Université de Montréal

Palladium-Catalyzed Intramolecular sp^3 C–H Functionalization

Studies in Cyclopropyl and Heterocyclic Motifs

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Résumé

La recherche d'approches novatrices, économique en atomes et durables pour former des liaisons C–C continue de stimuler la communauté chimique. En tant qu'approche émergente, la fonctionnalisation des liens C–H est une alternative complémentaire aux couplages traditionnels et à d'autres méthodes classiques néfastes pour l'environnement.

Par ailleurs, l'incorporation d'une unité cyclopropane dans une molécule peut être une stratégie bénéfique pour améliorer la stabilité métabolique et augmenter l'affinité pour un récepteur donné. En plus du profil pharmacologique diversifié, les cyclopropanes peuvent être utilisés comme précurseurs synthétiques pour préparer des architectures moléculaires plus complexes. Par rapport à d'autres centres sp^3 qui sont plus difficilement fonctionnalisables, ceux du cyclopropanes sont plus réactifs et sujets à réagir dans une réaction d'insertion C–H en raison de leur acidité accrue du à la tension de cycle.

Cette thèse présentera deux nouvelles méthodes de synthèse soit l'arylation intramoléculaire de liaisons C–H et l'alcénylation intramoléculaire de liaisons C–H des cyclopropanes catalysées par un complexe de palladium. Les résultats préliminaires pour des versions énantiosélectives d'insertion dans les liaisons C (sp^3)–H seront également présentés.

Le premier chapitre introduira les réactions de fonctionnalisation de liaisons C–H d'atomes de carbone sp^3 et de dérivés cyclopropanes catalysées par un complexe de palladium. De plus, les propriétés, les applications, les méthodes de synthèse et de fonctionnalisation des aminocyclopropanes seront discutées. Les travaux antérieurs effectués lors de la maîtrise seront discutés et mis en contexte dans le cadre des objectifs de cette thèse.

Le chapitre 2 décrira la fonctionnalisation intramoléculaire des liaisons C–H de cyclopropylbenzamides dérivés d'acides alpha-aminés pour accéder aux motifs tétrahydroquinolones et tétrahydroisoquinolones. Dans ce cas, une approche visant à minimiser le nombre de réactifs sera développée en explorant le rôle des additifs dans la fonctionnalisation des liaisons C–H. Notamment, ce système a servi de réaction modèle pour nos recherches initiales sur la fonctionnalisation asymétrique des liaisons C–H et sera donc revu (chapitre 4).

Le chapitre 3 visera à étendre la réaction développée au chapitre 2 aux systèmes moins plats c'est-à-dire ceux possédant un plus grand nombre d'atomes de carbone sp^3. La motivation à échapper au « *Flatland* » a contribué à l'étude de l'alcénylation intramoléculaire de dérivés cyclopropanes catalysée par un complexe de palladium. Au cours de notre étude, une réaction d'ouverture du cycle a été observée et le potentiel synthétique de cette transformation a été mis en évidence. Ce chapitre décrira nos efforts pour découvrir un nouveau système catalytique pour la version asymétrique de la réaction. Il sera démontré que les ligands de type monoxyde de bis(phosphine) peuvent être utilisés dans la fonctionnalisation énantiosélective des liaisons C–H. Des recherches initiales sur l'alcénylation asymétrique de dérivés cyclopropaniques ont démontré qu'un ligand de type phosphoramidite ou de type (*R, R*)-BozPhos est efficace.

Le chapitre 4 décrira que (*R, R*)-BozPhos peut être utilisé en combinaison avec le Pd(0) pour obtenir une induction asymétrique importante dans les réactions d'arylation et d'alcénylation d'atomes de carbone hybridés sp^3. Nos résultats seront comparés avec ceux de Kagan et nous démontrerons que le ligand actif est le monoxyde de bis(phosphine) et non la bis(phosphine). Enfin, l'utilisation de la 4ème génération de palladacycles dimèriques de Buchwald nous permettra d'atteindre des énantiosélectivités supérieures aux autres systèmes décrits dans la littérature pour ce type de transformation.

Mots-clés : le palladium, l'arylation, l'alcénylation, la fonctionnalisation des liaisons C–H, les cyclopropanes, la catalyse asymétrique, les hétérocycles, les indolines, les tétrahydroquinolones

Abstract

The search for novel, atom economical and sustainable approaches to form C–C bonds continues to stimulate the chemical community. As an emerging synthetic tool, C–H functionalization offers both alternative and complementary reactions to traditional cross-coupling and other environmentally hazardous classical methods.

Cyclopropane incorporation can offer a beneficial strategy to improve both target binding and metabolic stability. In addition to the diverse pharmacological profile, cyclopropanes can be used as valuable synthetic precursors *en route* to highly complex molecular architectures. Compared to other more challenging sp^3 centers, cyclopropanes are highly primed for C−H functionalization due to enhanced cyclopropyl C−H bond acidity and increased reactivity from ring strain. This thesis will disclose explorations towards both intramolecular palladium-catalyzed C−H arylation and alkenylation of cyclopropane systems, including recent efforts towards enantioselective C(sp^3)−H functionalization.

Chapter One will introduce key concepts regarding palladium-catalyzed C–H functionalization with emphasis on cyclopropanes and sp^3 centers. Additionally, properties, applications, synthetic approaches and functionalization of cyclopropanes will be discussed with a focus on aminocyclopropanes. Herein, previous Masters work on C–H arylation will be summarized and a context for the work presented in this dissertation will be established.

Chapter 2 will describe intramolecular palladium-catalyzed C–H functionalization of cyclopropyl α-amino acid-derived benzamides to access six-membered tetrahydroquinolones and tetrahydroisoquinolones motifs. Herein, a reductionist approach will be applied through exploring the role of additives in cyclopropyl C–H functionalization. Notably, this system served as a model reaction for our initial investigations into asymmetric C–H functionalization and will consequently be revisited (Chapter 4).

Chapter 3 will address the current paucity of methodologies targeting systems with increasing Fsp^3. The motivation to "escape Flatland" contributed to investigating intramolecular palladium-catalyzed cyclopropyl direct alkenylation. This chapter will also elaborate on our search for a novel asymmetric catalyst system and our discovery that bisphosphine monoxide ligands can be employed in enantioselective C–H functionalization. Initial investigations into

asymmetric cyclopropyl alkenylation using both a BINOL-based phosphoramidite ligand and (*R,R*)-BozPhos will be provided.

Chapter 4 will describe our discovery that (*R,R*)-BozPhos can be employed in combination with Pd(0) to achieve asymmetric induction of cyclopropyl and related sp^3 centers. Herein, we will readdress the work of Kagan, and demonstrate that (*R,R*)-BozPhos, not *(R,R)*-MeDUPHOS is the active ligand for this system. Finally, the use of Buchwald 4^{th} generation palladacycle dimer to achieve unprecedented enantioselectivities compared to other established literature benchmarks for sp^3 asymmetric arylation will be presented.

Keywords : palladium, arylation, alkenylation, ring-opening, direct functionalization, cyclopropanes, asymmetric catalysis, heterocycles, indolines, tetrahydroquinolones

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List of Abbreviations

AdOH: 1-adamantanecarboxylic acid

Ar : Aryl

aq : aqueous

BMPO: bisphosphine monoxide

BINOL: 1,1'-bi-2-napthol

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

2-BiPhOH: 2-biphenylcarboxylic acid

Boc: *tert*-butyloxycarbonyl

Cal : Calorie

CMD : Concerted-metallation deprotonation

cm : centimetre

CPME: cyclopentyl methyl ether

2-CypOH: 2-cyclopentylcarboxylic acid

2-CyOH: 2-cyclohexylcarboxylic acid

DABCO: 1,4-diazabicyclo[2.2.2]octane

dba: dibenzylideneacetone

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

dppf: 1,1'-Bis(diphenylphosphino)ferrocene

dppe: Bis(diphenylphosphino)ethane

dppm: 1,1-Bis(diphenylphosphino)methane

DIPEA: N, N-Diisopropylethylamine

DMA: N,N-Dimethylacetamide

DMF: Dimethylformamide

DFT : Density Field Theory

ee : enantiomeric excess

e.r : enantiomeric ratio

equiv : equivalent

FDA : US Food and Drug Administration

G2: 2^{nd} generation

G4: 4^{th} generation

3,3-GluOH: 3,3’-dimethylglutaric acid

g : gramO

h : hour

HOMO: Highest occupied molecular orbital

HRMS : High-resolution mass spectrometry

HSAB : Hard-soft acids and bases

Hz : Hertz

J : coupling constant

K : Kelvin

L : ligand

LUMO: Lowest unoccupied molecular orbital

M : molarity

mL : mililitre

mmol : milimol

mm : millimetre

mp : melting point

NHC: *N*-heterocyclic carbene

NMR : Nuclear-Magnetic Resonance

NNRTI: Non-nucleoside reverse-transcriptase inhibitors

PG : protecting group

PivOH: pivalic acid

PMB: 4-methoxybenzyl ether

rac : racemic

SEM: [2-(Trimethylsilyl)ethoxy]methyl

SET : Single-electron transfer

SFC : Supercritical Fluid Chromatography

T : temperature

TADDOL: α, α, α', α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol.

TFA: trifluoroacetic acid

To Lise and Brian, with love

In memory of Violet Margaret Tabler

Acknowledgements

"If you're going to try, go all the way. Otherwise, don't even start. This could mean losing girlfriends, wives, relatives and maybe even your mind. It could mean not eating for three or four days. It could mean freezing on a park bench. It could mean jail. It could mean derision. It could mean mockery--isolation. Isolation is the gift. All the others are a test of your endurance, of how much you really want to do it. And, you'll do it, despite rejection and the worst odds. And it will be better than anything else you can imagine. If you're going to try, go all the way. There is no other feeling like that. You will be alone with the gods, and the nights will flame with fire. You will ride life straight to perfect laughter. It's the only good fight there is."

–Charles Bukowski

I started my PhD thinking about this quote by Bukowski; however, I had no idea how many of these challenges I would have to face to finish. I have learned that isolation, although hard and sometimes painful can indeed be a gift. My love for chemistry, research and myself has been tried and tested. I have built character and resilience. Along this weird and crazy journey, I have gained the knowledge about how to interact with difficult people, how to deepen my compassion, how to persevere through challenging, dark times and how to rise above it all as a better person. And how to build stronger, healthier relationships: both in work and in life.

Here, at the end, the phrase that kept coming back to me as to why I should continue was simple: Love is always the answer.

This dissertation was made possible by the unconditional love, support and encouragement I have received from so many wonderful people in my life, since I first fell so madly in love with organic chemistry when I was 17.

I could not finish this journey without all of you. You are what matters.

I have had those beautiful nights of discovery! I have felt my heart light up with joy upon getting SFC results or seeing an NMR. Those nights where you can't eat, can't sleep, molecules weaving in and out of your dreams! Those nights are the nights that have flamed with fire and I have felt not alone with the gods, but like a demi-god (with the power to break and make bonds!). It is amazing to hold a new compound in your hand that no one has made before. It is wonderful

that we can create such complex molecules with the dual nature of life and death, and remarkable how a beautiful white solid can translate into an intimate conversation of hydrogen atoms whispering to each other across an NMR spectrum.

I have been so fortunate to experience those moments.

Chemistry continues to show me what a wonderfully intricate and delightful world we live in! Chemistry has taught me patience, perseverance, humility, and how to be adaptable.

You cannot control Chemistry (or Life for that matter!) but you can control your attitude and you can choose to not let anyone or anything steal your sunshine!

As a scientist, you learn that life is like an experiment. Even the bad experiences can offer important lessons to help you grow, if you choose to take the time to troubleshoot.

To my supervisor, Professor André B. Charette, thanks for allowing me to do my PhD. I appreciate the times you have given me advice when I've asked for it. Thanks for writing reference letters, for the opportunity to attend conferences, and for those subtle ways that you have been a mentor that perhaps have gone unrecognized. I know you've always been so busy with so many other responsibilities, yet I know you still do your best. I also appreciate all the tools and resources that you have provided. The moments when I've emailed you an exciting result and you've shared my enthusiasm, well, those are the good things I will remember!

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My best friend, Lise Malta. You have been an important part of my life for so many years! You continue to inspire me! You are so incredibly strong and resilient! I am so happy you are healthy again! Watching you battle leukemia changed me. It made me think deeper about my life and what it means to be a chemist. You reminded me that there's more to life than chemistry (although chemistry does play a very important role!).

Dearest Brian, such early days, but you were such an unexpected blessing from all the crazy! Thanks for your encouragement, acceptance, and affection! You provided a safe space for me to heal, to be vulnerable, to open my heart again, and to be my authentic, genuine self. Also, for those nights of writing in solidarity and for always delighting me with your use of punctuation, especially the colons! You have been a positive force in my life and have been instrumental in helping to change me for the better. I love you, and you are a wonderful, lovely man! I am so glad we found each other! Thank you for believing in me.

Although I could have dedicated this dissertation to so many people who have been there for me over the years of my PhD, both Lise and Brian actively supported me during the stressful period of thesis writing. Lise, thanks for all your messages and prayers! I would wake up to find you had texted me on a rough day, and it was such a blessing to hear your voice! Brian, thanks for truly, sincerely being there and supporting me. Thanks for seeing me through to the finish

line! My heart feels full having you both as part of my life, and I treasure you both immensely. I finished this thesis because of you and for you.

To my friends and roommates over the years, thanks for all the stress-relief! I have appreciated all the painting parties, dancing, Jeopardy, Sunday brunches, mutual comradery and other antics that have helped me cope with PhD life. Sometimes after a long day at the lab you feel like a lab robot, so it's great to remember your humanity when you come home!

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To my parents, thanks for raising me surrounded by a library of books and for pushing intellectual pursuits and achievements.

George, thanks for the love and the support you have provided to me over the last few years. I appreciate our life-long friendship. Love does not die; it is transformed. I also appreciate your family for welcoming me. Thanks to Fanny Orlemann for all the help and love she has provided over the years.

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To all my supervisors from my internships for providing the time and resources during my undergraduate degree! The little things that we do can have an impact in surprising ways. I

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Early in my PhD, I experienced a great loss for the first time in my life when my grandmother Violet Margaret Tabler passed away.

One of the phrases she would often say was “Mind over matter!”

These are the words that have given me that stoic-tough-love-push during my PhD.

She was a bright and intelligent woman whom I loved so much. I hope that she would be proud of my academic achievements.

This dissertation is also written in her memory.

"Great spirits have always encountered opposition from mediocre minds. The mediocre mind is incapable of understanding the man who refuses to bow blindly to conventional prejudices and chooses instead to express his opinions courageously and honestly."
—Albert Einstein

Chapter 1 General Introduction

This doctoral dissertation will describe the development of catalytic C–C bond formation targeting the cyclopropane core. Using intramolecular palladium-mediated C–H functionalization strategies, novel and privileged cyclopropyl-fused azines can be created. Additionally, the exploration of (*R,R*)-MeDUPHOS(O) (BozPHOS) as a chiral ligand for palladium-catalyzed sp^3 and cyclopropane asymmetric C–H arylation will also be presented.

This introduction will provide background regarding palladium catalysis; C–H functionalization; and the properties, synthesis and functionalization of cyclopropyl moieties. The presented concepts contained herein will provide a suitable framework to understand the approach and strategies employed in the subsequent chapters.

1.1 Motivations for Catalytic C–C Bond Formation

The discovery and development of new reactions can provide innovative synthetic solutions, can permit access to novel chemical motifs, and can offer important mechanistic insights for future reaction design. In particular, construction reactions such as C–C and C–heteroatom forming reactions are essential for synthesis.[1] Consequently, improved C-C bond forming reactions can significantly impact the synthetic efficiency and sustainability.

Over the years, C–C bond forming strategies have evolved, taking advantage of various reactive intermediates. Several Nobel Prizes have recognized these fruitful efforts towards C–C bond formation including cycloadditions, boron and phosphorous reagents, organometallics, and more recently, homogenous transition-metal catalysis. However, many of these methods are inconvenient due to the required stoichiometric, hazardous and toxic reagents; poor atom economy; functional group incompatibilities; and intolerance towards air and moisture.

Due to the associated environmental and economic benefits, improving reaction sustainability continues to drive new synthetic methods. As “the pillar of green chemistry,” catalysis is central as many catalytic processes can circumvent unnecessary waste production, achieve high atom economy, enable ambient and mild conditions, reduce unnecessary derivatization, and eliminate the need for hazardous and toxic reagents. [2]

Advances within organometallic chemistry have enabled crossover towards organic synthetic applications, ultimately resulting in the parallel development of two important classes of C–C bond forming reactions: palladium-catalyzed cross-coupling and palladium-catalyzed C–H functionalization. Key concepts regarding catalytic palladium C–C bond forming events will be highlighted in the following section.

1.2 Palladium-Catalyzed C–C Bond Formation

For the longest time, palladium was limited to heterogeneous processes using either Pd/C[3] or Lindlar's catalyst.[4] However, following the post-WWII discovery of the Wacker oxidation, the field of homogenous palladium catalysis has dramatically advanced and its impact acknowledged via the 2010 Nobel Prize, which was awarded to Suzuki, Heck, and Negishi for the development of palladium-catalyzed cross-coupling reactions.[5]

Figure 1 shows the extensive work investigating organometallic coupling partners leading to several useful palladium-catalyzed reactions.

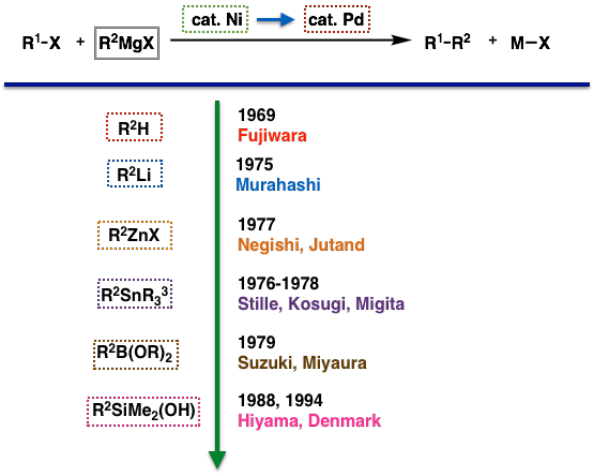


Figure 1. A summary of palladium-catalyzed cross-couplings

Although palladium cross-couplings have offered valuable strategies towards C–C bond formation, the need to prefunctionalize the coupling partner is a requirement. For example, some of the reagent preparations necessitate the use of toxic organotin reagents and hazardous organolithium compounds, which can produce undesirable stoichiometric waste. Instead, if one

of the coupling partners could be replaced with a C–H bond motif, both the reaction efficiency and sustainability could be improved.

Consequently, C–H functionalization has re-emerged an active research area, providing both complementary and alternative options for catalytic C–C bond formation. Many other metals have been explored and offer their own unique advantages; however, palladium remains a dominant force and will be the focus of this dissertation. A brief primer on palladium chemistry will be provided in the subsequent section.

1.2.1 Properties of Palladium

Palladium possesses a well-balanced reactivity compared to its group 10 counterparts, platinum and nickel. Platinum can be useful for isolating stable organometallic species for mechanistic studies; however, the high stability coupled with cost is undesirable for many practical applications.[6] In contrast, nickel is highly reactive and can undergo SET processes.[7] Consequently, nickel often requires specialized ligands to tame its reactivity. Although palladium is a more expensive metal compared to nickel, when increased catalyst loading and expensive ligand requirements are considered, palladium-based processes can often be more cost-effective. Toxicity can be another concern; however, in many cases nickel and other metals such as copper and iron can be more toxic compared to palladium.[8]

Most palladium chemistry involves two-electron processes; however, reports of one-electron processes via Pd(0)/Pd(I) and Pd(II)/Pd(III) manifolds have been documented. Most commonly, Pd(0)/Pd(II) catalytic cycles have been cited in popular reactions including cross-coupling, Heck–Mizoroki, and Tsuiji–Trost reactions.[9] Another common manifold involves Pd(II)/Pd(0) catalytic cycles and uses an oxidant to regenerate the active, more electrophilic Pd(II) species. Examples of these processes include Wacker-type oxidations, the Saegusa–Ito oxidation, and allylic oxidation reactions.[10] A less common manifold that has gained attention in recent years involves Pd(II)/Pd(IV) intermediates such as observed in the Catellani reaction.[11] Despite initial controversy, numerous studies support the formation of Pd(IV) intermediates.[12] This thesis will explore the common Pd(0)/Pd(II) platform.

1.2.2 Palladium-Catalysis and Ligand Design

Changing the ligand can have a powerful effect on catalyst properties including reactivity, selectivity, solubility and robustness. Although a broad range of ligand classes exist, this thesis will focus on phosphorous-based ligands.

Osborn observed significant catalytic activity for phosphanes such as PCy_3 and $Pi Pr_3$ that were both strongly basic ($pK_a > 6.5$) and possessed cone angles greater than 160º but less than 180º.[13] Based on this finding, both Koie[14] and Fu[15] demonstrated that trialkylphosphines could access highly reactive catalytic palladium species. Concurrently, the Buchwald group developed a set of dialkylbiarylphosphine ligands.[16] Recognizing the importance of electron-rich and sterically-bulky ligands in promoting challenging palladium-catalyzed transformations, other researchers designed ligands to maximize these desirable properties.[17]

As another distinct ligand class, hemilabile ligands are bidentate ligands containing a strongly coordinating group and a weakly coordinating group.[18] The weakly coordinating group is labile, and can easily detach from the metal center like an on-off switch, permitting other ligands to enter the metal's coordination sphere (**Figure 2**).

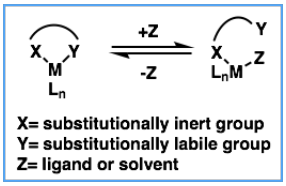


Figure 2. The fluxional properties of hemilabile ligands.

This flexibility can impart unique reactivity and stability to transition-metal complexes. Numerous types of hemilabile ligands exist; however, this thesis will focus on a particular class of *P,O*-based ligands known as bisphosphine monoxides (**Figure 3**).[19]

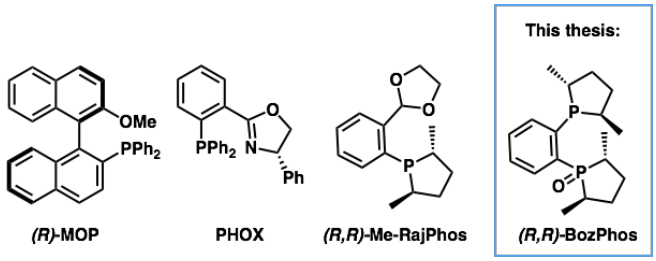
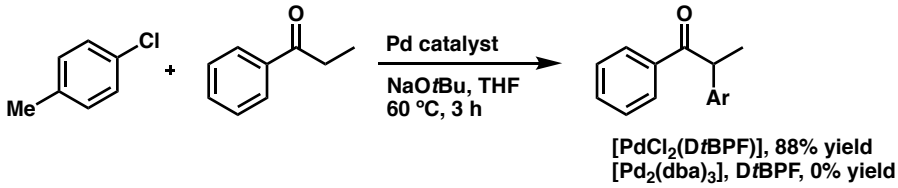


Figure 3. Examples of hemilabile ligands.

1.2.3 The Benefits of Palladium Precatalysts

The evolution in ligand design has played a critical role in expanding the scope of cross-coupling and related palladium-catalyzed reactions. In parallel, palladium precatalysts have equally evolved to consider new mechanistic information and to meet new demands.[20] To date, often the active catalytic species that forms upon mixing a precatalyst with ligand is not considered. However, a mixture of active catalytic species can form and can have a stark influence on reactivity and stereoselectivity. Investigations into the role of frequently considered spectator ligands from common precatalysts such as $Pd(OAc)_2$, $Pd(dba)_2$ and Pd_2dba_3 continue to support the noninnocent nature of spectator ligands. Additionally, catalytic precursors can show varying degrees of purity based on supplier and preparation method, leading to reproducibility errors. Scheme 1 illustrates how dba hinders reactivity and how using a precatalyst can restore reactivity.[21]

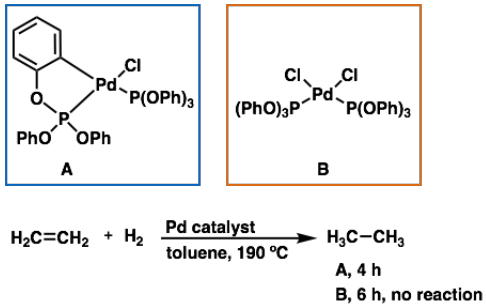
Scheme 1. The deleterious effects of dba on Pd-catalyzed alpha-arylation.



Advances within palladium catalysis continue towards milder, more efficient and more robust reaction conditions. Consequently, precatalysts that are facile to synthesize, are highly active, and are air- and moisture-tolerant can be synergistic in achieving such aims.

Precatalysts based on palladacycles have evolved from early preconceptions as deactivation products towards highly active and useful precatalysts for C–C and C–heteroatom bond construction.[22] In particular, seminal work by Lewis suggested superior reactivity of *ortho*-metallated precatalysts (**Scheme 2**).

Scheme 2. Lewis's comparison of Pd-based hydrogenation catalysts.



Catalyst A could actively hydrogenate ethylene to ethane; however, catalyst B failed to react, producing Pd mirror. Building on this discovery, several other groups have developed *ortho*-metallated palladacycles.[23] Notably, the Buchwald group has been highly active within precatalyst development. Figure 4 depicts the progression in the Buchwald precatalyst series.[24]

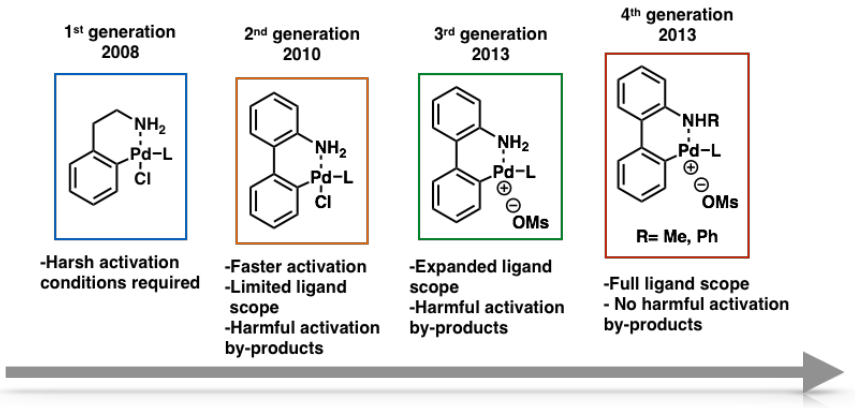
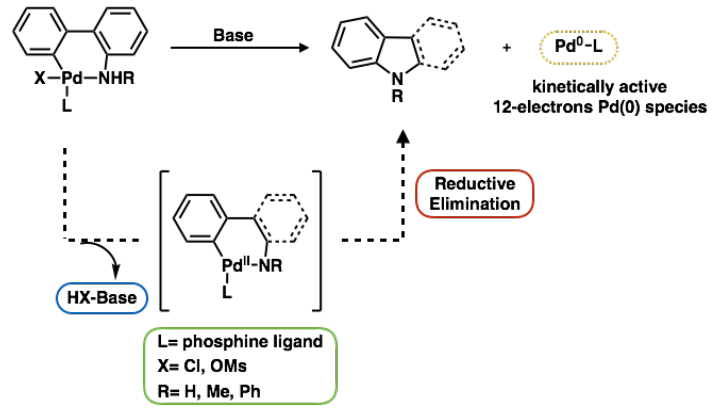


Figure 4. Evolution in Buchwald palladacycles.

The 4th generation precatalyst can be beneficial for reactions that are hampered by free NH-containing compounds, which can produce Buchwald-Hartwig amination products or can cause catalyst poisoning.[25] As an additional benefit, the 4th generation catalyst generates either NMe-carbazole or NPh-carbazole by-products, which are less toxic compared to carbazole, a

known human carcinogen.[26] This dissertation will employ the Buchwald 4th generation dimer as a dba-free Pd(0) source (**Chapter 4**). Scheme 3 shows the proposed preactivation mechanism for Buchwald palladacycles to generate Pd(0).

Scheme 3. Proposed activation for Buchwald palladacycles.



In summary, palladium precatalysts can act as alternative Pd(0) sources and can provide access to robust catalysts capable of functioning under mild reaction conditions, low catalyst loadings and high efficiencies.

1.3 C–H Functionalization: "Liberating Chemistry from the Tyranny of Functional Groups."

The C–H bond is the quintessential bonding motif within the realm of Organic Chemistry. Due to its prominence, the C–H bond was considered the default bond and was misconceived to be inert, leading to its reputation as the "unfunctional group."[27]

Recent improvements in reactivity and selectivity have established C–H functionalization as a novel synthetic tool.[28] By considering the C–H bond as a synthon, new synthetic disconnections can be unlocked, diversifying potential synthetic strategies. This change in mindset provides access to a new arsenal of reactions that can work in a complementary fashion with standard reaction classes in a more efficient, environmentally-conscious, and highly selective manner (**Figure 5**).

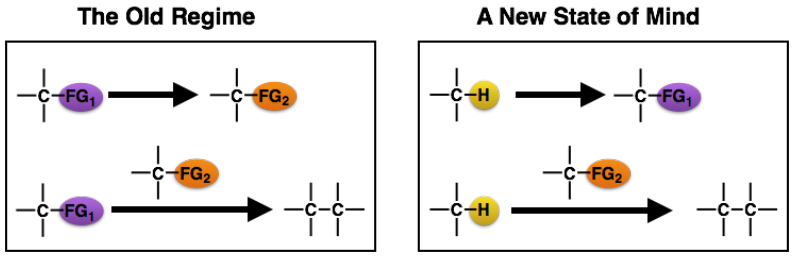


Figure 5. A) The traditional approach for functional group interconversions and C–C bond formation. B) The C–H bond as a functional group.

1.3.1 Defining C–H Functionalization and C–H Activation

C–H functionalization and C–H activation are distinct terms that have important mechanistic implications (**Figure 6**).

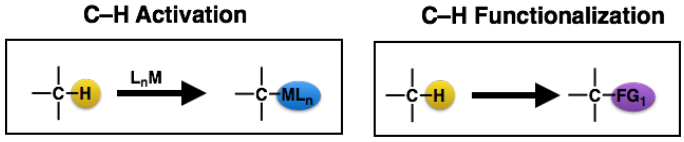


Figure 6. C–H Activation vs. C–H Functionalization.

C–H activation involves the cleavage of C–H bonds using transition-metals, resulting in the formation of organometallic intermediates. In contrast, C–H functionalization is a broader terminology, which can encompass various C–H cleavage pathways including C–H activation, where a C–H bond is transformed into another functional group.[29]

Considering the broad definition of C–H functionalization, various C–H functionalization reaction manifolds can be exploited in parallel and complementary fashions to avoid prefunctionalization.[30] Examples of approaches within this expansive reaction umbrella to form C–C bonds include radical-mediated C–H cleavage, electrophilic aromatic substitution, deprotonation of acidic C–H bonds, and carbene-mediated C–H insertions. Continual development across the spectrum of C–H functionalization reactions will provide chemists with a powerful armory to liberate chemistry from the need for functional groups in many cases and to offer unique reactivity and selectivity to work synergistically within existing reaction manifolds. Notably, many of the prescribed methods are not all catalytic and can require stoichiometric, hazardous, and harsh reactions conditions.

This thesis will focus on palladium-catalyzed C–H functionalization occurring via a concerted-metallation deprotonation event.

1.3.2 Challenges in Palladium-Catalyzed C–H Functionalization

The concept of C–H functionalization sounds like a practical, simple approach towards C–C bond formation; however, reactivity, selectivity and sustainability concerns can complicate methodology development. This dissertation will focus on C-(sp^3)–H bond functionalization, which has additional challenges.

C-(sp^3)–H bonds lack "active" HOMO or LUMO orbitals for beneficial transition-metal interactions, making such activation processes more energetically demanding. Additionally, C-(sp^3)–H systems commonly have higher bond dissociation energies, increasing the relative "inertness" compared to sp^2 centers.

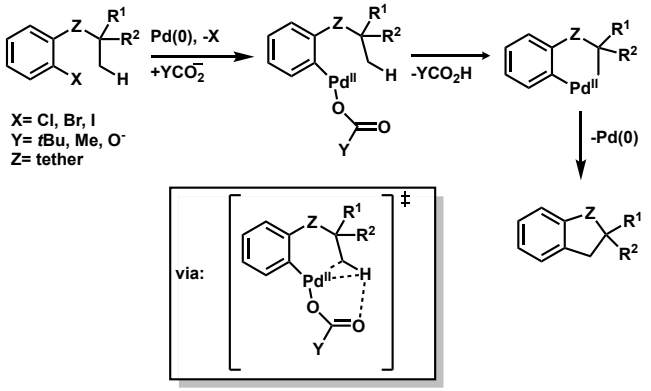
Selectivity is another challenge, which can encompass regioselectivity and stereoselectivity issues. Within an organic molecule several types of C–H bonds can exist; therefore, it is necessary to devise strategies to selectively functionalize one C–H group over another more reactive or equally reactive C–H bond. This selectivity problem can be exacerbated in cases where the functionalized product can often be more reactive than the initial starting material, leading to multiple undesired functionalizations.[31] Selectivity can be influenced via the substrate's innate reactivity,[32] or controlled via either catalyst design[33] or the use of directing groups.[34] Such parameters must also be considered for stereoselective C–H functionalization protocols, which will be addressed later in this dissertation (**Chapter 4**).

Finally, developing systems that are mild, avoid unnecessary oxidants and additives, and high temperatures are important for functional group compatibility, practical laboratory usage and environmental sustainability.[35] Like most methodology designs, a reductionist approach should be employed wherever possible to avoid the use of unnecessary reagents.[36]

1.3.3 Intramolecular Palladium-Catalyzed C–H Functionalization

This thesis will focus on intramolecular palladium-mediated C–H activation, which commonly employs carbon-or heteroatom based tethers (**Scheme 4**).

Scheme 4. Palladium-catalyzed C–H functionalization via an oxidative-addition-induced approach.

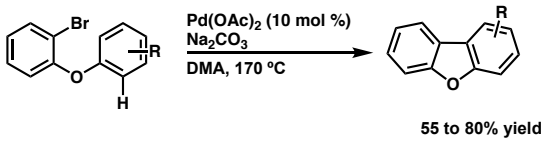


This approach requires strategic substrate design to place the C–H bond of interest near the metal center. Following oxidative addition and generation of a highly reactive palladium centre, C–H bond metalation is induced via a carboxylate-assisted, concerted-metalation deprotonation event (CMD). The thusly-formed palladacycle can then undergo further functionalization or reductive elimination to produce the desired product. Although this strategy eliminates the need to remove auxiliaries, it does require thoughtful design of the starting material and, consequently, can be synthetically restrictive.

Regioselectivity for intramolecular C–H functionalizations is controlled via palladacycle size. Five- and six-membered palladacycles are most commonly observed; however, the rarer seven-membered palladacycle has been postulated. This dissertation will explore reactions that proceed via both six- and seven-membered palladacycle intermediates. Below will describe key advances for C(sp^2)–H and C(sp^3)–H arylation using this approach.

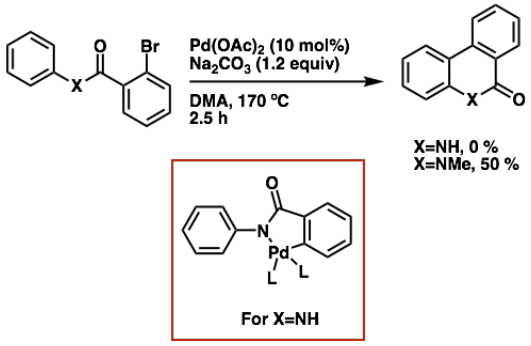
In 1983, Ames published one of the first examples of palladium-catalyzed intramolecular C(sp^2)–H arylation using 2-bromophenyl phenyl ethers (**Scheme 5**).[37]

Scheme 5. Early example of intramolecular C–H arylation by Ames.



Other heteroatom-containing tethers including amines, amides, and sulfonamides could also be employed to access both five and six-membered heterocyclic motifs.[38] Notably, the reaction failed when free NH-moieties were employed, which was attributed to catalyst sequestration via formation of a non-productive palladacycle (**Scheme 6**).

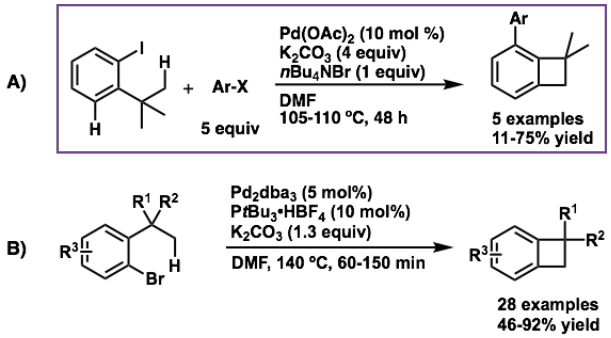
Scheme 6. Effect of using a Lewis-basic group on reactivity.



The Fagnou group revisited Ames's work and discovered that using electron-rich, sterically bulky ligands such as Davephos and trialkylphosphines in the presence of an inorganic base could lead to significant improvements in reactivity for intramolecular C(sp^2)–H arylation. These contributions provided the foundations to activate more difficult sp^3 centers.

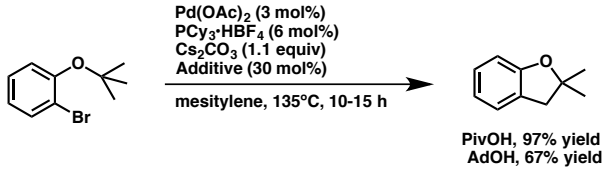
Inspired by Dyker's early work,[39] the Baudoin group developed a carbonate-mediated intramolecular process to generate benzocyclobutenes via C(sp^3)–H functionalization (**Scheme 7**).[40]

Scheme 7. Intramolecular Pd-catalyzed alkane arylation. A) Dyker's seminal work. B) Baudoin's revised conditions.



In earlier work, the Fagnou group observed enhanced reactivity when pivalic acid was employed in intermolecular C–H arylation.[41] This discovery was extended towards one of the first examples of C(sp^3)–H intramolecular alkane arylation using an ether tether (**Scheme 8**).[42]

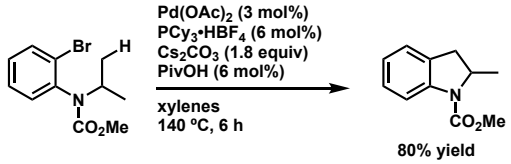
Scheme 8. Intramolecular alkane arylation using carboxylate-based additives.



Notably, pivalic acid outperformed its bulkier adamantane-based analogue, illustrating the steric limitations of the bulky carboxylate additive.

In a related methodology, Ohno developed a pivalate-assisted protocol using protected amine-based tethers to access indolines excellent yields.[43] Notably, sp^3 centers could be functionalized without an adjacent quaternary carbon (**Scheme 9**).

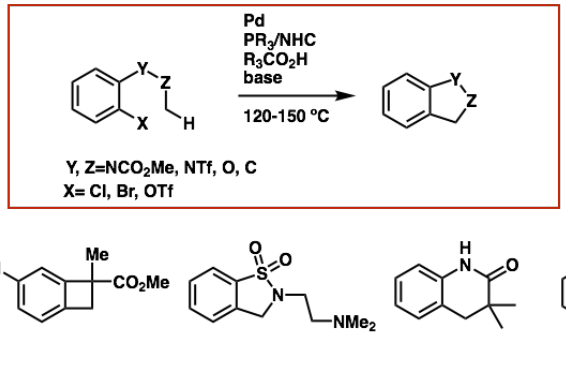
Scheme 9. A suitable model reaction for asymmetric C–H functionalization.



This transformation provided access to a model system for developing enantioselective C–H arylation reactions. To date, this reaction has been used as the benchmark for testing asymmetric conditions and will be discussed later (**Chapter 4**).

Since these important early findings, numerous groups have explored intramolecular Pd arylation of sp^3 centers to access 4, 5, 6 and 7-membered ring systems using generalized reaction conditions (**Scheme 10**).[44]

Scheme 10. Generalized intramolecular alkane arylation with selected examples.



Via an intramolecular Pd-catalyzed C–H functionalization strategy, new synthetic disconnections are viable, affording a diversity of novel and known heterocyclic motifs. This approach will be applied towards cyclopropyl C(sp^3)–H functionalization using amide-based tethers. The next section will provide a brief discussion of mechanistic considerations regarding palladium-catalyzed carboxylate-mediated C–H activation.

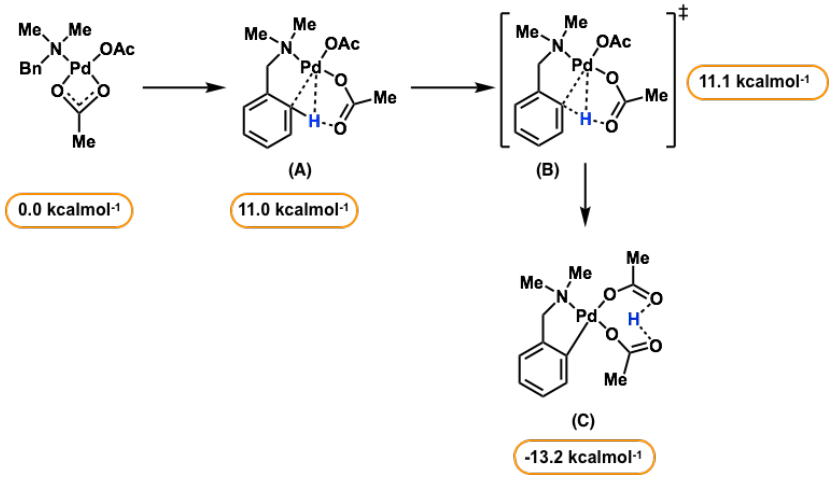
1.3.4 Mechanistic Considerations

Previous explanations for transition-metal mediated C–H bond functionalization included oxidative addition, σ-bond metathesis and electrophilic substitution; however, experimental results contradicted these mechanisms. Consequently, concerted-metalation deprotonation (CMD) was conceived to rationalized carboxylate-mediated C–H bond activation

By studying the *ortho*-palladation of *N,N*-dimethylbenzylamine with $Pd(OAc)_2$, Ryabov provided the first detailed mechanistic studies supporting a concerted-metalation deprotonation mechanism. Kinetic studies indicated that C–H metalation was rate-limiting and that the Pd(II) species was electrophilic. Additionally, a negative entropy of activation of 60 $calK^{-1}mol^{-1}$, indicated the presence of a highly ordered transition state, formed via acetate-mediated intramolecular proton abstraction. Crystallographic data of related palladium precursors also revealed possible agostic interactions.[45] Additionally, Davies, McGregor and Donald conducted density field theory (DFT) calculations, which disproved the possibility for a Wheland intermediate. Instead it was proposed that C–H metalation proceeds via an initial C–H agostic interaction (**A**), which enhances the acidity of the *ortho*-proton to promote facile intramolecular deprotonation by acetate. A six-membered cyclic transition state (**B**) was postulated and was

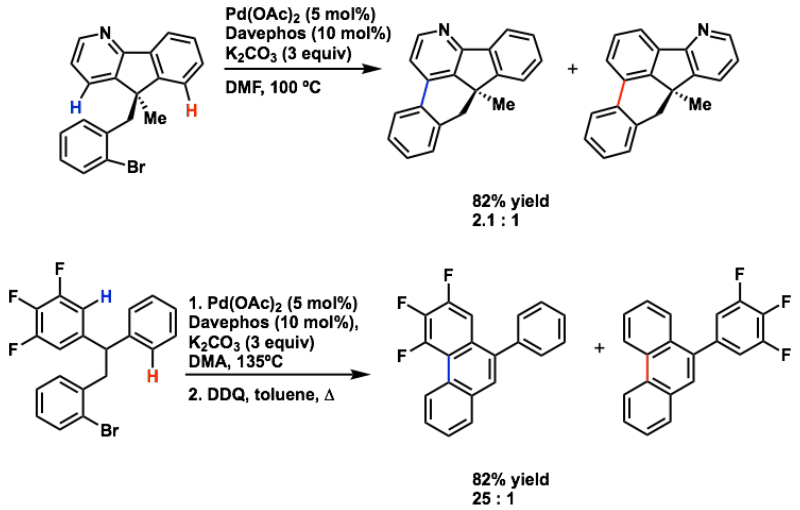
calculated to have a low energy barrier for proton transfer (ΔE_A= +0.1 kcalmol^{-1}), favoring palladacycle (**C**) (**Scheme 11**). [46]

Scheme 11. Calculated reaction profile for the cyclometalation of $Pd(OAc)_2$[DMBA-H].



In 2006, Echavarren and Maseras conducted experimental and theoretical studies to develop a modified mechanism for intramolecular palladium-catalyzed C–H arylation.[47] One key observation was the regiochemical ratios, which favoured electron-withdrawing substituents over electron-donating substituents, contrary to known electrophilic aromatic substitution patterns (**Scheme 12**).

Scheme 12. Regiochemical ratios disfavour electrophilic aromatic substitution.



