Palladium-Catalyzed Alkene Difunctionalization to Form Methylene Cyclobutanes, Methylene Cyclopentanes, and Tetrahydroberberines

by

Jessica E. Hatt

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Doctoral Committee:

Professor John P. Wolfe, Chair
Professor John Montgomery
Professor Melanie S. Sanford
Associate Professor Wenjing Wang

Jessica E. Hatt

jehatt@umich.edu

ORCID iD: 0000-0002-2082-0378

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Dedication

To all my friends and family-Thank you for your love and encouragement

.

Acknowledgements

I would like to begin my acknowledgements by thanking my PI, Dr. John P. Wolfe, without whom I would not be the scientist I am today. I have appreciated your consistent confidence in my work over the years and encouragement that I will always figure out the next roadblock in my chemistry. You gave me the freedom to figure out how I want to approach chemistry and have created an environment where I get to solve my own problems but always feel like I have your support, which I appreciate immensely. I've grown a lot in your lab and I will be forever grateful for the opportunity to be one of your students.

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eq 4-6 73

eq 5-1 82

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eq 5-3 95

List of Abbreviations

A ..... angstrom

α ..... alpha

acac ..... acetylacetone

aq .....aqueous

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

β ..... beta

Boc ..... tert-butyloxycarbonyl

Bn ..... benzyl

br. ..... Broad

Bz ..... benzoyl

ca ..... circa

calcd ..... calculated

CO……carbon monoxide

CO_3……carbonate

Cp..... cyclopentadienyl

Cy ..... cyclohexyl

°C ..... degrees Celsius

d .....doublet

dba ..... dibenzylideneacetone

DCM ..... dichloromethane/methylene chloride

dd ..... doublet of doublets

ddd ..... doublet of doublet of doublets

ddt ..... doublet of doublet of triplets

DMF ..... dimethylformamide

DMSO ..... dimethylsulfoxide

dr ..... diastereomeric ratio

ee.....enantiomeric excess

equiv ..... equivalents

eq .....equation

er ..... enantiomeric ratio

ESI ..... electrospray ionization

Et ..... ethyl

EtOH .....ethanol

(g) ..... gas

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

HPLC.....High Pressure Liquid Chromotagraphy

HRMS ..... high resolution mass spectrometry

IR..... infrared spectroscopy

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

J ..... coupling constant

Ln/L ..... general ligand

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

m ..... multiplet

Me ..... methyl

MeOH ..... methanol

m.p. ..... melting point

NMR ..... nuclear magnetic resonance

Nuc/Nuc-H ..... nucleophile

OAc .....acetate

OMe ..... methoxy

OtBu ..... tert-butoxide

OTf .....triflate

p ..... para

Pd ..... palladium

pent ..... pentet

PG/P ..... protecting group

Ph ..... phenyl

PMP ..... para-methoxyphenyl

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

q ..... quartet

rbf ..... round-bottom flask

rt ..... room temperature

s ..... singlet

satd. ..... Saturated

t ..... triplet

t ..... tert

t-butyl/^{t}Bu ..... tert-butyl

TEA ..... triethylamine

Tf ..... triflyl

TFA [$Pd(TFA)_2$] ..... trifluoroacetate

Tf_2O ..... triflic anhydride

THF ..... tetrahydrofuran

THB.....tetrahydroberberine

TLC ..... thin-layer chromatography

TMS ..... trimethylsilyl

Ts ..... tosyl

T. S. ..... transition state

R..... general functional group

rr.....regiomeric ratio

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

Y ..... general heteroatom

Z ..... general atom or substitution

Abstract

Carbocycles and heterocycles are highly valuable synthetic building blocks, especially when they incorporate functional handles, such as amines. Palladium-catalyzed alkene difunctionalization is a mild and versatile method for the construction of these sought after motifs. This thesis will primarily describe the development of this class of reactions for the synthesis of methylene cyclopentanes, methylene cyclobutanes and tetrahydroberberine (THB) alkaloids/analogs.

The first portion of this dissertation is focused on the construction of functionalized carbocycles. Therefore, Chapter 1 outlines the significance of functionalized cyclobutanes and cyclopentanes and developments towards their synthetic construction both by the Wolfe lab and other research groups. This introduction highlights the need for methodologies in which cyclization and functionalization are achieved in the same step. This need is initially addressed in Chapter 2 in which the regiodivergent methods for forming malonate functionalized cyclopentanes and cyclobutanes are summarized and my contributions in the mechanistic investigations are detailed. Chapter 3 expands upon this work by focusing on the development of a regiodivergent 4-exocyclization/functionalization for the synthesis of amine substituted methylene cyclobutanes; including the reaction optimization, substrate scope and mechanistic investigations.

The second portion of the thesis targets heterocycles, specifically tetrahydroberberines (THBs). The relevance of this class of natural products and previous synthetic routes to access these molecules are discussed in Chapter 4. Within this chapter, remaining challenges in the field are highlighted; such as the lack of a method that forms the two aliphatic rings of THBs and sets the stereocenter at the same time, and the limited substrate scope due to the electronic demands of existing reactions. Chapter 5 will describe my development of intramolecular palladium catalyzed carboamination to form THB derivatives, which not only offers efficient access to biologically active heterocycles, but is also one of the first examples of carboamination reactions with aliphatic amines. Within this chapter, the development of new chiral phosphite ligands derived from a combination of a TADDOL and a cinchona alkaloid are also described.

Overall, this thesis demonstrates that palladium-catalyzed alkene difunctionalization is an efficient strategy to access both carbocycles and heterocycles. As this field develops further, these and similar methods will be applied to a wider range of nucleophiles and electrophiles to access even more biologically active relevant scaffolds.

Chapter 1 Introduction into the Significance of Functionalized Cyclobutanes and Cyclopentanes and the Approaches Used to Access Them

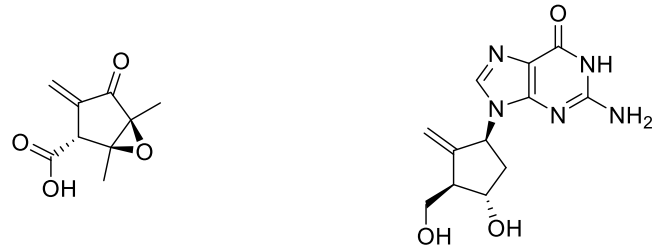
1.1 Introduction

Carbocycles are a common feature in biologically active and pharmaceutically relevant molecules, often being highlighted as a key structural motif. As such, there has been considerable interest in developing methods to access them in recent history, especially in ways that incorporate functional groups and synthetic handles during their construction. Despite continued interest, small ring systems (such as cyclopentanes and cyclobutanes) still remain challenging to synthesize. As an introduction to later chapters (2 & 3) which highlight my contributions to this area of research, this chapter will briefly discuss the importance of cyclopentanes (1.2) and cyclobutanes (1.4); and existing methods to make these carbocycles (1.3 and 1.5).

1.2 Natural Occurrences and Applications of Cyclopentanes

Cyclopentanes are a very common motif in natural products and biologically active materials. As of 2021, when I began working on making such compounds, five membered rings were the 7th most common ring structure in natural products and 18th in synthetic compounds.[1,2] Highly functionalized cyclopentanes regularly appear in the literature as notable compounds of interest. For example, the natural product methylenomycin A **1-1** has been shown to be an effective antibacterial agent, in part due to its complex functionalization pattern (eq 1-1).[3] 1,3-Disubstituted cyclopentanes specifically have also been identified as promising scaffolds and have been the focus of many research efforts in the recent years.[4] One example of such a

molecule is entecavir **1-2**, which is a synthetic drug from BMS used to treat hepatitis B that relies on a titanium mediated ring closing disconnection (eq 1-1).[5] Despite this continued interest, the synthesis of functionalized cyclopentanes continues to be more challenging than many other carbocyclic systems; primarily, because there is not a unified approach to making functionalized cyclopentanes like there is for other carbocycles, such as cyclohexanes.[6]

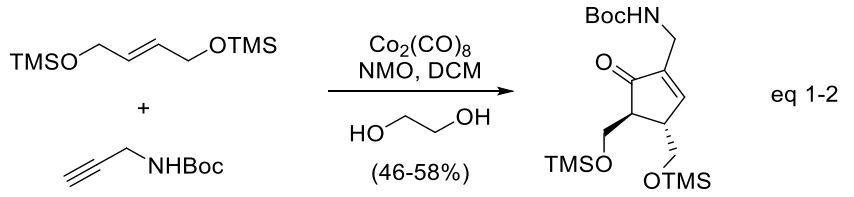


Methylenomycin A **1-1** Entecavir **1-2** eq 1-1

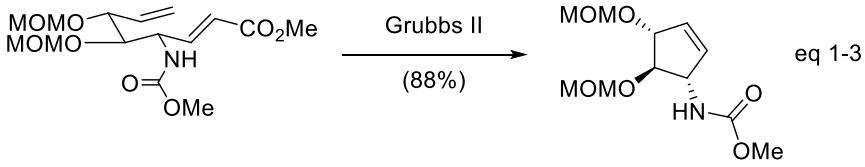
1.3 Methods to Synthesize Functionalized Cyclopentanes including Palladium Catalyzed Alkene Difunctionalization

Cyclopentanes are made through a wide variety of means; including rearrangements, cycloadditions, and intramolecular polar reactions.[7] Transition metals (TM) have been shown to be quite effective in mediating ring forming reactions to form functionalized cyclopentanes. As an example, the Pauson-Khand reaction is a [2+2+1] reaction enabled by cobalt catalysis that forms cyclopentanones, allowing for high degrees of functionalization [8,9] In 2011, the Baran group applied this strategy as their first step to build a core cyclopentanone in the construction of axenelleamines (eq 1-2).[10] Another example of TM mediated cyclopentane ring formation is ring closing metathesis (RCM). For example, Rosa and co-workers used RCM as a critical step in the formation of (−)-allosamizoline (eq 1-3).[11] In both of these cases, functional groups are retained and new handles are installed (a carbonyl and alkene respectively). However, a limitation in both

of these cases, and across existing TM mediated reactions, is that they do not create cyclopentanes directly and products need to be manipulated post-formation through reduction or other transformations to obtain the saturated carbocycle.

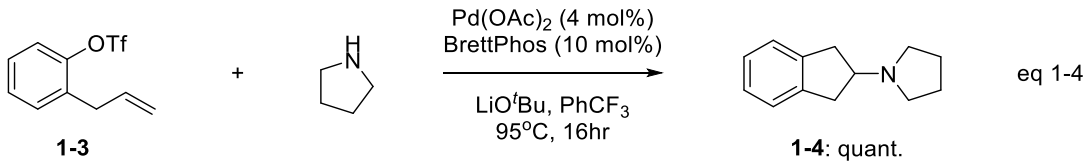


eq 1-2



eq 1-3

Beginning in 2015, our group began exploring the use of palladium-catalyzed alkene difunctionalization as a strategy to form functionalized cyclopentanes.[12] In these reactions, an alkene is tethered to an aryl triflate **1-3** which is then coupled to an external nucleophile. This was initially explored using amine nucleophiles to generate indane derivatives **1-4** (eq 1-4).[13] Since the original reaction development, this system has been applied to a vast array of nucleophiles, including indoles, malonates, enolates, and alcohols.[12] Additionally, the electrophile scope has been expanded to alkenyl triflates, and also to the formation of methylene cyclopentane **1-4a** products.



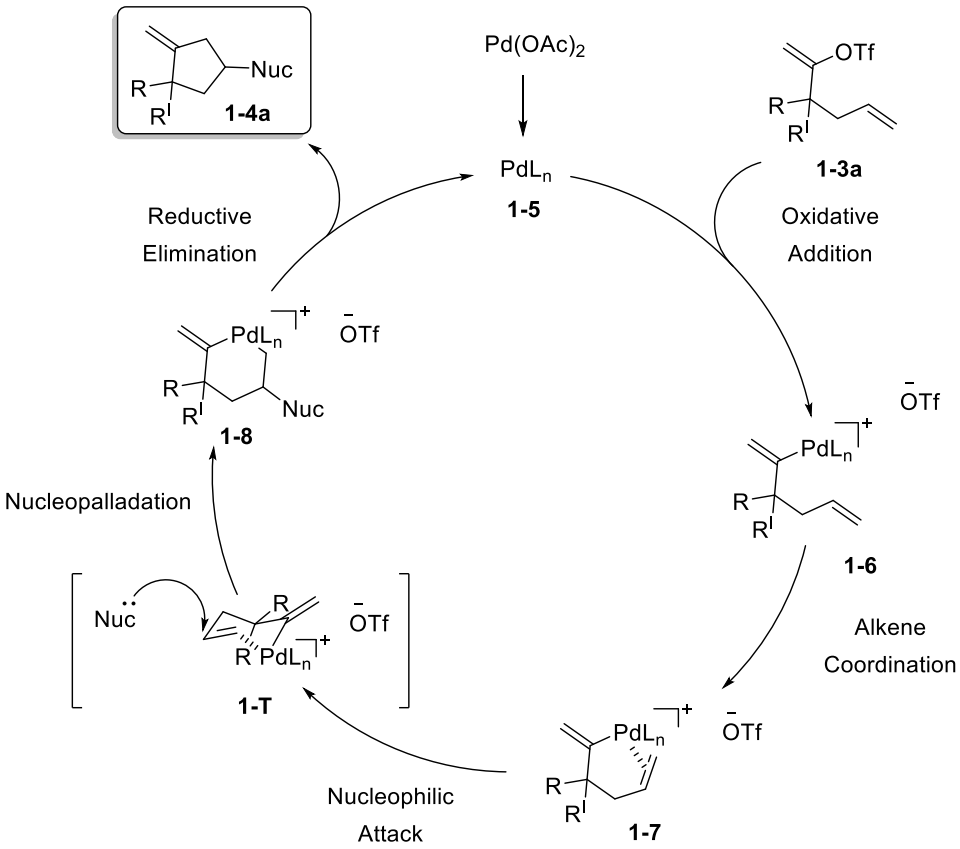
1-3

1-4: quant.

eq 1-4

This reaction proceeds through the following catalytic cycle shown below (Scheme 1-1). The palladium pre-catalyst is first converted to the active palladium (0) species **1-5**, ligated by a phosphine ligand. The electrophile, alkenyl/aryl triflate with a tethered alkene **1-3a**, undergoes oxidative addition to the palladium catalyst, forming Pd(II) species **1-6**. The palladium then coordinates to the tethered alkene forming, alkene complex **1-7**. The nucleophile then attacks the alkene *anti* to the palladium in a nucleopalladation step via transition state **1-T** to form the palladacycle **1-8**. This species undergoes reductive elimination to form the functionalized five-membered ring (**1-4**) and regenerate the active Pd(0) species **1-5**.

Scheme 1-1: Mechanism of Pd-Catalyzed Alkene Difunctionalization

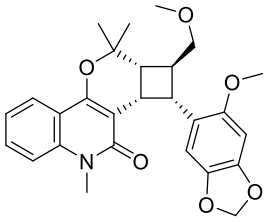


Palladium-catalyzed alkene difunctionalization offers an efficient approach to forming and functionalizing cyclopentanes all in one step. In general, this class of reactions proceeds with high

yield and diastereoselectivity to access functionalized carbocycles.[12] This is an area of research that continues to be explored in our group in an effort to expand the scope of nucleophiles and electrophiles that can be tolerated.

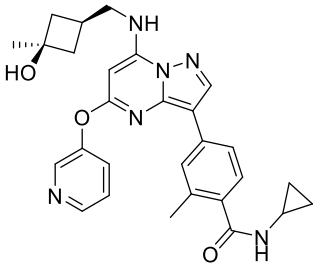
1.4 Natural Occurrences and Applications of Cyclobutanes

Similarly to cyclopentanes, cyclobutanes are a common motif in both natural products and drugs. They have garnered a lot of interest in recent years due to their strained nature and puckered 3-dimensional structure.[14] Their rigidity and non-planar confirmation is proposed to allow for a better fit in the active site of enzymes and improve metabolic properties.[15] This is demonstrated across the wide range of biologically active cyclobutanes currently in the literature. For example, melicodenine E **1-9** was isolated from *Melicope denhamii* which was used by indigenous peoples of the Solomon Island to treat skin conditions and it, along with others in this family of molecules, was shown to have activity against DLD-1 human colon cancer cells (eq 1-5).[16,17] In the pharmaceutical sector, cyclobutanes are incorporated in drug molecules frequently as well, typically during SAR studies as attractive bioisosteres for cyclohexanes.[14] This was the case for CFI-402257 **1-10**, a molecule effective against threonine tyrosine kinases in breast cancer cells (eq 1-5). [18] In its development, the cyclohexane version **1-11** was effective but prone to cis-trans isomerization, a problem solved by the substitution of a cyclobutane (eq 1-5).[14] Overall, cyclobutanes are common motifs in biologically active molecules due to their interesting shape and substitution capabilities. However, those are the aspects of these carbocycles that make them difficult to manipulate and incorporate into scaffolds of interest, a problem which has attracted a lot of interest of late from the organic chemistry community.



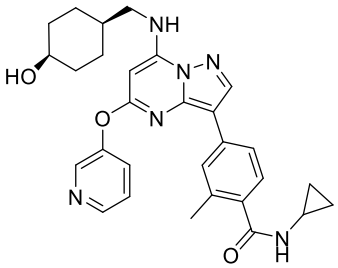
Melicodenine E

1-9



CFI-402257

1-10

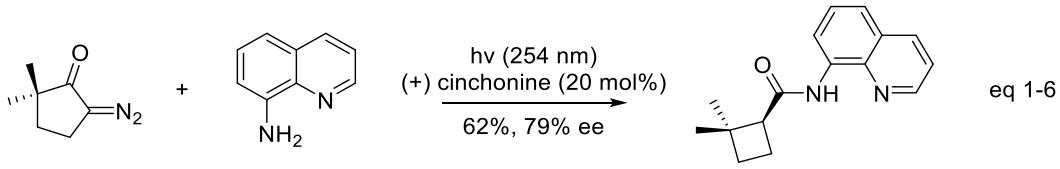


1-11

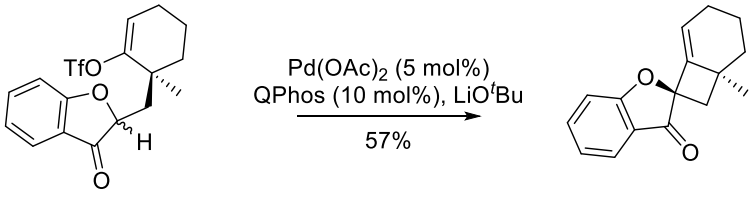
eq 1-5

1.5 Methods to Synthesize Functionalized Cyclobutanes

It is believed that most cyclobutanes in natural products are obtained biosynthetically through light or enzyme mediated [2+2] cycloadditions.[19] This is a trend that has been exploited in synthetic laboratories, in which [2+2] cycloadditions are the most common method for accessing cyclobutanes.[20] This is an active area of research where current investigators are addressing issues such as the necessity for at least one component of the reaction to be an activated olefin that is able to be excited, along with challenges associated with regioselectivity and diastereoselectivity.[21] More recently, new approaches have been developed and applied to natural product synthesis that circumvent these challenges. For example, in 2016, Reisman and co-workers published a Wolff rearrangement as the key cyclobutane forming step in the total synthesis (+)-psiguadial B. (eq 1-6).[22] In 2017, Dong and co-workers reported an intramolecular palladium-catalyzed alkenylation to form a key segment of phainanoid (eq 1-7).[23] Both of these strategies relied on reaction optimization for this step in the synthetic sequence, indicating a need for more general synthetic methods to access cyclobutanes.



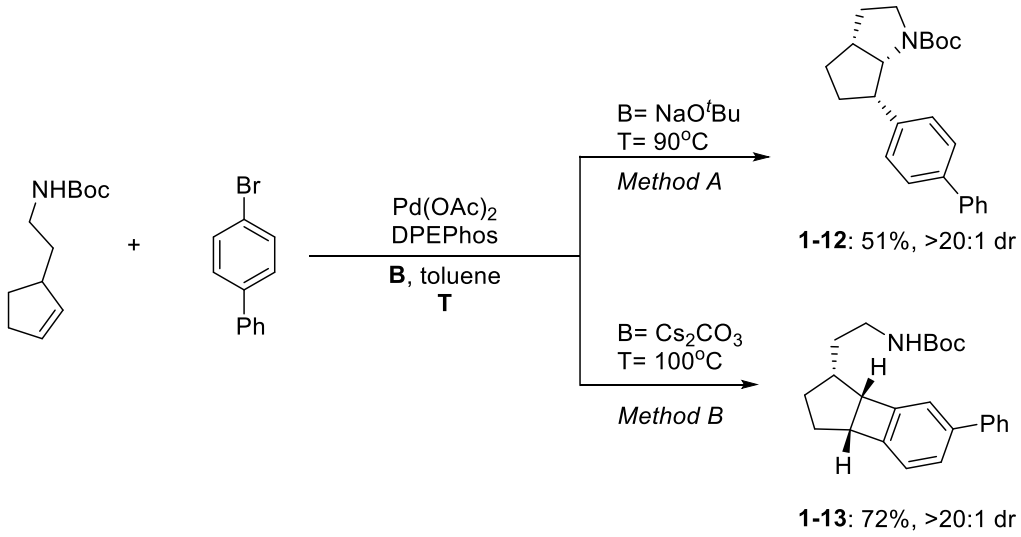
eq 1-6



eq 1-7

In the past, this has been a synthetic challenge that the Wolfe group has been interested in. Wolfe and co-workers previously developed a method that employs palladium alkene difunctionalization as a strategy to make cyclobutanes.[24] In this work, cyclopentane-fused benzocyclobutenes **1-13**, a regioisomer of the cyclopentane product **1-12** that arises from the same starting material, were formed via a carbopalladation and C-H activation (Scheme 1-2). Despite this exciting result, limited attempts were made in our group to expand upon this or similar methods to form cyclobutanes using Pd-catalyzed alkene difunctionalization in the 10 years following this publication, leaving a gap in the literature that was addressed by the projects detailed in chapters 2 & 3 of this thesis.

Scheme 1-2: Previous Regiodivergent Cyclobutane Forming Reaction



1.6 Conclusion

Cyclopentanes and cyclobutanes are an important motif in biologically relevant molecules. They appear frequently in both natural product and drug scaffolds, and there is a breadth of literature describing means for their construction. However, further development is required to continue to expand the scope of the literature such that more cyclopentane/cyclobutane containing targets can be accessed. Palladium-catalyzed alkene difunctionalization is a potentially, generally useful method for 4-5 membered ring synthesis that would achieve both ring formation and functionalization in the same step. The following chapters will address my contributions to this area of research through the mechanistic studies in the formation of malonate functionalized cyclopentanes (Chapter 2) and amine functionalized cyclobutanes (Chapter 3).

1.7 References

(1) Chen, Y.; Rosenkranz, C.; Hirte, S.; Kichmair, J. “Ring Systems in Natural Products: Structural Diversity, Physicochemical Properties, and Coverage by Synthetic Compounds” *Nat. Prod. Rep*., **2022,** *39*, 1544-1556.

(2) Shearer, J.; Castro, J. L.; Lawson, A. D. G.; MacCoss, M.; Taylor, R. D. “Rings in Clinical Trials and Drugs: Present and Future” *J. Med. Chem,* **2022***, 65* (13), 9699-8712.

(3) Gimazetdinov, A. M.; Gataullin, S. S.; Loza, V. V.; Miftakhov, M. S. “Synthesis of (+)-didesmethylmethyleneomycin A methyl ester” *Tetrahedron,* **2013***, 69* (46), 9540-9543.

(4) Paul, S.; Adelfinsky, D.; Salome, C.; Fessard, T.; Brown, M. K. “2,5-disubstituted bicyclo [2.1.1]hexanes as rigified cyclopentane variants” *ChemSci,* **2023.** 14.

(5) Velasco, J.; Ariza, X.; Badia, L.; Bartra, M.; Berenguer, R.; Farras, J.; Gallardo, J.; Garcia, J.; Gasanz, Y. “Total Synthesis of Entecavir” *J. Org. Chem*, **2013,** *78* (11), 5482–5491.

(6) Oelze, S.; Brauer, N.; Michel, T.; Schaumann, E.; Kirschning, A. “[4+1] Cyclizations to Enantiopure Multifunctional Cyclopentanes from D-Glucose using Formyl Dianion Synthons” *Synlett,* **2024,** *35* (09), 973-978.

(7) Ferreira, A. J.; Beaudry. C. M. “Synthesis of Natural Products Containing Fully Functionalized Cyclopentanes” *Tetrahedron,* **2017,** *73* (8), 965-1084.

(8) Brummond, K. M.; Kent, J. L. “Recent Advances in the Pauson-Khand Reaction and Related [2+2+1] Cycloadditions” *Tetrahedron,* **2000,** *56* (21), 3263-3283.

(9) Lledo, A.; Sola, J. “The Intermolecular Pauson-Khand Reaction: Applications, Challenges and Opportunities” *Advanced Synthesis & Catalysis,* **2023**, *366* (4), 574-592.

(10) Su, S.; Rodriguez, R. A.; Baran, P. S. “Scalable, Stereocontrolled Total Syntheses of (+)-Axinellamines A and B” *J. Am. Chem. Soc.* **2011,** *133* (35), 13922-13925.

(11) Donohoe, T. J.; Rosa, C. P. “Concise and Efficient Synthesis of (-)-Allosamizoline” *Org Lett,* **2007**, *9* (26), 5509-5511.

(12) White, D. R.; Bornowski, E. C.; Wolfe, J. P. “Pd-Catalyzed C-C, C-N, and C-O Bond Forming Difunctionalization Reactions of Alkenes Bearing Tethered Aryl/Alkenyl Triflates” *Isr. J. Chem.* **2020,** *60*, 259-267.

(13) White, D. R; Hutt, J. T; Wolfe, J. P. “Asymmetric Pd-Catalyzed Alkene Carboamination Reactions for the Syntehsis of 2-Aminoindane Derivatives” *J. Am. Chem. Soc*., **2015,** *137*(35). 11246-11249.

(14) Hui, C.; Liu, Y.; Jiang, M.; Wu, P. “Cyclobutane-Containing Scaffolds in Bioactive Small Molecules” *Trends in Chemistry Cell Press,* **2022,** *4* (8), 677-681.

(15) Van der Kolk, M. R.; Janssen, M. A. C. H.; Rutjes, F. P. J. T.; Blanco-Ania, D. B. “Cyclobutanes in Small-Molecule Drug Candidates” *ChemMedChem,* **2022,** *17* (9), e202200020.

(16) Dembitsky, V. M. “Naturally Occuring Bioactive Cyclobutane-Containing (CBC) Alkaloids in Fungi, Fungal Endophytes, and Plants” *Phytomedicine,* **2014,** *71* (12), 1559-1581.

(17) Nakahima, K.; Oyama, M.; Ito, T.; Akao, Y.; Witona, J. R.; Darnaedi, D.; Tanaka, T.; Murata, J.; Iinuma, M. “Novel Quinolinone Alkaloids Bearing a Lignoid Moiety and Related Constitutents in the Leaves of Melicope Denhamii” *Tetrahedron,* **2012**, *68*, 2421-2428.

(18) Liu, Y.; Laufer, R.; Patel, N. K.; Ng, G.; Sampson, P. B.; Li, S-W.; Lang, Y.; Feher, M.; Brokx, R.; Belestkaya, I.; Hodgson, R.; Plotnikova, O.; Awrey, D.E.; Qui, W.; Chirgadze, N. Y.; Mason, J. M.; Wei, X.; Lin, D. C-C.; Che, Y.; Kiarash, R.; Fletcher, G. C.; Mak, T. W.; Bray, M. R.; Pauls, H. W.

"Discovery of Pyrazolo[1,5-a] pyrimidine TTK Inhibitors: CFI-402257 is a Potent, Selective, Bioavailable Anticancer Agent" *ACS Med Chem Lett.*, **2016,** *7*(7), 671-675.

(19) Yang, P.; Jia, Q.; Song, S.; Huang, X. "[2+2] Cycloaddition-derived Cyclobutane Natural Products: Structural Diversity, Sources, Bioactivities, and Biomimetic Syntheses" *Nat. Prod. Rep.,* **2023**, *40*, 1094-1129.

(20) Li, J.; Gao, K.; Bian, M.; Ding, H. "Recent Advances in the Total Synthesis of Cyclobutane-Containing Natural Products" *Org. Chem. Front*., **2020,** *7*, 136-154.

(21) Poplate, S.; Troster, A.; Zou, Y-Q.; Bach, T. "Recent Advances in the Synthesis of Cyclobutanes by Olefin [2+2] Photocycloaddition Reactions" *Chemical Reviews,* **2016**, *116* (17), 9748-9793.

(22) Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. "Enantioselective Total Synthesis of (+)-Psiguadial B" *J. Am. Chem. Soc*., **2016,** *138*, 9803-9806.

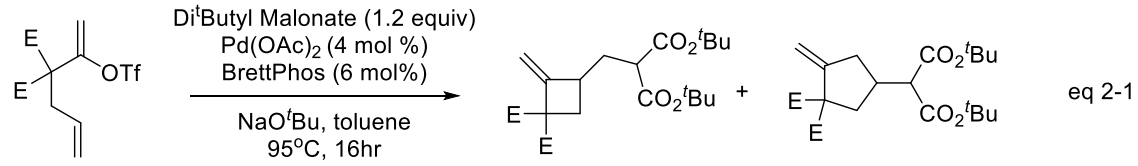
(23) Xie, J.; Wang, J.; Dong, G. "Synthetic Study of Phainanoids. Highly Diastereoselective Construction of the 4,5-Spirocycle via Palladium-Catalyzed Intramolecular Alkenylation" *Org Lett,* **2017**, *19* (11), 2777-3038.

(24) Bertrand, M. B.; Wolfe, J. P.; "Palladium-Catalyzed Synthesis of Cyclopentane-Fused Benzocyclobutenes via Tandem Directed Carbopalladation/C-H Bond Functionalization" *Org. Lett,* **2007**, *9* 3073-3075

Chapter 2 Mechanistic Insights into Regiodivergent Palladium-Catalyzed Alkene Difunctionalization Reactions for the Construction of Malonate Methylene Cyclopentanes and Other Studies

2.1 Introduction

As described in the previous chapter, our group has reported a series of palladium-catalyzed alkene difunctionalization reactions for the synthesis of functionalized methylene cyclopentanes.[1] In general, these transformations form carbocycles in good yield and diastereoselectivity through coupling reactions between 1,5-dien-2-yl triflates and an external nucleophile. In 2019, a version of this method was published which included malonates, ketones and esters in the nucleophile scope.[2] These substrates demonstrated a generally high selectivity for 5-endo-cyclization. However, upon probing this reaction with the gem-diester substrate **2-1a** with di-tert-butyl malonate under standard conditions, a new functionalized cyclobutane regioisomer was produced (eq 2-1)



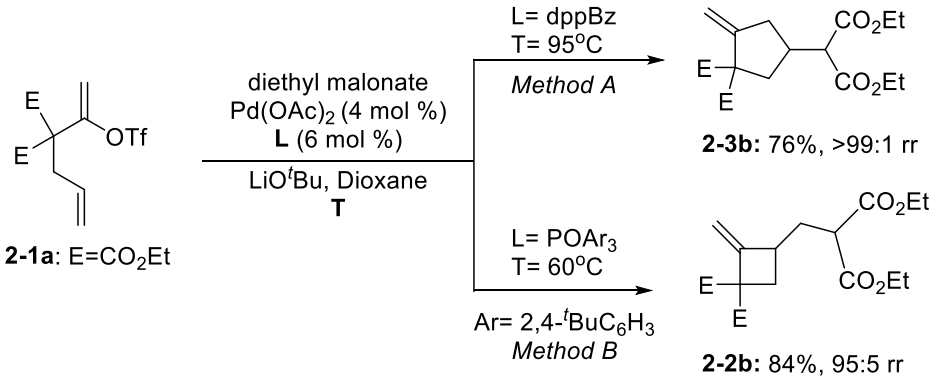
2-1a: E=CO_2Et **2-2a** **2-3a**

53% yield, 1:4 rr

Extensive optimization by previous Wolfe group members, Dr. Evan Bornowski, James Shepich, Paige Carpenter, and Dr. Derick White, indicated this reaction could be tuned to select for one regioisomer over the other from the same starting materials by altering ligand and

temperature.[3] The cyclopentane regioisomer **2-3b** could be selected for by using small bite angled bidentate ligands (e.g. dppBz) and higher temperatures (Method A, Scheme 2-1). These conditions are thought to prevent the migratory insertion step leading to the cyclopentane product. Yield and regiomeric ratios were also improved upon the use of additional equivalents of the diethyl malonate nucleophile. On the other hand, electron-deficient monodentate ligands (e.g. tris(2,4-di-*tert*-butylphenyl)phosphite) and lower temperatures demonstrated preference for the cyclobutane regioisomer **2-2b** (Method B, Scheme 2-1). The monodentate phosphite ligand presumably facilitates the migratory insertion, which likely occurs through an intermediate bearing a single ligand.

Scheme 2-1: Regiodivergent Methods

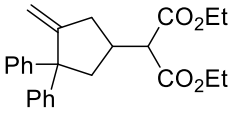


These conditions were then used to explore the 1,5-dien-2-yl triflate substrate scope by varying the geminal disubstituents at the C3 position. The selectivity was found to be largely dependent upon the identity of the groups beta to the triflate. Relatively large groups more readily formed the cyclobutane products in both methods. This can be attributed to the Thorpe-Ingold Effect in which larger groups favor the intermediary ring closure (migratory insertion) that is proposed to be the deviating step between the two pathways (Scheme 2-3). For example, when the C3 position was substituted with large phenyl groups, in Method A the regiomeric ratio was

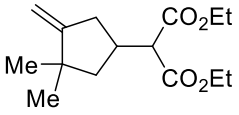
only moderate for the cyclopentane product **2-3c** (77:23) but in Method B, the cyclobutane product was formed in >99:1 rr **2-2c** (Scheme 2-2). The inverse is also true such that small groups favored the cyclopentane product. For example, geminal dimethyl substitution at C3 gave the cyclopentane product **2-3d** in >99:1 rr in Method A and the cyclobutane product **2-2d** in only 60:40 rr in Method B (Scheme 2-2).

Scheme 2-2: Representative Substrate Scope

Method A

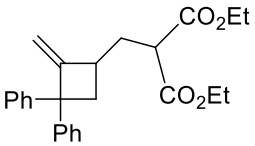


2-3c: 71%, 77:23 rr

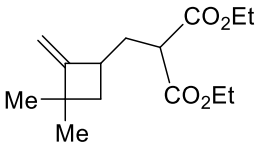


2-3d: 72%, >99:1 rr

Method B



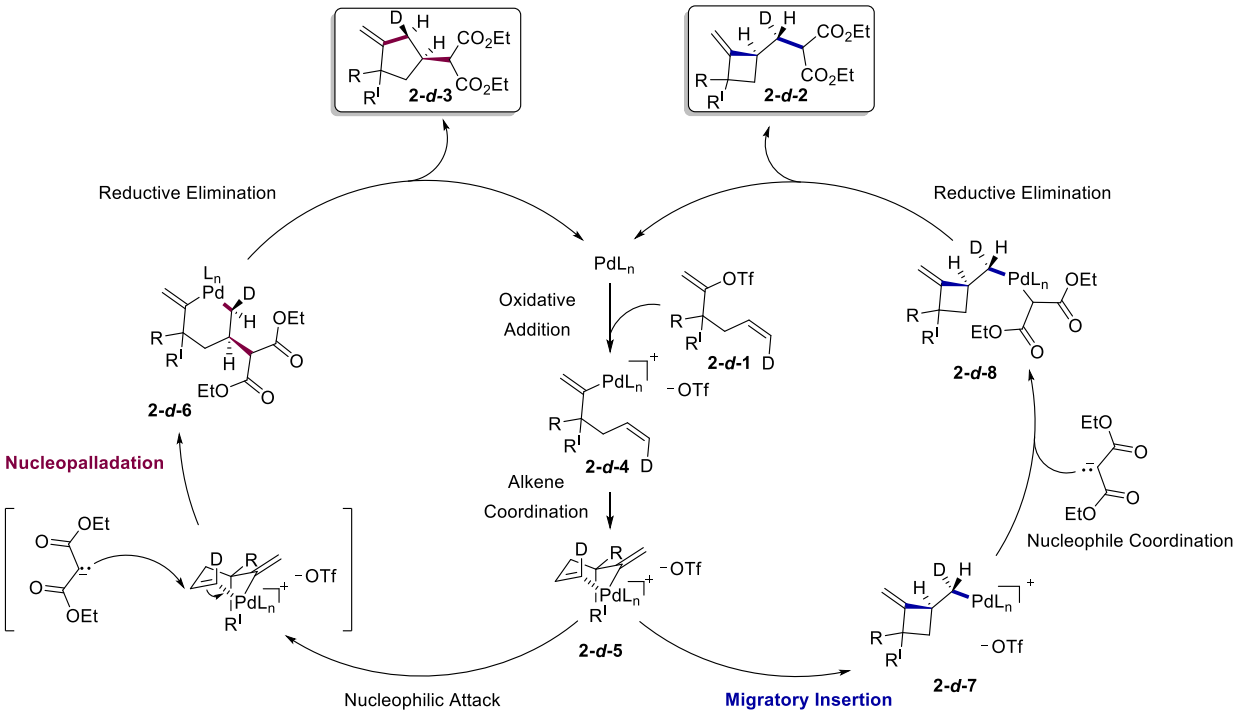
2-2c: 74%, >99:1 rr



2-2c: 86%, 60:40 rr

This reactivity was taken advantage of during mechanistic studies into the formation of the desired products for both Method A and Method B. The mechanism is proposed to be regiodivergent, with both pathways starting with oxidative addition of the alkenyl triflate **2-*d*-1** to the active palladium (0) species, ligated by a phosphine ligand, forming a Pd(II) species (**2-*d*-4,** Scheme 2-3). The palladium then coordinates to the tethered alkene forming, what is proposed to be, a six-membered intermediate **2-*d*-5**. At this point the pathway diverges. Method A was originally probed using dimethyl deuterated triflate (**2-*d*-1,** R = R^1 = Me) by Dr. Evan Bornowski. He found the nucleophile attacks the alkene in an *anti*-nucleopalladation step to form a palladacycle **2-*d*-6**. This species then undergoes reductive elimination to form the functionalized five-membered ring **2-*d*-3** and regenerate the active Pd(0) species. Method B was probed using diphenyl

Scheme 2-3: Regiodivergent Mechanism



deuterated triflate (**2-*d*-1,** R = R^1 = Ph). Dr. Bornowski proposed that after the alkene of the electrophile coordinates to the palladium (**2-*d*-5**), instead of the nucleophile attacking, the electrophile undergoes a 4-exo migratory insertion to form the carbocycle **2-*d*-7**. The nucleophile then captures the cyclobutane derived product **2-*d*-2** through reductive elimination. Currently, it is still unclear whether the nucleophile coordinates to the palladium center prior to, after (**2-*d*-8**), or in concert with the migratory insertion event.

