 MHz; $CDCl_3$, 55 °C): δ 5.35-5.30 (m, 1H), 5.17 (t, *J* = 9.7 Hz, 1H), 4.03 (d, *J* = 12.8 Hz, 2H), 2.77 (t, *J* = 12.6 Hz, 2H), 2.41-2.39 (m, 1H), 2.04 (t, *J* = 6.3 Hz, 2H), 1.55 (d, *J* = 12.4 Hz, 2H), 1.45 (s, 9H), 1.29 (s, 9H), 0.89 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 155.26, 134.09, 129.92, 79.62, 44.01, 34.84, 32.54, 32.14, 30.21, 29.34, 28.86, 27.88, 23.02, 14.48.

LRMS (ESI+) *m/z*: 318.5 [$M+Na^+$].



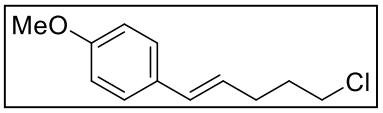
Ethyl 4-(cyclohex-1-en-1-yl)butanoate (2.19) General benchtop procedure was followed with ethyl-4-bromobutyrate (390 mg, 2.0 mmol, 1.0 equiv) and either 1-bromocyclohex-1-ene (322 mg, 2.0 mmol, 1.0 equiv) or cyclohex-1-en-1-yl trifluoromethanesulfonate (460 mg, 2.0 mmol, 1.0 equiv) at room temperature for 16 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 70% yield (275 mg) for X=Br and 73% yield (285 mg) for X=OTf.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.42 (d, *J* = 0.8 Hz, 1H), 4.14 (tt, *J* = 7.1, 3.6 Hz, 2H), 2.28 (td, *J* = 7.5, 4.0 Hz, 2H), 1.99 (d, *J* = 3.6 Hz, 4H), 1.92 (s, 2H), 1.76-1.73 (m, 2H), 1.63 (d, *J* = 3.5 Hz, 2H), 1.57-1.55 (m, 2H), 1.27 (td, *J* = 7.2, 4.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 174.22, 137.08, 122.11, 60.55, 37.74, 34.23, 28.46, 25.61,

23.35, 23.28, 22.90, 14.66.

GC-MS m/z (% relative intensity, ion): 196.15 (13.66, M^+), 108.10 (100.00, M^+-$C_4H_7O_2$), 95.10 (14.16, M^+-$C_5H_9O_2$).

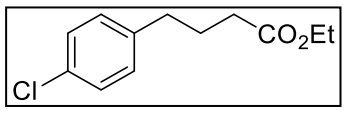


***(E)*-1-(5-chloropent-1-en-1-yl)-4-methoxybenzene (2.21)** General benchtop procedure was followed with 1-bromo-3-chloropropane (314 mg, 2.0 mmol, 1.0 equiv) and *(E)*-1-(2-bromovinyl)-4-methoxybenzene (426 mg, 2.0 mmol, 1.0 equiv) at room temperature for 24 hours. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 63% yield (265 mg).

^{1}**H-NMR** (400 MHz; $CDCl_3$): δ 7.27 (t, *J* = 6.1 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.38 (d, *J* = 15.8 Hz, 1H), 6.02 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.80 (s, 3H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.35 (q, *J* = 7.1 Hz, 2H), 1.93 (quintet, *J* = 6.9 Hz, 2H).

^{13}**C-NMR** (101 MHz, $CDCl_3$): δ 159.24, 130.95, 130.66, 127.48, 126.84, 114.34, 55.68, 44.79, 32.63, 30.42.

GC-MS m/z (% relative intensity, ion): 210.10 (32.31, M^+), 147.10 (100.00, M^+-C_2H_4Cl).



Ethyl 4-(4-chlorophenyl)butanoate (2.28) To a 250 mL round-bottom flask containing a teflon-coated stir-bar was sequentially added: nickel catalyst (51 mg of bpyNiI_2, 0.11 mmol), Mn^0 dust (2.42 g, 44 mmol), sodium iodide (813 mg, 5.5 mmol), 1-bromo-4-chlorobenzene (4.21 g, 22 mmol). The reaction flask was sealed with a rubber septum and purged with argon gas for two minutes. DMPU (90 mL), ethyl 4-bromobutyrate (4.29 g, 22 mmol), and trimethylsilyl chloride (560 µL, 4.4 mmol) were sequentially added via syringe, then the reaction was stirred on the benchtop (1200 rpm) at 40 °C under Ar for 21 hours. The reaction mixture

was poured into water (80 mL), and this aqueous mixture was then extracted with diethyl ether (3 × 100 mL). The organic layers were combined, washed with 100 mL of brine, and dried over anhydrous $MgSO_4$. After filtration of the organic layer, volatile materials were removed on a rotary evaporator. The product was isolated by flash column chromatography (10% ethyl ether/hexane) as colorless oil in 72% yield (3.6 g). The purified product contained a small amount (<5%) of diethyl suberate derived from dimerization of the alkyl bromide.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.93 (quintet, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.70, 140.25, 132.10, 130.21, 128.86, 60.72, 34.84, 33.90, 26.81, 14.64.

GC-MS m/z (% relative intensity, ion): 226.00 (23.46, M^+), 181.00 (39.25, M^+-C_2H_5O), 125.00 (71.87, M^+-$C_5H_9O_2$).

2.4.5. NMR Spectra

Copies of the spectral data have been published[58] and can be found at **https://doi.org/10.1002/chem.201601320**.

2.5. References

1. Huang, C. Y.; Doyle, A. G., Electron-deficient olefin ligands enable generation of quaternary carbons by Ni-catalyzed cross-coupling. *J. Am. Chem. Soc.* **2015,** *137* (17), 5638-41.
2. Siau, W.-Y.; Zhang, Y.; Zhao, Y., Stereoselective Synthesis of *Z*-Alkenes. In *Stereoselective Alkene Synthesis*, Wang, J., Ed. Springer Berlin Heidelberg: 2012; Vol. 327, pp 33-58.
3. Wittig, G.; Schöllkopf, U., Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien (I. Mitteil. *Chem. Ber.* **1954,** *87* (9), 1318-1330.
4. Edmonds, M.; Abell, A., The Wittig Reaction. In *Modern Carbonyl Olefination*, Wiley-VCH Verlag GmbH & Co. KGaA: 2004; pp 1-17.

5. Batesky, D. C.; Goldfogel, M. J.; Weix, D. J., Removal of Triphenylphosphine Oxide by Precipitation with Zinc Chloride in Polar Solvents. *J. Org. Chem.* **2017,** *82* (19), 9931-9936.
6. Still, W. C.; Gennari, C., Direct synthesis of *Z*-unsaturated esters. A useful modification of the horner-emmons olefination. *Tetrahedron Lett.* **1983,** *24* (41), 4405-4408.
7. Dong, D.-J.; Li, H.-H.; Tian, S.-K., A Highly Tunable Stereoselective Olefination of Semistabilized Triphenylphosphonium Ylides with N-Sulfonyl Imines. *J. Am. Chem. Soc.* **2010,** *132* (14), 5018-5020.
8. Fang, F.; Li, Y.; Tian, S.-K., Stereoselective Olefination of N-Sulfonyl Imines with Stabilized Phosphonium Ylides for the Synthesis of Electron-Deficient Alkenes. *Eur. J. Org. Chem.* **2011,** *2011* (6), 1084-1091.
9. Horner, L.; Hoffmann, H.; Wippel, H. G., Phosphororganische Verbindungen, XII. Phosphinoxyde als Olefinierungsreagenzien. *Chem. Ber.* **1958,** *91* (1), 61-63.
10. Wadsworth, W. S.; Emmons, W. D., The Utility of Phosphonate Carbanions in Olefin Synthesis. *J. Am. Chem. Soc.* **1961,** *83* (7), 1733-1738.
11. Ando, K., Highly Selective Synthesis of *Z*-Unsaturated Esters by Using New Horner−Emmons Reagents, Ethyl (Diarylphosphono)acetates. *J. Org. Chem.* **1997,** *62* (7), 1934-1939.
12. Ando, K., *Z*-Selective Horner−Wadsworth−Emmons Reaction of α-Substituted Ethyl (Diarylphosphono)acetates with Aldehydes1. *J. Org. Chem.* **1998,** *63* (23), 8411-8416.
13. Chinchilla, R.; Nájera, C., Chemicals from Alkynes with Palladium Catalysts. *Chem. Rev.* **2014,** *114* (3), 1783-1826.
14. Oger, C.; Balas, L.; Durand, T.; Galano, J.-M., Are Alkyne Reductions Chemo-, Regio-, and Stereoselective Enough To Provide Pure *(Z)*-Olefins in Polyfunctionalized Bioactive Molecules? *Chem. Rev.* **2013,** *113* (3), 1313-1350.
15. Lindlar, H., Ein neuer Katalysator für selektive Hydrierungen. *Helv. Chim. Acta* **1952,** *35* (2), 446-450.
16. Lu, Y.; Feng, X.; Takale, B. S.; Yamamoto, Y.; Zhang, W.; Bao, M., Highly Selective Semihydrogenation of Alkynes to Alkenes by Using an Unsupported Nanoporous Palladium Catalyst: No Leaching of Palladium into the Reaction Mixture. *ACS Catal.* **2017,** *7* (12), 8296-8303.
17. Hancker, S.; Neumann, H.; Beller, M., Development of a Palladium-Catalyzed Process for the Synthesis of *Z*-Alkenes by Sequential Sonogashira–Hydrogenation Reaction. *Eur. J. Org. Chem.* **2018,** *2018* (38), 5253-5259.
18. Slack, E. D.; Gabriel, C. M.; Lipshutz, B. H., A Palladium Nanoparticle–Nanomicelle Combination for the Stereoselective Semihydrogenation of Alkynes in Water at Room Temperature. *Angew. Chem. Int. Ed.* **2014,** *53* (51), 14051-14054.
19. Drost, R. M.; Bouwens, T.; van Leest, N. P.; de Bruin, B.; Elsevier, C. J., Convenient Transfer Semihydrogenation Methodology for Alkynes Using a PdII-NHC Precatalyst. *ACS Catal.* **2014,** *4* (5), 1349-1357.
20. Liu, Y.; Hu, L.; Chen, H.; Du, H., An Alkene-Promoted Borane-Catalyzed Highly Stereoselective Hydrogenation of Alkynes to Give *Z*- and E-Alkenes. *Chem. Eur. J.* **2015,** *21* (8), 3495-3501.

21. Kominami, H.; Higa, M.; Nojima, T.; Ito, T.; Nakanishi, K.; Hashimoto, K.; Imamura, K., Copper-Modified Titanium Dioxide: A Simple Photocatalyst for the Chemoselective and Diastereoselective Hydrogenation of Alkynes to Alkenes under Additive-Free Conditions. *ChemCatChem* **2016,** *8* (12), 2019-2022.
22. Rodríguez, A. R.; Spur, B. W., First total synthesis of 7(S),17(S)-Resolvin D5, a potent anti-inflammatory docosanoid. *Tetrahedron Lett.* **2005,** *46* (21), 3623-3627.
23. Hoveyda, A. H., Evolution of Catalytic Stereoselective Olefin Metathesis: From Ancillary Transformation to Purveyor of Stereochemical Identity. *J. Org. Chem.* **2014,** *79* (11), 4763-4792.
24. Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H., High-value alcohols and higher-oxidation-state compounds by catalytic *Z*-selective cross-metathesis. *Nature* **2015,** *517* (7533), 181-186.
25. Speed, A. W. H.; Mann, T. J.; O'Brien, R. V.; Schrock, R. R.; Hoveyda, A. H., Catalytic *Z*-Selective Cross-Metathesis in Complex Molecule Synthesis: A Convergent Stereoselective Route to Disorazole C1. *J. Am. Chem. Soc.* **2014,** *136* (46), 16136-16139.
26. Yu, M.; Schrock, R. R.; Hoveyda, A. H., Catalyst-Controlled Stereoselective Olefin Metathesis as a Principal Strategy in Multistep Synthesis Design: A Concise Route to (+)-Neopeltolide. *Angew. Chem. Int. Ed.* **2015,** *54* (1), 215-220.
27. Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H., The Growing Impact of Catalysis in the Pharmaceutical Industry. *Adv. Synth. Catal.* **2011,** *353* (11-12), 1825-1864.
28. Jana, R.; Pathak, T. P.; Sigman, M. S., Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011,** *111* (3), 1417-1492.
29. Crabtree, R. H., Oxidative Addition and Reductive Elimination. In *The Organometallic Chemistry of the Transition Metals*, John Wiley & Sons, Inc.: 2005; pp 159-182.
30. Lu, G.-p.; Voigtritter, K. R.; Cai, C.; Lipshutz, B. H., Ligand effects on the stereochemistry of Stille couplings, as manifested in reactions of *Z*-alkenyl halides. *Chem. Commun.* **2012,** *48* (69), 8661-8663.
31. Krasovskiy, A.; Lipshutz, B. H., Highly Selective Reactions of Unbiased Alkenyl Halides and Alkylzinc Halides: Negishi-Plus Couplings. *Org. Lett.* **2011,** *13* (15), 3822-3825.
32. Krasovskiy, A. L.; Haley, S.; Voigtritter, K.; Lipshutz, B. H., Stereoretentive Pd-catalyzed Kumada-Corriu couplings of alkenyl halides at room temperature. *Org. Lett.* **2014,** *16* (16), 4066-4069.
33. Lu, G.-P.; Voigtritter, K. R.; Cai, C.; Lipshutz, B. H., Ligand Effects on the Stereochemical Outcome of Suzuki–Miyaura Couplings. *J. Org. Chem.* **2012,** *77* (8), 3700-3703.
34. Krasovskiy, A.; Lipshutz, B. H., Ligand Effects on Negishi Couplings of Alkenyl Halides. *Org. Lett.* **2011,** *13* (15), 3818-3821.
35. Everson, D. A.; Jones, B. A.; Weix, D. J., Replacing conventional carbon nucleophiles with electrophiles: nickel-catalyzed reductive alkylation of aryl bromides and chlorides. *J. Am. Chem. Soc.* **2012,** *134* (14), 6146-6159.

36. Cheung, C. W.; Zhurkin, F. E.; Hu, X., *Z*-Selective Olefin Synthesis via Iron-Catalyzed Reductive Coupling of Alkyl Halides with Terminal Arylalkynes. *J. Am. Chem. Soc.* **2015,** *137* (15), 4932-4935.
37. Cherney, A. H.; Reisman, S. E., Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles. *J. Am. Chem. Soc.* **2014,** *136* (41), 14365-14368.
38. Everson, D. A.; Shrestha, R.; Weix, D. J., Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010,** *132* (3), 920-921.
39. Biswas, S.; Weix, D. J., Mechanism and selectivity in nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides. *J. Am. Chem. Soc.* **2013,** *135* (43), 16192-16197.
40. Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F., Fundamental Studies and Development of Nickel-Catalyzed Trifluoromethylthiolation of Aryl Chlorides: Active Catalytic Species and Key Roles of Ligand and Traceless MeCN Additive Revealed. *J. Am. Chem. Soc.* **2015,** *137* (12), 4164-4172.
41. Ge, S.; Green, R. A.; Hartwig, J. F., Controlling First-Row Catalysts: Amination of Aryl and Heteroaryl Chlorides and Bromides with Primary Aliphatic Amines Catalyzed by a BINAP-Ligated Single-Component Ni(0) Complex. *J. Am. Chem. Soc.* **2014,** *136* (4), 1617-1627.
42. Klein, A.; Kaiser, A.; Wielandt, W.; Belaj, F.; Wendel, E.; Bertagnolli, H.; Záliš, S., Halide Ligands—More Than Just σ-Donors? A Structural and Spectroscopic Study of Homologous Organonickel Complexes. *Inorg. Chem.* **2008,** *47* (23), 11324-11333.
43. Finkelstein, H., Darstellung organischer Jodide aus den entsprechenden Bromiden und Chloriden. *Ber. Dtsch. Chem. Ges.* **1910,** *43* (2), 1528-1532.
44. Yamamoto, T.; Wakabayashi, S.; Osakada, K., Mechanism of C-C coupling reactions of aromatic halides, promoted by Ni(COD)2 in the presence of 2,2′-bipyridine and PPh3, to give biaryls. *J. Organomet. Chem.* **1992,** *428* (1–2), 223-237.
45. Osakada, K.; Yamamoto, T., Transmetallation of alkynyl and aryl complexes of Group 10 transition metals. *Coord. Chem. Rev.* **2000,** *198* (1), 379-399.
46. Jutand, A.; Négri, S., Rate and Mechanism of the Oxidative Addition of Vinyl Triflates and Halides to Palladium(0) Complexes in DMF. *Organometallics* **2003,** *22* (21), 4229-4237.
47. Fegheh-Hassanpour, Y.; Arif, T.; Sintim, H. O.; Al Mamari, H. H.; Hodgson, D. M., Synthesis of (−)-6,7-Dideoxysqualestatin H5 by Carbonyl Ylide Cycloaddition–Rearrangement and Cross-electrophile Coupling. *Org. Lett.* **2017,** *19* (13), 3540-3543.
48. Boeckman, R. K.; Niziol, J. M.; Biegasiewicz, K. F., Scalable Synthesis of (−)-Rasfonin Enabled by a Convergent Enantioselective α-Hydroxymethylation Strategy. *Org. Lett.* **2018,** *20* (16), 5062-5065.
49. Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J., New ligands for nickel catalysis from diverse pharmaceutical heterocycle libraries. *Nat. Chem.* **2016,** *8* (12), 1126-1130.
50. Hansen, E. C.; Li, C.; Yang, S.; Pedro, D.; Weix, D. J., Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling. *J. Org. Chem.* **2017,** *82* (14), 7085-7092.

51. Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E., Nickel-Catalyzed Asymmetric Reductive Cross-Coupling To Access 1,1-Diarylalkanes. *J. Am. Chem. Soc.* **2017,** *139* (16), 5684-5687.
52. Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E., Nickel-Catalyzed Enantioselective Cross-Coupling of N-Hydroxyphthalimide Esters with Vinyl Bromides. *Org. Lett.* **2017,** *19* (8), 2150-2153.
53. Mao, J.; Bao, W., Palladium(0)-Catalyzed Methylenecyclopropanation of Norbornenes with Vinyl Bromides. *Org. Lett.* **2014,** *16* (10), 2646-2649.
54. Das, J. P.; Roy, S., Catalytic Hunsdiecker Reaction of α,β-Unsaturated Carboxylic Acids: How Efficient Is the Catalyst? *J. Org. Chem.* **2002,** *67* (22), 7861-7864.
55. Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L., Palladium-Catalyzed Intramolecular C−O Bond Formation. *J. Am. Chem. Soc.* **2001,** *123* (49), 12202-12206.
56. *Z*han, F.; Liang, G., Formation of Enehydrazine Intermediates through Coupling of Phenylhydrazines with Vinyl Halides: Entry into the Fischer Indole Synthesis. *Angew. Chem. Int. Ed.* **2013,** *52* (4), 1266-1269.
57. Martínez, A. G.; Herrera, A.; Martínez, R.; Teso, E.; García, A.; Osío, J.; Pargada, L.; Unanue, R.; Subramanian, L. R.; Hanack, M., A new and convenient synthesis of alkyl and aryl pyrimidines. *J. Heterocycl. Chem.* **1988,** *25* (4), 1237-1241.
58. Johnson, K. A.; Biswas, S.; Weix, D. J., Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides. *Chem. Eur. J.* **2016,** *22* (22), 7399-7402.

Chapter 3: Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Chlorides with Secondary Unactivated Alkyl Chlorides

3.1. Introduction

3.1.1. Coupling of Aryl Chlorides with Secondary Alkyl Organometallic Reagents

Due to the significant emphasis placed on palladium-catalyzed cross-coupling, palladium catalysis dominates secondary C(sp^3)-C(sp^2) bond formation reactions with aryl chlorides. Additionally, most of these examples utilize organoboron reagents as the organometallic coupling partner.

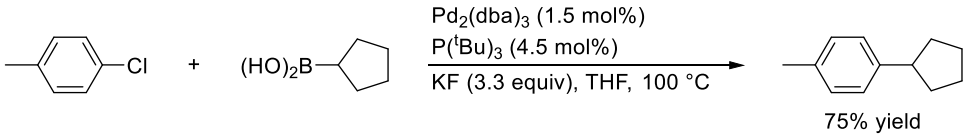


Figure 3.1. Early example of coupling secondary boronic acids.

Fu and coworkers reported the coupling of 4-chlorotoluene with cyclopentyl boronic acid in 75% isolated yield (Figure 3.1).[1] While this was the first example of coupling an aryl chloride with a secondary organometallic reagent, they did not follow up on this result. Santelli et al. later reported the coupling of cyclopropylboronic acid with aryl bromides and chlorides using a tetraphosphine ligand in combination with a palladium (II) precatalyst.[2] Molander and coworkers have reported several methods for the coupling of aryl and heteroaryl chlorides with potassium trifluoroborate salts (Figure 3.2, A).[3-7] After the report by Fu, they reported the coupling of both cyclopentyl and isopropyl trifluoroborates with a variety of aryl and heteroaryl chlorides.[3] In the same year, they reported the extension of this chemistry to cyclobutyl and cyclopropyl trifluoroborates.[4] Around this time, Burke and coworkers reported the coupling of the equally stable cyclopropyl *N*-methyliminodiacetic acid (MIDA) boronate ester with aryl chlorides

(Figure 3.2, B). These boronate esters work similarly to the trifluoroborate salts in that they allow for the controlled release of the boronic acid into the reaction.[8] Molander and Biscoe have also reported several stereospecific cross-couplings of enantioenriched potassium trifluoroborate salts.[5-7, 9] More recently, Biscoe, in collaboration with Sigman, reported the enantiodivergent coupling of these salts with aryl chlorides (Figure 3.2, C). They were able to control stereoretention vs. stereoinversion through statistical analysis and parameterization of ligands examined for the transformation.[10]

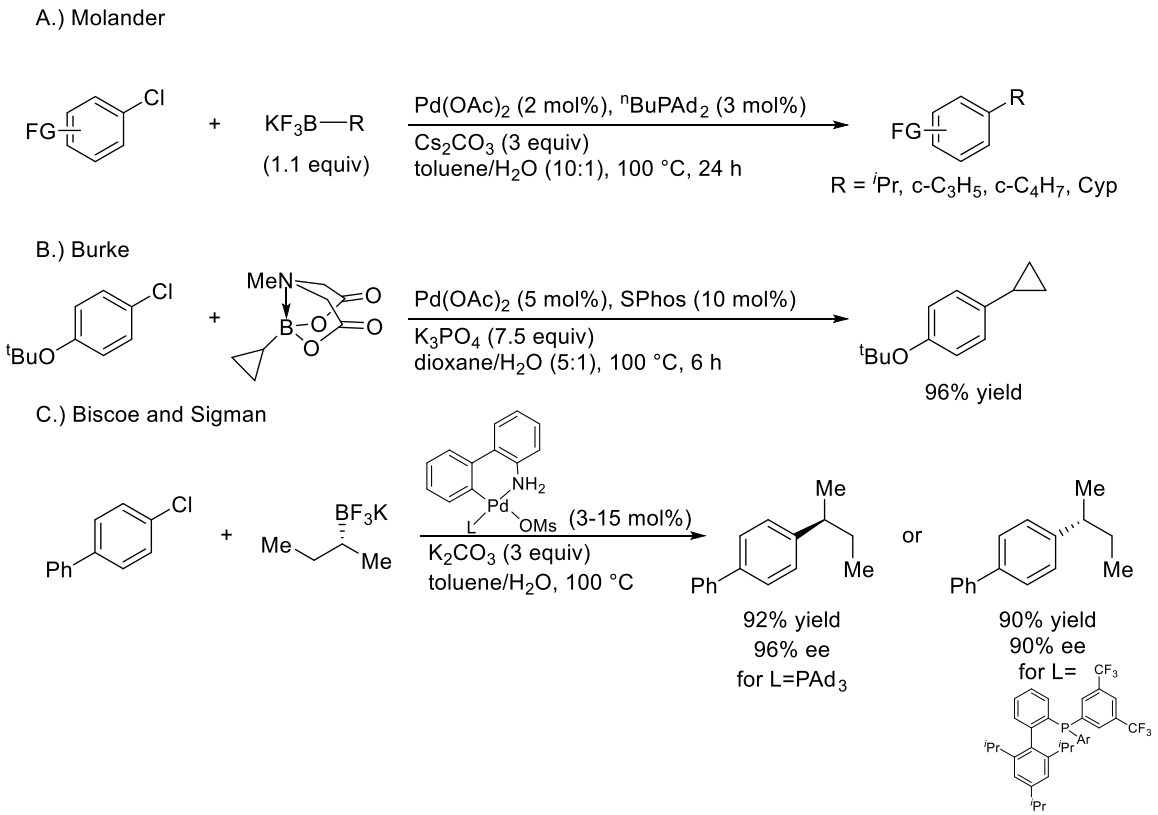


Figure 3.2. Palladium-catalyzed coupling of secondary alkyl organoboron derivatives.

3.1.2. Coupling of Secondary Alkyl Chlorides with Aryl Organometallic Reagents

Nakamura and coworkers have reported the coupling of both aryl Grignard reagents and the coupling of arylzinc reagents with primary and secondary alkyl halides catalyzed by $FeCl_3$.[11-12] While these methods boast high yields, there are only a few examples of

secondary alkyl chlorides presented, most of which are unfunctionalized hydrocarbons. Later, they were able to expand upon the scope of alkyl chlorides by utilizing an NHC ligand in place of the often used TMEDA (Figure 3.3, A).[13] While this report focused solely on the coupling of alkyl chlorides, again the alkyl scope lacked functionality. Shen and coworkers reported in 2016 the intra- and intermolecular coupling of aryl bromides and unactivated alkyl chlorides catalyzed by $Fe(PPh_3)_2Cl_3$.[14] The use of magnesium turnings forms the Grignard reagent in-situ, allowing for a broader aryl scope. However, due to the reactivity of the Grignard reagent, the transformation suffers the same limitations in the alkyl scope that were previously mentioned. More recently, Nakamura and coworkers have disclosed the synthesis of aryl *C*-glycosides via the iron-catalyzed cross-coupling of chlorosugars (Figure 3.3, B).[15] While the C-Cl bond is in an activated position on the ring, this is a marked improvement in terms of the reaction scope. They are able to arylate these carbohydrate rings with high α/β selectivities employing aryl zinc, aryl aluminum, and aryl boronate esters under similar reaction conditions.

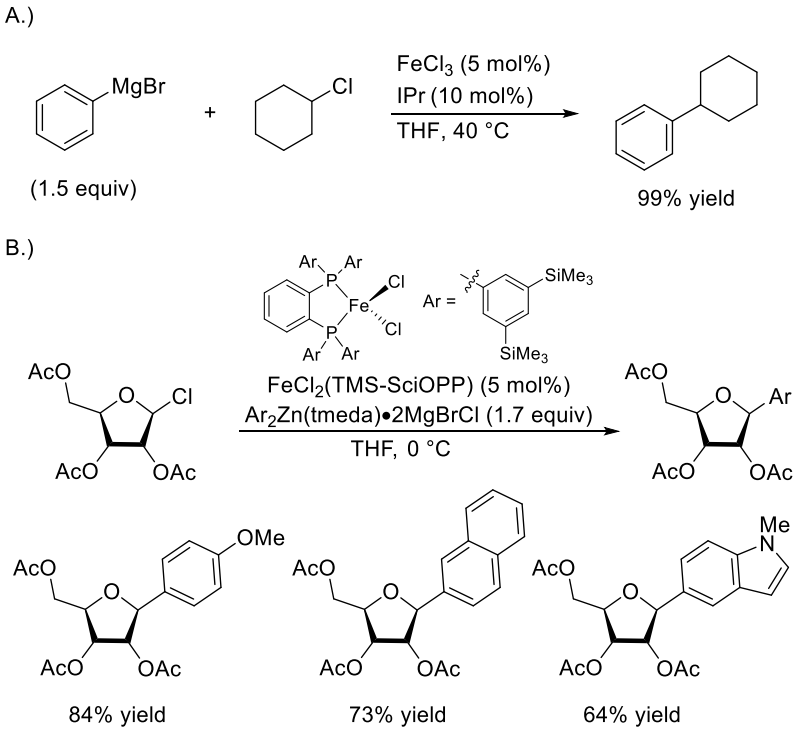


Figure 3.3. Iron-catalyzed coupling of secondary alkyl chlorides.

The Fu group have made significant efforts in the Ni-catalyzed couplings of alkyl electrophiles. In 2006, they reported the nickel-catalyzed Suzuki coupling of unactivated alkyl halides with aryl boronic acids (Figure 3.4, A).[16] The method is tolerant of both primary and secondary alkyl chlorides, furnishing the desired alkylated arenes in high yield. Key to the success of this method is the identification of prolinol, derived from the amino acid proline, as a competent ligand for nickel. Molander and coworkers also made this observation when they reported the coupling of potassium (hetero)aryltrifluoroborates (Figure 3.4, B).[17] While bathophenanthroline as a ligand for nickel was effective in the couplings of alkyl bromides and iodides, only the proline/Ni system was operative in coupling alkyl chlorides.

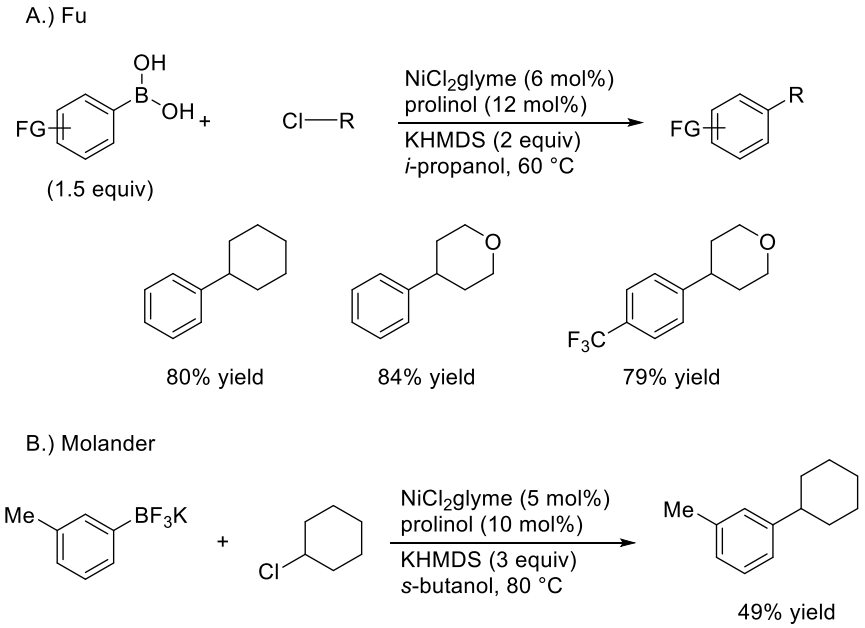


Figure 3.4. Nickel-catalyzed coupling of secondary alkyl chlorides.

3.1.3. Previous Results and Working Hypothesis

While there are a number of reports on the coupling of aryl halides with secondary benzyl chlorides,[18-22] α-chlorocarbonyls,[23-25] and other activated alkyl chlorides,[26-29] there are fewer examples of couplings employing aryl halides and non-activated alkyl chlorides.[30-36] All of these examples go through the stoichiometric formation of an organometallic reagent prior to coupling. Additionally, there are *no reported couplings* of aryl chlorides with non-activated secondary alkyl chlorides. Aryl chlorides represent the largest pool of aryl coupling partners (Figure 3.5), have higher stability compared to their iodide and bromide counterparts, and are relatively unreactive under most reaction conditions which can allow form subsequent functionalization. Alkyl chlorides share these advantages as well, and functionalization of these strong bonds would allow for substantial growth in the pool of compounds available through cross-coupling methods.

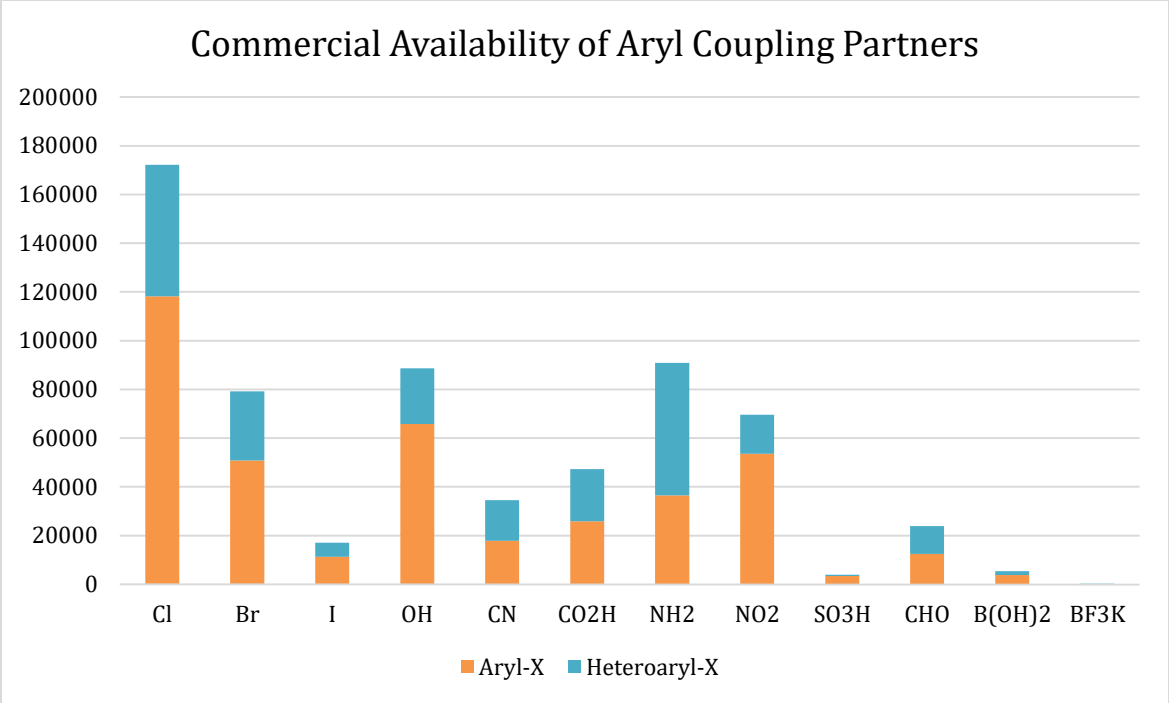


Figure 3.5. Availability of aryl coupling partners.

We hypothesized that in the coupling of aryl chlorides with secondary alkyl chlorides, the alkyl chloride would be the problematic coupling partner (Figure 3.6). We have shown that under previous conditions for cross-electrophile couplings alkyl chlorides remain unreactive,[37] both providing an impetus for realization of this coupling and highlighting the challenges to achieve it. Vicic et al. have shown that tridentate terpyridine ligands, in combination with a nickel catalyst, were effective in cross-couplings to form $C(sp^3)$-$C(sp^3)$ bonds and have provided mechanistic insight into how these reactions proceed.[38-39] We have found in our lab that using 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (ttbtpy, **L1**) as a ligand that we could dimerize alkyl bromides and primary alkyl chlorides.[40] Additionally, terpyridine ligands are effective in couplings that go through an allyl-Ni intermediate.[41-43] However, these ligands have not been thouroughly investigated

for aryl-alkyl cross-electrophile coupling. We posited that this ligand would allow us to achieve the goals of coupling alkyl chlorides with aryl chlorides.

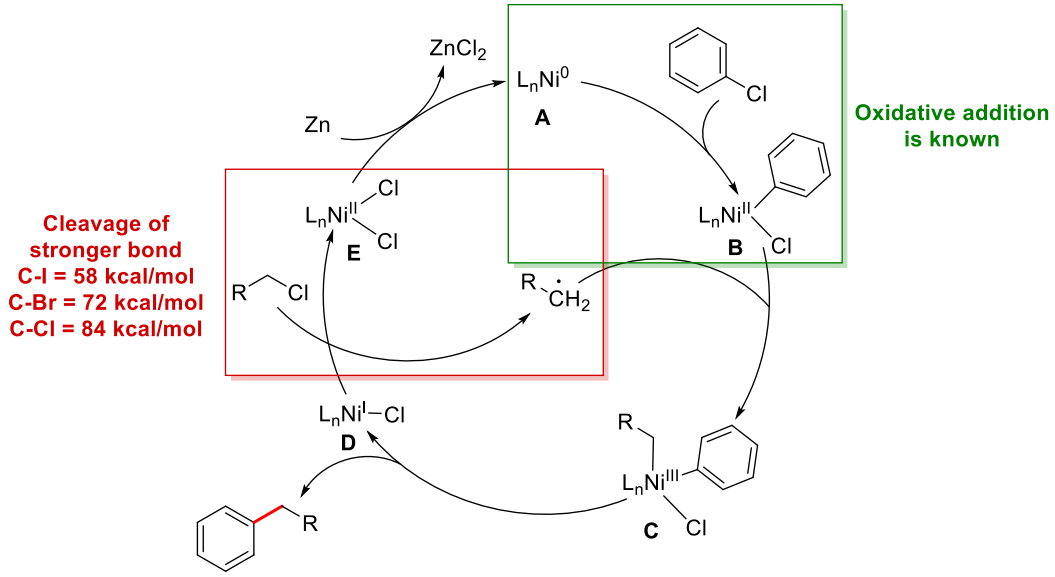


Figure 3.6. Challenge in coupling aryl and alkyl chlorides

3.2. Results

3.2.1. Preliminary Optimization

Initial investigations by Dr. Laura Ackerman and Seoyoung Kim found that **L1** with $NiBr_2$diglyme as precatalyst was able to couple chlorobenzene with cyclohexylchloride in 87% assay yield by GC. While this was a promising result, these conditions were not general (Figure 3.7). Other secondary alkyl chlorides coupled in significantly lower yields, displaying unique reactivity of cyclohexyl radicals that has been previously observed.[44-46]

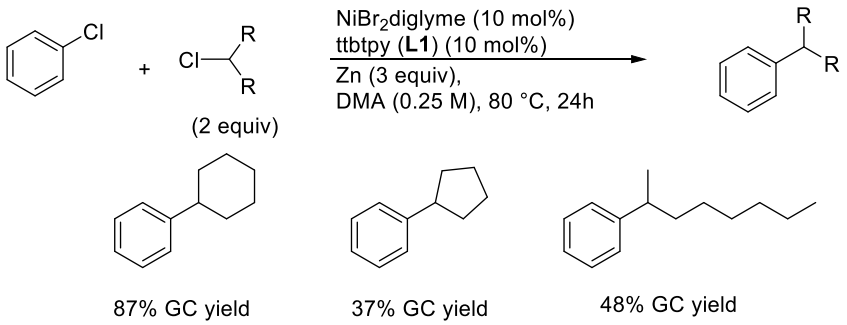
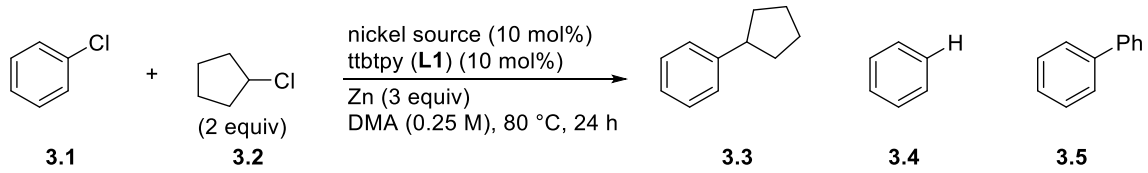


Figure 3.7. Initial Conditions.

In search of more general conditions, we decided to optimize the coupling of chlorobenzene with cyclopentyl chloride. Evaluation of various nickel (II) precatalysts revealed $NiCl_2$dme as the optimal nickel source, providing 48% yield of the desired product (Table 3.1). Reactions in NMP were comparable to those in DMA in terms of yield and selectivity.