Of interest, calculations suggested that both intramolecular (**A**) and intermolecular (**B**) concerted-deprotonation processes were feasible; however, the intermolecular process was more energetically favorable by 6.1 kcalmol^{-1}. The least energetically favorable state occurred without carbonate (**C**). Consequently, Echavarren and Maseras proposed that carbonate could assist as an external noncoordinated base via an intermolecular concerted-metalation deprotonation mechanism (**Figure 7**).

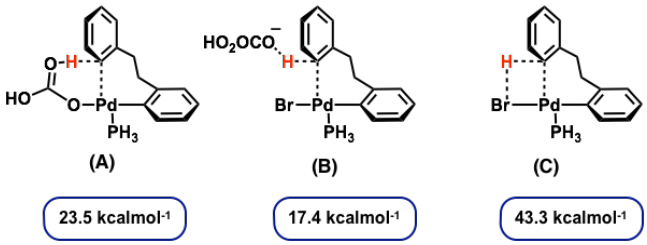
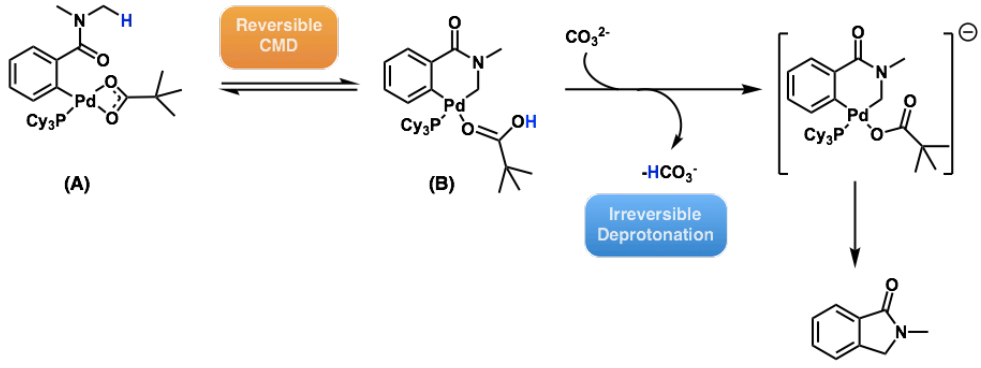


Figure 7. Calculations for potential mechanisms for carbonate-assisted direct arylation.

The Fagnou group has investigated the role of pivalate in promoting the CMD step. DFT studies showed that pivalate required less energy of activation compared to bicarbonate (24.9 kcalmol^{-1} vs. 26.2 kcalmol^{-1}). Further studies on the role of pivalate and carbonate were conducted via exploring the C(sp^3)–H arylation of *N*-methylamides.[48] Experimental results suggested that pivalate also promotes phosphine dissociation from Pd(II).

Scheme 13. Carbonate as a driving force via proton sequestration.



Excess pivalate impeded reactivity, which was rationalized by the formation of non-productive intermediate **A** (**Scheme 13**). Additionally, a synergistic relationship between carbonate and pivalate was observed; poor reactivity was detected in the absence of a carbonate-

containing base. To rationalize this dependence, it was proposed and supported by calculations that the concerted-metallation deprotonation event is reversible. Consequently, to prevent intermediate **B** from reverting back to **A**, carbonate drives the reaction to completion by sequestering the proton. Therefore, pivalate acts as a proton shuttle to transfer the proton from the substrate during C–H cleavage to the poorly soluble carbonate base.

Figure 8 summarizes these findings the following catalytic cycle

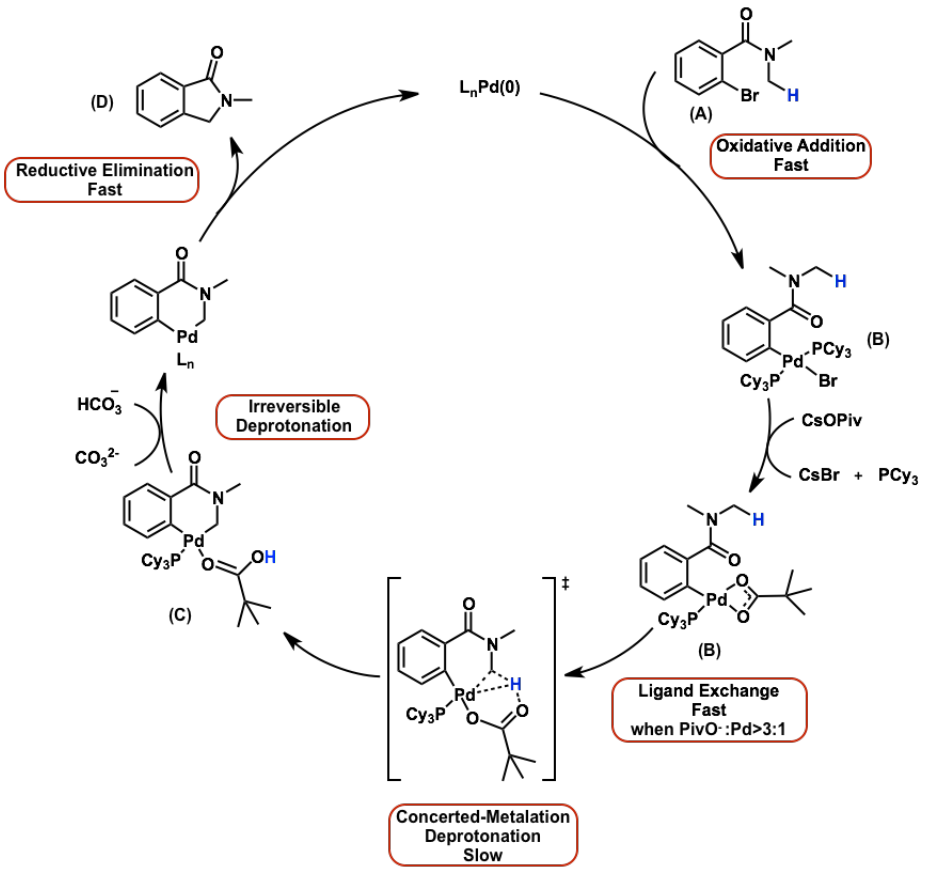


Figure 8. Proposed catalytic cycle for C(sp^3)–H arylation.

Amide (**A**) undergoes oxidative addition to form (**B**), followed by ligand exchange to form κ^2-intermediate (**C**). Pivalate mediates the concerted-metalation deprotonation event to form palladacycle (**D**), which undergoes irreversible deprotonation, then reductive elimination to produce (**E**)

In summary, a CMD process requires an electron-deficient metal centre, a proton shuttle such as pivalate, and an insoluble carbonate or phosphate base.[49] Additionally, in light of the proposed catalytic cycle, the fluxional ability to open and close coordination sites on the metal can be highly beneficial.[50]

1.4 Cyclopropanes: Relevance, Synthesis and Functionalization

1.4.1 Properties of Cyclopropanes

Cyclopropanes share similar properties with both alkane and alkene functionalities, which contributes to the wide-range of properties within the cyclopropane family. Strain plays a significant role in modulating reactivity and cyclopropanes contain both Bayer and Pitzer strain elements. Bayer strain results from internuclear bond angles of 60º whereas Pitzer strain results from the coplanar arrangement of cyclopropyl carbons forcing C–H bond to eclipse.[51] Consequently, cyclopropyl strain can function as a thermodynamic driving force in reactions to yield less-strained products. Strain also enhances reactivity due to the resulting orbital re-hybridization, forcing electrons to occupy higher energy orbitals.[52]

Two main bonding models rationalize cyclopropane bonding and properties: a) The Walsh Model, and b) The Coulson-Moffitt Model (**Figure 9**).

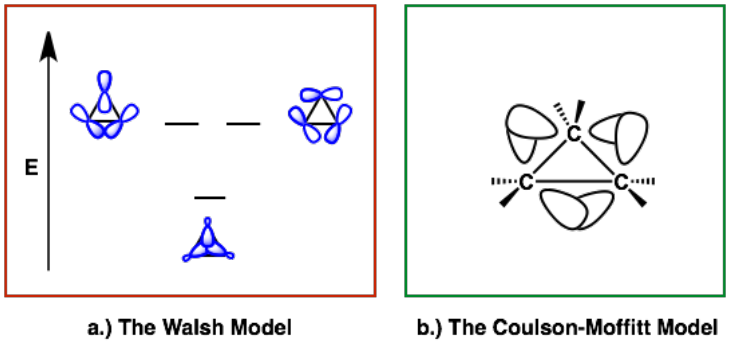


Figure 9. The two main bonding models for cyclopropanes.

Based on Hartree-Fock (HF) calculations, Walsh proposed that cyclopropyl bonding resulted from the overlap of three-sp^2 hybridized orbitals pointing towards the centre from each carbon, forming a delocalized MO-orbital. This stabilization gained from delocalization can

account for the similarity in strain energies between cyclopropanes and cyclobutanes (27.5 $kcalmol^{-1}$ vs. 26.5 $kcalmol^{-1}$), despite major geometrical differences.[53]

The Coulson and Moffitt model employs Valence Bond (VB) theory. As the smallest angle formed from s and p orbitals would be 90º, higher "p" character in the C–C bond could allow for "bent bonding," improving orbital overlap. Consequently, this model involves three orbitals pointing outward by 22º, leading to pseudo-sp^2 hybridization for the cyclopropyl orbitals, which can account for the similarities between cyclopropanes and alkenes.[54] The resulting increase in "p" character for cyclopropyl C–C bonds causes enhanced "s" character within the C–H bonds, creating shorter C–H bonds and enhancing acidity compared to alkanes.

1.4.2 Applications of Cyclopropanes

Cyclopropanes continue to demonstrate popularity across a broad spectrum of research fields. Nature has employed the cyclopropane motif into numerous novel and structurally astounding molecular architectures, which has offered interesting total synthesis challenges.[55] Figure 10 shows a selected example of cyclopropyl-containing natural products, including steroids, fatty acids, terpenes, amino acids and indoline alkaloids.

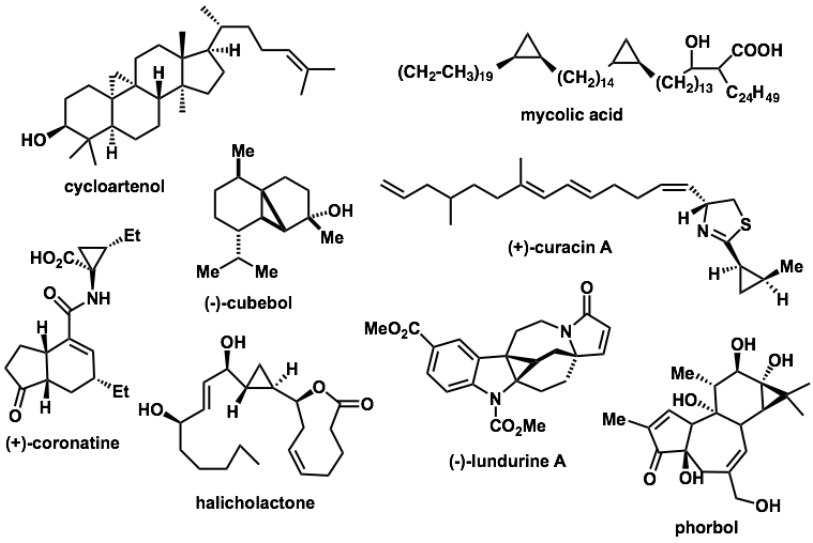


Figure 10. A wide range of the diversity of cyclopropyl-containing natural products.

The search for sustainable fuel sources has spurred biofuel research. By cyclopropanating terpenes and unsaturated fatty esters a 4% increase in energy density was

observed compared to the alkene analogues and the cyclopropane-derivatives exhibited increased resistance towards oxidation.[56] Cyclopropanes also have shown numerous applications as radical probes.[57] Additionally, the cyclopropane motif has been incorporated into catalyst and ligand design for use in Heck reactions,[58] enantioselective radical additions,[59] allylic alkylation,[60] asymmetric epoxidation and cyclopropanations.[61] Through productive ring-opening processes, cyclopropanes function as three-carbon synthons. The inherent ring strain provides a driving force for cycloadditions, ring-expansions, and related ring-opening transformations providing entrance to valuable synthetic intermediates and heterocyclic motifs.[62]

Since the 1960's, medicinal chemists have exploited the pharmacological benefits of cyclopropane incorporation. The cyclopropane ring remains the 10th most commonly-used ring system in small molecule drugs, and is present in 8 of the top 100 FDA-approved best-selling drugs.[63] Figure 11 shows some recent FDA-drugs containing the cyclopropyl moiety.

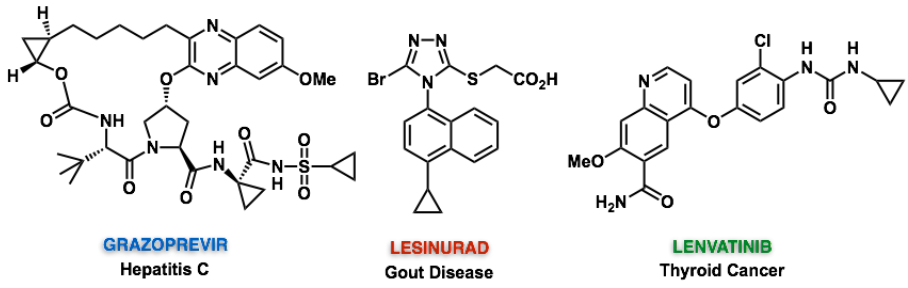


Figure 11. FDA-approved drugs from 2015 to 2017 containing a cyclopropyl-moiety.

Beneficial drug properties attributed to cyclopropyl incorporation include increases in potency, metabolic stability, bioavailability, aqueous solubility, brain permeability and enhanced target selectivity.

The cyclopropane moiety can impart a myriad of interesting properties across interdisciplinary fields. To access highly-functionalized cyclopropanes, a combination of de novo synthesis and functionalization strategies can be employed. The next two sections will highlight both approaches.

1.4.3 Synthesis of Cyclopropanes

Designing strategies to access highly-functionalized cyclopropane cores and simple cyclopropyl building blocks are two distinct goals to consider when developing cyclopropanation reactions. Access to simple cyclopropyl building blocks is important for functionalization strategies, whereas de novo-based cyclopropane syntheses remain reliable mainstays. Consequently, the synthesis and functionalization of cyclopropanes work in concert to provide access to highly-decorated cyclopropane scaffolds (**Figure 12**).

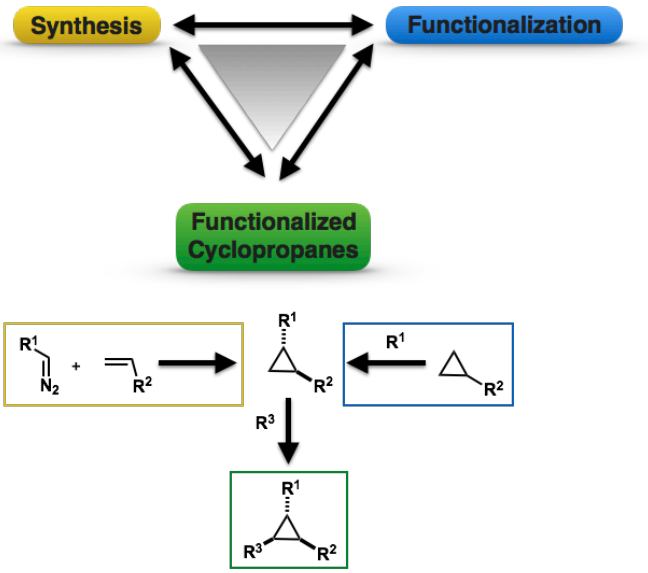


Figure 12. The synergy between cyclopropyl synthesis and functionalization.

Some common methods to synthesize cyclopropanes include metal carbenoid-based approaches such as the Simmons–Smith reaction[64] and metal-catalyzed decomposition of diazo reagents,[65-66] nucleophilic displacements reaction such as the Perkin, Corey–Chakovsky,[67] and Pirrung reactions,[68] and access to cyclopropanols and cyclopropylamines via the Kulinkovich reaction.[69] More recent approaches have employed cycloisomerizations,[70] biocatalysis,[71] photoredox,[72] and cross-coupling strategies.[73] Continual development of new protocols to access simple and highly-functionalized cyclopropanes will benefit many fields and provide valuable precursors for further structure elaboration via functionalization approaches. For this

reason, work towards improving the efficiency, sustainability and overcoming the limitations of current methodologies is essential for expanding the cyclopropane library.

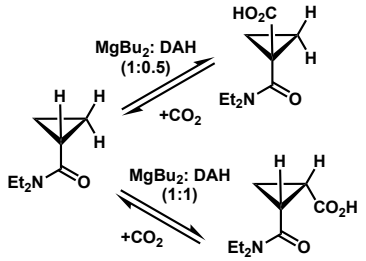
1.4.4 Functionalization of Cyclopropanes

Functionalization of the cyclopropane motif can offer distinct advantages over de novo synthetic approaches. It can enable researchers to start from a simple cyclopropane core and diversify the cyclopropyl ring to easily access various analogues, instead of having to separately synthesize each complex precursor. Selected strategies will be highlighted below.

1.4.4.1 Via Metalation Strategies

Examples of cyclopropane functionalization via metalation are rare; however, a few reports do exist. For example, Zhang and Eaton developed a protocol for alpha and beta cyclopropyl functionalization using Bu_2Mg and an amine-directing group (**Scheme 14**).[74]

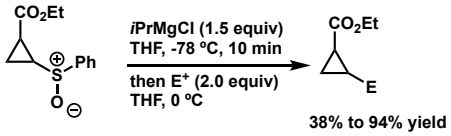
Scheme 14. Stoichiometric control influence alpha vs. beta functionalization



This strategy was used to access a key intermediate en route towards MIV-150, an NNRTI.[75]

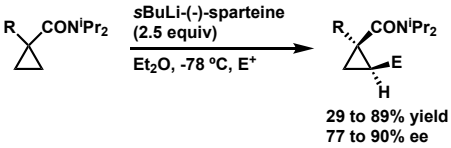
Knochel also achieved metalation via stereoselective bromine/magnesium and sulfoxide/magnesium exchange reactions.[76] Bull recently extended this magnesium/sulfoxide exchange strategy to towards accessing a broad-range of pharmacologically-interesting cyclopropanes (**Scheme 15**).[77]

Scheme 15. Sulfoxide-exchange followed by electrophile quench.



Simpkins developed an asymmetric metalation-substitution of cyclopropanes based on Eaton's amine-directing group concept using *s*BuLi-(-)-sparteine (**Scheme 16**). Various alpha-substituted cyclopropanes were accessible; albeit, variability within the yields for this methodology were observed, which was attributed to the tendency of lithiated cyclopropyl analogues to undergo decomposition and self-condensation.[78]

Scheme 16. Asymmetric lithiation-electrophile quench by Simpkins.

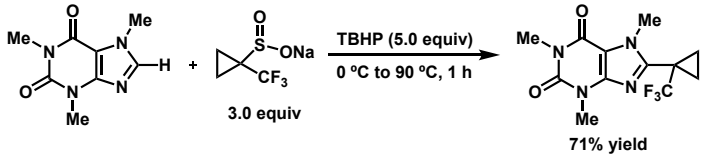


Although viable, metalation strategies require stoichiometric organometallics, which are air and moisture sensitive. Additionally, many of the metallated cyclopropane species are unstable, contributing to side-reactions and decomposition.[79] The scope remains limited for many of these procedures; albeit, improvements have been observed towards metalation-electrophile quench protocols. Notably, the directing group is often critical for enabling such reactivity, which parallels many transition-metal catalyzed C–H functionalization approaches.[80]

1.4.4.2 Via Radical-based Approaches

Due to the instability of many cyclopropyl radical species, there are limited examples of functionalization via radical pathways.[81] One example by the Baran group employs Barton chemistry to access sodium sulfinate salts from carboxylic acid precursors. The sodium sulfinate reagents could then be reacted under Minisci conditions to access heterocyclic-substituted cyclopropanes (**Scheme 17**).[82]

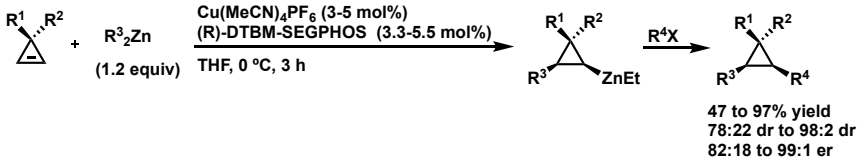
Scheme 17. Use of sodium sulfinate reagents to cyclopropanate caffeine.



1.4.4.3 Via Cyclopropenes[83]

Cyclopropenes can be employed as valuable synthetic intermediates to access functionalized cyclopropanes via addition reactions across the double bond. Some of these reactions include carbometalations, hydrometalations, hydrogenation, nucleophile additions, and Pauson–Khand reactions. Scheme 18 shows a recent example of a Cu-catalyzed asymmetric carbozincation.

Scheme 18. Cu-catalyzed carbozincation of cyclopropenes.

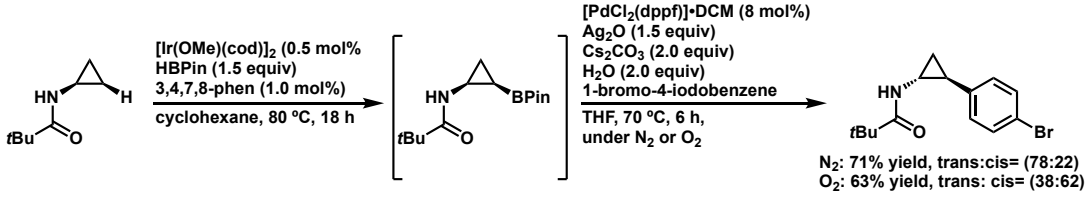


1.5 Palladium-Catalyzed Cross-Coupling of Cyclopropanes

Whereas transition-metal cross-couplings have permitted rapid diversification of numerous molecular cores, the cross-coupling of sp^3 centers continues to be challenging; albeit, significant progress has been made.[84] One issue in using this approach to functionalize cyclopropanes is the need to prefunctionalize, which can involve challenging de novo syntheses. Advances in cyclopropane synthesis have permitted expansion within this field; however, further research is required to reach a broad substrate scope.

Notably, most research has focused on the Suzuki–Miayura reaction.[85] The contributions from Buchwald and Fu in ligand and precatalyst design have been critical for improving these methodologies. Additionally, contributions from the Charette group and others towards accessing the required halocyclopropanes or cyclopropyl boronates have been instrumental in expanding the scope of the reaction. Scheme 19 illustrates an example of directed borylation, followed by subsequent Suzuki–Miayura cross-coupling.

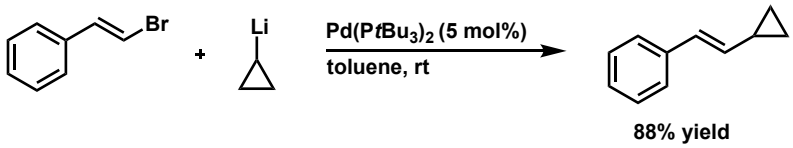
Scheme 19. Sequential C–H borylation, followed by Suzuki–Miayura cross-coupling.



This strategy demonstrates how C–H functionalization approaches can work in concert with other functionalization strategies to achieve highly decorated cyclopropane cores.

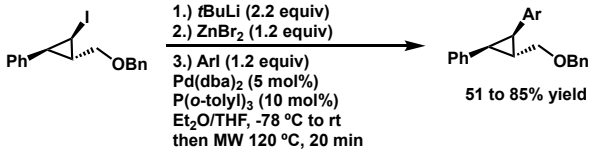
Limited examples of other cross-coupling methodologies have also been developed. To date, there are no examples of full methodologies employing Murahashi,[86] Kumada or Stille conditions. Scheme 20 shows a recent example from the Feringa group using cyclopropyllithium.

Scheme 20. Improved Murahashi conditions for cyclopropane functionalization.



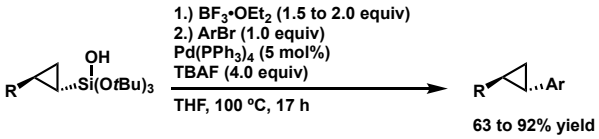
The Negishi reaction has showed more promise towards an expanded scope. It has been a viable strategy to transmetalate both organolithium and organomagnesium reagents into their zinc analogues with some success (**Scheme 21**).[87]

Scheme 21. Negishi reaction via a transmetalation approach.



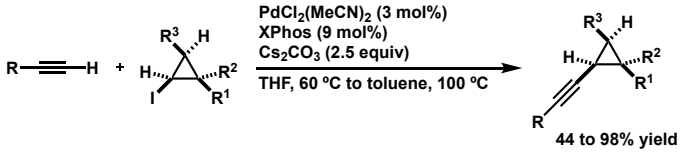
In 2010, the Charette group published a full methodology permitting access to the silanol precursors and their subsequent use in the Hiyama–Denmark cross coupling (**Scheme 22**).[88]

Scheme 22. Hiyama–Denmark cross-coupling of cyclopropanes



The Cossy group also published a copper-free Sonogashira coupling targeting cyclopropyl iodides using XPhos as a bulky, electron-rich ligand (**Scheme 23**).[89]

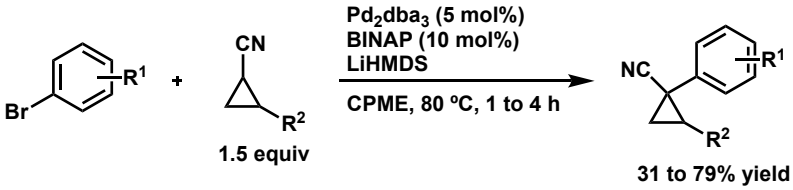
Scheme 23. Copper-free Sonogashira coupling of cyclopropyl iodides.



The bottlenecks for many cyclopropane cross-couplings include accessing the required organometallic reagents and developing mild reaction conditions to maintain the delicate cyclopropane core.

Transition-metal catalyzed alpha-arylation strategies have recently emerged with more potential in recent years as prefunctionalization of the cyclopropane core is not required. Both the Merck Process group and the Genentech Process group designed a protocol employing cyclopropyl and cyclic nitriles (**Scheme 24**).[90]

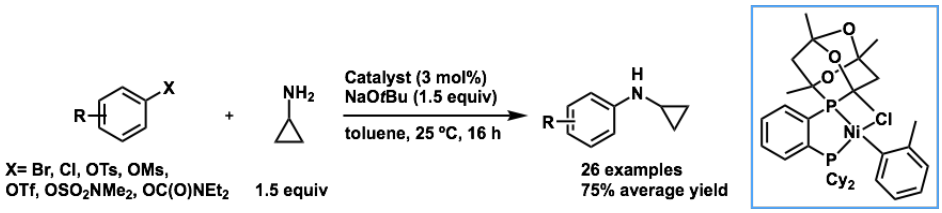
Scheme 24. Merck process for alpha-arylation of cyclopropyl nitriles



Notably, Genentech observed deleterious results using Pd_2dba_3 as a precatalyst, which was improved using Buchwald's G2 precatalyst with XPhos, further substantiating the benefits of avoiding dba-based precursors.

Most recently, the Stradiotto group published a Ni-catalyzed *N*-arylation of cyclopropylamines (**Scheme 25**). Notably, the cyclopropyl scaffold remains limited.[91]

Scheme 25. Ni-catalyzed *N*-arylation of cyclopropylamines



Catalytic methods towards cyclopropane functionalization continue to challenge researchers. Based on the described difficulties for prefunctionalization of cyclopropanes, direct functionalization of cyclopropanes could afford an improved strategy to access highly-functionalized cyclopropane cores. The development of better cyclopropane syntheses in combination with functionalization strategies will provide the arsenal necessary to meet niche cyclopropane market demands.

1.6 Palladium-Catalyzed C–H Functionalization of Cyclopropanes

As demonstrated, the advances in transition-metal cross-coupling have enabled C–H functionalization technology to expand. Additionally, the increased C–H bond acidity of the cyclopropyl unit makes cyclopropanes highly primed for C–H functionalization strategies. Considering the challenges presented by other functionalization strategies, avoiding complex de novo syntheses and prefunctionalization steps would provide simplified approaches toward building intricate cyclopropyl-scaffolds, late-stage diversifications, and diversity-oriented syntheses. Such benefits would help to streamline cyclopropane incorporation, while improving reaction efficiency and sustainability.

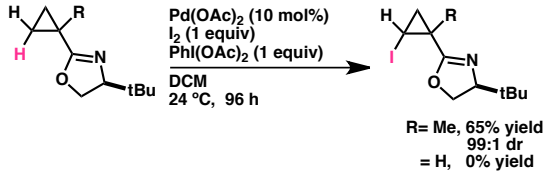
In recent years, there have been a growing number of papers addressing this subject, exploiting both directing-group and oxidative addition-induced metalation strategies. To date, there remains a dearth of full methodology papers devoted to cyclopropanes. This section will underline important contributions towards palladium-catalyzed cyclopropyl C–H

functionalization, will discuss our previous investigations within this field, and will highlight the research goals for this dissertation.

1.6.1 Intermolecular C–H Functionalization of Cyclopropanes[92]

In 2005, the Yu group published one of the first examples of cyclopropyl C–H functionalization involving a direct iodination procedures utilizing oxazoline as a directing group (**Scheme 26**).[93]

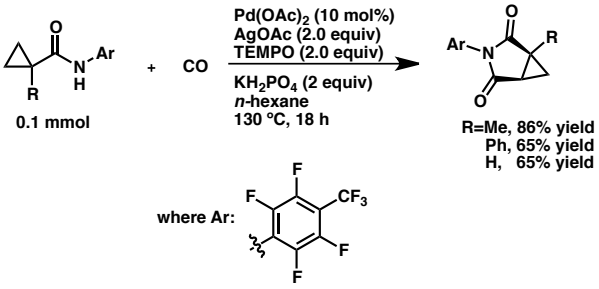
Scheme 26. Direct iodination of oxazoline-substituted cyclopropanes



Despite long reaction times and required alpha-substitution, the reaction could be conducted at room temperature. Cleavage of the auxiliary provided access to the corresponding enantiomers as carboxylic acids in >99% *ee*.

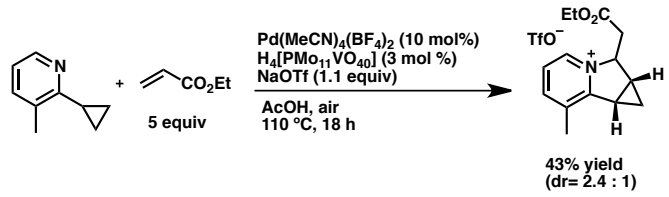
Tuning of the directing-group[94] enabled direct alkylation[95] and direct alkenylation reactions with limited cyclopropane examples.[96] One example enables access to cyclopropyl-fused succinimides via carbonylation using the Yu–Wasa auxiliary (**Scheme 27**).[97]

Scheme 27. Direct carbonylation of cyclopropanes using the Yu-Wasa auxiliary.



Using 3-picoline as a directing group, the Sanford group also developed an aerobic direct alkenylation protocol; however, yields were modest (**Scheme 28**).[98]

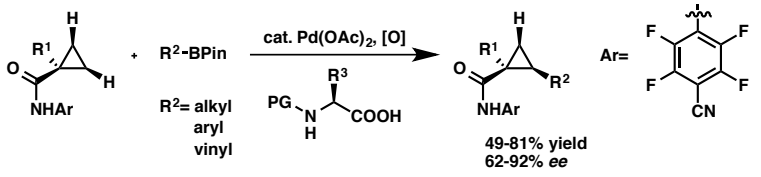
Scheme 28. Direct alkenylation protocol using 3-picoline as a directing group.



Sanford and Kubota also attempted to acetoxylate and iodinate cyclopropanes containing oxazoline, oxime ether and pyridines as directing groups; however, none of these attempts were successful and led to ring-opening of the cyclopropane in low yields.[99]

In 2011, Yu published the first full methodology paper focusing on enantioselective C–H activation of cyclopropanes using mono-protected amino acid ligands (MPAA's) and an electron-deficient directing group (**Scheme 29**).[100]

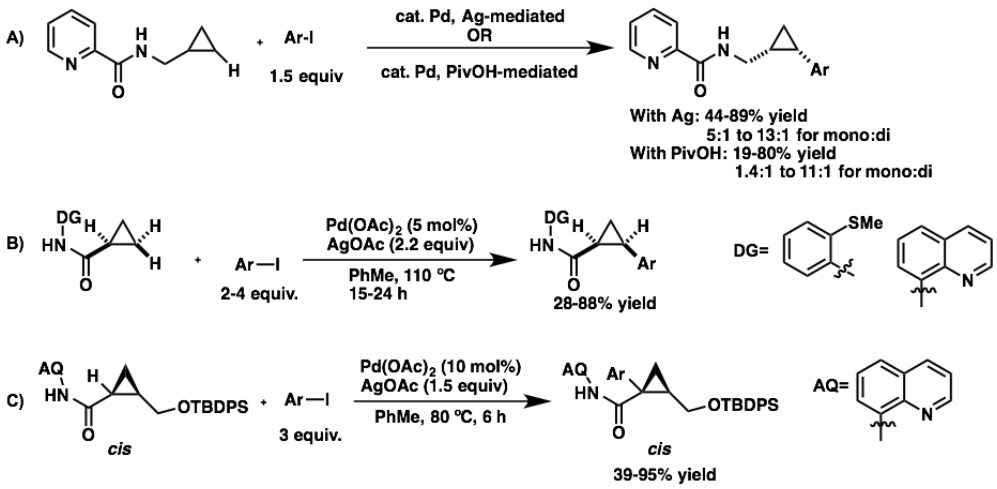
Scheme 29. First example of enantioselective intermolecular C–H activation of cyclopropanes



Various *cis*-substituted cyclopropanes could be accessed, and these products could be further arylated to give *cis*-1,2,3-substituted cyclopropanes, albeit in low yields (20-38%). The reaction temperatures could also be lowered to provide good conversions while producing good *ee's*. Notably, there were issues with mixtures of mono: di arylated products, which remains problematic for intermolecular arylation reactions.

Inspired by the work by Daugulis and others, there has also been investigations into cyclopropyl intermolecular C–H arylation employing other auxiliaries towards accessing the less common *cis*-substituted cyclopropane motif (**Scheme 30**).[101]

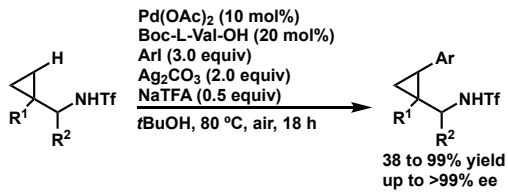
Scheme 30. Cyclopropyl C–H arylation employing other common directing groups. A) picolinamide. B) 2-(methylthio)aniline C) 8-aminoquinoline.



A common feature for all the examples presented is that all observed mixtures of mono: di-arylated products. Additionally, like many directing group strategies access to the less-common *cis*-substituted cyclopropane could be achieved and were proposed to occur via similar Pd(II)/Pd(IV) manifolds.

Yu additionally published a follow-up paper reporting enantioselective arylation of cyclopropylmethylamines (**Scheme 31**).[102]

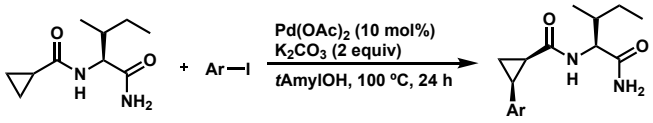
Scheme 31. Pd(II)-catalyzed enantioselective arylation cyclopropylmethylamines.



The monoarylated product was exclusively obtained and unlike previous Pd(II)/MPAA methodologies, this represented the first example of enantioselective arylation via a Pd(II)/Pd(IV) manifold.

There has also been work employing amino acid-based directing groups. A cyclopropyl variant was devised based on a similar methodology developed by Yu (**Scheme 32**).[103]

Scheme 32. Use of an isoleucine-NH_2 bidentate directing group for stereoselective cyclopropane C–H functionalization.



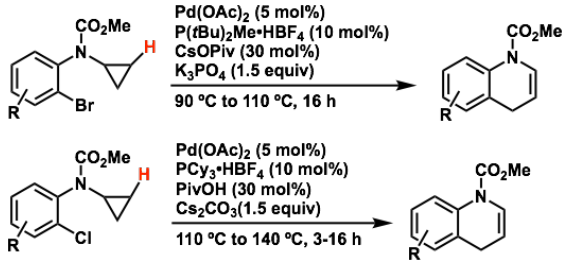
Issues with diarylation were also observed, but could be eliminated by decreasing the reaction time at the cost of product yields.

To date, there are still limited examples of cyclopropyl functionalization that proceed with primarily monoarylation. Additionally, transient directing group and catalyst-control strategies would be desirable for intermolecular approaches.

1.6.2 Intramolecular C–H Functionalization of Cyclopropanes

Using an amide-based tether, the Fagnou group reported the first example of intramolecular cyclopropyl C–H functionalization; however, ring-opening was observed, producing an unstable 1,4-dihydroquinoline intermediate (**Scheme 33**).[104]

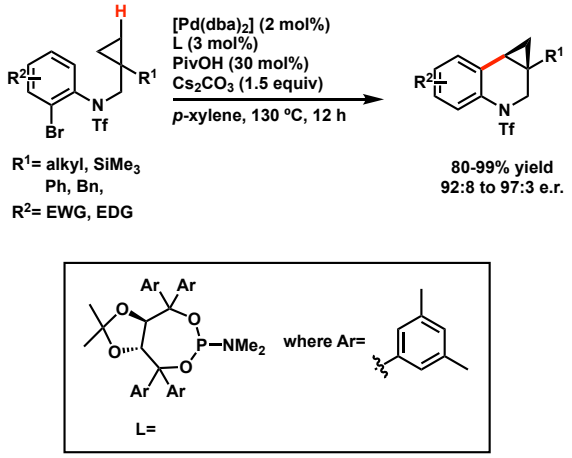
Scheme 33. Intramolecular C–H arylation/ring-opening employing cyclopropylamines.



Mechanistic studies supported that cyclopropyl C–H bond abstraction occurred prior to ring-opening.

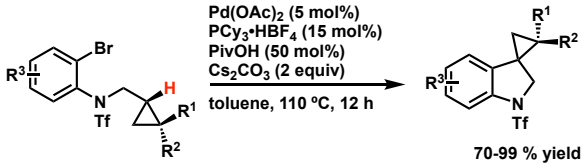
In 2012, using a similar amine-based tether, the Cramer group published the first example of an enantioselective intramolecular C–H arylation of cyclopropanes to form tetrahydroquinolines using a TADDOL-phosphoramidite ligand (**Scheme 34**).[105]

Scheme 34. Saget and Cramer's intramolecular enantioselective C–H arylation of cyclopropanes



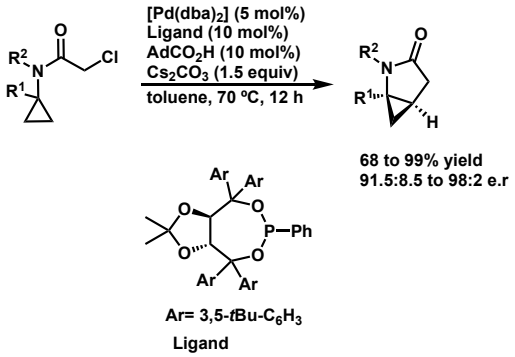
Simultaneously with the Charette group,[106] the Cramer group later discovered that if the alpha-position was not blocked, spiroindolines could be accessed (**Scheme 35**).[107]

Scheme 35. Synthesis of spiroindolines using pivalate-assisted conditions.



More recently, the Cramer group published a strategy to access gamma-lactams using chloroacetamide substrates and a TADDOL-phosphonite ligand. Azabicyclo [3.1.0] hexane scaffolds were accessible in excellent yields with excellent enantioselectivities (**Scheme 36**)

Scheme 36. Access to gamma-lactams via cyclopropyl C–H functionalization.



In recent years, intramolecular C–H functionalization of cyclopropanes has gained increasing attention. Via these processes, it is viable to access novel and pharmacologically-relevant cyclopropyl-fused heterocycles. Although there has been some progress in this field, there remains only a few methodologies, leaving room to develop novel reactions, which could offer interesting mechanistic insights and synthetic pathways towards novel cyclopropane scaffolds. The rest of this thesis will detail our contributions to this field through two examples of intramolecular C–H functionalization of cyclopropanes utilizing an oxidative-addition-induced approach and our work in expanding asymmetric C–H functionalization methodologies.

1.7 Master's Work[108]

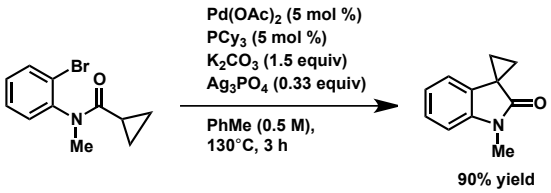
The foundations for the work presented in this doctoral dissertation were developed during the author's Master's research. Two key reactions were discovered and will be briefly summarized below.

1.7.1 Access to Spiro 3,3'-oxindoles via a Silver-Mediated, Palladium-Catalyzed Direct Arylation of 2-Bromoanilides[109]

At the time, we started investigations, there were no examples of intramolecular palladium-catalyzed cyclopropyl C–H arylation. Based on literature precedence, we postulated that an amide tether would perform superiorly compared to an amine tether because of reduced nitrogen basicity. Notably, we were the first to employ such an amide-based tether towards cyclopropyl C–H functionalization.

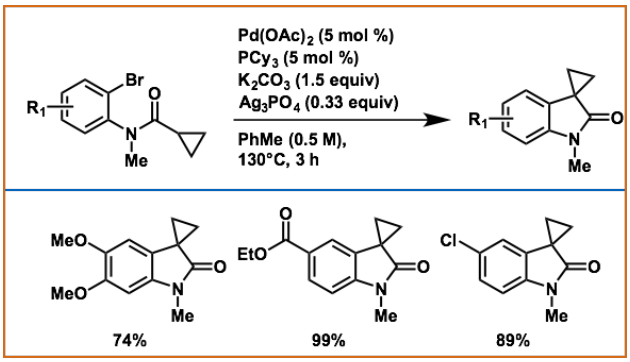
Initially, we pursued Ni-catalyzed radical-based methodologies employing an amide-based tether, based on a report by Beckwith and Storey.[110] However, such efforts were not fruitful, and consequently, we switched to Pd-based strategies. Initially, poor yields were achieved with the iodo analogues, which we attributed to catalyst poisoning. By adding 1 equivalent of Ag(I) to sequester the iodide, improved reactivity was attained. Extending the palladium-catalyzed, silver-mediated conditions to 2-bromoanilide substrates, a rate enhancement was observed (**Scheme 37**).[111]

Scheme 37. Palladium-catalyzed intramolecular arylation of 2-bromoanilides.



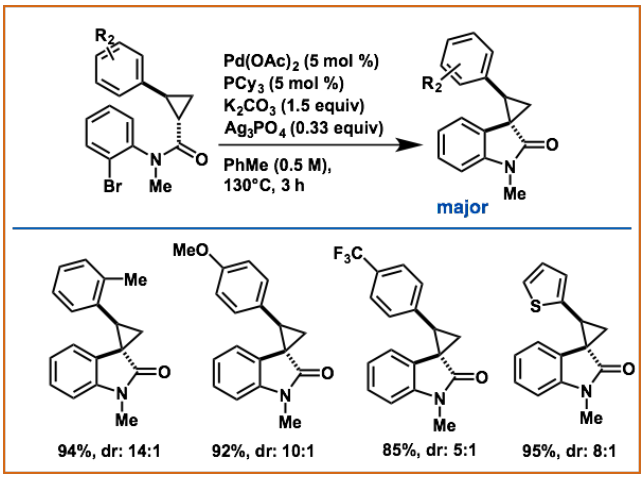
Using this methodology, we were able to access various spiro 3,3'-oxindoles. Notably, this cyclization strategy presents a safer, efficient and more sustainable synthetic route to access the spiro 3,3'-cyclopropyl oxindole core, a recurring structural motif present in several agrochemically and pharmacologically active compounds. Scheme 38 shows selected examples of aryl substitution. In line with a concerted-metallation deprotonation event, electron-withdrawing functionalities performed superiorly to electron-donating groups.

Scheme 38. Selected scope using aryl substituents.



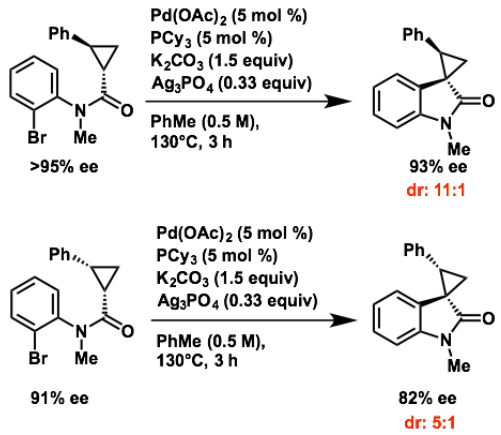
Substitution onto the cyclopropane moiety was also tolerated, providing access to a mixture of major and minor diastereomers. Electron-donating groups afforded slightly improved diastereoselectivities (**Scheme 39**).

Scheme 39. Selected scope with cyclopropane substitution.



To differentiate between direct arylation and enolate arylation, we performed epimerization experiments using enantiopure substrates (**Scheme 40**).

Scheme 40. Epimerization experiments.



