Cascade Palladium-Catalyzed Stereoselective Synthesis of Polycyclic Nitrogen Heterocycles via Reactions of Allylanilines

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
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Dedication

בס״ד

What does *dedication* mean? It is defined as a noun, meaning "a devoting or setting aside for a particular purpose" (Merriam Webster), "the willingness to give a lot of time and energy to something because it is important" (Cambridge Dictionary), and "to set apart and consecrate to a deity or to a sacred purpose" (Dictionary.com). I examined these definitions on Monday May 6, 2024 (28 *Nisan* 5784)—the Hebrew birthday of our first-born son, Zedekiah ("Z") Daveed Culberson (*Tzidkiyahu David ben Mattityahu Baruch*)—as I sat across from him and my wife, Kiara Joy Jackson Culberson (*Ayalah bat Avraham*) at South Quad *Kosher* (fit according to the Jewish law) Dining Hall. While we ate *Beit Yosef* (House of Joseph) burgers, I asked her, "who or what should my thesis dedication be to?" My initial internal obvious answers were the two sitting across from me, my mother, my grandmother, my father, my ancestors, *k'lal Yisrael* (the Jewish nation), etc. Given the third definition above, which indirectly captures everyone mentioned, this dissertation is dedicated to *HaKadosh Baruch Hu* (the Holy One, blessed be He).

Hashem (The Name) has blessed me to be born to a wonderful, G-d fearing mother and grandmother, supporting me throughout my education, as well as a hard-working father, guiding me throughout life. G-d has bestowed upon me an *eshet chayil* (woman of valor)—Ayalah—and righteous first-born (a *pidyon haben*)—Z. *Borei Olam* (Creator of the universe) has merited me to be born into a family with records dating back to our Alabama slave plantation, Latter-Day Saints of Utah, Native Americans of South Carolina, and Jewish immigrants. He chose me and my forefathers to be a part of an eternal *brit* (covenant)—for over 3,700 years—with Him and

his “first-born” nation, *Yisrael*, and I am forever grateful for Him redeeming us from *Mitzrayim* (Egypt) with a strong hand to be His servants. *Hashem* has guided me and my wife to be brought under the *Shechinah* (G-d’s presence) by phenomenal *shomer Torah mitzvot* (guarded Bible commandment) *rabbis* (teachers) with inspiring *middot* (characteristics). He allowed us to survive the pandemic, comforted me when I was unjustly incarcerated and when I lost my little brothers Justin C. Culberson to gun violence and Terry E. Edmerson to sudden circumstances, and protected me from workplace fabricated accusations. G-d has blessed me with the ability to speak *Leshon Hakodesh* (the Holy Language) and to live to walk the Land of Israel (*Eretez Yisrael*), opportunities my ancestors yearned for. He is the *mekor* (source) of my extravagant mind and set me apart. Hashem has brought me through over five years of graduate school with a surplus of inconceivable experiences and rewards; I never imagined becoming a religious Jew.

During my career, late rapper Nipsey Hussle’s song “Dedication” motivated me, asserting, “How long 'til opportunity meet preparation? To make it happen, you got to have it. Dedication, hard work plus patience. [*sic*]” My graduate school career and this work is dedicated to *HaKadosh Baruch Hu* for the ability to study and manipulate the essence of the matter that He spoke into existence eons ago—chemicals. I have doctored a science that connects many of His creations. As Nobel Laureate chemist Dr. Ben Feringa said, “When I draw a molecule in China or in Argentina, it is the same molecule. People understand immediately without knowing Spanish or Chinese. That is beautiful.” Studying this elegant science, I feel the humility of *Moshe Rabbeinu* (Moses) with strength to endure its rigor. As *Devarim* (Deuteronomy) 8:18 says, “But you must remember the L-rd your G-d, for it is He that gives you strength to make wealth, in order to establish His covenant which He swore to your forefathers, as it is this day

”.[וְזָכַרְתָּ֣ אֶת־יְהוָ֣ה אֱלֹהֶ֔יךָ כִּ֥י ה֛וּא הַנֹּתֵ֥ן לְךָ֖ כֹּ֣חַ לַעֲשׂ֑וֹת חֶ֚יל לְמַ֣עַן הָקִ֣ים אֶת־בְּרִית֗וֹ אֲשֶׁר־נִשְׁבַּ֤ע לַאֲבֹתֶ֙יךָ֙ כַּיּ֣וֹם הַזֶּֽה׃]

Acknowledgments

The nation credited with founding the Abrahamic faith of monotheism are colloquially called *Jews*. The word *Jew* is the anglicized form of the Hebrew word *Yehudi* (יְהוּדִי), which roots stem from the Hebrew word *hodaah* (הוֹדָאָה), meaning "acknowledge" and "express gratitude." Essentially, by definition, a Jew is coined to be grateful (*Yehudi* ≈ I am thankful). There are many people I want to express thanks to; please pardon if I unintentionally fail to mention you.

I would like to initially acknowledge the obvious: my advisor, mentor, principal investigator, coach, and guide—Dr. John P. Wolfe, Professor of Chemistry and Associate Chair of Undergraduate Studies. Dr. Wolfe has provided me the space, chemicals, and funding to have the luxury of practicing the scientific method in chemistry research. His laid-back personality, honest commentary, academic expertise, creative thinking, and enjoyable career stories granted me the ability to develop as an independent scientist, scholar, and student. Dr. Wolfe's authentic nature is comforting, and his practical, analytical thinking is unparalleled. He provided me with the opportunity and freedom to express myself as a researcher, make tons of mistakes in the laboratory, heal from my traumas before and during graduate school, and pick a fitting career pathway. Furthermore, many others have substantially supported my graduate school journey.

My Ph.D. thesis committee tremendously enhanced my educational experience. I thank Dr. Melanie S. Sanford for granting me the opportunity, over many other equally qualified students, to spend my first summer in Ann Arbor conducting research in her lab before the start of my first semester. Her continued strategic, academic guidance was impeccable. I thank Dr.

Charles C. L. McCrory for coaching me academically, professionally, and personally during my journey. He provided sound advice and was an advocate for me in abundance. I never imagined the honor of having a Black chemistry professor on my thesis board; his presence is indispensable. Finally, I thank Dr. Alison R. H. Narayan for her vibrant, sensitive, and professional character, coaching, and scientific critique. For me, there was no better cognate.

There is also another unofficial member of my thesis committee: Dr. Cherie R. Dotson, alumna of the University of Michigan (UMich) Department of Chemistry. Dr. Dotson has been an exceptional mentor, coach, counselor, advisor, supporter, advocate, guide, realist, and "mother away from home" to me since the day we met in 2019. She has a plethora of academic and personal experiences to educate and motivate students from underserved and underrepresented backgrounds, giving us the equity and opportunity to reach our fullest scholarly potential. I am forever grateful and indebted to Dr. Dotson for "getting me through grad school" and life. I have also had the privilege of gaining a rich administrative experience alongside her as a Graduate Student Staff Assistant (GSSA) for Rackham Merit Fellowship (RMF) Programming.

In 2019, UMich selected me to be a Rackham Merit Fellow with maximum resources to endure and thrive as a scholar. Thank you UMich Department of Chemistry for nominating me and the Rackham Finance and Fellowships Department and the Chem Student Services Staff for the seamless renewal awarding throughout my Ph.D. Also, the staff accommodated me to have *kosher* food for inclusion efforts. The Services for Students with Disabilities (SSD) additionally ensured my education was effortless; thank you for all the equitable resources with my struggles with Attention-Deficit/Hyperactivity Disorder (ADHD) and dyslexia. Relatedly, thank you to the Wolfe lab members for being patient with me as I wrestled with my personal and academic struggles. Although some lab members made is difficult for me to exist in this space, I appreciate

the ones that made efforts for friendship, gifted me, and celebrated a few *Shabbatot* (Sabbaths) with me. Lastly, I tremendously thank the Rackham Dean's Office for their professional and academic development resources and inducting me into the prestigious Bouchet Honor Society.

Including the aforementioned entities, my progression can be attributed to the National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (NOBCChE), UMich commUNITY pipeline program, and the UMich Chemistry Diversity Committee. Thank you Dr. Ginger V. Shultz, Dr. Stephen Maldonado, and Dr. John Montgomery for your unwavering allyship. Thank you Alma R. Perez, Dr. Scott Kim, Daisy Haas, Dr. Gloria D. De La Garza, Dr. Nicholas A. Glenn, Dr. Taylor A. Bramlett, Dr. Wesley L. Pein, Nagash Clarke, Dr. Maribel E. Okiye, Dr. Nicolas A. Diaz, Takana H. Tubo, Dr. Phoenix N. Williams, and Dr. Clarence & Jaquia Cochran for your friendship and support. I only know these great people because Dr. Rosalyn V. Kent and Dr. James L. Collins recruited me to UMich.

For mentorship, thank you Dr. Sidney Wilkerson-Hill, Dr. Jared T. Shaw, Lolita Adkins, Dr. Elbert Mock III, Dr. Richard Lynton, Vaughn Evans, Dr. Emma M. Flores, Dr. Connie Champagne, Dr. Gene G. Gurkoff, Kayton C. Carter, Dr. Enoch P. Baldwin, Sean Connel, Dr. Teresa Aldredge, Dr. Ralph C. Aldredge, Dr. Marnel and Matthew Goins, Dr. Kimberly (Linenberger) Cortes, and Dr. Animesh V. Aditya. A special thank you to my uncle and aunt Yancy Clark Jr. and Pamela D. Hodge-Clark for their graduate school assistance. I thank all the graduate scholarships, awards, grants, and fellowships for support—the list on my CV is extensive. For the dissertation writing process, thank you ScholarSpace team and Dr. Namoi Silver with the Sweetland Center. Thank you Elizabeth Oxford, Katie Foster, Alex Franklin, Emma Houle, and Heather Hanosh for supreme administrative help. Lastly, thanks Mozzy and late rappers Young Slo-be and Nipsey Hussle for music to endure long days and nights in the lab.

Thank you to my wife, soulmate, and best friend Kiara for holding on tight during this rocky journey of graduate school and being a wise voice of reason; I love you. Thank you to the literal best mom in the universe, Ambria E. Alston—no words suffice. Everything I am and have today is because of your investment and sacrifice; I love you. Thank you to the most inspiring father Ray C. Culberson Jr. Grandma, Peggy Alston, I love you so much; you know what's up! Thanks for everything cuddy Briana N. Wells and twin Jasmine M. Cabrera. Tiffany R. Jamison and Donald L. Williams Jr., you know the support! Best friend Karl M. Matienzo, aunts, uncles, cousins, and Fresno and Sacramento family, thank you. Thanks Stockton, CA for tough skin. "Saba" Reuben Rickman, G-ddad Vernon L. Fox, III, and g-dmom Dr. Dyoni Lyons, thank you.

Dr. Gurkoff said it's fair to give myself proper recognition when due. I would like to acknowledge me, Matthew (מתתיהו ברוך), for beating my historical socioeconomical disadvantaged background's statistical outcomes, becoming an African slave descendant doctor.

Lastly, my *Yahadut* (Jewishness) provided strength to my academic life. I must thank UMich O-minyan, Chabad House of Ann Arbor, the Jewish Resource Center (JRC), Hillel at UM, the Orthodox Union Jewish Learning Initiative on Campus (OU-JLIC), the Ann Arbor Orthodox Minyan (AAOM), Adat Shalom Synagogue, Badatz Mekor Haim (Rabbi Eliyahu BenHaim *shlt"a* & Rabbi Benjamin Golan), Rabbi Rod Glogower, Partners Detroit (Rabbi Avi Cohen), Keter Torah Synagogue, Bais Chabad Torah Center, my *chavrutot* (Torah learning partners), my *rabbeim* Rabbi Jared Anstandig and Rabbi Dan Raphael Tobaly, artist L'Chaim OG (Zechariah Y. O. D. Levine), Rabbi Mordechai Lebhar, Congregation Ner Hamizrach (Rabbi Shmuel Khoshkerman, Rabbi Raphael Darzi, Eli Maman), and our *chakhamim* (sages). Their spiritual and religious support and guidance has made my observance of *halacha* (Jewish law) enjoyable, which has reinforced me throughout my Ph.D. journey; I am Yehudi—so thankful!

Preface

My ability to know and appreciate chemistry on a deep level came from the instruction of my late college teacher Rolf Friedrich Unterleitner, M.S. (28 Apr 1959–22 Apr 2016). When I was first enrolled at UC Davis in 2013 and selected to participate in the Biology Undergraduate Scholars Program (BUSP) program led by Dr. Connie C. Champagne, Rolf Unterleitner tirelessly taught me fundamental chemistry topics in a way that reached my brain areas that no subject had before. I fell in love with chemistry and its appliances to every-day life. I found fulfillment in passing on my knowledge to students, especially African American students that often came from underserved science backgrounds. Additionally, Dr. Jared T. Shaw, through his chemistry research, gave me the foundation in laboratory synthesis and methodology development. Building on this, former Shaw group graduate students, Dr. Leslie A. Nickerson and Dr. Lucas W. Souza, assisted me in developing key laboratory skills to practice the scientific method. These combined efforts prepared me for Dr. John P. Wolfe's synthetic method development lab, exploring palladium-catalyzed alkene difunctionalization reactions.

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List of Abbreviations

°C ..... degrees Celsius

Å..... angstrom

α .....alpha

β .....beta

γ.....gamma

Ac.....acetyl

acac [Pd(acac)2].....acetylacetonate

acac-F_6..... hexafluoroacetylacetonate

acac .....acetylacetone

All ..... allyl

aq..... aqueous

Ar .....aryl (when bound to another atom)

Au ..... Gold

BINAP (rac.)..... (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene

Bn.....benzyl

Boc ..... *tert*-butyloxycarbonyl

BPO.....benzoyl peroxide

Br.....Broad

BrettPhos..... 2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl

brsm..... based on recovered starting material

Bt (BTA) .....benzotriazole

Bz .....benzoyl

^{13}C ..... carbon

C_6D_6 .....deuterated benzene

Ca .....circa

calcd ..... calculated

CAN ..... ceric ammonium nitrate

Cbz .....carboxybenzyl

$CDCl_3$ .....deuterated chloroform

CN .....cyano

cod..... 1,5-Cyclooctadiene

Cp.....cyclopentadienyl

CPhos ..... 2-Dicyclohexylphosphino-2′,6′-bis(*N,N*-dimethylamino)biphenyl

Cy.....cyclohexyl

Cy_4DPE-Phos..... Bis[2-(dicyclohexylphosphino)phenyl] ether

CyJohnPhos ..... 2-(Dicyclohexylphosphino)biphenyl

d..... doublet

DavePhos .....2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl

dba.....dibenzylideneacetone

DBU 1,8-diazabicycloundec-7-ene

DCE.....dichloroethane

DCM .....dichloromethane/methylene chloride

dd..... doublet of doublets

ddd..... doublet of doublet of doublets

ddt .....doublet of doublet of triplets

DMF .....dimethylformamide

DMSO ..... dimethylsulfoxide

DPE-Phos .....Bis[(2-diphenylphosphino)phenyl] ether

Dppb.....1,4-Bis(diphenylphosphino)butane

dppb.....1,4-Bis(diphenylphosphino)butane

dppBz ..... 1,2-Bis(diphenylphosphino)benzene

dppe..... 1,2-bis(diphenylphosphaneyl)ethane

dppf .....1,1'-bis(diphenylphosphino)ferrocene

dppm .....1,1-Bis(diphenylphosphino)methane

dr ..... diastereomeric ratio

EDG .....electron-donating group

eh.....2-ethylhexanoate

EPhos .....Dicyclohexyl(3-isopropoxy-2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphane

eq.....equation

equiv..... equivalents

er ..... enantiomeric ratio

ESI.....electrospray ionization

Et ..... ethyl

Et_2O..... diethyl ether

EtOH .....ethanol

EWG .....electron-withdrawing group

Furyl..... furan (when bound to another atom)

(g).....gas

^{1}H .....proton

h/hr .....hour(s)

HFIP.....hexafluoroisopropanol

HRMS ..... high resolution mass spectrometry

Hz..... hertz

IR.....infrared spectroscopy

J.....coupling constant

JackiePhos..... 2-{Bis[3,5-bis(trifluoromethyl)phenyl]phosphino}-3,6-dimethoxy -2′,4′,6′-triisopropyl-1,1′-biphenyl

JohnPhos ..... 2-(di-tert-butylphosphino)biphenyl

$KMnO_4$..... Potassium Permanganate (Stain)

LG ..... leaving group

LiHMDS/KHMDS..... lithium/potassium hexamethyldisilazide

L_n/L .....general ligand

M .....molar (mol/L)

m .....multiplet

m.p. .....melting point

*m*CPBA .....meta-chloroperoxybenzoic acid

Me ..... methyl

MeOH ..... methanol

MePhos ..... 2-Dicyclohexylphosphino-2′-methylbiphenyl

MHz .....mega hertz

MS..... molecular sieve

Ms ..... mesyl (methanesulfonyl)

n..... number (whole number)

n-butyl/*n*-Bu..... normal butyl (straight chain)

NBS.....*N*-bromosuccinimide

NHC ..... *N*-heterocyclic carbene

NMR .....nuclear magnetic resonance

nOe..... Nuclear Overhauser effect

Nuc/Nuc-H.....nucleophile

o/n ..... overnight

OAc ..... acetate

OMe ..... methoxy

O*t*Bu.....tert-butoxide

OTf.....triflate

p..... para

(*p*MeOPh)$_3$P..... tris(4-methoxyphenyl)phosphane

P(*o*-tol)$_3$.....tri-*p*-tolylphosphane

PCy$_3$•HBF$_4$.....tricyclohexylphosphonium tetrafluoroborate

Pd ..... palladium

Pd/C ..... palladium on carbon

pent.....pently/pentane

PG/P ..... protecting group

Ph ..... phenyl

PhDavePhos ..... 2-Diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl

PMA ..... Phosphomolybdic Acid

PMB ..... *para*-methoxybenzyl

PMP ..... *para*-methoxyphenyl

PPh_3 ..... triphenylphosphine

Pr ..... propyl

q ..... quartet

R ..... general functional group

rbf ..... round-bottom flask

RCM ..... ring-closing metathesis

rt ..... room temperature

RuPhos ..... 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

s ..... singlet

satd ..... saturated

sec-butyl ..... secondary carbon butyl chain

SPhos ..... 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl

selectfluor ..... 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

t-butyl/*t*-Bu ..... tert-butyl

T. S. ..... transition state

t ..... triplet

t ..... tert

*t*BuBrettPhos ..... 2-(Di-*tert*-butylphosphino)-2′,4′,6′- triisopropyl-3,6-dimethoxy-1,1′-biphenyl

*t*BuDavePhos..... 2-Di-*tert*-butylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl

*t*BuMePhos..... 2-Di-*tert*-butylphosphino-2′-methylbiphenyl

*t*BuXPhos ..... 2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl

TEA..... triethylamine

TEMPO 2,2,6,6-tetramethyl-1-piperidinyloxy

Tf..... triflyl (trifluoromethylsulfonyl)

Tf_2O..... triflic anhydride

TFA [Pd(TFA)2] ..... trifluoroacetate

TFA ..... trifluoroacetic acid

THF ..... tetrahydrofuran

TLC ..... thin-layer chromatography

TMS ..... trimethylsilyl

Tol ..... toluene

Tol-d8..... deuterated toluene

Tolyl..... toluene (when bound to another atom)

Ts..... tosyl

WeirdPhos (**24**) ..... 2′-Dicyclohexylphosphino-2-methoxy-1-phenylnaphthalene

X..... general halide, counterion, or atom

XantPhos ..... 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos..... 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

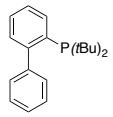
Y..... general heteroatom/functional group

Z ..... general atom or substitution

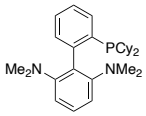
List of Ligands

The ligands listed in this section are named in their abbreviated form and are referenced throughout this dissertation. For conveince they are drawn here; full names can be found in the abbreviations section or through an online search.

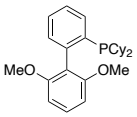
Buchwald Monodentate



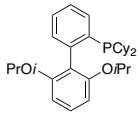
JohnPhos



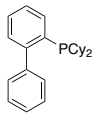
CPhos



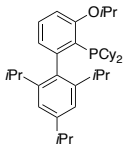
SPhos



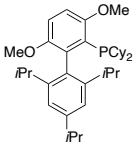
RuPhos



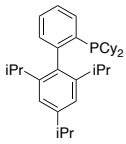
CyJohnPhos



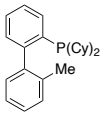
EPhos



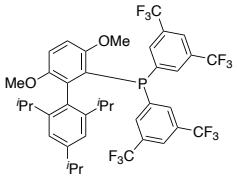
BrettPhos



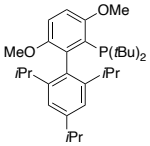
XPhos



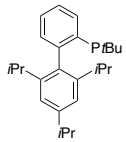
MePhos



JackiePhos



***t*BuBrettPhos**



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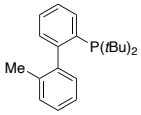

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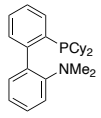
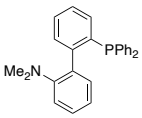
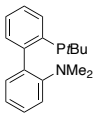


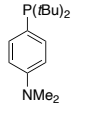
DavePhos



PhDavePhos



***t*BuDavePhos**



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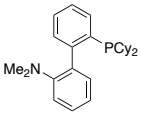

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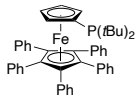

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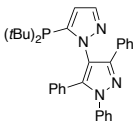

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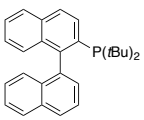

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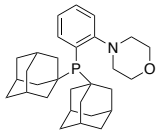

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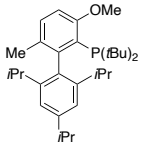

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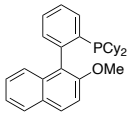
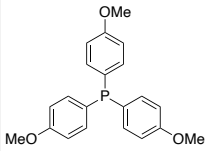
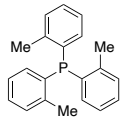


24 ("WeirdPhos")

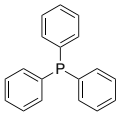
Other Monodentate



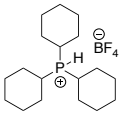
(*p*MeOPh)$_3$P



P(*o*-tolyl)$_3$

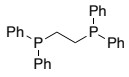


PPh$_3$



PCy$_3$·HBF$_4$

Bidentate



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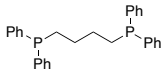
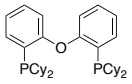
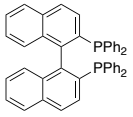


dppb



Cy$_4$DPE-Phos



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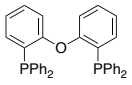
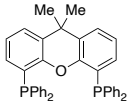
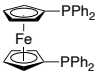


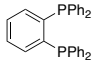
DPE-Phos



XantPhos



dppf



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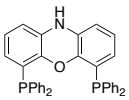
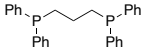


NiXantPhos



dppp

Abstract

Metal-catalyzed alkene difunctionalization reactions have been targeted and developed by chemists as a quintessential class of important and efficient transformations for both academic research and industry efforts. Specifically, many chemists have discovered and improved methods of metal-catalyzed diamination and carboamination reactions of unactivated alkenes to prepare nitrogen heterocycles that appear in natural products and drug candidates.

The Wolfe Lab at University of Michigan has developed a series of methods for the synthesis of nitrogen-containing heterocycles through palladium-catalyzed alkene carboamination reactions. In these transformations, alkenes bearing tethered amine nucleophiles are coupled with aryl or alkenyl halide electrophiles to rapidly generate nitrogen heterocycles from readily available starting materials. These reactions are valuable tools that can be used in drug discovery and chemical biology to produce a diverse library of compounds containing common pharmacophores. However, the optimization of these transformations can be challenging due to competing side reactions, as the intermediates in the catalytic processes can frequently react in more than one way. This can often be controlled by using very specific catalysts or ligands to minimize side reactions and provide optimal yields and stereoselectivities for products.

This Ph.D. dissertation describes the development of a new tandem intra/intermolecular *N*-arylation/alkene carboamination reaction between 2-allylaniline derivatives and 1,2-dihalobenzene electrophiles that generate polycyclic nitrogen heterocycles. These transformations generate two carbon-nitrogen bonds and one carbon-carbon bond, leading to the formation of two

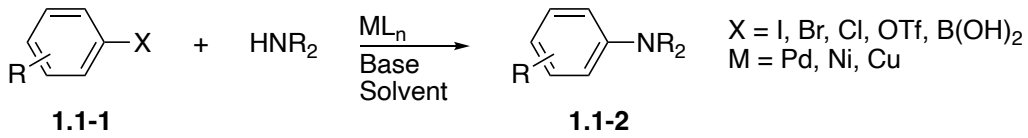
rings in a single process. These reactions form biologically relevant dihydroindoloindole derivative ring systems that are of considerable interest and utility. This method is a valuable tool that can be used in drug discovery and chemical biology to produce a diverse archive of molecules containing common scaffolds.

The transformations provide the heterocyclic products in good yield with up to 19:1 diastereoselectivity and allow for the construction of a rarely-described class of nitrogen heterocycles from substrates prepared in in only 1-2 steps from commercially available materials. This dissertation describes the background behind this work along with the synthesis of starting materials, reaction optimization, ligand effects, exploration of the scope of the chemistry, and isolation/purification of the products. The mechanism of the tandem reactions, which is analogous to previously described N-arylation and alkene carboamination reactions, is also presented.

Chapter 1 Palladium-Catalyzed N-Arylation and Carboamination Reactions

1.1 Introduction to Metal Catalyzed N-Arylation Reactions

For over 25 years, methods for the metal-catalyzed *N*-arylation of aryl halides (-I, -Br, -Cl) or pseudo aryl halides (-OTf, -$B(OH)_2$) using amines have been developed, studied, and optimized in different systems to produce *N*-aryl amines in high yields under mild reaction conditions.[1-2] These methods have been of interest in both academia and industry because the *N*-aryl moiety is found in the core of many biologically relevant compounds, and these processes contain interesting scientific explorations.[3] These transformations take a sp^3 or sp^2 nitrogen (HNR_2) and affix it to an aromatic compound (**1.1-1**), forming a new C–N bond (carbon-nitrogen) (**1.1-2**) using transition metal catalysts like palladium, nickel, and copper mixed with ligands of various structures in the presence of a base (Equation 1–1).[4]

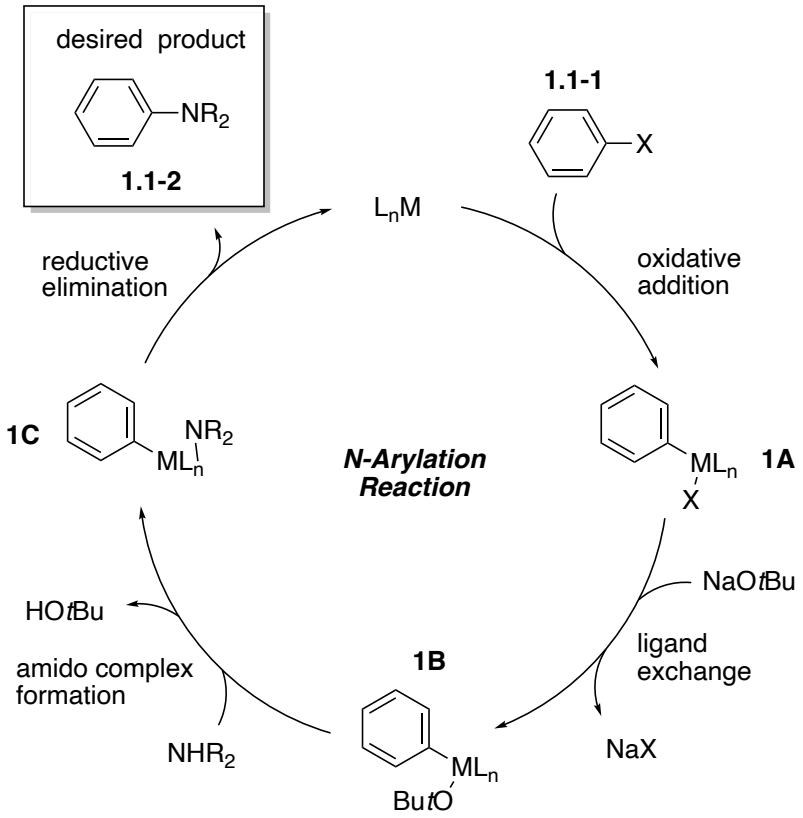


1.1-1 **1.1-2**

Equation 1–1 General Metal-Catalyzed N-Arylation Reaction

Specifically, the research groups of Dr. Stephen L. Buchwald and Dr. John F. Hartwig have collectively created Buchwald–Hartwig amination reactions using various metal catalysts; Buchwald described a new class of dialkylbiaryl phosphine ligands for promoting the transformations.[5] These methods employ a reliable and practical way of forming new C–N bonds from a simple cross-coupling reaction of amines and derivatives of aryl halides, as opposed to

other methods that require harsh conditions, stoichiometric quantities of metals or high catalyst loadings, or toxic metals.[5] The mechanism of the Pd-catalyzed *N*-arylation reactions has been heavily studied and proceeds through known organometallic transformations (Scheme 1–1).



Scheme 1–1 General Mechanism of N-Arylation Reaction

Traditionally, these *N*-arylation reactions precede through an initial formation of a metal catalyst *in situ* from a binding between a pre-catalyst and ligands. The catalyst then undergoes an oxidative addition into an aryl halide (**1.1-1**) to form Pd(Ar)(X) complex (**1A**). Then a ligand exchange between a butoxide base and the halogen occurs (**1B**). Next the amine reacts with **1B** to form amido complex **1C**. Finally, a reductive elimination leads to the desired product (**1.1-1**) and regenerates the palladium catalyst to continue the cycle.[6] Depending on the base used (e.g. Cs_2CO_3), amine binding can precede amido complex formation, before reductive elimination leading to the product.

