Studies on the Development of Palladium-Catalyzed Alkene Difunctionalization Reactions for the Synthesis of Nitrogen-Containing Heterocycles

By

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Dedication

To all my friends and family who pushed me to achieve my dreams – Thank you

To Blackie, Tesla, and Dalton – I feel you here with me everyday

Acknowledgements

To my loving mother: I want to thank you for all that you've done for me. You've taught me what it means to sacrifice for your family and to always have family in my heart. You, working multiple teaching jobs, coming home between 8-9 pm several days of the week, and supporting a family of five on a teacher's salary all while setting aside money for vacations and trips is something I will never forget. I try to emulate your work ethic in everything I do. In doing so, I believe I've become a better person even though I could never work as hard as you have. You are the definition of a super mom and I love you more than you'll know. I strive every day to make sure that you can look at me with pride and admiration. I'm sorry I didn't call more often. I can be forgetful at times and I'm not sure where I got that from since you and pops never seemed to forget anything. I love you and always will.

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Abuela Daisy, gracias por todo lo que has hecho por mí. Siempre has estado ahí para mí cuando te he necesitado y estoy muy feliz de tenerte en mi vida. Eres mi reina y nunca dejaré de amarte mientras viva.

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think of anything more important than that. I hope you continue to bring that energy to everything else that you do.

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Dr. Wolfe, I couldn't have asked for a better PI to work under. You inspired me to be the best scientist I could be. You displayed an excitement of chemistry that is second to none and willingness to teach that is unrivaled. I can't thank you enough for taking me in, letting me make mistakes, and learn and grow from them. I'll never forget the group meetings and problem-solving sessions that went on for a lot longer than they needed to because of the stories you'd share. I still think you need therapy from your days in the Buchwald lab but that's a different conversation for a different time.

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Dragons. I don't think I've ever told you, but you were one of the main reason why I started getting into it. I now have a ton of dice (it's getting bad).

I want to thank my undergraduate mentees, Kyle and Allison as well as my post-baccalaureate mentee, Glori. I've learned so much from being a mentor to you all and I really couldn't have asked a better group of minds to help cultivate. You all showed me what it means to be a part of a team and work hard together towards a common goal. I'm so proud of everything you all have accomplished and will continue to accomplish.

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lab. You four always managed to keep me on my toes and bring me joy and energy in the lab.

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Finally, thank you to Maitlin. I'm so lucky to have found you and I can't think of anyone else I would've wanted to spend the last 9 years with. You are my rock, my partner in crime, my other half. During my periods of crippling anxiety, you were always by my side and I can't thank you enough. I would not be here, both in grad school and in life, without you. Thank you for filling my life with laughter, love, happiness, and joy I never thought possible. Thank you for being an incredible, beautiful, intelligent, funny, and personable human being. Thank you for comforting me when I couldn't move because of my anxiety. Thank you for making me smile when I was going through severe depression. Thank you for always pushing me into being a better person. I can confidently say that everything I do is to make sure I can repay all the kindness that you've done for me with interest. Thank you for bringing Dusk (*Dusky*) and Nezuko (*Nezzy*) into my life. I'll never

forget the days when we got the both of them; they were such small kittens at the time. Thank you for loving me and starting this little family with me. I love you.

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List of Abbreviations

Å.....angstrom

α.....alpha

acac.....acetylacetone

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

acac-F6.....hexafluoroacetylacetonate

app.....apparent

aq.....aqueous

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

Au……Gold

β.....beta

BINAP…….... 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

Bn.....benzyl

Boc..... tert-butyloxycarbonyl

BPO.....benzoyl peroxide

br.....Broad

Bz.....benzoyl

C_6D_6……deuterated benzene

Ca.....circa

calcd.....calculated

$CDCl_3$……deuterated chloroform

CN.....cyano

Cp.....cyclopentadienyl

Cy.....cyclohexyl

°C.....degrees Celsius

d.....doublet

dba .....dibenzylideneacetone

DCM.....dichloromethane/methylene chloride

DCE……dichloroethane

dd..... doublet of doublets

ddd .....doublet of doublet of doublets

ddt .....doublet of doublet of triplets

DMF.....dimethylformamide

DMSO.....dimethylsulfoxide

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

DppBz……1,2-Bis(diphenylphosphino)benzene

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

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

dr.....diastereomeric ratio

EDG……..electron-donating group

eh.....2-ethylhexanoate

equiv.....equivalents

eq.....equation

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

G3……..Generation 3

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

HFIP.....hexafluoroisopropanol

HRMS.....high resolution mass spectrometry

Hz……hertz

IR.....infrared spectroscopy

LG……..leaving group

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

J.....coupling constant

Ln/L.....general ligand

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

m.....multiplet

mCPBA.....meta-chloroperoxybenzoic acid

Me.....methyl

MeOH.....methanol

MHz……..mega hertz

m.p.....melting point

MS.....molecule sieve

Ms.....mesyl

MTBE.....methyl tert-butyl ether

n……number (whole number)

nBu……butyl (straight chain)

NBS.....*N*-bromosuccinimide

NMR.....nuclear magnetic resonance

Nuc/Nuc-H.....nucleophile

OAc.....acetate

OMe.....methoxy

OtBu.....tert-butoxide

OTf.....triflate

p.....para

Pd.....palladium

Pd/C.....palladium on carbon

pent.....pentet

PG/P.....protecting group

Ph.....phenyl

PMP.....para-methoxyphenyl

prep TLC.....preparative thin-lay chromatography

q.....quartet

R.....general functional group

rbf.....round-bottom flask

rt.....room temperature

s .....singlet

satd.....Saturated

t.....triplet

t.....tert

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

TEA.....triethylamine

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

Tf.....triflyl

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

TFA.....trifluoroacetic acid

Tf_2O.....triflic anhydride

THF.....tetrahydrofuran

TLC.....thin-layer chromatography

TMS.....trimethylsilyl

Tol-d^8……..….deuterated toluene

Tolyl……toluene (when bound to another atom)

Ts.....tosyl

T. S.....transition state

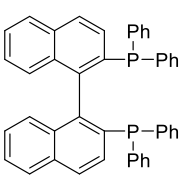
X.....general halide, counterion, or atom

Y.....general heteroatom/functional group

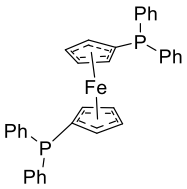
Z.....general atom or substitution

List of Ligands

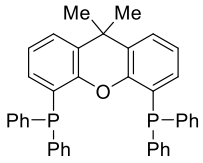
Chelating Phosphine Ligands



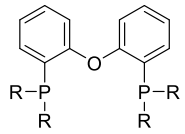
BINAP



DPPF

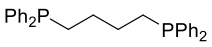


XantPhos

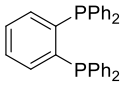


DPEPhos: R = Ph
Cy_4DPEPhos: R = Cy

dppm

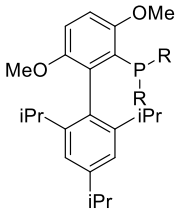


dppb

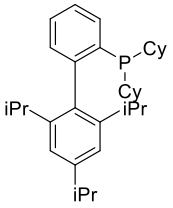


dppBz

Buchwald Ligands



BrettPhos: R = Cy
tBuBrettPhos: R = tBu



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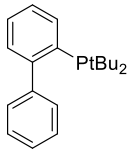

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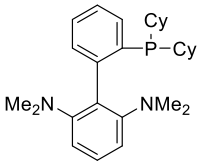
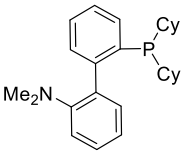
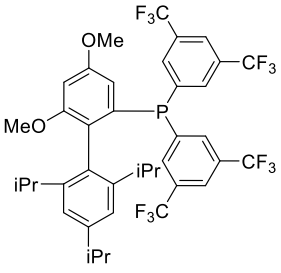


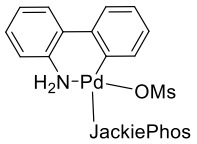
CPhos



DavePhos

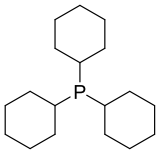


JackiePhos

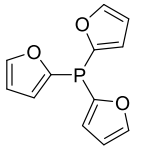


Pd(JackiePhos)G3

Monodentate Phosphine Ligands



PCy_3



$P(2\text{-furyl})_3$

Abstract

Alkene difunctionalization reactions have proved chemists with a valuable and versatile tool to efficiently increase the molecular complexity of carbocycles and heterocycles in a single synthetic step. This dissertation focuses on the study and development of Pd–catalyzed alkene diamination of *N*-heterocycles with an emphasis on alkene diamination to generate 1,2-diamines, ligand considerations for alkene diamination, and methods to generate polycyclic *N*-heterocycles. These reactions efficiently form 2 new bonds (C–N/C–N and C–N/C–C) and 1 – 2 new rings in a single step, up to 2 new stereoisomeric sites from simple starting materials and provides new and important methodology for the synthesis of functionalized heterocycles.

My work has involved the development of Pd–catalyzed alkene diamination reactions; the progress of this field by other labs is described in Chapter 1 and divided by the choice of the transition-metal catalyst. Typically, this chemical reactivity has shown to have some significant limitations such as stoichiometric transition metal sources, needed for added oxidants, limited nucleophile and electrophile scope, or lack of stereospecificity. My studies on alkene diamination (described in Chapter 2) have involved the coupling of aminobenzoate electrophiles with urea and guanidine nucleophiles that contain an unactivated alkene. These reactions produce cyclic ureas and guanidine heterocycles bearing a pendant (di)alkylamino group. During this study, through NMR studies and side product isolation, it was observed that 1,3-dicarbonyl ligands (β-diketones) were the active ligands in this transformation and the mechanistic data is most consistent with a

Pd(II)/(IV) catalytic sequence. Using acac derived ligands, we were able to expand the previously limited electrophile scope of the transformation and more efficiently promote the formation of cyclic ureas, guanidines, and lactams.

Structural and electronic considerations of 1,3–dicarbonyl derivatives were also investigated (described in Chapter 3). From these studies, it was found that keeping the alkyl backbone of acac-like derivatives unsubstituted was critical for a competent catalyst system. Additionally, o–hydroxyacetophenone (and their imine) derivatives mimicked the reactivity of acac-like derivatives. There was a general trend that increasing electron-donating capabilities of the ligand led to more competent reactivity. Exploring the reactivity of this ligand class, including our most optimized ligand, for the formation of other heterocyclic products did not lead to any competent reactivity.

The progress of transition-metal catalyzed C–N bond forming reactions, including early work in the Wolfe lab is described in Chapter 4. This work has shown that the synthesis of heterocycles can be accomplished through Pd–catalyzed N–arylation of primary amines as well as alkene carboamination reactions where a nucleophile with a tethered alkene is coupled with an exogenous electrophile. Later work has shown that the same reactivity is possible where the nucleophile, alkene, and electrophile is tethered into one substrate. My work in this field is described in Chapter 5 in which a sequential N–arylation/alkene carboamination strategy is described to generate polycyclic N–heterocycles commonly observed in therapeutic, natural product, and materials compounds. These reactions allow for the efficient synthesis of 6/6 and 5/6 polycyclic heterocycles from simple starting materials. Stereochemical explanation for the 6/6 and 5/6 ring systems is also described.

Chapter 1

Introduction to Transition Metal–Catalyzed Alkene Diamination Reactions

1.1 Significance of 1,2–Diamines

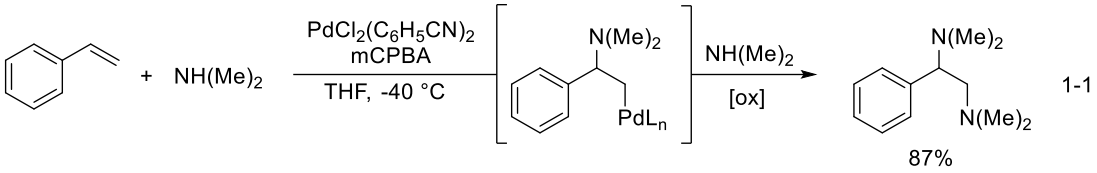
1,2-diamines have been continuously recognized as multipurpose motifs commonly observed in numerous therapeutic drug molecules,[1] ligands,[2] asymmetric catalysts,[3] and natural products.[4] As a result, strategic efforts have been made towards the synthesis of these motifs. However, many of these efforts often require the synthesis of complex starting materials and/or require multistep synthesis.

Over the last two decades, efforts have been made to develop 1,2-diamination methodologies through transition–metal catalyzed alkene difunctionalization. Through these efforts, a number of methodologies involving inter- and intra-molecular alkene diamination of simple starting materials have been established.[5] However, many of these strategies still suffer from key limitations such as i) need for stoichiometric metal sources, ii) need for added oxidants, iii) nucleophile/electrophile scope limitations, and iv) lack of stereospecificity due to the radical nature of the catalytic mechanism.

1.2 Palladium-Catalyzed Alkene Diamination Reactions, the Need for Added Oxidants, and Use of Nitrogen Nucleophiles/Electrophiles

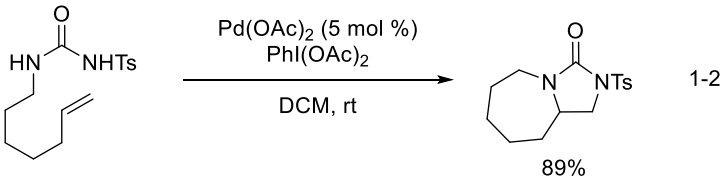
Pd-catalyzed alkene diamination reactions have been explored since the 1978 when Backvall et. al. published their findings on a stoichiometric Pd strategy where diamination occurs across activated and unactivated alkenes in the presence of an added

oxidant in up to 87% yield (eq 1-1).[6] Backvall proposes that alkene diamination is achieved through a Pd(II) intermediate that is oxidized to Pd(IV) by mCPBA, Br_2, NBS, or $Pb(OAc)_2$ followed by a S_N2-like reductive elimination to form the desired product.



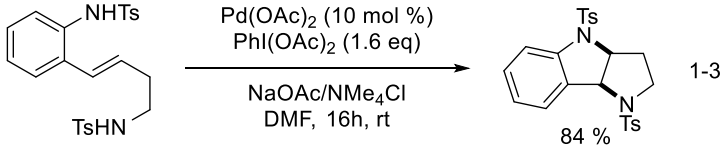
1-1

Since then, alkene diamination has experienced a resurgence within the last two decades. In 2005, Muñiz developed an intramolecular Pd-catalyzed alkene diamination that allowed for the formation of 5,5-, 6,5-, and 7,5-fused bicyclic ureas and guanidines (eq 1-2).[7] They were able to achieve this by employing hypervalent iodine reagent, $PhI(OAc)_2$.



1-2

In 2007, Muñiz reported the development of an intramolecular diamination of internal alkenes to synthesize bisindolines scaffolds using $Pd(OAc)_2$ and $NaOAc/Me_4NCl$ as a combinatory acetate base (1-3).[8] $PhI(OAc)_2$ was also needed as an additional oxidant to oxidize the Pd to Pd(IV). Additionally, they propose an *anti*-aminopalladation by way of the second amido group after the Pd-amido pre-coordination with the first amido group to explain the generally disfavored 5-endo-trig cyclization.

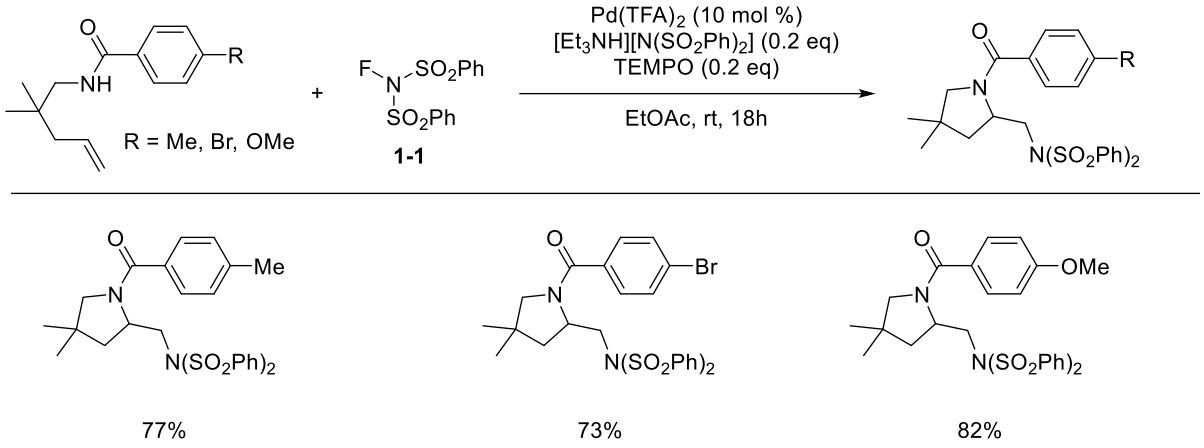


1-3

More recently, it has been found that alkene diamination reactions can be accomplished using nitrogen electrophiles. In 2009, an accidental discovery by Michael

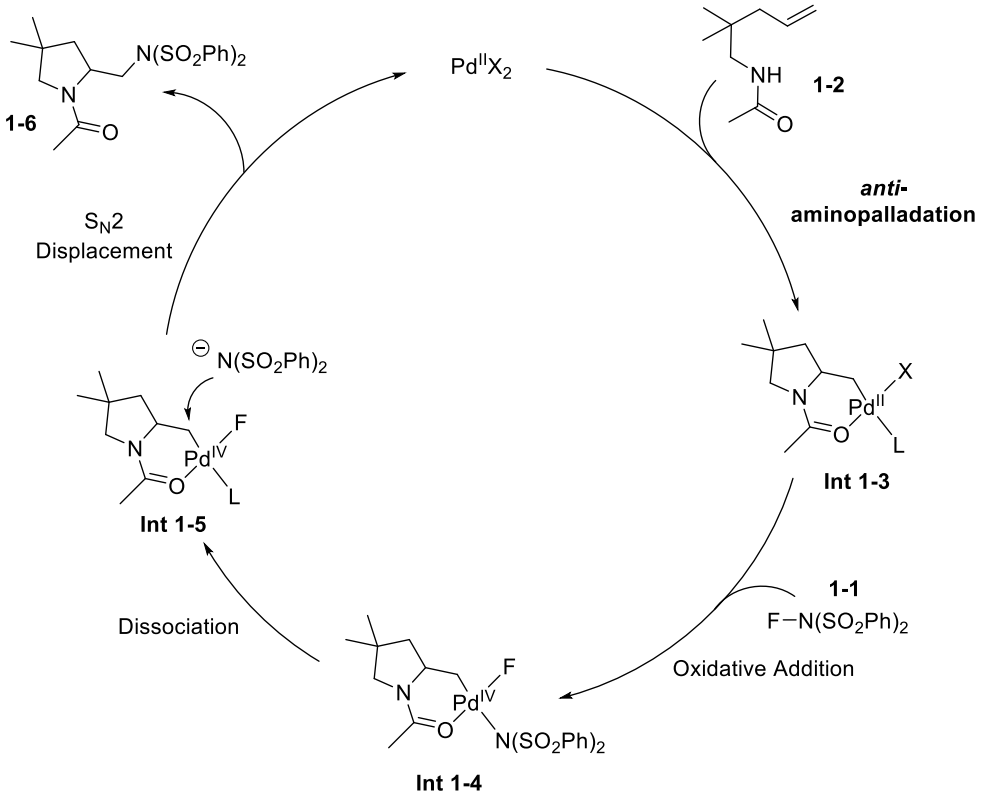
et. al found that employing *N*-fluorobenzenesulfonimide (**1-1**, NFBS), traditionally used as a source of electrophilic fluorine, as an electrophilic aminating reagent can generate pyrrolidine benzenesulfonimides through an intermolecular Pd-catalyzed alkene diamination strategy (Scheme 1-1).[9] In this system, NFBS is used as a strong oxidant to oxidize the Pd(II) to the Pd(IV) complex.

Scheme 1-1: Selected Scope of Michael Pd-Catalyzed Diamination



One limitation of this work, however, is the use of a single nitrogen source to perform the desired reaction. Attempts to use other nitrogen electrophile sources outside of NFBS, did not generate any desired product. This is significant as the limitation of the electrophile source limits the ability to produce a variety of heterocycles with the reported method.

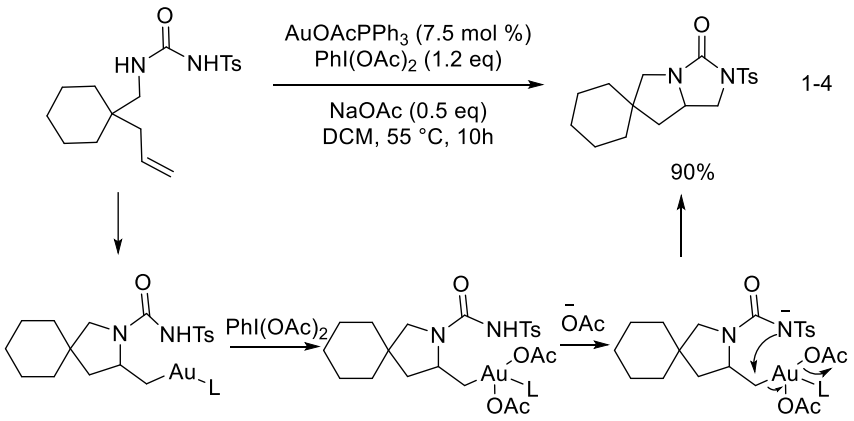
Scheme 1-2: Mechanism for Michael's Alkene Diamination



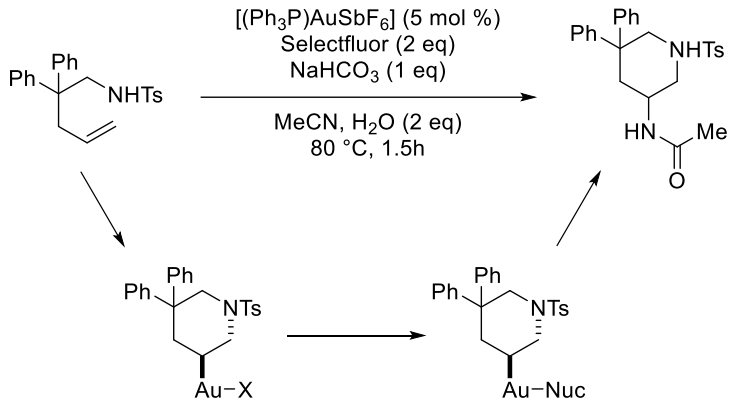
Following this discovery, Michael later reported a mechanistic study in which the stereochemical outcomes of the aminopalladation were elucidated, as well as an alternative to a previously expected reductive elimination step.[10] Michael's proposed mechanism for the alkene diamination (Scheme 1-2) begins with anti-aminopalladation of nucleophile **1-2** to Pd(II) intermediate **Int 1-3**. Oxidative addition of **1-1** leads to Pd(IV) intermediate **Int 1-4**. Afterwards, ligand dissociation of the benzenesulfonimide anion is proposed to reach **Int 1-5**. S_N2 substitution of the Pd(IV) species with the benzenesulfonimide anion is proposed to generate the desired product **1-6** while regenerating the Pd(II) species for catalytic turnover.

1.3 Gold-Catalyzed Alkene Diamination Reactions

In 2009, Muñiz reported a homogeneous Au(I/III)-catalyzed intramolecular alkene diamination to synthesize 5,5- and 6,5- fused bicyclic ureas (eq 1-4).[11] This reaction is one of the very few examples of homogeneous gold oxidation catalysis and proceeds with high selectivity under mild conditions when using hypervalent iodine reagents as an added oxidant. The key step involves intramolecular C–N bond formation from a Au(III) intermediate, which validates the concept of a reductive elimination from a high oxidation state for this type of C–N bond forming reaction.

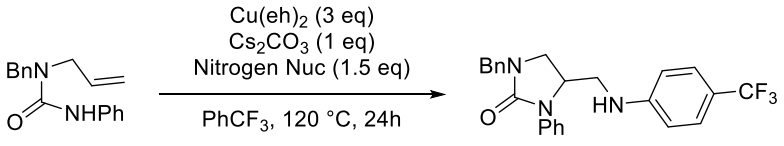


In 2011, Nevado et. al. reported a flexible Au-catalyzed oxidative diamination of unactivated alkenes with Selectfluor as an added oxidant and nitrile solvents acting as nucleophiles, which can then undergo hydrolysis to the corresponding amide (1-5).[12] A 6-endo *anti*-aminoauration is proposed and by using Selectfluor, the oxidation from Au(I) to Au(III) is possible and allows for a solvent-fluorine ligand exchange, due to the high electrophilicity of the Au(III) center, when an acetonitrile solvent is used. From there, a reductive elimination yields the desired product.



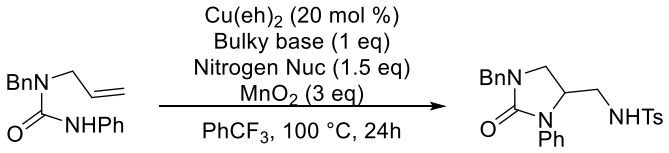
1-5

1.4 Copper-Catalyzed Alkene Diamination Reactions



1-6

97%

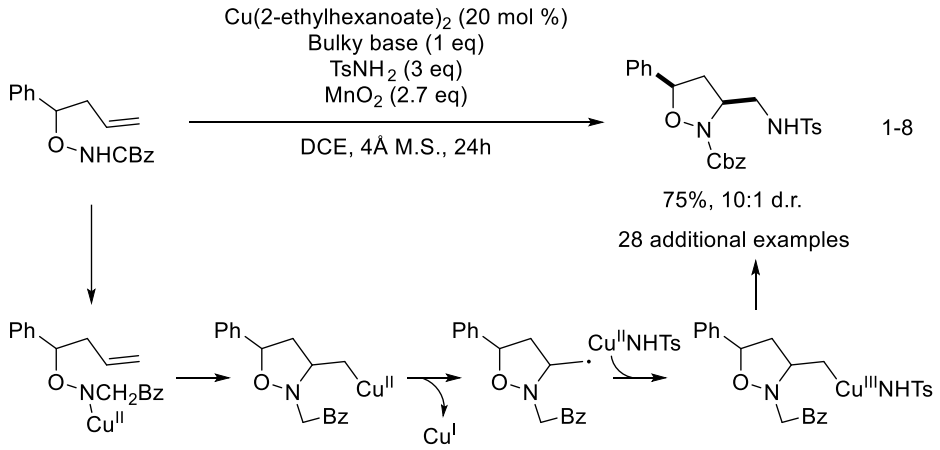


1-7

72%

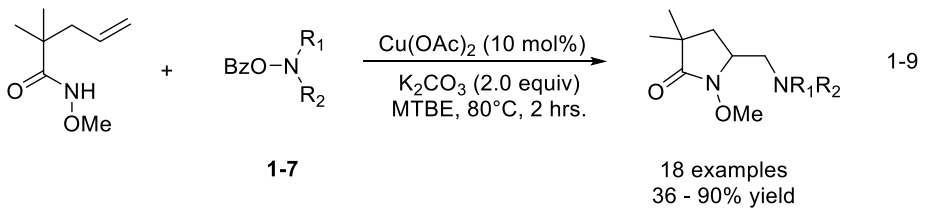
Aside from Pd- and Au- catalysis, Cu-catalysis has been widely studied in transition metal-catalyzed alkene diamination chemistry. In 2010, Chemler et. al., reported on a Cu-promoted (eq 1-6) and Cu-catalyzed (eq 1-7) method to form cyclic urea substrates using nitrogen nucleophiles.[813] One of the benefits of this method is that copper is more abundant and cheaper than palladium or gold catalysts. However, stoichiometric amounts of copper are often needed for the desired chemical reactivity to occur. When using aniline or azide nucleophiles as coupling partners, 3 equivalents of copper are required for desired reactivity. If the nucleophile is replaced with a sulfamide, catalytic inter- and intra-molecular alkene diamination proceeds efficiently. This finding significantly limits the nucleophile and electrophile scope as catalytic reactivity is preferred to limit cost.

Later in 2017, Chemler et. al. reported an elegant stereoselective Cu-catalyzed alkene diamination for the synthesis of isoxazolidines (eq 1-8).[14] This reported method is well tolerant of sulfonamide, aniline, and secondary cyclic amine nucleophiles (yields between 34% - 92%). The diastereoselectivity for this method also range from 3:1 – 20:1 d.r.. The proposed key catalytic step in this method involves a homolysis of the carbon-Cu(II) bond to give Cu(I) and a carbon radical which is then added to Cu(II) to generate

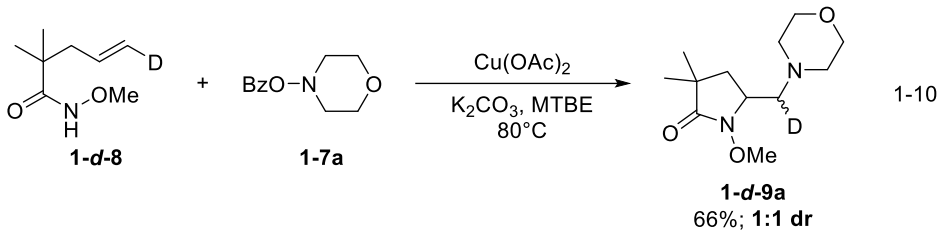


an amine-coordinated Cu(III) intermediate. From this intermediate, reductive elimination leads to the desired isoxazolidines and Cu(I) which then oxidizes to Cu(II) by way of MnO_2.

