THE DESIGN AND DEVELOPMENT OF PALLADIUM-CATALYZED AEROBIC OXIDATIVE TRANSFORMATIONS

Thesis by

Eric Matthew Ferreira

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To my parents

ACKNOWLEDGMENTS

I should have written this days ago. "No," I kept telling myself. "Save it for the end. You should end on the acknowledgments." And now here I am, late to turn this thing in, rushing. But it's important to get this right. This is the part that everyone reads. Sure, there's the person who wants to look up this specific reference or that similar procedure, but come on, it's this, followed by the remark, "It seems kinda long."

I have to first thank Professor Brian Stoltz for his support, guidance, and enthusiasm. For an assistant professor to take on so many responsibilities and put forth such a tremendous effort in everything he does is truly remarkable. I appreciate the personal interactions I have had with him over the years, both as a mentor and as a friend. I've been thankful for his continuous interest in science, and for allowing me to forge my own research path with a pretty long leash. I've learned so much from him and his advice, and he has really provided me with an excellent model of what an advisor should be. I also want to thank his wife Erna for her supportive discussions during my time here.

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Zhang, Dave Ebner, Dan Caspi, Ryan McFadden, Toyoki Nishimata, and JT Mohr. Although I never worked directly with anyone at any given time on this project, I know this project would be nothing without all of their efforts. Jeff has done an excellent job in developing the oxidative kinetic resolution beyond the initial work. Raissa has done some of the most profound work on the palladium chemistry while I've been here. I have a great deal of respect for her skills in experimental design and execution. Haiming came in and cranked on the C-H bond functionalization chemistry. God, he runs a ton of reactions. I love that. I think his efforts have really helped to outline where the project needs to go in the future. Dave and Toyoki have both started working on non-sparteine-based systems. I'm happy to see that people are excited about taking the chemistry in this direction, despite how difficult it may be, and I wish them the best. I really admire their willingness to work on projects that can be challenging, but could eventually lead to some thrilling outcomes. I think that although there's still a bunch to be done, the project has come a long way in a pretty short amount of time. I have tried to point out their specific contributions in the text of the thesis, but I wanted to thank them collectively here as well.

I've had three baymates while in the group. Sarah Spessard was the first back in the days of 264 Crellin. I enjoyed playing tennis a bunch with Sarah Spessard in the early days. Though she kicked my butt most of the time, it helped to release some of the built up tension from the day-to-day lab stuff. In 204 Church, I then had the luxury (yes, that's the right word) of working next to Richmond Sarpong. I could have done with less Steely Dan or Hall & Oates, but he was an excellent coworker. His enthusiasm about chemistry was contagious, and I thoroughly enjoyed the scientific discussions we had in the years he was here. I hope he does great as a professor at Berkeley; I can't think of anyone more deserving of success. Mike Krout has been my baymate for almost a year. Although we haven't had too much time to work next to each other, it's been a pleasure working near him. I'm also grateful to him for putting up with way more Sonic Youth than he should have felt obligated to.

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has been fun to talk to, vent to, complain about the Sacramento Kings to, etc. He knows a boatload of information and could always answer even my most mundane questions. I've always appreciated the level-headedness of Jeremy May. He seems to have such a reasonable and healthy perspective on things that I've found refreshing and helpful toward achieving my own version of rationality. Jenn Stockdill is always good for an ice cream break or hanging out with Sage and Lily. JT Mohr has been great to talk to about music, the Daily Show, or heck, chemistry. I want to thank the following for their insightful assistance with drafts of this thesis (and proposals, for that matter): JT, Eric A., Mike K., Raissa, Haiming, Jeremy, Jenn, and Dave. Finally, I want to thank the Stoltz Group as a whole for creating an environment always willing to discuss science in an engaging manner. It's this environment that allows the lab to be successful as it has been, and I'm sure that the success will continue for years to come.

I have to single out Mike Meyer for a second. First, he's a San Francisco Giants fan (big plus). Second, he's really the only person that I've worked with on a project at the same time. Although none of it is appearing in this thesis (okay, one reaction), it has been a true pleasure to have the opportunity to work with him for the past few months. I've really admired his excitement about chemistry and his eagerness to learn and then perform. His willingness to get things done quickly helped to push this project along, and I'm certain his optimism and enthusiasm will carry this project to the end. I just want to thank him for having a huge part in helping to restore my excitement about chemistry after a particularly discouraging stretch (Chapter 5, *vide infra*).

Caltech is a unique place in that people can be incredibly interactive with one another across research groups in both scientific and social manners. I've frequently enjoyed being able to talk to people in other areas of the Caltech community about science or about anything else. Rather than go into detail about each one, which would take way too long, I'll just list them here. Joel Austin (Scrabble rocks), Andrew Waltman, Erin Guidry, Ian Mangion, Jon Owen, Julie Park, Arnab Chatterjee, Vy Dong, Nick Paras, Connie Lu, Steve Brown, Ted Betley, and Lori Lee. I appreciated the occasional discussions with all of them about whatever was on our minds. Tehshik Yoon was immensely helpful in the first couple of years I was here. I think he gets a lot of appreciation for his selfless impact in the MacMillan Group, but he was also able to

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I need to thank the folks at anarchy@mit.edu. (No, we aren't anarchists.) The philosophical discussions, battle raps, and indie elitist posturing were incredibly entertaining and a frequently welcome distraction to work. Just names again: Mike Salamina, Mike Dewberry, Andy Stein, Ian Ross, Mike Perry, Jordan Gilliland, Mike O'Hara, Ian McCreery, Andy Kuziemko and Dan Amano.

Lastly, I need to thank my family for their continued support. Andrea and Henry have been hosting awesome Thanksgivings for many years now, and I've always enjoyed the chance to get away, even if only for a day, to visit with them. My parents have been continually supportive of me in helping me reach my goals. I think as I've gotten older, I've become more aware of the extent of their support, revealing itself in ways I never thought possible even just a couple of years ago. I am eternally thankful for their sage advice, and that's why this thesis is dedicated to them. Although I may not be visibly demonstrative of my appreciation all the time, I hope that they can recognize how much their support has meant to me.

Hmm. Even my acknowledgments section is too long.

ABSTRACT

Oxidation is a fundamental process in chemistry and biology. In synthetic chemistry, several developments have been made in catalytic asymmetric oxidative transformations that involve a heteroatom transfer from a reagent to a substrate (e.g., epoxidations, dihydroxylations). Enantioselective oxidations that do not involve a heteroatom transfer have been relatively less explored. These types of oxidative transformations were investigated using a general palladium(II) catalyst system.

A palladium-catalyzed oxidative kinetic resolution of secondary alcohols was developed. This catalytic system utilizes (–)-sparteine as the chiral ligand and molecular oxygen as the sole stoichiometric oxidant. Benzylic and allylic alcohols can be resolved to high enantiomeric excesses in excellent yields. The same selective process has been applied to the desymmetrization of meso diols.

This general palladium(II) oxidative system was applied to intramolecular Wacker oxidations to form a variety of heterocycles. Lactones, lactams, tetrahydrofurans, dihydrobenzofurans, and dihydrobenzopyrans were all accessed by this methodology. Importantly, this work provided entry into the development of asymmetric variants. Highly enantioselective cyclizations of phenolic substrates were realized with a palladium-sparteine catalyst, analogous to the kinetic resolution chemistry. The heterocyclization chemistry was employed in the context of the total synthesis of the *Cephalotxaxus* alkaloids.

Oxidative annulations for the synthesis of carbocycles were developed utilizing this general palladium system. Indoles with pendant olefin tethers were oxidatively

cyclized under palladium(II) catalysis to form annulated indoles. Electron-rich aromatic systems were also investigated, culminating in the syntheses of benzofurans and dihydrobenzofurans. These reactions were demonstrated to proceed by an initial C-H bond functionalization event, followed by olefin insertion and β-hydride elimination.

Enantioselective heterocyclizations using the general oxidative system were further explored. Promising results were realized in the heterocyclizations of sulfonamide-based compounds. Key experiments allowed for a firmer understanding of how the reaction was progressing and, specifically, how enantioselectivity was being induced by the palladium catalyst.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
t-Am	*tert*-amyl
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
br	broad, broadened
Bu	butyl
i-Bu	isobutyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for specific rotation measurements
° C	degrees Celsius
calc'd	calculated
cat.	catalytic
comp	complex
conv	conversion
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone

DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMFDMA	*N,N*-dimethylformamide dimethyl acetal
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ration
ee	enantiomeric excess
EI	electrospray ionization
equiv	equivalents
er	enantiomeric ratio
Et	ethyl
FAB	fast atom bombardment
g	grams
GC	gas chromatography
[H]	reduction
h	hours
HMDS	hexamethyldisilazane or hexamethyldisilazide
hν	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
imid.	imidazole
IR	infrared
J	coupling constant
kcal	kilocalories
L	liter

LAH	lithium aluminum hydride
LDA	lithium dicyclohexylamide
M	metal or molar
m	milli or multiplet or meters
m/z	mass to charge ratio
μ	micro
Me	methyl
Mes	mesityl
MHz	megahertz
min	minutes
mol	moles
mp	melting point
MS	molecular sieves
Ms	methanesulfonyl
N	normal
ν	frequency
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
[O]	oxidation
o	ortho
OKR	oxidative kinetic resolution
p	para
PCC	pyridinium chlorochromate
n-Pent	*n*-pentyl
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Piv	pivaloyl (trimethylacetyl)

pK_a	acidity constant
PPA	polyphosphoric acid
ppm	parts per million
PPTs	pyridinium *p*-toluenesulfonate
i-Pr	isopropyl
py	pyridine
pyr	pyridine
q	quartet
ref	reference
R_F	retention factor
s	singlet or selectivity factor
sat.	saturated
SEM	(trimethylsilyl)ethoxymethyl
stoich.	stoichiometric
Sub	substrate
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid or trifluoroacetate
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
TPAP	tetrapropylammonium perruthenate

Ts	*p*-toluenesulfonyl or tosyl
TsOH	*p*-toluenesulfonic acid or tosic acid
UV	ultraviolet
v/v	volume to volume
w/v	weight to volume

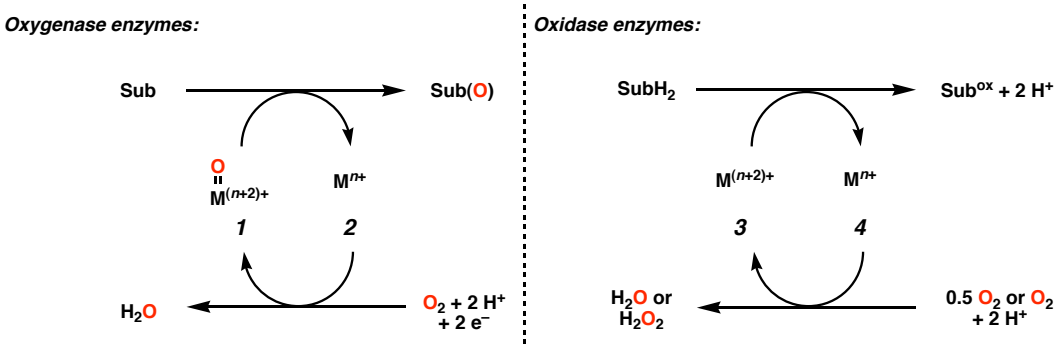
CHAPTER ONE

Enantioselective Oxidation Chemistry

1.1 Oxidation in Biological Systems

Oxidation is a fundamental process in chemistry and biology. In biological systems, a number of enzymes catalyze a diverse set of oxidative reactions through the use of molecular oxygen. Metalloenzymes that catalyze these aerobic oxidations are divided into two distinct types (Figure 1.1.1). Oxygenases involve the transfer of an oxygen atom from O_2 to the substrate, often via a high-valent metal oxo species (**1**). The reduced metal intermediate (**2**) is then oxidized by dioxygen back to the active species, mediated by two protons and two electrons. Importantly, one of the oxygen atoms from O_2 is incorporated into the oxidized substrate. Oxidases differ in that the metal oxidant (**3**) catalyzes the dehydrogenation of the substrate, releasing two protons. In this case, there is no oxygen atom transfer to the substrate—molecular oxygen is used simply as a proton and electron acceptor for the catalytic process. The atoms from O_2 are released as either water or hydrogen peroxide.

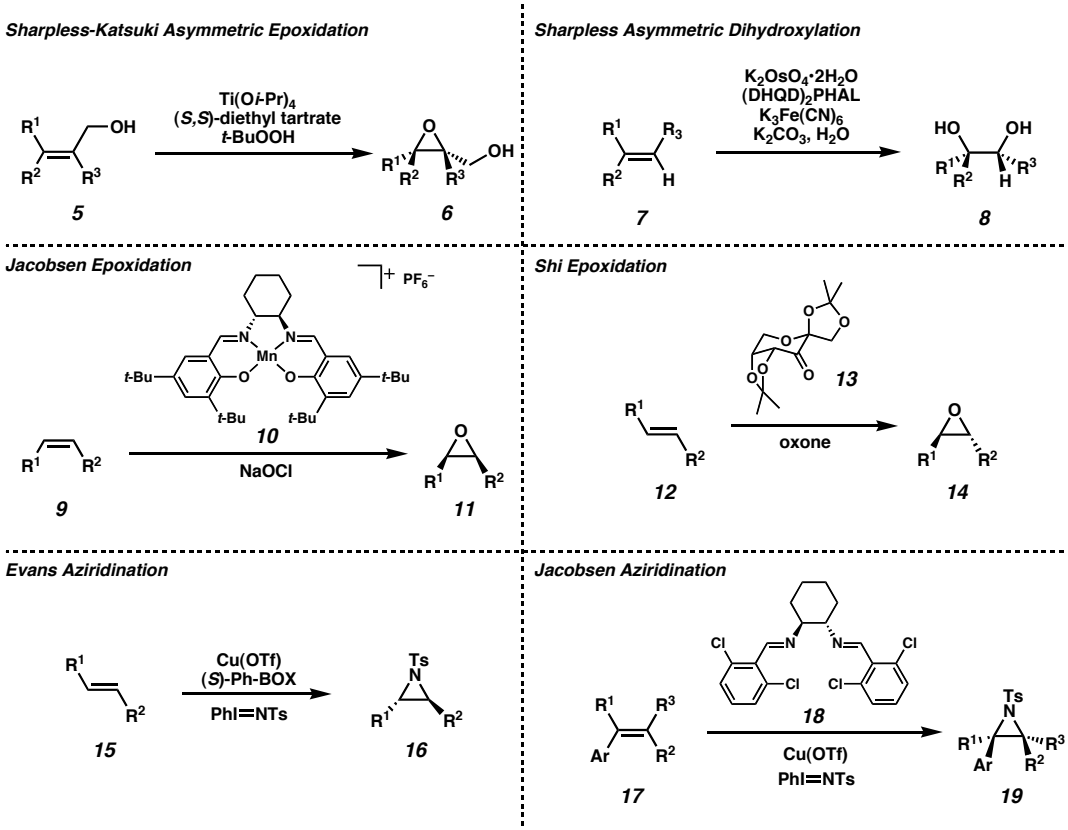
Figure 1.1.1 Oxygenase and oxidase metalloenzymes.



1.2 Oxidation in Chemical Synthesis

In chemical synthesis, there have been several developments regarding asymmetric oxidation catalysts that involve heteroatom transfer, i.e., catalysts that mimic the behavior of oxygenase enzymes. Some of the most notable examples are illustrated in Figure 1.2.1. The initial discovery of a highly enantioselective catalytic oxidation was reported by Sharpless and Katsuki.[1] Allylic alcohols were epoxidized (**5** → **6**) by a titanium-tartrate catalyst, using *tert*-butyl hydroperoxide as the stoichiometric oxidant. Sharpless later reported the asymmetric dihydroxylation of unfunctionalized olefins (**7** → **8**) using an osmium catalyst system.[2] Jacobsen and Shi have both disclosed examples of enantioselective epoxidations of simple olefins (**9** → **11**, **12** → **14**).[3] Highly asymmetric aziridinations (**15** → **16**, **17** → **19**) have also been described by both Evans and Jacobsen.[3b,4] Although these examples do not involve O_2 as the stoichiometric oxidant like oxygenase enzymes, they do all proceed by heteroatom transfer from a reagent to the substrate.

Figure 1.2.1 Asymmetric oxidations featuring heteroatom transfers.

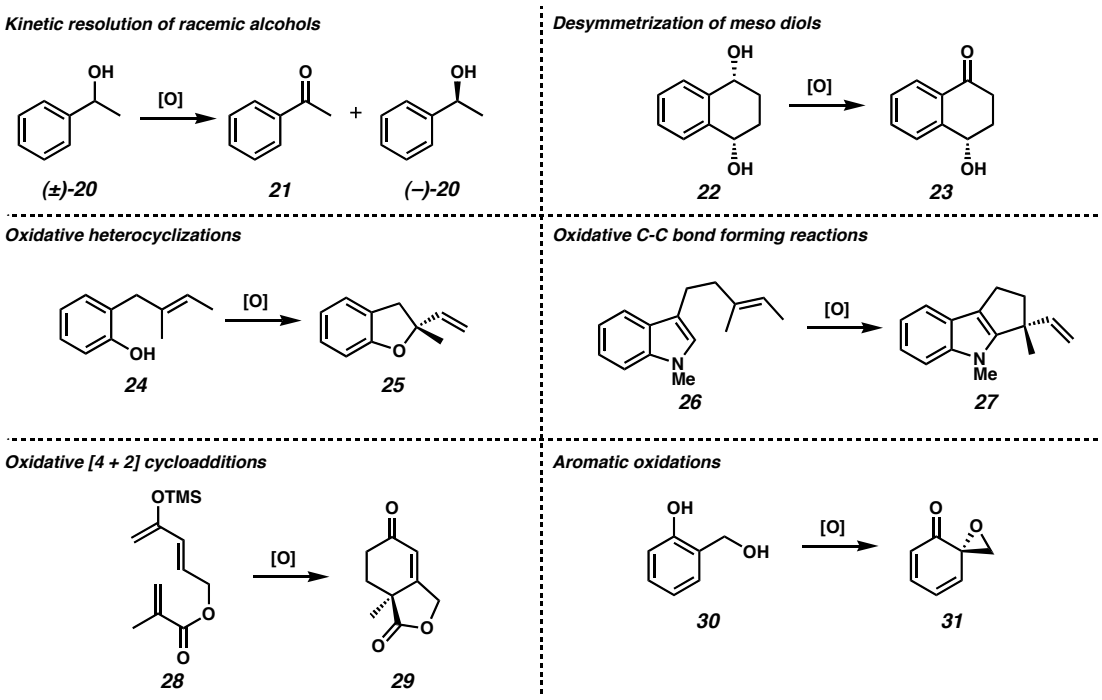


Chemical methods that mimic the reactions catalyzed by oxidase enzymes have also been developed. This class of transformations does not involve a heteroatom transfer to a substrate, but a dehydrogenative process instead. Fundamental reactions of this type include alcohol oxidations and alkane dehydrogenations, both ubiquitous in nature and in chemical synthesis. Although prevalent, asymmetric catalytic variants of this class of reactions have been relatively less explored in comparison to the oxygenase mimics.

Several enantioselective dehydrogenative reactions are illustrated in Figure 1.2.2. The kinetic resolution of racemic alcohols involves the selective oxidation of one enantiomer to produce a prochiral ketone (**21**) and an enantioenriched alcohol (**20**). This

same selective process can be applied to the desymmetrization of meso diols (**22** → **23**). Enantiopure heterocycles and carbocycles (e.g., **25** and **27**) can be envisioned to arise from asymmetric dehydrogenative processes. Other potential asymmetric non-heteroatom transfer oxidations include cycloadditions (**28** → **29**) and aromatic oxidations (**30** → **31**). The design and development of palladium(II) catalytic systems for investigations into this fertile area of enantioselective oxidation chemistry will be the focus of this thesis.[5]

Figure 1.2.2 Enantioselective dehydrogenative reactions.



1.3 Notes and References

(1) For discussions on the enantioselective epoxidation of allylic alcohols, see: (a) Katsuki, T. Epoxidation of Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 18.1, pp 621-648. (b) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Epoxidation of Allylic Alcohols. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 6A, pp 231-280.

(2) For discussions on the enantioselective dihydroxylation of olefins, see: (a) Markó, I. E.; Svendsen, J. S. Dihydroxylation of Carbon-Carbon Double Bonds. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 20, pp 713-787. (b) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation—Discovery and Development. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 6D, pp 357-398.

(3) For discussions on the enantioselective epoxidation of unfunctionalized olefins, see: (a) Jacobsen, E. N.; Wu, M. H. Epoxidation of Alkenes Other than Allylic Alcohols. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 18.2, pp 649-677. (b) Katsuki, T. Asymmetric Epoxidation of Unfunctionalized Olefins and

Related Reactions. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 6B, pp 649-677.

(4) For a discussion on enantioselective aziridinations, see: Jacobsen, E. N. Aziridination. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 17, pp 607-618.

(5) Palladium(II) dehydrogenative reactions have been the focus of several recent reviews. See: (a) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362-367. (b) Stahl, S. S. *Angew. Chem., Int. Ed*. **2004**, *43*, 3400-3420. (c) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem*. **2004**, *2*, 2551-2554.

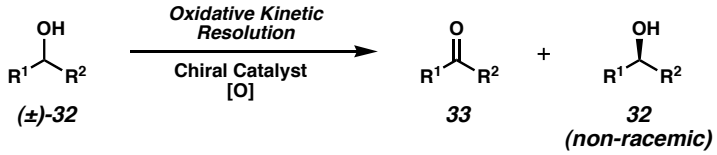
CHAPTER TWO

The Palladium-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols with Molecular Oxygen

2.1 Introduction

The oxidation of an alcohol to a carbonyl compound is one of the most ubiquitous reactions in organic chemistry.[1] Despite its prevalence, the enantioselective variant has been considerably less explored compared to other asymmetric oxidation processes (e.g., epoxidation, dihydroxylation, etc.). This relative neglect is somewhat understandable considering the nonintuitive nature of the problem—enantioselective alcohol oxidation involves the selective destruction of a stereocenter, in contrast to most asymmetric transformations, which involve the creation of stereogenicity. With the hope of developing a system that could be applicable to a broad range of dehydrogenative reactions, we first investigated the oxidative kinetic resolution of secondary alcohols using palladium(II) catalysis (Scheme 2.1.1).[2,3]

Scheme 2.1.1



2.2 Background

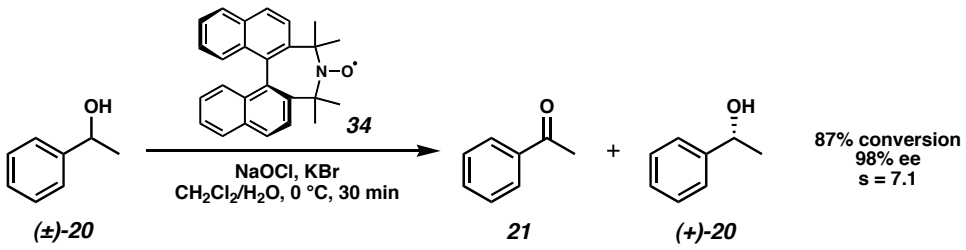
There have been numerous reports of nonenzymatic catalytic approaches to the kinetic resolution of secondary alcohols that do not involve alcohol oxidation.[4,5] The most extensively studied strategy toward kinetic resolution is via selective acylation,

pioneered by the works of Vedejs,[6] Fuji,[7] Fu,[8] Oriyama,[9] and Miller.[10] Other notable catalytic examples include resolutions via S_N2 displacements and allylic alcohol functionalizations (e.g., epoxidation, reduction).[11] One approach that has been relatively less explored is the resolution of secondary alcohols via enantioselective oxidation. At the onset of this project, there were only two general oxidative approaches to a resolution of this type.

2.2.1 Nitroxyl Radicals for the Oxidative Kinetic Resolution of Alcohols

The first approach toward a kinetic resolution via alcohol oxidation involves the use of nitroxyl radicals, which form the active *N*-oxoammonium species under oxidative conditions. Rychnovsky reported the oxidative kinetic resolution of secondary alcohols using chiral nitroxyl radical **34** (Scheme 2.2.1).[12] Sodium hypochlorite acts as the oxidizing agent for the nitroxyl radical. Modest selectivities were achieved across a range of substrates (s = 1.5-7.1).[13] This system represented the first example of a nonenzymatic catalytic enantioselective oxidation of secondary alcohols.

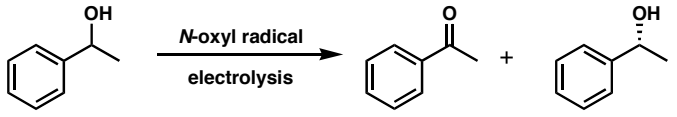
Scheme 2.2.1



Improvements to the nitroxyl radical approach were realized when electrolytic conditions were utilized. Some key examples of these systems are outlined in Table 2.2.1. Chiral nitroxyl radical **35** resolved *sec*-phenethyl alcohol (**20**) with some degree of selectivity,[14] while radical **34** (the same that was used by Rychnovsky) was significantly

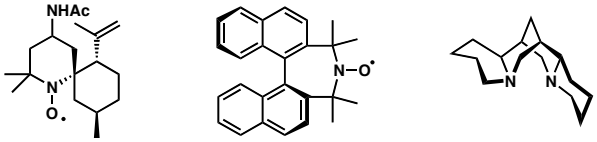
more selective.[15] The highly efficient TEMPO-(–)-sparteine system reported by Osa and Bobbitt is particularly noteworthy (entry 3).[16] In this system, (–)-sparteine is postulated to act as a chiral base in an enantioselective deprotonation step, conceptually different from the chiral nitroxyl radical examples (entries 1 and 2). Although high enantiomeric excesses can be obtained, this chemistry has yet to be utilized in any synthetic context.

Table 2.2.1 *N*-Oxyl radicals in oxidative kinetic resolutions of secondary alcohols.



(±)-20 ***21*** ***(+)-20***

entry	radical	% conversion	% ee *20*	s	ref
1	*35*	63.9	70.0	4.6	14
2	*34*	57.0	91.0	16	15
3	TEMPO (*+36*)	52.9	99.6	102	16

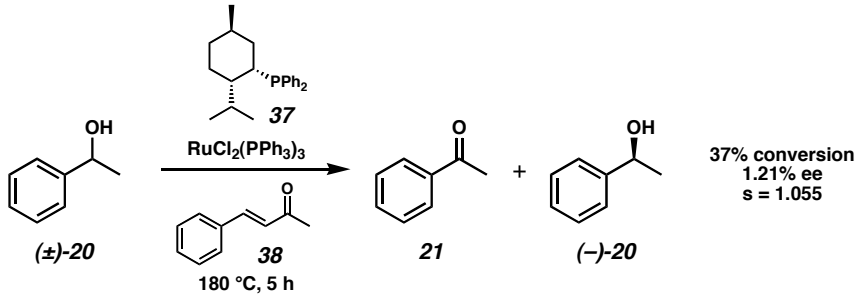


35 ***34*** ***36***

2.2.2 Transition Metal Approaches for the Oxidative Kinetic Resolutions of Alcohols

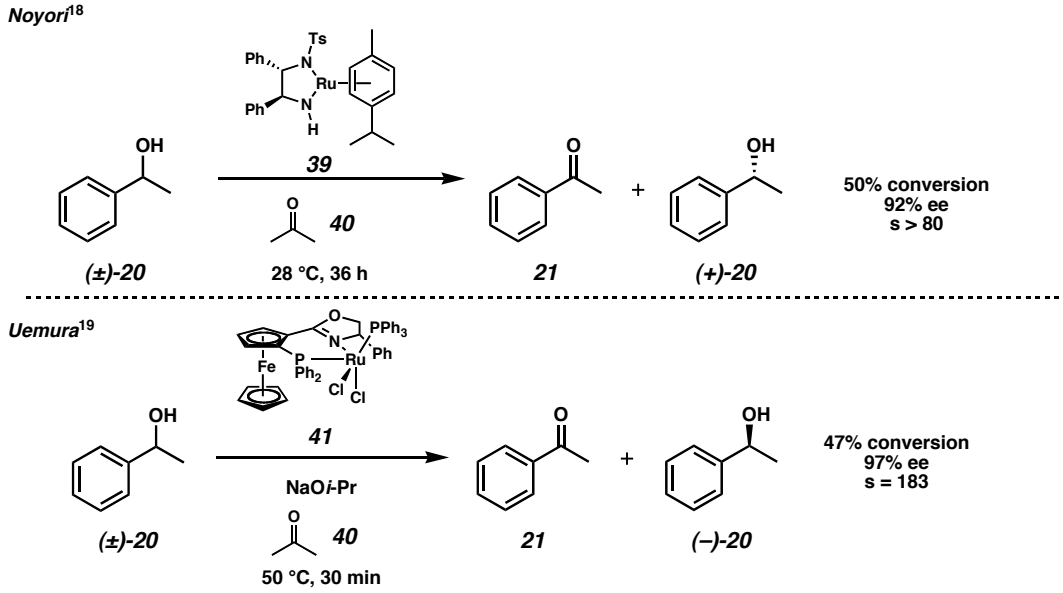
The other general approach to oxidative kinetic resolutions that has been investigated is transition metal catalysis. The first report of a metal-catalyzed enantioselective dehydrogenation was in 1976 by Ohkubo et al.[17] *sec*-Phenethyl alcohol (**20**) was oxidatively resolved via transfer hydrogenation in the presence of a ruthenium-phosphine catalyst with modest selectivity. Although the results were not synthetically useful (s = 1.055), this study demonstrated the viability of kinetic resolution through a transfer hydrogenation process.

Scheme 2.2.2



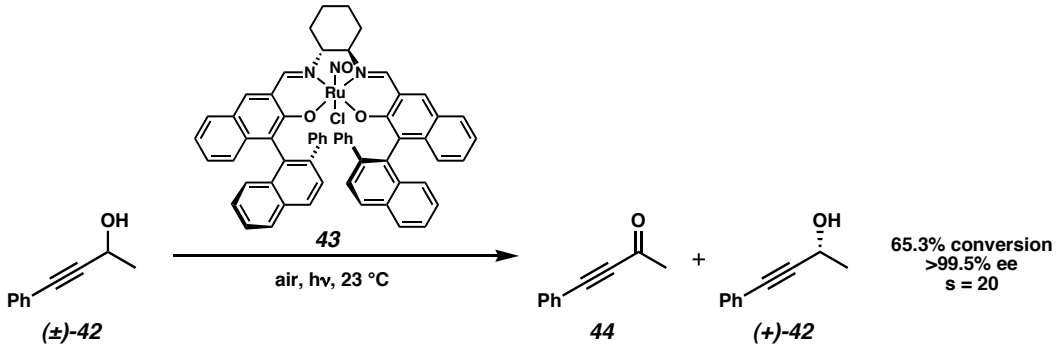
Noyori and Uemura have since developed highly enantioselective variants of the ruthenium-catalyzed kinetic resolution of secondary alcohols. Noyori demonstrated the use of ruthenium-diamine catalyst **39** to resolve secondary alcohols with acetone as the hydrogen acceptor (Scheme 2.2.3).[18] Uemura later reported a similar system using a ruthenium-ferrocenyloxazoline complex (**41**).[19] In both cases, an array of secondary alcohols were resolved to high enantiopurity with remarkable levels of selectivity (s > 100 for both).

Scheme 2.2.3



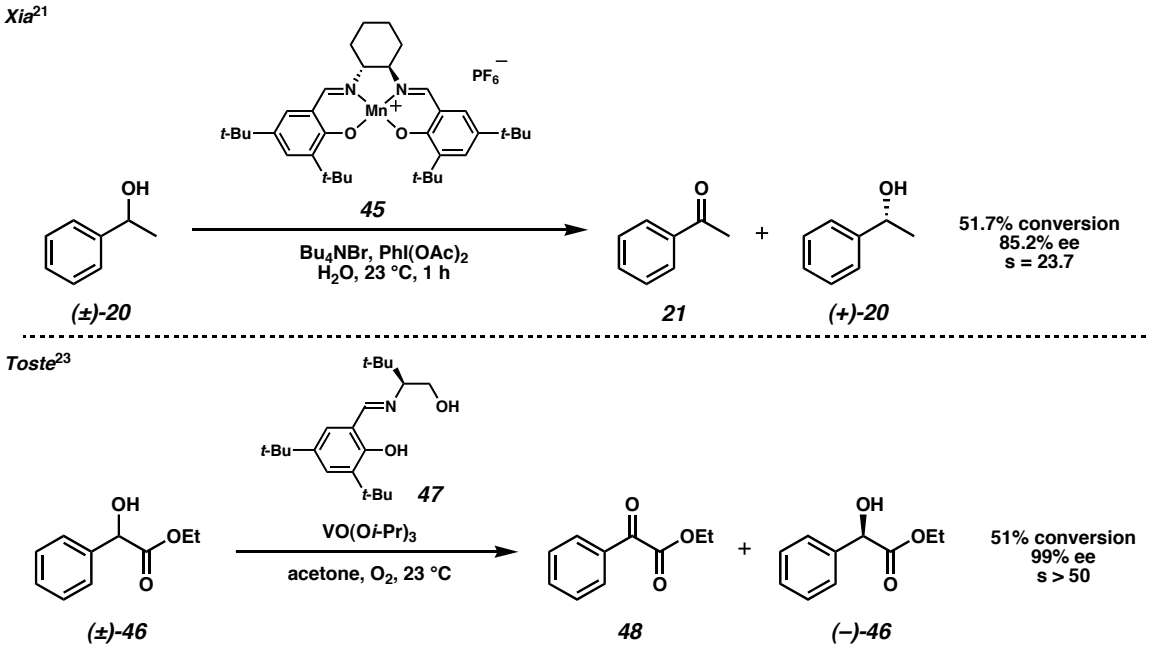
There have also been a few isolated reports of transition metal-catalyzed kinetic resolutions not involving direct transfer hydrogenation processes. Katsuki reported the oxidative kinetic resolution of secondary alcohols under air and irradiation using ruthenium-salen-derived catalyst **43**.[20] Only four alcohols (though structurally distinct from one another) were reported to be resolved by this system, and the reaction mechanism is presently unclear.

Scheme 2.2.4



Subsequent to our initial report on the kinetic resolution of secondary alcohols, more examples have surfaced. In 2003, Xia reported an oxidative kinetic resolution using a manganese-salen catalyst and iodobenzene diacetate as the stoichiometric oxidant (Scheme 2.2.5).[21] Selectivities up to 23.7 could be obtained by this system.[22] Toste recently described a vanadium-salicylaldimine catalyst system for the asymmetric oxidation of α-hydroxy esters.[23] High selectivities for a number of α-hydroxy esters were realized, though less activated alcohols (e.g., *sec*-phenethyl alcohol) were unreactive to this unique system.

Scheme 2.2.5



Despite these significant contributions, there still remained a need for a general catalytic enantioselective oxidation system. Importantly, we sought to develop a system that would be applicable to a variety of enantioselective oxidative transformations. Taking into consideration the ubiquitous nature of palladium catalysis in enantioselective reactions (e.g., Heck reactions,[24] π-allyl chemistry,[25] etc.), we decided to employ a palladium(II) system as our approach to this goal. Palladium(II) has been shown to catalyze the oxidation of alcohols to carbonyl compounds in the presence of a variety of stoichiometric cooxidants, including allyl carbonates, aryl halides, CCl_4, and molecular oxygen.[26] It was anticipated that a similar oxidative system consisting of a ligated palladium catalyst would be readily adaptable to asymmetric variants. Not only would this system serve as the basis for the development of an oxidative kinetic resolution of

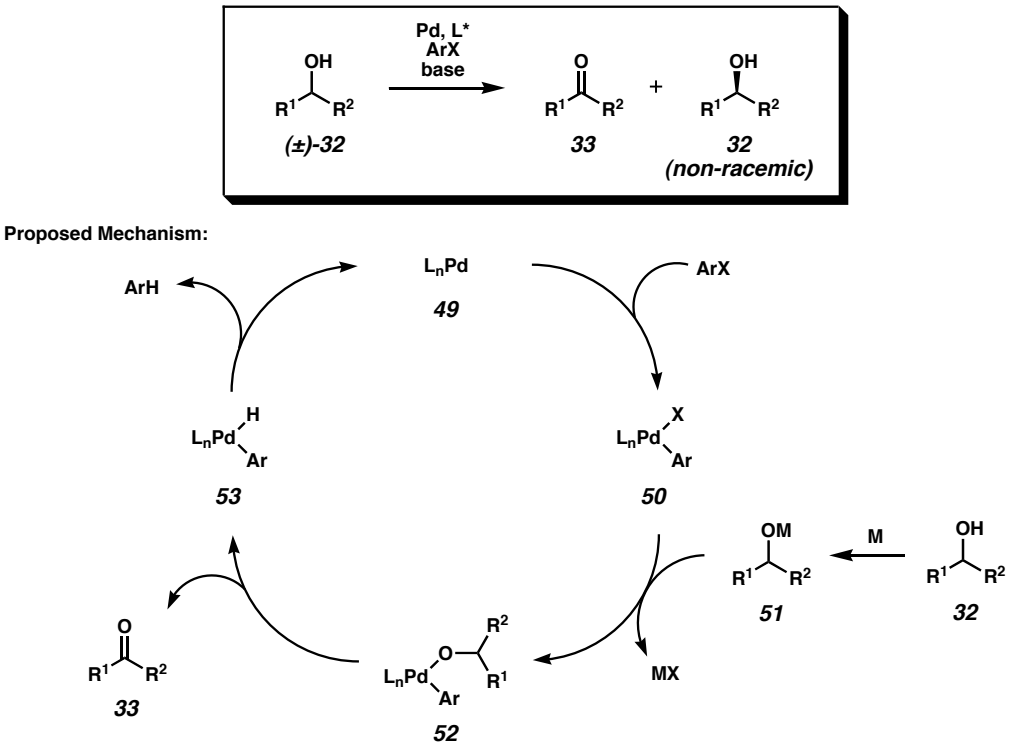
alcohols but also as a platform toward the development of several enantioselective dehydrogenation reactions.[27]

2.3 Reaction Development

2.3.1 Investigations of a Palladium/Aryl Halide System

Our initial strategy was to utilize an aryl halide as the stoichiometric oxidant with a ligated palladium catalyst. The mechanism envisioned for this reaction is outlined in Scheme 2.3.1. Starting with a palladium(0)-ligand complex (**49**), oxidative addition of the aryl halide affords Pd(II) intermediate **50**. Transmetallation with metal alkoxide **51** (generated from the alcohol and a metal base) produces a palladium alkoxide, which can undergo β-hydride elimination to afford palladium hydride **53**. Reductive elimination regenerates the Pd(0) catalytic species, with reduced arene as a byproduct. This system appeared especially attractive based on the number of variables that could potentially influence the asymmetric transformation (i.e., palladium source, chiral ligand, base, aryl halide, solvent, temperature, etc.).

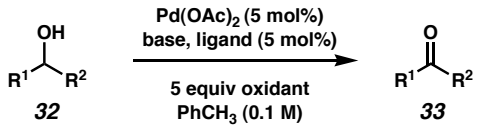
Scheme 2.3.1

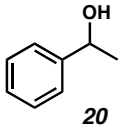
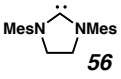
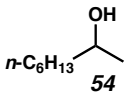
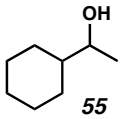


Most reports of palladium(II) oxidations of alcohols involved the use of highly coordinating solvents (e.g., DMSO, methanol). It was presumed that more mild conditions would be readily amenable to asymmetric catalysis—that is, in nonpolar solvents that would not disrupt any palladium-ligand intermediates, and preferably at reasonable temperatures for asymmetric reactions. Using *sec*-phenethyl alcohol (**20**) as our test substrate, a number of conditions were evaluated (Table 2.3.1). Starting with K_2CO_3 as the metal base, bromobenzene as the stoichiometric oxidant, and toluene as the solvent at 80 °C, oxidation to acetophenone was sluggish (entry 1). Switching to iodobenzene, which can undergo oxidative addition at lower temperatures, and from K_2CO_3 to the stronger NaO*t*-Bu as the metal base, the complete oxidation to acetophenone occurred in approximately 3 h at 30 °C (entry 3). Importantly, these

oxidative conditions were generally effective for a number of ligand types (monodentate, bidentate, carbene, pyridyl) and substrates, providing several options for asymmetric variants.

Table 2.3.1 Palladium-catalyzed alcohol oxidations with aryl halides as the stoichiometric oxidant.

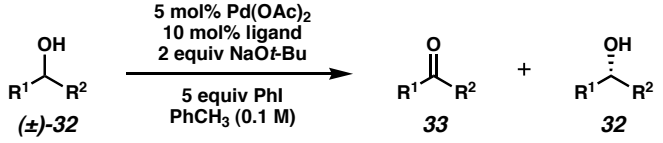


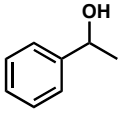
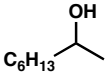
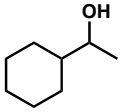
alcohol	entry	base	ligand	oxidant	temp./time	% conversion[a]
 20	1	K_2CO_3 (5 equiv)	dppe	PhBr	80 °C / 7.5 h	16
	2	Cs_2CO_3 (5 equiv)	dppe	PhI	80 °C / 5 h	75
	3	NaO*t*-Bu (2 equiv)	dppe	PhI	30 °C / 3 h	96
	4[b]	NaO*t*-Bu (2 equiv)	PPh_3	PhI	30 °C / 5 h	94
	5[b]	NaO*t*-Bu (2 equiv)	 56	PhI	30 °C / 2 h	97
	6	NaO*t*-Bu (2 equiv)	2,2'-dipyridyl	PhI	30 °C / 30 h	72
 54	7	NaO*t*-Bu (2 equiv)	dppe	PhI	30 °C / 1.5 h	65
 55	8	NaO*t*-Bu (2 equiv)	dppe	PhI	30 °C / 2 h	>99

[a] % conversion measured by ^{1}H NMR. [b] 10 mol% ligand added.

Having developed this mild oxidation system, an initial screen of chiral ligands was conducted, providing some promising results (Table 2.3.2). Although *sec*-phenethyl alcohol (**20**) was not resolved by any of the palladium-ligand complexes, aliphatic alcohols displayed modest levels of enantiodifferentiation. For example, 1-cyclohexylethanol was resolved to 65% ee at 58% conversion (s = 5.3) by treatment with (–)-Me-DUPHOS (**57**), $Pd(OAc)_2$, NaO*t*-Bu, and iodobenzene in CH_2Cl_2 at 30 °C (entry 10).

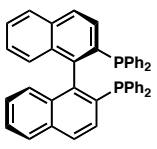
Table 2.3.2 Palladium-catalyzed enantioselective oxidations of secondary alcohols with iodobenzene.

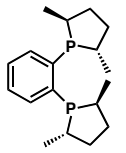


alcohol	entry	ligand	temp./time	% conversion[a]	% ee[b]	s
 (±)-20	1	(*R*)-BINAP	30 °C / 6 h	63	0	1.0
	2	(+)-Me-DUPHOS	30 °C / 96 h	66	0	1.0
	3	(*S,S*)-CHIRAPHOS	20 °C / 48 h	72	0	1.0
	4	(*R,R*)-DIOP	30 °C / 41 h	30	0	1.0
	5	(*R,R*)-Trost Ligand	30 °C / 65 h	17	0	1.0
 (±)-54	6	(+)-Me-DUPHOS	30 °C / 36 h	43	16	1.5
 (±)-55	7	(*R*)-BINAP	20 °C / 24 h	57	0	1.0
	8	(+)-Me-DUPHOS	30 °C / 65 h	51	20	1.8
	9	(*R,R*)-Trost Ligand	30 °C / 65 h	6	0	1.0
	10[c]	(+)-Me-DUPHOS	30 °C / 15 h	58[c]	65	5.3

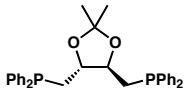
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by GC or HPLC. [c] CH_2Cl_2 as solvent.

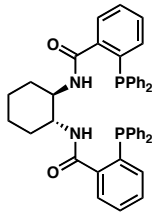
Figure 2.3.1 Ligands evaluated in Table 2.3.2.


(R)-BINAP (56)


(+)-Me-DUPHOS (57)


(S,S)-CHIRAPHOS (58)

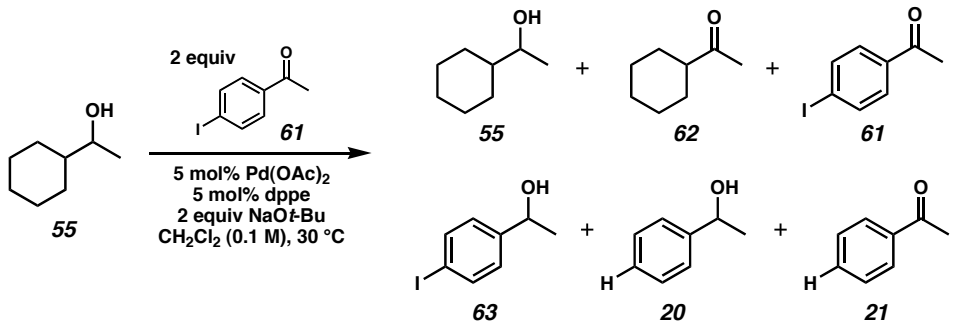

(R,R)-DIOP (59)


(R,R)-Trost Ligand (60)

Although the initial results were encouraging, it was soon found that these reactions were plagued by side reactions and inconsistencies. Specifically, during an investigation of the substituent effects on the aryl halide, an experiment with 4'-iodoacetophenone revealed a complicating side reaction (Scheme 2.3.2). In the oxidation

of alcohol **55**, three alcohols and their corresponding ketones were observed in the reaction mixture. Alcohols **63** and **20** could only arise from some reductive pathway. It was later found through control experiments that the presence of a metal base was promoting a background Meerwein-Ponndorf-Verley reduction/Oppenauer oxidation cycle between an alcohol and a ketone.[28] This nonselective process was likely racemizing the resolved alcohol in our systems to some extent, prohibiting high levels of enantiopurity. Moreover, the oxidation system showed a clear oxygen dependency; when these reactions were conducted under the rigorous exclusion of oxygen, alcohol oxidation barely proceeded. Recognizant of these difficulties and desirous of a simpler system, we decided to turn elsewhere.

Scheme 2.3.2

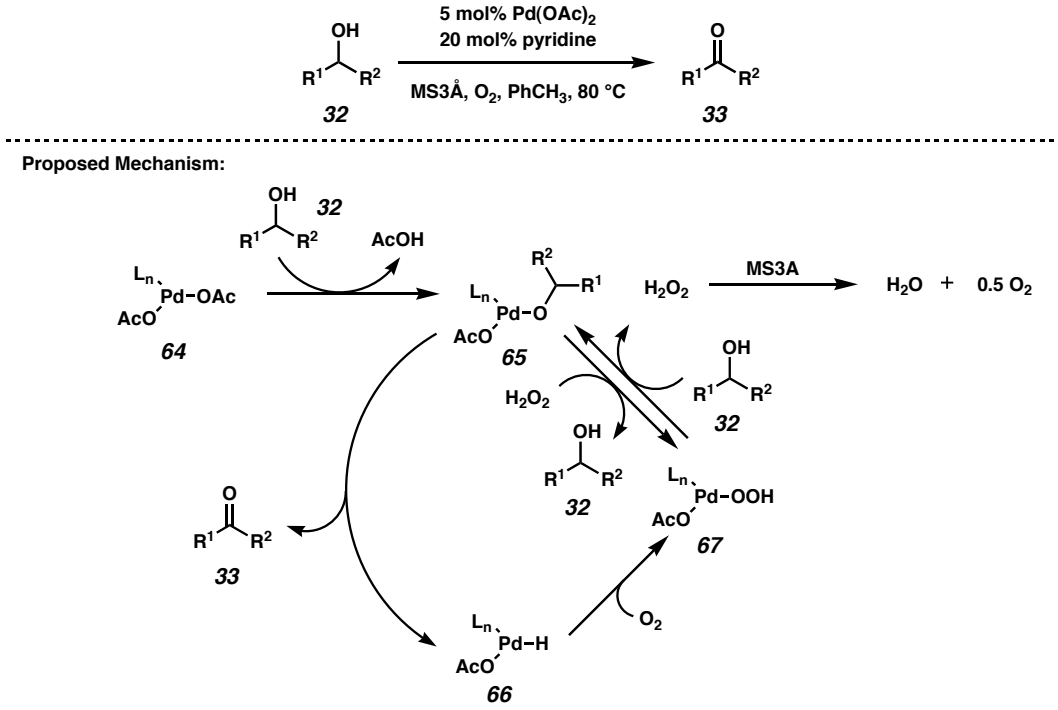


2.3.2 Oxidative Kinetic Resolution of Alcohols with a Palladium/Oxygen System

An alternative oxidative system that was considered was initially reported by Uemura in 1999 (Scheme 2.3.3).[26f] He described the oxidation of a number of alcohols to aldehydes and ketones using a palladium-pyridine (1:4 molar ratio) catalyst system in toluene at 80 °C. Molecular oxygen was used as the sole stoichiometric oxidant, and high yields were realized for an array of alcohol substrates. The mechanism proposed by Uemura (Scheme 2.3.3) begins with acetate exchange with an alcohol to provide

palladium alkoxide **65**. This intermediate can undergo β-hydride elimination to the resulting palladium hydride (**66**). Reoxidation of the palladium hydride by oxygen affords palladium peroxide **67**, which subsequently exchanges ligands with another alcohol to regenerate the palladium alkoxide. The byproduct, hydrogen peroxide, is proposed to disproportionate to H_2O and O_2 by the 3Å molecular sieves in the reaction mixture.

Scheme 2.3.3

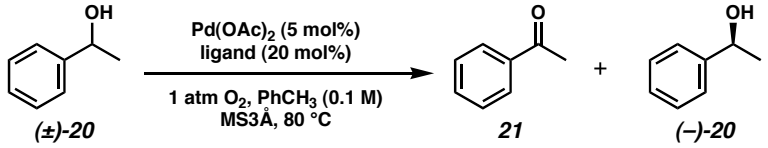


There were some important features to this system that made it particularly attractive for developing an oxidative kinetic resolution. No strong base was required, which would hopefully prevent the background reduction/oxidation cycle that had complicated the aryl halide system. Molecular oxygen is inexpensive and abundant, and the byproduct of the oxidation is water, both advantageous from an environmental and an

economical standpoint. Lastly, the system demonstrated a clear ligand dependence—when the reaction was performed in the absence of pyridine, the oxidation did not proceed efficiently. Because of this dependence on the ligand, it was anticipated that chiral ligands would have a significant enantioinducing effect on the alcohol oxidation.

Alcohol **(±)-20** was subjected to oxidative conditions analogous to Uemura's system, but substituting various chiral ligands for pyridine (Table 2.3.3). Each of these systems led to one of three results: (a) catalyst activity was completely suppressed (entries 1-6), (b) oxidation was observed but nonselective (entries 7 and 8), or (c) partial resolution via oxidation was achieved (entries 9 and 10). During this evaluation, (–)-sparteine (**36**) immediately emerged as a promising ligand for this transformation. After 24 h at 80 °C, *sec*-phenethyl alcohol was oxidized to acetophenone in 15.1% conversion, and alcohol **20** was recovered in 13.7% ee. Although those particular values are not synthetically useful, the selectivity factor of 8.8 was the highest observed in any of the systems studied up to this point.

Table 2.3.3 Initial ligand screen for the aerobic oxidative kinetic resolution of **20**.

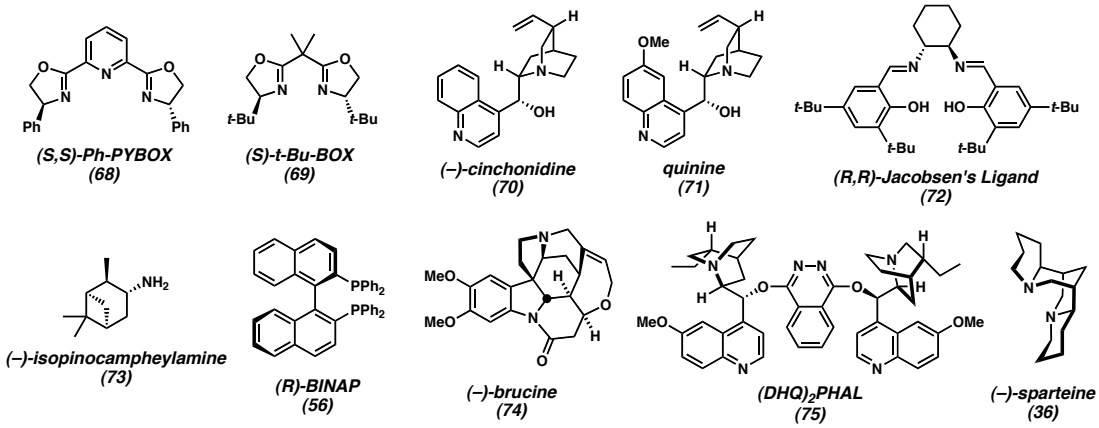


(±)-20 *21* *(–)-20*

entry	ligand	time	conversion (%)[a]	% ee *20*[b]	s
1	(*S,S*)-Ph-PYBOX	72 h	2	-	1
2	(S)-*t*-Bu-BOX	24 h	3	-	1
3	(–)-cinchonidine	72 h	2	-	1
4	quinine	24 h	0	-	1
5	(–)-isopinocampheylamine	24 h	0	-	1
6	(*R,R*)-Jacobsen's Ligand	24 h	3	-	1
7	(*R*)-BINAP	24 h	29.0	0	1
8	(–)-brucine	24 h	77.0	0	1
9	$(DHQ)_2PHAL$	24 h	31.6	8.7	1.6
10	(–)-sparteine	24 h	15 .1	13.7	8.8

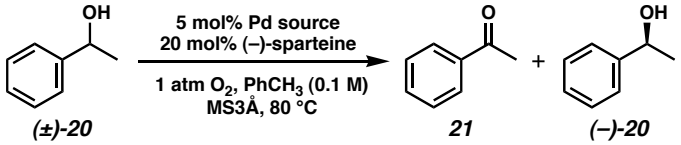
[a] % conversion measured by GC. [b] % ee measured by HPLC.

Figure 2.3.2 Ligands evaluated in Table 2.3.3.



Reexamination of the mechanism proposed by Uemura (Scheme 2.3.3) proved to be critical for the optimization of this reaction. In the mechanism, an acetoxy moiety is bound to the palladium center throughout the catalytic cycle. This moiety originates from the $Pd(OAc)_2$ used as a precatalyst. It was hypothesized that changing counterions by varying the palladium precursors would have marked effects on both the reactivity and selectivity of the oxidation. A variety of palladium sources were surveyed to test this hypothesis (Table 2.3.4). Indeed, palladium precatalysts with chloride counterions were found to be more reactive and selective than ones with acetate counterions. Eventually we found $Pd(nbd)Cl_2$ to be the most effective palladium precursor for this reaction, resulting in a selectivity of 23.1 for the oxidative kinetic resolution of *sec*-phenethyl alcohol (entry 7).[29]

Table 2.3.4 Palladium source examination for the oxidative kinetic resolution.



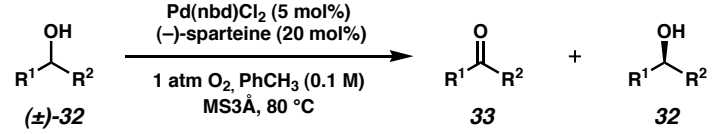
(±)-20 *21* *(–)-20*

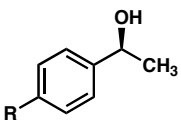
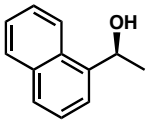
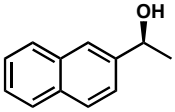
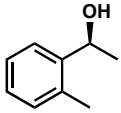
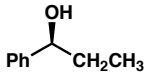
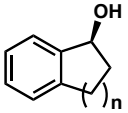
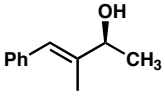
entry	Pd source	time	conversion (%)[a]	% ee *20*[b]	s
1	$Pd(OAc)_2$	24 h	15.1	13.7	8.8
2[c]	$Pd_2(dba)_3$	55 h	66.2	81.5	5.7
3	$PdCl_2$	96 h	62.6	98.0	16.3
4	$Pd(CH_3CN)_2Cl_2$	36 h	51.7	79.8	16.5
5	$Pd(PhCN)_2Cl_2$	36 h	57.4	92.1	16.9
6[c]	$[(allyl)PdCl]_2$	96 h	60.2	96.9	18.0
7	*$Pd(nbd)Cl_2$*[d]	*96 h*	*59.9*	*98.7*	*23.1*

[a] % conversion measured by GC. [b] % ee measured by HPLC. [c] 2.5 mol% Pd source (5 mol% Pd). [d] nbd: norbornadiene.

With the optimized resolution conditions in hand, investigations into the scope of the reaction were conducted. As shown in Table 2.3.5, a variety of activated alcohols (i.e., benzylic and allylic) can be resolved to high enantiomeric excess with good to excellent selectivities. 1-Phenylethanol derivatives are particularly good substrates for the kinetic resolution (entries 1-3). A number of different arenes can be substituted for the phenyl group, although steric hindrance from ortho substituents can significantly impact reactivity (entries 4-6). Endocyclic alcohols can be resolved to high levels of enantiopurity (entries 8 and 9). The resolution is not limited to benzylic alcohols, as demonstrated by the resolution of allylic alcohol **84** (entry 10).[30]

Table 2.3.5 The oxidative kinetic resolution of secondary alcohols with a palladium-sparteine system.



entry	unreacted alcohol, major enantiomer		time	conversion (%)[a]	isolated yield (%)[b]	% ee ROH[c]	s[d,e]
1		R = H *20*	96 h	59.9	37 (93)	98.7	23.1
2		R = OMe *76*	96 h	66.6	32 (96)	98.1	12.3
3		R = F *77*	54 h	63.3	32 (88)	97.4	14.4
4		*78*	192 h	55.9	43 (97)	78.4	9.8
5		*79*	112 h	55.2	44 (99)	99.0	47.1
6		*80*	144 h	48.4	49 (95)	68.7	13.1
7		*81*	192 h	59.3	40 (98)	93.1	14.8
8[f]		n = 1 *82*	54 h	67.5	30 (93)	93.4	8.3
9		n = 2 *83*	40 h	68.6	31 (99)	99.8	15.8
10		*84*	120 h	70.4	29 (99)	91.8	6.6

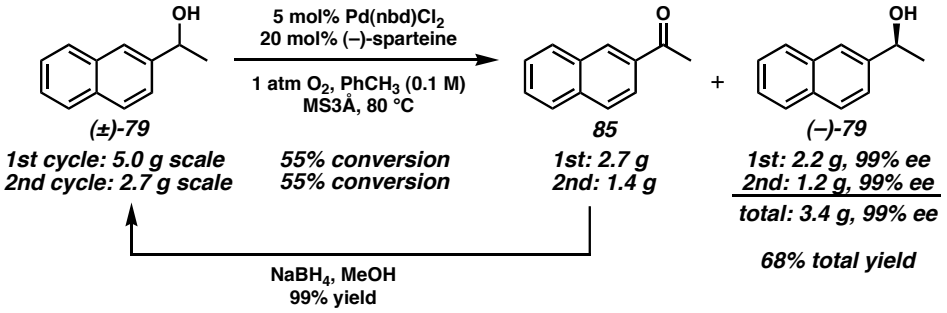
[a] % conversion measured by GC. [b] Isolated yield of enantioenriched alcohol is presented first. Number in parentheses refers to the total combined yield of alcohol and ketone. [c] % ee was measured by HPLC or GC. [d] Selectivity values represent an average of at least two experiments. [e] For each entry, comparable selectivities are observed through the course of the reaction. [f] Performed at 60 °C.

2.3.3 Scale up and Recycling

One of the major criticisms leveled on kinetic resolutions is that the theoretical maximum yield of the reaction is only 50%. The scale up experiment depicted in Scheme 2.3.4 demonstrates the simplicity with which this potential drawback is overcome. On a multigram kinetic resolution of **(±)-79**, we were able to recover alcohol **79** in 44% yield

and 99% ee after one resolution. The recovered ketone (**85**) was quantitatively reduced by sodium borohydride to regenerate the racemic alcohol, which was then subjected to a second resolution. After the two cycles, alcohol **79** was isolated in 68% total yield and 99% ee. A trivial ketone reduction and recycling sequence provides an opportunity to access >50% yield of a starting racemic alcohol from the oxidative resolution process.

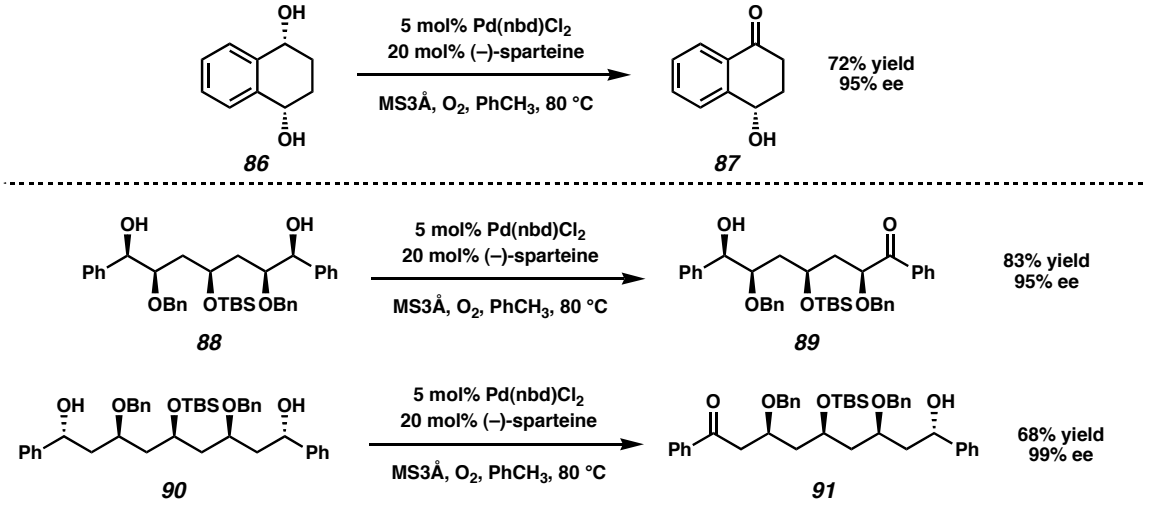
Scheme 2.3.4



2.3.4 Desymmetrization of Meso Diols

The palladium-catalyzed oxidative kinetic resolution can also be applied to the desymmetrization of meso diols by the same selective process. Meso diol **86** was subjected to the standard kinetic resolution to afford the hydroxyketone (**87**) in 72% yield and 95% ee. Jeffrey Bagdanoff, a graduate student in the Stoltz laboratory, later applied this desymmetrization concept toward the enantioselective synthesis of complex acyclic polyols.[31] In both of these transformations (**88** → **89**, **90** → **91**), four stereocenters are set enantioselectively in a single step. The desymmetrized ketone products were isolated in high yields and enantiopurities.

Scheme 2.3.5



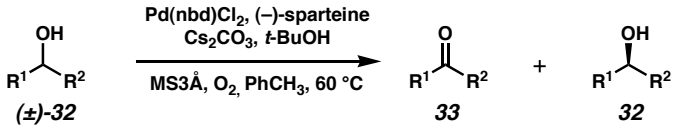
2.4 Further Developments

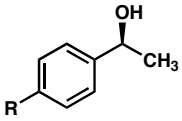
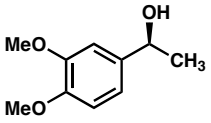
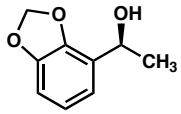
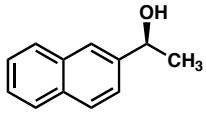
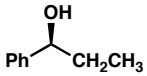
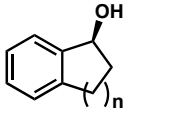
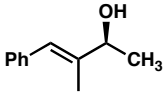
2.4.1 Improved Reaction Conditions

At this point, the palladium-catalyzed oxidative kinetic resolution could be utilized to access an array of enantiopure secondary alcohols. The conditions developed, however, were noticeably sluggish (approximately 2-8 days, see Table 2.3.5). During the course of these investigations, a palladium•sparteine complex was prepared to test its reactivity in the resolution. In general, we found that the reactivity of this complex was significantly lower than our optimized system, wherein a fourfold excess of (–)-sparteine relative to the palladium precursor is added, forming the complex in situ. Interestingly, the reactivity of the resolution with the palladium•sparteine complex could be restored to the optimal levels if 3 equivalents of (–)-sparteine relative to the complex were added. It could also be restored to near optimal levels by adding an achiral base (e.g., 4-methyl-2,6-di-*tert*-butylpyridine) instead of (–)-sparteine.

Based on these results, it was anticipated that the oxidative kinetic resolution could be affected by the presence of a stoichiometric base. Jeffrey Bagdanoff therefore sought to improve the reaction rates of the established system by probing the effects of bases and other additives. Eventually, it was found that the addition of both Cs_2CO_3 and *t*-BuOH to the standard conditions resulted in a dramatic rate acceleration.[32] As shown in Table 2.4.1, all of the resolutions are complete in less than 24 h, and the alcohols can be accessed in high enantiopurity.

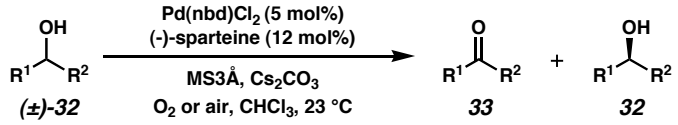
Table 2.4.1 The rate-accelerated palladium-catalyzed oxidative kinetic resolution.

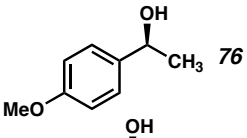
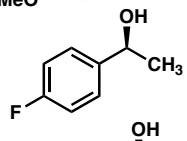
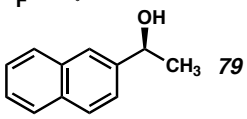
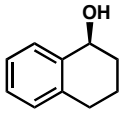
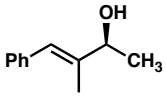
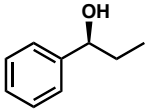


entry	unreacted alcohol, major enantiomer		time	conversion (%)	% ee ROH	s
1		R = H *20*	12.5 h	63.9	99.6	20.0
2		R = OMe *76*	9.5 h	67.4	99.5	14.9
3		R = F *77*	12.5 h	65.7	97.4	12.1
4		*92*	18 h	63.8	98.3	15.4
5		*93*	15 h	56.5	99.7	47.4
6		*79*	12 h	66.1	99.4	15.8
7		*81*	4.5 h	62.8	98.0	16.1
8		n = 1 *82*	12 h	74.0	99.5	10.1
9		n = 2 *83*	12 h	61.5	99.0	20.9
10		*84*	12 h	65.1	87.9	7.5

In hopes of further understanding the effects of the individual reaction parameters, Jeffrey Bagdanoff conducted a more thorough screening of various conditions for the oxidative kinetic resolution. Ultimately, it was found that chloroform was uniquely effective as a solvent for the reaction.[33,34] This modification allowed the resolution to be conducted at room temperature, resulting in a uniform increase in selectivity factors (Table 2.4.2). Moreover, the reactions could be performed in the presence of ambient air without an appreciable loss of selectivity. Curiously, the resolutions proceeded with faster reaction rates in ambient air; the reasons behind this observation are presently unclear.

Table 2.4.2 The palladium-catalyzed oxidative kinetic resolution at room temperature.

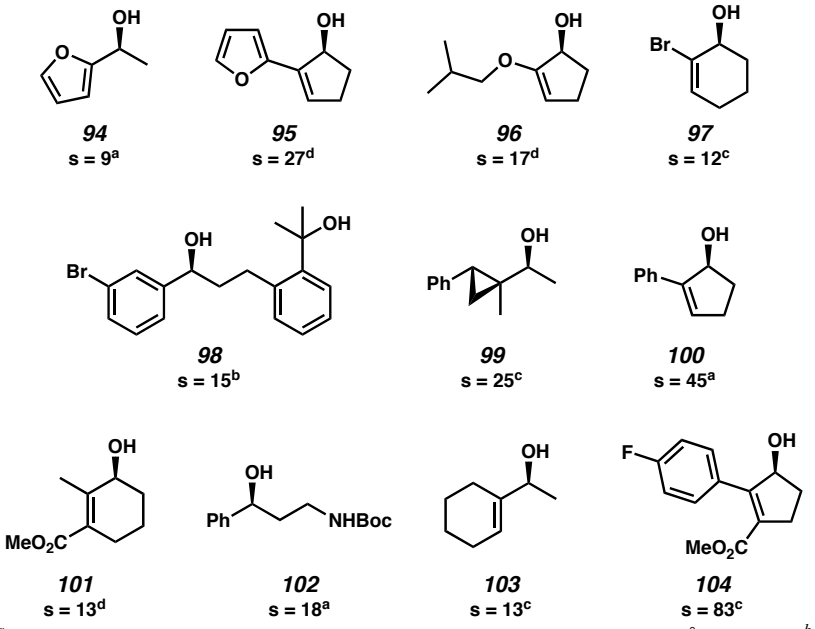


entry	unreacted alcohol, major enantiomer		atm	time	conversion (%)	% ee ROH	s
1		*76*	O_2	48 h	62.6	99.9	27.1
			air	24 h	62.3	99.8	25.4
2		*77*	O_2	48 h	59.3	98.0	23.0
			air	24 h	56.7	93.0	19.5
3		*79*	O_2	48 h	59.3	99.6	31.1
			air	24 h	55.5	98.0	37.3
4		*83*	O_2	24 h	57.5	98.0	27.6
			air	16 h	60.2	99.6	28.0
5		*84*	O_2	48 h	62.6	98.7	17.9
			air	44 h	64.7	98.9	15.7
6		*81*	O_2	72 h	62.6	98.2	24.4
			air	48 h	56.8	94.9	21.7

2.4.2 Expanding the Substrate Scope toward Total Synthesis Applications

Up to this point, the substrates that had been investigated in the development of conditions for the oxidative kinetic resolution were primarily simple secondary alcohols. A significant effort has been put forth in expanding this substrate scope, especially in light of the development of new conditions. Work by David Ebner, Daniel Caspi, and Ryan McFadden, graduate students in the Stoltz laboratory, has demonstrated that a variety of secondary alcohols can be resolved with high selectivities (Figure 2.4.1).[35] Functional groups such as enol ethers, vinyl and aryl bromides, esters, and carbamates are all compatible with the reaction conditions. It was also found that no single set of conditions is superior for every substrate. Some of the substrates investigated are key building blocks for important pharmaceuticals, such as monteleukast sodium (Singulair®),[36] fluoxetine hydrochloride (Prozac®),[37] and Merck's promising human neurokinin-1 receptor antagonist[38] (from alcohols **98**, **102**, and **104**, respectively).

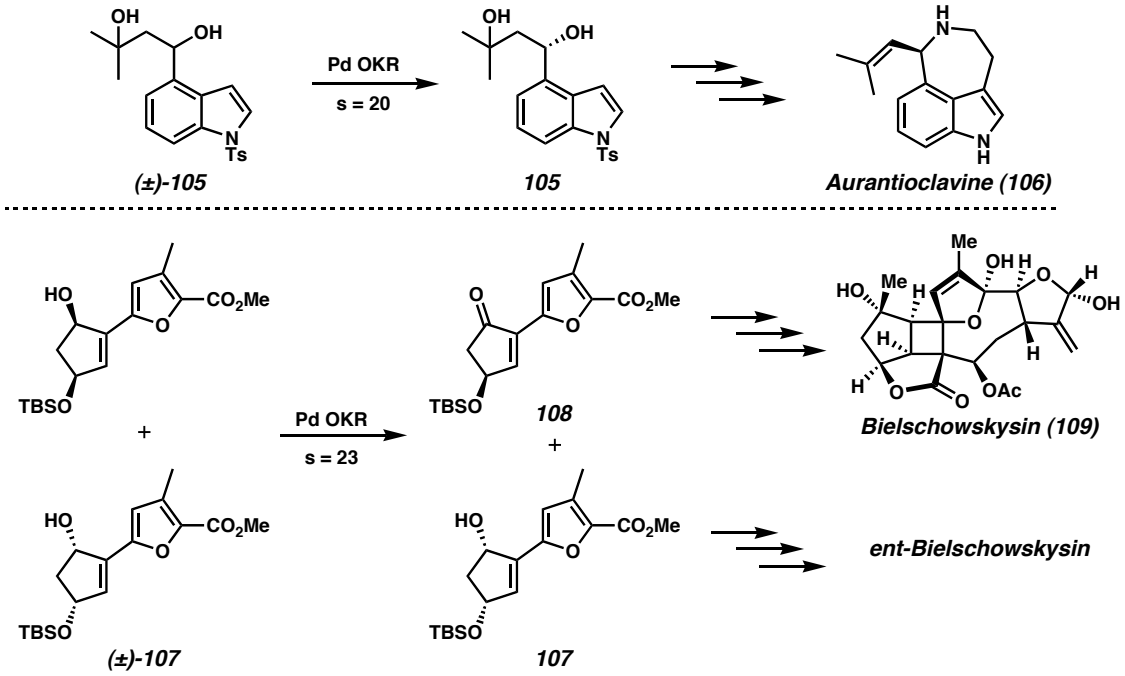
Figure 2.4.1 Enantioenriched substrates accessed by the oxidative kinetic resolution.



[a] 5 mol% $Pd(nbd)Cl_2$, 20 mol% (–)-sparteine, toluene, O_2, MS3Å, 80 °C. [b] 5 mol% $Pd(nbd)Cl_2$, 20 mol% (–)-sparteine, Cs_2CO_3, *t*-BuOH, toluene, O_2, MS3Å, 60 °C. [c] 5 mol% $Pd(nbd)Cl_2$, 12 mol% (–)-sparteine, Cs_2CO_3, $CHCl_3$, O_2, MS3Å, 23 °C. [d] 5 mol% $Pd(nbd)Cl_2$, 12 mol% (–)-sparteine, Cs_2CO_3, $CHCl_3$ air, MS3Å, 23 °C.

The palladium-catalyzed oxidative kinetic resolution has also been utilized in the context of total synthesis of bioactive natural products (Scheme 2.4.1). Yeeman Ramtohul, a former postdoctoral scholar in the Stoltz laboratory, has applied the resolution to secondary alcohol **105**, which we anticipated to be a viable intermediate in the enantioselective synthesis of aurantioclavine (**106**).[39] Michael Meyer, a graduate student in the Stoltz laboratory, has also performed a resolution of cyclopentenol **107** as a method of accessing both enantiomers of a key intermediate in work toward the total synthesis of bielschowskysin (**109**).[40]

Scheme 2.4.1



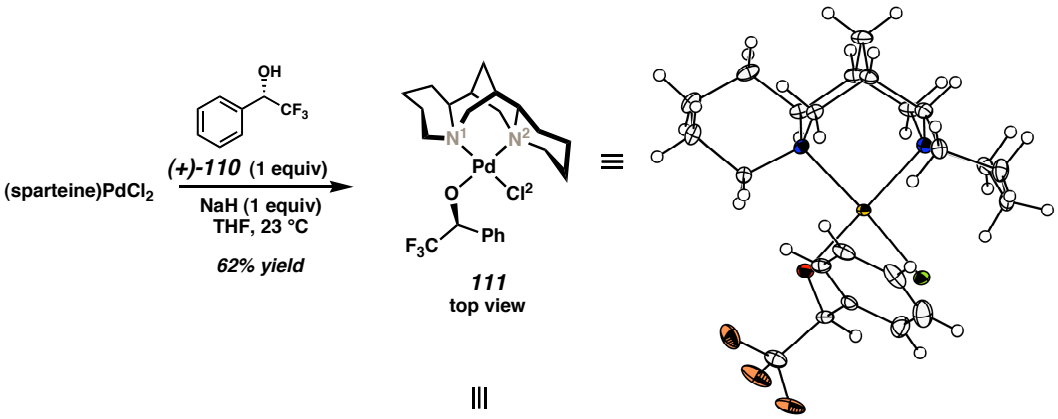
2.5 Mechanistic Studies

2.5.1 Coordination Studies on Palladium-Sparteine Systems

There have also been significant developments in understanding the mechanistic details and the origin of selectivity in the palladium-catalyzed oxidative kinetic resolution. Raissa Trend, a graduate student in the Stoltz laboratory, has studied a number of palladium•sparteine complexes to ascertain the mode of enantioinduction.[41] Specifically, (*S*)-(+)-α-(trifluoromethyl)benzyl alcohol (**(+)-110**) was reacted with sodium hydride and (sparteine)palladium dichloride to generate a single palladium species (Scheme 2.5.1). The alcohol chosen represents a steric model for the reactive enantiomer of *sec*-phenethyl alcohol (**20**) in the kinetic resolution. However, because of the low reactivity of alcohol **110** under the oxidative conditions, the palladium alkoxide could be isolated and characterized by X-ray crystallography. The crystal structure

vividly illustrates the orientation with which the alcohol binds to the palladium-sparteine catalyst. The phenyl (R_L) is positioned in the open region above the square plane of the metal complex (**111**, side view), and the benzylic C-H bond is pointed toward the metal plane parallel to the palladium-chloride bond. Importantly, the palladium-chloride bond is somewhat distorted out of the square plane, implicating how the chloride anion moves away from the metal center to reveal a site for β-hydride elimination.

Scheme 2.5.1

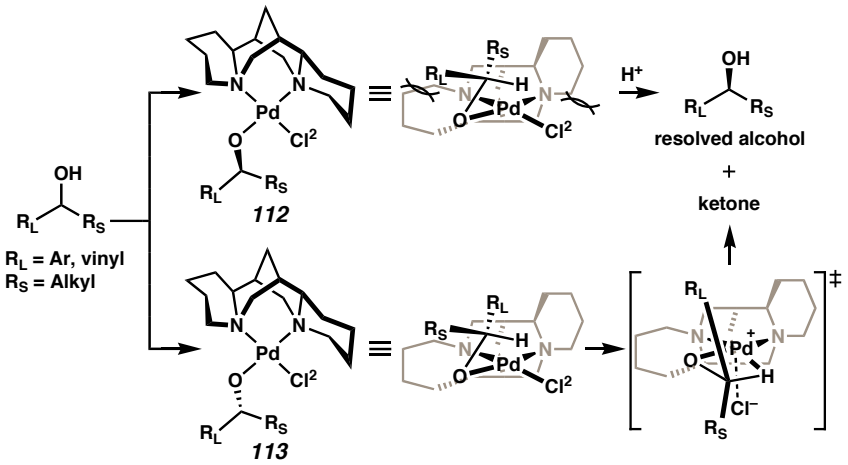


Atoms	Distance (Å)
Pd–N^1	2.1243(17)
Pd–N^2	2.0925(16)
Pd–O	2.0012(14)
Pd–Cl	2.3316(5)
N^1–Pd–Cl angle = 164.59(5)°	

Based on the above studies, a model for selectivity in the kinetic resolution was proposed (Scheme 2.5.2).[41] Both of the alcohols bind preferentially at the position indicated to form diastereomeric alkoxides **112** and **113**. Due to steric interactions with the sparteine ligand, alkoxide **112** cannot adopt the necessary orientation to undergo β-hydride elimination; it therefore protonates and dissociates from the complex.

Meanwhile, alkoxide **113** can undergo partial chloride dissociation and β-hydride elimination from a four-coordinate metal center with an axially disposed chloride.[42] Since alkoxide **113** leads to ketone production and alkoxide **112** leads to alcohol dissociation, an overall resolution results.

Scheme 2.5.2

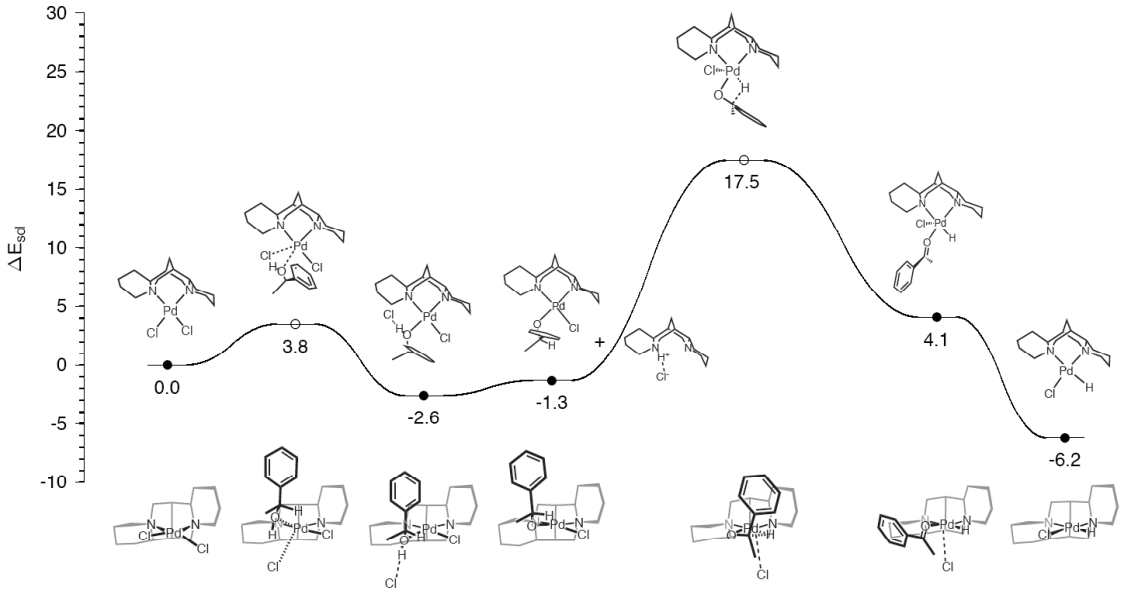


2.5.2 Computational Studies

The counterion effect seen in the initial studies (*vide supra*), with chloride being a much more effective anion than acetate, can be rationalized by these studies and those of Robert Nielsen, a graduate student in the Goddard research group at Caltech.[43] The chloride ion of the palladium alkoxide partially dissociates prior to β-hydride elimination. The anion is still associated to the metal center, however, via electrostatic interactions. This partially associated anion serves as another steric interaction to enhance the degree of selectivity. Calculations have shown that an acetate group presents a somewhat different, less selective steric environment, while the absence of an anion results in almost no selectivity. The observed association of the chloride ion to the metal center helps to explain the counterion effects in the kinetic resolution. The full mechanistic

profile up to ketone dissociation, with calculated energies of the intermediates, is depicted in Scheme 2.5.3.[43]

Scheme 2.5.3



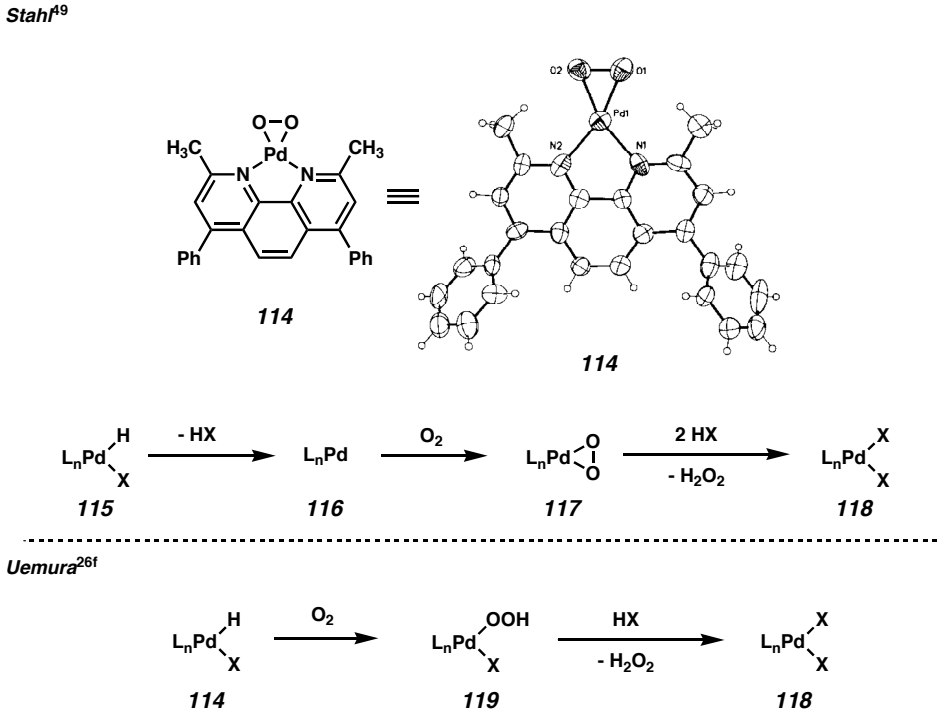
2.5.3 Kinetic Studies of Palladium(II) Oxidative Systems

Sigman and Stahl have recently reported detailed kinetic analyses on the palladium-catalyzed oxidation of alcohols. Stahl studied the palladium-pyridine oxidation system of Uemura, where he found that β-hydride elimination from a (py)Pd(OAc)(alkoxide) intermediate was rate-determining.[44] Sigman focused on the palladium-sparteine resolution system, where he observed that the rate-determining step was dependent on the sparteine stoichiometry.[45,46] At low sparteine levels, deprotonation of the intermediate alcohol complex is rate-limiting; on the other hand, at high sparteine concentrations, β-hydride elimination becomes rate-determining.[47] The origin of selectivity in reactions at high sparteine concentrations, relevant to our studies, was

believed to arise from a combination of the kinetic difference in the β-hydride elimination step and the thermodynamic difference in the diastereomeric alkoxides.[48]

Stahl has also investigated the catalyst turnover steps that follow β-hydride elimination.[49] By using a bathocuproine ligand, Stahl was able to oxidize a palladium(0) center to palladium(II) with molecular oxygen. He isolated and characterized palladium-peroxo species **114** (Scheme 2.5.4). **114** was converted to the diacetate in the presence of acetic acid, demonstrating how an intermediate diamine-palladium(0) species can regenerate the catalytically active diamine-palladium(II) species with molecular oxygen.[50] Uemura has proposed an alternative pathway, where dioxygen simply inserts into the palladium-hydride bond generated from the β-hydride elimination step, thereby avoiding a palladium(0) intermediate altogether.[26f]

Scheme 2.5.4



2.6 Conclusion

We have developed the first example of a palladium-catalyzed oxidative kinetic resolution of secondary alcohols. The reaction uses a simple system of $Pd(nbd)Cl_2$, (–)-sparteine, molecular sieves, and dioxygen to access a variety of secondary alcohols in high enantiopurity. The reaction performs remarkably well upon scale up and can be used to desymmetrize simple and complex meso diols. Further developments have led to improvements on the original system, and the substrate scope has been expanded to compounds relevant to both pharmaceuticals and natural product syntheses. The development of this reaction has also prompted intriguing mechanistic studies that have shed light on palladium(II) oxidative transformations. While developments are still ongoing, we began to explore new directions with this interesting catalytic system, the results of which will be discussed in later chapters of this thesis.

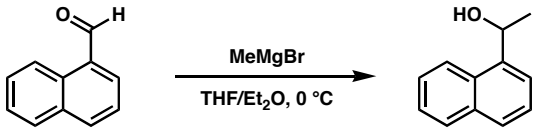
2.7 Experimental Section

2.7.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). ICN Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed on a Chiralcel OJ, AS, or OD-H column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical achiral GC was performed using an Agilent DB-WAX (30.0 m x 0.25 mm) column. Analytical chiral GC was carried out using either a Chiraldex B-DM column (30.0 m x 0.25 mm) or a Chiraldex G-TA column (30.0 m x 0.25 mm) purchased from Bodman Industries. Preparatory reversed-phase HPLC was performed on a Beckman HPLC with a Waters DeltaPak 25 x 100 mm, 100 μm C18 column equipped with a guard, 0.1% (w/v) TFA with CH_3CN/H_2O as the eluent. Bisphosphines in Figure 2.3.1 as well as **72** (Jacobsen's ligand) were purchased from Strem Chemicals, Inc., Newburyport, MA. All other organic compounds were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. $Pd(nbd)Cl_2$ was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI; all other palladium salts were purchased from Strem Chemicals, Inc., Newburyport, MA. Commercially available racemic alcohols in Table 2.3.5 (entries 1, 2, 3, 5, 7, 8, and 9), 1-cyclohexylethanol, and 2-octanol were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Commercially available samples of enantiopure alcohols for

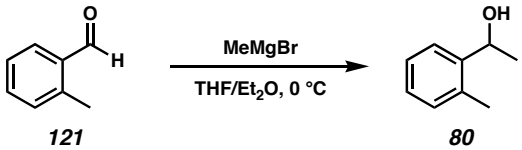
analytical comparison purposes (entries 1, 4, 7, 8, and 9) were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Non-commercially available enantiopure alcohols prepared by palladium-catalyzed oxidative kinetic resolution (Table 2.3.5, entries 2[51], 3[52], 5[53], 6[54], and 10[55]) were compared by optical rotation to known values.

2.7.2 Preparative Procedures



120 *78*

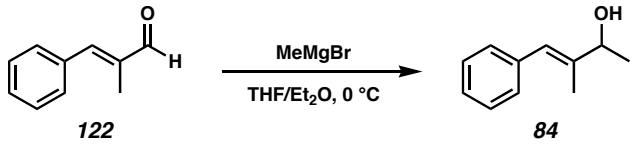
Alcohol 78. To a solution of 1-naphthaldehyde (2.72 mL, 20.0 mmol) in 20 mL THF at 0 °C was added MeMgBr (10.0 mL, 3.0 M in Et_2O, 30.0 mmol) dropwise over 10 min. The reaction mixture was maintained at 0 °C for 30 min, then poured into saturated NH_4Cl (100 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford alcohol **78** (R_F = 0.17 in 4:1 hexanes/EtOAc) as a yellow oil, which solidified upon refrigeration.



121 *80*

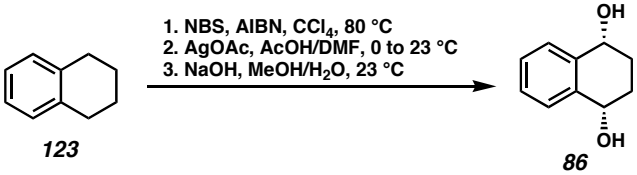
Alcohol 80. To a solution of *o*-tolualdehyde (3.16 mL, 27.3 mmol) in 27 mL THF at 0 °C was added MeMgBr (10.0 mL, 3.0 M in Et_2O, 30.0 mmol) dropwise over 10 min. The reaction mixture was maintained at 0 °C for 30 min, then poured into saturated

NH_4Cl (100 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford alcohol **80** (R_F = 0.19 in 4:1 hexanes/EtOAc) as a yellow oil.



122 *84*

Alcohol 84. To a solution of α-methyl-*trans*-cinnamaldehyde (3.81 mL, 27.3 mmol) in 27 mL THF at 0 °C was added MeMgBr (10.0 mL, 3.0 M in Et_2O, 30.0 mmol) dropwise over 10 min. The reaction mixture was maintained at 0 °C for 10 min, then poured into saturated NH_4Cl and ice (200 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford alcohol **84** (R_F = 0.31 in 4:1 hexanes/EtOAc) as a yellow oil.



123 *86*

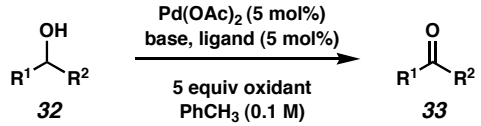
Meso Diol 86. Meso diol **86** was synthesized according to the procedure of Yamada.[56] A 200 mL round-bottom flask holding a solution of tetralin (4.08 mL, 30.0 mmol) in CCl_4 (40 mL) at 23 °C was wrapped in foil. NBS (10.7 g, 60.0 mmol) and AIBN (148 mg, 0.900 mmol) were added sequentially, and the mixture was heated to 80 °C. After

20 min, the reaction mixture turned from yellow to white. The mixture was cooled to room temperature, suction-filtered, and the filtrate was concentrated in vacuo. The crude dibromide was carried to the subsequent step without further purification.

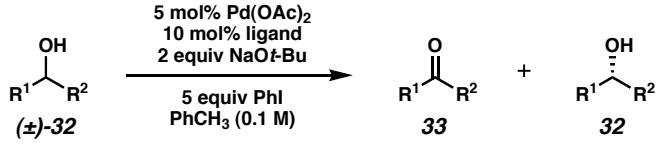
The crude dibromide (assume 30.0 mmol) was dissolved in DMF (10 mL) and AcOH (30 mL) at 23 °C. The mixture was cooled to 0 °C, and AgOAc (10.0 g, 60.0 mmol) was added. The yellow slurry was allowed to warm to 23 °C and stirred for 2.5 h. AgBr was removed by suction-filtration, and the filtrate was concentrated in vacuo. The residue was neutralized with saturated $NaHCO_3$ (30 mL), diluted with water (100 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 5% $Na_2S_2O_3$ (2 x 100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent) to provide the diacetate (2.86 g, 38% yield over 2 steps, R_F = 0.71 in 1:1 hexanes/EtOAc) as a mixture of dl and meso forms.

To a solution of the diacetate (3.53 g, 14.2 mmol) in 71 mL MeOH at 23 °C was added 2.0 M aq. NaOH (17.8 mL, 35.5 mmol). The mixture was stirred at 23 °C for 2.5 h, then acidified with 2.0 M HCl (~20 mL). The mixture was concentrated in vacuo, and the residue was dissolved in $CHCl_3$/EtOH (1:1, 60 mL). The solids were removed by filtration, and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (1:1 → 3:1 EtOAc/hexanes eluent) afforded the diol (R_F = 0.19 in 1:1 hexanes/EtOAc) as a mixture of dl and meso forms. The meso diol (**86**) was isolated by reversed-phase preparative HPLC (100% H_2O → 3:7 CH_3CN/H_2O eluent). The spectroscopic information for **86** was identical to the reported data.[56]

2.7.3 Palladium(II) Oxidation Procedures

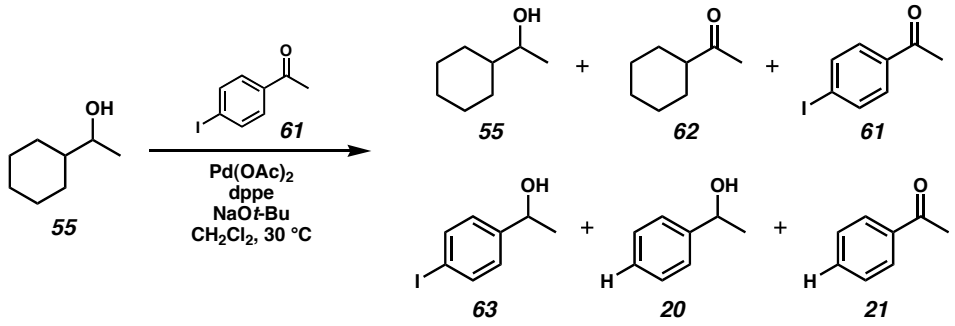


General Procedure for the Racemic Oxidation of Alcohols Using Aryl Halides (Table 2.3.1). To a solution of $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol), ligand (0.0500 mmol), and base (2.00 mmol) in 10 mL toluene at 23 °C was added the alcohol (1.00 mmol), then the aryl halide (5.00 mmol). The solution was heated to the specified temperature and stirred. After the listed time, the solution was cooled to room temperature and quenched with H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude material was analyzed by ^1H NMR to determine conversion values.

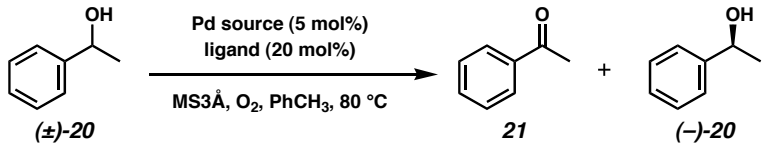


General Procedure for the Enantioselective Oxidation of Alcohols Using Aryl Halides (Table 2.3.2). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.0250 mmol), ligand (0.0500 mmol), and NaO*t*-Bu (1.00 mmol) in 5.0 mL toluene at 23 °C was added the alcohol (0.500 mmol), then the aryl halide (2.50 mmol). The solution was maintained at the specified temperature for the listed time. The solution was then cooled to room temperature and quenched with H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$,

and concentrated in vacuo. The crude material was analyzed by ^{1}H NMR to determine conversion values. Enantiomeric excess was determined by GC or HPLC analysis (see Table 2.7.2 for details).

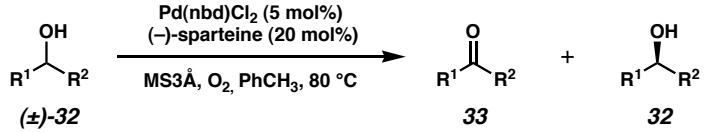


Observation of Background Oxidation/Reduction Pathways (Scheme 2.3.2). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.0250 mmol), dppe (10.0 mg, 0.0250 mmol), and NaO*t*-Bu (96.1 mg, 1.00 mmol) in 5.0 mL CH_2Cl_2 at 23 °C was added 1-cyclohexylethanol (69.0 μl, 0.500 mmol), then 4'-iodoacetophenone (246 mg, 1.00 mmol). The solution was heated to 30 °C and stirred. After 11 h, the solution was cooled to room temperature and quenched with H_2O (30 mL). The mixture was extracted with Et_2O (3 x 50 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Alcohols **55**, **63**, and **20**, and ketones **62**, **61**, and **21** were all detected by ^{1}H NMR.



General Procedure for the Oxidative Kinetic Resolution of Secondary Alcohols. Ligand and Palladium Source Screening Trials (Tables 2.3.4 and 2.3.5). A 25 mL

Schlenk flask equipped with a magnetic stir bar was charged with powdered molecular sieves (MS3Å, 0.25 g) and flame-dried under vacuum. After cooling under dry N_2, Pd complex (0.025 mmol, 0.05 equiv) was added followed by toluene (5.0 mL), and then an appropriate ligand (0.10 mmol, 0.20 equiv). The flask was vacuum-evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. The alcohol (0.50 mmol, 1.0 equiv) was introduced and the reaction monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values. Aliquots of the reaction mixture (0.2 mL) were collected after 24 h, 40 h, 72 h, 96 h, 120 h, and 144 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed.[57]

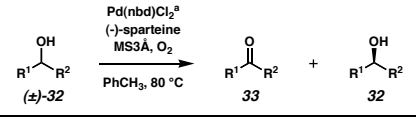


General Procedure for the Oxidative Kinetic Resolution of Secondary Alcohols. Preparative Runs (6.0 mmol) in Table 2.7.1. A 200 mL flask equipped with a magnetic stir bar was charged with powdered molecular sieves (MS3Å, 3.0 g) and flame-dried under vacuum. After cooling under dry N_2, Pd(nbd)Cl_2 (80.8 mg, 0.30 mmol, 0.05 equiv) was added followed by toluene (60.0 mL), and then (–)-sparteine (276 mL, 1.20 mmol, 0.20 equiv). The flask was vacuum-evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. The racemic alcohol (6.00 mmol, 1.0 equiv) was introduced, and the reaction was monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess

values. Aliquots of the reaction mixture (0.2 mL) were collected after 24 h, 40 h, 72 h, 96 h, 120 h, and 144 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed. Upon completion of the reaction, the reaction mixture was filtered through a pad of SiO_2 (EtOAc eluent) and purified by column chromatography on SiO_2 (see below for details).

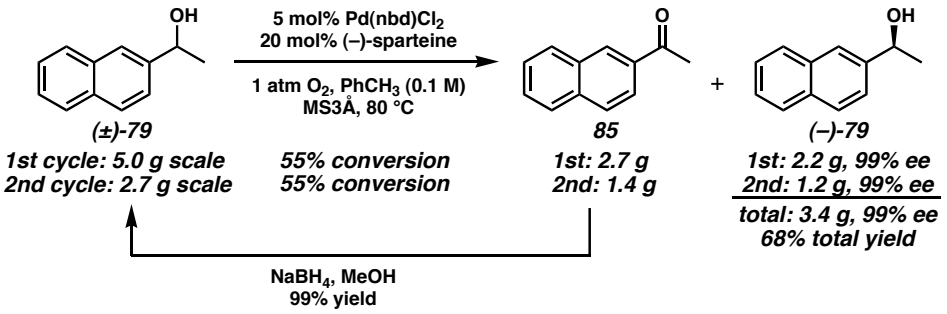
General Procedure for the Oxidative Kinetic Resolution of Secondary Alcohols. Preparative Runs (8.0 mmol) in Table 2.7.1. A 200 mL flask equipped with a magnetic stir bar was charged with powdered molecular sieves (MS3Å, 4.0 g) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (108 mg, 0.40 mmol, 0.05 equiv) was added followed by toluene (80.0 mL), and then (–)-sparteine (368 mL, 1.60 mmol, 0.20 equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. The alcohol (8.00 mmol, 1.0 equiv) was introduced and the reaction monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values. Aliquots of the reaction mixture (0.2 mL) were collected after 24 h, 40 h, 72 h, 96 h, 120 h, and 144 h depending on the course of the reaction (typically three aliquots per run). Each aliquot was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed. Upon completion of the reaction, the reaction mixture was filtered through a pad of SiO_2 (EtOAc eluent) and purified by column chromatography on SiO_2 (see below for details).

Table 2.7.1 Oxidative kinetic resolution on preparative scale.



entry	racemic alcohol	amount	time	conversion	chromatography eluent	isolated yield of ketone	unreacted alcohol, major enantiomer	isolated yield ROH	ee ROH[b]	s[c,d]
1	R = H	0.977 g (8.00 mmol)	96 h	59.9%	6:1→3:1 hexane/EtOAc	0.535 g (56%)	R = H	0.366 g (37%)	98.7%	23.1
2	R = OMe	1.22 g (8.00 mmol)	96 h	66.6%	6:1→3:1 hexane/EtOAc	0.773 g (64%)	R = OMe	0.392 g (32%)	98.1%	12.3
3	R = F	1.12 g (8.00 mmol)	54 h	63.3%	6:1→3:1 hexane/EtOAc	0.623 g (56%)	R = F	0.361 g (32%)	97.4%	14.4
4	Ar = 1-Naphthyl	1.03 g (6.00 mmol)	192 h	55.9%	6:1→3:1 hexane/EtOAc	0.555 g (54%)	Ar = 1-Naphthyl	0.443 g (43%)	78.4%	9.8
5	Ar = 2-Naphthyl	5.00 g (29.00 mmol)	112 h	55.2%	6:1→3:1 hexane/EtOAc	2.75 g (55%)	Ar = 2-Naphthyl	2.20 g (44%)	99.0%	47.1
6	Ar = *o*-tolyl	1.09 g (8.00 mmol)	144 h	48.4%	6:1→3:1 hexane/EtOAc	0.492 g (46%)	Ar = *o*-tolyl	0.533 g (49%)	68.7%	13.1
7		1.09 g (8.00 mmol)	192 h	59.3%	6:1→4:1 hexane/EtOAc	0.625 g (58%)		0.435 g (40%)	93.1%	14.8
8	n = 1	1.07 g (8.00 mmol)	54 h[e]	67.5%	6:1→3:1 hexane/EtOAc	0.662 g (63%)	n = 1	0.323 g (30%)	93.4%	8.3
9	n = 2	1.19 g (8.00 mmol)	40 h	68.6%	9:1→4:1 hexane/EtOAc	0.796 g (68%)	n = 2	0.370 g (31%)	99.8%	15.8
10		0.973 g (6.00 mmol)	120 h	70.4%	6:1→3:1 hexane/EtOAc	0.671 g (70%)		0.286 g (29%)	91.8%	6.6

[a]5 mol% $Pd(nbd)Cl_2$, 20 mol% (–)-sparteine, 1 atm O_2. [b]The degree of enantiomeric excess was measured directly by chiral HPLC or GC of the recovered alcohols.[58] [c]Selectivity (s) values represent an average of at least two experiments, while conversion and ee values are for specific cases. [d]For each entry, comparable selectivities are observed throughout the course of the run. [e]Experiment performed at 60 °C.



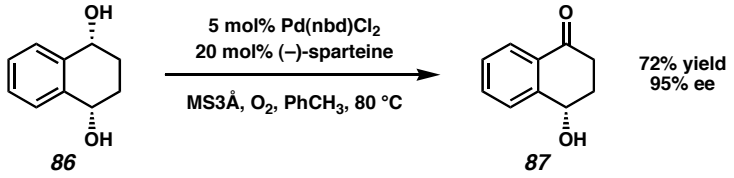
Scale-up Procedure for the Two-Cycle Oxidative Kinetic Resolution of α-methyl-2-naphthalenemethanol 79. 1st cycle: A 500 mL round bottom flask was charged with powdered molecular sieves (MS3Å, 14.5 g) and a magnetic stir bar and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (0.391 g, 1.45 mmol, 0.05 equiv) was added followed by toluene (290 mL), and then (–)-sparteine (1.34 mL, 5.81 mmol, 0.20

equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. Alcohol **(±)-79** (5.00 g, 29.0 mmol, 1.0 equiv) was introduced and the reaction mixture heated at 80 °C for 112 h. Progress of the reaction was monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values by the removal of small aliquots of the reaction mixture (0.2 mL), which were filtered through silica gel (EtOAc eluent), evaporated, and analyzed. After the reaction rate had significantly slowed (112 h, 55% conversion), and aliquot analysis showed a high level of enantiopurity for the remaining alcohol **(–)-79** (99.0% ee), the entire reaction mixture was filtered through a small column of silica gel (5 x 6 cm, EtOAc eluent). The filtrate was evaporated and purified by flash chromatography on silica gel (6:1 to 3:1 hexanes/EtOAc eluent) to provide ketone **85** (R_F = 0.42 in 4:1 hexanes/EtOAc, 2.75 g, 55% yield) and alcohol **(–)-79** (R_F = 0.22 in 4:1 hexanes/EtOAc, 2.20 g, 44% yield, 99.0% ee) as white solids.

Regeneration of alcohol (±)-79. A cooled (0 °C) solution of ketone **85** (2.75 g, 16.2 mmol, 1.0 equiv) in 1:1 CH_2Cl_2/MeOH (16.2 mL) was treated with $NaBH_4$ (733 mg, 19.4 mmol, 1.2 equiv) in four portions over 10 min. The reaction was stirred at 0 °C for 15 min and treated with 1 N HCl solution (30 mL) slowly over 15 min. After the evolution of gas was complete, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, evaporated, and purified by flash chromatography on silica gel (3:1 hexanes/EtOAc eluent) to provide alcohol **(±)-79** (2.76 g, 99% yield) as a white solid, which was used in cycle two.

2nd cycle: A 500 mL round bottom flask was charged with molecular sieves (MS3Å, 8.0 g) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (0.216 g,

0.800 mmol, 0.05 equiv) was added followed by toluene (160 mL), and then (–)-sparteine (0.735 mL, 3.20 mmol, 0.20 equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon), and the reaction mixture was heated to 80 °C for 10 min. Alcohol **(±)-79** (2.76 g, 16.0 mmol, 1.0 equiv) prepared above was introduced and the reaction mixture heated at 80 °C for 96 h. Progress of the reaction was monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values by the removal of small aliquots (0.2 mL), which were filtered through silica gel (EtOAc eluent), evaporated, and analyzed. After the reaction rate had significantly slowed (81 h, 55% conversion), and aliquot analysis showed a high level of enantiopurity for the remaining alcohol **(–)-79** (99.0% ee), the entire reaction mixture was filtered through a small column of silica gel (5 x 6 cm, EtOAc eluent). The filtrate was evaporated and purified by flash chromatography on silica gel (6:1 to 3:1 hexanes/EtOAc eluent) to provide ketone **85** (1.43 g, 54% yield) and alcohol **(–)-79** (1.20 g, 44% yield, 99.0% ee) as white solids. The combination of both cycles provided alcohol **(–)-79** (3.39 g, 68% yield, 99.0% ee).

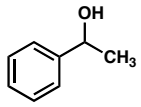
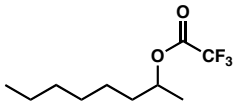
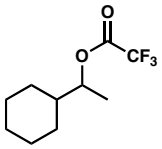
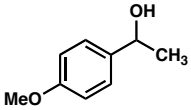
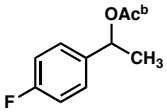
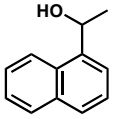
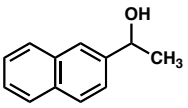


86 *87*

Oxidative Desymmetrization of Meso Diol 86. A 50 mL Schlenk flask equipped with a magnetic stir bar was charged with molecular sieves (MS3Å, 625 mg) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (16.8 mg, 0.0625 mmol, 0.05 equiv) was added followed by toluene (12.5 mL), and then (–)-sparteine (57 mL, 0.25 mmol, 0.20 equiv). The flask was vacuum evacuated and filled with O_2 (3x, balloon),

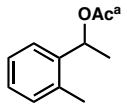
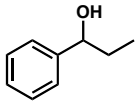
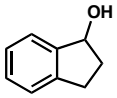
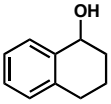
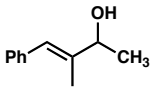
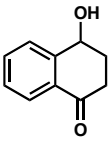
and the reaction mixture was heated to 80 °C for 10 min. Diol **86** (205 mg, 1.25 mmol, 1.0 equiv) was introduced and the reaction monitored by standard analytical techniques (TLC, GC, ^{1}H NMR, and HPLC) for % conversion and enantiomeric excess values. Upon completion of the reaction, the reaction mixture was filtered through a pad of SiO_2 (EtOAc eluent) and purified by column chromatography on SiO_2 (3:1 to 1:1 hexane/EtOAc eluent) to provide hydroxyketone **(+)-87** as an oil (145 mg, 72% yield, 95% ee); $[\alpha]_D^{23}$ +19.6 (*c* 1.0, MeOH).[59] See Table 2.7.2 for details regarding the ee assay.

Table 2.7.2 Methods utilized for the determination of enantiomeric excess.

entry	Substrate	ee Assay	Conditions	Retention Time of (*R*) isomer (min)	Retention Time of (*S*) isomer (min)
1	 *20*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	10.69	13.37
2	 *124*	GC Chiraldex G-TA	50 °C, 0 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	7.72[a]	7.94[a]
3	 *125*	GC Chiraldex G-TA	50 °C, 25 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	30.17[a]	30.45[a]
4	 *76*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	14.60	16.52
5	 *126*	GC Chiraldex B-DM	50 °C, 0 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	16.41	15.78
6	 *78*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	31.99	18.96
7	 *79*	HPLC Chiralcel OJ	4% 2-propanol/hexane 1.0 mL/min	38.69	31.32

a. Prepared by reaction of the alcohol with TFAA; absolute configuration not determined.
b. Prepared by reaction of the alcohol with Ac_2O and pyridine.

Table 2.7.2 (continued)

entry	Substrate	ee Assay	Conditions	Retention Time of (*R*) isomer (min)	Retention Time of (*S*) isomer (min)
8	 *127*	GC Chiraldex B-DM	85 °C, 45 min 1.0 mL/min carrier gas flow	42.17	40.71
9	 *81*	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	11.15	13.23
10	 *82*	HPLC Chiralcel OJ	3% EtOH/hexane 1.0 mL/min	17.35	14.76
11	 *83*	HPLC Chiralcel AS	2% EtOH/hexane 1.0 mL/min	15.55	12.68
12	 *84*	HPLC Chiralcel OD-H	4% 2-propanol/hexane 1.0 mL/min	13.44	15.44
13	 *87*	HPLC Chiralcel AS	6% 2-propanol/hexane 1.0 mL/min	37.97	30.44

a. Prepared by reaction of the alcohol with Ac_2O and pyridine.

Table 2.7.3 Selected experimental data for the determination of conversion, enantiomeric excess, and selectivity (s).

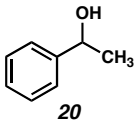
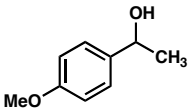
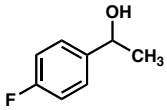
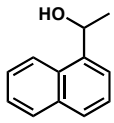
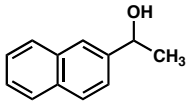
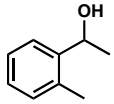
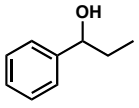
entry	Substrate	time (h)	% Conversion	Measured %ee, unreacted ROH	s
1	 *20*	19 40 96 96	35.7 47.4 59.9 57.1	48.6 75.7 98.7 96.6	24.3 26.1 23.1 24.8
2	 *76*	40 96 96 96 120	50.8 64.8 66.6 65.8 66.0	72.5 97.6 98.1 98.3 98.9	12.2 13.1 12.3 13.3 14.3
3	 *77*	48 54 60 72	63.9 63.3 65.7 65.2	96.1 97.4 96.9 97.9	12.3 14.4 11.6 13.2
4	 *78*	40 144 144 168 192	26.5 47.4 47.4 54.5 55.9	27.3 62.2 61.8 76.6 78.4	9.4 10.2 10.0 10.2 9.8
5	 *79*	81 112	55.1 55.2	99.0 99.0	48.0 47.1
6	 *80*	96 96 144 144	34.2 40.5 39.5 48.4	41.6 52.0 48.7 68.7	13.5 12.5 11.1 13.1
7	 *81*	40 48 96 96 192	30.3 41.6 57.2 55.7 59.3	34.4 55.0 89.0 86.8 93.1	12.0 13.4 14.4 15.0 14.8

Table 2.7.3 (continued)

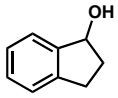
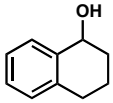
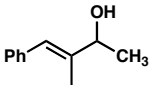
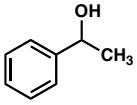
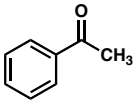
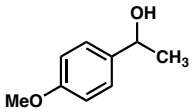
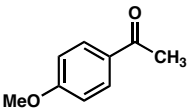
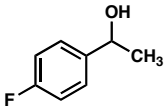
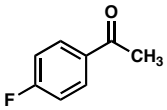
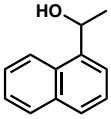
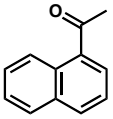
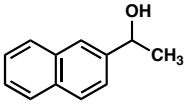
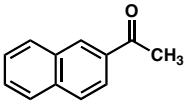
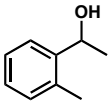
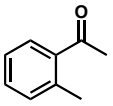
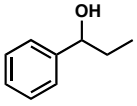
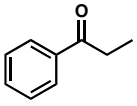
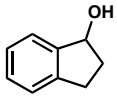
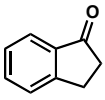
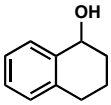
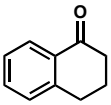
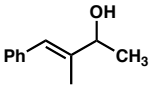
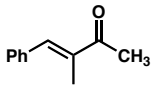
entry	Substrate	time (h)	% Conversion	Measured %ee, unreacted ROH	s
8	 *82*	48 54 96	65.2 67.5 68.0	92.5 93.4 90.0	9.1 8.3 6.9
9	 *83*	40 40 48 96 96	68.6 59.9 67.6 68.7 69.3	99.8 95.2 99.7 99.9 99.9	15.8 16.1 15.9 17.2 16.6
10	 *84*	40 96 120 144	46.0 66.2 70.4 68.4	54.5 85.9 91.8 90.7	7.7 6.6 6.6 7.0

Table 2.7.4 Methods utilized for the determination of % conversion.

entry	alcohol	ketone	GC Conditions[a]	Retention Time of alcohol (min)	Retention Time of ketone (min)
1	 ***20***	 ***21***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	29.03	26.02
2	 ***76***	 ***128***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	34.82	33.90
3	 ***77***	 ***129***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	29.82	25.93
4	 ***78***	 ***130***	70 °C, 0 min; 3.0 °C/min to 270 °C 1.0 mL/min carrier gas flow	50.74	44.91
5	 ***79***	 ***85***	70 °C, 0 min; 3.0 °C/min to 270 °C 1.0 mL/min carrier gas flow	36.17	35.96
6	 ***80***	 ***131***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	31.01	26.68
7	 ***81***	 ***132***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	30.06	27.43

[a]All assays performed on Agilent DB-WAX column.

Table 2.7.4 (continued)

entry	alcohol	ketone	GC Conditions[a]	Retention Time of alcohol	Retention Time of ketone
8	 ***82***	 ***133***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	33.12	32.20
9	 ***83***	 ***134***	70 °C, 15 min; 7.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	34.90	33.39
10	 ***84***	 ***135***	70 °C, 15 min; 5.0 °C/min to 220 °C 1.0 mL/min carrier gas flow	25.37	23.04

[a]All assays performed on Agilent DB-WAX column.

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(58) Enantiomeric excess was measured by chiral HPLC analysis using either a Chiralcel OJ, AS, or OD-H column or by chiral GC using a Bodman Chiraldex B-DM column. Conversion was measured by GC using a DB-WAX column.

(59) The assignment of absolute stereochemistry is based on analogy to the results in Table 2.7.1.

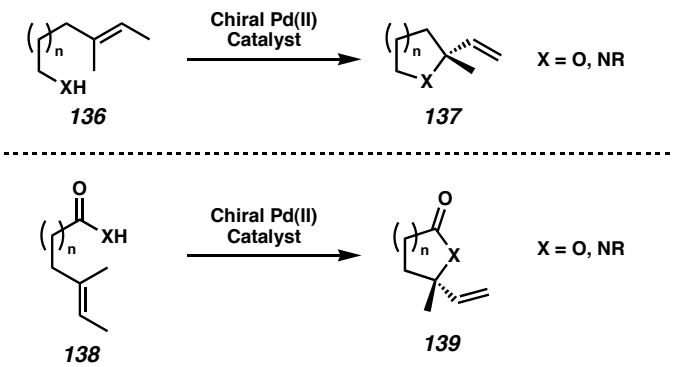
CHAPTER THREE

Palladium-Catalyzed Aerobic Wacker Cyclizations and the Formal Total Synthesis of Cephalotaxine

3.1 Introduction

The design of palladium-catalyzed dehydrogenative transformations is an important area of research for our laboratory.[1] The initial studies led to the development of an oxidative kinetic resolution of secondary alcohols using molecular oxygen as the sole stoichiometric oxidant.[2] The kinetic resolution, however, was just one example of the array of non-heteroatom transfer oxidations we were intent on developing. Oxidative heterocyclizations (Scheme 3.1.1) are another fundamental class of transformations that were of interest. These reactions involve the cyclization of a heteroatom nucleophile onto an olefin to afford a heterocycle. This process is in essence an intramolecular variant of a Wacker oxidation, where an olefin is activated by palladium(II) for subsequent nucleophilic attack.[3] Most of the systems developed for Wacker oxidations, however, are simply not amenable to asymmetric catalysis. Prompted by our studies of a palladium(II) oxidation system that clearly was amenable to enantioselective catalysis, we sought to apply this system toward oxidative heterocyclizations.[4]

Scheme 3.1.1



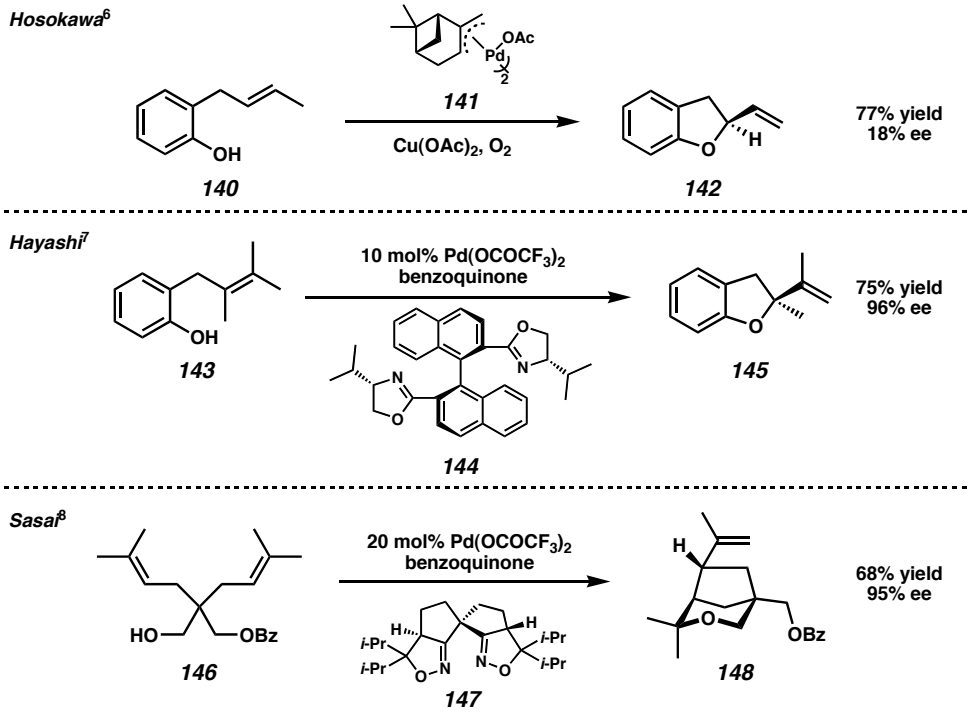
3.2 Background

Racemic intramolecular Wacker cyclizations to form heterocycles, variants of those depicted in Scheme 3.1.1, have been studied extensively.[5] A range of heteroatom nucleophiles have been investigated, including phenols, alcohols, amines, tosylamides, carboxylic acids, and amides. Palladium(II) catalysis, a general method for this process, provides heterocycles in typically excellent yields. Most of the reactions reported, however, utilize cooxidants such as copper(II) salts or benzoquinone to effect the reoxidation from palladium(0) to electrophilic palladium(II). These cooxidants would likely be problematic in the development of asymmetric heterocyclizations employing chiral palladium(II) complexes. Chiral ligands could preferentially bind to copper instead of palladium; benzoquinone and hydroquinone could act as competitive ligands to the palladium center.

Despite these complicating factors, works by Hosokawa,[6] Hayashi,[7] and Sasai[8] have demonstrated the possibility of enantioselective oxidative heterocyclizations via palladium catalysis (Scheme 3.2.1). Hosokawa and Murahashi reported the first case of an asymmetric heterocyclization using an isopinocampheyl-palladium acetate dimer (**141**), affording dihydrobenzofuran **142** in 18% ee.[6] Over fifteen years later, Hayashi disclosed the first highly enantioselective Wacker cyclization on a similar substrate using a binaphthyl-bisoxazoline ligand (BOXAX, **144**) with $Pd(OCOCF_3)_2$ and benzoquinone as the stoichiometric reoxidant.[7] With this system, dihydrobenzofurans such as **143** are obtained in >90% ee. More recently, Sasai described an asymmetric Wacker transformation of a non-phenolic substrate (**146**), which underwent a double cyclization

in the presence of a palladium-SPRIX (**147**) catalyst to afford bicycle **148** in good yield and high ee.[8] Analogous to Hayashi's system, benzoquinone was used as the stoichiometric cooxidant. The reports by Hayashi and Sasai were the only examples of highly enantioselective palladium-catalyzed Wacker cyclizations.

Scheme 3.2.1



Based on our successes in the palladium-catalyzed oxidative kinetic resolution of secondary alcohols,[2a] we speculated that a similar oxidation system could be utilized toward the development of asymmetric intramolecular Wacker reactions. Specifically, the alcohol oxidation system described by Uemura ($Pd(OAc)_2$, pyridine, O_2)[9] was used as a starting point for the discovery of the kinetic resolution ($Pd(nbd)Cl_2$, (–)-sparteine, O_2). We anticipated that an oxidation system similar to that of Uemura could catalyze oxidative heterocyclizations. The success of this strategy could facilitate the extension to

asymmetric variants in an analogous fashion to our kinetic resolution work. Described herein are our efforts to apply the palladium(II) aerobic oxidation system we had been studying toward intramolecular Wacker cyclizations to form heterocycles.

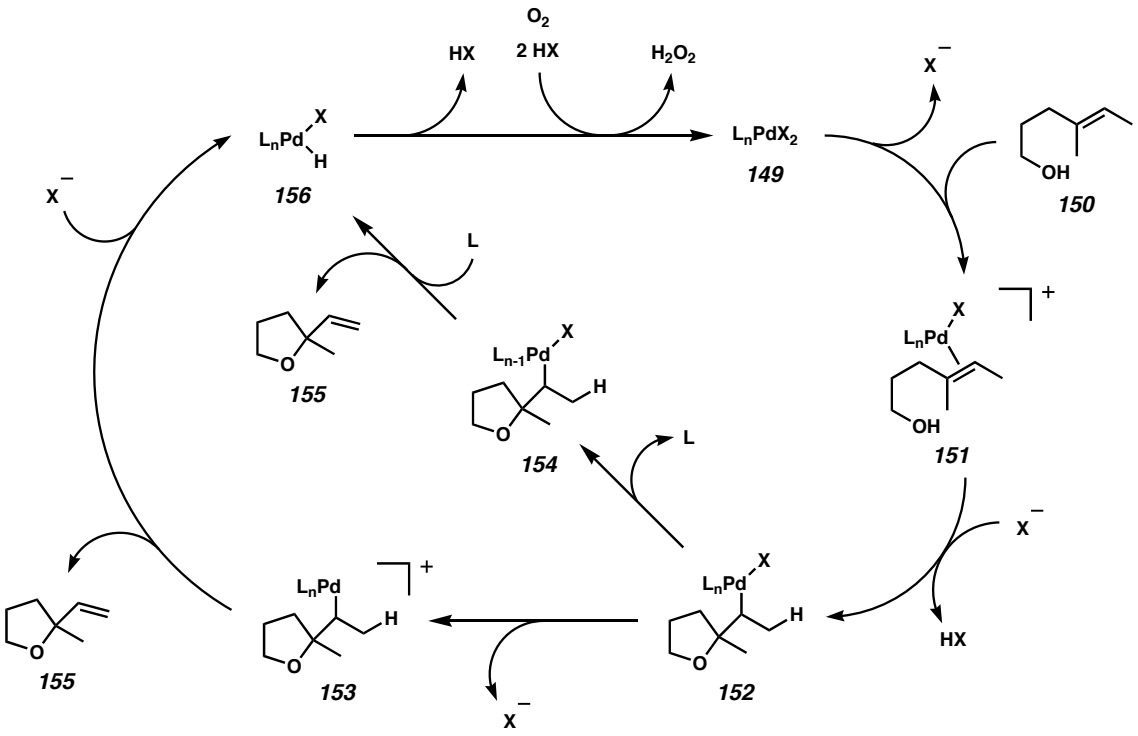
3.3 The Development of Palladium-Catalyzed Aerobic Heterocyclizations

3.3.1 Oxidative Cyclizations with Molecular Oxygen

Palladium-catalyzed heterocyclizations that use molecular oxygen as the sole stoichiometric oxidant are rare. The only aerobic system reported involves catalytic $Pd(OAc)_2$ in DMSO, pioneered by the investigations of Larock and Bäckvall.[10] The development of asymmetric variants based on these works would certainly be hindered by the ligating ability of DMSO to palladium, interfering with a palladium-chiral ligand catalyst. The system of Uemura, which uses toluene as the solvent, was considerably more attractive in this light.

The mechanism that was envisioned for the aerobic oxidative heterocyclization is depicted in Scheme 3.3.1. Ligated palladium(II) catalyst **149** dissociates an X-type ligand and binds an olefin to give cationic intermediate **151**. The olefin is activated for intramolecular nucleophilic attack with concomitant deprotonation by X^-, which leads to palladium-alkyl intermediate **152**. At this stage, an open site on the palladium center is likely necessary for β-hydride elimination; this occurs via dissociation of either an X-type ligand to cationic intermediate **153** or an L-type ligand to neutral intermediate **154**. The palladium hydride (**156**) generated from the elimination and dissociation of **155** is converted back to palladium(II) species **149** through an oxidation pathway involving molecular oxygen.[11]

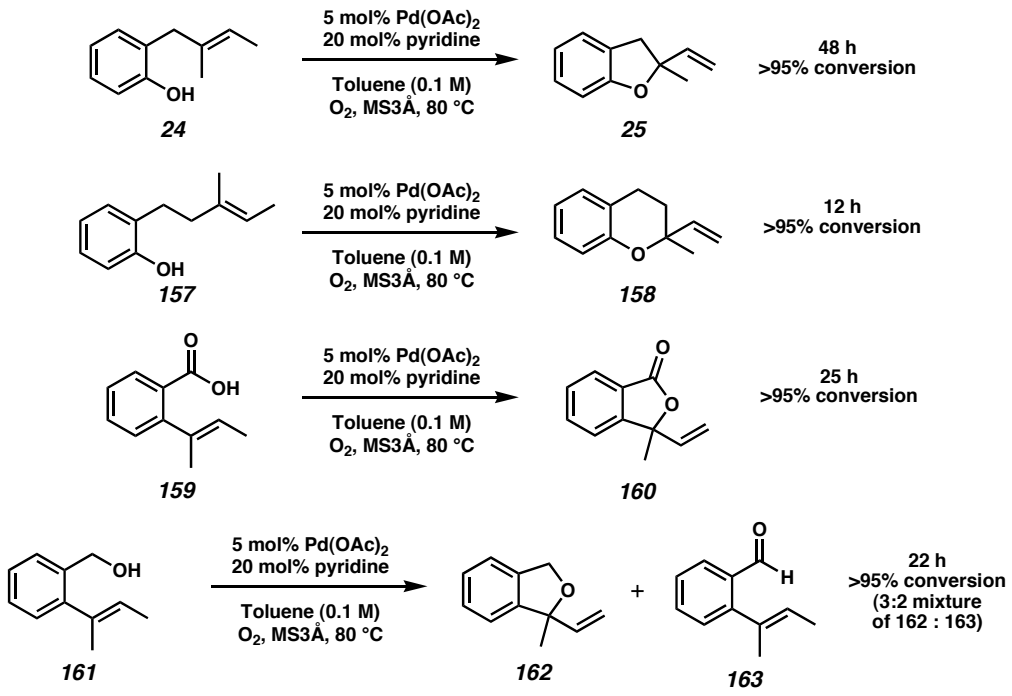
Scheme 3.3.1



3.3.2 Initial Experiments

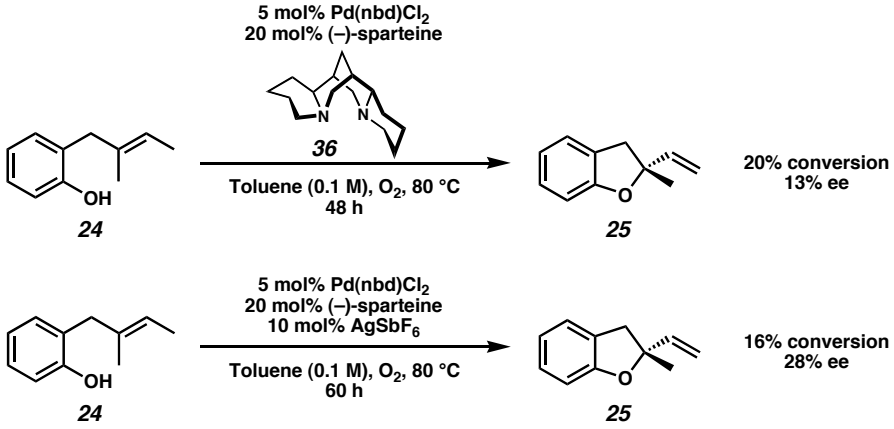
To test the feasibility of these cyclizations under the aerobic oxidation system described by Uemura,[9] a number of olefin substrates were synthesized and subjected to the standard conditions ($Pd(OAc)_2$, pyridine, O_2, toluene, 80 °C). As shown in Scheme 3.3.2, cyclizations proceeded to complete conversion for a variety of heteroatom nucleophiles. Phenols **24** and **157** cyclized to produce dihydrobenzofuran **25** and dihydrobenzopyran **158**, respectively. A carboxylic acid was also a competent nucleophile, cyclizing to afford lactone **160**. In the case of benzylic alcohol **161**, both dihydrofuran **162**, arising from oxidative cyclization, and aldehyde **163**, arising from alcohol oxidation, were observed.

Scheme 3.3.2



With the success of cyclization under the desired conditions, we then probed the possibility of asymmetric variants of these heterocyclizations. As a test experiment, the optimized conditions from the palladium-catalyzed kinetic resolution ($Pd(nbd)Cl_2$, (–)-sparteine, O_2, toluene, 80 °C, see Scheme 3.3.3) were employed. Although the reaction was extremely sluggish (20% conversion after 48 h), there was some observed enantioinduction (13% ee). Furthermore, when 10 mol% $AgSbF_6$ was added to the reaction mixture, the enantioselectivity increased measurably.[12] Although the selectivities were modest, these encouraging results demonstrated the viability of extending the simple palladium/ligand/oxygen/toluene system to enantioselective variants.

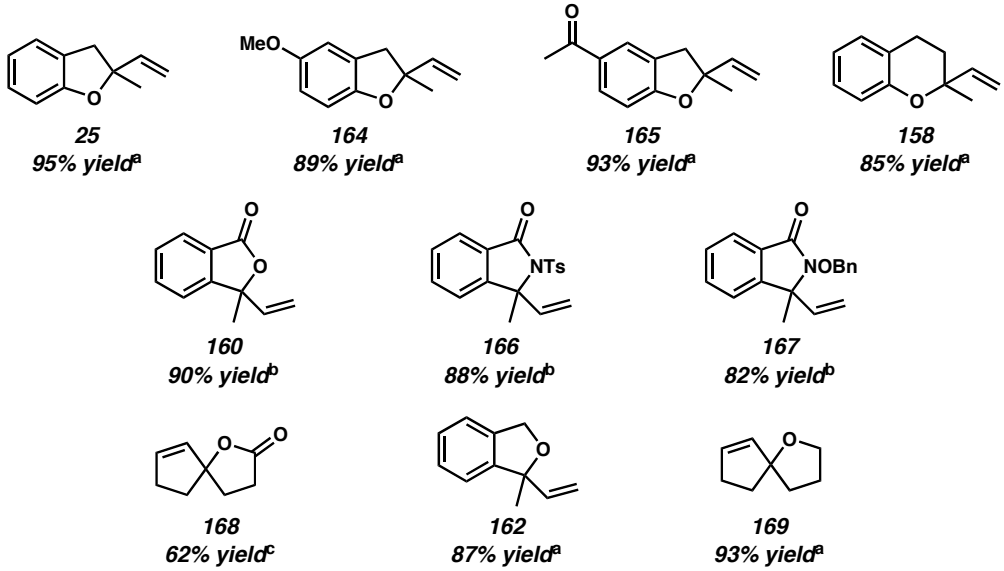
Scheme 3.3.3



3.3.3 Reaction Development

At this point, this project was carried to completion by Raissa Trend, a graduate student in the Stoltz laboratory, and Dr. Yeeman Ramtohul, a postdoctoral scholar in the same laboratory. After considerable investigation and optimization, an array of heterocycles could be synthesized in excellent yields by this oxidative system (Figure 3.3.1).[4,13] Analogous to the kinetic resolution chemistry, a significant counterion effect was observed during these studies. $Pd(OCOCF_3)_2$ was an especially effective palladium precursor for catalyzing these oxidative transformations.[14] Heterocycles including dihydrobenzofurans, dihydrobenzopyrans, lactones, and lactams were obtained using this palladium-catalyzed aerobic intramolecular Wacker cyclization. Interestingly, furans **162** and **169** could be accessed exclusively via these oxidative transformations; aldehyde products were not observed.

Figure 3.3.1 Heterocycles accessed via the palladium-catalyzed aerobic oxidative Wacker cyclization.



25 ***95% yield[a]*** ***164*** ***89% yield[a]*** ***165*** ***93% yield[a]*** ***158*** ***85% yield[a]***

160 ***90% yield[b]*** ***166*** ***88% yield[b]*** ***167*** ***82% yield[b]***

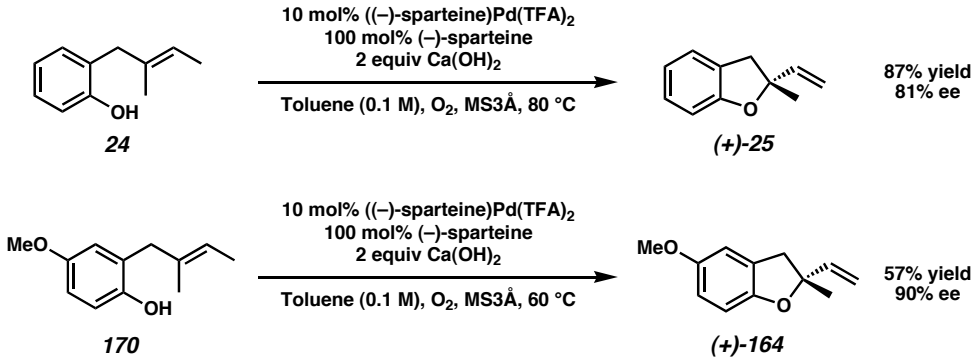
168 ***62% yield[c]*** ***162*** ***87% yield[a]*** ***169*** ***93% yield[a]***

[a] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, 2 equiv Na_2CO_3, MS3Å, 1 atm O_2, 0.1 M in toluene, 80 °C. [b] 5 mol% $Pd(TFA)_2$, 20 mol% pyridine, MS3Å, 1 atm O_2, 0.1 M in toluene, 80 °C. [c] 10 mol% $Pd(TFA)_2$, 40 mol% pyridine, MS3Å, 1 atm O_2, 0.1 M in toluene, 80 °C.

Importantly, highly enantioselective variants of these oxidative heterocyclizations could be realized under similar systems (Scheme 3.3.4).[4] Again, using (–)-sparteine as the chiral ligand, the cyclization of phenols **24** and **170** proceeded with high enantioinduction to afford dihydrobenzofurans **25** (81% ee) and **164** (90% ee), respectively. These results represented the first examples of palladium-catalyzed asymmetric heterocyclizations using molecular oxygen as the sole stoichiometric oxidant. They also demonstrate a critical proof of concept: the simple palladium/ligand/oxygen/toluene oxidative system provided a straightforward entry toward the discovery of highly selective asymmetric variants. Not only was this viable in the alcohol oxidation chemistry, but now it was possible in oxidative Wacker cyclizations as well. This versatile palladium(II) system clearly had wide potential in oxidative

transformations, and further extensions of this chemistry to novel asymmetric cyclizations is a promising future direction.

Scheme 3.3.4



3.4 The Formal Total Synthesis of Cephalotaxine

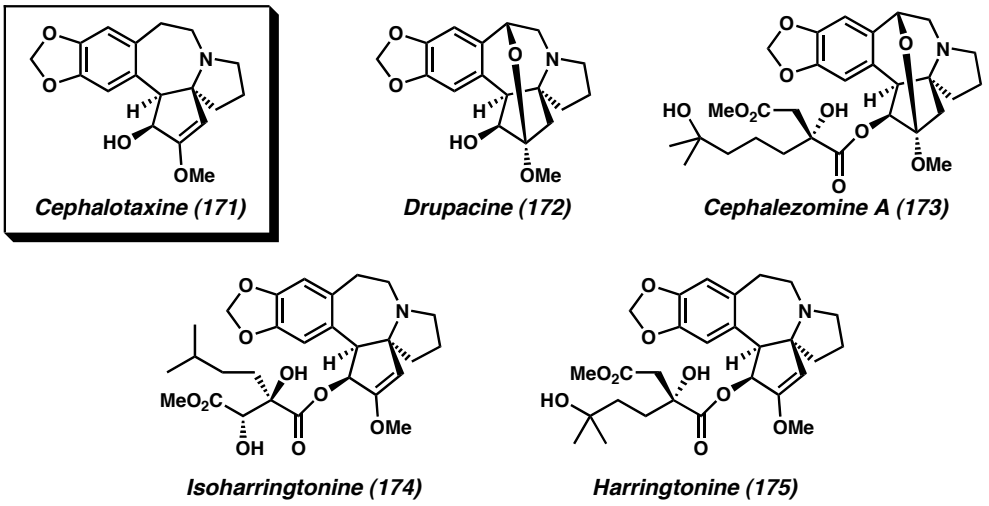
3.4.1 Introduction and Background

While the heterocyclization investigations were ongoing, we desired to demonstrate the utility of these palladium(II) oxidative transformations in natural product synthesis. To this end, we pursued the total synthesis of the *Cephalotaxus* alkaloids.[15] In the synthetic design, we wanted to exploit the potential of palladium(II) dehydrogenative reactions to build molecular architectures in a rapid, efficient fashion.

The *Cephalotaxus* alkaloids (Figure 3.4.1), first isolated in 1974,[16] are an interesting class of biologically active natural products. Although the parent compound, cephalotaxine (**171**), has shown no biological activity, esters of the C-3 hydroxyl have shown potent antileukemic activity. Additionally, cancer patients who have become resistant to other forms of chemotherapy responded positively to cephalotaxine esters, indicative of possible multiple drug resistance reversing activity.[17] With the clear

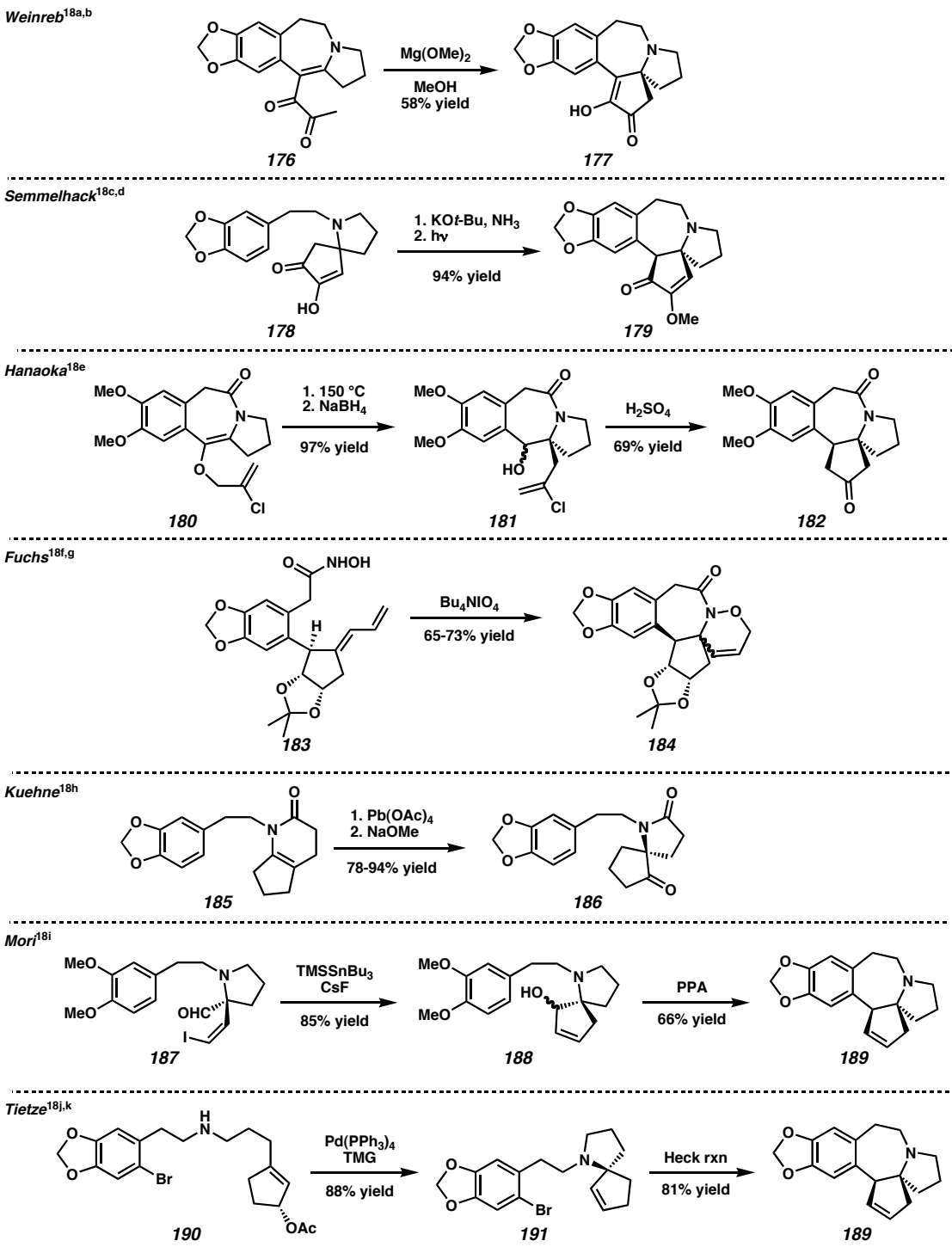
biological importance of these compounds, an efficient synthesis of the alkaloids is highly desirable.

Figure 3.4.1 Representative examples of the *Cephalotaxus* alkaloids.



The total synthesis of cephalotaxine has been pursued by several laboratories. Since the report of the first total synthesis by Weinreb in 1972, a number of syntheses have been reported in the literature.[18,19] The key transformation that was utilized in each individual synthesis is outlined in Scheme 3.4.1. Although the synthesis of cephalotaxine has been extensively investigated, we envisioned that the synthesis of this molecule would serve to illustrate the utility of the palladium(II) oxidative chemistry we had studied thus far.

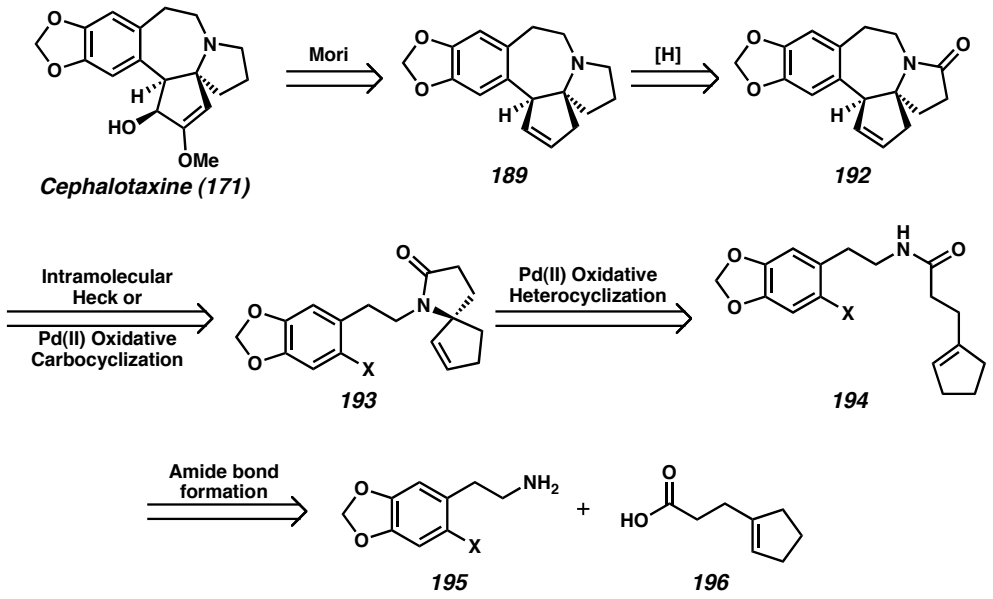
Scheme 3.4.1


Weinreb[18a,b]
Mg(OMe)2
MeOH
58% yield
176
177
Semmelhack[18c,d]
1. KOt-Bu, NH3
2. hν
94% yield
178
179
Hanaoka[18e]
1. 150 °C
2. NaBH4
97% yield
H2SO4
69% yield
180
181
182
Fuchs[18f,g]
Bu4NIO4
65-73% yield
183
184
Kuehne[18h]
1. Pb(OAc)4
2. NaOMe
78-94% yield
185
186
Mori[18i]
TMSSnBu3
CsF
85% yield
PPA
66% yield
187
188
189
Tietze[18j,k]
Pd(PPh3)4
TMG
88% yield
Heck rxn
81% yield
190
191
189

3.4.2 Retrosynthetic Plan

Outlined in Scheme 3.4.2 is our retrosynthetic plan. We first targeted the known olefin intermediate **189**, which has been converted to the natural product in enantiopure form by Mori.[18i] The amine could arise from a reduction of lactam **192**. This lactam could be formed from spirolactam **193** via a diastereoselective intramolecular Heck reaction (X = halogen). Another possibility is to use palladium(II) chemistry to form the seven-membered ring. If X = H, then under palladium(II) catalysis, arene palladation and subsequent diastereoselective olefin insertion and β-hydride elimination could occur, leading to the identical product arising from the Heck reaction (**192**).[20] The spirolactam could be formed from amide **194** by a palladium(II)-catalyzed intramolecular heterocyclization. Amide **194** could be synthesized from amine **195** and acid **196** through straightforward coupling chemistry.

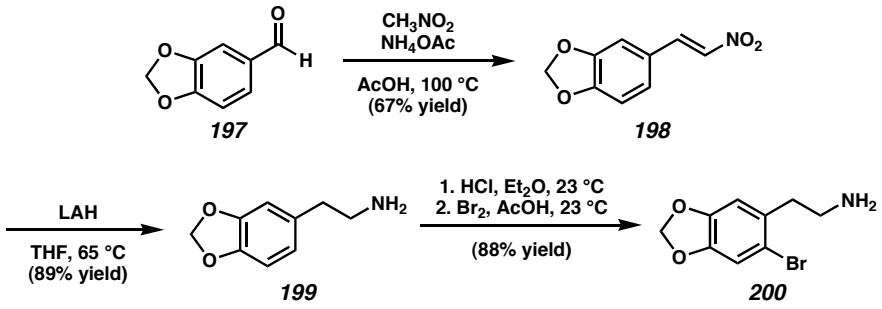
Scheme 3.4.2



3.4.3 Formal Total Synthesis of (±)-Cephalotaxine

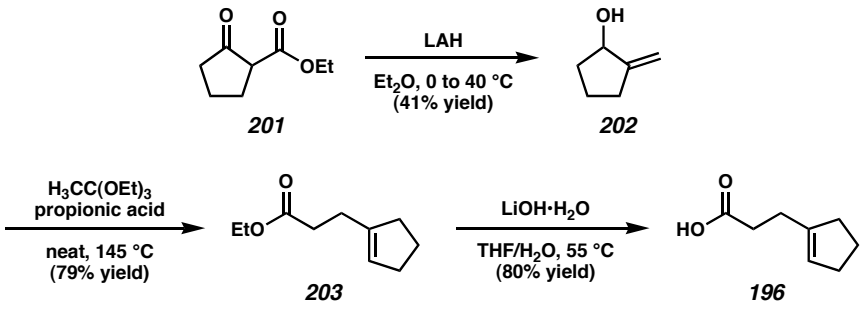
For our first approach, we decided to pursue the route involving the intramolecular Heck reaction since it was more precedented at the onset of this study. Amine **200** can be synthesized in three steps according to the procedures of Marsden and MacLean,[21] and of Tietze and Schirok (Scheme 3.4.3).[18k] Piperonal (**197**) is treated with nitromethane under Henry conditions[22] to afford β-nitrostyrene derivative **198**. Lithium aluminum hydride reduction to the amine followed by arene bromination provides amine **200** in excellent yield.

Scheme 3.4.3



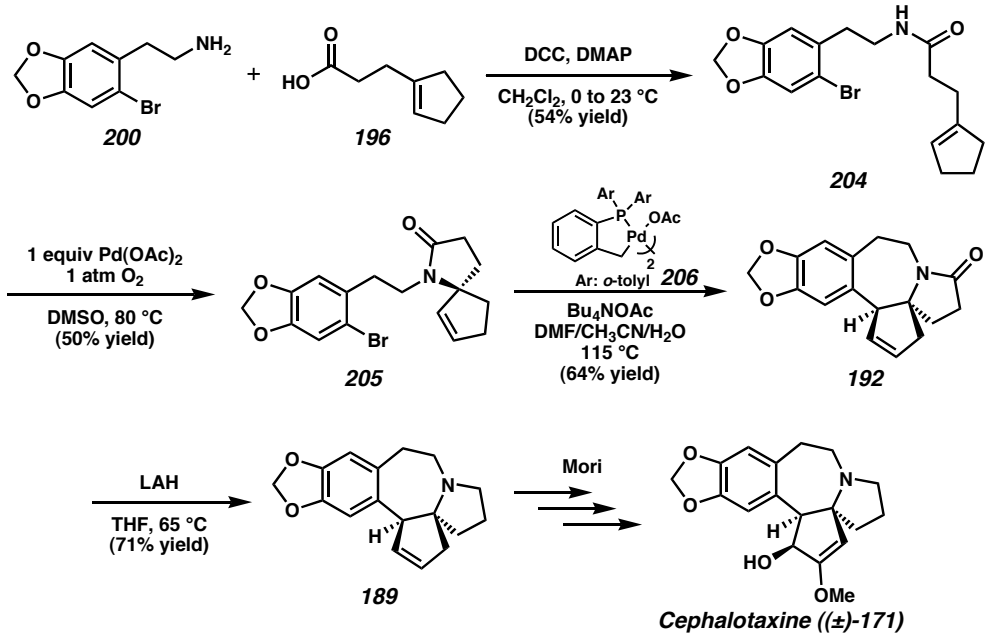
Carboxylic acid **196**[4] was readily synthesized from commercially available β-ketoester **201** (Scheme 3.4.4). The ketoester is reduced to allylic alcohol **202** by lithium aluminum hydride.[23] The allylic alcohol is treated with triethyl orthoacetate under Johnson orthoester Claisen conditions[24] to afford ethyl ester **203**,[25] which is subsequently saponified by base to produce acid **196**.

Scheme 3.4.4



The completion of the formal total synthesis of (±)-cephalotaxine is outlined in Scheme 3.4.5. DCC-mediated amide bond formation provided **204** in 54% yield. Unfortunately, the oxidative heterocyclization of **204** under catalytic palladium(II) conditions did not proceed efficiently. To our delight, however, spirolactam **205** was produced in 50% yield using 1 equiv $Pd(OAc)_2$ in DMSO at 80 °C. Notably, the aryl bromide did not react under these conditions. The intramolecular Heck reaction[26] proceeded cleanly and diastereoselectively to afford lactam **192**.[18h] LAH reduction of amide **192** afforded amine **189**, which Mori has shown can be converted to cephalotaxine in four steps.[18i]

Scheme 3.4.5

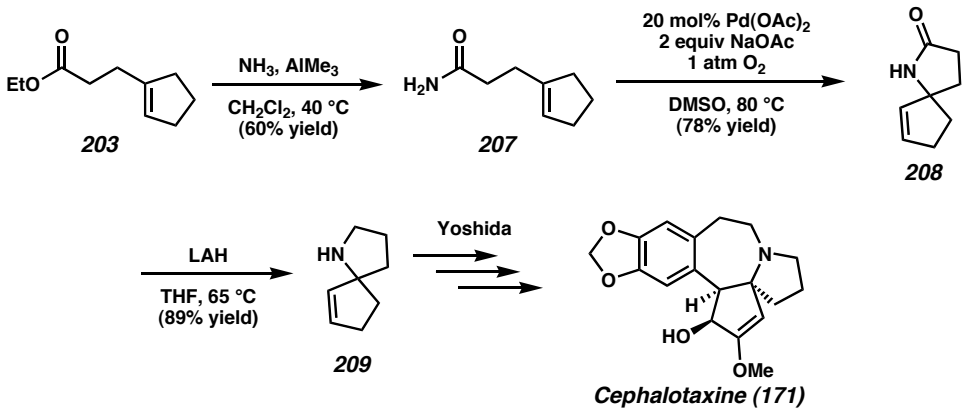


There are a number of aspects that warrant discussion with this synthesis. Currently, the spirolactam formation (**204** → **205**) requires stoichiometric quantities of palladium. The design of improved oxidative systems will be necessary in order to achieve catalyst turnover. Importantly, the synthesis can be carried out with complete diastereoselectivity based on the stereocenter formed in the palladium-mediated heterocyclization step. Therefore, in the event of the development of an asymmetric heterocyclization, it can readily be applied to an enantioselective total synthesis of (–)-cephalotaxine. Finally, as mentioned in the retrosynthetic plan, the seven-membered ring could alternatively be formed by a palladium(II)-mediated carbocyclization on a non-brominated arene. The development of similar reactions to form carbocycles will be discussed in Chapter 4 of this thesis.

3.4.4 A Second Formal Total Synthesis of (±)-Cephalotaxine

Regarding the first of these issues, we have investigated heterocyclizations that can proceed under catalytic conditions and can be applied to the synthesis of cephalotaxine (Scheme 3.4.6). Ethyl ester **203** was converted to amide **207** by treatment with NH_3 and trimethylaluminum.[27] In contrast to the more substituted system, the oxidative heterocyclization of **207** proceeded under catalytic conditions to afford spirolactam **208** in good yield.[28,29] Reduction of the lactam afforded pyrrolidine **209**, which Yoshida has shown is an intermediate in his recently reported total synthesis of cephalotaxine.[19d] This constituted a second formal total synthesis of (±)-cephalotaxine, with the advantage of using direct dioxygen-coupled palladium catalysis.

Scheme 3.4.6

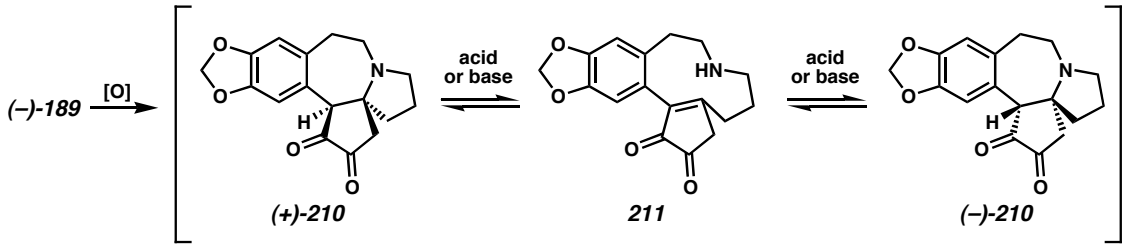


3.5 A Proposed Total Synthesis of Drupacine

Particularly noteworthy among the synthetic efforts toward cephalotaxine was the first asymmetric synthesis reported by Mori.[18i] In this report, diketone intermediate **210**, arising from olefin **189** via a two-step oxidation sequence, was shown to be susceptible to racemization under acidic or basic conditions (Scheme 3.5.1). Under carefully optimized

acidic conditions, this racemization event could be avoided, and (–)-cephalotaxine was thereby accessed. We anticipated that we could utilize the known racemization of this compound as a key transformation in the enantioselective total synthesis of (–)-drupacine (**172**), another member of the *Cephalotaxus* alkaloids.[30]

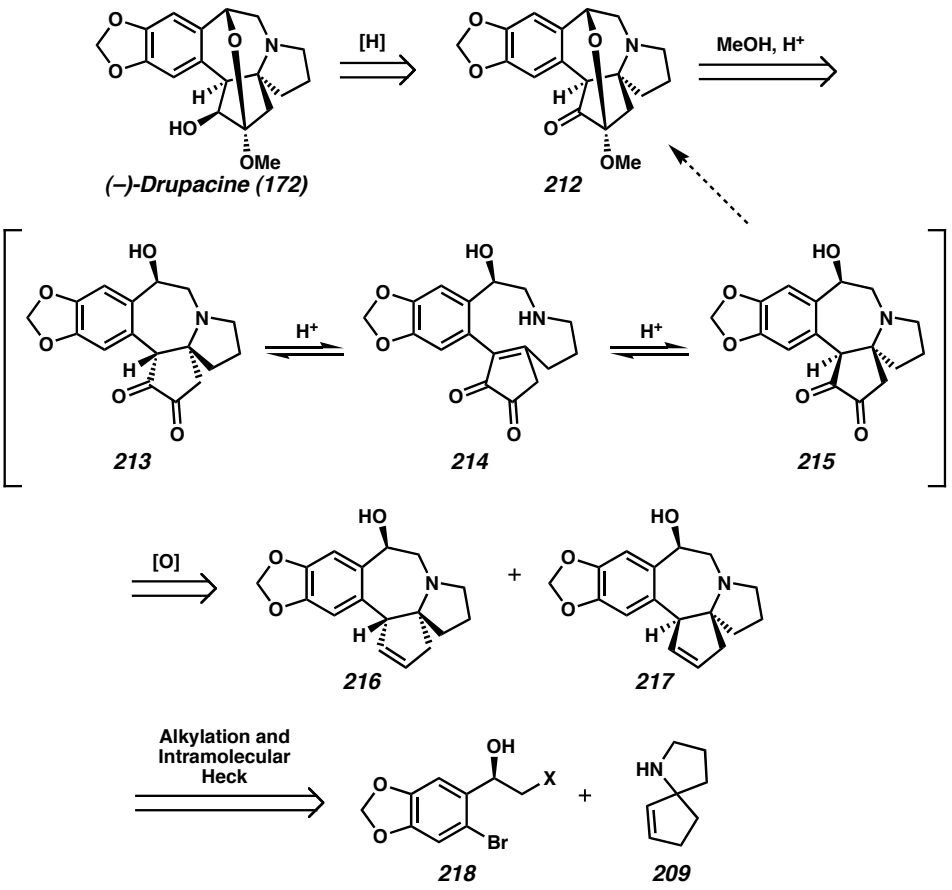
Scheme 3.5.1



A proposed retrosynthetic plan for the synthesis of (–)-drupacine is outlined in Scheme 3.5.2. The natural product is expected to arise from a ketone reduction of **212**. It is believed that this acetal can be derived from an equilibrating mixture of diketone diastereomers (**213** and **215**). The equilibration is expected to occur via an analogous racemization pathway to that described by Mori for the similar diketones **(+)-210** and **(–)-210** (see Scheme 3.5.1). The diketone moiety in diastereomer **215** is positioned in close proximity to the benzylic alcohol, thus allowing the formation of the acetal under acidic conditions. The same acetal cannot form in diastereomer **213** because the alcohol is too far away from the diketone moiety—it therefore undergoes the racemization step. This dynamic diastereomeric resolution is expected to eventually funnel all of the material to acetal **212**. These diketones (**213** and **215**) can be derived from diastereomeric olefins **216** and **217** through a straightforward oxidation sequence. These olefins are expected to arise from alcohol **218** and pyrrolidine **209** via an alkylation and subsequent intramolecular Heck reaction. We anticipate that enantiopure alcohol **218** can be

accessed from the palladium-catalyzed oxidative kinetic resolution, while we have already demonstrated that pyrrolidine **209** can be formed from the palladium(II)-catalyzed heterocyclization chemistry (*vide supra*). This synthesis would be highly illustrative of the synthetic utility of the aerobic palladium(II) transformations we have developed thus far.

Scheme 3.5.2



3.6 Conclusion

Following the discovery of the oxidative kinetic resolution of alcohols, we desired to extend this aerobic oxidation method to other transformations. Our efforts toward this goal resulted in the demonstration that similar catalytic systems can be used for

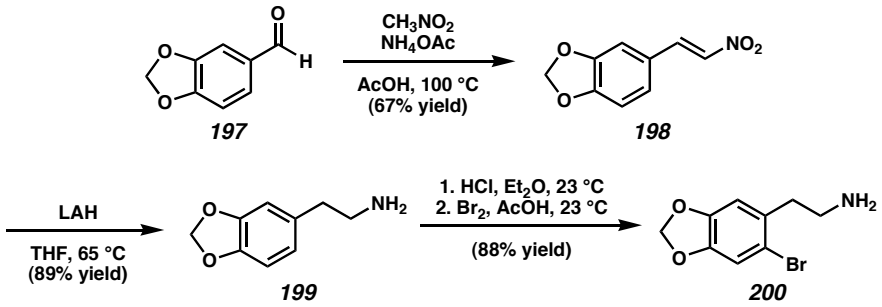
intramolecular Wacker cyclizations to form heterocycles. The reactions are remarkably simple, employing a palladium-pyridine catalyst and molecular oxygen as the sole stoichiometric oxidant. Furans, lactones, lactams, and pyrans can all be accessed in high yields via this method. Importantly, the developed system allowed for entry into asymmetric variants, which ultimately led to the highly enantioselective synthesis of dihydrobenzofurans using a palladium-sparteine catalyst. We have also begun to apply some of these reactions toward the synthesis of the *Cephalotaxus* alkaloids, completing two formal syntheses of (±)-cephalotaxine. In hopes of further developing palladium(II)-catalyzed dehyrogenative reactions, there were two key directions we believed were in need of substantial investigation. The first involved the development of novel enantioselective heterocyclizations to make chiral heterocycles beyond dihydrobenzofurans. Approaches to this goal will be discussed in Chapter 5. The other direction we wanted to pursue was the use of this palladium(II) oxidative system toward carbon-carbon bond forming reactions. Our efforts in this area will be described in the next chapter.

3.7 Experimental Section

3.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C spectra were recorded on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. $Pd(OAc)_2$ was purchased from Strem Chemicals, Inc., Newburyport, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

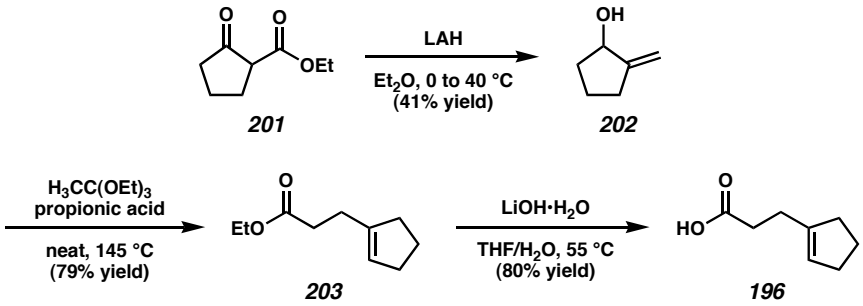
3.7.2 Preparative Procedures



Amine 200. Amine **199** was synthesized according to the procedure of Marsden and MacLean.[21] To a solution of piperonal (5.00 g, 33.3 mmol) in 49.7 mL acetic acid was added nitromethane (3.07 mL, 56.6 mmol), then NH_4OAc (6.68 g, 86.6 mmol). The reaction mixture was heated to 100 °C and stirred for 6 h. The mixture was then cooled to room temperature and poured over ice (200 mL). After 1 h, the yellow precipitate that formed was collected by filtration. The crude material was recrystallized from hot ethanol to afford β-nitrostyrene derivative **198** (4.31 g, 67% yield, R_F = 0.45 in 4:1 hexanes/EtOAc) as yellow needlelike crystals.

To a stirring suspension of LAH (1.18 g, 31.2 mmol) in 62.3 mL THF at 65 °C was added a solution of **198** (2.00 g, 10.4 mmol) in 41.7 mL THF dropwise via an addition funnel over 20 min. The resulting mixture was stirred at 65 °C for 15 h, then cooled to 0 °C and quenched slowly with 1.18 mL H_2O, 1.18 mL 15% aq. NaOH, and 3.54 mL H_2O, sequentially. The mixture was allowed to warm to room temperature and stirred vigorously. Once a white precipitate had formed, the mixture was filtered, and the filtrate was concentrated in vacuo. Amine **199**[21] (1.53 g, 89% yield, R_F = 0.00 in 4:1 hexanes/EtOAc) was sufficiently pure to be carried to the subsequent reaction.

Bromination of amine **199** was performed according to the procedure of Tietze and Schirok.[18k] HCl (g) was bubbled through a solution of the crude amine (9.27 mmol) in Et_2O at 23 °C for 5 min. The solution was then concentrated to a solid, which was then suspended in 10.3 mL AcOH at 23 °C. Bromine (951 μl, 18.5 mmol) was added dropwise, and the mixture was stirred at 23 °C for 10 h. The reaction was then quenched with 5% aq. Na_2SO_3 until the color dissipated, then basified with 20% aq. NaOH until pH >13. The mixture was extracted with CH_2Cl_2 (4 x 75 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated to an oil. Amine **200** (2.00 g, 88% yield, R_F = 0.00 in 4:1 hexanes/EtOAc) was carried on without further purification.

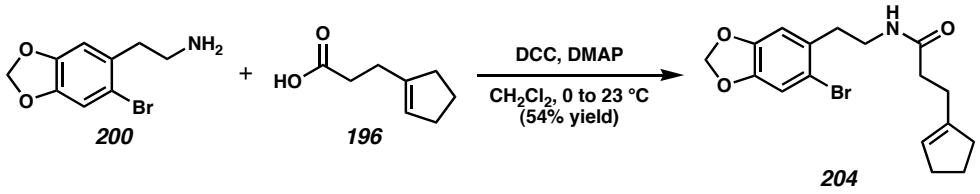


Carboxylic acid 196. Allylic alcohol **202** was synthesized according to the procedure of Dreiding and Hartman.[23a] To a stirring suspension of lithium aluminum hydride (13.6 g, 359 mmol) in Et_2O (120 mL) at 0 °C was added ethyl 2-oxocyclopentanecarboxylate (**201**, 25.0 mL, 169 mmol) in Et_2O (50 mL) dropwise via an addition funnel. The reaction mixture was heated to 40 °C and stirred 30 min. The mixture was then cooled to 0 °C and quenched by the slow addition of water. The resulting mixture was diluted with Et_2O (500 mL) and stirred vigorously with 20% aqueous solution of sodium potassium tartrate (150 mL) for 1 h. The phases were then separated, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried over $MgSO_4$

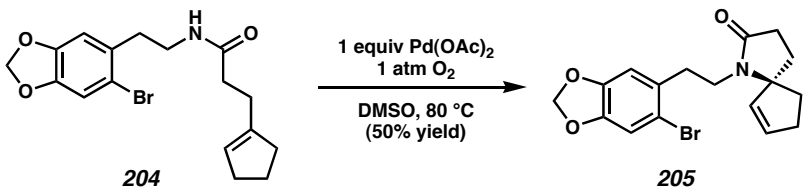
and concentrated to a yellow oil. Fractional distillation of the oil (bp 92 °C at 68 torr) provided allylic alcohol **202**[31] (6.83 g, 41% yield, R_F = 0.26 in 4:1 hexanes/EtOAc) as a colorless oil.

The allylic alcohol (2.50 mL, 24.3 mmol) was dissolved in triethylorthoacetate (35.6 mL, 194 mmol), and the solution was treated with propionic acid (660 μl, 8.31 mmol). The reaction was heated to 145 °C with distillative removal of ethanol. After distillation was complete, the reaction was stirred at 145 °C for an additional 60 min, then cooled to 23 °C and diluted with Et_2O (300 mL). The solution was stirred with 1.0 M aq. $KHSO_4$ (300 mL) for 8 h. The phases were separated, and the aqueous phase was extracted with ether (1 x 200 mL). The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (30:1 hexanes/Et_2O eluent) provided ester **203** (3.22 g, 79% yield, R_F = 0.62 in 4:1 hexanes/Et_2O) as a clear oil.

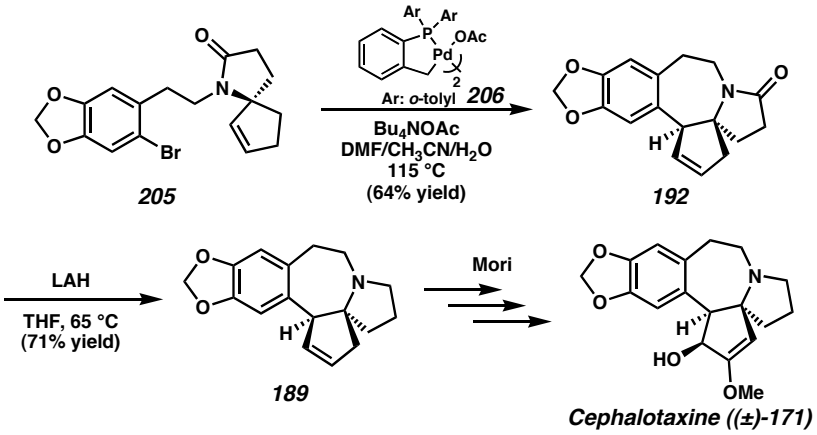
To a solution of ethyl ester **203** (2.99 g, 17.8 mmol) in THF/H_2O (89 mL, 1:1) at 23 °C was added LiOH•H_2O (3.73 g, 89.0 mmol). The mixture was heated to 50 °C and stirred overnight (12 h). The mixture was cooled to room temperature, and the volatile solvent was removed by rotary evaporation. The aqueous residue was cooled to 0 °C, acidified with 3.0 N HCl, then extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to an oil. The residue was purified by flash chromatography (100% CH_2Cl_2 → 9:1 CH_2Cl_2/MeOH eluent) to afford carboxylic acid **196**[4] (2.00 g, 80% yield, R_F = 0.35 in 4:1 hexanes/EtOAc) as a white solid.



Amide 204. To a solution of acid **196** (119 mg, 0.848 mmol) in 2.54 mL CH_2Cl_2 at 0 °C was added DCC (177 mg, 0.856 mmol), DMAP (5.2 mg, 0.0424 mmol), and a solution of amine **200** (207 mg, 0.848 mmol) in 1.70 mL CH_2Cl_2, sequentially. The mixture was stirred at 0 °C for 15 min, then allowed to warm to 23 °C and stirred 90 min. The reaction mixture was then diluted with CH_2Cl_2 (15 mL) and filtered through a plug of celite to remove the white precipitates. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford amide **204** (167 mg, 54% yield, R_F = 0.43 in 15:1 CH_2Cl_2/MeOH) as a yellow semisolid. **Amide 204**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.70 (s, 1H), 5.96 (s, 2H), 5.56 (br s, 1H), 5.33 (br s, 1H), 3.47 (app.q, *J* = 6.9 Hz, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.40-2.20 (comp m, 6H), 2.36 (t, 2H), 1.84 (app.quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 147.7, 147.4, 143.5, 131.5, 124.3, 114.8, 113.0, 110.6, 101.9, 39.6, 35.9, 35.3, 35.2, 32.6, 27.2, 23.6; IR (film) 1641, 1502, 1477, 1230 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{20}NO_3Br]^+$: 365.0627, found 365.0631.



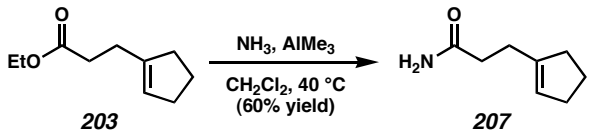
Spirolactam 205. To a solution of amide **204** (225 mg, 0.614 mmol) in 6.14 mL DMSO at 23 °C was added $Pd(OAc)_2$ (138 mg, 0.614 mmol). The mixture was cooled to 0 °C, evacuated and backfilled with O_2 three times, and then heated to 80 °C and stirred. After 90 min, the reaction was cooled to room temperature, diluted with EtOAc (100 mL), and washed with H_2O (2 x 75 mL). The aqueous phases were extracted with EtOAc (2 x 50 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provided spirolactam **205** (113 mg, 50% yield, R_F = 0.19 in 1:1 hexanes/EtOAc) as a yellow oil. **Spirolactam 205**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.77 (s, 1H), 5.94 (s, 2H), 5.92-5.90 (m, 1H), 5.27-5.25 (m, 1H), 3.35-3.25 (m, 1H), 3.10-3.01 (m, 1H), 2.98-2.86 (comp m, 2H), 2.54-2.29 (comp m, 4H), 1.96 (app.t, *J* = 7.8 Hz, 2H), 1.94 (comp m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 147.6, 147.2, 134.8, 134.2, 132.1, 114.8, 112.8, 111.0, 101.8, 76.4, 40.5, 35.3, 34.5, 33.2, 31.5, 30.5; IR (film) 1681, 1477, 1406, 1230 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{18}NO_3Br]^+$: 363.0470, found 363.0455.



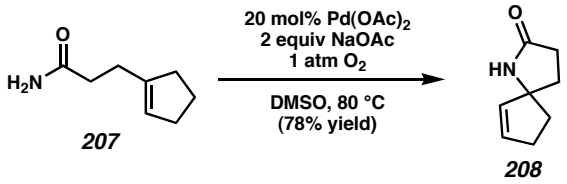
Amine 189. The intramolecular Heck reaction was performed according to a modified procedure of Tietze and Schirok.[18k] To a solution of spirolactam **205** (113 mg, 0.310 mmol) in DMF (3.1 mL), CH_3CN (3.1 mL), and H_2O (620 μl) under argon at 23 °C was added palladium-phosphine dimer **206**[32] (32.8 mg, 0.0310 mmol), then Bu_4NOAc (187 mg, 0.620 mmol). The reaction mixture was heated to 115 °C. After 19 h, the mixture was cooled to room temperature, and the volatile solvents were removed by rotary evaporation. The residue was partitioned between 75 mL EtOAc and 30 mL H_2O. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford amide **192**[18h] (56.2 mg, 64% yield, R_F = 0.27 in 3:1 EtOAc/hexanes) as a yellow solid.

To a stirring suspension of LAH (15.2 mg, 0.400 mmol) in 800 μl THF at 23 °C was added a solution of amide **192** (28.3 mg, 0.100 mmol) in 200 μl THF dropwise over 1 min. The mixture was heated to 65 °C and stirred for 1 h. It was then cooled to 0 °C, diluted with 4 mL Et_2O, and quenched with 15.2 μl H_2O, 15.2 μl 15% aq. NaOH, and 45.6 μl H_2O, sequentially. The mixture was allowed to warm to room temperature and stirred until a white precipitate formed. The precipitate was removed by filtration through a plug of celite (THF eluent), and the filtrate was concentrated in vacuo. Amine

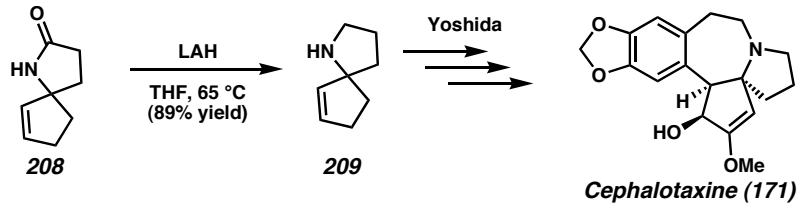
189[18i] (19.1 mg, 71% yield, R_F = 0.17 in 5:1 EtOAc/MeOH w/ 1% Et_3N) was isolated as a pale yellow oil.



Amide 207. 35.0 mL CH_2Cl_2 was saturated with NH_3 by bubbling ammonia gas for 3 min at 0 °C. The solution was warmed to 23 °C, and trimethylaluminum (12.2 mL, 2.5 M in hexanes, 30.6 mmol) was added dropwise over 10 min. The mixture was stirred for 15 min, then a solution of ethyl ester **203** (2.57 g, 15. 3 mmol) in 3.3 mL CH_2Cl_2 was added dropwise. The reaction mixture was heated to 40 °C and stirred for 46 h. The mixture was then cooled to 0 °C, quenched by slow addition of 1.0 N HCl, and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (100% EtOAc eluent) provided amide **207** (1.28 g, 60% yield, R_F = 0.39 in 100% EtOAc) as a white solid. **Amide 207**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (br s, 1H), 5.58 (br s, 1H), 2.38 (br s, 1H), 2.39 (app.s, 4H), 2.32-2.22 (comp m, 4H), 1.86 (app.quintet, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 143.3, 124.5, 35.3, 34.4, 32.6, 27.0, 23.6; IR (film) 3382, 3183, 1657, 1632, 1416 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{13}NO]^+$: 139.0997, found 139.0996.



Spirolactam 208. To a solution of amide **207** (209 mg, 1.50 mmol) in 15.0 mL DMSO at 23 °C was added $Pd(OAc)_2$ (67.3 mg, 0.300 mmol). The mixture was cooled to 0 °C, evacuated and backfilled with O_2 three times, and then heated to 80 °C and stirred. After 48 h, the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified by flash chromatography (100% EtOAc eluent) to provided spirolactam **208** (161 mg, 78% yield, R_F = 0.25 in 100% EtOAc) as a yellow solid. **Spirolactam 208**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (br s, 1H), 5.81-5.78 (m, 1H), 5.59-5.56 (m, 1H), 2.46-2.23 (comp m, 4H), 2.07-1.85 (comp m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 135.2, 133.2, 71.4, 37.9, 33.9, 30.9; IR (film) 3191, 1690, 1366, 753 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{11}NO]^+$: 137.0841, found 137.0835.



Amine 209. To a suspension of LAH (417 mg, 11.0 mmol) in 10.4 mL THF at 0 °C was added a solution of spirolactam **208** (504 mg, 3.68 mmol) in 8.0 mL THF dropwise over 2 min. The reaction mixture was heated to 65 °C and stirred. After 16 h, the mixture was cooled to 0 °C and quenched with 417 μl H_2O, 417 μL 15% aq. NaOH, and 1.25 μL H_2O, sequentially. The mixture was allowed to warm to room temperature and stirred vigorously until a white precipitate had formed. The mixture was then suction filtered,

and the filtrate was concentrated in vacuo to provide amine **209**[19d] (402 mg, 89% yield, R_F = 0.00 in 100% EtOAc) as a yellow oil.

3.8 Notes and References

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(6) (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S. -I. *J. Am. Chem. Soc*. **1981**, *103*, 2318-2323. (b) Hosokawa, T.; Okuda, C.; Murahashi, S. -I. *J. Org. Chem*. **1985**, *50*, 1282-1287.

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(10) For leading references on the Pd(II)/DMSO oxidative system for heterocyclizations, see: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem*. **1993**, *58*, 5298-5300. (b) Rönn, M.; Bäckvall, J. -E.; Andersson, P. G. *Tetrahedron Lett*. **1995**, *36*, 7749-7752. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem*. **1996**, *61*, 3584-3585.

(11) This mechanistic pathway was simply a proposed hypothesis based on similar literature examples. Another pathway involving O-H bond insertion to a palladium alkoxide intermediate followed by olefin insertion was not ruled out as operative. Mechanistic aspects of these heterocyclizations will be briefly discussed as part of Chapter 5 of this thesis.