My primary contributions to this published work[3] were in the elucidation of the mechanism for cyclopentane products under both Method A and Method B as detailed below (2.2, 2.3, 2.4). Additional studies included probing the effect of the palladium to ligand ratio on regiomeric ratios (2.5) and an additional example in the substrate scope (2.6)

Dr. Derick White, Dr. Evan Bornowski, Ms. Paige Carpenter, and Mr. Jim Shepich III made contributions to the work described in this chapter. Dr. White conducted initial preliminary

studies and identified the cyclobutane side product (eq 2-1). Dr. Bornowski conducted reaction optimization (Scheme 2-1), synthesized starting materials and applied the method to the substrate scope (Scheme 2-2), proposed the regiodivergent catalytic cycle (Scheme 2-3), and conducted the initial dimethyl deuterated triflate route (Scheme 2-4). Mr. Shepich and Ms. Carpenter assisted with substrate synthesis (Scheme 2-2).

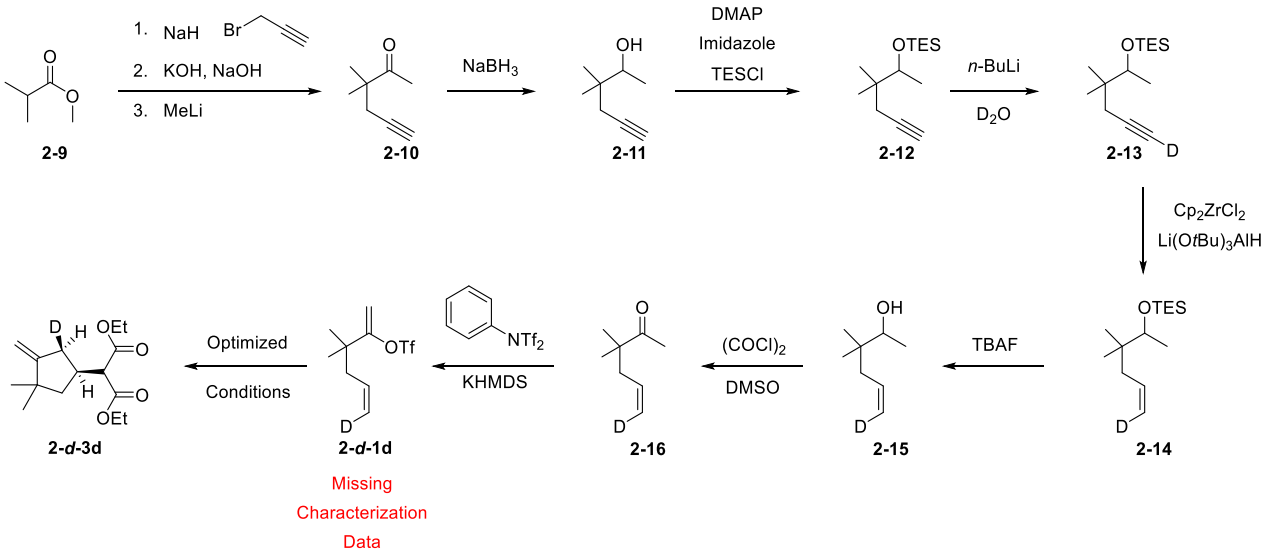
2.2 Mechanistic Study into Methylene Cyclopentanes Using Deuterated Diphenyl Triflate

As stated above, originally Method A was probed using dimethyl deuterated triflate **2-*d*-1d** by Dr. Evan Bornowski. This triflate was synthesized in 10 steps at an overall 0.25% yield (Scheme 2-4). The synthetic route started with an enolate alkylation to dimethyl acetate **2-9** with propargyl bromide, followed by conversion of the ester to a ketone **2-10** via an intermediate carboxylic acid. The ketone was reduced to the alcohol **2-11** and protected with a TES group (**2-12**, Scheme 2-4). The deuterium atom was installed by deprotonation with n-BuLi and quenching with D_2O. The alkyne **2-13** was reduced to the Z-alkene **2-14** using Schwartz's reagent. The alcohol was then deprotected (**2-15**) and oxidized back to the ketone **2-16**. The triflate **2-*d*-1d** was formed via the deprotonation to give the corresponding enolate followed by subsequent *O*-triflation. The substrate **2-*d*-1d** was then subjected to Method A conditions. Through nOe analysis of the resulting cyclopentane **2-d-3d** and comparison to the NMRs of the proteo version, Dr. Bornowski found the nucleophile attacks the alkene in an *anti*-nucleopalladation step (Scheme 2-3).

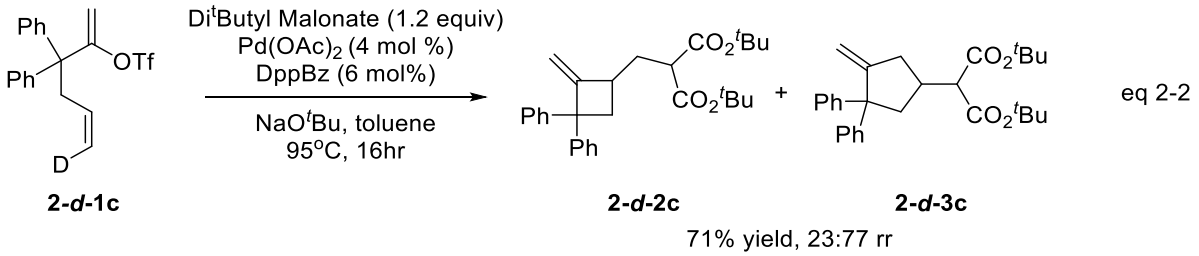
Unfortunately, the triflate **2-*d*-1d** was not fully characterized prior to use in the cyclopentane reaction and there was not enough compound remaining to obtain the necessary ^{13}C NMR, HRMS, and IR data needed for publication. Multiple individuals in the lab attempted the synthesis outlined above and were not able to produce enough material to characterize the

triflate **2-*d*-1d**. The primary issue was volatility of every intermediate due to their low molecular weights.

Scheme 2-4: Original Dimethyl Triflate Route



To address this challenge, I sought a method to determine the mechanism of nucleopalladation without the use of triflate **2-*d*-1d**. On hand was the deuterated diphenyl triflate ***d*-2-1c**. This compound was previously used to elucidate the mechanism Method B by Dr. Evan Bornowoski. It did not have the same volatility challenges as the triflate **2-*d*-1d** and as such, there was an excess of the material stored in the freezer and it had been fully characterized. This compound was not previously used in the investigation of Method A because when subjected to the optimized conditions, it did not selectively form the cyclopentane product ***2-d*-3c** (eq 2-2). This presented a potential issue, because if the regioisomers were inseparable it would convolute 2-dimensional NMR analysis and make stereochemical assignments challenging.

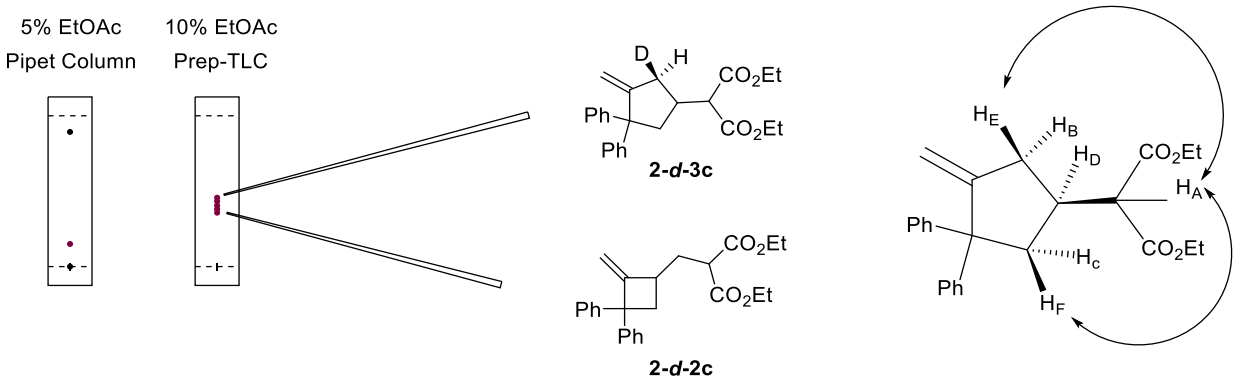


2-*d*-1c **2-*d*-2c** **2-*d*-3c**

71% yield, 23:77 rr

However, after carrying out the reaction, despite obtaining a mixture, I found that the regioisomers were separable under chromatography conditions (Scheme 2-5). I developed and utilized a two step purification method in which a pipette column (5:95 EtOAc:Hexanes) allowed for the mixture of regioisomers to be separated from all other impurities (starting material, phosphine oxide, intramolecular Heck cyclization by-product, etc.) The resulting crude material could then be subjected to preparative thin-layer chromatography (10:90 EtOAc:Hexanes). The spot containing the two products would streak on the plate, allowing for the top portion of the spot to be harvested as exclusively cyclopentane **2-*d*-3c.** The stereochemistry of **2-*d*-3c** was determined by assigning the regiochemistry/stereochemistry of each proton in **2-3c** via COSY/nOe, and then comparing the spectrum of the deuterated product to determine which H signal was absent. Through this method, the stereochemistry was consistent with what was observed previously in dimethyl cyclopentane **2-*d*-3c**, corroborating the mechanism proposed for Method A and thereby circumventing the need for the triflate **2-*d*-1d.**

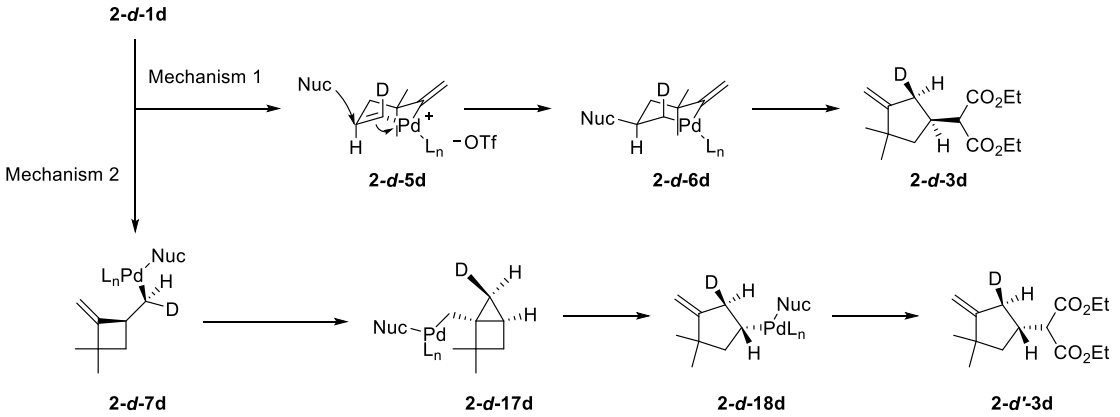
Scheme 2-5: Isolation of Regioisomers



2.3 Mechanistic Study into Methylene Cyclopentanes Using Deuterated Dimethyl Triflate

Upon submission of this paper into *Organic Letters*, a reviewer suggested a possible alternative mechanism for the formation of cyclopentane **2-3d** under Method B. As explained above, Method B promotes cyclobutane ring formation; however, when the groups at the C3 position are too small (e.g. methyls groups) the reaction has poor regioselectivity and forms cyclopentane **2-3d** as a major side product. The reviewer proposed that this cyclopentane may not be formed through Mechanism A, but rather an alternative pathway (Mechanism B, Scheme 2-6). In this proposed pathway, after **2-*d*-1d** undergoes oxidative addition followed by carbopalladation, intermediate **2-*d*-7d** could, in principle, undergo a second migratory insertion to afford housane **2-*d*-17d**, which could undergo beta-alkyl elimination to **2-*d*-18d**, followed by reductive elimination to yield **2-*d'*-3d**, a stereoisomer of **2-*d*-3d**.

Scheme 2-6: Possible Mechanisms



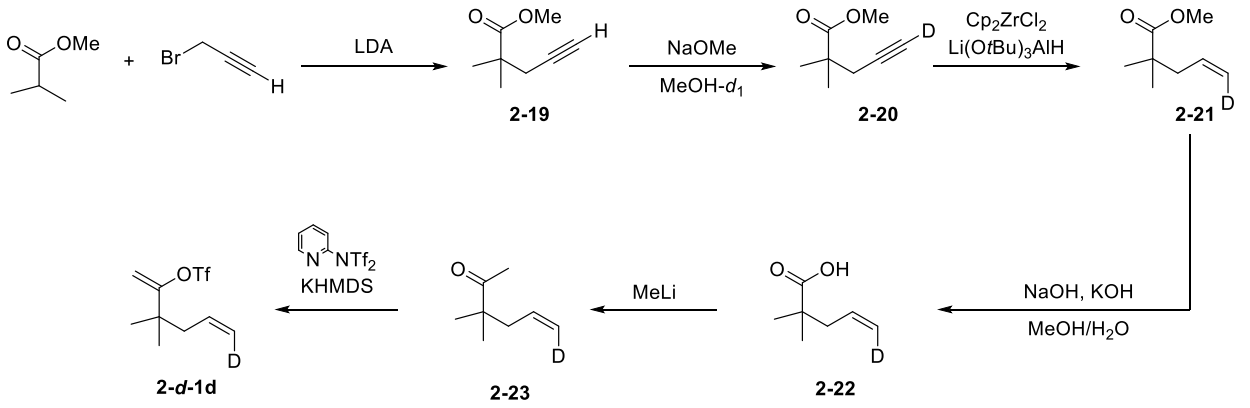
In order to probe whether the minor 5-membered regioisomer is formed via anti-aminopalladation under conditions that favor the 4-membered ring product, I carried out the coupling of **2-*d*-1d** (the revised synthesis of which is detailed in section 2.4) with diethyl malonate in the presence of the Pd/phosphite catalyst system. Under these conditions, minor regioisomer was formed with the same relative stereochemistry as **2-*d*-3d** (cis D/malonate relationship), which was prepared using the conditions optimized for 5-membered ring formation. This suggests the mechanism of 5-membered ring formation occurs via the same mechanism (nucleopalladation of **2-*d*-5d**), regardless of catalyst.

2.4 Deuterated Dimethyl Triflate

In order to accomplish the study detailed above, triflate **2-*d*-1d** needed to be synthesized. As previously stated, this compound was challenging to prepare due to its volatility, along with the volatility of every intermediate in the 10 step route. Therefore, we sought to revise the synthesis to reduce the number of steps and eliminate/improve purifications. The previous route (Scheme 2-4) installed the deuterium using n-BuLi, which required the use of oxidation state manipulations of the ketone and a protection/deprotection strategy, all of which required

purification steps and led to overall losses in yield. To circumvent these steps, I used a milder base (NaOMe) to install the deuterium. Additionally, to address the loss of product due to purification, I incorporated a saponification step which yielded a carboxylic acid which was less volatile and more readily purified, allowing for an intensive purification to be avoided on most other steps. Finally, I also revised the final triflation procedure to use a shorter reaction time and a more easily separable triflating reagent which helped eliminate purification challenges and degradation of the final product. With these changes, I was able to reduce the step count from 10 to 6 and improve the overall yield 10 fold (2.5% compared to 0.25%), thereby affording enough material to characterize triflate **2-*d*-1d** and subject it to the necessary experiments as detailed above.

Scheme 2-7: Revised Route to Dimethyl Triflate



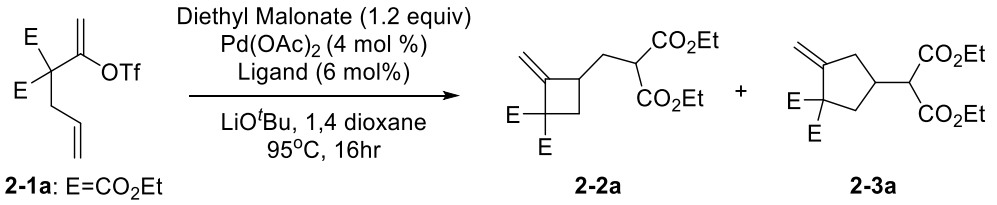
The revised synthesis of triflate **2-*d*-1d** is as follows (Scheme 2-7). The route started with alkylation of methyl isobutyrate with propargyl bromide to yield the ester **2-19**. The deuterium atom was installed using sodium methoxide as the base and MeOH-d^1 as the deuterium source. The alkyne **2-20** was reduced to the Z-alkene **2-21** using Schwartz's reagent. The ester **2-21** was saponified to the carboxylic acid **2-22** and subsequent methylation to obtain the ketone **2-23**.

Finally, the triflate **2-*d*-1d** was formed via the deprotonation of the enolate and subsequent *O*-triflation using *N*-pyridyl triflimide.

2.5 Palladium: Ligand Ratio Study

I also worked to address a second comment that arose during review of the manuscript. One referee noted that, in optimization studies, 6 mol% of ligand is employed with the same amount of palladium both when the ligand is monodentate and when it is bidentate (Table 2-1). This prompted the reviewer to ask if the palladium: ligand (Pd:Ln) ratio had an impact on the regiomeric ratios (rr). This experiment could potentially generate results that either supported, or conflicted with, our hypothesis about the effect of ligand denticity on rr and was worth a further investigation.

Table 2-1: Comparison of Conditions



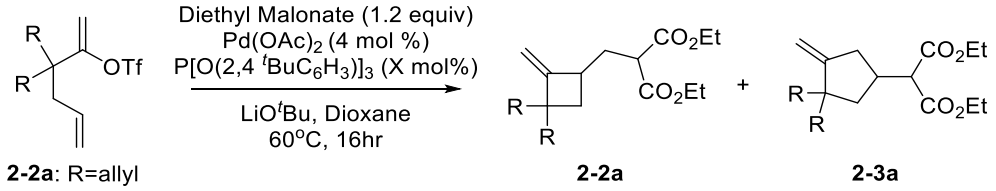
2-1a: E=CO_2Et **2-2a** **2-3a**

Entry	Ligand	**2-2a/2-3a**	Yield (%)[b]
1	dppbz	2:98	55
2	$HPCy_3BF_4$	85:15	40

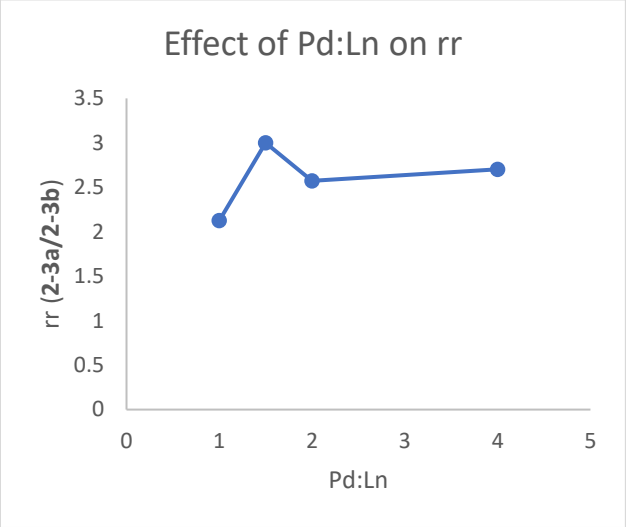
To address this inquiry, the coupling of alkenyl triflate **2-1b** with diethyl malonate was conducted under standard 4-membered ring forming conditions (Method B, Scheme 2-2). This substrate was chosen because under optimized conditions, the rr was moderate (75:25 rr) and the yield was good (80%), thus any changes, positive or negative, would be observable. The Pd:Ln ratio was varied from 1:1, 1:2 and 1:4 and compared against the optimized result. Across all conditions, neither the rr or yield varied significantly. This is consistent with our suggestion that

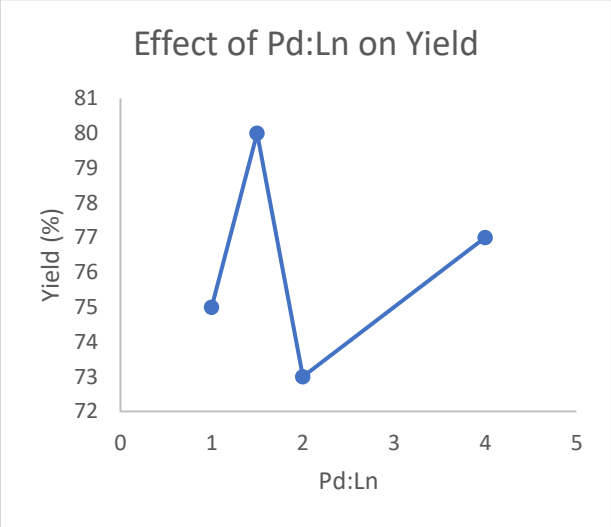
only one monodentate ligand is coordinated to the palladium center at a time during the migratory insertion step.

Scheme 2-8: Effect of Pd:Ln on Yield



2-2a: R=allyl **2-2a** **2-3a**

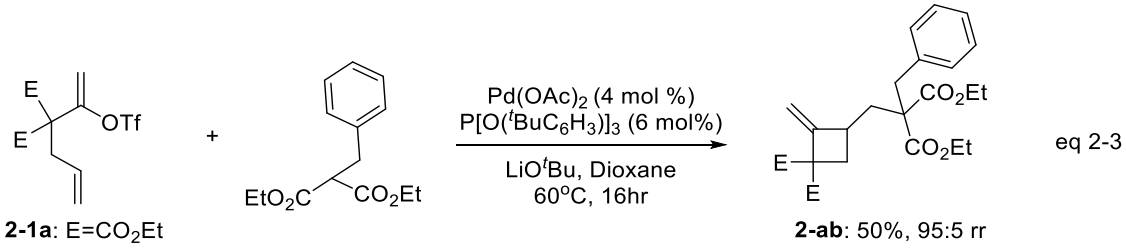




2.6 Nucleophile Scope

Initial studies on the scope of this methodology included a wide range of 10 different electrophiles. The nucleophile scope, on the other hand, was limited to only diethyl malonate and ethyl acetoacetate. We sought to expand this by incorporating more substituted malonate derivatives. Both phenyl diethyl malonate and diethyl benzyl malonate were screened in the optimized four-membered ring reaction conditions with the model triflate **2-1a**. Both afforded desired products, however, we only reproduced the result and characterized the product from the diethyl benzylmalonate reaction due to its' slightly better performance in the reaction (assessed by NMR yield) and cleaner crude reaction mixtures. The final product **2-2b** was

obtained in 50% yield 5:95 rr (eq 2-3) as an average of two reactions of the same scale and method. This result indicates that the method is able to be applied to malonate nucleophiles that are substituted at the internal methylene position.



2-1a: E=CO_2Et **2-ab**: 50%, 95:5 rr

2.7 Conclusions

In conclusion, previous group members developed a regiodivergent alkene difunctionalization reaction that selectively forms either functionalized methylene cyclobutanes or methylene cyclopentanes in good yield with high regioselectivities.[1] My contributions to this work enabled publication of these methods by resolving outstanding issues and addressing additional questions that arose during the revision process. The experiments I conducted provided support for claims made throughout the report and lead to additional insights into the mechanism of the transformation.

The work described in this chapter was published in *Organic Letters*.[3] This chapter was adapted with permission from Bornowski, E. C.; Shepich, J. H.; Carpenter, P. M.; White, D. W.; Hatt, J. E.; Wolfe, J. P. "Regiodivergent Palladium-Catalyzed Alkene Difunctionalization Reactions for the Construction of Methylene Cyclobutanes and Methylene Cyclopentanes." *Org. Lett*. **2022**, *24* (44), 8208–8212. Copyright (2022) American Chemical Society.

2.8 Experimental

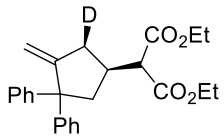
General Procedure A: Synthesis of Substituted Cyclobutanes

A 10 mL Schlenk tube equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (0.008 mmol, 1.8 mg, 0.04 equiv), tris(2,4-di-tert- butylphenyl)phosphite (0.012 mmol, 7.8 mg, 0.06 equiv), and lithium tert-butoxide (1.00 mmol, 80.1 mg, 5 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. The alkenyl triflate (0.2 mmol, 1.0 equiv) was weighed in a nitrogen-flushed dram vial capped with a septum and diluted with 1,4 dioxane (1 mL). This substrate solution was added to the Schlenk tube, followed by diethyl malonate (1 mmol, 160 µL, 5 equiv). Then 1,4 dioxane (1 mL) was used to rinse the dram vial and the resulting solution was transferred to the Schlenk tube. The Schlenk tube was then heated to 60 °C with stirring overnight until the starting material had been consumed. The mixture was then cooled to rt, quenched with saturated aqueous ammonium chloride (2 mL), then transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 1 mL), then the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel.

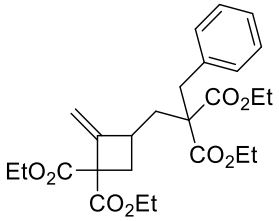
General Procedure B: Synthesis of Substituted Cyclopentanes

A 10 mL Schlenk tube equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with $Pd(OAc)_2$ (0.008 mmol, 1.8 mg, 0.04 equiv), 1,2-bis(diphenylphosphino)benzene (0.012 mmol, 5.4 mg, 0.06 equiv), and lithium tert-butoxide (1.00 mmol, 80.1 mg, 5 equiv). The Schlenk tube was evacuated and refilled with N_2 twice. The alkenyl triflate (0.2 mmol, 1.0 equiv) was weighed in a nitrogen-flushed dram vial capped with a septum and diluted with 1,4 dioxane (1 mL). This substrate solution was added to the Schlenk

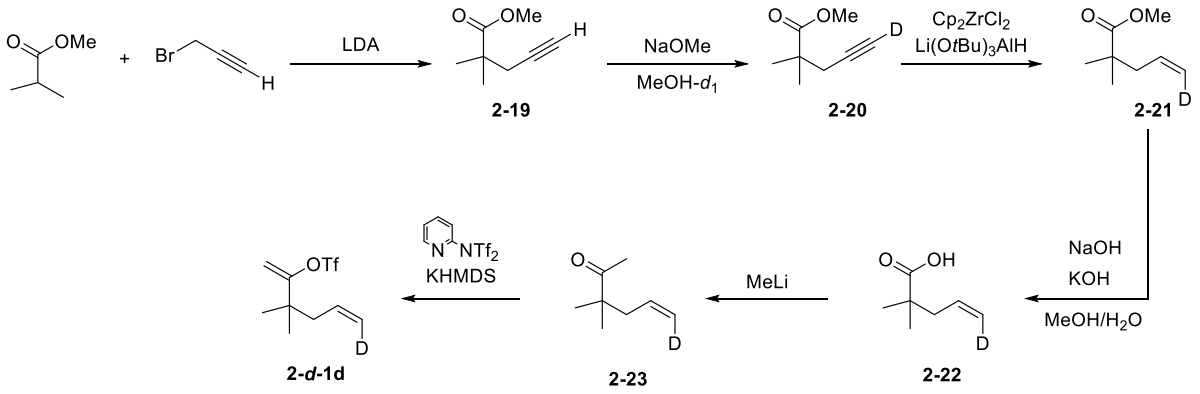
tube, followed by diethyl malonate (1 mmol, 160 µL, 5 equiv). Then 1,4 dioxane (1 mL) was used to rinse the dram vial and the resulting solution was transferred to the Schlenk tube. The Schlenk tube was then heated to 95 °C with stirring for 1 h until the starting material had been consumed. The mixture was then cooled to rt, quenched with saturated aqueous ammonium chloride (2 mL), then transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (3 x 1 mL), then the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel.



(±)-(1S*,5S*)-Diethyl 2-(4-methylene-3,3-diphenylcyclopentyl-5-D)malonate (2-*d*-3c) The title compound was prepared from (Z)-3,3-diphenylhexa-1,5-dien-2-yl-6-D trifluoromethanesulfonate (0.1 mmol, 38.3 mg) according to a modified version of General Procedure B where diethyl malonate (0.2 mmol, 32 µL), sodium tert-butoxide (0.2 mmol, 19.2 mg) and toluene (1 mL, 0.1 M) were used and the reaction stirred for 16 hr. The crude material was purified using column chromatography. This procedure afforded 4.4 mg (11%) of the title compound as a colorless oil. The reported peaks are for the title compound. 1 H NMR (500 MHz, CDCl3) d 7.25 – 6.95 (m, 10H), 5.13 (d, J = 1.8 Hz, 1H), 4.54 (d, J = 2.2 Hz, 1H), 4.19 – 4.03 (m, 4H), 3.21 (d, J = 9.9 Hz, 1H), 2.75 – 2.67 (m, 2H), 2.54 – 2.46 (m, 1H), 2.26 – 2.18 (m, 1H), 1.23 – 1.15 (m, 6H). 13C NMR (126 MHz, CDCl3) d 168.7, 168.6, 155.9, 146.8, 145.11 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 126.3, 126.0, 111.4, 61.4, 61.3, 60.6, 57.1, 46.1, 35.2, 29.7, 14.1. IR (film) 2980, 2922, 1748, 1733 cm-1 ; HRMS (EI+TOF) m/z: [M]+ calcd for C25H27DO4 393.2052; found 393.2058.



Diethyl3-(2-benzyl-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-2-methylenecyclobutane-1,1-dicarboxylate (2-2b) The title compound was prepared from 2-allyl-2-(1 -{[(trifluoromethyl) sulfonyl]oxy}vinyl)malonate (0.1 mmol, 37.4 mg) using General Procedure A with diethyl benzylmalonate. The crude material was purified via column chromatography on silica gel using 85:15 hexanes:ethyl acetate as the eluent. This procedure afforded 23.7 mg (50%) of the title compound (95:5 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 3H), 7.10 – 7.05 (m, 2H), 5.31 (d, J = 3.0 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.28 – 4.10 (m, 8H), 3.31 – 3.20 (m, 3H), 2.62 (dd, J = 11.8, 9.0 Hz, 1H), 2.28 (dd, J = 11.7, 8.2 Hz, 1H), 2.13 – 1.99 (m, 2H), 1.31 – 1.16 (m, 12H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.20, 170.98, 169.92, 169.45, 168.72, 147.88, 135.83, 130.36, 129.95, 128.28, 128.11, 127.14, 127.03, 109.58, 62.57, 61.77, 61.54, 61.36, 59.68, 57.32, 40.46, 38.70, 36.85, 36.31, 33.57, 14.09 – 13.93 (m). IR (film) 2982, 1727, 1239, 1096 cm-1; HRMS (EI+) m/z: calcd for C26H34O8 474.2254; found 474.2238.



(*Z*)-3,3-Dimethylhexa-1,5-dien-2-yl-6-d trifluoromethanesulfonate (2-*d*-1d). A flask equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with diisopropylamine (47.9 mmol, 6.75 mL, 1.45 equiv) and THF (50 mL, 1 M). The mixture was cooled to -78°C and *n*BuLi (36.3 mmol, 2.5 M in hex, 15.5 mL, 1.1 equiv) was added dropwise. The mixture was stirred for 10 minutes and a solution of methyl isobutyrate (33 mmol, 3.78 mL, 1.0 equiv) in THF (25 mL, 1 M) was added dropwise. The mixture was stirred for 1 hr at -78 °C, then d^3-propargyl bromide[4] (80% wt in toluene, 33 mmol, 4 g, 1 equiv) was added dropwise, and the mixture was stirred for 1 hr at -78 °C. The mixture was warmed to rt and allowed to stir overnight (15 h), then the reaction was quenched with aqueous ammonium chloride (50 mL), the mixture was stirred briefly, then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow oil. The crude material was purified on silica gel using 15:85 ethyl acetate:hexanes as an elutent. This procedure afforded 1.48 g (32%) of methyl 2,2-dimethylpent-4-ynoate (**2-19**) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$) □ 3.70 (s, 3 H), 2.44 (dd, *J* = 2.8, 1.2 Hz, 2 H), 2.00 (td, *J* = 2.7, 1.2 Hz, 1 H), 1.28 (s, 6 H).

A flask equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with sodium methoxide (2.1mmol, 0.113 g, 0.21 equiv) and d^1-methanol (10 mL). **2-19** was added in a solution of d^1-methanol (10 mL, 1M). The mixture was stirred at rt for 48 hr. d^1-acetic acid (1 mL) was added to quench the reaction. Water (50 mL) was added and the aqueous layer was extracted with DCM (3x 20mL). The combined organic layers

were dried over $MgSO_4$ and concentrated carefully in vacuo to yield methyl 2,2-dimethylpent-4-ynoate-5-*d* (**2-20**) as a yellow oil (>99% deuterium incorporation). Due to the volatility of the title compound, significant amounts of solvent remained and this material was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.44 (s, 2H), 1.28 (s, 6H).

A flask equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with bis(cyclopentadienyl)zirconium(iv) dichloride (14.7 mmol, 4.3 g, 1.4 equiv), followed by a solution of **2-20** (10.5 mmol, 1 equiv) in THF (16 mL, 0.65 M). The mixture was stirred for 10 minutes, then a solution of lithium tri tert-butoxy aluminum hydride (14.7 mmol, 3.74 g, 1.4 equiv) in THF (19 mL, 0.8 M) and was added to the mixture. The mixture was stirred for 12 minutes at rt, then the reaction was placed in an ice water bath and immediately quenched with saturated ammonium chloride (10 mL) and stirred for 10 minutes. THF was removed under reduced pressure and then the mixture was transferred to a separatory funnel. The aqueous layer was extracted with DCM (3 x 20 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated carefully in vacuo to yield methyl (Z)-2,2-dimethylpent-4-enoate-5-d (**2-21**) as a yellow oil. Due to the volatility of the title compound, significant amounts of solvent remained and this material was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.75 – 5.66 (m, 1H), 5.02 (d, J = 10.1 Hz, 1H), 3.65 (d, J = 1.5 Hz, 3H), 2.27 (d, J = 7.3, 1.0 Hz, 2H), 1.17 (s, 6H).