In 2015, Wang et. al. reported a Cu-catalyzed regio- and stereoselective diamination of unactivated alkenes using aminobenzoates **1-7** as electrophilic nitrogen sources (eq 1-9).[1015] The electrophiles are synthesized from their amine precursors allowing for a wide array of products to be formed. However, the method requires α-substitution on the amide to instill the Thorpe-Ingold effect. In addition, when a single

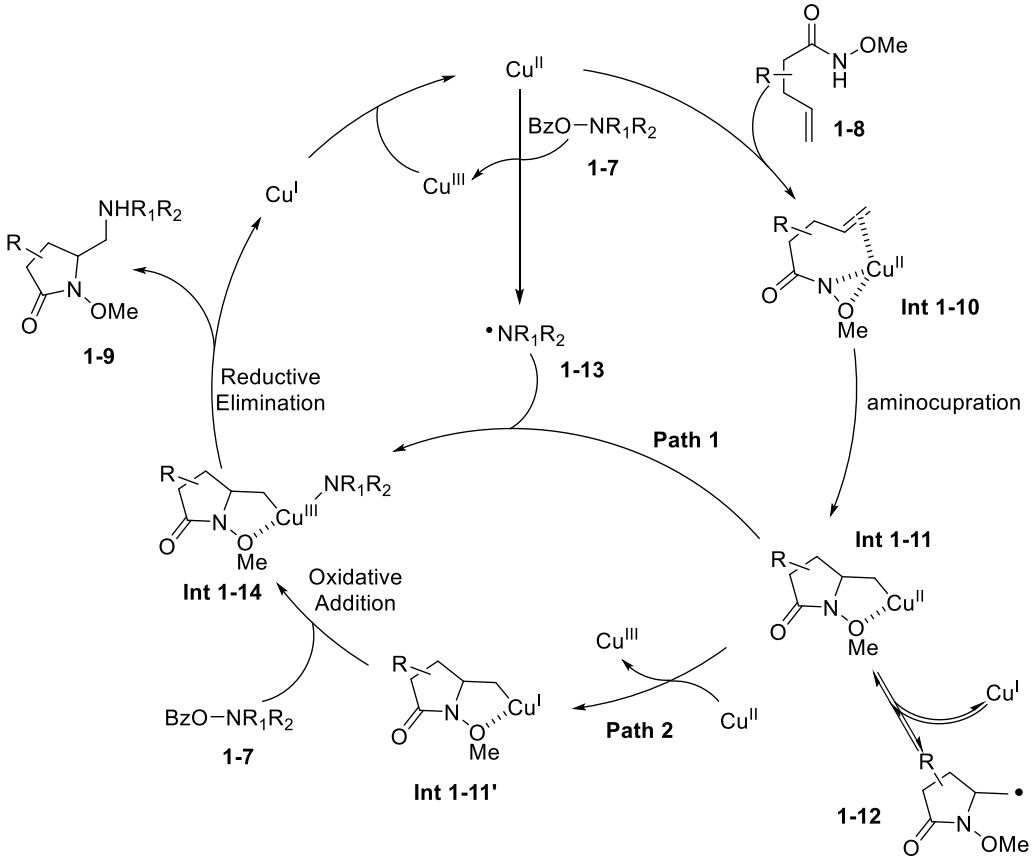


stereoisomer of the deuterium-labeled homoallyic amide **1-*d*-8** and morpholinobenzoate **1-7a** is used, they obtain a 1:1 mixture of diastereoisomers **1-*d*-9a** (eq 1-10). This lack of stereospecificity is likely due to the radical mechanism of the Cu catalysis as observed in the work by Chemler.



The proposed mechanism (Scheme 3-5) begins with association of the Cu(II) species to the alkene, nitrogen, and oxygen of 1-8 to yield **Int 1-10** followed by aminocupration to give **Int 1-11**. **Int 3-11** combines with amino radical **1-13** to form Cu(III) intermediate **1-14** and reductive elimination yields desired product **1-9** and Cu(I). The

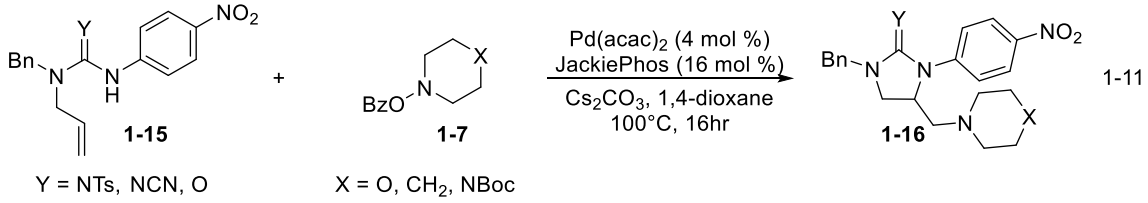
Scheme 1-3: Mechanism for Wang's Cu-Catalyzed Alkene Diamination



Cu(I) can be oxidized by Cu(III) that is formed by the reduction of **1-7**. There is a second proposed pathway in which **1-11** is reduced by Cu(II) to form Cu(III) and **1-11'**. From here, **1-11'** can undergo oxidative addition with **1-7** and then follow the same pathway previously discussed from **1-14**. It is theorized that presence of Cu(I) in the system can react with **1-11** by an equilibrated homolysis of the carbon-Cu(II) bond to generate the carbon radical species **1-12**. This equilibrium would explain the 1:1 dr of **1-*d*-9a** as the formation of the carbon radical would scramble the stereocenter of **1-*d*-8**.

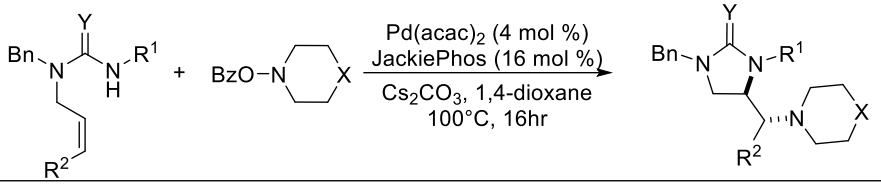
1.5 Our Lab's Initial Studies Regarding Pd-Catalyzed Alkene Diamination

In 2018, Peterson, Kirsch, and Wolfe reported the Pd-catalyzed alkene diamination of guanidines and ureas bearing tethered alkenes **1-15** with aminobenzoate derivatives **1-7** such as morpholinobenzoate **1-7a** (eq 1-11).[16] These transformations provide cyclic guanidines or ureas bearing appended aminoalkyl groups **1-16** in good to excellent chemical yield. However, cyclic aminobenzoate electrophiles were the only suitable electrophiles for this transformation. Attempting to use an acyclic aminobenzoate or primary aminobenzoate electrophile resulted in no product formation, oftentimes resulting ina complex mixture of products.



In addition, reactions involving deuterated alkene substrates proceed with modest diastereoselectivity, favoring products resulting from *anti*-addition of the two nitrogen atoms to the alkene (Table 1-1).

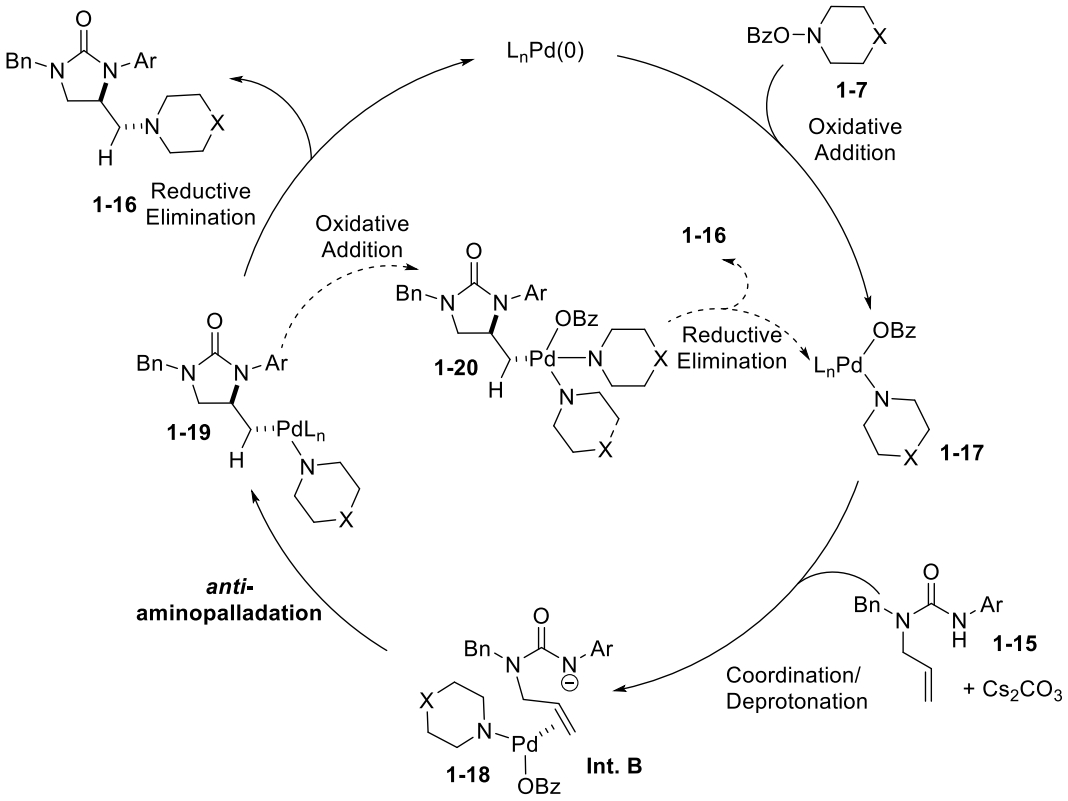
Table 1-1: Scope of Previously Reported Alkene Diamination



Entry	Y	R^1	R^2	X	diasteriomeric ratio, dr	Yield (%)[b]
1	O	C_6H_4-*p*-NO_2	D	O	6:1	75
2	N-Ts	Bn	D	O	6:1	75
3	N-Ts	Bn	D	CH_2	7:1	76
4	N-CN	Bn	D	O	3:1	67
5	O	C_6H_4-*p*-NO_2	H	O	-	90
6	O	C_6H_4-*p*-Cl	H	O	-	45
7	N-CN	Bn	H	CH_2	-	92
8	N-CN	Bn	H	NBoc	-	61

It was initially hypothesized that the mechanism of these reactions is similar to that of related alkene carboamination reactions between **1-15** and aryl halide or triflate electrophiles and likely involves a typical Pd(0)/Pd(II) catalytic cycle (Scheme 1-4, Path A) that is initiated by oxidative addition of **1-7** to the Pd metal center to afford **1-17**.[17] Subsequent coordination of the alkene group of **1-15** to the metal followed by alkene aminopalladation[18] (**1-18** – **1-19**) and then reductive elimination from **1-19** would afford the product **1-16**.[19] However, a Pd(II)/Pd(IV) catalytic cycle in which **1-19** was oxidized to **1-20** by additional **1-7**[20] followed by reductive elimination to generate **1-16** and **1-17** also seemed plausible.

Scheme 1-4: Previously Proposed Mechanism of Wolfe's Alkene Diamination



1.6 Conclusions

Transition metal-catalyzed alkenes (such as Pd-, Au, and Cu-catalyzed systems to name a few) have been reported for the synthesis of *N*-heterocycles such as ureas, guanidines, lactams, piperidines, and isoxazolidines to name a few. However, most of these methods suffer from i) the necessity of external oxidants such as hypervalent iodine, Cu oxidants, or MnO_2, ii) limited nucleophile and electrophile scope due to limited access of nitrogen electrophile sources or the intrinsic reactivity of the system such as in the cases of Scheme 1-1 and iii) lack of stereospecificity due to potential radical pathways such as eq 1-10. We are interested in tackling some of these key limitations and building upon these alkene diamination methods in our group using Pd-catalysis.

In the following chapter, I describe new experiments that have to a revision of this original mechanistic hypothesis, along with the discovery that acac (2,4-pentanedione) and simple acac derivatives bearing substituted arenes serve as highly effective ligands for this transformation. These discoveries have also allowed for significant expansion in scope with respect to the electrophile structure. The results of this work are detailed in Chapter 2.

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Chapter 2

Pd-Catalyzed Alkene Diamination Reactions with O-Benzoylhydroxylamine Electrophiles: Evidence Supporting a Pd(II/IV) Catalytic Cycle, the Role of 2,4-Pentanedione Derivatives as Ligands, and Expanded Substrate Scope

2.1 Introduction

As previously discussed in Chapter 1, in 2018 we reported the Pd-catalyzed alkene diamination of guanidines and ureas bearing tethered alkenes with *O*-acylated hydroxylamine derivatives to provide cyclic guanidines or ureas bearing appended aminoalkyl groups in good to excellent chemical yield (Chapter 1, Table **1-1**).[13] In addition, reactions involving deuterated alkene substrates proceed with modest diastereoselectivity favoring products resulting from anti-addition of the two nitrogen atoms to the alkene.

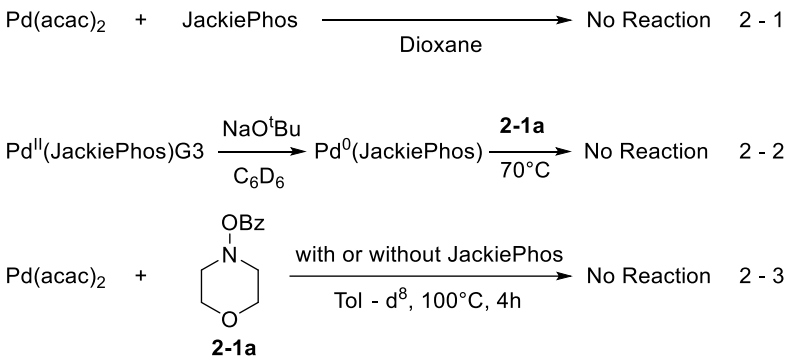
It was initially hypothesized that the mechanism of these reactions is similar to alkene carboamination reactions, involving a Pd(0)/Pd(II) catalytic cycle (Chapter 1, Scheme **1-5**).[13] In this chapter, we describe new experiments that have led us to revise our mechanistic hypothesis, along with the discovery that acac (2,4- pentanedione) and simple acac derivatives that serve as highly effective ligands for this transformation leading to an expanded nucleophile and electrophile scope for the transformation.

The work described in this chapter was published in the Journal of Organic Chemistry[23] and was adapted with permission from Kirsch, J. K.; Gonzalez, G. A., Faculak, M. S.,

Wolfe. J. P. “Pd-Catalyzed Alkene Diamination Reactions with O-Benzoylhydroxylamine Electrophiles: Evidence Supporting a Pd(II/IV) Catalytic Cycle, the Role of 2,4-Pentanedione Derivatives as Ligands, and Expanded Substrate Scope” *J. Org. Chem*, **2021**, *86*, 11378. Copyright (2021) American Chemical Society.

2.2 Control Experiments and Precatalyst Effects.

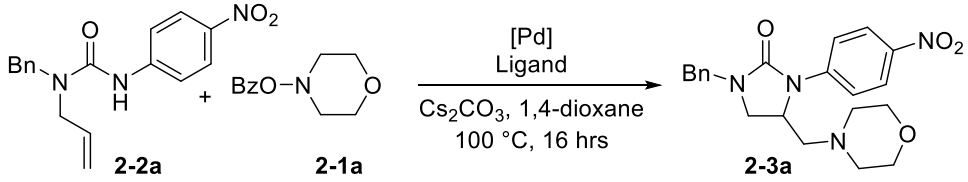
Following our preliminary studies, we set out to further examine this reaction and its mechanism (Equations 2-1 – 2-3). We elected to first explore the putative oxidative addition of the morpholinobenzoate electrophile **2-1a** to either Pd(0) or Pd(II). However, in initial scouting experiments, we were surprised to find that the phosphine ligand JackiePhos did not bind to $Pd(acac)_2$ as judged by a lack of change in the ^{31}P nuclear magnetic resonance (NMR) chemical shift of JackiePhos versus the mixture of JackiePhos and $Pd(acac)_2$ (eq 2-1).



In order to explore the possibility of oxidative addition to a Pd(0)/JackiePhos complex, we carried out NMR studies, in which the Buchwald Pd(II)(JackiePhos) G3 precatalyst was reduced in situ, as judged by ^{31}P NMR analysis,[1] and then treated with **2-1a** (eq 2-2). Surprisingly, we saw no evidence for oxidative addition of 2a to this Pd(0) complex. In addition, we did not observe any evidence for oxidative addition of **2-1a** to

the Pd(II) complex $Pd(acac)_2$ at 100°C, either with or without JackiePhos present (eq 2-3).[2] The results of these experiments immediately suggested two things: (i) since JackiePhos does not appear to bind to $Pd(acac)_2$, it may not be the actual ligand for Pd in these alkene diamination reactions and (ii) our original mechanistic hypothesis is likely incorrect, as the proposed initial oxidative addition step does not appear to be viable with this catalyst system. Given these results, we decided to revisit the influence of the precatalyst and ligand on the outcome of the coupling reactions between **2-1a** and *N*-allylurea substrate **2-2a**. We had previously reported that the coupling of **2-1a** with **2-2a** in the presence of Cs_2CO_3, $Pd(acac)_2$, and JackiePhos afforded a 90% yield of the desired product **2-3a** (Table 2-1, entry 1). We first carried out the key control experiment, in which JackiePhos was omitted from these conditions,[3] and obtained essentially the same result as that when JackiePhos was included (entry 2). This result suggests that the actual ligand for Pd is acac, not JackiePhos, and is further supported by the fact that $Pd(TFA)_2$ or other simple palladium precatalysts alone gave poor results (entries 3−5), but use of $Pd(TFA)_2$ and acac provided **2-3a** in 95% yield (entry 6).

Table 2-1: Precatalyst Effects on Yield of **2-3a**[a]



2-2a **2-1a** **2-3a**

entry	[Pd]	Ligand (mol %)	Yield (%)[b]
1	$Pd(acac)_2$	JackiePhos (16 mol %)	90[c]
2	$Pd(acac)_2$	none	95
3	$Pd_2(dba)_3$	none	43
4	$Pd(OAc)_2$	none	24
5	$Pd(TFA)_2$	none	35
6	**$Pd(TFA)_2$**	**acac (8 mol %)**	**95**

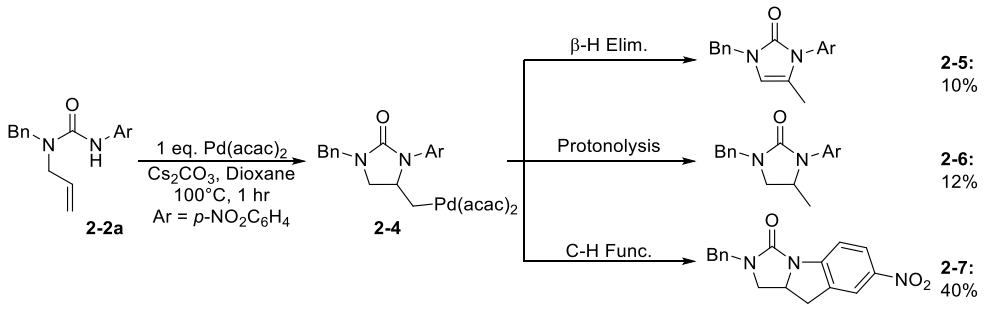
[a]Conditions: 1.0 equiv **2-2a**, 3.0 equiv **2-1a**, 4 mol % [Pd], 2 equiv Cs_2CO_3, dioxane (0.1 M), 100°C, and 16 h. [b]Yields were determined by 1H NMR analysis using phenanthrene as an internal standard. [c]Isolated yield reported in *Org. Lett.*, **2018**, *20*, 3513. Thank you to Janelle Kirsch for conducting these experiments

2.3 Revised Mechanistic Hypothesis and Stereochemical Details.

Given that the experiments described in Equations 2-1 – 2-3 and in Table 2-1 indicated that our initial mechanistic hypothesis (Chapter 1: Scheme 5) is not correct, we sought to gain additional information about the mechanism of these transformations. Michael's previously reported Pd-catalyzed alkene diamination reactions of protected amino alkenes with *N*-fluorobenzenesulfonimide have been shown to proceed via initial anti-aminopalladation of the alkene, followed by oxidative addition of the electrophile to an alkyl Pd(II) complex and subsequent reductive elimination with inversion of configuration from the resulting Pd(IV) intermediate.[3] In order to probe whether our

reactions may proceed via a similar mechanism, we first sought to confirm that alkene aminopalladation could occur in the absence of the electrophile. As such, **2-2a** was treated with Cs_2CO_3 and a stoichiometric amount of $Pd(acac)_2$. These conditions afforded a roughly 1:1:4 mixture of products **2−5 – 2-7** in 62% combined NMR yield (Scheme 2-1). All three of these products likely arise from alkene aminopalladation (**2-2a to 2-4**), with **2-5** likely derived from β-hydride elimination of **2-4** followed by alkene isomerization. The β-hydride elimination generates an equivalent of H-Pd(acac), which can react with **2-4** to afford **2-6**. Finally, **2-7** derives from aryl C−H functionalization of **2-4**. As such, the presence of the electrophile is not required for alkene aminopalladation to occur, and $Pd(acac)_2$ is effective at inducing alkene aminopalladation of **2-2a** under our otherwise standard reaction conditions.

Scheme 2-1: Stoichiometric Reaction in the Absence of Electrophile

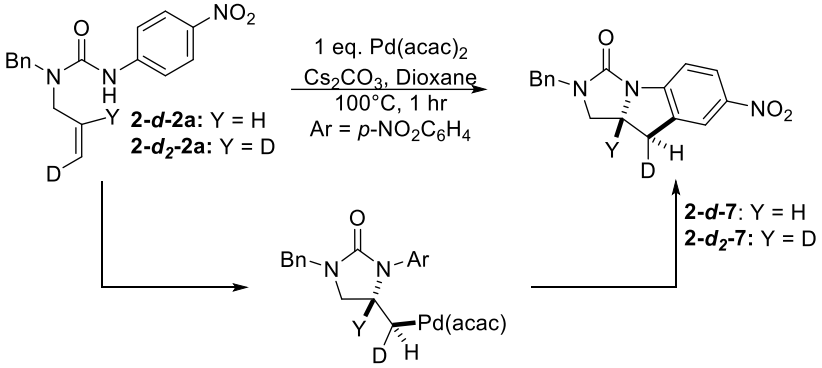


Experimentation Done by Janelle Kirsch

Since product **2-*d*-3a** results from net anti-addition to the alkene, we sought to gain additional information about the stereochemistry of alkene aminopalladation and reductive elimination. The overall anti-addition could result from either anti-aminopalladation followed by reductive elimination with retention of configuration or may derive from syn-amino-palladation and subsequent reductive elimination with inversion of configuration.[4] In order to determine the alkene addition stereochemistry, we elected to

take advantage of the relatively facile aminopalladation/C−H functionalization sequence described above (**2-2a to 2-4**). As shown in Scheme 2-2, treatment of deuterated alkene substrate **2-*d*-2a** with $Pd(acac)_2$ and Cs_2CO_3 in the presence or absence of JackiePhos afforded **2-*d*-7** in modest yields (37% and 20%, respectively), with ca. 1.5:1 diastereoselectivity favoring the product resulting from anti-aminopalladation.[5]

Scheme 2-2: Stereochemistry of Alkene Aminopalladation[a]

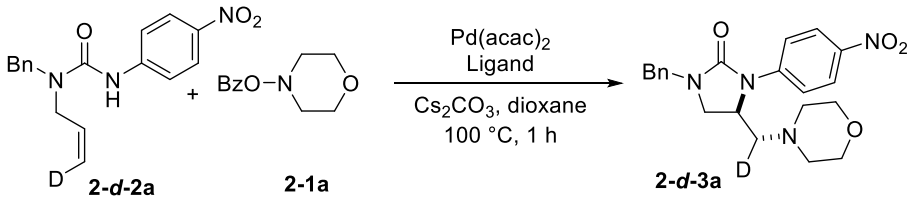


entry	Y	ligand	dr	yield[b]
1	H	JackiePhos	1.7:1	37%
2	H	none	1.5:1	20%
3	D	none	1.6:1	38%

[a]Conditions: 1.0 equiv 1d or 1e, 1 equiv $Pd(acac)_2$, 2 equiv ligand, 2 equiv Cs_2CO_3, dioxane (0.1 M), 100°C, and 1 h. [b]Yields for entries 1and 2 are isolated yields, whereas the yield for entry 3 was determined by 1H NMR analysis using phenanthrene as an internal standard. Thank you to Janelle Kirsch for conducting these experiments.

Given the low diastereoselectivity of the conversion of **2-*d*-2a** to **2-*d*-7** (ca. 1.5:1 dr) relative to that for the conversion of **2-*d*-2a** to **2-*d*-3a** (Table 2-2 and 6:1 dr), it seemed possible that the aminopalladation stereoselectivity was being eroded by reversible β-hydride elimination from complex **2-*d*-4**.[6]

Table 2-2: Effect of Electrophile Concentration and the Ligand on Anti-Addition Stereoselectivity[a]



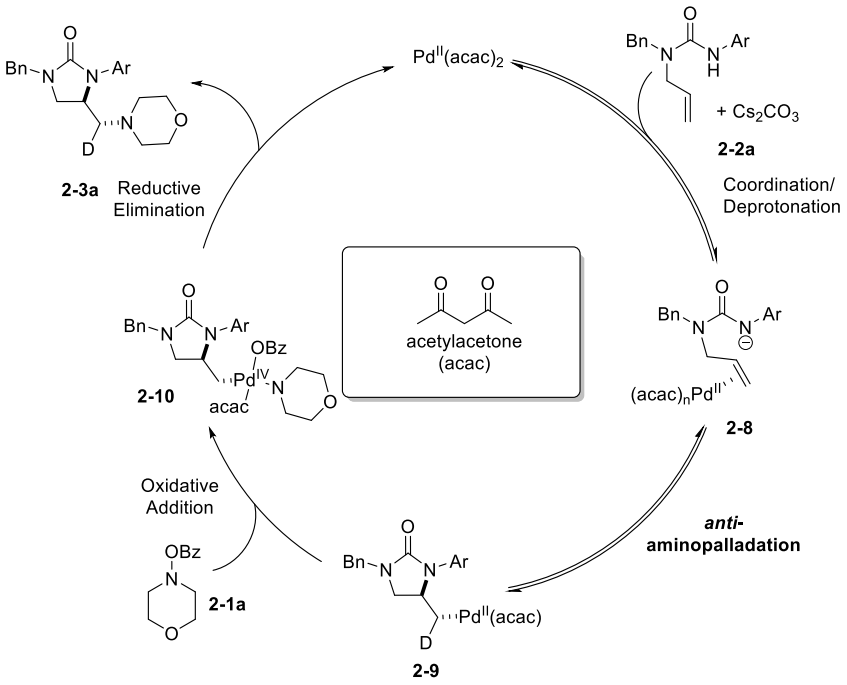
entry	equiv **2-1a**	Ligand	dr	Yield (%)[b]
1	3.0	JackiePhos	6:1	75[c]
2	3.0	none	6:1	74
3	1.5	JackiePhos	2.2:1	79
4	1.5	none	2.8:1	76

[a]Conditions: 1.0 equiv **2-*d*-2a**, 3.0 equiv **2-1a**, 4 mol % [Pd], 2 equiv Cs_2CO_3, dioxane (0.1M), 100°C, and 16 h. [b]Isolated Yield. [c]Isolated yield reported in *Org. Lett.*, **2018**, *20*, 3513.

However, the cyclization/C−H functionalization of di-deuterated substrate **2-*d*$_2$-2a**, which should undergo much slower β-deuterium elimination from complex **2-*d*$_2$-4** than the rate for β-hydride elimination from complex **2-*d*-4**,[7] proceeded with comparable (1.6:1) diastereoselectivity (Scheme 2-2, entry 3). Although the selectivity for anti- versus syn-aminopalladation is modest, this result suggests that since the overall conversion of **2-*d*-2a** to **2-*d*-3a** proceeds with net anti-addition, the C−N bond-forming reductive elimination must occur with retention of configuration. Thus, although these transformations are mechanistically similar to the reactions previously described by Michael,[6] the nature of the nitrogen nucleophile has an impact on the stereochemistry of reductive elimination. Transformations of the more electron-rich *O*-benzoyl hydroxylamine-derived electrophiles appear to involve stereoretentive reductive elimination, rather than stereoinvertive reductive elimination as observed with *N*-fluorobenzenesulfonimide by Michael.[6]

Collectively, the results of the experiments shown above suggest that the mechanism of this transformation involves initial and likely reversible anti-aminopalladation of the alkene to generate intermediate **2-*d*-4** from **2-*d*-2a** (Scheme 2-3).[8] Oxidative addition of the amine electrophile **2-1a** to **2-9** provides Pd(IV) intermediate **2-10**, and then, reductive elimination affords the observed product **2-3a** with regeneration of the Pd(II) catalyst.[9] Although our control experiments illustrate that **2-1a** does not undergo oxidative addition to $Pd(acac)_2$, the alkylpalladium complex **2-9** is considerably more electron-rich than $Pd(acac)_2$ and should undergo much more facile oxidative addition.