As stereochemical fidelity was maintained and no racemization was observed, it could be concluded that a putative enolate species did not form. We also calculated the KIE to be 3.9 using parallel experiments, indicating that the H-abstraction was the rate-determining step,

which provided further support against enolate arylation where oxidative insertion is typically the rate-limiting step.

As the reaction was dependent on silver, we postulated that in light of previous studies,[112] the reaction could proceed via a cationic palladium species. Figure 13 shows our postulated mechanism.

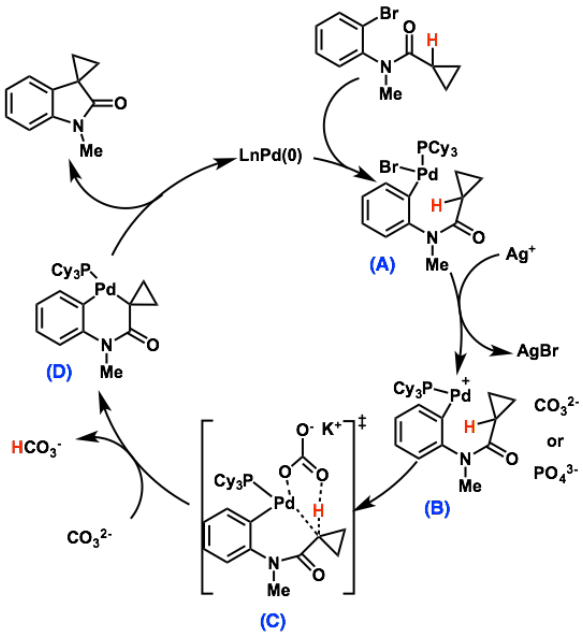


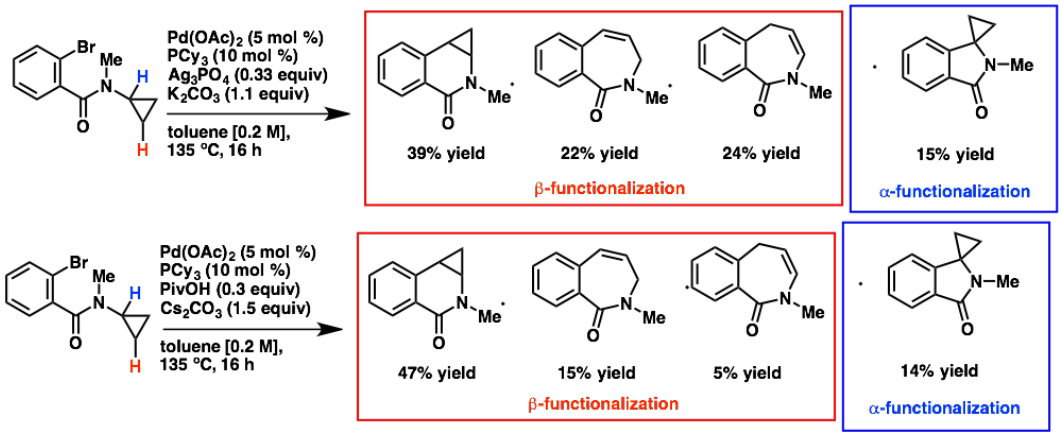
Figure 13. Proposed Catalytic Cycle.

Oxidative addition of Pd(0) into the Ar–Br bond generates intermediate **A**. Silver(I) abstracts bromide, forming highly electrophilic cationic Pd-species **B**. Carbonate serves as the external base, resulting in irreversible deprotonation (**C**) to form six-membered palladacycle **D**, which undergoes reductive elimination to regenerate Pd(0) and yield the cyclized product.

1.7.2 Palladium-Catalyzed, Silver-Promoted Ring-Opening of Cyclopropyl Benzamides[113]

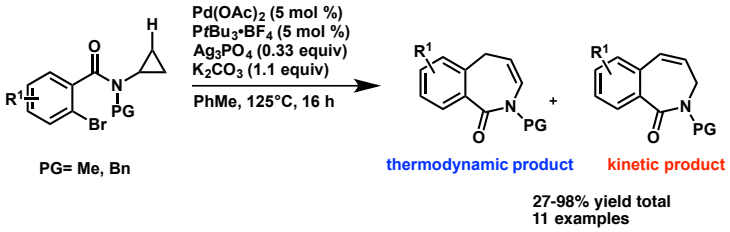
Delighted with the success of our previous methodology, we decided to switch the position of the amide, focusing on 2-bromobenzamides. However, we were surprised to observe the formation of four different products under both silver and pivalate conditions, favoring beta-functionalization over alpha-functionalization (**Scheme 41**).

Scheme 41. Ring-opening of cyclopropyl-derived 2-bromobenzamides.



Aiming to access the fused-cyclopropane system, we conducted a brief ligand screen. Unfortunately, we were unable to maintain the cyclopropyl moiety; however, by employing sterically bulky P*t*Bu$_3$•HBF$_4$, complete ring-opening produced novel 7-membered benzazepinones as a mixture of two stable separable isomers (**Scheme 42**).

Scheme 42. Ring-opening of cyclopropyl-derived 2-bromobenzamides.



When the fused cycle was resubjected to the reaction conditions, no ring-opening products were detected, supporting a mechanism involving C–H activation, followed by subsequent ring-opening (**Scheme 43**)

Scheme 43. Support for cyclopropyl C–H activation, then ring-opening.

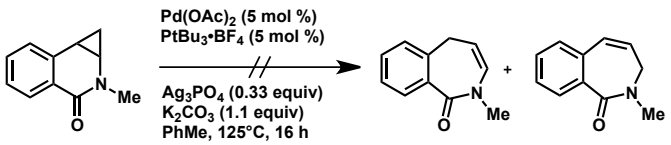


Figure 14 demonstrates a proposed mechanism involving oxidative addition (**A**), halide abstraction (**B**), and a CMD step to render the seven-membered palladacycle (**C**). Palladacycle

C then undergoes a ring-opening event (**D**), followed by reductive elimination to generate the resulting ring-opened products.

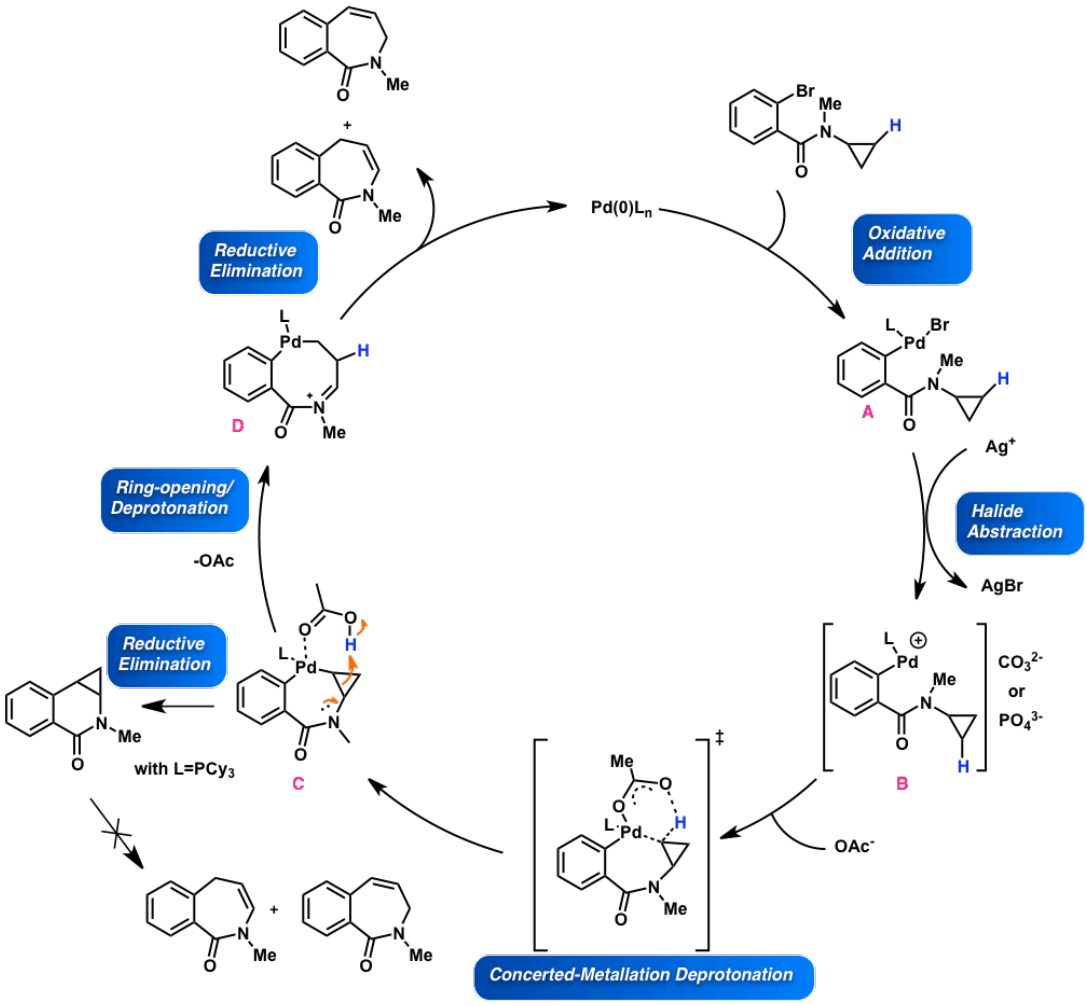


Figure 14. Proposed catalytic cycle for benzazepinone formation.

Scope explorations indicated that the reaction was general towards both electron-donating and electron-withdrawing substituents, producing the separable isomers in high yields; albeit, cyclopropyl substitution inhibited the reaction. Notably, the mixture of benzazepinones could be hydrogenated to access benzolactams via a one-pot procedure.

1.8 Research Goals

Figure 15 summarizes mechanistic explorations into alpha- and beta-cyclopropane functionalization via intramolecular palladium-catalyzed arylation. Access to novel five-, six- and seven-membered heterocyclic motifs were viable.

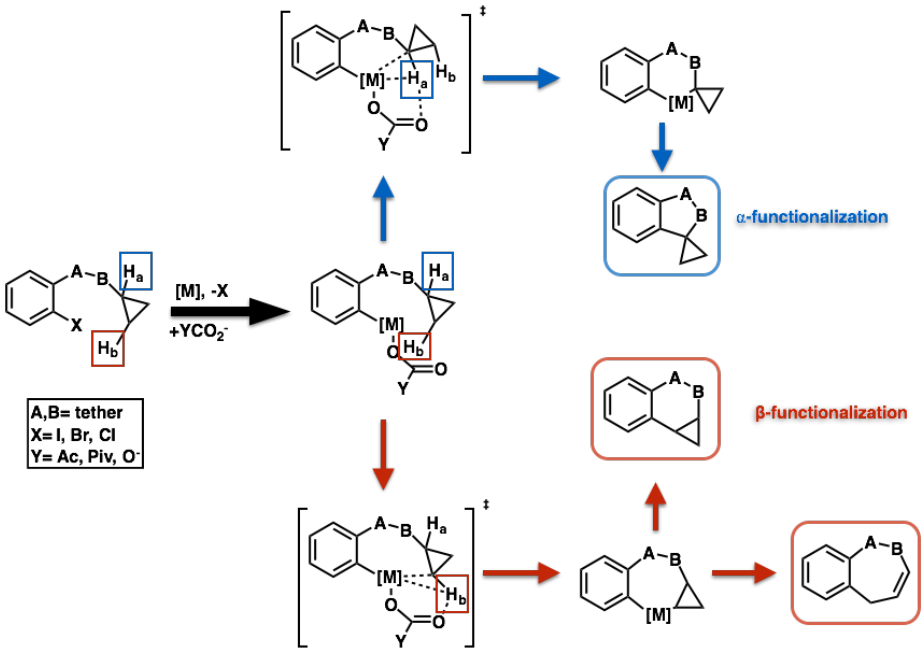


Figure 15. Cyclopropyl C–H activation pathways pursued during Masters work.

For this PhD dissertation, investigations into intramolecular palladium-catalyzed C–H functionalization were continued with emphasis on developing new approaches towards enantioselective functionalization. Based on the results using our 2-bromobenzamide system, we pursued access towards novel tetraisohydroquinolones scaffolds, using this transformation as a model system to test potential asymmetric strategies. Chapter 2 describes the development of this system using 2-bromobenzamides derived from alpha-cyclopropyl amino acids. Chapter 3 describes our synthetic adventures to "escape Flatland" via direct cyclopropyl alkenylation. Finally, Chapter 4 describes our efforts towards enantioselective C–H arylation of sp^3 centers employing *(R,R)*-BozPhos, a hemilabile, bisphosphine monoxide as a chiral ligand in combination with the Buchwald G4 dimer as a dba-free source of Pd(0).

Chapter 2 Intramolecular Palladium-Catalyzed sp^3 Functionalization of α-Cyclopropyl Amino Acid-Derived Benzamides

Within medicinal chemistry, nitrogen represents an essential design element and is known as the "necessary nitrogen atom." Substituting the CH group with N can increase pharmacological properties by >10 fold.[114] Consequently, it is no surprise that nitrogen-based heterocycles are present within 59% of USA FDA-approved small-molecule drugs, surpassing both sulfur and fluorine atoms (26% and 13% respectively).[115] Furthermore, six-membered azines represent the largest portion of heterocycles (59%) and fused ring systems comprise 14%. Amongst nitrogen-based heterocycles, tetrahydroisoquinoline ranks 19th within the top 25 most frequently encountered heterocycles. Figure 16 shows a selected example of this core, which is a commonly known drug metabolite, and a few recent FDA-approved drugs and drug candidates.[116]

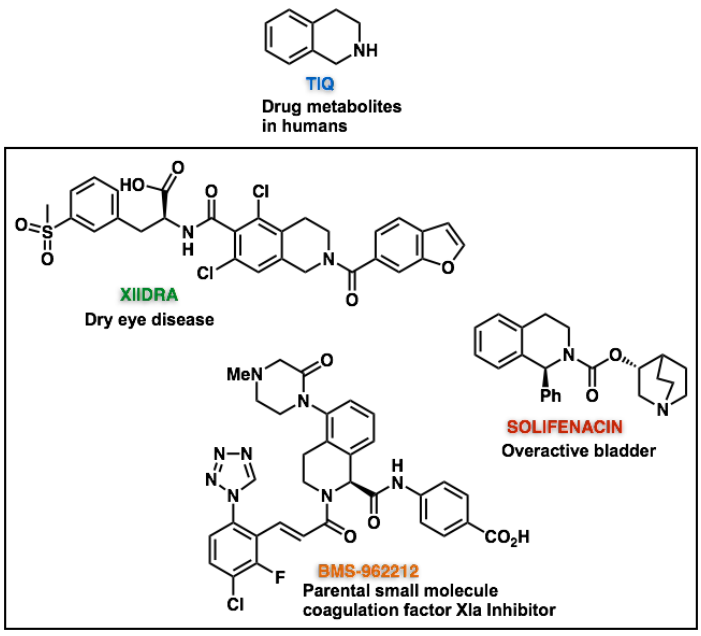


Figure 16. The tetrahydroisoquinoline motif within pharmacological scaffolds.

Cyclopropane amino acids have been explored due to the ability to impart desirable steric restraints and have demonstrated interesting applications in peptidomimetics.[117] The simplest

cyclopropyl amino acid, is naturally-occurring 1-aminocylcopropane-1-carboxylic acid (ACC) and is responsible for regulating plant growth via controlling ethylene-release.[118] Figure 17 shows a sampling of cyclic cyclopropane-fused prolines and pipecolic acids.[119]

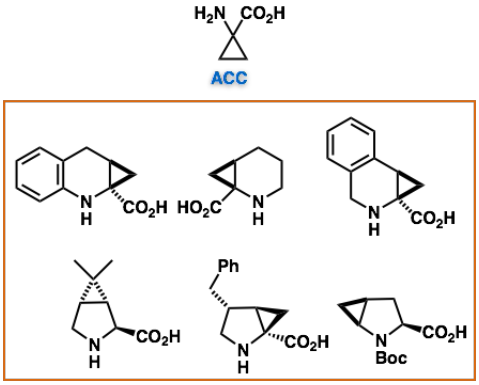


Figure 17. Cyclic proline and pipecolic acid derivatives.

De Kimpe has investigated strategies to constrain 1,2,3,4-tetrahydroisoquinoline-3-carboxlic acid (TiC). Additionally, TiC is a useful precursor to access bradykinin antagonists, ACE inhibitors, renin inhibitors and opioid antagonists.[120] To reduce the structural promiscuity of TiC, a cyclopropane-analogue was proposed (Figure 18).

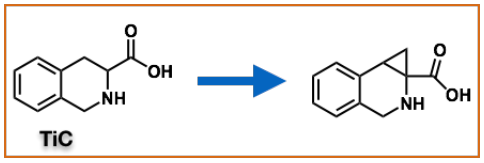


Figure 18. De Kimpe's modification to access a doubly constricted bicyclic amino acid.

Notably, potential alkene precursors are notoriously unstable and difficult to purity, complicating alkene-based cyclopropanation strategies (Figure 19).[121]

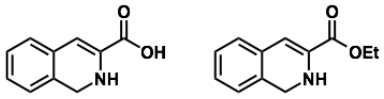


Figure 19. Unstable alkene precursors.

Additionally, tetrahydroquinolone analogues have demonstrated interesting bioactivity (**Figure 20**).[122]

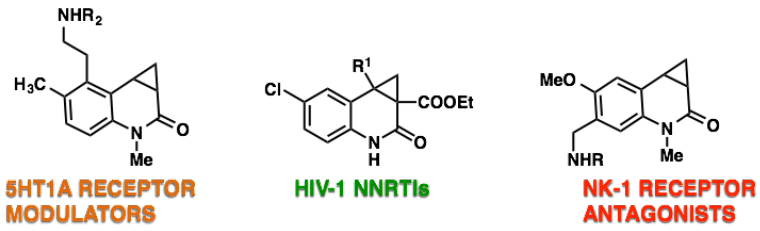


Figure 20. Biologically-relevant cyclopropyl-containing tetrahydroquinolone cores.

By accessing the related tetrahydroisoquinolone core, a novel class of unexplored cyclopropane-fused heterocycles could be developed.

Considering the beneficial pharmacological properties and the difficulty in accessing such a moiety, a direct C–H functionalization pathway could provide a strategy to avoid the unstable alkene intermediates and provide a more sustainable pathway to access this potentially valuable core (Figure 21).

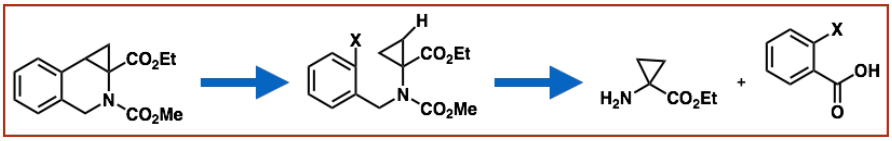
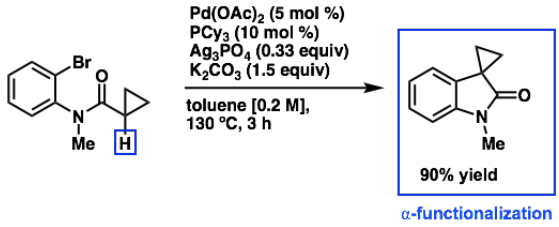


Figure 21. Route to access tetrahydroquinolines via C–H functionalization logic.

2.1 Project Origins and Research Goals

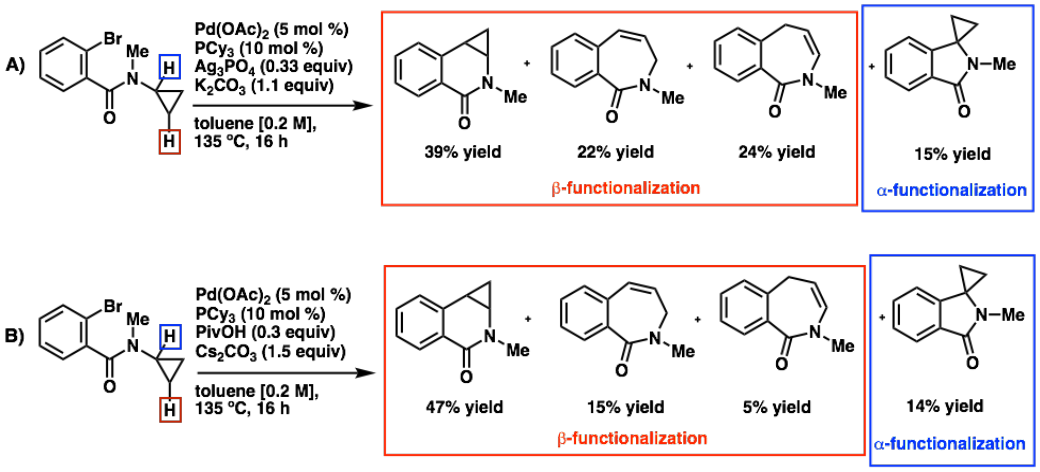
This project originated from the author's MSc work exploring palladium-catalyzed C–H functionalization of cyclopropanes using amide-based tether systems and silver additives (**1.7**). Using 2-bromo anilides, only alpha-functionalization was observed (**Scheme 44**).

Scheme 44. Alpha-functionalization using 2-bromoanilides.



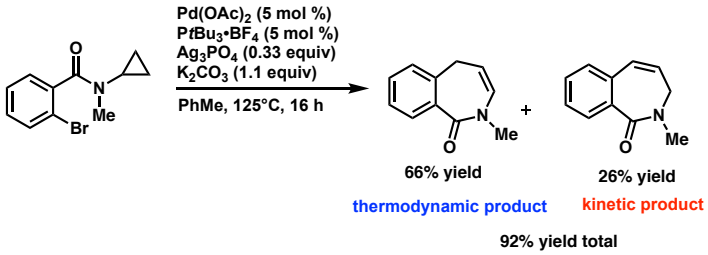
By switching the position of the nitrogen and employing 2-bromobenzamide systems, we observed a strong preference for beta-functionalization over alpha-functionalization with both pivalate and silver conditions (**Scheme 45**).

Scheme 45. A) C–H functionalization of cyclopropyl benzamides under silver-conditions. B) C–H functionalization of cyclopropyl benzamides under silver-conditions.



A preliminary ligand screen indicated that although the undesired ring-opening process could not be circumvented, using P*t*Bu$_3$•HBF$_4$ could achieve complete conversion to the ring-opened benzazeapinone products (**Scheme 46**).

Scheme 46. Access to ring-opened benzazepinones

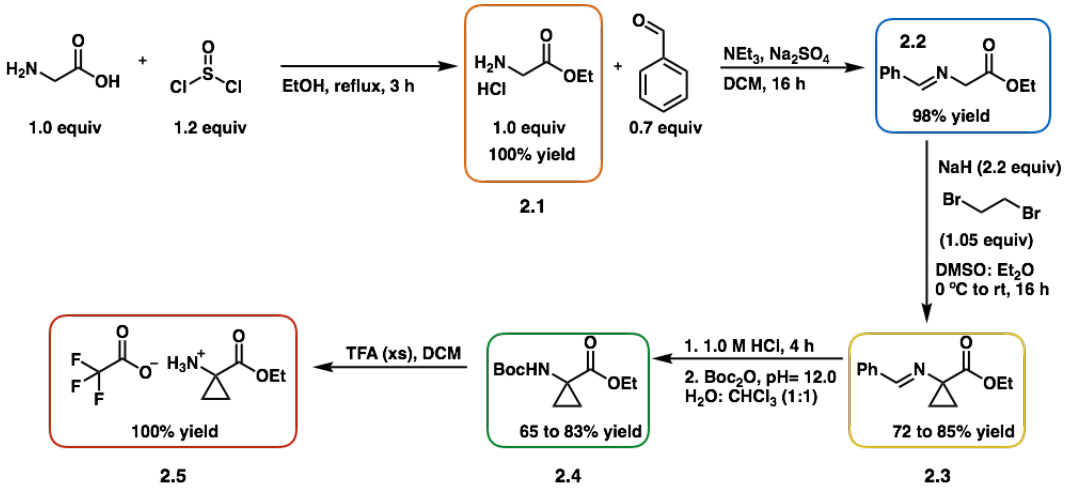


Inspired by cyclopropyl amino acids, we modified our benzamide substrate to feature an ester moiety that we postulated could access both a milder, less-energetically demanding process for cyclopropyl C–H insertion, providing access to the 6-membered cyclopropyl-fused tetrahydroisoquinolinones. Additionally, with the aim of pursuing enantioselective cyclopropyl C–H functionalization, we postulated that the reaction would be a suitable model system to test potential asymmetric strategies (**Chapter 4**).

2.2 Synthesis of Starting Materials

We decided that the use of an amino acid ester as our precursor would provide a highly amenable strategy to access a diversity of products. Although this amino acid ester is now commercially available,[123] at the time we synthesized the TFA salt via a six-step synthesis from glycine modified from a literature procedure (**Scheme 47**).[124]

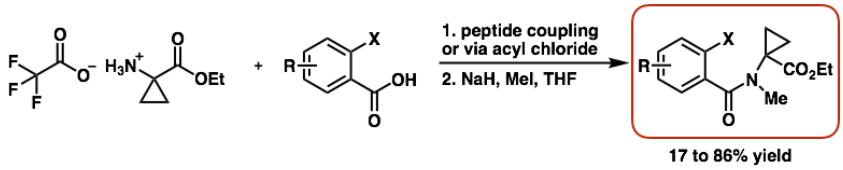
Scheme 47. Synthesis of TFA salt precursor.



The first step involved esterification of the glycine and conversion to its hydrochloride salt (**2.1**).[125] Then, **2.1** was converted to the aldimine (**2.2**) via condensation.[126] Bisalkylation, followed by aldimine hydrolysis, Boc-deprotection, and conversion to the TFA salt produced desired precursor **2.5** in 38% yield from **2.1**. The yield matched literature precedence for a similar pathway and for the project, this synthesis was scaled to 20g.

Precursor **2.5** could then be coupled either via a peptide coupling protocol or acyl chloride process. Due to issues in removing the peptide reagent by-products, we switched to an acyl chloride approach. Subsequent protection of the nitrogen could then access a variety of 2-bromobenzamide precursors (**Scheme 48**).

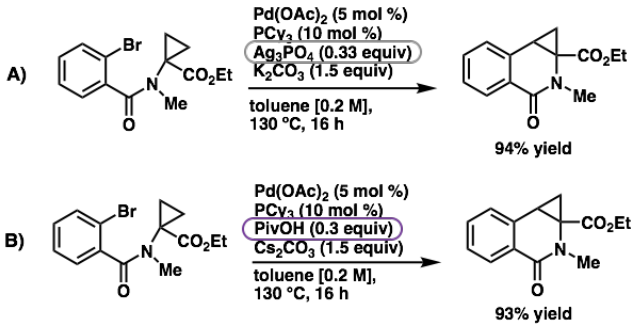
Scheme 48. Synthesis of starting 2-halobenzamides.



2.3 First Reactions

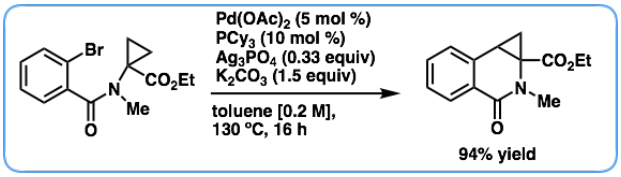
First, we subjected the starting material to both silver and pivalate-mediated conditions and we could obtain the desired six-membered product as the sole-product in excellent yield (**Scheme 49**).

Scheme 49. Initial efforts using A) silver-mediated conditions, B) pivalate-mediated conditions.



As there was no clear preference between silver and pivalate-mediated conditions, control reactions were conducted to further explore the role of reagents (**Table 1**).

Table 1. Control Reactions



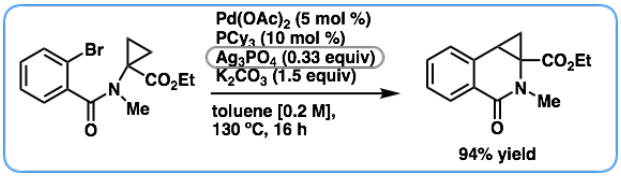
Entry	Variation from Standard Conditions	Yield[%][a]
1	No Ag_3PO_4	91
2	No $Pd(OAc)_2$	SM
3	Without ligand (PCy_3)	SM
4	No Ag_3PO_4 or $Pd(OAc)_2$	SM
5	Only K_2CO_3	SM does not decompose
6	Without K_2CO_3	64 + SM

[a] Yields determined via ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

In the absence of silver, the reaction still proceeds in excellent yield (**entry 1**). Both catalyst and ligand are required for reactivity (**entry 1-4**), and the starting material was found to be stable when heated with base and solvent (**entry 5**). Notably, the reaction does proceed without base in modest yields (**entry 6**), substantiating the need for potassium carbonate to function as an insoluble base to regenerate the proton shuttle for the concerted-metallation deprotonation event. Most importantly, no background reactions resulting from the absence of ligand were observed (**entry 3**), which was important for our enantioselective reaction design.

Table 2 shows preliminary catalyst optimization conditions.

Table 2. Catalyst Investigations.



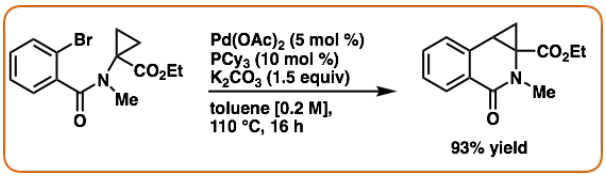
Entry	Variation from Standard Condition	Yield[%][a]
1	$Pd(dba)_2$, instead of $Pd(OAc)_2$	80
2	$Pd(dba)_2$ + K_2CO_3 + 10 mol% KOAc	65
3	$Pd(TFA)_2$, instead of $Pd(OAc)_2$	91
4	$PdBr_2$, instead of $Pd(OAc)_2$	54
5	2.5 mol% Pd:L loading, with $Pd(OAc)_2$	80
6	1:1 Pd:L, not 1:2 Pd:L, with $Pd(OAc)_2$	89

[a] Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The reaction works with Pd(0) sources such as $Pd(dba)_2$ (**entry 1**); albeit, with slightly decreased yields. However, **entry 2** demonstrates that the reaction does not proceed in high conversions without the silver additive, even when additional acetate is added, suggesting that $Pd(OAc)_2$ is much better as a catalyst precursor compared to $Pd(dba)_2$. Other Pd(II) sources such as $Pd(TFA)_2$ and $PdBr_2$ both worked; albeit, $Pd(TFA)_2$ performed superiorly.[127] Reducing the catalyst loading was also feasible (**entry 5**) and the catalyst to ligand ratio did not have a significant effect on reactivity **(entry 6**).

These preliminary optimizations produced the optimal conditions (**Scheme 50**). Notably reaction temperatures could be reduced from 130 ºC to 110 ºC.

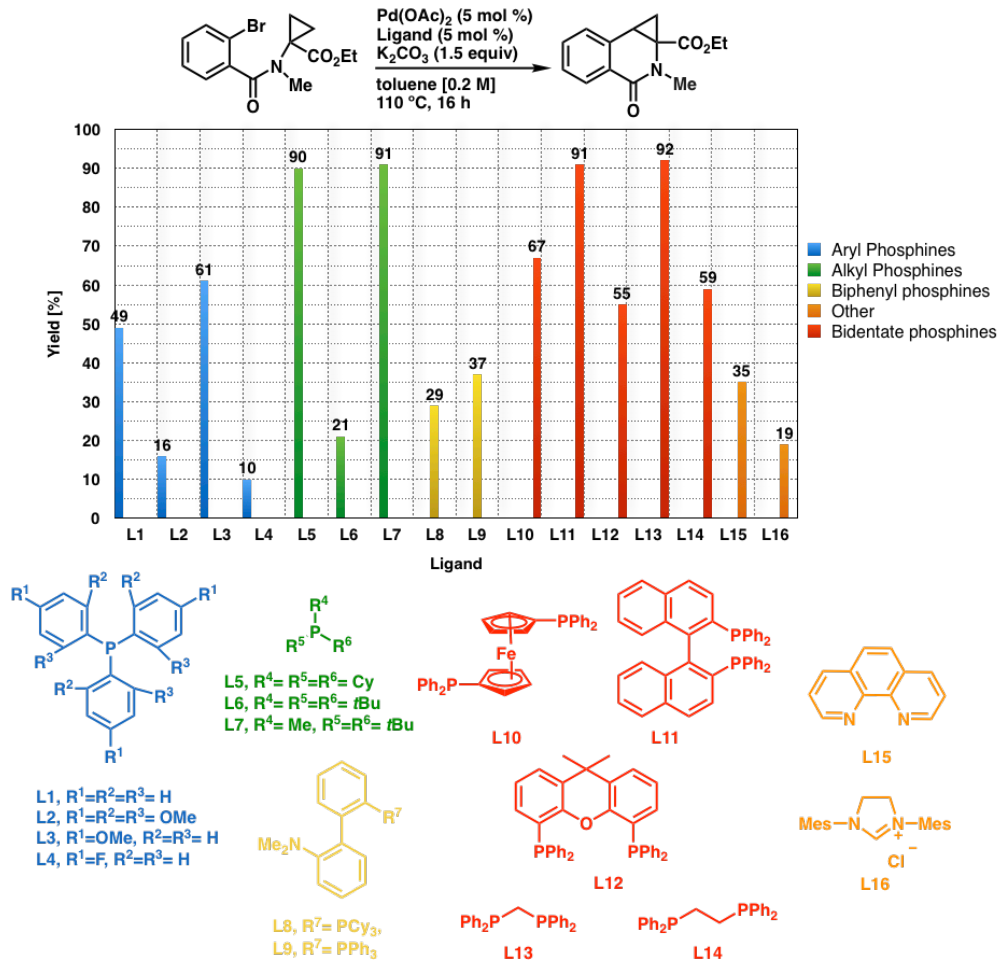
Scheme 50. Reaction in absence of silver and pivalate additives.



2.4 Reaction Optimization

We conducted a full optimization to further understand our reaction. Figure 22 shows the results from the ligand screening.

Figure 22. Ligand Screening[a]

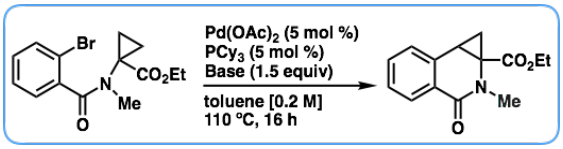


[a] Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Some general trends can be observed.[128] Alkyl phosphines outperformed aryl phosphines. Within aryl phosphines, electron-donating P(4-OMePh)$_3$ gave a slightly better yield (61% yield) compared to PPh_3 (49% yield) and to the slightly electron-withdrawing P(4-FPh)$_3$ (10% yield). Within the alkyl phosphines, steric limitations were observed as P*t*Bu$_3$•HBF$_4$ (21% yield) failed to give good yields. Buchwald-type ligands such as Davephos and PhDavephos performed inferiorly compared to other ligand classes (29 and 37% yield, respectively). Other

ligands such as 1,10-phenanthroline (35% yield) and IMes (19% yield) also gave poor conversions. One observation that was peculiar was the excellent reactivities were observed for the bisphosphine ligands. Although Echavarren previously rationalized this reactivity based on an intermolecular deprotonation mechanism, we began to speculate the possibility that the bisphosphine might not be the active ligand and that its bisphosphine monoxide counterpart may in fact be formed *in situ* from oxidation from Pd(II). This theme will emerge over the course of this thesis and will be elaborated in full detail in **Chapter 4**. Notably, *rac*-BINAP and dppm performed superiorly compared to Xantphos, dppe, and dppf. For the purposes of this methodology we chose PCy_3 due to its excellent reactivity and relatively low cost.

Table 3. Base Screening.[a]



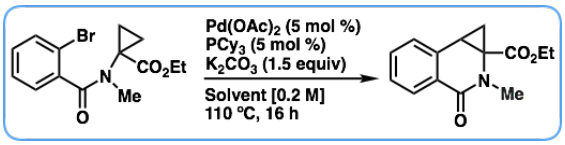
Entry	Base	Yield [%][a]
1	K_2CO_3	90
2	Na_2CO_3	79
3	Rb_2CO_3	66
4	Cs_2CO_3	85
5	K_3PO_4	80
6	KOAc	39
7	CsOPiv	Trace
8	NaO*t*Bu	Trace
9	NEt_3	18
10	DIPEA	11

[a] Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

We then screened bases varying in counterion and base strength (**Table 3**). All the carbonate bases performed well (**entries 1-4**) with Rb_2CO_3 (**entry 3**) providing the lowest conversion. Surprisingly, Na_2CO_3 also performed well (**entry 2**), suggesting that the counterion has only subtle effects on reactivity. Notably, even K_3PO_4 afforded the product in good yield (80%), despite being a weaker base (**entry 5**). Bases such as KOAc and CsOPiv performed

poorly (**entries 6-7**), suggesting the need for the insoluble carbonate or phosphate base to help regenerate the proton shuttle. Notably, NaO*t*Bu decomposed the starting material (**entry 8**). Organic bases such as NEt_3 and DIPEA gave poor conversions (**entry 9-10**), which suggests H-abstraction occurs via a carboxylate-mediated CMD event. Due to the cost and mild nature, we chose K_2CO_3 as the optimal base.

Table 4. Solvent Screening[a]



Entry	Solvent	Yield[%][a]
1	pyridine	12
2	DMA	38
3	dioxane	58
4	chlorobenzene	62
5	mesitylene	75
6	*n*-butanol	trace
7	DMF	54
8	toluene	90

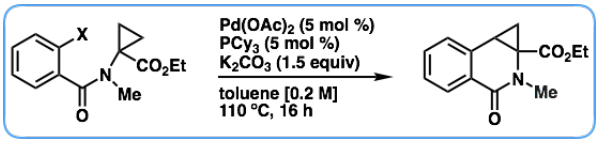
[a] Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

We next conducted a brief solvent screen (**Table 4**). Aromatic solvents performed superiorly to other solvents (**entries 4,5,8**). Polar protic solvents such as *n*-butanol gave trace conversions (**entry 6**). Polar aprotic solvents such as DMF, DMA, and pyridine in addition to nonpolar solvent such as 1,4-dioxane provided moderate yields (**entries 1, 2 and 7**). Consequently, toluene was maintained as the choice solvent.

2.5 Scope of Reaction

Using our optimized conditions, the scope of the reaction was then explored. The effect of halide analogue was first examined (**Table 5**).

Table 5. Halide Effect.



Entry	Halide (X=)	Yield[%][a]
1	Br	90
2	Cl	49 (97)[b]
3	I	29(46)[c]

[a] Isolated yields [b] Yield in parenthesis at 140 ºC [c] Yield in parenthesis with 1.0 equivalents of Ag_2CO_3

The chloro analogue (**entry 2**) also provided high yields; however, higher temperatures were required.[129] The iodo analogue produced diminished conversions due dehalogenation and the poisoning effect of iodide ion on palladium; however, the addition of 1.0 equiv of cationic silver as a halide sequestration reagent improved the yield.[130]

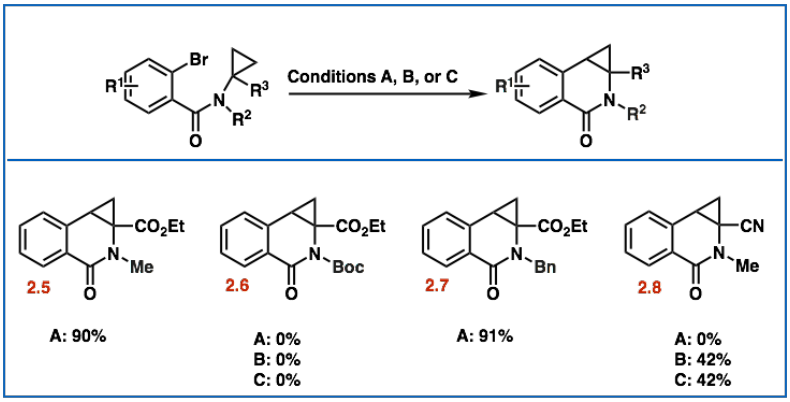
Although adopting a reductionist approach towards methodology design was advantageous, some substrates required additional additives to achieve improved yields. In general, both electron-withdrawing and electron-donating substrates furnished good to excellent yields under additive-free conditions (**Conditions A**).[131] Low-yielding substrates produced dehalogenation or starting materials as identifiable by-products, with no detected no ring-opening products. Pivalate and silver conditions (**Conditions B and C**) were additionally screened for substrates providing yields less than 70%.

In general, the pivalate additive was more beneficial compared to adding silver, suggesting that the reaction does not proceed via a cationic palladium species. Notably, the silver additive showed negligible effects on reactivity. Only the *bis*-methoxy substrate showed reduced performance compared to the standard conditions (**Conditions A**). More specific classes of the scope are discussed below (**Scheme 52**).

We first began investigating the role of the *N*-protecting group and alpha-substituent (**Scheme 51**). The *N*-Boc group (**2.6**) was incompatible; however, the *N*-benzyl derivative could be employed providing product **2.7** in excellent yield.[132] Replacing the ester moiety with a cyano

group (**2.8**) gave trace conversions; albeit, both silver and pivalate additives enhanced reactivity.[133]

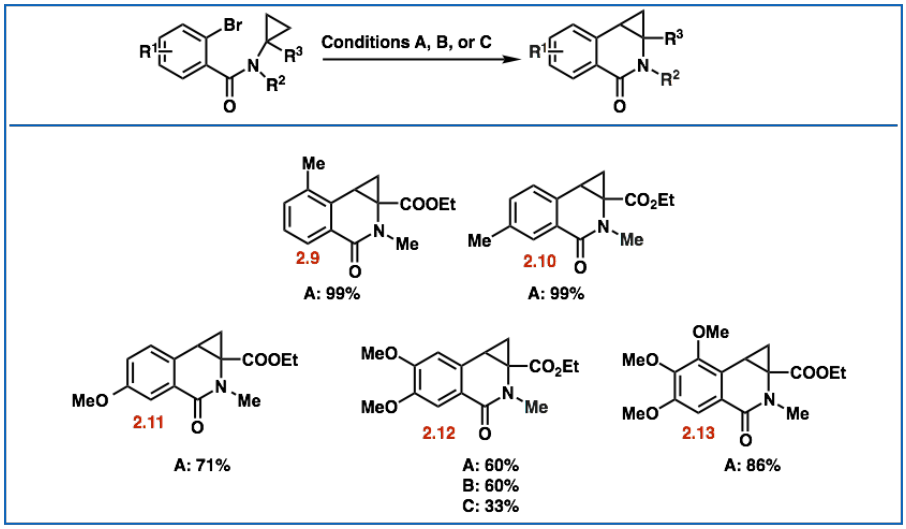
Scheme 51. Effect of protecting group and alpha-substituents.[a]



[a]Isolated yields. **Conditions A:** $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h. **Conditions B:** $Pd(OAc)_2$ (5 mol%), $PtBu_2Me{\bullet}HBF_4$ (5 mol%), CsOPiv (0.3 equiv), K_3PO_4 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h. **Conditions C:** $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), Ag_3PO_4 (0.3 equiv), toluene [0.2 M], 110 ºC, 16 h.

Electron-donating groups could be incorporated (**Scheme 52, 2.9-2.33**). *Bis*-methoxy-substitution produced moderate yields (**2.12**) and additional additives were not beneficial.[134] Notably, *tris*-methoxy-substitution was well-tolerated, affording **2.13** in good yield.

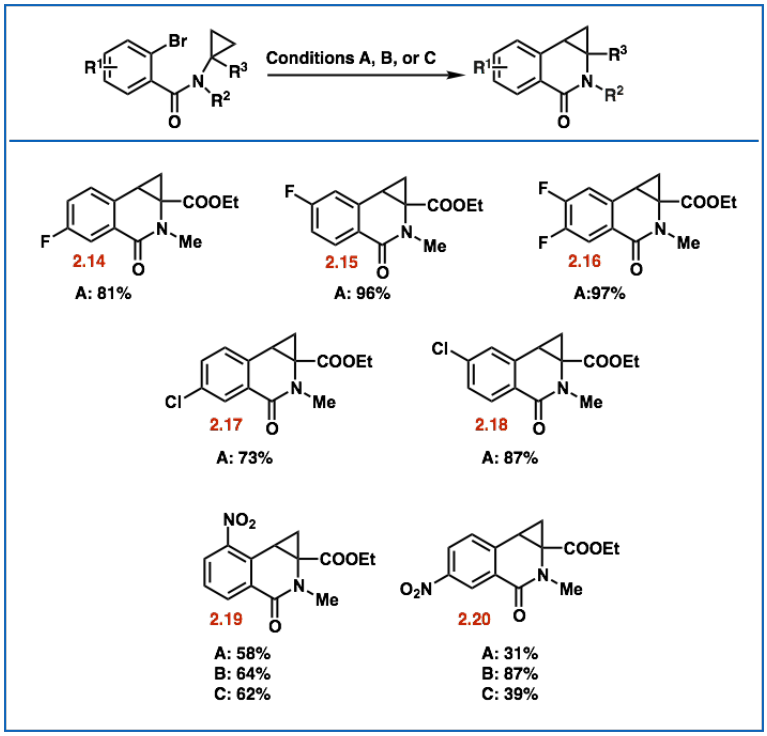
Scheme 52. Scope of Reaction for Electron-donating groups



[a]Isolated yields. **Conditions A:** $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h. **Conditions B**: $Pd(OAc)_2$ (5 mol%), P*t*Bu_2Me•HBF_4 (5 mol%), CsOPiv (0.3 equiv), K_3PO_4 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h**. Conditions C:** $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), Ag_3PO_4 (0.3 equiv), toluene [0.2 M], 110 ºC, 16 h.

