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Rhodium Catalyzed C–H Bond Functionalization: Development of Methods and
Applications in Organic Synthesis

by

Andy Siu-Chun Tsai

A dissertation submitted in partial satisfaction of the
requirements for the degree of
Doctor of Philosophy
in
Chemistry
in the
Graduate Division
of the
University of California, Berkeley

Committee in charge:

Professor Robert G. Bergman, Chair
Professor Dean F. Toste
Professor Chris D. Vulpe

Spring 2011

Abstract

Rhodium Catalyzed C-H Bond Functionalization: Development of Methods and Applications in Organic Synthesis

By

Andy Siu-Chun Tsai

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Robert G. Bergman, Chair

Chapter 1. A sequence of research projects beginning with studies in diastereoselective C–H bond functionalization applied to the synthesis of (–)-incarvillateine to the Rh(III) catalyzed arylation of imines, are described. Some theory and mechanistic considerations are discussed in relation to the genesis of these projects. Research directions are summarized and rationalized.

Chapter 2. The synthesis of (–)-incarvillateine utilizing a key C–H bond alkylation step is described as a means to highlight the synthetic utility of a newly reported olefinic C–H bond functionalization methodology. Elements of diastereoselectivity are also explored in the key step which allows for the concise, stereoselective synthesis of the natural product. Progress in the area of enantioselective C–H alkylations are also summarized as it applies to the synthesis of other natural products.

Chapter 3. A method for the enantioselective cyclization of *N*-allylimidazoles is developed. The reaction is thought to proceed via a novel, reactive *N*-heterocyclic carbene. High enantioselectivities are achieved, which is unusual in view of the elevated temperatures of the reaction.

Chapter 4. The first general method for the oxidative coupling of unactivated alkenes via C–H bond functionalization is reported using a methyl oxime directing group. A silver abstractor is important to obtain reactivity. Several functional groups are compatible with the reaction and no precautions to exclude air are required.

Chapter 5. A rare example of C–H activation and intermolecular coupling to *N*-protected-imines is achieved using a cationic Rh(III) catalyst. The reaction is directed by pyridines and related heterocycles and produces a variety of aryl-branched amines. The reaction accommodates several reactive functional groups and is mild enough to even couple with sensitive alkyl *N*-sulfonyl-imines.

Table of Contents

Chapter 1. Introduction	
Introduction	1
Synthesis of (–)-Incarvillateine	2
Enantioselective Cyclization of <i>N</i> -Allylimidazoles	4
Oxidative Coupling of Unactivated Alkenes	4
Arylation of <i>N</i> -Boc-Imines	5
Tandem Reactions	7
Conclusion	9
References	9
Chapter 2. Asymmetric Synthesis of (–)-Incarvillateine Employing an Intramolecular Alkylation via Rh-Catalyzed Olefinic C–H Bond Activation	
Introduction	12
Results and Discussion	12
Enantioselective C–H Alkylation	16
Conclusion	18
Experimental	18
References	26
Chapter 3. Rhodium Catalyzed Enantioselective Cyclization of Substituted Imidazoles via C–H Bond Activation	
Introduction	28
Results and Discussion	28
Conclusion	30
Experimental	31
References	38
Appendix: X-ray Crystal Data	40
Chapter 4. Rh(III)-Catalyzed Oxidative Coupling of Unactivated Alkenes via C–H Activation	
Introduction	48
Results and Discussion	48
Conclusion	51
Experimental	51
References	60
Chapter 5. Rhodium(III) Catalyzed Arylation of Boc-Imines via C–H Bond Functionalization	
Introduction	62
Results and Discussion	62
Conclusion	66
Experimental	66
References	80

Acknowledgments

I will organize this roughly by descending ages which allows me to begin with thanking Prof. Jon Ellman and Prof. Bob Bergman, my two advisors. I was given a fantastic first project which introduced me to organic synthesis and organometallic chemistry in equal measure. Their patience, encouragement and the sense of freedom I felt in subsequent (sometimes not so successful) projects allowed me to progress from a student to a researcher in these four-odd years. The suggestions, advice, and perspectives I received were always invaluable and have shaped the way I approach problems.

Jason Rech taught me how to run 2D NMRs, Jared Lewis showed me how much work can actually be accomplished in a week, and Hillary Peltier was always a friendly and comforting presence. Matt Soellner was my labmate across the bench and whom I would often ask how to do basic things in lab. I wish him the best as a professor at Michigan and regret that I will not be able to postdoc for him. Matt was replaced by Somenath Chowdhury who would keep me company in lab for the rest of my time at Berkeley and then at Yale. The hours he kept while juggling a family never ceases to amaze and I hope to have a fraction of his dedication. Ashley Berman had a car, drove me around, and let me play with his cat. He showed me the area outside the Bay. I am grateful for the hikes he took me to and my first camping experience at Joshua National Park. Becca Wilson patiently introduced me to how to work in a glovebox and I somehow fumbled through sealing NMR tubes under her guidance. I thank Andrew Patterson for giving me the dubious nickname of “double A” and asking how my chemistry was going once in a while. I looked up to him as a senior researcher and have tried to emulate his positive influence as I become one myself. Regretfully, I neither have his level of clout nor respect amongst the group to be able to rally them to meet up at a bar on a random Friday night.

Denise Colby will always hold my greatest respect and gratitude. Not only have I learned a lot from her, but she consistently placated the seemingly daily crises that a new researcher encounters. Her knowledge, skill, eagerness to help, and open ear combine to make a chemist who I have tried to model myself after. Melissa Beenen-Herbage has always treated me with much appreciated familiarity and has contributed much to the sense of comfort I have felt in the Ellman Group. I've always appreciated her rational, step by step analyses of my problems.

Then there are the five grad students directly above me: Katrien Brak, MaryAnn Robak, Melissa Leyva, Katherine Rawls, and Michael Gribble. I have always been awed by Katrien for the amount of work she has accomplished; and even more so now as I stare at her thesis and compare it to mine own. I thank MaryAnn for the dinners and parties she has hosted at her house. She is an excellent teacher and my own erratic teaching style has been tempered by following her patience, pace, and preparation. Leyva's love of baseball has showed me that you can also have passions outside of the chemistry lab. I watched all of the 2010 World Series quietly hoping that the Rangers might win it all. Next year Leyva. Katherine Rawls adeptly took on the groups jobs of Safety and Inventory. From her I have learned assertiveness. Gribble might be the most careful and observant scientist I have met. He speaks in prose and is unintentionally hilarious.

I have shared the most time in lab with my contemporaries Sirilata Yotphan (Van) and Pete Marsden. We somehow made it through our first few years in adjoining rooms, collectively stumbling past classes, 1st year reports, and prelims. They were always someone who I could come by to chat, vent, and get away from chemistry in the middle of the day. With Van, whose palette is similar to mine, we shared many good lunches and dinners. Pete was a constant friend and source of distraction. It is sad that we are separate now when we were so close to finishing together. But that is grad school. People leave and you leave people.

Speaking of which, I will be leaving behind Rhia Martin, Kyle Kimmel, and Tyler Baguley. Rhia single handedly taught me about diversity. Thank you for Thanksgiving and the various dinners you have hosted. It was a pleasure to clean up your vomit after you passed your prelim. Kyle, you were my work out partner at the gym. I leave the pull up bar in your care. Tyler joined the group with the confidence and competence which took me awhile to acquire. I taught him nothing. He taught me about devotion...for your alma mater.

My best opportunity to be a mentor, in the loosest sense of the word, was for Andrew Bruesking, Jason Ji, and Vivian Lin. Jason and Vivian were lost to us early which I regret. I sincerely wish them the best. Andrew is me four years ago but far more mature. In turn, I'm Andrew Patterson four years ago. In that tradition (*vide supra*), I hereby officially assign your nickname to be "Ace." Take care of it well and take care Ellman Group.

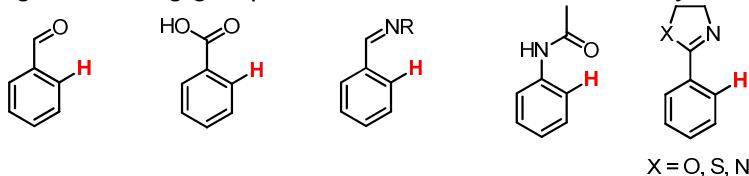
Chapter 1. Introduction

Following the synthesis of (-)-incarvillateine via a diastereoselective C–H bond alkylation, a method for the enantioselective cyclization of imidazoles was developed. Continuing on the theme of exploring selectivity, regioselectivity in C–H bond alkylations was investigated and subsequently led to a method for the oxidative coupling of unactivated alkenes using a cationic Rh(III) catalyst. This catalyst was also found to effect the arylation of N-Boc-imines via C–H bond activation of 2-aryl-pyridines. A tangentially related topic in the area of tandem chemistry is also discussed.

Introduction

Carbon-hydrogen bonds represent the most common bond in organic chemistry. However, except for acidic C–H bonds, they are generally unreactive and are not used as “functional handles” in synthesis. Methods for selective activation and functionalization of these unreactive C–H bonds potentially open up many new possibilities for efficient synthesis. One challenge in the area of C–H activation is that of selectively activating one particular C–H bond in the presence of several other nearly identical ones. Chelation assistance has been used to overcome this problem for transition-metal catalyzed reactions. Through the use of heteroatom “directing groups” which guide the transition-metal to a specific C–H bond, selective activation can be achieved. A wide variety of directing groups such as aldehydes, carboxylic acids, imines, amides, and various heterocycles have been utilized for this purpose (Figure 1.1). Once selective activation is attained, a suitable coupling partner such as an alkene or an aryl halide is used to functionalize the C–H bond and close the catalytic cycle.¹

Figure 1.1. Sampling of directing groups used for transition-metal catalyzed C–H activation



As C–H functionalization is a relatively new field, priorities in this area are to improve generality (i.e. wider types of substrates) and increase reaction scope (ie more coupling partners) to make other useful products. My research has focused the use of rhodium for elaboration of C–H functionalization substrates and the types of coupling partners for these reactions. In my synthesis of (–)-incarvillateine, an potent analgesic natural product, I demonstrated that α,β -unsaturated imines can be activated and intramolecularly coupled to a trisubstituted alkene in a diastereoselective fashion. The concise synthesis of this natural product highlights the value of C–H functionalization as a simplifying method in organic synthesis. I then developed a method for the enantioselective alkylation of *N*-allylimidazoles. Such enantioselective reactions in the field of C–H functionalization are rare and this method demonstrates that further progress in the field will enable new strategies to assemble molecules stereoselectively.

In efforts to expand the range of coupling partners in C–H functionalization, I developed conditions which allowed for the oxidative coupling of *unactivated* alkenes and the coupling of protected imines. Up to this point, oxidative coupling of alkenes via C–H activation have been limited to “activated” olefins such as styrenes and acrylates. However, in using a $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ system, coupling of simple aliphatic olefins was accomplished for the first time. The same catalyst system was also shown to activate C–H bonds and couple to imines, making branched amine products. Such reactivity with imines has not been observed before for these systems and produce products which are common motifs in many drugs and natural products.

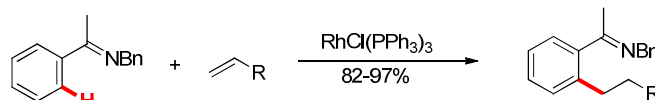
Synthesis of (–)-incarvillateine

One of the first synthetically useful rhodium catalyzed C–H functionalization methodologies was reported by Jun and coworkers. They found that using Wilkinson’s catalyst, *ortho* C–H bonds can be activated and added across the double bond in terminal alkenes to form *ortho* alkylated products (Scheme 1.1A).² Later, our group showed that if the reaction was

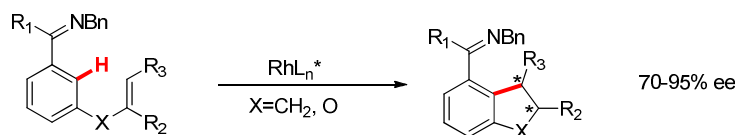
performed intramolecularly, the substrate scope could be dramatically broadened to include di- and tri-substituted alkenes. Furthermore, using chiral ligands, the alkylation could be accomplished with high enantioselectivity (Scheme 1.1B)³

Scheme 1.1. Early examples of C–H bond functionalizations

A. Rh catalyzed C–H bond alkylation by Jun



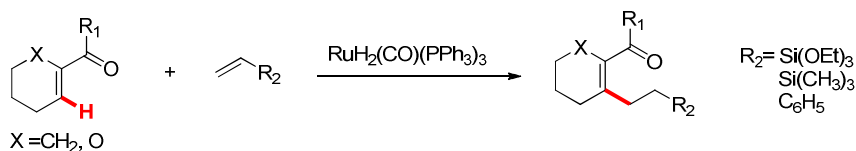
B. Enantioselective C–H bond alkylations by Ellman and Bergman groups



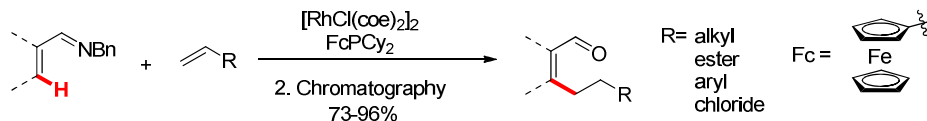
While functionalization of *aromatic* C–H bonds has been fairly well explored, the analogous functionalization of *olefinic* C–H bonds has been less well developed. Early examples from the Trost and Murai groups were limited to cyclic substrates and only to terminal, non-isomerizable alkenes (Scheme 1.2A).⁴ Our group showed that using electron rich rhodium catalysts, aliphatic α,β -unsaturated imines could be activated at the β C–H bond and coupled to a wide range of terminal alkenes.⁵ The resulting products after hydrolysis are highly substituted alkenes that would be difficult to synthesize stereoselectively through other methods (Scheme 1.2B).

Scheme 1.2. Functionalization of olefinic C–H bonds

A. Olefinic C–H bond functionalization of cyclic α,β -unsaturated ketones from Trost and Murai groups

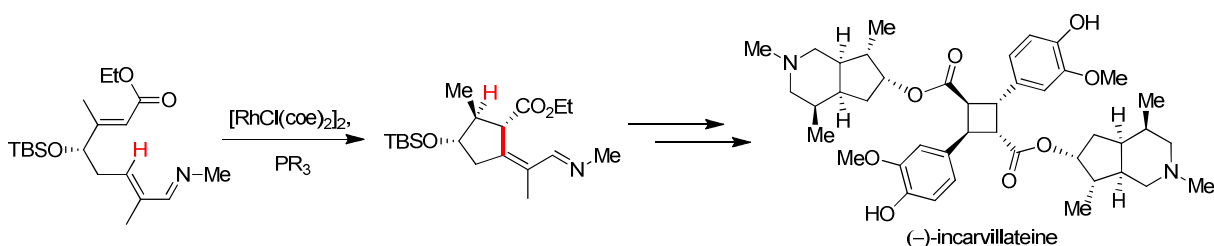


B. Olefinic C–H bond functionalization of aliphatic α,β -unsaturated imines from Ellman and Bergman Groups



My first project was to apply the olefinic C–H bond functionalization to a natural product (Chapter 2).⁶ The goals of this were three fold. First was to demonstrate the synthetic utility of the reaction. Also through the synthesis, we hoped to be able to elaborate the reaction scope. Finally, the target we chose, (–)-incarvillateine, allowed us to explore elements of diastereoselectivity in the key C–H bond functionalization step (Scheme 1.3). As a follow on to this synthesis, enantioselective alkylations were also explored as a means to access several other natural products.

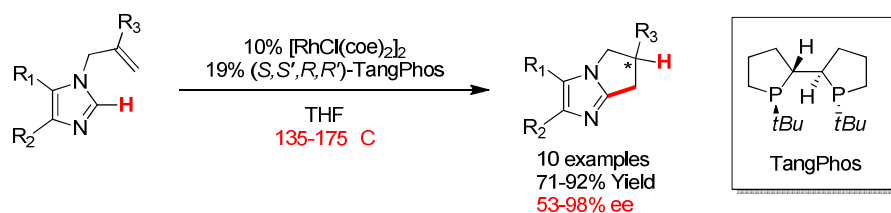
Scheme 1.3. Synthesis of (-)-incarvillateine via C–H bond functionalization



Enantioselective Cyclization of *N*-Allylimidazoles

Continuing on the theme of stereoselectivity, enantioselective cyclization of *N*-allyl imidazoles was also achieved using TangPhos as a chiral ligand (Chapter 3).⁷ This ligand was singularly active and selective for the title reaction. Excellent enantioselectivities up to 98% were achieved even at the elevated temperatures of the reaction (Scheme 1.4).

Scheme 1.4. Enantioselective cyclization of imidazoles via C–H bond functionalization



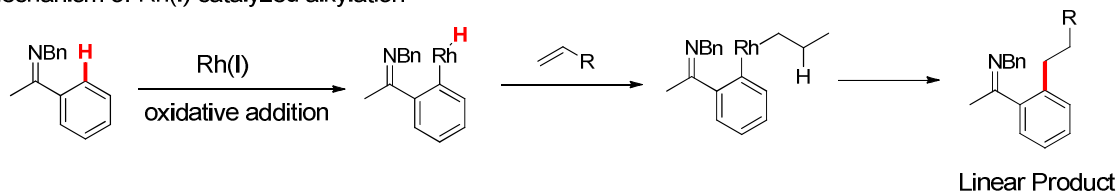
Oxidative Coupling of Unactivated Alkenes

Having investigated the diastereoselectivity and enantioselectivity of C–H bond alkylations, regioselectivity was next explored. In particular, we wanted to reverse the regioselectivity normally observed in the coupling of terminal alkenes. Generally, C–H activation and coupling with terminal alkenes provide linear products when using Rh(I) catalysts. This can be explained by the fact that the regio-determining insertion of the alkene into the rhodium hydride bond of the intermediate occurs such that the bulky rhodium complex is placed at the less sterically hindered terminal position. This naturally leads to the linear product after reductive elimination (Scheme 1.5A). However, whereas Rh(I) catalysts activate C–H bonds by oxidative addition to form Rh(III)-hydrides, Rh(III) catalysts activate C–H bonds by electrophilic deprotonation.⁸ This leads to an aryl-Rh(III) species with no hydride ligand. Thus, insertion of the alkene can only occur across the aryl-Rh(III) bond. Again, the regioselectivity of this insertion places the bulky rhodium complex at the terminal position of the alkane. However, in this case, a branched product is formed after protonolysis (Scheme 1.5B).

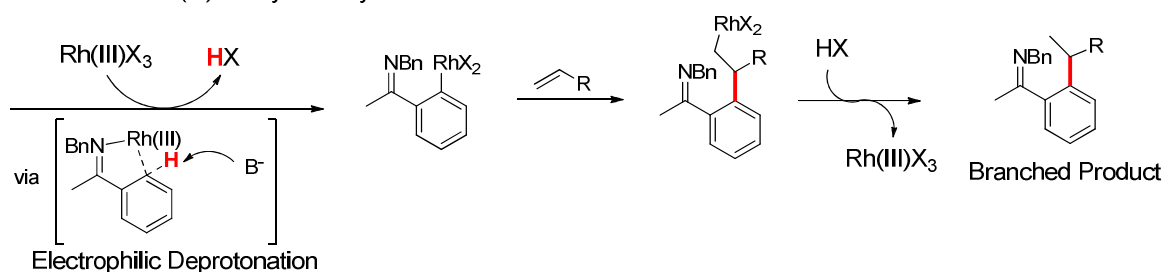
Adapting conditions from the Jones group, **1.1** was exposed to $[\text{Cp}^*\text{RhCl}_2]_2$ and NaOAc in CH_2Cl_2 (Scheme 1.6).⁸ Small amounts of the five membered ring (**1.3**) were observed by NMR. This is significant because the regioselectivity of this Rh(III) catalyzed alkylation is the reverse of that observed for Rh(I) catalyzed reactions which generate the six membered ring (**1.2**, Scheme 1.6).

Scheme 1.5. Mechanisms of Rh(I) and Rh(III) catalyzed alkylations

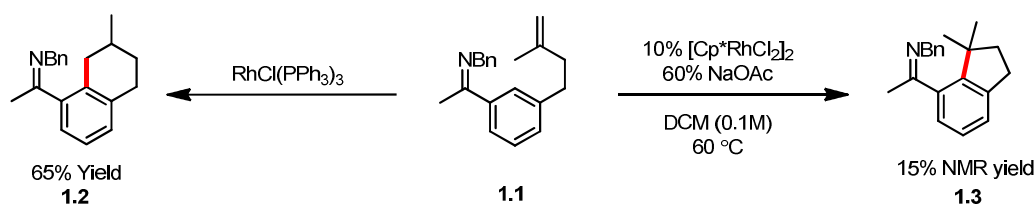
A. Mechanism of Rh(I) catalyzed alkylation



B. Mechanism of Rh(III) catalyzed alkylation

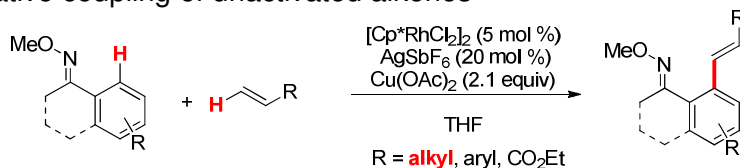


Scheme 1.6. Regioselectivity of alkylation with Rh(I) and Rh(III) catalysts



Unfortunately, conditions for the synthesis of **1.3** did not translate to intermolecular couplings. However, subsequent exploration with Rh(III) catalysts lead to a method for the oxidative coupling of unactivated alkenes, which up to this point were generally unknown (Scheme 1.7).⁹ Good yields are achieved and several commonly encountered functional groups are compatible with the method (Chapter 4).

Scheme 1.7. Oxidative coupling of unactivated alkenes

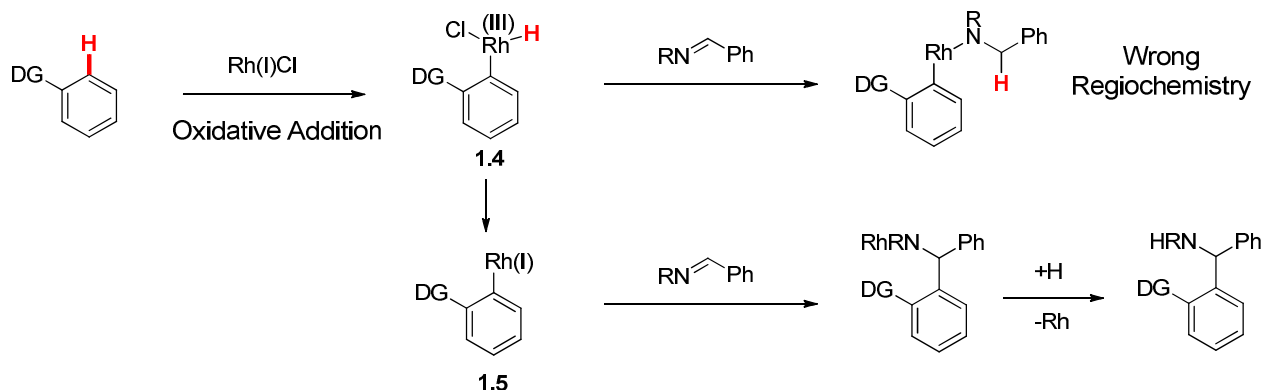


Arylation of *N*-Boc-Imines

Rh(III) catalysts also became instrumental for the arylation of imines via C–H bond activation. Previous attempts to accomplish this transformation focused on Rh(I) catalysts that were not reactive toward imines. This could possibly be due to the fact that the imine would insert across the intermediate rhodium-hydride bond with regiochemistry opposite to that would be required to make a C–C bond. Instead, the insertion leads to a rhodium amide that may be a catalytic dead end (Scheme 1.8). Thus, attempts were made to convert intermediate **1.4** to a species that would be able to arylate imines with the desired regiochemistry. In

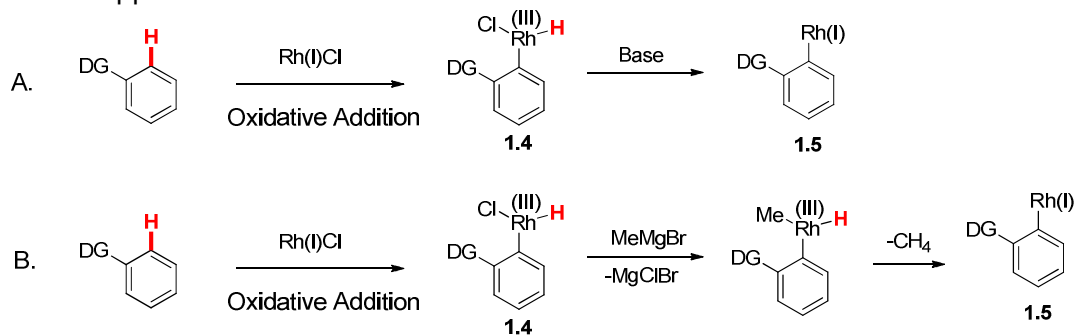
particular, converting **1.4** to an aryl-rhodium (I) species (**1.5**, Scheme 1.8), should then allow for arylation of imines in a manner similar to that observed with aryl boronic acids.¹⁰

Scheme 1.8. Initial proposition for the arylation of imines via C-H bond activation



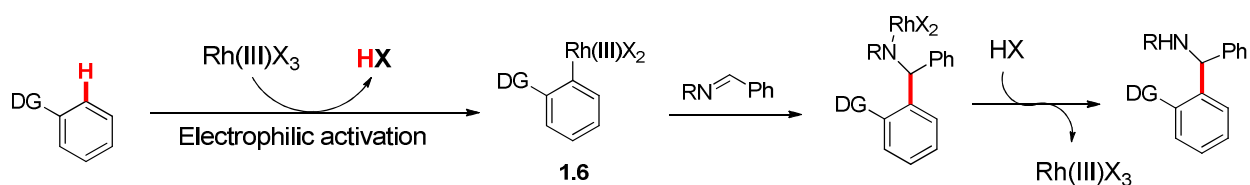
Two methods were explored to convert **1.4** to **1.5** (Scheme 1.9). The first attempted to promote reductive elimination of HCl from **1.4** through the addition of bases (Scheme 1.9A). When that failed, halide abstractors were also added, but no Rh(I) complex was ever observed and arylation of polar functional groups were not detected. The second strategy involved displacement of the Cl ligand with a methyl group (Scheme 1.9B). The new complex would then reductively eliminate methane gas to generate **1.5**. This method also gave a species that failed to react with imines, aldehydes, or nitriles.