Scheme 2-3: Revised Mechanistic Hypothesis

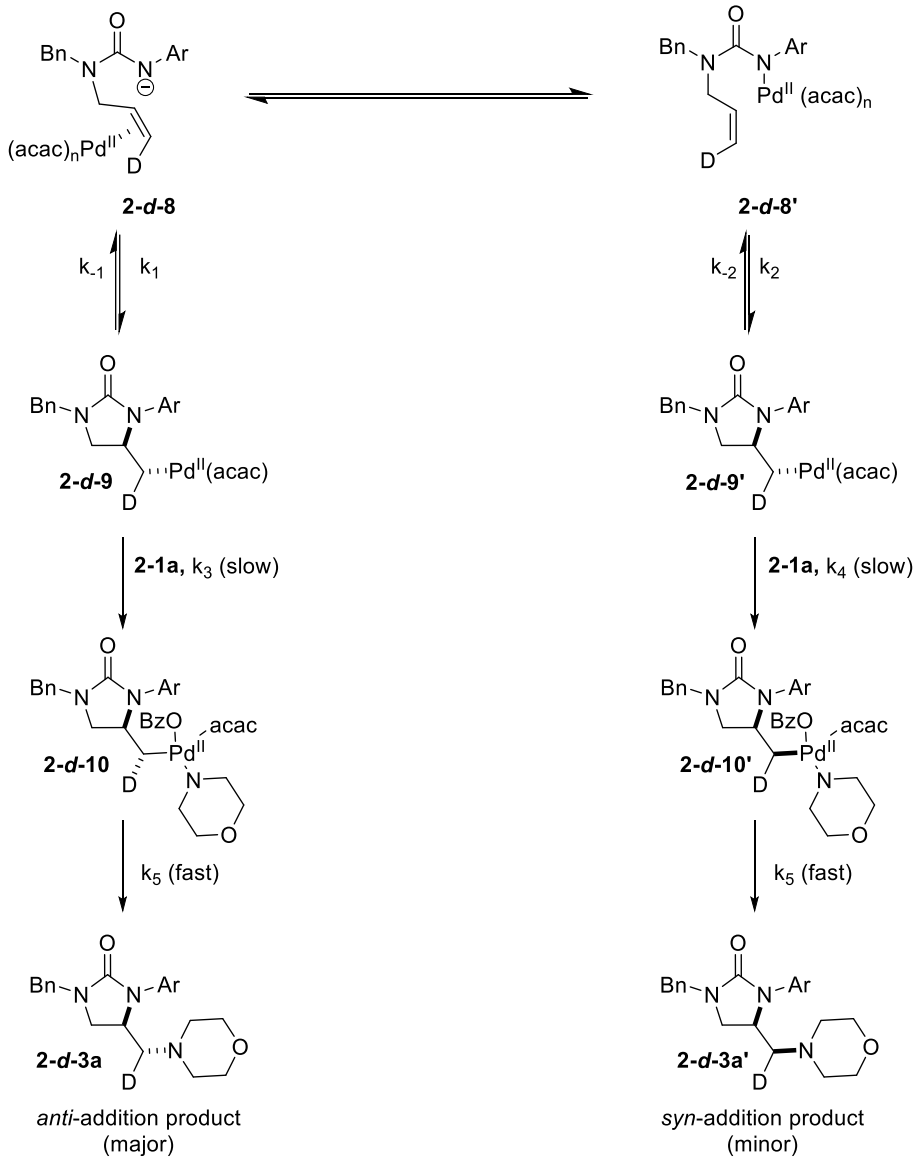


2.4 Effect of Electrophile Concentration on Stereoselectivity.

In our initial studies, we found that the $Pd(acac)_2$/JackiePhos-catalyzed coupling of **2-*d*-2a** with **2-1a** afforded **2-*d*-3a** in 75% yield and 6:1 dr (Table 2-2, entry 1).10 A similar outcome was obtained when $Pd(acac)_2$ alone (no phosphine) was used as the catalyst

for this reaction (entry 2). However, when the amount of **2-1a** was decreased to only 1.5 equiv, **2-*d*-3a** was generated in much lower diastereoselectivity (2.2:1 − 2.8:1 dr; entries 3 − 4), regardless of whether or not JackiePhos was present. This suggests that the stereoselectivity of this transformation is dependent at least to some extent on the rate of the oxidative addition step in the catalytic cycle. The influence of electrophile concentration on diastereoselectivity may be due to the relative rates of anti-aminopalladation/oxidative addition versus syn-aminopalladation, coupled with kinetic versus thermodynamic control of selectivity. As illustrated in Scheme 2-4, it is possible for **2-*d*-8** and **2-*d*-8′** to equilibrate through exchange of the coordinated alkene for the anionic urea nitrogen, with displacement of an acac ligand. If anti-aminopalladation of **2-*d*-8** to **2-*d*-9** is faster than syn-aminopalladation of **2-*d*-8′** to **2-*d*-9’** ($k_1 > k_2$) and if the oxidative addition sequence from **2-*d*-9** to **2-*d*-10** is faster than retro-aminopalladation of **2-*d*-9** to **2-*d*-8** ($k_3 > k_{-1}$), then, the selectivity for the anti-addition stereoisomer **2-*d*-3a** should be relatively high.[10] On the other hand, anti-aminopalladation complex **2-*d*-9** and its syn-addition diastereomer **2-*d*-9’** are expected to be very close in energy, since they differ only in the configuration of an H/D stereocenter, and if oxidative addition is slow enough that **2-*d*-9** and **2-*d*-9′** equilibrate through reversible aminopalladation (k_{-1} and $k_2 > k_3$), stereoselectivity should be relatively low, as it would reflect the thermodynamic ratio of **2-*d*-9** and **2-*d*-9′**. The data shown in Table 2-2 are consistent with those in the former scenario ($k_1 > k_2$ and $k_3 > k_{-1}$) when the concentration of **2-1a** is relatively high. However, if the concentration of **2-1a** is relatively low, the rate k_3 of the bimolecular oxidative addition should decrease, and selectivity for the anti-addition product **2-*d*-3a** should erode, as is observed.

Scheme 2-4: Competing Stereochemical Pathways

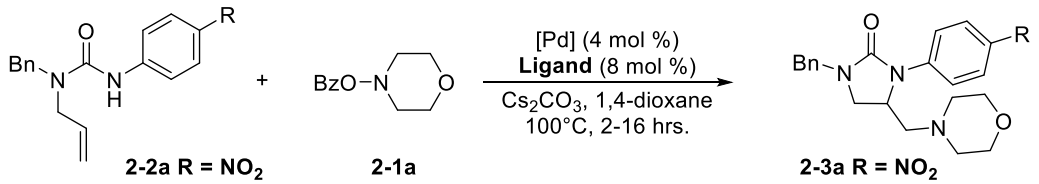


2.5 Influence of the acac Structure on Reactivity.

The use of acac as a "standalone" (no added phosphine) ligand in Pd-catalyzed cross-coupling reactions is extremely rare, and the influence of the acac ligand structure on reactivity in Pd-catalyzed reactions has not thoroughly been explored.[11] In order to determine whether the acac structure has an impact on reactivity or yield, we quickly screened Pd(acac-F_6)$_2$ as a catalyst for the coupling of **2-2a** with **2-1a** to afford **2-3a** (Table

2-3; entry 2). Interestingly, this complex bearing an electron-deficient acac derivative gave very poor results in comparison to the results obtained with $Pd(acac)_2$ (entry 1, 90% yield). This result indicated that the structure of the acac ligand does influence reactivity, in a profound manner. Accordingly, we explored the coupling of more challenging urea substrates **2-2b** and **2-2c** with several different acac-derived ligands (Table 2-3). With our original catalyst system of $Pd(acac)_2$/JackiePhos, the coupling of **2-2b** with **2-1a** afforded **2-3b** in only 45% isolated yield (entry 3).[10] By omitting JackiePhos and using only $Pd(acac)_2$ as a catalyst, we observed 74% NMR yield of **2-3b** (entry 4). Changing the ligand to **2-11, 2-12a,** or **2-12c** (entries 5, 6, and 8) resulted in significantly reduced yields. However, improved results were obtained with **2-12d** – **2-12f** (83−88%; entries 9−11). Finally, the best result was obtained with electron-rich analogue **2-12f** (84% isolated yield, entry 11). This ligand also provided considerably improved results in the reaction of **2-2c** with **2-1a**. Under our original conditions with JackiePhos as a ligand, only a trace amount of the desired product **2-3c** was obtained (entry 12). However, use of **2-12f** as a ligand in this reaction provided **2-3c** in 42% isolated yield (entry 14). Thus, it appears that JackiePhos inhibits catalysis for some substrate combinations.

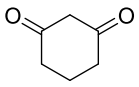
Table 2-3: Acac Ligand Effects[a]



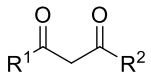
2-2a R = NO_2
2-2b R = Cl
2-2c R = OMe

2-1a

2-3a R = NO_2
2-3b R = Cl
2-3c R = OMe



2-11



2-12a: R^1 = N(H)Ph, R^2 = CH_3
2-12b: R^1, R^2 = CH_3
2-12c: R^1, R^2 = (*p*-CF_3)Ph
2-12d: R^1, R^2 = ^{t}Bu
2-12e: R^1, R^2 = Ph
2-12f: R^1, R^2 = (*p*-MeO)Ph

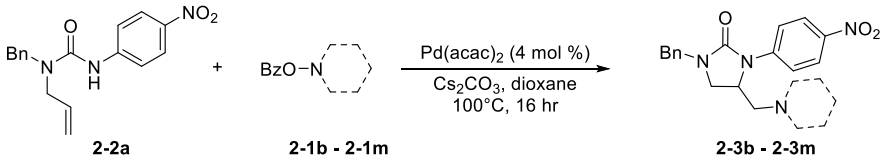
Entry	*R*	[Pd]	Ligand	Yield (%)[b]
1	NO_2	$Pd(acac)_2$	none	>95, (69)[c]
2	NO_2	$Pd(acac\text{-}F_6)_2$	none	11[d]
3	Cl	$Pd(acac)_2$	JackiePhos	87, (45)
4	Cl	$Pd(acac)_2$	none	74
5	Cl	$Pd(TFA)_2$	**2-11**	16[e]
6	Cl	$Pd(TFA)_2$	**2-12a**	24
7	Cl	$Pd(TFA)_2$	**2-12b**	77
8	Cl	$Pd(TFA)_2$	**2-12c**	trace
9	Cl	$Pd(TFA)_2$	**2-12d**	83
10	Cl	$Pd(TFA)_2$	**2-12e**	88
11	Cl	$Pd(TFA)_2$	**2-12f**[f]	94, (84)
12	OMe	$Pd(acac)_2$	JackiePhos	<5
13	OMe	$Pd(acac)_2$	none	30[e]
14	OMe	$Pd(TFA)_2$	**2-12f**[f]	75[e], (42)[e]

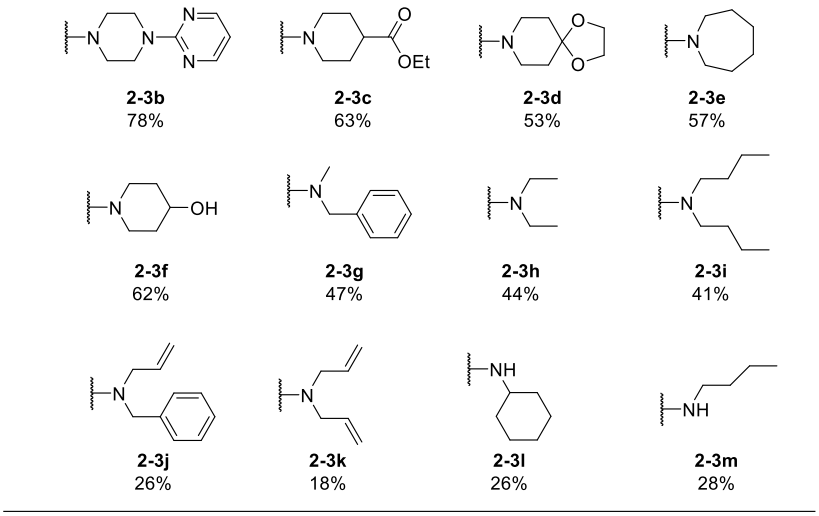
[a]Conditions: 1.0 equiv **2-2a, 2-2b, or 2-2c**, 1.5 equiv **2-1a**, 4 mol % [Pd], 8 mol % ligand, 2.0 equiv Cs_2CO_3, dioxane (0.1 M), 100°C, and 16 h .[b]Yields were determined by 1H NMR analysis using phenanthrene as an internal standard. Yields in parentheses are isolated yields. [c]The reaction was conducted for 1 h. [d]The reaction was conducted with 3.0 equiv **2-1a.** [e]Isolated yield from *Org. Lett.*, **2018**, *20*, 3513. Thank you to Janelle Kirsch (Entries 1-5), Mason Faculak (Entries 6-9), and Michael Gatazka (Entries 9-11) for helping conduct these experiments.

2.6 Further Exploration of Substrate Scope.

Given the observation that JackiePhos may inhibit catalysis in some systems, along with the fact that we have only successfully coupled electrophiles derived from cyclic amines, JackiePhos was omitted from the reaction and various nitrogen electrophiles (**2-1b** – **2-1m**) were employed to expand on the scope (Table 2-4). Fruitfully, upon omission of JackiePhos, the alkene diamination reaction now supports a variety of electrophiles with various functionality. Cyclic six-membered aminobenzoate electrophiles (**2-1b** – **2-1d, 2-1f**) were well tolerated. Coupling **2-2a** and azepan-1-yl benzoate electrophile **2-1e** afforded the corresponding product **2-3e** in 57% yield. This is in contrast with prior experimentation where employing JackiePhos as ligand did not provide any desired product. Coupling **2-2a** with acyclic aliphatic amine electrophiles (**2-1g** – **2-1i**) afforded the corresponding products **2-3g** – **2-3i**, whereas with JackiePhos as ligand no desired product was observed. Coupling **2-2a** with acyclic unsaturated aminobenzoate electrophiles (**2-1j** – **2-1k**) and primary aminobenzoate electrophiles (**2-1l** – **2-1m**) afforded the corresponding products (**2-3j – 2-3m**) albeit in depreciated yields. This is due to the reactive alkene and reactive N-H protons that can coordinate with the Pd/acac complex and undergo undesirable side reactions. This confirmed our suspicion that JackiePhos was debilitating for the reaction transformation.

Table 2-4: Electrophile Scope Upon Removal of JackiePhos[a,b]

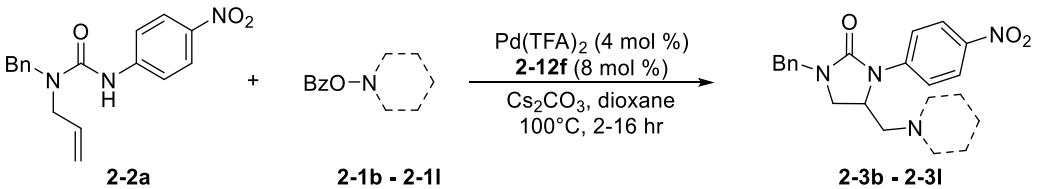




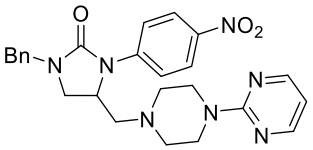
[a]Conditions: 1.0 equiv **2-2a**, 1.5 equiv **2-1b - 2-1m**, 4 mol % [Pd], 8 mol % ligand, 2.0 equiv Cs_2CO_3, dioxane (0.1 M), 100°C, and 16 h. [b]Yields represent unaveraged isolated yields.

With an optimized catalyst/ligand system in hand, the electrophile scope was revisited to explore the change in yield of selected products. As shown in Table 2-5, this catalyst system was effective for the preparation of cyclic ureas (**2-3b** – **2-3l**) with noticeably higher yields in all cases.

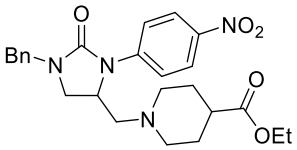
Table 2-5: Yield of Electrophile Scope with Optimized Ligand[a,b]



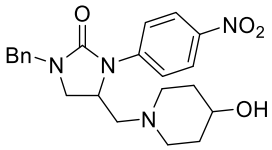
2-2a **2-1b - 2-1l** **2-3b - 2-3l**



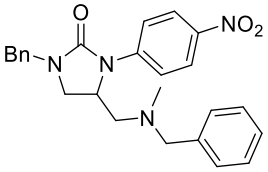
2-3b
85%



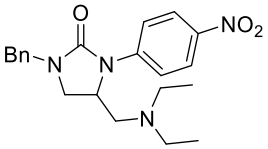
2-3c
75%



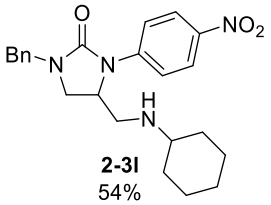
2-3f
64%



2-3g
78%



2-3h
72%

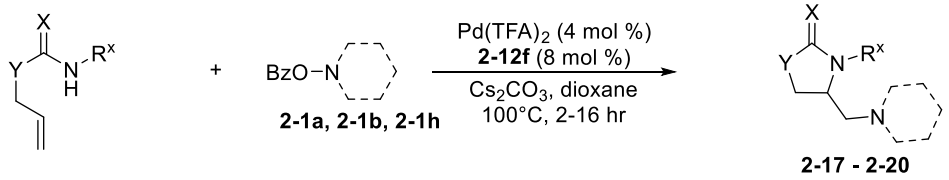


2-3l
54%

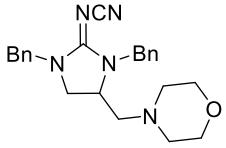
[a]Conditions: 1.0 equiv **2-2a**, 3.0 equiv **2-1b - 2-1m**, 4 mol % $Pd(TFA)_2$, 8 mol % **2-12f**, 2.0 equiv Cs_2CO_3, dioxane (0.1 M), 100°C, and 2-16 h. [b]Yields represent unaveraged isolated yields.

Next, an exploration into the nucleophile scope was conducted. Fortunately, the catalyst system was effective for the preparation of cyclic guanidines (**2-17a,h** and **2-18b,h**) and amides (**2-19a** and **2-20a**). However, the presence of a gem-dimethyl group adjacent to the amide carbonyl was necessary to obtain satisfactory results; a substrate lacking the gem-dimethyl group failed to react. This is presumably the result of a Thorpe−Ingold effect that facilitates the alkene aminopalladation step.

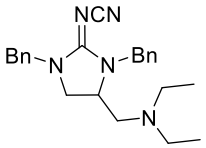
Table 2-6: Yield of Nucleophile Scope with Optimized Ligand[a,b]



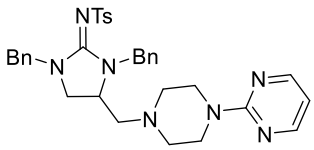
2-13: Y = NBn, X = NCN, R^1 = Bn **2-15:** Y = CMe_2, X = O, R^2 = OMe
2-14: Y = NBn, X = NTs, R^1 = Bn **2-16:** Y = CMe_2, X = O, R^3 = *p*-NO_2-C_6H_4



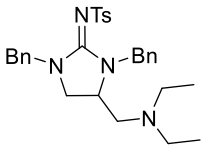
2-17a
74%



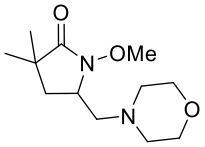
2-17h
55%



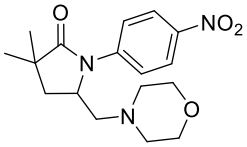
2-18b
75%



2-18h
64%



2-19a[c]
68%



2-20a[c]
68%

[a]Conditions: 1.0 equiv **2-13 - 2-16**, 3.0 equiv **2-1a, 2-1b, or 2-1h**, 4 mol % $Pd(TFA)_2$, 8 mol % **2-12f**, 2.0 equiv Cs_2CO_3, dioxane (0.1 M), 100°C, and 2-16 h. [b]Yields represent averaged isolated yields. [c]Experiments run by Mason Faculak

2.7 Summary and Considerations

In conclusion, through continued studies on Pd-catalyzed alkene diamination reactions involving *O*-benzoyl hydroxylamine electrophiles, we have demonstrated that phosphine ligands are not required and in some cases inhibit catalysis. Instead, acac or acac derivatives serve as the actual ligand for palladium that promotes reactivity in these transformations. In addition, we have illustrated that the structure of the acac ligand has a significant influence on reactivity, and this observation will likely find utility in other Pd-catalyzed reactions. We have also found that these transformations do not proceed via

our originally postulated Pd(0/II) catalytic cycle that was initiated by oxidative addition of the *N*-electrophile to Pd(0). Instead, catalysis cycles through Pd(II)/Pd(IV) oxidation states and is initiated by alkene amino-palladation. In comparison of our results with those of Michael, it appears that the stereochemical outcome of the reductive elimination from Pd(IV) is dependent on the nucleophilicity/basicity of the *N*-electrophile, with basic amines favoring reductive elimination with retention of configuration. Finally, this new catalyst system has allowed for a significant expansion of the scope of electrophiles that can be employed as coupling partners; now incorporating secondary acyclic aliphatic amines, secondary acyclic unsaturated amines, and primary aliphatic amines. The primary reason for this is because of the favorability of the catalyst system towards the Pd(II/IV) pathway.

2.8 Experimental

General: All reactions were carried out under a nitrogen atmosphere using oven or flame-dried glassware. All palladium sources and reagents including **2-11** and **2-12a-e** were obtained from commercial sources and used without further purification unless otherwise noted. *N*-Allylureas and guanidines **2-2a-c, 2-*d*-2a, 2-*d*$_2$-2a, 2-13, 2-14, 2-15, and 2-16**[12-14] ligands **2-12f**[15], and electrophiles **2-1a-l**[16-22] were prepared according to previously reported procedures. Dioxane was purified by distillation from Na metal and benzophenone. All yields refer to isolated compounds that are estimated to be ≥95% pure as judged by 1H NMR analysis unless otherwise noted. *The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in Schemes 2-5 & 2-6.*

Procedures for eq 2-1-3:

For eq 5-1: JackiePhos was added to an NMR tube and a ^{31}P NMR was taken. We observed two peaks, leading us to believe that the bottle contained both JackiePhos and JackiePhos-oxide. ^{31}P NMR (dioxane) δ 18.687, -19.401 ppm. Triphenylphosphine oxide was added to an NMR tube and a ^{31}P NMR was taken. ^{31}P NMR (dioxane) δ 20.950. JackiePhos and Triphenylphosphine oxide were added to an NMR tube and a ^{31}P NMR was taken. ^{31}P NMR (dioxane) δ 20.950, 18.546, -19.609

In an NMR tube, JackiePhos (104.5 mg, 0.13 mmol, 4 equiv), $Pd(acac)_2$ (10 mg, 0.033 mmol, 1 equiv), triphenylphosphine oxide (as a NMR reference std), and dioxane (2 mL) were shaken and a ^{31}P NMR was taken. ^{31}P NMR (dioxane) δ 20.950, 18.696, -19.429.

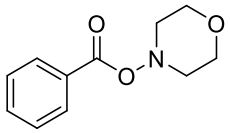
For eq 5-2: In an NMR tube, JakiePhosPdG3 (20 mg, 0.017 mmol, 1 equiv) and 1 mL of C_6D_6 were added and ^{31}P NMR and ^{1}H NMR were taken. NaOtBu (3 mg, 0.031 mmol, 1.8 equiv) was added and the NMR tube shaken and then ^{31}P NMR and ^{1}H NMR were taken. **2-1a** (3.6 mg, 0.017 mmol, 1 equiv) was added and the NMR tube shaken and then ^{31}P NMR and ^{1}H NMR were taken. The NMR tube was placed in an oil bath heated to 70 °C for 30 min and then ^{31}P NMR and ^{1}H NMR were taken. Evidence for oxidative addition was not observed.

For eq 5-3: $Pd(acac)_2$ (20 mg, 0.066 mmol, 1 equiv), **2-1a** (13.7 mg, 0.066 mmol, 1 equiv), and 1 mL of d_8-toluene were added to an NMR tube. A ^{1}H NMR was taken of the mixture at rt, after 15 minutes of heating at 95 °C, and after an additional 30 minutes of heating at 95 °C. Evidence of oxidative addition was not observed. A similar reaction was repeated by JPW and evidence of oxidative addition was not observed. $Pd(acac)_2$ (5 mg, 0.0164 mmol, 1 equiv), JackiePhos (26.1 mg, 0.0328 mmol, 2 equiv), **2-1a** (3.4 mg, 0.0164 mmol,

1 equiv), triphenylphosphine oxide (as a NMR reference std) and 1 mL of dioxane were added to an NMR tube. A ^{31}P NMR was taken of the mixture at rt, and after 15 minutes of heating at 95 °C. Evidence of oxidative addition was not observed.

Synthesis and Characterization of Substrates and Ligands:

General Procedure for the Synthesis of Amino Benzoate Electrophiles (2-1a – 2-1m)

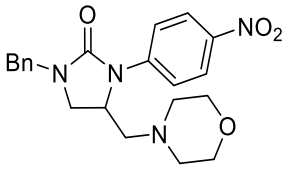


Morpholino benzoate (**2-1a**). Morpholine (.455 mL, 5.28 mmol, 1.2 equiv) was added to a stirring mixture of K_2HPO_4 (1.15 g, 6.59 mmol, 1.5 equiv), benzoyl peroxide (1.42 g, 4.40 mmol, 1.0 equiv) and DMF (11 mL, 0.4M). The reaction was stirred under Nitrogen atmosphere for 18 h. 50 mL of satd. Na_2CO_3 (aq) was added to the reaction and stirred for 20 minutes. 25 mL of EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc 3x 25 mL. The combined organic layers were washed with brine 1x 50 mL. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to afford 534 mg (58%) of the title compound as a white solid. The characterization data matched previously reported literature.[17]

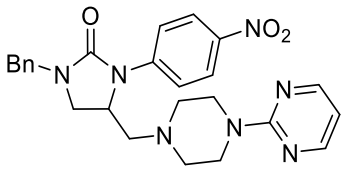
Preparation and Characterization of Products

General Procedure for Pd-Catalyzed Alkene Diamination Reactions: Tables 2-2-6, Schemes 2-2

A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of N_2 and charged with the appropriate palladium source (4 mol %), the appropriate ligand if used (8 mol %), the appropriate urea or guanidine (0.2 mmol, 1 equiv), the appropriate electrophile (0.6 mmol, 3.0 equiv) and cesium carbonate (0.4 mmol, 2 equiv). After purging the Schlenk tube with N_2, dioxane (2 mL, 0.1 M) was added and the reaction was headed to 100 ^oC for 16 h. The crude reaction mixture was filtered through cotton with diethyl ether and concentrated in vacuo. The crude product was then purified by flash chromatography on silica gel.

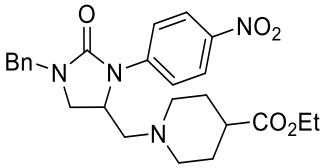


1-Benzyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (**2-3a**). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with morpholino benzoate (**2-1a**) (62.2mg, 0.3 mmol, 1.5 equiv) using a catalyst composed of $Pd(acac)_2$ (2.4mg, 0.008 mmol, 4 mol %), except the reaction was run for 1 h. The crude product was purified by flash chromatography on silica gel [10% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 56.5 mg (71%) of the title compound as a yellow solid. The characterization data matched previously reported literature.[13]



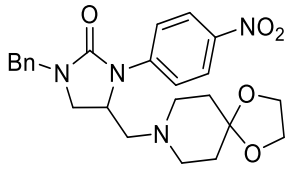
1-Benzyl-4-(morpholinomethyl)-3-(4-nitrophenyl)imidazolidin-2-one (**2-3b**). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with 4-

(pyrimidin-2-yl)piperazin-1-yl benzoate (**2-1b**) (113.7 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.5 mg, 0.016mmol, 8 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 85.9 mg (91%) of the title compound as a yellow oil. Omission of the ligand and using $Pd(acac)_2$ (0.008 mmol, 4 mol%) afforded 72.2 mg (78%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, 2 H), 8.21 (d, *J* = 9.3 Hz, 2 H), 7.76 (d, J = 9.2 Hz, 2 H), 7.40−7.29 (m, 5 H), 6.49 (dd, *J* = 6.6, 2.9 Hz, 1H), 4.51 (q, *J* = 14.9 Hz, 2H), 4.40 (m, 1 H), 3.75 (m, 4 H),3.53 (t, *J* = 8.8 Hz, 1H), 3.41 (d, *J* = 9.2 Hz, 1H), 2.64 (d, *J* = 13.0 Hz, 1 H), 2.59−2.53 (m, 2 H), 2.49−2.35 (m, 3 H); ^{13}C {^{1}H} NMR (126MHz, $CDCl_3$): δ 157.9, 129.0, 128.4, 128.1, 125.2, 117.6, 110.3, 59.2, 53.9, 51.3, 48.0, 46.1, 43.7; IR (film) 2925, 2851, 1709, 1585, 1548,1501 cm^{-1}; HRMS (ESI TOF)m/z: $[M+H]^+$ calcd for $C_{25}H_{28}N_7O_3$, 474.2255; found, 474.2251.



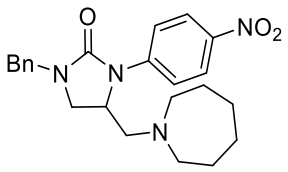
Ethyl 1-{[1-Benzyl-3-(4-nitrophenyl)-2-oxoimidazolidin-4-yl]-methyl}piperidine-4-carboxylate (**2-3c**). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with ethyl piperidine-4-carboxylate (**2-1c**) (111.0 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.5mg, 0.016 mmol, 8 mol %). The

crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 75.0 mg (81%) of the title compound as a yellow oil. Omission of the ligand and using $Pd(acac)_2$ (0.008 mmol, 4 mol%) afforded 58.8 mg (63%) of the title compound as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.3 Hz, 2 H), 7.75 (d, *J* = 9.3 Hz, 2 H), 7.39−7.29 (m, 5 H), 4.49 (q, *J* = 14.9 Hz, 2 H), 4.36−4.28 (m, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.48 (t, *J* = 8.9 Hz, 1 H), 3.34 (dd, *J* = 9.2, 2.6 Hz, 1 H), 2.86 (d, *J* = 11.1 Hz, 1 H), 2.64−2.51 (m, 2 H), 2.36 (dd, *J* = 12.9, 9.4 Hz, 1 H), 2.28−2.05 (m, 3 H), 1.84 (t, *J* = 14.8 Hz, 2 H), 1.73−1.61 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H); ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ 174.8, 156.4, 145.4, 141.9, 136.2, 128.9,128.6, 128.3, 128.1, 124.9, 117.4, 117.2, 60.4, 59.0, 54.5, 52.9, 51.4,51.3, 47.8, 46.0, 40.7, 28.2, 28.1, 14.3, 14.1; IR (film) 2927, 1714,1595, 1503 cm^{-1}; HRMS (ESI TOF) m/z: $[M+H]^+$ calcd for $C_{25}H_{31}N_4O_5$, 467.2296; found, 467.2297.

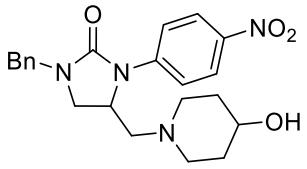


4-((1,4-dioxa-8-azaspiro[4.5]decan-8-yl)methyl)-1-benzyl-3-(4-nitrophenyl) imidazolidin-2-one (**2-3d**). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with 1,4-dioxa-8-azaspiro[4.5]decan-8-yl benzoate (**2-1d**) (79.0 mg, 0.4 mmol, 2.0 equiv) using a catalyst composed of $Pd(acac)_2$ (0.008 mmol, 4 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [20% 3:1 (ethyl acetate/ethanol) in hexanes]

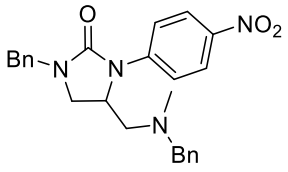
to afford 47.9 mg (53%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 11.5 Hz, 2H), 7.75 (d, *J* = 9.3 Hz, 2H), 7.39 – 7.24 (m, 5H), 4.48 (q, *J* = 8.6, 2H), 4.36 – 4.32 (m, 1H), 3.92 (s, 4H), 3.50 (t, *J* = 8.9 Hz, 1H), 3.36 (dd, *J* = 9.2, 2.9 Hz, 1H), 2.67 – 2.58 (m, 2H), 2.50 – 2.44 (m, 3H), 2.42 (dd, *J* = 13.1, 9.0 Hz, 2H), 1.73 – 1.60 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 221.9, 188.0, 181.4, 156.4, 145.3, 142.0, 136.2, 128.8, 128.3, 127.9, 125.0, 117.4, 111.2, 106.6, 64.3, 58.6, 52.2, 51.4, 47.8, 46.2, 34.7, 30.5, 19.8.