1.2 Importance & Significance of Aryl Amines and Their Syntheses

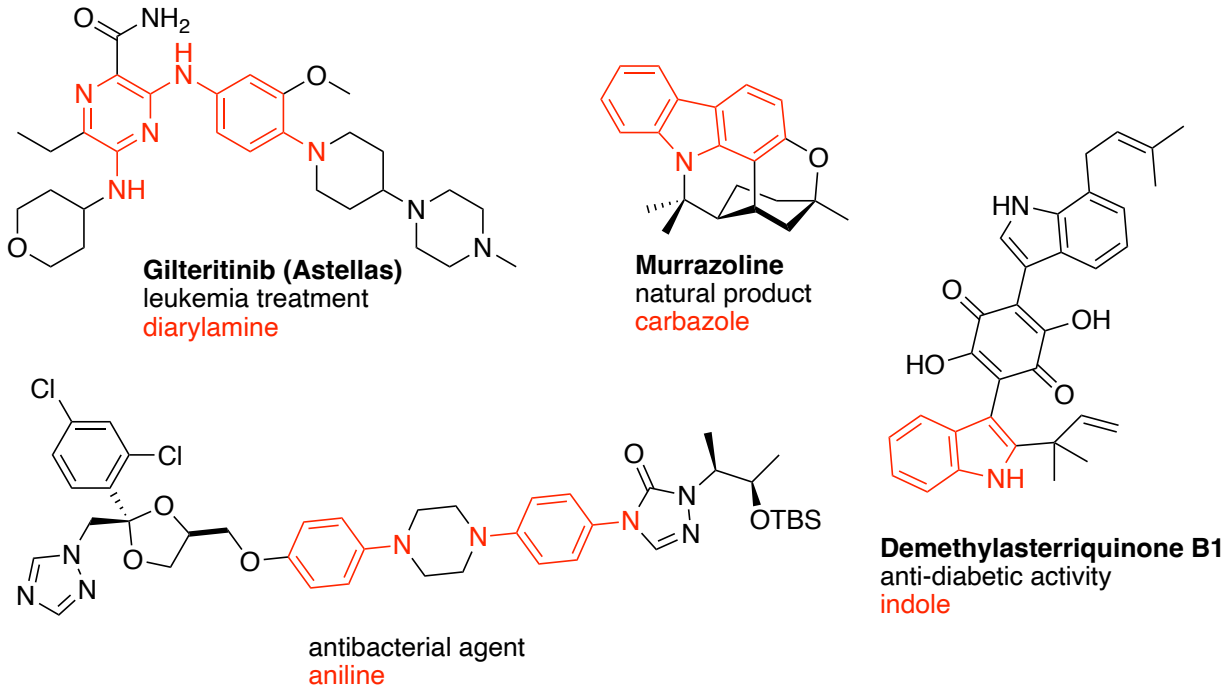
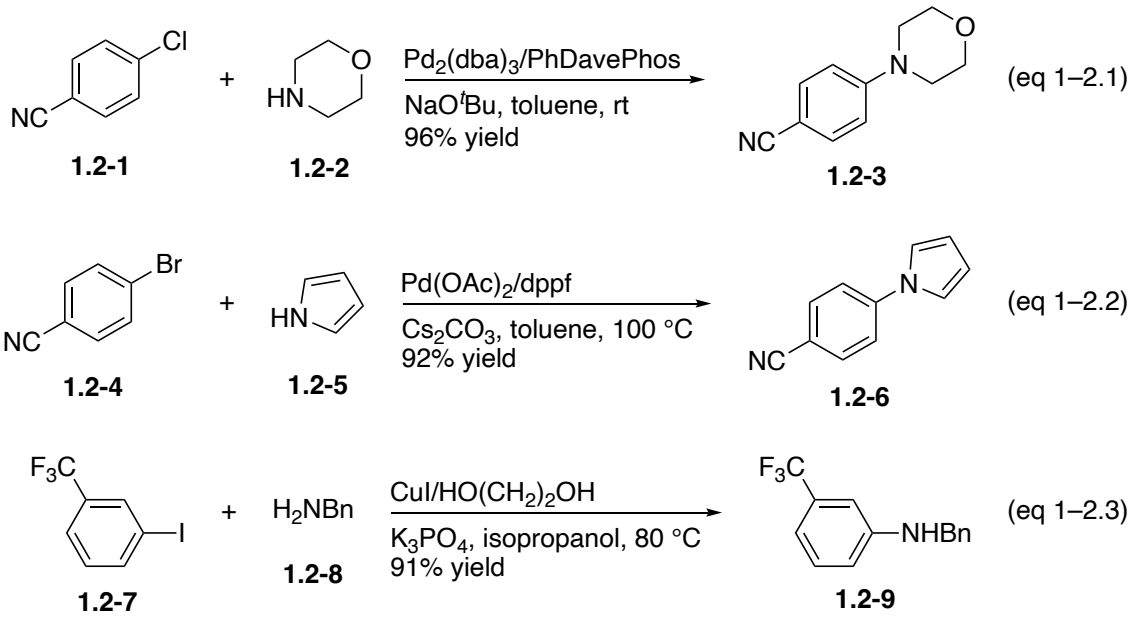


Figure 1–1 Select Biologically Relevant Aryl Amines

Aryl amines are ubiquitous in natural products, pharmaceuticals, materials, synthetic intermediates, academic research as ligands, and medicinal agents.[7] The *N*-aryl moiety is diverse in applications and properties across chemical-related fields and are sometimes biologically active in heterocycles. This structural element is present in many biologically-active and pharmaceutical compounds as listed in Figure 1–1. For example, the leukemia treatment *gilteritinib* contains a diarylamine and *murrazoline* is natural product that contains a carbazole with a C–N bond that can be achieved through *N*-arylation chemistry.

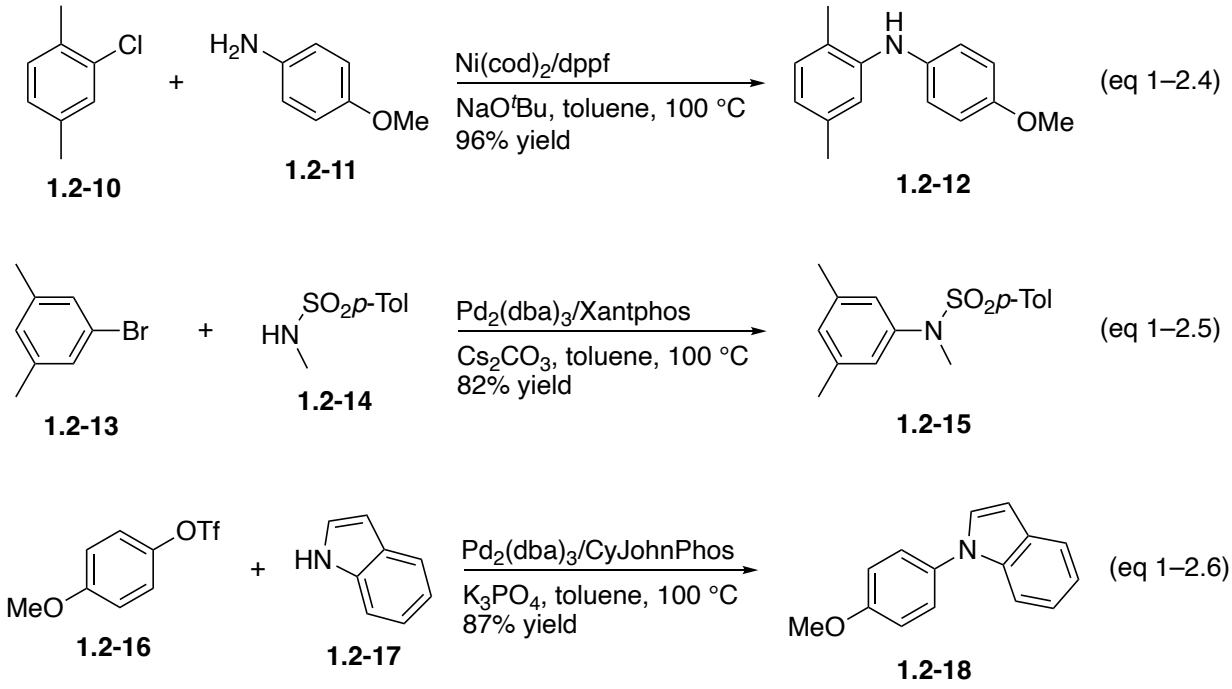
Scheme 1–2 contains select examples of *N*-arylation reactions with cyclic and acyclic sp^3 or sp^2 amines and aryl halides in high yields with dialkylbiaryl phosphine ligands or ethylene glycol as a ligand.[8] For example, eq 1–2.1 demonstrates a cross-coupling of aryl chloride (**1.2-1**) to morpholine (**1.2-2**) using palladium *dba* as a pre catalyst and PhDavePhos as a phosphine ligand. At room temperature, the *N*-arylation product (**1.2-3**) was able to be achieve in excellent yield

(96%) in toluene. These reactions work best with sodium butoxide as the base in solution for deprotonation and interaction with the metal complex. However, high yields (92%) of *N*-arylation products (**1.2-5**) were accomplished using a carbonate base with the cross coupling of aryl bromide (**1.2-4**) and pyrrole (**1.2-5**) in the presence of a palladium catalyst heated to 100 degrees Celsius (eq 1–2.2). Lastly, copper has successfully catalyzed the coupling of alkylamines (**1.2-8**) and aryl iodides (**1.2-7**) at 80 degrees Celsius with diols as ligands and potassium phosphate as the base to produce *N*-arylamine **1.2-9** in high yield (eq 1–2.3).



Scheme 1–2 Select N-Arylation Reactions Example 1

The utility of this method has also been demonstrated (Scheme 1–3) with nickel and palladium catalysts forming diaryl amines (**1.2-12**) from anilines (**1.2-11**), aryl amines (**1.2-15**) from free amines (**1.2-14**)—both acyclic nitrogens as starting materials—and aryl indoles (**1.2-18**) from indoles (**1.2-17**).[9] Bidentate ligands dppf and Xantphos and monodentate ligand CyJohnPhos were used for these transformations in the presence of base to achieve high yields (up to 96%). The structures of these ligands are displayed in Figure 1–2, and the ligand structure is highly important for performing specific chemical transformations.



Scheme 1–3 Select N-Arylation Reactions Example 2

The structural features of dialkylbiaryl phosphine ligands heavily control the rates of mechanistic steps in the catalytic cycle, catalyst stability, ligand stability, and inhibition of undesired products.[10] For example, substituents attached to the arenes can prevent cyclometalation, accelerate reductive elimination, prevent oxidation of the phosphorous atom, encourage formation of complexes, and enhance binding of amines to the metal center. Another component of these ligands are the substituents attached to the phosphorus. For example, electron-rich groups enhance the rate of oxidative addition.

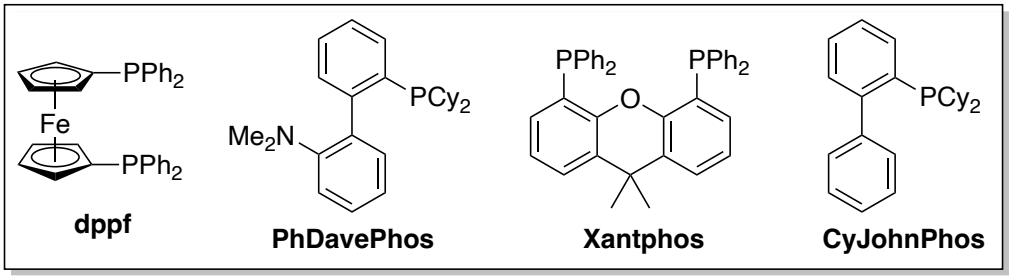


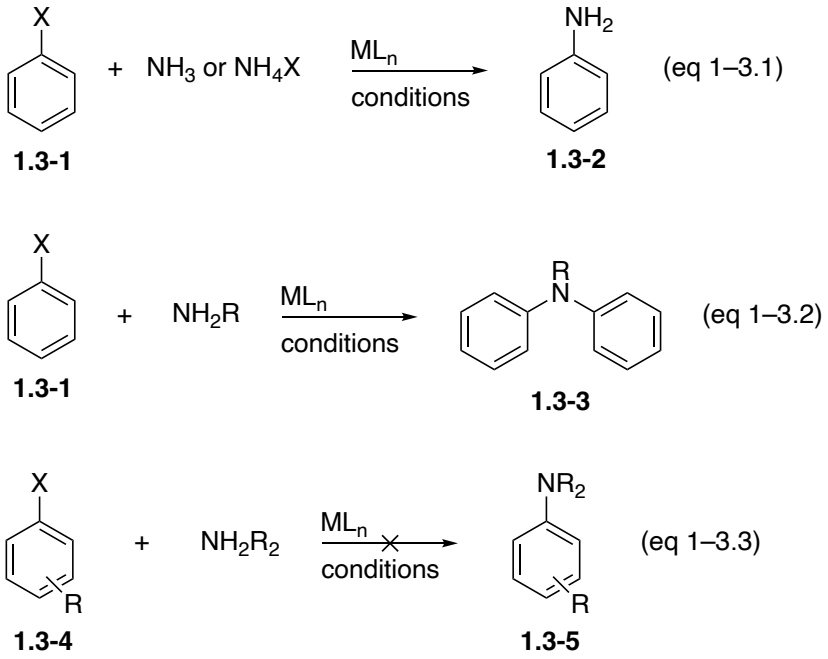
Figure 1–2 Ligands Involved with N-Arylation

Generally, factors that influence palladium catalyzed amination reactions include the type of electrophile arene and its substituents, the type of nitrogen-based nucleophile, the palladium precatalyst source, the electronics and sterics of the ligand, the choice base, the solvent, and the temperature of the system. For example, the type of halide (I, Br, OTf) influences the rate of oxidative addition and amine binding, the electronics and sterics of the amine influence reductive elimination, the temperature and solvent control the solubility of materials and formation of products, and the types of bases influence rate of catalytic steps and functional group tolerance. Adjusting each parameter for *N*-arylation reactions can access diverse substrates.

Palladium-catalyzed *N*-arylation chemistry can be utilized to possibly generate *γ*-*N*-arylamino alkenes, and these products can be used as substrates for alkene carboamination reactions that produce nitrogen heterocycles. For example, if *p*-anisidine **1.2-11** was allylated at C2 and subsequently *N*-arylated, the resulting *N*-aryl-2-allylaniline derivative can be converted to an indoline product as described further below in Section 1.5 (Scheme 1–5).

1.3 Limitations & Challenges of N-Arylation Reactions

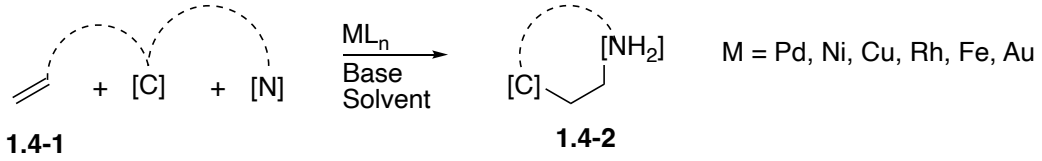
Despite the utility of *N*-arylation chemistry, this methodology does have some limitations. For example, ammonia is one of the most abundant nitrogen sources on earth but handling it for *N*-arylation reactions opens safety concerns.[11] Additionally, direct use of ammonia is generally not effective in Buchwald–Hartwig aryl-amine couplings, due to the strong Lewis basicity leading to inactive metal complexes from the strong coordination (eq 1–3.1); therefore, free amine alternatives or multistep catalyst systems are required for those *N*-arylation reactions.[11] Additional limitations to *N*-arylation chemistry include β-hydride (β-H) elimination side reactions (eq 1–3.3), diarylation (over arylation) of the nucleophile (eq 1–3.2), functional group tolerance from the base and/or temperature used, and other substrate structure limitations (Scheme 1–4).[11] Nonetheless,



Scheme 1–4 N-Arylation Challenges Example

the *N*-arylation method remains a powerful tool and is exhibited in intermediate pathways of other transformations like carboamination reactions.

1.4 Introduction to Metal-Catalyzed Carboamination Reactions

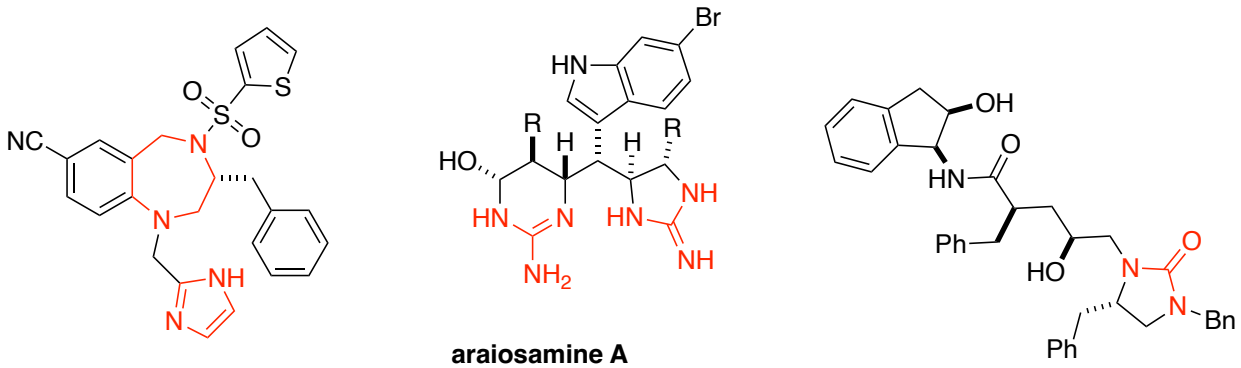


Equation 1–2 General Metal-Catalyzed Carboamination Reaction

Simple molecules like *N*-aryl aminoalkenes can be synthesized first from *N*-arylation reactions then subjected to carboamination reactions to synthesize multifaceted heterocycles.[12] Carboamination reactions involve the formation of C–N and C–C bonds to substrates in sequence, usually through metal catalysis. Particularly, carboamination reactions have strong utility in difunctionalization of alkenes, adding these two new bonds across different sides of an olefin (Equation 1–2).[13] In a single transformation, this powerful method can strategically build complex

molecules with up to two stereocenters. This transformation can proceed through modes of bimolecular cyclization of amines and alkenes, intramolecular aminocyclization via an aminoalkene, or fully intermolecular multi-component functionalization of alkenes for acyclic compounds.[13]

1.5 Importance & Significance of Carboamination Reactions, Methods, and Products



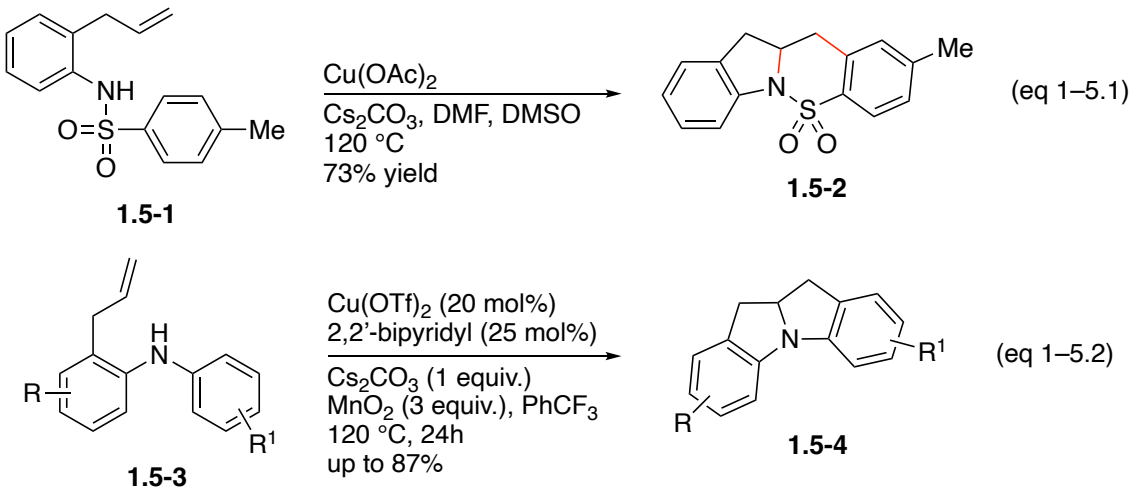
BMS-214662
antitumor
diazepane & imidazole-based

araiosamine A
natural product
Guanidine-based
R = 3-(7-bromo)indolyl

HIV-protease inhibitor
urea-based

Figure 1–3 Biologically Relevant Nitrogen Heterocycle Carboamination Prospective Products

Carboamination reactions affect construction of a variety of *N*-heterocycles, forming two or more bonds (C–N and C–C) in one step, converting simple molecules to more complex ones. Biologically relevant nitrogen heterocycles (Figure 1–5)[14] can theoretically be synthesized by using metal-catalyzed alkene carboamination reactions. In the case of the molecules shown above, for example an aminoalkene substrate would be coupled with an aryl halide or arene to form a C–N bond along with one ring, and a carbon-carbon bond to the aryl group external to the ring. Although most of this chapter is focused on palladium-catalyzed carboamination reactions, a brief discussion of copper-, gold-, and nickel-catalyzed reactions that are related to the work in this dissertation (Chapter 2) is included below.



Scheme 1–5 Select Copper-Promoted/Catalyzed Alkene Carboaminations Examples 1

Copper-promoted alkene carboamination reactions were first reported in 2004 by the Chemler group (Scheme 1–5).[15] They took *N*-tosyl-2-allylanilines (**1.5-1**) with $Cu(OAc)_2$ in the presence of Cs_2CO_3 at 120 °C in a DMF/DMSO mixture to produce tetracyclic indoline derivatives **1.5-2** in 73% yield (eq 1–5.1). This carboamination method forms a polycyclic nitrogen heterocycle through aminocupration of the alkene and C–H activation of the arene. This transformation proceeds by formation of copper-amido complex **1D** followed by *cis*-aminocupration (**1E**), homolysis to form an alkyl radical (**1F**), ring addition, and rearomatization for product synthesis (Scheme 1–6). Chemler also used copper to catalyze this type of transformation via intramolecular carboamination chemistry to synthesize polycyclic nitrogen heterocycles **1.5-4** from *N*-aryl-2-allylaniline derivatives **1.5-3** (eq 1–5.2).[16] Their allylaniline undergoes a similar C–H amination (C–H activation) during catalysis.

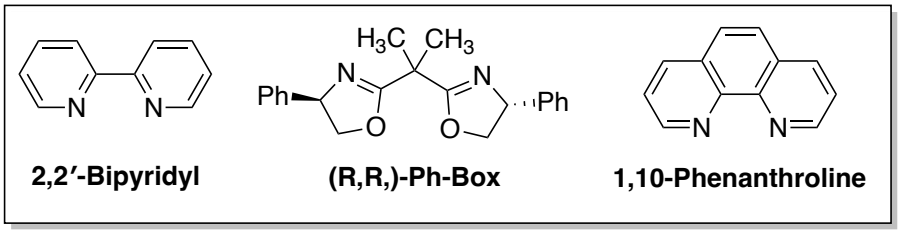
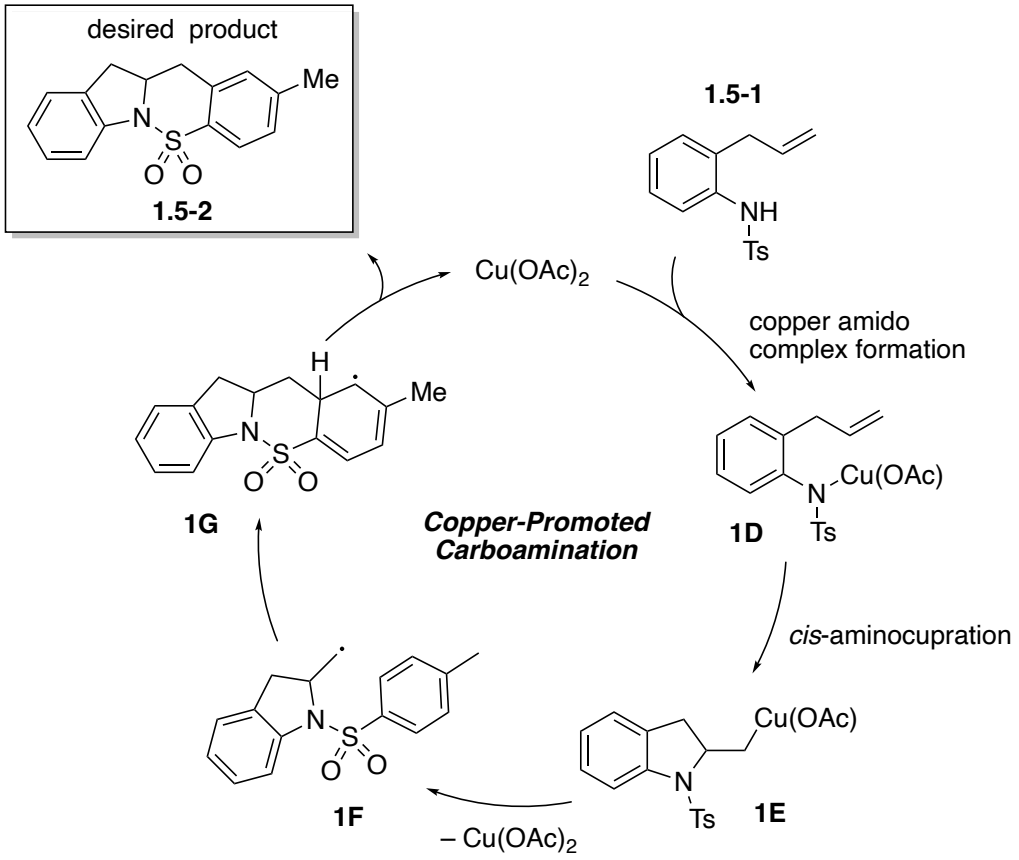


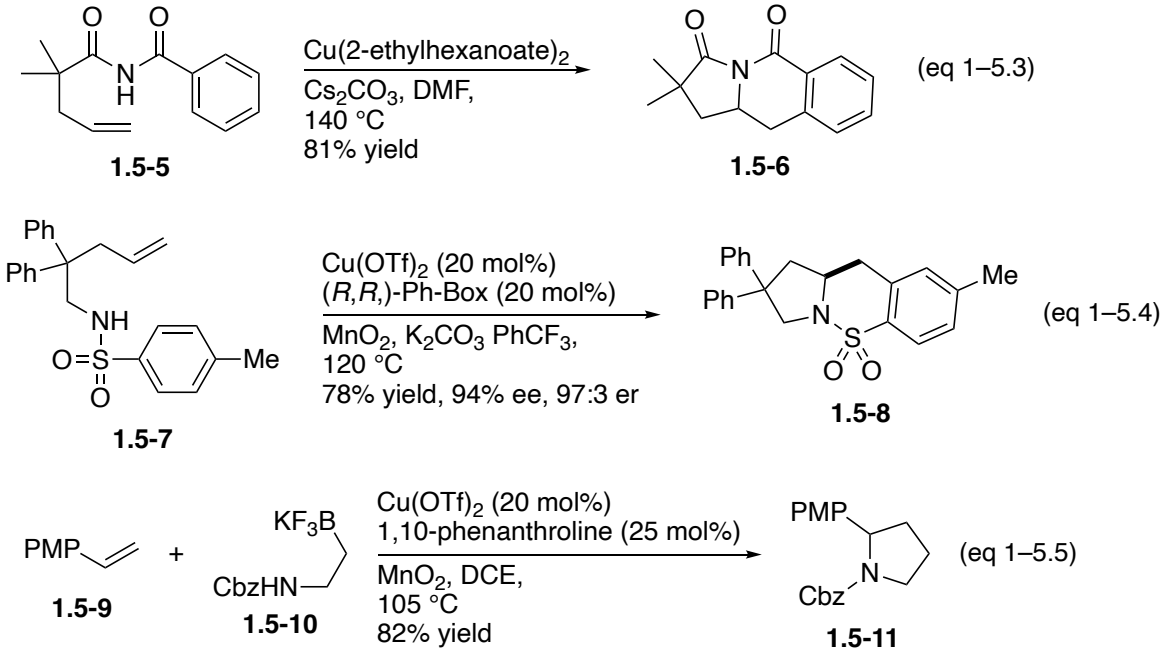
Figure 1–4 Ligands Involved with Copper-Mediated Carboaminations

There have also been reports of other fully intramolecular (eq 1–5.3), fully intermolecular, and intra-/intermolecular reactions utilizing copper and ligands such as phenanthroline or Ph-Box derivatives, along with enantioselective versions of these reactions (1–5.4).[17] As shown in Scheme 1–7, the scope of synthesis of polycycles via copper-mediated carboamination of alkene is not limited to 2-allylaniline derivates. For example, amides tethered to olefins **1.5-5**, or tosyl-



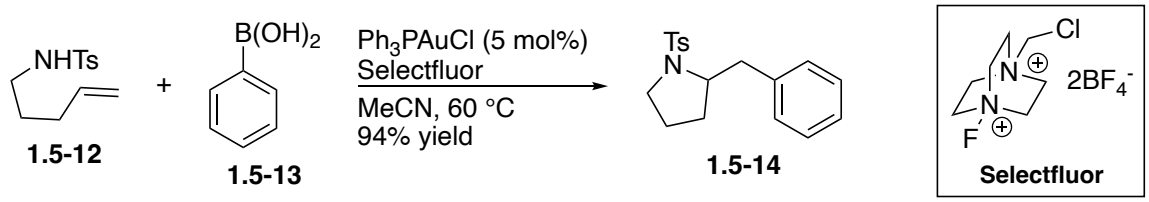
Scheme 1–6 Copper Promoted Carboamination

protected aminoalkenes **1.5-7** are converted to tricyclic nitrogen heterocycles (**1.5-6** and **1.5-8**) in good yield and selectivity. Cu-catalysts can also be used for the synthesis of other nitrogen heterocycles such as pyrrolidines, β-lactams, and, oxoiminopyrroles.[17] For example, eq 1–5.5 demonstrates paramethoxystyrene **1.5-9** can be coupled to *N*-Cbz-β-aminoethyltrifluoroborate **1.5-10** to synthesize pyrrolidines **1.5-11** in high yield using copper catalysis with a strong oxidant.



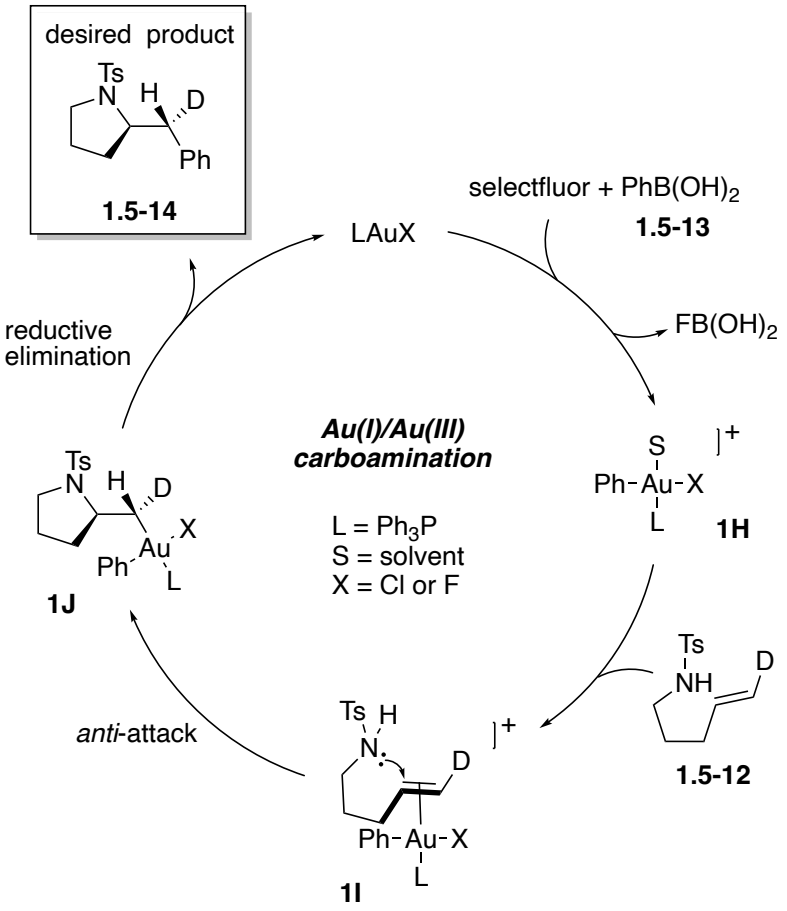
Scheme 1–7 Select Copper-Promoted/Catalyzed Alkene Carboaminations Examples 2

This method is considered to be intermolecular two-component alkene carboamination. Similar pyrrolidines can be created through gold catalysis.



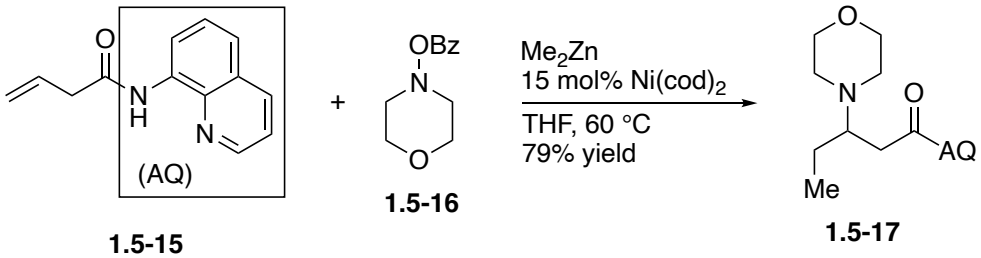
Equation 1–3 Rare Gold-Catalyzed Carboamination Reaction

In 2010 Zhang reported rare examples of homogeneous Au-catalyzed alkene carboamination reactions between aminoalkenes **1.5-12** and arylboronic acids **1.5-13** in high yields and mild conditions to synthesize pyrrolidines **1.5-14** (Equation 1–3).[18] This oxidative carboheterofunctionalization proceeds through an unusual mechanism involving Au(I)/(III) redox cycles. As shown in Scheme 1–8, the mechanism of this reaction involves initial oxidation of Au(I) to Au(III) to provide **1H**, followed by transmetalation to afford an arylgold(III) intermediate **1I**.



Scheme 1–8 Gold-Catalyzed Carboamination

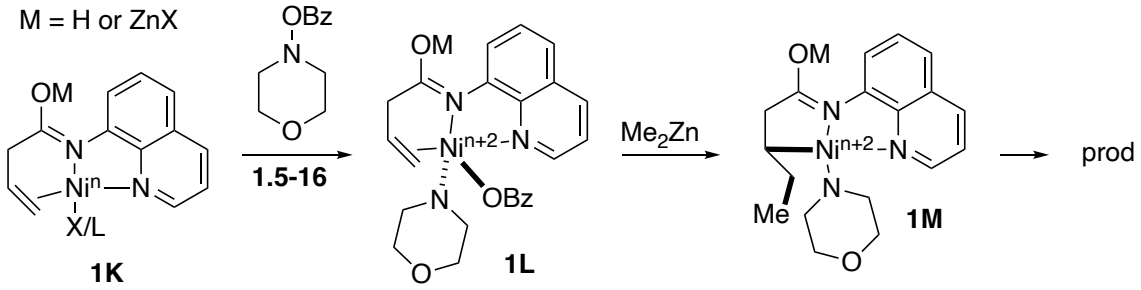
Thereafter, the arylgold(III) intermediate performs an *anti*-aminometalation of the alkene to yield **1J**, and subsequent reductive elimination then provides the desired product **1.5-14**. Similar products have been synthesized with a nickel catalyst.