Table 3.1. Nickel Precatalyst Screening.



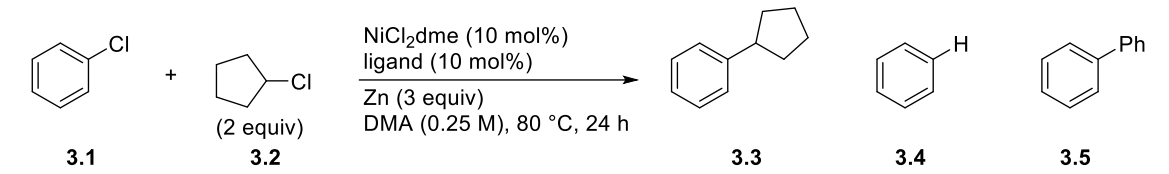
Entry	Nickel Source	**3.1** (%)[a]	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	$NiBr_2$diglyme	6	31	12	3
2	$NiBr_2$	20	27	9	1
3	$NiCl_2$	12	26	13	1
4	NiI_2	21	16	14	1
5	$NiCl_2$•$2H_2O$	-	14	14	5
6	$NiBr_2$•$3H_2O$	5	14	20	3
7	$NiCl_2$dme	2	48	12	2
8	$NiBr_2$dme	18	29	11	1

[a]GC yields vs. dodecane as internal standard.

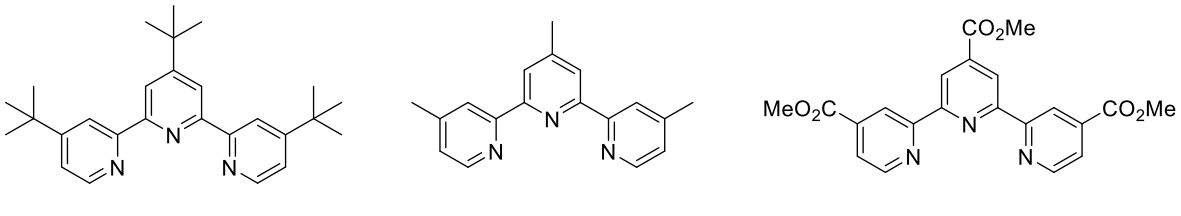
We observed dramatic differences in selectivity when ligands were examined. We found that while ttbtpy remained the optimal ligand, all the terpyridines tested resulted in complete conversion of the alkyl chloride and incomplete conversion of the aryl chloride (Table 3.2, 1-5). Interestingly, when we examined bidentate bipyridine ligands we

observed the opposite trend; complete conversion of the aryl chloride and incomplete conversion of the alkyl chloride (Table 3.2, 6-8). This is consistent with the results seen during our mechanistic studies on the coupling of aryl and alkyl iodides.[47] Oxidative addition is faster of aryl iodides than alkyl iodides for bipyridine-ligated nickel. This trend appears to be opposite for terpyridine ligated nickel, where oxidative addition of the alkyl chloride is faster. Given our previous success utilizing dual catalyst systems where each catalyst is selective for a different coupling partner,[48-50] we speculated that a combination of both a bipyridine and a terpyridine ligand could provide high yield and selectivity.

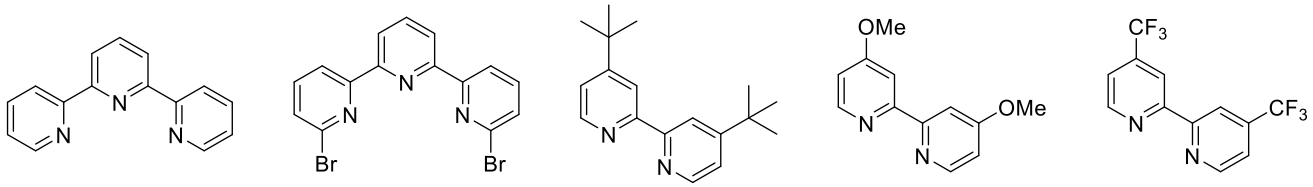
Table 3.2. Ligand Screening.



3.1 **3.2** **3.3** **3.4** **3.5**



L1 **L2** **L3**



L4 **L5** **L6** **L7** **L8**

Entry	Ligand	**3.1** (%)[a]	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	**L1**	5	48	28	2
2	**L2**	32	26	23	4
3[b]	**L3**	29	11	7	1
4	**L4**	26	26	24	-
5	**L5**	43	1	54	-
6[c]	**L6**	-	3	15	19
7[c]	**L7**	-	4	8	24
8[c]	**L8**	-	-	34	12

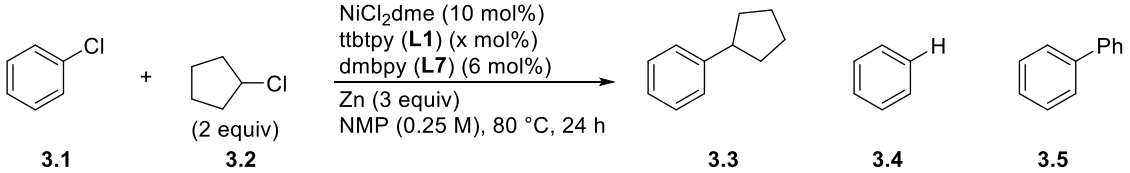
[a]GC yields vs. dodecane as internal standard. Alkyl chloride completely consumed. [b]Reaction in NMP as solvent. [c]Sodium iodide (50 mol%) added. 12 mol% of ligand. Alkyl chloride remaining.

3.2.2. Evaluation of the Dual Ligand System

We chose 4,4'-dimethoxy-2,2'-bipyridine (dmbpy, **L7**) as our bidentate ligand as it resulted in the lowest amount of alkyl chloride conversion. When we used a 1:1 ratio of ttbtpy and dmbpy we achieved a similar yield as ttbtpy alone, but complete conversion of both starting materials (Table 3.3, 1). Since the terpyridine ligand appeared to have the greater influence on the reaction, we looked at varying the concentration of ttbtpy while

keeping the loading of dmbpy constant. We observed that as the amount of terpyridine is increased, the yield of product also increased from 25% to 72% yield at 7 mol% ttbtpy (Table 3.3, 2-4). If dmbpy is omitted from the reaction, the yield drops significantly. Additionally, when we examined other bidentate ligands in combination with ttbtpy we observed a range of results (Table 3.4). This data supports the hypothesis that the bipyridine ligand is playing an active role in catalysis and that both ligands are necessary for high yields.

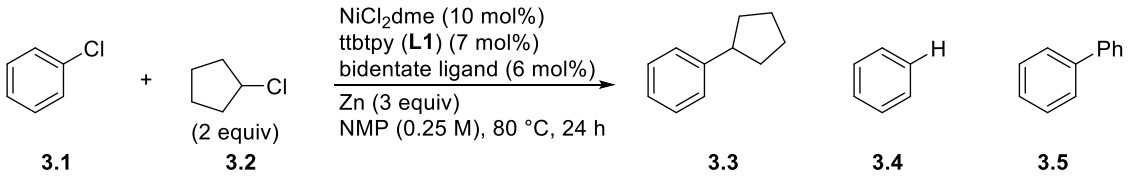
Table 3.3. Evaluation of Dual Ligand System.



Entry	mol% ligand	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	6 mol%	51	4	11
2	3 mol%	25	11	16
3	5 mol%	41	9	13
4	7 mol%	72	18	6
5[b]	7 mol%	32	29	4
6[bc]	7 mol%	40	48	5

[a]GC yields vs. dodecane as internal standard. Starting materials completely consumed. [b]dmbpy omitted from reaction. [c]7 mol% $NiCl_2$dme used.

Table 3.4. Effects of Bidentate Ligand

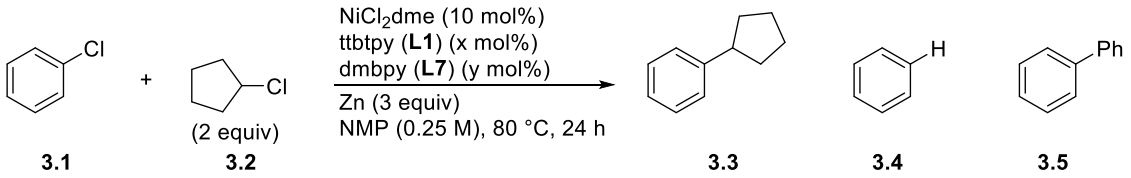


Entry	Ligand	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	**L6**	58	6	4
2	**L7**	68	2	3
3	**L8**	46	19	2
4	2,2'-bipyridine	63	8	6
5	phenanthroline	76	7	1
6	neocuproine	10	27	1
7	bathophenanthroline	58	10	-
8	bathocuproine	18	23	4

[a]GC yields vs. dodecane as internal standard. Starting materials completely consumed.

As the total amount of ligands was in excess compared to nickel, it was unclear as to how much nickel was ligated by each nickel. Our initial hypothesis was that ttbtpy ligated nickel stoichiometrically and excess nickel was ligated with dmbpy. In this case, the extra 3 mol% of dmbpy might be unnecessary. We explored the ligand ratio further, keeping the total ligand concentration constant and stoichiometric with nickel (Table 3.5).

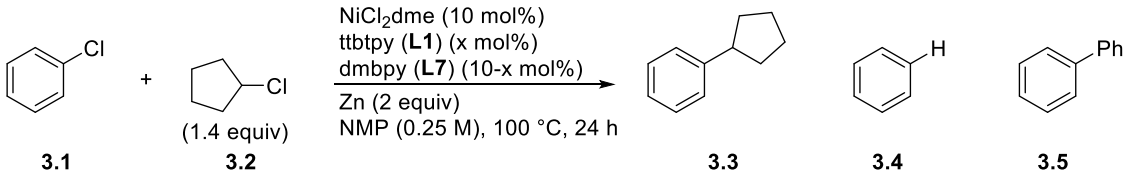
Table 3.5. Effect of Ligand Ratio.



Entry	Ligand ratio (x:y)	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	1:9	15	6	23
2	2:8	25	5	19
3	3:7	27	4	17
4	4:6	39	4	14
5	5:5	46	5	15
6	6:4	52	6	12
7	7:3	67	5	6
8	8:2	86	5	1
9	9:1	85	5	-

[a]GC yields vs. dodecane as internal standard. Starting materials completely consumed.

As we previously observed, as the amount of terpyridine increases we see a steady increase in product yield and decrease in aryl dimer. A ligand ratio of 4:1 ttbtpy to dmbpy appeared to be the optimal ratio for the transformation, with higher concentrations of terpyridine resulting in lower yields. We also found that a slight increase in the temperature (80 °C to 100 °C) allowed for less reductant and a smaller excess of alkyl chloride to be used while keeping the same trend observed before (Figure 3.8). We also examined electronic effects on the ligand ratio by using aryl chlorides with varying electronic properties. We found that while electron-rich aryl chlorides follow the same trend as chlorobenzene (albeit at a lower yield), electron-poor aryl chlorides coupled in higher yields with increasing terpyridine ligand, the highest yield being in the absence of the bipyridine ligand (Figure 3.9).



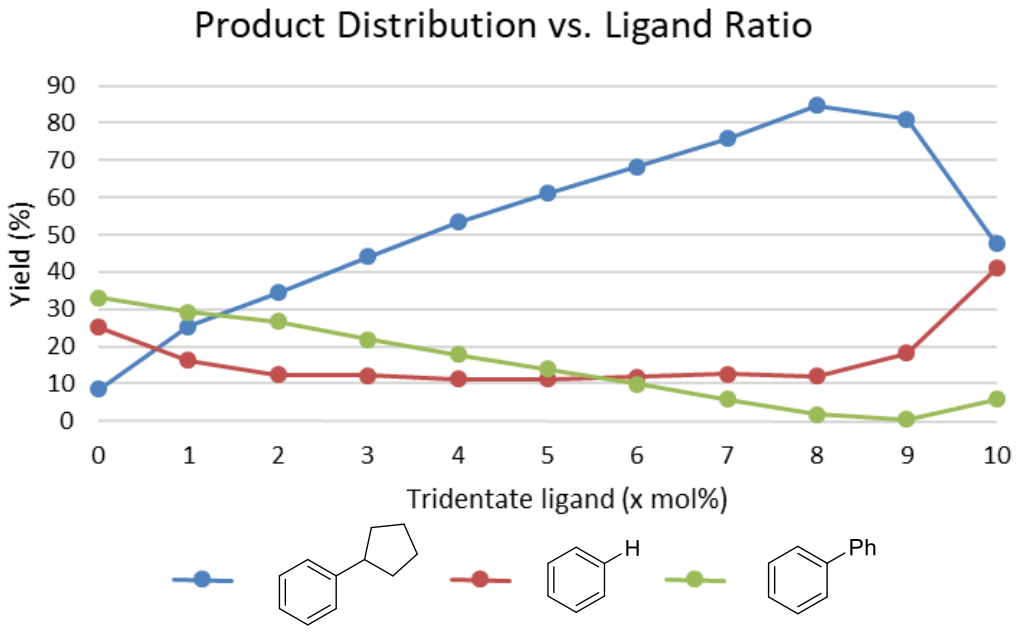
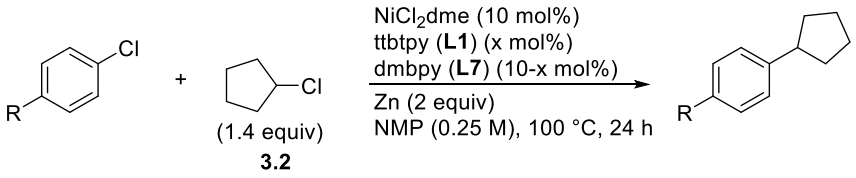


Figure 3.8. Effect of ligand ratio on product selectivity.



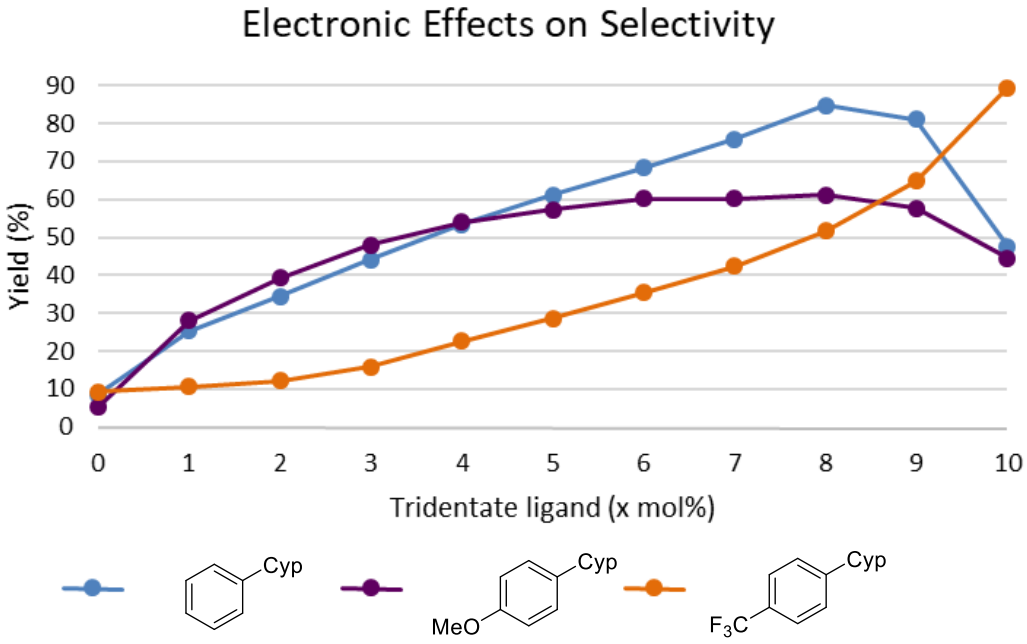
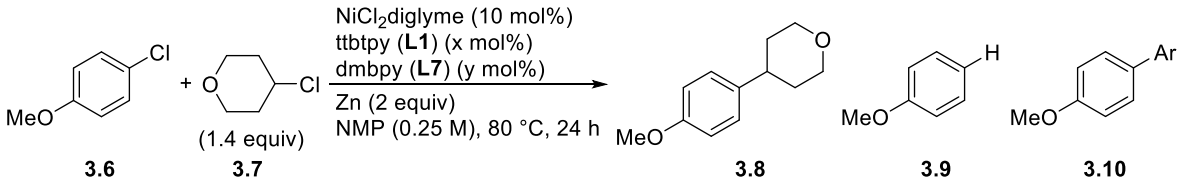


Figure 3.9. Effect of aryl electronics on product selectivity.

3.2.3. Investigation of Dimethoxyethane and Diglyme Nickel Precatalysts

While investigating the effect of the ligand ratios on the reaction, we became curious about the supporting ligand on the precatalyst, as this can play a role in the initial ligation of the ligand. We reinvestigated the ligand ratio with a new set of substrates (chosen for facile separation) and $NiCl_2$diglyme as the nickel precatalyst (Table 3.6). We observed, once again, that the product yield increases with increasing terpyridine concentration (Figure 3.10). However, high yields were obtained in the absence of the bipyridine ligand (Table 3.6, 11). We decided to take these new conditions forward to evaluate the substrate scope.

Table 3.6. Effect of Ligand Ratio with $NiCl_2$diglyme



Entry	Ligand ratio (x:y)	**3.6** (%)[a]	**3.8** (%)[a]	**3.9** (%)[a]	**3.10** (%)[a]
1	0:10	0	5	16	84
2	1:9	17	15	16	58
3	2:8	19	31	16	44
4	3:7	28	41	14	30
5	4:6	23	55	10	25
6	5:5	31	59	10	13
7	6:4	18	75	11	12
8	7:3	21	77	10	6
9	8:2	8	83	12	6
10	9:1	0	87	13	11
11	10:0	0	82	11	16

[a]GC yields vs. trimethoxybenzene as internal standard.

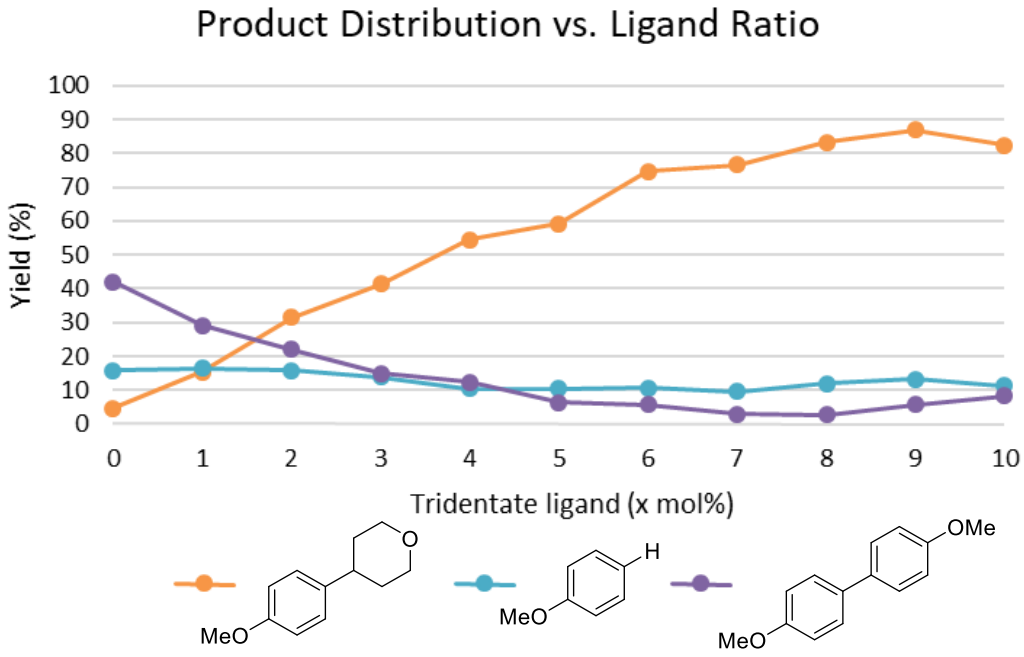
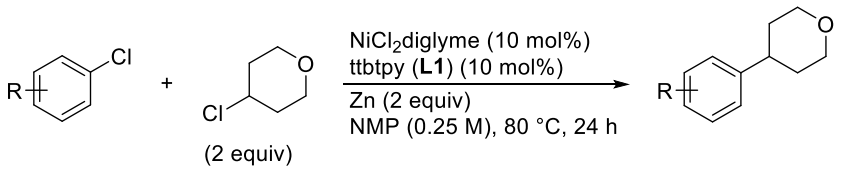
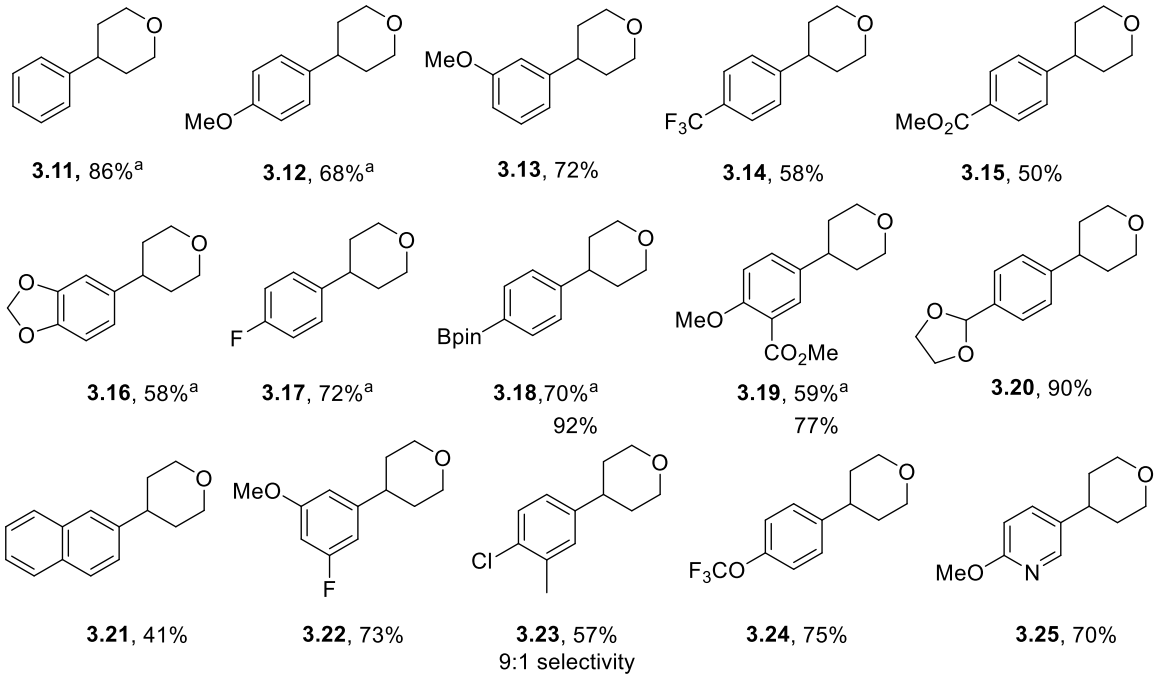


Figure 3.10. Effect of ligand ratio on product selectivity with $NiCl_2$diglyme.

3.2.4. Preliminary Substrate Scope

Table 3.7. Substrate Scope



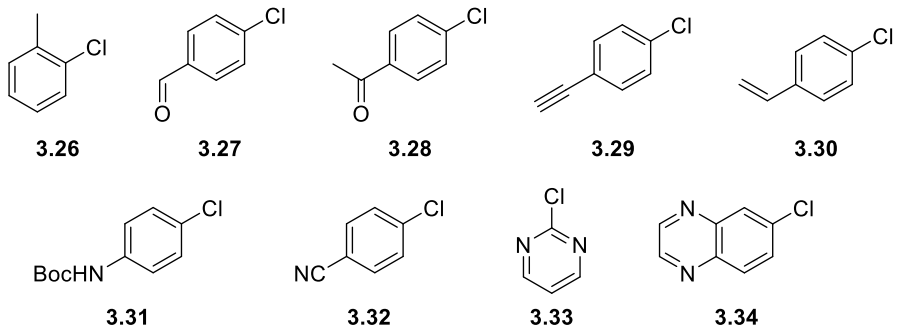


Reactions were performed on 0.5 mmol scale. Yields are of isolated products. [a]1.4 equivalents of alkyl chloride used.

A variety of aryl chlorides were successfully coupled under these conditions. Electron-rich and electron-poor aryls are well tolerated (Table 3.7, **3.12-17**). In a few cases, an improvement in yield was seen when 2.0 equivalents of the alkyl coupling partner was used (**3.18-19**). An aryl chloride with a boronic ester coupled in 92% yield, allowing for further functionalization through palladium catalysis. 4-Chlorobenzaldehyde decomposed under the reaction conditions, but protection as the ethylene glycol acetal furnished the coupled product **3.20** in high yield. The reaction is sensitive to steric hindrance at the C(sp^2)-Cl bond, but leveraging that sensitivity allowed for **3.23** to be produced in good

selectivity. Finally, 2-methoxy-5-chloropyridine was able to be coupled in high yield (**3.25**).

3.2.5. Unsuccessful Substrates

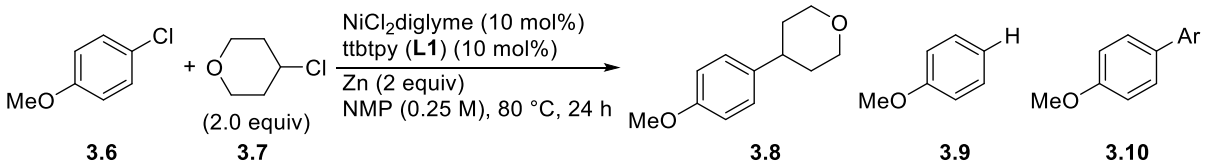


3.26 **3.27** **3.28** **3.29** **3.30** **3.31** **3.32** **3.33** **3.34**

Figure 3.11. Problematic coupling partners.

As discussed in the previous section, sterically hindered aryl chlorides did not perform well in the reaction. Additionally, aldehydes and ketones resulted in complex mixtures of unidentified products. Substrates with unsaturated C-C bonds, such as **3.29** and **3.30**, also underwent unproductive side reactions, even when **3.29** was protected with a silyl group. Protected amines also proved problematic, perhaps due to the increased acidity of the N-H bond. Substrates with coordinating groups (**3.32-3.34**) are challenging due to possible deactivation of the catalyst by the substrate. This hypothesis was tested by adding benzonitrile, similar to **3.32**, to the optimized reaction. We observed that the nitrile has a negative effect on the reaction, leading to significant amounts of unreacted aryl chloride, consistent with our hypothesis (Table 3.8). We plan to investigate if this effect is general amongst some of the unsuccessful substrates tested.

Table 3.8. Effect of PhCN on Reaction Selectivity.



3.6 **3.7** **3.8** **3.9** **3.10**

Entry	Added PhCN (equiv)	**3.6** (%)[a]	**3.8** (%)[a]	**3.9** (%)[a]	**3.10** (%)[a]
1	0 equiv	4	81	15	6
2	1 equiv	85	8	16	0

[a]GC yields vs. trimethoxybenzene as internal standard.

3.3. Conclusion and Future Work

We have established reaction conditions for the coupling of aryl chlorides with unactivated secondary alkyl chlorides. The significant selectivity differences between bipyridine and terpyridine ligands were investigated, and a synergistic effect of both ligand types was observed. The method allows for the coupling of a variety of aryl chlorides in high yields and provides the opportunity for subsequent functionalization. We plan to further investigate the scope of the reaction by evaluating various secondary alkyl chlorides as coupling partners (Figure 3.12). While the synergy between ligands was not necessary for the aryl scope, we hypothesize that it will play a major role for the alkyl scope. Seoyoung Kim and Dr. Matthew Goldfogel have developed conditions for the coupling of aryl chlorides with primary alkyl chlorides; however, secondary alkyl chlorides couple in low yield. This method offers complimentary reactivity as it is able to couple secondary alkyl chlorides in high yield. Alkyl chlorides can also remain unreacted under previous cross-electrophile coupling conditions, and we plan to exploit this by performing subsequent couplings on alkyl and aryl dihalides (Figure 3.13).

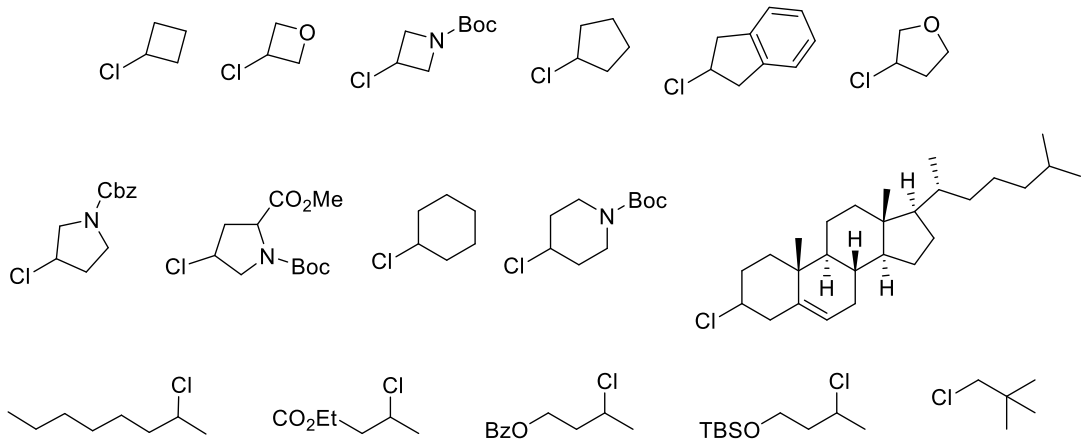


Figure 3.12. Potential alkyl chloride scope.

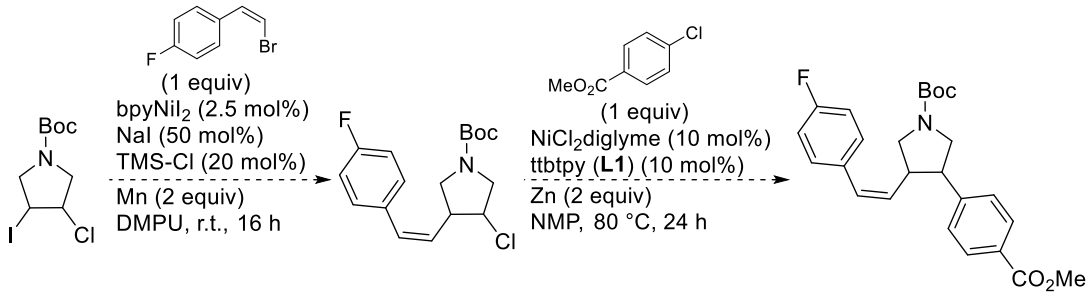
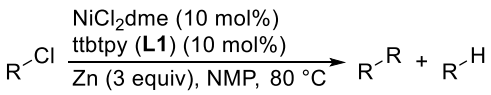


Figure 3.13. Difunctionalization via successive nickel-catalyzed cross-electrophile couplings.

Based on the results presented in this chapter, it is unlikely that the coupling of aryl and alkyl chlorides is proceeding via our previously posited reaction mechanism (Figure 3.6). It appears that activation of the alkyl chloride via oxidative addition is faster than reaction with the aryl chloride when a terpyridine is used as the ligand (Table 3.9).

Table 3.9. Catalyst Selectivity.



Entry	R =	Conversion at 3 h (%)[a]	Conversion at 24 h (%)[a]
1	Ph	11	96
2	Cyclopentyl	100	100
3	2-heptyl	77	100
4	Cyclohexyl	23	91

[a]% Conversion by GC.

We plan to confirm this with a stoichiometric nickel complex with an excess of **3.6** and **3.7**. We will also conduct this experiment with a mixture of cyclopentyl chloride (**3.2**) and **3.7** (Figure 3.14, A). Once confirmed, we will investigate the reactivity of analogous Ni-alkyl complexes with aryl and alkyl chlorides (Figure 3.14, B). Vicic has shown that the (tpy)Ni(I)-Me complex **3.36** can react with alkyl iodides via oxidative addition.[38] We hypothesize that we are making a similar intermediate that can undergo oxidative addition into the aryl chloride and plan to directly test this hypothesis. Finally, based on the results in Table 3.2, we hypothesize that the role of the second ligand is to facilitate oxidative addition of the aryl chloride, and that product is formed through a transmetallation between a Ni-aryl and a Ni-alkyl species. We plan to synthesize both intermediates to investigate whether transmetallation is feasible under the reaction conditions (Figure 3.14, C).

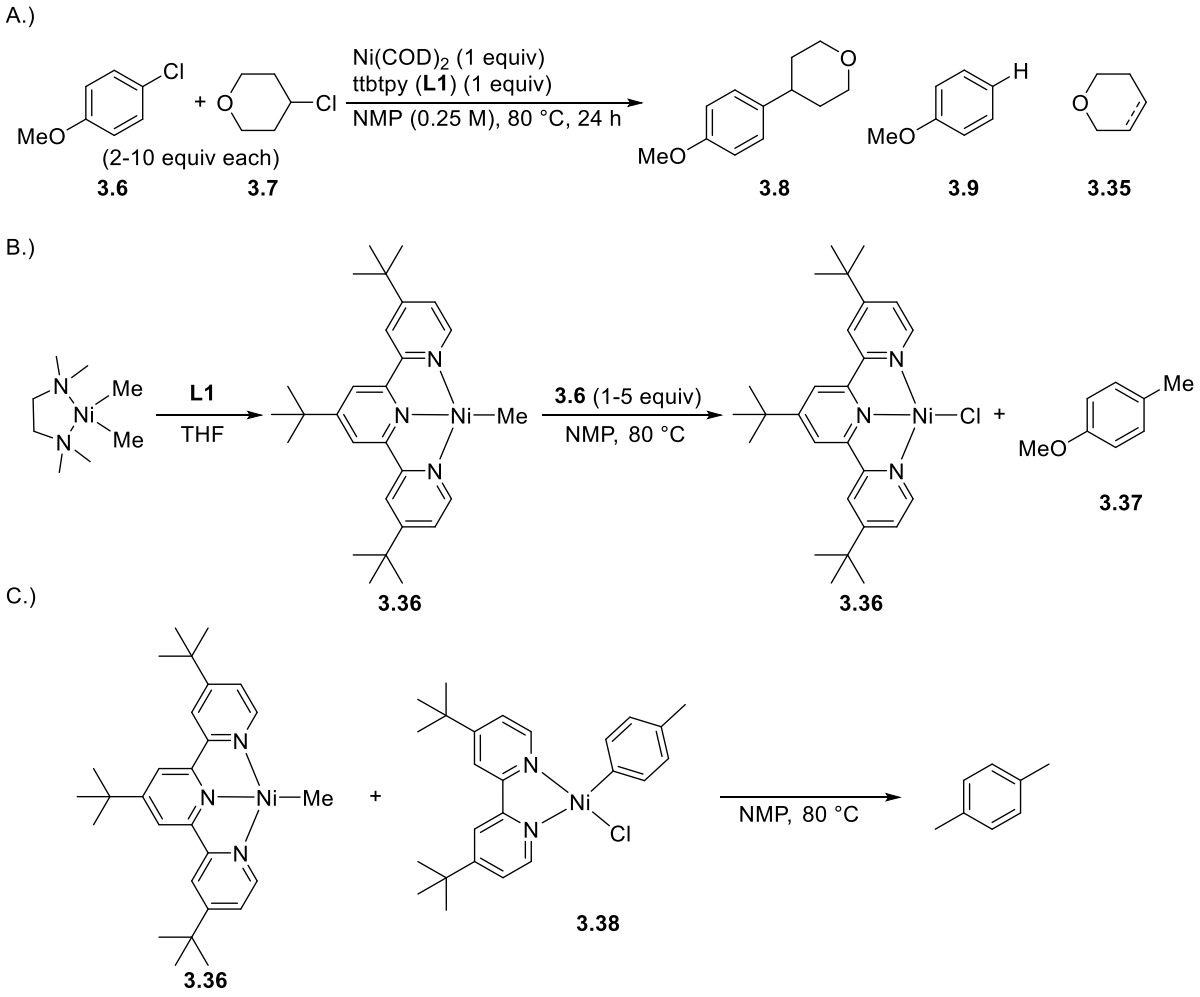


Figure 3.14. Proposed mechanistic experiments.

3.4. Experimental

3.4.1. Materials

$NiCl_2$diglyme was prepared according to literature procedure.[51] 4,4'-dimethoxy-2,2'-bypyridine (dmbpy), 4,4',4"-tri-tert-butyl-2,2',6',2"-terpyridine (ttbtpy), and zinc flake (-325 mesh) were purchased from commercial suppliers and used as received.

The following substrates were synthesized according to a literature procedure:[52] 2-chloro-2,3-dihydro-1H-indene, tert-butyl 4-chloropiperidine-1-carboxylate, tert-butyl 3-chloroazetidine-1-carboxylate, benzyl 3-chloropyrrolidine-1-carboxylate, benzyl 4-chloropiperidine-1-carboxylate, 3-chlorooxetane, 3-chlorotetrahydrofuran, ((2-

chlorocyclohexyl)oxy)(methyl)diphenylsilane, 1-(tert-butyl) 2-methyl 3-chloropyrrolidine-1,2-dicarboxylate, ethyl 3-chlorobutanoate, (2-chloropropoxy)benzene, tert-butyl(3-chlorobutoxy)dimethylsilane, and 3-chlorobutyl benzoate.

4-chlorotetrahydropyran was purchased from Millipore-Sigma or TCI and used as received. 4-chlorotetrahydropyran purchased from Combi-Blocks led to inconsistent results.

4-chlorobenzonitrile, 3-chloroanisole, 1-chloronaphthalene, 4-chloro-(N-Boc)aniline, cyclobutyl chloride, chlorocyclopentane, (-)-menthyl chloride, 1-chloroadamantane, and 4-chlorobenzeneboronic acid pinacol ester were purchased from Millipore-Sigma and used as received.

Methyl 4-chlorobenzoate, methyl 5-chloro-2-methoxybenzoate, 4'-chloroacetophenone, 5-chloro-1,3-benzodioxole, chlorobenzene, diethyl 4-chlorobenzylphosphonate, 4-chlorophenol, and 4-chlorobenzotrifluoride, 1-chloro-2-methylbenzene, chlorocyclohexane, and cholesteryl chloride were purchased from Alfa Aesar and used as received.

2-chloronaphthalene, 1-chloro-4-(1,1-dimethylethyl)benzene, and 3-chloro-5-fluoroanisole were purchased from Combi-Blocks and used as received.

4-chloroanisole was purchased from Oakwood Chemicals and used as received.

1-chloro-4-fluorobenzene and 2-chlorocyclohexanol were purchased from Acros and used as received.

NMP (1-methyl-2-pyrrolidinone, anhydrous) was purchased from Millipore Sigma and used as received. All other dry solvents were prepared from ACS grade, inhibitor free solvents by passage through activated alumina and molecular sieves in an Inert

Technologies solvent purification system. Water content was routinely measured using Karl-Fisher titration (Metrohm) and was less than 50 ppm in all cases.

3.4.2. General Methods

NMR Spectroscopy.

^{1}H and ^{13}C NMR spectra were acquired on 400 and 500 MHz Bruker NMR instrument. NMR chemical shifts are reported in ppm and referenced to tetramethylsilane at 0.00 ppm (^{1}H) and 0.00 ppm (^{13}C) or the residual solvent peaks for $CDCl_3$ at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C). Coupling constants (*J*) are reported in Hertz.

Gas Chromatography.

Instrument. GC analyses were performed on an Agilent 7890A GC equipped with dual DB-5 columns (20 m x 180 μm x 0.18 μm), dual FID detectors, and using hydrogen as the carrier gas.