Scheme 1.9. Approaches to form **1.5**

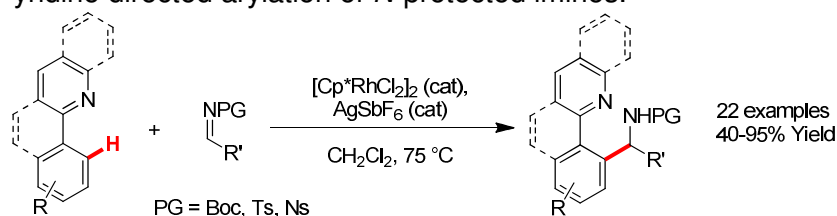


Rh(III) catalysts provide a straight-forward route to **1.6**, a Rh(III) analogue of **1.5** (Scheme 1.10). While an aryl-Rh(III) species should theoretically insert across imines with the correct regiochemistry to form a C–C bond, such a transformation has not been demonstrated. Nonetheless, the approach was explored and was successful for the pyridine directed arylation of *N*-Boc-imines (Scheme 1.11, Chapter 5).¹¹

Scheme 1.10. Mechanism of Rh(III) catalyzed arylation of imines



Scheme 1.11. Pyridine directed arylation of *N*-protected imines.

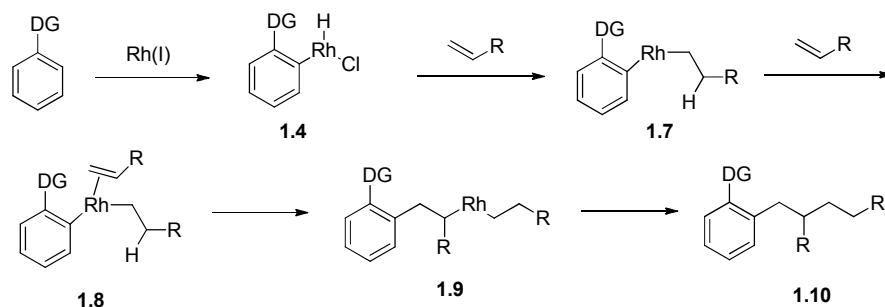


The demonstration that Rh(III) catalysts are able to activate C-H bonds for additions across imines suggest that several analogous reactions that lead to addition across other common polarized unsaturates (aldehydes, nitriles, isonitriles, isocyanides, etc) might also be possible. Continuing work is also focused on expanding from a pyridine directing group to more synthetically versatile directing groups and on lowering catalyst loadings.

Tandem Reactions

Tandem reactions provide a rapid method to achieve high molecular complexity. The strategy investigated to achieve this type of reactivity in the area of C-H functionalization involved transformations designed to intercept intermediates for the arylation of imines. Specifically, it was postulated that interception of species such as **1.7** with a second alkene might result in an additional insertion event to yield **1.9** which would ultimately lead to incorporation of multiple alkenes (**1.10**, Scheme 1.12).

Scheme 1.12. Mechanistic proposal for tandem reactivity via C-H activation

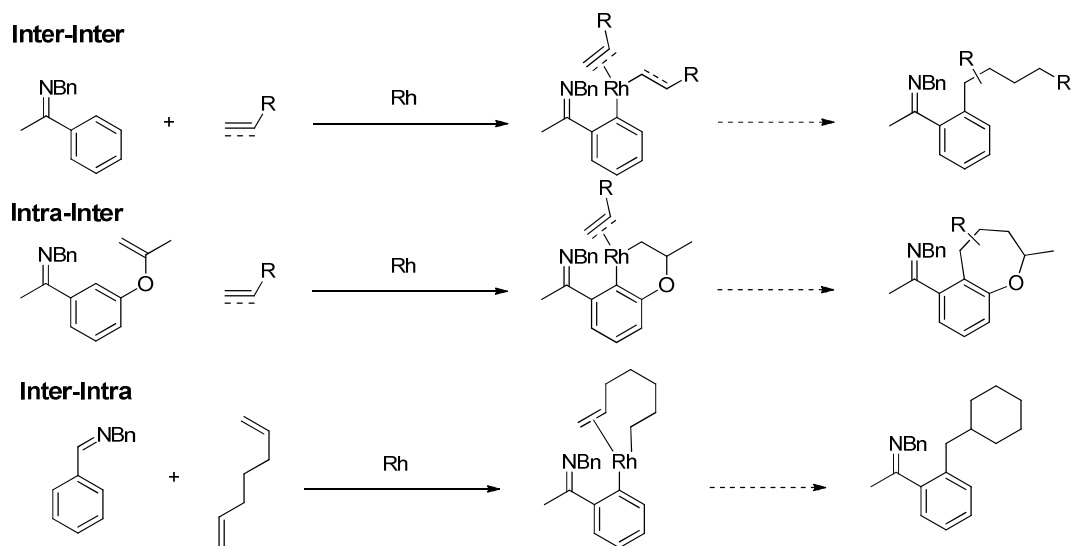


Three approaches were initially explored (Scheme 1.13). Benzyl imines were used as the directing group as the Bergman and Ellman groups have had the most experience and success in developing alkylations using this moiety. The precatalyst $[\text{RhCl}(\text{coe})_2]_2$ (coe: cis-cyclooctene) in combination with various electron rich $[\text{FcPCy}_2]$ and poor $[\text{P}(\text{O}i\text{Pr})_3, \text{PPh}_3]$ phosphines were used as the catalyst. The “inter-inter” approach simply used a high concentration of an alkene (neohexene, ethyl acrylate, norbornene) or alkyne (1-hexyne, 4-octyne, diphenyl-acetylene) in hopes of intercepting the key aryl-Rh-alkyl species for an additional insertion event. However, only the mono alkylated product was observed. The intra-inter strategy used a tethered alkene and an external alkene/alkyne (neohexene, ethyl acrylate, norbornene, 1-hexyne, 4-octyne, diphenyl-acetylene) to try to attain tandem reactivity. This tactic also failed and only gave the five-membered dihydrofuran. At this point, it was hypothesized that coordination and insertion of a second alkene/alkyne was unfavorable and slow. Thus, reductive elimination occurs prior to the targeted second insertion. To address this issue, attempts were made to couple simple dienes (1,7-heptadiene) (inter-intra approach). It was hoped that because the two alkenes were tethered, coordination of the second alkene would be favorable due to the formation of a stable metallacycle. Unfortunately, no coupled

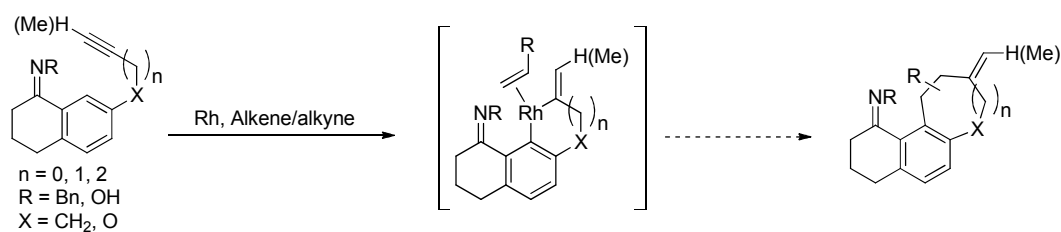
product was observed when dienes were used as coupling partners. This might possibly be due to chelation of the diene to the rhodium center, leading to an inactive catalyst. A similar phenomena was previously observed when $[\text{RhCl}(\text{cod})]_2$ was used in place of $[\text{RhCl}(\text{coe})_2]_2$ for previously successful alkylation reactions. It is postulated that the chelating nature of 1,4-cyclooctadiene (cod) prevents its displacement by phosphine ligands.

The common issue with all three previous strategies is that reductive elimination is faster than the second insertion event. One tactic that may address this issue is to make a rhodium species that *cannot* reductively eliminate. Such a species might be obtained through insertion of a tethered alkyne into the Rh–H bond. If the tether is of an appropriate length, reductive elimination might be prevented by formation of a strained four-member ring (Scheme 1.14). Experiments were performed using imine and oxime directing groups, terminal and internal alkenes with varied methylene tethers, $[\text{RhCl}(\text{coe})_2]_2$ as the precatalyst, with electron rich and poor ligands (FcPCy_2 , $\text{P}(\text{O}/\text{Pr})_3$, PPh_3), and various alkene/alkyne tandem partners (neohexene, ethyl acrylate, norbornene 1-hexyne, 4-octyne, diphenyl-acetylene). None of the experiments showed any coupled or tandem products. The reason for the lack of reactivity is not clear. However, while intramolecular olefination using tethered alkynes has been demonstrated,¹² it has never been done with such short linkers. This may prevent coordination of the alkyne in an appropriate manner for insertion to occur.

Scheme 1.13. Initial approaches to achieve tandem reactivity



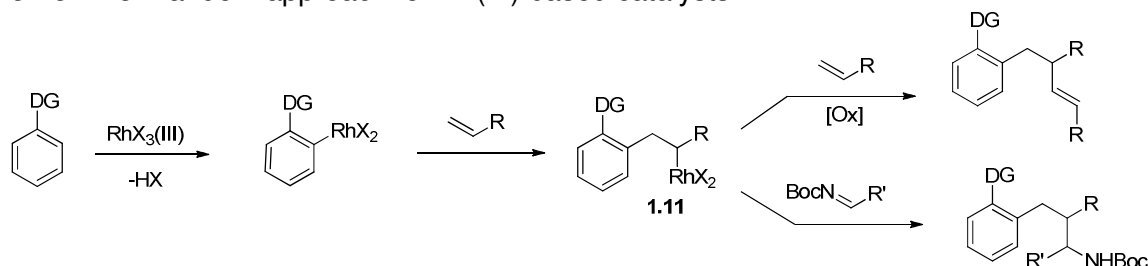
Scheme 1.14. Alternate approach for tandem reactivity



Though Rh(I) based catalysts thus far have proven unfruitful for tandem reactions, the Rh(III) catalysts that were used for the oxidative coupling of alkenes and the arylation of imines may provide a different method to achieve such reactivity. The mechanistic proposal for tandem

chemistry with Rh(III) catalysts is shown in Scheme 1.15. Instead of intercepting an intermediate such as **1.7** (Scheme 1.12), the species targeted for interception of the Rh(III) catalyst would be **1.11**. The advantage of using a Rh(III) catalysis for tandem reactions is that one would simply need to outcompete protonolysis which is an *intermolecular* process. This is in contrast to Rh(I) catalysts where reductive elimination, a potentially faster *intramolecular* process, needs to be avoided.

Scheme 1.15. Tandem approach for Rh(III) based catalysts



Conclusion

An olefinic C–H bond functionalization was utilized as the key step in the stereoselective synthesis of (–)-incarvillateine. With continuing interest in stereoselectivity and regiochemistry in C–H functionalization reactions, enantioselective cyclization of imidazoles was developed as well as, serendipitously, a method for oxidative coupling of unactivated alkenes. Up to this point, only alkenes have been explored as coupling partners. However, using the same Rh(III)/AgSbF₆ catalyst system for oxidative coupling, a method for the pyridine directed arylation of *N*-Boc-imines was developed. This is a rare example in which a C–H activated intermediate is coupled with a polarized functional group. This potentially allows for the diversification of possible coupling partners in this type of chemistry. Using the same strategy of intercepting organometallic intermediates for new reactivity, tandem reactions were also explored. The results thus far have been disappointing, but new catalysts that operate under different mechanisms may provide the key to achieving such reactions.

References

- (1) (a) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094-5115; (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624-655; (c) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987-6001; (d) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, *9*, 1399-1427; (e) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212-11222; (f) Wang, X.; Zhou, L.; Lu, W. *Curr. Org. Chem.* **2010**, *14*, 289.
- (2) Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440-3442.
- (3) (a) Harada, H.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772-6779; (b) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692-9693; (c) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 6775-6781; (d) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192-7193.
- (4) (a) Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679-680; (b) Trost, B. M.; Iml, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371-5372.

- (5) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604-5605.
- (6) Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316-6317.
- (7) Tsai, A. S.; Wilson, R. M.; Harada, H.; Bergman, R. G.; Ellman, J. A. *Chem Commun* **2009**, 3910-3912.
- (8) (a) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414-12419; (b) Li, L.; Jiao, Y.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2010**, *29*, 4593-4605.
- (9) Tsai, A. S.; Brasse, M. I.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2010**, ASAP.
- (10) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169-196.
- (11) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, ASAP.
- (12) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452-2453.

Chapter 2. Asymmetric Synthesis of (-)-Incarvillateine Employing an Intramolecular Alkylation via Rh-Catalyzed Olefinic C–H Bond Activation

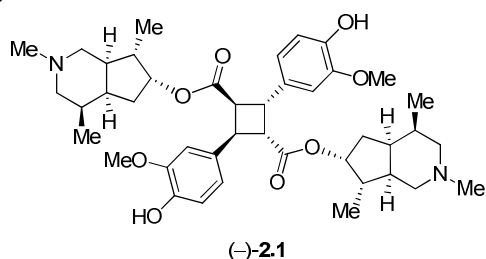
*An asymmetric total synthesis of (-)-incarvillateine, a natural product with potent analgesic properties, was achieved in 11 steps and 15.4% overall yield. The key step was a rhodium-catalyzed intramolecular alkylation of an olefinic C–H bond to set two stereocenters. Additionally, this transformation produced an exocyclic, tetrasubstituted alkene through which the bicyclic piperidine moiety could readily be accessed. A majority of this work has been published in a communication (Tsai, A. S.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. **2008**, 130, 6316-6317).*

As a follow on to this work, enantioselective cyclization of a derivative of the key intermediate in the synthesis of (-)-incarvillateine was also explored as a route to other natural products.

Synthesis of (–)-Incarvilleine: Introduction

(–)-Incarvilleine (–)-**2.1** (Figure 2.1) is a monoterpene alkaloid that has attracted attention due to its potent analgesic properties.¹ The first enantioselective synthesis of this natural product was recently achieved,² but required a number of steps to correctly set the stereochemistry of the five contiguous stereocenters on the bicyclic piperidine moiety.³ Herein, we report a concise asymmetric synthesis of (–)-incarvilleine employing an intramolecular alkylation of an olefinic C–H bond to set two of the stereocenters with simultaneous stereospecific introduction of an exocyclic, tetrasubstituted alkene framework upon which the bicyclic piperidine could rapidly be assembled.^{4,5,6}

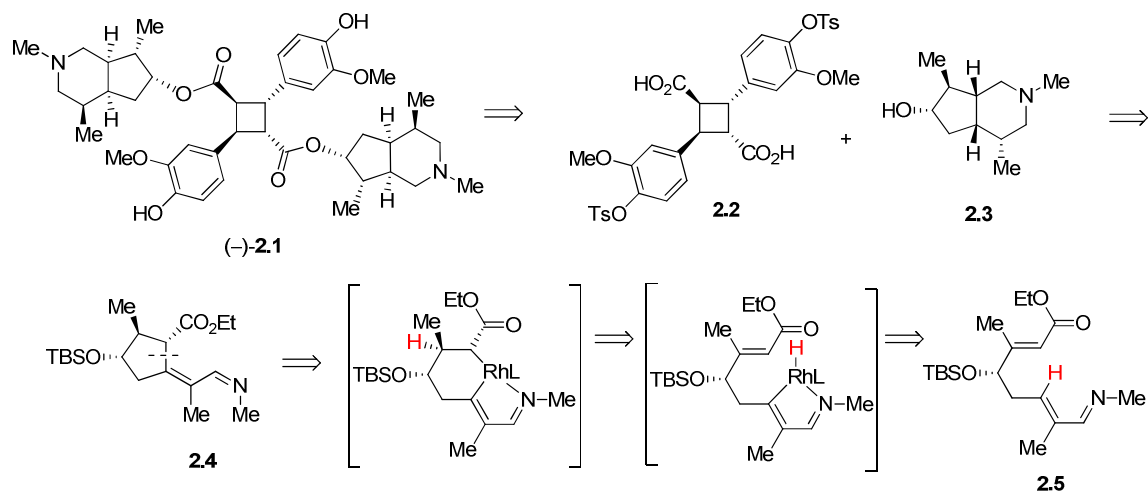
Figure 2.1. (–)-Incarvilleine



Results and Discussion

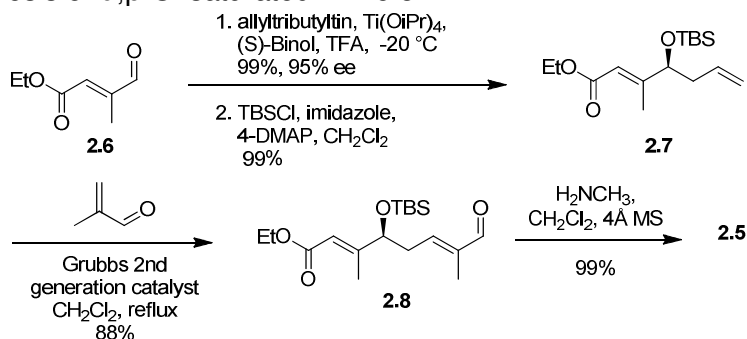
(–)-Incarvilleine may be retrosynthetically disconnected to cyclobutane **2.2** and piperidine **2.3** (Scheme 2.1). The synthesis of **2.2** can be accomplished in two steps from commercially available ferulic acid through a light promoted [2+2] photodimerization.⁷ Piperidine **2.3** could be obtained from **2.4** through reduction of the imine, lactamization, and reduction of the resulting amide and alkene. Cyclopentane **2.4** should be accessible in a key step by the intramolecular alkylation of **2.5** via Rh-catalyzed C–H activation followed by syn-alkene insertion and reductive elimination⁷ with retention of configuration. This is reasoned to exclusively provide the desired exocyclic double bond geometry and the anti-relationship of the methyl and ester functionalities. Furthermore, the secondary TBS ether should result in diastereoselective alkylation to install the correct absolute stereochemistry at the methyl and ester stereocenters.

Scheme 2.1. Retrosynthesis of (–)-Incarvilleine



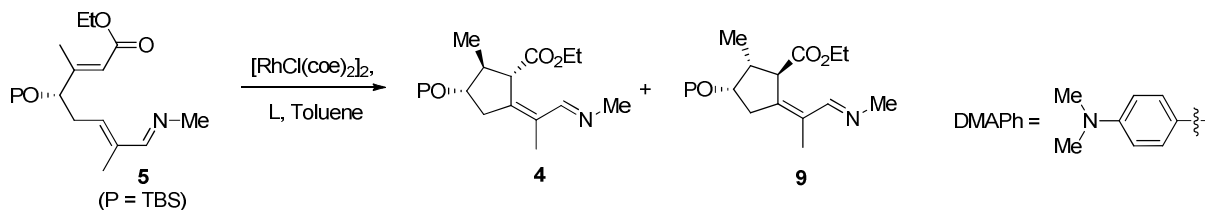
Asymmetric allylation of commercially available **2.6** with allyltributyltin under Keck conditions proceeded in quantitative yield and with excellent enantioselectivity (Scheme 2.2).⁸ The resulting alcohol was subsequently protected as a TBS ether (**2.7**). Cross metathesis of **2.7** with methacrolein using Grubbs' 2nd generation catalyst provided **2.8** in good yield as a single isomer.⁹ Imine **2.5** was then formed through condensation of **2.8** with methylamine in the presence of molecular sieves.

Scheme 2.2. Synthesis of α,β -Unsaturated Imine **5**



The diastereoselective intramolecular alkylation of **2.5** was explored using conditions recently reported for the intermolecular β -alkenylation of α,β -unsaturated imines with alkynes (Table 2.1).¹⁰ Ferrocenyl (Fc) dialkyl phosphines (entries 1-2) as well as 4-(dimethylamino)phenyl (DMAPh) based phosphines (entries 3-8) were evaluated. Though many of the ligands explored were active, resulting in quantitative cyclization of **2.5**, (DMAPh)-PEt₂ was the most selective ligand, providing diastereomers **2.4** and **2.9** in a ~5:1 ratio (entry 7).¹¹ It is interesting to note that the sterics of this ligand provided the “sweet spot” in terms of diastereoselectivity as both more (entry 5) and less bulky (entry 4) analogues eroded the diastereoselectivity. The high catalyst activity of (DMAPh)-PEt₂ also allowed the catalyst loading to be reduced to 2.5 mol% (entry 8).

Table 2.1. Ligand screen for the diastereoselective alkylation of **2.5**

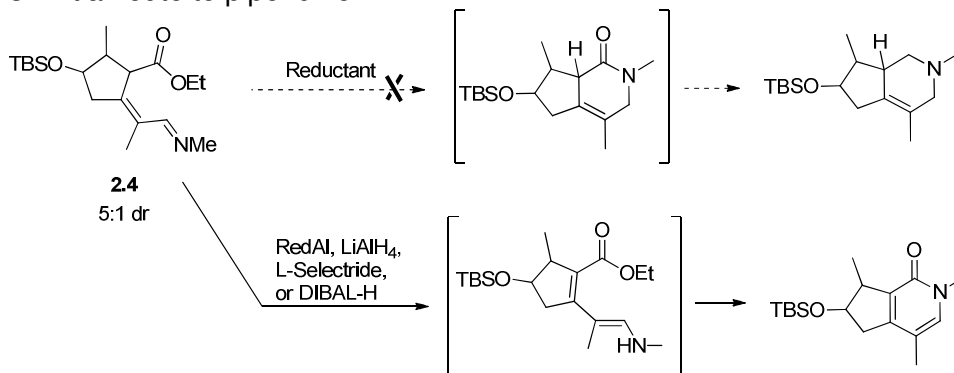


entry	ligand	% Rh	% L	T (°C)	t (h)	4 + 9 (%) ^a	4:9 dr ^b
1	FcPCy ₂	5	11	45	25	100	53:47
2	FcPEt ₂	5	11	25	21	100	69:31
3	(DMAPh) ₂ PMe	10	22	25	8	100	75:25
4	(DMAPh)PMe ₂	10	22	45	19	100	75:24
5	(DMAPh)PCy ₂	5	11	45	21	34	62:38
6	(DMAPh)PEt ₂	5	11	22	54	100	86:14
7	(DMAPh)PEt ₂	5	11	45	6	100	83:17
8	(DMAPh)PEt₂	2.5	5.5	45	6	100	83:17

^a Yields based on ¹H NMR integration relative to residual protio toluene as an internal standard. ^b Diastereomeric ratio determined by ¹H NMR. Fc: ferrocenyl. DMAPh: 4-(dimethylamino)phenyl.

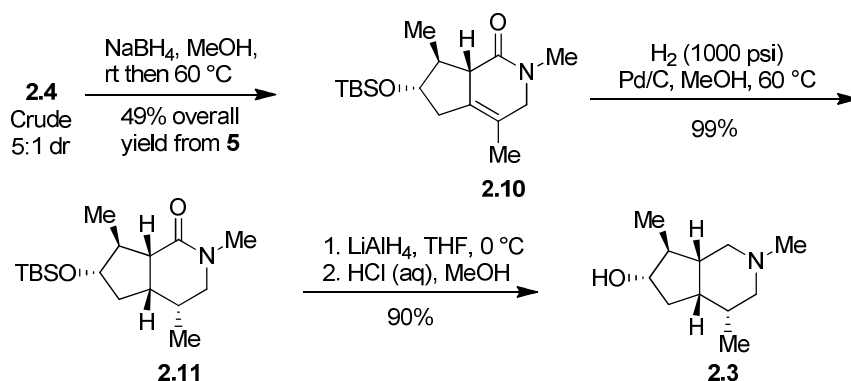
Initial attempts to obtain the piperidine focused on using a strong reductant that would be able to reduce the imine and subsequently formed lactam (Scheme 2.3). Unfortunately, use of such reductants as RedAl, LiAlH₄, L-selectride, and DIBAL-H all failed, giving instead, a pyridone via tautomerization to the enamine and cyclization.

Scheme 2.3. Initial route to piperidine



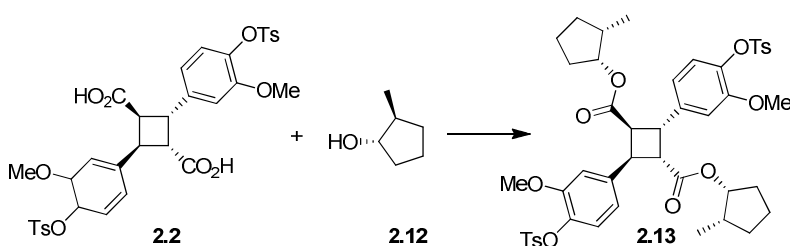
Due to facile tautomerization of **2.4** to the ester conjugated dienamine, it was necessary to directly convert the crude compound to a more stable intermediate. This was accomplished through imine reduction with NaBH₄ followed by lactamization upon heating to provide **2.10**, which after chromatography was isolated as a single diastereomer in 49% overall yield from **5** (Scheme 2.4). Hydrogenation of the tetrasubstituted olefin required high pressure and elevated temperature, but occurred exclusively on the less hindered face to yield **2.11**. Reduction of **2.11** with LiAlH₄, followed by cleavage of the TBS protecting group under acidic conditions gave **2.3**.

Scheme 2.4. Synthesis of bicyclic piperidine **2.3**



Completion of the synthesis of (–)-incarvillateine was carried out in accordance with the previously reported sequence: Mitsunobu coupling between **2.3** and **2.2** followed by removal of the tosyl protecting groups.² The low reported yield in the Mitsunobu coupling reaction (30% based on the more valuable fragment **2.3**), encouraged us to optimize this step. Commercially available trans-2-methylcyclopentanol (**2.12**) was used as the model substrate for **2.3** (Table 2.2). In addition to DEAD/PPh₃ (entries 1-5), ADDP/PBu₃ (1,1'-(azodicarbonyl)dipiperidine)¹² was explored as coupling reagents but showed diminished reactivity (entries 6-7). A range of temperatures and solvents was also investigated. Refluxing conditions reported in the prior synthesis were found to be unnecessary and in fact resulted in reduced yield for the model system (entry 1). Dioxane and CH₂Cl₂ were found to be poor solvents for the reaction due to limited solubility of **2.2** at low temperatures (entries 4-5). Use of DEAD/PPh₃ at low temperatures in THF provided the highest yield (entry 3).