Equation 1–4 Nickel-Catalyzed Carboaminations of β,γ-Unsaturated Amides

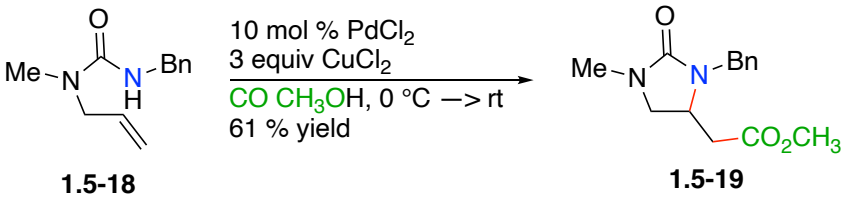
In recent years, Engle has demonstrated a coupling of β,*γ*-unsaturated amides bearing 8-aminoquinoline **1.5-15** with *O*-benzoyl hydroxylamine electrophiles **1.5-16** and aryl/alkylzinc

nucleophiles via *syn*-1,2-carboamination (Equation 1–4).[19] In these transformations nickel catalysts are used, and this method provides access to acyclic β-amino amides **1.5-17** in good yield under mild conditions. One mechanism suggested by the group involves a substrate-bound nickel complex **1K** that would first undergo oxidative addition with **1.5-16** to form intermediate **1L**. The group deduced that two plausible redox manifolds—Ni(0)/Ni(II) or Ni(I)/Ni(III) catalysis as Ni(*n*)/N(*n*+2)—could be functioning. Transmetalation followed by insertion to the alkene would form **1M**, which could reductively eliminate to form products **1.5-17** and regenerate the active catalyst.



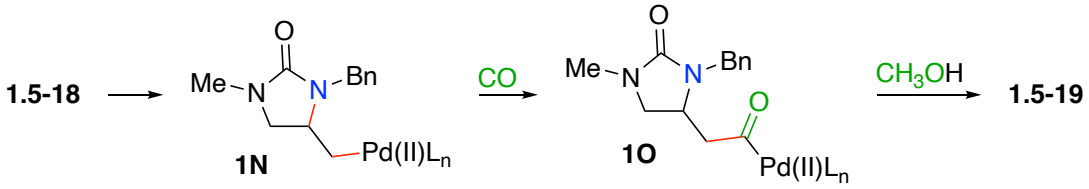
Scheme 1–9 Nickel-Catalyzed Carboamination Mechanism

Although metals such as copper, gold, and nickel have been used to catalyzed alkene carboamination reactions, palladium is the most utilized for several reasons. For example, alkylcopper intermediates have radical character (are not configurationally stable), and stereocontrol in Cu-catalyzed carboamination reactions can be modest. In addition, although the Cu-catalyzed reactions have an advantage to effect C–C bond formation via C–H functionalization, they also produce mixtures of regioisomers in reactions involving substrates with substituents on the aromatic ring. However, many phosphine ligands are commercially available that have been shown to be useful for various regio-, chemo-, and stereoselective transformations in palladium catalysis, which allows for easy tuning of *in situ* generated catalyst from pre-catalysts such as $Pd(OAc)_2$ and Buchwald ligands.



Equation 1–5 Early Example of Palladium-Catalyzed Carboamination Reaction

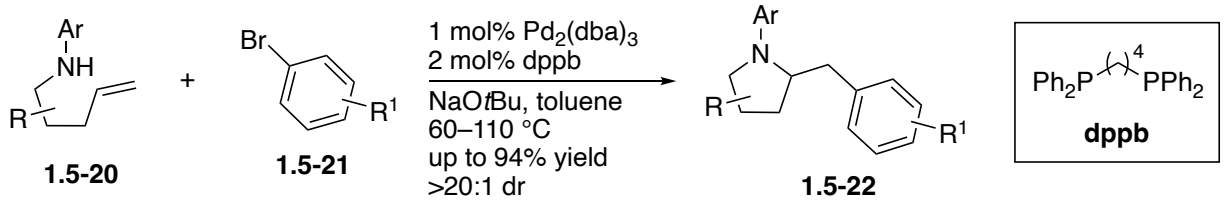
One of the earliest examples of a Pd-catalyzed alkene carboamination reaction is from the 1980s when Hegedus and Tamaru independently reported the synthesis of urea-based nitrogen heterocycles (**1.5-19**) in moderate yields through palladium-catalyzed alkene carbonylation reactions (Equation 2–1).[20] They discovered that, after deprotonation, a nitrogen nucleophile (**1.5-18**) could form a new bond to one end of a tethered alkene and the other end of the alkene could be intercepted to form a new bond to a carbon substituent. Hegedus and Tamaru were able to synthesize a cyclic urea bearing a pendant ester with formation of three new bonds from acyclic *N*-allylureas (**1.5-18**). Copper (II) chloride in this instance serves to re-oxidize the palladium catalyst from Pd(0) to Pd(II) *in situ*. The mechanism[21] of this reaction involves σ-alkylpalladium(II) complex formation **1N** from aminopalladation of the urea derivative with a tethered olefin. Carbon monoxide then inserts (**1O**) and methanolysis occurs to produce the desire product **1.5-19** (Scheme 1–10). The first example of intercepting a cyclic aminopalladium complex



Scheme 1–10 Palladium-Catalyzed Alkoxycarbonylation

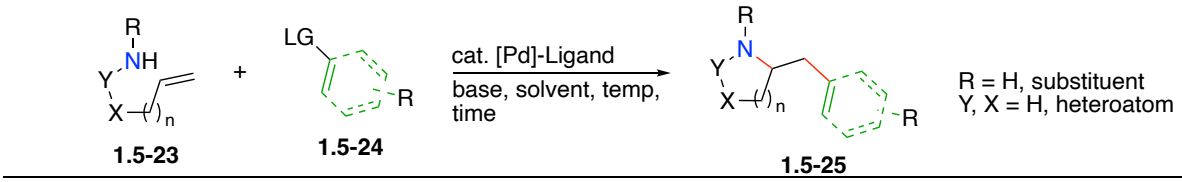
with an aryl halide instead of CO was reported in the early 2000's.

Since 2004, the Wolfe group have developed a robust series of carboamination reactions involving aryl or alkenyl halides and *γ*-*N*-arylamino alkenes. The group was the first to report stereoselective synthesis of *N*-aryl pyrrolidines (**1.5-22**) in high yields and light conditions with this methodology (Equation 1–6).[12] These types of reactions generally involve a *N*-substituted amine or aniline tethered to an alkene (**1.5-23**) as a nucleophile cross-coupled with an aryl or alkenyl halides or pseudohalide (**1.5-24**) in the presence of a palladium catalyst and exogenous base with an elevated temperature system to produce nitrogen heterocycles (**1.5-25**) as shown in Scheme 1–11.

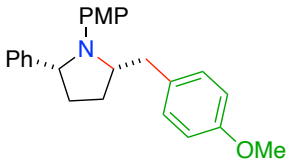


Equation 1–6 Palladium-Catalyzed Carboamination Reaction with Aryl Halide and Aminoalkene

Scaffolds to biologically-relevant nitrogen heterocycles have been created over the years by the Wolfe group.[22] Through palladium catalysis, difunctionalization of alkenes via carboamination reactions has been reported in high yield and great selectivity to produce cyclic nitrogen heterocycles, such as *pyrazolidines*, *oxazolidines*, and *morpholines* (Scheme 1–11). The method had even been expanded to revisit ureas possessing a tethered olefin to synthesize cyclic ureas as demonstrated by Hegedus and Tamaru.



Pyrrolidines



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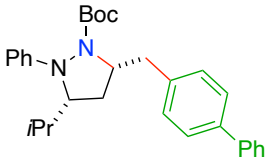
Pyrazolidines



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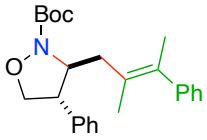
J. Am. Chem. Soc. **2008**, 130, 12907

Isoxazolidines



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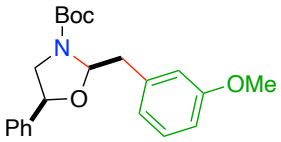
J. Org. Chem. **2009**, 74, 2533

Oxazolidines



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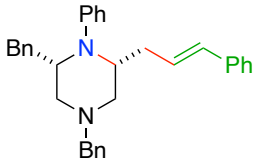
Org. Lett. **2011**, 13, 4728

Piperazines



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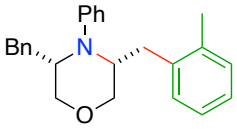
Tetrahedron **2009**, 65, 6549

Morpholines



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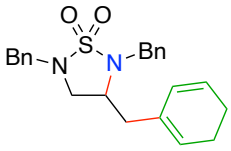
J. Org. Chem. **2009**, 74, 5107

Cyclic Sulfonamides



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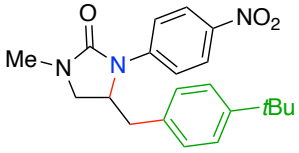
Chem. Eur. J. **2014**, 20, 8782

Cyclic Ureas



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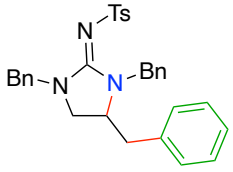
Cyclic Guanidines



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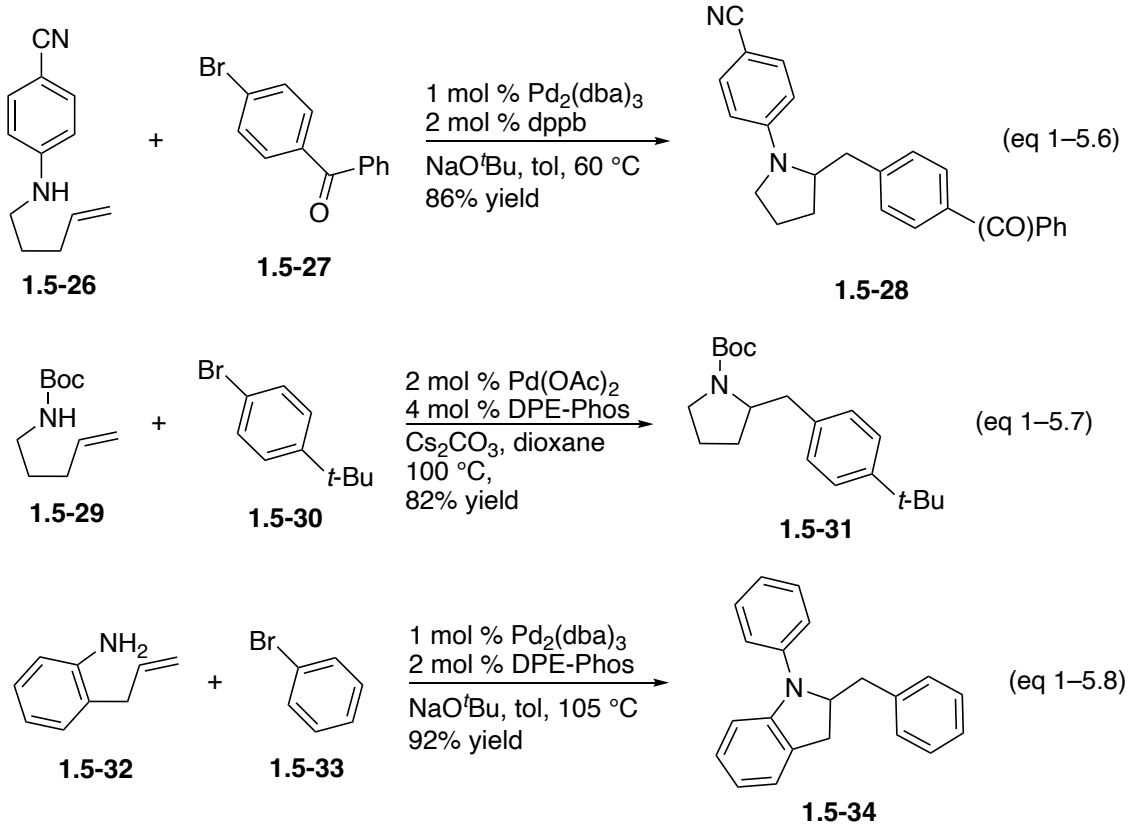
Org. Lett. **2017**, 19, 2817

Scheme 1–11 Selected Examples of Nitrogen Heterocycles Synthesized Through Pd-Catalyzed Alkene Difunctionalization Reactions

For example, *N*-aryl aminoalkene **1.5-26** was combined with aryl bromide **1.5-27** in the presence of $Pd_2(dba)_3$, *dppb*, and sodium *tert*-butoxide to produce *N*-aryl pyrrolidine **1.5-28** in high yield (eq 1–5.6). The utility of this transformation can be expanded to *Boc* protected amines **1.5-29** and anilines **1.5-32** to synthesize other nitrogen heterocycles in high yield with a different precatalyst, bidentate ligand, base, and solvent (Scheme 1–12).[22] The respective ligands' structures are displayed in Figure 1–5, demonstrating that relatively simple bidentate phosphine ligands are suitable for these robust reactions.



Scheme 1–12 Select Examples of Pd-Cat. Carboamination Reactions

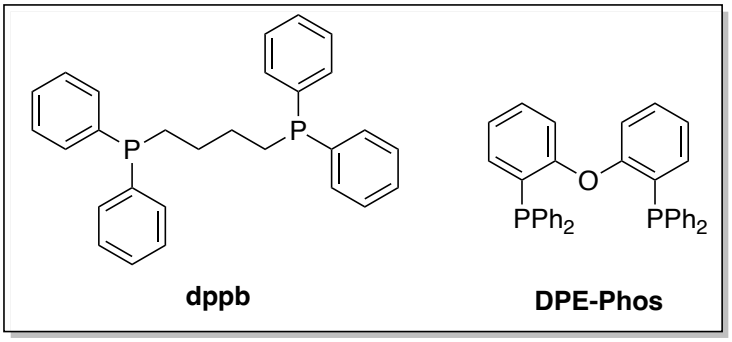
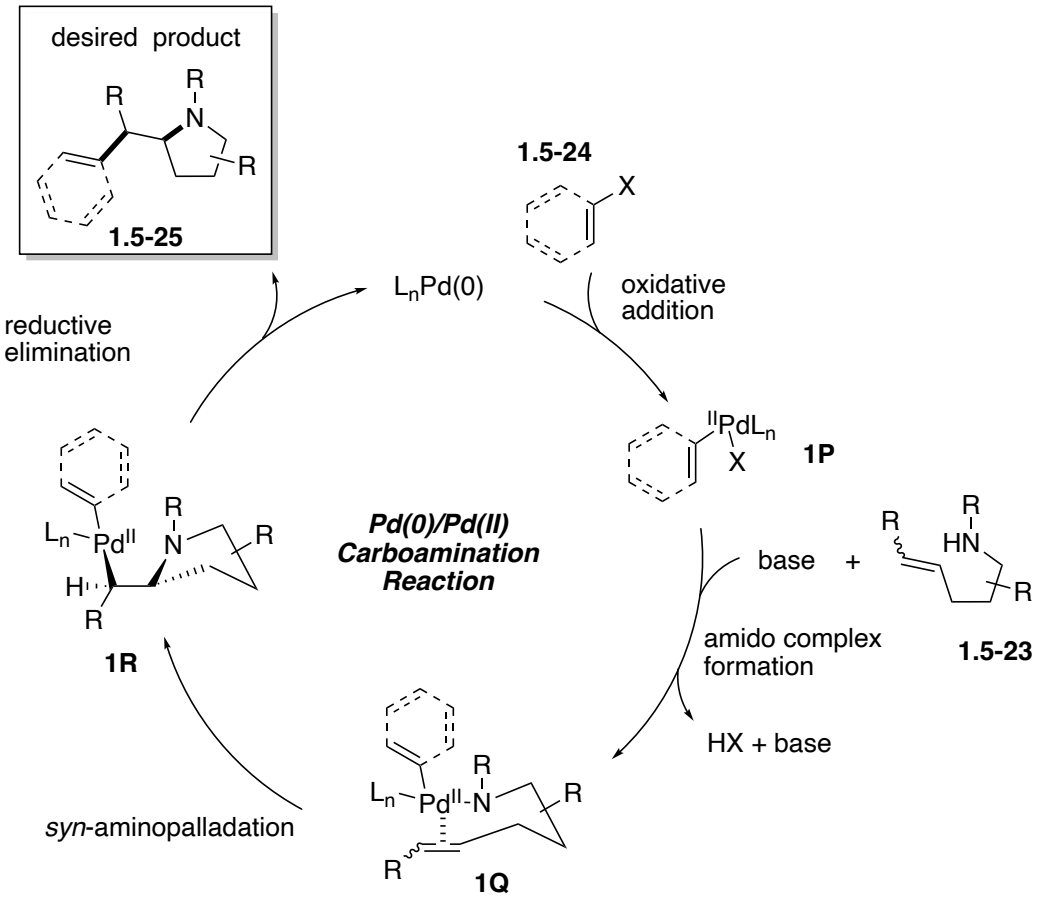


Figure 1–5 Ligands Involved in Pd-Cat. Carboamination

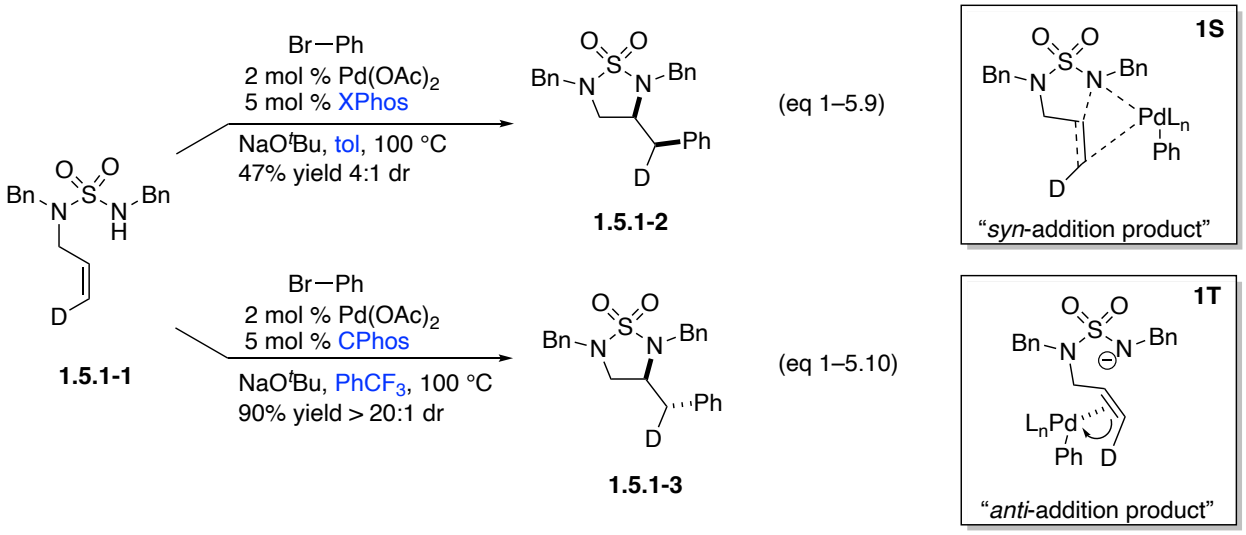
It has been found from research studies that phosphine ligands are highly specific for chemical reactions and assist in key steps of the mechanism.[23] The mechanism of the carboamination reaction is believed to begin with catalyst oxidative addition into an aryl or alkenyl



Scheme 1–13 Pd-Cat. Carboamination Reaction Mechanism

halide (**1.5-24**) to form complex (**1P**). There is then a base-mediated amido complex formation with the addition of the amine (**1.5-23**) to the metal center, creating complex **1Q**. Then a syn-aminopalladation on the tethered alkene forms complex **1R**. Finally, a reductive elimination leads to the desired product (**1.5-25**) and recycles the palladium catalyst to continue the cycle. The stereoselectivity of these reactions for syn- versus anti-aminopalladation can be influenced based on the reaction systems' parameters.

1.5.1 Syn- and Anti-Aminopalladation Products



Scheme 1–14 Syn- and Anti-Addition Products

The palladium-catalyzed alkene difunctionalization reactions can selectively provide *syn*- or *anti*-addition products based on the reaction conditions. In studies involving *N*-allyl sulfamides (**1.5.1-1**) the stereoselectivity for the *syn*-aminopalladation pathway (Pd coordination to the nucleophilic nitrogen prior to the aminopalladation step **1S**) instead of the *anti*-aminopalladation pathway (no coordination of Pd to the nucleophilic nitrogen **1T**) was controlled by reaction conditions that favor a neutral palladium center during the mechanism (Scheme 1–14).[24] In the case of *syn*-addition, the palladium and nitrogen form bonds on same side of the alkene in a concerted fashion (eq 1–5.9). Depending on the counterion of the electrophile, counterion of the base, and polarity of solvent coupled with the ligand, you will get *syn*- or *anti*-aminopalladation. For example, when triflates are used as electrophiles and trifluorotoluene as solvent, this facilitates the generation of cationic intermediate palladium complexes that favor the *anti*-aminopalladation pathway. In contrast, conditions that lead to a less electrophilic metal center and/or neutral intermediates (aryl bromide substrates, nonpolar solvents) favor the *syn*-addition pathway. Ligands from *syn*- and *anti*-aminopalladation products are listed in Figure 1–6 for reference.

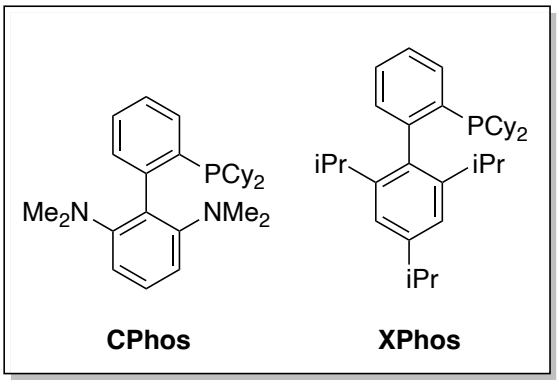
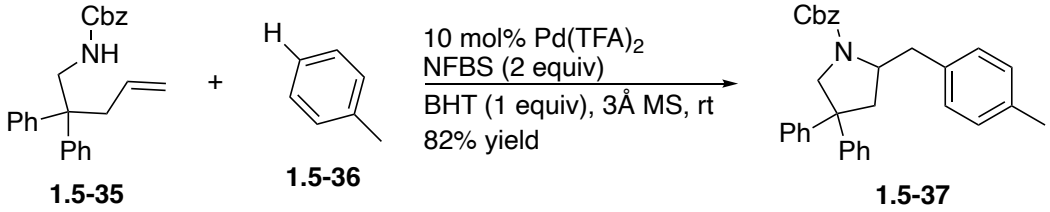
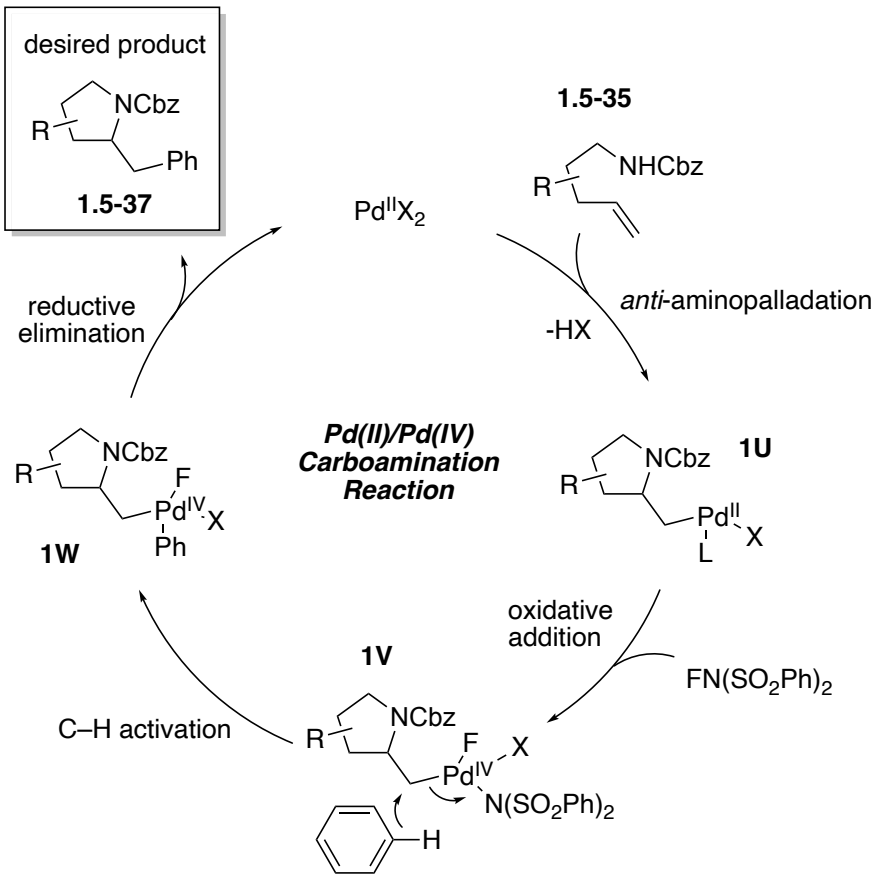


Figure 1–6 Syn- vs Anti-Carboamination Ligands

The Michael group developed an *anti*-addition Pd-catalyzed alkene carboamination reaction in 2009 that cross-couples Cbz-protected aminoalkenes **1.5-35** and arenes **1.5-36** to synthesize pyrrolidines (Equation 1–7).[25] This carboamination reaction relies on a high oxidation state palladium (IV) complex to promote C–H functionalization of an arene, which is used the reaction's solvent. The mechanism initiates with *anti*-aminopalladation of the alkene to form complex **1U**, followed by oxidative addition of *N*-fluorobenzenesulfonimide (NFBS) to provide the Pd(IV) complex **1V**. Next, C–H activation of the arene solvent occurs (**1W**) followed by reductive elimination to synthesize product (**1.5-37**). *Anti*-aminopalladation is influenced by the slightly acidic conditions, preventing Pd-amido complex formation.

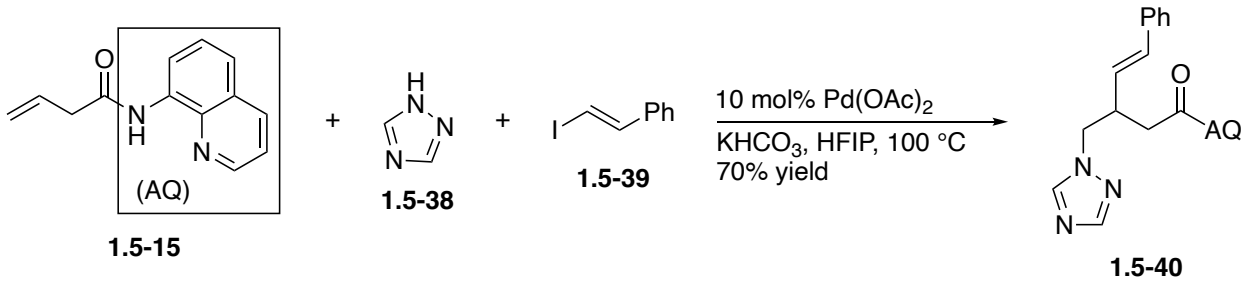


Equation 1–7 Palladium-Catalyzed Carboamination Reactions via C–H Activation

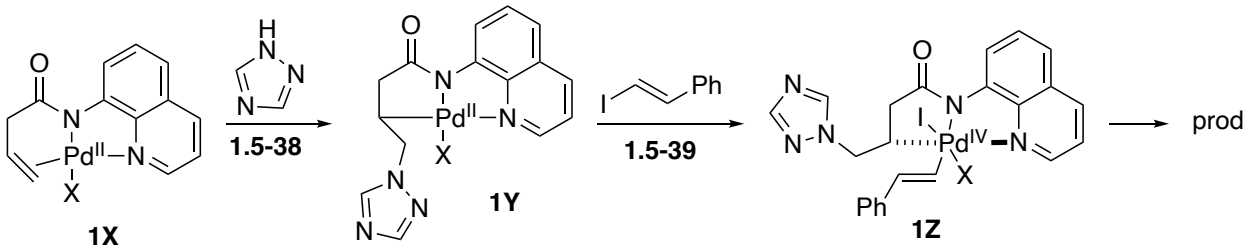


Scheme 1–15 Mechanism Palladium-Catalyzed Carboamination via C–H Activation

High valent palladium complexes have also used by Engle in carboamination reactions to synthesize acyclic amines (Equation 1–8).[26] This transformation is a regiocontrolled three component coupling reaction between unactivated alkenes **1.5-15**, nitrogen nucleophiles (**1.5-38**), and aryl, alkenyl, or alkyl iodides (**1.5-39**) to synthesize *γ*-aminocarboxylic acid derivatives **1.5-40** in moderate to good yield. The reaction begins with initial binding of the alkene and 8-aminoquinoline (AQ) directing group to Pd(II) to form complex **1X**. This influences the reactivity and regioselectivity. Next *anti*-aminopalladation (**1Y**) then oxidative addition of the alkyl iodide to produce a Pd(IV) complex **1Z** occurs. Lastly, reductive elimination and substrate exchange releases the product to regenerates the initial Pd(II) amide alkene complex (Scheme 1–16).