Scheme 53 shows the scope for electron-withdrawing groups. Both fluoro- and chloro-substitution (**2.14-2.18**) did not require additional additives. Strongly electron-withdrawing functionalities such as the nitro group were tolerated (**2.19-2.20**). The addition of pivalate contributed to significantly improved yields for product **2.20**; however, the effects of additives on **2.19** were negligible.[135]

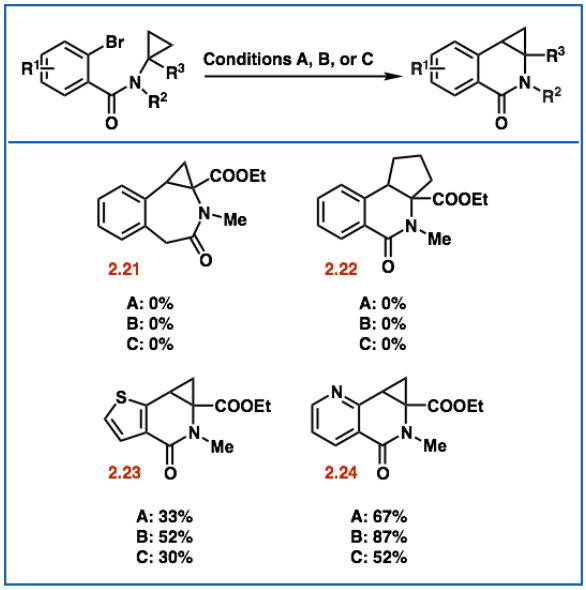
Scheme 53. Scope of Reaction for Electron-withdrawing groups.



[a]Isolated yields. **Conditions A:** $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h. **Conditions B:** $Pd(OAc)_2$ (5 mol%), $PtBu_2Me{\bullet}HBF_4$ (5 mol%), CsOPiv (0.3 equiv), K_3PO_4 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h. **Conditions C:** $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), Ag_3PO_4 (0.3 equiv), toluene [0.2 M], 110 ºC, 16 h.

Other ring sizes and heterocycles were also investigated (**Scheme 54**). Homologated benzamide **2.21** and cyclopentyl derivative **2.22** did not work under the reaction conditions.[136137] Notably, using pivalate-conditions thienyl and pyridyl substrates (**2.23-2.24**) afforded modest to good yields.[138-139]

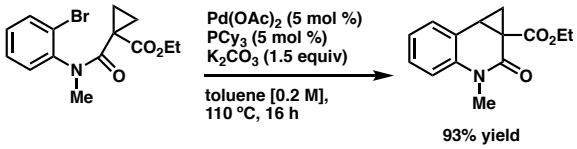
Scheme 54. Scope of reaction for other ring sizes and heterocycles.



[a]Isolated yields. **Conditions A:** $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h. **Conditions B**: $Pd(OAc)_2$ (5 mol%), $PtBu_2Me{\bullet}HBF_4$ (5 mol%), CsOPiv (0.3 equiv), K_3PO_4 (1.5 equiv), toluene [0.2 M], 110 ºC, 16 h. **Conditions C**: $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), K_2CO_3 (1.5 equiv), Ag_3PO_4 (0.3 equiv), toluene [0.2 M], 110 ºC, 16 h.

It was also possible to synthesize the biologically-relevant tetrahydroquinolone core (**Scheme 55**).

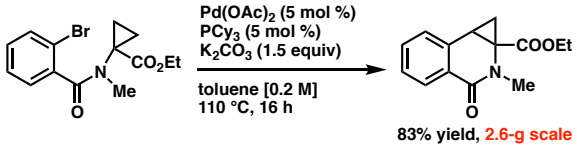
Scheme 55. Access to tetrahydroquinolones.



2.6 Reaction Scale-up

Additionally, the reaction could be scaled to 2.6 grams in good yield using a reflux condenser exposed to air and moisture, demonstrating the robust nature of the reaction (**Scheme 56**).

Scheme 56. Robust gram-scale synthesis.



2.7 Proposed Catalytic Cycle

Based on our findings, we postulate that the reaction without pivalate or silver occurs via a Pd(0)-Pd(II) cycle (**Figure 23**).[140]

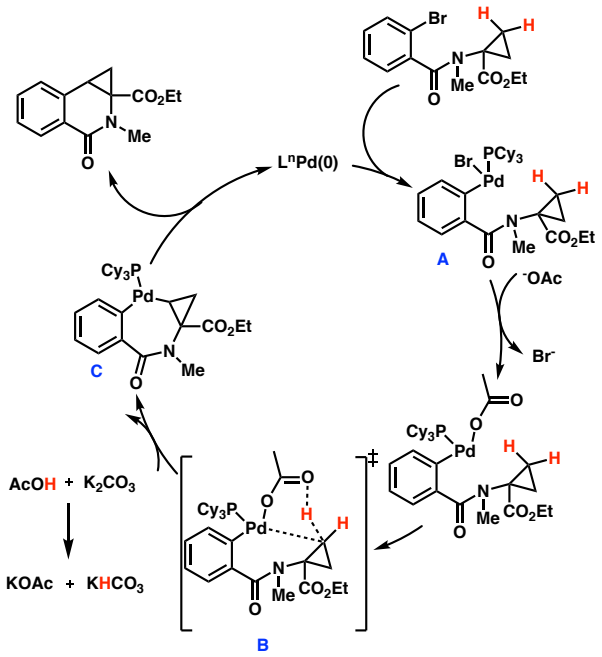


Figure 23. Proposed catalytic cycle.

Oxidative addition into the Ar–Br bond by palladium produces complex **A**. After ligand exchange with bromide, acetate functions as a the proton shuttle to mediate the concerted metalation-deprotonation event **B**,[141] producing seven-membered palladacycle **C,** stabilized by the rigid cyclopropyl moiety.[142] Finally, reductive elimination regenerates Pd(0), liberating the final product.

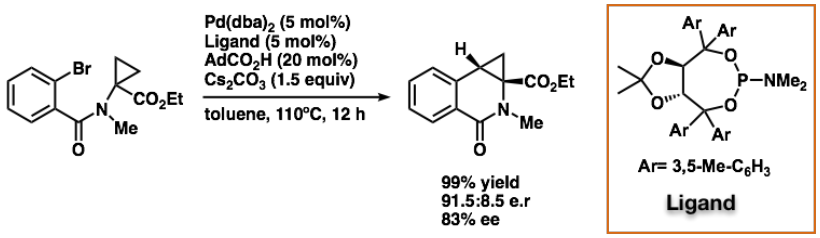
2.8 Conclusion

In conclusion, β–functionalization of cyclopropyl α–amino-acid-derived benzamides was achieved to access ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates. The role of pivalate and silver additives was explored and more challenging substrates required pivalate. If possible, a reductionist approach towards reaction design and development should be adopted and the subtle role of additives in C–H functionalization should be considered.

2.9 Related Work

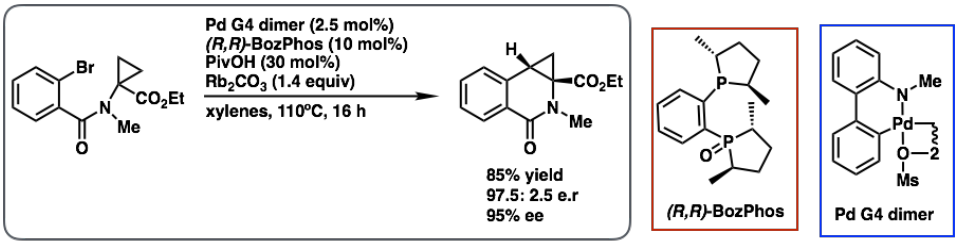
During our investigations into this system, the Cramer group published a similar methodology employing TADDOL-phosphoramidite ligands to achieve enantioselective cyclopropyl arylation (**Scheme 57**).[143]

Scheme 57. Related enantioselective methodology by the Cramer group.



The enantioselective version of this reaction will be examined using a Pd(0)-(*R,R*)-BozPhos system (**Scheme 58**) (**Chapter 4**).

Scheme 58. Optimized conditions using Pd(0)-*(R,R)*-BozPhos



Chapter 3 Access to Cyclopropyl-Fused Azacycles via a Palladium-Catalyzed Direct Alkenylation Strategy

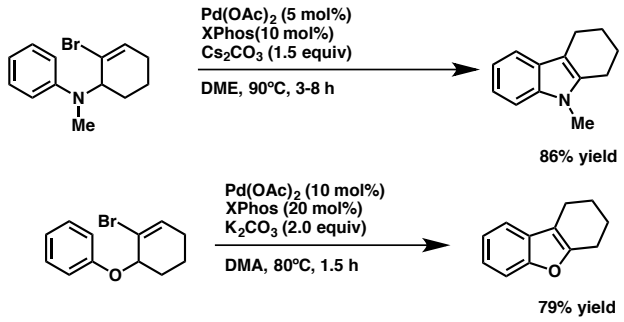
3.1 Motivations to "Escape Flatland"

To date, most C–H functionalization methodologies have concentrated on arylation reactions. However, the continuing demand for pharmaceutical drug candidates with increased Fsp^3 centers necessitates new reactions to access saturated systems. This trend towards "escaping Flatland" is attributed to improved molecular properties with higher Fsp^3 including better metabolic stability, improved solubility, greater complexity without increasing molecular weight, and improved target specificity.[144] Based on these motivations, devising C–H functionalizations to access 3D-systems via alkenylation or alkylation approaches could provide chemists with the tools to synthesis diverse chemical libraries with increased Fsp^3

3.2 Previous Work on Intramolecular Direct Alkenylation

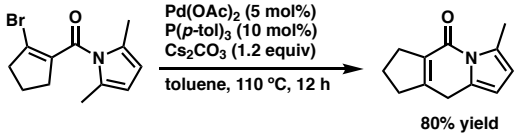
Willis reported one of the first examples of direct alkenylation using amine and ether tethers.[145] Using bulky XPhos as a ligand, access towards indole and benzofuran analogues were viable (**Scheme 59**).

Scheme 59. Early example of direct alkenylation of sp^2 centers.



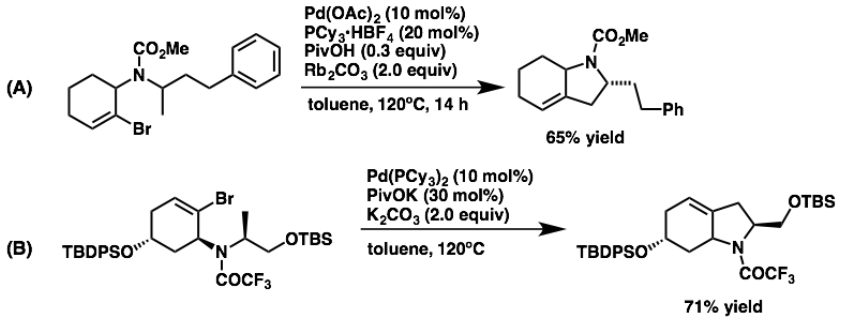
The Knochel group also published a direct alkenylation report for benzylic C–H bonds, providing access to novel fused-heterocyclic motifs (**Scheme 60**).[146]

Scheme 60. Early example of direct alkenylation of sp^3 centers.



Finally, the Baudoin group has actively pursued direct alkenylation strategies targeting sp^3 centres (**Scheme 61**).[147]

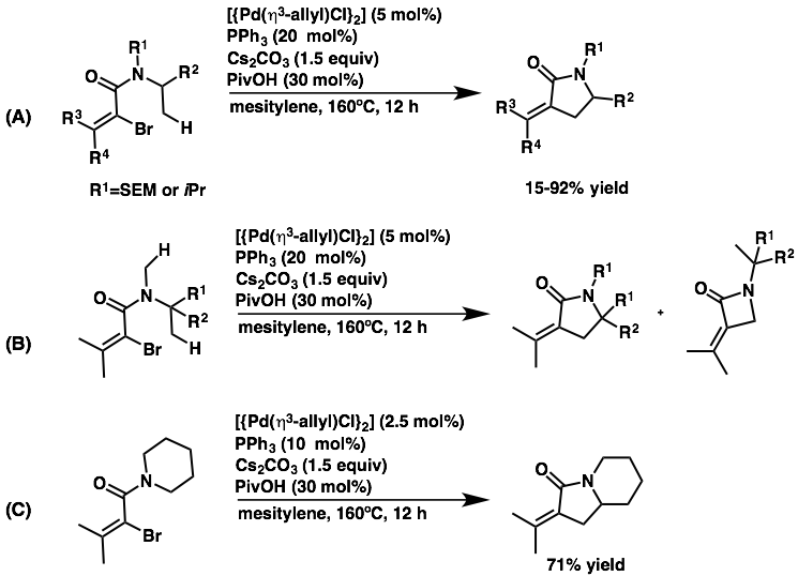
Scheme 61. A) Initial report by Baudoin. B) Application to synthesis of the aeruginosin core.



Although useful, the scope was limited to only cyclohexyl bromides and electronically-neutral systems. Additionally, high catalyst and loadings were required in addition to excess base, and only moderate yields could be achieved.

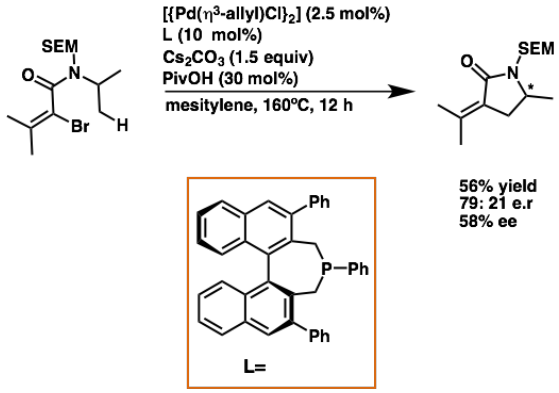
More recently, Baudoin published a methodology employing acyclic alkenes to access alpha-alkylidene-gamma-lactams (**Scheme 62**).[148]

Scheme 62. A) Access to alpha-alkylidene-gamma-lactams. B) Selectivity issues between primary and secondary C–H bonds. C) Access to bicyclic alkaloids



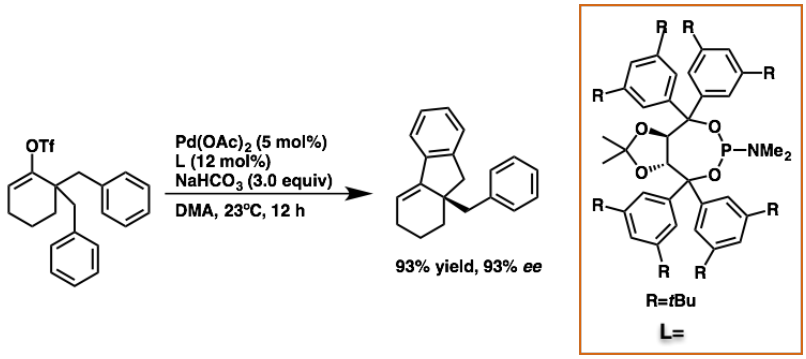
High temperatures were required and most substrates required the expensive SEM-protecting group for reactivity. Additionally, regioselectivity issues were observed. Enantioselective alkenylation was also explored; however, both yields and enantioselectivities were only modest (**Scheme 63**).

Scheme 63. Efforts towards enantioselective alkenylation.



The Cramer group has also explored enantioselective intramolecular alkenylation; however, this system is much easier due increased reactivity of the benzylic protons (**Scheme 64**).[149]

Scheme 64. Early example of enantioselective benzylic alkenylation.



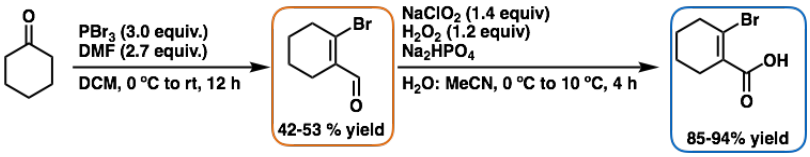
3.3 Research Goals

At the time of our work, there was a lack of methods targeting intramolecular direct alkenylations and no full cyclopropane methodologies. Cognizant of this dearth in the literature, we decided to address this deficiency, which would additionally offer a point of comparison between our previously studied direct cyclopropane arylation methodologies (**Chapter 2**). A final motivation was to develop a new model system to apply enantioselective conditions employing Pd(0) and (*R,R*)-BozPhos. Consequently, we synthesized a related 2-bromocyclohexene analogue.

3.4 Synthesis of Starting Materials

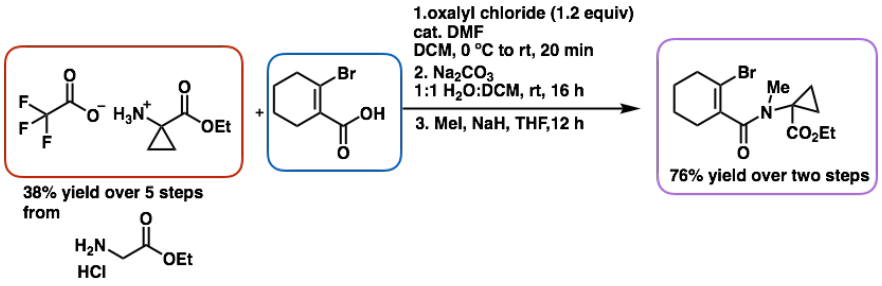
To access the desired precursor, we synthesized the 2-bromo cycloalkenyl moiety via a Vismaier-Haak bromoformylation approach,[150] followed by subsequent Pinnick-Lindgren-Kraus Oxidation of the resulting aldehyde (**Scheme 65**).[151] Via this pathway, we could access both six-membered ring-systems and five-membered ring-systems; albeit, in modest yields. The chloro analogue could be accessed via a similar method by replacing PBr_3 with $POCl_3$.

Scheme 65. Synthesis of 2-bromocycloalkenyl carboxylic acid precursors.



Both of precursors were then coupled via in situ acid chloride formation under Schötten-Baumann conditions. Subsequent protection of free NH-group provided the desired precursor (**Scheme 66**).

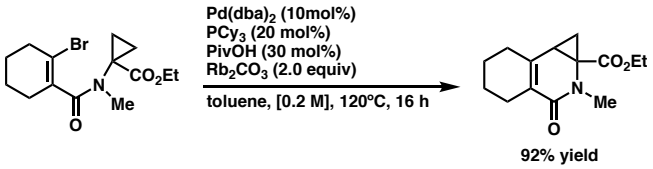
Scheme 66. Synthesis of 2-bromocycloalkenyl carboxylic acid precursors.



3.5 First Reactions

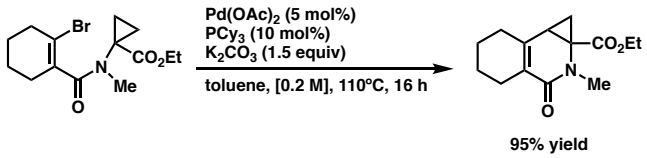
We first employed Baudoin's published conditions, which provided our fused-cyclopropyl azacycle in excellent yield (**Scheme 67**).

Scheme 67. Use of conditions inspired by Baudoin *et al.*



Based on this initial success, we tested our optimized arylation conditions (**Chapter 2**) to avoid using the more expensive Rb_2CO_3 base (**Scheme 68**).

Scheme 68. "Additive-free" direct alkenylation.

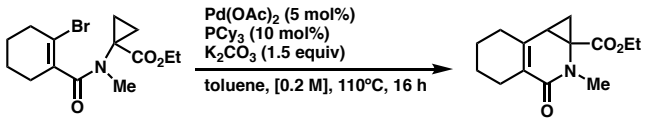


Based on our previous investigations (**Chapter 2**), we similarly decided to study the role of additives in dictating reactivity. We also performed an extensive optimization to potentially observe trends between the direct arylation and direct alkenylation of both systems.

3.6 Reaction Optimization

Our first step was to run control reactions to confirm the role of reagents (**Table 6**). As previously observed, all reagents were required for the reaction. A trace amount of conversion was observed in the absence of potassium carbonate, which can be attributed to the lack of an insoluble base sink for proton shuttle regeneration.

Table 6. Control Reactions.

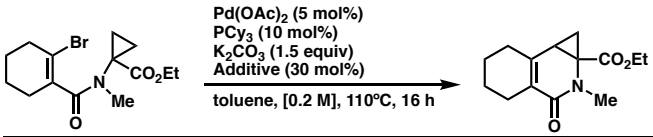


Entry	Conditions	Yield[%][a]
1	No Pd	0
2	No ligand	0
3	No base	12
4	With solvent + base	0

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

We next explored the effect of additives on the reaction (**Table 7**). No enhancement in yield was observed using PivOH or AdOH compared to the conditions without an additive (**entries 1-2,4**). Notably silver performed poorly compared to the carboxylate-based additives (**entry 3**), and hindered reactivity.

Table 7. Effect of Additives on the Reaction[a]

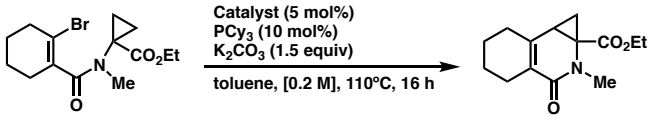


Entry	Additive	Yield[%][a]
1	PivOH	91
2	AdOH	87
3	Ag_2CO_3	39
4	none	90

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

We next screened a series of Pd(0) and Pd(II) catalysts (**Table 8**). Notably, all catalysts gave good conversions; albeit, Pd(0) catalysts containing dba gave slightly diminished conversions (**entry 1-2**). $PdBr_2$ was also low performing (76% yield) compared to the other catalysts screened (**entry 3**).

Table 8. Catalyst Screening[a]

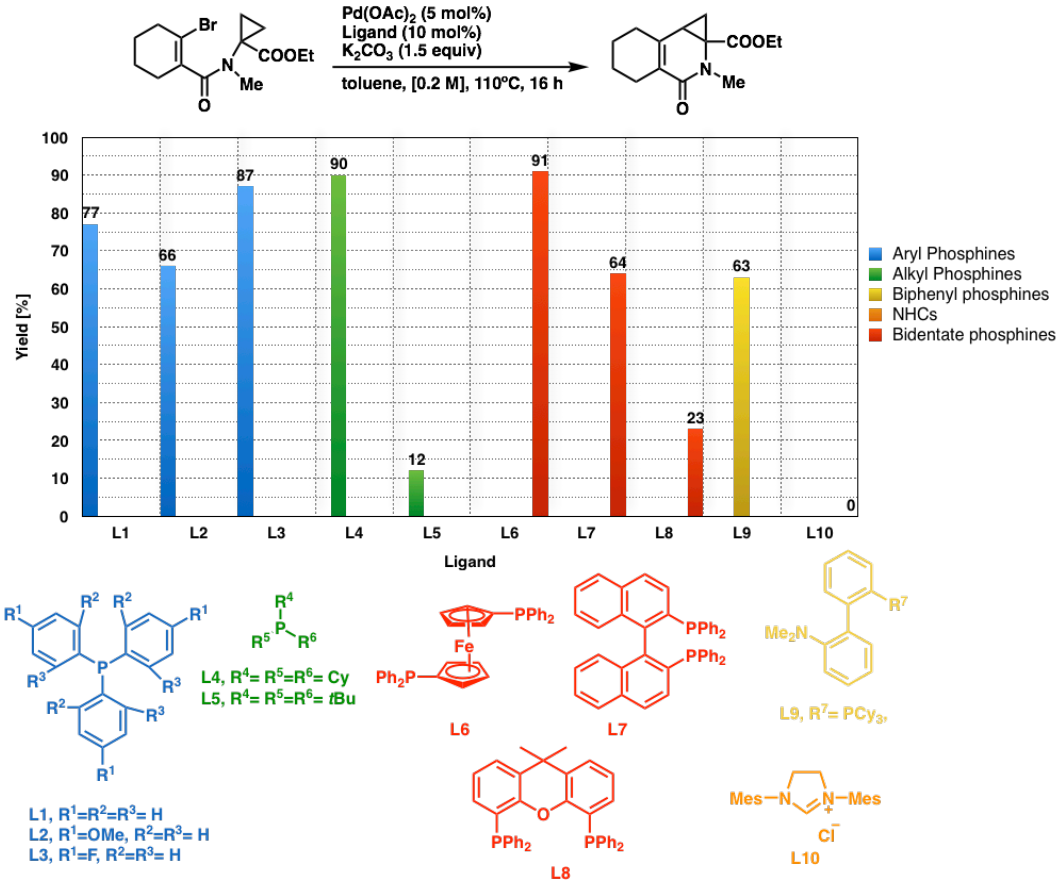


Entry	Catalyst	Yield[%][a]
1	$Pd(dba)_2$	68
2	Pd_2dba_3 (2.5 mol%)	72
3	$PdBr_2$	76
4	$Pd(PPh_3)_4$	80
5	$Pd(TFA)_2$	79

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

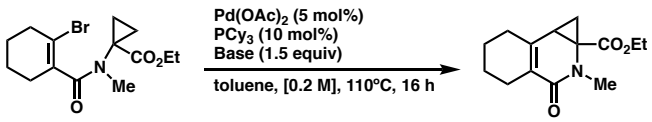
An extensive ligand screen was also performed (Figure 24).

Figure 24. Ligand Screening.



Unlike our direct arylation protocol, direct alkenylation could tolerate more ligands. For example, aryl phosphines worked equally well compared to alkyl phosphines; however, electron-withdrawing aryl phosphines slightly outperformed electron-donating aryl phosphines (87% for P(4-FPh)$_3$ compared to 77% and 66% for PPh$_3$ and P(4-OMePh)$_3$ respectively). A similar steric limitation was also observed for P*t*Bu$_3$•HBF$_4$ (12% yield). As observed previously, bidentate phosphines worked well; albeit, dppf worked better compared to *rac*-BINAP and Xantphos. Additionally, Davephos gave good yield (63%); however, IMes gave no conversion.

Table 9. Base Screening.[a]



Entry	Ligand	Yield[%][a]
1	Na_2CO_3	14
2	K_2CO_3	90
3	Rb_2CO_3	79
4	Cs_2CO_3	67
5	K_3PO_4	45
6	KOtBu	26
7	KOAc	26
8	DIPEA	12
9	DBU	34
10	DABCO	15

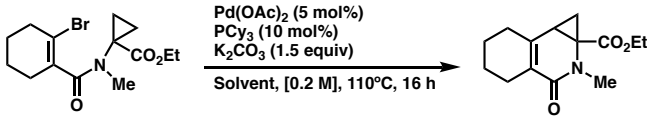
[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

We then studied the effects of base strength and counterion. Unlike the arylation conditions, the alkenylation showed sensitivity to strong bases. Only K_2CO_3 gave excellent yields (**entry 2**), whereas other carbonates gave inferior performances, indicating the need for a mild base.[152] K_3PO_4 produced only moderate yield (**entry 5**, 45%), and KOAc also gave modest yield (**entry 7**, 26%). Potassium *tert*-butoxide decomposed the starting material via protodebromination. Organic bases such as DIPEA, DBU, DABCO were ineffective, indicative that the reaction requires a carboxylate-mediated concerted-metallation deprotonation event for hydrogen-abstraction.

A variety of solvents were also screened (**Table 10**). Unlike the arylation protocol, a wider range of solvents were tolerated; albeit, aromatic solvents such as *p*-xylene were still high performing solvent choices. 1,4-Dioxane also worked well, providing the desired product in 83% yield. Notably, protic polar solvents such as *t*-amyl alcohol worked well (68% yield).[153]

Polar aprotic solvents were also well-tolerated as DMF gave 75% yield; albeit, MeCN produced diminished yields.[154] Chlorobenzene also showed diminished yields and DCE failed to produce any product.

Table 10. Solvent Screening[a]

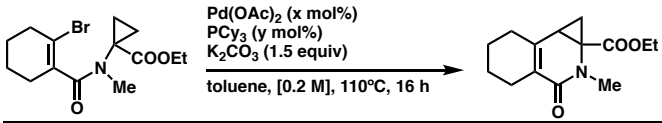


Entry	Solvent	Yield[%][a]	dielectric constant[b]
1	chlorobenzene	59	5.69
2	DMF	75	38.25
3	*t*-amylOH	68	17.93
4	dioxane	83	2.21
5	MeCN	56	36.64
6	DCE	trace	10.4
7	*p*-xylene	84	2.27

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

We also explored the effect of catalyst and ligand loading (**Table 11**). A 1:2 catalyst: ligand ratio was optimal with no change in yield observed with increasing the ligand loading. A reduced yield was observed when a 1:1 catalyst: ligand ratio was employed. Notably, good conversions could still be achieved at lower loadings, with a slight enhancement of yield when operating at higher catalyst: ligand loadings (10:20).

Table 11. Catalyst and Ligand Loading.[a]



Entry	Conditions	Yield[%][a]
1	10:20 [Pd:L] (1:2)	98
2	2.5: 5 [Pd:L] (1:2)	70
3	5:5 [Pd:L] (1:1)	66
4	5:10 [Pd:L] (1:2)	90
5	5:15 [Pd:L] (1:3)	93
6	5:20 [Pd:L] (1:4)	93
7	5:25 [Pd:L] (1:5)	93

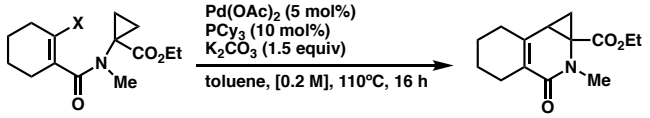
[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.7 Scope of Reaction

We then explored the reaction scope and although some substrates could afford good yields without additional additives, more challenging substrates required pivalate for complete conversion. For yields <80%, we also ran the reaction with pivalate for comparison.

Table 12 shows the effect of the halide partner, including the scale-up for the bromo analogue. The chloro analogue was also viable, albeit pivalate was required.

Table 12. Effect of Halide[a,b]

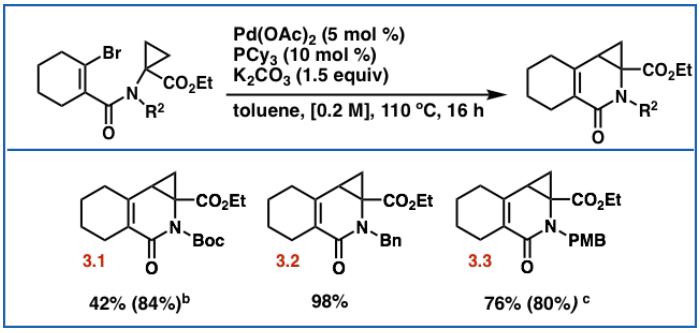


Entry	Halide (X=)	Yield[%][a]
1	Br	95 (98)[b]
2	Cl	12 (75)[c]

[a]Isolated yield, 0.2 mmol scale.
[b]Yield in parenthesis on 1.0 mmol scale. [a]Yield in parenthesis with 30 mol% PivOH added.

Other *N*-protecting groups were also employed (**Scheme 69**).

Scheme 69. Scope of Reaction, Protecting Group[a]

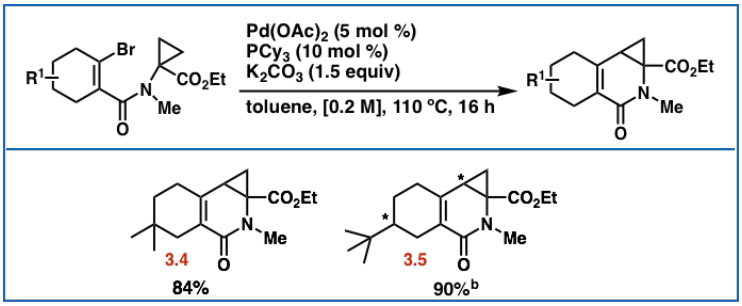


[a]Isolated yield, 0.2 mmol scale.
[b]Yield in parenthesis on 0.72 mmol scale with 30% mol PivOH. [a]Yield in parenthesis on 1.9 mmol scale with 30 mol% PivOH added.

Despite previous difficulties, Boc-protected product **3.1** formed efficiently with pivalate and could be scaled. Both benzyl and PMB also exhibited excellent reactivity (**3.2–3.3**); pivalate showed little improvement in reactivity when added to **3.3**.

gem-Dimethyl and *tert*-butyl substitution afforded cyclized products in good yield without additional additive (**3.4-3.5**) (**Scheme 70**).

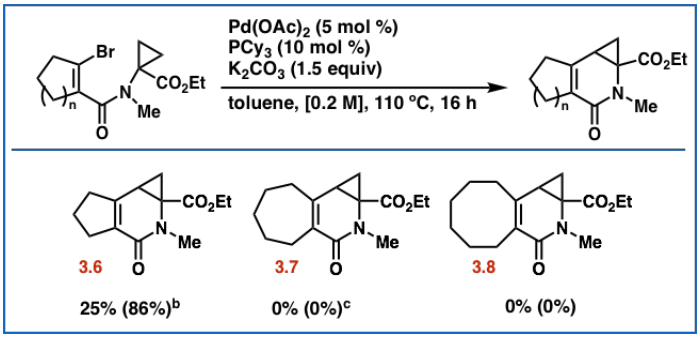
Scheme 70. Scope of Reaction, Cyclohexyl Substitution[a,b]



[a]Isolated yield, 0.2 mmol scale.
[b]Isolated as a mixture of inseparable diastereomers.

We also employed other ring-sizes, and observed excellent conversion with pivalate for the cyclopentyl derivative; however, both cycloheptyl and cyclooctyl derivatives **3.7-3.8** gave no conversion (**Scheme 71**).

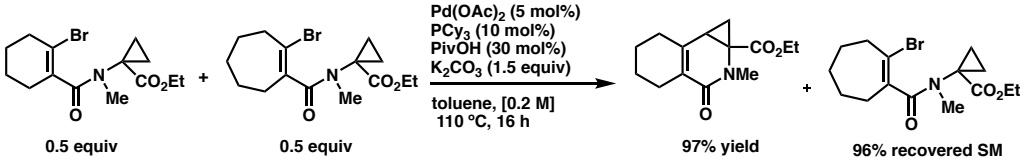
Scheme 71. Scope of Reaction, Ring Size[a]



[a]Isolated yield, 0.2 mmol scale, yield in parenthesis with 30 mol%PivOH
[b]Isolated on a 1.2 mmol scale, yield in parenthesis with 30 mol% PivOH
[c]88% of starting material recovered.

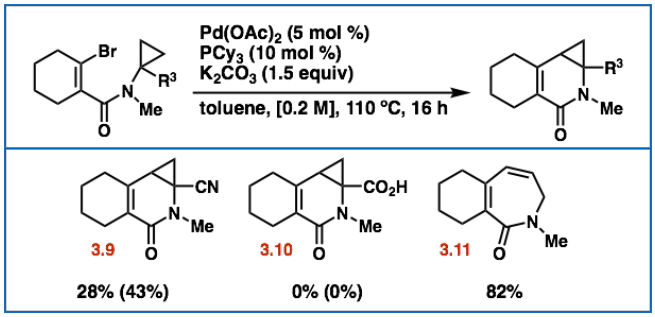
A catalyst sequestration experiment with the 7-membered ring system indicated that catalyst poisoning by the alkene precursor is not a contributing factor (**Scheme 72**).

Scheme 72. Catalyst poisoning experiment.



Scheme 73 shows the effect of alpha-substitution. The cyano group (**3.9)** impeded reactivity and free carboxylic acid **3.10** also failed to cyclize.[155] In parallel with previous findings,[156] without alpha-substitution, ring-opening occurred, providing access to **3.11**. Notably, the ring-opened product was formed exclusively, with no additional isomer.[157]

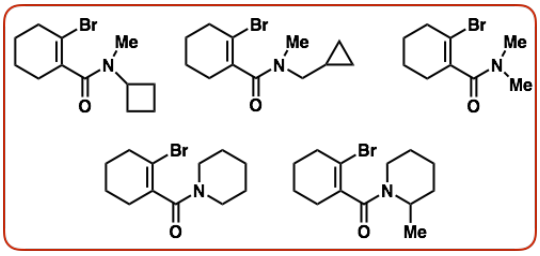
Scheme 73. Effect of Alpha Substituent.[a]



[a]Isolated yield, 0.2 mmol scale, yield in parenthesis with 30 mol% pivalate.

No reaction with other related sp^3 systems was observed, illustrating the orthogonal reactivity of the cyclopropyl moiety under the optimized reaction conditions (**Scheme 74**).

Scheme 74. Substrates that failed to cyclize.

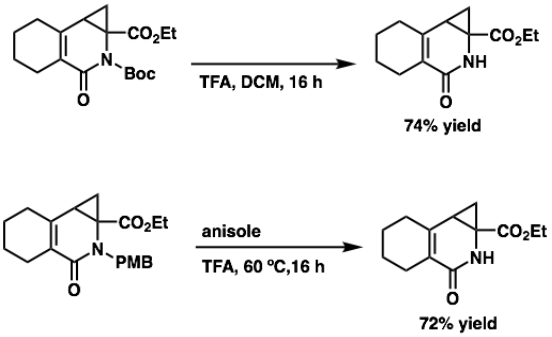


Higher temperatures (up to 160 ºC) were employed with and without pivalate; however only dehalogenation or starting materials were recovered.

3.8 Liberation of Free Amine

Cleavage of both the Boc and PMB groups to access the free NH-product was also viable (**Scheme 75**).

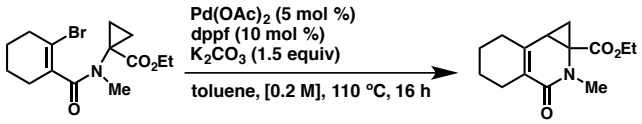
Scheme 75. Deprotection of Boc and PMB groups.



3.9 Revisiting Ligand Screening

As previously mentioned (**Chapter 2**), we were interested in why bisphosphine ligands were producing excellent yields. Table 13 shows ligand studies performed with dppf, the highest performing bisphosphine. Entries 1-2 illustrate the importance of using a Pd(II) source, and the slight inhibition by dba on reactivity. Notably, dppf was inactive as a ligand when a Pd(0) source was employed, even with additional pivalate (entries 3-4). These preliminary experiments suggest that dppf(O) and BINAP(O) may be the active ligands in this transformation.

Table 13. Ligand Studies with dppf[a]



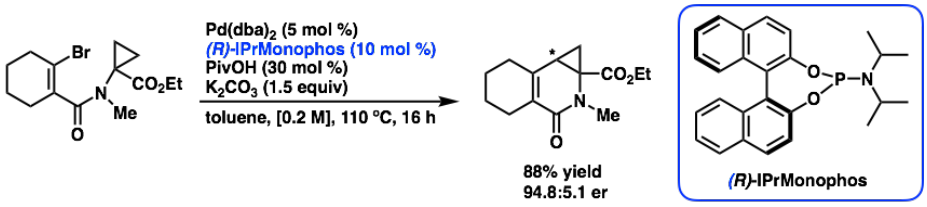
Entry	Variation from Standard Conditions	Yield[%][a]
1	none	85
2	with 10 mol% dba	73
3	$Pd(dba)_2$ instead of $Pd(OAc)_2$	<20
4	$Pd(dba)_2$ instead of $Pd(OAc)_2$, with 30% PivOH	<20

[a]Yields determined via ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

3.10 Preliminary Asymmetric Alkenylation Results

Based on the ligand studies with dppf, we postulated that bisphosphine monoxides could be used as chiral ligands in our alkenylation reaction. Additionally, in parallel with Cramer's use of Feringa-based TADDOL-phosphoramidites, we discovered that Feringa-based BINOL phosphoramidite (IPrMonophos) produced excellent enantioselectivities and yields (**Scheme 76**).[158] Enantiomeric ratios were determined via SFC analysis on a chiral stationary phase ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar).

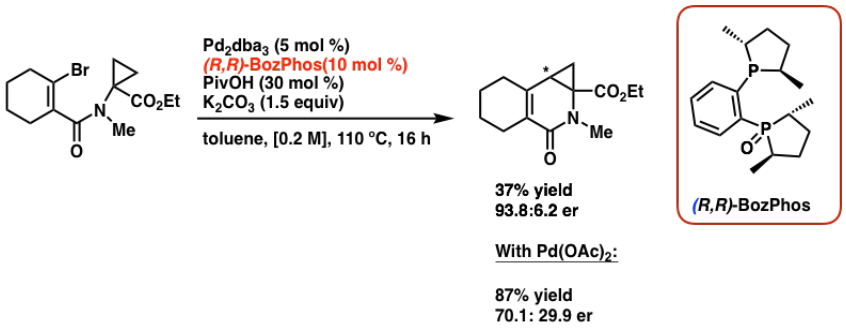
Scheme 76. Use of BINOL-phosphoramidite, (*R*)-IPrMonophos in asymmetric alkenylation.



This reaction represents a rare example of asymmetric direct alkenylation.

Testing our hypothesis, we also employed (*R,R*)-BozPhos as a chiral bisphosphine monoxide, which produced excellent enantioselectivities; however, poor yields were obtained. We could improve our yields using $Pd(OAc)_2$ with costs to enantioselectivity (**Scheme 77**).[159]

Scheme 77. Use of *(R,R)*-BozPhos in asymmetric alkenylation.



Both of these reactions demonstrate the first examples applying both IPrMonophos and (*R,R*)-BozPhos towards asymmetric C–H functionalization processes.

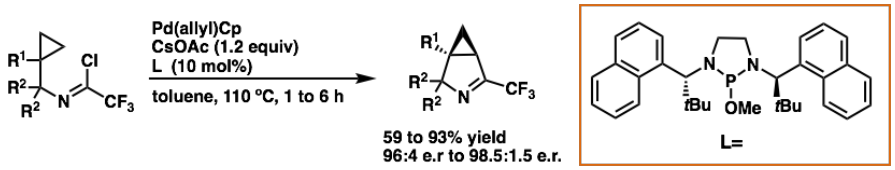
3.11 Conclusion

In conclusion, one of the first examples of palladium-catalyzed intramolecular cyclopropyl direct alkenylation was developed. This method affords novel azacycles with increased Fsp^3 content. Ligand studies suggested that bisphosphine monoxides, not their bisphosphine counterparts were responsible for reactivity. Testing this hypothesis, we achieved enantioselective direct alkenylation employing both IPrMonophos and *(R,R)*-BozPhos. This represents the first example of enantioselective C–H functionalization employing a chiral bisphosphine monoxide ligand, the first example of enantioselective cyclopropyl C–H alkenylation and demonstrates the potential for other bifunctional ligand classes to be applied towards C–H functionalization methodologies.

3.12 Related Work

The Cramer group recently published a related methodology using trifluoroacetimidoyl chlorides as electrophilic partners, affording 3-azabicyclo[3.1.0]hexanes (**Scheme 78**).[160]

Scheme 78. Access to 3-azabicyclo[3.1.0]hexanes via asymmetric C-H alkenylation.



Chapter 4 A Pd(0)-BozPhos System Catalyzes Intramolecular Enantioselective C(sp^3)–H Arylation

Chiral natural products and pharmacological agents possess important activity and function; therefore, generating chiral centers is essential for the synthesis of bioactive scaffolds.[161-162] Asymmetric catalysis represents one solution to access chiral molecules in a highly selective manner.[163] As only catalytic materials are required, access to the desired stereoisomer can be achieved, while avoiding the waste produced from other strategies such as chiral resolution and chiral auxiliary-based approaches. Despite the theoretical benefits, asymmetric catalysis can be a challenging endeavour. First, background reactions must be minimized and avoided. Secondly, the desired product must be stereochemically stable. Finally, dicovering a suitable catalyst-ligand system to access both high enantioinduction and excellent yields can be an arduous task.

4.1 Stereoselective C–H Functionalization[164]

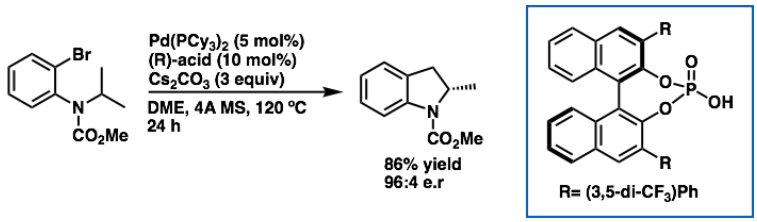
In the last decade, strategies to create chiral centres via C–H functionalization have employed chiral or prochiral directing groups, chiral counterions, kinetic resolutions, and chiral ligands. This chapter will focus on chiral anion and chiral ligand-based approaches, which are the strategies we investigated in our asymmetric C–H functionalization studies.