4-(azepan-1-ylmethyl)-1-benzyl-3-(4-nitrophenyl)imidazolidin-2-one (**2-3e**). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with azepan-1-yl benzoate (**2-1e**) (79.0 mg, 0.4 mmol, 2.0 equiv) using a catalyst composed of $Pd(acac)_2$ (0.008 mmol, 4 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [20% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 46.7 mg (57%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.4, 2.5 Hz, 2H), 7.76 (d, *J* = 9.5, 2.5 Hz, 2H), 7.40 – 7.24 (m, 5H), 4.54 (q, *J* = 14.9, 2.4 Hz, 2H), 4.28 – 4.24 (m, 1H), 3.46 (t, *J* = 8.54, 1H), 3.38 (d, *J* = 9.2, 2.6 Hz, 1H), 2.81 (d, *J* = 13.3, 3.6 Hz, 1H), 2.68 – 2.51 (m, 4H), 2.45 (t, *J* = 10.7, 9.4 Hz, 1H), 1.59 – 1.45 (m, 8H).

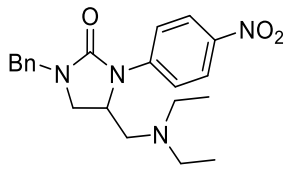


1-benzyl-4-((4-hydroxypiperidin-1-yl)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (**2-3f**). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with 4-hydroxypiperidin-1-yl benzoate (**2-1f**) (79.0 mg, 0.6 mmol, 3 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol%) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [35% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 52.4 mg (64%) of the title compound as a yellow oil. Omission of the ligand and using $Pd(acac)_2$ (0.008 mmol, 4 mol%) afforded 50.8 mg (62%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 9.0 Hz, 2H), 7.76 (t, *J* = 8.9 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.29 (m, 3H), 4.49 (q, *J* = 15.2 Hz, 2H), 4.41 – 4.24 (m, 1H), 3.74 – 3.61 (m, 1H), 3.57 – 3.44 (m, 1H), 3.41 – 3.31 (m, 1H), 2.79 (s, 1H), 2.67 – 2.52 (m, 2H), 2.47 – 2.11 (m, 3H), 1.88 – 1.75 (m, 2H), 1.46 (s, 2H).



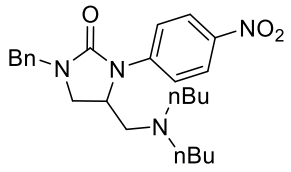
1-benzyl-4-((benzyl(methyl)amino)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (**2-3g**) The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with *N*-methylbenzylamino benzoate (**2-1g**) (97.0 mg, 0.4 mmol, 2 equiv) using a

catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol%) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 70.3 mg (82%) of the title compound as a yellow oil. Omission of the ligand and using $Pd(acac)_2$ (0.008 mmol, 4 mol%) afforded 40.3 mg (47%) of the title compound as a yellow oil. 1H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 9.3 Hz, 2H), 7.64 (d, *J* = 9.3 Hz, 2H), 7.38−7.25 (m, 8H), 7.21 (d, *J* = 6.6 Hz, 2H), 4.41 (q, *J* = 10.8 Hz, 2H), 4.21 (m, 1H), 3.52 (d, *J* = 12.9 Hz, 1H), 3.47−3.39 (m, 2H), 3.30 (dd, *J* = 9.1, 2.5 Hz, 1H), 2.60 (d, *J* = 2.7 Hz, 1H), 2.48−2.41 (m, 1H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 156.5, 145.5, 141.9, 138.5, 136.3, 129.2, 128.9, 128.6,128.4, 128.0, 127.7, 125.1, 117.3, 63.5, 57.6, 52.0, 47.9, 45.8, 44.0; IR(film) 2921, 2850, 1712, 1595, 1503 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{27}N_4O_3$, 431.2085; found, 431.2063



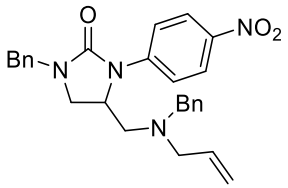
1-benzyl-4-((diethylamino)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (2-3h) The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with *N,N*-diethylaminobenzoate (**2-1h**) (97.0 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash

chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 56.6mg (74%) of the title compound as a yellow oil. Omission of the ligand and using $Pd(acac)_2$ (0.008 mmol, 4 mol%) afforded 33.5 mg (44%) of the title compound as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 2H), 7.77 (d, 2H), 7.39−7.27 (m, 5H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.37 (d, *J* = 14.8 Hz, 1H), 4.32−4.23 (m, 1H), 3.45 (t, *J* = 8.8 Hz, 1H), 3.37 (d, *J* = 9.1 Hz, 1H), 2.62 (d, *J* = 13.1 Hz,1H), 2.58−2.49 (m, 2H), 2.46−2.36 (m, 3H), 0.91 (t, *J* = 7.0 Hz, 6H); ^{13}C {^1H} NMR (126 MHz, CDCl3): δ156.4, 145.5, 141.8,136.3, 128.8, 128.3, 127.8, 125.0, 117.2, 53.9, 52.0, 47.8, 47.7, 45.7,11.8; IR (film) 2969, 1712, 1595, 1503 cm^{-1}; HRMS (ESI TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{27}N_4O_3$, 383.2085; found, 383.2078.

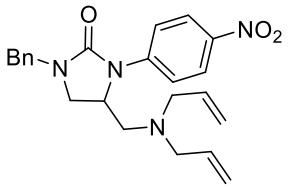


1-benzyl-4-((dibutylamino)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (2-3i). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with *O*-benzoyl-*N,N*-dibutylhydroxylamine (**2-1i**) (59.8 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(acac)_2$ (0.008 mmol, 4 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [15% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 36.3 mg (41%) of the title compound as a yellow oil. ^1H NMR (401 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.4 Hz, 2H), 7.77 (d, *J* = 9.1 Hz, 2H), 7.33 (h, *J* = 7.4, 6.9 Hz, 5H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.32 (d, *J* = 14.8 Hz, 1H),

4.29 – 4.21 (m, 1H), 3.48 – 3.35 (m, 2H), 2.64 – 2.57 (m, 1H), 2.46 – 2.37 (m, 3H), 2.34 – 2.25 (m, 2H), 1.32 – 1.14 (m, 8H), 0.90 – 0.82 (m, 6H).

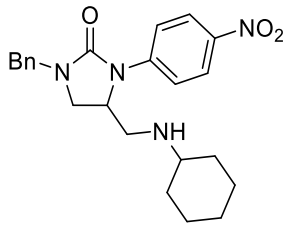


4-((allyl(benzyl)amino)methyl)-1-benzyl-3-(4-nitrophenyl)imidazolidin-2-one (2-3j). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with *N*-allyl-*O*-benzoyl-*N*-benzylhydroxylamine (**2-1j**) (59.8 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(acac)_2$ (0.008 mmol, 4 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 36.3 mg (41%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.3 Hz, 2H), 7.59 (d, *J* = 9.3 Hz, 2H), 7.40 – 7.27 (m, 5H), 5.83 – 5.69 (m, 1H), 5.22 – 5.12 (m, 2H), 4.37 (s, 2H), 4.13 – 4.04 (m, 1H), 3.60 (q, 2H), 3.37 – 3.23 (m, 2H), 3.16 (dd, *J* = 14.0, 6.1 Hz, 1H), 3.04 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.67 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.57 – 2.46 (m, 1H).



1-benzyl-4-((diallylamino)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (2-3k). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with

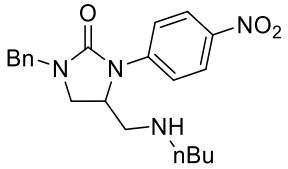
N,N-diallyl-*O*-benzoylhydroxylamine (**2-1k**) (130 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(acac)_2$ (0.008 mmol, 4 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 18 mg (18%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.1 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.37 – 7.29 (m, 5H), 5.74 – 5.63 (m, 2H), 5.40 – 5.27 (m, 1H), 5.20 – 5.04 (m, 4H), 4.60 (d, *J* = 9.5 Hz, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.47 – 3.32 (m, 2H), 3.19 – 3.08 (m, 2H), 3.05 – 2.94 (m, 2H), 2.62 (d, *J* = 13.2 Hz, 1H), 2.48 (t, *J* = 11.6 Hz, 1H).



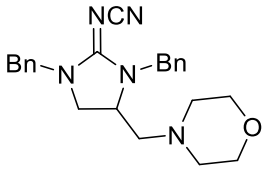
1-benzyl-4-((cyclohexylamino)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (2-3l)

The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with *O*-benzoyl-*N*-cyclohexylhydroxylamine (**2-1l**) (132 mg, 0.6 mmol, 3 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol 2%) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [40% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 46.2 mg (54%) of the title compound as a yellow oil. Omission of the ligand and using $Pd(acac)_2$ (0.008 mmol, 4 mol%) afforded 21.5 mg (26%) of the title compound as a yellow oil. 1H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.3 Hz, 2H), 7.77 (d, *J* = 9.2 Hz, 2H),

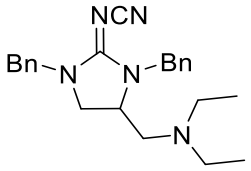
7.38−7.28 (m, 5H), 4.57 (d, *J* = 15.0 Hz, 1H), 4.42(d, *J* = 15.0 Hz, 1H), 4.33−4.25 (m, 1H), 3.49 (t, *J* = 9.1 Hz, 1H), 3.37 (dd, *J* = 8.9, 3.2 Hz, 1H), 2.86 (dd, *J* = 12.5, 2.6 Hz, 1H), 2.76(dd, *J* = 12.5, 7.7 Hz, 1H), 2.29 (m, 1H), 1.78−1.62 (m, 4H), 1.60−1.54 (m, 1H), 1.24−1.08 (m, 4H), 1.01−0.87 (m, 2H); ^{13}C {^{1}H}NMR (126 MHz, $CDCl_3$): δ 156.5, 145.2, 142.0, 136.2, 128.7, 128.2,127.8, 124.9, 117.6, 56.8, 53.3, 47.8, 46.9, 45.5, 33.7, 26.0, 24.8; IR(film) 2926, 2852, 1698, 1596 cm^{-1}; HRMS (ESI TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{29}N_4O_3$, 409.2234; found, 409.2230.



1-benzyl-4-((butylamino)methyl)-3-(4-nitrophenyl)imidazolidin-2-one (2-3m). The general procedure was used for the coupling of **2-2a** (62.3 mg, 0.2 mmol, 1 equiv) with *O*-benzoyl-*N*-butylhydroxylamine (**2-1m**) (130 mg, 0.4 mmol, 2 equiv) using a catalyst composed of $Pd(acac)_2$ (0.008 mmol, 4 mol %). The crude reaction mixture was filtered through Celite. The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 21.3 mg (28%) of the title compound as a yellow oil. ^1H NMR (401 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.3 Hz, 2H), 7.78 (d, *J* = 9.3 Hz, 2H), 7.40 – 7.26 (m, 5H), 4.50 (q, *J* = 15.1, 10.8 Hz, 2H), 4.39 – 4.28 (m, 1H), 3.50 (t, *J* = 8.9 Hz, 1H), 3.36 (dd, *J* = 9.0, 3.4 Hz, 1H), 2.84 (dd, *J* = 12.6, 3.2 Hz, 1H), 2.76 (dd, *J* = 12.6, 7.5 Hz, 1H), 2.62 – 2.47 (m, 2H), 1.43 – 1.17 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H).

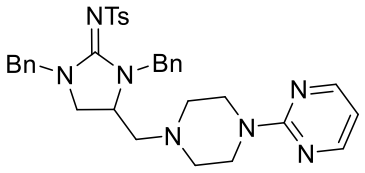


***N*-(1,3-Dibenzyl-4-(morpholinomethyl)imidazolidin-2-ylidene)-cyanamide** (**2-17a**). The general procedure was used for the coupling of **2-13** (30.4 mg, 0.1 mmol, 1 equiv) with morpholino benzoate (**2-1a**) (103.6 mg, 0.5 mmol, 5 equiv) using a catalyst composed of $Pd(TFA)_2$ (1.3 mg, 0.004 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (2.3 mg, 0.008 mmol, 8mol %), except the reaction was conducted on a 0.1 mmol scale with 1mL of dioxane. The crude product was purified by flash chromatography on silica gel [10% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 62.0 mg (80%) of the title compound as a yellow oil. 1H NMR (500 MHz, $CDCl_3$): δ 7.29−6.95 (m, 10 H), 5.24 (d, *J* = 15.5 Hz, 1 H), 4.56−4.46 (m, 2 H) 4.05 (d, *J* = 15.5 Hz, 1 H), 3.33−3.24 (m, 4 H), 3.01 (m, 1 H), 2.64 (app t, *J* = 9.5 Hz, 1 H), 2.52 (dd, *J* = 9.6, 7.1 Hz, 1 H), 1.87 (dd, *J* = 12.8, 5.6 Hz, 1 H), 1.77−1.66 (m, 4 H), 1.53 (dd, *J* = 12.8, 6.9 Hz, 1 H); ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ 158.4, 135.9, 135.4, 128.9, 128.8, 128.2, 128.1, 128.0, 127.9, 116.5, 66.7, 61.0, 54.1, 51.9, 49.5, 49.3, 47.8; IR (film) 2919, 2171, 1596 cm^{-1}; HRMS (ESI TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{27}N_5O$, 390.2288; found, 390.2292



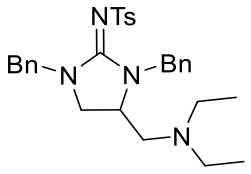
***N*-{1,3-Dibenzyl-4-[(diethylamino)methyl]imidazolidin-2-ylidene}cyanamide** (**2-17h**). The general procedure was used for the coupling of **2-13** (60.9 mg, 0.2 mmol, 1 equiv) with *N,N*-diethylamino benzoate (**2-1h**) (116.0 mg, 0.6 mmol, 3 equiv) using a catalyst composed of $Pd(TFA)_2$ (2.7 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.5 mg, 0.016 mmol, 8 mol %). The crude

product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to give the desired product. The compound was dissolved in ethyl acetate and extracted with 1 M HCl (3×ca. 3 mL).The combined aqueous layers were basified to a pH of 14 using 3 M NaOH (ca. 5 mL) and then extracted with EtOAc (3×ca. 3 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford 41.5 mg (55%) of the title compound as a clear oil. 1H NMR (500 MHz, $CDCl_3$): δ 7.36−7.33 (m, 4H), 7.30−7.27 (m, 6H), 5.29−5.26 (d, *J* = 15.5, 1H), 4.81−4.78 (d, *J* = 15.1 Hz, 1H), 4.65−4.62 (d, *J* = 15.2 Hz, 1H), 4.33−4.29 (d, *J* = 15.5, 1H), 3.56−3.50 (m, 1H), 3.38−3.35 (t, 1H), 3.14−3.11 (m, 1H), 2.55−2.51 (dd, *J* = 13.0 Hz, 4.9 Hz, 1H), 2.39−2.30 (m, 4H), 2.28−2.24 (m, 1H), 0.85−0.82 (t, 6H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ 158.2, 136.0, 135.5, 128.8, 128.3, 128.2, 128.1, 128.0, 116.7, 55.3, 53.2, 49.5, 49.4, 47.7, 47.6, 11.6. IR (film) 3030, 2967, 2169, 1593, 1507 cm^{-1}; HRMS (ESI TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{30}N_5$, 376.2496; found, 376.2487



***N*-(1,3-Dibenzyl-4-{[4-(pyrimidin-2-yl)piperazin-1-yl]methyl}-imidazolidin-2-ylidene)-4-methylbenzenesulfonamide** (**2-18b**). The general procedure was used for the coupling of **2-14** (86.7 mg, 0.2 mmol) and 4-(pyrimidin-2-yl)piperazin-1-yl benzoate (**2-1b**) (170.6 mg, 0.6 mmol) using a catalyst composed of $Pd(TFA)_2$ (2.66 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.55 mg, 0.016 mmol, 8 mol %). The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 89.1 mg (75%) of the title compound

as a clear oil. 1H NMR (500 MHz, C_6D_6): δ 8.30 (d, 2H), 8.21 (d, *J* = 9.3 Hz, 2H), 7.76 (d, *J* = 9.2 Hz, 2H), 7.40−7.29 (m, 5H), 6.49 (dd, *J* = 6.6, 2.9 Hz, 1H), 4.51 (q, *J* = 14.9 Hz, 2H), 4.40(m, *J* = 8.6 Hz, 1H), 3.75 (m, 4H), 3.53 (t, *J* = 8.8 Hz, 1H), 3.41 (d, *J* = 9.2 Hz, 1H), 2.64 (d, *J* = 13.0 Hz, 1H), 2.59−2.53 (m, 2H), 2.49−2.35 (m, 3H); ^{13}C {^1H} NMR (126 MHz, C_6D_6): δ 161.8, 157.4, 156.2, 144.2, 140.5, 137.0, 136.4, 128.8, 128.6, 128.5, 128.5, 128.4, 127.5, 126.2, 109.7, 60.2, 53.2, 51.6, 50.8, 48.8, 48.5, 43.4, 20.7; IR(film) 3028, 2924, 1585, 1564, 1497 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{33}H_{38}N_7O_2S$, 596.2802; found, 596.2801



***(Z)-N*-(1,3-dibenzyl-4-((diethylamino)methyl)imidazolidin-2-ylidene)-4-methylbenzenesulfonamide (2-18h)** The general procedure was used for the coupling of *N*-{[allyl(benzyl)amino][benzylamino]-methylene}-4-methylbenzenesulfonamide **2-14** (86.7 mg, 0.2 mmol) with *N,N*-diethylamino benzoate (**2-1h**) (116.0 mg, 0.6 mmol) using a catalyst composed of $Pd(TFA)_2$ (2.66 mg, 0.008 mmol, 4 mol %) and 1,3-bis(4-methoxyphenyl)propane-1,3-dione (**2-12f**) (4.55 mg, 0.016 mmol, 8mol%). The crude product was purified by flash chromatography on silica gel [30% 3:1 (ethyl acetate/ethanol) in hexanes] to afford 83.4 mg (83%) of the title compound as a yellow oil.1H NMR (500 MHz, C_6D_6): δ 8.29 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.15−7.08 (m, 4H), 7.07−7.02 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 5.51 (d, *J* = 15.2 Hz, 1H), 4.94 (d, *J* = 14.9 Hz, 1H), 4.51 (d, *J* = 14.9 Hz, 1H), 4.20 (d, *J* = 15.2 Hz, 1H), 3.23−3.13 (m, 1H), 2.86−2.75 (m, 2H), 2.15 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.06−1.95

(m, 4H), 1.90 (s, 3H), 1.89−1.85 (m, 1H), 0.60 (t, J = 7.1 Hz, 6H); ^{13}C {^{1}H} NMR (126 MHz, C_6D_6): δ 156.1,144.3, 140.4, 137.0, 136.5, 128.8, 128.6, 128.5, 128.5, 128.0, 127.6, 126.2, 55.1, 52.8, 50.6, 49.0, 48.6, 47.2, 20.7, 11.4; IR (film) 2968, 1563, 1497, 1453 cm^{-1}; HRMS (ESI TOF) m/z: $[M+H]^+$ calcd for $C_{29}H_{37}N_4O_2S$, 505.2632; found, 505.2629

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Collect. Czech. Chem. Commun. **1983**, *48*, 1430. However, we cannot rule out an alternate pathway in which deprotonation occurs after aminopalladation

(9) The fact that the coupling of **2-2a** with **2-1a** provided comparable results when conducted open to air (82% NMR yield) is also more consistent with Pd(II)/(IV) catalysis than a Pd(0)/(II) catalytic cycle given the air-sensitivity of most Pd(0) complexes.

(10) Due to the high energy of Pd(IV) intermediates, oxidative addition from Pd(II) to Pd(IV) tends to be relatively slow, and reductive elimination from Pd(IV) to Pd(II) tends to be relatively fast. For a general review on Pd(IV) catalysis, see: Sehnal, P.; Taylor, RJ; Fairlamb, IJ Emergence of Palladium(IV) Chemistry in Synthesis and Catalysis. *Chem. Rev.* **2010**, *110*, 824.

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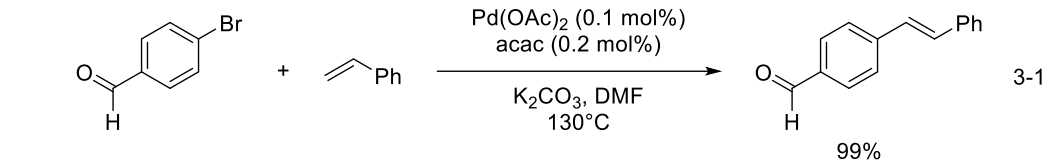
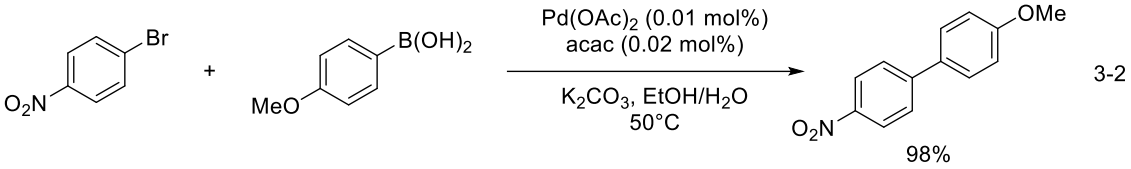
Chapter 3
Ligand Studies Regarding Palladium-Catalyzed Diamination of Unactivated Alkenes

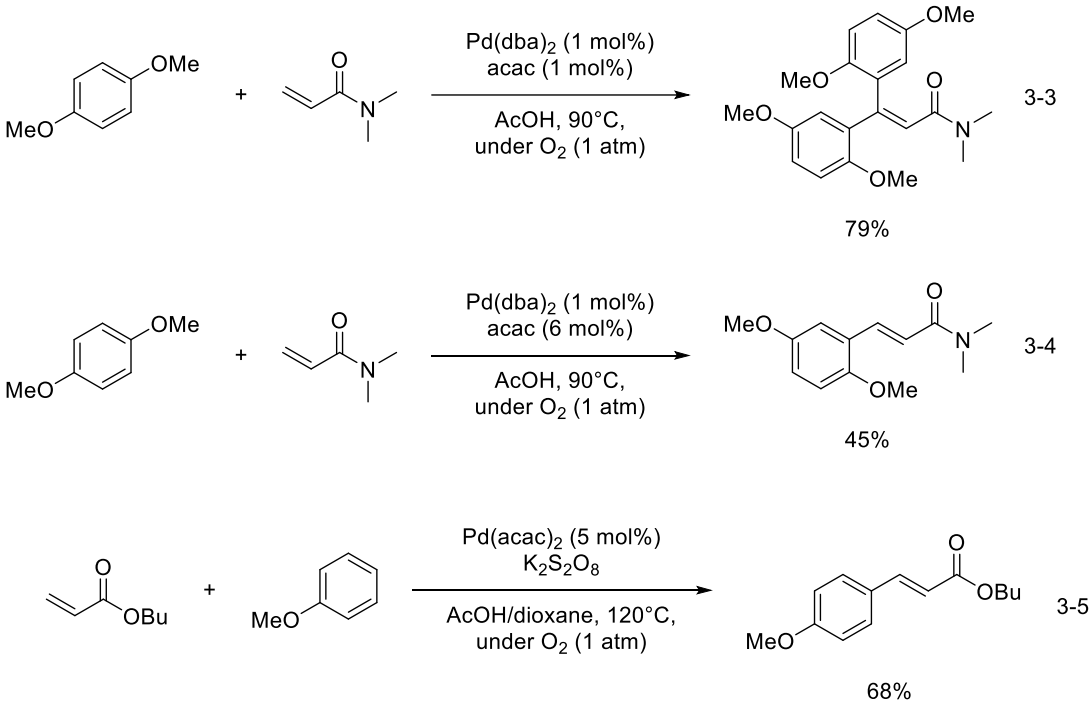
3.1 Introduction and Background

As previously mentioned (Chapter 2; Section 5), the use of acetylacetone (acac) as a standalone and active ligand in Pd-catalyzed cross coupling reactions is extremely uncommon, and the influence of the acac ligand structure on reactivity in Pd-catalyzed reactions has not been thoroughly explored. β-diketone ligands have mainly found applications in Cu-catalyzed Ullmann diaryl ether synthesis[1] and Ullmann C-N coupling reactions.[2] Regarding Pd-catalyzed cross-coupling procedures, Cui et. al. in 2007 showed that β-diketones are effective ligands for Heck reactions of aryl bromides with styrenes (Equation 3-1) and Suzuki reactions of aryl halides and aryl boronic acids (Equation 3-2),[3] and feature low reaction times (between 2-10 hours), low catalyst loadings, excellent functional group tolerance, and high yields. This is in contrast with traditional Heck and Suzuki coupling transformations that typically use phosphine ligands which can be expensive, toxic, air sensitive, and prone to degrade.

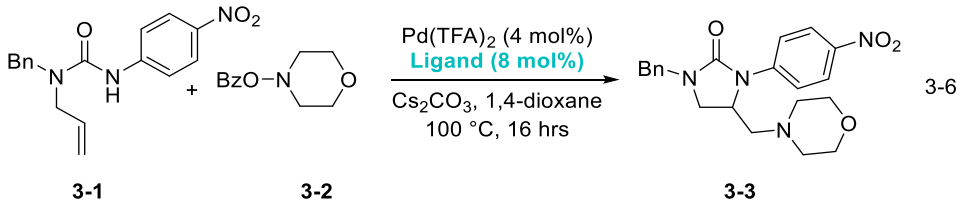




Pd-catalyzed Fujiwara-Moritani-like reactions have also been reported. In 2013, Obora and coworkers, published their findings on Pd-catalyzed chemoselective oxidative coupling reaction of benzene derivatives with acrylamides under an oxygen atmosphere using acac as an added ligand (Equation 3-3).[4] By increasing the ligand loading from 1 mol% to 6 mol% acac, monoarylation of the acrylamide, opposed to diarylation, can be achieved in moderate to excellent yields (Equation 3-4). Later in 2020, Jones and coworkers reported a similar Fujiwara-Moritani reaction using alkylacrylates with electron-rich arenes using $Pd(acac)_2$ in 5 mol% and potassium persulfate as an added oxidant (Equation 3-5).[5] This gave electron-rich, monoarylated acrylates in excellent yields. It was also observed that, in some cases, increasing the reaction time from 3 to 24 hours allowed for the formation of diarylated alkenes as undesired products.



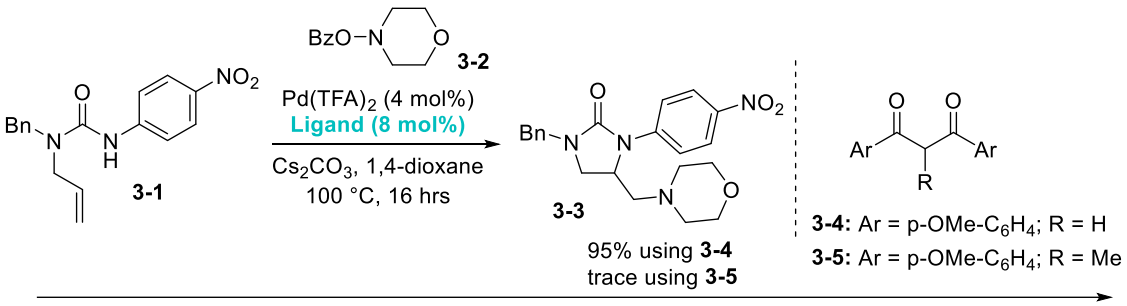
With the discovery that β-diketone ligands are critical for the desired reactivity of our Pd-catalyzed alkene diamination reaction, I was interested in further exploring the structural and electronic properties of this ligand class with the goal of expanding the nucleophile scope to generate other *N*-heterocycles. In order to properly explore ligand reactivity in our system, we chose to incorporate all synthesized ligands into the coupling of cyclic urea precursor **3-1** and morpholinobenzoate **3-2** with our most recently optimized conditions for the formation of desired product **3-3** (Equation 3-6).



3.2 Ligand Structural Considerations

We began by exploring the structural considerations of our most optimized ligand, 1,3-bis(4-methoxyphenyl)propane-1,3-dione (Scheme 3-1, **3-4**). It is believed that the reason for the enhanced reactivity of this optimized ligand, and acac ligands as a whole, in our system is due to the planar, chelating nature, and narrow bite angle of the ligand.

Scheme 3-1: Diamination Result From Using Optimized and Methylated Ligand[ab]

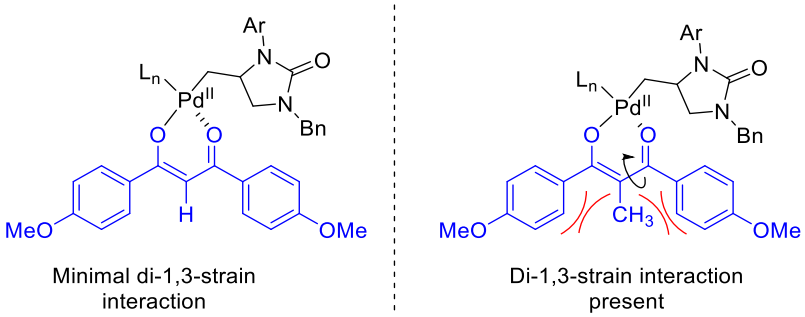


[a]Conditions: 1.0 equiv **3-1**, 3.0 equiv **3-2**, 4 mol % $Pd(TFA)_2$, 8 mol % Ligand, 2 equiv Cs_2CO_3, dioxane (0.1M), 100°C, and 16 h. [b]Yields represent NMR yields

This minimizes the steric hindrance around the metal center and allows oxidative addition of the aminobenzoate, bringing the oxidation state of the metal to Pd(IV). To test this, I decided to methylate the methylene backbone of the bis(4-methoxyphenyl)propane-1,3-dione (**3-5**) with the expectation that the reaction would fail due to the di-1,3-strain of the methyl group with both phenyl groups of the ligand (Scheme 3-2). This can be explained in one of two ways: i) This di-1,3-strain would cause the phenyl groups to rotate out of a planar face and cause additional steric hindrance of the metal center to prevent oxidative addition and ii) prevent the dissociation of one of the oxygens on the palladium by increasing the energy required for conformational rotation which prevents the palladium from freeing a necessary coordination site for oxidative addition. When subjecting the methylated ligand to our optimized diamination conditions the reaction only gave trace

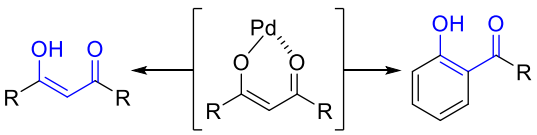
amounts of desired product, indicating that planar conformation is indeed important for the success of the ligand.