Table 2.2. Mitsunobu Coupling of Model Substrate

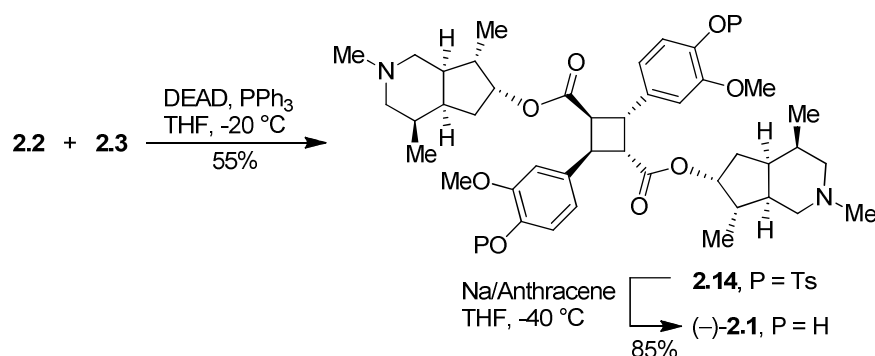


entry	reagents	T ($^{\circ}\text{C}$)	solvent	% 2.13 ^a
1	DEAD, PPh ₃	65	THF	36
2	DEAD, PPh ₃	0	THF	61
3	DEAD, PPh₃	-20	THF	72
4	DEAD, PPh ₃	25	Dioxane	29
5	DEAD, PPh ₃	0	CH ₂ Cl ₂	33
6	ADDP, PBU ₃	65	Toluene	28
7	ADDP, PBU ₃	25	THF	0

^a Isolated yield based on 2-methylcyclopentanol. DEAD: (diethyl diazocarbonylate), ADDP: (1,1'-(azodicarbonyl)dipiperidine)

Employing the optimal Mitsunobu coupling conditions from the model study, **2.14** was obtained from **2.2** and **2.3** in 55% yield (Scheme 4). The major byproduct (22%) resulted from competitive amidation of one of the carboxylic acids in **2.2** with the hydrazine of reduced DEAD. Alternatives to sodium amalgam for removal of the tosyl protecting groups in **2.14** were also explored because the yield reported in the literature was not satisfactory (58%).² Sodium/anthracene¹³ proved to be optimal and provided (–)-incarvillateine (**2.1**) in high yield (Scheme 2.5).

Scheme 2.5. Synthesis of (–)-incarvillateine



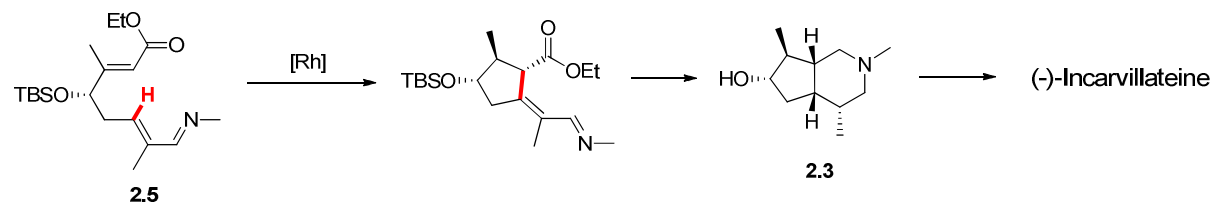
In summary, a concise asymmetric synthesis of (–)-incarvillateine was accomplished in 11 steps and 15.4% overall yield representing a substantial improvement over the previously reported synthesis.^{2,15} The Rh-catalyzed alkylation of **2.5** simultaneously installed two out of the five necessary stereocenters in the bicyclic piperidine while also stereospecifically introducing the tetrasubstituted, exocyclic alkene that enabled the rapid assembly of (–)-**2.1**.

Enantioselective C–H Alkylation

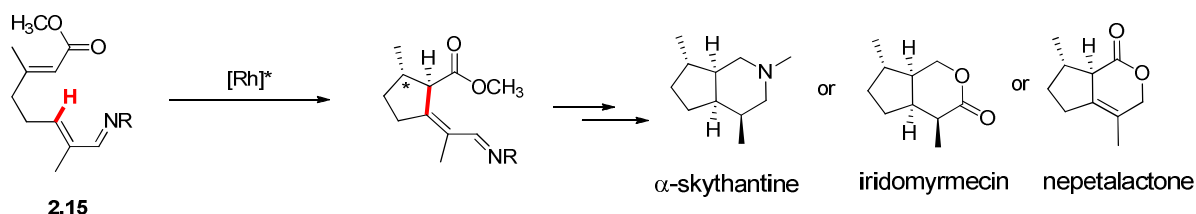
As a follow on to the diastereoselective alkylation employed in the synthesis of (-)-incarvillateine, enantioselective alkylations were also explored as a route to access other natural products. In particular, enantioselective cyclization of **2.15**, a derivative of **2.3** which lacks the hydroxyl-substituted stereocenter, should lead to an intermediate that could be diverted to several natural products (α -skythantine, iridomyrmecin, and nepetalactone) (Scheme 2.6).

Scheme 2.6. Natural product targets via enantioselective alkylation

Diastereoselective Alkylation

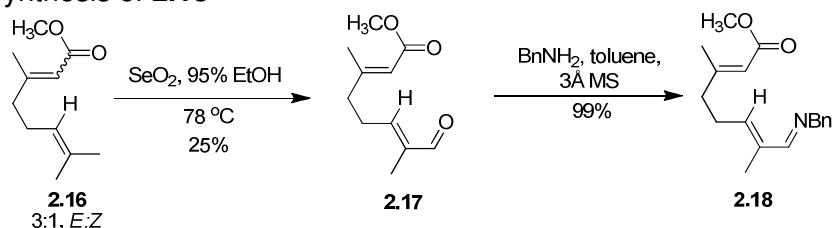


Enantioselective Alkylation



Synthesis of the benzyl imine **2.18** was achieved in two steps from commercially available **2.16** which is sold as a 3:1 E:Z mixture via an SeO₂ allylic oxidation and imine condensation with benzyl amine (Scheme 2.7).

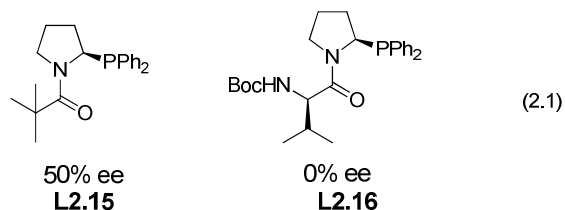
Scheme 2.7. Synthesis of **2.18**



Chiral ligands were then explored in the rhodium catalyzed intramolecular alkylation of **2.18**. To evaluate the enantioselectivity, the lactam (**2.19**) was isolated via NaBH₄ reduction of the unstable cyclic intermediate. The initial ligand screen focused on phosphines used in previous enantioselective alkylations with aromatic imines (Scheme 2.8).¹⁴ Binol based ligands (**L2.1**) which were active for the alkylation of aromatic imines, were inactive for **2.18**. Taddol based phosphite **L2.2** however, was an effective ligand, generating the 5-membered ring in 71% ee. The diastereomer **L2.3** was also active but provided the product with reduced enantioselectivity. To probe the steric effect of the aryl moiety on the taddol backbone, **L2.4** and **L2.5** were synthesized. Less bulky **L2.4** was inactive for the alkylation while the more bulky **L2.5** provided the alkylated product in only 58% ee. Taddol based phosphoramidite (**L2.6**) was inactive in the transformation while phosphonites **L2.7** and **L2.8** resulted in reduced enantioselectivity.

While the results with the taddol based ligands were promising, several derivatives of **L2.2** failed to improve the enantioselectivity. Thus, other ligand classes were explored. Tropos ligands refer to ligand architectures where axial chirality is fluxional. Incorporation of a fixed chiral element enforces a preferred diastereomeric conformation.¹⁵ While tropos ligand **L2.9** (Scheme 2.9) was inactive for the rhodium catalyzed alkylation, more bulky phosphites **L2.10** and **L2.11** did provide the expected product, albeit in a nearly racemic manner. Despite this result, the fact that increasing the steric bulk of **L2.9** restored reactivity to this biaryl series suggested that by similarly increasing the steric bulk of previously inactive binol phosphites, activity might also be restored. To test this hypothesis, increasingly bulky ligands **L2.12–L2.14** were synthesized. Unfortunately, none of these ligands was active.

Work in this area has since focused on proline based ligands that were identified in the initial ligand screen. Ligand **L2.15**, for example, provided the alkylated product in 50% ee. However, replacement of the achiral pivalate with *N*-Boc-valine provided the product in racemic form (eq 2.1). This result could possibly be a case of a mis-match pair between (*S*)-proline and *N*-Boc-(*L*)-valine. Thus, the diastereomer might generate the product with high enantioselectivity.



Conclusion

Through the application of an olefinic C–H alkylation, the concise synthesis of (–)-incarvillateine was achieved. Notable features include the diastereoselectivity and the result that the insertion step in the key transformation occurs with a sterically hindered tri-substituted olefin. Enantioselective alkylations were also explored with 77% ee being the highest obtained so far. Higher enantioselectivities may be achieved via easily modifiable amino acid based phosphines.

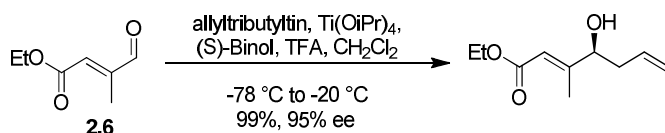
Experimental

I. General Methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Molecular sieves were heated at 300 °C under 0.5 mm Hg vacuum overnight or flame dried during three vacuum/purge cycles. Toluene, dichloromethane, and tetrahydrofuran were passed through a column of activated alumina under nitrogen. Methanol was distilled from CaH₂ under N₂. All reactions of air- and moisture-sensitive materials were carried out using syringe, cannula and/or inert atmosphere box techniques. All glassware was dried overnight at 150 °C or flame-dried under vacuum immediately prior to use. During workup procedures, organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure with a rotary evaporator. Chromatography was performed on Merck 60 230-240 mesh silica gel. NMR chemical shifts are reported in ppm relative to CHCl₃ (7.26 ppm for ¹H, and 77.23 ppm for ¹³C) or C₆D₆ (7.16 ppm for ¹H, and 128.39 ppm for ¹³C) as noted. Chiral HPLC analyses were performed on an Agilent 1100 system with a Chiral PAK OD column (250 mm 4.6 mm) with a flow rate of 1 mL/min and with *i*-PrOH/hexanes as the mobile phase. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. A

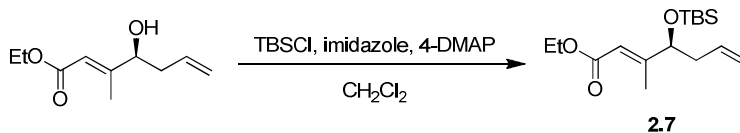
Perkin-Elmer 241 polarimeter with a sodium lamp was used to determine specific rotations and concentrations are reported in g/dL. Mass spectra (HRMS) were obtained by the University of California at Berkeley Mass Spectrometry Facility.

II. General Procedure for C–H Activation Experiments Monitored by NMR. In a nitrogen-filled inert atmosphere box, $[\text{RhCl}(\text{coe})_2]_2$,¹⁶ ligand, substrate (0.05 mmol), and toluene- d_8 (0.5 mL) were combined in a thin-walled NMR tube. The tube was fitted with a Cajon adapter, frozen with liquid nitrogen, and flame-sealed under vacuum. The tube was then placed in an oil bath set to the desired temperature. Periodically, the tube was removed from the bath, cooled to room temperature, and analyzed by $^1\text{H-NMR}$ spectroscopy to monitor the progress of the reaction based on integration relative to toluene as an internal standard. All optimization reactions were carried out via this procedure by varying temperature, ligand, and catalyst loading.

III. Synthesis of (–)-Incarvillateine.

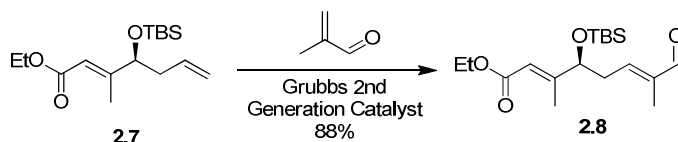


(S,E)-ethyl 4-hydroxy-3-methylhepta-2,6-dienoate. (S)-(-)-1,1-Bi(2-naphthol) (0.60 g, 2.1 mmol, 0.3 equiv), 4Å molecular sieves (6.3 g), CH_2Cl_2 (30 mL), distilled trifluoroacetic acid (5 μL , 0.08 mmol, 0.01 equiv), and distilled $\text{Ti}(\text{O}i\text{Pr})_4$ (0.32 mL, 1.1 mmol, 0.15 equiv) were added to a 100 mL round bottom flask equipped with a stir bar and reflux condenser. The red mixture was heated at reflux for 2 h and cooled to room temperature. **2.6** (1.00 g, 7.04 mmol, 1 equiv) was added and the reaction mixture was cooled to $-78\text{ }^\circ\text{C}$. Allyltri-*n*-butyltin (3.50 mL, 10.4 mmol, 1.5 equiv) was added dropwise via syringe over 20 min. The solution was stirred at $-78\text{ }^\circ\text{C}$ for 20 min and transferred to a $-20\text{ }^\circ\text{C}$ freezer. After 16 h, the reaction mixture was quenched with 1 M aq NaOH (15 mL), and the mixture was stirred at room temperature for 45 min. The mixture was filtered through Celite, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude material was chromatographed on SiO_2 (hexanes/EtOAc, 3:1, $R_f = 0.30$) to afford a clear oil (1.3 g, 99%) with an enantiomeric excess of 95% (determined by chiral HPLC analysis). IR (film): 3452, 1714 cm^{-1} . $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 5.93 (s, 1H), 5.82-5.67 (m, 1H), 5.19-5.09 (m, 2H), 4.19-4.07 (m, 3H), 2.48-2.36 (m, 1H), 2.32-2.12 (m, 2H), 2.10 (s, 3H), 1.26 (t, $J = 4.17$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 166.7, 160.0, 133.7, 117.33, 114.8, 75.3, 60.2, 39.2, 14.6, 13.3. HPLC analysis (OD column, 95% hexanes: 5% *i*-PrOH, 20 min wait time): peak 1 = 8.4 min (major enantiomer) and peak 2 = 10.4 min (minor enantiomer). $[\alpha]_D^{23} -29.9$ (c 1.03, CHCl_3). HRMS (FAB+) Calcd for $\text{C}_{10}\text{H}_{17}\text{O}_3$ $[\text{MH}]^+ 185.1172$; Found 185.1177.

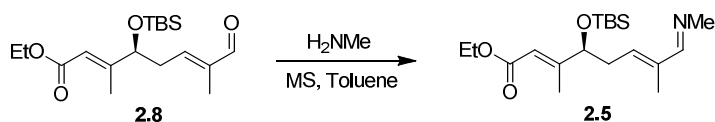


(S,E)-ethyl 4-(tert-butyldimethylsilyloxy)-3-methylhepta-2,6-dienoate (2.7). To a 100 mL round bottom flask equipped with a stir bar was added (S,E)-ethyl 4-hydroxy-3-methylhepta-2,6-dienoate (2.00 g, 10.8 mmol, 1 equiv), *tert*-butyldimethylsilyl chloride (1.80 g, 11.9 mmol, 1.1 equiv), imidazole (1.40 g, 20.5 mmol, 1.9 equiv), 4-dimethylaminopyridine (0.12

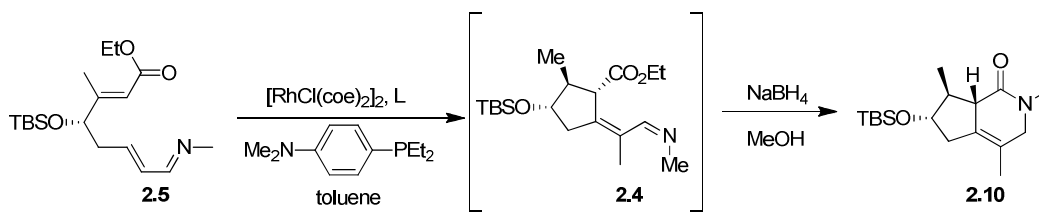
g, 1.0 mmol, 0.1 equiv), and CH₂Cl₂ (40 mL). The white heterogeneous solution was stirred at room temperature for 18 h. To the solution was added water (50 mL) and CH₂Cl₂ (20 mL). The layers were separated. The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried, concentrated, and purified by column chromatography (hexane/EtOAc, 3:1, R_f = 0.82) to yield a clear oil (3.2 g, 99%). IR (film): 1717, 1086 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 5.84 (s, 1H), 5.84-5.65 (m, 1H), 5.06-5.03 (m, 1H), 5.02-5.00 (m, 1H), 4.14 (q, *J* = 6.9 Hz, 2H), 4.06 (t, *J* = 6 Hz, 1H), 2.28 (m, 2H), 2.08 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 166.8, 160.1, 134.4, 117.4, 115.5, 77.3, 59.6, 41.1, 25.9, 18.3, 14.7, 14.4, -4.7, -4.9. [α]_D²³ -3.4 (*c* 1.07, CHCl₃). HRMS (FAB+) Calcd for C₁₆H₃₁O₃Si [MH]⁺ 299.2037; Found 299.2048.



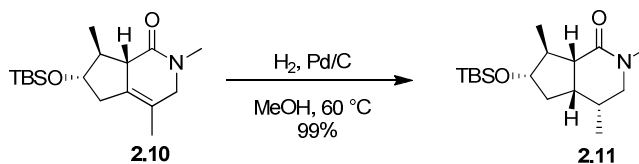
(S,2E,6E)-ethyl 4-(tert-butyldimethylsilyloxy)-3,7-dimethyl-8-oxoocta-2,6-dienoate (2.8). Distilled methacrolein (4.1 mL, 50 mmol, 10 equiv), Grubbs 2nd generation catalyst [benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium] (322 mg, 0.379 mmol, 0.075 equiv), **2.7** (1.5 g, 5.0 mmol, 1 equiv), and CH₂Cl₂ (45 mL) were added to a 100 mL round bottom flask equipped with a stir bar and reflux condenser. The red/brown solution was heated at reflux for 5 h, cooled to room temperature, and concentrated under reduced pressure. The crude material was chromatographed on SiO₂ (hexanes/EtOAc, 10:1, R_f = 0.24) to afford a light brown oil (1.5 g, 88%). IR (film): 1716, 1689, 1217 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 9.36 (s, 1H), 6.45 (t, *J* = 7.0 Hz, 1H), 5.88 (s, 1H), 4.20 (t, *J* = 6.2 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.63-2.51 (m, 2H), 2.09 (s, 3H), 1.70 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 194.8, 166.6, 158.9, 149.4, 140.9, 115.9, 75.8, 59.8, 35.7, 25.7, 18.1, 14.8, 14.3, 9.4, -4.8, -4.7.



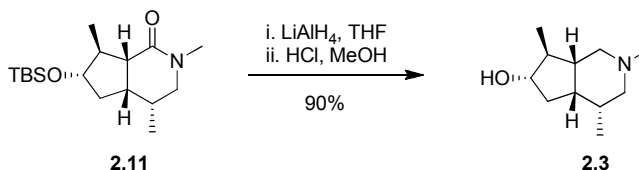
(S,2E,6E)-ethyl-4-(tert-butyldimethylsilyloxy)-3,7-dimethyl-8-(methylimino)octa-2,6-dienoate (2.5). To a 100 mL round bottom flask equipped with a stir bar was combined **2.8** (1.0 g, 2.9 mmol, 1 equiv), methylamine (2M in THF, 8.0 mL, 16 mmol, 5 equiv), molecular sieves (3 g), and toluene (40 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was filtered through Celite and concentrated under reduced pressure to yield an orange oil (1.0 g, 99%). IR (film): 1716, 1652 cm⁻¹. ¹H NMR (400 MHz, C₆D₆): δ 7.68 (s, 1H), 6.19 (s, 1H), 5.73 (t, *J* = 7.2 Hz, 1H), 4.08-3.95 (m, 3H), 3.22 (s, 3H), 2.45-2.25 (m, 2H), 2.23 (s, 3H), 1.99 (s, 3H), 0.97 (t, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), -0.02 (s, 6H). ¹³C{¹H} NMR (100 MHz, C₆D₆): δ 166.5, 165.8, 159.9, 138.8, 135.1, 116.1, 76.9, 59.8, 47.7, 35.4, 25.9, 18.4, 15.0, 14.3, 12.2, -4.7, -4.9. [α]_D²³ +0.7 (*c* 1.10, CHCl₃). HRMS (FAB+) Calcd for C₁₉H₃₆NO₃Si [MH]⁺ 354.2459; Found 354.2454.



(6*S*,7*S*,7*aS*)-6-(tert-butyldimethylsilyloxy)-2,4,7-trimethyl-2,3,5,6,7,7*a*-hexahydrocyclopenta[*c*]pyridin-1-one (2.10). In a nitrogen atmosphere glove box, to a 6 mL vial was added **2.5** (100 mg, 0.283 mmol, 1 equiv), [RhCl(coe)₂]₂ (5.1 mg, 0.0071 mmol, 0.025 equiv), 4-(diethylphosphino)-*N,N*-dimethylaniline¹⁰ (3.0 mg, 0.014 mmol, 0.05 equiv), and toluene (2.8 mL). The orange solution was transferred to a 20 mL Schlenk vessel, removed from the inert atmosphere box, and heated at 45 °C for 7 h. The reaction mixture was concentrated under reduced pressure and dissolved in methanol (4.2 mL). To the solution was added NaBH₄ (41 mg, 1.1 mmol, 3.9 equiv) and the dark solution was stirred at room temperature for 5 h. The solution was then heated at reflux for 40 h. The reaction solution was cooled to room temperature and methanol was removed *in vacuo*. Water was added to the residue and the resulting mixture was extracted three times with CH₂Cl₂. The organic layers were combined, concentrated under reduced pressure, and purified by column chromatography (hexane/EtOAc, 5:1, R_f = 0.15). **2.10** was isolated as a yellow oil (44 mg, 49%). IR (film): 1651 cm⁻¹. ¹H NMR (400 MHz, C₆D₆): δ 3.63-3.49 (m, 1H), 3.43-3.28 (m, 1H), 2.84-2.73 (m, 1H), 2.69 (s, 3H), 2.48-2.33 (m, 1H), 2.28-2.12 (m, 2H), 2.11-1.96 (m, 1H), 1.54 (d, *J* = 5.5 Hz, 3H), 1.27 (s, 3H), 0.97 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ¹³C{¹H} NMR (100 MHz, C₆D₆): δ 169.5, 132.0, 119.9, 79.0, 54.8, 48.6, 45.8, 37.1, 33.5, 26.1, 18.4, 18.3, 16.4, -4.3, -4.6. HRMS (FAB+) Calcd for C₁₇H₃₂NO₂Si [MH]⁺ 310.2197; Found 310.2195.

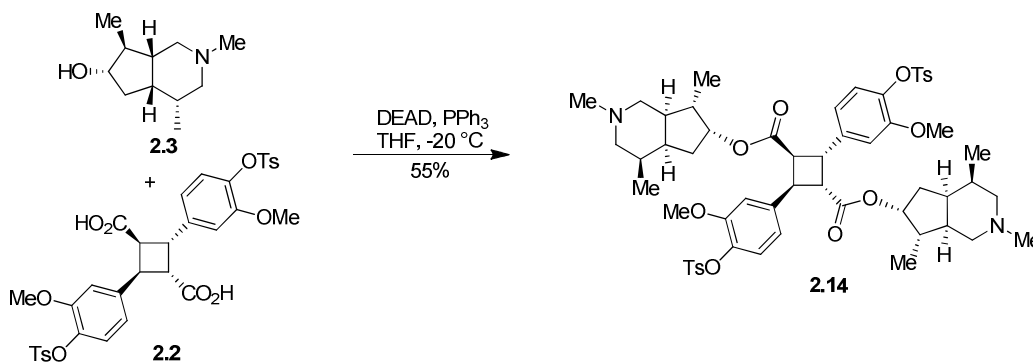


(4*R*,4*aS*,6*S*,7*S*,7*aR*)-6-(tert-butyldimethylsilyloxy)-2,4,7-trimethyl-octahydrocyclopenta[*c*]pyridin-1-one (2.11). To a 50 mL Parr bomb equipped with a stir bar was combined **2.10** (240 mg, 0.776 mmol, 1 equiv), 10% Pd/C (100 mg), and MeOH (10 mL). The bomb was pressurized with H₂ (1000 psi) and heated at 60 °C for 16 h. The reaction mixture was cooled to room temperature, filtered through Celite, and concentrated under reduced pressure to yield a clear oil (241 mg, 99%). IR (film): 1635 cm⁻¹. ¹H NMR (400 MHz, C₆D₆): δ 3.54-3.42 (m, 1H), 2.79-2.62 (m, 1H), 2.72 (s, 3H), 2.31-2.20 (m, 2H), 2.18-2.07 (m, 1H), 1.93-1.77 (m, 1H), 1.70-1.51 (m, 2H), 1.40-1.23 (m, 1H), 1.27 (d, *J* = 9.0 Hz, 3H), 0.97 (s, 9H), 0.52 (d, *J* = 9.3 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H). ¹³C{¹H} NMR (100 MHz, C₆D₆): δ 171.2, 78.8, 50.9, 49.0, 48.4, 37.8, 34.7, 34.0, 20.0, 25.8, 18.2, 18.0, 15.6, -4.7, -4.9. [α]_D²³ +26.6 (c 1.08, CHCl₃). HRMS (FAB+) Calcd for C₁₇H₃₄NO₂Si [MH]⁺ 312.2353; Found 312.2360.