4.1.1 Use of Chiral Anions[165]

Previously, asymmetric counteranion-directed catalysis has offered a powerful way to achieve enantioinduction across numerous reaction platforms by employing privileged chiral motifs such as chiral phosphoric acids possessing BINOL- or TADDOL-based backbones. As previously described (**1.3.4**), the carboxylate additive substantially influences concerted-metallation deprotonation, which is the enantiodetermining step for enantioselective C–H functionalization. Consequently, a chiral carboxylate or chiral phosphate additive could serve as a vessel to transfer chirality. Since 2015, several notable contributions have been made using

chiral anions for enantioselective C–H functionalization, including towards the Ohno benchmark (**Scheme 79**).[166]

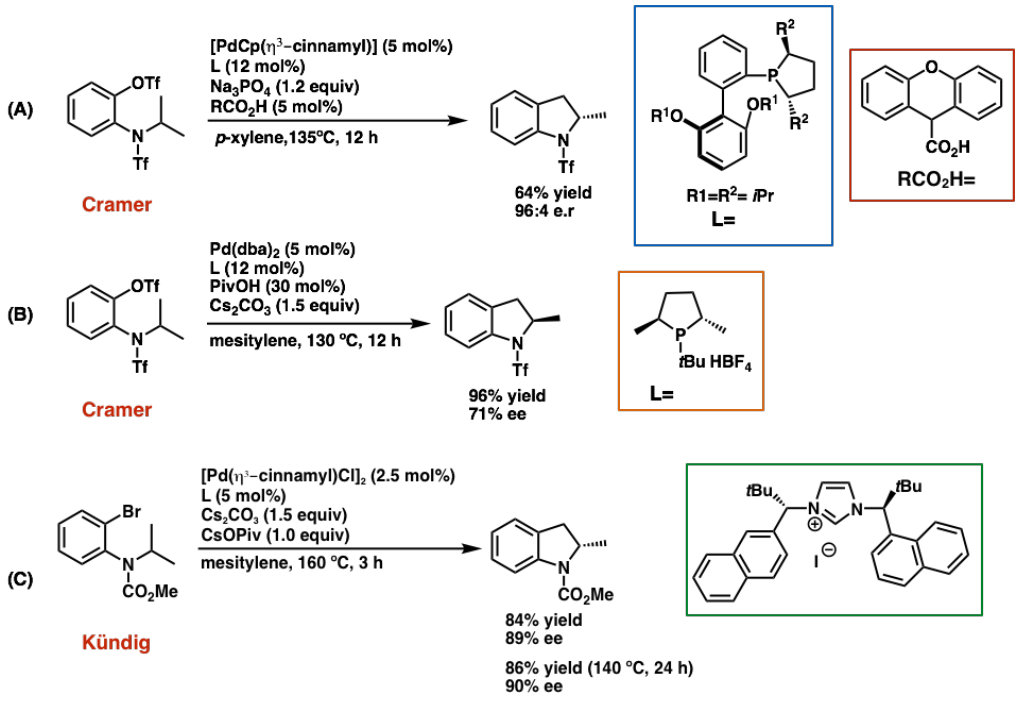
Scheme 79. Application of a chiral phosphate anion strategy to the Ohno benchmark.



4.1.2 Use of Chiral Ligands

The design, discovery and application of chiral ligands has encompassed the core of methodologies targeting enantioselective C–H functionalization.[167] The Ohno benchmark has served as the model system. Scheme 80 summarizes this work for acyclic indolines.[168]

Scheme 80. Asymmetric synthesis of 2-methyl indolines. A) SagePhos B) Phospholanes C) *N*-Heterocyclic Carbenes (NHCs).



4.2 Background on Bisphosphine Monoxides

To date, chiral bisphosphine monoxides (BPMOs) have not been explored in asymmetric C–H functionalization. [169-170] Within this type of ligand, the P atom functions as the soft site, which coordinates strongly to palladium as a soft metal in accordance with Pearson's HSAB theory (**Figure 25**). In contrast, O is the hard site, which can switch on and off the metal due to its weaker palladium-oxygen interaction. The result is a catalytic species that can open and close coordination sites, which can help facilitate both oxidative addition and reductive elimination amongst other steps during the catalytic cycle. The second important feature is that this opening-closing mechanism can allow for ligand displacement by external molecules such as pivalate, allowing the metal to switch ligands on and off. This second feature is key for why BPMOs can be highly applicable towards C–H functionalization processes: an empty coordination site for the carboxylate ligand can be created and the metal can be stabilized once this ligand departs.

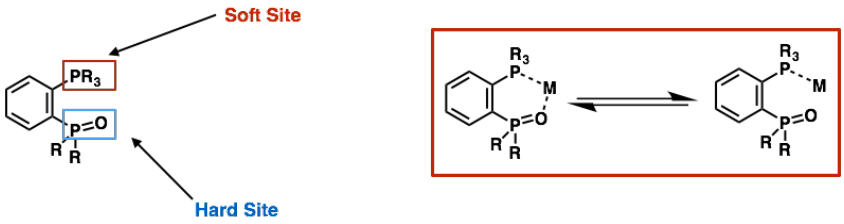
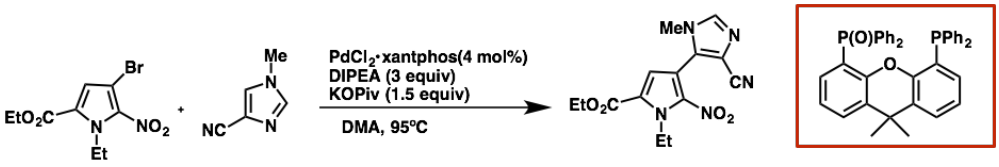


Figure 25. Features of BPMOs and their adaptable nature within catalysis.

Despite the discovery of BPMOs in the 1970's, the applications of BPMOS in transition-metal and palladium-catalysis remain in the nascent stages. More recently, industrial interests have shifted towards BPMOs. One benefit is that BPMOs can be easily accessed via selective oxidation of commercially available bisphosphines. Despite the inherent benefits of BPMOS ligands, the only example of applying BPMOs to C–H functionalization was published by Blackmond and Eastgate.[171] Additional studies into the intermolecular direct arylation of azines heterocycles suggested Xantphos(O) was the active ligand.

Scheme 81. Reaction investigated by Blackmond and Eastgate.



The findings from this paper suggested that: 1) the bisphosphine monoxide was the active ligand, not the bidentate ligand,[172] 2) the hemilabile nature helps to stabilize the Pd metal in between reductive elimination and oxidative addition steps.[173] Additionally, it was shown that the carboxylate helps to both form the active phosphine monoxide catalyst and to displace the P=O moiety in addition to mediating the concerted-metallation deprotonation step.

4.3 Kagan's Seminal Report[174]

In 2011, Kagan developed an enantioselective variant of Ohno's achiral reaction (**Scheme 82**) exploring both DIOP and DUPHOS ligands. This reaction was considered one of the seminal reports of enantioselective sp^3 C–H activation and to date has 91 citations.

Scheme 82. Ohno's system, the asymmetric benchmark.

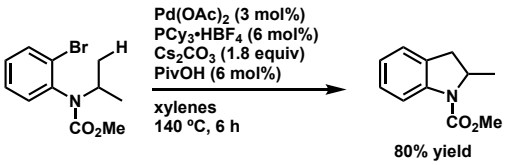
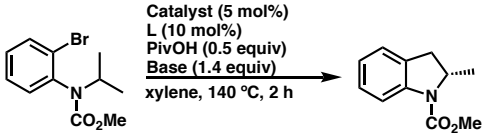


Table 14 shows selected optimization performed for this system. Lower yields and ee's were obtained with $Pd_2(dba)_3$ (**entry 1**). Surprisingly, despite the mixture of pivalate, acetate and carbonate, Kagan reports quantitative conversion and high ee's using $Pd(OAc)_2$ with *(R,R)*-MeDUPHOS. Using a weaker base led to a dramatic reduction in both yield and ee.

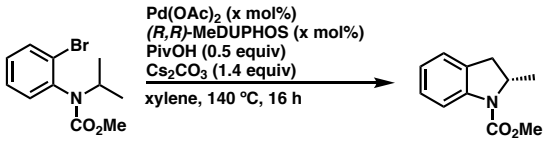
Table 14. Selected optimization by Kagan



Entry	Catalyst	Ligand	Base	Yield[%]	ee (%)
1	$Pd_2(dba)_3$	(S,S)-MeDUPHOS	Cs_2CO_3	80	84
2	$Pd(OAc)_2$	(R,R)-MeDUPHOS	Cs_2CO_3	>99	93%
3	$Pd(OAc)_2$	(R,R)-MeDUPHOS	K_2CO_3	61	58
4	$Pd(OAc)_2$	(R,R)-MeDUPHOS	NEt_3	6	80

An interesting observation was made in the paper that "argon [was] not necessary for the reaction." Issues with reproducibility were also reported within the supporting information. Table 15 shows the difference in yield and ee depending on the ratio of catalyst: ligand.

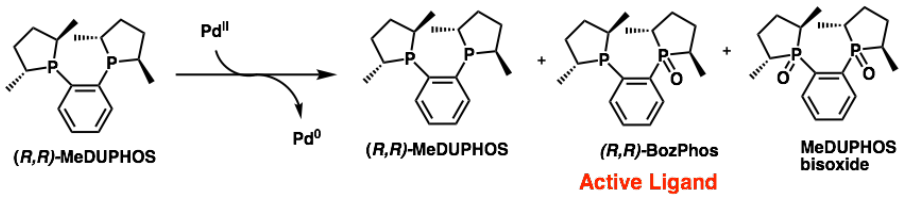
Table 15. Kagan's study of the effect of catalyst: ligand ratio on yield and ee's.



Entry	Catalyst (mol%)	Ligand (mol%)	Yield (%)	ee (%)
1	5	2.5	87	19
2	5	5	77	17
3	5	7.5	25	44
4	5	10	55	82

Although yields decrease with increasing ligand, the ee's observe a substantial increase. Considering these results and our own investigations that we will present within this chapter, we propose the following assertions: 1) The enantioselectivities reported within Kagan's paper are incorrect. The presence of acetate and carbonate compete with pivalate, and consequently, it would be impossible to achieve 93% *ee* due to these literature-supported background reactions. 2) *(R,R)*-MeDUPHOS is not the active ligand for this transformation. Instead, *(R,R)*-MeDUPHOS is oxidized in situ to *(R,R)*-BozPhos (**Scheme 83**).

Scheme 83. Proposed oxidation process for *(R,R)*-MeDUPHOS by Pd(II).



This would explain why yields decrease and enantioselectivities increase: the required catalyst for the transformation is depleted in order to oxidize the ligand; however, *(R,R)*-BozPhos as the active ligand still enables high enantioinduction. It would also explain the reproducibility errors, which could result from variable amounts of air and moisture.

Considering the importance of this reaction within the field of asymmetric C–H functionalization, which continues to be highly cited in numerous reviews, it is important to correct this error within the scientific literature. By fixing this misnomer, it will help other researchers on their quests towards developing asymmetric C–H functionalization protocols.

4.4 Project Origins and Research Goals

From the onset of this doctoral work, we desired to create a new catalytic system capable of achieving enantioselective sp^3 C–H functionalization. As previously mentioned (**Chapter 2**) we developed an intramolecular cyclopropane arylation reaction to serve as a model system for testing several strategies. Through careful considerations of our ligand screening, we realized that *(R,R)*-BozPHOS, not *(R,R)*-MeDUPHOS was the active ligand species.

Upon re-examining the literature, we observed Kagan's reference to reproducibility issues within their own enantioselective C–H arylation reaction using (*R,R*)-MeDUPHOS. Taking these cues, we decided a re-examination of Kagan's conditions was warranted. As the 2-methyl indoline moiety has been employed by several groups as a benchmark for testing new catalytic systems, we decided to optimize our own set of asymmetric conditions employing *(R,R)*-BozPhos to compare to the literature precedence. In summary, we desired to achieve 3 main goals: 1) to demonstrates that bisphosphine monoxides could be employed as a novel ligands for asymmetric C–H functionalization 2) to re-examine Kagan's work and provide support that *(R,R)*-BozPhos, not *(R,R)*-MeDUPHOS is responsible for asymmetric induction. 3)

to develop a general catalyst system capable of intramolecular asymmetric arylation for both cyclopropyl and sp^3 centers.

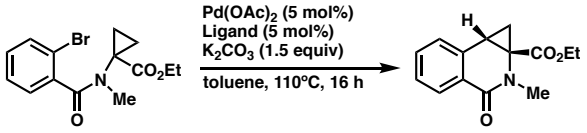
As discussed throughout this dissertation, the proton shuttle plays a key role in controlling reactivity. For asymmetric processes, the carboxylate base additionally tunes the catalyst, dictating enantioselectivity. To achieve high enantioinduction, it is necessary to select a bulky base as the concerted-metallation deprotonation step serves as the enantiodetermining step via irreversible deprotonation.[175] Additionally, a key background reaction for enantioselective C–H functionalization involving a CMD step is the competition of carboxylates. As demonstrated earlier (**Chapter 2–3**), acetate and carbonate can also act as proton shuttles. Consequently, this mixture of carboxylates in solution can lead to erosions in enantioselectivities due to background reactions mediated by these species. This is one of the challenges that makes it difficult to achieve high enantioinduction.

4.5 First Reactions

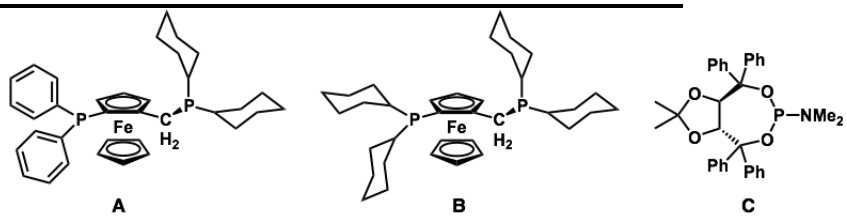
4.5.1 Enantioselective C–H Arylation of Cyclopropanes

When we originally discovered our arylation reaction (**Chapter 2**), we performed a small screen of chiral ligands (**Table 16**). Notably, this was performed without pivalate additive. Only *(R)*-BINAP provided an acceptable yield; however, no enantioinduction was observed (Entry 1).[176] Although we had initially screened (*R,R*)-MeDUPHOS, no yield was observed without pivalate. The simplest TADDOL-based phosphoramidite also failed to provide yields.

Table 16. Preliminary chiral ligand screening.[a,b]



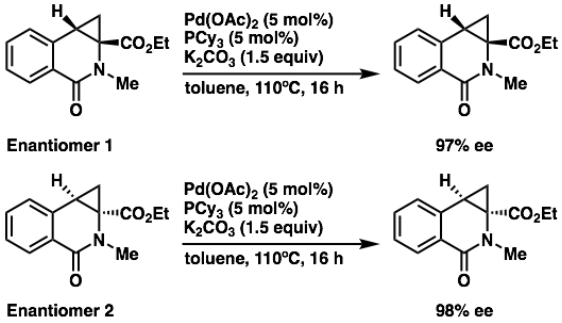
Entry	Chiral Ligand	Yield[%], ee%
1	*(R)*-(+) BINAP	80 (racemic)
2	*(S)*- (-) BINAP	16 (racemic)
3	*(R,S)*-PPF-PCy_2 (**A**)	0
4	(R,S)-Cy_2PF-PCy_2 (**B**)	12 (N/A)
5	**C**	0
6	*(R,R)*-Me-DUPHOS	0



[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

After these initial efforts, we decided to double-check the stability of our product. The enantiomers were separated via preparative SFC and then each of the enantiomers were resubjected to our reaction conditions to check for racemization (**Scheme 84**).

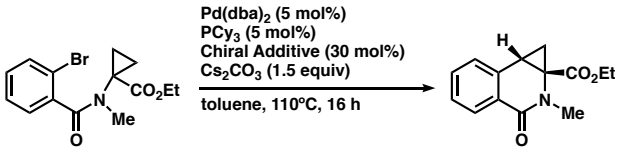
Scheme 84. Racemization experiment to check stereochemical stability.



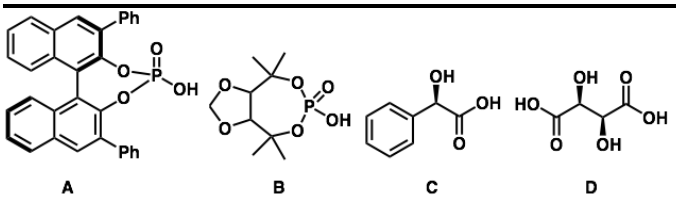
The enantiomeric integrity was maintained; therefore, we continued our pursuit of suitable asymmetric conditions.

Our second strategy was to use chiral additives such as chiral carboxylates or chiral phosphates. One key point is that selecting a proper palladium precatalyst is important. As previously mentioned, the competition of carboxylate ligands can contribute to reduced ee's. For this reason, we used $Pd(dba)_2$ as a precatalyst to avoid possible background competition from acetate. Table 17 illustrates our efforts exploring other chiral additives.

Table 17. Initial explorations into chiral additives.[a,b]



Entry	Chiral Additive	Yield [%]
1	A	47
2	A + Ag_2CO_3 (0.5 equiv)	45
3	C (*R)-(-)* mandelic acid	57
4	D, D-(-) tartaric acid	78
5	B (at 140 ºC)	49



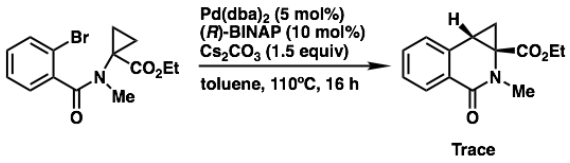
[a]Yields determined via ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

Unfortunately, although yields could be achieved with many additives, all the products were racemic. Considering Baudoin's recent report, it is probable that this strategy could still work with this system; however, a screening of various phosphoric acids and conditions would be required to find the ideal candidate. Additionally, the dba precatalyst is not ideal and the use

of PCy_3 as an achiral ligand and carbonate as a proton shuttle are both dominant background processes, hindering enantioinduction.

At this point our best results in terms of yield was achieved with *(R)*-BINAP, consequently, we decided to modify these reaction conditions to remove background reactions, hopefully improving the enantioselectivities. When we replaced $Pd(OAc)_2$ with $Pd(dba)_2$, we were surprised to observe no reaction (**Scheme 85**).

Scheme 85. Lack of reactivity for *(R)*-BINAP with Pd(0).

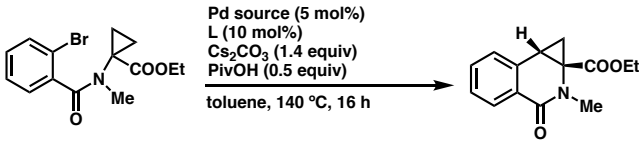


Although arguably the difference in reactivity could be attributed to the lack of pivalate, we had already shown that the achiral reaction works with Pd(0) sources under the prescribed "additive free" conditions (**Chapter 2**).

A basic literature search revealed an interesting paper by Grushin, which described the Pd-mediated oxidation of BINAP in situ to generate BINAP(O).[177] We postulated that a similar process could be occurring for our system, and that the BINAP(O) could be the active ligand.

Concurrently, we also used Kagan's published conditions using *(R,R)*-MeDUPHOS (**Table 18**).

Table 18. Exploring the nature of the ligand[a,b]



Entry	Pd source	Ligand	Yield [%]	e.r.	ee (%)
1	$Pd(OAc)_2$	(*R,R*)-MeDUPHOS	77	82.6:17.4	65.2
2	$Pd(dba)_2$	(*R,R*)-MeDUPHOS	0	0	0
3	$Pd(OAc)_2$	(*R,R*)-BozPhos	73	85.3: 14.7	70.6
4	$Pd(dba)_2$	(*R,R*)-BozPhos	95	88.6: 11.4	77.2

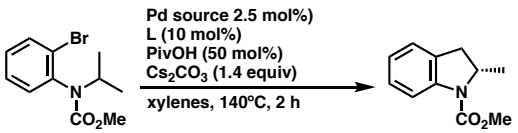
[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

Much to our delight, we were finally observing enantioselectivities; albeit, they were much lower than the values described by Kagan for the amine-based system (**Table 1, entry 1**). We also ran these conditions with $Pd(dba)_2$ and observed no conversion, which paralleled our BINAP results (**Table 1, entry 2**). Based on the precedence in the Charette group with Cu and (*R,R*)-BozPhos, we wondered if perhaps Pd(II) was oxidizing *(R,R)*-MeDUPHOS in situ to *(R,R*)-BozPhos, and if this was the active ligand. As support for our hypothesis, we found that indeed, both Pd(0) and Pd(II) sources could produce enantioselectivities using *(R,R*)-BozPhos; albeit, substantial optimization was required (**entries 3–4**). Notably, the highest ee's could be achieved using $Pd(dba)_2$, showing the detrimental effects of acetate on ee's. With these results in hand, we proceeded to perform a full-optimization.

4.5.2 Enantioselective C–H Arylation of sp^3 centres

After completing the studies of our cyclopropyl system, we decided to re-examine Kagan's system (**Table 19**).

Table 19. Re-examination of Kagan's system[a,b]



Entry	Pd source	Ligand	Yield [%]	e.r. (%ee)
1	$Pd(OAc)_2$	(*R,R*)-MeDUPHOS	92	86.6:13.4 (73.2)
2	$Pd(dba)_2$	(*R,R*)-MeDUPHOS	0	0
5	$Pd(OAc)_2$	(*R,R*)-BozPhos	36	79: 21 (58)
6	$Pd(dba)_2$	(*R,R*)-BozPhos	35	95.2:4.8 (90.4)

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

Notably, we were unable to achieved the high yield and excellent ee's reported, and instead our results paralleled with our cyclopropyl results (**Entry 1**). $Pd(dba)_2$ failed to provide any conversion (**Entry 2**). *(R,R)*-BozPhos gave poor yields with both $Pd(OAc)_2$ and $Pd(dba)_2$; however, $Pd(dba)_2$ gave better ee's.[178] Considering the contradictions observed and the reproducibility issues, we decided this system was also worthy of closer examination and consequently, performed a full optimization for deeper study.

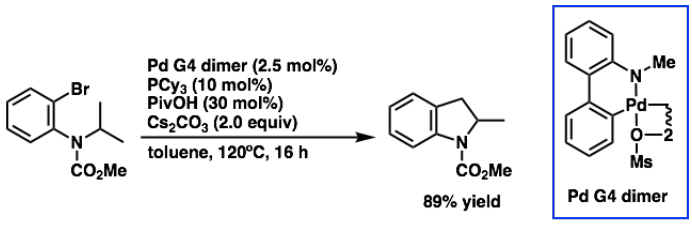
4.6 Development of Achiral Conditions

For the purposes of our enantioselective methodology, we also decided it might be worth re-examining the original conditions proposed by Ohno.[179]

Despite the notable efficiencies of these protocols, we contemplated developing modified achiral conditions to meet the demands of our asymmetric project. We hoped to access milder conditions, to improve the reaction sustainability reaction, or to decrease catalyst loading. To do this, we made a few simple modifications: a) we switched the Pd source to a Buchwald precatalyst, b) we opted to change solvent from the aromatic solvents to a more sustainable solvent derived from biomass, CPME.[180]

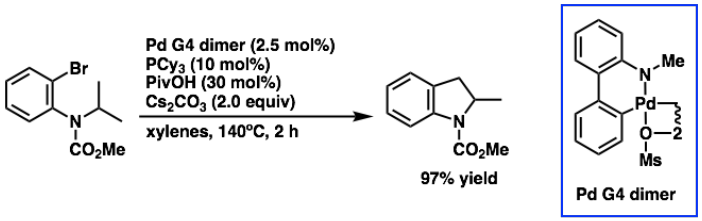
Our first effort employed similar conditions to the enantioselective version, except we switched the ligand for achiral PCy_3 (**Scheme 86**). Notably, the yield was better compared to Ohno's conditions (80% yield, 140 ºC, 6 h).

Scheme 86. Revised sp^3-arylation conditions with G4-dimer.



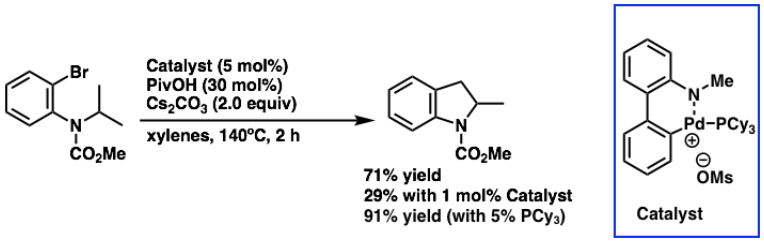
Excellent conversions were achieved at 140 ºC using xylenes and a 2 h reaction time (**Scheme 87**).

Scheme 87. Reaction after modifications.



We also synthesized and employed the PCy_3-G4 catalyst (**Scheme 88**). [181]

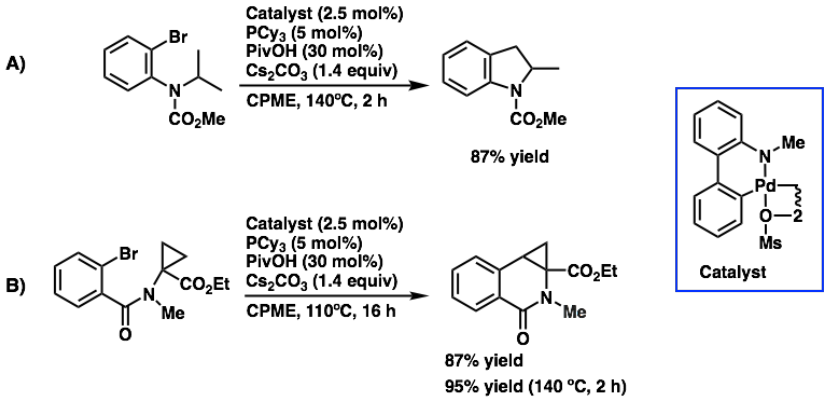
Scheme 88. sp^3 arylation employing PCy_3-G4 catalyst



Further experiments indicated that extra ligand was required for full conversion.[182]

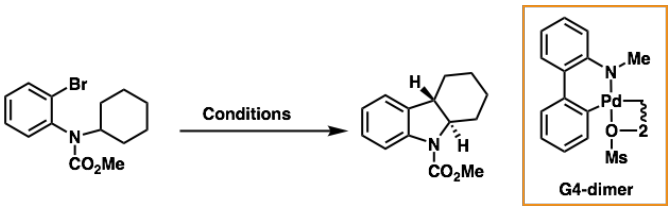
We also switched to a greener, biomass-based solvent and chose CMPE due its success in other Pd-based methodologies (**Scheme 89**).

Scheme 89. Reaction conditions employing CPME as a biomass-derived solvent.



We also tried conditions on the more challenging cyclic indoline system. Even with longer reaction times, only 66% yield could be achieved (**Table 20**).

Table 20. Brief explorations into the cyclic indolines.[a]



Entry	Conditions	Yield[%]
1	2.5 mol% G4 dimer, 10 mol% PCy_3, 30 mol% PivOH, 2.0 equiv Cs_2CO_3, 160ºC, 3 h	65
2	2.5 mol% G4 dimer, 10 mol% PCy_3, 30 mol% PivOH, 2.0 equiv Cs_2CO_3, 140ºC, 16 h	55
3	2.5 mol% G4 dimer, 10 mol% PCy_3, 30 mol% CsOPiv, 2.0 equiv Cs_2CO_3, 140ºC, 24	66

[a]Yields determined via ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Considering this brief optimization, it became evident that either the Pd dimer could be used with 10% ligand or the PCy_3-precatalyst could be used with extra ligand. For simplicity, we decided to use the dimer with the ligand as additional ligand was required for full reactivity.

These details were useful for understanding the nature of the Buchwald precatalyst and a parallel observation was detected for the BozPhos precatalyst.

Overall, although fast reaction times and a biomass-derived solvent can be employed, it is probable that a milder base can be employed using longer reaction times. This would be slightly more optimal compared to current conditions using cesium carbonate. We do not advocate that these conditions are necessarily an improvement compared to Ohno's well-established protocol, but demonstrate that the Buchwald G4 dimer can function as a viable source of Pd(0) for this transformation.

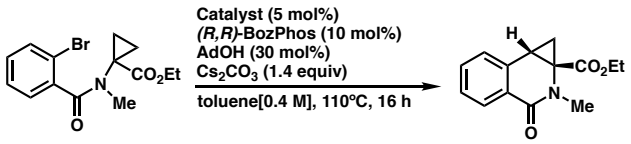
4.7 Reaction Optimization

With our achiral conditions in hand, we then pursued the optimizations for our asymmetric systems. It is noteworthy that the conditions for the cyclopropane motif were developed before the sp^3 conditions.

4.7.1 For Cyclopropanes

After the initial reaction discovery, we optimized our cyclopropyl conditions. We began using AdOH as our carboxylate in line with Cramer's observations that a bulky carboxylate was required to maximize enantioselectivities. Notably, all the Pd(II) catalysts worked well under the prescribed reaction conditions; however, a pronounced counterion effect was observed on enantioselectivities (**Table 21**).

Table 21. Catalyst Screening[a,b]



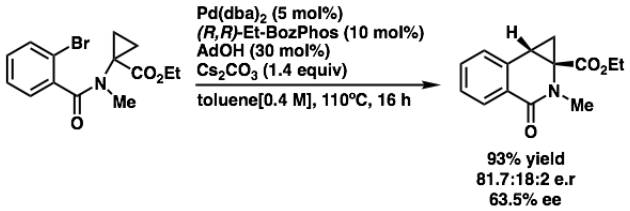
Entry	Catalyst	Yield[%]	e.r(%ee)
1	$Pd(OAc)_2$	84	90.3:9.6 (81)
2	$Pd(TFA)_2$	100	77.9:22.1 (55.8)
3	$PdBr_2$	99	89:11(78)
4	$PdCl_2$•2MeCN	99	84.7:15.3(69.4)
5	$Pd(PPh_{3)4}$	99	62.7:37.3(25.4)

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

$Pd(OAc)_2$ still exhibited the best ee (**entry 1**); however, $Pd(TFA)_2$ a showed pronounced erosion in ee (**entry 2**). The ee's for entry 3-4 were similar, with greater erosion observed for $PdCl_2$•2MeCN. The lowest ee was from $Pd(Ph_3)_4$, which results from the competition between the chiral and achiral ligand (**entry 5**).

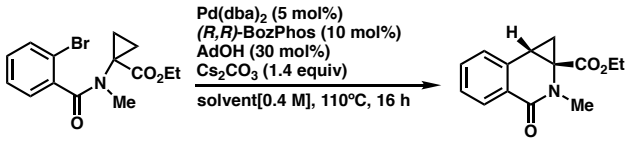
Aside from our original ligand investigations, we also screened the slightly more sterically hindered *(R,R)*-Et-BozPhos (**Scheme 90**)

Scheme 90. The use of *(R,R)*-Et-BozPhos



Notably, although the yield was high, the ee's were much lower than *(R,R)*-BozPhos, indicative that the extra sterics appeared to hinder, not help with enantioinduction.

Table 22. Solvent Screening[a,b]



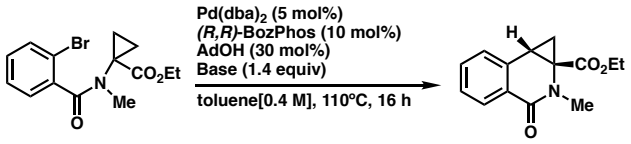
Entry	Solvent	Yield[%]	e.r (%ee)
1	chlorobenzene	47	82.4:17.6 (64.8)
2	DMA	trace	NA
3	mesitylene	trace	NA
4	t-amyl alcohol	trace	NA

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

We also screened other solvents, and notably only trace yields were observed for other protic solvent, sterically-hindered aromatics, and protic highly polar solvents (**Table 22**). Chlorobenzene gave modest yields; albeit, in reduced enantioselectivities (**entry 1**).

We also screened other bases to explore counterion effects (**Table 23**).

Table 23. Base Screening.[a,b]



Entry	Base	Yield[%]	e.r (%ee)
1	KOtBu	15	93.6:6.5 (87.1)
2	KOAc	33	87.9:12.1 (75.8)
3	K_3PO_4	58	95.6:4.4 (91.2)
4	K_2CO_3	63	88.4:11.5 (76.9)
5	Rb_2CO_3	97	92.5:7.5 (85)
6	Na_2CO_3	0	NA
7	Cs_2CO_3	95	88.6: 11.4 (77.2)

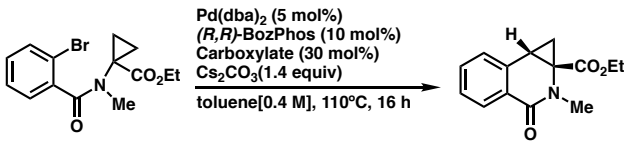
[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

As previously observed, Na_2CO_3 afforded no reaction (**Chapter 2**). KO*t*Bu produced good ee, but poor yield due to decomposition of the starting material (**entry 1**).[183] KOAc also failed to provide good yield (**entry 2**),[184] and notably gave lower ee compared to KO*t*Bu, supporting the notion that competition for the coordination site by acetate contributes to eroding ee's. Other carbonate bases exhibited better reactivities with Rb_2CO_3 being optimal for both yield and ee (**entry 5**). This trend with carbonates could be either attributed to solubility or counterion effects. If it is solubility, the erosion in ee's could be explained by cesium carbonate being more soluble; therefore, a higher concentration of carbonate is available to compete for the coordination site, contributing to a loss in ee. If it is counterion effects, it is possible that a smaller counterion contributes to greater charge balance, contributing to a more energetically favorable transition state for the chiral reaction compared to the background reaction, leading to enhanced ee's. Notably, although the yields were low for weaker bases such as potassium phosphate (**entry 3**), the highest ee was observed. The poor yield could be indicative that

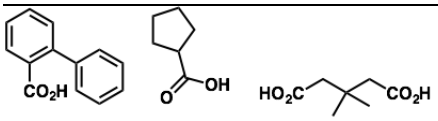
phosphate is not as competitive as carbonate as a proton shuttle; therefore, the background reaction is not as pronounced as compared to carbonate and acetate, leading to enhanced ee's.

We also screened other carboxylate ligands (**Table 24**).

Table 24. Carboxylate Screening.[a,b]



Entry	Carboxylate	Yield[%]	e.r (%ee)
1	None	31	86.6: 13.4 (73.2)
2	2-BiPhOH	33	87.9:12.1 (75.8)
3	2-CypOH	65	91.5:8.5 (83)
4	DL-Pipecolic acid	0	NA
5	$(Ph)_3CO_2H$	0	NA
6	Benzoic acid	32	92.5:7.5 (85)
7	*p*-anisic acid	41	93.5: 6.4 (87)
8	*p*-nitrobenzoic acid	26	91.5:8.5 (83)
9	3,3-GluOH	40	90.0:9.9 (80.1)



2-BiPhOH **2-CypOH** **3,3-GluOH**

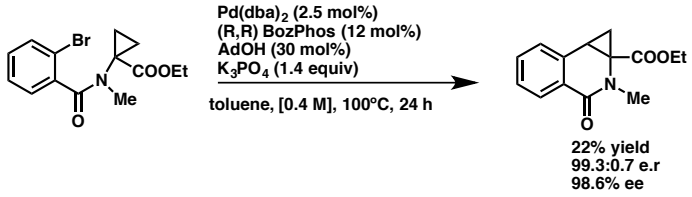
[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

Without any additional additive, the reactivity was impaired; albeit, only a slight reduction in ee was observed (**entry 1**). Most of the yields for the carboxylate ligands ranged

from 30-40% yield with the highest yield obtained for 2-CypOH (**entry 3**). *DL*-pipecolic acid failed to provide yields, possibly due to the free NH functionality resulting in catalyst sequestration (**entry 4**). $(Ph)_3CO_2H$ also failed to product due to being too sterically encumbered (**entry 5**). Although subtle, electron-donating *p*-anisic acid gave better yields and slightly improved ee's compared to benzoic acid and *p*-nitrobenzoic acid (**entry 6–8**). Overall, no significant ee changes were observed based on the carboxylate ion screened, with ee's ranging from 80% to 87%.

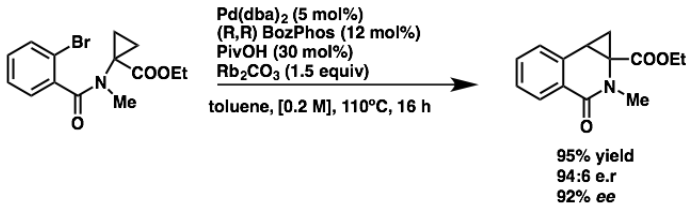
We next tried to increase our ee's by dropping the temperature, extending the reaction time, and using potassium phosphate (**Scheme 91**).

Scheme 91. Efforts to increase ee by decreasing temperature.



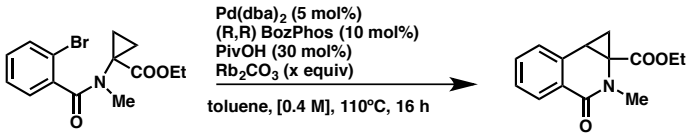
Although this gave excellent ee's, the reactivity was poor. After our carboxylate screen, we realized that AdOH did not appear to substantially improve our ee's. Upon switching to pivalic acid, increasing our ligand loading and increasing concentration, we could obtain good yields and excellent ee's (**Scheme 92**).

Scheme 92. Switch to PivOH and increase in ligand loading.



We then decided to assess the effect of base stoichiometry (**Table 25**).

Table 25. Effect of Base Stoichiometry.[a,b]



Entry	Base Equiv	Yield[%]	e.r(%ee)
1	2.0	93	91.2: 8.8 (82.4)
2	1.7	98	94.1:5.9 (88.2)
3	1.3	88	95.4:4.6 (90.8)
4	1.1	88	96.6: 3.4(93.2)

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 10% MeOH.

We also tried decreasing the amount of carbonate present in the reaction mixture, and although we could observe a notable influence on ee's with increasing base, we could not manage to further increase our ee's.

We continued to explore the role of the ligand on ee's. Notably a significant increase was observed when increasing the amount of ligand. Having explored all other variables, we postulated that dba might be contributing to diminished ee's. As BozPhos is a hemilabile ligand, it does not bind as strongly compared to bisphosphines and consequently, may be forming other non-cooperative catalytic species in solutions contributing to reductions in ee. Based on Jutand and Amatore's research on BINAP and PPh_3, it is known that although the first equivalent of dba is easily displaced, it is much more difficult to displace the second ligand.[185]

Figure 26 shows the relevant equations involved when mixing $Pd(dba)_2$ with PPh_3

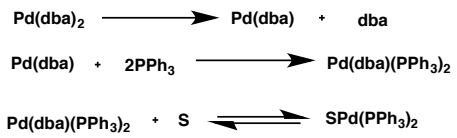
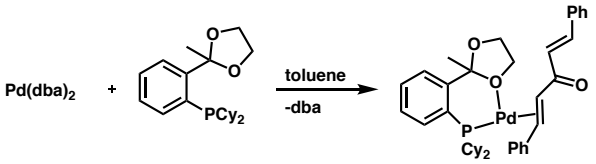


Figure 26. Equations involved explaining dba-displacement.

Additionally, dba-based precatalysts are notorious for containing a large portion of Pd nanoparticles, the dba unit can be difficult to remove during purifications, and detrimental effects on reactivity have been noted.[186] Scheme 93 reveals an interesting non-productive complex formed from a related *P,O*-type ligand..[187]

Scheme 93. Isolated LPd(dba) complex with a *P,O*-type ligand.

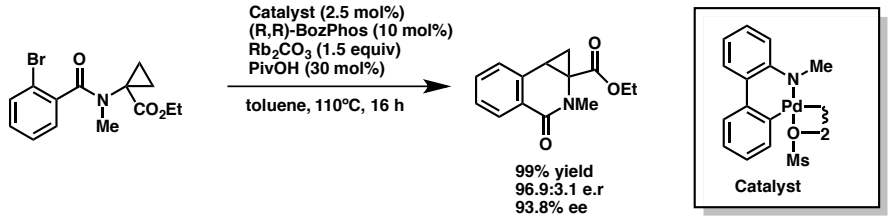


It is possible that a similar complex may form with *(R,R)*-BozPhos that could affect both reactivity and enantioselectivity. Further mechanistic studies are warranted.

Notably, we tried adding free dba to our system, which had no effect, supporting that the displacement was the issue, which parallel Amatore and Jutand's investigations.

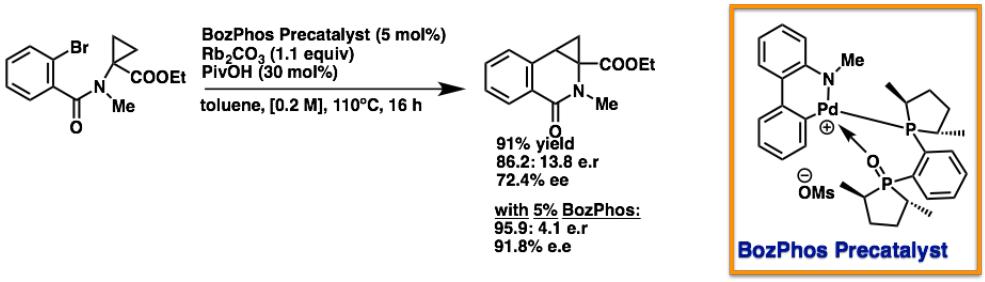
These investigations prompted us to consider a different source of Pd(0) and consequently, we decided to employ Buchwald's 4th generation dimer. The 4th generation has the added benefit of not producing the harmful carcinogenic free-carbazole by-product, which can also cause side reactions. We could achieve high yields and the highest ee's to date employing these modified conditions, while being able to reduce our ligand loading (**Scheme 94**).

Scheme 94. Improved results by switching to G4-dimer as source of Pd(0).



We also synthesized the BozPhos precatalyst and tested this in the reaction, and observed good yield, but diminished ee's (**Scheme 95**).

Scheme 95. Reactivity differences with BozPhos precatalyst.



When 5% BozPhos was added, ee's were restored, supporting the need for extra ligand to stabilize the catalyst.

In parallel with our previous observations for the achiral conditions, employing the Buchwald dimer as a source of Pd(0) with 10 mol % ligand provided the most optimal performance. Consequently, although interesting, there is no actual benefit from using the prepared catalyst versus using the dimer, as additional ligand must be added anyways.

4.7.2 For Indolines

With the experience from optimizing the cyclopropyl moiety, we next turned to the Ohno benchmark. Using our previous conditions, using $Pd(dba)_2$ and *(R,R)*-BozPhos gave good ee's and yields (**Scheme 96**), but we decided to also explore the differences using this amine-based tether system compared to the amide motif we had previously explored.

Scheme 96. Initial conditions for acyclic indoline.

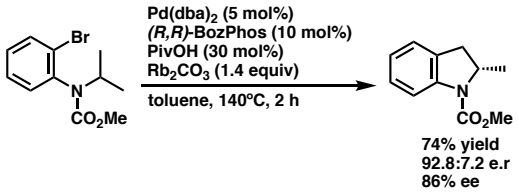
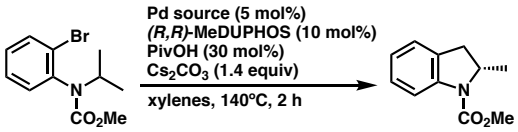


Table 26 shows different Pd(II) sources used for the in situ oxidation of *(R,R)*-MeDUPHOS. Notably, $Pd(OPiv)_2$ gave no reaction, whereas $PdCl_2$ gave modest yield with reduced ee's.

Table 26. Screening of Pd sources[a,b]

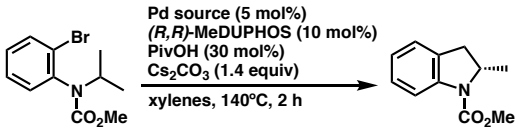


Entry	Pd source	Yield [%]	e.r (%ee)
1	$Pd(OAc)_2$	92	86.6:13.4 (73.2)
2	$Pd(OPiv)_2$	0	0
3	$PdCl_2$	50	74.9:25.1 (49.8)

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

We also explored other Pd sources (**Table 27**).

Table 27. Catalyst Screening.[a,b]



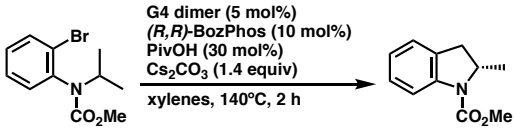
Entry	Catalyst	Yield[%]	e.r
1	$Pd(dba)_2$	35	95.2:4.8
2	Pd_2dba_3	38	95.2: 4.8
3	$PdCl_2$•MeCN	44	72.8:27.2
4	$Pd(OAc)_2$	36	79: 21
5	$Pd(TFA)_2$	100	86.1:13.9
6	G4 dimer	93	93.3:6.7
7	G4 dimer + 50 mol% NMe-carbazole	92	92.8: 7.2
8	$Pd(PCy_3)_2$	85	69.7: 30.3
9	$[PdCl(allyl)]_2$	67	87:12.
10	G3 dimer	92	87.2:12.7

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

For this catalyst screen, we used two new bottles for the dba precursors from Strem. Both bottles produced low reaction yields, but good ee's (**entries 1–2**). As observed previously, other Pd(II) sources were viable, but produced diminished ee's (**entries 3–5**). We additionally doped the reaction using the G4 dimer with the carbazole by-product, which had no significant effect on reactivity or ee (**entries 6–7**). Entry 8 demonstrates the competition of the achiral PCy_3 ligand with *(R,R)*-BozPhos, leading to the worst er's (**entry 8**). We also tried the G3 dimer, and although the yields were good the e.r was inferior. From a safety standpoint, it is also better to employ the G4 dimer to avoid the production carcinogenic carbazole.

We also ran a series of controls. Notably without base, some conversion is observed; albeit, the ee's are reduced (**Table 28**).