Sample preparation. A 50 μL aliquot was removed from the reaction mixture using a gas-tight syringe and quenched with 1.5 mL each of water and diethyl ether, and the resulting mixture was then passed through a 1-inch pipette column of silica. The filtrate is used for GC and GC-MS analysis.

Analysis Method. 1 μL inj. of sample, inj. temp of 300 °C, 100:1 split ratio, initial inlet pressure was 20.3 psi but varied as the column flow was held constant at 1.8 mL/min for the duration of the run. Initial oven temperature of 50 °C was held for 0.46 min followed by a temperature ramp up to 300 °C at 65 °C/min and finally the temperature was held at 300 °C for 0.69 min. Total run time was ~ 5 min. FID temperature was 325 °C.

High Resolution Mass Spectrometry (HRMS) Analysis

Mass spectrometry data was collected on a Thermo Q Exactive Plus (thermofisher.com) via flow injection with electrospray ionization or via ASAP-MS (asap-ms.com) by the chemistry mass spectrometry facility at the University of Wisconsin – Madison. The purchase of the Thermo Q Exactive Plus in 2015 was funded by NIH Award 1S10 OD020022 to the Department of Chemistry.

Chromatography

Chromatography was performed on a Biotage Isolera One (detection at 200-400 nm). Products were visualized by UV or analyzed by GC.

3.4.3. General Reaction Procedures

General procedure for Nickel-catalyzed cross-coupling reactions

Preparation of nickel solution: In a nitrogen-filled glovebox, to an oven-dried 20 mL scintillation vial containing a teflon-coated stir-bar was added $NiCl_2$diglyme (247 mg, 0.95 mmol), ttbtpy (380 mg, 0.95 mmol), and NMP (19 mL). The resulting solution was used for the catalytic reactions described. The solution was tested against *in-situ* formed precatalyst and no differences in yield or selectivity were observed. The solution is stable for >3 months in the glovebox. NOTE: After initial dissolution, the dark green homogeneous solution turns into an opaque light green slurry. Stirring the slurry prior to use is necessary for the correct stoichiometry of catalyst(s).

General procedure: In a nitrogen-filled glovebox, to an oven-dried 1-dram vial containing a teflon-coated stir-bar was sequentially added: Zn^0 flake (65 mg, 1.00 mmol, 2 equiv), NMP (1 mL), nickel/ligand solution (1 mL, 0.05 mmol Ni and 0.05 mmol ttbtpy), 1,3,5-trimethoxybenzene (if used, 10 µL of a 0.44 M solution as internal GC standard),

aryl chloride (0.50 mmol, 1 equiv), and alkyl chloride (1.0 mmol, 2 equiv). The reaction vials were capped with a PTFE-faced silicone septum cap, removed from the glove box, and stirred on the benchtop (1200 rpm) at 80 °C.

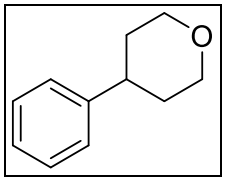
GC analysis

After 24 h reaction time, 50 µL aliquots of the reaction mixture were removed with a 250 µL gas-tight syringe and quenched with water (1.5 mL), extracted with ethyl ether (1.5 mL), and filtered through a short silica pad (1.5 cm) in a pipette packed with glass wool. The filtrate was analyzed by gas chromatography and percent yield was calculated vs. the internal standard (dodecane or 1,3,5-trimethoxybenzene) if applicable.

Isolation and purification

After 24 h reaction time, the reaction mixture was filtered through a pad of silica gel which was subsequently rinsed with diethyl ether or dichloromethane (15 ml). After filtration, volatile materials were removed on a rotary evaporator. The crude material was purified by flash chromatography to afford the pure product.

3.4.4. Product Characterization



4-phenyltetrahydro-2H-pyran (3.11) General procedure was followed with chlorobenzene (56 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (84 mg, 0.7 mmol, 1.4 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/acetone gradient) as a white crystalline solid in 86% yield (69.8 mg).

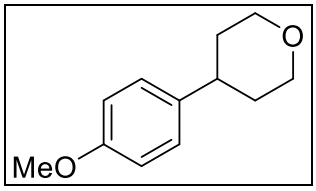
^{1}**H-NMR** (500 MHz, Chloroform-*d*) δ 7.32 (td, *J* = 7.2, 1.4 Hz, 2H), 7.25 – 7.19 (m, 3H),

4.09 (ddt, *J* = 11.6, 4.4, 1.1 Hz, 2H), 3.54 (td, *J* = 11.6, 2.5 Hz, 2H), 2.76 (tt, *J* = 11.8, 4.2 Hz, 1H), 1.89 – 1.73 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 145.87, 128.52, 126.75, 126.32, 68.43, 41.59, 33.95.

HRMS (ESI): m/z calculated for $[M+H]^+$ 163.1117, found 163.1117

Spectroscopic data matches with previously reported data.[53]



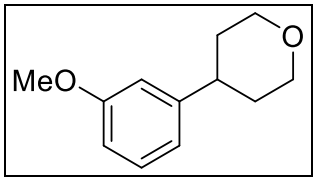
4-(4-methoxyphenyl)tetrahydro-2H-pyran (3.12) General procedure was followed with 4-chloroanisole (71 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (84 mg, 0.7 mmol, 1.4 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 68% yield (65.2 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.11 – 4.02 (m, 2H), 3.79 (s, 3H), 3.52 (td, *J* = 11.4, 3.3 Hz, 2H), 2.70 (tt, *J* = 11.2, 4.6 Hz, 1H), 1.85 – 1.70 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 158.03, 138.12, 127.60, 113.88, 68.47, 55.28, 40.71, 34.22.

HRMS (ESI): m/z calculated for $[M+H]^+$ 193.1223, found 193.1223

Spectroscopic data matches with previously reported data.[53]



4-(3-methoxyphenyl)tetrahydro-2H-pyran (3.13) General procedure was followed with 3-chloroanisole (71 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The

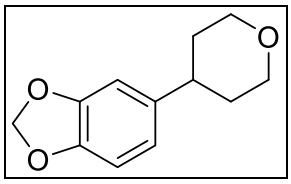
product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 72% yield (71.1 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.20 (m, 1H), 6.83 (ddt, *J* = 7.6, 1.5, 0.7 Hz, 1H), 6.80 – 6.73 (m, 2H), 4.12 – 4.04 (m, 2H), 3.81 (s, 3H), 3.52 (td, *J* = 11.5, 2.6 Hz, 2H), 2.73 (tt, *J* = 11.6, 4.3 Hz, 1H), 1.88 – 1.72 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 159.73, 147.60, 129.49, 119.15, 112.81, 111.28, 68.40, 55.17, 41.64, 33.90.

HRMS (ESI): m/z calculated for $[M+H]^+$ 193.1223, found 193.1223

Spectroscopic data matches with previously reported data.[53]



5-(tetrahydro-2H-pyran-4-yl)benzo[d][1,3]dioxole (3.16)

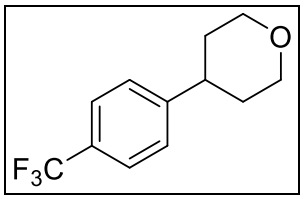
General procedure was followed with 5-chloro-1,3-benzodioxole (78 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (84 mg, 0.7 mmol, 1.4 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 58% yield (59.4 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 6.76 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 6.67 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.93 (s, 2H), 4.13 – 4.00 (m, 2H), 3.57 – 3.43 (m, 2H), 2.67 (td, *J* = 10.7, 4.8 Hz, 1H), 1.84 – 1.68 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 147.67, 145.85, 140.03, 119.51, 108.24, 107.23, 100.86, 68.39, 41.37, 34.26.

HRMS (ESI): m/z calculated for $[M+H]^+$ 207.1016, found 207.1014

Spectroscopic data matches with previously reported data.[54]



4-(4-(trifluoromethyl)phenyl)tetrahydro-2H-pyran (3.14)

General procedure was followed with 4-chlorobenzotrifluoride (90 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 58% yield (66.8 mg).

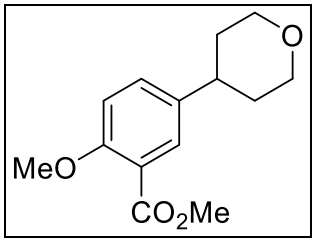
^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.14 – 4.05 (m, 2H), 3.54 (td, *J* = 11.6, 2.6 Hz, 2H), 2.82 (ddt, *J* = 11.6, 8.5, 4.1 Hz, 1H), 1.89 – 1.73 (m, 4H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 149.76 (d, $J_{C,F}$ = 1.6 Hz), 128.66 (q, $J_{C,F}$ = 32.4 Hz), 125.48 (q, $J_{C,F}$ = 3.8 Hz), 124.25 (q, $J_{C,F}$ = 271.8 Hz), 68.20, 41.51, 33.65.

^{19}F-NMR (377 MHz, $CDCl_3$) δ -62.37.

HRMS (ESI): m/z calculated for $[M+H]^+$ 231.0991, found 231.0989

Spectroscopic data matches with previously reported data.[53]



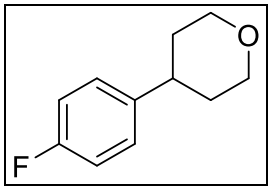
Methyl 2-methoxy-5-(tetrahydro-2H-pyran-4-yl)benzoate (3.19) General procedure was followed with methyl 5-chloro-2-methoxybenzoate (100 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a colorless oil in 77% yield (96.7 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 2.4 Hz, 1H), 7.33 (dd, *J* = 8.6, 2.5 Hz,

1H), 6.94 (d, *J* = 8.6 Hz, 1H), 4.11 – 4.04 (m, 2H), 3.89 (d, *J* = 2.7 Hz, 6H), 3.52 (td, *J* = 11.3, 3.0 Hz, 2H), 2.73 (td, *J* = 11.0, 4.8 Hz, 1H), 1.85 – 1.70 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 166.80, 157.62, 137.62, 131.61, 129.93, 119.86, 112.24, 68.32, 56.15, 52.07, 40.48, 33.97.

HRMS (ESI): m/z calculated for $[M+H]^+$ 251.1278, found 251.1275



4-(4-fluorophenyl)tetrahydro-2H-pyran (3.17) General procedure was followed with 4-fluorochlorobenzene (65 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (84 mg, 0.7 mmol, 1.4 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a pale oil in 72% yield (65.1 mg).

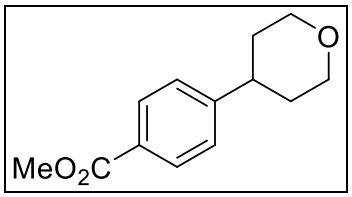
^{1}H-NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.13 (m, 2H), 7.04 – 6.95 (m, 2H), 4.13 – 4.03 (m, 2H), 3.52 (td, *J* = 11.3, 3.6 Hz, 2H), 2.74 (tt, *J* = 10.8, 5.3 Hz, 1H), 1.86 – 1.69 (m, 4H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ 161.39 (d, $J_{C,F}$ = 244.0 Hz), 141.53, 128.06 (d, $J_{C,F}$ = 7.8 Hz), 115.23 (d, $J_{C,F}$ = 21.0 Hz), 68.35, 40.87, 34.12.

^{19}F-NMR (377 MHz, $CDCl_3$) δ -117.06.

HRMS (ESI): m/z calculated for $[M+H]^+$ 181.1023, found 181.1023

Spectroscopic data matches with previously reported data.[53]



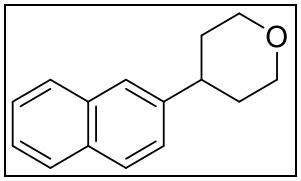
Methyl 4-(tetrahydro-2H-pyran-4-yl)benzoate (3.15) General procedure was followed with methyl 4-chlorobenzoate (85 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 50% yield (54.6 mg).

^{1}**H-NMR** (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 4.15 – 4.01 (m, 2H), 3.91 (s, 3H), 3.54 (td, *J* = 11.6, 2.5 Hz, 2H), 2.82 (tt, *J* = 11.7, 4.2 Hz, 1H), 1.93 – 1.71 (m, 4H).

^{13}**C-NMR** (101 MHz, $CDCl_3$): δ 173.87, 131.27, 128.53, 60.33, 33.92, 31.91, 29.82, 29.13, 27.37, 26.69, 25.08, 22.79, 14.39, 14.23.

HRMS (ESI): m/z calculated for $[M+H]^+$ 221.1172, found 221.1172

Spectroscopic data matches with previously reported data.[53]



4-(naphthalen-2-yl)tetrahydro-2H-pyran (3.21) General procedure was followed with 2-chloronapthalene (81 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 41% yield (43.3 mg).

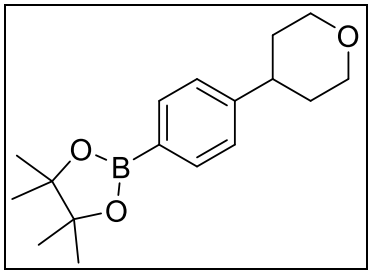
^{1}**H-NMR** (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.4 Hz, 3H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.38 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.21 – 4.06 (m, 2H), 3.59 (td, *J* = 11.7,

2.3 Hz, 2H), 2.93 (tt, *J* = 11.8, 4.0 Hz, 1H), 2.01 – 1.80 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 167.02, 151.08, 129.91, 128.30, 126.80, 68.23, 52.04, 41.68, 33.60.

HRMS (ESI): m/z calculated for $[M+H]^+$ 213.1274, found 213.1272

Spectroscopic data matches with previously reported data.[55]

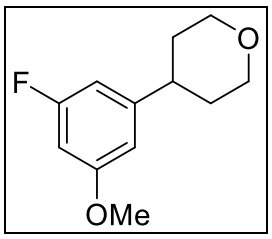


4,4,5,5-tetramethyl-2-(4-(tetrahydro-2H-pyran-4-yl)phenyl)-1,3,2-dioxaborolane (3.18) General procedure was followed with 4-chlorophenyl boronic acid pinacol ester (119 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 92% yield (132.9 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.18 – 4.00 (m, 2H), 3.53 (td, *J* = 11.7, 2.3 Hz, 2H), 2.77 (tt, *J* = 11.9, 4.1 Hz, 1H), 1.97 – 1.66 (m, 4H), 1.34 (s, 12H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 149.14, 135.10, 126.23, 83.70, 68.37, 41.80, 33.74, 24.86.

HRMS (ESI): m/z calculated for $[M+NH_4]^+$ 306.2235, found 306.2232



4-(3-fluoro-5-methoxyphenyl)tetrahydro-2H-pyran (3.22) General procedure was followed with 3-chloro-5-fluoroanisole (80 mg, 0.5 mmol, 1.0

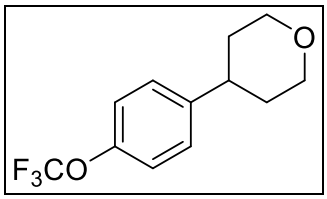
equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a colorless oil in 73% yield (77 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 6.58 – 6.50 (m, 2H), 6.47 (dt, *J* = 10.6, 2.3 Hz, 1H), 4.11 – 4.03 (m, 2H), 3.79 (s, 3H), 3.55 – 3.46 (m, 2H), 2.71 (td, *J* = 10.4, 5.3 Hz, 1H), 1.83 – 1.72 (m, 4H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 163.74 (d, *J* = 244.4 Hz), 160.91 (d, *J* = 11.4 Hz), 149.00 (d, *J* = 8.8 Hz), 108.63 (d, *J* = 2.5 Hz), 105.89 (d, *J* = 21.6 Hz), 99.14 (d, *J* = 25.2 Hz), 68.22, 55.47, 41.58 (d, *J* = 2.1 Hz), 33.68.

^{19}F-NMR (377 MHz, $CDCl_3$) δ -111.88.

HRMS (ESI): m/z calculated for $[M+H]^+$ 211.1129, found 211.1128



4-(4-(trifluoromethoxy)phenyl)tetrahydro-2H-pyran (3.24)

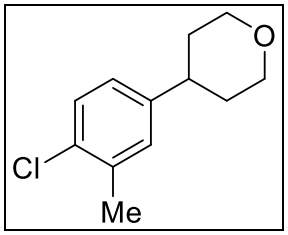
General procedure was followed with 1-chloro-4-(trifluoromethoxy)benzene (98 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a pale oil in 75% yield (92 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.20 (m, 2H), 7.20 – 7.12 (m, 2H), 4.14 – 4.02 (m, 2H), 3.53 (td, *J* = 11.4, 3.1 Hz, 2H), 2.77 (td, *J* = 11.0, 4.8 Hz, 1H), 1.87 – 1.70 (m, 4H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 147.60 (q, *J* = 1.9 Hz), 144.52, 127.97, 121.07, 120.50 (q, *J* = 256.7 Hz), 68.27, 40.99, 33.91.

^{19}F-NMR (377 MHz, $CDCl_3$) δ -57.92.

HRMS (ESI): m/z calculated for $[M+H]^+$ 247.0940, found 247.0939



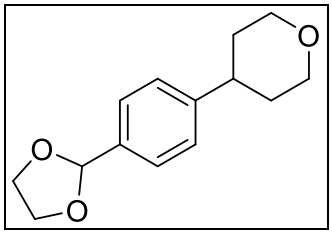
4-(4-chloro-3-methylphenyl)tetrahydro-2H-pyran (3.23)

General procedure was followed with 2,5-dichlorotoluene (80 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as colorless oil in 57% yield (59.8 mg) as a 9:1 mixture of regioisomers.

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.98 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.12 – 4.03 (m, 2H), 3.51 (td, *J* = 11.5, 2.8 Hz, 2H), 2.69 (tt, *J* = 11.4, 4.5 Hz, 1H), 2.36 (s, 3H), 1.84 – 1.68 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 144.40, 135.95, 132.08, 129.41, 129.05, 125.42, 68.32, 41.00, 33.91, 20.15.

HRMS (ESI): m/z calculated for $[M+H]^+$ 211.0884, found 211.0883



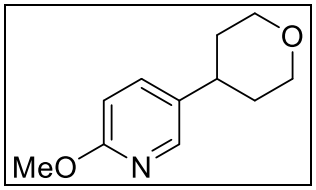
4-(4-(1,3-dioxolan-2-yl)phenyl)tetrahydro-2H-pyran (3.20)

General procedure was followed with 2-(4-chlorophenyl)-1,3-dioxolane (92 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a white crystalline solid in 90% yield (105.7 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.80 (s, 1H), 4.22 – 3.94 (m, 6H), 3.53 (td, *J* = 11.6, 2.4 Hz, 2H), 2.77 (tt, *J* = 11.8, 4.1 Hz, 1H), 1.90 – 1.68 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 146.98, 135.91, 126.82, 126.63, 103.67, 68.37, 65.34, 41.44, 33.88.

HRMS (ESI): m/z calculated for $[M+H]^+$ 235.1329, found 235.1327



2-methoxy-5-(tetrahydro-2H-pyran-4-yl)pyridine (3.25)

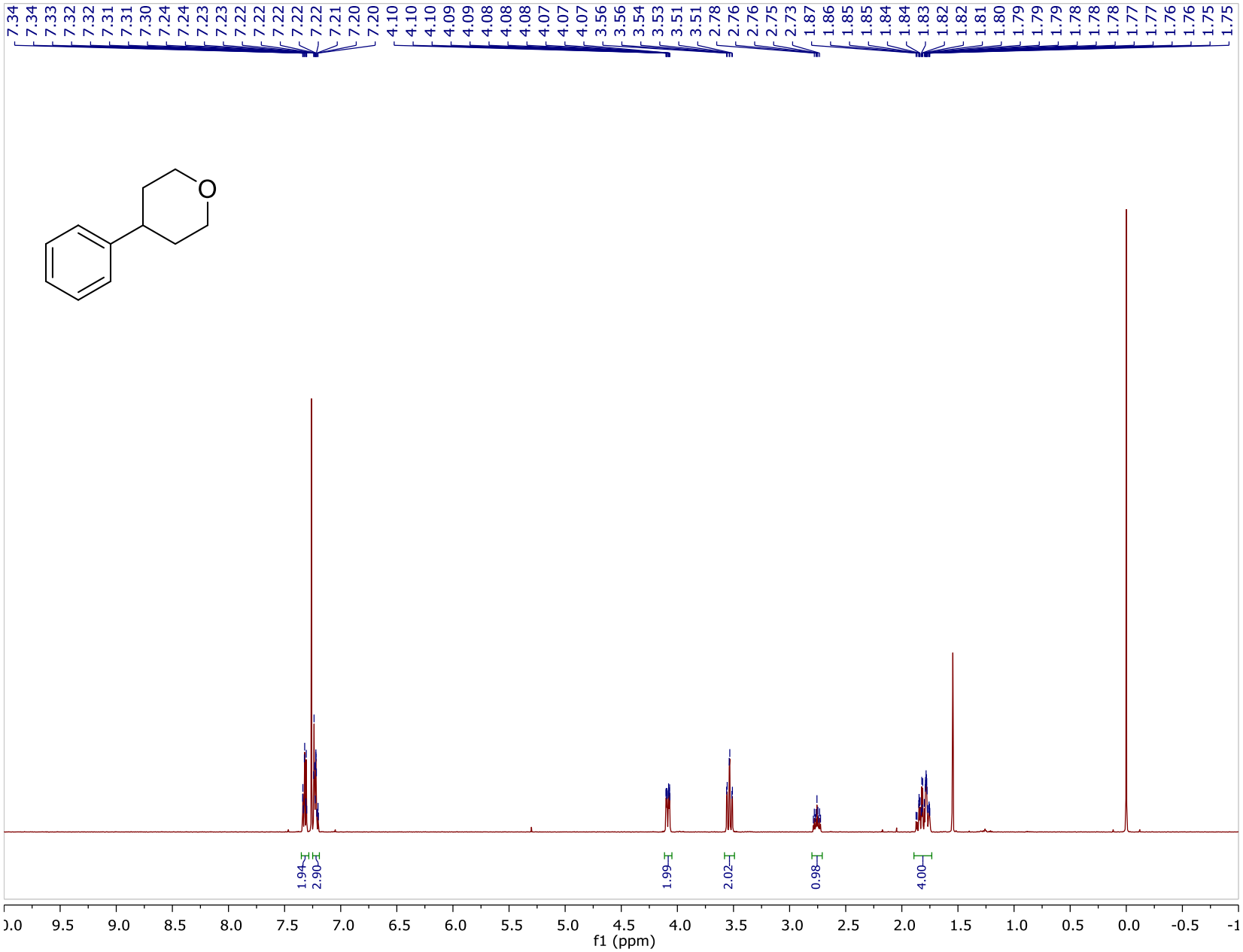
General procedure was followed with 2-methoxy-5-chloropyridine (72 mg, 0.5 mmol, 1.0 equiv) and 4-chlorotetrahydro-2H-pyran (120 mg, 1.0 mmol, 2.0 equiv) at 80 °C for 24 hours. The product was isolated by flash column chromatography (hexane/ethyl acetate gradient) as a colorless oil in 70% yield (67.5 mg).

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 2.5 Hz, 1H), 7.45 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 4.13 – 4.03 (m, 2H), 3.92 (s, 3H), 3.52 (td, *J* = 11.5, 2.8 Hz, 2H), 2.72 (tt, *J* = 11.3, 4.6 Hz, 1H), 1.84 – 1.66 (m, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 162.96, 144.86, 137.15, 133.73, 110.70, 68.25, 53.36, 38.28, 33.85.

HRMS (ESI): m/z calculated for $[M+H]^+$ 194.1176, found 194.1176.

3.4.5. NMR Spectra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4.10 4.10 4.10 4.09 4.09 4.08 4.08 4.08 4.07 4.07 4.07 3.56 3.56 3.54 3.53 3.51 3.51 2.78 2.76 2.76 2.75 2.73 1.87 1.86 1.85 1.85 1.84 1.84 1.83 1.82 1.82 1.81 1.80 1.79 1.79 1.79 1.78 1.78 1.77 1.77 1.76 1.76 1.75 1.75
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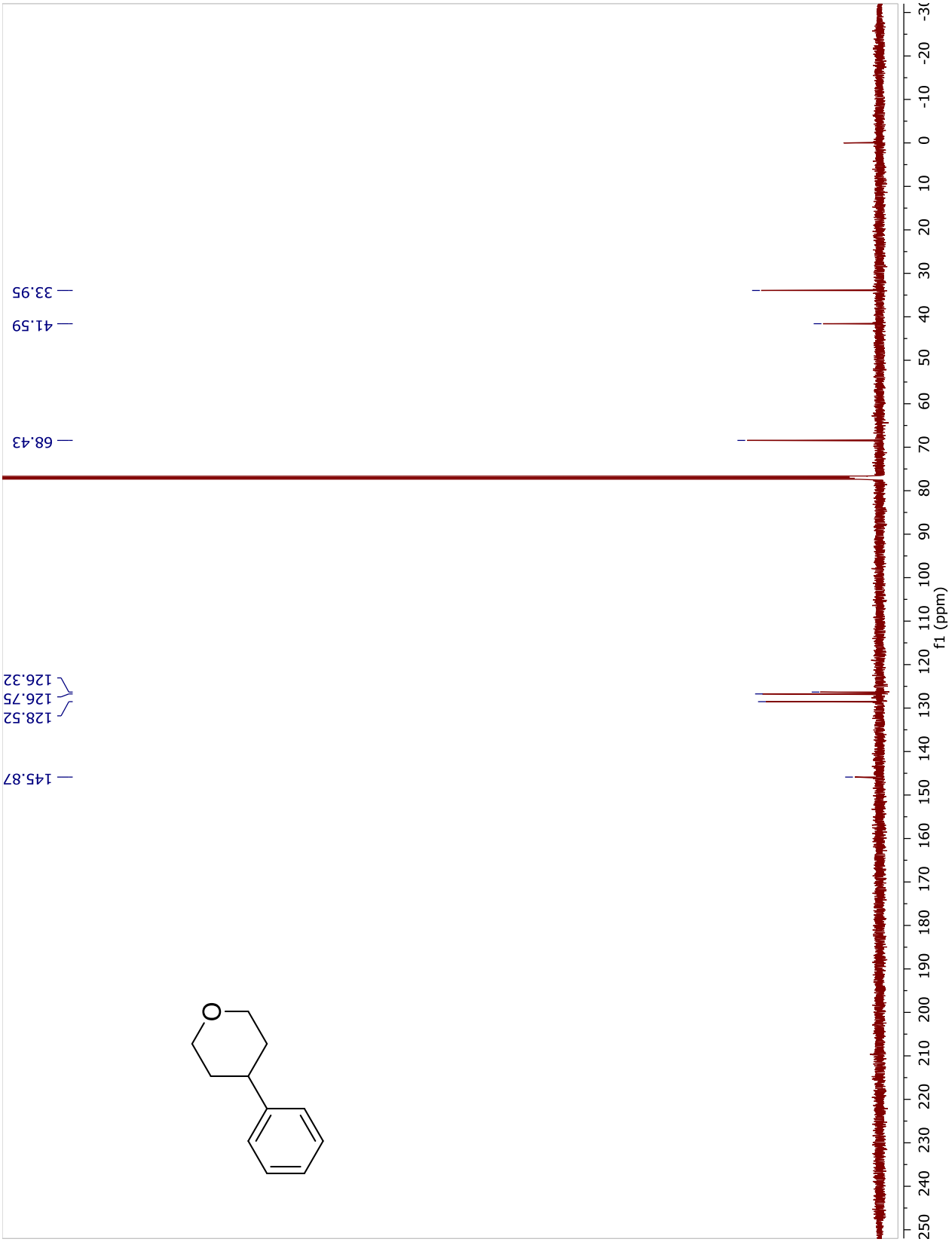
1.94
2.90
1.99
2.02
0.98
4.00
f1 (ppm)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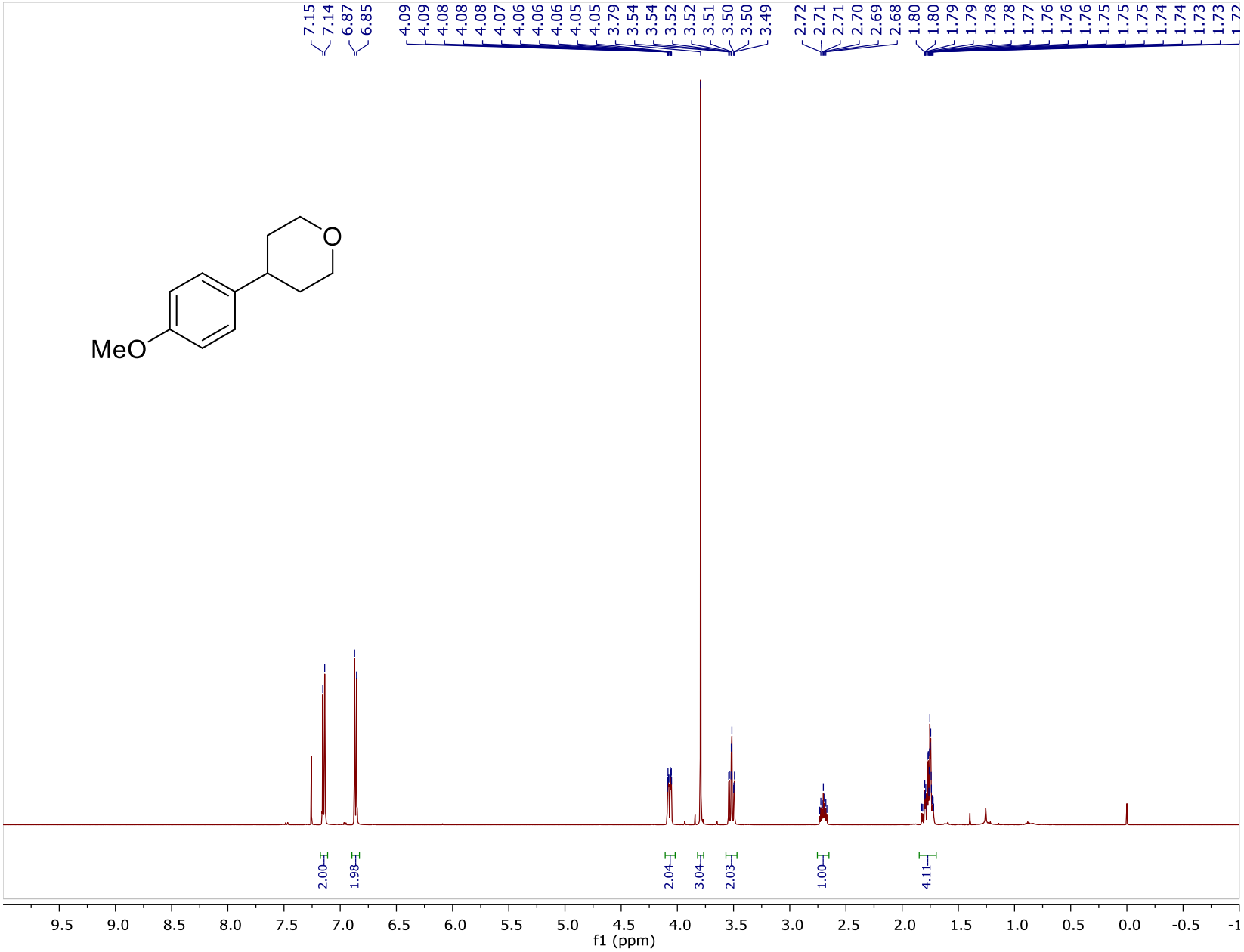
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7.14
6.87
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4.08
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4.07
4.06
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4.05
4.05
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1.78
1.77
1.76
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1.76
1.75
1.75
1.75
1.74
1.74
1.73
1.73
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O
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3.04
2.03
1.00
4.11
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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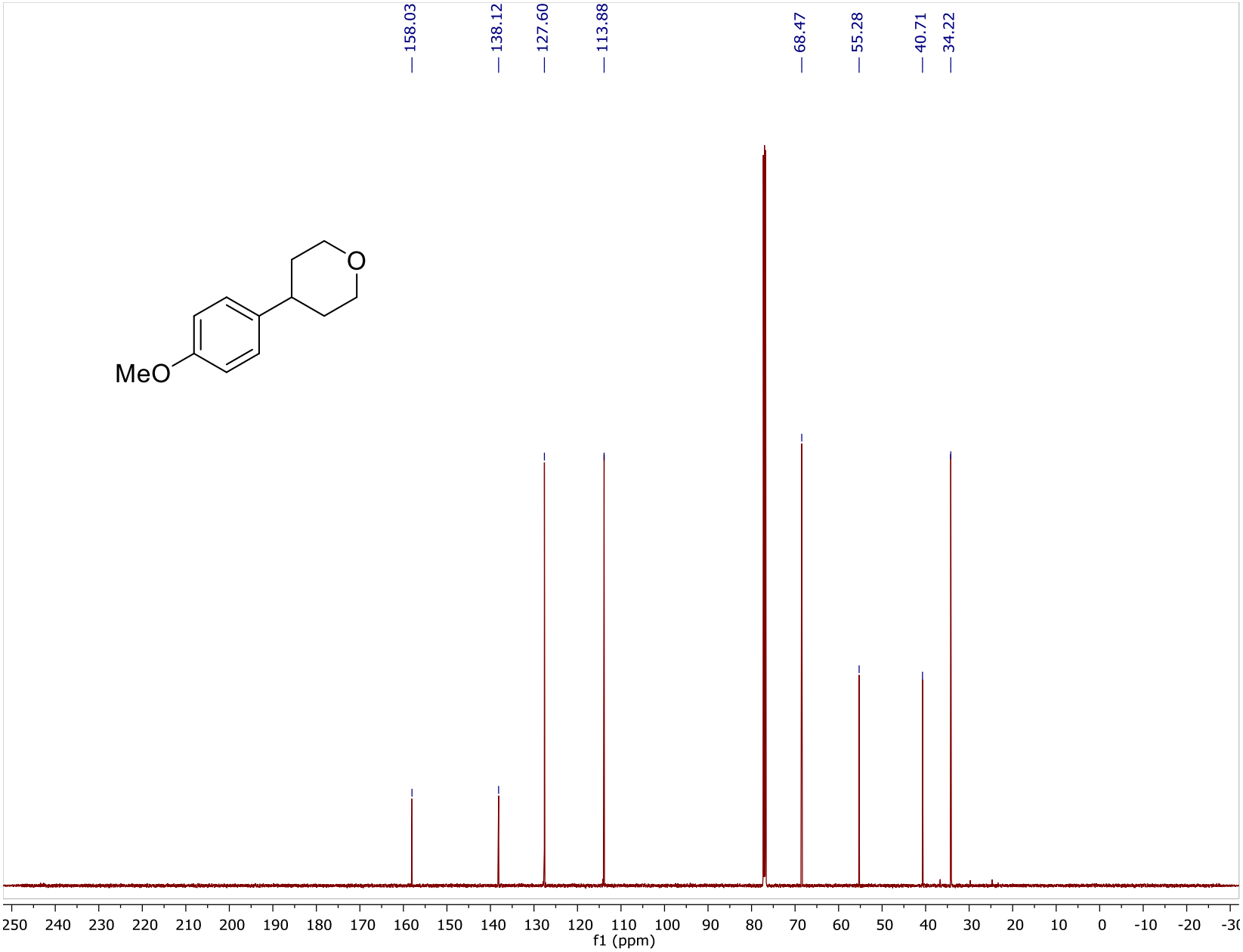
f1 (ppm)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138.12
127.60
113.88
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55.28
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34.22
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MeO
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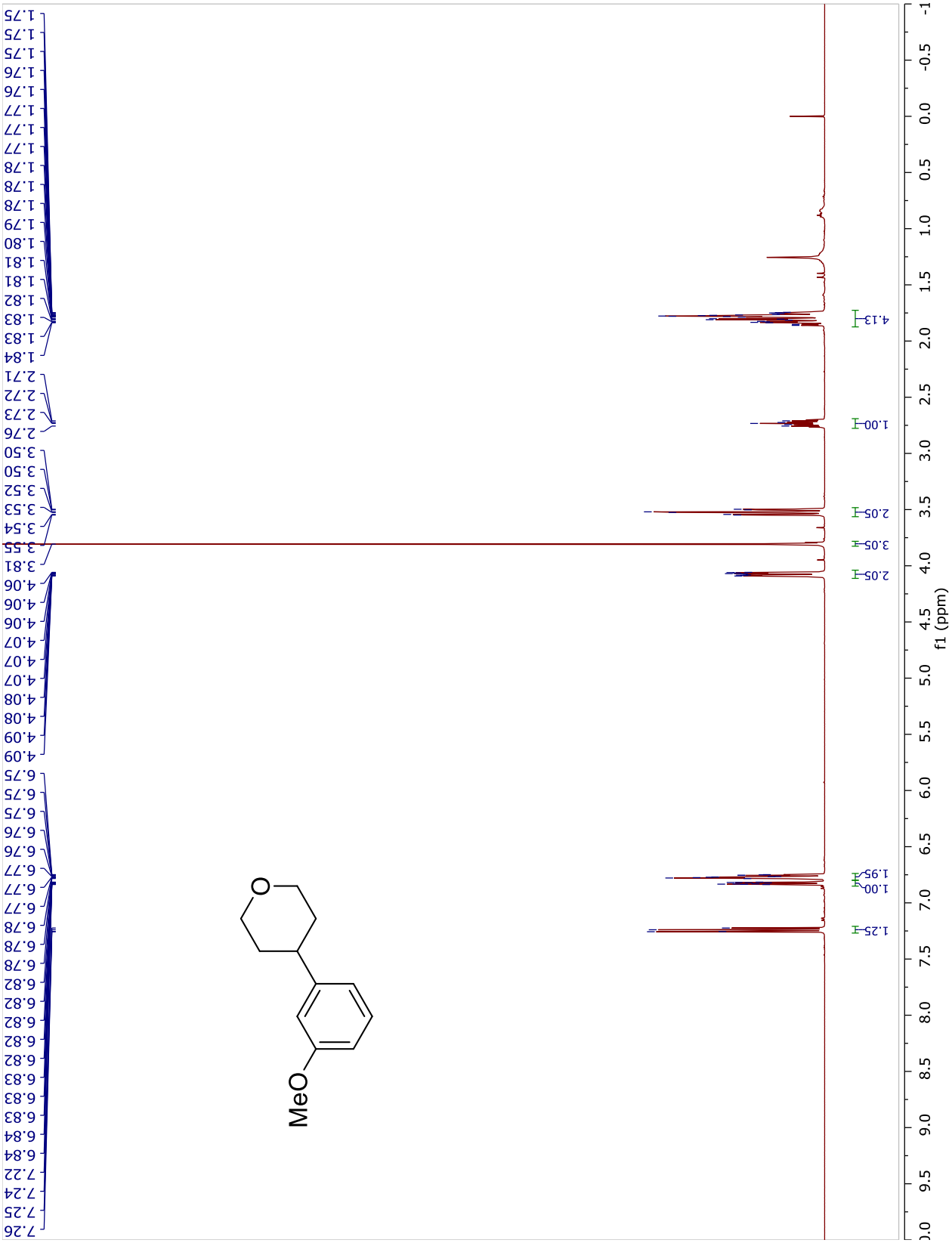
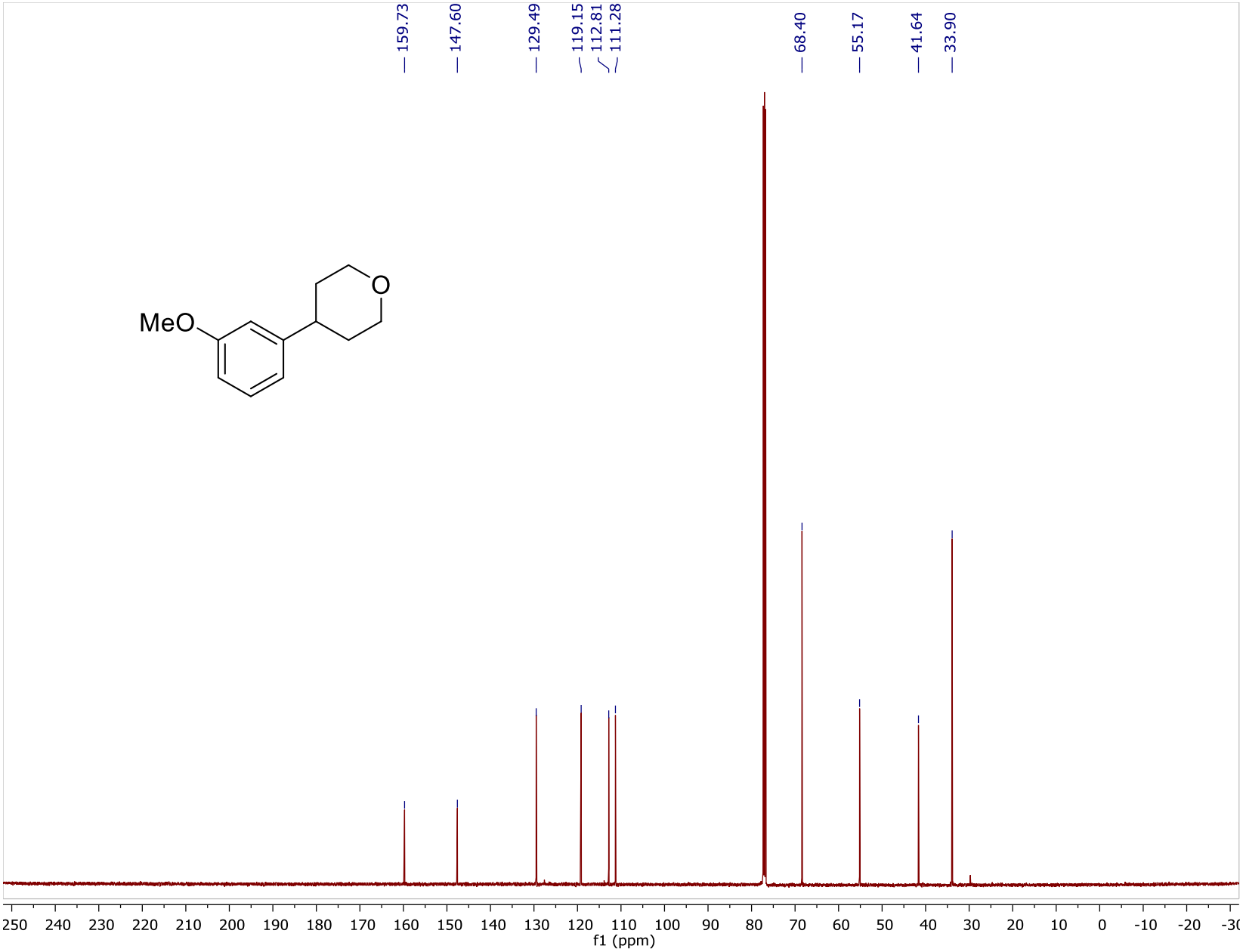
f1 (ppm)