Equation 1–8 Palladium-Catalyzed Three Component Carboamination Reaction

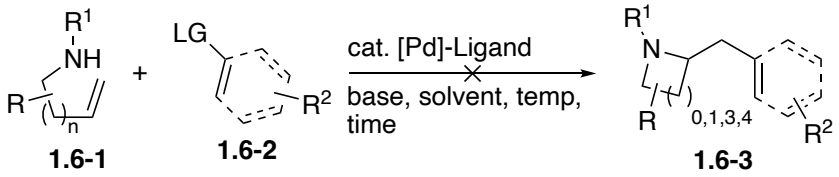


Scheme 1–16 Mechanism of Directed Multi-Component Carboamination Reaction

1.6 Limitations & Challenges to Carboamination Chemistry

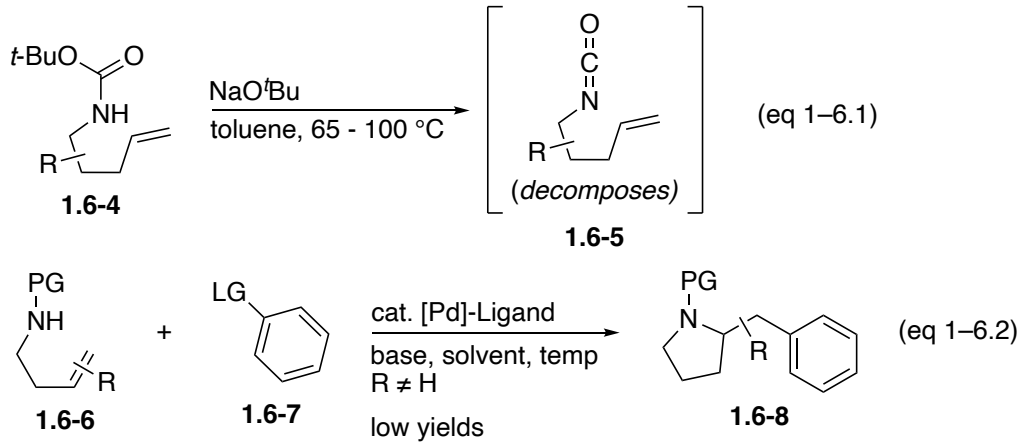
Several different metals, including palladium, copper, gold, and nickel, have been used as catalysts for alkene carboamination reactions, each with advantages and disadvantages. For example, Cu-catalyzed reactions frequently involve C–H functionalization, obsoleting the requirement for aryl halides. Some limitations to copper-involved carboamination reactions include the need for high catalyst loadings, external oxidants, and low stereoselectivity due to radical intermediates. Nickel carboamination reactions of alkenes demonstrated strengths of synthesizing cyclic and acyclic nitrogen compounds in good yield and mild conditions. Nickel is a relatively small metal, and hindered substrates can pose challenges. Many nickel or gold precatalysts are extremely air sensitive and difficult to handle. Also, nickel- and gold-catalyzed reactions are very limited in scope. Palladium is the most utilized metal for alkene carboamination reactions due to its ease of handling, low air-sensitivity, suburb stereoselectivity, short reaction rate times, and access to nitrogen-based compounds. However, competing β–hydride elimination

side reactions tend to be more facile with palladium; correct choice of ligand is necessary to obtain good results.[5,8]



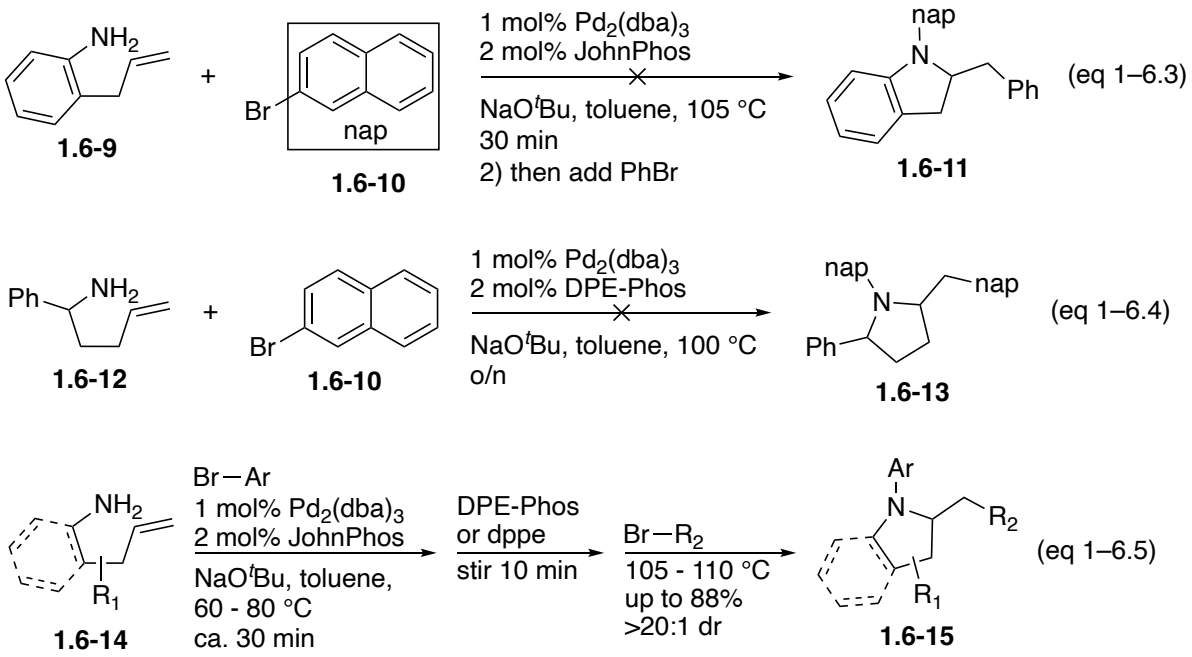
Equation 1–9 Limited Examples of 3-, 4-, 6-, and 7-membered Ring Products

Although there have been successes in Pd-cat carboamination reactions of aminoalkenes to synthesize nitrogen heterocycles,[27] the Wolfe group has observed challenges and limitations. Some of those challenges include the production of 3-, 4-, 6-, and 7-membered ring nitrogen heterocycles (Equation 1–9). Also, the requirement for a strong base can limit functional group tolerance (Scheme 1–17). For example, some protecting groups, such as *Boc*-groups, undergo base-mediated decomposition under certain conditions (eq 1–6.1).[28] In addition, substitution of the tethered olefin is not generally well tolerated (eq 1–6.2).[29]



Scheme 1–17 Limitations and Challenges to Carboamination Example 1

There are also relatively few examples of the synthesis of polycyclic nitrogen heterocycles via alkene carboamination.[27] Cascade reactions[30] in in which amines undergo both an *N*-arylation reaction and subsequent carboamination reaction have been reported but remain rare and



Scheme 1–18 Limitations and Challenges to Carboamination Example 2

challenging (Scheme 1–18). In previously reported examples, an *in situ* ligand exchange protocol was required (eq 1–6.5) because no one ligand performed well for both the *N*-arylation and the carboamination steps (eq 1–6.3 & eq 1–6.4).

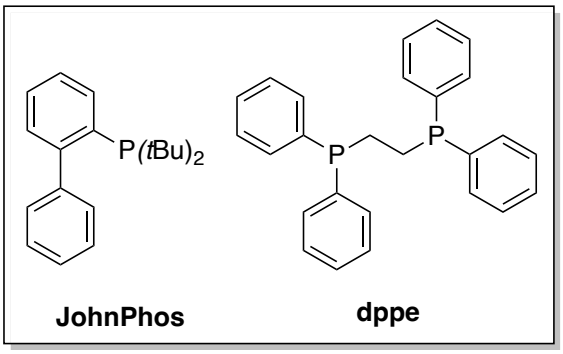
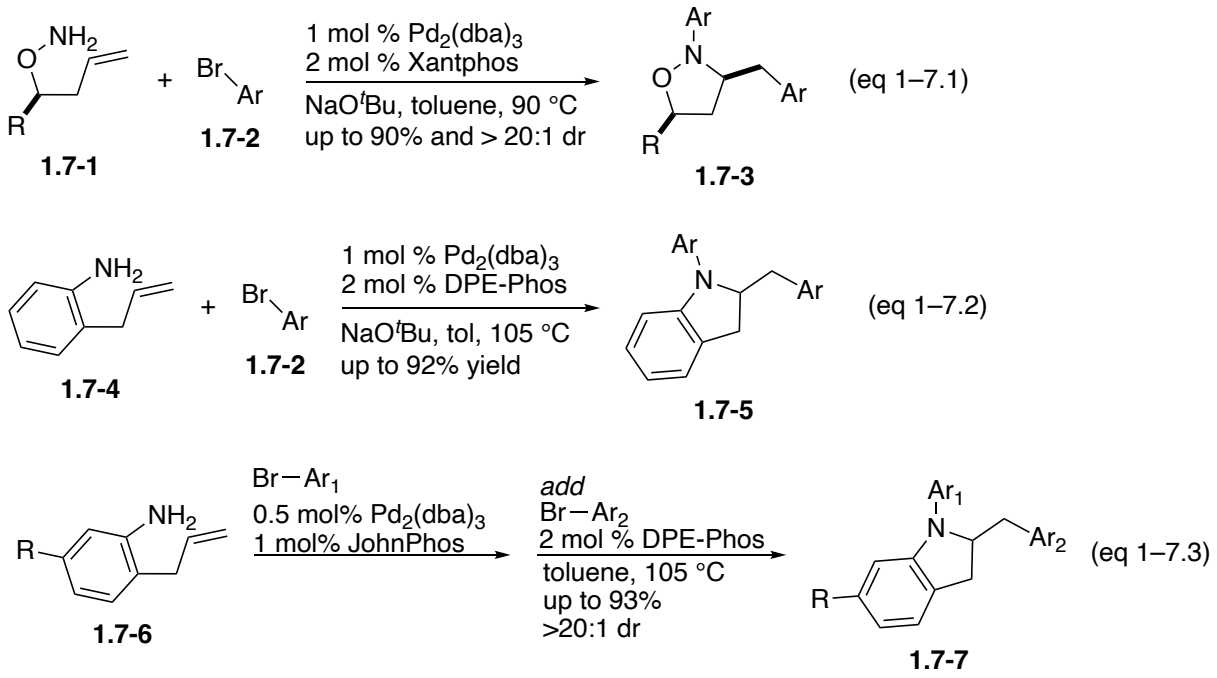


Figure 1–7 Ligands Involved with Carboamination Challenges

1.7 Cascade/Tandem Palladium Catalyzed Carboamination Reactions

Cascade reactions that combine the use of intermolecular and intramolecular functionalization are highly attractive to science, technology, and medicine. Performing these transformations as one-pot catalytic processes can rapidly build complex and diverse molecules

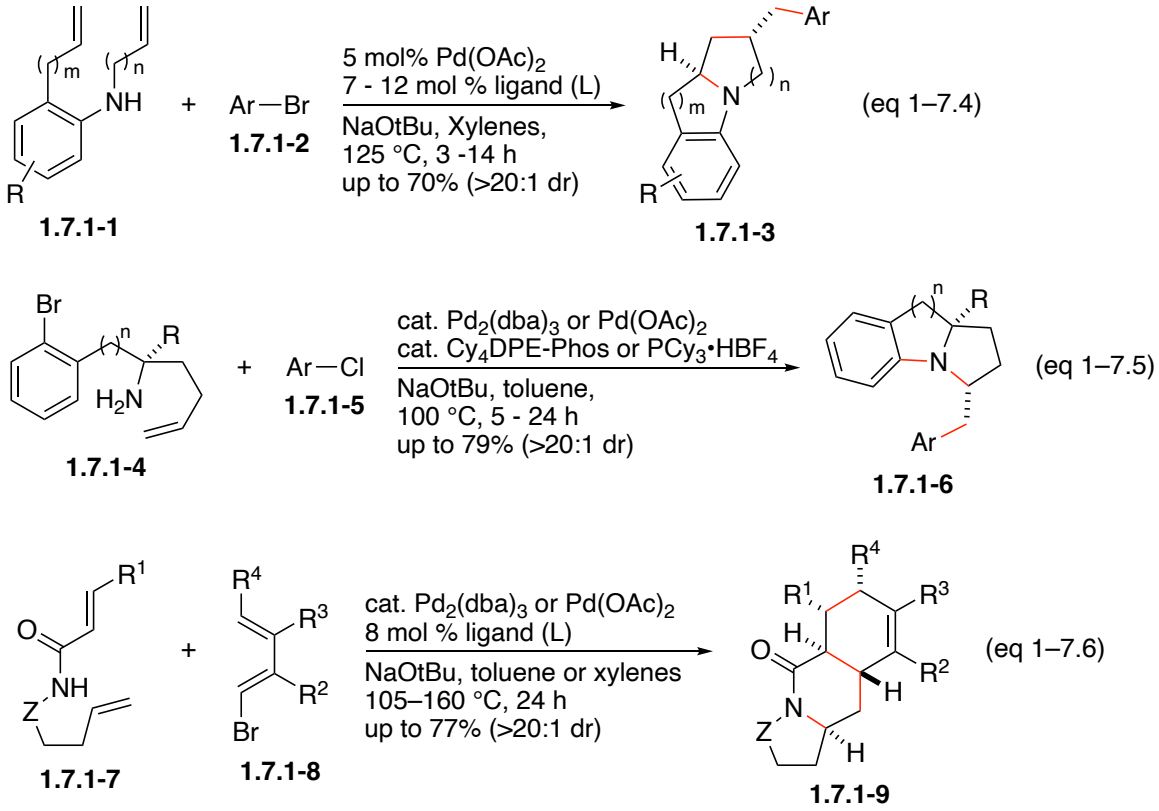
with ease. Particularly, palladium-catalyzed tandem reactions on alkenes form multiple bonds, stereocenters, and rings to synthesize *N*-heterocycles that are otherwise difficult to create.



Scheme 1–19 Select Examples of Palladium-Catalyzed Cascade/Tandem Reactions

Palladium-catalyzed *N*-arylation and carboamination reactions in tandem with aminoalkenes and aryl halides to produce nitrogen heterocycles in good yield with high chemoselectivity have been reported over the last few years (Scheme 1–19).[31] For example, hydroxylamine **1.7-1** cross-coupled to arylbromide **1.7-2** in the presence of a palladium catalyst, butoxide base, and toluene as solvent has synthesized isoxazolidines **1.7-3** in high yield and great selectivity (eq 1–7.1). Allylanilines (**1.7-4**) perform similarly to produce hydroindoles (**1.7-5**). These cascade reactions involve an intermolecular *N*-arylation to the amine and a subsequent carboamination on the tethered alkene to form mono- and dicyclic nitrogen heterocycles (Scheme 1–19). Furthermore, other types of polycyclic heterocycles can be synthesized under similar conditions using palladium catalysis.

1.7.1 Select Syntheses of Polycyclic Nitrogen Heterocycles via Cascade/Tandem Pd-Cat. Carboamination Reactions



Scheme 1–20 Cascade/Tandem Reactions to Produce Polycyclic Nitrogen Heterocycles

Benzene-fused polycyclic *N*-heterocycles and their derivatives represent scaffolds of interest in industrial and academic applications. The Wolfe group has reported three different methods for the synthesis of polycyclic nitrogen heterocycles in good yield utilizing intramolecular palladium carboamination chemistry (Scheme 1–20).[31,32] Two cases require an aryl halide and olefin for inter-/intramolecular reactivity (eq 1–7.4 & eq 1–7.5). Equation 1–7.4 also utilizes *para*-substituted triphenylphosphine ligands for a successful transformation instead of Buchwald ligands (Figure 1–8). Reaction 1–7.6 couples carboamination to a Diels–Alder [4+2] cycloaddition with a γ-aminoalkene derivative and bromodiene in the presence of a Pd-catalyst and base to synthesize stereoselective polycyclic heterocycles. Different Buchwald ligands were

used for this chemistry and the group also reported using ureas, sulfamides, and phenylenediamines as substrates for highly complex and diverse products.

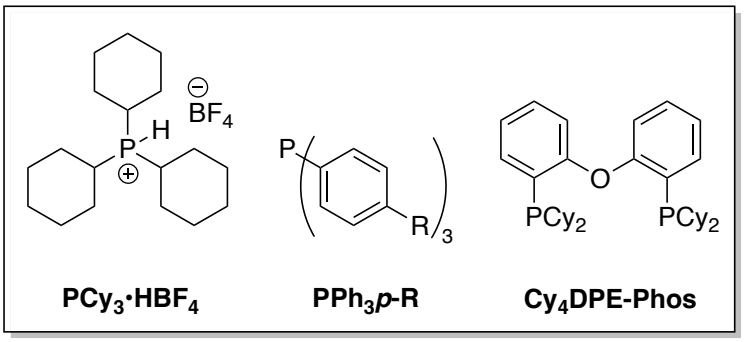
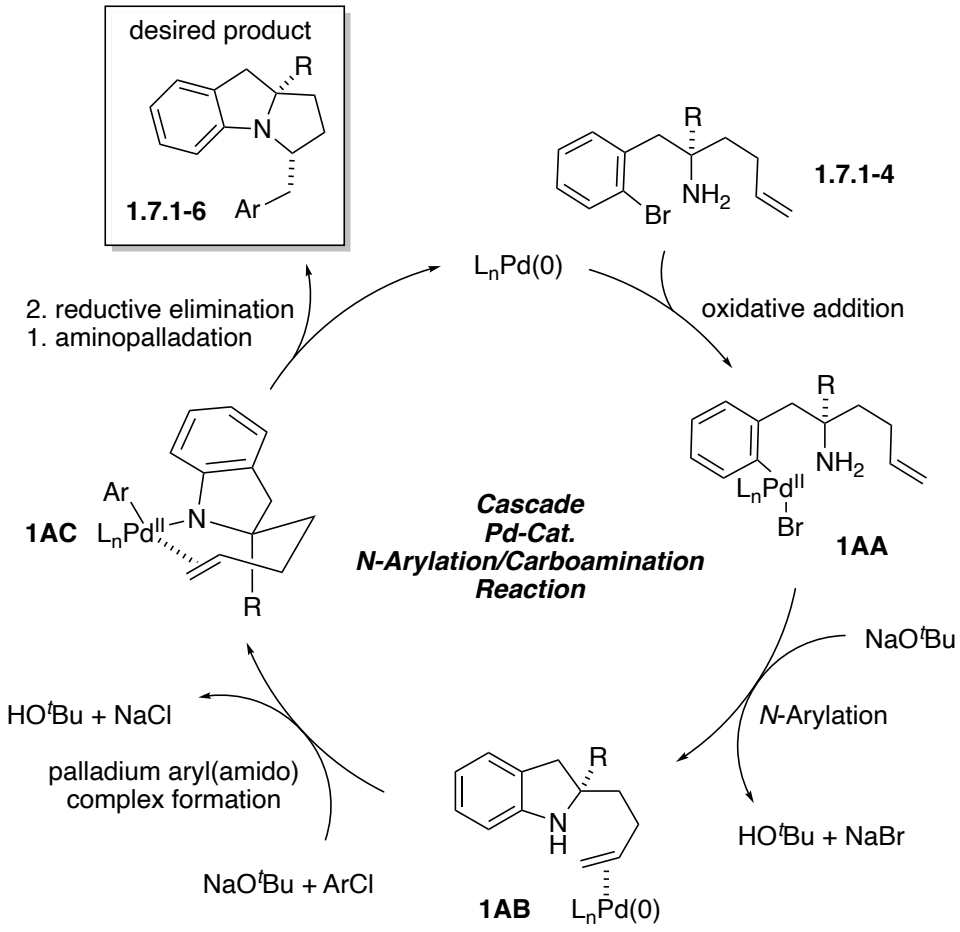


Figure 1–8 Select Ligands in Tandem Catalysis

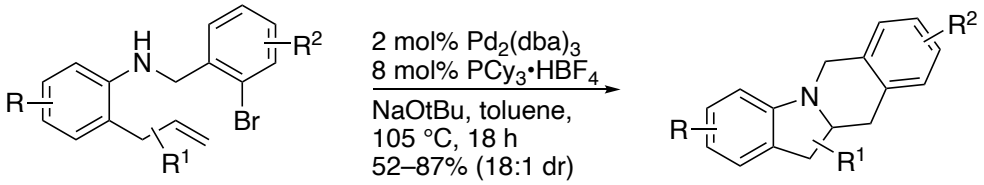
Generally, cascade palladium-catalyzed synthesis of polycyclic nitrogen heterocycles proceeds through the general steps of previously reported carboamination chemistry.[32,33] For example, the mechanism of eq 1–7.5 is believed to begin with oxidative addition of the palladium catalyst into the tethered aryl halide of **1.7.1-4** to form an organometal complex (**1AA**). There is then a base-mediated *N*-arylation reaction to create complex **1AB** followed by a base-mediated amido complex formation of complex **1AC**. Subsequent aminopalladation and reductive elimination leads to the desired product (**1.7.1-6**) and recycles the palladium catalyst to continue the cycle (Scheme 1–21). This system was strategically designed to control the rates of steps in the mechanism based on both the electronic ease of metal insertion into an aryl bromide and intramolecular activity followed by aryl chloride oxidative addition for favored products.



Scheme 1–21 Cascade Intramolecular N-Arylation/Intermolecular Carboamination Strategy

The Wolfe group has also reported the synthesis of polycyclic nitrogen heterocycles through fully intramolecular alkene carboaminations of substrates in which the amine is tethered to both the alkene and the aryl bromide with a pre-*N*-arylated substrate. For example, an infrequent class of fused bicyclic heterocycles, tetrahydroindoloisoquinolines and their substituted derivates **1.7.1-11**, have been synthesized in good yield through Pd-catalyzed alkene carboamination reactions of substrates **1.7.1-10**, which were prepared through reductive amination reactions between 2-allylanilines and 2-bromobenzaldehyde derivatives (Equation 1–10).[27] At the time of publication, there had only been one ring-forming method for the synthesis of tetrahydroindoloisoquinolines. This new method afford polycyclic nitrogen heterocycle

derivatives **1.7.1-11** and allows for facile installation of diverse functionality at C6, C11, C11a, or C12 through substrate modifications. However, the use of a two-step substrate synthesis, which sometimes afforded modest yields of starting materials, is a limitation. Competing intramolecular Heck arylation was also problematic in some cases, and low stereoselectivity was obtained with some substrates. This transformation proceeds through a standard *syn*-addition alkene carboamination mechanism that is analogous to the one shown above in Scheme 1–21.



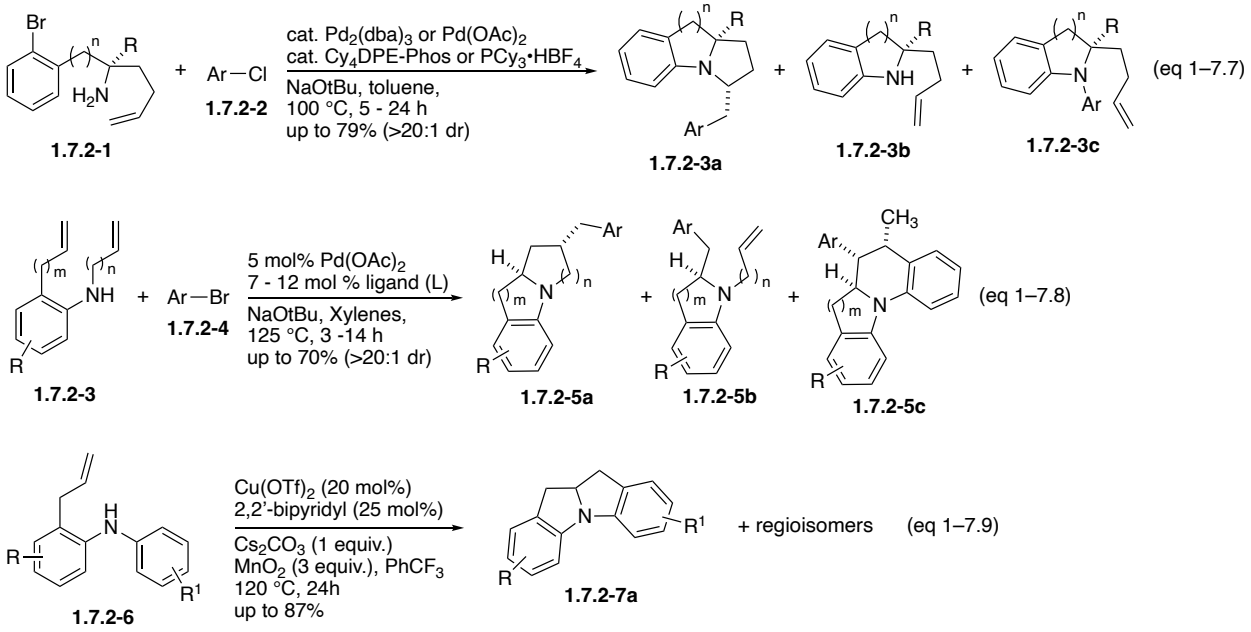
1.7.1-10 **1.7.1-11**

Equation 1–10 Synthesis of Tetrahydroindoloisoquinolines via Palladium Catalysis

1.7.2 Limitations & Challenges of Select Cascade/Tandem Polycycle Syntheses

As seen in previously reported cascade synthesis of polycyclic nitrogen heterocycles, there are a few limitations to current selected methods in Scheme 1–20 and Chemler's reaction in Scheme 1–5.[31-33] For example, equation 1–7.7 requires the arene to be fused to the amine nucleophile, limiting the scope of products. The starting material also required multi-step synthesis and cumbersome conditions in cases. This method sometimes had to run for two days, and it was reported that reactivity toward aryl chlorides was poor in some cases, including chlorothiophenes. There were also small amounts of unidentifiable side products formed with byproducts **1.7.2-3b** and **1.7.2-3c**. Similar limitations existed for eq 1–7.8 whereas the reaction time was improved for polycycle synthesis, but there were high temperature requirements, low yields in cases, undesired side products like **1.7.2-5b**, and substrate limitations from pre-functionalized allylic groups. Also, this method required different triphenylphosphine derivatives for individual product derivatives

(eq 1–7.8). Lastly, as described in **Section 1.5**, Chemler's copper-catalyzed reactions provide mixtures of regioisomers when the non-allylated ring is substituted (R^1) at the *m*-position, and the radical intermediate prior to C–C bond formation is not configurationally stable with respect to stereochemistry (eq 1–7.9).



Scheme 1–22 Recent Cascade Reaction Limitations for Synthesis of Polycyclic Nitrogen Heterocycles

To address some of these issues, Dr. Wolfe and I developed a new method of cascade palladium-catalyzed stereoselective synthesis of nitrogen polycycles. Our chemoselective method is discussed in the following chapter and provides analogous products to those obtained by Chemler in reactions of *N*-aryl-2-allylanilines (Scheme 1–22). Our method uses a low loading of Pd (2 mol % metal) whereas Chemler uses 20 mol% of Cu catalyst. Our method also does not require the use of oxidants such as MnO_2, uses lower reaction temperatures, achieves shorter reaction times, provides comparable or better yields (Table 1–1), and does not generate mixtures of product regioisomers.

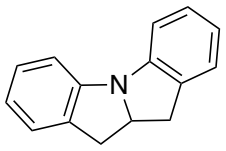
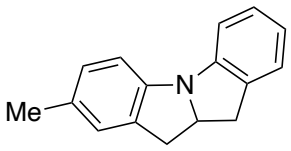
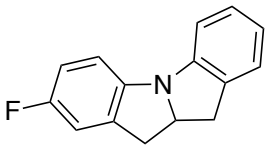
Product	Yield
	**Wolfe:** 92% **Chemler:** 87%
	**Wolfe:** 77% **Chemler:** 59%
	**Wolfe:** 66% **Chemler:** 64%

Table 1–1 Preview of Select Heterocycle Products' Comparison Between Chemler and Wolfe

1.8 Summary of Palladium Catalyzed N-Arylation and Carboamination Reactions

Metal-catalyzed *N*-arylation of amines and aryl halides or pseudo aryl halides has been developed, studied, and optimized in different systems to produce *N*-aryl amines in high yields and mild reaction conditions. These methods have been of interest in both academia and industry, because the *N*-aryl moiety is found in the core of many biologically relevant compounds and these processes contain interesting scientific explorations. Research groups of Dr. Stephen L. Buchwald and Dr. John F. Hartwig have collectively created Buchwald–Hartwig amination reactions and discovered a class of dialkylbiaryl phosphine ligands for promoting transformations. These methods employ a reliable and practical way of forming new C–N bonds from a simple cross-coupling reaction of amines and derivatives of aryl halides. The mechanism of these processes has been heavily studied and proceed through known organometallic chemistry.

Arylamines are ubiquitous in natural products, pharmaceuticals, materials, synthetic intermediates, academic research as ligands, and medicinal agents. The *N*-aryl moiety is diverse in applications and properties across chemical-related fields and are sometimes biologically active in heterocycles. *N*-arylation reactions with cyclic and acyclic sp^3 or sp^2 amines and aryl halides

has been demonstrated in high yields with dialkylbiaryl phosphine ligands. The structure of ligands are highly important for controlling the rates of mechanistic steps in the catalytic cycle, catalyst stability, ligand stability, and inhibition of undesired products. These reactions work best with butoxides as the base in solution.

Generally, factors that influence palladium catalyzed amination reactions include the type of electrophile arene and its substituents, the type of nitrogen-based nucleophile, the palladium precatalyst source, the electronics and sterics of the ligand, the choice base, the solvent, and temperature of the system. With these parameters come some limitations and challenges to *N*-arylation chemistry. Therefore, free amines alternatives or multistep catalyst systems are required for *N*-arylation reactions with reagents like ammonia. Additional limitations to *N*-arylation chemistry include β-H elimination side reactions, diarylation (over arylation) of the nucleophile, functional group tolerance from the base and/or temperature used, and other substrate structure limitations. Nonetheless, the *N*-arylation method remains a powerful tool and is exhibited in intermediate pathways of other transformations like carboamination reactions.

Palladium-catalyzed alkene carboamination reactions are powerful tools in organic synthesis. They permit the construction of a variety of *N*-heterocycles, forming two or more bonds in one step. These types of reactions couple an *N*-substituted amine or aniline tethered to an alkene with an aryl or alkenyl halides or pseudohalide in the presence of a palladium catalyst and exogenous base. Specific phosphine ligands are required for these transformations and facilitate key steps of the mechanism.

The research described in chapter 2 of this dissertation addresses a specific limitation of current alkene carboamination chemistry, which is the inability to conduct cascade *N*-arylation/carboamionation reactions with a single ligand for sp^2 aminoalkenes. In addition, the

work described in chapter 3 provides entry into a specific class of heterocycles—substituted 10a,11-dihydro-10*H*-indolo[1,2-*a*]indoles—that have not been previously prepared using alkene carboamination chemistry.

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Chapter 2 Development of Cascade Palladium-Catalyzed N-Arylation/Alkene Carboamination Reactions between Allylanilines and 1,2-Dihaloarenes for the Synthesis of Polycyclic Nitrogen Heterocycles

2.1 Importance & Significance of Polycyclic Nitrogen Heterocycles

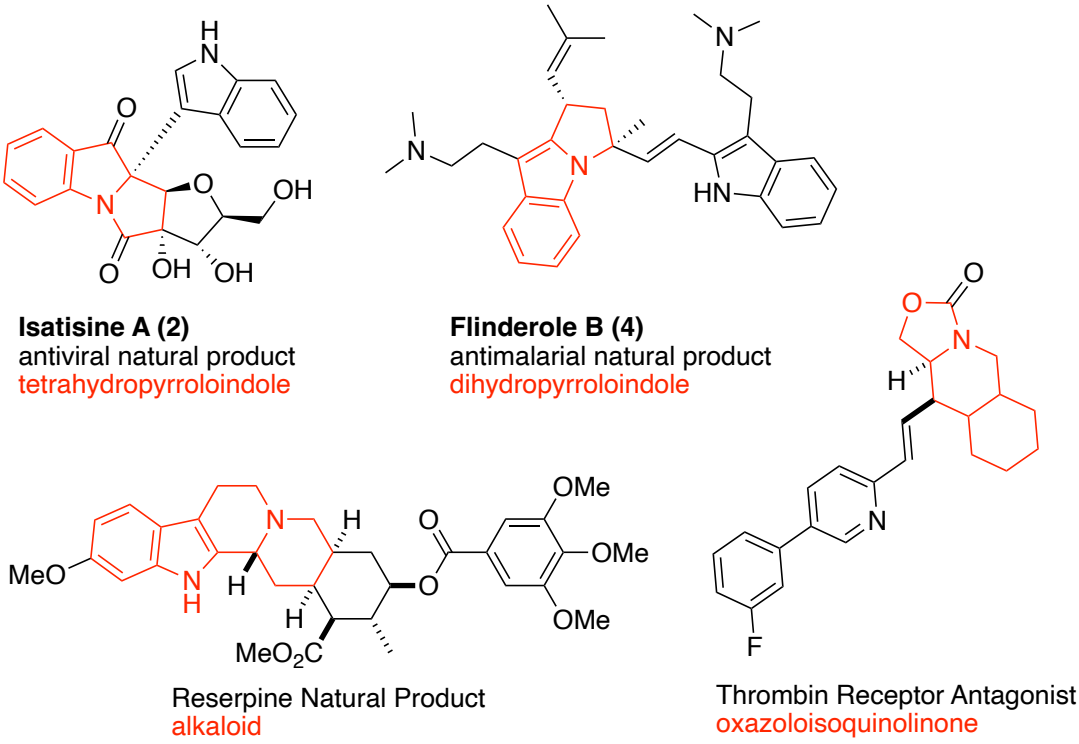


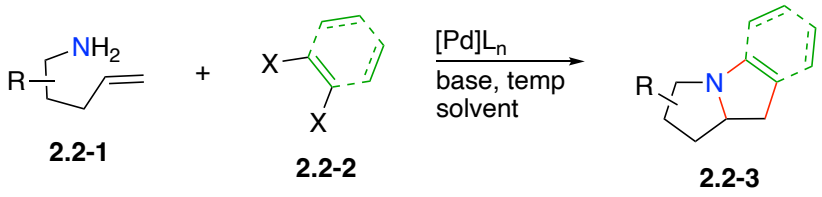
Figure 2–1 Biologically Relevant Polycyclic Nitrogen Heterocycles

Polycyclic nitrogen heterocycles scaffolds are abundant in biologically active molecules and natural products (Figure 3–1).[1] For example, Isatisine A (2) is isolated from the leaves of Isatis Indigotica Fort (Cruciferae) roots & leaves, has been used for traditional Chinese medicine for treatment of viral diseases for hundreds of years, and contains a polycyclic nitrogen heterocycle core. Many of these cores contain at least one 5-membered heterocycle, and often an arene-fused ring. Some examples of these products include tetrahydropyrroloindole,

hexahydropyrroloquinoline, and indoline cores. New methods for the synthesis of fused *N*-heterocycles are of particular interest in academia and industry to access new classes of compounds and study their properties and bioactivity.[1] An efficient sequential palladium-catalyzed *N*-arylation/carboamination reaction can selectively synthesize polycycles in one step with multiple new bonds, rings, and stereocenters, while addressing challenges and limitations to previous methods.