Table 28. Control reactions[a,b]

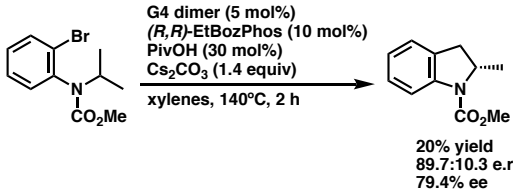


Entry	Conditions	Yield	e.r (%ee)
1	No Pd	0	N/A
2	No ligand	0	N/A
3	No base	19	19 (64.5:35.5)
4	With solvent + base	0	N/A

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

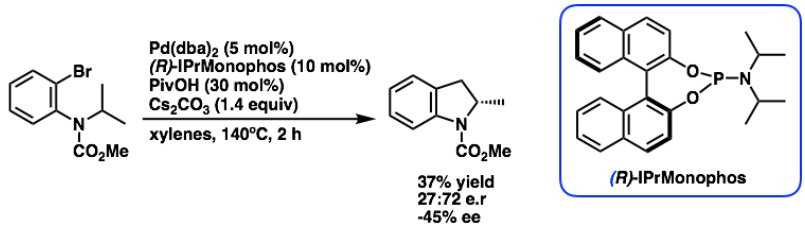
We also employed the more sterically *(R,R)*-EtBozPHOS ligand, which afforded poor yields and diminished enantioselectivity (**Scheme 97**).

Scheme 97. Ligand screen with *(R,R)*-EtBozPHOS.



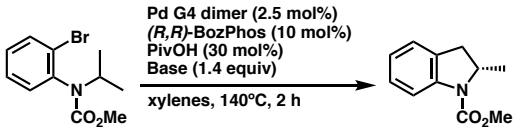
Notably, we also tried *(R)*-IPrMonophos, which gave low yield and the reversed selectivity (**Scheme 98**).

Scheme 98. Ligand screen with *(R)*-IPrMonophos.



We also screened other bases (**Table 29**).

Table 29. Base Screening.[a,b]



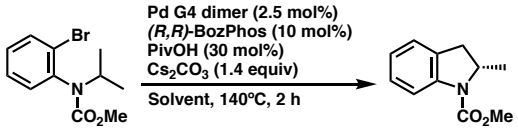
Entry	Base	Yield[%]	e.r
1	KO*t*Bu	41	53.7: 46.3
2	K_2CO_3	92	91.1:8.8
3	Rb_2CO_3	97	94.0: 6.0
4	Na_2CO_3	0	n/a
5	Cs_2CO_3	93	93.3:6.7
6	DIPEA	16	97.6:2.4
7	NEt_3	17	97.1: 2.9

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

KO*t*Bu gave poor yield and poor enantioinduction (**entry 1**). Compared to the other carbonates (**entries 2–5**), Na_2CO_3 gave no conversion. Out of the counterions, K_2CO_3 produced the worst e.r's (entry 2) compared to Rb_2CO_3 (**entry 3**) and Cs_2CO_3 (**entry 5**). Although organic bases gave poor yields, the highest e.r's could be achieved, supporting the notion that carbonate competes with pivalate and that this background reaction leads to reduced e.r's.

We also screened other solvents (**Table 30**).

Table 30. Solvent Screening.[a,b]



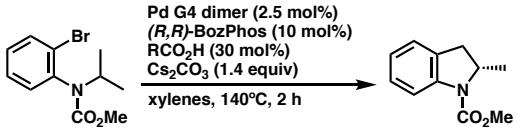
Entry	Solvent	Yield[%]	e.r
1	Xylene	93	93.3:6.7
2	CPME	92	88.7: 11.3
3	Mesitylene	52	78.8: 21.2
4	Dioxane	22	92.6: 7.3
5	DMF	0	0

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

Both xylene and CPME gave the best yields (**entries 1–2**); however, CPME gave decreased e.r. Mesitylene produced diminished yields (**entry 3**) and lower e.r's, whereas dioxane afforded low yield (**entry 4**) and good e.r. DMF failed to give conversions (**entry 5**).

We also screened a few other acid additives for comparison (**Table 31**).

Table 31. Carboxylate Screening.[a,b]



Entry	Carboxylate	Yield[%]	e.r
1	$AdCO_2H$	40	58.2:41.8
2	Ph_3CO_2H	23	76.8: 23.2
3	Benzoic acid	35	91.3: 8.7
4	Cyclopropyl CO_2H	80	93.7:6.3
5	Cyclobutyl CO_2H	82	90.0:9.1
6	$CypCO_2H$	97	90.9: 9.1
7	$CyCO_2H$	99	78.7: 21.3
8	2-norbornane CO_2H	77	92.5:7.5
9	*Cis*-*tert*-butyl $CyCO_2H$	80	90.6:9.4
10	*Trans*-*tert*-butyl $CyCO_2H$	92	89.7:10.3

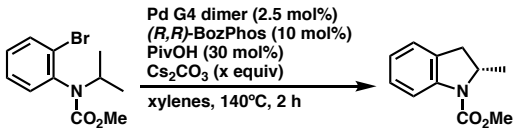
[a]Yields determined via ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

Notably, AdOH gave both poor yield and e.r (**entry 1**). Triphenylcarboxylic acid (**entry 2**) gave poor conversion Benzoic acid gave poor yield, but good e.r (**entry 3**).In general, alkyl carboxylates afforded both better yields and e.r's (**entries 4–10**). It is apparent that the more rigid the carboxylic acid, the greater the enantioinduction. This trend can be observed by comparing the more flexible cyclobutyl carboxylic acid to the more rigid cyclopropyl carboxylic acid (**entries 4–5**), and additionally by comparing the more flexible cyclohexylcarboxylic acid to the more rigid cyclopentylcarboxylic acid (**entries 6–7**). Additionally, adding rigidity to the cyclohexyl ring also improved e.r, as can be demonstrated by 2-norbornanecarboxylic acid (**entry 8**), and by added bulky substituents such as *tert*-butyl onto the cyclohexyl ring (**entries**

9–10). No apparent difference was observed between the *cis* and *trans*-substitution (**entries 9–10**).

In parallel with our previous observations, we also noticed an increase in e.r with decreasing base, indicative of the carboxylate competition as a background reaction (**Table 32**).

Table 32. Base Loading.[a,b]

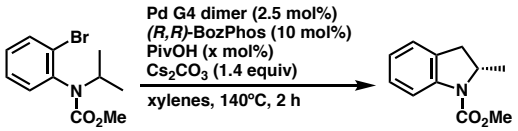


Entry	Base Equiv	Yield[%]	e.r
1	1.0	61	94.7:5.3
2	1.4	93	93.3:6.7
3	2.0	91	89.9:10.1
4	2.5	83	88.7: 11.3

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

We also explored the effect of pivalate loading and did not noticed a substantial increase in ee with increasing pivalate loading; albeit, literature reports suggest at least 30 mol% should be added to achieved good reactivity (**Table 33**).

Table 33. Pivalate Loading[a,b]

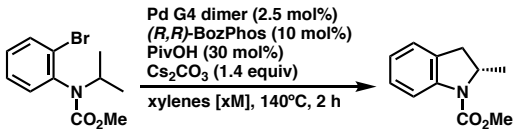


Entry	PivOH Loading (mol%)	Yield[%]	e.r
1	10	49	92.5:7.4
2	30	93	93.3:6.7
3	50	97	95.5:4.5
4	100	94	94:6

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH

We also managed to slightly improve ee's with increasing concentration (**Table 34**).

Table 34. Concentration Effects[a,b]

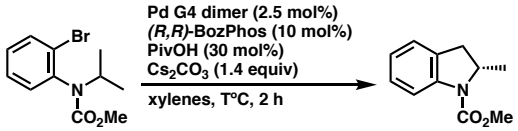


Entry	Conc [M]	Yield[%]	e.r
1	0.05	88	84.9: 15.1
2	0.1	93	93.3:6.7
3	0.2	86	94.4: 5.5

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

We also tried decreasing the temperature and increasing the reaction time (**Table 35**). The reaction does not proceed below 120 ºC; however, much higher ee's can be obtained at 120 ºC.

Table 35. Effect of temperature.[a,b]

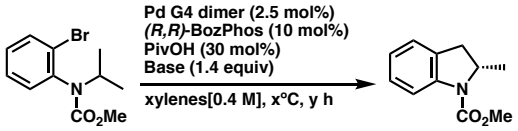


Entry	T [ºC]	Yield [%]	e.r
1	140	93	93.3:6.7
2	120 (16 h)	96	97:3
3	110 (16 h)	0	N/A

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

Table 36 shows the fine tuning of the reaction conditions. Notably, at lower temperatures using K_2CO_3, excellent e.r could be obtained (**entry 4**).

Table 36. Final optimization indolines[a,b]

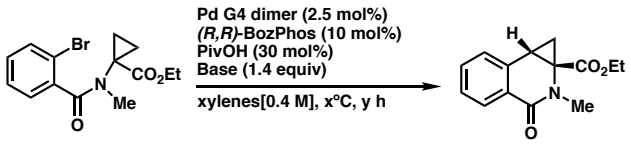


Entry	Base	T(ºC)	Time (h)	Yield[%]	e.r
1	Cs_2CO_3	140	2	93	93.3:6.7
2	Cs_2CO_3	120	16	96	95:8:4.2
3	Rb_2CO_3	120	16	91	96.6:3.5
4	K_2CO_3	120	16	93	97.1:2.9

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

Table 37 shows the fine tuning of the reaction conditions for the cyclopropane substrate. Notably, at lower temperatures using K_2CO_3 and Rb_2CO_3 afforded excellent e.r; however, Rb_2CO_3 was employed to achieved good reactivity (**entry 3**).

Table 37. Final optimization cyclopropanes[a,b]



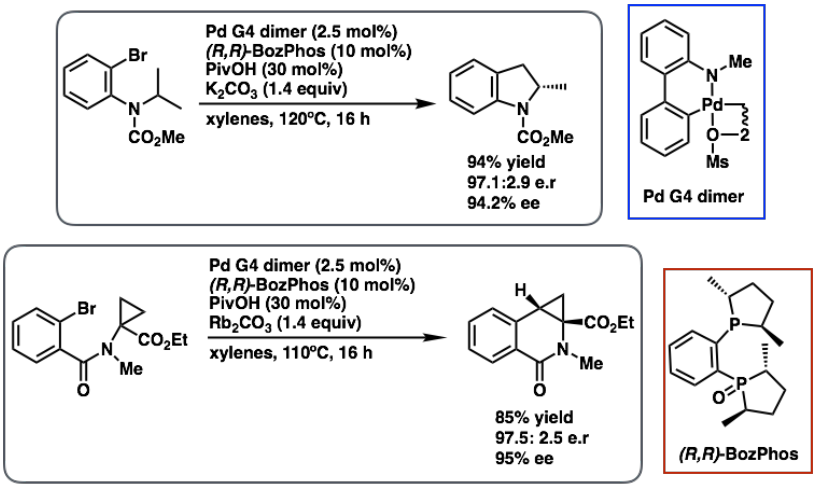
Entry	Base	T(°C)	Time (h)	Yield[%]	e.r
1	Cs_2CO_3	110	16	87	95.8:4.2
2	Cs_2CO_3	140	2	95	94.4:5.6
3	Rb_2CO_3	110	16	85	97.5:2.5
4	K_2CO_3	110	16	73	97.5:2.9

[a]Yields determined via ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[a]ee's were determined via SFC using a ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar), 5% MeOH.

4.8 Comparison to Literature Benchmarks

After careful tuning of our reaction conditions for both systems, the final optimized yields and ee's are shown for both systems as isolated yields (**Scheme 99**).

Scheme 99. Optimized conditions for cyclopropyl and sp^3 arylation using *(R,R)*-BozPhos.



To date, these systems are competitive with the current literature, indicative of the immense potential of bisphosphine monoxide ligands for enantioselective C–H functionalization and related Pd-transformations.

4.9 Conclusions

In conclusion, we demonstrated that *(R,R)*-BozPhos, not *(R,R)*-MeDUPHOS is the active ligand for Kagan's system. By careful optimization and switching from $Pd(dba)_2$ to Buchwald's G4 dimer, improved enantioselectivities could be achieved. Compared to other systems, the developed systems allow for the use of commercially available ligands and catalyst, and a cheap inexpensive base while maximizing yield and enantioselectivity. Notably, this system demonstrates the successful application of hemilabile bisphosphine monoxides towards enantioselective sp^3 C–H arylation.

Chapter 5 Concluding Remarks and Future Work

5.1 Chapter 2 Conclusions

In Chapter 2, a β–functionalization process for cyclopropyl α–amino-acid-derived benzamides was achieved to provide ethyl 1,2,3,4-tetrahydroisoquinolone-3-carboxylates and related six-membered valuable fused-heterocyclic cores. Through exploring the influence of additives, we discovered that pivalate or silver additives may not always be required for direct functionalization processes; however, more challenging substrates can benefit from pivalate. Consequently, the subtle role of such additives in reaction development should be considered to avoid employing unnecessary reagents.

For this system, there are several investigation and applications can could be performed. First, the role of the ester was not fully explored. As a small extension, modifications to the ester moiety could be investigated, which could provide another point of influence for enantioinduction. In particular, one could envision using chiral cations instead of chiral anions as an alternative strategy to create a chiral space.

In terms of applications, as this core is a modified version of TiC, it is highly probable that the compounds present in this paper are pharmacologically active. Consequently, structure-activity relationship studies would be of interest to discover if this tetraisohydroquinolone core could be of use in drug development. Cleavage of the ester moiety would provide access to a linker. It would be equally interesting to see how this building block could be incorporated into peptides for peptidomimetic applications.

Additionally, one issue with this system like many cyclopropane systems is that the alpha-position must often be blocked to prevent ring-opening or regioselectivity issues. Design of a suitable catalyst to select between the alpha and beta positions by overcoming innate reactivity via a catalyst-control strategy would be highly desirable.

5.2 Chapter 3 Conclusions

In Chapter 3, we developed one of the few examples of Pd-catalyzed, intramolecular cyclopropyl direct alkenylation, providing access to novel azacycles. To date, this represents one of the only full methodology papers targeting direct alkenylation of cyclopropanes. Ligand studies suggested that bisphosphine monoxides, not bisphosphines were the active ligands. In light of these findings, we reported rare examples of enantioselective direct alkenylation employing both *(R)*-IPrMonophos and *(R,R)*-BozPhos ligands.. To date, this is the first example of enantioselective C–H functionalization employing a chiral bisphosphine monoxide ligand and the first enantioselective cyclopropyl direct alkenylation example, demonstrating the potential for bifunctional ligands to be applied towards C–H functionalization processes.

One of the major issues with this project was substrate scope limitations, resulting from the starting material synthesis, which must use symmetric cycloalkanones to access the required 2-alkenylbromide systems. Additionally, the yields are notoriously low yielding and the reaction is not environmentally benign. To circumvent these issues, two improvements could be made: 1) improved synthesis to access the alkenyl halides or related cross-coupling partners, 2) development of cross-dehydrogenative cross-couplings to enable use of H as a both coupling partners and avoid the need for the halide precursor.

Additionally, the enantioselective variant of this reaction employing IPrMonophos has yet to be fully optimized and the scope to be completed. Issues were also observed for reactivity with (*R,R*)-BozPhos, and consequently, further investigations into finding a suitable system for this process are warranted.

It is highly important that chemists continue developing improved strategies to access molecules with increased Fsp^3 character. Considering the importance in "escaping Flatland" for drug candidate design, improving synthetic methods to enable facile parallel synthesis will help promote the development and explorations into more complex 3D-structures.

5.3 Chapter 4 Conclusions

In Chapter 4, we demonstrate that *(R,R)*-BozPhos, not *(R,R)*-MeDUPHOS is the active ligand for Kagan's system. Due to the importance of Kagan's seminal discovery, it was importance to determine if *(R,R)*-MeDUPHOS was the active ligand to correct this misnomer within the literature. By careful optimization and switching from $Pd(dba)_2$ to Buchwald's G4 dimer, improved enantioselectivities and reproducibility could be achieved. Compared to other systems, the developed systems allow for the use of commercially available ligands and catalyst, and a cheap inexpensive base while maximizing yield and enantioselectivity. The reported systems for both amides and amines are both competitive with the literature reports. Notably, this system demonstrates the successful first application of hemilabile bisphosphine monoxides for an enantioselective sp^3 C–H arylation process.

There is still a substantial amount of work required to fully understand how bisphosphine monoxides function within a direct functionalization manifold. Extensive mechanistic studies including DFT calculations for this system would be highly valuable. Several factors are still unclear including: 1) the carboxylate competition, 2) the active and noncooperative species formed when $Pd(dba)_2$ is employed 3) the catalytic intermediates responsible for the CMD step, 4) the role of the BPMOs in stabilizing the catalyst. By further understanding how this reaction works, it can potentially enable the design of a new type of precatalyst tuning towards the unique properties of the BPMO systems. Ultimately, design of a viable chiral catalyst could enable enantioselective C–H functionalization via catalyst control.

5.4 General Conclusions

Within the duration of this dissertation, we have witnessed the rise and re-discovery of new technologies including high-throughput screening (HTS), flow chemistry, photoredox and electrochemical methods.

It will be highly important to adopt an interdisciplinary approach to allow transition-metal C–H functionalization processes to be transferred into flow chemistry applications. Careful design of solid-supported catalysts and homogenous conditions will require communication between experts in chemistry, engineering and materials science.

For future reaction optimizations, the use of high-throughput screening (HTS) will play a key role in rapidly obtaining data to enable greater time investments towards mechanistic understandings and deeper thinking about reaction manifolds.

We have also witnessed a renaissance of radical chemistry. Many of these reactions remain problematic for cyclopropanes due to the instability of many cyclopropyl radical species. Investigations into radical-based cyclopropyl C-H functionalization would produce novel reactions employing photoredox, HAS, electrochemistry, and other metals that employ SET mechanisms such as Fe and Ni.

Despite the privileged status of the cyclopropane motif, it is evident that the literature still shows an immense paucity for methodologies to access highly-functionalized cyclopropane architectures. Although significant advances have been made in the field of de novo synthesis, many of these processes can be time-consuming, air- and moisture-sensitive and limited in substrate scope, including the lengthy starting material syntheses. As illustrated, functionalization of cyclopropanes via traditional cross-couplings and C–H activation approaches are both still in their infancy. Consequently, greater synergy between the synthesis and functionalization is required to fully actualize the synthetic potential of these molecular triangle motifs, which empower greater cyclopropyl applications across disciplines.

As observed within the context of transition-metal cross-coupling development, work towards employing alternative, halide-free coupling partners is also of interest. Additionally, the importance of ligand design continues to drive reaction design and possibilities. As demonstrated herein, hemilabile/bifunctional ligands can be highly useful in stabilizing catalytic species. Consequently, applying hemilabile ligand systems towards other metals such as nickel chemistry could offer solutions to taming this "spirited horse."

Within this dissertation phosphine-based ligands were explored; however, their NHC counterparts produced highly active and useful catalysts. Consequently, one could imagine designing hemilabile/bifunctional NHC ligands, perhaps even possessing a P=O motif, and exploring the new reactivity modes that could be unlocked.

This dissertation began by describing the impact that methodology development can have on total synthesis by creating construction reactions. There continues to be few examples

of applying C–H functionalization strategies towards total synthesis. Consequently, it would be of interest to find a suitable natural product to employ some of the cyclopropane C–H functionalization methodologies that we and others have explored. Such applications would expose and further test the limitations of such construction reactions and provide important feedback for future methodology development.

Overall, since the rise of homogenous catalysis, the chemical community has revisited old reaction patterns and been inspired to design new reaction platforms. We have emerged from using chisels towards using lasers as sophisticated synthetic tools to make and break bonds and that evolution will continue to impart greater control over both reactivity, selectivity and the complexity in our molecular design

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(137) The reaction was run at higher temperatures (140 °C) and failed to react. This may be a consequence of decreased C−H bond acidity compared to cyclopropanes.

(138) This is possibly due to the strong binding of Pd to N- and S- atoms of the pyridyl and thienyl moiety forming noncooperative Pd- complexes, causing catalyst poisoning.

(139) The reaction was run at higher temperatures (140 °C) and failed to react. This may be a consequence of decreased C−H bond acidity compared to cyclopropanes.

(140) The absence of a silver salt indicates that the reaction does not proceed via a cationic palladium intermediate. For more details on a carboxylate-assisted process

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Annex

Experimental Section for Chapter 2

Materials.

Commercial reagents were used as supplied or purified by standard techniques where necessary. Starting materials not listed below were obtained commercially and the reagents were used without further purification. Ethyl 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylate was synthesized according to literature procedure[1] and converted to its TFA salt for subsequent use.[2] 2-bromoanilide **1u** was synthesized in the same fashion as previously reported from 2-bromo aniline and 1-(ethoxycarbonyl)cyclopropane-1-carboxylic acid.[3] Benzyl-protected substrate **2b** was synthesized by the general procedure and benzylated as previously reported. [4]

General procedure for cyclopropyl benzamide synthesis
Ethyl 1-[N-methyl(2-bromophenyl)amido]cyclopropane-1-carboxylate (1a)

To a 100-mL round bottom flask flame-dried and cooled under Ar (g) was added 2-bromobenzoic acid (1.91 g, 12.19 mmol) dissolved in either MeCN or DCM (25 mL). To this was added EDC•HCl (1.89 g, 12.19 mmol and HOBt (1.71 g, 11.18 mmol). In a separate 50 mL round-bottom flask containing the cyclopropane TFA salt (2.45 g, 10.16 mmol) dissolved in MeCN or DCM was added DIPEA (4.20 mL, 25.40 mmol), evolving white fumes; this mixture was canulated into the reaction mixture and subsequently stirred for 24 h at ambient temperature. The reaction was transferred into a separatory funnel and diluted with 75 mL of EtOAc. The organics were then washed in the following order: HCl 1.0 N (50 mL), distilled water (50 mL), saturated $NaHCO_3$ (50 mL) and brine (2x's, 50 mL each). The combined organics were dried with sodium

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sulfate anhydrous, filtered and concentrated *in vacuo* to give a golden brown solid, which was used crude in the following methylation step.

To a 250-mL round bottom flask containing ethyl 1-[(2-bromophenyl)amido]cyclopropane-1-carboxylate (1.94 g, 6.22 mmol) and purged with argon was added anhydrous THF (50 mL) and NaH (22.4 mg, 9.33 mmol) (bubbling was observed) The reaction was stirred for 10 min. MeI (1.5 mL, 24.88 mmol) was added and this was stirred overnight at room temperature. The reaction was quenched with 50 mL of water and then transferred into a separatory funnel. The aqueous layer was extracted (3x's, 50 mL) with EtOAc. The combined organics were washed with brine (50 mL), dried with sodium sulfate, filtered and concentrated *in vacuo* to give a dark-orange brown oil.

The crude was then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes. The desired product was isolated as a pale yellow oil (1.59 g, 4.86 mmol, 78% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.58 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.48-7.42 (m, 1H), 7.29-7.08 (m, 3H), 4.13-4.06 (q, *J*=7.3 Hz, 2H), 3.08 (s, 1.3H), 2.75 (s, 1.8H), 1.65-1.04 (m, 7H). **^{13}C NMR** ($CDCl_3$, 75MHz): δ 172.1, 171.6, 170.63, 170.43, 139.3, 138.4, 133.0, 132.7, 130.3, 130.1, 127.9, 127.8, 127.1, 126.4, 119.5, 118.7, 77.7, 77.3, 76.9, 61.6, 61.3, 43.1, 40.4, 36.9, 34.7, 20.6, 19.1 (br), 18.4, 17.3(br), 14.2, -2.4 (br). **FTIR** (cm^{-1}) (neat): 2979, 1725, 1435, 1296, 1023, 770.5, 748.9, 501.3, 448.6; **HRMS** (ESI, Pos) calcd for $C_{14}H_{16}BrNO_3$ $(M+H)^+$: 326.03959, found: 326.03863

Ethyl 1-(2-chloro-*N*-methylbenzamido)cyclopropanecarboxylate (1ab)

The title compound was prepared by the general synthesis on a 10.16-mmol scale and then purified via column chromatography (10-30% EtOAc/Hex) to give a golden yellow oil (2.298 g, 8.16 mmol, 80% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.39 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.42-7.16 (m, 4H), 4.20 (q, *J*=7.1 Hz, 2H), 3.17 (s, 1.4H), 2.85 (s, 1.6H), 1.94-1.10 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 171.9, 171.4, 169.8, 169.6, 137.1, 136.2, 130.0, 129.83, 129.78, 129.65, 129.3, 127.6, 127.0, 126.4, 126.2, 61.4, 61.1, 42.9, 40.3, 36.6, 34.4, 20.1, 18.7 (br), 18.1, 17.6 (br), 14.0, -2.6 (br); **FTIR** (cm^{-1}) (neat): 2981, 1725, 1654, 1382, 1186, 1134, 1039, 748; **HRMS** (ESI, Pos) calcd for $C_{14}H_{16}ClNO_3$ $(M+H)^+$: 282.08811, found: 282.08915 *m/z*.

Ethyl 1-(2-iodo-*N*-methylbenzamido)cyclopropanecarboxylate (1ac)

The title compound was prepared by the general synthesis on a 12.71-mmol scale and then purified via column chromatography (10-30% EtOAc/Hex) to give a yellow oil (0.666 g, 1.78 mmol, in 14% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.41 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.77-7.64 (m, 1H), 7.37-7.24 (m, 1H), 7.23-7.04 (m, 1H), 7,02-6.90 (m, 1H), 4,10 (q, *J*=7.1 Hz, 2H), 3.08 (s, 1.1H), 2.74 (s, 1.9H), 1.86-0.94 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 172.0, 171.9, 171.7, 171.4, 143.0, 142.2, 139.3, 138.9, 130.1, 130.0, 128.3, 127.6, 127.2, 125.8, 93.7, 91.7, 61.5, 61.2, 43.0, 40.3, 37.0, 34.7, 21.1, 18.9 (br), 18.4, 17.2 (br), 14.1, -2.4 (br); **FTIR** (cm^{-1}) (neat): 2981, 1725, 1650, 1384, 1186, 1014, 730, 440; **HRMS** (ESI, Pos) calcd for $C_{14}H_{16}INO_3$ $(M+H)^+$: 374.02331, found: 374.02476 *m/z.*

Ethyl 1-(*N*-benzyl-2-bromobenzamido)cyclopropane-1-carboxylate (1b)

The title compound was prepared by the general synthesis on a 2.568-mmol scale and then purified via column chromatography (10-60% EtOAc/Hexanes) to give a clear oil (0.9298 g, 2.311 mmol, 90% yield). Reported as a mixture of rotamers. **R_f:** 0.46 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.67-7.24 (m, 10H), 5.53 (d, *J* = 15.4 Hz, 0.7H), 4.45-4.15 (m, 3.7H), 1.45-1.08 (m, 7H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 172.6, 171.8, 171.5, 139.4, 138.5, 133.3, 132.9, 130.43, 130.28, 128.60, 128.43, 127.7, 127.2, 126.6, 119.9, 119.4, 61.9, 61.4, 53.8, 52.46, 52.41, 43.3, 19.5, 17.5, 14.4; **FTIR** (cm^{-1}) (neat): 2980, 1724, 1652, 1177, 1156, 747.5, 501.5; **HRMS** (ESI, Pos) calcd for $C_{20}H_{20}BrNO_3$ $(M+H)^+$: 402.07141, found: 402.06993 *m/z.*

Ethyl 1-(*N*-benzyl-2-bromobenzamido)cyclopropane-1-carboxylate (1b)

The title compound was prepared by the general synthesis on a 2.568-mmol scale and then purified via column chromatography (10-60% EtOAc/Hexanes) to give a clear oil (0.9298 g, 2.311 mmol, 90% yield). Reported as a mixture of rotamers. **R_f:** 0.46 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.67-7.24 (m, 10H), 5.53 (d, J = 15.4 Hz, 0.7H), 4.45-4.15 (m, 3.7H), 1.45-1.08 (m, 7H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 172.6, 171.8, 171.5, 139.4, 138.5, 133.3, 132.9, 130.43, 130.28, 128.60, 128.43, 127.7, 127.2, 126.6, 119.9, 119.4, 61.9, 61.4, 53.8, 52.46, 52.41, 43.3, 19.5, 17.5, 14.4; **FTIR** (cm^{-1}) (neat): 2980, 1724, 1652, 1177, 1156, 747.5, 501.5; **HRMS** (ESI, Pos) calcd for $C_{20}H_{20}BrNO_3$ $(M+H)^+$: 402.07141, found: 402.06993 *m/z.*

2-bromo-*N*-(1-cyanocyclopropyl)-*N*-methylbenzamide (1d)

The title compound was prepared by the general synthesis on a 4.434-mmol scale and then purified via column chromatography (10-60% EtOAc/Hexanes) to give a clear oil (0.389 g, 1.394 mmol, 31% yield). Reported as a mixture of rotamers. **R_f:** 0.46 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.66-7.28 (m, 4H), 3.24 (s, 1.09H), 2.92 (s, 1.72H), 1.70-1.27 (m, 4H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.1, 136.7, 132.9, 132.5, 130.64, 130.53, 127.6, 127.29, 127.24, 127.04, 119.5, 119.03, 118.85, 118.6, 35.9, 33.6, 27.5; **FTIR** (cm^{-1}) (neat): 2921, 2237,1657, 1369, 1076, 695, 565 ; **HRMS** (ESI, Pos) calcd for $C_{12}H_{11}BrN_2O$ $(M+H)^+$: 279.01275, found: 279.01407 *m/z.*

Ethyl 1-(2-bromo-*N*-methyl-3-nitrobenzamido)cyclopropane-1-carboxylate (1f)

The title compound was prepared by the general synthesis on a 6.272-mmol scale and then purified via column chromatography (10-60% EtOAc/Hexanes) to give an orange oil (0.773 g, 3.596 mmol, 57% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.59 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.42-6.92 (m, 4H), 4.27-4.18 (m, 2H), 3.28-3.20 (m, 0.8H), 2.93 (s, 1.7H), 1.89-1.19 (m, 7H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.5, 170.5, 165.9, 159.9, 157.4, 131.91, 131.83, 131.23, 131.14, 131.04, 128.8, 128.5, 127.1, 126.9, 119.89, 119.85, 115.1, 114.9, 61.84, 61.74, 61.5, 40.5, 36.4, 14.14, 14.01; **FTIR** (cm^{-1}) (neat): 2982, 1724,

1661,1445, 1188, 871.9, 676.6, 662.6, 469.1 **; HRMS** (ESI, Pos) calcd for $C_{14}H_{15}BrN_2O_5$ $(M+H)^+$: 371.02554, found: 371.02371 *m/z*.

Ethyl 1-(2-bromo-*N*-methyl-5-nitrobenzamido)cyclopropanecarboxylate (1g)

The title compound was prepared by the general synthesis on a 4.26-mmol scale and then purified via column chromatography (10-30% EtOAc/Petroleum Et2O) to give a yellow solid (0.773 g, 2.08 mmol, 55% yield over two steps). Reported as a mixture of rotamers. **mp:** 80-86 °C; **R_f:** 0.39 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 8.11-7.94 (m, 2H), 7.74-7.65 (m, 1H), 4.12 (q, *J*=7.1 Hz, 2H), 3.11 (s, 1.6H), 2.80 (s, 1.4H), 1.77-1.03 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz); δ 171.7, 171.1, 168.4, 168.3, 147.1, 146.6, 140.6, 139.8, 134.4, 134.2, 127.1, 126.2, 124.8, 124.7, 122.9, 121.6, 62.3, 61.5, 43.1, 40.6, 36.9, 34.7, 20.7, 19.0 (br), 18.3, 17.4 (br), 14.2, 14.12, 14.07; **FTIR** (cm^{-1}) (neat): 2982, 1654, 1526, 1338, 1183, 1135, 1026, 752, 739; **HRMS** (ESI, Pos) calcd for $C_{14}H_{15}BrN_2O_5$ $(M+H)^+$: 371.02429, found: 371.02371 *m/z*.

Ethyl 1-(2-bromo-5-fluoro-*N*-methylbenzamido)cyclopropane-1-carboxylate (1h)

The title compound was prepared by the general synthesis on a 4.822-mmol scale and then purified via column chromatography (10-30% EtOAc/Hex) to give a white solid (1.044 g, 3.032 mmol, 63% yield over two steps). Reported as a mixture of rotamers. **mp:** 66-68 °C **R_f:** 0.52 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.54-7.45 (m, 1H), 7.03-6.90 (m, 2H), 4.26-4.13 (m, 2H), 3.15 (s, 1.4H), 2.86 (s, 1.6H), 1.42-1.17 (m, 7H); **^{13}C NMR** ($CDCl_3$, 101MHz) δ 172.1, 171.6, 169.5, 169.3, 162.3 (d, *J*=249.6 Hz), 161.6 (d, *J*=249.5 Hz), 141.0 (d, *J*=7.4 Hz), 140.1 (d, *J*=6.9 Hz), 134.7 (d, *J*=8.0 Hz), 134.5(d, *J*=8.1 Hz), 117.8 (d, *J*=22.5 Hz), 117.5 (d, *J*=22.4 Hz),115.4 (d, *J*=24.2 Hz),114.3, (d, *J*=24.5 Hz), 113.2, 62.0, 61.6, 43.2, 40.7, 37.0, 34.9, 20.7, 18.4, 14.3; **^{19}F NMR** ($CDCl_3$, 282MHz):δ -114.7 (m), -115.2 (m); **FTIR** (cm^{-1}) (neat): 2984, 1729, 1658, 1407, 1193, 1148, 868, 749, 591; **HRMS** (ESI, Pos) calcd for $C_{14}H_{15}BrFNO_3$ $(M+H)^+$: 344.03039, found: 344.02921 *m/z*.

Ethyl 1-(2-bromo-4-fluoro-*N*-methylbenzamido)cyclopropanecarboxylate (1i)

The title compound was prepared by the general synthesis on a 3.09-mmol scale and then purified via column chromatography (10-30% EtOAc/Hex) to give a light yellow oil (0.235 g, 0.68 mmol, 22% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.38 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.38-7.22 (m, 2H), 7.04 (dtd, *J*=30.9, 10.7, 2.4 Hz, 1H), 4.20 (q, *J*=7.1 Hz, 2H), 3.18 (s, 1.3H), 2.86 (s, 1.7H), 1.86-1.12 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 172.0, 171.5 170.0, 169.8, 164.0 (d, *J*=253.2 Hz), 160.6 (d, *J*=252.9 Hz), 135.7 (d, *J*=4.0 Hz), 134.9 (d, *J*=4.0 Hz), 129.5 (d, *J*=8.7 Hz), 127.9 (d, *J*=8.7 Hz), 120.7 (d, *J*=24.6 Hz), 120.4 (d, *J*=9.4 Hz), 120.2 (d, *J*=24.7 Hz), 119.5 (d, *J*=9.4 Hz), 115.3 (d, *J*=21.4 Hz), 114.5 (d, *J*=21.3 Hz), 61.7, 61.3, 43.1, 40.5, 36.9, 34.7, 20.6, 19.1 (br), 18.3, 17.6 (br), 14.1; **^{19}F NMR** ($CDCl_3$, 282MHz): δ -109.5 (m), -109.8 (m); **FTIR** (cm^{-1}) (neat): 2981, 1726, 1655, 1381, 1189, 1027, 752; **HRMS** (ESI, Pos) calcd for $C_{14}H_{15}BrFNO_3$ $(M+H)^+$: 344.03021, found: 344.02921 *m/z*

Ethyl 1-(2-bromo-4,5-difluoro-*N*-methylbenzamido)cyclopropane-1-carboxylate (1j)

The title compound was prepared by the general synthesis on a 5.882-mmol scale and then purified via column chromatography (10-30% EtOAc/Hex) to give a clear oil (1.605 g, 4.431 mmol, 75 % yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.48 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz):δ 7.41-7.35 (m, 1H), 7.14-7.09 (m, 1H), 4.17-4.12 (m, 2H), 3.10 (s, 1.4H), 2.83 (s, 1.6H), 1.65-1.18 (m, 7H) ; **^{13}C NMR** ($CDCl_3$, 101MHz): δ 172.0, 171.4, 168.80, 168.61, 151.65, 151.52, 151.37, 151.23, 151.10, 150.58, 150.46, 149.11, 148.98, 148.83, 148.70, 148.0, 136.00, 135.95, 135.11, 135.06, 122.5, 122.27, 122.13, 121.93, 117.2, 117.0, 115.95, 115.75, 113.88, 62.03, 61.55, 43.18, 40.68, 36.96, 34.85, 29.71, 20.72, 18.25, 14.29,14.26; **^{19}F NMR** ($CDCl_3$, 282MHz): δ -133.2 (m), -133.5 (m), -136.8(m), -137.5(m); **FTIR** (cm^{-1}) (neat): 2981, 1724, 1651, 1287, 1149, 750.1, 576.1, 458.0 ; **HRMS** (ESI, Pos)calcd for $C_{14}H_{15}BrF_2NO_3$ $(M+H)^+$: 362.02137, found: 362.01979 *m/z.*

Ethyl 1-(2-bromo-5-chloro-*N*-methylbenzamido)cyclopropanecarboxylate (1k)

The title compound was prepared by the general synthesis on a 3.87-mmol scale and then purified via column chromatography (10-40% EtOAc/Hex) to give a cream white solid (0.681 g, 7.89 mmol, 49% yield over two steps). Reported as a mixture of rotamers. **mp:** 98-104 °C; **R_f:** 0.48 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.49 (t, *J*=8.3 Hz, 1H), 7.33-7.16 (m, 2H), 4.21 (q, *J*=7.1 Hz, 2H), 3.17 (s, 1.4H), 2.88 (s, 1.6H), 1.93-1.08 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz); δ 172.1, 171.5, 169.4, 169.2, 140.7, 139.9, 134.3, 134.1, 133.5, 130.6, 130.3, 128.1, 126.9, 117.6, 116.8, 62.1, 61.6, 61.3, 43.2, 40.6, 37.0, 34.8, 28.3, 20.7, 19.0 (br), 18.4, 17.7 (br), 14.4, 14.3; **FTIR** (cm^{-1}) (neat): 3341, 2979, 1718, 1645, 1389, 1595, 1026, 754, 502; **HRMS** (ESI, Pos) calcd for $C_{14}H_{15}BrClNO_3$ $(M+H)^+$: 360.00014, found: 359.99966 *m/z*.

Ethyl 1-(2-bromo-4-chloro-*N*-methylbenzamido)cyclopropane-1-carboxylate (1l)

The title compound was prepared by the general synthesis on a 5.962-mmol scale and then purified via column chromatography (10-40% EtOAc/Hex) to give a light yellow oil (0.8074 g, 2.239 mmol, 38% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.62-7.58 (m, 1H), 7.38-7.20 (m, 2H), 4.24-4.19 (m, 2H), 3.18 (s, 1.3H), 2.87 (s, 1.6H), 1.47-1.19 (m, 7H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.7, 171.1, 169.55, 169.37, 137.5, 136.6, 135.2, 134.9, 132.5, 132.1, 128.5, 127.8, 127.07, 127.03, 119.9, 119.0, 61.5, 61.1, 42.8, 40.2, 36.6, 34.5, 20.4, 18.1, 13.9 ; **FTIR** (cm^{-1}) (neat): 2980, 1725, 1652, 1367, 1327, 1078, 725.8, 507.2, 445.3; **HRMS** (ESI, Pos) calcd calcd for $C_{14}H_{15}BrClNO_3$ $(M+H)^+$: 360.00086, found: 359.99966 *m/z*.

Ethyl 1-(2-bromo-5-methoxy-*N*-methylbenzamido)cyclopropanecarboxylate (1m)

The title compound was prepared by the general synthesis on a 4.04-mmol scale and then purified via column chromatography (10-30% EtOAc/Hex) to give a light yellow oil (0.486 g, 1.37 mmol, 34% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.41 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.40-7.30 (m, 1H), 6.79-6.65 (m, 2H), 4.13 (q, *J*=7.1 Hz, 2H), 3.72

(s, 1.7H), 3.64 (s, 1.3H), 3.10 (s, 1.3H), 2.80 (s, 1.7H), 1.83-1.07 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 172.0, 171.5, 170.9, 170.6, 139.7, 138.90, 138.89, 138.6, 130.8, 130.7, 127.4, 126.8, 124.9, 123.6, 121.6, 120.7, 61.4, 61.1, 43.0, 40.2, 36.7, 34.4, 23.1, 22.9, 20.2, 18.9 (br), 18.2, 17.3 (br), 14.1, 14.0; **FTIR** (cm^{-1}) (neat): 2980, 1726, 1655, 1467, 1291, 1238, 1040, 751; **HRMS** (ESI, Pos) calcd for $C_{15}H_{18}BrNO_4$ $(M+H)^+$: 356.04746, found: 356.0492 *m/z.*

Ethyl 1-(2-bromo-4,5-dimethoxy-*N*-methylbenzamido)cyclopropanecarboxylate (1n)

The title compound was prepared by the general synthesis on a 6.71-mmol scale and then purified via column chromatography (50-75% EtOAc/Petroleum Et_2O) to give a white solid (0.879 g, 2.28 mmol, 34% yield over two steps). Reported as a mixture of rotamers. **mp:** 104-106 °C; **R_f:** 0.19 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.01 (d, *J*=13.8 Hz, 1H), 6.87-6.71 (m, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 3.94-3.70 (m, 6H), 3.16 (s, 1.3H), 2.89 (s, 1.5H), 1.85-1.13 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 172.0, 171.2, 170.08, 170.06, 149.5, 149.2, 148.4, 147.5, 130.8, 129.8, 115.2, 114.8, 110.1, 109.6, 109.2, 108.8, 61.2, 60.8, 55.8, 55.74, 55.72, 55.4, 42.8, 40.1, 36.5, 34.3, 20.2, 18.5 (br), 18.0, 17.2 (br), 13.85, 13.79; **FTIR** (cm^{-1}) (neat): 2981, 1720, 1506, 1255, 1160, 1027, 863, 754; **HRMS** (ESI, Pos) calcd for $C_{16}H_{20}BrNO_5$ $(M+H)^+$: 386.06031, found: 386.05976 *m/z.*

Ethyl 1-(2-bromo-3,4,5-trimethoxy-*N*-methylbenzamido)cyclopropanecarboxylate (1o)

The title compound was prepared by the general synthesis on a 3.75-mmol scale and then purified via column chromatography (20-50% EtOAc/Petroleum Et_2O) to give a clear oil (0.996 g, 2.39 mmol, 63% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.54 (1:1 ethyl acetate: petroleum ether); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 6.63-6.51 (m, 1H), 4.09 (q, J=7.1 Hz, 2H), 3.87-3.70 (m, 8H), 3.65 (s, 1H), 3.06 (s, 1.3H), 2.78 (s, 1.7H), 1.81-1.04 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz); δ 172.2, 171.5, 170.2, 170.1, 153.4, 152.7, 151.2, 150.8, 143.4, 143.1, 134.5, 133.6, 106.3, 106.0, 105.6, 105.2, 61.5, 61.2, 61.0, 60.0, 56.1, 55.8, 43.1, 40.4, 36.8, 34.6, 20.3, 19.0 (br), 18.2, 17.2 (br), 14.09, 14.07; **FTIR** (cm^{-1}) (neat): 2939, 1726, 1656, 1382, 1242, 1106, 1009, 752; **HRMS** (ESI, Pos) calcd for $C_{17}H_{22}BrNO_6$ $(M+H)^+$: 416.0706, found: 416.07033 *m/z.*

Ethyl 1-(2-bromo-*N*,3-dimethylbenzamido)cyclopropanecarboxylate (1p)

The title compound was prepared by the general synthesis on a 5.61-mmol scale and then purified via column chromatography (10-40% EtOAc/Hex) to give a yellow oil (0.495 g, 1.46 mmol, 26% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.37 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.25-7.03 (m, 3H), 4.21 (q, J=7.1 Hz, 2H), 3.19 (s, 1.2H), 2.85 (s, 1.8H), 2.42 (s, 3H), 1.91-1.22 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz); δ 172.2, 171.6, 170.4, 170.2, 159.1, 158.5, 139.9, 139.0, 133.7, 133.5, 116.6, 116.2, 113.0, 112.1, 109.6, 108.8, 61.6, 61.3, 55.5, 55.3, 43.1, 40.4, 36.8, 34.6, 20.5, 19.1 (br), 18.3, 17.4 (br), 14.17, 14.15, -2.4 (br); **FTIR** (cm^{-1}) (neat): 2980, 1727, 1656, 1383, 1193, 1138, 1026, 791, 749; **HRMS** (ESI, Pos) calcd for $C_{15}H_{18}BrNO_3$ $(M+H)^+$: 340.05468, found: 340.05428 *m/z.*

Ethyl 1-(2-bromo-*N*,4-dimethylbenzamido)cyclopropanecarboxylate (1q)

The title compound was prepared by the general synthesis on a 5.68-mmol scale and then purified via column chromatography (10-30% Et_2O/Hex) to give a cream yellow solid (0.975 g, 2.87 mmol, 50% yield over two steps). Reported as a mixture of rotamers. **mp:** 70-74 °C; **R_f:** 0.39 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.38 (d, *J*=9.4 Hz, 1H), 7.22-7.01 (m, 2H), 4.19 (q, *J*=7.1 Hz, 2H), 3.17 (s, 1.3H), 2.85 (s, 1.7H), 2.32 (s, 3H), 1.85-1.11 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 171.9, 171.4, 170.5, 170.4, 140.5, 140.2, 136.2, 135.3, 133.1, 132.7, 128.2, 127.5, 127.4, 126.0, 119.0, 118.3, 61.3, 61.0, 42.9, 40.2, 36.7, 34.4, 20.64, 20.62, 20.4, 18.7 (br), 18.2, 17.7 (br), 14.0, -2.5 (br); **FTIR** (cm^{-1}) (neat): 2980, 1726, 1653, 1380, 1186, 1029, 752; **HRMS** (ESI, Pos) calcd for $C_{15}H_{18}BrNO_3$ $(M+H)^+$: 340.05298, found: 340.05428 *m/z.*

Ethyl 1-(2-bromo-*N*-methylthiophene-3-carboxamido)cyclopropane-1-carboxylate (1r)

The title compound was prepared by the general synthesis on a 5.28-mmol scale and then purified via column chromatography (10-60% EtOAc/Hexanes) to give a clear oil (0.7096 g, 2.136 mmol, 40% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.46 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.32-7.26 (m, 1H), 6.92 (s, 1H), 4.16 (t, *J* = 6.5 Hz, 2H), 3.06 (d, *J* = 37.3 Hz, 3H), 1.64-1.16 (m, 7H); **^{13}C NMR** ($CDCl_3$, 75MHz); δ 171.8, 171.0, 164.9, 132.36,

132.33, 131.7, 129.88, 129.78, 127.2, 126.2, 110.5, 109.4, 61.6, 61.0, 43.1, 40.6, 37.2, 34.9, 21.5, 18.4, 13.8; **FTIR** (cm^{-1}) (neat): 2980, 1725, 1643, 1123, 909.6, 751.4, 551.1; **HRMS** (ESI, Pos) calcd for $C_{12}H_{14}BrNO_3S$ $(M+H)^+$: 331.99659, found: 331.99505 *m/z.*

Ethyl 1-(2-bromo-*N*-methylnicotinamido)cyclopropane-1-carboxylate (1s)

The title compound was prepared by the general synthesis on a 9.111-mmol scale and then purified via column chromatography (10-60% EtOAc/Hexanes) to give a brown oil (0.770 g, 2.354 mmol, 28% yield over two steps). Reported as a mixture of rotamers. **R_f:** 0.46 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 8.43-8.38 (m, 1H), 7.67-7.24 (m, 2H), 4.25-4.19 (m, 2H), 3.19 (s, 1.6H), 2.92 (s, 1.8H), 1.52-1.21 (m, 7H); **^{13}C NMR** ($CDCl_3$, 101MHz); δ 172.0, 171.4, 169.2, 168.7, 150.4, 150.1, 139.2, 138.1, 136.7, 136.4, 135.6, 134.9, 123.1, 122.2, 61.9, 61.60, 61.55, 43.2, 40.7, 37.0, 34.8, 20.9, 18.4, 14.30, 14.28; **FTIR** (cm^{-1}) (neat): 2980, 1724, 1652, 1381, 1036, 754.1, 454.1; **HRMS** (ESI, Pos) calcd for $C_{13}H_{15}BrN_2O_3$ $(M+H)^+$: 327.03505, found: 327.03388 *m/z.*

1-(2-bromophenyl) 1-ethyl cyclopropane-1,1-dicarboxylate (1u)

The title compound was prepared as directed (see SM synthesis) on a 8.283-mmol scale and then purified via column chromatography (10-60% EtOAc/Hexanes) to give a light yellow oil (1.729 g, 5.301 mmol, 64% yield over two steps). **R_f:** 0.48 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.68-7.63 (m, 1H), 7.39-7.20 (m, 3H), 4.35-4.02 (m, 2H), 3.33 (s, 0.9H), 3.26 (s, 2H), 1.67-0.97 (m, 7H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.3, 171.0, 168.1, 167.8, 142.4, 141.8, 134.0, 133.6, 130.3, 129.8, 129.32, 129.30, 128.8, 128.5, 123.2, 122.4, 61.7, 61.3, 37.8, 37.3, 30.2, 29.3, 17.1, 16.5, 16.2, 14.9, 14.4, 14.2; **FTIR** (cm^{-1}) (neat): 2979, 1720, 1655, 1584, 1476,1436, 1368, 1057, 765.0, 729.7, 455.6; **HRMS** (ESI, Pos) calcd for $C_{14}H_{16}BrNO_3$ $(M+H)^+$: 326.03966, found: 326.03863 *m/z.*

General Procedure A for Pd-Catalyzed Cyclization

A 5.0-mL microwave vial containing 2-halobenzamide (0.5 mmol) was taken into a glovebox and to this was added in the following order: $Pd(OAc)_2$ (5 mol %, 0.025 mmol, 5.6 mg), PCy_3 (5 mol %, 0.025 mmol, 7.0 mg), and K_2CO_3 (1.5 equiv, 0.75 mmol, 104 mg). The vial was crimped shut. Outside of the glovebox was added 2.5 mL of toluene. The yellowish-orange solution was then heated to 110 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% Ethyl Acetate/Hexanes to give the desired products**.**

General Procedure B for Pd-Catalyzed Cyclization

A 5.0-mL microwave vial containing 2-bromobenzamide (0.5 mmol) was taken into a glovebox and to this was added in the following order: $Pd(OAc)_2$ (5 mol %, 0.025 mmol, 5.6 mg), P*t*Bu_2Me•HBF_4 (5 mol %, 0.025 mmol, 6.2 mg), CsOPiv (0.3 equiv, 0.15 mmol, 35.1 mg), K_3PO_4 (1.5 equiv, 0.75 mmol, 159 mg). The vial was crimped shut. Outside of the glovebox was added 2.5 mL of toluene. The yellowish-orange solution was then heated to 110 °C in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% Ethyl Acetate/Hexanes to give the resulting products.