MeO
f1 (ppm)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119.15
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111.28
68.40
55.17
41.64
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MeO
O
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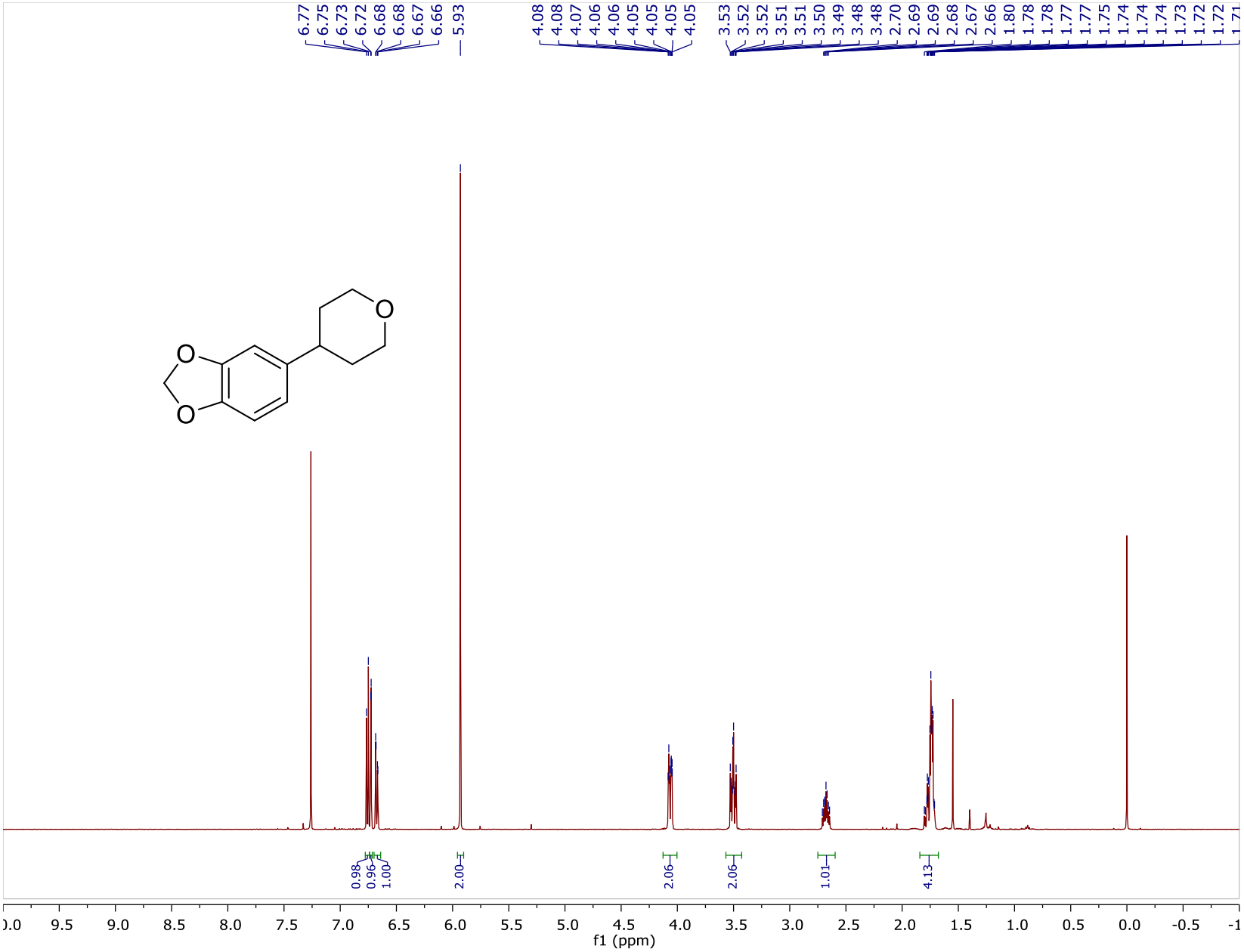
f1 (ppm)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4.05
4.05
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1.72
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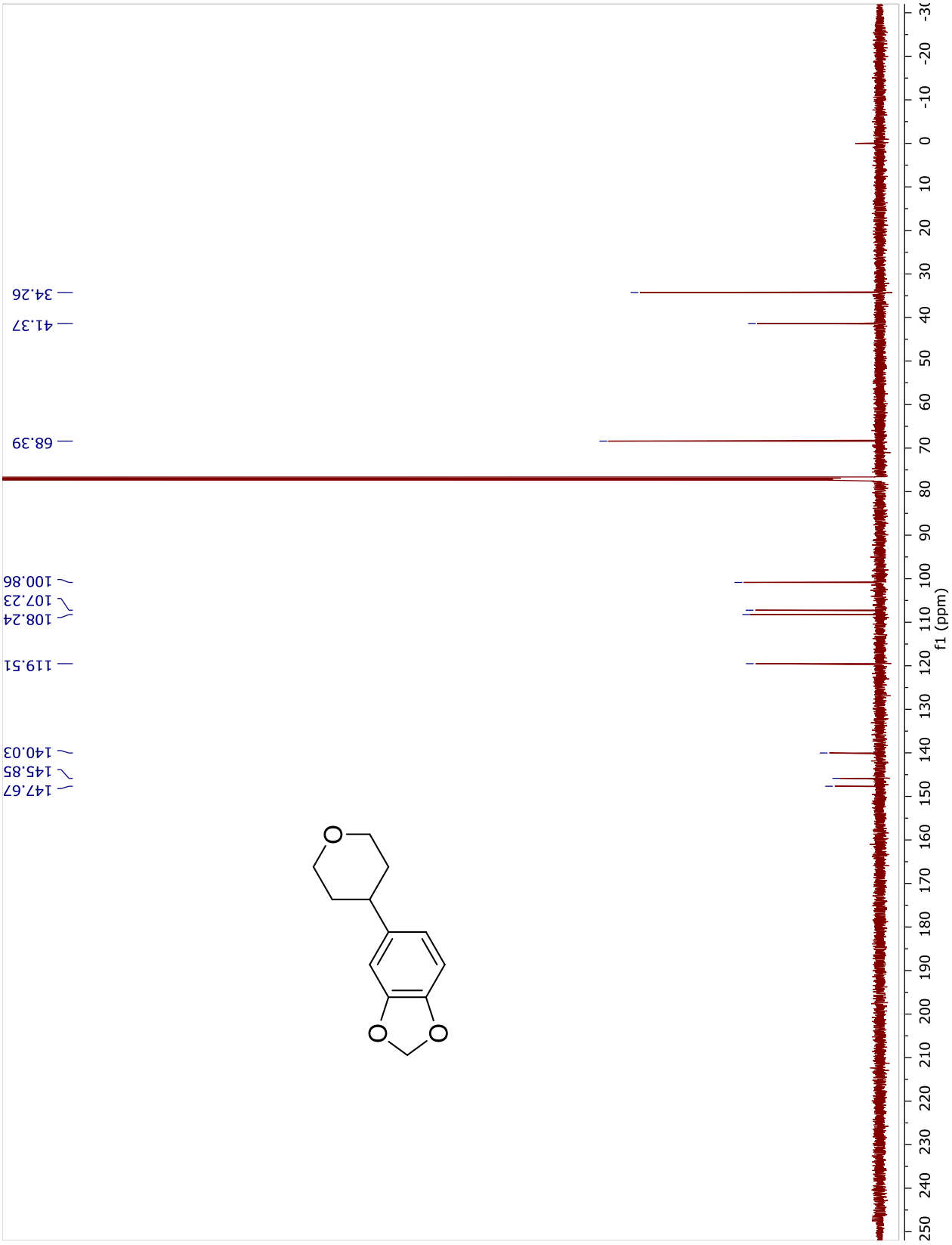
f1 (ppm)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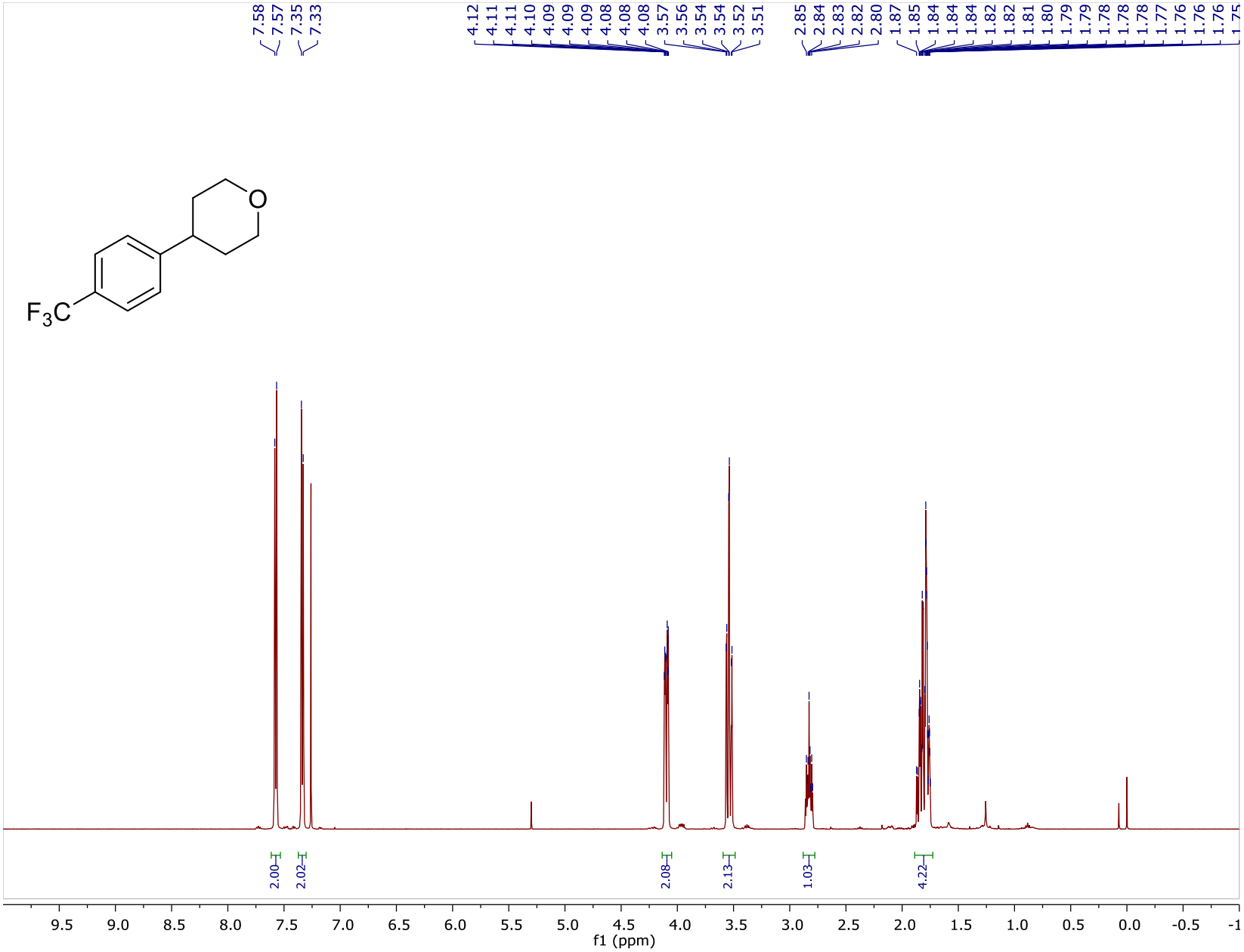
147.67
f1 (ppm)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2.08
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1.03
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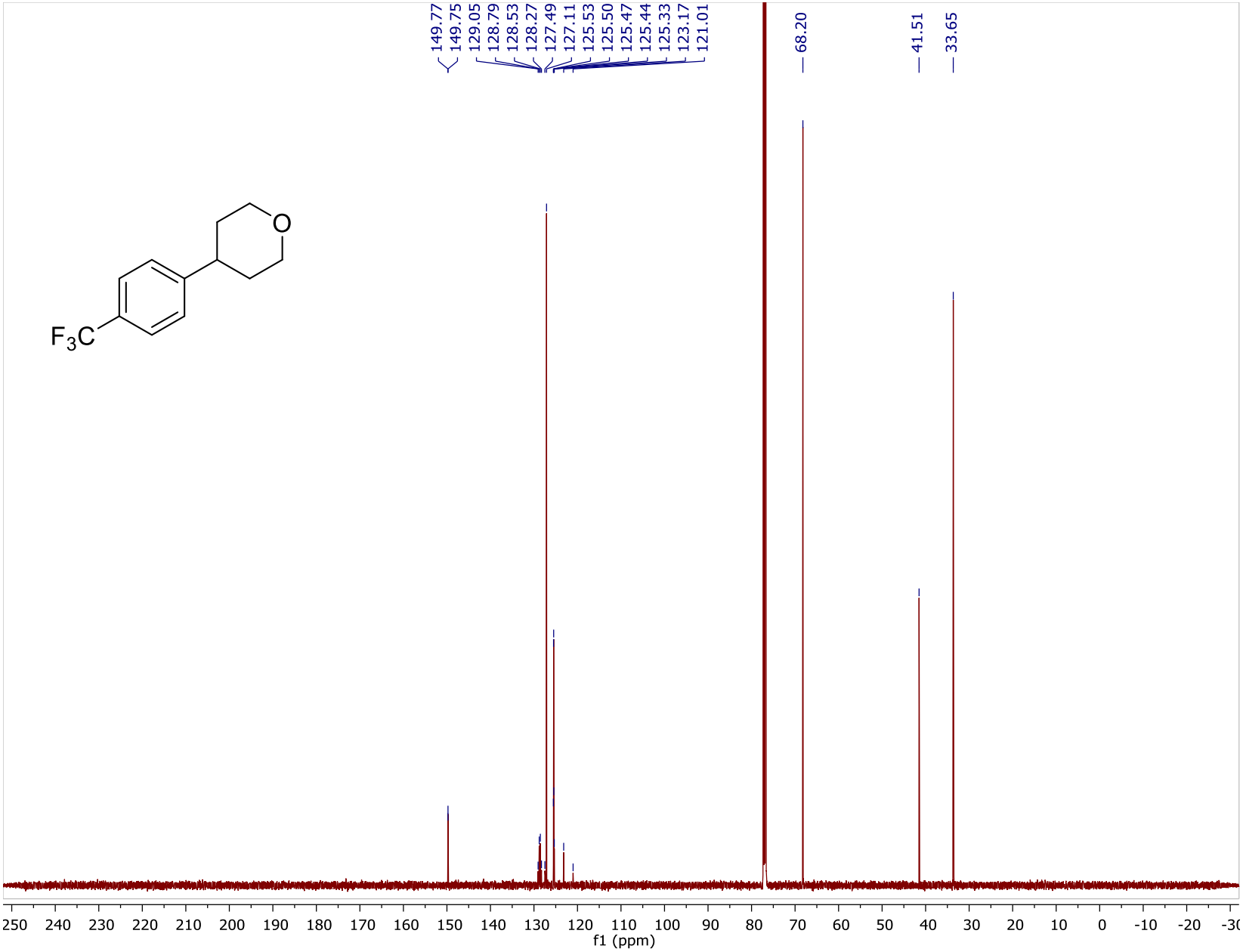
f1 (ppm)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123.17
121.01
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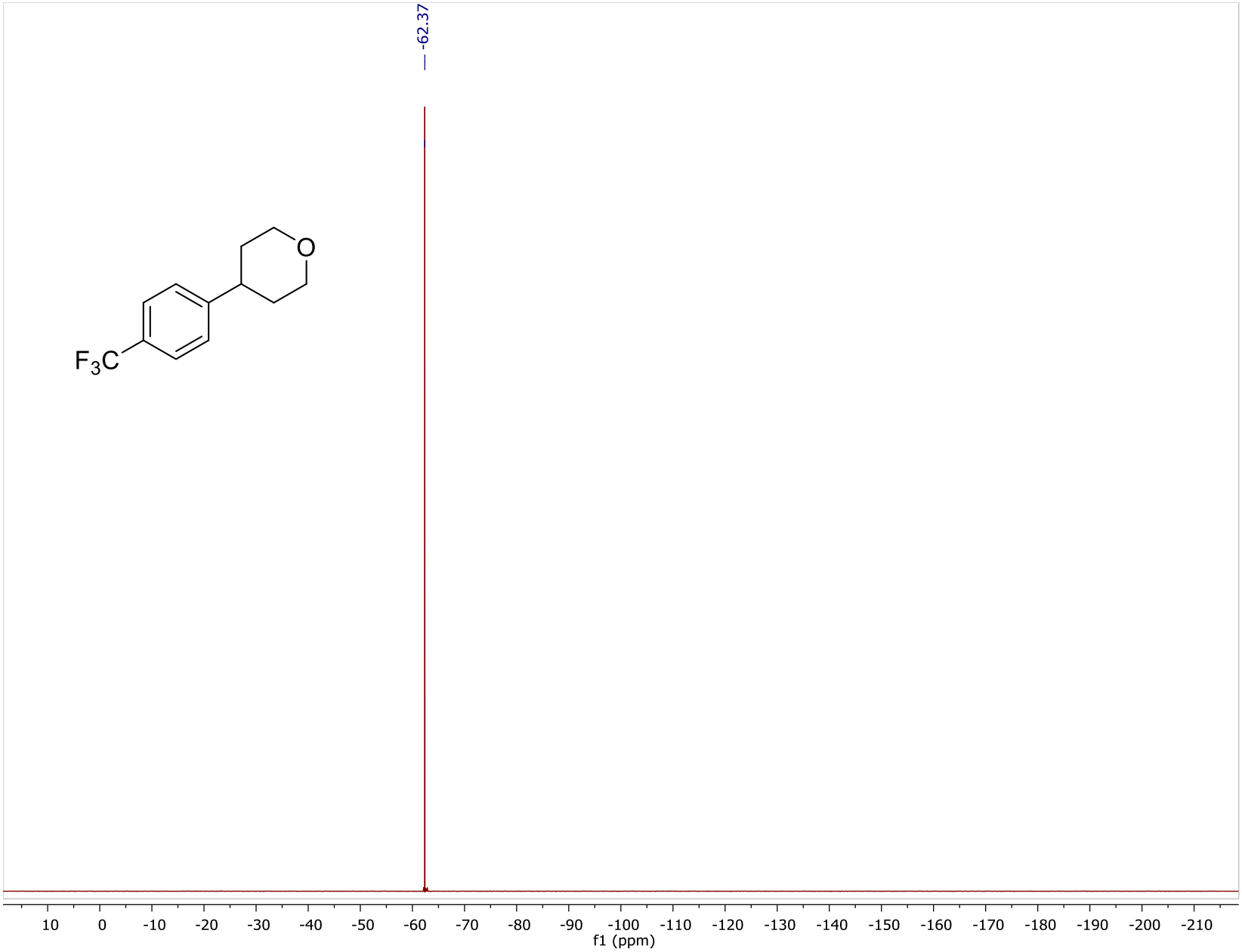
f1 (ppm)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-60
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-80
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-140
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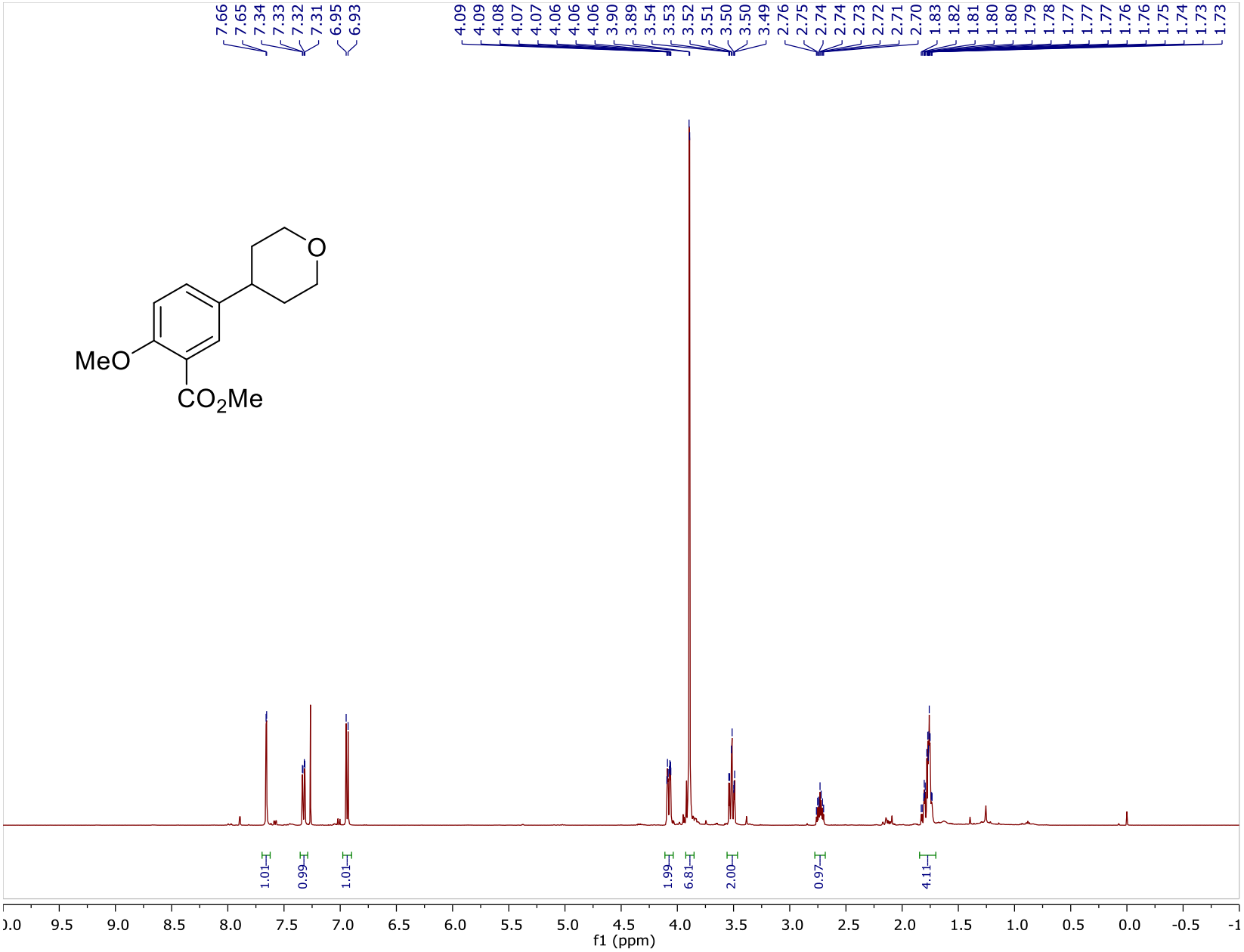
-170
-180
-190
-200
-210
f1 (ppm)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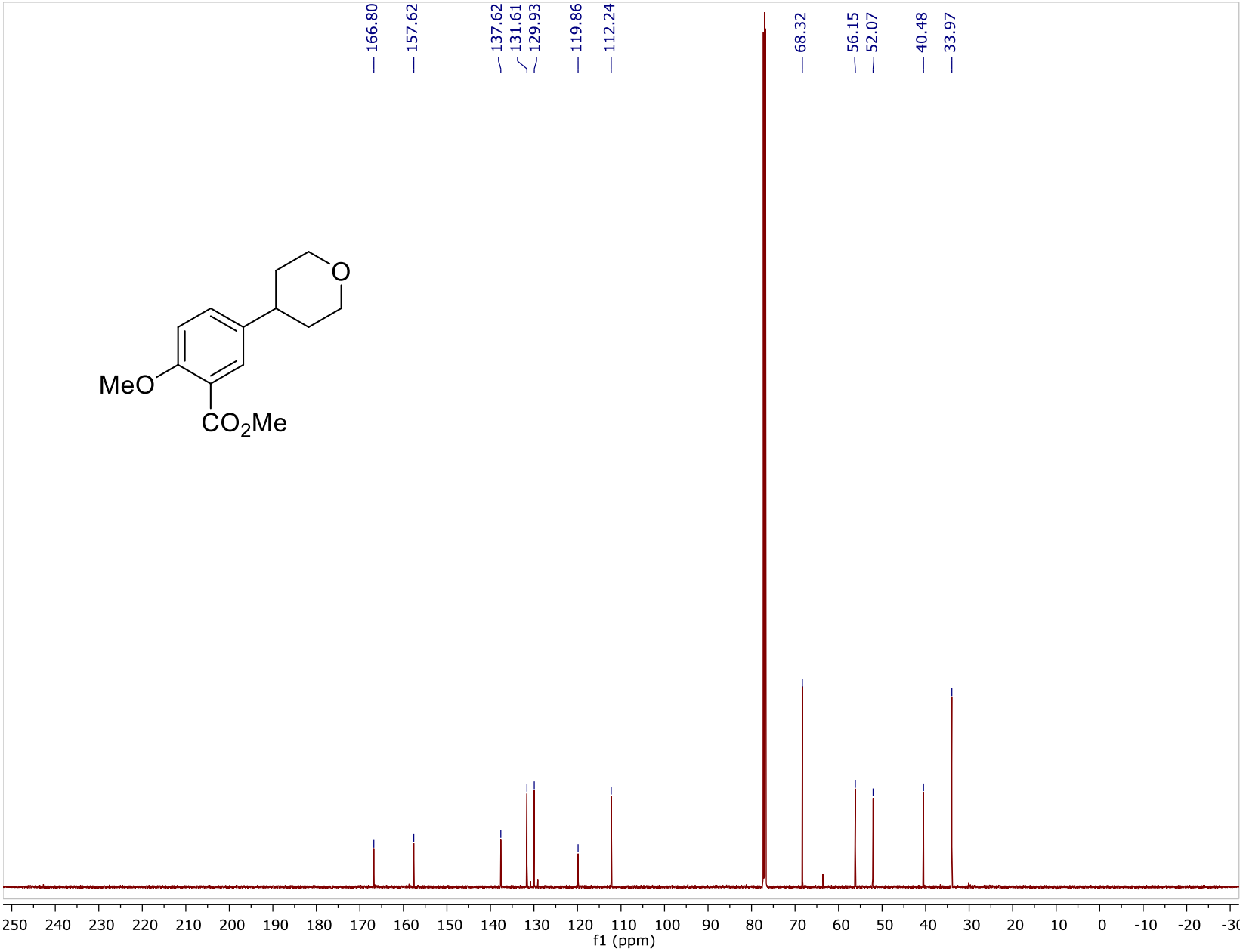
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CO2Me
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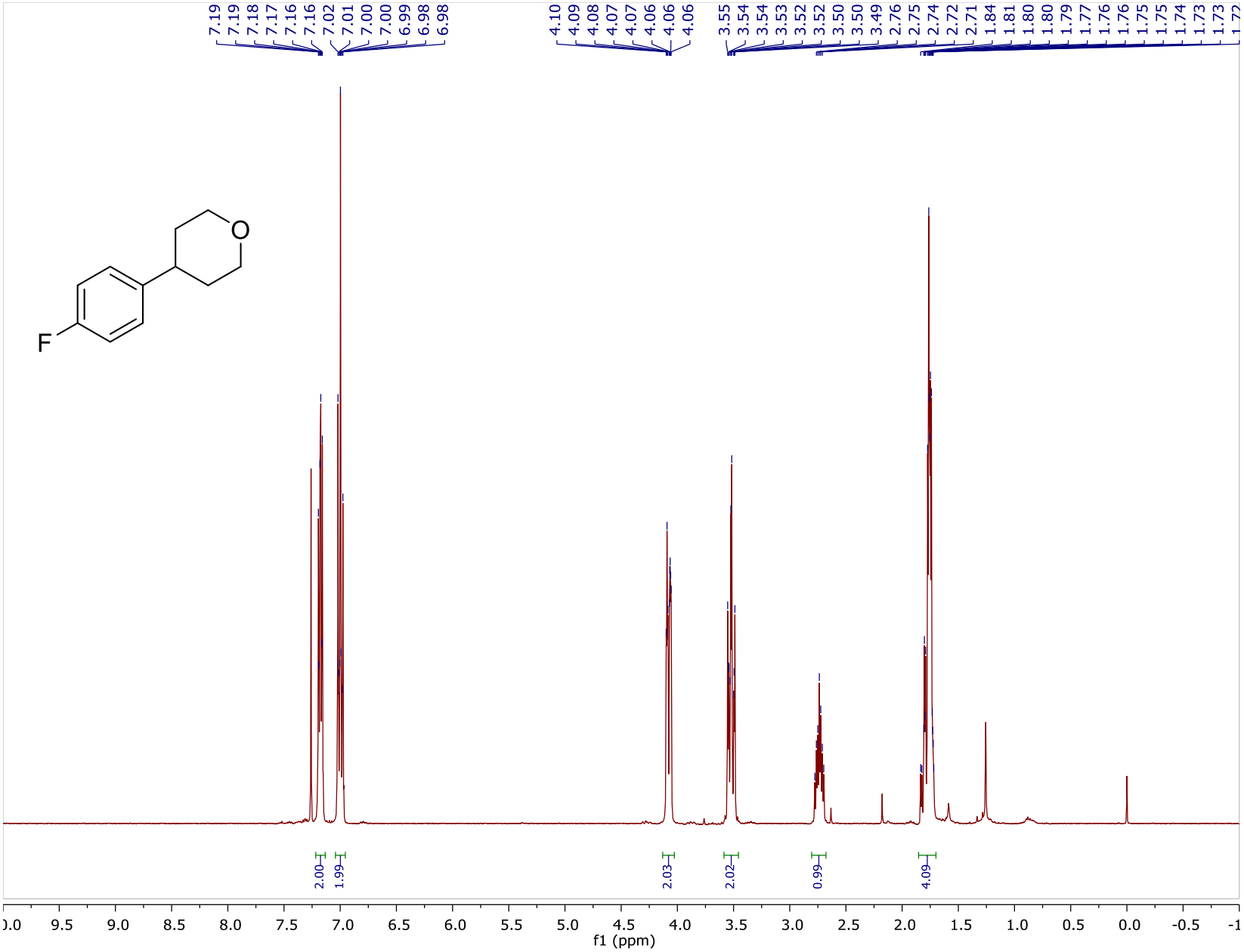
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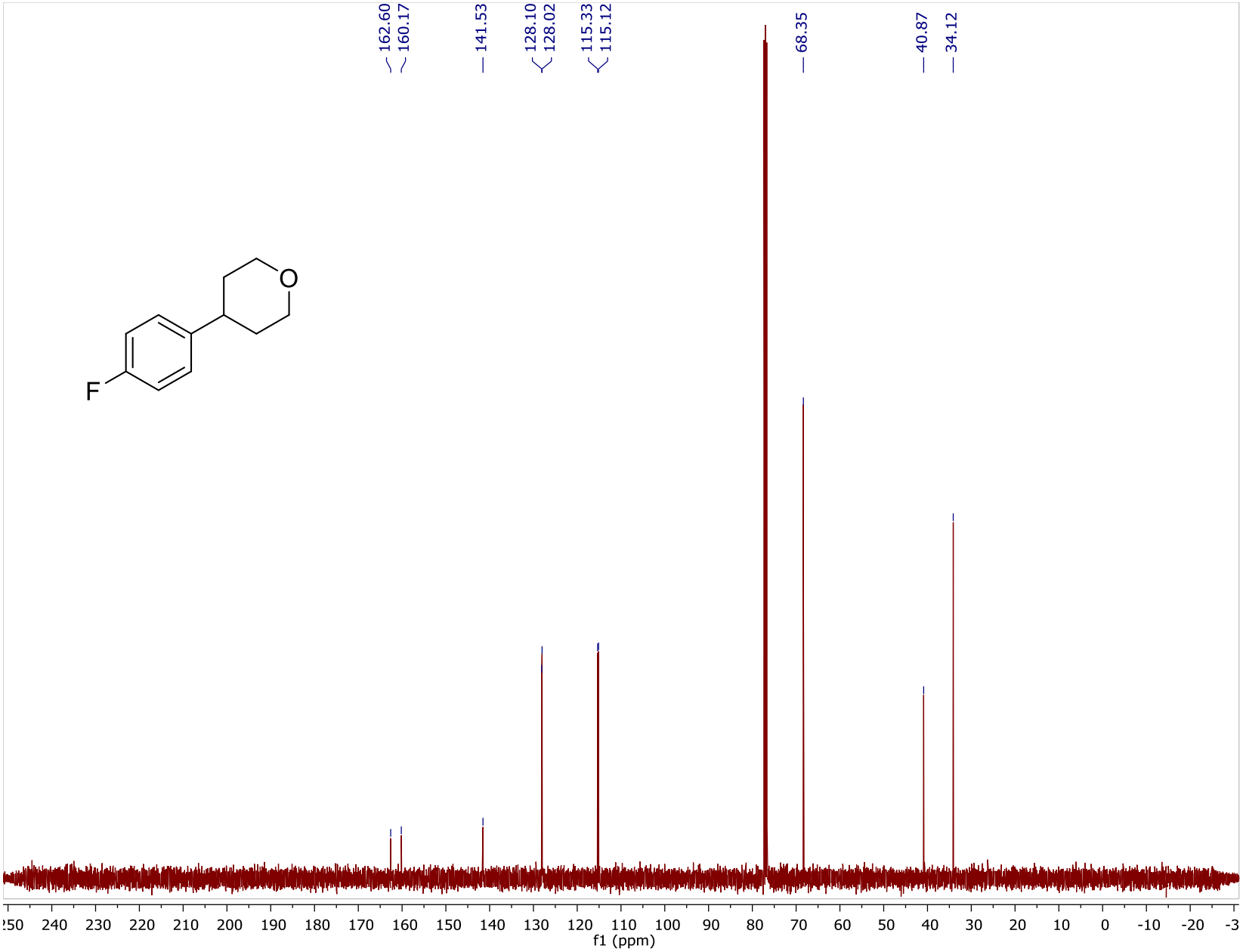
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F
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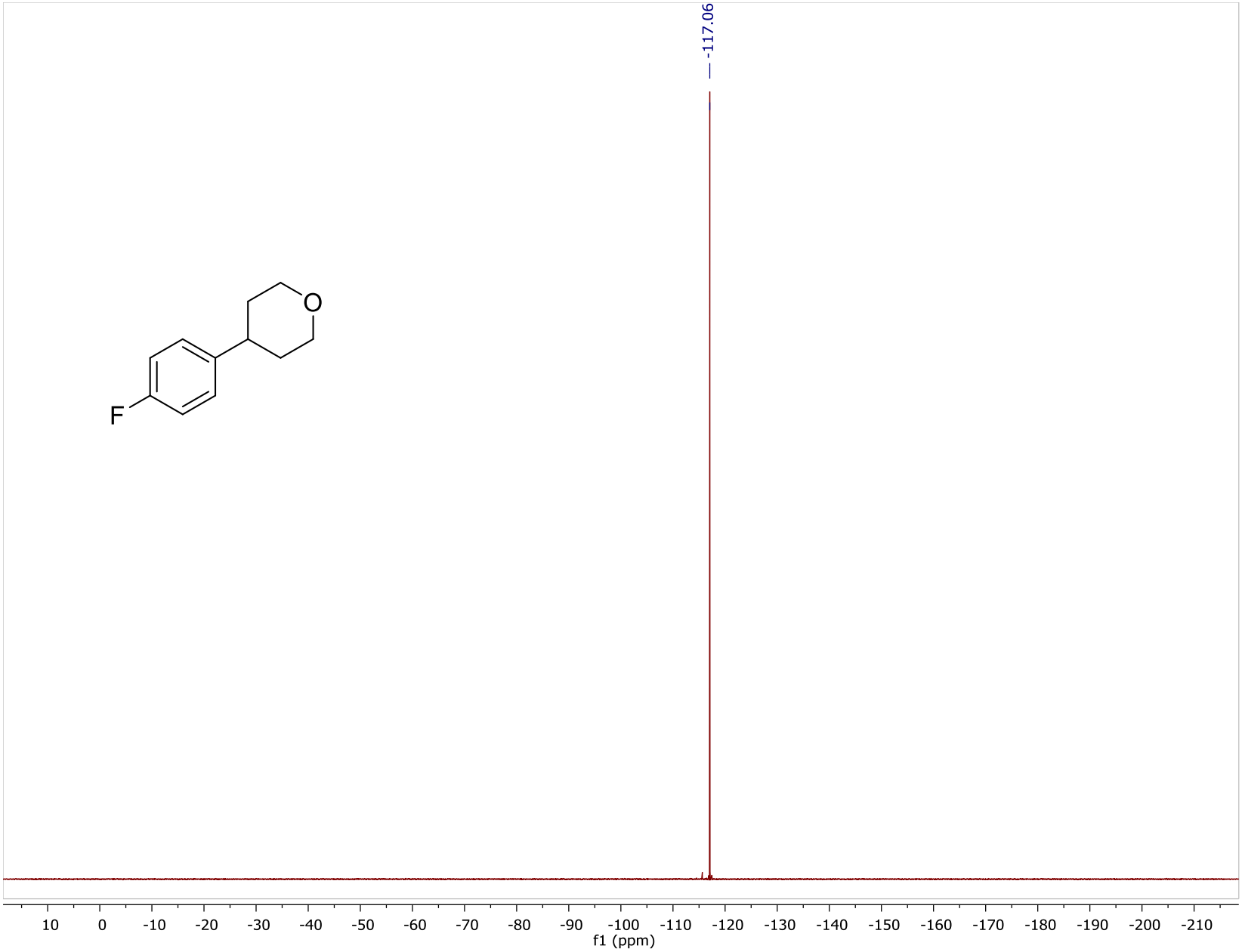
f1 (ppm)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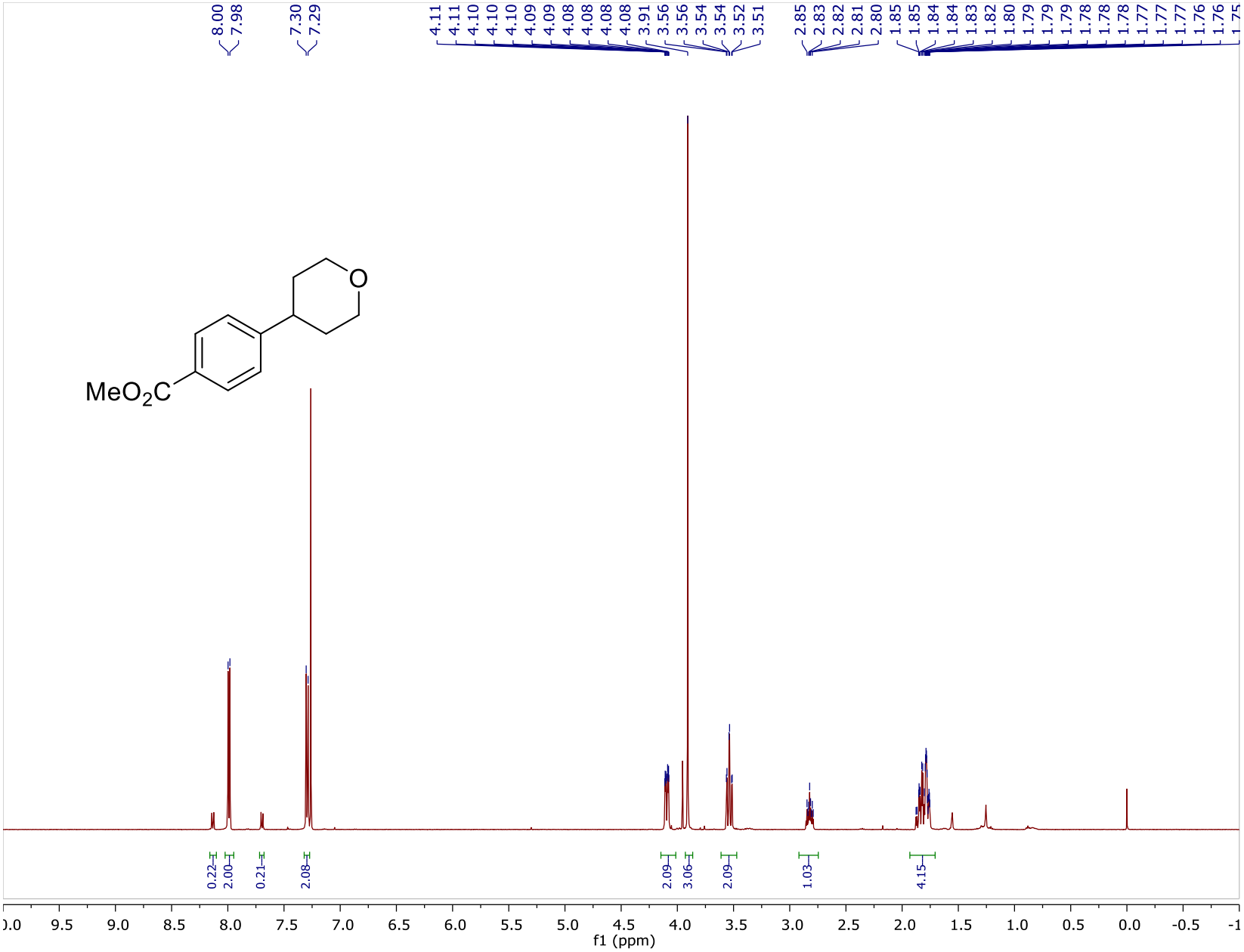
-210
f1 (ppm)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1.76