(12) The silver salt is believed to at least partially abstract the chloride counterion(s) from the palladium center. This contributed to the notion that the palladium counterion would have an effect on the selectivity and reactivity of the reaction, as we had seen in the kinetic resolution chemistry.

(13) While this research was underway, a similar cyclization of tosylamides was reported. See: Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed*. **2002**, *41*, 164-166.

(14) The efficacy of $Pd(OCOCF_3)_2$ is attributed to its electron-deficient nature compared to $Pd(OAc)_2$ or $PdCl_2$, making it more reactive toward reactions involving electrophilic activation pathways.

(15) For reviews on the *Cephalotaxus* alkaloids, see: (a) Miah, M. A. J.; Hudlicky, T.; Reed, J. W. Cephalotaxus alkaloids. In *The Alkaloids*; Academic Press: New York,

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(19) For other syntheses of cephalotaxine not illustrated in Scheme 3.4.1, see: (a) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull*. **1993**, *41*, 276-281. (b) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Am. Chem. Soc*. **1994**, *116*, 9791-9792. (c) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem*. **1996**, *61*, 7335-7347. (d) Suga, S.; Watanabe, M.; Yoshida, J. -I. *J. Am. Chem. Soc*. **2002**, *124*, 14824-14825. (e) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett*. **2002**, *4*, 885-888. (f) Li, W. -D. Z.; Wang, Y. -Q. *Org. Lett*. **2003**, *5*, 2931-2934. (g) Li. W. -D. Z.; Ma, B. -C. *J. Org. Chem*. **2005**, *70*, 3277-3280.

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(28) The catalyst loading could be reduced to 5 mol% on small scale reactions (ca. 100 mg substrate). When larger scale reactions were conducted, the catalyst loading needed to be increased.

(29) The oxidative heterocyclization of **207** was also investigated using the palladium/pyridine/toluene system. The reaction proceeded to completion with stoichiometric palladium, and modest turnover was observed under catalytic conditions. For the purposes of accessing large quantities of material, however, the palladium/DMSO conditions were more effective.

(30) There has been only one total synthesis of (±)-drupacine reported. See reference 18g.

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APPENDIX ONE

Spectra Relevant to Chapter Three: Palladium-Catalyzed Aerobic Wacker Cyclizations and the Formal Total Synthesis of Cephalotaxine

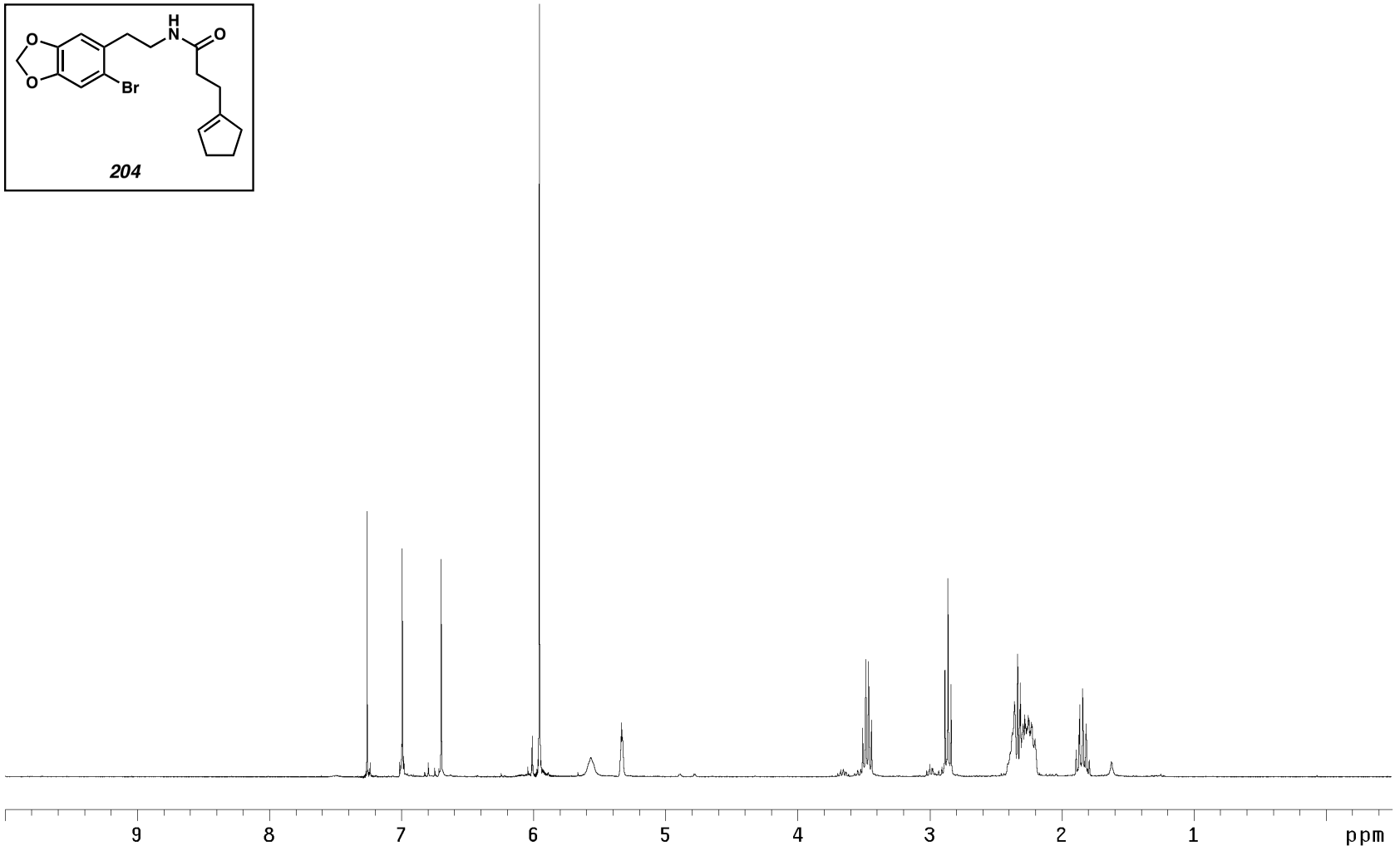


Figure A1.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **204**.

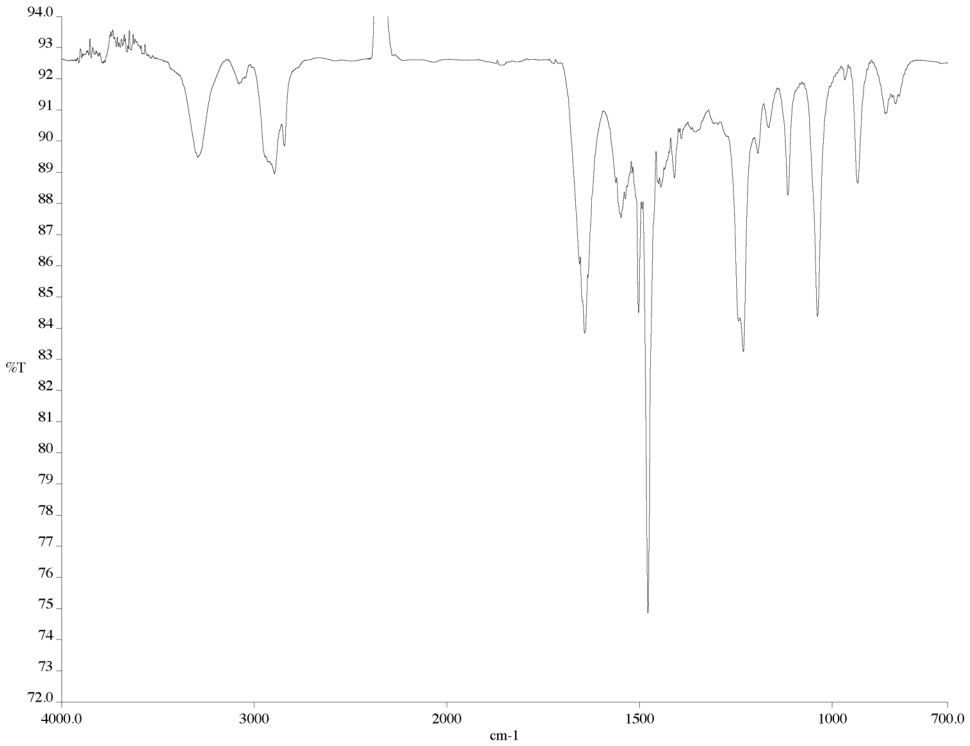


Figure A1.2 Infrared spectrum (thin film/NaCl) of compound **204**.

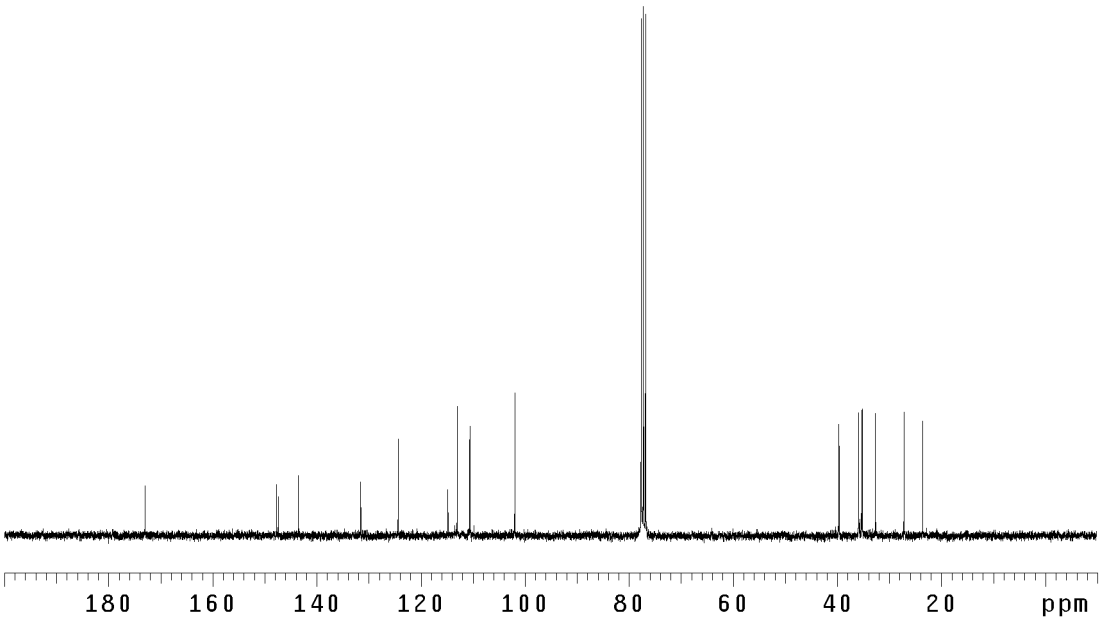


Figure A1.3 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **204**.

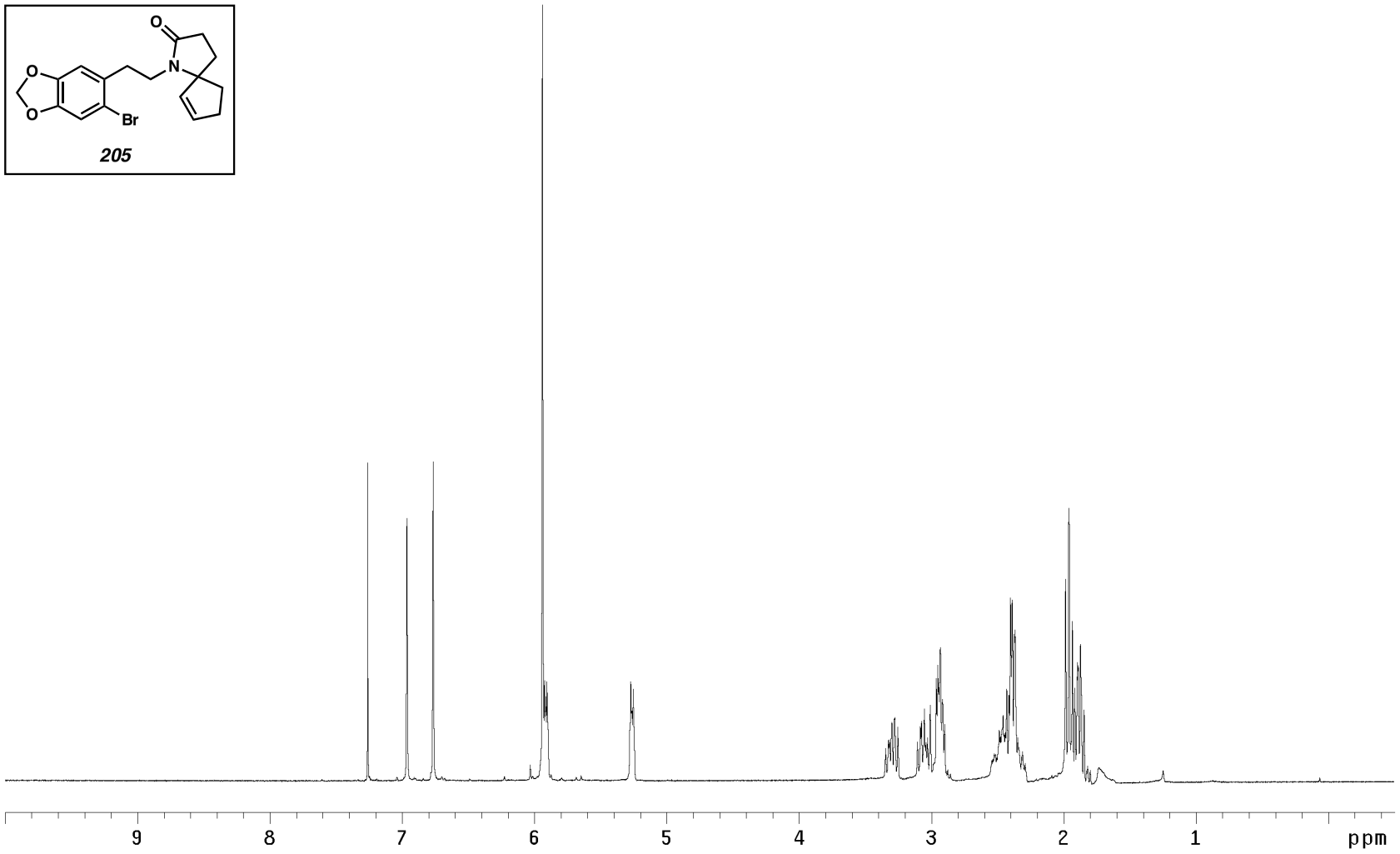


Figure A1.4 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **205**.

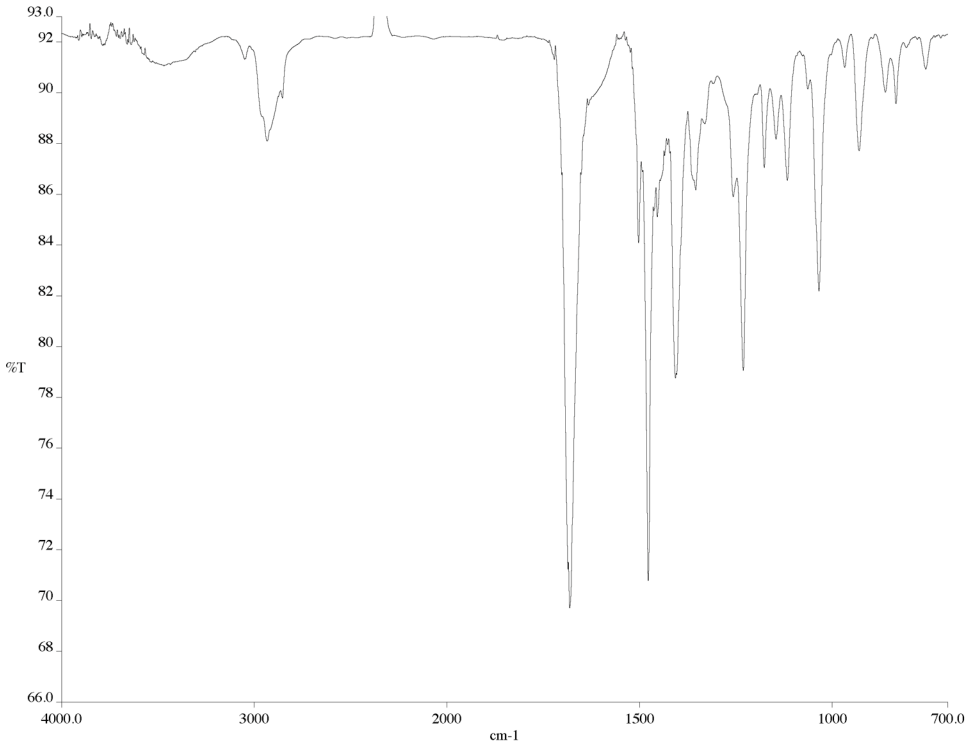


Figure A1.5 Infrared spectrum (thin film/NaCl) of compound **205**.

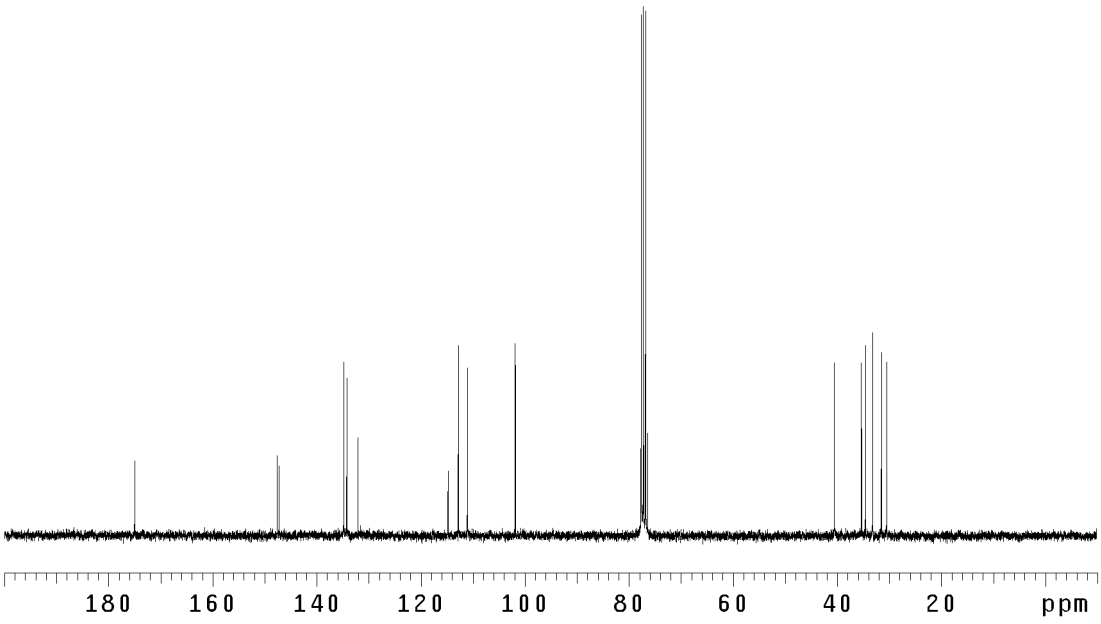


Figure A1.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **205**.

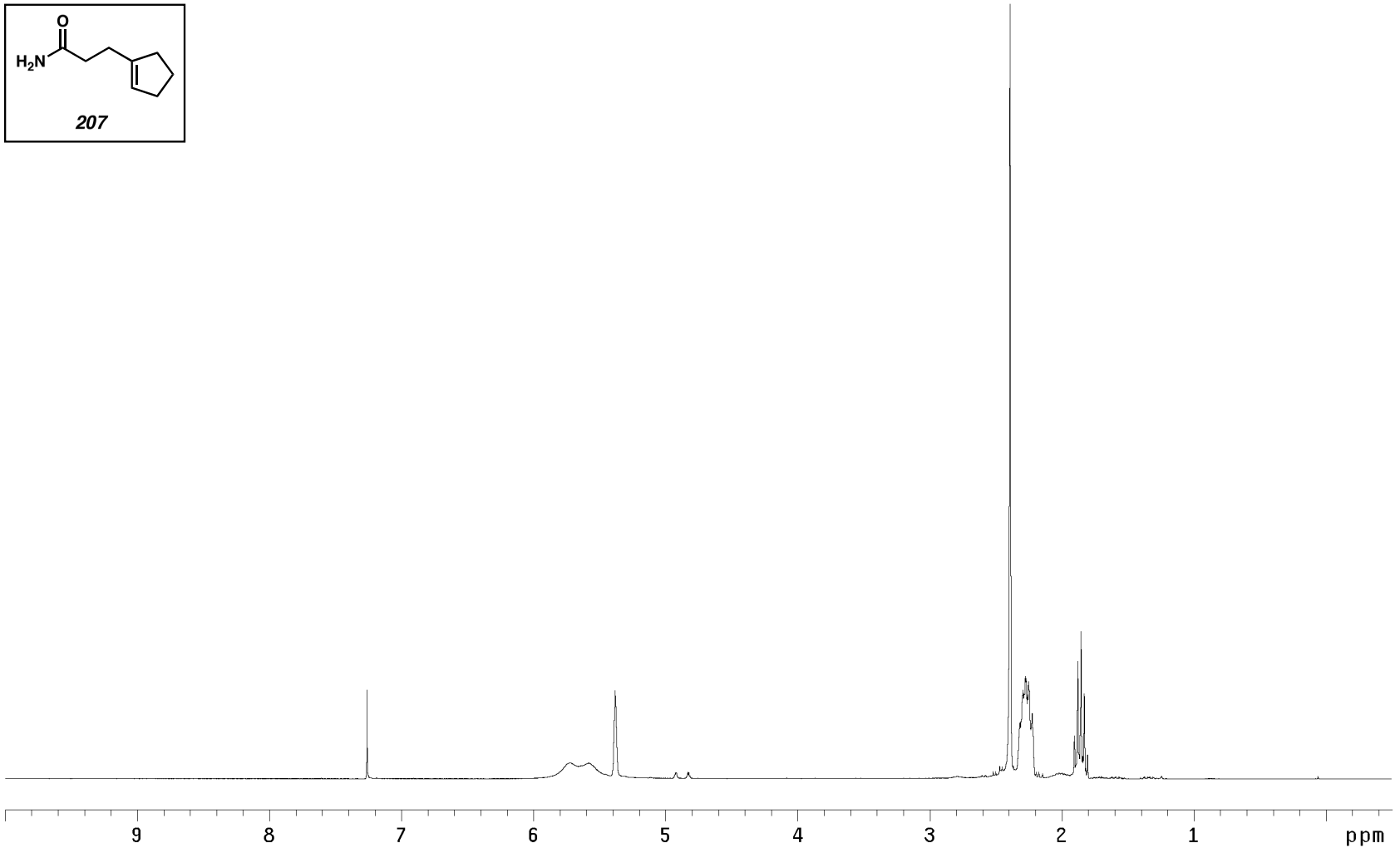


Figure A1.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **207**.

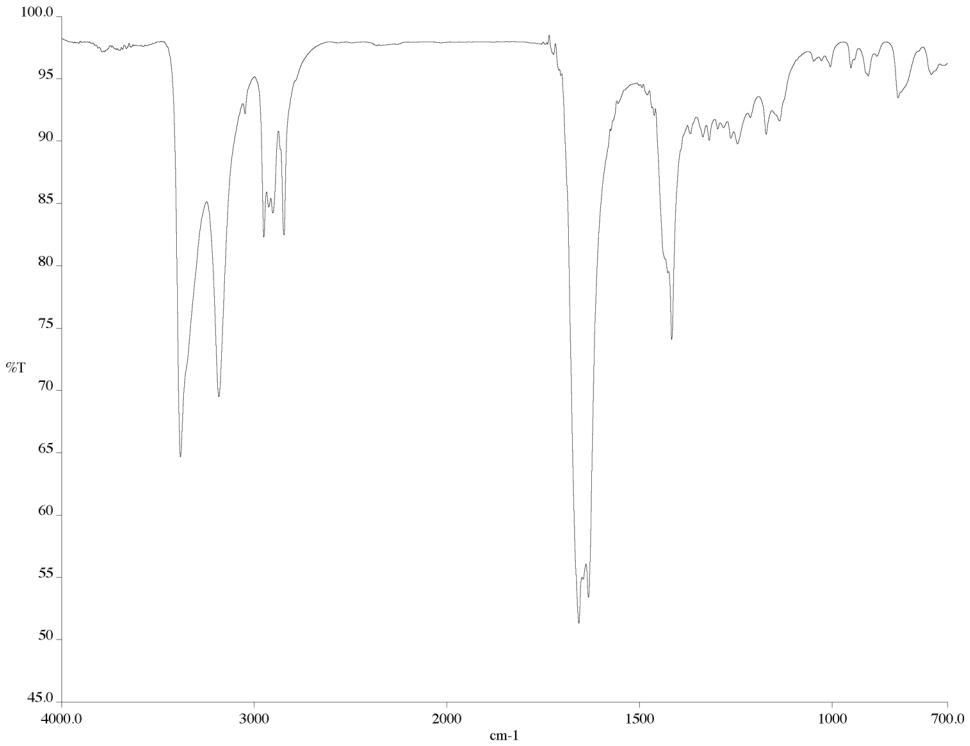


Figure A1.8 Infrared spectrum (thin film/NaCl) of compound **207**.

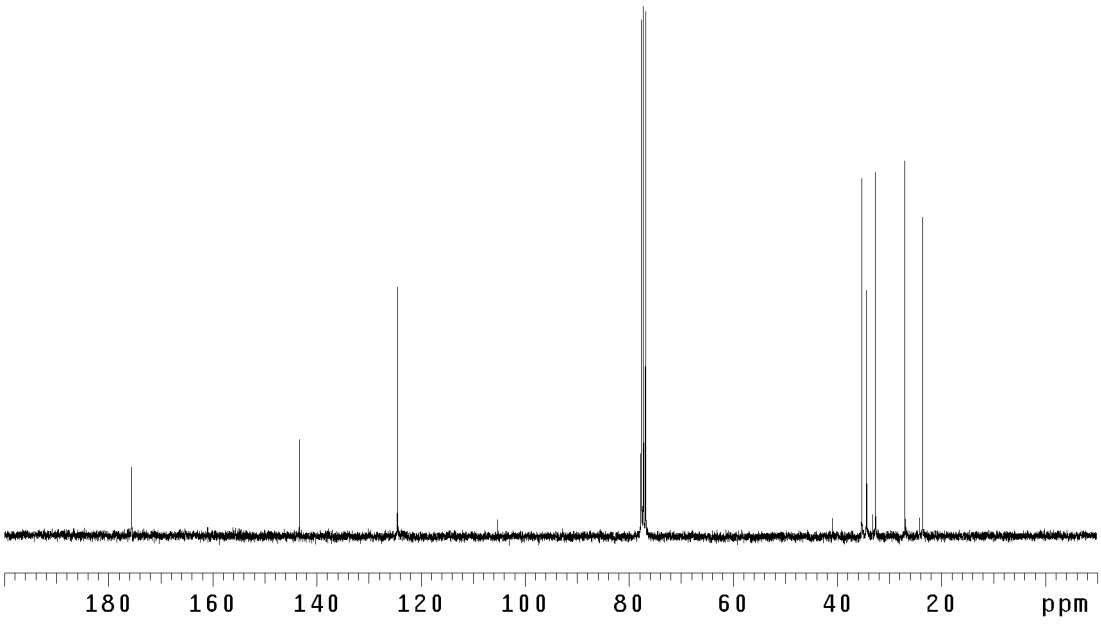


Figure A1.9 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **207**.

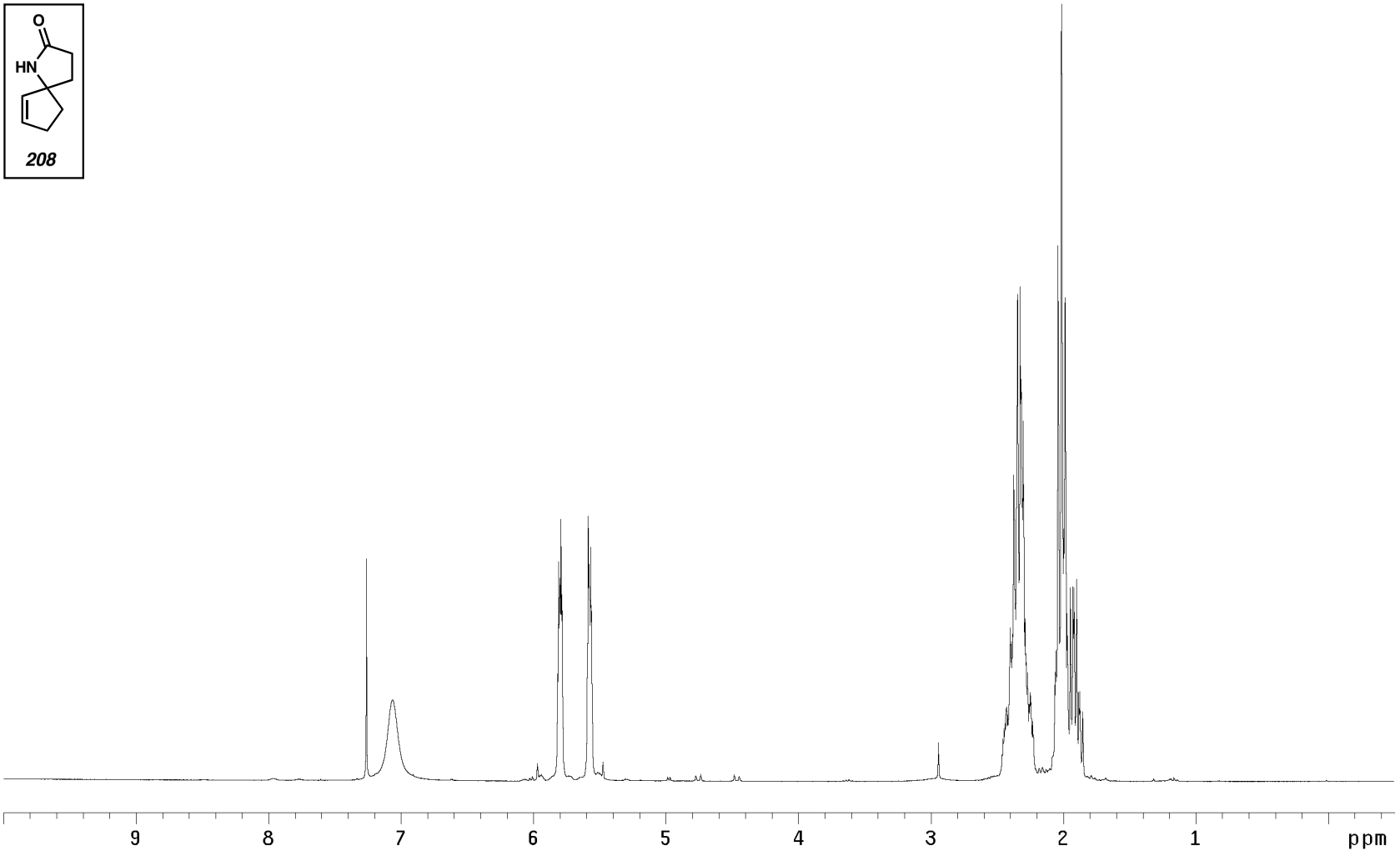


Figure A1.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **208**.

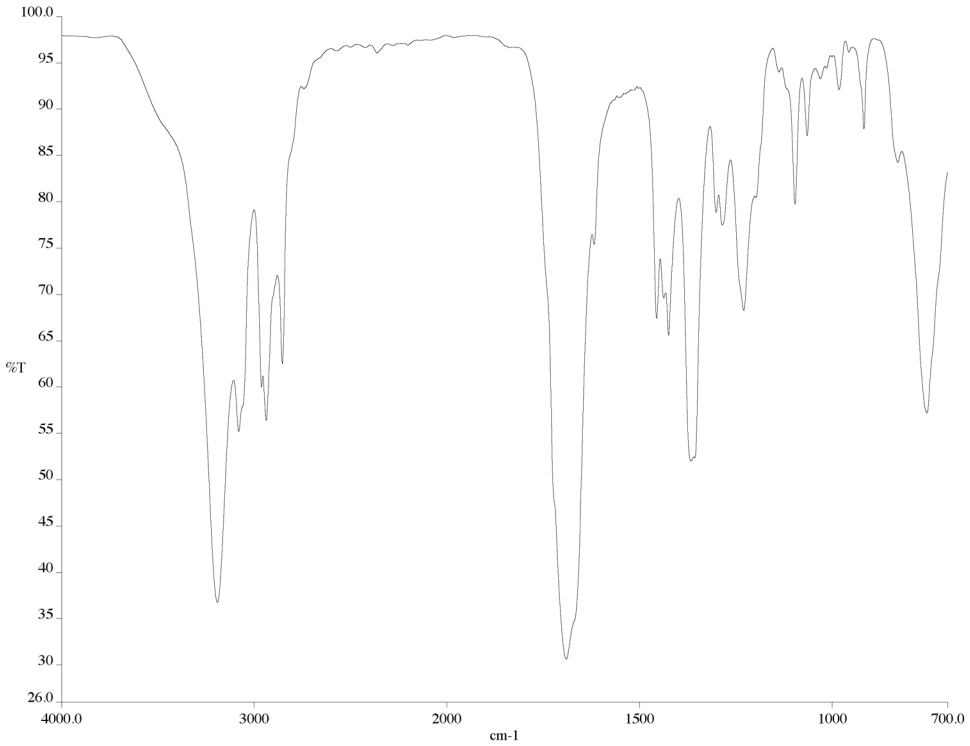


Figure A1.11 Infrared spectrum (thin film/NaCl) of compound **208**.

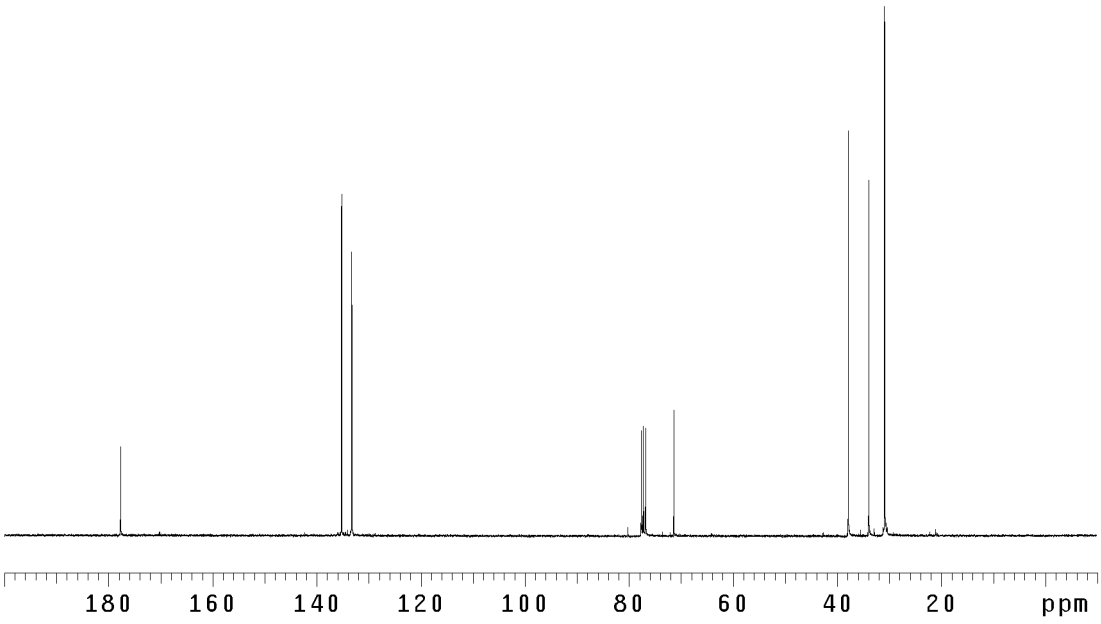


Figure A1.12 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **208**.

CHAPTER FOUR

C-H Bond Functionalizations with Palladium(II): Intramolecular Annulations of Arenes

4.1 Introduction

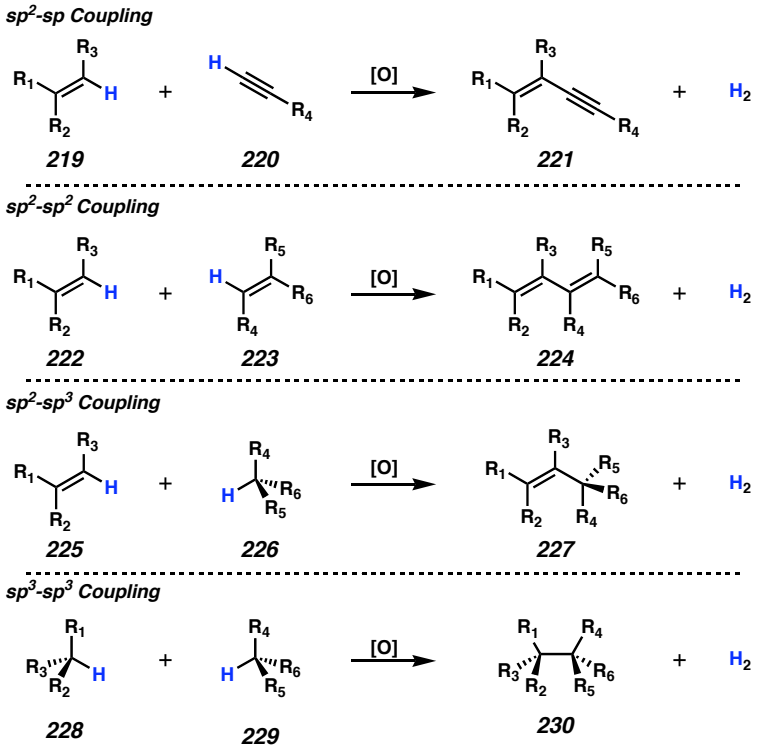
As detailed in Chapters 2 and 3, the development of palladium(II) oxidative transformations that do not involve heteroatom transfer was a principal focus of our research. We had discovered and developed the oxidative kinetic resolution of secondary alcohols using a palladium/sparteine/O_2 system.[1] This oxidative system was then used as a starting point for the development of oxidative heterocyclization reactions in both the racemic and enantioselective sense.[2] It was anticipated that our understanding of these systems could be applied to the development of novel oxidative transformations. Specifically, we sought to extend the palladium/ligand/O_2 catalytic oxidation system to C-C bond forming reactions.

4.1.1 Carbon-Carbon Bond Forming Reactions via Palladium Catalysis

Palladium(0)-catalyzed carbon-carbon bond forming reactions have been well-established in synthetic chemistry.[3] Processes such as the Heck reaction,[4] Stille and Suzuki couplings,[5,6] and the Sonogashira reaction[7] have been widely used for the efficient construction of carbon-carbon bonds. All of these transformations are initiated by the oxidative addition of a palladium(0) catalyst to a carbon-halogen bond, the byproducts of these reactions being either HX (for the Heck and Sonogashira reactions) or MX (for the cross-coupling reactions).

Comparatively, dehydrogenative carbon-carbon bond forming reactions have seen little use in synthetic chemistry. A number of oxidative transformations that can be envisioned by such a process are depicted in Figure 4.1.1. These transformations result in the functionalization of two C-H bonds and the formation of a new C-C bond. Carbons of any hybridization (*sp*, sp^2, or sp^3) can be viewed as coupling partners for these dehydrogenative bond forming reactions.

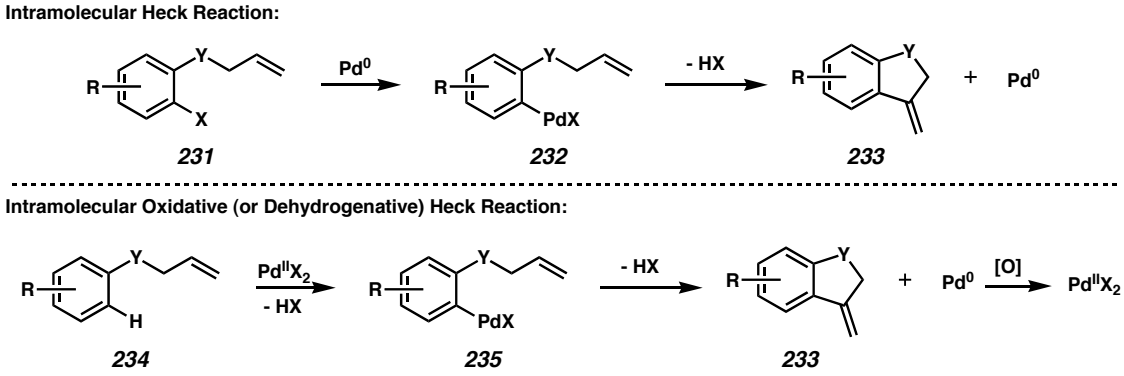
Figure 4.1.1 Oxidative carbon-carbon bond forming reactions.



As a starting point, we decided to investigate intramolecular dehydrogenative couplings between two sp^2 carbons. A reaction of this type is directly analogous to the intramolecular Heck reaction, wherein a halogenated arene (**231**) undergoes an oxidative addition by palladium(0), followed by olefin insertion and β-hydride elimination (Scheme 4.1.1). In a dehydrogenative version, a C-H bond of an arene is directly

functionalized by palladium(II), leading to a similar aryl-palladium intermediate (**235**). The reaction then proceeds in the same fashion as the Heck reaction. This oxidative coupling can be considered more efficient, obviating the need to first install the halide functionality required for a Heck process. Described herein are our efforts toward this goal, culminating in the palladium-catalyzed oxidative annulations of indoles and the syntheses of benzofuran and dihydrobenzofuran derivatives, all involving a C-H bond functionalization event.[8]

Scheme 4.1.1



4.2 Background

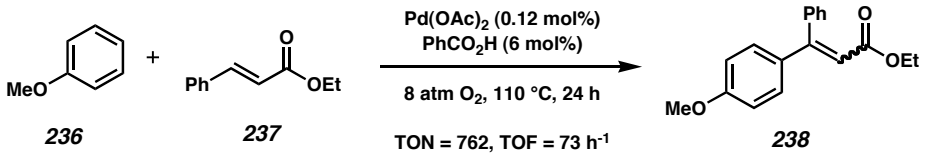
High C-H bond strengths (e.g., methane: 105 kcal/mol; benzene: 110 kcal/mol) significantly limit their reactivity toward functionalization. Despite this barrier, a massive effort has been put forth over the past twenty-five years toward transition metal activation of C-H bonds.[9] One successful reaction manifold is the oxidative coupling of an arene and an olefin by palladium(II), pioneered by Fujiwara.[10] Although successful in several intermolecular cases, examples of intramolecular reactions are rare. We postulated that the aerobic oxidative systems we had been studying could be utilized in

intramolecular C-C bond forming reactions between an arene and an olefin that involve an initial C-H bond functionalization.

4.2.1 Palladium(II) Oxidative Arene-Olefin Couplings

The first aerobic palladium-catalyzed C-C bond forming reaction was reported by Shue in 1971.[11] Benzene and styrene were coupled in the presence of $Pd(OAc)_2$ and approximately 20 atm O_2 at 100 °C to provide stilbene. Up to 110 catalytic turnovers were observed under these conditions. More recently, Jacobs has described a similar system in the oxidative coupling of benzene derivatives and activated esters (Scheme 4.2.1).[12] In the presence of $Pd(OAc)_2$ and a cocatalytic amount of benzoic acid under approximately 8 atm O_2, benzene derivatives could be oxidatively coupled to afford styrenyl compounds. Under these conditions, turnover number and turnover frequency were both remarkably high.

Scheme 4.2.1

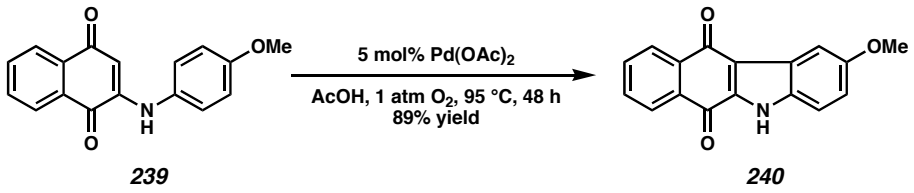


236 *237* *238*

Oxidative C-C bond forming reactions using oxygen as the sole stoichiometric oxidant almost exclusively involved intermolecular examples wherein a solution of an activated olefin (e.g., acrylate esters) in neat arene was stirred under high pressures of oxygen. One notable exception was reported by Åkermark in 1999 (Scheme 4.2.2).[13] Arylaminoquinone **239** was oxidatively cyclized under catalytic $Pd(OAc)_2$ and 1 atm O_2

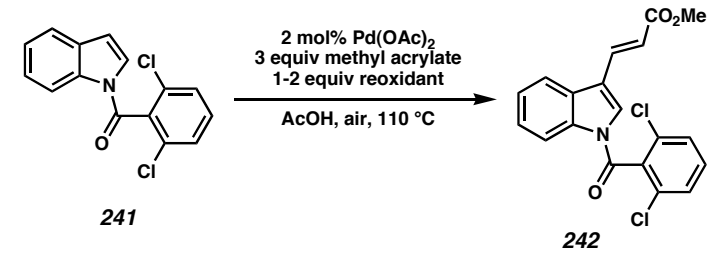
in AcOH at 95 °C to afford product **240**, resembling the core structures of a number of natural products (e.g., murrayquinone A and kinamycin A).

Scheme 4.2.2



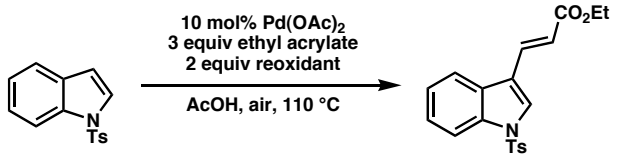
Palladium-mediated oxidative coupling reactions involving the indole nucleus have been studied extensively by Itahara and coworkers.[14] Catalytic examples, however, were consistently plagued by low yields (Scheme 4.2.3). *N*-2,6-Dichlorobenzoylindole (**241**) was oxidatively coupled with methyl acrylate by catalytic $Pd(OAc)_2$ and a number of stoichiometric oxidants (e.g., AgOAc, $Cu(OAc)_2$, $Na_2S_2O_8$, and $NaNO_2$),[14a] but the yield never exceeded 20% in these systems. Alternatively, the oxidative coupling of *N*-tosylindole (**243**) was examined, in this case with higher catalyst loadings.[14b] Although the yields were marginally improved (up to 42%), they were still not particularly useful synthetically. Fujiwara recently described a single example of a catalytic intermolecular oxidative coupling using the indole nucleus.[15] Under $Pd(OAc)_2$ and a benzoquinone/TBHP reoxidation system, indole (**245**) was coupled to methyl acrylate to provide **246** in 52% yield.

Scheme 4.2.3



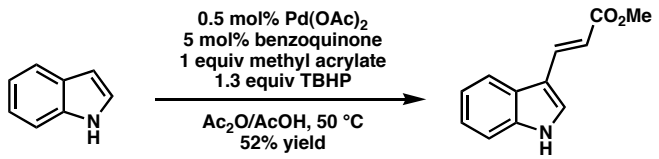
241 242

Reoxidant	TON	Yield (%)
stoich. $Pd(OAc)_2$	--	25
AgOAc	8.8	18
$Cu(OAc)_2$	5.2	10
$Na_2S_2O_8$	3.2	6
$NaNO_2$	3.4	7



243 244

Reoxidant	TON	Yield (%)
stoich. $Pd(OAc)_2$	--	48
AgOAc	3.2	31
$Cu(OAc)_2$	4.1	41
$Na_2S_2O_8$	4.2	42
$NaNO_2$	1.6	16

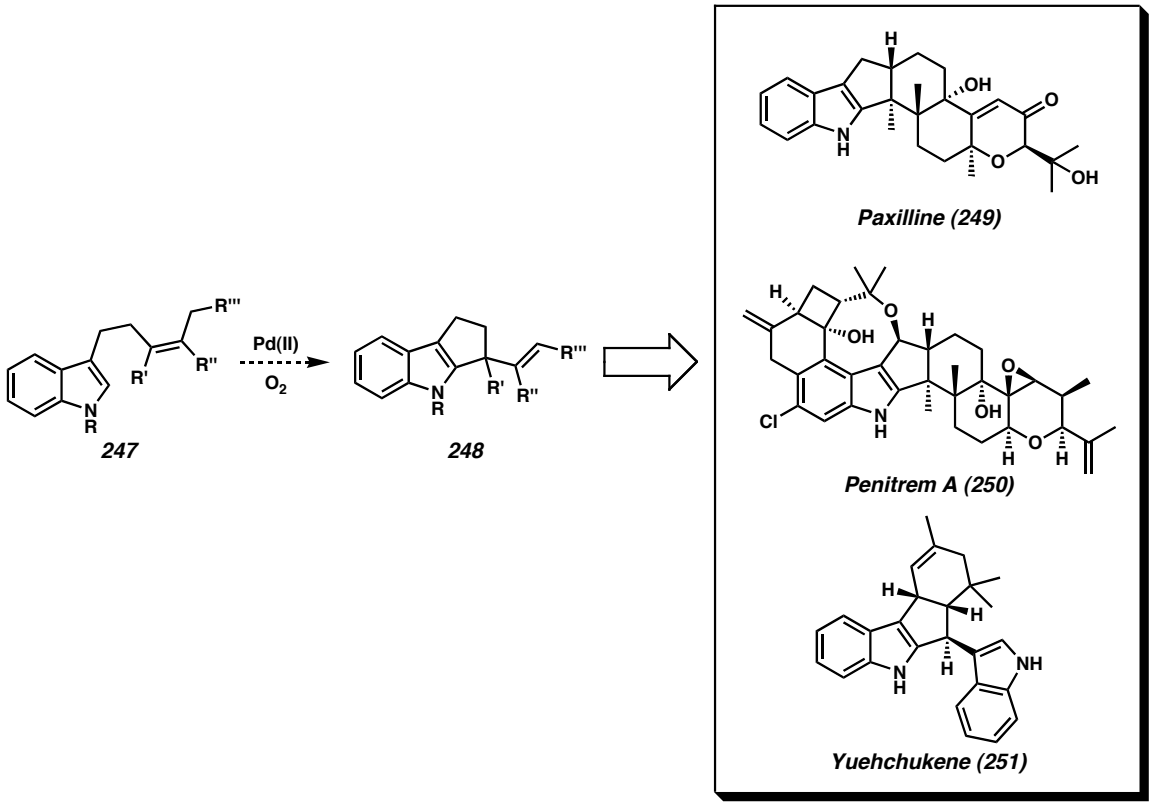


245 246

4.2.2 Synthetic Importance of Annulated Indoles

Although some success has been achieved in oxidative couplings involving the indole nucleus, intramolecular catalytic examples have never been reported. In a general reaction scheme, indole **247** would cyclize onto a tethered olefin to afford annulated indole **248** (Scheme 4.2.4). A reaction of this type would be immensely useful to the synthetic community. Several biologically active natural products (e.g., paxilline,[16] penitrem A,[17] and yuehchukene[18]) containing the core annulated indole structural motif could be accessed by such a reaction.

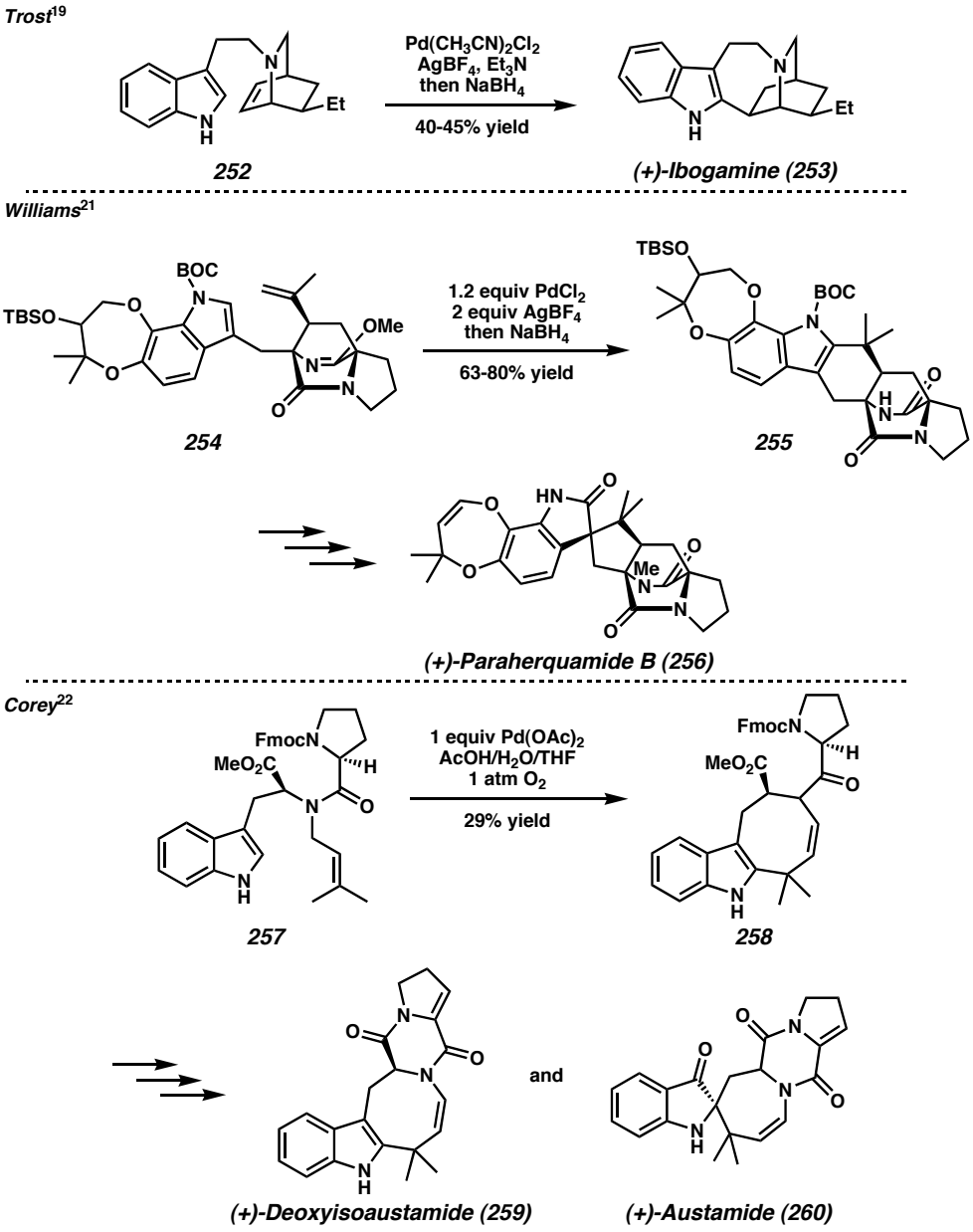
Scheme 4.2.4



We were not the first to recognize the potential utility of an intramolecular indole annulation in natural product synthesis. In 1978, Trost reported the palladium-mediated cyclization and subsequent reduction of indole **252** to produce (+)-ibogamine.[19,20] Fifteen years later, Williams described the total synthesis of paraherquamide B using a similar palladium(II)-promoted cyclization/reduction sequence of indole **254** as the key transformation.[21] More recently, Corey has reported the oxidative cyclization of indole **257** using palladium(II) in the syntheses of members of the austamide class of natural products.[22,23] Although the cyclizations were all effective in the synthetic context, they all required stoichiometric amounts of palladium(II) salts. By comparison, the catalytic palladium/pyridine/O_2 system we had been studying had proven quite effective in a

number of oxidative transformations. We therefore sought to extend this system to catalytic C-C bond forming reactions, specifically oxidative indole annulations.[24,25]

Scheme 4.2.5

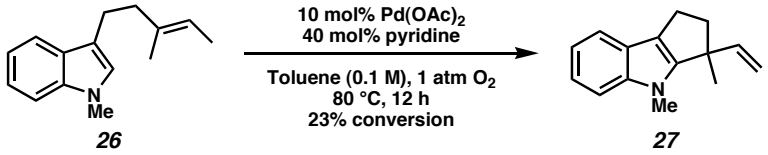


4.3 The Synthesis of Annulated Indoles via Palladium-Catalyzed Oxidative Carbocyclization

4.3.1 Reaction Development

As an initial test of the viability of a catalytic oxidative indole annulation, indole **26** was treated with 10 mol% $Pd(OAc)_2$ and 40 mol% pyridine under 1 atm O_2 in toluene at 80 °C (Scheme 4.3.1).[26] Gratifyingly, oxidative cyclization to annulated indole **27** occurred;[27] the overall reactivity, however, was noticeably sluggish (23% conversion after 12 h) relative to the other oxidative processes studied thus far (i.e., alcohol oxidation[1] and various heterocyclizations[2]). It was hypothesized that the catalyst center was not sufficiently electron-deficient for substrate activation. By increasing the electrophilicity of the catalyst, potentially higher reaction rates could be achieved.

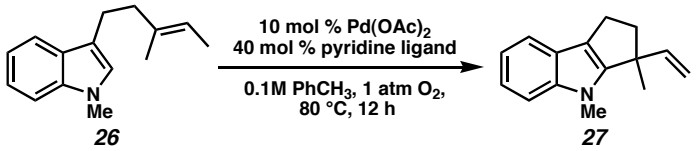
Scheme 4.3.1



To that end, we surveyed a range of electronically differentiated pyridine ligands with $Pd(OAc)_2$ (Table 4.3.1). Interestingly, there was a noticeable correlation between the electronic nature of the ligand (estimated by the measured pK_a of their respective pyridinium ions)[28] and the overall reactivity. More electron-rich pyridine ligands shut down the reaction (entries 1 and 2), while switching to pyridines substituted with electron-withdrawing groups effected an increase in the reactivity, peaking with ethyl nicotinate (entry 5). Further increasing the electron-deficiency, however, was detrimental to the overall reaction (entries 6-9). These ligands are likely unable to sufficiently

coordinate to the palladium center, hampering the catalyst's reactivity and/or palladium(0) reoxidation. Because ethyl nicotinate appeared to strike the appropriate electronic balance for overall reactivity, it was selected as the ligand for further studies.

Table 4.3.1 Examination of electronic effects of the pyridyl ligand.



26 *27*

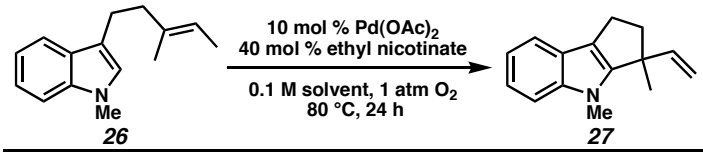
entry	pyridine ligand	pK_a (PyrH$^+$)[a]	conversion (%)[b]
1	4-MeO	6.47	3
2	4-*t*-Bu	5.99	1
3	unsubstituted	5.25	23
4	4-CO_2Et	3.45	52
5	*3-CO_2Et*	*3.35*	*76*
6	3-$COCH_3$	3.18	58
7	3-F	2.97	64
8	3-CN	1.39	55
9	3,5-di-Cl	0.90	22

[a] Reference 28. [b] % conversion measured by GC relative to an internal standard.

With the optimal ligand in hand, other parameters in the oxidative cyclization of indole **26** were investigated. The choice of palladium(II) salt was found to be important; $Pd(OAc)_2$ was more effective than $Pd(TFA)_2$, in contrast to the heterocyclization chemistry.[2] $PdCl_2$ and other palladium(II) halides were completely unreactive. The most significant effects on the reaction outcome were determined by the solvent (Table 4.3.2). Moving from nonpolar aromatic solvents (entries 1-3) to more polar solvents moderately increased the reactivity and overall yield of annulated indole **27**. There was still a noticeable discrepancy, however, between the conversion of **26** and the overall yield of **27**.[29] At this point, the combined yield of **26** and **27** (starting material and product) was observed to decrease in a nonlinear fashion over time. One possible rationalization of this observation is that the product decomposes over the course of the reaction.[30] Interestingly, this problem could be minimized by the addition of AcOH as a cosolvent

(entries 10 and 11). Ultimately, we found that employing a 4:1 mixture of *t*-amyl alcohol and AcOH as the solvent resulted in an 82% isolated yield of annulated indole **27**.

Table 4.3.2 Solvent effects in the indole annulation.



26 *27*

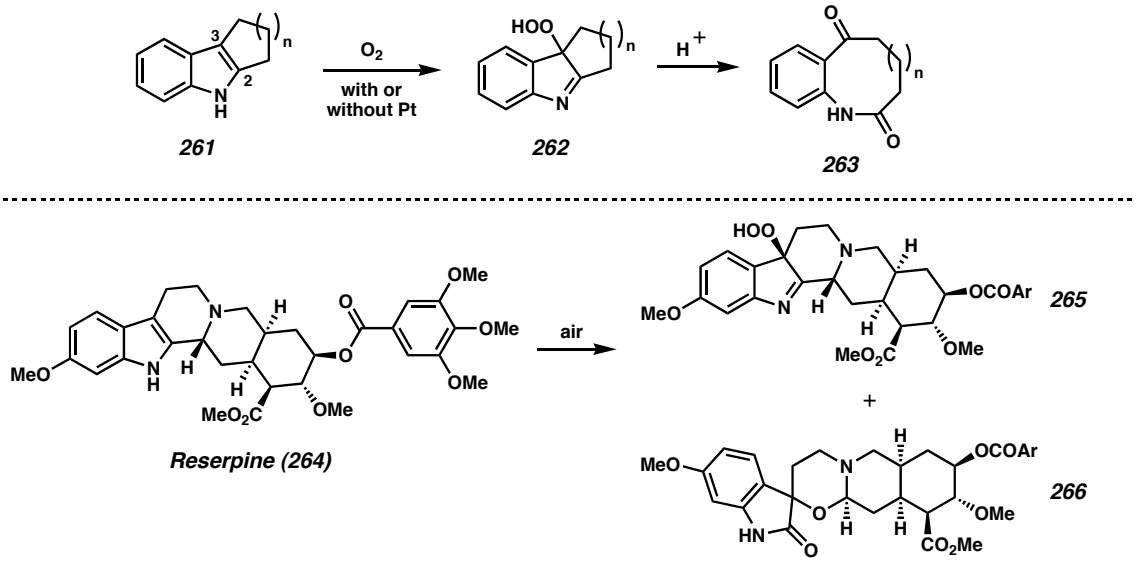
entry	solvent	conversion (%)[a]	% yield[a]
1	toluene	88	33
2	xylenes	88	31
3	chlorobenzene	85	40
4	dioxane	87	42
5	diglyme	99	37
6	butyl acetate	95	49
7	*t*-amyl alcohol	94	53
8	pinacolone	95	58
9	AcOH	86	25
10	pinacolone/AcOH (4:1)	91	76
11	*t*-amyl alcohol/AcOH (4:1)	99	82[b]

[a] % conversion and % yield measured by GC relative to an internal standard. [b] Isolated yield.

4.3.2 Susceptibility of Annulated Indoles to Oxygen

This difficulty with product decomposition was somewhat anticipated considering previous reports on reactions of 2,3-disbustituted indoles with oxygen.[31] In 1951, Witkop described the autoxidation of indoles with fused rings attached to the C-2 and C-3 positions (**261**, Scheme 4.3.2).[32] Under an oxygen atmosphere with or without reduced platinum oxide, the indoles were converted to intermediate peroxides by addition at the C-3 position, which upon workup afford keto lactams (**263**). More recently, the oxidation of reserpine (**264**), which contains an annulated indole core, under an atmosphere of oxygen was investigated by Awang (Scheme 4.3.2).[33] Two products were observed, peroxide **265** and dioxyreserpine (**266**), that arose from reaction with oxygen at ambient temperature.

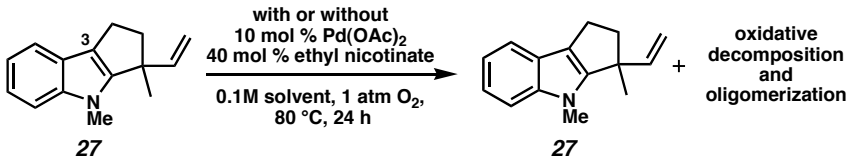
Scheme 4.3.2

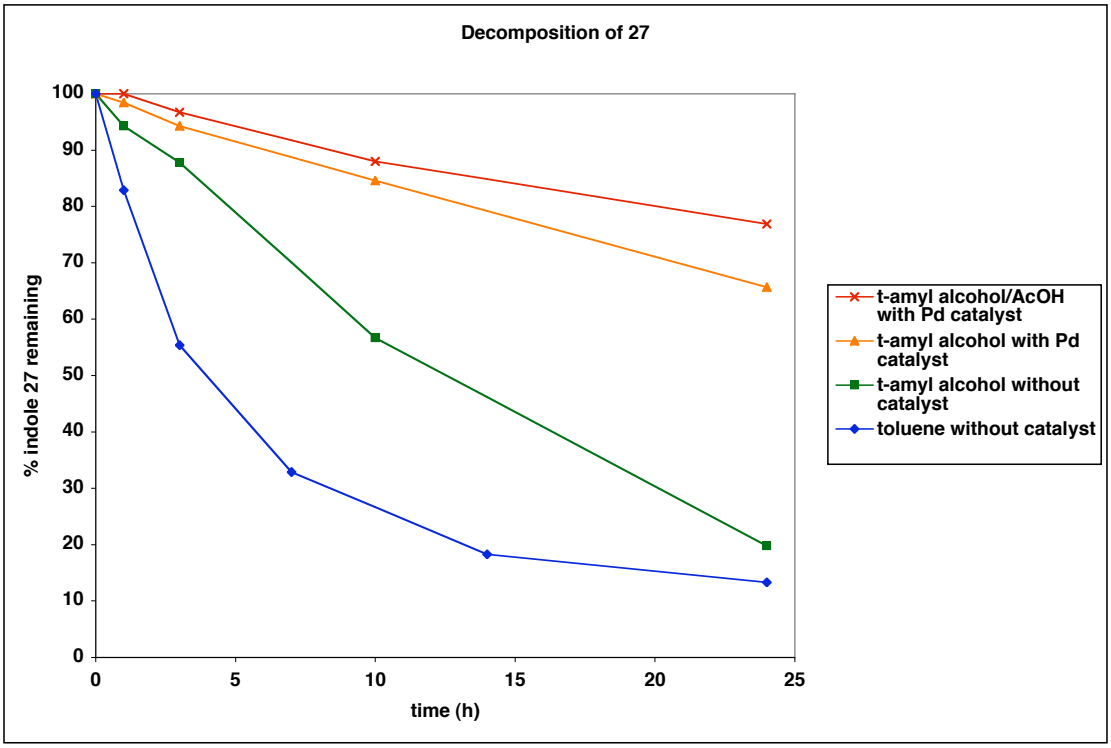


The product decomposition of our oxidative indole cyclization was probed in more detail (Scheme 4.3.1). Annulated indole **27** was subjected to the reaction conditions for 24 h, and the decomposition was monitored by GC analysis relative to an internal standard (tridecane).[34] A slight increase in product stability was observed in *t*-amyl alcohol versus toluene, consistent with our observations of the cyclization reaction. Addition of the catalyst (10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate) had a remarkable impact, limiting product decomposition to approximately 30% over 24 h. The stability was improved further by addition of AcOH as a cosolvent. The reasons behind the beneficial nature of the catalyst and AcOH toward the suppression of oxidative decomposition are currently unclear. One potential explanation is that since oxidative decomposition is initiated by nucleophilic addition of indole into dioxygen, the electrophilic palladium center may act as a competitive inhibitor via palladation at C-3. AcOH could act either as a second competitive inhibitor via association at C-3 or as an

ionizing agent for $L_nPd(OAc)_2$, protonating off an acetate ligand to afford a more reactive cationic palladium(II) center.[35]

Figure 4.3.1 Oxidative decomposition studies of indole **27**.



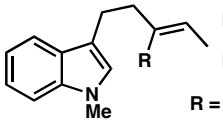
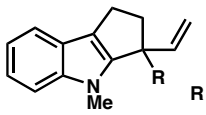
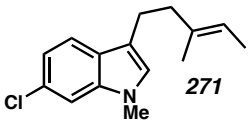
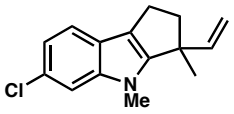
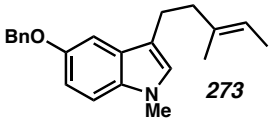
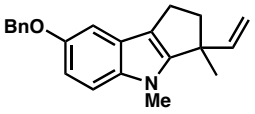
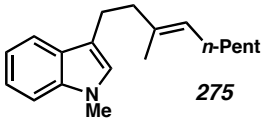
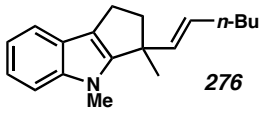
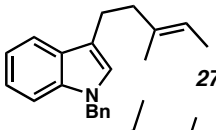
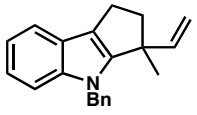
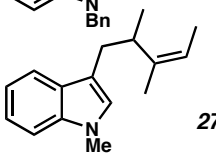
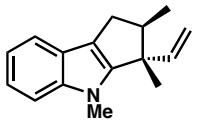
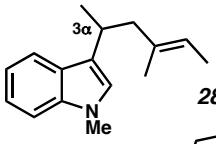
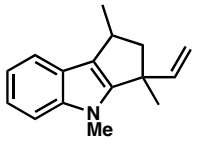
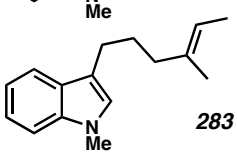
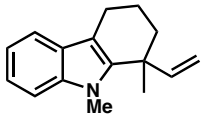
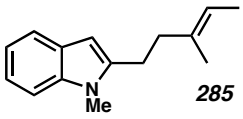
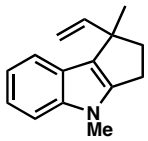
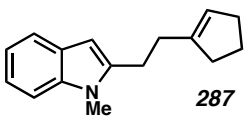
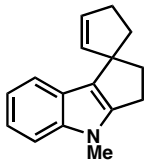
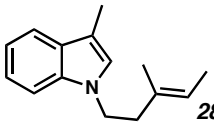
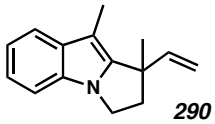


4.3.3 Substrate Scope

With this optimized system now in hand, the substrate scope was investigated. As shown in Table 4.3.3, good to excellent yields can be obtained across a range of substituted indoles. Indoles substituted with electron-withdrawing or electron-donating groups on the arene cyclize efficiently (entries 4 and 5). Substitution on the tether α to the olefin resulted in a diastereoselective cyclization (entry 8), whereas substitution at the

C-3α site imparted no diastereoselectivity (entry 9). Ring sizes of 5 or 6 (entry 10) can be accessed via the oxidative cyclization. The annulation is not limited to bond formation at the C-2 position. The cyclization can proceed from the C-2 to C-3 positions (entries 11 and 12), as well as from N-1 to C-2 (entry 13).[36]

Table 4.3.3 The palladium-catalyzed oxidative indole annulation.[a]

entry	substrate[b]	product	time	% yield[c]
1	 R = Me ***26***	 R = Me ***27***	24 h	82
2	R = Et ***267***	R = Et ***268***	18 h	74
3	R = CH_2OBn ***269***	R = CH_2OBn ***270***	24 h	60
4	 ***271***	 ***272***	32 h	62
5	 ***273***	 ***274***	20 h	73
6	 ***275***	 ***276***	30 h	79[d]
7	 ***277***	 ***278***	48 h	69
8	 ***279***	 ***280***	18 h	76 (6:1 dr)
9	 ***281***	 ***282***	53 h	64 (1:1 dr)
10	 ***283***	 ***284***	39 h	66[e]
11	 ***285***	 ***286***	6 h	73[f]
12	 ***287***	 ***288***	5 h	68[f]
13	 ***289***	 ***290***	18 h	74

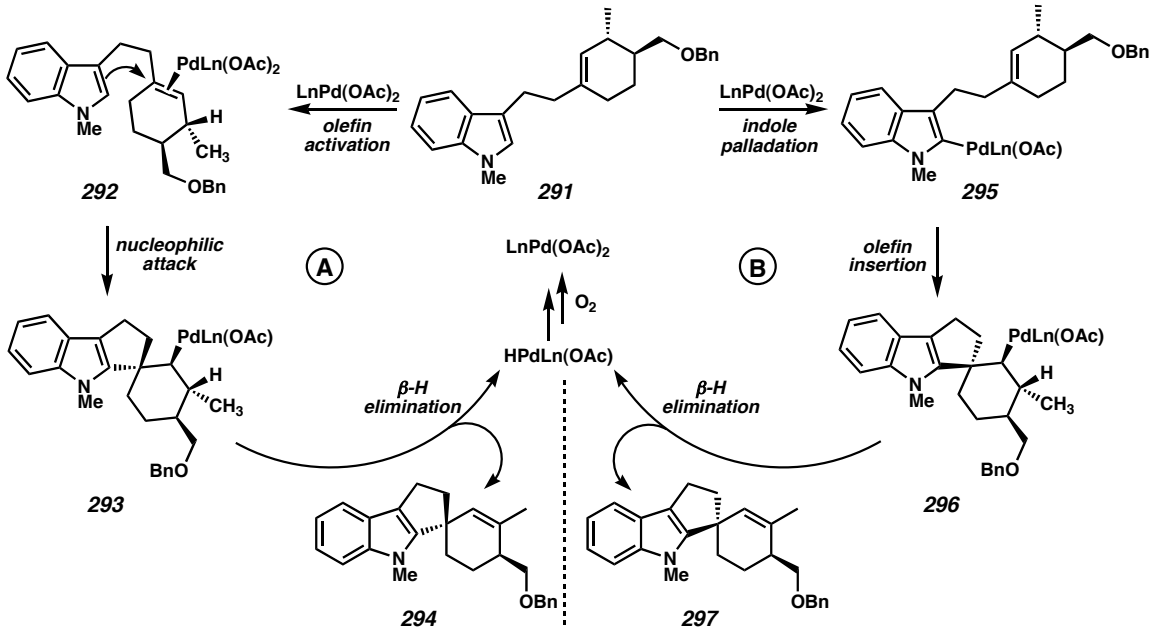
[a] 10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1). [b] Typically used as a mixture of olefin isomers; see Experimental Section. [c] Isolated yields. [d] Product isolated as a 58:42 mixture of olefin isomers. [e] 0.1 M in pinacolone. [f] 0.1 M in *tert*-amyl alcohol.

4.3.4 Mechanistic Insights

The relative rates of reactivity of the substrates with substitutions on the tethering carbons between the indole nucleus and the olefin (i.e., entries 8 and 9) were particularly interesting; substrate **281** was considerably slower in the cyclization than substrate **279**. This observation pointed toward a mechanism involving initial palladation at C-2, followed by olefin insertion and β-hydride elimination. Branching at the C-3α position (as in substrate **281**) would be expected to sterically interfere with the palladation event, which would cause a decrease in the overall rate. An alternative mechanism involves palladium(II) electrophilic activation of the olefin, intramolecular nucleophilic attack by the indole, and β-hydride elimination akin to the Wacker-type mechanism, which we believed was operative in our heterocyclization studies.[37]

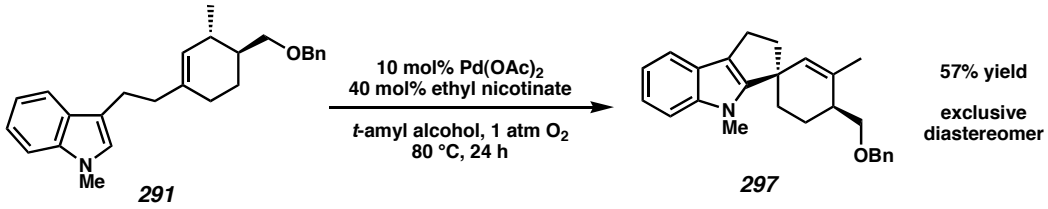
In order to differentiate between these two possible pathways, we designed a cyclization substrate that could act as a mechanistic probe (**291**, Scheme 4.3.3). In pathway A, the cyclization of diastereomerically pure indole **291** proceeds via olefin activation, anti nucleophilic attack, and syn β-hydride elimination to afford annulated indole **294**. The availability of only one β-hydrogen and the general assumption of both an anti nucleophilic attack and a syn β-hydride elimination explain the expected stereochemistry of the product indole. Pathway B proceeds by initial palladation, followed by syn olefin insertion and syn β-hydride elimination. In this case, a syn insertion and elimination are assumed to be operative, as is typical for palladium-catalyzed reactions, ultimately resulting in product indole **297**, which is diastereomerically distinct from **294**.

Scheme 4.3.3



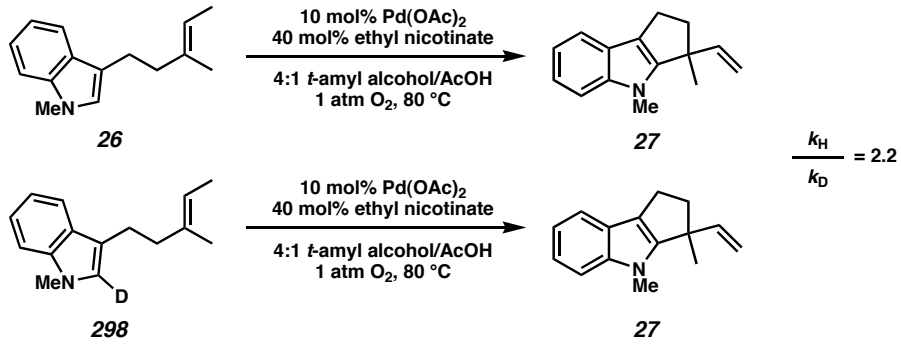
Indole **291** was subjected to the standard indole annulation conditions (10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C in *t*-amyl alcohol[38]). Annulated indole **297** was thus obtained in 57% yield as a single diastereomer.[39] This result strongly suggested that the reaction was proceeding through initial palladation (net C-H bond functionalization), followed by olefin insertion and β-hydride elimination (pathway B). The mechanism elucidated here is in full agreement with those previously proposed for related reactions.[14a,19] Additionally, this reaction highlights the capacity of this chemistry to set quaternary carbon centers diastereoselectively via a chirality transfer from a tertiary carbon center.

Scheme 4.3.4



To further verify the C-H bond functionalization pathway, the rate of cyclization of indole **26** was compared to that of (C-2)-deuteroindole **298** (Scheme 4.3.5). The rates of consumption of **26** and **298** were measured by GC analysis. The kinetic isotope effect for this cyclization was measured to be 2.2, which is consistent with kinetic isotope effects measured for other palladium(II)-catalyzed reactions involving C-H bond functionalization events.[40] This value also suggests that C-H bond functionalization is a slow step in the catalytic cycle.

Scheme 4.3.5

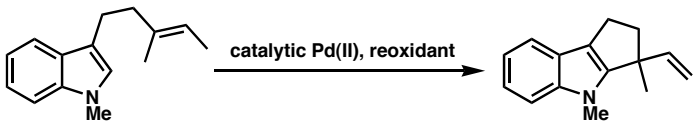


4.3.5 Methodology Comparisons

A direct comparison of the indole annulation method we have developed to other known oxidative palladium(II)-catalyzed C-C bond forming reactions highlights the remarkable efficacy of our system (Table 4.3.4). Indole **26** was subjected to a variety of

previously reported oxidative systems employing different solvent systems and oxidants.[14,15,41] Clearly, the $Pd(OAc)_2$/ethyl nicotinate/O_2/*t*-amyl alcohol/AcOH conditions are vastly superior at catalyzing this annulation. The desired product was observed in only three other cases, with the highest yield reaching just 13%. Even the conditions that were highly successful for the indole oxidative coupling reported by Fujiwara[15] were ineffective for this transformation (entry 8). The oxidative system described herein holds immense potential for other oxidative C-C bond forming reactions, where previously developed conditions may be too harsh or simply ineffective.

Table 4.3.4 Comparison of methods for the oxidative annulation of **26**.



26 ***27***

entry	conditions[a]	ref	% yield[b]
1	$Pd(OAc)_2$, AgOAc, AcOH, air, 110 °C	14a	4
2	$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, air, 110 °C	14a	0
3	$Pd(OAc)_2$, $K_2S_2O_8$, AcOH, air, 110 °C	14a	0
4	$Pd(OAc)_2$, $NaNO_2$, AcOH, air, 110 °C	14a	0
5	$Pd(OAc)_2$, $Cu(OAc)_2$, Dioxane/AcOH (4:1), O_2, 100 °C	40a	13
6	$Pd(OAc)_2$, benzoquinone, $TsOH{\cdot}H_2O$, Toluene/AcOH (2:1), O_2, 23 °C	40b	0
7	$Pd(OAc)_2$, $H_6PMo_9V_3O_{40}$, acetylacetonate, NaOAc AcOH, O_2, 90 °C	40c	0
8	$Pd(OAc)_2$, cat. benzoquinone, TBHP $AcOH/Ac_2O$ (4:1), 50 °C	15	5
9	$Pd(OAc)_2$, ethyl nicotinate, t-amyl alcohol/AcOH (4:1), O_2, 80 °C		82

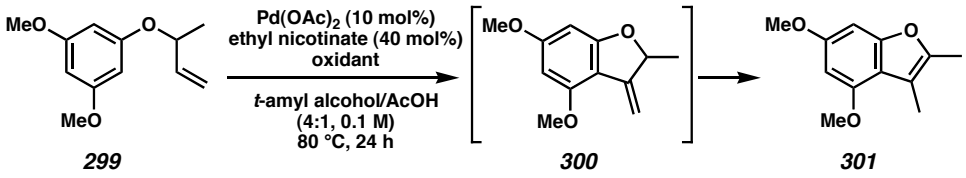
[a] For details, see Experimental Section. [b] % yield measured by GC relative to an internal standard.

4.4 The Synthesis of Benzofurans and Dihydrobenzofurans via Oxidative Carbocyclizations

In hopes of further developing the oxidative C-H bond functionalization systems, Dr. Haiming Zhang, a postdoctoral scholar in our laboratory, extended the chemistry toward the synthesis of benzofurans and dihydrobenzofurans. Discussed herein is a brief account of his work on this project.[8b]

Aryl allyl ether **299** was subjected to the optimized conditions from the indole annulation chemistry (10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 4:1 *t*-amyl alcohol/AcOH, 1 atm O_2, 80 °C) to provide benzofuran **301** in 56% yield (Table 4.4.1, entry 1). This reaction presumably proceeds via an initial C-H bond functionalization, followed by 5-exo cyclization and β-hydride elimination to afford intermediate **300**. The intermediate then isomerizes to the more thermodynamically stable aromatic compound **301**.[42] With this promising result, a variety of oxidants were evaluated in this oxidation system. Although moderate yields of **301** were obtained with a number of oxidants, oxygen and benzoquinone provided the highest yields (entries 1 and 2). Benzoquinone led to the greatest yield of **301** and was therefore used in subsequent optimization studies.

Table 4.4.1 Oxidant screen for the synthesis of benzofuran **301**.



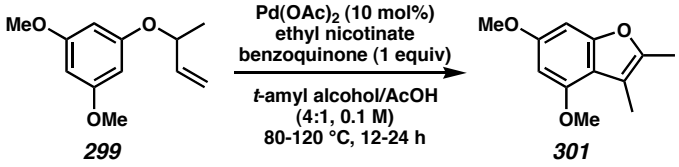
299 ***300*** ***301***

entry	oxidant (1 equiv)	% yield[a]	entry	oxidant (1 equiv)	% yield[a]
1	O_2 (1 atm)	56	5	$Tl(O_2CCF_3)_3$	<10
2	benzoquinone	62	6	$K_2S_2O_8$	30
3	$Cu(OAc)_2$	31	7	$H_2NC(S)NH_2$	<10
4	$Ag(OAc)_2$	29	8	$PhCO_3$-*t*-Bu	42

[a] % yield measured by GC relative to an internal standard.

Other parameters were then examined in the oxidative cyclization of aryl allyl ether **299** (Table 4.4.2). The ratio of ligand:palladium was found to be important for this reaction, a 2:1 system being optimal. This is likely reflective of a balance between the sufficient ligation of the palladium center for Pd(0) reoxidation and the suppression of competitive binding caused by the presence of excess ligand. Further optimization studies revealed that adding 20 mol% NaOAc and increasing the temperature to 100 °C were both beneficial to the overall transformation, providing the highest yield of benzofuran **301** (77% isolated yield, entry 7).

Table 4.4.2 Optimization studies for the synthesis of benzofuran **301**.

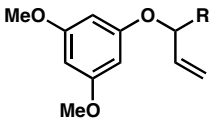
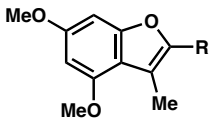
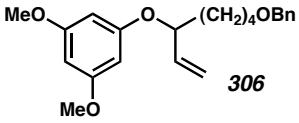
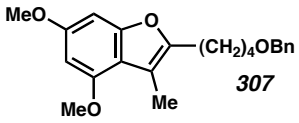
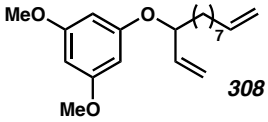
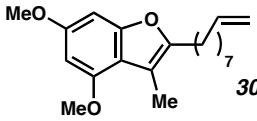
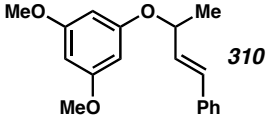
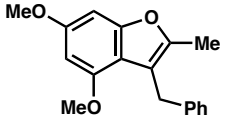
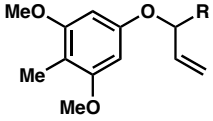
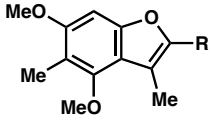
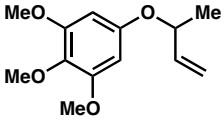
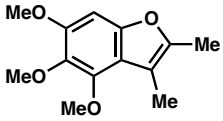
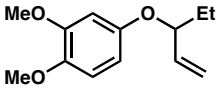
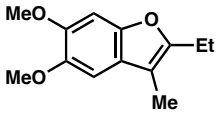
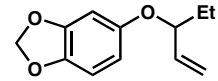
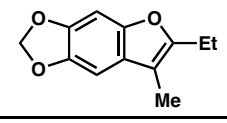


entry	ethyl nicotinate	additive	temp (°C)	time (h)	% yield[a]
1	40 mol%	–	80	24	62
2	20 mol%	–	80	24	66
3	10 mol%	–	80	24	59
4	0 mol%	–	80	24	55
5	20 mol%	NaOAc (1 equiv)	80	24	70
6	20 mol%	NaOAc (20 mol %)	80	24	74
7	20 mol%	NaOAc (20 mol %)	100	12	80 (77)[b]
8	20 mol%	NaOAc (20 mol %)	120	12	67

[a] % yield measured by GC relative to an internal standard.
[b] Isolated yield in parentheses.

The generality of the palladium-catalyzed benzofuran synthesis was then explored. As shown in Table 4.4.3, this process works for a variety of allyl aryl ethers with various substitution patterns, all resulting in good yields. This reaction is currently limited to electron-rich aryl groups; the palladation event requires a sufficiently nucleophilic arene in order to occur. The aryl subunit, however, tolerates various alkyl and alkoxy substitution patterns within the electronic requirements. The allyl moiety can also accommodate several substituents (aryl, alkyl, alkoxy) at both the proximal and distal positions.

Table 4.4.3 The palladium(II)-catalyzed oxidative benzofuran synthesis.[a]

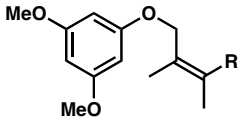
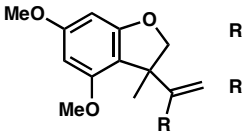
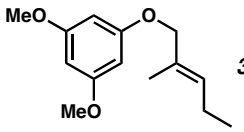
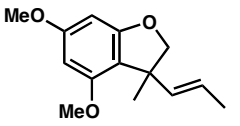
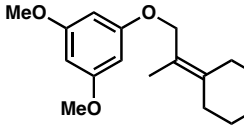
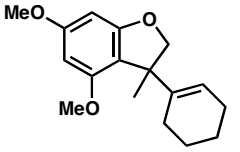
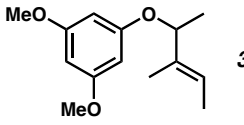
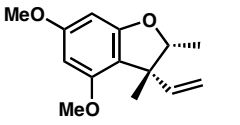
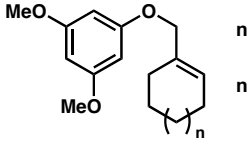
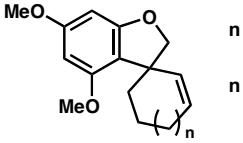
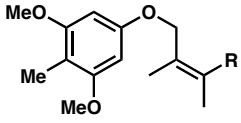
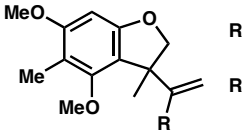
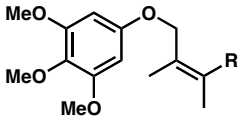
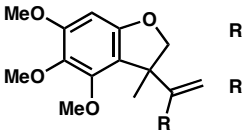
entry	substrate	product	time (h)	% yield[b]
1	 R = Me ***299***	 R = Me ***301***	12	77
2	R = Et ***302***	R = Et ***303***	12	74
3	R = *n*-C_5H_{11} ***304***	R = *n*-C_5H_{11} ***305***	13	72
4	 ***306***	 ***307***	12	62
5	 ***308***	 ***309***	14	54
6	 ***310***	 ***311***	12	61
7	 R = Me ***312***	 R = Me ***313***	14	75
8	R = Et ***314***	R = Et ***315***	12	79
9	 ***316***	 ***317***	12	61
10	 ***318***	 ***319***	16	56[c]
11	 ***320***	 ***321***	16	52[c]

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. [c] Produced as a single regioisomer.

This methodology was then extended to aryl allyl ethers in which the allyl group possessed tri- and tetrasubstituted olefins. The dihydrobenzofuran products of these reactions can be obtained in good to excellent yields (Table 4.4.4). Dihydrobenzofurans are produced in these reactions because the substitution patterns lack hydrogens at the point of C-C bond formation that could eliminate to intermediates similar to **300** (*vide*

supra, Table 4.4.1). An array of aryl and allyl substitution patterns are tolerated in this reaction.

Table 4.4.4 The palladium(II)-catalyzed oxidative dihydrobenzofuran synthesis.[a]

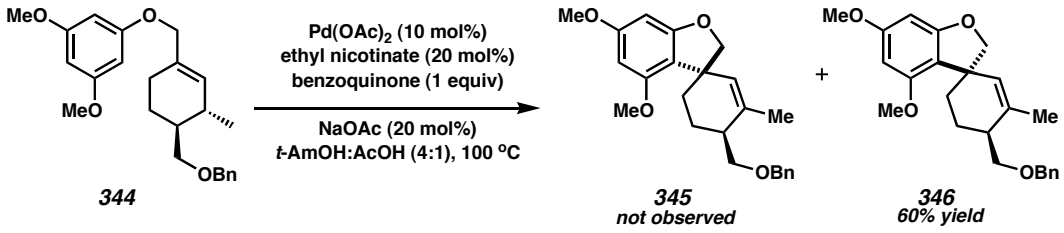
entry	substrate		product		time (h)	% yield[b]
1		R = H ***322***		R = H ***323***	16	74
2[c]		R = Me ***324***		R = Me ***325***	12	71
3		***326***		***327***	30	58[d]
4		***328***		***329***	28	55
5		***330***		***331***	15	74[e]
6		n = 1 ***332***		n = 1 ***333***	24	80
7		n = 0 ***334***		n = 0 ***335***	18	78
8		R = H ***336***		R = H ***337***	15	50
9		R = Me ***338***		R = Me ***339***	15	63
10		R = H ***340***		R = H ***341***	15	60
11		R = Me ***342***		R = Me ***343***	15	66

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. [c] Performed with 5 mol% $Pd(OAc)_2$ and 10 mol% ethyl nicotinate. [d] An inseparable mixture of roughly 66% product (*E*/*Z* = 3:1) and 10% starting material was isolated after 18 h. This mixture was subjected to another reaction with 5 mol% $Pd(OAc)_2$, 10 mol% ethyl nicotinate, 20 mol% NaOAc, and 50 mol% benzoquinone for 12 h, after which only the *E* isomer was observed. The yield presented is the overall yield of isolated product. [e] A 2.3:1 mixture of diastereomers was isolated with the major isomer shown.

Analogous to the indole annulation studies (*vide supra*), aryl allyl ether **344** was subjected to the cyclization conditions as a mechanistic probe (Scheme 4.4.1). As in the

indole case, this experiment differentiates between an olefin activation/nucleophilic attack pathway (to produce **345)** and an arene palladation/olefin insertion pathway (to produce **346**). In the event, the product dihydrobenzofuran (**346**) was isolated as a single diastereomer.[43] This experiment strongly suggests that the palladation pathway (a net C-H bond functionalization) is operative, which correlates with the result from the indole study.

Scheme 4.4.1

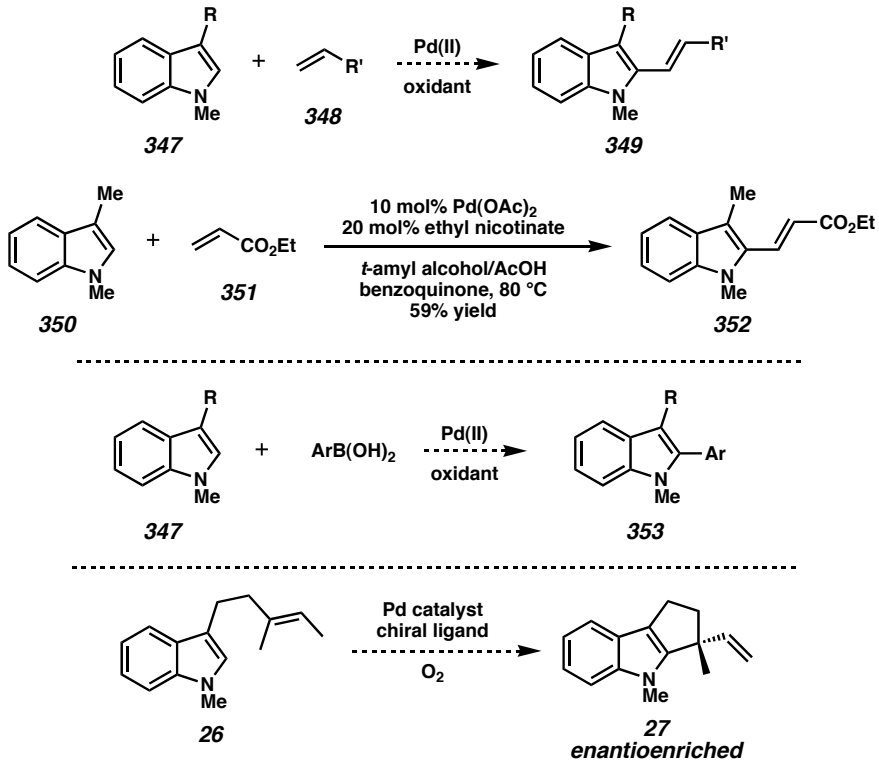


4.5 Future Directions

There are a number of future directions for this chemistry. Currently, only intramolecular oxidative reactions have been studied in detail. Intermolecular examples that initiate with a similar C-H bond functionalization followed by olefin insertion and β-hydride elimination can be envisioned (Scheme 4.5.1). This transformation is similar to the lone indole example reported recently by Fujiwara.[15,44] As an initial test, 1,3-dimethylindole was oxidatively coupled to ethyl acrylate under conditions similar to those utilized in the benzofuran chemistry.[45] This promising lead establishes that intermolecular examples are indeed possible. The C-H bond functionalization event could also be followed by transmetallation and reductive elimination processes (e.g., **347** → **353**), analogous to cross-couplings such as Suzuki and Stille reactions. The research described herein opens the possibility of extending these annulations to asymmetric

variants. We have demonstrated that the Pd/pyridine system can be readily modified to enantioselective versions in other reaction manifolds.[1,2] Perhaps the same concept can be applied to the carbocyclization chemistry described herein (e.g., **26** → **27**) to set quaternary centers enantioselectively.[46]

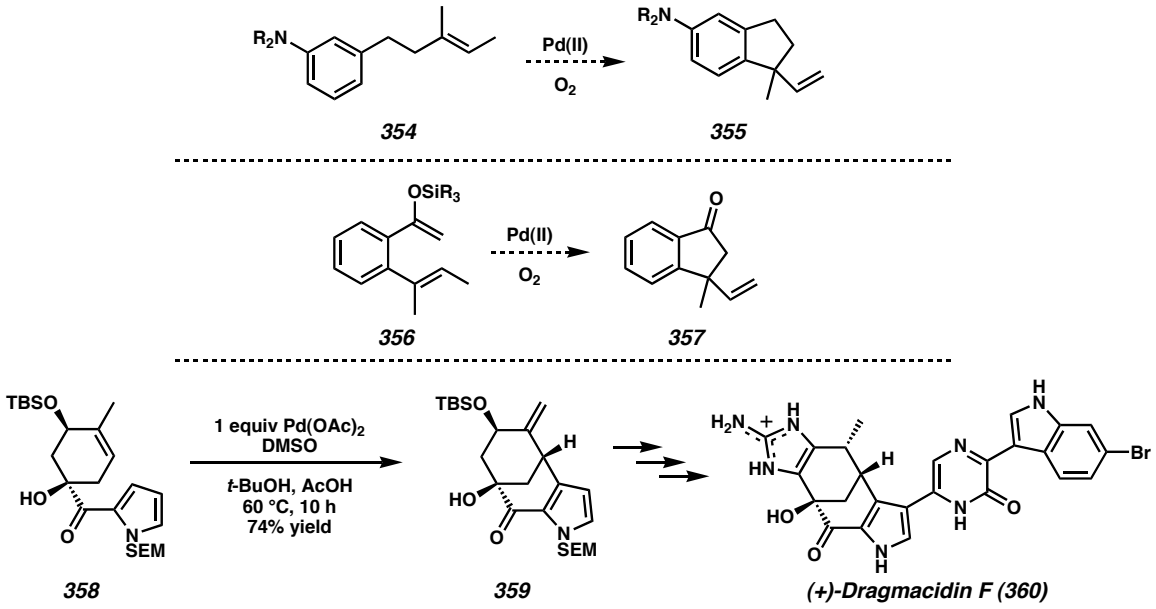
Scheme 4.5.1



Another interesting extension would be to apply this chemistry to other electron-rich systems (Scheme 4.5.2). Currently, we have only studied indoles and oxygenated aryl groups as the carbon nucleophile in these cyclizations. These oxidative systems could potentially be extended to aniline derivatives (e.g., **354**) or silyl enol ethers (e.g., **356**).[47] One example, discovered by Neil Garg and Daniel Caspi in our laboratories, has been utilized in the total synthesis of dragmacidin F (**360**).[48] In one of the key transformations of the synthesis, acyl pyrrole **358** was oxidatively cyclized to tricycle **359**

using stoichiometric palladium(II) conditions.[49] Substrate variation or parameter optimization could lead to the discovery of catalytic variants more similar to our cyclization studies. The carbocyclization studies outlined above have clear and immediate impacts in total synthesis and methodology.

Scheme 4.5.2



4.6 Conclusion

We have developed a remarkably mild oxidative system for C-C bond forming reactions that involves a C-H bond functionalization event. Annulated indoles, benzofurans, and dihydrobenzofurans can all be accessed through this chemistry, which could have widespread implications in total synthesis. In the indole carbocyclizations, molecular oxygen is the sole stoichiometric oxidant, the inexpensive and abundant reagent affording only water as a byproduct. These cyclizations are also the first examples to demonstrate the use of electronically tuned pyridine ligands in the standard

Pd/pyridine system. This electronic tuning has led to the discovery of unique reactivities that were unavailable under the original conditions.

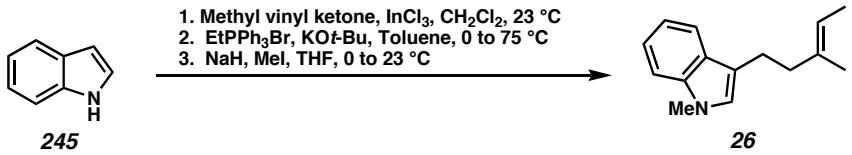
C-H bond functionalization continues to be an active and engaging area of research. Outlined herein is an oxidative catalytic approach to C-C bond forming reactions that involves an initial C-H bond functionalization step, followed by an intramolecular cyclization onto an unactivated olefin. This is directly analogous to the corresponding intramolecular Heck reaction, but does not involve the prior halogenation necessary for the palladium(0) process. Furthermore, the oxidative carbocyclization can be considered orthogonal to the Heck reaction, as the electron-rich aromatic systems utilized in this study can be employed directly. Generally, selectively halogenated derivatives of these types of arenes can be difficult to access; additionally, electron-rich aryl halides are typically poor reactants toward oxidative addition to palladium(0) species. Both of these complicating factors are circumvented by the oxidative cyclization chemistry. The transformations described herein provide a promising future area for the development of powerful catalytic dehydrogenative carbon-carbon bond forming reactions.

4.7 Experimental Section for the Oxidative Annulation of Indoles

4.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical GC was carried out using a DB-1701 column (30.0 m x 0.25 mm) from Agilent Technologies. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C spectra were recorded on a Varian Mercury 500 (at 125 MHz) or on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. Unless otherwise noted, compounds that are mixtures of *E* and *Z* olefin isomers are reported as the mixture as seen by ^{1}H NMR. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. $Pd(OAc)_2$ was purchased from Strem Chemicals, Inc., Newburyport, MA. Titanium(III) chloride solution in 3% HCl was purchased from Alfa Aesar, Ward Hill, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

4.7.2 Preparative Procedures

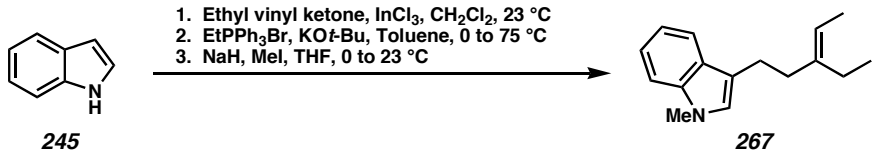


245 *26*

Indole 26. Indium catalyzed conjugate additions of indoles were done according to the procedure of Yadav et al.[50] To a solution of indole (5.00 g, 42.7 mmol) in 85.4 mL CH_2Cl_2 at 23 °C was added methyl vinyl ketone (3.55 mL, 42.7 mmol) and $InCl_3$ (944 mg, 4.27 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (160 mL), and extracted with CH_2Cl_2 (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. The solid was dissolved in CH_2Cl_2 and passed through a plug of SiO_2 (5 x 5 cm, 4:1 CH_2Cl_2/hexanes eluent). The filtrate was evaporated to provide the ketone[50] (6.49 g, 81% yield, R_F = 0.22 in 100% CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (5.00 g, 26.7 mmol) was added as a solid, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin[51] (4.31 g, 81% yield, R_F = 0.67 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (4.31 g, 21.6 mmol) in THF (86.4 mL) at 0 °C was added NaH (1.73 g, 60% dispersion in mineral oil, 43.2 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (2.02 mL, 32.4 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (100 mL), and extracted with ether (2 x 250 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **26** (3.67 g, 80% yield, R_F = 0.48 in 9:1 hexanes/EtOAc, 59:41 mixture of olefin isomers) as a clear oil. **Indole 26**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.33 (app.t, *J* = 7.7 Hz, 1H), 7.33 (app.t, *J* = 7.7 Hz, 1H), 7.31-7.25 (m, 1H), 7.31-7.25 (m, 1H), 7.20-7.13 (comp m, 1H), 7.20-7.13 (comp m, 1H), 6.90 (s, 1H), 6.88 (s, 1H), 5.37 (app.q, *J* = 6.6 Hz, 1H), 5.33 (app.q, *J* = 6.6 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.90 (t, *J* = 8.8 Hz, 2H), 2.88 (t, *J* = 8.5 Hz, 2H), 2.52-2.42 (comp m, 2H), 2.52-2.42 (comp m, 2H), 1.84 (s, 3H), 1.77 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H), 1.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 136.3, 136.2, 128.1, 126.1, 121.6, 119.5, 119.2, 118.7, 115.6, 109.3, 40.7, 32.8, 32.7, 24.2, 23.6, 16.0, 13.6, 13.5; IR (film) 2916, 1473, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1514.



245 *267*

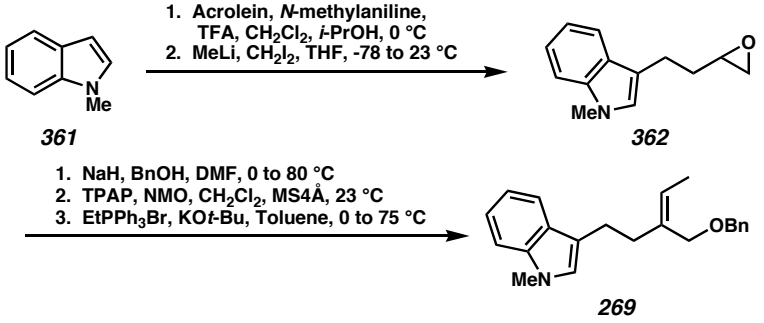
Indole 267. Indium-catalyzed conjugate additions of indoles were done according to the procedure of Yadav et al.[50] To a solution of indole (1.61 g, 13.7 mmol) in CH_2Cl_2 (27.4

mL) at 23 °C was added ethyl vinyl ketone (1.36 mL, 13.7 mmol) and $InCl_3$ (303 mg, 1.37 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (50 mL), and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (2:1 to 4:1 CH_2Cl_2/hexanes eluent) to provide the ketone[52] (2.25 g, 82% yield, R_F = 0.38 in CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (1.39 g, 12.4 mmol) in toluene (49.7 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (4.60 g, 12.4 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (1.00 g, 4.97 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (990 mg, 93% yield, R_F = 0.32 in 9:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (990 mg, 4.64 mmol) in THF (18.6 mL) at 0 °C was added NaH (297 mg, 60% dispersion in mineral oil, 7.42 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (375 μl, 6.03 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL), and extracted with ether (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was

purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **267** (830 mg, 79% yield, R_F = 0.69 in 4:1 hexanes/EtOAc, 56:44 mixture of olefin isomers) as a clear oil. **Indole 267**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.25 (m, 1H), 7.25 (m, 1H), 7.17-7.11 (comp m, 1H), 7.17-7.11 (comp m, 1H), 6.89 (s, 1H), 6.87 (s, 1H), 5.33 (app.q, *J* = 6.6 Hz, 1H), 5.31 (app.q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.90-2.80 (comp m, 2H), 2.90-2.80 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.22-2.11 (comp m, 2H), 2.22-2.11 (comp m, 2H), 1.66 (app.d, *J* = 6.6 Hz, 3H), 1.65 (app.d, *J* = 6.6 Hz, 3H), 1.09 (app.t, *J* = 7.7 Hz, 3H), 1.06 (app.t, *J* = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 142.0, 137.2, 128.0, 126.1, 121.6, 119.2, 118.7, 118.1, 117.8, 115.7, 109.3, 37.7, 32.7, 31.3, 30.0, 24.4, 24.1, 23.2, 13.4, 13.2, 13.1; IR (film) 2964, 2930, 1472, 736 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1678.



Indole 269. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then

filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/EtOAc eluent) provided the aldehyde[53] (3.54 g, 80% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a yellow oil.

The epoxide was synthesized according to a modified procedure of Cainelli et al.[54] To a solution of the aldehyde (500 μl, 2.91 mmol) and diiodomethane (422 μl, 5.24 mmol) in THF (11.6 mL) at –78 °C was added methyllithium (3.28 mL, 1.6 M in Et_2O, 5.24 mmol) dropwise over 3 min. The reaction was stirred for 30 min at –78 °C and 2 h at 23 °C. It was then cooled to 0 °C and quenched by slow addition of saturated NH_4Cl (40 mL). Et_2O (50 mL) was added, the phases separated, and the aqueous layer extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (5:1 hexanes/EtOAc eluent) afforded epoxide **362** (314 mg, 54% yield, R_F = 0.54 in 2:1 hexanes/EtOAc) as a yellow oil.

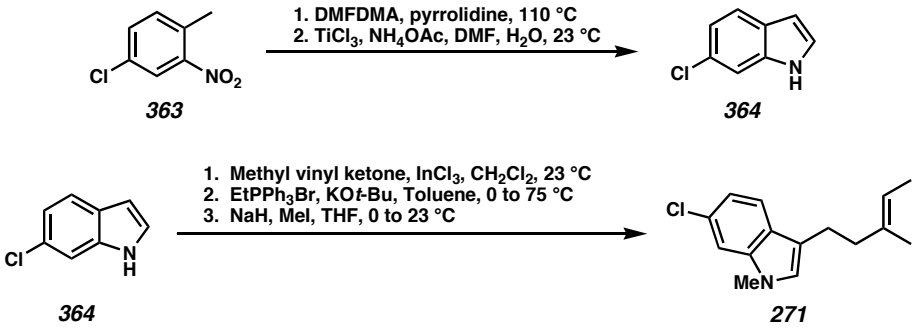
To a solution of benzyl alcohol (475 μl, 4.59 mmol) in DMF (8.5 mL) at 0 °C was added NaH (184 mg, 60% dispersion in mineral oil, 4.59 mmol). The solution was stirred at 0 °C for 10 min and 23 °C for 1 h. The resulting solution of sodium benzyloxide was added to a solution of epoxide **362** (308 mg, 1.53 mmol) in DMF (2.13 mL) at 0 °C. The reaction mixture was then heated to 80 °C and stirred 3 h. The reaction was cooled to 0 °C and quenched with saturated NH_4Cl (50 mL). Et_2O (75 mL) was added, the phases separated, and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to an oil. Purification

of the residue by flash chromatography (1:1 hexanes/Et_2O eluent) afforded the alcohol (304 mg, 64% yield, R_F = 0.30 in 2:1 hexanes/EtOAc) as a yellow oil.

To a solution of the alcohol (304 mg, 0.981 mmol) in CH_2Cl_2 (1.96 mL) at 23 °C was added 4Å molecular sieves (491 mg, 500 mg/mmol substrate), then NMO (172 mg, 1.47 mmol). The suspension was stirred for 15 min, at which point TPAP (17.2 mg, 0.0491 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad of silica gel (2 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. Purification of the oil by flash chromatography (4:1 hexanes/EtOAc eluent) afforded α-benzyloxyketone (265 mg, 86% yield, R_F = 0.50 in 2:1 hexanes/EtOAc) as a clear oil.

To a suspension of potassium *tert*-butoxide (230 mg, 2.05 mmol) in toluene (8 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (761 mg, 2.05 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, a solution of the ketone (294 mg, 0.956 mmol) in toluene (1.56 mL) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (30 mL, 1:1), and extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (2:1 hexanes/CH_2Cl_2 eluent) to provide indole **269** (243 mg, 80% yield, R_F = 0.48 in 4:1 hexanes/EtOAc, 88:12 mixture of olefin isomers) as a clear oil. **Indole 269**: (Major isomer only) ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 1H), 7.40-7.26 (comp m, 6H), 7.22 (app.t, *J* = 7.4 Hz, 1H), 7.09 (app.t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H), 5.58 (q, *J* = 6.8 Hz, 1H), 4.52 (s, 2H), 4.14 (s, 2H), 3.73 (s, 3H), 2.89 (t, *J* = 8.1

Hz, 2H), 2.53 (t, J = 8.1 Hz, 2H), 1.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 137.2, 136.9, 128.6, 128.1, 128.0, 127.7, 126.2, 124.1, 121.6, 119.3, 118.7, 115.4, 109.3, 72.2, 67.2, 36.5, 32.7, 24.3, 13.6; IR (film) 1472, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{25}NO]^+$: 319.1936, found 319.1938.



Indole 271. A solution of 4-chloro-2-nitrotoluene (1.00 g, 5.83 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (2.32 mL, 17.5 mmol) and pyrrolidine (1.46 mL, 17.5 mmol) was heated to 110 °C for 1 h. The dark red mixture was cooled to 23 °C and carried on without isolation.

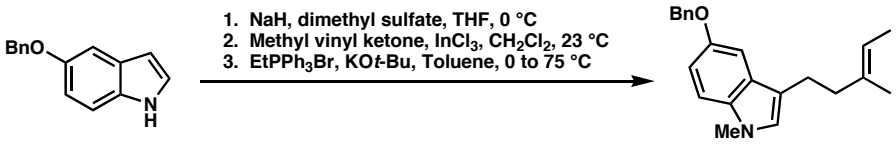
The red mixture was dissolved in DMF (58.3 mL), and to the solution was added NH_4OAc (25 mL, 4.0 M in water) followed by dropwise addition of $TiCl_3$ (21.1 mL, 20% w/v in 3% HCl, 27.4 mmol) over 15 minutes. The temperature was kept at 23 °C by an external water bath. After the addition was complete, the reaction was quenched with 1.0 M NaOH (300 mL) and extracted with ether (5 x 250 mL). The organic layers were combined, washed with water, passed through a plug of SiO_2 (5 x 8 cm, Et_2O eluent), dried over $MgSO_4$, and evaporated to an oil. Purification of the residue by flash chromatography (5:1 hexanes/EtOAc eluent) provided 6-chloroindole[55] (400 mg, 45% yield over 2 steps, R_F = 0.46 in 4:1 hexanes/EtOAc) as a brown solid.

To a solution of 6-chloroindole (400 mg, 2.64 mmol) in CH_2Cl_2 (5.28 mL) at 23 °C was added methyl vinyl ketone (220 μl, 2.64 mmol) and $InCl_3$ (58.4 mg, 0.264 mmol). The reaction mixture was stirred at 23 °C for 2 h, quenched with water (30 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. Purification of the residue by flash chromatography (4:1 CH_2Cl_2/hexanes eluent) provided the ketone (309 mg, 53% yield, R_F = 0.33 in 2:1 hexanes/EtOAc) as a yellow solid.

To a suspension of potassium *tert*-butoxide (230 mg, 2.05 mmol) in toluene (8.21 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (761 mg, 2.05 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (182 mg, 0.821 mmol) was added, and the solution was heated to 75 °C. After stirring for 4 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (20 mL, 1:1), and extracted with EtOAc (2 x 35 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin (128 mg, 67% yield, R_F = 0.50 in 4:! hexanes/EtOAc) as a clear oil.

To a solution of the olefin (74.0 mg, 0.317 mmol) in THF (1.27 mL) at 0 °C was added NaH (25.4 mg, 60% dispersion in mineral oil, 0.634 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (29.6 μl, 0.476 mmol), and allowed to warm to 23 °C. After 30 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (20 mL), and extracted with ether (2 x 30 mL). The organic layers were combined,

washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **271** (70.3 mg, 90% yield, R_F = 0.47 in 9:1 hexanes/EtOAc, 57:43 mixture of olefin isomers) as a clear oil. **Indole 271**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.27 (s, 1H), 7.26 (s, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 5.29 (app.q, *J* = 6.6 Hz, 1H), 5.26 (app.q, *J* = 6.6 Hz, 1H), 3.70 (s, 3H), 3.70 (s, 3H), 2.80 (t, *J* = 8.2 Hz, 2H), 2.78 (t, *J* = 8.2 Hz, 2H), 2.42-2.32 (comp m, 2H), 2.42-2.32 (comp m, 2H), 1.76 (s, 3H), 1.69 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.53 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 136.0, 135.9, 127.7, 126.8, 120.1, 120.0, 119.7, 119.4, 118.9, 115.8, 109.3, 40.6, 32.8, 32.6, 24.0, 23.6, 23.5, 16.0, 13.6, 13.5; IR (film) 2917, 1477, 799 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{18}NCl]^+$: 247.1128, found 247.1123.



365 *273*

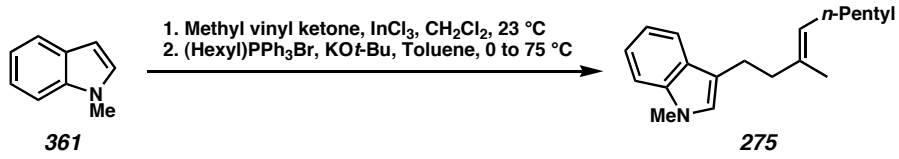
Indole 273. To a solution of 5-benzyloxyindole (500 mg, 2.24 mmol) in THF (8.96 mL) at 0 °C was added NaH (179 mg, 60% dispersion in mineral oil, 4.48 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and at 23 °C for 1 h. The mixture was then cooled to 0 °C and treated with dimethyl sulfate (320 μl, 3.36 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (40 mL) and extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash

chromatography (5:1 hexanes/EtOAc eluent) to provide the methyl indole[56] (493 mg, 93% yield, R_F = 0.49 in 4:1 hexanes/EtOAc) as a white solid.

To a solution of 5-benzyloxy-*N*-methyl indole (493 mg, 2.08 mmol) in CH_2Cl_2 (4.16 mL) at 23 °C was added methyl vinyl ketone (173 µl, 2.08 mmol) and $InCl_3$ (46.0 mg, 0.208 mmol). The reaction mixture was stirred at 23 °C for 2.5 h, quenched with water (25 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide the ketone (450 mg, 70% yield, R_F = 0.42 in 2:1 hexanes/EtOAc) as a white solid.

To a suspension of potassium *tert*-butoxide (328 mg, 2.92 mmol) in toluene (14.6 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (1.08 g, 2.92 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the ketone (450 mg, 1.46 mmol) was added, and the solution was heated to 75 °C. After stirring for 4 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (3:1 hexanes/CH_2Cl_2 eluent) to provide indole **273** (418 mg, 90% yield, R_F = 0.64 in 4:1 hexanes/EtOAc, 59:41 mixture of olefin isomers) as a clear oil. **Indole 273**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (app.d, *J* = 7.7 Hz, 2H), 7.51 (app.d, 7.7 Hz, 2H), 7.43-7.31 (comp m, 3H), 7.43-7.31 (comp m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 5.0 Hz, 1H), 7.15 (d, *J* = 5.5 Hz, 1H), 7.00 (s, 1H), 6.97 (s, 1H), 6.85 (s, 1H), 6.82 (s, 1H), 5.32 (app.q, *J* = 6.6 Hz, 1H), 5.27 (app.q, *J* = 6.6 Hz, 1H), 5.14 (s, 2H), 5.14 (s, 2H), 3.73

(s, 3H), 3.72 (s, 3H), 2.83-2.75 (comp m, 2H), 2.83-2.75 (comp m, 2H), 2.44-2.34 (comp m, 2H), 2.44-2.34 (comp m, 2H), 1.79 (s, 3H), 1.72 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H), 1.57 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 138.1, 136.3, 136.2, 132.9, 128.7, 128.4, 127.9, 127.8, 126.8, 119.5, 118.7, 115.1, 112.5, 110.0, 103.2, 103.1, 71.4, 40.6, 32.9, 32.6, 24.2, 23.7, 16.0, 13.6, 13.5; IR (film) 1489, 1208 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{25}NO]^+$: 319.1936, found 319.1947.

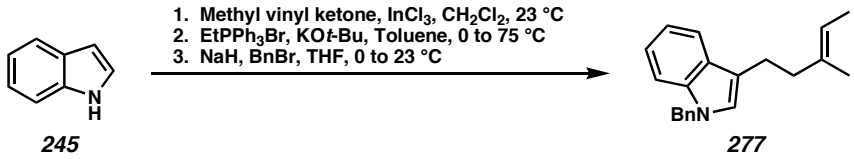


361 *275*

Indole 275. To a solution of 1-methylindole (1.00 mL, 7.82 mmol) in CH_2Cl_2 (15.6 mL) at 23 °C was added methyl vinyl ketone (651 μl, 7.82 mmol) and $InCl_3$ (173 mg, 0.782 mmol). The reaction mixture was stirred at 23 °C for 2.5 h, quenched with water (30 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting solid was purified by flash chromatography (5:1 hexanes/THF eluent) to provide the ketone[57] (1.57 g, 99% yield, R_F = 0.17 in 2:1 CH_2Cl_2/hexanes) as a colorless oil.

To a suspension of potassium *tert*-butoxide (1.63 g, 14.5 mmol) in toluene (53.7 mL) at 0 °C was added (hexyl)triphenylphosphonium bromide (6.20 g, 14.5 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (1.08 g, 5.37 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and

concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) to provide indole **275** (666 mg, 46% yield, R_F = 0.50 in 9:1 hexanes/EtOAc, 60:40 mixture of olefin isomers) as a clear oil. **Indole 275**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.31 (app.t, *J* = 8.2 Hz, 1H), 7.29-7.23 (m, 1H), 7.29-7.23 (m, 1H), 7.18-7.11 (comp m, 1H), 7.18-7.11 (comp m, 1H), 6.88 (s, 1H), 6.86 (s, 1H), 5.24 (app.q, *J* = 7.1 Hz, 1H), 5.24 (app.q, *J* = 7.1 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.89 (app.t, *J* = 8.5 Hz, 2H), 2.85 (app.t, *J* = 8.0 Hz, 2H), 2.48-2.39 (comp m, 2H), 2.48-2.39 (comp m, 2H), 2.05 (app.q, *J* = 6.9 Hz, 2H), 2.00 (app.q, *J* = 6.9 Hz, 2H), 1.83 (s, 3H), 1.74 (s, 3H), 1.40-1.23 (comp m, 6H), 1.43-1.23 (comp m, 6H), 0.94 (t, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 135.1, 128.1, 126.2, 125.3, 121.6, 119.2, 118.7, 115.5, 109.3, 40.7, 33.1, 32.7, 31.8, 30.0, 29.8, 28.1, 24.2, 24.0, 23.7, 22.9, 16.3, 14.3; IR (film) 2924, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{27}N]^+$: 269.2143, found 269.2136.



245 *277*

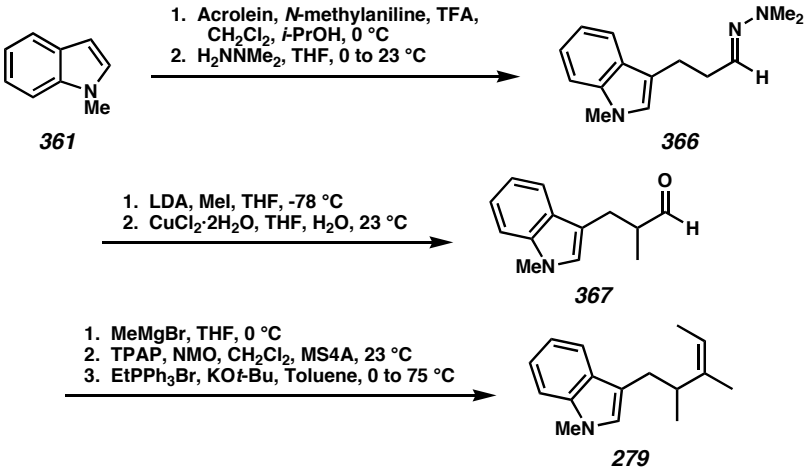
Indole 277. To a solution of indole (5.00 g, 42.7 mmol) in 85.4 mL CH_2Cl_2 at 23 °C was added methyl vinyl ketone (3.55 mL, 42.7 mmol) and $InCl_3$ (944 mg, 4.27 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (160 mL), and extracted with CH_2Cl_2 (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. The solid was dissolved in CH_2Cl_2 and passed through a plug of SiO_2 (5 x 5 cm, 4:1 CH_2Cl_2/hexanes eluent). The filtrate was

evaporated to provide the ketone[50] (6.49 g, 81% yield, R_F = 0.22 in 100% CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (5.00 g, 26.7 mmol) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin[51] (4.31 g, 81% yield, R_F = 0.67 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (982 mg, 4.93 mmol) in THF (19.7 mL) at 0 °C was added NaH (394 mg, 60% dispersion in mineral oil, 9.86 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with benzyl bromide (880 μl, 7.40 mmol), and allowed to warm to 23 °C. After 4 h, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (100 mL), and extracted with ether (2 x 250 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide benzyl indole **277** (872 mg, 61% yield, R_F = 0.42 in 9:1 hexanes/EtOAc, 57:43 mixture of olefin isomers) as a clear oil. **Indole 277**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.6 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.33-7.26 (comp m, 4H), 7.33-7.26 (comp m, 4H), 7.22-7.11 (comp m,

4H), 7.22-7.11 (comp m, 4H), 6.95 (s, 1H), 6.92 (s, 1H), 5.34-5.24 (m, 1H), 5.34-5.24 (m, 1H), 5.30 (s, 2H), 5.30 (s, 2H), 2.89 (t, J = 8.2 Hz, 2H), 2.86 (t, J = 8.2 Hz, 2H), 2.49-2.39 (comp m, 2H), 2.49-2.39 (comp m, 2H), 1.80 (s, 3H), 1.72 (s, 3H), 1.61 (d, J = 7.1 Hz, 3H), 1.56 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 136.9, 136.2, 136.0, 128.9, 128.4, 127.7, 127.0, 125.5, 121.8, 119.5, 119.3, 119.0, 116.2, 109.8, 50.0, 40.5, 32.6, 24.2, 23.6, 16.0, 13.6, 13.5; IR (film) 2917, 1467, 1453, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{21}H_{23}N]^+$: 289.1830, found 289.1820.



Indole 279. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/EtOAc eluent) provided the aldehyde[53] (3.54 g, 80% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a yellow oil.

Aldehyde alkylation was accomplished using dimethylhydrazone chemistry according to the procedure of Corey and Enders.[58] To a solution of the aldehyde (2.00 mL, 11.6 mmol) in THF (58 mL) at 0 °C was added 1,1-dimethylhydrazine (973 μl, 12.8 mmol) dropwise. The resulting solution was stirred at 0 °C for 30 min, then allowed to warm to 23 °C, and was stirred overnight (12 h). The solution was concentrated to an oil, which was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide hydrazone **366** (1.84 g, 69% yield, R_F = 0.41 in 1:1 hexanes/EtOAc) as a yellow oil.

To a solution of LDA (26.0 mmol) in THF (13.7 mL) at –78 °C was added the hydrazone (5.43 g, 23.7 mmol) in THF (10 mL) dropwise via cannula. The reaction mixture was allowed to warm to 0 °C, and was stirred 2.5 h. The mixture was then cooled to –78 °C, and methyl iodide (2.30 mL, 37.0 mmol) was added. After 1 h, the reaction was quenched by quick addition of saturated NH_4Cl (75 mL) and Et_2O (75 mL). The mixture was allowed to warm to 23 °C, the phases were separated, and the aqueous phase extracted with Et_2O (2 x 75 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the α-methyl dimethylhydrazone (3.64 g, 63% yield, R_F = 0.52 in 1:1 hexanes/EtOAc) as a yellow oil.

The dimethylhydrazone was converted to the aldehyde by the procedure outlined by Yamashita et al.[59] To a solution of copper(II) chloride dihydrate (2.81 g, 16.5 mmol) in water (150 mL) at 23 °C was added a solution of the α-methyl dimethylhydrazone (3.64 g, 15.0 mmol) in THF (224 mL). The reaction was stirred vigorously for 16 h, then quenched with 3.0 M NH_4OH. EtOAc (200 mL) was added, the phases were separated, and the aqueous layer was extracted with EtOAc (1 x 150 mL). The combined organic

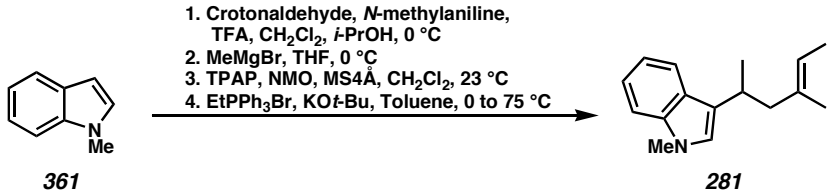
phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 to 1:1 hexanes/EtOAc eluent) afforded aldehyde **367** (1.85 g, 61% yield, R_F = 0.67 in 2:1 hexanes/EtOAc) as a clear oil.

To a solution of **367** (1.85 g, 9.19 mmol) in THF (18.4 mL) at 0 °C was added methylmagnesium bromide (3.67 mL, 3.0 M in Et_2O, 11.0 mmol) dropwise over 5 min. The reaction was stirred for 30 min, and then quenched with saturated NH_4Cl (30 mL). The reaction mixture was partitioned between Et_2O (100 mL) and water (75 mL), and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the alcohol (1.50 g, 75% yield, R_F = 0.36 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alcohol (593 mg, 2.73 mmol) in CH_2Cl_2 (5.46 mL) at 23 °C was added 4Å molecular sieves (1.36 g, 500 mg/mmol substrate), then NMO (479 mg, 4.09 mmol). The suspension was stirred for 15 min, at which point TPAP (47.8 mg, 0.136 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad of silica gel (3 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. The resulting ketone (374 mg) was used without further purification (R_F = 0.59 in 2:1 hexanes/EtOAc).

To a suspension of potassium *tert*-butoxide (526 mg, 4.69 mmol) in toluene (12.4 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (1.74 g, 4.69 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, a solution of the ketone (from above) in toluene (5.00 mL) was added, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was

cooled to 0 °C, quenched with saturated NH_4Cl/water (50 mL, 1:1), and extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil (product indole contaminated with PPh_3) was dissolved in THF (10 mL), and to the solution was added methyl iodide (292 µl, 4.69 mmol). After stirring 2 h, the mixture was filtered through a pad of celite (2 x 7 cm, Et_2O eluent), and the filtrate was concentrated to an oil. This oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **279** (290 mg, 47% yield over 2 steps, R_F = 0.61 in 9:1 hexanes/EtOAc, 73:27 mixture of olefin isomers) as a clear oil. **Indole 279**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (app.t, *J* = 7.2 Hz, 1H), 7.23 (app.t, *J* = 7.2 Hz, 1H), 7.12 (app.t, *J* = 7.2 Hz, 1H), 7.12 (app.t, *J* = 7.2 Hz, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 5.31 (q, *J* = 6.8 Hz, 1H), 5.22 (q, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 3.12 (m, 1H), 2.94-2.59 (comp m, 2H), 2.94-2.59 (comp m, 2H), 2.52 (m, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.61 (d, *J* = 6.6 Hz, 3H), 1.55 (d, *J* = 8.2 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 140.5, 137.1, 128.4, 126.9, 126.8, 121.5, 119.3, 119.2, 118.9, 118.6, 117.6, 114.4, 114.2, 109.2, 43.6, 34.5, 32.8, 31.4, 30.6, 19.5, 18.8, 18.6, 13.5, 13.2, 13.0; IR (film) 2960, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1675.



361 *281*

Indole 281. To a solution of crotonaldehyde (5.83 mL, 70.4 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (178 μl, 1.64 mmol) and trifluoroacetic acid (126 μl, 1.64 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 15 h, then filtered through a pad of SiO_2 (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) provided the aldehyde[60] (3.13 g, 66% yield, R_F = 0.35 in 4:1 hexanes/EtOAc) as a yellow oil.

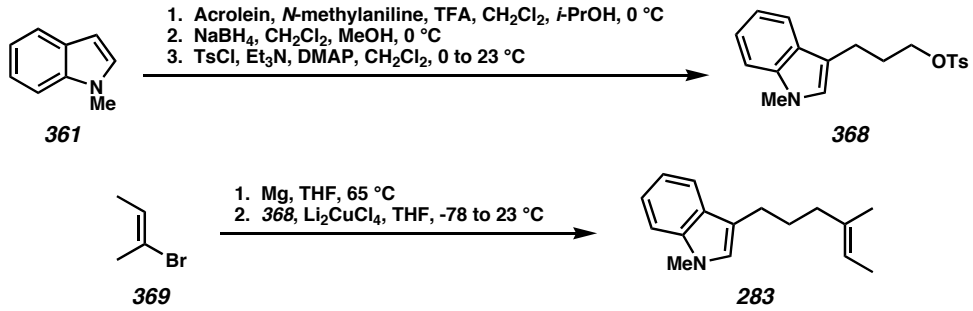
To a solution of the aldehyde (2.85 g, 14.2 mmol) in THF (28.4 mL) at 0 °C was added methylmagnesium bromide (5.67 mL, 3.0 M in Et_2O, 17.0 mmol) dropwise over 5 minutes. The reaction was stirred for 30 min, and then quenched with saturated NH_4Cl (50 mL). The reaction mixture was partitioned between Et_2O (125 mL) and water (75 mL), and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the alcohol (1.53 g, 50% yield, R_F = 0.35 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alcohol (1.50 g, 6.90 mmol) in CH_2Cl_2 (13.8 mL) at 23 °C was added 4Å molecular sieves (3.45 g, 500 mg/mmol substrate), then NMO (1.22 g, 10.4 mmol). The suspension was stirred for 15 min, at which point TPAP (121 mg, 0.345 mmol) was added. After stirring 15 min, the reaction mixture was filtered through a pad

of SiO_2 (5 x 7 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. The resulting ketone[61] (1.28 g, R_F = 0.57 in 2:1 hexanes/EtOAc) was used without further purification.

To a suspension of potassium *tert*-butoxide (1.81 g, 16.1 mmol) in toluene (49.5 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (5.98 g, 16.1 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, a solution of the ketone (1.28 g, 5.95 mmol) in toluene (10 mL) was added, and the solution was heated to 75 °C. After stirring for 9 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (150 mL, 1:1), and extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil (product indole contaminated with PPh_3) was dissolved in THF (32 mL), and to the solution was added methyl iodide (1.00 mL, 16.1 mmol). After stirring 2 h, the mixture was filtered through a pad of celite (3 x 7 cm, Et_2O eluent), and the filtrate was concentrated to an oil. This oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **281** (1.35 g, 99% yield, R_F = 0.65 in 4:1 hexanes/EtOAc, 53:47 mixture of olefin isomers) as a clear oil. **Indole 281**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 5.30 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.27 (m, 1H), 3.27 (m, 1H), 2.59 (br dd, *J* = 4.7, 13.4 Hz, 1H), 2.47 (app.d, *J* = 7.2 Hz, 1H), 2.47 (app.d, *J* = 7.2 Hz, 1H), 2.20 (app.dd, *J* = 9.9, 13.2 Hz, 1H), 1.79 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 135.3, 134.8, 127.4, 124.9, 124.8, 121.6, 120.6, 120.4, 120.3, 119.6, 118.6, 109.4, 48.5, 39.9, 32.8, 29.3, 28.9, 23.9, 20.7, 15.8, 13.8, 13.6; IR (film) 2960, 1473, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1676.



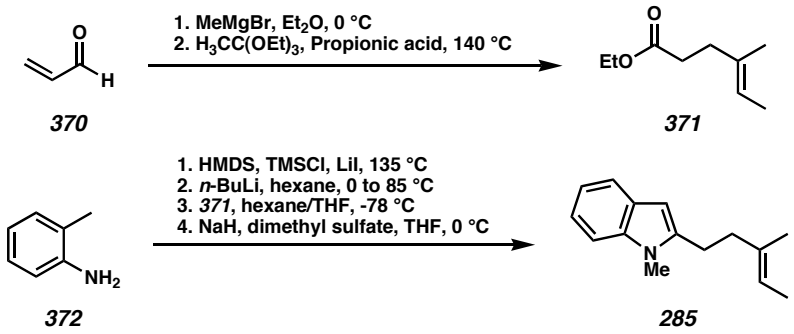
Indole 283. To a solution of acrolein (4.62 mL, 70.5 mmol) in 85:15 CH_2Cl_2/*i*-PrOH (47 mL) at 23 °C was added *N*-methylaniline (179 μl, 1.65 mmol) and trifluoroacetic acid (127 μl, 1.65 mmol). The resulting solution was cooled to 0 °C, and *N*-methylindole (3.00 mL, 23.5 mmol) was added dropwise. The reaction was stirred at 0 °C for 4 h, then filtered through a pad of silica gel (5 x 6 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/EtOAc eluent) provided the aldehyde[53] (3.54 g, 80% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a yellow oil.

To a solution of the aldehyde (2.00 mL, 11.6 mmol) in 1:1 CH_2Cl_2/MeOH (11.6 mL) at 0 °C was added $NaBH_4$ (526 mg, 13.9 mmol) in four portions over 10 min. The resulting solution was quenched at 0 °C with 1.0 M HCl and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to an oil, which was used immediately without further purification (R_F = 0.28 in 2:1 hexanes/EtOAc).

The oil was dissolved in CH_2Cl_2 (58 mL), cooled to 0 °C, and treated with tosyl chloride (3.32 g, 17.4 mmol), triethylamine (3.23 mL, 23.2 mmol), and DMAP (142 mg, 1.16 mmol), sequentially. The solution was allowed to warm to 23 °C and stirred 10 h. The mixture was cooled to 0 °C and quenched with saturated NH_4Cl (75 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 75 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (1:1 hexanes/CH_2Cl_2 eluent) afforded tosylate **368** (2.62 g, 66% yield over 2 steps, R_F = 0.59 in 2:1 hexanes/EtOAc) as a colorless oil.

Copper-catalyzed coupling of vinyl Grignard reagents with alkyl sulfonates was accomplished using the procedure outlined by Foquet and Schlosser.[62] To a stirring suspension of magnesium turnings (260 mg, 10.7 mmol) in THF (21.4 mL) at 23 °C was added 2-bromo-2-butene (1.09 mL, 10.7 mmol). The mixture was heated to 65 °C and stirred 1 h, at which point the Grignard reagent had been fully generated. The solution was cooled to 23 °C, and then added via syringe to a solution of **368** (2.62 g, 7.63 mmol) in THF (7.63 mL) at –78 °C. Lithium tetrachlorocuprate (763 μl, 0.1 M in THF, 0.0763 mmol) was then added, and the reaction mixture was allowed to warm to 23 °C. After stirring for 32 h, the reaction was cooled to 0 °C and quenched by slow addition of 1.0 N HCl. The mixture was partitioned between 150 mL Et_2O and 150 mL H_2O. The organic phase was washed with H_2O (100 mL), and the aqueous layers were combined and extracted with Et_2O (150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (30:1 hexanes/Et_2O eluent) provided indole **283** (1.35 g, 78% yield, R_F =

0.63 in 4:1 hexanes/Et_2O, single olefin isomer of undetermined geometry) as a clear oil. **Indole 283**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.24 (app.t, *J* = 7.3 Hz, 1H), 7.12 (app.t, *J* = 7.7 Hz, 1H), 6.86 (s, 1H), 5.27 (q, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.18 (t, *J* = 7.7 Hz, 2H), 1.83 (comp m, 2H), 1.74 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 136.3, 128.2, 126.1, 121.6, 119.3, 119.2, 118.7, 115.6, 109.3, 32.7, 31.6, 28.7, 25.2, 23.6, 13.5; IR (film) 2930, 1473, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{21}N]^+$: 227.1674, found 227.1680.



Indole 285. To a solution of MeMgBr (4.43 mL, 3.0 M in Et_2O, 13.3 mmol) in Et_2O (4 mL) at 0 °C was added methacrolein (1.00 mL, 12.1 mmol) in Et_2O (7 mL) dropwise via cannula. After 30 min, the reaction was quenched by dropwise addition of 1.0 N HCl (15 mL) and extracted with Et_2O (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to a colorless oil, which was carried on without further purification.

The allylic alcohol (assume 12.1 mmol) was dissolved in triethylorthoacetate (15.5 mL, 84.7 mmol), and the solution was treated with propionic acid (271 μl, 3.63 mmol). The reaction was heated to 140 °C with distillative removal of ethanol. After

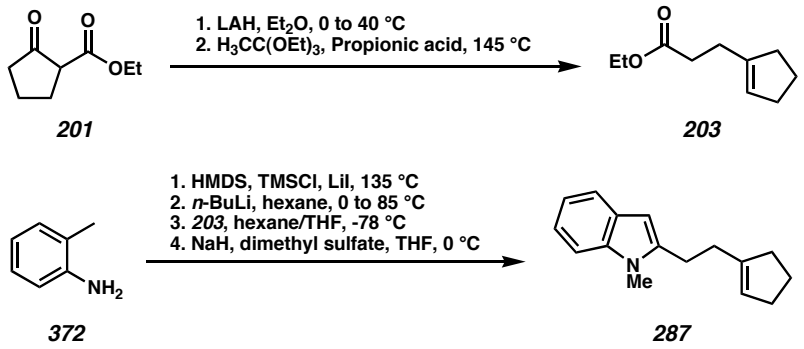
distillation was complete, the reaction was stirred at 140 °C for an additional 60 min, then cooled to 23 °C and diluted with ether (100 mL). The solution was stirred with 1.0 M aq. $KHSO_4$ (100 mL) for 8 h. The phases were separated, and the aqueous phase was extracted with ether (1 x 75 mL). The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (3:2 hexanes/CH_2Cl_2 eluent) provided ester **371**[63] (895 mg, 47% yield over 2 steps, R_F = 0.33 in 1:1 hexanes/CH_2Cl_2) as a colorless oil.

2-substituted indoles were synthesized according to the procedure of Smith et al.[64] A 50 mL flask was charged with hexamethydisilazane (17.7 mL, 84.0 mmol), *o*-toluidine (2.99 mL, 28.0 mmol), TMSCl (197 μl, 1.68 mmol), and lithium iodide (75.0 mg, 0.560 mmol). The mixture was heated to 135 °C and stirred 20 h. The reaction mixture was treated with cyclohexene oxide (1.13 mL, 11.2 mmol) in two equal portions over 15 minutes, then cooled to 23 °C. The volatile materials were removed by distillation under atmospheric pressure. The trimethylsilylaniline was then isolated as a clear oil by vacuum distillation (bp 50 °C at 1 torr).

To a solution of the trimethylsilylaniline (757 μl, 3.88 mmol) in hexane (34.6 mL) at 0 °C was added *n*-butyllithium (3.71 mL, 2.3 M solution in hexane, 8.54 mmol) dropwise. The orange solution was heated to 85 °C and stirred for 6 h. The resulting heterogeneous mixture was cooled to –78 °C and treated with a solution of ester **371** (709 mg, 4.54 mmol) in THF (45.4 mL) quickly. The solution was allowed to warm to 23 °C, stirred 1 h, and quenched with brine. The layers were separated, and the aqueous phase was extracted with 2 x 150 mL Et_2O, 2 x 150 mL EtOAc, and 150 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification

of the oil by flash chromatography (2 columns: 9:1 hexanes/Et_2O eluent, then 3:1 hexanes/CH_2Cl_2 eluent) provided the indole (372 mg, 48% yield, R_F = 0.52 in 4:1 hexanes/EtOAc) as a yellow solid.

To a solution of the indole (116 mg, 0.582 mmol) in THF (2.33 mL) at 0 °C was added NaH (46.4 mg, 60% dispersion in mineral oil, 1.16 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C and treated with dimethyl sulfate (83.1 μl, 0.873 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ether (2 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash chromatography (15:1 hexanes/Et_2O eluent) to provide indole **285** (106 mg, 85% yield, R_F = 0.50 in 9:1 hexanes/EtOAc) as a clear oil. **Indole 285**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.17 (app.t, *J* = 7.4 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 5.35 (app.q, *J* = 6.6 Hz, 1H), 3.69 (s, 3H), 2.84 (app.t, *J* = 8.2 Hz, 2H), 2.42 (app.t, *J* = 8.2 Hz, 2H), 1.72 (s, 3H), 1.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 137.6, 135.1, 128.2, 120.7, 120.0, 119.5, 119.4, 108.9, 98.8, 38.9, 29.6, 26.0, 16.0, 13.6; IR (film) 2917, 1468, 745 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1514.



Indole 287. To a stirring suspension of lithium aluminum hydride (13.6 g, 359 mmol) in Et_2O (120 mL) at 0 °C was added ethyl 2-oxocyclopentanecarboxylate (25.0 mL, 169 mmol) in Et_2O (50 mL) dropwise via an addition funnel. The reaction mixture was heated to 40 °C and stirred 30 min. The mixture was then cooled to 0 °C and quenched by the slow addition of water. The resulting mixture was diluted with Et_2O (500 mL) and stirred vigorously with 20% aqueous solution of sodium potassium tartrate (150 mL) for 1 h. The phases were then separated, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to a yellow oil. Fractional distillation of the oil (bp 92 °C at 68 torr) provided the allylic alcohol[65] (6.83 g, 41% yield, R_F = 0.26 in 4:1 hexanes/EtOAc) as a colorless oil.

The allylic alcohol (2.50 mL, 24.3 mmol) was dissolved in triethylorthoacetate (35.6 mL, 194 mmol), and the solution was treated with propionic acid (660 μl, 8.31 mmol). The reaction was heated to 145 °C with distillative removal of ethanol. After distillation was complete, the reaction was stirred at 145 °C for an additional 60 min, then cooled to 23 °C and diluted with Et_2O (300 mL). The solution was stirred with 1.0 M aq. $KHSO_4$ (300 mL) for 8 h. The phases were separated, and the aqueous phase was extracted with ether (1 x 200 mL). The organic layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification of the

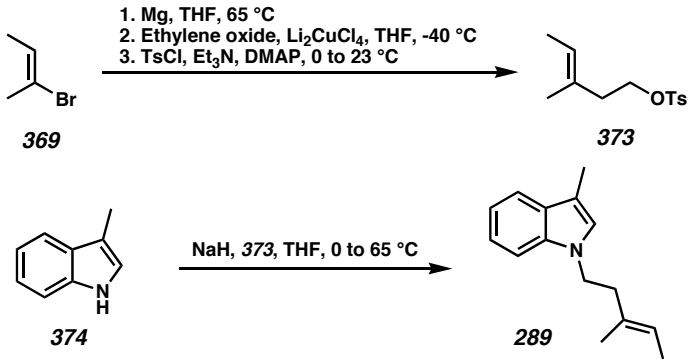
residue by flash chromatography (30:1 hexanes/Et_2O eluent) provided ester **203**[66] (3.22 g, 79% yield, R_F = 0.62 in 4:1 hexanes/Et_2O) as a clear oil.

A 50 mL flask was charged with hexamethydisilazane (17.7 mL, 84.0 mmol), *o*-toluidine (2.99 mL, 28.0 mmol), TMSCl (197 μl, 1.68 mmol), and lithium iodide (75.0 mg, 0.560 mmol). The mixture was heated to 135 °C and stirred 20 h. The reaction mixture was treated with cyclohexene oxide (1.13 mL, 11.2 mmol) in two equal portions over 15 minutes, then cooled to 23 °C. The volatile materials were removed by distillation under atmospheric pressure. The trimethylsilylaniline was then isolated as a clear oil by vacuum distillation (bp 50 °C at 1 torr).

To a solution of the trimethylsilylaniline (408 μl, 2.09 mmol) in hexane (18.7 mL) at 0 °C was added *n*-butyllithium (2.00 mL, 2.3 M solution in hexane, 4.60 mmol) dropwise. The orange solution was heated to 85 °C and stirred for 6 h. The resulting heterogeneous mixture was cooled to –78 °C and treated with a solution of ester **203** (412 mg, 2.45 mmol) in THF (24.5 mL) quickly. The solution was allowed to warm to 23 °C, stirred 1 h, and quenched with brine. The layers were separated, and the aqueous phase was extracted with 2 x 100 mL Et_2O, 2 x 100 mL EtOAc, and 100 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (2 columns: 4:1 hexanes/CH_2Cl_2 eluent, then 9:1 hexanes/Et_2O eluent) provided the indole (172 mg, 39% yield, R_F = 0.56 in 4:1 hexanes/EtOAc) as a white solid.

To a solution of the indole (139 mg, 0.658 mmol) in THF (2.63 mL) at 0 °C was added NaH (52.8 mg, 60% dispersion in mineral oil, 1.32 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to

0 °C and treated with dimethyl sulfate (94.0 μl, 0.987 mmol). After 30 min, the reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ether (2 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) to provide indole **287** (127 mg, 86% yield, R_F = 0.57 in 4:1 hexanes/EtOAc) as a white solid. **Indole 287**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.16 (app.t, *J* = 7.4 Hz, 1H), 7.07 (app.t, *J* = 7.4 Hz, 1H), 6.28 (s, 1H), 5.47 (m, 1H), 3.69 (s, 3H), 2.93-2.88 (comp m, 2H), 2.54-2.49 (comp m, 2H), 2.37 (comp m, 4H), 1.91 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 141.4, 137.5, 128.1, 124.3, 120.7, 120.0, 119.4, 108.9, 98.8, 35.5, 32.7, 30.5, 29.6, 25.6, 23.7; IR (film) 2842, 1468, 744 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1513.



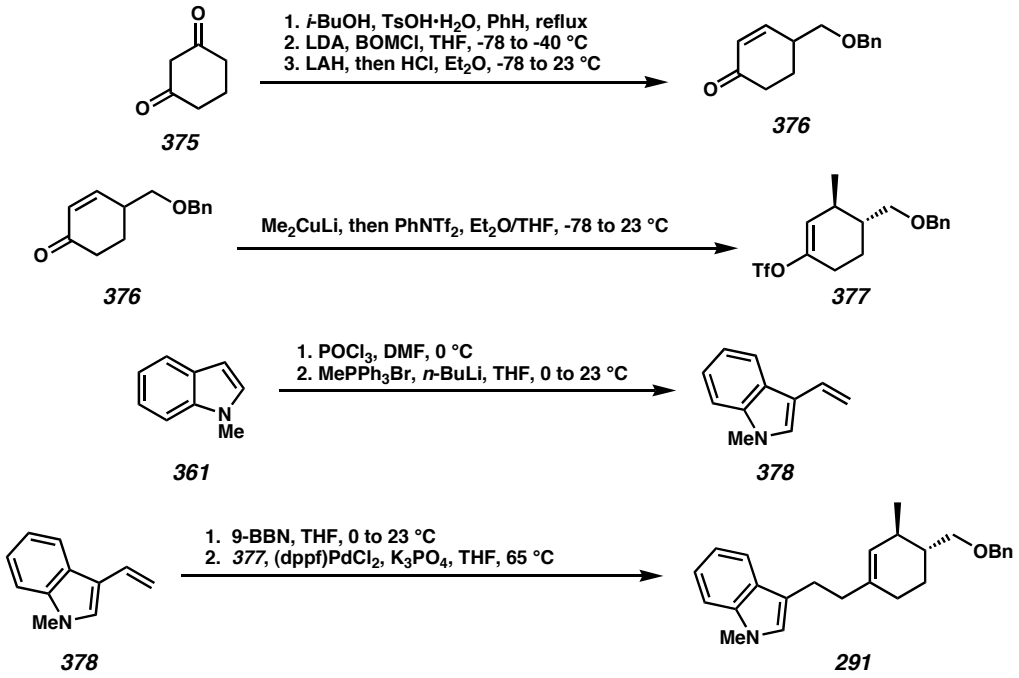
Indole 289. To a stirring suspension of magnesium turnings (146 mg, 6.00 mmol) in THF (12 mL) at 23 °C was added 2-bromo-2-butene (610 μl, 6.00 mmol). The mixture was heated to 65 °C and stirred 1 h, at which point the Grignard reagent had been fully generated. The solution was cooled to 23 °C, and then added via syringe to a solution of ethylene oxide (300 μl, 6.00 mmol) in THF (12 mL) at –40 °C. Lithium

tetrachlorocuprate (3.00 mL, 0.1 M in THF, 0.300 mmol) was then added, and the reaction mixture was stirred at –40 °C for 8 h. The reaction was then quenched by the addition of saturated NH_4Cl (30 mL), allowed to warm to 23 °C, and partitioned between 100 mL Et_2O and 100 mL water. The aqueous phase was extracted with Et_2O (1 x 100 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The resulting homoallylic alcohol[67] (R_F = 0.28 in 4:1 hexanes/EtOAc) was used without further purification.

The alcohol (assume 6.00 mmol) was dissolved in CH_2Cl_2 (30 mL), cooled to 0 °C, and treated with tosyl chloride (1.72 g, 9.00 mmol), Et_3N (1.67 mL, 12.0 mmol), and DMAP (73.3 mg, 0.600 mmol), sequentially. The solution was allowed to warm to 23 °C and stirred 12 h. The mixture was cooled to 0 °C and quenched with saturated NH_4Cl (30 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 hexanes/CH_2Cl_2 eluent) afforded tosylate **373**[68] (458 mg, 30% yield over 2 steps, R_F = 0.46 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of 3-methylindole (227 mg, 1.73 mmol) in THF (5.00 mL) at 0 °C was added NaH (138 mg, 60% dispersion in mineral oil, 3.46 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C and treated with alkyl tosylate **373** (483 mg, 1.90 mmol) in THF (1.92 mL). The reaction was heated to 65 °C and stirred 8 h. The reaction was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL), and extracted with ether (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The

resulting solid was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide indole **289** (259 mg, 70% yield, R_F = 0.82 in 4:1 hexanes/EtOAc, single olefin isomer of undetermined geometry) as a clear oil. **Indole 289**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.25 (app.t, *J* = 7.7 Hz, 1H), 7.14 (app.t, *J* = 7.7 Hz, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 4.12 (t, *J* = 7.7 Hz, 2H), 2.54 (t, *J* = 7.7 Hz, 2H), 2.37 (s, 3H), 1.77 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 132.5, 129.0, 125.6, 122.1, 121.5, 119.2, 118.6, 110.3, 109.2, 44.5, 32.8, 23.8, 13.4, 9.8; IR (film) 2918, 1468, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{19}N]^+$: 213.1517, found 213.1513.



Trifluoromethanesulfonate 377. To a solution of 1,3-cyclohexanedione (10.0 g, 89.2 mmol) and isobutyl alcohol (25.0 mL, 270 mmol) in benzene (110 mL) at 23 °C was added TsOH•H_2O (77.0 mg, 0.446 mmol). The reaction was heated to reflux with azeotropic removal of water. After 4.5 h, the solution was concentrated to an oil and

distilled (bp 93 °C at 1 torr) to provide the vinylogous ester[69] (14.6 g, 97% yield, R_F = 0.23 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of LDA (7.50 mmol) in THF (10.1 mL) at –78 °C was added a solution of the vinylogous ester (1.00 mL, 6.25 mmol) in THF (10 mL) dropwise via cannula. The reaction mixture was stirred at –78 °C for 2 h, at which point benzyl chloromethyl ether (1.30 mL, 9.38 mmol) was added. The reaction was allowed to warm to –40 °C over 1 h, then stirred at –40 °C for 4 h. The reaction mixture was then quenched by quick addition of saturated $NaHCO_3$ (50 mL) and allowed to warm to 23 °C. Et_2O (75 mL) was added, the phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the alkylated vinylogous ester (1.32 g, 73% yield, R_F = 0.45 in 2:1 hexanes/EtOAc) as a colorless oil.

To a stirring suspension of LAH (115 mg, 3.02 mmol) in Et_2O (11 mL) at –78 °C was added a solution of the vinylogous ester (1.16 g, 4.02 mmol) in Et_2O (5.0 mL) via cannula. The cold bath was removed, and the reaction mixture was allowed to warm over 30 min. The reaction was then cooled to 0 °C, and to the mixture was added slowly 115 μl water, 115 μl, 15% aq. NaOH, and 345 μl water, sequentially. Et_2O (30 mL) was added, and the heterogeneous mixture was stirred for 30 min at 23 °C, at which point a white precipitate had formed. The mixture was filtered through a pad of celite (Et_2O eluent), and to the filtrate was added 1.0 N HCl (25 mL). The biphasic solution was stirred vigorously for 1 h. The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with

saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded enone **376**[70] (654 mg, 75% yield, R_F = 0.41 in 2:1 hexanes/EtOAc) as a colorless oil.

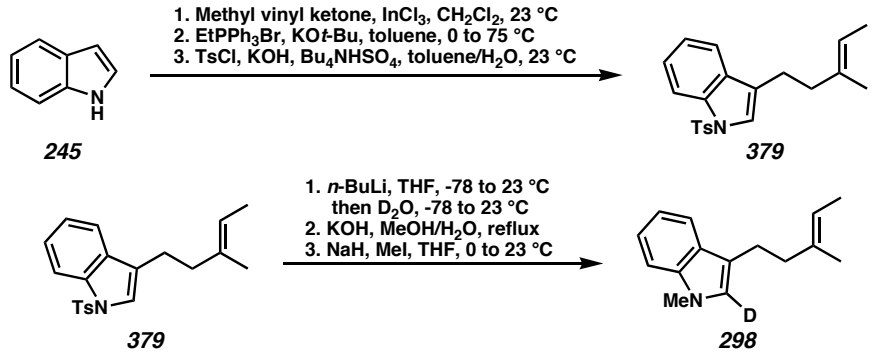
Trifluoromethanesulfonate **377** was generated regioselectively by the procedure of McMurry and Scott.[71] To a stirring suspension of copper(I) iodide (159 mg, 0.833 mmol) in Et_2O (14.1 mL) at 0 °C was added methyllithium (1.04 mL, 1.6 M in Et_2O, 1.67 mmol) dropwise over 1 min. The pale yellow solution was stirred 30 min, then cooled to –78 °C. A solution of enone **376** (120 mg, 0.555 mmol) in THF (12.3 mL) was added dropwise over 3 min, and the resulting solution was stirred at –78 °C for 45 min and 0 °C for 45 min. A solution of $PhNTf_2$ (208 mg, 0.583 mmol) in THF (9 mL) was added via cannula, and the reaction mixture was stirred at 0 °C for 2 h, then 90 min at 23 °C. The reaction was quenched with saturated NH_4OH (50 mL, saturated with NH_4Cl) and diluted with Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) afforded the vinyl triflate (**377**) (146 mg, 72% yield, R_F = 0.43 in 9:1 hexanes/EtOAc) as a clear oil. Relative stereochemistry was determined based on similar dimethyl cuprate conjugate additions to 4-substituted enones.[72] **Trifluoromethanesulfonate 377**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (comp m, 5H), 5.58 (br s, 1H), 4.51 (ABq, J = 12.3, Δν = 14.3 Hz, 2H), 3.51 (dd, J = 4.5, 9.3 Hz, 1H), 3.38 (dd, J = 6.9, 9.3 Hz, 1H), 2.42-2.23 (comp m, 3H), 2.06-1.97 (m, 1H), 1.76-1.63 (m, 1H), 1.61-1.51 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 138.5, 128.6, 127.9, 127.8, 123.7, 118.7 (q, J = 318 Hz), 73.4, 72.0, 39.9, 31.7,

26.7, 25.0, 20.1; IR (film) 1416, 1209, 1143 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{16}H_{20}O_4SF_3]^+$: 365.1034, found 365.1036.

Vinyl indole 378. $POCl_3$ (437 μl, 4.69 mmol) was added dropwise to 1.02 mL DMF at 0 °C. The mixture was stirred for 30 min, and then a solution of *N*-methylindole (500 μl, 3.91 mmol) in DMF (3.91 mL) was added dropwise. The mixture turned thick and heterogeneous. The reaction mixture was stirred vigorously for 6 h, then poured over ice water (75 mL). The mixture was basified with 5% aq. NaOH (color changed from red to yellow), and the solution was extracted with EtOAc (3 x 75 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to an oil. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc eluent) afforded the aldehyde[73] as a yellow oil (R_F = 0.27 in 1:1 hexanes/EtOAC), which was carried on to the subsequent reaction.

To a stirring suspension of $MePPh_3Br$ (1.92 g, 5.38 mmol) in 11.5 mL THF at 0 °C was added *n*-BuLi (1.88 mL, 2.4 M in hexane, 4.52 mmol) dropwise. The resulting yellow solution was stirred at 0 °C for 30 min, and then a solution of the aldehyde (assume 3.91 mmol) in THF (5.7 mL) was added dropwise. The reaction mixture was maintained at 0 °C for 20 min, then allowed to warm to 23 °C and stirred 6 h. The mixture was poured into ice water (75 mL) and extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide the vinyl indole[74] (**378**, 535 mg, 87% yield over 2 steps, R_F = 0.71 in 2:1 hexanes/EtOAc) as a colorless oil. The indole was stored frozen in PhH to prevent decomposition.

Indole 291. Suzuki cross-coupling was carried out according to the procedure of Suzuki et al.[75] 9-BBN dimer (203 mg, 0.830 mmol) was dissolved in THF (1.66 mL) at 23 °C under an argon atmosphere. Once fully in solution, it was cooled to 0 °C, and to the solution was added a solution of indole **378** (261 mg, 1.66 mmol) in THF (1.66 mL). The reaction mixture was warmed to 23 °C and stirred for 3 h. To the solution was then added a solution of triflate **377** (552 mg, 1.51 mmol) in THF (7.55 mL), (dppf)$PdCl_2$ (30.8 mg, 0.0378 mmol), and K_3PO_4 (482 mg, 2.27 mmol), and the reaction was heated to 65 °C. After 5 h, the reaction was cooled to 23 °C and quenched with 1 mL NaOH (3.0 M aq.) and 1 mL 30% H_2O_2, and the resulting mixture was stirred 1 h. The mixture was then partitioned between Et_2O (50 mL) and water (40 mL), and the aqueous phase was extracted with Et_2O (1 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 → 1:1 hexanes/CH_2Cl_2 eluent) afforded Suzuki product **291** (467 mg, 75% yield, R_F = 0.20 in 4:1 hexanes/CH_2Cl_2) as a clear oil. **Indole 291**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.34 (app.d, *J* = 4.4 Hz, 4H), 7.36-7.30 (comp m, 2H), 7.25 (app.t, *J* = 7.4 Hz, 1H), 7.13 (app.t, *J* = 7.4 Hz, 1H), 6.85 (s, 1H), 5.29 (s, 1H), 4.56 (ABq, *J* = 12.1 Hz, Δν = 17.7 Hz, 2H), 3.75 (s, 3H), 3.59 (dd, *J* = 4.4, 9.3 Hz, 1H), 3.38 (dd, *J* = 7.2, 9.3 Hz, 1H), 2.88 (app.t, *J* = 8.0 Hz, 2H), 2.37 (app.t, *J* = 7.7 Hz, 2H), 2.10-1.98 (comp m, 3H), 1.58-1.46 (comp m, 2H), 1.03 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 137.2, 137.1, 128.5, 128.2, 127.7, 127.6, 127.2, 126.1, 121.6, 119.2, 118.7, 115.5, 109.3, 73.8, 73.3, 41.2, 38.6, 32.7, 32.5, 27.7, 25.5, 23.9, 21.0; IR (film) 2921, 1453, 1114, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{26}H_{31}NO]^+$: 373.2406, found 373.2410.



To a solution of indole (5.00 g, 42.7 mmol) in 85.4 mL CH_2Cl_2 at 23 °C was added methyl vinyl ketone (3.55 mL, 42.7 mmol) and $InCl_3$ (944 mg, 4.27 mmol). The reaction mixture was stirred at 23 °C for 4 h, quenched with water (160 mL), and extracted with CH_2Cl_2 (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to a brown solid. The solid was dissolved in CH_2Cl_2 and passed through a plug of SiO_2 (5 x 5 cm, 4:1 CH_2Cl_2/hexanes eluent). The filtrate was evaporated to provide the ketone[50] (6.49 g, 81% yield, R_F = 0.22 in 100% CH_2Cl_2) as a white solid.

To a suspension of potassium *tert*-butoxide (7.50 g, 66.8 mmol) in toluene (267 mL) at 0 °C was added (ethyl)triphenylphosphonium bromide (24.8 g, 66.8 mmol). The suspension was stirred vigorously for 10 min at 0 °C and 1 h at 23 °C. The resulting red solution was cooled to 0 °C, the indolyl ketone (5.00 g, 26.7 mmol) was added as a solid, and the solution was heated to 75 °C. After stirring for 6 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl/water (250 mL, 1:1), and extracted with EtOAc (2 x 250 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5:1 hexanes/CH_2Cl_2 eluent) to provide the olefin[51] (4.31 g, 81% yield, R_F = 0.67 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the olefin (730 mg, 3.66 mmol) in toluene (3.66 mL) at 23 °C was added Bu_4NHSO_4 (86.9 mg, 0.256 mmol), aq. KOH (4.57 mL, 50% w/v), and a solution of TsCl (934 mg, 4.90 mmol) in toluene (9.80 mL), sequentially. The biphasic mixture was stirred vigorously for 1 h, then partitioned between EtOAc (125 mL) and H_2O (75 mL). The organic layer was washed with H_2O (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 → 1:1 hexanes/CH_2Cl_2 eluent) to provide the *N*-tosyl indole (**379**, 1.29 g, 100% yield, R_F = 0.43 in 1:1 hexanes/CH_2Cl_2), which was carried to the subsequent reaction.

To a solution of the *N*-tosyl indole (1.29 g, 3.66 mmol) in THF (14.9 mL) at –78 °C was added *n*-BuLi (3.11 mL, 2.4 M in hexane, 7.46 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to 23 °C and stirred 2 h. The mixture was then cooled to –78 °C, and D_2O (445 μl, 24.6 mmol) was added. The mixture was allowed to warm to 23 °C, stirred for 1.5 h, then diluted with Et_2O (150 mL). The solution was washed with saturated NH_4Cl (50 mL), and the aqueous phase was extracted with Et_2O (1 x 75 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 hexanes/CH_2Cl_2 eluent) afforded the deuterated indole (748 mg, 58% yield, R_F = 0.43 in 1:1 hexanes/CH_2Cl_2), which was taken to the next reaction.

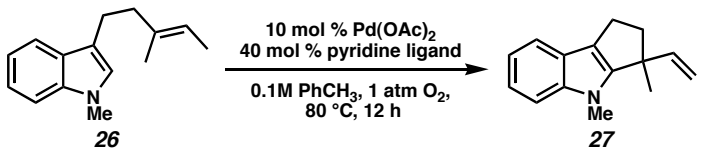
To a solution of the deuterated indole (748 mg, 2.11 mmol) in MeOH (16.5 mL) and H_2O (1.83 mL) at 23 °C was added KOH (3.08 g, 54.9 mmol). The reaction mixture was heated to 75 °C and stirred 1 h. The solution was cooled to room temperature, partitioned between Et_2O (125 mL) and H_2O (75 mL), and the aqueous phase was extracted with Et_2O (2 x 50 mL). The organic phases were combined, washed with brine,

dried over $MgSO_4$, and concentrated in vacuo. The *N*-H indole (R_F = 0.46 in 1:1 hexanes/CH_2Cl_2) was carried to the subsequent reaction without further purification.

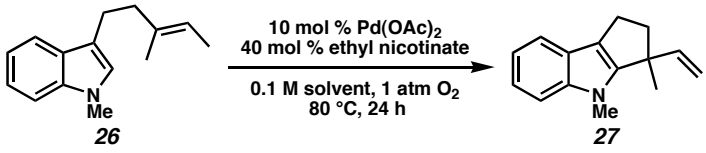
To a solution of the indole (assume 2.11 mmol) in THF (8.44 mL) at 0 °C was added NaH (169 mg, 60% dispersion in mineral oil, 4.22 mmol). The mixture was stirred 15 min at 0 °C, then allowed to warm to 23 °C and stirred an additional 45 min. The reaction was then cooled to 0 °C and treated with MeI (197 μl, 3.17 mmol). The reaction was allowed to warm to 23 °C and stirred 30 min. It was then quenched at 0 °C with D_2O (1 mL) and partitioned between Et_2O (100 mL) and saturated NH_4Cl (60 mL). The aqueous phase was extracted with Et_2O (50 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the *N*-methyl indole (355 mg, 79% yield, R_F = 0.51 in 9:1 hexanes/CH_2Cl_2) as a colorless oil. Deuterium incorporation was measured to be 90% by ^{1}H NMR.

Indole 298. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.31 (app.t, *J* = 8.4 Hz, 1H), 7.31 (app.t, *J* = 8.4 Hz, 1H), 7.25 (app.d, *J* = 8.1 Hz, 1H), 7.25 (app.d, *J* = 8.1 Hz, 1H), 7.18-7.12 (m, 1H), 7.18-7.12 (m, 1H), 5.35 (q, *J* = 6.6 Hz, 1H), 5.31 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.92-2.83 (comp m, 2H), 2.92-2.83 (comp m, 2H), 2.50-2.40 (comp m, 2H), 2.50-2.40 (comp m, 2H), 1.82 (s, 3H), 1.75 (s, 3H), 1.65 (d, *J* = 6.6 Hz, 3H), 1.61 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 136.2, 136.2, 128.1, 126.1, 125.8 (t, *J* = 26.9 Hz), 121.6, 121.6, 119.5, 119.2, 119.2, 118.7, 118.7, 115.5, 115.4, 109.3, 109.3, 40.7, 32.7, 32.7, 24.2, 23.7, 23.6, 16.0, 13.6, 13.5; IR (film) 2915, 1469, 1373, 738 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{18}ND]^+$: 214.1580, found 214.1574.

4.7.3 Palladium-Catalyzed Indole Annulations



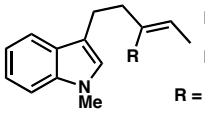
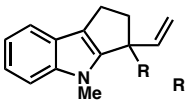
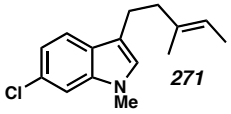
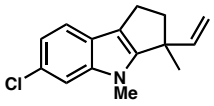
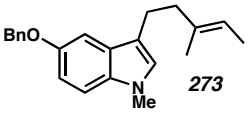
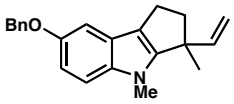
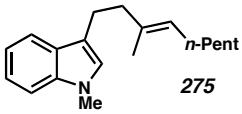
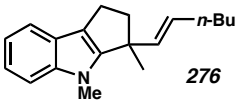
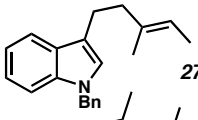
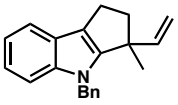
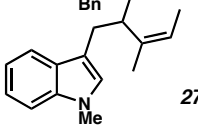
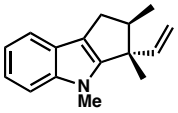
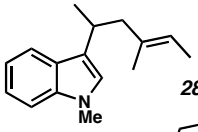
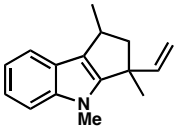
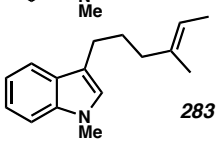
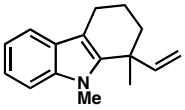
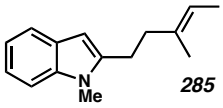
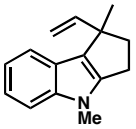
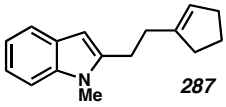
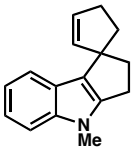
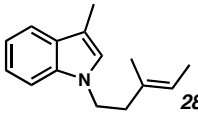
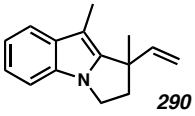
General procedure for the optimization of pyridine ligand (Table 4.3.1): A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by toluene (1.63 mL) and ligand (0.0732 mmol, 0.40 equiv). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) in toluene (200 μl), and then tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2 for 12 h. An aliquot (approx. 200 μl) was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.



General procedure for the optimization of solvent (Table 4.3.2): A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by solvent (1.63 mL) and ethyl nicotinate (10.0 μl, 0.0732 mmol). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) in solvent (200 μl), and then tridecane (25.0 μl, 0.103 mmol, internal

standard) were then added via syringe, and the reaction was stirred under O_2 for 24 h. An aliquot (approx. 200 μl) was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Table 4.3.3 (reproduced). The palladium-catalyzed oxidative indole cyclization.[a]

entry	substrate[b]	product	time	% yield[c]
1	 R = Me *26*	 R = Me *27*	24 h	82
2	R = Et *267*	R = Et *268*	18 h	74
3	R = CH_2OBn *269*	R = CH_2OBn *270*	24 h	60
4	 *271*	 *272*	32 h	62
5	 *273*	 *274*	20 h	73
6	 *275*	 *276*	30 h	79[d]
7	 *277*	 *278*	48 h	69
8	 *279*	 *280*	18 h	76 (6:1 dr)
9	 *281*	 *282*	53 h	64 (1:1 dr)
10	 *283*	 *284*	39 h	66[e]
11	 *285*	 *286*	6 h	73[f]
12	 *287*	 *288*	5 h	68[f]
13	 *289*	 *290*	18 h	74

[a] 10 mol% $Pd(OAc)_2$, 40 mol% ethyl nicotinate, 1 atm O_2, 80 °C, 0.1 M substrate in *t*-amyl alcohol:AcOH (4:1). [b] Typically used as a mixture of olefin isomers. [c] Isolated yields. [d] Product isolated as a 58:42 mixture of *E* and *Z* isomers. [e] 0.1 M in pinacolone. [f] 0.1 M in *t*-amyl alcohol.

General procedure for the oxidative annulation of indoles (Entry 1 is used as an example): A flame-dried 25 mL round bottom flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (17.2 mg, 0.0769 mmol, 0.100 equiv), *t*-amyl alcohol (5.15 mL), acetic acid (1.54 mL), and ethyl nicotinate (42.0 μl, 0.308 mmol, 0.400 equiv), sequentially. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole (164 mg, 0.769 mmol) in *t*-amyl alcohol (1.00 mL) was then added via syringe, and the reaction was stirred under O_2 for the listed time. Filtration of the reaction mixture through a small pad of silica gel (1 x 5 cm, EtOAc eluent), concentration, and purification of the oil by flash chromatography afforded pure annulated indole.

Entry 1: 24 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (133 mg, 82% yield, R_F = 0.76 in 4:1 hexanes/acetone) as a clear oil.

Indole 27. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.1 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.16 (app.t, *J* = 8.2 Hz, 1H), 7.09 (app.t, *J* = 7.1 Hz, 1H), 6.09 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.06 (dd, *J* = 1.7, 10.4 Hz, 1H), 4.98 (dd, *J* = 1.7, 17.0 Hz, 1H), 3.64 (s, 3H), 2.83 (app.t, *J* = 6.9 Hz, 2H), 2.57-2.48 (m, 1H), 2.40-2.32 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 145.3, 141.8, 124.1, 120.5, 119.2, 119.0, 117.6, 112.1, 109.5, 46.5, 46.2, 30.2, 24.0, 22.7; IR (film) 1468, 742 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1363.

Entry 2: 18 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (123 mg, 74% yield, R_F = 0.80 in 4:1 hexanes/acetone) as a clear oil.

Indole 268. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.16 (app.t, *J* = 8.2 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 6.11 (dd, *J* = 10.5, 17.3 Hz, 1H), 5.03 (dd, *J* = 1.1, 10.5 Hz, 1H), 4.89 (dd, *J* = 1.1, 17.3 Hz, 1H), 3.63 (s, 3H), 2.80 (app.t, *J* = 7.2 Hz, 2H), 2.54-2.37 (comp m, 2H), 2.00-1.81 (comp m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 144.8, 142.0, 124.2, 120.4, 119.1, 119.0, 118.9, 112.1, 109.4, 50.9, 42.8, 30.5, 30.4, 23.1, 9.4; IR (film) 2964, 2925, 1466, 738 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1510.

Entry 3: 24 h. Purification of the residue by flash chromatography (9:1 to 4:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (96.5 mg, 60% yield, R_F = 0.63 in 4:1 hexanes/Et_2O) as a clear oil.

Indole 270. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.7 Hz, 1H), 7.36-7.26 (comp m, 6H), 7.19 (app.t, *J* = 7.6 Hz, 1H), 7.11 (app.t, *J* = 7.3 Hz, 1H), 6.20 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.17 (dd, *J* = 1.1, 10.7 Hz, 1H), 5.01 (dd, *J* = 1.1, 17.6 Hz, 1H), 4.54 (ABq, *J* = 12.1 Hz, Δν = 14.2 Hz, 2H), 3.74 (ABq, *J* = 9.1 Hz, Δν = 18.5 Hz, 2H), 3.66 (s, 3H), 2.85 (app.t, *J* = 6.9 Hz, 2H), 2.62-2.53 (m, 1H), 2.49-2.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 142.2, 142.0, 138.5, 128.5, 127.8, 127.7, 124.1, 120.6, 119.2, 119.1, 119.0, 114.2, 109.7, 75.6, 73.7, 51.9, 42.2, 31.3, 22.7; IR (film) 2855, 1467, 739 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{23}NO]^+$: 317.1780, found 317.1774.

Entry 4: 32 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (61.2 mg, 62% yield, R_F = 0.72 in 4:1 hexanes/acetone) as a clear oil.

Indole 272. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.07 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.08 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.97 (dd, *J* = 1.1, 17.0 Hz, 1H), 3.60 (s, 3H), 2.80 (app.t, *J* = 6.9 Hz, 2H), 2.56-2.47 (m, 1H), 2.40-2.31 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 145.0, 142.2, 126.5, 122.7, 119.7, 117.7, 112.3, 109.6, 46.4, 46.3, 30.4, 23.9, 22.6; IR (film) 1471, 1375 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{16}NCl]^+$: 245.0971, found 245.0970.

Entry 5: 20 h. Purification of the residue by flash chromatography (3:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (118 mg, 73% yield, R_F = 0.62 in 4:1 hexanes/Et_2O) as a clear oil.

Indole 274. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (app.d, *J* = 6.6 Hz, 2H), 7.43-7.30 (comp m, 3H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H), 6.90 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.08 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.12 (s, 2H), 5.06 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.98 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.61 (s, 3H), 2.80 (app.t, *J* = 6.9 Hz, 2H), 2.55-2.46 (m, 1H), 2.38-2.30 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 149.8, 145.3, 138.2, 137.4, 128.7, 127.9, 127.7, 124.3, 117.2, 112.0, 111.1, 110.1, 103.2, 71.4, 46.4, 46.2, 30.3, 23.9, 22.7; IR (film) 1482, 1204 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{22}H_{23}NO]^+$: 317.1780, found 317.1774.

Entry 6: 30 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (133 mg, 79% yield, R_F = 0.81 in 4:1 hexanes/EtOAc) as a clear oil.

Indole 276. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.16 (app.t, *J* = 7.7 Hz, 1H), 7.15 (app.t, *J* = 7.7 Hz, 1H), 7.09 (app.t, *J* = 7.7 Hz, 1H), 7.08 (app.t, *J* = 7.7 Hz, 1H), 5.71 (s, 1H), 5.66 (s, 1H), 5.39 (t, *J* = 6.9 Hz, 1H), 5.33 (t, *J* = 6.9 Hz, 1H), 3.64 (s, 3H), 3.64 (s, 3H), 2.81 (app.t, *J* = 6.6 Hz, 2H), 2.81 (app.t, *J* = 6.6 Hz, 2H), 2.54-2.45 (m, 1H), 2.54-2.45 (m, 1H), 2.39-2.31 (m, 1H), 2.39-2.31 (m, 1H), 2.04 (app.q, *J* = 6.6 Hz, 2H), 2.04 (app.q, *J* = 6.6 Hz, 2H), 1.48 (s, 3H), 1.48 (s, 3H), 1.37-1.30 (comp m, 4H), 1.37-1.30 (comp m, 4H), 0.90 (app.t, *J* = 7.1 Hz, 3H), 0.90 (app.t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 141.8, 137.1, 128.2, 124.2, 120.3, 119.1, 118.9, 117.2, 109.4, 47.0, 45.4, 32.4, 32.0, 30.2, 24.8, 22.7, 22.4, 14.2; IR (film) 2927, 1466, 736 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{19}H_{25}N]^+$: 267.1987, found 267.1990.

Entry 7: 48 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (132 mg, 68% yield, R_F = 0.76 in 4:1 hexanes/acetone) as a clear oil.

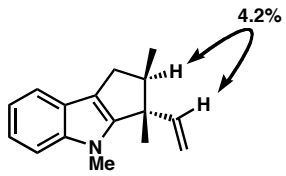
Indole 278. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 1H), 7.29-7.21 (comp m, 4H), 7.12-7.06 (comp m, 3H), 6.99 (app.d, *J* = 7.1 Hz, 2H), 6.04 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.28 (s, 2H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 17.6 Hz, 1H), 2.88 (app.t, *J* = 7.1 Hz, 2H), 2.59-2.50 (m, 1H), 2.40-2.31 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 145.0, 141.6, 138.5, 128.7, 127.2, 126.2, 124.4, 120.8, 119.5, 119.0, 118.1, 112.2,

110.5, 47.4, 46.5, 46.3, 23.9, 22.8; IR (film) 2930, 1453, 739 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{21}N]^+$: 287.1674, found 287.1671.

Entry 8: 18 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (109 mg, 76% yield, R_F = 0.78 in 4:1 hexanes/acetone) as a clear oil.

Indole 280. Major diastereomer only: ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.18 (app.t, *J* = 7.7 Hz, 1H), 7.11 (app.t, *J* = 7.7 Hz, 1H), 6.09 (dd, *J* = 11.0, 17.0 Hz, 1H), 5.25 (dd, *J* = 1.4, 11.0 Hz, 1H), 5.24 (dd, *J* = 1.4, 17.0 Hz, 1H), 3.66 (s, 3H), 3.02 (dd, *J* = 7.1, 13.7 Hz, 1H), 2.78 (m, 1H), 2.47 (dd, *J* = 9.3, 13.7 Hz, 1H), 1.22 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 145.2, 141.2, 124.2, 120.4, 119.2, 118.9, 115.9, 113.5, 109.5, 50.3, 48.2, 31.4, 30.0, 17.0, 13.9; IR (film) 2960, 2928, 1464, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1520.

Figure 4.7.1 NOE measurements of the major diastereomer of **280**:



Entry 9: 53 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (94.6 mg, 64% yield, R_F = 0.76 in 4:1 hexanes/acetone) as a clear oil. The indole was isolated as a 55:45 mixture of diastereomers.