General Procedure C for Pd-Catalyzed Cyclization

Preocedure C was identical to Procedure A except 0.3 equivalents of Ag_3PO_4 was additionally added in a glovebox.

Ethyl 2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2a)

The title compound was prepared by general procedure A on a 0.9921-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a pale yellow solid in 96% yield (0.2339g, 0.9536 mmol). **R_f:** 0.46 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 8.14-8.12 (m, 1H), 7.48-7.41 (m, 1H), 7.36-7.30 (m, 2H), 4.33-4.14 (m, 2H), 3.24 (s, 3H), 2.72 (dd, *J* = 10.4, 7.2 Hz, 1H), 2.15 (dd, *J* = 10.4, 4.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.86 (dd, *J* = 7.2, 4.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz) δ 170.0, 162.3, 136.4, 132.1, 129.1, 128.2, 127.5, 125.1, 62.1, 45.0, 34.7, 26.4, 20.1, 14.3; **FTIR** (cm^{-1}) (neat): 2981, 1720, 1648, 1249, 798.1, 748.9, 523.9; **HRMS** (ESI, Pos) calcd for $C_{14}H_{15}NO_3$ $(M+H)^+$: 246.11316, found: 246.11247 *m/z.*

Ethyl 2-benzyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2b)

The title compound was prepared by general procedure A on a 0.4994-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a yellow crystalline solid in 96% yield (0.1282 g, 0.4944 mmol). **mp:** 98-101 °C; **R_f:** 0.45 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 8.25 (d, *J* = 7.8 Hz, 1H), 7.47-7.27 (m, 8H), 5.79 (d, *J* = 14.6 Hz, 1H), 4.49 (d, *J* = 14.6 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.61 (dd, *J* = 10.4, 7.3 Hz, 1H), 1.99 (dd, *J* = 10.5, 5.0 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.46 (dd, *J* = 7.2, 5.0 Hz, 1H);**^{13}C NMR** ($CDCl_3$, 101MHz) δ 169.7, 161.8, 136.5, 136.3, 132.2, 129.43, 129.35, 128.3, 128.0, 127.5, 127.3, 125.3, 61.9, 49.2, 43.0, 25.1, 21.4, 14.1; **FTIR** (cm^{-1}) (neat): 3002, 2926, 1722, 1647, 1359, 1105, 7021, 455.8; **HRMS** (ESI, Pos) calcd for $C_{20}H_{19}NO_3$ $(M+Na)^+$: 344.12571, found: 344.12704 *m/z.*

6-methyl-5-oxo-5*H*,6*H*,6a*H*,7*H*,7a*H*-cyclopropa[*c*]isoquinoline-6a-carbonitrile (2d)

The title compound was prepared by general procedure B on a 0.1975-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light cream-colored solid in 42% yield (0.01644 g, 0.08295 mmol). **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz); δ 8.17-8.15 (m, 1H), 7.54-7.51

(m, 1H), 7.44-7.39 (m, 2H), 3.38 (s, 3H), 3.02-2.97 (m, 1H), 2.01-1.97 (m, 1H), 0.99-0.96 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75MHz): δ 160.6, 134.4, 132.6, 129.4, 128.19, 128.10, 124.2, 117.5, 77.4, 77.0, 76.5, 33.1, 23.5, 21.4**; FTIR** (cm^{-1}) (neat): 3095, 2921, 2237, 1655, 1369, 1049, 1027, 753.9, 533.8 ; **HRMS** (ESI, Pos) calcd for $C_{12}H_{10}N_2O$ $(M+H)^+$: 199.08659, found: 199.08733 *m/z.*

Ethyl 2-methyl-7-nitro-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2f)

The title compound was prepared by general procedure A on a 0.4995-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light brown crystalline solid in 31% yield (0.0444 g, 0.153 mmol). **mp:** 144-146 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz δ 7.45-7.38 (m, 1H), 7.17-7.14 (m, 1H), 7.06-6.99 (m, 1H), 4.32-4.18 (m, 2H), 3.19 (s, 3H), 2.75-2.71 (m, 1H), 2.17-2.12 (m, 1H), 1.33-1.28 (m, 3H), 0.91-0.87 (m, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 169.8, 161.1, 134.8, 133.7, 132.2, 129.7, 129.1, 126.7, 62.3, 45.1, 34.9, 25.9, 20.2, 14.3 **FTIR** (cm^{-1}) (neat): 3101, 2989, 2908, 1718, 1649, 1214, 1034, 687.4, 483.5; **HRMS** (ESI, Pos) calcd for $C_{14}H_{14}N_2O_5$ $(M+H)^+$: 291.09842, found: 291.09827 *m/z.*

Ethyl 2-methyl-5-nitro-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2g)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a crystalline light brown solid in 58% yield (0.0838 g, 0.2887 mmol). **mp:** 116-117 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 8.97-8.96 (m, 1H), 8.30 (ddd, *J* = 8.4, 2.5, 1.4 Hz, 1H), 7.56 (dd, *J* = 8.4, 1.3 Hz, 1H), 4.35-4.20 (m, 2H), 3.29 (s, 3H), 2.85-2.80 (m,, 1H), 2.33-2.28 (m, 1H), 1.34-1.30 (m, 3H), 1.01-0.98 (m, 1H).; **^{13}C NMR** ($CDCl_3$, 101MHz): δ 169.1, 160.1, 147.6, 143.3, 129.7, 126.65, 126.48, 124.7, 62.5, 45.6, 35.0, 26.0, 21.0, 14.3; **FTIR** (cm^{-1}) (neat): 2931, 1728, 1645, 1242, 1034, 783.1, 504.1, 448.7; **HRMS** (ESI, Pos) calcd for $C_{14}H_{14}N_2O_5$ $(M+H)^+$: 291.09842, found: 291.09755 *m/z.*

Ethyl 5-fluoro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2h)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline solid in 81% yield (0.1071 g, 0.4068 mmol). **mp:** 80-82 °C; **R_f:** 0.5 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.85 (dt, *J* = 9.3, 2.2 Hz, 1H), 7.38-7.35 (m, 1H), 7.19 (ddd, *J* = 9.1, 7.4, 2.8 Hz, 1H), 4.32-4.21 (m, 2H), 3.27 (s, 3H), 2.76-2.72 (m, 1H), 2.17 (ddd, *J* = 10.3, 4.7, 1.6 Hz, 1H), 1.35-1.31 (m, 3H), 0.87 (ddd, *J* = 7.2, 4.7, 1.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 169.7, 162.4 (d, *J*=246.3 Hz), 161.1, 132 (d, *J*= 3.2 Hz), 130 (d, *J*= 7.6 Hz), 127.1 (d, *J*= 7.7 Hz), 119.4 (d, *J*= 22.3 Hz), 115.6 (d, *J*= 23.8 Hz), 62.1, 44.9, 34.7, 25.7, 19.9, 14.2; **^{19}F NMR** ($CDCl_3$, 282MHz): δ -113.5 (m); **FTIR** (cm^{-1}) (neat): ; 2928, 1722, 1646, 1194, 1077, 533.9, 447.2; **HRMS** (ESI, Pos) calcd for $C_{14}H_{14}FNO_3$ $(M+H)^+$: 264.10432, found: 264.10305 *m/z*.

Ethyl 6-fluoro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2i)

The title compound was prepared by general procedure A on a 0.4838-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a yellow solid in 96% yield (0.1224 g, 0.4649 mmol). **R_f:** 0.48 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 8.16-8.11 (m, 1H), 7.05-6.97 (m, 2H), 4.32-4.17 (m, 2H), 3.22 (s, 3H), 2.71-2.65 (m, 1H), 2.20-2.14 (m, 1H), 1.32-1.27 (m, 3H), 0.89 (m, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 169.7, 165.1 (d, *J* = 253.7 Hz), 161.5, 139.1 (d, *J*=9.4Hz), 132.1 (d, *J*=9.6 Hz), 121.5 (d, *J*=2.7 Hz), 115.1 (d, *J*=21.7 Hz), 114.8 (d, *J*= 22.5 Hz), 62.2, 45.2, 34.7, 26.12, 26.09, 20.3, 14.3 ; **^{19}F NMR** ($CDCl_3$, 282MHz): δ -107.2 (m); **FTIR** (cm^{-1}) (neat): 2924, 1727, 1646, 1242, 995.2, 685.2, 497.1; **HRMS** (ESI, Pos) calcd for $C_{14}H_{14}FNO_3$ $(M+H)^+$: 264.10424, found: 264.10305 *m/z*.

Ethyl 5,6-difluoro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2j)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a yellow solid in 81% yield (0.1365 g, 0.4853 mmol). **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.99-7.93 (m, 1H), 7.21-7.16 (m, 1H), 4.35-4.20 (m, 2H), 3.25 (s, 3H), 2.68 (ddd, *J* = 11.2, 6.0, 2.2 Hz, 1H), 2.21-2.17 (m, 1H), 1.35-1.31 (m, 3H), 0.91 (ddd, *J* = 7.0, 4.8, 2.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 169.4, 160.4, 154.4 (d, *J*= 13.5 Hz), 153 (d, *J*=235.4 Hz), 151.3 (d, *J*= 12.8 Hz), 152.8 (d, *J*= 234.7 Hz), 151.1 (d, *J*= 13.5 Hz), 148 (d, *J*= 12.8 Hz), 133.6 (d, *J*= 3.7 Hz), 133.5 (d, *J*= 3.8 Hz), 122.4 (d, J= 3.2 Hz), 122.3 (d, J= 3.2), 118.3 (d, J=19.2 Hz), 118.3 (d, J=19.2 Hz), 116.9 (d, J= 18.5 Hz), 62.2, 45.0, 34.6, 19.9, 14.1; **^{19}F NMR** ($CDCl_3$, 282MHz): δ -133.1 (m), -139.5 (m); **FTIR** (cm^{-1}) (neat): 3055, 2931, 1727, 1650, 1337, 1267, 720.4, 504.1, 411.7; **HRMS** (ESI, Pos) calcd for $C_{14}H_{13}F_2NO_3$ $(M+H)^+$: 282.0945, found: 282.09363 *m/z*.

Ethyl 5-chloro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2k)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline yellow solid in 73% yield (0.1024 g, 0.3661 mmol). **mp:** 79-80 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 8.08-8.08 (m, 1H), 7.38 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.28-7.22 (m, 1H), 4.28-4.15 (m, 2H), 3.21 (s, 3H), 2.67 (dd, *J* = 10.3, 7.2 Hz, 1H, 2.14 (dd, *J* = 10.4, 4.7 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.83 (dd, *J* = 7.2, 4.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 169.8, 161.1, 134.8, 133.7, 132.2, 129.7, 129.1, 126.7, 62.3, 45.1, 34.9, 25.9, 20.2, 14.3 **FTIR** (cm^{-1}) (neat): 2977, 1727, 1596, 1170, 974.9, 791.4, 695.3, 458.6 ; **HRMS** (ESI, Pos) calcd for $C_{14}H_{14}ClNO_3$ $(M+H)^+$: 280.07436, found: 280.0735 *m/z*.

Ethyl 6-chloro-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2l)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light yellow solid in 87% yield (0.1217 g, 0.4351 mmol). **mp:** 108-110 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.50 (s, 1H), 4.32-4.20 (m, 2H), 3.96-3.91 (m, 9), 3.24 (s, 3H), 2.90-2.83 (m, 1H), 2.22-2.12 (1H), 1.38-129 (m, 3H), 0.83-0.80 (m, 1H).; **^{13}C NMR** ($CDCl_3$, 75MHz): δ 170.3, 162.0, 152.8, 150.8, 145.5, 123.5, 120.8, 107.5, 62.1, 61.4, 61.1, 56.3, 44.9, 34.8, 21.8, 19.1, 14.3; **FTIR** (cm^{-1}) (neat): 2919, 1724, 1650, 1246, 1216, 927.5, 738.9, 546.1, 449.0; **HRMS** (ESI, Pos) calcd for $C_{14}H_{14}ClNO_3$ $(M+H)^+$: 280.07433, found: 280.0735 *m/z*.

Ethyl 5-methoxy-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2m)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give an off-white crystalline solid in 71% yield (0.0982 g, 0.3567 mmol). **mp:** 78-80 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.66 (d, J = 2.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.4, 2.8 Hz, 1H), 4.24 (dtd, J = 19.8, 12.6, 7.2 Hz, 2H), 3.83 (s, 3H), 3.25 (s, 3H), 2.69 (dd, J = 10.2, 7.2 Hz, 1H), 2.11 (dd, J = 10.2, 4.5 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 0.81 (dd, J = 7.2, 4.5 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.1, 162.2, 159.1, 129.3, 128.5, 126.1, 119.9, 112.0, 62.0, 55.6, 44.8, 34.7, 25.9, 19.8, 14.2; **FTIR** (cm^{-1}) (neat): 2933, 1726, 1650, 1278, 1079, 859.0, 576.7; **HRMS** (ESI, Pos) calcd for $C_{15}H_{17}NO_4$ $(M+H)^+$: 276.12383, found: 276.12303 *m/z*.

Ethyl 5,6-dimethoxy-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2n)

The title compound was prepared by general procedure A on a 0.4971-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light beige crystalline solid in 93% yield (0.1413 g, 0.4628 mmol). **mp:** 124-126 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.62 (s, 1H), 6.80 (s, 1H), 4.30-4.17 (m, 2H), 3.91 (d, *J* = 7.9 Hz, 6H), 3.22 (s, 3H), 2.66 (dd, *J* = 10.1, 7.2 Hz, 1H), 2.13-2.09 (m, 1H), 1.32-1.28 (m, 3H), 0.81 (dt, *J* = 7.5, 2.9 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.1, 162.3, 152.3, 148.4, 130.1, 117.9, 111.0, 110.0, 62.0, 56.17, 56.14, 44.9, 34.6, 26.2, 19.5, 14.2; **FTIR** (cm^{-1}) (neat): 3000, 2840, 1712, 1646, 1265, 847.9, 649.4, 514.1 ; **HRMS** (ESI, Pos) calcd for $C_{16}H_{19}NO_5$ $(M+H)^+$: 306.1346, found: 306.1336 *m/z.*

Ethyl-5,6,7-trimethoxy-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H* cyclopropa[*c*]isoquinoline-1a-carboxylate (2o)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a white solid in 86% yield (0.1448 g, 0.4318 mmol). **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.50 (s, 1H), 4.32-4.20 (m, 2H), 3.96-3.91 (m, 9), 3.24 (s, 3H), 2.90-2.83 (m, 1H), 2.22-2.12 (1H), 1.38-129 (m, 3H), 0.83-0.80 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75MHz): δ 170.3, 162.0, 152.8, 150.8, 145.5, 123.5, 120.8, 107.5, 62.1, 61.4, 61.1, 56.3, 44.9, 34.8, 21.8, 19.1, 14.3; **FTIR** (cm^{-1}) (neat): 2939, 1727, 1649, 1595, 1415, 1096, 700, 519.4; **HRMS** (ESI, Pos) calcd for $C_{17}H_{21}NO_6$ $(M+H)^+$: 336.14416, found: 336.14524 *m/z.*

Ethyl 2,7-dimethyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2p)

The title compound was prepared by general procedure A on a 0.4994-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light orange solid in 99% yield (0.1282 g, 0.4944 mmol). **R_f:** 0.45 (1:1

ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 300MHz): δ 7.95-7.92 (m, 1H), 7.24-7.13 (m, 2H), 4.27-4.10 (m, 2H), 3.16 (s, 3H), 2.57 (dd, *J* = 10.3, 7.3 Hz, 1H), 2.34 (s, 3H), 2.11 (dd, *J* = 10.4, 4.3 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.78 (dd, *J* = 7.3, 4.4 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz) δ 170.4, 162.5, 136.1, 134.9, 133.3, 127.1, 62.1, 44.7, 34.7, 24.3, 18.89, 18.81, 14.2; **FTIR** (cm^{-1}) (neat): 2922, 2852, 1715, 1645, 1368, 750.1, 723.7, 431.4; **HRMS** (ESI, Pos) calcd for $C_{15}H_{17}NO_3$ $(M+H)^+$: 260.12922, found: 260.12812 *m/z*.

Ethyl 2,6-dimethyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2q)

The title compound was prepared by general procedure A on a 0.4988-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline yellow solid in 99% yield (0.128 g, 0.4938 mmol). **mp:** 104-105 ºC; **R_f:** 0.45 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.99 (d, *J* = 7.5 Hz, 1H), 7.14-7.10 (m, 2H), 4.29-4.15 (m, 2H), 3.21 (s, 3H), 2.66 (dd, *J* = 9.8, 7.2 Hz, 1H), 2.34 (s, 3H), 2.11 (dd, *J* = 10.4, 7.2 Hz, 1H), 1.29-1.25 (m, 3H), 0.83-0.80 (m, 1H); **^{13}C NMR** ($CDCl_3$, 101MHzδ 169.9, 162.3, 142.6, 136.3, 129.0, 128.5, 128.3, 122.4, 61.9, 44.9, 34.4, 26.3, 21.4, 19.9, 14.1; **FTIR** (cm^{-1}) (neat): 2975, 1719, 1649, 1210, 1138, 613.4, 501.3; **HRMS** (ESI, Pos) calcd for $C_{15}H_{17}NO_3$ $(M+H)^+$: 260.12916, found: 260.12812 *m/z*.

Ethyl 5-methyl-4-oxo-4,5,6,6a-tetrahydro-5a*H*-cyclopropa[*b*]thieno[2,3-*d*]pyridine-5a-carboxylate (2r)

The title compound was prepared by general procedure A on a 0.4985-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light crystalline yellow solid in 33% yield (0.04134 g, 0.1645 mmol). **mp:** 78-80 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.49 (d, *J* = 5.0 Hz, 1H), 7.05 (d, *J* = 5.0 Hz, 1H), 4.30-4.17 (m, 2H), 3.21 (s, 3H), 2.73 (dd, *J* = 10.1, 7.1 Hz, 1H), 2.15 (dd, *J* = 10.1, 4.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.84 (dd, *J* = 7.1, 4.8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 169.8, 159.3, 141.9, 132.2, 129.3, 127.2, 62.2, 46.6, 33.7, 25.2, 18.2,

14.3 ; **FTIR** (cm^{-1}) (neat): 3097, 2981, 1719, 1635, 1234, 1166, 485.6, 468.2; **HRMS** (ESI, Pos) calcd for $C_{12}H_{13}NO_3S$ $(M+H)^+$: 252.06988, found: 252.06889 *m/z.*

Ethyl 6-methyl-5-oxo-5,6,7,7a-tetrahydro-6a*H*-cyclopropa[*h*][1,6]naphthyridine-6a-carboxylate (2s)

The title compound was prepared by general procedure A on a 0.5-mmol scale and then purified via column chromatography over silica gel using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a bright yellow crystalline solid in 67% yield (0.0821 g, 0.3334 mmol). **mp:** 78-80 ºC; **R_f:** 0.44 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz) δ 8.63 (d, *J* = 3.2 Hz, 1H), 8.40-8.37 (m, 1H), 7.35-7.28 (m, 1H), 4.33-4.17 (m, 2H), 3.27 (s, 3H), 3.02-2.96 (m, 1H), 2.32-2.26 (m, 1H), 1.30 (m, 3H), 1.02-0.94 (m, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 169.2, 161.6, 155.5, 152.5, 136.8, 122.8, 121.1, 62.1, 44.9, 34.4, 28.5, 19.8, 14.1; **FTIR** (cm^{-1}) (neat): 3105, 2981, 1725, 1585, 1446, 1421, 726.1, 489.3; **HRMS** (ESI, Pos) calcd for $C_{13}H_{14}N_2O_3$ $(M+H)^+$: 247.10895, found: 247.10772 *m/z.*

Ethyl 3-methyl-2-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]quinoline-1a-carboxylate (2u)

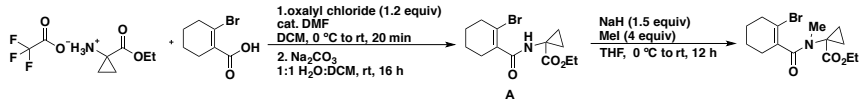
The title compound was prepared by general procedure A on a 0.4936-mmol scale and then purified via column chromatography over silica using a solvent gradient of 10% to 50% ethyl acetate/hexanes to give a light yellow solid in 93% yield (0.1129 g, 0.4603 mmol). **R_f:** 0.48 (1:1 ethyl acetate: hexanes); **^{1}H NMR** ($CDCl_3$, 400MHz): δ 7.37-7.35 (m, 1H), 7.31-7.27 (m, 1H), 7.10-7.06 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 4.30-4.24 (m, 2H), 3.39 (d, *J* = 1.1 Hz, 3H), 2.83-2.79 (m, 1H), 2.32 (ddd, *J* = 9.3, 4.6, 1.2 Hz, 1H), 1.35-1.29 (m, 3H), 1.07 (ddd, *J* = 6.7, 4.2, 1.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 168.9, 165.0, 137.3, 128.5, 127.9, 122.9, 122.1, 114.8, 30.8, 29.6, 29.1, 17.2, 14.3; **FTIR** (cm^{-1}) (neat): 2928, 1718, 1655, 1363, 1303, 1048, 747.4, 679.5; **HRMS** (ESI, Pos) calcd for $C_{14}H_{15}NO_3$ $(M+H)^+$: 246.11366, found: 246.11247 *m/z.*

Experimental Section for Chapter 3

Synthesis of Starting Materials.

Starting materials not listed below were obtained commercially and the reagents were used without further purification. Ethyl 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylate was synthesized according to literature procedure[5] and converted to its TFA salt for subsequent use.[6] 2-bromocycloalkenyl carboxylic acids were synthesized via a Vilsmeier-Haack formylation[7] followed by Pinnick oxidation as reported in the literature (Scheme 1).[8][9]

General procedure for synthesis of 2-bromocycloalkenyl amides (example for 1a shown below)



To a 100 mL flask flamed-dried and cooled under Ar was added DCM, cat. DMF, and 2-bromocyclohex-1-ene-1-carboxylic acid (3.07 g, 14.97 mmol). To this was added oxalyl chloride (1.5 mL, 17.97 mmol) (bubbling observed). The reaction was stirred for 45 minutes (opaque white turned bright yellow). To a 500 mL flask was added sodium carbonate (31.7 g, 299.4 mmol) and distilled water (300 mL), followed by 1-(ethoxycarbonyl)cyclopropan-1-aminium trifluoroacetate (3.82 g, 15.72 mmol) and stirred for 15 min. The acyl chloride was then added via canula into the TFA salt solution (gas evolved), then the mixture was stirred for 16 h. The reaction was poured into a 500 mL separatory funnel, the layers were separated, and the aqueous layer extracted with DCM (3x's, 150 mL each). The combined organics were then washed with brine (200 mL), dried over Mg_2SO_4 anhydrous, filtered and concentrated *in vacuo* to give an off-white solid in 72% yield (3.42 g, 10.84 mmol) after column chromatography (0-30% hexanes:ethyl acetate). Intermediate **A** could also be used crude in subsequent *N*-protections.

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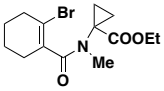
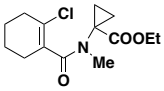
[5] Allwein, S. P.; Secord, E. A.; Martins, A.; Mitten, J. V.; Nelson, T. D.; Kress, M. H.; Dolling, U. H. *Synlett* **2004**, 2489.
[6] Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc,* **1988**, *110*, 2237.
[7] Gogoi, Junali; Gogoi, Pranjal; Boruah, Romesh C. *Eur. J. Org. Chem*., **2014** , *16*, 3483.
[8] Gogoi, Junali; Gogoi, Pranjal; Boruah, Romesh C. *Eur. J. Org. Chem*., **2014** , *16*, 3483.
[9] Ren, H.; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 3462.

To a 250 mL rbf containing 150 mL of THF was added intermediate **A** (6.88g, 21.75 mmol). The reaction was cooled to 0 ºC, and NaH (1.31 g, 32.62 mmol) was then added. After stirring for 15 min, MeI (6.8 mL, 108.8 mmol) was then added dropwise. The reaction was then let stir for 16 h before quenching with 75 mL brine and 75 mL of EtOAc. The reaction was transferred to a 250 mL separatory funnel. The layers were then separated and the aq. layer was then extracted with EtOAc (3x's, 200 mL). The combined organics were then washed with brine (1x, 150 mL), dried over Na_2SO_4 anhydrous, filtered and concentrated *in vacuo* to give **1a** as pale yellow solid (76% yield, 5.48 g, 16.58 mmol) after column chromatography (0-30% hexanes:ethyl acetate). All starting materials are reported as mixtures of rotamers.



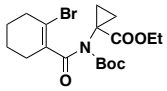
Ethyl 1-[*N*-methyl(2-bromocyclohex-1-en-1-yl)amido]cyclopropane-1-carboxylate (1a)
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11 (q, *J* = 7.1 Hz, 2H), 2.99 (s, 3H), 2.46-2.39 (m, 3H), 2.22-1.91 (m, 1H), 1.72-1.63 (m, 5H), 1.49-1.33 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.15-1.13 (m, 1H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 172.1, 171.9, 171.6, 136.7, 134.7, 120.9, 119.5, 66.9, 61.8, 61.3, 42.3, 40.1, 35.9, 35.6, 35.3, 34.9, 28.4, 24.21, 24.17, 22.0, 21.51, 21.35, 20.4 (br), 19.3 (br), 18.9, 17.2, 14.3, 10.5 **FTIR** (cm^{-1}) (neat): 2954, 1718, 1646, 1384, 1189, 1019, 681.0, 458.6; **HRMS** (ESI, Pos) calcd for $C_{14}H_{21}BrNO_3$ $(M+H)^+$ 330.06993: found: 330.07102 *m/z.*



Ethyl 1-(2-chloro-*N*-methylcyclohex-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1ab)

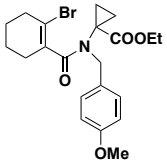
The title compound **1ab** was prepared by the general synthesis on a 4.71 mmol scale and then purified via column chromatography (0-30% Hex:EtOAc) to give a light yellow oil in 62% yield (1.02 g, 3.58 mmol) over two steps. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.02 (s, 3H), 2.42-2.39 (m, 3H), 2.18-2.14 (m, 1H), 1.74-1.60 (m, 5H), 1.48-1.35 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.15-1.14 (m, 1H). ; **^{13}C NMR** ($CDCl_3$, 75MHz): δ 171.9, 171.6, 171.4, 136.52, 136.51, 134.52, 134.48, 120.6, 119.2, 66.7, 61.6, 60.2, 42.1, 39.9, 35.7, 35.4, 34.7, 30.8, 28.2, 24.00, 23.96, 21.8, 21.3, 19.0, 18.6, 16.9, 14.0, 10.3; **FTIR** (cm^{-1}) (neat): 2956, 1717, 1477, 1075,

989.9, 857.9, 642.8, 459.1; **HRMS** (ESI, Pos) calcd for $C_{14}H_{21}ClNO_3$ $(M+H)^+$: 286.12045 found: 286.12126 *m/z.*



Ethyl 1-(2-bromo-*N*-(*tert*-butoxycarbonyl)cyclohex-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1b)

To a 50 mL rbf containing DCM was added intermediate **A** (0.28 g, 0.8855 mmol), DMAP (0.177 g, 1.45 mmol), Boc_2O (1.16 g, 5.313 mmol) and NEt_3 (0.17 mL, 1.274 mmol). The reaction was then let stir for 16 h at rt before quenching with 50 mL brine. 50 mL of DCM was then added, and the reaction was transferred to a 250 mL separatory funnel. The layers were then separated and the aqueous layer was then extracted with DCM (3x's, 50 mL). The combined organics were then washed with brine (1x, 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a white solid in 77% yield (0.2839 g, 0.6819 mmol) after flash (0-30% hexanes: ethyl acetate). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.05 (s, 3H), 2.72-2.39 (m, 4H), 2.06-2.00 (m, 2H), 1.64-1.45 (m, 2H), 1.27-1.23 (m, 5H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 14.21, 19.08, 20.71, 21.25, 23.95, 27.98, 28.97, 35.85, 38.23, 61.35, 83.13, 84.17, 118.29, 135.81, 151.96, 163.47, 171.59, 171.87;**FTIR (cm^{-1})** (neat): 2935, 1726, 1667, 1317, 1150, 770.7, 439.7 ; **HRMS** (ESI, Pos) calcd for $C_{18}H_{25}NNaO_5$ $(M+H)^+$: 358.16249 found: 358.16137 *m/z.*

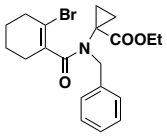


Ethyl 1-(2-bromo-*N*-(4-methoxybenzyl)cyclohex-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1c)

The title compound **1c** was prepared by the general synthesis on a 7.581 mmol scale, except ethyl 1-{[(4-methoxyphenyl)methyl]amino}cyclopropane-1-carboxylate[10] was substituted for the TFA salt and the product was then purified via column chromatography (30% Hex: EtOAc) to give a

[10] Pedroni, J.; Cramer, N. *Angew. Chem. Int. Ed.* **2015**, *54*,11826.

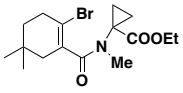
pale yellow solid in 53% yield (1.753 g, 4.017 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.32-7.24 (s, 2H), 6.88-6.85 (m, 2H), 5.36-4.62 (m, 2H), 4.39-3.96 (m, 2H), 3.81 (d, *J* = 3.3 Hz, 3H), 2.50-2.30 (m, 3H), 2.05-1.70 (m, 6H), 1.27-1.14 (m, 5H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 173.0, 172.7, 171.9, 171.3, 159.2, 158.7, 135.1, 133.3, 130.7, 130.34, 130.32, 129.14, 129.05, 128.7, 120.1, 113.8, 69.6, 68.8, 65.0, 61.9, 61.2, 55.37, 55.29, 52.98, 52.81, 51.78, 51.68, 42.1, 39.4, 37.3, 35.73, 35.55, 35.52, 29.3, 28.9, 28.6, 24.26, 24.09, 21.71, 21.58, 21.52, 21.45, 21.27, 19.2, 17.74, 17.71, 17.63, 14.22, 14.11; **FTIR** (cm^{-1}) (neat): 2936, 1716, 1626, 1512, 1246, 1028, 812.6, 586.9 ; **HRMS** (ESI, Pos) calcd for $C_{21}H_{26}BrNO_4$ $(M+H)^+$: 436.1118 found: 436.11367 *m/z.*



Ethyl 1-(*N*-benzyl-2-bromocyclohex-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1d)

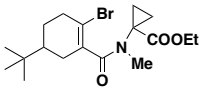
To a 50 mL rbf containing THF was added intermediate **A** (0.3162 g, 1.0 mmol). The reaction was cooled to 0ºC, and NaH (60.0 mg, 1.5 mmol) was then added. After stirring for 15 min, benzyl bromide (0.48 mL, 4.0 mmol) was then added dropwise. The reaction was then let stir for 16 h before quenching with 50 mL brine. EtOAc was then added (50 mL), and the reaction was transferred to a 250 mL separatory funnel. The layers were then separated and the aqueous layer was then extracted with EtOAc (3x's, 50 mL). The combined organics were then washed with brine (1x, 50 mL), dried over Na2SO4, filtered and concentrated *in vacuo* to give a clear oil in 85% yield (0.3438 g, 0.8461 mmol) after flash (0-30% hexanes: ethyl acetate).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.29 (m, 5H), 5.45-4.41 (m, 2H), 4.19-3.95 (m, 2H), 2.57-2.30 (m, 3H), 2.08-1.93 (m, 1H), 1.70-1.65 (m, 6H), 1.29-0.87 (m, 5H). **^{13}C NMR** ($CDCl_3$, 101MHz): δ 173.0, 172.7, 171.98, 171.89, 138.6, 136.71, 136.55, 135.1, 128.9, 128.49, 128.43, 127.82, 127.69, 127.0, 121.1, 120.2, 67.5, 66.8, 61.9, 61.2, 53.7, 42.3, 39.8, 35.76, 35.58, 31.0, 29.4, 28.7, 24.3, 24.0, 21.96, 21.93, 21.6, 21.2, 19.2, 17.8, 14.24, 14.13, 10.56, 10.44; **FTIR** (cm^{-1}) (neat): 2935, 1724, 1646, 1393, 1176, 734.8, 505.6, 453.9; **HRMS** (ESI, Pos) calcd for $C_{20}H_{25}BrNO_3$ $(M+H)^+$: 406.10123 found: 406.10253 *m/z.*



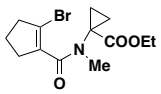
Ethyl 1-(2-bromo-*N*,5,5-trimethylcyclohex-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1e)

The title compound **1e** was prepared by the general synthesis on a 2.087 mmol scale and then purified via column chromatography (30% Hex:EtOAc) to give a golden oil in 39% yield over 2-steps (0.2911 g, 0.8125 mmol). δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.00-2.93 (m, 3H), 2.47-2.46 (m, 2H), 2.26-2.22 (m, 1H), 1.92-1.40 (m, 8H), 1.24-1.20 (m, 5H), 0.98-0.88 (m, 6H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 171.92, 171.84, 171.42, 171.37, 133.80, 133.78, 118.2, 66.9, 61.8, 61.3, 42.2, 41.9, 40.3, 36.78, 36.71, 35.8, 33.6, 33.3, 29.8, 28.67, 28.53, 28.51, 28.46, 27.78, 27.66, 27.0, 22.0, 19.3, 19.0, 14.36, 14.28, 10.5; **FTIR** (cm^{-1}) (neat): 2927, 1728, 1650, 1384, 1190, 1038, 761.1, 541.4; **HRMS** (ESI, Pos) calcd for $C_{16}H_{24}BrNO_3$ $(M+H)^+$: 358.10123 found: 358.1009 *m/z.*



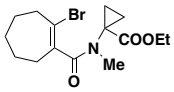
Ethyl 1-(2-bromo-5-(*tert*-butyl)-*N*-methylcyclohex-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1f)

The title compound **1f** was prepared by the general synthesis on a 1.904 mmol scale and then purified via column chromatography (30% Hex:EtOAc) to give a light golden oil in 63% yield over two steps (0.4624 g, 1.197 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.14-4.03 (m, 2H), 2.98 (d, *J* = 19.7 Hz, 3H), 2.50-2.12 (m, 4H), 1.81-1.58 (m, 3H), 1.40-1.13 (m, 7H), 0.83 (d, *J* = 23.5 Hz, 10H); **^{13}C NMR** ($CDCl_3$, 75MHz): δ 171.94, 171.83, 134.8, 134.4, 119.5, 119.0, 67.4, 66.9, 61.8, 61.3, 43.2, 42.93, 42.92, 42.3, 40.1, 36.82, 36.66, 36.58, 36.1, 35.7, 30.1, 27.2, 25.8, 25.5, 22.0, 19.30, 19.27, 17.25, 17.15, 17.12, 14.2, 10.5; **FTIR** (cm^{-1}) (neat): 2959, 1729, 1651, 1383, 1186, 750.6, 680.9; **HRMS** (ESI, Pos) calcd for $C_{18}H_{29}BrNO_3$ $(M+H)^+$: 386.13253 found: 386.1321 *m/z.*



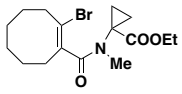
Ethyl 1-(2-bromo-*N*-methylcyclopent-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1g)

The title compound **1g** was prepared by the general synthesis on a 7.795 mmol scale and then purified via column chromatography (0-30% Hex:EtOAc) to give a brown solid in 86% yield (2.124 g, 6.716 mmol) over two steps. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.05 (s, 3H), 2.72-2.39 (m, 4H), 2.06-2.00 (m, 2H), 1.64-1.45 (m, 2H), 1.27-1.23 (m, 5H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.8, 171.1, 169.4, 168.9, 138.8, 136.7, 120.1, 119.0, 77.4, 61.3, 60.8, 41.6, 40.2, 39.9, 39.6, 35.6, 34.15, 34.06, 33.8, 22.7, 21.8, 20.1, 17.9, 13.8; **FTIR** (cm^{-1}) (neat): 2964, 1725,1642, 1187, 1131, 816.9, 691.8, 538.1; **HRMS** (ESI, Pos) calcd for $C_{13}H_{18}BrNO_3$ $(M+H)^+$: 316.05428 found: 316.05407 *m/z.*



Ethyl 1-(2-bromo-*N*-methylcyclohept-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1h)

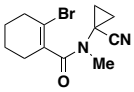
The title compound **1h** was prepared by the general synthesis on a 6.181 mmol scale and then purified via column chromatography (0-30% Hex:EtOAc) to give a bright yellow oil in 13% yield (0.2814 g, 0.8174 mmol) over two steps **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.05 (s, 3H), 2.72-2.39 (m, 4H), 2.06-2.00 (m, 2H), 1.64-1.45 (m, 2H), 1.27-1.23 (m, 5H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.8, 171.1, 169.4, 168.9, 138.8, 136.7, 120.1, 119.0, 61.3, 60.8, 41.6, 40.2, 39.9, 39.6, 35.6, 34.14, 34.06, 33.8, 22.7, 21.8, 20.1, 17.9 (br), 13.8; **FTIR** (cm^{-1}) (neat): 2925, 1727, 1647, 1382, 1185, 1039, 753.2, 644.5, 502.5; **HRMS** (ESI, Pos) calcd for $C_{15}H_{22}BrNO_3$ $(M+H)^+$: 344.08558 found: 344.08457 *m/z.*



Ethyl 1-(2-bromo-*N*-methylcyclooct-1-ene-1-carboxamido)cyclopropane-1-carboxylate (1i)

The title compound **1i** was prepared by the general synthesis on a 1.507 mmol scale and then

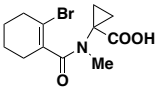
purified via column chromatography (0-30% Hex:EtOAc) to give a golden oil in 38% yield (0.205 g, 0.5708 mmol) over two steps. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.05 (s, 3H), 2.72-2.39 (m, 4H), 2.06-2.00 (m, 2H), 1.64-1.45 (m, 2H), 1.27-1.23 (m, 5H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.8, 171.1, 169.4, 168.9, 138.8, 136.7, 120.1, 119.0, 61.3, 60.8, 41.6, 40.2, 39.9, 39.6, 35.6, 34.14, 34.06, 33.8, 22.7, 21.8, 20.1, 17.9, 13.8; **FTIR** (cm^{-1}) (neat): 2927, 1728, 1647, 1383, 1186, 1110, 1030, 752.5, 637.3; **HRMS** (ESI, Pos) calcd for $C_{16}H_{25}BrNO_3$ $(M+H)^+$: 358.10123 found: 358.10091 *m/z.*



2-Bromo-*N*-(1-cyanocyclopropyl)-*N*-methylcyclohex-1-ene-1-carboxamide (1j)

The title compound **1j** was prepared by the general synthesis using on a 4.682 mmol scale, except 1-amino-1-cyclopropanecarbonitrile hydrochloride was substituted for the TFA salt and then purified via column chromatography (30% Hex:EtOAc) to give a pale light oil in 57% yield over two steps (0.7496 g, 2.647 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz); δ 3.01-2.99 (m, 3), 2.44-2.32 (m, 3H), 2.07-2.04 (m, 1H), 1.68 (s, 6H), 1.34-1.30 (m, 2H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.5, 135.7, 133.6, 121.6, 121.1, 119.76, 119.75, 119.3, 37.3, 35.53, 35.34, 35.27, 35.19, 34.1, 33.9, 29.5, 28.61, 28.44, 27.4, 24.10, 23.98, 21.36, 21.16, 19.2(br), 17.6(br), 16.9(br) **FTIR** (cm^{-1}) (neat): 2935, 2236, 1650, 1370, 1026, 738.9, 593.2, 499.1; **HRMS** (ESI, Pos) calcd for $C_{12}H_{15}BrN_2O$ $(M+H)^+$: 283.04405 found: 283.04471 *m/z.*

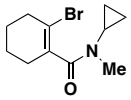
The high temperature ^{1}H NMR for cyano substrate **1j** was additionally taken in d^6-DMSO $(CD_3)_2SO$ as proof of principle for the rotamer nature (ref page XX). Notably, the rotamer peaks coalesce with increasing to a maximum temperature of 110 ºC (identical to the reaction).