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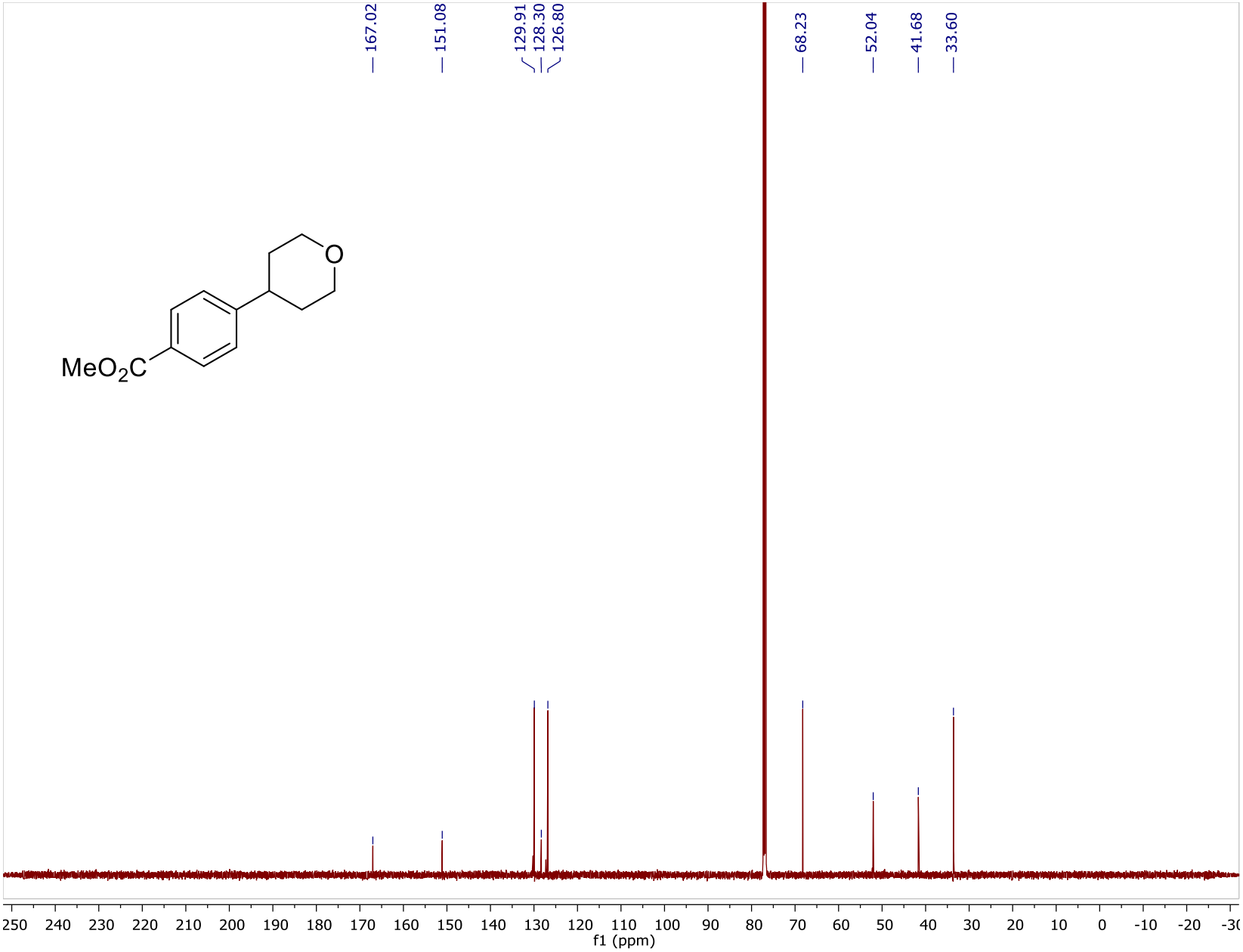
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33.60
O
MeO2C
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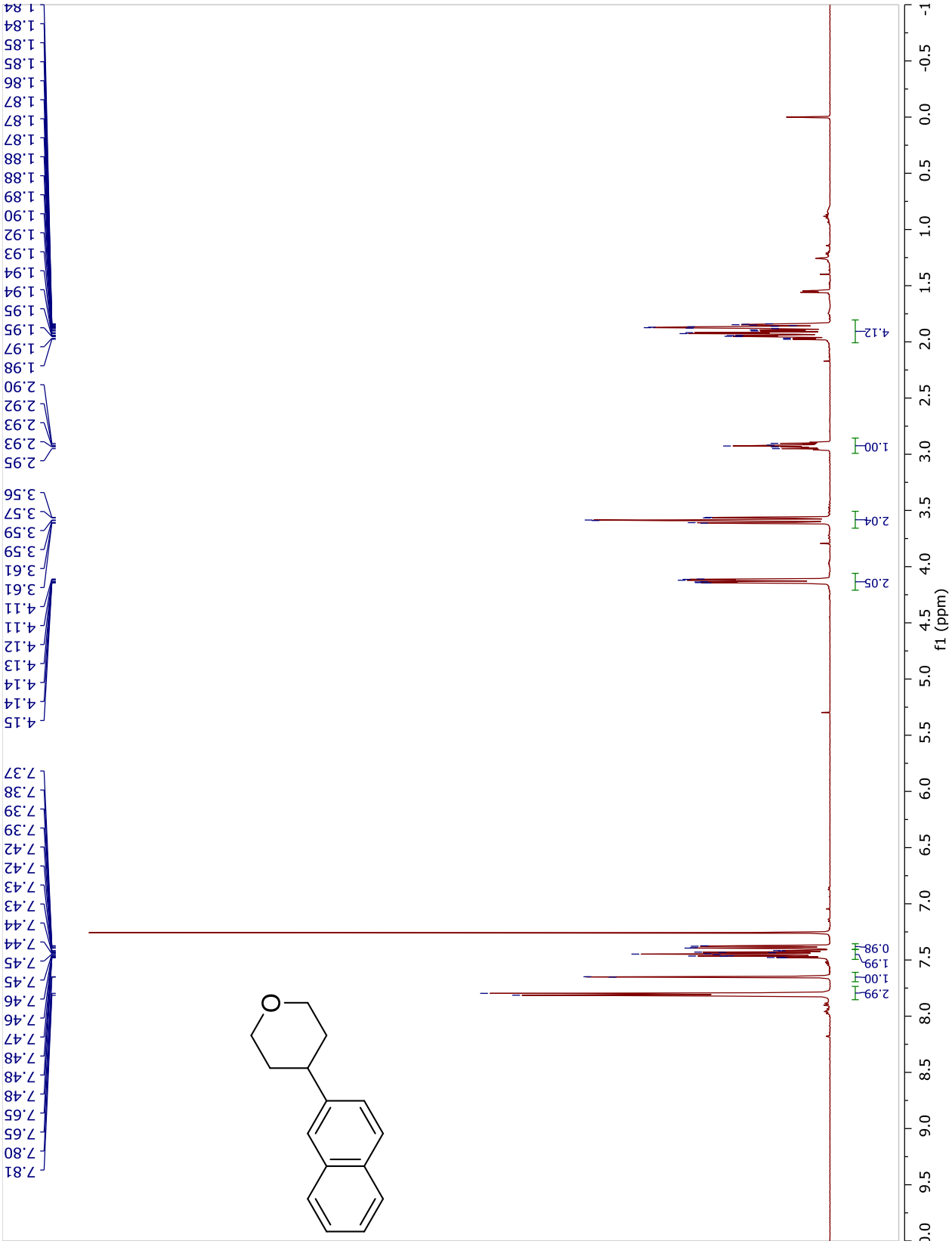
f1 (ppm)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2.05
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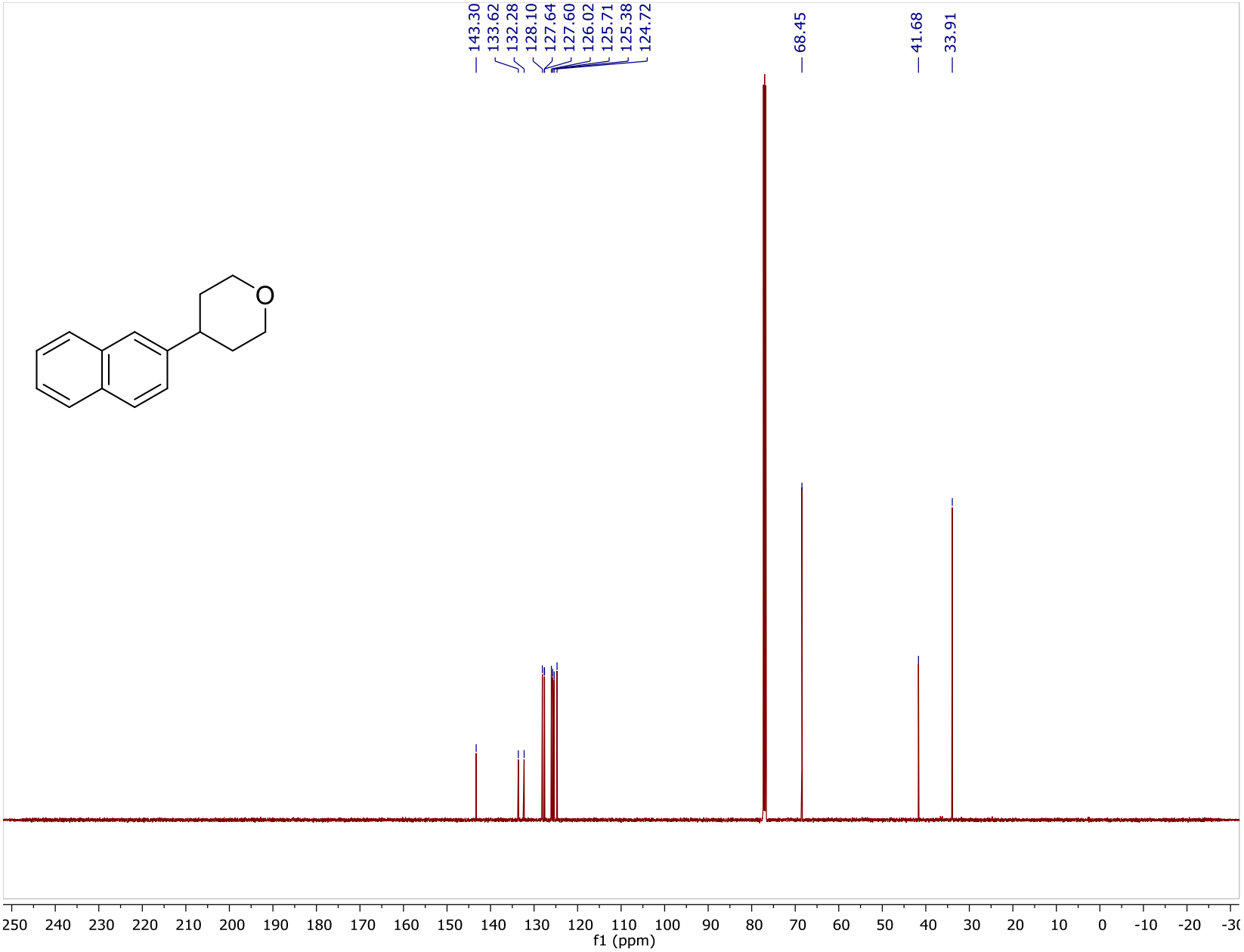
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125.71
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124.72
68.45
41.68
33.91
O
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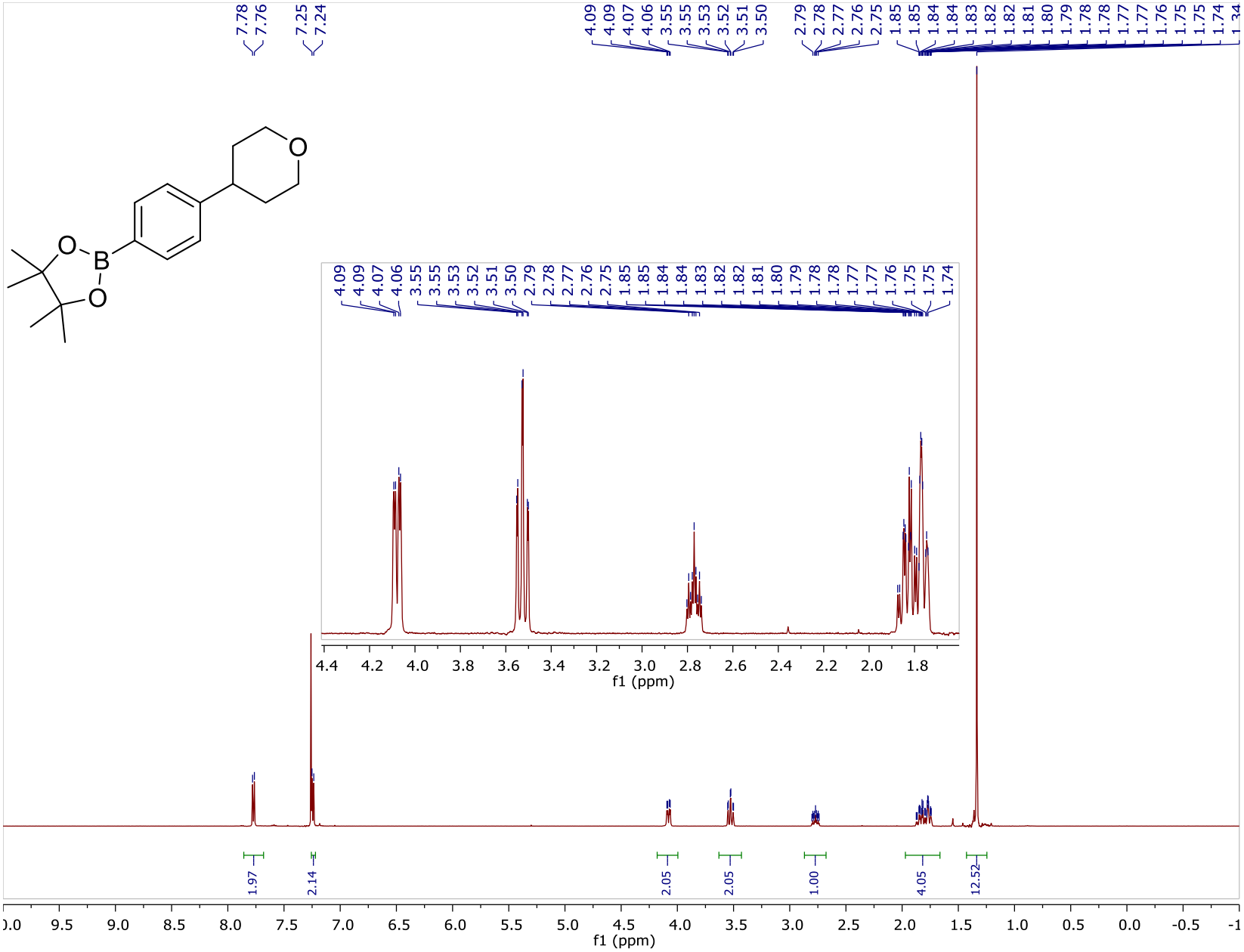
f1 (ppm)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O
B
O
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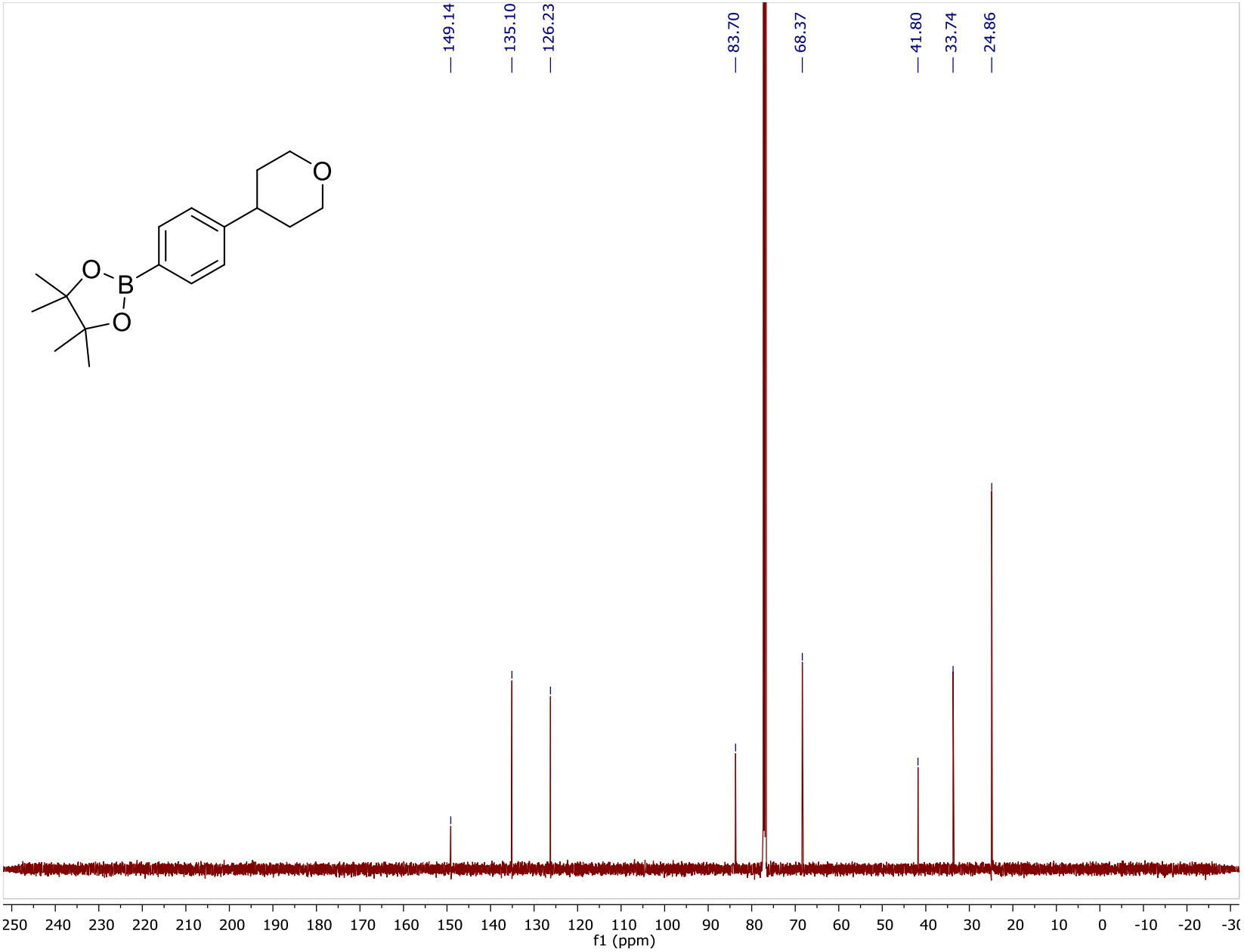
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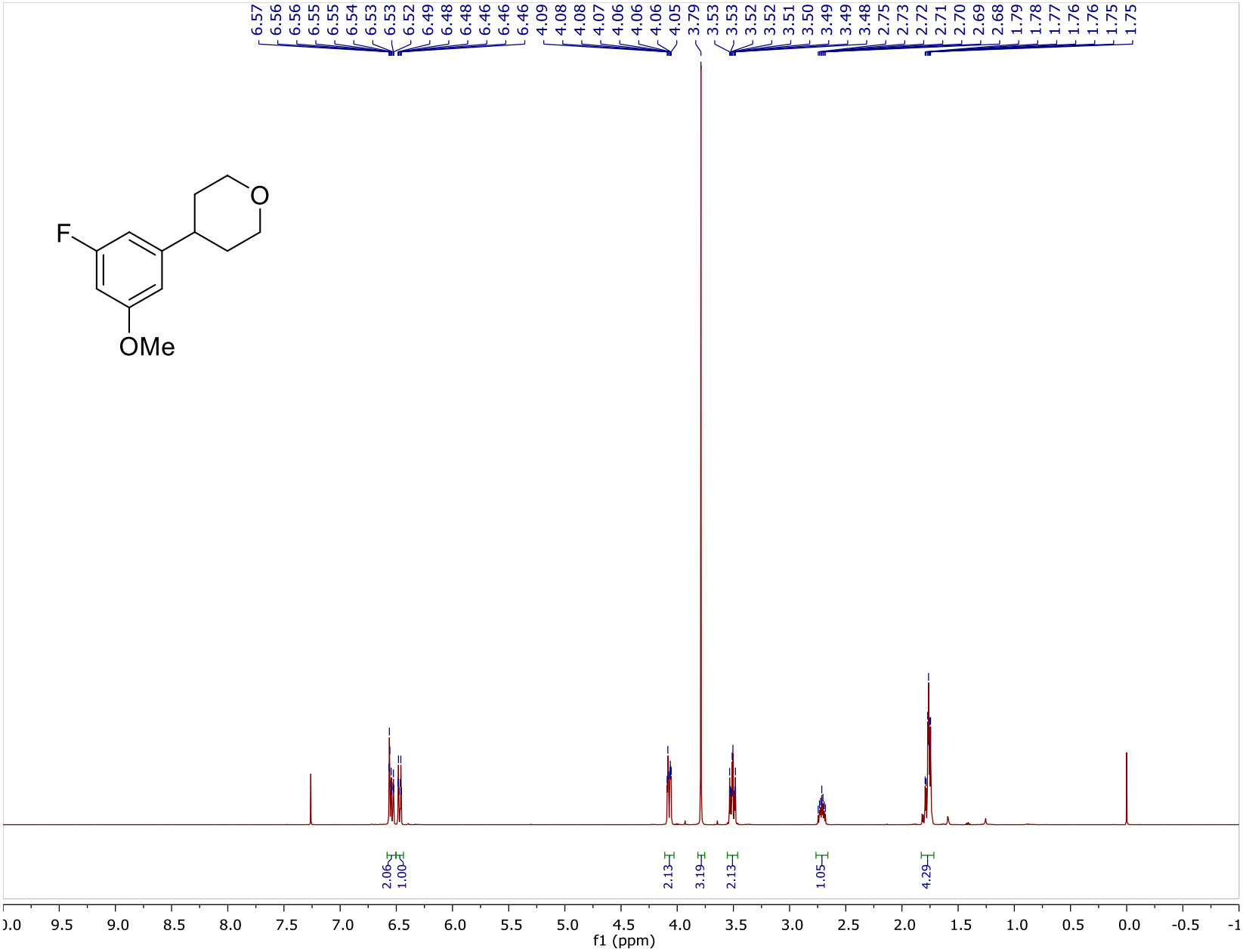
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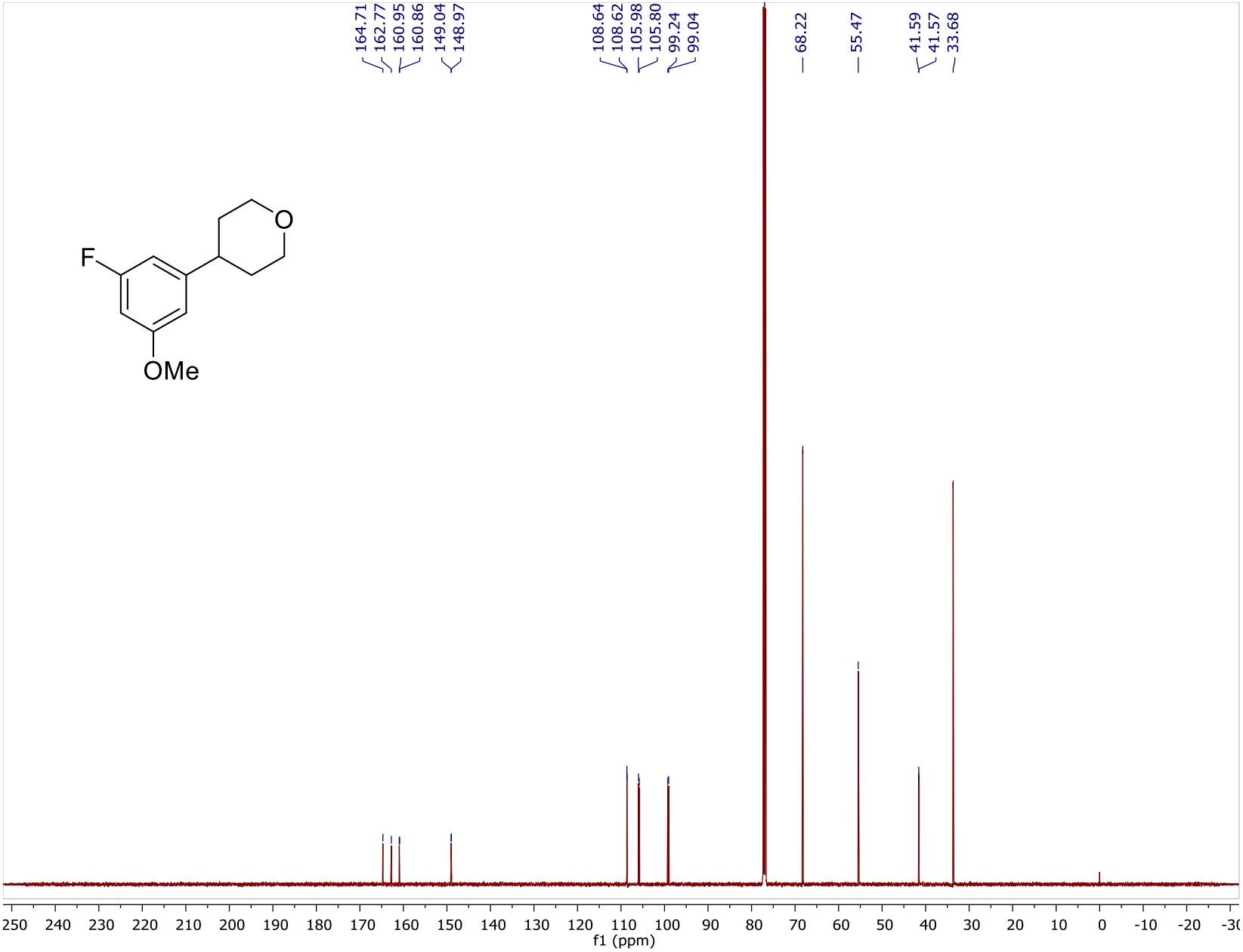
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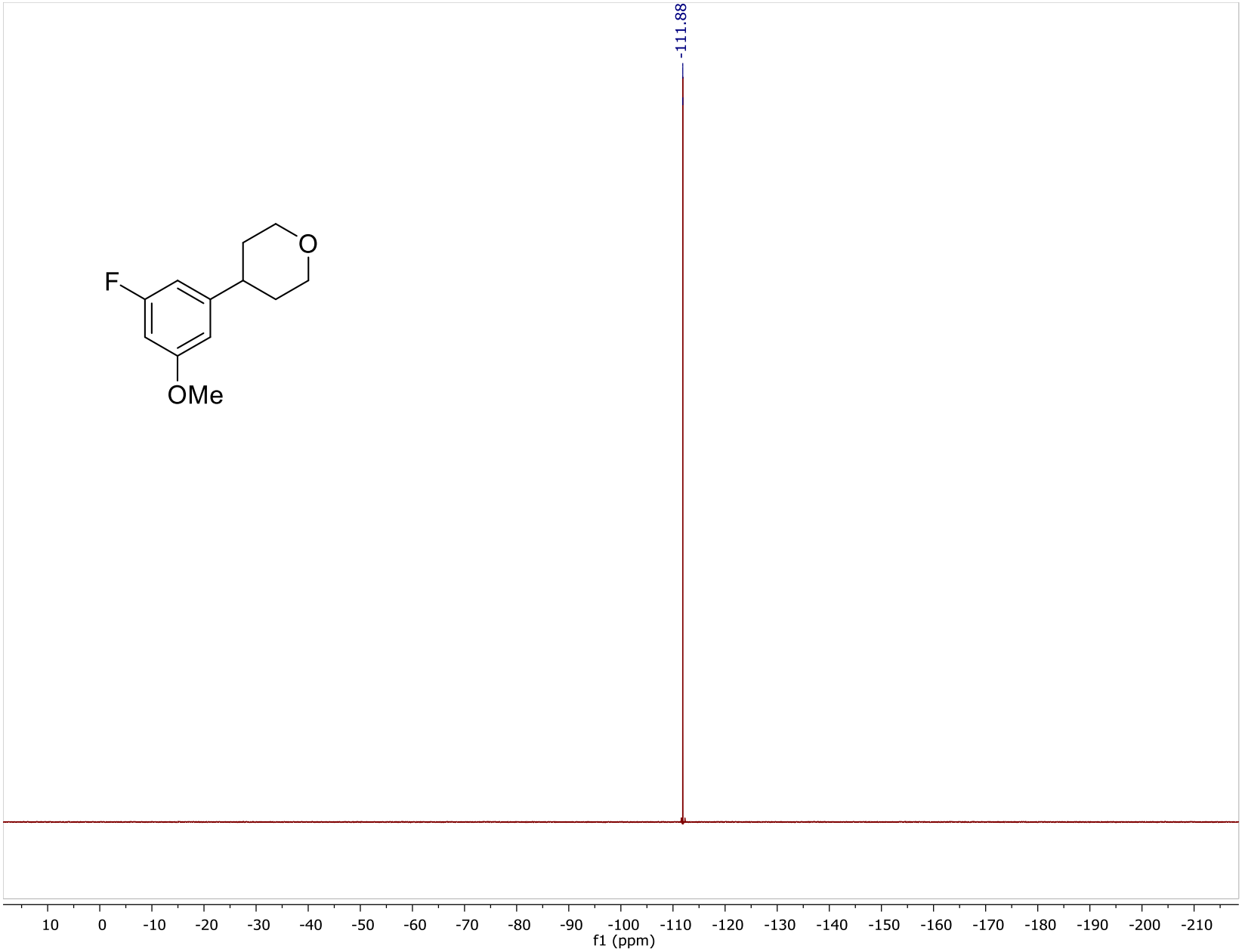
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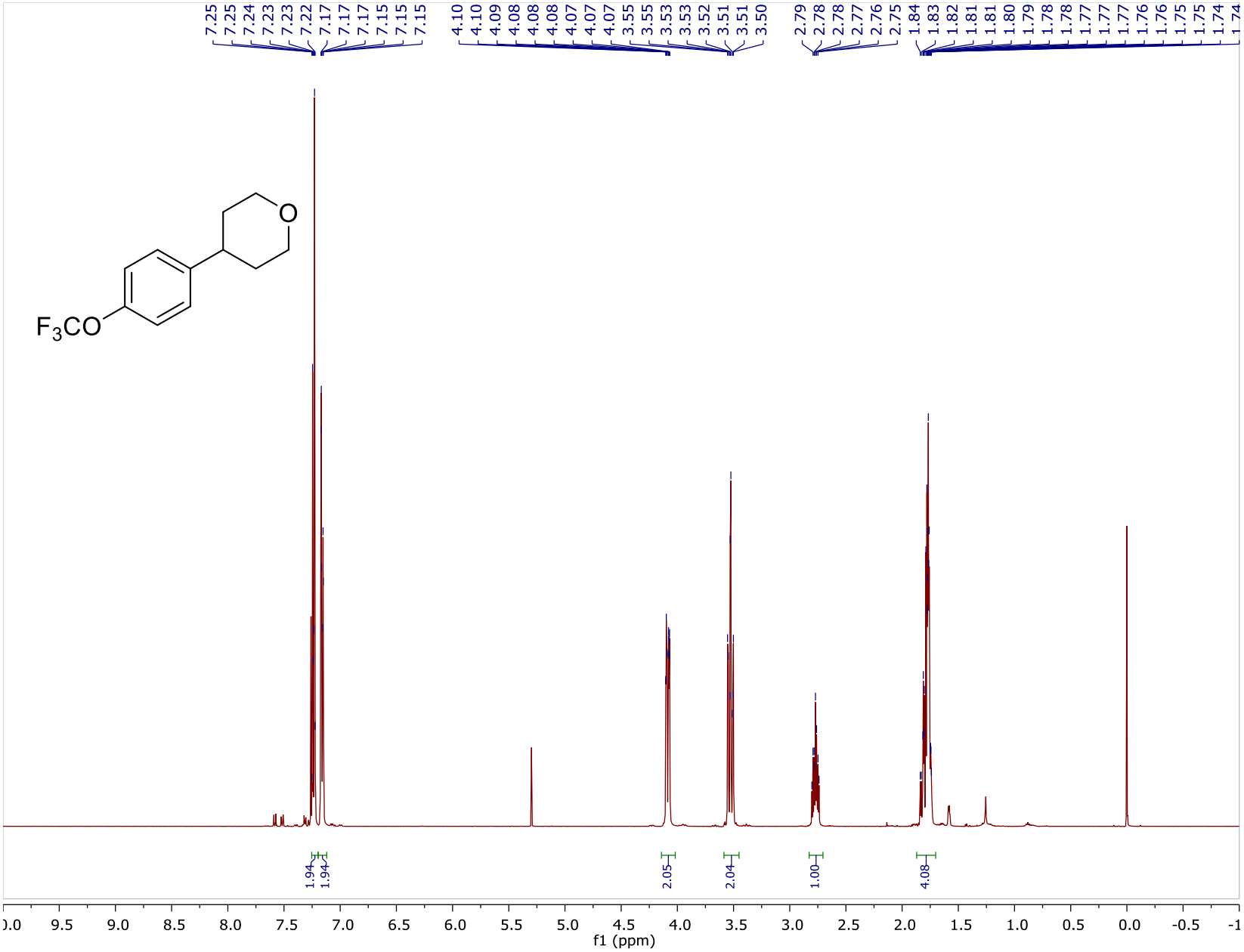
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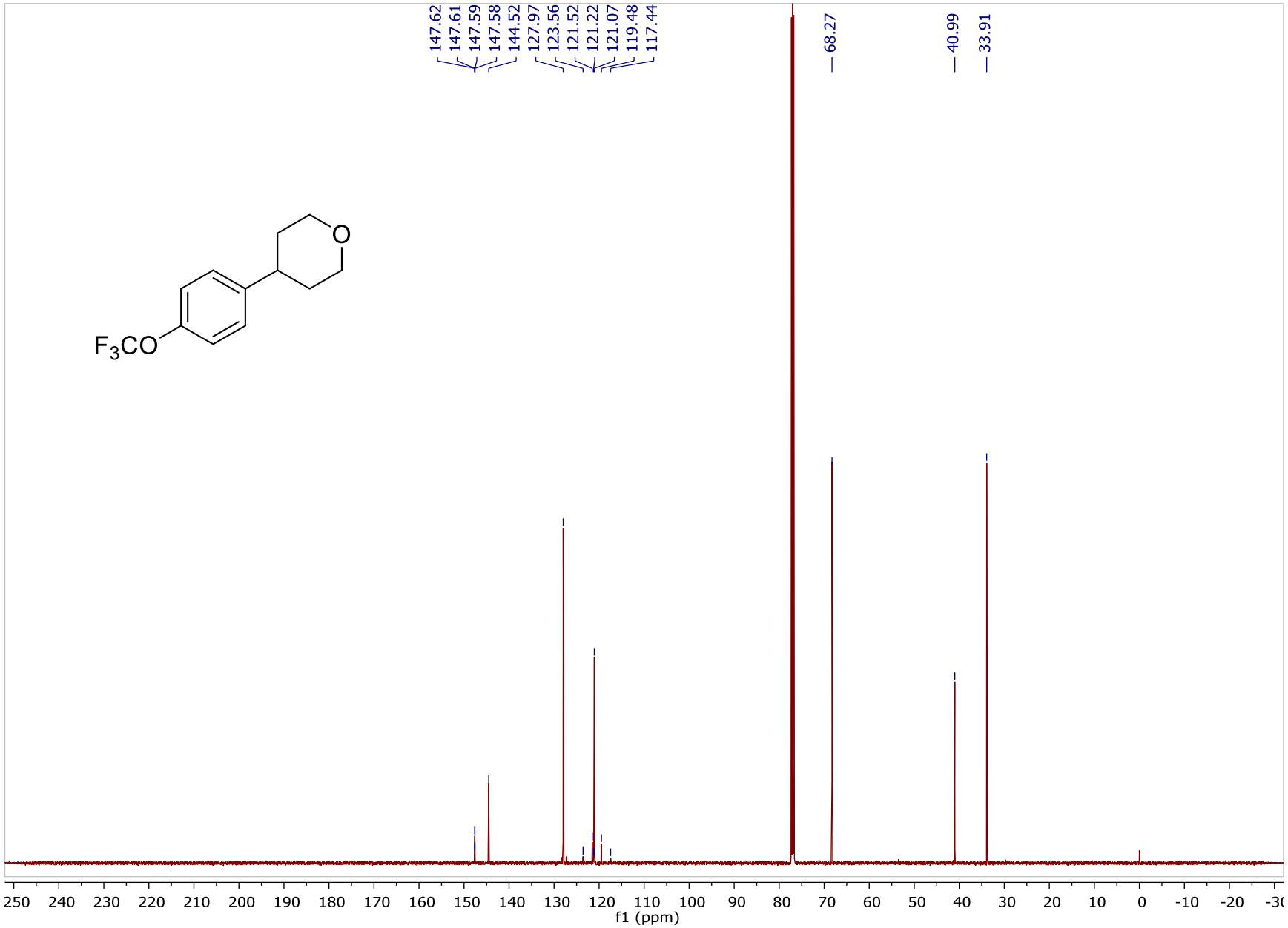
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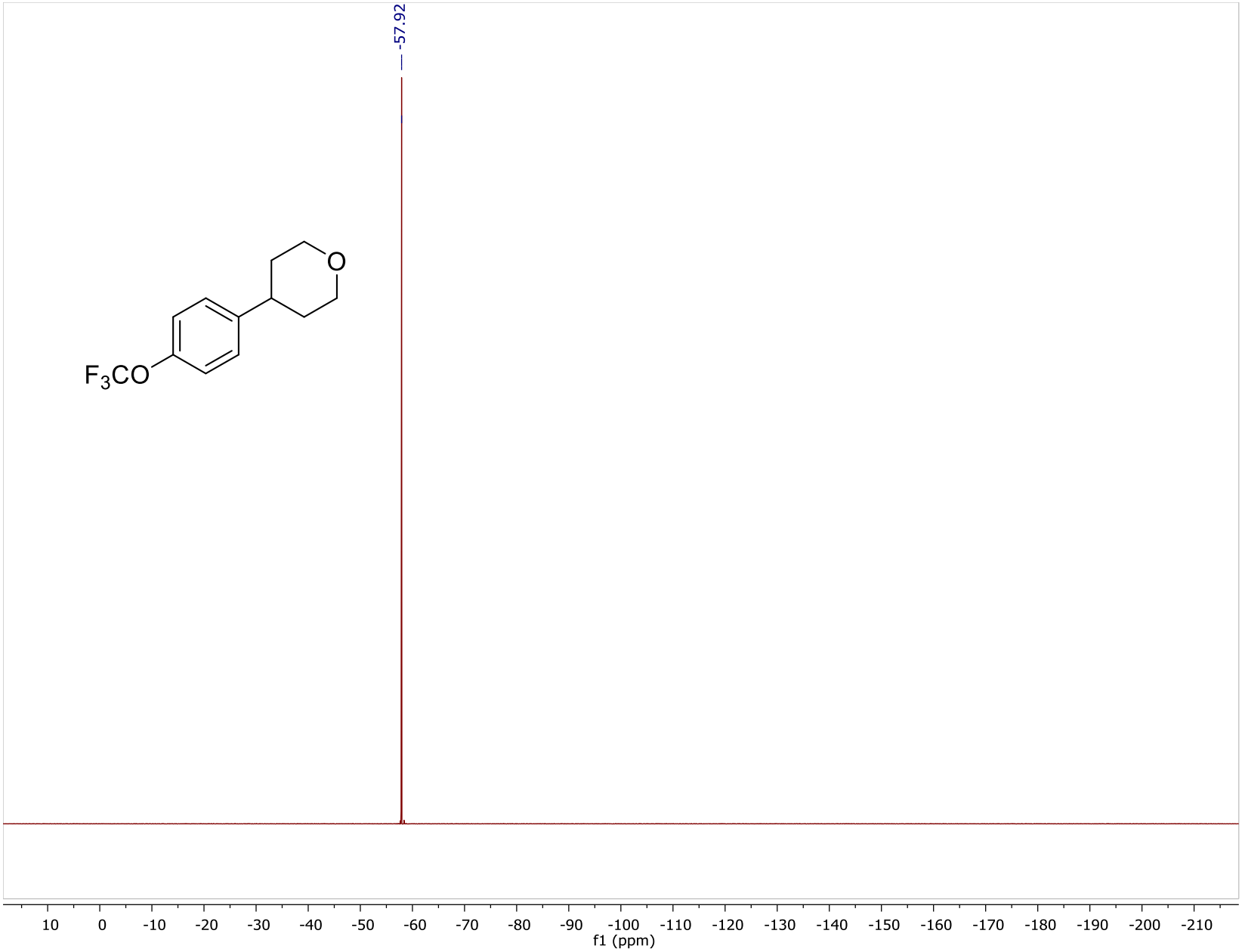
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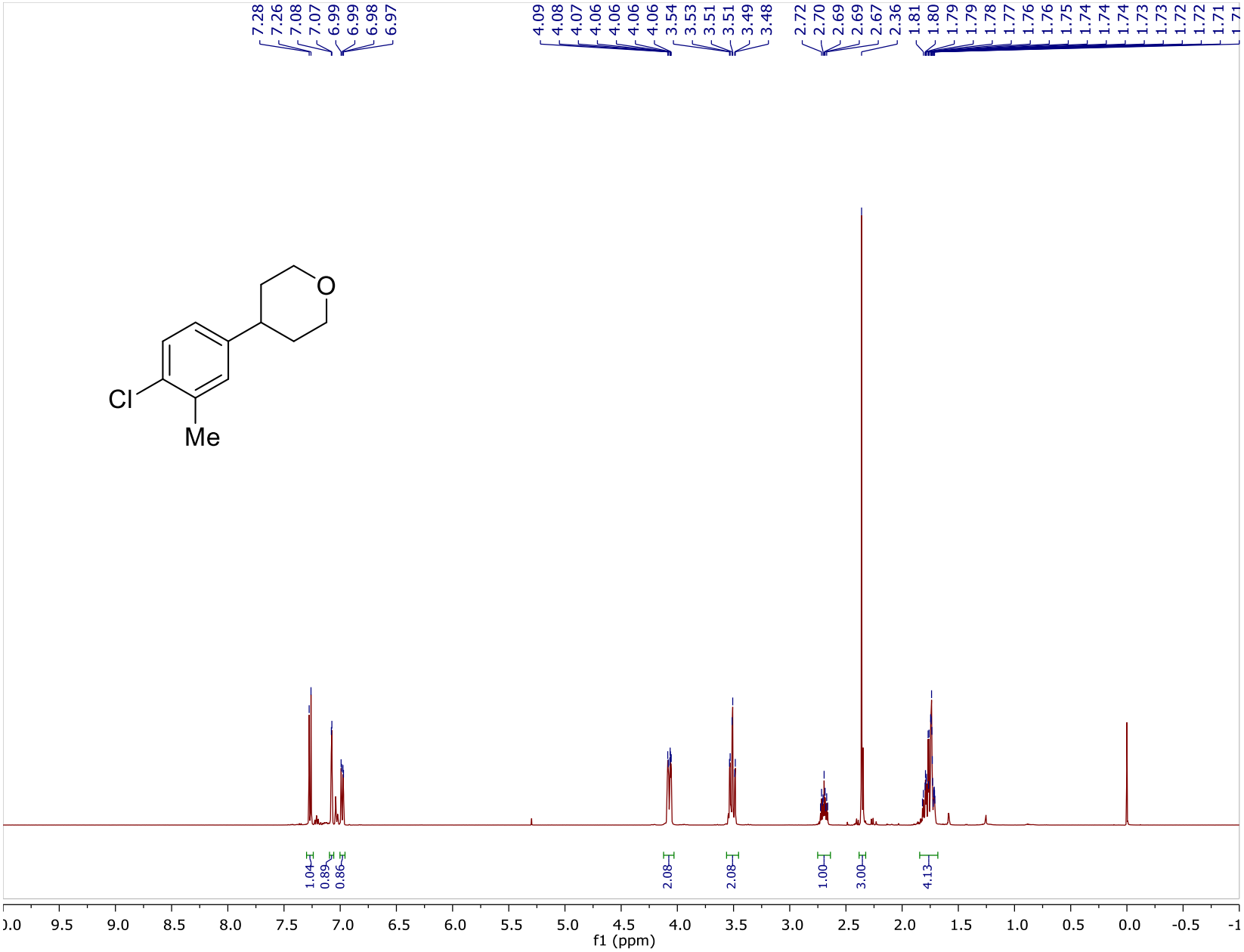
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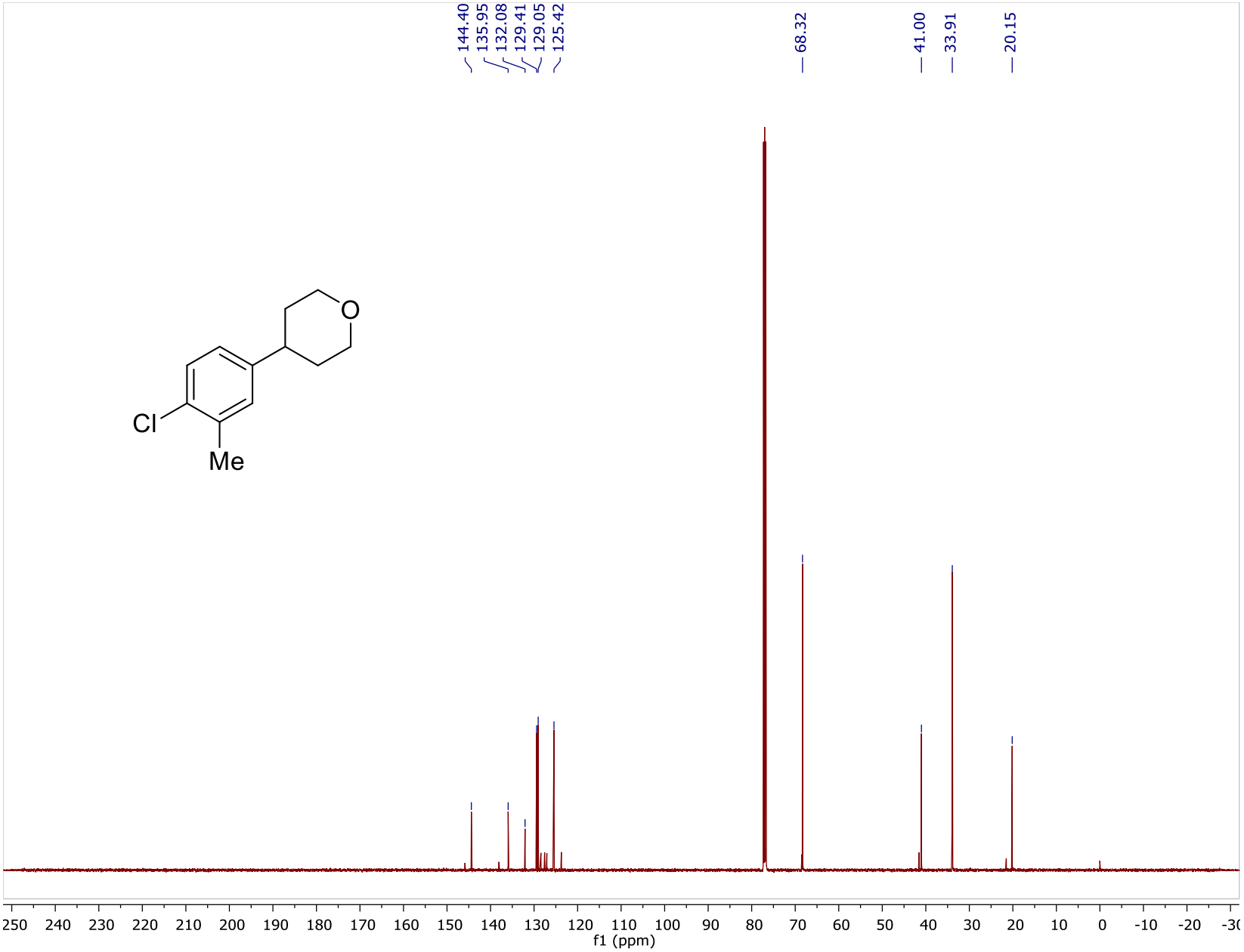
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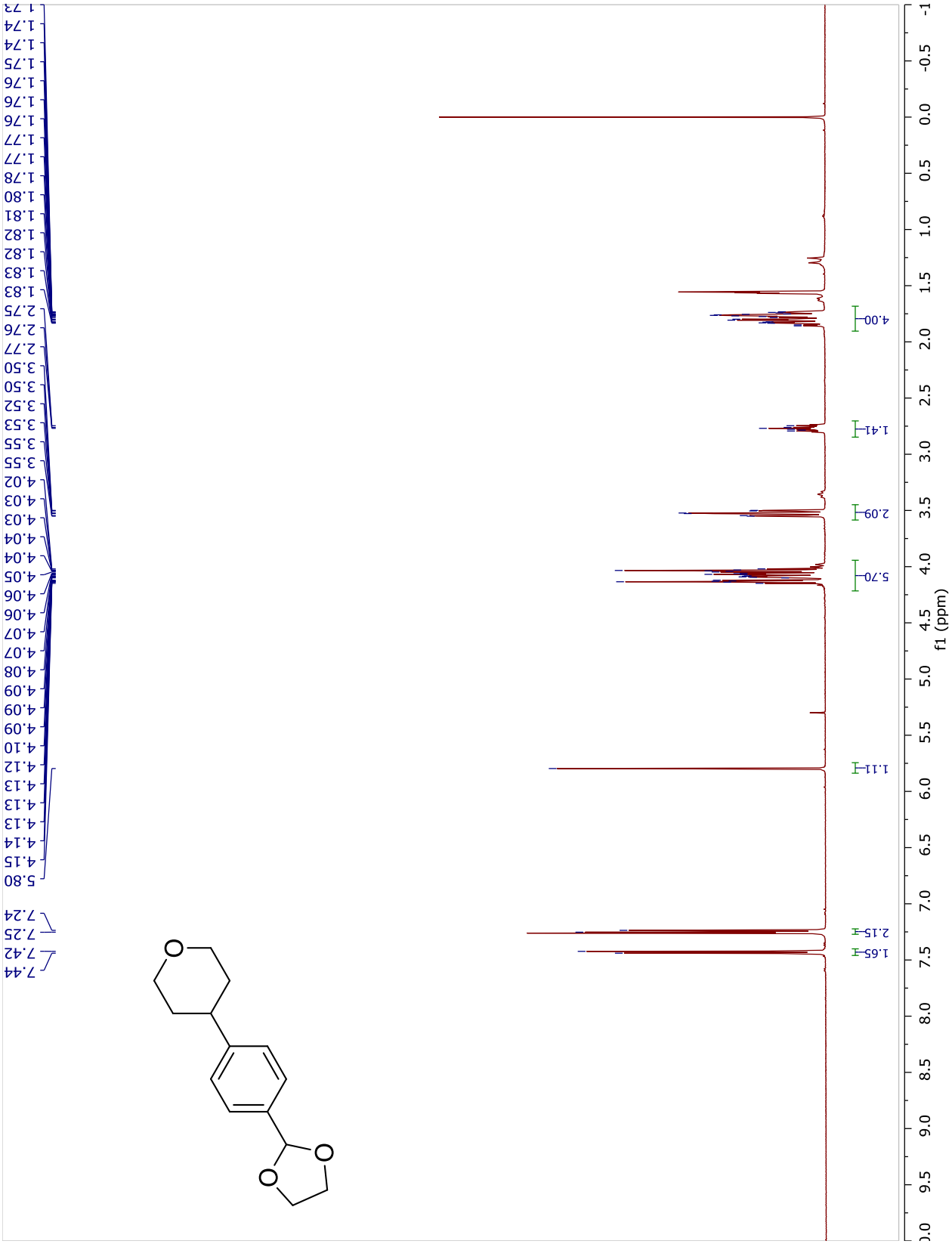
f1 (ppm)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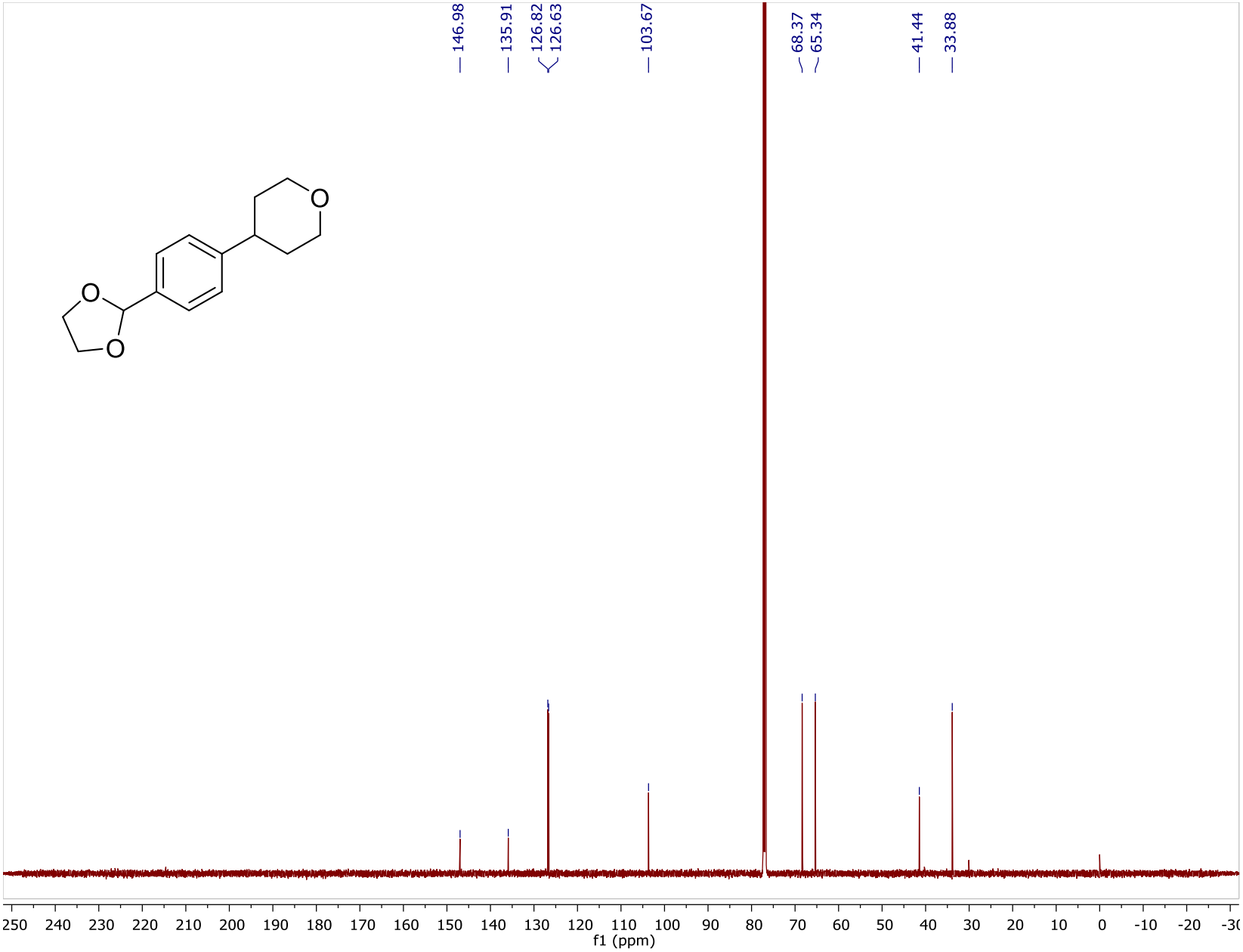
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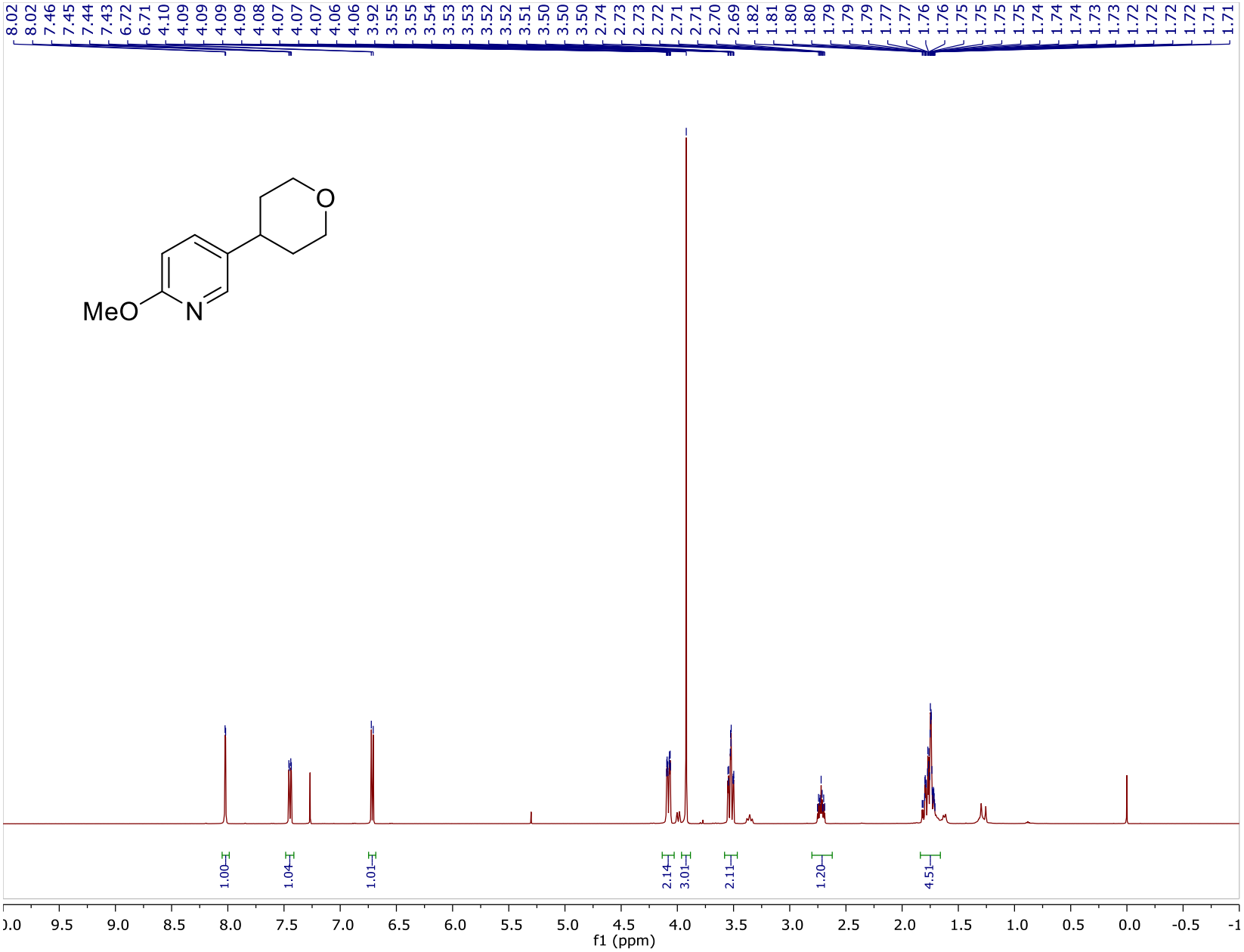
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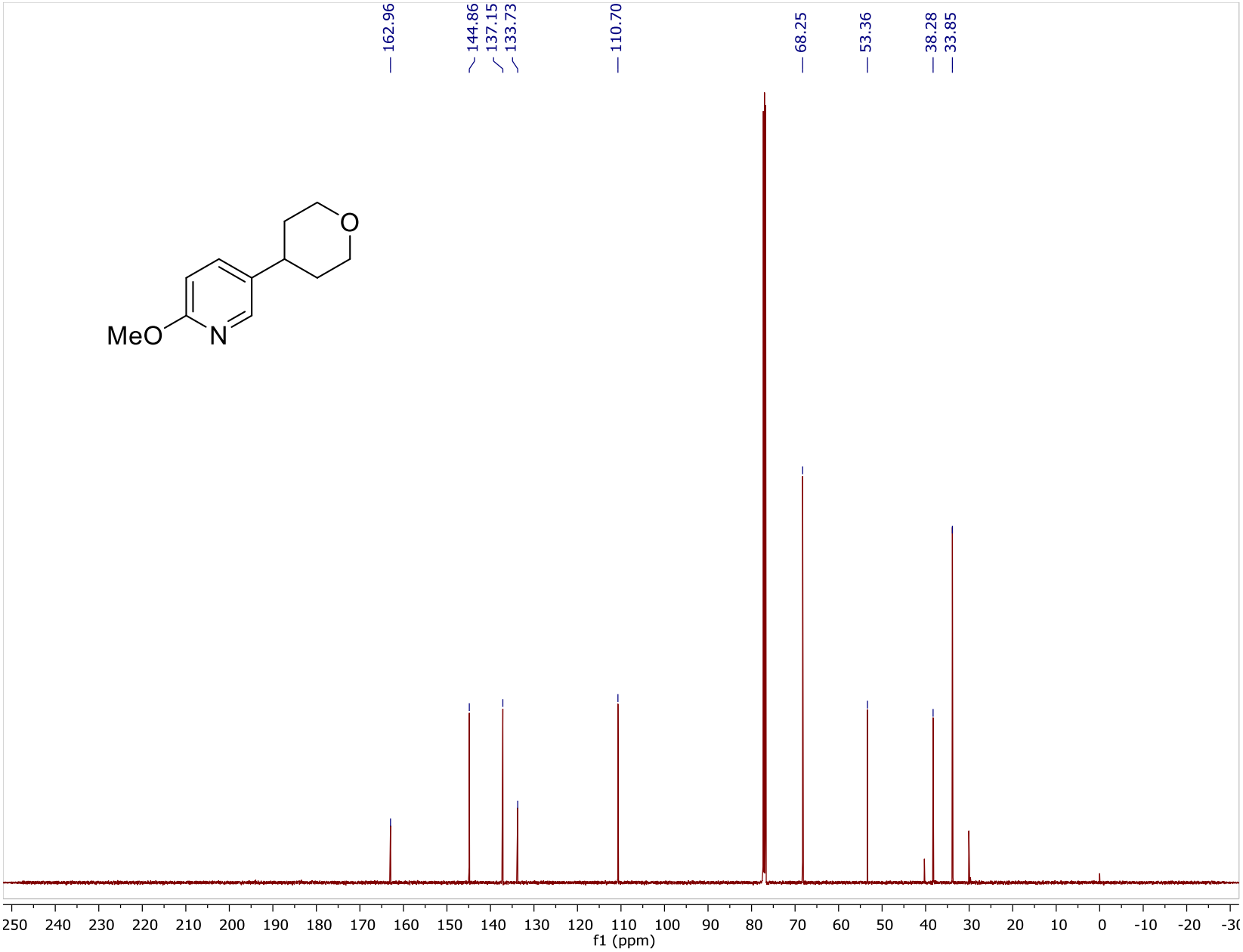
4.51
f1 (ppm)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f1 (ppm)