A flask equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with potassium hydroxide (50 mmol, 2.8 g, 5 equiv) and sodium hydroxide (11 mmol, 0.44 g, 1.1 equiv). Water (20mL) was added to the flask, followed by a solution of **2-21** (10 mmol, 1 equiv) in methanol (40 mL, 0.25 M). The flask was equipped with a

reflux condenser and the mixture was refluxed at 90 °C overnight (16hr). The mixture was then cooled to rt and then the mixture was transferred to a separatory funnel. The solution was extracted with DCM (3 x 20 mL), then 1 M HCl was added to the solution until the aqueous layer turned acidic (pH 3), and the acidic aqueous layer was extracted with DCM (3 x 20 mL). The combined, organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a brown oil. The crude material was dissolved in DCM and washed with 1 M NaOH. The organic layer was discarded and the aqueous layer was washed with 3 M HCl until the solution was acidic (pH 3). The acidic aqueous layer was extracted with DCM (3x 20mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. This procedure afforded 0.648 g (47% over 3 steps) of (Z)-2,2-dimethylpent-4-enoic-5-d acid (**2-22**) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.79 – 5.73 (m, 1H), 5.07 (d, J = 9.9 Hz, 1H), 2.31 (d, J = 7.3 Hz, 2H), 1.22 – 1.18 (m, 6H).

A flask equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with **2-22**(4.5 mmol, 1 equiv) and diethyl ether (5 mL, 1 M). The mixture was cooled to -78 °C and methyllithium (9 mmol, 1.6 M in Et_2O, 5.6 mL, 2.2 equiv) was added dropwise. The mixture was stirred for 10 minutes at -78 °C, then allowed to warm to room temperature. The flask was then equipped with a reflux condenser, and the reaction was refluxed at 50 °C while stirring rapidly for 3 hours. The mixture was cooled to rt, quenched with saturated ammonium chloride (20 mL), and transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (3 x 10 mL), then the combined, extracted organic layers were washed with brine, dried over $MgSO_4$, filtered and carefully concentrated in vacuo to yield a yellow oil. The crude material was purified via column chromatography on silica gel using 95:5

hexanes:diethyl ether as the eluent to afford 0.64g (50%) of (Z)-3,3-dimethylhex-5-en-2-one-6-d (**2-23**) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 – 5.62 (m, 1H), 5.03 (d, *J* = 10.0, 1.1 Hz, 1H), 2.26 (d, *J* = 7.4, 1.1 Hz, 2H), 2.12 (s, 3H), 1.12 (s, 6H).

A flask equipped with a stir bar was flame-dried under vacuum, then cooled under a stream of nitrogen and charged with potassium hexamethyldisilazane (2.37 mmol, 0.474 g, 1.2 equiv) and THF (15 mL). The mixture was cooled to -78 °C, then a solution of **2-23** (1.98 mmol, 0.252 g, 1 equiv) in THF (4 mL) was added dropwise. The mixture was stirred for 1 hr at -78 °C, then a solution of *N*-(2-pyridyl)bis(trifluoromethanesulfonimide) (2.17 mmol, 0.777 g, 1.1 equiv) in THF (4.7 mL) was added to the mixture at -78 °C. The mixture was stirred for 2 hrs at -78 °C. The cold solution was poured over saturated sodium bicarbonate (20 mL) in a separatory funnel. The aqueous layer was extracted with pentanes (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to yield a yellow-orange oil. The crude material was purified via column chromatography on silica gel using 100% pentanes as the eluent. This procedure afforded 0.167 g (33%) of the title compound as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.76 – 5.65 (m, 1H), 5.12 (d, *J* = 3.3 Hz, 1H), 5.08 (d, *J* = 10.2, 2.2 Hz, 1H), 4.92 (d, *J* = 4.7, 2.1 Hz, 1H), 2.19 (d, *J* = 7.5, 2.2 Hz, 2H), 1.15 (s, 6H).^{13}C NMR (176 MHz, $CDCl_3$) δ 162.6, 133.1, 118.3, 118.2, 101.1, 43.6, 39.5, 25.2. IR (film) 1417, 1210, 926 cm^{-1}; HRMS (APCI^{+}TOF) m/z: [M + H^{+}]$^{+}$ calcd for $C_9H_{13}DF_3O_3S$ 260.0673; found 260.0686.

2.9 References

(1) White, D. R.; Bornowski, E. C.; Wolfe, J. P. “Pd-Catalyzed C−C, C−N, and C−O Bond-Forming Difunctionalization Reactions of Alkenes Bearing Tethered Aryl/Alkenyl Triflates” *Isr. J. Chem*., **2020**, *60*, 259-267.

(2) Bornowski, E. C.; Hinds, E. M.; White, D. R.; Nakamura, Y.; Wolfe, J. P. “Pd-Catalyzed Alkene Difunctionalization Reactions of Enolates for the Synthesis of Substituted Bicyclic Cyclopentanes” *Org. Process Res. Dev*., **2019**, *23*, 1610-1630.

(3)Bornowski, E. C.; Shepich, J. H.; Carpenter, P. M.; White, D. W.; Hatt, J. E.; Wolfe, J. P. “Regiodivergent Palladium-Catalyzed Alkene Difunctionalization Reactions for the Construction of Methylene Cyclobutanes and Methylene Cyclopentanes.” *Org. Lett*. **2022**, *24* (44), 8208–8212.

(4) Ollis, W. D.; Sutherland, I. O.; Thebtaranonth, Y. “Base Catalyzed Rearrangements Involving Ylide Intermediates. Part 12. The Preparation and Reactions of 2-Oxoiodoanilinium Ylides.” *J. Chem. Soc., Perkin Trans. 1,* **1981**, 1981-1993.

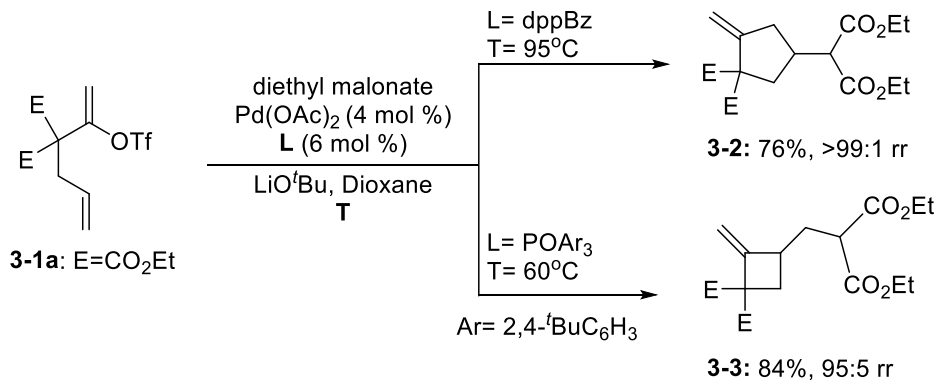
Chapter 3 Palladium-Catalyzed Synthesis of 1-Alkylidene-2- dialkylaminomethyl Cyclobutane Derivatives via Pd-Catalyzed Alkene Difunctionalization Reactions: Influence of Nucleophile and Water on the Reaction Mechanism

3.1 Introduction

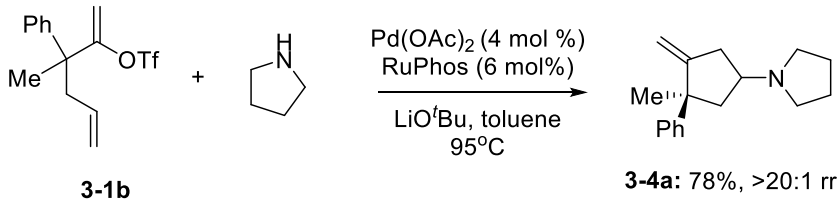
Regiodivergent reactions that can selectively provide different products are both interesting and useful, because they allow for facile generation of different molecular architectures from a single set of starting materials.[1] However, achieving selectivity can be very challenging, especially if a change in the reaction mechanism is required to obtain different regioisomeric products.[2] As described in Chapter 2, we recently reported a regiodivergent synthesis of either exomethylene cyclopentanes or exomethylene-cyclobutanes bearing malonate functional groups via Pd-catalyzed cross coupling reactions of 1,5-diene-2-yl triflates (e.g, **3-1a**) with malonate nucleophiles.[3] For example (Scheme 3-1), treatment of compound **3-1a** with diethyl malonate in the presence of a Pd/dppBz catalyst afforded cyclobutane derivative **3-2** in 76% yield with >99:1 regioselectivity. In contrast, when the bulky phosphite P[O(2,4-$tBuC6H_3]_3$ was used as a ligand, cyclobutane **3-3** was obtained in 84% yield with 95:5 regioselectivity. In this system, regioselectivity was controlled using ligands to modulate the relative rates of migratory insertion versus alkene anti-carbopalladation after oxidative addition of the triflate electrophile.[4] We have also shown that amines can be employed as nucleophiles in alkene difunctionalization reactions of 1,5-dienyl triflates (e.g., **3-1b**), and cyclopentane products

(e.g., **3-4a**, Scheme 3-2) are obtained with high regioselectivity and good to excellent diastereoselectivity.

Scheme 3-1: Regiodivergent Malonate Functionalization



Scheme 3-2: Previous Amine Alkene Difunctionalization



The synthesis of four-membered carbocycles has attracted considerable attention in recent years,[5] but the stereocontrolled synthesis of these compounds remains a considerable challenge. We were interested in extending the scope of our four-membered ring-forming reactions to allow for the incorporation of amine nucleophiles. Aminoalkylcyclobutane units are displayed in both natural products such as benzosceptrin A,[6] and biologically active molecules of pharmaceutical relevance such as butorphanol[7] and sibutramine.[8] Approaches to the synthesis of cyclobutylmethylamine derivatives typically involve reduction or alkylation/reduction of the corresponding nitriles or amides, which in turn require preparation via multi-step synthesis. The functionalized four-membered ring is most commonly generated via double S_N2 alkylation of

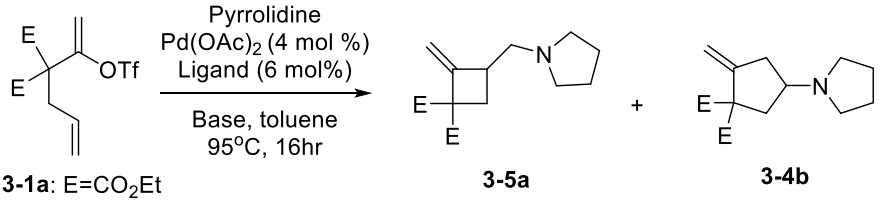
diethyl malonate, ethyl cyanoacetate, or related compounds, with 1,3-dibromopropane derivatives.[9b,10]

Mr. Jim Shepich III, Dr. Evan Bornowski and Ms. Mackenzie Clemons made contributions to the work described in this chapter. Mr. Shepich and Dr. Bornowski conducted initial preliminary studies (omitted for clarity). Ms. Clemons aided in starting material synthesis (**3-1a**, **3-1o**, **3-1n**, Scheme 3-3).

3.2 Optimization of Amine Functionalized Exomethylene Cyclobutanes

At the outset of our studies, it seemed that development of the four-membered ring-forming reactions of amine nucleophiles may be particularly challenging. Our prior work with malonate nucleophiles indicated the final step in the catalytic cycle was an sp^3C-Csp^3 bond-forming reductive elimination of an allyl palladium (II) malonate complex.[3] However, reductive elimination reactions that generate C-N bonds are typically more difficult to affect than the analogous C-C bond-forming processes.[11]

Table 3-1:Reaction Optimization



3-1a: E=CO_2Et **3-5a** **3-4b**

Entry	Ligand	Base	**3-5a/3-4b**	Yield (%)[b]
1	$POAr_3$[c]	LiO^tBu	0:100	38[d]
2	RuPhos	LiO^tBu	0:100	22
3	CyJohnPhos	LiO^tBu	37:63	86
4	P^tBu_3	LiO^tBu	47:53	70
5	P^tBu_3	Cs_2CO_3	68:32	quant
6	P^tBu_3	Cs_2CO_3	80:20	74[e]
7	P^tBu_3	Cs_2CO_3	86:14	86[f]

[a]Conditions: 1.0 equiv **3-1a**, 1.2 equiv pyrrolidine, 1.4 equiv Cs_2CO_3, 4 mol % $Pd(OAc)_2$, 6 mol % ligand, toluene (0.1 M), 95 °C, 16 h. [b]Determined by ^1H NMR using phenanthrene as an internal standard; combined yield of both products. [c] Ar = 2,4-$^tBuC_6H_3$. [d]The reaction was conducted at 95 °C; no reaction was observed at 60 °C. [e]The reaction was conducted in 1:3 water:toluene as solvent at 0.05 M substrate concentration. [f]The reaction was

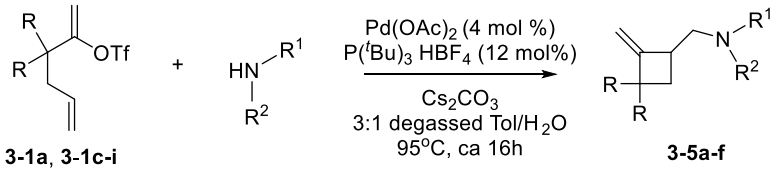
In preliminary studies, we simply replaced diethyl malonate with pyrrolidine in Pd-catalyzed coupling reactions of compound **3-1a**. Unfortunately, when the reaction was conducted at 60 °C, no conversion was observed, and at 95 °C, only the five-membered product **3-4b** was generated. We subsequently examined a series of other phosphine ligands, and after some experimentation discovered that P^tBu_3 provided a roughly 1:1 mixture of the two products **3-5a**/**3-4b** under otherwise standard conditions. Further screening revealed that higher selectivity for product **3-5a** was obtained when Cs_2CO_3 was used as a base. Finally, after examination of the influence of water on the reaction, we found that use of P^tBu_3 as a ligand, Cs_2CO_3 as a base, and a 1:3 mixture of water/degassed toluene provided 86:14 selectivity for the formation of cyclobutane **3-5a**.

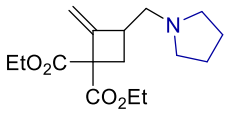
3.3 Reaction Scope

Once we had identified reaction conditions that provided seemingly maximal selectivity for the cyclobutane product **3-5a**, we examined the scope of these transformations with respect to the structure of both the amine nucleophile and the 1,5-diene-2-yl triflate derivative. As shown in Scheme 3-3, the transformations are effective with a range of amine nucleophiles, including cyclic and acyclic secondary amines. However, reactions of primary amines were not successful. The regioselectivities are generally good, with most examples providing 80:20 regioselectivity. The presence of esters, acetals, and additional alkenes is well-tolerated. As we previously observed in reactions with malonate nucleophiles, the selectivity for four-membered ring formation is dependent on the size of the substitutents adjacent to the triflate-bearing alkene in the starting material. With relatively small R-groups the regioselectivities were lowest (ca 70:30;

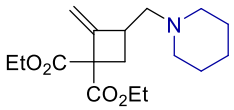
3-5n and **3-5o**), whereas the highest selectivities were obtained with gem diphenyl substrate **3-1c** (>95:5 rr). A similar electronic effect on regioselectivity was also observed, with the electron-withdrawing ester R-groups providing considerably higher selectivity (ca 85:15 to >95:5) than with methyl R-groups. In some instances, the products were difficult to isolate due to the basicity of the amine and its tendency to co-elute on silica gel with the phosphine ligand. For example, although **3-5c** was generated in 88% NMR yield, only 40% could be cleanly isolated after chromatography. Although most experiments were conducted on a 0.1 mmol scale, compound **3-5f** was produced with identical selectivities and comparable yields when run on either a 0.1 or a 1.0 mmol scale.

Scheme 3-3: Substrate Scope

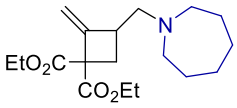




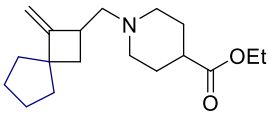
3-5a: 40%, 17:83
[88%]



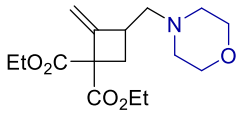
3-5b: 82%, 21:79



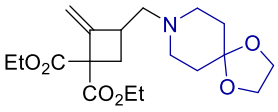
3-5c: 84%, 19:81



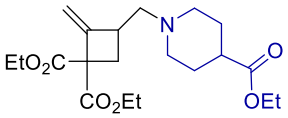
3-5n: 48%, 30:70
[66%]



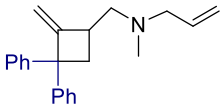
3-5d: 80%, 17:83



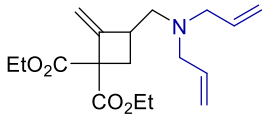
3-5e: 85%, 12:88



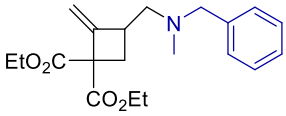
3-5g: 86%, 11:89



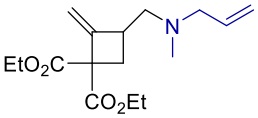
3-5l: 52%, >5:95



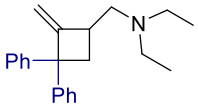
3-5j: 54%, 4:96
[83%]



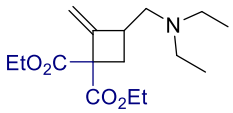
3-5h: 65%, 26:73
[99%]



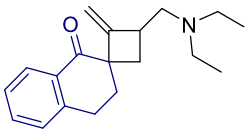
3-5l: 79%, 9:91



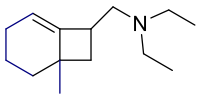
3-5k: 45%, 5:95



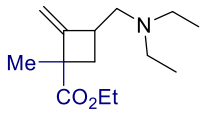
3-5f: 84% (75%)[c], 5:95



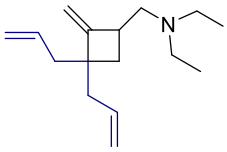
3-5r*: 53%, 9:91
[87%], >20:1 dr



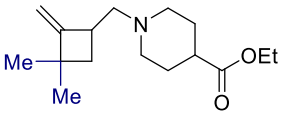
3-5p: 40%, >5:95
[89%]



3-5q: 50%, >5:95
[90%],1:1 dr



3-5m: 44%, 12:88
[75%]



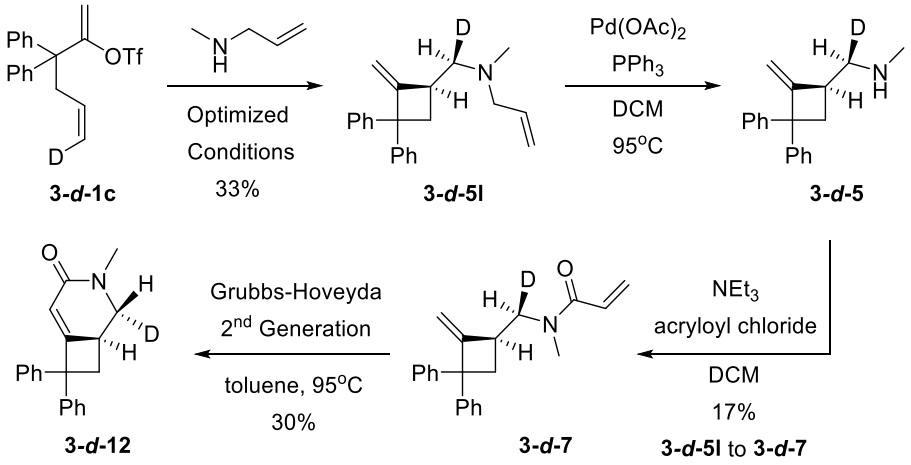
3-5o: 71%, 28:72

[a]Conditions: 1.0 equiv **1**, 1.2 equiv amine, 1.4 equiv Cs_2CO_3, 4 mol % $Pd(OAc)_2$, 6 mol % ligand, 3:1 toluene:water (0.05 M), 95 °C, 16 h. [b]Isolated yield (average of two or more experiments). Yields in parentheses are NMR yields using phenanthrene as an internal standard. [c]The reaction was conducted on a 1.0 mmol scale.

3.4 Mechanism

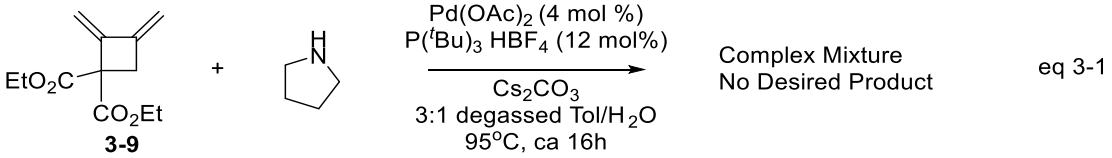
In order to gain insight into the mechanism of these reactions, we prepared deuterated substrate **3-*d*-1c**, and carried out its coupling with N-methyl allylamine to afford **3-*d*-5l** (Scheme 3-4).[12] Deallylation **of 3-*d*-5l** afforded **3-*d*-6**, which was then transformed to unsaturated amide **3-*d*-7** by acylation with acryloyl chloride. Finally, ring-closing metathesis afforded **3-*d*-8**,[13] the stereochemistry of which indicates the conversion of **3-*d*-1c** to **3-*d*-5l** occurred with net *anti*-addition to the alkene.

Scheme 3-4: Post-Reaction Manipulations for Mechanistic Insights



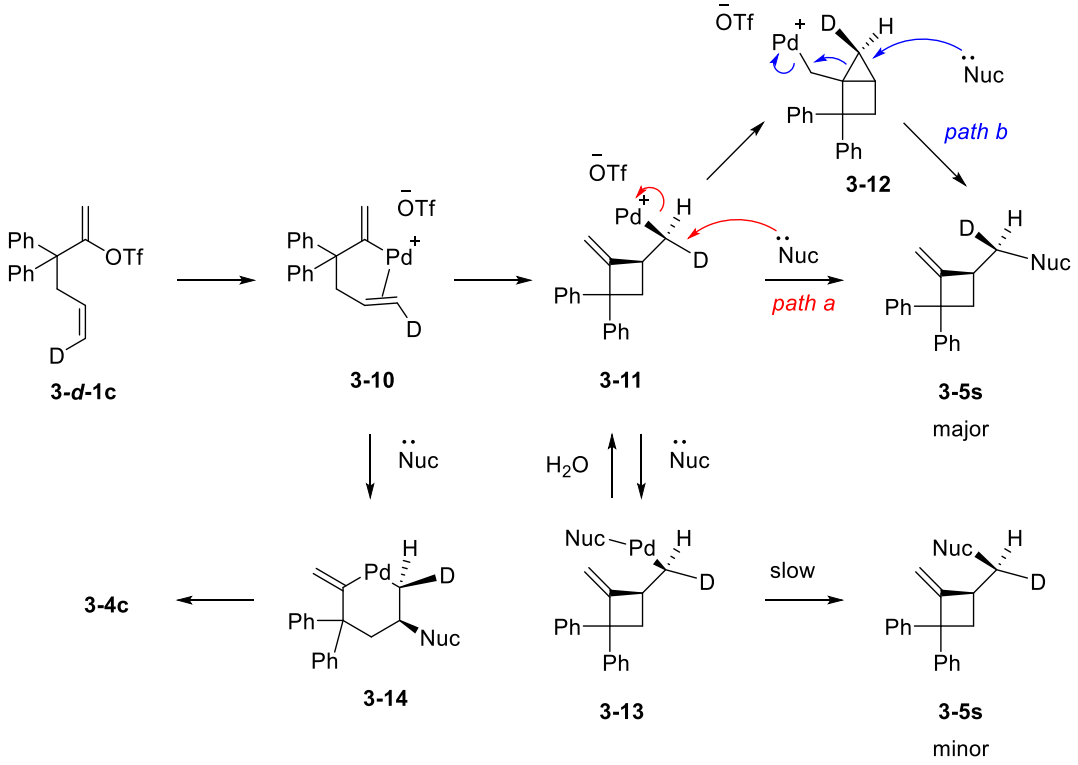
Diene side products of general structure **3-9** are observed in these transformations, and prior studies by Mulzer have shown that 1,5-diene-2-yl triflates can undergo intramolecular Heck reactions to afford diene products.[14] However, our control experiments have shown that these dienes are not converted to the observed aminomethyl cyclobutane products when resubjected to our standard reaction conditions (eq 3-1), which indicates these are not intermediates in the transformations of compound **3-1** to compound **3-5**

.



On the basis of these observations, and the stereochemical outcome of the reaction of **3-*d*-1c**, the transformations are likely initiated by oxidative addition of the alkenyl triflate to a Pd(0)/P(^{t}Bu)$_3$ phosphine complex to afford compound **3-10** (Scheme 3-5; ligands are omitted for clarity). Migratory insertion of the alkene into the Pd–C bond of compound **3-10** would then provide compound **3-11**;[15,16] observed diene side products result from β-hydride elimination reactions of compound **3-11**.[14] Intermediate **3-11** could be transformed to **3-5s** major either by direct S_N2 displacement of the metal by the nucleophile (path a), or by migratory insertion to compound **3-12**, followed by S_N2' reductive elimination from the housane-type intermediate.[15]

Scheme 3-5: Proposed Possible Mechanisms



Interestingly, despite the apparent similarities in the transformations of malonates (Scheme 3-1) and amines, reactions of the two different types of nucleophiles provide different stereochemical outcomes, and involve different mechanisms for the final reductive elimination step. In the case of malonate nucleophiles, overall *syn*-addition to the alkene is observed, and the nucleophile-carbon bond is generated by reductive elimination from a cyclobutylmethyl-Pd-Malonate complex.[3] In contrast, with amine nucleophiles *anti*-addition is observed, and reductive elimination is an outer-sphere S_N2 or S_N2' process. This result is in stark contrast with prior studies on reductive elimination of alkylamines from Pd(II) complexes, which are known to proceed with retention of configuration.[11] In this system, it is possible that formation of the requisite palladium amido complex **3-13** occurs, but is reversible, and the outer-sphere S_N2 pathway is simply faster than the inner-sphere reductive elimination (**3-13** to **3-5s** minor). In addition, water may play a role in the change in mechanism, because hydrogen-bonding to the palladium amido-complex should slow the rate of reductive elimination by decreasing the nucleophilicity of the amido ligand,[17] and also facilitate the reversion of amido complex **3-13** back to compound **3-11** via protonolysis.[18] Water may also serve to decrease the rate of *anti*-aminopalladation of compound **3-10** to compound **3-14**, which leads to five-membered side products, by decreasing the nucleophilicity of the amine through hydrogen-bonding, by decreasing the effective concentration of the amine through partial water solubility, or both.[19]

The failure of the bulky triarylphosphite ligand, which was highly effective with malonate nucleophiles, to provide satisfactory results with amines (entry 1 in Table 3-1) may be due to its facile displacement from the metal by the amine nucleophile. In contrast, the more basic P^tBu_3 ligand is not as easily displaced, but is still sufficiently labile to allow for the initial alkene

migratory insertion to occur in preference to either cyclopentane formation, or competing N-alkenylation of the starting triflate.

3.5 Conclusion

In conclusion, we have developed a new method for the preparation of medicinally relevant cyclobutylmethylamine derivatives by the coupling of 1,5-dienyl triflates with amines. These modular reactions provide access to cyclobutylmethylamines that cannot be generated with existing methods, and represent the first examples of metal-catalyzed alkene carboamination reactions that afford cyclobutane products. These results also illustrate that water can play a key role in modulating relative rates of alkene aminopalladation versus alkene migratory insertion, as well as potentially influencing the pathway for C–N bond forming reductive elimination.

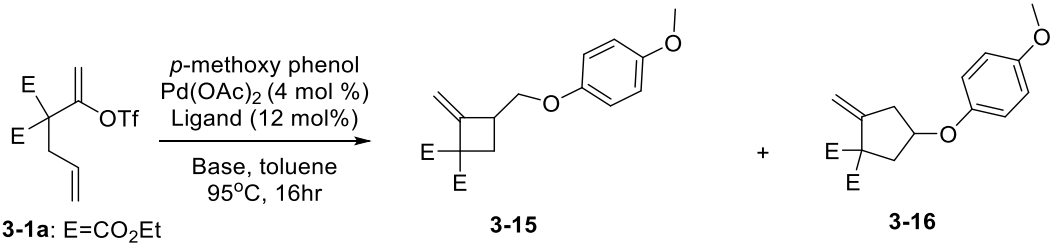
The work described in this chapter was published in *Organic Letters*.[22] This chapter was adapted with permission from Hatt, J. E.; Shepich, J. H.; Clemons, M. N.; Bornoski, E. C.; Wolfe, J. P. "Palladium-Catalyzed Synthesis of 1-Alkylidene-2-dialkylaminomethyl Cyclobutane Derivatives via Pd-Catalyzed Alkene Difunctionalization Reactions: Influence of Nucleophile and Water on the Reaction Mechanism" *Org. Lett*. **2023**, *25*(18), 3245-3248. Copyright (2023) American Chemical Society.

3.6 Future Directions and Unpublished Results

Upon the successful development of methods to form exomethylene cyclobutanes functionalized with carbon and nitrogen nucleophiles, respectively, oxygen nucleophiles were the next obvious target. Initial screens of 1,5-diene-2-yl triflate **3-1a** with para-methoxy phenol indicated that conditions similar to the amine nucleophiles only gave the diene product **3-9** and

starting material (Table 3-2, entry 1). Omitting water allowed for the formation of some the desired cyclobutane product **3-15** (Table 3-2, entry 2). The highest yield (c.a. 37%,>95:5rr) was achieved by lowering the temperature, changing the base to NaO^{t}Bu, and changing the Pd pre-catalyst to Pd(F_6acac)$_2$. Any changes to ligand gave a lower yield or higher amount of cyclopentane product **3-16**. Additional studies are required to further optimize these results.

Table 3-2: Preliminary Alcohol Nucleophile Optimization



3-1a: E=CO_2Et

3-15

3-16

Entry	Ligand	Base	**3-15/3-16**	Yield (%)[b]
1	P^{t}Bu$_3$[c]	Cs_2CO_3	N/A	0
2	P^{t}Bu$_3$	Cs_2CO_3	N/A	19
3	XantPhos	NaO^{t}Bu	0:100	70
4	P^{t}Bu$_3$	NaO^{t}Bu	100:0	34[d]
5	P^{t}Bu$_3$	NaO^{t}Bu	100:0	37[def]

[a]Conditions: 1.0 equiv **3-1a**, 1.2 equiv *p*-methoxy phenol, 1.4 equiv Cs_2CO_3, 4 mol % Pd(OAc)$_2$, 12 mol % ligand, toluene (0.1 M), 95 °C, 16 h. [b]Determined by ^{1}H NMR using phenanthrene as an internal standard; combined yield of both products. [c]The reaction was conducted in 1:3 water:degassed toluene as solvent. [d] The reaction was conducted at 85 °C [e] The pre-catalyst was switched to Pd(F_6acac)$_2$ (2 mol%) [f] The reaction was run for only 8

3.7 Experimental

General Considerations: All reactions were carried out under a nitrogen atmosphere in vacuum and flame-dried glassware. All reagents, palladium pre-catalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. The substrates **3-1a**,[20] **3-1c**,[3] **3-1d**,[4a] **3-1e**,[20] **3-1f-g**,[4a] and **3-1h-i**[3] were prepared by previously published methods. Alkenyl triflate starting materials were stored in a freezer under nitrogen. Bulk quantities of cesium carbonate, lithium tert-butoxide, and lithium hexamethyldisilazide

were stored in nitrogen-filled glove box and small amounts were removed within a few days of use, then quickly weighed in the open atmosphere before being added to reaction vessels. Toluene, tetrahydrofuran (THF), dichloromethane (DCM), and diethyl ether were purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY and nOe experiments. Ratios of diastereomers were determined by 1 H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by 1 H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Scheme 2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Scheme 2.

Preparation and Characterization of Products

General Procedure 1 for Pd-Catalyzed Alkene Difunctionalization:

A 4 mL vial was equipped with a stir bar, flame dried, and cooled to rt under a flow of nitrogen. The vial was charged with palladium acetate (0.9 mg, 0.004 mmol, 4 mol%), tri-*tert*-butylphosphine tetrafluoroborate (3.5 mg, 0.012 mmol, 12 mol %), and cesium carbonate (45.6 mg, 0.14 mmol, 1.4 equiv). The alkenyl triflate (0.1 mmol, 1 equiv) was added in a solution of toluene (2 mL). The amine (0.12 mmol, 1.2 equiv) was added. The vial was capped with a rubber-lined screw cap, then placed in a heating block and stirred at 95 ^{o}C for 16 h. The mixture was then cooled to rt and was quenched with 2 mL of saturated aqueous sodium bicarbonate solution. The organic layer was extracted with ethyl acetate (3 x 1 mL), passed through a plug of sodium sulfate, and concentrated in vacuo.

General Procedure 2 for Pd-Catalyzed Alkene Difunctionalization:

An oven dried 10 mL culture tube was equipped with a stir bar, fitted with a septa cap, and cooled to rt under a flow of nitrogen. The tube was charged with palladium acetate (0.9 mg, 0.004 mmol, 4 mol%), tri-*tert*-butylphosphine tetrafluoroborate (3.5 mg, 0.012 mmol, 12 mol%), and cesium carbonate (45.6mg, 0.14 mmol, 1.4 equiv). The alkenyl triflate (0.1 mmol, 1 equiv) was added in a solution of degassed toluene (1.5 mL). DI water (0.5 mL) was added, followed by the amine (0.12 mmol, 1.2 equiv). The nitrogen line and venting needle were removed and the septa cap was replaced with a rubber-lined screw cap, then placed in a heating block and stirred at 95 ^{o}C for 16 h. *Note: Vigorous stirring was required to obtain optimal yield and regioisomeric ratios.* The mixture was then cooled to rt and was quenched with 2 mL of saturated aqueous sodium bicarbonate solution. The organic layer was extracted with ethyl acetate (3 x 1 mL), passed through a plug of sodium sulfate, and concentrated in vacuo.

Purification Method A:

p-toluensulfonic acid (1 eq) was dissolved in DCM (1 M) in a small screwcap vial. The crude product obtained after workup was dissolved in DCM (1 M) and added. The mixture was stirred for 30 minutes. Solvent was removed under reduced pressure and the resulting crystals were washed with ethyl acetate (3 x 1 mL). The crystals were dissolved in aqueous 2M NaOH (5mL) and the organic layer was extracted with ethyl acetate (3 x 1 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to afford the pure product.

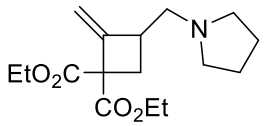
Purification Method B:

The crude product obtained after workup was dissolved in diethyl ether (1 mL) in a small screwcap vial. Saturated aqueous copper (II) sulfate (2mL) was added, the vial was shaken, the

layers were allowed to separate, and the organic layer was removed. Ammonium hydroxide (2 mL) was added to the aqueous phase, which was then extracted with diethyl ether (3 x 1 mL). The organic layer was dried over sodium sulfate, filtered twice, and concentrated in vacuo. The process described above was then repeated to afford the pure product.

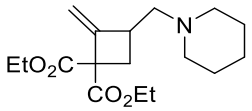
Purification Method C:

A cotton plug was inserted into a short stem glass pipet. The pipet was filled ¾ with dry silica gel. The silica get was then moistened with 2 mL of a 15:85 EtOAc:Hexanes solution. The sample was loaded onto the pipet column with ½ mL of 15:85 EtOAc:Hexanes, then the column was eluted with 5 mL 15:85 EtOAc:Hexanes, which was collected in a vial, and discarded. The pipet was then eluted with 10mL of 60:40 EtOAc:Hexanes, which was collected in a vial, then concentrated in vacuo to afford the pure product.

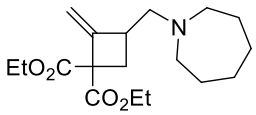


Diethyl 2-methylene-3-(pyrrolidin-1-ylmethyl)cyclobutane-1,1-dicarboxylate (5a). The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.2 mmol, 74.8 mg) using General Procedure 2. The crude material was purified using Purification Method B. This procedure afforded 31.8 mg (54%) of the title compound (85:15 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound.^{1}H NMR (700 MHz, $CDCl_3$) d 5.33 – 5.28 (m, 1H), 5.16 – 5.07 (m, 1H), 4.27 – 4.11 (m, 4H), 3.26 – 3.18 (m, 1H), 2.75 – 2.67 (m, 2H), 2.54 – 2.43 (m, 5H), 2.41 – 2.36 (m, 1H), 1.79 – 1.71 (m, 4H), 1.29 – 1.20 (m, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) d 169.6, 169.1, 147.1, 110.1, 61.64, 61.63, 61.4, 60.1, 59.4, 54.4,

53.1, 40.1, 32.4, 23.5, 14.0, 14.0. IR (film) 2964, 2783, 1730, 1240 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C16H25NO4 295.1784; found 295.1781.