Scheme 3-2: Conformational Explanation for Methylation of the Dicarbonyl Ligand Backbone



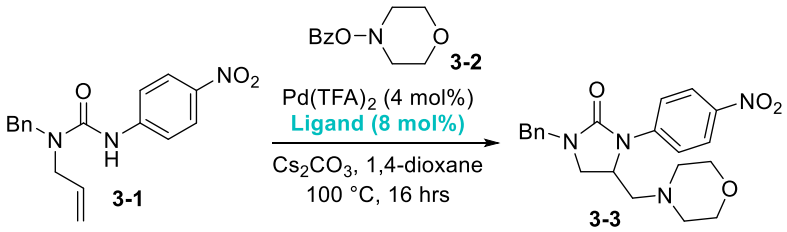
Next, we explored using *o*-hydroxyacetophenone derivatives as ligands in the transformation. In solution and in the presence of base, acac (along with other 1,3 dicarbonyls previously synthesized and investigated) undergo deprotonation to afford the corresponding enolate, which binds to the metal center as a monoanionic LX-type chelating ligand. An *o*-hydroxyacetophenone derivative has a pKa that is comparable to that of a malonate, and I reasoned that it may be possible to use these compounds as ligands for this transformation (Scheme 3-3). This can be advantageous as *o*-hydroxyacetophenone derivatives are commercially available or easily synthesizable in 1-2 steps. This would make it possible to further probe the influence of ligand steric and electronic properties by preparing differently substituted derivavtives.

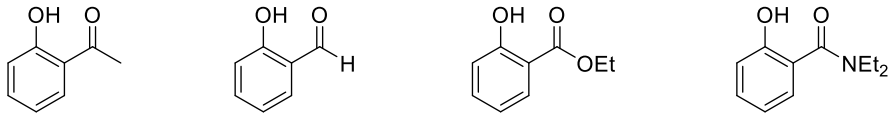
Scheme 3-3: Structural Similarities Between Ligands



First, we explored the use of unsubstituted *o*-hydroxyacetophenone as a ligand in the transformation (Table 3-1). This ligand gave the desired product in 10% NMR yield along with a complex mixture of side products that could not be purified. However, attempting to incorporate other acetophenone derivatives such as **3-7-9** gave only trace amounts of desired product and a complex mixture of side products. Other structurally similar ligands were explored, however these ligands also failed to provide satisfactory results. With this in mind, we decided to explore the electronic trends of these ligands by examining substituted derivatives and their corresponding imines.

Table 3-1: Select Examples of *o*-Hydroxyacetophenone Derivatives as Ligands[ab]





3-6; 10% **3-7;** trace **3-8;** trace **3-9;** trace

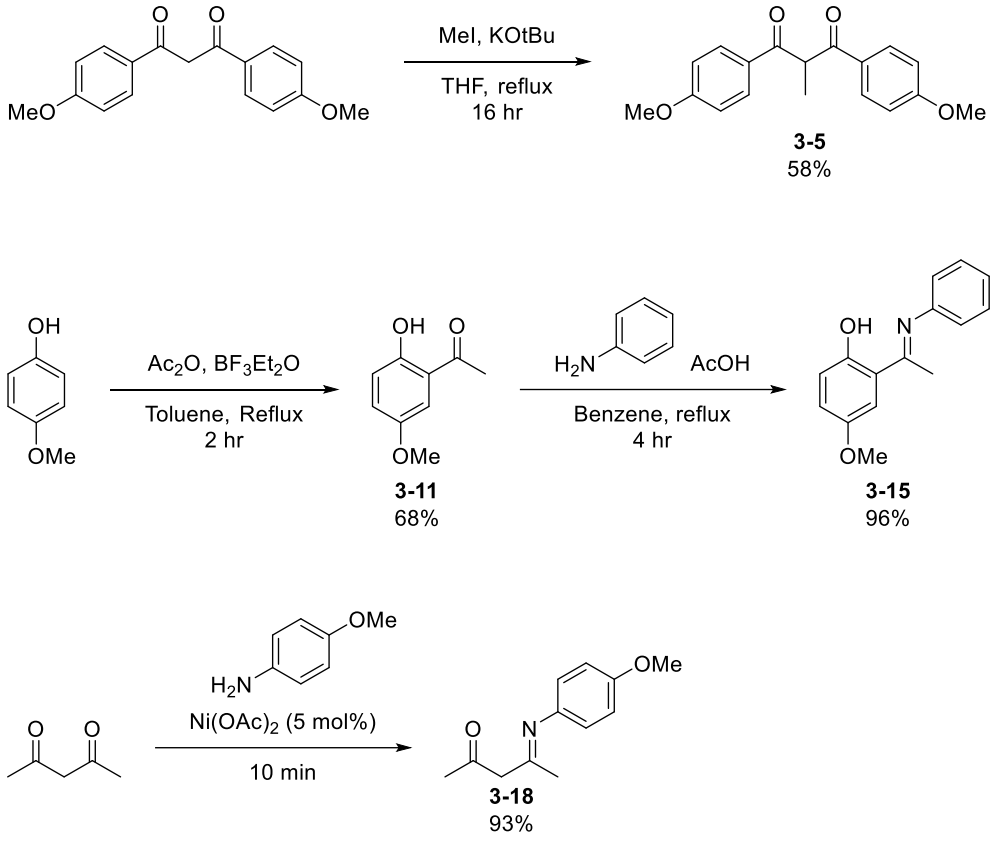
[a]Conditions: 1.0 equiv **3-1**, 3.0 equiv **3-2**, 4 mol % $Pd(TFA)_2$, 8 mol % Ligand, 2 equiv Cs_2CO_3, dioxane (0.1M), 100°C, and 16 h. [b]Yields represent NMR yields

3.3 Ligand Synthesis and Electronic Trends

Various synthetic methods were used to develop *o*-hydroxyacetophenone and *o*-hydroxyimine derivatives (Scheme 3-4). *o*-Hydroxyacetophenone derivatives were synthesized from corresponding phenols using acetic anhydride and boron trifluoride etherate (Scheme 3-4; **3-11**). From this, imine condensation using aniline and acetic acid

can generate the desired o-hydroxyimine derivatives (Scheme 3-4; **3-15**). β-dicarbonyls were also used to synthesize β-ketoimines using a method involving $Ni(OAc)_2$.

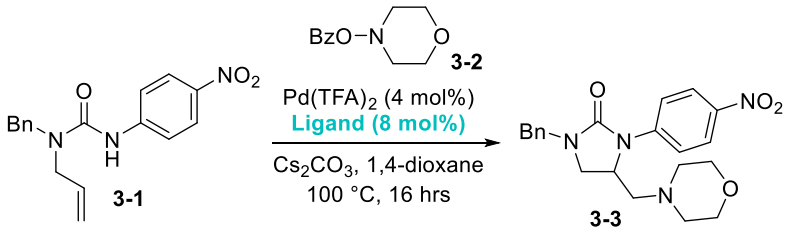
Scheme 3-4: Representative Synthesis of Ligands

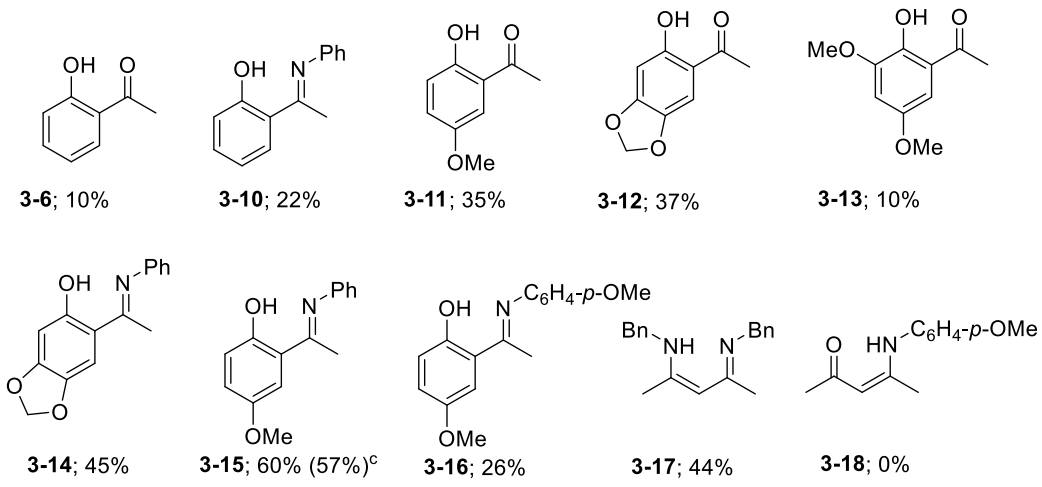


As previously observed in the Chapter 2, Section 5, there was a general trend that increasing the electron-donating capabilities of the ligand improved reaction performance. With this in mind, we began exploring substituting the aryl ring of *o*-hydroxyacetophenone with electron-donating groups and changing one of the associating atoms from oxygen to nitrogen (Table 3-2). Using the phenylimine **3-10**, we noticed an increase in NMR yield of **3-3** to 22%. When alkyl ethers were present in the aryl ring meta and/or para to the hydroxyl group (**3-11** and **3-12**), the NMR yield of the transformation was further increased to 37%. However, when a methoxy group is ortho to the hydroxyl group (**3-13**), only 10%

of the desired product is observed. This observation suggests that the electronics of the aryl ring are important for ligand reactivity in the system. However, when the coordinating atom of the ligand becomes more sterically hindered, the reactivity of the ligand is diminished. Replacing the carbonyl functionality in **3-11** and **3-12** for imine functionality (**3-14** and **3-15**) further increased the yield of the reaction. This suggests that

Table 3-2: Select Examples of the Electronic Effects of *o*-Hydroxyacetophenone Derivatives as Ligands[ab]



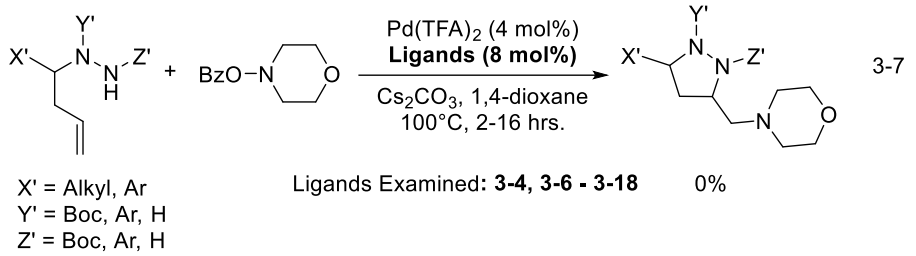


[a]Conditions: 1.0 equiv **3-1**, 3.0 equiv **3-2**, 4 mol % $Pd(TFA)_2$, 8 mol % Ligand, 2 equiv Cs_2CO_3, dioxane (0.1M), 100°C, and 16 h. [b]Yields represent NMR yields. [c]Yield in parenthesis represents isolated yield. Thank you to Kyle Palka and Allison Rackowski for helping conduct these experiments.

incorporating less electronegative atoms as binding atoms are advantageous most likely due to the ligand making the metal center more electron rich comparatively. However, further attempts to increase the electron-donating capabilities of the ligand did not result in an increase in yield (**3-16-18**) and resulted in either degradation of the starting material or β-hydride elimination after aminopalladation.

3.4 Attempts to Expand the Diamination Nucleophile Scope Using This New Ligand Class

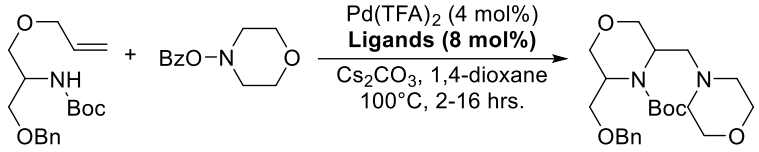
Although the studies described above revealed that ligand 3-15 provided the best results of those explored, the yields were not as good as those obtained with acac or simple acac derivatives. In hopes that this new class of ligands may help us overcome another limitation of the deamination reactions, which is they are limited to urea and guanidine nucleophiles, we began to explore the reactivity of these ligands when transformations of other nucleophiles that would generate different 5- or 6 -membered ring *N*-heterocycles. To this end, we examined the reactivity of pyrazolidines (Equation 3-7), morpholines (Equation 3-8), oxazolidines (Equation 3-9), and cyclic carbamates (Equation 3-10) precursors as a general screen of nucleophiles in our diamination chemistry. However, regardless of the ligand that was chosen, including our most optimized ligand **3-4**, no desired product was observed in all cases.



3-7

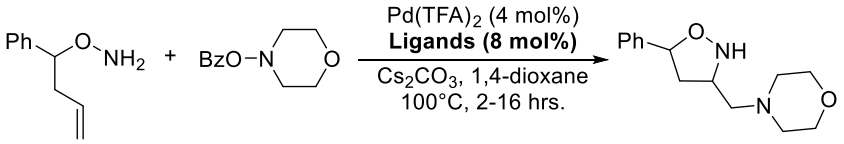
X' = Alkyl, Ar
Y' = Boc, Ar, H
Z' = Boc, Ar, H

Ligands Examined: **3-4, 3-6 - 3-18** 0%



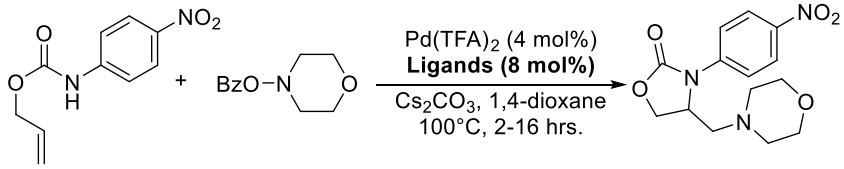
3-8

Ligands Examined: **3-4, 3-6 - 3-18** 0%



3-9

Ligands Examined: **3-4, 3-6 - 3-18** 0%

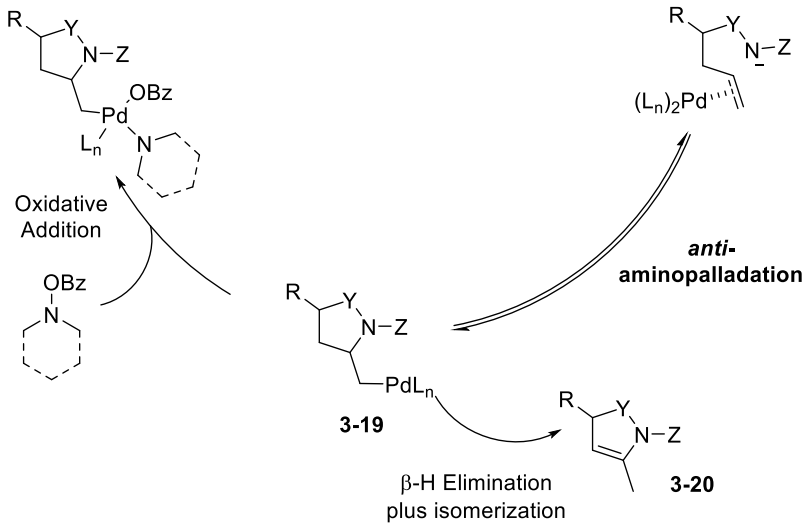


3-10

Ligands Examined: **3-4, 3-6 - 3-18** 0%

NMR analysis showed that in all of the transformations described above side products **3-20** were present, along with a mixture of other products that could not be isolated by column chromatography or identified from the crude NMR spectrum. Products **3-20** result from β-hydride elimination from **3-19** (Scheme 3-5), which suggests the rate of oxidative addition is slow with these nucleophiles as compared to ureas and guanidines. Given these unsatisfactory results, and the fact that the new ligands had no advantages over the simple acac derivatives, we elected to move away from this project.

Scheme 3-5: Explanation of Observed Side Products in Nucleophile Scope



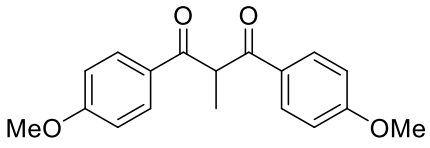
3.5 Conclusion

β-diketones are an extremely rare class of ligands used as standalone ligands in Pd-catalyzed cross-couplings. This is in part due to their underexplored reactivity and the use of more versatile phosphine ligands. With the discovery that 1,3-dicarbonyl ligands were critical for the observed reactivity of our Pd-catalyzed alkene diamination, I wanted to explore the structural and electronic considerations of this ligand class more. Despite the fact that these ligands were not superior to simple acac derivatives, we still gleaned significant information from these studies. Our experiments with these ligands showed that i) substitution of the methylene backbone is not tolerated in the system, ii) *o*-hydroxyacetophenone derivatives and their corresponding imines are able to mimic the reactivity of acac in this method and iii) increasing the electron-donating properties of the ligand, while keeping the associating atoms relatively sterically unhindered, also increased the yields of desired product.

3.6 Experimental

General: All reactions were carried out under a nitrogen atmosphere using oven or flame-dried glassware. All palladium sources and reagents including **3-6** - **3-9** and **3-11** were obtained from commercial sources and used without further purification unless otherwise noted. Ligands **3-5,**[6] **3-10,**[7] and **3-12** - **3-18**[8-10] were prepared according to previously reported procedures. Dioxane was purified by distillation from Na metal and benzophenone. No isolated yields were taken for the formation of ligands. *All o-hydroxyacetophenone derivatives were examined by NMR prior to use to ensure no water or trace impurities were present. Ligands that were found to have water were passed through a sodium sulfate plug and ligands that contained trace impurities were purified by column chromatography.*

Synthesis and Characterization of Ligands



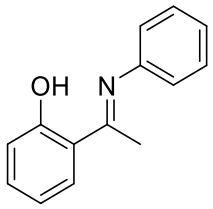
1,3-bis(4-methoxyphenyl)-2-methylpropane-1,3-dione (3-5).

Substrate **3-4** (0.2 mmol; 1 equiv.) was dissolved in THF (0.3 M). Potassium tert-butoxide (0.22 mmol, 1.1 equiv.) was added and allowed to stir for 1 hour at room temperature. Afterwards, MeI (0.22 mmol, 1.1 equiv) was added the solution was allowed to reflux for 16 hours. The reaction was quenched with aqueous NH_4Cl. The quenched mixture was diluted with EtOAc and the organic layer was separated 3 times. Crude product was purified by column chromatography using 20% EtOAc in hexanes to afford the desired product in 58% yield. The characterization data matched those of known methods.[6]

General Procedure A: To a flame-dried round bottom flask was added the corresponding phenol derivative (10.0 mmol, 1 equiv.) diluted in toluene (1.0 M). The solution was placed under N_2 atmosphere and acetic acid (10.0 mmol, 1 equiv.) was added followed by BF_3Et_2O (12.0 mmol, 1.2 equiv.). The reaction was heated to reflux and allowed to stir for 2 hours. Afterwards, the reaction was cooled to room temperature and the reaction mixture was poured into an ice water solution to allow precipitation. The solution was filtered and recrystallized in absolute ethanol to obtain the resulting *o*-hydroxyacetophenone in good to excellent yields. From here, the *o*-hydroxyacetophenone derivative (1.0 mmol, 1 equiv.) was then dissolved in benzene (0.3 M) and the solution was placed under N_2 atmosphere. Aniline derivative (1.5 mmol, 1.5 equiv.) was added dropwise along with a catalytic amount of AcOH (0.10 mmol, 10 mol%). The reaction was allowed to reflux and stir for 16 hours. The reaction was quenched with H_2O and diluted with Et_2O. The layers were separated, and the organic layer was dried with Na_2SO_4, filtered and rotovaped. The crude mixture was purified via column chromatography to give the corresponding *o*-hydroxyimines in good to excellent yields.

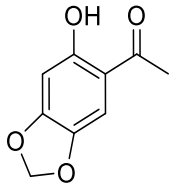
General Procedure B: To a flame-dried round bottom flask was added the corresponding β-dicarbonyl derivative (1.0 mmol, 1 equiv.). The corresponding aniline derivative (1.0 mmol, 1 equiv.) and $Ni(OAc)_2$ (0.05 mmol, 5 mol%) was added and the reaction was allowed to stir for 10 minutes to 1 hour as a neat solution. After completion of the reaction, ethyl acetate (10 ml) was added and the heterogeneous mixture was filtered. The organic phase was washed with water (2 × 15 ml) and dried over anhydrous MgSO4. The solvent was evaporated under reduced pressure to provide the crude product. Further purification

was carried out by column chromatography to afford pure β-enamino ketones or esters in moderate to excellent yields.



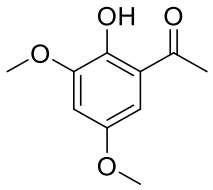
(E)-2-(1-(Phenylimino)ethyl)phenol (3-10).

General Procedure A was used for the synthesis of **3-10**. The crude mixture was purified via recrystallization in absolute ethanol to afford the desired substrate in 93% yield. NMR Data: ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.47 – 7.38 (m, 3 H), 7.28 – 7.24 (s, 1 H), 7.21 (d, *J* = 8.3 Hz, 1 H), 6.98 (dd, *J* = 8.4, 1.2 Hz, 2 H), 6.95 – 6.89 (m, 1 H), 2.41 (s, 3 H).



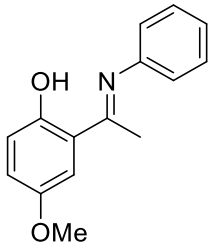
1-(6-Hydroxybenzo[d][1,3]dioxol-5-yl)ethan-1-one (3-12).

General Procedure A was used for the synthesis of **3-12**. The crude mixture was purified via recrystallization in absolute ethanol to afford the desired substrate in 78% yield. NMR Data: ^{1}H NMR (401 MHz, $CDCl_3$) δ 13.03 (s, 1 H), 7.05 (s, 1 H), 6.45 (s, 1 H), 5.98 (s, 2 H), 2.52 (s, 3 H).



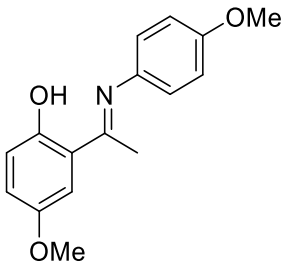
1-(2-Hydroxy-3,5-dimethoxyphenyl)ethan-1-one (3-13).

General Procedure A was used for the synthesis of **3-13**. The crude mixture was purified via recrystallization in absolute ethanol to afford the desired substrate in 85% yield. NMR Data: ^{1}H NMR (401 MHz, $CDCl_3$) δ 12.70 (s, 1 H), 7.36 (s, 1 H), 6.49 (s, 1 H), 3.86 (s, 3 H), 2.53 (s, 3 H), 2.31 (s, 3 H).



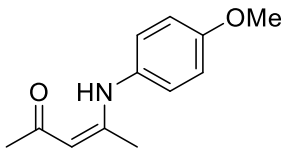
(E)-4-Methoxy-2-(1-(phenylimino)ethyl)phenol (3-15).

General Procedure A was used for the synthesis of **3-15**. The crude mixture was purified via recrystallization in absolute ethanol to afford the desired substrate in 81% yield over two steps. NMR Data: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.3, 7.4 Hz, 2 H), 7.20 – 7.17 (m, 1 H), 7.14 (d, *J* = 2.9 Hz, 1 H), 7.01 (dd, *J* = 9.0, 3.0 Hz, 1 H), 6.96 (d, *J* = 9.0 Hz, 1 H), 6.93 – 6.88 (m, 2 H), 3.81 (s, 3 H), 2.31 (s, 3 H).



(E)-4-Methoxy-2-(1-((4-methoxyphenyl)imino)ethyl)phenol (3-16).

General Procedure A was used for the synthesis of **3-10**. The crude mixture was purified via recrystallization in absolute ethanol to afford the desired substrate in 87% yield over two steps. NMR Data: ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.13 (d, *J* = 2.8 Hz, 1 H), 7.03 – 6.89 (m, 4 H), 6.90 – 6.82 (m, 2 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.34 (s, 3 H).



(Z)-4-((4-Methoxyphenyl)amino)pent-3-en-2-one (**3-18**).

General Procedure B was used for the synthesis of **3-18**. The crude mixture was purified via column chromatography using 20% EtOAc/Hexanes to afford the desired substrate in 94% yield. NMR Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1 H), 7.04 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.15 (s, 1 H), 3.81 (s, 3 H), 2.09 (s, 3 H), 1.90 (s, 3 H).

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Chapter 4
Introduction to Transition Metal-Catalyzed Alkene Carboamination Reactions and Polycyclic *N*-Heterocycles

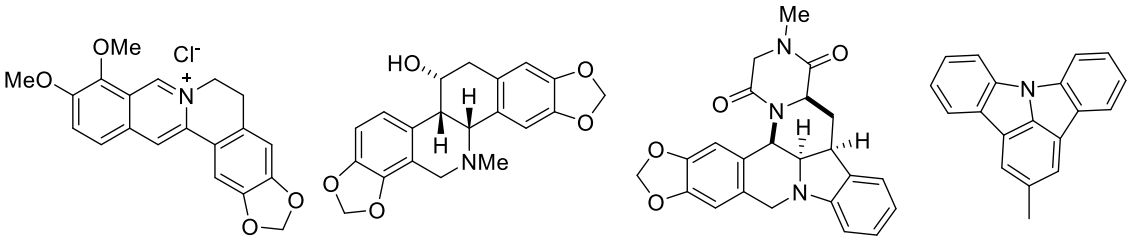
4.1 Polycyclic Nitrogen Heterocycles and Their Applications

Fused polycyclic *N*-heterocycles comprise a large sum of biologically active molecules and natural products, and the development of methods for their formation as been of particular interest.[1] Moreover, new methods for the formation of uncommon, fused *N*-heterocycles can lead to newer classes of compounds whose reactivity profile is not fully understood.[2] In particular, polycyclic indolines, tetrahydroisoquinolines and their derivatives represent scaffolds displayed in various alkaloid natural products.

Berberine and other protoberberine alkaloids are a pharmacologically important class of alkaloids due to their broad and potent biological activities (Scheme 4-1).[3] For example, berberine effected 99% suppression (P less than 0.001) of total ventricular premature beats (VPCs) by 12 hours[4] and exhibits a variety of other biological properties such as anti-inflammatory, antibacterial, neuroprotective, anticholesterol, and antilipemic.[5] Chelidonine possess antitumor properties that result from promoting apoptosis of advanced hepatocellular carcinoma (HCC) cells.[6] Compound **1** features a tetrahydroisoquinoline motif and is a synthetic class of alkaloids patented by Eli Lilly as potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE), in particular PDE5, and have utility in a variety of therapeutic areas where such inhibition is considered beneficial, including the

treatment of cardiovascular disorders and erectile dysfunction.[7] Compound **2** features a di-indoline scaffold and is a part of a synthetic class of alkaloids patented by the Universal Display Corporation as potentially useful in organic light emitting devices (OLEDs) which may have performance advantages over conventional materials. With this in mind, developing synthetic methods to access polycyclic *N*-heterocycles efficiently and selectively is an ever-growing and evolving field.[8]

Scheme 4-1: Select Examples of Industrially Relevant Polycyclic Tetrahydroisoquinoline and Indoline Products



Berberine
Suppresses Ischemic Arrythmias; antilipemic agent

Chelidonine
antitumor properites

1
Patented potent and selective inhibitor of cyclic guanosine phosphosdiesterase

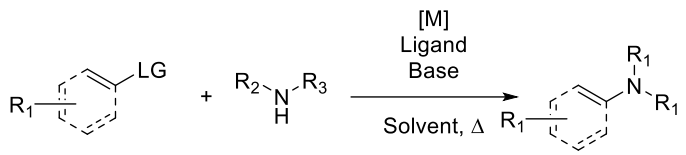
2
Patented OLED material

4.2 Palladium-Catalyzed C-N Bond Formation Reactions

The first example of a Pd-catalyzed C-N cross coupling was initially published in 1983 by Migita and coworkers.[9] In this report, they were able to successfully couple *N,N*-diethylamino-tributyltin with aryl bromides in the presence of $PdCl_2$(*o*-tolyl$_3$P)$_2$ to give the corresponding *N,N*-diethylaminobenzene derivatives. However, these reactions provided poor yields and limited reaction scope. Afterwards, between 1994 through the early 2000s, Stephen Buchwald and John Hartwig developed and optimized a Pd-catalyzed amination using aryl/alkyl phosphines as ligands (the Buchwald-Hartwig Amination) which features a significant amount of generality including aryl/vinyl, (pseudo)halide electrophiles. This along with the wide availability of nitrogen nucleophiles such as primary/secondary, alkyl/aryl amines of various complexity (Scheme 4-2) has made these

catalytic approaches much more desirable as opposed to more traditional methods for the synthesis of arylamines due to their high efficiency, scope, selectivity, and relatively mild reaction conditions.[10] It is for these reasons that the Buchwald-Hartwig amination has become a staple transformation in industrial settings such as medicinal, natural product, and materials research;[10] so much so that almost all available industrial-based synthesis methodologies contain at least one Pd-catalyzed C-N cross coupling transformation.[11]

Scheme 4-2: General Reaction Scheme for Metal-Catalyzed C-N Cross Couplings



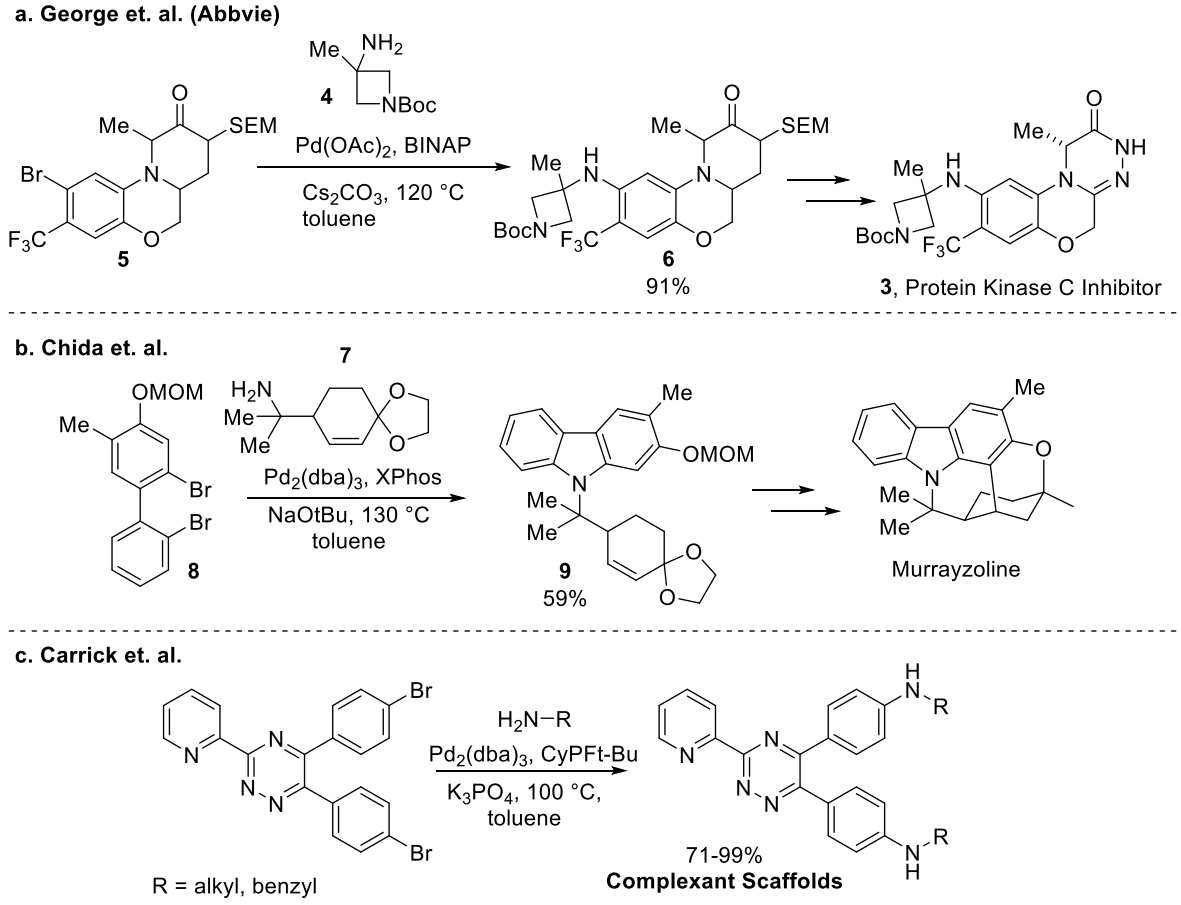
LG = Halide, -SO_2R
R = Alkyl, Aryl
R_1 = H, Alkyl, Aryl, Halide,Heteroatom
R_2 = R_3 = H, Alkyl, Aryl, Heteroaryl

Although other transition metals such as copper[12] and nickel,[13] have been used in Buchwald-Hartwig type reactions, this chapter is focused solely on Pd-catalyzed transformations as they are the most common and most relevant to the work described in the following chapter.