3.5. References

1. Littke, A. F.; Dai, C.; Fu, G. C., Versatile catalysts for the Suzuki cross-coupling of arylboronic acids with aryl and vinyl halides and triflates under mild conditions. *J. Am. Chem. Soc.* **2000,** *122* (17), 4020 - 4028.
2. Lemhadri, M.; Doucet, H.; Santelli, M., Suzuki coupling of cyclopropylboronic acid with aryl halides catalyzed by a palladium-tetraphosphine complex. *Synth. Commun.* **2006,** *36* (1), 121 - 128.
3. Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A., Efficient cross-coupling of secondary alkyltrifluoroborates with aryl chlorides-reaction discovery using parallel microscale experimentation. *J. Am. Chem. Soc.* **2008,** *130* (29), 9257 - 9259.
4. Molander, G. A.; Gormisky, P. E., Cross-coupling of cyclopropyl- and cyclobutyltrifluoroborates with aryl and heteroaryl chlorides. *J. Org. Chem.* **2008,** *73* (19), 7481 - 7485.
5. Sandrock, D. L.; Jean-Gerard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A., Stereospecific cross-coupling of secondary alkyl beta- trifluoroboratoamides. *J. Am. Chem. Soc.* **2010,** *132* (48), 17108 - 17110.
6. Molander, G. A.; Wisniewski, S. R., Stereospecific cross-coupling of secondary organotrifluoroborates: Potassium 1-(benzyloxy)alkyltrifluoroborates. *J. Am. Chem. Soc.* **2012,** *134* (40), 16856 - 16868.
7. Molander, G. A.; Wisniewski, S. R.; Hosseini-Sarvaria, M., Synthesis and Suzuki-Miyaura cross-coupling of enantioenriched secondary potassium beta-trifluoroboratoamides: Catalytic, asymmetric conjugate addition of bisboronic acid and tetrakis(dimethylamino)diboron to alpha,beta- unsaturated carbonyl compounds. *Adv. Synth. Catal.* **2013,** *355* (14-15), 3037 - 3057.
8. Knapp, D. M.; Gillis, E. P.; Burke, M. D., A general solution for unstable boronic acids: Slow-release cross-coupling from air-stable MIDA boronates. *J. Am. Chem. Soc.* **2009,** *131*, 6961 - 6963.
9. Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R., Stereospecific Pd-catalyzed cross-coupling reactions of secondary alkylboron nucleophiles and aryl chlorides. *J. Am. Chem. Soc.* **2014,** *136* (40), 14027 - 14030.
10. Zhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. R., Enantiodivergent Pd-catalyzed C–C bond formation enabled through ligand parameterization. *Science* **2018,** *362* (6415), 670-674.
11. Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E., Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2004,** *126* (12), 3686 - 3687.
12. Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E., Iron-catalyzed chemoselective cross-coupling of primary and secondary alkyl halides with arylzinc reagents. *Synlett* **2005,** (11), 1794 - 1798.
13. Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M., Cross-Coupling of Non-activated Chloroalkanes with Aryl Grignard Reagents in the Presence of Iron/N-Heterocyclic Carbene Catalysts. *Org. Lett.* **2012,** *14* (4), 1066-1069.
14. Li, Z.; Sun, H.-M.; Shen, Q., Iron-mediated inter- and intramolecular reductive cross-coupling of unactivated alkyl chlorides with aryl bromides. *Org. Biomol. Chem.* **2016,** *14* (12), 3314-3321.

15. Adak, L.; Kawamura, S.; Toma, G.; Takenaka, T.; Isozaki, K.; Takaya, H.; Orita, A.; Li, H. C.; Shing, T. K. M.; Nakamura, M., Synthesis of Aryl C-Glycosides via Iron-Catalyzed Cross Coupling of Halosugars: Stereoselective Anomeric Arylation of Glycosyl Radicals. *J. Am. Chem. Soc.* **2017,** *139* (31), 10693 - 10701.
16. Gonzalez-Bobes, F.; Fu, G. C., Amino alcohols as ligands for nickel-catalyzed Suzuki reactions of unactivated alkyl halides, including secondary alkyl chlorides, with arylboronic acids. *J. Am. Chem. Soc.* **2006,** *128* (16), 5360 - 5361.
17. Molander, G. A.; Argintaru, O. A.; Aron, I.; Dreher, S. D., Nickel-catalyzed cross-coupling of potassium aryl- and heteroaryltrifluoroborates with unactivated alkyl halides. *Org. Lett.* **2010,** *12* (24), 5783 - 5785.
18. Pal, S.; Chowdhury, S.; Rozwadowski, E.; Auffrant, A.; Gosmini, C., Cobalt-Catalyzed Reductive Cross-Coupling Between Benzyl Chlorides and Aryl Halides. *Adv. Synth. Catal.* **2016,** *358* (15), 2431-2435.
19. Durandetti, M.; Nédélec, J.-Y.; Périchon, J., Nickel-Catalyzed Direct Electrochemical Cross-Coupling between Aryl Halides and Activated Alkyl Halides. *J. Org. Chem.* **1996,** *61* (5), 1748-1755.
20. Zhang, J.; Lu, G.; Xu, J.; Sun, H.; Shen, Q., Nickel-Catalyzed Reductive Cross-Coupling of Benzyl Chlorides with Aryl Chlorides/Fluorides: A One-Pot Synthesis of Diarylmethanes. *Org. Lett.* **2016,** *18* (12), 2860-2863.
21. Zhang, Q.; Wang, X.; Qian, Q.; Gong, H., Nickel-Catalyzed Reductive Cross-Coupling of Benzyl Halides with Aryl Halides. *Synthesis* **2016,** *48* (17), 2829-2836.
22. Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E., Nickel-Catalyzed Asymmetric Reductive Cross-Coupling To Access 1,1-Diarylalkanes. *J. Am. Chem. Soc.* **2017,** *139* (16), 5684-5687.
23. Durandetti, M.; Gosmini, C.; Perichon, J., Ni-catalyzed activation of alpha-chloroesters: a simple method for the synthesis of alpha-arylesters and beta-hydroxyesters. *Tetrahedron* **2007,** *63* (5), 1146 - 1153.
24. Conan, A.; Sibille, S.; d'Incan, E.; Périchon, J., Nickel-catalysed electroreductive coupling of α-halogenoesters with aryl or vinyl halides. *J. Chem. Soc., Chem. Commun.* **1990,** (1), 48-49.
25. Durandetti, M.; Sibille, S.; Nédélec, J.-Y.; Périchon, J., A Novel Method of Arylation of α-Chloroketones. *Synth. Commun.* **1994,** *24* (2), 145-151.
26. Kadunce, N. T.; Reisman, S. E., Nickel-Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles. *J. Am. Chem. Soc.* **2015,** *137* (33), 10480-10483.
27. Wang, X.; Wang, S.; Xue, W.; Gong, H., Nickel-Catalyzed Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2015,** *137* (36), 11562-11565.
28. Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H., Ni-Catalyzed Reductive Coupling of Electron-Rich Aryl Iodides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2018,** *140* (43), 14490-14497.
29. Zhang, Z.; Xu, L. J.; Chen, Z. K.; Liu, Z. B.; Miao, M. Z.; Song, J. Y.; Ren, H. J., Nickel-Catalyzed Regioselective Reductive Cross-Coupling of Aryl Halides with Polysubstituted Allyl Halides in the Presence of Imidazolium Salts. *Synlett* **2015,** *26* (20), 2784-2788.

30. Chen, B.-Z.; Zhi, M.-L.; Wang, C.-X.; Chu, X.-Q.; Shen, Z.-L.; Loh, T.-P., Synthesis of Alkyl Indium Reagents by Using Unactivated Alkyl Chlorides and Their Applications in Palladium-Catalyzed Cross-Coupling Reactions with Aryl Halides. *Org. Lett.* **2018,** *20* (7), 1902-1905.
31. Melzig, L.; Dennenwaldt, T.; Gavryushin, A.; Knochel, P., Direct aminoalkylation of arenes, heteroarenes, and alkenes via Ni-catalyzed Negishi cross-coupling reactions. *J. Org. Chem.* **2011,** *76* (21), 8891 - 8906.
32. Melzig, L.; Gavryushin, A.; Knochel, P., Direct Aminoalkylation of Arenes and Hetarenes via Ni-Catalyzed Negishi Cross-Coupling Reactions. *Org. Lett.* **2007,** *9* (26), 5529-5532.
33. Huo, S., Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents from Unactivated Alkyl Bromides and Chlorides. *Org. Lett.* **2003,** *5* (4), 423-425.
34. Barluenga, J.; Montserrat, J. M.; Flórez, J., Direct coupling between β-functionalized organolithium compounds and aryl and vinyl halides. *Tetrahedron Lett.* **1992,** *33* (41), 6183-6186.
35. Barluenga, J.; Montserrat, J. M.; Florez, J., Direct coupling of functionalized organolithium compounds with aryl and vinyl halides. *J. Org. Chem.* **1993,** *58* (22), 5976-5980.
36. Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A., Domino Iron Catalysis: Direct Aryl–Alkyl Cross-Coupling. *Angew. Chem. Int. Ed.* **2009,** *48* (3), 607-610.
37. Johnson, K. A.; Biswas, S.; Weix, D. J., Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides. *Chem. Eur. J.* **2016,** *22* (22), 7399-7402.
38. Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A., Ligand Redox Effects in the Synthesis, Electronic Structure, and Reactivity of an Alkyl−Alkyl Cross-Coupling Catalyst. *J. Am. Chem. Soc.* **2006,** *128* (40), 13175-13183.
39. Budnikova, Y.; Vicic, D.; Klein, A., Exploring Mechanisms in Ni Terpyridine Catalyzed C–C Cross-Coupling Reactions—A Review. *Inorganics* **2018,** *6* (1), 18.
40. Prinsell, M. R.; Everson, D. A.; Weix, D. J., Nickel-catalyzed, sodium iodide-promoted reductive dimerization of alkyl halides, alkyl pseudohalides, and allylic acetates. *Chem. Commun.* **2010,** *46* (31), 5743-5745.
41. Shrestha, R.; Weix, D. J., Reductive Conjugate Addition of Haloalkanes to Enones To Form Silyl Enol Ethers. *Org. Lett.* **2011,** *13* (10), 2766-2769.
42. Huihui, K. M.; Shrestha, R.; Weix, D. J., Nickel-Catalyzed Reductive Conjugate Addition of Primary Alkyl Bromides to Enones To Form Silyl Enol Ethers. *Org. Lett.* **2017,** *19* (2), 340-343.
43. Anka-Lufford, L. L.; Prinsell, M. R.; Weix, D. J., Selective Cross-Coupling of Organic Halides with Allylic Acetates. *J. Org. Chem.* **2012,** *77* (22), 9989-10000.
44. Loginova, K. A.; Knyazev, V. D., Kinetics of the Self Reaction of Cyclohexyl Radicals. *J. Phys. Chem. A* **2011,** *115* (31), 8616-8622.
45. Freitas, J. E.; Jin Hwang, H.; Ticknor, A. B.; El-Sayed, M. A., The structure of the cyclohexyl radical from state-selective photofragment translational spectroscopy of the axial and equatorial conformers of iodocyclohexane. *Chem. Phys. Lett.* **1991,** *183* (3), 165-170.