Indole 282. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.18 (app.t, *J* = 7.4 Hz, 1H), 7.18 (app.t, *J* = 7.4 Hz, 1H), 7.11 (app.t, *J* = 6.6 Hz, 1H), 7.11 (app.t, *J* = 6.6 Hz, 1H), 6.16 (dd, *J* = 10.2, 17.9 Hz, 1H), 6.05 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.14 (dd, *J* = 1.1, 9.9 Hz, 1H), 5.14 (dd, *J* = 1.1, 17.6 Hz, 1H), 5.00 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.86 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.38 (m, 1H), 3.38 (m, 1H), 2.72 (dd, *J* = 7.7, 12.6 Hz, 1H), 2.55 (dd, *J* = 7.7, 12.6 Hz, 1H), 2.11 (dd, *J* = 6.6, 12.6 Hz, 1H), 1.98 (dd, *J* = 6.6, 12.6 Hz, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.8, 146.5, 145.1, 141.8, 123.9, 122.6, 122.1, 120.5, 119.2, 119.1, 118.7, 112.3, 111.5, 109.6, 109.5, 55.9, 55.8, 46.3, 46.1, 31.8, 31.5, 30.2, 30.1, 25.7, 23.7, 21.9, 21.8; IR (film) 2955, 1466, 740 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1517.

Entry 10: 39 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (98.3 mg, 66% yield, R_F = 0.84 in 4:1 hexanes/acetone) as a clear oil.

Indole 284. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.20 (app.t, *J* = 7.4 Hz, 1H), 7.09 (app.t, *J* = 7.4 Hz, 1H), 6.01 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.14 (dd, *J* = 1.1, 10.4 Hz, 1H), 4.89 (dd, *J* = 1.1, 17.6 Hz, 1H), 3.69 (s, 3H), 2.75 (app.t, *J* = 6.1 Hz, 2H), 1.88-1.70 (comp m, 4H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 139.3, 137.7, 126.9, 121.2, 118.8, 118.3, 113.6, 110.5, 108.7, 41.2, 39.3, 31.7, 25.4, 22.0, 20.0; IR (film) 2929, 1471, 738 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{19}N]^+$: 225.1517, found 225.1509.

Entry 11: 6 h. Purification of the residue by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (88.8 mg, 73% yield, R_F = 0.65 in 4:1 hexanes/THF) as a white solid.

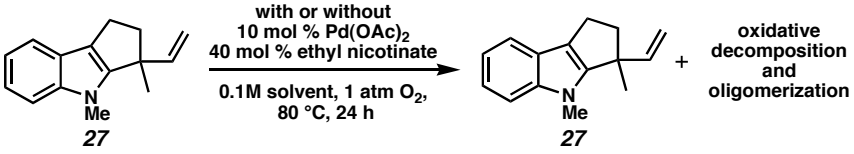
Indole 286. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.14 (app.t, *J* = 7.7 Hz, 1H), 7.06 (app.t, *J* = 7.7 Hz, 1H), 6.15 (dd, *J* = 10.4, 17.6 Hz, 1H), 5.02 (dd, *J* = 1.7, 17.6 Hz, 1H), 4.95 (dd, *J* = 1.7, 10.4 Hz, 1H), 3.68 (s, 3H), 2.89 (app.t, *J* = 6.9 Hz, 2H), 2.55-2.46 (m, 1H), 2.40-2.31 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 145.1, 141.6, 124.0, 122.8, 120.2, 119.1, 118.4, 110.5, 109.7, 46.6, 44.5, 30.9, 26.3, 23.8; IR (film) 2956, 740 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1367.

Entry 12: 5 h. Purification of the residue by flash chromatography (6:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (75.7 mg, 68% yield, R_F = 0.62 in 4:1 hexanes/THF) as a white solid.

Indole 288. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.13 (app.t, *J* = 7.7 Hz, 1H), 7.05 (app.t, *J* = 7.4 Hz, 1H), 5.84-5.81 (m, 1H), 5.77-5.74 (m, 1H), 3.68 (s, 3H), 2.98-2.82 (comp m, 2H), 2.71-2.43 (comp m, 4H), 2.31-2.22 (m, 1H), 2.07-1.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 141.7, 139.1, 129.0, 123.8, 123.4, 120.2, 119.1, 118.3, 109.6, 56.2, 43.5, 38.0, 32.5, 30.8, 24.3; IR (film) 2942, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{17}N]^+$: 223.1361, found 223.1366.

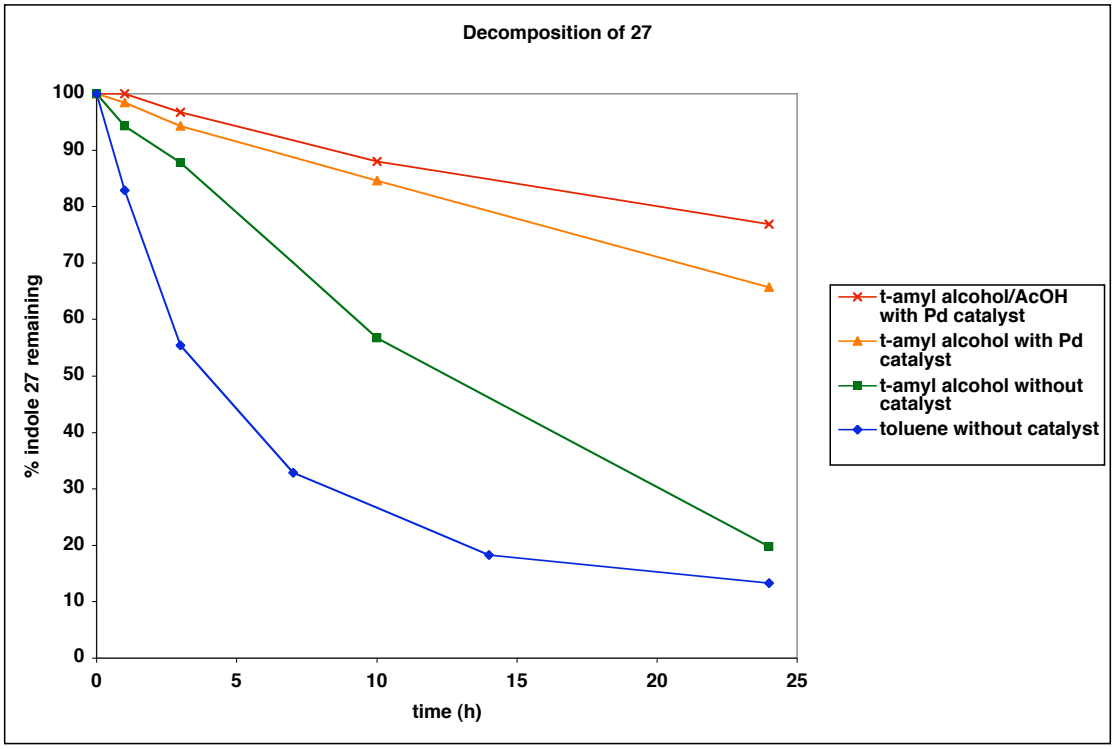
Entry 13: 18 h. Purification of the residue by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) provided the desired annulated indole (114 mg, 74% yield, R_F = 0.45 in 4:1 hexanes/benzene) as a clear oil.

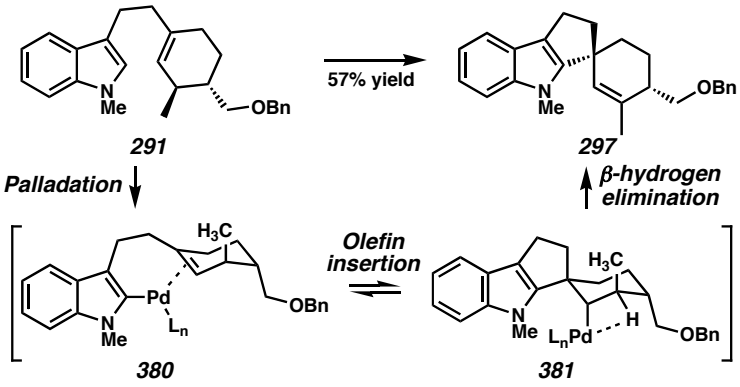
Indole 290. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.16 (app.t, *J* = 7.7 Hz, 1H), 7.10 (app.t, *J* = 7.7 Hz, 1H), 6.06 (dd, *J* = 10.4, 17.0 Hz, 1H), 5.09 (dd, *J* = 1.1, 10.4 Hz, 1H), 5.01 (dd, *J* = 1.1, 17.0 Hz, 1H), 4.10-3.98 (comp m, 2H), 2.61-2.53 (m, 1H), 2.48-2.39 (m, 1H), 2.27 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 143.2, 133.4, 132.2, 120.6, 118.7, 118.6, 112.6, 109.4, 101.6, 44.8, 43.8, 42.0, 24.3, 8.2; IR (film) 2966, 2867, 1461, 737 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{17}N]^+$: 211.1361, found 211.1360.



Control experiments to examine product stability: A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (2.6 mg, 0.0118 mmol) if applicable, followed by solvent (918 μl) and ethyl nicotinate (6.4 μl, 0.0472 mmol) if applicable. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **27** (25.0 mg, 0.118 mmol) in solvent (200 μl), and then tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2 for 24 h. Aliquots (approx. 200 μl) were withdrawn periodically, filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The data collected were plotted on a graph to illustrate decomposition.

Graph from Figure 4.3.1 *(reproduced)*

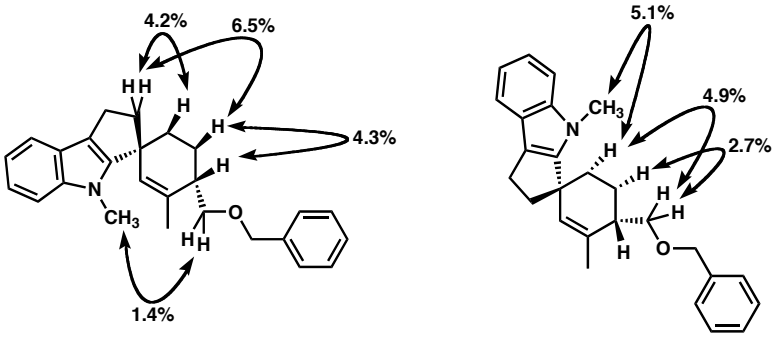


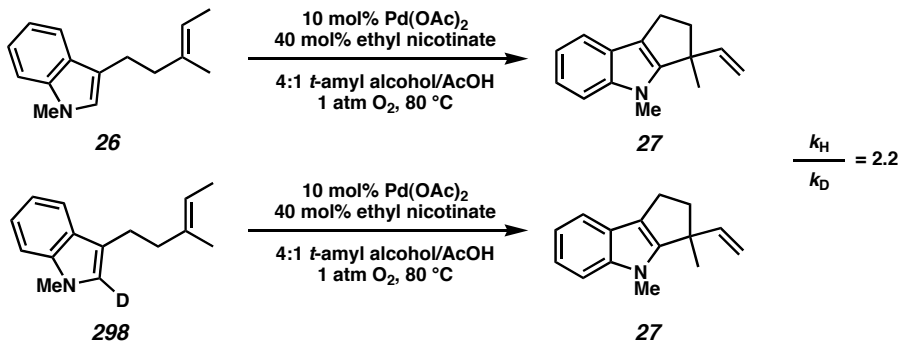


Procedure for the oxidative annulation of diastereomerically pure indole 291. A flame-dried 25 mL round bottom flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.5 mg, 0.0202 mmol) followed by *t*-amyl alcohol (1.52 mL) and ethyl nicotinate (11.0 μl, 0.0808 mmol), sequentially. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **291** (75.5 mg, 0.202 mmol) in *t*-amyl alcohol (500 μl) was then added via syringe, and the reaction was stirred under O_2 for 24 h. The reaction mixture was filtered through a small pad of silica gel (1 x 5 cm, EtOAc eluent) and concentrated in vacuo. Purification of the oil by flash chromatography (1:1 hexane/PhH eluent) afforded diastereomerically pure annulated indole **297** (42.8 mg, 57% yield, R_F = 0.59 in 4:1 hexanes/Et_2O) as a colorless oil. The relative stereochemistry of the product was determined by NOE analysis. **Indole 297**: ^{1}H NMR (300 MHz, C_6D_6) δ 7.64-7.61 (m, 1H), 7.25-7.20 (comp m, 3H), 7.15-7.09 (comp m, 3H), 7.08-7.02 (comp m, 2H), 5.37 (s, 1H), 4.27 (ABq, *J* = 12.1 Hz, Δν = 22.2 Hz, 2H), 3.43-3.32 (comp m, 2H), 3.14 (s, 3H), 2.77 (dd, *J* = 5.2, 8.0 Hz, 2H), 2.33-2.21 (comp m, 2H), 2.16-2.09 (m, 1H), 1.99-1.91 (m, 1H), 1.83 (dd, *J* = 2.5, 13.5 Hz, 1H), 1.68 (ddd, *J* = 3.3, 5.5, 13.2 Hz, 1H), 1.61 (s, 3H), 1.53 (app.dt, *J* = 2.9, 12.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 141.7, 138.6, 134.4, 130.8, 128.6, 128.0, 127.9, 124.2, 120.2, 119.1, 118.8, 117.1, 109.4, 73.4,

71.4, 44.8, 44.0, 39.0, 30.0, 28.5, 23.7, 23.0, 22.7; IR (film) 2929, 2855, 1466, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{26}H_{29}NO]^+$: 371.2249, found 371.2241.

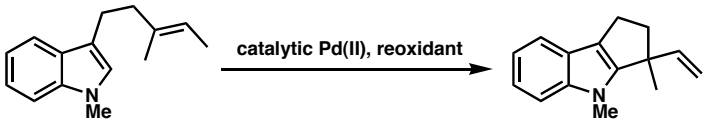
Figure 4.7.2 NOE measurements of annulated indole **297**:





Procedure to examine the kinetic isotope effect: A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by *t*-amyl alcohol (1.26 mL), AcOH (366 μl), and ethyl nicotinate (10.0 μl, 0.0732 mmol). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) or **298** (39.2 mg, 0.183 mmol) in *t*-amyl alcohol (200 μl), and tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2. Aliquots (approx. 100 μl) were taken hourly, filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Table 4.3.4 (reproduced) Comparison of methods for the oxidative annulation of **26**.



26 ***27***

entry	conditions[a]	ref	% yield[b]
1	$Pd(OAc)_2$, AgOAc, AcOH, air, 110 °C	14a	4
2	$Pd(OAc)_2$, $Cu(OAc)_2$, AcOH, air, 110 °C	14a	0
3	$Pd(OAc)_2$, $K_2S_2O_8$, AcOH, air, 110 °C	14a	0
4	$Pd(OAc)_2$, $NaNO_2$, AcOH, air, 110 °C	14a	0
5	$Pd(OAc)_2$, $Cu(OAc)_2$, Dioxane/AcOH (4:1), O_2, 100 °C	40a	13
6	$Pd(OAc)_2$, benzoquinone, $TsOH{\cdot}H_2O$, Toluene/AcOH (2:1), O_2, 23 °C	40b	0
7	$Pd(OAc)_2$, $H_6PMo_9V_3O_{40}$, acetylacetonate, NaOAc AcOH, O_2, 90 °C	40c	0
8	$Pd(OAc)_2$, cat. benzoquinone, TBHP $AcOH/Ac_2O$ (4:1), 50 °C	15	5
9	$Pd(OAc)_2$, ethyl nicotinate, t-amyl alcohol/AcOH (4:1), O_2, 80 °C		82

Entries 1-4. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (2.1 mg, 0.00917 mmol). The solid was dissolved in AcOH (3.67 mL), and to the solution was added oxidant (0.183 mmol), followed by indole **26** (20.0 μl, 0.0917 mmol) and tridecane (25.0 μl, 0.103 mmol, internal standard). The reaction was heated to 110 °C under air and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The GC yield is listed in the table.

Entry 5. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.8 mg, 0.00366 mmol). The solid was dissolved in dioxane (1.83 mL) and AcOH (458 μl), and to the solution was added $Cu(OAc)_2$ (66.5 mg, 0.366 mmol), followed by indole **26** (40.0 μl, 0.183 mmol) and tridecane (25.0 μl, 0.103 mmol, internal standard). The flask was evacuated and back-filled with O_2 (3 x, balloon), heated

to 100 °C under O_2, and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The GC yield is listed in the table.

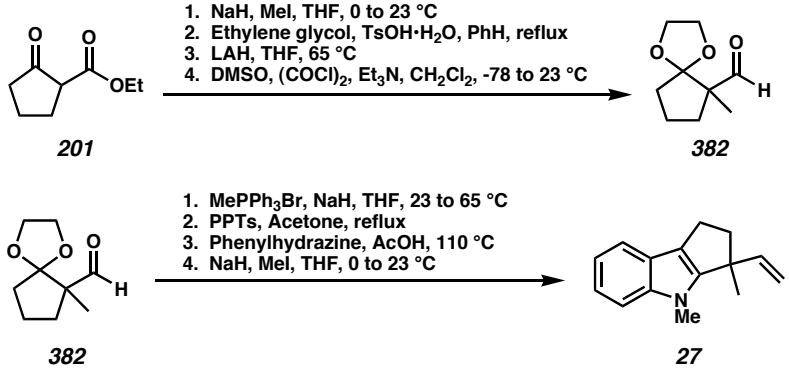
Entry 6. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.8 mg, 0.00366 mmol). The solid was dissolved in toluene (137 μl) and AcOH (275 μl), and to the solution was added benzoquinone (19.8 mg, 0.183 mmol), $TsOH•H_2O$ (17.4 mg, 0.0915 mmol), indole **26** (40.0 μl, 0.183 mmol), and tridecane (25.0 μl, 0.103 mmol, internal standard), sequentially. The reaction was stirred at room temperature. Complete decomposition was observed after 5 min.

Entry 7. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol) followed by AcOH (485 μl), NaOAc (0.8 mg, 0.00975 mmol), acetylacetonate (1.3 μl, 0.0122 mmol), and $H_6PMo_9V_3O_{40}$ (5.5 mg), sequentially. The flask was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon) for 10 min. A solution of indole **26** (40.0 μl, 0.183 mmol) in AcOH (125 μl), and then tridecane (25.0 μl, 0.103 mmol, internal standard) were then added via syringe, and the reaction was stirred under O_2. Aliquots (approx. 100 μl) were taken at 5h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC.

Entry 8. A flame-dried 25 mL schlenk flask equipped with magnetic stir bar was charged with $Pd(OAc)_2$ (0.3 mg, 0.00138 mmol). The solid was dissolved in Ac_2O (91.7 μl) and AcOH (275 μl), and to the solution was added benzoquinone (1.5 mg, 0.0138

mmol), TBHP (50 μl, 70% in H_2O, 0.358 mmol), indole **26** (60.0 μl, 0.275 mmol), and tridecane (25.0 μl, 0.103 mmol, internal standard), sequentially. The flask was heated to 50 °C and allowed to stir. Aliquots (approx. 100 μl) were taken at 5 h and at 24 h, partitioned between H_2O and EtOAc, and the organic phase was filtered through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by GC. The GC yield is listed in the table.

4.7.4 Independent Synthesis



Independent synthesis of annulated indole 27. To a solution of ethyl 2-oxocyclopentanecarboxylate (500 μl, 3.37 mmol) in THF (13.5 mL) at 0 °C was added NaH (162 mg, 60% dispersion in mineral oil, 4.04 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (273 μL, 4.38 mmol), and allowed to warm to 23 °C. After 5 h, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (50 mL), and extracted with ether (2 x 75 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide the ketoester[76] (491 mg, 85% yield, R_F = 0.45 in 4:1 hexanes/EtOAc) as a clear oil.

To a solution of the ketoester (491 mg, 2.88 mmol) in benzene (8 mL) at 23 °C was added ethylene glycol (321 μl, 5.76 mmol) and TsOH•H_2O (54.8 mg, 0.288 mmol). The reaction mixture was heated to reflux with azeotropic removal of water. After stirring 10 h, the reaction was cooled to room temperature and diluted with Et_2O (75 mL). The solution was washed sequentially with water, saturated $NaHCO_3$, and brine (50 mL each). It was dried over $MgSO_4$, and concentrated to an oil. Purification of the residue

by flash chromatography (6:1 hexanes/EtOAc eluent) afforded the ketal[77] (593 mg, 96% yield, R_F = 0.23 in 4:1 hexanes/Et_2O) as a colorless oil.

To a stirring suspension of LAH (210 mg, 5.54 mmol) in THF (3.5 mL) at 0 °C was added a solution of the ketal (593 mg, 2.77 mmol) in THF (2.5 mL) via cannula. The cold bath was removed, and the reaction mixture was heated to 65 °C and stirred 1 h. The reaction was then cooled to 0 °C, and to the mixture was added slowly 210 μl water, 210 μl NaOH (15% aq. solution), and 630 μl water, sequentially. Et_2O (50 mL) was added, and the heterogeneous mixture was stirred for 30 min at 23 °C, at which point a white precipitate had formed. The mixture was filtered through a pad of celite (Et_2O wash), and the filtrate was concentrated to an oil. The resulting alcohol was used in the next reaction without further purification (R_F = 0.28 in 2:1 hexanes/EtOAc).

To a solution of DMSO (325 μl, 4.58 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added oxalyl chloride (191 μl, 2.19 mmol) dropwise. The reaction mixture was stirred at –78 °C for 45 min, and then crude alcohol (342 mg, 1.99 mmol) in CH_2Cl_2 (2 mL) was added. After stirring for 1.5 h, triethylamine (1.39 mL, 9.95 mmol) was added, and the reaction was allowed to gradually warm to 23 °C over 2 h. The mixture was then diluted with CH_2Cl_2 (40 mL) and quenched with saturated NH_4Cl (40 mL). The organic layer was separated and washed with water (30 mL) and brine (30 mL), sequentially. The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 40 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) provided aldehyde **382** (300 mg, 64% yield over 2 steps, R_F = 0.58 in 2:1 hexanes/EtOAc) as a clear oil.

To a solution of NaH (141 mg, 60% dispersion in mineral oil, 3.52 mmol) in THF (9 mL) at 23 °C was added (methyl)triphenylphosphonium bromide (943 mg, 2.64 mmol). The heterogeneous mixture was stirred vigorously for 15 min, and then a solution of aldehyde **382** (300 mg, 1.76 mmol) in THF (2.7 mL) was added dropwise via cannula. The reaction mixture was heated to 65 °C and stirred 8 h. The reaction was then cooled to 0 °C, quenched with saturated NH_4Cl (10 mL), and partitioned between Et_2O (50 mL) and saturated NH_4Cl (35 mL). The aqueous phase was extracted with Et_2O (1 x 40 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (14:1 hexanes/EtOAc eluent) afforded the olefin (134 mg, 45% yield, R_F = 0.49 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the olefin (134 mg, 0.796 mmol) in wet acetone (7.96 mL, 5% H_2O) at 23 °C was added pyridinium *p*-toluenesulfonate (60.1 mg, 0.239 mmol). The solution was heated to 60 °C and stirred 10 h. Acetone was then removed in vacuo, and the residue was partitioned between Et_2O (35 mL) and saturated $NaHCO_3$ (30 mL). The organic phase was washed with brine (25 mL), dried over $MgSO_4$, and concentrated to an oil, which was used without further purification (R_F = 0.48 in 9:1 hexanes/EtOAc).

Phenylhydrazine (78.3 μl in 0.796 mmol) was dissolved in AcOH (174 μl) at 23 °C, and the solution was heated to 110 °C. A solution of the crude ketone in AcOH (100 μl) was added dropwise, and the resulting mixture was stirred at 110 °C for 72 h. The dark mixture was cooled to 23 °C and diluted with Et_2O. The solution was then partitioned between Et_2O and 5% saturated $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The organic phases were combined, washed with brine, dried over

$MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 to 2:1 hexanes/CH_2Cl_2 eluent) afforded the annulated indole (56.8 mg, 36% yield over 2 steps, R_F = 0.66 in 1:1 hexanes/CH_2Cl_2) as a pink oil.

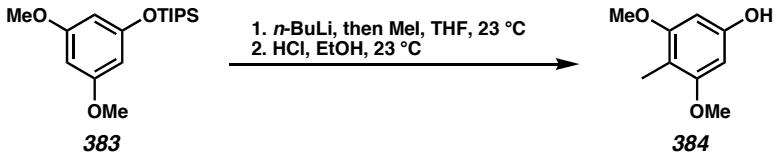
To a solution of the indole (17.9 mg, 0.0907 mmol) in THF (364 μl) at 0 °C was added NaH (7.2 mg, 60% dispersion in mineral oil, 0.181 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and 1 h at 23 °C. The mixture was then cooled to 0 °C, treated with iodomethane (8.5 μl, 0.136 mmol), and allowed to warm to 23 °C. After 15 min, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (15 mL), and extracted with ether (2 x 20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to provide the methyl indole (5.6 mg, 29% yield, R_F = 0.48 in 4:1 hexanes/CH_2Cl_2) as a clear oil. This compound matched the product of Table 4.3.3, entry 1 in both TLC and ^{1}H NMR .

4.8 Experimental Section for the Synthesis of Benzofurans and Dihydrobenzofurans

4.8.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an argon or nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, potassium permanganate, and anisaldehyde staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. Preparative HPLC was performed on a Waters HPLC with an Agilent ZORBAX S1L 4.6 x 250 mm, 5 μm column utilizing a flow rate of 1.5 mL/min and a ramp of 0.11% B/min (A eluent = hexanes, B eluent = EtOAc) with visualization at 270 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass were obtained from the California Institute of Technology Mass Spectral Facility. $Pd(PPh_3)_4$ and $Pd(OAc)_2$ were purchased from Strem Chemicals, Inc., Newburyport, MA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

4.8.2 Preparative Procedures



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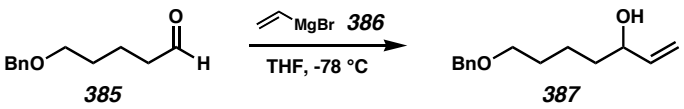
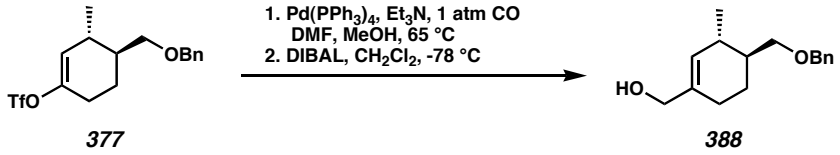
Phenol 384. To a solution of (3,5-dimethoxyphenoxy)triisopropylsilane[78] (1.36 g, 4.54 mmol) in THF (20.0 mL) was added *n*-BuLi (2.00 mL, 2.50 M in hexanes, 1.10 equiv) dropwise at 23 °C. The resulting mixture was stirred at 23 °C for 1 h and MeI (0.570 mL, 2.00 equiv) was added dropwise. After the addition was complete, the mixture was stirred for an additional 30 min and quenched with saturated aq. NH_4Cl. The mixture was extracted with Et_2O, dried ($MgSO_4$), evaporated, and purified by flash chromatography using 50:1 hexanes/EtOAc to afford (3,5-dimethoxy-4-methyl-phenoxy)triisopropylsilane (1.33 g, 93% yield, R_F = 0.30 in 50:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (s, 2H), 3.76 (s, 6H), 2.01 (s, 3H), 1.22 (m, 3H), 1.12 (d, J = 6.6 Hz, 18H). To a solution of (3,5-dimethoxy-4-methylphenoxy)triisopropylsilane (1.32 g, 4.20 mmol) in 95% EtOH (20.0 mL) was added conc. HCl (1.70 mL). The mixture was stirred at 23 °C for 20 h, concentrated, and extracted with EtOAc. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash chromatography using 2:1 hexanes/EtOAc to afford 3,5-dimethoxy-4-methylphenol (706 mg, 100% yield, R_F = 0.28 in 2:1 hexanes/EtOAc) as a white solid: mp 149-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 2H), 4.96 (br s, 1H), 3.77 (s, 6H), 2.00 (s, 3H).

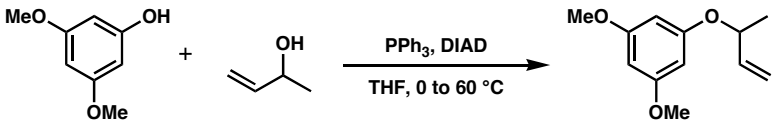


Alcohol 387. To a solution of 5-benzyloxy-1-pentanal[79] (1.65 g, 8.58 mmol) in THF (20.0 mL) at –78 °C was added vinyl magnesium bromide (9.50 mL, 1.00 M in THF, 1.10 equiv) dropwise. After the addition was complete, the reaction was stirred at –78 °C for an additional 30 min. The reaction mixture was quenched with saturated aq. NH_4Cl, extracted with Et_2O, dried ($MgSO_4$), concentrated, and purified by flash chromatography using 3:1 hexanes/EtOAc to afford the alcohol (1.17 g, 62% yield, R_F = 0.27 in 3:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 5.91 (m, 1H), 5.26 (dt, *J* = 1.5, 17.4 Hz, 1H), 5.14 (dt, *J* = 1.5, 10.2, 1H), 4.54 (s, 2H), 4.14 (q, *J* = 6.0 Hz, 1H), 3.52 (t, *J* = 6.6 Hz, 2H), 1.75-1.40 (m, 6H).



Alcohol 388. A flame-dried 25 mL round-bottom flask was sequentially charged with $Pd(PPh_3)_4$ (66.0 mg, 5 mol %), *trans*-4-benzyloxymethyl-3-methylcyclohex-1-enyl triflate (**377**, 400 mg, 1.15 mmol), DMF (10.0 mL), MeOH (2.50 mL), and Et_3N (320 μl, 2.00 equiv). The flask was sealed with a septum and flushed with CO. The mixture was stirred under CO (balloon) at 65 °C for 12 h. The reaction mixture was passed through a plug of celite (0.6 × 5 cm), diluted with ether, and washed with saturated aq. NH_4Cl. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash chromatography using 12:1 hexanes/EtOAc to afford *trans*-4-benzyloxymethyl-3-methyl-cyclohex-1-enecarboxylic acid methyl ester (236 mg, 75% yield, R_F = 0.21 in 12:1 hexanes/EtOAc)

as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.80 (br s, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 3.77 (s, 3H), 3.55 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.40 (dd, *J* = 9.0, 6.6 Hz, 1H), 2.40 (m, 1H), 2.22 (m, 2H), 1.98 (m, 1H), 1.55 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 3H). To a solution of *trans*-4-benzyloxymethyl-3-methyl-cyclohex-1-enecarboxylic acid methyl ester (236 mg, 0.86 mmol) in CH_2Cl_2 (5.00 mL) under N_2 at –78 °C was added DIBAL (353 μl, 2.30 equiv) dropwise. The reaction mixture was stirred at –78 °C for 30 min, quenched with 10% aq. NaOH (2.00 mL), and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), evaporated, and purified by flash chromatography using 2:1 hexanes/EtOAc to afford *trans*-(4-benzyloxymethyl-3-methylcyclohex-1-enyl)methanol (158 mg, 75% yield, R_F = 0.28 in 2:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.50 (br s, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.03 (s, 2H), 3.58 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.39 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.15-1.95 (m, 4H), 1.46 (m, 2H), 1.42 (br s, 1H), 1.06 (d, *J* = 7.2 Hz, 3H).



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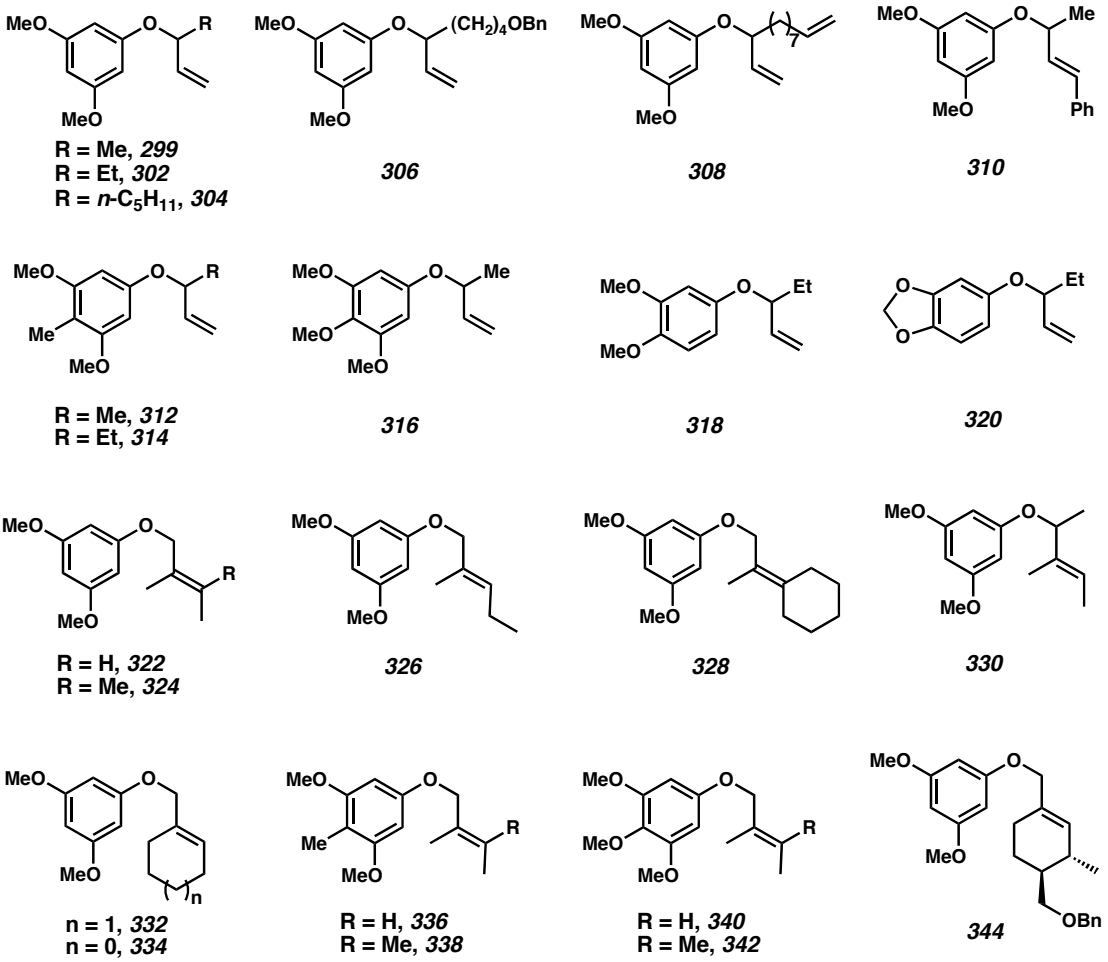
Representative procedure for the preparation of starting substrates. To a 25 mL flame-dried round bottom flask were added 3,5-dimethoxyphenol (308 mg, 2.00 mmol), triphenylphosphine (788 mg, 3.00 mmol), 3-buten-2-ol (216 mg, 3.00 mmol), and THF (10.0 mL). The mixture was stirred until the solids were completely dissolved, and diisopropyl azodicarboxylate (DIAD, 607 mg, 3.00 mmol) was added dropwise at 0 °C. The resulting yellow solution was heated at 60 °C. After the reaction was complete

judged by TLC analysis, the reaction mixture was concentrated in vacuo, triturated with hexanes/EtOAc (20:1), and filtered. The filtrates were concentrated in vacuo, and the residue was purified using hexanes/EtOAc (20:1) by flash chromatography to afford 1,3-dimethoxy-5-(1-methylallyloxy)benzene (287 mg, 69% yield) as a colorless oil.

Substrates for Oxidative Heck Cyclizations



Ether 299. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to the desired product (69% yield, R_F = 0.20 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 1H), 5.90 (m, 1H), 5.30 (m, 1H), 5.20 (m, 1H), 4.80 (m, 1H), 3.79 (s, 6H), 1.46 (d, *J* = 6.3 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 161.6, 160.1, 139.3, 115.8, 95.0, 93.2, 74.8, 55.5, 21.5; IR (film) 2960, 2839, 1598, 1150 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{16}O_3]^+$: 208.1100, found 208.1107.

Ether 302. The compound was prepared using 3,5-dimethoxyphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (58% yield, R_F = 0.20 in 20:1 hexanes/EtOAc) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 2.1 Hz, 2H), 6.10 (t, *J* = 2.1 Hz, 1H), 5.87 (m, 1H), 5.26 (m, 2H), 4.52 (m, 1H), 3.79 (s, 6H), 1.79 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.3, 137.8, 116.6, 94.8, 93.0, 80.3, 55.3, 28.5, 9.7; IR (film) 2936, 1598, 1205, 1151 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1256.

Ether 304. The compound was prepared using 3,5-dimethoxyphenol and 1-octen-3-ol. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (58% yield, R_F = 0.21 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, *J* = 2.1 Hz, 2H), 6.05 (t, *J* = 2.1 Hz, 1H), 5.82 (m, 1H), 5.25 (d, *J* = 17.4 Hz, 1H), 5.19 (d, *J* = 10.5 Hz, 1H), 4.55 (q, *J* = 6.0 Hz, 1H), 3.73 (s, 6H), 1.82-1.58 (m, 2H), 1.50-1.23 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.5, 138.3, 116.5, 95.0, 93.2, 79.3, 55.5, 35.7, 31.9, 25.2, 22.8, 14.3; IR (film) 2932, 1596, 1465, 1152 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{16}H_{24}O_3]^+$: 264.1726, found 264.1731.

Ether 306. The compound was prepared using 3,5-dimethoxyphenol and 7-benzyloxy-1-hepten-3-ol. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford the desired product (48% yield, R_F = 0.25 in 6:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.09 (d, *J* = 1.8 Hz, 2H), 6.05 (t, *J* = 1.8 Hz, 1H), 5.82 (m, 1H), 5.21 (m, 2H), 4.56 (m, 1H), 4.50 (s, 2H), 3.75 (s, 6H), 3.48 (m, 2H), 1.82-1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 160.2, 139.0, 138.0, 128.4, 127.7, 127.5, 116.5, 94.8, 93.0, 78.9, 72.9, 70.2, 55.3, 35.4, 29.6, 22.1; IR (film) 2932, 1595, 1205, 1152 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{22}H_{28}O_4]^+$: 356.1988, found 356.1995.

Ether 308. The compound was prepared using 3,5-dimethoxyphenol and 1,11-dodecadien-3-ol.[80] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (50% yield, R_F = 0.27 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10-6.05 (m, 3H), 5.86-5.76 (m, 2H), 5.28-5.18 (m, 2H), 5.03-4.91 (m, 2H), 4.55 (q, *J* = 6.6 Hz, 1H), 3.75 (s, 6H), 2.10-2.00 (m, 2H), 1.82-1.54 (m, 2H), 1.50-1.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.5, 139.4, 138.3, 116.5, 114.4, 95.0, 93.1, 79.3, 55.5, 35.8, 34.0, 29.6, 29.4, 29.3, 29.1, 25.5; IR (film) 2932, 2855, 1560, 1157 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{20}H_{30}O_3]^+$: 318.2195, found 318.2209.

Ether 310. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-4-phenyl-3-buten-2-ol.[81] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (58% yield, R_F = 0.20 in 20:1 hexanes/EtOAc) as a pale yellow

oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 5H), 6.65 (d, *J* = 16.5 Hz, 1H), 6.30 (dd, *J* = 6.3, 16.5 Hz, 1H), 6.23-6.10 (m, 3H), 4.98 (m, 1H), 3.79 (s, 6H), 1.56 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 159.9, 136.5, 130.7, 130.6, 128.5, 127.7, 126.5, 94.9, 93.2, 74.6, 55.3, 21.7; IR (film) 2980, 2836, 1595, 1190, 1148 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{18}H_{20}O_3]^+$: 284.1413, found 284.1424.

Ether 312. The compound was prepared using 3,5-dimethoxy-4-methylphenol and 3-buten-2-ol. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (41% yield, R_F = 0.25 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (s, 2H), 5.93 (m, 1H), 5.29 (d, *J* = 17.4 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.78 (quintet, *J* = 6.3 Hz, 1H), 3.78 (s, 6H), 2.01 (s, 3H), 1.44 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.4, 148.9, 139.8, 115.7, 93.0, 75.2, 55.9, 21.6, 7.9; IR (film) 2922, 1560, 1459, 1143 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1246.

Ether 314. The compound was prepared using 3,5-dimethoxy-4-methylphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (34% yield, R_F = 0.20 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 2H), 5.90 (m, 1H), 5.32 (d, *J* = 18.9 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.53 (m, 1H), 3.82 (s, 6H), 2.04 (s, 3H), 1.80 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 157.7, 138.3, 116.5, 106.8, 92.7, 80.6, 55.7, 28.6, 9.7, 7.7; IR (film) 2940, 1605, 1454, 1133 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1413.

Ether 316. The compound was prepared using 3,4,5-trimethoxyphenol and 3-buten-2-ol. The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford the desired product (51% yield, R_F = 0.25 in 8:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 2H), 5.89 (m, 1H), 5.26 (dt, *J* = 1.2, 17.1 Hz, 1H), 5.16 (dt, *J* = 1.2, 10.5 Hz, 1H), 4.71 (quintet, *J* = 6.3 Hz, 1H), 3.79 (s, 6H), 3.76 (s, 3H), 1.40 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.8, 139.6, 132.2, 115.8, 94.1, 75.5, 61.2, 56.2, 21.5; IR (film) 2940, 1594, 1234, 1135 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{18}O_4]^+$: 238.1205, found 238.1205.

Ether 318. The compound was prepared using 3,4-dimethoxyphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford the desired product (34% yield, R_F = 0.27 in 6:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, J = 9.0 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, 1H), 6.48 (dd, *J* = 3.0, 9.0 Hz, 1H), 5.90 (m, 1H), 5.25 (m, 2H), 4.48 (q, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 1.80 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 138.2, 116.6, 111.7, 106.2, 102.3, 101.2, 81.2, 56.4, 55.8, 28.5, 9.7; IR (film) 2965, 1596, 1509, 1229 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1255.

Ether 320. The compound was prepared using 3,4-methylenedioxyphenol and 1-penten-3-ol. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (56% yield, R_F = 0.22 in 25:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.39 (dd, *J*

= 2.1, 8.4 Hz, 1H), 5.93 (s, 2H), 5.83 (m, 1H), 5.25 (m, 2H), 4.40 (q, *J* = 7.2 Hz, 1H), 1.77 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 148.0, 141.6, 138.0, 116.6, 108.2, 107.9, 101.1, 99.6, 81.9, 28.5, 9.7; IR (film) 2969, 2879, 1630, 1486, 1189 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{14}O_3]^+$: 206.0943, found 206.0941.

Ether 322. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-2-methyl-2-buten-1-ol.[82] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (77% yield, R_F = 0.30 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, *J* = 1.8 Hz, 2H), 6.08 (t, *J* = 1.8 Hz, 1H), 5.63 (q, *J* = 6.6 Hz, 1H), 4.34 (s, 2H), 3.76 (s, 6H), 2.17 (s, 3H), 1.73 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.9, 131.7, 123.6, 93.7, 93.0, 74.2, 55.3, 13.7, 13.3; IR (film) 2924, 1594, 1207, 1153 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1248.

Ether 324. The compound was prepared using 3,5-dimethoxyphenol and 2,3-dimethyl-2-buten-1-ol.[83] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (44% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a colorless oil. Also the compound was prepared as follows: To a flame-dried vial were added 3,5-dimethoxyphenol (308 mg, 2.00 mmol), 1-bromo-2,3-dimethyl-2-butene[84] (489 mg, 3.00 mmol), Cs_2CO_3 (978 mg, 3.00 mmol), and acetone (6.00 mL). The mixture was sealed and heated at 75 °C for 10 h. The mixture was cooled, filtered, concentrated, and chromatographed using 20:1 hexanes/EtOAc to afford the desired product (68% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, *J* = 2.4 Hz, 2H), 6.12 (t, *J* = 2.4

Hz, 1H), 4.49 (s, 2H), 3.80 (s, 6H), 1.82 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.2, 131.3, 123.8, 93.5, 93.0, 69.3, 55.3, 21.0, 20.3, 16.8; IR (film) 2997, 2935, 1601, 1474, 1151 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1405.

Ether 326. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-2-methyl-2-peten-1-ol.[85] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (67% yield, R_F = 0.20 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.59 (t, *J* = 6.6 Hz, 1H), 4.38 (s, 2H), 3.80 (s, 6H), 2.13 (m, 2H), 1.77 (s, 3H), 1.03 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.0, 131.1, 130.3, 93.7, 93.0, 74.3, 55.3, 21.0, 13.9, 13.8; IR (film) 2953, 1597, 1461, 1199, 1150 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1415.

Ether 328. The compound was prepared using 3,5-dimethoxyphenol and 2-cyclohexylidene-1-propanol.[86] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (66% yield, R_F = 0.21 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 4.50 (s, 2H), 3.80 (s, 6H), 2.29 (m, 4H), 1.84 (s, 3H), 1.60 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.2, 139.7, 120.4, 93.6, 93.0, 68.8, 55.3, 30.9, 30.5, 28.3, 27.8, 26.8, 16.4; IR (film) 2917, 1592, 1199, 1150 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{17}H_{24}O_3]^+$: 276.1726, found 276.1717.

Ether 330. The compound was prepared using 3,5-dimethoxyphenol and (*E*)-3-methyl-3-penten-2-ol.[87] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (43% yield, R_F = 0.21 in 25:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (d, *J* = 2.1 Hz, 1H), 6.09 (t, *J* = 2.1 Hz, 1H), 5.59 (m, 1H), 4.66 (q, *J* = 6.6 Hz, 1H), 3.78 (s, 6H), 1.65 (m, 6H), 1.43 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 160.1, 136.3, 121.0, 94.7, 92.8, 79.1, 55.3, 20.5, 13.1, 11.0; IR (film) 2935, 1599, 1205, 1153 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1418.

Ether 332. The compound was prepared using 3,5-dimethoxyphenol and 1-cyclohexene-1-methanol.[88] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (73% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.85 (br s, 1H), 4.35 (s, 2H), 3.80 (s, 6H), 2.12 (m, 4H), 1.80-1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 161.0, 133.8, 125.9, 93.7, 93.0, 72.9, 55.3, 25.9, 25.1, 22.5, 22.3; IR (film) 2931, 2838, 1600, 1152 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{20}O_3]^+$: 248.1413, found 248.1404.

Ether 334. The compound was prepared using 3,5-dimethoxyphenol and 1-cyclopentene-1-methanol.[89] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (67% yield, R_F = 0.28 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.79 (br s, 1H), 4.57 (s, 2H), 3.80 (s, 6H), 2.43 (m, 4H),

1.98 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 160.9, 140.4, 128.4, 93.6, 93.0, 67.2, 55.3, 32.9, 32.5, 23.3; IR (film) 2952, 1599, 1205, 1152 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1246.

Ether 336. The compound was prepared using 3,5-dimethoxy-4-methylphenol and (*E*)-2-methyl-2-buten-1-ol.[82] The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (49% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (s, 2H), 5.70 (q, J = 6.6 Hz, 1H), 4.41 (s, 2H), 3.83 (s, 6H), 2.05 (s, 3H), 1.79 (s, 3H), 1.71 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 158.3, 132.0, 123.6, 106.7, 91.4, 74.4, 55.7, 13.7, 13.3, 7.7; IR (film) 2936, 1611, 1195, 1141 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_3]^+$: 236.1413, found 236.1421.

Ether 338. The compound was prepared using 3,5-dimethoxy-4-methylphenol and 2,3-dimethyl-2-buten-1-ol.[83] The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (52% yield, R_F = 0.26 in 25:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 2H), 4.53 (s, 2H), 3.84 (s, 6H), 2.06 (s, 3H), 1.84 (s, 6H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 158.6, 131.1, 124.0, 106.6, 91.3, 69.3, 55.7, 21.0, 20.3, 16.8, 7.7; IR (film) 2935, 1611, 1459, 1195, 1142 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{22}O_3]^+$: 250.1569, found 250.1571.

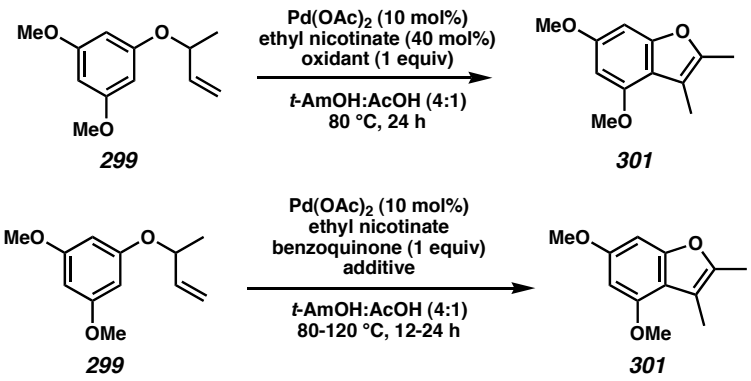
Ether 340. The compound was prepared using 3,4,5-trimethoxyphenol and (*E*)-2-methyl-2-buten-1-ol.[82] The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford the desired product (57% yield, R_F = 0.25 in 7:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 2H), 5.64 (q, *J* = 6.6 Hz, 1H), 4.34 (s, 2H), 3.83 (s, 6H), 3.78 (s, 3H), 2.16 (s, 3H), 1.74 (s, 3H), 1.67 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 15.6, 132.3, 131.8, 123.8, 92.5, 74.6, 61.0, 56.1, 13.7, 13.3; IR (film) 2938, 1593, 1506, 1225, 1130 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{20}O_4]^+$: 252.1362, found 252.1352.

Ether 342. To a flame-dried vial were added 3,4,5-trimethoxyphenol (368 mg, 2.00 mmol), 1-bromo-2,3-dimethyl-2-butene (489 mg, 3.00 mmol), Cs_2CO_3 (978 mg, 3.00 mmol), and acetone (6.00 mL). The mixture was sealed and heated at 75 °C for 10 h. The mixture was cooled, filtered, concentrated, and chromatographed using 5:1 hexanes/EtOAc to afford the desired product (65% yield, R_F = 0.30 in 5:1 hexanes/EtOAc) as a white solid: mp 60-61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 2H), 4.50 (s, 2H), 3.87 (s, 6H), 3.82 (s, 3H), 1.83 (s, 6H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.7, 132.2, 131.3, 123.8, 92.4, 69.5, 61.1, 56.1, 21.0, 20.3, 16.8; IR (film) 2936, 1593, 1505, 1226, 1129 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{15}H_{22}O_4]^+$: 266.1518, found 266.1518.

Ether 344. The compound was prepared using 3,5-dimethoxyphenol and *trans*-(4-benzyloxymethyl-3-methylcyclohex-1-enyl)methanol. The reaction mixture was chromatographed using 12:1 hexanes/EtOAc to afford the desired product (63% yield, R_F

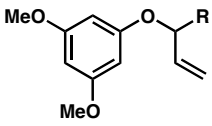
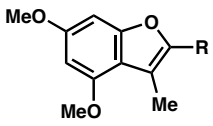
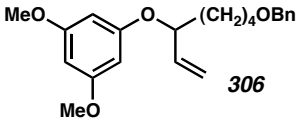
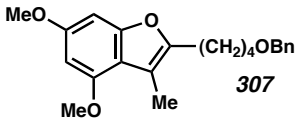
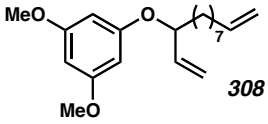
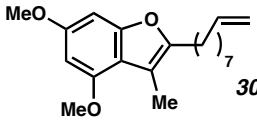
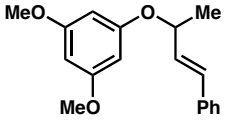
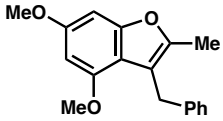
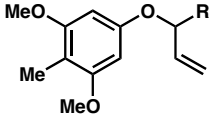
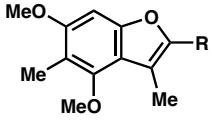
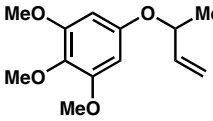
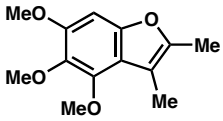
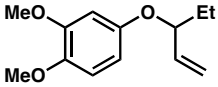
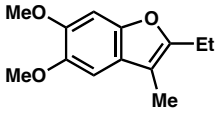
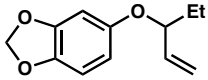
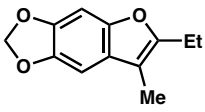
= 0.28 in 12:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.14 (d, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 1H), 5.63 (br s, 1H), 4.55 (m, 2H), 4.37 (s, 2H), 3.80 (s, 6H), 3.58 (m, 1H), 3.40 (m, 1H), 2.15-1.95 (m, 4H), 1.56 (m, 2H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 161.0, 138.8, 132.8, 131.2, 128.4, 127.5, 127.5, 93.7, 93.1, 73.3, 73.1, 72.5, 55.3, 40.9, 32.2, 24.9, 20.3, 15.3; IR (film) 2927, 2870, 1600, 1153 cm^{-1}; HRMS (FAB^{+}) *m/z* calc'd for $[C_{24}H_{30}O_4]^{+}$: 382.2144, found 382.2146.

4.8.3 Palladium-Catalyzed Benzofuran and Dihydrobenzofuran Synthesis



Representative procedure for optimization (Tables 4.4.1 and 4.4.2): A flame-dried 1-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (2.3 mg, 0.0100 mmol), followed by ethyl nicotinate (0-40 mol%), tridecane (12.0 μl, 0.049 mmol, internal standard), **299** (20.8 mg, 0.100 mmol), NaOAc (1 equiv or 20 mol%), and a mixture of *t*-amyl alcohol and acetic acid (1.0 mL, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then oxidant (1 equiv) was added. The reaction mixture was heated at 100 °C for 12 h. The reaction mixture was then cooled, filtered through a short plug of silica gel (Et_2O as eluent), and analyzed by GC.

Table 4.4.3 (reproduced) The palladium(II)-catalyzed oxidative benzofuran synthesis.[a]

entry	substrate	product	time (h)	% yield[b]
1	 R = Me ***299***	 R = Me ***301***	12	77
2	R = Et ***302***	R = Et ***303***	12	74
3	R = *n*-C_5H_{11} ***304***	R = *n*-C_5H_{11} ***305***	13	72
4	 ***306***	 ***307***	12	62
5	 ***308***	 ***309***	14	54
6	 ***310***	 ***311***	12	61
7	 R = Me ***312***	 R = Me ***313***	14	75
8	R = Et ***314***	R = Et ***315***	12	79
9	 ***316***	 ***317***	12	61
10	 ***318***	 ***319***	16	56[c]
11	 ***320***	 ***321***	16	52[c]

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. [c] Produced as a single regioisomer.

Representative procedure for the Pd-catalyzed synthesis of benzofurans: (Table 4.4.3): A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (11.3 mg, 0.0500 mmol), followed by ethyl nicotinate (13.8 μl, 0.100 mmol), **299** (104.1 mg, 0.500 mmol), NaOAc (8.2 mg, 0.100 mmol), and a mixture of *t*-amyl alcohol and acetic acid (5.00 mL, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then benzoquinone (54.1 mg, 0.500 mmol) was added. The reaction mixture

was heated at 100 °C for 12 h. The reaction mixture was then cooled, filtered through a short plug of silica gel (0.6 × 5 cm, Et_2O as eluent), evaporated, and purified by flash chromatography on a silica gel column.

Benzofuran 301. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (79 mg, 77% yield, R_F = 0.26 in 20:1 hexanes/EtOAc) as a white sold: mp 53-54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, *J* = 2.1 Hz, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 155.5, 154.4, 147.6, 113.2, 109.5, 93.5, 88.0, 55.7, 55.4, 11.4, 9.8; IR (film) 2917, 1602, 1427, 1108 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{14}O_3]^+$: 206.0943, found 206.0939.

Benzofuran 303. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (81 mg, 74% yield, R_F = 0.26 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (d, *J* = 2.1 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.71 (q, *J* = 7.5 Hz, 2H), 2.29 (s, 3H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 155.5, 154.5, 152.8, 113.2, 108.6, 93.5, 88.0, 55.7, 55.4, 19.3, 13.0, 9.6; IR (film) 2969, 1603, 1501, 1208, 1149 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1110.

Benzofuran 305. The reaction mixture was chromatographed using 25:1 hexanes/EtOAc to afford the desired product (95 mg, 72% yield, R_F = 0.30 in 25:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d, *J* = 2.1 Hz, 1H), 6.26 (d, *J* = 2.1

Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.63 (t, J = 7.2 Hz, 2H), 2.25 (s, 3H), 1.66 (quintet, J = 7.2 Hz, 2H), 1.31 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 155.8, 154.7, 152.0, 113.4, 109.5, 93.7, 88.2, 55.9, 55.6, 31.5, 28.4, 26.0, 22.7, 14.2, 9.9; IR (film) 2930, 1603, 1501, 1148, 1113 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{16}H_{22}O_3]^+$: 262.1569, found 262.1570.

Benzofuran 307. The reaction was carried out in 0.40 mmol scale and chromatographed using 10:1 hexanes/EtOAc to afford the desired product (88 mg, 62% yield, R_F = 0.32 in 10:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 6.60 (d, J = 1.8 Hz, 1H), 6.32 (d, J = 1.8 Hz, 1H), 4.55 (s, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.54 (t, J = 6.6 Hz, 3H), 2.73 (t, J = 6.6 Hz, 2H), 2.30 (s, 3H), 1.84-1.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 155.6, 154.5, 151.3, 138.7, 128.4, 127.7, 127.5, 113.2, 109.6, 93.6, 88.0, 73.0, 70.1, 55.7, 55.4, 29.2, 25.6, 25.2, 9.8; IR (film) 2939, 2860, 1602, 1500, 1202 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{22}H_{26}O_4]^+$: 354.1831, found 354.1824.

Benzofuran 309. The reaction mixture was chromatographed using 2:1 hexanes/$CHCl_3$ to afford the desired product (86 mg, 54% yield, R_F = 0.25 in 2:1 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d, J = 2.1 Hz, 1H), 6.26 (d, J = 2.1 Hz, 1H), 5.81 (m, 1H), 5.02-4.91 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 2.63 (t, J = 7.2 Hz, 2H), 2.24 (s, 3H), 2.04 (m, 2H), 1.65 (m, 2H), 1.32 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 155.8, 154.7, 151.9, 139.4, 114.4, 113.4, 109.5, 93.7, 88.2, 55.9, 55.6, 34.0, 29.5, 29.3, 29.1, 28.6, 26.1, 10.0; IR (film) 2927, 2854, 1602, 1148 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{20}H_{28}O_3]^+$: 316.2039, found 216.2040.

Benzofuran 311. The reaction mixture was chromatographed using 3:1 hexanes/$CHCl_3$ to afford the desired product (86 mg, 61% yield, R_F = 0.26 in 3:1 hexanes/$CHCl_3$) as a white solid: mp 72-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 6.60 (d, *J* = 2.1 Hz, 1H), 6.28 (d, *J* = 2.1 Hz, 1H), 4.09 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 155.7, 154.1, 148.9, 141.6, 128.3, 128.2, 125.7, 113.0, 112.6, 93.8, 88.0, 55.7, 55.2, 30.2, 11.9; IR (film) 2917, 1603, 1501, 1217, 1148 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{18}H_{18}O_3]^+$: 282.1256, found 282.1252.

Benzofuran 313. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (83 mg, 75% yield, R_F = 0.31 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.7, 151.7, 148.3, 116.2, 113.9, 108.4, 90.4, 62.0, 55.9, 11.5, 9.3, 8.6; IR (film) 2942, 1593, 1223, 1149 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1107.

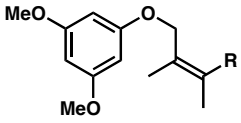
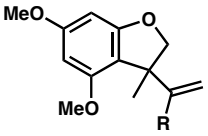
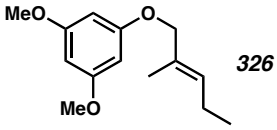
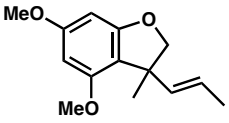
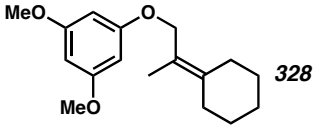
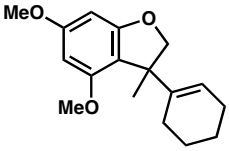
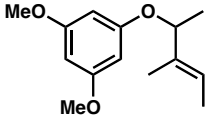
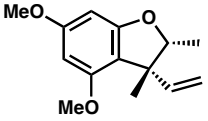
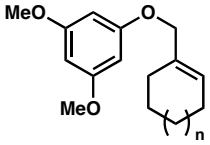
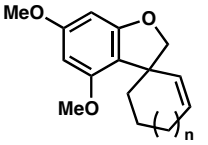
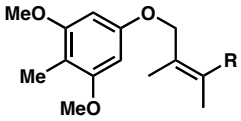
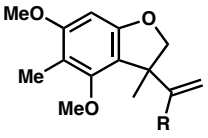
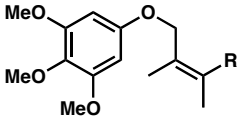
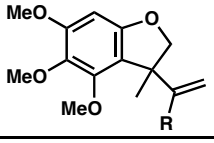
Benzofuran 315. The reaction mixture was chromatographed using 4:1 hexanes/$CHCl_3$ to afford the desired product (93 mg, 79% yield, R_F = 0.25 in 4:1 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.72 (q, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.7, 153.5, 151.9, 116.3, 113.9, 107.5, 90.5, 62.0, 55.9, 19.4, 12.9, 9.2, 8.6; IR (film) 2938, 1594, 1461, 1149 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1248.

Benzofuran 317. The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford the desired product (72 mg, 61% yield, R_F = 0.29 in 10:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H), 3.96 (s, 3H), 3.86 (s, 6H), 2.29 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 150.5, 148.8, 146.5, 138.2, 116.5, 109.3, 91.1, 61.8, 61.3, 56.3, 11.5, 9.3; IR (film) 2937, 1620, 1468, 1199 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_4]^+$: 236.1049, found 236.1051.

Benzofuran 319. The reaction mixture was chromatographed using 2:3 hexanes/$CHCl_3$ to afford the desired product (62 mg, 56% yield, R_F = 0.25 in 2:3 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.89 (s, 1H), 3.96 (s, 3H), 3.94 (s, 6H), 2.74 (q, *J* = 7.5 Hz, 2H), 2.16 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 148.1, 147.0, 146.0, 122.3, 108.7, 100.7, 95.3, 56.5, 56.3, 19.8, 12.9, 7.9; IR (film) 2938, 1621, 1489, 1212 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1103.

Benzofuran 321. The reaction mixture was chromatographed using 5:1 hexanes/$CHCl_3$ to afford the desired product (53 mg, 52% yield, R_F = 0.29 in 5:1 hexanes/$CHCl_3$) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.83 (s, 1H), 5.98 (s, 3H), 2.73 (q, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 148.6, 145.0, 143.8, 123.8, 109.0, 101.0, 97.6, 93.2, 19.8, 12.9, 7.9; IR (film) 2973, 1463, 1292, 1170 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{12}O_3]^+$: 204.0787, found 204.0795.

Table 4.4.4 (reproduced) The palladium(II)-catalyzed oxidative dihydrobenzofuran synthesis.

entry	substrate	product	time (h)	% yield[b]
1	 R = H ***322***	 R = H ***323***	16	74
2[c]	R = Me ***324***	R = Me ***325***	12	71
3	 ***326***	 ***327***	30	58[d]
4	 ***328***	 ***329***	28	55
5	 ***330***	 ***331***	15	74[e]
6	 n = 1 ***332***	 n = 1 ***333***	24	80
7	n = 0 ***334***	n = 0 ***335***	18	78
8	 R = H ***336***	 R = H ***337***	15	50
9	R = Me ***338***	R = Me ***339***	15	63
10	 R = H ***340***	 R = H ***341***	15	60
11	R = Me ***342***	R = Me ***343***	15	66

[a] 10 mol% $Pd(OAc)_2$, 20 mol% ethyl nicotinate, 20 mol% NaOAc, 1 equiv benzoquinone, 0.1 M substrate in *tert*-amyl alcohol/AcOH (4:1), 100 °C. [b] Isolated yield. c Performed with 5 mol% $Pd(OAc)_2$ and 10 mol% ethyl nicotinate. [d] An inseparable mixture of roughly 66% product (*E*/*Z* = 3:1) and 10% starting material was isolated after 18 h. This mixture was subjected to another reaction with 5 mol% $Pd(OAc)_2$, 10 mol% ethyl nicotinate, 20 mol% NaOAc, and 50 mol% benzoquinone for 12 h, after which only the *E* isomer was observed. The yield presented is the overall yield of isolated product. [e] A 2.3:1 mixture of diastereomers was isolated with the major isomer shown.

Representative procedure for the Pd-catalyzed synthesis of dihydrobenzofurans (Table 4.4.4): A flame-dried 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (11.3 mg, 0.0500 mmol), followed by ethyl nicotinate (13.8 μl, 0.100 mmol), **322** (111 mg, 0.500 mmol), NaOAc (8.2 mg, 0.100 mmol), and a mixture of *t*-amyl alcohol and acetic acid (5.00 mL, 4:1 v/v). The resulting mixture was stirred at 23 °C for 2 min, and then benzoquinone (54.1 mg, 0.500 mmol) was added. The reaction mixture was heated at 100 °C for 12 h. The reaction mixture was then cooled, filtered through a short plug of silica gel (0.6 × 5 cm, Et_2O as eluent), evaporated, and purified by flash chromatography on a silica gel column.

Dihydrobenzofuran 323. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (81 mg, 74% yield, R_F = 0.24 in 20:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17-6.05 (m, 3H), 5.09-4.98 (m, 2H), 4.44 (d, *J* = 9.0 Hz, 1H), 4.22 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 6H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.6, 157.4, 142.9, 112.1, 91.7, 88.6, 83.6, 55.5, 55.3, 48.1, 23.2; IR (film) 2961, 1601, 1500, 1151, 1098 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1100, found 220.1098.

Dihydrobenzofuran 325. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc and further purified by preparative HPLC to afford the desired product (83 mg, 71% yield, R_F = 0.26 in 20:1 hexanes/EtOAc) as a colorless oil: . ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, *J* = 2.1 Hz, 1H), 6.04 (d, *J* = 2.1 Hz, 1H), 4.88 (s, 1H), 4.81 (s, 1H), 4.43 (d, *J* = 8.7 Hz, 1H), 4.18 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 1.74 (s,

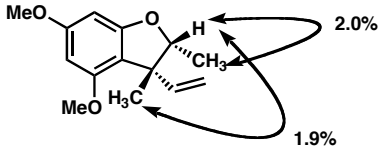
3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.8, 157.3, 148.2, 112.5, 110.3, 91.5, 88.4, 83.6, 55.5, 55.3, 50.6, 23.4, 20.2; IR (film) 2964, 1601, 1500, 1201, 1151 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1267.

Dihydrobenzofuran 327. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired product (68 mg, 58% yield, R_F = 0.25 in 20:1 hexanes/EtOAc) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (d, *J* = 2.1 Hz, 1H), 6.02 (d, *J* = 2.1 Hz, 1H), 5.69 (dq, *J* = 1.8, 15.3 Hz, 1H), 5.36 (dq, *J* = 6.3, 15.3 Hz, 1H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.16 (d, *J* = 8.4 Hz, 1H), 3.76 (s, 6H), 1.67 (dd, *J* = 1.5, 6.3 Hz, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.7, 157.6, 136.1, 123.0, 113.0, 91.9, 88.8, 84.4, 55.7, 55.5, 47.6, 24.1, 18.2; IR (film) 2960, 1604, 1499, 1150, 1095 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1245.

Dihydrobenzofuran 329. The reaction mixture was chromatographed using 30:1 hexanes/EtOAc and further purified by preparative HPLC to afford the desired product (60 mg, 55% yield, R_F = 0.22 in 30:1 hexanes/EtOAc) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, *J* = 2.1 Hz, 1H), 6.04 (d, *J* = 2.1 Hz, 1H), 5.48 (m, 1H), 4.38 (d, *J* = 8.7 Hz, 1H), 4.14 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.08-1.55 (m, 8H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.6, 157.3, 139.8, 120.6, 112.9, 91.5, 88.4, 83.8, 55.5, 55.3, 50.6, 25.6, 25.5, 23.3, 23.1, 22.4; IR (film) 2931, 1622, 1150, 1097 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{17}H_{22}O_3]^+$: 274.1569, found 274.1580.

Dihydrobenzofuran 331. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford the desired products (81 mg, 74% yield, R_F = 0.28 in 20:1 hexanes/EtOAc) in a 2.3:1 ratio as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) major isomer: δ 6.07 (m, 3H), 5.80 (dd, *J* = 10.5, 17.4 Hz, 1H), 5.12 (m, 2H), 4.42 (q, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 1.52 (s, 3H), 1.34 (d, *J* = 6.6 Hz, 3H); minor isomer: δ 4.80 (dd, *J* = 1.5, 17.4 Hz, 2H), 4.55 (q, *J* = 6.6 Hz, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.27 (s, 3H), other peaks overlapped with peaks of major isomer; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 161.6, 161.0, 160.5, 157.7, 157.0, 143.2, 139.5, 114.2, 112.7, 112.3, 91.7, 91.7, 90.1, 88.6, 88.5, 88.5, 87.6, 55.5, 55.3, 55.3, 50.2, 49.9, 22.1, 17.5, 14.9, 14.0; IR (film) 2970, 1606, 1500, 1148 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1258.

Figure 4.8.1 NOE measurements of dihydrobenzofuran **331**.



Dihydrobenzofuran 333. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc and recrystallized from hexanes to afford the desired product (99 mg, 80% yield, R_F = 0.30 in 20:1 hexanes/EtOAc) as a white solid: mp 80-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (d, *J* = 2.1 Hz, 1H), 6.05 (d, *J* = 2.1 Hz, 1H), 5.85 (m, 1H), 5.70 (m, 1H), 4.36 (d, *J* = 8.7 Hz, 1H), 4.21 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.20-2.00 (m, 3H), 1.83 (m, 2H), 1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.7, 157.4, 131.2, 127.7, 113.5, 91.7, 88.5, 82.6, 55.5, 55.4, 46.5, 32.5, 24.4, 20.1; IR

(film) 2934, 1603, 1200, 1146 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{15}H_{18}O_3]^+$: 246.1256, found 246.1252.

Dihydrobenzofuran 335. The reaction mixture was chromatographed using 20:1 hexanes/EtOAc and recrystallized from hexanes to afford the desired product (91 mg, 78% yield, R_F = 0.28 in 20:1 hexanes/EtOAc) as a white solid: mp 49-50 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, *J* = 2.1 Hz, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 5.83 (m, 1H), 5.67 (m, 1H), 4.35 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.65-2.55 (m, 1H), 2.50-2.35 (m, 2H), 1.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.7, 157.4, 134.4, 130.9, 112.3, 91.7, 88.4, 83.2, 55.6, 55.4, 45.0, 36.0, 32.0; IR (film) 2938, 1602, 1145, 1095 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{16}O_3]^+$: 232.1100, found 232.1091.

Dihydrobenzofuran 337. The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford the desired product (59 mg, 50% yield, R_F = 0.20 in 40:1 hexanes/EtOAc) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 1H), 6.15 (dd, *J* = 10.5, 16.8 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 5.09 (d, *J* = 16.8 Hz, 1H), 4.38 (d, *J* = 8.4 Hz, 1H), 4.19 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.09 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 159.1, 156.1, 143.5, 117.2, 112.4, 111.7, 90.3, 83.5, 61.3, 55.8, 48.4, 23.0, 8.8; IR (film) 2939, 1614, 1471, 1134, 1072 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{14}H_{18}O_3]^+$: 234.1256, found 234.1250.

Dihydrobenzofuran 339. The reaction mixture was chromatographed using 1:1 hexanes/$CHCl_3$ to afford the desired product (78 mg, 63% yield, R_F = 0.25 in 1:1

hexanes/$CHCl_3$) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (s, 1H), 4.92 (s, 1H), 4.88 (s, 1H), 4.43 (d, *J* = 8.4 Hz, 1H), 4.16 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.09 (s, 3H), 1.75 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 155.9, 148.9, 117.2, 111.5, 110.5, 90.0, 83.3, 60.7, 55.7, 50.8, 23.8, 20.0, 8.8; IR (film) 2940, 1614, 1471, 1130 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{20}O_3]^+$: 248.1413, found 248.1416.

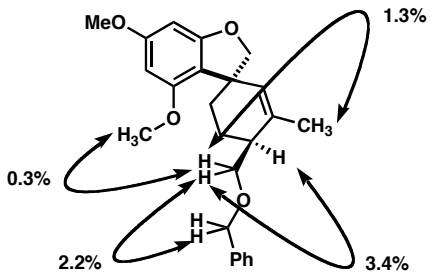
Dihydrobenzofuran 341. The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford the desired product (72 mg, 60% yield, R_F = 0.30 in 8:1 hexanes/EtOAc) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.13 (dd, *J* = 10.5, 17.4 Hz, 1H), 5.12 (dd, *J* = 0.9, 10.5 Hz, 1H), 5.05 (dd, *J* = 0.9, 17.4 Hz, 1H), 4.39 (d, *J* = 8.4 Hz, 1H), 4.19 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 154.3, 150.7, 143.1, 136.2, 116.9, 112.4, 90.6, 83.5, 61.0, 60.9, 56.1, 48.8, 23.4; IR (film) 2937, 1614, 1472, 1197, 1105 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{14}H_{18}O_4]^+$: 250.1205, found 250.1207.

Dihydrobenzofuran 343. The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford the desired product (87 mg, 66% yield, R_F = 0.30 in 8:1 hexanes/EtOAc) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.86 (s, 1H), 4.78 (s, 1H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.11 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 1.70 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 154.3, 150.6, 148.5, 136.1, 117.1, 110.7, 90.5, 83.5, 61.2, 60.9, 56.4, 51.6, 24.1, 20.4; IR

(film) 2939, 1614, 1472, 1199, 1103 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{15}H_{20}O_4]^+$: 264.1362, found 264.1364.

Dihydrobenzofuran 346. The reaction was carried out in a 0.34 mmol scale, and the crude material was chromatographed using 12:1 hexanes/EtOAc and recrystallized from hexanes/EtOAc (to remove a small amount of the starting material) to afford the desired product (78 mg, 60% yield, R_F = 0.29 in 12:1 hexanes/EtOAc) as a white solid: mp 99-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 6.06 (d, *J* = 2.1 Hz, 1H), 5.99 (d, *J* = 2.1 Hz, 1H), 5.43 (s, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.58 (m, 2H), 2.35 (m, 1H), 2.09 (m, 2H), 1.78 (s, 3H), 1.60 (m, 2H); ^{1}H NMR (300 MHz, C_6D_6) δ 7.34-7.30 (m, 2H), 7.20-7.04 (m, 3H), 6.26 (d, *J* = 2.1 Hz, 1H), 6.06 (d, *J* = 2.1 Hz, 1H), 5.45 (q, *J* = 1.2 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 4.14 (dd, *J* = 1.2, 9.0 Hz, 1H), 3.60 (m, 2H), 3.31 (s, 3H), 3.19 (s, 3H), 2.34-2.22 (m, 2H), 2.16-2.06 (m, 1H), 1.68-1.60 (m, 4H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.7, 157.2, 138.7, 134.4, 128.4, 128.1, 127.6, 127.5, 113.5, 91.7, 88.5, 83.1, 73.0, 70.4, 55.5, 55.2, 46.8, 38.6, 27.7, 23.0, 22.5; IR (film) 2937, 1605, 1499, 1147, 1098 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{24}H_{28}O_4]^+$: 380.1988, found 380.1981.

Figure 4.8.2 NOE measurements of dihydrobenzofuran **346 (**in C_6D_6).



4.9 Notes and References

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(26) The conditions for initial investigation were derived from the alcohol oxidation work of Uemura, similar to how we began the heterocyclization studies. See: Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem*. **1999**, *64*, 6750-6755.

(27) The structure of the annulated indole product (**27**) was confirmed by an independent synthesis. See the Experimental Section for details.

(28) (a) Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965; pp 141-183. (b) Rogne, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 489-492. (c) Ramsey, B. G.; Walker, F. A. *J. Am. Chem. Soc*. **1974**, *96*, 3314-3316.

(29) GC conversion was measured by consumption of indole **26** relative to an internal standard (tridecane). GC yield was measured by amount of annulated indole **27** relative to an internal standard (tridecane).

(30) Another possible scenario is that a new decomposition pathway for the starting material arises during the course of the reaction.

(31) For discussions of reactions of indoles with oxygen, see: (a) Hino, T.; Nakagawa, M. *Heterocycles* **1977**, *8*, 743-782. (b) Dave, V.; Warnhoff, E. W. *Can. J. Chem*. **1971**, *49*, 1911-1920. (c) Kunapuli, S. P.; Khan, N. U.; Divakar, N. G.; Vaidyanathan, C. S. *J. Indian Inst. Sci.* **1981**, *63*, 167-202.

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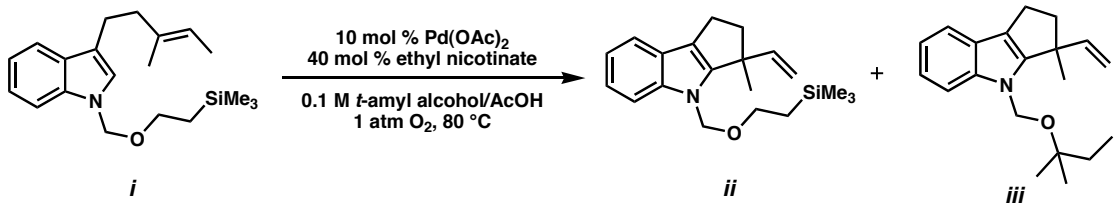
(34) Because the decomposition products were oligomeric, highly polar, and numerous, none were isolated and characterized. Oligomerizations of indole compounds under oxidative conditions have been discussed.[20b]

(35) AcOH has also been used frequently as a solvent in aryl palladation reactions. Therefore, other possible beneficial effects, such as favorable interactions with reaction intermediates, cannot be ruled out.

(36) Other *N*-substituted indoles were not as effective. Acetyl, tosyl, or *tert*-butyldimethylsilyl groups all shut down reactivity. *N*-H indole was prone to heavy decomposition under the reaction conditions. SEM-protected indoles cyclized, but were complicated by an acetalization side reaction (e.g., **i** → **ii** + **iii**).



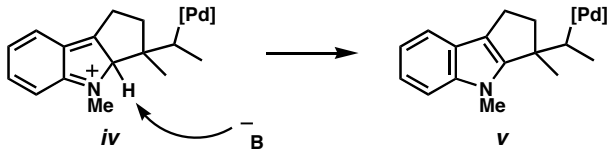
i *ii* *iii*

(37) Interestingly, the mechanism of the oxidative heterocyclization reactions proved to be more complicated than we initially expected, showing a dependence on the nucleophile and the conditions. See Chapter 5 for details of this study.

(38) When AcOH was used as a cosolvent, the yield of the annulated product was lower than when it was not used. Still, only one diastereomer (**297**) was produced even when AcOH was added.

(39) The relative stereochemistry of **297** was confirmed by NOE analysis. See the Experimental Section for details.

(40) It should be noted that it is not clear what the deuterium isotope effect would be in the Wacker-type mechanism, and consequently this result does not necessarily rule out such a pathway. The deprotonation event (**iv** → **v**) would need to be rate-determining in order for an effect to be observed.



(41) (a) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem*. **1981**, *46*, 851-855. (b) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc*.

2002, *124*, 1586-1587. (c) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc*. **2003**, *125*, 1476-1477.

(42) The isomerization process could be mediated by the catalyst, but it could also occur thermally.

(43) The relative stereochemistry of **346** was confirmed by NOE analysis. See the Experimental Section for details.

(44) Recently, an intermolecular oxidative coupling of indoles and alkenes was described. See, Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew, Chem., Int. Ed*. **2005**, *44*, 2-6.

(45) This experiment was performed by Haiming Zhang and presently remains unoptimized.

(46) To our knowledge, there is only one report of an enantioselective palladium(II) oxidative C-C bond forming reaction (up to 49% ee). See, Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett*. **1999**, 55-56.

(47) Silyl enol ethers would likely not proceed via a C-H bond functionalization event, but still can be considered in the category of carbon nucleophiles.

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(49) The necessity for stoichiometric palladium in this reaction is unclear. An acyl pyrrole is certainly more electron-poor than any of the other arenes we have investigated, but there may be complications arising from a lack of regioselectivity in the palladation step. An alternative mechanistic pathway could also account for the requirement of 1 equiv $Pd(OAc)_2$.

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APPENDIX TWO

Spectra Relevant to Chapter Four:
C-H Bond Functionalizations with Palladium(II): Intramolecular Annulations of Arenes

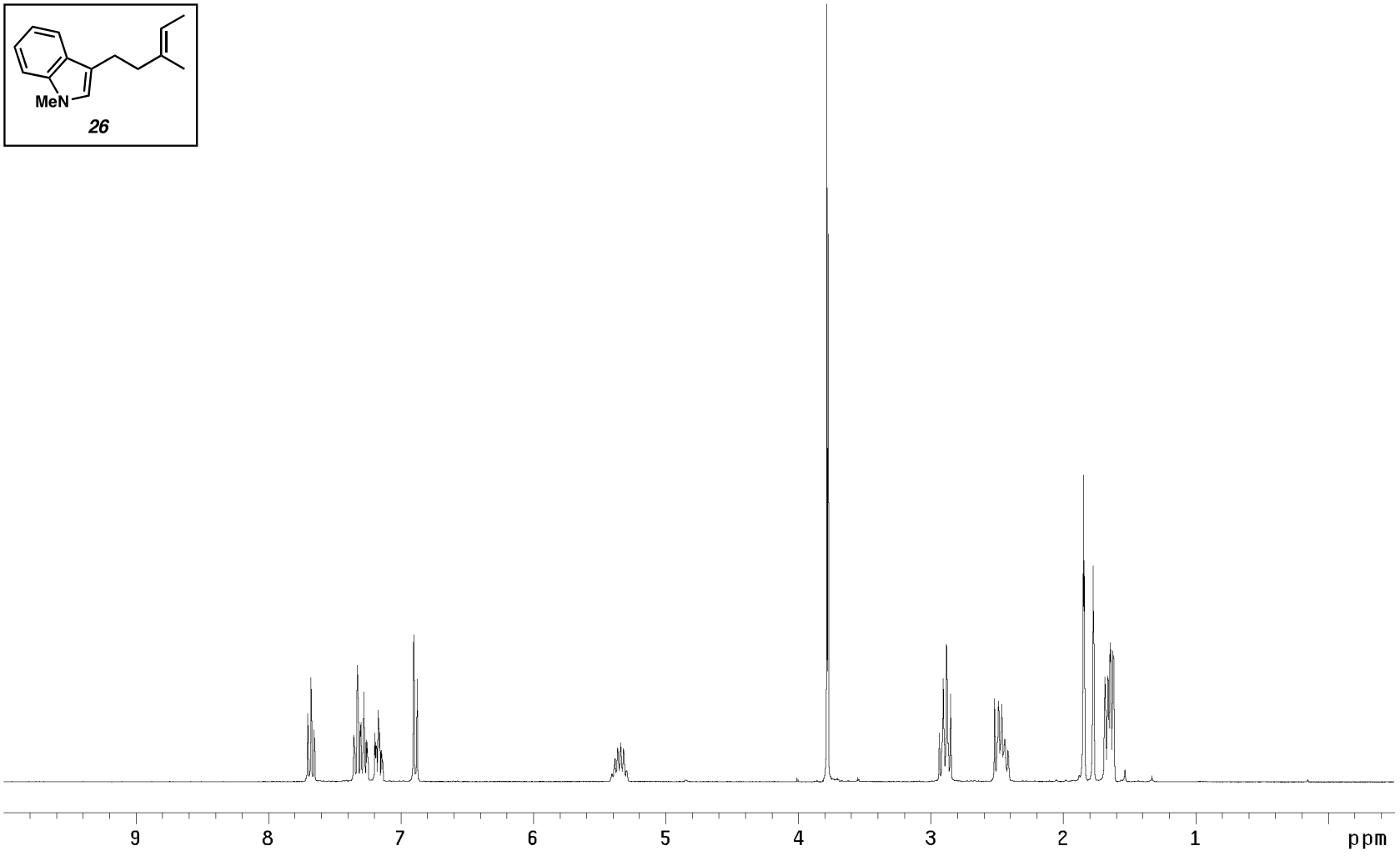

Figure A2.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **26**.

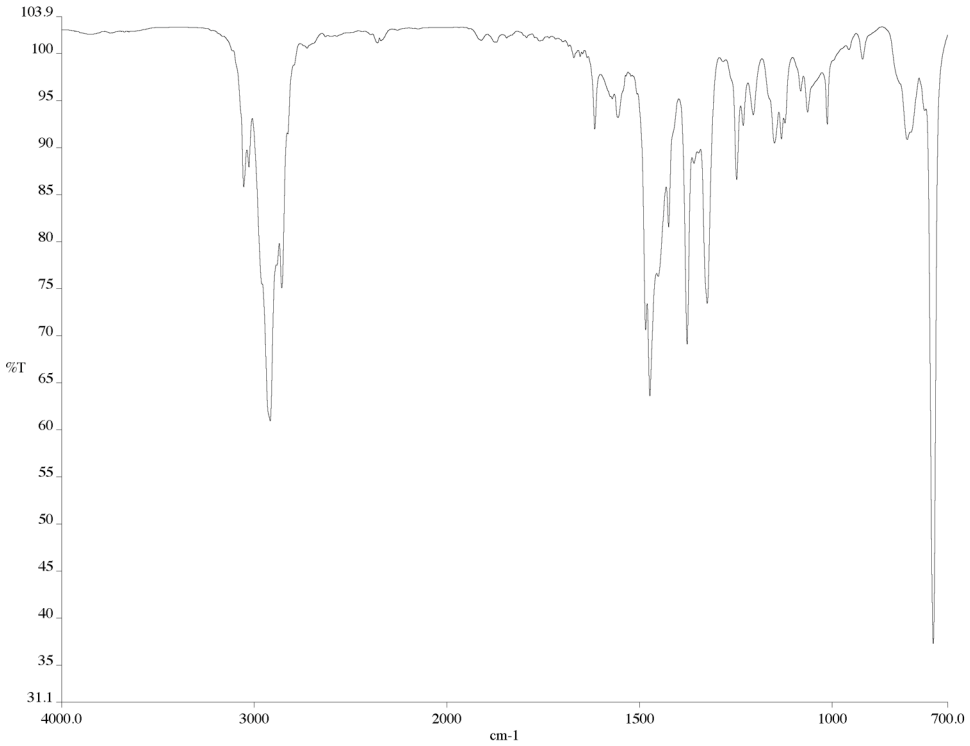

Figure A2.2 Infrared spectrum (thin film/NaCl) of compound **26**.

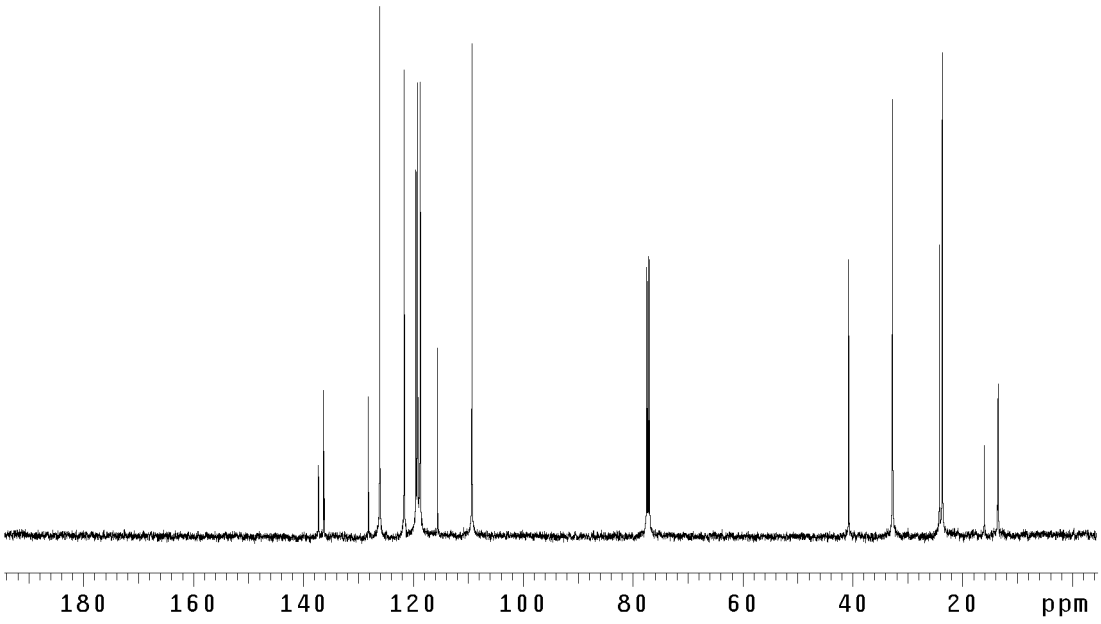

Figure A2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **26**.

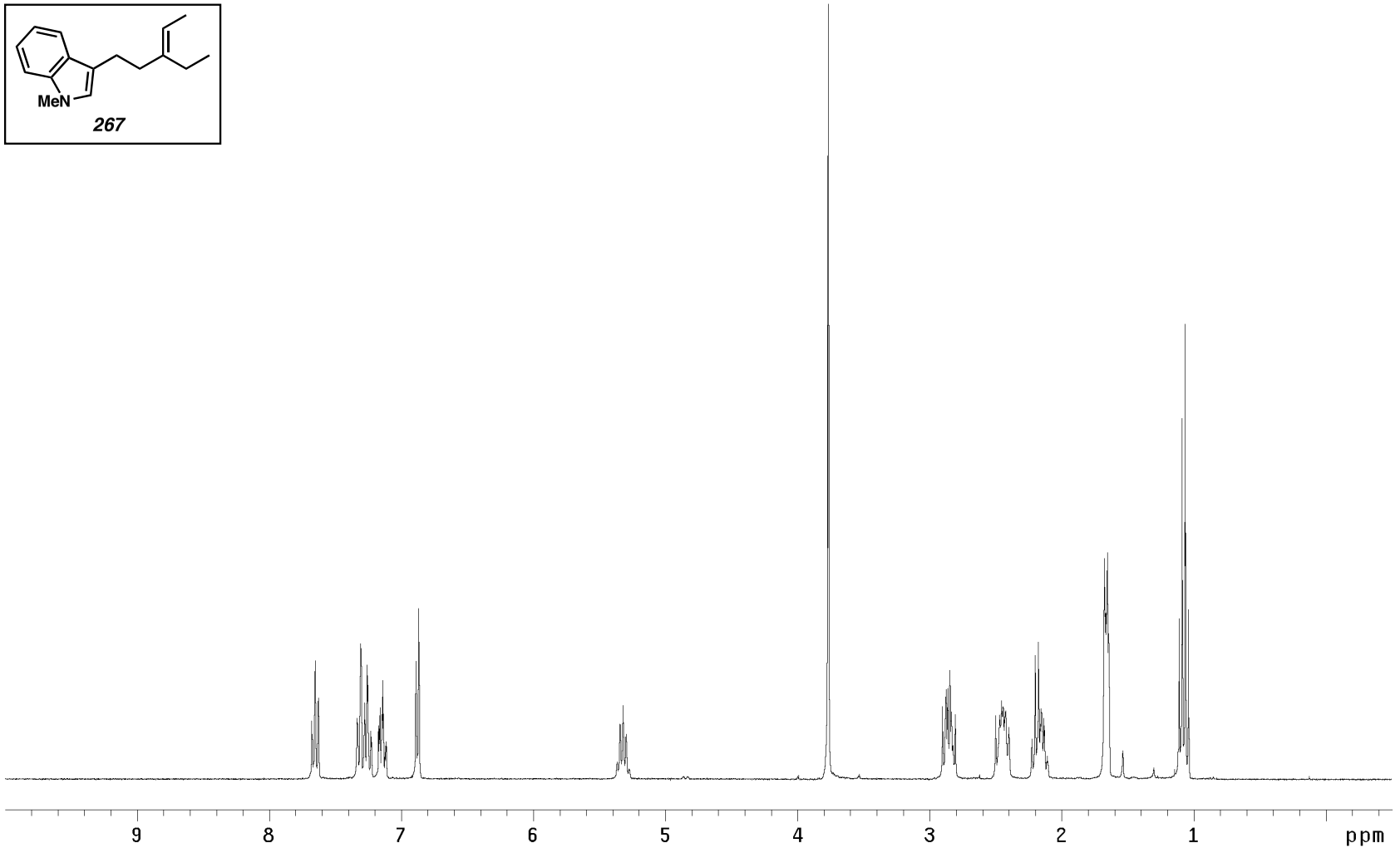

Figure A2.4 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **267**.

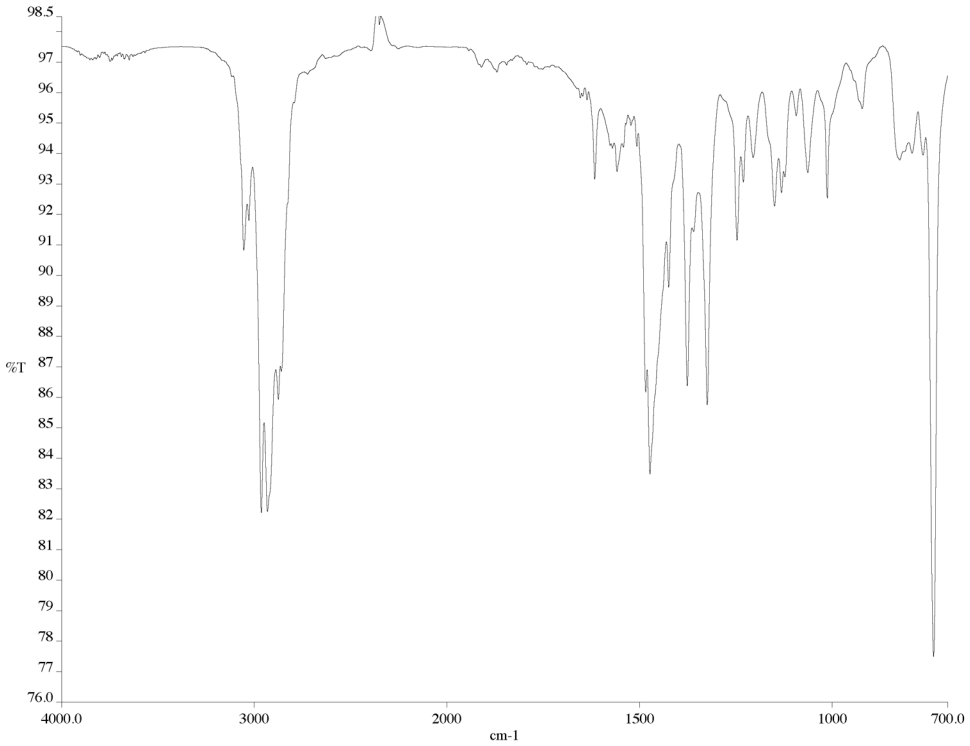

Figure A2.5 Infrared spectrum (thin film/NaCl) of compound **267**.

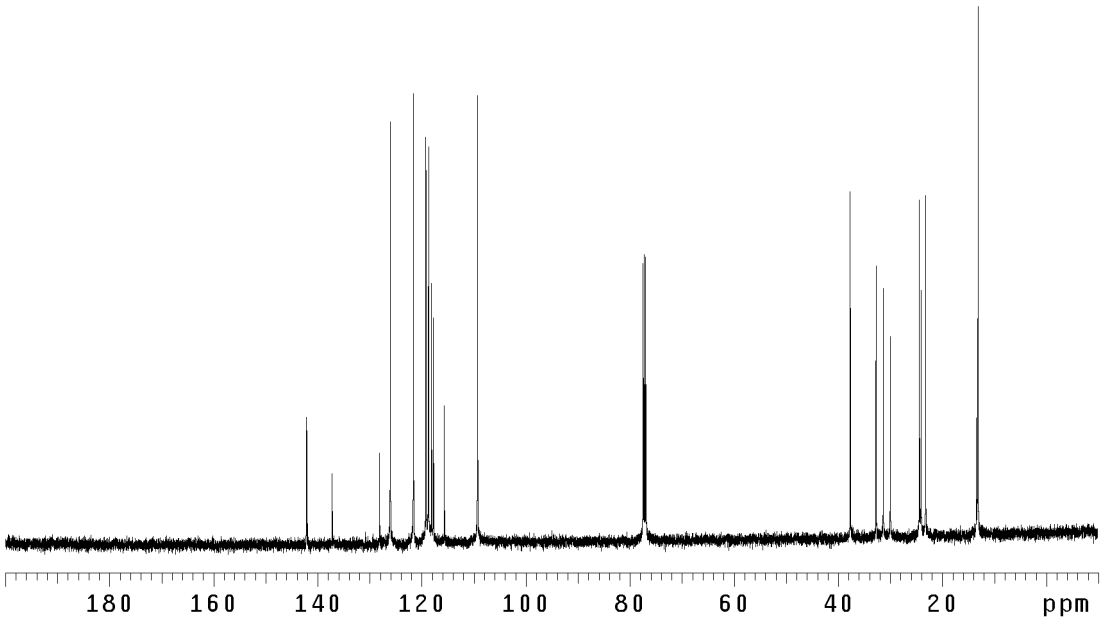

Figure A2.6 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **267**.

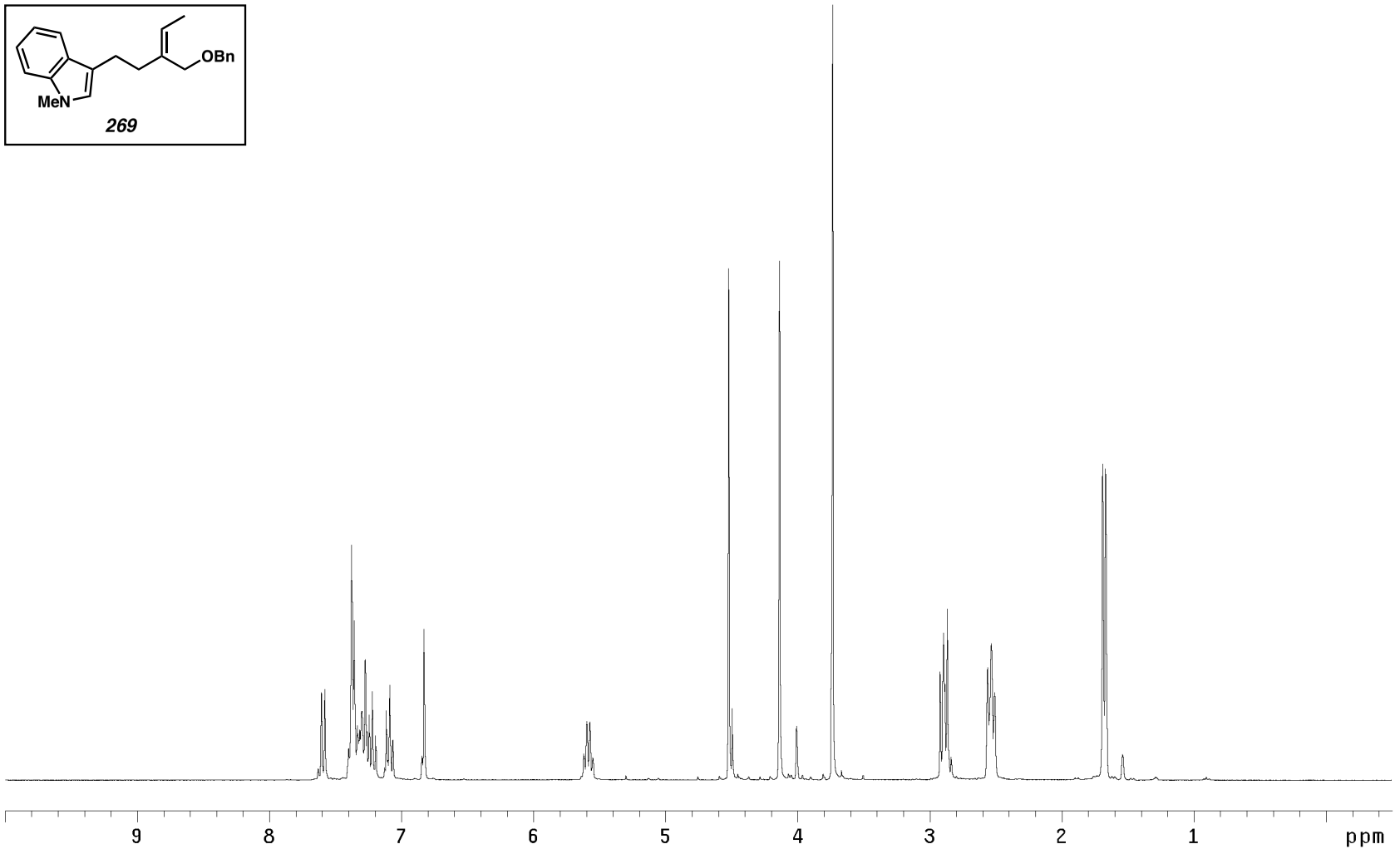

Figure A2.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **269**.

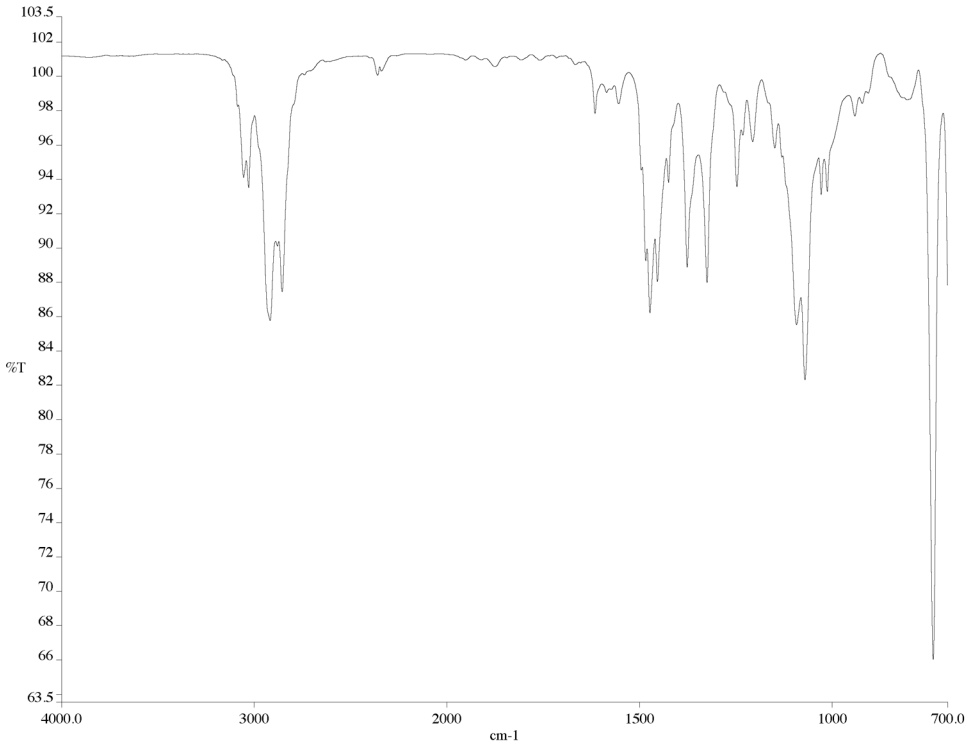

Figure A2.8 Infrared spectrum (thin film/NaCl) of compound **269**.

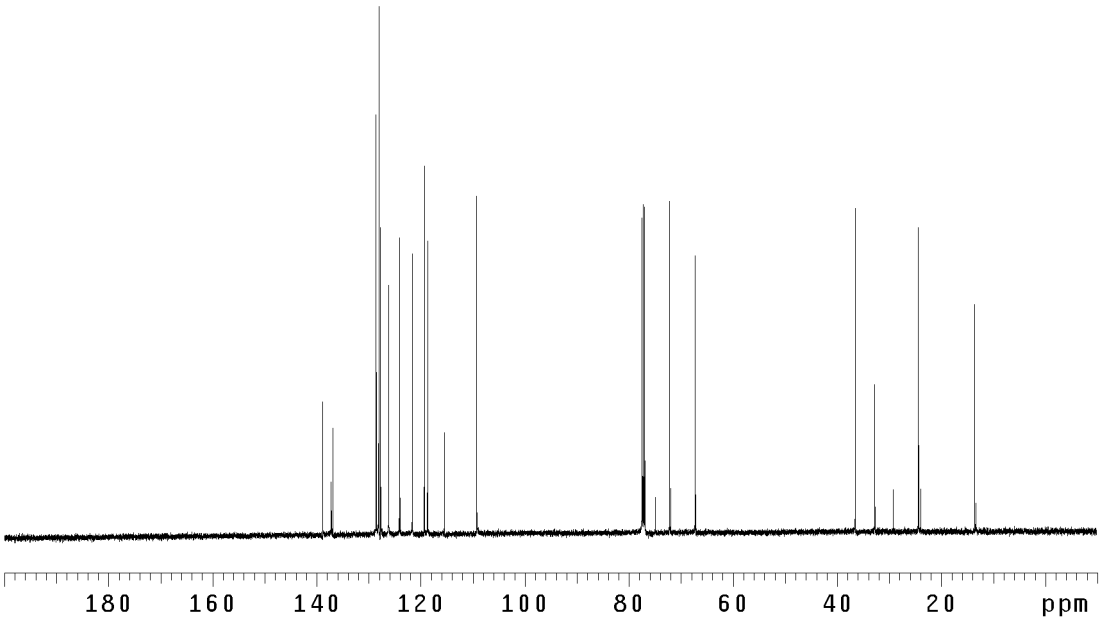

Figure A2.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **269**.

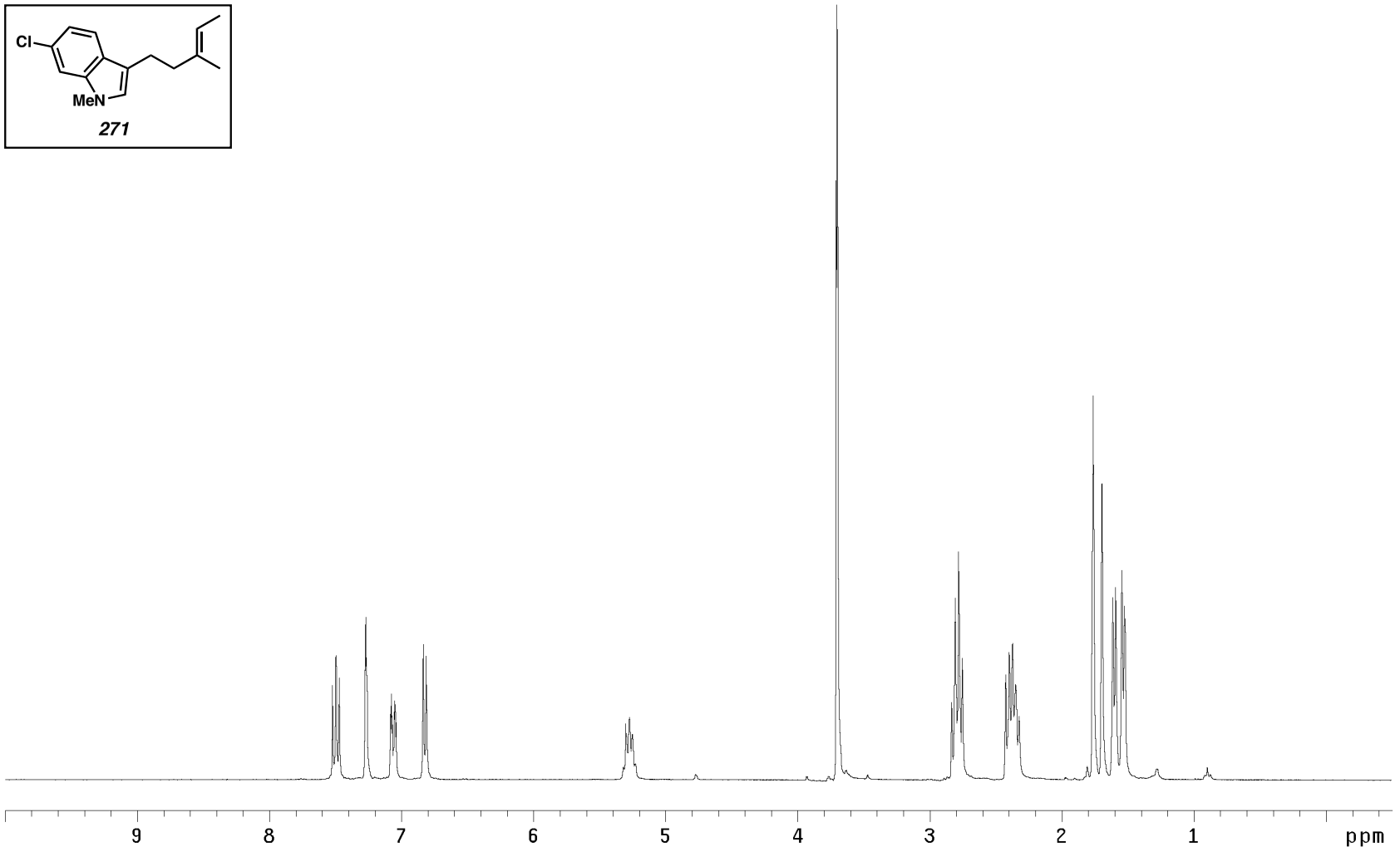

Figure A2.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **271**.

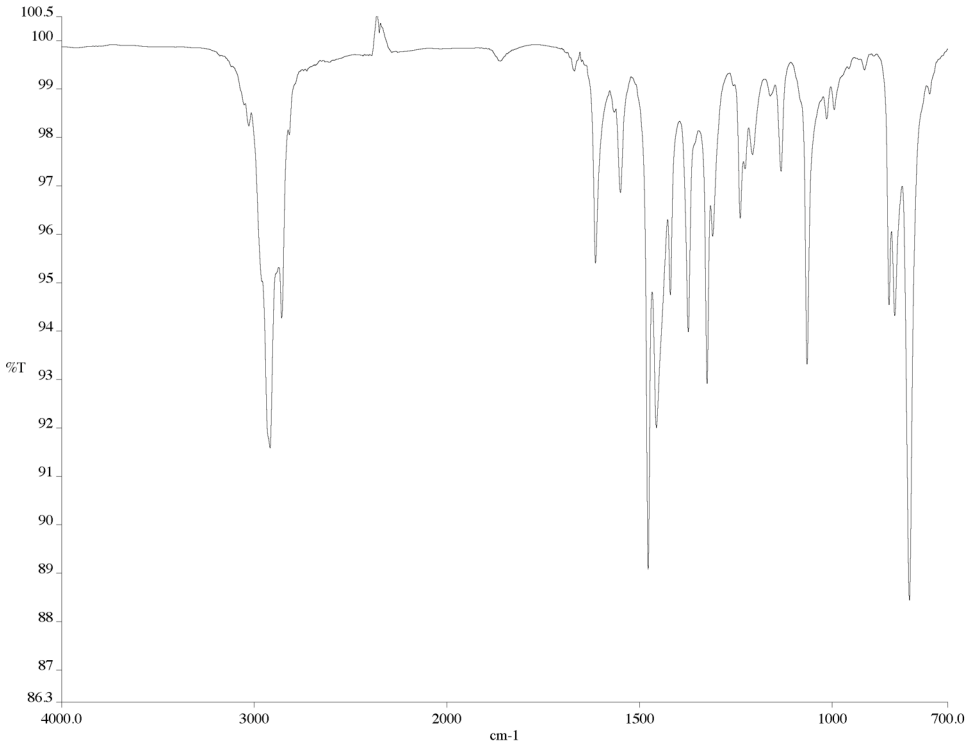

Figure A2.11 Infrared spectrum (thin film/NaCl) of compound **271**.

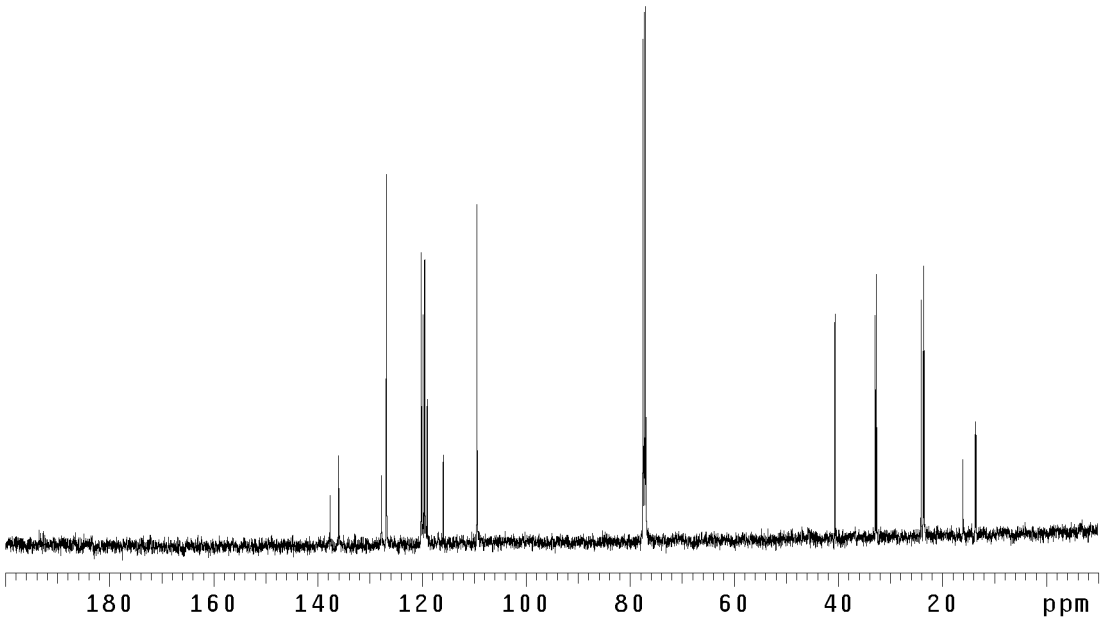

Figure A2.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **271**.

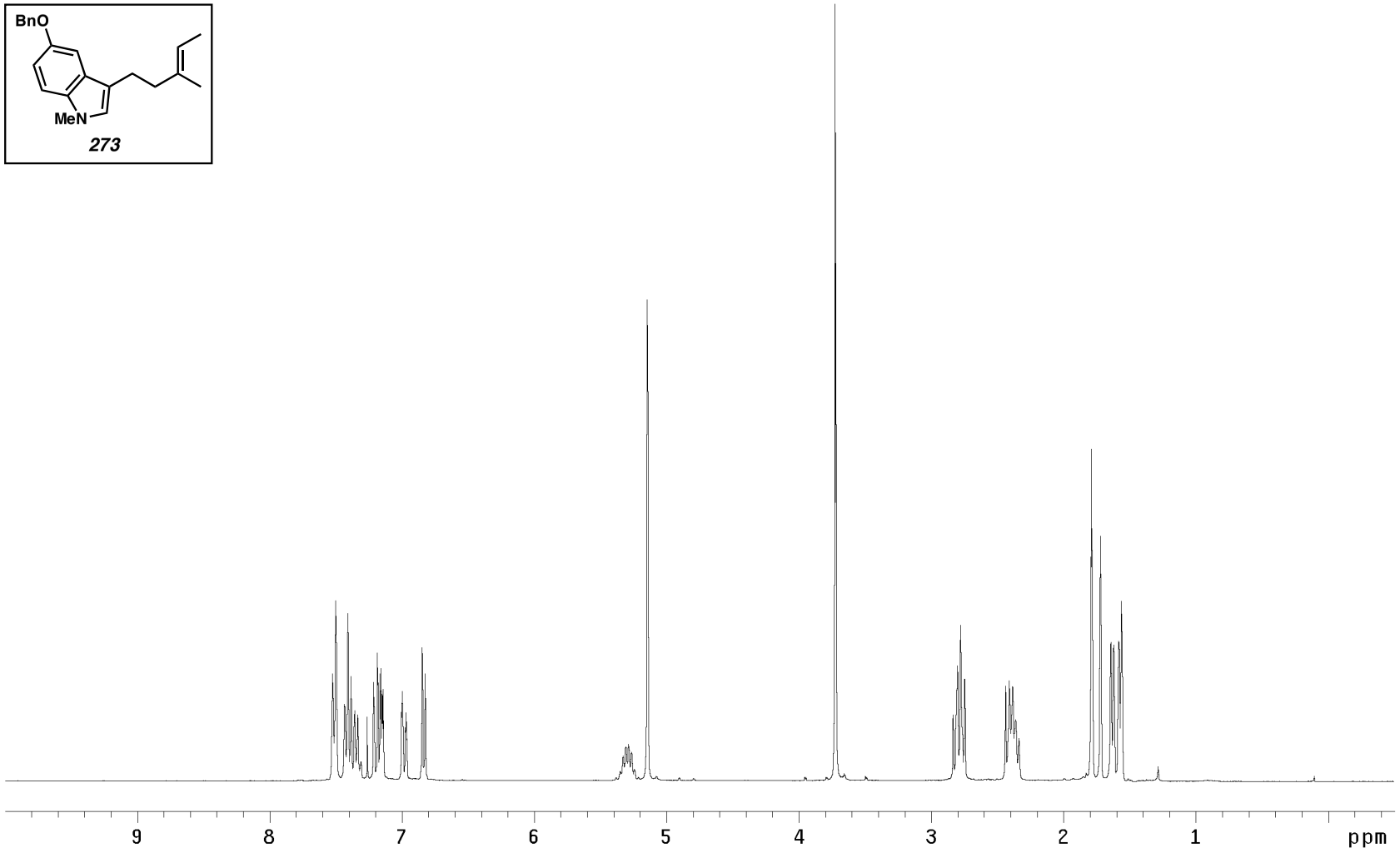

Figure A2.13 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **273**.

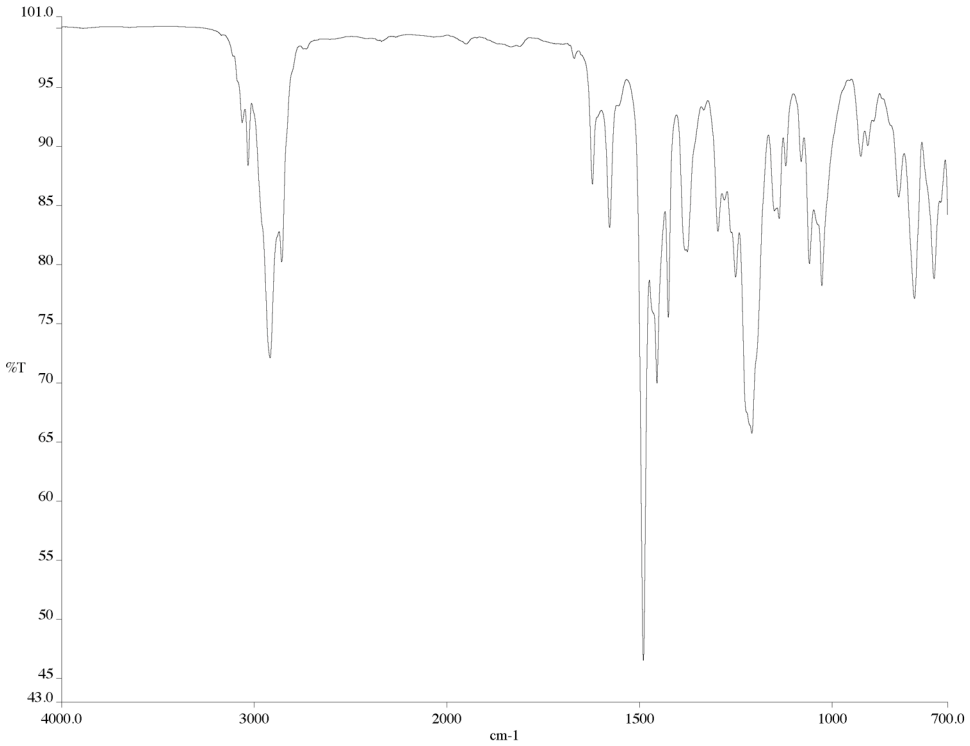

Figure A2.14 Infrared spectrum (thin film/NaCl) of compound **273**.

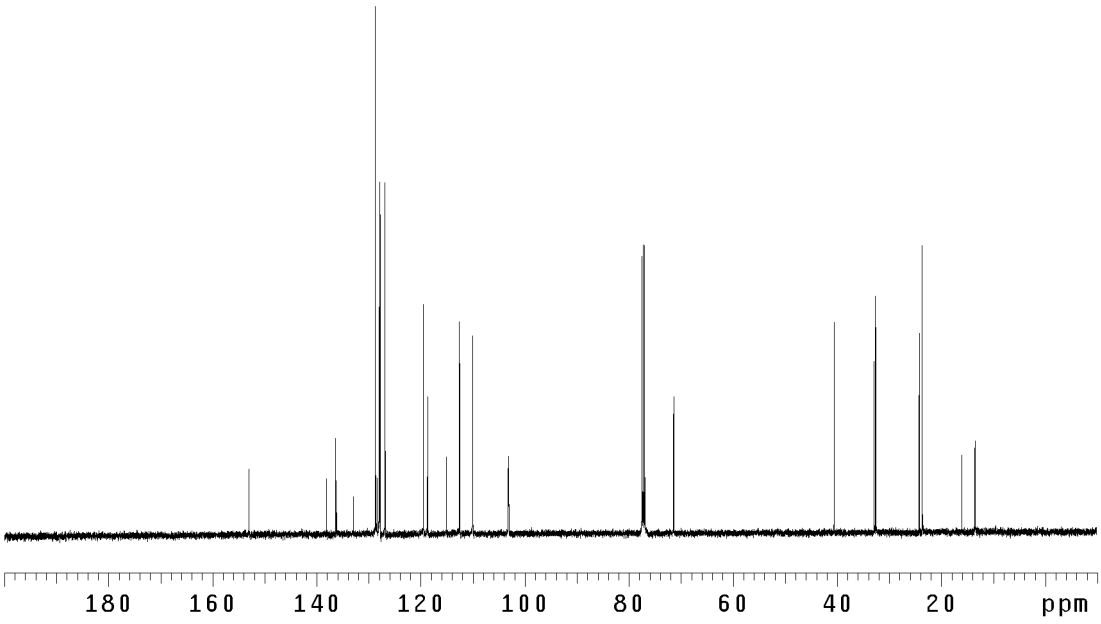

Figure A2.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **273**.

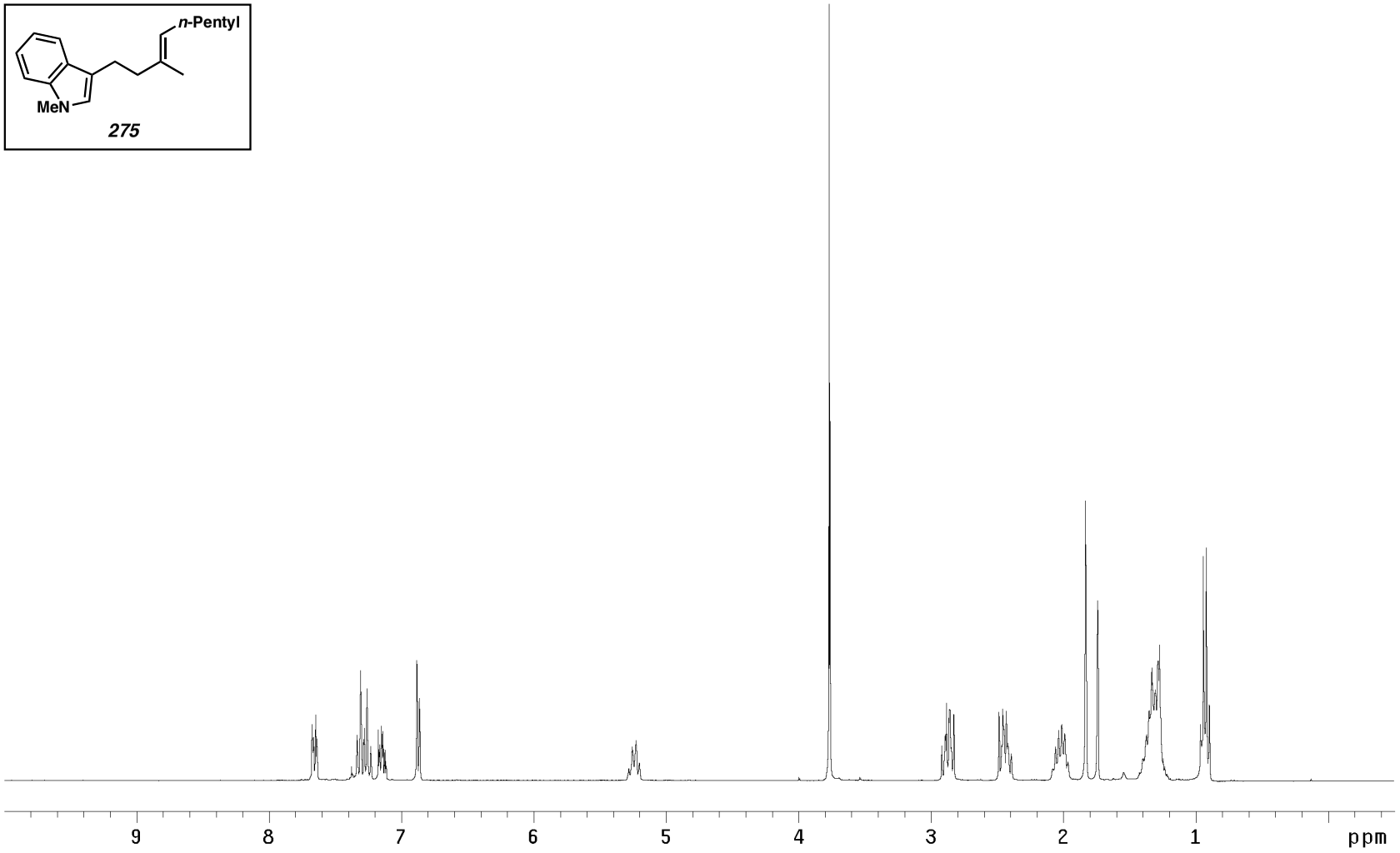

Figure A2.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **275**.

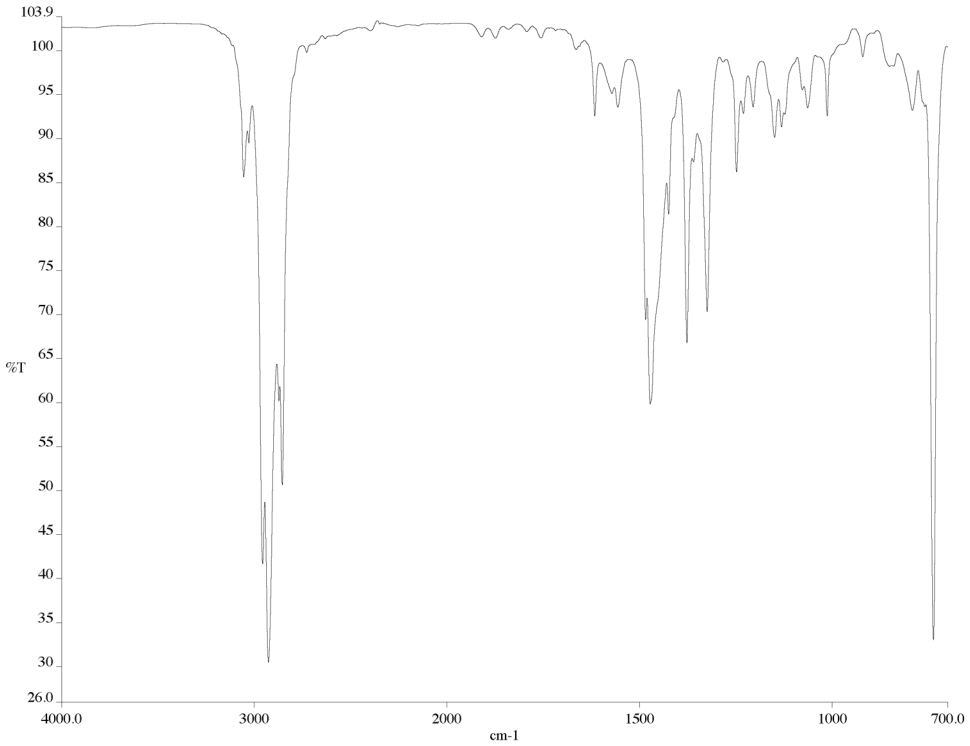

Figure A2.17 Infrared spectrum (thin film/NaCl) of compound **275**.

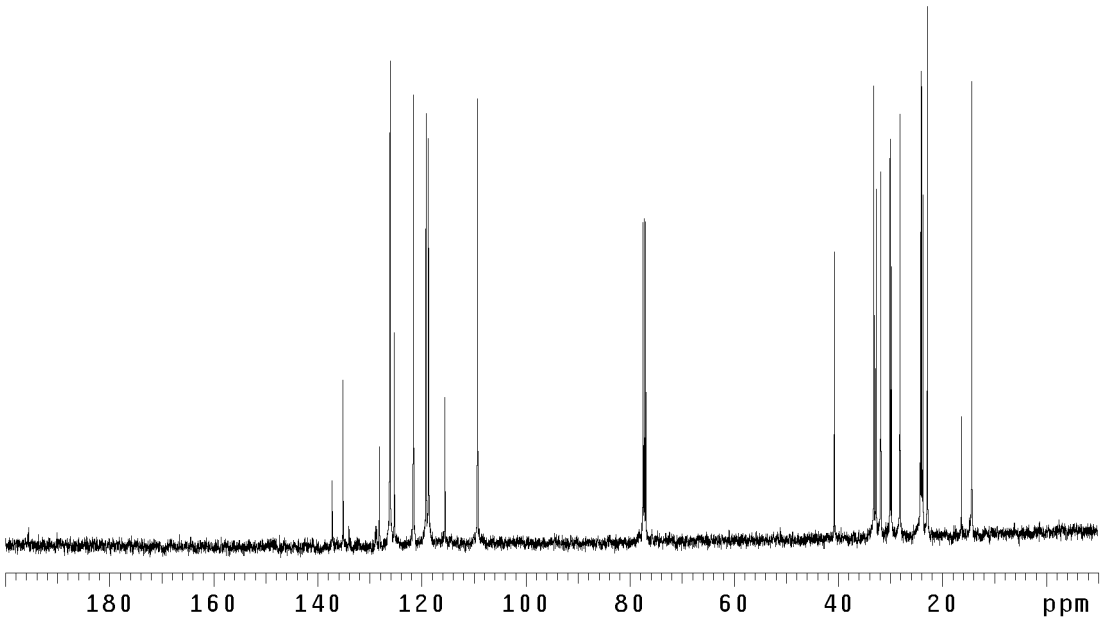

Figure A2.18 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **275**.

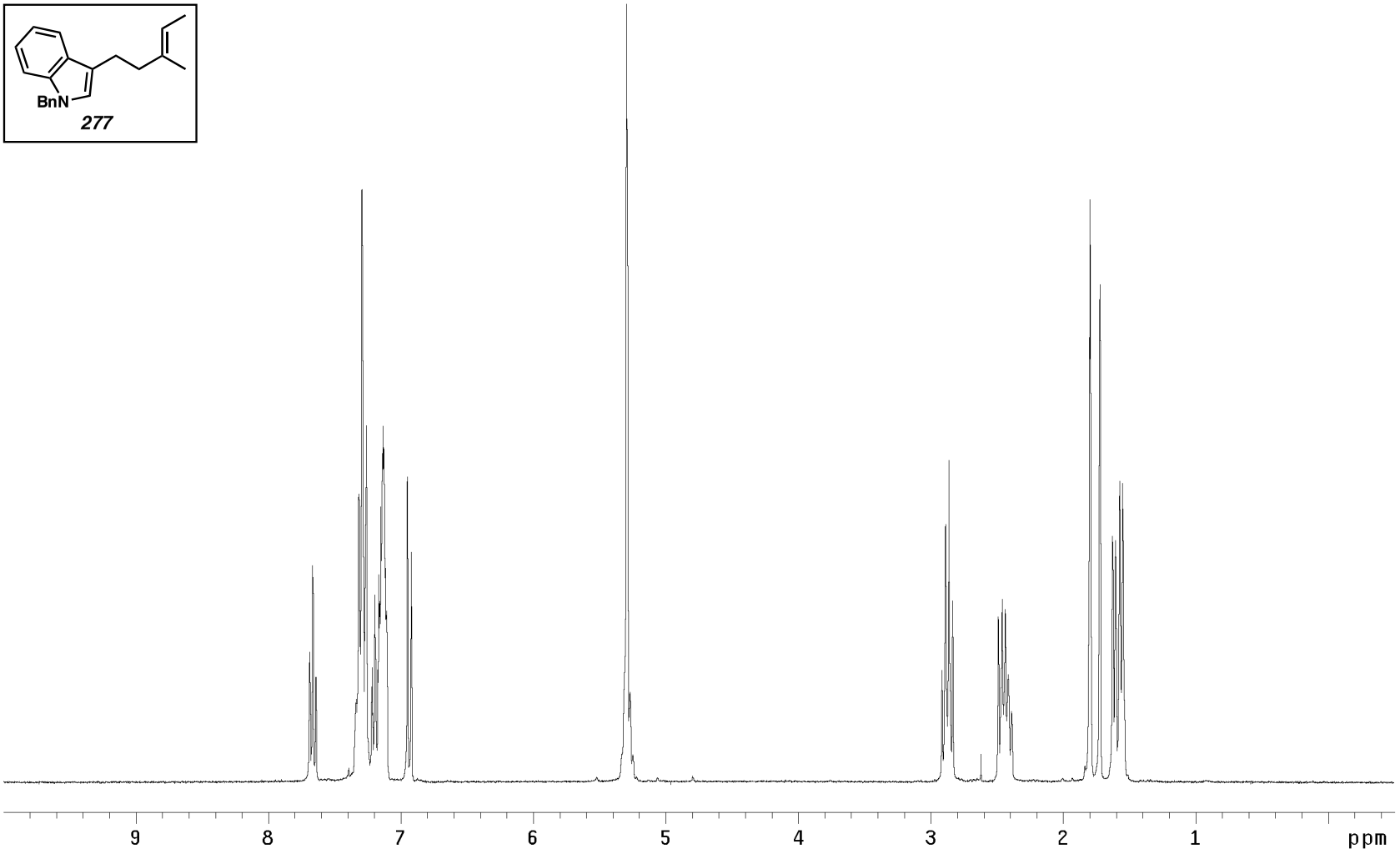

Figure A2.19 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **277**.

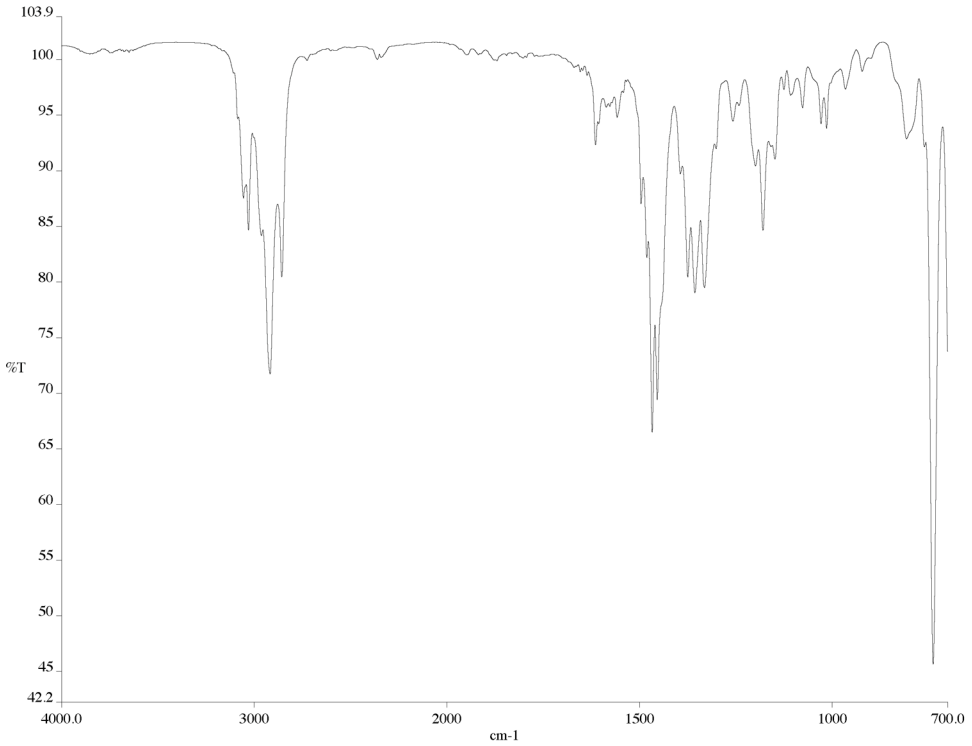

Figure A2.20 Infrared spectrum (thin film/NaCl) of compound **277**.

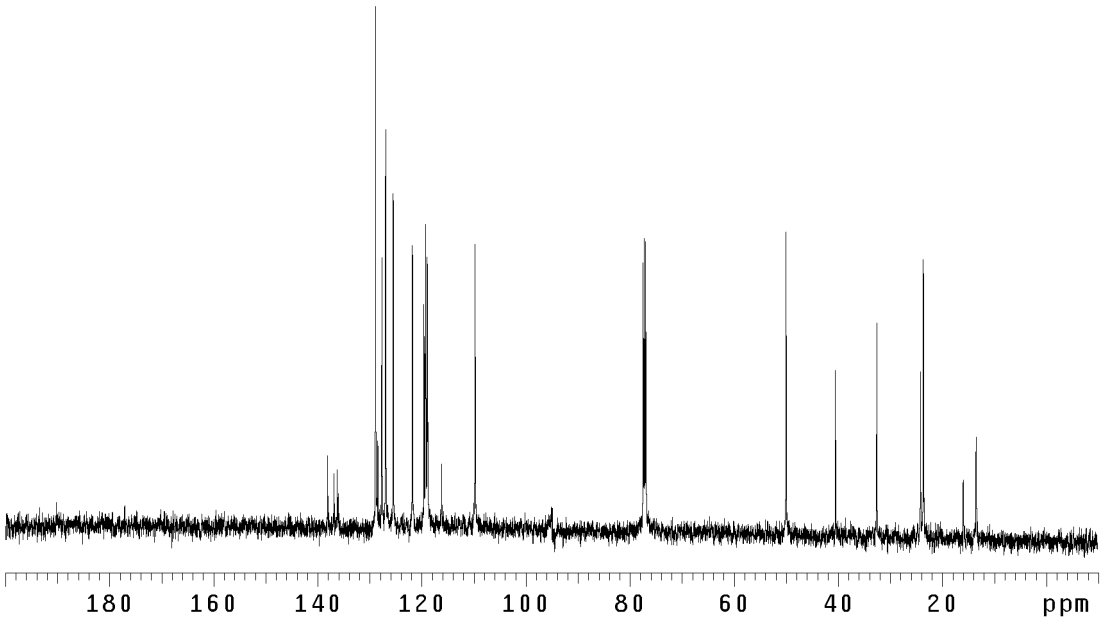

Figure A2.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **277**.

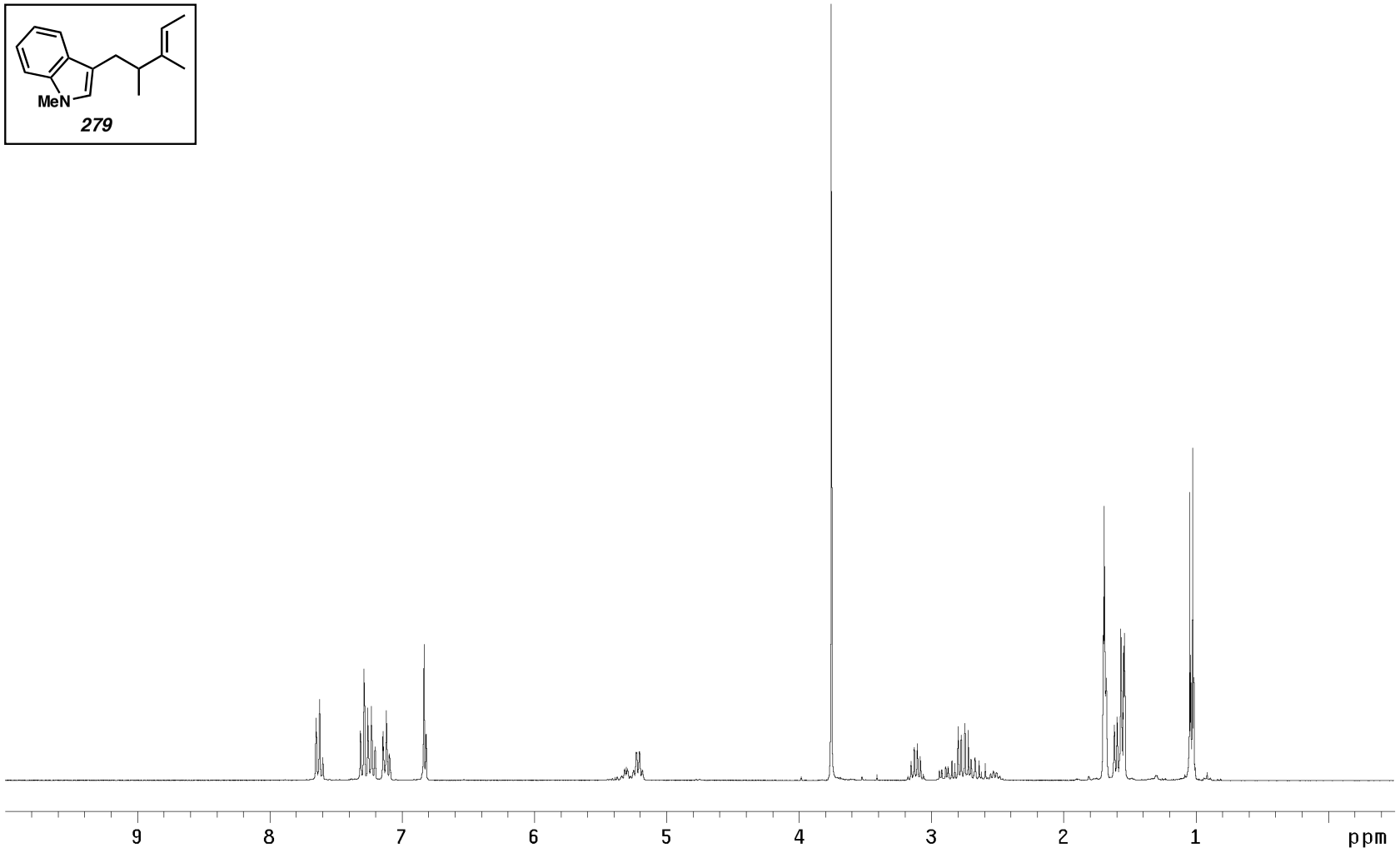

Figure A2.22 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **279**.

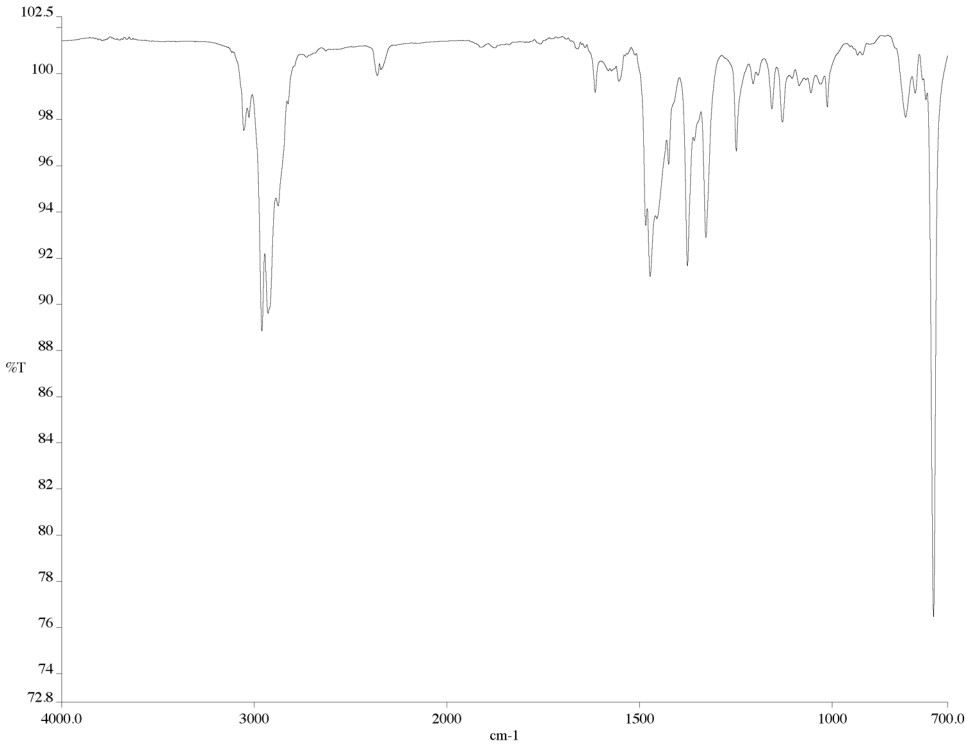

Figure A2.23 Infrared spectrum (thin film/NaCl) of compound **279**.

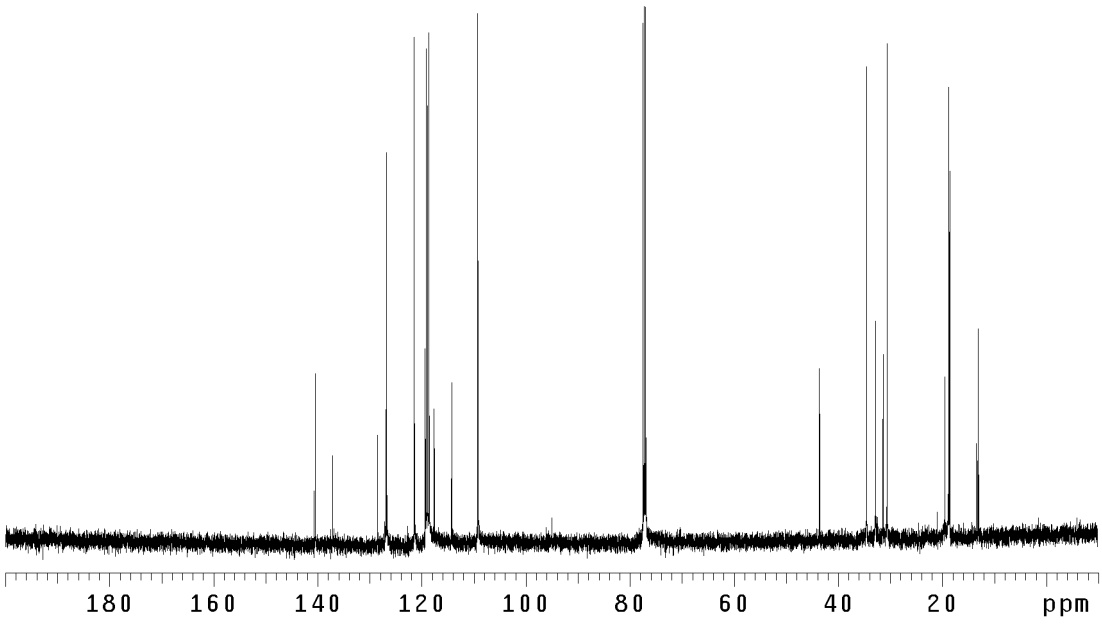

Figure A2.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **279**.

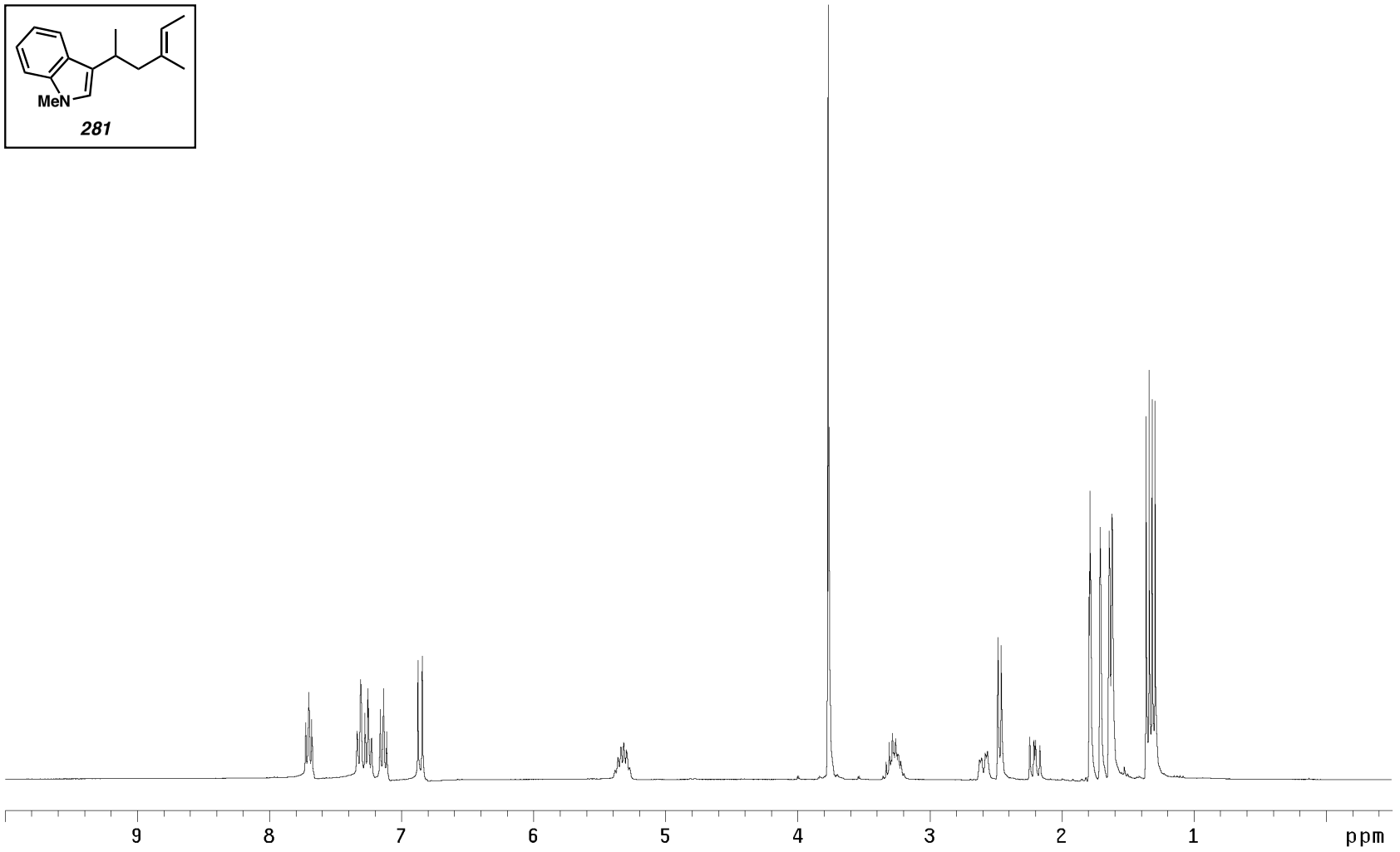

Figure A2.25 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **281**.

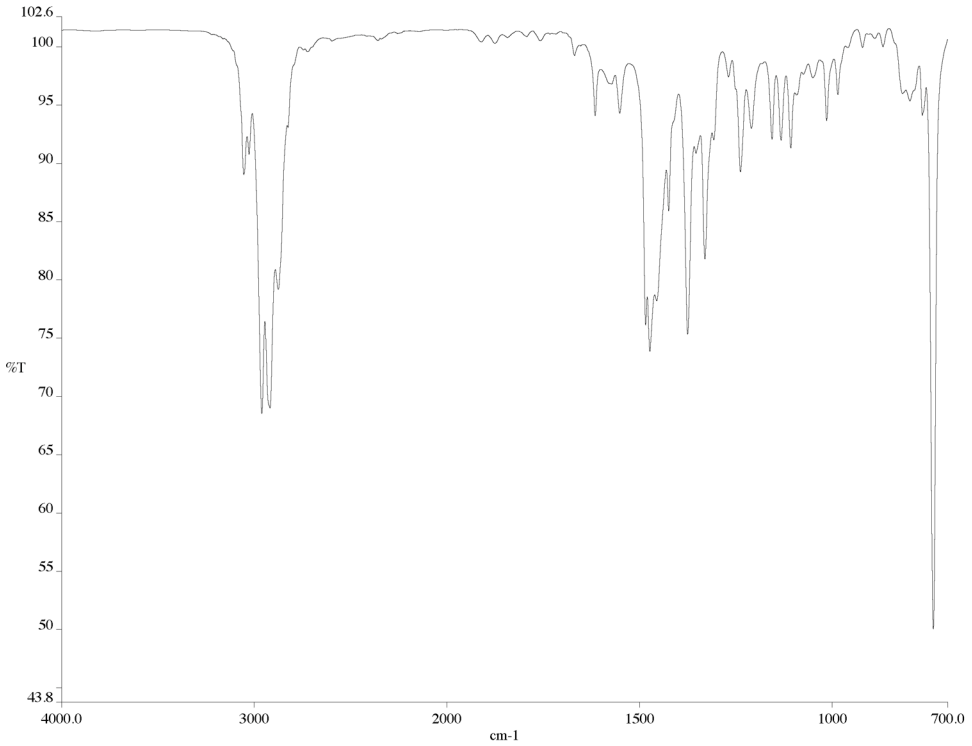

Figure A2.26 Infrared spectrum (thin film/NaCl) of compound **281**.

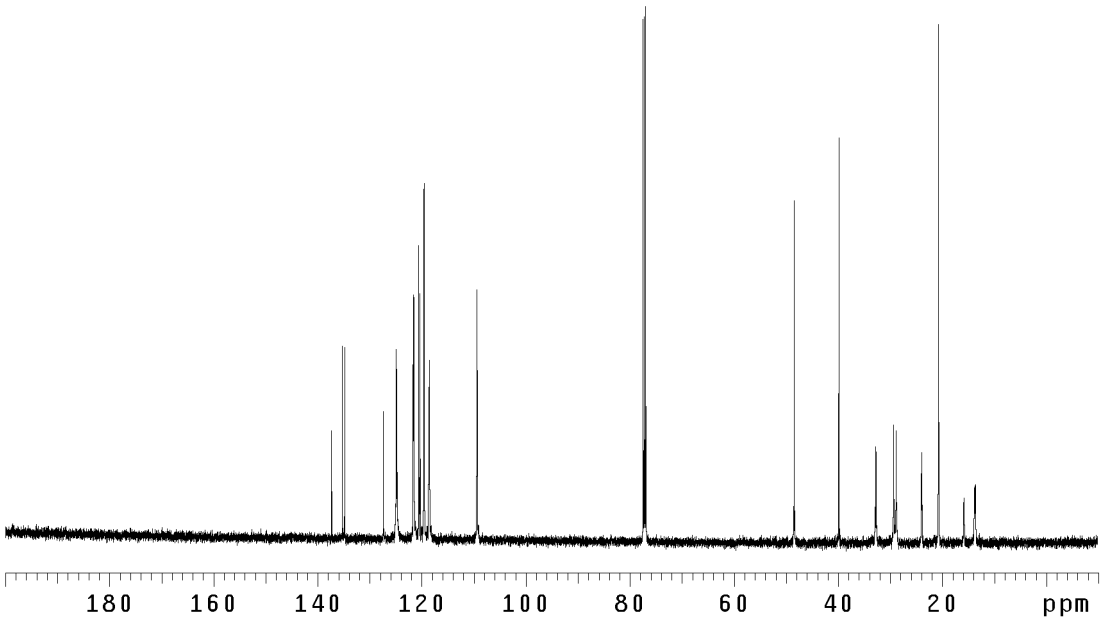

Figure A2.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **281**.

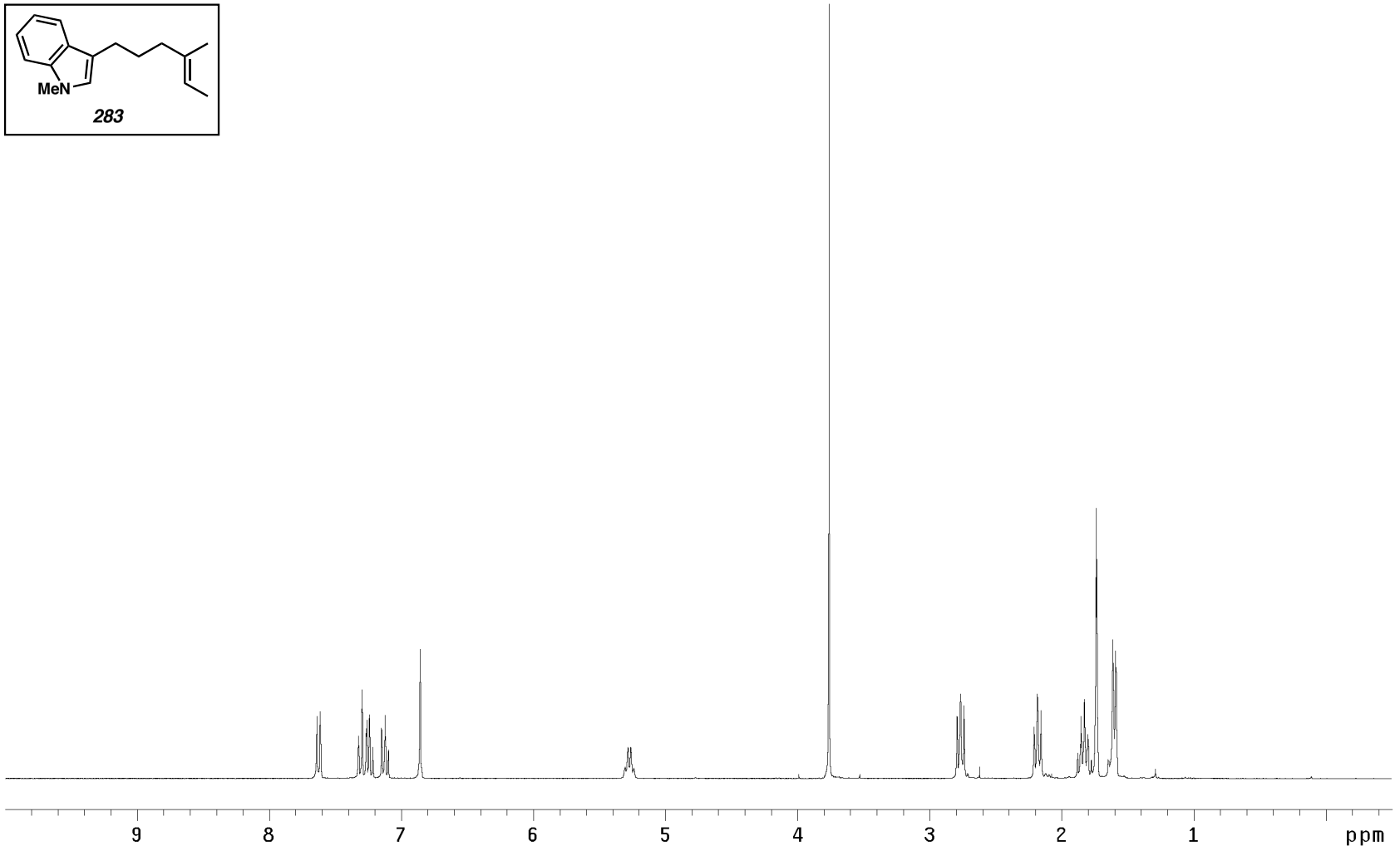

Figure A2.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **283**.

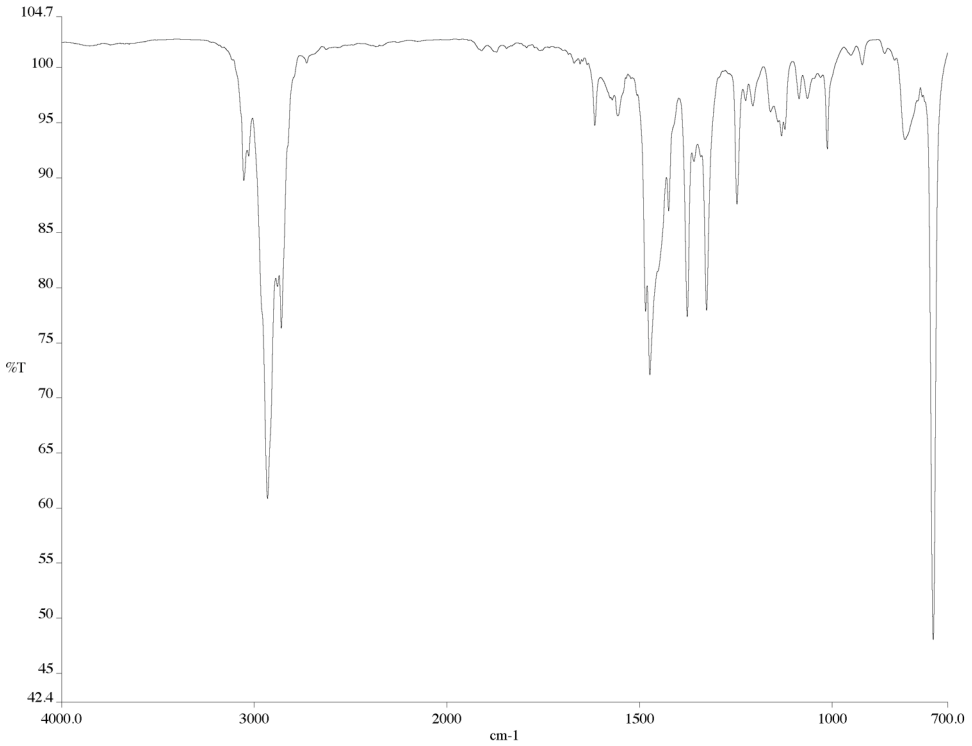

Figure A2.29 Infrared spectrum (thin film/NaCl) of compound **283**.

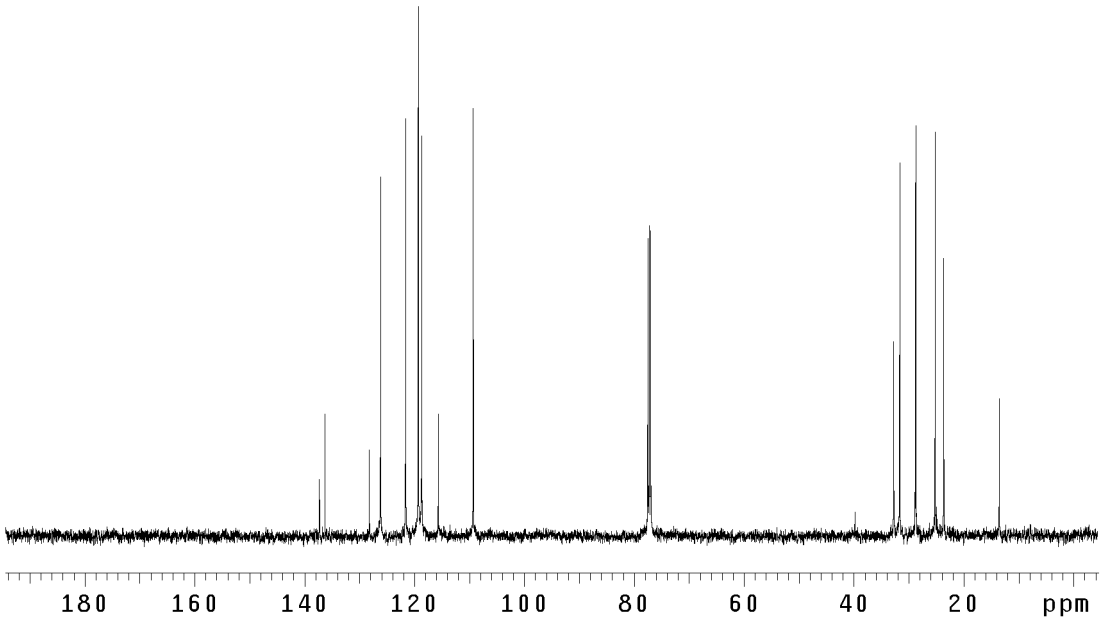

Figure A2.30 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **283**.

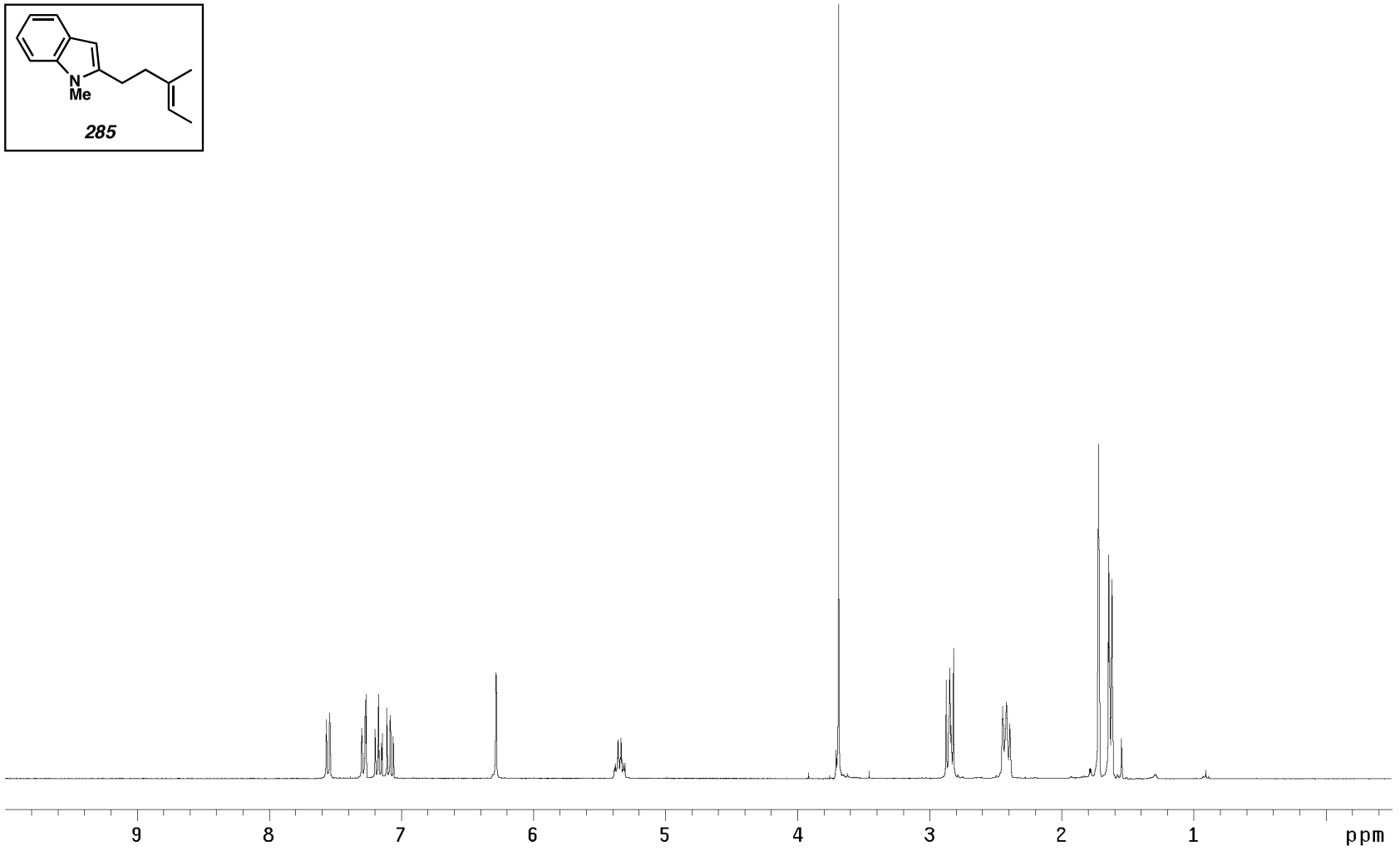

Figure A2.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **285**.

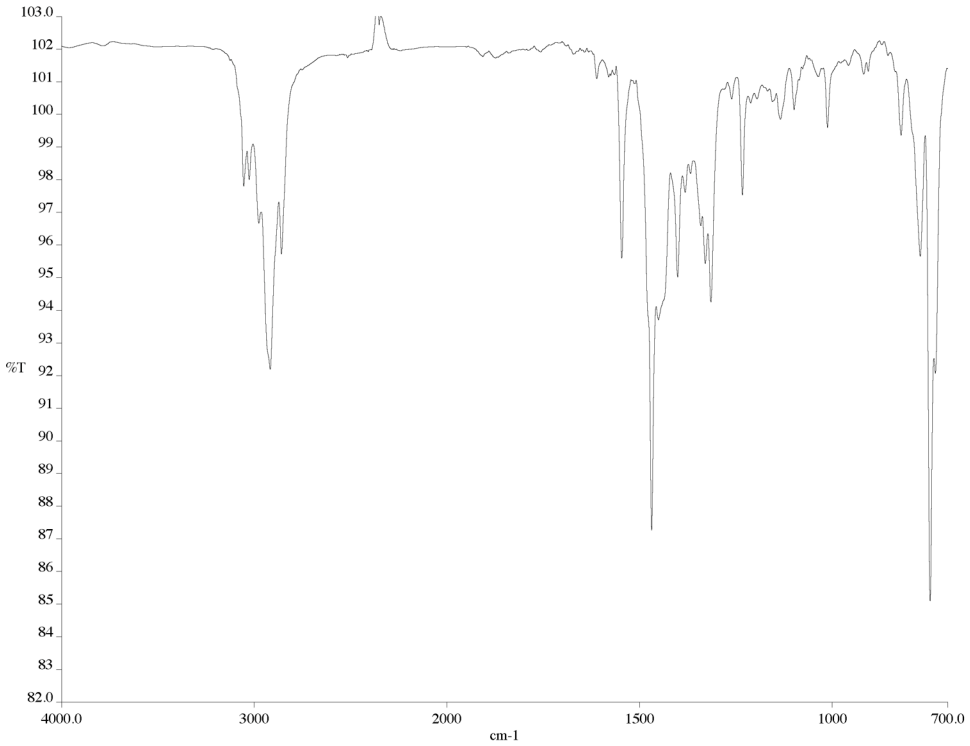

Figure A2.32 Infrared spectrum (thin film/NaCl) of compound **285**.

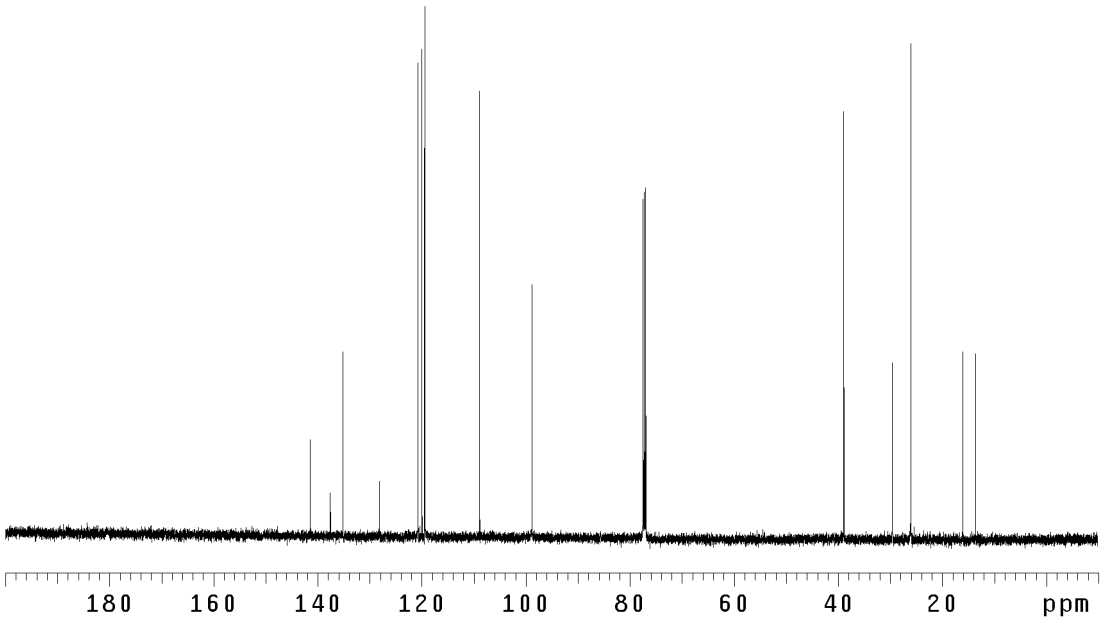

Figure A2.33 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **285**.

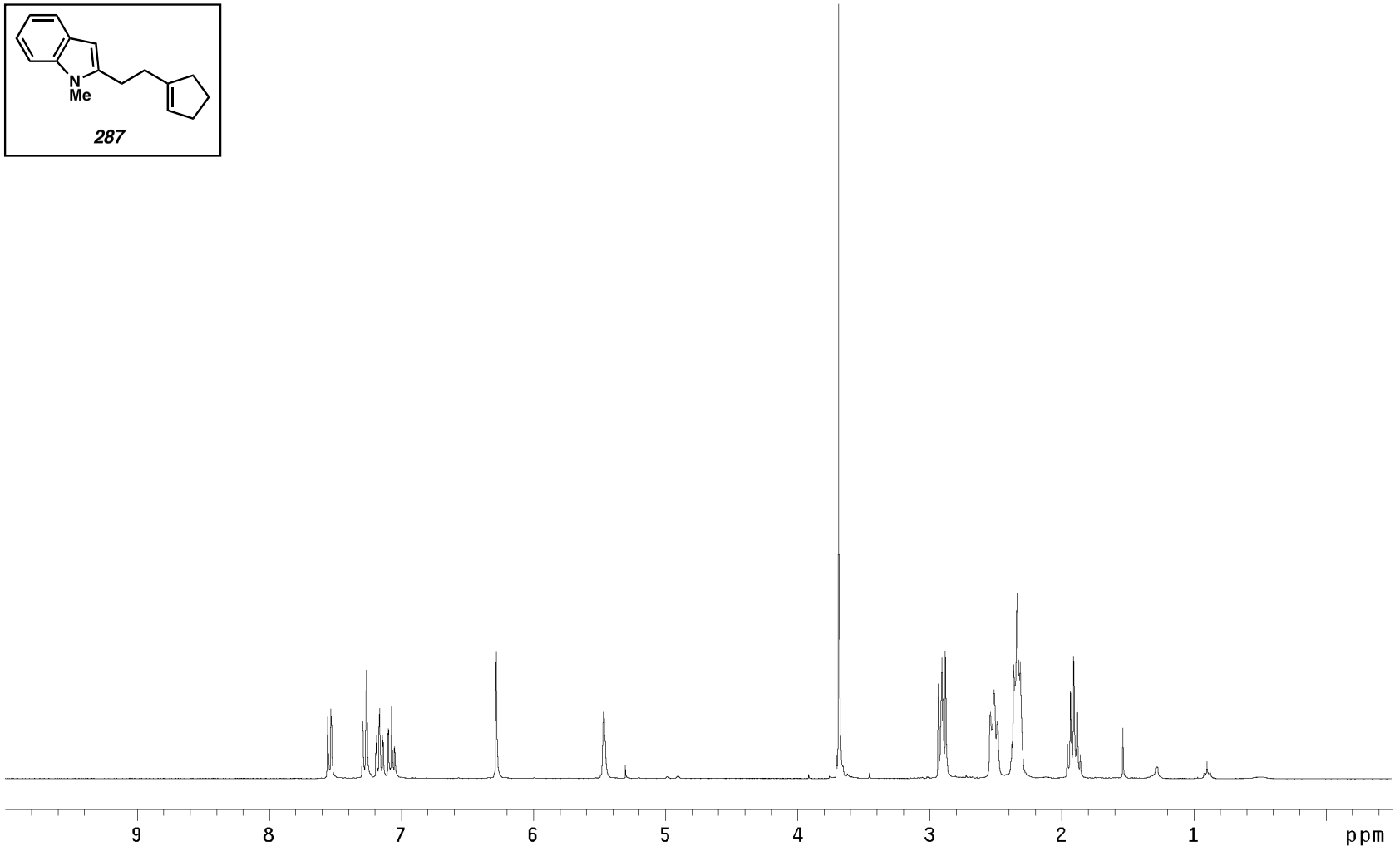

Figure A2.34 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **287**.

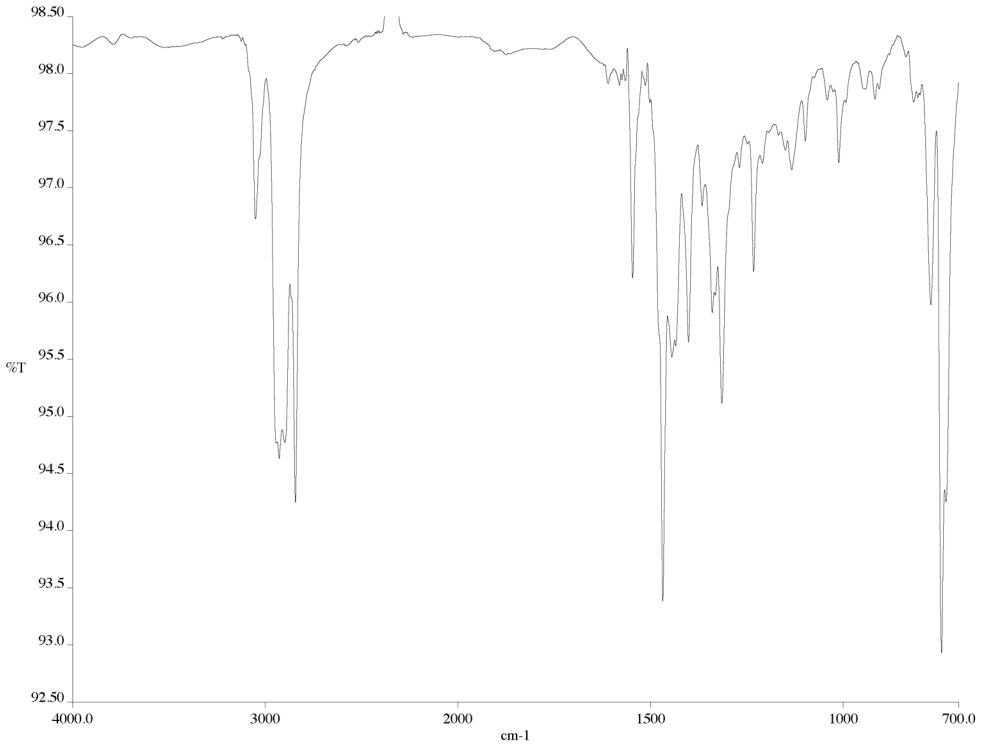

Figure A2.35 Infrared spectrum (thin film/NaCl) of compound **287**.

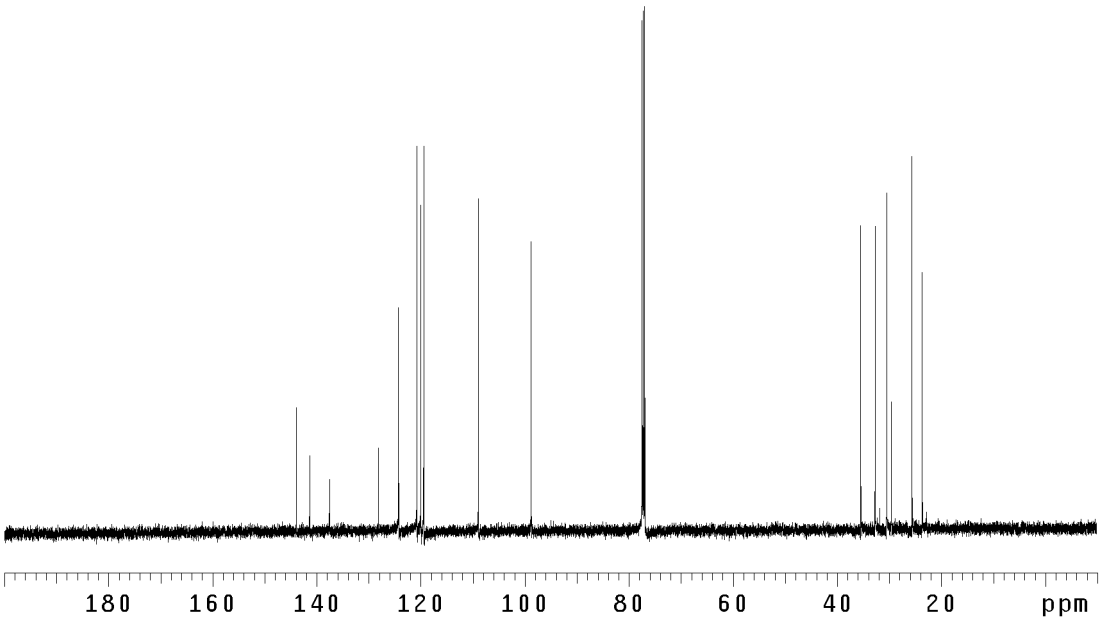

Figure A2.36 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **287**.