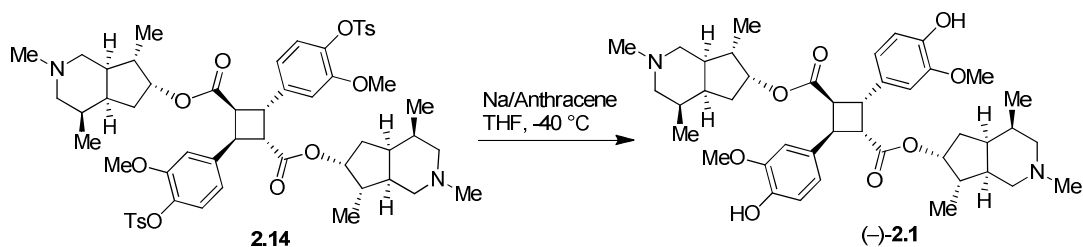
(4R,4aS,6S,7S,7aR)-2,4,7-trimethyl-octahydro-1H-cyclopenta[c]pyridin-6-ol (2.3).

To a 50 mL round bottom flask equipped with a stir bar was added **2.11** (230 mg, 0.74 mmol, 1 equiv) and THF (20 mL). The solution was cooled to 0 °C and LiAlH₄ (110 mg, 2.9 mmol, 4 equiv) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. To the reaction mixture was added saturated sodium bicarbonate (aq) and the layers were separated. The aqueous layer was washed with CH₂Cl₂ and the combined organic layers were concentrated under reduced pressure. The residue was transferred to a 50 mL round bottom flask and dissolved in MeOH (20 mL). 12 N HCl (aq) (0.4 mL, 4.8 mmol, 6.5 equiv) was added to the solution and the resulting mixture was stirred at room temperature for 16 h. MeOH was removed under reduced pressure. To the residue was added saturated sodium bicarbonate (aq) and the resulting mixture was extracted three times with CH₂Cl₂. The combined organic layers were concentrated under reduced pressure and the crude material was chromatographed on SiO₂ (CH₂Cl₂/MeOH/NH₄OH, 100:10:1, R_f = 0.30) to afford a clear oil (122 mg, 90%). IR (film): 3370 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.80 (dt, *J* = 7.17, *J* = 3.1 Hz 1H), 2.90-2.67 (m, 1H), 2.72-2.65 (m, 1H), 2.58-2.50 (m, 1H), 2.28 (s, 3H), 2.19-2.00 (m, 3H), 1.99-1.80 (m, 3H), 1.59-1.47 (m, 2H), 1.03 (d, *J* = 7.56 Hz, 3H), 0.85 (d, *J* = 6.78, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 80.4, 58.0, 57.6, 47.3, 46.2, 45.6, 38.5, 33.0, 30.6, 20.1, 17.7. [α]_D²³ +20.0 (*c* 0.90, CHCl₃). HRMS (FAB+) Calcd for C₁₁H₂₂NO [MH]⁺ 184.1701; Found 184.1699.



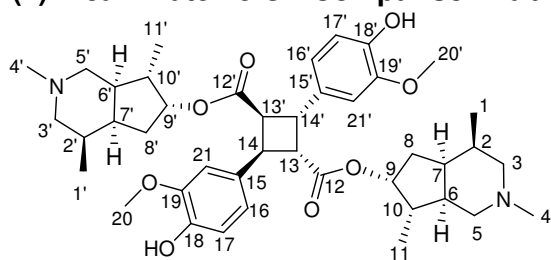
(1R,2S,3S,4R)-bis((4R,4aS,6R,7S,7aR)-2,4,7-trimethyl-octahydro-1H-cyclopenta[c]pyridin-6-yl)2,4-bis(3-methoxy-4-(tosyloxy)phenyl)cyclobutane-1,3-dicarboxylate (2.14). To a 10 mL round bottom flask was combined **2.2** (174 mg, 0.250 mmol, 1 equiv), **2.3** (96 mg, 0.52 mmol, 2.2 equiv), PPh₃ (157 mg, 0.599 mmol, 2.4 equiv), and THF (3 mL). The solution was cooled to -40 °C and diethyl azodicarboxylate (91 mL, 57 mmol, 2.3 equiv) was added dropwise. The reaction solution was transferred to a -20 °C freezer. After 30 h, the reaction solution was quenched with sodium bicarbonate (aq), and the resulting mixture was warmed to room temperature. The mixture was extracted three times with CH₂Cl₂. The combined organic layers were concentrated under reduced pressure and the crude material was chromatographed on SiO₂ (CH₂Cl₂/MeOH/NH₄OH, 500:10:1, R_f = 0.00) then (100:10:1, R_f = 0.36) to afford an amorphous solid (148 mg, 55% based on **2.3**). IR (film): 1723 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.77-7.70 (m, 4H), 7.33-7.27 (m, 4H), 7.08-7.01 (m, 2H), 6.87-6.70 (m, 4H), 4.90-4.78 (m, 2H), 4.40-4.25 (2H), 3.90-3.73 (m, 2H), 3.58 (s, 3H), 3.57 (s, 3H), 2.58-2.48 (m, 2H), 2.48-2.34 (m, 2H), 2.43 (m, 6H), 2.16 (s, 3H), 2.15 (s, 3H), 2.08-1.87 (m, 4H), 1.87-1.73 (m, 4H), 1.62-1.49 (m, 3H), 1.44-1.33 (m, 2H), 1.18-1.11 (m, 1H), 1.04-0.99 (m, 1H), 0.80-0.64 (m, 9H), 0.54 (d, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 171.3, 171.2, 151.7, 145.1, 139.1, 139.0, 137.5, 137.5, 133.8, 129.4, 128.5, 123.9, 119.6, 119.2, 112.5, 112.4, 77.0, 57.7, 57.6, 57.5, 57.3, 55.6, 47.4, 46.8, 46.3, 46.1, 46.0, 41.7, 41.3, 40.5, 40.3, 37.5, 30.6, 30.0,

29.3, 21.7, 17.3, 17.1, 14.8, 14.5. $[\alpha]_D^{23} -9.8$ (c 1.62, CHCl_3). HRMS (ESI-TOF) Calcd for $\text{C}_{56}\text{H}_{71}\text{N}_2\text{O}_{12}\text{S}_2$ $[\text{MH}]^+$ 1027.4448; Found 1027.4445.



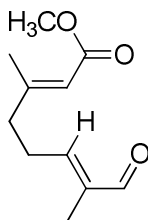
(-)-Invarvillateine (-)-2.1. To a 10 mL round bottom flask was combined sodium metal (21 mg, 0.91 mmol, 1.2 equiv), anthracene (133 mg, 0.747 mmol, 1 equiv), and THF (1.5 mL). The mixture was stirred for 1 h during which time the solution turned blue. The Na/anthracene solution (0.30 mL, 0.15 mmol, 3 equiv), was added to a 10 mL round bottom flask containing **2.14** (49.7 mg, 0.0484 mmol, 1 equiv) in THF (4 mL) at -40 °C. The solution was stirred at -40 °C for 3 h, and immediately quenched with saturated ammonium chloride. Ethyl acetate was added, and the layers were separated. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were concentrated under reduced pressure and the crude material was chromatographed on SiO_2 ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$, 500:10:1 $R_f = 0.00$) then (100:10:1, $R_f = 0.20$) to afford a white solid (30 mg, 86%). The solid was recrystallized from MeOH to give colorless crystals: mp $216\text{--}217$ °C (lit. 217 °C)¹⁷; IR (KBr): 3386, 2955, 1720, 1517 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 6.89–6.71 (m, 6H), 4.95–4.80 (m, 2H), 4.42–4.26 (m, 2H), 3.95–3.75 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 2.61–2.50 (m, 2H), 2.49–2.39 (m, 2H), 2.32–2.05 (m, 2H), 2.18 (s, 6H), 2.03–1.88 (m, 4H), 1.87–1.77 (m, 3H), 1.77–1.64 (m, 2H), 1.64–1.49 (m, 3H), 1.47–1.35 (m, 2H), 1.10–0.99 (m, 1H), 0.80 (d, $J = 7.33$ Hz, 3H), 0.76 (d, $J = 6.82$ Hz, 3H), 0.71 (d, $J = 6.32$ Hz, 3H), 0.60 (d, $J = 7.07$ Hz, 3H), 0.56–0.48 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 172.0, 171.8, 146.7, 146.6, 145.2, 145.0, 130.7, 130.6, 120.4, 119.9, 114.5, 110.8, 110.7, 77.4, 76.6, 57.6, 57.5, 57.4, 57.2, 55.8, 55.7, 47.9, 47.3, 46.2, 46.2, 46.0, 45.9, 41.8, 41.2, 40.4, 37.4, 37.3, 30.4, 29.8, 29.2, 17.1, 16.9, 15.1, 14.7. $[\alpha]_D^{23} -10.1$ (c 1.40, CHCl_3). HRMS (ESI-TOF) Calcd for $\text{C}_{42}\text{H}_{59}\text{N}_2\text{O}_8$ $[\text{MH}]^+$ 719.4271; Found 719.4240.

(-)-Incarvillateine C¹³ Comparison Table

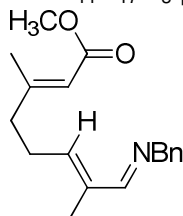


	Synthetic 100 MHz	Reported 125 MHz ^{1a}
C-12, 12'	172.0	171.9
	171.8	171.7
C-18, 18'	146.7	146.9
	146.6	146.8
C-19, 19'	145.2	145.5
	145.0	145.3
C-15, 15'	130.7	130.4
	130.6	130.2
C-16, 16'	120.4	120.3
	119.9	119.8
C-17, 17'	114.5	114.7
C-21, 21'	110.8	110.9
	110.7	110.8
C-9, 9'	77.4	77.2
	76.6	76.5
C-3, 3'	57.6	57.4
	57.5	57.3
C-5, 5'	57.4	57.1
	57.2	57.0
C-20, 20'	55.8	55.7
	55.7	55.6
C-13, 13'	47.9	47.8
	47.3	47.2
C-4, 4'	46.2	46.0
	46.2	45.9
C-6, 6'	46.0	45.7
	45.9	45.6
C-14, 14'	41.8	41.7
	41.2	40.3
C-10, 10'	40.4	40.1
C-7, 7'	37.4	37.3
	37.3	37.2
C-2, 2'	30.4	30.1
C-8, 8'	29.8	29.6
	29.2	29.1
C-1, 1'	17.1	17.0
	16.9	16.8
C-11, 11'	15.1	14.8
	14.7	14.4

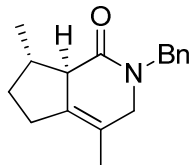
Other Enantioselective Cyclizations



(2E,6E)-Methyl 3,7-dimethyl-8-oxoocta-2,6-dienoate (2.17). Aldehyde **2.12** was prepared according to literature precedent¹⁸ to afford a yellow oil in 25% yield. IR (film): 1715, 1683, 1435, 1148 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 9.38 (s, 1H), 6.41 (t, $J = 7.2$ Hz, 1H), 5.69 (s, 1H), 3.69 (s, 3H), 2.60-2.5 (m, 2H), 2.34 (t, $J = 7.8$ Hz, 2H), 2.19 (s, 3H), 1.75 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 195.14, 167.07, 158.01, 152.34, 140.2, 116.34, 51.18, 39.27, 26.82, 18.88, 9.49. HRMS (FAB+) Calcd for $\text{C}_{11}\text{H}_{17}\text{O}_3$ $[\text{MH}]^+$ 197.1172; Found 197.1174.



(2E,6E)-Methyl 8-(benzylimino)-3,7-dimethylocta-2,6-dienoate (2.18). In a nitrogen-filled inert atmosphere box, to a 20 mL vial containing aldehyde **2.12** (217 mg, 1.11 mmol) was added benzene (3.7 mL), 3Å molecular sieves (1.84 g) and freshly distilled benzyl amine (1.18 g, 1.11 mmol). The vial was capped, and the reaction mixture was stirred for 16 h at room temperature. The mixture was filtered to remove molecular sieves, and the resulting solution was concentrated *in vacuo* to yield a yellow oil (311 mg, 99%). IR (film): 1716, 1645, 1628, 1222.93, 1146 cm^{-1} . ^1H NMR (300 MHz, C_6D_6): δ 7.68 (s, 1H), 7.42-7.08 (m, 5H), 5.76 (s, 1H), 5.47 (t, $J = 6.6$ Hz, 1H), 4.56 (s, 2H), 3.41 (s, 3H), 2.28 (s, 3H), 2.05-1.96 (m, 2H), 1.91 (s, 3H), 1.81 (t, $J = 7.8$ Hz, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6): δ 166.40, 165.08, 158.43, 140.33, 139.02, 137.23, 128.36, 127.99, 126.71, 115.91, 64.40, 50.25, 39.49, 25.93, 18.35, 11.59. Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_2\text{N}$ $[\text{MH}]^+$ 286.1802; Found 286.1813.



(7S,7aR)-2-benzyl-4,7-dimethyl-2,3,5,6,7,7a-hexahydro-1H-cyclopenta[c]pyridin-1-one (2.19). In an nitrogen-filled inert atmosphere box to a 6 mL vial was added **2.6** (85 mg, 0.30 mmol), $[\text{RhCl}(\text{coe})_2]_2$ (21 mg, 0.030 mmol), 4-(dimethylphosphino)-N,N-dimethylaniline (16 mg, 0.090 mmol), and toluene (3 mL). The orange solution was transferred to a Schlenk vessel which was taken out of the glove box, and heated to 75 $^\circ\text{C}$ for 1 h. The solution was then directly concentrated *in vacuo*. Methanol (1.2 mL) was added to the residue and the solution was cooled to 0 $^\circ\text{C}$. NaBH_4 (13.6 mg, 0.36 mmol) was added in one portion and the resulting solution was stirred at 0 $^\circ\text{C}$ for 30 min and at room temperature for 1 h. The solution was then concentrated and washed with water (2 mL). The solution was extracted four times with 1 mL of ethyl acetate. The combined organic layers were concentrated, dissolved in methanol, and stirred for 24 h at room temperature. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to yield an oil (15.0 mg, 18%). IR (film): 1777, 1647, 1159, 697 cm^{-1} . ^1H NMR (400 MHz, C_6D_6): δ 7.34-7.10 (m, 5H), 4.59-4.40 (m, 2H), 3.40-3.35 (m, 1H), 3.01-2.97 (m, 1H), 2.24-2.17 (m, 2H), 2.02-1.93 (m, 2H), 1.75-1.68 (m,

1H), 1.54 (d, $J = 6$ Hz, 3H), 1.23 (s, 3H), 1.16-1.06 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6): δ 172.25, 137.77, 135.96, 129.07, 128.39, 127.98, 127.88, 118.97, 53.06, 51.85, 34.36, 33.90, 26.81, 20.87, 16.28. Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}$ $[\text{MH}]^+$ 256.1696; Found 256.1693. HPLC (Chiralcel AS-H column, 5% iPrOH/hexanes, 1mL/min): Peak 1, 5.72 min; Peak 2, 6.24 min; 0% ee

References

- (1) (a) Chi, Y.; Yan, W.; Li, J. *Phytochemistry* **1990**, *29*, 2376-2378; (b) Chi, Y.-M.; Nakamura, M.; Yoshizawa, T.; Zhao, X.-Y.; Yan, W.-M.; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. *Biol. Pharm. Bull.* **2005**, *28*, 1989-1991.
- (2) Ichikawa, M.; Takahashi, M.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2004**, *126*, 16553-16558.
- (3) (a) Cid, M. M.; Pombo-Villar, E. *Helvetica Chimica Acta* **1993**, *76*, 1591-607; (b) Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, *117*, 5757-5762; (c) Wroblewski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475-5481.
- (4) (a) Jun, C.-H.; Lee, J. H. *Pure Appl. Chem.* **2004**, *76*, 577-587; (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826-834; (c) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 6775-6781.
- (5) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1-16.
- (6) (a) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485-2490; (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417-424; (c) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849-2852; (d) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496-13497; (e) Wehn, P. M.; DuBois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950-12951; (f) Wiedemann, S. H.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2006**, *71*, 1969-1976; (g) Wilson, R. M.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2006**, *8*, 1745-1747.
- (7) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604-5605.
- (8) Keck, G. E.; Welch, D. S.; Vivian, P. K. *Org. Lett.* **2006**, *8*, 3667-3670.
- (9) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784; (b) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155-13164.
- (10) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645-3651.
- (11) Alternative hydroxyl protecting groups such as a benzyl ether were also examined, but resulted in decreases in both the yield and diastereoselectivity of the Rh-catalyzed alkylation.
- (12) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763-2772.
- (13) Suzuki, H.; Unemoto, M.; Hagiwara, M.; Ohyama, T.; Yokoyama, Y.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1717-1724.
- (14) (a) Harada, H.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772-6779; (b) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192-7193.
- (15) Facchetti, S.; Cavallini, I.; Funaioli, T.; Marchetti, F.; Iuliano, A. *Organometallics* **2009**, *28*, 4150-4158.
- (16) Van der Ent, A.; Onderdelinden, A. L. *Inorg. Syn.* **1973**, *14*, 92-95.
- (17) Chi, Y.-M.; Zhao, X.-Y.; Yoshizawa, T.; Nakamura, M.; Yan, W.-M.; Hashimoto, F.; Chi, Y.-C.; Kinjo, J.; Nohara, T. *Chem. Pharm. Bull.* **2005**, *53*, 1472-1474.
- (18) Gramatica, P.; Manitto, P.; Monti, D.; Speranza, G. *Tetrahedron* **1987**, *43*, 4481.

Chapter 3. Rhodium Catalyzed Enantioselective Cylization of Substituted Imidazoles via C–H Bond Activation

*The enantioselective intramolecular alkylation of substituted imidazoles with enantiomeric excesses up to 98% has been accomplished by rhodium catalyzed C–H bond functionalization with (S,S',R,R')TangPhos as the chiral ligand. A majority of this work has been published in a communication (Tsai, A. S.; Wilson, B. M.; Harada, H.; Bergman, R. G.; Ellman, J. A. Chem. Commun. **2009**, 3910-3912.)*

Authorship

The work on the enantioselective cyclization of imidazoles was conducted in collaboration with Rebecca Wilson and Hitoshi Harada.

Introduction

Carbon-hydrogen and carbon-carbon bonds represent the two most common linkages in organic chemistry. Thus, the formation of C–C bonds via catalytic activation of C–H bonds has the potential to be highly general, practical and atom economical. Great progress has been achieved in this area from fundamental study to chemical application.¹ However, only a limited number of catalytic enantioselective transformations have been reported to date. The two most common methods for asymmetric C–H functionalization have been via chelation-assistance² or carbenoid insertion.^{3,4} Our group previously disclosed a unique C-2 functionalization of benzimidazoles that proceeds through an N-heterocyclic-carbene intermediate obtained via C–H activation.⁵ Herein, we disclose a catalytic asymmetric benzimidazole functionalization that provides remarkably high enantioselectivities (up to 98%) despite the elevated temperatures (135 °C) of the reaction.

Results and Discussion

Investigation into the catalytic asymmetric alkylation of imidazoles began with *N*-methallyl benzimidazole **3.1** as the model substrate. Reaction parameters were adapted from previously reported conditions for the alkylation of this substrate with achiral catalysts.^{5a} With [RhCl(coe)₂]₂ (coe = cis-cyclooctene) as the rhodium pre-catalyst, a variety of chiral ligands were screened to explore reactivity and enantioselectivity.

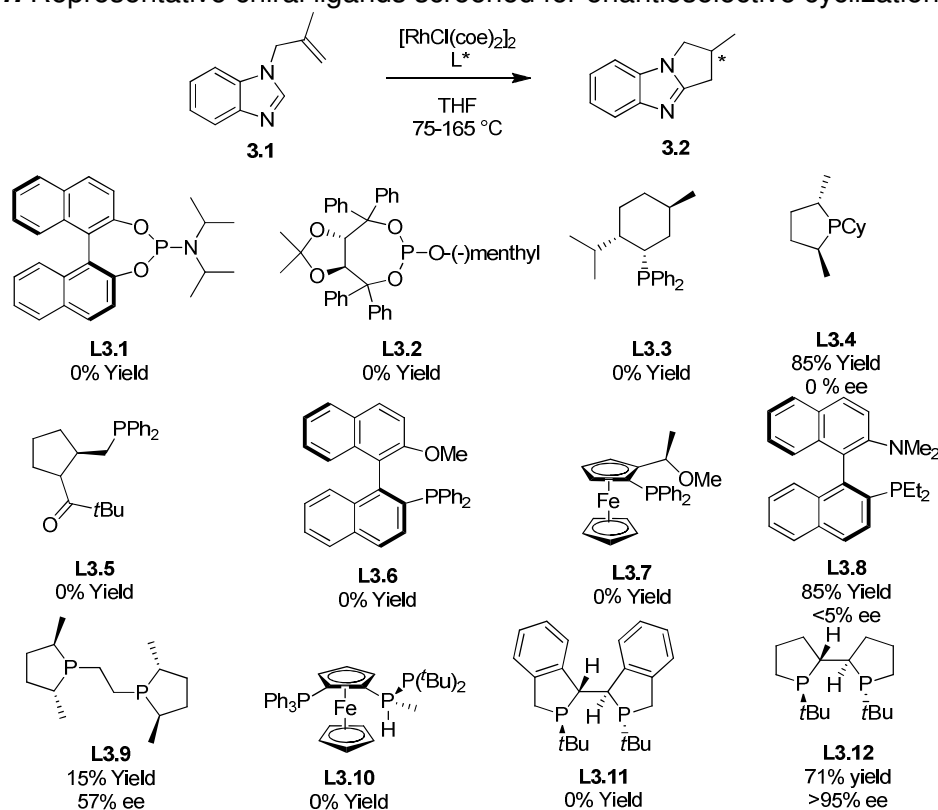
Results obtained using a representative subset of screened chiral ligands are summarized in Scheme 3.1. Monodentate ligands were initially explored (**L3.1-L3.4**) because only this type of ligand architecture provided successful reactions in past alkylation studies. Phosphoramidites and phosphites (**L3.1-L3.2**), which were successful in asymmetric imine directed alkylations, were not active for this system.^{2b, 2d} Previous work into the alkylations of imidazoles established that electron rich phosphines were required.⁵ Indeed, trialkyl phosphine **L3.4** provided the desired product in good yield, but in racemic form.

Given the limited number of chiral, monodentate electron rich phosphines that are commercially available, hemi-labile bidentate ligands were explored (**L3.5-L3.8**). Though from past studies, bidentate ligands consistently inhibited the reaction most likely by blocking a necessary metal coordination site,^{5d} we hoped that the weaker coordination of the nitrogen or oxygen heteroatom on the hemilabile ligands would allow partial dissociation. This hypothesis seemed to be operative as some ligands in this class (**L3.8**) did generate the cyclized product, albeit in nearly racemic form. A more sterically demanding di-isopropyl analogue of **L3.8** also showed activity but no improvement in enantioselectivity.

Although we were encouraged by the reactivity of some hemilabile ligands, the chiral induction was still deficient and therefore more rigid chiral bidentate phosphines were explored in hopes of improving the enantioselectivity. Indeed, **L3.9**, the bidentate analogue of **L3.4**, did provide the cyclized product with moderate enantioselectivity. However, the bidentate ligand architecture suppressed the reaction, possibly by occupying a metal coordination site necessary for the reaction. Next, the electron rich diphosphine **L3.12** ((*S,S'*,*R,R'*)-TangPhos) was evaluated.⁶ Not only was high reaction conversion observed, but exceptional enantioselectivity was also achieved, which is notable considering the elevated reaction temperature (135 °C). Interestingly, the close analogue (*S,S'*,*R,R'*)-DuanPhos (**L3.11**) showed no activity for the

alkylation of **3.1**. Furthermore, a less bulky isopropyl analogue of **L3.12** resulted in only trace reaction.

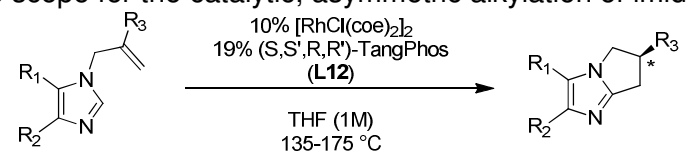
Scheme 3.1. Representative chiral ligands screened for enantioselective cyclization of **3.1**

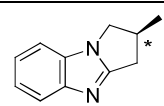
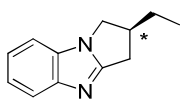
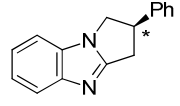
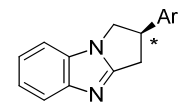
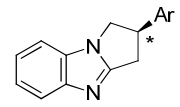
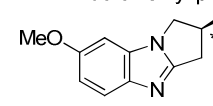
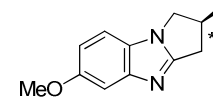
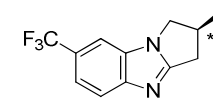
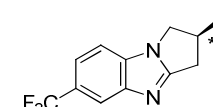
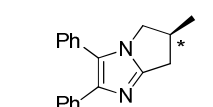


Considering the results from the ligand screen, electron rich phosphines seem to be necessary for activity though it is not the only requirement. Partial ligand dissociation to form a monodentate diphosphine may be occurring with **L3.12** to allow for the formation of an open coordination site necessary to provide catalytic activity.⁷ This process may be slow for **L3.9** and inaccessible for **L3.11** or the **L3.12** analogue. Moreover, the factors that determine the degree of chiral induction are unclear. Of the ligands that were evaluated, only TangPhos incorporated all of the characteristics necessary for a successful and highly enantioselective transformation.