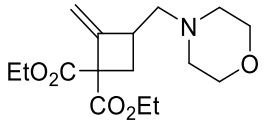


Diethyl 2-methylene-3-(piperidin-1-ylmethyl)cyclobutane-1,1-dicarboxylate (5b). The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.1 mmol, 37.4 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 25.9 mg (84%) of the title compound (82:18 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound.^{1}H NMR (500 MHz, $CDCl_3$) d 5.31 (d, 1H), 5.14 (d, *J* = 2.5 Hz, 1H), 4.26 – 4.14 (m, 4H), 3.31 – 3.21 (m, 1H), 2.75 – 2.67 (m, 1H), 2.64 – 2.56 (m, 1H), 2.46 – 2.39 (m, 1H), 2.42 – 2.33 (m, 5H), 1.61 – 1.51 (m, 4H), 1.44 – 1.36 (m, 2H), 1.30 – 1.21 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) d 169.6, 169.1, 147.4, 110.1, 63.3, 61.6, 61.4, 59.6, 54.6, 52.9, 38.6, 32.9, 25.98, 25.89, 24.3, 14.1, 14.0. IR (film) 2934, 1730 1243, 1110 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C17H27NO4 309.1940; found 309.1953.

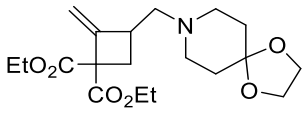


Diethyl 3-(azepan-1-ylmethyl)-2-methylenecyclobutane-1,1-dicarboxylate (5c) The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.1 mmol, 37.4 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 26.7 mg (83%) of the title compound (80:20 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound.^{1}H NMR (500 MHz, $CDCl_3$) d 5.30 (d, *J* = 2.9 Hz, 1H), 5.17 (d, *J* = 2.4 Hz, 1H), 4.26 – 4.14 (m, 4H), 3.26 – 3.16 (m,

1H), 2.77 – 2.63 (m, 2H), 2.63 – 2.49 (m, 5H), 2.41 – 2.32 (m, 1H), 1.64 – 1.53 (m, 8H), 1.29 – 1.22 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) d 169.7, 169.2, 147.7, 110.1, 62.1, 61.62, 61.59, 61.4, 59.4, 55.5, 53.1, 39.2, 32.2, 28.2, 27.05, 27.03, 14.1, 14.0. IR (film) 2925, 1729, 1240. 1095 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C18H29NO4 323.2097; found 323.2094.

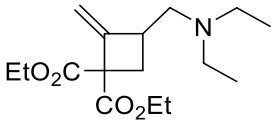


Diethyl 2-methylene-3-(morpholinomethyl)cyclobutane-1,1-dicarboxylate (5d) The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.2 mmol, 74.8 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 50.2 mg (81%) of the title compound (87:13 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound.^{1}H NMR (500 MHz, $CDCl_3$) d 5.30 (dd, *J* = 2.9, 0.9 Hz, 1H), 5.15 (dd, *J* = 2.4, 0.9 Hz, 1H), 4.24 – 4.12 (m, 4H), 3.72 – 3.61 (m, 4H), 3.29 – 3.16 (m, 1H), 2.73 – 2.62 (m, 2H), 2.62 – 2.51 (m, 1H), 2.46 – 2.37 (m, 4H), 2.37 – 2.29 (m, 1H), 1.29 – 1.20 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) d 169.5, 169.0, 147.0, 110.5, 66.9, 62.7, 61.72, 61.67, 61.5, 59.4, 53.7, 37.9, 32.1, 14.0, 13.97, 13.92. IR (film) 2958, 1728, 1239 cm^{--1}; HRMS (EI+TOF) m/z: Calcd for C16H25NO5 311.1733; found 311.1743.



Diethyl 3-[(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)methyl]-2-methylenecyclobutane-1,1-dicarboxylate (5e) The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.2 mmol, 74.8 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 60.9 mg

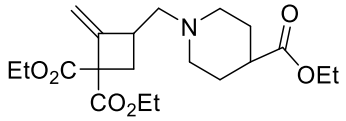
(83%) of the title compound (91:9 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) d 5.32 (d, *J* = 2.8 Hz, 1H), 5.16 (d, *J* = 2.4 Hz, 1H), 4.25 – 4.13 (m, 4H), 3.94 (s, 4H), 3.29 – 3.19 (m, 1H), 2.75 – 2.67 (m, 1H), 2.67 – 2.60 (m, 1H), 2.55 – 2.44 (m, 5H), 2.41 – 2.32 (m, 1H), 1.79 – 1.65 (m, 4H), 1.29 – 1.21 (m, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) d 169.6, 169.0, 147.2, 110.3, 107.2, 64.2, 62.0, 61.7, 61.5, 59.5, 51.4, 49.7, 38.6, 34.8, 32.5, 14.1, 14.0. IR (film) 2955, 1729, 1242, 1083 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C19H29NO6 367.1995; found 367.2000.



Diethyl 3-[(diethylamino)methyl]-2-methylenecyclobutane-1,1-dicarboxylate (5f). The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.1 mmol, 37.4 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 22.1mg (74%) of the title compound (96: 4 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) d 5.30 (d, *J* = 2.8 Hz, 1H), 5.13 (d, *J* = 2.4 Hz, 1H), 4.24 – 4.15 (m, 4H), 3.27 – 3.15 (m, 1H), 2.73 – 2.61 (m, 2H), 2.61 – 2.45 (m, 5H), 2.41 – 2.29 (m, 1H), 1.29 – 1.22 (m, 6H), 1.05 – 0.94 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) d 169.6, 169.1, 147.4, 128.9, 110.2, 61.6, 61.4, 59.4, 56.9, 47.1, 38.7, 32.2, 14.04, 13.99, 13.94, 11.6. IR (film) 2970, 1730, 1242 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C16H27NO4 297.1940; found 297.1946.

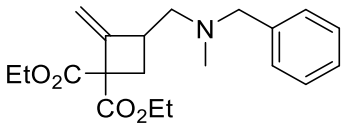
Diethyl 3-[(diethylamino)methyl]-2-methylenecyclobutane-1,1-dicarboxylate (5f). A 250mL round bottom was equipped with a large stir bar and septa. The round bottom was flamed dried under vacuum and cooled to rt under a flow of nitrogen. The flask was charged with palladium

acetate (8.9 mg, 0.04 mmol, 4 mol%), tri-*tert*-butylphosphine tetrafluoroborate (35 mg, 0.12 mmol, 12 mol%), and cesium carbonate (456 mg, 1.4 mmol, 1.4 equiv). Diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.374 g, 1 mmol, 1 equiv) was added as a solution in 5 mL of degassed toluene. Additional degassed toluene (10 mL) and DI water (5 mL) were added, followed by diethylamine (0.12 mL,1.2 mmol, 1.2 equiv). The venting needle was removed and the septa cap was removed for 30 seconds and replaced. The reaction mixture was then placed in a silicon oil bath and stirred at 95 ^{o}C for 16 h. *Note: Vigorous stirring was required to obtain optimal yield and regioisomeric ratios.* The mixture was then cooled to rt and was quenched with 20 mL of saturated aqueous sodium bicarbonate solution. The organic layer was extracted with ethyl acetate (3 x 10 mL), dried over sodium sulfate, and concentrated in vacuo. The crude material was purified via column chromatography on silica gel. This procedure afforded 224.3 mg (75 %) of the title compound (>95: 5 ratio of regioisomers) as a colorless oil. Data were identical to those reported above.

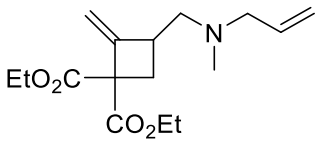


Diethyl 3-{[4-(ethoxycarbonyl)piperidin-1-yl]methyl}-2-methylenecyclobutane-1,1-dicarboxylate (5g) The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.2 mmol, 74.8 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 64.9 mg (85%) of the title compound (89:11 ratio of regioisomers) as a yellow oil. The reported peaks are for the title compound. ^{1}H NMR (700 MHz, $CDCl_3$) d 5.28 (d, *J* = 2.9 Hz, 1H), 5.12 (d, *J* = 2.4 Hz, 1H), 4.22 – 4.11 (m, 4H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.26 – 3.14 (m, 1H), 2.82 – 2.74 (m, 2H), 2.70 –

2.63 (m, 1H), 2.59 – 2.53 (m, 1H), 2.44 – 2.35 (m, 1H), 2.35 – 2.26 (m, 1H), 2.24 – 2.17 (m, 1H), 2.03 – 1.94 (m, 2H), 1.87 – 1.79 (m, 2H), 1.74 – 1.62 (m, 2H), 1.26 – 1.16 (m, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) d 175.0, 169.5, 169.0, 147.1, 110.4, 62.5, 61.6, 61.4, 60.2, 59.4, 53.2, 52.9, 41.0, 38.3, 32.4, 28.18, 28.15,14.2, 14.0, 14.0. IR (film) 2942, 1727, 1247, 1046 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C20H31NO6 381.2151; found 381.2148.

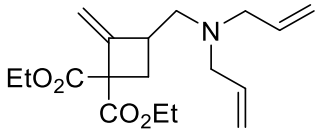


Diethyl 3-{[benzyl(methyl)amino]methyl}-2-methylenecyclobutane-1,1-dicarboxylate (5h) The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.2 mmol, 74.8 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 43.2 mg (63%) of the title compound (79:21 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.34 – 7.28 (m, 4H), 5.32 (dd, *J* = 2.9, 0.9 Hz, 1H), 5.16 (dd, *J* = 2.4, 0.9 Hz, 1H), 4.29 – 4.12 (m, 4H), 3.53 – 3.40 (m, 2H), 3.36 – 3.24 (m, 1H), 2.74 – 2.66 (m, 1H), 2.66 – 2.60 (m, 1H), 2.55 – 2.45 (m, 2H), 2.39 – 2.33 (m, 1H), 2.18 (s, 3H), 1.31 – 1.16 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) d 169.6, 169.1, 147.3, 139.1, 128.9, 128.21, 128.17, 126.9, 110.3, 62.4, 61.7, 61.5, 61.4, 59.4, 42.3, 39.78, 39.71, 38.7, 32.0, 14.1. IR (film) 2981, 2787, 1729, 1243 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C20H27NO4 345.1940; found 345.1944.

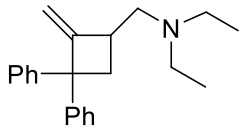


Diethyl 3-{[allyl(methyl)amino]methyl}-2-methylenecyclobutane-1,1-dicarboxylate (5i) The title compound was prepared from diethyl 2-allyl-2-(1-

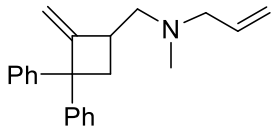
{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.1 mmol, 37.4 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 23.3 mg (79%) of the title compound (91:9 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound. ^{1}H NMR (600 MHz, $CDCl_3$) d 5.90 – 5.75 (m, 1H), 5.35 – 5.28 (m, 1H), 5.20 – 5.09 (m, 3H), 4.27 – 4.13 (m, 4H), 3.29 – 3.19 (m, 1H), 3.04 – 2.93 (m, 2H), 2.75 – 2.66 (m, 1H), 2.62 – 2.52 (m, 1H), 2.50 – 2.42 (m, 1H), 2.40 – 2.30 (m, 1H), 2.21 (s, 3H), 1.30 – 1.16 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) d 169.6, 169.1, 147.1, 135.4, 117.6, 110.4, 61.7, 61.5, 61.03, 61.00, 59.4, 42.3, 38.7, 32.3, 14.1, 14.0. IR (film) 2980, 2785, 1730, 1245 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C16H25NO4 295.1784; found 295.1776.



Diethyl 3-[(diallylamino)methyl]-2-methylenecyclobutane-1,1-dicarboxylate (5j) The title compound was prepared from diethyl 2-allyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)malonate (**1a**) (0.2 mmol, 74.8 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 46.6 mg (72%) of the title compound (>95:5 ratio of regioisomers) as a yellow oil. The reported peaks are for the title compound. ^{1}H NMR (700 MHz, $CDCl_3$) d 5.86 – 5.73 (m, 2H), 5.29 (d, *J* = 2.8 Hz, 1H), 5.16 – 5.06 (m, 5H), 4.25 – 4.12 (m, 4H), 3.25 – 3.18 (m, 1H), 3.09 – 3.01 (m, 4H), 2.69 – 2.61 (m, 2H), 2.56 – 2.50 (m, 1H), 2.35 – 2.29 (m, 1H), 1.27 – 1.20 (m, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) d 169.6, 169.1, 147.2, 135.6, 117.3, 110.3, 61.6, 61.4, 59.3, 57.2, 57.0, 38.5, 31.9, 14.03, 13.98. IR (film) 2980, 1730, 1241 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C18H27NO4 321.1940; found 321.1944.

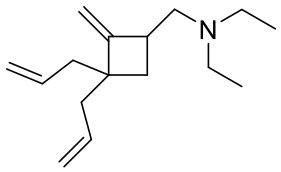


***N*-Ethyl-*N*-[(2-methylene-3,3-diphenylcyclobutyl)methyl]ethanamine (5k)** The title compound was prepared from 3,3-diphenylhexa-1,5-dien-2-yl trifluoromethanesulfonate (**1c**) (0.1 mmol, 38.2 mg) using General Procedure 2. The crude material was purified using Purification Method A. This procedure afforded 13.7 mg (45%) of the title compound (>95:5 ratio of regioisomers) as a yellow oil. The reported peaks are for the title compound. ^{1}H NMR (700 MHz, $CDCl_3$) d 7.43 – 7.11 (m, 10H), 5.20 – 5.18 (m, 1H), 5.04 – 5.01 (m, 1H), 3.21 – 3.07 (m, 1H), 2.85 – 2.77 (m, 2H), 2.66 – 2.61 (m, 1H), 2.61 – 2.56 (m, 1H), 2.56 – 2.46 (m, 4H), 1.01 (t, J = 7.1 Hz, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) d 158.4, 146.7, 146.6, 128.2, 128.1, 127.6, 127.3, 126.0, 125.8, 106.4, 58.6, 56.5, 47.1, 39.5, 38.2, 11.7. IR (film) 2969, 1491, 1445, 699 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C22H27N 305.2144; found 305.2132.

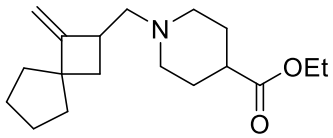


***N*-Methyl-*N*-[(2-methylene-3,3-diphenylcyclobutyl)methyl]prop-2-en-1-amine (5l)** The title compound was prepared from 3,3-diphenylhexa-1,5-dien-2-yl trifluoromethanesulfonate (**1c**) (0.1 mmol, 38.2 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 14.3 mg (47%) of the title compound (>95:5 ratio of regioisomers) as a yellow oil. The reported peaks are for the title compound. ^{1}H NMR (600 MHz, $CDCl_3$) d 7.42 – 7.13 (m, 10H), 5.90 – 5.79 (m, 1H), 5.20 – 5.09 (m, 3H), 5.03 – 5.01 (m, 1H), 3.22 – 3.12 (m, 1H), 3.07 – 3.01 (m, 1H), 3.00 – 2.94 (m, 1H), 2.86 – 2.80 (m, 1H), 2.74 – 2.70 (m, 1H), 2.67 – 2.60 (m, 1H), 2.56 – 2.48 (m, 1H), 2.22 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) d 158.1,

146.56, 146.51, 135.6, 128.2, 128.1, 127.6, 127.2, 126.1, 125.8, 117.6, 106.5, 61.1, 60.7, 42.4, 39.4, 38.2. IR (film) 2782, 1491, 1445, 698 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C22H25N 303.1987; found 303.1976.

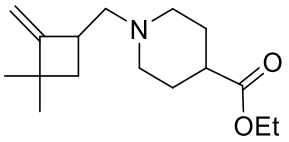


***N*-[(3,3-Diallyl-2-methylenecyclobutyl)methyl]-N-ethylethanamine (5m)** The title compound was prepared from 3,3-diallylhexa-1,5-dien-2-yl trifluoromethanesulfonate (**1d**) (0.1 mmol, 32.4 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 9.8mg (42%) of the title compound (83:17 ratio of regioisomers) as a yellow oil. The reported peaks are for the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) d 5.92 – 5.67 (m, 2H), 5.09 – 4.99 (m, 4H), 4.86 (d, *J* = 2.4 Hz, 1H), 4.75 (d, *J* = 2.8 Hz, 1H), 3.04 – 2.96 (m, 1H), 2.71 – 2.58 (m, 2H), 2.54 – 2.45 (m, 4H), 2.27 – 2.22 (m, 2H), 2.22 – 2.17 (m, 2H), 1.99 – 1.92 (m, 1H), 1.69 – 1.63 (m, 1H), 1.04 – 0.94 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) d 159.3, 135.1, 135.0, 117.07, 117.05, 117.0, 103.7, 57.1, 47.1, 45.0, 44.9, 42.7, 42.3, 37.2, 34.6, 11.7. IR (film) 3075 2970 912 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C16H27N 233.2144; found 233.2137.

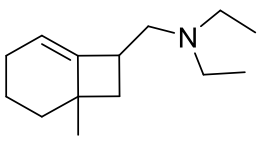


Ethyl 1-[(1-methylenespiro[3.4]octan-2-yl)methyl]piperidine-4-carboxylate (5n) The title compound was prepared from 1-(1-allylcyclopentyl)vinyl trifluoromethanesulfonate (**1e**) (0.1 mmol, 28.4 mg) using General Procedure 2. The crude material was purified using Purification Method B. This procedure afforded 14.1 mg (48%) of the title compound (72:28 ratio of

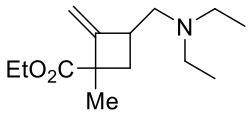
regioisomers) as a color-less oil. The reported peaks are for the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) d 4.75 – 4.70 (m, 2H), 4.18 – 4.07 (m, 2H), 3.15 – 3.05 (m, 1H), 3.00 – 2.88 (m, 1H), 2.88 – 2.80 (m, 2H), 2.68 – 2.61 (m, 1H), 2.40 – 2.32 (m, 1H), 2.12 – 2.04 (m, 2H), 1.77 – 1.62 (m, 8H), 1.65 – 1.56 (m, 6H), 1.28 – 1.18 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) d 175.2, 162.2, 100.9, 63.2, 60.26, 60.24, 53.3, 53.0, 52.8, 42.0, 41.1, 40.0, 39.8, 38.5, 38.1, 28.2, 24.60, 24.58, 24.4, 14.2. IR (film) 2948, 1731, 1171, 1047 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C18H29NO2 291.2198; found 291.2200.



Ethyl 1-((3,3-dimethyl-2-methylenecyclobutyl)methyl)piperidine-4-carboxylate (5o) The title compound was prepared from 3,3-dimethylhexa-1,5-dien-2-yl trifluoromethanesulfonate (**1f**) (0.1 mmol, 25.8 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 16.7 mg (63%) of the title compound (78:22 ratio of regioisomers) as a yellow oil. The reported peaks are for the title compound. ^{1}H NMR (700 MHz, $CDCl_3$) d 4.76 – 4.68 (m, 2H), 4.15 – 4.06 (m, 2H), 3.21 – 3.10 (m, 1H), 2.87 – 2.76 (m, 2H), 2.69 – 2.63 (m, 1H), 2.39 – 2.30 (m, 1H), 2.28 – 2.21 (m, 1H), 2.05 – 1.96 (m, 3H), 1.90 – 1.83 (m, 2H), 1.79 – 1.71 (m, 2H), 1.57 – 1.50 (m, 1H), 1.26 – 1.21 (m, 3H), 1.17 (s, 3H), 1.14 – 1.09 (m, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) d 175.2, 162.7, 126.5, 101.1, 63.5, 60.2, 53.3, 53.0, 41.9, 40.3, 37.5, 30.5, 29.2, 28.1, 27.5, 14.2. IR (film) 2953, 1732, 1175, 1048 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C16H27NO2 265.2042; found 265.2040.

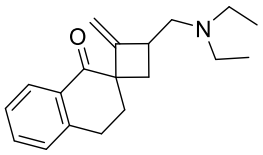


***N*-Ethyl-*N*-[(1-methylbicyclo[4.2.0]oct-5-en-7-yl)methyl]ethanamine (5p)** The title compound was prepared from 6-allyl-6-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (**1g**) (0.1 mmol, 28.5 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 12.3 mg (59%) of the title compound (>95:5 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound. ^{1}H NMR (700 MHz, $CDCl_3$) d 5.28 – 5.24 (m, 1H), 3.37 – 3.31 (m, 1H), 2.79 – 2.74 (m, 1H), 2.59 – 2.52 (m, 1H), 2.54 – 2.47 (m, 4H), 2.46 – 2.40 (m, 1H), 2.09 – 2.00 (m, 2H), 1.98 – 1.90 (m, 1H), 1.72 – 1.54 (m, 2H), 1.56 – 1.51 (m, 1H), 1.39 – 1.33 (m, 1H), 1.23 (s, 3H), 1.03 – 0.96 (m, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) d 148.1, 111.8, 56.5, 47.1, 43.7, 42.76, 42.73, 42.3, 35.4, 25.2, 24.7, 23.8, 19.5, 11.7. IR (film) 2962, 2927, 1371 cm^{-1} ; HRMS (EI+TOF) m/z: Calcd for C14H25N 207.1987; found 207.1987.



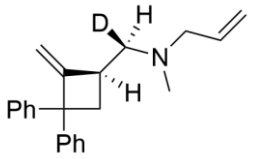
Ethyl 3-[(diethylamino)methyl]-1-methyl-2-methylenecyclobutane-1-carboxylate (5q) The title compound was prepared from Ethyl 2-methyl-2-(1-{[(trifluoromethyl)sulfonyl]oxy}vinyl)pent-4-enoate (**1h**) (0.1 mmol, 31.6 mg) using General Procedure 2. The crude material was purified using Purification Method C. This procedure afforded 11.9 mg (50%) of the title compound (1:1 ratio of diastereomers) as a yellow oil. The reported peaks are for both diastereomers of title compound. ^{1}H NMR (500 MHz, $CDCl_3$) d 5.03 (d, *J* = 2.8 Hz, 1H), 4.98 (d, *J* = 2.9 Hz, 1H), 4.93 (d, *J* = 2.4 Hz, 1H), 4.90 (d, *J* = 2.3 Hz, 1H), 4.20 – 4.09 (m, 4H), 3.26 – 3.17 (m, 1H), 3.17 – 3.09 (m, 1H), 2.83 – 2.75 (m, 1H), 2.73 – 2.63 (m, 2H), 2.59 – 2.54 (m, 1H), 2.54 – 2.47 (m, 9H), 2.43 – 2.36 (m, 1H), 2.03 – 1.95 (m, 1H), 1.63 – 1.56 (m, 1H), 1.46 (s, 3H), 1.40 (s, 3H), 1.30 – 1.22 (m, 6H), 1.05 – 0.97 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) d 175.0, 174.6, 156.0, 155.4, 105.6, 105.4, 60.7, 60.6,

57.7, 57.0, 50.7, 49.8, 47.2, 47.0, 39.0, 37.5, 36.3, 34.5, 24.3, 23.7, 14.2, 14.1, 11.71, 11.69. IR (film) 2969 1735 1143 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C14H25NO2 239.1885; found 239.1876.



3-[(Diethylamino)methyl]-2-methylene-3',4'-dihydro-1'H-spiro[cyclobutane-1,2'-naphthalen]-1'-one (5r) The title compound was prepared from 1-(2-allyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)vinyl trifluoromethanesulfonate (**1i**) (0.2 mmol, 72.1 mg) using General Procedure 2. The crude material was purified using Purification Method B. This procedure afforded 31.1mg (55%) of the title compound (92:8 ratio of regioisomers) as a colorless oil. The reported peaks are for the title compound. ^{1}H NMR (700 MHz, $CDCl_3$) d 8.04 (d, 1H), 7.45 (t, 1H), 7.29 (t, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 4.92 (d, *J* = 2.4 Hz, 1H), 4.57 (d, *J* = 2.8 Hz, 1H), 3.27 – 3.16 (m, 2H), 2.95 – 2.87 (m, 1H), 2.71 – 2.65 (m, 2H), 2.65 – 2.58 (m, 1H), 2.58 – 2.47 (m, 4H), 2.35 – 2.30 (m, 1H), 2.28 – 2.21 (m, 1H), 1.93 – 1.87 (m, 1H), 1.05 – 0.95 (m, 6H). ^{13}C NMR (176 MHz, $CDCl_3$) d 196.8, 154.0, 143.9, 133.20, 133.19, 132.1, 128.8, 128.0, 126.68, 126.63, 106.3, 56.9, 47.2, 37.5, 34.2, 33.2, 30.9, 26.2, 11.8. IR (film) 2967, 2931, 1681, 1223, 743 cm^{-1}; HRMS (EI+TOF) m/z: Calcd for C19H25NO 283.1936; found 283.1936.

Preparation and Characterization of Deuterated Product (*d*-5l)

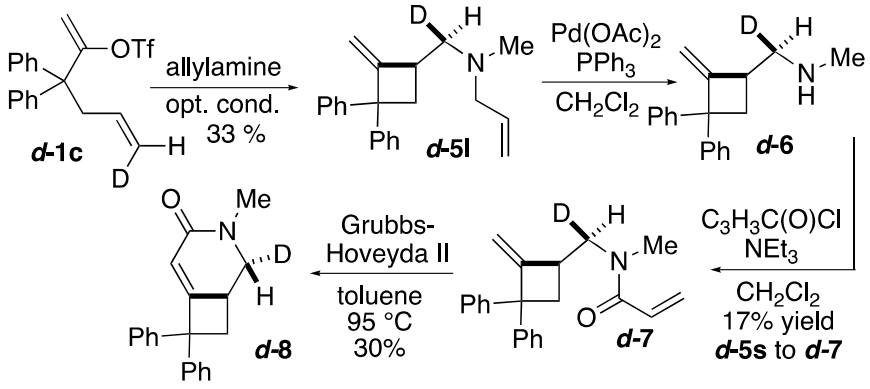


(1*R*,2*S*)-*N*-Methyl-N-[(2-methylene-3,3-diphenylcyclobutyl)methyl-*d*]prop-2-en-1-amine (*d*-5l)

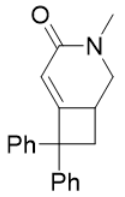
The title compound was prepared from (E)-3,3-diphenylhexa-1,5-dien-2-yl-6-d trifluoromethanesulfonate (***d*-1c**) (0.165 mmol, 63 mg) using General Procedure 2. The crude material was purified using Purification Method A. This procedure afforded 5.8 mg (12%) of the title compound as a yellow oil in 93% purity (>95:5 ratio of regioisomers). Due to limited availability of ***d*-1c**, this compound was used for the analysis of stereochemistry without further purification. The reported peaks are for the title compound. ^{1}H NMR (600 MHz, $CDCl_3$) d 7.40 – 7.14 (m, 10H), 5.89 – 5.78 (m, 1H), 5.19 – 5.08 (m, 3H), 5.02 (d, J = 2.76 Hz, 1H), 3.21 – 3.12 (m, 1H), 3.07 – 2.99 (m, 1H), 2.99 – 2.91 (m, 1H), 2.85 – 2.78 (m, 1H), 2.70 – 2.60 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) d 158.2, 146.6, 146.5, 135.8, 128.2, 128.1, 127.6, 127.2, 126.1, 125.8, 117.5, 106.5, 61.2, 60.5, 42.4, 39.3, 38.2. IR (film) 2781, 1491, 1446, 700 cm^{-1}. HRMS (EI+TOF) m/z: Calcd for C22H24DN 304.2050; found 304.2040.

Assignment of Stereochemistry of Deuterated Product (*d*-5l):

The stereochemistry of ***d*-5l** was assigned through comparison of ***d*-5l** and **5l**. **5l** was converted to bicycle (***d*-8**) below, which was then characterized by ^{1}H NMR nOe experiments. Key nOe signals, provided below, lead to the assignment of each proton in the all-proteo bicyclic product. The signal of H_E and H_f disappeared in a >20: 1 ratio, indicating the relative stereochemistry of the product. The synthesis of both all-proteo (**8**) and deuterated version (***d*-18**) of the bicycle are provided.



Procedure for Bicycle formation:



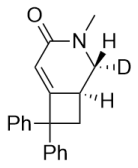
3-methyl-7,7-diphenyl-3-azabicyclo[4.2.0]oct-5-en-4-one (8) An 25mL round bottom was equipped with a stir bar and septa. The round bottom was flamed dried under vacuum and cooled to rt under a flow of nitrogen. The reaction flask was charged with palladium acetate (2.7 mg, 0.012 mmol, 5 mol%), triphenylphosphine (12.7 mg, 0.05 mmol, 20 mol %), and 1,3-dimethylbarbituric acid (113 mg, 0.73 mmol, 3 equiv). N-methyl-N-((2-methylene-3,3-diphenylcyclobutyl)methyl)prop-2-en-1-amine (**5l**) (73.5 mg, 0.24 mmol, 1 eq) was added in a solution of DCM (5 mL). The mixture was heated to 35°C and allowed to stir 16 hours. The reaction was cooled and the solvent removed under reduced pressure. The crude reaction mixture was dissolved in diethyl ether (50 mL) and washed with a saturated aqueous solution of potassium carbonate (2 x 50 ML). The organic layer was dried over sodium sulfate and concentrated in vacuo to yield N-methyl-1-(2-methylene-3,3-diphenylcyclobutyl)methanamine (**6**) as a yellow oil. This material was used without any further purification. ^{1}H NMR (700 MHz,

$CDCl_3$) d 7.39 – 7.34 (m, 2H), 7.32 – 7.28 (m, 2H), 7.28 – 7.24 (m, 2H), 7.23 – 7.18 (m, 3H), 7.17 – 7.13 (m, 1H), 5.15 (d, J = 2.37 Hz, 1H), 5.05 (d, J = 2.92 Hz, 1H), 3.20 – 3.12 (m, 1H), 2.90 – 2.84 (m, 1H), 2.82 – 2.78 (m, 1H), 2.75 – 2.70 (m, 2H), 2.69 – 2.65 (m, 1H), 2.43 (s, 3H).

A 10 mL round bottom was equipped with a stir bar and septa. The round bottom was flamed dried under vacuum and cooled to rt under a flow of nitrogen. **6** was added in a solution of DCM (0.34mL). The mixture was cooled to 0°C in an ice bath. Triethylamine (0.05 mL, 0.36 mmol, 1.5 eq) was added followed by acroyl chloride (0.02 mL, 0.28 mmol, 1.2 eq). The reaction was allowed to warm to rt and stir for 3 hrs. Water (5mL) was added to quench and the aqueous layer was extracted with DCM (3 x 5mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to yield a yellow oil. The crude material was purified via preparative thin layer chromatography with a mixture of 90% ethyl acetate and 10% hexanes as the eluent to afford 13.1 mg (17%) of N-methyl-N-((2-methylene-3,3-diphenylcyclobutyl)methyl)acrylamide (**7**) as a yellow oil. The reported peaks are for the mixture of rotamers. ^{1}H NMR (700 MHz, $CDCl_3$) d 7.37 – 7.26 (m, 12H), 7.25 – 7.14 (m, 8H), 6.55 (dd, J = 16.73, 10.45 Hz, 1H), 6.43 (dd, J = 16.69, 10.42 Hz, 1H), 6.34 – 6.26 (m, 2H), 5.68 (dd, J = 10.41, 1.98 Hz, 1H), 5.59 (dd, J = 10.42, 2.07 Hz, 1H), 5.19 – 5.13 (m, 3H), 5.06 (d, J = 2.78 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.67 – 3.60 (m, 2H), 3.50 – 3.44 (m, 1H), 3.30 – 3.22 (m, 2H), 3.06 (s, 3H), 2.99 (s, 3H), 2.87 – 2.83 (m, 1H), 2.81 – 2.71 (m, 2H), 2.62 – 2.55 (m, 1H).

Grubbs-Hoveyda II complex (0.5 mg, 0.002 mmol) was added to a Schlenk tube with a stir bar and septa in a glove box. The Schlenk tube was removed from the glove box and connected to the Schlenk line and opened to nitrogen. **7** (4.7 mg, 0.015 mmol) was added in solution of degassed toluene (2.4 mL). The tube was heated to 95°C and stir for 16 hours. The reaction

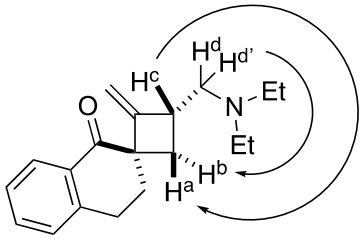
mixture was cooled to room temperature and filtered through celite with ethyl acetate. The crude was purified via preparative thin layer chromatography with a mixture of 50% ethyl acetate and 50% hexanes as the eluent to afford 1.3 mg (30%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.30 – 7.19 (m, 6H), 7.18 – 7.09 (m, 4H), 5.83 (d, J = 2.33 Hz, 1H), 3.47 (t, J = 12.02 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.25 – 3.15 (m, 1H), 2.90 (s, 3H), 2.85 – 2.79 (m, 1H), 2.58 – 2.52 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 165.9, 161.1, 144.5, 144.1,128.8, 128.5, 127.3, 126.9, 126.6, 126.4, 114.3, 61.6, 54.5, 37.8, 34.8, 33.0. IR (film) 3202, 2940,1683, 1632 cm^{-1}. HRMS (EI+TOF) m/z: Calcd for C20H19NO 289.1467; found 289.1461.



(±)-(1*S*,2*R*)-3-Methyl-7,7-diphenyl-3-azabicyclo[4.2.0]oct-5-en-4-one-2-*d* (*d*-8) The title compound was prepared from (1*R*,2*S*)-*N*-Methyl-N-[(2-methylene-3,3-diphenylcyclobutyl)methyl-*d*]prop-2-en-1-amine (***d*-5l**) (0.068 mmol, 21 mg) using the procedure detailed above. The crude material was purified using column chromotagraphy. This procedure afforded 3.7 mg (74%) of the title compound as a yellow oil, which contained some minor grease impurities. The reported peaks are for the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.30 – 7.19 (m, 6H), 7.18 – 7.09 (m, 4H), 5.83 (d, J = 2.33 Hz, 1H), 3.47 (t, J = 12.02 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.90 (s, 3H), 2.85 – 2.79 (m, 1H), 2.58 – 2.52 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) d 165.9, 161.0, 144.5, 144.1, 128.8, 128.5, 127.3, 126.9, 126.8, 126.6, 126.4, 114.3, 61.6, 54.2, 37.8, 34.8, 32.9. IR (film) 3201, 2939,1683, 1632 cm^{-1}. HRMS (EI+TOF) m/z: Calcd for C20H18DNO 290.1529; found 290.1521.

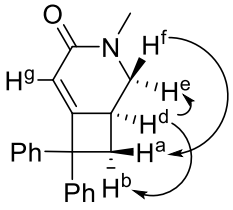
Description of Stereochemical Assignments

The stereochemistry of product **5r** was assigned through a combination of ^{1}H NMR COSY and nOe experiments. The methylene protons (H^a and H^b) appear at chemicals shifts of 1.64 and 2.94 ppm, respectively.[21] The significant upfield shift of H^a is a result of its positioning above the carbonyl pi-system. With the stereochemistry of H^a relative to the carbonyl established, the stereochemistry of the molecule was assigned based on the nOe enhancements shown below.



Proton	Chemical Shift
H^a	1.64
H^b	2.94
H^c	3.08
H^d H^e	2.3-2.4

The relative stereochemistry of key protons in all-proteo bicycle **8** was established through a combination of ^{1}H NMR COSY and nOe experiments. Key nOe enhancements are shown below. The stereochemistry of ***d*-8** was assigned based on the disappearance of the signal at 3.36 ppm.



Proton	Chemical Shift
H^a	2.56
H^b	2.81
H^d	3.19
H^e	3.36
H^f	3.46
H^g	5.83

3.8 References

(1) Najera, C.; Beletskaya, I. P.; Yus, M. “Metal−Catalyzed Regiodivergent Organic Reactions” *Chem. Soc. Rev.* **2019**, *48*, 4515. 10.1039/C8CS00872H.

(2) (a) Maraswami, M.; Diggins, T.; Goh, J.; Tio, R.; Ong, W. T. R.; Hirao, H.; Loh, T. −P. “Intramolecular Alkene−Alkene Coupling via Rh(III)−Catalyzed Alkenyl sp^2C−H Functionalization: Divergent Pathways to Indene or α−Naphthol Derivatives” *ACW. Catal*. **2021**, *11*, 11494 10.1021/acscatal.1c03175. (b) Yang, M. −H.; Orsi, D. L.; Altman, R. A. “Ligand−Controlled Regiodivergent Palladium−Catalyzed Decarboxylative Allylation Reaction to Access α, α−Difluoroketones” *Angew. Chem., Int. Ed*. **2015**, *54*, 2361 10.1002/anie.201410039. (c) Locascio, T. M.; Tunge, J. A. “Palladium−Catalyzed Regiodivergent Substitution of Propargylic Carbonates” *Chem.−Eur. J.* **2016**, *22*, 18140 10.1002/chem.201603481. (d) Yang, Y.; Buchwald, S. L. “Ligand−Controlled Palladium− Catalyzed Regiodivergent Suzuki−Miyaura Cross−Coupling of Allylboronates and Aryl Halides” *J. Am. Chem. Soc*. **2013***, 135*, 10642 10.1021/ja405950c.