46. Currie, J.; Sidebottom, H.; Tedder, J., The reaction of cyclohexyl radicals with carbon tetrachloride. *Int. J. Chem. Kinet.* **1974,** *6* (4), 481-492.
47. Biswas, S.; Weix, D. J., Mechanism and selectivity in nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides. *J. Am. Chem. Soc.* **2013,** *135* (43), 16192-16197.
48. Zhao, Y.; Weix, D. J., Nickel-catalyzed regiodivergent opening of epoxides with aryl halides: co-catalysis controls regioselectivity. *J. Am. Chem. Soc.* **2014,** *136* (1), 48-51.
49. Zhao, Y.; Weix, D. J., Enantioselective Cross-Coupling of meso-Epoxides with Aryl Halides. *J. Am. Chem. Soc.* **2015,** *137* (9), 3237-3240.
50. Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J., Cobalt co-catalysis for cross-electrophile coupling: diarylmethanes from benzyl mesylates and aryl halides. *Chem. Sci.* **2015,** *6* (2), 1115-1119.
51. Petriček, S.; Demšar, A., Syntheses and crystal structures of manganese, nickel and zinc chloride complexes with dimethoxyethane and di(2-methoxyethyl) ether. *Polyhedron* **2010,** *29* (18), 3329-3334.
52. Zhang, J.; Wang, H.; Ma, Y.; Wang, Y.; Zhou, Z.; Tang, C., CaF2 catalyzed SN2 type chlorodehydroxylation of chiral secondary alcohols with thionyl chloride: a practical and convenient approach for the preparation of optically active chloroalkanes. *Tetrahedron Lett.* **2013,** *54* (18), 2261-2263.
53. Zhang, P.; Le, C. C.; MacMillan, D. W. C., Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2016,** *138* (26), 8084-8087.
54. Hofmayer, M. S.; Hammann, J. M.; Haas, D.; Knochel, P., Cobalt-Catalyzed C(sp2)–C(sp3) Cross-Coupling Reactions of Diarylmanganese Reagents with Secondary Alkyl Iodides. *Org. Lett.* **2016,** *18* (24), 6456-6459.
55. Knauber, T.; Chandrasekaran, R.; Tucker, J. W.; Chen, J. M.; Reese, M.; Rankic, D. A.; Sach, N.; Helal, C., Ru/Ni Dual Catalytic Desulfinative Photoredox Csp2–Csp3 Cross-Coupling of Alkyl Sulfinate Salts and Aryl Halides. *Org. Lett.* **2017,** *19* (24), 6566-6569.

Chapter 4: Efforts Towards the Total Synthesis of (±)-Recifeiolide

4.1. Introduction

Macrocycles, especially macrocyclic peptides, are gaining increased interest in medicinal chemistry and chemical biology due to their ability to target protein-protein interactions, their improved metabolic stability, and the balance of flexibility and rigidness that these molecules possess.[1-3] For these reasons, the development of methods for macrocyclization continues to be of significant importance. However, there are major challenges associated with ring-closing reactions of bifunctional molecules that do not exist for intermolecular bond-forming reactions.[4-5] For example, the concentration of the reaction can have substantial influence over the reaction selectivity for ring closing over intermolecular bond forming.[6] Nonetheless, many advances have been made in the synthesis of large cyclic systems.

4.1.1. Non-Transition Metal Catalyzed Macrocyclization

While any intermolecular reaction can be applied to cyclization, the earliest examples of macrocyclization reactions involve the formation of a carbonyl compound. In 1926, Ruzicka reported the formation of a cyclic ketones through the dehydration/decarboxylation of a dicarboxylic acid catalyzed by thorium oxide.[7] Since this discovery, there has been substantial work on the use of carboxylic acids for the synthesis of macrocycles. This was spurred by the fact that most macrocyclic natural products contained either an ester or an amide bond in the ring. Great efforts were directed towards the activation of the carboxylic acid towards macrolactonization (Figure 4.1).[8] The most notable (and synthetically applied) methods of this type are the Shiina macrolactonization,[9] the Yamaguchi macrolactonization,[10] and the Corey-Nicolaou macrolactonization.[11]

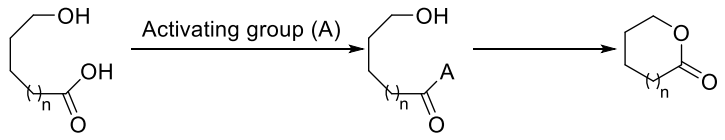


Figure 4.1. General strategy for macrolactonization.

Even with the advent of ring-closing olefin metathesis methods (see section 4.1.2.1), contemporary syntheses of various natural products still employ these methods for macrocyclization.[12] Macrolactamization has found significant utility in the synthesis of macrocyclic peptides, where amide bonds are abundant.[13-14] It has also found use in the synthesis of natural products,[15-17] and in some cases provides superior results compared to macrolactonization.[18-19]

4.1.2. Transition-Metal Catalyzed Macrocyclization

4.1.2.1. Ring Closing Olefin Metathesis

The earliest example of olefin metathesis being used for macrocyclization is a report from Villemin in 1980. They describe the synthesis of a precursor to Exaltolide, a 15-membered macrolide, and compare strategies for ring closure (Figure 4.2).[20] They reported the formation of the 15-membered ring in 60% yield using WCl_6 and $SnMe_4$ as catalyst. Tsuji also reported the synthesis of Civetone using a W/Ti system for ring closing olefin metathesis.[21]

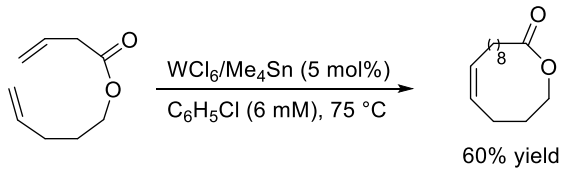


Figure 4.2. Synthesis of Exaltolide.

These initial reports generated an increasing interest in the use of olefin metathesis for the synthesis of macrocycles. However, certain challenges prevented the initial widespread use of ring closing metathesis in a synthetic environment; namely catalyst

availability, stability, and activity. These obstacles were overcome through the development of well-defined Mo and Ru-based catalyst that are bench stable, highly reactive, and commercially available.[22-26] The development of these catalysts, which was spearheaded by Grubbs, Hoveyda, and Schrock, has made ring closing metathesis one of the more reliable and accessible methods for the synthesis of macrocyclic olefins.[27] This reliability and accessibility has led to the application of ring closing metathesis in a numerous total syntheses.[28-30] One of the major challenges with ring closing olefin metathesis is the formation of oligomers rather than the desired macrocycle. While this challenge exists for all ring forming reactions, olefin metathesis differs in that the formed product can also participate in metathesis.[31-32] Conversely, the formed oligomers can also participate to form the desired cyclic compound.[33] This is usually addressed by lowering the reaction concentration, however the ring closing metathesis then competes with catalyst deactivation.[31] Recently, Grela and coworkers developed conditions that allow for ring-closing metathesis at high concentrations to synthesize macrocycles.[34] Key to this advance is the use of high molecular weight cyclization precursors and the removal of the desired product from the reaction via vacuum distillation (Figure 4.3).

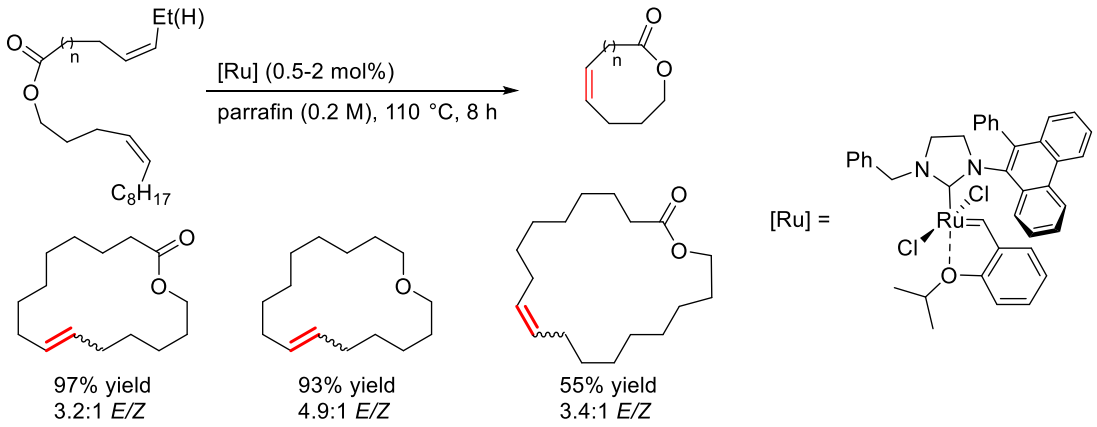


Figure 4.3. Olefin metathesis macrocyclization at high concentration

4.1.2.2. Intramolecular Cross-Coupling

For the formation of macrocyclic rings via cross-coupling, the Stille coupling has found extensive use.[35] Stille reported the intramolecular cyclization of esters containing a vinyl triflate and a vinyl stannane catalyzed by $Pd(PPh_3)_4$ (Figure 4.4, A).[36] This is one of the first examples of using palladium-catalyzed cross-coupling to synthesize large rings, and was followed by a number of reports that utilized the coupling of vinyl stannanes for macrocyclization.[37-39] Of particular note is the total synthesis of (+)-mycotrienol, which involves a double Stille coupling utilizing a bis-stannyl reagent (Figure 4.4, B).[40]

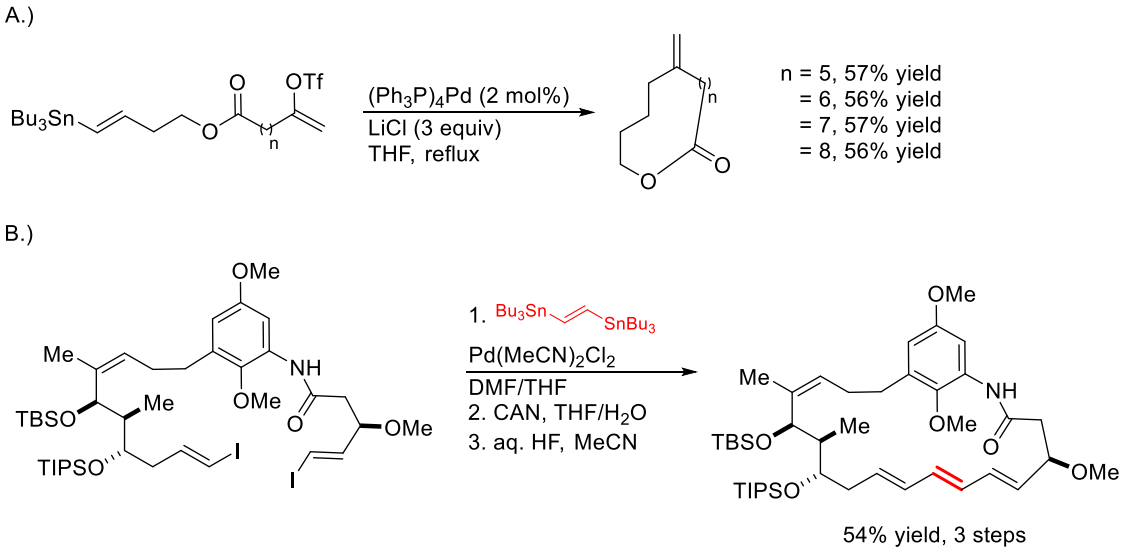


Figure 4.4. Intramolecular Stille coupling.

While these methods efficiently furnish the macrocycle, the organotin reagents present purification and toxicity concerns.[41] Therefore, the application of other palladium-catalyzed cross-coupling reactions to macrocyclization has gained increasing interest.[35] Nicolaou and coworkers evaluated the Stille, Suzuki, and Heck reactions for the total syntheses of marinomycins A-C and monomarinomycin A (Figure 4.5, A).[42] They found that while all three methods effectively furnished monomarinomycin A, only the Suzuki reaction was able to give the desired dimeric product. Denmark reported the synthesis of macrolactones through the intramolecular coupling of a vinyl iodide tethered to a cyclic vinyl siloxane catalyzed by allylpalladium chloride dimer.[43] The method allows for the synthesis of 11- through 14-membered rings with no loss in efficiency due to ring size. More recently, Baran has reported oxidative coupling in the cyclization of peptides to synthesize arylomycins on scale (Figure 4.5, B).[44]

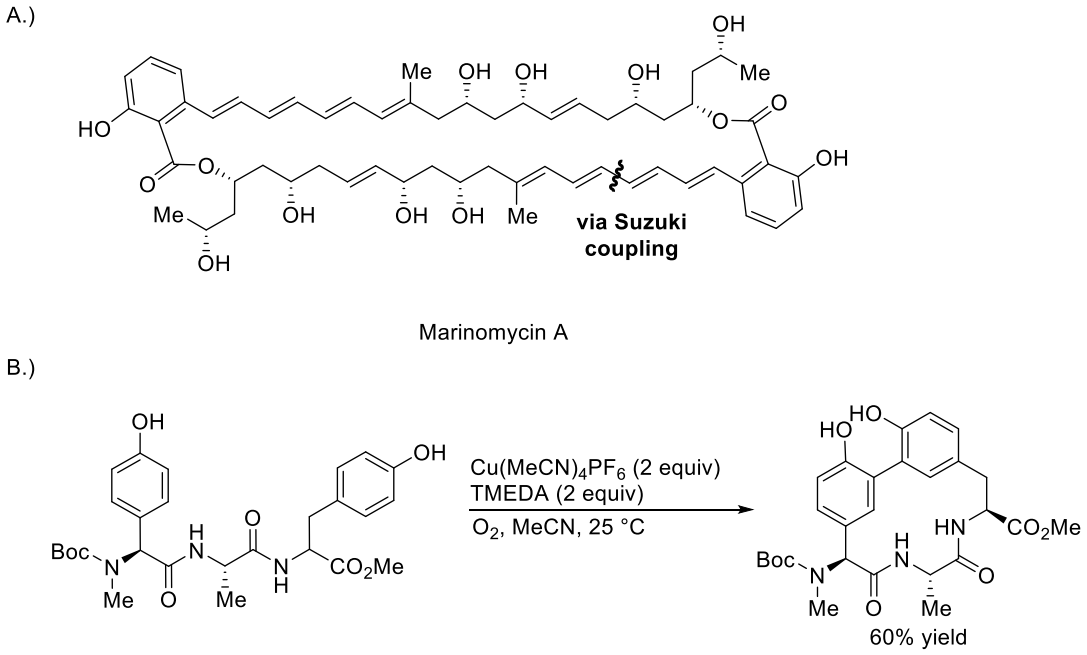


Figure 4.5. Other transition metal mediated strategies for macrocyclization.

4.1.3. Strategies for the Total Synthesis of (±)-Recifeiolide

First isolated in 1976,[45] the 12-membered lactone (±)-recifeiolide **4.1** has been a proving ground for cyclization reactions. Corey reported the first synthesis of the macrocycle utilizing macrolactonization of an activated carboxylic acid (Figure 4.6).[46] Schreiber later reported a radical fragmentation pathway mediated by $FeSO_4$ and $Cu(OAc)_2$ that leads to ring-expansion, furnishing the macrolide in three synthetic steps from cyclononanone (Figure 4.6).[47] This remains the shortest reported synthesis to date, although cyclononanone isn't readily available in useful quantities. Since these initial reports, syntheses of recifeiolide have been reported using macrolactonization,[48-51] olefin metathesis,[27, 52-54] and other methods for forming the ring.[55] Interestingly, there are no reports of intramolecular cross-coupling to form the macrolide.

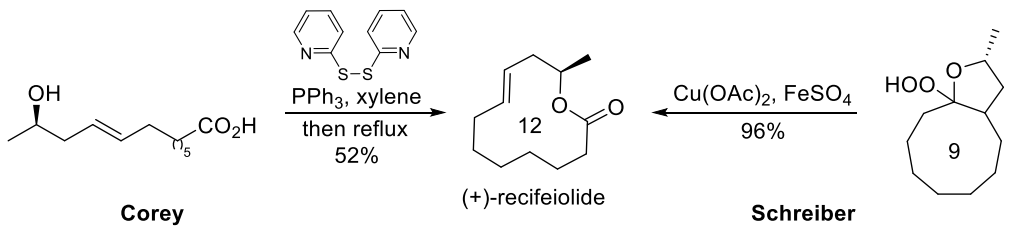


Figure 4.6. Synthesis of (+)-recifeiolide.

Peng has reported the nickel mediated intramolecular coupling of alkyl and aryl halides (Figure 4.7, A),[56] and have since provided several reports on the tandem cyclization of aryl and alkyl halides to form tricyclic ring systems.[57-60] Gong and coworkers reported the cyclization of alkyl dihalides catalyzed by nickel (Figure 4.7, B),[61] and more recently Jarvo has reported the intramolecular reductive cross-electrophile coupling of benzylic esters with aryl halides (Figure 4.7, C).[62] In all these cases, the methods are limited to the formation of medium-sized (5-7 membered) rings. A general method that would allow for the formation of larger rings from simple starting materials would be advantageous. We sought to apply cross-electrophile coupling to macrocyclization and identified recifeiolide as an appropriate target molecule. We envisioned the target molecule coming from the cyclization of the dihalide precursor shown (Figure 4.8), which can be readily furnished in four synthetic steps from commercially available starting materials.

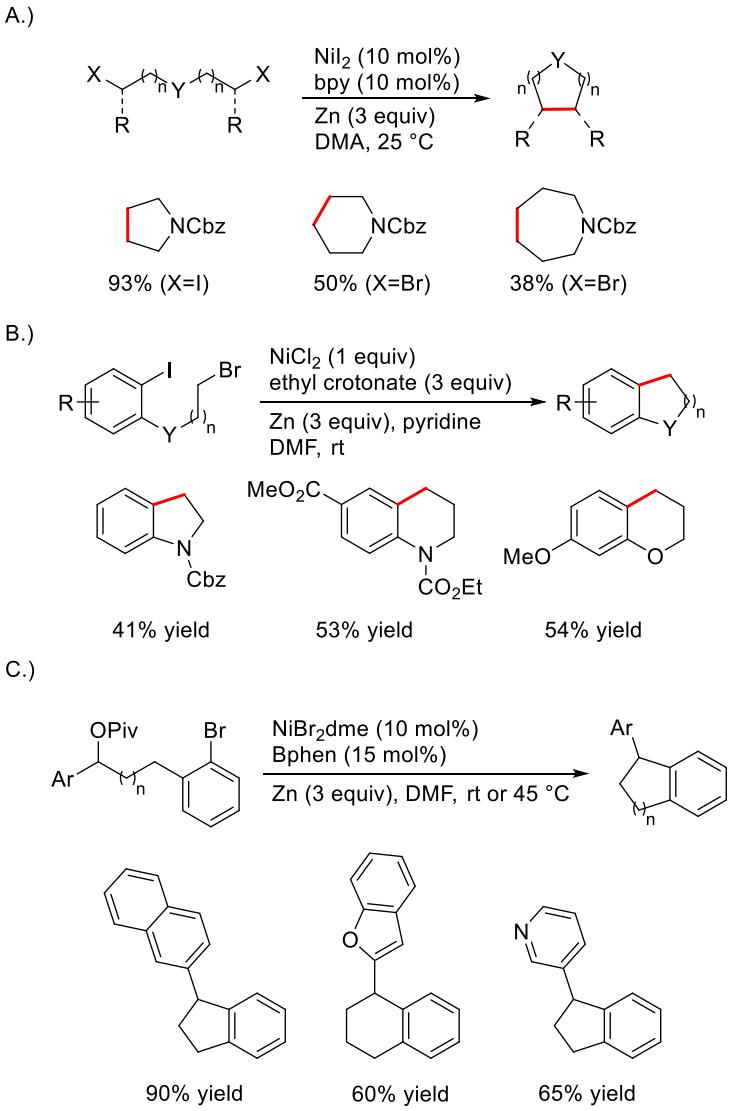


Figure 4.7. Nickel-catalyzed reductive cyclization methods.

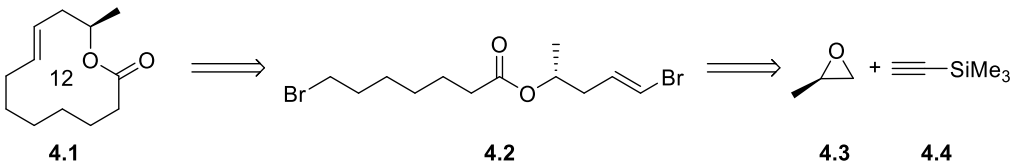


Figure 4.8. Proposed retrosynthesis of (+)-recifeiolide.

4.2. Results

We began our synthesis of recifeiolide with the ring opening reaction of (±)-propylene oxide with the lithiate of trimethylsilyl acetylene (Figure 4.9). Application of this synthetic

sequence to the enantiomerically pure natural product would simply require starting from the enantiopure epoxide, which is readily available ($7/g). We observed that the BF_3•OEt_2 must be freshly distilled prior to use. We obtained the desired alcohol in 50% yield and took it forward to the next step. The reported reduction of **4.5** with diisobutylaluminum hydride (DIBAL-H) in refluxing ether gave a mixture of (*E*)- and (*Z*)-isomers (Figure 4.9). Fortunately, conducting the reaction at room temperature gave exclusive formation of the desired (*Z*)-isomer of the vinyl silane in 55% yield. Esterification of the homoallylic alcohol with 7-bromoheptanoic acid, which was prepared from the hydrolysis of ethyl 7-bromoheptanoate in 90% yield, gave the ester in 54% yield (Figure 4.9). Finally, the (*Z*)-vinyl silane was converted to the (*E*)-vinyl bromide through bromination with elemental bromine followed by desilylative elimination using TBAF (Figure 4.9). Unfortunately, displacement of the alkyl bromide by fluorine was observed to be significant. We overcame this by performing the reaction at -78 °C which led to only 21% yield of the desired dihalide.

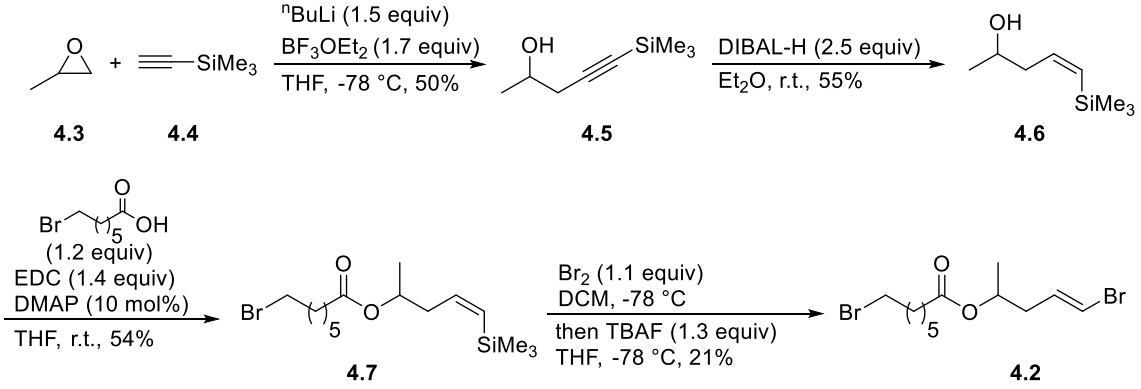


Figure 4.9. Synthesis of (±)-recifeiolide precursor

4.3. Conclusions and Future Directions

We have evaluated a synthetic route to the 12-membered macrolide (±)-recifeiolide. The penultimate intermediate can be synthesized in four steps from readily available in

starting materials in modest yields. Optimization of these reaction conditions will allow for the assessment of cross-electrophile coupling towards macrocyclization. Early investigations with simple precursors found that oligomerization of the starting material was preferred over cyclization, consistent with previous reports (Figure 4.10).[56]

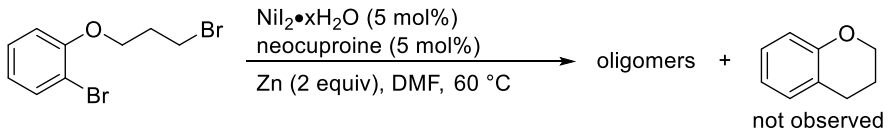


Figure 4.10. Preliminary results for reductive cyclization.

When taking into account the mechanistic studies on the intermolecular coupling of aryl and alkyl halides,[63] two conflicting challenges become apparent: (1) at high catalyst concentrations dimerization of the aryl/vinyl halide is rapid, consistent with studies done by Osakada and Yamamoto,[64-65] however, (2) the mechanism requires that two discrete nickel centers react with the same molecule in order for cyclization to occur, which is favored at high nickel concentrations (Figure 4.11).

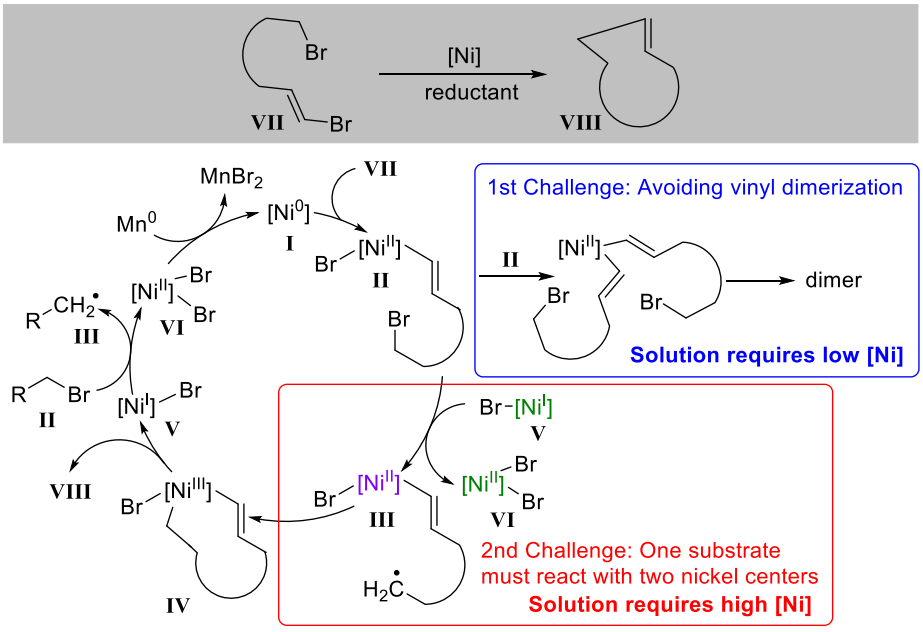


Figure 4.11. Challenges for reductive macrocyclization.

To overcome these challenges, the strategies described in Chapter 2 and Chapter 3 will be applied in unison to intramolecular cross-electrophile coupling to form macrocycles. We envision that we will achieve macrocyclization by utilizing a low concentration of two discrete catalytic species (Section 2.2.1.3), one responsible for oxidative addition into the C(sp^2)-X bond and the other responsible for radical formation (Section 3.2.2). We also plan to investigate tethering the catalysts together as a way to encourage cyclization over oligomerization by bringing the nickel centers within proximity of one another (Figure 4.12). A similar strategy was applied by Kishi and coworkers for Ni/Cr cross-coupling reactions.[66] By applying these strategies, we ae confident that we will be able to realize macrocyclization and the synthesis of (±)-recifeiolide in five synthetic steps, making it one of the shortest synthesis of the natural product reported.

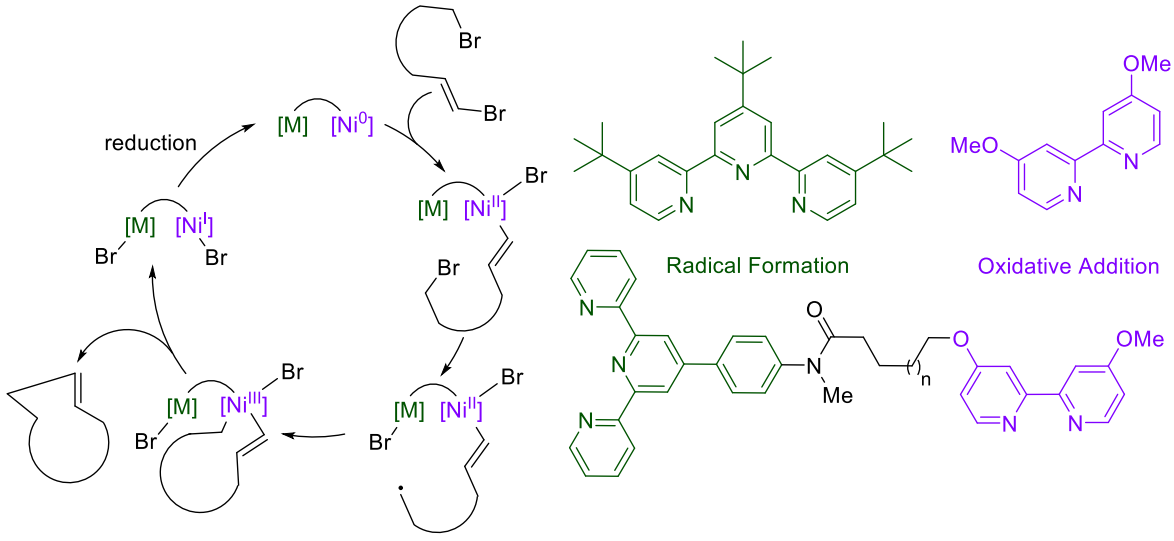


Figure 4.12. New strategies for reductive macrocyclization.

4.4. Experimental

4.4.1. Materials

Reagents were purchased from commercial sources and used as received. All dry solvents were prepared from ACS grade, inhibitor free solvents by passage through

activated alumina and molecular sieves in a Vacuum Atmospheres solvent purification system. Water content was routinely measured using Karl-Fisher titration (Metrohm) and was less than 50 ppm in all cases.

4.4.2. General Methods

NMR Spectroscopy

^{1}H and ^{13}C NMR spectra were acquired on 400 and 500 MHz Bruker NMR instruments. NMR chemical shifts are reported in ppm and referenced to tetramethylsilane at 0.00 ppm (^{1}H) and 0.00 ppm (^{13}C), α, α, α-trifluorotoluene at 0.00 ppm (^{19}F), or the residual solvent peaks for $CDCl_3$ at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C). Coupling constants (*J*) are reported in Hertz. For substrates that existed as rotamers at ambient temperature, the ^{1}H NMR spectrum was obtained at 55 °C.

Gas Chromatography

Instrument. GC analyses were performed on an Agilent 7890A GC equipped with dual DB-5 columns (20 m × 180 μm × 0.18 μm), dual FID detectors, and using hydrogen as the carrier gas.

Sample preparation. A 50 μL aliquot was removed from the reaction mixture using a gas-tight syringe and quenched with 1.5 mL each of water and diethyl ether, and the resulting mixture was then passed through a 1-inch pipette column of silica. The filtrate is used for GC and GC-MS analysis.

Analysis Method. 1 μL injection of sample, injection temp of 300 °C, 100:1 split ratio, initial inlet pressure was 20.3 psi but varied as the column flow was held constant at 1.8 mL/min for the duration of the run. Initial oven temperature of 50 °C was held for 0.46 min followed by a temperature ramp up to 300 °C at 65 °C/min and finally the temperature

was held at 300 °C for 0.69 min. Total run time was ~ 5 min. FID temperature was 325 °C.

GC/MS Analysis

GC/MS analyses were performed on a Shimadzu GCMS-QP2010 equipped with an RTX-XLB column (30 m × 0.25 mm × 0.28 μm) with a quadrupole mass analyzer using helium as the carrier gas. The analysis method used in all cases was 5 μL injection of sample, injection temp of 225 ºC, 25:1 split ratio, initial inlet pressure was 7.8 psi, but varied as the column flow was held constant at 1.0 mL/min for the duration of the run, the interface temperature was held at 250 ºC, and the ion source (EI+, 30 eV) was held at 250 ºC. Initial oven temperature was held at 50 ºC for 3 min with the detector off followed by a temperature ramp, with the detector on, to 280 ºC at 40 ºC/min, and finally the temperature was held at 280 ºC for 3 min. Total run time was 11.75 min.

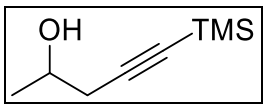
Chromatography

Chromatography was performed on silica gel (EMD, silica gel 60, particle size 0.040-0.063 mm) using standard flash techniques Products were visualized by one of the following methods: UV light, $KMnO_4$ stain, or by GC.

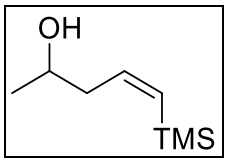
4.4.3. General Reaction Procedures

All reactions were performed in flame- or oven-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. All reaction mixtures were stirred throughout the course of each procedure using Teflon-coated magnetic stir bars. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula.

4.4.4. Product Characterization

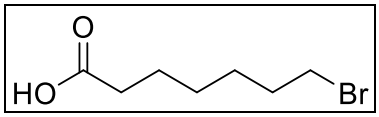


5-(trimethylsilyl)pent-4-yn-2-ol (4.5) To a 500 mL round-bottom flask containing a teflon-coated stir-bar was added THF (150 mL) and trimethylsilyl acetylene (5.6 g, 57.6 mmol, 1.2 equiv). The reaction flask was sealed with a rubber septum and purged with argon gas for ten minutes. The reaction flask was then cooled to -78 °C. n-butyllithium (2.3 M in hexanes, 26 mL, 60 mmol, 1.25 equiv) was added dropwise via syringe, followed by (±)-propylene oxide (2.79 g, 48 mmol, 1 equiv), then freshly distilled boron trifluoride etherate (10.2 g, 72 mmol, 1.5 equiv). The reaction was stirred at -78 °C under positive argon pressure for 3 hours. The reaction mixture was poured into aqueous ammonium chloride (150 mL), and this mixture was then extracted with methyl *tert*-butyl ether (3 × 100 mL). The organic layers were combined, washed with 100 mL of brine, and dried over anhydrous Na_2SO_4. After filtration of the organic layer, volatile materials were removed on a rotary evaporator. The product was isolated by flash column chromatography (1:3 ethyl ether/hexane) and distillation to afford a colorless oil in 50% yield (3.73 g). Spectroscopic data matches with previously reported data.[67]

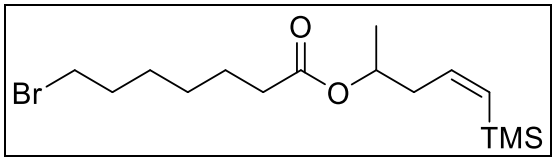


(*Z*)-5-(trimethylsilyl)pent-4-en-2-ol (4.6) To a 100 mL round-bottom flask containing a teflon-coated stir-bar under argon was added Et_2O (15 mL) and **4.5** (1.0 g, 6.4 mmol, 1 equiv). The reaction flask was then cooled to 0 °C. Diisobutylaluminum hydride (1.23 M in hexanes, 13 mL, 16 mmol, 2.5 equiv) was added dropwise via syringe. The reaction was

stirred at room temperature under positive argon pressure for 24 hours. The reaction mixture was poured into aqueous Rochelle's salt solution (30 mL), and this mixture was then extracted with diethyl ether (3 × 20 mL). The organic layers were combined, washed with 20 mL of brine, and dried over anhydrous $MgSO_4$. After filtration of the organic layer, volatile materials were removed on a rotary evaporator. The product was isolated by flash column chromatography (1:3 ethyl ether/hexane) to afford a colorless oil in 55% yield (546 mg). Spectroscopic data matches with previously reported data.[68]



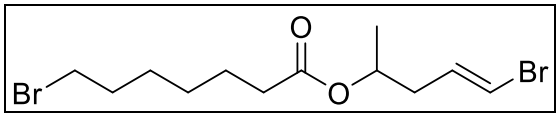
7-bromoheptanoic acid To a 250 mL round-bottom flask containing a teflon-coated stir-bar was added THF (25 mL), H_2O (25 mL), EtOH (25 mL), lithium hydroxide monohydrate (2.0 g, 48 mmol, 2.0 equiv), and ethyl 7-bromoheptanoate (5.7 g, 24 mmol, 1 equiv). The reaction was stirred at room temperature for 4 hours. The reaction mixture was then acidified with 1 M HCl (60 mL), and this mixture was then extracted with dichloromethane (3 × 50 mL). The organic layers were combined, washed with 20 mL of brine, and dried over anhydrous $MgSO_4$. After filtration of the organic layer, volatile materials were removed on a rotary evaporator. The pure product was obtained as a colorless oil in 90% yield (4.48 g). Spectroscopic data matches with previously reported data.[69]



(*Z*)-5-(trimethylsilyl)pent-4-en-2-yl 7-bromoheptanoate (4.7) To a 100 mL round-bottom flask containing a teflon-coated stir-bar was added 4-(dimethylamino)pyridine (39 mg, 0.32 mmol, 0.01 equiv) and *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide

hydrochloride (843 mg, 4.4 mmol, 1.4 equiv). The reaction flask was sealed with a rubber septum and purged with argon gas for ten minutes. THF (30 mL), 7-bromoheptanoic acid (794 mg, 3.8 mmol, 1.2 equiv), and **4.6** (500 mg, 3.15 mmol, 1 equiv) were added sequentially via syringe. The reaction was stirred at room temperature under positive argon pressure for 24 hours. The reaction mixture was poured into H_2O (30 mL), and this mixture was then extracted with diethyl ether (3 × 20 mL). The organic layers were combined, washed with 20 mL of brine, and dried over anhydrous $MgSO_4$. After filtration of the organic layer, volatile materials were removed on a rotary evaporator. The product was isolated by flash column chromatography (1:5 ethyl ether/hexane) to afford a colorless oil in 54% yield (590 mg).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 14.4, 7.3 Hz, 1H), 5.61 (dt, *J* = 14.2, 1.4 Hz, 1H), 4.97 (q, *J* = 6.3 Hz, 1H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.46 – 2.30 (m, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.85 (p, *J* = 7.0 Hz, 2H), 1.62 (p, *J* = 7.3 Hz, 2H), 1.51 – 1.40 (m, 2H), 1.38 – 1.31 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.12 (s, 9H).



(*E*)-5-bromopent-4-en-2-yl 7-bromoheptanoate (4.2) To a 25 mL round-bottom flask containing a teflon-coated stir-bar under argon was added DCM (5 mL) and **4.7** (590 mg, 1.7 mmol, 1 equiv). The reaction flask was then cooled to -78 °C. Bromine (303 mg, 1.9 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred at -78 °C under positive argon pressure for 20 minutes. The reaction mixture was poured into aqueous sodium bisulfite (10 mL), and this mixture was then extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, washed with 100 mL of brine, and dried over anhydrous $MgSO_4$. After filtration of the organic layer, volatile materials were removed on

a rotary evaporator. The crude mixture was transferred to a 25 mL round-bottom flask containing a teflon-coated stir-bar. The reaction flask was sealed with a rubber septum and purged with argon gas for ten minutes. THF (5 mL) was added via syringe. The reaction flask was then cooled to -78 °C. Tetrabutylammonium fluoride (1.0 M in hexanes, 2.2 mL, 2.2 mmol, 1.3 equiv) was added dropwise via syringe. The reaction was stirred at -78 °C under positive argon pressure for 30 minutes. The reaction mixture was poured into aqueous ammonium chloride (10 mL), and this mixture was then extracted with diethyl ether (2 × 100 mL). The organic layers were combined, washed with 100 mL of brine, and dried over anhydrous $MgSO_4$. After filtration of the organic layer, volatile materials were removed on a rotary evaporator. The product was isolated by flash column chromatography (1:3 ethyl ether/hexane) to afford a colorless oil in 21% yield (130 mg).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.17 – 6.05 (m, 2H), 4.94 (h, *J* = 6.4 Hz, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.36 – 2.21 (m, 4H), 1.86 (p, *J* = 7.0 Hz, 2H), 1.62 (p, *J* = 7.5 Hz, 2H), 1.45 (p, *J* = 7.3 Hz, 2H), 1.35 (q, *J* = 8.0 Hz, 2H), 1.21 (dd, *J* = 6.3, 1.2 Hz, 3H).