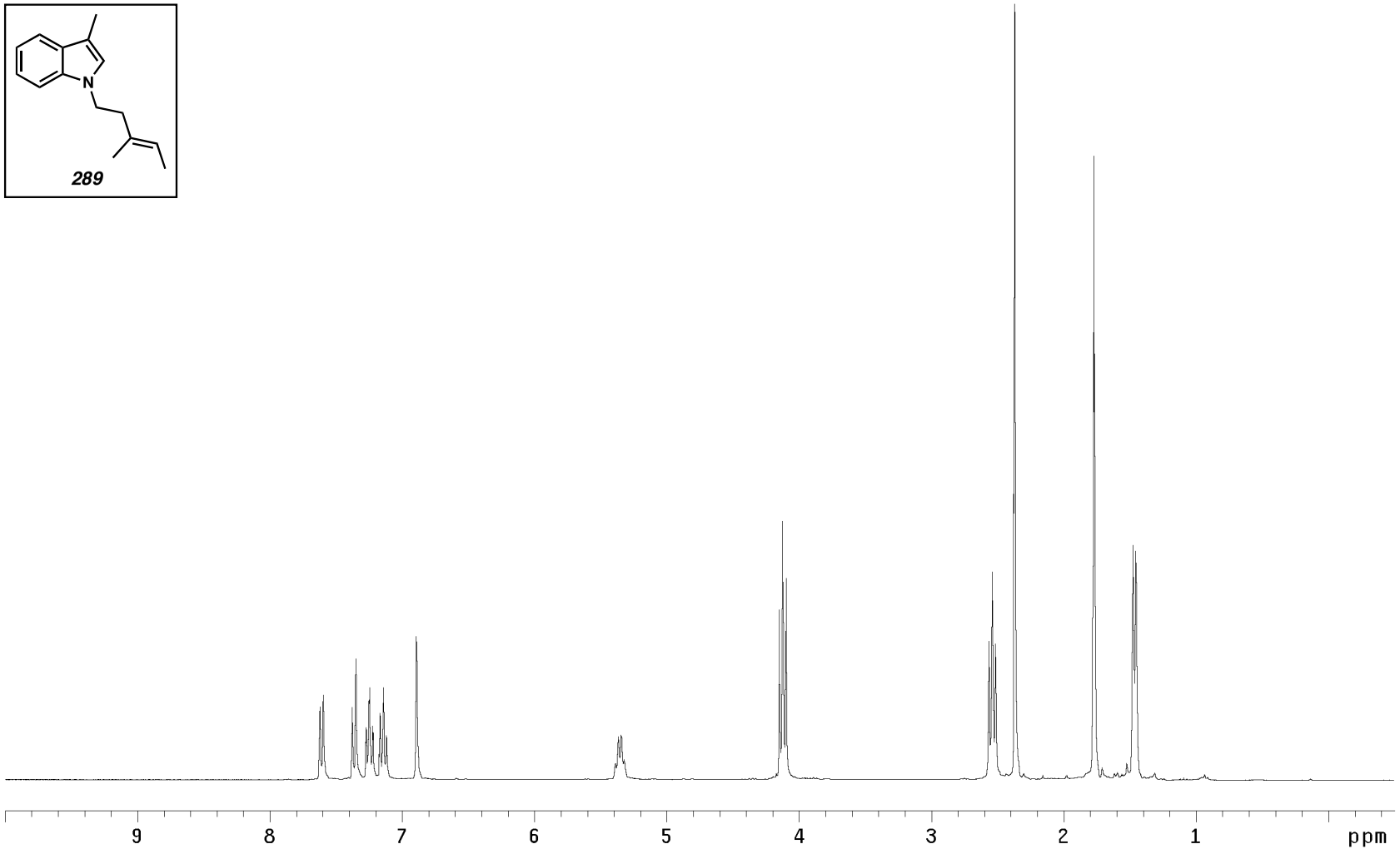

Figure A2.37 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **289**.

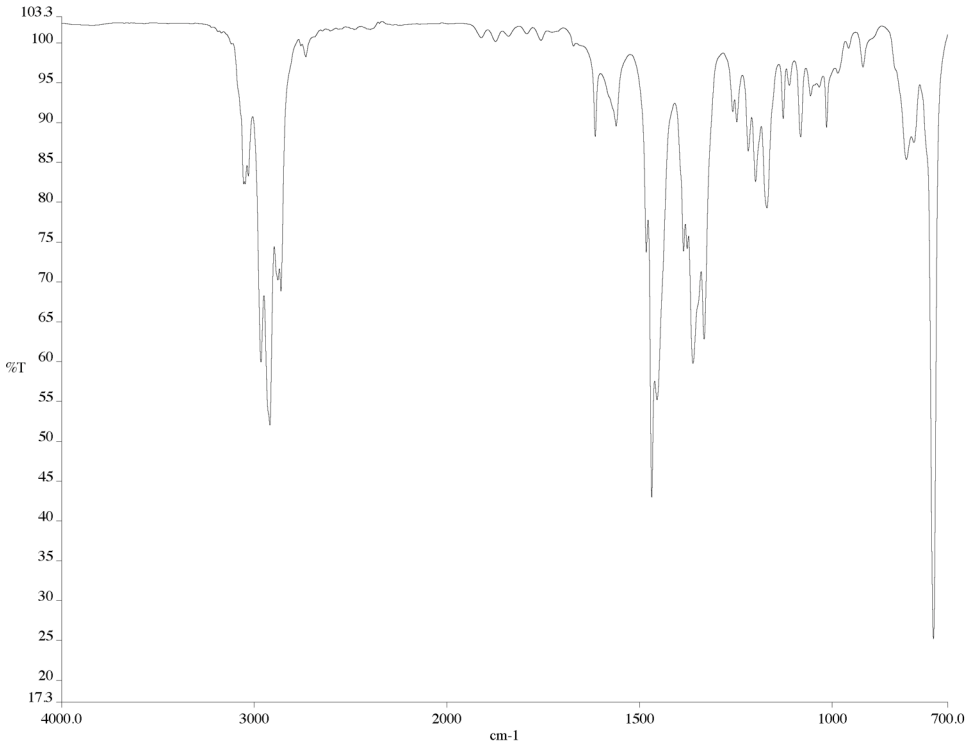

Figure A2.38 Infrared spectrum (thin film/NaCl) of compound **289**.

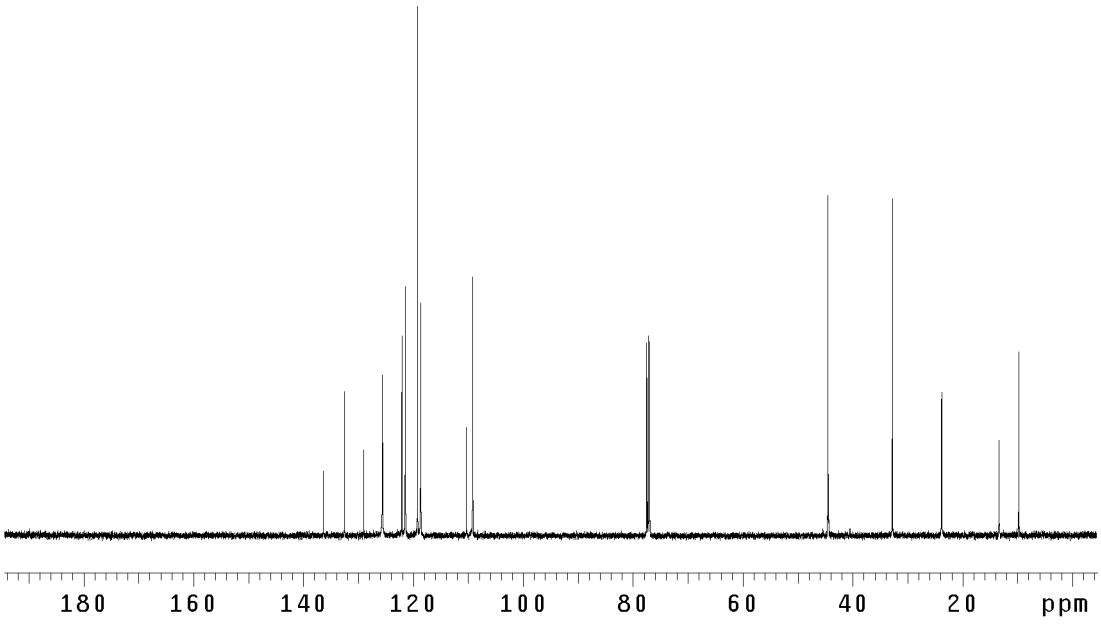

Figure A2.39 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **289**.

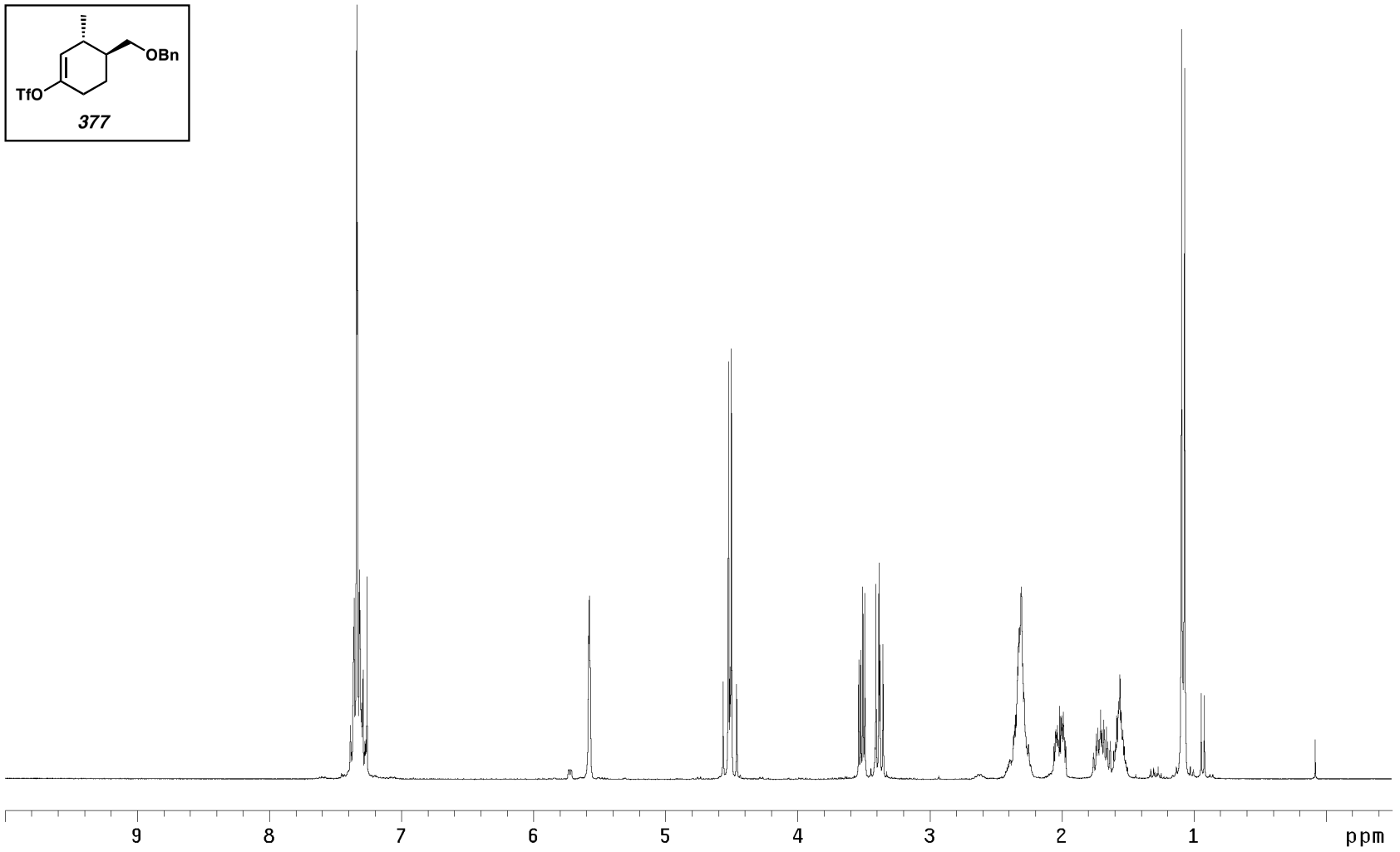

Figure A2.40 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **377**.

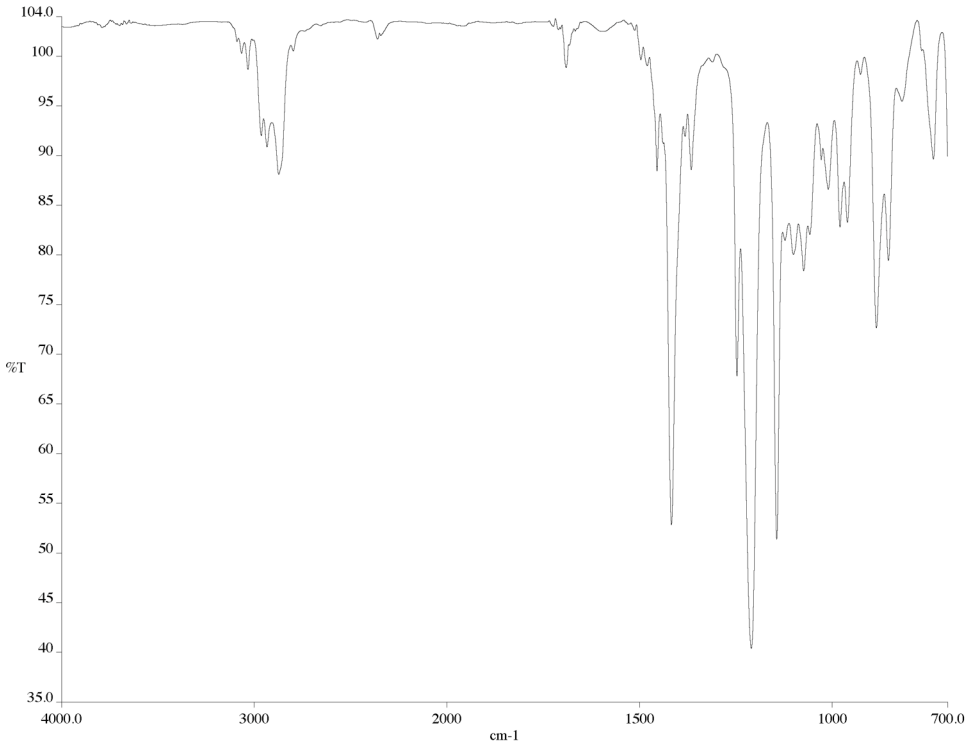

Figure A2.41 Infrared spectrum (thin film/NaCl) of compound **377**.

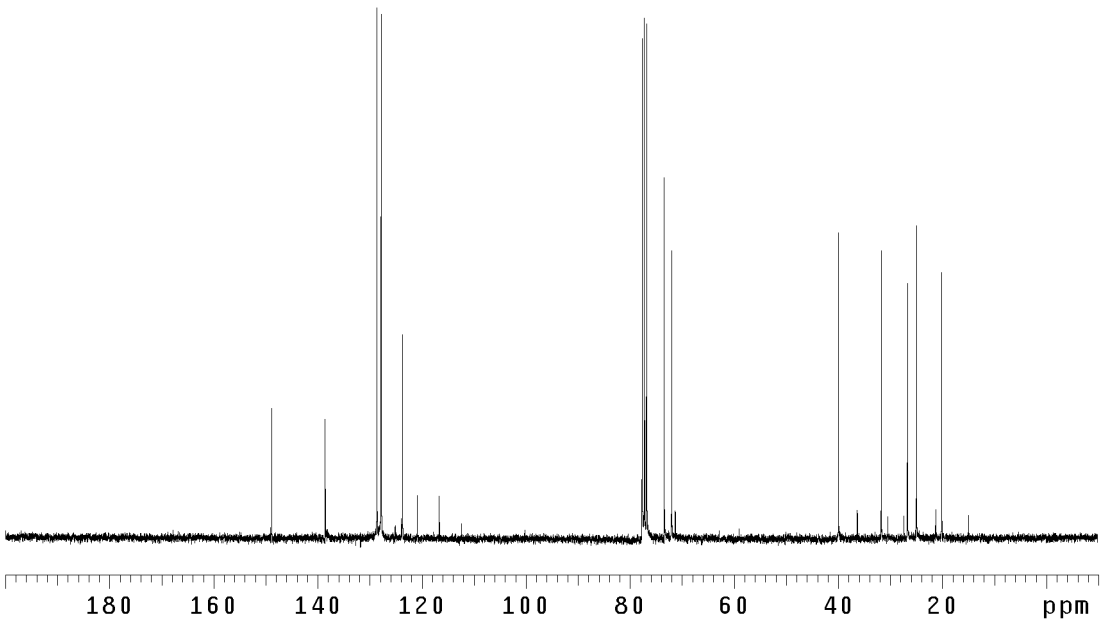

Figure A2.42 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **377**.

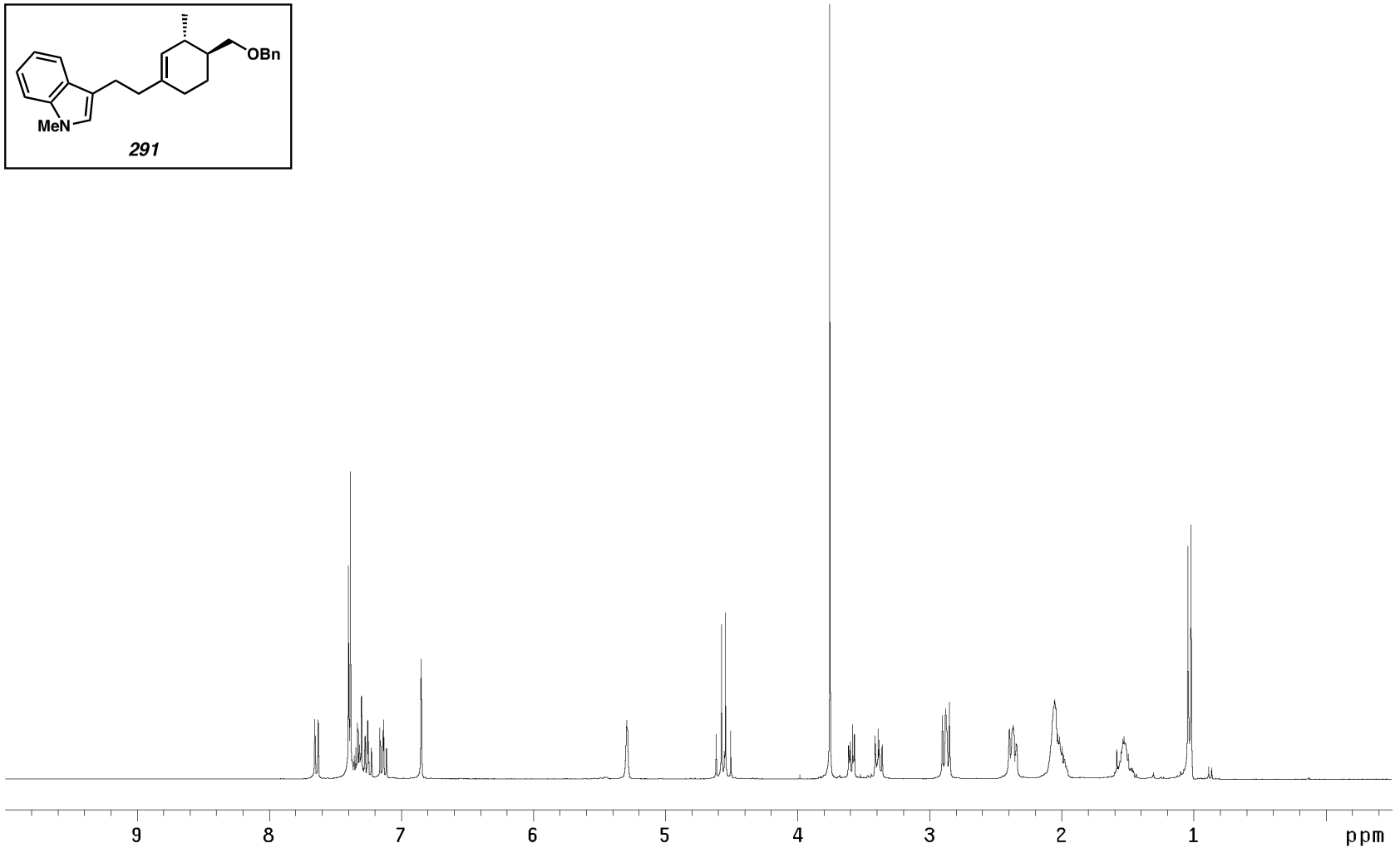

Figure A2.43 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **291**.

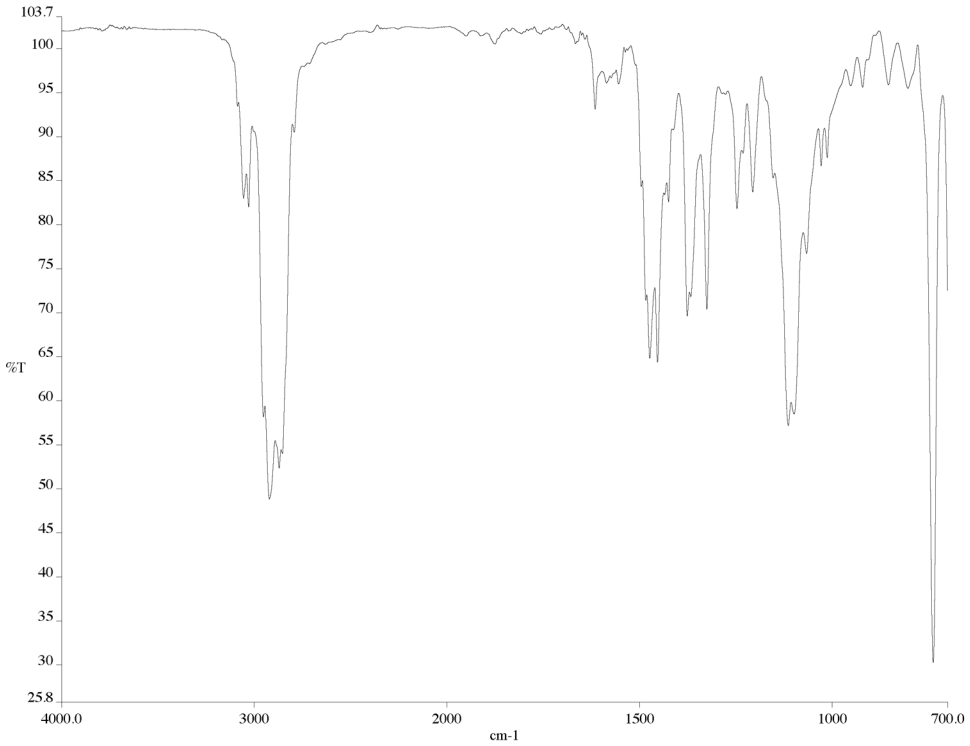

Figure A2.44 Infrared spectrum (thin film/NaCl) of compound **291**.

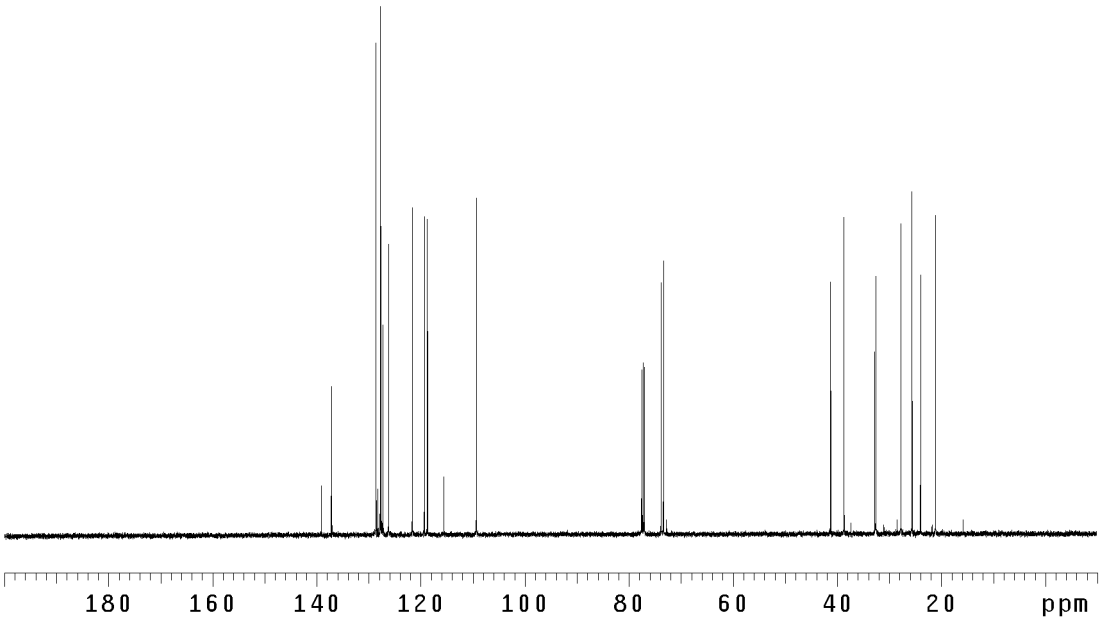

Figure A2.45 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **291**.

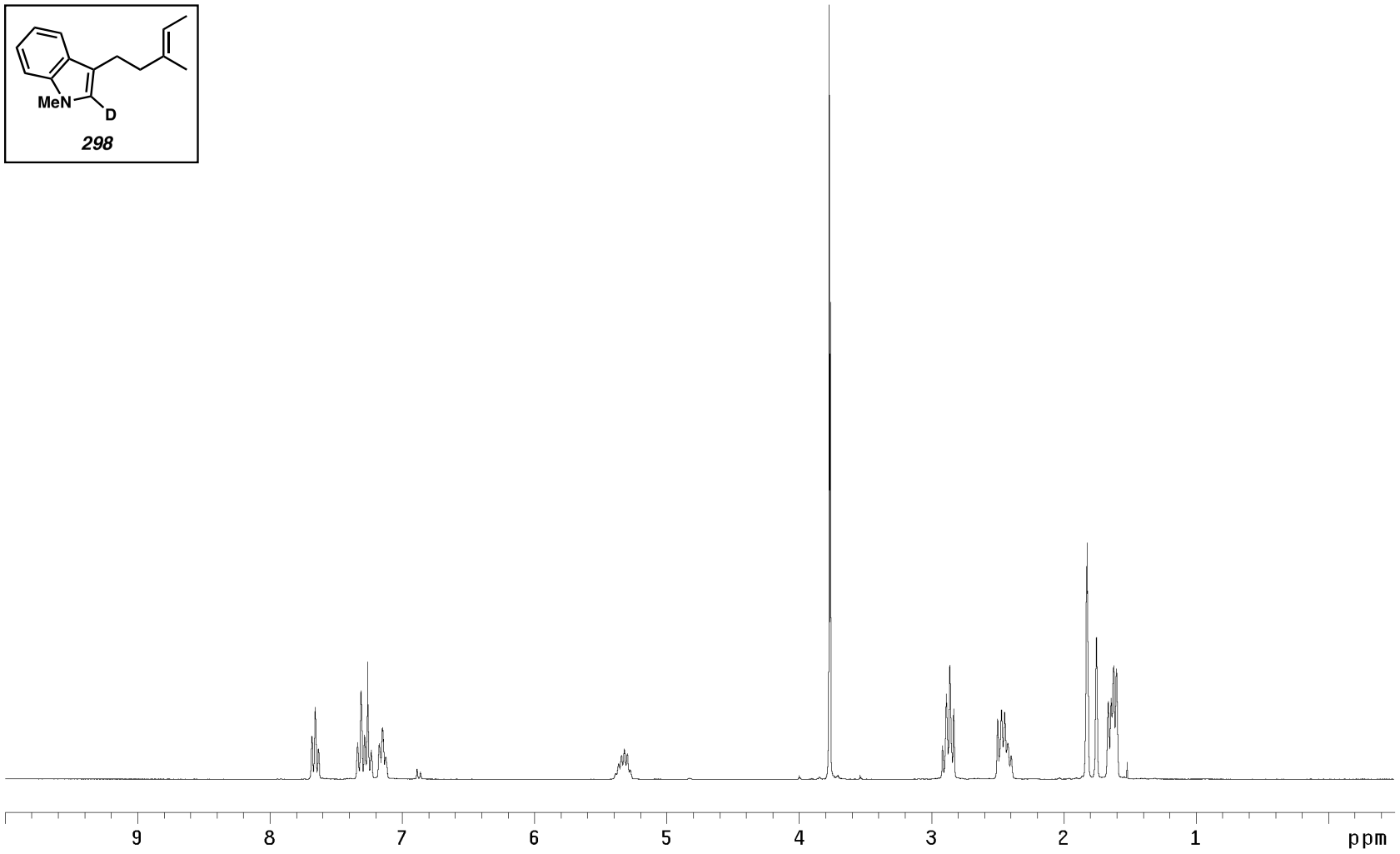

Figure A2.46 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **298**.

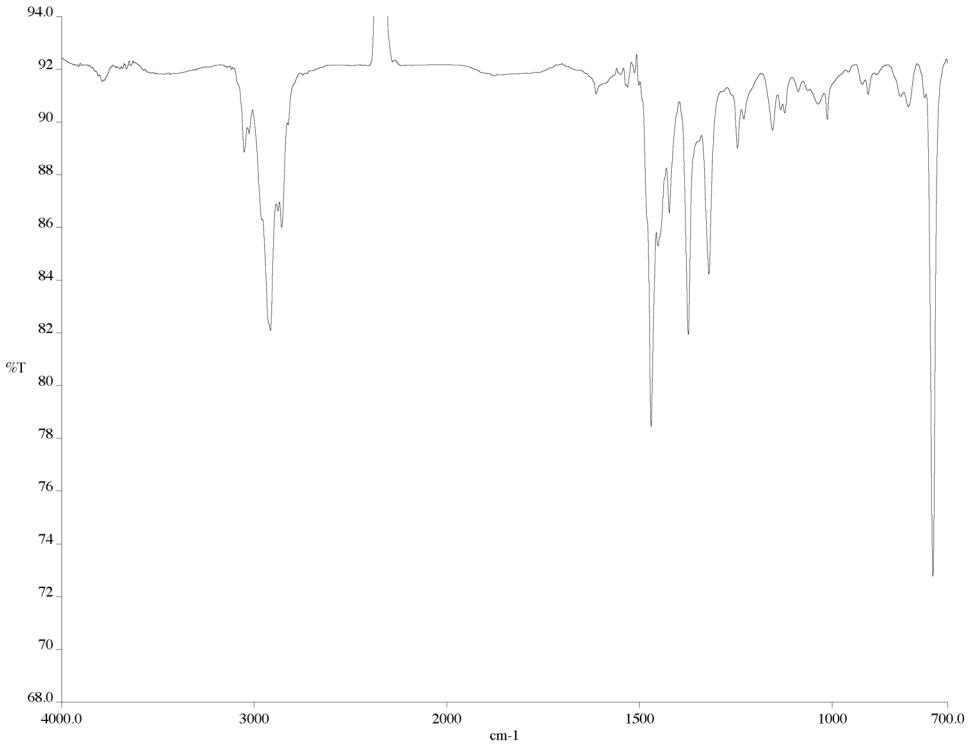

Figure A2.47 Infrared spectrum (thin film/NaCl) of compound **298**.

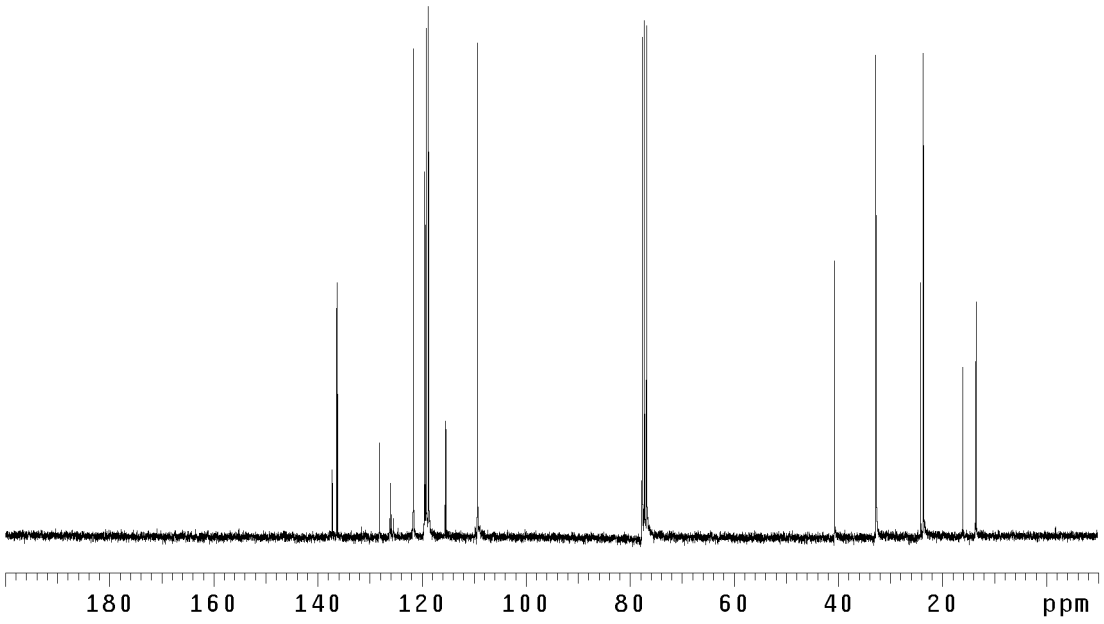

Figure A2.48 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **298**.

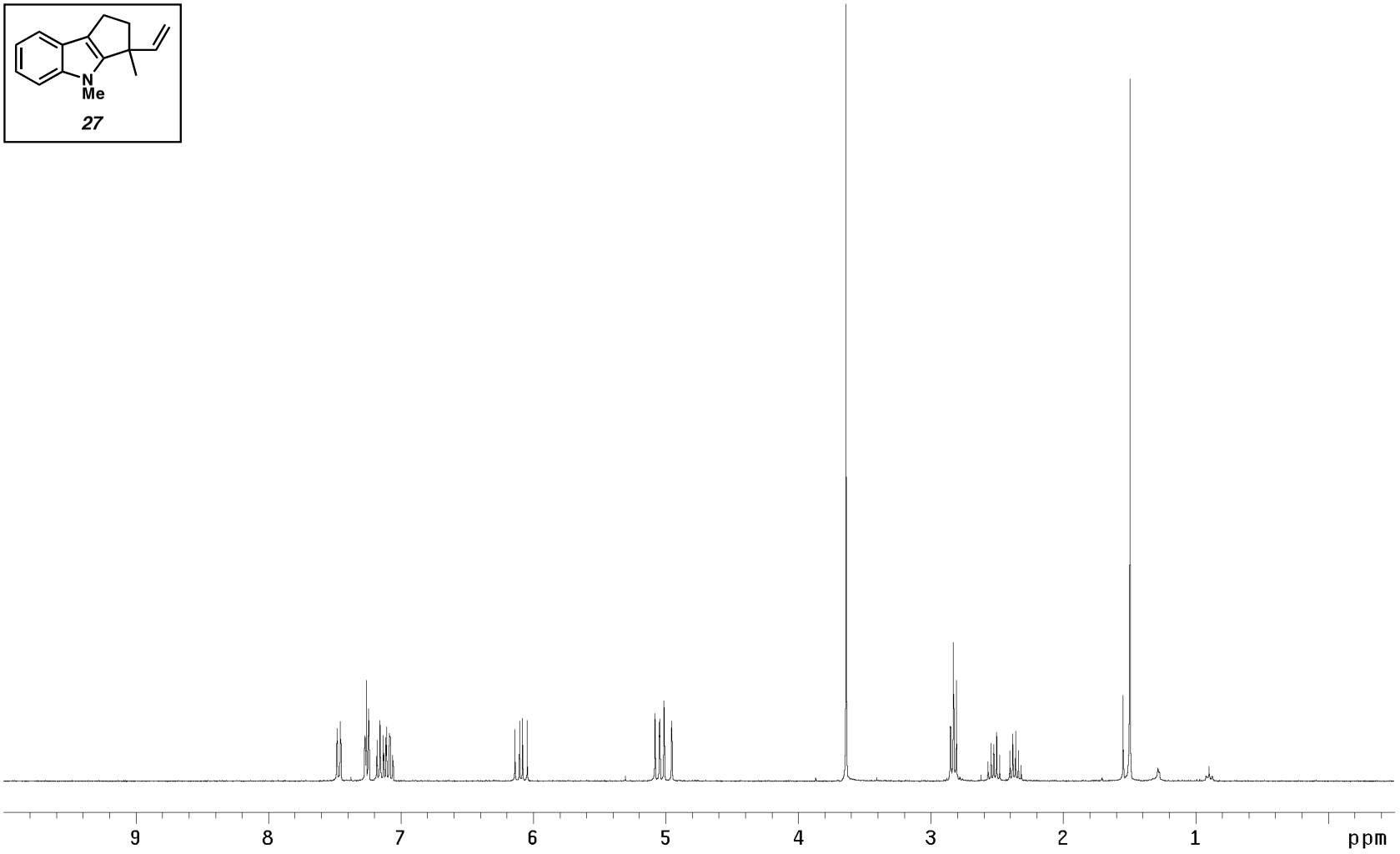

Figure A2.49 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **27**.

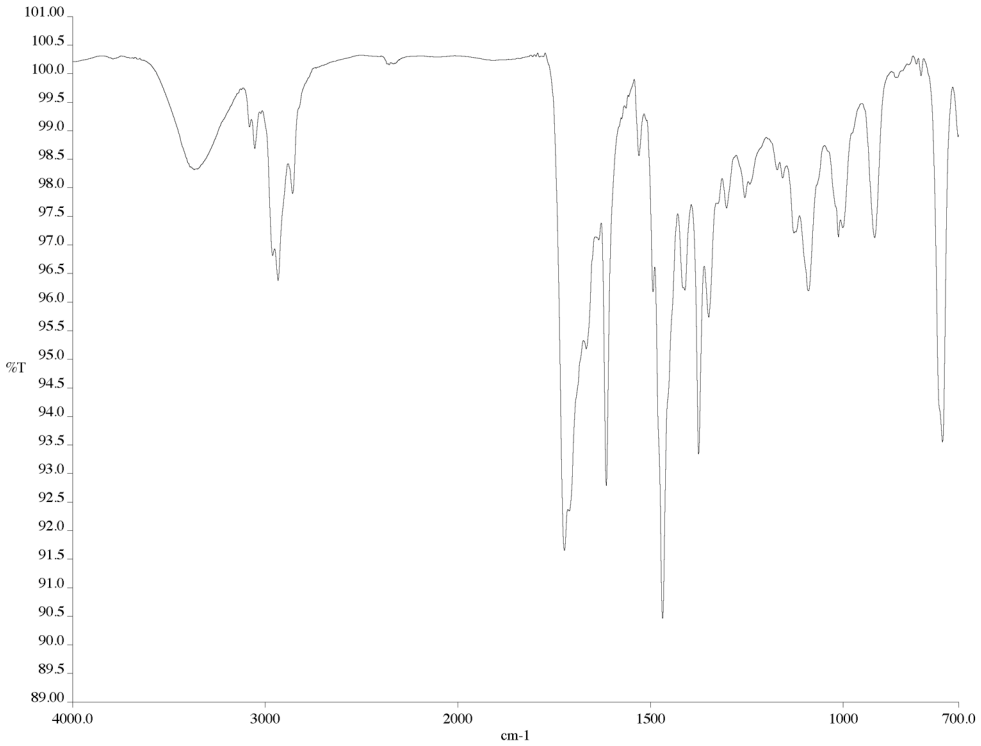

Figure A2.50 Infrared spectrum (thin film/NaCl) of compound **27**.

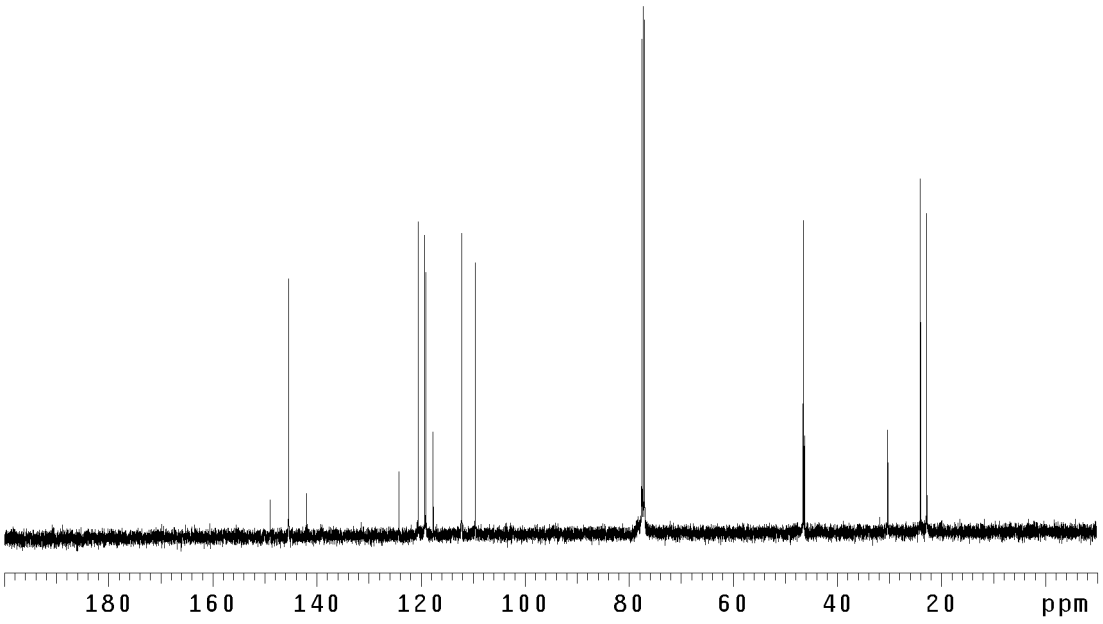

Figure A2.51 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **27**.

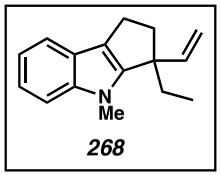

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Figure A2.52 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **268**.

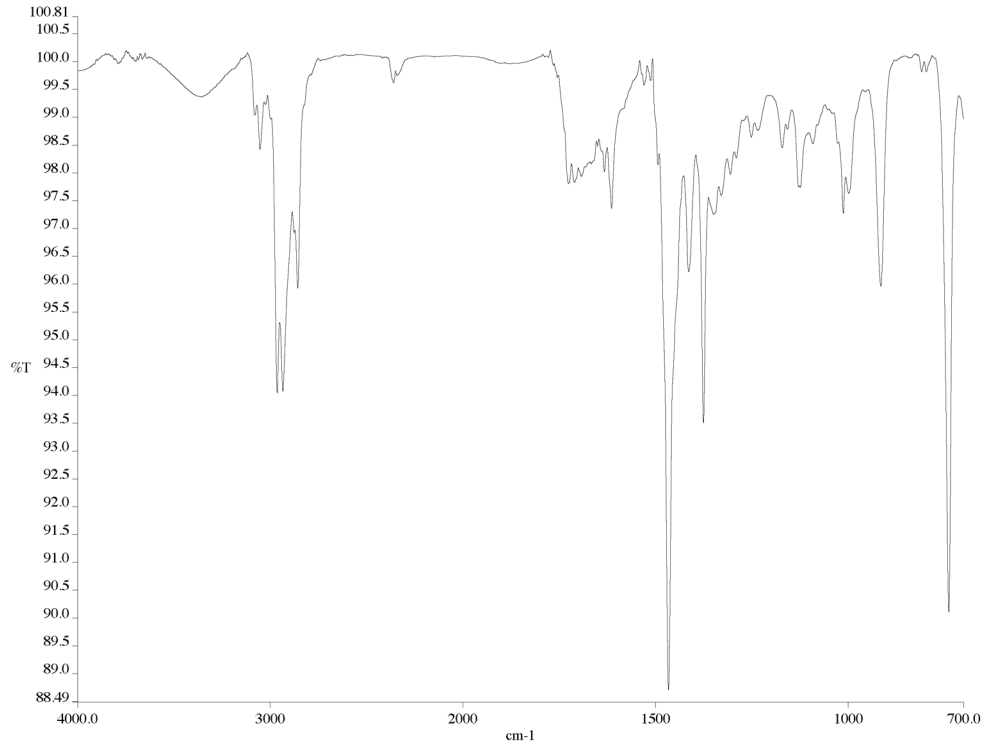


Figure A2.53 Infrared spectrum (thin film/NaCl) of compound **268**.

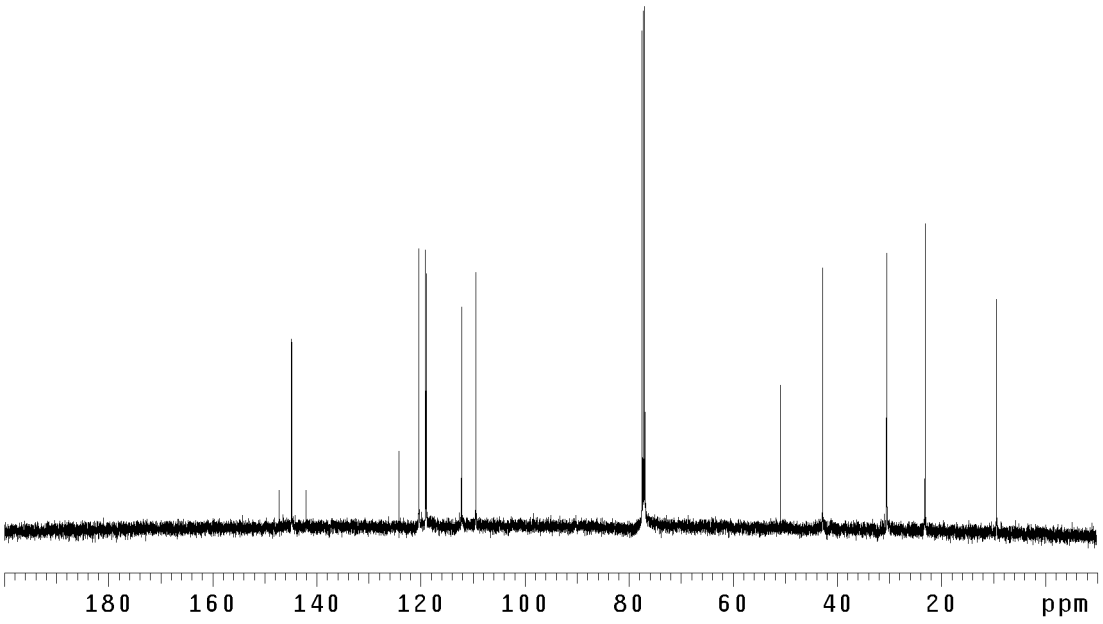


Figure A2.54 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **268**.

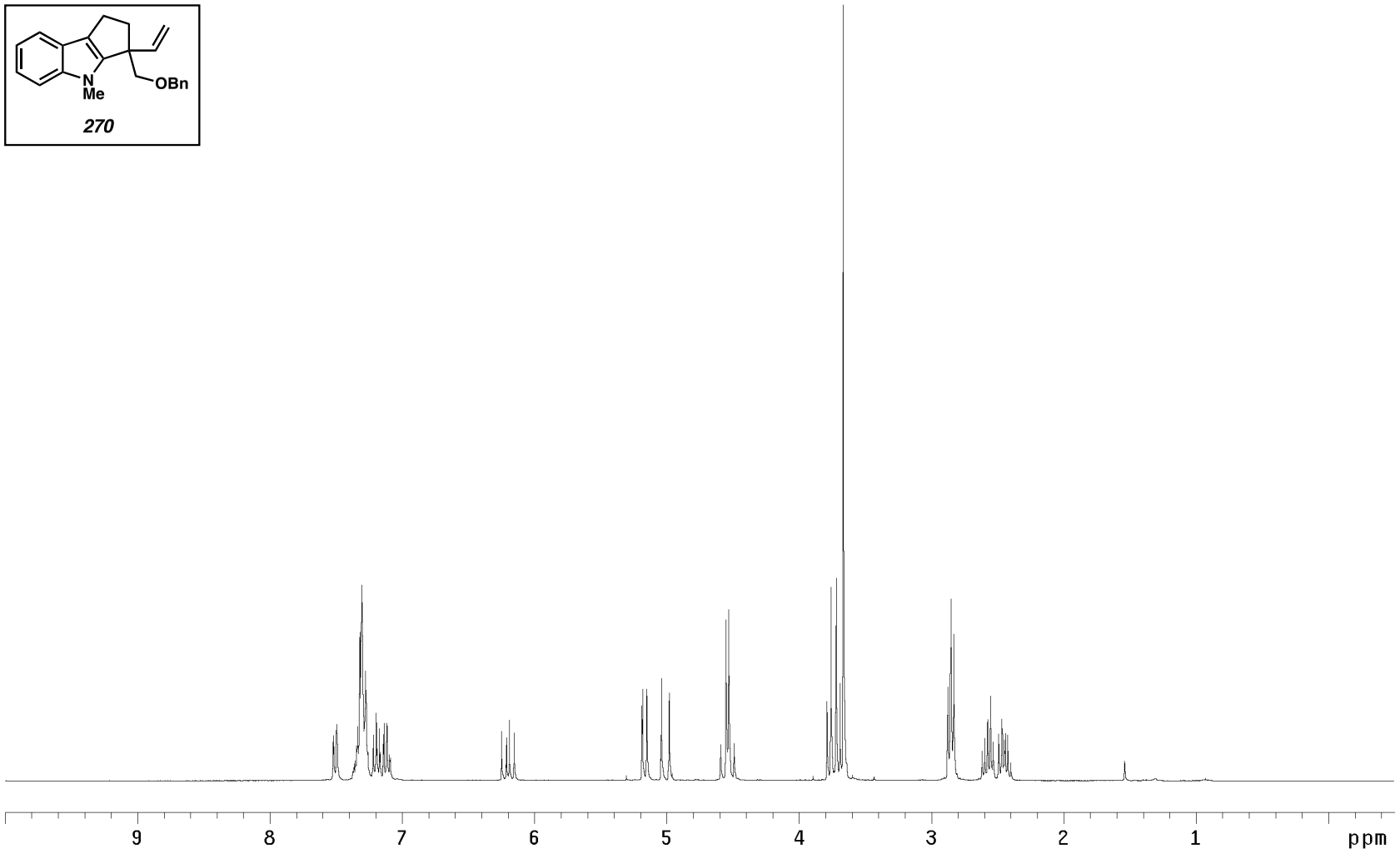


Figure A2.55 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **270**.

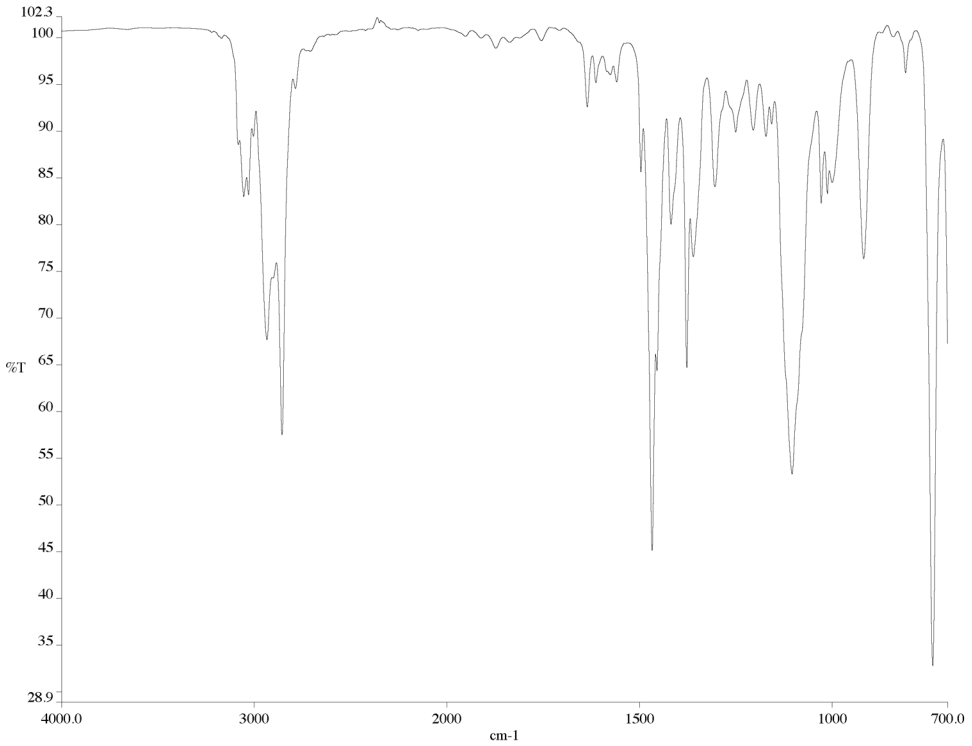


Figure A2.56 Infrared spectrum (thin film/NaCl) of compound **270**.

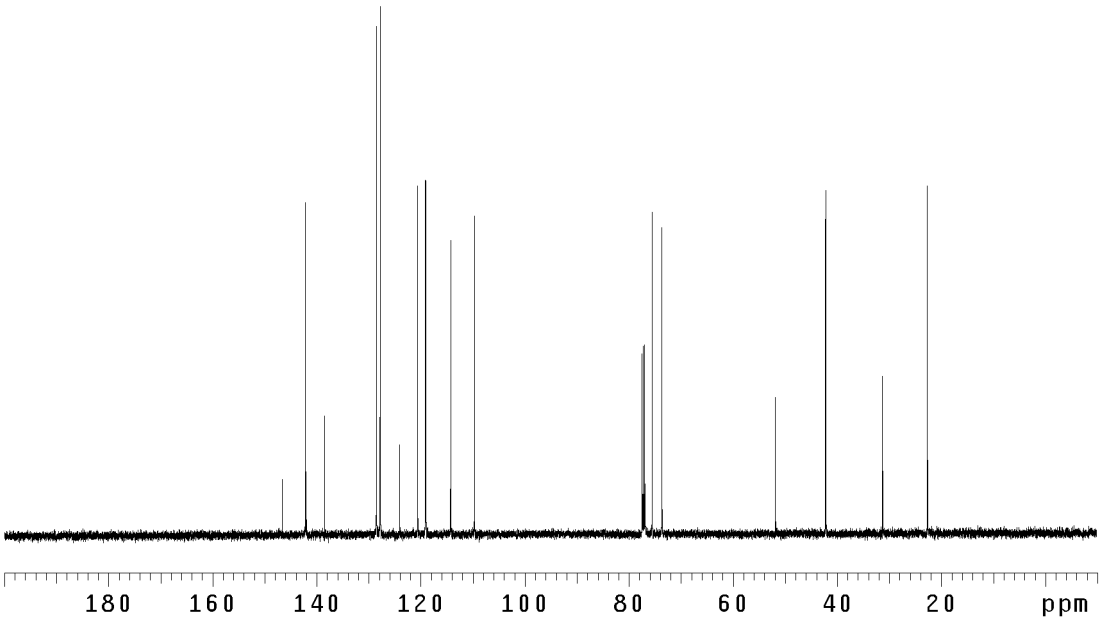


Figure A2.57 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **270**.

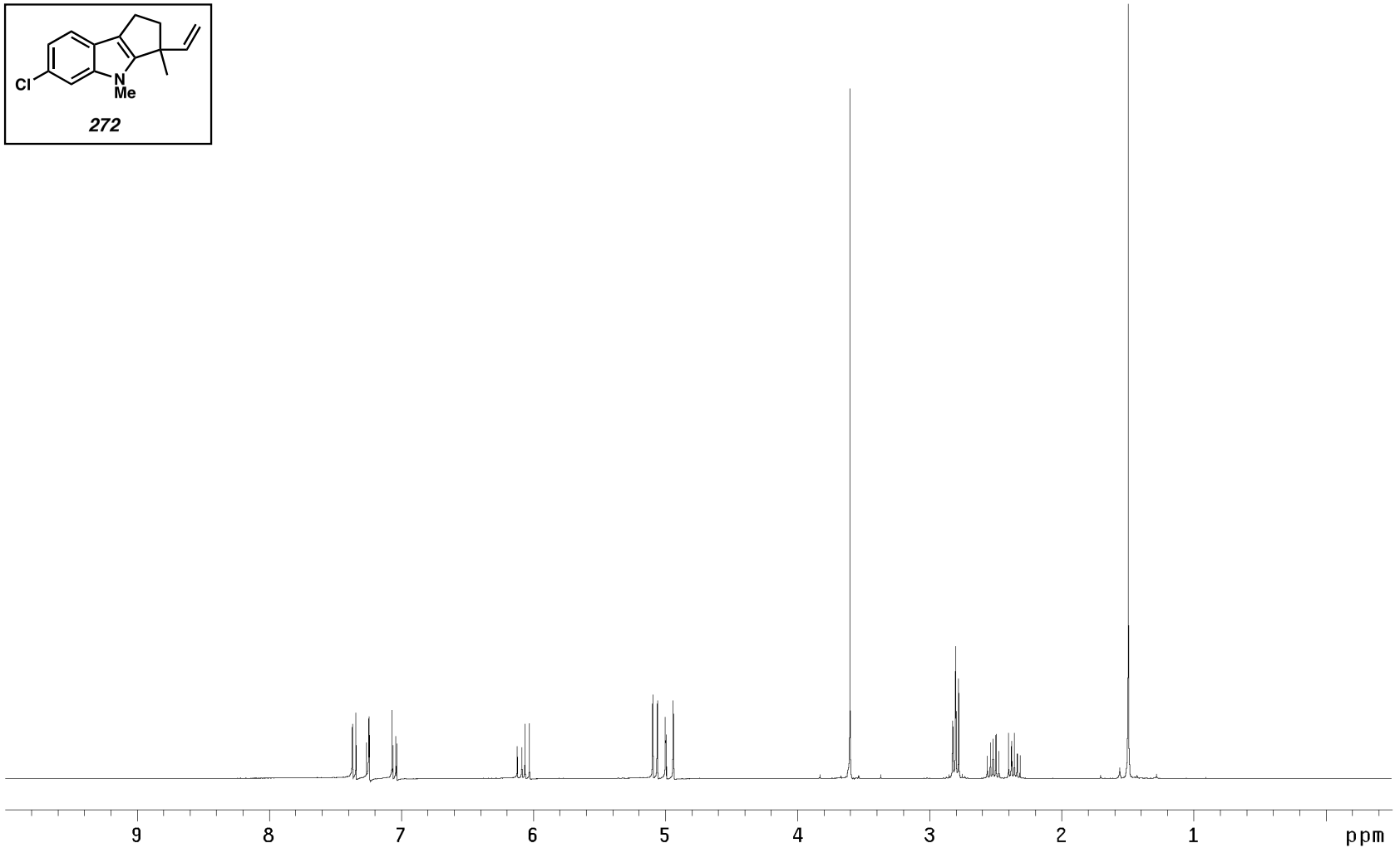


Figure A2.58 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **272**.

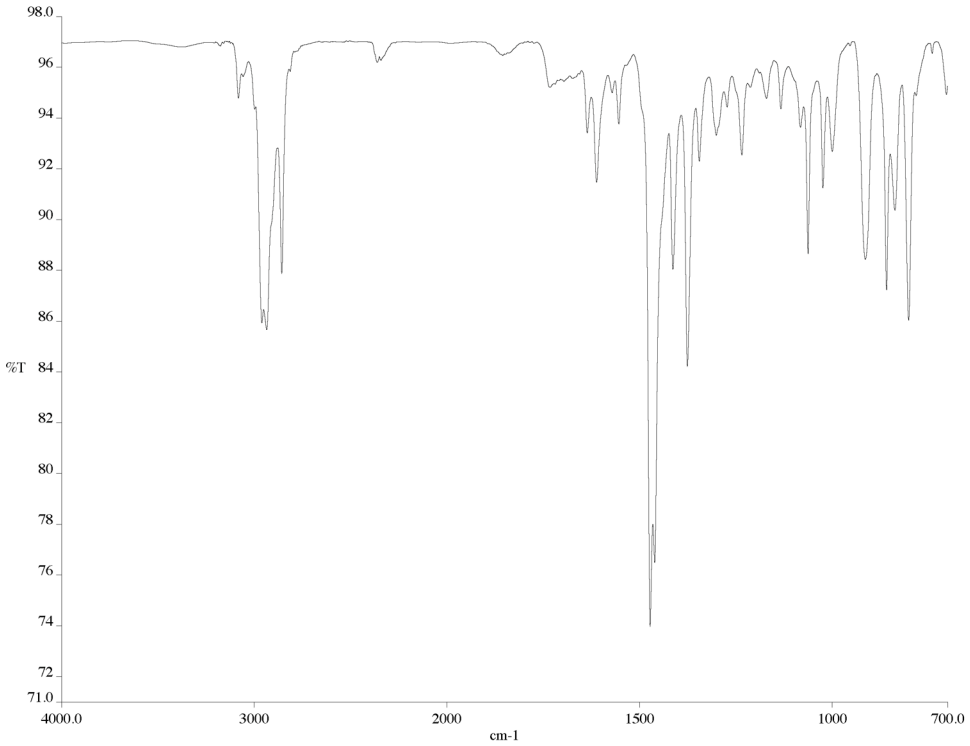


Figure A2.59 Infrared spectrum (thin film/NaCl) of compound **272**.

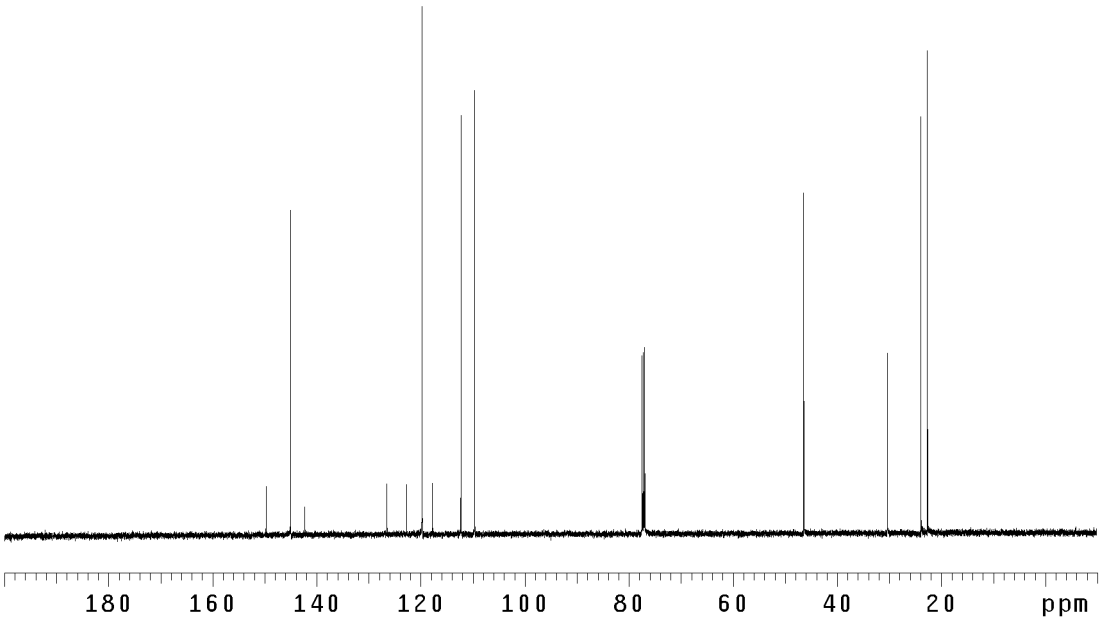


Figure A2.60 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **272**.

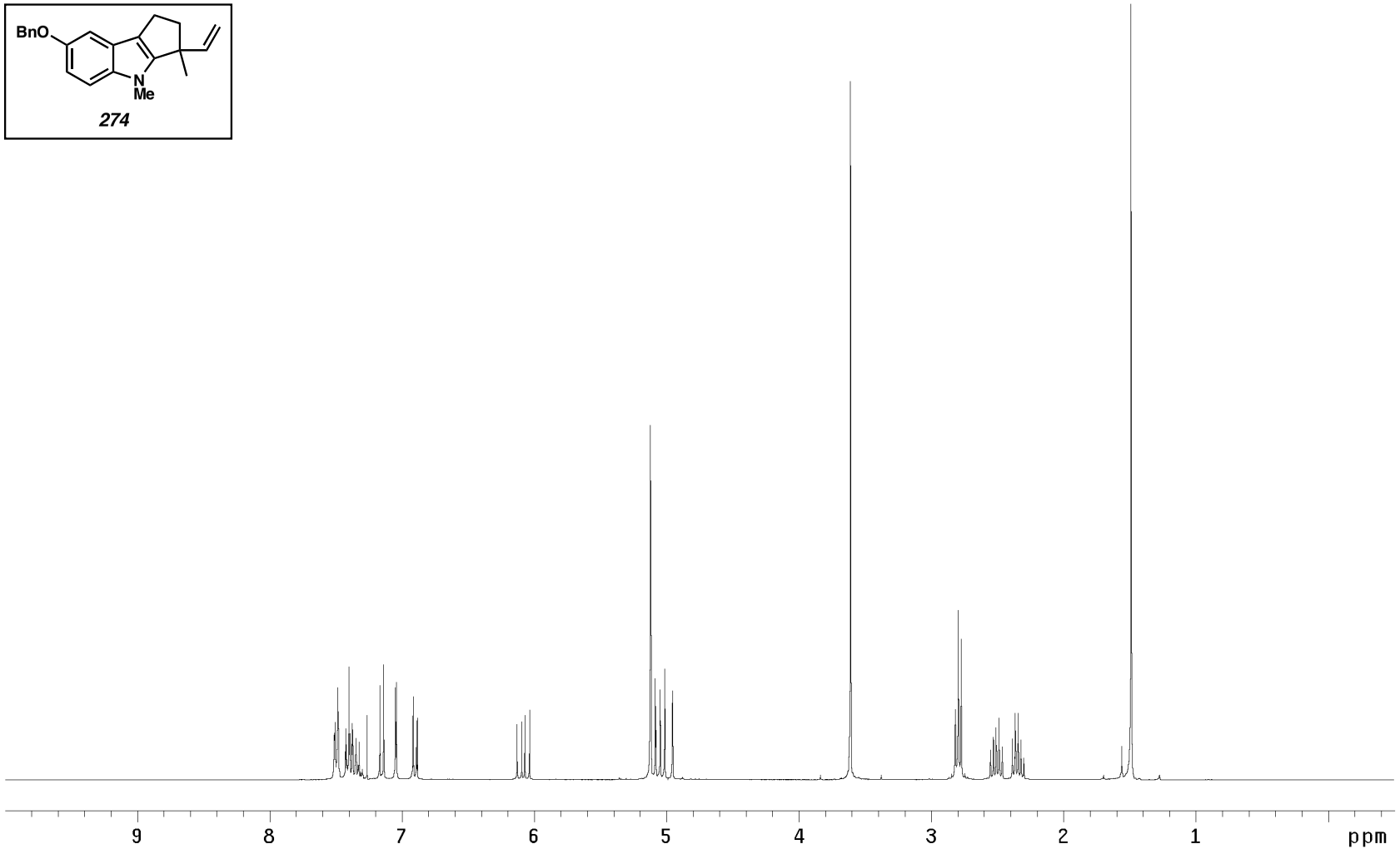


Figure A2.61 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **274**.

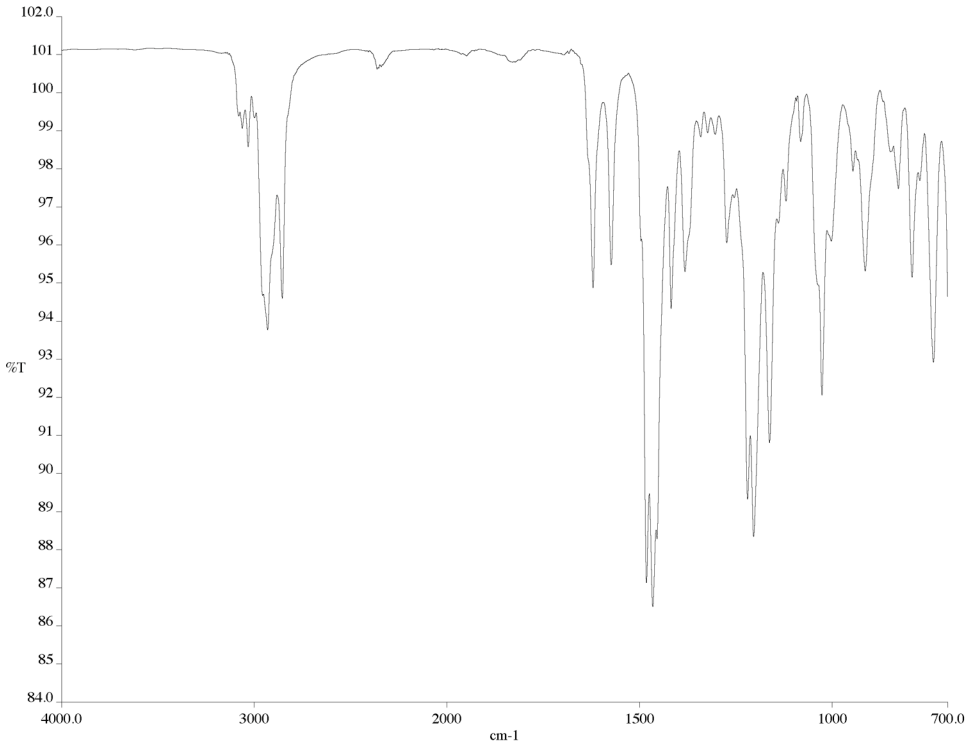


Figure A2.62 Infrared spectrum (thin film/NaCl) of compound **274**.

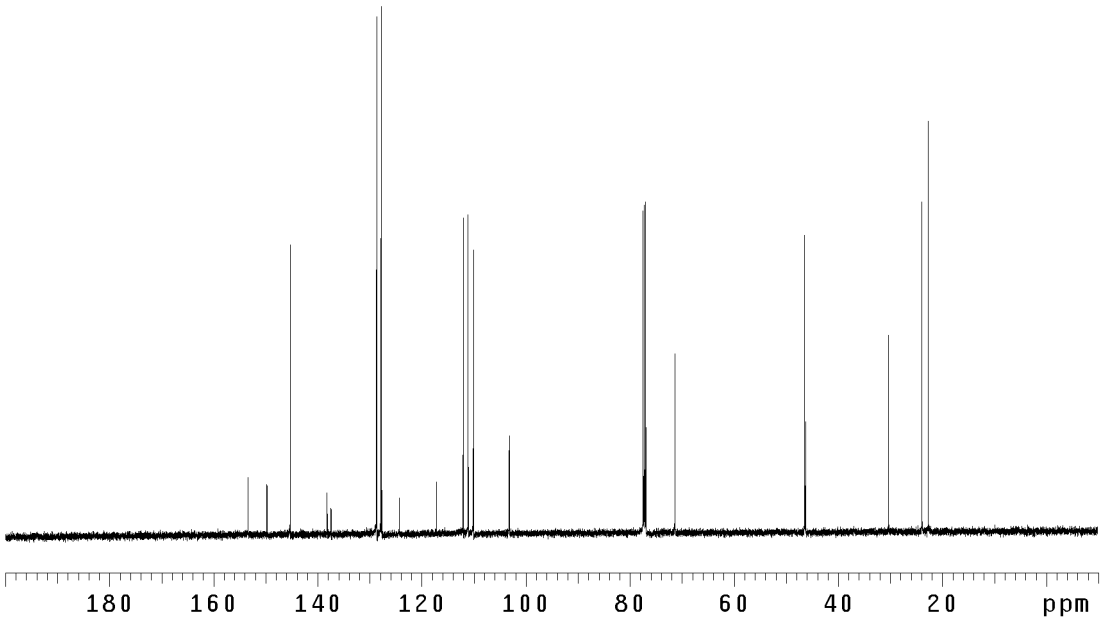


Figure A2.63 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **274**.

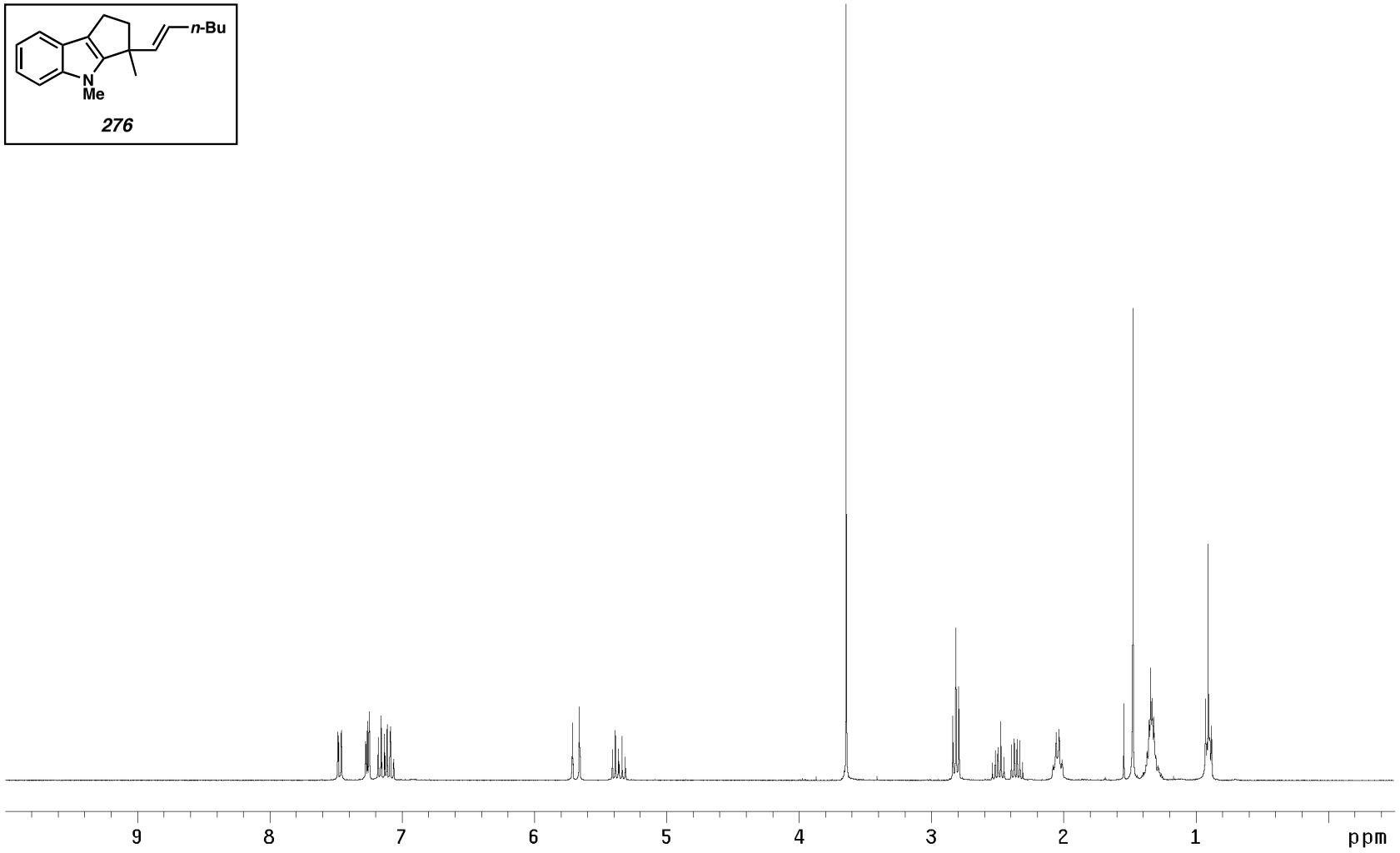


Figure A2.64 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **276**.

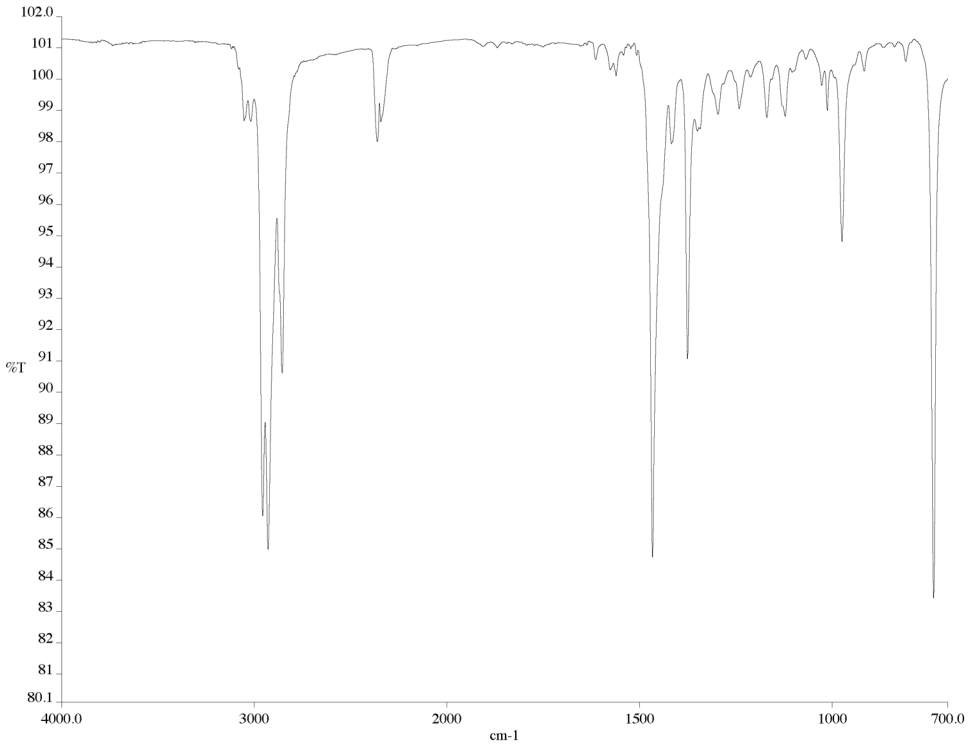


Figure A2.65 Infrared spectrum (thin film/NaCl) of compound **276**.

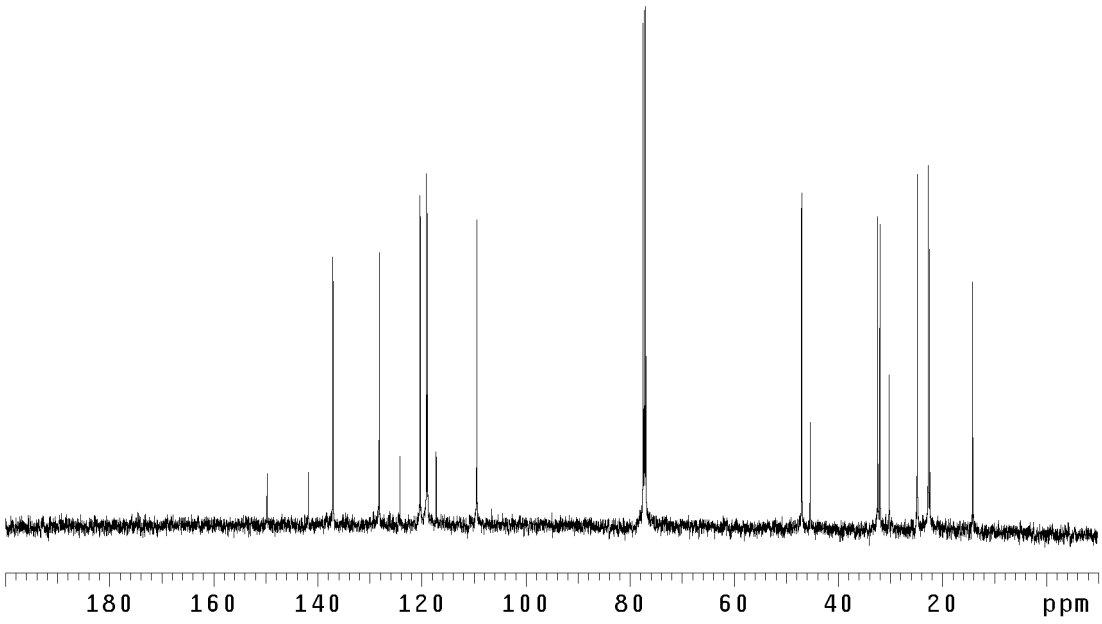


Figure A2.66 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **276**.

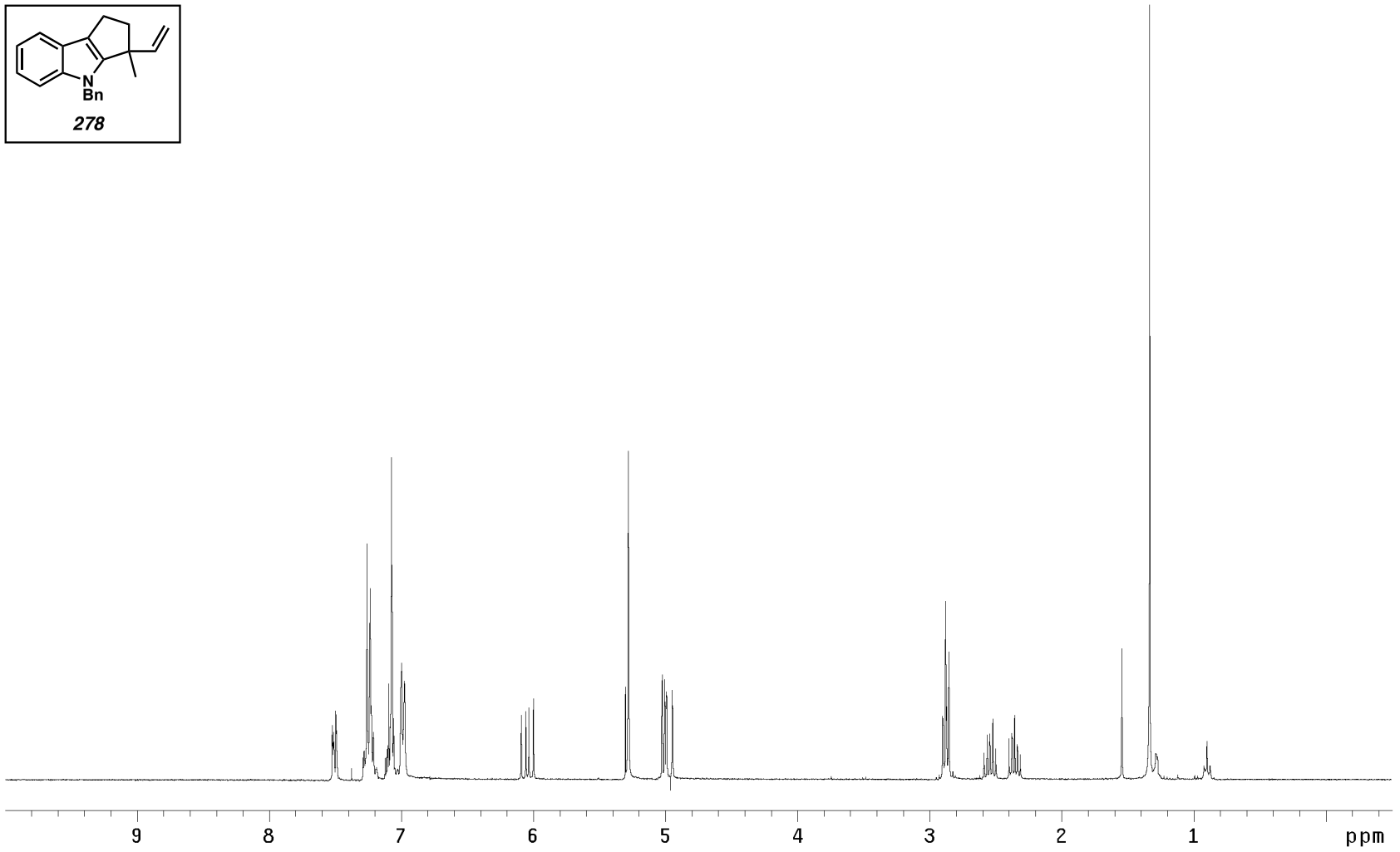


Figure A2.67 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **278**.

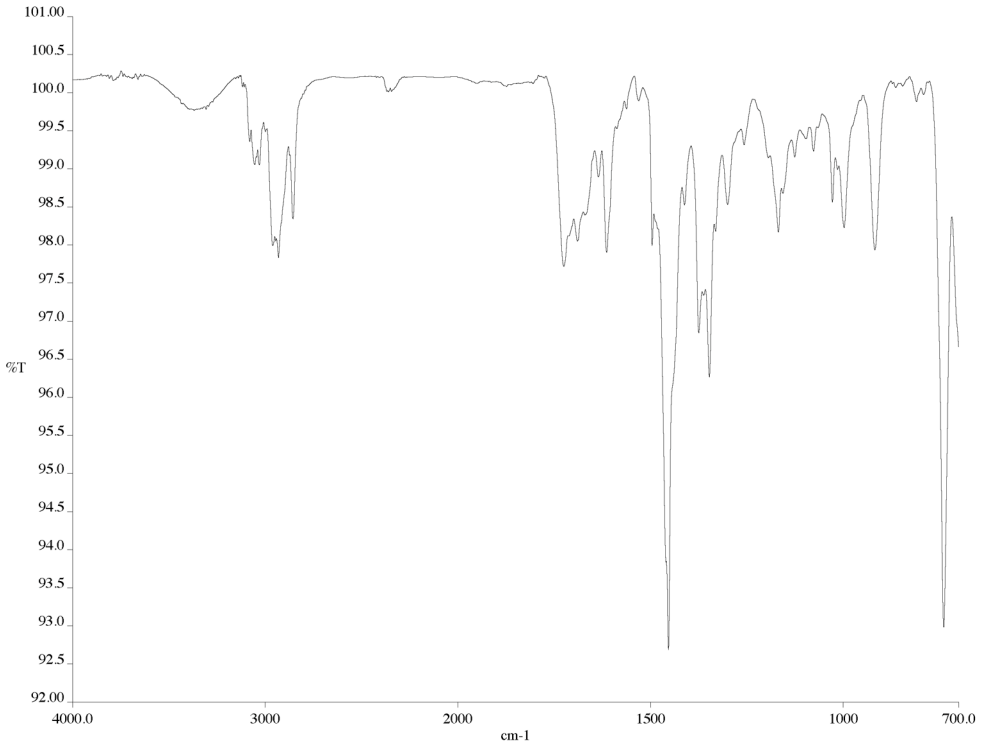


Figure A2.68 Infrared spectrum (thin film/NaCl) of compound **278**.

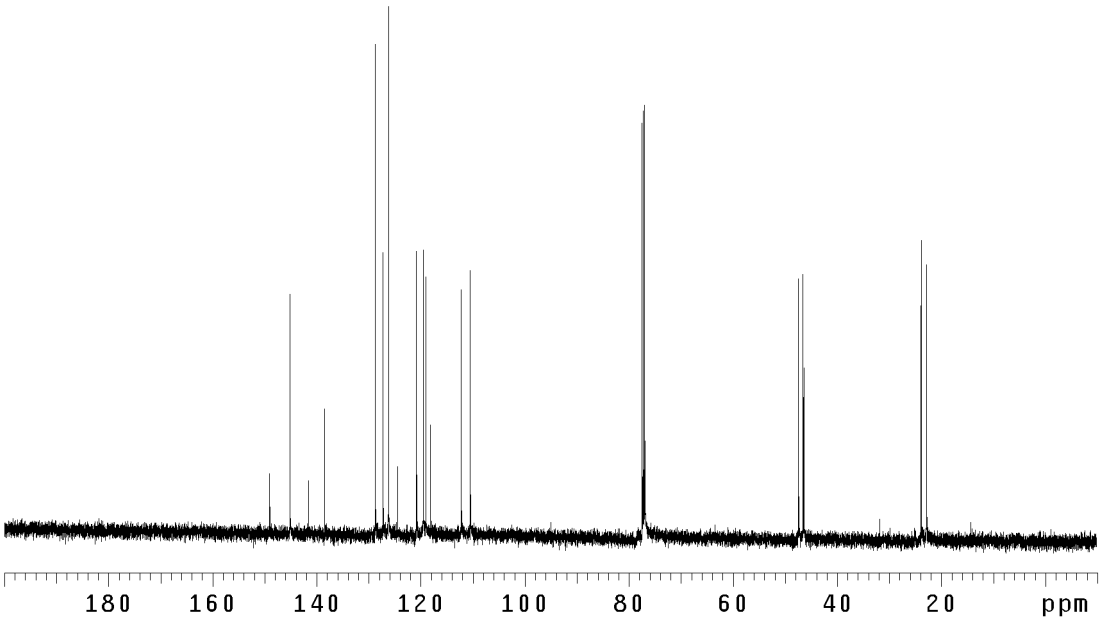


Figure A2.69 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **278**.

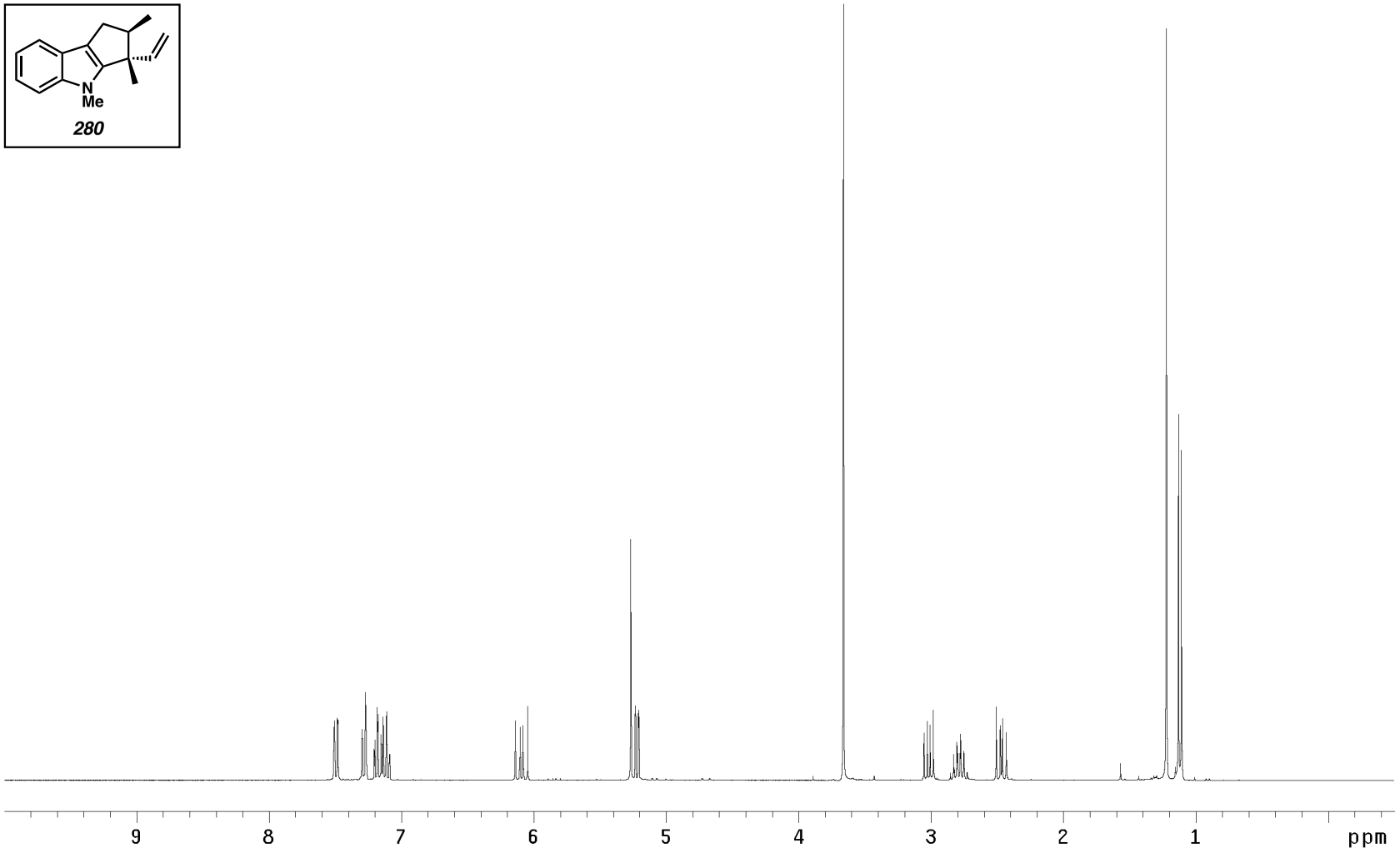


Figure A2.70 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **280**.

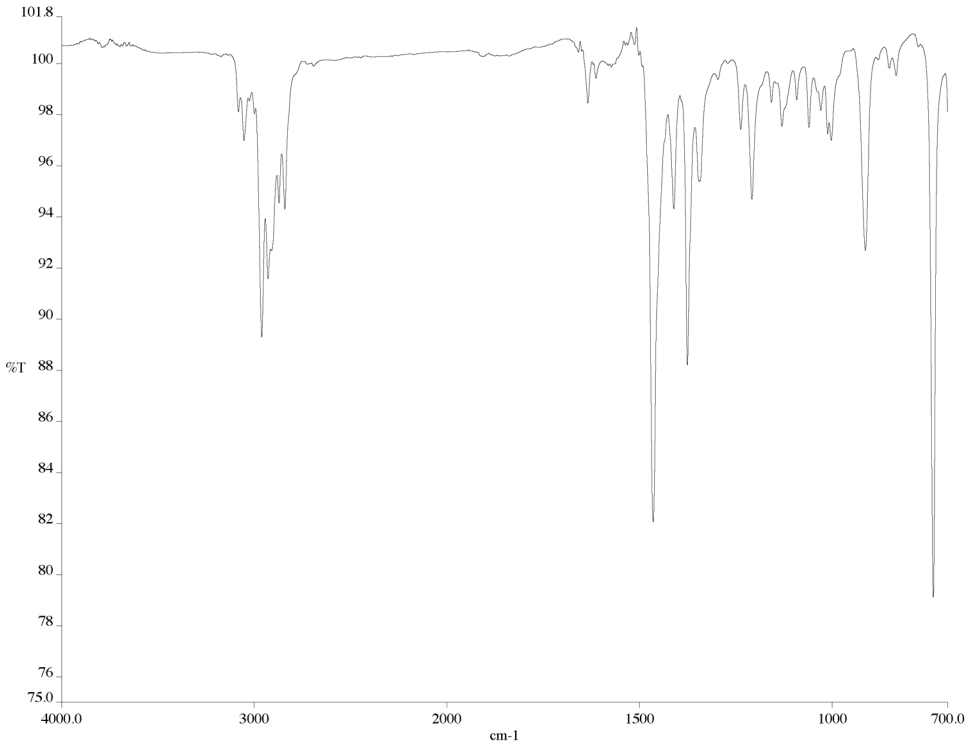


Figure A2.71 Infrared spectrum (thin film/NaCl) of compound **280**.

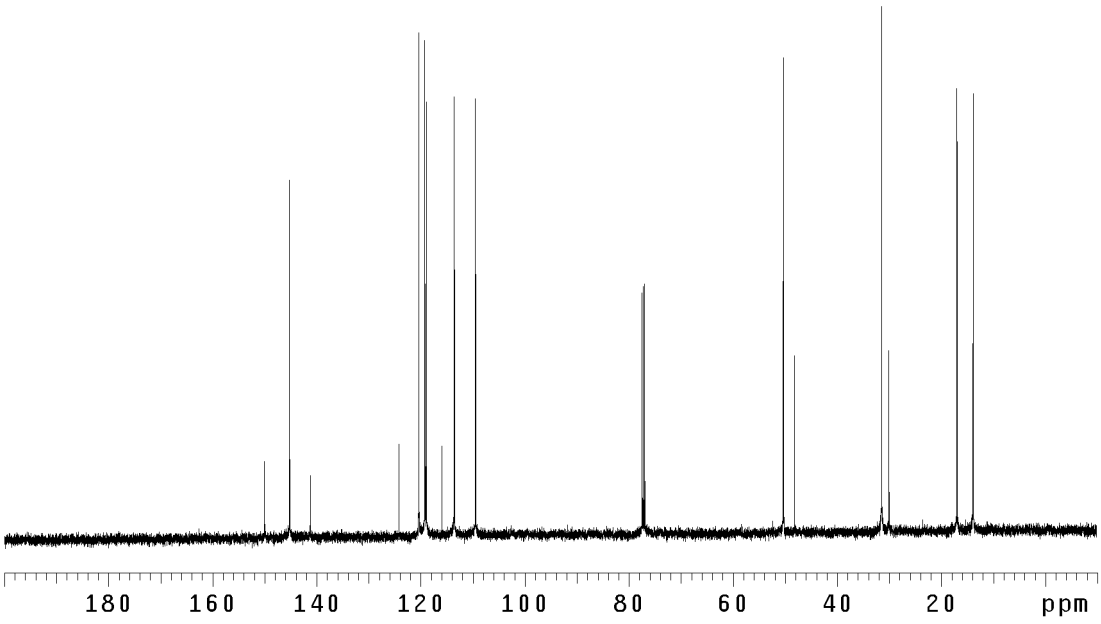


Figure A2.72 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **280**.

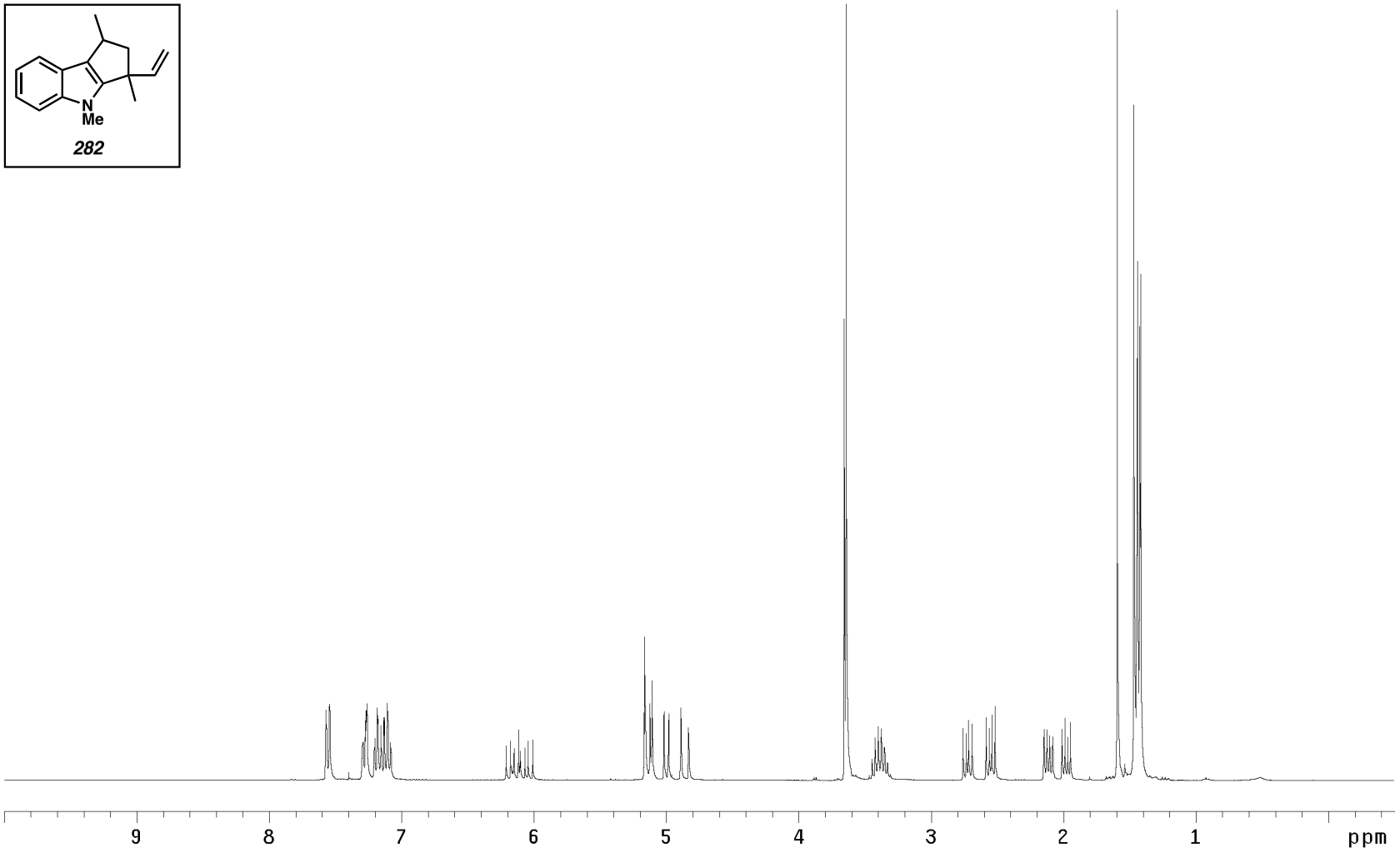


Figure A2.73 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **282**.

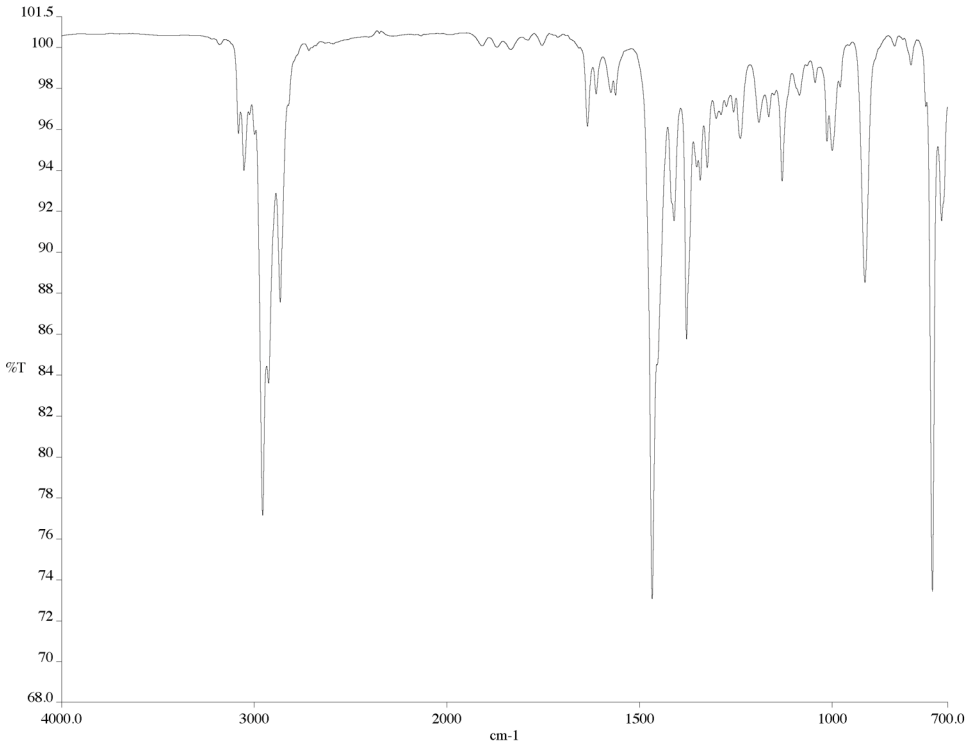


Figure A2.74 Infrared spectrum (thin film/NaCl) of compound **282**.

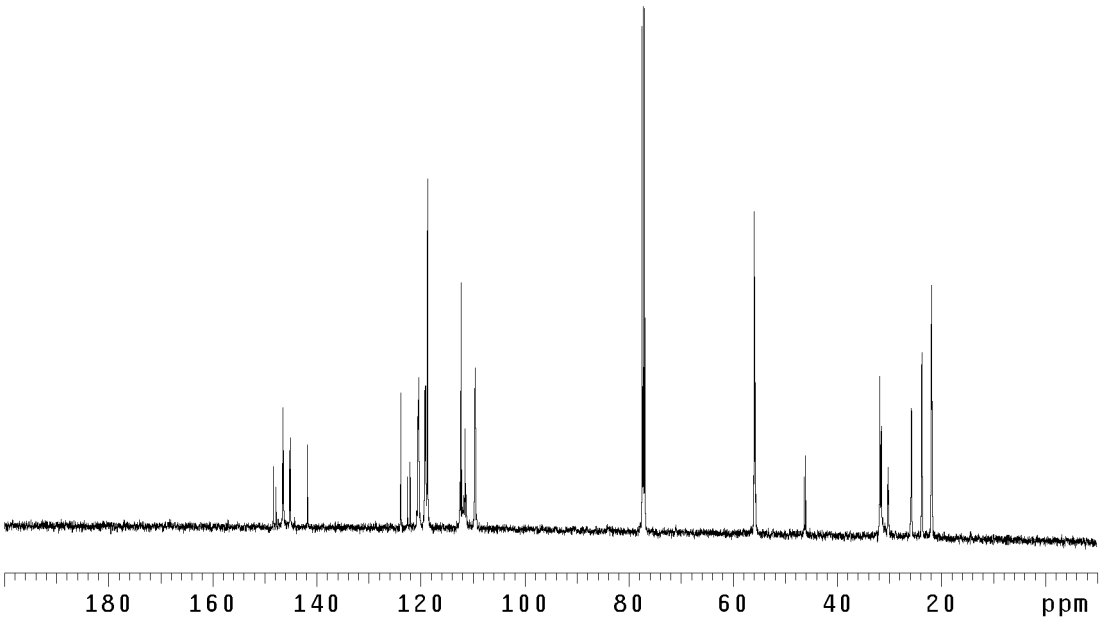


Figure A2.75 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **282**.

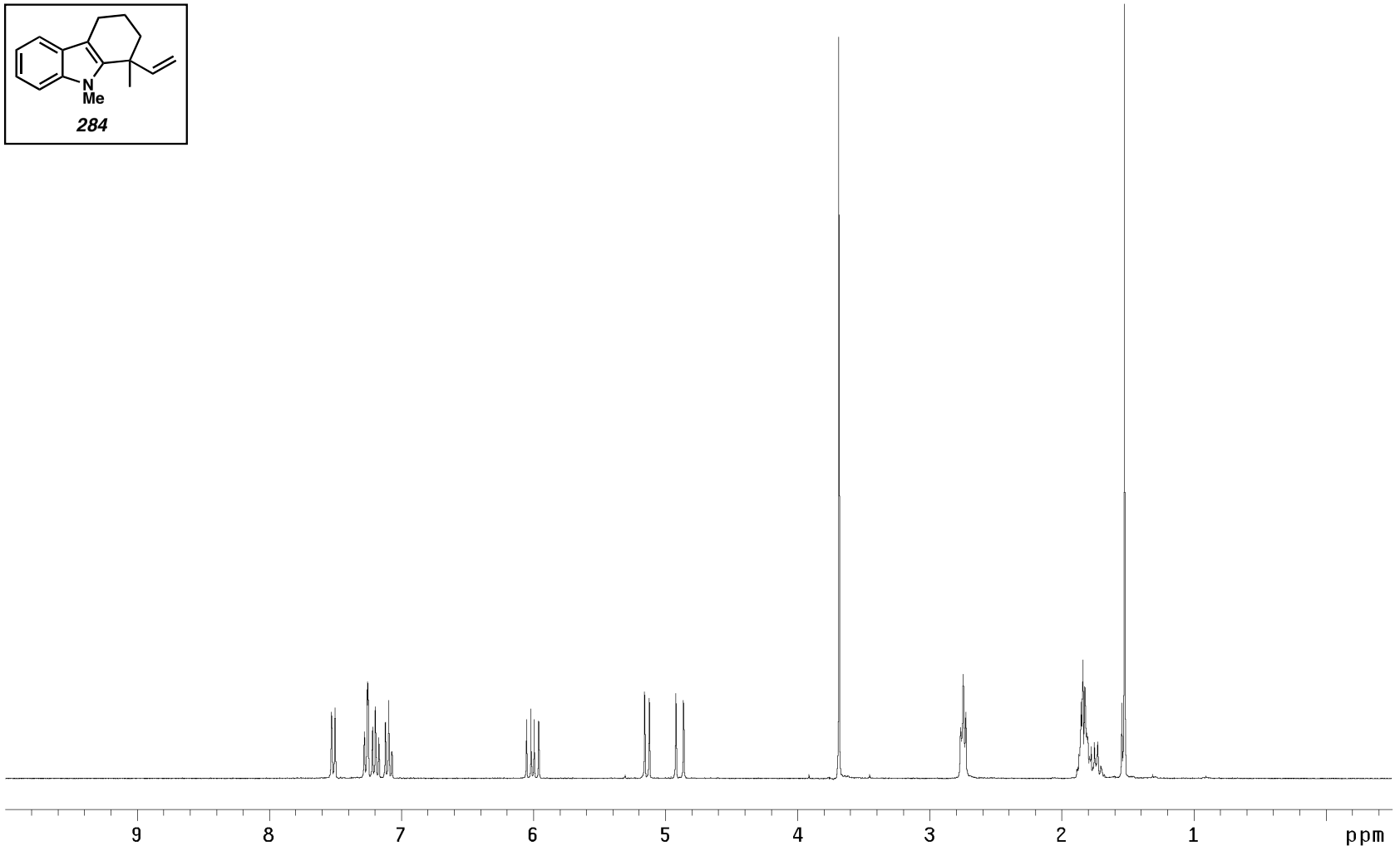


Figure A2.76 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **284**.

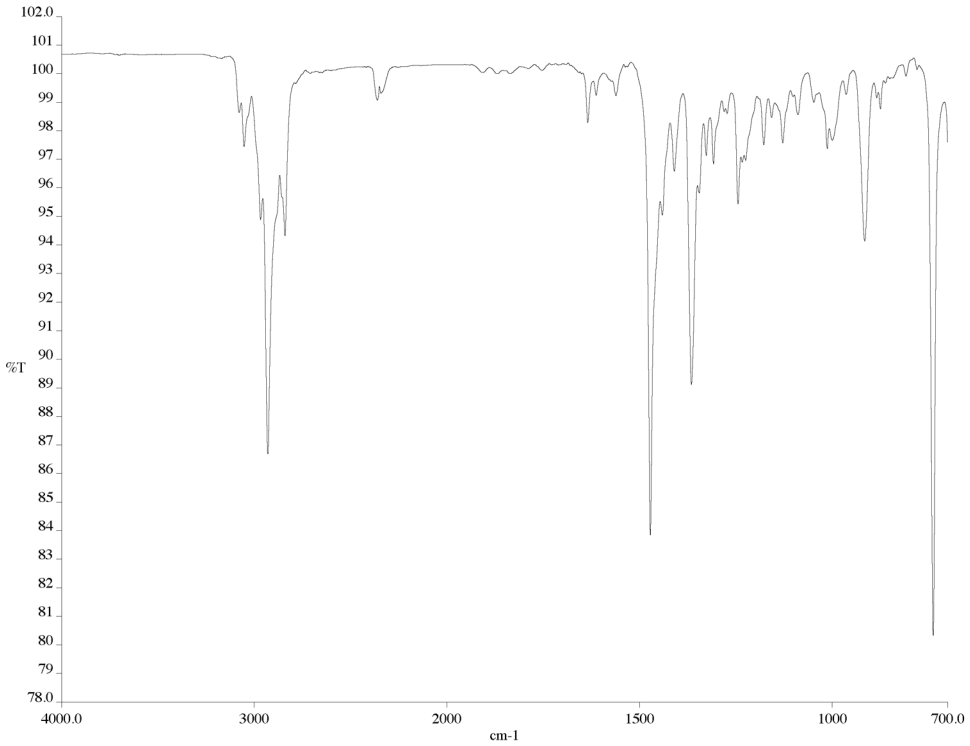


Figure A2.77 Infrared spectrum (thin film/NaCl) of compound **284**.

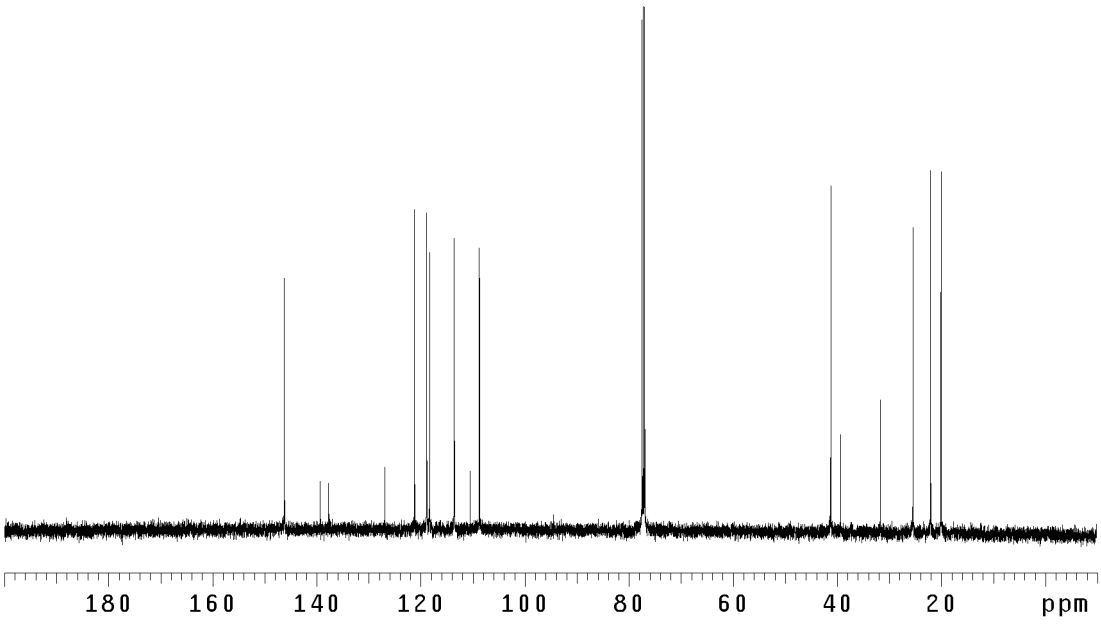


Figure A2.78 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **284**.

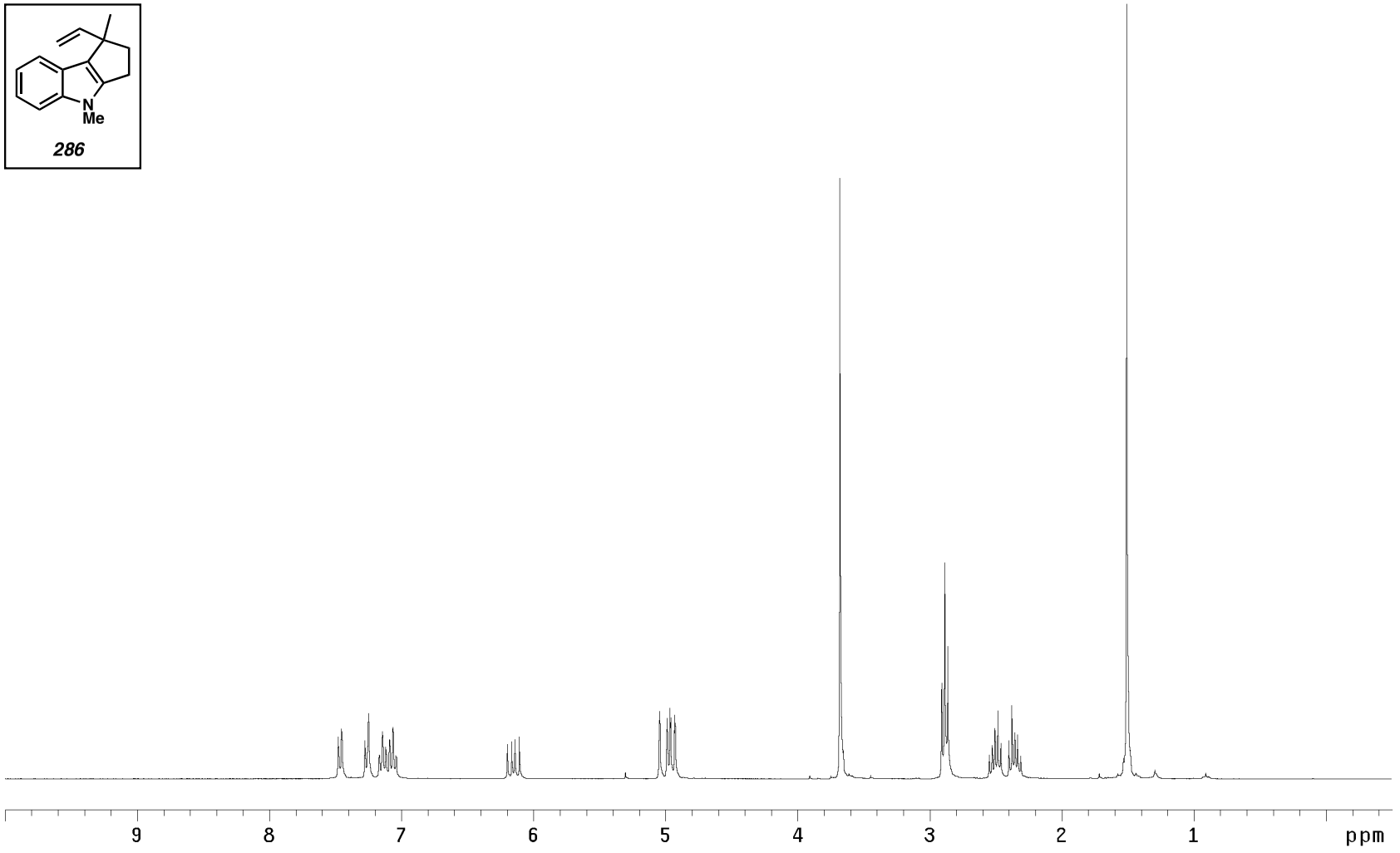


Figure A2.79 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **286**.

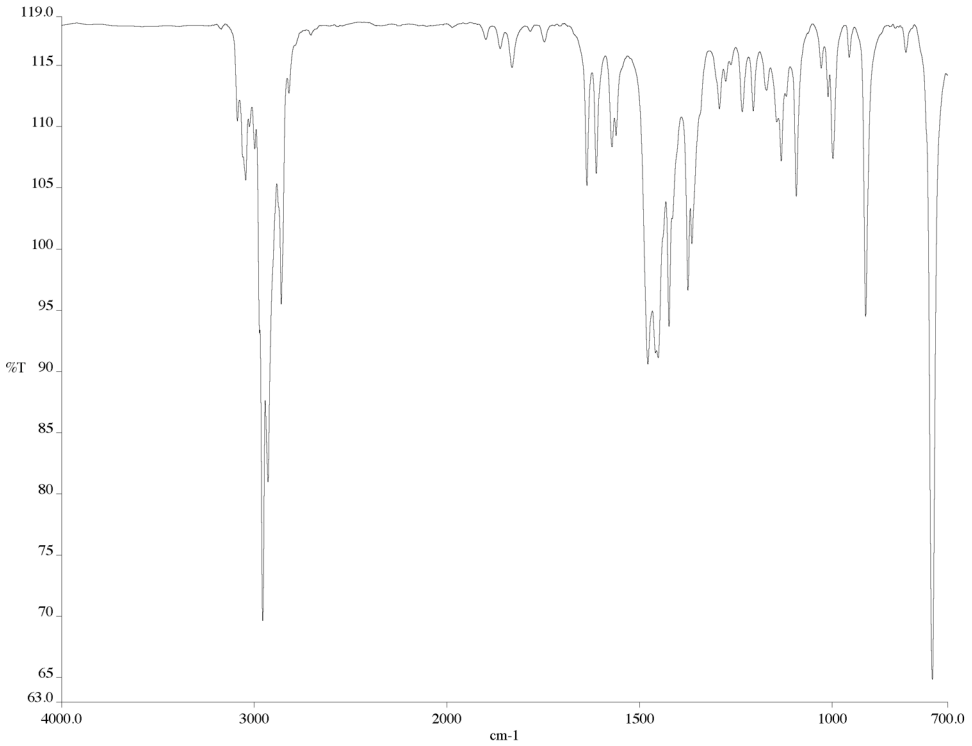


Figure A2.80 Infrared spectrum (thin film/NaCl) of compound **286**.

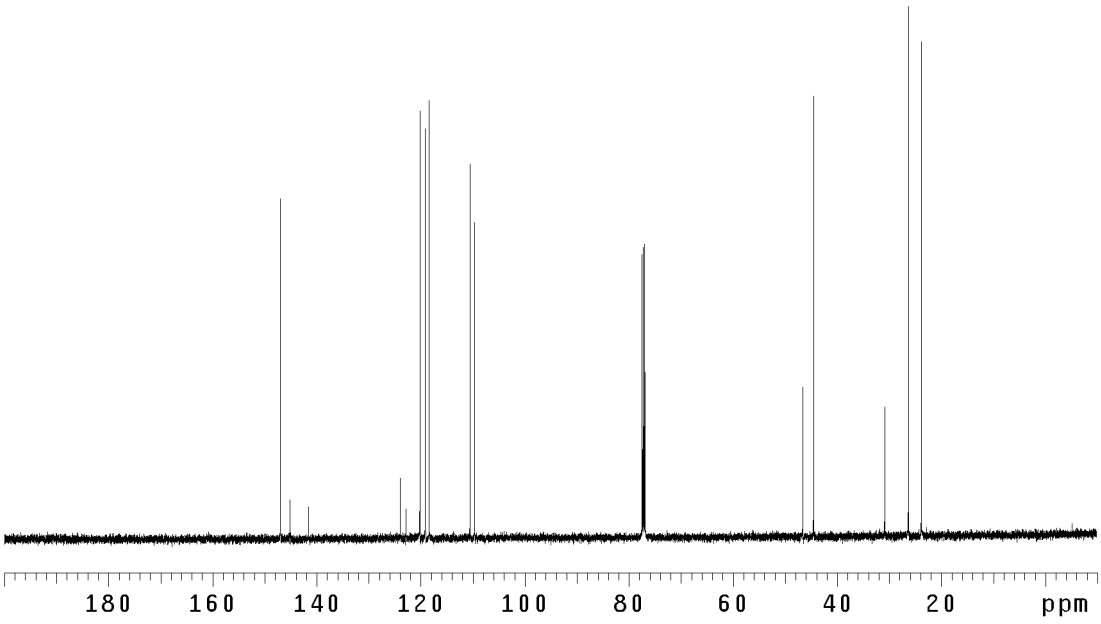


Figure A2.81 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **286**.

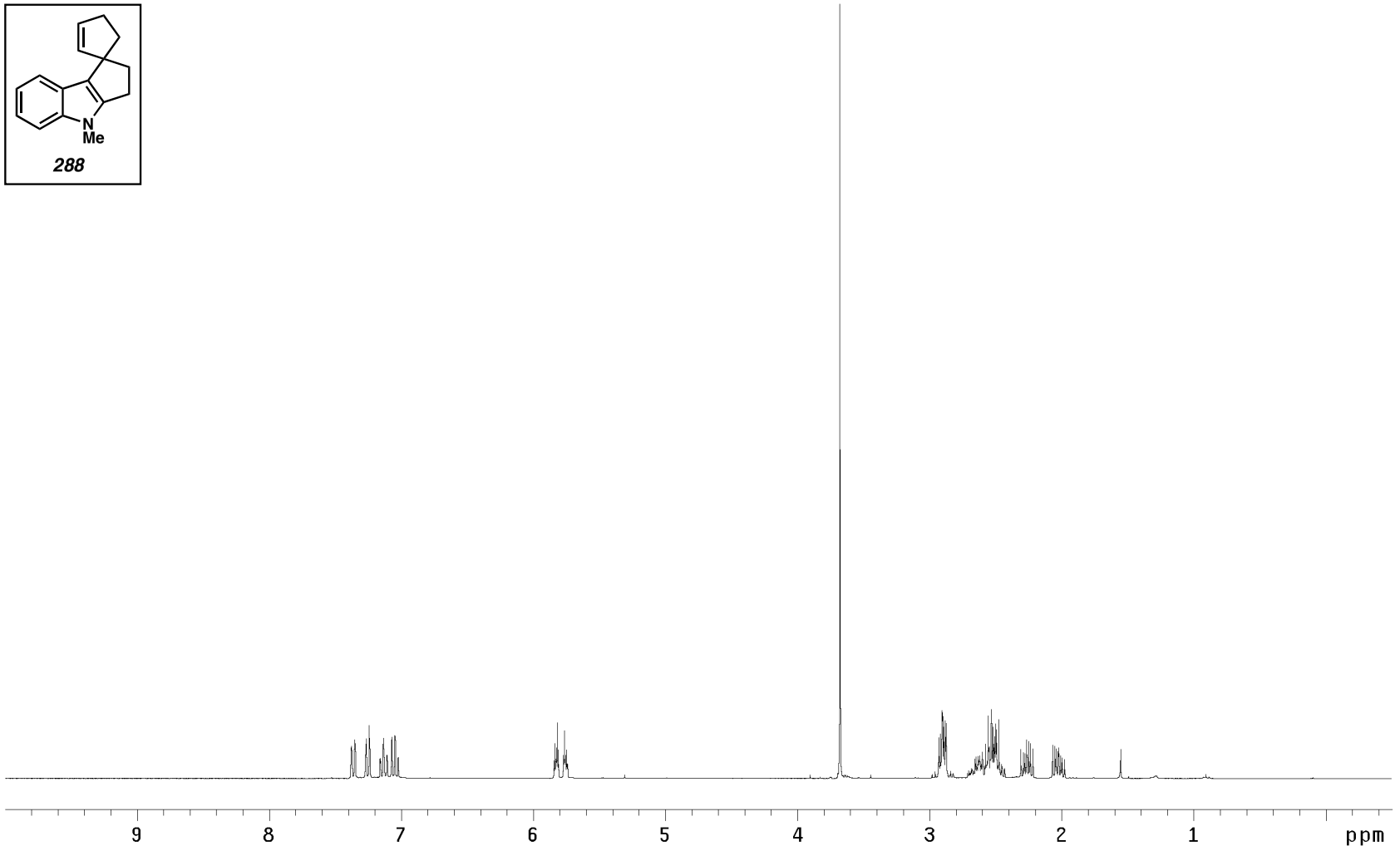


Figure A2.82 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **288**.

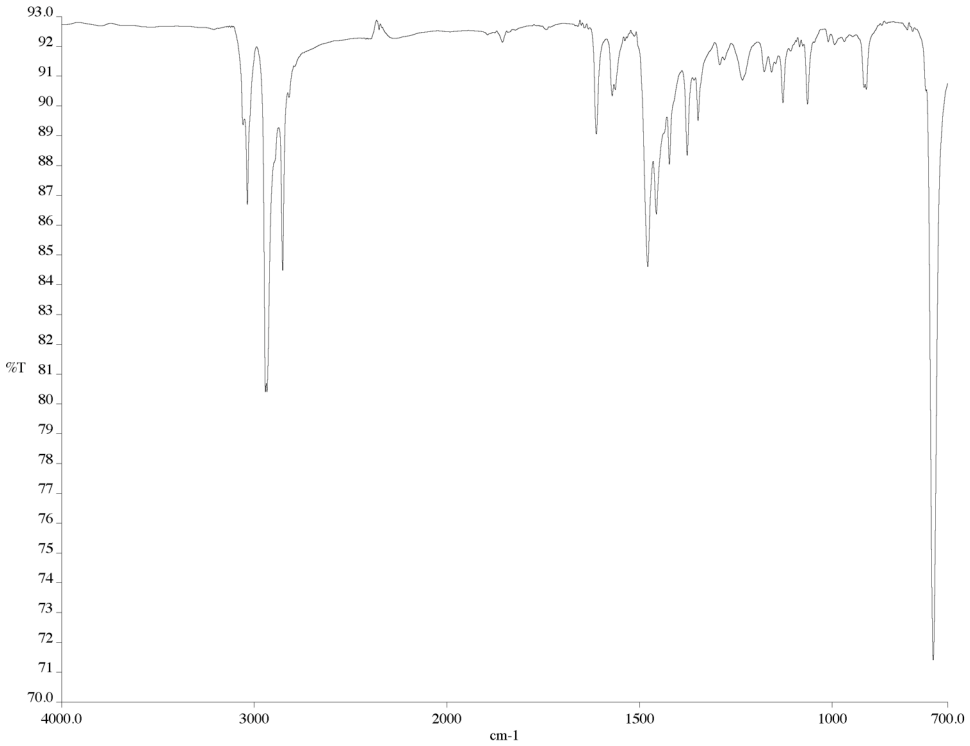


Figure A2.83 Infrared spectrum (thin film/NaCl) of compound **288**.

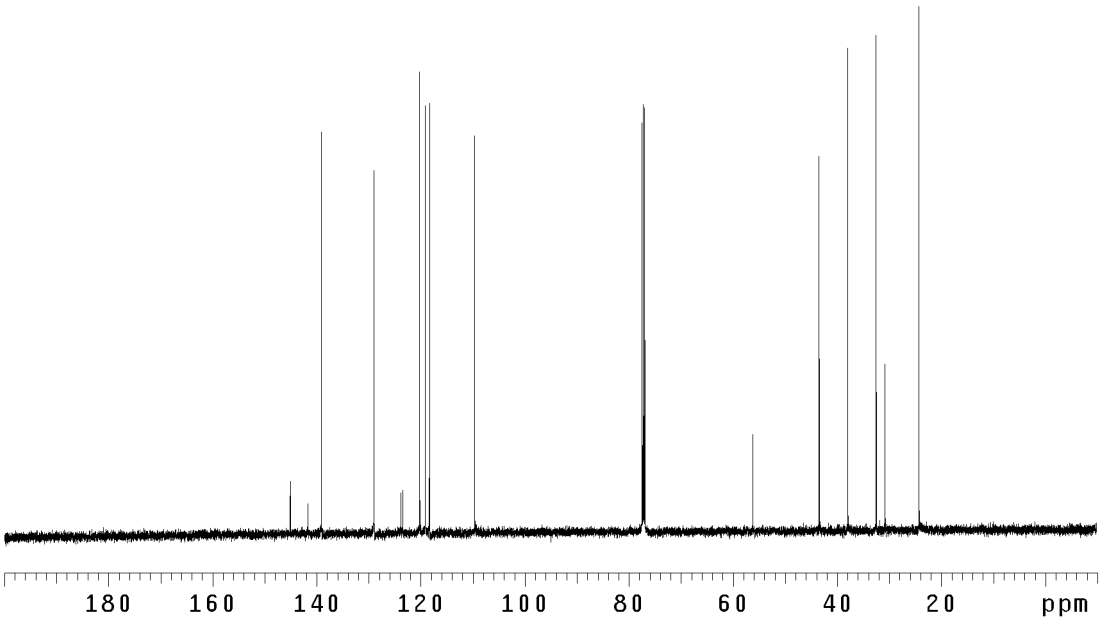


Figure A2.84 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **288**.

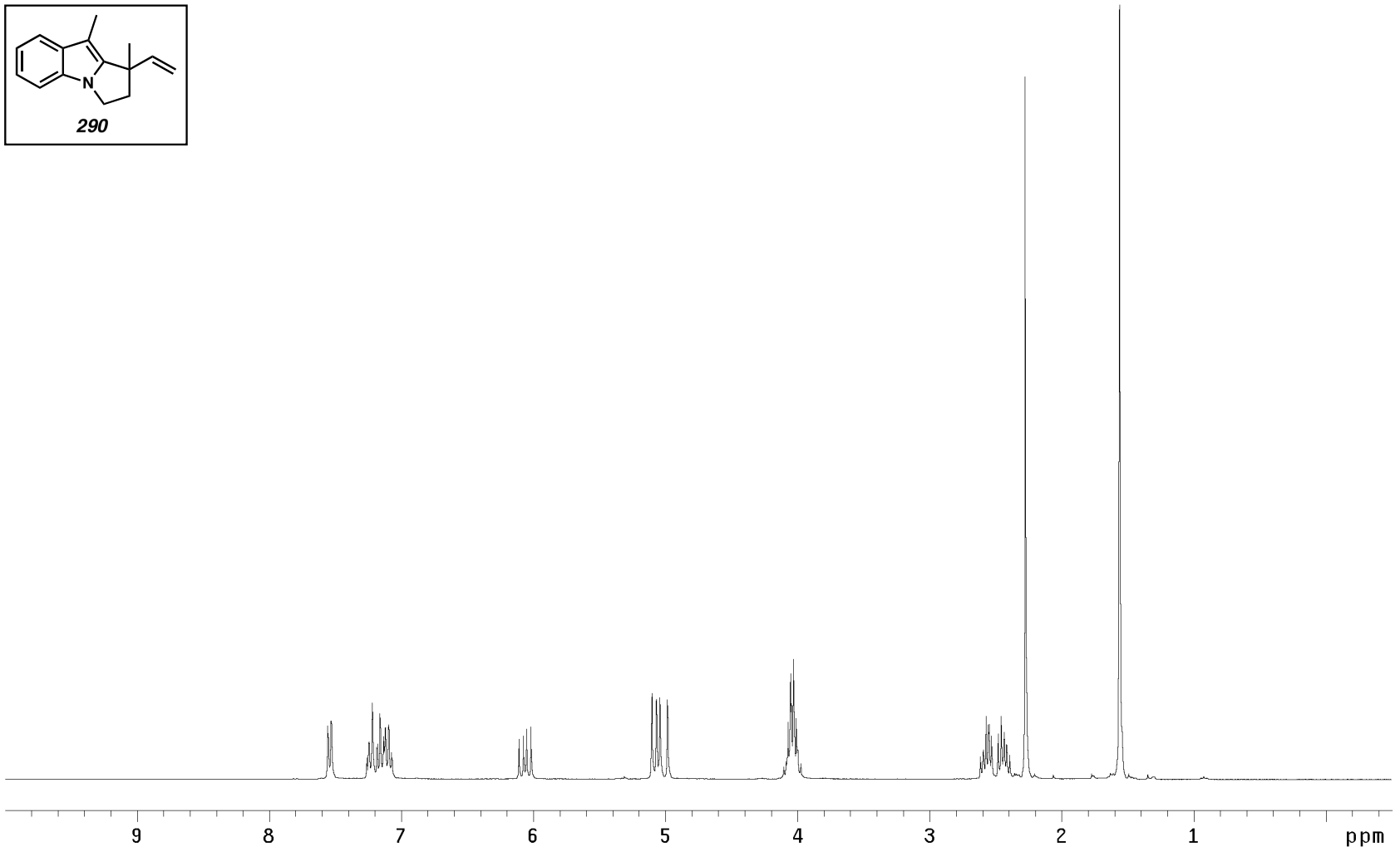


Figure A2.85 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **290**.

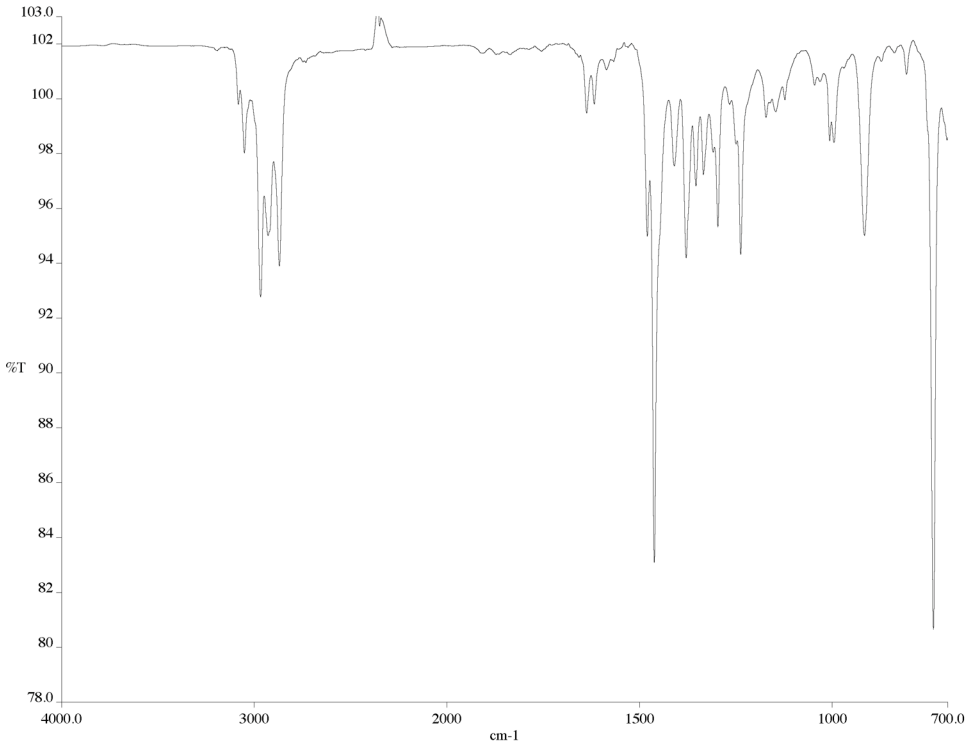


Figure A2.86 Infrared spectrum (thin film/NaCl) of compound **290**.

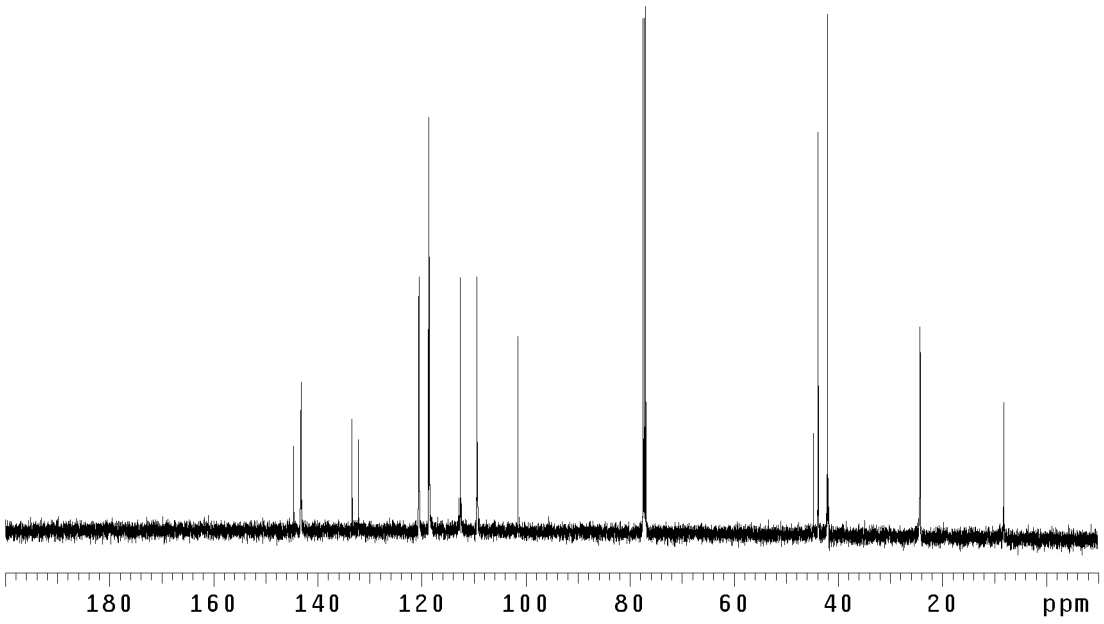


Figure A2.87 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **290**.

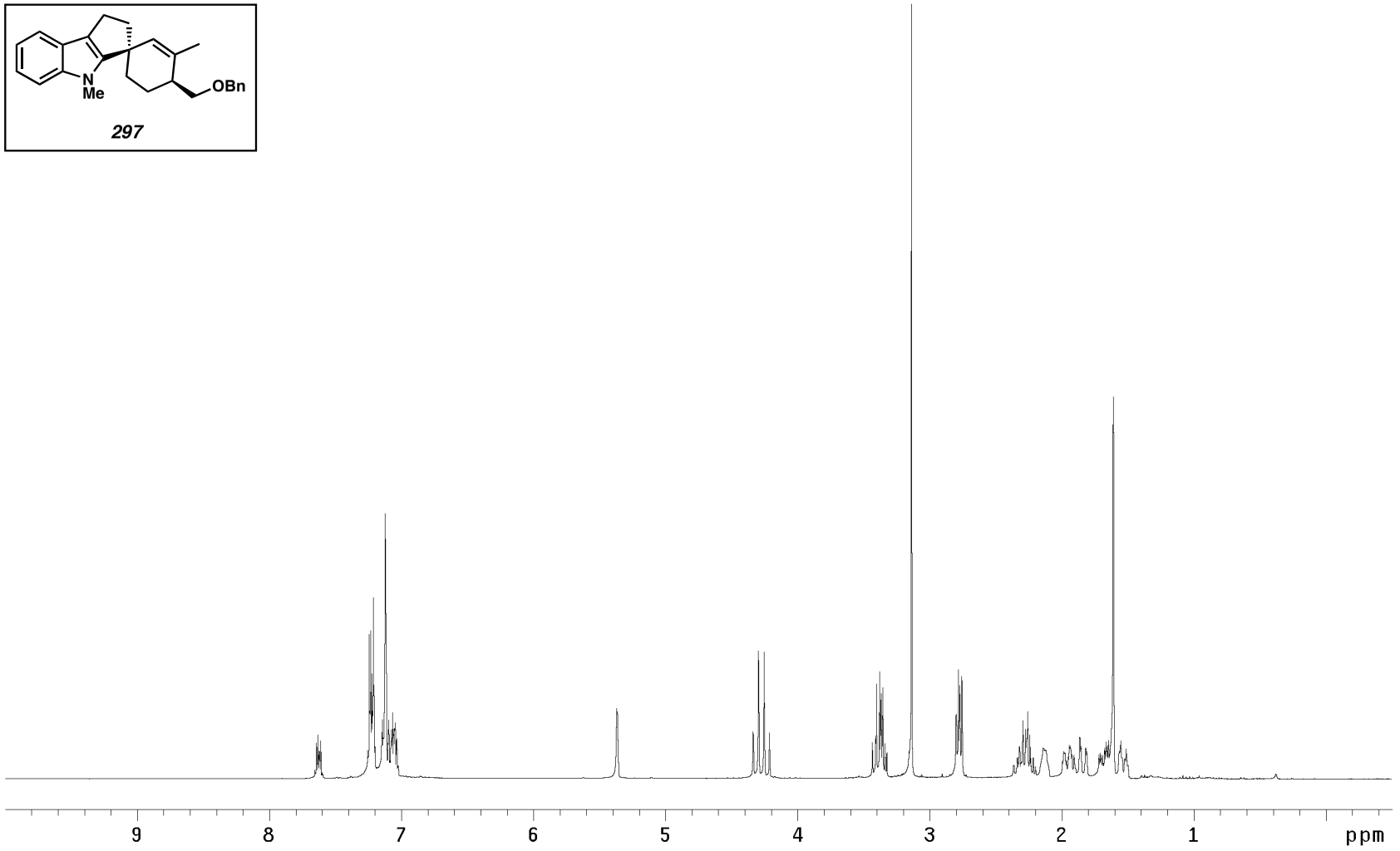


Figure A2.88 ^{1}H NMR (300 MHz, C_6D_6) of compound **297**.

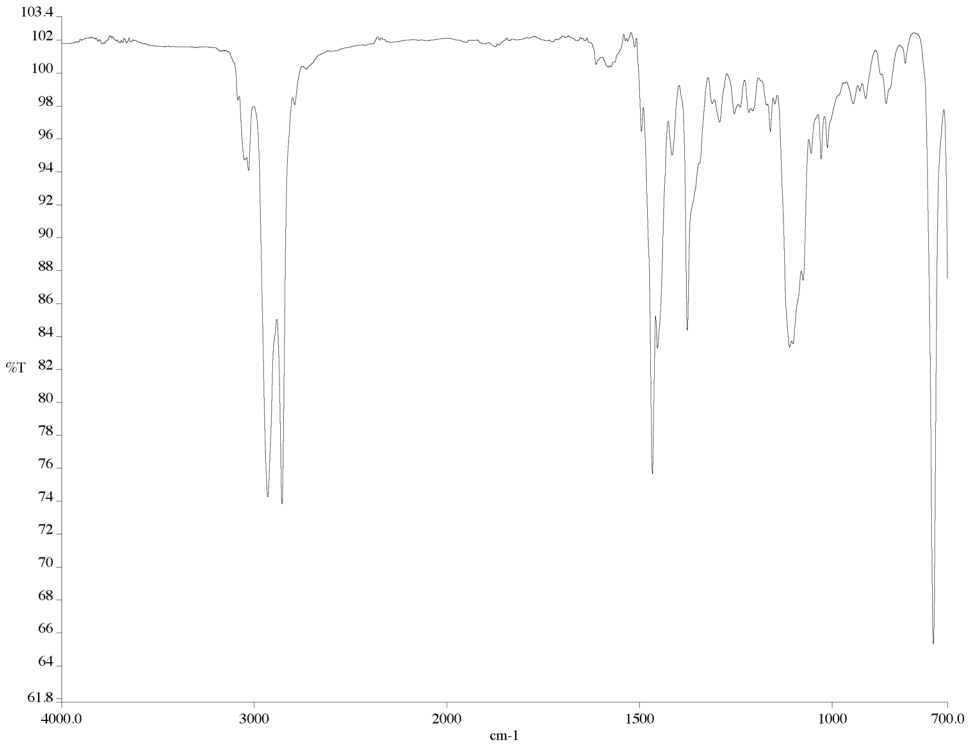


Figure A2.89 Infrared spectrum (thin film/NaCl) of compound **297**.

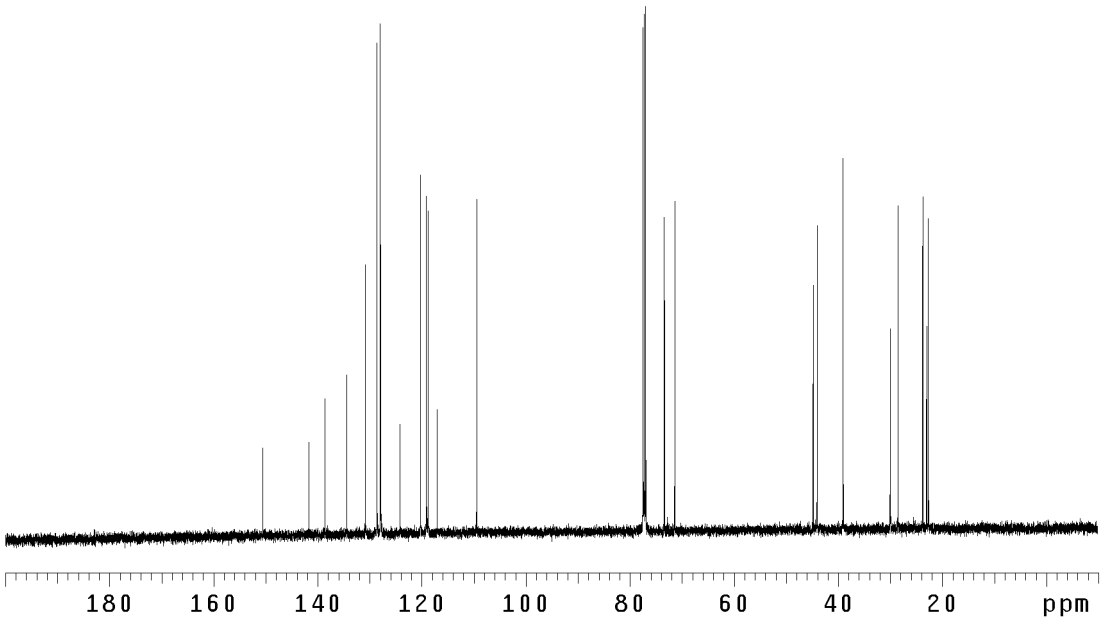


Figure A2.90 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **297**.

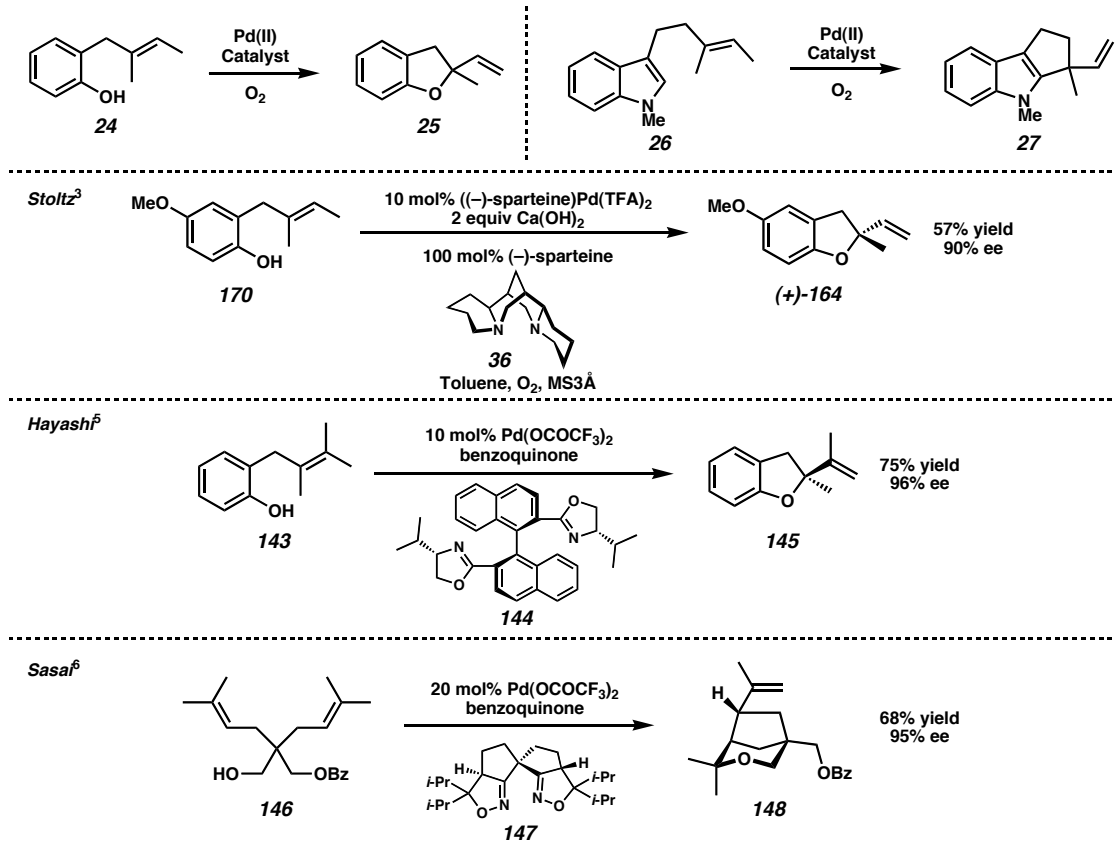
CHAPTER FIVE

Further Investigations into Palladium(II)-Catalyzed Asymmetric Oxidative Heterocyclizations

5.1 Introduction

Although significant progress had been made in a number of directions, the palladium(II) oxidation chemistry we had been investigating was at a crossroads (Scheme 5.1.1). The palladium/pyridine/O_2 system discovered by Uemura[1] for the oxidation of alcohols was used as a platform to develop the oxidative kinetic resolution of secondary alcohols.[2] Further investigations of the palladium/pyridine/O_2 system eventually led to the development of efficient cyclization reactions to form both heterocycles and carbocycles.[3,4] Importantly, one of these cyclization systems could be extended to a highly asymmetric variant by switching from pyridine to the chiral ligand (–)-sparteine. Although sparteine was effective for this isolated case, there was a significant lack of generality across a number of substrates. Moreover, the work by Hayashi[5] and Sasai[6] represent the only other cases where highly asymmetric heterocyclizations were realized. An important direction for this chemistry, therefore, is the development of asymmetric catalytic systems that can selectively cyclize new types of substrates. Described herein are our initial investigations of novel asymmetric oxidative heterocyclizations with chiral palladium(II) complexes.

Scheme 5.1.1



5.2 Heterocyclizations of Carboxylic Acids

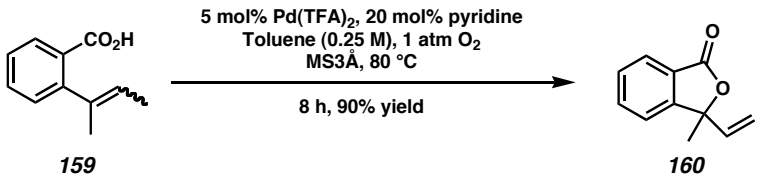
The first new substrate class that we chose to investigate for the heterocyclization chemistry was carboxylic acids. Based on our previous findings[3] and those of others,[7] it was well established that carboxylic acids with tethered olefin moieties will cyclize to lactones under palladium(II) oxidative conditions. We anticipated that the palladium/pyridine catalyst system could again be used as a platform to develop enantioselective variants. Moreover, there are few examples of enantioselective lactonization reactions deriving from the cyclization of carboxylic acids onto olefins, and of those reported, all exhibit modest selectivity.[8] Lactones are prevalent in countless

important bioactive molecules; the development of an efficient enantioselective lactonization would be highly useful for the synthetic community.

As a starting point, we decided to use catalysts possessing oxazoline ligands instead of sparteine-based derivatives. This decision was based both on the synthetic ease and availability of the oxazoline moiety (arising directly from chiral amino acids) and on its modular nature (allowing for straightforward variability). Both of these features were considerable advantages over the sparteine system we had previously investigated.

We first examined the cyclization of benzoic acid **159**. We had previously shown that under the standard $Pd(TFA)_2$/pyridine/O_2 conditions, **159** cyclized efficiently to lactone **160** (Scheme 5.2.1).[3] It should be noted that at the onset of this project, we hypothesized that it was important to use substrates as pure olefin isomers. It was anticipated that enantioselectivity would arise from face-selective binding of the olefin to the catalytic complex. Mixtures of olefin isomers would complicate the system because geometrical isomers have the potential to behave very differently in the reaction.

Scheme 5.2.1

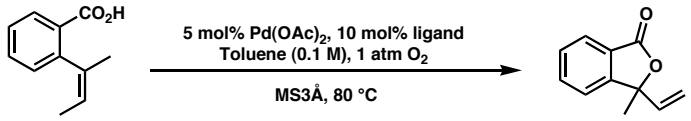


159 ***160***

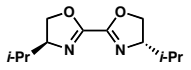
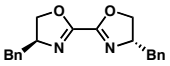
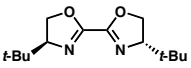
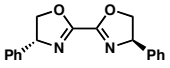
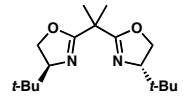
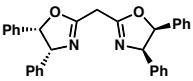
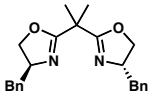
The $Pd(TFA)_2$/pyridine catalyst was substituted for $Pd(OAc)_2$/oxazoline catalysts in the cyclization of carboxylic acid **(*Z*)-159**, and the results of this preliminary screen are listed in Table 5.2.1. In general, oxazoline ligands did not suppress the reaction, and the cyclizations proceeded in the same timeframe as the pyridine systems. Enantioinduction

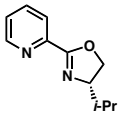
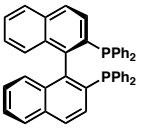
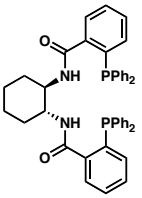
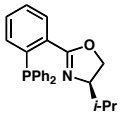
by the chiral ligands, however, was quite poor. Only in the case of ligand **393** (entry 3) did the ee exceed 10%. Ligands with phosphine moieties completely suppressed the oxidative cyclization to **160** (entries 9-11). Though the ee values were very low, these results still supported our hope that enantioinduction could occur in these reaction manifolds.

Table 5.2.1 Ligand screen for the oxidative cyclization of **(*Z*)-159**.



(Z)-159 *160*

Entry	Ligand		time	Conv (%)[a]	% ee[b]
1		*391*	5 h	73	7
			16 h	>95	8
2		*392*	5 h	75	0
			16 h	>95	0
3		*393*	5 h	65	12
			22 h	>95	11
4		*394*	5 h	30	4
			26 h	31	--[c]
5		*69*	5 h	55	0
			20 h	>95	0
6		*395*	20 h	>95	0
7		*396*	24 h	NR	--

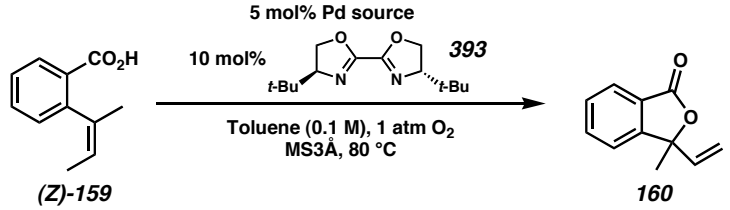
Entry	Ligand		time	Conv (%)[a]	% ee[b]
8		*397*	5 h	39	2
			20 h	>95	2
9		*56*	24 h	NR	--
10		*60*	24 h	NR	--
11		*398*	24 h	NR	--

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral GC. [c] % ee not measured.

We had observed significant effects on both reactivity and enantioselectivity depending on the palladium source during our previous studies on asymmetric palladium(II) reactions.[2a,3] We therefore examined the effect of the palladium source on the cyclization of carboxylic acid **(*Z*)-159** (Table 5.2.2). Although switching to $Pd(TFA)_2$ proved to be remarkably effective in our previous heterocyclization studies, it

did not prove fruitful here (entry 2). Reactivity was increased somewhat, but enantioselectivity was eroded. Chloride-based palladium precursors were much less reactive than $Pd(OAc)_2$ (entries 3 and 4). Following this initial screen, it appeared that $Pd(OAc)_2$ was the most effective palladium source for these cyclizations.[9]

Table 5.2.2 Palladium source screen for the oxidative cyclization of **(*Z*)-159**.

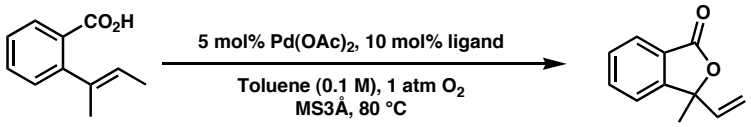


Entry	Pd source	time	Conv (%)[a]	% ee[b]
1	$Pd(OAc)_2$	5 h	65	12
		22 h	>95	11
2	$Pd(TFA)_2$	5 h	>90	6
3	$Pd(CH_3CN)_2Cl_2$	24 h	9	5
4	$Pd(nbd)Cl_2$	24 h	NR	--

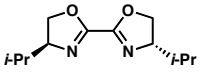
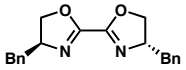
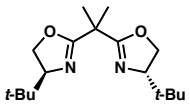
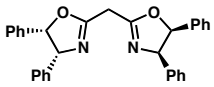
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral GC.

As mentioned above, we anticipated it was important to examine both olefin isomers of a cyclization substrate. Carboxylic acid **(*E*)-159** was thus subjected to Pd(II) cyclizations with several bisoxazoline ligands (Table 5.2.3). Again, the enantioselectivity in these reactions was found to be quite poor. The reactivity of this substrate was noticeably lower than the (*Z*)-olefin counterpart (compare to Table 5.2.1), confirming the notion that olefin geometry did indeed have an impact on the reactivity and would need to be considered in these studies.

Table 5.2.3 Ligand screen for the oxidative cyclization of **(*E*)-159**.



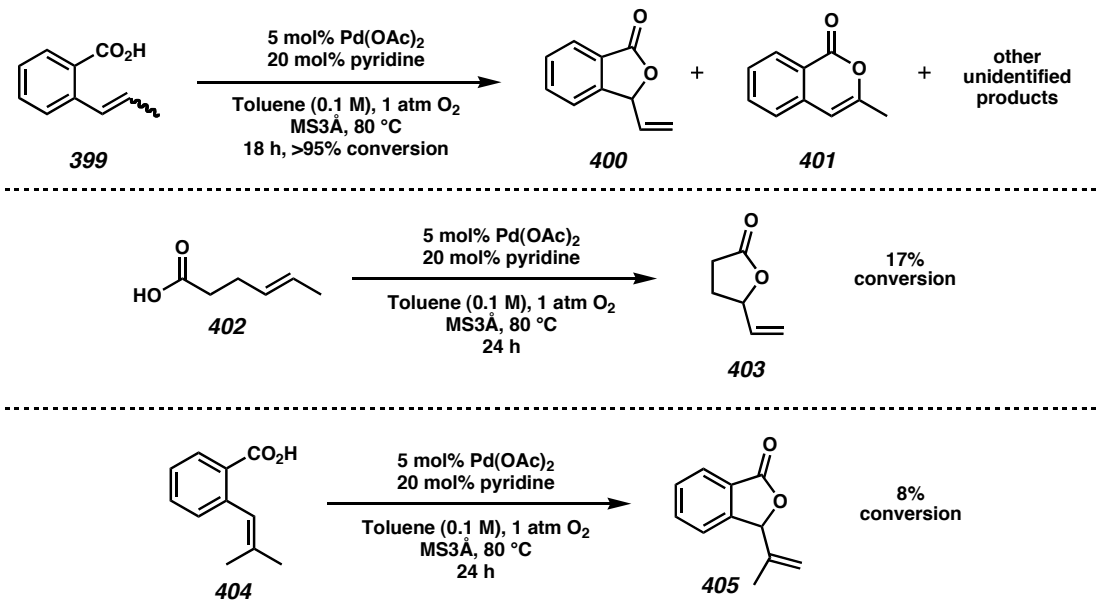
(E)-159 *160*

Entry	Ligand		time	Conv (%)[a]	% ee[b]
1		*391*	5 h	35	7
			20 h	54	6
2		*392*	5 h	43	2
			20 h	59	2
3		*69*	5 h	23	--[c]
			21 h	44	0
4		*395*	21 h	33	0

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral GC. [c] % ee not measured.

Other carboxylic acids (i.e., **399**, **402**, and **404**) were investigated in the early stages of experimentation. It was observed, however, that these acids had more complications than benzoic acids **(*Z*)-159** and **(*E*)-159**. Benzoic acid **399** did cyclize efficiently under the standard $Pd(OAc)_2$/pyridine conditions, but afforded multiple products arising from both exo and endo cyclization pathways (Scheme 5.2.2). Carboxylic acids **402** and **404** cyclized to lactones, but the reaction rates were quite sluggish compared to the other acids examined. Most of the substrates investigated have the alkene and the carboxyl group positioned on ortho substituents of a benzene ring. Carboxylic acid **402** may be relatively slow to react because it does not have the same conformational restrictions. It is not clear why carboxylic acid **404** was so unreactive; perhaps the olefin substitution pattern is simply not suited for this lactonization.

Scheme 5.2.2



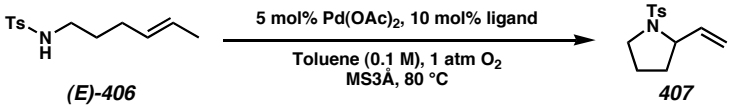
5.3 Heterocyclizations of Amines

5.3.1 Studies of the Cyclizations of Tosylamides

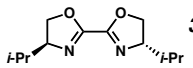
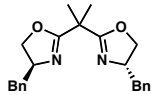
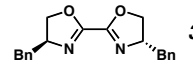
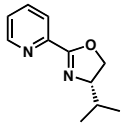
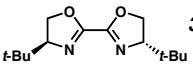
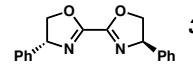
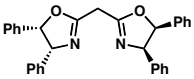
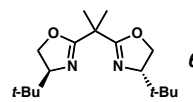
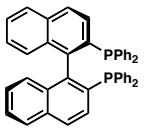
Although there were some promising leads in the lactonization reactions, both the low levels of enantioselectivity and the lack of substrate generality were discouraging. Consequently, we decided to investigate asymmetric intramolecular amination reactions. The palladium-catalyzed oxidative amination of olefins has been studied extensively.[10] Most relevant are reports by Larock ($Pd(OAc)_2$, DMSO, O_2)[11] and Stahl ($Pd(OAc)_2$, pyridine, O_2)[12] that have demonstrated that intramolecular cyclizations of tosylamides proceed efficiently under aerobic oxidative conditions. Both of these reports highlighted the importance of a *p*-toluenesulfonyl (tosyl) group on the nitrogen nucleophile. The tosyl group is electron-withdrawing, presumably preventing a nitrogen binding event that would preclude cyclization. We therefore began our studies of the intramolecular amination reactions by utilizing tosylamides as our substrates.

Tosylamide **(*E*)-406** was subjected to palladium(II) oxidative conditions with a variety of chiral ligands (Table 5.3.1).[13] As in the cases of the carboxylic acids, the bisoxazolines that are directly attached to each other through a single sigma bond (**391-394**, entries 1-4) were the most effective at enantioinduction (up to 23% ee). Pyridine-oxazoline **397** was promising as well (entry 7), providing moderate levels of reactivity with modest enantioselectivity (20% ee). Bisoxazolines with a bridging carbon were less effective ligands for this reaction, both in reactivity and selectivity (entries 5, 6, and 8). Though the levels of reactivity and selectivity in the tosylamide cyclizations were still lower than hoped, these cyclizations still represented a significant improvement over the aforementioned lactonization reactions.

Table 5.3.1 Ligand screen for the oxidative cyclization of **(*E*)-406**.



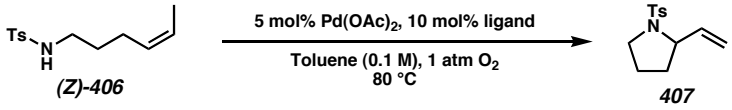
(E)-406 *407*

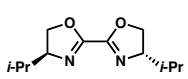
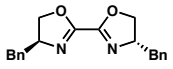
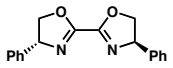
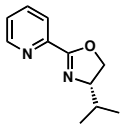
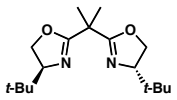
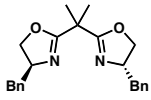
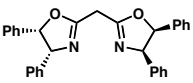
Entry	Ligand		time	Conv (%)[a]	% ee[b,c]	Entry	Ligand		time	Conv (%)[a]	% ee[b,c]
1		*391*	4 h 24 h	33 43	10 6	6		*396*	24 h	NR	--
2		*392*	4 h 24 h	10 25	23 20	7[d]		*397*	4 h 24 h	17 42	--[e] 20
3		*393*	4 h 24 h	15 20	10 8						
4[d]		*394*	5 h 24 h	<5 9	-12 -15	8[d]		*395*	24 h	NR	--
5		*69*	4 h 24 h	12 13	-3 3	9[d]		*56*	4 h 24 h	<5 7	-- --[e]

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. It does not necessarily correspond to the sign of optical rotation, which was not measured. [d] Reaction run without MS3Å. [e] % ee not measured.

We also examined the cis isomer of the tosylamide (**(*Z*)-406**) under various cyclization catalysts (Table 5.3.2). Again, the bisoxazolines deriving from oxalate (**391**, **392**, and **394**, entries 1-3) and the pyridine-oxazolines (**397** and **408**, entries 4 and 5) were somewhat effective ligands for these cyclizations, achieving moderate reactivity and modest enantioselectivity. Additionally, there were measurable differences in both reactivity and selectivity between the cis and trans isomers of the tosylamide (**(*E*)-406** and **(*Z*)-406**, Tables 5.3.1 and 5.3.2). In general, the (*Z*)-olefin cyclized more efficiently and selectively than the (*E*)-olefin, though there were exceptions, and the differences were not particularly large.

Table 5.3.2 Ligand screen for the oxidative cyclization of **(*Z*)-406**.



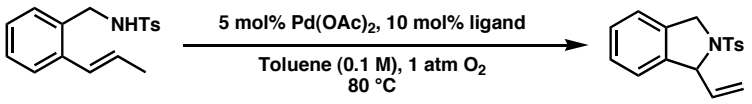
Entry	Ligand		time	Conv (%)[a]	% ee[b,c]
1		*391*	5 h 24 h	17 29	--[d] -7
2		*392*	5 h 24 h	32 44	--[d] 29
3		*394*	5 h 24 h	<5 <5	-- --
4		*397*	5 h 24 h	20 59	--[d] 36
5		*408*	5 h 24 h	12 40	--[d] 18
6		*69*	5 h 24 h	34 49	--[d] -2
7		*396*	24 h	NR	--
8		*395*	5 h 24 h	<5 38	-- -24

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. It does not necessarily correspond to the sign of optical rotation, which was not measured. [d] % ee not measured.

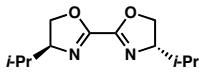
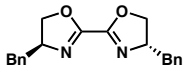
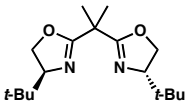
In an attempt to increase the reactivity of these systems, we investigated the cyclization of tosylamide **409**. By attaching the nucleophile and the olefin in an ortho

substitution pattern on a benzene ring, we hypothesized that the reactive partners would be forced into close proximity to each other and would therefore interact more readily. This proved to be true, as the oxidative cyclization of **409** proceeded more efficiently than the cyclization of tosylamide **406**. Tosylamide **409** was examined under a few catalyst systems (Table 5.3.3), all of which showed increased reactivity and selectivity compared to **406** under the same metal-ligand systems. Although this represented a promising lead for future work, the cyclizations of tosylanilines were even more selective (*vide infra*), and we consequently focused our attention on those substrates.

Table 5.3.3 Ligand screen for the oxidative cyclization of **409**.



409 ***410***

Entry	Ligand		time	Conv (%)[a]	% ee[b]
1		***391***	5 h 24 h	39 53	25 20
2		***392***	5 h 24 h	38 63	30 27
3		***69***	5 h	31	10

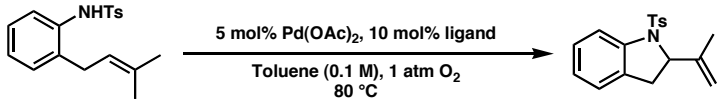
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

5.3.2 Studies of the Cyclizations of Tosylanilines and Derivatives

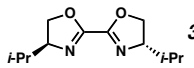
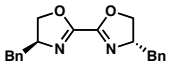
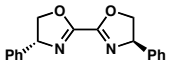
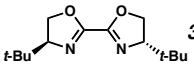
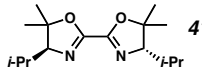
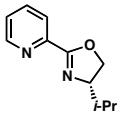
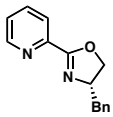
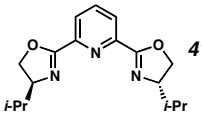
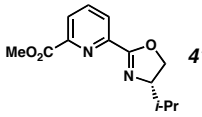
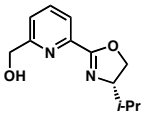
The asymmetric oxidative cyclization of tosylaniline **411** was investigated under a variety of palladium-ligand systems (Table 5.3.4). Although most of the ligands that were tested provided only marginal results, some interesting observations were made. Consistent with our previous results, bisoxazolines **391**-**393** and **413** were the most effective ligands with regard to reactivity and enantioselectivity (entries 1-5).

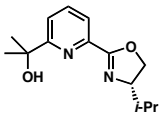
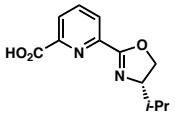
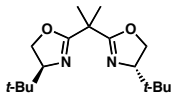
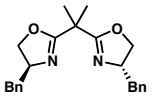
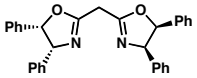
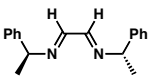
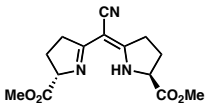
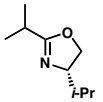
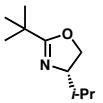
Bisoxazolines with larger backbones (entries 13-15, 20-25, and 36) afforded tosylindolines with much lower ee levels. Curiously, monooxazolines **421** and **422** hindered reactivity, in contrast to our findings with monodentate and bidentate pyridyl ligands (*vide infra*). Any ligand with an X-type donor (carboxylate, amide) completely shut down the cyclization reaction (entries 12, 17, and 32);[14] however, a tertiary alcohol moiety in the ligand framework caused a dramatic increase in the reactivity of the system (entries 11 and 27). This effect will be addressed in more detail later. Bisphosphine **56** (entry 33) and phosphoramidite **436** (entry 35) suppressed reactivity, suggesting that nitrogen-based ligands were more suited for this transformation than phosphorus-based ligands. Because valine-based bisoxazoline **391** provided the best combination of reactivity and selectivity (entry 1, 44% conversion and 34% ee after 24 h), it was utilized in further optimization studies.[15]

Table 5.3.4 Ligand screen for the oxidative cyclization of **411**.



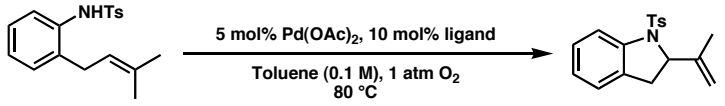
411 ***412***

Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
1	 ***391***	5 h 24 h	30 44	34 34
2	 ***392***	5 h 24 h	13 20	41 37
3	 ***394***	5 h 24 h	8 15	-24 -27
4	 ***393***	5 h 24 h	33 69	25 24
5	 ***413***	5 h 24 h	51 71	34 33
6	 ***397***	5 h 24 h	12 22	-12 -24
7	 ***408***	5 h 24 h	17 29	6 -2
8	 ***414***	5 h 24 h	9 21	21 18
9	 ***415***	5 h 24 h	<5 7	-- 27
10	 ***416***	5 h 24 h	<5 5	-- 37

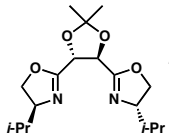
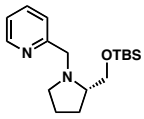
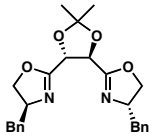
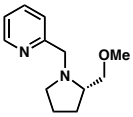
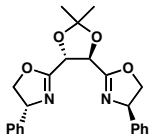
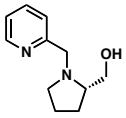
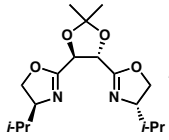
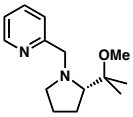
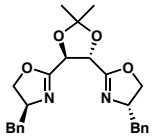
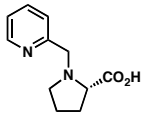
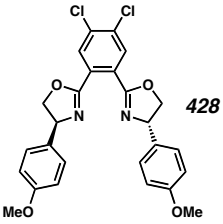
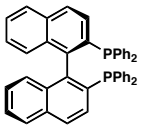
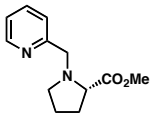
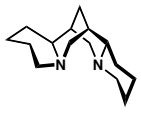
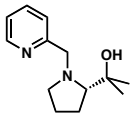
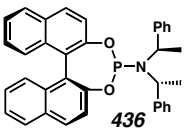
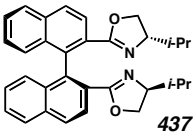
Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
11	 ***417***	5 h 24 h	35 77	24 24
12	 ***418***	24 h	NR	--
13	 ***69***	5 h 24 h	48 53	9 11
14	 ***396***	24 h	<5	--
15	 ***395***	24 h	NR	--
16	 ***419***	6 h	9	-3
17	 ***420***	24 h	NR	--
18[d]	 ***421***	5 h 24 h	NR <5	-- 4
19[d]	 ***422***	5 h 24 h	<5 8	-- -12

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. The sign corresponds to the sign of optical rotation, which was measured. [d] 20 mol% ligand.

Table 5.3.4 (continued)



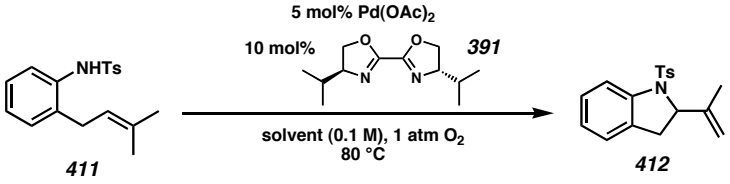
411 **→** ***412***

Entry	Ligand	time	Conv (%)[a]	% ee[b,c]	Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
20	 ***423***	6 h	20	2	28	 ***431***	5 h	18	-2
21	 ***424***	5 h	20	0	29	 ***432***	5 h	10	-4
22	 ***425***	5 h 48 h	29 65	-9 -9	30	 ***433***	5 h 24 h	66 79	8 9
23	 ***426***	5 h	26	7	31	 ***434***	5 h 24 h	26 31	-9 -9
24	 ***427***	5 h	36	6	32	 ***435***	24 h	NR	--
25	 ***428***	5 h 48 h	12 38	-8 -7	33	 ***56***	4 h 24 h	4 10	7 2
26	 ***429***	5 h 24 h 48 h	<5 12 16	16 25 25	34	 ***36***	5 h 24 h	<5 12	-12 -7
27	 ***430***	5 h 14 h	79 >95	-5 -4	35	 ***436***	5 h	<5	-2
					36	 ***437***	24 h	<5	--

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. The sign corresponds to the sign of optical rotation, which was measured.

Having found a promising ligand, we then investigated other parameters of the cyclization of tosylaniline **411**.[16] The solvent had a noticeable effect on the selectivity of the reaction (Table 5.3.5). Solvents with modest electron-donating capabilities (*t*-amyl alcohol, pinacolone) resulted in marginal decreases in reactivity and selectivity (entries 3 and 4). Solvents with stronger electron-donating moieties (DMF, CH_3CN) essentially shut down enantioselectivity (entries 7 and 8). In these instances, the solvent is most likely binding to the metal center, perhaps completely displacing the bisoxazoline ligand. The effects of various solvents seemed to imply that the bisoxazoline ligand was somewhat weakly bound to the metal center, potentially preventing high levels of enantioinduction in the cyclization reaction. Toluene, lacking any coordinative moieties, appeared to be the solvent of choice for this system and was used in subsequent optimization.

Table 5.3.5 Solvent screen for the oxidative cyclization of **411**.

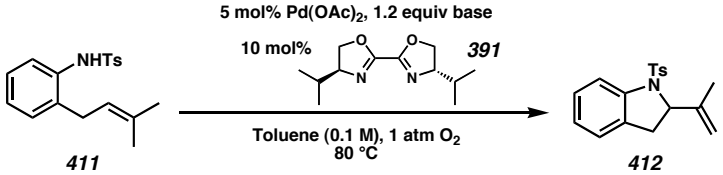


Entry	Solvent	time	Conv (%)[a]	% ee[b]
1	toluene	5 h	30	34
		24 h	44	34
2	DCE	5 h	5	18
		24 h	7	18
3	*t*-amyl alcohol	5 h	23	24
		29 h	34	26
4	pinacolone	5 h	15	20
		24 h	17	20
5	chlorobenzene	5 h	21	27
		24 h	25	25
6	dioxane	5 h	c	--
7	DMF	5 h	44	4
8	CH_3CN	5 h	12	1

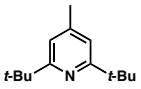
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] Substantial decomposition was observed.

The effect of a base additive was also examined in the oxidative cyclization of **411** (Table 5.3.6). It was hypothesized that an exogenous base could partially deprotonate the tosylaniline, increasing its nucleophilicity and thus the overall reactivity. Some bases did in fact increase the level of reactivity, but only marginally. LiOAc provided the largest improvement over the base-free conditions (entry 2 vs. entry 1). Some bases resulted in a dramatic erosion in enantioselectivity (entries 7, 8, and 14); it is not clear whether this erosion stems from a change in catalyst activity or an epimerization of product tosylindoline **412**. Stronger bases simply resulted in heavy decomposition (entries 11-13 and 15). Because the improvements caused by mild base additives were essentially insignificant, bases were not used in further optimizations.

Table 5.3.6 Base additives in the oxidative cyclization of **411**.



411 412

Entry	Base	time	Conv (%)[a]	% ee[b]	Entry	Base	time	Conv (%)[a]	% ee[b]
1	none	5 h	30	34	10	$KHCO_3$	5 h	42	30
		24 h	44	34			24 h	58	25
2	LiOAc	5 h	33	37	11	NaO*t*-Bu	5 h	d	--
		24 h	54	38					
3	NaOAc	5 h	35	36	12	KO*t*-Bu	5 h	d	--
		24 h	59	37					
4	KOAc	5 h	37	32	13	KHMDS	5 h	d	--
		24 h	57	31					
5	Li_2CO_3	5 h	35	33	14	$LiOH{\cdot}H_2O$	5 h	30	0
		24 h	51	35					
6	Na_2CO_3	5 h	29	32	15	NaOH	5 h	d	--
		24 h	49	31					
7	K_2CO_3	5 h	34	0	16	$Ca(OH)_2$	5 h	35	33
		24 h	67	0			24 h	54	34
8[c]	Cs_2CO_3	5 h	12	8	17[c]		5 h	32	37
		24 h	20	12			24 h	44	35
9	$NaHCO_3$	5 h	30	34					
		24 h	50	34					

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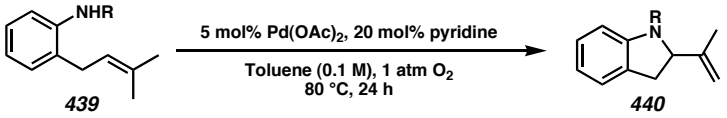
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] 2 equiv base were used. [d] Substantial decomposition was observed.