(3) Bornowski, E. C.; Shepich, J. H.; Carpenter, P. M.; White, D. R.; Hatt, J. E.; Wolfe, J. P. “Regiodivergent Palladium−Catalyzed Alkene Difunctionalization Reactions for the Construction of Methylene Cyclobutanes and Methylene Cyclopentanes” *Org. Lett*. **2022**, *24*, 8208 10.1021/acs.orglett.2c03308.

(4) (a) White, D. R.; Wolfe, J. P. “Stereocontrolled Synthesis of Amino−Substituted Carbocycles by Pd− Catalyzed Alekene Carboamination Reactions” *Chem. − Eur. J*. **2017**, *23*, 5419 10.1002/chem.201700466. (b) White, D. R.; Hutt, J. T.; Wolfe, J. P. “Asymmetric Pd−Catalyzed

Alkene Carboamination Reaction for the Synthesis of 2−Aminoindane Derivatives" *J. Am. Chem. Soc*. **2015**, *137*, 11246 10.1021/jacs.5b07203.

(5) (a) Poplata, S.; Troster, A.; Zou, Y. −Q.; Bach, T. "Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions" *Chem. Rev*. **2016**, *116*, 9748 10.1021/acs.chemrev.5b00723. (b) Li, J.; Gao, K.; Bian, M.; Ding, H. "Recent advances in the total synthesis of cyclobutane−containing natural products" *Org. Chem. Front*. **2020**, *7*, 136 10.1039/C9QO01178A.

(6) Appenzeller, J.; Tilvi, S.; Martin, M.−T.; Gallard, J.−F.; El−bitar, H.; Dau, E. T. H.; Debitus, C.; Laurent, D.; Moriou, C.; Al−Mourabit, A. "Benzosceptrins A and B with a Unique Benzocyclobutane Skeleton and Nagelamide S and T from Pacific Sponges" *Org. Lett*. **2009**, *11*, 4874 10.1021/ol901946h.

(7) Monkovic, I.; Wong, H.; Pircio, A. W.; Perron, Y. G.; Pachter, I. J.; Belleau, B. "Oxilorphan and butorphanol. Potent narcotic antagonists and nonaddicting analgesics in the 3,14−dihydroxymorphinan series. Part V" *Can. J. Chem*. **1975**, *53*, 3094 10.1139/v75−439

(8) Buckett, W. R.; Thomas, P. C.; Luscombe, G. P. "The pharmacology of sibutramine hydrochloride (BTS 54 524), a new antidepressant which induces rapid noradrenergic down−regulation. Prog. Neuropsychopharm" *Biol. Psych*. **1988**, *12*, 575 10.1016/0278−5846(88)90003−6.

(9) (a) Giblin, G. M. P.; O'Shaughnessy, C. T.; Naylor, A.; Mitchell, W. L.; Eatherton, A. J.; Slingsby, B. P.; Rawlings, A.; Goldsmith, P.; Brown, A. J.; Haslam, C. P.; Clayton, N.; Wilson, A. W.; Chessell, I. P.; Wittington, A. R.; Green, R. "Discovery of 2−[(2,4−Dichlorophenyl)amino]−N−[(tetrahydro−2H−pyran−4−yl) methyl]−4−(trifluoromethyl)−5−pyrimidinecarboxamide, a

Selective CB2 Receptor Agonist for the Treatment of Inflammatory Pain" *J. Med. Chem*. **2007**, 50, 2597 10.1021/jm061195+. (b) Reddy, G. O.; Sarma, M. R.; Chandrasekhar, B.; Babu, J. M.; Prasad, A. S. R.; Raju, C. M. H. "A Study and Identification of Potential By−Products of Sibutramine" *Org. Process Res. Dev*. **1999**, *3*, 488 10.1021/op980093t.

(10) (a) Jiang, Y.; Zhang, K.; Gao, S.; Wang, G.; Huang, J.; Wang, J.; Chen, L. "Discovery of Potent c−MET Inhibitors with New Scaffold Having Different Quinazoline, Pyridine, and Tetrahydropyridothienopyrimidine Headgroups" *Molecules* **2016**, *21*, 612 10.3390/molecules21050612 (b) Dobrydnev, A.; Popova, M.; Saffon−Merceron, N.; Listunov, D.; Volovenko, Y. "Synthesis of the First Representatives of Spiro−1λ6−isothiazolidine−1,1,4−triones" *Synthesis* **2015**, *47*, 2523 10.1055/s−0034−1380434.

(11) (a) Hanley, P. S.; Marquard, S. L.; Cundari, T. R.; Hartwig, J. F. "Reductive Elimination of Alkylamines from Low−Valent, Alkylpalladium (II) Amido Complexes" *J. Am. Chem. Soc*. **2012**, *134*, 15281 10.1021/ja307558x. (b) Peacock, D. M.; Jiang, Q.; Cundari, T. R.; Hartwig, J. F. "Reductive 11 Elimination to Form C(sp^3)−N Bonds from Palladium(II) Primary Alkyl Complexes" *Organometallics* **2018**, *37*, 3243 10.1021/acs.organomet.8b00617.

(12) The lower yield obtained with the deuterated substrate **3-d−1c** compared to the all −proteo analogue was due to the presence of small amounts of (Z)−methyl 2,2−diphenylpent−4−enoate−5−d, which was an intermediate in the preparation of compound **3-d−1c**.

(13) Product stereochemistry was determined by preparing the all−proteo analogue of compound **3-d−8** and then assigning the relative stereochemistry of all protons through ^{1}H NMR nuclear Overhauser effect (NOE) experiments. The relative stereochemistry of compound **3-d−8**

was then established by determining which of the proton signals in the NMR spectrum of compound **3-8** was absent in the spectrum of compound **3-d−8**.

(14) (a) Innitzer, A.; Brecker, L.; Mulzer, J. "Functionalized Cyclobutanes via Heck Cyclization" *Org. Lett*. **2007**, *9*, 4431 −4434 10.1021/ol701697r. (b) Bour, C.; Suffert, J. "4−Exo−digcyclocarbopalladation: A straightforward synthesis of cyclobutanediols from acyclic γ− bromopropargylic diols under microwave irradiation conditions" *Eur. J. Org. Chem*. **2006**, *2006* 139010.1002/ejoc.200500813.

(15) (a) Yi, H.; Hu, P.; Snyder, S. A. "Development and elucidation of a Pd−based cyclization oxygenation sequence for natural product synthesis" *Angew. Chem., Int. Ed*. **2020**, *59*, 2674 10.1002/anie.201913730. (b) Lee, C. −W.; Oh, K. S.; Kim, K. S.; Ahn, K. H. "Suppressed β−hydride elimination in palladium−catalyzed cascade cyclization−coupling reactions: An efficient synthesis of 3−arylmethylpyrrolidines" *Org. Lett.* **2000,** *2*, 1213 10.1021/ol0056426. and references cited therein.

(16) In principle the products could be generated by a mechanism involving alkene aminopalladation with the opposite regioselectivity observed in five−membered ring−forming reactions. However, we disfavor this mechanism because a Pd−complexed monosubstituted alkene is polarized such that the more substituted carbon bears the partial positive charge. In addition, this pathway would generate a five −membered palladacycle bearing an exocyclic CH_2NR_2 group with β−hydrogens that would likely undergo rapid β−hydride elimination side reactions to generate side products that we do not observe.

(17) Driver, M. S.; Hartwig, J. F. “Carbon−Nitrogen−Bond−Forming Reductive Elimination of Arylamines from Palladium(II) Phosphine Complexes” *J. Am. Chem. Soc*. **1997**, *119*, 8232 10.1021/ja971057x.

(18) Driver, M. S.; Hartwig, J. F. “Energetics and Mechanism of Alkylamine N−H Bond Cleavage by Palladium Hydroxides: N−H Activation by Unusual Acid−Base Chemistry” *Organometallics* **1997**, *16*, 5706 10.1021/om970856l.

(19) When the reaction of compound **3-d−1c** was conducted without added water, only the five−membered ring regioisomer was formed.

(20) White, D. R.; Herman, M. I.; Wolfe, J. P. “Palladium-catalyzed alkene carboalkoxylation reactions of phenols and alcohols for the synthesis of carbocycles” *Org. Lett*. **2017**, *19*, 4311.

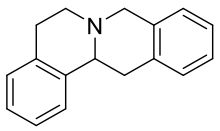
(21) Martin, N. H.; Allen III, N. W.; Brown, J. D.; Kmiec Jr., D. M.; Vo, L. “An NMR shielding model for protons above the plane of a carbonyl group*” J. Molec. Graph. Model*. **2003**, *22*, 127.

(22) Hatt, J. E.; Shepich, J. H.; Clemons, M. N.; Bornoski, E. C.; Wolfe, J. P. “Palladium-Catalyzed Synthesis of 1-Alkylidene-2-dialkylaminomethyl Cyclobutane Derivatives via Pd-Catalyzed Alkene Difunctionalization Reactions: Influence of Nucleophile and Water on the Reaction Mechanism” *Org. Lett*. **2023**, *25*(18), 3245-3248.

Chapter 4 Introduction Into Tetrahydroberberine Alkaloids

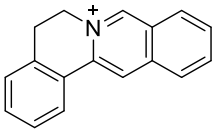
4.1 Introduction

Heterocycles, particularly those containing nitrogen, are a common motif in biologically active molecules.[1] One such family of molecules are the tetrahydroberberine (THB) alkaloids, which includes tetrahydroprotoberberine (THPB) **4-1** and functionalized derivatives. These compounds feature a fused, polycyclic ring system with a tetrahydroisoquinoline core (eq 4-1). This class of molecules has been shown to have anti-oxidant, anti-inflammatory, and neuroprotective behavior.[2] In addition, the fully oxidized versions of this scaffold, berberines such as protoberberine **4-2** (eq 4-1), have demonstrated cytotoxic activity, indicating a clear relationship between structural features and biological properties.[2] This class of molecules is an interesting synthetic target and this chapter will offer a brief introduction into the biological activity of THBs (4.2) and current approaches used to synthesize them (4.3). My own contributions to this work through palladium catalyzed alkene difunctionalization will be detailed in the following chapter (5) and, to scaffold this discussion, previous advances in carboamination reactions in the synthesis of polycyclic heterocycles (4.4) will also be discussed in this introduction.



Tetrahydroprotoberberine

4-1



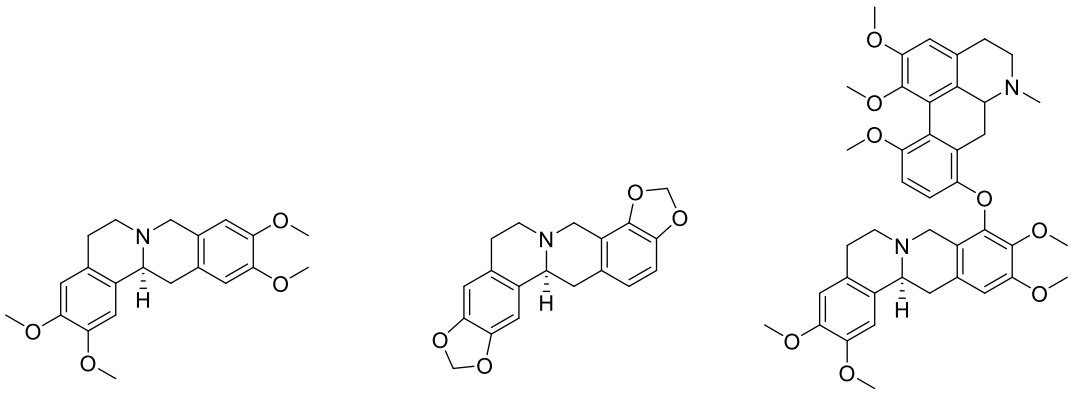
Protoberberine

4-2

eq 4-1

4.2 Significance of Tetrahydroberberine Alkaloids

Tetrahydroberberines (THBs) are a large class of natural products, the members of which demonstrate a wide variety of biological activity.[2] For example, levo-tetrahydropalmatine **4-3** can aide in substance use disorders as a dopamine receptor antagonist that can help reduce patients' cravings of elicit substances. [3] Whereas, Stylopine **4-4** and Acutiaporerine **4-5** were reactive against distinct cancer cell lines through different modes, osteosarcoma and non-small cell lung cancer, respectively. [4,5] These are just a few examples of naturally occurring THBs that have demonstrated promise in many disease areas due to different substitution patterns. Along this line of thought, there has also been movement to structurally diversify the THB structure and functionality through synthetic means to access even more competent



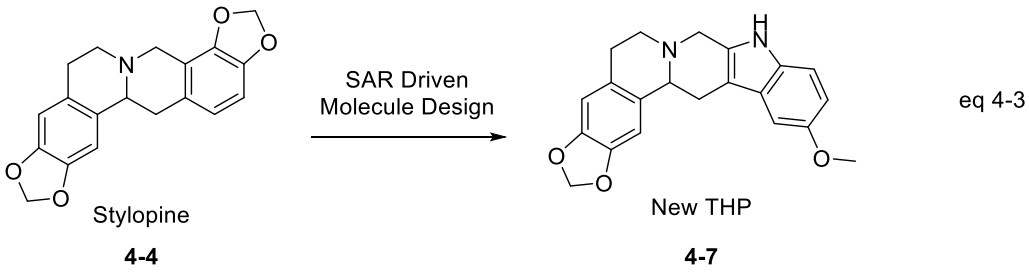
Levo-tetrahydropalmatine **4-3**

Stylopine **4-4**

Acutiaporberine **4-5**

eq 4-2

therapeutics. For example, after discovering some promising bioactivity of **4-3** as an adrenergic receptor antagonist that is implicated for the treatment of benign prostatic hyperplasia, researchers substituted one of the aryl rings with an indole, which improved activity and the pharmokinetic profile (eq 4-3).[6] Results such as these indicate a pressing need to synthesize more THB derivatives with untraditional substitution patterns.

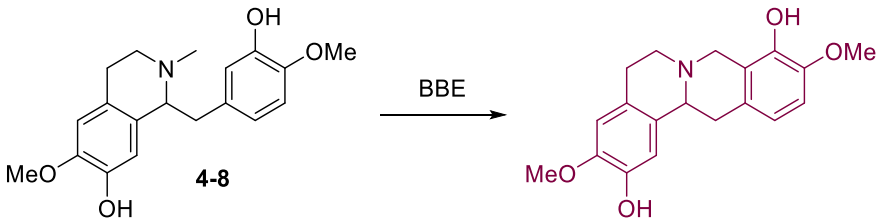


eq 4-3

4.3 Methods for Synthesis of Tetrahydroberberine Alkaloids

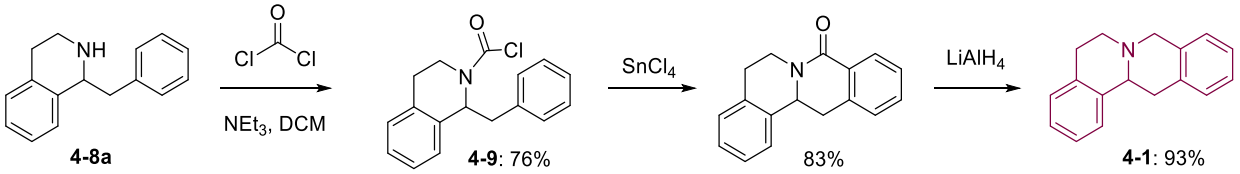
As discussed in the previous section, tetrahydroberberines (THBs) are a biologically active class of natural products and researchers are interested in accessing them synthetically.[7] Biosynthetically, THBs are formed in 9 steps using 10 enzymes from dopamine.[8] In this approach, a tetrahydroisoquinoline core **4-8** is formed first and then the second internal ring is formed using a berberine bridge enzyme (BBE) that affects an electrophilic aromatic substitution to close the final ring (Scheme 4-1). This strategy has been frequently employed in fully synthetic pathways as well, and are prevalent in the older examples of synthetic approaches in the literature.[7] For example, in 1985 Jung and Stambach used phosgene as an acylating agent on **4-8a** to form intermediate **4-9** so that they could then conduct a Friedel-Crafts acylation and reduction to form

Scheme 4-1: Biosynthetic Pathway



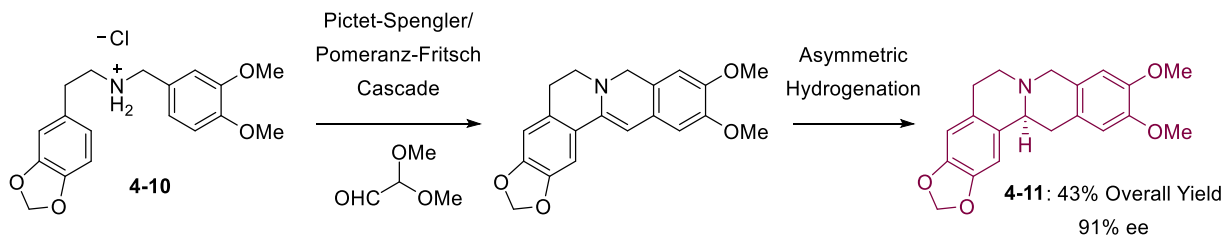
the desired product **4-1** (Scheme 4-2).[9] While this disconnection is effective, only one bond is formed in this step, and more recent reports have sought methods to form both rings in tandem in an effort to reduce overall step count.

Scheme 4-2: 1985 Jung and Stambach Method



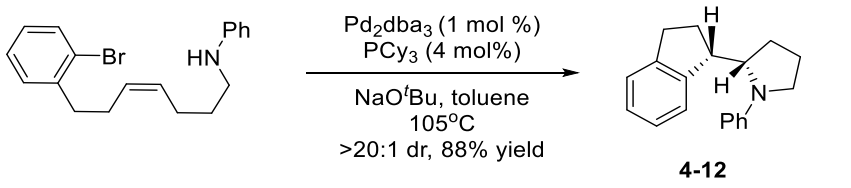
For example, recently in the literature Chen and co-workers published a method in which both rings are formed from **4-10** in a "Pictet–Spengler reaction/Friedel–Crafts hydroxyalkylation/dehydration cascade" (Scheme 4-3). [10] The desired product **4-11** is subsequently formed through an asymmetric hydrogenation. While this method is effective, a limitation still exists in that this approach, like most reports, employs an electrophilic aromatic substitution as a key step which typically only tolerates electron rich aromatic systems, limiting the applicability to unnatural THPs. Additionally, while the rings are formed in tandem, the single stereocenter is installed in a subsequent synthetic step, which lengthens the route to the target. Palladium-catalyzed alkene difunctionalization offers a solution to this problem, but it is so far underdeveloped. [11] My contributions to this area, as outlined in Chapter 5, will address how an intramolecular palladium-catalyzed alkene difunctionalization reaction can address the identified gaps in existing methodology through a tandem cyclization that: (a) installs the key stereocenter in the same step that one ring and two bonds are formed; and (b) exhibits much greater functional group tolerance than traditional electrophilic aromatic substitution approaches.

Scheme 4-3: Chen and Co-workers' Cascade Approach



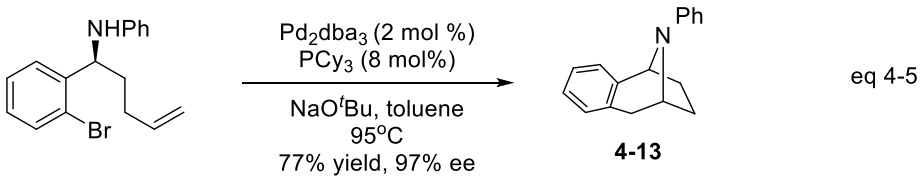
4.4 Intramolecular Carboamination Alkene Difunctionalization Reaction for the Synthesis of Polycyclic Heterocycles

Palladium-catalyzed alkene difunctionalization was identified as a potential solution to the gaps in the literature outlined in the previous section (4.3), given the Wolfe group's extensive history in making heterocycles in this manner. However, despite there being many examples of intermolecular carboamination reactions between amines bearing tethered alkenes and aryl/alkenyl halide/triflate electrophiles, fully intramolecular reactions in which all three components (amine, alkene, and electrophile) are tethered remain under developed.[12] To the best of my knowledge, in the published literature, there are only three examples that have been previously described. The first example was published in 2006 which formed 2-indan-1-yl pyrrolidines **4-12** through a syn-carboamination reaction (eq 4-4).[13] This work demonstrated the feasibility of this approach, and is a useful approach to the synthesis of attached ring systems, but does not generate fused-ring heterocycles. In 2011, bridged bicycles were synthesized using an intramolecular carboamination approach, allowing access to benzo-fused tropanes **4-13**, an interesting class of natural products (eq 4-5). [14] A feature of this reaction that is important to note is that while this work allowed access to enantiomerically enriched products, it did so through the use of chiral starting materials, not chiral ligands. Although these two examples deliver products that behave and look distinct from the THPs, they still represent critical foundational work in the development of intramolecular carboamination reactions.



4-12

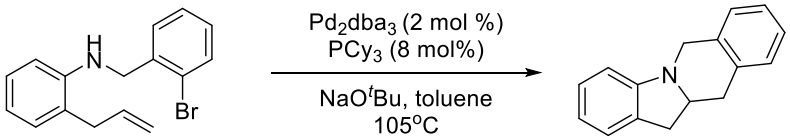
eq 4-4



4-13

eq 4-5

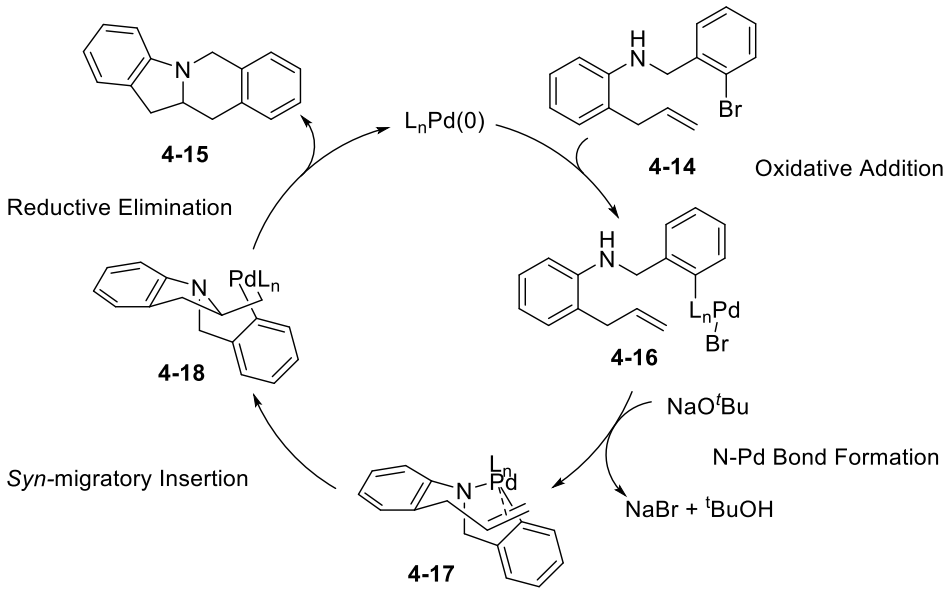
In 2014, the electrophile, nucleophile and alkene were rearranged again, to now form tetrahydroindoloisoquinolines **4-15** (eq 4-6)`.[15] This reaction occurs via the following catalytic cycle (Scheme 4-4). First, the starting material **4-14** undergoes oxidative addition to a palladium (0) species. This intermediate **4-16** next undergoes a ligand exchange to form a nitrogen-palladium bond and coordinates to the alkene. This intermediate **4-17** undergoes a syn-migratory insertion to form palladacycle **4-18**, which can undergo reductive elimination to form the desired product **4-15**.[15]



4-14 **4-15**

eq 4-6

Scheme 4-4: Catalytic Cycle to Form Tetrahydroindoloisoquinolines



This system is the most similar to the proposed reaction of Chapter 5. However, it is important to note the key differences. First, all three-previously reported fully intramolecular reactions, including that of **4-14** involve aniline nucleophiles rather than aliphatic amines. This changes the nucleophilicity of the amine and, therefore, it's reactivity in potentially competing bimolecular N-arylation reactions, and also reduces the likelihood of beta-hydride elimination side reactions that are a major potential issue for the project outlined in Chapter 5. Finally, this is a racemic method, and no ligand has yet been reported to be able to control the enantioselectivity of this transformation, a major goal of the THP project. These key differences offer an opportunity to not only expand the scope of products that can be made through intramolecular carboamination, but also expand understanding of the generality and demands of previously unexplored intramolecular alkene difunctionalization reaction systems.

4.5 Conclusion

In the field of organic chemistry, there has been significant interest in developing methods to access interesting classes of heterocycles in efficient and stereoselective ways.[16] This is an area of research that continues to be developed and is showcased in the synthetic literature surrounding Tetrahydroberberines (THBs). However, there still remain many gaps in this body of literature. For example, in the field of THBs, there are limited examples of methods that will form both rings at the same time that the stereocenter is set. Also, most methods rely on the electron donating character of the aryl rings to encourage ring-forming reactions, limiting tolerance of functionalization in positions that do no stabilize developing positive charge during the EAS reaction, including electron-withdrawing or electron-neutral groups on the aryl rings. These are problems that can be potentially addressed through an intramolecular palladium catalyzed alkene difunctionalization reaction as the key disconnection. However, there are limited examples of these systems in the literature, which leaves remaining questions as to the generality of this approach. For example, aliphatic amines are under explored and ligand controlled enantioselectivity in fully intramolecular Pd-catalyzed alkene carboamination reactions has not been described. Current research projects in the Wolfe lab are targeted towards addressing these gaps in the literature and my contributions to answering these scientific questions will be outlined in the following chapter (Chapter 5).

4.6 References

(1) Chen, Y.; Rosenkranz, C.; Hirte, S.; Kirchmair, J. “Ring systems in natural products: structural, diversity, physiochemical properties, and coverage by synthetic compounds” *Nat. Prod. Rep*. **2022**, 39, 1544–1556.

(2) Pingali, S.; Donahue, J. P.; Payton-Stewart, F. “Tetrahydroberberine, a pharmacologically active naturally occurring alkaloid” *Acta Crystallogr C Struct Chem*, **2015**, *71*, 262-265.

(3) Gong, X.; Yue, K.; Ma, B.; Xing, J.; Gan, Y.; Wang, D.; Jin, G.; Li, C. “Levo- Levo-tetrahydropalmatine, a natural, mixed dopamine receptor antagonist, inhibits methamphetamine self-administration and methamphetamine-induced reinstatement” *Pharmacol. Biochem. Behav,* **2016**, *144*, 67-72.

(4) Velayutham, N. K.; Thamaraikani, T.; Wahab, S.; Khalid, M.; Ramachawolran, G.; Abullais, S. S.; Wong, L. S.; Sekar, M.; Gan, S. H.; Ebenezer, A. J.; Ravikumar, M.; Subramaniyan, V.; Mat Rani, N. N. I.; Wu, Y. S.; Jeyabalan, S. “Stylopine: A potential natural metabolite to block vascular endothelial growth factor receptor 2 (VEGFR2) in osteosarcoma therapy” *Front Pharmacol* **2023,** *14*, 1150270.

(5) Chen, Q.; Peng, W.; Xu, A. “Apoptosis of a human non-small cell lung cancer (NSCLC) cell line, PLA-801, induced by acutiaporberine, a novel bisalkaloid derived from Thalictrum acutifolium (Hand.-Mazz.) Boivin” *Biochemical Pharmacology,* **2002,** *63* (8), 1389-1396.

(6) Guo, D.; Li, J.; Lin, H.; Zhou, Y.; Chem, Y.; Zhao, F.; Sun, H.; Zhang, D.; Li, H.; Shoichet, B. K.; Shan, L.; Zhang, W.; Xie, X.; Jiang, H.; Liu, H. “Design, Synthesis, and Biological Evaluation of

Novel Tetrahydroprotoberberine Derivatives (THPBs) as Selective α1A-Adrenoceptor Antagonists" *J. Med. Chem.* **2016,** *59* (20), 9489–9502

(7) Niu, Z-X.; Wang, T-W.; Wang, J. F. "Retracted Article: Recent advances in total synthesis of protoberberine and chiral tetrahydroberberine alkaloids." Retraction notice: *Nat. Prod. Rep*. **2024**. *41,* 1457-1457.

(8) Zhao, W.; Liu, M.; Shen, C.; Liu, K.; Liu, H.; Ou, C.; Dai, W.; Liu, X.; Liu, J. "Biosynthesis of plant-specific alkaloids tetrahydroprotoberberines in engineered Escherichia coli" *Green Chem.,* **2021**,*23*, 5944-5955.

(9) Stambach, J. F.; Jung, L. "Phosgenation of benzyltetrahydroisoquinolines: A new method of berbines and berbin-8-ones synthesis" *Tetrahedron,* **1985,** *41* (3), 169-172.

(10) Li, W.; Jiang, M.; Chen, W.; Chen, Y.; Yang, Z.; Tang, P.; Chen, F. "Total Synthesis of (−)-Canadine, (−)-Rotundine, (−)-Sinactine, and (−)-Xylopinine Using a Last-Step Enantioselective Ir-Catalyzed Hydrogenation" *J. Org. Chem*. **2021**, *86*, 12, 8143–8153

(11) Song, Y.; Li, R.; Bai, J.; Li, X.; Zhou, S.; Zhang, Y. "Carboxylic Acid-Enabled Vinylene Transfer Reaction by Co(III) Catalyst: Scope and Applications to the Five-Step Total Synthesis of Protoberberine Alkaloids Containing Free Hydroxyl Group without Protection" *J. Org. Chem.* **2024**, *89*, 5, 3238–3250.

(12) White, D. R.; Bornowski, E. C.; Wolfe, J. P. "Pd-Catalyzed C-C, C-N, and C-O Bond-Forming Reactions of Alkenes Bearing Tethered Aryl/Alkenyl Triflates." *Isr. J. Chem*. **2020**, *60*, 259–267.

(13) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. "Intramolecular Pd-Catalyzed Carboetherification and Carboamination. Influence of Catalyst Structure on Reaction Mechanism and Product Stereochemistry. *J. Am. Chem. Soc*. **2006**, *128*, 2893–2901.

(14) Schultz, D. M.; Wolfe, J. P. “Intramolecular Alkene Carboamination Reactions for the Synthesis of Enantiomerically Enriched Tropane Derivatives”. *Org. Lett.* **2011**, *13*, 2962–2965.

(15) Alicea, J.; Wolfe, J. P. “Synthesis of Substituted Tetrahydroindoloisoquinoline Derivatives via Intramolecular Pd-Catalyzed Alkene Carboamination Reactions.” *J. Org. Chem*. **2014**, *79*, 4212–4217.

(16) Vo, C. T.; Bode, J. W. “Synthesis of Saturated N-Heterocycles” *J. Org. Chem*. **2014**, *79*, 2

Chapter 5 Palladium-Catalyzed Synthesis of Tetrahydroberberine Derivatives via Pd-Catalyzed Alkene Difunctionalization Reactions

5.1 Introduction

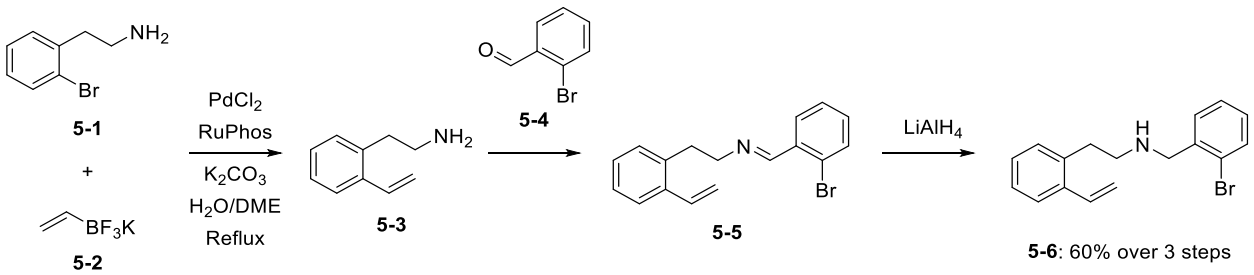
As discussed in the previous chapter, tetrahydroberberine (THB) alkaloids are a synthetically interesting class of molecules due to their biological activity (Chapter 4, Section 2).[1] Despite continued interest, very few methods used to make THBs form both rings at the same time that the stereocenter is set, and most methods rely on the electron donating character of the aryl rings to encourage ring-forming reactions (Chapter 4, Section 3). These are limitations as they add to the step count and limit the type of structures that can potentially be generated with these methods. The following unpublished work will address these current limitations through the development of an intramolecular palladium-catalyzed alkene difunctionalization reaction to directly form THBs.

Mr. Jeremiah Alicea, Dr. Brett Hopkins, Dr. Josh Neukom, Dr. Peter Mai, and Ms. Ellie White made contributions to the work described in this chapter. Mr. Alicea conducted some initial preliminary optimization reactions (Table 5-1, entry 1). Dr. Hopkins, Dr. Neukom and Dr. Mai synthesized some of the TADDOL Cinchona Phosphite ligands (**BAH-7-80** and **BAH-9-51**, Table 5-3; **BAH-8-76**, Scheme 5-5; **BAH-9-122**, **BAH-9-121A**, and **BAH-7-165**, Scheme 5-6). Ms. White aided in the synthesis of starting materials (**5-1a**, Scheme 5-10) and some initial preliminary optimization reactions of the partially intramolecular variation of this transformation (**5-24**, Scheme 5-12).

5.2 Starting Material Synthesis

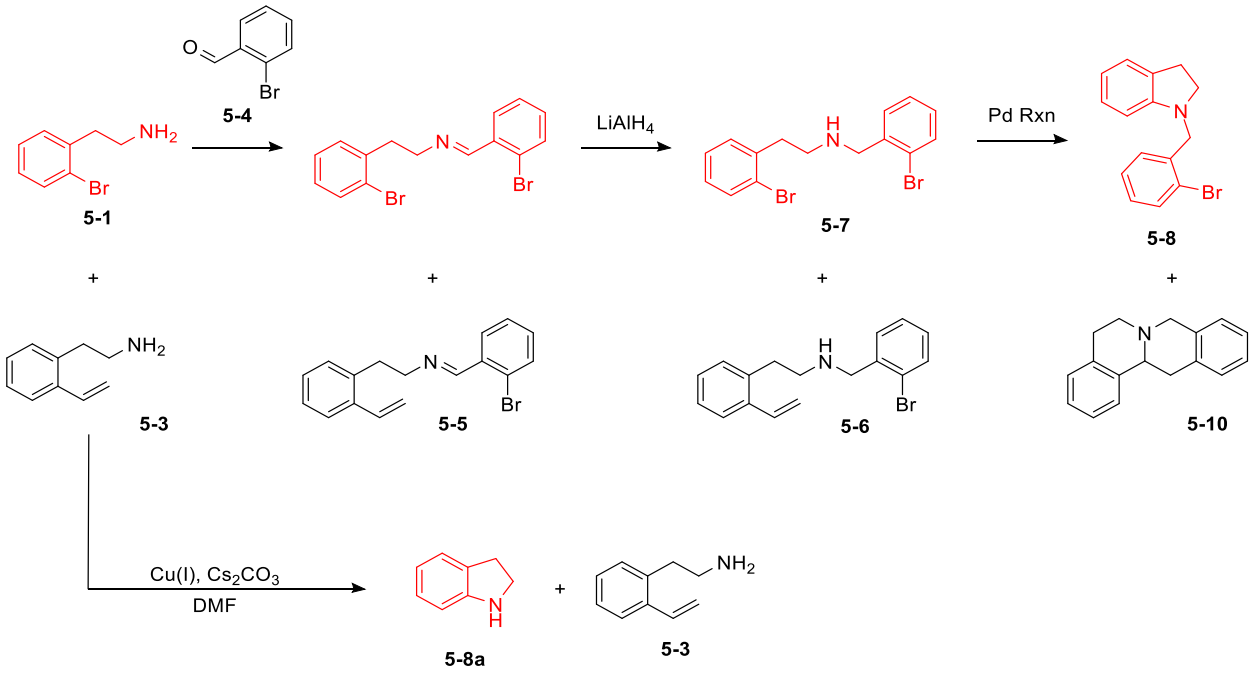
The model starting material for the following experiments was synthesized in 3 steps (Scheme 5-1). The synthetic route starts with a Suzuki cross coupling with 2-bromophenylethyl amine **5-1** and potassium trifluoro(vinyl)borate **5-2** to give the styrene **5-3**. Next, the electrophilic portion was installed using a reductive amination, in which 2-bromo benzaldehyde **5-4** was condensed on **5-3** and the resulting imine **5-5** was reduced using lithium aluminum hydride to give the desired product **5-6** in a 60% overall yield. This modular approach was used to synthesize other substrates described in Section 5.5 by using variations of starting materials **5-4** or **5-1**.