With the identification of TangPhos as an active and selective ligand, reaction optimization was performed to establish THF as the optimal solvent and a slight excess of rhodium to Tangphos as the optimal stoichiometry (Table 3.1, entry 1). With these optimized conditions identified, substrate scope was next explored (Table 3.1). The reaction conditions accommodated the alkylation of isomerizable and arylsubstrates (entries 2-3). The electronics of the N-allyl tether and benzimidazole were also examined (entries 4-9). Both electron-poor and rich substrates required higher temperatures for satisfactory reaction rates, leading to an erosion of enantioselectivity. Finally, the 4,5-diphenyl substituted imidazole could also be alkylated with high enantioselectivities (entry 10), although the corresponding 4,5-dimethyl imidazole was found to be inactive (not shown). Yields were high for most substrates examined. Starting material and products arising from hydrogenation of the starting alkene comprised the remaining mass balance. Alkylation of **3.1** could also be successfully carried out with 2.5% $[\text{RhCl}(\text{coe})_2]_2$ and 4.9% TangPhos. Higher temperature (175 °C) is required for a convenient rate. The same yields by NMR and similar enantioselectivities (90%) were obtained in 36 h under these conditions.

Table 3.1. Substrate scope for the catalytic, asymmetric alkylation of imidazoles^a



Entry	Product	Temp (°C)	Time (h)	Yield (%) ^{b,c}	ee (%) ^d
1		135	20	89	98
2		135	60	71	90
3		135	46	91	97
4	 Ar = 4-methoxy-phenyl	175	24	83	87
5	 Ar = 4-trifluoromethyl-phenyl	175	24	87	79
6		175	36	89	71
7		175	24	92	81
8		175	24	83	53
9		175	24	81	71
10		135	98	90	95

^a Absolute stereochemistry of the HCl salt of **3.2** was determined by X-ray crystallography (see appendix). Remaining products are assigned by analogy ^b Reactions were carried out on 0.15 mmol scale. ^c Isolated yield after chromatography. ^d Determined by chiral HPLC analysis.

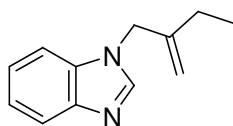
Conclusion

In summary, a method for the catalytic asymmetric cyclization of substituted imidazoles via C–H bond activation has been achieved. A ligand screen identified TangPhos (**L3.12**) as a highly active ligand for the asymmetric cyclization of N-allylic imidazoles to yield products with moderate to high enantioselectivities even at elevated temperatures.

Experimental:

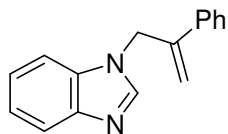
General Procedures. All organic reactions were performed under an atmosphere of N₂ in flame- or oven-dried glassware unless otherwise stated. All preparations for all C–H activation experiments were carried out in a N₂-filled Vacuum Atmospheres inert atmosphere box (glovebox). Thin-layer chromatography was performed on Merck 60 F₂₅₄ 250-nm silica gel plates. Visualization of the developed chromatograms was performed by fluorescence quenching. Flash chromatography was carried out using Merck 60 230-240 mesh silica gel or a Biotage SP Flash Purification System (Biotage No. SP1-B1A). IR spectra were recorded on a Thermo Nicolet Avatar 370 fitted with a single bounce ZnSe ATR plate; stretching frequencies are reported in cm⁻¹ and the data shown include only major absorptions. ¹H, and ¹³C NMR measurements were conducted using a Bruker AV-300, AVB-400, or DRX-500 spectrometer as noted at room temperature. NMR chemical shifts are reported in ppm and referenced to residual protonated solvent or added internal standard, and coupling constants are reported in Hz. High resolution mass spectra (HRMS) and elemental analyses were performed by the University of California, Berkeley Micro-Mass Facility using ProSpec equipped with an EI source (EI), ZAB equipped with a FAB (FAB), or LTQ Orbitrap (ESI). X-ray crystal structures were obtained by the University of California, Berkeley X-ray Crystallography Facility. Chiral HPLC analyses were performed on a Shimadzu VP Series with a Chiralcel AD-H column (250 mm x 4.6 mm) or Chiralcel AS-H (250 mm x 4.6 mm) using a flow rate of 1 mL/min. A Perkin-Elmer 241 polarimeter with a sodium lamp was used to determine specific rotations and concentrations are reported in g/dL. Melting points of the compounds obtained as solids were measured with a Laboratory Devices Inc. MEL-TEMP 3.0.

Materials. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was obtained from a Seca Solvent System by Glass Contour (solvents were passed through activated alumina columns under nitrogen pressure). (1*S*,1'*S*',2*R*,2'*R*')-1,1'-di-*tert*-butyl-(2,2')-diphospholane ((*S*,*S*',*R*,*R*')-Tangphos) was purchased from Sigma-Aldrich. [RhCl(coe)₂]₂ (also available from Strem Chemical) was prepared according to referenced literature procedure.⁸ Tetrahydrofuran-*d*₈, dioxane-*d*₈, toluene-*d*₈ were dried over sodium/benzophenone ketyl and distilled using vacuum transfer procedures. All liquid reagents and deuterated solvents were thoroughly degassed using three freeze-pump-thaw cycles prior to transfer into the glovebox. Racemic samples of the cyclized products for chiral HPLC analysis were prepared by using PCy₃ as a ligand instead of (*S*,*S*',*R*,*R*')-Tangphos.

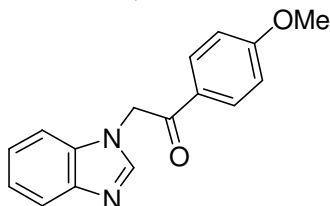


1-(2-methylenebutyl)-1H-benzimidazole. To an ice-water cooled solution of 1*H*-benzimidazole (132 mg, 1.13 mmol) in THF (5 mL) was added NaH (60%/mineral oil) (81 mg, 2.0 mmol). The mixture was stirred under the same conditions for 15 minutes. 3-bromo-2-ethylpropene (200 mg, 1.35 mmol) was added as a solution in THF (2mL) and the mixture was stirred at rt for 18 h. The reaction was quenched with sat. NaHCO₃ (aq), and the resulting mixture was extracted three times with ethyl acetate. The organic layers were combined, dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (200:10:1 CH₂Cl₂: MeOH: NH₄OH) to give the title compound as a clear oil (126 mg, 60% yield). ; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1493, 1457; ¹H NMR (400 MHz, CDCl₃): δ 7.88 (s, 1H), 7.86-7.81 (m, 1H), 7.39-7.32 (m, 1H), 7.31-7.23 (m, 2H), 4.99 (s, 1H), 4.81 (s, 1H), 4.71 (s, 2H), 1.99 (q, 2H, *J* = 7.4 Hz), 1.06 (t, 3H, *J* = 7.4 Hz); ¹³C {¹H } NMR (100 MHz, CDCl₃): δ 145.3,

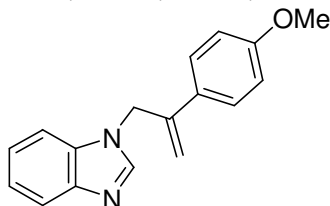
144.1, 143.7, 134.3, 123.2, 122.4, 120.6, 112.0, 110.3, 50.3, 26.4, 12.1; HRMS (FAB+) Calcd for C₁₂H₁₅N₂ [MH]⁺ 187.1235; Found 187.1233.



1-(2-Phenylallyl)-1H-benzimidazole. To a ice-water cooled solution of 1H-benzimidazole (249 mg, 2.11 mmol) in THF (10 mL) was added NaH (60%/mineral oil) (128 mg, 3.20 mmol). The mixture was stirred under the same conditions for 15 minutes. (1-bromomethylvinyl)benzene (389 mg, 1.98 mmol) was added as a solution in THF (3 mL), and the mixture was stirred at rt for 18 h. The reaction was quenched with sat. NaHCO₃ (aq), and the resulting mixture was extracted three times with ethyl acetate. The organic layers were combined, dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (0-70% gradient of ethyl acetate in hexanes) followed by washing with diethyl ether to give the title compound as a white solid (326 mg, 66% yield). mp 126-127 °C; ν_{max} (film)/cm⁻¹ 1490; ¹H NMR (400 MHz, CDCl₃): δ 7.90 (s, 1H), 7.84-7.77 (m, 1H), 7.45-7.26 (m, 8H), 5.55 (s, 1H), 5.18 (s, 2H), 4.98 (s, 1H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 143.8, 143.3, 142.2, 137.9, 133.9, 128.7, 128.5, 125.9, 123.0, 122.2, 120.4, 115.3, 110.0, 48.7; HRMS (EI): Calcd for C₁₆H₁₄N₂ [M]⁺ 234.1157; Found 234.1162.

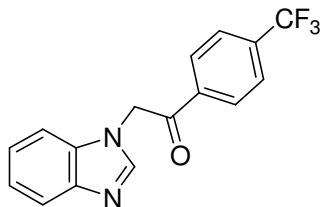


2-(1H-benzo[d]imidazol-1-yl)-1-(4-methoxyphenyl)ethanone. To a 25 mL round bottom flask was added benzimidazole (890 mg, 7.54 mmol), 2-bromo-1-(4-methoxyphenyl)ethanone (695 mg, 3.05 mmol), and DMF (4 mL). The solution was stirred at rt for 16 h during which time the solution became cloudy. DMF was removed via high-vac at 0.05 mmHg, and the resulting crude solid was suspended in CH₂Cl₂ and washed with sat. NaHCO₃ (aq). The layers were separated and the aqueous layer was washed three times with CH₂Cl₂. The organic layers were combined, dried over anhydrous MgSO₄, concentrated, and purified by silica column chromatography (200:10:1 CH₂Cl₂: MeOH: NH₄OH) to yield a white solid (350 mg, 43% yield). Physical data were consistent with the previously reported characterization.⁹ ¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, 2H, *J* = 8.8 Hz) 7.97 (s, 1H), 7.92-7.83 (m, 1H), 7.37-7.24 (m, 3H), 7.05 (d, 2H, *J* = 8.8 Hz), 5.55 (d, 2H), 3.95 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 189.9, 164.6, 144.0, 143.5, 134.5, 130.5, 127.3, 123.3, 122.4, 120.4, 114.4, 109.5, 55.7, 50.1;

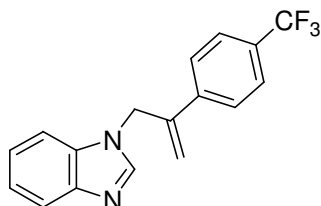


1-(2-(4-methoxyphenyl)allyl)-1H-benzo[d]imidazole. In a 25 mL Schlenk flask equipped with a stir bar was combined 2-(1H-benzo[d]imidazol-1-yl)-1-(4-methoxyphenyl)ethanone (280 mg, 1.05 mmol), methyl triphenylphosphonium bromide (756 mg, 2.12 mmol), and K₂CO₃ (336 mg, 2.43 mmol), and THF (10 mL). The suspension was heated at 135 °C for 24 h. The reaction vessel was cooled to rt, filtered through celite, and the celite was washed with THF. The filtrate was concentrated and purified by silica column chromatography (95:5 methyl *tert*-butyl ether: triethylamine) to yield a white solid (159 mg, 57%). mp 121-

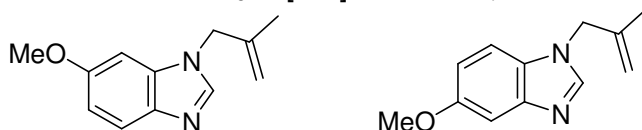
123 °C; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1605, 1513; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.89 (s, 1H), 7.84-7.76 (m, 1H), 7.45-7.38 (m, 1H), 7.37-7.22 (m, 4H), 6.86 (d, 2H, $J = 8.9$ Hz), 5.47 (s, 1H), 5.13 (s, 2H), 4.91 (s, 1H), 3.79 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 159.8, 143.9, 143.4, 141.5, 134.0, 130.3, 127.1, 123.0, 122.2, 120.4, 114.1, 113.4, 110.0, 55.3, 48.8; HRMS (FAB+) Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}$ $[\text{MH}]^+$ 265.1341; Found 265.1339.



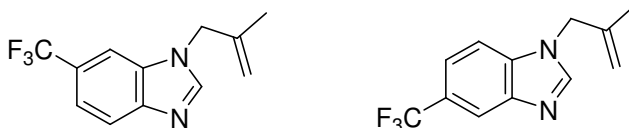
2-(1H-benzo[d]imidazol-1-yl)-1-(4-(trifluoromethyl)phenyl)ethanone. To a 25 mL round bottom flask was combined benzimidazole (231 mg, 1.96 mmol), 2-bromo-1-(4-(trifluoromethyl)phenyl)ethanone (200 mg, 0.75 mmol), and DMF (1 mL). The solution was stirred at rt for 16 h during which time it became cloudy. DMF was removed via high-vac at 0.05 mmHg, and the resulting crude solid was suspended in CH_2Cl_2 and washed with sat. NaHCO_3 (aq). The layers were separated and the aqueous layer was washed three times with CH_2Cl_2 . The organic layers were combined, dried over anhydrous MgSO_4 , concentrated, and purified by silica column chromatography (200:10:1 CH_2Cl_2 : MeOH: NH_4OH) to yield a white solid (200 mg, 87% yield). mp 169-172 °C; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1706, 1323; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.81 (d, 2H, $J = 8.1$ Hz), 7.98 (s, 1H), 7.93-7.82 (m, 3H) 7.40-7.22 (m, 3H), 5.64 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 8.81 (d, 2H, $J = 8.1$ Hz), 7.98 (s, 1H), 7.93-7.82 (m, 3H), 7.40-7.22 (m, 3H), 5.64 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 190.6, 143.6, 143.5, 135.9 (q, $J_{\text{C-F}} = 31.5$ Hz), 136.8, 134.1, 128.5, 126.3 (q, $J_{\text{C-F}} = 3.7$ Hz), 123.5, 123.4 (q, $J_{\text{C-F}} = 271.5$ Hz), 122.6, 120.7, 109.2, 50.7; $^{19}\text{F NMR}$ (375 Mhz, CDCl_3): δ -62.5; HRMS (FAB+) Calcd for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{N}_2\text{O}$ $[\text{MH}]^+$ 305.0896; Found 305.0899.



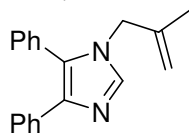
1-(2-(4-(trifluoromethyl)phenyl)allyl)-1H-benzo[d]imidazole. To a 25 mL Schlenk flask equipped with a stir bar was combined 2-(1H-benzo[d]imidazol-1-yl)-1-(4-(trifluoromethyl)ethanone (450 mg, 1.47 mmol), methyl triphenylphosphonium bromide (1.06 g, 2.96 mmol), K_2CO_3 (470 mg, 3.40 mmol), and THF (15 mL). The suspension was heated at 135 °C for 24 h. The reaction vessel was cooled to rt, the reaction mixture was filtered through celite, and the celite pad was washed with THF. The filtrate was concentrated, and the crude product purified by activity III neutral alumina chromatography (2:1 hex: EtOAc) to yield a white solid (190 mg, 42%). mp 119-121 °C; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1498, 1325; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.91 (s, 1H), 7.88-7.81 (m, 1H), 7.63 (d, 2H, $J = 8.1$ Hz), 7.52 (d, 2H, $J = 8.1$ Hz), 7.45-7.49 (m, 1H), 7.38-7.29 (m, 2H), 5.64 (s, 1H), 5.19 (s, 2H), 5.14 (s, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 143.9, 143.2, 141.5, 141.4, 133.8, 130.5, (q, $J_{\text{C-F}} = 32.9$ Hz), 126.3, 125.8 (q, $J_{\text{C-F}} = 3.7$ Hz), 123.9 (q, $J_{\text{C-F}} = 271.5$ Hz), 123.3, 122.4, 120.6, 117.4, 109.8, 48.6; $^{19}\text{F NMR}$ (375 Mhz, CDCl_3): δ -61.5; HRMS (FAB+) Calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_2$ $[\text{MH}]^+$ 303.1109; Found 303.1111.



6-methoxy-1-(2-methylallyl)-1H-benzo[d]imidazole and **5-methoxy-1-(2-methylallyl)-1H-benzo[d]imidazole**. To an ice-water cooled solution of 6-methoxy-1H-benzo[d]imidazole (300 mg, 2.0 mmol) in THF (5 mL) was added NaH (60%/mineral oil) (136 mg, 3.40 mmol). The mixture was stirred under the same conditions for 15 minutes. 3-Bromo-2-methylprop-1-ene (300 mg, 2.24 mmol) was added, and the mixture was stirred at rt for 18 h. The reaction was quenched with sat. NaHCO₃ (aq), and the resulting mixture was extracted three times with ethyl acetate. The organic layers were combined, dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (10:1 *t*-butyl methyl ether: triethylamine) to obtain two clear oils. **Less polar product (6-methoxy-1-(2-methylallyl)-1H-benzo[d]imidazole)**: 100 mg (24% yield); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1491, 1438, 1224; ¹H NMR (300 MHz, CDCl₃): δ 7.76 (s, 1H), 7.66 (d, 1H, *J* = 8.6 Hz), 6.90 (dd, 1H, *J* = 8.6, 2.0 Hz), 6.78 (d, 1H, *J* = 2.0 Hz), 4.97 (s, 1H), 4.79 (s, 1H), 3.83 (s, 2H), 3.83 (s, 3H), 1.69 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 157.0, 142.9, 139.7, 138.6, 134.9, 121.0, 114.1, 111.6, 93.9, 56.1, 51.3, 20.1; HRMS (FAB+) Calcd for C₁₂H₁₅N₂O [MH]⁺ 203.1184; Found 203.1185. **More polar product (5-methoxy-1-(2-methylallyl)-1H-benzo[d]imidazole)**: 60 mg (14%); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1492, 1430, 1224; ¹H NMR (300 MHz, CDCl₃): δ 7.81 (s, 1H), 7.26 (d, 1H, *J* = 2.3 Hz), 7.22 (d, 1H, *J* = 8.9 Hz), 6.91 (dd, 1H, *J* = 8.9, 2.3 Hz), 4.97 (s, 1H), 4.81 (s, 1H), 4.53 (s, 2H), 3.84 (s, 3H), 1.67 (s, 3H); ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 156.4, 145.0, 143.8, 139.9, 128.9, 114.2, 113.5, 110.7, 102.6, 56.0, 51.53, 20.0; HRMS (FAB+) Calcd for C₁₂H₁₅N₂O [MH]⁺ 203.1184; Found 203.1187.



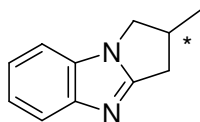
1-(2-methylallyl)-6-(trifluoromethyl)-1H-benzo[d]imidazole and **1-(2-methylallyl)-5-(trifluoromethyl)-1H-benzo[d]imidazole**. To an ice-water cooled solution of 6-(trifluoromethyl)-1H-benzo[d]imidazole¹⁰ (250 mg, 1.34 mmol) in THF (5 mL) was added NaH (60%/mineral oil) (91 mg, 2.28 mmol). The mixture was stirred under the same conditions for 15 minutes. 3-Bromo-2-methylprop-1-ene (216 mg, 1.61 mmol) was added, and the mixture was stirred at rt for 18 h. The reaction was quenched with sat. NaHCO₃ (aq), and the resulting mixture was extracted three times with ethyl acetate. The organic layers were combined, dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (200:10:1 CH₂Cl₂: MeOH: NH₄OH) to obtain two white solids. **Less polar product (1-(2-methylallyl)-5-(trifluoromethyl)-1H-benzo[d]imidazole)**: 50 mg (16%); mp 42-43 °C; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1503, 1326; ¹H NMR (400 MHz, CDCl₃): δ 8.07 (s, 1H), 7.97 (s, 1H), 7.50 (d, 1H, *J* = 8.4 Hz), 7.42 (d, 1H, *J* = 8.4 Hz), 5.00 (s, 1H), 4.77 (s, 1H), 4.69 (s, 2H), 1.67 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 145.2, 143.2, 139.0, 135.9, 124.7, (q, *J*_{C-F} = 31.5 Hz), 124.0 (q, *J*_{C-F} = 271.4 Hz), 119.9 (q, *J*_{C-F} = 2.9 Hz), 118.0 (q, *J*_{C-F} = 3.7 Hz), 114.3, 110.6, 51.2, 19.7; ¹⁹F NMR (375 MHz, CDCl₃): δ -59.8; HRMS (FAB+) Calcd for C₁₂H₁₂F₃N₂ [MH]⁺ 241.0953; Found 241.0954. **More polar product (1-(2-methylallyl)-6-(trifluoromethyl)-1H-benzo[d]imidazole)**: 50 mg (16%); mp 35-37 °C; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1486, 1325; ¹H NMR (400 MHz, CDCl₃): δ 8.01 (s, 1H), 7.88 (d, 1H, *J* = 8.4 Hz), 7.64 (s, 1H), 7.52 (d, 1H, *J* = 8.4 Hz), 5.02 (s, 1H), 4.80 (s, 1H), 4.73 (s, 2H), 1.71 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 145.9, 145.6, 138.9, 133.4, 125.2 (q, *J*_{C-F} = 32.5 Hz), 124.8 (q, *J*_{C-F} = 270.2 Hz), 120.8, 119.2 (q, *J*_{C-F} = 3.7 Hz), 114.4, 107.9 (q, *J*_{C-F} = 4.1 Hz), 51.2, 19.7; ¹⁹F NMR (375 MHz, CDCl₃): δ -59.9 HRMS (FAB+) Calcd for C₁₂H₁₂F₃N₂ [MH]⁺ 241.0953; Found 241.0952.



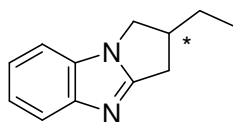
1-(2-Methylallyl)-4,5-diphenyl-1H-imidazole. To an ice-water cooled solution of 4,5-diphenyl-1H-imidazole (1.00 g, 4.54 mmol) in THF (20 mL) was added NaH (60%/mineral oil) (284 mg, 7.10 mmol). The mixture was stirred under the same conditions for 15 minutes. 3-Bromo-2-methylpropene (0.49 mL, 4.9 mmol) was added, and the mixture was stirred at rt for 18 h. The reaction was quenched with sat. NaHCO₃ (aq), and the resulting mixture was extracted three times with ethyl acetate. The organic layers were combined, dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (0-50% gradient of ethyl acetate in hexanes) followed by washing with diethyl ether to give the title compound as a white solid (671 mg, 54% yield). mp 94-95 °C; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1600, 1503; ¹H NMR (400 MHz, CDCl₃): δ 7.60 (s, 1H), 7.52-7.46 (m, 2H), 7.45-7.39 (m, 3H), 7.35-7.29 (m, 2H), 7.24-7.17 (m, 2H), 7.17-7.10 (m, 1H), 4.90 (s, 1H), 4.60 (s, 1H), 4.28 (s, 2H), 1.64 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 140.9, 137.9, 137.2, 134.6, 130.8, 130.6, 128.9, 128.7, 128.6, 128.1, 126.5, 126.2, 113.0, 50.5, 19.9; HRMS (EI): Calcd for C₁₉H₁₈N₂ [M]⁺ 274.1470; Found 274.1471.

General Procedure for ligand screen and reaction optimization. In a nitrogen-filled inert atmosphere box, [RhCl(coe)₂]₂ (2.9 mg, 0.0040 mmol), ligand, substrate (0.05 mmol), and solvent (0.4 mL) were combined in a medium-walled NMR tube. The tube was fitted with a Cajon adapter, frozen with liquid nitrogen, and flame-sealed under vacuum. The tube was then placed in an oil bath set to the desired temperature. Periodically, the tube was removed from the bath, cooled to room temperature, and analyzed by ¹H-NMR spectroscopy. All optimization reactions were carried out via this procedure by varying temperature, solvent, ligand, ligand loading, and additives.

General procedure for asymmetric alkylation. To a scintillation vial in a glovebox, was added (*S,S',R,R'*)-Tangphos (8.1 mg, 0.028 mmol), [RhCl(coe)₂]₂ (10.8 mg, 0.0150 mmol), substrate (0.15 mmol) and THF (1.5 mL). The solution was then transferred to a 15 mL Schlenk tube, heated for the specified time, cooled to rt, and concentrated. The residue was purified by silica gel column chromatography (200:10:1 CH₂Cl₂: MeOH: NH₄OH) to yield the desired product.

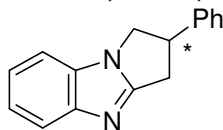


2-Methyl-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (3.2). The general procedure was applied using 1-(2-methylallyl)-1H-benzo[d]imidazole as the substrate. The reaction vial was heated at 135 °C for 20 h, and after purification the product was obtained as a white solid (23 mg, 89%). mp 85-87 °C; $[\alpha]_{\text{D}}^{25}$ +21.43 (c 0.19, CHCl₃); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1615, 1521, 1453; ¹H NMR (400 MHz, CDCl₃): δ 7.73-7.66 (m, 1H), 7.32-7.17 (m, 3H), 4.26 (dd, 1H, *J* = 7.6, 10.0 Hz), 3.66 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.29-3.12 (m, 2H), 2.69 (dd, 1H, *J* = 6.0, 15.6 Hz), 1.35 (d, 3H, *J* = 6.8 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 160.6, 148.5, 132.4, 121.8, 121.6, 119.6, 109.4, 50.1, 35.7, 32.2, 20.0; HRMS (EI): *m/z* calcd. for C₁₁H₁₂N₂ (M⁺): 172.1000; found: 172.1006; HPLC (Chiralcel AD-H column, 5% *i*PrOH/hexanes, 1mL/min): major, 18.45 min; minor, 21.50 min; 98% ee. X-ray quality crystals of the HCl salt of **2** (CCDC 727522) were obtained by dissolving the compound in a minimal amount of Et₂O, precipitation with 1M HCl in Et₂O, and recrystallation from CH₂Cl₂/hexanes.