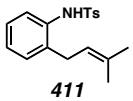
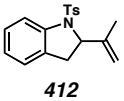
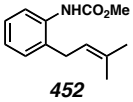
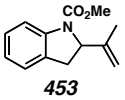
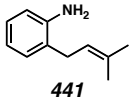
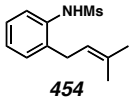
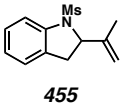
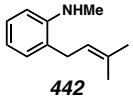
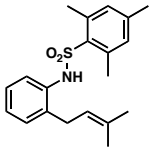
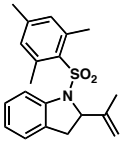
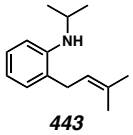
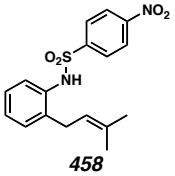
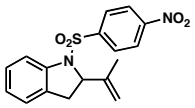
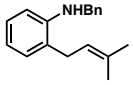
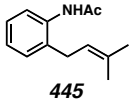
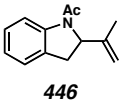
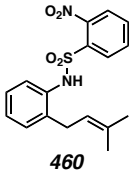
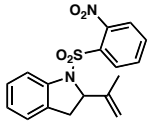
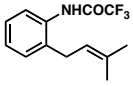
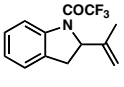
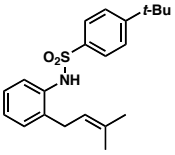
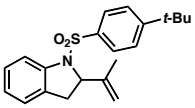
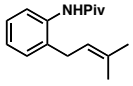
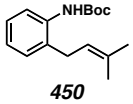
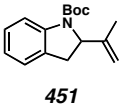
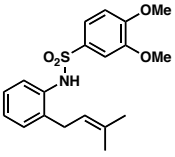
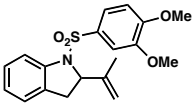
Substrate variations of tosylaniline **411** were investigated next. The *p*-toluenesulfonyl group was substituted by a variety of functional groups. These anilines were then cyclized under the standard palladium/pyridine conditions (Table 5.3.7). Some general trends were observed. Both free aniline (entry 2) and alkyl-substituted anilines (entries 3-5) were completely unreactive to oxidative cyclization. This could be because the nitrogen is now electron-rich enough to act as a ligand to the metal center. Another possibility is that the pK_a of the amine nitrogen is too high in the alkyl anilines to undergo deprotonation.[17] Amide functionalities could act as nucleophiles for the cyclization (entries 6-8), although the reactivities were noticeably lower. Carbamates were

comparable in reactivity to the parent sulfonamide (entries 9 and 10), and other sulfonamides also demonstrated comparable reactivity (entries 11-16). The only exceptions were arylsulfonamides with ortho substituents (entries 12 and 14), which appeared to hinder cyclization. This was somewhat surprising, as it was anticipated that the sterics were far enough removed from the nucleophilic center that they would not interfere with the cyclization.

Table 5.3.7 Examination of different aniline substituents in racemic cyclizations.



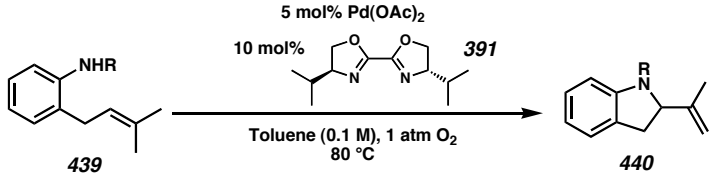
439 440

Entry	Substrate	Product	Conv (%)[a]	Entry	Substrate	Product	Conv (%)[a]
1	 411	 412	69	10	 452	 453	69
2	 441		NR	11	 454	 455	71
3	 442		NR	12	 456	 457	19
4	 443		NR	13	 458	 459	70
5	 444		NR[b]				
6	 445	 446	50	14	 460	 461	10
7	 447	 448	10	15	 462	 463	>95
8	 449		NR				
9	 450	 451	85	16	 464	 465	79

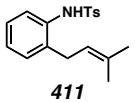
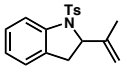
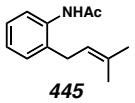
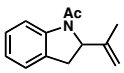
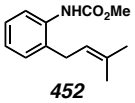
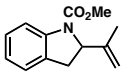
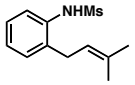
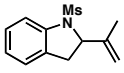
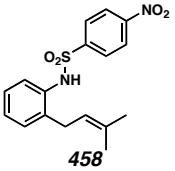
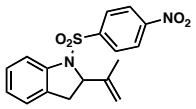
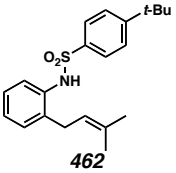
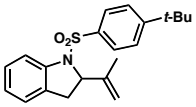
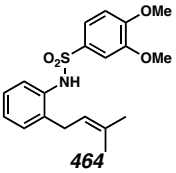
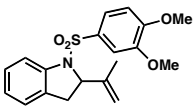
[a] % conversion measured by ^{1}H NMR. [b] Oxidation to the imine was observed.

The substrates that were effective in the racemic cyclization were then investigated under our best asymmetric cyclization conditions (Table 5.3.8). Both acetanilide **445** and methyl carbamate **452** were unreactive under these conditions (entries 2 and 3), and amides and carbamates were not explored further. Other sulfonamides were similarly reactive to tosylaniline **411** (entries 4-7). The enantioselectivities were also about the same as that of tosylaniline **411**, with the exception of the marginally lower *p*-nitrobenzenesulfonamide (**458**). It appeared from these experiments that altering the substituent on the nitrogen was not a good strategy for optimization because interchanging sulfonamides caused little to no change, while replacing the sulfonamide with another type of substituent shut down the reactivity.

Table 5.3.8 Examination of different aniline substituents in asymmetric cyclizations.



439 440

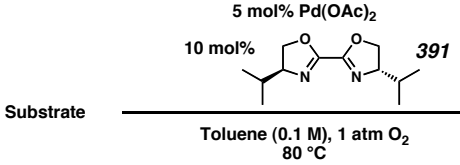
Entry	Substrate	Product	time	Conv (%)[a]	% ee[b]
1	 411	 412	5 h 24 h	42 56	34 34
2	 445	 446	24 h	<5	7
3	 452	 453	24 h	<5	--
4	 454	 455	5 h 24 h	36 50	28 28
5	 458	 459	5 h 24 h	44 56	20 23
6	 462	 463	5 h 24 h	31 45	32 27
7	 464	 465	5 h 24 h	34 47	34 33

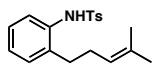
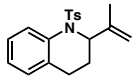
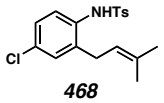
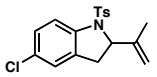
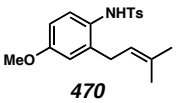
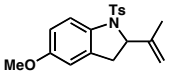
[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

Other substrate variations were also met with no improvement (Table 5.3.9). The one carbon homolog of the original tosylaniline was less reactive and less selective. Aryl substitutions on the aniline ring also proved less effective. An electron-withdrawing group caused a decrease in reactivity (entry 2), likely due to the reduced nucleophilicity

of the nitrogen atom. The electron-donating methoxy group also had a negative effect, both on reactivity and selectivity. The origin of this effect is not clear, but it could arise from substrate ligation to the metal center via the oxygen atom or the more electron-rich nitrogen atom. Nonetheless, these variations were not investigated further.

Table 5.3.9 Examination of substrate variations in the asymmetric cyclization.



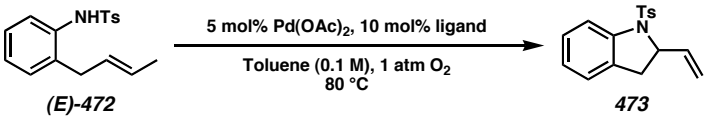
Entry	Substrate	Product	time	Conv (%)[a]	% ee[b]
1	 **466**	 **467**	24 h	17	11
2	 **468**	 **469**	5 h 24 h	14 19	36 33
3	 **470**	 **472**	5 h 24 h	21 30	26 18

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

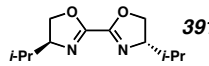
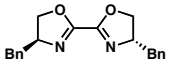
The final substrate variation that was investigated was the olefin substitution pattern. Specifically, trans and cis substituted olefins **(*E*)-472** and **(*Z*)-472** were subjected to asymmetric oxidative conditions (Tables 5.3.10 and 5.3.11). Both of these substrates cyclized significantly faster than the trisubstituted olefin. This is consistent with what has been found by Larock[11] and Stahl[12] in their tosylamide cyclization studies—a disubstituted olefin is generally more reactive because there are fewer steric interactions in the Pd(II) olefin activation event. The levels of enantioselectivity, however, were markedly lower in these cyclizations. These substrates were not

optimized further, but it is possible that conditions more favorable for enantioselective reactions (i.e., lower temperatures) could lead to improvements.[18]

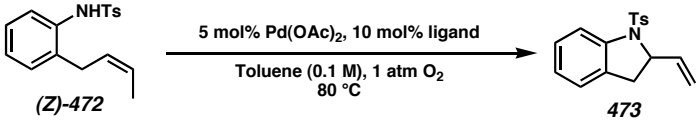
Tables 5.3.10 and 5.3.11 Oxidative cyclizations of disubstituted olefin substrates.



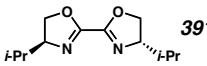
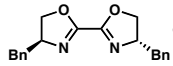
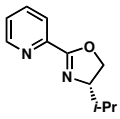
(E)-472 *473*

Entry	Ligand	time	Conv (%)[a]	% ee[b]
1	 *391*	5 h	>95	20
		10 h	>95	19
2	 *392*	5 h	>95	13
		24 h	>95	12

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.



(Z)-472 *473*

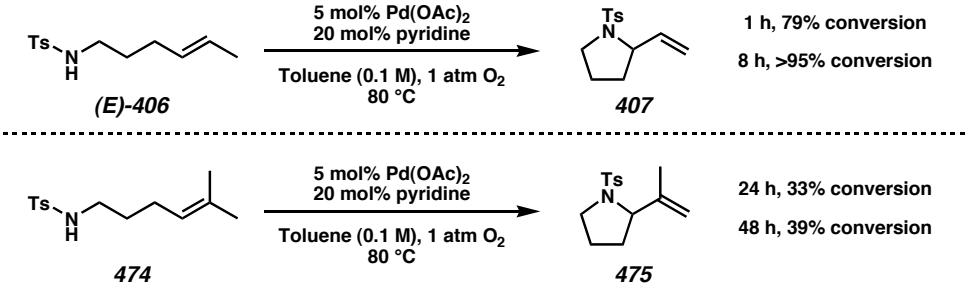
Entry	Ligand	time	Conv (%)[a]	% ee[b,c]
1	 *391*	5 h	92	22
		24 h	>95	22
2	 *392*	5 h	80	6
		24 h	>95	6
3	 *397*	5 h	92	-16
		24 h	>95	-15

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC. [c] +/- distinction is intended to represent different enantioenrichments. It does not necessarily correspond to the sign of optical rotation, which was not measured.

Regarding the alkene substitution pattern and its impact on overall reactivity, we also compared disubstituted olefin **(*E*)-406** and trisubstituted olefin **474** in the oxidative cyclization (Scheme 5.3.1). Under the standard $Pd(OAc)_2$/pyridine conditions, tosylamide **(*E*)-406** cyclized efficiently to pyrrolidine **407**. The trisubstituted olefin

(**474**), however, reacted much more sluggishly. This comparison further demonstrated the impact of alkene substitution on these Pd(II) catalyzed oxidative cyclizations.

Scheme 5.3.1



5.4 Probing the Mechanism

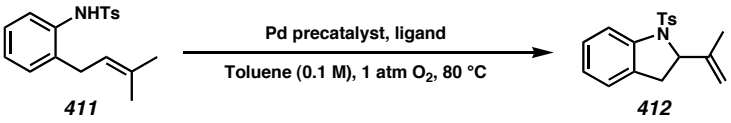
Although the screening of various ligand-substrate combinations had proven effective in finding initial leads, the overall improvement was modest. High enantioselectivities could not be realized under any of these systems, and reactivity was quite variable. It became clear that this screening process was limited in potential, and a firmer understanding of how the reaction was proceeding was needed. We therefore embarked on a more detailed study of this cyclization in hopes of rationalizing some of our observations to ultimately provide a stronger basis for further explorations.

5.4.1 Monodentate and Bidentate Ligand Effects

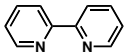
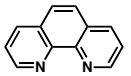
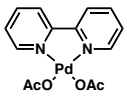
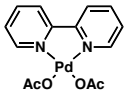
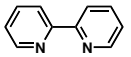
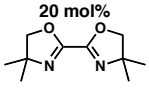
The first aspect of the oxidative cyclization we studied was the effect of monodentate versus bidentate ligands. In the racemic oxidative cyclizations studied by our group[3] and Stahl,[12] it was found that pyridine, a monodentate ligand, served as the optimal ligand. Bidentate ligands on metals are generally more effective at inducing asymmetry in enantioselective catalytic transformations because of the increased organization of the catalyst complex. Monodentate and bidentate variants of both

pyridine and oxazoline ligands were examined in the oxidative cyclization of tosylaniline **411** (Table 5.4.1). In the pyridine class, systems with monodentate ligands were clearly more reactive than bidentate ones (entry 1 vs. entries 2-5). Importantly, added bipyridine slowed down the reaction (compare entries 4 and 5). Stahl has found that in detailed mechanistic studies of the palladium(II)-catalyzed oxidation of alcohols, several catalytic intermediates only have one pyridine ligand bound to the metal center.[19] It could be that the second pyridyl moiety in the bidentate ligands is hindering the ability to access these intermediates, resulting in sluggish reactions.

Table 5.4.1 Monodentate and bidentate ligands in the cyclization of **411**.



411 ***412***

Entry	Pd precatalyst	Added Ligand	time	Conv (%)[a]
1	5 mol% $Pd(OAc)_2$	20 mol% pyridine	5 h	33
			24 h	69
			44 h	>95
2	5 mol% $Pd(OAc)_2$	10 mol%  ***476***	8 h	3
			24 h	9
3	5 mol% $Pd(OAc)_2$	10 mol%  ***477***	8 h	3
			24 h	8
4	5 mol%  ***478***	none	5 h	7
			24 h	17
5	5 mol%  ***478***	5 mol%  ***476***	5 h	2
			24 h	8
6	5 mol% $Pd(OAc)_2$	20 mol%  ***479***	5 h	<5
			24 h	12
7	10 mol% $Pd(OAc)_2$	20 mol%  ***480***	24 h	62

[a] % conversion measured by ^{1}H NMR.

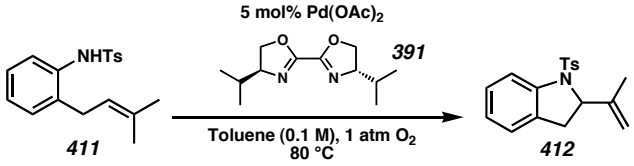
Surprisingly, the same monodentate-bidentate comparison did not extend to oxazolines (entries 6 and 7, Table 5.4.1). Monodentate oxazoline **479** hindered the reaction, whereas bisoxazoline **480** was a competent ligand for this reaction. The difference between these two ligands compared to the differences in the pyridine class is remarkable. It is currently unclear why this reversal occurs, but it could represent a change in mechanism. More detailed mechanistic studies would need to be conducted to explain this effect, but for the purposes of this study, it should be noted that bidentate ligands are not necessarily worse in catalyst design.

5.4.2 Ligand:Palladium Ratio Studies

We also investigated the effect of the ligand to palladium ratio in the oxidative cyclization of tosylaniline **411** (Table 5.4.2). There was a subtle increase in enantioselectivity in moving from 5 to 15 mol% ligand (entries 1-3). At 100 mol% ligand, the level of enantioselectivity was about the same as at 15 mol%, but the reactivity was significantly lower. A dynamic equilibrium between ligated and nonligated palladium centers is consistent with these observations (Scheme 5.4.1). At low ligand concentrations (5 mol%), an unselective background pathway involving nonligated palladium complexes **481** or **482** could be more prevalent and would account for the decreased enantioselectivity. At higher concentrations, this background reaction is suppressed. The low reactivity at 100 mol% ligand could be attributed to a second bisoxazoline competitively binding to the metal center (**484**), preventing catalysis. Another possible explanation is that the Pd-bisoxazoline complex **483**, heavily favored at

high ligand concentration, is exceptionally slow to react compared to free palladium catalysts **481** or **482**.[20]

Table 5.4.2 Examination of ligand **391** stoichiometry.

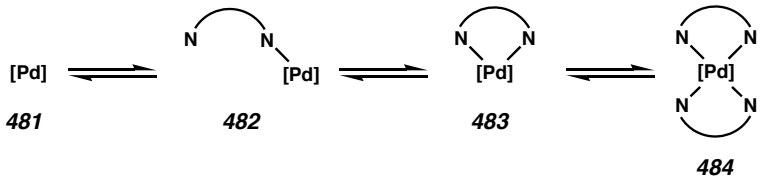


411 412

Entry	Ligand amt	time	Conv (%)[a]	% ee[b]
1	5 mol%	5 h	34	31
		24 h	46	29
2	10 mol%	5 h	42	34
		24 h	56	34
3	15 mol%	5 h	35	36
		24 h	50	36
4	100 mol%	5 h	16	37
		29 h	28	35

[a] % conversion measured by ^{1}H NMR. [b] % ee measured by chiral HPLC.

Scheme 5.4.1



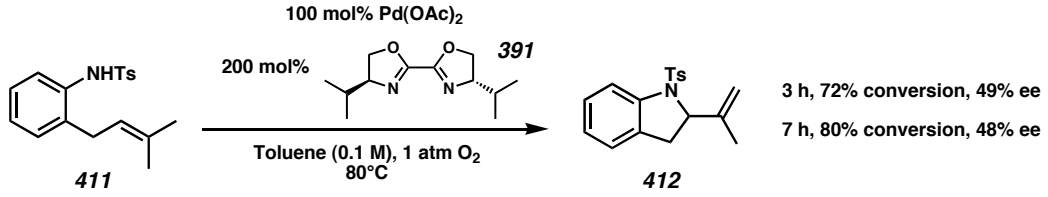
481 482 483 484

5.4.3 Stoichiometric Palladium Cyclizations

The oxidative cyclization of tosylaniline **411** was performed using a stoichiometric amount of the catalyst complex (Scheme 5.4.2). A significant increase in both conversion and enantioselectivity was observed. Conversion, albeit higher, seemed to stall after a short time. The enantioselectivity was also measurably higher than in the catalytic reactions. Both of these observations imply that the active, selective catalyst is not persisting in the reaction. Stahl has demonstrated that palladium catalysts can

undergo bimolecular decomposition by aggregation in Pd(II) oxidative reactions, which would be more likely at high catalyst concentration.[21] It is possible that this deactivation is occurring in this stoichiometric reaction (as well as in the catalytic reactions), which would help to explain the incomplete conversion.

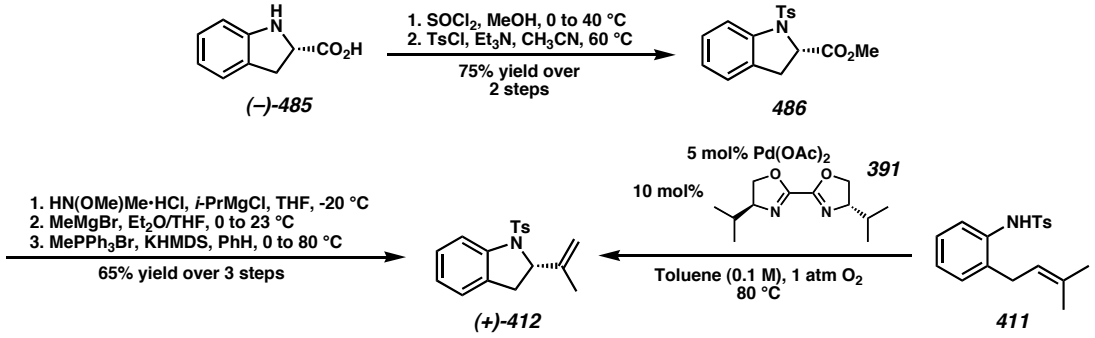
Scheme 5.4.2



5.4.4 Independent Synthesis of Tosylindoline 412

With a better understanding of the nature of the catalyst in these reactions, we hoped to investigate how the catalyst was interacting with the substrate in order to develop a clearer picture of the mode of enantioinduction. We first determined which enantiomer of tosylindoline **412** was preferentially being formed. This was accomplished via an independent synthesis (Scheme 5.4.3). Starting with (*S*)-indoline-2-carboxylic acid, methyl esterification and tosylation afforded indoline **486**. Indoline **486** was then converted to the Weinreb amide, which was treated with MeMgBr to afford the methyl ketone. Treatment with $MePPh_3Br$ provided enantiomerically pure tosylindoline **(+)-412**, which corresponds to the major enantiomer produced with the $Pd(OAc)_2$/bisoxazoline **391** catalyst.

Scheme 5.4.3

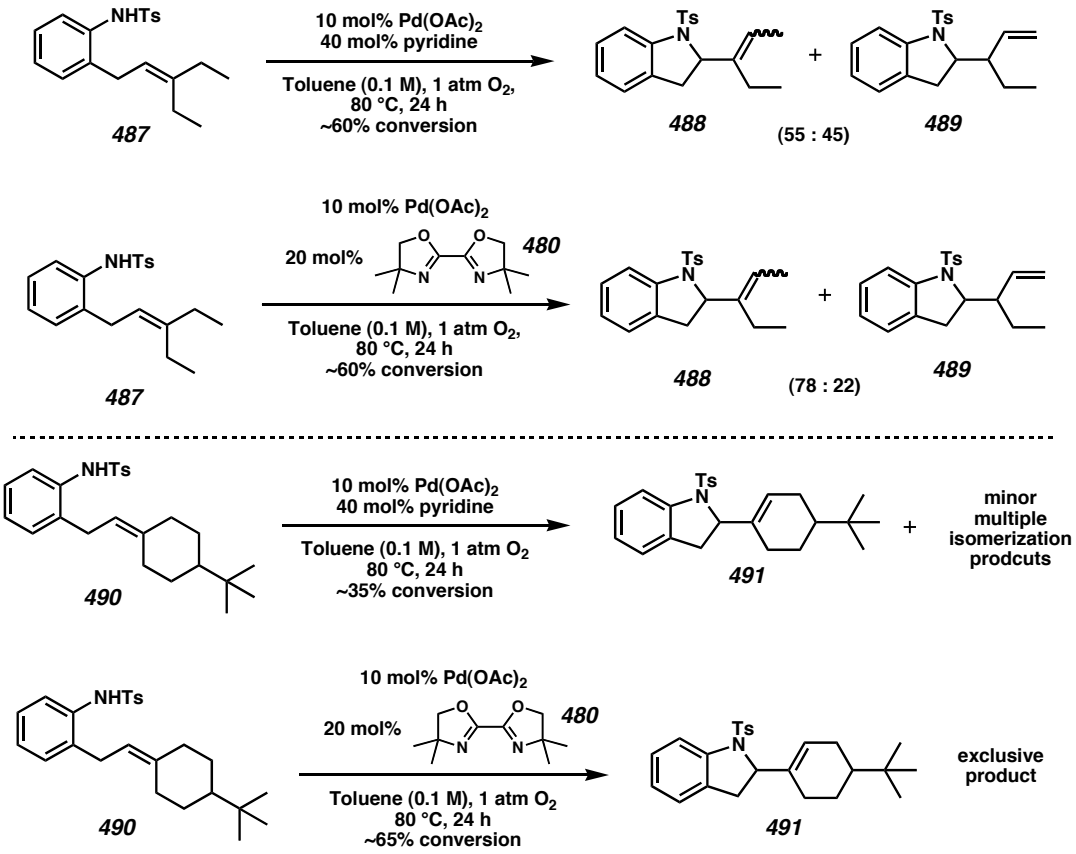


5.4.5 Palladium Hydride Mediated Olefin Isomerizations

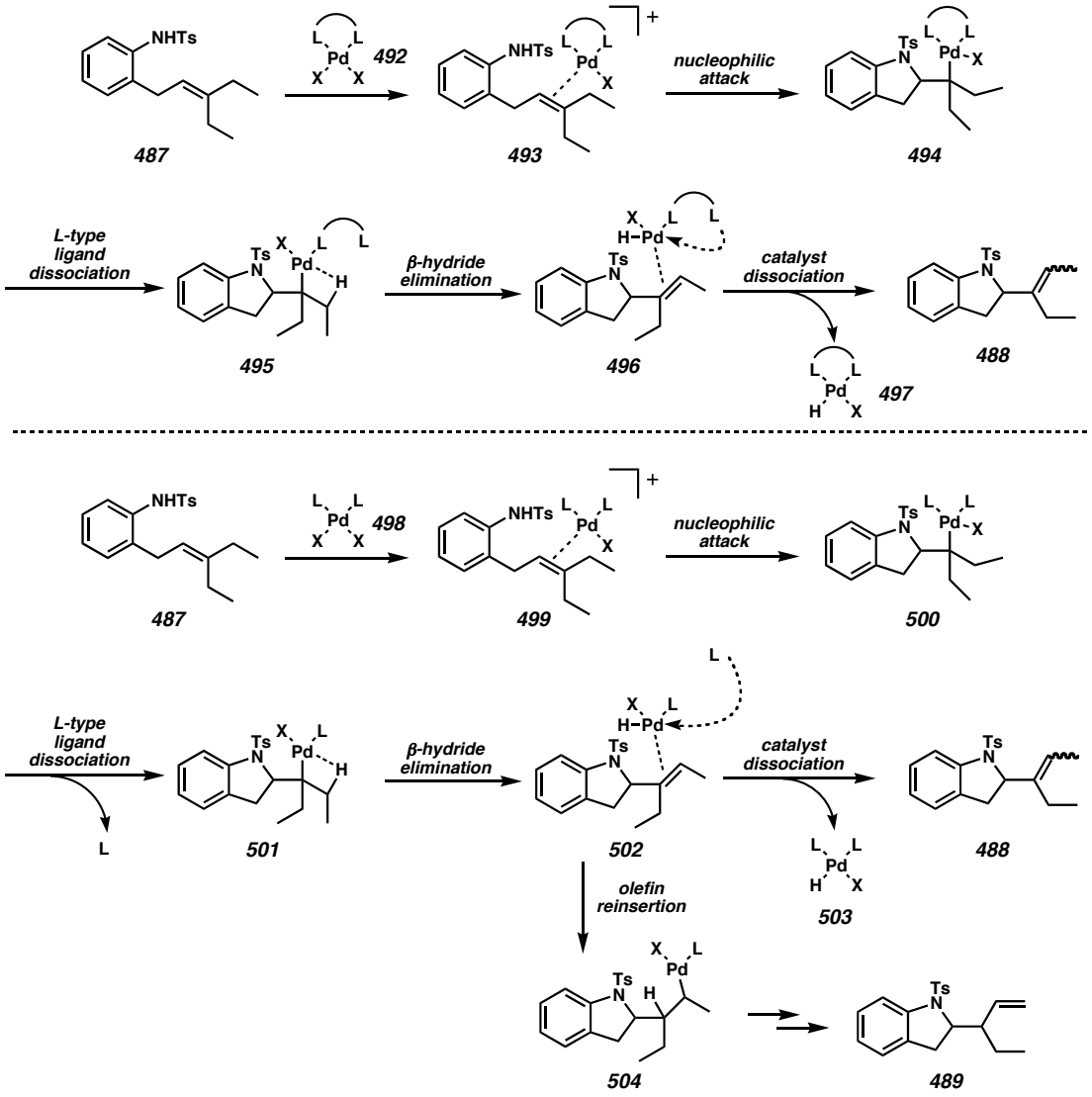
Palladium hydride intermediates, generated from the β-hydride elimination step, have been known to undergo olefin insertion reactions to form mixtures of olefin products. Olefin isomerization reactions were observed in some substrate tosylanilines (Scheme 5.4.4). Specifically, tosylaniline **487**, under the $Pd(OAc)_2$/pyridine conditions, afforded a mixture of tosylindolines **488** and **489**. **489** most likely arises from the palladium hydride reinsertion of the initial product olefin (**488**) and β-hydride elimination at the terminal methyl. The product distribution was different when bisoxazoline **480** was used as the ligand. In this case, palladium hydride reinsertion of the olefin was much less prevalent, and tosylindoline **488** was therefore the major isolated product. Olefin isomerizations also occurred in the oxidative cyclization of tosylaniline **490**. In this case, multiple isomerization products were observed in the $Pd(OAc)_2$/pyridine system, whereas no isomerizations were observed with the $Pd(OAc)_2$/bisoxazoline system. This result is consistent with the first example—palladium hydride mediated isomerizations occur more readily with monodentate pyridine ligands. The origin of this effect is unclear; one possible explanation is that L-type ligand dissociation must occur before β-hydride

elimination can happen (Scheme 5.4.5). Once the elimination occurs, the olefin ligand is readily displaced by the second coordinating atom of the bidentate ligand (intermediate **496**). In the pyridine case, this displacement must happen intermolecularly (intermediate **502**), which we expected to be slower than the intramolecular case. Therefore, olefin reinsertion to intermediate **504** would be more kinetically competitive, leading to increased levels of isomerization.

Scheme 5.4.4



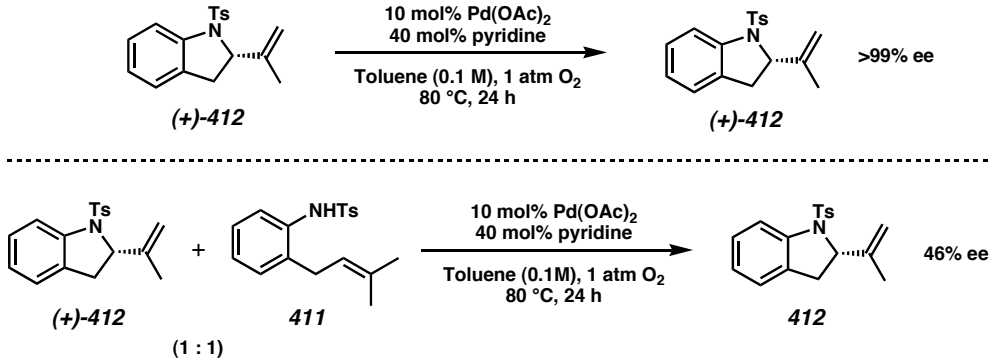
Scheme 5.4.5



To test whether palladium hydride species are detrimental to the overall enantioselectivity, enantiopure tosylindoline **(+)-412** was subjected to racemic reaction conditions (Scheme 5.4.6). After 24 h, the tosylindoline was reisolated without any evident racemization. The effect of intermediate palladium hydride species was also examined by subjecting a 1:1 mixture of enantiopure tosylindoline **(+)-412** and tosylaniline **411** to racemic cyclization conditions. The product tosylindoline was

isolated in 46% ee (73:27 er), within error of what was expected if palladium hydride species did not cause racemization in an intermolecular fashion. Once the palladium hydride dissociates from the product olefin, it proceeds to the catalyst reoxidation step rather than associate to a new olefin.

Scheme 5.4.6

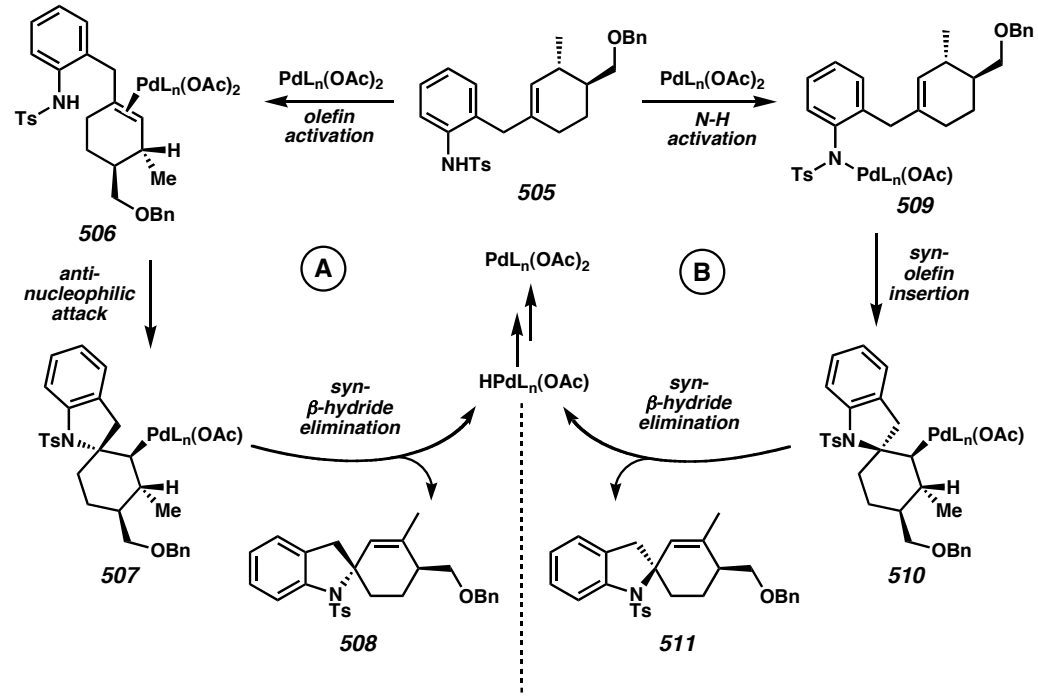


5.4.6 Distinguishing between a Wacker Mechanism and an Olefin Insertion Mechanism

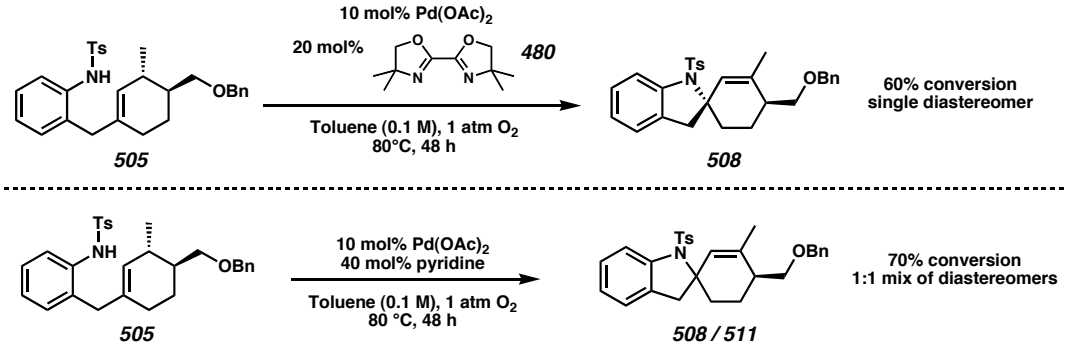
The final experiment conducted to provide insight into the asymmetric oxidation reaction was the cyclization of tosylaniline **505** (Scheme 5.4.7). As shown in our oxidative C-C bond forming chemistry, cyclization of this substrate can distinguish between two possible mechanistic pathways. Pathway A (Wacker-type mechanism) involves olefin activation, anti nucleophilic attack, and syn β-hydride elimination. Pathway B consists of an "N-H activation" step,[22] followed by a syn olefin insertion and a syn β-hydride elimination. When substrate **505** is subjected to the $Pd(OAc)_2$/bisoxazoline **480** catalyst system, tosylindoline **508** is isolated as a single diastereomer (Scheme 5.4.8). This outcome is consistent with a Wacker-type mechanism (pathway A). Interestingly, when substrate **505** is subjected to the $Pd(OAc)_2$/pyridine

system, both diastereomers were observed in an approximately 1:1 mixture. It remains unclear whether this mixture arises from both mechanisms being operative or palladium hydride mediated isomerizations of the initial product.[23]

Scheme 5.4.7



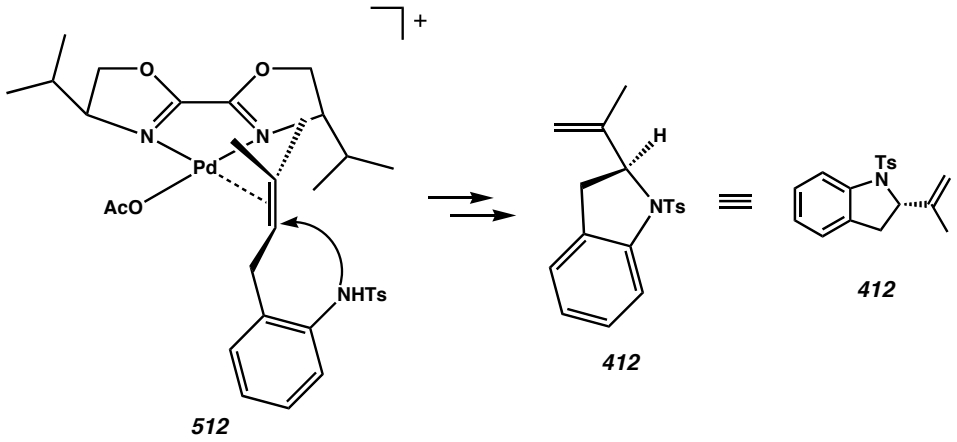
Scheme 5.4.8



5.4.7 A Proposed Stereochemical Model for the Observed Selectivity

Based on this outcome, a model describing the origin of enantioselectivity based on facially-selective olefin binding can be derived. It is believed that the alkene of tosylaniline **411** binds to the palladium center in the orientation depicted in Figure 5.4.1. The olefin binds to orient the proton of the less substituted carbon in the vicinity of the isopropyl group of the oxazoline. Anti selective nucleophilic attack on this bound olefin leads to the product with the stereocenter as drawn. This model is most consistent with the observed results[24] and could potentially be utilized in further ligand design.

Figure 5.4.1 Model for the observed selectivity in the asymmetric cyclization of **411**.



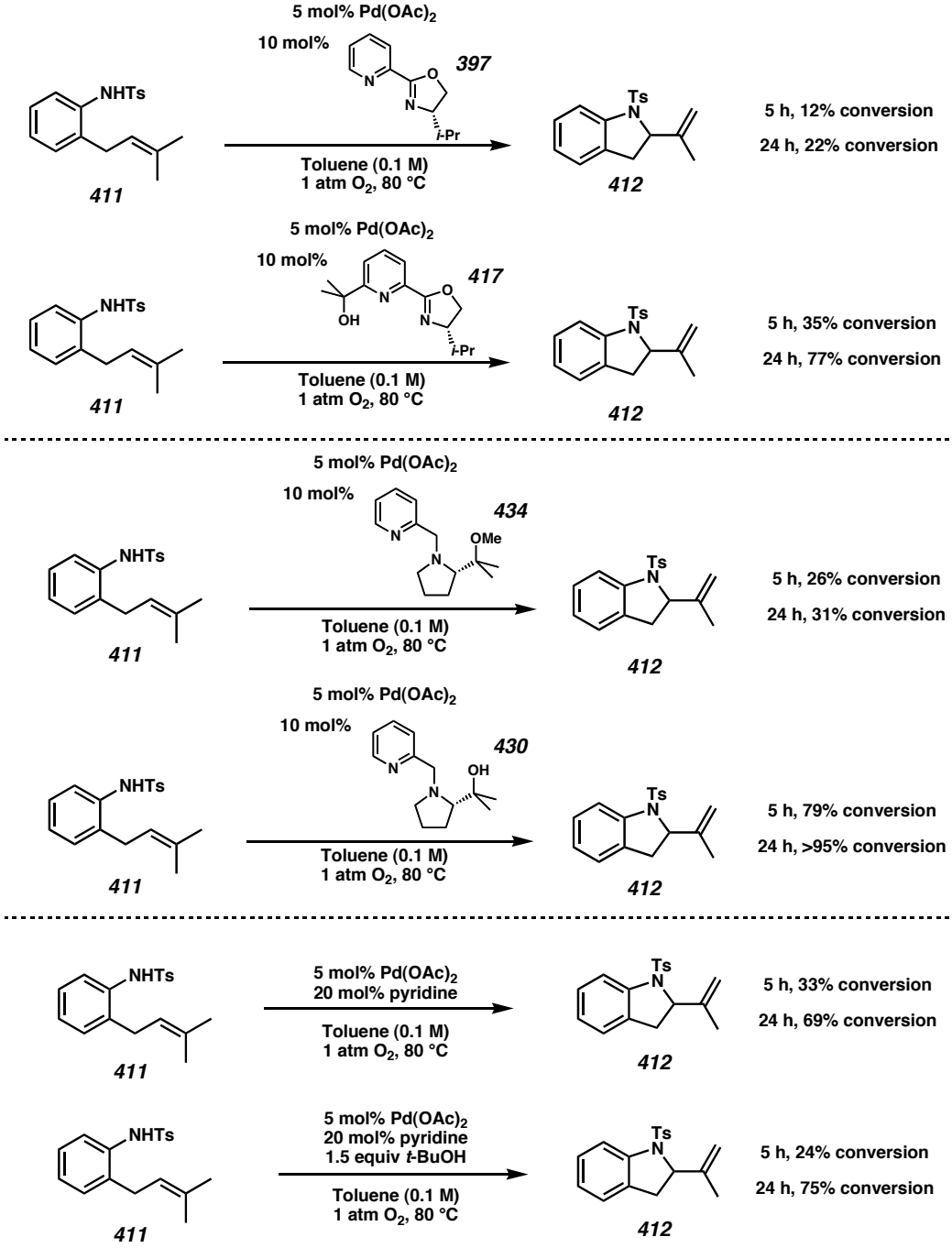
5.5 Further Developments

Although we have developed a reasonably clear picture of what is occurring in the oxidative cyclization of tosylaniline **411**, the levels of reactivity and enantioselectivity are not optimal. The largest obstacle in developing these reactions has been the effect of ligands on overall reactivity. Stahl has demonstrated that in palladium(II)-catalyzed alcohol oxidations, pyridine ligands accelerate the reoxidation of Pd(0), but decelerate the substrate oxidation.[19] The reactivity of Pd(II) centers toward substrate oxidation depends

highly on the electrophilicity of the metal center; bound ligands will increase the electron density of the metal center and thereby decrease its electrophilicity. Because of this ligand effect, the cyclizations typically need to be performed at high temperatures (i.e., 80 °C) for long periods of time, which are typically undesirable conditions for asymmetric transformations. Nonligated palladium centers, which would catalyze nonselective cyclizations, are expected to be more electrophilic (and consequently more reactive) than their ligated counterparts, further complicating the situation. Solutions to overcome these difficulties remain undiscovered.

A promising lead to this end is depicted in Scheme 5.5.1. During the ligand screening process of the cyclization of tosylaniline **411**, substantial increases in reactivity were observed when ligands possessing a tertiary alcohol were utilized (*vide supra*). Our previous studies on the palladium(II)-catalyzed oxidative kinetic resolution have demonstrated a dramatic rate effect caused by the presence of a tertiary alcohol in the reaction mixture.[2b] Direct comparisons of ligands **397** and **417** (with the tertiary alcohol moiety absent) and ligands **434** and **430** (with the tertiary alcohol replaced by a methyl ether) demonstrate the dramatic effects of this alcohol moiety. Importantly, when *t*-BuOH was added to the standard cyclization conditions, there was no noticeable effect on the rate, in contrast to our observations in the kinetic resolution chemistry. Though the origin of its effect remains to be elucidated, incorporation of a tertiary alcohol into the ligand framework could prove beneficial in the design of more reactive and selective systems.

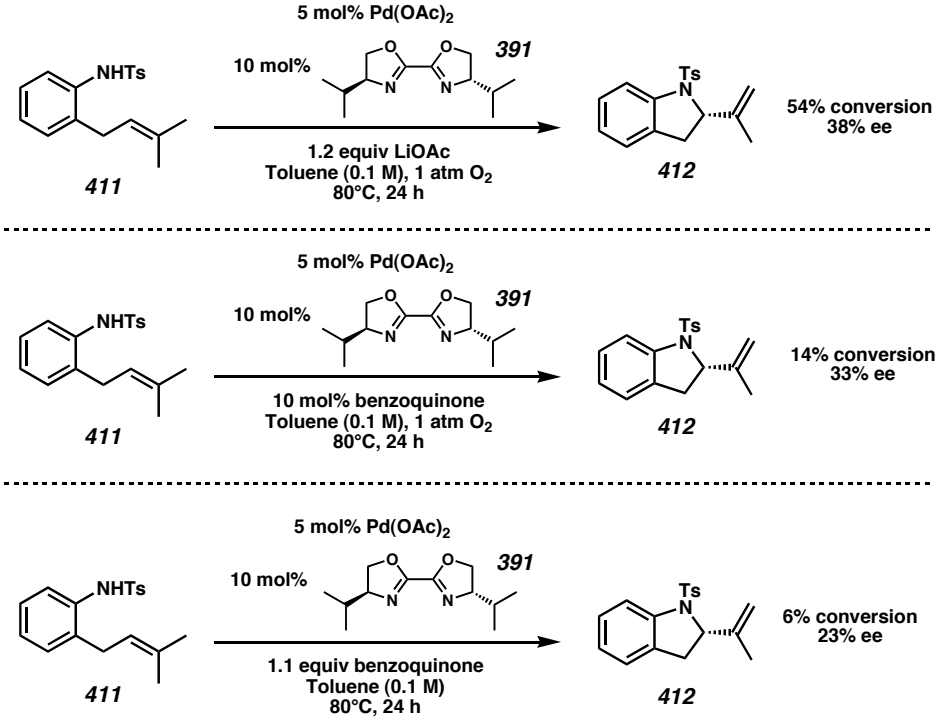
Scheme 5.5.1


5 mol% Pd(OAc)2
10 mol%
397
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
Ts
N
412
5 h, 12% conversion
24 h, 22% conversion
5 mol% Pd(OAc)2
10 mol%
417
OH
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 35% conversion
24 h, 77% conversion
5 mol% Pd(OAc)2
10 mol%
434
OMe
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 26% conversion
24 h, 31% conversion
5 mol% Pd(OAc)2
10 mol%
430
OH
NHTs
411
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 79% conversion
24 h, >95% conversion
NHTs
411
5 mol% Pd(OAc)2
20 mol% pyridine
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 33% conversion
24 h, 69% conversion
NHTs
411
5 mol% Pd(OAc)2
20 mol% pyridine
1.5 equiv t-BuOH
Toluene (0.1 M)
1 atm O2, 80 °C
412
5 h, 24% conversion
24 h, 75% conversion

5.6 Conclusion

We have investigated further extensions into the palladium catalyzed asymmetric oxidative heterocyclization reactions. Although the levels of reactivity and enantioselectivity are modest at this point, our findings still represent the most selective examples of cyclizations of this type. A demonstration of the advantage of using the palladium/ligand/O_2 system is illustrated in Scheme 5.6.1. Under our best conditions to date, the cyclization of tosylaniline **411** proceeds in 54% conversion and 38% ee. Using the same system, but including 10 mol% benzoquinone as a cooxidant, both reactivity and selectivity drop measurably. When benzoquinone is used as the sole stoichiometric oxidant—currently the most utilized reoxidation system in asymmetric Pd(II) cyclization chemistry[5,6]—the levels of reactivity and selectivity are even lower. The palladium/ligand/O_2 system clearly provides an entry into new asymmetric oxidative transformations and holds promise for future developments.

Scheme 5.6.1


5 mol% Pd(OAc)2
10 mol%
391
NHTs
411
1.2 equiv LiOAc
Toluene (0.1 M), 1 atm O2
80°C, 24 h
Ts
N
412
54% conversion
38% ee
5 mol% Pd(OAc)2
10 mol%
391
NHTs
411
10 mol% benzoquinone
Toluene (0.1 M), 1 atm O2
80°C, 24 h
Ts
N
412
14% conversion
33% ee
5 mol% Pd(OAc)2
10 mol%
391
NHTs
411
1.1 equiv benzoquinone
Toluene (0.1 M)
80°C, 24 h
Ts
N
412
6% conversion
23% ee

5.7 Experimental Section

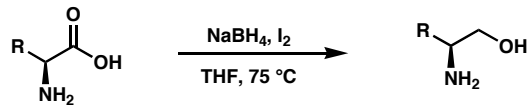
5.7.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received, except for benzoquinone, which was sublimed. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral GC was carried out using a Chiraldex B-DM column (30.0 m x 0.25 mm) purchased from Bodman Industries. Analytical chiral HPLC was performed on a Chiralcel AD or OD-H column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) or on a Varian Mercury 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C spectra were recorded on a Varian Mercury 300 (at 75 MHz) or on a Varian Mercury 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. Unless otherwise noted, compounds that are mixtures of *E* and *Z* olefin isomers are reported as the mixture as seen by ^{1}H NMR. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

$Pd(nbd)Cl_2$ was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Lindlar's catalyst (5% palladium on $CaCO_3$ with lead poison) was purchased from Alfa Aesar, Ward Hill, MA. All other palladium salts were purchased from Strem Chemicals, Inc., Newburyport, MA. Ligands **56**, **60**, **398**, and **572** were purchased from Strem Chemicals, Inc., Newburyport, MA. Diimine **419** was acquired from Ryan McFadden in the Stoltz group. Phosphoramidite **436** was acquired from Douglas Behenna in the Stoltz group. Bisoxazoline **428** was acquired from Tehshik Yoon in the MacMillan group at the California Institute of Technology, Pasadena, CA. All other chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

5.7.2 Preparative Procedures

5.7.2.1 Synthesis of Ligands



R = i-Pr (513)
R = Bn (515)
R = t-Bu (517)

R = i-Pr (514)
R = Bn (516)
R = t-Bu (518)

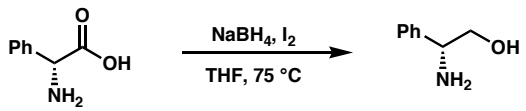
Synthesis of amino alcohols

L-Valinol. The reduction of amino acids was performed according to the procedure of McKennon et al.[25] To a suspension of $NaBH_4$ (6.20 g, 164 mmol) in 166 mL THF at 23 °C was added L-valine (8.00 g, 68.3 mmol) in one portion. The resulting suspension was cooled to 0 °C, and a solution of I_2 (17.3 g, 68.3 mmol) in 41.4 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 125 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 150 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by distillation (35 °C/1 mm) to afford L-valinol[26] as a colorless oil.

L-Phenylalaninol. To a suspension of $NaBH_4$ (1.37 g, 36.2 mmol) in 36.2 mL THF at 23 °C was added L-phenylalanine (2.50 g, 15.1 mmol) in one portion. The resulting suspension was cooled to 0 °C, and a solution of I_2 (3.83 g, 15.1 mmol) in 9.1 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was

allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 30 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by recrystallization from hot toluene to afford L-phenylalaninol[27] as a white solid.

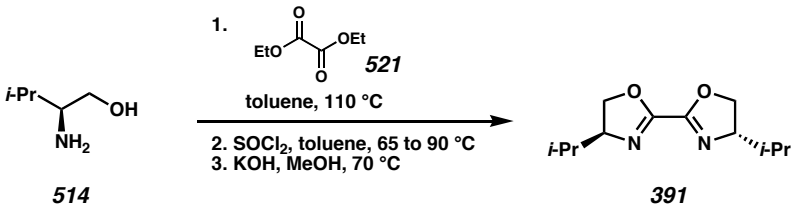
L-*tert*-Leucinol. To a suspension of $NaBH_4$ (692 mg, 18.3 mmol) in 18.3 mL THF at 23 °C was added L-*tert*-leucine (1.00 g, 7.62 mmol) in one portion. The resulting suspension was cooled to 0 °C, and a solution of I_2 (1.93 g, 7.62 mmol) in 4.6 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 15 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude L-*tert*-leucinol[28] was carried on without further purification.



519 ***520***

(*R*)-Phenylglycinol. To a suspension of $NaBH_4$ (1.50 g, 39.6 mmol) in 40 mL THF at 23 °C was added (*R*)-(–)-phenylglycine (2.50 g, 16.5 mmol) in one portion. The resulting

suspension was cooled to 0 °C, and a solution of I_2 (4.19 g, 16.5 mmol) in 10 mL THF was added dropwise over 10 min. Once the red color had dissipated, the mixture was allowed to warm to 23 °C, then heated to 75 °C and stirred. After 18 h, the reaction was cooled to room temperature, and MeOH was added dropwise until the mixture was clear. After stirring for 30 min, the solvent was removed by rotary evaporation, and the residue was dissolved in aqueous KOH (20%, 30 mL). The mixture was stirred for 4 h, then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by recrystallization from toluene to afford (*R*)-phenylglycinol[29] as a white solid.



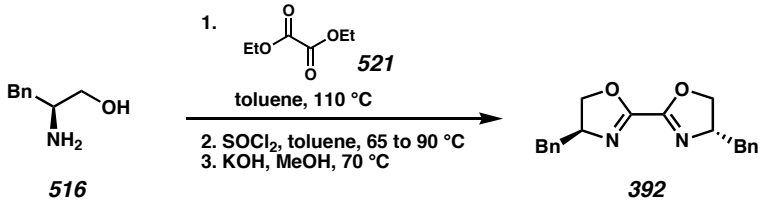
514 391

Bisoxazoline 391. Bisoxazoline **391** was synthesized according to a modified procedure of Denmark et al.[30] To a solution of L-valinol (500 μl, 4.49 mmol) in 32.9 mL toluene at 23 °C was added diethyl oxalate (291 μl, 2.14 mmol). The mixture was heated to 110 °C and stirred 6 h. After cooling to room temperature, 50 mL hexanes was added, and the mixture was stirred overnight (8 h). The white diamide that precipitated (472 mg, 85% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (100 mg, 0.384 mmol) in 2.56 mL toluene at 65 °C was added $SOCl_2$ (61.6 μl, 0.845 mmol) quickly. The resulting mixture was maintained at 65 °C for 30 min, then heated to 90 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction

mixture was then cooled to room temperature and partitioned between EtOAc (50 mL) and brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated to a white solid, which was carried directly to the next reaction.

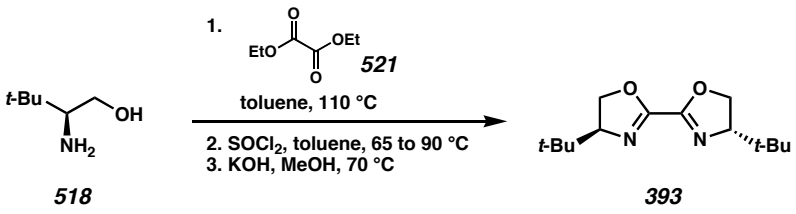
A suspension of the bis alkyl chloride (assume 0.384 mmol) and KOH (53.9 mg, 0.960 mmol) in 4.80 mL MeOH was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 1 h, and then it was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 30 mL CH_2Cl_2 and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (1:1 → 3:2 EtOAc/hexanes eluent) to provide the bisoxazoline[30] (74.1 mg, 86% over 2 steps, R_F = 0.42 in 2:1 hexanes/acetone) as a white solid.



Bisoxazoline 392. Bisoxazoline **392** was synthesized according to a modified procedure of Denmark et al.[30] To a solution of L-phenylalaninol (600 mg, 3.97 mmol) in 31.1 mL toluene at 23 °C was added diethyl oxalate (270 μl, 1.99 mmol). The mixture was heated to 110 °C and stirred 12 h. After cooling to room temperature, 50 mL hexanes was added, and the mixture was stirred for 1 h. The white diamide that precipitated (548 mg, 77% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (548 mg, 1.54 mmol) in 11.0 mL toluene at 65 °C was added $SOCl_2$ (325 μl, 4.46 mmol) quickly. The resulting mixture was maintained at 65 °C for 30 min, then heated to 90 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction mixture was then cooled to room temperature and partitioned between EtOAc (150 mL) and brine (75 mL). The organic phase was dried over Na_2SO_4 and concentrated to a white solid, which was carried directly to the next reaction.

A suspension of the bis alkyl chloride (assume 1.54 mmol) and KOH (216 mg, 3.85 mmol) in 19.3 mL MeOH was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 1 h, and then it was cooled to room temperature and filtered through a plug of celite (1.5 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 50 mL CH_2Cl_2 and filtered through a plug of celite (1.5 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to provide the bisoxazoline[30] (300 mg, 61% over 2 steps, R_F = 0.14 in 1:1 hexanes/EtOAc) as a white solid.

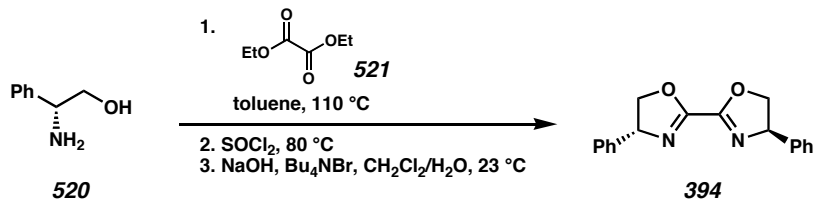


Bisoxazoline 393. Bisoxazoline **393** was synthesized according to a procedure analogous to that of Denmark et al.[30] To a solution of L-*tert*-leucinol (183 mg, 1.70 mmol) in 13.1 mL toluene at 23 °C was added diethyl oxalate (116 μl, 0.851 mmol). The mixture was

heated to 110 °C and stirred 10 h. After cooling to room temperature, 40 mL hexanes was added, and the mixture was stirred overnight (8 h). The white diamide that precipitated (147 mg, 60% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (88.5 mg, 0.307 mmol) in 2.05 mL toluene at 65 °C was added $SOCl_2$ (49.2 μl, 0.675 mmol) quickly. The resulting mixture was maintained at 65 °C for 30 min, then heated to 90 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was concentrated from PhH (3 x 15 mL) and carried directly to the next reaction.

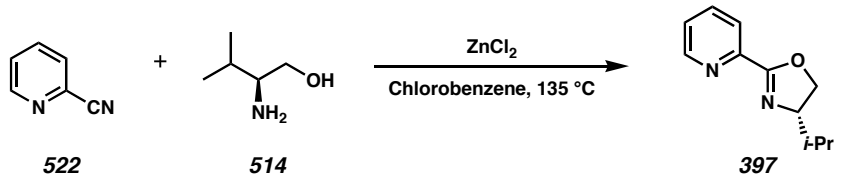
A suspension of the bis alkyl chloride (assume 0.307 mmol) and KOH (43.1 mg, 0.768 mmol) in 3.84 mL MeOH was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 3 h, and then it was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 30 mL CH_2Cl_2 and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provide the bisoxazoline[31] (43.2 mg, 56% over 2 steps, R_F = 0.17 in 2:1 hexanes/EtOAc) as a white solid.



Bisoxazoline 394. To a solution of (*R*)-phenylglycinol (500 mg, 3.64 mmol) in 26.6 mL toluene at 23 °C was added diethyl oxalate (235 μl, 1.73 mmol). The mixture was heated to 110 °C and stirred 9 h. After cooling to room temperature, 100 mL hexanes was added, and the mixture was stirred 1 h. The white diamide that precipitated (447 mg, 79% yield) was collected by suction filtration and carried on to the subsequent reaction.

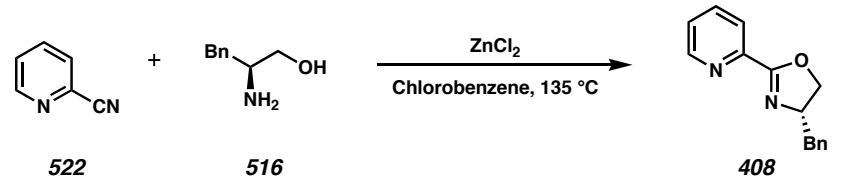
A solution of the diamide (431 mg, 1.31 mmol) in 6.0 mL $SOCl_2$ was stirred at 80 °C for 2 h. The bright yellow mixture was cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was concentrated from PhH (3 x 20 mL), and the crude material was taken directly to the next reaction.

Bisoxazoline formation was performed according to the procedure of Patra et al.[32] To a solution of NaOH (1.31 g, 32.8 mmol) in 4.0 mL H_2O and 26.2 mL CH_2Cl_2 at 23 °C was added Bu_4NBr (422 mg, 1.31 mmol). The mixture was stirred for 30 min, at which point the bis alkyl chloride (assume 1.31 mmol) was added portionwise over 5 min. The resulting mixture was stirred at 23 °C for 4 h. It was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:2 hexanes/EtOAc eluent) to afford the bisoxazoline[32] (276 mg, 72% yield over 2 steps, R_F = 0.12 in 2:1 hexanes/EtOAc) as a white semisolid.



522 *514* *397*

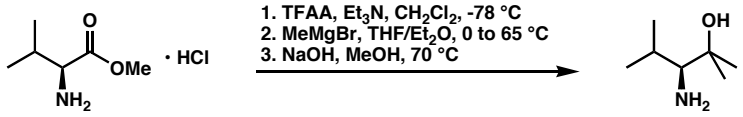
Oxazoline 397. Oxazoline **397** was synthesized according to the procedure of Bolm et al.[33] $ZnCl_2$ (8.2 mg, 0.0605 mmol) was flamed in a 50 mL round-bottom flask under vacuum. The flask was cooled to room temperature under nitrogen. It was then charged with L-valinol (200 μl, 1.81 mmol), chlorobenzene (3.63 mL), and 2-cyanopyridine (117 μl, 1.21 mmol), sequentially. The mixture was heated to 135 °C and stirred. After 6 h, the reaction was cooled to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between 125 mL CH_2Cl_2 and 75 mL H_2O. The organic phase was washed with H_2O (50 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (29:1 CH_2Cl_2/MeOH eluent) to provide the oxazoline[33] (207 mg, 90% yield, R_F = 0.06 in 2:1 hexanes/EtOAc) as a white solid.



522 *516* *408*

Oxazoline 408. Oxazoline **408** was synthesized according to a procedure analogous to that of Bolm et al.[33] $ZnCl_2$ (14.2 mg, 0.104 mmol) was flamed in a 50 mL round-bottom flask under vacuum. The flask was cooled to room temperature under nitrogen. It was then charged with L-phenylalaninol (472 mg, 3.12 mmol), chlorobenzene (6.30 mL), and

2-cyanopyridine (200 μl, 2.08 mmol), sequentially. The mixture was heated to 135 °C and stirred. After 6 h, the reaction was cooled to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between 125 mL CH_2Cl_2 and 75 mL H_2O. The organic phase was washed with H_2O (50 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 EtOAc/hexanes w/ 1% Et_3N eluent) to provide the oxazoline[34] (437 mg, 88% yield, R_F = 0.03 in 1:1 hexanes/EtOAc) as an orange oil.

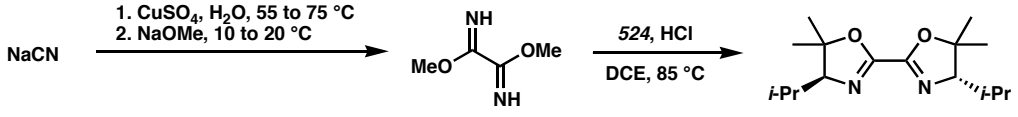


523 ***524***

Amino alcohol 524. Amino alcohol **524** was synthesized according to the procedure of Denmark et al.[30] To a suspension of L-valine methyl ester hydrochloride (1.00 g, 5.97 mmol) in 11.9 mL CH_2Cl_2 at 0 °C was added Et_3N (1.74 mL, 12.5 mmol) dropwise over 3 min. The mixture was maintained at 0 °C for 5 min, then cooled to –78 °C. Trifluoroacetic anhydride (860 μl, 6.09 mmol) was added over 1 min, and the resulting mixture was stirred at –78 °C. After 1 h, the reaction was quenched with saturated NH_4Cl (15 mL) and warmed to room temperature. Saturated $NaHCO_3$ (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide the trifluoroacetamide (1.26 g, 93% yield, R_F = 0.75 in 1:1 hexanes/EtOAc), which was carried on to the next reaction.

To a solution of MeMgBr (9.43 mL, 3.0 M in Et_2O, 28.3 mmol) 9.43 mL in THF at 0 °C was added a solution of the trifluoroacetamide (1.26 g, 5.55 mmol) in 6.24 mL THF dropwise. The resulting mixture was heated to 65 °C and stirred 6 h. The reaction was then cooled to 0 °C, quenched with saturated NH_4Cl (75 mL), and extracted with EtOAc (4 x 75 mL). The combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded the tertiary alcohol (1.26 g, 100% yield, R_F = 0.50 in 2:1 hexanes/EtOAc), which was taken on to the subsequent reaction.

A solution of the tertiary alcohol (215 mg, 0.946 mmol) in 5% NaOH (w/v) in MeOH (1.89 mL) was heated to 70 °C. After 4 h, the mixture was cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (50 mL) and 1 M NaOH (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (5 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The amino alcohol[30] (**524**, R_F = 0.00 in 2:1 hexanes/EtOAc) was taken on to the next reaction without purification.



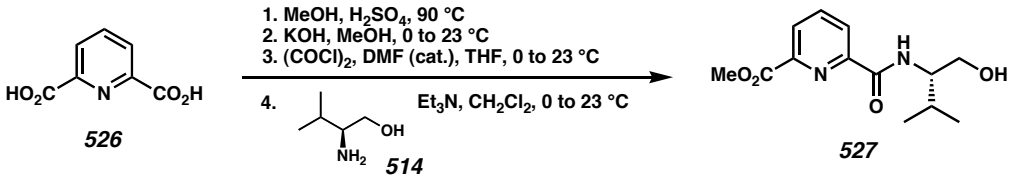
525 *413*

Bisoxazoline 413. Cyanogen was generated according to the procedure of Janz,[35] and the gas was trapped by methoxide according to the reported procedures.[36] To a solution of $CuSO_4$•$5H_2O$ (6.24 g, 25.0 mmol) in 25 mL H_2O at 55 °C was added a solution of NaCN (2.45 g, 50.0 mmol) in 50 mL H_2O dropwise via addition funnel over 40 min. The mixture was then heated to 75 °C and stirred an additional 30 min. The gas evolved over

the course of the reaction (cyanogen) was passed through a drying tube ($CaCl_2$) and bubbled directly into a solution of NaOMe in MeOH (50 mL, 0.5 M, 25.0 mmol, generated from Na metal in MeOH) at 10 °C. Once cyanogen evolution was complete, the methanol solution was concentrated to an oil, which was partitioned between brine (100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 75 mL), and the combined organic phases were dried over K_2CO_3 and concentrated in vacuo. Bisimidate **525**[37] (435 mg, 24% yield, R_F = 0.32 in 2:1 hexanes/acetone) was carried directly to the next reaction without purification.

Bisoxazoline **413** was synthesized according to a procedure analogous to that of Ukaji et al.[38] To a solution of amino alcohol **524** (100 mg, 0.762 mmol) in 3.0 mL Et_2O at 0 °C was added HCl (400 μl, 0.800 mmol). The solvent was removed by rotary evaporation, and the white solid was dissolved in 1.50 mL dichloroethane. To this solution at 23 °C was added bisimidate **525** (43.4 mg, 0.374 mmol), and the resulting mixture was heated to 85 °C. After stirring for 24 h, the brown solution was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were washed with H_2O (30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford the bisoxazoline (13.9 mg, 13% yield, R_F = 0.51 in 2:1 hexanes/acetone) as a white solid. **Bisoxazoline 413**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (d, *J* = 8.7 Hz, 2H), 1.95-1.79 (d of septets, *J* = 6.6, 8.7 Hz, 2H), 1.52 (s, 6H), 1.38 (s, 6H), 1.12 (d, *J* = 6.6 Hz, 6H), 0.99 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 88.6, 81.0, 29.3, 29.0, 21.4, 21.2, 21.0; IR (film) 1615,

1089 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{28}O_2N_2]^+$: 280.2151, found 280.2154; $[\alpha]^{23}_D$ –55.60° (*c* 0.50, $CHCl_3$).



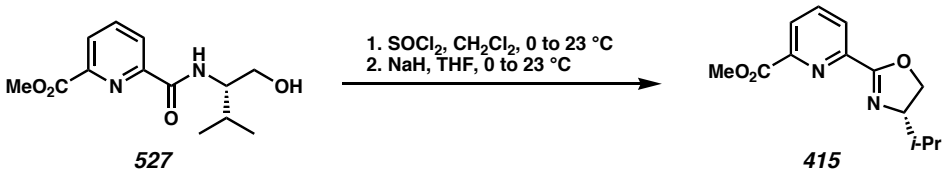
Amide 527. Esterification was performed according to the procedure of Chrystal et al.[39] To a suspension of 2,6-pyridinedicarboxylic acid (1.00 g, 5.98 mmol) in 12.5 mL MeOH at 23 °C was added 2.49 mL conc. H_2SO_4 dropwise. The reaction was heated to 90 °C and stirred for 40 h. The mixture was cooled to 0 °C, diluted with 10 mL H_2O, and quenched by adding Na_2CO_3 portionwise until bubbling ceased. The mixture was then reacidified with conc. HCl and extracted with $CHCl_3$ (4 x 75 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The bis methyl ester[39] (781 mg, 69% yield, R_F = 0.16 in 2:1 hexanes/EtOAc) was carried to the next reaction without further purification.

Monosaponification was performed according to a modified procedure of Hull et al.[40] To a suspension of the bis methyl ester (1.00 g, 5.12 mmol) in 34.1 mL MeOH at 0 °C was added KOH (287 mg, 5.12 mmol). The reaction was stirred at 0 °C for 3 h, then allowed to warm to 23 °C and stirred an additional 3 h. The solvent was then removed by rotary evaporation, and the residue was dissolved in H_2O (30 mL). Conc. HCl was added to acidify the mixture, and it was then extracted with $CHCl_3$ (4 x 50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was then dissolved in EtOAc (100 mL) and extracted with saturated $NaHCO_3$ (3 x 50 mL). The combined aqueous layers were acidified at 0 °C with conc. HCl and extracted with

$CHCl_3$ (4 x 75 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The mono methyl ester[40] (573 mg, 62% yield, R_F = 0.00 in 2:1 hexanes/EtOAc) was isolated as a white solid.

To a solution of the mono methyl ester (294 mg, 1.62 mmol) in 8.10 mL THF at 0 °C was added oxalyl chloride (707 μl, 8.10 mmol), then DMF (~20 μl). The mixture was stirred at 0 °C for 5 min, then allowed to warm to 23 °C. After 1 h, the mixture was concentrated in vacuo. The residue was concentrated from PhH (3 x 15 mL) and carried to the subsequent reaction.

To a solution of L-valinol (216 μl, 1.94 mmol) and Et_3N (677 μl, 4.86 mmol) in 8.20 mmol CH_2Cl_2 at 0 °C was added a solution of the crude acid chloride (assume 1.62 mmol) in 8.00 mL CH_2Cl_2 dropwise over 5 min. The mixture was maintained at 0 °C for 10 min, then allowed to warm to 23 °C and stirred for 1 h. The reaction was quenched with 0.5 N HCl (30 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (4:1 EtOAc/hexanes → 9:1 EtOAc/MeOH eluent) to afford the amide (406 mg, 94% yield over 2 steps, R_F = 0.49 in 9:1 CH_2Cl_2/MeOH), which was carried on to the next reaction.

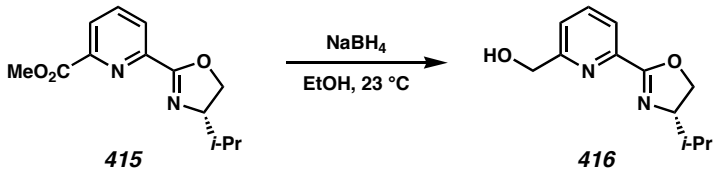


527 *415*

Oxazoline 415. To a solution of amide **527** (278 mg, 1.04 mmol) in 6.93 mL CH_2Cl_2 at 0 °C was added $SOCl_2$ (945 μl) dropwise. The reaction was allowed to warm to 23 °C and stirred. After 2 h, the mixture was quenched at 0 °C with H_2O (30 mL) and extracted with CH_2Cl_2 (2 x 60 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 hexanes/EtOAc eluent) provided the alkyl chloride (258 mg, 87% yield, R_F = 0.70 in 3:1 EtOAc/hexanes) as a colorless oil.

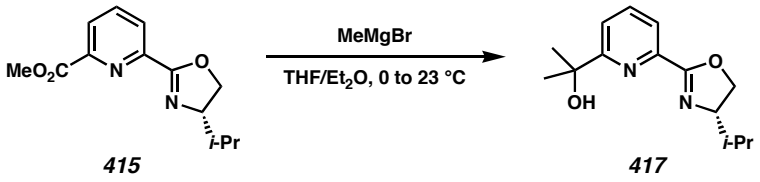
To a solution of the alkyl chloride (258 mg, 0.906 mmol) in 7.25 mL THF at 0 °C was added NaH (72.4 mg, 60% dispersion in mineral oil, 1.81 mmol). The mixture was stirred for 5 min at 0 °C, then allowed to warm to 23 °C. After 9 h, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl (30 mL), and extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (3:1 EtOAc/hexanes eluent) to afford the oxazoline (144 mg, 64% yield, R_F = 0.26 in 3:1 EtOAc/hexanes) as a white solid. **Oxazoline 415**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.8 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.93 (app.t, *J* = 7.8 Hz, 1H), 4.55 (dd, *J* = 8.1, 9.6 Hz, 1H), 4.25 (app.t, *J* = 8.1 Hz, 1H), 4.20-4.11 (m, 1H), 4.00 (s, 3H), 1.88 (app.octet, *J* = 6.6 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 162.1, 148.2, 147.4, 137.9, 127.4, 126.9, 73.2, 71.3,

53.3, 33.1, 19.3, 18.5; IR (film) 1737, 1248 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{16}O_3N_2]^+$: 248.1161, found 248.1156; $[\alpha]^{23}_D$ –88.00° (*c* 1.0, $CHCl_3$).

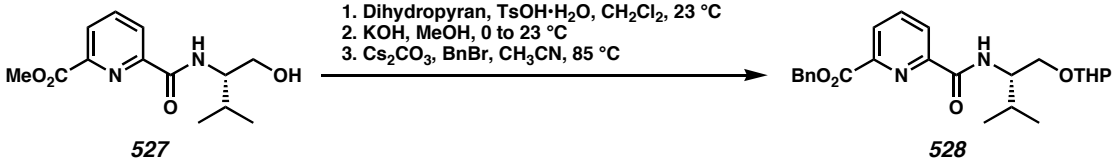


415 *416*

Oxazoline 416. To a solution of oxazoline **415** (45.3 mg, 0.182 mmol) in 1.82 mL EtOH at 23 °C was added $NaBH_4$ (31.1 mg, 0.822 mmol) portionwise over 3 min. The reaction was stirred at 23 °C for 2 h, and then it was quenched with 10 mL H_2O. The mixture was then partitioned between $CHCl_3$ (50 mL) and H_2O/brine (30 mL, 1:1), and the aqueous phase was extracted with $CHCl_3$ (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (19:1 CH_2Cl_2/MeOH eluent) afforded the alcohol (40.1 mg, 99% yield, R_F = 0.34 in 9:1 CH_2Cl_2/MeOH) as a colorless oil. **Oxazoline 416**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.5 Hz, 1H), 7.77 (app.t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 4.85 (s, 2H), 4.49 (dd, *J* = 7.8, 9.0 Hz, 1H), 4.22 (app.t, *J* = 8.1 Hz, 1H), 4.19-4.11 (m, 1H), 1.90 (app.octet, *J* = 6.6 Hz, 1H), 1.04 (d, *J* = 6.9 Hz, 1H), 0.93 (6.9, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 160.4, 146.1, 137.5, 122.8, 122.7, 73.0, 70.9, 65.0, 32.9, 19.3, 18.3; IR (film) 3306, 2960, 1643, 1587, 1365 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{16}O_2N_2]^+$: 220.1212, found 220.1203; $[\alpha]^{23}_D$ –71.64° (*c* 0.50, $CHCl_3$).



Oxazoline 417. To a solution of MeMgBr (305 μl, 3.0 M in Et_2O, 0.915 mmol) in 1.03 mL THF at 0 °C was added a solution of oxazoline **415** (45.5 mg, 0.183 mmol) in 1.00 mL THF dropwise over 1 min. The reaction was maintained at 0 °C for 10 min, then allowed to warm to 23 °C. After 30 min, the mixture was quenched at 0 °C with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (29:1 CH_2Cl_2/MeOH eluent) to afford the tertiary alcohol (38.7 mg, 85% yield, R_F = 0.40 in 9:1 CH_2Cl_2/MeOH) as a colorless oil. **Oxazoline 417**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.78 (app.t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 4.51 (dd, *J* = 7.8, 9.3 Hz, 1H), 4.23 (app.t, *J* = 8.1 Hz, 1H), 4.20-4.13 (m, 1H), 1.91 (app.octet, *J* = 6.6 Hz, 1H), 1.57 (s, 3H), 1.56 (s, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 162.8, 145.2, 137.7, 122.5, 121.0, 73.0, 72.1, 70.9, 33.0, 30.9, 30.8, 19.2, 18.4; IR (film) 2967, 1365, 965 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_2N_2]^+$: 248.1525, found 248.1533; $[\alpha]^{23}_D$ –82.40° (*c* 0.25, $CHCl_3$).

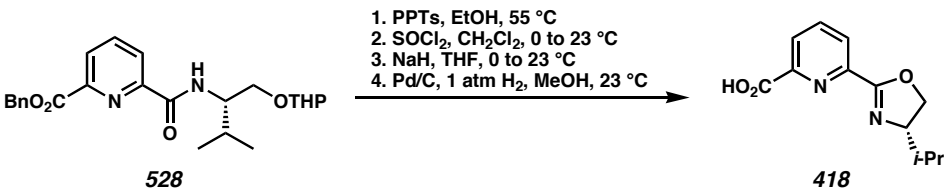


Ester 528. To a solution of amide **527** (80.3 mg, 0.302 mmol) and dihydropyran (30.3 μl, 0.332 mmol) in 1.51 mL CH_2Cl_2 at 23 °C was added TsOH•H_2O (0.6 mg, 0.00302

mmol). The solution was maintained at 23 °C for 11 h. The mixture was then diluted with 50 mL EtOAc and washed with saturated $NaHCO_3$ (25 mL), then brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc eluent) provided the THP ether (87.1 mg, 82% yield, R_F = 0.56 in 3:1 EtOAc/hexanes) as a colorless oil.

To a solution of the THP ether (87.1 mg, 0.249 mmol) in 860 μl MeOH at 0 °C was added a solution of KOH (27.9 mg, 0.498 mmol) in 800 μl MeOH. The resulting mixture was stirred at 0 °C for 30 min, then was allowed to warm to 23 °C. After 5 h, the MeOH was removed by rotary evaporation, and the residue was partitioned between $CHCl_3$ (50 mL) and H_2O/brine (30 mL, 1:1). The aqueous phase was extracted with $CHCl_3$ (4 x 25 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The carboxylic acid (R_F = 0.00 in 1:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

The benzyl ester was synthesized according to the procedure of Lee et al.[41] A suspension of the carboxylic acid (assume 0.249 mmol), Cs_2CO_3 (148 mg, 0.453 mmol), and BnBr (39.5 ml, 0.332 mmol) in 3.02 mL CH_3CN was heated to 85 °C. After 30 min, the reaction mixture was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_3CN eluent). The solvent was removed by rotary evaporation, and the residue was dissolved in 50 mL EtOAc and washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (3:2 hexanes/EtOAc eluent) to afford the benzyl ester (74.3 mg, 70% yield over 2 steps, R_F = 0.47 in 1:1 hexanes/EtOAc), which was taken on to the subsequent reaction.



528 *418*

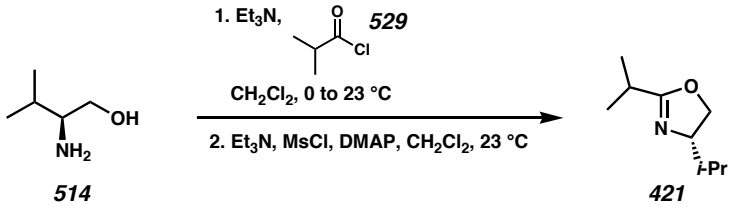
Oxazoline 418. To a solution of ester **528** (76.5 mg, 0.179 mmol) in 1.99 mL EtOH at 23 °C was added PPTs (4.5 mg, 0.0179 mmol). The reaction mixture was heated to 55 °C and stirred. After 2 h, the mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 EtOAc/hexanes eluent) afforded the alcohol (R_F = 0.13 in 1:1 hexanes/EtOAc), which was carried to the next reaction.

To a solution of the alcohol (assume 0.179 mmol) in 1.31 mL CH_2Cl_2 at 0 °C was added $SOCl_2$ (179 μl) dropwise over 1 min. The reaction was maintained at 0 °C for 10 min, then allowed to warm to 23 °C and stirred for 2 h. The mixture was then quenched with 15 mL H_2O at 0 °C and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the alkyl chloride (54.5 mg, 84% yield over 2 steps, R_F = 0.58 in 1:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alkyl chloride (207 mg, 0.574 mmol) in 4.59 mL THF at 0 °C was added NaH (45.9 mg, 60% dispersion in mineral oil, 1.15 mmol). The reaction was stirred at 0 °C for 10 min, then allowed to warm to 23 °C and stirred for 20 h. The mixture was then quenched at 0 °C with saturated NH_4Cl (50 mL) and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (50 mL),

dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc eluent) afforded the oxazoline (88.1 mg, 47% yield, R_F = 0.25 in 1:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

A solution of the oxazoline (23.6 mg, 0.0728 mmol) and Pd/C (2.4 mg, 10%) in 2.91 mL MeOH at 23 °C was stirred under 1 atm H_2. After 15 min, the mixture was filtered through a plug of celite (pipet, MeOH eluent), and the filtrate was concentrated in vacuo. The crude material (R_F = 0.00 in 1:1 hexanes/EtOAc) was used immediately in the subsequent palladium reaction to avoid forming insoluble materials.

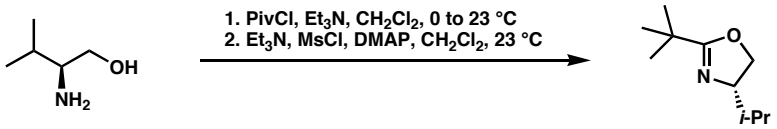


514 421

Oxazoline 421. To a solution of L-valinol (100 µl, 0.898 mmol) and *i*-Pr_2NEt (427 µl, 2.45 mmol) in 8.16 mL CH_2Cl_2 at 0 °C was added isobutyryl chloride (85.5 µl, 0.816 mmol). The reaction mixture was stirred for 5 min, then allowed to warm to 23 °C and stirred for 75 min. The reaction was then cooled to 0 °C, quenched with 0.5 N HCl (25 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL) and then brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude amide (63.2 mg, 45% yield, R_F = 0.13 in 1:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

To a solution of the amide (63.2 mg, 0.365 mmol) in 1.83 mL CH_2Cl_2 at 23 °C was added DMAP (4.5 mg, 0.0365 mmol), Et_3N (224 µl, 1.61 mmol), and MsCl (31.1 µl, 0.402 mmol), sequentially. The resulting mixture was stirred at 23 °C for 24 h. The

reaction was then partitioned between 50 mL CH_2Cl_2 and 30 mL saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were washed with saturated $NaHCO_3$ (30 mL). The basic aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL), and the organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to afford the oxazoline[42] (7.0 mg, 12% yield, R_F = 0.64 in 2:1 hexanes/EtOAc) as a colorless oil.

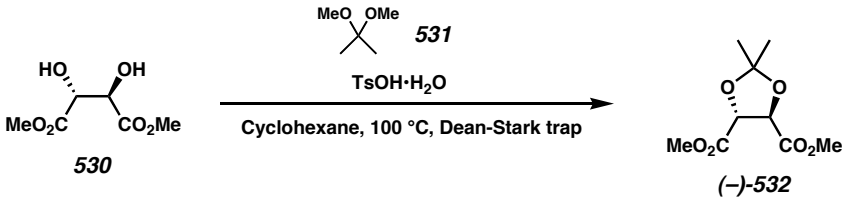


514 ***422***

Oxazoline 422. To a solution of L-valinol (100 μl, 0.898 mmol) and Et_3N (341 μl, 2.45 mmol) in 8.16 mL CH_2Cl_2 at 0 °C was added trimethylacetyl chloride (101 μl, 0.816 mmol). The reaction mixture was stirred for 5 min, then allowed to warm to 23 °C and stirred for 75 min. The reaction was then cooled to 0 °C, quenched with 0.5 N HCl (25 mL), and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL) and then brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude amide[43] (135 mg, 88% yield, R_F = 0.07 in 2:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

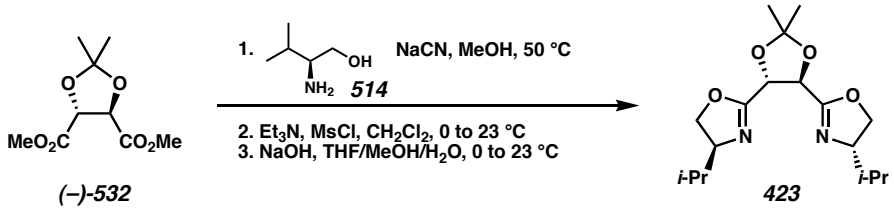
To a solution of the amide (135 mg, 0.721 mmol) in 3.61 mL CH_2Cl_2 at 23 °C was added DMAP (8.8 mg, 0.0721 mmol), Et_3N (442 μl, 3.17 mmol), and MsCl (61.4 μl, 0.793 mmol), sequentially. The resulting mixture was stirred at 23 °C for 24 h. The reaction was then partitioned between 50 mL CH_2Cl_2 and 30 mL saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases

were washed with saturated $NaHCO_3$ (30 mL). The basic aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL), and the organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to afford the oxazoline (61.0 mg, 50% yield, R_F = 0.64 in 2:1 hexanes/EtOAc) as a colorless oil. **Oxazoline 422**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 7.8, 9.3 Hz, 1H), 4.01 (app.t, *J* = 7.2 Hz, 1H), 3.99-3.92 (m, 1H), 1.89-1.78 (m, 1H), 1.23 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.1, 69.9, 33.5, 32.3, 28.1, 18.7, 17.4; IR (film) 2965, 1731, 1151 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{10}H_{19}NO]^+$: 169.1467, found 169.1479; $[\alpha]^{23}_D$ –18.64° (*c* 0.50, $CHCl_3$).



Acetonide (–)-532. Acetonide **(–)-532** was synthesized according to a modified procedure of Mash et al.[44] To a solution of dimethyl L-tartrate (500 mg, 2.81 mmol) and 2,2-dimethoxypropane (1.04 mL, 8.43 mmol) in 14 mL cyclohexane was added TsOH•H_2O (53.5 mg, 0.281 mmol). The reaction was heated to 100 °C with azeotropic removal of MeOH via a Dean-Stark trap. The mixture turned dark red over the course of the reaction (16 h). The mixture was then cooled to room temperature, and 100 mg K_2CO_3 was added. The solution was stirred for 1.5 h (red color dissipated to pale yellow), and then it was partitioned between EtOAc (100 mL) and saturated $NaHCO_3/H_2O$ (60 ml, 1:2). The aqueous phase was extracted with EtOAc (50 mL), and

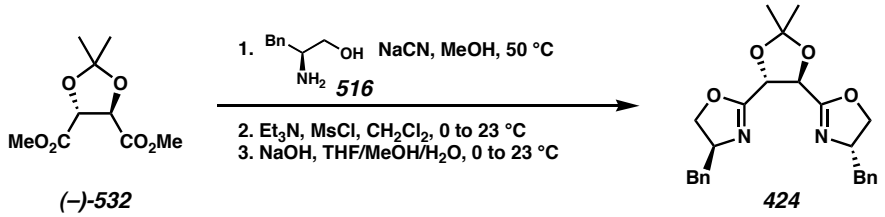
the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) provided the acetonide[44] (602 mg, 98% yield, R_F = 0.24 in 4:1 hexanes/EtOAc) as a yellow oil.



Bisoxazoline 423. The synthesis of bisoxazoline **423** was performed according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(–)-532** (103 mg, 0.472 mmol) and L-valinol (116 μl, 1.04 mmol) in 1.57 mL MeOH at 50 °C was added NaCN (2.3 mg, 0.0472 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.02 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.472 mmol) and Et_3N (295 μl, 2.12 mmol) in 2.15 mL CH_2Cl_2 at 0 °C was added MsCl (91.3 μl, 1.18 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.21 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

To a solution of the bis mesylate (assume 0.472 mmol) in THF (2.43 mL), MeOH (2.78 mL), and H_2O (2.78 mL) at 0 °C was added NaOH (56.8 mg, 1.42 mmol). The mixture was stirred at 0 °C for 2 h, then allowed to warm to 23 °C and stirred for an additional 4 h. The reaction was then cooled to 0 °C, quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (3:2 hexanes/EtOAc w/ 1% Et_3N eluent) to afford the bisoxazoline[45] (49.7 mg, 32% yield over 3 steps, R_F = 0.37 in 1:1 hexanes/EtOAc) as a colorless oil.

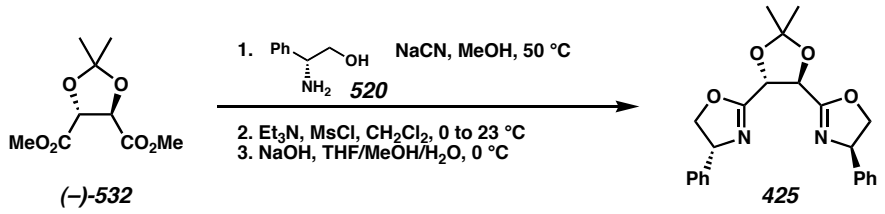


Bisoxazoline 424. Bisoxazoline **424** was synthesized according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(–)-532** (85.2 mg, 0..390 mmol) and L-phenylalaninol (130 mg, 0.858 mmol) in 1.30 mL MeOH at 50 °C was added NaCN (1.9 mg, 0.0390 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.03 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.390 mmol) and Et_3N (245 μl, 1.76 mmol) in 1.77 mL CH_2Cl_2 at 0 °C was added MsCl (75.5 μl, 0.975 mmol) dropwise over 1 min.

The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.25 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

To a solution of the bis mesylate (assume 0.390 mmol) in THF (2.01 mL), MeOH (2.29 mL), and H_2O (2.29 mL) at 0 °C was added NaOH (46.8 mg, 1.17 mmol). The mixture was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for an additional 6 h. The reaction was then cooled to 0 °C and quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (3:2 hexanes/EtOAc w/ 1% Et_3N eluent) to afford the bisoxazoline[45] (87.9 mg, 54% yield over 3 steps, R_F = 0.51 in 3:1 EtOAc/hexanes) as a colorless oil.

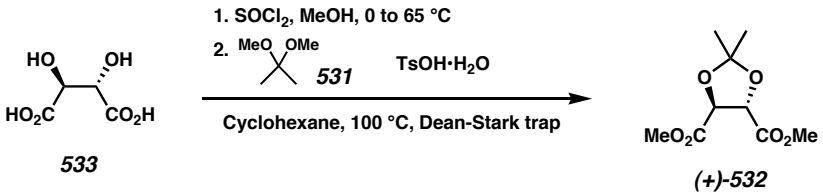


Bisoxazoline 425. The synthesis of bisoxazoline **425** was performed according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(–)-532** (103 mg, 0.472 mmol) and (*R*)-phenylglycinol (136 mg, 0.991 mmol) in 3.75 mL MeOH at 50 °C was added NaCN (4.3 mg, 0.0661 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and

30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.05 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.472 mmol) and Et_3N (296 μl, 2.12 mmol) in 2.15 mL CH_2Cl_2 at 0 °C was added MsCl (91.3 μl, 1.18 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.33 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

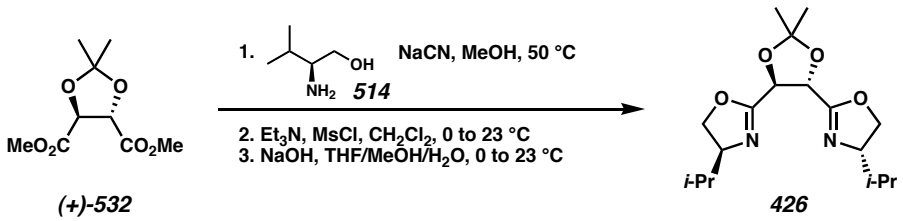
To a solution of the bis mesylate (assume 0.472 mmol) in THF (2.43 mL), MeOH (2.78 mL), and H_2O (2.78 mL) at 0 °C was added NaOH (56.8 mg, 1.42 mmol). The mixture was stirred at 0 °C for 2.5 h. The reaction was then quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (2:1 hexanes/EtOAc w/ 1% Et_3N eluent) to afford bisoxazoline **425** (88.0 mg, 47% yield over 3 steps, R_F = 0.79 in 3:1 EtOAc/hexanes) as a colorless oil. The spectroscopic data, with the exception of the sign of optical rotation, were identical to the reported information for the opposite enantiomer.[46]



Acetonide (+)-532. Dimethyl D-tartrate was synthesized according to the procedure of Kim et al.[47] To a solution of D-tartaric acid (500 mg, 3.33 mmol) in 1.67 mL MeOH at 0 °C was added $SOCl_2$ (1.26 mL, 17.3 mmol) dropwise over 2 min. The mixture was maintained at 0 °C for 1 h, then heated to 65 °C. After 3 h, the reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$ (30 mL). The solvent was removed by rotary evaporation, and the aqueous residue was extracted with EtOAc (4 x 40 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Dimethyl D-tartrate (515 mg, 87% yield, R_F = 0.02 in 4:1 hexanes/EtOAc) was carried on to the subsequent reaction without further purification.

Acetonide **(+)-532** was synthesized according to a modified procedure of Mash et al.[44] To a solution of dimethyl D-tartrate (515 mg, 2.89 mmol) and 2,2-dimethoxypropane (1.07 mL, 8.67 mmol) in 14 mL cyclohexane was added TsOH•H_2O (55.0 mg, 0.289 mmol). The reaction was heated to 100 °C with azeotropic removal of MeOH via a Dean-Stark trap. The mixture turned dark red over the course of the reaction (16 h). The mixture was then cooled to room temperature, and 100 mg K_2CO_3 was added. The solution was stirred for 1.5 h (red color dissipated to pale yellow), and then it was partitioned between EtOAc (100 mL) and saturated $NaHCO_3/H_2O$ (60 ml, 1:2). The aqueous phase was extracted with EtOAc (50 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash

chromatography (4:1 hexanes/EtOAc eluent) provided the acetonide[44] (624 mg, 99% yield, R_F = 0.24 in 4:1 hexanes/EtOAc) as a yellow oil.

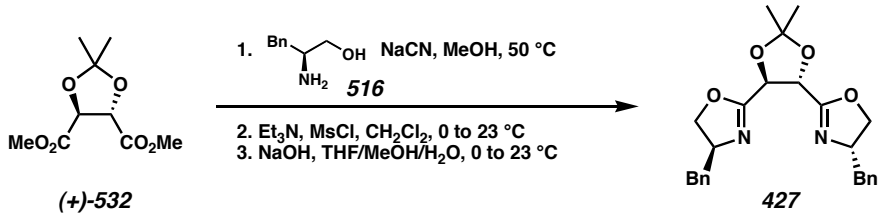


Bisoxazoline 426. The synthesis of bisoxazoline **426** was performed according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(+)-532** (112 mg, 0.513 mmol) and L-valinol (126 μl, 1.13 mmol) in 1.71 mL MeOH at 50 °C was added NaCN (2.5 mg, 0.0513 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.03 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.513 mmol) and Et_3N (322 μl, 2.31 mmol) in 2.33 mL CH_2Cl_2 at 0 °C was added MsCl (99.1 μl, 1.28 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.21 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

To a solution of the bis mesylate (assume 0.513 mmol) in THF (2.64 mL), MeOH (3.02 mL), and H_2O (3.02 mL) at 0 °C was added NaOH (61.6 mg, 1.54 mmol). The

mixture was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for an additional 6 h. The reaction was then cooled to 0 °C and quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (2:1 hexanes/EtOAc w/ 1% Et_3N eluent) to afford bisoxazoline **426**[45] (96.8 mg, 58% yield over 3 steps, R_F = 0.57 in 3:1 EtOAc/hexanes) as a white solid.

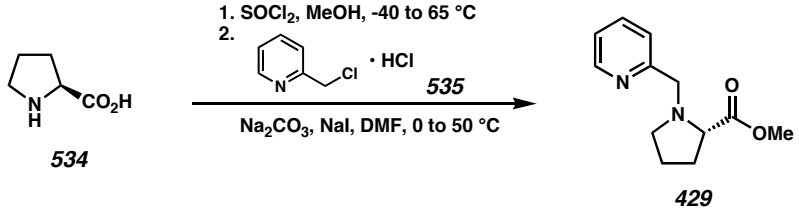


Bisoxazoline 427. Bisoxazoline **427** was synthesized according to a modified procedure of Bedekar et al.[45] To a solution of acetonide **(+)-532** (110 mg, 0.504 mmol) and L-phenylalaninol (168 mg, 1.11 mmol) in 1.68 mL MeOH at 50 °C was added NaCN (2.5 mg, 0.0504 mmol). The resulting mixture was heated to 50 °C and stirred for 24 h. The reaction was then cooled to room temperature, and the solvent was removed via rotary evaporation. The residue was partitioned between 60 mL EtOAc and 30 mL H_2O. The organic phase was dried over $MgSO_4$ and concentrated to an oil. The diamide (R_F = 0.03 in 3:1 EtOAc/hexanes) was carried on to the next reaction without further purification.

To a solution of the diamide (assume 0.504 mmol) and Et_3N (316 μl, 2.27 mmol) in 2.29 mL CH_2Cl_2 at 0 °C was added MsCl (97.5 μl, 1.26 mmol) dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then partitioned between 50 mL CH_2Cl_2 and 30 mL H_2O, and the organic layer was dried over

Na_2SO_4 and concentrated to an oil. The bis mesylate (R_F = 0.26 in 3:1 EtOAc/hexanes) was taken directly to the subsequent reaction.

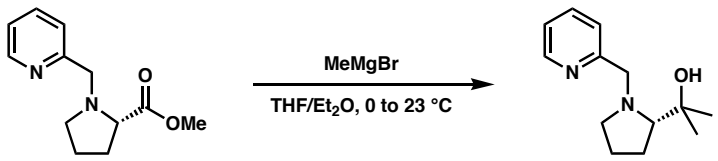
To a solution of the bis mesylate (assume 0.504 mmol) in THF (2.60 mL), MeOH (2.96 mL), and H_2O (2.96 mL) at 0 °C was added NaOH (60.4 mg, 1.51 mmol). The mixture was stirred at 0 °C for 1 h, then allowed to warm to 23 °C and stirred for an additional 6 h. The reaction was then cooled to 0 °C and quenched with 10 mL saturated NH_4Cl, and the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (30 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (2:1 → 1:1 hexanes/EtOAc w/ 1% Et_3N eluent) to afford bisoxazoline **427** (103 mg, 49% yield over 3 steps, R_F = 0.57 in 3:1 EtOAc/hexanes) as a colorless oil. **Bisoxazoline 427**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (comp m, 10H), 4.96 (s, 2H), 4.53-4.43 (m, 2H), 4.29 (app.t, *J* = 9.0 Hz, 2H), 4.09 (dd, *J* = 7.2, 8.4 Hz, 2H), 3.15 (dd, *J* = 5.1, 13.8 Hz, 2H), 2.67 (dd, *J* = 8.4, 13.8 Hz, 2H), 1.50 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 137.7, 129.5, 128.8, 126.8, 112.9, 74.1, 72.7, 67.6, 41.5, 26.4; IR (film) 1667, 976 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{25}H_{28}O_4N_2]^+$: 420.2049, found 420.2068; $[\alpha]^{23}_D$ +29.22° (*c* 1.0, $CHCl_3$).



Ester 429. L-Proline methyl ester hydrochloride was synthesized according to the procedure of Xin et al.[48] To a solution of L-proline (100 mg, 0.869 mmol) in 869 μl

MeOH at –40 °C was added $SOCl_2$ (87.5 μl, 1.20 mmol). The reaction mixture was allowed to warm to 23 °C, then heated to 65 °C. After 1.5 h, the reaction was cooled to room temperature, and the solvent was removed by rotary evaporation. The crude residue was concentrated from MeOH (2 x 10 mL) and the ester hydrochloride salt (R_F = 0.10 in 9:1 CH_2Cl_2/MeOH) was carried on to the subsequent reaction without further purification.

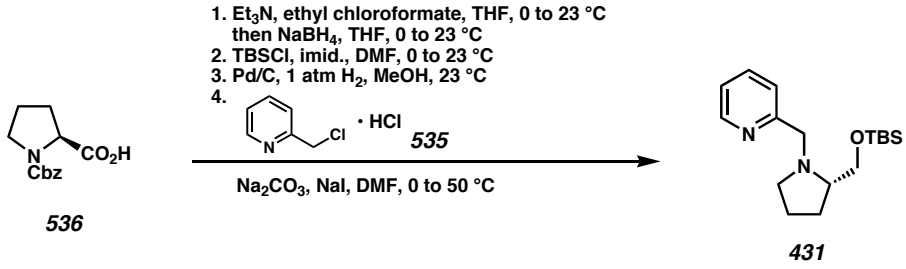
Ester **429** was synthesized according to the procedure of Chelucci et al.[49] To a solution of L-proline methyl ester hydrochloride (assume 0.869 mmol), 2-picolyl chloride hydrochloride (95.0 mg, 0.579 mmol), and NaI (4.3 mg, 0.0290 mmol) in 1.35 mL DMF at 0 °C was added Na_2CO_3 (220 mg, 2.08 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (3:1 EtOAc/hexanes w/ 1% Et_3N eluent) afforded alkylated proline methyl ester **429**[49] (120 mg, 94% yield, R_F = 0.40 in 9:1 CH_2Cl_2/MeOH) as a pale yellow oil.



429 *430*

Alcohol 430. The synthesis of tertiary alcohol **430** was performed according to the procedure of Chelucci et al.[49] To a solution of MeMgBr (653 ml, 3.0 M in Et_2O, 1.96 mmol) in 327 μl THF at 0 °C was added a solution of methyl ester **429** (108 mg, 0.490

mmol) in 522 μl THF dropwise over 1 min. The reaction was allowed to warm to 23 °C and stirred for 1 h. The mixture was then quenched with 1 N HCl 10 mL and stirred an additional 1 h. Aqueous NaOH (10%, 30 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, filtered through a pad of celite (CH_2Cl_2 eluent), dried over K_2CO_3, and concentrated to an oil. The residue was purified by flash chromatography (9:1 CH_2Cl_2/MeOH eluent) to provide the tertiary alcohol[49] (94.4 mg, 87% yield, R_F = 0.22 in 9:1 CH_2Cl_2/MeOH) as a yellow oil.



Pyrrolidine 431. Carboxylic acid reduction was performed according to the procedure of Seijas et al.[50] To a solution of *N*-carbobenzyloxy-L-proline (800 mg, 3.21 mmol) in 8.23 mL THF at 0 °C was added Et_3N (581 μl, 4.17 mmol). After 35 min at 0 °C, ethyl chloroformate (368 μl, 3.85 mmol) was added. The mixture was allowed to warm to 23 °C and stirred 45 min. The mixture was then cooled back to 0 °C, and a solution of $NaBH_4$ (243 mg, 6.42 mmol) in 5.44 mL H_2O was added dropwise. The reaction was allowed to warm to 23 °C and stirred overnight (8 h). The reaction mixture was then quenched at 0 °C with saturated NH_4Cl (20 mL), and 1 N HCl was added until the solution was slightly acidic (pH = 5). The THF was removed by rotary evaporation, and the residue was partitioned between H_2O (30 mL) and EtOAc (150 mL). The aqueous phase was extracted with EtOAc (50 mL), and the combined organic layers were washed

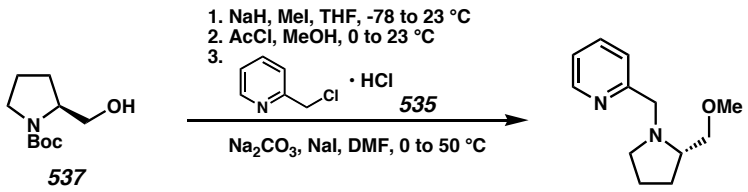
with 10% aq. NaOH (50 mL) and then brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to provide the alcohol[50] (653 mg, 86% yield, R_F = 0.10 in 2:1 hexanes/EtOAc), which was carried directly to the subsequent reaction.

Silylation and carbamate cleavage were performed according to the procedure of Vedejs and Lee.[51] To a solution of the alcohol (336 mg, 1.43 mmol) in 3.98 mL DMF at 23 °C was added imidazole (244 mg, 3.58 mmol). The mixture was then cooled to 0 °C, and TBSCl (259 mg, 1.72 mmol) was added. The reaction was allowed to warm to 23 °C and stirred. After 2 h, the mixture was diluted with 100 mL Et_2O and washed with 1 N HCl (2 x 30 mL), then brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford the silyl ether (450 mg, 90% yield, R_F = 0.76 in 2:1 hexanes/EtOAc), which was taken to the next reaction.

A mixture of the silyl ether (79.3 mg, 0.227 mmol) and Pd/C (2.3 mg, 10%) in 2.27 mL MeOH was stirred under 1 atm H_2 at 23 °C. After 1 h, the suspension was filtered through a plug of celite (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. The crude pyrrolidine[51] (R_F = 0.00 in 4:1 hexanes/EtOAc) was carried to the subsequent reaction without purification.

Pyrrolidine alkylation was performed according to the procedure of Chelucci et al.[49] To a solution of the pyrrolidine (assume 0.227 mmol), 2-picolyl chloride hydrochloride (37.2 mg, 0.227 mmol), and NaI (1.7 mg, 0.0114 mmol) in 535 μl DMF at 0 °C was added Na_2CO_3 (50.6 mg, 0.477 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room

temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (2:1 hexanes/EtOAc w/ 1% Et_3N eluent) afforded alkylated pyrrolidine **431** (51.2 mg, 74% yield over 2 steps, R_F = 0.40 in 9:1 CH_2Cl_2/MeOH) as a pale yellow oil. **Pyrrolidine 431**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (br d, *J* = 4.5 Hz, 1H), 7.64 (br t, *J* = 7.8 Hz, 1H), 7.50-7.43 (br m, 1H), 7.14 (br t, *J* = 6.0 Hz, 1H), 4.25 (br d, *J* = 13.5 Hz, 1H), 3.66 (br, 2H), 3.50 (br, 1H), 3.00 (br, 1H), 2.77 (br, 1H), 2.34 (br, 1H), 2.00-1.88 (br m, 1H), 1.72 (br, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 136.5, 123.2, 122.0, 67.2, 65.7, 62.0, 55.2, 28.5, 26.2, 23.3, 18.5, -5.1, -5.1; IR (film) 2954, 1088, 836 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{17}H_{31}ON_2Si]^+$: 307.2206, found 307.2202; $[\alpha]^{23}_D$ –65.12° (*c* 0.25, $CHCl_3$).

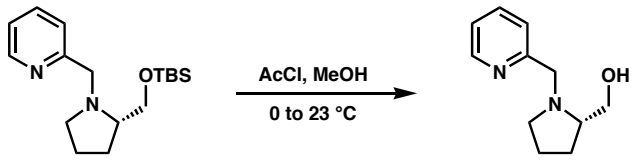


Pyrrolidine 432. Methylation of *N*-*t*-Boc-L-prolinol was performed according to the procedure of Kurokawa et al.[52] To a solution of *N*-*t*-Boc-L-prolinol (400 mg, 1.99 mmol) in 7.96 mL THF at –78 °C was added MeI (215 μl, 3.42 mmol), then NaH (134 mg, 60% dispersion in mineral oil, 3.34 mmol). The reaction was allowed to warm to 23 °C over 1 h. The mixture was then quenched at 0 °C with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 50 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (6:1

hexanes/EtOAc eluent) to provide the methyl ether[52] (401 mg, 93% yield, R_F = 0.60 in 2:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

Anhydrous HCl was generated by addition of 2.45 mL AcCl dropwise slowly to 7.91 mL MeOH at 0 °C. After 3 min, a solution of the methyl ether (120 mg, 0.557 mmol) in 1.00 mL MeOH was added. The resulting mixture was stirred for 5 min, then allowed to warm to 23 °C. After 90 min, the solution was concentrated in vacuo, and the crude hydrochloride salt (R_F = 0.00 in 4:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

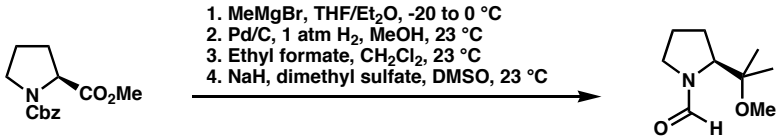
To a solution of the pyrrolidine hydrochloride salt (assume 0.557 mmol), 2-picolyl chloride hydrochloride (91.4 mg, 0.557 mmol), and NaI (4.0 mg, 0.0279 mmol) in 1.31 mL DMF at 0 °C was added Na_2CO_3 (183 mg, 1.73 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc w/ 1% Et_3N eluent) afforded alkylated pyrrolidine **432**[49] (95.2 mg, 83% yield over 2 steps, R_F = 0.19 in 9:1 CH_2Cl_2/MeOH) as an orange oil.



431 *433*

Alcohol 433. Anhydrous HCl was generated by addition of 3.15 mL AcCl dropwise slowly to 47.4 mL MeOH at 0 °C. After 3 min, a solution of pyrrolidine **431** (315 mg,

1.03 mmol) in 47.4 mL MeOH was added to the HCl solution. The mixture was allowed to warm to 23 °C and stirred. After 1 h, the reaction was cooled to 0 °C and quenched with saturated $NaHCO_3$ (50 mL). The MeOH was removed by rotary evaporation, and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The organic phases were combined, dried over K_2CO_3, and concentrated to an oil. The residue was purified by flash chromatography (19:1 → 3:1 CH_2Cl_2/MeOH eluent) to afford the primary alcohol[49] (138 mg, 70% yield, R_F = 0.11 in 9:1 CH_2Cl_2/MeOH) as an orange oil.



538 *539*

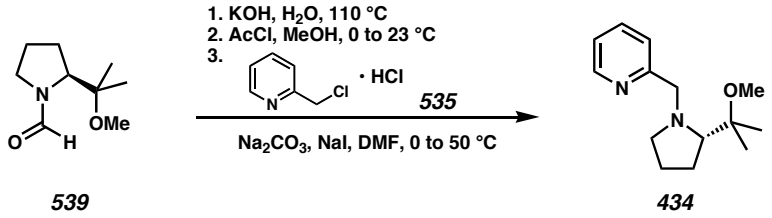
Pyrrolidine 539. *N*-formyl pyrrolidine **539** was synthesized according to the procedure of Nakayama and Thompson.[53] To a solution of *N*-carbobenzyloxy-L-proline methyl ester (500 μl, 2.23 mmol) in 3.34 mL THF at –20 °C was added MeMgBr (2.23 mL, 3.0 M in Et_2O, 6.69 mmol) dropwise over 5 min. The reaction was maintained at –20 °C for 30 min, then warmed to 0 °C and stirred for an additional 1 h. The mixture was then quenched with saturated NH_4Cl (30 mL) and extracted with Et_2O (4 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/EtOAc eluent) afforded the tertiary alcohol (549 mg, 93% yield, R_F = 0.26 in 2:1 hexanes/EtOAc), which was taken on to the subsequent reaction.

A mixture of the tertiary alcohol (549 mg, 2.08 mmol) and Pd/C (20.8 mg, 10%) in 20.8 mL MeOH was stirred under 1 atm H_2 at 23 °C. After 1 h, the suspension was filtered through a plug of celite (1.5 x 5 cm, Et_2O eluent), and the filtrate was

concentrated in vacuo. The crude pyrrolidine (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried to the subsequent reaction without purification.

To a solution of the crude pyrrolidine (assume 2.08 mmol) in 1.30 mL CH_2Cl_2 at 23 °C was added ethyl formate (1.03 mL, 12.7 mmol). The reaction was maintained at 23 °C for 45 h. The mixture was then concentrated to an oil, and the residue was dissolved in 30 mL EtOAc and passed through a plug of SiO_2 (1 x 5 cm, EtOAc eluent). The filtrate was concentrated in vacuo, and the product formamide (248 mg, 76% yield over 2 steps) was carried on to the next reaction without further purification.

Sodium dimsylate was generated by adding NaH (350 mg, 60% dispersion in mineral oil, 8.75 mmol) to 3.40 mL DMSO and heating the mixture at 70 °C for 1 h. To a solution of the formamide (248 mg, 1.58 mmol) and triphenylmethane (5 mg) in 1.58 mL DMSO at 23 °C was added the sodium dimsylate solution dropwise. Once the red color persisted, dimethyl sulfate (165 μl, 1.74 mmol) was added. The mixture was stirred at 23 °C for 90 min, and then it was quenched with H_2O (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 EtOAc/hexanes → 100% EtOAc eluent) to afford the tertiary methyl ether[53] (225 mg, 99% yield, R_F = 0.35 in 100% EtOAc), which was taken to the next reaction.

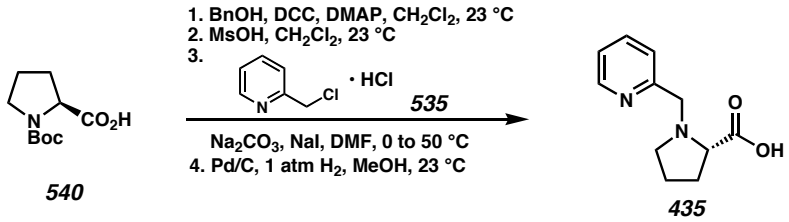


Pyrrolidine 434. Deformylation of **539** was performed according to the procedure of Nakayama and Thompson.[53] A solution of formamide **539** (75.4 mg, 0.440 mmol) in aqueous KOH (10%, 942 μl) was heated at 110 °C. After 1.5 h, the reaction was cooled to room temperature and extracted with CH_2Cl_2 (5 x 20 mL). The combined organic phases were dried over K_2CO_3 and concentrated to an oil. The pyrrolidine (R_F = 0.00 in 100% EtOAc) was carried to the subsequent reaction.

Anhydrous HCl was generated by addition of 156 μl AcCl (2.20 mmol) dropwise slowly to 2.20 mL MeOH at 0 °C. After 3 min, a solution of the pyrrolidine (assume 0.440 mmol) in 2.20 mL MeOH was added. The resulting mixture was stirred for 5 min, then allowed to warm to 23 °C. After 30 min, the solution was concentrated in vacuo, concentrated from PhH (3 x 15 mL), and the crude hydrochloride salt was carried directly to the subsequent reaction.

The pyrrolidine alkylation was performed according to the procedure of Chelucci et al.[49] To a solution of the pyrrolidine hydrochloride salt (assume 0.440 mmol), 2-picolyl chloride hydrochloride (72.2 mg, 0.440 mmol), and NaI (3.3 mg, 0.0220 mmol) in 1.04 mL DMF at 0 °C was added Na_2CO_3 (144 mg, 1.36 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 5 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (1:1 hexanes/EtOAc w/ 1% Et_3N

eluent) afforded alkylated pyrrolidine **434** (69.2 mg, 67% yield over 3 steps, R_F = 0.30 in 9:1 CH_2Cl_2/MeOH) as a yellow oil. **Pyrrolidine 434**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (br d, *J* = 4.5 Hz, 1H), 7.65 (br t, *J* = 6.9 Hz, 1H), 7.55 (br d, *J* = 7.5 Hz, 1H), 7.12 (br t, *J* = 5.7 Hz, 1H), 4.46 (d, *J* = 14.7 Hz, 1H), 3.63 (br d, *J* = 14.7 Hz, 1H), 3.22 (s, 3H), 2.99-2.84 (br m, 2H), 2.38-2.28 (br m, 1H), 1.92-1.82 (br m, 3H), 1.22 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 136.5, 122.7, 121.7, 70.3, 63.9, 55.8, 49.3, 28.0, 24.4, 22.0, 21.4; IR (film) 2970, 1146 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{23}N_2O]^+$: 235.1810, found 235.1821; $[\alpha]^{23}_D$ –77.04° (*c* 0.25, $CHCl_3$).

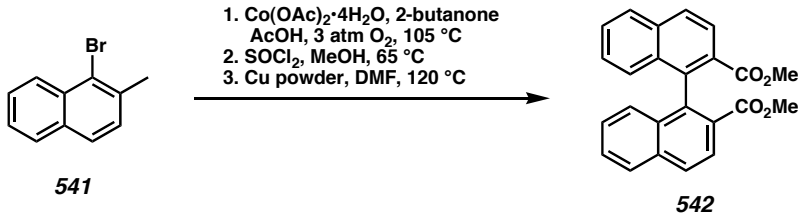


Carboxylic acid 435. Esterification was performed according to the procedure of Gardner and Gellman.[54] To a solution of *N*-*t*-Boc-L-proline (200 mg, 0.929 mmol) in 4.65 mL CH_2Cl_2 at 23 °C (maintained with an external water bath) was added DCC (229 mg, 1.11 mmol), DMAP (13.6 mg, 0.111 mmol), and BnOH (207 μl, 2.00 mmol), sequentially. The resulting heterogeneous mixture was stirred at 23 °C for 2 h. The mixture was suction-filtered through a pad of celite (5 x 5 cm, CH_2Cl_2 eluent), and the filtrate was concentrated to an oil. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford the benzyl ester[54] (R_F = 0.48 in 2:1 hexanes/EtOAc) contaminated with benzyl alcohol. The mixture was carried on without further purification.

To a solution of the benzyl ester mixture (assume 0.929 mmol) in 2.32 mL CH_2Cl_2 at 23 °C was added methanesulfonic acid (229 μl, 3.53 mmol) dropwise over 1 min. The reaction mixture was maintained at 23 °C for 5 min, then cooled to 0 °C and quenched with saturated $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (2 x 40 mL), and the combined organic layers were dried over K_2CO_3 and concentrated to an oil. This residue was partitioned between 30 mL 0.5 N HCl and 30 mL Et_2O to separate the benzyl alcohol from the previous step. The organic phase was extracted with 0.5 N HCl (2 x 20 mL), and the combined aqueous phases were basified with solid Na_2CO_3. The mixture was then extracted with CH_2Cl_2 (3 x 40 mL), and the combined organic phases were dried over K_2CO_3 and concentrated in vacuo. The benzyl ester (121 mg, 63% yield over 2 steps, R_F = 0.00 in 2:1 hexanes/EtOAc) was sufficiently pure to be taken to the next reaction.

The pyrrolidine was alkylated according to the procedure of Chelucci et al.[49] To a solution of the pyrrolidine benzyl ester (78.2 mg, 0.381 mmol), 2-picolyl chloride hydrochloride (56.8 mg, 0.346 mmol), and NaI (2.6 mg, 0.0173 mmol) in 816 μl DMF at 0 °C was added Na_2CO_3 (80.7 mg, 0.761 mmol). The reaction was allowed to warm to 23 °C after 5 min, then heated to 50 °C. After 4 h, the mixture was cooled to room temperature, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (1:1 → 3:1 EtOAc/hexanes eluent) afforded the alkylated pyrrolidine (97.0 mg, 95% yield, R_F = 0.44 in 9:1 CH_2Cl_2/MeOH) as a pale yellow oil.

A mixture of the benzyl ester (34.0 mg, 0.115 mmol) and Pd/C (3.4 mg, 10%) in 4.60 mL MeOH was stirred under 1 atm H_2 at 23 °C. After 45 min, the suspension was filtered through a plug of celite (1.5 x 5 cm, MeOH eluent), and the filtrate was concentrated in vacuo. The crude carboxylic acid (23.7 mg, 100% yield, R_F = 0.00 in 9:1 CH_2Cl_2/MeOH) was sufficiently pure to be used in the next reaction. **Carboxylic acid 435**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.64 (d, *J* = 5.1 Hz, 1H), 7.87 (app.t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 5.1, 7.8 Hz, 1H), 4.61 (d, *J* = 14.1 Hz, 1H), 4.40 (d, *J* = 14.1 Hz, 1H), 4.07 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.72 (ddd, *J* = 4.5, 7.2, 11.4 Hz, 1H), 3.22 (ddd, *J* = 7.2, 8.7, 11.4 Hz, 1H), 2.52-2.40 (m, 1H), 2.25-1.94 (comp m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 154.4, 149.6, 137.5, 124.0, 123.6, 68.0, 59.4, 54.6, 29.8, 24.3; IR (film) 3400, 1631 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{11}H_{15}N_2O_2]^+$: 207.1134, found 207.1142; $[\alpha]^{23}_D$ –46.22° (*c* 1.0, MeOH).



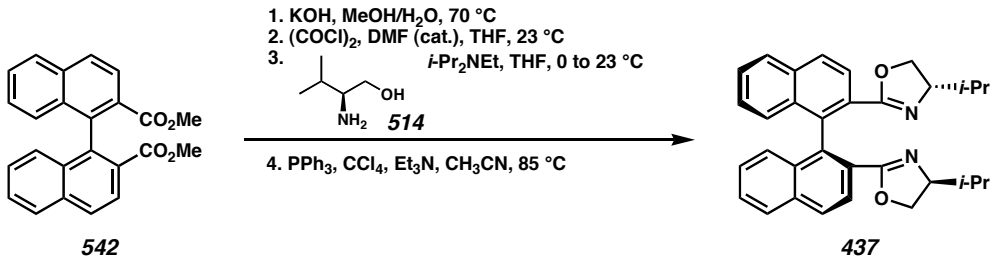
541 ***542***

Binaphthyl 542. Binaphthyl **542** was synthesized according to the procedure of Seki et al.[55] A solution of 1-bromo-2-methylnaphthalene (1.00 mL, 6.42 mmol), 2-butanone (173 μl, 1.93 mmol), and $Co(OAc)_2$•$4H_2O$ (319 mg, 1.28 mmol) in 5.35 mL AcOH under 3 atm O_2 was heated to 105 °C. The mixture was stirred overnight (10 h), then cooled to room temperature and partitioned between 100 mL EtOAc and 50 mL 1 N HCl. The aqueous phase was extracted with EtOAc (75 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash

chromatography (7:1 CH_2Cl_2/MeOH eluent) to afford the carboxylic acid[55] (1.48 g, 92% yield, R_F = 0.07 in 4:1 hexanes/EtOAc) as a brown solid.

To a solution of the carboxylic acid (206 mg, 0.820 mmol) in 683 μl MeOH at 23 °C was added $SOCl_2$ (71.8 μl, 0.984 mmol) dropwise over 1 min. The reaction was heated to 65 °C and stirred 3 h. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between 50 mL EtOAc and 30 mL H_2O, and the organic phase was washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude methyl ester[56] (R_F = 0.42 in 4:1 hexanes/EtOAc) was taken directly to the subsequent reaction without purification.

A solution of the methyl ester (assume 0.820 mmol) and Cu powder (88.3 mg, 1.39 mmol) in 293 μl DMF was heated to 120 °C for 2 h. The mixture was then cooled to room temperature, diluted with 30 mL CH_2Cl_2, and filtered through a pad of celite (2 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was partitioned between H_2O (30 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (30 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (4:1 hexanes/EtOAc) to provide **542**[56] (127 mg, 90% yield over 2 steps, R_F = 0.25 in 4:1 hexanes/EtOAc).



542 *437*

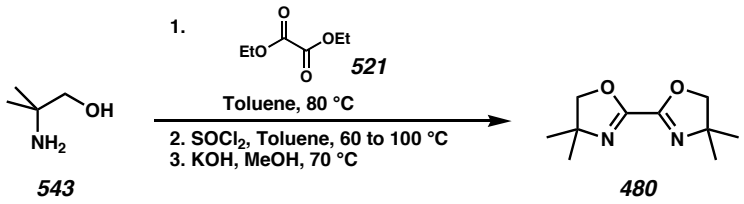
Bisoxazoline 437. The saponification of **542** was performed according to the procedure of Seki et al.[55] To a solution of the bis methyl ester (480 mg, 1.30 mmol) in 3.61 mL MeOH and 722 μl H_2O at 23 °C was added KOH (263 mg, 4.68 mmol). The reaction was heated to 70 °C and stirred for 2 h. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between H_2O (60 mL) and toluene (60 mL). The organic phase was extracted with 3 N NaOH (50 mL), and the combined aqueous phases were acidified with conc. HCl and extracted with EtOAc (3 x 75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The bis carboxylic acid[55] (411 mg, 92% yield, R_F = 0.00 in 1:1 hexanes/EtOAc) was carried on directly to the next reaction without purification.

Bisoxazoline **437** was synthesized according to a modified procedure of Uozumi et al.[57] To a solution of the bis carboxylic acid (97.4 mg, 0.285 mmol) in 1.43 mL THF at 23 °C was added oxalyl chloride (125 μl, 1.43 mmol), then DMF (~10 μl). The reaction was stirred at 23 °C for 90 min. The mixture was then concentrated in vacuo, and the residue was concentrated from PhH (2 x 15 mL). The bis acid chloride was taken on to the next reaction.

To a solution of L-valinol (94.2 μl, 0.855 mmol) and Et_3N (119 μl, 0.855 mmol) in 1.00 mL THF at 0 °C was added a solution of the bis acid chloride (assume 0.285

mmol) in 600 μl THF dropwise over 1 min. The mixture was allowed to warm to 23 °C and stirred. After 1 h, the mixture was concentrated to an oil, which was dissolved in 50 mL EtOAc. The solution was washed sequentially with 0.5 N HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude diamide (R_F = 0.40 in 7:1 CH_2Cl_2/MeOH) as a mix of diastereomers was taken directly to the subsequent reaction.

To a solution of PPh_3 (194 mg, 0.741 mmol), CCl_4 (179 μl, 1.85 mmol), and Et_3N (139 μl, 0.998 mmol) in1.85 mL CH_3CN at 23 °C was added a solution of the diamide (assume 0.285 mmol) in 1.00 mL CH_3CN. The resulting mixture was heated to 85 °C and stirred for 3 h. The mixture was then cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was dissolved in 50 mL EtOAc and washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (2 columns: 6:1 hexanes/EtOAc, then 9:1 → 3:1 CH_2Cl_2/EtOAc eluent) to provide the diastereomerically and enantiomerically pure (*S,S*)-bisoxazoline (34.3 mg, 50% yield over 3 steps, R_F = 0.52 in 7:1 CH_2Cl_2/MeOH) as a pale yellow semisolid. Optical rotation matched the reported value.[57]



Bisoxazoline 480. Bisoxazoline **480** was synthesized according to a modified procedure of Butula and Karlovic.[58] To a solution of 2-amino-2-methyl-1-proapanol (702 μl, 7.36

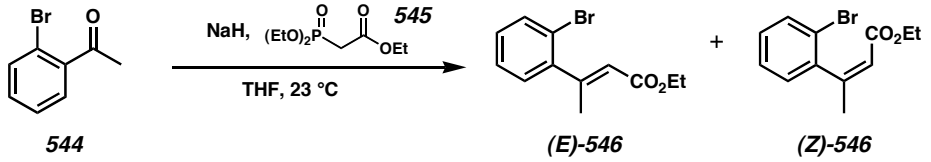
mmol) in 3.68 mL toluene at 23 °C was added diethyl oxalate (500 μl, 3.68 mmol). The mixture was heated to 110 °C and stirred 40 h. After cooling to room temperature, 50 mL hexanes was added, and the mixture was stirred 1 h. The white diamide that precipitated (802 mg, 94% yield) was collected by suction filtration and carried on to the subsequent reaction.

To a suspension of the diamide (3.14 g, 13.5 mmol) in 13.5 mL toluene at 60 °C was added $SOCl_2$ (6.14 mL). The resulting mixture was maintained at 60 °C for 30 min, then heated to 100 °C and stirred an additional 90 min. The solids gradually went into solution over the course of the reaction. The reaction mixture was then cooled to room temperature and partitioned between EtOAc (150 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated to a white solid, which was carried directly to the next reaction.

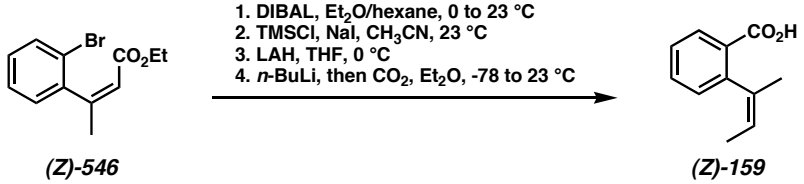
A suspension of the bis alkyl chloride (assume 13.5 mmol) in methanolic KOH (27.0 mL, 1.0 M, 27.0 mmol) was stirred at 70 °C. KCl began to precipitate almost immediately. The reaction mixture was stirred for 90 min, and then it was cooled to room temperature and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated in vacuo, and the residue was dissolved in 30 mL CH_2Cl_2 and filtered through a plug of celite (1 x 5 cm, CH_2Cl_2 eluent) to remove the excess KOH. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography (3:1 hexanes/acetone eluent) to provide the bisoxazoline (2.30 g, 87% over 2 steps, R_F = 0.32 in 2:1 hexanes/acetone) as a white solid. **Bisoxazoline 480**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (s, 4H), 1.35 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

153.5, 80.0, 68.7, 28.3; IR (film) 2967, 1613, 1103, 949 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{10}H_{16}N_2O_2]^+$: 196.1212, found 196.1216.

5.7.2.2 Synthesis of Carboxylic Acid Substrates



Esters (*E*)-546 and (*Z*)-546. To a suspension of NaH (1.35 g, 60% dispersion in mineral oil, 33.7 mmol) in 36.0 mL THF at 23 °C (kept at that temperature with an external water bath) was added triethyl phosphonoacetate (6.61 mL, 33.3 mmol) dropwise. After stirring for 30 min, the solution was cooled to 0 °C, and a solution of 2-bromoacetophenone (3.00 mL, 22.2 mmol) in 53.0 mL THF was added. The resulting mixture was maintained at 0 °C for 3 h, then allowed to warm to 23 °C and stirred 8 h. The reaction was then quenched at 0 °C with saturated $NaHCO_3$ (100 mL) and extracted with Et_2O (3 x 125 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (14:1 → 4:1 hexanes/Et_2O eluent) afforded the pure olefin isomers of the α,β-unsaturated ester[59] (*E* isomer: 3.55 g, 59% yield, R_F = 0.65 in 4:1 hexanes/EtOAc; *Z* isomer: 1.92 g, 32% yield, R_F = 0.58 in 4:1 hexanes/EtOAc) as colorless oils.



Carboxylic acid (*Z*)-159. To a solution of the (*Z*)-unsaturated ester (1.92 g, 7.13 mmol) in 16.1 mL Et_2O at 0 °C was added DIBAL (14.2 mL, 1.0 M in hexane, 14.2 mmol)

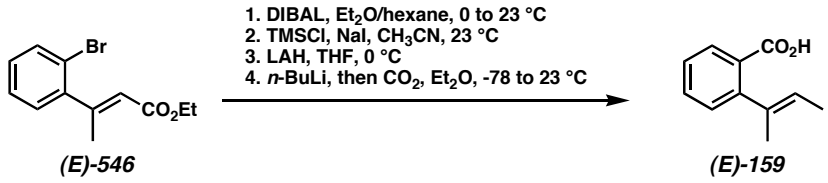
dropwise over 10 min. The reaction was allowed to warm to 23 °C and stirred for 90 min. The mixture was then quenched at 0 °C with brine (20 mL) and diluted with 3 N HCl and aqueous sodium potassium tartrate (10%) until the aqueous phase was clear. The solution was then extracted with Et_2O (3 x 100 mL), and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the allylic alcohol (1.59 g, 98% yield, R_F = 0.18 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the allylic alcohol (1.59 g, 7.00 mmol) in 14.0 mL CH_3CN at 23 °C in the dark was added NaI (2.62 g, 17.5 mmol), then TMSCl (1.78 mL, 14.0 mmol). The reaction was stirred at 23 °C for 30 min, and then it was diluted with 150 mL EtOAc and washed sequentially with H_2O (50 mL), 10% aq. sodium thiosulfate (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The allylic iodide (R_F = 0.79 in 4:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

To a suspension of LAH (1.33 g, 35.0 mmol) in 40 mL THF at 0 °C was added a solution of the crude allylic iodide (assume 7.00 mmol) in 20 mL THF dropwise over 5 min. The reaction was stirred at 0 °C for 30 min. The mixture was then quenched by sequential addition of 1.33 mL H_2O, 1.33 mL 15% aq. NaOH, and 4.00 mL H_2O. The slurry was allowed to warm to room temperature and was stirred vigorously. Once a white precipitate had fully formed (~30 min), the suspension was suction-filtered through a pad of celite (5 x 3 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/CH_2Cl_2 eluent) to provide

the bromoarene (986 mg, 67% yield over 2 steps, R_F = 0.80 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the bromoarene (986 mg, 4.67 mmol) in 46.7 mL THF at –78 °C was added *n*-BuLi (2.14 mL, 2.4 M in hexane, 5.14 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (40 mL) and extracted with Et_2O (3 x 75 mL). The organic layers were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (6:1 hexanes/acetone eluent) afforded carboxylic acid **(*Z*)-159**[3] (671 mg, 82% yield, R_F = 0.23 in 4:1 hexanes/EtOAc) as a white solid.



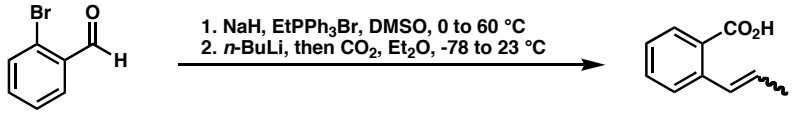
Carboxylic acid (*E*)-159. To a solution of the (*E*)-unsaturated ester (2.35 g, 8.73 mmol) in 19.8 mL Et_2O at 0 °C was added DIBAL (17.5 mL, 1.0 M in hexane, 17.5 mmol) dropwise over 10 min. The reaction was allowed to warm to 23 °C and stirred for 90 min. The mixture was then quenched at 0 °C with brine (20 mL) and diluted with 3 N HCl and aqueous sodium potassium tartrate (10%) until the aqueous phase was clear. The solution was then extracted with Et_2O (3 x 100 mL), and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the allylic alcohol (1.98 g, 99% yield, R_F = 0.17 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the allylic alcohol (2.00 g, 8.81 mmol) in 17.6 mL CH_3CN at 23 °C in the dark was added NaI (3.30 g, 22.0 mmol), then TMSCl (2.23 mL, 17.6 mmol). The reaction was stirred at 23 °C for 30 min, and then it was diluted with 150 mL EtOAc and washed sequentially with H_2O (50 mL), 10% aq. sodium thiosulfate (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The allylic iodide (R_F = 0.76 in 4:1 hexanes/EtOAc) was taken on directly to the subsequent reaction.

To a suspension of LAH (1.67 g, 44.1 mmol) in 50 mL THF at 0 °C was added a solution of the crude allylic iodide (assume 8.81 mmol) in 24 mL THF dropwise over 5 min. The reaction was stirred at 0 °C for 30 min. The mixture was then quenched by sequential addition of 1.67 mL H_2O, 1.67 mL 15% aq. NaOH, and 5.00 mL H_2O. The slurry was allowed to warm to room temperature and was stirred vigorously. Once a white precipitate had fully formed (~30 min), the suspension was suction-filtered through a pad of celite (5 x 3 cm, Et_2O eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/CH_2Cl_2 eluent) to provide the bromoarene (1.39 g, 75% yield over 2 steps, R_F = 0.80 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the bromoarene (1.31 g, 6.21 mmol) in 18.8 mL THF at –78 °C was added *n*-BuLi (3.10 mL, 2.4 M in hexane, 7.45 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (50 mL) and extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in

vacuo. Purification of the residue by flash chromatography (4:1 hexanes/acetone eluent) afforded carboxylic acid **(*E*)-159**[3] (577 mg, 53% yield, R_F = 0.23 in 4:1 hexanes/EtOAc) as a white solid.

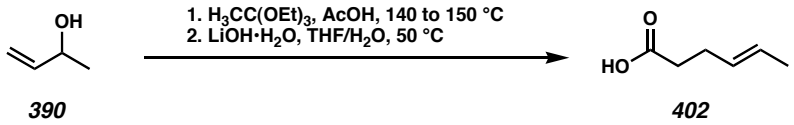


547 ***399***

Carboxylic acid 399. Wittig olefination was performed according to the procedure of Bleckmann and Hanack.[60] Sodium dimsylate was generated by adding NaH (75.2 mg, 60% dispersion in mineral oil, 1.88 mmol) to 940 μl DMSO and heating the mixture at 70 °C for 1 h. The mixture was cooled to 0 °C, and a solution of $EtPPh_3Br$ (668 mg, 1.80 mmol) in 1.00 mL DMSO was added dropwise. The red mixture was allowed to warm to 23 °C and stirred 20 min. A solution of 2-bromobenzaldehyde (200 μl, 1.71 mmol) in 950 μl DMSO was added, and the reaction was heated to 60 °C. After 2.5 h, the mixture was cooled to room temperature, poured into ice water (50 mL), and extracted with hexanes (3 x 50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (100% hexanes eluent) to afford the olefin[61] (153 mg, 45% yield, R_F = 0.61 in 100% hexanes) as a mix of geometrical isomers.

To a solution of the bromoarene (153 mg, 0.776 mmol) in 7.76 mL THF at –78 °C was added *n*-BuLi (342 μl, 2.5 M in hexane, 0.854 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (30 mL) and extracted with Et_2O (3 x 50 mL). The organic layers

were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 → 3:1 hexanes/acetone eluent) afforded carboxylic acid **399**[62] (101 mg, 80% yield, R_F = 0.10 in 4:1 hexanes/EtOAc) as a white solid.

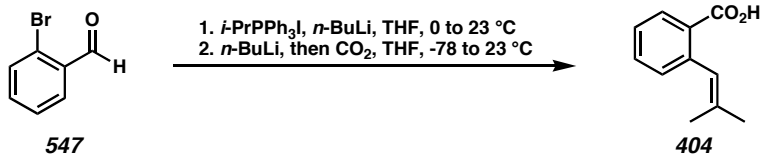


390 *402*

Carboxylic acid 402. Johnson orthoester Claisen rearrangement was performed according to the procedure of Noack and Göttlich.[63] A solution of 3-buten-2-ol (2.00 mL, 23.1 mmol), triethyl orthoacetate (6.36 mL, 34.7 mmol), and AcOH (52.3 μl, 0.924 mmol) was heated to 140 °C with distillative removal of EtOH. Once distillation ceased, the reaction mixture was heated to 150 °C and stirred for 3 h. The solution was then cooled to room temperature and poured into a mixture of 200 mL 1 M $KHSO_4$ and 200 mL Et_2O. The mixture was stirred vigorously for 8 h, and then the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and concentrated in vacuo. The crude oil was purified by flash chromatography (29:1 hexanes/Et_2O eluent) to afford the ester (1.72 g, 52% yield, R_F = 0.32 in 19:1 hexanes/Et_2O) as a colorless oil.

To a solution of the ester (364 mg, 2.56 mmol) in 6.4 mL THF and 6.4 mL H_2O at 23 °C was added $LiOH•H_2O$ (537 mg, 12.8 mmol). The reaction was heated to 50 °C and stirred vigorously. After 4 h, the mixture was cooled to room temperature, and the THF was removed by rotary evaporation. The aqueous residue was acidified at 0 °C with 2 N HCl and extracted with Et_2O (3 x 60 mL). The organic phases were combined, washed

with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/acetone eluent) to provide carboxylic acid **402**[64] (232 mg, 79% yield, R_F = 0.23 in 4:1 hexanes/EtOAc) as a colorless oil.



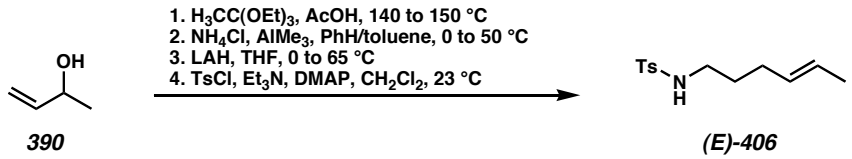
547 *404*

Carboxylic acid 404. To a suspension of *i*-$PrPPh_3I$ (389 mg, 0.900 mmol) in 1.29 mL THF at 0 °C was added *n*-BuLi (360 μl, 2.5 M in hexane, 0.900 mmol) dropwise. The dark red mixture was allowed to warm to 23 °C and stirred for 15 min. The mixture was then cooled to 0 °C, and a solution of 2-bromobenzaldehyde (100 μl, 0.857 mmol) in 429 μl THF was added. The resulting orange mixture was allowed to warm to 23 °C and stirred overnight (8 h). The mixture was then poured into 100 mL pentane with ~3 g celite, and the suspension was stirred 15 min. It was then filtered (pentane eluent), and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) to afford the olefin[65] (138 mg, 76% yield, R_F = 0.78 in 9:1 hexanes/EtOAc), which was carried on to the next reaction.

To a solution of the bromoarene (138 mg, 0.654 mmol) in 6.54 mL THF at –78 °C was added *n*-BuLi (262 μl, 2.5 M in hexane, 0.654 mmol) dropwise. The reaction was stirred at –78 °C for 1 h, and then CO_2 was bubbled into the solution for 30 min. The mixture was then allowed to warm to 23 °C over 1 h. The reaction was then quenched at 0 °C with 1 N HCl (30 mL) and extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (4:1 hexanes/acetone eluent)

afforded carboxylic acid **404**[66] (94.1 mg, 82% yield, R_F = 0.17 in 4:1 hexanes/EtOAc) as a white solid.

5.7.2.3 Synthesis of Amine Substrates



390 *(E)-406*

Tosylamide (*E*)-406. Johnson orthoester Claisen rearrangement was performed according to the procedure of Noack and Göttlich.[63] A solution of 3-buten-2-ol (2.00 mL, 23.1 mmol), triethyl orthoacetate (6.36 mL, 34.7 mmol), and AcOH (52.3 μl, 0.924 mmol) was heated to 140 °C with distillative removal of EtOH. Once distillation ceased, the reaction mixture was heated to 150 °C and stirred for 3 h. The solution was then cooled to room temperature and poured into a mixture of 200 mL 1 M $KHSO_4$ and 200 mL Et_2O. The mixture was stirred vigorously for 8 h, and then the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and concentrated in vacuo. The crude oil was purified by flash chromatography (29:1 hexanes/Et_2O eluent) to afford the ester (1.72 g, 52% yield, R_F = 0.32 in 19:1 hexanes/Et_2O) as a colorless oil.

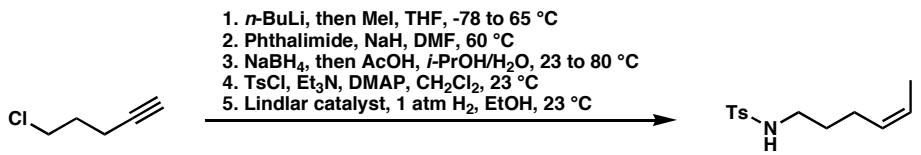
Conversion of the ester to a primary amide was performed according to the procedure of Levin et al.[67] To a suspension of NH_4Cl (1.67 g, 31.2 mmol) in 31.2 mL PhH at 0 °C was added $AlMe_3$ (15.6 mL, 2.0 M in toluene, 31.2 mmol) dropwise over 10 min. The mixture was allowed to warm to 23 °C and stirred for 90 min. Gas evolution was observed during this time. This solution was then added via cannula to a solution of the ester (1.48 g, 10.4 mmol) in 104 mL PhH at 23 °C. The resulting mixture was heated to 50 °C and stirred. After 16 h, the mixture was cooled to room temperature and quenched with 0.5 N HCl (100 mL). The mixture was extracted with EtOAc (3 x 150

mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The amide[64] (R_F = 0.05 in 4:1 hexanes/EtOAc) was carried on without purification.

To a solution of the amide (assume 10.4 mmol) in 52.0 mL THF at 0 °C was added LAH (1.18 g, 31.2 mmol) portionwise slowly. The reaction was heated to 70 °C and stirred for 7 h. The mixture was then cooled to 0 °C and quenched by sequential addition of 1.18 mL H_2O, 1.18 mL 15% NaOH, and 3.54 mL H_2O. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The product amine[64] (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried on to the next reaction without purification.

To a solution of the amine (assume 10.4 mmol) in 52.0 mL CH_2Cl_2 at 23 °C was added Et_3N (2.90 mL, 20.8 mmol), TsCl (2.38 g, 12.5 mmol), and DMAP (63.5 mg, 0.520 mmol), sequentially. The reaction was stirred at 23 °C for 8 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/Et_2O eluent) to afford tosylamide **(*E*)-406** (1.16 g, 44% yield over 3 steps, R_F = 0.23 in 4:1 hexanes/EtOAc) as an orange oil. **Tosylamide (*E*)-406**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.43-5.22 (comp m, 2H), 4.56 (br s, 1H), 2.92 (app.q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.95 (app.q, *J* = 7.5 Hz, 2H), 1.60 (d, *J* = 7.2 Hz, 3H), 1.53 (app.quint, J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.2,

129.9, 129.9, 127.3, 126.4, 42.8, 29.7, 29.4, 21.7, 18.0; IR (film) 3284, 1326, 1160 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{13}H_{20}O_2NS]^+$: 254.1215, found 254.1202.



548 ***(Z)-406***

Tosylamide (*Z*)-406. The first three steps of this synthetic sequence were performed according to a modified procedure of Li and Marks.[68] To a solution of 5-chloro-1-pentyne (2.00 mL, 18.9 mmol) in 18.9 mL THF at –78 °C was added *n*-BuLi (7.92 mL, 2.5 M in hexane, 19.8 mmol) dropwise over 10 min. The reaction was stirred for 1 h, at which point MeI (1.23 mL, 19.8 mmol) was added dropwise. The reaction was allowed to warm to 23 °C, then heated to 65 °C. After 1 h at 65 °C, the mixture was cooled to 0 °C, quenched with saturated NH_4Cl (75 mL), and extracted with Et_2O (3 x 75 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude chloride was carried to the next reaction without purification.

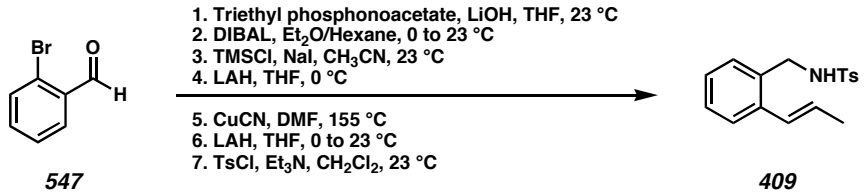
To a solution of phthalimide (1.39 g, 9.45 mmol) in 12.3 mL DMF at 0 °C was added NaH (378 mg, 60% dispersion in mineral oil, 9.45 mmol). The mixture was stirred at 0 °C for 10 min and at 23 °C for 1 h. The chloride (assume 18.9 mmol) was then added to the reaction mixture, and the reaction was heated to 60 °C and stirred overnight (10 h). The mixture was then cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic phases were washed with brine (75 mL), dried over

Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) provided the alkylated phthalimide (1.63 g, 76% yield, R_F = 0.63 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the phthalimide (1.63 g, 7.17 mmol) in 61.5 mL *i*-PrOH and 10.2 mL H_2O at 23 °C was added $NaBH_4$ (1.36 g, 35.9 mmol). The resulting mixture was stirred at 23 °C for 24 h. AcOH (7.50 mL, 131 mmol) was then added slowly, and the mixture was heated to 80 °C. After 3.5 h, the mixture was cooled to 0 °C and quenched with 1 N HCl (25 mL). After stirring at room temperature for 30 min, the *i*-PrOH was removed by rotary evaporation, and the residue was partitioned between Et_2O (100 mL) and 1 N HCl (50 mL). The organic layer was extracted with 1 N HCl (2 x 25 mL). The combined aqueous phases were basified at 0 °C with KOH pellets (pH > 13), and then extracted with CH_2Cl_2 (3 x 75 mL). The organic phases were combined, dried over K_2CO_3, and concentrated in vacuo. The free amine[68] (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried on to the next reaction without purification.

To a solution of the amine (assume 7.17 mmol) in 36.0 mL CH_2Cl_2 at 23 °C was added Et_3N (1.99 mL, 14.3 mmol), TsCl (1.64 g, 8.60 mmol), and DMAP (43.9 mg, 0.359 mmol), sequentially. The reaction was stirred at 23 °C for 10 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 75 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash chromatography (4:1 → 2:1 hexanes/EtOAc eluent) to afford the tosylamide (1.24 g, 69% yield over 2 steps, R_F = 0.42 in 2:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alkyne (863 mg, 3.43 mmol) in 17.2 EtOH at 23 °C was added Lindlar catalyst (34.3 mg, 5% $Pd/CaCO_3$ with lead poison). The mixture was put under 1 atm H_2 and stirred vigorously. After 75 min, the mixture was filtered through a plug of celite (1 x 5 cm, EtOAc eluent), and the filtrate was concentrated to an oil. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) afforded *cis*-tosylamide **(*Z*)-406** (834 mg, 96% yield, R_F = 0.25 in 4:1 hexanes/EtOAc) as a colorless oil. **Tosylamide (*Z*)-406**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 5.50-5.35 (m, 1H), 5.33-5.21 (m, 1H), 4.60 (br s, 1H), 2.94 (app.q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.02 (app.q, *J* = 7.5 Hz, 2H), 1.56-1.52 (m, 3H), 1.52 (app.quintet, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.2, 129.9, 129.1, 127.3, 125.4, 43.1, 29.5, 24.1, 21.7, 12.9; IR (film) 3283, 1325, 1160 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{13}H_{20}O_2NS]^+$: 254.1215, found 254.1217.



547 ***409***

Tosylamide 409. Phosphonoacetate addition was performed according to the procedure of Dyker and Grundt.[59] To a solution of 2-bromobenzaldehyde (100 μl, 0.857 mmol) and triethyl phosphonoacetate (179 ml, 0.900 mmol) in 1.07 mL THF at 23 °C was added LiOH (22.6 mg, 0.943 mmol). The reaction mixture was stirred for 1 h, at which point it was partitioned between 50 mL Et_2O and 30 mL saturated $NaHCO_3$. The aqueous phase was extracted with Et_2O (30 mL), and the organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an oil. The residue was purified

by flash chromatography (19:1 hexanes/EtOAc eluent) to provide the *trans*-(α,β)-unsaturated ester[59] (180 mg, 82% yield, R_F = 0.57 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the ester (1.16 g, 4.55 mmol) in 10.3 mL Et_2O at 0 °C was added DIBAL (9.09 mL, 1.0 M in hexane, 9.09 mmol) dropwise over 5 min. The reaction was allowed to warm to 23 °C and stirred. After 90 min, the mixture was cooled to 0 °C, diluted with Et_2O (100 mL), and quenched with 20 mL brine. Aqueous sodium potassium tartrate (10%) and 3 M HCl were added until the layers were clear, and the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The oil was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the allylic alcohol[69] (774 mg, 80% yield, R_F = 0.11 in 4:1 hexanes/EtOAc) as a colorless oil, which was carried to the next reaction.

To a solution of the alcohol (744 mg, 3.63 mmol) in 7.26 mL CH_3CN at 23 °C in the dark was added NaI (925 mg, 6.17 mmol), then TMSCl (783 μl, 6.17 mmol) dropwise. The reaction mixture was stirred for 40 min, then quenched with 40 mL H_2O. The mixture was extracted with EtOAc (100 mL), and the organic phase was washed with aqueous sodium thiosulfate (10%, 40 mL) and then brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting iodide (R_F = 0.67 in 4:1 hexanes/EtOAc) was carried directly to the next reaction without further purification.

To a suspension of LAH (689 mg, 18.2 mmol) in 18.2 mL THF at 0 °C was added a solution of the iodide (assume 3.63 mmol) in 12.1 mL THF dropwise. The resulting mixture was stirred at 0 °C. After 30 min, the reaction was quenched by adding 690 μl

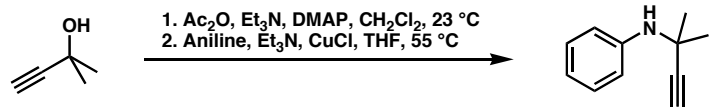
H_2O, 690 μl 15% aqueous NaOH, and 2.07 mL H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (hexanes eluent) provided the (*E*)-alkene[70] (493 mg, 69% yield over 2 steps, R_F = 0.72 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of the alkene (509 mg, 2.58 mmol) in 5.16 mL DMF at 23 °C was added CuCN (347 mg, 3.87 mmol). The heterogeneous mixture was heated to 155 °C and stirred. After 9 h, the mixture was cooled to room temperature and quenched with 720 μl Et_2NH and 30 mL H_2O. The mixture was extracted with Et_2O (5 x 30 mL), and the organic phases were combined, washed with aqueous NaCN (10%, 30 mL) and then brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/Et_2O eluent) to afford the nitrile (316 mg, 86% yield, R_F = 0.41 in 9:1 hexanes/EtOAc) as a colorless oil.

To a suspension of LAH (151 mg, 3.98 mmol) in 11.0 mL THF at 0 °C was added a solution of the nitrile (316 mg, 2.21 mmol) in 7.40 mL THF over 2 min. The resulting mixture was stirred at 0 °C for 15 min, then allowed to warm to 23 °C. After 1 h at 23 °C, the reaction was quenched by adding 151 μl H_2O, 151 μl 15% aqueous NaOH, and 453 mL H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The free amine (R_F = 0.00 in 4:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

To a solution of the amine (assume 2.21 mmol) in 11.1 CH_2Cl_2 at 23 °C was added Et_3N (616 μl, 4.42 mmol), then TsCl (505 mg, 2.65 mmol). The reaction was

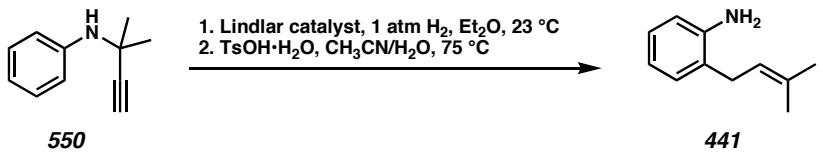
allowed to stir for 11 h. The mixture was quenched with saturated NH_4Cl/H_2O (1:1, 30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided tosylamide **409** (438 mg, 66% yield over 2 steps, R_F = 0.58 in 2:1 hexanes/EtOAc) as a colorless oil. **Tosylamide 409**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.37-7.29 (comp m, 3H), 7.24-7.19 (m, 1H), 7.14-7.07 (comp m, 2H), 6.37 (d, *J* = 13.8 Hz, 1H), 6.08 (dq, *J* = 6.6, 15.6 Hz, 1H), 4.51 (br s, 1H), 4.13 (d, *J* = 6.0 Hz, 2H), 2.44 (s, 3H), 1.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 137.5, 136.8, 132.2, 129.9, 129.7, 129.5, 128.7, 127.5, 127.4, 127.3, 126.5, 45.5, 21.7, 18.9; IR (film) 1328, 1160 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{19}NO_2S]^+$: 301.1143, found 301.1136.



549 *550*

Aniline 550. Aniline **550** was synthesized according to the reported procedure.[71] To a solution of 2-methyl-3-butyn-2-ol (3.00 mL, 31.0 mmol) in 31.0 mL CH_2Cl_2 at 23 °C was added Et_3N (4.67 mL, 33.5 mmol), Ac_2O (3.37 mL, 35.7 mmol), and DMAP (174 mg, 1.55 mmol), sequentially. The reaction was stirred at 23 °C overnight (8 h). The reaction was then poured over saturated NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic phases were combined, washed with 1 N HCl (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.51 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 31.0 mmol) in THF (40.3 mL) at 23 °C under nitrogen was added Et_3N (3.65 mL, 26.2 mmol), aniline (2.17 mL, 23.8 mmol), and CuCl (236 mg, 2.38 mmol), sequentially. The reaction was heated to 55 °C and stirred for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 100 mL EtOAc and 75 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (50 mL), then brine (50 mL). The combined aqueous phases were extracted with EtOAc (75 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (15:1 hexanes/EtOAc eluent) to provide aniline **550** (3.41 g, 90% yield, R_F = 0.55 in 4:1 hexanes/EtOAc) as a pale yellow oil, which was carried on.

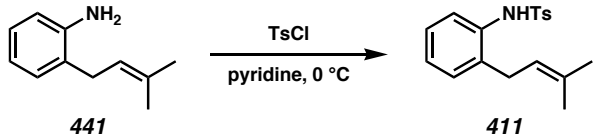


550 ***441***

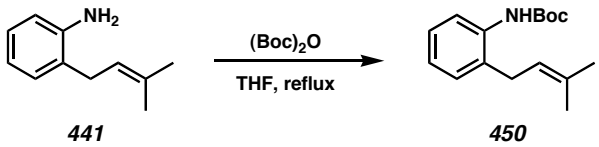
Aniline 441. Free aniline **441** was synthesized according to the procedure of Cooper et al.[72] Aniline **550** (1.02 g, 6.41 mmol) was dissolved in Et_2O (32.1 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 64.1 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 30 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.63 in 4:1 hexanes/EtOAc) was carried on directly to the subsequent reaction.

To a solution of alkene (assume 6.41 mmol) in CH_3CN/H_2O (64.1 mL, 9:1) was added $TsOH•H_2O$ (122 mg, 0.641 mmol). The solution was heated to 75 °C and stirred. After 12 h, the mixture was cooled to room temperature, and the CH_3CN was removed by

rotary evaporation. The aqueous residue was extracted with Et_2O (125 mL), and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (14:1 hexanes/EtOAc eluent) afforded aniline **441**[72] (879 mg, 85% yield over 2 steps, R_F = 0.24 in 4:1 hexanes/Et_2O) as a colorless oil.

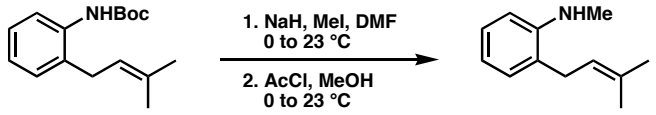


Tosylaniline 411. To a solution of aniline **441** (1.39 g, 8.62 mmol) in 12.3 mL pyridine at 0 °C was added TsCl (1.96 g, 10.3 mmol) portionwise over 2 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 100 mL EtOAc and quenched with 2 N HCl (40 mL). The phases were separated, and the organic phase was washed with 2 N HCl (40 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 → 4:1 hexanes/EtOAc eluent) to provide tosylaniline **411**[73] (1.69 g, 62% yield, R_F = 0.34 in 4:1 hexanes/EtOAc) as a white semisolid.



Carbamate 450. To a solution of aniline **411** (237 mg, 1.47 mmol) in 1.47 mL THF at 23 °C was added di-*tert*-butyl dicarbonate (354 mg, 1.62 mmol). The reaction mixture was heated to 70 °C. After 2 h, the mixture was cooled to room temperature and

concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and saturated NH_4Cl (30 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to an oil. The residue was purified by flash chromatography (25:1 hexanes/EtOAc eluent) to provide carbamate **450**[74] (374 mg, 97% yield, R_F = 0.41 in 9:1 hexanes/EtOAc) as a colorless oil.

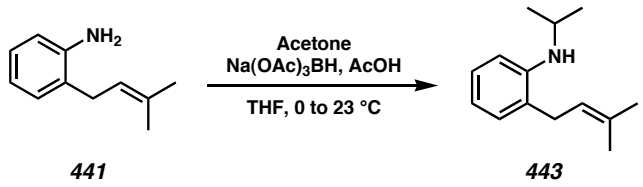


450 ***442***

Aniline 442. To a solution of carbamate **450** (347 mg, 1.33 mmol) in 6.65 mL DMF at 23 °C was added MeI (108 μl, 1.73 mmol). The solution was cooled to 0 °C, and NaH (69.2 mg, 60% dispersion in mineral oil, 1.73 mmol) was added. The reaction mixture was allowed to warm to 23 °C and stirred. After 2 h, the mixture was cooled to 0 °C and quenched with H_2O (25 mL). The mixture was extracted with EtOAc (2 x 50 mL), and the combined organic phases were washed with H_2O (2 x 25 mL), then brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (19:1 hexanes/EtOAc eluent) afforded the *N*-methyl carbamate (292 mg, 80% yield, R_F = 0.35 in 9:1 hexanes/EtOAc), which was carried on to the next reaction.

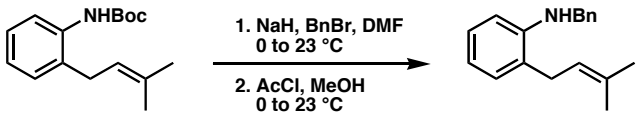
To a solution of the *N*-methyl carbamate (223 mg, 0.810 mmol) in 8.10 mL MeOH at 0 °C was added AcCl (576 μl, 8.10 mmol). The reaction was allowed to warm to 23 °C and stirred for 6 h. The mixture was then quenched with saturated $NaHCO_3$ (30 mL). The methanol was removed by rotary evaporation, and the aqueous residue was extracted with 100 mL EtOAc. The organic phase was washed with brine (40 mL), dried

over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (40:1 hexanes/EtOAc) to provide *N*-methyl aniline **442**[75] (128 mg, 90% yield, R_F = 0.48 in 9:1 hexanes/EtOAc) as a colorless oil.



441 ***443***

Aniline 443. To a solution of aniline **441** (114 mg, 0.707 mmol) in 3.54 mL THF at 0 °C was added acetone (115 μl, 1.56 mmol), AcOH (80.7 μl, 1.41 mmol), and $Na(OAc)_3BH$ (449 mg, 2.12 mmol), sequentially. The reaction mixture was allowed to warm to 23 °C and stirred. After 23 h, the mixture was cooled to 0 °C, quenched with 30 mL H_2O, and extracted with EtOAc (60 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (40:1 hexanes/EtOAc eluent) afforded *N*-isopropyl aniline **443** (128 mg, 89% yield, R_F = 0.53 in 9:1 hexanes/EtOAc) as a colorless oil. **Aniline 443**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (app.t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.65 (app.t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 5.24-5.18 (m, 1H), 3.64 (septet, *J* = 6.3 Hz, 1H), 3.62 (br s, 1H), 3.20 (d, *J* = 6.9 Hz, 2H), 1.78 (s, 3H), 1.76 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 133.4, 129.7, 127.5, 125.6, 122.5, 116.8, 111.1, 44.2, 31.5, 25.9, 23.3, 18.1; IR (film) 2967, 1604, 1510, 745 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{21}N]^+$: 203.1674, found 203.1680.

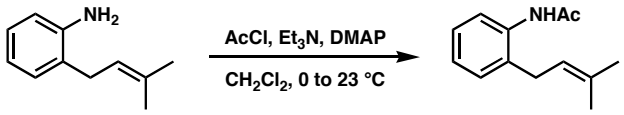


450 *444*

Aniline 444. To a solution of carbamate **450** (317 mg, 1.21 mmol) in 6.05 mL DMF at 23 °C was added BnBr (187 μl, 1.57 mmol). The solution was cooled to 0 °C, and NaH (62.8 mg, 60% dispersion in mineral oil, 1.57 mmol) was added. The reaction mixture was allowed to warm to 23 °C and was stirred. After 2 h, the mixture was cooled to 0 °C and quenched with H_2O (25 mL). The mixture was extracted with EtOAc (2 x 50 mL), and the combined organic phases were washed with H_2O (2 x 25 mL), then brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) afforded the *N*-benzyl carbamate (356 mg, 84% yield, R_F = 0.45 in 4:1 hexanes/Et_2O), which was carried on to the next reaction.

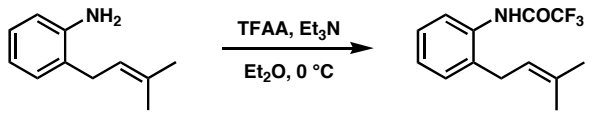
To a solution of the *N*-benzyl carbamate (356 mg, 1.01 mmol) in 10.1 mL MeOH at 0 °C was added AcCl (718 μl, 10.1 mmol). The reaction was allowed to warm to 23 °C and stirred for 8 h. The mixture was then quenched with saturated $NaHCO_3$ (40 mL). The methanol was removed by rotary evaporation, and the aqueous residue was extracted with 100 mL EtOAc. The organic phase was washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (30:1 hexanes/EtOAc eluent) to provide *N*-benzyl aniline **444** (218 mg, 86% yield, R_F = 0.56 in 9:1 hexanes/EtOAc) as a colorless oil. **Aniline 444**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 7.14 (app.t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.72 (app.t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.27-5.21 (m, 1H), 4.34 (s, 2H), 4.11 (br s, 1H), 3.25 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4,

139.6, 133.9, 129.5, 128.8, 127.9, 127.6, 127.5, 125.7, 122.1, 117.6, 110.7, 48.6, 31.4, 25.9, 17.9; IR (film) 1509, 747 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{18}H_{21}N]^+$: 251.1674, found 251.1675.



441 *445*

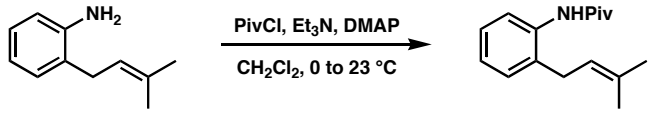
Acetanilide 445. To a solution of aniline **441** (88.2 mg, 0.547 mmol) in 2.24 mL CH_2Cl_2 at 0 °C was added Et_3N (229 μl, 1.64 mmol), DMAP (3.3 mg, 0.0274 mmol), and AcCl (46.6 μl, 0.656 mmol), sequentially. The reaction mixture was allowed to warm to 23 °C. After 30 min, the mixture was quenched with saturated NH_4Cl (25 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic phases were combined and washed with saturated $NaHCO_3$ (25 mL), then brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provide acetanilide **445**[76] (88.9 mg, 80% yield, R_F = 0.07 in 4:1 hexanes/EtOAc) as a white solid.



441 *447*

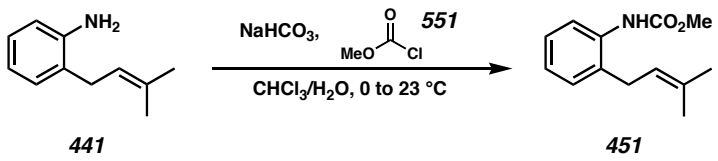
Trifluoroacetamide 447. To a solution of aniline **441** (111 mg, 0.688 mmol) in 3.44 mL Et_2O at 0 °C was added Et_3N (287 μl, 2.06 mmol), then trifluoroacetic anhydride (126 μl, 0.894 mmol). The reaction was stirred at 0 °C. After 1 h, the mixture was quenched with saturated NH_4Cl (25 mL) and extracted with Et_2O (2 x 35 mL). The organic phases were

combined, washed with brine (25 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (14:1 hexanes/Et_2O eluent) to provide trifluoroacetamide **447**[76] (152 mg, 86% yield, R_F = 0.48 in 4:1 hexanes/Et_2O) as a white solid.

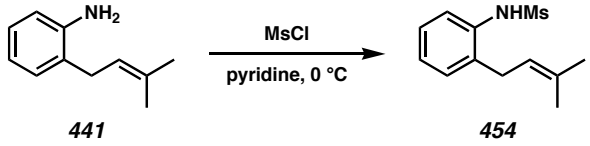


441 *449*

Amide 449. To a solution of aniline **441** (90.8 mg, 0.563 mmol) in 2.82 mL CH_2Cl_2 at 0 °C was added Et_3N (236 µl, 1.69 mmol), DMAP (3.4 mg, 0.0282 mmol), and trimethylacetyl chloride (83.3 µl, 0.676 mmol), sequentially. The mixture was allowed to warm to 23 °C and stirred for 1 h. The reaction was quenched with saturated NH_4Cl/H_2O (30 mL, 1:1) and extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined and washed with saturated $NaHCO_3$, then brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) provided amide **449** (119 mg, 86% yield, R_F = 0.10 in 1:1 hexanes/CH_2Cl_2) as a white solid. **Amide 449**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.51 (br s, 1H), 7.23 (app.t, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.05 (app.t, *J* = 7.5 Hz, 1H), 5.24-5.18 (m, 1H), 3.33 (d, *J* = 6.3 Hz, 2H), 1.77 (app.s, 6H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 136.5, 135.3, 131.6, 129.9, 127.3, 124.7, 122.8, 122.2, 39.8, 31.7, 27.7, 25.8, 18.6; IR (film) 1655, 1520, 1450 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{16}H_{23}NO]^+$: 245.1780, found 245.1777.

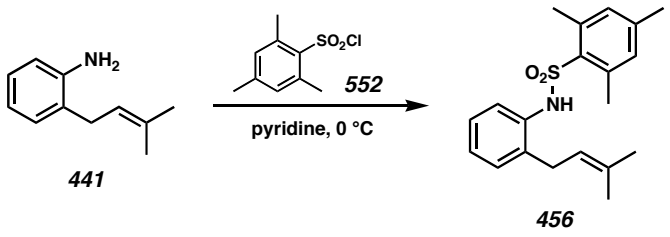


Carbamate 451. To a solution of aniline **441** (105 mg, 0.651 mmol) in 1.30 mL $CHCl_3$ at 23 °C was added 2.60 mL aqueous saturated $NaHCO_3$. The mixture was cooled to 0 °C, and methyl chloroformate (121 μl, 1.56 mmol) was added. The reaction was allowed to warm to 23 °C and was stirred. After 1.5 h, the mixture was partitioned between 50 mL CH_2Cl_2 and 30 mL saturated $NaHCO_3$. The organic layer was washed with water (25 mL) and then brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (15:1 hexanes/EtOAc eluent) to afford methyl carbamate **451** (143 mg, 99% yield, R_F = 0.45 in 2:1 hexanes/Et_2O) as a colorless oil. **Carbamate 451**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.23 (app.t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.04 (app.t, *J* = 7.2 Hz, 1H), 6.65 (br s, 1H), 5.22-5.16 (m, 1H), 3.77 (s, 3H), 3.30 (d, *J* = 6.9 Hz, 2H), 1.80 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 136.3, 134.4, 131.0, 129.8, 127.3, 124.3, 121.8, 52.5, 31.7, 25.9, 18.0; IR (film) 1740, 1524, 1454, 1226 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{17}NO_2]^+$: 219.1259, found 219.1251.



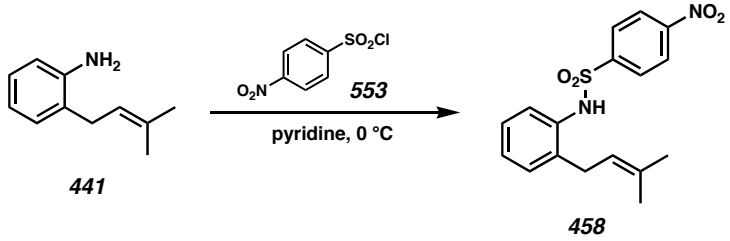
Sulfonamide 454. To a solution of aniline **441** (100 mg, 0.620 mmol) in 2.07 mL pyridine at 0 °C was added MsCl (57.6 μl, 0.744 mmol) dropwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 40 mL

EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide sulfonamide **454** (141 mg, 95% yield, R_F = 0.24 in 4:1 hexanes/EtOAc) as a white semisolid. **Sulfonamide 454**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 1H), 7.27-7.20 (comp m, 2H), 7.14 (app.t, *J* = 7.2 Hz, 1H), 6.48 (br s, 1H), 5.21-5.14 (m, 1H), 3.37 (d, *J* = 7.2 Hz, 2H), 2.99 (s, 3H), 1.81 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 135.3, 132.8, 130.7, 127.9, 126.0, 122.1, 121.4, 39.9, 31.8, 25.9, 18.1; IR (film) 1326, 1154 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{17}O_2NS]^+$: 239.0980, found 239.0986.



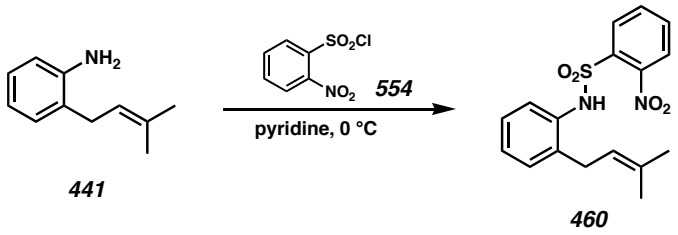
Sulfonamide 456. To a solution of aniline **441** (112 mg, 0.695 mmol) in 2.32 mL pyridine at 0 °C was added 2-mesitylenesulfonyl chloride (182 mg, 0.834 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (12:1 hexanes/EtOAc eluent)

to provide sulfonamide **456** (204 mg, 85% yield, R_F = 0.34 in 4:1 hexanes/acetone) as a white solid. **Sulfonamide 456**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.11 (m, 1H), 7.07-7.01 (comp m, 2H), 6..94 (s, 2H), 6.87-6.84 (m, 1H), 6.63 (br s, 1H), 5.14-5.08 (m, 1H), 3.27 (d, *J* = 6.9 Hz, 2H), 2.56 (s, 6H), 2.30 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 139.4, 135.5, 135.2, 134.7, 133.8, 132.3, 130.3, 127.2, 125.6, 122.5, 121.7, 31.5, 25.9, 23.2, 21.2, 18.2; IR (film) 1330, 1154 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{25}NO_2S]^+$: 343.1606, found 343.1596.



Sulfonamide 458. To a solution of aniline **441** (124 mg, 0.769 mmol) in 2.56 mL pyridine at 0 °C was added 4-nitrobenzenesulfonyl chloride (228 mg, 0.923 mmol) portionwise over 1 min. The dark red mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide sulfonamide **458** (241 mg, 90% yield, R_F = 0.31 in 4:1 hexanes/EtOAc) as an orange oil. **Sulfonamide 458**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.22 (app.t, *J* = 7.8 Hz, 1H), 7.14 (app.t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.72 (br s, 1H), 4.99-4.93 (m, 1H), 2.96 (d, *J* = 7.2 Hz,

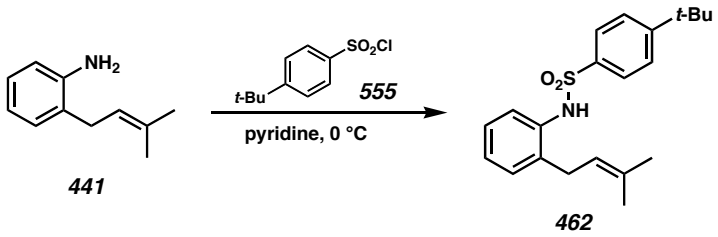
2H), 1.74 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 145.5, 135.4, 134.2, 134.1, 130.6, 128.5, 127.9, 127.0, 124.4, 124.1, 121.2, 31.5, 25.9, 18.1; IR (film) 1531, 1349, 1167 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{18}N_2O_4S]^+$: 346.0987, found 346.0971.



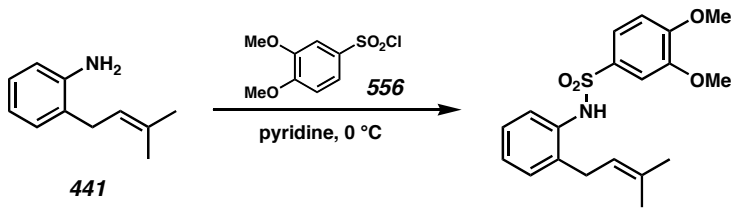
441 *460*

Sulfonamide 460. To a solution of aniline **441** (130 mg, 0.806 mmol) in 2.69 mL pyridine at 0 °C was added 2-nitrobenzenesulfonyl chloride (214 mg, 0.967 mmol) portionwise over 1 min. The dark red mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide sulfonamide **460** (215 mg, 77% yield, R_F = 0.26 in 4:1 hexanes/EtOAc) as an orange oil. **Sulfonamide 460**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.73 (app.t, *J* = 7.8 Hz, 1H), 7.64 (app.t, *J* = 7.8 Hz, 1H), 7.25-7.20 (comp m, 2H), 7.18-7.11 (comp m, 2H), 7.16 (br s, 1H), 5.07-5.01 (m, 1H), 3.30 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 136.3, 134.8, 133.8, 133.7, 132.7, 131.3, 130.1, 127.0, 126.9, 125.3, 124.8, 121.0, 30.3, 25.7, 17.9; IR (film)

1541, 1169 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{18}N_2O_4S]^+$: 346.0987, found 346.0983.

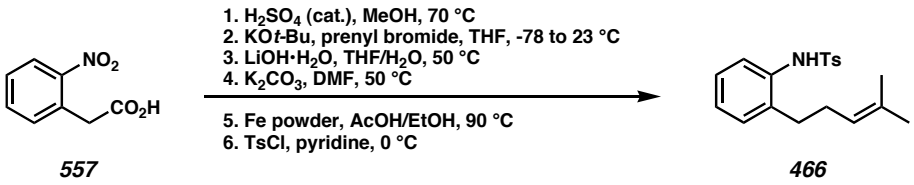


Sulfonamide 462. To a solution of aniline **441** (101 mg, 0.626 mmol) in 2.09 mL pyridine at 0 °C was added 4-*tert*-butylbenzenesulfonyl chloride (175 mg, 0.751 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide sulfonamide **462** (203 mg, 91% yield, R_F = 0.39 in 4:1 hexanes/acetone) as a white solid. **Sulfonamide 462**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.21-7.16 (m, 1H), 7.11-7.05 (comp m, 2H), 6.55 (br s, 1H), 5.00-4.95 (m, 1H), 2.96 (d, *J* = 6.9 Hz, 2H), 1.73 (s, 3H), 1.68 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 137.0, 135.3, 135.0, 133.5, 130.1, 127.5, 127.1, 126.1, 126.0, 123.7, 121.4, 35.3, 31.3, 31.2, 25.9, 18.1; IR (film) 2966, 1166 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{27}NO_2S]^+$: 357.1762, found 357.1750.



441 464

Sulfonamide 464. To a solution of aniline **441** (108 mg, 0.670 mmol) in 2.23 mL pyridine at 0 °C was added 3,4-dimethoxybenzenesulfonyl chloride (190 mg, 0.804 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 40 mL EtOAc and quenched with 2 N HCl (25 mL). The phases were separated, and the organic phase was washed with 2 N HCl (25 mL). The aqueous layers were combined and extracted with EtOAc (40 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/Et_2O eluent) to provide sulfonamide **464** (231 mg, 95% yield, R_F = 0.11 in 4:1 hexanes/EtOAc) as a white solid. **Sulfonamide 464**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.20 (app.t, *J* = 7.2 Hz, 1H), 7.10 (app.t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.51 (br s, 1H), 5.00-4.94 (m, 1H), 3.90 (s, 3H), 3.70 (s, 3H), 2.91 (d, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 148.9, 135.4, 135.0, 134.3, 131.5, 130.1, 127.5, 126.3, 124.5, 121.4, 121.0, 110.6, 109.7, 56.3, 56.2, 31.3, 25.9, 18.0; IR (film) 1509, 1263, 1156 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{19}H_{23}NO_4S]^+$: 361.1348, found 361.1348.



557 *466*

Tosylaniline 466. Methyl 2-nitrophenylacetate was synthesized according to the procedure of Lee et al.[77] To a solution of 2-nitrophenylacetic acid (200 mg, 1.10 mmol) in 1.10 mL MeOH at 23 °C was added 1 drop (pipet) conc. H_2SO_4. The solution was heated to 70 °C and stirred. After 2 h, the reaction was cooled to room temperature, and the solvent was removed by rotary evaporation. The residue was partitioned between 75 mL EtOAc and 50 mL saturated $NaHCO_3$. The organic layer was washed with H_2O (35 mL) and then brine (35 mL), dried over $MgSO_4$, and concentrated in vacuo. The oil was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to afford the methyl ester (181 mg, 84% yield, R_F = 0.25 in 4:1 hexanes/EtOAc) as a colorless oil.

The monoalkylation of methyl 2-nitrophenylacetate was performed according to the procedure of Prasad et al.[78] To a solution of the methyl ester (369 mg, 1.89 mmol) in 28.2 mL THF at 23 °C was added prenyl bromide (266 μl, 2.08 mmol). The solution was cooled to –78 °C, and KO*t*-Bu (233 mg, 2.08 mmol) was added. After 10 min at –78 °C, the mixture was allowed to warm to 23 °C. After 1 h, the mixture was quenched at 0 °C with saturated NH_4Cl (40 mL) and extracted with Et_2O (2 x 60 mL). The organic layers were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide the alkylated ester (480 mg, 96% yield, R_F = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

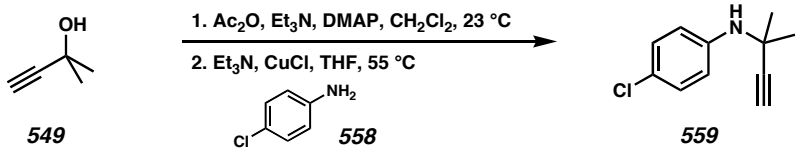
The saponification-decarboxylation sequence was performed according to a modified procedure of Bull et al.[79] To a solution of the ester (480 mg, 1.82 mmol) in THF/H_2O (9.10 mL, 1:1) at 23 °C was added LiOH•H_2O (382 mg, 9.10 mmol). The mixture was heated to 50 °C. After 4 h, the reaction was cooled to room temperature and partitioned between Et_2O (60 mL) and 1 N HCl (30 mL). The aqueous phase was extracted with Et_2O (50 mL), and the organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The product acid (R_F = 0.00 in 9:1 hexanes/EtOAc) was carried on directly to the next reaction.

To a solution of the acid (assume 1.82 mmol) in 5.52 mL DMF at 23 °C was added K_2CO_3 (252 mg, 1.82 mmol). The mixture was heated to 50 °C and stirred for 2 h. The mixture was then cooled to room temperature and partitioned between 50 mL Et_2O and 40 mL 0.5 N HCl. The aqueous phase was extracted with Et_2O (30 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (14:1 hexanes/Et_2O eluent) to afford the decarboxylated product (257 mg, 69% yield over 2 steps, R_F = 0.48 in 9:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

To a solution of the nitroarene (274 mg, 1.33 mmol) in EtOH/AcOH (35.0 mL, 1:1) at 80 °C was added iron powder (670 mg, 12.0 mmol). The resulting slurry was heated to 90 °C. After 1 h, the mixture was cooled to 40 °C, and solid Na_2CO_3 was added slowly to neutralize the reaction. The mixture was then partitioned between EtOAc (100 mL) and H_2O (50 mL), and the aqueous phase was extracted with EtOAc (50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (14:1 hexanes/EtOAc eluent) to

provide the aniline (181 mg, 77% yield, R_F = 0.26 in 9:1 hexanes/EtOAc), which was carried to the next reaction.