In particular, the Buchwald-Hartwig aminations of primary amines and aryl (pseudo)halides have been of critical importance (Scheme 4-3). In the context of medicinal chemistry, one example is the synthesis of **3,** a protein kinase C inhibitor for autoimmune disease therapy, by George et. al. at AbbVie.[14] One of the key synthetic steps involves the coupling of primary aminoazetadine **4** with aryl bromide **5** using $Pd(OAc)_2$ and BINAP as the catalyst system yielding the key intermediate **6** in 91%. In the context of natural product synthesis, one example is the total synthesis of (±)-

Murrayazoline by Chida et. al. where the key synthetic step involved a double *N*-arylation of the sterically bulky primary alkylamine **7** and biarylhalide **8** yielding the key intermediate **9** in 59% yield.[15] In the context of materials research, one example is the synthesis of 1,2,4-triazinyl complexant scaffolds by Carrick and coworkers. Through a facile *N*-arylation procedure, they were able to generate the desired complexant scaffolds in excellent yields (70-99%).[16] These complexant scaffolds act as effective complexants for chemoselective minor actinide extraction from used nuclear fuel.

Scheme 4-3: Select Examples of Buchwald-Hartwig Amination in Medicinal, Natural Product, and Materials Research



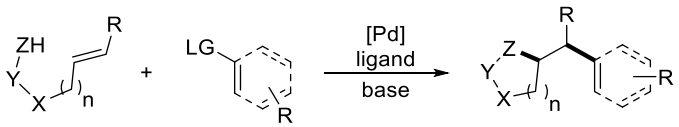
In many of these reported primary amine *N*-arylation reactions, the preferred ligands are sterically bulky, electron-deficient, chelating ligands such as BINAP, tol-

BINAP, and DPPF (For structures see List of Ligands; page xxv). The relatively large size of these chelating ligands prevent double *N*-arylation from occurring while making reductive elimination more kinetically favorable.

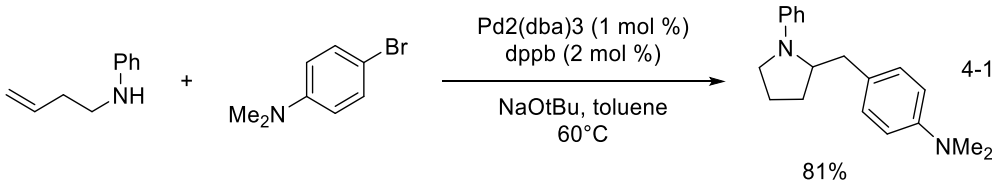
4.3 Palladium-Catalyzed Alkene Carboamination Reactions

The stereocontrolled synthesis of heterocycles remains an important challenge for synthetic chemists. Over the last two decades, Pd-catalyzed alkene carboamination has proven to be efficient and robust transformations to address this problem. Typically, these reactions feature the coupling of an alkene that contains a pendant heteroatom **10** with an aryl or alkenyl halide or triflate **11**, often in the presence of an exogenous ligand and base, for the formation of substituted heterocycles with excellent stereocontrol (Scheme 4-4).[17]

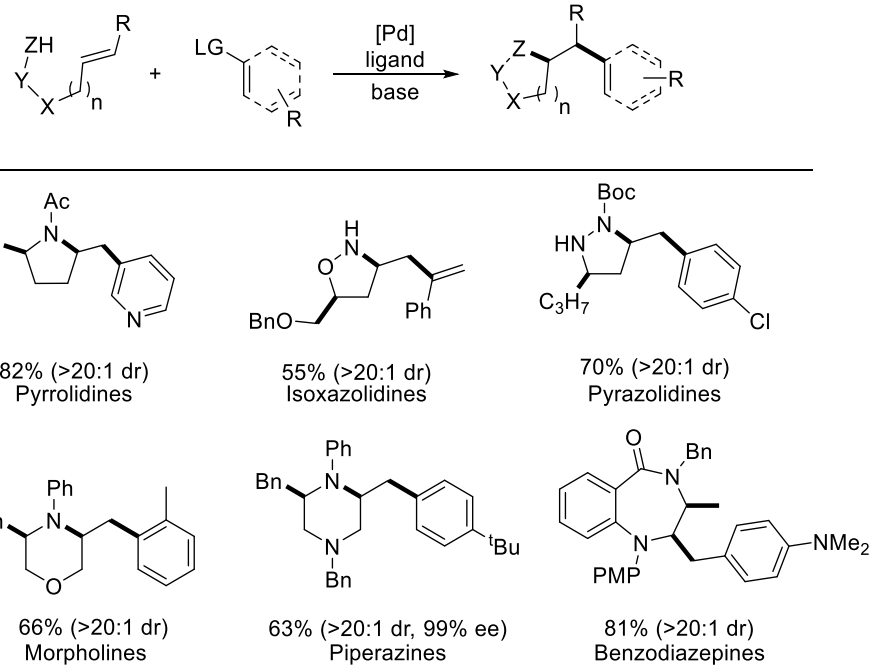
Scheme 4-4: General Reaction Scheme for Pd-Catalyzed Alkene Carboamination



The first related publication in the area of alkene carboamination by the Wolfe lab was in 2004 with the synthesis of pyrrolidines from aryl bromides and alkenylamines (Eq 4-1).[18] This method has since been developed for the synthesis of various heterocyclic scaffolds including piperazines, oxazolidines, isoxazolidines, morpholines, pyrazolidines, benzodiazepines, and other structures commonly found in bioactive compounds (Scheme 4-5).[19]



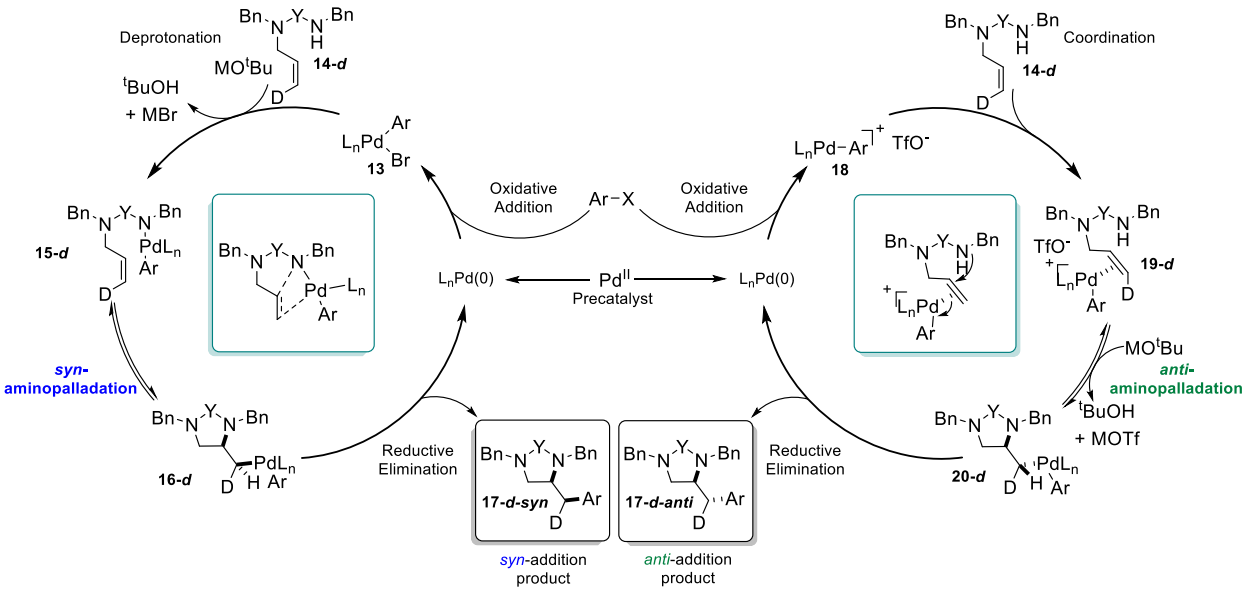
Scheme 4-5: Select Examples of Heterocycles Prepared Through Alkene Carboamination



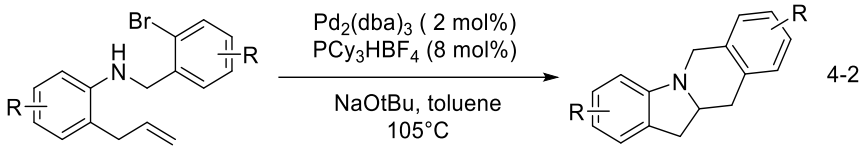
The most common ligands for these transformations typically are smaller, electron-rich, monodentate ligands such as PCy_3, $P(2\text{-furyl})_3$, or Buchwald ligands such as CPhos and DavePhos (For structures see List of Ligands; page xxv). It is important to note that, while there is precedence for alkene carboamination promoted by chelating ligands,[22] there is little reported literature of these ligands overlapping with *N*-arylation of primary amines. For this reason, it is anticipated that the best ligand for *N*-arylation may not be the best ligand for alkene carboamination. Therefore, any cascade reaction method may need to address this issue; if the issue is possible to address.

Additionally, in some systems such as sulfamides[21] and ureas,[23] the *syn* versus *anti* stereoselectivity of alkene carboamination can be influenced by the choice of catalyst and reaction conditions, allowing selective formation of different heterocycle stereoisomers from a single starting material. Early studies in the Wolfe lab showed that alkene carboamination reactions of aryl halides proceeded by oxidative addition of aryl halide to Pd(0), followed by substation of **13** with **14-*d*** to give **15-*d*** (Scheme 4-6). From this intermediate, syn-aminopalladation (syn-migratory insertion of the alkene into the Pd-N bond) generates **16-*d*** then reductive elimination affords the *syn*-addition adduct **17-*d*-*syn***. However, when employing aryl triflates under slightly different reaction conditions (switching from NaOtBu to LiOtBu, use of more polar solvents) that facilitate formation of cationic palladium intermediates, oxidative addition intermediate **18** undergoes coordination with **14-*d*** to give **19-*d*.** From this intermediate, anti-aminopalladation to give **20-*d*** occurs, then reductive elimination leads to the observed *anti*-addition adduct **17-*d*-*anti*** selectively. This trend was also observed when *N*-allylureas are used in the reaction.

Scheme 4-6: Comparative Mechanisms of Syn- vs Anti-Aminopalladation



In 2014, the Wolfe group published their findings on the synthesis of tetrahydroindoloisoquinoline derivatives through an alkene carboamination strategy (Equation 4-2).[24] This approach is the only example of making fused polycyclic *N*-heterocycles by this strategy thus far. However, there are some significant limitations to this approach: i) there is no possibility for tandem catalysis as the substrates are made via reductive amination of *o*-allylaniline and *o*-bromobenzaldehyde derivatives, ii) no exploration of ring size (4/6/7-membered rings), and iii) no exploration of heteroaryl coupling partners. These limitations will be addressed in the work described in Chapter 5.



4-2

4.4 Conclusion

Fused polycyclic *N*-heterocycles comprise many biologically active molecules and natural products. Synthetic methods to develop these scaffolds are of significant importance for the advancement of medicine and technology. Of these methods, arguably the most well-studied transformation to this end is C-N bond formation, particularly the Buchwald-Hartwig amination which has allowed the efficient yet mild synthesis of arylamines of varying complexity and functionality. Moreover, Pd-catalyzed alkene carboamination allows for the expeditious synthesis of biologically relevant heterocyclic scaffolds using aryl/alkenyl (pseudo)halides and alkenylamines. These efficient reactions typically involve the formation of (i) one new sp^3C-sp^3N bond and one new sp^3C-sp^2C bond (ii) one ring (iii) up to 2 new stereocenters stereoselectively in one efficient step from

easily synthesizable or commercially available starting materials. The work described in the following chapter (Chapter 5) will describe a method involving a sequential Pd-catalyzed *N*-arylation and alkene carboamination to synthesize isoquinolinoquinoline, a fused poly-*N*-heterocyclic scaffold, derivatives that have rarely been synthetically explored and otherwise difficult to generate.

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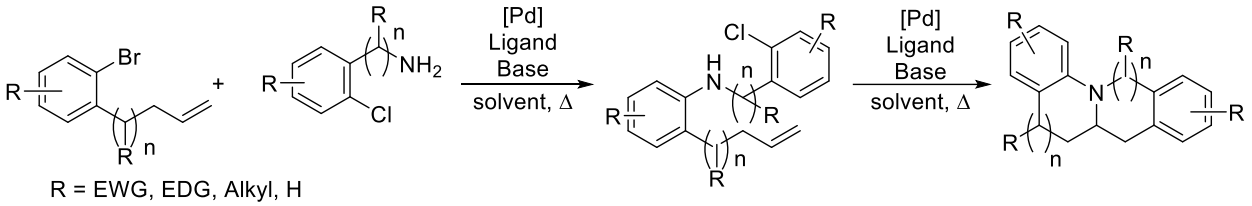
Chapter 5
Synthesis of Tetrahydroquinolinoquinoline Derivatives by a Sequential Pd-Catalyzed *N*-Arylation and Alkene Carboamination Strategy

5.1 Introduction

As mentioned in Chapter 4, fused poly-*N*-heterocyclic scaffolds are common motifs in a number of biologically active small molecule drugs, natural products, and materials, making their synthesis and reactivity profile of particular interest to many industries (Chapter 4, Section 1).[1] Furthermore, the Buchwald-Hartwig amination has allowed the efficient yet mild synthesis of arylamines of varying complexity and functionality (Chapter 4, Section 2).[2] Additionally, our group has previously illustrated that Pd-catalyzed alkene carboamination reactions of aryl and alkenyl (pseudo)halides with exogenous and/or pendant nitrogen nucleophiles are an efficient, high-yielding, and stereoselective means of generating nitrogen heterocycles (Chapter 4, Section 3).[3] It was reasoned that performing an *N*-arylation between *o*-homoallylbromobenzene and *o*-chlorobenzylamine derivatives would generate an isolatable tethered alkenylamine as a key intermediary substrate. This intermediary substrate would then undergo a subsequent alkene carboamination reaction to generate tetrahydroisoquinolinoquinoline derivatives (Scheme 5-1).

Scheme 5-1: General N-Arylation/Alkene Carboamination Reaction Scheme



R = EWG, EDG, Alkyl, H
n = 0,1

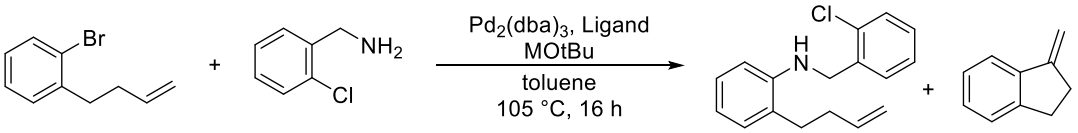
As described in Chapter 4, previous studies conducted in the Wolfe have illustrated that many Pd-catalyzed alkene carboamination reactions proceed with high diastereoselectivity.[3] Importantly, given the broad scope of both N-arylation and alkene carboamination reactions, this reaction should not be limited to synthesis of 6/6 membered ring systems but the 5/6, 6/5, and 5/5 systems should also be accessible depending on the length of the alkyl tether in the respective starting materials (n= 0,1).

5.2 Optimization of *N*-Arylation and Alkene Carboamination

In our initial reaction optimization, we elected to employ *o*-homoallylbromobenzene **5-1a** as the electrophilic alkene source as this compound is readily synthesized in 2 steps; the synthesis of this substrate and others employed in these transformations is described below in section 5.3. *O*-chlorobenzylamine **5-2a** was used as the nucleophilic substrate due to its commercial availability. $Pd_2(dba)_3$ was used as the [Pd] source for the reaction along with toluene as solvent and tert-butoxide as base. Based on the literature precedence of primary amine *N*-arylations, we first examined a catalyst system composed of $Pd_2(dba)_3$, and BINAP (Table 5-1; entry 12) to give desired intermediate **5-3a** in excellent yield. For the sake of being thorough, we explored other ligands in hopes of performing the *N*-arylation/alkene carboamination in a one-pot fashion. Buchwald ligands were first explored in the reaction optimization but

provided unsatisfactory conversion of **5-1a** and often promoted an intramolecular Heck cyclization to give **5-4a** (Table 5-1; Entry 1-3). Additionally, switching the base from sodium tert-butoxide to lithium tert-butoxide gave diminished yields (Table 5-1; Entry 3-4). Next, chelating phosphine ligands were explored as they are heavily precedented ligands for the coupling of aryl bromides with alkylamine and aniline derivatives with high conversion. More flexible chelating ligands like dppm and dppb gave little to no conversion of the starting materials (Entry 5-6). DppBz, a more rigid ligand also provided little to no conversion of the alkene substrate. This is in part due to its smaller natural bite angle when compared to other larger chelating ligands such as XantPhos (83° and 108° respectively) which gave full conversion and 67% NMR yield of the substrate (Entry 7-8). To explore the optimal bite angle and electronics for the catalyst system, bulky chelating ligands with smaller bite angle were also explored. DPEPhos gave improved results both in the conversion of the starting materials to the desired intermediate and in reducing intramolecular Heck cyclization (Entry 9). Replacing the electron-withdrawing phenyl groups on the phosphine with comparably more electron-donating cyclohexyl groups gave low conversion of the starting materials which indicated that having a more electron poor catalyst system was preferential. Finally, dppf (bite angle 99°) and BINAP (bite angle 93°) were employed and successfully gave full conversion of the starting materials (Entry 11-12). Ultimately BINAP was chosen due to the added benefit of providing no intramolecular Heck cyclization. Increasing the equivalents of base from 2.0 to 3.0 equivalents gave diminished yields and increased Heck cyclization.

Table 5-1: N-Arylation Reaction Optimization[ab]



5-1a **5-2a** **5-3a** **5-4a**

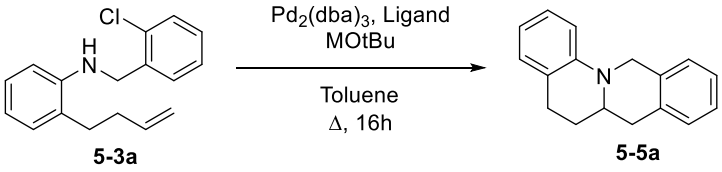
Entry	Ligand	MOtBu	NMR Yield	
1	BrettPhos	NaOtBu	trace	32%
2	tBuBrettPhos	NaOtBu	24%	26%
3	JohnPhos	NaOtBu	54%	17%
4	JohnPhos	LiOtBu	trace	63%
5	dppm	NaOtBu	0%	32%
6	dppb	NaOtBu	0%	0%
7	dppBz	NaOtBu	0%	18%
8	XantPhos	NaOtBu	67%	10%
9	DPEPhos	NaOtBu	75%	5%
10	Cy_4DPEPhos	NaOtBu	trace	10%
11	dppf	NaOtBu	90%	6%
12	BINAP	NaOtBu	quant. (95%)[b]	0%
13	BINAP	NaOtBu	51%[c]	18%

[a]Reaction conditions: 1 equiv of **5-1a**, 1.2 equiv **5-2a**, 1 mol % $Pd_2(dba)_3$, 1:2 $Pd_2(dba)_3$ to ligand ratio, 2 equiv base, 0.1 M toluene, 105 °C, 16h. [b]Yield in paranthesis represents an unaveraged isolated yield. [c]3.0 equiv base was used. Thank you to Glorimar Miranda for helping conduct these experiments.

Optimization for the alkene carboamination was then conducted. Fortunately, our lab has shown precedence for intramolecular alkene carboamination reactions using electron-rich bidentate and monodentate ligands.[5] PCy_3HBF_4 has frequently been used in the alkene carboamination and, when used in our system, gave excellent yields of **5-5a**. However, for the sake of being thorough, other commonly explored alkene

carboamination ligands were explored as well. Electron-withdrawing and electron-donating bidentate ligands were first explored but none provided the desired fused poly-heterocycle due to poor conversion of the starting material (Table 5-2; Entry 1-3). Switching to the electron-rich monodentate phosphine ligand PCy_3HBF_4 allowed for the conversion of **5-3a** and gave **5-5a** in excellent yield (Entry 4). Again, switching from sodium tert-butoxide to lithium tert-butoxide only gave diminished yields. Attempting to lower the reaction temperature from 105°C to 80°C only resulted in partial conversion of the **5-3a** and only 59% of **5-5a**. In all cases, no other side product was detected by NMR.

Table 5-2: Alkene Carboamination Reaction Optimization[ab]



5-3a **5-5a**

Entry	Ligand	MOtBu	NMR Yield
1	DPEPhos	NaOtBu	0%
2	XantPhos	NaOtBu	trace
3	CyDPEPhos	NaOtBu	trace
4	PCy_3HBF_4	NaOtBu	93% (85%)[b]
5	PCy_3HBF_4	LiOtBu	27%
6	PCy_3HBF_4	NaOtBu	59%[c]

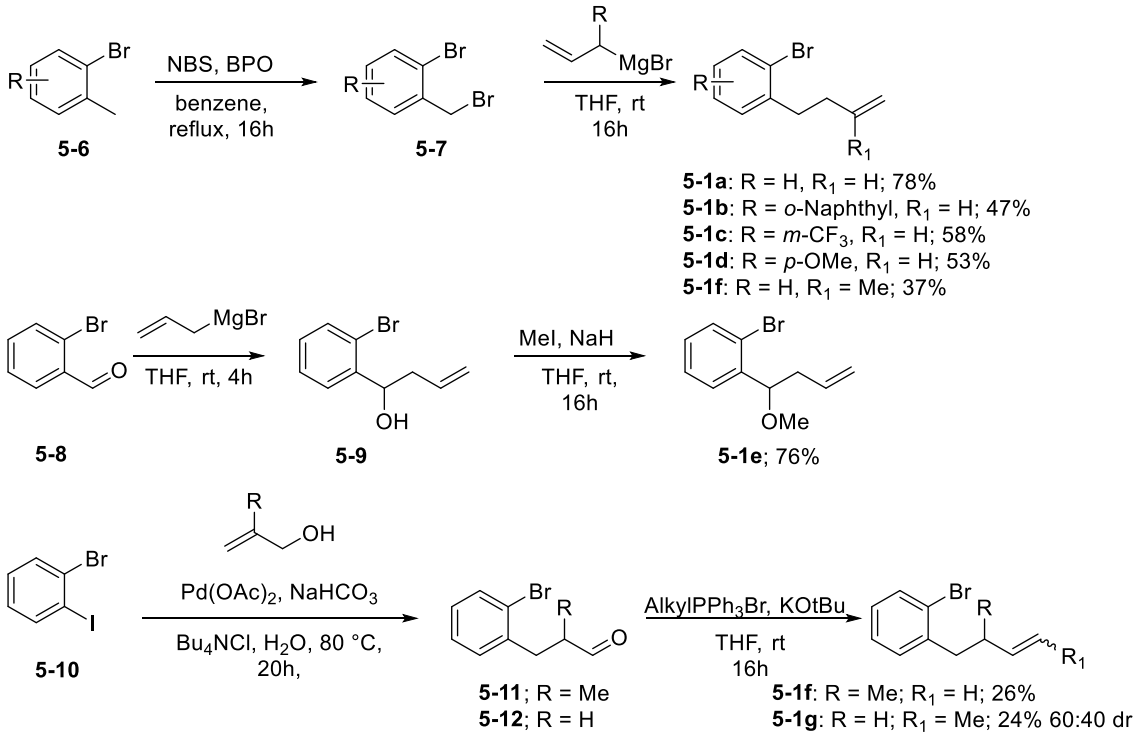
[a]Reaction conditions: 1 equiv of **5-3a**, 2 mol % $Pd_2(dba)_3$, 1:2 Pd to ligand ratio, 2 equiv base, 0.1 M toluene, 105 °C, 16h. [b]Yield in paranthesis represents an unaveraged isolated yield. [c]Reaction run at 80°C. Thank you to Glorimar Miranda for helping conduct these experiments.

5.3 Synthesis of Starting Materials and Reaction Scope

The starting materials for these studies can be readily synthesized from simple starting materials in two through four synthetic steps. For **5-1**, cheap and functionalized

o-bromotoluene derivatives can be transformed via bromination to generate *o*-bromobenzylbromide derivatives **5-7**. Allyl Grignard can then be used to perform the necessary alkyl S_N2 (Scheme 5-2). Functionalizing the benzylic position can be easily done from the corresponding *o*-bromobenzaldehyde **5-8** by subjecting it to allyl Grignard to give the free alcohol **5-9**. For there, S_N2 substitution with iodomethane can be done to generate **5-1e**. Synthesis of **5-1f-g** can be done by coupling *o*-bromoiodobenzene **5-10** with either 2-Methyl-2-propen-1-ol or allyl alcohol via a Heck arylation to give the respective aldehydes **5-11** and **5-12**. From there, a Wittig olefination can be done to generate the terminal or internal alkene.

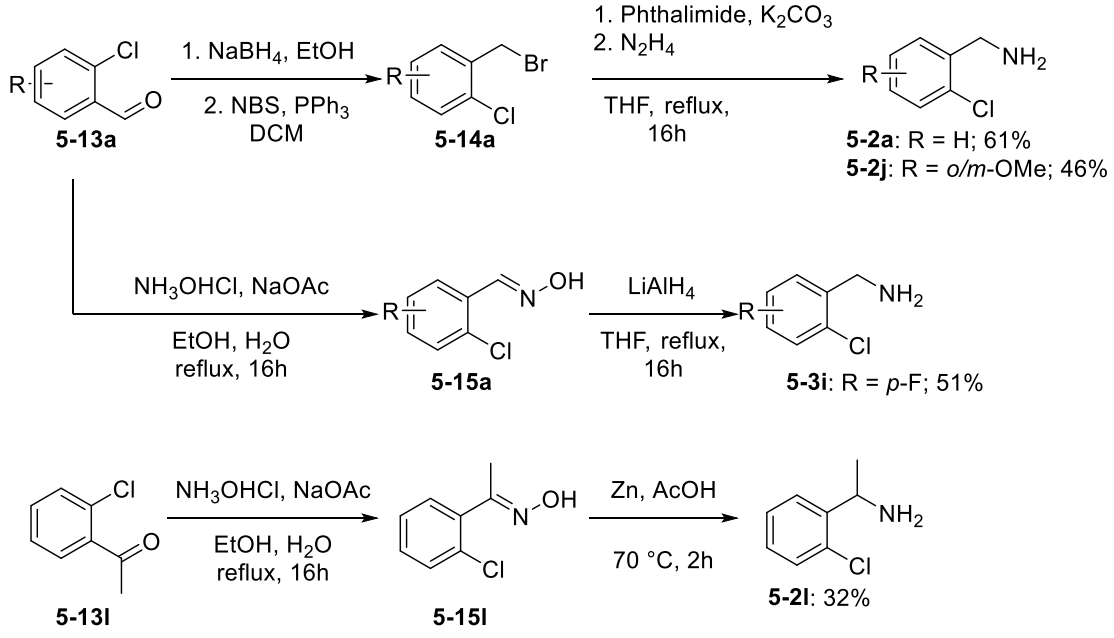
Scheme 5-2: Representative Synthesis of Alkenyl Substrate



Derivatives of substrates **5-2** were either commercially available (such as **5-2a**) or readily synthesized from corresponding functionalized *o*-chlorobenzaldehydes in two to four steps. *There was not a consensus way of making these derivatives so multiple*

synthetic pathways were explored. While 5-2a is commercially available, it can also be synthesized through the following route and will be shown as the representative synthesis in Scheme 5-3. The most reliable synthesis was reduction of **5-13a** with sodium borohydride, followed by bromination to **5-14a**. A Gabriel amine synthesis can be conducted to give the corresponding benzylamine **5-2a** in four steps. In favor of a shorter synthetic route, *o*-chlorobenzaldehydes can be condensed with hydroxylamine salt to give the free oxime **5-15a**. Reduction of the oxime with lithium aluminum hydride afforded the corresponding benzylamine **5-2a** derivatives in two steps. In the case of α-substitution, reduction with lithium aluminum hydride generally gave little to no desired product. Fortunately, dissolving metal reduction conditions involving zinc dust and acetic acid allowed for complete reduction to give α-substituted benzylamine derivative **5-2c**.