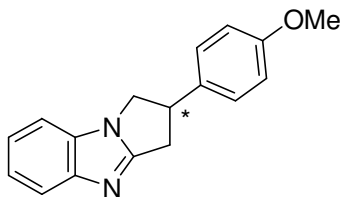


2-Ethyl-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using 1-(2-methylenebutyl)-1H-benzo[d]imidazole as the substrate. The reaction vial was heated at 135 °C for 60 h, and after purification the product was obtained as a yellowish oil

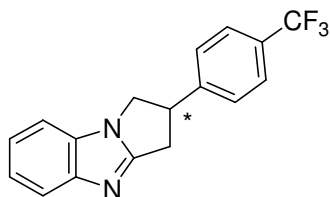
(20 mg, 71%). $[\alpha]_D^{25} +7.28$ (c 0.38, CHCl_3); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1525, 1451; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.77-7.69 (m, 1H), 7.35-7.29 (m, 1H), 7.29-7.20 (m, 2H), 4.29 (dd, 1H, $J = 10.1, 8.1$ Hz), 3.75 (dd, 1H, $J = 10.1, 6.8$ Hz), 3.26 (dd, 1H, $J = 16.6, 8.6$ Hz), 3.06 (apparent septet, 1H), 2.77 (dd, 1H, $J = 16.6, 7.1$ Hz), 1.75 (m, 2H), 1.09 (t, 3H, $J = 7.3$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 160.6, 148.5, 132.4, 121.8, 121.6, 119.6, 109.4, 48.4, 42.8, 30.1, 27.8, 12.1; HRMS (EI): m/z calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_2$ $[\text{MH}]^+$ 187.1232; Found 187.1230; HPLC (Chiralcel AD-H column, 5% EtOH/hexanes, 1mL/min): major, 30.85 min; minor, 28.20 min; 90% ee.



2-Phenyl-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using 1-(2-Phenylallyl)-1H-benzoimidazole as the substrate. The reaction vial was heated at 135 °C for 46 h, and after purification the product was obtained as a white solid (32 mg, 91%). mp 144-146 °C; $[\alpha]_D^{25} +64.55$ (c 0.44, CHCl_3); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1618, 1516; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.78-7.70 (m, 1H), 7.46-7.19 (m, 8H), 4.54 (dd, 1H, $J = 8.4, 10.0$ Hz), 4.28 (m, 1H), 4.10 (dd, 1H, $J = 7.2, 10.0$ Hz), 3.53 (dd, 1H, $J = 8.4, 16.8$ Hz), 3.21 (dd, 1H, $J = 7.2, 16.8$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 159.9, 148.6, 141.8, 132.3, 129.1, 127.6, 126.9, 122.1, 121.9, 119.8, 109.6, 50.4, 46.2, 32.4; HRMS (EI): m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2$ (M^+): 234.1157; found: 234.1160; HPLC (Chiralcel AD-H column, 10% *i*PrOH/hexanes, 1mL/min): major, 41.78 min; minor, 35.43 min; 97% ee.

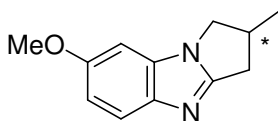


2-(4-methoxyphenyl)-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using 1-(2-(4-methoxyphenyl)allyl)-1H-benzo[d]imidazole as the substrate. The reaction vial was heated at 175 °C for 24 h, and after purification the product was obtained as a yellowish solid (33 mg, 83%). mp 115-117 °C; $[\alpha]_D^{25} +48.11$ (c 0.9, CHCl_3); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1513; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.77-7.69 (m, 1H), 7.35-7.15 (m, 5H), 6.88 (d, 2H, $J = 8.6$ Hz), 4.47 (dd, 1H, $J = 10.1, 8.1$ Hz), 4.21 (m, 1H), 4.02 (dd, 1H, $J = 10.1, 8.1$ Hz), 3.80 (s, 3H), 3.48 (dd, 1H, $J = 16.9, 8.8$ Hz), 3.14 (dd, 1H, $J = 16.9, 8.6$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 159.9, 158.8, 148.5, 133.6, 132.2, 127.9, 121.9, 121.7, 119.6, 114.3, 109.5, 55.3, 50.4, 45.4, 32.5; HRMS (FAB+): m/z calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}$ (MH^+): 265.1335; found: 265.1333; HPLC (Chiralcel AD-H column, 10% EtOH/hexanes, 1mL/min): major, 47.10 min; minor, 32.32 min; 87% ee.

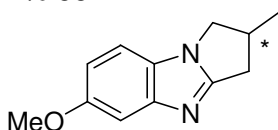


2-(4-trifluoromethylphenyl)-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using 1-(2-(4-(trifluoromethyl)phenyl)allyl)-1H-benzo[d]imidazole as the substrate. The reaction mixture was heated at 175 °C for 24 h, and after purification the product was obtained as a yellowish solid (39 mg, 87%). mp 162-165 °C; $[\alpha]_D^{25} +36.63$ (c 0.8, CHCl_3); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1538, 1412, 1324; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.80-7.71 (m, 1H), 7.62 (d, 2H, $J = 8.2$ Hz), 7.39 (d, 2H, $J = 8.2$ Hz), 7.34-7.21 (m, 3H), 4.56 (dd, 1H, $J = 10.4, 8.1$ Hz), 4.33 (m, 1H), 4.10 (dd, 1H, $J = 10.4, 7.9$ Hz), 3.56 (dd, 1H, $J = 16.9, 8.8$ Hz), 3.19 (dd, 1H, $J =$

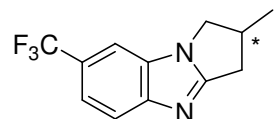
16.9, 7.3 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 159.4, 148.7, 145.9, 132.2, 130.0 (q, $J_{\text{C-F}} = 33.0$ Hz), 127.4, 126.3 (q, $J_{\text{C-F}} = 3.9$ Hz), 124.0 (q, $J_{\text{C-F}} = 272.3$ Hz), 122.3, 122.1, 119.9, 109.6, 50.1, 45.8, 32.2; ^{19}F NMR (375 MHz, CDCl_3): δ -61.7; HRMS (FAB+) Calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_2$ $[\text{MH}]^+$ 303.1109; Found 303.1106; HPLC (Chiralcel AD-H column, 10% EtOH/hexanes, 1mL/min): major, 26.66 min; minor, 22.43 min; 79% ee.



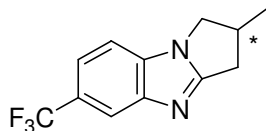
2-Methyl-2,3-dihydro-1H-7-methoxy-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using (6-methoxy-1-(2-methylallyl)-1H-benzo[d]imidazole) as the substrate. The reaction vial was heated at 175 °C for 36 h, and after purification the product was obtained as a yellowish solid (27 mg, 89%). mp 100-103 °C; $[\alpha]_{\text{D}}^{25} +22.95$ (c 0.9, CHCl_3); $u_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1626, 1457, 1408; ^1H NMR (500 MHz, CDCl_3): δ 7.54 (d, 1H, $J = 8.1$ Hz), 6.83 (dd, 1H, $J = 8.1, 2.3$ Hz), 6.74 (d, 1H, $J = 2.3$ Hz), 4.17 (dd, 1H, 1H, $J = 9.9, 7.6$ Hz), 3.83 (s, 3H), 3.58 (dd, 1H, $J = 9.9, 6.9$ Hz), 3.22-3.07 (m, 2H), 2.68-2.56 (m, 1H), 1.31 (d, 3H, $J = 6.7$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 159.7, 155.8, 142.8, 132.8, 119.8, 110.2, 93.5, 55.8, 49.9, 35.6, 32.0, 19.9; HRMS (FAB+): m/z calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$ (MH^+): 203.1179; found: 203.1175; HPLC (Chiralcel AS-H column, 2% EtOH/hexanes w/ 0.1% diethylamine, 1mL/min): major, 33.96 min; minor, 40.53 min; 71% ee.



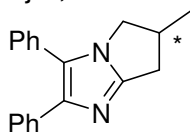
2-Methyl-2,3-dihydro-1H-6-methoxy-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using (5-methoxy-1-(2-methylallyl)-1H-benzo[d]imidazole) as the substrate. The reaction vial was heated at 175 °C for 24 h, and after purification the product was obtained as a yellowish solid (28 mg, 92%). mp 119-122 °C; $[\alpha]_{\text{D}}^{25} +12.56$ (c 0.7, CHCl_3); $u_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1522, 1282, 1442; ^1H NMR (400 MHz, CDCl_3): δ 7.19 (d, 1H, $J = 2.3$ Hz), 7.14 (d, 1H, $J = 8.8$ Hz), 6.84 (dd, 1H, $J = 8.8, 2.3$ Hz), 4.21 (dd, 1H, $J = 10.0, 7.7$ Hz), 3.85 (s, 3H), 3.62 (dd, 1H, $J = 10.0, 6.0$ Hz), 3.26-3.09 (m, 2H), 2.72-2.59 (m, 1H), 1.33 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 162.4, 155.7, 149.2, 127.0, 111.2, 109.6, 102.3, 55.8, 50.2, 35.6, 32.3, 20.0; HRMS (FAB+): m/z calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$ (MH^+): 203.1184; found: 203.1177; HPLC (Chiralcel AS-H column, 2% EtOH/hexanes w/ 0.1% diethylamine, 1mL/min): major, 33.67 min; minor, 38.65 min; 81% ee.



2-Methyl-2,3-dihydro-1H-7-trifluoromethyl-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using (1-(2-methylallyl)-6-(trifluoromethyl)-1H-benzo[d]imidazole) as the substrate. The reaction vial was heated at 175 °C for 24 h, and after purification the product was obtained as a yellowish solid (30 mg, 83%). mp 80-83 °C; $[\alpha]_{\text{D}}^{25} +10.89$ (c 0.9, CHCl_3); $u_{\text{max}}(\text{film})/\text{cm}^{-1}$ 1523, 1454, 1309; ^1H NMR (400 MHz, CDCl_3): δ 7.76 (d, 1H, $J = 8.6$ Hz), 7.58 (s, 1H), 7.48 (d, 1H, $J = 8.6$ Hz), 4.32 (dd, 1H, $J = 10.2, 7.8$ Hz), 3.73 (dd, 1H, $J = 10.2, 6.3$ Hz), 3.36-3.17 (m, 2H), 2.72 (dd, 1H, $J = 15.1, 5.6$ Hz), 1.37 (d, 3H, $J = 6.6$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 163.3, 150.6, 131.8, 124.9 (q, $J_{\text{C-F}} = 271.5$ Hz), 124.0 (q, $J_{\text{C-F}} = 32.2$ Hz), 119.8, 118.7 (q, $J_{\text{C-F}} = 3.7$ Hz), 107.2 (q, $J_{\text{C-F}} = 4.4$ Hz), 50.3, 35.7, 32.2, 19.9; HRMS (FAB+): m/z calcd. for $\text{C}_{12}\text{H}_{12}\text{F}_3\text{N}_2$ (MH^+): 241.0953; found: 241.0944; HPLC (Chiralcel AS-H column, 2% EtOH/hexanes, 1mL/min): major, 22.75 min; minor, 17.55 min; 53% ee.



2-Methyl-2,3-dihydro-1H-6-trifluoromethyl-benzo[d]pyrrolo[1,2-a]imidazole. The general procedure was applied using (1-(2-methylallyl)-5-(trifluoromethyl)-1H-benzo[d]imidazole) as the substrate. The reaction vial was heated at 175 °C for 24 h, and after purification the product was obtained as a yellowish solid (29 mg, 81%). mp 107-110 °C; $[\alpha]_D^{25} +4.02$ (c 1.0, CHCl₃); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1531, 1322; ¹H NMR (400 MHz, CDCl₃): δ 7.95 (s, 1H), 7.46 (d, 1H, *J* = 8.3 Hz), 7.3 (d, 1H, *J* = 8.3 Hz), 4.29 (dd, 1H, *J* = 10.1, 7.6 Hz), 3.69 (dd, 1H, *J* = 10.1, 6.3 Hz), 3.32-3.15 (m, 2H), 2.72 (dd, 1H, *J* = 15.7, 5.8 Hz), 1.36 (d, 3H, *J* = 6.6 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 162.7, 147.9, 134.4, 125.0 (q, *J*_{C-F} = 271.5 Hz), 124.1 (q, *J*_{C-F} = 3.1 Hz), 118.9 (q, *J*_{C-F} = 3.6 Hz), 117.1 (q, *J*_{C-F} = 3.7 Hz), 109.7, 50.2, 35.8, 32.2, 19.9; HRMS (FAB+): *m/z* calcd. for C₁₂H₁₂F₃N₂ (MH⁺): 241.0953; found: 241.0947; HPLC (Chiralcel AS-H column, 2% EtOH/hexanes, 1mL/min): major, 13.44 min; minor, 14.75 min; 71% ee.



6-Methyl-2,3-diphenyl-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole. The general procedure was applied using 1-(2-Methylallyl)-4,5-diphenyl-1H-imidazole as the substrate. The reaction vial was heated at 135 °C for 98 h, and after purification the product was obtained as a white solid (37 mg, 90%). mp 139-141 °C; $[\alpha]_D^{25} +4.09$ (c 0.29, CHCl₃); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1599; ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, 2H, *J* = 7.2 Hz), 7.42-7.12 (m, 8H), 4.08 (dd, 1H, *J* = 7.6, 10.4 Hz), 3.53 (dd, 1H, *J* = 6.4, 10.4 Hz), 3.23-3.04 (m, 2H), 2.63 (dd, 1H, *J* = 6.4, 15.6 Hz), 1.30 (d, 3H, *J* = 6.8 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 153.1, 141.2, 135.2, 131.3, 128.9, 128.8, 128.2, 127.7, 127.1, 126.4, 125.2, 51.8, 35.6, 32.3, 19.8; HRMS (EI): *m/z* calcd. for C₁₉H₁₈N₂ (M⁺): 274.1470; found: 274.1474; HPLC (Chiralcel AD-H column, 3% EtOH/hexanes, 1mL/min): major, 18.40 min; minor, 16.20 min; 95% ee.

References

- (1) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238; (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67-72; (c) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013-3039; (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731-1769.
- (2) (a) Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1997**, 425-426; (b) Harada, H.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772-6779; (c) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882-4886; (d) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192-7193.
- (3) (a) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861-2903; (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417-424.
- (4) (a) Han, X.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801-3804; (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997-4999.
- (5) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685-2686; (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964-13965; (c) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202-3203; (d) Wiedemann, S. H.; Lewis, J. C.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2006**, *128*, 2452-2462.
- (6) (a) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612-1614; (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029-3069.

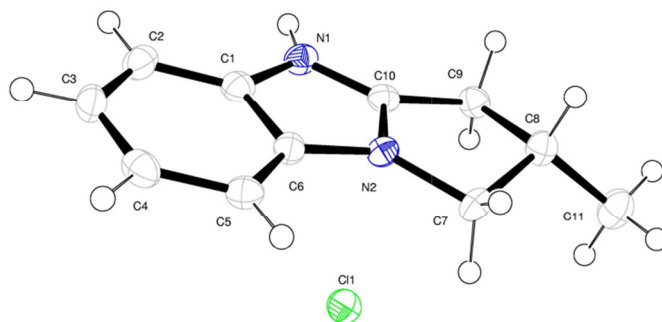
(7) (a) Gridnev, I. D.; Imamoto, T. *Organometallics* **2001**, *20*, 545-549; (b) James, B. R.; Mahajan, D. *J. Organomet. Chem.* **1985**, *279*, 31-48.

(8) Van der Ent, A.; Onderdelinden, A. L. *Inorg. Syn.* **1973**, *14*, 92-95.

(9) Yanez, E. C.; Serrano, J. M.; Huert, G.; Muchowski, J. M.; Almanza, R. C. *Tetrahedron* **2004**, *60*, 9391-9396.

(10) Moore, C. L.; Zivkovic, A.; Engels, J. W.; Kuchta, R. D. *Biochemistry* **2004**, *43*, 12367-12374.

Appendix: Chapter 3. X-ray Crystal Data



A colorless plate 0.06 x 0.05 x 0.02 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 0.5°. Data collection was 99.7% complete to 67.00° in ϕ . A total of 9520 reflections were collected covering the indices, $-13 \leq h \leq 17$, $-8 \leq k \leq 8$, $-12 \leq l \leq 11$. 1990 reflections were found to be symmetry independent, with an R_{int} of 0.0186. Indexing and unit cell refinement indicated a primitive, Orthorhombic lattice. The space group was found to be P2(1)2(1)2 (No. 18). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97. Absolute stereochemistry at C(8) was determined to be S.

Table 1. Crystal data and structure refinement for ellman03.

X-ray ID	ellman03	
Sample/notebook ID	HHII-149a	
Empirical formula	C ₁₁ H ₁₃ Cl N ₂	
Formula weight	208.68	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2	
Unit cell dimensions	a = 14.8792(16) Å	α = 90°.
	b = 7.4397(8) Å	β = 90°.
	c = 10.0119(11) Å	γ = 90°.
Volume	1108.3(2) Å ³	
Z	4	
Density (calculated)	1.251 Mg/m ³	
Absorption coefficient	2.737 mm ⁻¹	
F(000)	440	
Crystal size	0.06 x 0.05 x 0.02 mm ³	
Crystal color/habit	colorless plate	
Theta range for data collection	4.42 to 68.24°.	
Index ranges	-13 ≤ h ≤ 17, -8 ≤ k ≤ 8, -12 ≤ l ≤ 11	
Reflections collected	9520	
Independent reflections	1990 [R(int) = 0.0186]	
Completeness to theta = 67.00°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9473 and 0.8530	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	1990 / 0 / 128	
Goodness-of-fit on F ²	1.082	
Final R indices [I > 2σ(I)]	R1 = 0.0353, wR2 = 0.0933	
R indices (all data)	R1 = 0.0357, wR2 = 0.0936	
Absolute structure parameter	0.03(2)	
Largest diff. peak and hole	0.452 and -0.195 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ellman03. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	778(2)	8203(3)	904(2)	22(1)
C(2)	36(2)	7627(3)	169(2)	27(1)
C(3)	-693(2)	7010(3)	892(3)	29(1)
C(4)	-700(2)	6980(3)	2288(3)	26(1)
C(5)	25(2)	7563(3)	3027(2)	22(1)
C(6)	766(1)	8162(3)	2307(2)	20(1)
C(7)	2077(2)	9181(3)	3946(2)	23(1)
C(8)	2853(1)	10402(3)	3474(2)	23(1)
C(9)	2958(1)	10033(3)	1958(2)	23(1)
C(10)	2058(2)	9305(3)	1611(2)	20(1)
C(11)	3711(2)	10135(4)	4260(2)	33(1)
N(1)	1599(1)	8918(2)	517(2)	22(1)
N(2)	1586(1)	8885(2)	2689(2)	19(1)
Cl(1)	2941(1)	5171(1)	2300(1)	26(1)

Table 3. Bond lengths [Å] and angles [°] for ellman03.

C(1)-N(1)	1.388(3)	C(4)-C(5)-C(6)	116.3(2)
C(1)-C(2)	1.394(3)	C(4)-C(5)-H(5)	121.8
C(1)-C(6)	1.405(3)	C(6)-C(5)-H(5)	121.8
C(2)-C(3)	1.383(4)	N(2)-C(6)-C(5)	132.7(2)
C(2)-H(2)	0.95	N(2)-C(6)-C(1)	104.9(2)
C(3)-C(4)	1.398(4)	C(5)-C(6)-C(1)	122.3(2)
C(3)-H(3)	0.95	N(2)-C(7)-C(8)	101.41(16)
C(4)-C(5)	1.378(3)	N(2)-C(7)-H(7A)	111.5
C(4)-H(4)	0.95	C(8)-C(7)-H(7A)	111.5
C(5)-C(6)	1.390(3)	N(2)-C(7)-H(7B)	111.5
C(5)-H(5)	0.95	C(8)-C(7)-H(7B)	111.5
C(6)-N(2)	1.387(3)	H(7A)-C(7)-H(7B)	109.3
C(7)-N(2)	1.472(3)	C(11)-C(8)-C(7)	113.26(18)
C(7)-C(8)	1.542(3)	C(11)-C(8)-C(9)	113.66(18)
C(7)-H(7A)	0.99	C(7)-C(8)-C(9)	105.70(17)
C(7)-H(7B)	0.99	C(11)-C(8)-H(8)	108
C(8)-C(11)	1.513(3)	C(7)-C(8)-H(8)	108
C(8)-C(9)	1.551(3)	C(9)-C(8)-H(8)	108
C(8)-H(8)	1	C(10)-C(9)-C(8)	101.73(17)
C(9)-C(10)	1.485(3)	C(10)-C(9)-H(9A)	111.4
C(9)-H(9A)	0.99	C(8)-C(9)-H(9A)	111.4
C(9)-H(9B)	0.99	C(10)-C(9)-H(9B)	111.4
C(10)-N(1)	1.322(3)	C(8)-C(9)-H(9B)	111.4
C(10)-N(2)	1.325(3)	H(9A)-C(9)-H(9B)	109.3
C(11)-H(11A)	0.98	N(1)-C(10)-N(2)	110.43(19)
C(11)-H(11B)	0.98	N(1)-C(10)-C(9)	137.7(2)
C(11)-H(11C)	0.98	N(2)-C(10)-C(9)	111.88(18)
N(1)-H(1)	0.88	C(8)-C(11)-H(11A)	109.5
N(1)-C(1)-C(2)	131.8(2)	C(8)-C(11)-H(11B)	109.5
N(1)-C(1)-C(6)	107.3(2)	H(11A)-C(11)-H(11B)	109.5
C(2)-C(1)-C(6)	120.8(2)	C(8)-C(11)-H(11C)	109.5
C(3)-C(2)-C(1)	116.5(2)	H(11A)-C(11)-H(11C)	109.5
C(3)-C(2)-H(2)	121.7	H(11B)-C(11)-H(11C)	109.5
C(1)-C(2)-H(2)	121.7	C(10)-N(1)-C(1)	107.90(18)
C(2)-C(3)-C(4)	122.3(2)	C(10)-N(1)-H(1)	126
C(2)-C(3)-H(3)	118.8	C(1)-N(1)-H(1)	126
C(4)-C(3)-H(3)	118.8	C(10)-N(2)-C(6)	109.45(19)
C(5)-C(4)-C(3)	121.7(2)	C(10)-N(2)-C(7)	113.46(16)
C(5)-C(4)-H(4)	119.1	C(6)-N(2)-C(7)	136.92(19)
C(3)-C(4)-H(4)	119.1		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ellman03. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(1)	18(1)	23(1)	-1(1)	-1(1)	4(1)
C(2)	31(1)	23(1)	25(1)	-3(1)	-8(1)	6(1)
C(3)	25(1)	23(1)	38(1)	-3(1)	-12(1)	0(1)
C(4)	19(1)	21(1)	39(1)	2(1)	2(1)	0(1)
C(5)	22(1)	21(1)	24(1)	2(1)	1(1)	3(1)
C(6)	20(1)	17(1)	24(1)	-2(1)	-2(1)	3(1)
C(7)	24(1)	28(1)	16(1)	-1(1)	-3(1)	1(1)
C(8)	22(1)	26(1)	23(1)	-1(1)	-1(1)	-1(1)
C(9)	23(1)	23(1)	22(1)	0(1)	2(1)	-2(1)
C(10)	23(1)	17(1)	20(1)	-1(1)	2(1)	4(1)
C(11)	25(1)	41(1)	33(1)	0(1)	-6(1)	-1(1)
N(1)	26(1)	22(1)	16(1)	0(1)	1(1)	3(1)
N(2)	19(1)	21(1)	16(1)	1(1)	0(1)	1(1)
Cl(1)	31(1)	25(1)	22(1)	-2(1)	3(1)	0(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for ellman03.

	x	y	z	U(eq)
H(2)	32	7657	-780	32
H(3)	-1208	6592	424	34
H(4)	-1218	6546	2740	32
H(5)	20	7556	3976	27
H(7A)	2305	8037	4322	27
H(7B)	1697	9790	4618	27
H(8)	2659	11679	3588	28
H(9A)	3088	11152	1459	27
H(9B)	3438	9144	1782	27
H(11A)	3594	10350	5210	49
H(11B)	4168	10981	3943	49
H(11C)	3926	8901	4137	49
H(1)	1781	9085	-310	26

Chapter 4. Rh(III)-Catalyzed Oxidative Coupling of Unactivated Alkenes via C–H Activation

*Oxime directed aromatic C–H bond activation and oxidative coupling to alkenes is reported using a cationic Rh(III) catalyst. Significantly, the method can be used to oxidatively couple unactivated, aliphatic alkenes. A majority of this work has been published in a communication (Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. Org. Lett. **2010**, ASAP)*

Authorship

This work was conducted in collaboration with Mikael Brasse

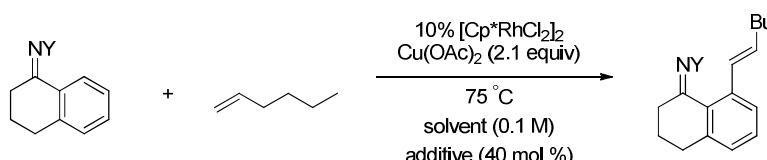
Introduction

Directed C–H bond activation and oxidative coupling with alkenes provides an atom economical alternative to traditional transformations such as the Heck reaction. Palladium,^{1,2} ruthenium,³ and rhodium^{4,5} have been reported to effect the former transformation. However, nearly all oxidative couplings have employed “activated” alkenes such as acrylates and styrenes.^{2e,2m} Herein, we report a general method for the oxidative coupling of aryl *O*-methyl oximes with unactivated alkenes via C–H bond functionalization using a cationic Rh(III) catalyst.

Results and Discussion

We began our exploration with attempts to oxidatively couple 1-hexene with imine **4.1a**. We initially employed conditions reported by Miura for the oxidative coupling of 1-phenylpyrazole with acrylates using [Cp*RhCl₂]₂ as the catalyst in the presence of Cu(OAc)₂ as an oxidant and with DMF as the solvent (Table 4.1, entry 1).^{5e} Only trace amounts of the coupled product were observed, and none of the desired product was obtained with other solvents (entries 2 and 3). Prompted by reports that noted a positive effect of halide abstractors for rhodium catalysis, AgSbF₆ was added⁶ and resulted in improved yields (entries 4-7) with the highest yield being obtained with ethanol as the solvent (entry 6). The combination of rhodium with silver was next tested without copper acetate or using other oxidants (Ag₂CO₃, benzoquinone, PhI(OAc)₂), bases (NaOAc, lutidine) or acids (AcOH), but all of these modifications resulted either in a reduced yield or no coupled product (not shown). A survey of other directing groups established that *O*-methyl oxime **4.1b** (entries 8-10) is superior to the corresponding *N*-benzyl imine **4.1a**, providing good yields of the trans alkene product in THF (entry 10).