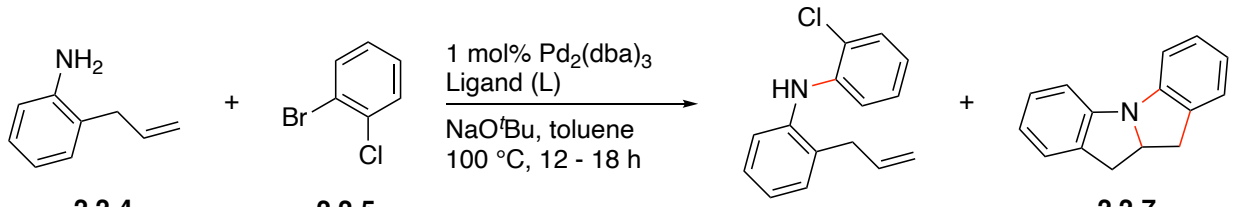
2.2 Optimization of Cascade Palladium-Catalyzed Stereoselective Synthesis of Polycyclic Nitrogen Heterocycles via Reactions of Allylanilines

To develop a method to synthesize polycyclic nitrogen heterocycles through cascade alkene *N*-arylation/carboamination reactions, we planned to cross-couple a functionalized sp^3 or sp^2 amine bearing a pendant alkene (**2.2-1**) to a dihaloarene, dipseudohaloarene, or dihaloalkene (**2.2-2**) to afford polycycles (**2.2-3**) (Equation 2–1).



Equation 2–1 General Pd-Cat. Cascade Synthesis of Polycyclic Nitrogen Heterocycle

We chose 2-allylanilines as the starting material for initial studies as some are commercially available, and others can be made in a few steps. In addition, the absence of beta hydrogens makes the *N*-arylation chemistry more succinct. Due to the important role phosphine ligands play in both *N*-arylation and alkene carboamionation reactions, we screened ligands for the coupling of 2-allylaniline (**2.2-4**) with 1-bromo-2-chlorobenzene (**2.2-5**) in the presence of 1 mol% $Pd_2(dba)_3$, sodium butoxide, and toluene at 100 °C overnight (Table 3–1). We chose this specific electrophile to control the rates of oxidative addition such that the *N*-arylation reaction



2.2-4 **2.2-5** **2.2-6** **2.2-7**

Entry[a]	Ligand (L)	Product Ratio[b] **4**:**6**:**7**	Entry[a]	Ligand (L)	Product Ratio[b] **4**:**6**:**7**
1	dppb	0:0:0	14	XantPhos	2:98:0
2	(pMeOPh)$_3$P	0:0:0	15	PhDavePhos	2:98:0
3	PPh_3	0:0:0	16	tBuDavePhos	2:96:2
4	P(o-tol)$_3$	0:0:0	17	DPE-Phos	2:98:0
5	PCy_3•HBF_4	0:0:0	18	Cy_4DPE-Phos	3:97:0
6	XPhos	0:0:0	19	tBuXPhos	2:96:2
7	dppe	0:0:0	20	BINAP (rac.)	2:98:0
8	CyJohnPhos	2:98:0	21	JohnPhos	2:94:4
9	MePhos	2:98:0	22	BrettPhos	2:98:0
10	tBuMePhos	48:4:48	23	tBuBrettPhos	2:98:0
11	SPhos	2:98:0	24	DavePhos	0:0:100
12	EPhos	2:98:0	25	RuPhos	0:0:100
13	JackiePhos	2:98:0	26	CPhos	0:0:100

[a]Conditions: 2 - 4 mol % Ligand, 1 eq. substrate (0.25 mmol), 1.2 eq. electrophile (35 μL), 0.25 M solution (1 mL solvent), and 2.4 eq. of base. All reactions one-pot, no pre-stir, elongated 20mL vials. [b]Product ratios were determined by ^{1}H NMR analysis of crude reaction mixtures based on recovered starting material (brsm). If **2.2-4**, **6**, or **7** were not recovered, undetermined sideproducts were formed (0:0:0).

Table 2–1 Ligand Screen for Cascade Palladium-Catalyzed Synthesis of Polycyclic Nitrogen Heterocycles via Reactions of Allylanilines

could proceed to completion before the carboamination step started; this also should help to minimize potential side products. We assayed reactions via NMR, looking for both disappearance of starting material (**2.2-4**) and appearance of the desired dihydroindoloindole (**2.2-7**). We initially hypothesized that ligands such as PCy_3•HBF_4 or dialkylphosphinobiphenyl derivatives may provide good results for transforming 2-allylaniline to the desired 10a,11-dihydro-10*H*- indolo[1,2-*a*]indole (**2.2-7**), as these ligands previously showed utility in related

intramolecular palladium-catalyzed reactions (Scheme 1–20).[2] However, several simple ligands failed to produce the desired product (Entries 1–7). Instead, we observed isomerization of the olefin, Heck reaction products (2-methylindole), and other unidentifiable side products in crude NMR assays. The indole formation suggests that beta-hydride elimination is a problem with some of these ligands.[2] Since Buchwald-type biarylphosphine ligands have been successfully used in both *N*-arylation and carboamination chemistry,[2] we screened an array of them in our system. Although we did not observe desired product, we did observe the formation of *N*-arylation product (**2.2-6**) (Entries 8–23). Surprisingly, *t*BuMePhos underperformed (Entry 10) to produce arylation byproduct as compared to other Buchwald ligands tested, though it is sterically similar to *t*BuDavePhos (Entry 16). The notable difference between the two ligands is a heteroatom at the 2' position on *t*BuDavePhos. This observation proved to be key, as the ligands DavePhos, RuPhos, and CPhos led to complete consumption of starting material and construction of desired dihydroindoloindole (**2.2-7**) product (Entries 24–26). The architecture of these ligands is displayed in Figure 2–2, and all contain dicyclohexylphosphine groups and an electron-donating group at the 2' position. We hypothesize the latter feature keeps the catalyst functioning and stable enough for the second oxidative addition into the chloro-arene bond, in addition to increasing electron density for otherwise traditionally difficult oxidative addition into the aryl C–Cl bond.[3] The cycloalkyl groups on the phosphorus increase electron density, which

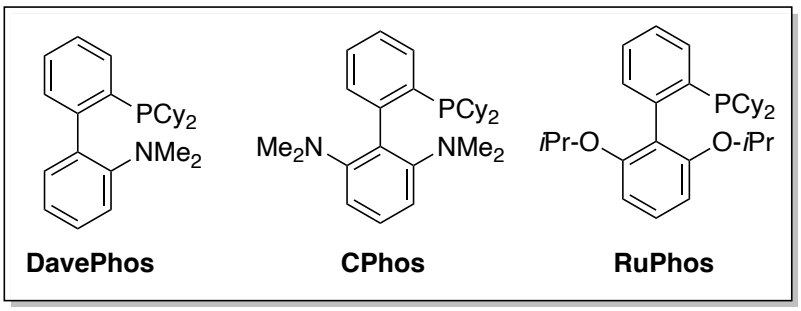
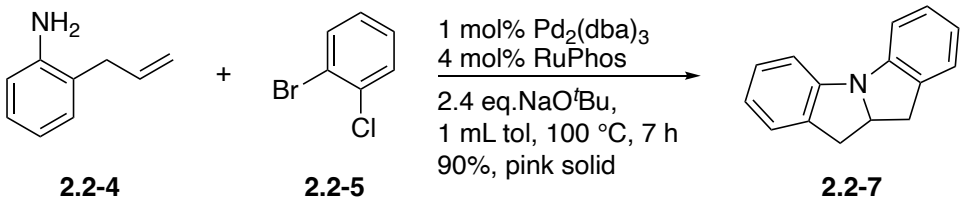


Figure 2–2 Successful Ligands for Tandem Synthesis of Polycyclic Nitrogen Heterocycles via Palladium Catalysis

improves rates of oxidative addition, and their size enhances rates of reductive elimination.[3] The dicyclohexyl groups, as opposed to *tert*-butyl, are best for a high turnover number for catalyst. Generally, bulky groups promote L_1Pd complex formation which increases the rates of all steps in the catalytic cycle. Substituents at the 2' position in the RuPhos, C-Phos, and DavePhos also prevent cyclometallation of the ligand, which increases catalyst stability.[3] Though SPhos (Entry 11) is structurally comparable to the three, it gave mainly *N*-arylation intermediate, rather than the desired tetracyclic product for reasons that are not clear. After screening several different ligands, we elected to use RuPhos in transformations of other substrates since that ligand provided cleaner crude NMR spectra as compared to C-Phos and DavePhos. RuPhos is also the least expensive per gram of the three, which is attractive to industrial efforts.

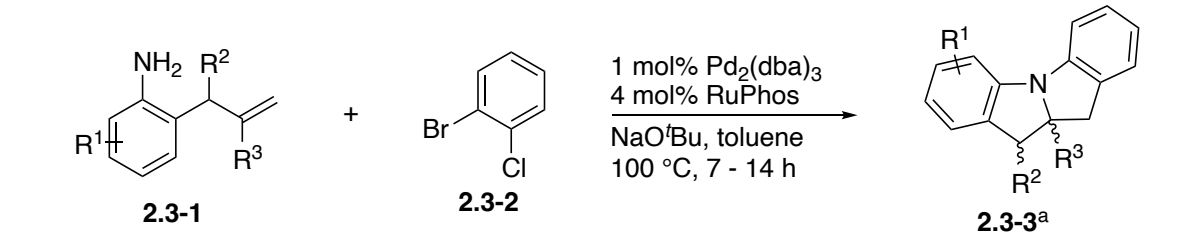


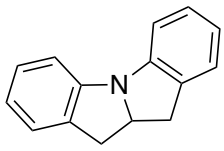
Equation 2–2 Optimal Cascade Palladium-Catalyzed Synthesis of Polycyclic Nitrogen Heterocycle

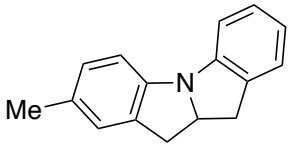
From these findings, we aimed to optimize the other reactions parameters and isolate the product via column chromatograph and/or recrystallization. We optimized the cascade palladium-catalyzed synthesis of polycyclic nitrogen heterocycles via reactions of 2-allylanilines at 0.25 mmolar using 1 mol% palladium *dba*, 4 mol% RuPhos, 2.4 equivalents of sodium butoxide, 0.25M toluene at 100 °C for 7 hours (Equation 2–2). The unsubstituted product was isolated at 90% yield as a pink solid after column chromatography using either a mixture of 1% EtOAc/Hexanes or 20% DCM/Hexanes as the eluant. Our next objective was to evaluate the scope of this transformation by changing the electronics of the nucleophile's benzene ring and the steric interactions around the olefin, separately.

2.3 Scope and Challenges of Reactions between Allylanilines and 1,2-Dihaloarenes for the Synthesis of Polycyclic Nitrogen Heterocycles

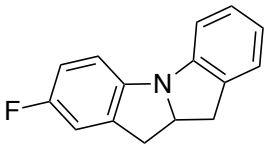
We varied the substituent *para* to the amine to gauge the influence of electronic properties on the reaction (Table 2–2). Products **2.3-3b**, **2.3-3c**, and **2.3-3d** were isolated in moderate to good yield with the trend indicating that heteroatoms on the ring reduce yield. Prior studies have shown that the rates of both *N*-arylation[4] and alkene aminopalladation[5] increase with increasing



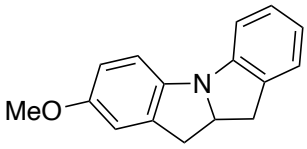

2.3-3a 92%



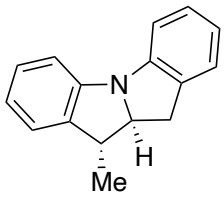
2.3-3b 77%



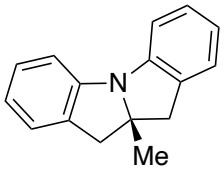
2.3-3c66%



2.3-3d 58%



2.3-3e 42%
> 95:5 dr



2.3-3f 44%

[a]Average yields from two or more repeated reactions. Reactions performed with 1 eq. substrate (0.25 mmol), 1.2 eq. electrophile, 0.25 M solution (1 mL solvent), and 2.4 eq. of base. All reactions one-pot, no pre-stir, elongated 20mL vials, and sealed tubes under nitrogen atmosphere.

Table 2–2 Scope of Stereoselective Pd-Catalyzed Cascade N-Arylation/Carboamination Reactions of Allylanilines to Synthesize Nitrogen Heterocycles

nucleophilicity of the amine. Thus, the lower yields with π-electron donors *para* to the nitrogen atom are likely due to increased rates of β-hydride elimination, which generates an indole side product. This is consistent with related transformations previously reported by the Chemler group.[6]

Based on our observed crude NMR spectra from reactions, unidentified byproducts are forming along with an indole side product. Additionally, isolation proved more challenging for substituted products. Next we evaluated stereoselectivity and sterics of the system by adding methylene groups near the reaction center (Table 2–2). Although we observed a significant reduction in yield of products **2.3-3e** and **2.3-3f**, we achieved excellent selectivity with diastereomer ratios at over 95% favoring one stereoisomer; the stereochemistry of this product was assigned using a combination of ^{1}H NMR COSY and nOe experiments—see experimental section **2.6.4** of dissertation. Essentially, we believe that the *N*-arylated intermediate complex **2A** goes through a chair-like transition state with the methyl group in the favorable equatorial position for aminopalladation to produce product **2.3-3e** (Figure 2–3).

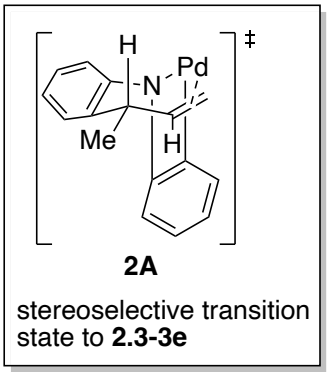
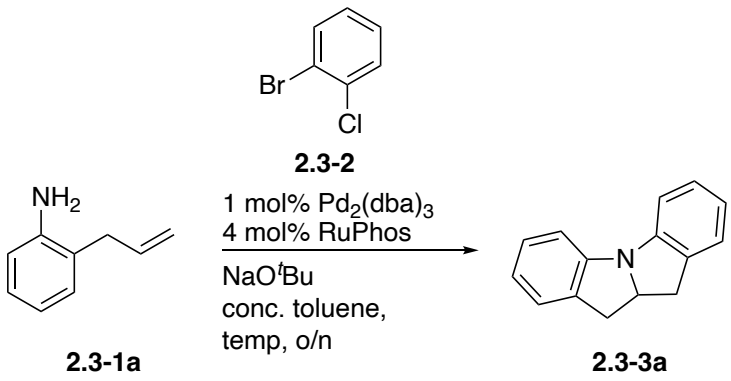


Figure 2–3 Stereoselective Transition State for Nitrogen Polycycle

In our attempt to improve product yields, we examined the influence of temperature and concentration on the system (Table 2–3). Generally, β–H elimination reactions and other undesired side products occur at higher temperatures,[5] so we hypothesized that reduction in temperature could improve yields, given that the starting material was being fully consumed and *N*-arylation reactions have been demonstrated to occur at temperatures as low as room temperature.[5] We theorized that reducing the system concentration would also improve product synthesis, since it would increase opportunity for the intramolecular carboamination reaction to occur without

competing intermolecular carboamination reactions. This hypothesis proved to be correct, as lowering the temperature and diluting the system improved crude yields (Entry 2); however, there was no *significant* increase in product yield observed via NMR based on the experimentation of these parameters. On the contrary, we noticed the product NMR yield was significantly different from the isolated yield, yet there was no starting material nor *N*-arylation peaks present in the crude NMR spectra; this suggested potentially that a side product may be forming with spectra that is not obvious.



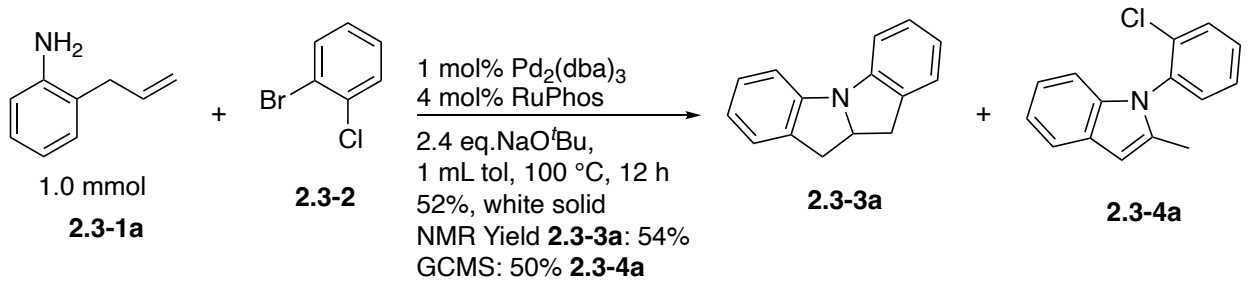
Entry[a]	Concentration	Temperature	NMR Yield
1	2 mL	100 °C	52%
2	2 mL	90 °C	59%
3	1 mL	90 °C	46%

[a]Phenanthrene as NMR internal standard. Reactions performed with 1 eq. substrate (0.25 mmol), 1.2 eq. electrophile (35 μL), and 2.4 eq. of base. All reactions one-pot, no pre-stir, elongated 20mL vials, and sealed tubes under nitrogen atmosphere. Starting material consumed for each.

Table 2–3 Concentration and Temperature Screen for Pd-Cat. Cascade Synthesis of Nitrogen Heterocycles

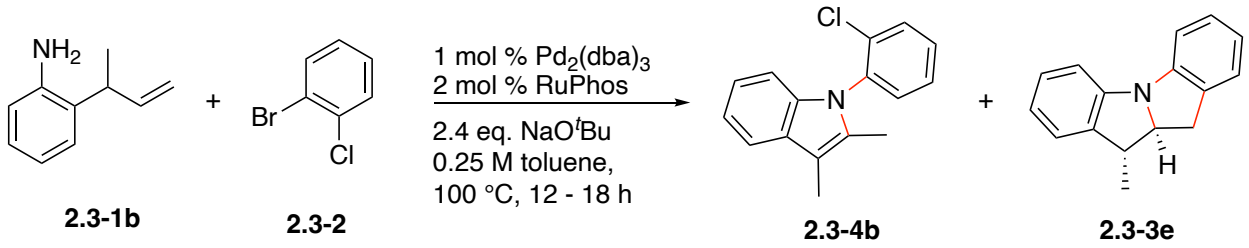
To rule out product loss during isolation that is related to working on a small scale, we increased reaction scale from 0.25 mmol to 1.0 mmol. The NMR yield was consistent to what we had observed on a smaller scale, but the isolated yield was almost halved. There were no immediately identifiable side-product peaks in the crude NMR, so we decided to assay the crude

reaction using GCMS. After analyzing all data on hand, we concluded that yield loss is due to the formation of byproduct **2.3-4a** (Equation 2–3). To our dismay, we observed a similar side product (**2.3-4b**) with the benzylic methyl aniline (**2.3-1b**) (Equation 2–4). Our working hypothesis is that the product of the initial *N*-arylation reaction undergoes a subsequent Wacker-type cyclization,[7] which proceeds via aminopalladation of **2C** followed by β-hydride elimination to provide **2.3-4c** and subsequent isomerization to **2.3-4a**. A second molecule of *o*-bromochlorobenzene likely serves as the oxidant for the Wacker cyclization (Scheme 2–1).

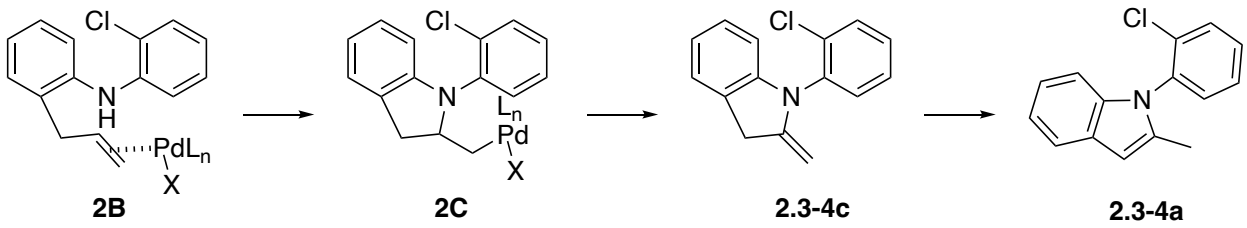


Equation 2–3 Scaled Cascade Reaction

These findings help us better understand the mechanism of this transformation and suggest that further optimization may lead to conditions where the Wacker cyclization can be suppressed (Scheme 2–1).



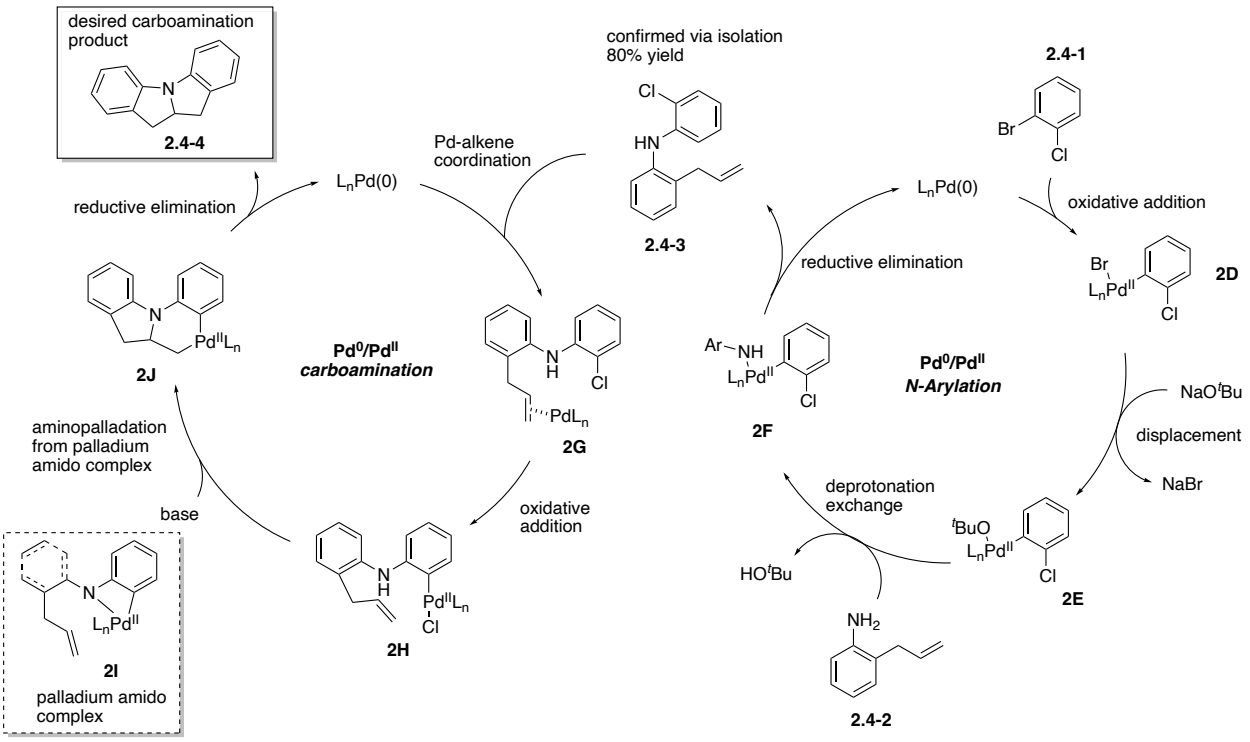
Equation 2–4 Challanges to Casacde Catalysis of Allylanilines



Scheme 2–1 Waker-Type Cyclization of Nitrogen Polycycles

2.4 Proposed Mechanism of Cascade Palladium-Catalyzed N-Arylation/Alkene Carboamination Reactions for Polycyclic Nitrogen Heterocycle Synthesis

Based on our findings and related literature precedent,[8-9] we propose the mechanism of the cascade reactions starts with an oxidative addition into the carbon-bromine bond of the dihaloarene (**2.4-1**) to form complex (**2D**). Then a displacement of the halide with a butoxide base occurs to produce complex **2E**. Next the amine inserts into the metal complex, displacing the butoxide base to form complex **2F**. A reductive elimination ensues, leading to the *N*-arylation product (**2.4-3**) bringing the oxidation state of the palladium back down to 0 from 2. We confirmed that the *N*-arylation product maintains the chlorine from isolating **2.4-3** from a reaction with a Buchwald ligand that did not lead to the formation of desired final product.



Scheme 2–2 Mechanism of Cascade Palladium-Catalyzed Stereoselective Synthesis of Polycyclic Nitrogen Heterocycles via Reactions of Allylanilines

After the *N*-arylation has proceeded to completion, the alkene carboamination mechanism potentially begins with palladium coordination to the olefin (**2G**) followed by catalyst oxidative addition into chloride to form complex **2H**. There is then a base-mediated amido complex formation (**2I**), trailed by a syn-aminopalladation on the tethered alkene to form complex **2J**. Finally, a reductive elimination leads to the desired product (**2.4-4**) and recycles the palladium catalyst to continue the cycle. We have successfully conducted cascade palladium-catalyzed stereoselective synthesis of polycyclic nitrogen heterocycles via reactions of allylanilines. Our new method improves previous challenges in cascade reactions such as multi-step synthesis to starting materials, daily reaction times, high temperature requirements, high catalyst loading, external oxidants, and generally harsh conditions. In addition, these reactions may proceed via an unusual migratory insertion of an alkene into a 4-membered palladium-amido complex.

2.5 Conclusions of Cascade Palladium-Catalyzed Reactions for the Synthesis of Polycyclic Nitrogen Heterocycles

Palladium-catalyzed tandem reactions on alkenes form multiple bonds, stereocenters, and rings to synthesize *N*-heterocycles. The Pd-catalyzed coupling of 2-allylanilines and 1-Bromo-2-chlorobenzene provides rapid access to substituted 10a,11-dihydro-10*H*-indolo[1,2-*a*]indole derivatives. The RuPhos ligand provides optimal results, although yields in some transformations are modest due to the formation of *N*-(2-chlorophenyl)-2-methyl indoles via competing Wacker cyclization after *N*-arylation. However, this route provides access to compounds that are difficult to generate with other methods, and the reactions appear to involve alkene aminopalladation from a strained 4-membered palladium-amido complex.

2.6 Experimental Section for the Synthesis of Polycyclic Nitrogen Heterocycles

2.6.1 General Procedures

General: All reactions were carried out under a nitrogen atmosphere inside of immediately oven- or flame-dried glassware. All reagents, palladium precatalysts, ligands, and aryl halides were purchased from commercial sources and were used without purification unless otherwise noted. Toluene and THF were purified using a GlassContour solvent purification system. Xylenes were dried from distillation with calcium hydride. DMF was anhydrous, 99.8%, packaged under argon or nitrogen in resealable ChemSeal™ Sure/Seal™ bottle and taken under nitrogen. Structural and stereochemical assignments were made based on 2-D COSY and NOESY experiments. Ratios of diastereomers were determined by ^{1}H NMR. All yields refer to isolated yields of compounds that are estimated to be ≥95% pure as determined by ^{1}H NMR unless otherwise noted (i.e. average yield of two or more experiments). Sensitive starting materials like triflates were stored in a freezer

under nitrogen. Bulk quantities of cesium carbonate, sodium *tert*-butoxide, and other moisture-sensitive compounds like bases were stored in nitrogen-filled glove box, and small amounts were removed and used.

2.6.1.1 General Procedure for Palladium Catalysis Reactions

A flame-dried modified 10 mL vial (cylinder shaped) equipped with a 10 μm magnetic stir bar was cooled under a stream of nitrogen and charged with the appropriate base (0.6 mmol, 2.4 equiv), palladium pre-catalyst (0.0025 mmol, 0.0025 equiv, 1 mol %), the appropriate ligand (0.001 mmol, 0.01 equiv, 4 mol %). The vial was purged with nitrogen and charged with toluene (0.25 M, 1 mL) and the appropriate aniline derivative (0.25 mmol, 1 equiv) and dihaloarene (0.3 mmol, 1.2 equiv). The vial was capped and heated to the appropriate temperature with stirring overnight. The mixture was then cooled to rt, charged with phenanthrene (1 equiv; NMR internal standard), diluted with diethyl ether (2 mL), and quenched with saturated ammonium chloride (2 mL). The aqueous layer was extracted with diethyl ether (3 x 2 mL), filtered through celite and sand, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified via flash chromatography on silica gel to afford the product. Product shows blue with PMA on TLC.

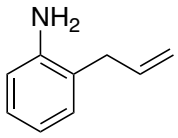
2.6.1.2 General Procedure for Aniline Substrates

2-allylaniline derivatives were prepared according to previously published procedures and sometimes slightly modified based on reactivity. Allyl chloride (or crotyl bromide for **S6**) (2.65 mL, 32.5 mmol, 1 equiv.) was added dropwise to a flame-dried 250 mL round bottom flask containing a solution of aniline derivatives (4.00 g, 32.5 mmol, 1 equiv.) and potassium carbonate (10.75 g, 78 mmol, 2.4 equiv.) in DMF (74 mL, 0.44 M) under nitrogen that was pre-stirred for 5 minutes prior to addition. The solution was heated to 80 °C and was stirred at this temperature overnight under nitrogen. The reaction was then cooled to room temperature, filtered, and diluted

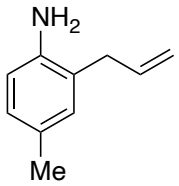
with EtOAc (150 mL). The organic layer was washed with water (4×50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% EtOAc/Hexanes) to afford the respective *N*-aniline derivative.

A flame-dried glass pressure tube equipped with a magnetic stir bar and a rubber septum was cooled under a stream of nitrogen and charged with a solution of corresponding *N*-allyl aniline derivatives (0.700 g, 4.63 mmol) in xylenes (5 mL). The solution was cooled to 0 °C and BF_3•OEt_2 (0.69 mL, 5.56 mmol, 1.2 equiv.) was added slowly. The reaction mixture was warmed to rt and stirred for 15 min, then the tube was sealed with a Teflon screwcap stopper and placed in a 180 °C oil bath for 3-5 h. The mixture was then cooled to rt, the stopper was removed, and a solution of 2 M NaOH (5 mL) was added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with diethy ether (3 x 10 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography 5-10% EtOAc/Hexanes.

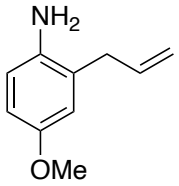
2.6.2 Preparation and Characterization of Substrates



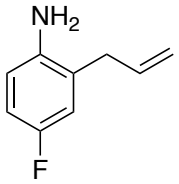
2-allylaniline S1 (2.3-1) General Procedure found in section **3.8.1.2**. The procedure afforded 2.04 g (81%) of the title compound from 18.727 mmol as a yellow oil. Spectroscopic properties are identical to those previously reported.[1a]



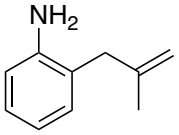
2-allyl-4-methylaniline S2 General Procedure found in section **3.8.1.2**. The procedure afforded 0.4765 g (68%) of the title compound from 5.56 mmol as a yellow oil. Spectroscopic properties are identical to those previously reported.[1a]



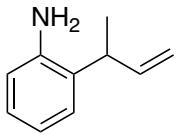
2-allyl-4-methoxyaniline S3 General Procedure found in section **3.8.1.2**. The procedure afforded 0.5313 g (75%) of the title compound from 4.29 mmol as an orange oil. Spectroscopic properties are identical to those previously reported.[1a,2a]



2-allyl-4-fluoroaniline S4 General Procedure found in section **3.8.1.2**. The procedure afforded 0.4868 g (70%) of the title compound from 4.63 mmol as a yellow oil. Spectroscopic properties are identical to those previously reported.[1a]

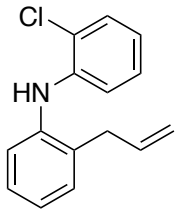


2-(2-methylallyl)aniline S5 General Procedure found in section **3.8.1.2**. The procedure afforded 0.208 g (45%) of the title compound from 5.23 mmol as an orange oil. Spectroscopic properties are identical to those previously reported.[3a]

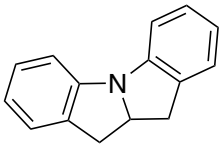


2-(but-3-en-2-yl)aniline S6 (2.3-1b) General Procedure found in section **3.8.1.2**. The procedure afforded 0.5624 g (73%) of the title compound from 5.23 mmol as a yellow oil. Spectroscopic properties are identical to those previously reported.[4a]

*General product procedure found in section **3.8.1.1**.*

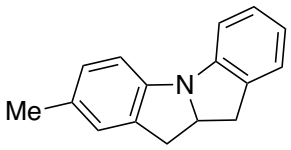


2-allyl-*N*-(2-chlorophenyl)aniline (**2.2-6**) Performed in flame dried schleck tube from 2-allylaniline (0.75 mmol), 1.2 equiv. bromochlorobeneze, 1 mol% $Pd_2(dba)_3$, 4 mol% BrettPhos, 1.4 equiv. NaO*t*Bu, 0.25 M toluene, 60 °C, 16 h to 80% yield as clear oil. Column 1% EtOAc/Hexanes. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.31 (td, *J* = 7.3, 6.7, 1.4 Hz, 2H), 7.25 – 7.16 (m, 3H), 7.11 – 6.97 (m, 3H), 6.74 (td, *J* = 7.6, 1.7 Hz, 1H), 6.06 (s, 1H), 5.96 (ddt, *J* = 16.5, 10.0, 6.1 Hz, 1H), 5.18 – 5.05 (m, 2H), 3.38 (dt, *J* = 6.2, 1.7 Hz, 2H). HRMS (ESI+ TOF) m/z: [M + H+]+ calcd for $C_{15}H_{14}ClN$ 243.0815; found 244.0886.