To a solution of the aniline (181 mg, 1.03 mmol) in 3.43 mL pyridine at 0 °C was added TsCl (236 mg, 1.24 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 1 h. The mixture was then diluted with 75 mL EtOAc and quenched with 2 N HCl (30 mL). The phases were separated, and the organic phase was washed with 2 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide tosylaniline **466** (266 mg, 78% yield, R_F = 0.15 in 9:1 hexanes/EtOAc) as a white solid. **Tosylaniline 466**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 6.9 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.17-7.07 (comp m, 3H), 6.56 (br s, 1H), 5.10-5.04 (m, 1H), 2.38 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.10 (app.q, *J* = 7.2 Hz, 2H), 1.70 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 137.0, 135.6, 134.4, 134.3, 130.2, 129.8, 127.3, 127.2, 126.5, 124.7, 123.1, 31.2, 28.8, 25.9, 21.7, 17.8; IR (film) 3276, 1329, 1161 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{19}H_{24}O_2NS]^+$: 330.1528, found 330.1534.

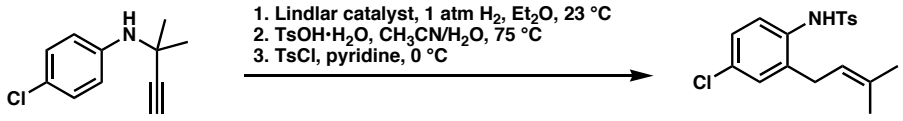


549 *558* *559*

Aniline 559. To a solution of 2-methyl-3-butyn-2-ol (500 μl, 5.16 mmol) in 5.16 mL CH_2Cl_2 at 23 °C was added Et_3N (776 μl, 5.57 mmol), Ac_2O (561 μl, 5.93 mmol), and DMAP (28.9 mg, 0.258 mmol), sequentially. The reaction was stirred at 23 °C overnight

(8 h). The reaction was then poured over saturated NH_4Cl (50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed with 1 N HCl (2 x 35 mL) and brine (35 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.51 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 5.16 mmol) in THF (5.16 mL) at 23 °C under nitrogen was added Et_3N (609 μl, 4.37 mmol), 4-chloroaniline (506 mg, 3.97 mmol), and CuCl (39.3 mg, 0.397 mmol), sequentially. The reaction was heated to 55 °C and stirred for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 75 mL EtOAc and 50 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide aniline **559** (651 mg, 85% yield, R_F = 0.49 in 4:1 hexanes/EtOAc) as a pale yellow oil, which was carried on.

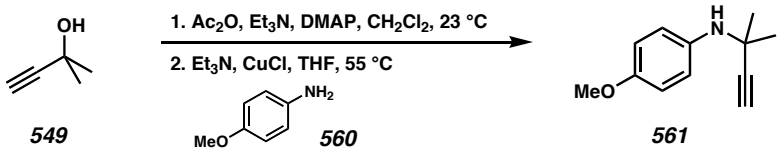


559 ***468***

Tosylaniline 468. Aniline **559** (364 mg, 1.88 mmol) was dissolved in Et_2O (9.40 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 18.8 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 40 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.60 in 4:1 hexanes/EtOAc) was carried on directly to the subsequent reaction.

To a solution of the alkene (assume 1.88 mmol) in CH_3CN/H_2O (18.8 mL, 9:1) was added $TsOH•H_2O$ (35.7 mg, 0.188 mmol). The solution was heated to 75 °C and stirred. After 24 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (75 mL), and the organic layer was washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent) afforded the rearranged aniline[80] (255 mg, 69% yield over 2 steps, R_F = 0.44 in 4:1 hexanes/EtOAc) as a colorless oil.

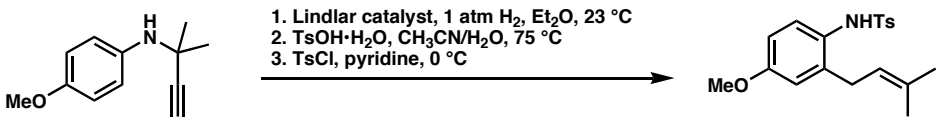
To a solution of the aniline (255 mg, 1.30 mmol) in 4.33 mL pyridine at 0 °C was added TsCl (297 mg, 1.56 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 75 mL EtOAc and quenched with 2 N HCl (30 mL). The phases were separated, and the organic phase was washed with 2 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to provide tosylaniline **468** (363 mg, 80% yield, R_F = 0.25 in 4:1 hexanes/EtOAc) as a colorless semisolid. **Tosylaniline 468**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.14 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.04 (d, *J* = 2.7 Hz, 1H), 6.48 (br s, 1H), 4.96-4.89 (m, 1H), 2.91 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 136.7, 135.8, 135.8, 133.8, 131.5, 130.0, 129.9, 127.5, 127.3, 125.4, 120.5, 31.0, 25.9, 21.8, 18.1; IR (film) 1162 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{18}H_{20}NO_2SCl]^+$: 349.0907, found 349.0903.



549 *560* *561*

Aniline 561. To a solution of 2-methyl-3-butyn-2-ol (500 μl, 5.16 mmol) in 5.16 mL CH_2Cl_2 at 23 °C was added Et_3N (776 μl, 5.57 mmol), Ac_2O (561 μl, 5.93 mmol), and DMAP (28.9 mg, 0.258 mmol), sequentially. The reaction was stirred at 23 °C overnight (8 h). The reaction was then poured over saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed with 1 N HCl (2 x 35 mL) and brine (35 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.51 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 5.16 mmol) in THF (5.16 mL) at 23 °C under nitrogen was added Et_3N (609 μl, 4.37 mmol), *p*-anisidine (489 mg, 3.97 mmol), and CuCl (39.3 mg, 0.397 mmol), sequentially. The reaction was heated to 55 °C and stirred for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 75 mL EtOAc and 50 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (50 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide aniline **561** (646 mg, 86% yield, R_F = 0.37 in 4:1 hexanes/EtOAc) as an orange oil, which was carried on.



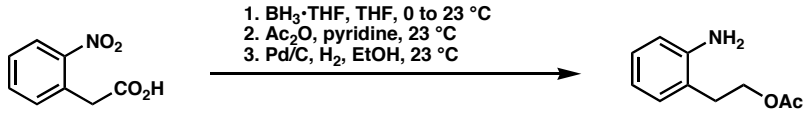
561 ***470***

Tosylaniline 470. Aniline **561** (324 mg, 1.72 mmol) was dissolved in Et_2O (8.56 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 17.1 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 10 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The resulting oil was purified by flash chromatography (5:1 hexanes/EtOAc) to provide the alkene (279 mg, 85% yield, R_F = 0.40 in 4:1 hexanes/acetone), which was carried on directly to the subsequent reaction.

To a solution of the alkene (279 mg, 1.46 mmol) in CH_3CN/H_2O (15.7 mL, 9:1) was added $TsOH•H_2O$ (27.8 mg, 0.146 mmol). The solution was heated to 75 °C and stirred. After 24 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (75 mL), and the organic layer was washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (5:1 hexanes/EtOAc eluent) afforded the rearranged aniline[80] (233 mg, 84% yield, R_F = 0.58 in 2:1 hexanes/EtOAc) as a yellow oil.

To a solution of the aniline (233 mg, 1.22 mmol) in 4.07 mL pyridine at 0 °C was added TsCl (278 mg, 1.46 mmol) portionwise over 1 min. The bright yellow mixture was stirred at 0 °C for 45 min. The mixture was then diluted with 75 mL EtOAc and quenched with 2 N HCl (30 mL). The phases were separated, and the organic phase was washed with 2 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried

over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide tosylaniline **470** (383 mg, 91% yield, R_F = 0.19 in 4:1 hexanes/acetone) as a yellow oil. **Tosylaniline 470**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 1H), 6.60 (s, 1H), 6.24 (br s, 1H), 4.97-4.90 (m, 1H), 3.76 (s, 3H), 2.85 (d, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 143.8, 137.7, 137.0, 134.7, 129.7, 127.6, 127.5, 127.4, 121.3, 115.7, 111.9, 55.5, 31.1, 25.9, 21.8, 18.0; IR (film) 1496, 1161 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{23}NO_3S]^+$: 345.1399, found 345.1388.



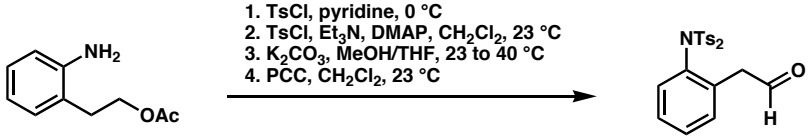
557 ***562***

Aniline 562. Aniline **562** was synthesized according to the procedure of Yamashita et al.[81] To a solution of 2-nitrophenylacetic acid (1.00 g, 5.52 mmol) in 3.25 mL THF at 0 °C was added BH_3•THF (11.0 mL, 1.0 M in THF, 11.0 mmol) dropwise over 3 min. The mixture was allowed to warm to 23 °C and stirred overnight. After 12 h, the reaction was cooled to 0 °C and quenched with H_2O (15 mL). The mixture was partitioned between 100 mL EtOAc and 50 mL saturated $NaHCO_3$. The organic phase was washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) provided the alcohol[82] (915 mg, 99% yield, R_F = 0.19 in 2:1 hexanes/EtOAc) as a pale yellow oil.

To a solution of the alcohol (915 mg, 5.47 mmol) in 6.59 mL pyridine at 23 °C was added 6.59 mL Ac_2O. The mixture was stirred for 30 min, and then concentrated to

an oil. The residue was azeotroped with MeOH (3 x 20 mL), then toluene (2 x 20 mL). The residue was then dissolved in 125 mL $CHCl_3$ and washed with 75 mL saturated $NaHCO_3$. The aqueous phase was extracted with 50 mL $CHCl_3$, and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The acetate[83] (1.08 g, 94% yield, R_F = 0.54 in 2:1 hexanes/EtOAc) was carried directly to the subsequent reaction.

To a solution of the acetate (1.08 g, 5.16 mmol) in 51.6 mL EtOH at 23 °C was added Pd/C (108 mg, 10%). The suspension was put under 1 atm H_2 and stirred vigorously for 90 min. The mixture was filtered through a plug of celite (1.5 x 5 cm, EtOAc eluent), and the filtrate was concentrated to an oil. Aniline **562** (R_F = 0.19 in 4:1 hexanes/EtOAc) was carried on directly to the next reaction.



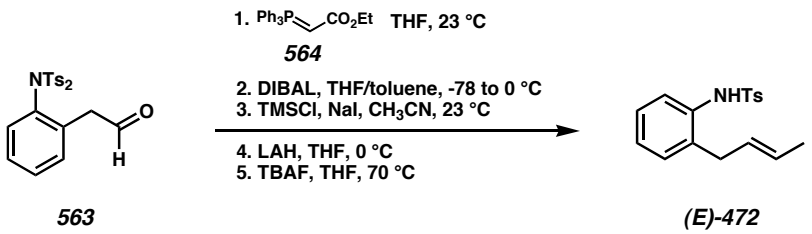
562 ***563***

Aldehyde 563. To a solution of the aniline (assume 5.16 mmol) in 12.9 mL pyridine at 0 °C was added TsCl (1.18 g, 6.19 mmol) portionwise over 2 min. The reaction was stirred for 1 h at 0 °C. The mixture was then diluted with 100 mL EtOAc and quenched with 1 N HCl (30 mL). The phases were separated, and the organic phase was washed with 1 N HCl (30 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to afford the tosylaniline (1.58 g, 92% yield over 2 steps, R_F = 0.34 in 2:1 hexanes/EtOAc), which was carried to the next reaction.

To a solution of the tosylaniline (1.58 g, 4.74 mmol) in 47.4 mL CH_2Cl_2 at 23 °C was added Et_3N (1.98 mL, 14.2 mmol), TsCl (1.08 g, 5.69 mmol), and DMAP (29.0 mg, 0.237 mmol), sequentially. The reaction was stirred at 23 °C for 45 min, at which point it was diluted with 100 mL CH_2Cl_2 and washed with saturated NH_4Cl/H_2O (1:1, 50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc eluent) to provide the bis(tosyl)aniline (2.31 g, 100% yield, R_F = 0.43 in 2:1 hexanes/EtOAc) as a white solid.

To a solution of the bis(tosyl)aniline (213 mg, 0.437 mmol) in THF/MeOH (3.36 mL, 1:1) at 40 °C was added K_2CO_3 (66.5 mg, 0.481 mmol). The reaction was stirred at 40 °C for 1 h, then cooled to room temperature and quenched with saturated $NaHCO_3$ (10 mL). The organic solvents were removed by rotary evaporation, and the aqueous residue was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) provided the alcohol (189 mg, 97% yield, R_F = 0.14 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a suspension of PCC (535 mg, 2.48 mmol) in 3.30 mL CH_2Cl_2 at 23 °C was added a solution of the alcohol (735 mg, 1.65 mmol) in 3.30 mL CH_2Cl_2 dropwise over 1 min. The reaction was stirred at 23 °C for 1 h. The solution was then diluted with 50 mL Et_2O, and the heterogeneous mixture was filtered through a plug of SiO_2 (1.5 x 10 cm, Et_2O eluent). The filtrate was concentrated in vacuo, and the crude residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide aldehyde **563** (545 mg, 75% yield, R_F = 0.42 in 2:1 hexanes/EtOAc) as a white foam.



563 *(E)-472*

Tosylaniline (*E*)-472. Wittig olefination was performed according to the procedure of Matsumori et al.[84] To a solution of aldehyde **563** (545 mg, 1.23 mmol) in 12.3 mL THF at 23 °C was added (carbethoxymethylene)triphenylphosphorane (557 mg, 1.60 mmol). The reaction was stirred at 23 °C for 12 h, then partitioned between 100 mL Et_2O and 50 mL H_2O. The aqueous phase was extracted with Et_2O (50 mL), and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/Et_2O eluent) to afford the *trans*-α,β-unsaturated ester (412 mg, 65% yield, R_F = 0.48 in 2:1 hexanes/EtOAc), which was carried on to the next reaction.

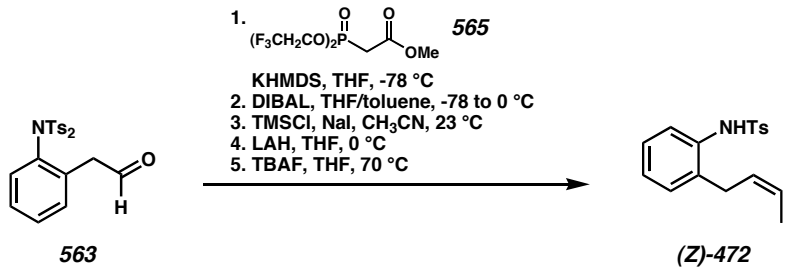
To a solution of the ester (412 mg, 0.802 mmol) in 3.21 mL THF at –78 °C was added DIBAL (1.39 mL, 1.5 M in toluene, 2.09 mmol) dropwise over 3 min. The reaction was stirred for 1 h at –78 °C, then allowed to warm to 0 °C and stirred for an additional 1 h. The reaction mixture was then quenched with 1 N HCl (30 mL) at 0 °C, and it was extracted with EtOAc (3 x 75 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 → 3:2 hexanes/EtOAc eluent) to provide the allylic alcohol (R_F = 0.13 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the alcohol (assume 0.802 mmol) in 1.61 mL CH_3CN at 23 °C in the dark was added NaI (301 mg, 2.01 mmol), then TMSCl (203 μl, 1.60 mmol) dropwise. The reaction mixture was stirred for 15 min, then quenched with 30 mL H_2O. The mixture was extracted with EtOAc (75 mL), and the organic phase was washed with aqueous sodium thiosulfate (10%, 30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting iodide (R_F = 0.55 in 2:1 hexanes/EtOAc) was carried directly to the next reaction without further purification.

To a suspension of LAH (152 mg, 4.01 mmol) in 3.34 mL THF at 0 °C was added a solution of the iodide (assume 0.802 mmol) in 3.34 mL THF dropwise. The resulting mixture was stirred at 0 °C. After 30 min, the reaction was quenched by adding 152 μl H_2O, 152 μl 15% aqueous NaOH, and 456 μl H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided the *E*-alkene (299 mg, 82% yield over 3 steps, R_F = 0.58 in 2:1 hexanes/EtOAc) as a white solid.

Selective monodesulfonylation was carried out according to the procedure of Yasuhara et al.[85] To a solution of the bis(tosyl)aniline (362 mg, 0.795 mmol) in 7.95 mL THF at 23 °C was added TBAF (1.59 mL, 1.0 M in THF, 1.59 mmol). The reaction was heated to 70 °C and stirred. After 2 h, the reaction was cooled to room temperature, and 30 mL H_2O was added. The mixture was extracted with EtOAc (3 x 40 mL), and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1

hexanes/Et_2O eluent) to provide tosylaniline **(*E*)-472**[86] (213 mg, 89% yield, R_F = 0.26 in 2:1 hexanes/Et_2O) as a white semisolid.



Tosylaniline (*Z*)-472. The Still-modification of the Horner-Wadsworth-Emmons reaction was performed according to the procedure of Gleave and Brickner.[87] To a solution of phosphonate **565** (116 μl, 0.545 mmol) in 3.88 mL THF at –78 °C was added KHMDS (545 μl, 1.0 M in THF, 0.545 mmol). The mixture was stirred for 5 min, and then a solution of aldehyde **563** (230 mg, 0.514 mmol) in 3.88 mL THF was added. The reaction was stirred at –78 °C for 1 h, and then it was quenched with saturated NH_4Cl (30 mL) and allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 30 mL), and the combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (2:1 hexanes/Et_2O) to provide the *cis*-α,β-unsaturated ester (183 mg, 71% yield, R_F = 0.54 in 2:1 hexanes/EtOAc), which was carried on to the subsequent reaction.

To a solution of the ester (487 mg, 0.975 mmol) in 3.90 mL THF at –78 °C was added DIBAL (1.69 mL, 1.5 M in toluene, 2.54 mmol) dropwise over 3 min. The reaction was stirred for 1 h at –78 °C, then allowed to warm to 0 °C and stirred for an additional 1 h. The reaction mixture was then quenched with 1 N HCl (40 mL) at 0 °C, and it was extracted with EtOAc (3 x 75 mL). The organic layers were combined,

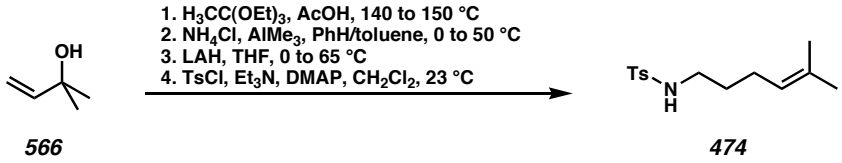
washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (2:1 → 3:2 hexanes/EtOAc eluent) to provide the allylic alcohol (R_F = 0.13 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the alcohol (assume 0.975 mmol) in 1.95 mL CH_3CN at 23 °C in the dark was added NaI (366 mg, 2.44 mmol), then TMSCl (247 μl, 1.95 mmol) dropwise. The reaction mixture was stirred for 15 min, then quenched with 30 mL H_2O. The mixture was extracted with EtOAc (75 mL), and the organic phase was washed with aqueous sodium thiosulfate (10%, 30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting iodide (R_F = 0.60 in 2:1 hexanes/EtOAc) was carried directly to the next reaction without further purification.

To a suspension of LAH (185 mg, 4.88 mmol) in 4.07 mL THF at 0 °C was added a solution of the iodide (assume 0.975 mmol) in 4.07 mL THF dropwise. The resulting mixture was stirred at 0 °C. After 30 min, the reaction was quenched by adding 185 μl H_2O, 185 μl 15% aqueous NaOH, and 555 μl H_2O, sequentially. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc eluent) provided the *Z*-alkene (397 mg, 89% yield over 3 steps, R_F = 0.62 in 2:1 hexanes/EtOAc) as a white solid.

Selective monodesulfonylation was carried out according to the procedure of Yasuhara et al.[85] To a solution of the bis(tosyl)aniline (397 mg, 0.871 mmol) in 8.71 mL THF at 23 °C was added TBAF (1.74 mL, 1.0 M in THF, 1.74 mmol). The reaction was heated to 70 °C and stirred. After 2 h, the reaction was cooled to room temperature, and

30 mL H_2O was added. The mixture was extracted with EtOAc (3 x 40 mL), and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (3:1 hexanes/Et_2O eluent) to provide tosylaniline **(*Z*)-472**[86] (244 mg, 93% yield, R_F = 0.26 in 2:1 hexanes/Et_2O) as a white semisolid.



Tosylamide 474. Johnson orthoester Claisen rearrangement was performed according to the procedure of Noack and Göttlich.[63] A solution of 2-methyl-3-buten-2-ol (1.00 mL, 9.57 mmol), triethyl orthoacetate (2.64 mL, 14.4 mmol), and AcOH (21.9 μl, 0.383 mmol) was heated to 140 °C with distillative removal of EtOH. Once distillation ceased, the reaction mixture was heated to 150 °C and stirred for 3 h. The solution was then cooled to room temperature and poured into a mixture of 150 mL 1 M $KHSO_4$ and 150 mL Et_2O. The mixture was stirred vigorously for 8 h, and then the phases were separated. The aqueous phase was extracted with Et_2O (75 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (75 mL) and concentrated in vacuo. The crude oil was purified by flash chromatography (19:1 hexanes/Et_2O eluent) to afford the ester (297 mg, 20% yield, R_F = 0.48 in 9:1 hexanes/EtOAc) as a colorless oil.

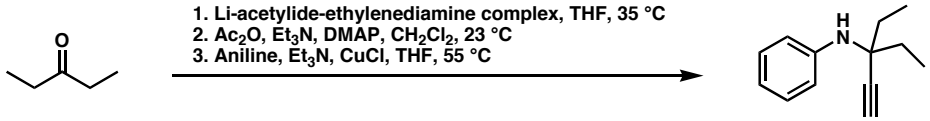
Conversion of the ester to a primary amide was performed according to the procedure of Levin et al.[67] To a suspension of NH_4Cl (266 mg, 4.98 mmol) in 4.98 mL PhH at 0 °C was added $AlMe_3$ (2.49 mL, 2.0 M in toluene, 4.98 mmol) dropwise over 10 min. The mixture was allowed to warm to 23 °C and was stirred for 90 min. Gas

evolution was observed during this time. This solution was then added via cannula to a solution of the ester (259 mg, 1.66 mmol) in 16.6 mL PhH at 23 °C. The resulting mixture was heated to 50 °C and stirred. After 16 h, the mixture was cooled to room temperature and quenched with 0.5 N HCl (50 mL). The mixture was extracted with EtOAc (3 x 60 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The amide (R_F = 0.02 in 4:1 hexanes/EtOAc) was carried on without purification.

To a solution of the amide (assume 1.66 mmol) in 8.30 mL THF at 0 °C was added LAH (189 mg, 4.98 mmol) portionwise slowly. The reaction was heated to 70 °C and stirred for 7 h. The mixture was then cooled to 0 °C and quenched by sequential addition of 189 μl H_2O, 189 μl 15% NaOH, and 567 μl H_2O. The resulting slurry was stirred vigorously at room temperature until a white precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The product amine[88] (R_F = 0.00 in 2:1 hexanes/EtOAc) was carried on to the next reaction without purification.

To a solution of the amine (assume 1.66 mmol) in 8.30 mL CH_2Cl_2 at 23 °C was added Et_3N (463 μl, 3.32 mmol), TsCl (379 mg, 1.99 mmol), and DMAP (10.1 mg, 0.0830 mmol), sequentially. The reaction was stirred at 23 °C for 10 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 30 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to afford tosylamide **474** (299 mg, 67% yield over 3 steps, R_F = 0.24 in 4:1 hexanes/EtOAc) as a colorless oil. **Tosylamide 474**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74

(d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.01-4.95 (m, 1H), 4.57 (br t, *J* = 6.0 Hz, 1H), 2.92 (app.q, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 1.94 (app.q, *J* = 7.2 Hz, 2H), 1.64 (s, 3H), 1.53 (s, 3H), 1.48 (app.quintet, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 137.2, 133.0, 129.9, 127.3, 123.2, 43.1, 29.8, 25.9, 25.3, 21.7, 17.9; IR (film) 3283, 1325, 1160 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{22}O_2NS]^+$: 268.1371, found 268.1363.

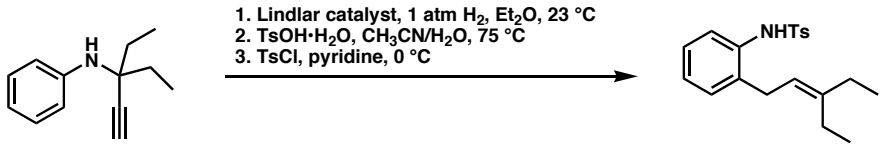


567 ***568***

Aniline 568. Aniline **568** was synthesized according to the literature procedure.[71] To a suspension of lithium acetylide ethylenediamine complex (483 mg, 4.72 mmol) in 4.72 mL THF at 35 °C was added 3-pentanone (500 μl, 4.72 mmol). The reaction mixture was stirred at 35 °C for 3 h. The mixture was then cooled to 0 °C, quenched with saturated NH_4Cl (30 mL), and extracted with Et_2O (2 x 50 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The alcohol[89] (R_F = 0.39 in 4:1 hexanes/EtOAc) was carried crude to the next reaction.

To a solution of the propargylic alcohol (assume 4.72 mmol) in 4.72 mL CH_2Cl_2 at 23 °C was added Et_3N (711 μl, 5.10 mmol), Ac_2O (513 μl, 5.43 mmol), and DMAP (26.5 mg, 0.236 mmol), sequentially. The reaction was stirred at 23 °C overnight (8 h). The reaction was then poured over saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The organic phases were combined, washed with 1 N HCl (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.59 in 4:1 hexanes/EtOAc) was carried on crude.

To a solution of the acetate (assume 4.72 mmol) in THF (6.13 mL) at 23 °C under nitrogen was added Et_3N (556 μL, 3.99 mmol), aniline (331 μL, 3.63 mmol), and CuCl (35.9 mg, 0.363 mmol), sequentially. The reaction was heated to 55 °C and stirred for 3 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 50 mL EtOAc and 35 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (35 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (14:1 hexanes/EtOAc eluent) to provide aniline **568**[72] (253 mg, 37% yield, R_F = 0.62 in 4:1 hexanes/EtOAc) as a pale yellow oil, which was carried on.



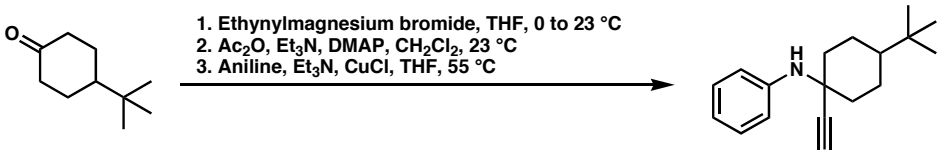
568 ***487***

Tosylaniline 487. Aniline **568** (101 mg, 0.539 mmol) was dissolved in Et_2O (2.70 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 5.4 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 20 min. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.68 in 4:1 hexanes/EtOAc) was carried on directly to the subsequent reaction.

To a solution of the alkene (assume 0.539 mmol) in CH_3CN/H_2O (5.80 mL, 9:1) was added $TsOH•H_2O$ (10.3 mg, 0.0539 mmol). The solution was heated to 75 °C and stirred. After 8 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (50 mL),

and the organic layer was washed with brine (35 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (14:1 hexanes/EtOAc eluent) afforded the rearranged aniline[72] (75.4 mg, 74% yield over 2 steps, R_F = 0.30 in 4:1 hexanes/Et_2O) as a colorless oil, which was carried on directly to the subsequent reaction.

To a solution of the free aniline (226 mg, 1.19 mmol) in 3.97 mL pyridine at 0 °C was added TsCl (273 mg, 1.43 mmol) portionwise over 1 min. The bright yellow solution was stirred at 0 °C for 1 h. The mixture was diluted with 75 mL EtOAc and quenched with 1 N HCl (30 mL). The phases were separated, and the organic phase was washed with 1 N HCl (30 mL). The combined aqueous layers were extracted with 40 mL EtOAc, and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (4:1 hexanes/Et_2O eluent) afforded tosylaniline **487** (329 mg, 80% yield, R_F = 0.39 in 4:1 hexanes/EtOAc) as a pale yellow oil. **Tosylaniline 487**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.19-7.15 (m, 1H), 7.11-7.05 (comp m, 2H), 6.56 (br s, 1H), 4.94 (t, *J* = 6.9 Hz, 1H), 2.99 (d, *J* = 6.9 Hz, 2H), 2.39 (s, 3H), 2.09 (q, *J* = 7.8 Hz, 2H), 2.06 (q, *J* = 7.8 Hz, 2H), 1.00 (app.t, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 143.4, 137.0, 135.3, 133.8, 130.1, 129.8, 127.5, 127.3, 126.0, 123.8, 119.2, 30.6, 29.3, 23.5, 21.8, 13.1, 12.9; IR (film) 2965, 1335, 1163 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{25}O_2NS]^+$: 343.1606, found 343.1601.



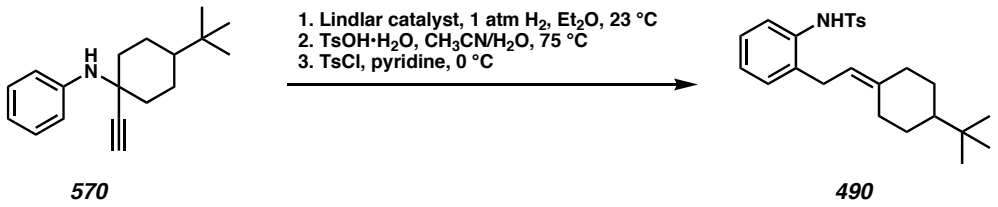
569 ***570***

Aniline 570. Ethynyl Grignard addition was performed according to the reported procedure.[90] To a solution of 4-*t*-butylcyclohexanone (500 mg, 3.24 mmol) in 16.2 mL THF at 0 °C was added ethynylmagnesium bromide (13.0 mL, 0.5 M in THF, 6.48 mmol) dropwise over 5 min. The reaction was allowed to warm to 23 °C over 15 min. After 15 min at 23 °C, the mixture was cooled to 0 °C and quenched with 1 N HCl (40 mL). The mixture was extracted with Et_2O (2 x 100 mL), and the organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford the *syn*-propargylic alcohol (402 mg, 69% yield, R_F = 0.13 in 9:1 hexanes/EtOAc), which was carried to the subsequent reaction. Only the major diastereomer was isolated.

To a solution of the alcohol (402 mg, 2.23 mmol) in 2.23 mL CH_2Cl_2 at 23 °C was added Et_3N (336 μl, 2.41 mmol), Ac_2O (242 μl, 2.56 mmol), and DMAP (13.7 mg, 0.112 mmol), sequentially. The reaction was stirred at 23 °C for 16 h. The reaction was then poured over saturated NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed with 1 N HCl (2 x 40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated to an oil. The acetate (R_F = 0.59 in 4:1 hexanes/EtOAc) was carried on crude to the next reaction.

To a solution of the acetate (assume 2.23 mmol) in THF (2.23 mL) at 23 °C under nitrogen was added Et_3N (263 μL, 1.89 mmol), aniline (157 μL, 1.72 mmol), and CuCl (17.0 mg, 0.172 mmol), sequentially. The reaction was heated to 55 °C and stirred for 6

h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude residue was partitioned between 50 mL EtOAc and 35 mL saturated NH_4Cl. The organic phase was washed with saturated NH_4Cl (35 mL), then brine (35 mL). The combined aqueous phases were extracted with EtOAc (35 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by flash chromatography (29:1 hexanes/EtOAc eluent) to provide aniline **570** (403 mg, 71% yield, R_F = 0.63 and 0.70 in 4:1 hexanes/EtOAc), a mixture of diastereomers, as a white solid, which was carried on to the next reaction.



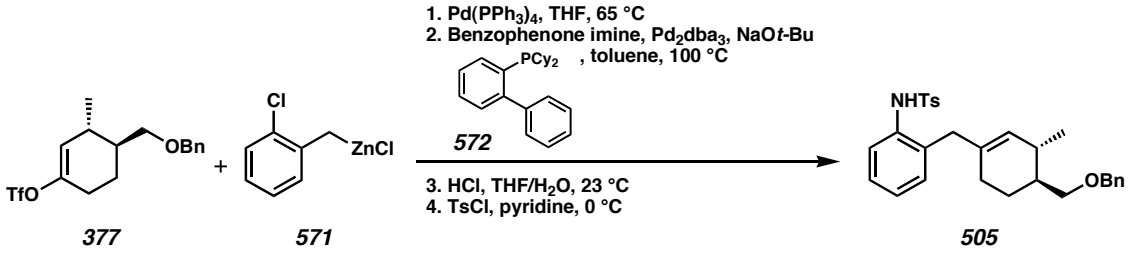
570 ***490***

Tosylaniline 490. Aniline **570** (403 mg, 1.58 mmol) was dissolved in Et_2O (7.90 mL) at 23 °C. Lindlar catalyst (5% $Pd/CaCO_3$ with lead poison, 15.8 mg) was added, and the reaction was put under 1 atm of H_2. The reaction mixture was stirred vigorously at 23 °C for 1 h. The mixture was then passed through a plug of SiO_2 (1 x 5 cm, Et_2O eluent), and the filtrate was concentrated to an oil. The alkene (R_F = 0.45 and 0.80 in 4:1 hexanes/Et_2O) was carried on directly to the subsequent reaction.

To a solution of the alkene (assume 1.58 mmol) in CH_3CN/H_2O (17.2 mL, 9:1) was added $TsOH•H_2O$ (30.6 mg, 0.0161 mmol). The solution was heated to 75 °C and stirred. After 16 h, the mixture was cooled to room temperature, and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with Et_2O (100 mL), and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, and

concentrated in vacuo. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) afforded the rearranged aniline (190 mg, 47% yield over 2 steps, R_F = 0.28 in 9:1 hexanes/EtOAc) as a colorless oil, which was carried on directly to the subsequent reaction.

To a solution of the free aniline (190 mg, 0.738 mmol) in 1.48 mL pyridine at 0 °C was added TsCl (169 mg, 0.886 mmol) portionwise over 1 min. The bright yellow solution was stirred at 0 °C for 45 min. The mixture was diluted with 75 mL EtOAc and quenched with 1 N HCl (30 mL). The phases were separated, and the organic phase was washed with 1 N HCl (30 mL). The combined aqueous layers were extracted with 40 mL EtOAc, and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (6:1 hexanes/Et_2O eluent) afforded tosylaniline **490** (291 mg, 96% yield, R_F = 0.24 in 9:1 hexanes/EtOAc) as a pale yellow oil. **Tosylaniline 490**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.21-7.15 (m, 1H), 7.10-7.04 (comp m, 2H), 6.60 (br s, 1H), 4.91 (t, *J* = 7.2 Hz, 1H), 2.96 (d, *J* = 7.2 Hz, 2H), 2.62 (app.d, *J* = 13.2 Hz, 1H), 2.38 (s, 3H), 2.20 (app.d, *J* = 12.6 Hz, 1H), 2.06 (app.t, *J* = 10.5 Hz, 1H), 1.98-1.79 (comp m, 3H), 1.27-1.00 (comp m, 3H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 142.8, 137.0, 135.4, 133.5, 130.2, 129.7, 127.5, 127.2, 126.0, 123.7, 117.7, 48.5, 37.1, 32.7, 30.6, 29.3, 28.7, 28.6, 27.8, 21.8; IR (film) 2945, 1164 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{25}H_{33}O_2NS]^+$: 411.2232, found 411.2228.



377 *571* *505*

Tosylaniline 505. To a solution of trifluoromethanesulfonate **377** (815 mg, 2.24 mmol) in 11.2 mL THF at 23 °C under argon was added $Pd(PPh_3)_4$ (77.7 mg, 0.0672 mmol), then 2-chlorobenzylzinc chloride (5.38 mL, 0.5 M in THF, 2.69 mmol) dropwise over 5 min. The reaction mixture was heated to 65 °C and stirred. After 90 min, the reaction was cooled to room temperature, diluted with 100 mL EtOAc, and quenched with 1 N HCl (50 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (50 mL). The organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (29:1 hexanes/EtOAc eluent) to provide the aryl chloride (767 mg, 100% yield, R_F = 0.56 in 9:1 hexanes/EtOAc) as a colorless oil.

Palladium-catalyzed aryl amination with benzophenone imine was performed according to the procedure of Wolfe et al.[91] A flame-dried sealable schlenk tube was charged with $Pd_2(dba)_3$ (49.3 mg, 0.0538 mmol), phosphine **572** (75.4 mg, 0.215 mmol), and NaO*t*-Bu (362 mg, 3.77 mmol). A solution of the aryl chloride (767 mg, 2.24 mmol) in 5.38 mL toluene was added, then benzophenone imine (542 μl, 3.23 mmol) was introduced. The reaction mixture was subjected to three freeze-pump-thaw cycles, the tube was sealed under argon, and it was heated to 100 °C. After 24 h, the reaction was cooled to room temperature, diluted with 25 mL Et_2O, and filtered through a plug of celite (1 x 5 cm, Et_2O eluent). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (29:1 hexanes/EtOAc eluent) to provide the *N*-aryl

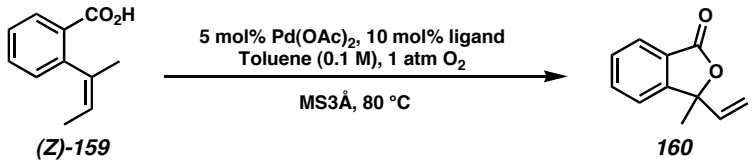
imine (R_F = 0.46 in 9:1 hexanes/EtOAc), which was immediately carried to the subsequent reaction.

To a solution of the imine (assume 2.69 mmol) in 8.97 mL THF at 23 °C was added 1.0 M HCl (897 μl, 0.897 mmol) dropwise. The reaction was stirred vigorously for 2 h, and the mixture was then partitioned between 100 mL EtOAc and 50 mL 1 N NaOH. The aqueous phase was extracted with EtOAc (50 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (12:1 → 6:1 hexanes/EtOAc eluent) to provide the aniline (524 mg, 73% yield over 2 steps, R_F = 0.17 in 4:1 hexanes/Et_2O) as a colorless oil.

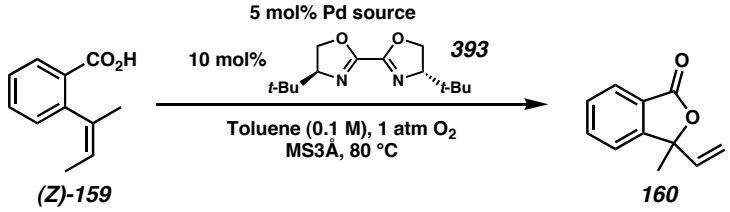
To a solution of the aniline (124 mg, 0.386 mmol) in 3.86 mL pyridine at 0 °C was added TsCl (88.3 mg, 0.463 mmol) portionwise over 1 min. The mixture was stirred for 1 h, at which point it was partitioned between 100 mL EtOAc and 40 mL 1 N HCl. The aqueous phase was extracted with EtOAc (2 x 30 mL), and the organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (8:1 hexanes/EtOAc eluent) afforded tosylaniline **505** (134 mg, 73% yield, R_F = 0.27 in 4:1 hexanes/acetone) as a colorless oil. **Tosylaniline 505**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.35-7.25 (comp m, 5H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.19 (app.t, *J* = 7.2 Hz, 1H), 7.07 (app.t, *J* = 7.5 Hz, 1H), 6.85 (br s, 1H), 5.23 (br s, 1H), 4.51 (ABq, *J* = 12.0, Δν = 16.1 Hz, 2H), 3.52 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.34 (dd, *J* = 6.9, 9.0 Hz, 1H), 2.87 (s, 2H), 2.38 (s, 3H), 2.10-2.02 (m, 1H), 1.89-1.81 (m, 1H), 1.74-1.66 (comp m, 2H), 1.52-1.32 (comp m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 138.9, 137.2, 135.9, 135.2, 131.2,

130.5, 129.8, 128.5, 127.8, 127.7, 127.7, 127.2, 125.8, 123.7, 73.3, 73.3, 41.1, 41.0, 32.5, 27.3, 25.2, 21.7, 20.7; IR (film) 1163, 1092 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{29}H_{33}NO_3S]^+$: 475.2181, found 475.2186.

5.7.3 Palladium(II) Heterocyclizations

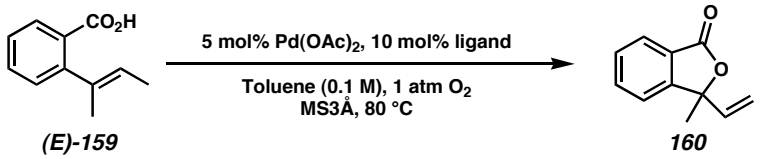


General procedure for the ligand screen in the cyclization of (*Z*)-159 (Table 5.2.1). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (56.5 mg) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.3 mg, 0.00565 mmol) was added, and the solids were taken up in toluene (813 μl). Ligand (0.0113 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of carboxylic acid **(*Z*)-159** (20.0 mg, 0.113 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and GC (See Table 5.7.1 for assay method). The spectroscopic data for lactone **160** (R_F = 0.36 in 4:1 hexanes/EtOAc) was identical to that reported.[3]

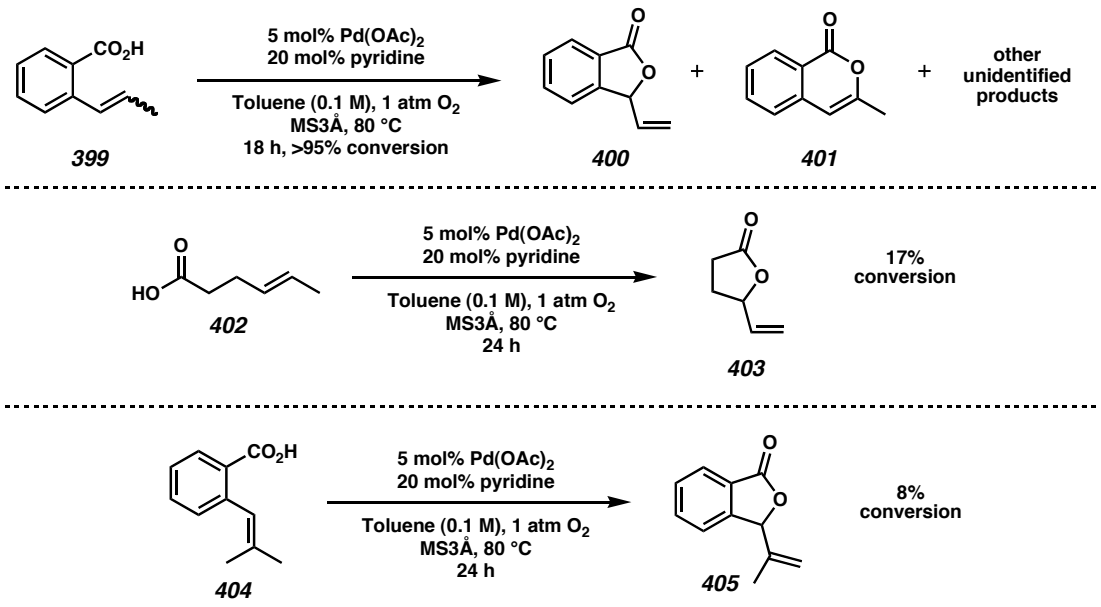


General procedure for the palladium source screen in the cyclization of (*Z*)-159 (Table 5.2.2). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (56.5 mg) and flame-dried under vacuum. After cooling under N_2, Pd source (0.00565

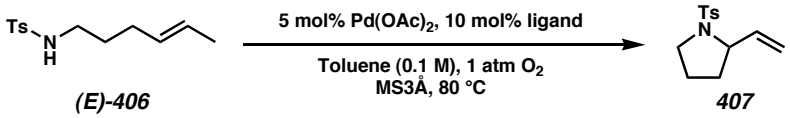
mmol) was added, and the solids were taken up in toluene (813 μl). Ligand **393** (2.9 mg, 0.0113 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of carboxylic acid **(*Z*)-159** (20.0 mg, 0.113 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and GC (See Table 5.7.1 for assay method).



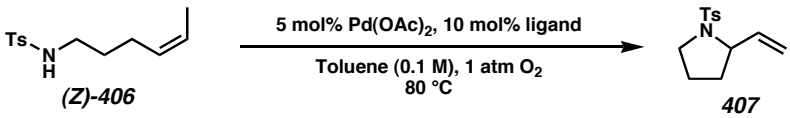
General procedure for the ligand screen in the cyclization of (*E*)-159 (Table 5.2.3). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (56.5 mg) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.3 mg, 0.00565 mmol) was added, and the solids were taken up in toluene (813 μl). Ligand (0.0113 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of carboxylic acid **(*E*)-159** (20.0 mg, 0.113 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and GC (See Table 5.7.1 for assay method).



General procedure for investigation of the substrate scope of the acid cyclization (Scheme 5.2.2). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (500 mg/mmol substrate) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the solids were taken up in toluene (approximately 75% of total amount to make 0.1 M in substrate). Pyridine (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of the carboxylic acid in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. Lactones **400**,[92] **401**[93] (both R_F = 0.38 in 4:1 hexanes/EtOAc), **403**[94] (R_F = 0.25 in 4:1 hexanes/Et_2O), and **405**[7c] (R_F = 0.42 in 4:1 hexanes/EtOAc) were identical spectroscopically to the literature reports.

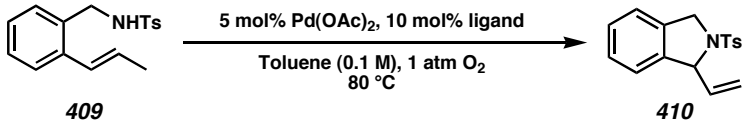


General procedure for the ligand screen in the cyclization of (*E*)-406 (Table 5.3.1). A 25 mL reaction tube with a magnetic stirbar was charged with MS3Å (49.4 mg) and flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00494 mmol) was added, and the solids were taken up in toluene (687 μl). Ligand (0.00987 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide **(*E*)-406** (25.0 mg, 0.0987 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for pyrrolidine **407** (R_F = 0.33 in 4:1 hexanes/EtOAc) was identical to that reported.[10f]



General procedure for the ligand screen in the cyclization of (*Z*)-406 (Table 5.3.2). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00494 mmol) was added, and the compound was dissolved in toluene (687 μl). Ligand (0.00987 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide **(*Z*)-406** (25.0 mg, 0.0987

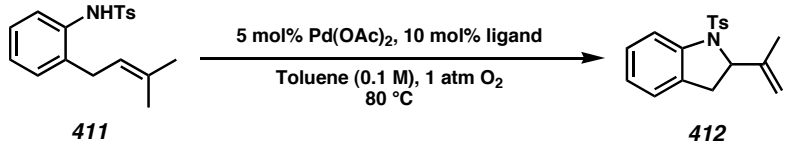
mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



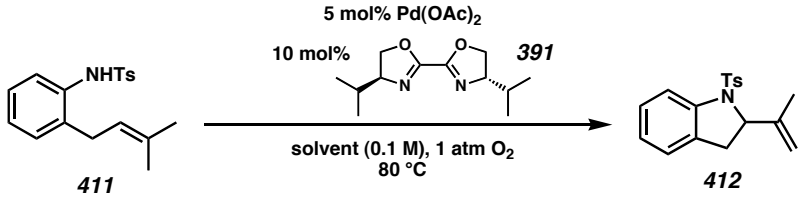
409 *410*

General procedure for the ligand screen in the cyclization of 409 (Table 5.3.3). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00498 mmol) was added, and the compound was dissolved in toluene (695 μl). Ligand (0.00995 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide **409** (30.0 mg, 0.0995 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). Pyrrolidine **410** (R_F = 0.38 in 4:1 hexanes/EtOAc) was further isolated by flash chromatography (5:1 hexanes/Et_2O eluent) for characterization analysis. **Pyrrolidine 410**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.25-7.23 (comp m, 2H), 7.18-7.15 (m, 1H), 7.08-7.05 (m, 1H), 5.90 (ddd, *J* = 8.1, 9.9, 17.1 Hz, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.26-5.24 (m, 1H), 5.24 (d, *J* = 9.9 Hz, 1H), 4.73 (d, *J* = 13.5 Hz, 1H), 4.63 (d, *J* = 13.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 139.0, 138.4, 135.5, 135.1, 129.9, 128.3, 128.0, 127.8, 123.6,

122.7, 116.8, 68.7, 54.0, 21.7; IR (film) 1347, 1164 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{17}NO_2S]^+$: 299.0980, found 299.0983.

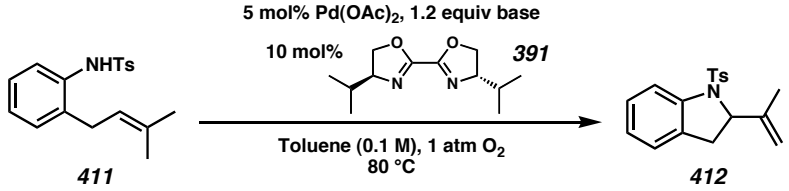


General procedure for the ligand screen in the cyclization of 411 (Table 5.3.4). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Ligand (0.0111 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^1H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for tosylindoline **412** (R_F = 0.45 in 4:1 hexanes/EtOAc) was identical to that reported.[73]

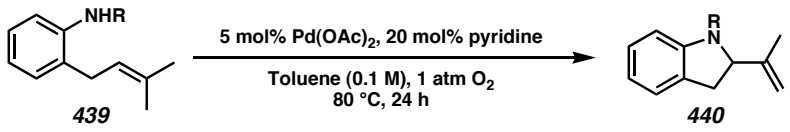


General procedure for the solvent screen in the cyclization of 411 (Table 5.3.5). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was

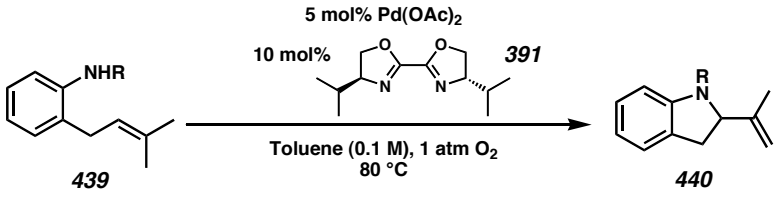
dissolved in solvent (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl solvent was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



General procedure for the base screen in the cyclization of 411 (Table 5.3.6). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, followed by the addition of base (0.132 mmol, 1.20 equiv), and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).

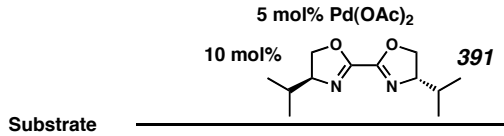


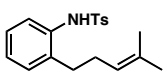
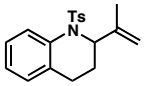
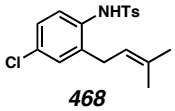
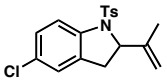
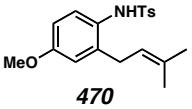
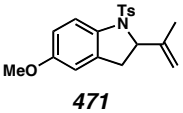
General procedure for the aniline substituent examination in the racemic cyclizations (Table 5.3.7). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Pyridine (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of aniline in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The products of these reactions were verified by independent syntheses (see Section 5.7.4).



General procedure for the aniline substituent examination in the asymmetric cyclizations (Table 5.3.8). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Bisoxazoline **391** (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to

80 °C under O_2 for 10 min. A solution of aniline in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



Entry	Substrate	Product	time	Conv (%)	% ee
1	 *466*	 *467*	24 h	17	11
2	 *468*	 *469*	5 h 24 h	14 19	36 33
3	 *470*	 *471*	5 h 24 h	21 30	26 18

General procedure for the asymmetric cyclizations of 466, 468, and 470 (Table 5.3.9). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Bisoxazoline **391** (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of aniline in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots

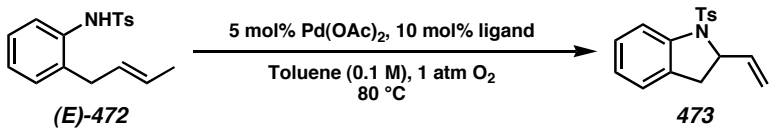
(approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).

The spectroscopic data for tosylaniline **467** (R_F = 0.32 in 9:1 hexanes/EtOAc) was identical to that reported.[95]

Tosylindoline **469** (R_F = 0.43 in 4:1 hexanes/EtOAc) was further isolated by flash chromatography (6:1 hexanes/Et_2O eluent) for characterization analysis. **Tosylindoline 469**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.57 (comp m, 3H), 7.21 (d, 7.8.2H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 5.06 (s, 1H), 4.87 (s, 1H), 4.66 (dd, *J* = 3.6, 10.2 Hz, 1H), 2.95 (dd, *J* = 10.2, 16.5 Hz, 1H), 2.66 (dd, *J* = 3.6, 16.5 Hz, 1H), 2.38 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 144.1, 141.0, 135.0, 133.6, 129.9, 129.7, 128.0, 127.3, 125.3, 117.5, 112.8, 67.3, 34.3, 21.8, 17.9; IR (film) 1357, 1167 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{18}H_{18}NO_2SCl]^+$: 347.0747, found 347.0747.

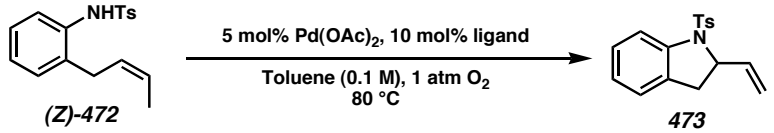
Tosylindoline **471** (R_F = 0.25 in 4:1 hexanes/acetone) was further isolated by flash chromatography (3:1 hexanes/Et_2O eluent) for characterization analysis. **Tosylindoline 471**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.75 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.58 (br s, 1H), 5.06 (br s, 1H), 4.85 (br s, 1H), 4.60 (dd, *J* = 3.3, 9.9 Hz, 1H), 3.75 (s, 3H), 2.82 (dd, *J* = 9.9, 16.5 Hz, 1H), 2.60 (dd, *J* = 3.3, 16.5 Hz, 1H), 2.36 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 144.4, 143.9, 135.5, 135.0, 133.8, 129.7, 127.4, 118.1, 112.9, 112.3,

110.9, 67.1, 55.8, 34.5, 21.7, 18.2; IR (film) 1167 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{19}H_{21}NO_3S]^+$: 343.1242, found 343.1255.



(E)-472 *473*

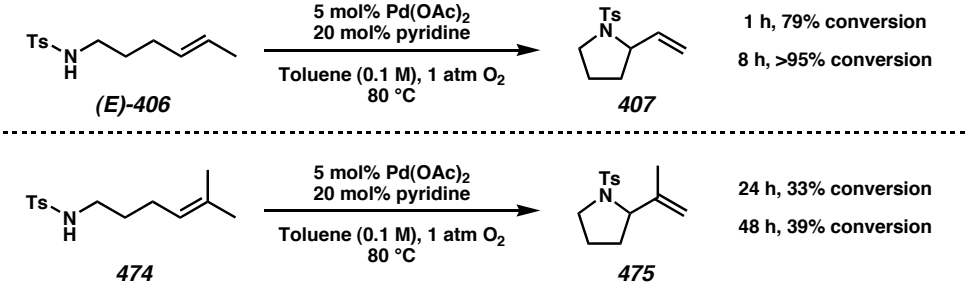
General procedure for the ligand screen in the cyclization of (*E*)-472 (Table 5.3.10). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00498 mmol) was added, and the compound was dissolved in toluene (665 μl). Ligand (0.00995 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **(*E*)-472** (30.0 mg, 0.0995 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^1H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for tosylindoline **473** (R_F = 0.31 in 2:1 hexanes/EtOAc) was identical to that reported.[11]



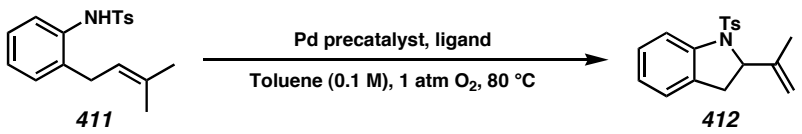
(Z)-472 *473*

General procedure for the ligand screen in the cyclization of (*Z*)-472 (Table 5.3.11). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.1 mg, 0.00498 mmol) was added, and the compound was dissolved in toluene (665 μl). Ligand (0.00995 mmol) was added, and the mixture was

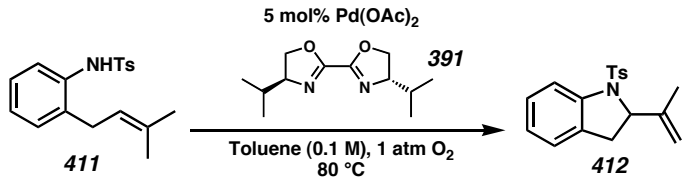
cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **(*Z*)-472** (30.0 mg, 0.0995 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). The spectroscopic data for tosylindoline **473** was identical to that reported.[11]



Procedure for the cyclization of (*E*)-406 and 474 (Scheme 5.3.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (0.0500 equiv) was added, and the compound was dissolved in toluene (approximately 75% of total amount to make 0.1 M in substrate). Pyridine (0.200 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylamide in toluene (approximately 25% of total amount to make 0.1 M in substrate) was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The spectroscopic data for pyrrolidine **475** (R_F = 0.48 in 1:1 hexanes/Et_2O) was identical to that reported.[96]

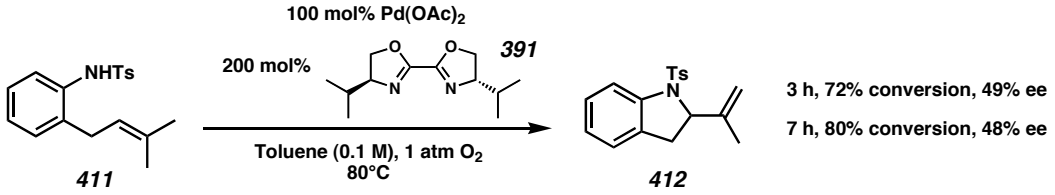


General procedure for the comparison of monodentate and bidentate ligands in the cyclization of 411 (Table 5.4.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, palladium precatalyst (0.0500–0.100 equiv) was added, and the compound was dissolved in toluene (810 μl). Ligand (0.0500 –0.200 equiv) was added if listed, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR.

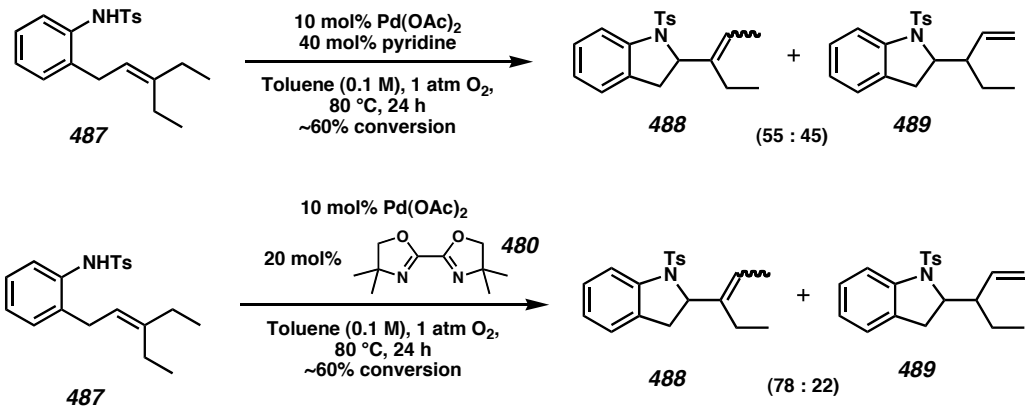


General procedure for the examination of ligand stoichiometry for the cyclization of 411 (Table 5.4.2). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (0.0500–1.00 equiv) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of

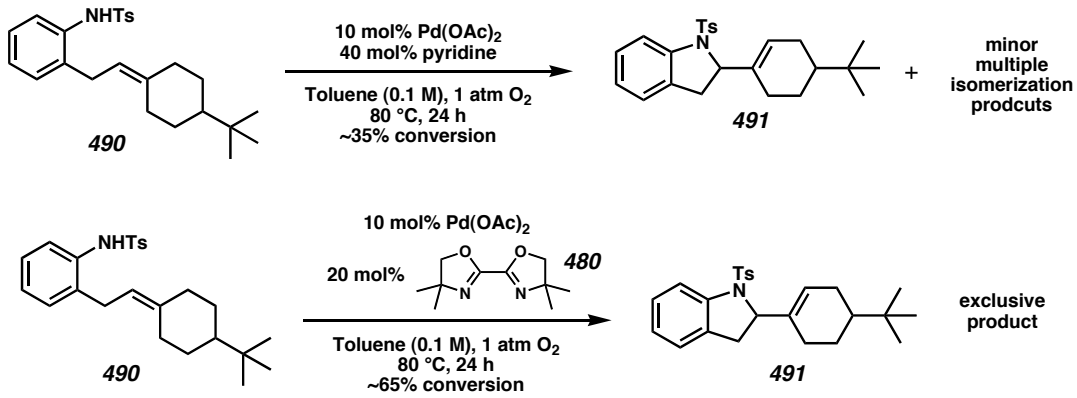
tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



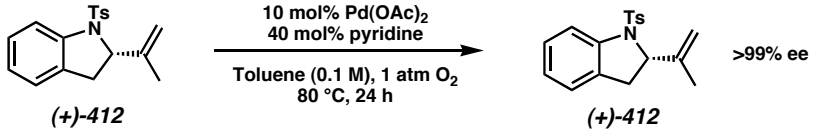
Cyclization of 411 with stoichiometric palladium (Scheme 5.4.2). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (7.1 mg, 0.0317 mmol) was added, and the compound was dissolved in solvent (217 μl). Bisoxazoline **391** (14.2 mg, 0.0634 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (10.0 mg, 0.0317 mmol) in 100 μl solvent was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 50 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



Cyclization of 487 with either pyridine or bisoxazoline 480 as the ligand (Scheme 5.4.4). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.3 mg, 0.0102 mmol) was added, and the compound was dissolved in toluene (720 μl). Pyridine (3.3 μl, 0.0408 mmol) or bisoxazoline **480** (4.0 mg, 0.0204 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **487** (35.0 mg, 0.102 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The product mixture was characterized by independent syntheses of the individual compounds (see Section 5.7.4).

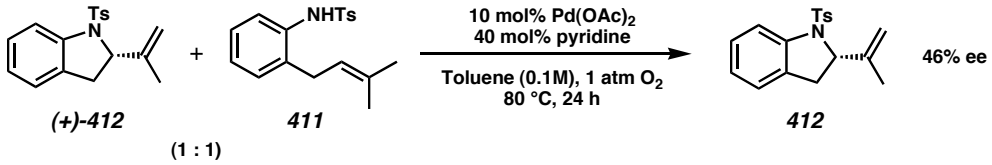


Cyclization of 490 with either pyridine or bisoxazoline 480 as the ligand (Scheme 5.4.4). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.2 mg, 0.00972 mmol) was added, and the compound was dissolved in toluene (672 μl). Pyridine (3.1 μl, 0.0389 mmol) or bisoxazoline **480** (3.8 mg, 0.0194 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **490** (40.0 mg, 0.0972 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The major product (**491**, R_F = 0.54 in 4:1 hexanes/EtOAc) was identical spectroscopically to the compound reported in the literature.[86]

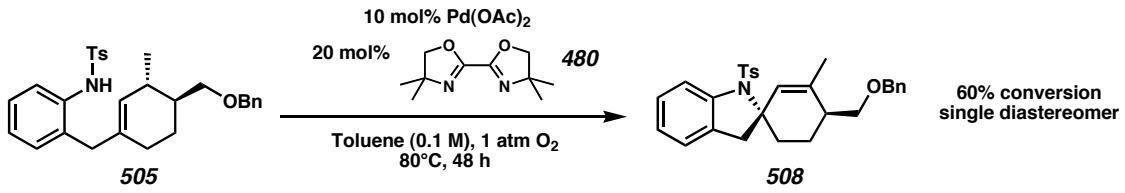


Subjection of tosylindoline (+)-412 to racemic cyclization conditions (Scheme 5.4.6). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.1 mg, 0.00957 mmol) was added, and the compound was

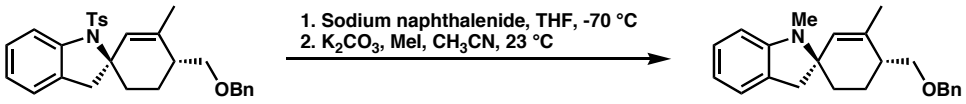
dissolved in toluene (657 μl). Pyridine (3.1 μl, 0.0383 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylindoline **(+)-412** (30.0 mg, 0.0957 mmol, see Section 5.7.4 for synthesis) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken after 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by HPLC (see Table 5.7.1 for assay method). Tosylindoline **(+)-412** was found to be >99% ee.



Racemic cyclization of 411 in the presence of (+)-412 (Scheme 5.4.6). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.1 mg, 0.00957 mmol) was added, and the compound was dissolved in toluene (657 μl). Pyridine (3.1 μl, 0.0383 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylindoline **(+)-412** (15.0 mg, 0.0479 mmol) and tosylaniline **411** (15.1 mg, 0.0479 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken after 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method). Conversion was complete and tosylindoline **412** was measured at 46% ee.



Cyclization of 505 with bisoxazoline ligand 480 (Scheme 5.4.8). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.4 mg, 0.0105 mmol) was added, and the compound was dissolved in toluene (750 μl). Bisoxazoline **480** (4.1 mg, 0.0210 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **505** (50.0 mg, 0.105 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. The reaction was cooled after 48 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The crude material was purified by flash chromatography (6:1 hexanes/Et_2O eluent) to afford tosylindoline **508** (R_F = 0.44 in 2:1 hexanes/Et_2O) as a single diastereomer. **Tosylindoline 508**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.38-7.26 (comp m, 5H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.16 (app.t, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.95 (app.t, *J* = 7.5 Hz, 1H), 5.38 (s, 1H), 4.52 (app.s, 2H), 3.54 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.48 (dd, *J* = 6.0, 9.3 Hz, 1H), 3.00 (app.s, 2H), 2.55 (dt, *J* = 3.3, 12.9 Hz, 1H), 2.52-2.42 (m, 1H), 2.38 (s, 3H), 2.06-1.96 (m, 1H), 1.95-1.88 (m, 1H), 1.75-1.62 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 142.3, 139.8, 138.7, 137.4, 129.6, 129.1, 128.5, 127.8, 127.7, 127.7, 127.6, 127.1, 125.1, 123.0, 114.9, 73.3, 72.6, 72.1, 44.9, 39.2, 34.5, 24.8, 21.7, 21.5; IR (film) 1356, 1166 cm^{-1}; HRMS (EI+) *m/z* calc'd for $[C_{29}H_{31}NO_3S]^+$: 473.2025, found 473.2045.



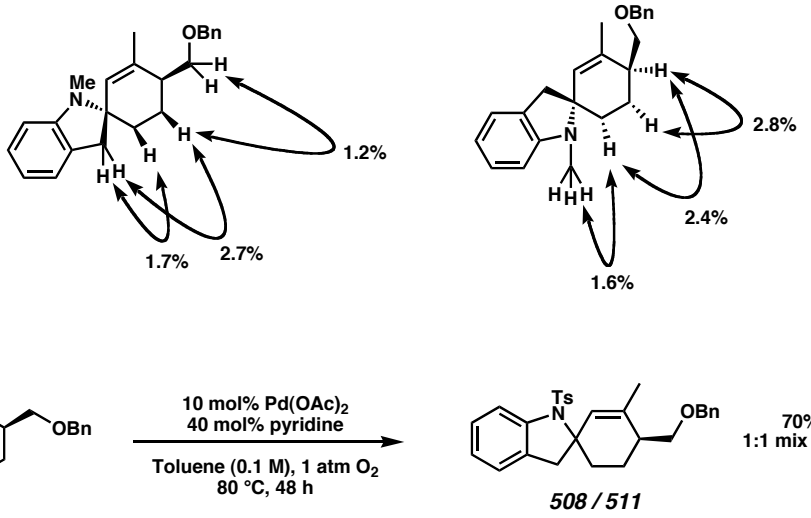
508 *573*

Derivatization of tosylindoline 508 for determination of relative stereochemistry. To a solution of tosylindoline **508** (11.8 mg, 0.0249 mmol) in 175 μl THF at –70 °C was added a solution of sodium naphthalenide (0.2 M in THF, generated from naphthalene and Na metal) dropwise until the dark green color persisted. The reaction mixture was immediately quenched with saturated NH_4Cl (15 mL), and it was allowed to warm to room temperature. The mixture was extracted with Et_2O (3 x 15 mL), and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC (3:1 hexanes/Et_2O eluent) to provide the deprotected indoline (6.2 mg, 78% yield, R_F = 0.53 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the indoline (4.8 mg, 0.0150 mmol) in 543 μl CH_3CN at 23 °C was added K_2CO_3 (10.4 mg, 0.0750 mmol), then MeI (109 μl). The reaction was stirred at 23 °C for 7 h. The mixture was then diluted with 10 mL CH_2Cl_2 and filtered through a plug of celite (pipet), and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (4:1 hexanes/EtOAc eluent) to provide methyl indoline **573** (2.2 mg, 44% yield, R_F = 0.66 in 4:1 hexanes/EtOAc) as a colorless oil. **Indoline 573**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.37-7.29 (comp m, 5H), 7.01 (app.t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.57 (app.t, *J* = 7.0 Hz, 1H), 6.34 (d, *J* = 7.5 Hz, 1H), 5.45 (br s, 1H), 4.53 (ABq, *J* = 12.0, Δν = 15.2 Hz, 2H), 3.58 (dd, *J* = 3.5, 9.0 Hz, 1H), 3.52 (dd, *J* =

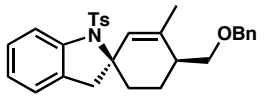
6.5, 9.5 Hz, 1H), 2.85 (ABq, J = 15.5, Δν = 9.1 Hz, 2H), 2.62 (s, 3H), 2.36-2.33 (m, 1H), 1.93-1.88 (m, 1H), 1.85-1.74 (comp m, 2H), 1.75 (s, 3H), 1.68-1.64 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 153.3, 140.0, 139.9, 130.3, 129.5, 129.4, 129.0, 128.8, 128.5, 125.0, 118.3, 107.3, 74.3, 73.3, 70.0, 44.1, 41.2, 29.9, 29.8, 25.9, 21.9; IR (film) 1607, 1486 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{23}H_{27}NO]^+$: 333.2093, found 333.2090.

Figure 5.7.1 Relevant NOE interactions for indoline **573**.



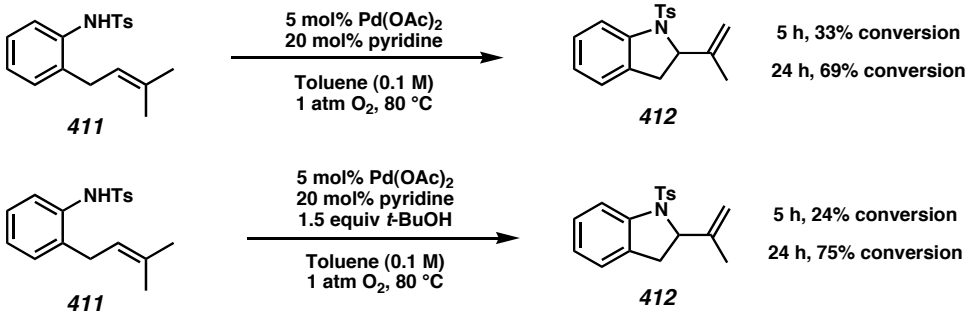
Cyclization of 505 with pyridine as the ligand (Scheme 5.4.8). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (2.4 mg, 0.0105 mmol) was added, and the compound was dissolved in toluene (750 μl). Pyridine (3.4 μl, 0.0420 mmol) was added, and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **505** (50.0 mg, 0.105 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. The reaction was cooled after 48 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR. The diastereomer not observed in the analogous bisoxazoline

reaction was isolated by flash chromatography (9:1 → 4:1 hexanes/Et_2O eluent) to afford tosylindoline **511** (R_F = 0.47 in 2:1 hexanes/Et_2O).



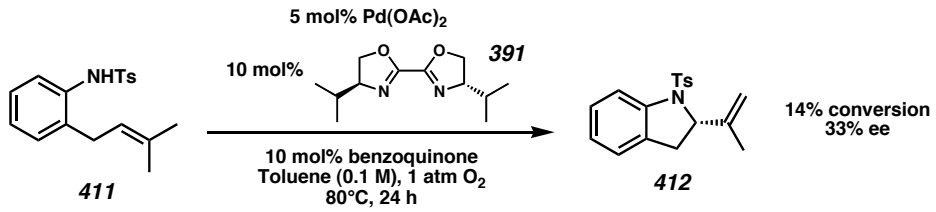
511

Tosylindoline 511: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.39-7.25 (comp m, 5H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.15 (app.t, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.94 (app.t, *J* = 7.5 Hz, 1H), 5.31 (s, 1H), 4.57 (app.s, 2H), 3.70 (app.d, *J* = 7.8 Hz, 2H), 2.99 (app.s, 2H), 2.61 (dt, *J* = 2.7, 14.1 Hz, 1H), 2.38 (s, 3H), 2.36-2.28 (m, 1H), 2.10-2.02 (m, 1H), 1.78-1.65 (comp m, 2H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 142.3, 139.7, 138.8, 136.7, 129.6, 128.9, 128.6, 127.9, 127.9, 127.7, 127.4, 127.2, 125.1, 122.9, 114.6, 73.4, 72.5, 70.7, 44.7, 39.3, 30.6, 23.1, 22.9, 21.7; IR (flm) 1351, 1165, 1091 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{29}H_{32}NO_3S]^+$: 474.2103, found 474.2099.

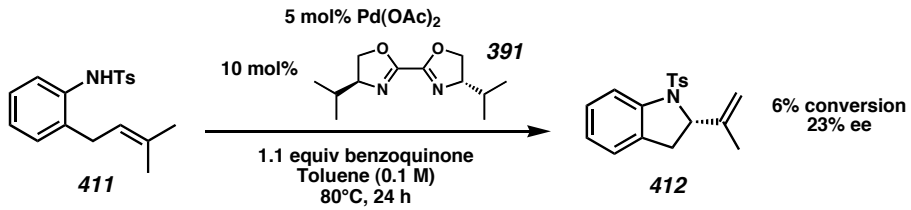


Racemic cyclization of 411 with or without added *t*-BuOH (Scheme 5.5.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Pyridine (1.8 μl, 0.0222 mmol) was added, and the mixture was cooled

to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, followed by the addition of *t*-BuOH (16.0 μl, 0.167 mmol) if necessary, and the reaction was stirred under O_2. Aliquots (approximately 100 μl) were taken at the listed times, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR.



Asymmetric cyclization of 411 with catalytic benzoquinone (Scheme 5.6.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, followed by the addition of benzoquinone (1.2 mg, 0.0111 mmol), and the mixture was cooled to –78 °C and evacuated and filled with O_2 three times. The mixture was then heated to 80 °C under O_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under O_2. An aliquot (approximately 100 μl) was taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).



Asymmetric cyclization of 411 with stoichiometric benzoquinone (Scheme 5.6.1). A 25 mL reaction tube with a magnetic stirbar was flame-dried under vacuum. After cooling under N_2, $Pd(OAc)_2$ (1.2 mg, 0.00555 mmol) was added, and the compound was dissolved in toluene (810 μl). Bisoxazoline **391** (2.5 mg, 0.0111 mmol) was added, followed by the addition of benzoquinone (13.2 mg, 0.122 mmol), and the mixture was heated to 80 °C under N_2 for 10 min. A solution of tosylaniline **411** (35.0 mg, 0.111 mmol) in 300 μl toluene was then introduced, and the reaction was stirred under N_2. An aliquot (approximately 100 μl) was taken at 24 h, passed through a small plug of silica gel (EtOAc eluent), evaporated, and analyzed by ^{1}H NMR and HPLC (see Table 5.7.1 for assay method).

Table 5.7.1. GC/HPLC assays for determining enantiomeric excess.

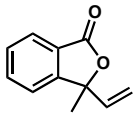
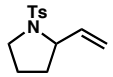
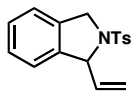
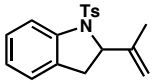
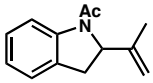
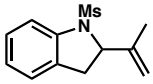
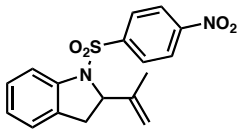
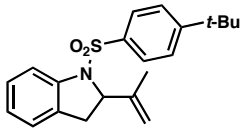
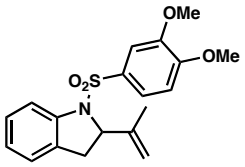
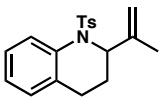
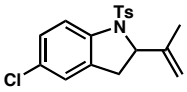
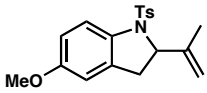
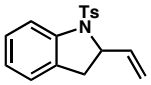
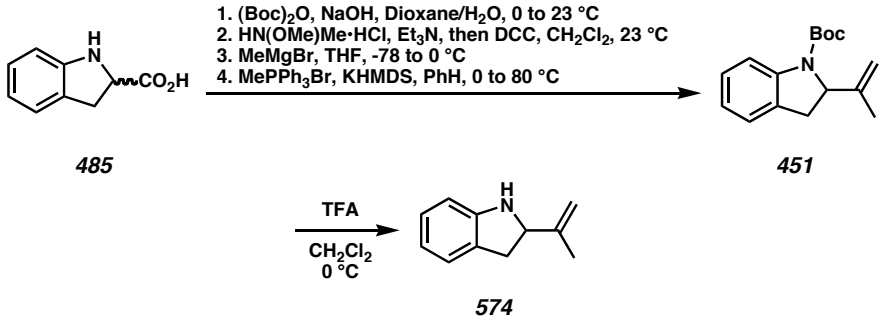
entry	Substrate	ee assay	conditions	retention times
1	 ***160***	GC Chiraldex B-DM	50 °C, 5 min 5 °C/min to 200 °C 1.0 mL/min carrier gas flow	28.67, 28.85
2	 ***407***	HPLC Chiralcel AD	8% EtOH/hexane 1.0 mL/min	14.47, 18.73
3	 ***410***	HPLC Chiralcel AD	8% EtOH/hexane 1.0 mL/min	16.00, 21.62
4	 ***412***	HPLC Chiralcel AD	3% *i*-PrOH/hexane 1.0 mL/min	13.06, 23.49
5	 ***446***	HPLC Chiralcel OD-H	6% EtOH/hexane 1.0 mL/min	8.46, 12.29
6	 ***455***	HPLC Chiralcel OD-H	3% EtOH/hexane 1.0 mL/min	15.97, 24.40
7	 ***459***	HPLC Chiralcel AD	4% EtOH/hexane 1.0 mL/min	17.26, 23.39
8	 ***463***	HPLC Chiralcel OD-H	3% *i*-PrOH/hexane 1.0 mL/min	7.14, 7.74

Table 5.7.1 (continued)

entry	Substrate	ee assay	conditions	retention times
9	 ***465***	HPLC Chiralcel OD-H	6% EtOH/hexane 1.0 mL/min	13.04, 14.03
10	 ***467***	HPLC Chiralcel AD	5% *i*-PrOH/hexane 1.0 mL/min	10.62, 13.79
11	 ***469***	HPLC Chiralcel AD	3% *i*-PrOH/hexane 1.0 mL/min	12.69, 21.47
12	 ***471***	HPLC Chiralcel AD	6% EtOH/hexane 1.0 mL/min	13.08, 18.84
13	 ***473***	HPLC Chiralcel AD	3% *i*-PrOH/hexane 1.0 mL/min	13.99, 20.53

5.7.4 Independent Syntheses of Heterocycles



Independent syntheses of the products from Table 5.3.7.

Carbamate 451. Carbamate synthesis was performed according to the procedure of Sato et al.[97] To a suspension of indoline-2-carboxylic acid (200 mg, 1.23 mmol) in 1.23 mL dioxane and 2.46 mL 0.5 M NaOH at 0 °C was added a solution of di-*tert*-butyl dicarbonate (295 mg, 1.35 mmol) in 1.35 mL dioxane. The reaction mixture was allowed to warm to 23 °C and stirred for 16 h. The mixture was then partitioned between 30 mL hexanes and 50 mL 0.5 M NaOH. The aqueous phase was acidified with saturated citric acid and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH eluent) to provide the carbamate (301 mg, 93% yield, R_F = 0.27 in 9:1 CH_2Cl_2/MeOH) as a brown oil.

To a solution of the carbamate (301 mg, 1.14 mmol) in 6.16 mL CH_2Cl_2 was added *N*,*O*-dimethylhydroxylamine hydrochloride (111 mg, 1.14 mmol), then Et_3N (159 μl, 1.14 mmol). After stirring for 5 min, DCC (235 mg, 1.14 mmol) was added. A white solid began to precipitate. After 2.5 h, the solvent was removed via rotary evaporation, and the solid residue was triturated with acetone (4 x 20 mL). The solution was then concentrated in vacuo. The crude material was purified by flash chromatography (2:1

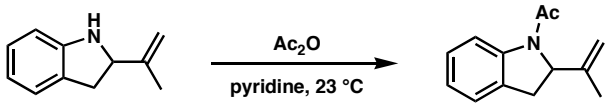
hexanes/EtOAc) to provide the Weinreb amide (276 mg, 79% yield, R_F = 0.68 in 3:1 EtOAc/hexanes), which was carried on to the subsequent reaction.

Grignard reagent addition to the Weinreb amide was performed according to the procedure of Toda et al.[98] To a solution of the amide (1.21 g, 3.95 mmol) in 39.5 mL THF was added MeMgBr (3.97 mL, 3.0 M in Et_2O, 11.9 mmol) dropwise over 5 min. The reaction was warmed to 0 °C and stirred for 3 h. The mixture was then quenched with saturated NH_4Cl (75 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (75 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide the methyl ketone (920 mg, 89% yield, R_F = 0.60 in 2:1 hexanes/EtOAc), which was carried on to the next reaction.

To a suspension of $MePPh_3Br$ (3.79 g, 10.6 mmol) in 19.5 mL PhH at 23 °C was added KHMDS (2.11 g, 10.6 mmol). The yellow mixture was stirred for 15 min, then cooled to 0 °C. A solution of the methyl ketone (920 mg, 3.52 mmol) in 9.78 mL PhH was added dropwise over 5 min, and the mixture was allowed to warm to 23 °C over 30 min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 150 mL Et_2O and 50 mL H_2O. The organic layer was washed with H_2O (2 x 50 mL) and then brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (14:1 hexanes/Et_2O eluent) provided the olefin (866 mg, 95% yield, R_F = 0.58 in 4:1 hexanes/EtOAc) as a white solid. **Carbamate 451**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.17 (app.t, *J* = 7.5 Hz, 1H), 7.11 (d, 1H), 6.93 (app.t, *J* = 7.2 Hz, 1H), 4.81 (s, 1H), 4.75 (s, 1H), 4.81-4.75 (m, 1H), 3.42 (dd, *J* = 10.5, 16.2 Hz, 1H), 2.79 (dd, *J* = 3.6, 16.2 Hz, 1H), 1.67 (s,

3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 145.6, 130.1, 127.7, 124.8, 122.7, 122.5, 115.0, 109.9, 80.9, 64.1, 34.6, 28.6, 18.1; IR (film) 1703, 1485, 1388 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{16}H_{21}NO_2]^+$: 259.1572, found 259.1576.

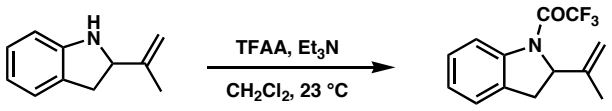
Indoline 574. To a solution of the olefin (137 mg, 0.528 mmol) in 1.32 mL CH_2Cl_2 at 0 °C was added 1.32 mL TFA dropwise. The reaction was maintained at 0 °C for 30 min, at which point it was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. The free indoline[99] (**574**, R_F = 0.47 in 4:1 hexanes/Et_2O) was sufficiently pure to use in further reactions.



574 *446*

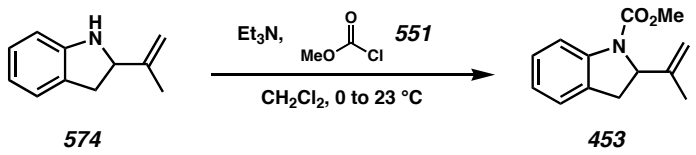
Acetanilide 446. To a solution of indoline **574** (14.9 mg, 0.0936 mmol) in 312 μl pyridine at 23 °C was added Ac_2O (17.6 μl, 0.187 mmol). The mixture was stirred at 23 °C for 30 min, at which point it was diluted with 30 mL EtOAc and washed with 0.5 N HCl (25 mL). The aqueous phase was extracted with EtOAc (30 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to afford the acetanilide (R_F = 0.49 in 1:1 hexanes/EtOAc) as a colorless oil. **Acetanilide 446**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.20 (app.t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.01 (app.t, *J* = 7.2 Hz, 1H), 4.85 (br s, 2H), 4.74 (br d, *J* = 9.9 Hz, 1H), 3.53 (br dd, *J* = 10.5, 16.5 Hz, 1H), 2.87 (br d, *J* = 15.9 Hz, 1H), 2.18 (br s, 3H), 1.69 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 144.6, 143.3, 130.0, 127.8,

124.6, 124.0, 117.3, 111.6, 65.1, 35.3, 23.9, 18.1; IR (film) 1662, 1482, 1396 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{15}NO]^+$: 201.1154, found 201.1149.

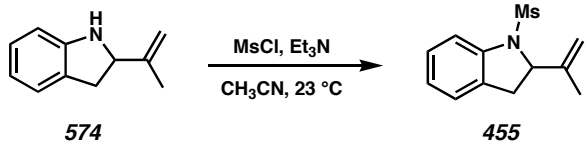


574 ***448***

Trifluoroacetanilide 448. To a solution of indoline **574** (22.0 mg, 0.138 mmol) and Et_3N (67.3 μl, 0.483 mmol) in 690 μl CH_2Cl_2 at 23 °C was added trifluoroacetic anhydride (68.2 μl, 0.483 mmol) dropwise. The solution was maintained at 23 °C for 30 min, and then it was quenched with 30 mL H_2O and extracted with CH_2Cl_2 (50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to provide trifluoroacetanilide **448** (R_F = 0.40 in 1:1 hexanes/CH_2Cl_2) as a white solid. **Trifluoroacetanilide 448**: ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.8 Hz, 1H), 7.29 (app.t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.16 (app.t, *J* = 7.5 Hz, 1H), 5.05 (br d, *J* = 9 Hz, 1H), 4.78 (s, 1H), 4.71 (s, 1H), 3.56 (dd, *J* = 9.3, 15.6 Hz, 1H), 2.93 (d, *J* = 15.6 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 142.2, 130.7, 128.1, 126.2, 125.3, 118.2, 118.2, 114.3, 110.9, 64.2, 35.9, 19.0; IR (film) 1691, 1202 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{12}NOF_3]^+$: 255.0871, found 255.0881.

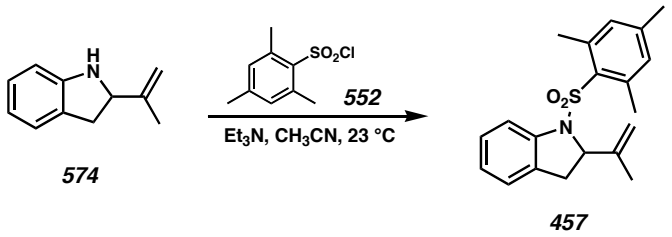


Carbamate 453. To a solution of indoline **574** (17.3 mg, 0.109 mmol) in 653 μl CH_2Cl_2 at 0 °C was added Et_3N (18.3 μl, 0.131 mmol), then methyl chloroformate (10.1 μl, 0.131 mmol). The reaction was allowed to warm to 23 °C and stirred for 16 h. The mixture was then quenched with saturated NH_4Cl/H_2O (1:1, 25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to an oil, which was purified by flash chromatography (19:1 hexanes/Et_2O eluent) to afford the methyl carbamate (R_F = 0.33 in 4:1 hexanes/Et_2O) as a colorless oil. **Carbamate 453**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.19 (app.t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 1H), 6.96 (app.t, *J* = 7.5 Hz, 1H), 4.85 (m, 1H), 4.81 (br s, 1H), 4.76 (br s, 1H), 3.81 (s, 3H), 3.45 (dd, *J* = 10.5, 16.2 Hz, 1H), 2.82 (dd, *J* = 3.0, 16.2 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 144.9, 127.8, 124.9, 123.0, 115.1, 110.2, 64.0, 52.8, 34.7, 18.1; IR (film) 1710, 1486, 1387 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{13}H_{15}NO_2]^+$: 217.1103, found 217.1105.



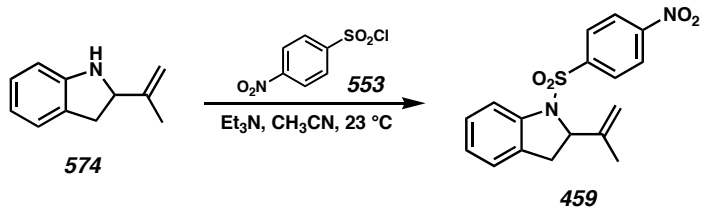
Sulfonamide 455. To a solution of indoline **574** (20.4 mg, 0.128 mmol) in 985 μl CH_3CN at 23 °C was added Et_3N (21.5 μl, 0.154 mmol), then methanesulfonyl chloride (11.9 μl, 0.154 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The

combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to provide indoline **455** (R_F = 0.10 in 9:1 hexanes/EtOAc) as a pale yellow oil. **Sulfonamide 455**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 1H), 7.23-7.17 (comp m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 5.07 (s, 1H), 4.88 (s, 1H), 4.82 (dd, *J* = 3.9, 10.5 Hz, 1H), 3.50 (dd, *J* = 10.2, 16.5 Hz, 1H), 2.90 (dd, *J* = 3.9, 16.5 Hz, 1H), 2.89 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 142.1, 130.6, 128.3, 125.4, 124.2, 114.8, 112.9, 67.2, 37.1, 34.9, 17.6; IR (film) 1347, 1158 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{12}H_{15}NO_2S]^+$: 237.0823, found 237.0820.



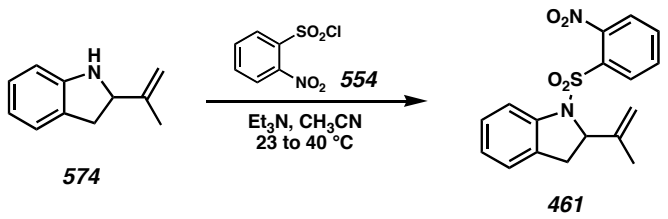
Sulfonamide 457. To a solution of indoline **574** (13.9 mg, 0.0873 mmol) in 672 μl CH_3CN at 23 °C was added Et_3N (14.6 μl, 0.105 mmol), then 2-mesitylenesulfonyl chloride (24.4 mg, 0.105 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (11:1 hexanes/Et_2O eluent) to provide indoline **457** (R_F = 0.36 in 4:1 hexanes/Et_2O) as a white solid. **Sulfonamide 457**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 1H), 7.13-7.07 (comp m, 2H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.93 (s, 2H), 4.84 (s, 1H), 4.78 (dd, *J* = 3.0, 10.2 Hz, 1H), 4.67 (s, 1H), 3.44 (dd, *J* = 9.9, 16.2 Hz, 1H), 2.77 (dd, *J* = 3.0, 16.2 Hz, 1H), 2.60 (s, 6H), 2.29 (s, 3H),

1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 143.1, 140.7, 133.4, 132.3, 130.1, 127.7, 125.1, 123.6, 115.3, 112.4, 66.5, 35.1, 23.1, 21.2, 17.4; IR (film) 1158 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{23}NO_2S]^+$: 341.1449, found 341.1454.

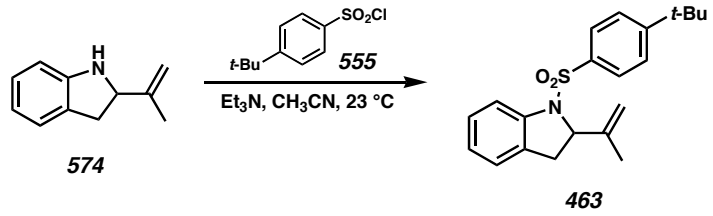


574 459

Sulfonamide 459. To a solution of indoline **574** (13.6 mg, 0.0854 mmol) in 657 μl CH_3CN at 23 °C was added Et_3N (14.2 μl, 0.102 mmol), then 4-nitrobenzenesulfonyl chloride (22.6 mg, 0.102 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/Et_2O eluent) to provide indoline **459** (R_F = 0.32 in 2:1 hexanes/Et_2O) as a yellow solid. **Sulfonamide 459**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.27-7.22 (m, 1H), 7.09-7.04 (comp m, 2H), 5.08 (s, 1H), 4.89 (s, 1H), 4.71 (dd, *J* = 3.3, 9.9 Hz, 1H), 3.03 (dd, *J* = 9.9, 16.5 Hz, 1H), 2.74 (dd, *J* = 3.3, 16.5 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 143.9, 143.8, 141.2, 131.4, 128.5, 128.3, 125.5, 125.3, 124.4, 116.2, 113.1, 67.3, 34.4, 17.8; IR (film) 1530, 1350, 1172 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{16}N_2O_4S]^+$: 344.0831, found 344.0822.

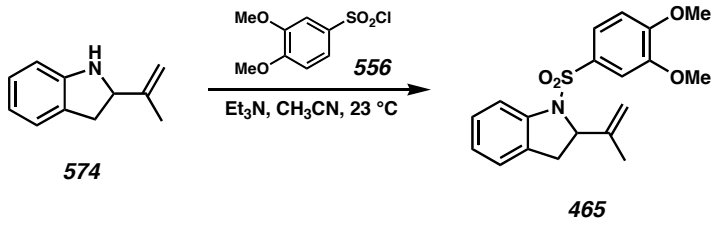


Sulfonamide 461. To a solution of indoline **574** (14.5 mg, 0.0911 mmol) in 701 μl CH_3CN at 23 °C was added Et_3N (15.2 μl, 0.109 mmol), then 2-nitrobenzenesulfonyl chloride (24.2 mg, 0.109 mmol). The reaction was heated to 40 °C and stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide indoline **461** (R_F = 0.08 in 2:1 hexanes/Et_2O) as an orange solid. **Sulfonamide 461**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.69-7.53 (comp m, 3H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.19 (app.t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.03 (app.t, *J* = 7.5 Hz, 1H), 5.07 (br s, 1H), 5.05 (dd, *J* = 2.1, 10.2 Hz, 1H), 4.83 (br s, 1H), 3.40 (dd, *J* = 9.9, 16.2 Hz, 1H), 2.80 (dd, *J* = 2.1, 16.2 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 144.2, 140.8, 134.1, 131.9, 131.5, 131.5, 131.5, 128.0, 125.5, 124.8, 124.4, 115.3, 112.5, 67.4, 34.5, 18.1; IR (film) 1544, 1371, 1170 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{17}H_{16}N_2O_4S]^+$: 344.0831, found 344.0840.

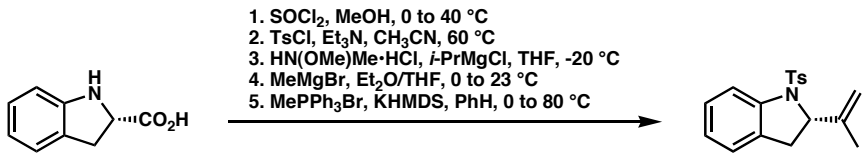


574 463

Sulfonamide 463. To a solution of indoline **574** (14.0 mg, 0.0879 mmol) in 676 μl CH_3CN at 23 °C was added Et_3N (14.6 μl, 0.105 mmol), then 4-*tert*-butylbenzenesulfonyl chloride (24.4 mg, 0.105 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (11:1 hexanes/Et_2O eluent) to provide indoline **463** (R_F = 0.36 in 4:1 hexanes/Et_2O) as a white solid. **Sulfonamide 463**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.21 (app.t, *J* = 7.5 Hz, 1H), 7.06-6.98 (comp m, 2H), 5.07 (s, 1H), 4.86 (s, 1H), 4.66 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.02 (dd, *J* = 10.2, 16.2 Hz, 1H), 2.71 (dd, *J* = 4.2, 16.2 Hz, 1H), 1.70 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 144.6, 142.3, 135.3, 131.5, 128.0, 127.2, 126.1, 125.0, 124.4, 116.4, 112.5, 67.0, 35.3, 34.6, 31.2, 17.8; IR (film) 1356, 1171 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{25}NO_2S]^+$: 355.1606, found 355.1610.



Sulfonamide 465. To a solution of indoline **574** (17.9 mg, 0.112 mmol) in 862 μl CH_3CN at 23 °C was added Et_3N (18.7 μl, 0.134 mmol), then 3,4-dimethoxybenzenesulfonyl chloride (31.7 mg, 0.134 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (2:1 CH_2Cl_2/hexanes eluent) to provide indoline **465** (R_F = 0.13 in 2:1 hexanes/Et_2O) as a colorless oil. **Sulfonamide 465**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.21 (app.t, *J* = 6.0 Hz, 1H), 7.03 (app.t, *J* = 6.9 Hz, 1H), 7.02 (d, *J* = 6.9 Hz, 1H), 6.98 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 5.06 (s, 1H), 4.85 (s, 1H), 4.60 (dd, *J* = 3.6, 9.9 Hz, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 2.91 (dd, *J* = 9.9, 16.2 Hz, 1H), 2.67 (dd, *J* = 3.6, 16.2 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 148.9, 144.5, 142.4, 132.1, 129.7, 127.8, 125.1, 124.8, 121.2, 117.1, 112.4, 110.5, 109.6, 66.9, 56.3, 56.1, 34.4, 18.0; IR (film) 1509, 1264, 1162 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{19}H_{21}NO_4S]^+$: 359.1191, found 359.1188.



(–)-485 *(+)-412*

Independent synthesis of enantiopure (+)-412. Methyl (*S*)-indoline-2-carboxylate was synthesized according to the procedure of Jones et al.[100] To a solution of (*S*)-indoline-2-carboxylic acid (500 mg, 3.06 mmol) in 2.55 mL MeOH at 0 °C was added $SOCl_2$ (268 μl, 3.67 mmol) dropwise over 3 min. The reaction was heated to 40 °C and stirred. After 4 h, the mixture was cooled to 0 °C and quenched with H_2O (30 mL). Saturated $NaHCO_3$ was added to basify the mixture, and it was extracted with EtOAc (100 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to provide the methyl ester (519 mg, 96% yield, R_F = 0.28 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the methyl ester (519 mg, 2.93 mmol) in 22.5 mL CH_3CN at 23 °C was added Et_3N (449 μl, 3.22 mmol), then TsCl (614 mg, 3.22 mmol). The mixture was heated to 60 °C and stirred for 5 h. The red mixture was then cooled to room temperature and quenched with saturated NH_4Cl/H_2O (1:1, 30 mL), and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided the tosylindoline[101] (759 mg, 78% yield, R_F = 0.19 in 4:1 hexanes/EtOAc) as a colorless oil.

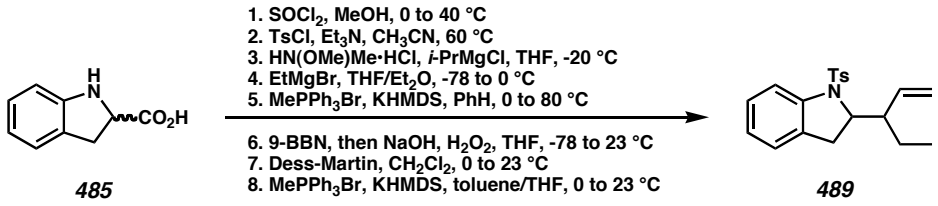
The Weinreb amide synthesis was performed according to the procedure of Williams et al.[102] To a solution of the tosylindoline (348 mg, 1.05 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (153 mg, 1.57 mmol) in 2.10 mL THF at –20 °C

was added *i*-PrMgCl (1.58 mL, 2.0 M in THF, 3.16 mmol) dropwise over 2 min. The mixture was stirred for 30 min at –20 °C, quenched with 30 mL saturated NH_4Cl, and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford the Weinreb amide (255 mg, 67% yield, R_F = 0.06 in 2:1 hexanes/EtOAc) as a white solid.

To a solution of MeMgBr (461 μl, 3.0 M in Et_2O, 1.38 mmol) in 3.07 mL THF at –78 °C was added a solution of the Weinreb amide (166 mg, 0.461 mmol) in 1.54 mL THF dropwise over 2 min. The reaction was allowed to warm to 0 °C. After 30 min at 0 °C, the mixture was quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 50 mL). The organic phases were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide the methyl ketone (145 mg, 99% yield, R_F = 0.32 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a suspension of $MePPh_3Br$ (493 mg, 1.38 mmol) in 2.56 mL PhH at 23 °C was added KHMDS (275 mg, 1.38 mmol). The yellow mixture was stirred for 15 min, then cooled to 0 °C. A solution of the methyl ketone (145 mg, 0.461 mmol) in 1.28 mL PhH was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C over 30 min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 75 mL Et_2O and 40 mL H_2O. The organic layer was washed with H_2O (2 x 30 mL) and then brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/EtOAc eluent)

provided the olefin[73] (142 mg, 98% yield, R_F = 0.41 in 4:1 hexanes/EtOAc) as a white semisolid. **Optical rotation of (+)-412**: $[\alpha]^{23}_D$ +141.36° (*c* 1.0, $CHCl_3$).



485 ***489***

Independent synthesis of the products from Scheme 5.4.4.

Tosylindoline 489. Methyl indoline-2-carboxylate was synthesized according to the procedure of Jones et al.[100] To a solution of indoline-2-carboxylic acid (500 mg, 3.06 mmol) in 2.55 mL MeOH at 0 °C was added $SOCl_2$ (268 μl, 3.67 mmol) dropwise over 3 min. The reaction was heated to 40 °C and stirred. After 4 h, the mixture was cooled to 0 °C and quenched with H_2O (30 mL). Saturated $NaHCO_3$ was added to basify the mixture, and it was extracted with EtOAc (100 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide the methyl ester (536 mg, 99% yield, R_F = 0.28 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the methyl ester (536 mg, 3.02 mmol) in 23.2 mL CH_3CN at 23 °C was added Et_3N (463 μl, 3.32 mmol), then TsCl (633 mg, 3.32 mmol). The mixture was heated to 60 °C and stirred for 5 h. The red mixture was then cooled to room temperature, quenched with saturated NH_4Cl/H_2O (1:1, 30 mL), and the CH_3CN was removed by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in

vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) provided the tosylindoline[101] (837 mg, 84% yield, R_F = 0.19 in 4:1 hexanes/EtOAc) as a colorless oil.

The Weinreb amide synthesis was performed according to the procedure of Williams et al.[102] To a solution of the tosylindoline (837 mg, 2.53 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (371 mg, 3.80 mmol) in 5.06 mL THF at –20 °C was added *i*-PrMgCl (3.80 mL, 2.0 M in THF, 7.59 mmol) dropwise over 2 min. The mixture was stirred for 30 min at –20 °C, quenched with 60 mL saturated NH_4Cl, and extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (1:1 hexanes/EtOAc eluent) to afford the Weinreb amide (821 mg, 90% yield, R_F = 0.06 in 2:1 hexanes/EtOAc) as a white solid.

To a solution of the Weinreb amide (365 mg, 1.01 mmol) in 10.1 mL THF at –78 °C was added EtMgBr (1.01 mL, 3.0 M in Et_2O, 3.03 mmol) dropwise over 2 min. The reaction was allowed to warm to 0 °C. After 45 min at 0 °C, the mixture was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (2 x 75 mL). The organic phases were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/EtOAc eluent) to provide the ethyl ketone (329 mg, 99% yield, R_F = 0.53 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

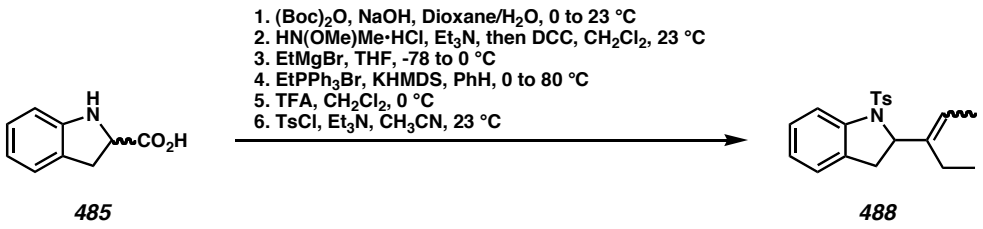
To a suspension of $MePPh_3Br$ (249 mg, 0.696 mmol) in 1.29 mL PhH at 23 °C was added KHMDS (139 mg, 0.696 mmol). The yellow mixture was stirred for 15 min, then cooled to 0 °C. A solution of the ethyl ketone (76.4 mg, 0.232 mmol) in 643 μl PhH was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C over 30

min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 50 mL Et_2O and 25 mL H_2O. The organic layer was washed with H_2O (2 x 20 mL) and then brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/CH_2Cl_2 → 9:9:2 hexanes/CH_2Cl_2/EtOAc eluent) provided the olefin (35.8 mg, 47% yield, R_F = 0.42 in 4:1 hexanes/EtOAc) as a white solid.

To a solution of the olefin (35.8 mg, 0.109 mmol) in 559 μl THF at –78 °C was added 9-BBN (828 μl, 0.5 M in THF, 0.414 mmol) dropwise over 2 min. The mixture was stirred for 10 min, then allowed to warm to 23 °C. After 2.5 h, the reaction was cooled to 0 °C and quenched by addition of 373 μl EtOH, 187 μl 3 M NaOH, and 187 μl H_2O_2 (30% aq.), sequentially. The mixture was stirred at room temperature for 7 h, then diluted with EtOAc (50 mL) and washed with 1 N NaOH (2 x 25 mL), then saturated NH_4Cl (2 x 25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) afforded the primary alcohol (26.6 mg, 71% yield, R_F = 0.31 in 2:1 hexanes/EtOAc), which was carried to the subsequent reaction.

To a solution of the alcohol (26.6 mg, 0.0770 mmol) in 2.57 mL CH_2Cl_2 at 0 °C was added Dess-Martin periodinane (91.6 mg, 0.216 mmol). The reaction was stirred for 20 min, then allowed to warm to 23 °C. After 5 h, the mixture was diluted with 30 mL EtOAc and washed with saturated $NaHCO_3$ (25 mL), then brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (7:1 hexanes/EtOAc) to afford the aldehyde (13.9 mg, 53% yield, R_F = 0.61 in 2:1 hexanes/EtOAc), which was carried to the next reaction.

To a suspension of $MePPh_3Br$ (21.7 mg, 0.0608 mmol) in 529 μl toluene at 23 °C was added KHMDS (12.1 mg, 0.0608 mmol). The yellow mixture was stirred for 30 min, then cooled to 0 °C. A solution of the aldehyde (13.9 mg, 0.0405 mmol) in 203 μl THF was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C. After 20 min at 23 °C, the mixture was partitioned between 50 mL Et_2O and 25 mL H_2O. The organic layer was washed with H_2O (20 mL) and then brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (9:1 hexanes/Et_2O eluent) provided the olefin (7.9 mg, 57% yield, R_F = 0.53 in 4:1 hexanes/EtOAc) as a white solid. **Tosylindoline 489** (characterized as a 57:43 mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.23-7.16 (comp m, 2H), 7.12 (d, *J* = 7.8 Hz, 4H), 7.05-6.95 (comp m, 4H), 5.56-5.41 (comp m, 2H), 5.07-4.98 (comp m, 4H), 4.25 (app.quintet, *J* = 4.2 Hz, 1H), 4.13 (ddd, *J* = 2.1, 7.5, 9.0 Hz, 1H), 2.67-2.41 (comp m, 4H), 2.34 (s, 6H), 2.30-2.12 (comp m, 2H), 1.87-1.74 (m, 1H), 1.68-1.54 (m, 1H), 1.46-1.21 (comp m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 142.7, 142.1, 137.7, 137.7, 135.5, 135.3, 133.6, 133.6, 129.9, 129.6, 127.7, 127.3, 127.3, 125.2, 125.2, 124.9, 124.8, 118.7, 118.4, 118.0, 117.4, 65.7, 52.3, 50.9, 31.8, 31.5, 23.7, 21.8, 21.7, 12.1, 12.0; IR (film) 1353, 1168 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{20}H_{23}NO_2S]^+$: 341.1449, found 341.1447.



485 ***488***

Tosylindoline 488. Carbamate synthesis was performed according to the procedure of Sato et al.[97] To a suspension of indoline-2-carboxylic acid (200 mg, 1.23 mmol) in 1.23 mL dioxane and 2.46 mL 0.5 M NaOH at 0 °C was added a solution of di-*tert*-butyl dicarbonate (295 mg, 1.35 mmol) in 1.35 mL dioxane. The reaction mixture was allowed to warm to 23 °C and stirred for 16 h. The mixture was then partitioned between 30 mL hexanes and 50 mL 0.5 M NaOH. The aqueous phase was acidified with saturated citric acid and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 CH_2Cl_2/MeOH eluent) to provide the carbamate (301 mg, 93% yield, R_F = 0.27 in 9:1 CH_2Cl_2/MeOH) as a brown oil.

To a solution of the carbamate (301 mg, 1.14 mmol) in 6.16 mL CH_2Cl_2 was added *N*,*O*-dimethylhydroxylamine hydrochloride (111 mg, 1.14 mmol), then Et_3N (159 μl, 1.14 mmol). After stirring for 5 min, DCC (235 mg, 1.14 mmol) was added. A white solid began to precipitate. After 2.5 h, the solvent was removed via rotary evaporation, and the solid residue was triturated with acetone (4 x 20 mL). The solution was then concentrated in vacuo. The crude material was purified by flash chromatography (2:1 hexanes/EtOAc) to provide the Weinreb amide (276 mg, 79% yield, R_F = 0.68 in 3:1 EtOAc/hexanes), which was carried on to the subsequent reaction.

Grignard reagent addition to the Weinreb amide was performed according to the procedure of Toda et al.[98] To a solution of the amide (425 mg, 1.39 mmol) in 13.9 mL

THF was added EtMgBr (1.39 mL, 3.0 M in Et_2O, 4.17 mmol) dropwise over 2 min. The reaction was warmed to 0 °C and stirred for 3.5 h. The mixture was then quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (2 x 75 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 → 2:1 hexanes/EtOAc eluent) to provide the ethyl ketone (186 mg, 49% yield, R_F = 0.68 in 2:1 hexanes/EtOAc), which was carried on to the next reaction.

To a suspension of $EtPPh_3Br$ (133 mg, 0.357 mmol) in 662 μl PhH at 23 °C was added KHMDS (71.2 mg, 0.357 mmol). The mixture was stirred for 15 min, then cooled to 0 °C. A solution of the ethyl ketone (32.9 mg, 0.119 mmol) in 331 μl PhH was added dropwise over 1 min, and the mixture was allowed to warm to 23 °C over 30 min. It was then heated to 80 °C and stirred for 4 h. The mixture was cooled to room temperature and partitioned between 50 mL Et_2O and 25 mL H_2O. The organic layer was washed with H_2O (2 x 20 mL) and then brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/CH_2Cl_2 → 2:1 hexanes/CH_2Cl_2 w/ 5% EtOAc eluent) provided the mixture of cis and trans olefins (25.3 mg, 74% yield, R_F = 0.44 in 9:1 hexanes/EtOAc) as a white solid.

To a solution of the olefin (25.3 mg, 0.0880 mmol) in 440 μl CH_2Cl_2 at 0 °C was added 440 μl TFA dropwise. The reaction was maintained at 0 °C for 30 min, at which point it was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil. The free indoline (R_F = 0.51 in 9:1 hexanes/EtOAc) was carried to the next reaction without further purification.

To a solution of the indoline (assume 0.0880 mmol) in 677 μl CH_3CN at 23 °C was added Et_3N (14.8 μl, 0.106 mmol), then TsCl (20.2 mg, 0.106 mmol). The reaction was stirred for 1 h, and then it was quenched with 25 mL saturated NH_4Cl/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (11:1 hexanes/Et_2O eluent) to provide tosylindoline **488** (17.9 mg, 60% yield over 2 steps, R_F = 0.27 in 9:1 hexanes/EtOAc) as a white solid. **Tosylindoline 488** (characterized as a 58:42 mixture of olefin isomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.55 (comp m, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.32-7.15 (comp m, 6H), 7.04-6.95 (comp m, 4H), 5.52 (q, *J* = 6.9 Hz, 1H), 5.31 (q, *J* = 6.9 Hz, 1H), 5.18 (dd, *J* = 4.8, 10.8 Hz, 1H), 4.67 (dd, *J* = 3.3, 10.2 Hz, 1H), 3.13 (dd, *J* = 10.5, 16.5 Hz, 1H), 2.95 (dd, *J* = 10.2, 16.5 Hz, 1H), 2.64 (dd, *J* = 3.3, 16.2 Hz, 1H), 2.62 (dd, *J* = 5.1, 16.5 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 2.09-1.92 (comp m, 4H), 1.78 (d, *J* = 6.9 Hz, 3H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.03 (t, *J* = 7.8 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 143.8, 142.8, 142.4, 142.0, 141.0, 135.6, 135.2, 132.1, 131.6, 129.9, 129.8, 129.7, 128.7, 127.9, 127.8, 127.4, 127.3, 125.1, 124.9, 124.5, 124.1, 122.6, 120.9, 118.7, 116.8, 116.0, 67.0, 60.9, 35.2, 35.1, 23.1, 21.7, 20.6, 13.6, 13.3, 13.2, 12.3; IR (film) 1356, 1169 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{20}H_{23}NO_2S]^+$: 341.1449, found 341.1436.

5.8 Notes and References

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(9) We also investigated other standard reaction parameters. Lowering the temperature slowed the reaction rate, but did not increase enantioselectivity. Toluene appeared to be the optimal solvent for these reactions among the solvents screened.

(10) For leading references on the amination of olefins with palladium, see: (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc*. **1978**, *100*, 5800-5807. (b) Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett*. **1986**, *27*, 6009-6012. (c) Fox, D. N. A.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4697-4710. (d) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc*. **1982**, *104*, 2444-2451. (e) Kimura, M.; Harayama, H.; Tanaka, S.; Tamaru, Y. *J. Chem. Soc., Chem. Commun*. **1994**, *21*, 2531-2533. (f) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org.*

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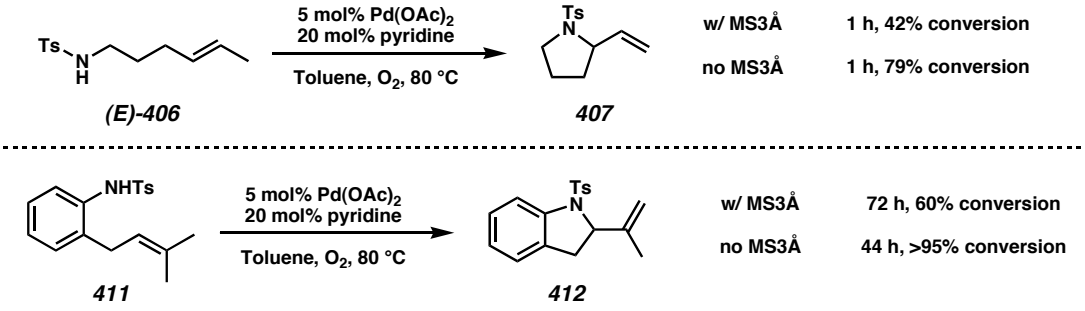
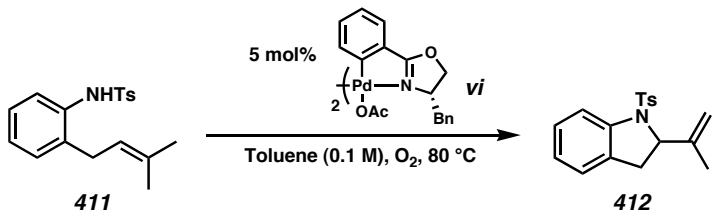
(13) Some of the reactions in this table are run without MS3Å. It was found during these reactions that added MS3Å provided no increased selectivity and in fact hindered reactivity in the cyclizations of tosylamides and tosylanilines.



(14) This observation was further validated by the oxidative cyclization with catalyst **vi**.



(15) Bisoxazoline **413** (entry 5) provided higher levels of conversion with the same degree of enantioselectivity; however, the synthetic difficulty of this ligand compared to bisoxazoline **391** thwarted its use in further studies.

(16) The palladium source had a dramatic effect on the reaction, $Pd(OAc)_2$ being the most effective precatalyst investigated. $Pd(TFA)_2$ resulted in a decrease in selectivity, while all other palladium sources were ineffective at catalyzing the transformation. See the experimental section for details.

(17) It is not clear if the deprotonation event occurs before or after nucleophilic attack on the activated olefin. It is believed, however, that deprotonation from an anilinium intermediate arising from the nucleophilic attack should be facile regardless of the nitrogen substituent.

(18) The synthetic difficulty of accessing these substrates (see Experimental Section) prevented us from further exploring these reactions.

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(20) This would be rather unsurprising. Nonligated palladium centers are more electron-deficient, likely increasing their reactivity toward olefin activation.

(21) (a) The aggregative decomposition occurs at palladium(0) and is therefore more prevalent in the Pd/DMSO/O_2 systems, where Pd(0) is the resting state for the catalyst. See, Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc*. **2002**, *124*, 766-767. (b) Pd(II) was found to be the resting state for the Pd/pyridyl/O_2 oxidation systems, which helps to prevent the same aggregative decomposition. See reference 19b. It is not clear what the resting state of the catalyst is in the bisoxazoline systems described herein.

(22) "N-H activation" is used figuratively in this explanation. A net N-H activation would most likely involve coordination of the nitrogen atom to the metal center followed by deprotonation of the cationic intermediate with concomitant loss of an acetate ligand.

(23) The latter scenario is less likely, but cannot be completely ruled out. No other olefin isomers were observed in the reaction mixture. Additionally, unpublished results by Raissa Trend and results by Hayashi et al. have shown that in the case of

oxygen atom nucleophiles, insertion of an olefin into a palladium-oxygen bond is the most likely mechanism. (a) Trend, R. M.; Stoltz, B. M. California Institute of Technology, Pasadena, CA. Unpublished work, 2005. (b) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc*. **2004**, *126*, 3036-3037.

(24) This model is not fully in agreement with every element of data. In particular, the reversal of enantioselectivity with pyridine-oxazoline **397** (Table 5.3.4, entry 6) is inconsistent with the enantioinduction model and cannot be rationalized at this time.

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APPENDIX THREE

Spectra Relevant to Chapter Five: Further Investigations into Palladium(II)-Catalyzed Asymmetric Oxidative Heterocyclizations

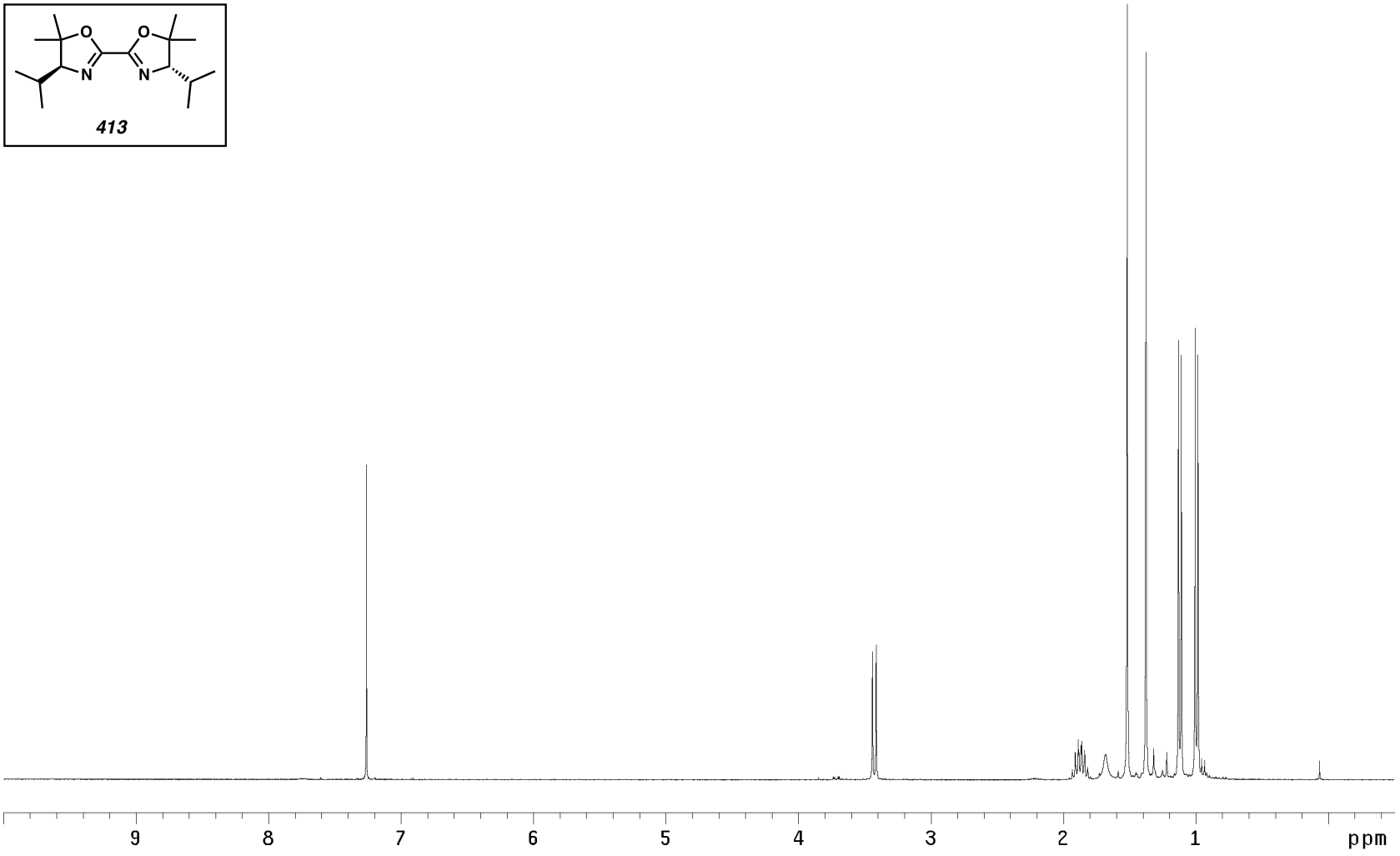


Figure A3.1 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **413**.

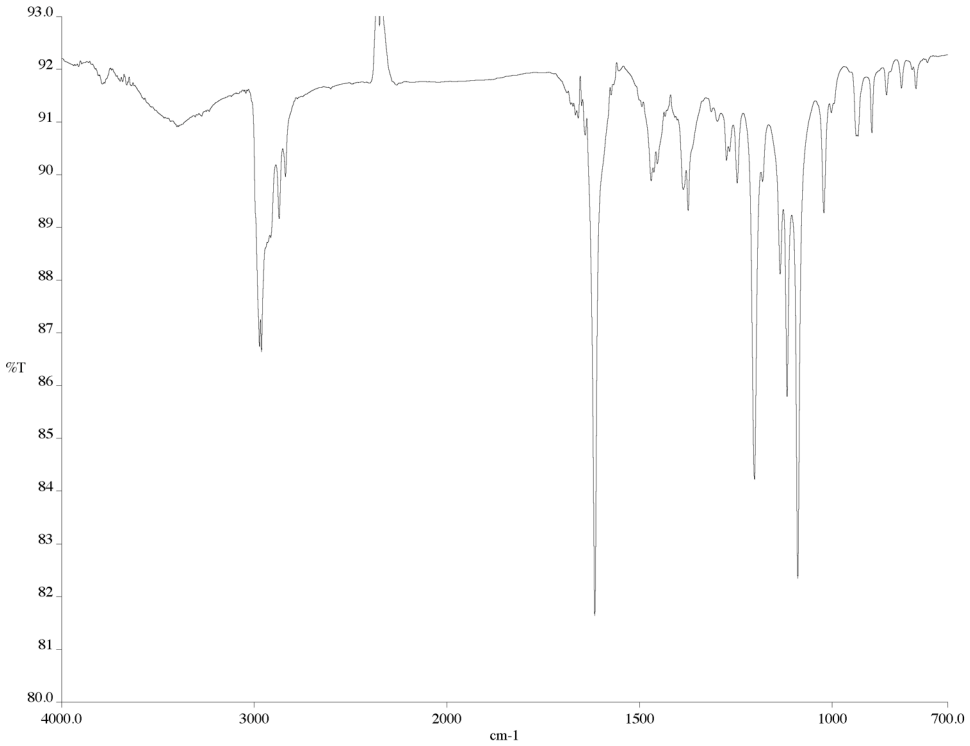


Figure A3.2 Infrared spectrum (thin film/NaCl) of compound **413**.

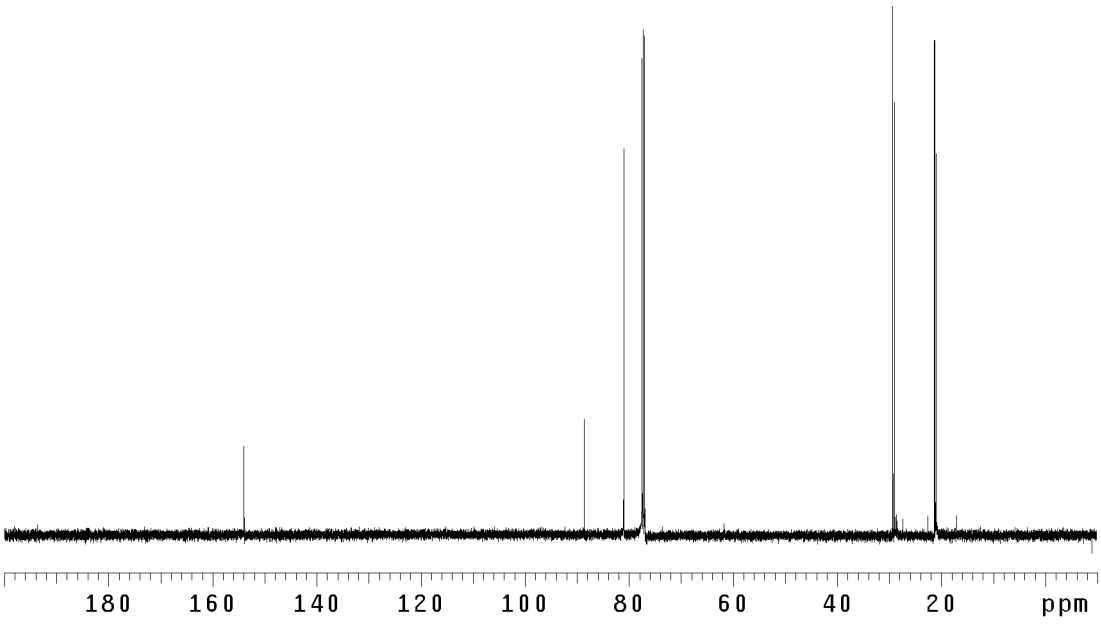


Figure A3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **413**.

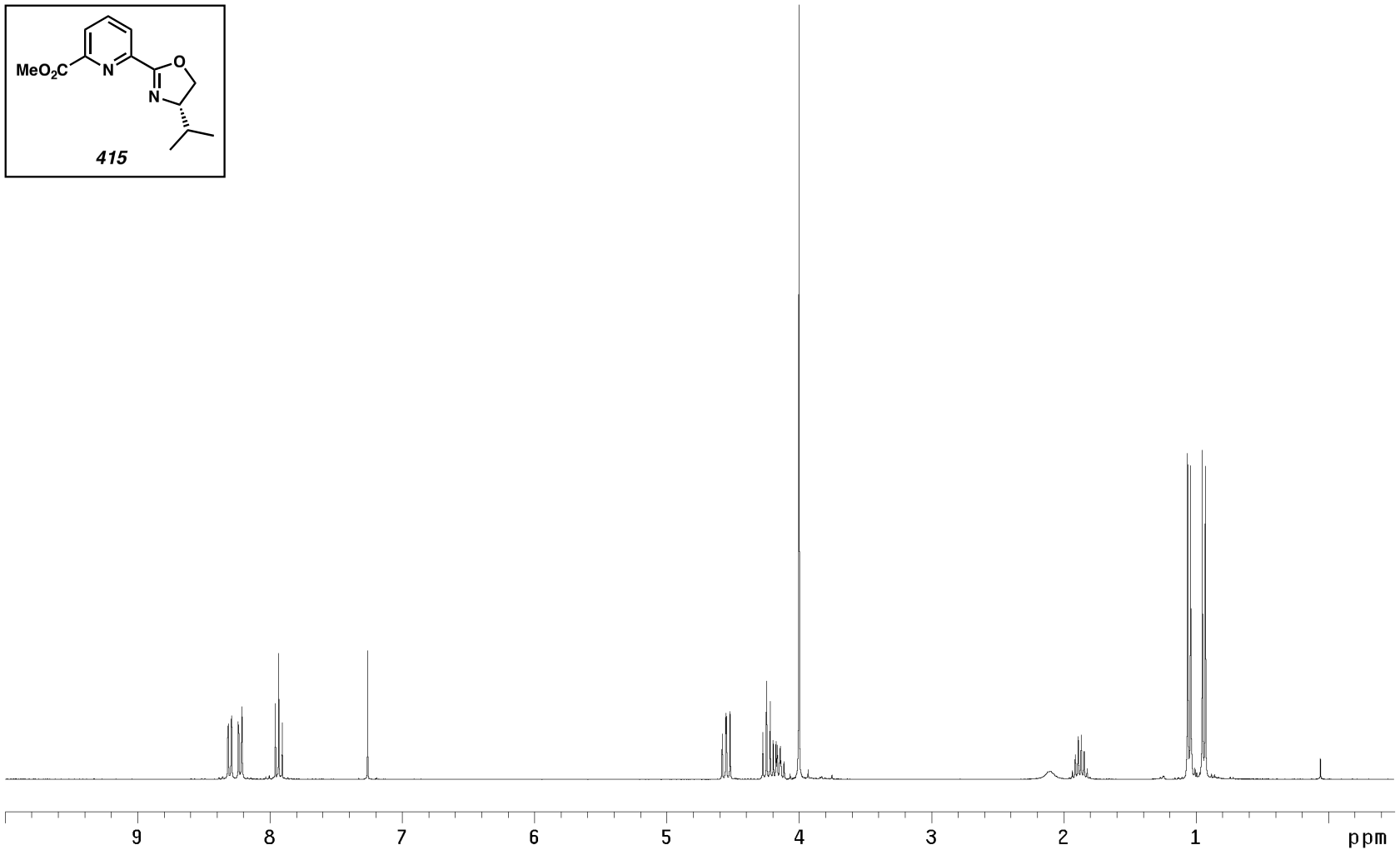


Figure A3.4 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **415**.

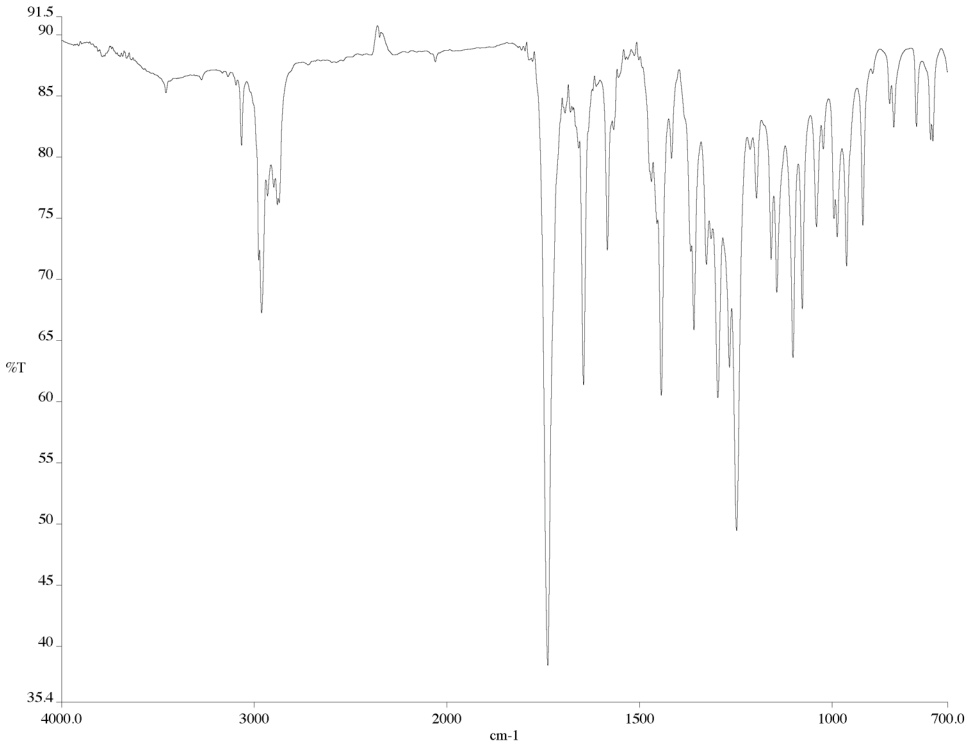


Figure A3.5 Infrared spectrum (thin film/NaCl) of compound **415**.

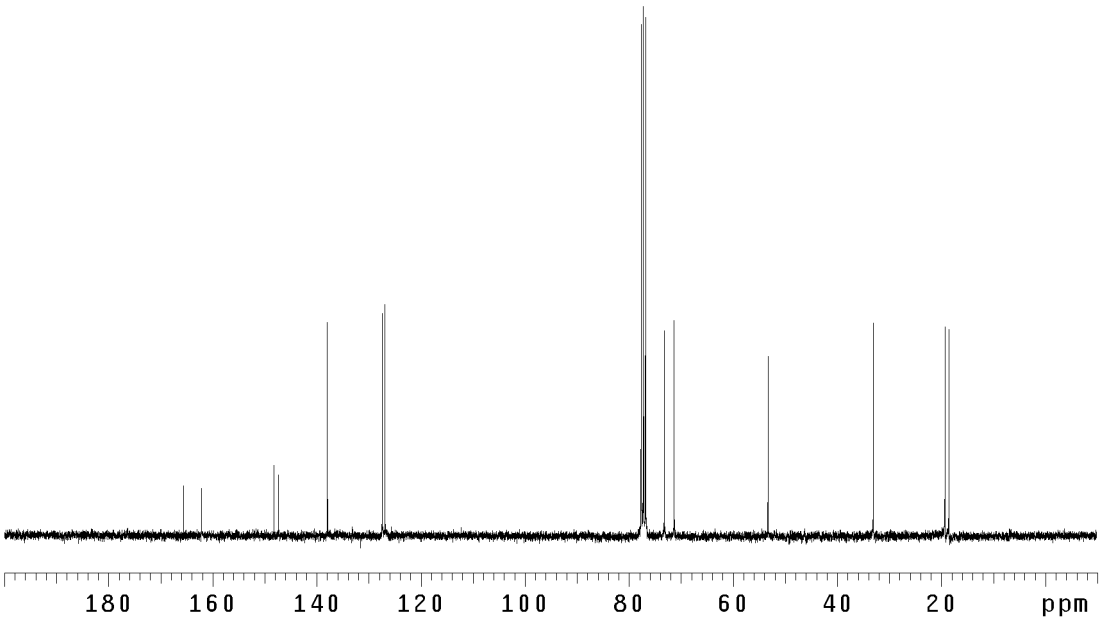


Figure A3.6 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **415**.

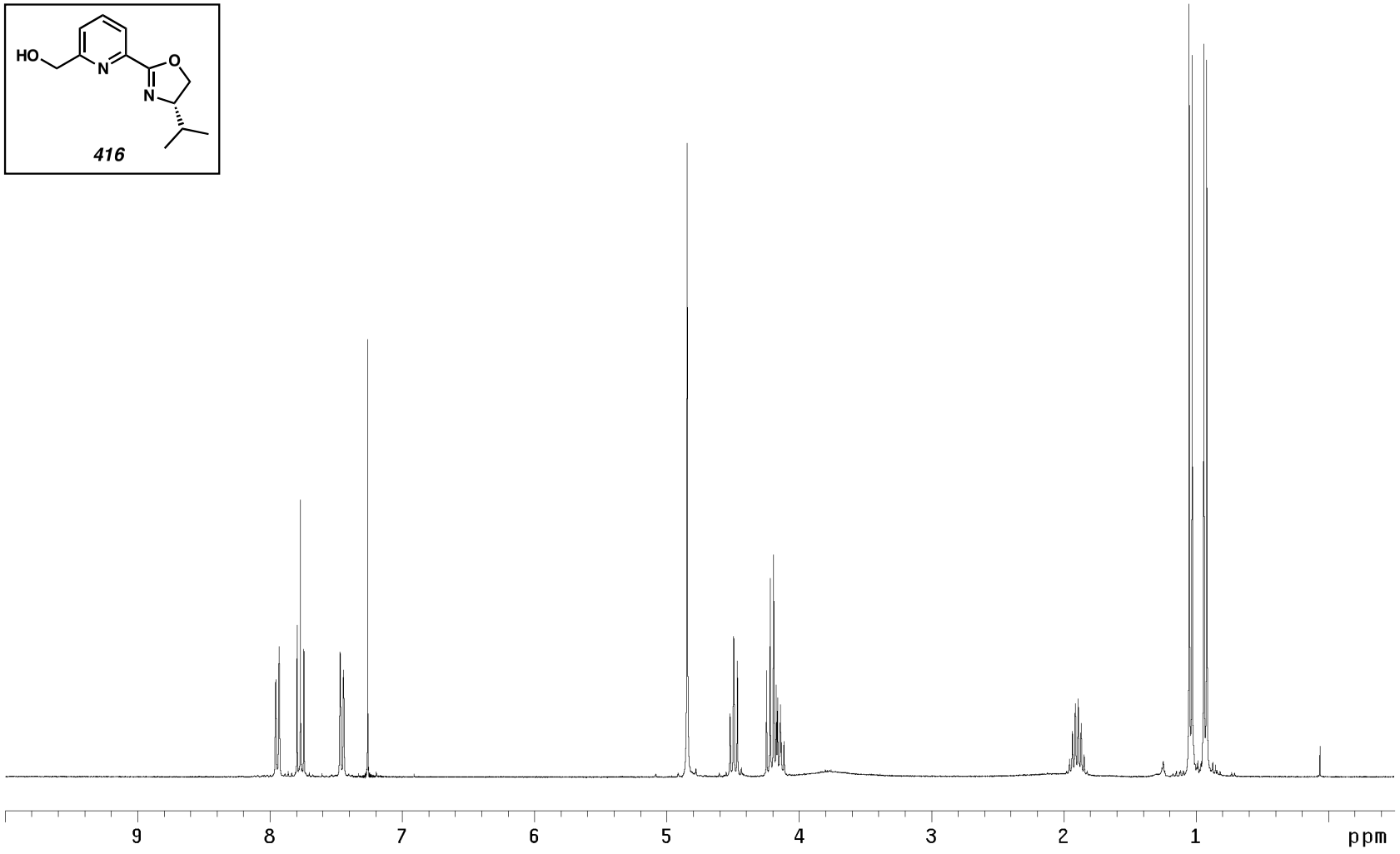


Figure A3.7 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **416**.

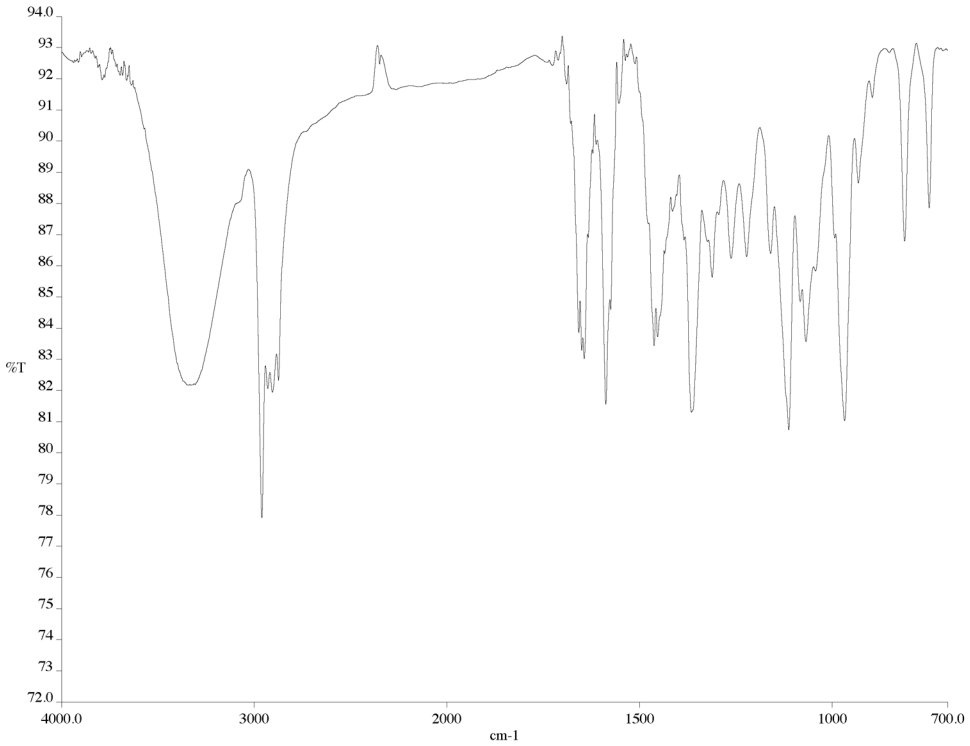


Figure A3.8 Infrared spectrum (thin film/NaCl) of compound **416**.

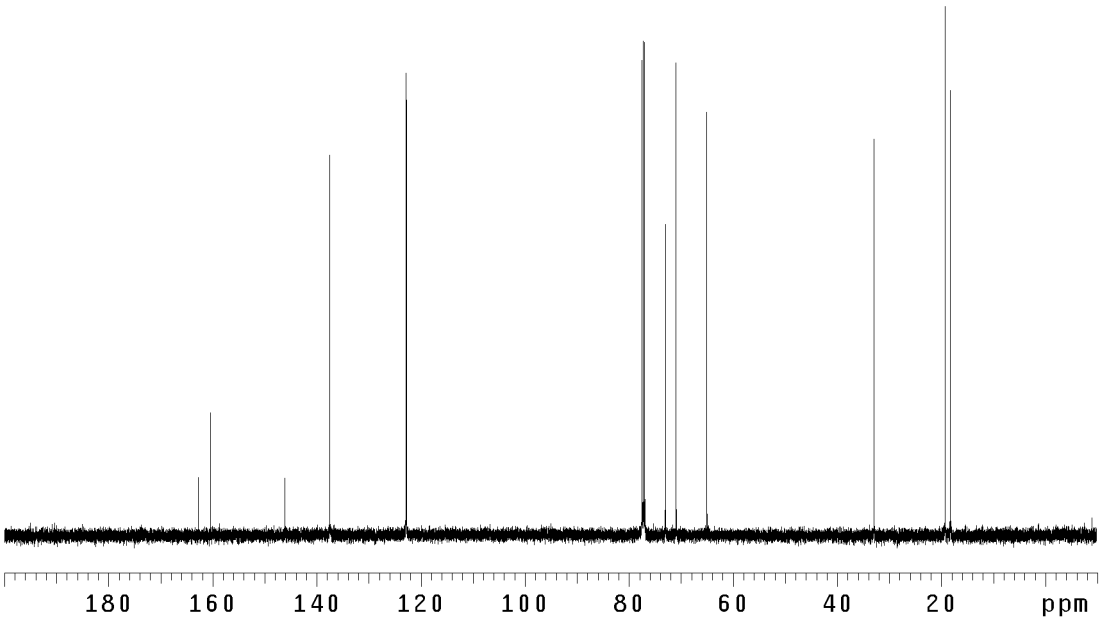


Figure A3.9 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **416**.

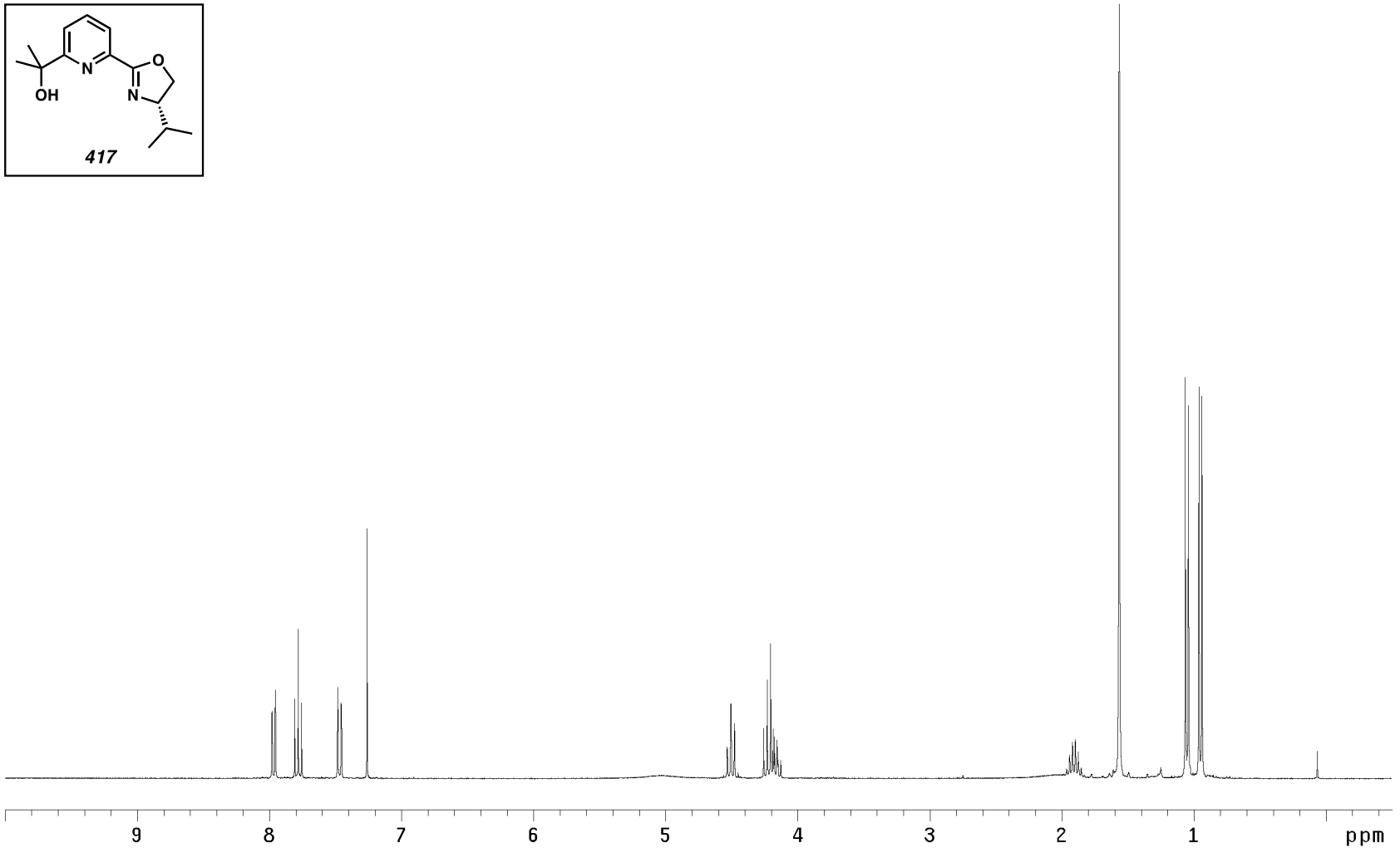


Figure A3.10 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **417**.

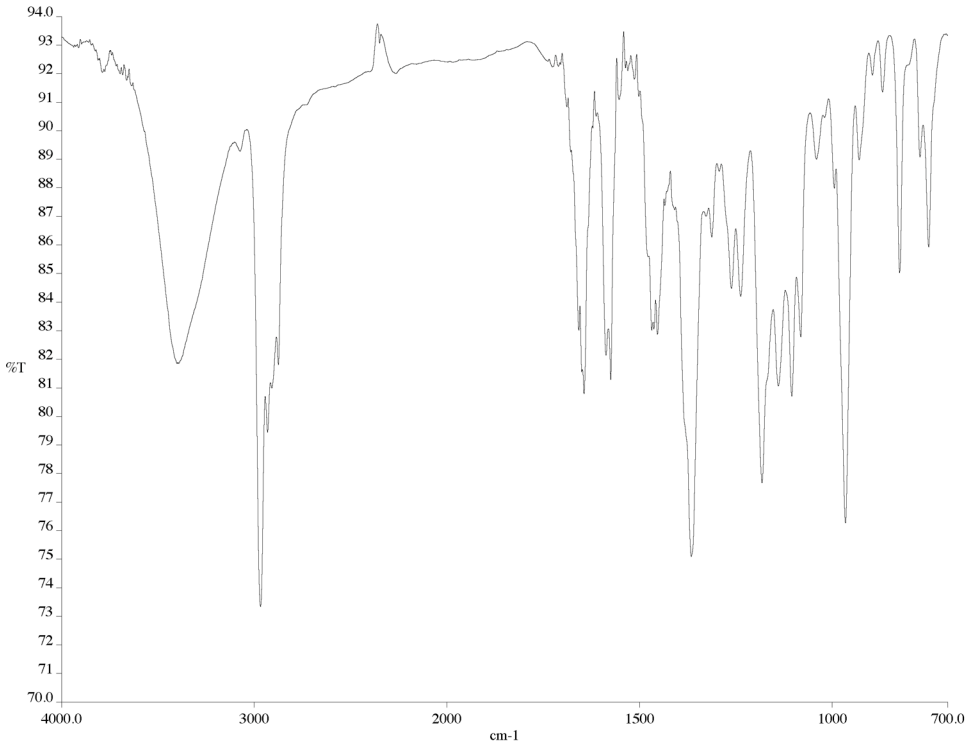


Figure A3.11 Infrared spectrum (thin film/NaCl) of compound **417**.

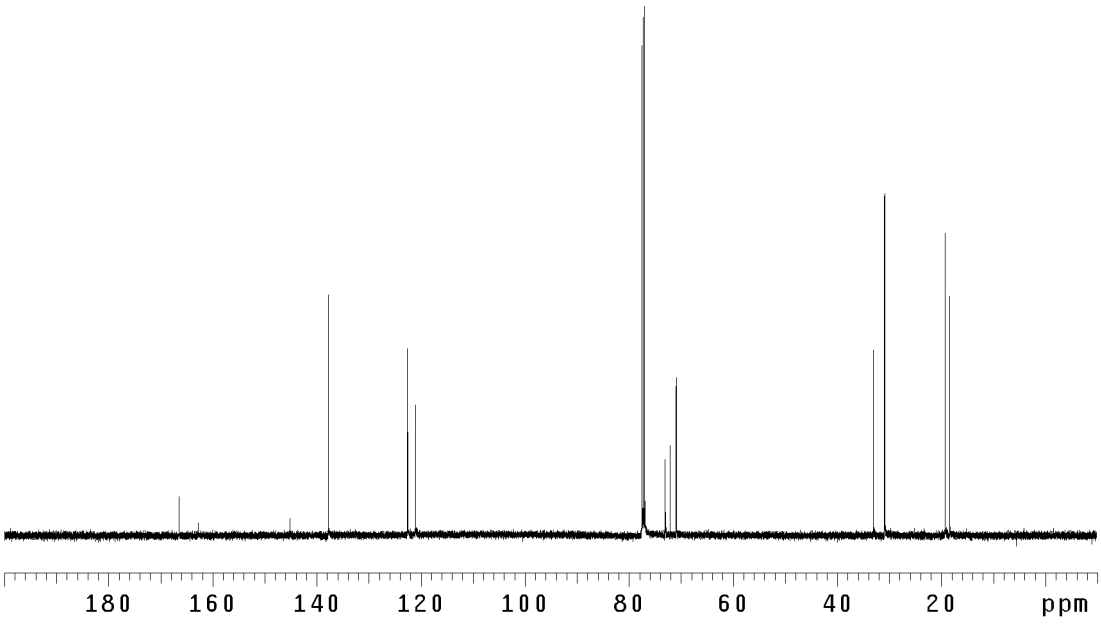


Figure A3.12 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **417**.

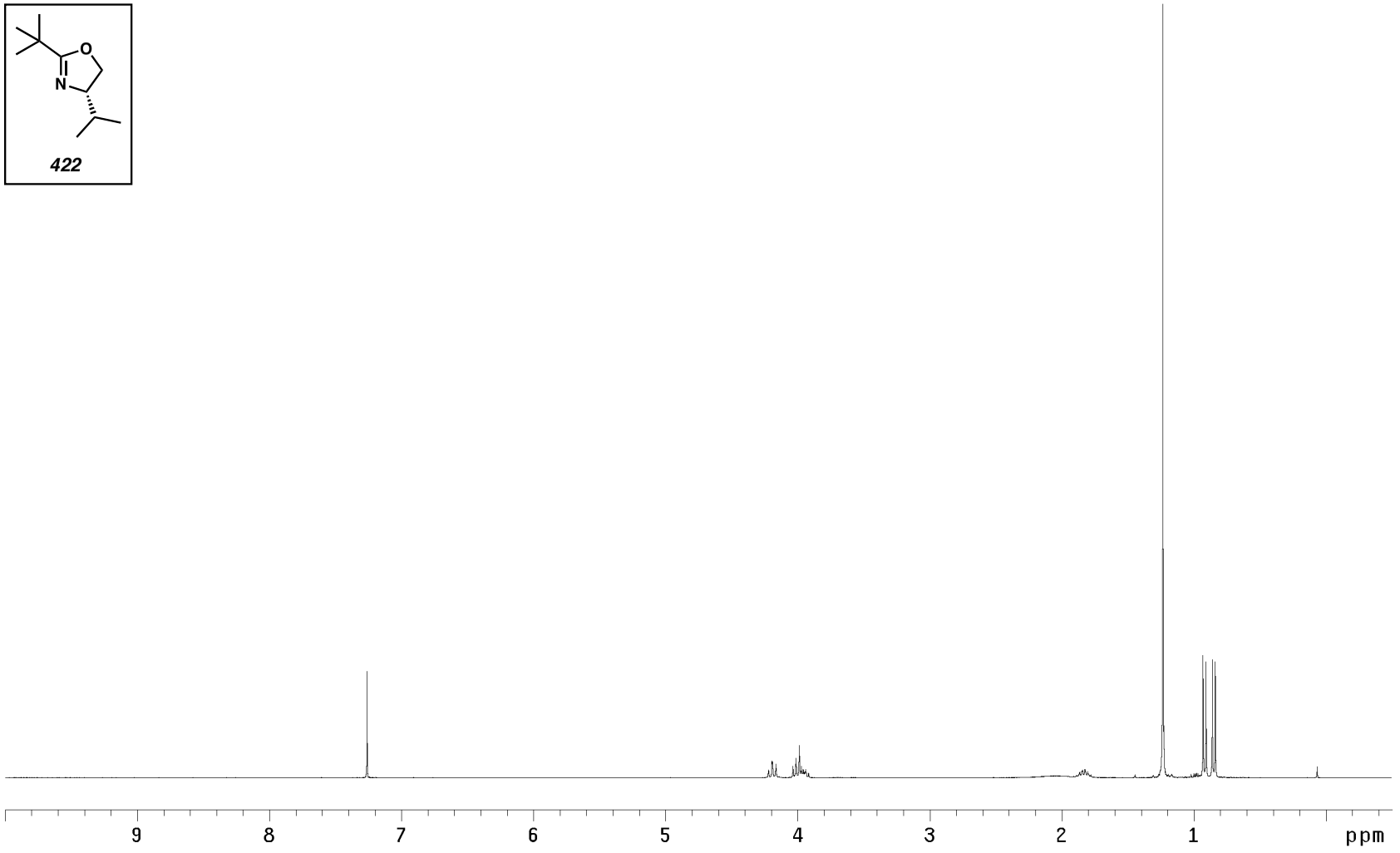


Figure A3.13 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **422**.

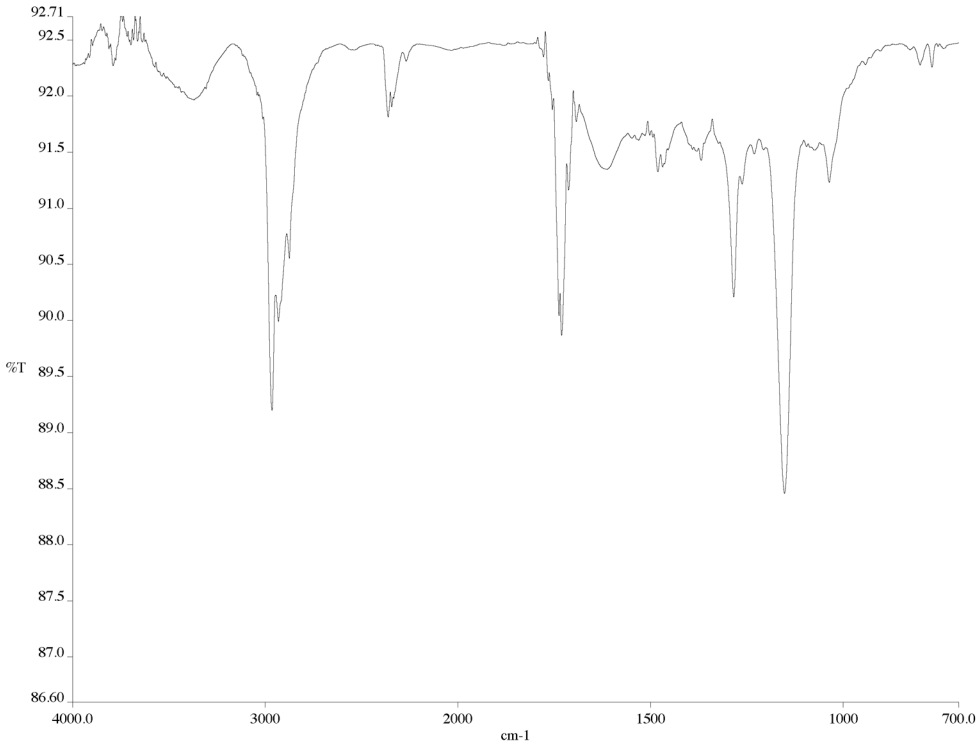


Figure A3.14 Infrared spectrum (thin film/NaCl) of compound **422**.

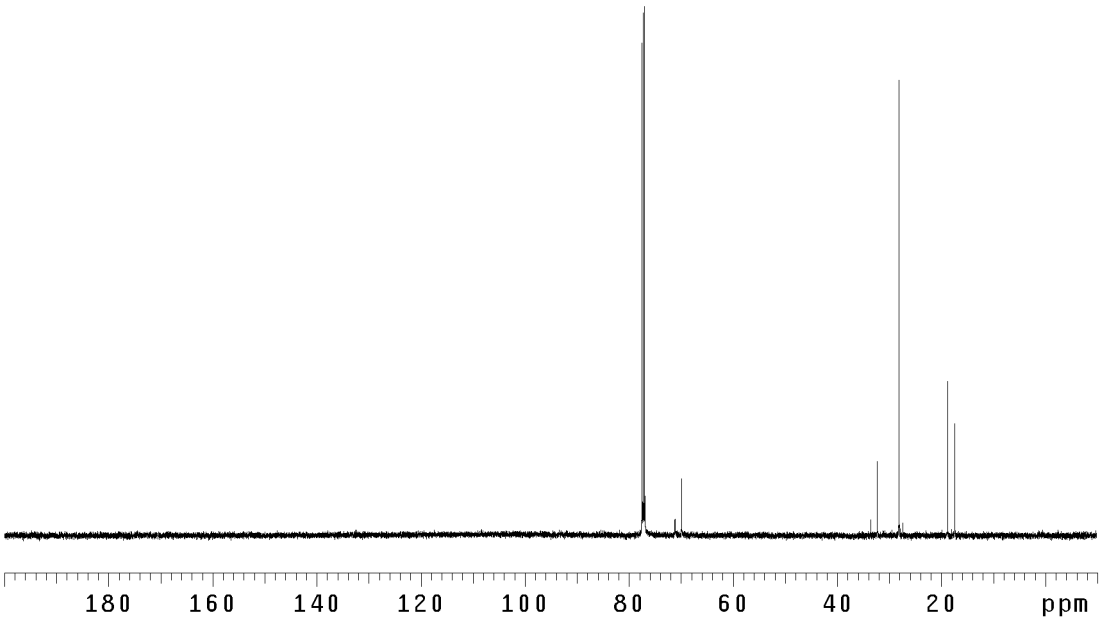


Figure A3.15 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **422**.

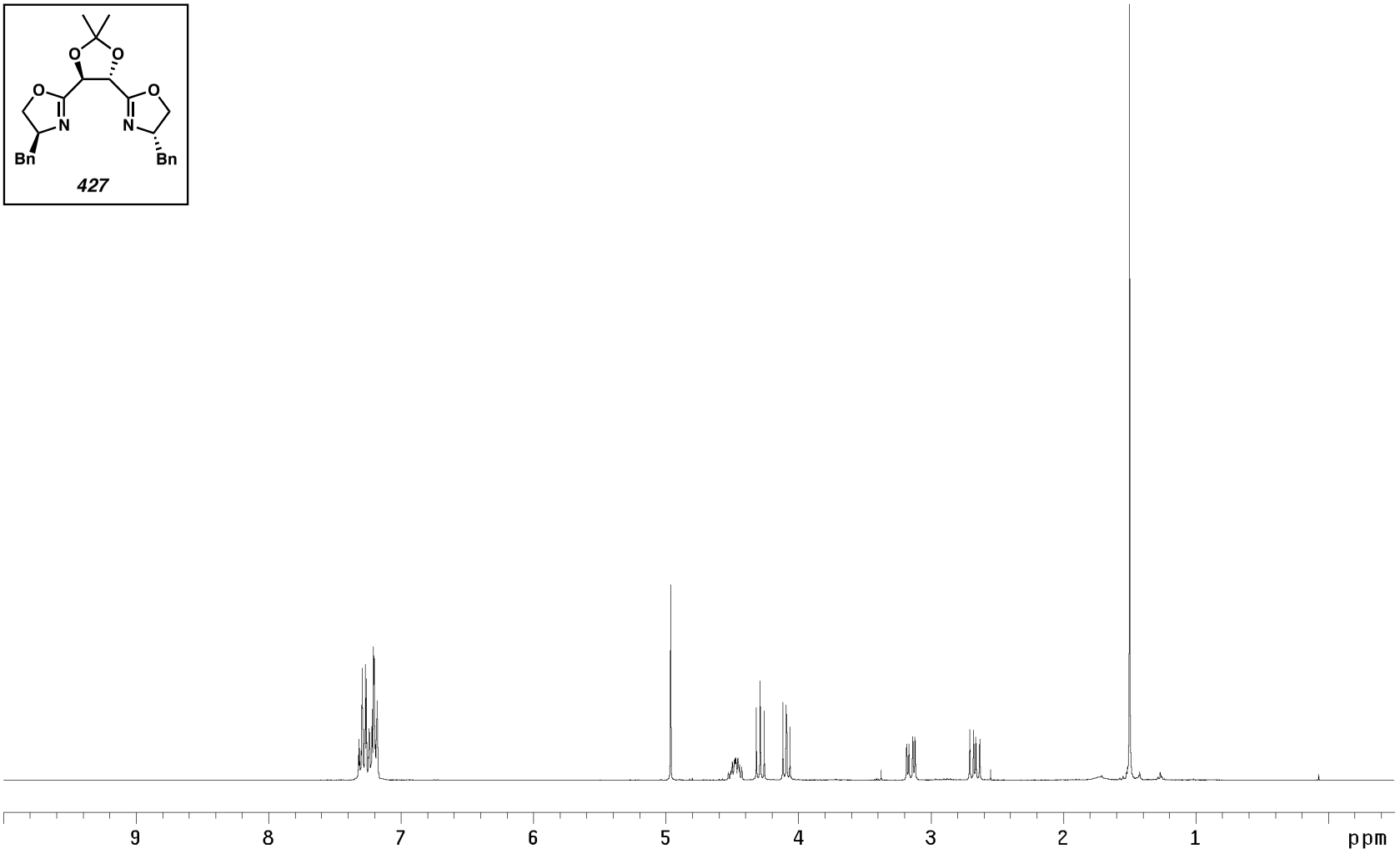


Figure A3.16 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **427**.

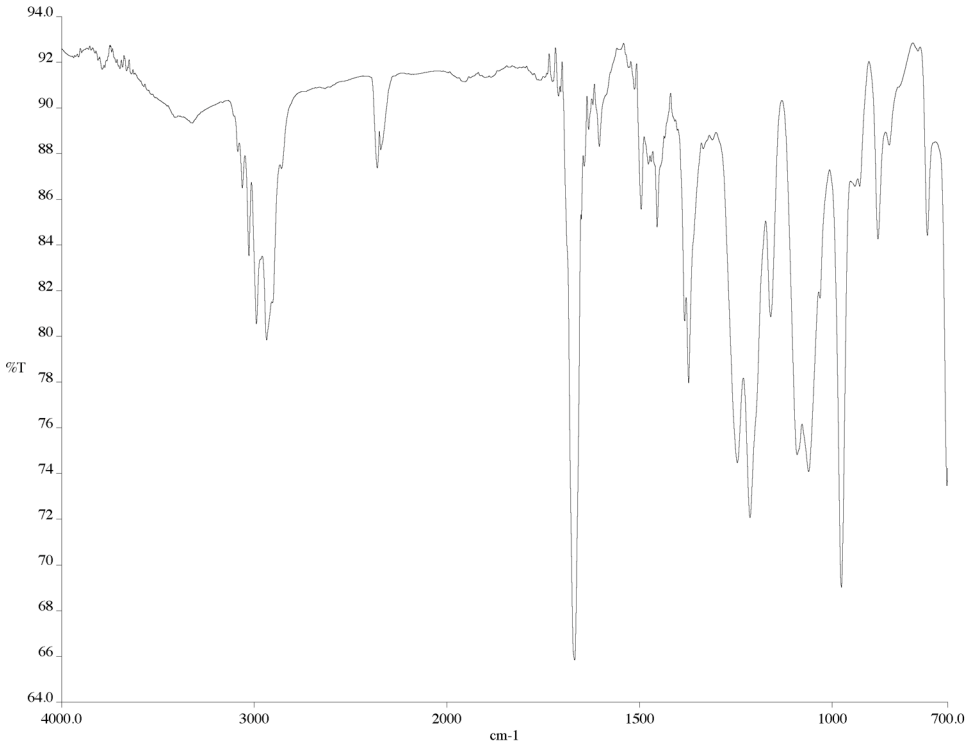


Figure A3.17 Infrared spectrum (thin film/NaCl) of compound **427**.

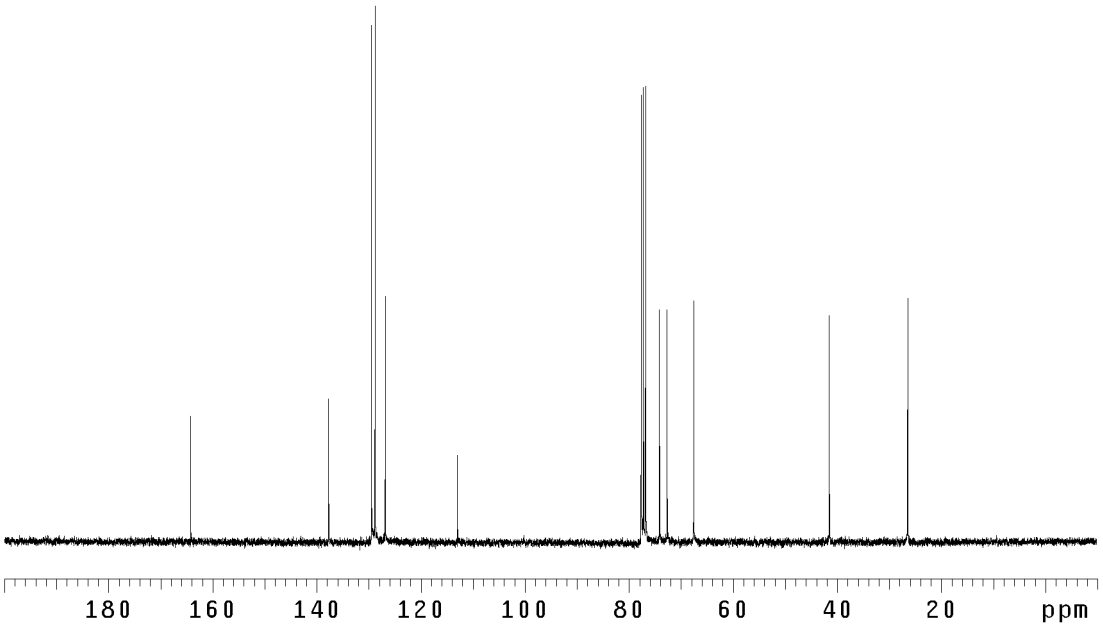


Figure A3.18 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **427**.

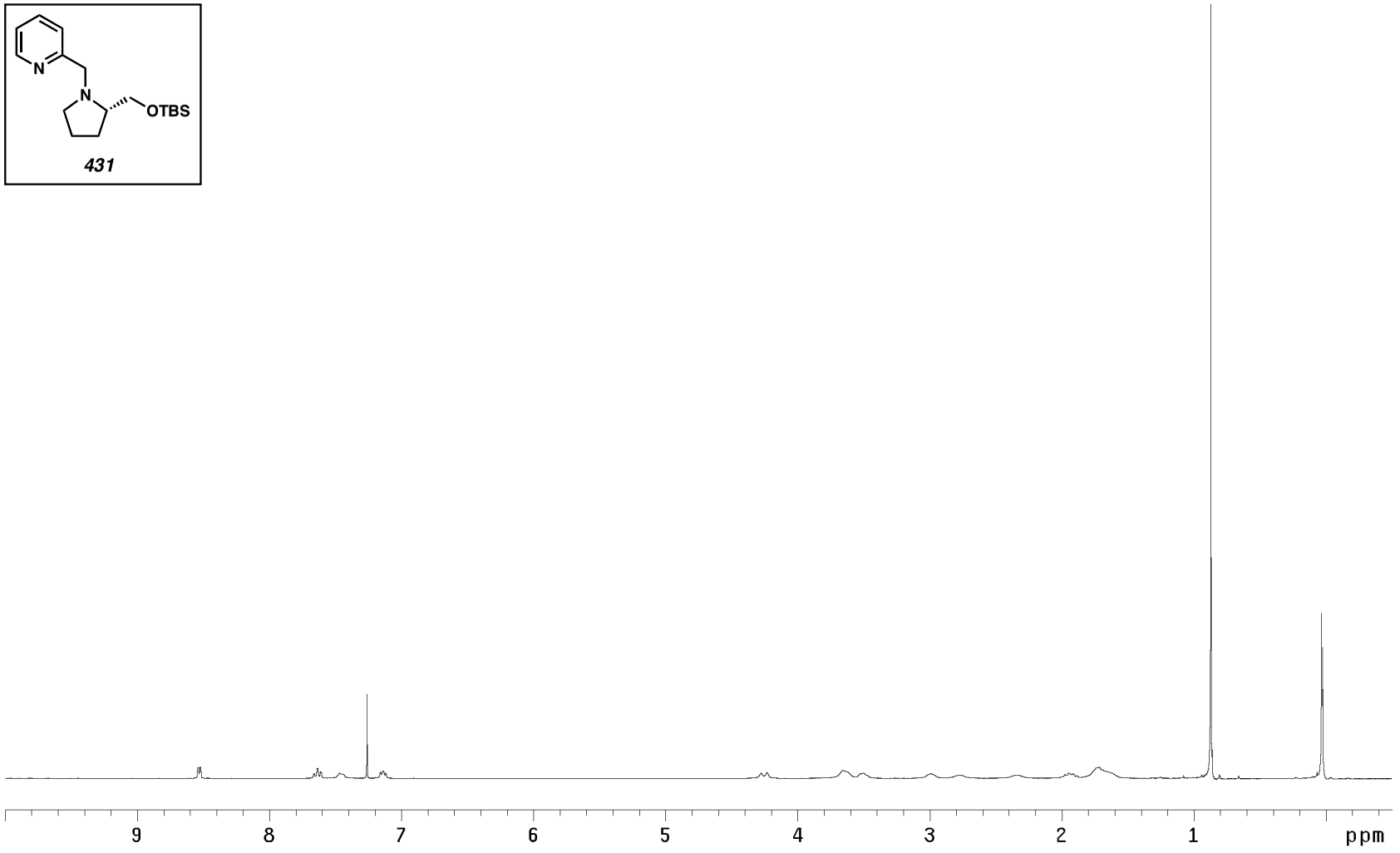


Figure A3.19 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **431**.

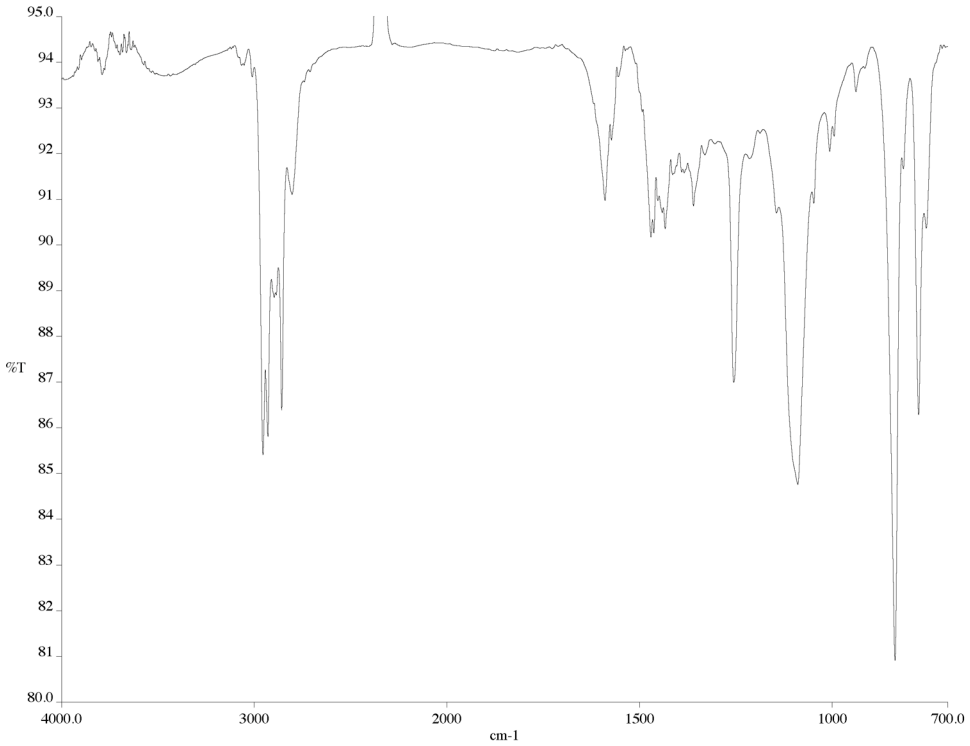


Figure A3.20 Infrared spectrum (thin film/NaCl) of compound **431**.

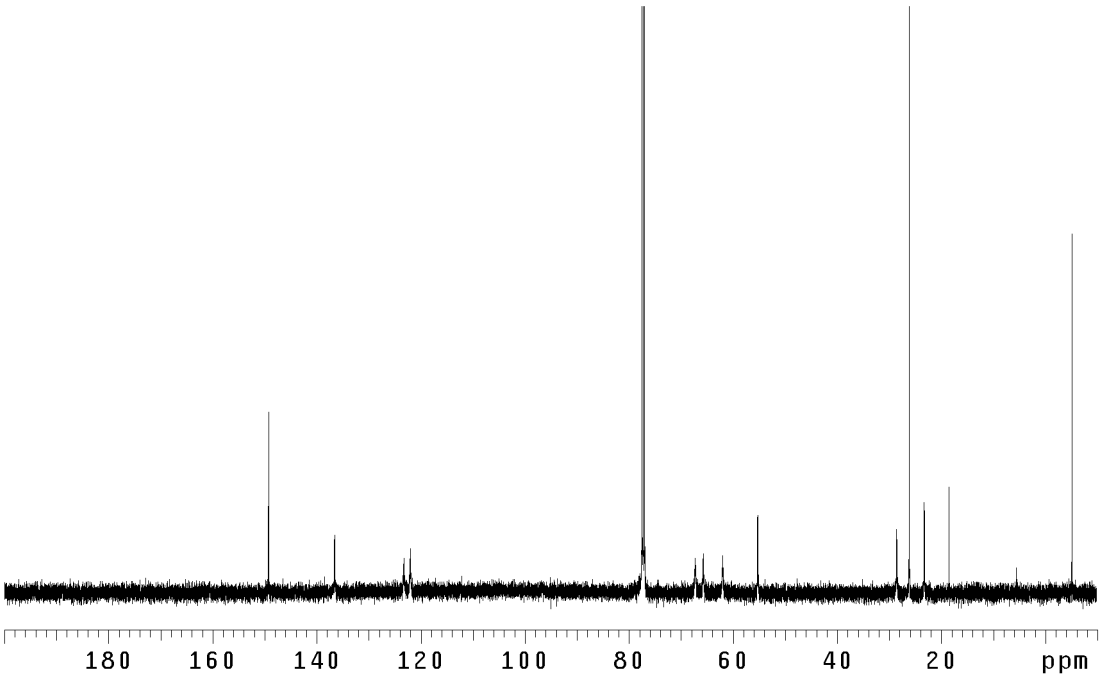


Figure A3.21 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **431**.

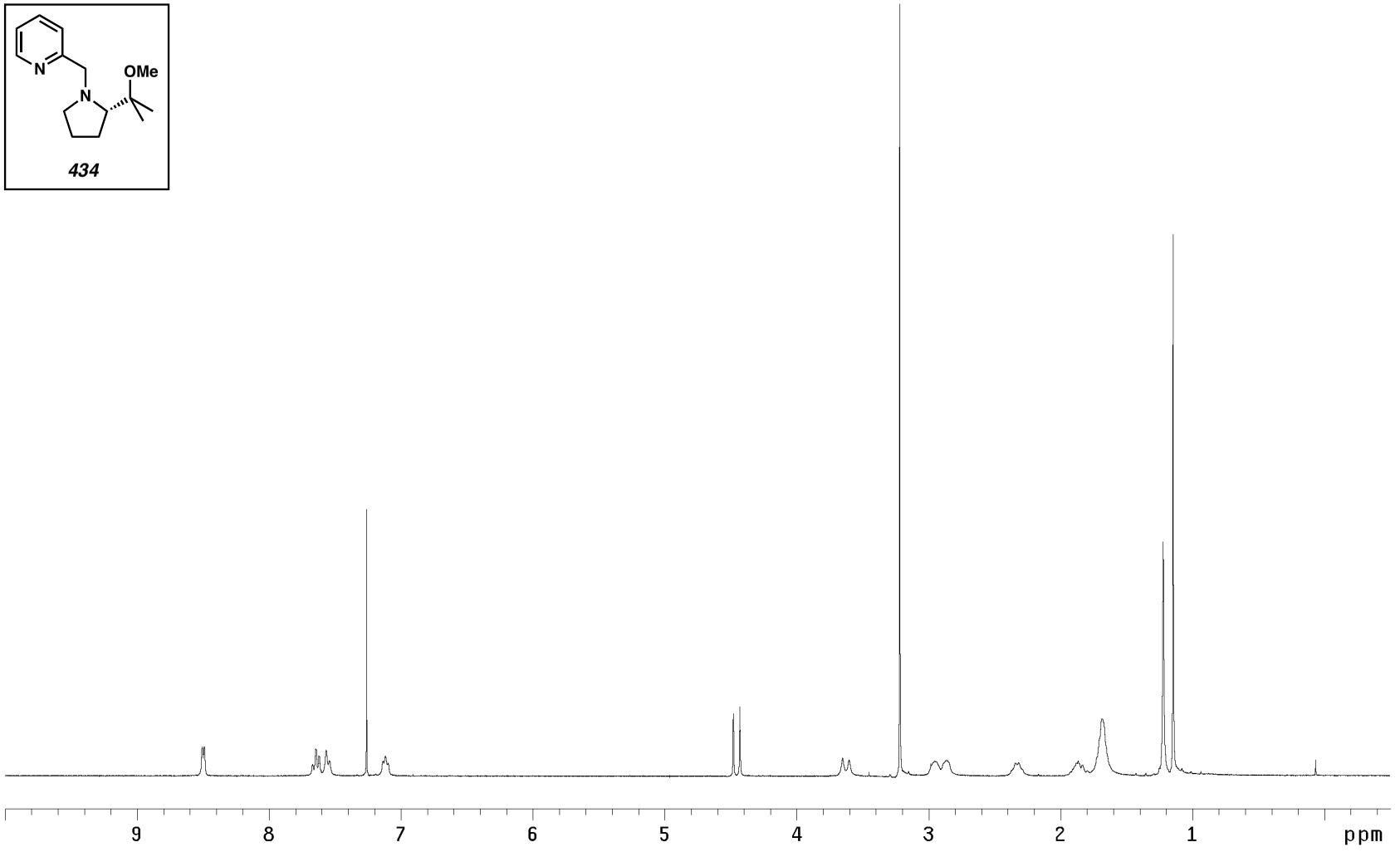


Figure A3.22 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **434**.