Table 4.1. Optimization of the Oxidative Coupling Reaction



entry	substrate	additive	solvent	yield ^a
1	Y = Bn (4.1a)	-	DMF	Trace
2	Y = Bn (4.1a)	-	THF	0
3	Y = Bn (4.1a)	-	<i>t</i> AmOH	0
4	Y = Bn (4.1a)	AgSbF ₆	DMF	11%
5	Y = Bn (4.1a)	AgSbF ₆	<i>t</i> AmOH	27%
6	Y = Bn (4.1a)	AgSbF ₆	EtOH	45%
7	Y = Bn (4.1a)	AgSbF ₆	THF	10%
8	Y = OMe (4.1b)	AgSbF ₆	<i>t</i> AmOH	60%
9	Y = OMe (4.1b)	AgSbF ₆	DMF	30%
10	Y = OMe (4.1b)	AgSbF ₆	THF	85%
11	acetanilide	AgSbF ₆	THF	0%

^a NMR yield relative to 2,6-dimethoxytoluene as an internal standard

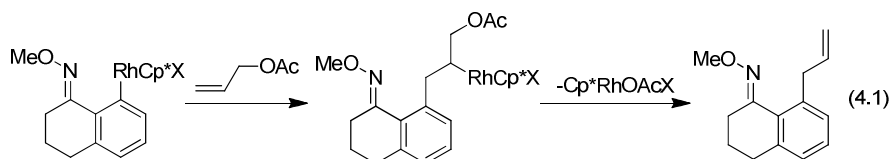
Trace amounts of the cis product could also be detected under these conditions (5-10%) and no migration of the double bond was observed. Of note, while the reaction is water sensitive, it is not air sensitive. The reaction mixture could be exposed to the atmosphere with no decrease in yield. No coupled product was observed for acetanilide which has been reported to direct the oxidative coupling of styrenes using the same $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ system (entry 11).^{5c}

Alkene scope was next explored (Table 4.2). A β -branched alkene provided the coupled product in high yield (entry 2), while an α -branched alkene resulted in a somewhat lower yield (entry 3). The reaction is compatible with chloro and ester functionalities (entries 4 and 5). Notably, diene **4.2e** preferentially couples at the terminal alkene position in preference to the more electronically activated α,β -unsaturated ester (entry 5). Reactions with activated alkenes such as styrene and ethyl acrylate proceed well to give good yields of the alkenylated products (entries 6 and 7). Interestingly, use of allyl acetate as the coupling partner lead to formation of the unconjugated terminal alkene **4.3h** (entry 8). This allylated product presumably forms via a concerted elimination from a rhodium-acetate complex obtained upon insertion of the alkene in the initially generated rhodium-aryl species (eq 4.1).⁷ While this transformation is redox neutral, only trace amounts of product are obtained when $\text{Cu}(\text{OAc})_2$ is omitted. However, the reaction can be performed using substoichiometric amounts of $\text{Cu}(\text{OAc})_2$ (40 mol %) without loss in yield.

Table 4.2. Alkene Scope^a

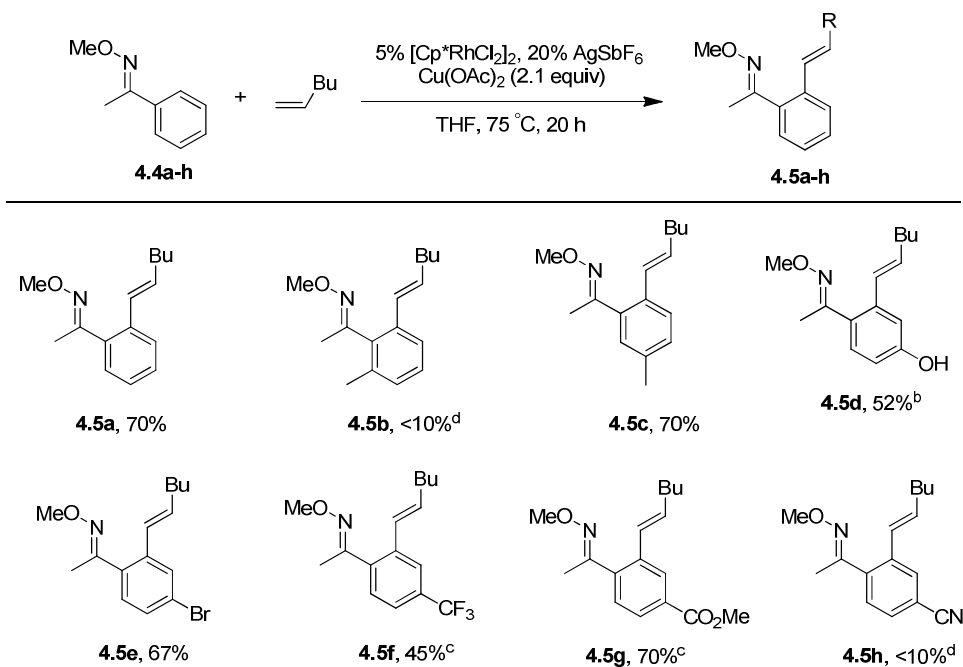
entry	alkene	product	yield ^b	entry	alkene	product	yield ^b
1			75%	5			80%
2			84%	6			98%
3			53%	7			81%
4			85%	8			46%

^a All reactions were performed by heating the oxime (1 equiv), alkene (3 equiv), $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mol %), AgSbF_6 (20 mol %), $\text{Cu}(\text{OAc})_2$ (2.1 equiv), and THF (0.1 M) in a sealed vial for 20 h at 75 °C. ^b Isolated yields after purification by chromatography are reported.



Under the optimized conditions, a variety of different aryl *O*-methyl oximes could be coupled with alkenes in good yield (Scheme 4.1). Substrates with *para* (**4.4d-g**) or *meta* (**4.4c**) substitution patterns and both electron withdrawing (**4.4e-g**) and releasing (**4.4d**) substituents were effective coupling partners. However, the electron poor substrates **4.4f** and **4.4g** required longer reaction times to achieve full conversion. The brominated analogue **4.4e** not only coupled efficiently but also did not suffer any Heck coupling or proto-debromination. In contrast, the *para*-cyano aryl oxime **4.4h** gave only a poor yield of coupled product (10% by NMR), probably due to coordination of the nitrile to the catalyst. A small amount of the bis-alkenylated product, less than 10% by NMR, was observed for oximes **4.4a** and **4.4e**, and under the standard reaction conditions **4.4d** resulted in 30% of the bis-alkenylated product. However, this undesired product could be reduced to trace amounts using 1.5 equiv of the alkene. *Ortho*-methyl substituted aryl oxime **4.4b** resulted in poor conversion, likely due to steric congestion between the directing group and the methyl substituent.^{5c}

Scheme 4.1. Aryl *O*-Methyl Oxime Scope^a



^a All reactions were performed by heating oxime (1 equiv), 1-hexene (3 equiv), [Cp*RhCl₂]₂ (5 mol %), AgSbF₆ (20 mol %), Cu(OAc)₂ (2.1 equiv), and THF (0.1 M) in a sealed vial for 20 h at 75 °C. Isolated yields after purification by chromatography are reported. ^b 1-hexene (1.5 equiv). ^c 36 h. ^d NMR yield relative to 2,6-dimethoxytoluene as an internal standard

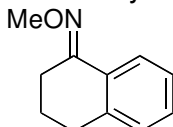
Conclusion

Recent reports have shown that Rh(III) complexes are efficient catalysts for the oxidative coupling of C–H bonds with acrylates and styrenes. However, the analogous transformation with non-activated olefins has not previously been demonstrated for Rh catalysts and is generally unknown. We have shown that given an appropriate directing group, the coupling of unactivated as well as functionalized terminal alkenes can be accomplished in moderate to good yields and under conditions that are compatible with commonly encountered functional groups.

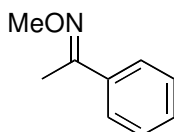
Experimental

I. General Methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran was passed through a column of activated alumina under nitrogen. Ethanol and *t*AmOH were refluxed overnight with magnesium turnings and distilled prior to use. Extra dry DMF (<50 ppm water) was purchased from Acros organics and used without further purification. All reactions of air- and moisture-sensitive materials were carried out using syringe, cannula and/or inert atmosphere box techniques. All glassware was dried overnight at 150 °C or flame-dried under vacuum immediately prior to use. During workup procedures, organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure with a rotary evaporator. Chromatography was performed on Merck 60 230-240 mesh silica gel. Reverse phase column chromatography was carried out using a Biotage SP Flash Purification System (Biotage No. SP1-B1A) with Flash Cartridges (Biotage No. KP-C18-HS 12+M) using Acetonitrile Water gradient. NMR chemical shifts are reported in ppm relative to CHCl₃ (7.26 ppm for ¹H, and 77.23 ppm for ¹³C) or benzene (7.16 ppm for ¹H, and 128.06 ppm for ¹³C). IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory or a Nicolet 6700 FT-IR equipped with an attenuated total reflectance accessory, and only partial data are listed. Mass spectra (HRMS) were obtained by the University of California at Berkeley Mass Spectrometry Facility or the Keck Center of Yale University.

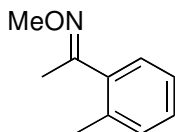
II. General Procedure for the Synthesis of *O*-methyl oximes. To a 50 mL round bottom flask equipped with a stir bar was combined ketone (1.7 mmol, 1 equiv), MeONH₂·HCl (380 mg, 4.6 mmol, 2.7 equiv), NaOAc (610 mg, 7.5 mmol, 4.4 equiv), H₂O (15 mL), and EtOH (5 mL). The flask was equipped with a reflux condenser and heated at 70°C for 2 h. After cooling to rt, the mixture was extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried with Na₂SO₄, and concentrated to yield the desired analytically pure oxime.



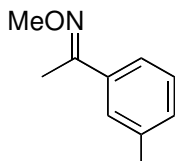
3,4-Dihydronaphthalen-1(2H)-one *O*-methyl oxime (4.1b). 1-Tetralone was subjected to the standard procedure to yield *O*-methyl oxime as a red oil (85% yield) ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.17-7.14 (m, 1H), 4.02 (s, 3H), 2.80-2.73 (m 4H), 1.91-1.83 (m, 2H). Spectral data matched those previously reported.⁸



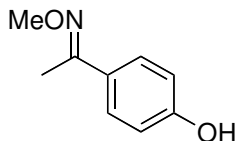
Acetophenone O-methyl oxime (4.4a). Acetophenone was subjected to the standard procedure to yield *O*-methyl oxime as a clear oil (87% yield) ^1H NMR (400 MHz, CDCl_3): δ 7.68-7.59 (m, 2H), 7.40-7.32 (m, 3H), 3.99 (s, 3H), 2.21 (s, 3H). Spectral data matched those previously reported.⁹



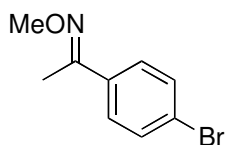
1-(*o*-Tolyl)ethanone O-methyl oxime (4.4b). 2-Methyl-acetophenone was subjected to the standard procedure to yield *O*-methyl oxime as a clear oil (87% yield) ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.19 (m, 4H), 4.02 (s, 3H), 2.41 (s, 3H), 2.22 (s, 3H). Spectral data matched those previously reported.¹⁰



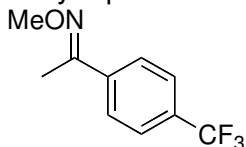
1-(3-Tolyl)ethanone O-methyl oxime (4.4c). 3-Methyl acetophenone was subjected to the standard procedure to yield *O*-methyl oxime as a yellow oil (78% yield) ^1H NMR (400 MHz, CDCl_3): δ 7.51 (s, 1H), 7.46 (d, $J = 7.7$ Hz, 1H), 7.30 (m, 1H), 7.21 (d, $J = 7.4$ Hz, 1H), 4.04 (s, 3H), 2.42 (s, 3H), 2.26 (s, 3H). Spectral data matched those previously reported.¹¹



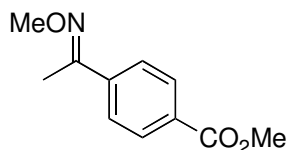
1-(4-Hydroxyphenyl)ethanone O-methyl oxime (4.4d). 4-Hydroxy-acetophenone was subjected to the standard procedure to yield *O*-methyl oxime as a clear oil (80% yield) ^1H NMR (400 MHz, CDCl_3): δ 7.52 (d, $J = 8.5$ Hz, 2H), 6.78 (d, $J = 8.5$ Hz, 2H), 3.97 (s, 3H), 2.19 (s, 3H). Spectral data matched those previously reported.¹²



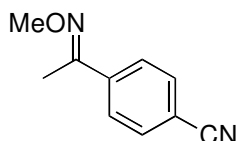
1-(4-Bromophenyl)ethanone O-methyl oxime (4.4e). 4-Bromo-acetophenone was subjected to the standard procedure to yield *O*-methyl oxime as a yellow oil (87% yield) ^1H NMR (400 MHz, CDCl_3): δ 7.56 (d, $J = 8.6$ Hz, 2H), 7.55 (d, $J = 8.6$ Hz, 2H), 4.03 (s, 3H), 2.24 (s, 3H). Spectral data matched those previously reported.¹³



1-(4-(Trifluoromethyl)phenyl)ethanone O-methyl oxime (4.4f). 4-(Trifluoromethyl)-acetophenone was subjected to the standard procedure to yield *O*-methyl oxime as a colorless oil (70% yield) ^1H NMR (400 MHz, CDCl_3): δ 7.80 (d, $J = 8.3$ Hz, 2H), 7.66 (d, $J = 8.4$ Hz, 2H), 4.06 (s, 3H), 2.28 (s, 3H). Spectral data matched those previously reported.¹⁴



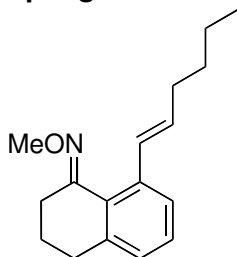
Methyl 4-(1-(methoxyimino)ethyl)benzoate (4.4g). 4-Acetylbenzoic acid was subjected to the standard procedure to yield *O*-methyl oxime as a white solid (95% yield). ^1H NMR (400 MHz, CDCl_3): δ 8.07 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 4.06 (s, 3H), 3.97 (s, 3H), 2.28 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 167.2, 154.1, 141.2, 130.8, 130.1, 126.3, 62.6, 52.6, 12.9. HRMS (EI): Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_3$: 207.0895; observed: 207.0895.



4-(1-(Methoxyimino)ethyl)benzonitrile (4.4h) 4-Acetylbenzonitrile was subjected to the standard procedure to yield *O*-methyl oxime as a white solid (75% yield). ^1H NMR (400 MHz, CDCl_3): δ 7.80 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 4.07 (s, 3H), 2.26 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 153.2, 141.2, 132.6, 126.9, 119.1, 112.8, 62.8, 12.6. HRMS (ES+): Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$: 174.0793; observed: 174.0794.

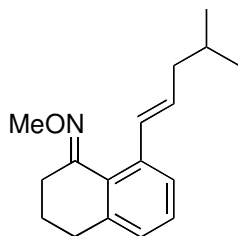
III. General Procedure for Oxidative Coupling Experiments Monitored by NMR. In a nitrogen-filled inert atmosphere box, to a vial was combined $[\text{Cp}^*\text{RhCl}_2]_2$, AgSbF_6 , substrate (0.05 mmol), 1-hexene (12.6 mg, 0.150 mmol, 3 equiv), 2,6-dimethoxytoluene (7.6 mg, 0.050 mmol) and solvent (0.5 mL). The reaction mixture was transferred to a 1 mL sealable vial equipped with a stir bar and was heated to the desired temperature with stirring. After the desired reaction time, the vial was cooled to rt, the reaction was quenched with sat. NH_4OH , and then the resulting mixture was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. Yields were based on NMR integration relative to 2,6-dimethoxytoluene as an internal standard. All optimization reactions were carried out via this procedure by varying substrate, oxidant, additive, and solvent.

IV. Rh(III) Catalyzed Oxidative Coupling of Alkenes



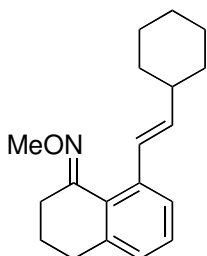
8-(Hex-1-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (4.3a). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF_6 (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one *O*-methyl oxime (44 mg, 0.25 mmol, 1 equiv), 1-hexene (63 mg, 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH_4OH , and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with Na_2SO_4 , concentrated, and purified by column chromatography (30:1 Hex:Et₂O) to yield a clear oil (49 mg, 75% yield). IR (film): 2931, 1599, 1460 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.39 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 15.8 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.08 (dt, J = 15.8, 6.8 Hz, 1H), 4.00 (s, 3H), 2.70 (t, J = 6.7 Hz, 2H), 2.66-2.61 (m, 2H), 2.23 (dq, J = 6.8, 1.1

Hz, 2H), 1.79-1.73 (m, 2H), 1.53-1.46 (m, 2H), 1.46-1.37 (m, 2H), 0.94 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 155.4, 142.2, 137.7, 131.7, 131.1, 128.7, 128.6, 126.9, 126.3, 62.4, 33.2, 31.9, 31.4, 25.9, 22.8, 21.6, 14.5. HRMS (ES+) Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}$ $[\text{MH}]^+$ 258.1853; Found 258.1849.



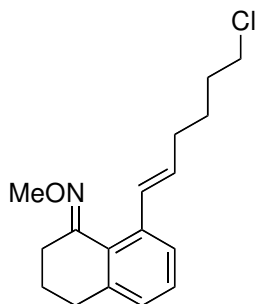
8-(4-Methylpent-1-en-1-yl)-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (4.3b).

To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF_6 (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (44 mg, 0.25 mmol, 1 equiv), 4-methylpent-1-ene (63 mg, 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75°C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH_4OH , and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with Na_2SO_4 , concentrated, and purified by column chromatography (3:1 Hex:EtOAc) to yield a clear oil (54 mg, 84% yield). IR (film): 2950, 1599, 1461, 1049 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.44 (d, $J = 8.4$ Hz, 1H), 7.22 (t, $J = 8.4$ Hz, 1H), 7.11-7.03 (m, 2H), 6.10 (dt, $J = 15.2, 7.3$ Hz, 1H), 4.01 (s, 3H), 2.80 (t, $J = 6.8$ Hz, 2H), 2.70-2.65 (m, 2H), 2.15 (t, $J = 7.3$ Hz, 2H), 1.85-1.76 (m, 3H), 1.02 (d, $J = 6.6$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 154.9, 141.9, 137.3, 132.5, 129.4, 128.4, 128.2, 126.5, 126.0, 62.1, 42.7, 31.0, 28.8, 25.5, 22.6, 21.2. HRMS (ES+) Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}$ $[\text{MH}]^+$ 258.1853; Found 258.1839.

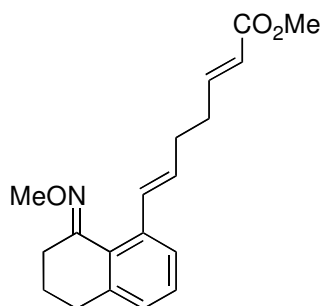


8-(2-Cyclohexylvinyl)-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (4.3c). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF_6 (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (44 mg, 0.25 mmol, 1 equiv), vinylcyclohexane (83 mg, 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75°C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH_4OH , and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with Na_2SO_4 , concentrated, and purified by column chromatography (5:1 Hex:EtOAc) to yield a clear oil (38 mg, 53% yield). IR (film): 2922, 1599, 1460, 1048 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.41 (d, $J = 7.6$ Hz, 1H), 7.20 (t, $J = 7.6$ Hz, 1H), 7.10 (d, $J = 15.8$ Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 1H), 6.06 (dd, $J = 15.8, 6.4$ Hz, 1H), 4.03 (s, 3H), 2.79 (t, $J = 6.8$ Hz, 2H), 2.70-2.63 (m, 2H), 2.23-2.14 (m, 1H), 1.94-1.86 (m, 2H), 1.84-1.75 (m, 4H), 1.75-1.67 (m, 1H), 1.42-1.36 (m, 2H), 1.36-1.19 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 154.9, 141.7, 137.5, 136.1, 129.0, 128.4, 128.2, 126.4,

125.8, 62.0, 41.0, 32.9, 31.0, 26.3, 26.2, 25.4, 21.2. HRMS (ES+) Calcd for C₁₉H₂₆NO [MH]⁺ 284.2009; Found 284.1994.

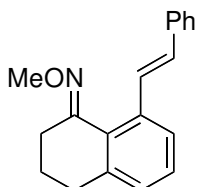


8-(2-Cyclohexylvinyl)-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (4.3d). To a vial in a glovebox was combined [Cp*RhCl₂]₂ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF₆ (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (44 mg, 0.25 mmol, 1 equiv), 6-chlorohexene (89 mg, 0.75 mmol, 3 equiv), Cu(OAc)₂ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH₄OH, and the resulting mixture was extracted with CH₂Cl₂ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, concentrated, and purified by column chromatography (2:1 Hex:EtOAc) to yield a clear oil (62 mg, 85% yield). IR (film): 2935, 1599, 1459, 1047 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 15.7 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.08 (dt, *J* = 15.7, 6.8 Hz, 1H), 4.04 (s, 3H), 3.62 (t, *J* = 6.7 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.70-2.66 (m, 2H), 2.35-2.26 (m, 2H), 1.95-1.86 (m, 2H), 1.84-1.76 (m, 2H), 1.75-1.65 (m, 2H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 154.9, 141.8, 137.0, 132.1, 129.4, 128.4, 128.2, 126.7, 125.9, 62.0, 45.0, 32.2, 32.1, 30.9, 26.5, 25.5, 21.1. HRMS (ES+) Calcd for C₁₇H₂₃ClNO [MH]⁺ 292.1463; Found 292.1440.

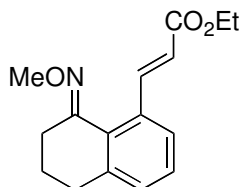


(2E,6E)-Methyl 7-(8-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-1-yl)hepta-2,6-dienoate (4.3e). To a vial in a glovebox was combined [Cp*RhCl₂]₂ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF₆ (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (44 mg, 0.25 mmol, 1 equiv), (E)-methyl hepta-2,6-dienoate (105 mg, 0.750 mmol, 3 equiv), Cu(OAc)₂ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH₄OH, and the resulting mixture was extracted with CH₂Cl₂ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, concentrated, and purified by column chromatography (20:1 Hex:EtOAc) to yield a clear oil (63 mg, 80% yield). IR (film): 2937, 1720, 1656, 1599, 1460, 1046 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.39 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 15.8 Hz, 1H), 7.12 – 7.01 (m, 2H), 6.06 (dt, *J* = 15.8, 6.2 Hz, 1H), 5.92 (d, *J* = 15.7 Hz, 1H), 4.02 (s, 3H), 3.76 (s, 3H), 2.79 (t, *J* = 6.8 Hz, 2H), 2.70 – 2.63 (m, 2H), 2.52 – 2.36 (m, 4H),

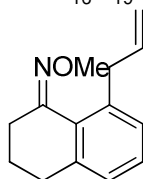
1.83-1.73 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 167.1, 154.9, 148.9, 141.8, 136.8, 132.6, 128.5, 128.3, 128.2, 126.9, 126.0, 121.3, 62.1, 51.4, 32.1, 31.5, 31.0, 25.5, 21.2. HRMS (ES+) Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_3$ $[\text{MH}]^+$ 314.1751; Found 314.1772.



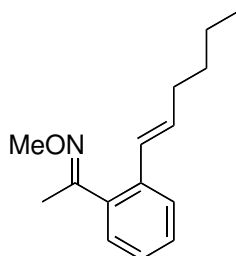
8-Styryl-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (4.3f). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF_6 (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (44 mg, 0.25 mmol, 1 equiv), styrene (78 mg, 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH_4OH , and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with Na_2SO_4 , concentrated, and purified by column chromatography (20:1 Hex:EtOAc) to yield a clear oil (67 mg, 98% yield). IR (film): 2933, 1597, 1494, 1045 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 7.79 (d, J = 16.2 Hz, 1H), 7.50-7.38 (m, 3H), 7.29-7.24 (m, 2H), 7.18-7.12 (m, 2H), 6.99 (d, J = 7.4 Hz, 1H), 6.84 (d, J = 16.2 Hz, 1H), 3.90 (s, 3H), 2.72 (t, J = 6.8 Hz, 2H), 2.61-2.57 (m, 2H), 1.74-1.67 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 155.0, 142.0, 138.3, 136.8, 131.0, 129.2, 128.6, 128.4, 128.1, 127.3, 127.1, 126.5, 125.8, 62.4, 31.0, 25.6, 21.2. HRMS (ES+) Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}$ $[\text{MH}]^+$ 278.1540; Found 278.1539.



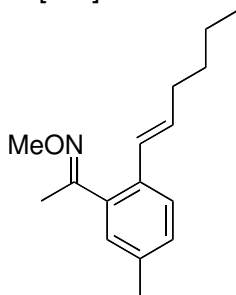
(2E)-Ethyl 3-(8-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-1-yl)acrylate (4.3g). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF_6 (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (44 mg, 0.25 mmol, 1 equiv), ethyl acrylate (75 mg, 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH_4OH , and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with Na_2SO_4 , concentrated, and purified by column chromatography (20:1 Hex:EtOAc) to yield a clear oil (56 mg, 81% yield). IR (film): 2936, 1705, 1631, 1599, 1460, 1044 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 8.28 (d, J = 15.8 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.17 (d, J = 15.8 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 2.70 (t, J = 6.8 Hz, 2H), 2.65-2.60 (m, 2H), 1.76-1.69 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 167.3, 154.1, 147.1, 141.9, 134.1, 130.3, 129.3, 128.4, 126.5, 117.8, 62.4, 60.2, 30.7, 25.3, 21.0, 14.4. HRMS (ES+) Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{MNa}]^+$ 296.1257; Found 296.1244.