Scheme 5-1: Starting Material Synthesis



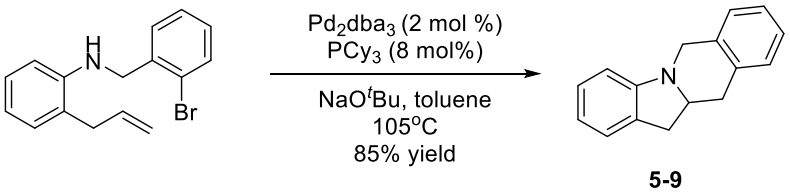
One unexpected challenge in synthesizing **5-6** were impurities resulting from left over **5-1** after the Suzuki cross-coupling (Scheme 5-2). This material was inseparable from the desired product **5-3** and, when carried forward, reacted comparably in the following reductive amination reactions. This led to side product **5-7** that was inseparable from the final product **5-6** which inhibited palladium reactions as it was prone to *N*-arylation, forming indoline **5-8**. This was avoided by improving the conversions of the Suzuki reaction by refluxing with DME instead of using THF in a bomb flask, inspired by a 2006 report.[2] Any additional starting material could be purged by carrying out an intramolecular Cu-catalyzed *N*-arylation directly after the Suzuki reaction, resulting in an indoline **5-8a** that could be separated from the desired product **5-3** using column chromatography (60% MeOH in DCM). [3]

Scheme 5-2: Unexpected Side Product and Prevention



5.3 Racemic Optimization

Our group previously reported an intramolecular carboamination for the construction of racemic tetrahydroindoloisoquinolines **5-9** (eq 5-1).[4] This work provided inspiration for initial studies in forming THBs; both by myself in 2024 and by Jeremiah Alicea in 2014. However, in both of these instances, the catalyst system previously employed for the formation of **5-9** did not give satisfactory results in the reaction of **5-6**; providing at most 9% NMR yield in the THB system (Entry 1, Table 5-1). Through optimization, Alicea was able to obtain up to a 66% yield using PPh_3 as the ligand (Entry 2, Table 5-1). However, this catalyst system suffered from a lack of consistency across runs and led to issues with purification. Alicea graduated with his MS degree shortly after obtaining this preliminary result, and the project was discontinued due to a lack of personnel in the group at the time, eventually forgotten with the passage of time.[5]



5-9

eq 5-1

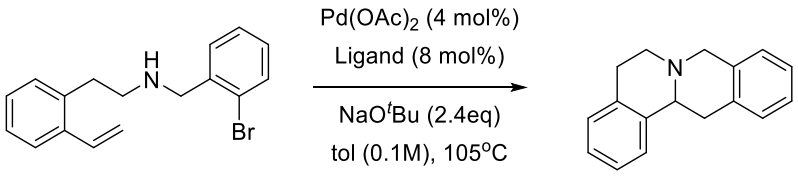
While, at the time, I was unaware of Alicea's attempts at synthesizing **5-10**, I also started optimization by way of a comprehensive ligand screen. I found that the desired product could be obtained in moderate yield using DPEPhos or Xantphos (Entry 3 and 4, Table 5-1). This indicated a preference for bulky bidentate ligands with large bite-angles. When mono-dentate or bidentate ligands with smaller bite angles were employed, the yields were lower; the rest of the mass balance was either starting material or de-halogenated starting material.

Since Xantphos produced significant amounts of product, I began to examine other reaction parameters. Through a base screen, I found that bases other than NaO^{t}Bu were not compatible (Entry 5, Table 5-1). No solvents outperformed toluene. However, improvements in yield were observed when the concentration of the reaction was doubled (Entry 6, Table 5-1). Similar effects were also observed when the amount of palladium was doubled and the temperature raised to 120^{o}C. This indicates that the reaction needed to be pushed in some way to convert the remaining starting material and not stall out. Concentration was chosen as the parameter to do so with, due to the green process chemistry implications that arise from using less solvent rather than increasing the amount of precious metals or energy employed in heating, thereby leading to an overall more desirable method.

Despite obtaining a respectable yield of 67% (Entry 7, Table 5-1) through parameter optimization, a problem remained that this yield was not consistent. As mentioned above, this

was also a problem for Alicea. Taking this into consideration, I thought that perhaps not all of my Xantphos was ligated to the metal, and in other Pd-catalyzed reactions involving Pd(OAc) studies have shown that pre-stirring the pre-catalyst and ligand in solvent has a large impact on reactivity. As such, I began using a pre-stir with a Pd pre-catalyst, ligand and base to ensure that the chosen ligand was fully on the palladium before the starting material **5-6** was added and the catalytic cycle began. This change improved yields and lead to more consistent results, forming the desired product in a 78% yield, albeit with some impurities observable in the baseline of the NMR (Entry 7, Table 5-1). Both the palladium loading and ligand loading could be reduced to 3 mol% and the amount of base could be reduced to 2 equiv without significant erosion of yield, thereby leading to the most optimized racemic conditions. It is important to note that at this time, the samples were not being purified effectively through acid/base washes, and all of these yields were inflated with residual ligand and undesired side products. When the crude reaction mixture purified using techniques described in the next section (**5.4**), the reaction gave a clean, average yield of 55% over 2 trials (Eq 5-2).

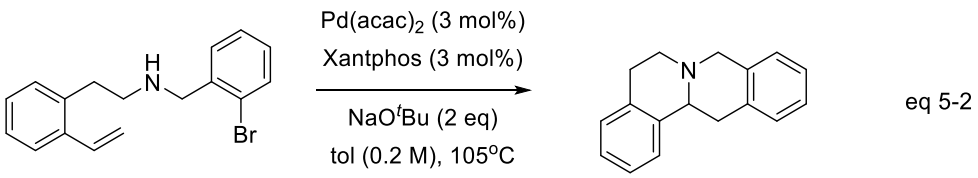
Table 5-1: Racemic Optimization



5-6 **5-10**

Entry	Ligand	Condition Variations	Yield (%)
1	PCy_3	N/A	9
2	PPh_3	N/A	66
3	DPEPhos	N/A	30
4	XantPhos	N/A	48
5	XantPhos	NaHMDS	0
6	XantPhos	0.2 M	67

7	XantPhos	0.2 M, Prestir with $Pd(acac)_2$	78

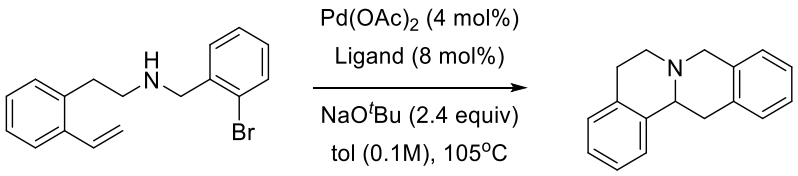


5-6 **5-10**: 55% isolated yield eq 5-2

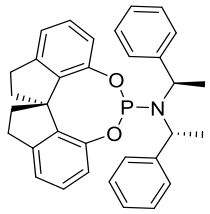
5.4 Chiral Optimization: Purchased and Found Ligands

With a racemic method established, I next turned my attention to developing an enantioselective version of the reaction by using a chiral ligand. Initial screening was conducted using the commercially available chiral ligands that were on hand and had provided useful results in previously reported carboamination reactions, such as *S*-Siphos-PE.[7] This ligand did provide the desired product **5-10**, albeit not with high enantioselectivity (Table 5-2). I expanded the screen and identified that bulky bidentate ligands were the only ones to consistently afford significant amounts of **5-10**; and the ligands that had larger bite angles and bigger backbones provided higher chemical yields (a representative few are included in Table 5-2, (S)-H8 BINAP, (S,S)-BDPP, (S,S,S)-(-)-Xyl-SKP). However, when these products were purified and assayed by chiral HPLC, it was determined that these ligands, too, did not provide products with a sufficiently high level of asymmetric induction.

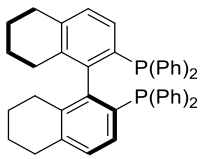
Table 5-2: Representative Initial Chiral Ligand Screen



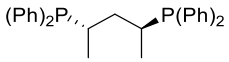
5-6 **5-10**



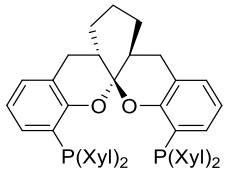
S-SiPhos-PE
65% yield, 20%ee



(S)-H_8 BINAP
38% yield, 31%ee



(S,S)-BDPP
38% yield, 31%ee

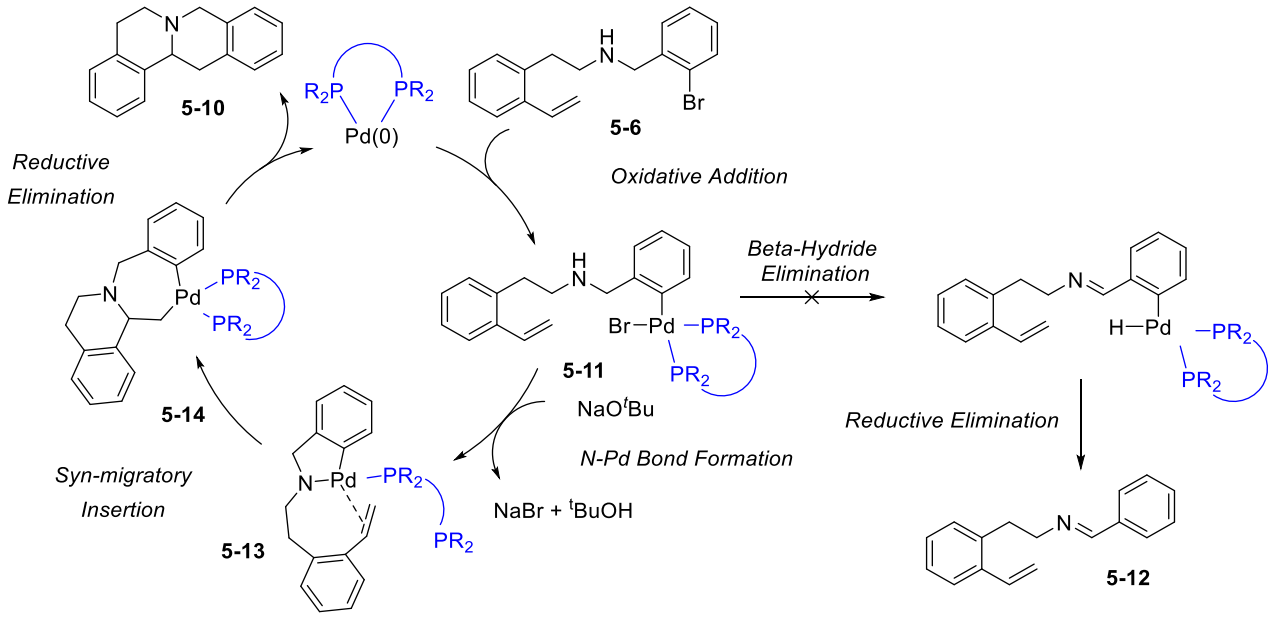


(S,S,S)-(-)-Xyl-SKP
70% yield, 27% ee

The disconnect between yield and enantioselectivity can be explained through the proposed catalytic cycle (Scheme 5-1). The cycle starts with oxidative addition of the aryl bromide portion of the starting material **5-6** to the active palladium (0) species, ligated by, presumably, both arms of the bidentate phosphine ligand, forming a Pd(II) species (**5-11,** Scheme 5-3). At this stage, having no open coordination sites is advantageous because it inhibits off path reactivity of B-Hydride elimination to obtain the dehalogenated side product **5-12**. However, deligation of one arm of the bis-phosphine ligand is required for alkene coordination to occur to intermediate **5-13** and syn-migratory insertion to form palladacycle **5-14**. This limits the ability for the ligand to impart enantioselectivity in the likely enantiodetermining step since the ligand is only partially coordinated and loses the rigidity which typically contributes to such phenomena. The palladacycle **5-14** then undergoes reductive elimination to form the desired **5-10** and regenerate the active Pd(0) species. Through this assessment, the previously selected bidentate ligands are not well-suited for this reaction because they are technically acting as hemi-labile ligands, in which both arms of the ligand are attached in some intermediates of the cycle (**5-11**, **5-14**) but

other intermediates only coordinate to one arm (**5-13**), which inhibits their overall ability to impart enantioselectivity.

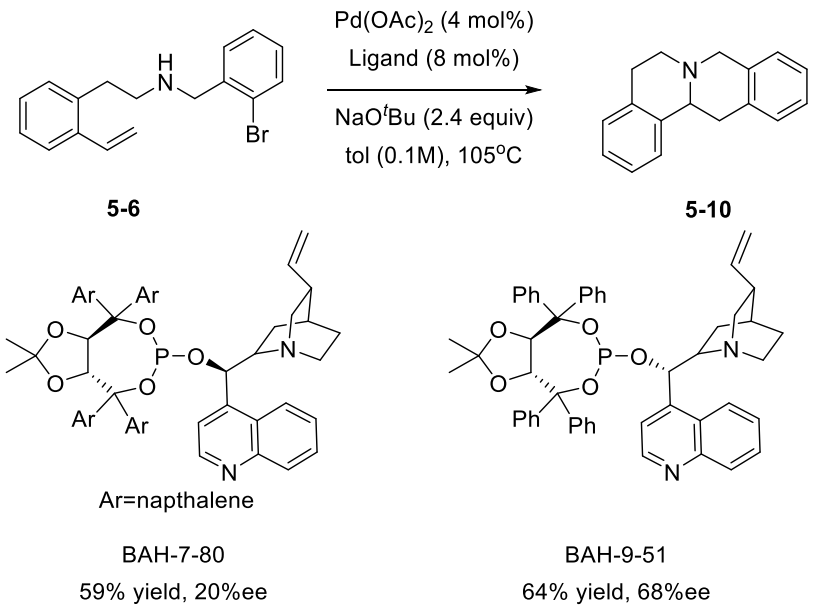
Scheme 5-3: Catalytic Cycle



With the evaluation that bidentate ligands are not effective at inducing high levels of asymmetry in this system, I resumed screening ligands, focusing in particular, on chiral monodentate ligands bearing groups that may serve as hemi-labile ligands. Within this search, I identified **BAH-7-80** as a potential candidate (Figure 5-1). This was a home-made ligand, originally synthesized by Dr. Brett Hopkins in March of 2014, ten years prior to when my screen was conducted. This ligand is characterized by its TADDOL backbone, with naphthalene functionality and a phosphite core to which the chiral cinchonidine is appended. This compound was never fully characterized and unpublished outside of Dr. Hopkin's thesis, which reports only the yield and ee resulting from using this ligand.[8] This compound was not originally screened in preliminary studies, as other chiral phosphites, such as ones with BINAP backbones, did not provide

satisfactory results. Additionally, as the campaign in which this TADDOL Cinchona Phosphite was originally synthesized involved an oxygen nucleophile, suggesting this ligand was never tested with, and may not be compatible with, a nitrogen containing system.[6] Fortunately, when **BAH-7-80** was tested, it proved more successful than anticipated, giving a 59% yield and 20% ee (Table 5-3). Inspired by this preliminary result, I next began trying other TADDOL Cinchona phosphite ligands on hand. While most of these ligands worked to varying degrees, **BAH-9-51** stood out by giving a 64% yield and 68% ee, surpassing all other ligands tested previously (Table 5-3).

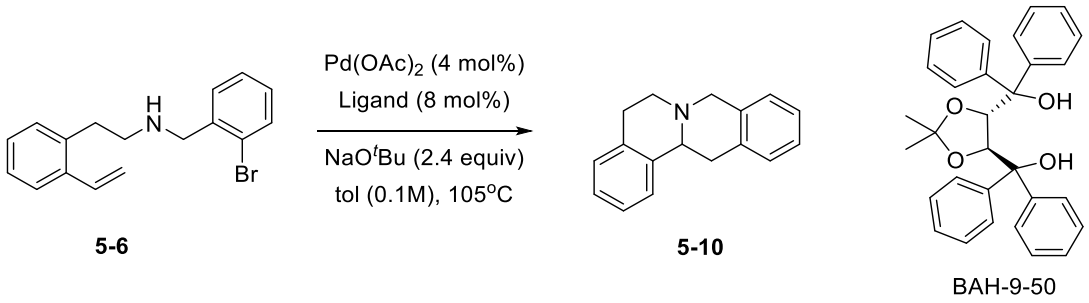
Table 5-3:Inital Success with TADDOL Cinchona Phosphite Ligands



Before fully pursuing these ligands, I conducted control experiments to ensure that it was the phosphite ligand itself responsible for asymmetric induction and not the chiral components (cinchonine or TADDOL **BAH-9-50**) that make up the ligand and could conceivable be present in the reaction mixture if ligand decomposition occurs under the reaction conditions. I found no evidence to support that either component can operate as an additive as none of the tests gave ee, and measurable yield of desired products was only observed when a second ligand (Xantphos)

was added to the reaction (Table 5-4). This indicates that cinchonine and TADDOL are not acting as ligands but the phosphite derived from them is.

Table 5-4: Component Test of Ligand



5-6 **5-10** BAH-9-50

Entry	Ligand	Additive	Yield (%)	ee(%)
1	N/A	Cinchonine	0	N/A
2	N/A	BAH-9-50	0	N/A
3	N/A	Cinchonine + BAH-9-50	0	N/A
4	XantPhos	Cinchonine	54	0
5	XantPhos	BAH-9-50	41	0

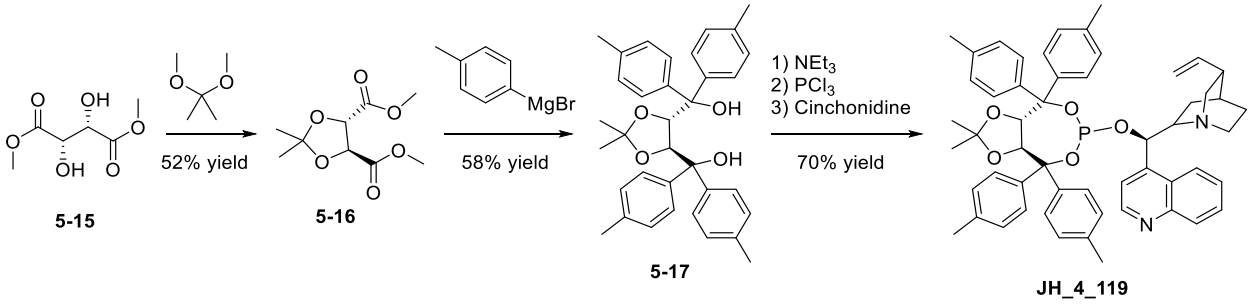
With this promising result, I optimized the reaction further using **BAH-9-51** as my ligand. I found I could reduce my palladium and ligand loading to 3% without erosion of yield or ee, as long as the pre-stir with palladium, ligand and base was incorporated into the procedure. Through time studies, I found the reaction was complete after 24 h, making them necessary to run overnight. Many types of work-up were well tolerated, including LLE and filtration through celite or flurosil. However, they did not increase product purity or ease of isolation, so filtration through a Kimwipe with DCM was selected as the ideal work-up due to ease and time considerations. Many purification methods were tested, including Acid/Base work ups, pipette columns, flash chromatography with EtOAc:Hex mixtures. However, 0-2% MeOH in DCM was found to be most effective. Most byproducts either come off in the initial pure DCM wash (such as acac or decomposition products from the ligand) or remain on the baseline (such as

dehalogenated starting material or palladium) even through the introduction of 2% MeOH. However, this method is not as effective if there is left over starting material as it will coelute with the desired product. While these changes helped optimize the process in which this reaction was run, the yield and ee were still only moderate throughout all these changes, leading to the next step of this project, synthesizing and testing new TADDOL cinchona phosphite ligands.

5.5 Chiral Optimization: TADDOL Cinchona Phosphite Ligands

TADDOL cinchona phosphite ligands are not available for purchase, nor is a procedure for their synthesis published. However, a procedure was described in the laboratory notebooks (7, 8, & 9) of previous group member, Dr. Brett Hopkins and the first two steps to make the TADDOL backbone are well documented.[9] The synthetic route is as follows, demonstrated by the preparation of *p*-tol-TADDOL cinchonidine ligand (**JH_4_119**, Scheme 5-4). Dimethyl-D-tartrate **5-15** is first protected as a cyclic acetal using dimethoxy propane to obtain intermediate **5-16** that can then be converted to various TADDOL derivatives through subsequent Grignard additions (in this case of *p*-tol- Grignard) to form the TADDOL **5-17.** The TADDOL **5-17** is then treated with triethylamine and trichlorophosphine to install the phosphorus atom. Subsequent addition of the cinchona alkaloid (cinchonidine) in a method similar to that documented in Dr. Hopkin's thesis leads to the formation of **JH_4_119** or related TADDOL-derived chiral phosphite ligands. [6]

Scheme 5-4: Representative Route to Make TADDOL Cinchona Phosphites

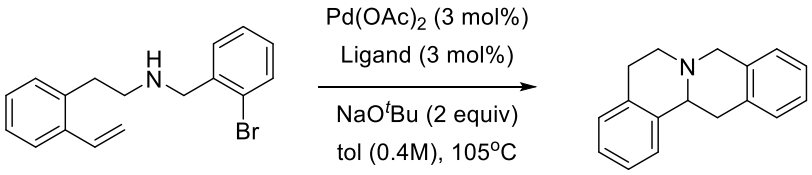


My first studies on the relationship between ligand structure and asymmetric induction were conducted to determine which portion of the ligand would impact ee most significantly. The phenyl cinchona ligand was made using dimethyl-D-tartrate and the cinchona alkaloid was varied between the two different pseudo enantiomers (**JH_4_113** and **JH_4_114**, Table 5-5). The yields and ee were comparable to the previous observed diastereomer **BAH-9-51**. It was significant to note that both ligands gave the same major enantiomer, indicating that the ee was derived from the TADDOL backbone and that is where initial optimization should be focused.

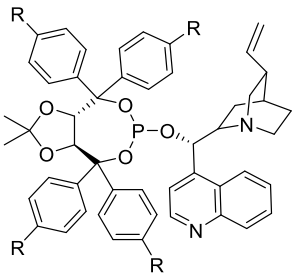
Initial studies were encouraged by promising results of improved ee when employing steric bulk on the TADDOL, toluene **JH-4-119** giving 89% ee (Table 5-5). This inspired a campaign in which the TADDOL backbone was systematically changed to probe the effect of electronics and sterics on yield and ee of the reaction, which initially appeared to support the theory that weakly electron donating groups at the para position that added steric bulk, were beneficial (such as biphenyl **JH_4_151** which gave 93% ee, Table 5-5). However, upon further inspection, these enantioselectivities were not found to be reproducible. The original false positive was most likely due to issues with the HPLC instrument that led to tailing peaks and inaccurate integrations. After additional HPLC analysis, all ligands were determined to provide roughly the same moderate yield and ee (~50-60% yield, ~60-70% ee). Despite this setback, many important lessons were learned through this campaign. Electron-withdrawing groups were not well tolerated such as the para-trifluorotoluene in **JH_4_123**, indicating that electron donation to the phosphite is a requirement for conversion (Table 5-5). Also, some ligands appear to be difficult or impossible to generate, such as very sterically bulky versions of the ligand (e.g., R=^{t}Bu). With this knowledge the next step of the campaign was to systematically look at other components of the TADDOL cinchona ligand

that might influence the reaction other than the aryl groups adjacent to the phosphorus-bound oxygen atoms.

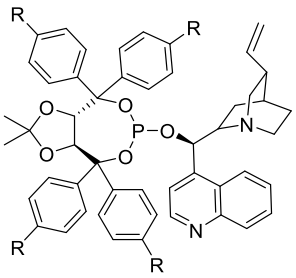
Table 5-5: Reactivity of Synthesized TADDOL Cinchona Phosphite Ligands



5-6 **5-10**



JH_4_113: R=H 62% yield, 74% ee



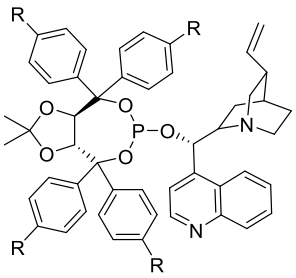
JH_4_114: R= H, 60% yield, 71% ee

JH_4_119: R= Me, 60% yield, 89% ee

* Revised to 68% yield, 58%ee

JH_4_123: R=CF_3, ~15% NMR yield

JH_4_146: R=Ph, 68% yield, 64% ee



JH_4_126: R=Me, 74% yield, -71% ee

JH_4_132: R=OMe, 51% yield, -62% ee

JH_4_151: R=Ph, 78% yield, -93%ee

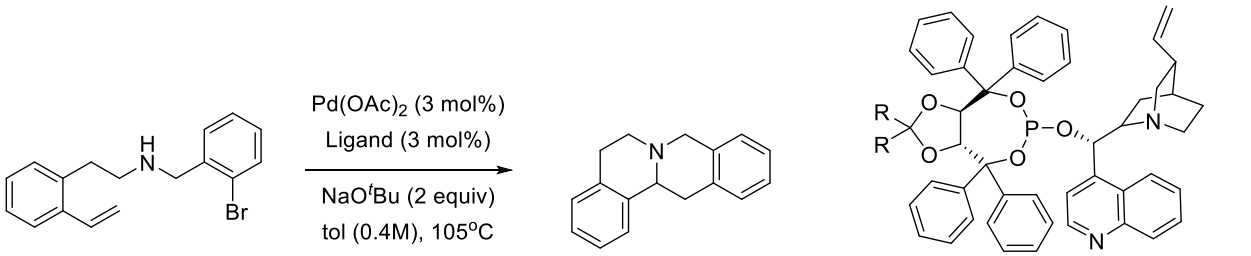
*Revised to: 52% yield, -74% ee

JH_4_176: R=iPr, 73% yield, -60% ee

Returning to the initial prediction that the TADDOL portion was controlling absolute sterochemistry, I next sought to test the effect of altering the other easily modified aspects of the TADDOL backbone, specifically the substituents on the TADDOL acetal. In 2014, Dr. Hopkins synthesized **BAH-8-76**, which contains a diphenyl acetal protection on the TADDOL backbone rather than the traditional dimethyl acetal, such as in **BAH-9-51**.[8] I employed this ligand in my reaction system and found that **BAH-8-76** provided comparable yield and ee to **BAH-9-51** (Scheme 5-5); thereby indicating that this portion of the ligand does not make a significant difference in the effectiveness of the transformation. At this point, it was determined that other

modifications of the TADDOL would be synthetically more difficult to access, so future effort should be focused on altering the cinchona alkaloid portion of the ligand rather than the TADDOL component.

Scheme 5-5: Test of Functionalization on TADDOL Backbone



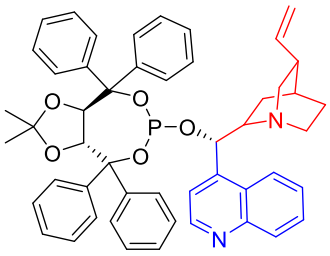
5-6 **5-10**

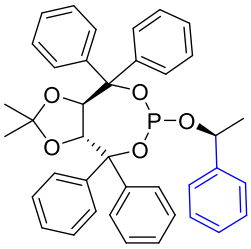
BAH-9-51: R=CH_3, 64% yield, 68% ee

BAH-8-76: R=Ph, 56% yield, 73% ee

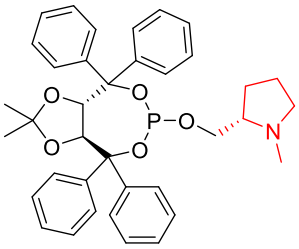
In 2014, Dr. Hopkins proposed that you can mentally break the cinchona alkaloid into 2 chiral portions, the 1,2 amino alcohol (represented in red) and the benzylic alcohol (represented in blue).[8] He synthesized ligands meant to isolate the effects of these two portions (**BAH-9-122A**, where the sec-phenethyl alcohol would mimic the chiral benzylic alcohol, and **BAH-9-121B**, where the N-Me-L-prolinol would mimic the chiral 1,2-aminoalcohol, Scheme 5-6).[8] These ligands gave low yield in his original system, as well as in my reaction system. This suggests that the alkene or quinoline portion may be the most important aspect of the cinchona for control of asymmetric induction, and may serve as hemi-labile groups that ligate at different points during the catalytic cycle. This was encouraged by the similar lack of reactivity of ligand **BAH-7-165** which has the same 1,2 amino alcohol and benzylic alcohol components as a cinchona alkaloid but lacks the quinoline and alkene (Scheme 5-6).

Scheme 5-6: Probe of the Significance of Cinchona Components

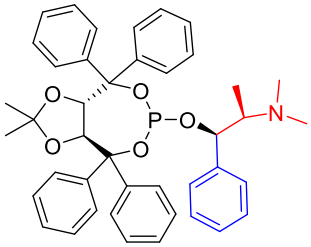




BAH-9-122A



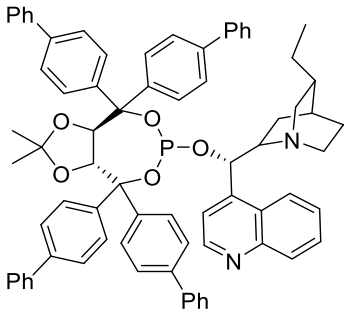
BAH-9-121A



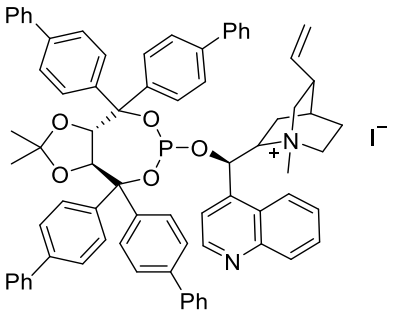
BAH-7-165

To further determine the influence of various components of the cinchona alkaloid with the quinoline present, I synthesized ligands in which the alkene had been reduced (**JH_4_152**) or the quincoridine had been methylatated (**JH_4_193**). The results obtained were nearly identically with the reduced and non-reduced version of the alkene, indicating that the alkene is not important for reactivity or selectivity (Scheme 5-7). On the other hand, the methylated version of **JH_4_146** performed poorly, giving mostly starting material. This data gave the possibility of two conclusions: 1) the quincoridine is important for reactivity in concert with the heteroaryl system, or 2) the positively charged ligand was not compatible with the reaction conditions.

Scheme 5-7: Modified TADDOL Cinchona Phosphites



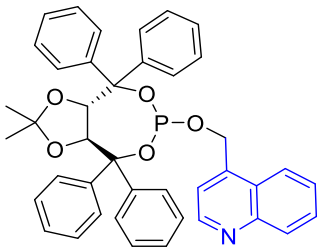
JH_4_152



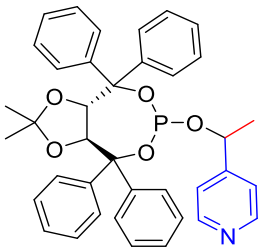
JH_4_193

To enable further clarification, I synthesized three new ligands that contained a pyridinyl component to mimic the benzyl alcohol of the cinchona alkaloids without the quincoridine (**JH-4-195**, **JH-4-196**, **JH_5_004** and **JH_5_009**, Scheme 5-8). While I was unable to obtain chiral versions of some of the pyridine alcohols, the achiral or non-chiral versions were commercially available and could be applied to the ligand synthesis effectively. This was not expected to negatively influence results because Dr. Hopkins previously observed near-identical reactivity between TADDOL derived phosphites in which the third alcohol was either a chiral and an a-chiral alcohol.[8] Additionally, as mentioned previously, I observed nearly identical results from the two different pseudo enantiomers (**JH_4_113** and **JH_4_114**, Table 5-5). Unlike **BAH-9-122A** and **BAH-7-165**, these three ligands contained at least one heteroaryl system, however, a similar lack of reactivity occurred in which the reactions returned mostly starting materials. These results indicate that having both nitrogen components of the cinchona alkaloid are required for reactivity, making the cinchona alkaloid special in its ability to give significant yield and ee.

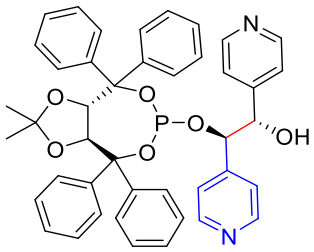
Scheme 5-8: Pyridinyl TADDOL Phosphite Ligands



JH_4_195



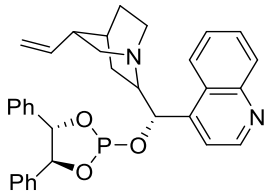
JH_4_196



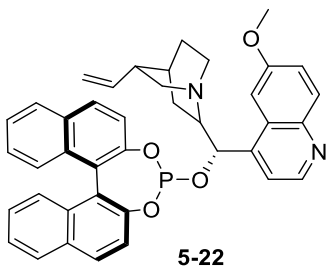
JH_5_009

5.6 Non-TADDOL Cinchona Phosphite Ligands

While considerable effort has been made in the course of this project to develop TADDOL Cinchona Phosphite ligands as a ligand class, future effort should be focused in changing the TADDOL functional group to alternative cyclic systems. While cinchona alkaloids are a prominent feature in asymmetric catalysis, to my knowledge, there are currently limited examples of cinchona alkaloid P,N ligands in the literature and only two that have a cyclic phosphite backbone. The first example (**5-21**)[13] uses a C2-symmetric 1,2-diol based scaffold and the second (**5-22**)[14] employs a BINOL backbone (eq 5-3). These backbones are interesting alternatives to TADDOL because they result in variable ring sizes around the phosphite. This is an attractive variable to manipulate as based upon previous investigations detailed above, the environment directly surrounding the phosphorus appears to be the component that is determining which is the major enantiomer that will form in the carboamination reaction.



5-21

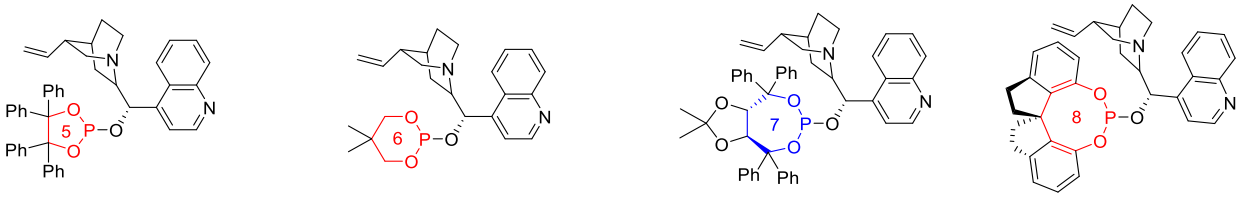


5-22

eq 5-3

To test the effect of backbones/ring sizes, three ligands were synthesized in which the backbone was varied from TADDOL to a commercially-available diol (Scheme 5-9, benzopinacol: **JH_5_041**, 2,2 dimethyl propanediol: **JH_5_048**, R-SPINOL: **JH_5_043**). Preliminary results indicate that the TADDOL ring size/backbone is critical in encouraging product formation. The 5-membered ring, **JH_5_041**, the 6-membered ring, **JH_5_048**, and the 8-membered ring, **JH_5_043**, gave only trace yield, returning mostly starting material and dehalogenation product. Thereby indicating that the TADDOL in unique in its positioning and ligation to the palladium such that it can participate productively in the reaction.