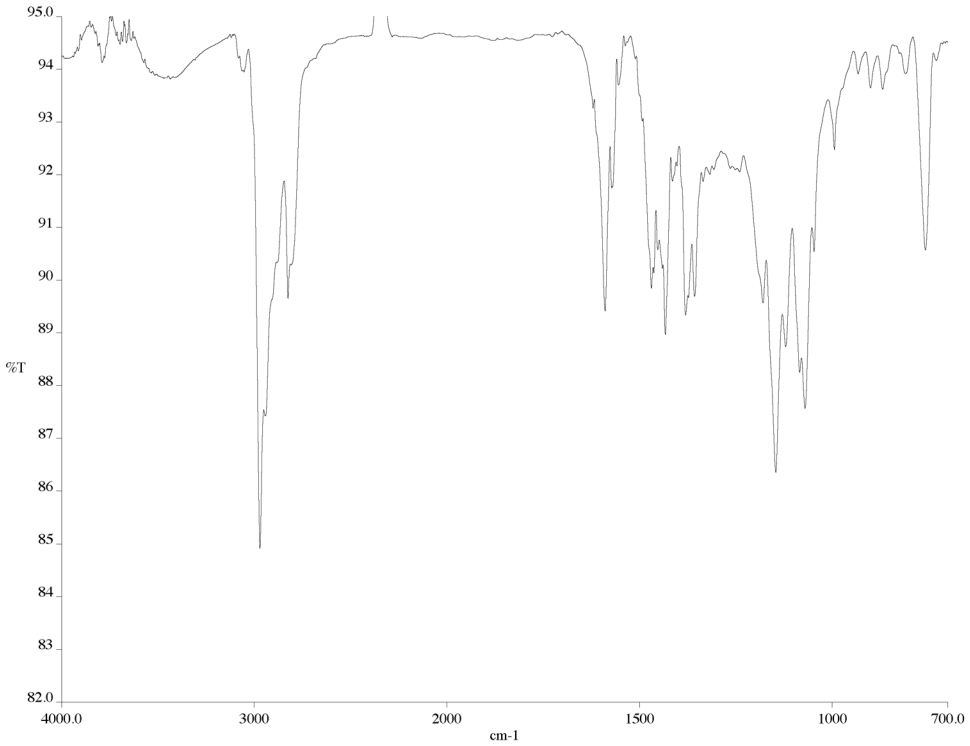


Figure A3.23 Infrared spectrum (thin film/NaCl) of compound **434**.

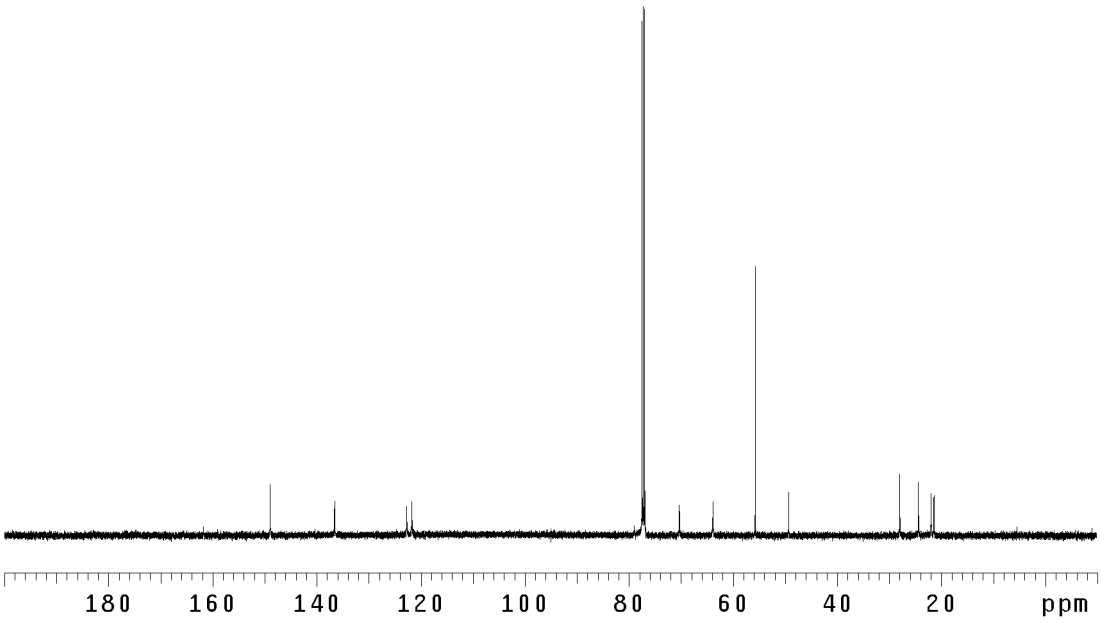


Figure A3.24 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **434**.

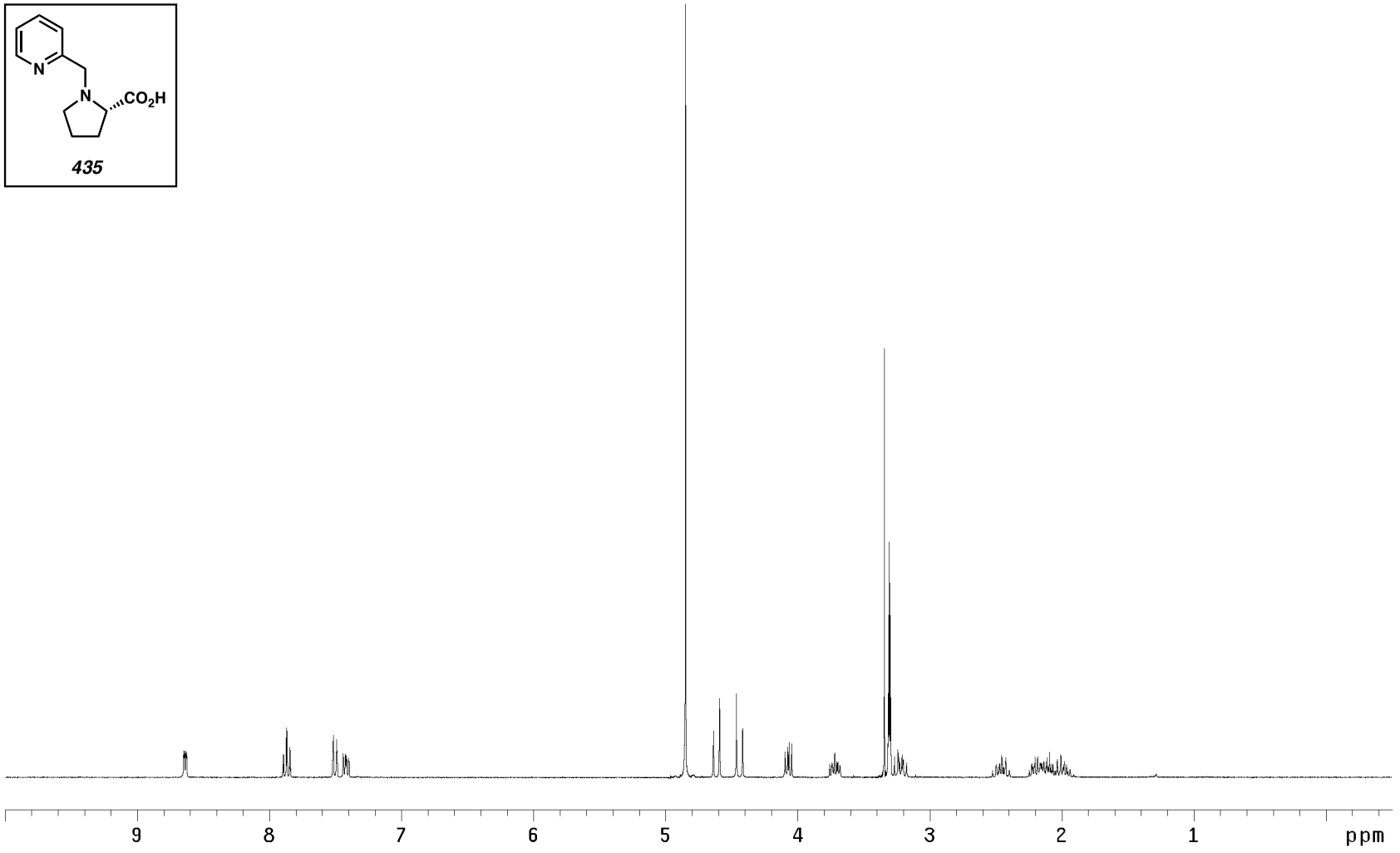


Figure A3.25 ^{1}H NMR (300 MHz, CD_3OD) of compound **435**.

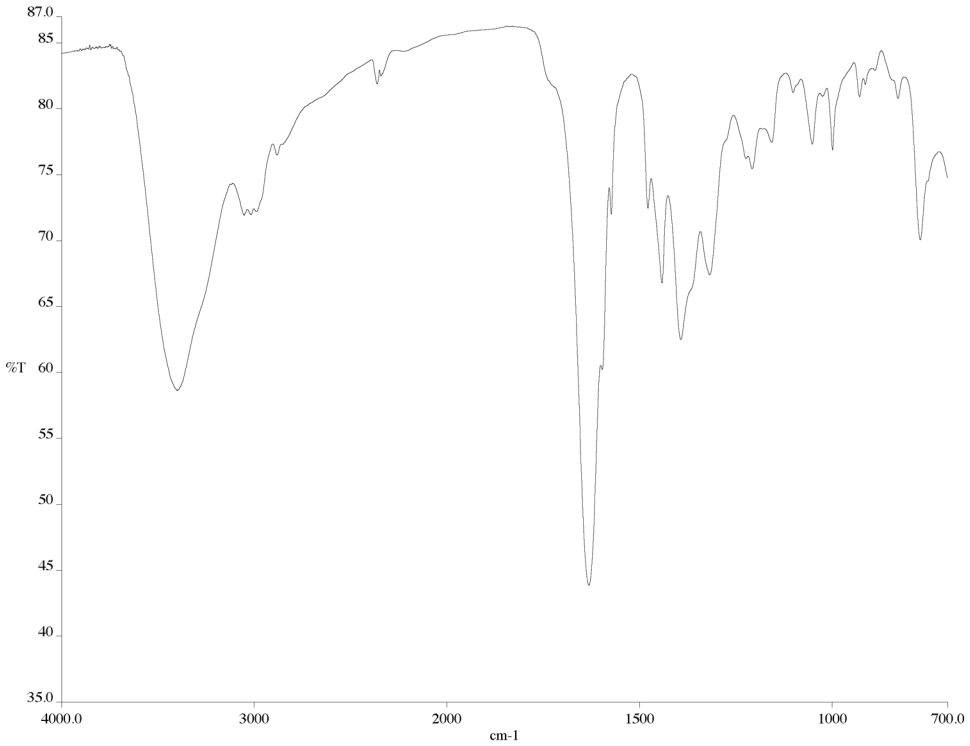


Figure A3.26 Infrared spectrum (thin film/NaCl) of compound **435**.

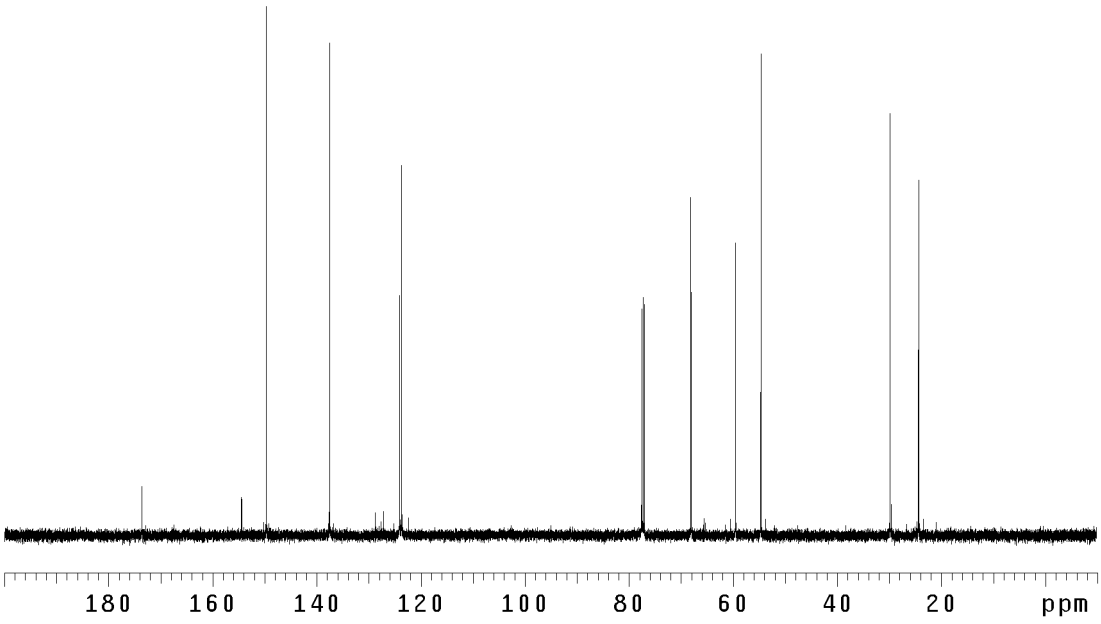


Figure A3.27 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **435**.

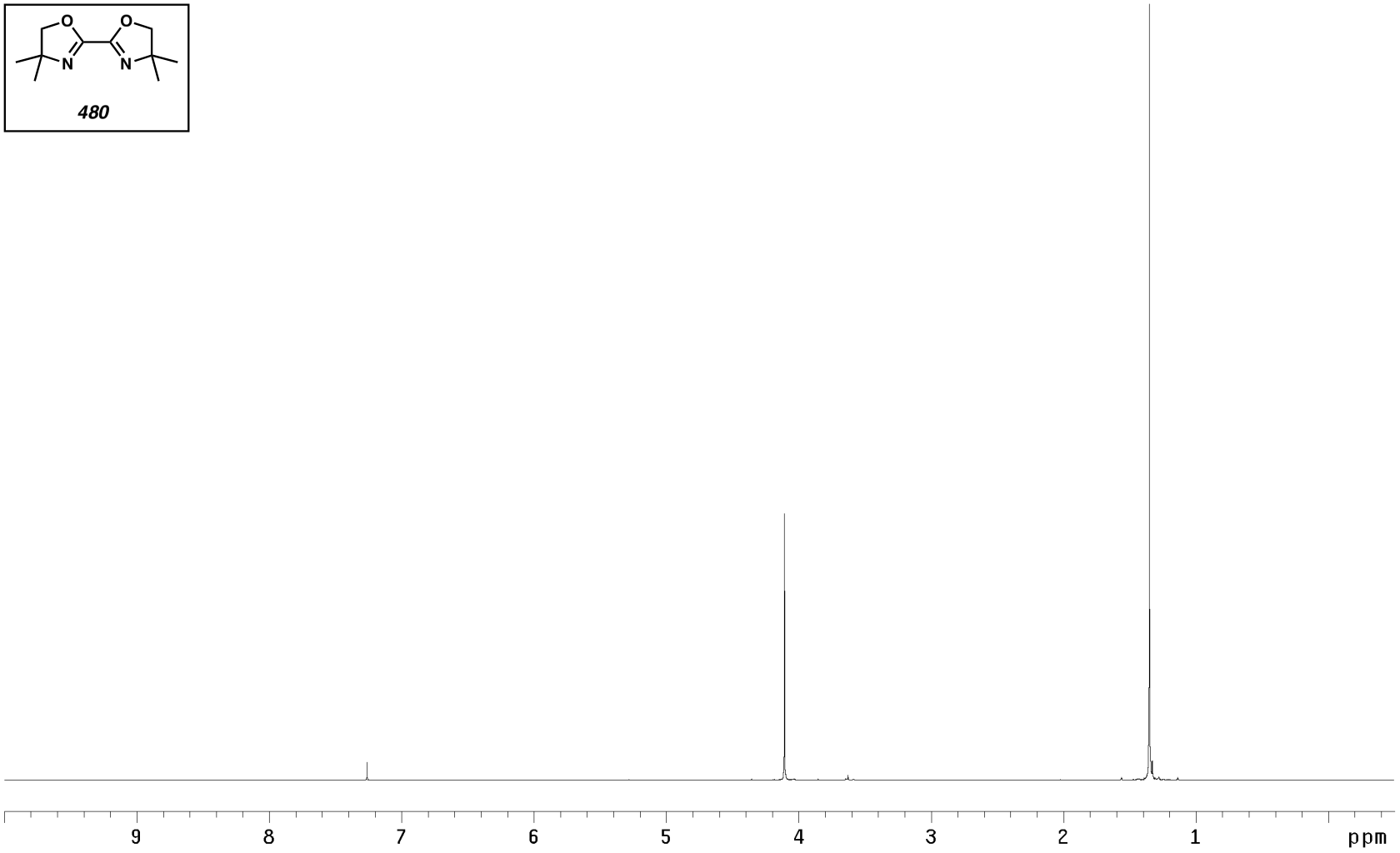


Figure A3.28 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **480**.

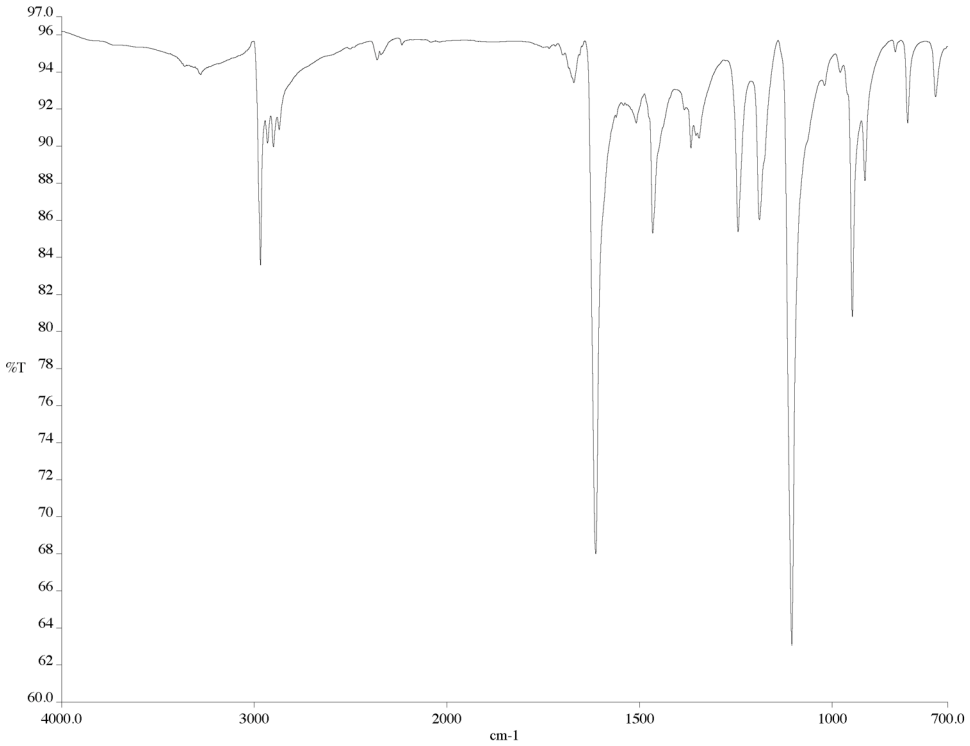


Figure A3.29 Infrared spectrum (thin film/NaCl) of compound **480**.

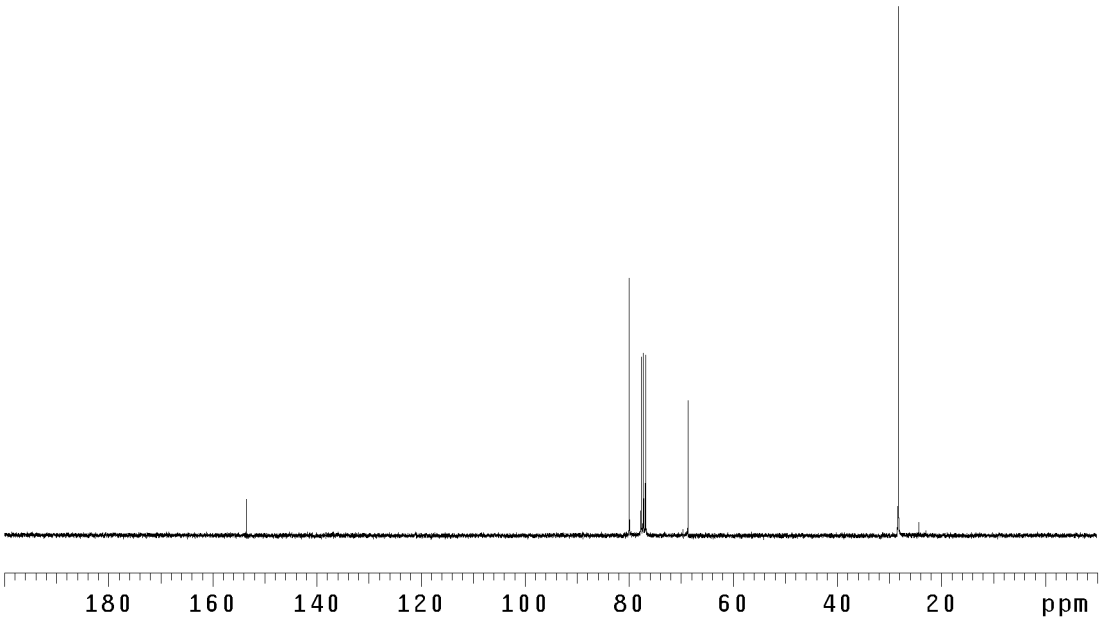


Figure A3.30 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **480**.

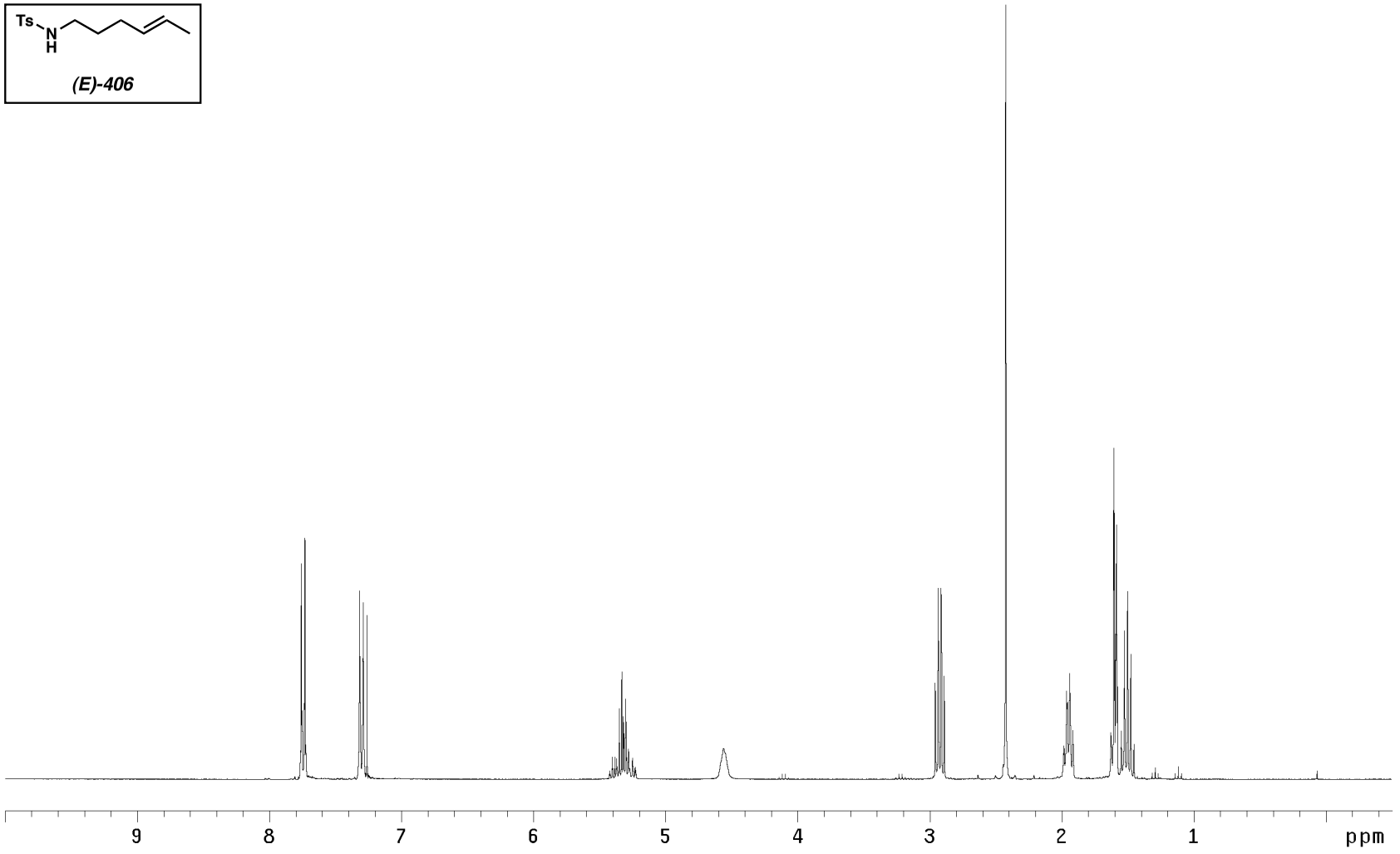


Figure A3.31 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **(*E*)-406**.

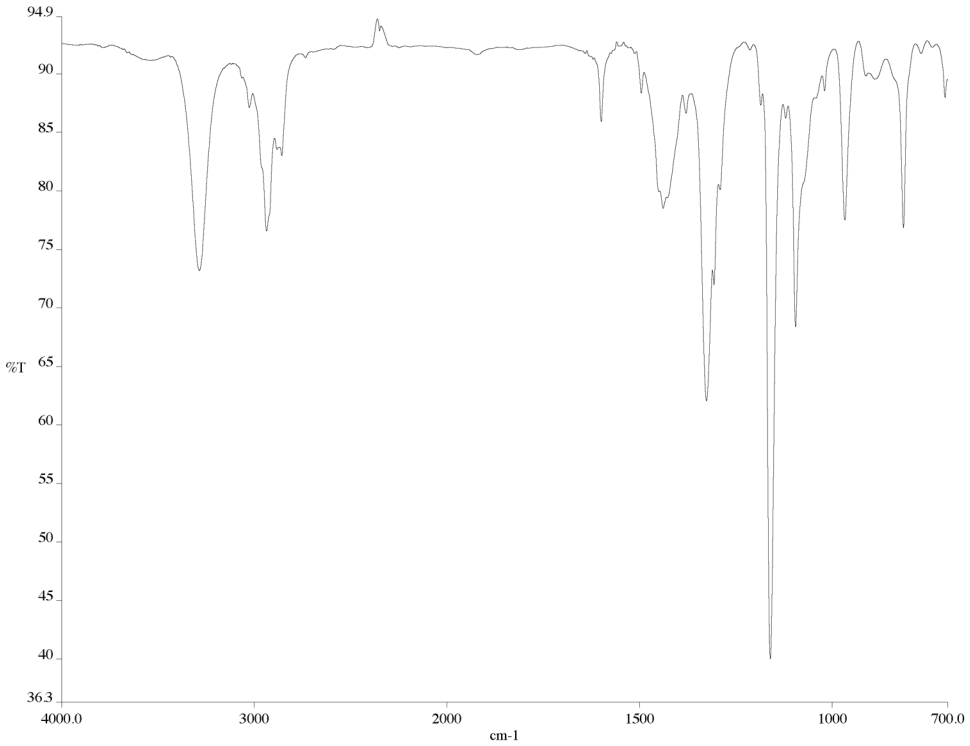


Figure A3.32 Infrared spectrum (thin film/NaCl) of compound **(*E*)-406**.

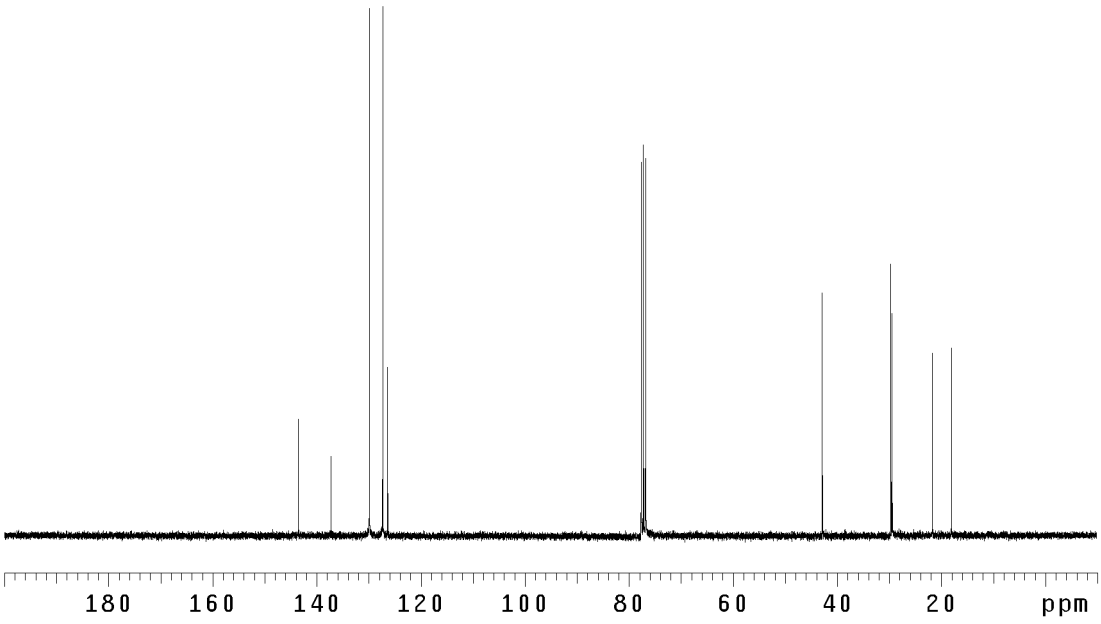


Figure A3.33 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **(*E*)-406**.

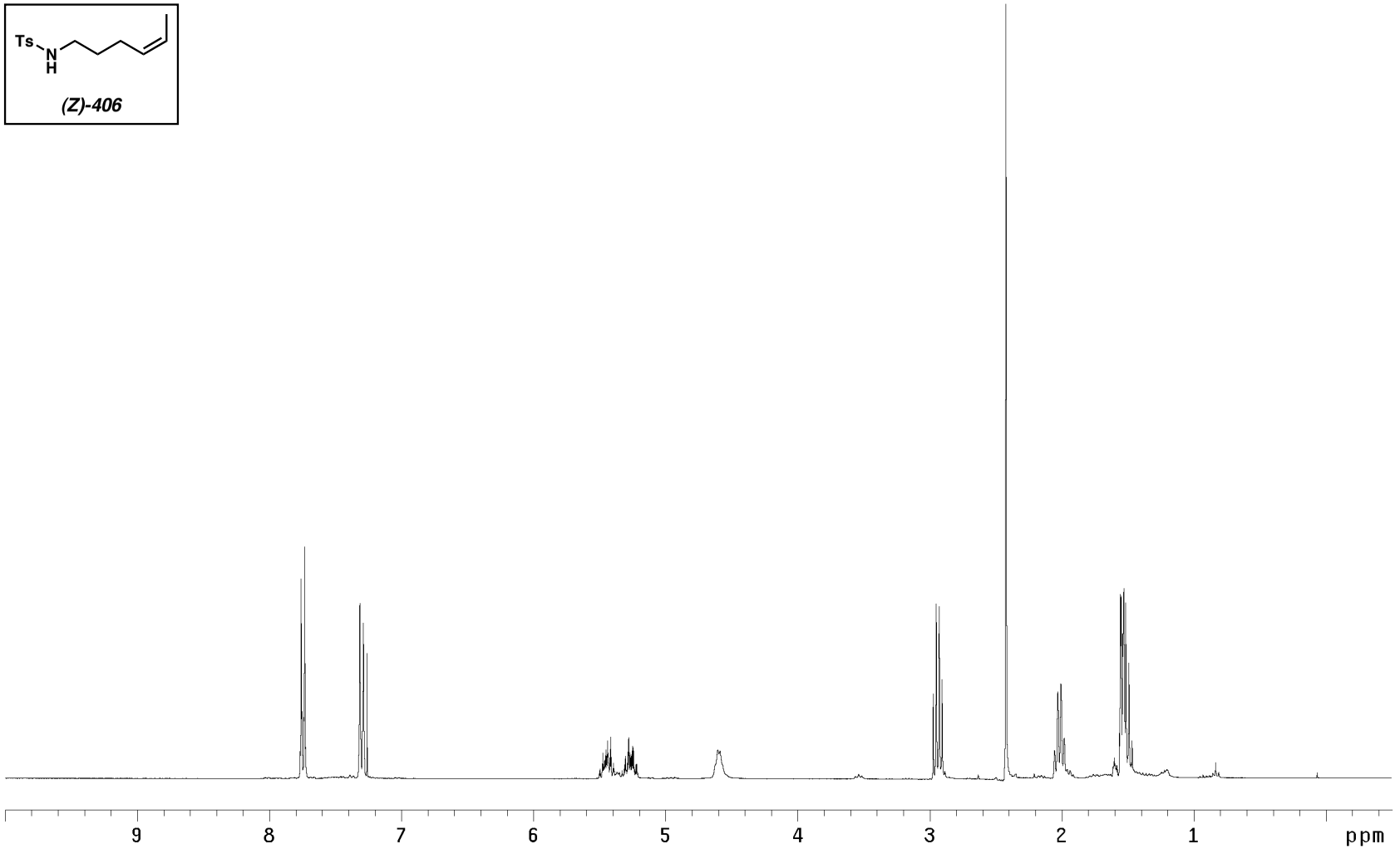


Figure A3.34 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **(*Z*)-406**.

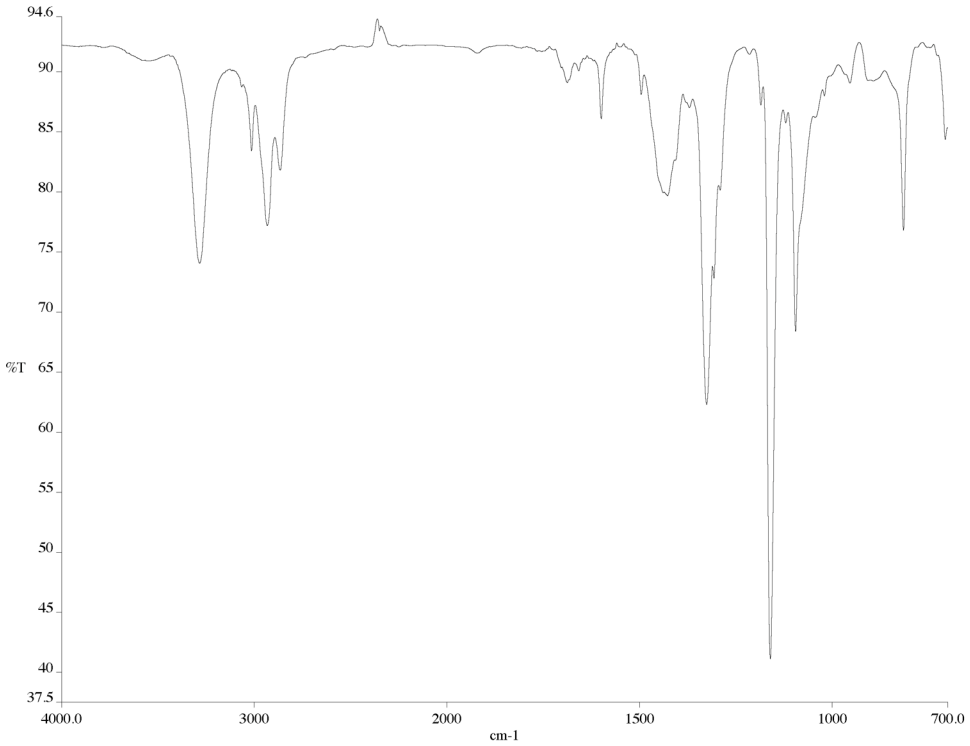


Figure A3.35 Infrared spectrum (thin film/NaCl) of compound **(*Z*)-406**.

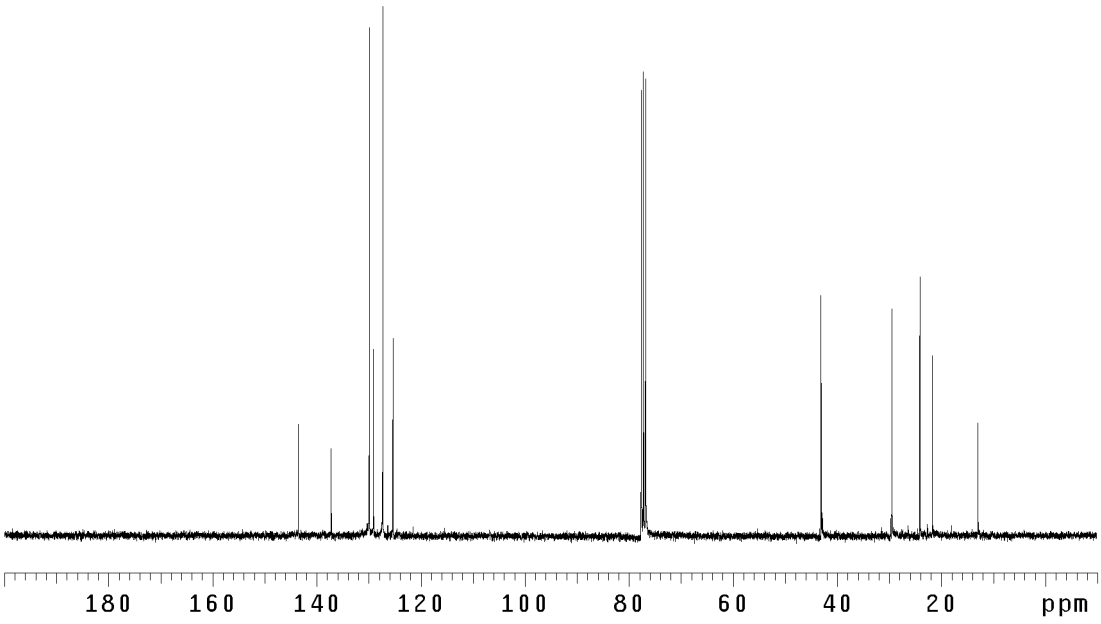


Figure A3.36 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **(*Z*)-406**.

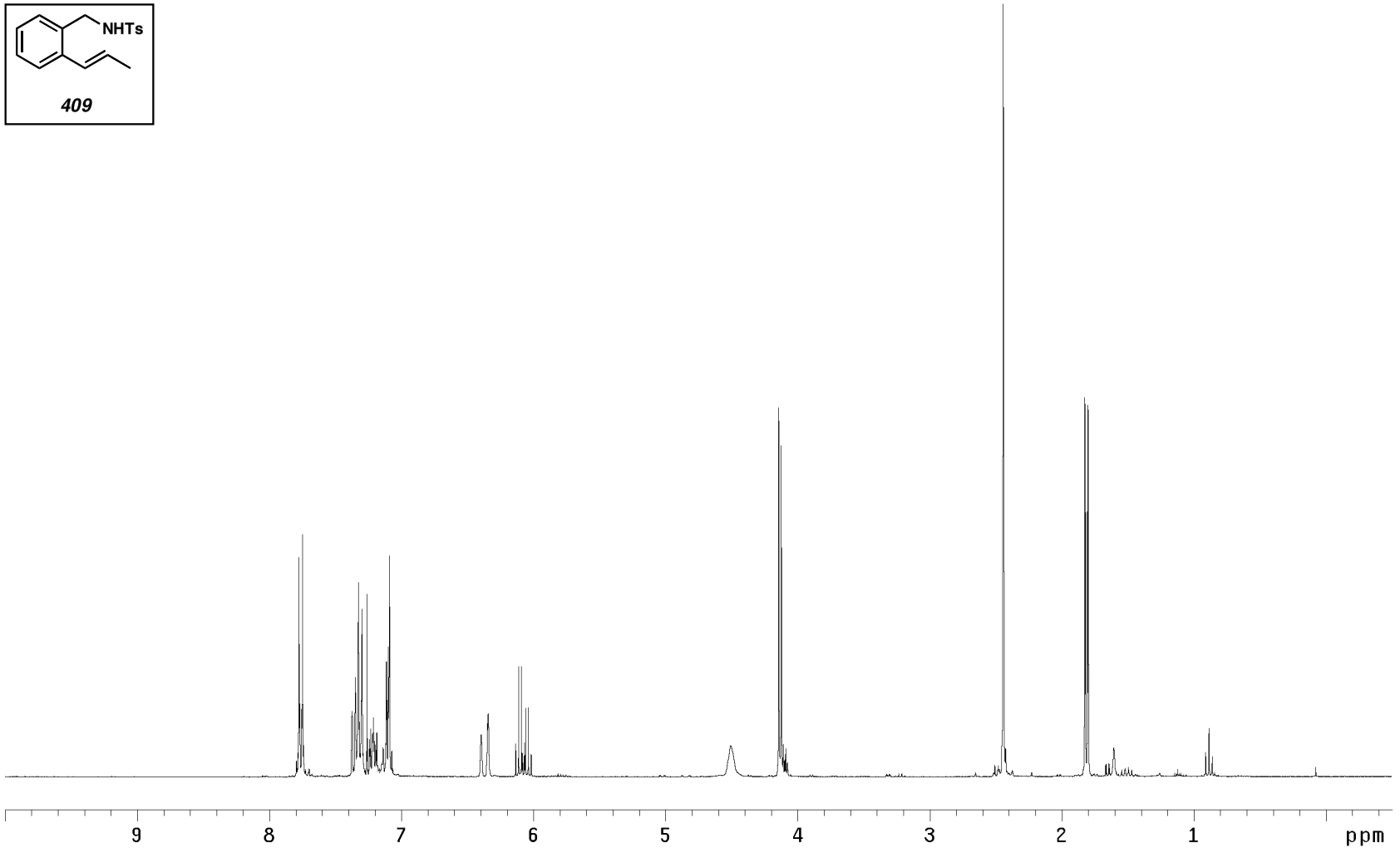


Figure A3.37 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **409**.

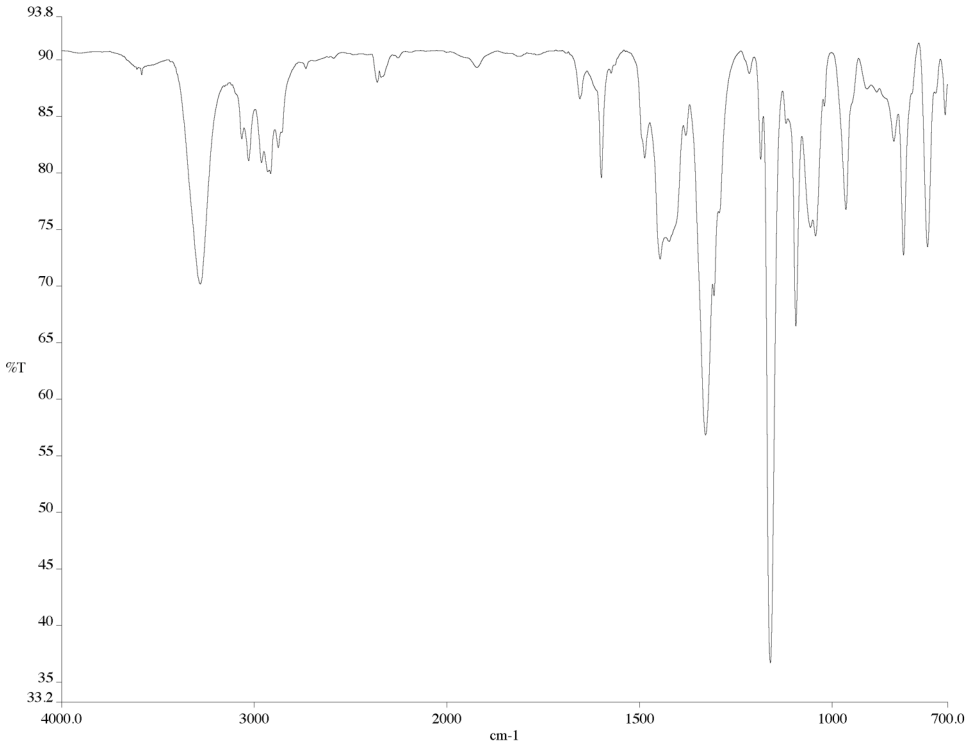


Figure A3.38 Infrared spectrum (thin film/NaCl) of compound **409**.

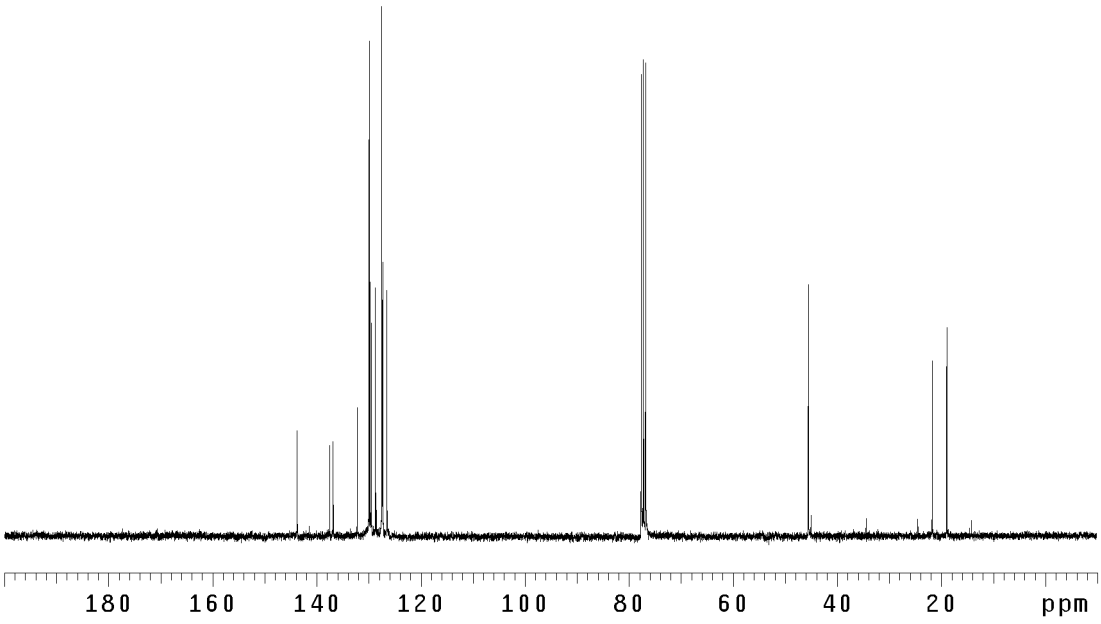


Figure A3.39 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **409**.

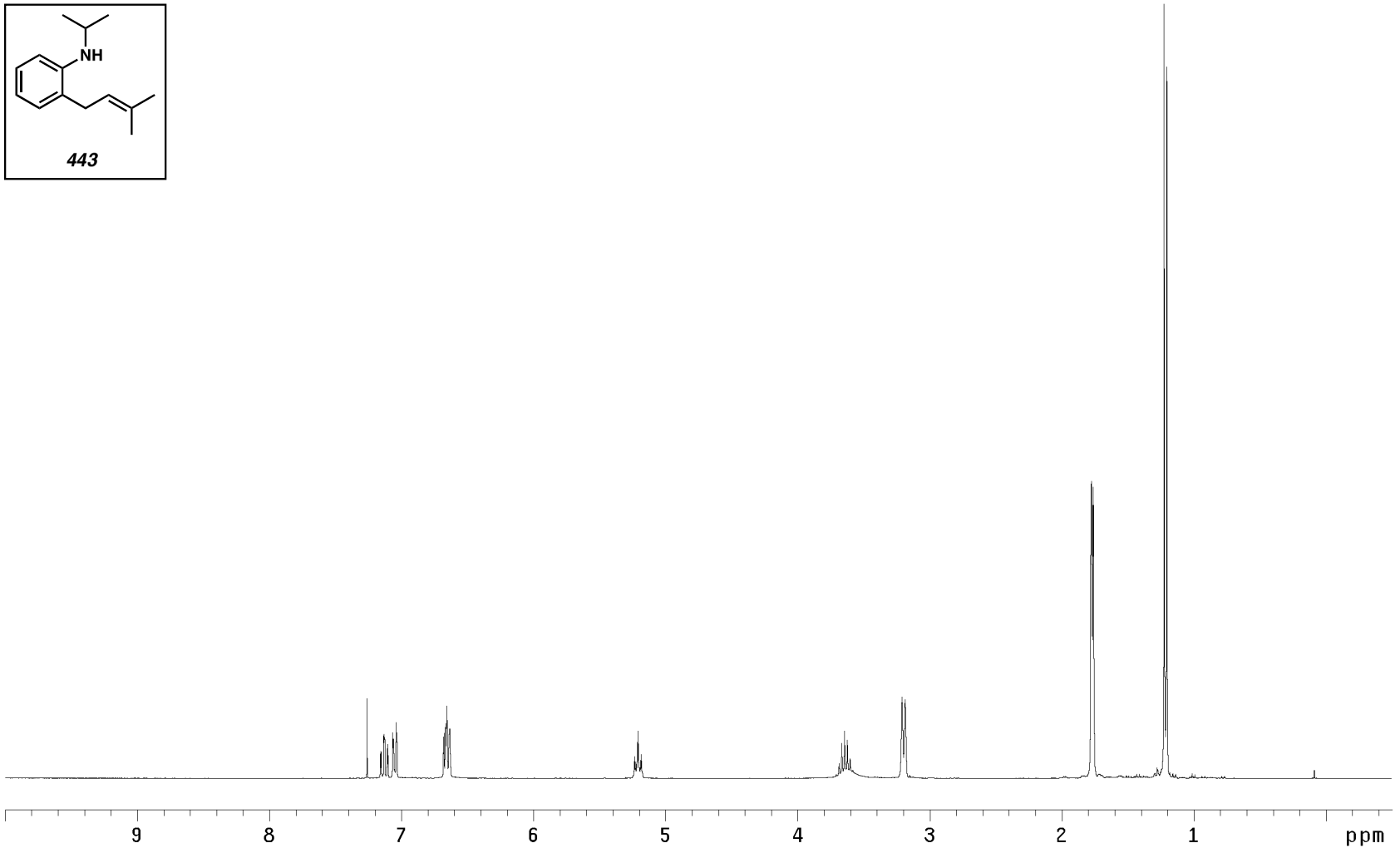


Figure A3.40 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **443**.

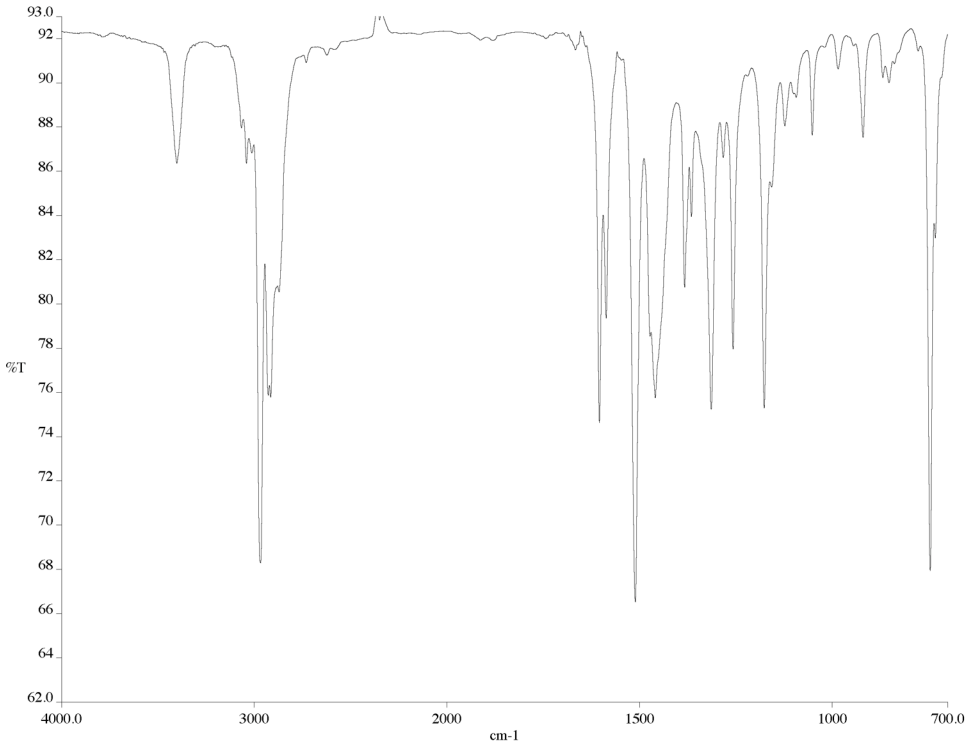


Figure A3.41 Infrared spectrum (thin film/NaCl) of compound **443**.

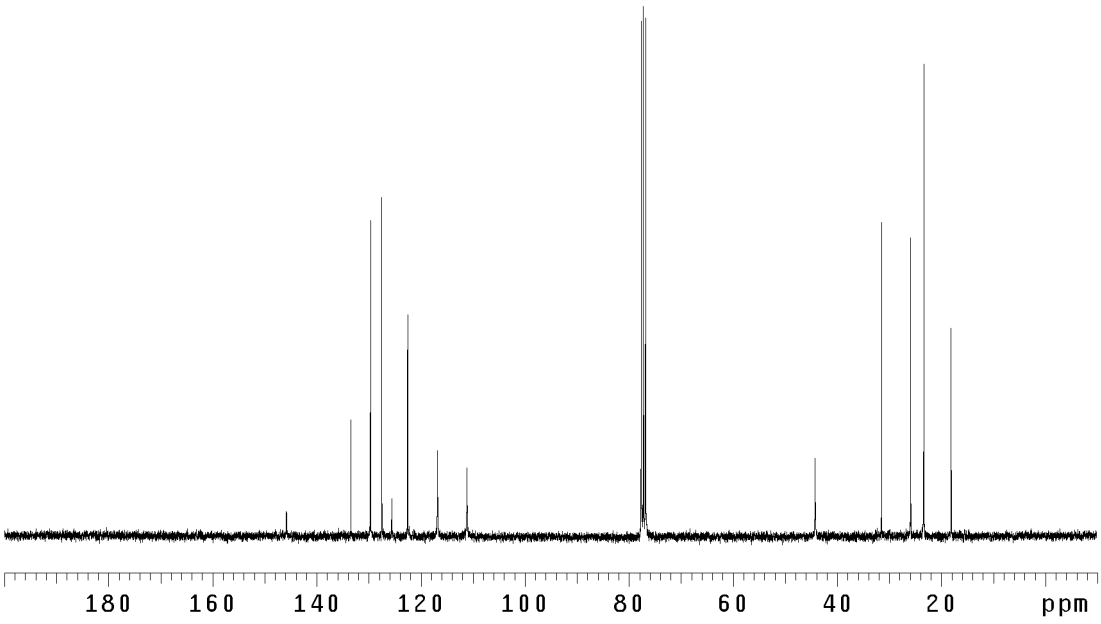


Figure A3.42 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **443**.

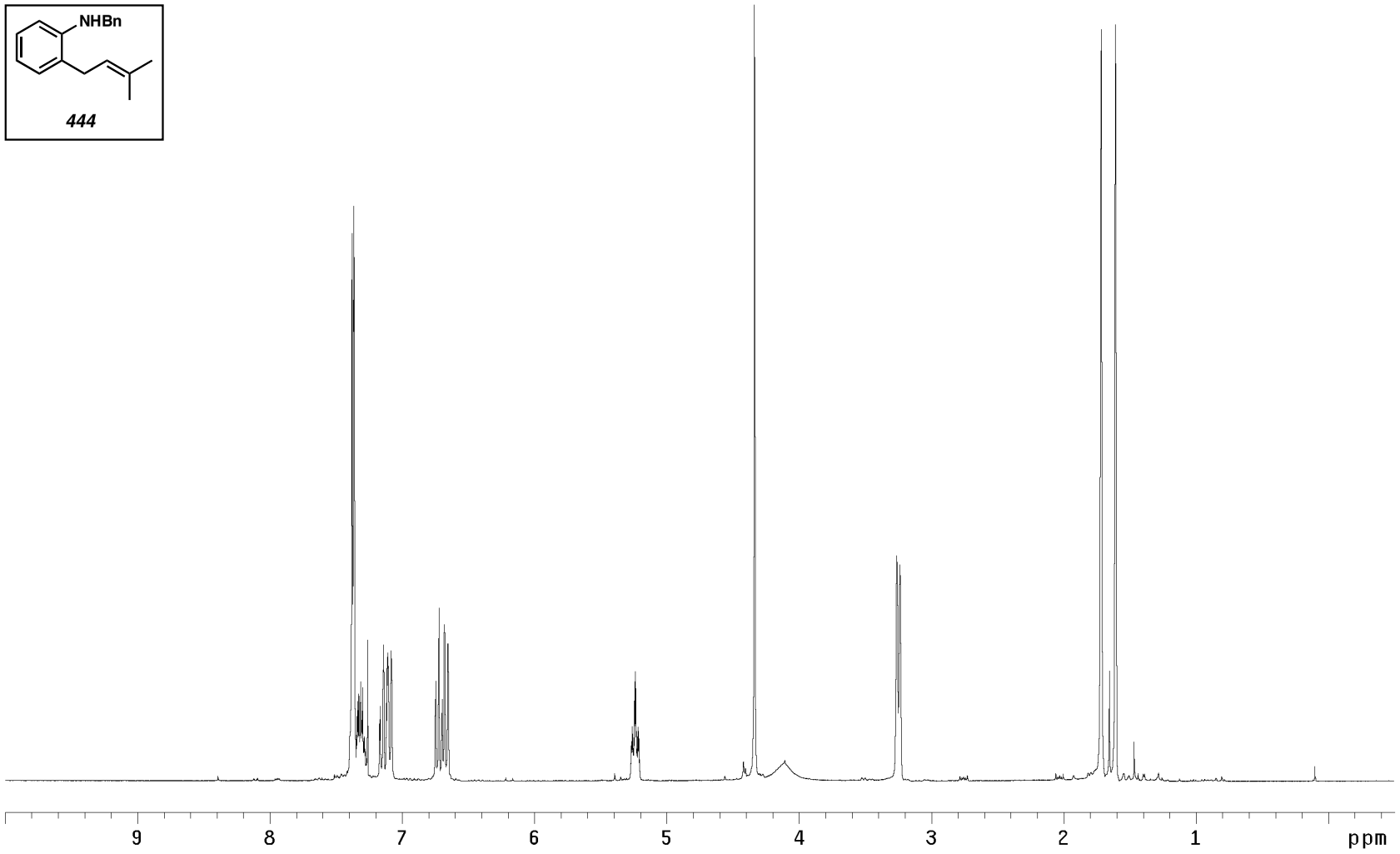


Figure A3.43 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **444**.

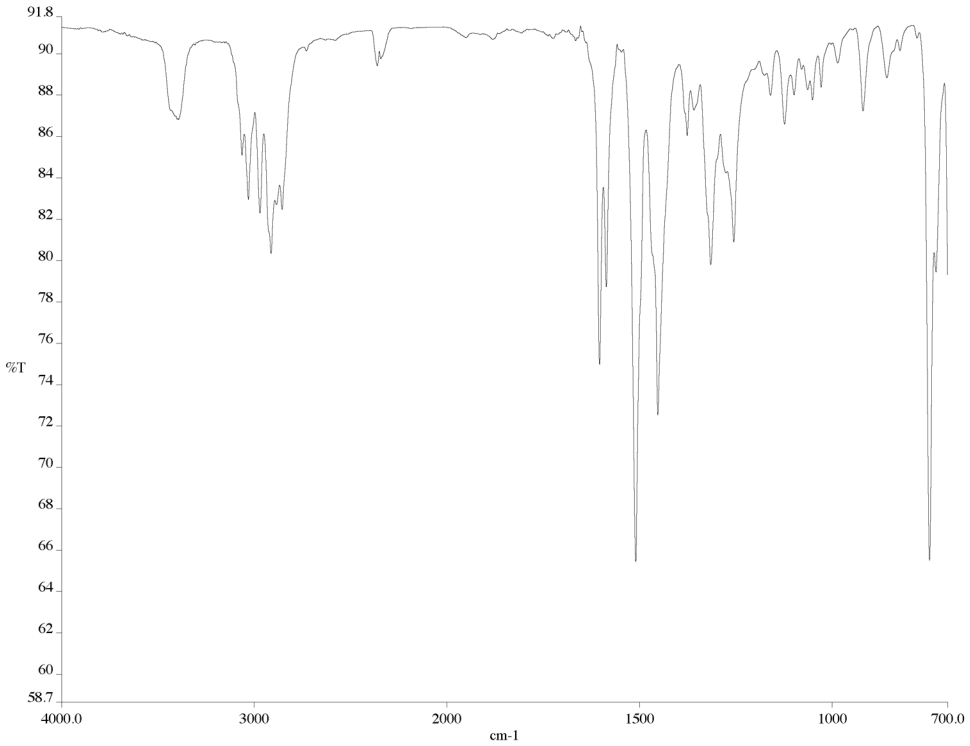


Figure A3.44 Infrared spectrum (thin film/NaCl) of compound **444**.

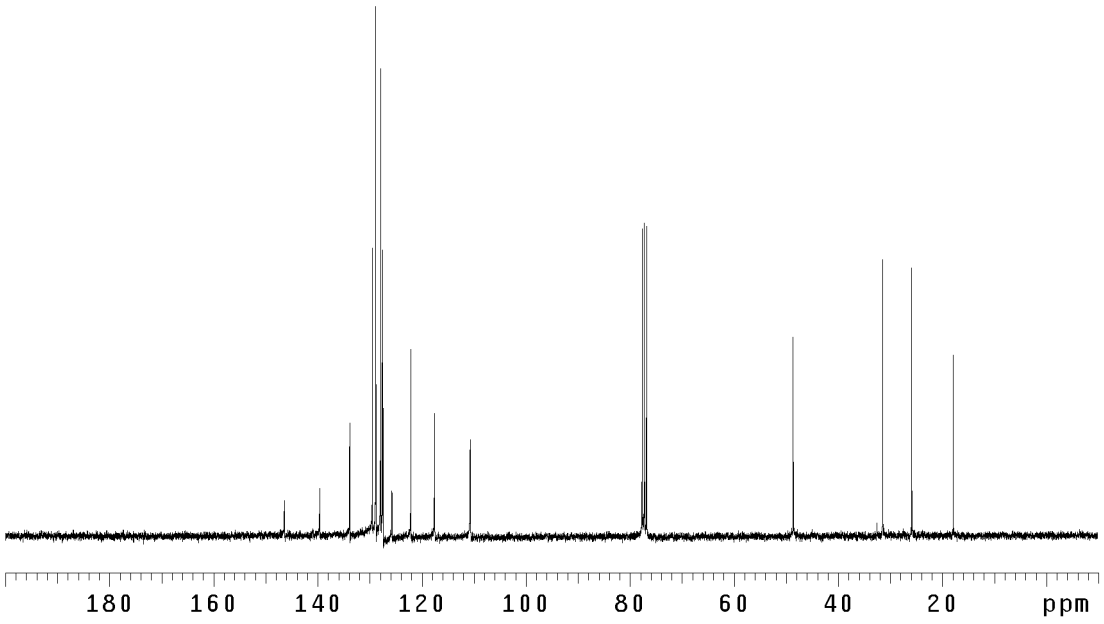


Figure A3.45 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **444**.

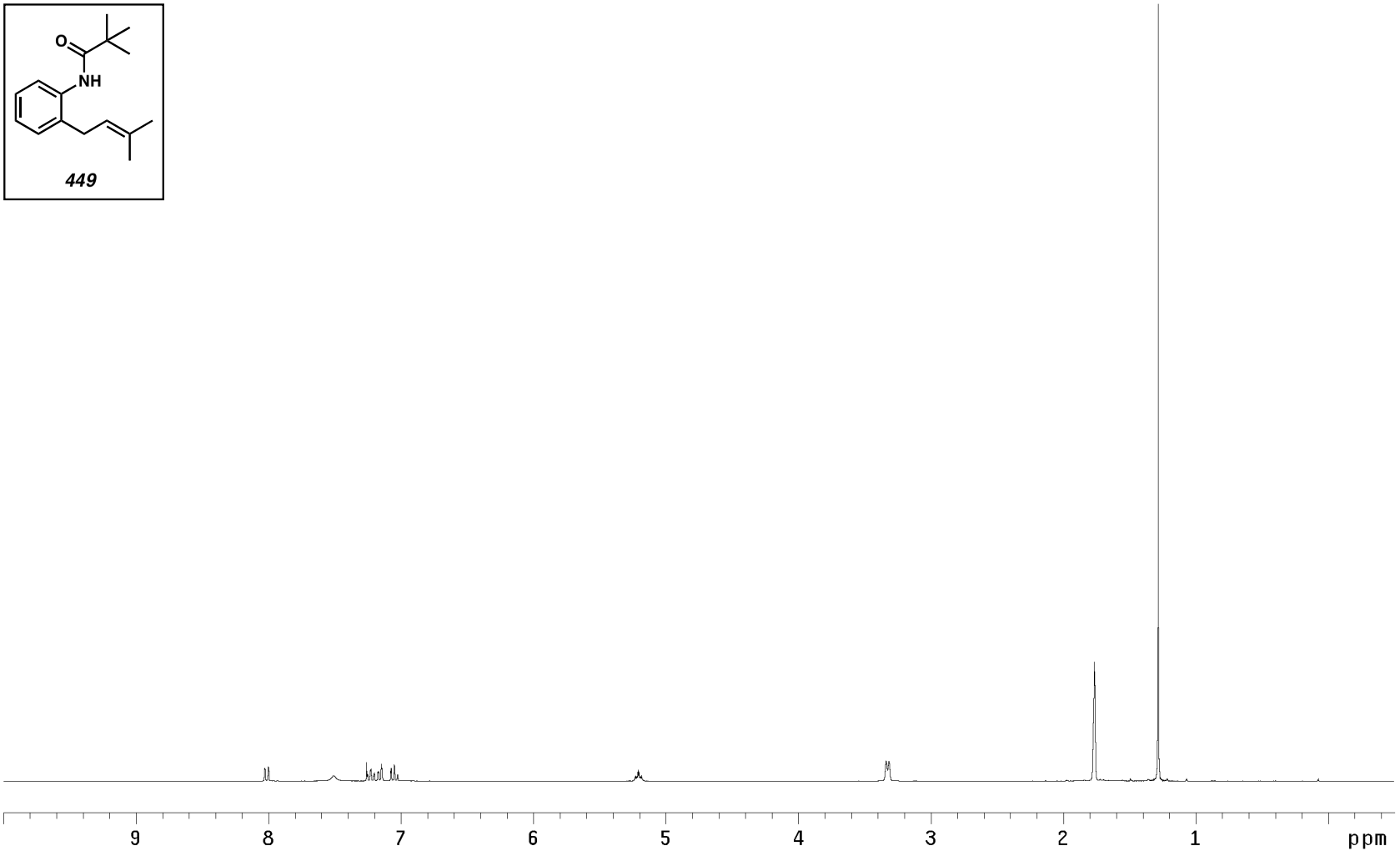


Figure A3.46 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **449**.

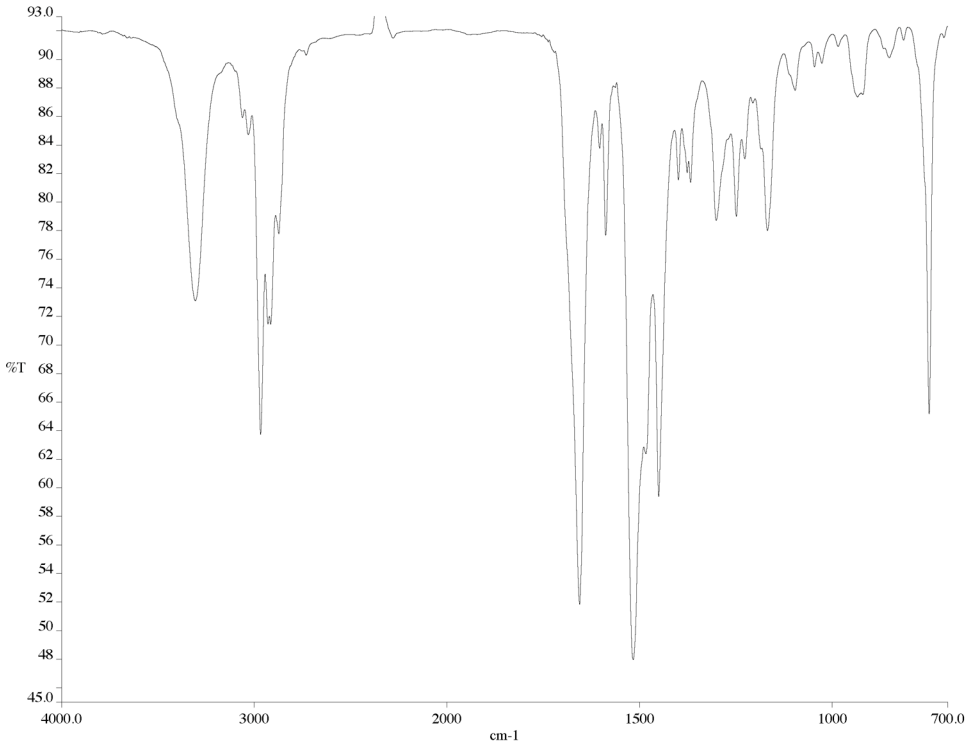


Figure A3.47 Infrared spectrum (thin film/NaCl) of compound **449**.

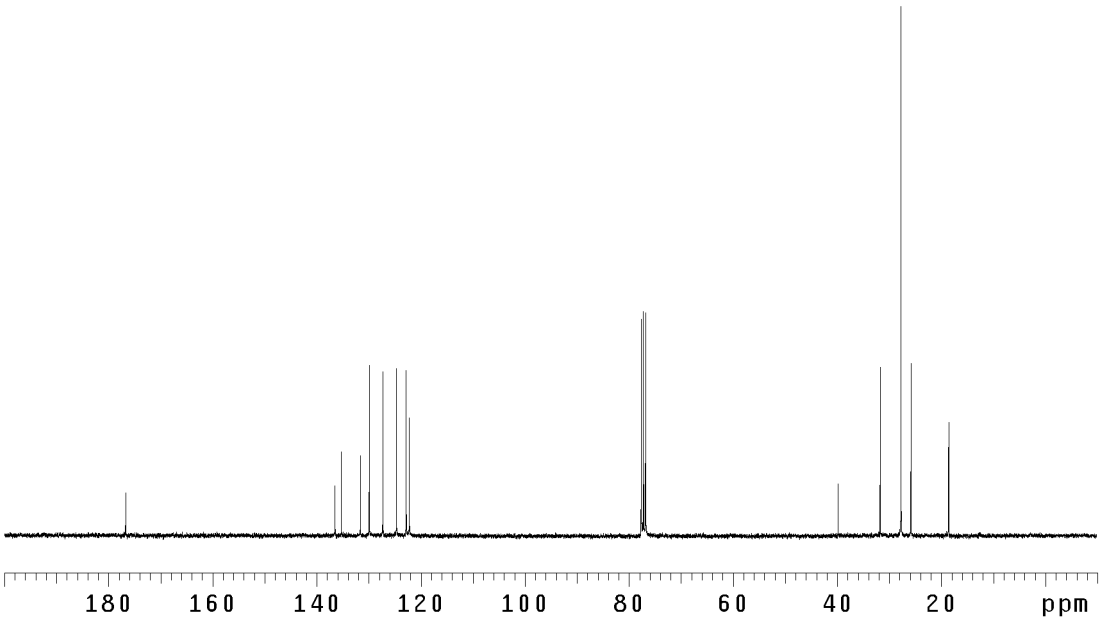


Figure A3.48 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **449**.

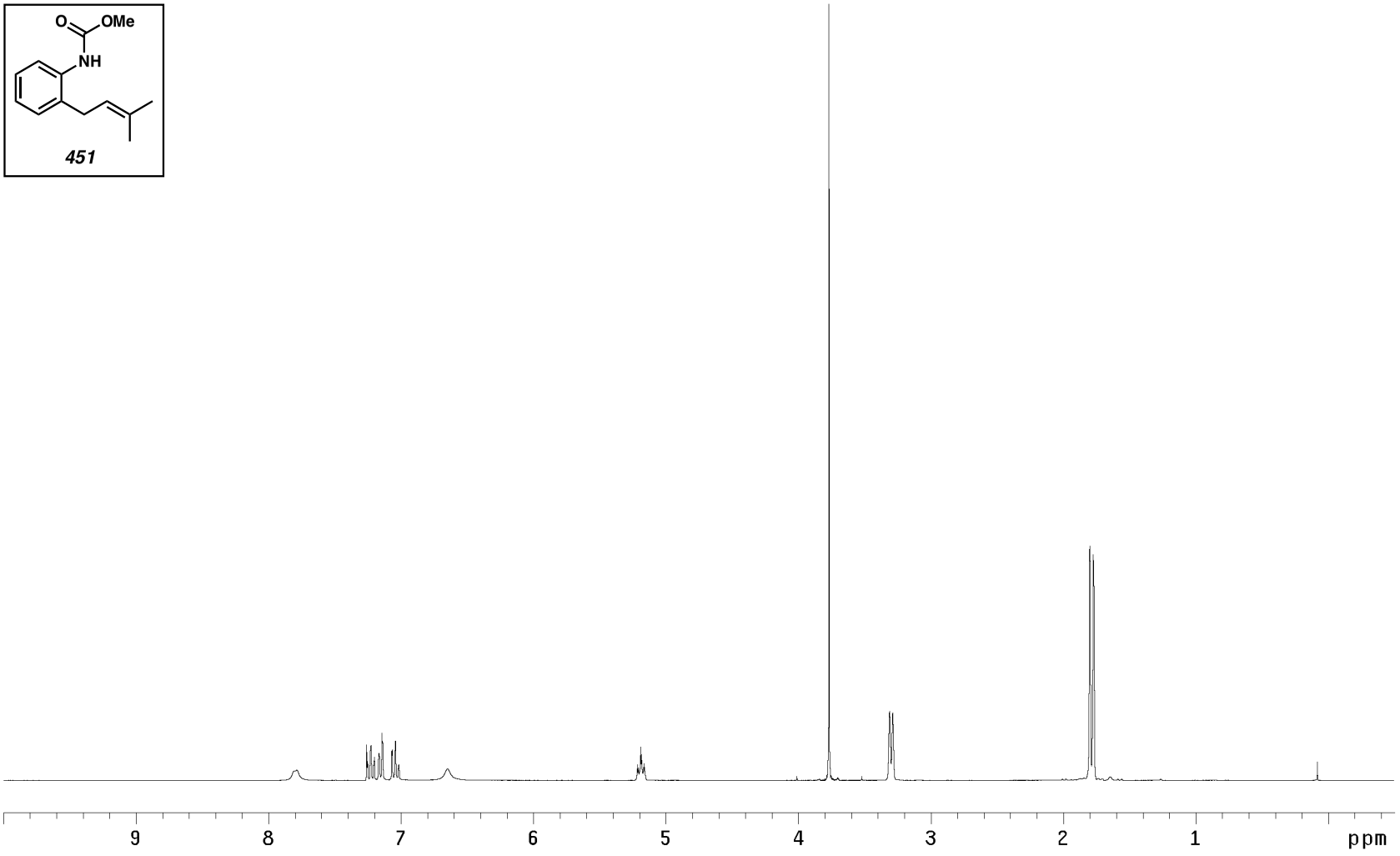


Figure A3.49 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **451**.

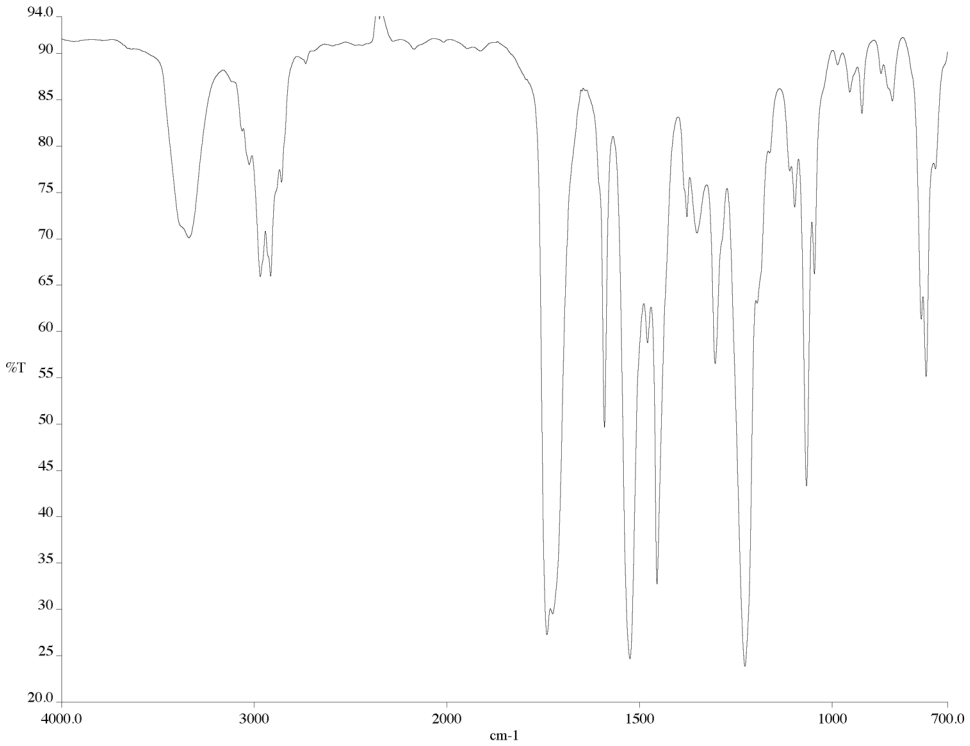


Figure A3.50 Infrared spectrum (thin film/NaCl) of compound **451**.

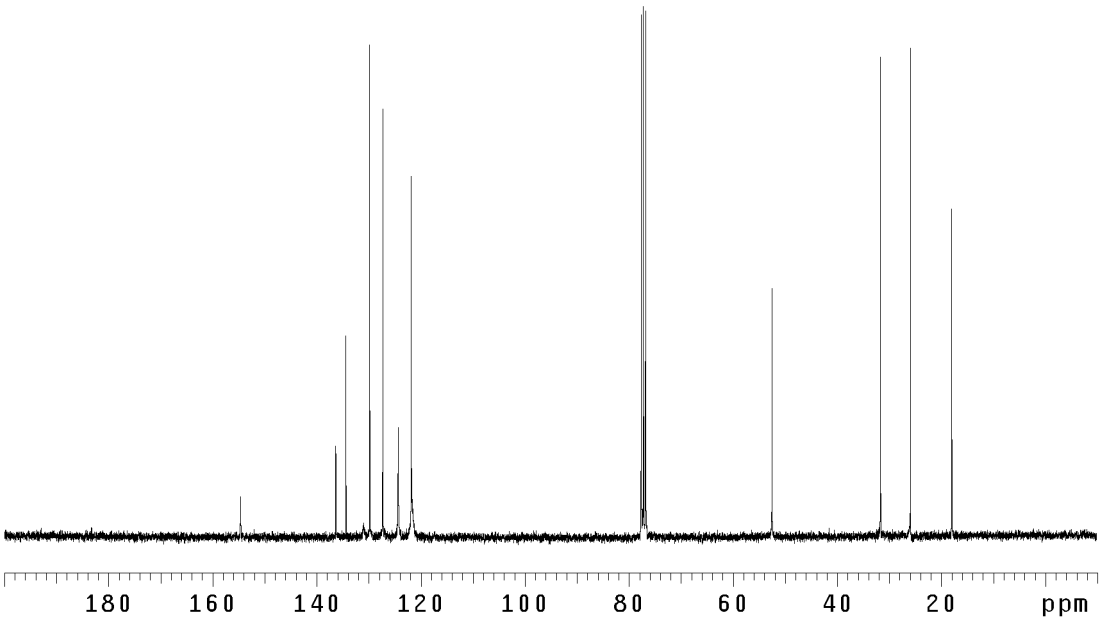


Figure A3.51 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **451**.

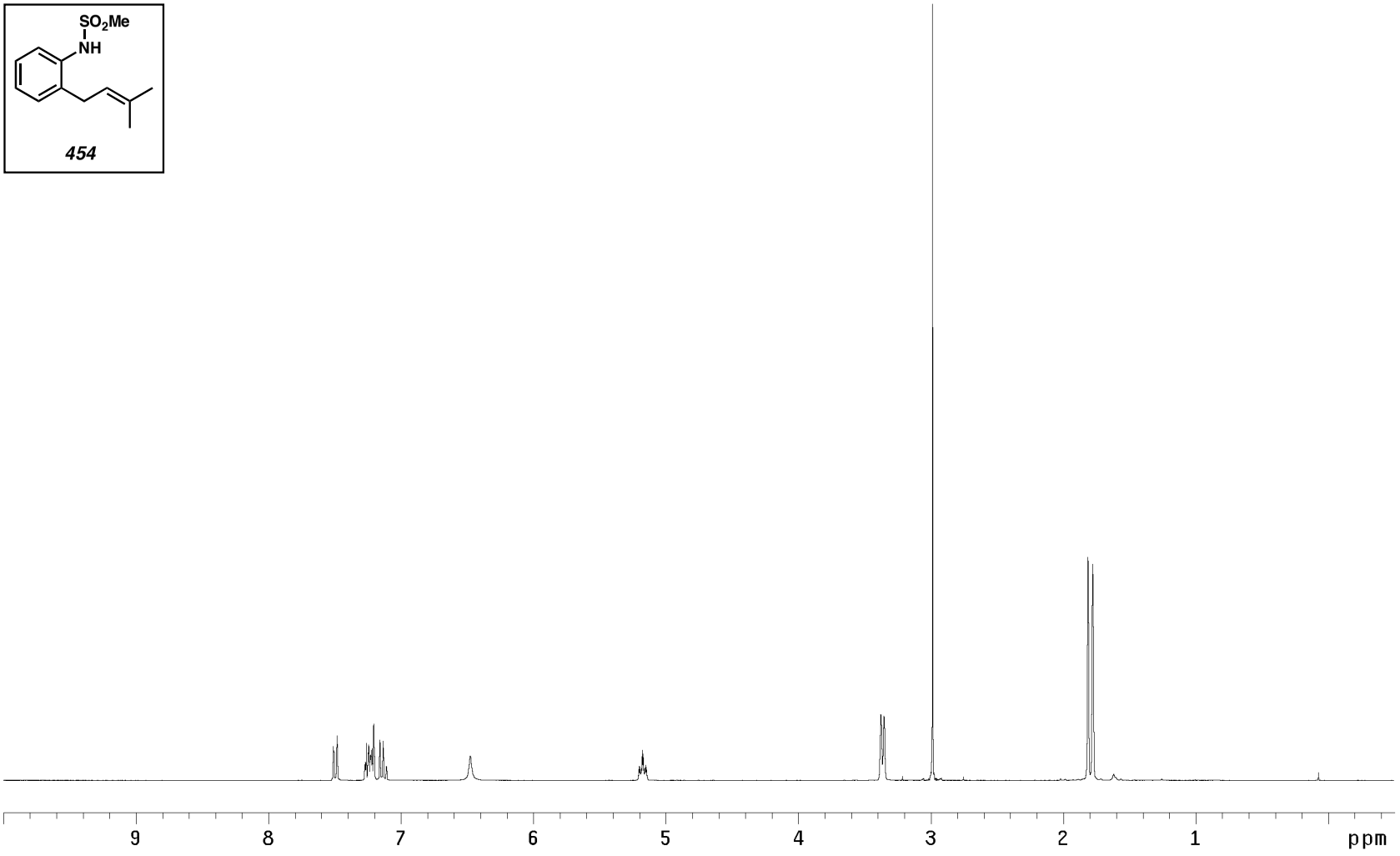


Figure A3.52 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **454**.

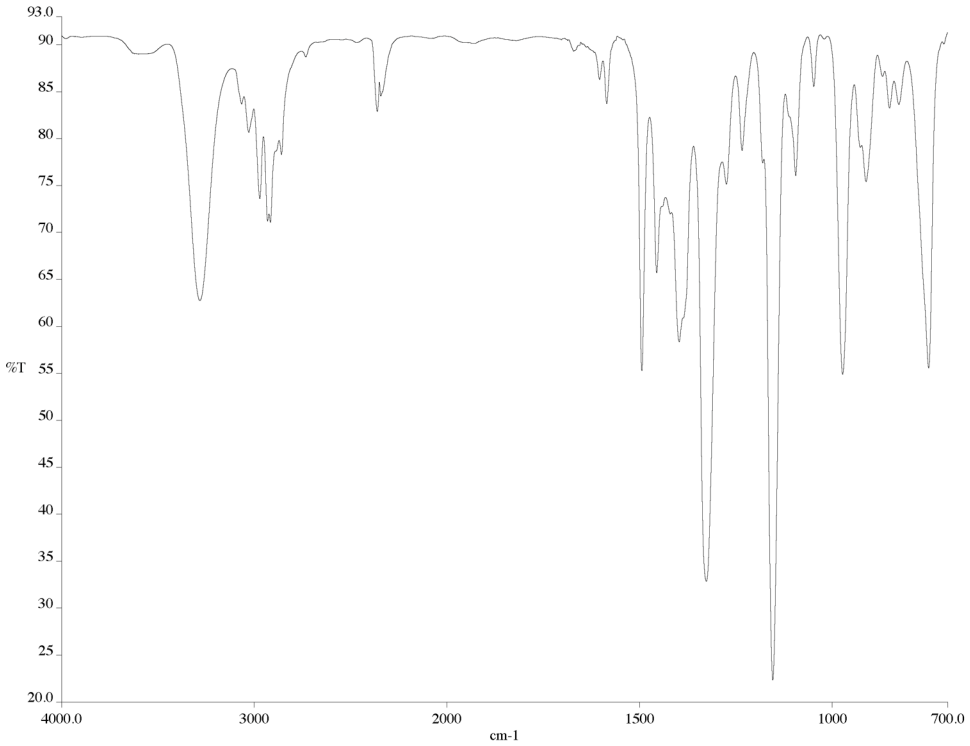


Figure A3.53 Infrared spectrum (thin film/NaCl) of compound **454**.

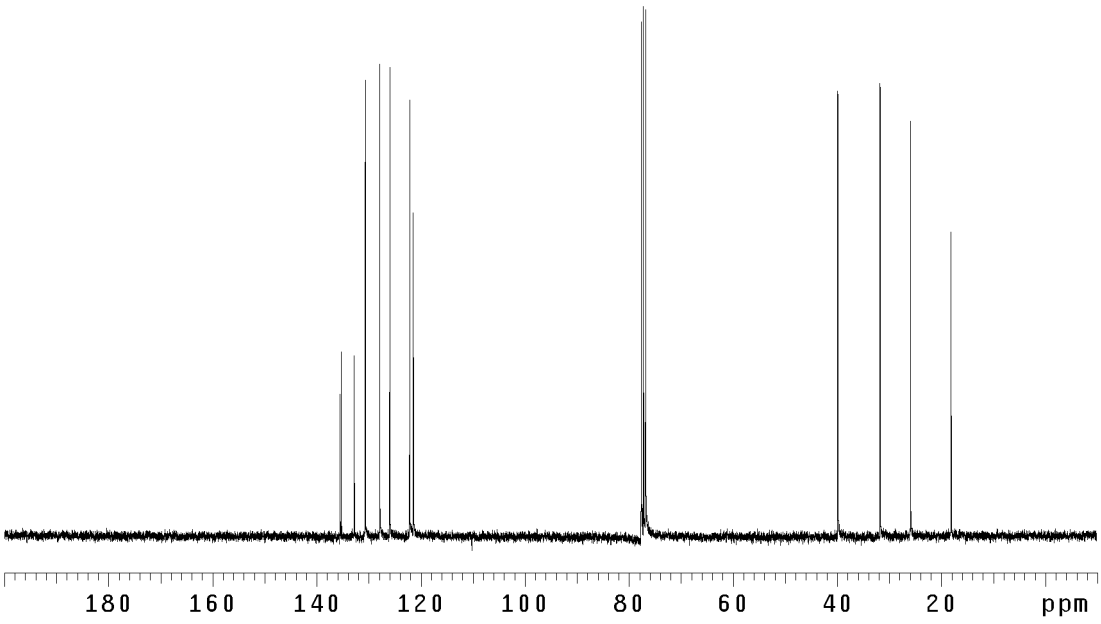


Figure A3.54 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **454**.

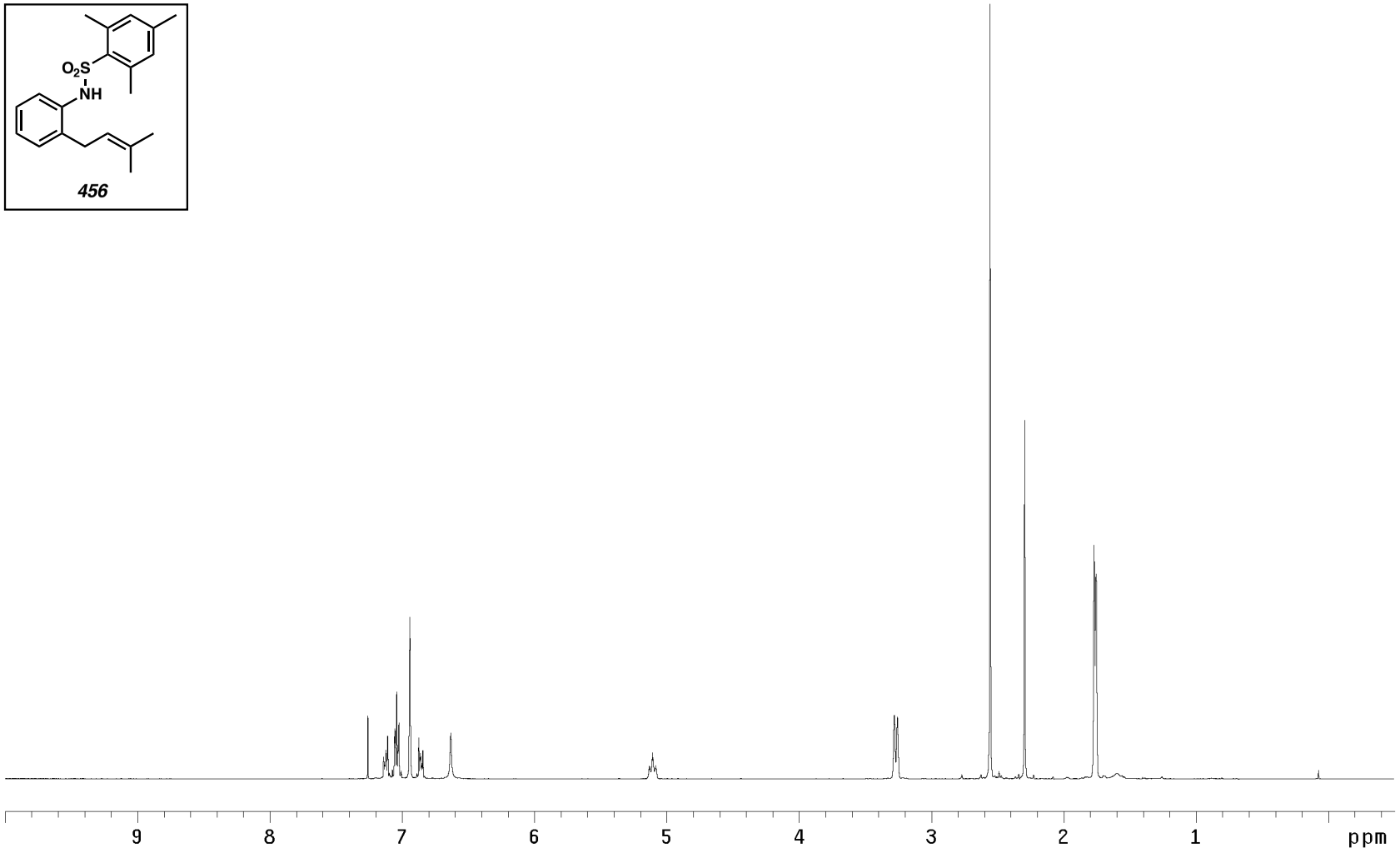


Figure A3.55 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **456**.

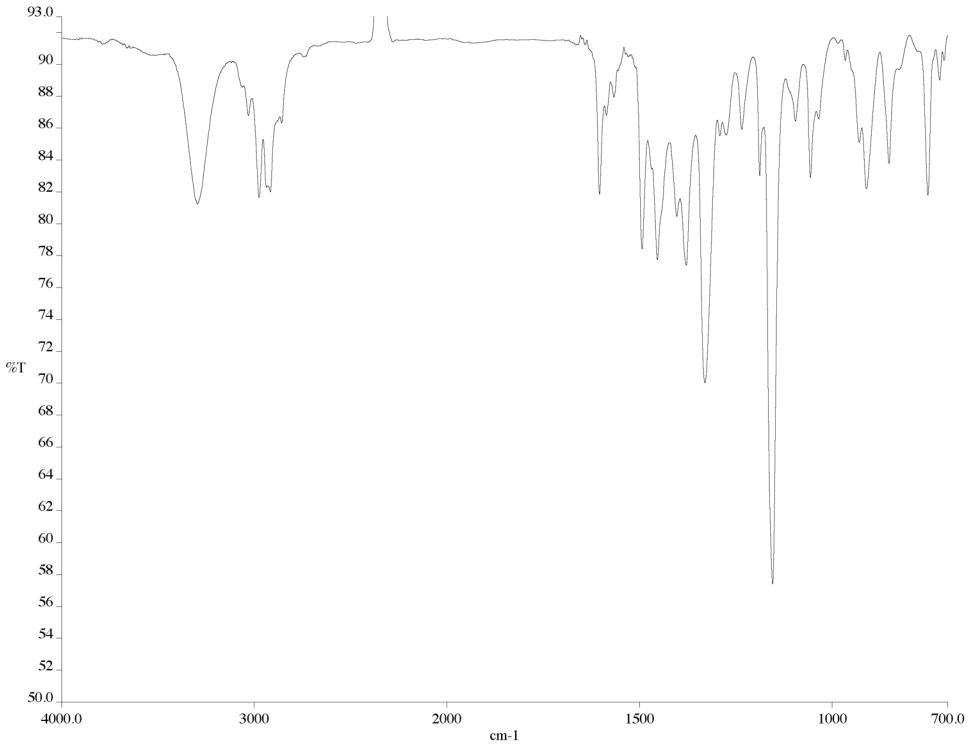


Figure A3.56 Infrared spectrum (thin film/NaCl) of compound **456**.

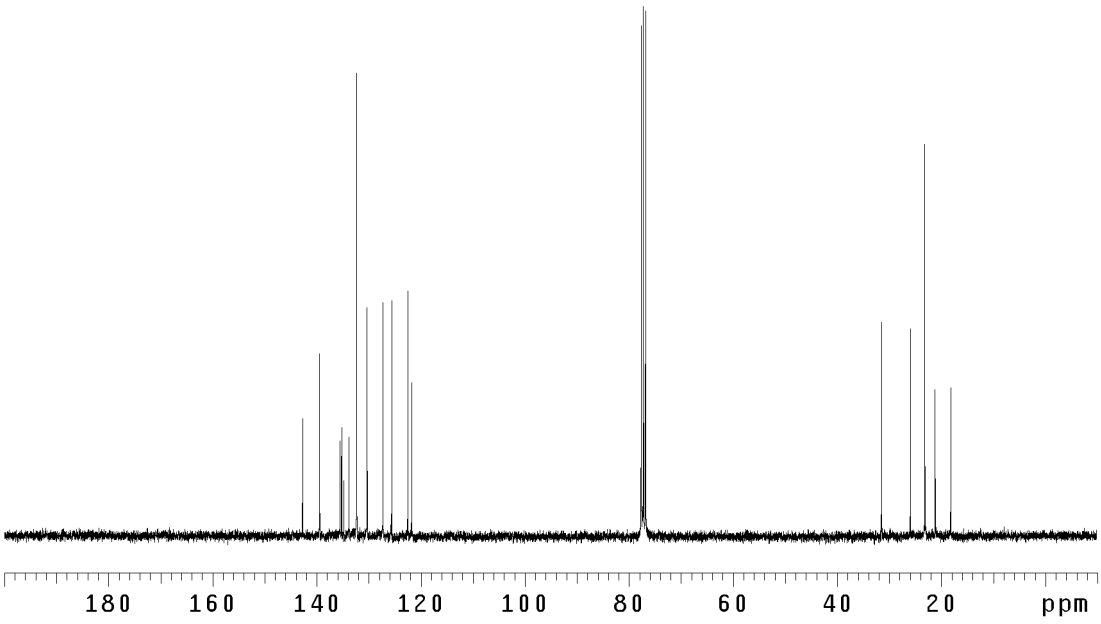


Figure A3.57 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **456**.

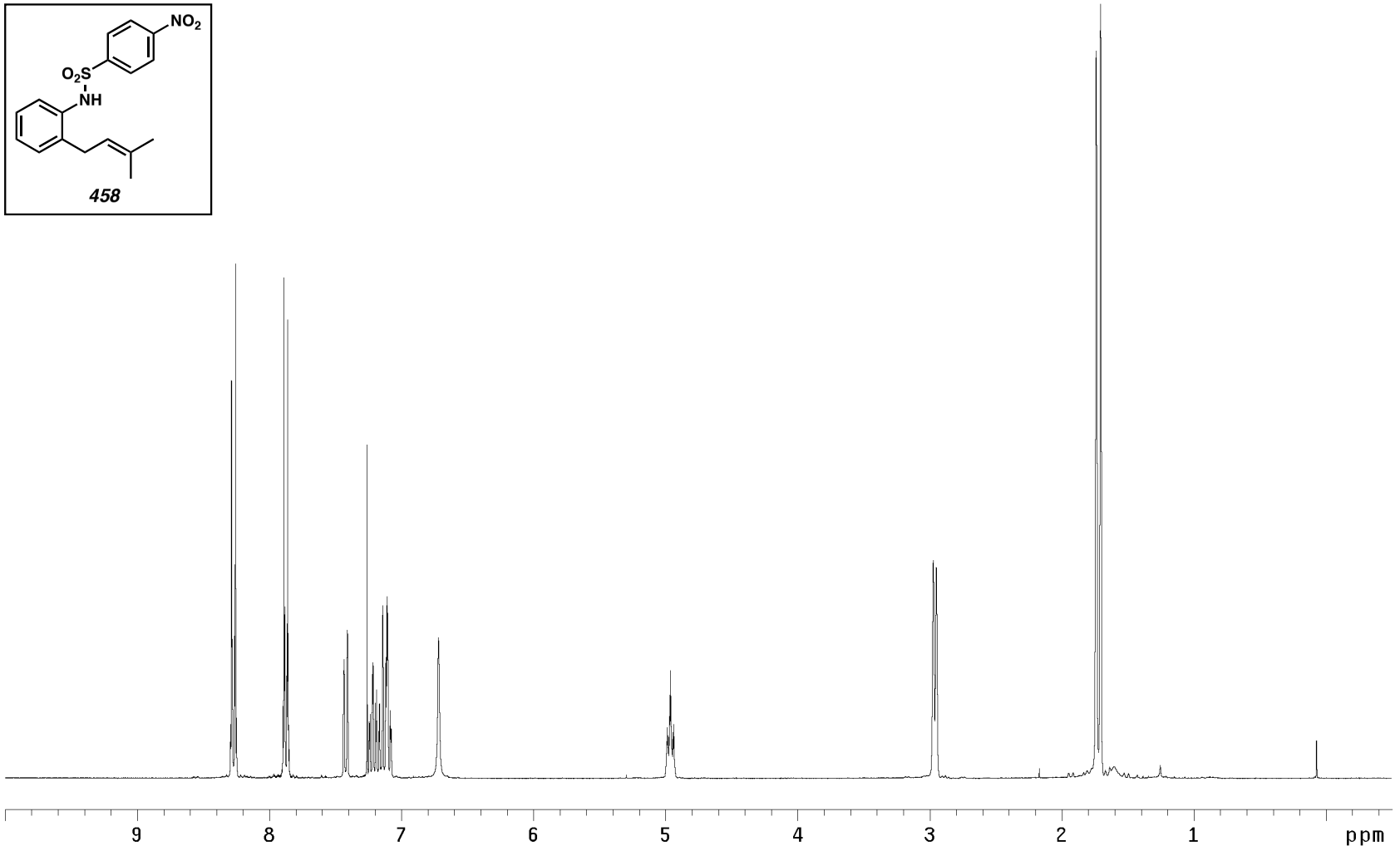


Figure A3.58 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **458**.

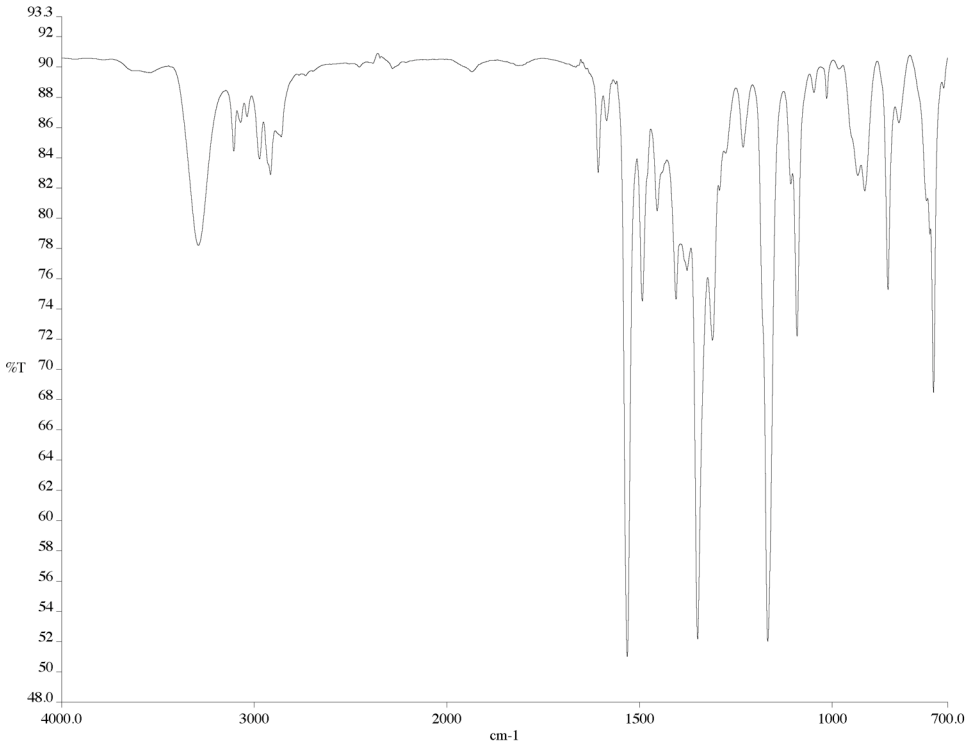


Figure A3.59 Infrared spectrum (thin film/NaCl) of compound **458**.

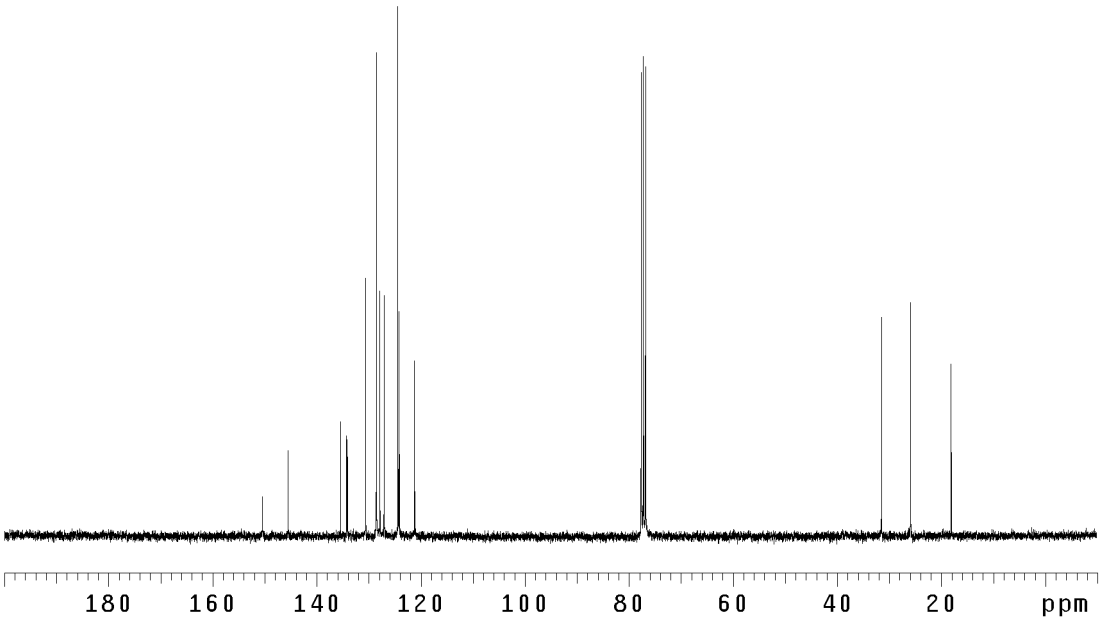


Figure A3.60 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **458**.

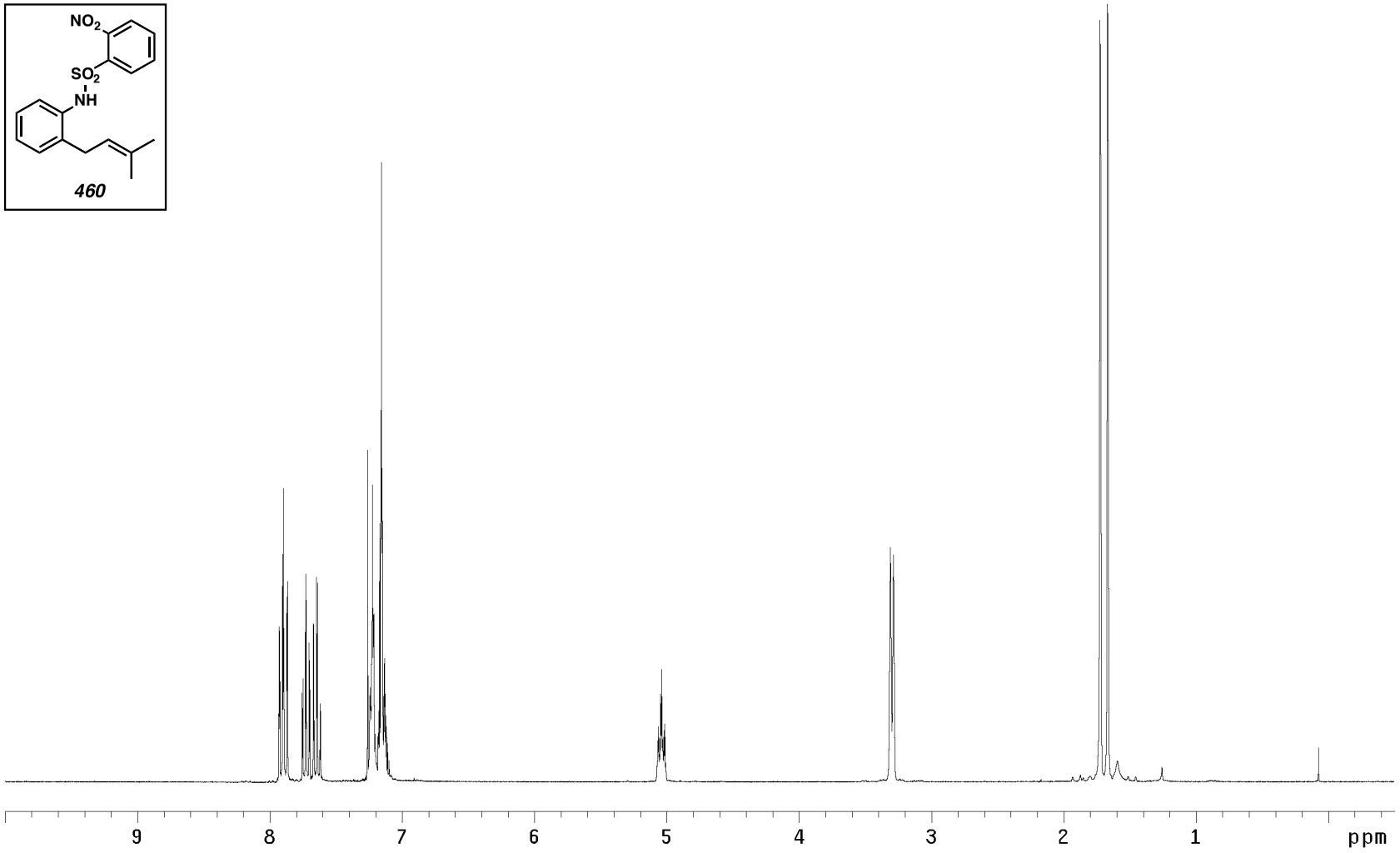


Figure A3.61 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **460**.

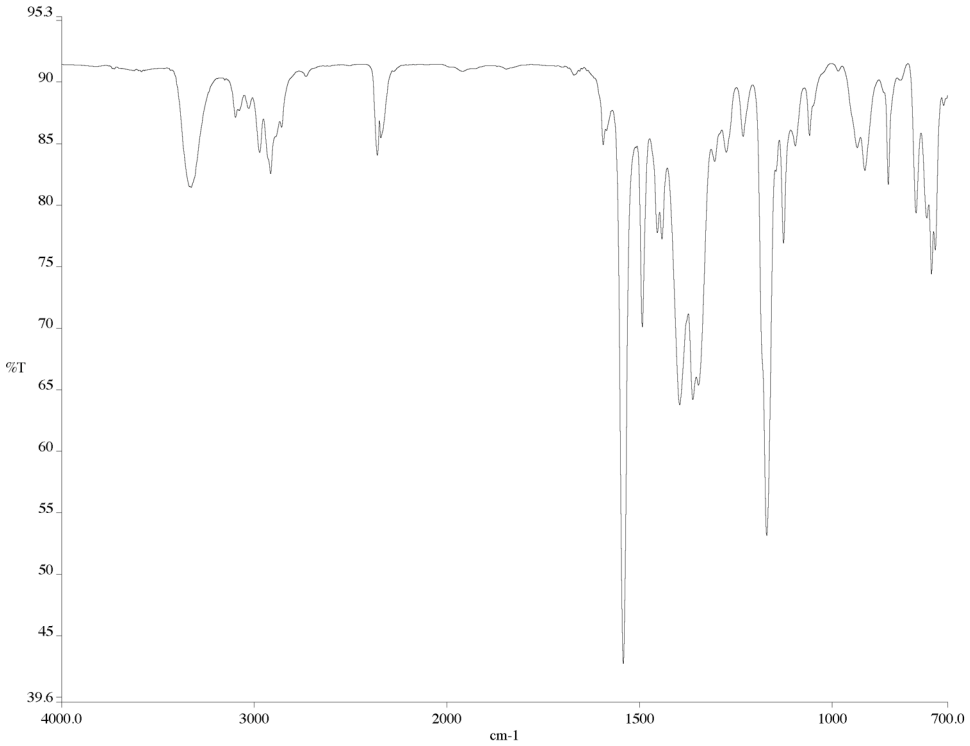


Figure A3.62 Infrared spectrum (thin film/NaCl) of compound **460**.

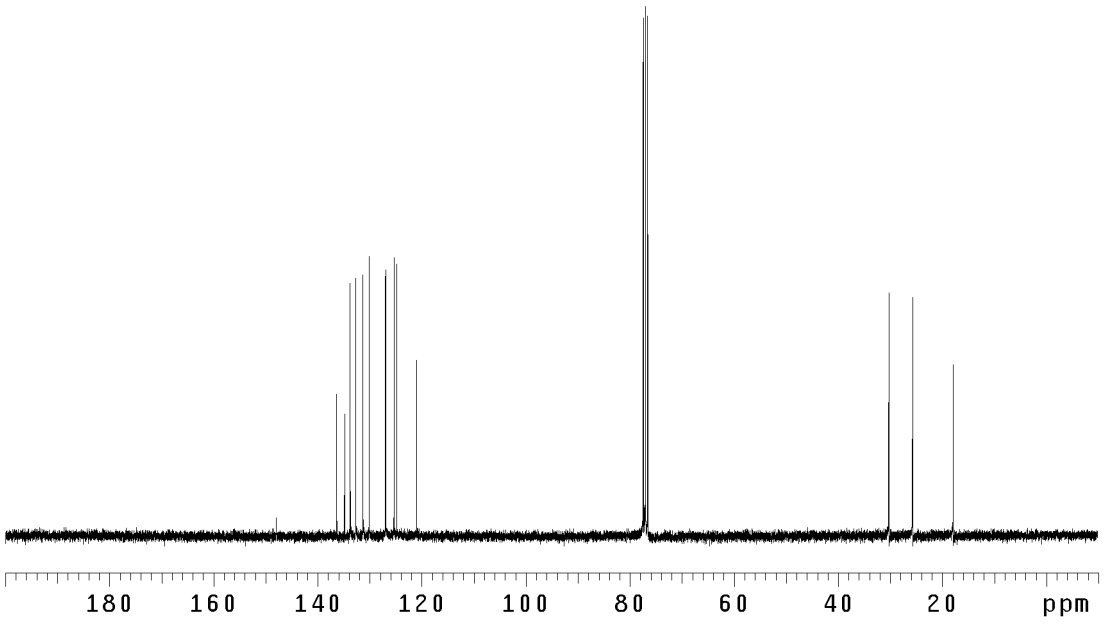


Figure A3.63 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **460**.

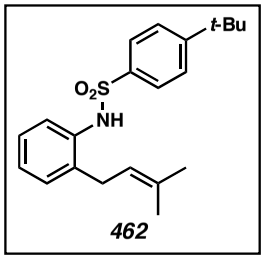


Figure A3.64 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **462**.

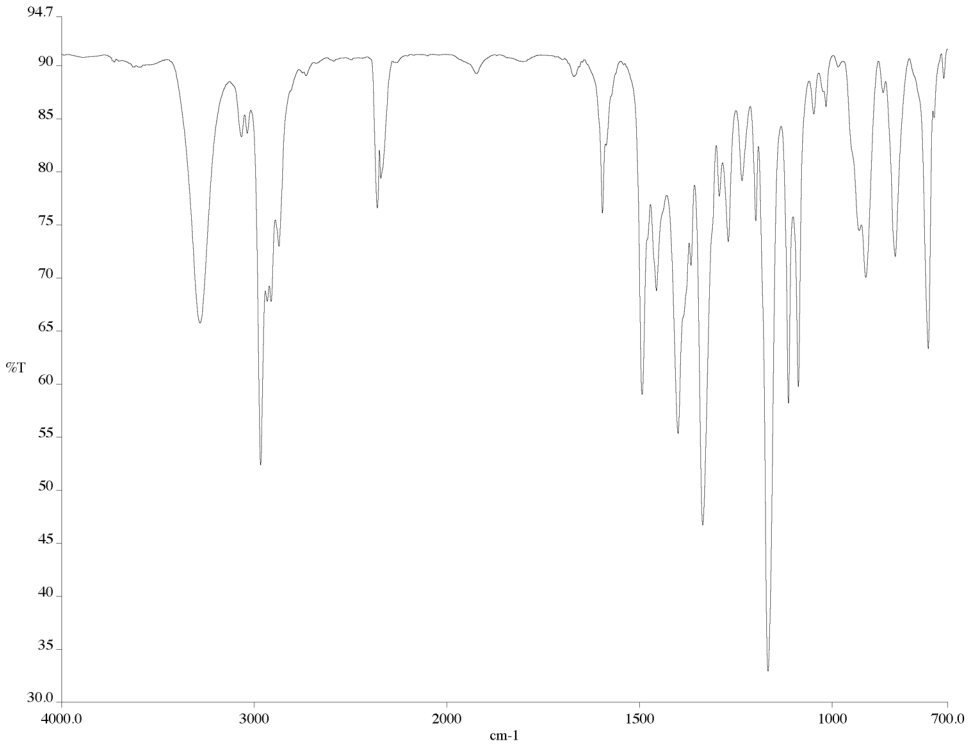


Figure A3.65 Infrared spectrum (thin film/NaCl) of compound **462**.

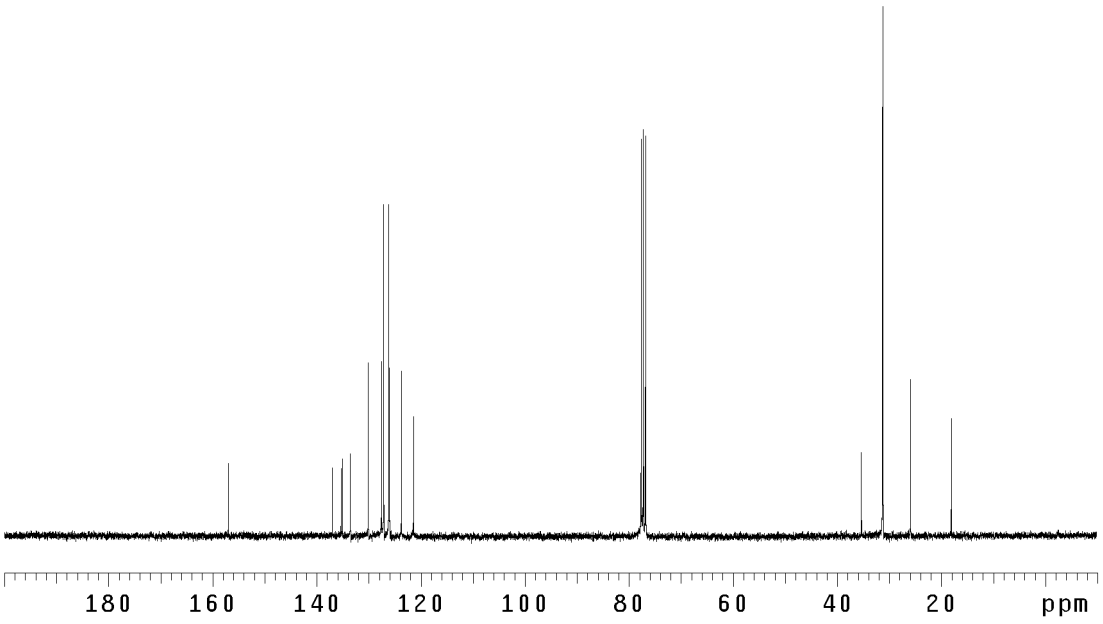


Figure A3.66 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **462**.

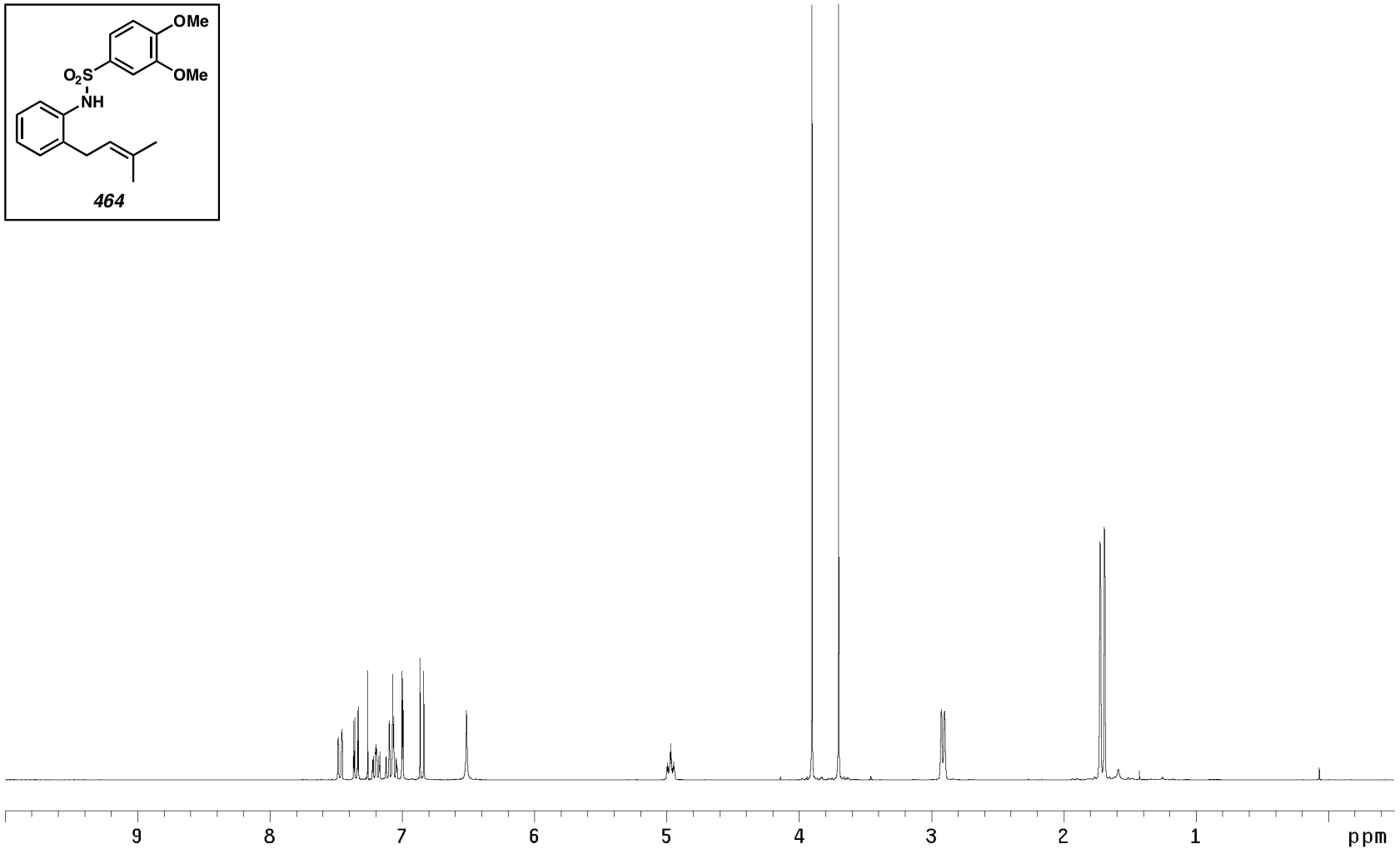


Figure A3.67 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **464**.

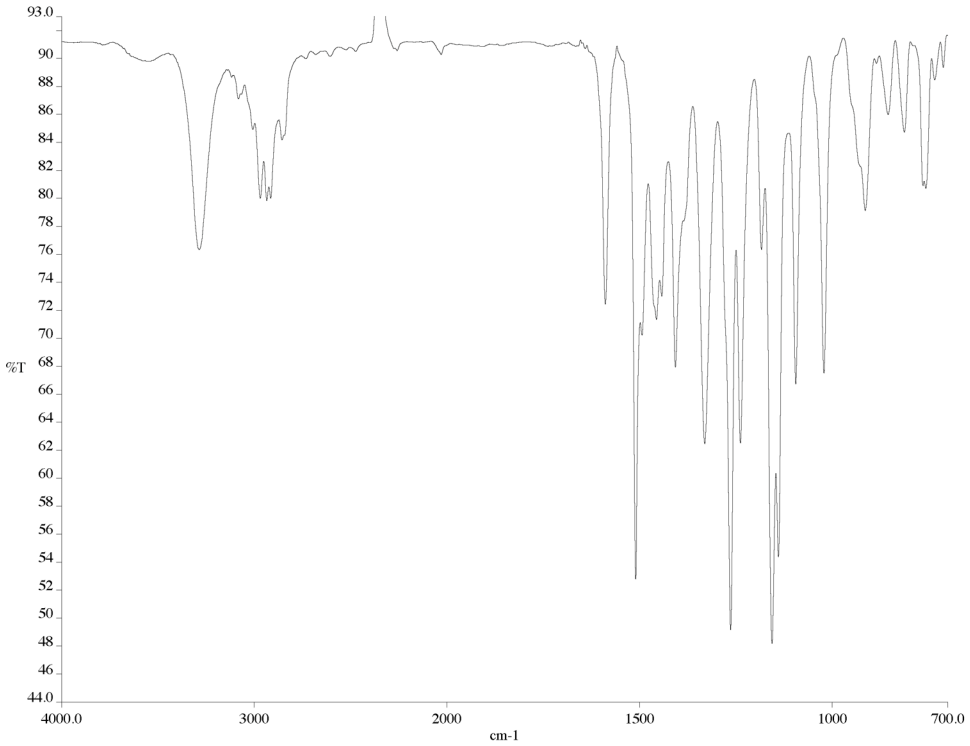


Figure A3.68 Infrared spectrum (thin film/NaCl) of compound **464**.

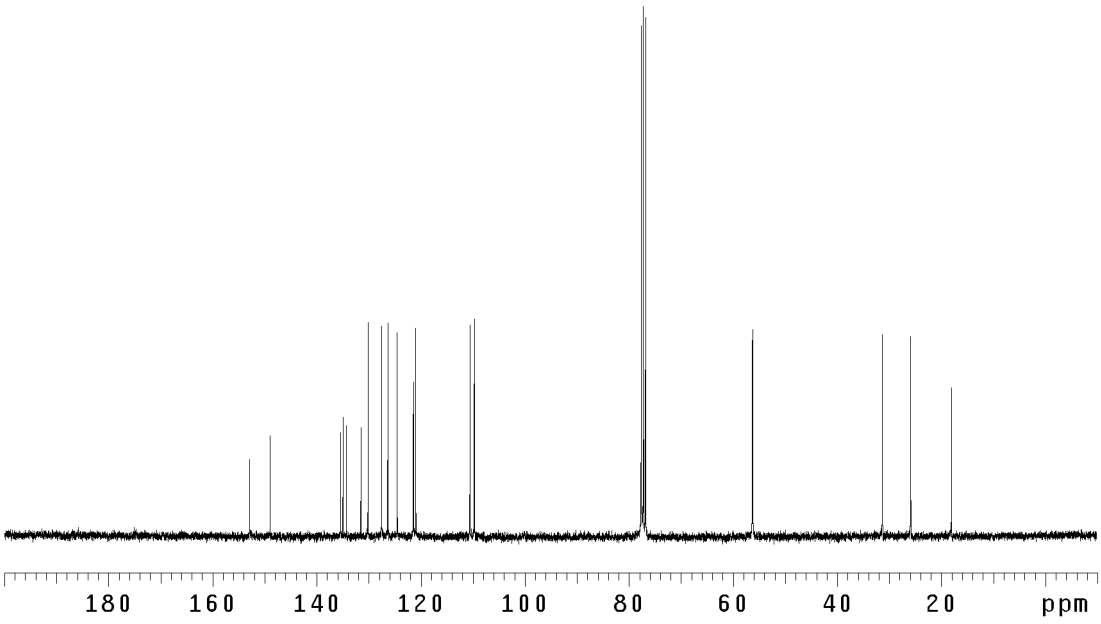


Figure A3.69 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **464**.

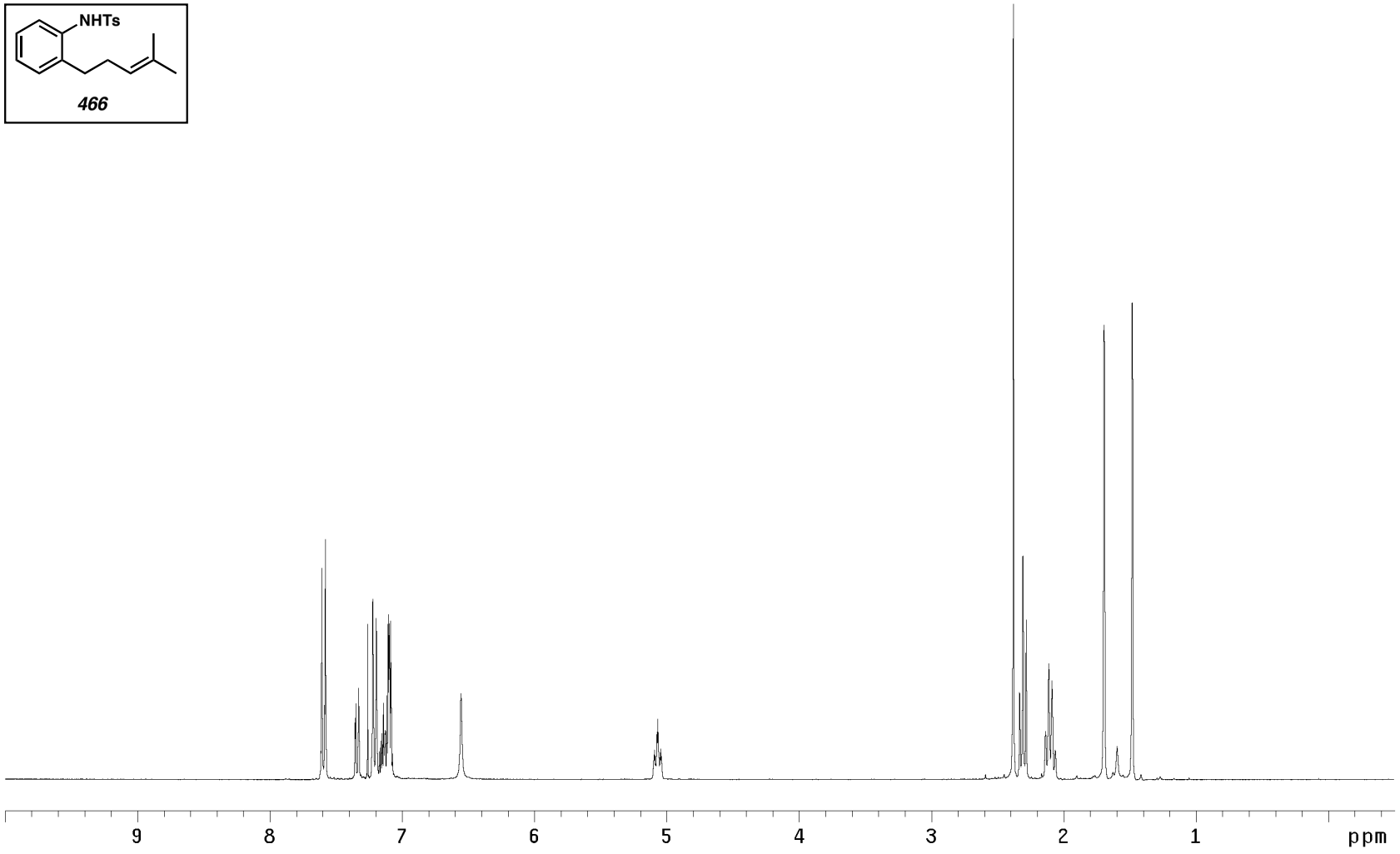


Figure A3.70 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **466**.

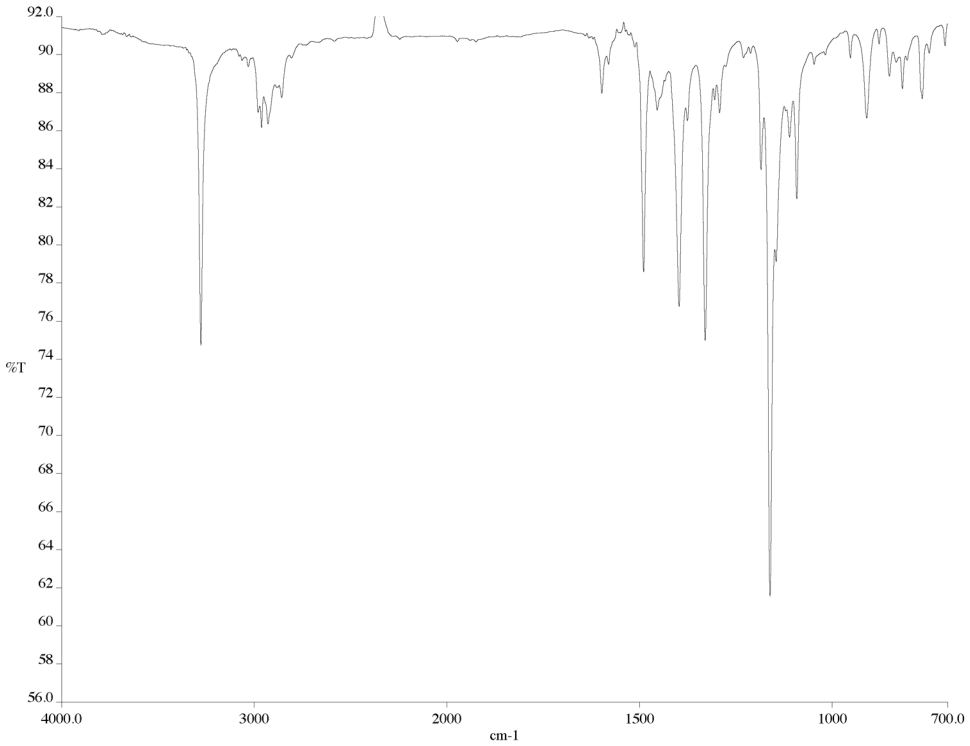


Figure A3.71 Infrared spectrum (thin film/NaCl) of compound **466**.

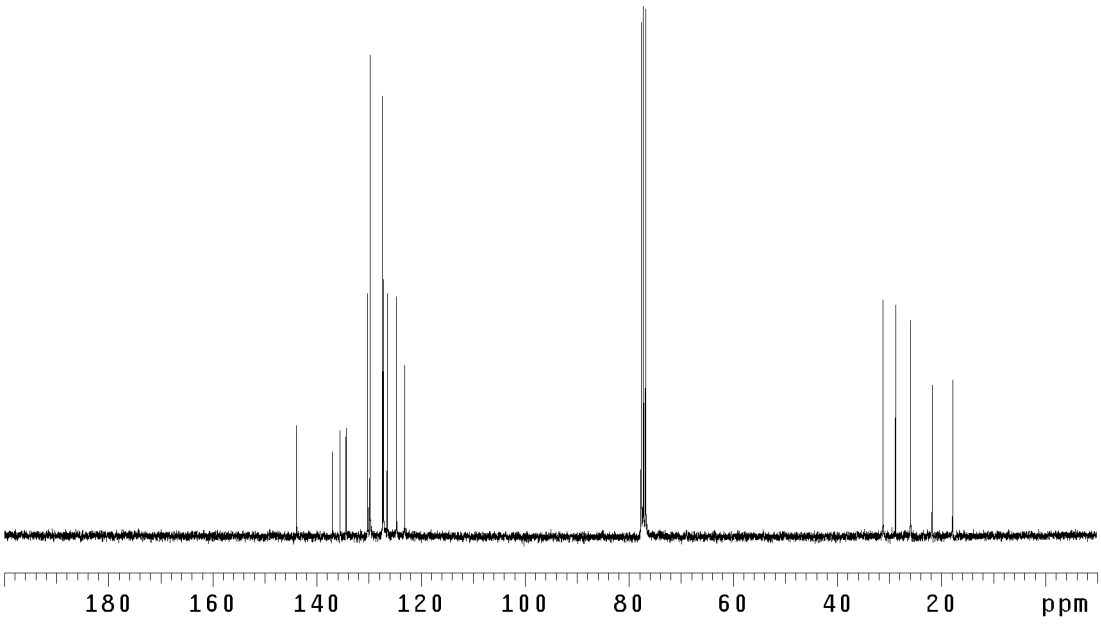


Figure A3.72 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **466**.

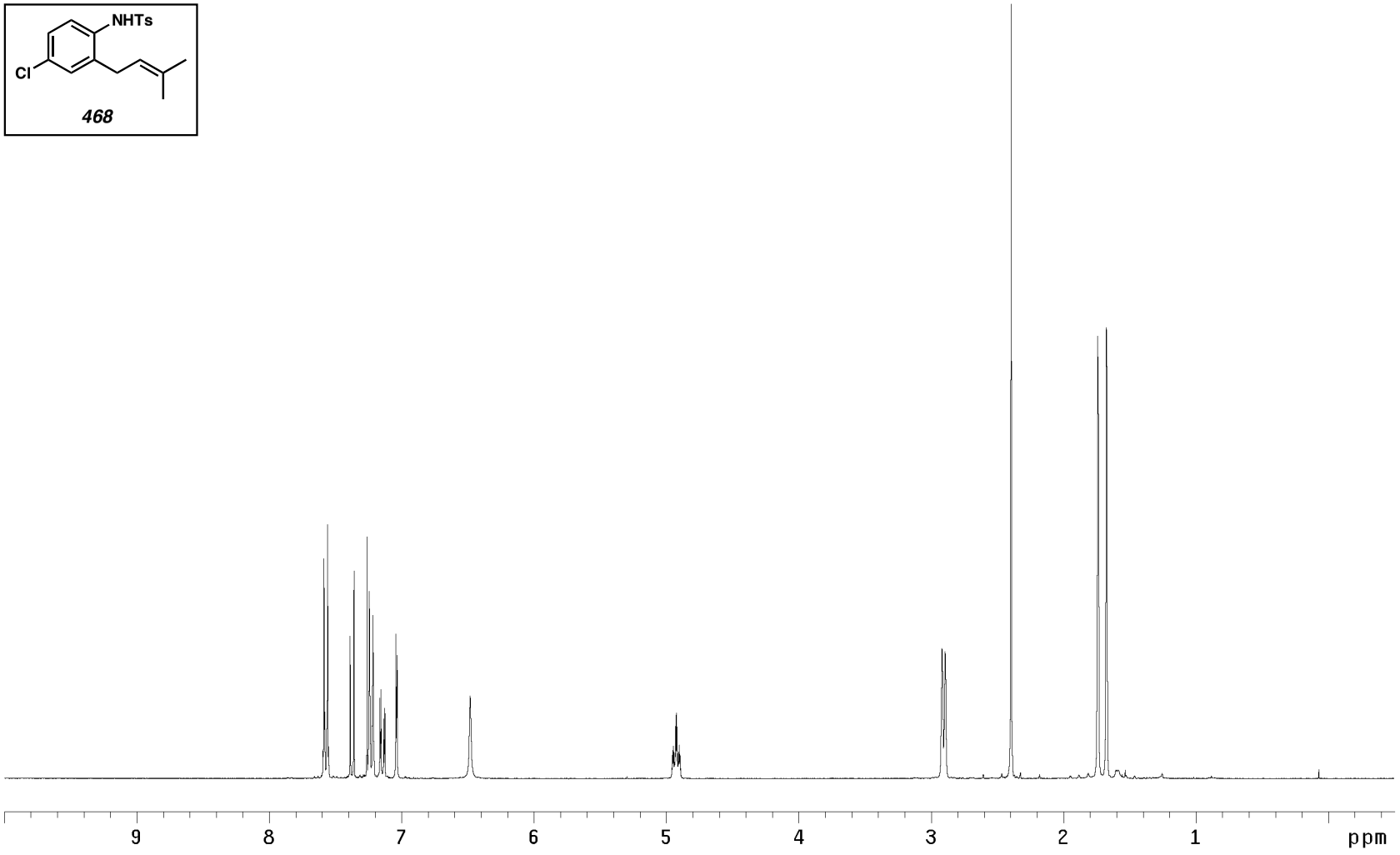


Figure A3.73 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **468**.

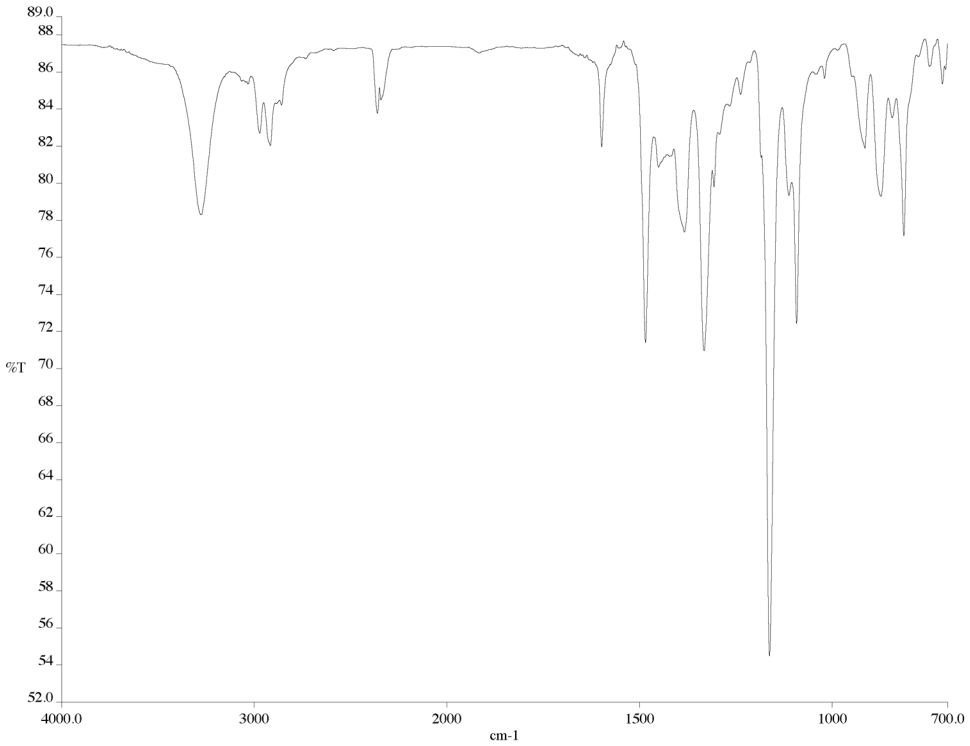


Figure A3.74 Infrared spectrum (thin film/NaCl) of compound **468**.

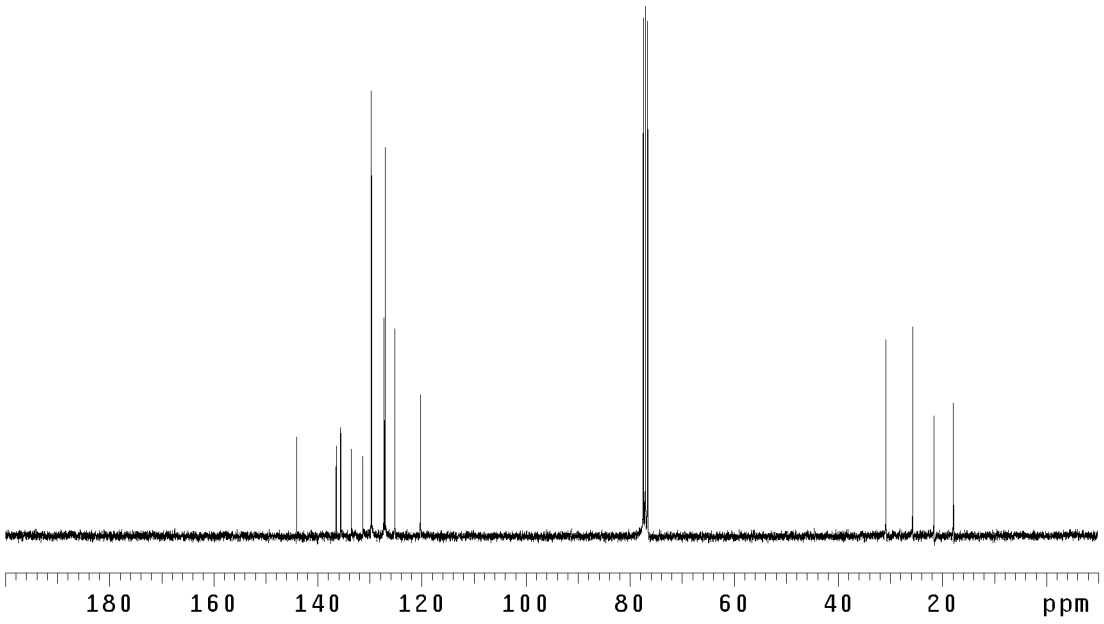


Figure A3.75 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **468**.

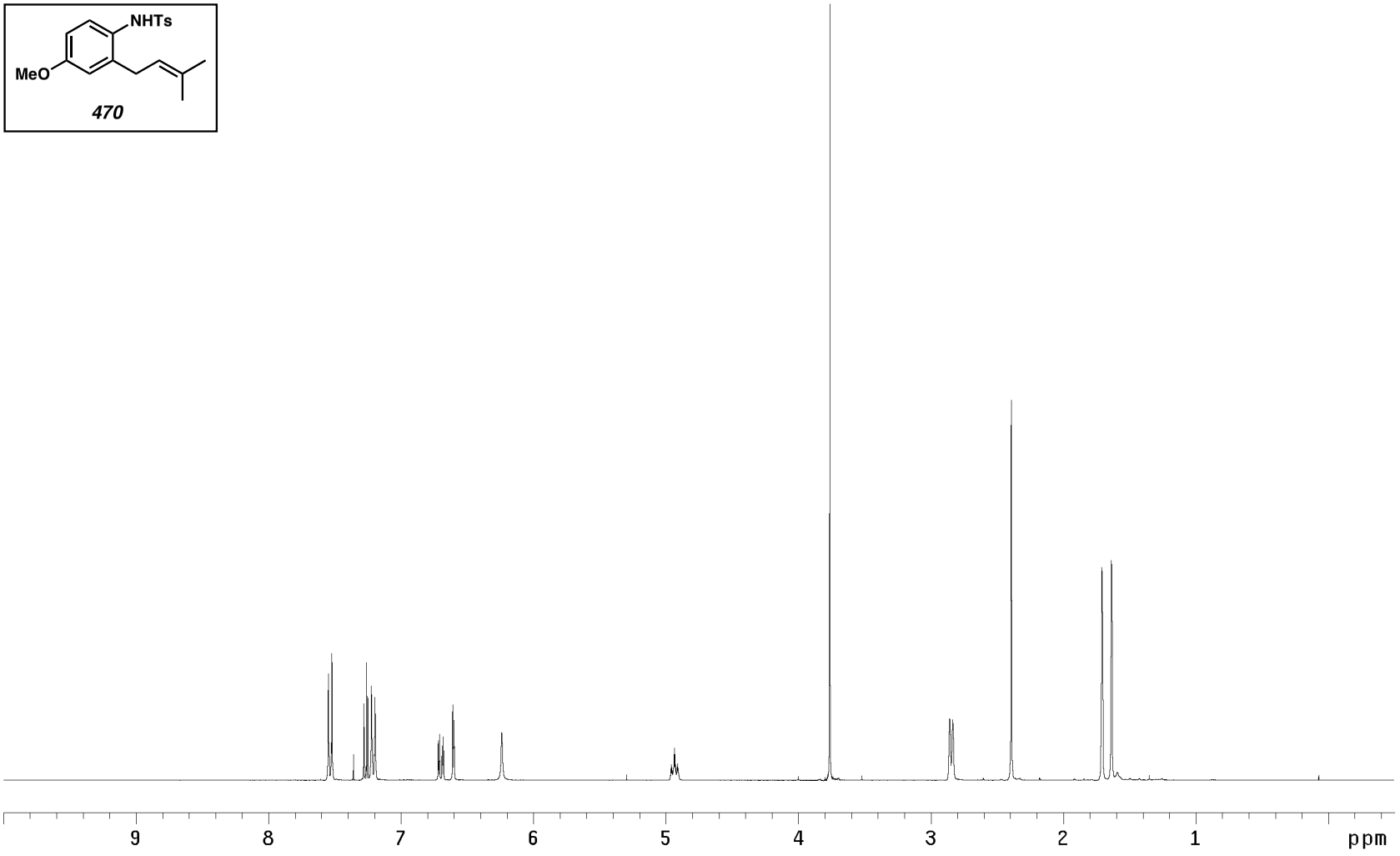


Figure A3.76 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **470**.

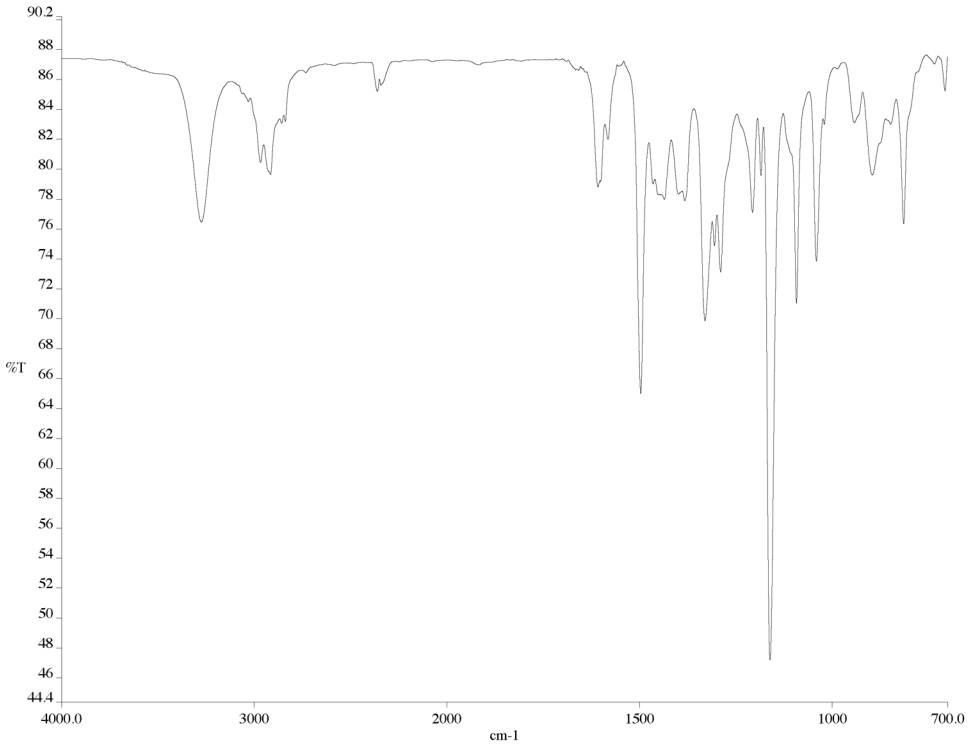


Figure A3.77 Infrared spectrum (thin film/NaCl) of compound **470**.

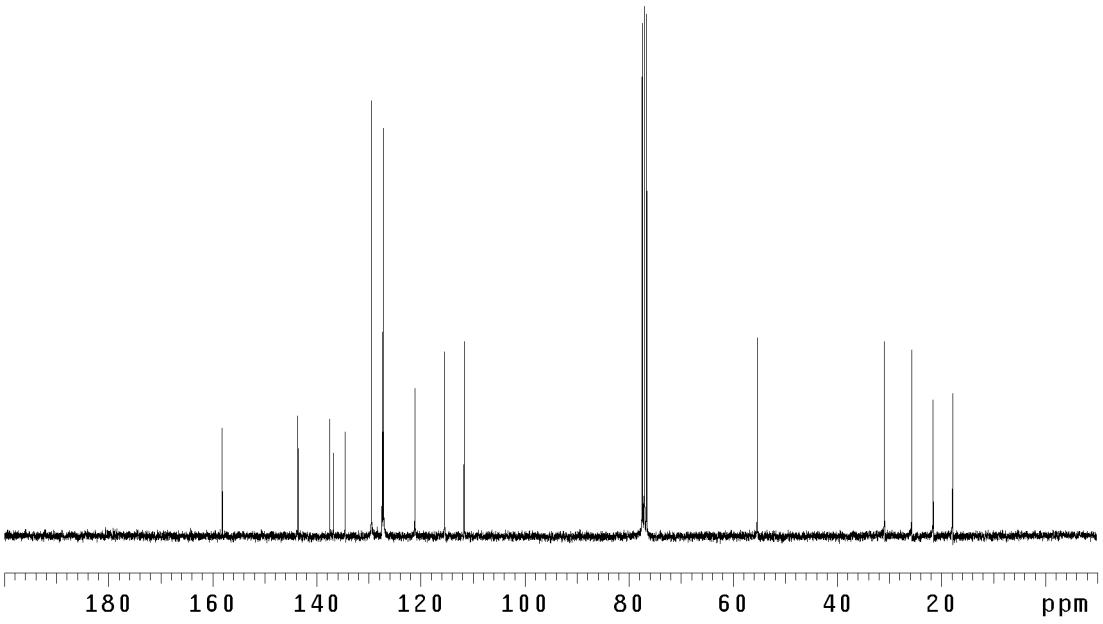


Figure A3.78 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **470**.

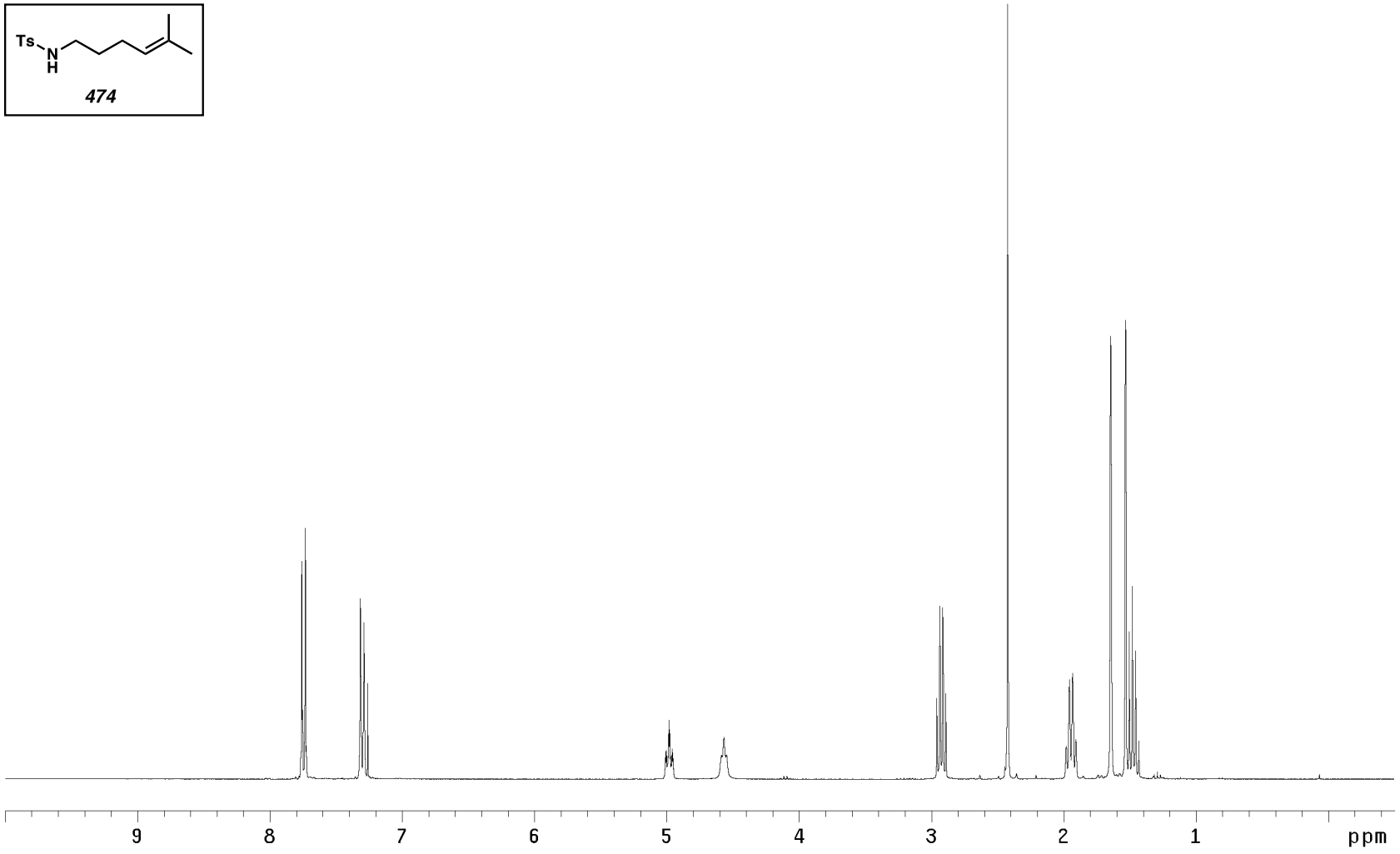


Figure A3.79 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **474**.

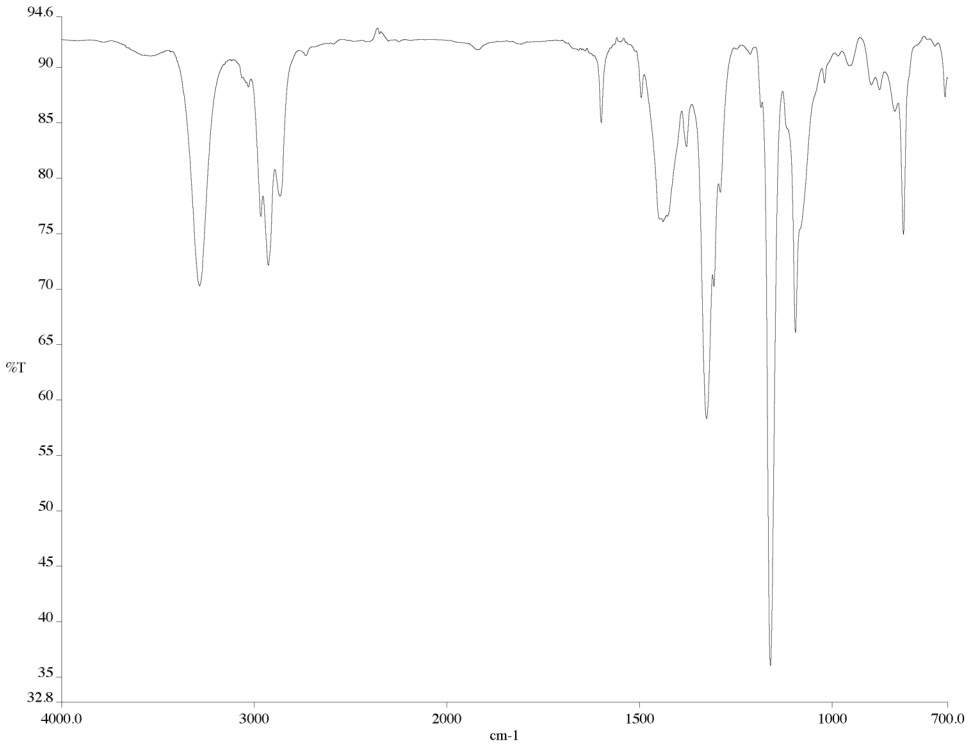


Figure A3.80 Infrared spectrum (thin film/NaCl) of compound **474**.

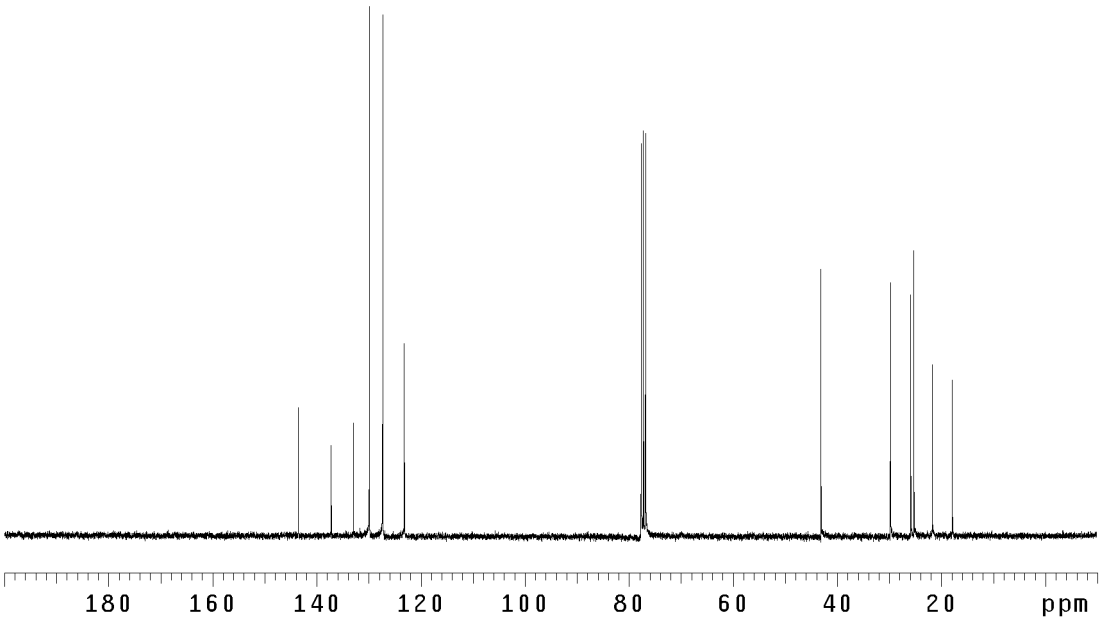


Figure A3.81 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **474**.

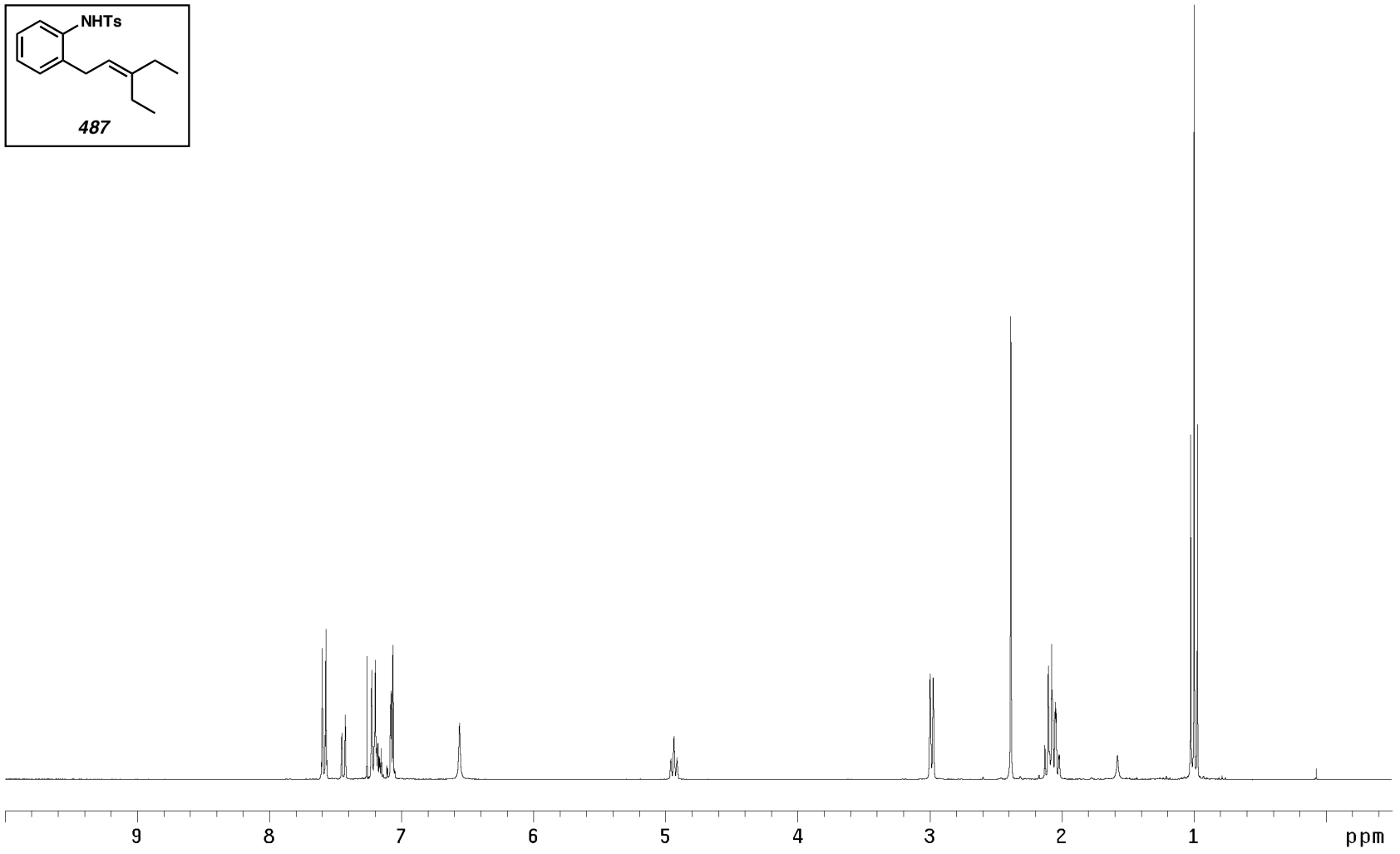


Figure A3.82 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **487**.

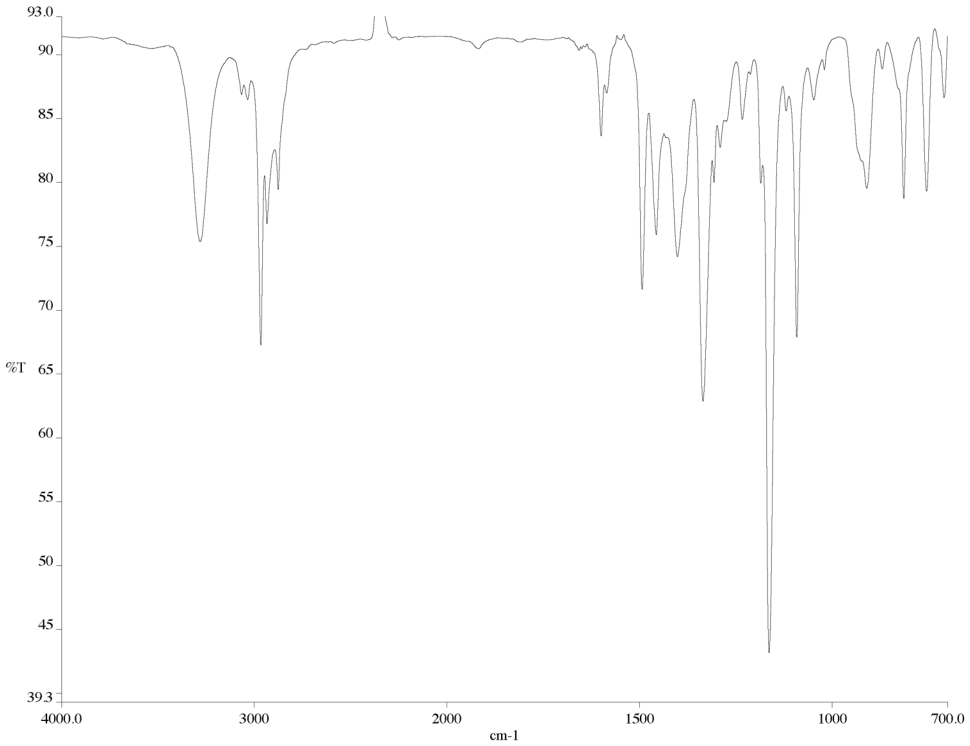


Figure A3.83 Infrared spectrum (thin film/NaCl) of compound **487**.

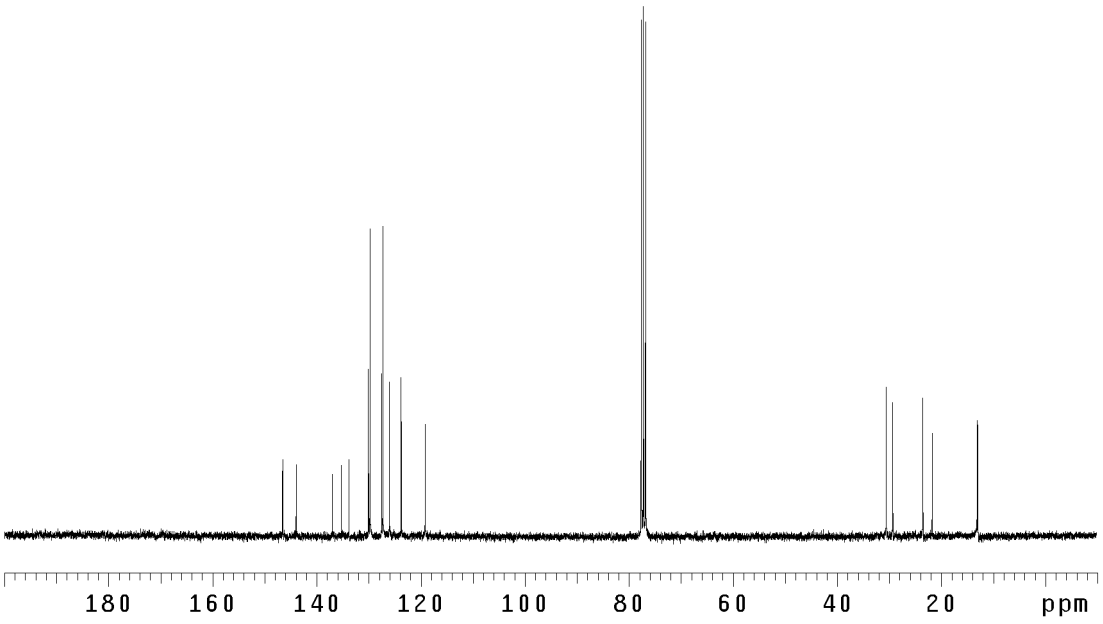


Figure A3.84 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **487**.

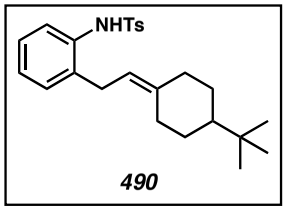


Figure A3.85 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **490**.

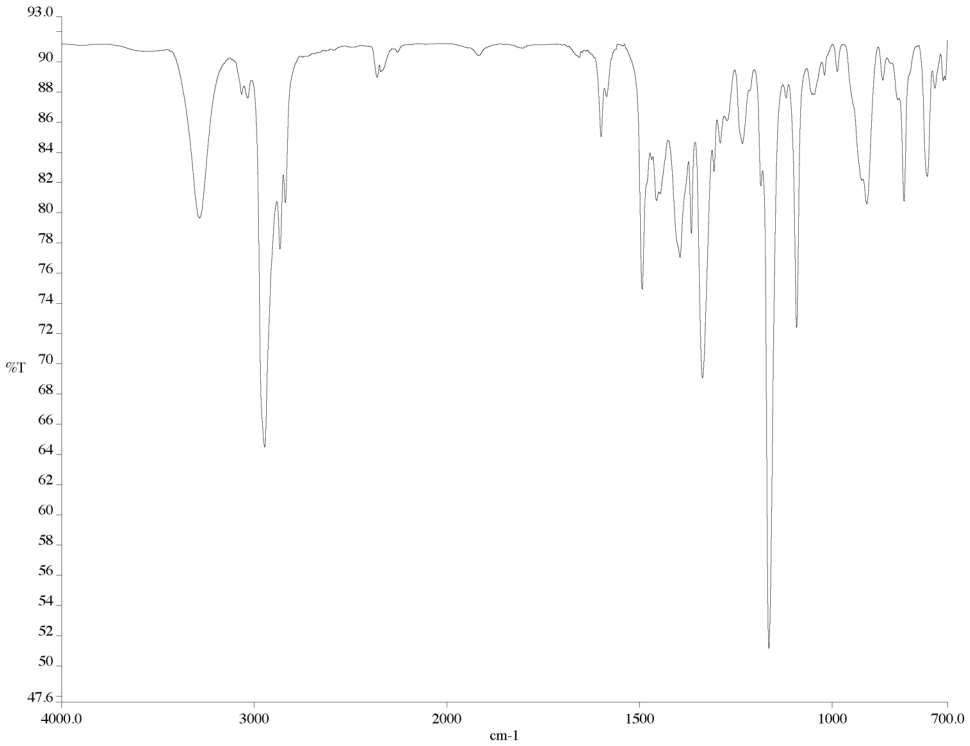


Figure A3.86 Infrared spectrum (thin film/NaCl) of compound **490**.

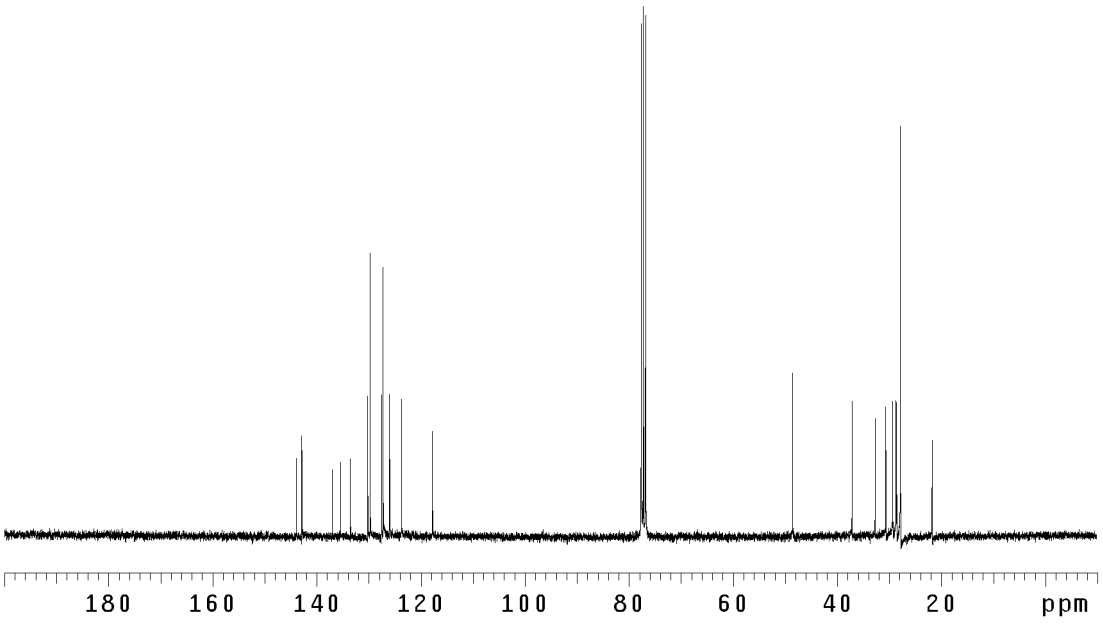


Figure A3.87 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **490**.

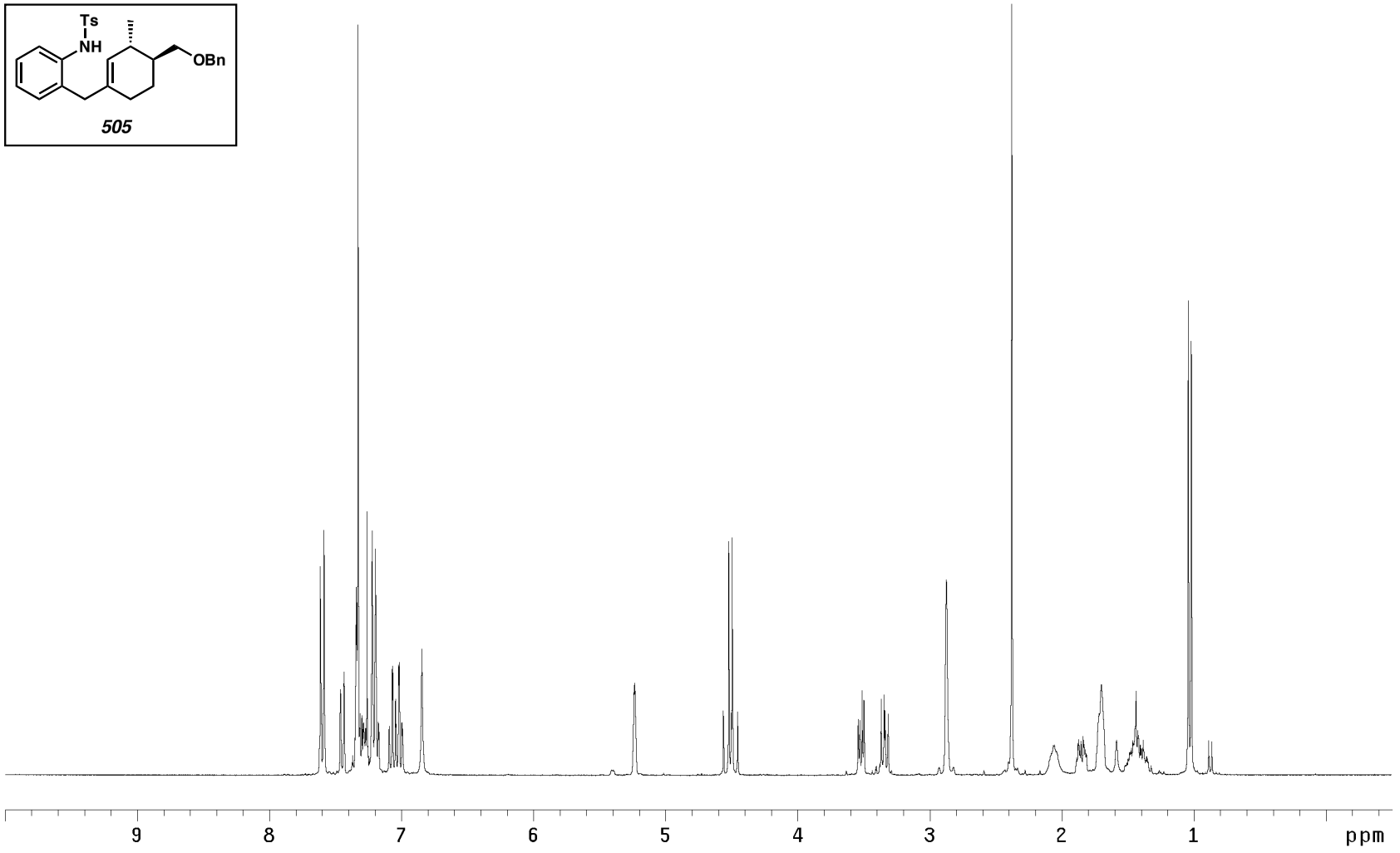


Figure A3.88 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **505**.

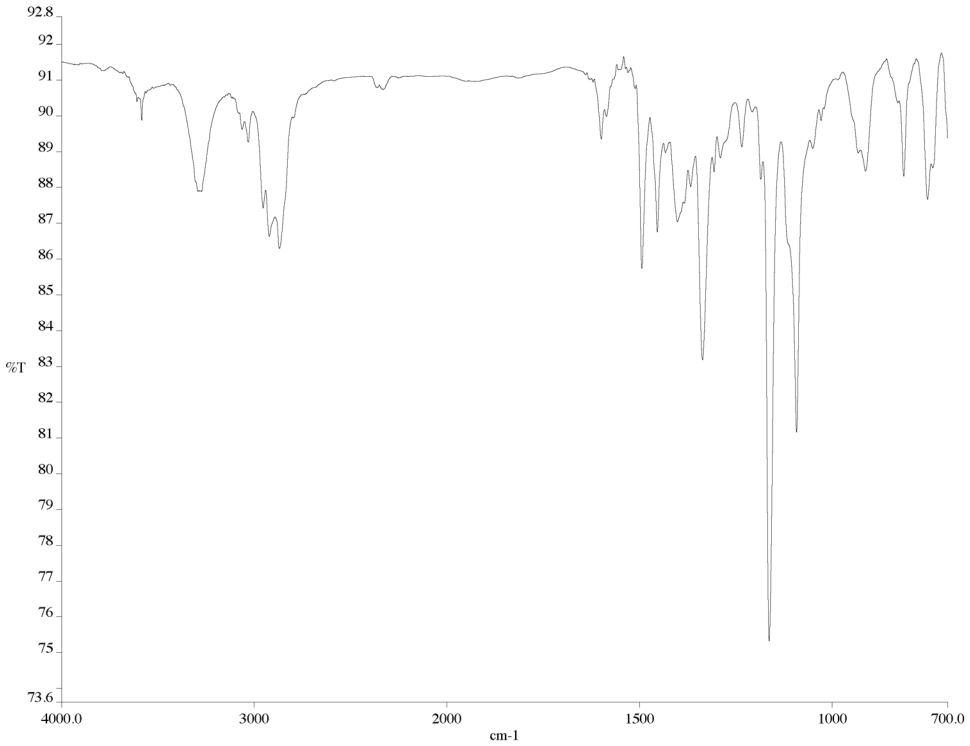


Figure A3.89 Infrared spectrum (thin film/NaCl) of compound **505**.

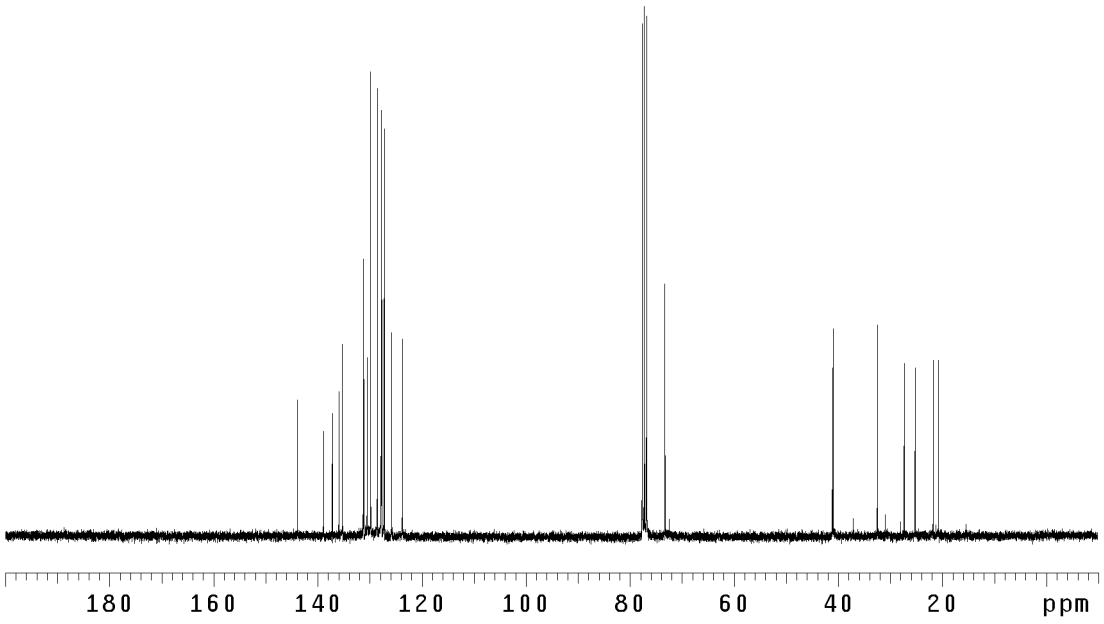


Figure A3.90 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **505**.