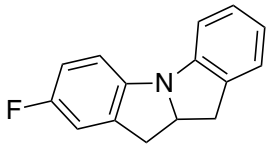


10a,11-dihydro-10*H*-indolo[1,2-*a*]indole (**2.3-3a**) 90% yield as pink solid. Column 20% DCM/Hexanes. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.20 – 7.14 (m, 5H), 6.91 (ddd, *J* = 8.1, 5.2, 3.1 Hz, 2H), 4.93 – 4.82 (m, 1H), 3.35 (dd, *J* = 15.9, 9.4 Hz, 2H), 3.08 (dd, *J* = 15.9, 7.8 Hz, 2H).

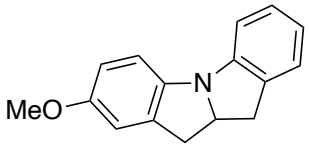
^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.82, 132.29, 127.56, 125.06, 121.66, 112.99, 65.23, 36.66. HRMS (ESI+ TOF) m/z: [M + H+]+ calcd for $C_{15}H_{13}N$ 207.1048; found 208.1118. Melting Point 130.1 °C



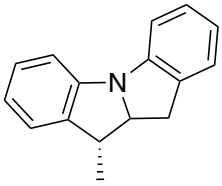
2-methyl-10a,11-dihydro-10*H*-indolo[1,2-*a*]indole (2.3-3b) 77% yield as orange-yellow solid. Column 20% DCM/Hexanes or 1% EtOAc. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.23 – 7.10 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.89 (td, *J* = 7.2, 1.5 Hz, 1H), 4.85 (tt, *J* = 9.4, 7.5 Hz, 1H), 3.31 (ddd, *J* = 33.0, 15.9, 9.4 Hz, 2H), 3.11 – 2.99 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 149.32, 146.71, 132.53, 131.99, 131.43, 127.89, 127.52, 125.76, 125.00, 121.41, 113.27, 112.73, 65.46, 36.85, 36.39, 20.91. HRMS (ESI+ TOF) m/z: [M + H+]+ calcd for $C_{16}H_{15}N$ 221.1204; found 222.1270. Melting Point 75.6 °C



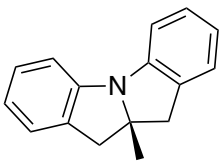
2-fluoro-10a,11-dihydro-10*H*-indolo[1,2-*a*]indole (2.3-3c) 66% yield as a gold solid. Column 20% DCM/Hexanes. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.16 (dt, *J* = 7.2, 1.3 Hz, 2H), 7.12 – 7.05 (m, 2H), 6.95 – 6.82 (m, 3H), 4.94 – 4.83 (m, 1H), 3.32 (ddd, *J* = 32.1, 16.1, 9.4 Hz, 2H), 3.07 (ddd, *J* = 16.1, 12.0, 7.5 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.80, 157.90, 149.09, 145.21 (d, *J* = 1.9 Hz), 134.25, 131.80, 127.60, 125.15, 121.75, 113.93, 113.87, 113.74, 113.56, 112.61, 112.38, 112.19, 65.88, 36.97 (d, *J* = 2.0 Hz), 36.27. HRMS (ESI+ TOF) m/z: [M + H+]+ calcd for $C_{15}H_{12}FN$ 225.0954; found 226.1038. Melting Point 107.05 °C



2-methoxy-10a,11-dihydro-10*H*-indolo[1,2-*a*]indole (2.3-3d) 58% yield as yellow-orange solid. Column 1% EtOAc/Hexanes. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.17 – 7.13 (m, 2H), 7.15 – 7.06 (m, 1H), 6.88 (td, *J* = 7.3, 1.2 Hz, 1H), 6.78 – 6.71 (m, 2H), 4.86 (qd, *J* = 9.0, 6.2 Hz, 1H), 3.77 (s, 3H), 3.36 (dd, *J* = 16.0, 9.5 Hz, 1H), 3.25 (dd, *J* = 15.9, 9.1 Hz, 1H), 3.07 (td, *J* = 16.6, 16.0, 7.3 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 155.78, 149.77, 143.00, 134.11, 131.61, 127.53, 125.05, 121.30, 114.59, 112.30 (d, *J* = 5.4 Hz), 111.47, 65.86, 55.79, 37.40, 35.99. HRMS (ESI+ TOF) m/z: [M + H+]+ calcd for $C_{16}H_{15}NO$ 237.1154; found 238.1198. Melting Point 118.6 °C



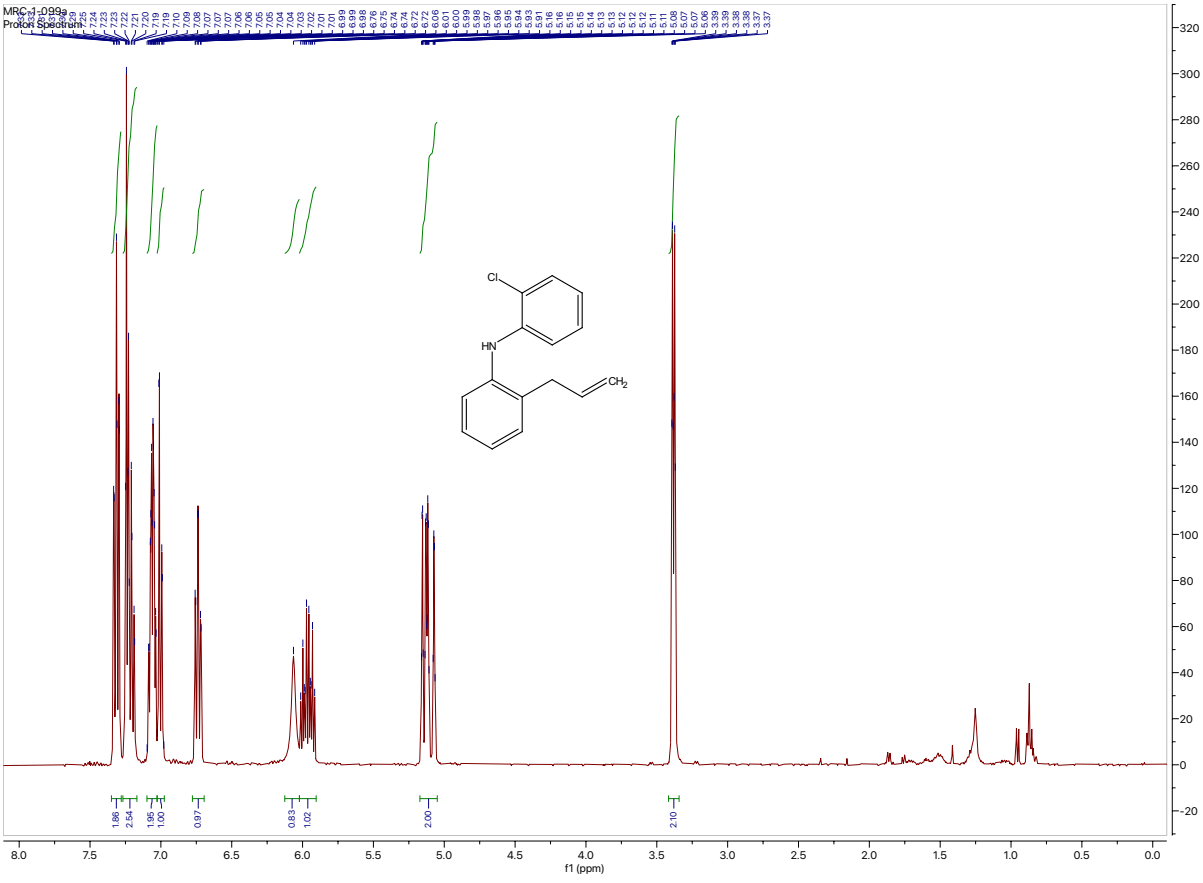
(10*R*)-10-methyl-10a,11-dihydro-10*H*-indolo[1,2-*a*]indole (2.3-3e) 42% as a pink oil. dr > 95:5, stereochemistry R* (cis). Column 1% EtOAc/Hexanes. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.24 – 7.03 (m, 6H), 7.01 – 6.92 (m, 1H), 6.88 (t, *J* = 7.3 Hz, 1H), 4.37 (td, *J* = 9.0, 6.2 Hz, 1H), 3.35 (td, *J* = 15.1, 14.1, 8.5 Hz, 2H), 3.08 (dd, *J* = 16.0, 6.2 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.59, 148.47, 137.94, 131.71, 127.58 (d, *J* = 9.5 Hz), 125.20, 123.59, 122.26, 121.12, 114.14, 111.73, 73.78, 43.90, 34.68, 18.08. HRMS (ESI+ TOF) m/z: [M + H+]+ calcd for $C_{16}H_{15}N$ 221.1204; found 222.1274.

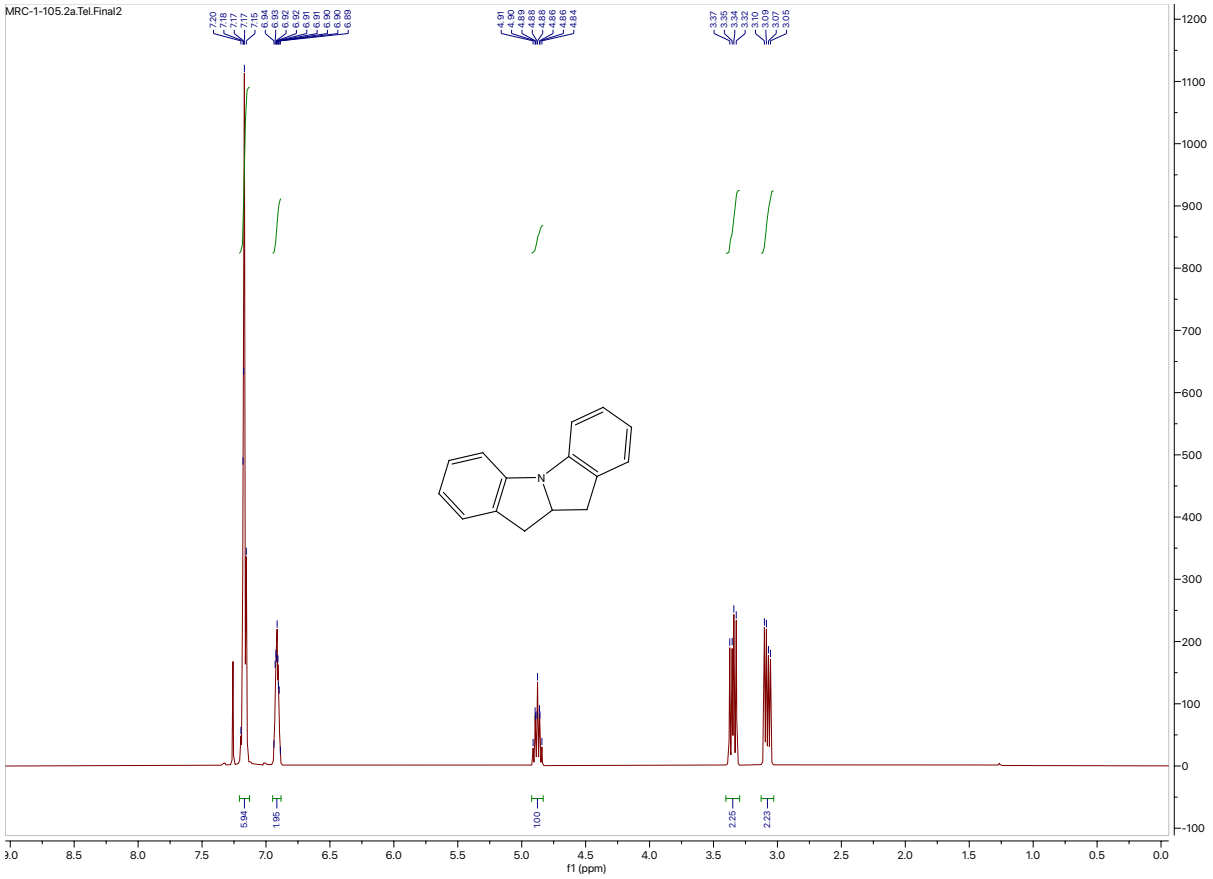


10a-methyl-10a,11-dihydro-10*H*-indolo[1,2-*a*]indole (2.3-3f) 44% as a yellow oil. Column 20% DCM/Hexanes. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.22 – 7.09 (m, 5H), 7.00 – 6.89 (m, 2H), 3.27 (d, *J* = 15.9 Hz, 2H), 3.03 (d, *J* = 15.8 Hz, 2H), 1.44 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.18, 131.50, 125.23, 113.08, 43.64, 28.86. HRMS (ESI+ TOF) m/z: [M + H+]+ calcd for $C_{16}H_{15}N$ 221.1204; found 222.1275.

(1a) *J. Am. Chem. Soc.* **2006**, 128, *10*, 3130–3131
(2a) *J. Am. Chem. Soc.* **2010**, 132, *42*, 14757–14759
(3a) *Adv. Synth. Catal*. **2015**, 357, *10*, 2339–2344
(4a) *J. Org. Chem.* **2013**, 78, *12*, 6245–6252

2.6.3 Unpublished Spectra

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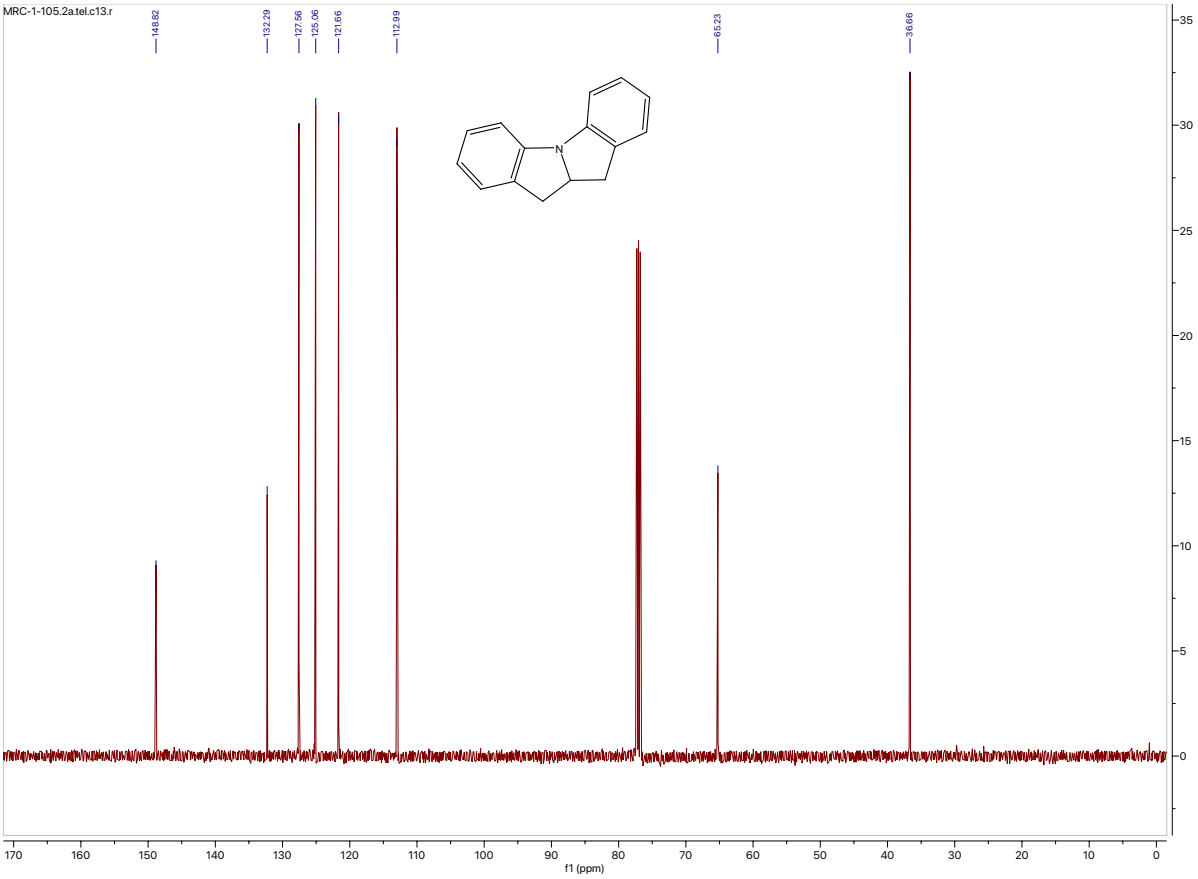
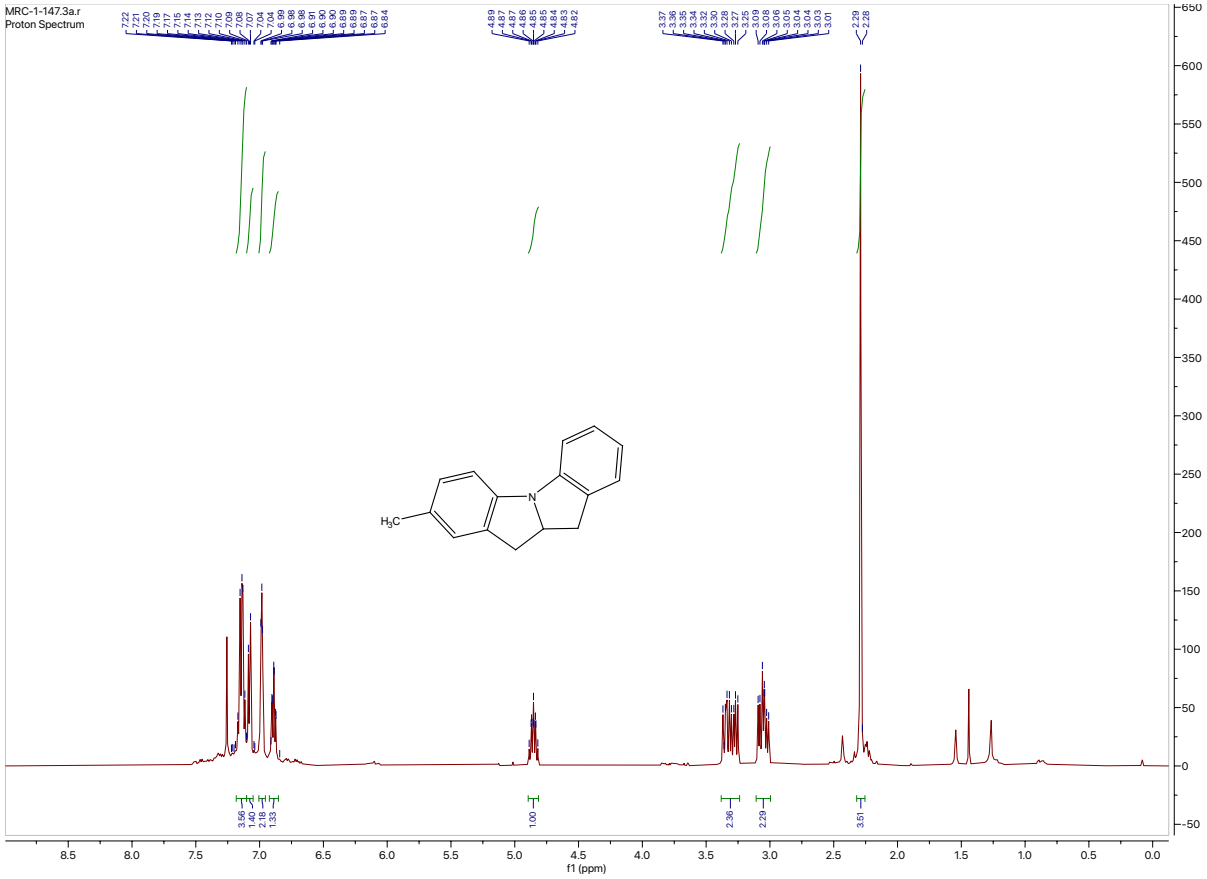
7.20
7.18
7.17
7.17
7.15
6.94
6.93
6.92
6.92
6.91
6.91
6.90
6.90
6.89
4.91
4.90
4.89
4.88
4.88
4.86
4.86
4.84
3.37
3.35
3.34
3.32
3.10
3.09
3.07
3.05
5.94
1.95
1.00
2.25
2.23
N
f1 (ppm)


MRC-1-105.2a.tel.c13.r
148.82
132.29
127.56
125.06
121.66
112.99
65.23
36.66
N
f1 (ppm)


MRC-1-147.3a.r
Proton Spectrum
7.22
7.21
7.20
7.19
7.17
7.15
7.14
7.13
7.12
7.10
7.09
7.08
7.07
7.04
7.04
6.99
6.98
6.96
6.91
6.90
6.89
6.89
6.87
6.87
6.84
4.89
4.87
4.87
4.86
4.85
4.85
4.84
4.83
4.82
3.37
3.36
3.35
3.34
3.32
3.30
3.28
3.27
3.25
3.09
3.08
3.06
3.05
3.04
3.04
3.03
3.01
2.29
2.28
N
H3C
3.56
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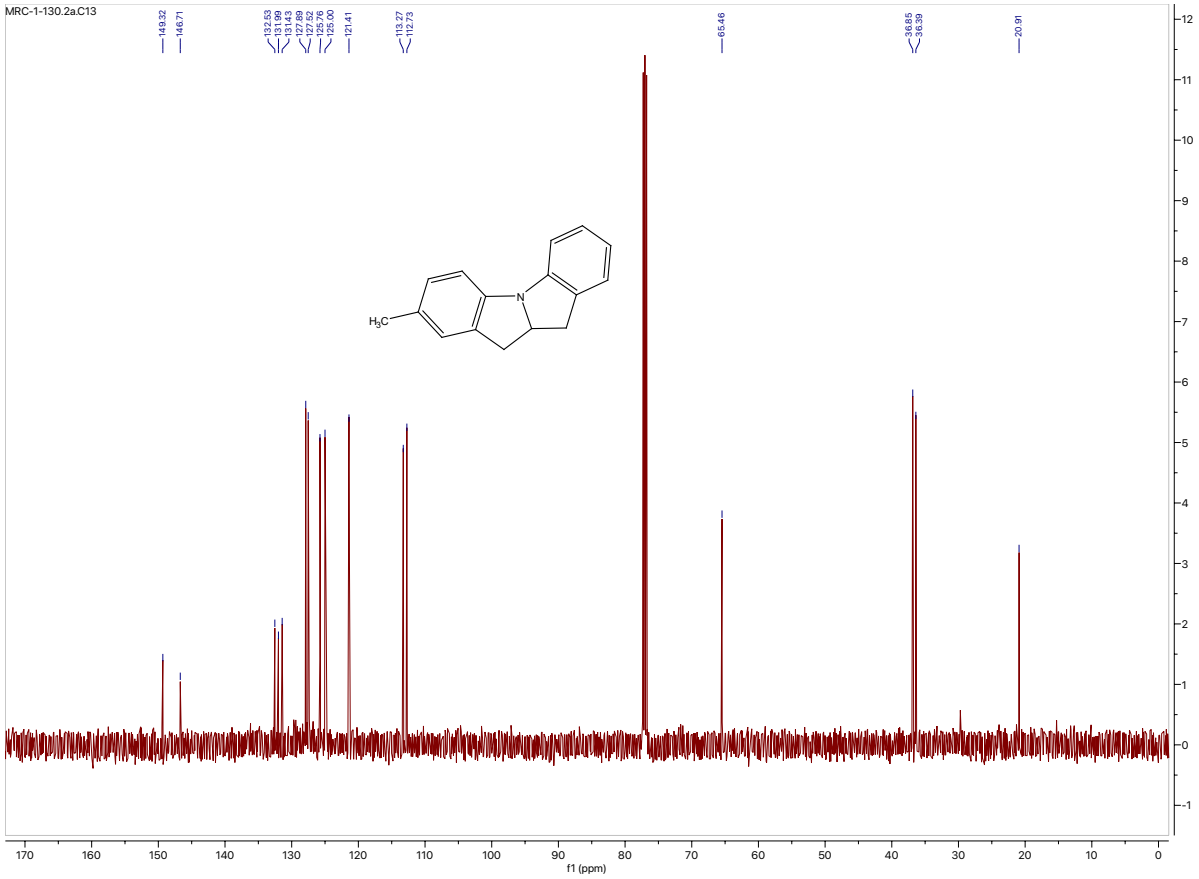
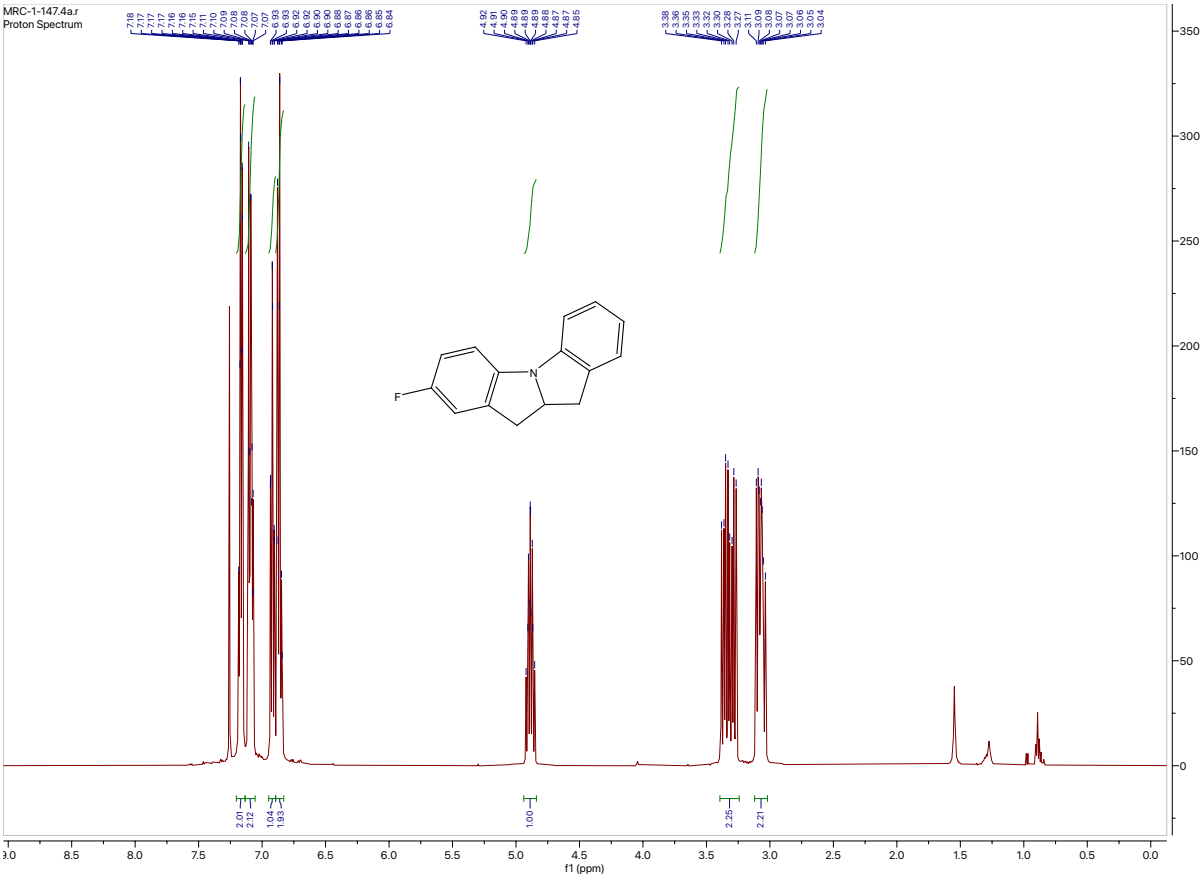
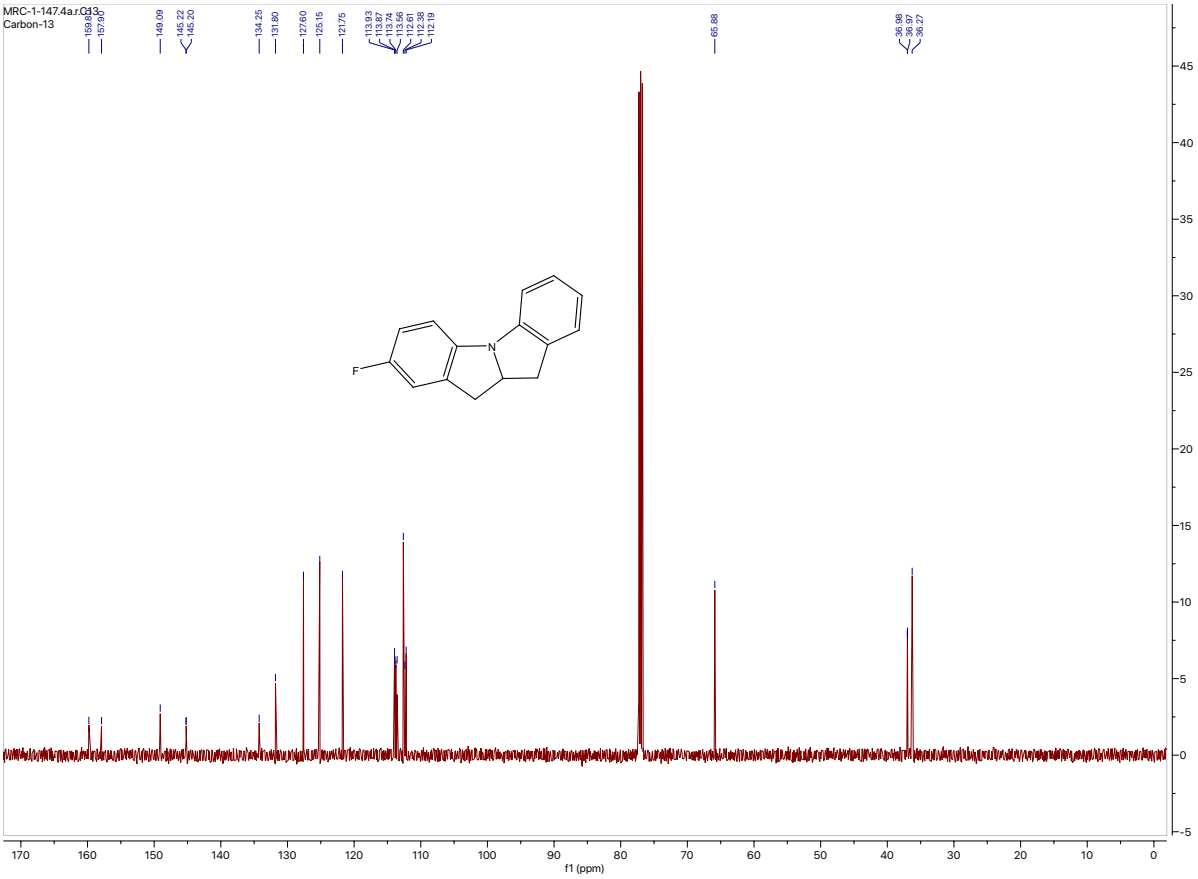
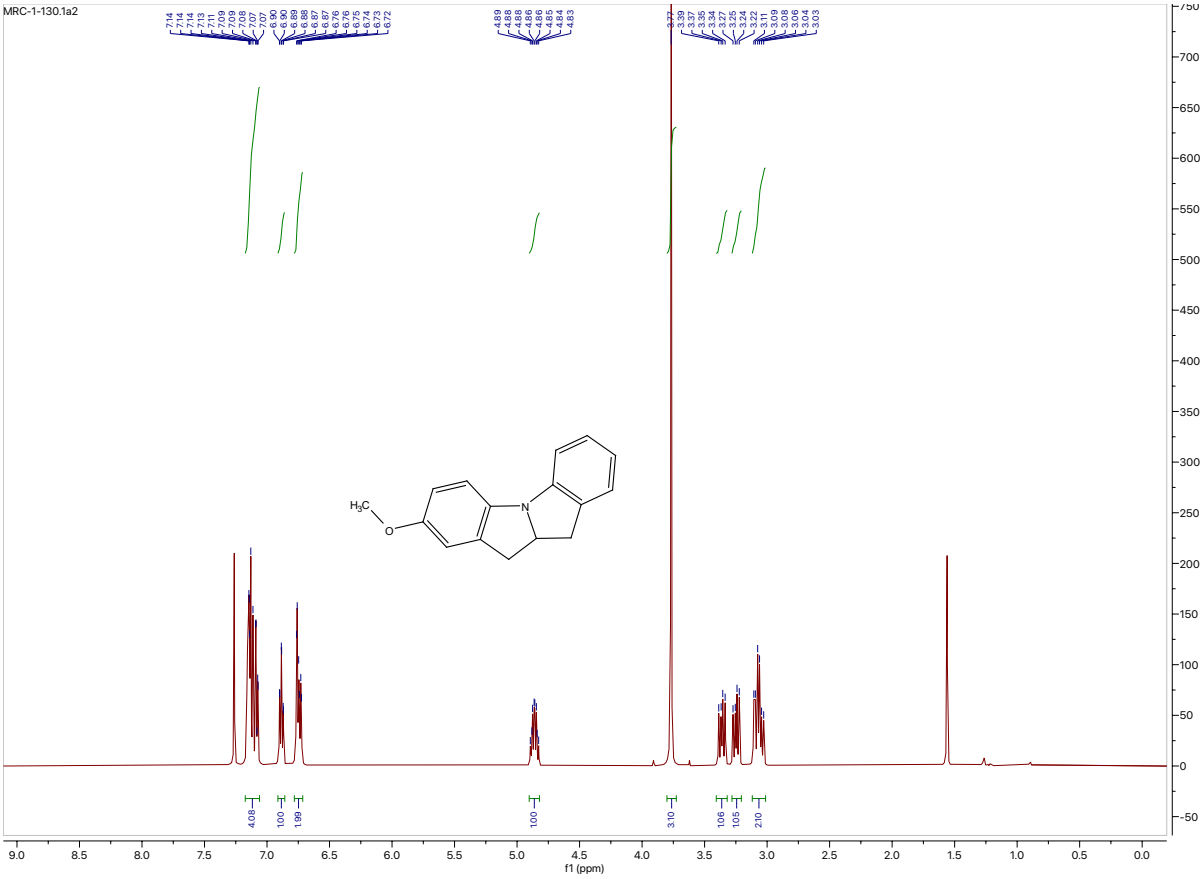
1.00
2.36
2.29
3.51
f1 (ppm)