1-(2-Bromo-*N*-methylcyclohex-1-ene-1-carboxamido)cyclopropane-1-carboxylic acid (1k)

The title compound **1k** was prepared from **1a** using the saponification procedure described in the

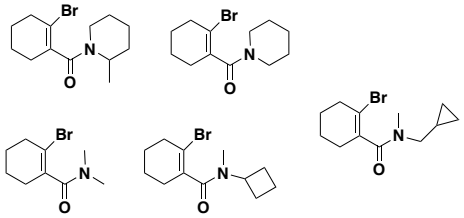
literature[11] on a 1.302 mmol scale and then purified via column chromatography (0-70% Hex:EtOAc) to give a white solid in 50% yield (0.1978 g, 0.6546 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.52 (br s, 1H), 3.01 (s, 3H), 2.48-2.18 (m, 4H), 1.74-1.21 (m, 8H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 177.6, 172.2, 134.5, 120.0, 42.1, 40.0, 36.0, 35.7, 35.4, 28.5, 24.2, 21.4; **FTIR** (cm^{-1})(neat): 2942, 1717, 1580, 1396, 1274, 1200, 948.0, 678.3, 461.6 ; **HRMS** (ESI, Pos) calcd for C12H17BrNO3 $(M+H)^+$: 302.03863 found: 302.03958 *m/z.*



2-Bromo-*N*-cyclopropyl-*N*-methylcyclohex-1-ene-1-carboxamide (1l)

The title compound **1l** was prepared by the general synthesis on a 10.14 mmol scale except cyclopropylamine was substituted for the TFA salt and then purified via column chromatography (30% Hex:EtOAc) to give a golden oil in 40% yield over 2 steps (1.332 g, 4.033 mmol); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.95-2.74 (m, 4H), 2.52-2.36 (m, 3H), 2.22-2.19 (m, 1H), 1.73-1.70 (m, 4H), 0.74 (ddt, *J* = 1.5, 0.8, 0.4 Hz, 4H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 172.7, 172.1, 136.0, 135.1, 132.7, 128.2, 119.5, 35.5, 33.6, 33.0, 31.3, 31.0, 29.5, 29.1, 28.6, 28.2, 24.27, 24.17, 23.5, 21.51, 21.39, 8.5, 6.4 **FTIR** (cm^{-1}) (neat): 2933, 1632, 1383, 1027, 735.3, 647.4 ; **HRMS** (ESI, Pos) calcd for $C_{11}H_{16}BrNO$ $(M+Na)^+$: 258.0488 found: 258.04897 *m/z.*

List of Compounds that Failed to Cyclize



These starting materials were additionally tested under the reaction conditions, with 30% pivalic acid, and at increased temperatures (140 ºC to 160 ºC). No cyclized products were observed, and at higher temperatures a large proportion of protodebromination was observed (>140ºC).

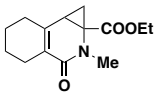
[11] Pieroni, M.; Annunziato, G.; Azzali, E.; Dessanti, P.; Mercurio, C.; Meroni, G.; Trifiró, P.; Vianello, P.; Villa, M.; Beato, C.; Varasi, M.; Costantino, G. *Eur. J. Med. Chem.* **2015**, *92*, 377.

General Procedure A for Pd-Catalyzed Cyclization

A 5.0-mL microwave vial containing 2-cycloalkenyl bromide (0.2 mmol) was taken into a glovebox and to this was added in the following order: $Pd(OAc)_2$ (5 mol%, 0.02 mmol, 2.2 mg), PCy_3 (10 mol%, 0.05 mmol, 5.6 mg), and K_2CO_3 (1.5 equiv, 0.3 mmol, 41.5 mg). The vial was crimped shut. Outside of the glovebox was added 1.0 mL of toluene. The yellowish-orange solution was then heated to 110 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) using a solvent gradient of 10% to 50% Ethyl Acetate/Hexanes to give products **2a-2l.**

General Procedure B for Pd-Catalyzed Cyclization (with Pivalic Acid)

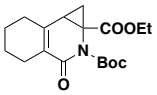
A 5.0-mL microwave vial containing 2-cycloalkenyl bromide (0.2 mmol) and pivalic acid (30 mol%, 0.06 mmol, 6.1 mg) was taken into a glovebox and to this was added in the following order: $Pd(OAc)_2$ (5 mol%, 0.02 mmol, 2.2 mg), PCy_3 (10 mol%, 0.05 mmol, 5.6 mg), and K_2CO_3 (1.5 equiv, 0.3 mmol, 41.5 mg). The vial was crimped shut. Outside of the glovebox was added 1.0 mL of toluene. The yellowish-orange solution was then heated to 110 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) using a solvent gradient of 10% to 50% Ethyl Acetate/Hexanes to give products **2a-2l.**



Ethyl 2-methyl-3-oxo-1,2,3,4,5,6,7,7b-octahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2a)

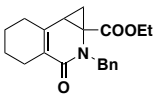
The title compound **2a** was prepared by the general synthesis on a 0.2 mmol scale and then purified via column chromatography (30% Hex:EtOAc) to give a golden oil in 95% yield (47.3 mg, 0.19

mmol). It was also scaled to 1.0 mmol scale to yield **2a** in 98% yield (0.2443 g, 0.98 mmol). Using chloro analogue **1ab** and **procedure B**, access to **2a** in 75% yield was also obtained. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.25-4.09 (m, 2H), 3.06 (s, 3H), 2.28-2.15 (m, 4H), 1.96-1.84 (m, 2H), 1.59 (dd, *J* = 7.1, 4.0 Hz, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.59 (dd, *J* = 6.6, 3.9 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.2, 163.6, 144.2, 124.0, 61.8, 44.2, 34.1, 30.4, 27.6, 23.2, 22.2, 21.7, 17.7, 14.2; **FTIR** (cm^{-1}) (neat): 2930, 1727, 1628, 1368, 1278, 1131, 1021, 750.9, 552.6, 493.6; **HRMS** (ESI, Pos) calcd for $C_{14}H_{19}NO_3$ $(M+H)^+$: 250.14377 found: 250.14309 *m/z.*



2-(*tert*-Butyl) 1a-ethyl 3-oxo-3,4,5,6,7,7b-hexahydro-1*H*-cyclopropa[*c*]isoquinoline-1a,2-dicarboxylate (2b)

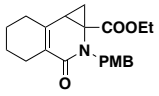
The title compound **2b** was prepared by the general synthesis on a 0.2 mmol scale and then purified via column chromatography (0%-20% Hex:EtOAc) to give a brown oil in 42% yield (28.17 mg, 0.084 mmol). It was also scaled to 0.724 mmol **using procedure B** to yield **2b** in 84% yield (0.205 g, 0.6115 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.22-4.17 (m, 2H), 2.35-2.26 (m, 4H), 2.21 (dd, *J* = 10.2, 4.8 Hz, 1H), 1.92-1.88 (m, 1H), 1.70-1.58 (m, 5H), 1.54 (s, 8H), 1.47 (d, *J* = 1.4 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.89 (dd, *J* = 7.0, 4.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.3, 161.7, 151.8, 147.2, 125.6, 83.4, 62.0, 61.4, 42.8, 30.5, 28.4, 28.1, 26.6, 23.2, 22.1, 21.6, 20.1, 14.2; **FTIR** (cm^{-1}) (neat):2957, 1730, 1631, 1445, 1273, 1132, 751.3, 435.5; **HRMS** (ESI, Pos) calcd for $C_{18}H_{25}NNaO_5$ $(M+Na)^+$: 358.16137, found: 358.16249.



Ethyl 2-benzyl-3-oxo-1,2,3,4,5,6,7,7b-octahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2c)

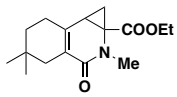
The title compound **2c** was prepared by the general synthesis on a 0.2 mmol scale (81.26 mg) and then purified via column chromatography (30% Hex:EtOAc) to give a pale yellow solid in 98% yield (64.0 mg, 0.1967 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.29 (s, 5H), 5.59 (d, *J* = 14.6 Hz, 1H), 4.37 (d, *J* = 14.6 Hz, 1H), 4.25-4.19 (m, 2H), 2.34-2.27 (m, 4H, 1.85-1.75 (m, 2H), 1.67-1.65 (m, 5H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.23 (dd, *J* = 6.4, 4.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ

170.0, 163.2, 144.4, 136.9, 129.56, 129.51, 128.4, 127.5, 124.5, 61.9, 48.8, 42.5, 30.5, 26.7, 23.5, 22.3, 21.8, 19.3, 14.3, 10.6; **FTIR** (cm^{-1}) (neat): 2936,1717, 1665, 1628, 1289, 1185, 719.2, 693.6, 501.11, 455.4; **HRMS** (ESI, Pos) calcd for $C_{20}H_{23}NO_3$ $(M+H)^+$: 326.17507 found: 326.17397 *m/z.*



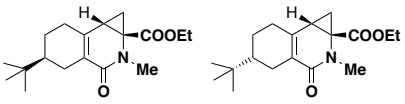
Ethyl 2-benzyl-3-oxo-1,2,3,4,5,6,7,7b-octahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2d)

The title compound **2d** was prepared by the general synthesis on a 0.1987 mmol scale and then purified via column chromatography (30% Hex:EtOAc) to give a pale yellow oil in 69% yield (48.5 mg, 0.1365 mmol). Using **procedure B**: 76% yield (52.9 mg, 0.1488 mmol). It was also scaled to 1.02 g scale using **procedure B** to yield **2d** in 80% yield (661 mg, 1.86 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.84-6.82 (m, 2H), 5.61 (dd, *J* = 14.5, 10.0 Hz, 1H), 5.09 (t, *J* = 6.3 Hz, 0.3H), 4.28-4.22 (m, 2.4H, 3.81 (s, 3H), 2.32-2.24 (m, 4H), 1.85-1.60 (m, 7H), 1.31-1.28 (m, 4H), 0.18 (ddd, *J* = 7.8, 6.6, 6.1 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 169.9, 169.3, 162.8, 158.8, 144.0, 130.7, 128.8, 124.3, 113.5, 69.4, 61.7, 55.2, 47.7, 42.1, 30.3, 26.4, 23.3, 22.1, 21.6, 19.2, 14.1; **FTIR** (cm^{-1}) (neat): 2934, 1725, 1626, 1511, 1247, 1030, 819.3, 746.9, 595.3, 520.4; **HRMS** (ESI, Pos) calcd for $C_{21}H_{25}NO_4$ $(M+H)^+$: 356.18563 found: 356.18677 *m/z.*



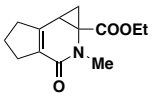
1a-((Ethylperoxy)-λ^2-methyl)-2,5,5-trimethyl-1,1a,2,4,5,6,7,7b-octahydro-3*H*-cyclopropa[*c*]isoquinolin-3-one (2e)

The title compound **2e** was prepared by the general synthesis on a 0.1987 mmol scale and then purified via column chromatography (30% Hex:EtOAc) to give a pale light oil in 84% yield (46.3 mg, 0.1669 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.28-4.15 (m, 2H), 3.10 (s, 3H), 2.35-2.28 (m, 2H), 2.14-2.04 (m, 2H), 2.00-1.92 (m, 2H), 1.41-1.35 (m, 2H), 1.32-1.25 (m, 3H), 0.93 (s, 3H), 0.89 (s, 3H), 0.61 (dd, *J* = 6.4, 3.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.1, 163.7, 142.8, 122.9, 61.7, 44.2, 36.6, 34.27, 34.09, 28.9, 28.4, 28.06, 27.88, 27.1, 17.7, 14.1; **FTIR** (cm^{-1}) (neat): 3266, 2955, 1729, 1666, 1629, 1265, 1132, 1021, 753.8, 514.8; **HRMS** (ESI, Pos) calcd for $C_{16}H_{23}NO_3$ $(M+H)^+$: 278.17507 found: 278.17569 *m/z.*



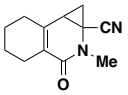
Ethyl (1a*S*,5*S*,7b*S*)-5-(*tert*-butyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,7b-octahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2f) and ethyl (1a*S*,5*R*,7b*S*)-5-(*tert*-butyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,7b-octahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (2f')

The title compounds **2f** and **2f'** was prepared by the general synthesis on a 0.2 mmol scale and then purified via column chromatography (30% Hex:EtOAc) to give a light golden oil in 90% yield (55.0 mg, 0.18 mmol). Product isolated as 2 inseparable diastereomers (1.6:1 d.r). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.24-4.16 (m, 1H), 3.09 (d, *J* = 6.7 Hz, 3H), 2.61-2.26 (m, 3H), 2.02-1.98 (m, 1H), 1.90-1.84 (m, 2H), 1.73-1.72 (m, 2H), 1.30-1.24 (m, 3H), 1.16-1.12 (m, 3H, 0.89 (s, 9H), 0.64-0.56 (m, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz) δ 170.3, 170.0, 164.0, 163.6, 144.0, 143.8, 124.22, 124.03, 61.8, 44.5, 44.20, 44.03, 34.2, 33.9, 32.39, 32.35, 32.26, 31.6, 27.5, 27.3, 27.1, 25.1, 24.7, 23.13, 23.04, 17.9, 17.3, 14.2; **FTIR** (cm^{-1}) (neat): 2957, 2868, 1730, 1631, 1445, 1273, 1132, 751.3, 435.5; **HRMS** (ESI, Pos) calcd for $C_{18}H_{27}NO_3$ $(M+H)^+$: 306.20637 found: 306.20537 *m/z*.



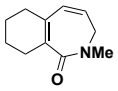
Ethyl 2-methyl-3-oxo-2,3,4,5,6,6b-hexahydrocyclopenta[*d*]cyclopropa[*b*]pyridine-1a(1*H*)-carboxylate (2g)

The title compound **2g** was prepared by the general synthesis on a 0.2 mmol scale and then purified via column chromatography (30% Hex:EtOAc) to give a light brown solid in 25% yield (11.7 mg, 0.050 mmol). Using **procedure B**: 84% yield (39.5 mg, 0.168 mmol). It was also scaled to 1.4 mmol scale using **procedure B** to yield **2h** in 86% yield (285 mg, 1.211 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.26-4.15 (m, 2H), 3.09 (s, 3H), 2.65-2.56 (m, 4H), 2.07 (dt, *J* = 3.2, 0.3 Hz, 2H), 1.95-1.93 (m, 2H), 1.301.27 (m, 3H), 0.69-0.67 (m, 1H). **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.1, 162.6, 151.3, 129.5, 61.9, 46.4, 36.6, 33.4, 30.5, 25.3, 22.3, 17.8, 14.3; **FTIR** (cm^{-1}) (neat): 2980, 1715, 1772, 1622,1263, 1137,420.2 ; **HRMS** (ESI, Pos) calcd for C13H17NO3 $(M+H)^+$: 236.12812 found: 236.12769 *m/z*.



2-Methyl-3-oxo-1,2,3,4,5,6,7,7b-octahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carbonitrile (2j)

The title compound **2j** was prepared by the general synthesis on a 0.2 mmol scale (56.6 mg) and then purified via column chromatography (30% Hex:EtOAc) to give a light yellow solid in 28% yield (13.4 mg, 0.056 mmol). Using **procedure B**: 43% yield (21.4 mg, 0.086 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 3.21 (s, 3H), 2.34-2.24 (m, 4H), 2.19-2.14 (m, 1H), 1.77 (dd, *J* = 10.4, 5.2 Hz, 1H), 1.66-1.64 (m, 4H), 0.77 (dd, *J* = 7.0, 5.2 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 161.8, 143.5, 124.8, 117.8, 32.7, 30.5, 29.9, 24.7, 23.3, 22.1, 21.7, 19.3; **FTIR** (cm^{-1}) (neat):2923, 2853, 2237, 1660, 1627, 1447, 1030, 7487, 538.5; **HRMS** (ESI, Pos) calcd for $C_{12}H_{15}N_2O$ $(M+H)^+$: 203.11789 found: 203.11833 *m/z.*



2-Methyl-2,3,6,7,8,9-hexahydro-1*H*-benzo[*c*]azepin-1-one (2l)

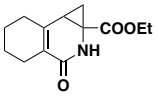
The title compound **2l** was prepared by the general synthesis on a 0.2 mmol scale (46 mg) and then purified via column chromatography (30% Hex:EtOAc) to give an orange oil in 82% yield (29.1 mg, 0.164 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.96-5.94 (m, 1H), 5.46-5.44 (m, 1H), 3.20 (s, 3H), 2.54-2.51 (m, 2H), 2.37-2.34 (m, 2H), 2.24-2.22 (m, 2H), 1.63-1.62 (m, 4H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 171.0, 147.2, 131.1, 128.0, 115.7, 36.2, 32.0, 31.1, 26.7, 22.8, 22.4; **FTIR** (cm^{-1}) (neat): 2923, 2853, 2237, 1660, 1627, 1447, 1030, 7487, 538.5; **HRMS** (ESI, Pos) calcd for $C_{11}H_{15}NO$ $(M+H)^+$: 178.12264 found: 178.1233 *m/z.*

Procedure for Boc-Deprotection of 2b

To a sealed microwave vial containing **2b** (37.6 mg, 0.121 mmol) and a stir bar was added DCM (0.5 mL), followed by TFA (7.0 mL). The reaction was stirred for 16 min at room temperature, diluted with DCM (10 mL) and then concentrated in vacuo to give the crude product. The crude reaction mixture was then flashed via column chromatography (0-70% Hex:EtOAc) to give the resulting product (**3**) as a brown solid in 74% yield(19.5 mg, 0.083 mmol).

Procedure for PMB-Deprotection of 2d.

To a sealed microwave vial containing **2d** (70 mg, 0.1969mmol) and a stir bar was added anisole (4.0 equiv), followed by TFA (4.0 mL). The reaction was stirred for 15 min at room temperature and then heated to 50ºC for 16 hours. The reaction was cooled to room temperature and then diluted with DCM (10 mL) and then concentrated in vacuo to give the crude product. The crude reaction mixture was then flashed via column chromatography (0-70% Hex:EtOAc) to give the resulting product (**3**) as a brown solid in 72% yield (33.3 mg, 0.1415 mmol).



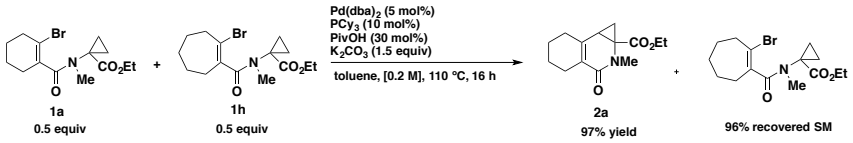
Ethyl 3-oxo-1,2,3,4,5,6,7,7b-octahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate (3)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.49 (br s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.49-2.28 (m, 4H), 2.20 (dd, *J* = 10.0, 6.5 Hz, 1H), 1.87 (dd, *J* = 10.1, 4.1 Hz, 1H), 1.74-1.59 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H), 0.64 (dd, *J* = 6.3, 4.1 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 101MHz): δ 170.2, 163.0, 147.5, 123.8, 62.2, 40.2, 30.8, 25.6, 22.8, 22.2, 22.0, 21.3, 14.3; **FTIR** (cm^{-1}) (neat): 3182, 2925, 1726, 1661, 1625, 1093, 785.5, 514.0; **HRMS** (ESI, Pos) calcd for $C_{13}H_{17}NO_3$ $(M+H)^+$: 236.12812 , found: 236.12914 m/z.

Procedure for Intermolecular Competition Experiment

A 5.0-mL microwave vial containing **1a** (0.1 mmol, 0.5 equiv), **1h** (0.1 mmol, 0.5 equiv) and pivalic acid (30 mol%, 0.06 mmol, 6.1 mg) was taken into a glovebox and to this was added in the following order: $Pd(OAc)_2$ (5 mol%, 0.02 mmol, 2.2 mg), PCy_3 (10 mol%, 0.05 mmol, 5.6 mg), and K_2CO_3 (1.5 equiv, 0.3 mmol, 41.5 mg). The vial was crimped shut. Outside of the glovebox was added 1.0 mL of toluene. The yellowish-orange solution was then heated to 110 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The ratio and yields of the two products was determined via ^{1}H NMR employing 1,3,5-trimethoxybenzene as an internal standard.

Yield: 97% yield for **2a**, 96% **1h** recovered.



This result indicates that the starting material does not poison the catalyst, as **2a** can be formed in high conversion in the presence of **1h**. Due to the high amount of **1h** that can be recovered, the oxidative addition appears to be challenging for ring sizes >6.

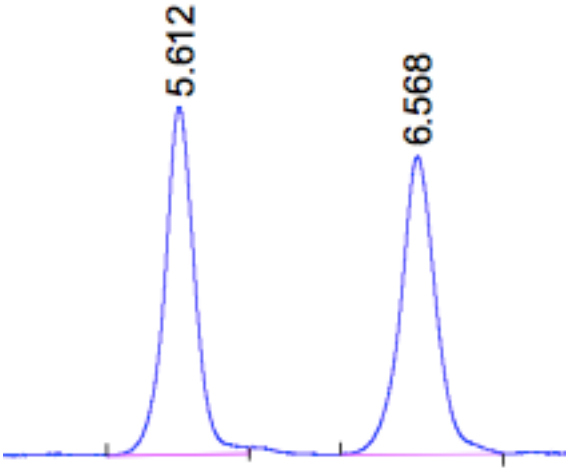
Procedure for Enanatioselective Cyclopropyl Alkenylation

A 5.0-mL microwave vial containing 2-bromocyclohexenyl amide (**1a,** 0.2 mmol) was taken into a glovebox and to this was added in the following order: $Pd(dba)_2$ (5 mol%, 0.025 mmol, 5.6 mg), BozPhos (5 mol%, 0.025 mmol, 7.0 mg) or IPrMonophos (5 mol%, 0.025 mmol, 8.0 mg), and K_2CO_3 (1.5 equiv, 0.75 mmol, 104 mg). The vial was crimped shut. Outside of the glovebox was added 1.0 mL of toluene. The green solution was then heated to 110 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) using a solvent gradient of 10% to 50% Hex:EtOAc to give product **2a.** Enantiomeric excess was determined via SFC analysis on a chiral stationary phase ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar). The enantiomers for **2a** were separated via SFC (supercritical fluid chromatography) using identical conditions for the analysis.

Attached are the SFC traces for: **(1)** the racemic mixture **(2)** each of the enantiomers **(3)** reaction conditions using *(R)*-IPrMonophos **(4)** reaction using *(R,R)*-BozPhos.

Note: For the racemic mixture and enantiopure traces, the major enantiomer (rt=7.062 min) showed tailing. This demonstrates that there is no impurity hidden underneath the peak inflating the enatiomeric excess.

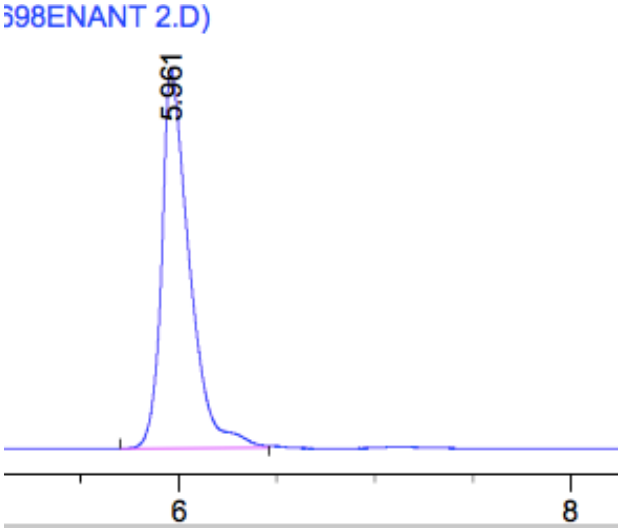
(1) Racemic mixture for **1a**.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.612	BV	0.1217	1248.49365	149.06386	49.6594
2	6.568	BV	0.1301	1265.62000	127.71049	50.3406
Totals :				2514.11365	276.77435	

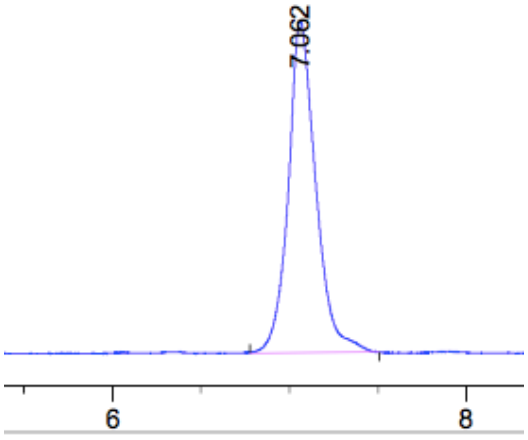
(2) Enantiomer 1 and 2, from SFC separation of racemic mixture.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.961	BV	0.1334	6336.70117	643.55243	100.0000
Totals :				6336.70117	643.55243	

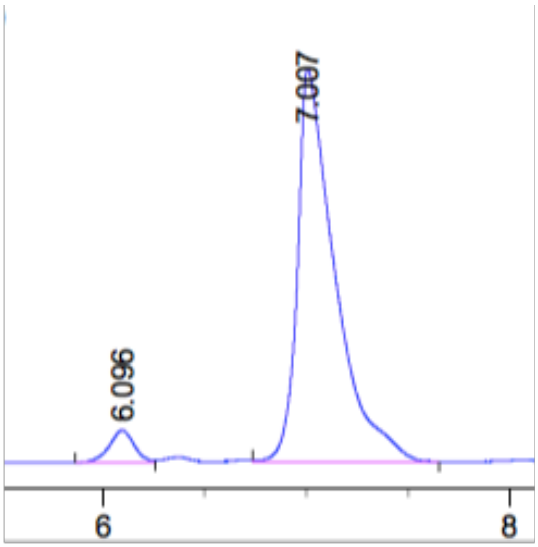
:NANT 1.D)



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.062	BB	0.1372	2700.11157	249.58971	100.0000
Totals :				2700.11157	249.58971	

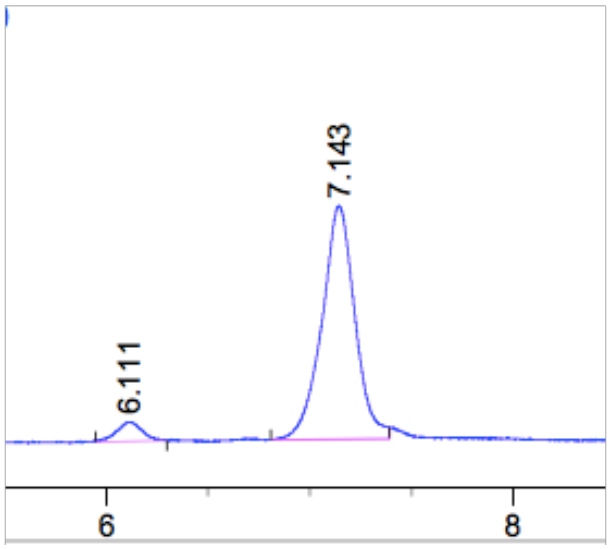
(3) SFC Trace using IPrMonophos as a Ligand:



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.096	BV	0.1050	514.43860	59.73563	5.1754
2	7.007	VV	0.1720	9425.65918	732.98364	94.8246
Totals :				9940.09778	792.71927	

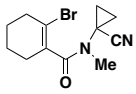
SFC Trace using BozPhos as a Ligand (with $Pd(dba)_2$):

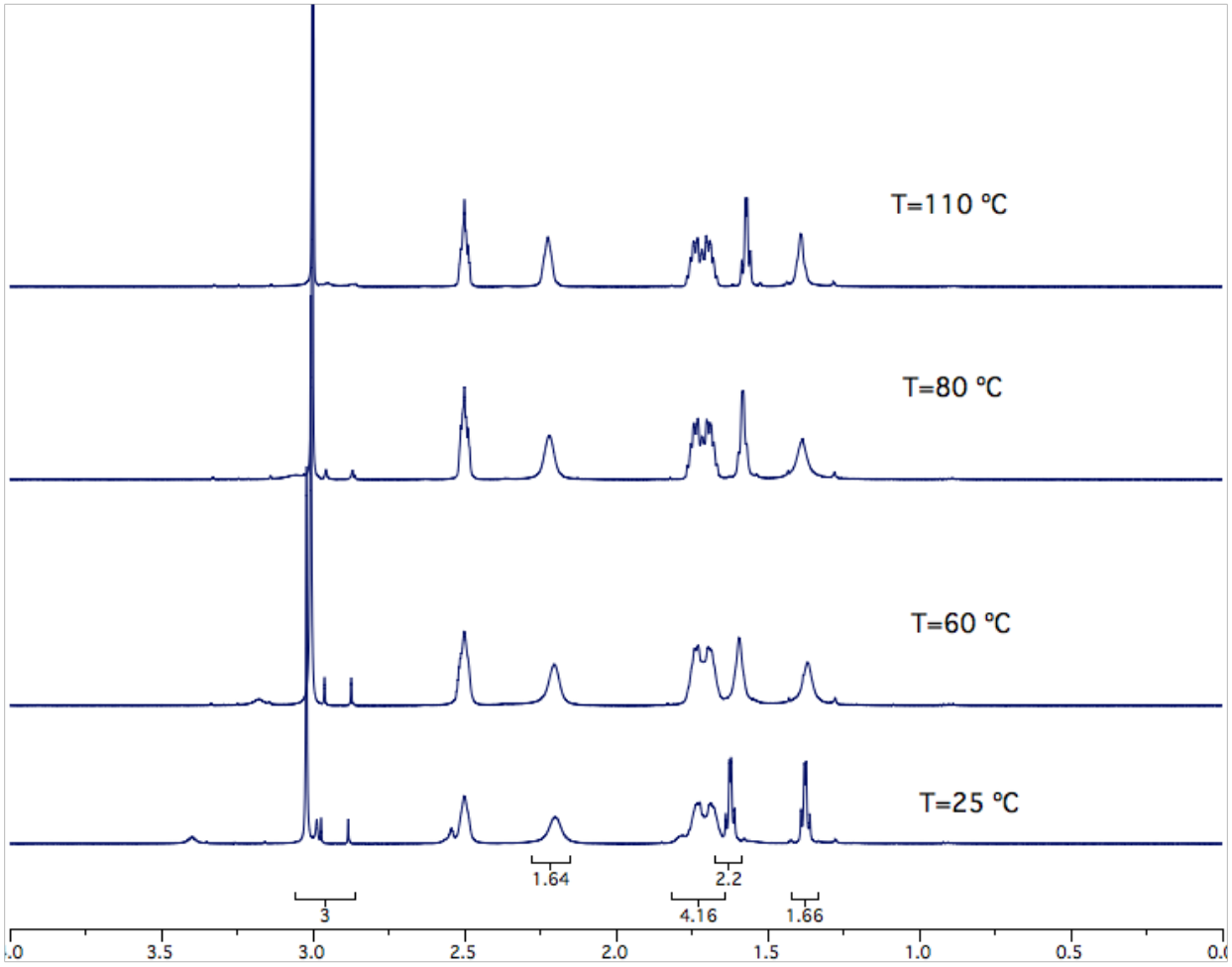


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.111	VV	0.1045	85.19999	9.60016	6.1679
2	7.143	VV	0.1395	1296.13696	114.51780	93.8321
Totals :				1381.33695	124.11796	

High temperature experiments for **1j** were performed on a 500 MHz NMR using d6-DMSO as a solvent. As the temperature increases, the rotamer peaks coalesce until a single conformer is present at the reaction temperature (110 ºC).





Experimental Section for Chapter 4[12]

Materials.

Commercial reagents were used as supplied or purified by standard techniques where necessary. Starting materials not listed below were obtained commercially and the reagents were used without further purification. Ethyl 1-((*tert*-butoxycarbonyl)amino)cyclopropane-1-carboxylate was synthesized according to literature procedure and converted to its TFA salt for subsequent use. **Ethyl 1-[N-methyl(2-bromophenyl)amido]cyclopropane-1-carboxylate** was prepared as described for Chapter 3. **Methyl (2-bromophenyl)(isopropyl)carbamate** was prepared as described in the literature and characterization matched that of the literature.[13] **Methyl (2-bromophenyl)(cyclohexyl)carbamate** was prepared via the literature procedure and the characterization matched that of the literature.[14] *(R,R)*-BozPhos was prepared via *(R,R)*-MeDUPHOS as described in the literature. [15] The product, methyl (*R*)-2-methylindoline-1-carboxylate was previously reported and characterization matched the literature values.[16] The product ethyl (1a*S*,7b*S*)-2-methyl-3-oxo-1,2,3,7b-tetrahydro-1a*H*-cyclopropa[*c*]isoquinoline-1a-carboxylate was previously reported and characterization matched the literature values.[17]

Procedure for Pd-Catalyzed C-H Arylation using CPME

A 5.0-mL microwave vial containing the starting material (0.2 mmol) was taken into a glovebox and to this was added in the following order: Pd G4 dimer (5 mol%, 0.05 mmol), PCy_3 (10 mol%, 0.025 mmol, 7.0 mg), and K_2CO_3 (1.5 equiv, 0.75 mmol, 104 mg). The vial was crimped shut. Outside of the glovebox was added 1.0 mL of CPME. The green solution was then heated to 110 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) using a solvent gradient of 10% to 30% Hex:EtOAc to give the cyclized product**.**

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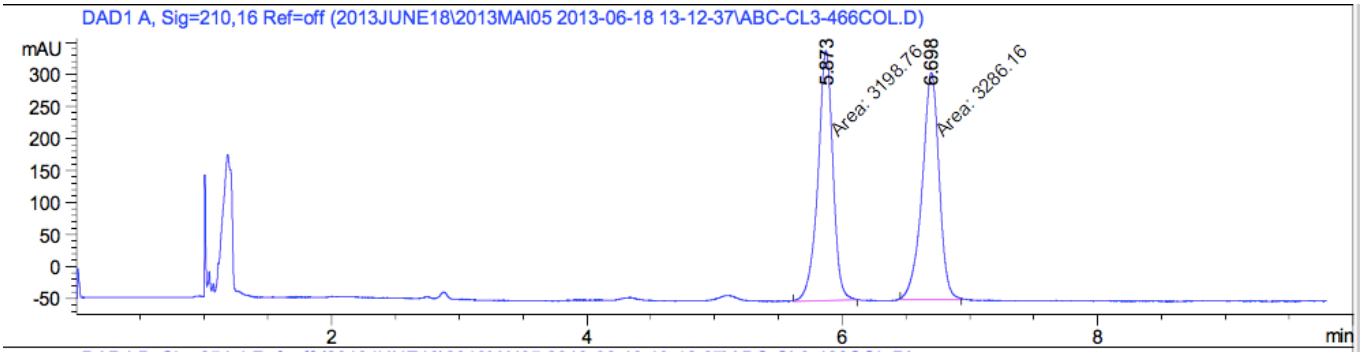
[13] (a) Reddy, T. J.; Leclair, M.; Proulx, M. *Synlett* **2005**, No. 4, 583. (b) Yang, L.; Melot, R.; Neuburger, M.; Baudoin, O. *Chem Sci* **2017**, *8*, 1344.
[14] (a) Pletz, J.; Berg, B.; Breinbauer, R. *Synthesis* **2016**, *48* (09), 1301. (b) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem.* **2011**, *123* (32), 7576.
[15] Cote, A.; Desrosiers, J-N.; Bpezio, A.A.; Charette, A.B. *Org. Synth.* **2006**, *83*, 1.
[16] Yang, L.; Melot, R.; Neuburger, M.; Baudoin, O. *Chem Sci* **2017**, *8*, 1344.
[17] Pedroni, J.; Saget, T.; Donets, P. A.; Cramer, N. *Chem Sci* **2015**, *6*, 5164. The absolute configuration still needs to be confirmed.

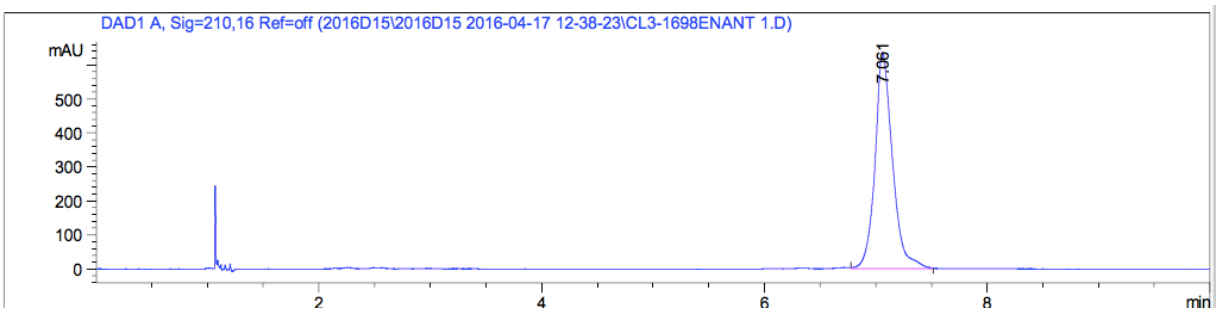
Procedure for Enanatioselective Cyclopropyl Arylation

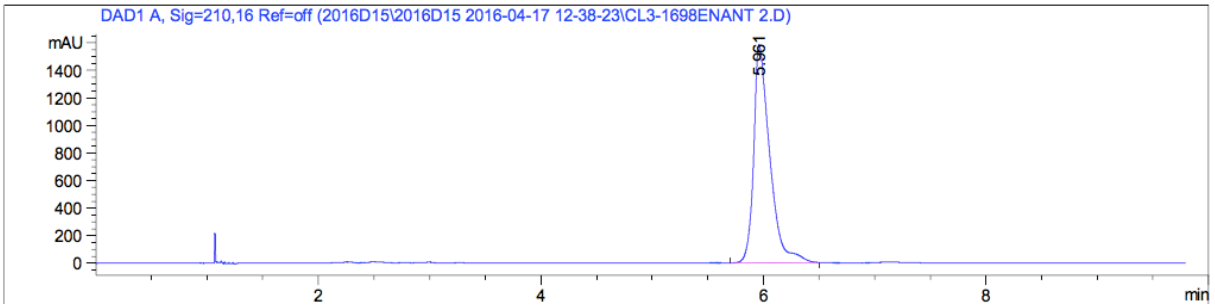
A 5.0-mL microwave vial containing ethyl 1-[*N*-methyl(2-bromophenyl)amido]cyclopropane-1-carboxylate (0.2 mmol) was taken into a glovebox and to this was added in the following order: G4-dimer (2.5 mol%, 0.025 mmol, 5.6 mg), (*R,R*)-BozPhos (5 mol%, 0.025 mmol, 7.0 mg), and Rb_2CO_3 (1.5 equiv, 0.75 mmol). The vial was crimped shut. Outside of the glovebox was added 1.0 mL of xylenes The green solution was then heated to 110 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) using a solvent gradient of 10% to 50% Hex:EtOAc to give product **2a.** Enantiomeric excess was determined via SFC analysis on a chiral stationary phase ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar). Attached are the SFC traces for: **(1)** the racemic mixture (2) the enantiopure products after separation **(3)** reaction conditions using *(R,R)*-BozPhos.

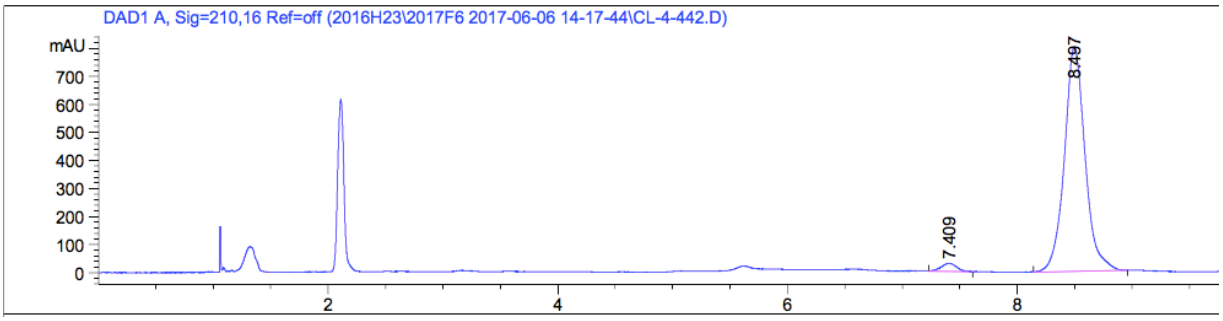


Signal 1: DAD1 A, Sig=210,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.873	MM	0.1363	3198.75928	391.19434	49.3261
2	6.698	MM	0.1542	3286.15894	355.27341	50.6739
Totals :				6484.91821	746.46774	







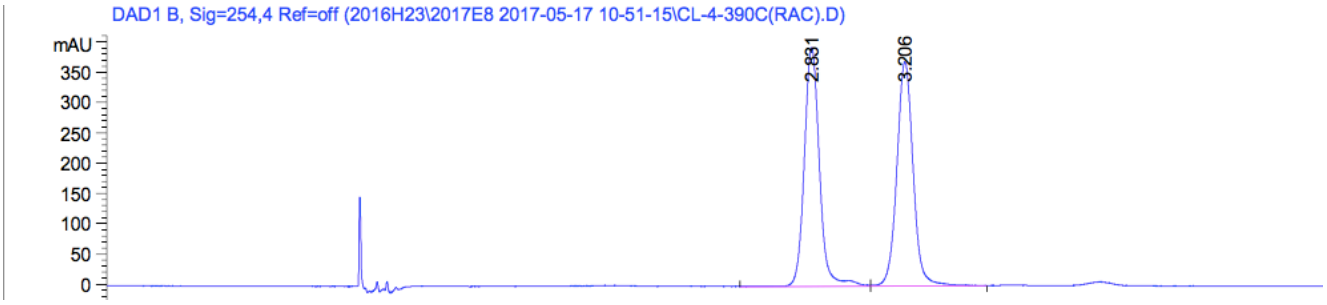
Signal 1: DAD1 A, Sig=210,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.409	VB	0.1085	258.50659	28.30954	2.5087
2	8.497	VV	0.1779	1.00459e4	800.47327	97.4913
Totals :				1.03044e4	828.78281	

Procedure for Enanatioselective sp^3 Arylation

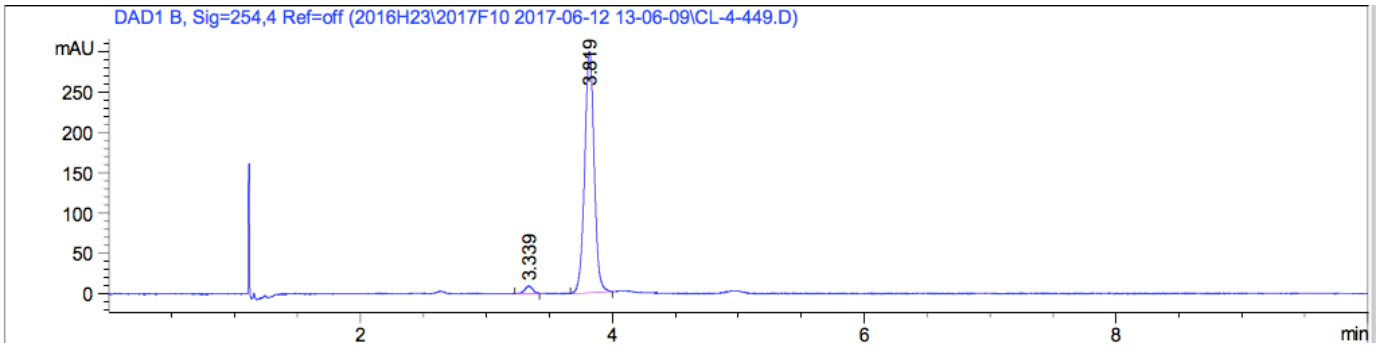
A 5.0-mL microwave vial containing **methyl (2-bromophenyl)(isopropyl)carbamate** (0.2 mmol) was taken into a glovebox and to this was added in the following order: G4-dimer (2.5 mol%, 0.025 mmol, 5.6 mg), (*R,R*)-BozPhos (5 mol%, 0.025 mmol, 7.0 mg) and K_2CO_3 (1.5 equiv, 0.75 mmol, 104 mg). The vial was crimped shut. Outside of the glovebox was added 1.0 mL of

xylenes. The green solution was then heated to 120 ºC in an oil bath for 16 h. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with 25 mL of ethyl acetate. It was then concentrated *in vacuo* to give the crude product. The crude was then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) using a solvent gradient of 10% to 30% Hex:EtOAc to give the product**.** Enantiomeric excess was determined via SFC analysis on a chiral stationary phase ((*R,R*)-WHELKO-01 15 cm x 4.6 mm, 3.0 mL/min, 20 ºC, 150 bar).
Attached are the SFC traces for: **(1)** the racemic mixture **(2)** reaction using *(R,R)*-BozPhos.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.831	BV	0.0666	1672.29858	393.51089	49.8349
2	3.206	VB	0.0701	1683.38171	369.59589	50.1651
Totals :				3355.68030	763.10678	



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.339	BV	0.0581	46.26177	9.87992	2.8732
2	3.819	BB	0.0771	1563.83911	298.83475	97.1268
Totals :				1610.10088	308.71466	