Scheme 5-9: Non-TADDOL Cinchona Ligands



JH_5_041
trace yield

JH_5_048
tbd

JH_4_113
62% yield, 74% ee

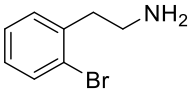
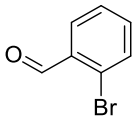
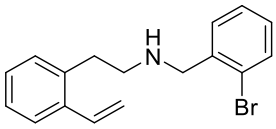
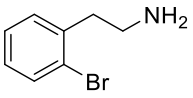
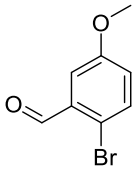
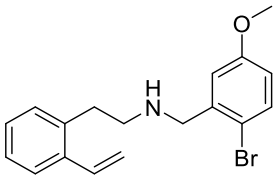
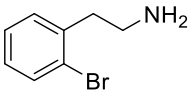
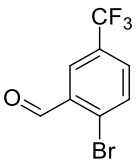
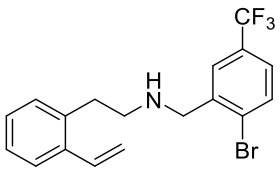
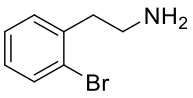
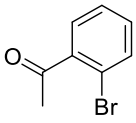
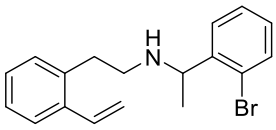
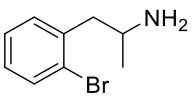
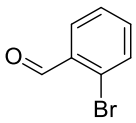
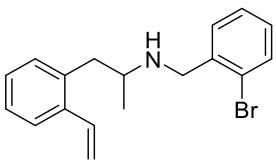
JH_5_043
trace yield

5.7 Substrate Scope

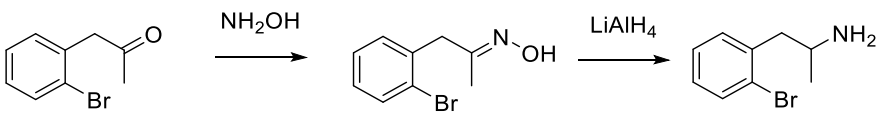
One of the initial goals of this project was to expand the scope of THBs that can be accessed. As discussed in the previous chapter, current methods are limited in that they do not often tolerate non-traditional functionalization, such as additions upon the cyclohexane rings or electron-withdrawing groups on the aromatic rings (Chapter 4). While the aforementioned carboamination method was being developed, it was important for its efficacy towards different substrates to be tested, to ensure the project was still aligned with its original goals. Therefore, four test substrates were synthesized to begin to examine the scope of the method while it was being optimized.

Each substrate was synthesized using the same synthetic route outline in Scheme 5-1 in which either the nucleophile **5-1** or electrophile **5-4** was modified as described in **Table 5-6.** Substrate **5-6a** incorporated a methoxy group para to the oxidative addition site to test tolerance of electron-donating groups on the aryl ring. Substrate **5-6b** tested the effect of electron-withdrawing groups through the incorporation of the trifluoromethyl group in the same position. Functionalization of the internal rings was executed by incorporating methyl groups on either side of the amine (**5-6c** and **5-6d**). For substrates **5-6a**, **5-6b**, and **5-6c**, these changes were straightforward to adopt because all of the coupling partners were commercially available and easily swapped with 2-bromobenzaldehyde **5-4**. In contrast, **5-6d** was slightly more challenging to prepare as **5-1a** was not commercially available and had to be synthesized through a hydroxylamine condensation with 2-bromophenyl acetone **5-19** and subsequent reduction using lithium aluminum hydride. (Scheme 5-5)

Table 5-6: Starting Materials for Substrate Scope

Nucleophile	Electrophile	Final Starting Material
		
5-1	**5-4**	**5-6:** 60% yield
		
5-1	**5-4a**	**5-6a:** 52% yield
		
5-1	**5-4b**	**5-6b:** 44% yield
		
5-1	**5-4c**	**5-6c:** 33% yield
		
5-1a	**5-4**	**5-6d:** 26% yield

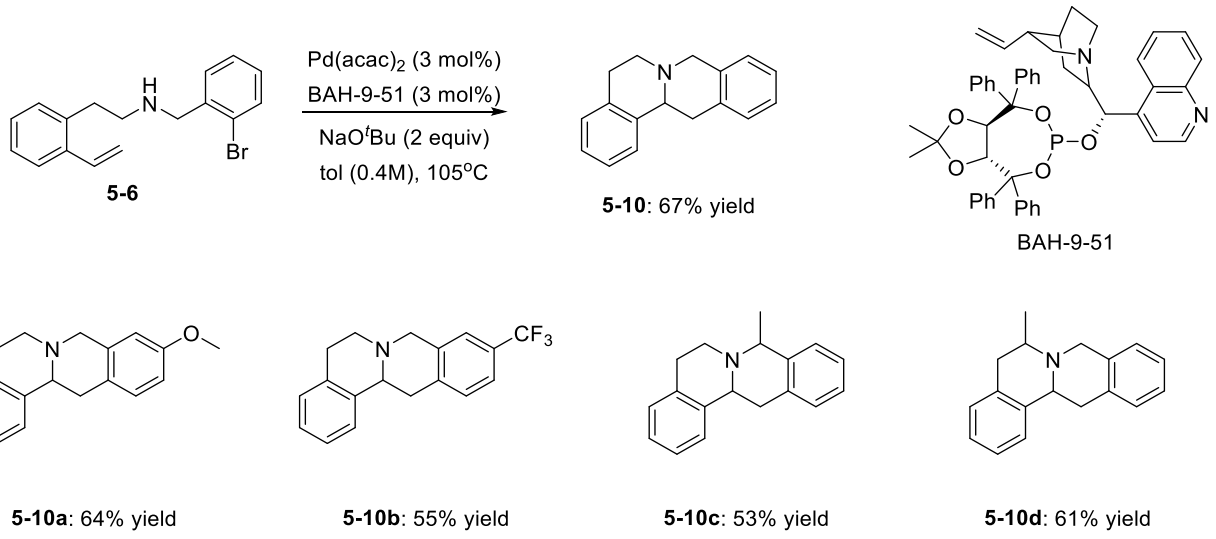
Scheme 5-10: Synthetic Sequence for 5-1a



5-19 **5-20** **5-1a**

Substrates **5-6a-d** showed preliminary reactivity in Pd/Xantphos catalyzed reactions, but in order to conserve material, were conducted on small scales and not isolated in complete purity until reaction parameter optimization was complete with **BAH-9-51**. In this system, all substrates afforded product in similar yields (Table 5-7, 53-67% yield, note: compounds were purified via acid/base wash so yields are slightly inflated due to the presence of small impurities). Despite using a chiral ligand, stereo-control was not assessed at this time, although it was noted that in product **5-10c** and **5-10d**, both diastereomers were observed and separable using the ethyl acetate: hexanes eluent. This snapshot indicated alignment with the overall project goals, and confirmed that the model substrate, was in general, a good representation for reactivity trends.

Table 5-7: Preliminary Substrate Scope



Once the exploration of the TADDOL cinchona phosphite ligands had been exhausted, the substrate scope was partially revisited to assess both yield and enantioselectivity of different substrates. The reaction conditions were scaled up to 0.2 mmol and tested across Xantphos, as a racemic standard, and four different TADDOL Cinchona phosphite ligands, **JH_4_114**, **JH_4_119**, **JH_4_146,** and **BAH-9-51)**. Each substrate was purified using MeOH/DCM flash chromatography,

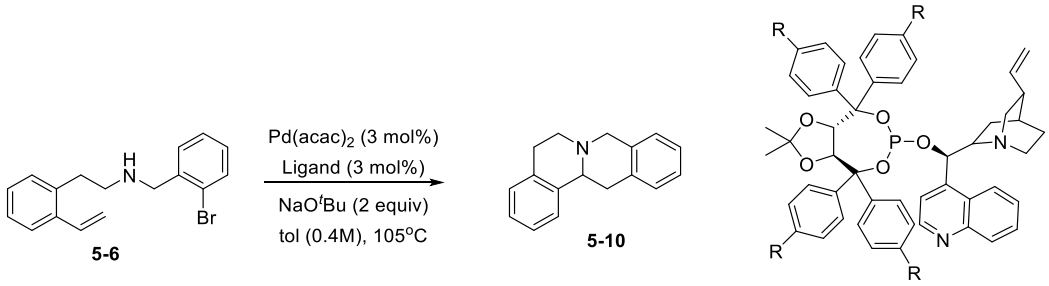
and diastereomers (where applicable) were separated using EtOAc/Hexanes flash chromatography. The enantiomers of all compounds tested were found to be separable on the HPLC using an AD-H column with a 99:1 Hexanes:iPrOH solvent mixture. However, the flow rate and time of each method was variable, depending on the compound, and most compounds suffered from tailing/broad peaks of at least one of the enantiomers that could not be remedied. Further HPLC method development is required to improve ee readings, and inclusion of an amine base additive in the HPLC solvent mixture may help with the tailing issue.

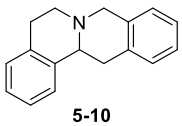
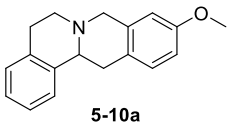
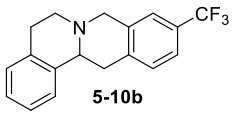
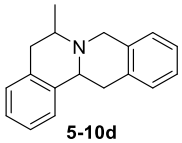
Despite having mostly full consumption of the starting material in all cases, the substrates tested gave higher yields with the TADDOL cinchona phosphite ligands than Xantphos by about 15% (Table 5-8). This discrepancy is most likely due to less of the starting material being converted to deleterious products such as the dehalogenated side product **5-12** when using the TADDOL cinchona phosphite ligands. This supports the conclusion that these ligands are favorable for product formation, in general.

The enantioselectivity of this reaction was universally moderate when employing the TADDOL cinchona phosphite ligands; ees varied from 60-75% (Table 5-8). No major difference was observed upon varying the para-substituent on the phenyl of the TADDOL. Some substrates had slight preferences, but no trend was observed that could be exploited to give better yields/ees systematically, and most likely these discrepancies were due to experimental error in reaction set-up, purification or analysis. As expected, when the pseudo enantiomer of the ligand, **BAH-9-51** in comparison to **JH_4_114**, was employed, the enantiomeric ratios inverted, resulting in negative ee values.

Diastereoselectivity was analyzed in the system that produced diastereomers, **5-10d** (Table 5-8). The ratio of diastereomers was 1:1 in the reactions that employed achiral ligands indicating that the methyl groups had no effect on the relative stereochemistry of the newly formed stereocenter, giving equal opportunity to form the cis and the trans products. As expected, the ratio of diastereomers was very close to 1:1 with a chiral TADDOL cinchona phosphite ligands. Small discrepancies (~1.5:1 dr rather than 1:1) were most likely due to either experimental error or preference of one enantiomer of starting material to react when the chiral ligand was employed, thereby also leading to the relative lower yield when compared to other substituted substrates. Despite the lack of selectivity, it is important to note the diastereomers can be separated from each other through flash column chromatography, so both diastereomers can be obtained in enantioenriched form from racemic starting materials.

Table 5-8: Revisited Substrate Scope



	XantPhos	R=H, **JH_4_114**	R=Me, **JH_4_119**	R=Ph, **JH_4_146**	**BAH-9-51**
 **5-10**	55% yield	68% yield, 61% ee	76% yield, ~75% ee	76% yield, 62% ee	64% yield, -68% ee
 **5-10a**	55% yield	66% yield, 63% ee	71% yield, 59% ee	70% yield, 60% ee	62% yield, -75% ee
 **5-10b**	68% yield	74% yield, 55% ee	71% yield, 41% ee	Coellution with ligand by-product prevents accurate yield assesment, 60% ee	68% yield, -67% ee
 **5-10d**	32% yield	47% yield, 74% ee 1.46:1 dr	48% yield, 65% ee 1.47:1 dr	45% yield, 72% ee 1.65:1 dr	52% yield, -77% ee 1.37:1 dr

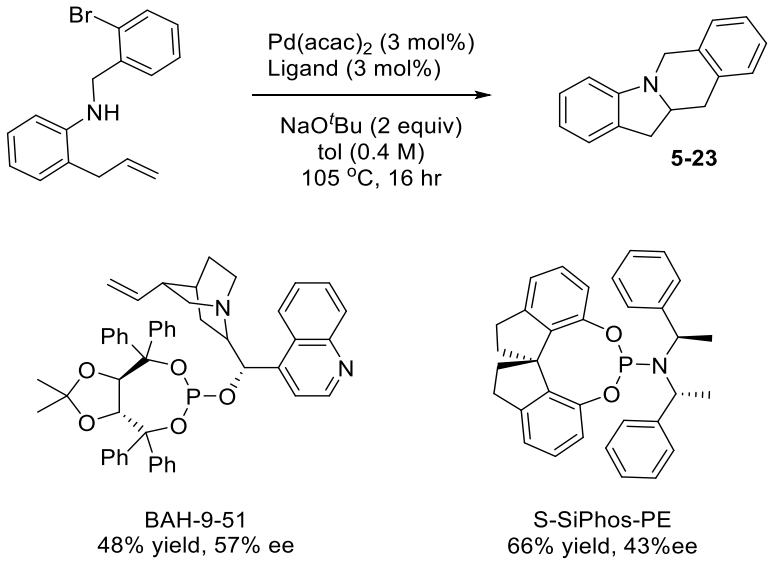
5.8 Future Directions and Conclusions

While considerable progress has been made in the development of the methodology outlined above, there is still work that must be done on this project. Further experimentation is needed to continue optimizing this reaction to produce higher yields and enantioselectivity, most likely through the exploration of different ligand classes. Additionally, the substrate scope will need to be further explored to include functionalization of the ring tethered to the alkene and, the efficacy of the method should be further demonstrated through application to the synthesis

of natural products. Additional preliminary studies have also indicated potential use of this methodology in new contexts and that could be elaborated on and further developed.

The TADDOL Cinchona Phosphite ligands have shown potential in other reaction systems. In unoptimized conditions, the ligands have been successfully applied to the synthesis of a tetrahydroindoloisoquinoline derivative, **5-23**. The racemic version of this reaction was developed by Jeremiah Alicea in 2014, in which the model substrate **5-23** was synthesized in up to 85% yield.[4] Initial screens were conducted with **BAH-9-51** and S-SiPhos PE, both giving considerable yield (48% and 66% respectively) and some enantioselectivity (57%ee and 43%ee respectively, Scheme 5-10). This data indicates the potential for further optimization to form a highly enantioselective version of the tetrahydroisoquinoline synthesis.

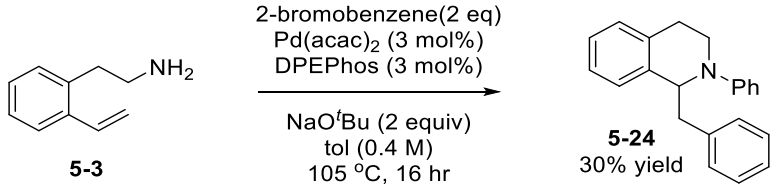
Scheme 5-11: Preliminary Result of Tetrahydroisoquinoline Derivatives



Finally, preliminary data has indicated that an intramolecular version of this reaction to form monocyclic tetrahydroisoquinoline derivatives may be possible. Initial experiments indicates that when **5-3** is subjected to the racemic reaction conditions developed above with 2 equiv of 2-bromo benzene, a tetrahydroisoquinoline derivative **5-24** can be formed through N-

arylation followed by an intramolecular carboamination (Scheme 5-11). This scaffold is an important substructure in a large family of natural products.[11] Future development is needed to optimize this reaction, as well as a version in which the starting material is either methylated or contains an N-protecting group that can be subsequently removed followed by N-methylation to generate the desired alkaloids.

Scheme 5-12:Preliminary Result of Intramolecular Tetrahydroisoquinoline Derivative



5.9 Overarching Conclusions

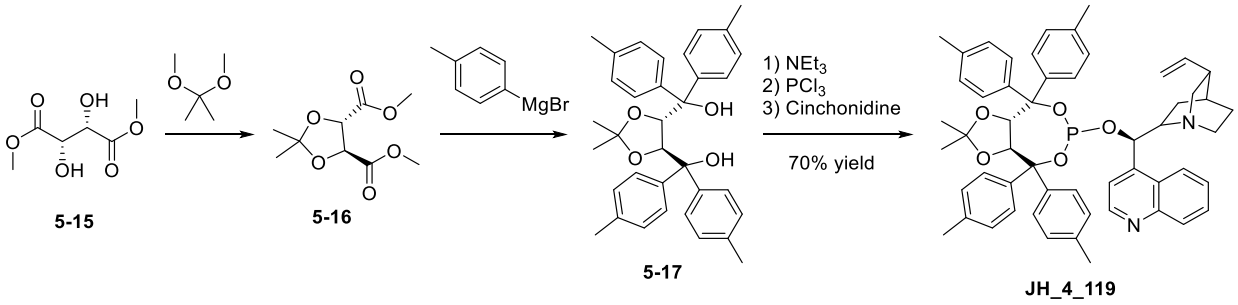
The work in this thesis demonstrates that palladium-catalyzed alkene difunctionalization is a powerful tool for synthesizing both carbocycles and heterocycles. We are able to access scaffolds for natural products and previously unexplored molecular motifs. Despite this success, a common theme throughout this thesis is the unexpected challenges that arise during methodology development. These challenges were best addressed through the systemic exploration of variable conditions and development of creative new solutions.

5.10 Experimental

General Considerations: All reactions were carried out under a nitrogen atmosphere in vacuum and flame-dried glassware. All reagents, palladium pre-catalysts, and ligands were purchased from commercial sources and were used without purification unless otherwise noted. Bulk quantities of cesium carbonate, lithium tert-butoxide, and lithium hexamethyldisilazide were stored in nitrogen-filled glove box and small amounts were removed within a few days of use,

then quickly weighed in the open atmosphere before being added to reaction vessels. Toluene, tetrahydrofuran (THF), dichloromethane (DCM), and diethyl ether were purified using a GlassContour solvent purification system. Structural and stereochemical assignments were made on the basis of 2-D COSY and nOe experiments. Ratios of diastereomers were determined by ^{1} H NMR analysis. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the supporting information describe the result of a single experiment, whereas yields reported in Eq 5-2 are average yields of two or more experiments. Thus, the yields reported in the supporting information may differ from those shown in Eq 5-2.

Preparation and Characterization of Cinchona TADDOL Phosphite ligands



General Procedure for Ligand Preparation Represented by JH_4_119

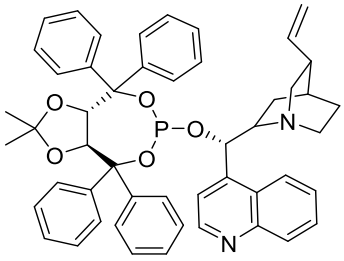
(1S,4S,5R)-2-((R)-(((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetra-p-tolyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (JH_4_119)

A round bottom flask, equipped with a stir bar, was flame dried under vacuum, then cooled under a stream of nitrogen and charged with dimethyl-D-tartrate (4.45 g, 25 mmol,1 eq) and p-TsOH (0.7115 g, 3.75 mmol, 0.15 eq). Toluene (0.5 M) and dimethoxy propane (6.15 mL, 50 mmol, 2 eq) were added. The septa cap was replaced with a reflux condenser and the reaction was heated to 90°C and stirred for 16h. The reaction was allowed to cool to rt and quenched with

water. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to yield a yellow-orange oil. The resulting crude was cleaned via flash chromatography on silica gel using 0-15% EtOAc: Hexanes to obtain the known compound **5-16** in 52% yield and used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.8 (s, 2H), 3.8 (s, 6H), 1.5 (s, 6H).

A round bottom, equipped with a stir bar, was flame dried under vacuum, then cooled under a stream of nitrogen and charged with freshly ground magnesium (0.334 g, 13.75 mmol, 5.5 eq) and a catalytic amount of iodine. THF (5 mL) was added and the reaction was cooled to 0°C. 4-Bromo-toluene (2.22 g, 13 mmol, 5.2 eq) was dissolved in 5 mL of THF and added dropwise. The reaction was allowed to warm to rt and stir until most of the magnesium dissolved. The reaction was cooled using an ice bath to prevent auto-reflux, once the temperature of the reaction elevated above rt. A second round bottom, equipped with a stir bar, was flame dried under vacuum, then cooled under a stream of nitrogen and charged with **5-16** (0.55 g, 2.5 mmol, 1 eq) and THF (6 mL). The solution was cooled to 0°C and the Grignard was added dropwise. The reaction was allowed to warm to rt and stir overnight. The reaction was cooled to 0°C and quenched carefully with water dropwise. The crude product was extracted from the aqueous layer with EtOAc (3 x 20 mL) and the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude product was then cleaned via flash chromatography on silica gel using 0-5% EtOAc: Hexanes to obtain the known compound **5-17** in 58% yield and used without further purification. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.4 (d, J = 7.90 Hz, 4H), 7.2 – 7.2 (m, 4H), 7.1 (d, J = 7.93 Hz, 4H), 7.0 (d, J = 7.98 Hz, 4H), 4.6 (s, 2H), 2.4 (s, 3H), 2.3 (s, 6H), 1.1 (s, 6H).

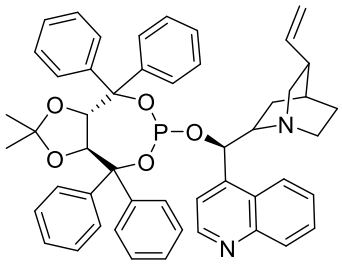
A 2-neck round bottom, equipped with a stir bar, was flame dried under vacuum, then cooled under a stream of nitrogen and charged with **5-17** (0.275 g, 0.5 mmol, 1 eq), DCM (5 mL), and recently distilled NEt_3 (0.28 mL, 2 mmol, 4 eq). The reaction was cooled to 0°C. PCl_3 (0.05 mL, 0.53 mmol, 1.05 eq) was added dropwise. The reaction was allowed to warm to rt and stir for 1 hr. Cinchonidine (0.155 g, 0. 53 mmol, 1.05 eq) was added directly through one of the necks of the flask while N_2 blew through the other. The reaction was allowed to stir at rt overnight. Additional DCM was added and the reaction was concentrated in vacuo. The crude product was then purified via flash chromatography on silica gel using 100% EtOAc to afford 0.297 g (70%) of the title compound as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.16 (d, J = 8.47 Hz, 1H), 7.99 (d, J = 8.40 Hz, 1H), 7.73 (t, J = 7.65 Hz, 1H), 7.53 (t, J = 7.71 Hz, 1H), 7.40 – 7.25 (m, 7H), 7.03 (t, J = 6.78 Hz, 4H), 6.99 – 6.77 (m, 6H), 5.72 (dd, J = 17.17, 8.90 Hz, 1H), 5.03 (d, J = 8.18 Hz, 1H), 4.93 (t, J = 13.32 Hz, 2H), 4.83 (s, 1H), 3.43 (s, 1H), 3.02 (dd, J = 30.63, 18.33 Hz, 2H), 2.62 (d, J = 14.28 Hz, 1H), 2.50 (s, 1H), 2.31 – 2.21 (m, 12H), 1.76 – 1.65 (m, 3H), 1.45 (s, 1H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 139.68.



JH_4_113

(1S,4S,5R)-2-((S)-(((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (JH_4_113)

The coupling of the TADDOL (derived from dimethyl-D-tartrate and phenyl Grignard) and cinchona alkaloid (cinchonine) was conducted according to General Procedure for ligands. This procedure afforded 39.8 mg (19%) of the title compound as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.86 (d, J = 4.51 Hz, 1H), 8.14 (d, J = 8.50 Hz, 1H), 7.71 (d, J = 7.99 Hz, 1H), 7.58 (d, J = 7.14 Hz, 2H), 7.53 (dd, J = 11.70, 7.50 Hz, 3H), 7.43 (d, J = 11.01 Hz, 1H), 7.39 (t, J = 7.58 Hz, 2H), 7.33 (dd, J = 15.42, 7.97 Hz, 1H), 7.31 – 7.14 (m, 8H), 6.98 (t, J = 7.46 Hz, 1H), 6.85 (d, J = 38.08 Hz, 2H), 6.49 (s, 2H), 6.03 (dt, J = 19.85, 8.98 Hz, 1H), 5.09 – 4.96 (m, 2H), 4.73 (d, J = 8.27 Hz, 1H), 2.80 (t, J = 11.76 Hz, 1H), 2.75 – 2.60 (m, 2H), 2.37 (s, 3H), 2.23 (t, J = 8.80 Hz, 1H), 1.78 (s, 1H), 1.51 (q, J = 9.80, 8.20 Hz, 3H), 1.27 (s, 1H), 1.04 (s, 3H), 0.29 (s, 3H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 137.99

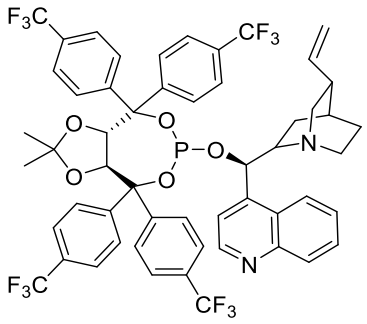


JH_4_114

(1S,4S,5R)-2-((R)-(((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (JH_4_114)

The coupling of the TADDOL (derived from dimethyl-D-tartrate and phenyl Grignard) and cinchona alkaloid (cinchonidine) was conducted according to General Procedure for ligands. This procedure afforded 40.3 mg (19%) of the title compound as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.81 (d, J = 4.58 Hz, 1H), 8.17 (d, J = 8.40 Hz, 1H), 8.03 (s, 1H), 7.74 (t, J = 7.62 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.53 – 7.42 (m, 4H), 7.39 (dd, J = 12.76, 7.31 Hz, 3H), 7.33 – 6.74 (m, 12H),

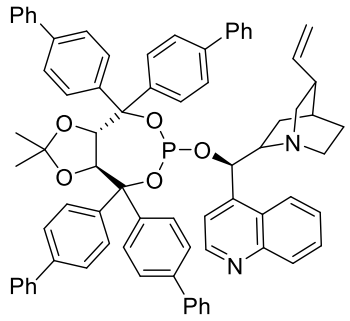
5.77 – 5.66 (m, 1H), 5.11 (d, J = 8.24 Hz, 1H), 5.03 – 4.87 (m, 4H), 3.06 (d, J = 31.85 Hz, 2H), 2.65 (s, 1H), 2.59 – 2.47 (m, 1H), 2.36 (s, 3H), 2.24 (d, J = 14.08 Hz, 1H), 1.85 (s, 1H), 1.72 (s, 2H), 1.48 (d, J = 12.09 Hz, 2H), 1.27 (s, 1H), 0.56 (s, 1H), 0.32 (s, 3H).^{31}P NMR (283 MHz, $CDCl_3$) δ 139.85



JH_4_123

(1S,4S,5R)-2-((R)-(((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetrakis(4-(trifluoromethyl)phenyl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (JH_4_123)

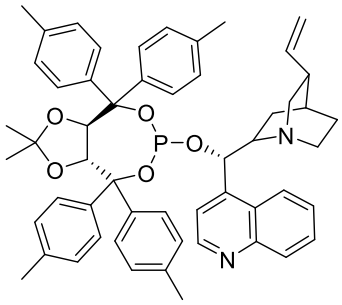
The coupling of the TADDOL (derived from dimethyl-D-tartrate and 4-trifluoro phenyl Grignard) and cinchona alkaloid (cinchonidine) was conducted according to General Procedure for ligands. This procedure afforded 52 mg (29%) of the title compound as a yellow solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.25 – 8.11 (m, 1H), 7.80 – 6.99 (m, 20H), 5.29 (s, 1H), 5.12 – 4.93 (m, 3H), 2.35 (s, 3H), 1.60 – 1.49 (m, 1H), 1.30 – 1.24 (m, 1H), 1.09 – 1.03 (m, 1H), 0.97 (s, 1H), 0.88 (td, J = 13.48, 12.05, 4.32 Hz, 1H), 0.83 – 0.76 (m, 2H), 0.70 (d, J = 6.18 Hz, 1H), 0.61 (d, J = 6.79 Hz, 1H), 0.46 (s, 3H), 0.29 (s, 1H), 0.08 (s, 1H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 150.31



JH_4_146

(1S,4S,5R)-2-((R)-quinolin-4-yl(((3aS,8aS)-4,4,8,8-tetra([1,1'-biphenyl]-4-yl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)methyl)-5-vinylquinuclidine (JH_4_146)

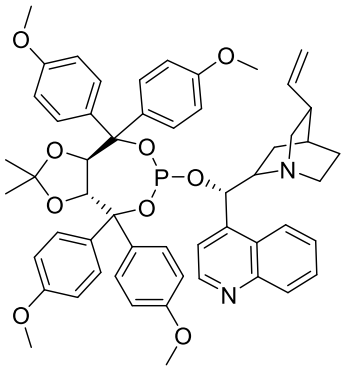
The coupling of the TADDOL (derived from dimethyl-D-tartrate and bi-phenyl Grignard) and cinchona alkaloid (cinchonidine) was conducted according to General Procedure for ligands. This procedure afforded 42.3 mg (26%) of the title compound as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.16 (d, J = 8.40 Hz, 1H), 8.06 (d, J = 8.45 Hz, 1H), 7.62 – 7.29 (m, 39H), 5.70 (dt, J = 17.50, 9.25 Hz, 1H), 5.20 (d, J = 8.25 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.92 (d, J = 17.12 Hz, 1H), 4.85 (d, J = 10.49 Hz, 1H), 3.13 (s, 1H), 3.02 (s, 1H), 2.67 (d, J = 14.28 Hz, 1H), 2.51 (s, 1H), 2.36 (s, 1H), 2.27 – 2.18 (m, 1H), 1.79 (d, J = 52.65 Hz, 2H), 1.49 (d, J = 11.28 Hz, 1H), 1.35 – 1.20 (m, 3H), 1.06 (s, 1H), 0.91 – 0.81 (m, 2H), 0.44 (s, 3H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 139.98



JH_4_126

(1S,4S,5R)-2-((S)-(((3aR,8aR)-2,2-dimethyl-4,4,8,8-tetra-p-tolyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (JH_4_126)

The coupling of the TADDOL (derived from dimethyl-L-tartrate and tolyl Grignard) and cinchona alkaloid (cinchonine) was conducted according to General Procedure for ligands. This procedure afforded 14.8 mg (6%) of the title compound as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.81 (d, J = 4.69 Hz, 1H), 8.15 (t, J = 8.76 Hz, 1H), 7.99 (s, 1H), 7.72 (t, J = 7.71 Hz, 1H), 7.52 (t, J = 7.86 Hz, 1H), 7.49 – 7.38 (m, 1H), 7.32 (td, J = 17.49, 15.77, 8.03 Hz, 4H), 7.26 – 6.90 (m, 9H), 6.77 (s, 1H), 6.70 (s, 1H), 6.04 (dd, J = 17.45, 9.21 Hz, 1H), 5.07 – 4.96 (m, 3H), 4.79 (d, J = 8.48 Hz, 1H), 3.03 (s, 1H), 2.88 (t, J = 11.79 Hz, 1H), 2.78 (d, J = 14.47 Hz, 1H), 2.70 (s, 1H), 2.62 (s, 1H), 2.40 (s, 1H), 2.36 (s, 2H), 2.32 – 2.13 (m, 12H), 1.77 (s, 1H), 1.52 – 1.39 (m, 3H), 1.26 (s, 3H), 1.08 (s, 3H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 140.08

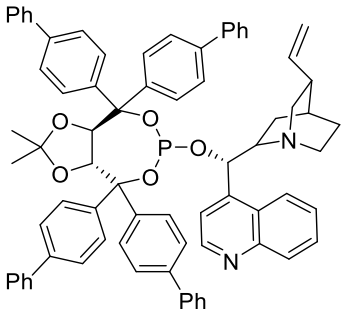


JH_4_132

(1S,4S,5R)-2-((R)-quinolin-4-yl(((3aS,8aS)-4,4,8,8-tetrakis(4-methoxyphenyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)methyl)-5-vinylquinuclidine (JH_4_132)

The coupling of the TADDOL (derived from dimethyl-L-tartrate and 4-methoxy phenyl Grignard) and cinchona alkaloid (cinchonine) was conducted according to General Procedure for ligands.

This procedure afforded 41.6 mg (17%) of the title compound as a yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.86 – 8.80 (m, 1H), 8.15 (dd, J = 13.58, 8.47 Hz, 1H), 7.72 (t, J = 7.42 Hz, 1H), 7.55 (t, J = 7.18 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.35 (dd, J = 25.88, 8.39 Hz, 4H), 7.27 – 7.24 (m, 2H), 7.16 (dd, J = 16.18, 7.70 Hz, 2H), 7.07 (dd, J = 26.17, 9.51 Hz, 1H), 6.83 (s, 2H), 6.76 (dq, J = 9.30, 5.90, 3.52 Hz, 4H), 6.69 (q, J = 7.95 Hz, 2H), 6.43 (s, 2H), 6.06 (dt, J = 18.23, 9.06 Hz, 1H), 5.09 – 4.97 (m, 2H), 3.88 – 3.66 (m, 12H), 3.05 (s, 1H), 2.91 (s, 1H), 2.82 (t, J = 11.84 Hz, 1H), 2.73 (s, 1H), 2.64 (s, 1H), 2.36 (s, 3H), 2.24 (dd, J = 19.36, 10.40 Hz, 1H), 1.78 (s, 1H), 1.44 (dd, J = 21.84, 11.41 Hz, 1H), 1.28 (d, J = 18.15 Hz, 1H), 1.09 (s, 2H), 0.68 (s, 1H), 0.36 (s, 3H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 140.38

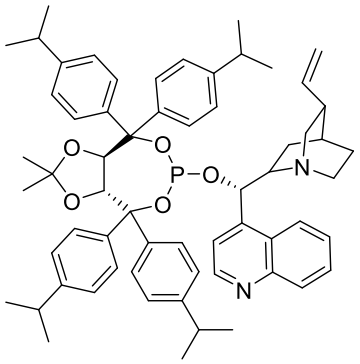


JH_4_151

(1S,4S,5R)-2-((S)-quinolin-4-yl(((3aR,8aR)-4,4,8,8-tetra([1,1'-biphenyl]-4-yl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)methyl)-5-vinylquinuclidine (JH_4_151)

The coupling of the TADDOL (derived from dimethyl-L-tartrate and bi-phenyl Grignard) and cinchona alkaloid (cinchonine) was conducted according to General Procedure for ligands. This procedure afforded 38.4 mg (13.5%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J = 4.58 Hz, 1H), 8.11 (d, J = 8.92 Hz, 2H), 7.68 – 7.28 (m, 35H), 7.20 (s, 2H), 7.07 (s, 2H), 6.09 (dd, J = 17.32, 8.83 Hz, 1H), 5.20 (d, J = 8.11 Hz, 1H), 5.08 (dd, J = 28.90, 13.84 Hz, 2H), 4.95 (s, 1H), 3.12 (s, 1H), 2.99 (s, 1H), 2.86 (s, 2H), 2.76 (s, 1H), 2.36 – 2.18 (m, 2H), 1.94 (s,

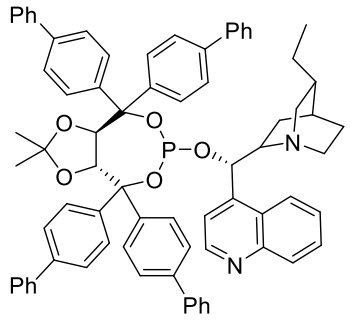
1H), 1.50 – 1.39 (m, 3H), 1.37 – 1.28 (m, 3H), 1.18 (s, 3H), 1.01 – 0.82 (m, 5H), 0.40 (s, 3H).^{31}P NMR (202 MHz,$CDCl_3$) δ 140.87,



JH_4_176

(1S,4S,5R)-2-((S)-quinolin-4-yl(((3aR,8aR)-4,4,8,8-tetrakis(4-isopropylphenyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)methyl)-5-vinylquinuclidine (JH_4_176)

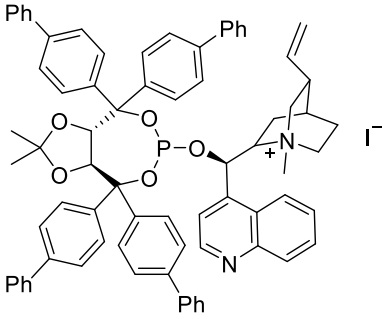
The coupling of the TADDOL (derived from dimethyl-L-tartrate and 4-isopropyl phenyl Grignard) and cinchona alkaloid (cinchonine) was conducted according to General Procedure for ligands. This procedure afforded 90.4 mg (36%) of the title compound as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.83 (d, J = 4.60 Hz, 1H), 8.17 (d, J = 8.43 Hz, 1H), 8.06 (d, J = 8.53 Hz, 1H), 7.73 (t, J = 7.63 Hz, 1H), 7.57 (t, J = 7.68 Hz, 1H), 7.40 (d, J = 7.95 Hz, 2H), 7.34 (d, J = 7.82 Hz, 2H), 7.08 (t, J = 7.86 Hz, 5H), 6.99 (d, J = 7.83 Hz, 2H), 6.90 (d, J = 16.54 Hz, 5H), 6.07 (dt, J = 17.74, 8.93 Hz, 1H), 5.10 (d, J = 8.34 Hz, 1H), 5.05 (d, J = 17.07 Hz, 1H), 4.98 (d, J = 10.27 Hz, 1H), 4.78 (d, J = 8.30 Hz, 1H), 3.11 – 2.97 (m, 1H), 2.97 – 2.63 (m, 6H), 2.23 (q, J = 8.45 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.78 (s, 1H), 1.54 – 1.41 (m, 2H), 1.28 – 1.12 (m, 27H), 1.03 (s, 3H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 140.94



JH_4_152

(1S,4S,5R)-5-ethyl-2-((S)-quinolin-4-yl(((3aR,8aR)-4,4,8,8-tetra([1,1'-biphenyl]-4-yl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)methyl)quinuclidine (JH_4_152)

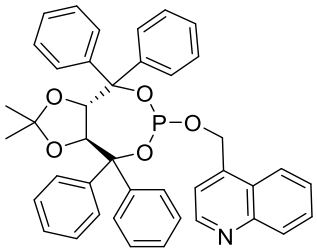
The coupling of the TADDOL (derived from dimethyl-L-tartrate and bi-phenyl Grignard) and cinchona alkaloid (reduced cinchonine BAH-7-136) was conducted according to General Procedure for ligands. This procedure afforded 38.4 mg (13.5%) of the title compound as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.90 (d, J = 4.49 Hz, 1H), 8.16 (q, J = 15.84, 12.23 Hz, 2H), 7.73 – 7.08 (m, 39H), 5.23 (d, J = 8.23 Hz, 1H), 4.97 (s, 1H), 3.03 (d, J = 94.35 Hz, 2H), 2.75 (d, J = 46.53 Hz, 2H), 2.23 – 2.01 (m, 1H), 1.61 – 1.36 (m, 6H), 1.18 (s, 3H), 0.90 (dt, J = 14.97, 7.42 Hz, 3H), 0.43 (s, 3H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 140.69



JH_4_193

(1S,4S,5R)-1-methyl-2-((R)-quinolin-4-yl(((3aS,8aS)-4,4,8,8-tetra([1,1'-biphenyl]-4-yl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)methyl)-5-vinylquinuclidin-1-ium iodide (JH_4_193)

A 4 mL vial equipped with a stir bar, was flame dried under vacuum, then cooled under a stream of nitrogen and charged with JH_4_155 (0.026 g, 0.024 mmol, 1 eq) and MeOH (0.2mL). Methyl iodide (0.00148 mL, 0.024 mmol, 1 eq) was added dropwise. The reaction stirred at room temperature overnight. The mixture was concentrated in vacuo to give a yellow solid in full conversion and was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, J = 4.52 Hz, 1H), 8.29 (d, J = 8.49 Hz, 1H), 8.14 (d, J = 8.45 Hz, 1H), 8.05 (t, J = 7.76 Hz, 1H), 7.76 (t, J = 7.65 Hz, 1H), 7.71 – 7.23 (m, 41H), 7.14 (d, J = 8.04 Hz, 2H), 7.06 (d, J = 7.56 Hz, 1H), 6.85 (d, J = 8.01 Hz, 2H), 5.46 (ddd, J = 17.27, 10.81, 6.64 Hz, 1H), 5.33 – 5.25 (m, 1H), 5.19 (d, J = 17.17 Hz, 1H), 4.94 (d, J = 8.37 Hz, 1H), 4.82 (d, J = 10.44 Hz, 1H), 4.21 (d, J = 11.76 Hz, 1H), 4.09 (t, J = 8.23 Hz, 2H), 3.96 (s, 3H), 3.00 – 2.88 (m, 1H), 2.20 – 1.95 (m, 4H), 1.24 (s, 3H), 0.35 (s, 3H). ^{31}P NMR (202 MHz, $CDCl_3$) δ 144.11.