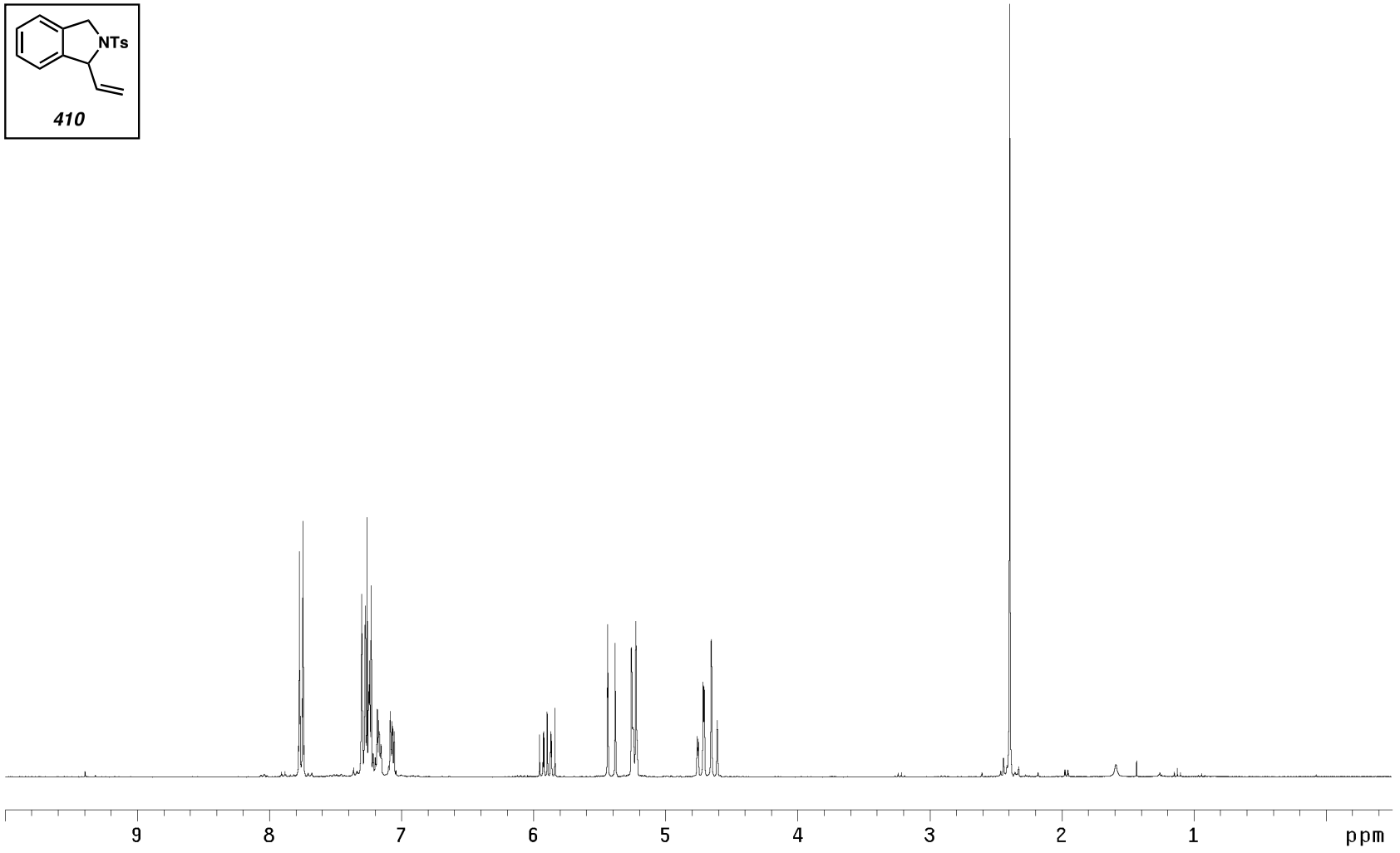


Figure A3.91 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **410**.

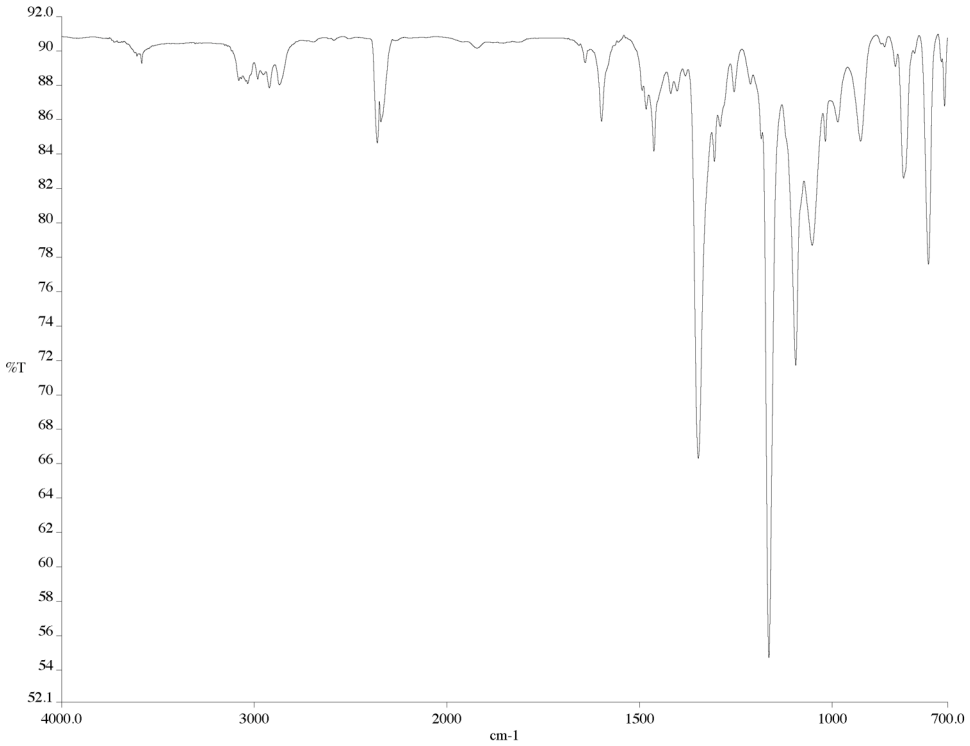


Figure A3.92 Infrared spectrum (thin film/NaCl) of compound **410**.

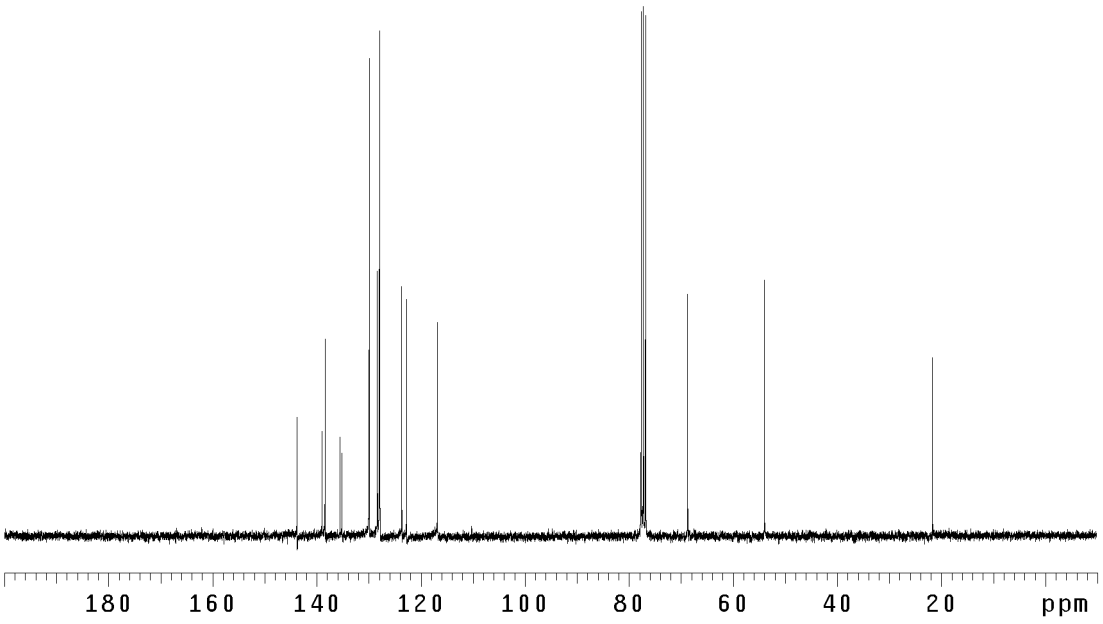


Figure A3.93 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **410**.

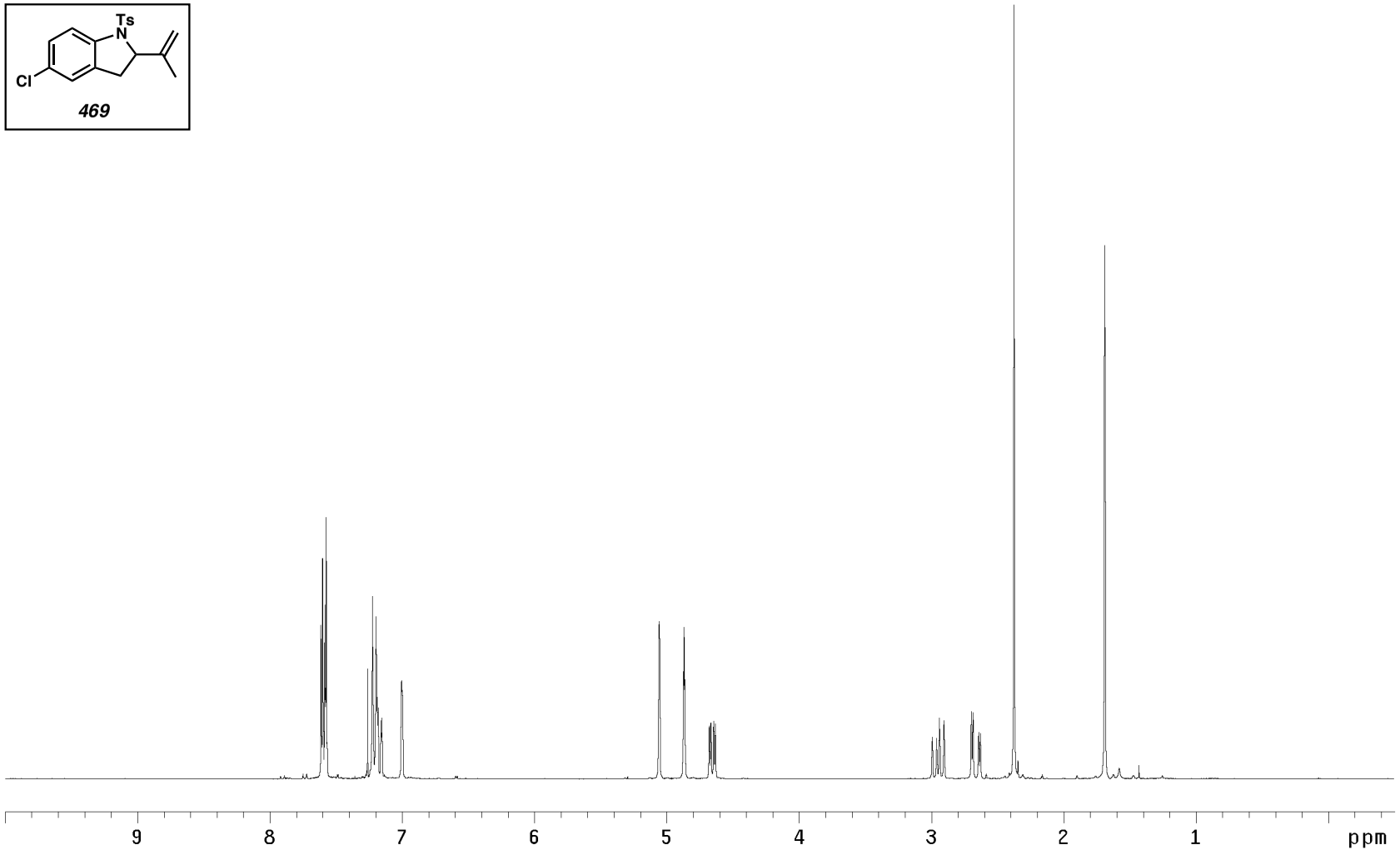


Figure A3.94 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **469**.

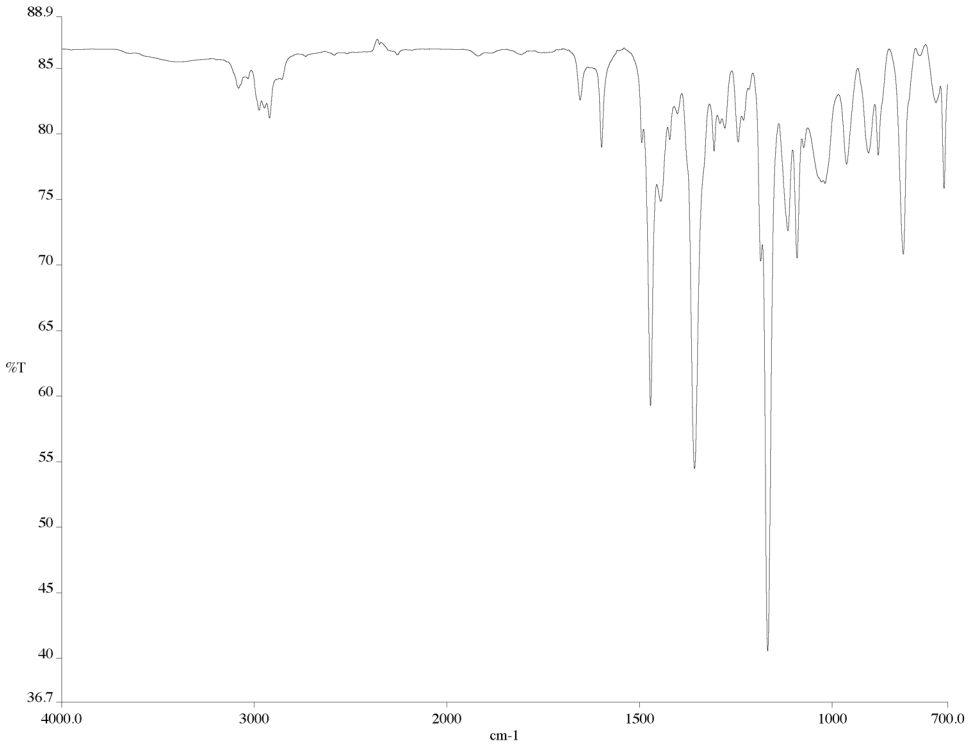


Figure A3.95 Infrared spectrum (thin film/NaCl) of compound **469**.

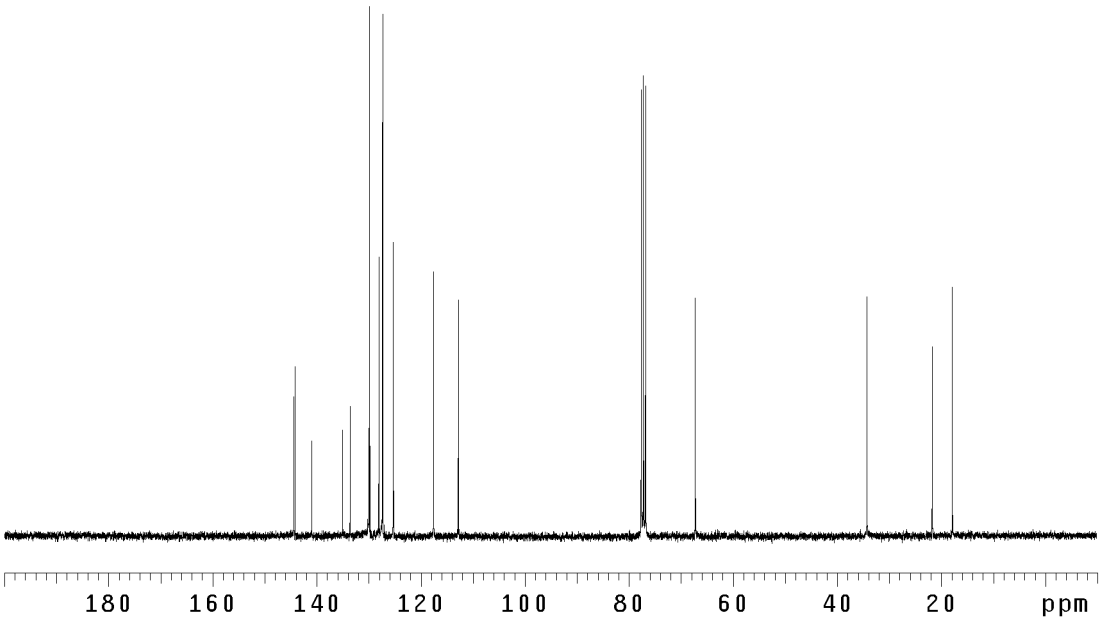


Figure A3.96 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **469**.

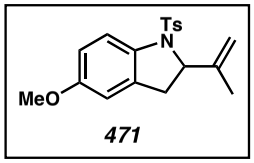


Figure A3.97 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **471**.

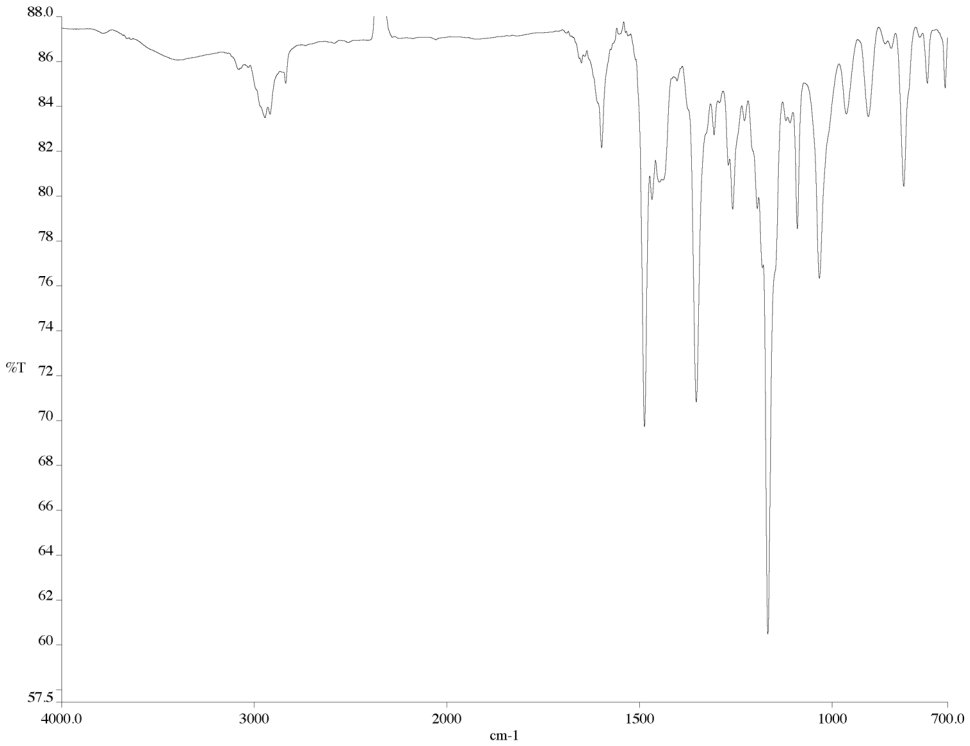


Figure A3.98 Infrared spectrum (thin film/NaCl) of compound **471**.

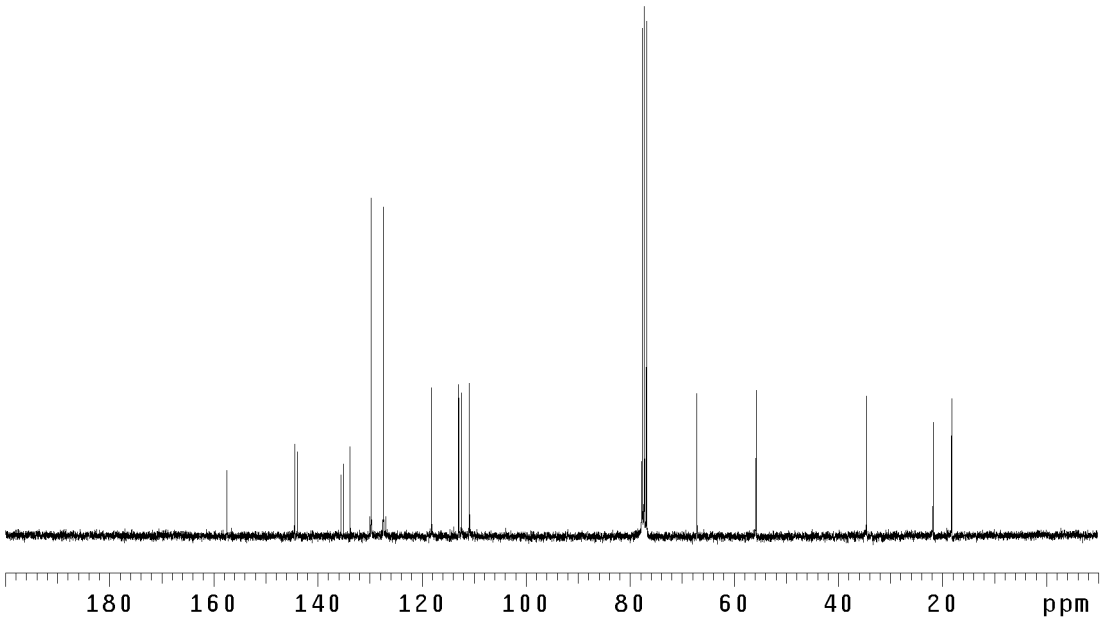


Figure A3.99 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **471**.

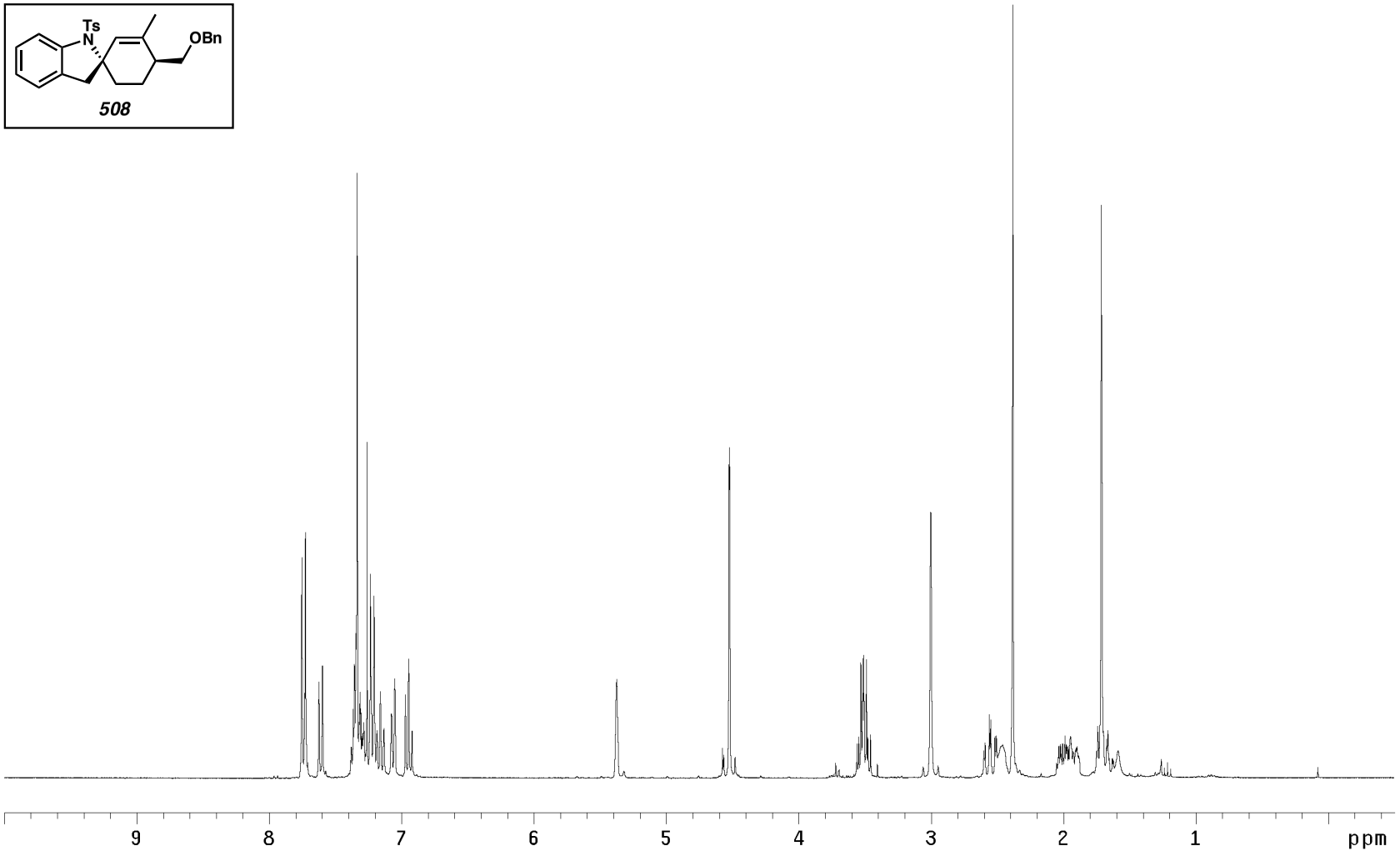


Figure A3.100 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **508**.

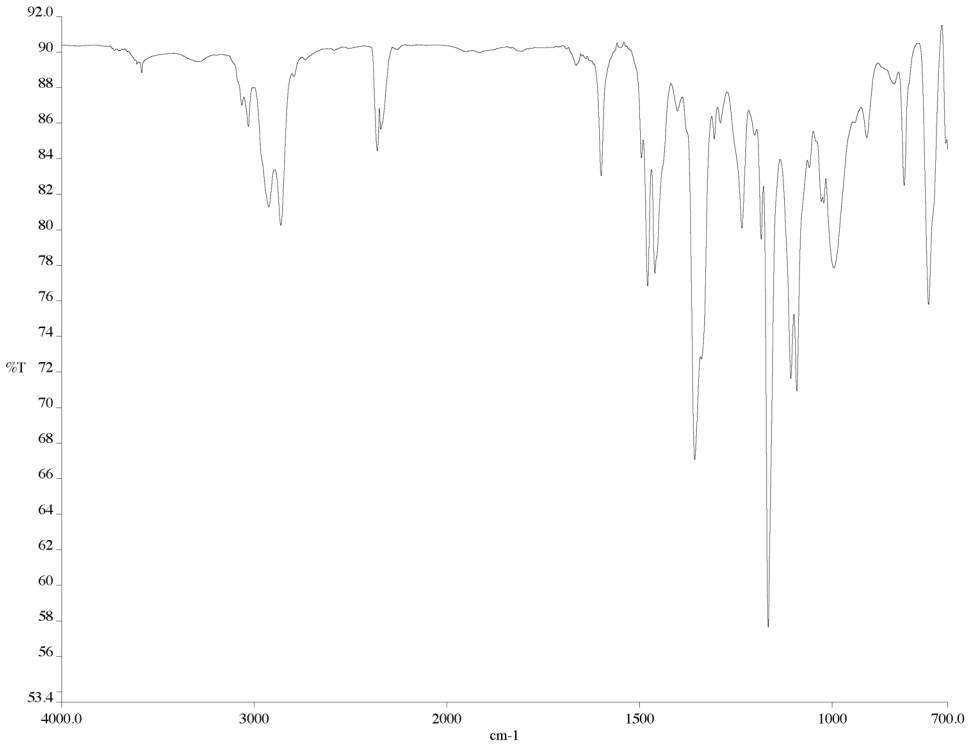


Figure A3.101 Infrared spectrum (thin film/NaCl) of compound **508**.

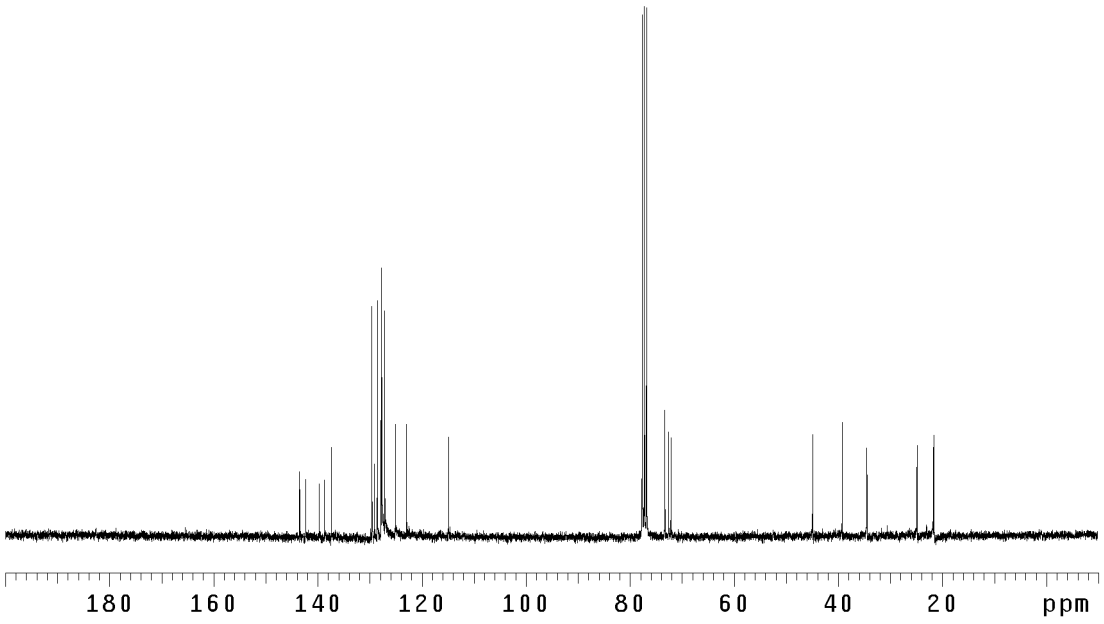


Figure A3.102 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **508**.

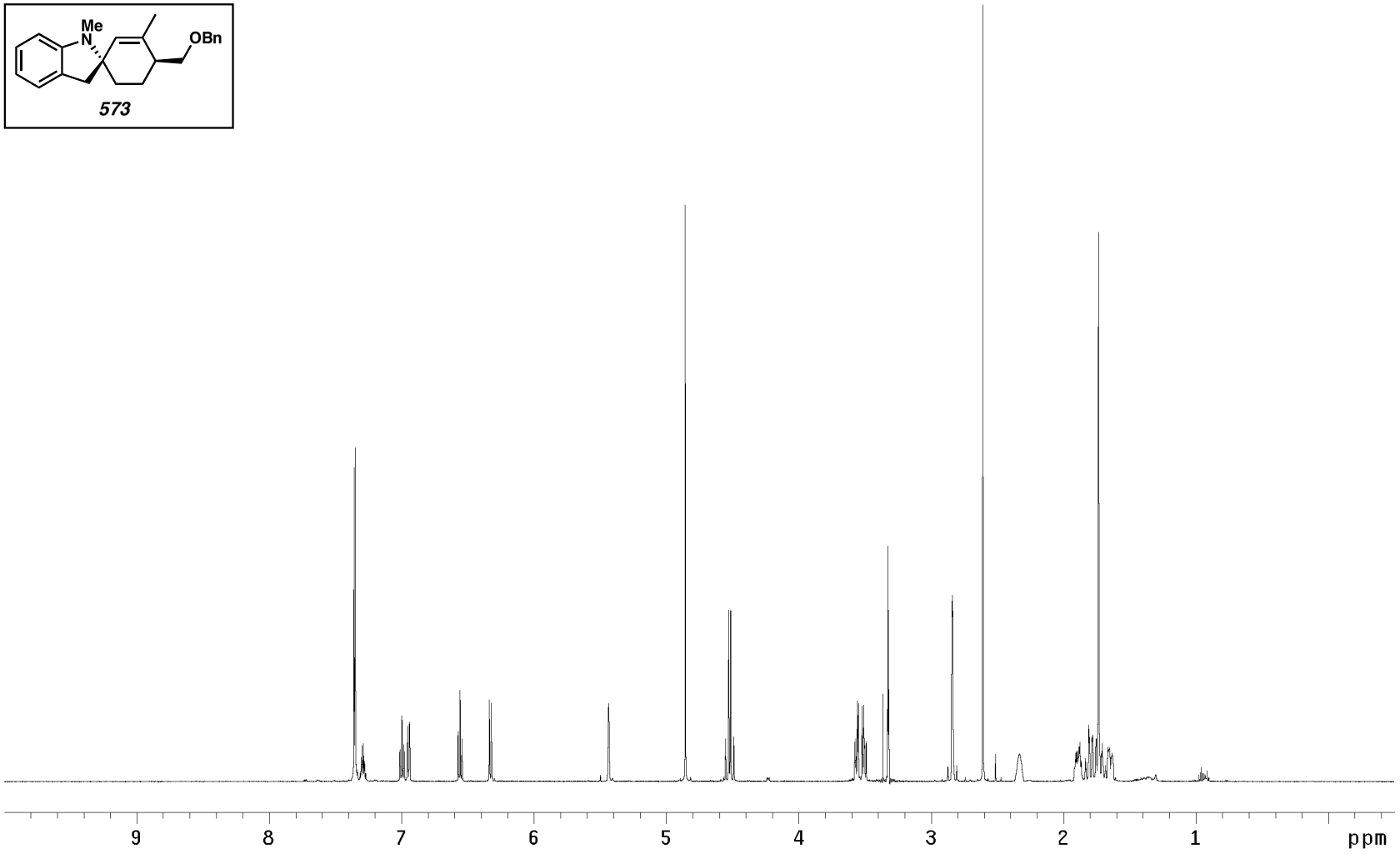


Figure A3.103 ^{1}H NMR (500 MHz, CD_3OD) of compound **573**.

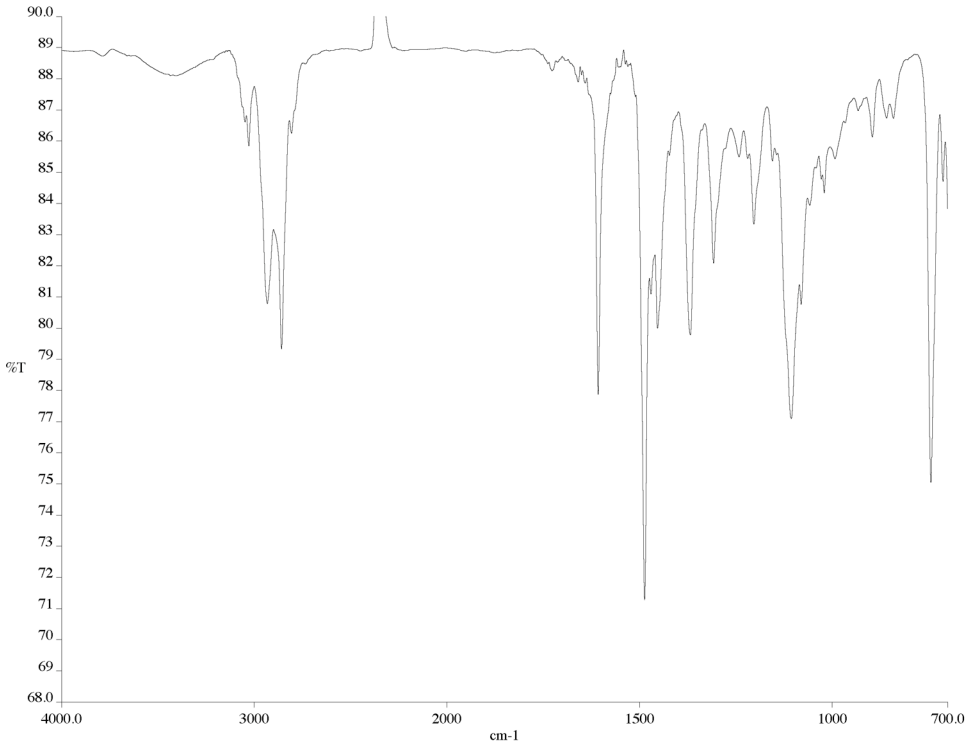


Figure A3.104 Infrared spectrum (thin film/NaCl) of compound **573**.

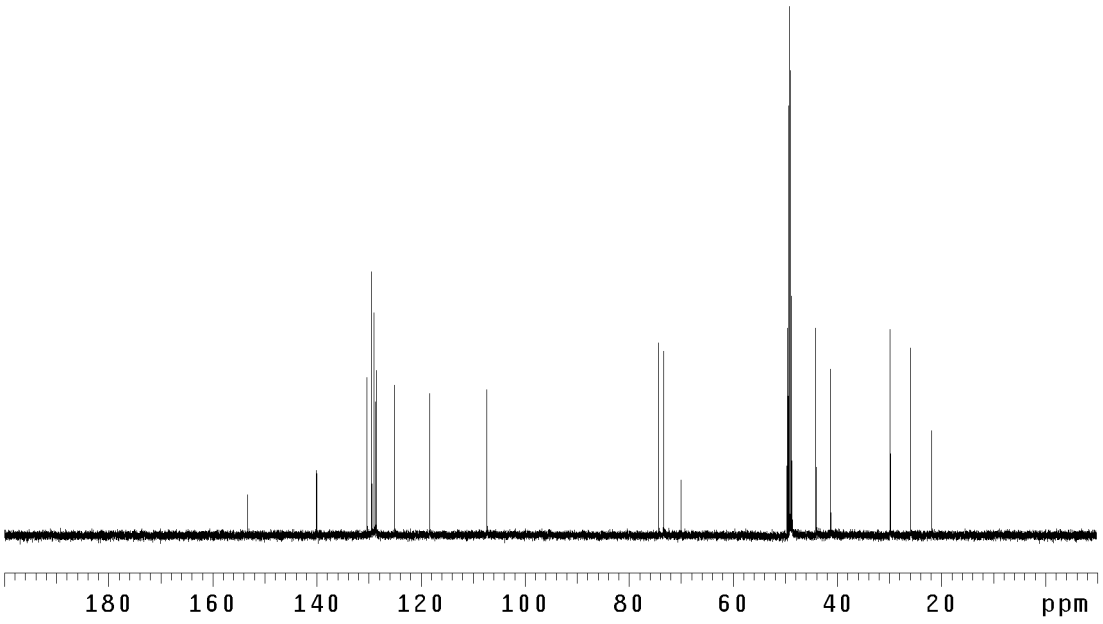


Figure A3.105 ^{13}C NMR (125 MHz, CD_3OD) of compound **573**.

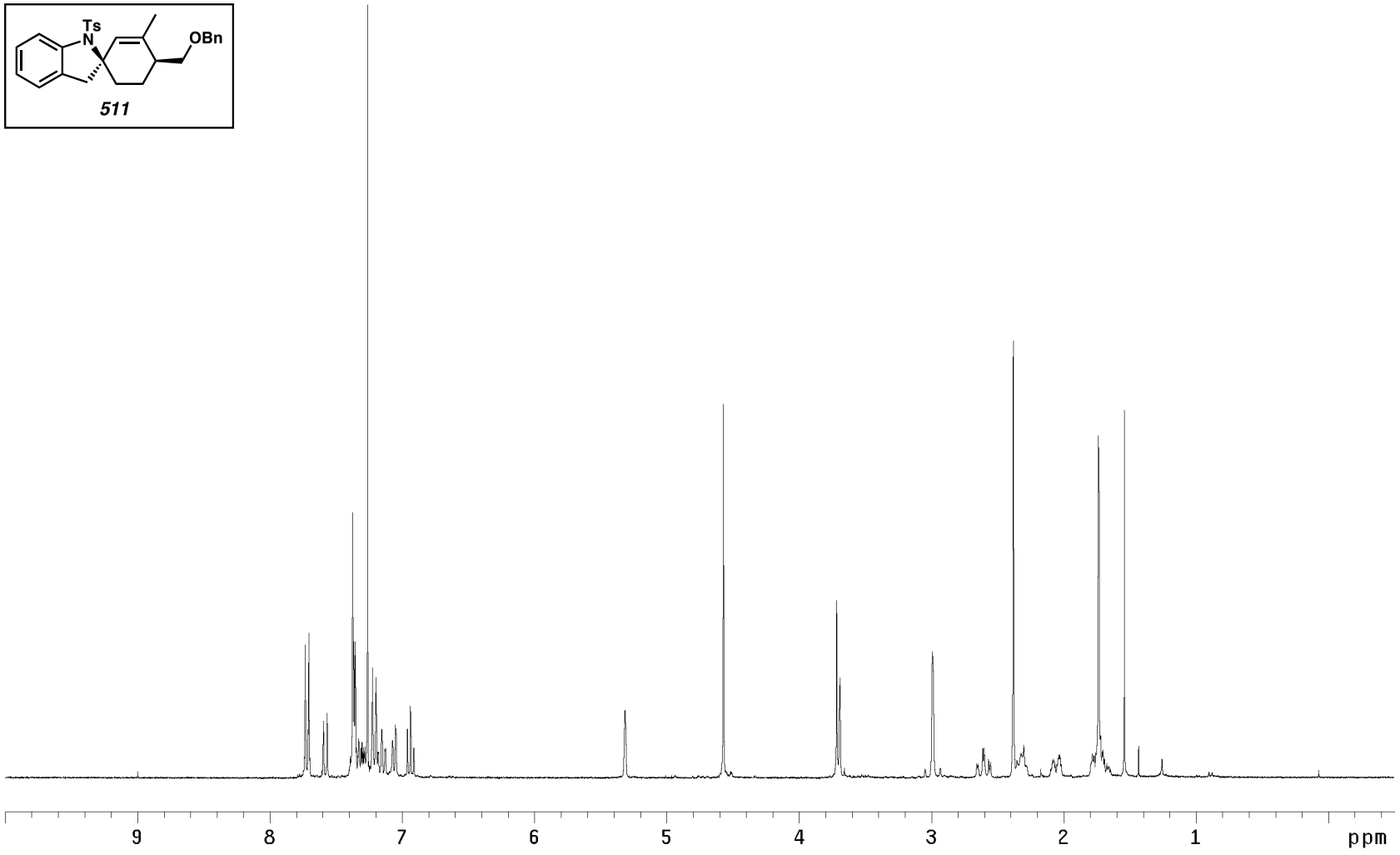


Figure A3.106 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **511**.

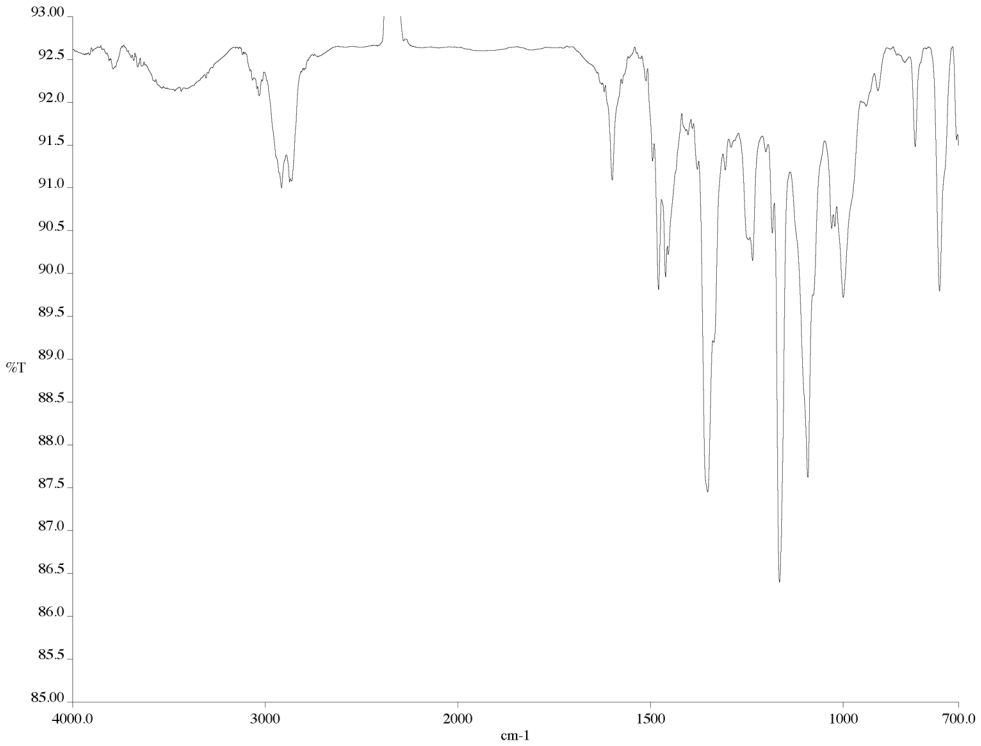


Figure A3.107 Infrared spectrum (thin film/NaCl) of compound **511**.

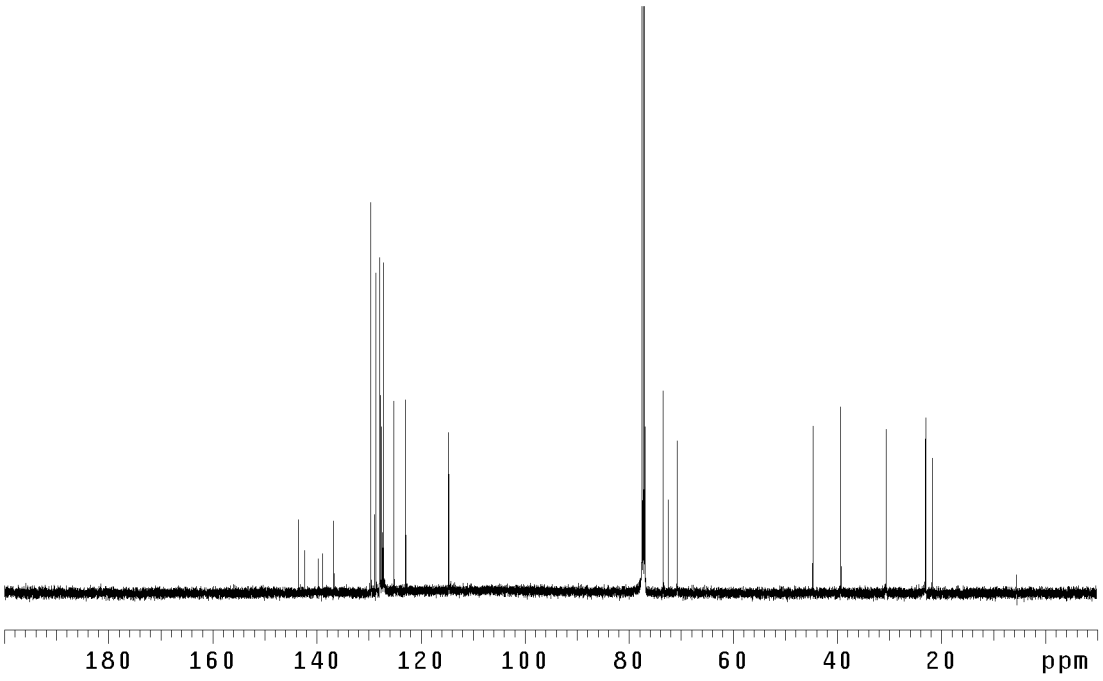


Figure A3.108 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **511**.

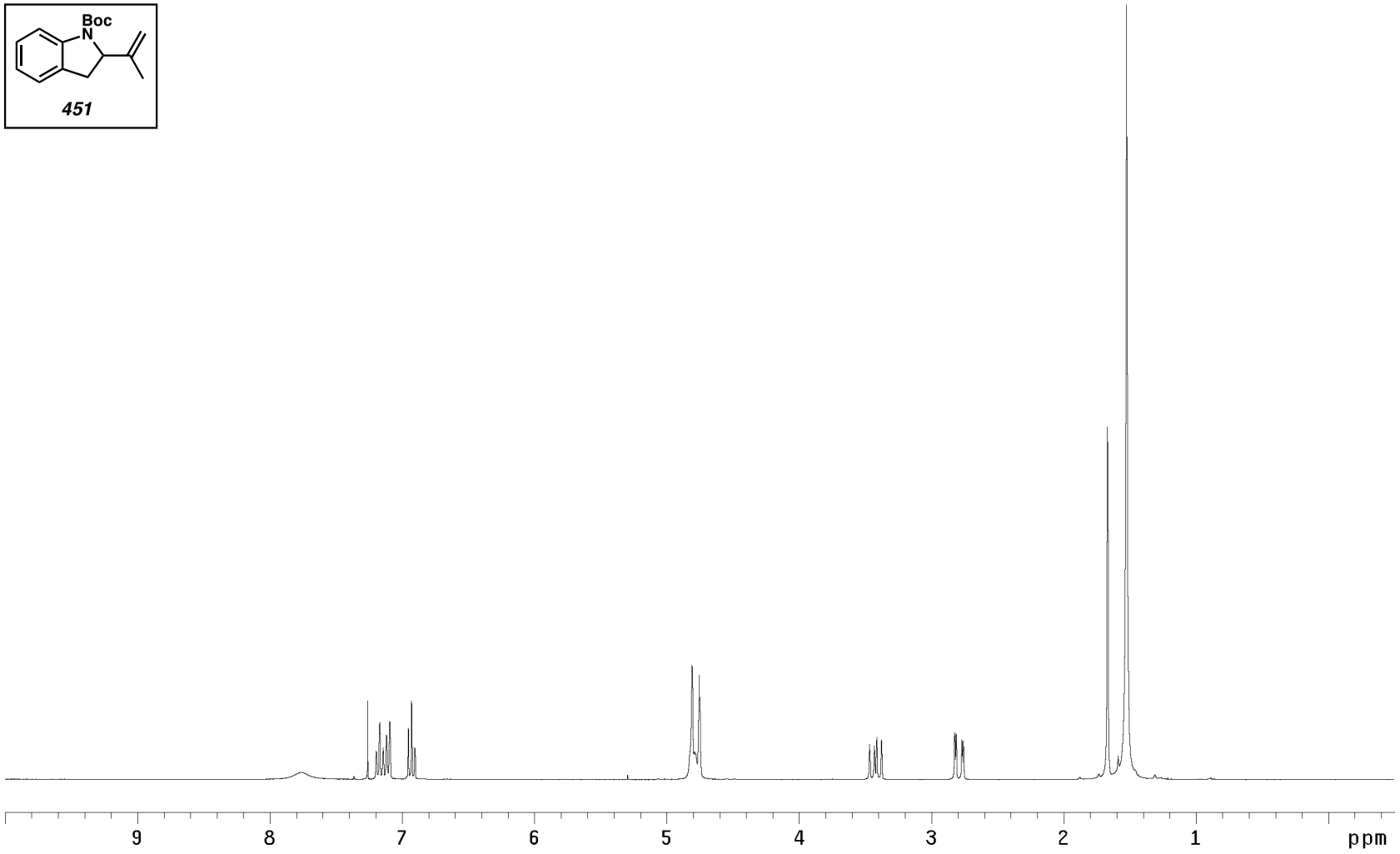


Figure A3.109 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **451**.

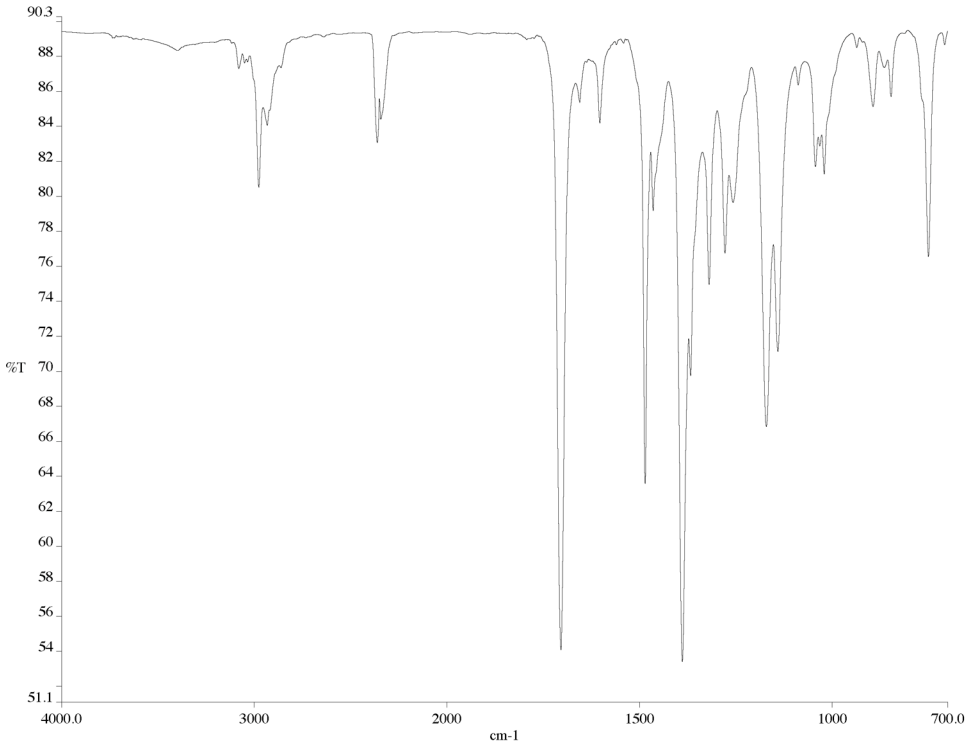


Figure A3.110 Infrared spectrum (thin film/NaCl) of compound **451**.

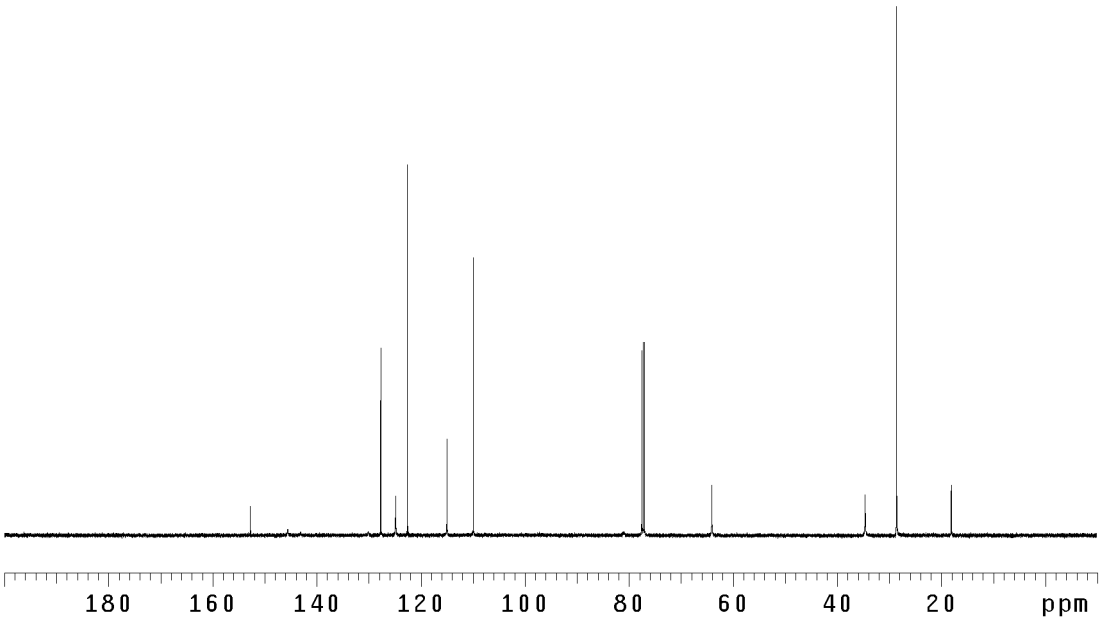


Figure A3.111 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **451**.

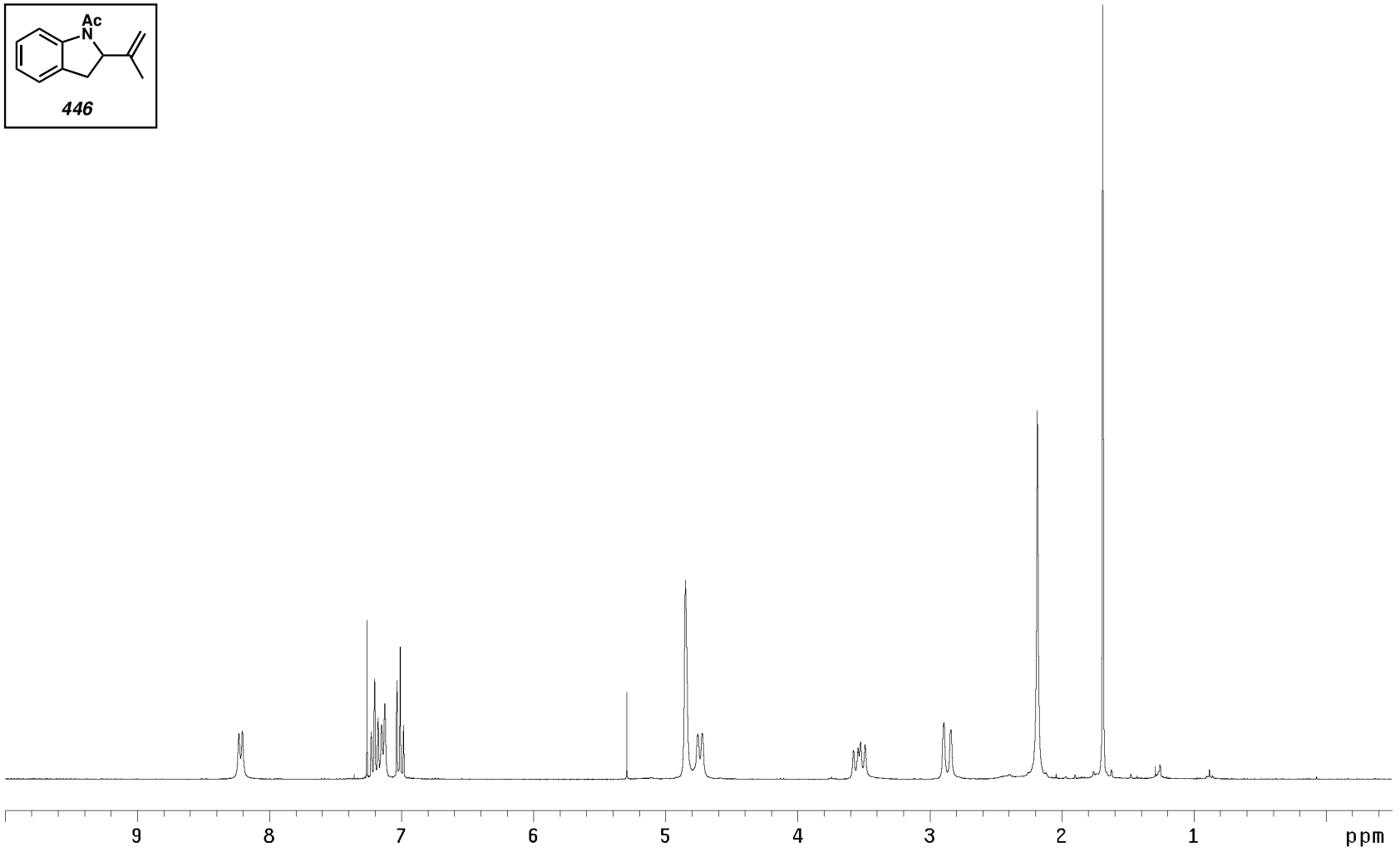


Figure A3.112 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **446**.

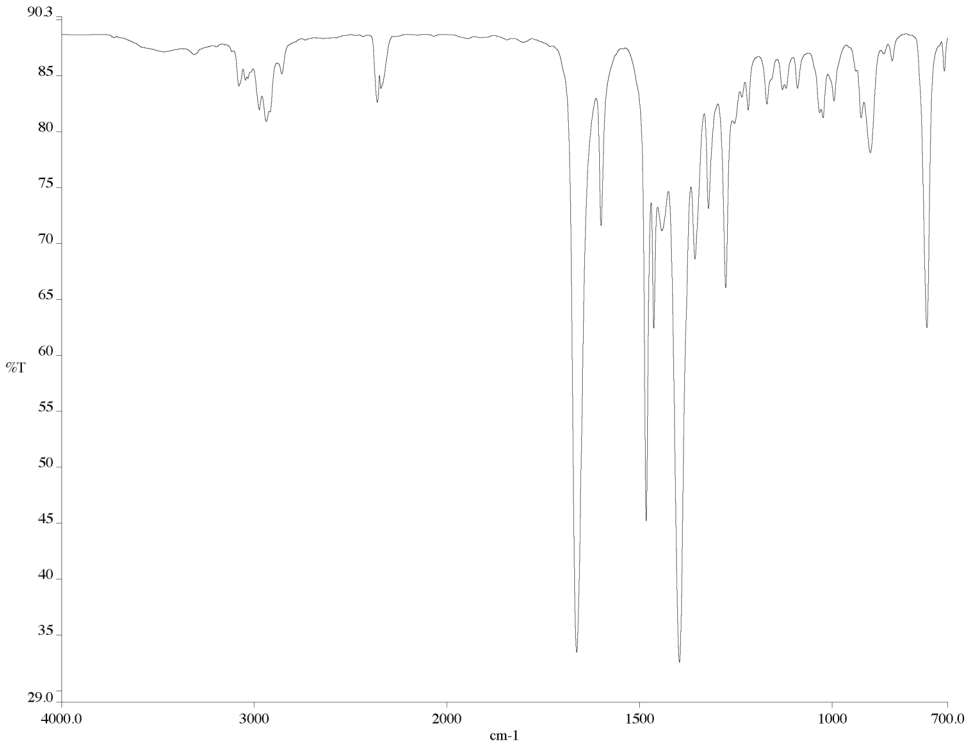


Figure A3.113 Infrared spectrum (thin film/NaCl) of compound **446**.

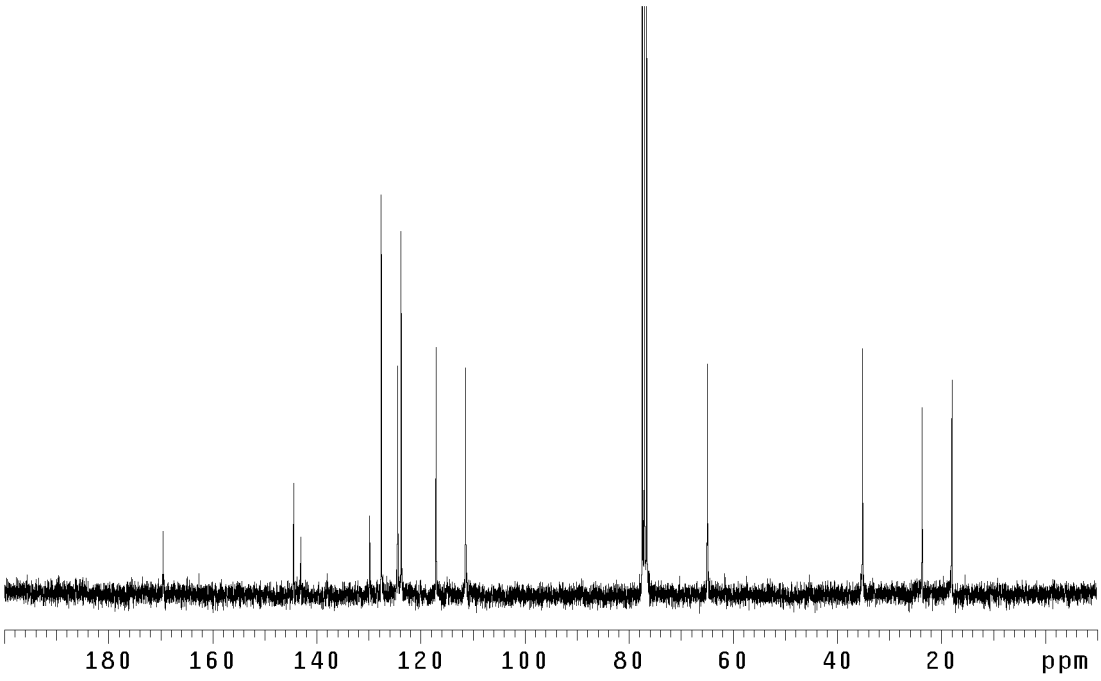


Figure A3.114 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **446**.

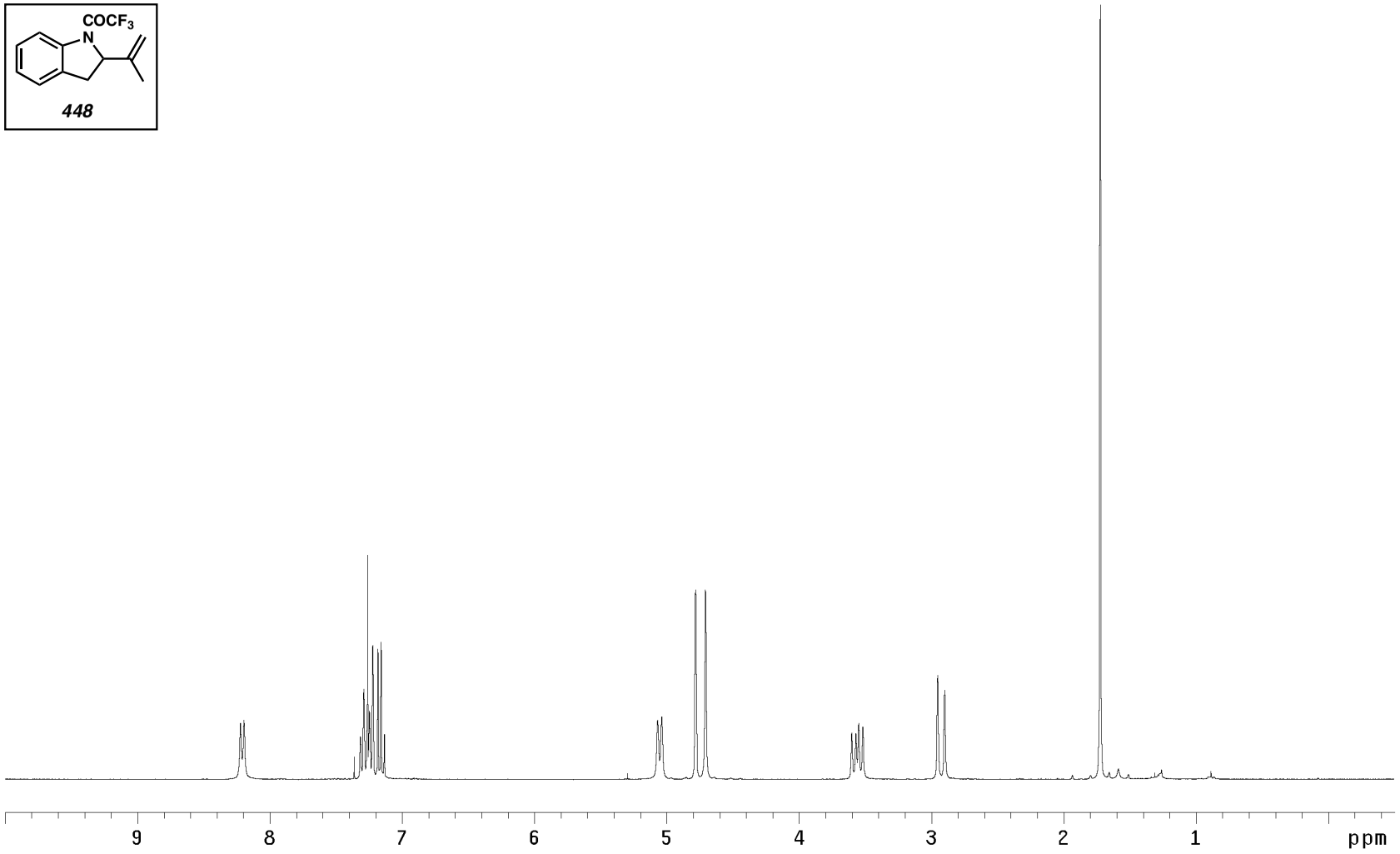


Figure A3.115 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **448**.

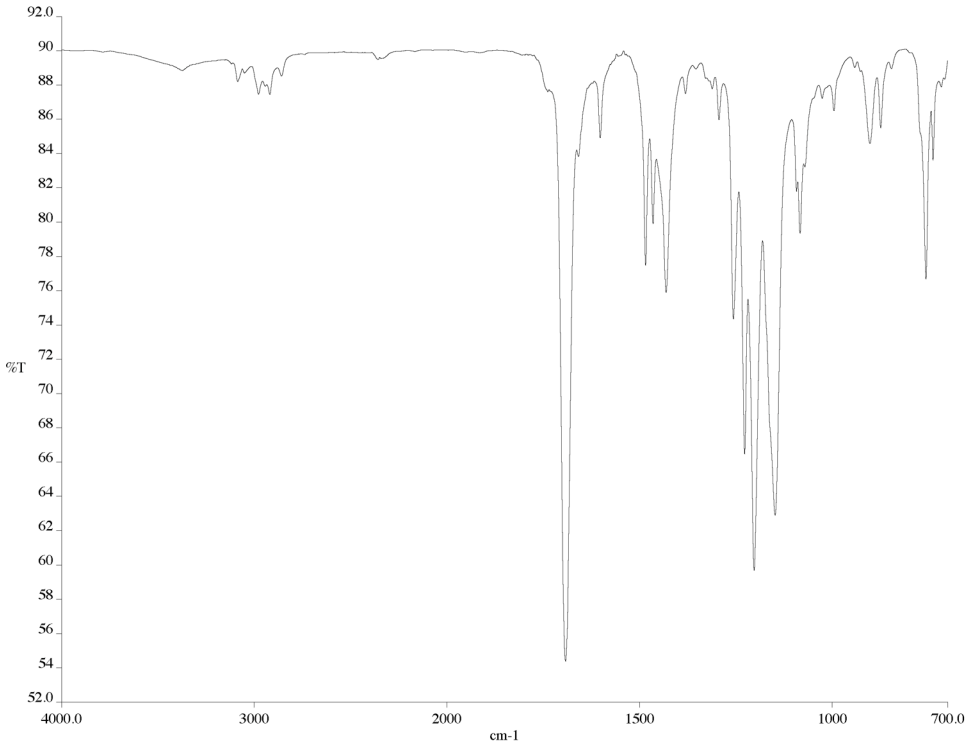


Figure A3.116 Infrared spectrum (thin film/NaCl) of compound **448**.

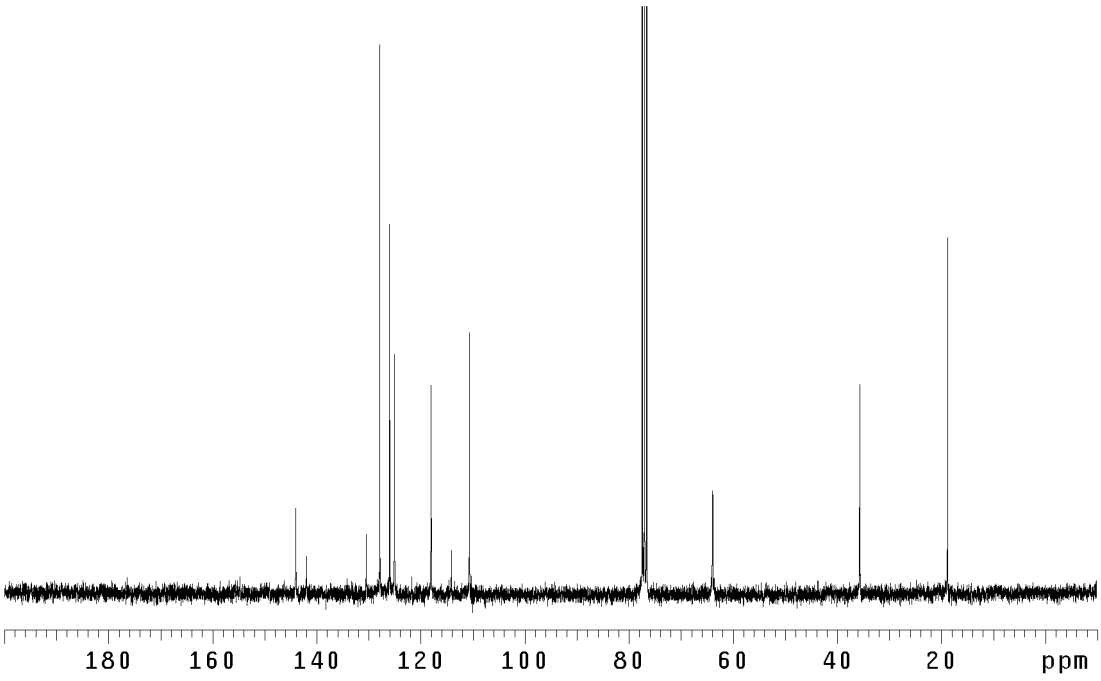


Figure A3.117 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **448**.

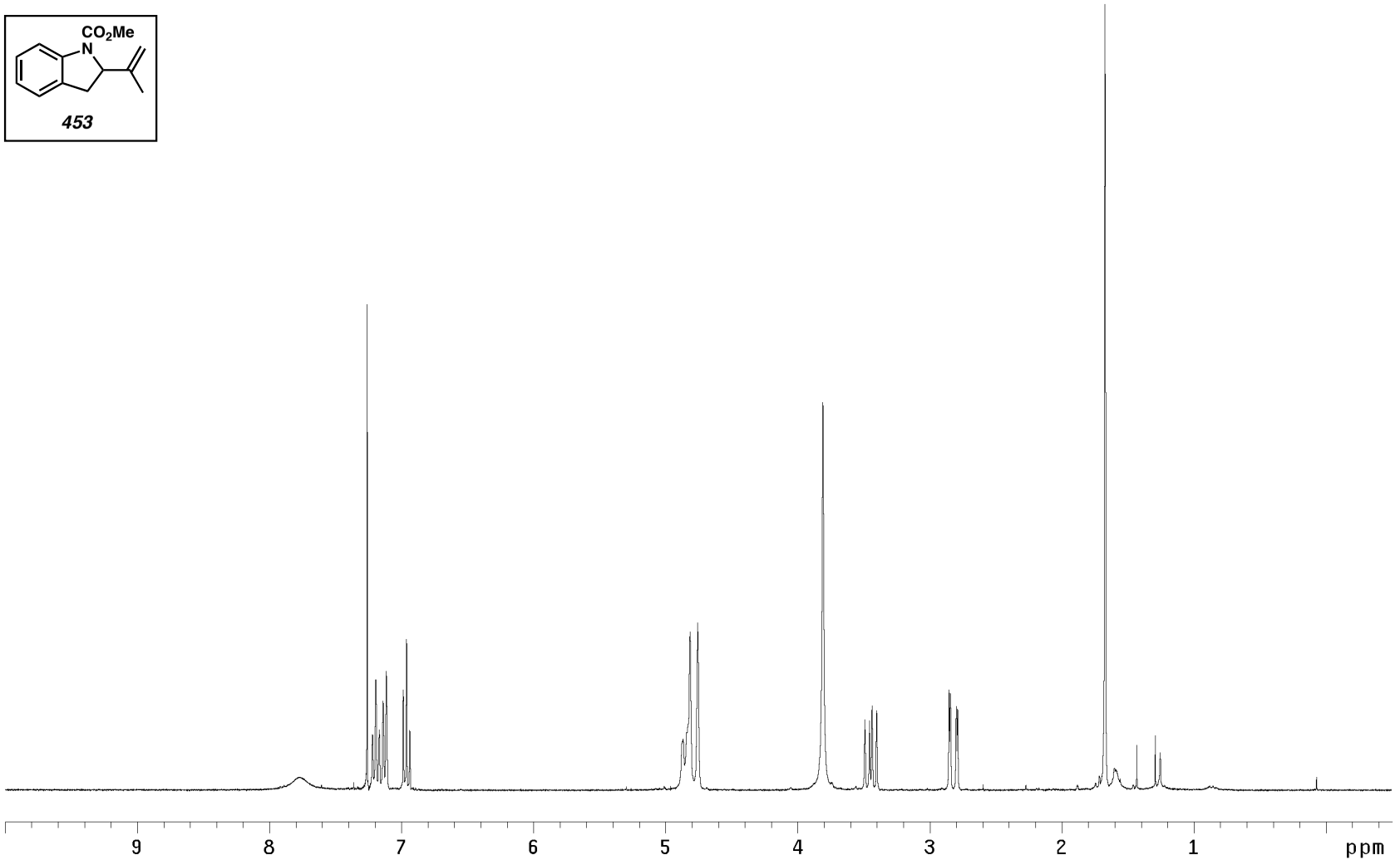


Figure A3.118 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **453**.

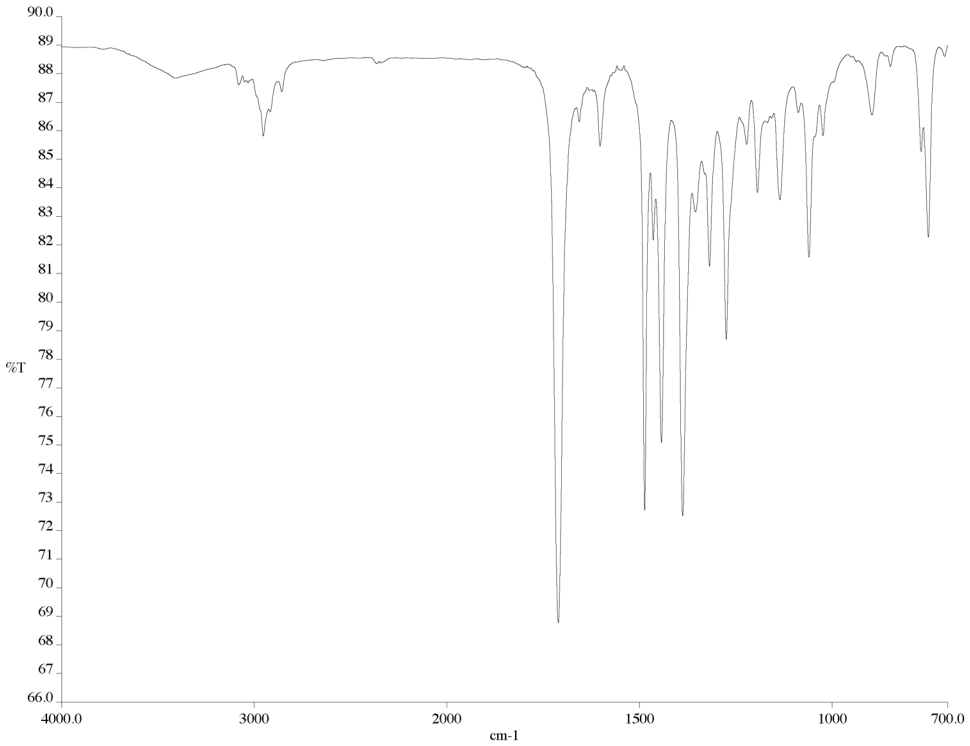


Figure A3.119 Infrared spectrum (thin film/NaCl) of compound **453**.

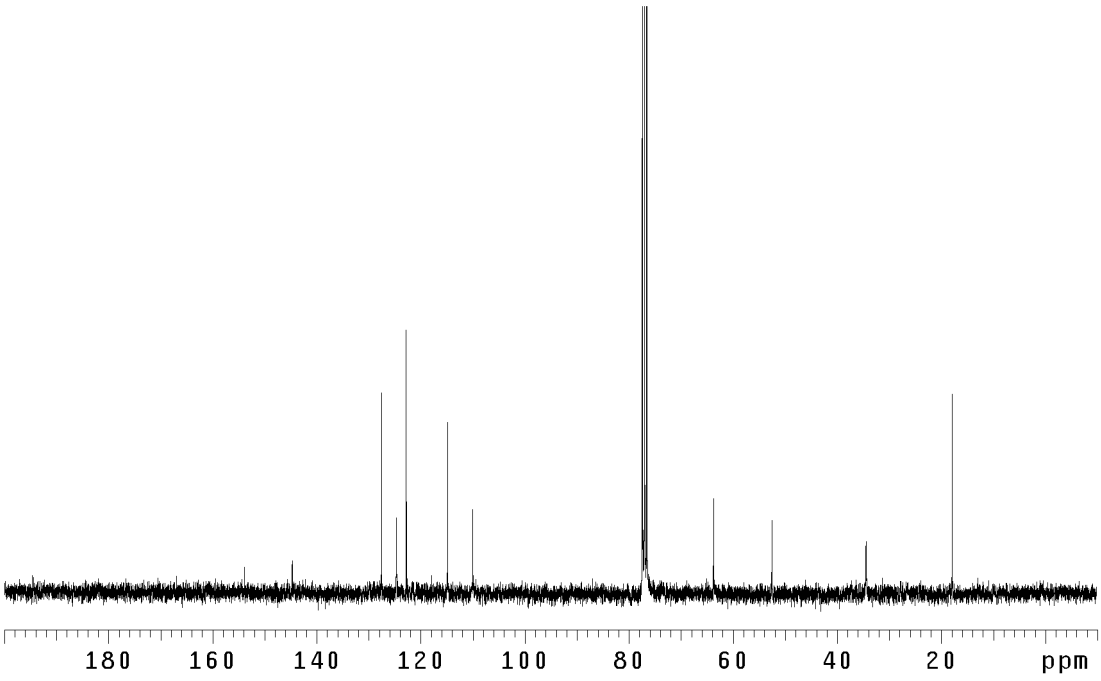


Figure A3.120 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **453**.

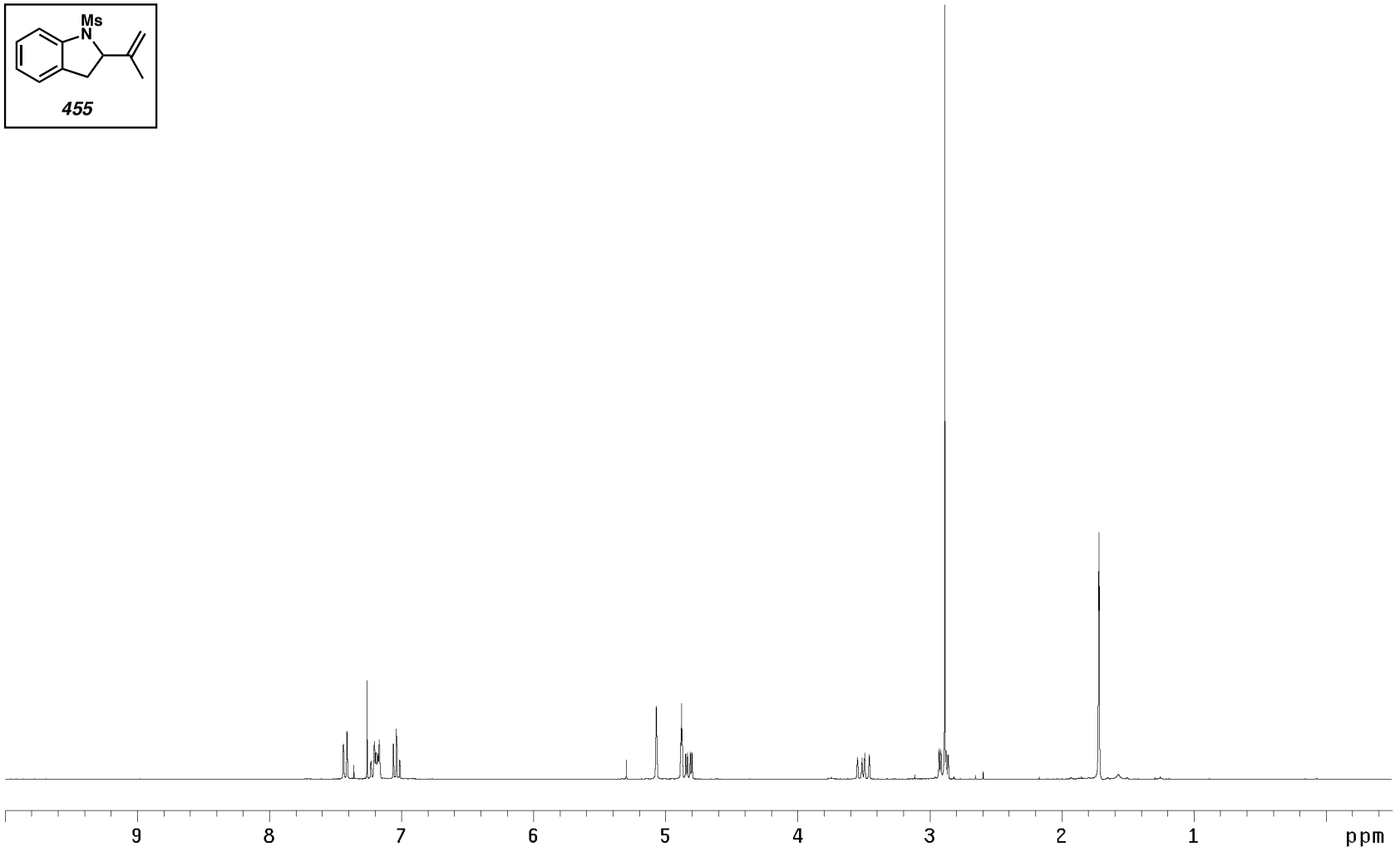


Figure A3.121 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **455**.

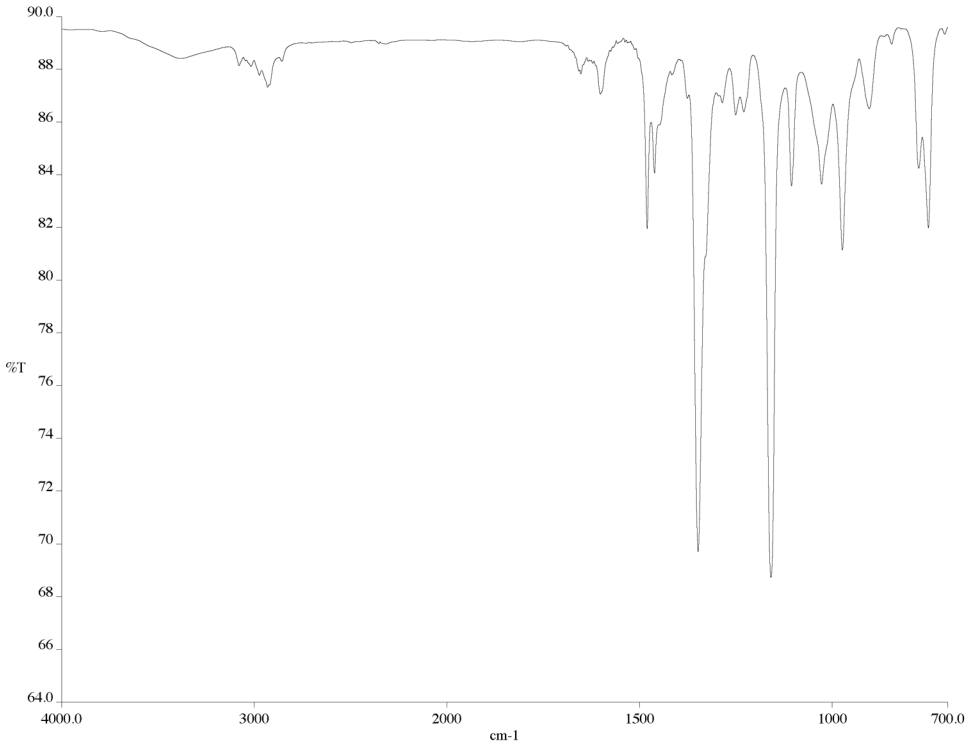


Figure A3.122 Infrared spectrum (thin film/NaCl) of compound **455**.

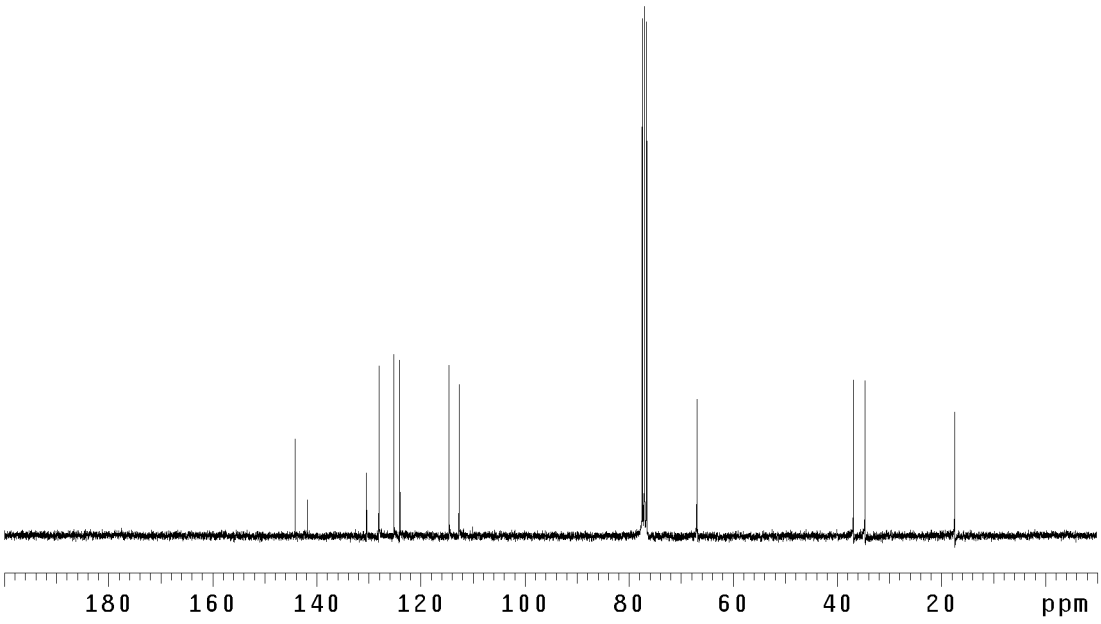


Figure A3.123 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **455**.

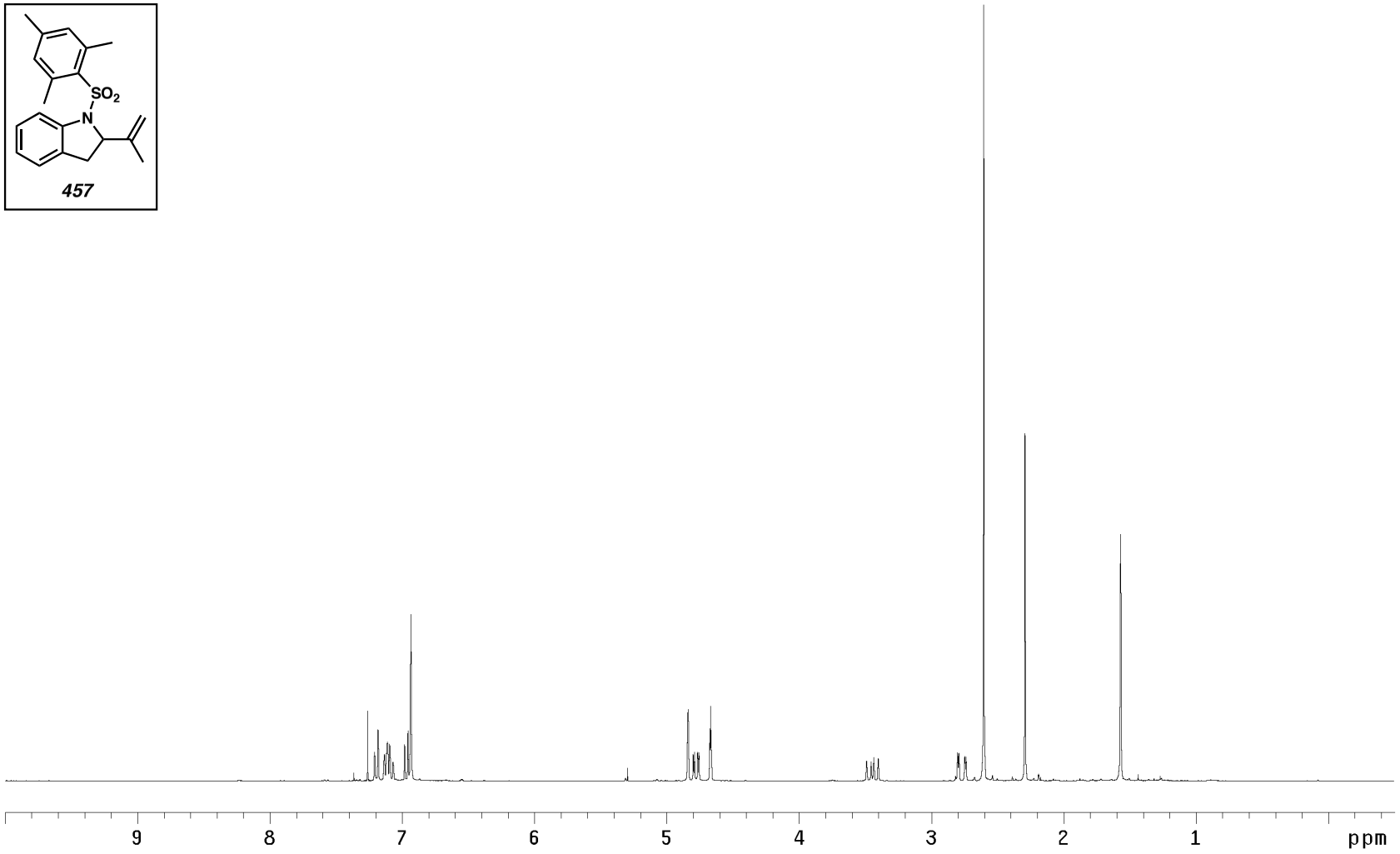


Figure A3.124 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **457**.

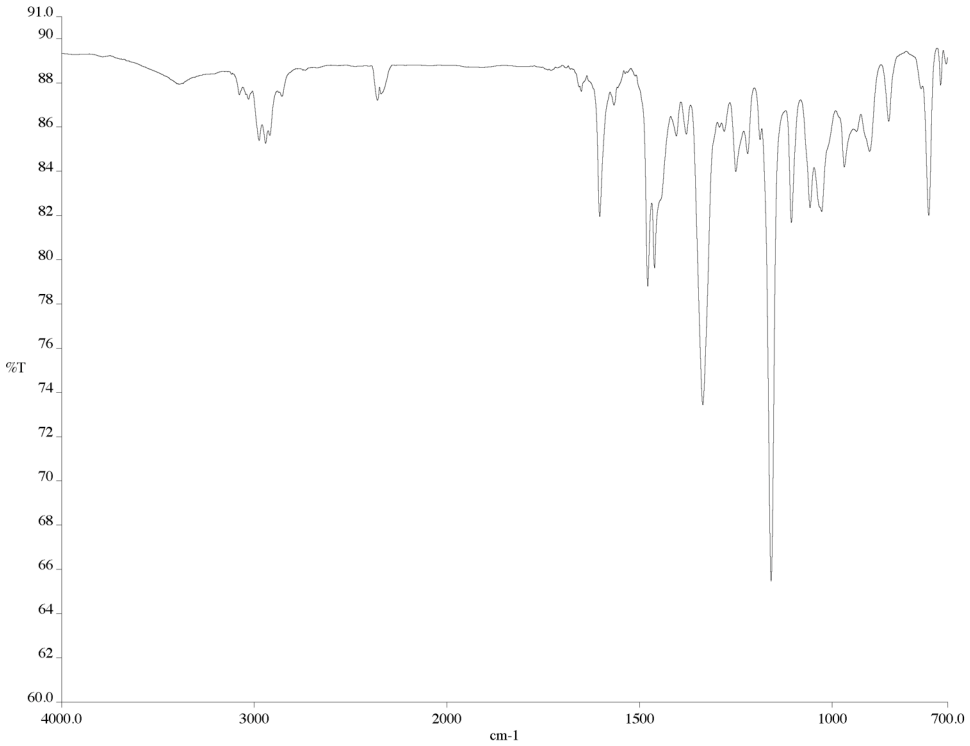


Figure A3.125 Infrared spectrum (thin film/NaCl) of compound **457**.

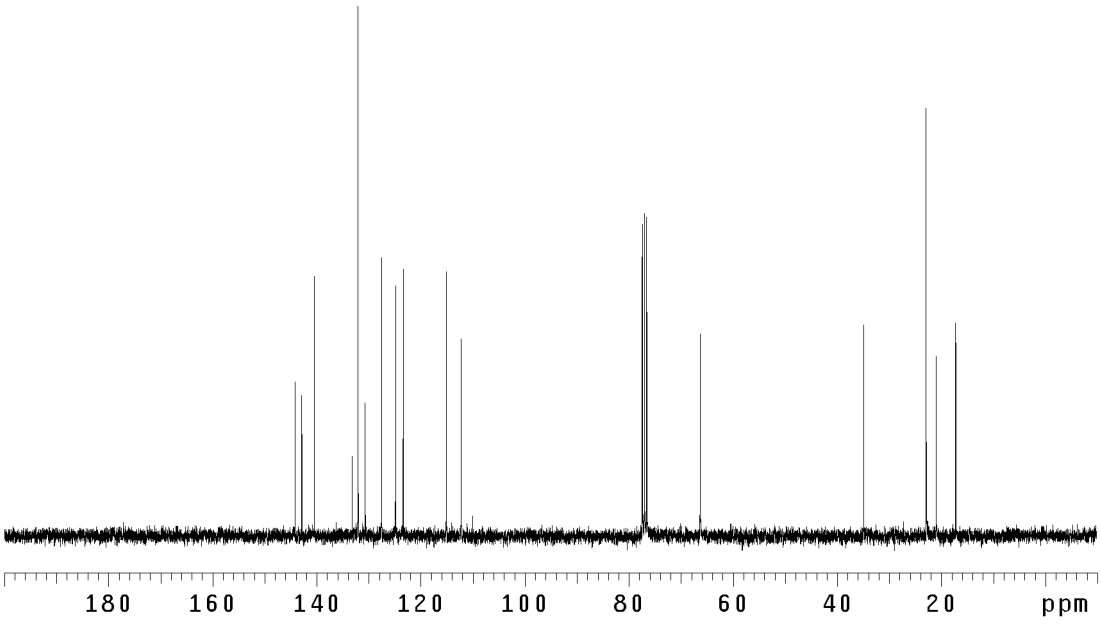


Figure A3.126 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **457**.

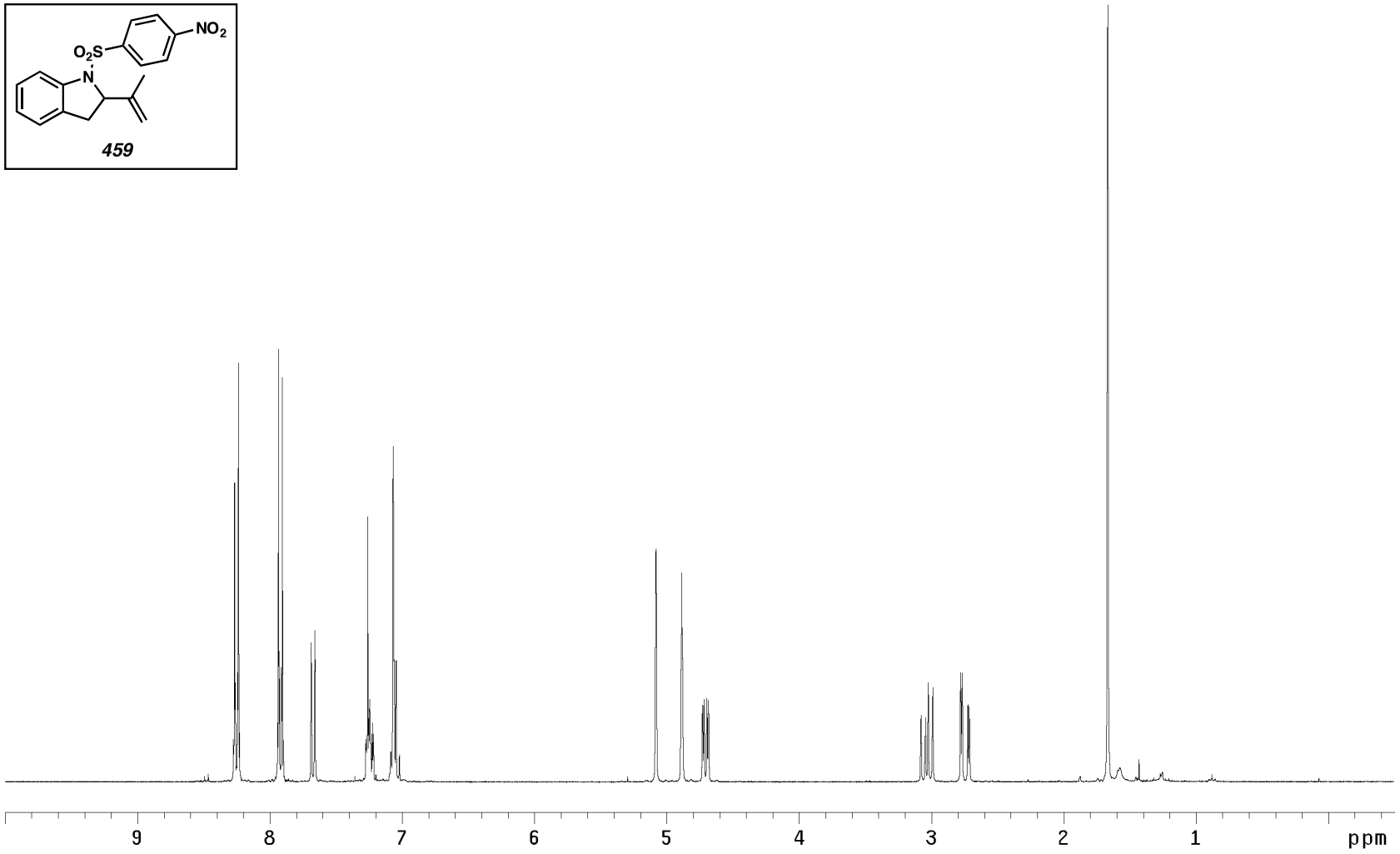


Figure A3.127 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **459**.

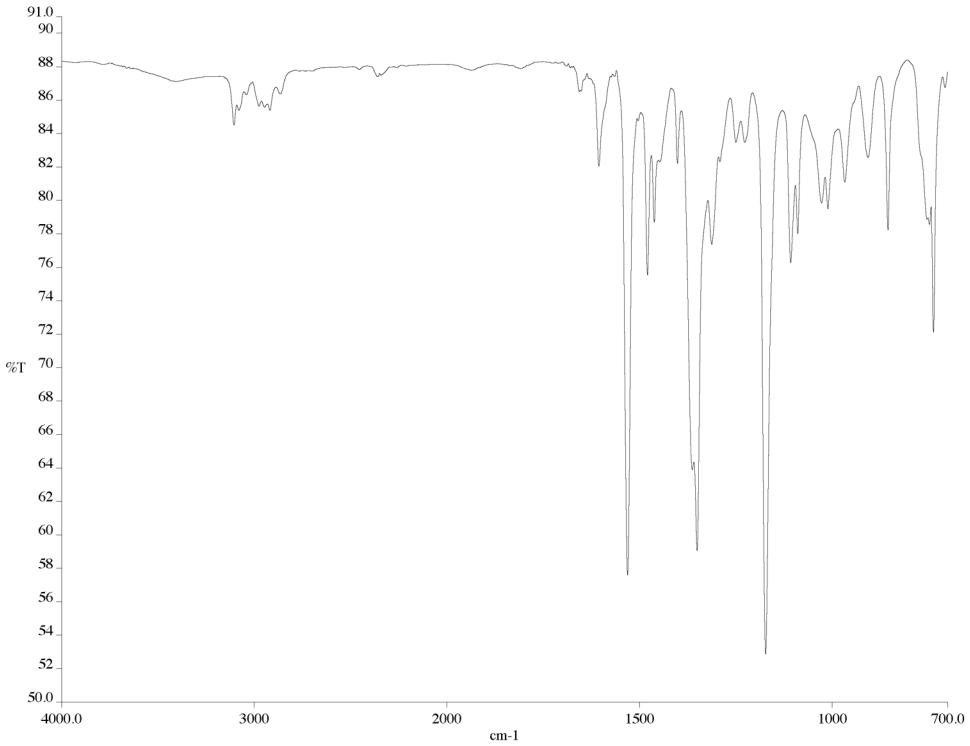


Figure A3.128 Infrared spectrum (thin film/NaCl) of compound **459**.

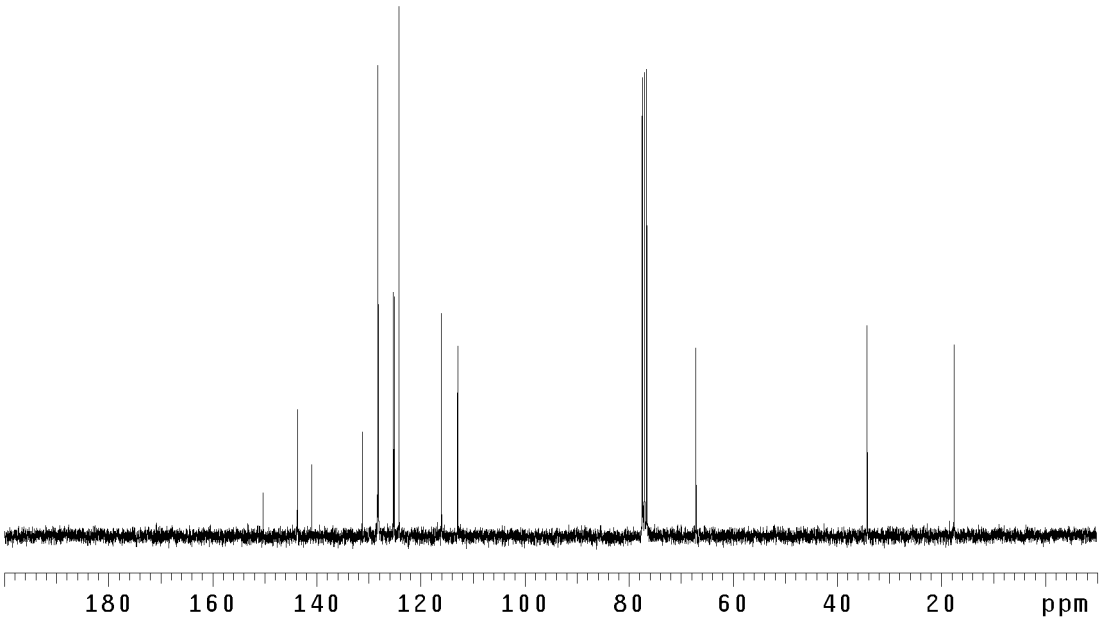


Figure A3.129 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **459**.

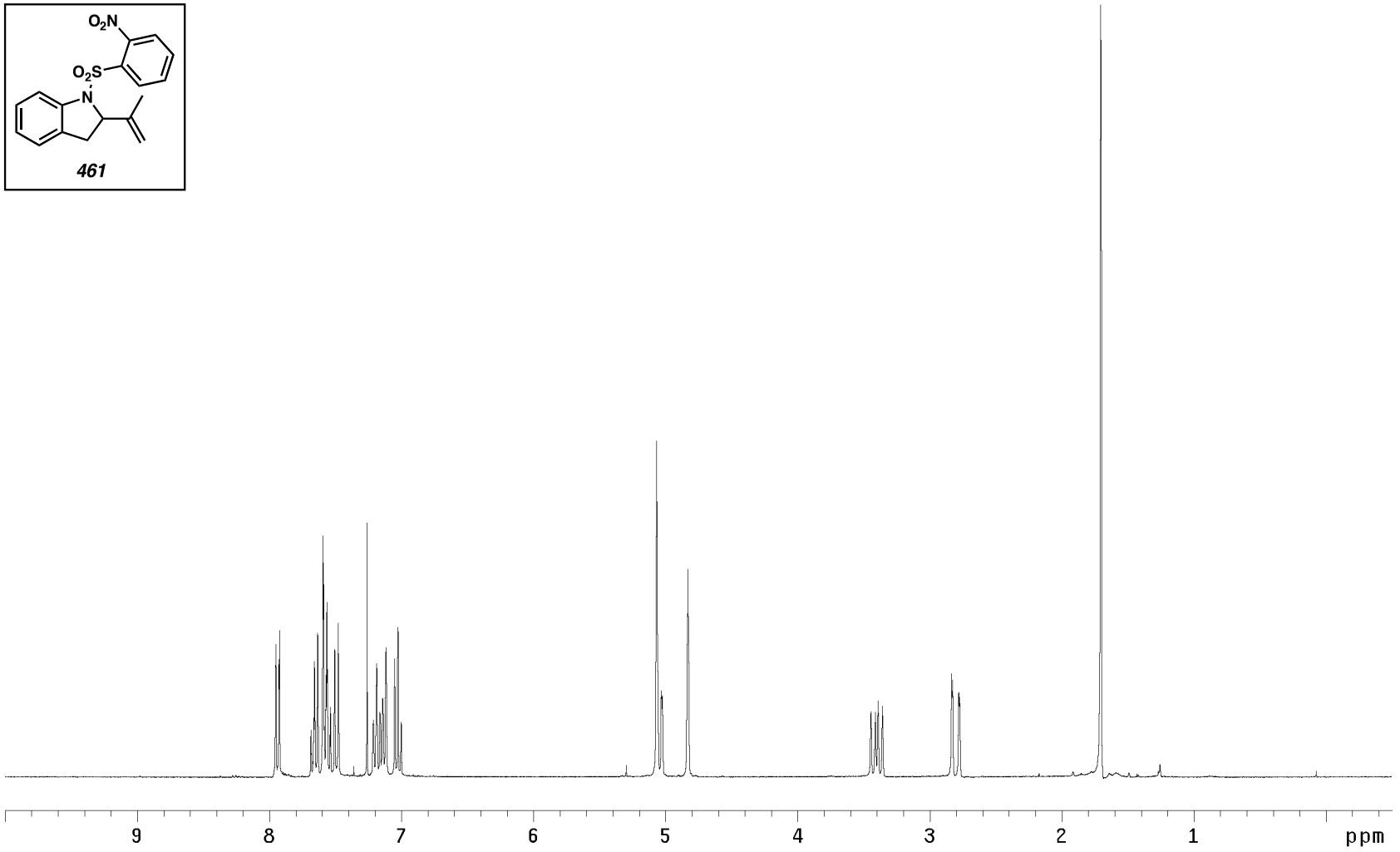


Figure A3.130 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **461**.

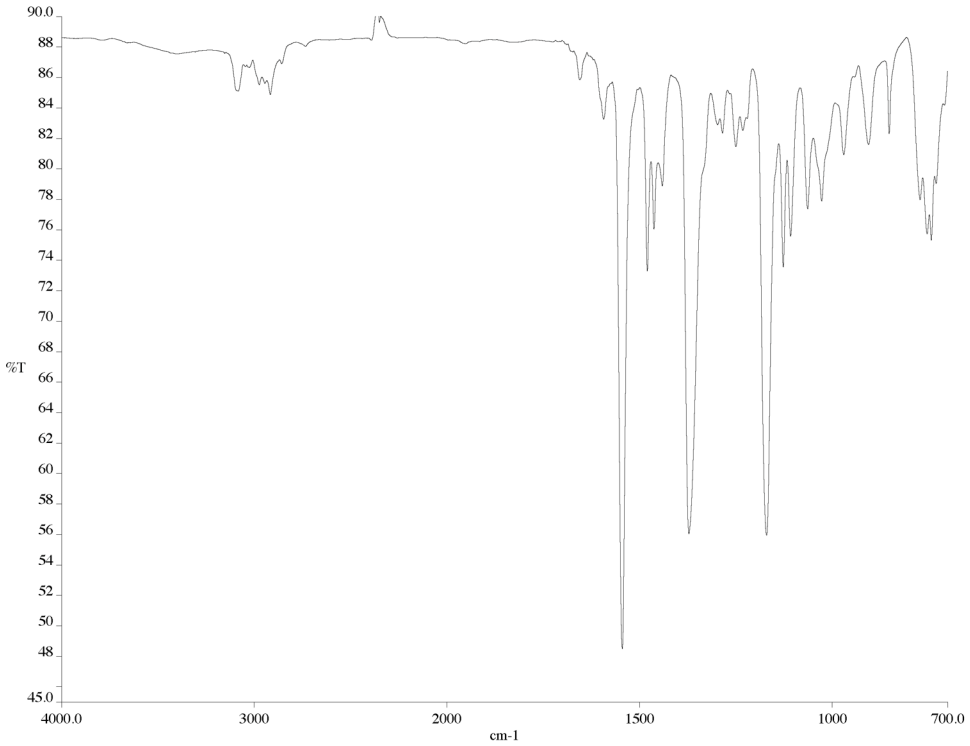


Figure A3.131 Infrared spectrum (thin film/NaCl) of compound **461**.

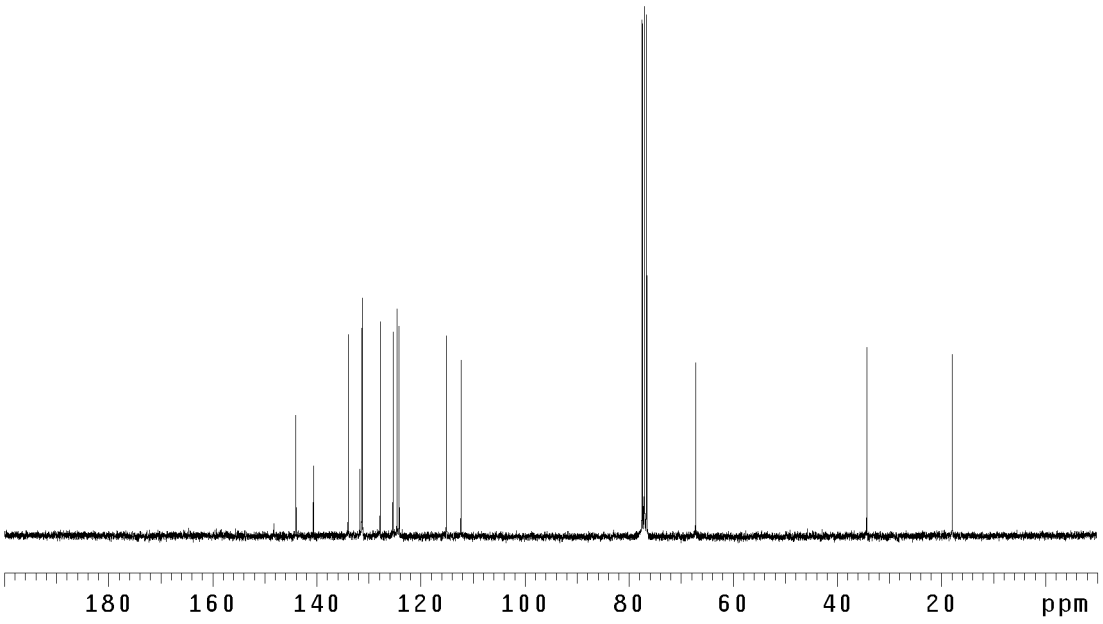


Figure A3.132 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **461**.

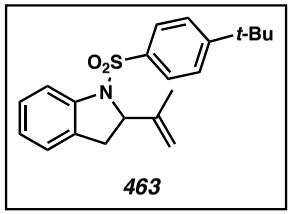


Figure A3.133 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **463**.

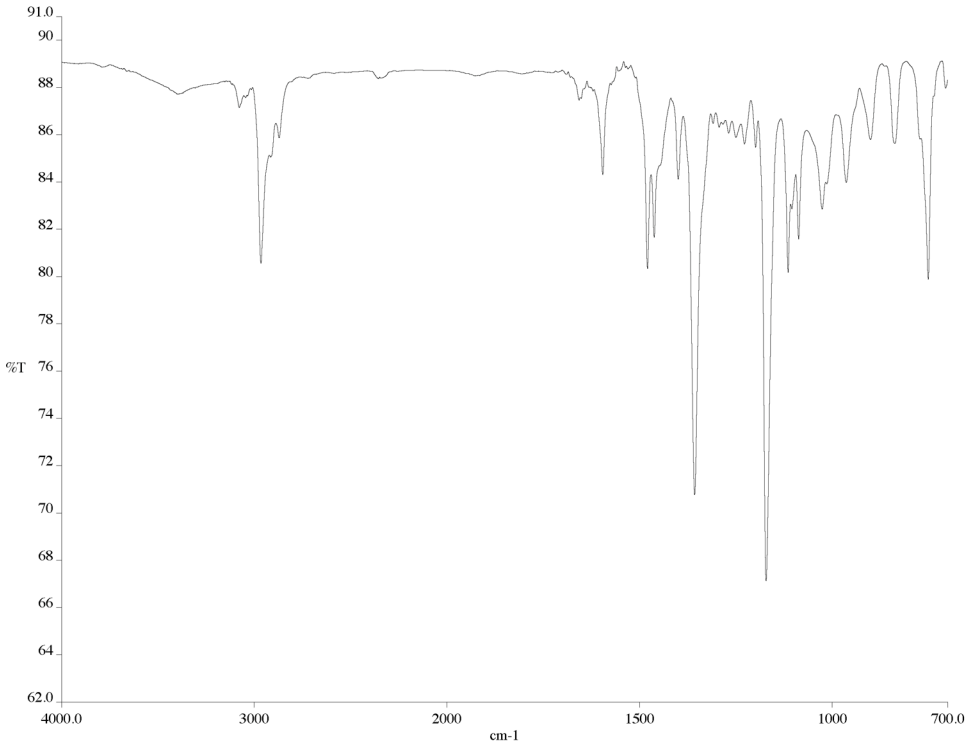


Figure A3.134 Infrared spectrum (thin film/NaCl) of compound **463**.

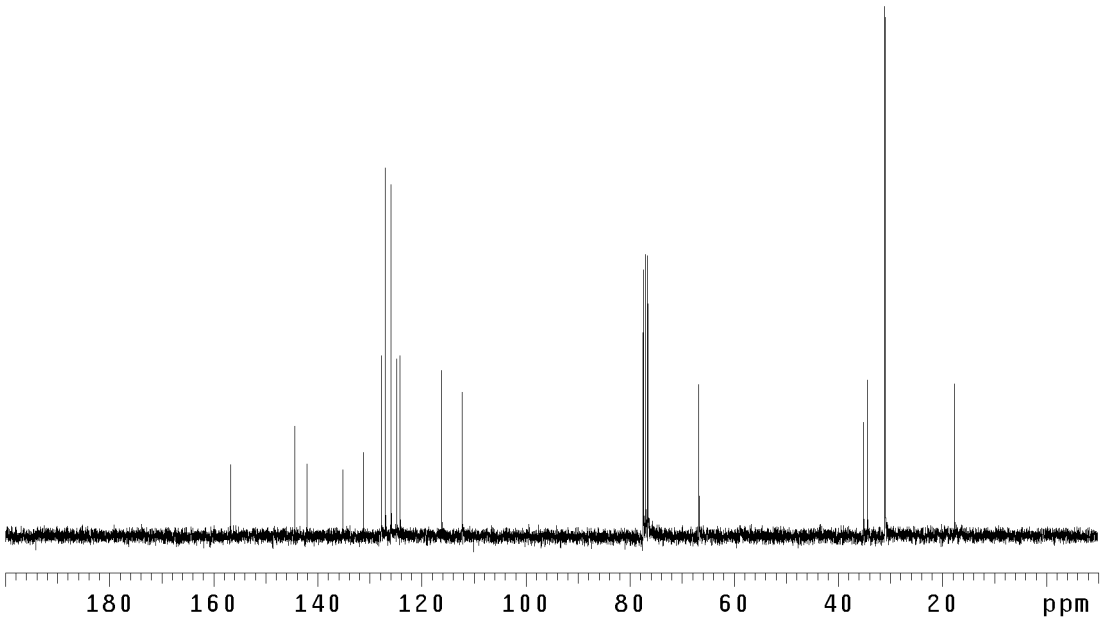


Figure A3.135 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **463**.

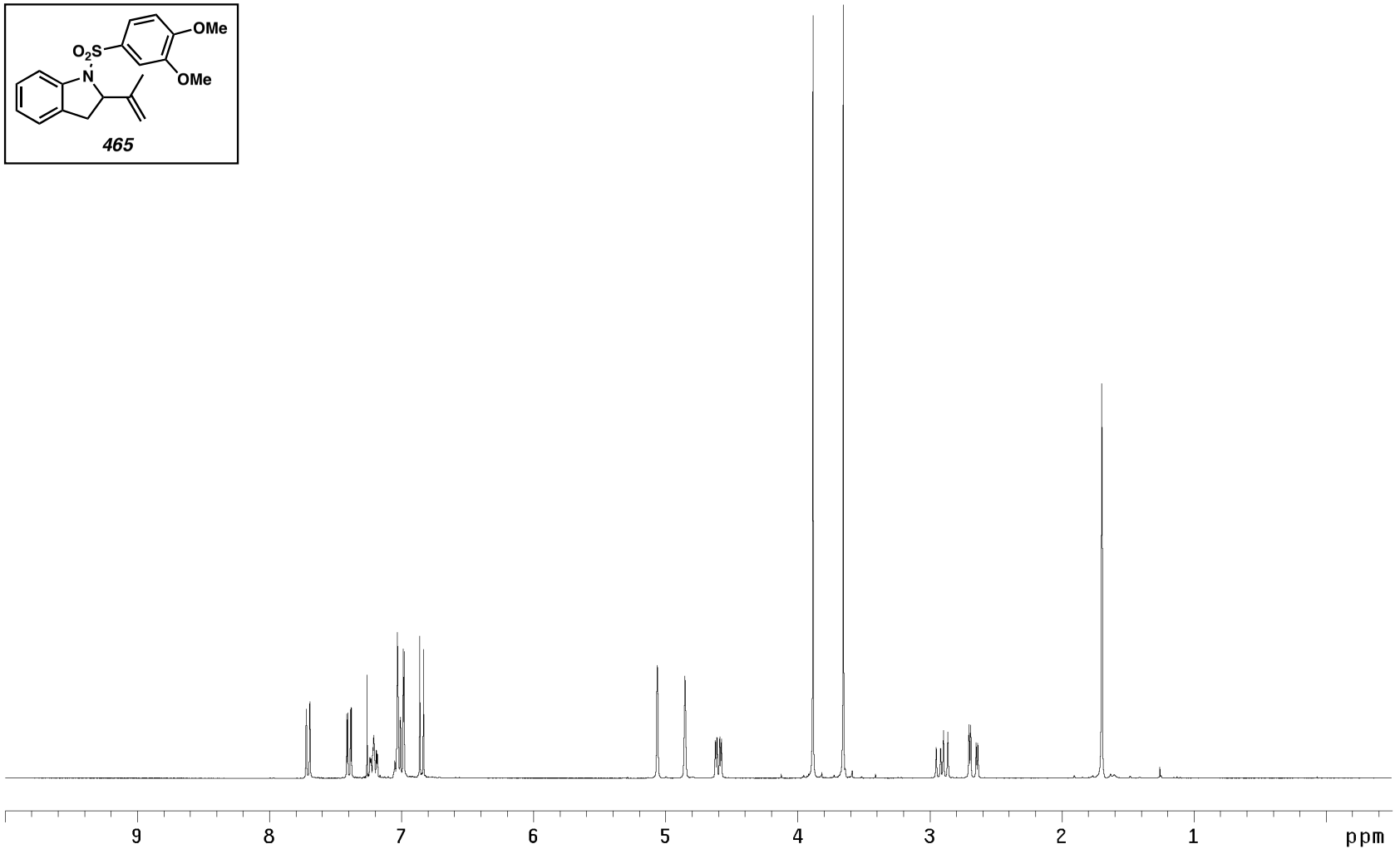


Figure A3.136 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **465**.

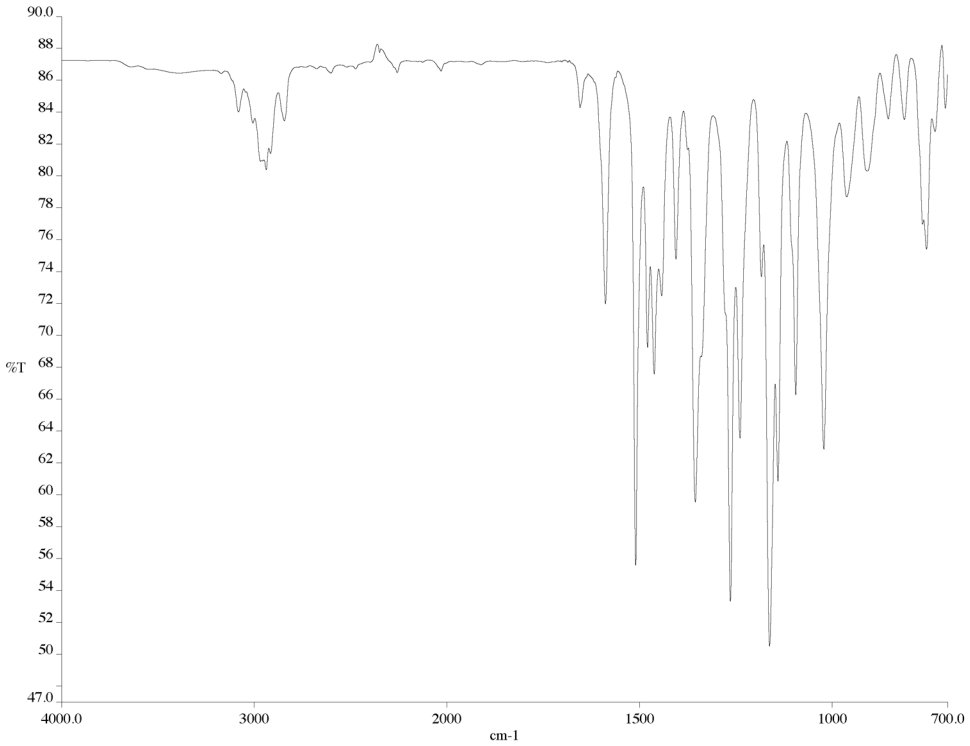


Figure A3.137 Infrared spectrum (thin film/NaCl) of compound **465**.

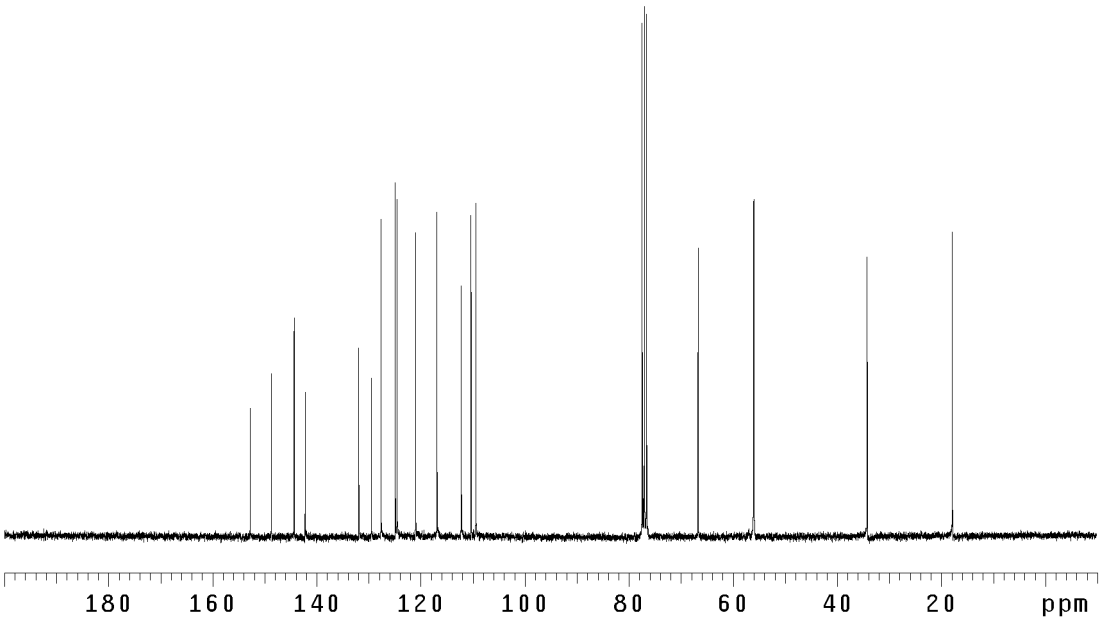


Figure A3.138 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **465**.

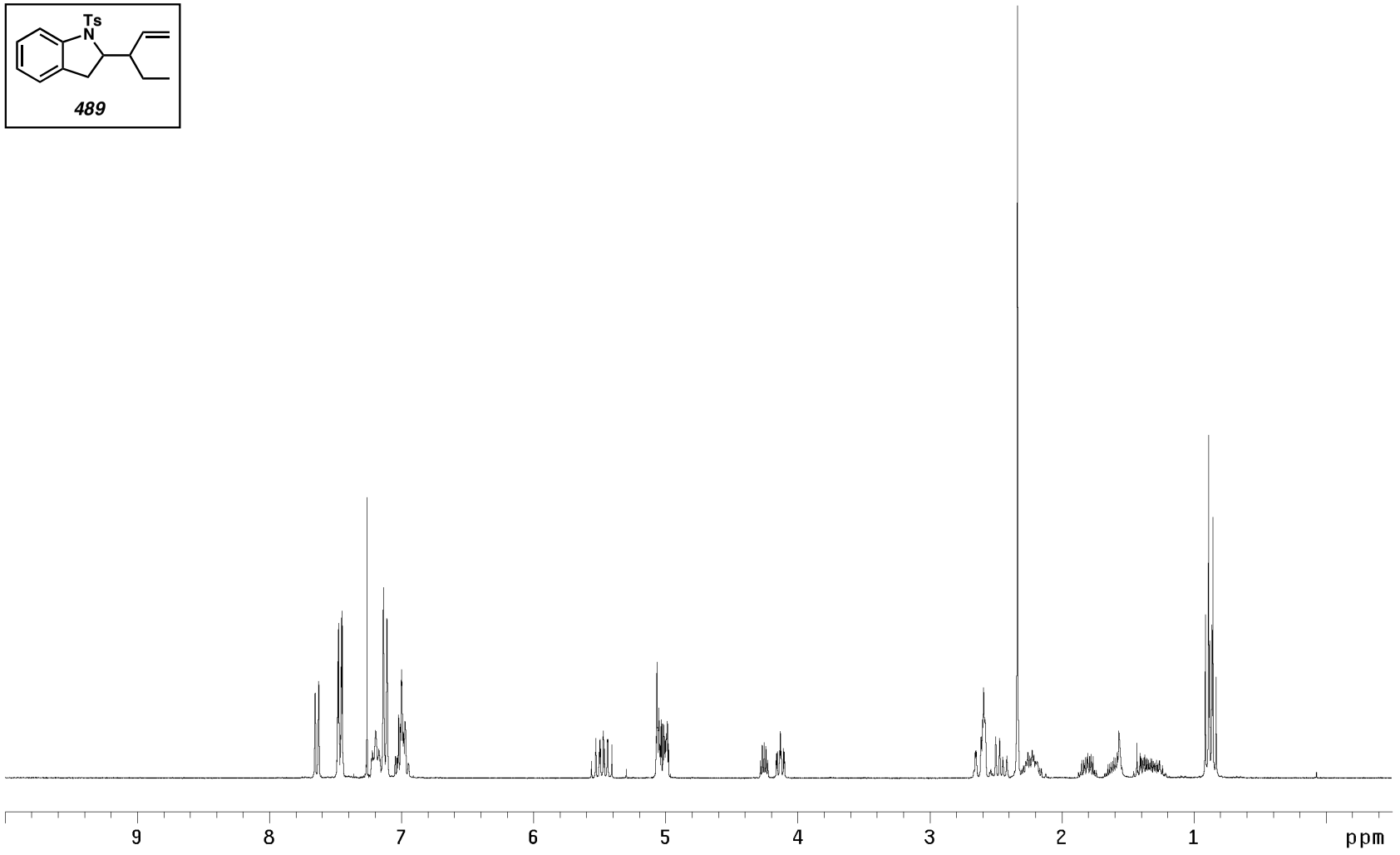


Figure A3.139 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **489**.

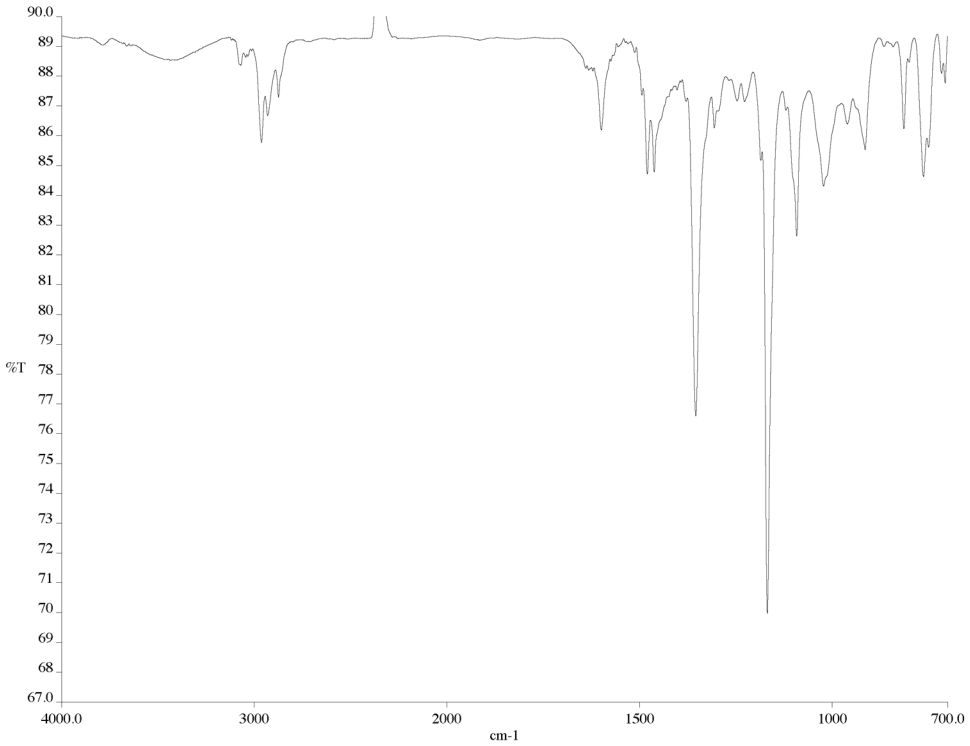


Figure A3.140 Infrared spectrum (thin film/NaCl) of compound **489**.

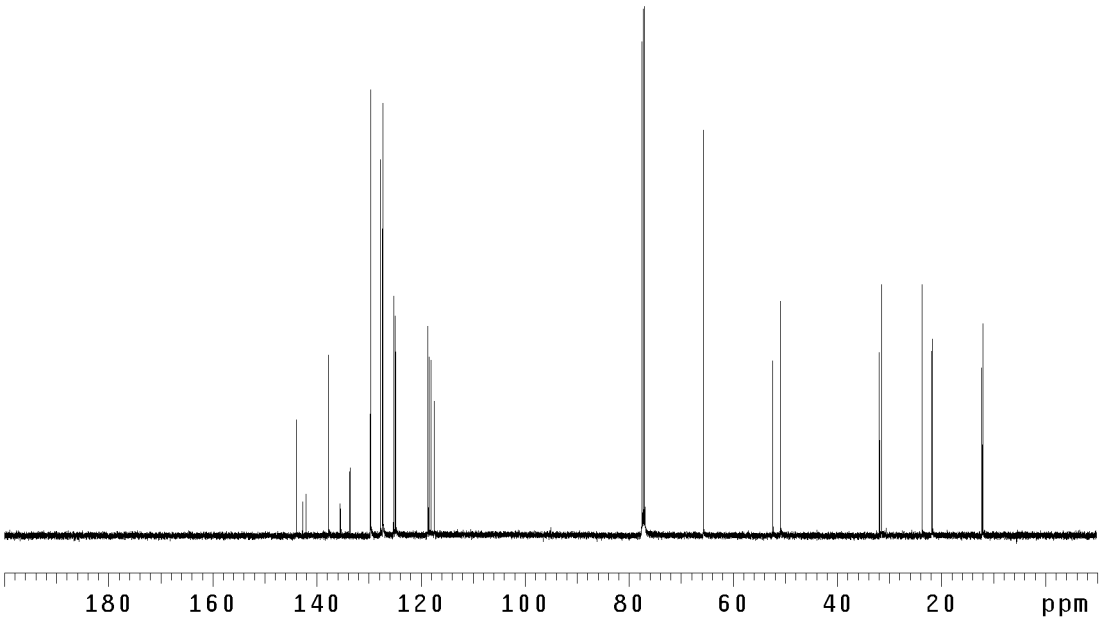


Figure A3.141 ^{13}C NMR (125 MHz, $CDCl_3$) of compound **489**.

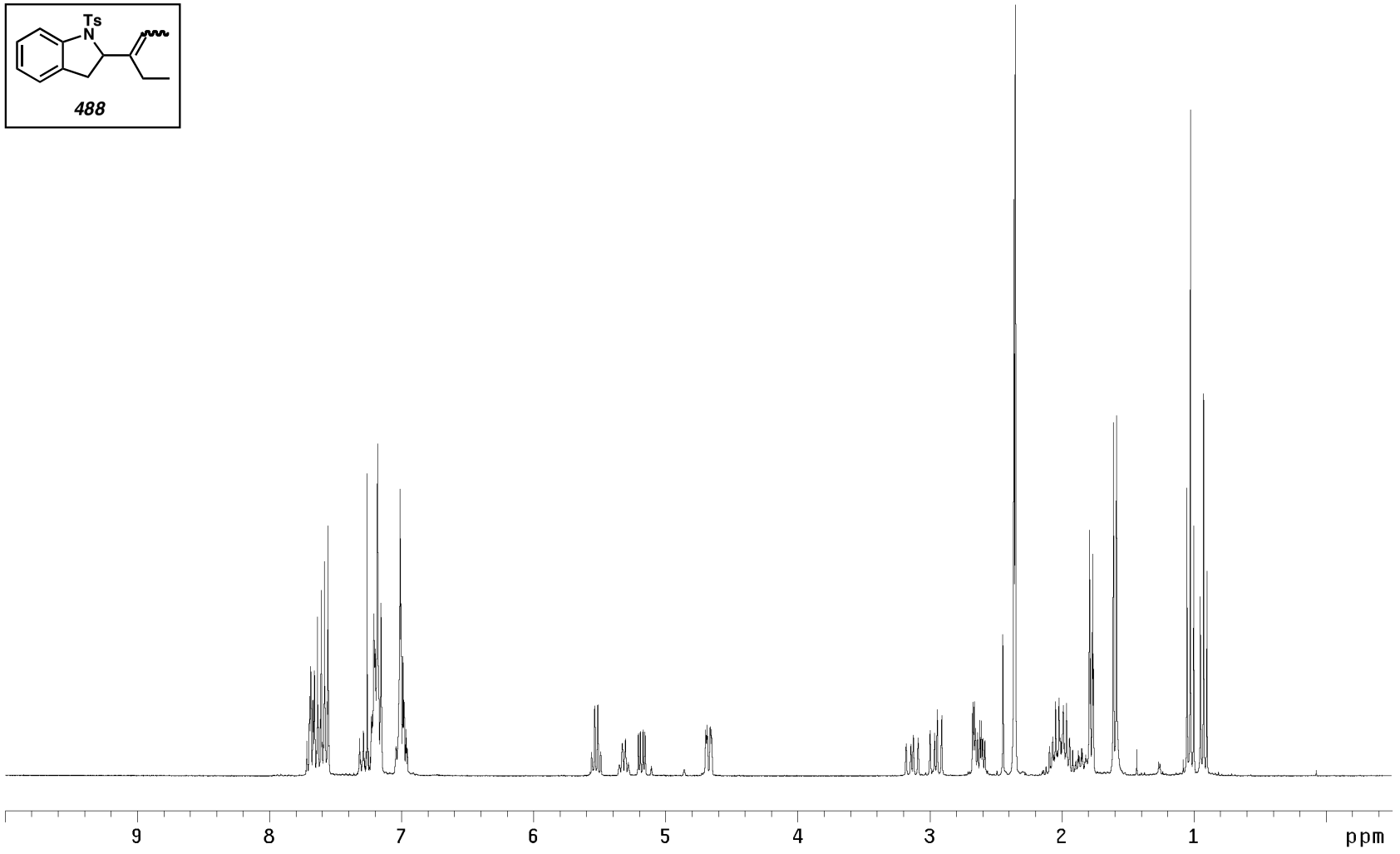


Figure A3.142 ^{1}H NMR (300 MHz, $CDCl_3$) of compound **488**.

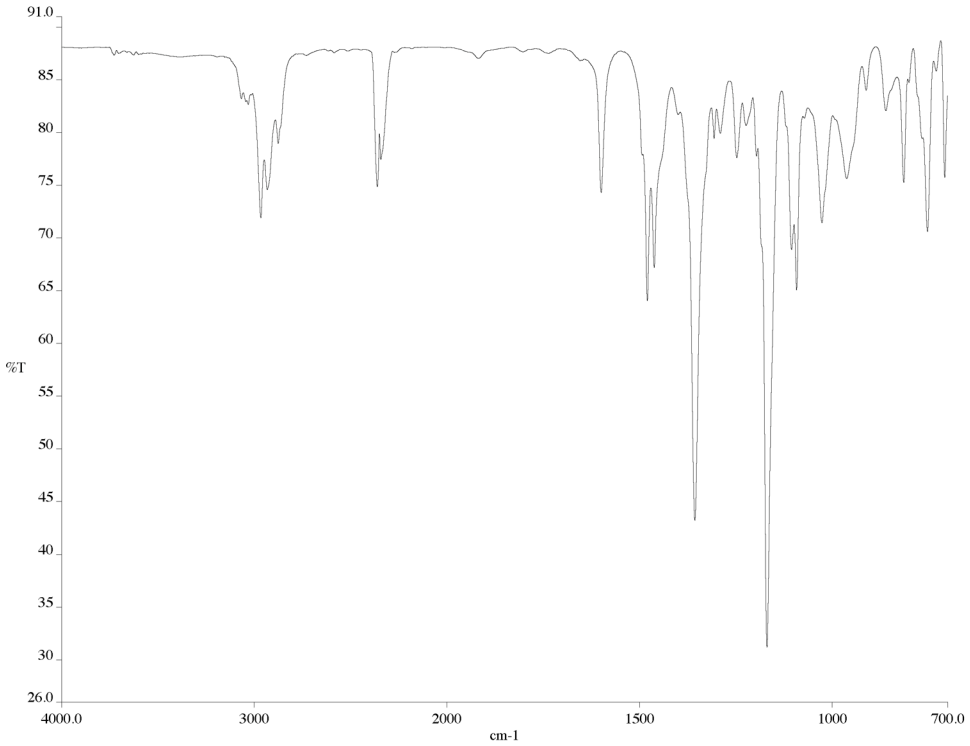


Figure A3.143 Infrared spectrum (thin film/NaCl) of compound **488**.

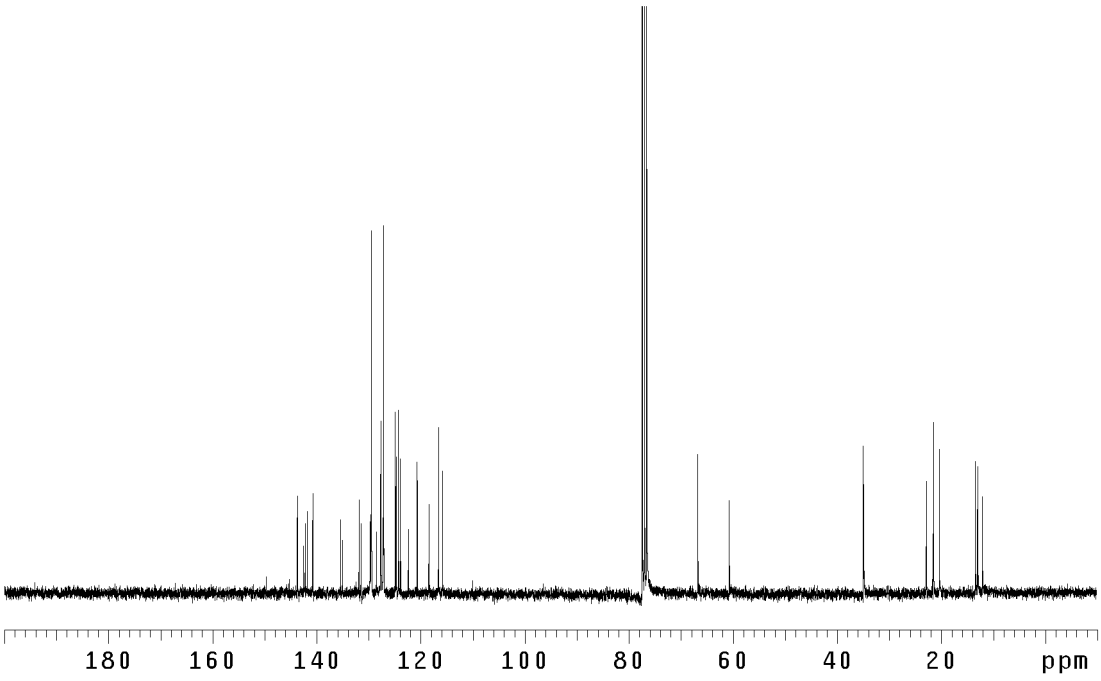


Figure A3.144 ^{13}C NMR (75 MHz, $CDCl_3$) of compound **488**.

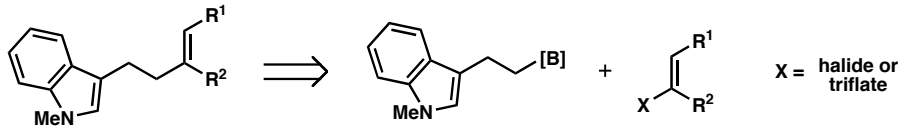
APPENDIX FOUR

The Synthesis of C-3β Functionalized Indoles via a Hydroboration/Suzuki-Miyaura Coupling Sequence

A4.1 Introduction

Indoles are important structural moieties in a number of biologically relevant compounds.[1] The development of synthetic methods involving indole-containing compounds remains an active area of research.[1a,2] During the course of our studies on the palladium-catalyzed oxidative annulation of indoles,[3] it became necessary to synthesize substrates with olefin tethers at the C-3 position. Specifically, we desired compounds where the indole tethers had olefins attached to the β carbon. We envisioned that indoles of this type could arise via sp^2-sp^3 palladium-catalyzed cross coupling chemistry. The Suzuki-Miyaura reaction has proven widely effective in the construction of carbon-carbon bonds.[4] We anticipated that a sequence consisting of a hydroboration of a 3-vinyl indole followed by a palladium-catalyzed cross coupling with a halide or triflate would afford the desired indole products (Scheme A4.1.1).

Scheme A4.1.1



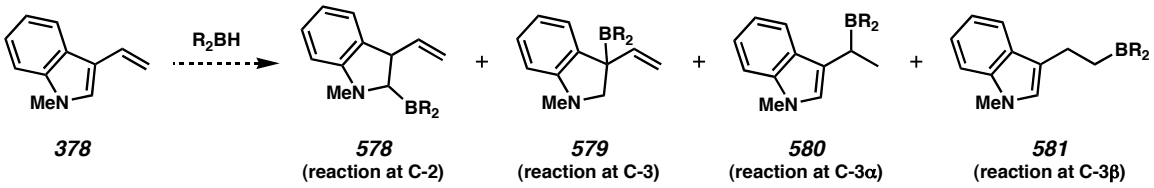
575 ***576*** ***577***

A4.2 Reaction Development

A4.2.1 Regioselectivity of Hydroboration

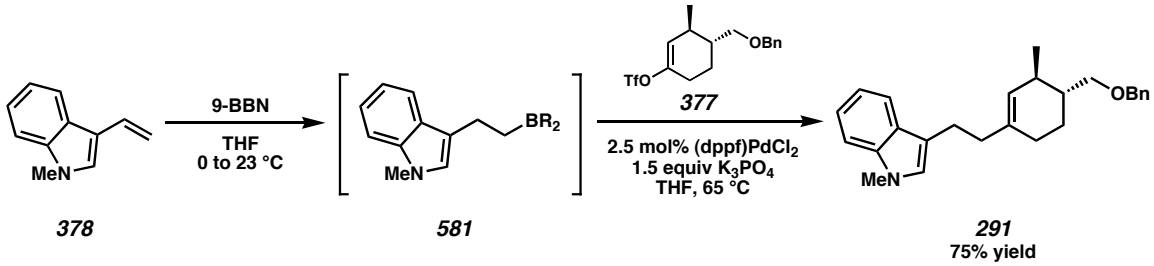
The regioselectivity of a hydroboration on a vinyl indole compound was uncertain at the beginning of this study. Styrenyl compounds generally react with hydroborating agents to afford compounds with boron substitution at the terminal (β) position. The hydroboration of more electron-rich heteroarenes, however, could potentially be complicated by the numerous nucleophilic sites. It could be envisioned that the hydroboration of *N*-methyl-3-vinyl indole could result in boron substitution at four different sites, C-2, C-3, C-3α, and C-3β, the desired location (Scheme A4.2.1).

Scheme A4.2.1



In the event, the hydroboration/Suzuki-Miyaura coupling sequence proved to be remarkably effective. Starting with *N*-methyl-3-vinyl indole (**378**), hydroboration with 9-BBN afforded B-alkyl intermediate **581**, which was treated with triflate **377** under standard Suzuki-Miyaura coupling conditions.[5] After the reaction was complete, analysis of the crude material revealed that there was only one compound present arising from boron substitution at C-3β. No products arising from hydroboration at any other sites on **378** were observed. This outcome is strongly suggestive that the regioselectivity of the hydroboration event was extremely high for the terminal position of the vinyl group.

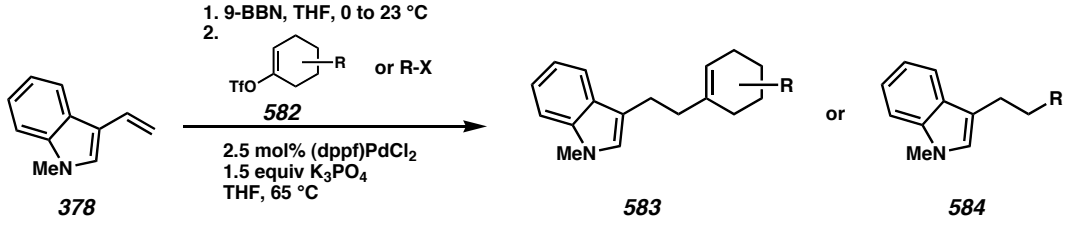
Scheme A4.2.2



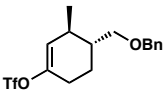
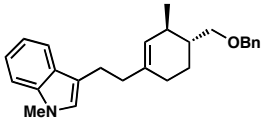
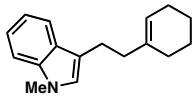
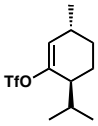
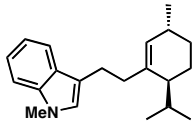
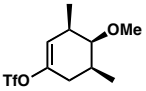
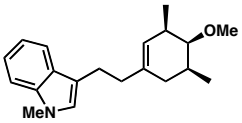
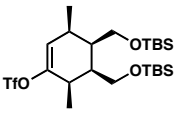
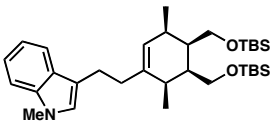
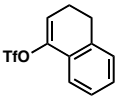
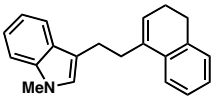
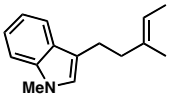
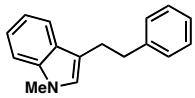
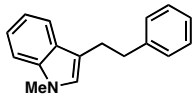
A4.2.2 Applications of the Hydroboration/Suzuki-Miyaura Coupling Sequence

A variety of C-3β substituted indoles can be synthesized via this hydroboration/Suzuki-Miyaura method (Table A4.2.1). Triflates derived from cyclohexanone derivatives are efficient coupling partners for this reaction (entries 1-6). Vinyl and aryl halides are also viable substrates for the construction of C-3β substituted indoles (entries 7-9).

Table A4.2.1. The synthesis of C-3β substituted indoles via a hydroboration/Suzuki-Miyaura coupling sequence.



378 ***583*** ***584***

entry	triflate or R-X		product		yield (%)[a]
1		***377***		***291***	75
2		***585***		***586***	46
3		***587***		***588***	56
4		***589***		***590***	61
5		***591***		***592***	73
6[b]		***593***		***594***	72
7		***369***		***26***	57
8[b]		***595***		***596***	63
9[b]		***597***		***596***	56

[a] Yields listed are isolated. [b] See footnote 6.

A general procedure is as follows: 9-BBN dimer (203 mg, 0.830 mmol) was dissolved in THF (1.66 mL) at 23 °C under an argon atmosphere. Once fully in solution, it was cooled to 0 °C, and to the solution was added a solution of indole **378** (261 mg, 1.66 mmol) in THF (1.66 mL). The reaction mixture was warmed to 23 °C and stirred for 3 h. To the solution was then added a solution of triflate **377** (552 mg, 1.51 mmol) in THF (7.55 mL), (dppf)$PdCl_2$ (30.8 mg, 0.0378 mmol), and K_3PO_4 (482 mg, 2.27 mmol), and the reaction was heated to 65 °C. After 5 h, the reaction was cooled to 23 °C and quenched with 1 mL NaOH (3.0 M aq.) and 1 mL 30% H_2O_2, and the resulting mixture was stirred 1 h. The mixture was then partitioned between Et_2O (50 mL) and water (40 mL), and the aqueous phase was extracted with Et_2O (1 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 → 1:1 hexanes/CH_2Cl_2 eluent) afforded Suzuki product **291** (467 mg, 75% yield, R_F = 0.20 in 4:1 hexanes/CH_2Cl_2) as a colorless oil.

A4.3 Conclusion

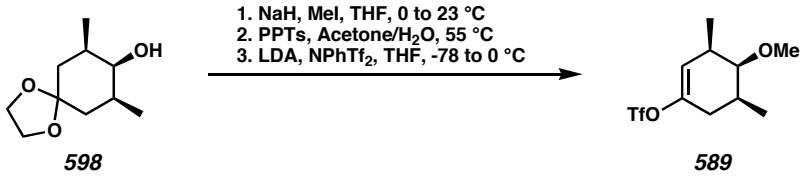
In summary, a hydroboration/Suzuki-Miyaura method was utilized to functionalize 3-vinyl indoles. An array of indole-containing compounds arising from triflates or halides can be synthesized via this protocol. It is anticipated that this method could be applied to the synthesis of a number of biologically interesting compounds featuring the indole nucleus.

A4.4 Experimental Section

A4.4.1 Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with dry solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. ^{1}H spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C spectra were recorded on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. All chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

A4.4.2 Triflate Synthesis

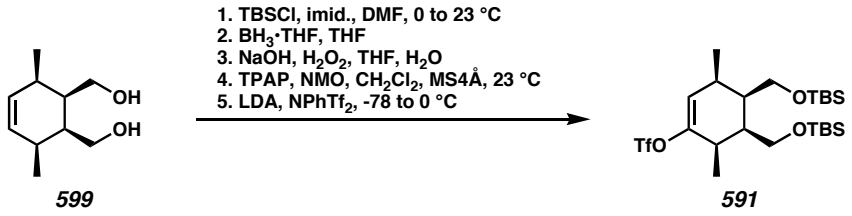


598 *589*

Triflate 589. To a solution of alcohol **598**[7] (286 mg, 1.54 mmol) in 6.16 mL THF at 0 °C was added NaH (123 mg, 60% dispersion in mineral oil, 3.08 mmol). The mixture was stirred for 5 min, then allowed to warm to 23 °C and stirred for 1 h. The reaction mixture was then cooled to 0 °C, and MeI (144 μl, 2.31 mmol) was introduced. The mixture was allowed to warm to 23 °C and maintained at room temperature for 3 h. The reaction was then cooled to 0 °C, quenched with saturated NH_4Cl (40 mL), and extracted with Et_2O (2 x 75 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) afforded the methyl ether (241 mg, 78% yield, R_F = 0.49 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the methyl ether (282 mg, 1.41 mmol) in acetone (12.7 mL) and H_2O (1.41 mL) was added PPTs (106 mg, 0.423 mmol). The mixture was heated to 55 °C and stirred. After 4.5 h, the mixture was cooled to room temperature, and the acetone was removed by rotary evaporation. The residue was partitioned between Et_2O (75 mL) and saturated $NaHCO_3$ (50 mL). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (6:1 hexanes/EtOAc eluent) to afford the ketone (157 mg, 71% yield, R_F = 0.41 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of LDA (1.20 mmol) in 1.20 mL THF at –78 °C was added a solution of the ketone (157 mg, 1.00 mmol) in 1.00 mL THF dropwise over 1 min. The reaction mixture was maintained at –78 °C for 3 h, then a solution of $NPhTf_2$ (393 mg, 1.10 mmol) in 1.10 mL THF was added via cannula. The mixture was allowed to warm to 0 °C and maintained for 3 h. The reaction was then quenched with saturated NH_4Cl (30 mL) and extracted with Et_2O (2 x 50 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) afforded triflate **589** (211 mg, 73% yield, R_F = 0.43 in 9:1 hexanes/EtOAc) as a yellow oil. **Triflate 589**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (br s, 1H), 3.49 (s, 3H), 3.12 (m, 1H), 2.61-2.51 (m, 1H), 2.34-2.12 (comp m, 2H), 2.04-1.91 (m, 1H), 1.14 (d, *J* = 7.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 120.6, 118.7 (q, *J* = 318.2 Hz), 82.1, 62.2, 36.5, 35.1, 31.3, 18.1, 16.6; IR (film) 1417, 1246, 1210, 1145, 1096, 919 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{10}H_{15}O_4F_3S]^+$: 288.0643, found 288.0633.



Triflate 591. To a solution of diol **599**[8] (316 mg, 1.86 mmol) in 3.72 mL DMF at 0 °C was added imidazole (317 mg, 4.65 mmol), then TBSCl (589 mg, 3.91 mmol). The mixture was allowed to warm to 23 °C and stirred for 4 h. The reaction was then quenched with water (30 mL) and extracted with Et_2O (2 x 75 mL). The combined organic phases were washed with 1 N HCl (2 x 30 mL) and then brine, dried over

$MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (25:1 hexanes/EtOAc eluent) to provide the bis(silyl ether) (571 mg, 77% yield, R_F = 0.90 in 4:1 hexanes/EtOAc) as a colorless oil.

To a solution of the bis(silyl ether) (571 mg, 1.43 mmol) in 14.3 mL THF at 0 °C was added BH_3•THF (2.00 mL, 1.0 M in THF, 2.00 mmol) dropwise. The reaction mixture was allowed to warm to 23 °C and stirred for 3 h. The mixture was then cooled to 0 °C, and aq. NaOH (5.72 mL, 15% w/v) and H_2O_2 (3.97 mL, 30% in H_2O) were added sequentially. The reaction mixture was allowed to warm to 23 °C and stirred 18 h. The mixture was then quenched by addition of 230 mg sodium metabisulfite, stirred 15 min, and partitioned between Et_2O (100 mL) and brine (50 mL). The aqueous layer was extracted with Et_2O (2 x 40 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting alcohol (581 mg, 97% yield, R_F = 0.16 in 9:1 hexanes/EtOAc) was sufficiently pure to carry on to the next reaction.

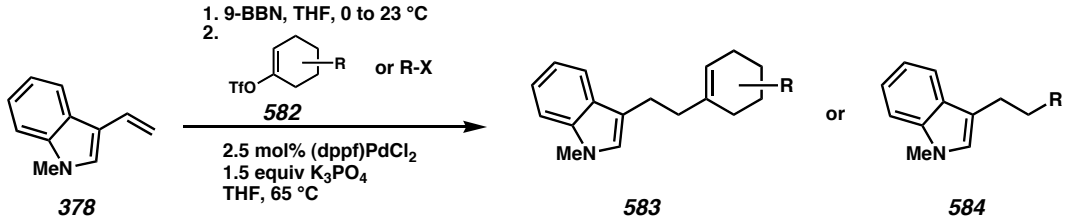
To a solution of the alcohol (581 mg, 1.39 mmol) in CH_2Cl_2 (2.78 mL) at 23 °C was added MS4Å (695 mg, 500 mg/mmol), then NMO (245 mg, 2.09 mmol). The resulting suspension was stirred for 15 min, and then TPAP (24.4 mg, 0.0695 mmol) was added. The mixture was stirred for 10 min, then diluted with CH_2Cl_2 (30 mL) and filtered through a plug of SiO_2 (1 x 5 cm, CH_2Cl_2 eluent). The filtrate was concentrated to an oil, which was purified by flash chromatography (19:1 hexanes/EtOAc eluent) to afford the ketone (521 mg, 90% yield, R_F = 0.40 in 9:1 hexanes/EtOAc) as a colorless oil.

To a solution of LDA (0.656 mmol) in 656 μl THF at –78 °C was added a solution of the ketone (227 mg, 0.547 mmol) in 547 μl THF dropwise over 1 min. The

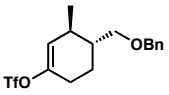
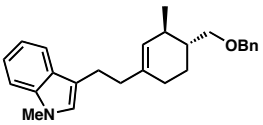
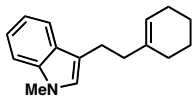
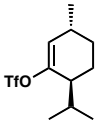
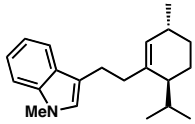
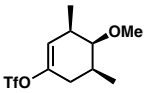
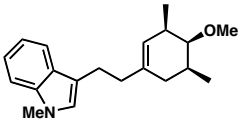
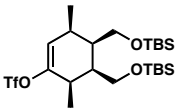
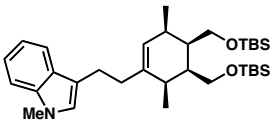
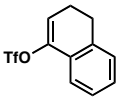
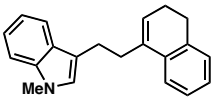
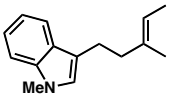
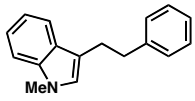
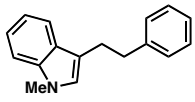
reaction mixture was maintained at –78 °C for 3 h, then a solution of $NPhTf_2$ (215 mg, 0.602 mmol) in 602 μl THF was added via cannula. The mixture was allowed to warm to 0 °C and maintained for 3 h. The reaction was then quenched with saturated NH_4Cl (25 mL) and extracted with Et_2O (2 x 50 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (29:1 hexanes/EtOAc eluent) afforded triflate **591** (201 mg, 67% yield, R_F = 0.70 in 9:1 hexanes/EtOAc) as a yellow oil. **Triflate 591**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (m, 1H), 3.88 (dd, *J* = 8.7, 10.5 Hz, 1H), 3.70-3.55 (comp m, 3H), 2.80-2.65 (comp m, 2H), 2.24-2.16 (m, 1H), 2.05-1.98 (m, 1H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 7.5 Hz, 3H), 0.89 (app.s, 18H), 0.05 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 122.5, 118.7 (q, J = 317.9 Hz), 62.6, 60.9, 44.8, 41.6, 34.0, 33.6, 26.1, 18.4, 18.3, 17.9, 12.8, -5.2, -5.2, -5.3, -5.3; IR (film) 2956, 2931, 1418, 1249, 1210, 1146, 1087, 838 cm^{-1}; HRMS (FAB$^+$) *m/z* calc'd for $[C_{23}H_{46}O_5SSi_2F_3]^+$: 547.2557, found 547.2562.

A4.4.3 Hydroboration/Suzuki-Miyaura Couplings

Table A4.2.1 (reproduced)



378 ***583*** ***584***

entry	triflate or R-X		product		yield (%)
1		***377***		***291***	75
2		***585***		***586***	46
3		***587***		***588***	56
4		***589***		***590***	61
5		***591***		***592***	73
6		***593***		***594***	72
7		***369***		***26***	57
8		***595***		***596***	63
9		***597***		***596***	56

General Procedure for the Hydroboration/Suzuki Cross-Coupling Sequence for Table A4.2.1. Entry 1 is used as an example. 9-BBN dimer (203 mg, 0.830 mmol) was dissolved in THF (1.66 mL) at 23 °C under an argon atmosphere. Once fully in solution, it was cooled to 0 °C, and to the solution was added a solution of indole **378** (261 mg, 1.66 mmol) in THF (1.66 mL). The reaction mixture was warmed to 23 °C and stirred for 3 h. To the solution was then added a solution of triflate **377** (552 mg, 1.51 mmol) in THF (7.55 mL), (dppf)$PdCl_2$ (30.8 mg, 0.0378 mmol), and K_3PO_4 (482 mg, 2.27 mmol), and the reaction was heated to 65 °C. After 5 h, the reaction was cooled to 23 °C and quenched with 1 mL NaOH (3.0 M aq.) and 1 mL 30% H_2O_2, and the resulting mixture was stirred 1 h. The mixture was then partitioned between Et_2O (50 mL) and water (40 mL), and the aqueous phase was extracted with Et_2O (1 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 → 1:1 hexanes/CH_2Cl_2 eluent) afforded Suzuki product **291** (467 mg, 75% yield, R_F = 0.20 in 4:1 hexanes/CH_2Cl_2) as a clear oil. (See Chapter 4.7.2 for characterization data.)

Indole 586 (Entry 2). Starting from triflate **585**[9] (179 mg, 0.778 mmol), purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) afforded indole **586** in 46% yield (85 mg, R_F = 0.51 in 9:1 hexanes/EtOAc) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.24 (app.t, *J* = 8.1 Hz, 1H), 7.13 (app.t, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 5.53 (br s, 1H), 3.76 (s, 3H), 2.88 (app.t, *J* = 7.8 Hz, 2H), 2.36 (app.t, *J* = 7.8 Hz, 2H), 2.08-2.04 (comp m, 4H), 1.73-1.58 (comp m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.2, 128.1, 126.1, 121.6, 121.1, 119.2, 118.6, 115.6,

109.3, 39.1, 32.7, 28.7, 25.5, 23.9, 23.3, 22.8; IR (film) 2923, 2360, 736 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{21}N]^+$: 239.1674, found 239.1679.

Indole 588 (Entry 3). Starting from triflate **587**[10] (245 mg, 0.856 mmol), purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) afforded indole **588** in 56% yield (143 mg, R_F = 0.54 in 9:1 hexanes/EtOAc) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.24 (app.t, *J* = 8.1 Hz, 1H), 7.13 (app.t, *J* = 8.1 Hz, 1H), 6.87 (s, 1H), 5.42 (br s, 1H), 3.76 (s, 3H), 2.94 (ddd, *J* = 5.1, 10.8, 14.7 Hz, 1H), 2.75 (ddd, *J* = 6.3, 10.2, 14.4 Hz, 1H), 2.49-2.06 (comp m, 5H), 1.86-1.69 (comp m, 2H), 1.40-1.27 (m, 1H), 1.09-1.01 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 137.2, 130.9, 128.1, 126.1, 121.6, 119.2, 118.7, 115.7, 109.3, 42.3, 36.0, 32.7, 31.8, 31.1, 27.8, 24.2, 22.6, 22.0, 21.1, 16.1; IR (film) 2954, 2926, 1472, 736 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{29}N]^+$: 295.2300, found 295.2309.

Indole 590 (Entry 4). Starting from triflate **589** (211 mg, 0.732 mmol), purification by flash chromatography (3:2 hexanes/CH_2Cl_2 eluent) afforded indole **590** in 61% yield (132 mg, R_F = 0.43 in 9:1 hexanes/EtOAc) as a brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.22 (app.t, *J* = 7.8 Hz, 1H), 7.11 (app.t, *J* = 7.8 Hz, 1H), 6.85 (s, 1H), 5.15 (br s, 1H), 3.74 (s, 3H), 3.54 (s, 3H), 3.18 (m, 1H), 2.94-2.83 (comp m, 2H), 2.46-2.26 (comp m, 3H), 2.04-1.94 (comp m, 2H), 1.91-1.81 (m, 1H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 137.1, 128.1, 126.2, 124.0, 121.5, 119.2, 118.6, 115.5, 109.2, 84.2, 62.0, 38.2,

37.0, 34.5, 32.8, 32.7, 23.6, 18.9, 17.4; IR (film) 2928, 1470, 1101, 737 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{20}H_{27}NO]^+$: 297.2093, found 297.2101.

Indole 592 (Entry 5). Starting from triflate **591** (201 mg, 0.368 mmol), purification by flash chromatography (12:1 → 6:1 hexanes/CH_2Cl_2 eluent) afforded indole **592** in 73% yield (148 mg, R_F = 0.55 in 9:1 hexanes/EtOAc) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.23 (app.t, *J* = 8.4 Hz, 1H), 7.11 (app.t, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 5.22 (br s, 1H), 3.90 (dd, *J* = 8.4, 10.2 Hz, 1H), 3.75 (s, 3H), 3.72-3.57 (comp m, 3H), 2.97-2.88 (m, 1H), 2.84-2.74 (m, 1H), 2.52-2.36 (comp m, 4H), 2.11-2.00 (comp m, 2H), 1.01 (app.d, *J* = 7.5 Hz, 6H), 0.92 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 137.2, 128.1, 126.4, 126.1, 121.6, 119.3, 118.7, 115.7, 109.3, 64.1, 61.5, 45.1, 42.5, 36.0, 34.8, 33.2, 32.8, 26.2, 26.2, 24.3, 18.9, 18.5, 18.3, 14.6, -5.1, -5.1, -5.2, -5.2; IR (film) 2955, 2929, 1086, 836, 774 cm^{-1}; HRMS (FAB^+) *m/z* calc'd for $[C_{33}H_{57}NO_2Si_2]^+$: 555.3928, found 555.3919.

Indole 594 (Entry 6). Starting from triflate **593**[11] (150 mg, 0.539 mmol), purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) afforded indole **594** in 73% yield (111 mg, R_F = 0.45 in 9:1 hexanes/EtOAc) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.28-7.18 (comp m, 4H), 7.13 (app.t, *J* = 7.8 Hz, 1H), 6.89 (s, 1H), 5.95 (t, *J* = 4.5 Hz, 1H), 3.77 (s, 3H), 3.05-2.99 (comp m, 2H), 2.89-2.83 (comp m, 2H), 2.79 (app.t, *J* = 8.4 Hz, 2H), 2.32-2.25 (comp m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 137.0, 136.6, 135.2, 128.1,

127.9, 126.8, 126.6, 126.2, 125.2, 122.8, 121.7, 119.3, 118.8, 115.4, 109.3, 33.9, 32.8, 28.7, 24.6, 23.3; IR (film) 2930, 1485, 736 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{21}H_{21}N]^+$: 287.1674, found 287.1678.

Indole 26 (Entry 7). Starting from 2-bromo-2-butene (47.1 μl, 0.463 mmol), purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) afforded indole **26** in 57% yield (56.6 mg, R_F = 0.54 in 9:1 hexanes/EtOAc) as a colorless oil. (See Chapter 4.7.2 for characterization data.)

Indole 596 (Entry 8). Starting from bromobenzene (48.8 μl, 0.463 mmol), purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) afforded indole **596** in 63% yield (69.0 mg, R_F = 0.48 in 9:1 hexanes/EtOAc) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.38-7.25 (comp m, 7H), 7.16 (app.t, *J* = 7.5 Hz, 1H), 6.83 (s, 1H), 3.76 (s, 3H), 3.15-3.03 (comp m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 137.2, 128.7, 128.5, 128.0, 126.3, 126.0, 121.7, 119.2, 118.8, 114.9, 109.3, 37.0, 32.7, 27.4; IR (film) 738, 699 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{17}N]^+$: 235.1361, found 235.1366.

Indole 596 (Entry 9). Starting from iodobenzene (51.8 μl, 0.463 mmol), purification by flash chromatography (9:1 hexanes/CH_2Cl_2 eluent) afforded indole **596** in 56% yield (60.5 mg, R_F = 0.43 in 9:1 hexanes/EtOAc) as a colorless oil.

A4.5 Notes and References

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(5) The conditions for the palladium-catalyzed coupling were derived from a procedure described by Suzuki et al. See, Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem*. **1993**, *58*, 2201-2208.

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APPENDIX FIVE

Notebook Cross-Reference

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hardcopy and electronic characterization folders have been created that contain copies of the original ^{1}H NMR, ^{13}C NMR, and IR spectra. All notebooks and spectral data are stored in the Stoltz archives.

Table A5.1 Compounds Appearing in Chapter 3: Palladium-Catalyzed Aerobic Wacker Cyclizations and the Formal Total Synthesis of Cephalotaxine

Compound	^{1}H NMR	^{13}C NMR	IR
204	EMF-VI-289	EMF-VI-289	EMF-VI-289
205	EMF-XXVII-101	EMF-XXVII-101	EMF-XXVII-101
207	EMF-VII-299	EMF-VII-299	EMF-VII-299
208	EMF-IX-143	EMF-IX-143	EMF-IX-143

Table A5.2 Compounds Appearing in Chapter 4:

C-H Bond Functionalizations with Palladium(II): Intramolecular

Annulations of Arenes

Compound	^{1}H NMR	^{13}C NMR	IR
26	EMF-X-135	EMF-X-135	EMF-X-135
267	EMF-X-133	EMF-X-133	EMF-X-133
269	EMF-XIV-227	EMF-XIV-227	EMF-XIV-227
271	EMF-XIV-231	EMF-XIV-231	EMF-XIV-231
273	EMF-XIV-273	EMF-XIV-273	EMF-XIV-273
275	EMF-IX-293	EMF-IX-293	EMF-IX-293
277	EMF-XI-269	EMF-XI-269	EMF-XI-269
279	EMF-XII-59	EMF-XII-59	EMF-XII-59
281	EMF-XI-101	EMF-XI-101	EMF-XI-101
283	EMF-X-225	EMF-X-225	EMF-X-225
285	EMF-XIV-303	EMF-XIV-303	EMF-XIV-303
287	EMF-XIV-239	EMF-XIV-239	EMF-XIV-239
289	EMF-XIII-263	EMF-XIII-263	EMF-XIII-263
377	EMF-XX-155	EMF-XX-155	EMF-XX-155
291	EMF-XV-115	EMF-XV-115	EMF-XV-115
298	EMF-XVII-223	EMF-XVII-223	EMF-XVII-223
27	EMF-XI-279	EMF-XI-279	EMF-XI-279
268	EMF-XII-71	EMF-XII-71	EMF-XII-71
270	EMF-XIV-167	EMF-XIV-167	EMF-XIV-167
272	EMF-XIV-269	EMF-XIV-269	EMF-XIV-269
274	EMF-XIV-281	EMF-XIV-281	EMF-XIV-281
276	EMF-XII-81	EMF-XII-81	EMF-XII-81
278	EMF-XII-63	EMF-XII-63	EMF-XII-63
280	EMF-XII-93	EMF-XII-93	EMF-XII-93

Compound	1H NMR	13C NMR	IR
282	EMF-XIII-297	EMF-XIII-297	EMF-XIII-297
284	EMF-XII-135	EMF-XII-135	EMF-XII-135
286	EMF-XIV-165	EMF-XIV-165	EMF-XIV-165
288	EMF-XIV-237	EMF-XIV-237	EMF-XIV-237
290	EMF-XIV-25	EMF-XIV-25	EMF-XIV-25
297	EMF-XV-113	EMF-XV-139	EMF-XV-139

Table A5.3 Compounds Appearing in Chapter 5:

Further Investigations into Palladium(II)-Catalyzed Asymmetric Oxidative Heterocyclizations

Compound	^{1}H NMR	^{13}C NMR	IR
413	EMF-XXIII-217	EMF-XXIII-217	EMF-XXIII-217
415	EMF-XXIV-65	EMF-XXIV-65	EMF-XXIV-65
416	EMF-XXIV-85	EMF-XXIV-85	EMF-XXIV-85
417	EMF-XXIV-87	EMF-XXIV-87	EMF-XXIV-87
422	EMF-XXIII-107	EMF-XXIII-107	EMF-XXIII-107
427	EMF-XXII-303	EMF-XXII-303	EMF-XXII-303
431	EMF-XXIII-103	EMF-XXIII-103	EMF-XXIII-103
434	EMF-XXIII-177	EMF-XXIII-177	EMF-XXIII-177
435	EMF-XXVII-99	EMF-XXVI-273	EMF-XXVI-273
480	EMF-XVII-59	EMF-XVII-59	EMF-XVII-59
(*E*)-406	EMF-XIX-49	EMF-XIX-49	EMF-XIX-49
(*Z*)-406	EMF-XIX-229	EMF-XIX-229	EMF-XIX-229
409	EMF-XX-289	EMF-XX-289	EMF-XX-289
443	EMF-XXII-171	EMF-XXII-171	EMF-XXII-171

Compound	^{1}H NMR	^{13}C NMR	IR
444	EMF-XXII-203	EMF-XXII-203	EMF-XXII-203
449	EMF-XXI-277	EMF-XXI-277	EMF-XXI-277
451	EMF-XXII-51	EMF-XXII-51	EMF-XXII-51
454	EMF-XXII-31	EMF-XXII-31	EMF-XXII-31
456	EMF-XXII-111	EMF-XXII-111	EMF-XXII-111
458	EMF-XXII-215	EMF-XXII-215	EMF-XXII-215
460	EMF-XXII-255	EMF-XXII-255	EMF-XXII-255
462	EMF-XXIII-29	EMF-XXIII-29	EMF-XXIII-29
464	EMF-XXIII-37	EMF-XXIII-37	EMF-XXIII-37
466	EMF-XXI-295	EMF-XXI-295	EMF-XXI-295
468	EMF-XXIII-261	EMF-XXIII-261	EMF-XXIII-261
470	EMF-XXIII-289	EMF-XXIII-289	EMF-XXIII-289
474	EMF-XIX-197	EMF-XIX-197	EMF-XIX-197
487	EMF-XXI-173	EMF-XXI-173	EMF-XXI-173
490	EMF-XXVII-81	EMF-XXVII-81	EMF-XXVII-81
505	EMF-XXI-115	EMF-XXI-115	EMF-XXI-115
410	EMF-XXVII-73	EMF-XXVII-73	EMF-XXVII-73
469	EMF-XXVII-59	EMF-XXVII-59	EMF-XXVII-59
471	EMF-XXVII-61	EMF-XXVII-61	EMF-XXVII-61
508	EMF-XXVII-77	EMF-XXVII-77	EMF-XXVII-77
573	EMF-XXVII-89	EMF-XXVII-89	EMF-XXVII-89
511	EMF-XXVII-93	EMF-XXVII-93	EMF-XXVII-93
451	EMF-XXVI-237	EMF-XXVI-237	EMF-XXVI-237
446	EMF-XXVI-249	EMF-XXVI-249	EMF-XXVI-249
448	EMF-XXVI-243	EMF-XXVI-243	EMF-XXVI-243
453	EMF-XXVI-269	EMF-XXVI-269	EMF-XXVI-269
455	EMF-XXVI-265	EMF-XXVI-265	EMF-XXVI-265
457	EMF-XXVI-257	EMF-XXVI-257	EMF-XXVI-257

Compound	^{1}H NMR	^{13}C NMR	IR
459	EMF-XXVI-259	EMF-XXVI-259	EMF-XXVI-259
461	EMF-XXVI-261	EMF-XXVI-261	EMF-XXVI-261
463	EMF-XXVI-253	EMF-XXVI-253	EMF-XXVI-253
465	EMF-XXVI-267	EMF-XXVI-267	EMF-XXVI-267
489	EMF-XXVII-27	EMF-XXVII-27	EMF-XXVII-27
488	EMF-XXVI-301	EMF-XXVI-301	EMF-XXVI-301

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ABOUT THE AUTHOR

Eric Matthew Ferreira was born on March 16, 1978 in Gilroy, California (The Garlic Capital of the World). He was the second child (behind sister Andrea) of Phil and Marna Ferreira. Shortly thereafter, the family moved to Sonora, California, nestled in the foothills of the Sierra Nevada, where Eric was raised for the next seventeen years. Eric attended Sonora High School, where he played on the tennis team and was a trumpet player in the Golden Regiment and in the jazz band. He also spent significant amounts of time not wanting to be in Sonora.

Desperate to accomplish this goal, he set out for college across the country to the Massachusetts Institute of Technology in Cambridge, Massachusetts. Although he initially was interested in biomedical engineering, he quickly became excited about chemistry. His first research experience was a summer stint at Oregon State University in Corvallis, where he studied food chemistry in the laboratories of Ronald Wrolstad. Later at MIT, he became very interested in organometallic chemistry. He spent over a year in the laboratories of Stephen Buchwald, working on both palladium and copper catalysis. He also was a member of the lightweight crew team (one of the eleven teams in the elite Eastern Sprints league), which pretty much meant he had no time to do anything else. He graduated in 2000 with an S.B. in Chemistry with a concentration in writing.

He then moved to Pasadena, California to pursue Ph.D. studies at the California Institute of Technology. He received his degree in 2005 for his work in palladium-catalyzed oxidation chemistry. He will begin postdoctoral studies later in 2005 at Stanford University under the direction of Professor Barry Trost.