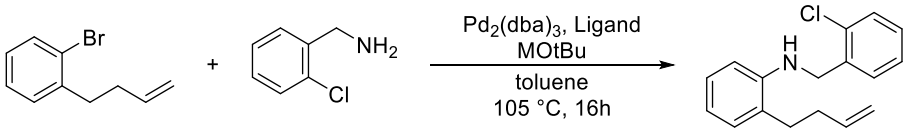
Scheme 5-3: Representative Synthesis of Benzylamine Substrates



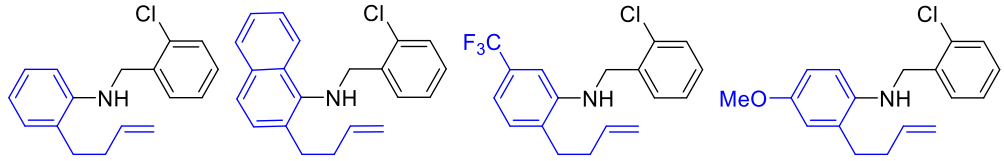
In our initial studies, we elected to examine the *N*-arylation reactivity of *o*-homoallylbromobenzene derivatives **5-1.** Simple, unfunctionalized **5-1a** gave 98%

averaged isolated yield (Table 5-3). When incorporating a naphthyl substitution ortho to the bromine we were pleased to see that reactivity was well-tolerated (88%) as oxidative addition and aminopalladation of the more hindered substrate was expected to be challenging. We were also pleased to see that, although adding electron withdrawing and electron donating substituents to the substrate led to slightly reduced yields, the reduction in yields were roughly comparable in reactions of substrates bearing either electron-withdrawing (**5-3c**) or electron-donating (**5-3d**) groups. Substitution along the alkyl chain (**5-3e-h**) was also tolerated. It is worth noting that, generally, the closer the substitution is to the oxidative addition site, the worse the yield of the **5-1.** This issue was remedied when 2.0 equivalents of benzylamine were used and the reaction was concentrated to 0.5 M (**5-3e and 5-3f**).

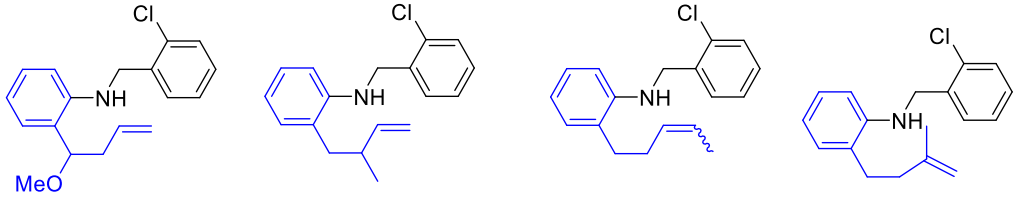
Table 5-3: N-Arylation Reaction Scope[ab]



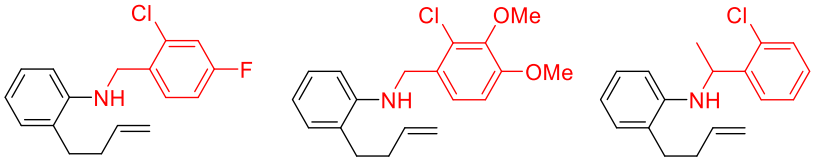
5-1a + **5-2a** → **5-3a**



5-3a 98% | **5-3b** 88% | **5-3c** 78% | **5-3d** 74%



5-3e 64%[c] | **5-3f** 61%[c] | **5-3g** 80%[d] | **5-3h** 95%



5-3i 79% | **5-3j** 66% | **5-3k** 45%[e]

[a]Reaction conditions: 1 equiv of **5-1**, 1.2 equiv **5-2**, 1 mol % $Pd_2(dba)_3$, 1:2 Pd to ligand ratio, 2 equiv base, 0.1 M toluene, 105°C, 16h. [b]Yields represent averaged isolated yield based on two runs. [c]2 equiv of **5-2** was used, 0.5M toluene [d]Unaveraged isolated yield. [e]NMR Yield**.** Thank you to Glorimar Miranda for helping conduct these experiments.

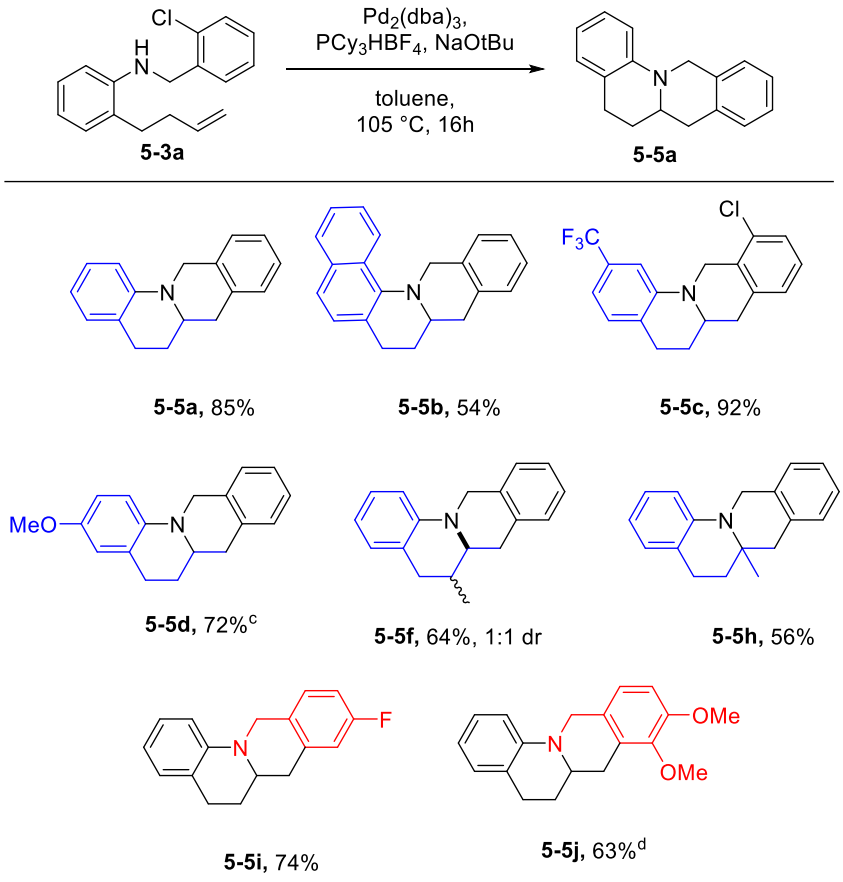
Next, we examined the reactivity of *o*-chlorobenzylamine substrates (**5-2**). We were pleased to see that electron-withdrawing and electron donating groups were also well tolerated on the amine coupling partner (**5-3i** and **5-3j**). A methyl group substituent at the alpha position of the benzylamine was also tolerated although the reaction proceeded in a lower yield (**5-3k;** 45%). It is anticipated that increasing the concentration

of the reaction from 0.1 M to 0.5 M and increasing the equivalencies of benzylamine from 1.2 to 2.0 will help to mitigate this problem.

We also explored the reactivity of **5-3** in the intramolecular alkene carboamination step. Simple, unfunctionalized **5-3a** was smoothly converted to **5-5a** in 85% yield (Table 5-4). The naphthyl-substituted intermediary substrate **5-3b** was also converted to **5-5b** in 54% yield. The current explanation for the reduced yield is the steric clashing of the naphthyl group with the 5-membered palladium-amido complex which hinders the aminopalladation of the alkene. We were also pleased to see that electron- withdrawing (**5-5c**) and donating (**5-5d**) substituents on the aryl ring bearing the amine were well-tolerated in the reaction. In the case of **5-5d**, substrate purification has proven to be an issue because the comparatively electron rich nitrogen readily undergoes oxidative decomposition in air to form a mixture of complex side products that are difficult to isolate. Attempting to run a silica column on the crude mixture also decomposed the product, most likely due to the slightly acidic nature of the column. In addition, attempting to purify through acid/base also readily decomposes the product. This issue is currently being investigated but encouraging early results show that spiking the column with a basic amine such as triethylamine or ammonia helps to slow or completely shut down degradation on silica. Substitution of the allylic position (**5-5f**) and internal alkene position were also well tolerated (**5-5h**). We were somewhat surprised that **5-5f** generated as a 1:1 mixture of diastereomers as these alkene carboamination reactions tend to be diastereoselective.[10] An explanation for the stereochemistry is given in Chapter 5, Section 5. Electron-withdrawing (**5-5i**) and electron-donating (**5-5j**) groups were on the aryl ring bearing the chlorine were also well tolerated. However, ortho substitution of the aryl

chloride required longer reaction times and did not give full conversion of **5-3j**. Exploration of both reaction scopes are still ongoing in the lab.

Table 5-4: Alkene Carboamination Scope[ab]



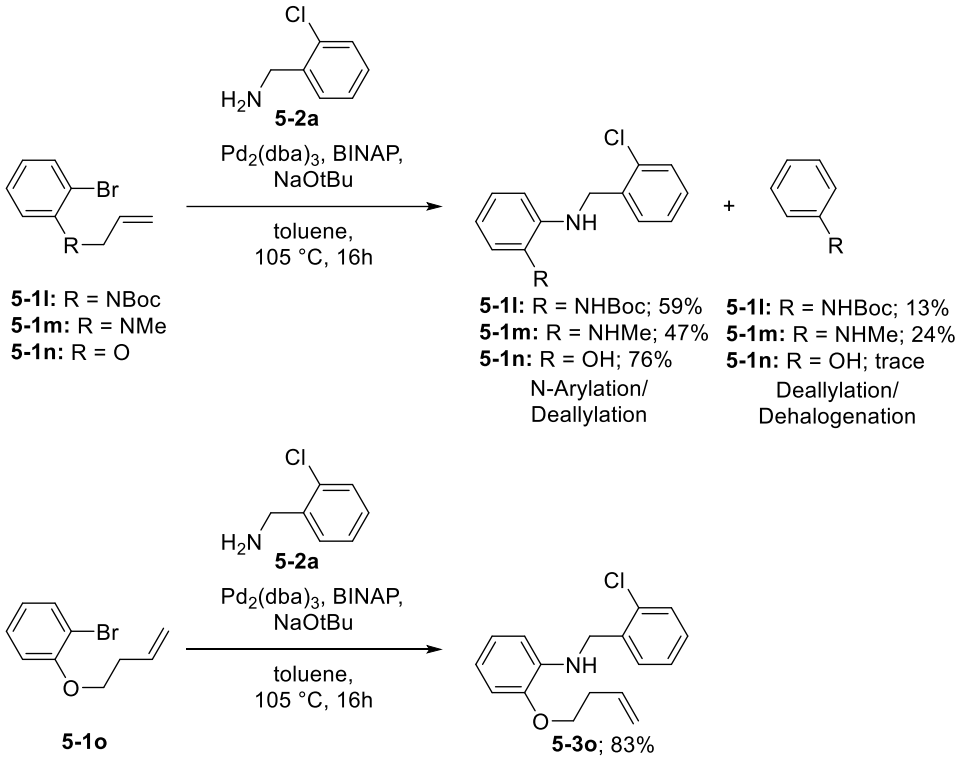
[a]Reaction conditions: 1 equiv of **5-3**, 2 mol % $Pd_2(dba)_3$, 1:2 Pd to ligand ratio, 2 equiv base, 0.1 M toluene, 105 °C, 16h. [b]Yields represent averaged isolated yield based on two runs. [c]Yield represents an NMR Yield. [d]Yield represents an unaveraged isolated yield. Thank you to Glorimar Miranda for helping conduct these experiments.

5.4 Scope Limitations

Although the explored *N*-arylation and alkene carboaminations reactions were reasonably efficient, efforts to extend this pathway to **5-1** derivatives where the benzylic position is replaced by a heteroatom (**5-1l-n**) were unsuccessful (Scheme 5-4). In all

cases, a mixture of *N*-arylated/deallylated and deallylated/dehalogenated substrates were observed. Performing a screen of ligands and reaction parameters did not yield any desired reactivity. To confirm that the heteroallylic substitution was the issue, we synthesized **5-1o** which has an additional methylene separating the oxygen from the allyl substituent and subjected it to the optimized *N*-arylation conditions. We were pleased to see that **5-3o** was formed in 83% and no dealkylation of the oxygen was present.

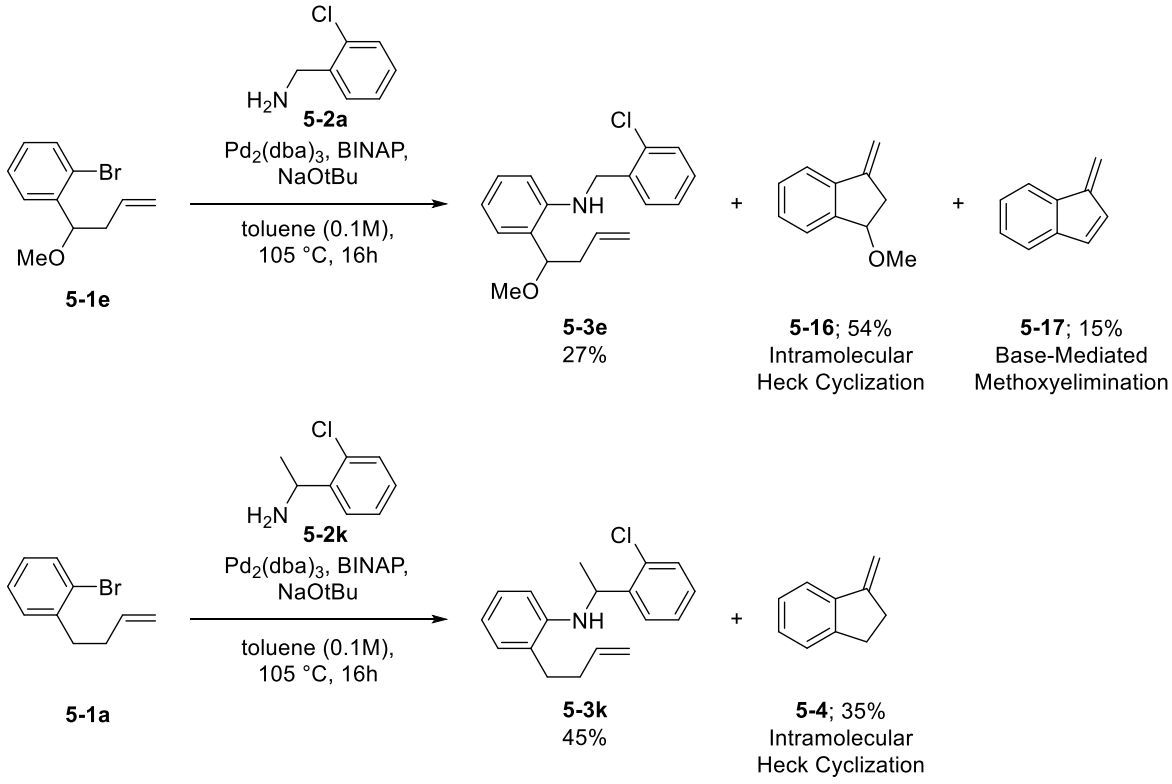
Scheme 5-4: Deallylation of Heteroatom-Substituted Benzylic Position



As mentioned earlier, substitution at the benzylic and allylic positions of **5-1** and **5-2** often resulted in poor conversion of the starting materials to **5-3**. **5-1e**, which bears a methoxy substituent at the benzylic position, favored the intramolecular Heck cyclization and base-mediated elimination of the methoxy group. This is because of added steric hindrance around the oxidative addition site. **5-2l**, which bears a methyl substituent at the benzylic position, gave reduced yields of **5-3k** because formation of the palladium-amido

complex after oxidative addition is higher in energy with a more sterically hindered amine. To solve this issue, the concentration of both the reaction and the benzylamine were increased from 0.1 M to 0.5 M and from 1.2 equivalents to 2.0 equivalents, respectively. In similar chemical systems, intramolecular reactions tend to have higher reaction rates than intermolecular reactions due to the highly effective concentration of the nucleophile and electrophile. By further increasing the concentration of both the reaction and **5-2**, we were pleased to see that yield of **5-3e** was increased (Table 5-3). The same method will also be applied to the formation of **5-3k**.

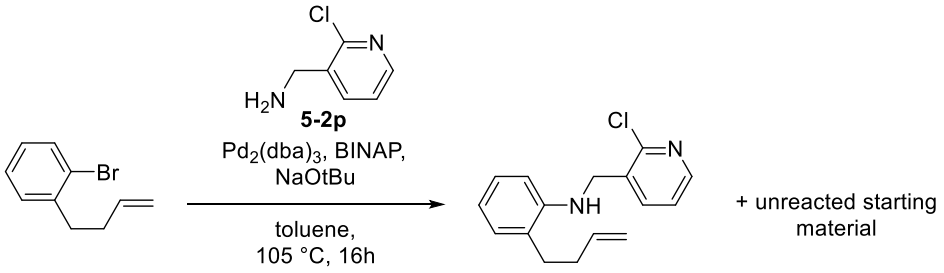
Scheme 5-5: Intramolecular Heck Cyclization of Sterically Hindered Starting Materials



When employing *o*-chloropyridinylethylamine **5-2p**, **5-3p** was not observed and quantitative amounts of starting materials were detected by NMR (Scheme 5-6). This is because 2-halopyridines are very reactive in oxidative addition processes and typically

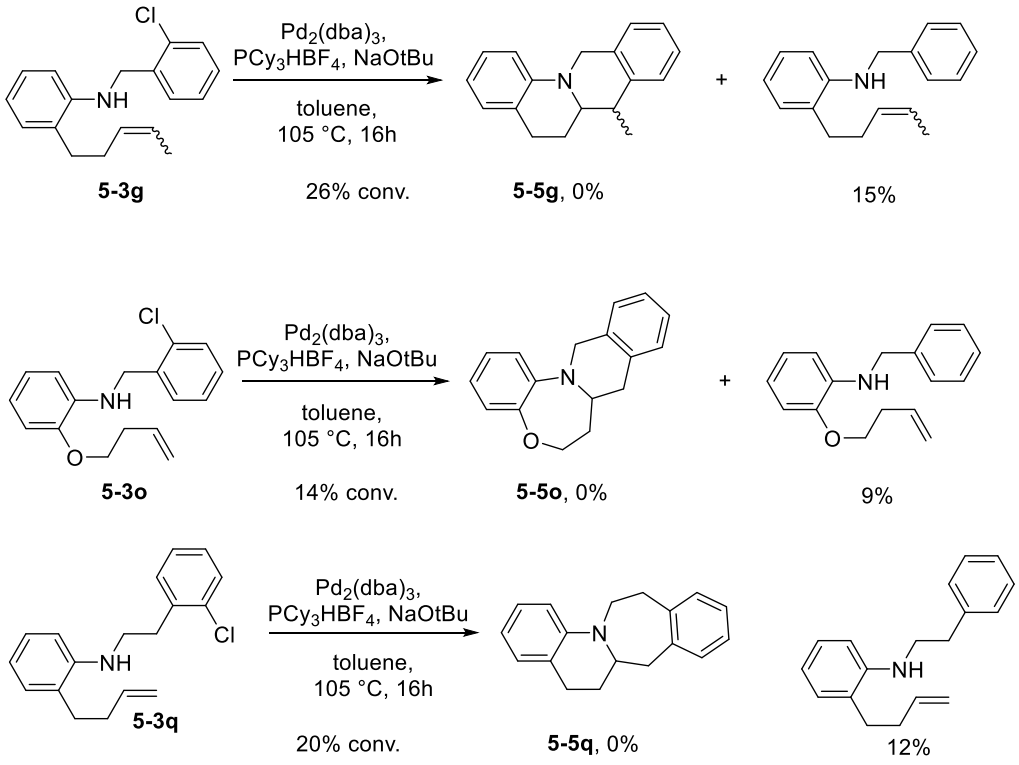
are more reactive than aryl halides.[6] A potential solution to this problem could be switching from an aryl bromide to an aryl triflate as they generally have higher rates of oxidative addition than 2-chloropyridinyl coupling partners.[6a]

Scheme 5-6: No Reactivity When Using o-Chloropyridinyl Starting Materials



Based on the current scope shown in Table 5-4, the scope of our alkene carboamination has been robust. However, some limitations of the reaction in this system include no reactivity when an internal alkene is used (Scheme 5-7; **5-3g**). This stems from a disfavorable aminopalladation from the palladium-amido complex which slows down the rate of migratory insertion. The main side product of the reaction consists of dehalogenation of the intermediary substrate and mostly unreacted starting material. Intermediary substrates, **5-3p** and **5-3r**, which lead to seven-membered ring products also gave no conversion. This was unsurprising as there are very few reported methods of alkene carboamination reactions leading to seven-membered heterocycles. This is due to two main issues: 1) As the ring size increases, syn-aminopalladation of the alkene becomes more difficult because of entropic and stereoelectronic effects[7] and 2) competing formation of enamine side products via β-hydride elimination becomes more problematic.[7] In both cases, the main side product is dehalogenation and mostly unreacted starting material.

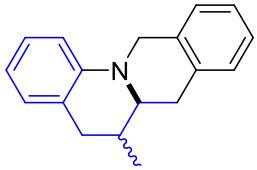
Scheme 5-7: No Reactivity with Internal Alkenes and 7-Membered Ring Precursors



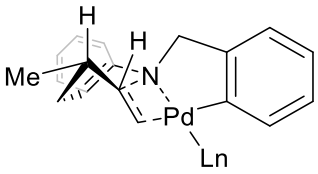
5.5 Stereochemical Explanation

The explanation for the stereoselectivity, or lack thereof, in the reaction to generate **5-5f** likely arises during the alkene aminopalladation step of the catalytic cycle. In the conversion of **5-3f** to **5-5f**, the alkene insertion step most likely proceeds via the boat-like transition states **5-18** and **5-19** (Scheme 5-8) which may be relatively close in energy as there is little axial strain resulting from the allylic methyl group in both, leading to the poor observed selectivity. For the formation of six-membered rings resulting from syn-aminopalladation, the transition state typically goes through boat-like transition states because of the difficulty to have the alkene and the amino-palladium bond to be eclipsed which is required for the alkene insertion to occur.[7a-b]

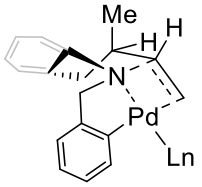
Scheme 5-8: Boat-like Transition States for Alkene Carboamination



5-5f, 64%, 1:1 dr



5-18



5-19

5.6 Conclusion and Future Work

In conclusion, we have demonstrated that fused polycyclic *N*-heterocycles such as tetrahydroisoquinolinoquinolines can be readily synthesized through a sequential *N*-arylation/alkene carboamination strategy. The *N*-arylation step is fairly robust, tolerating both electron-donating and withdrawing groups on the aryl ring of both starting substrates. In the case of substitution on the alkyl chain of both substrates, increasing the concentration of the reaction and benzylamine improved starting material conversion and mitigated unwanted intramolecular Heck cyclization. The alkene carboamination step also proved to be fairly robust, tolerating both electron-donating and withdrawing groups on the aryl rings of the intermediary substrate as well as substitution on the allylic and internal alkene position. The poor stereocontrol resulting from methyl substitution at the allylic position most likely results from competing boat-like transition states of relatively close energetic stability.

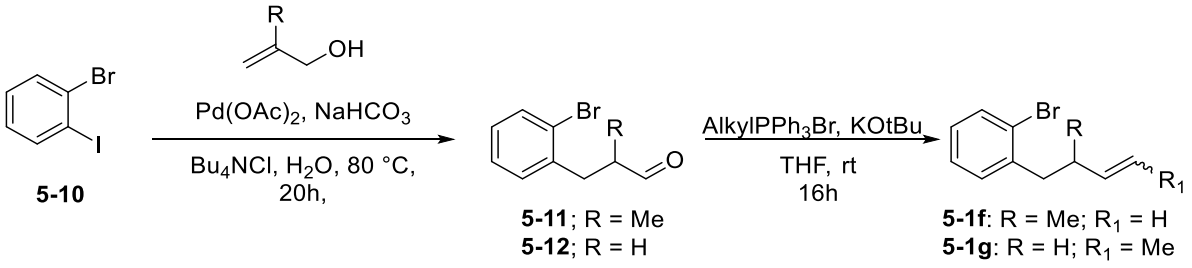
Future directions will be geared towards further expanding the substrate scope of both the *N*-arylation and alkene carboamination step, particularly in regards to substitution at the benzylic position of **5-1**, exploring synthesis of the 5/6, 6/5, and 5,5 ring systems, and investigating the stereocontrol regarding other positions across the molecule. This strategy will also be implemented for the coupling of 5-1 derivatives with alkenyl

(pseudo)halides. Finally, this alkene carboamination strategy will be used towards the synthesis of berberine natural product derivatives.

5.7 Experimental

General: All reactions were carried out under a nitrogen atmosphere using oven or flame-dried glassware. All palladium sources and reagents including **5-2a** were obtained from commercial sources and used without further purification unless otherwise noted. *o*-Bromohomoallybenzene substrates **5-1a-h,**[8a-e] **5-1m-p**[8f] and *o*-chlorobenzylamines **5-2i-k,**[9a-b] **5-2p**[9c] were synthesized according to known procedures were prepared according to previously reported procedures. Toluene was purified using a GlassContour solvent purification system. All yields refer to isolated compounds that are estimated to be ≥ 95% pure as judged by ^{1}H NMR analysis unless otherwise noted. *The yields reported in the experimental section describe the result of a single experiment, whereas yields reported in Table 5-3 and 5-4 are average yields of two or more experiments. Thus, the yields reported in the experimental section may differ from those shown in Tables 5-3 and 5-4.*

Preparation and Characterization of Starting Materials



5-10

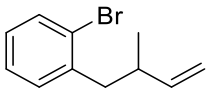
5-11; R = Me
5-12; R = H

5-1f: R = Me; R_1 = H
5-1g: R = H; R_1 = Me

A flame-dried roundbottom flask equipped with a stir bar was cooled under a stream of N_2 and charged with $Pd(OAc)_2$ (63.5 mg, 0.28 mmol, 2 mol%), $NaHCO_3$ (3.0 g, 35.4 mmol, 2.5 eq), and tBu_4NCl (3.9 g, 14.1 mmol, 1.0 eq). *o*-Bromoiodobenze and allyl alcohol

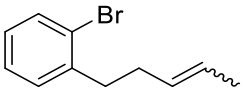
derivative was diluted in deionized water and syringed into the reaction vessel. The reaction was lowered into an oil bath at 80°C and allowed to stir for 20h. The crude mixture was filtered over celite to remove solid impurities and diluted in Et_2O. The layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and rotavaped. The crude material was purified via column chromatography using 15% EtOAc in Hexanes to give the corresponding aldehyde (**5-11/5-12** depending on allyl alcohol derivative used). **5-11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 3.25 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.90 – 2.77 (m, 1H), 2.69 (dd, *J* = 13.7, 8.1 Hz, 1H), 1.12 (d, *J* = 7.1 Hz, 3H). **5-12**: ^{1}H NMR (401 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.09 (ddd, *J* = 8.1, 5.4, 3.7 Hz, 1H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H).

Alkyltriphenylphosphonium bromide (15.7 mmol, 2.0 eq) was dissolved in THF and cooled to 0°C under N_2 atmosphere. nBuLi (15.7 mmol, 2.0 eq) was added dropwise over the course of 30 minutes and the reaction was allowed to stir for an additional 1 hour. **5-11/5-12** (7.84 mmol, 1.0 eq) was dissolved in 5 mL of THF and added dropwise. The reaction was stirred for an additional 2-16 hours at 0°C. The reaction mixture was quenched with NH_4Cl, diluted with Et_2O and H_2O. The layers we separated 3 times, and the organic layer was dried with Na_2SO_4, filtered, and rotavaped. The crude mixture was purified via column chromatography using 1% EtOAc in Hexanes to give the corresponding alkene (**5-1f/5-1g** depending on which alkyltriphenylphosphonium bromide was used; **5-1g** was formed in 60:40 d.r.).



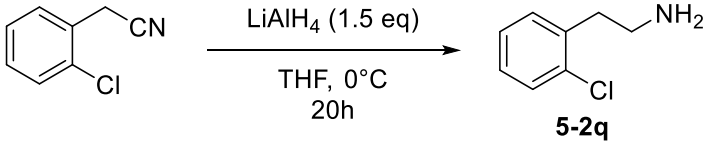
1-Bromo-2-(2-methylbut-3-en-1-yl)benzene (5-1f).

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.12 (m, 1H), 7.05 (td, *J* = 7.6, 1.9 Hz, 1H), 5.88 – 5.74 (m, 1H), 4.98 – 4.88 (m, 1H), 2.79 (dd, *J* = 13.3, 7.1 Hz, 1H), 2.73 – 2.64 (m, 1H), 2.57 (p, *J* = 7.0 Hz, 1H), 1.03 (d, *J* = 6.7 Hz, 3H).



1-Bromo-2-(pent-3-en-1-yl)benzene (5-1g).

^{1}H NMR (401 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.11 – 6.99 (m, 1H), 5.55 – 5.39 (m, 2H), 2.78 (dd, *J* = 9.0, 6.7 Hz, 2H), 2.42 – 2.32 (m, 1.5H), 2.32 – 2.25 (m, 0.5H), 1.66 (d, *J* = 4.1 Hz, 0.5H), 1.57 (d, *J* = 5.0 Hz, 2.5H).



5-2q

2-(2-Chlorophenyl)ethan-1-amine (5-2q).