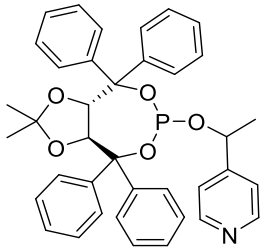


JH_4_195

4-((((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)methyl)quinoline (JH_4_195)

The coupling of the TADDOL (derived from dimethyl-D-tartrate and phenyl Grignard) and 4-hydroxy methyl quinoline was conducted according to General Procedure for ligands. This

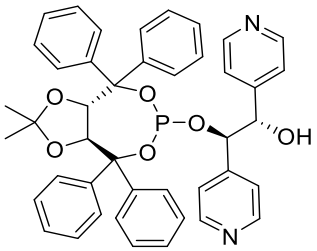
procedure afforded 31.3 mg (18%) of the title compound as a white solid**.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 4.43 Hz, 1H), 8.15 – 8.09 (m, 1H), 7.71 (ddd, J = 8.38, 6.72, 1.44 Hz, 1H), 7.62 – 7.14 (m, 18H), 6.93 (d, J = 4.41 Hz, 1H), 5.52 (d, J = 8.26 Hz, 1H), 5.06 – 5.02 (m, 1H), 0.79 (s, 3H), 0.68 (s, 3H). ^{31}P NMR (202 MHz, $CDCl_3$) δ 129.14



JH_4_196

4-(1-(((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)ethyl)pyridine (JH_4_196)

The coupling of the TADDOL (derived from dimethyl-D-tartrate and phenyl Grignard) and 4-hydroxy ethyl pyridine was conducted according to General Procedure for ligands. This procedure afforded 37.9 mg (23%) of the title compound as a mixture of diastereomers as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.47 (dd, J = 12.68, 5.12 Hz, 2H), 7.54 (d, J = 7.75 Hz, 1H), 7.49 (d, J = 7.71 Hz, 3H), 7.44 (s, 1H), 7.43 – 7.30 (m, 6H), 7.23 (dddd, J = 43.97, 23.43, 11.98, 4.63 Hz, 12H), 7.00 (d, J = 5.04 Hz, 1H), 6.88 (d, J = 4.99 Hz, 1H), 5.36 (dt, J = 13.27, 6.49 Hz, 1H), 5.29 (dd, J = 26.42, 8.28 Hz, 1H), 5.16 – 5.09 (m, 1H), 4.99 (dd, J = 33.14, 8.26 Hz, 1H), 1.40 (d, J = 6.53 Hz, 1H), 0.84 (s, 2H), 0.73 (d, J = 15.49 Hz, 3H), 0.61 (s, 1H). ^{31}P NMR (283 MHz, cdcl3) δ 132.83, 130.81

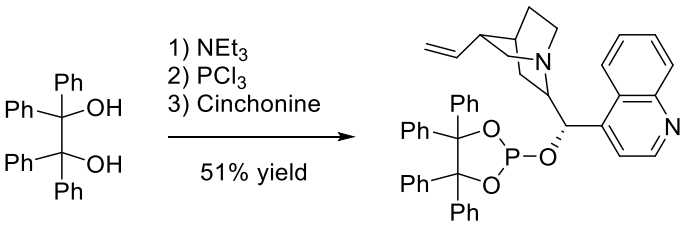


JH_5_009

(1S,2R)-2-(((3aS,8aS)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)-1,2-di(pyridin-4-yl)ethan-1-ol (JH_5_009)

The coupling of the TADDOL (derived from dimethyl-D-tartrate and phenyl Grignard) and trans-1,2- dipyridine-4-yl ethan-1,2-diol was conducted according to General Procedure for ligands. This procedure afforded 41.8 mg (22%) of the title compound as an orange solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.62 – 8.55 (m, 2H), 8.51 (d, J = 5.05 Hz, 2H), 7.55 (d, J = 5.05 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.43 (dd, J = 6.99, 3.16 Hz, 2H), 7.36 (d, J = 7.61 Hz, 2H), 7.34 – 7.28 (m, 6H), 7.22 (dd, J = 12.09, 5.50 Hz, 7H), 7.16 (q, J = 8.39 Hz, 3H), 7.05 (d, J = 7.22 Hz, 2H), 6.41 (s, 1H), 5.08 (d, J = 8.27 Hz, 1H), 4.95 (d, J = 8.33 Hz, 1H), 2.04 (s, 2H), 1.07 (s, 3H), 0.31 (s, 3H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 145.29

Preparation and Characterization of Cinchona Diol Phosphite ligands

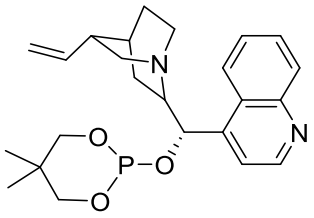


JH_5_041

General Procedure for Ligand Preparation Represented by JH_5_041

2-((S)-quinolin-4-yl((4,4,5,5-tetraphenyl-1,3,2-dioxaphospholan-2-yl)oxy)methyl)-5-vinylquinuclidine (JH_5_041)

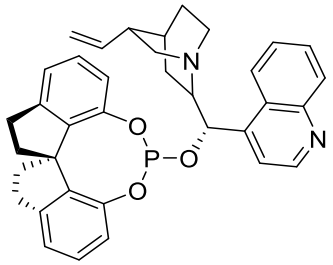
A 2-neck round bottom, equipped with a stir bar, was flame dried under vacuum, then cooled under a stream of nitrogen and charged with the diol, benzopinacol, (0.366 g, 1 mmol, 1 eq), THF (10 mL), and recently distilled NEt_3 (0.56 mL, 4 mmol, 4 eq). The reaction was cooled to 0°C. PCl_3 (0.1 mL, 1.05 mmol, 1.05 eq) was added dropwise. The reaction was allowed to warm to rt and stir for 1 hr. Cinchonidine (0.309 g, 1.05 mmol, 1.05 eq) was added directly through one of the necks of the flask while N_2 blew through the other. The reaction was allowed to stir at rt overnight. DCM was added and the reaction was concentrated in vacuo. The crude product was then purified via flash chromatography on silica gel using 15% to 100% EtOAc in Hexanes to 100% Acetone to afford 0.349 g (51%) of the title compound as an off-white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.45 (d, J = 4.53 Hz, 1H), 8.06 (d, J = 8.39 Hz, 1H), 7.98 (d, J = 8.45 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.66 – 7.60 (m, 1H), 7.53 (q, J = 7.72 Hz, 1H), 7.49 (d, J = 7.91 Hz, 2H), 7.33 (t, J = 7.30 Hz, 1H), 7.30 – 7.22 (m, 5H), 7.12 – 7.04 (m, 3H), 7.04 – 6.95 (m, 3H), 6.94 – 6.89 (m, 3H), 6.24 – 6.17 (m, 1H), 6.01 (ddd, J = 17.40, 10.32, 7.27 Hz, 1H), 5.85 (s, 1H), 5.10 (dt, J = 17.20, 1.55 Hz, 1H), 4.94 (d, J = 10.28 Hz, 1H), 3.38 (dd, J = 13.86, 8.24 Hz, 1H), 3.09 (dd, J = 13.77, 9.86 Hz, 1H), 2.95 – 2.85 (m, 2H), 2.76 (dt, J = 13.27, 8.88 Hz, 1H), 2.25 (q, J = 8.61 Hz, 1H), 2.12 (d, J = 16.10 Hz, 1H), 1.72 – 1.62 (m, 2H), 1.49 – 1.42 (m, 1H), 1.39 – 1.29 (m, 1H). ^{31}P NMR (283 MHz, $CDCl_3$) δ 150.94.



JH_5_048

((S)-((5,5-dimethyl-1,3,2-dioxaphosphinan-2-yl)oxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (JH_5_048)

The coupling of 2,2 dimethyl propanediol and cinchona alkaloid (cinchonine) was conducted according to General Procedure for ligands on a 1 mmol scale. This procedure afforded 85 mg (20%) of the title compound as an off white oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, J = 4.46 Hz, 1H), 8.21 (d, J = 8.96 Hz, 1H), 8.13 – 8.05 (m, 1H), 7.70 – 7.62 (m, 1H), 7.54 (dt, J = 8.64, 6.80 Hz, 1H), 7.43 (d, J = 4.45 Hz, 1H), 5.98 (ddd, J = 20.66, 9.88, 7.28 Hz, 1H), 5.12 – 5.01 (m, 2H), 4.15 (dd, J = 10.61, 3.03 Hz, 1H), 3.51 (s, 1H), 3.39 – 3.17 (m, 3H), 2.98 (q, J = 11.16, 9.90 Hz, 2H), 2.86 (dd, J = 13.91, 9.77 Hz, 1H), 2.78 – 2.60 (m, 2H), 2.23 (q, J = 8.49 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.80 (s, 1H), 1.58 – 1.38 (m, 3H), 1.12 (d, J = 3.71 Hz, 3H), 0.56 (d, J = 10.27 Hz, 3H). ^{31}P NMR (202 MHz, $CDCl_3$) δ 121.83.



JH_5_043

2-((S)-quinolin-4-yl((4,5,6,7-tetrahydrodiindeno[7,1-de:1',7'-fg][1,3,2]dioxaphosphocin-12-yl)oxy)methyl)-5-vinylquinuclidine (JH_5_043)

The coupling of R-SPINOL and cinchona alkaloid (cinchonine) was conducted according to General Procedure for ligands on a 0.4 mmol scale. This procedure afforded 79 mg (34%) of the title compound as an off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.96 (d, J = 4.49 Hz, 1H), 8.17 (d, J = 8.39 Hz, 1H), 8.10 (d, J = 8.51 Hz, 1H), 7.72 (t, J = 7.58 Hz, 1H), 7.57 (t, J = 7.70 Hz, 1H), 7.51 (s, 1H), 7.16 (t, J = 7.66 Hz, 1H), 7.02 (dd, J = 13.99, 7.59 Hz, 3H), 6.88 (d, J = 8.00 Hz, 1H),

6.23 (s, 1H), 5.64 (s, 1H), 4.97 (dd, J = 18.65, 13.63 Hz, 2H), 3.23 (s, 1H), 3.04 (ddt, J = 16.10, 10.99, 5.45 Hz, 3H), 2.96 (s, 1H), 2.80 (tq, J = 15.74, 7.74 Hz, 4H), 2.63 (d, J = 34.16 Hz, 2H), 2.26 – 2.11 (m, 4H), 2.00 – 1.86 (m, 2H), 1.85 – 1.77 (m, 1H), 1.51 – 1.40 (m, 2H).^{31}P NMR (243 MHz, $CDCl_3$) δ 128.87.

Preparation and Characterization of Starting Materials

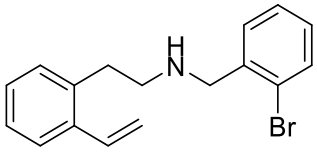
General Procedure for Starting Materials:

A round bottom flask, equipped with a stir bar, was flame dried under vacuum, then cooled under a stream of nitrogen and charged with palladium chloride (2 mol%), RuPhos (6 mol%), potassium carbonate (3 eq), and potassium vinyltrifluoroborate (20 mmol, 2.68 g, 2 eq). Ethylene glycol (0.4 M) and water (2M) were added. The appropriate 2-bromo phenethylamine derivative (1 eq) was added with stirring. The septa cap was replaced with a reflux condenser and the reaction was heated to 90°C and stirred for 16h. The reaction was allowed to cool to rt and quenched with water. The aqueous layer was extracted with Et_2O (3x). HCl (2M) was added to the combined organic layers, and the resulting aqueous layer was collected. NaOH (3 M) was added until the aqueous layer was sufficiently basic (~ pH 14) and crude was extracted with Et_2O (3x). The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to yield a yellow-orange oil. The resulting crude was used without additional purification. *(Note: if less than 90% conversion was achieved, the remaining 2- bromo phenylamine derivative was converted to 1-benzylindoline using established procedures[3] and the desired product isolated through silica flash chromatography (short column, 60% MeOH:DCM)*)

A flask equipped with a stir bar was flame dried under vacuum and cooled under a stream of nitrogen. The crude vinyl amine (1.25 eq), appropriate 2- bromo benzaldehyde (1eq) and

toluene (0.5M) were charged to the flask. The round bottom was equipped with a dean-stark condenser and refluxed until the expected amount of water was collected in the dean-stark trap (~2 h to ~16 h). The flask was cooled to room temperature. The solution was filtered, rinsed with EtOAc and the resulting organic layers concentrated in vacuo and the crude imine (yellow oil) was moved directly into the next step without further purification.

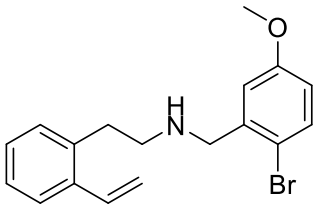
A flask equipped with a stir bar was flame dried under vacuum and cooled under a stream of nitrogen. The crude imine (1 eq) and Et_2O (0.5 M) were charged to the flask and cooled to 0°C. Lithium aluminum hydride (2eq of 1M solution in Et_2O) was added dropwise. The reaction was allowed to warm to rt and stir 16h. The reaction was cooled to 0°C and quenched carefully with water dropwise. NaOH was added dropwise, followed by additional water. The crude product was extracted from the aqueous layer with Et_2O (3x) and the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude product was then purified via flash chromatography on silica gel using 5-90% EtOAc: Hexanes.



N-(2-bromobenzyl)-2-(2-vinylphenyl)ethan-1-amine (5-6)

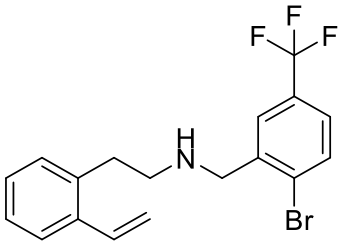
The coupling of 2-bromo phenethylamine (1.43 mL, 10 mmol) and 2-bromobenzaldehyde (0.93 mL, 8 mmol) was conducted according to General Procedure for Starting Materials. This procedure afforded 1.90 g (60%) of the title compound as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.34 (dd, J = 7.62, 1.72 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.23 – 7.15 (m, 3H), 7.11 (td, J = 7.63, 1.73 Hz, 1H), 7.00 (dd, J = 17.32, 10.94 Hz, 1H), 5.63 (dd, J = 17.35, 1.39 Hz, 1H), 5.29 (dd, J = 11.00, 1.39 Hz, 1H), 3.88 (s, 2H), 2.95 – 2.89 (m, 2H), 2.85 (dd, J = 7.87, 6.48 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 139.2, 137.2, 136.8, 134.5, 132.7, 130.1, 129.9, 128.5, 127.8, 127.4, 126.6, 125.9, 123.9, 115.7, 53.6, 49.8, 33.8. IR (film) 2936, 2831,1441, 1024 cm^{-1}.



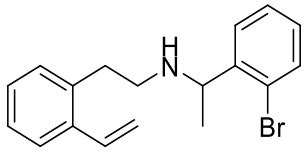
N-(2-bromo-5-methoxybenzyl)-2-(2-vinylphenyl)ethan-1-amine (5-6a)

The coupling of 2-bromo phenethylamine (1.43 mL, 10 mmol) and 5- methoxy 2-bromobenzaldehyde (1.72 mL, 8 mmol) was conducted according to General Procedure for Starting Materials. This procedure afforded 1.81 g (52%) of the title compound as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 1H), 7.40 (d, J = 8.72 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.20 – 7.15 (m, 1H), 7.01 (dd, J = 17.33, 10.97 Hz, 1H), 6.94 (d, J = 3.05 Hz, 1H), 6.67 (dd, J = 8.69, 3.07 Hz, 1H), 5.64 (dd, J = 17.32, 1.42 Hz, 1H), 5.29 (dd, J = 10.90, 1.43 Hz, 1H), 3.83 (s, 2H), 3.77 (s, 3H), 2.95 – 2.89 (m, 2H), 2.89 – 2.82 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.0, 140.2, 137.2, 136.8, 134.5, 133.2, 129.9, 127.8, 126.6, 125.9, 115.7, 115.5, 114.2, 114.1, 55.4, 53.7, 49.9, 33.8. IR (film) 2935, 2833,1465, 1295 cm^{-1}. HRMS (EI+TOF) m/z:345.0728 Calcd for $C_{18}H_2OBrN$. Found 345.0574.



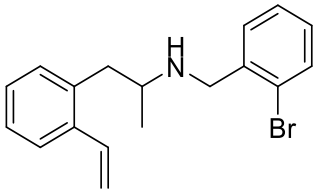
N-(2-bromo-5-(trifluoromethyl)benzyl)-2-(2-vinylphenyl)ethan-1-amine (5-6b)

The coupling of 2-bromo phenethylamine (0.34 mL, 2.4 mmol) and 2- bromo 5- trifluoromethyl benzaldehyde (0.29 mL, 1.9 mmol) was conducted according to General Procedure for Starting Materials. This procedure afforded 0.42 g (44%) of the title compound as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.64 (d, J = 8.26 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.36 (dd, J = 8.40, 2.22 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.21 – 7.16 (m, 1H), 7.01 (dd, J = 17.34, 10.97 Hz, 1H), 5.64 (dd, J = 17.32, 1.78 Hz, 1H), 5.30 (dd, J = 10.92, 1.79 Hz, 1H), 3.90 (s, 2H), 2.97 – 2.92 (m, 2H), 2.91 – 2.85 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.5, 137.0, 136.8, 134.4, 133.1, 129.9, 127.8, 127.5, 126.7, 126.4, 126.4, 126.0, 125.0, 125.0, 115.8, 53.1, 49.9, 33.7. IR (film) 2826, 1327,1168, 1126 cm^{-1}. ^{19}F NMR (564 MHz, $CDCl_3$) δ -62.63.



1-(2-bromophenyl)-N-(2-vinylphenethyl)ethan-1-amine (5-6c)

The coupling of 2-bromo phenethylamine (0.86 mL, 6 mmol) and 2'- bromo acetophenone (0.67 mL, 5 mmol) was conducted according to General Procedure for Starting Materials. This procedure afforded 0.66 g (33%) of the title compound as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 1H), 7.46 (dd, J = 6.13, 3.02 Hz, 1H), 7.39 (dd, J = 7.74, 1.77 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.22 – 7.15 (m, 2H), 7.15 – 7.11 (m, 1H), 7.07 (td, J = 7.63, 1.70 Hz, 1H), 6.92 (dd, J = 17.31, 10.94 Hz, 1H), 5.59 (dt, J = 17.47, 1.49 Hz, 1H), 5.27 – 5.21 (m, 1H), 4.27 (qd, J = 6.59, 2.07 Hz, 1H), 2.92 – 2.78 (m, 2H), 2.75 – 2.68 (m, 1H), 2.68 – 2.59 (m, 1H), 1.30 (dd, J = 6.75, 1.77 Hz, 3H). IR (film) 3061, 2970,1439, 1022 cm^{-1}.



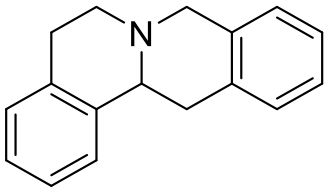
N-(2-bromobenzyl)-1-(2-vinylphenyl)propan-2-amine (5-6d)

The coupling of 1-(2-bromophenyl)propan-2-amine (1.71 g, 8 mmol) and 2- bromo benzaldehyde (0.78 mL, 7 mmol) was conducted according to General Procedure for Starting Materials. This procedure afforded 0.19 g (9%) of the title compound as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.40 – 7.34 (m, 1H), 7.27 – 7.14 (m, 4H), 7.14 – 7.11 (m, 1H), 7.08 (td, J = 7.49, 2.06 Hz, 1H), 6.96 (dd, J = 17.33, 10.92 Hz, 1H), 5.58 (dd, J = 17.30, 1.46 Hz, 1H), 5.23 (dd, J = 10.90, 1.41 Hz, 1H), 3.88 (d, J = 13.88 Hz, 1H), 3.79 (d, J = 13.91 Hz, 1H), 2.94 – 2.84 (m, 2H), 2.74 – 2.67 (m, 1H), 1.15 – 1.08 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.3, 137.1, 136.8, 134.7, 132.7, 130.7, 130.2, 128.5, 127.7, 127.3, 126.7, 125.9, 123.9, 115.5, 53.0, 51.3, 41.1, 20.3. IR (film) 2963, 2926,1440, 1025 cm^{-1}.

General Procedure for Intramolecular Pd-catalyzed Alkene Carboamination reactions:

A 4 mL vial was equipped with a stirbar, flame dried and cooled under a flow of nitrogen. The vial was charged with $Pd(acac)_2$ (0.9 mg, 0.003 mmol, 3 mol%), ligand (0.003 mmol, 3 mol%), and NaO^tBu (19.2 mg, 0.02 mmol, 2 equiv). Toluene (0.1mL) was added and the vial was stirred at room temperature for 10 minutes. The substrate was transferred into the vial in a solution of toluene (0.15 mL, total 0.4M). The vial was capped with a rubber-lined screw cap, then placed in a heating block and stirred at 105°C for 20 h. The reaction was cooled to room temperature,

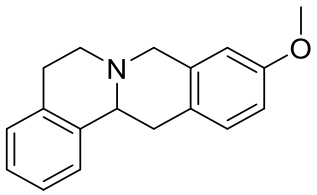
filtered with DCM and concentrated in vacuo. The reaction was purified in a short column of 0 to 2% MeOH in DCM.



5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline (5-10)

The cyclization of **5-6** was conducted according to General Procedure Intramolecular Pd-catalyzed Alkene Carboamination reactions on a 0.1 mmol scale using BAH-9-51 as a ligand to afford 15.9 mg (67%) of the title compound as an orange oil. The compound is known and previously reported.[9] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, J = 7.70 Hz, 1H), 7.26 – 7.13 (m, 6H), 7.12 – 7.07 (m, 1H), 4.05 (d, J = 14.88 Hz, 1H), 3.74 (ddd, J = 26.79, 13.13, 2.88 Hz, 2H), 3.40 (dd, J = 16.20, 3.97 Hz, 1H), 3.28 – 3.16 (m, 2H), 2.95 (ddd, J = 16.30, 11.38, 1.82 Hz, 1H), 2.79 (dt, J = 15.22, 2.13 Hz, 1H), 2.66 (td, J = 11.47, 10.98, 3.52 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.9, 134.5, 134.5, 134.4, 128.9, 128.8, 126.3, 126.1, 126.1, 126.0, 125.8, 125.5, 59.9, 58.6, 51.2, 36.7, 29.5.

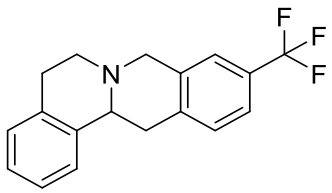
e.e. determined by HPLC analysis Daicel AD-H column: 99:1 Hexanes:iPrOH, flow rate 1.23 mL/min, rt, λ=210 nm, minor= 5.22 min, major= 11.53 min



10-methoxy-5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline (5-10a)

The cyclization of **5-6a** was conducted according to General Procedure Intramolecular Pd-catalyzed Alkene Carboamination reactions on a 0.2 mmol scale using BAH-9-51 as a ligand to afford 32.6 mg (61%) of the title compound as an orange oil. ^{1}H NMR (700 MHz,$CDCl_3$) δ 7.29 (d, J = 7.71 Hz, 1H), 7.22 (t, J = 7.44 Hz, 1H), 7.18 (t, J = 7.30 Hz, 1H), 7.15 (d, J = 7.49 Hz, 1H), 7.09 (d, J = 8.36 Hz, 1H), 6.76 (dd, J = 8.46, 2.63 Hz, 1H), 6.63 (d, J = 2.63 Hz, 1H), 4.01 (d, J = 14.89 Hz, 1H), 3.79 (s, 3H), 3.74 (d, J = 14.88 Hz, 1H), 3.69 (dd, J = 11.47, 3.96 Hz, 1H), 3.33 (dd, J = 15.85, 4.03 Hz, 1H), 3.26 – 3.19 (m, 1H), 3.21 – 3.15 (m, 1H), 2.86 (dd, J = 15.78, 11.37 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.65 (td, J = 11.18, 3.49 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 157.8, 138.0, 135.4, 134.5, 129.7, 128.8, 126.6, 126.1, 126.0, 125.5, 112.6, 110.9, 60.1, 58.8, 55.3, 51.1, 35.8, 29.5.

e.e. determined by HPLC analysis Daicel AD-H column: 99:1 Hexanes:iPrOH, flow rate 1.23 mL/min, rt, λ=210 nm, minor= 11.55 min, major= 29.75 min

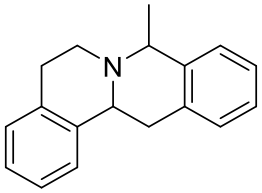


10-(trifluoromethyl)-5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline (5-10b)

The cyclization of **5-6b** was conducted according to General Procedure Intramolecular Pd-catalyzed Alkene Carboamination reactions on a 0.2 mmol using BAH-9-51 as a ligand to afford 41.0 mg (68%) of the title compound as an orange oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42 (d, J = 8.03 Hz, 1H), 7.36 (s, 1H), 7.28 (d, J = 3.61 Hz, 1H), 7.26 – 7.18 (m, 3H), 7.16 (d, J = 7.58 Hz, 1H), 4.09 (d, J = 15.08 Hz, 1H), 3.78 (d, J = 15.06 Hz, 1H), 3.74 (dd, J = 11.45, 3.82 Hz, 1H), 3.44 (dd, J = 16.64, 3.89 Hz, 1H), 3.26 – 3.18 (m, 2H), 2.98 (dd, J = 16.54, 11.42 Hz, 1H), 2.79 (dd, J = 16.94, 4.74 Hz, 1H), 2.72 – 2.65 (m, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 138.7, 137.3, 135.2, 134.4, 129.2,

129.0, 126.3, 126.1, 125.4, 123.1, 123.1, 123.0, 123.0, 59.5, 58.2, 51.0, 36.6, 29.4. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.37.

e.e. determined by HPLC analysis Daicel AD-H column: 99:1 Hexanes:iPrOH, flow rate 0.7 mL/min, rt, λ=210 nm, major= 12.50 min, minor= 18.83 min

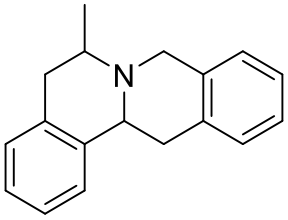


8-methyl-5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline (5-10c)

The cyclization of **5-6c** was conducted according to General Procedure Intramolecular Pd-catalyzed Alkene Carboamination reactions using BAH-9-51 as a ligand to afford 13.2 mg (53%) of the title compound as a 1:1.4 mix of diastereomers as an orange oil. The trans-compound is known and reported.[11] The cis and trans isomers are separable via flash chromatography on silica gel using 15% EtOAc: Hexanes.

Trans: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 – 7.10 (m, 8H), 3.84 (dd, J = 13.30, 8.50 Hz, 2H), 3.40 (ddd, J = 11.41, 5.31, 3.10 Hz, 1H), 3.27 (dd, J = 15.89, 3.28 Hz, 1H), 3.17 (ddd, J = 14.25, 9.48, 4.78 Hz, 2H), 2.98 (dd, J = 15.86, 11.29 Hz, 1H), 2.83 (dt, J = 16.15, 3.40 Hz, 1H), 2.52 (td, J = 11.19, 3.60 Hz, 1H), 1.58 (d, J = 6.39 Hz, 3H).

Cis: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30-7.10 (m, 8H), 4.36 (dd, J = 11.42, 4.46 Hz, 1H), 4.21 (q, J = 6.89 Hz, 1H), 3.15 (dq, J = 16.02, 6.18, 5.25 Hz, 2H), 3.08 – 3.02 (m, 2H), 2.93 – 2.87 (m, 2H), 1.43 (d, J = 6.85 Hz, 3H).



6-methyl-5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline (5-10d)

The cyclization of **5-6d** was conducted according to General Procedure Intramolecular Pd-catalyzed Alkene Carboamination reactions on a 0.2 mmol scale to afford 25.8 mg (52%) of the title compound as a 1:1.37 mix of diastereomers as an orange oil. The cis and trans isomers are separable via flash chromatography on silica gel using 15% EtOAc: Hexanes.

Isomer 1 (Top): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.07 (m, 8H), 4.37 (d, J = 14.67 Hz, 1H), 3.82 – 3.72 (m, 1H), 3.52 (d, J = 14.84 Hz, 1H), 3.41 (d, J = 16.24 Hz, 1H), 2.93 (dd, J = 28.06, 13.86 Hz, 2H), 2.79 – 2.63 (m, 2H), 1.26 (d, J = 1.91 Hz, 3H).

Isomer 2 (Bottom): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.06 (m, 8H), 4.18 – 4.08 (m, 1H), 4.05 – 3.86 (m, 2H), 3.44 (s, 1H), 3.31 (td, J = 16.92, 16.45, 4.41 Hz, 2H), 2.95 (d, J = 13.84 Hz, 1H), 2.64 (d, J = 16.00 Hz, 1H), 1.07 (d, J = 6.51 Hz, 3H).

e.e. determined of isomer 2 by HPLC analysis Daicel AD-H column: 99:1 Hexanes:iPrOH, flow rate 0.7 mL/min, rt, λ=210 nm, minor= 8.25 min, major= 12.89 min

5.11 References

(1) Pingali, S.; Donahue, J. P.; Payton-Stewart, F. “Tetrahydroberberine, a pharmacologically active naturally occurring alkaloid” *Acta Crystallogr C Struct Chem*, **2015**, *71*, 262-265.

(2) Bennasar, M. L.; Roca, T.; Monerris, M.; Garcia-Diaz, D. “Sequential N-Acylamide Methylenation−Enamide Ring-Closing Metathesis: Construction of Benzo-Fused Nitrogen Heterocycles” *J. Org. Chem.* **2006**, *71*, 18, 7028–7034.

(3) Shafir, A.; Buchwald, S. L.;“Highly Selective Room-Temperature Copper-Catalyzed C−N Coupling Reactions“ *J. Am. Chem. Soc.* **2006***, 128,* 27, 8742–8743.

(4) Alicea, J.; Wolfe, J. P. “Synthesis of Substituted Tetrahydroindoloisoquinoline Derivatives via Intramolecular Pd-Catalyzed Alkene Carboamination Reactions.” *J. Org. Chem*. **2014**, *79*, 4212–4217.

(5) Wolfe, J. P., Personal Communication

(6) Hopkins, B. A.; Garlets, Z. J.; Wolfe, J. P. “Development of Enantioselective Palladium-Catalyzed Alkene Carboalkoxylation Reactions for the Synthesis of Tetrahydrofurans” *Angew. Chem. Int. Ed.* **2015**, *54*, 13390–13392.

(7)a) Mai, D. N.; Wolfe, J. P “Asymmetric Palladium-Catalyzed Carboamination Reactions for the Synthesis of Enantiomerically Enriched 2-(Arylmethyl)- and 2-(Alkenylmethyl)pyrrolidines.” *J. Am. Chem. Soc.* **2010**, *132,* 12157-12159. b) Mai, D. N.; Rosen, B. R.; Wolfe, J. P “Enantioconvergent Synthesis of (+)-Aphanorphine via Asymmetric Pd-Catalyzed Alkene Carboamination.” *Org. Lett*. **2011**, *13*, 2932-2935. c) Hopkins, B. A.; Wolfe, J. P. “Synthesis of Enantiomerically Enriched Imidazolidin-2-Ones through Asymmetric Palladium-Catalyzed Alkene Carboamination Reactions” *Angew. Chem. Int. Ed.* **2012**, *51*, 9886–9890. d) Hopkins, B. A.; Wolfe, J. P. “Enantioselective synthesis of tetrahydroquinolines, tetrahydroquinoxalines, and tetrahydroisoquinolines via Pd-Catalyzed alkene carboamination reactions” *Chem. Sci*. **2014**, *5*, 4840–4844.

(8) Hopkins, B. A. “Enantioselective Synthesis of Heterocycles via Palladium Catalyzed Alkene Difunctionalization Reactions.” *University of Michigan.* **2015***, PhD Thesis*, 143.

(9) Gao, X.; Han, J.; Wang, L. “Design of Highly Stable Iminophosphoranes as Recyclable Organocatalysts: Application to Asymmetric Chlorinations of Oxindoles.” *Org. Lett.* **2015**, *17* (18), 4596-4599.

(10) Kraus, G. A.; Wu,T. “A three-component reaction between benzynes, the enolate of acetaldehyde, and unsaturated esters and dihydroisoquinolines” *Tetrahedron,* **2010,** *66*(3), 569-572.

(11) Kim, A. N.; Du, E.; Stoltz, B. M. “Recent Advances in the Total Synthesis of the Tetrahydroisoquinoline Alkaloids (2002−2020).” *Chem. Rev.* **2023**. *123*. 9448-9496.

(12) Reimann, E., Benend, H. “Synthese von Dibenzo[a,g]chinolizinen — Ein neuer Zugang zu Protoberberinen.” *Monatsh Chem.* **1992,** 123, 939–948. https://doi.org/10.1007/BF00811549

(13) Wang, Q-F.; He, W.; Liu, X-Y.; Chen, H.; Qin, X-Y.; Zhang, S-Y. “Facile one-pot synthesis of cinchona alkaloid-based P,N ligands and their application to Pd-catalyzed asymmetric allylic alkylation” *Tetrahedron: Asymmetry*. **2008**. *19* (21). 2447-2450.

(14) Khumsubdee, S. Burgess, K. “Metathesis for catalyst design: metacatalysis.” *Tetrahedron*. **2014**. *70* (6) 1326-1335.