MRC-1-130.2a.C13
149.32
146.71
132.63
131.99
131.65
127.89
127.62
125.76
125.00
121.41
113.27
112.73
65.46
36.85
36.59
20.91
H3C
N
f1 (ppm)


MRC-1-147.4a.r
Proton Spectrum
F
N
2.01
2.12
1.04
1.93
1.00
2.25
2.21
f1 (ppm)


MRC-1-147.4a.rC13
Carbon-13
159.81
157.91
149.09
145.22
145.20
134.25
131.80
127.60
125.15
121.75
113.93
113.87
113.74
113.68
112.61
112.38
112.19
65.88
36.98
36.97
36.27
F
N
f1 (ppm)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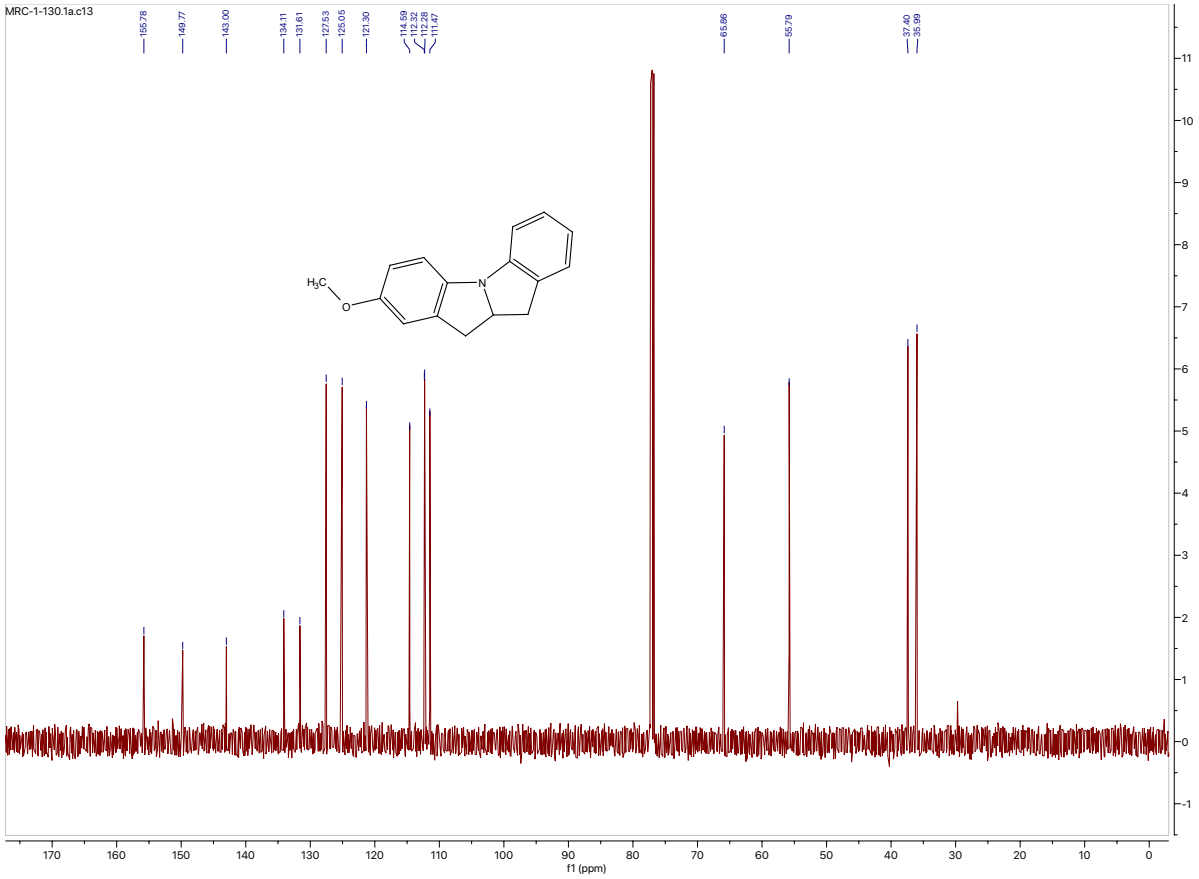
7.14
7.14
7.14
7.13
7.11
7.09
7.09
7.08
7.07
7.07
6.90
6.89
6.88
6.87
6.76
6.76
6.76
6.75
6.74
6.73
6.72
4.89
4.88
4.88
4.86
4.86
4.85
4.84
4.83
3.72
3.39
3.37
3.37
3.35
3.34
3.27
3.26
3.24
3.22
3.11
3.10
3.08
3.06
3.04
3.03
4.08
1.00
1.99
1.00
3.10
1.06
1.05
2.10
H3C
O
N
f1 (ppm)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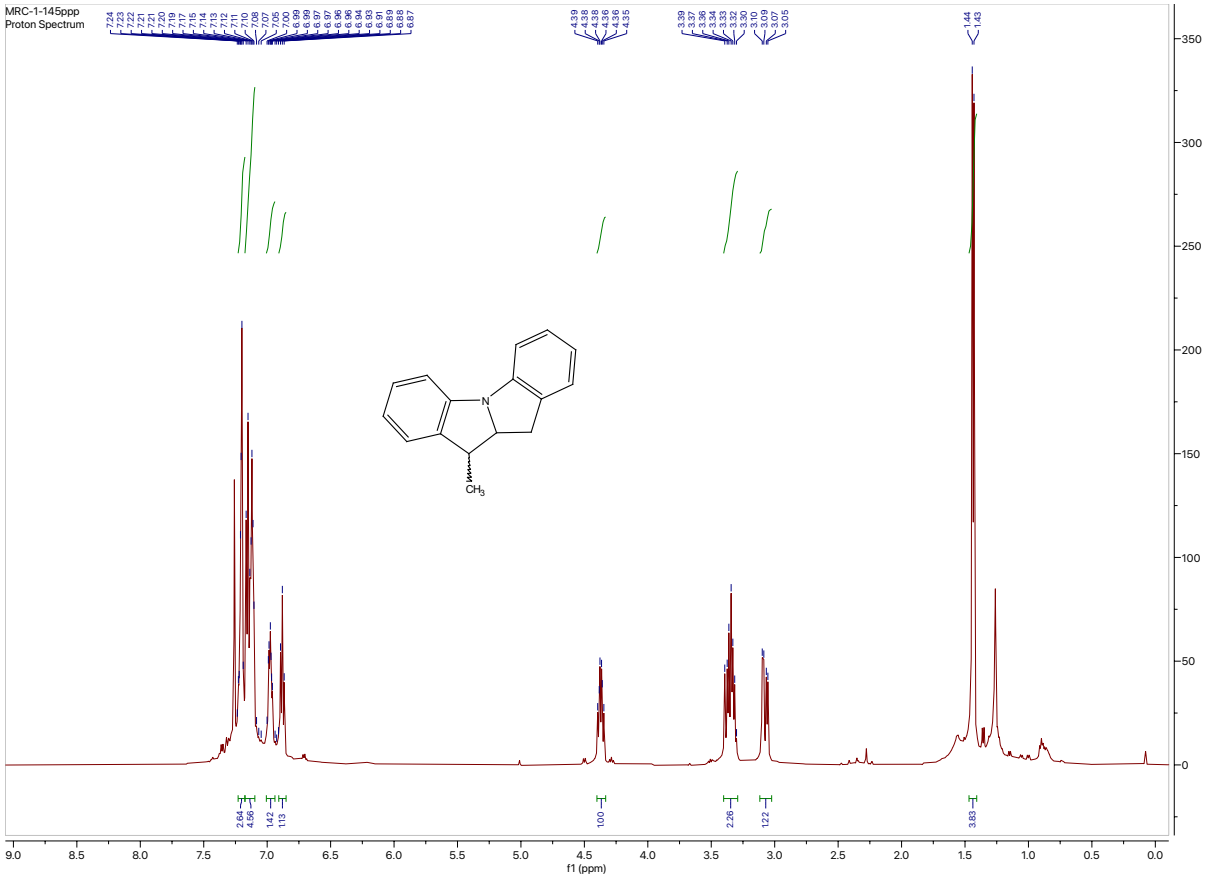
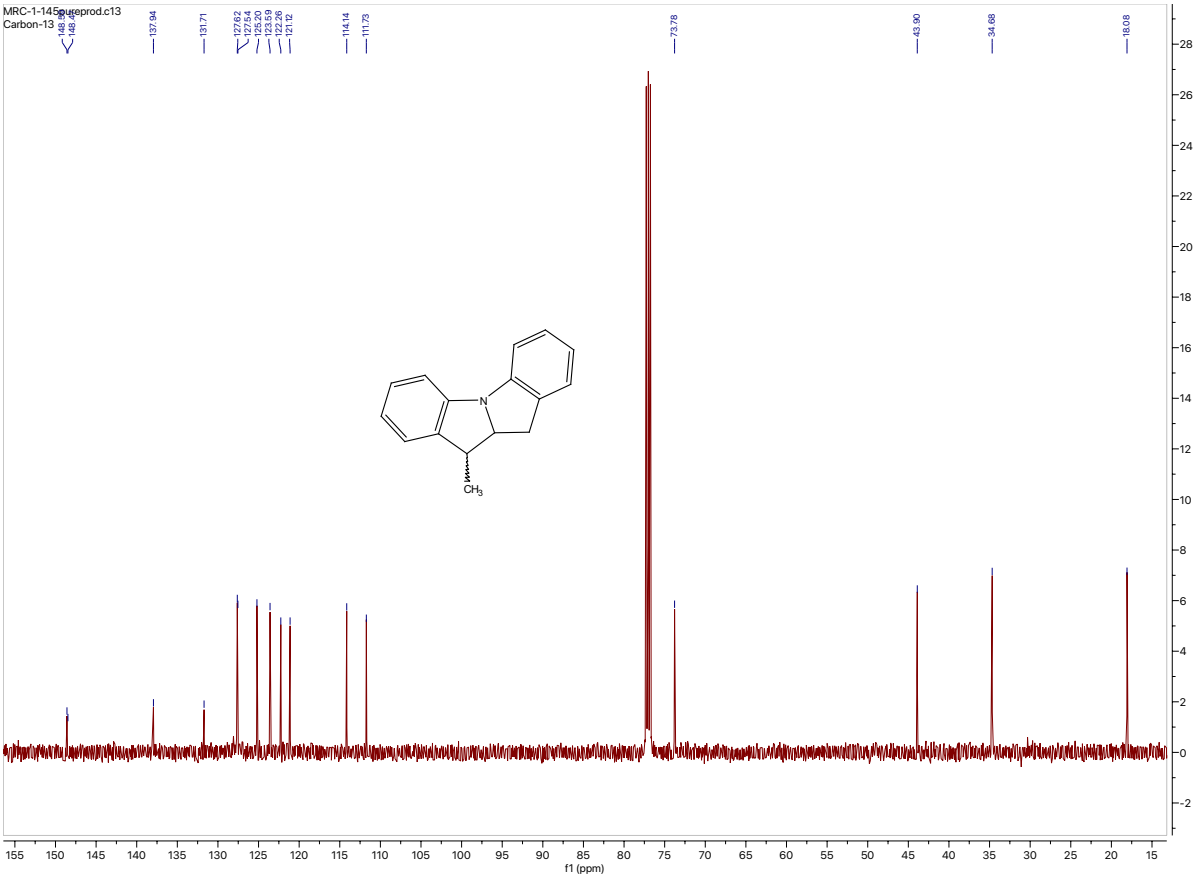
155.78
149.77
143.00
134.11
131.61
127.53
125.05
121.30
114.89
112.33
112.28
111.47
65.86
55.79
37.40
35.99
H3C
O
N
f1 (ppm)


MRC-1-145ppp
Proton Spectrum
7.24
7.23
7.22
7.21
7.21
7.20
7.20
7.19
7.17
7.15
7.14
7.13
7.12
7.11
7.10
7.08
7.07
7.05
7.05
6.99
6.99
6.97
6.97
6.96
6.96
6.94
6.93
6.91
6.89
6.88
6.88
6.87
4.39
4.38
4.38
4.36
4.36
4.35
3.39
3.37
3.36
3.34
3.33
3.32
3.30
3.10
3.09
3.07
3.05
1.44
1.43
N
CH3
2.64
4.56
1.42
1.13
1.00
2.26
1.22
3.83
f1 (ppm)


MRC-1-145pureprod.c13
Carbon-13
148.45
148.13
137.94
131.71
127.62
127.54
125.30
123.59
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121.12
114.14
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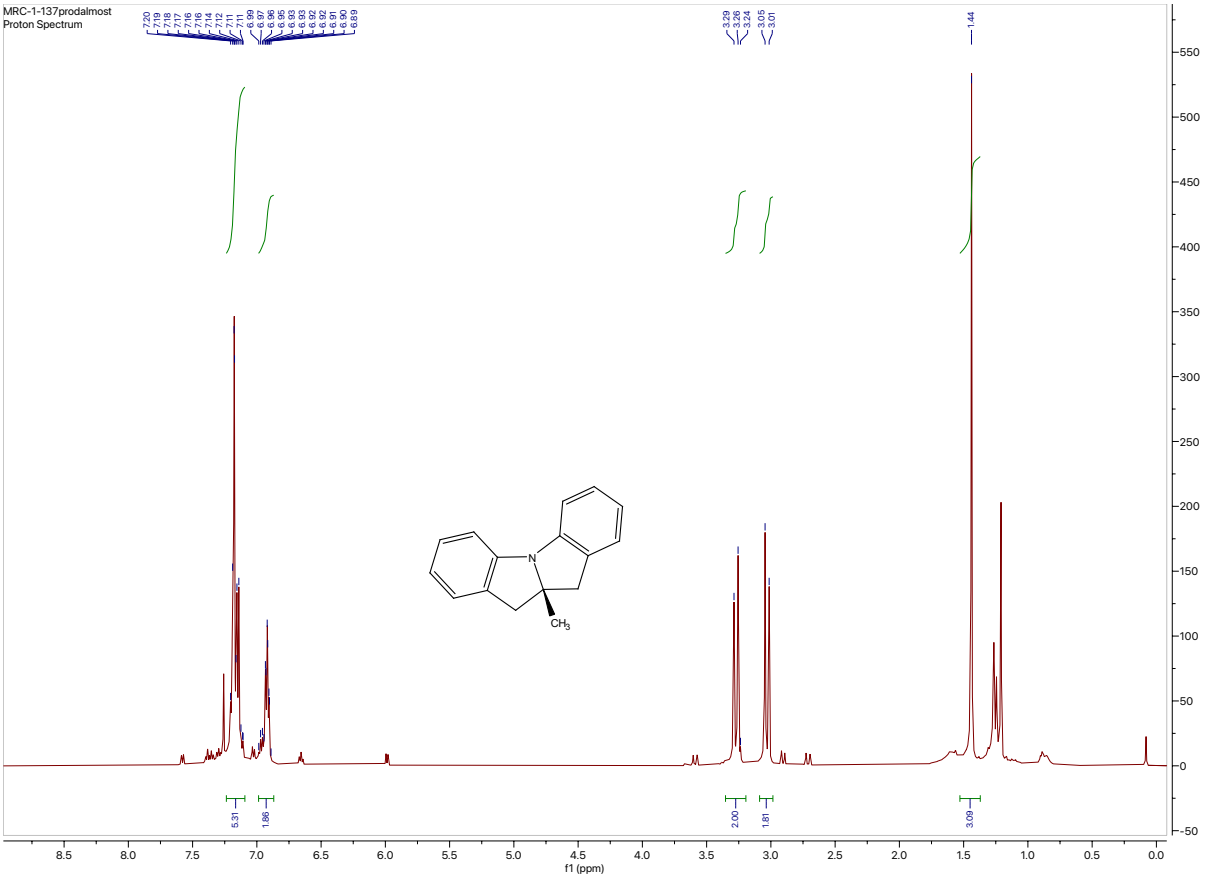
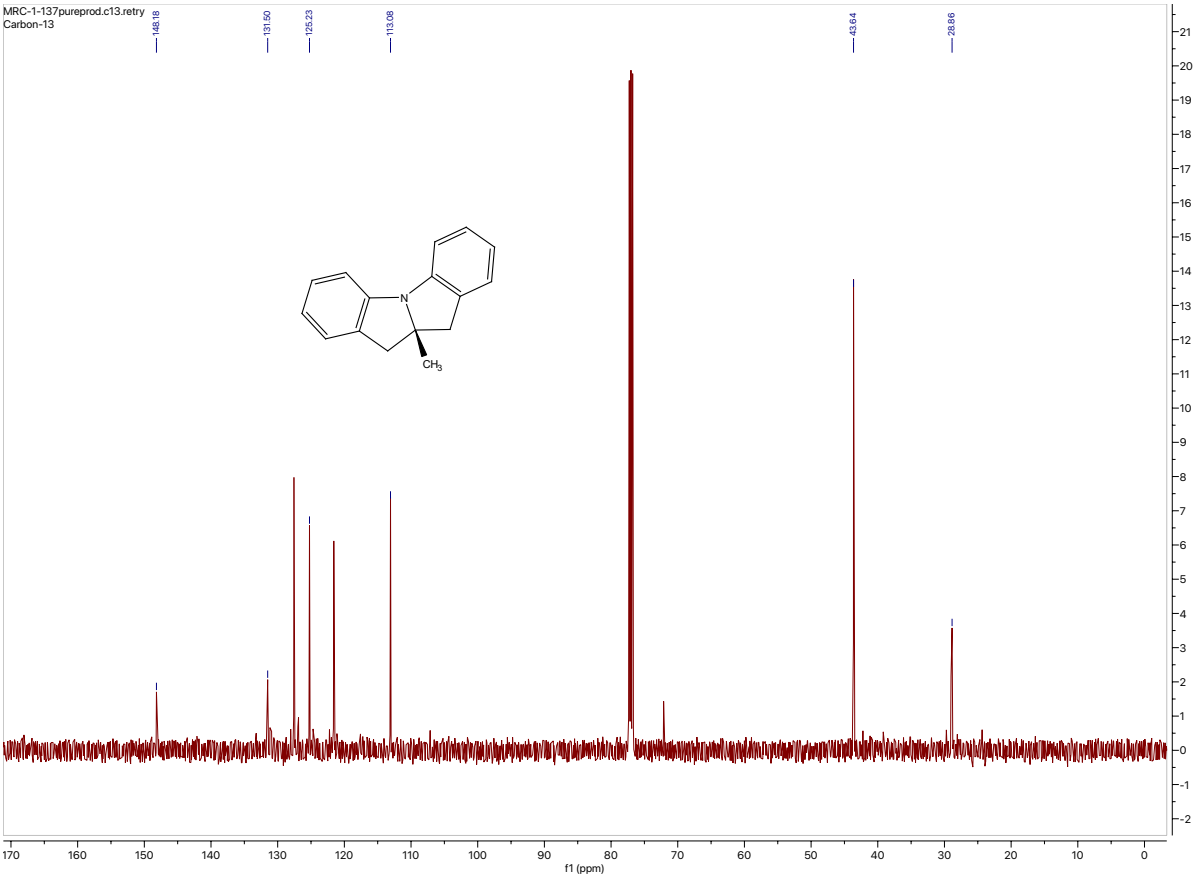
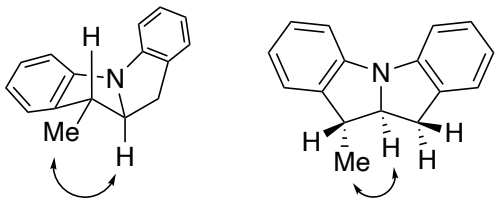
43.90
34.68
18.08
N
CH3
f1 (ppm)

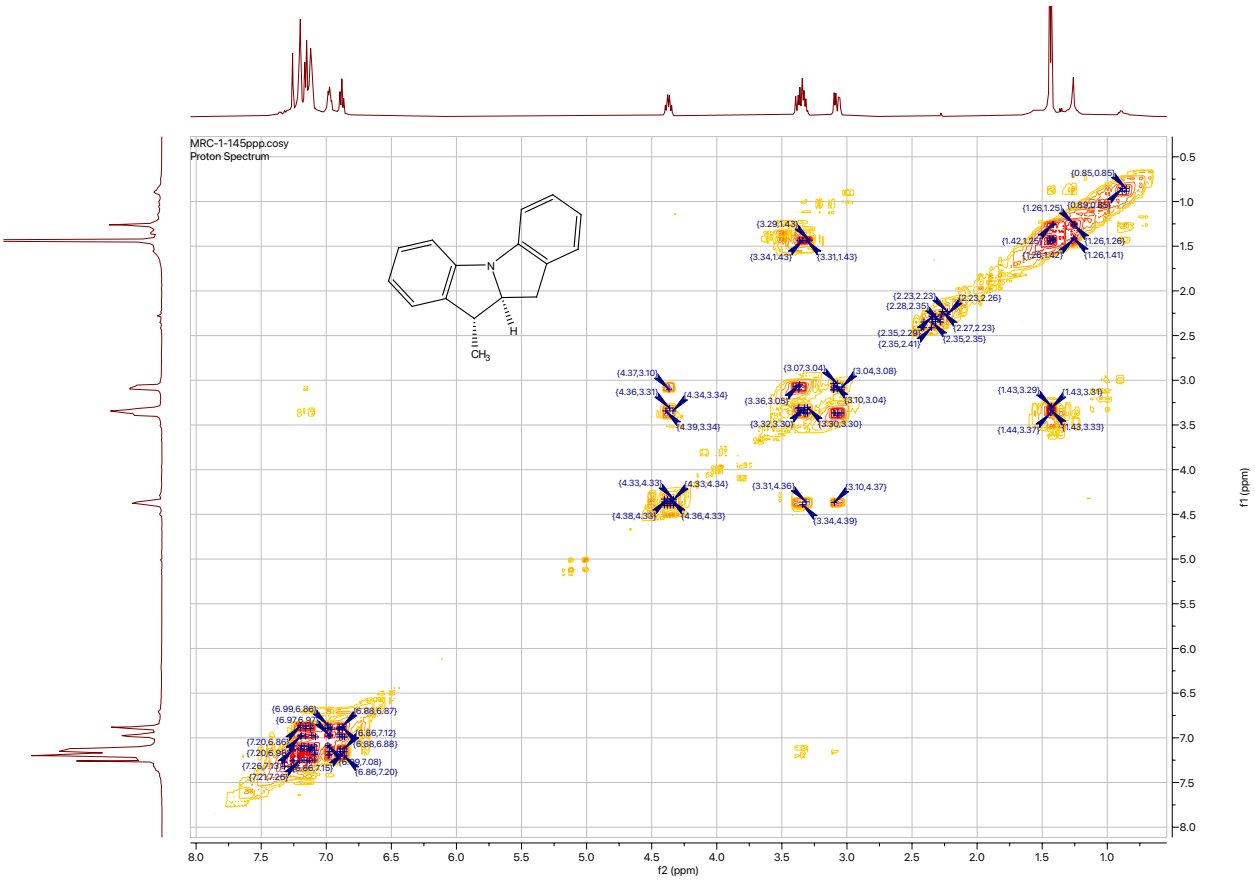

MRC-1-137prodalmost
Proton Spectrum
7.20
7.19
7.18
7.17
7.17
7.16
7.16
7.14
7.12
7.11
7.11
6.99
6.97
6.96
6.95
6.93
6.93
6.92
6.91
6.90
6.89
3.29
3.26
3.24
3.05
3.01
1.44
N
CH3
5.31
1.86
2.00
1.81
3.09
f1 (ppm)

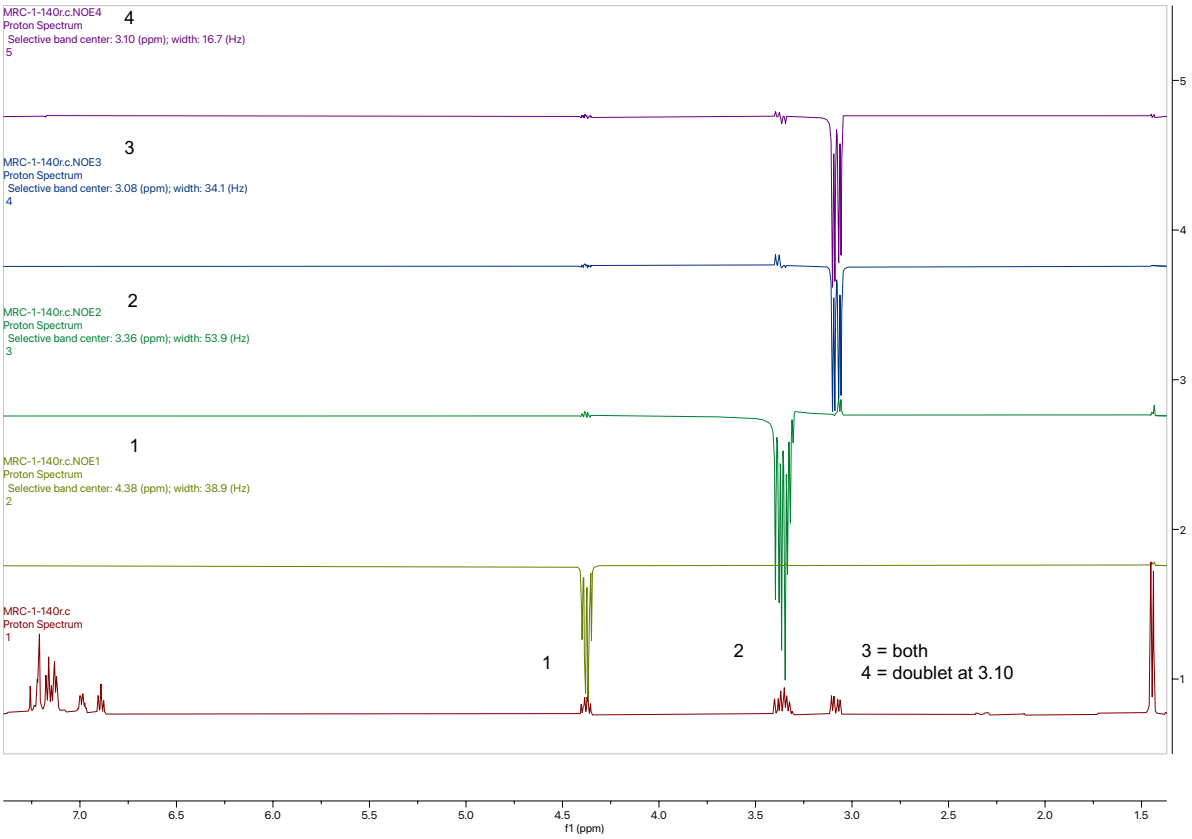


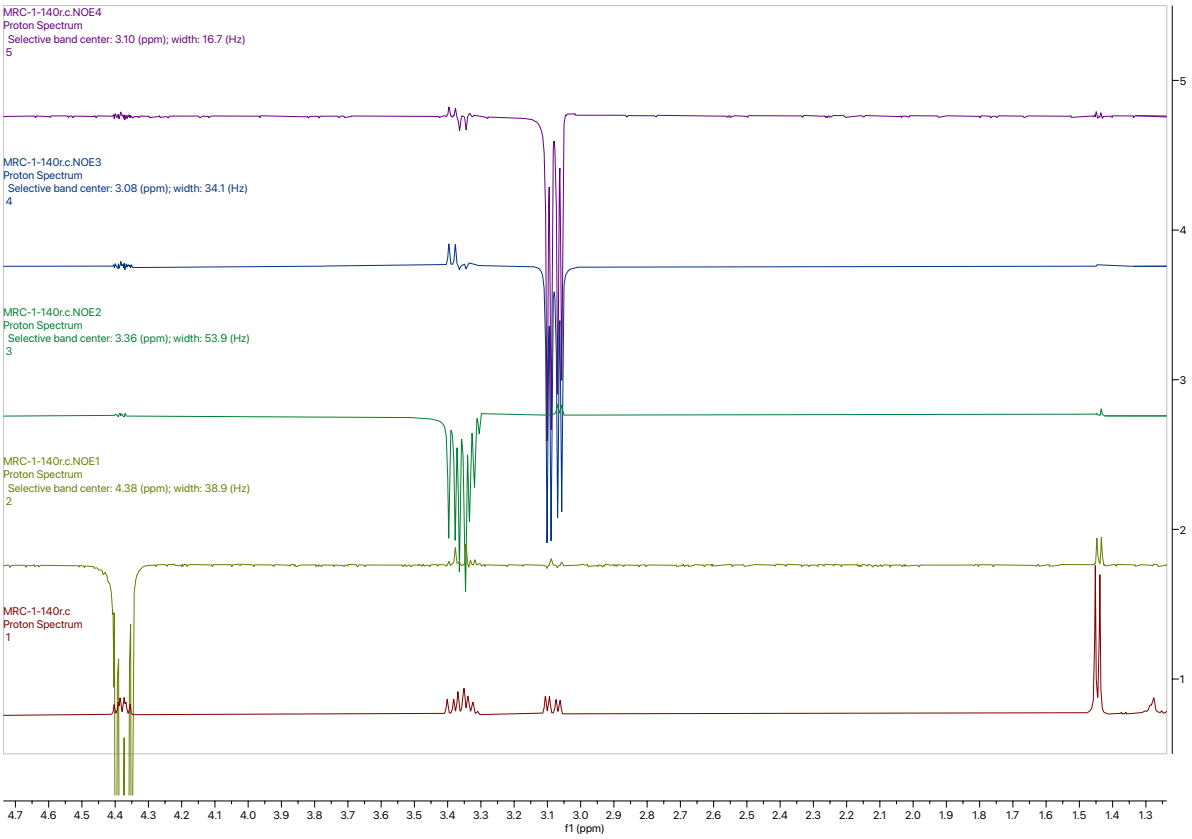
2.6.4 Assignment of Relative Stereochemistry

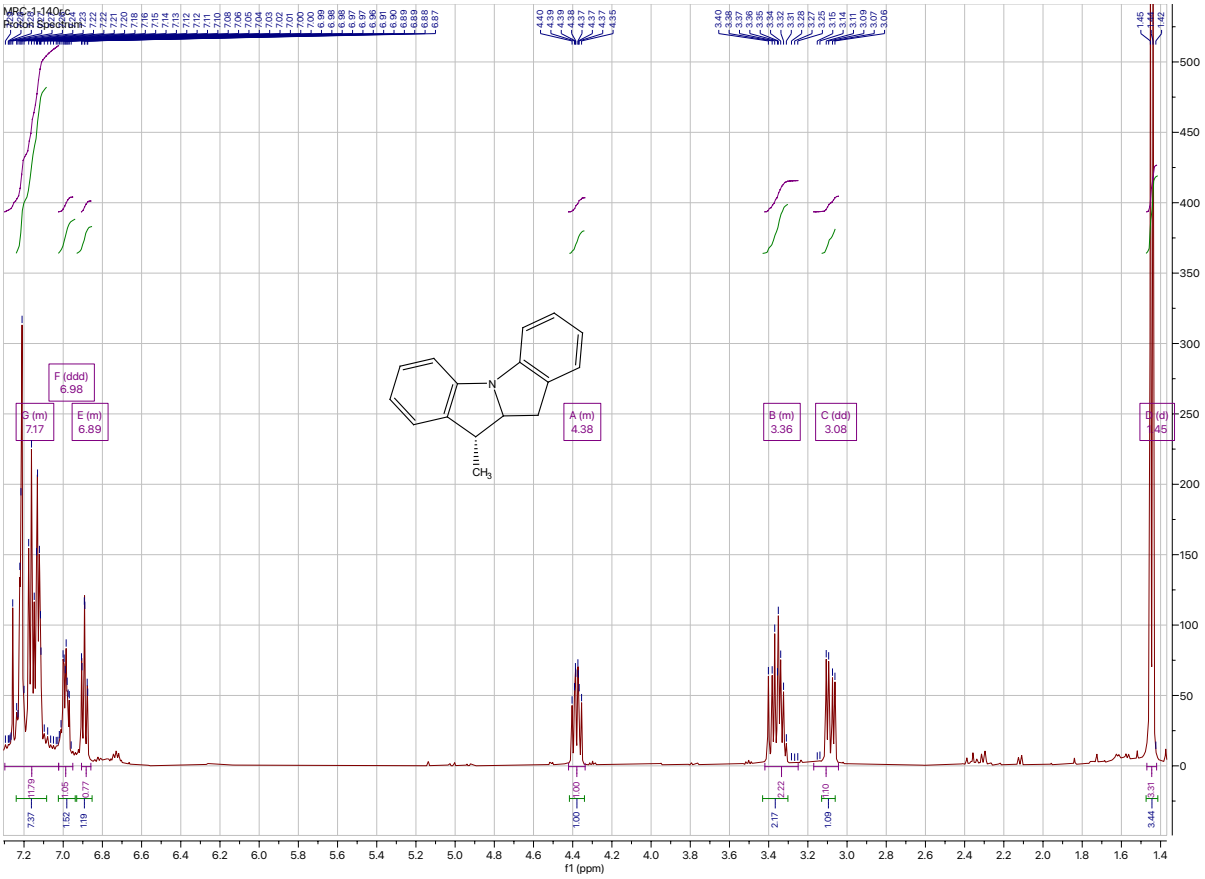
The relative stereochemistry of product **2.3-3e** was assigned based on ^{1}H NMR nOe studies. The data for these studies is provided below, along with the significant nOe signals.