4.5. References

1. Yudin, A. K., Macrocycles: lessons from the distant past, recent developments, and future directions. *Chem. Sci.* **2015,** *6* (1), 30-49.
2. Marsault, E.; Peterson, M. L., Macrocycles Are Great Cycles: Applications, Opportunities, and Challenges of Synthetic Macrocycles in Drug Discovery. *J. Med. Chem.* **2011,** *54* (7), 1961-2004.
3. Giordanetto, F.; Kihlberg, J., Macrocyclic Drugs and Clinical Candidates: What Can Medicinal Chemists Learn from Their Properties? *J. Med. Chem.* **2013,** *57* (2), 278-295.
4. Yu, X.; Sun, D., Macrocyclic drugs and synthetic methodologies toward macrocycles. *Molecules* **2013,** *18* (6), 6230-6268.
5. Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V., Macrocyclization Reactions: The Importance of Conformational, Configurational, and Template-Induced Preorganization. *Chem. Rev.* **2015,** *115* (16), 8736-8834.
6. Illuminati, G.; Mandolini, L., Ring closure reactions of bifunctional chain molecules. *Acc. Chem. Res.* **1981,** *14* (4), 95-102.

7. Ruzicka, L.; Stoll, M.; Schinz, H., Zur Kenntnis des Kohlenstoffringes II. Synthese der carbocyclischen Ketone vom Zehner- bis zum Achtzehnerring. *Helv. Chim. Acta* **1926,** *9* (1), 249-264.
8. Parenty, A.; Moreau, X.; Campagne, J. M., Macrolactonizations in the Total Synthesis of Natural Products. *Chem. Rev.* **2006,** *106* (3), 911-939.
9. Shiina, I.; Mukaiyama, T., A Novel Method for the Preparation of Macrolides from ω-Hydroxycarboxylic Acids. *Chem. Lett.* **1994,** *23* (4), 677-680.
10. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M., A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization. *Bull. Chem. Soc. Jpn.* **1979,** *52* (7), 1989-1993.
11. Corey, E. J.; Nicolaou, K. C., Efficient and mild lactonization method for the synthesis of macrolides. *J. Am. Chem. Soc.* **1974,** *96* (17), 5614-5616.
12. Zhang, Y.; Guo, Q.; Sun, X.; Lu, J.; Cao, Y.; Pu, Q.; Chu, Z.; Gao, L.; Song, Z., Total Synthesis of Bryostatin 8 Using an Organosilane-Based Strategy. *Angew. Chem. Int. Ed.* **2018,** *57* (4), 942-946.
13. Hewitt, W. M.; Leung, S. S. F.; Pye, C. R.; Ponkey, A. R.; Bednarek, M.; Jacobson, M. P.; Lokey, R. S., Cell-Permeable Cyclic Peptides from Synthetic Libraries Inspired by Natural Products. *J. Am. Chem. Soc.* **2015,** *137* (2), 715-721.
14. Vinogradov, A. A.; Yin, Y.; Suga, H., Macrocyclic Peptides as Drug Candidates: Recent Progress and Remaining Challenges. *J. Am. Chem. Soc.* **2019,** *141* (10), 4167-4181.
15. Terwilliger, D. W.; Trauner, D., Selective Synthesis of Divergolide I. *J. Am. Chem. Soc.* **2018,** *140* (8), 2748-2751.
16. Gorges, J.; Kazmaier, U., Matteson Homologation-Based Total Synthesis of Lagunamide A. *Org. Lett.* **2018,** *20* (7), 2033-2036.
17. Suto, T.; Yanagita, Y.; Nagashima, Y.; Takikawa, S.; Kurosu, Y.; Matsuo, N.; Sato, T.; Chida, N., Unified Total Synthesis of Madangamines A, C, and E. *J. Am. Chem. Soc.* **2017,** *139* (8), 2952-2955.
18. Wen, S.; Packham, G.; Ganesan, A., Macrolactamization versus Macrolactonization: Total Synthesis of FK228, the Depsipeptide Histone Deacetylase Inhibitor. *J. Org. Chem.* **2008,** *73* (23), 9353-9361.
19. Fitzgerald, M. E.; Mulrooney, C. A.; Duvall, J. R.; Wei, J.; Suh, B.-C.; Akella, L. B.; Vrcic, A.; Marcaurelle, L. A., Build/Couple/Pair Strategy for the Synthesis of Stereochemically Diverse Macrolactams via Head-to-Tail Cyclization. *ACS Comb. Sci.* **2012,** *14* (2), 89-96.
20. Villemin, D., Synthese de macrolides par methathese. *Tetrahedron Lett.* **1980,** *21* (18), 1715-1718.
21. Tsuji, J.; Hashiguchi, S., Application of olefin metathesis to organic synthesis. Syntheses of civetone and macrolides. *Tetrahedron Lett.* **1980,** *21* (31), 2955-2958.
22. Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H., Design and Stereoselective Preparation of a New Class of Chiral Olefin Metathesis Catalysts and Application to Enantioselective Synthesis of Quebrachamine: Catalyst Development Inspired by Natural Product Synthesis. *J. Am. Chem. Soc.* **2009,** *131* (3), 943-953.

23. Hoveyda, A. H., Evolution of Catalytic Stereoselective Olefin Metathesis: From Ancillary Transformation to Purveyor of Stereochemical Identity. *J. Org. Chem.* **2014,** *79* (11), 4763-4792.
24. Speed, A. W. H.; Mann, T. J.; O'Brien, R. V.; Schrock, R. R.; Hoveyda, A. H., Catalytic Z-Selective Cross-Metathesis in Complex Molecule Synthesis: A Convergent Stereoselective Route to Disorazole C1. *J. Am. Chem. Soc.* **2014,** *136* (46), 16136-16139.
25. Yu, M.; Schrock, R. R.; Hoveyda, A. H., Catalyst-Controlled Stereoselective Olefin Metathesis as a Principal Strategy in Multistep Synthesis Design: A Concise Route to (+)-Neopeltolide. *Angew. Chem. Int. Ed.* **2015,** *54* (1), 215-220.
26. Ahmed, T. S.; Grubbs, R. H., A Highly Efficient Synthesis of Z-Macrocycles Using Stereoretentive, Ruthenium-Based Metathesis Catalysts. *Angew. Chem. Int. Ed.* **2017,** *56* (37), 11213-11216.
27. Fürstner, A.; Langemann, K., Macrocycles by Ring-Closing Metathesis. *Synthesis* **1997,** *1997* (07), 792-803.
28. Gupta, P.; Kumar, P., An Efficient Total Synthesis of Decarestrictine D. *Eur. J. Org. Chem.* **2008,** *2008* (7), 1195-1202.
29. Sudina, P. R.; Motati, D. R.; Seema, A., Stereocontrolled Total Synthesis of Nonenolide. *J. Nat. Prod.* **2018,** *81* (6), 1399-1404.
30. Sakamoto, K.; Hakamata, A.; Tsuda, M.; Fuwa, H., Total Synthesis and Stereochemical Revision of Iriomoteolide-2a. *Angew. Chem. Int. Ed.* **2018,** *57* (14), 3801-3805.
31. van Lierop, B. J.; Lummiss, J. A. M.; Fogg, D. E., Ring-Closing Metathesis. *Olefin Metathesis* **2014**.
32. Deryn, E. F.; Jay, C. C., Ruthenium-Catalyzed Ring-Closing Metathesis: Recent Advances, Limitations and Opportunities. *Curr. Org. Chem.* **2006,** *10* (2), 185-202.
33. Conrad, J. C.; Eelman, M. D.; Silva, J. A. D.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E., Oligomers as Intermediates in Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2007,** *129* (5), 1024-1025.
34. Sytniczuk, A.; Dąbrowski, M.; Banach, Ł.; Urban, M.; Czarnocka-Śniadała, S.; Milewski, M.; Kajetanowicz, A.; Grela, K., At Long Last: Olefin Metathesis Macrocyclization at High Concentration. *J. Am. Chem. Soc.* **2018,** *140* (28), 8895-8901.
35. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D., Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005,** *44* (29), 4442-4489.
36. Stille, J. K.; Tanaka, M., Intramolecular palladium-catalyzed cyclizations of esters containing vinyl triflate and vinylstannane groups at the termini. Synthesis of large ring lactones. *J. Am. Chem. Soc.* **1987,** *109* (12), 3785-3786.
37. Smith, A. B.; Condon, S. M.; McCauley, J. A.; Leazer, J. L.; Leahy, J. W.; Maleczka, R. E., A Unified Total Synthesis of the Immunomodulators (−)-Rapamycin and (−)-27-Demethoxyrapamycin: Assembly of the Common C(1−20) Perimeter and Final Elaboration. *J. Am. Chem. Soc.* **1997,** *119* (5), 962-973.
38. Smith, A. B.; Ott, G. R., Total Syntheses of (−)-Macrolactin A, (+)-Macrolactin E, and (−)-Macrolactinic Acid: An Exercise in Stille Cross-Coupling Chemistry. *J. Am. Chem. Soc.* **1998,** *120* (16), 3935-3948.
39. Li, Q.; Seiple, I. B., Modular, Scalable Synthesis of Group A Streptogramin Antibiotics. *J. Am. Chem. Soc.* **2017,** *139* (38), 13304-13307.

40. Masse, C. E.; Yang, M.; Solomon, J.; Panek, J. S., Total Synthesis of (+)-Mycotrienol and (+)-Mycotrienin I: Application of Asymmetric Crotylsilane Bond Constructions. *J. Am. Chem. Soc.* **1998,** *120* (17), 4123-4134.
41. Graf, G. G., Tin, Tin Alloys, and Tin Compounds. *Ullmann's Encyclopedia of Industrial Chemistry* **2000**.
42. Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J., Total Synthesis of Marinomycins A−C and of Their Monomeric Counterparts Monomarinomycin A and iso-Monomarinomycin A. *J. Am. Chem. Soc.* **2007,** *129* (6), 1760-1768.
43. Denmark, S. E.; Muhuhi, J. M., Development of a General, Sequential, Ring-Closing Metathesis/Intramolecular Cross-Coupling Reaction for the Synthesis of Polyunsaturated Macrolactones. *J. Am. Chem. Soc.* **2010,** *132* (33), 11768-11778.
44. Peters, D. S.; Romesberg, F. E.; Baran, P. S., Scalable Access to Arylomycins via C–H Functionalization Logic. *J. Am. Chem. Soc.* **2018,** *140* (6), 2072-2075.
45. Vesonder, R. F.; Stodola, F. H.; Wickerham, L. J.; Ellis, J. J.; Rohwedder, W. K., 11-Hydroxy-trans-8-dodecenoic Acid Lactone, a 12-Membered-Ring Compound from a Fungus. *Can. J. Chem.* **1971,** *49* (12), 2029-2032.
46. Corey, E. J.; Ulrich, P.; Fitzpatrick, J. M., A stereoselective synthesis of (+-)-11-hydroxy-trans-8-dodecenoic acid lactone, a naturally occurring macrolide from Cephalosporium recifei. *J. Am. Chem. Soc.* **1976,** *98* (1), 222-224.
47. Schreiber, S. L., Fragmentation reactions of .alpha.-alkoxy hydroperoxides and application to the synthesis of the macrolide (.+-.)-recifeiolide. *J. Am. Chem. Soc.* **1980,** *102* (19), 6163-6165.
48. Di Franco, T.; Epenoy, A.; Hu, X., Synthesis of E-Alkyl Alkenes from Terminal Alkynes via Ni-Catalyzed Cross-Coupling of Alkyl Halides with B-Alkenyl-9-borabicyclo[3.3.1]nonanes. *Org. Lett.* **2015,** *17* (19), 4910-4913.
49. Miftakhov, M. S.; Akbutina, F. A.; Tolstikov, G. A., Synthesis of (±)-recifeiolide. *Chem. Nat. Compd.* **1982,** *18* (3), 267-270.
50. Mochizuki, N.; Yamada, H.; Sugai, T.; Ohta, H., A synthesis of (R-recifeiolide by the aid of biochemical reaction as the key-step. *Bioorg. Med. Chem.* **1993,** *1* (1), 71-75.
51. Okuma, K.; Hirabayashi, S.-i.; Ono, M.; Shioji, K.; Matsuyama, H.; Bestmann, H. J., An efficient synthesis of (R)-(+)-recifeiolide and related macrolides by using enantiomerically pure (R)-(−)-5-methyl-2,2,2-triphenyl-1,2λ5-oxaphospholane. *Tetrahedron* **1998,** *54* (17), 4243-4250.
52. Montgomery, T. P.; Ahmed, T. S.; Grubbs, R. H., Stereoretentive Olefin Metathesis: An Avenue to Kinetic Selectivity. *Angew. Chem. Int. Ed.* **2017,** *56* (37), 11024-11036.
53. Ahmed, T. S.; Montgomery, T. P.; Grubbs, R. H., Using stereoretention for the synthesis of E-macrocycles with ruthenium-based olefin metathesis catalysts. *Chem. Sci.* **2018,** *9* (14), 3580-3583.
54. Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H., Kinetically E-selective macrocyclic ring-closing metathesis. *Nature* **2017,** *541*, 380.
55. Zubrytski, D. M.; Kananovich, D. G.; Kulinkovich, O. G., A highly stereoselective route to medium-ring-sized trans-alkenolides via oxidative fragmentation

of bicyclic oxycyclopropane precursors: application to the synthesis of (+)-recifeiolide. *Tetrahedron* **2014,** *70* (18), 2944-2950.
56. Yan, C. S.; Peng, Y.; Xu, X. B.; Wang, Y. W., Nickel-mediated inter- and intramolecular reductive cross-coupling of unactivated alkyl bromides and aryl iodides at room temperature. *Chem. Eur. J.* **2012,** *18* (19), 6039-6048.
57. Peng, Y.; Xu, X.-B.; Xiao, J.; Wang, Y.-W., Nickel-mediated stereocontrolled synthesis of spiroketals via tandem cyclization–coupling of β-bromo ketals and aryl iodides. *Chem. Commun.* **2014,** *50* (4), 472-474.
58. Peng, Y.; Xiao, J.; Xu, X.-B.; Duan, S.-M.; Ren, L.; Shao, Y.-L.; Wang, Y.-W., Stereospecific Synthesis of Tetrahydronaphtho[2,3-b]furans Enabled by a Nickel-Promoted Tandem Reductive Cyclization. *Org. Lett.* **2016,** *18* (19), 5170-5173.
59. Xiao, J.; Cong, X.-W.; Yang, G.-Z.; Wang, Y.-W.; Peng, Y., Divergent Asymmetric Syntheses of Podophyllotoxin and Related Family Members via Stereoselective Reductive Ni-Catalysis. *Org. Lett.* **2018,** *20* (6), 1651-1654.
60. Xiao, J.; Cong, X.-W.; Yang, G.-Z.; Wang, Y.-W.; Peng, Y., Stereoselective synthesis of a Podophyllum lignan core by intramolecular reductive nickel-catalysis. *Chem. Commun.* **2018,** *54* (16), 2040-2043.
61. Xue, W.; Xu, H.; Liang, Z.; Qian, Q.; Gong, H., Nickel-catalyzed reductive cyclization of alkyl dihalides. *Org. Lett.* **2014,** *16* (19), 4984-7.
62. Konev, M. O.; Hanna, L. E.; Jarvo, E. R., Intra- and Intermolecular Nickel-Catalyzed Reductive Cross-Electrophile Coupling Reactions of Benzylic Esters with Aryl Halides. *Angew. Chem. Int. Ed.* **2016,** *55* (23), 6730-6733.
63. Biswas, S.; Weix, D. J., Mechanism and selectivity in nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides. *J. Am. Chem. Soc.* **2013,** *135* (43), 16192-16197.
64. Yamamoto, T.; Wakabayashi, S.; Osakada, K., Mechanism of C-C coupling reactions of aromatic halides, promoted by Ni(COD)2 in the presence of 2,2′-bipyridine and PPh3, to give biaryls. *J. Organomet. Chem.* **1992,** *428* (1–2), 223-237.
65. Osakada, K.; Yamamoto, T., Transmetallation of alkynyl and aryl complexes of Group 10 transition metals. *Coord. Chem. Rev.* **2000,** *198* (1), 379-399.
66. Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y., Dramatic Improvement in Catalyst Loadings and Molar Ratios of Coupling Partners for Ni/Cr-Mediated Coupling Reactions: Heterobimetallic Catalysts. *J. Am. Chem. Soc.* **2009,** *131* (46), 16678-16680.
67. Markó, I. E.; Bayston, D. J., The Intramolecular Silyl-Modified Sakurai (ISMS) reaction. Synthetic studies towards ambruticine. *Tetrahedron* **1994,** *50* (24), 7141-7156.
68. Dobbs, A. P.; Guesné, S. J. J., Rapid Access to trans-2,6-Disubstituted Piperidines: Expedient Total Syntheses of (-)-Solenopsin A and (+)-epi-Dihydropinidine. *Synlett* **2005,** *2005* (13), 2101-2103.
69. Subbaraman, S. A.; Mithran, S.; Mamdapur, R. V., An Expedient Synthesis of the Sugarcane Borer Pheromone Components. *Molecules* **1998,** *3* (2), 35-40

Appendix A: Additional Experiments for Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Chlorides with Secondary Unactivated Alkyl Chlorides

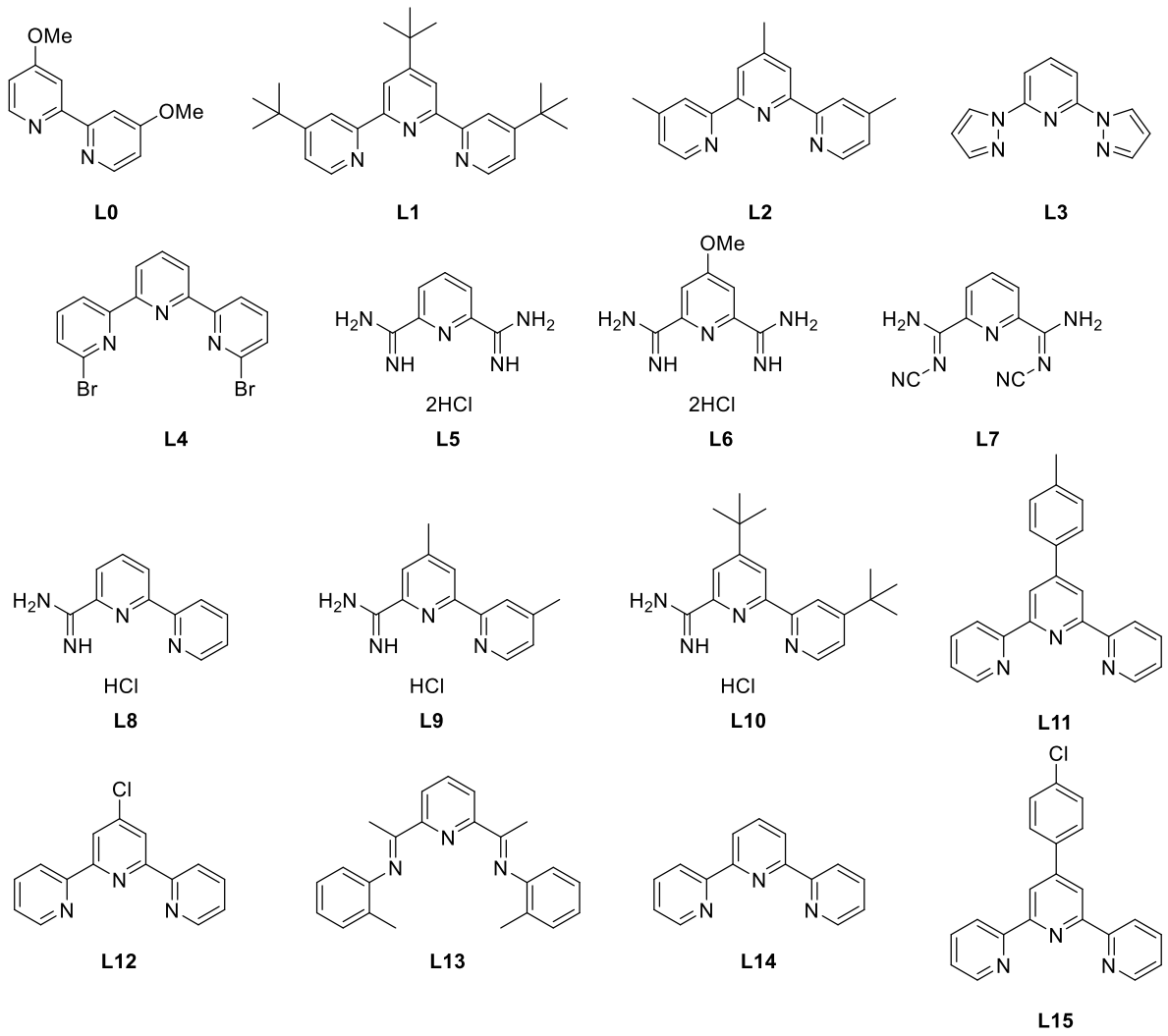
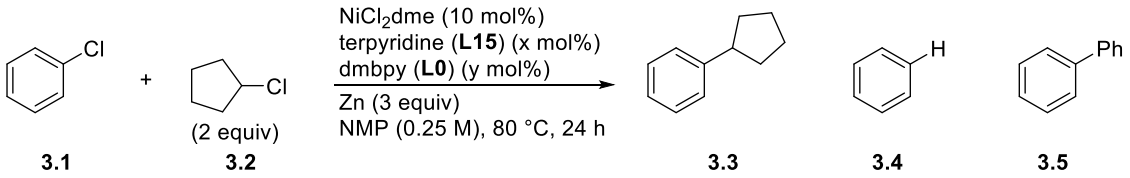


Figure A.1. Ligands evaluated in this section.

When evaluating the dual ligand system, it was observed that a ligand ratio of 4:1 ttbtpy (**L1**) to dmbpy (**L0**) was optimal for the transformation. This trend held constant for different combinations of terpyridine ligands with dmbpy (Tables A.1-3, Figures A.2-4). This trend also holds true for different alkyl chlorides (Figure A.5).

Table A.1. Effect of ligand ratio with **L15.**



Entry	Ligand ratio (x:y)	**3.2** (%)[a]	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	1:9	-	10	4	18
2	2:8	-	19	5	18
3	3:7	4	32	6	14
4	4:6	6	35	5	9
5	5:5	-	44	7	8
6	6:4	10	52	8	4
7	7:3	7	55	9	2
8	8:2	13	57	10	-
9	9:1	11	54	10	-

[a]GC yields vs. dodecane as internal standard.

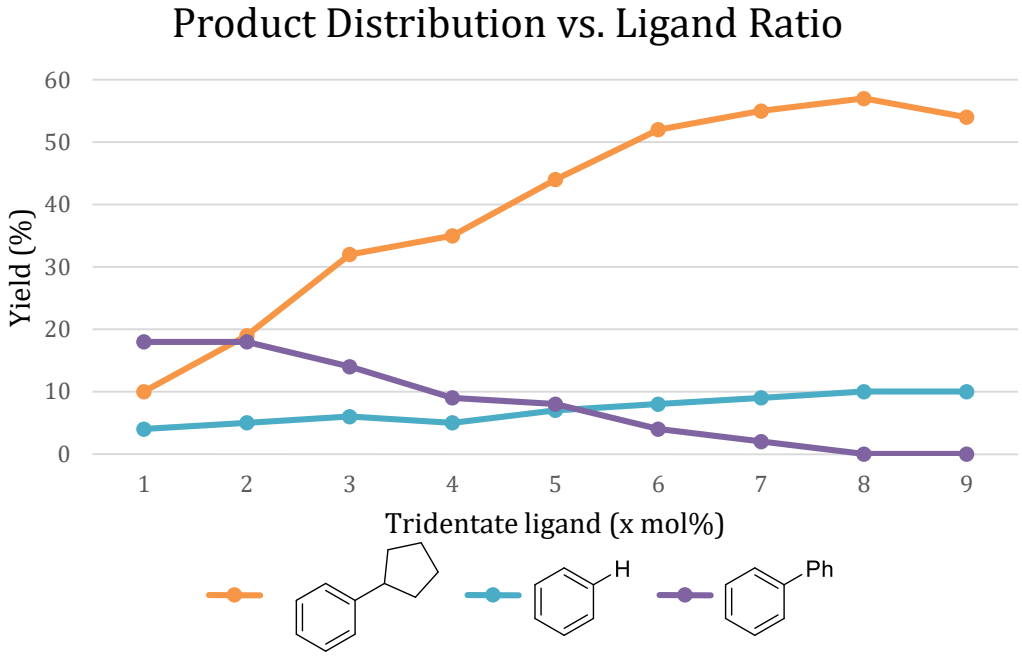
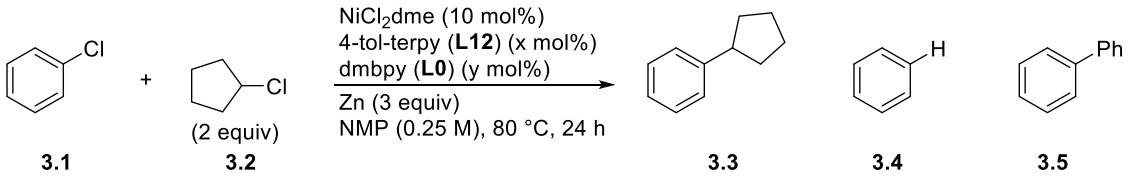


Figure A.2. Effect of ligand ratio on product selectivity with **L15.**

Table A.2. Effect of ligand ratio with **L12.**



Entry	Ligand ratio (x:y)	**3.2** (%)[a]	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	1:9	1	12	6	18
2	2:8	2	20	7	15
3	3:7	-	24	6	14
4	4:6	4	32	6	10
5	5:5	-	35	8	9
6	6:4	24	46	10	4
7	7:3	-	54	12	5
8	8:2	-	65	13	1
9	9:1	4	62	13	-

[a]GC yields vs. dodecane as internal standard.

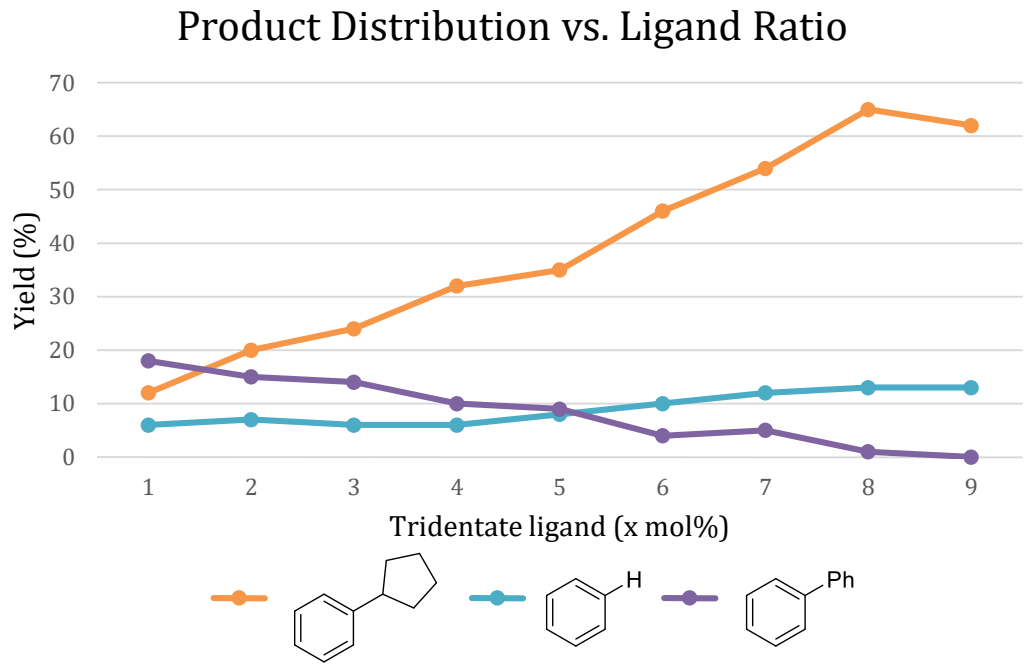
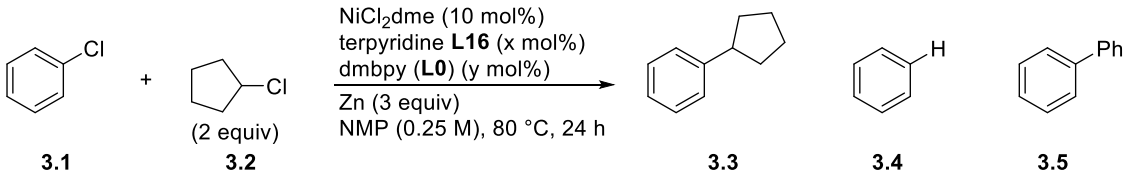


Figure A.3. Effect of ligand ratio on product selectivity with **L12.**

Table A.3. Effect of ligand ratio with **L16**.



Entry	Ligand ratio (x:y)	**3.2** (%)[a]	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	1:9	11	12	7	17
2	2:8	10	21	9	18
3	3:7	-	17	9	17
4	4:6	-	30	10	13
5	5:5	-	31	11	11
6	6:4	-	40	11	6
7	7:3	12	51	13	4
8	8:2	6	51	14	1
9	9:1	11	54	14	-

[a]GC yields vs. dodecane as internal standard.

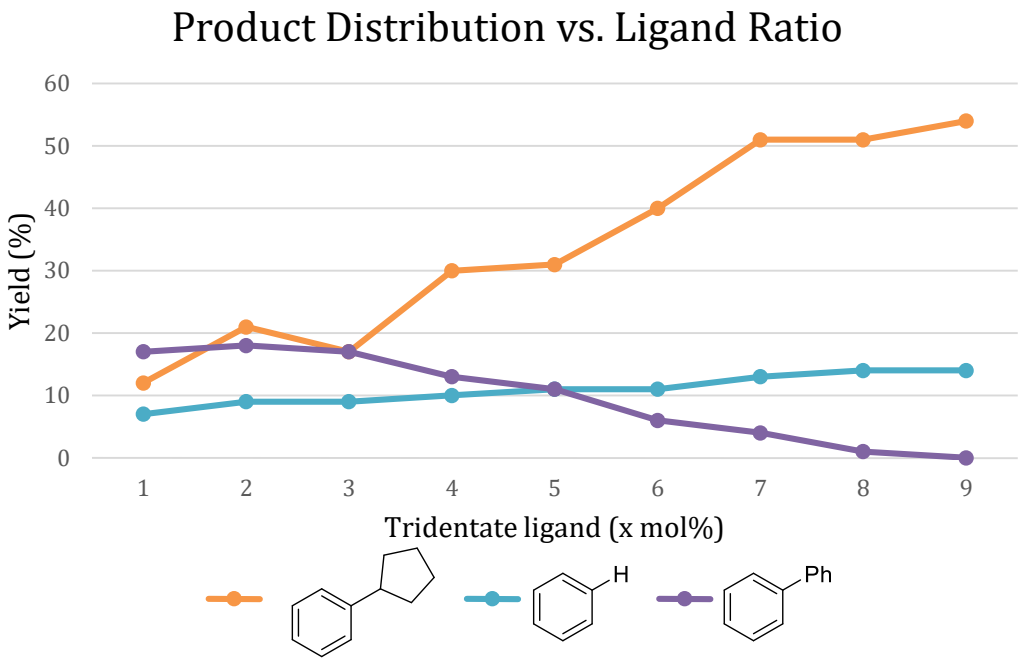


Figure A.4. Effect of ligand ratio on product selectivity with **L16**.

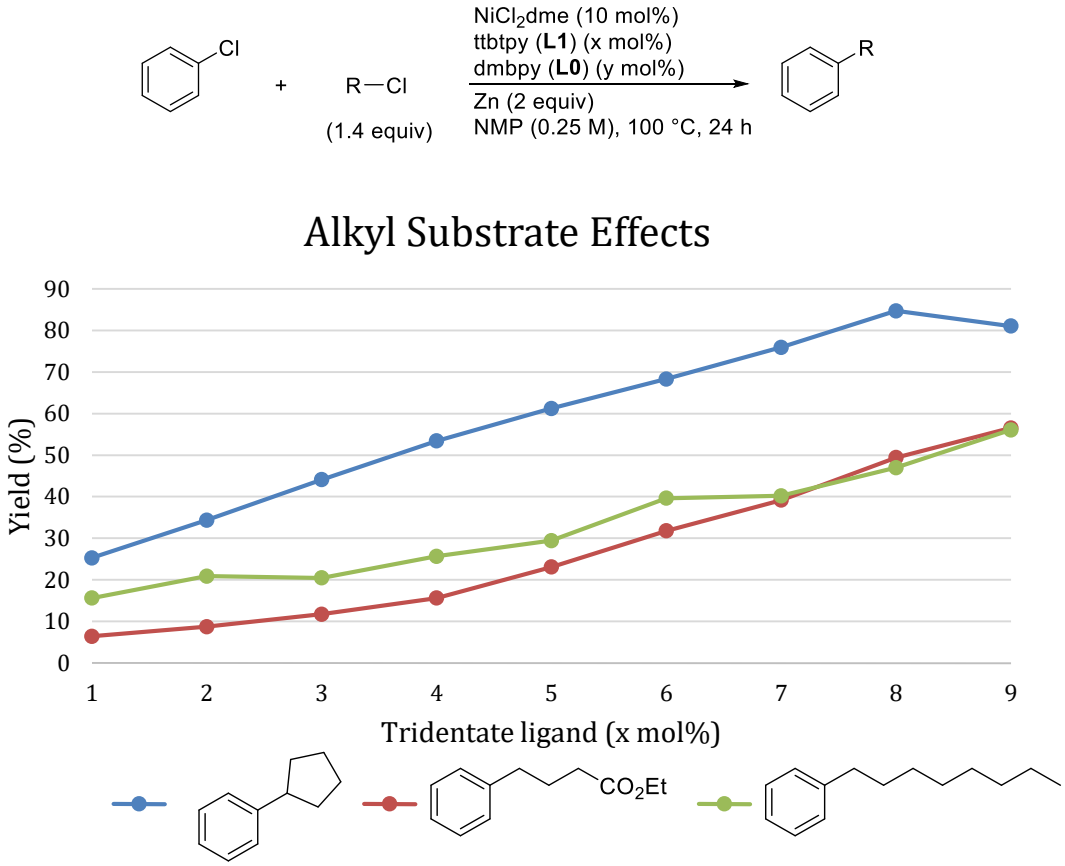
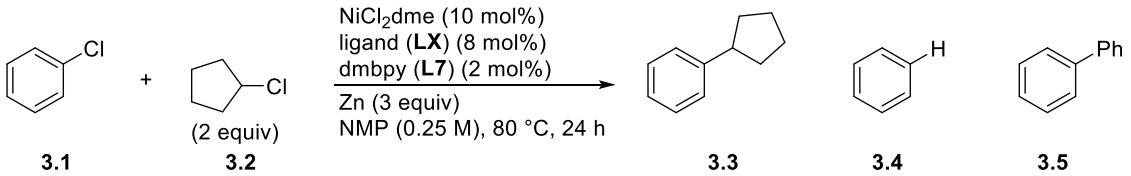


Figure A.5. Effect of ligand ratio on selectivity for different alkyl chlorides.

At the optimal ligand ratio, various terpyridine ligands were evaluated (Table A.4). While ttbtpy remained the best terpyridine ligand for the transformation, a few other ligands gave comparable results (**L2**, **L12**).

Table A.4. Effect of tridentate ligand.

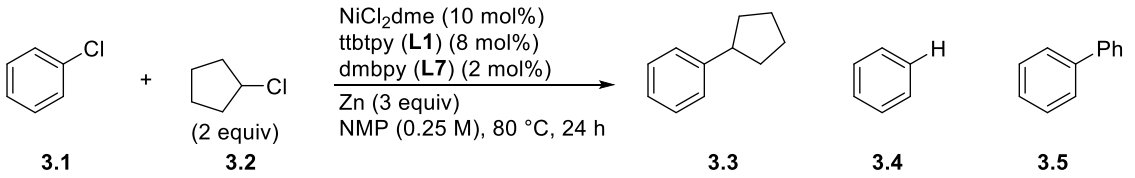


Entry	Ligand	**3.1** (%)[a]	**3.2** (%)[a]	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	**L1**	-	-	77	4	3
2	**L2**	-	-	64	6	5
3	**L3**	17	-	9	13	-
4	**L4**	27	-	3	22	1
5	**L5**	44	67	10	3	-
6	**L6**	32	60	21	8	-
7	**L7**	53	75	2	-	-
8	**L8**	2	-	16	23	1
9	**L9**	24	34	9	13	-
10	**L10**	13	55	30	12	4
11	**L11**	34	37	16	9	-
12	**L12**	-	3	69	13	1
13	**L13**	2	14	50	16	3
14	**L14**	3	1	23	22	2

[a]GC yields vs. dodecane as internal standard.

Control reactions show that both the nickel precatalyst and ligands are necessary for the reaction to occur (Table A.5, 1-2). Additionally, both ligands are necessary in the correct ratio for desired selectivity to be observed (Table A.5, 3-6).

Table A.5. Control reactions.

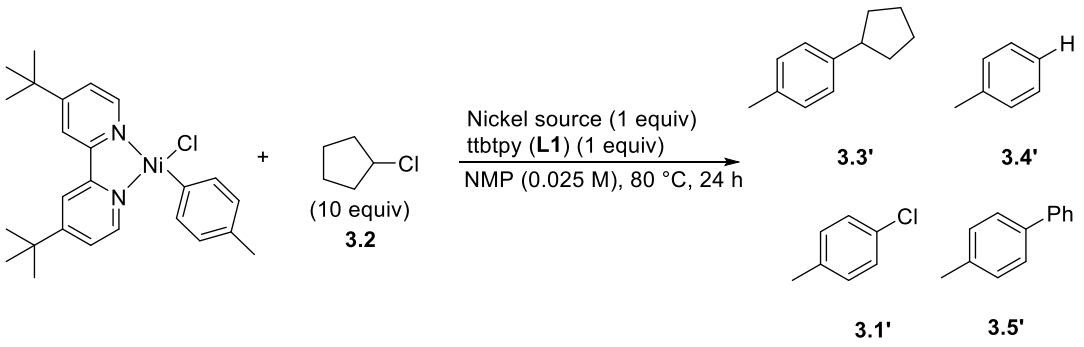


Entry	Deviation	**3.1** (%)[a]	**3.2** (%)[a]	**3.3** (%)[a]	**3.4** (%)[a]	**3.5** (%)[a]
1	no Ni	100	126	-	-	-
2	no ligands	100	124	-	-	-
3	no dmbpy	-	-	57	30	7
4	8 mol% Ni, no dmbpy	-	-	64	26	5
5	10 mol% dmbpy, no ttbtpy	-	37	8	25	33
6	no ttbtpy	28	82	5	44	12
7	Mn instead of Zn	-	-	66	23	6
8	no changes	-	-	78	15	4

[a]GC yields vs. dodecane as internal standard.

An isolated Ni(II) aryl complex was reacted with an excess of alkyl chloride independently and in the presence of Ni(0) and Ni(II) precatalysts (Table A.6). It was observed that the complex is capable of forming the desired product, although aryl dimer is preferred (Table A.6, 1). The desired product was only favored in the presence of the Ni(II) precatalyst (Table A.6, 3). These experiments should be expanded upon to provide a more complete mechanistic picture. Reaction of a stoichiometric amount of alkyl chloride with the isolated complex and reaction of the alkyl chloride in the absence of the complex would give insight into the reactivity of the alkyl chloride. The use of a deuterated alkyl chloride will aid in the determination of the source of aryl hydrodehalogenation (Table A.6, 2).

Table A.6. Stoichiometric reactions.



Entry	Nickel source	**3.1´**[a]	**3.3´**[a]	**3.4´**[a]	**3.5´**[a]
1	no Nickel	1.87	3.75	1	7.76
2	$Ni(COD)_2$	0.23	0.22	1	0.46
3	$NiCl_2$dme	2.95	4.34	1	3.09

[a]GC ratios of products with respect to toluene (**3.4´**).