In a flame-dried roundbottom flask was equipped a stir bar and cooled under a N_2 atmosphere. 2-(2-chlorophenyl)acetonitrile (1.0 g, 6.60 mmol, 1 eq) was dissolved in Et_2O and added to the reaction vessel, purged again with N_2 gas, and cooled to 0°C. $LiAlH_4$ (751 mg, 19.8 mmol, 3.0 eq)was added dropwise over the course of 15 minutes and the reaction was allowed to stir for 20h. The crude mixture was quenched with aqueous NH_4Cl and diluted with Et_2O. The layers were separated, and the organic layer was dried with

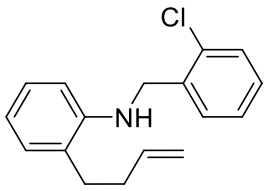
Na_2SO_4, filtered, and rotavaped. The crude mixture was purified by acid/base extraction using 1M HCl and 3M NaOH. The organic layer was again dried over Na2SO4, filtered and rotavaped to give **5-2q** in 46% yield. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.36 (d, *J* = 9.2 Hz, 1H), 7.27 – 7.11 (m, 3H), 3.03 – 2.94 (m, 2H), 2.93 – 2.85 (m, 2H), 1.29 (s, 2H).

Preparation and Characterization of Products

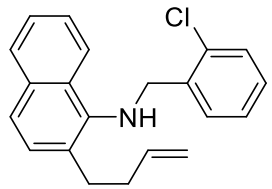
General Procedure 1: Pd-Catalyzed *N*-Arylation Reactions. A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of N_2 and charged with $Pd_2(dba)_3$ (1 mol %), BINAP (4 mol %), and NaOtBu (0.6 mmol, 2 equiv). The tube was capped with a rubber septum, then was evacuated and back-filled with N_2 gas three times. The appropriate *o*-bromohomoallybenzene (0.3 mmol, 1 equiv) and the appropriate *o*-chlorobenzylamines (.36 mmol, 1.2 equiv) were dissolved in toluene (3 mL, 0.1 M) and added via syringe. The reaction mixture was heated to 105 ˚C for 16 hours unless otherwise specified . The mixture was then cooled to room temperature, diluted with either Et_2O or DCM and filtered through a packed pad of celite. Additional Et_2O or DCM was eluted through the celite to ensure minimal compound loss. The resulting solution was concentrated *in* vacuo, and the crude product was purified by flash chromatography on silica gel.

General Procedure 2: Pd-Catalyzed Alkene Carboamination Reactions. A flame-dried Schlenk tube equipped with a stir bar was cooled under a stream of N_2 and charged with the $Pd_2(dba)_3$ (2 mol %), PCy_3HBF_4 (8 mol %), and NaOtBu (0.6 mmol, 2 equiv). The tube was capped with a rubber septum, then was evacuated and back-filled with N_2 gas three times. The appropriate intermediate (0.3 mmol, 1 equiv) was dissolved in toluene

(3 mL, 0.1 M) and added via syringe. The reaction mixture was heated to 105˚C for 16 hours unless otherwise specified. The mixture was then cooled to room temperature, diluted with either Et_2O or DCM and filtered through a packed pad of celite. Additional Et_2O or DCM was eluted through the celite to ensure minimal compound loss. The resulting solution was concentrated *in* vacuo, and the crude product was purified by flash chromatography on silica gel.

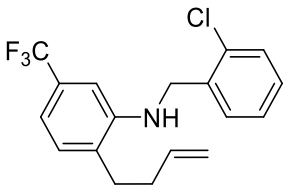


2-(But-3-en-1-yl)-*N*-(2-chlorobenzyl)aniline (5-3a). General procedure 1 was used for the coupling of **5-1a** (63.3 mg, 0.3 mmol, 1 equiv.) with **5-2a** (51.0 mg, 0.3 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.36 (m, 2 H), 7.24–7.18 (m, 2 H), 7.12–7.05 (m, 2 H), 6.71 (t, *J* = 7.5 Hz, 1 H), 6.57 (d, J = 8.2 Hz, 1 H), 5.99 – 5.87 (m, 1 H), 5.11 (d, *J* = 17.9 Hz, 1 H), 5.03 (d, *J* = 10.5 Hz, 1 H), 4.49 (s, 2 H), 4.14 (s, 1 H), 2.63 (t *J* = 7.6 Hz, 2 H), 2.47 – 2.38 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 138.1, 136.7, 133.3, 129.6, 129.1, 129.0, 128.4, 127.3, 126.9, 125.6, 117.5, 115.1, 110.7, 46.0, 32.8, 30.7. IR (film) 3446, 3069, 2925, 1604, 1509 cm^{-1}; HRMS (ESI^+) m/z: $[M + H]^+$ calcd for $C_{17}H_{18}ClN$ 272.1180; found 272.1172.



2-(But-3-en-1-yl)-*N*-(2-chlorobenzyl)naphthalen-1-amine (5-3b).

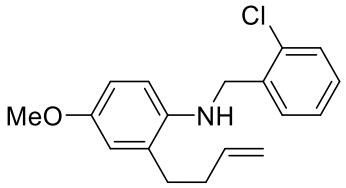
General procedure 1 was used for the coupling of **5-1b** (78.4 mg, 0.3 mmol, 1 equiv.) with **5-2a** (51.0 mg, 0.3 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 92% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.6 Hz, 1 H), 7.80 (d, J = 7.6 Hz, 1 H), 7.52 (d, J = 8.4 Hz, 1 H), 7.48 (t, J = 7.1 Hz, 1 H), 7.46 – 7.40 (m, 2 H), 7.37 (m, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.25 – 7.20 (m, 2 H), 5.91 – 5.81 (m, 1 H), 5.05 (d, *J* = 17.4 Hz, 1 H), 5.00 (d, *J* = 9.7 Hz, 1 H), 4.39 (s, 2 H), 3.92 (s, 1 H), 2.75 (t, J = 7.6 Hz, 2 H), 2.35 – 2.30 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.6, 138.0, 137.7, 133.8, 133.7, 130.6, 130.2, 129.7, 129.4, 128.8, 128.5, 128.2, 127.2, 125.8, 125.3, 123.6, 123.5, 115.5, 52.6, 35.2, 31.2. IR (film) 3378, 3083, 2946, 1606, 1511 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{20}ClN$, 322.1364; found, 322.1362



2-(But-3-en-1-yl)-*N*-(2-chlorobenzyl)-5-(trifluoromethyl)aniline (5-3c).

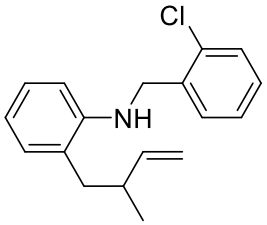
General procedure 1 was used for the coupling of **5-1c** (83.7 mg, 0.3 mmol, 1 equiv.) with **5-2a** (51.0 mg, 0.3 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 78% yield. ^{1}H

NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 1 H), 7.40 – 7.33 (m, 1 H), 7.27 – 7.23 (m, 2 H), 7.15 (d, *J* = 7.7 Hz, 1 H), 6.95 (d, *J* = 6.0 Hz, 1 H), 6.80 (s, 1 H), 5.95 – 5.83 (m, 1 H), 5.06 (m, 2 H), 4.50 (d, *J* = 5.6 Hz, 2 H), 4.25 (s, 1 H), 2.63 (t, J = 7.8 Hz, 2 H), 2.41 (q, *J* = 6.4 Hz, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.6, 137.7, 136.0, 133.8, 130.0, 129.8, 129.6, 129.4, 129.4, 129.1, 127.3, 125.6, 123.8, 115.8, 114.2, 114.2, 114.2, 114.2, 107.0, 106.9, 106.9, 106.9, 46.1, 32.5, 30.7. IR (film) 3364, 3115, 2918, 1517, 1437, 1325 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}ClF_3N$, 340.1080; found, 340.1052



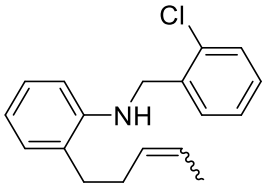
2-(But-3-en-1-yl)-*N*-(2-chlorobenzyl)-4-methoxyaniline (5-3d).

General procedure 1 was used for the coupling of **5-1d** (72.3 mg, 0.3 mmol, 1 equiv.) with **5-2a** (51.0 mg, 0.3 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 5% EtOAc in Hexanes to give the title compound in 74% yield. ^{1}H NMR (600 MHz, $CDCl_3$) d 7.42 – 7.34 (m, 2 H), 7.24 – 7.18 (m, 2 H), 6.71 (d, J = 2.6 Hz, 1 H), 6.66 (dd, *J* = 8.7 Hz, 1 H), 6.51 (d, J = 8.5 Hz, 1 H), 5.96 – 5.87 (m, 1 H), 5.06 (dd, *J* = 47.4 Hz, 2 H), 4.43 (s, 2 H), 3.84 (s, 1 H), 3.74 (s, 3 H), 2.64 – 2.58 (m, 2 H), 2.44 – 2.38 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) d 152.0, 139.4, 138.0, 137.0, 133.3, 129.5, 129.1, 128.3, 127.7, 126.9, 116.0, 115.2, 112.1, 111.5, 55.7, 46.8, 32.9, 30.8. IR (film) 3437, 2929, 1640, 1508, 1468, 1224 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}ClNO$, 302.1311; found, 302.1256.



***N*-(2-Chlorobenzyl)-2-(2-methylbut-3-en-1-yl)aniline (5-3f).**

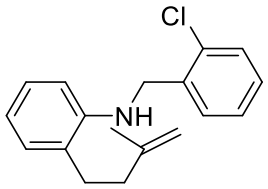
General procedure 1 was used for the coupling of **5-1f** (113.1 mg, 0.5 mmol, 1 equiv.) with **5-2a** (85 mg, 0.6 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 3% EtOAc in Hexanes to give the title compound in 61%. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 2 H), 7.21 (dd, *J* = 5.9, 3.5 Hz, 2 H), 7.12 – 7.00 (m, 2 H), 6.69 (td, *J* = 7.4, 1 H), 6.56 (d, *J* = 8.1 Hz, 1 H), 5.91 – 5.78 (m, 1 H), 5.02 – 4.90 (m, 2 H), 4.48 (s, 2 H), 4.21 (s, 1 H), 2.66 – 2.42 (m, 3 H), 1.06 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 145.4, 144.0, 136.8, 133.2, 130.7, 129.5, 129.0, 128.3, 127.3, 126.9, 124.7, 117.3, 112.9, 110.8, 46.0, 38.8, 36.9, 19.8.



***N*-(2-Chlorobenzyl)-2-(pent-3-en-1-yl)aniline (5-3g).**

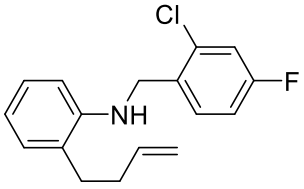
General procedure 1 was used for the coupling of **5-1g** (113.1 mg, 0.5 mmol, 1 equiv.) with **5-2a** (85 mg, 0.6 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 3% EtOAc in Hexanes to give the title compound in 80%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 3 H), 7.24 – 7.19 (m, 3 H), 7.11 – 7.04 (m, 3 H), 6.74 – 6.67 (m, 2 H), 6.58 – 6.52 (m, 2 H), 5.54 – 5.50 (m, 1 H), 5.52 – 5.46 (m, 2 H), 4.48 (d, *J* = 5.2 Hz, 3 H), 4.15 (s, 2 H), 2.57 (dd, *J* = 9.1, 6.4 Hz, 3 H), 2.45 – 2.38 (m, 2 H), 2.37

– 2.31 (m, 1 H), 1.66 (d, *J* = 4.9 Hz, 1 H), 1.57 (d, *J* = 4.7 Hz, 3 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 145.2, 145.2, 136.8, 136.8, 133.3, 130.7, 129.6, 129.6, 129.6, 129.1, 129.1, 129.0, 128.4, 128.4, 127.2, 127.2, 127.0, 126.0, 125.9, 125.7, 124.8, 117.5, 117.5, 110.6, 110.6, 46.0, 45.9, 31.8, 31.4, 31.1, 26.0, 18.0, 12.8. HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}ClN$, 286.1362; found, 286.1317



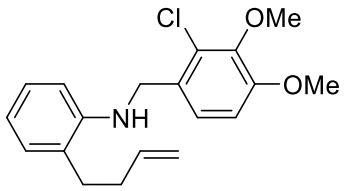
***N*-(2-Chlorobenzyl)-2-(3-methylbut-3-en-1-yl)aniline (5-3h).**

General procedure 1 was used for the coupling of **5-1h** (45.0 mg, 0.2 mmol, 1 equiv.) with **5-2a** (34.0 mg, 0.24 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 2 H), 7.24 – 7.19 (m, 2 H), 7.11 – 7.05 (m, 2 H), 6.71 (t, *J* = 7.3 Hz, 1 H), 6.56 (d, *J* = 8.1 Hz, 1 H), 4.76 (d, J = 7.1 Hz, 2 H), 4.50 (s, 2 H), 4.14 (s, 1 H), 2.66 (t, J = 8.7 Hz, 2 H), 2.35 (t, J = 8.4 Hz, 2 H), 1.79 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6, 129.6, 129.1, 128.9, 128.4, 127.2, 126.9, 110.3, 46.0, 36.7, 29.7, 22.7. IR (film) 3321, 3106, 2862, 1601, 1488 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}ClN$, 286.1362; found, 286.1296



2-(But-3-en-1-yl)-*N*-(2-chloro-4-fluorobenzyl)aniline (5-3i).

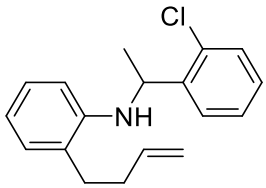
General procedure 1 was used for the coupling of **5-1a** (105.6 mg, 0.5 mmol, 1 equiv.) with **5-2i** (95.8 mg, 0.6 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 79% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.6, 6.1 Hz, 1 H), 7.16 (dd, *J* = 8.4, 2.6 Hz, 1 H), 7.10 – 7.06 (m, 2 H), 6.93 (td, *J* = 8.3, 2.6 Hz, 1 H), 6.75 – 6.69 (m, 1 H), 6.52 (dd, *J* = 8.6, 1.2 Hz, 1 H), 5.97 – 5.87 (m, 1 H), 5.07 (m, 2 H), 4.44 (d, *J* = 5.3 Hz, 2 H), 4.11 (s, 1 H), 2.65 – 2.59 (m, 2 H), 2.47 – 2.36 (m, 2 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 162.4, 160.9, 144.9, 138.1, 132.6, 129.1, 127.3, 125.7, 117.7, 117.0, 115.2, 114.1, 110.6, 53.4, 45.4, 32.8, 30.7. IR (film) 3391, 2984, 1601, 1488, 1227 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{17}ClFN$, 290.1104; found, 290.1112



2-(But-3-en-1-yl)-*N*-(2-chloro-3,4-dimethoxybenzyl)aniline (5-3j).

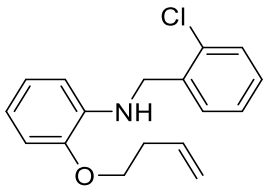
General procedure 1 was used for the coupling of **5-1a** (211.1 mg, 1.0 mmol, 1 equiv.) with **5-2j** (242 mg, 1.2 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 10% EtOAc in Hexanes to give the title compound in 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.05 (m, 3 H), 6.78 (d, *J* = 8.6 Hz, 1 H), 6.70 (t, *J* = 7.4 Hz, 1 H), 6.58 (d, *J* = 8.0 Hz, 1 H), 5.97 – 5.85 (m, 1 H), 5.10 (dd, *J* = 151.7, 16.9 Hz, 2 H), 4.41 (s, 2 H), 4.09 (s, 1 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 2.61 (t, *J* = 7.0 Hz, 2 H), 2.44 – 2.36 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 145.7, 145.2, 138.1, 129.5, 129.0, 127.7, 127.2, 125.6, 123.8, 117.4, 115.1, 110.7, 110.4, 60.6, 56.1, 45.8, 32.8, 30.7. IR (film):

3438, 2930, 2836, 1447, 1290, 1263 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{17}ClFN$, 332.1417; found, 332.1362



2-(But-3-en-1-yl)-*N*-(1-(2-chlorophenyl)ethyl)aniline (5-3k).

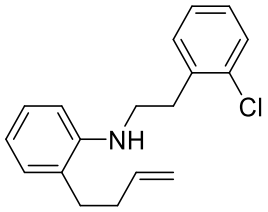
General procedure 1 was used for the coupling of **5-1a** (63.3 mg, 0.3 mmol, 1 equiv.) with **5-2k** (56.0 mg, 0.5 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 54%. ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.45 – 7.33 (m, 2H), 7.20 – 7.13 (m, 2H), 7.04 (d, *J* = 5.8 Hz, 1H), 6.94 (t, *J* = 7.7 Hz, 1H), 6.63 (t, *J* = 6.8 Hz, 1H), 6.22 (d, *J* = 8.1 Hz, 1H), 6.05 – 5.90 (m, 1H), 5.15 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.06 (d, *J* = 10.3 Hz, 1H), 4.92 (q, *J* = 6.7 Hz, 1H), 4.02 (s, 1H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.56 – 2.38 (m, 2H), 1.54 (d, *J* = 6.6 Hz, 3H).



2-(But-3-en-1-yloxy)-*N*-(2-chlorobenzyl)aniline (5-3o).

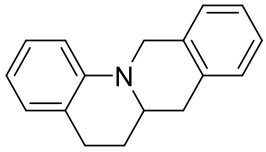
General procedure 1 was used for the coupling of **5-1o** (570.0 mg, 2.5 mmol, 1 equiv.) with **5-2a** (56.0 mg, 1.2 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 83%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 2H), 7.24 – 7.16 (m, 2H), 6.85 – 6.78 (m, 2H), 6.66 (d, *J* = 7.1 Hz, 0H), 6.52 (d, *J* = 6.3 Hz, 1H), 5.91 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.18

(dd, *J* = 17.2, 1.7 Hz, 1H), 5.10 (dd, *J* = 10.3, 1.6 Hz, 1H), 4.92 (s, 1H), 4.47 (s, 2H), 4.08 (t, *J* = 6.6 Hz, 2H), 2.57 (d, *J* = 6.6 Hz, 1H).



2-(But-3-en-1-yl)-*N*-(2-chlorophenethyl)aniline (5-3q).

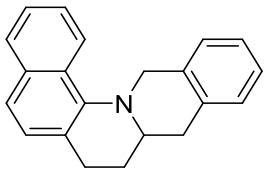
General procedure 1 was used for the coupling of **5-1a** (63.3 mg, 0.3 mmol, 1 equiv.) with **5-2q** (56.0 mg, 0.4 mmol, 1.2 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 58%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.24 (dd, *J* = 7.2, 2.3 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.73 – 6.66 (m, 2H), 5.86 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.70 – 3.67 (m, 1H), 3.47 (t, *J* = 6.9 Hz, 2H), 3.11 (t, *J* = 6.9 Hz, 2H), 2.51 – 2.45 (m, 2H), 2.28 (dt, *J* = 7.8, 6.4 Hz, 2H), 1.53 (s, 1H).



6,6a,7,12-Tetrahydro-5H-isoquinolino[2,3-a]quinoline (5-5a).

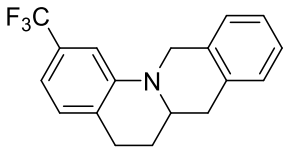
General procedure 2 was used for the cyclization of **5-3a** (81.5 mg, 0.3 mmol, 1 equiv.) The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 5

H), 7.02 (d, 1 H), 6.87 (d, 1 H), 6.71 (t, 1 H), 4.79 (d, *J* = 15.6 Hz, 1 H), 4.24 (d, *J* = 15.6 Hz, 1 H), 3.37 (s, 1 H), 3.00 – 2.77 (m, 3 H), 2.76 – 2.68 (m, 1 H), 2.15 – 2.05 (m, 1 H), 2.00 – 1.89 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 134.8, 134.1, 128.4, 128.3, 127.2, 126.4, 126.2, 126.0, 125.3, 117.3, 112.2, 52.9, 50.1, 37.4, 29.6, 26.7. IR (film) 3023, 2929, 2838, 2360, 1602, 1495 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{17}N$, 236.1439; found, 236.1388



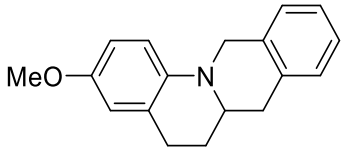
8,8a,9,14-Tetrahydro-7H-benzo[h]isoquinolino[2,3-a]quinoline (5-5b).

General procedure 2 was used for the cyclization of **5-3b** (81.2 mg, 0.25 mmol, 1 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 54% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 1 H), 7.81 – 7.75 (m, 1 H), 7.44 – 7.36 (m, 3 H), 7.28 – 7.17 (m, 4 H), 7.07 (d, *J* = 7.4 Hz, 1 H), 4.52 (s, 1 H), 4.24 (d, *J* = 15.7 Hz, 1 H), 3.53 – 3.46 (m, 1 H), 3.30 (d, *J* = 16.2 Hz, 1 H), 3.12 (m, 1 H), 2.96 (dd, *J* = 16.2 Hz, 1 H), 2.88 (d, *J* = 16.6 Hz, 1 H), 2.08 – 1.94 (m, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9, 135.0, 134.5, 133.7, 128.9, 128.3, 127.9, 126.5, 126.0, 125.7, 125.2, 124.9, 123.8, 121.8, 56.7, 55.1, 35.8, 28.5, 25.6. IR (film) 3046.79, 2931.81, 2823.20, 2790.64 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N$, 286.1595; found, 286.1552



2-(Trifluoromethyl)-6,6a,7,12-tetrahydro-5H-isoquinolino[2,3-a]quinoline (5-5c).

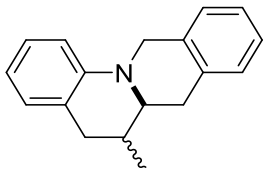
General procedure 2 was used for the cyclization of **5-3c** (92.6 mg, 0.27 mmol, 1 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 88% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 3 H), 7.16 (d, *J* = 7.4 Hz, 1 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 7.00 (s, 1 H), 6.94 (d, *J* = 7.7 Hz, 1 H), 4.75 (d, *J* = 15.5 Hz, 1 H), 4.31 (d, *J* = 15.4 Hz, 1 H), 3.49 – 3.39 (m, 1 H), 2.99 – 2.92 (m, 1 H), 2.92 – 2.84 (m, 1 H), 2.84 – 2.79 (m, 1 H), 2.80 – 2.72 (m, 1 H), 2.15 – 2.06 (m, 1 H), 2.00 – 1.88 (m, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.3, 134.8, 133.7, 129.6, 128.9, 128.5, 128.5, 126.6, 126.6, 126.5, 125.8, 124.0, 113.7, 113.6, 113.6, 113.6, 108.1, 108.1, 108.1, 108.1, 52.9, 49.9, 37.5, 29.9, 29.2, 26.7. IR (film) 2926, 2858, 1326, 1118; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}F_3N$, 304.1313; found, 304.1260



3-Methoxy-6,6a,7,12-tetrahydro-5H-isoquinolino[2,3-a]quinoline (5-5d).

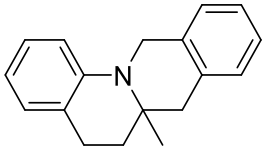
General procedure 2 was used for the cyclization of **5-3d** (90.5 mg, 0.3 mmol, 1 equiv.). The crude product has yet to be purified. ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 (d, *J* = 3.7 Hz, 3 H), 7.13 (d, *J* = 7.4 Hz, 1 H), 6.83 (d, *J* = 8.9 Hz, 1 H), 6.77 – 6.72 (m, 1 H), 6.65 (s, 1 H), 4.76 (d, *J* = 15.5 Hz, 1 H), 4.15 (d, *J* = 15.5 Hz, 1 H), 3.77 (s, 3 H), 3.25 (s, 1 H), 2.96 – 2.83 (m, 2 H), 2.80 (d, *J* = 15.8 Hz, 1 H), 2.70 (d, *J* = 15.6

Hz, 1 H), 2.08 (dd, *J* = 13.1, 5.2 Hz, 1 H), 1.96 – 1.88 (m, 1 H). IR (film) 2929.20, 2849.39, 1500.44, 1243.04; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{20}NO$, 266.1545; found, 266.1502



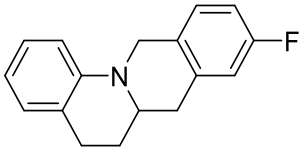
6-Methyl-6,6a,7,12-tetrahydro-5H-isoquinolino[2,3-a]quinoline (5-5f).

General procedure 2 was used for the cyclization of **5-3f** (48.0 mg, 0.168 mmol, 1 equiv.). The crude product was purified via column chromatography using 35% DCM in Hexanes to give the title compound in 65% yield and 1.3:1 diastereoselectivity. ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 7 H), 7.14 – 7.08 (m, 1 H), 7.02 (d, *J* = 7.3, 1.5 Hz, 1 H), 7.00 (d, *J* = 7.3, 1.5 Hz, 0.69 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 6.79 (d, *J* = 8.2 Hz, 0.75 H), 6.70 (t, *J* = 7.3, 1.1 Hz, 1 H), 6.65 (t, *J* = 7.3, 1.1 Hz, 0.71 H), 4.84 (d, *J* = 7.9 Hz, 0.81 H), 4.81 (d, *J* = 8.2 Hz, 1 H), 4.36 (d, *J* = 16.0 Hz, 0.79 H), 4.26 (d, *J* = 15.7 Hz, 1 H), 3.54 (dt, *J* = 11.8, 3.8 Hz, 0.74 H), 3.04 – 2.98 (m, 2 H), 2.91 (dd, *J* = 15.6, 11.8 Hz, 1 H), 2.87 – 2.68 (m, 4 H), 2.64 – 2.55 (m, 2 H), 2.32 – 2.24 (m, 0.76 H), 2.04 – 1.95 (m, 1 H), 1.13 (d, *J* = 6.9 Hz, 2.27 H), 1.11 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.7, 145.0, 135.3, 134.8, 134.5, 134.1, 128.9, 128.9, 128.7, 128.4, 127.2, 127.1, 126.3, 126.2, 126.2, 126.1, 126.0, 125.9, 124.0, 123.6, 117.2, 116.7, 112.3, 111.6, 59.8, 56.8, 50.6, 50.1, 35.7, 35.2, 33.7, 33.1, 31.0, 30.4, 19.3, 15.9. IR (film) 3027, 2925, 1603, 1494 cm^{-1};



6a-Methyl-6,6a,7,12-tetrahydro-5H-isoquinolino[2,3-a]quinoline (5-5h).

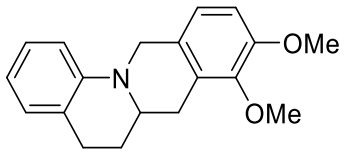
General procedure 2 was used for the cyclization of **5-3h** (111 mg, 0.39 mmol, 1 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 55% yield. ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.27 – 7.13 (m, 5 H), 7.07 (d, *J* = 7.3 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.72 (t, *J* = 7.4 Hz, 1 H), 4.70 (d, *J* = 15.9 Hz, 1 H), 4.18 (d, *J* = 15.9 Hz, 1 H), 3.07 (d, *J* = 15.4 Hz, 1 H), 2.97 – 2.90 (m, 1 H), 2.79 – 2.73 (m, 1 H), 2.67 (d, *J* = 15.4 Hz, 1 H), 2.04 – 1.97 (m, 1 H), 1.93 – 1.87 (m, 1 H), 1.05 (s, 3 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 145.3, 133.59, 133.6, 128.8, 128.6, 127.2, 126.2, 126.1, 125.9, 124.2, 116.8, 112.0, 51.8, 46.8, 43.6, 36.9, 24.6, 20.4. IR (film) 3027, 2926, 1601, 1494 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^{+}$ calcd for $C_{18}H_{20}N$, 250.1596; found, 250.1546



9-Fluoro-6,6a,7,12-tetrahydro-5H-isoquinolino[2,3-a]quinoline (5-5i).

General procedure 2 was used for the cyclization of **5-3i** (93.0 mg, 0.32 mmol, 1 equiv.). The crude product was purified via column chromatography using 1% EtOAc in Hexanes to give the title compound in 66% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 – 7.11 (m, 2 H), 7.03 (d, *J* = 5.8 Hz, 1 H), 6.94 – 6.87 (m, 1 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 6.72 (t, *J* = 6.8 Hz, 1 H), 4.75 (d, *J* = 15.4 Hz, 1 H), 4.19 (d, *J* = 15.4 Hz, 1 H), 3.38 – 3.31 (m, 1 H),

2.97 – 2.90 (m, 1 H), 2.90 – 2.82 (m, 1 H), 2.80 – 2.68 (m, 2 H), 2.09 (dd, *J* = 13.1, 6.6 Hz, 1 H), 1.97 – 1.88 (m, 1 H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 161.9, 160.5, 145.9, 136.8, 136.8, 129.7, 128.4, 127.8, 127.8, 127.2, 125.4, 117.5, 114.7, 114.6, 113.3, 113.2, 112.3, 52.7, 49.7, 37.3, 29.4, 26.5. IR (film) 3022.52, 2926.63, 2847.68, 1602.85, 1276.00 cm^{-1}; HRMS (ESI TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{17}FN$, 254.1345; found, 254.1299



8,9-Dimethoxy-6,6a,7,12-tetrahydro-5H-isoquinolino[2,3-a]quinoline (5-5j).

General procedure 2 was used for the cyclization of **5-3j** (60.0mg, 0.18 mmol, 1 equiv.). The crude product was purified via column chromatography using 5% EtOAc in Hexanes to give the title compound in 63% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 – 7.12 (m, 1H), 7.02 (d, *J* = 6.3 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.83 (dd, *J* = 15.6, 8.3 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 4.17 (d, *J* = 15.1 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.31 – 3.24 (m, 1H), 3.04 (dd, *J* = 16.2, 3.1 Hz, 1H), 2.90 – 2.82 (m, 1H), 2.76 – 2.64 (m, 2H), 2.15 – 2.07 (m, 1H), 2.01 – 1.92 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.6, 146.2, 146.1, 129.2, 128.4, 127.4, 127.1, 125.5, 121.7, 117.3, 112.4, 110.6, 77.2, 77.0, 76.8, 60.3, 55.9, 52.75, 49.8, 31.6, 29.6, 26.6. IR (film) 2934, 2834, 1603, 1497, 1280 cm^{-1};

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