MRC-1-145ppp.cosy
Proton Spectrum
f2 (ppm)
f1 (ppm)


MRC-1-140r.c.NOE4
Proton Spectrum
Selective band center: 3.10 (ppm); width: 16.7 (Hz)
5
4
MRC-1-140r.c.NOE3
Proton Spectrum
Selective band center: 3.08 (ppm); width: 34.1 (Hz)
4
3
MRC-1-140r.c.NOE2
Proton Spectrum
Selective band center: 3.36 (ppm); width: 53.9 (Hz)
3
2
MRC-1-140r.c.NOE1
Proton Spectrum
Selective band center: 4.38 (ppm); width: 38.9 (Hz)
2
1
MRC-1-140r.c
Proton Spectrum
1
1
2
3 = both
4 = doublet at 3.10
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


MRC-1-140r.c.NOE4
Proton Spectrum
Selective band center: 3.10 (ppm); width: 16.7 (Hz)
5
MRC-1-140r.c.NOE3
Proton Spectrum
Selective band center: 3.08 (ppm); width: 34.1 (Hz)
4
MRC-1-140r.c.NOE2
Proton Spectrum
Selective band center: 3.36 (ppm); width: 53.9 (Hz)
3
MRC-1-140r.c.NOE1
Proton Spectrum
Selective band center: 4.38 (ppm); width: 38.9 (Hz)
2
MRC-1-140r.c
Proton Spectrum
1
5
4
3
2
1
4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3
f1 (ppm)



2.7 References

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Chapter 3 Continuing Cascade Pd-Catalyzed N-Arylation/Carboamination Research

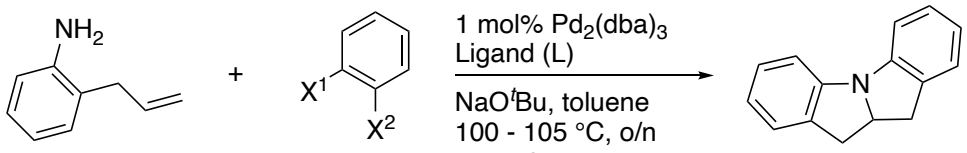
3.1 Scope of Electrophile and Nucleophile for Polycyclic Nitrogen Heterocycle Synthesis

As described in Chapter 2, we have developed a new cascade *N*-arylation/alkene carboamination reaction between 2-allylanilines and 1,2-bromochlorobenzene that afford tetracyclic nitrogen heterocycles in good yield. We theorize that it will be easier synthetically to prepare 1,2-dihalobenzene derivatives with additional substituents if the two halogens are the same. We were also interested if it is possible to form a 6-membered ring during the alkene carboamination step and were curious if the scope of this chemistry could be extended to *γ*-aminoalkenes. Aliphatic aminoalkenes would provide tricyclic pyrrolidine derivatives in the cascade reactions. Our preliminary studies in these areas are described below.

3.1.1 Diversifying the Electrophile

To expand the scope of the electrophile in our system, we sought to vary the leaving groups of the dihaloarene (**3.1.1-1**). In addition to halogenated electrophiles, we also wanted to examine 2-chlorophenyl triflates, since the 2-halophenols are easier to prepare than 1,2-dihalobenzenes.

In preliminary experiments, we attempted to couple 2-allylaniline (**3.1.1-1**) with several different 1,2-dibromo- or 1,2-dichlorobenzene and 2-chlorophenyl trifluoromethanesulfonate electrophiles (**3.1.1-2**) using a variety of ligands (Table 3–1). We evaluated the three ligands that provided the best results in our studies with 2-allylaniline—SPhos, RuPhos, and DavePhos—(Entries 1–3,5–10) and DPE-Phos (Entry 4) from its success with similar carboamination



3.1.1-1 **3.1.1-2** **3.1.1-3**

Entry[a]	X^1	X^2	Ligand (L)	Outcome[b]
1	Br	Br	SPhos	50:50 aniline:arylation
2	Br	Br	RuPhos	30:65:05 isomerization:arylation:prod
3	Br	Br	DavePhos	40:60 aniline:arylation
4	Br	Br	DPE-Phos	30:70 aniline:arylation
5	Cl	OTf	RuPhos	10:90 isomerization:arylation
6	Cl	OTf	DavePhos	25:75 isomerization:arylation
7	Cl	OTf	CPhos	20:80 isomerization:arylation
8	Cl	Cl	RuPhos	50:50 arylation:prod
9	Cl	Cl	DavePhos	95:05 arylation:prod
10	Cl	Cl	CPhos	80:20 arylation:prod

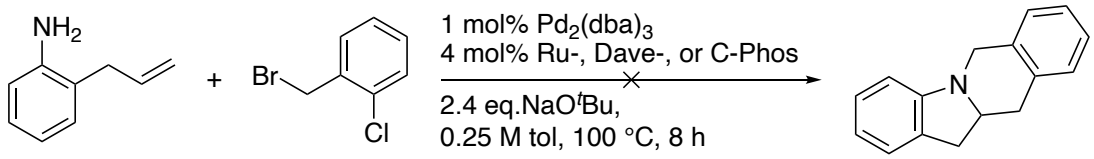
[a]Conditions: 2 - 4 mol % Ligand, 1 eq. substrate (0.25 mmol), 1.2 eq. electrophile (35 μL), 0.25 M solution (1 mL solvent), and 2.4 eq. of base. All reactions one-pot, no pre-stir, elongated 20mL vials. [b]Outcome determined by ^{1}H NMR analysis of crude reaction mixtures. Product ratios are brsm. If desired product, arylation, or alkene isomerization were not observed then undetermined sideproducts were formed.

Table 3–1 Electrophile Screen for Cascade Palladium-Catalyzed Synthesis of Polycyclic Nitrogen Heterocycles

reactions. To our surprise, reactions involving these various electrophiles (**3.1.1-2**) failed to produce desired product (**3.1.1-3**) in substantial yields. The dibromobenzene starting material did not undergo complete reaction in most cases. It is possible the second aryl bromide undergoes oxidative addition after *N*-arylation before the 2-allylaniline substrate has been completely consumed, which may lead to catalytically inactive metal complexes. RuPhos did provide trace amounts of the desired product, but the major product was still the *N*-arylation product (Entry 2). We anticipated that replacing one bromo with the chloro substituent and the other bromo with a pseudohalide would perform similarly to bromochlorobenzene, but at best we observed high *N*-

arylation yields without further conversion to product (Entries 5–7). The reasons for this are not clear, but it is possible that the triflate counterion is causing catalyst deactivation in some manner. Lastly, efforts to use 1,2-dichlorobenzene revealed that trace amounts of desired product were formed, but reactivity was poor and the formation of palladium black was observed (Entries 8–10). The low reactivity of 1,2-dichlorobenzene may be due to relatively slow oxidative addition into the chloro-arene bond.[1]

We also briefly explored the synthesis of an expanded ring product (**3.1.1-5**) using 1-(bromomethyl)-2-chlorobenzene as the electrophile (**3.1.1-4**). We hypothesized that the S_N2 reaction between aniline **3.1.1-1** and the benzylic halide would be fast, and the resulting *N*-(2-chlorobenzyl)-2-allylaniline could potentially undergo intramolecular alkene carboamination to generate **3.1.1-6**. We attempted this reaction using the ligands that were optimal for our coupling of 2-allylaniline with 2-bromochlorobenzen. However the crude NMR from the reaction of 2-allylaniline with **3.1.1-4** did not provide clear indication that any of the desired 6,11,11a,12-tetrahydroindolo[1,2-*b*]isoquinoline product had formed (Equation 3–1). Instead, the spectra and TLC revealed an almost even distribution of undetermined side products with evidence of alkene isomerization. We theorize that with a more extensive ligand screen, change in temperature, and/or concentration adjustment, the substituted tetrahydroindoloisoquinoline derivatives can be achieved. Given successes with similar products produced in the Wolfe group under similar conditions,[2] changing the chloro of **3.1.1-4** to bromo is also worth investigating.



3.1.1-1 **3.1.1-4** **3.1.1-5**

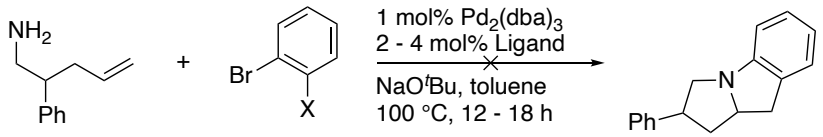
Equation 3–1 Attempt at Cascade 6-membered Ring Synthesis

3.1.2 Diversifying the Nucleophile

We also briefly explored the extension of this chemistry to the synthesis of tetrahydropyrroloindole products (**3.1.2-3**) from alkylaminoalkene derivatives (**3.1.2-1**). The Wolfe group has previously shown that *N*-aryl-pent-4-enylamines undergo alkene carboamination reactions when treated with aryl bromides and a palladium catalyst to generate substituted pyrrolidines.[3] In addition, related cascade intermolecular *N*-arylation/intermolecular alkene carboamination reactions of pentenylamines have been previously described.[3] We hypothesized, based on our success with anilines, that pentenylamine derivatives could undergo related cascade intermolecular *N*-arylation/intramolecular carboamination reactions with the optimal ligand.

Unfortunately, after trying various combinations of nucleophiles, parameters, and ligands, we were unsuccessful in producing the desired products (Table 3–2 and Table 3–3). Instead, most ligands produced an *N*-arylation product (**3.1.2-7**) in high yields (Scheme 3–1). In some cases, there was mostly unreacted starting material. In other instances, we observed evidence of Heck products and isomerization of the olefin in the crude NMR assays. Based on the wide range of electron-rich and -poor ligands and varying degrees of steric interactions with ligand substituents, with failure to produce even traces amount of product, we theorize that this transformation will require a different ligand for the alkene carboamination step than is optimal for the *N*-arylation step. For example, dppBz, NiXantPhos, *t*BuDavePhos, dppf, WeirdPhos, and DavePhos produced an abundance of *N*-arylation products, while Me_4*t*BuXPhos, PMe_3•HBF_4, CyAPhos, PhAPhos, P(2-furyl)$_3$, PPh_3, CPhos, dppp, CyDPE-Phos, P(*t*Bu)$_2$Me•HBF_4, dppe, dppb, P(*o*-Tol)$_3$, and PCy_3•HBF_4 returned unreacted starting material. Previous research in carboamination chemistry

suggests the palladium amido complex (**3F**) is the key feature to subsequent reactions (Scheme 3–1), and it is possible that electronic differences in the 4-membered amido complexes are



3.1.2-1 **3.1.2-2** **3.1.2-3**

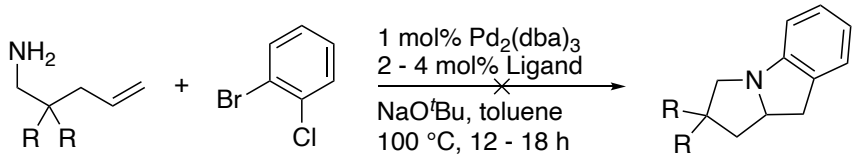
Entry[a]	Ligand (L)	X	Outcome	Entry[a]	Ligand (L)	X	Outcome
1	dppp	Cl	**3.1.2-1**	22	Me_4*t*BuXPhos	Cl	**3.1.2-1**
2	dppf	Cl	*N*-Arylation	23	APhos	Cl	*N*-Arylation
3	dppBz	Cl	*N*-Arylation	24	CyAPhos	Cl	**3.1.2-1**
4	BINAP (rac.)	Cl	*N*-Arylation	25	PhAPhos	Cl	**3.1.2-1**
5	Cy_4DPE-Phos	Cl	side prods + **1**	26	WeirdPhos	Cl	*N*-Arylation
6	DPE-Phos	Cl	*N*-Arylation	27	QPhos	Cl	*N*-Arylation
7	P(*t*Bu)$_2$Me•HBF_4	Cl	side prods + **1**	28	NiXantPhos	Cl	*N*-Arylation
8	PMe_3•HBF_4	Cl	**3.1.2-1**	29	RockPhos	Cl	*N*-Arylation
9	MePhos	Cl	*N*-Arylation	30	BippyPhos	Cl	side prods
10	*t*BuMePhos	Cl	*N*-Arylation	31	CyBippyPhos	Cl	side prods
11	SPhos	Cl	*N*-Arylation	32	MorDalPhos	Cl	side prods
12	EPhos	Cl	*N*-Arylation	33	Xantphos	Br	*N*-Arylation
13	JackiePhos	Cl	side prods	34	JohnPhos	Br	mixture
14	RuPhos	Cl	mixture	35	DPE-Phos	Br	*N*-Arylation
15	PhDavePhos	Cl	*N*-Arylation + **1**	36	CPhos	Br	mixture
16	*t*BuDavePhos	Cl	*N*-Arylation	37	RuPhos	Br	**3.1.2-1**
17	DavePhos	Cl	mixture	38	DavePhos	Br	**3.1.2-1**
18	BrettPhos	Cl	*N*-Arylation	39	CyJohnPhos	Br	*N*-Arylation
19	*t*BuBrettPhos	Cl	*N*-Arylation	40	P(2-furly)$_3$	Br	**3.1.2-1**
20	XPhos	Cl	*N*-Arylation	41	PPh_3	Br	**3.1.2-1**
21	*t*BuXPhos	Cl	*N*-Arylation	42	TrixiePhos (rac.)	Br	*N*-Arylation

[a]Conditions: 2 - 4 mol % Ligand, 1 eq. substrate (0.25 mmol), 1.2 eq. electrophile (35 μL), 0.25 M solution (1 mL solvent), and 2.4 eq. of base. All reactions one-pot, no pre-stir, elongated 20mL vials. [b]Outcome determined by ^{1}H NMR analysis of crude reaction mixtures.

Table 3–2 Ligand and Electrophile Screen of Aminoalkene Pd-Cat. Reactions

influencing the rates of the alkene aminopalladation step.[4]

There are challenges reported involving palladium(aryl)(amido) complexes in terms of intramolecular insertion of an unactivated alkene into the Pd–N bond of an intermediate with amidoarylation success only happening in specific conditions.[5] We theorize that there is also a



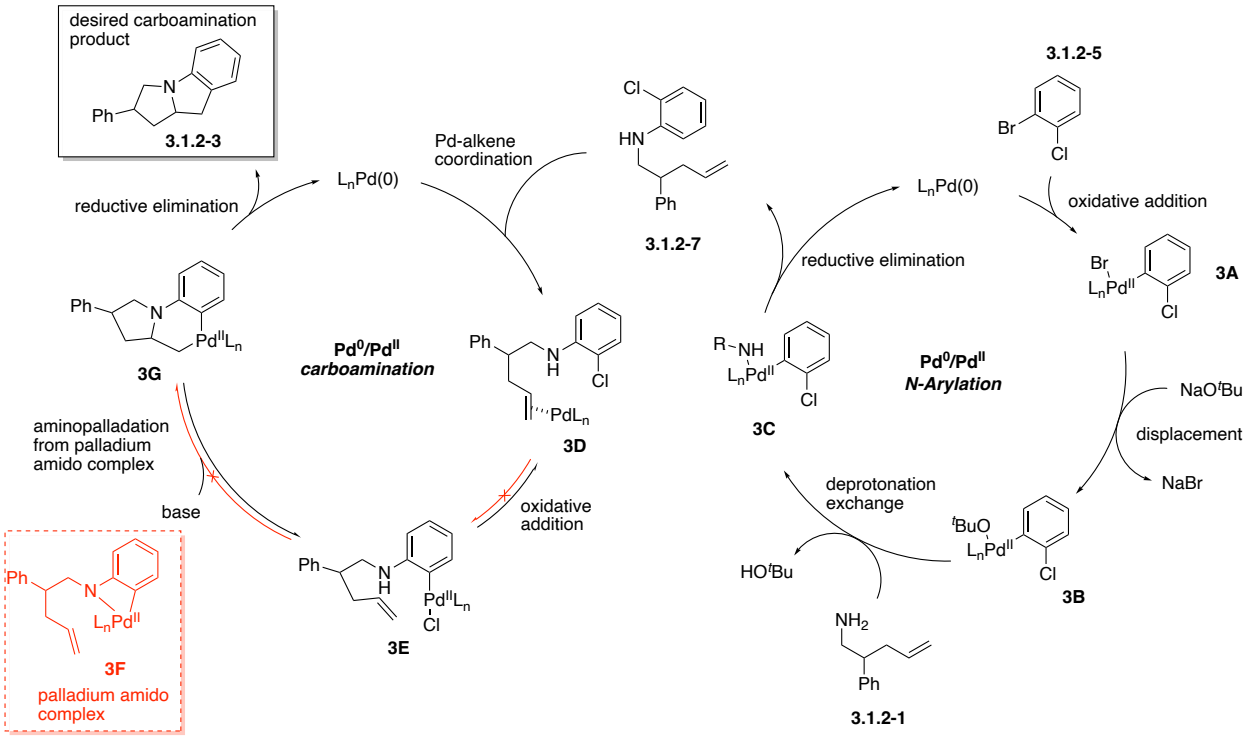
3.1.2-4 **3.1.2-5** **3.1.2-6**

Entry[a]	Ligand (L)	R	Outcome	Entry[a]	Ligand (L)	R	Outcome
1	RuPhos	Ph	mixture	7	Xantphos	Ph	*N*-Arylation
2	DavePhos	Ph	*N*-Arylation	8	P(*o*-tol)$_3$	Ph	**3.1.2-4**
3	CPhos	Ph	mixture	9	PCy$_3$•HBF$_4$	Ph	**3.1.2-4**
4	DPE-Phos	Ph	*N*-Arylation	10	RuPhos	Me	mixture
5	dppb	Ph	*N*-Arylation + **4**	11	DPE-Phos	Me	*N*-Arylation
6	dppe	Ph	**3.1.2-4**				

[a]Conditions: 2 - 4 mol % Ligand, 1 eq. substrate (0.25 mmol), 1.2 eq. electrophile (35 μL), 0.25 M solution (1 mL solvent), and 2.4 eq. of base. All reactions one-pot, no pre-stir, elongated 20mL vials. [b]Outcome determined by ^{1}H NMR analysis of crude reaction mixtures.

Table 3–3 Ligand and Nucleophile Screen of Aminoalkene Pd-Cat. Reactions

possibility that the pKa of intermediate **3D** is not in the optimal range for a subsequent aminopalladation, as prior studies have shown that the alkene carboamination is very sensitive to the electronic properties of the nitrogen atom.[3] It is also possible that the catalyst is dying before the second oxidative addition, or that we simply have not yet discovered a viable ligand or reaction conditions for this particular transformation. In the future, studies on the effects of changing the solvent of the system to a higher dielectric constant, increasing the temperature, and/or changing other parameters, such as the nature of the base. It is also possible to tune the electronic properties of the nitrogen atom by adding an electron-donating or withdrawing substituent to the 2-chlorophenyl group to modify the rates of alkene aminopalladation (faster with electron-rich *N*-substituents) or β-hydride elimination (slower with electron-withdrawing *N*-substitutents).[6] In the future, it may be possible to carry out this transformation over two steps and examine synthesis



Scheme 3–1 Mechanism N-Arylation of Aminoalkenes

and isolation of the *N*-arylated intermediate, followed by studying the effect of different ligands on the carboamination step alone. Therefore, more research needs to be conducted to evaluate the roadblocks in this cascade transformation.

3.2 Summary of Challenges with Cascade Pd-Catalyzed N-Arylation/Carboamination Reactions and Continued Research

To expand the scope of the electrophile in our system, we sought to vary the leaving groups of the dihaloarene so that we could attach substituents to the electrophile via aromatic substitution reactions. To our surprise, 1,2-dibromobenzene, 1,2-dichlorobenzene, or 2-chlorophenyl trifluoromethanesulfonate electrophiles did not produce the desired product. We also tested our ability to synthesize an expanded ring products using 1-(bromomethyl)-2-chlorobenzene, yet there was no clear indication of the formation of product via NMR. Our next study was to expand the

scope of the nucleophile. Unfortunately, after trying various combinations of parameters and ligands, we were unsuccessful in producing the desired product. At best, we produced *N*-arylation products in high yields. Therefore, more research needs to be conducted to evaluate the roadblocks in this cascade transformation. We believe the palladium amido complex is the key feature for tetrahydropyrroloindoles synthesis. Future work entails expanding the nucleophile scope of cascade palladium-catalyzed *N*-arylation/alkene carboamination reactions to sp^3 *γ*-*N*-arylamino alkenes. Particularly there is research opportunity to screen different solvents, bases, and ligands with a functionalized electrophile (i.e. electron-withdrawing or -donating group) to successfully synthesize polycyclic tetrahydropyrroloindoles. Under the right conditions, the challenge associated with the palladium amido complex can be overcome for aminopalladation and subsequent reductive elimination.

3.3 Experimental Section for Continued Research

3.3.1 General Procedures

General: All reactions were carried out under a nitrogen atmosphere inside of immediately oven- or flame-dried glassware. All reagents, palladium precatalysts, ligands, and aryl halides (including 2-chlorobenzyl bromide) were purchased from commercial sources and were used without purification unless otherwise noted. Toluene and THF were purified using a GlassContour solvent purification system. Xylenes were dried from distillation with calcium hydride. DMF was anhydrous, 99.8%, packaged under argon or nitrogen in resealable ChemSeal™ Sure/Seal™ bottle and taken under nitrogen. All yields refer to isolated yields of compounds that are estimated to be ≥95% pure as determined by ^{1}H NMR unless otherwise noted (i.e. average yield of two or more experiments). Sensitive starting materials like triflates were stored in a freezer under nitrogen. Bulk quantities of cesium carbonate, sodium *tert*-butoxide, and other moisture-sensitive

compounds like bases were stored in nitrogen-filled glove box, and small amounts were removed and used.

3.3.1.1 General Procedure for Palladium Catalysis Reactions

A flame-dried modified 10 mL vial (cylinder shaped) equipped with a 10 μm magnetic stir bar was cooled under a stream of nitrogen and charged with the appropriate base (0.6 mmol, 2.4 equiv), palladium pre-catalyst (0.0025 mmol, 0.0025 equiv, 1 mol %), the appropriate ligand (0.001 mmol, 0.01 equiv, 4 mol %). The vial was purged with nitrogen and charged with toluene (0.25 M, 1 mL) and the appropriate amine derivative (0.25 mmol, 1 equiv) and dihaloarene (0.3 mmol, 1.2 equiv). The vial was capped and heated to the appropriate temperature with stirring overnight. The mixture was then cooled to rt, charged with phenanthrene (1 equiv; NMR internal standard), diluted with diethyl ether (2 mL), and quenched with saturated ammonium chloride (2 mL). The aqueous layer was extracted with diethyl ether (3 x 2 mL), filtered through celite and sand, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified via flash chromatography on silica gel to afford the product.

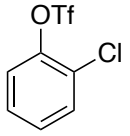
3.3.1.2 General Procedure for Amine Substrates

γ-N-arylamino alkenes were prepared according to previously published procedures. A solution of 2-alkylacetonitrile derivative (10 mmol) in dry DMF (10 mL) was added slowly to a suspension of NaH (0.48 g, 12 mmol, 60 % in oil) or to a solution of LDA generated *in situ* from *n*-BuLi (4 mL in hexanes, 2.5 M, 10 mmol) and NH(*i*Pr)$_2$ (11 mmol) in 8 mL dry THF at -78 ℃ and the resulting mixture was stirred at room temperature for 1 h. The resulting bright yellow suspension was cooled to 0 °C, a solution of allyl bromides (10 mmol) in dry DMF (3 mL) was added dropwise. Then the reaction warmed to room temperature overnight with stirring. The resulting solution was poured into an ice/water mixture (30 mL) and extracted with ethyl acetate (3 × 20

mL). The combined extracts were washed with brine (2 × 15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% EtOAc/Hexanes) to afford the respective pentenenitrile derivative.

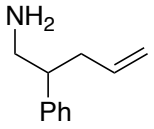
A flame-dried glass pressure tube equipped with a magnetic stir bar and a rubber septum was cooled under a stream of nitrogen. To a stirring solution of pentenenitrile (5 mmol) in ethyl ether (20 mL) at 0 °C was added 0.56 g $LiAlH_4$ (15 mmol) dropwise. The solution was warmed to room temperature overnight with stirring. The resulting suspension was cooled to 0 °C and quenched by slow addition of 6 M NaOH (20 mL). After filtering off the solid, the filtrate was extracted with ethyl ether (3 × 10 mL) and combined ether extracts were dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo and purified by silica gel chromatography (30% EtOAc/Hexanes) to afford the corresponding products.

3.3.2 Preparation and Characterization of Substrates

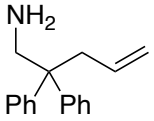


2-chlorophenyl trifluoromethanesulfonate S7 To a solution of 2-bromophenol (5 mmol) in dry dichloromethane (15 mL) was added pyridine (20 mmol) at room temperature. Then the reaction mixture was cooled to 0 ºC and Tf_2O (6 mmol) was added slowly. The reaction mixture was slowly warmed up to room temperature and stirred for 3 h. After consumption of starting material, water (15 mL) was added, and the organic layer was separated. The aq. layer was extracted with dichloromethane (15 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography on silica

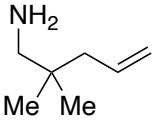
gel (1.2164 g, 93% as a clear oil). Spectroscopic properties are identical to those previously reported.[1a]



2-phenylpent-4-en-1-amine S8 General Procedure found in section **3.3.1.2**. Spectroscopic properties are identical to those previously reported.[2a]



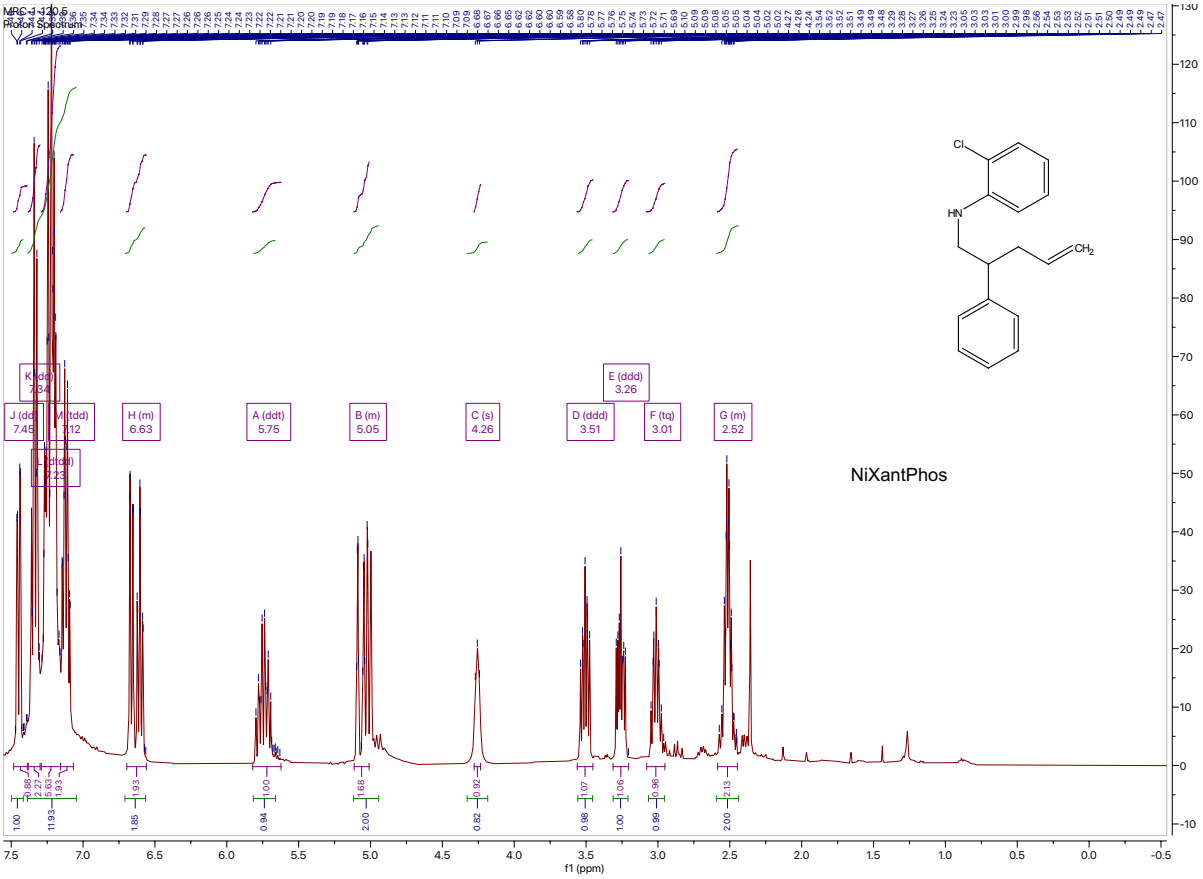
2,2-diphenylpent-4-en-1-amine S9 General Procedure found in section **3.3.1.2**. Spectroscopic properties are identical to those previously reported.[2a]



2,2-dimethylpent-4-en-1-amine S10 General Procedure found in section **3.3.1.2**. Spectroscopic properties are identical to those previously reported.[2a]

(1a) *Org. Lett.* **2015**, 17, *8*, 2034–2037
(2a) *Org. Lett.* **2015***,* 17, *4*, 1018–1021

3.3.3 Unpublished Crude Spectra



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