8-Allyl-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (4.3h). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF_6 (17 mg, 0.050 mmol, 0.2 equiv), 3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (44 mg, 0.25 mmol, 1 equiv), allyl acetate (75 mg, 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH_4OH , and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with Na_2SO_4 , concentrated, and purified by column chromatography (50:1 Hex:Et₂O) to yield a clear oil (25 mg, 46% yield). IR (film): 2940, 1598 cm^{-1} . ¹H NMR (500 MHz, CDCl_3): δ 7.20-7.10 (m, 2H), 7.04-6.98 (m, 1H), 6.07 (ddt, $J = 16.8, 10.0, 6.7$ Hz, 1H), 5.07 (dd, $J = 16.8, 3.6$ Hz, 1H), 5.01 (dd, $J = 10.0, 3.6$ Hz, 1H), 3.98 (s, 3H), 3.78 (d, $J = 6.7$ Hz, 2H), 2.75 (t, $J = 6.9$ Hz, 2H), 2.68-2.60 (m, 2H), 1.78-1.70 (m, 2H). ¹³C{¹H} NMR (125 MHz, CDCl_3): δ 155.1, 142.1, 139.2, 138.9, 129.6, 129.3, 128.2, 126.1, 114.9, 62.0, 39.6, 31.2, 25.4, 21.3. HRMS (ES+) Calcd for $\text{C}_{14}\text{H}_{18}\text{NO}$ $[\text{MH}]^+$ 216.1383; Found 216.1394

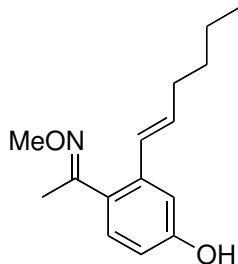


1-(2-(Hex-1-en-1-yl)phenyl)ethanone O-methyl oxime (4.5a). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF_6 (17 mg, 0.050 mmol, 0.2 equiv), acetophenone O-methyl oxime (37 mg, 0.25 mmol, 1 equiv), 1-hexene (63 mg, 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH_4OH , and the resulting mixture was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried with Na_2SO_4 , concentrated, and purified by column chromatography (30:1 Hex:Et₂O) to yield a clear oil (40 mg, 70% yield). IR (film): 2956, 1465, 1047 cm^{-1} . ¹H NMR (500 MHz, CDCl_3): δ 7.51 (d, $J = 7.8$ Hz, 1H), 7.41-7.19 (m, 3H), 6.52 (d, $J = 15.3$ Hz, 1H), 6.18 (dt, $J = 15.3, 6.9$ Hz, 1H), 4.02 (s, 3H), 2.25 (q, $J = 7.0$ Hz, 2H), 2.19 (s, 3H), 1.53-1.45 (m, 2H), 1.45-1.37 (m, 2H), 0.96 (t, $J = 7.2$ Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl_3): δ 157.2, 136.4, 135.9, 133.3, 128.7, 128.6, 127.8, 126.8, 126.2, 61.8, 32.9, 31.4, 22.3, 17.0, 14.0. HRMS (ES+) Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}$ $[\text{MH}]^+$ 232.1696; Found 232.1695.

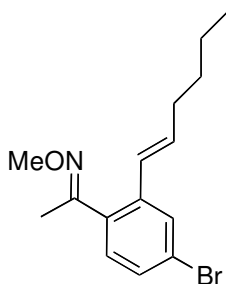


1-(2-(Hex-1-en-1-yl)-5-methylphenyl)ethanone O-methyl oxime (4.5c). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (9.3 mg, 0.015 mmol, 0.05 equiv), AgSbF_6 (20 mg, 0.060 mmol, 0.2 equiv), 1-(3-tolyl)ethanone O-methyl oxime (**4c**, 49 mg, 0.30 mmol, 1 equiv), 1-hexene (111.7 μL , 0.75 mmol, 3 equiv), $\text{Cu}(\text{OAc})_2$ (108 mg, 0.600 mmol, 2 equiv), and THF (3

mL). The mixture was transferred to a Schlenk tube equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was cooled to rt, diluted with sat. NH₄OH, and then extracted with CH₂Cl₂ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, concentrated, and purified by reverse phase column chromatography (MeCN:H₂O gradient) to yield a clear oil (53 mg, 73% yield). ¹H NMR (500 MHz, C₆D₆): δ 7.36 (d, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 0.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.65 (d, *J* = 15.7 Hz, 1H), 6.03 (dt, *J* = 15.6 Hz, 7.0 Hz, 1H), 3.92 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H), 2.04 (m, 2H), 1.28 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H). ¹³C{¹H} NMR (126 MHz, C₆D₆): δ 156.4, 136.5, 136.1, 133.7, 131.8, 129.6, 129.2, 128.2, 126.2, 61.3, 32.9, 31.4, 22.2, 20.6, 16.8, 13.8. HRMS (EI): Calcd for C₁₆H₂₃NO: 245.1780; observed: 245.1778.

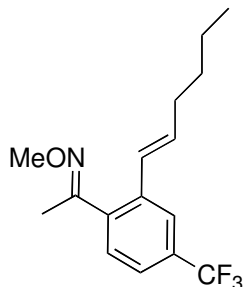


1-(2-(Hex-1-en-1-yl)-4-hydroxyphenyl)ethanone O-methyl oxime (4.5d). To a vial in a glovebox was combined [Cp**Rh*Cl₂]₂ (7.7 mg, 0.013 mmol, 0.05 equiv), AgSbF₆ (17 mg, 0.050 mmol, 0.2 equiv), 1-(4-hydroxyphenyl)ethanone O-methyl oxime (37 mg, 0.25 mmol, 1 equiv), 1-hexene (63 mg, 0.75 mmol, 3 equiv), Cu(OAc)₂ (96 mg, 0.53 mmol, 2 equiv), and THF (2.5 mL). The mixture was transferred to a 4 mL sealable vial equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The mixture was then cooled to rt, the reaction was quenched with sat. NH₄OH, and the resulting mixture was extracted with CH₂Cl₂ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, concentrated, and purified by column chromatography (7:1 Hex:EtOAc) to yield a clear oil (32 mg, 52% yield). IR (film): 2956, 2928, 1601, 1569, 1042 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.10 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.10 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.96 (s, 3H), 2.20 (q, *J* = 7.0 Hz, 2H), 2.12 (s, 3H), 1.49-1.40 (m, 2H), 1.39-1.33 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 157.6, 156.1, 138.0, 133.5, 129.9, 128.4, 127.5, 114.1, 112.9, 61.6, 32.8, 31.3, 22.3, 17.3, 13.9. HRMS (ES+) Calcd for C₁₅H₂₂NO₂ [MH]⁺ 248.1646; Found 248.1640.

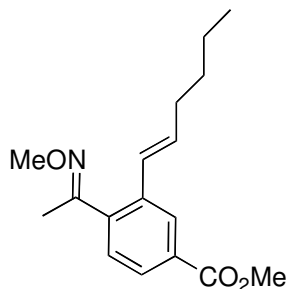


1-(4-Bromo-2-(hex-1-en-1-yl)phenyl)ethanone O-methyl oxime (4.5e). To a vial in a glovebox was combined [Cp**Rh*Cl₂]₂ (9.3 mg, 0.015 mmol, 0.05 equiv), AgSbF₆ (20 mg, 0.060 mmol, 0.2 equiv), 1-(4-bromophenyl)ethanone O-methyl oxime (**4e**, 68 mg, 0.30 mmol, 1 equiv), 1-hexene (111.7 μL, 0.75 mmol, 3 equiv), Cu(OAc)₂ (108 mg, 0.60 mmol, 2 equiv), and THF (3 mL). The mixture was transferred to a Schlenk tube equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 20 h with stirring. The reaction mixture was cooled to rt, diluted with sat. NH₄OH, and then extracted with CH₂Cl₂ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, concentrated, and purified by reverse phase column chromatography (MeCN:H₂O gradient) to yield a clear oil (62 mg, 67% yield). ¹H NMR (500

MHz, C₆D₆): δ 7.62 (d, *J* = 1.9 Hz, 1H), 7.11 (dd, *J* = 8.2 Hz, 2.0 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 5.78 (dt, *J* = 15.6 Hz, 7.0 Hz, 1H), 3.86 (s, 3H), 2.00 (s, 3H), 1.90 (q, *J* = 6.5 Hz, 2H), 1.19 (m, 4H), 0.82 (t, *J* = 6.8 Hz, 3H). ¹³C{¹H} (126 MHz, C₆D₆): δ 155.2, 138.6, 135.2, 134.2, 130.4, 129.5, 129.1, 126.9, 122.8, 61.4, 32.7, 31.1, 22.2, 16.4, 13.7. HRMS (EI): Calcd for C₁₅H₂₀BrNO: 309.0728; observed: 309.0723.



1-(2-(Hex-1-en-1-yl)-4-(trifluoromethyl)phenyl)ethanone O-methyl oxime (4.5f) To a vial in a glovebox was combined [Cp*RhCl₂]₂ (9.3 mg, 0.015 mmol, 0.05 equiv), AgSbF₆ (20 mg, 0.060 mmol, 0.2 equiv), 1-(4-(trifluoromethyl)phenyl)ethanone O-methyl oxime (**4f**, 68 mg, 0.30 mmol, 1 equiv), 1-hexene (111.7 μL, 0.75 mmol, 3 equiv), Cu(OAc)₂ (108 mg, 0.60 mmol, 2 equiv), and THF (3 mL). The mixture was transferred to a Schlenk tube equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 36 h with stirring. The reaction mixture was cooled to rt, diluted with sat. NH₄OH, and then extracted with CH₂Cl₂ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, concentrated, and purified by reverse phase column chromatography (MeCN:H₂O gradient) to yield a clear oil (40 mg, 45% yield). ¹H NMR (500 MHz, C₆D₆): δ 7.73 (s, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 5.85 (dt, *J* = 15.7 Hz, 7.0 Hz, 1H), 3.87 (s, 3H), 2.00 (s, 3H), 1.91 (q, *J* = 6.5 Hz, 2H), 1.19 (m, 4H), 0.83 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (126 MHz, C₆D₆): δ 155.1, 139.4, 137.3, 134.8, 130.5 (q, *J*_{CF} = 32.1 Hz, C-CF₃), 129.5, 126.9, 124.6 (q, *J*_{CF} = 272.3 Hz, CF₃), 123.1 (m, 1C), 123.0 (m, 1C) 61.5, 32.7, 31.0, 22.2, 16.2, 13.7. ¹⁹F{¹H} NMR (376.5 MHz, C₆D₆): δ -61.5. HRMS (EI): Calcd for C₁₆H₂₀F₃NO: 299.1497; observed: 299.1494.



Methyl 3-(hex-1-en-1-yl)-4-(1-(methoxyimino)ethyl)benzoate (4.5g). To a vial in a glovebox was combined [Cp*RhCl₂]₂ (9.3 mg, 0.015 mmol, 0.05 equiv), AgSbF₆ (20 mg, 0.060 mmol, 0.2 equiv), methyl-4-(1-(methoxyimino)ethyl)benzoate (**4g**, 62 mg, 0.30 mmol, 1 equiv), 1-hexene (111.7 μL, 0.75 mmol, 3 equiv), Cu(OAc)₂ (108 mg, 0.60 mmol, 2 equiv), and THF (3 mL). The mixture was transferred to a Schlenk tube equipped with a stir bar, removed from the glovebox, and heated at 75 °C for 36 h with stirring. The reaction mixture was cooled to rt, diluted with sat. NH₄OH, and then extracted with CH₂Cl₂ (3 x 4 mL). The combined organic layers were dried with Na₂SO₄, concentrated, and purified by reverse phase column chromatography (MeCN:H₂O gradient) to yield a clear oil (67 mg, 70% yield). ¹H NMR (500 MHz; C₆D₆): δ 8.44 (d, *J* = 1.6 Hz, 1H), 7.96 (dd, *J* = 8.0 Hz, 1.7 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 15.7 Hz, 1H), 6.05 (dt, *J* = 15.7 Hz, 6.9 Hz, 1H), 3.87 (s, 3H), 3.49 (s, 3H), 2.04 (s, 3H), 1.94 (qd, *J* = 6.7 Hz, 1.3 Hz, 2H), 1.20 (m, 4H), 0.82 (t, *J* = 6.8 Hz, 3H). ¹³C{¹H} NMR (126 MHz; C₆D₆): δ 166.1, 155.5, 140.3, 136.9, 134.1, 130.6, 129.1, 127.6 (Localized with

HMQC), 127.4 (Localized with HMQC), 127.3, 61.5, 51.3, 32.8, 31.1, 22.2, 16.3, 13.7. HRMS (EI): Calcd for C₁₇H₂₃NO₃: 289.1678; observed: 289.1674.

References

- (1) (a) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094-5115; (b) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987-6001.
- (2) (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586-1587; (b) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666-7673; (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256; (d) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512-3515; (e) Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169-6173; (f) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578-9579; (g) Grimster, N. P.; Cauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125-3129; (h) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097-2100; (i) Miura, M.; Tsuda, T.; Satoh, T.; Nomura, M. *Chem. Lett.* **1997**, 1103-1104; (j) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211-5215; (k) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972-1975; (l) Rubia-Garcia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511-6515; (m) Shi, B. F.; Zhang, Y. H.; Lam, J. K.; Wang, D. H.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 460-461; (n) Wang, D. H.; Engle, K. M.; Shi, B. F.; Yu, J. Q. *Science* **2010**, *327*, 315-319; (o) Wasa, M.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680-3681; (p) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230-7233; (q) Yokaota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476-1477; (r) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144-6148; (s) Zhang, Y. H.; Shi, B. F.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072-5074.
- (3) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337-338.
- (4) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212-11222.
- (5) (a) Chen, J.; Song, G.; Pan, C. L.; Li, X. *Org. Lett.* **2010**, *48*, 5430-5433; (b) Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Cat.* **2002**, *272*, 206-280; (c) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982-9983; (d) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407-1409; (e) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094-7099; (f) Wang, F.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5426-5429.
- (6) (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475; (b) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581-584.
- (7) (a) Song, J.; Shen, Q.; Xu, F.; Lu, X. *Tetrahedron* **2007**, *63*, 5148-5153; (b) Williams, B. S.; Leatherman, M. D.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **2005**, *127*, 5132-5146; (c) Zhang, Q.; Xu, W.; Lu, X. *J. Org. Chem.* **2005**, *70*, 1505-1507.
- (8) Itsuno, S.; Nakano, M.; Kyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039-2044.
- (9) Lijser, H. J.; Tsai, C. K. *J. Org. Chem.* **2004**, *69*, 3057-3067.
- (10) Sun, C. L.; Liu, N.; Li, B. J.; Yu, D. G.; Wang, Y.; Shi, Z. *Org. Lett.* **2010**, *12*, 184-187.
- (11) Desai, L.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141-1144.
- (12) Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.* **2002**, *67*, 6406-6414.
- (13) Chan, C. W.; Zhou, Z.; Chan, A. S. C.; Yu, W. Y. *Org. Lett.* **2010**, *12*, 3926-3929.
- (14) Haley, M. F.; Yates, K. *J. Org. Chem.* **1987**, *52*, 1817-1824.

Chapter 5. Rhodium(III) Catalyzed Arylation of Boc-Imines via C–H Bond Functionalization

*The first rhodium catalyzed arylation of imines proceeding via a C–H bond functionalization is reported. Use of a non-coordinating halide abstractor is important to obtain reactivity. Aryl branched N-Boc-amines are formed and a wide range of functionality is compatible with the reaction. A majority of this work has been published in a communication (Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. **2011**, ASAP)*

Authorship

This work was conducted in collaboration with Michael Tauchert

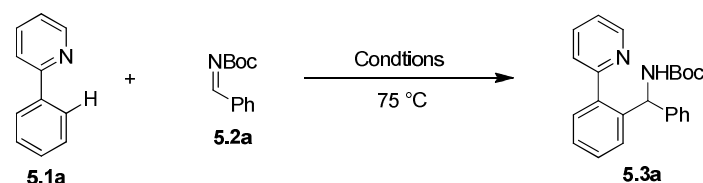
Introduction

In the area of C–H bond functionalization, arylation of alkenes and alkynes have been well explored.¹ In contrast, analogous additions across C–O² or C–N^{3,4,5} multiple bonds are rare. Due to the prevalence of α -branched amines in drugs and natural products,⁶ we sought a method for the arylation of imines via C–H bond functionalization. The most closely related transformations are Pd-catalyzed additions to *N*-tosyl imines that rely on the functionalization of acidic C–H bonds.⁵ Herein, we report the high-yielding 2-pyridyl-directed arylation of a wide range of aromatic *N*-Boc-imines with a Rh(III) catalyst.

Results and Discussion

Our investigations focused on additions to *N*-Boc-imines due to the convenience and ease of removal of the exceedingly popular Boc protecting group. As the test substrate for arylation, we chose 2-phenylpyridine (**5.1a**) because of the pyridyl directing group's high chemical stability and rich history in C–H functionalization with a variety of transition metals.^{1a,b,7}

Table 5.1. Screening of Reaction conditions^a



Entry	Catalyst	Additive	Solvent	% Yield ^b
1	[Cp*RhCl ₂] ₂	none	CH ₂ Cl ₂	0
2	[Cp*RhCl ₂] ₂	AgSbF ₆	CH ₂ Cl ₂	55
3	[Cp*RhCl ₂] ₂	AgSbF ₆	THF	30
4	[Cp*RhCl ₂] ₂	AgSbF ₆	DMF	0
5	[Cp*RhCl ₂] ₂	AgSbF ₆	C ₆ H ₆	0
6	[Cp*IrCl ₂] ₂	AgSbF ₆	CH ₂ Cl ₂	0
7	[Cp*RuCl ₂] _n	AgSbF ₆	CH ₂ Cl ₂	0
8 ^c	[Cp*RhCl ₂] ₂	AgSbF ₆	CH ₂ Cl ₂	60
9^d	[Cp*RhCl₂]₂	AgSbF₆	CH₂Cl₂	87
10 ^d	[Cp*RhCl ₂] ₂	AgOAc	CH ₂ Cl ₂	trace
11 ^d	[Cp*RhCl ₂] ₂	AgOTs	CH ₂ Cl ₂	30
12 ^d	[Cp*RhCl ₂] ₂	AgBF ₄	CH ₂ Cl ₂	54
13 ^d	[Cp*RhCl ₂] ₂	AgClO ₄	CH ₂ Cl ₂	69
14 ^d	[Cp*RhCl ₂] ₂	NaBPh ₄	CH ₂ Cl ₂	0

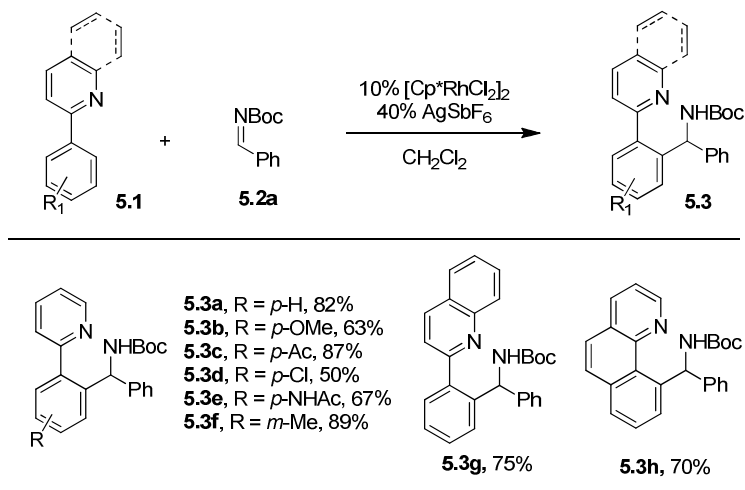
^a All reactions were run by employing 0.05 mmol of 2-phenylpyridine, 0.05 mmol of imine in 0.5 mL of solvent with 10 mol % catalyst and 40 mol % additive. ^b Yields are based on NMR using 2,6-dimethoxytoluene as an internal standard. ^c 0.1 mmol of imine. ^d 0.1 mmol of 2-phenylpyridine.

We began our reaction exploration with Rh(III) catalysts. This type of catalyst has been proposed to activate C–H bonds via an electrophilic deprotonation mechanism to generate an aryl-Rh(III) species.⁸ However, upon heating 10% [Cp*RhCl₂]₂ (Cp*: pentamethyl cyclopentadienyl) with 2-phenylpyridine and *N*-Boc-benzaldimine in CH₂Cl₂, no product was

observed (entry 1, Table 5.1). Theorizing that the lack of reactivity may be due to the chloride ligands on the metal, which could prevent coordination of the *N*-Boc-imine, AgSbF₆ was added as a halide abstractor and provided the desired product (**5.3a**) in 55% yield (entry 2).⁹ Utilizing coordinating solvents such as THF (entry 3) and DMF (entry 4) resulted in lower activity while solvents such as benzene failed due to insolubility of the catalyst system (entry 5). Analogous iridium (entry 6) and ruthenium (entry 7) based complexes were found to be inactive for this transformation. Substrate stoichiometries were also explored (entries 8 and 9) with the highest yield being achieved by employing two equivalents of 2-phenylpyridine (entry 9). Under these conditions, remaining aryl pyridine is recovered. Unreacted *N*-Boc imine is not observed and only small amounts of the hydrolyzed aldehyde product are detected. Other halide abstractors were also explored (entries 10-14) but AgSbF₆ proved to be optimal.

Evaluation of substituted 2-arylpyridines established that both electronically rich and deficient derivatives are effective arylation substrates and that the reaction is compatible with chloro, keto and acetanilide functional groups (Scheme 5.1). For 2-(3-methylphenyl)pyridine, functionalization occurred solely *para* to the methyl group to provide **5.3f**. Quinoline could also be used as a directing group in this chemistry (**5.3g**) and the more rigid benzo[*h*]quinoline provided the expected product (**5.3h**) in good yield. Notably, for all of the 2-arylpyridine substrates, products resulting from bis-arylation were not detected.

Scheme 5.1. Arylpyridine substrate scope^a



^a All reactions were run by heating 2-phenylpyridine (2 equiv), imine (1 equiv), [Cp^{*}RhCl₂]₂ (10 mol %), AgSbF₆ (40 mol %), and CH₂Cl₂ (0.1 M) in a sealed tube for 20 h at 75 °C. Isolated yields are reported.

The substrate scope was further extended to a broad variety of substituted aromatic *N*-Boc imines (Table 5.2, entries 1-12). Both electron-poor (entries 3, 5, 8 and 11) and electron-rich (entry 7) aromatic imines provided branched amine products in high yields. Substitution at the *ortho*- (entries 9 and 10), *meta*- (entry 11), and *para*- (entries 2-8) positions were all well tolerated. Moreover, the reaction showed excellent functional group compatibility with *N*-Boc-imines substituted with chloro (entries 2 and 9), nitro (entry 3), methoxy (entry 7), ester (entry 8) and even the electrophilic carboxaldehyde (entry 11) functionality all providing branched amine products in high yields. In addition, the 2-thienyl substituted branched amine product **5.3s** was obtained by addition to a heteroaromatic imine substrate (entry 12). Of the functionalities evaluated, only the nitrile group (entry 4) gave a low yield, likely due to competitive coordination of the CN group to the Rh(III) center. In support of this explanation, a dramatic reduction in yield was observed upon addition of benzonitrile to a previously successful substrate combination

(see entry 13 versus 6). While a 1:4 ratio of $[\text{Cp}^*\text{RhCl}_2]_2$ to AgSbF_6 gave consistently good results, we found that ratio could be decreased to 1:2 for most substrates with no effect on rates or yields (see entries 7, 9, 10 and 12). However, the reaction failed to work when the ratio was below 1:2. For more reactive imines, good yields may be obtained with 5 mol % $[\text{Cp}^*\text{RhCl}_2]_2$ (entry 5). This lower catalyst loading provided moderate yields when applied to other substrates as imine decomposition pathways become competitive with product formation (entries 1-2, 7). Further decreasing the catalyst loading to 2.5 mol % $[\text{Cp}^*\text{RhCl}_2]_2$ resulted in low yields.

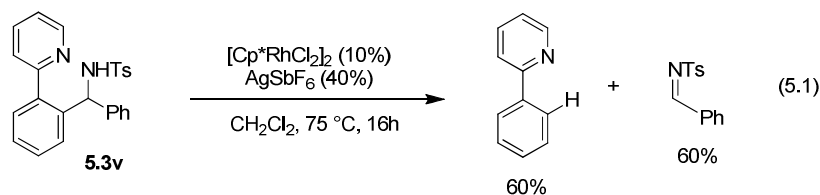
Table 5.2. Substrate scope of substituted imines^a

Entry	R	PG	Product	% Yield ^b
1	C ₆ H ₅	Boc	5.3a	82 (70) ^c
2	4-ClC ₆ H ₄	Boc	5.3i	77 (64) ^c
3	4-NO ₂ C ₆ H ₄	Boc	5.3j	77
4	4-CNC ₆ H ₄	Boc	5.3k	50
5	4-CF ₃ C ₆ H ₄	Boc	5.3l	95 (81) ^c
6	4-MeC ₆ H ₄	Boc	5.3m	70
7 ^d	4-MeOC ₆ H ₄	Boc	5.3n	70 (51) ^c
8	4-CO ₂ MeC ₆ H ₄	Boc	5.3o	70
9 ^d	2-ClC ₆ H ₄	Boc	5.3p	76
10 ^d	2-MeC ₆ H ₄	Boc	5.3q	92
11	3-CHOC ₆ H ₄	Boc	5.3r	81
12 ^d	2-thiophene	Boc	5.3s	71
13 ^e	4-MeC ₆ H ₄	Boc	5.3m	27
14 ^f	<i>n</i> Bu	P(O)Ph ₂	5.3t	0
15 ^f	<i>n</i> Bu	Ts	5.3u	72
16	C ₆ H ₅	Ts	5.3v	40
17	C ₆ H ₅	Ns	5.3w	51

^a All reactions were run by heating 2-phenylpyridine (2 equiv), imine (1 equiv), $[\text{Cp}^*\text{RhCl}_2]_2$ (10 mol %), AgSbF_6 (40 mol %), and CH_2Cl_2 (0.1 M) in a sealed tube for 20 h at 75 °C. ^b Isolated yield. ^c Values in parentheses are isolated yields after 40h at 75 °C using $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mol %) AgSbF_6 (20 mol %). ^d AgSbF_6 (20 mol %). ^e PhCN (1 equiv) added. ^f 2-phenylpyridine (1 equiv)

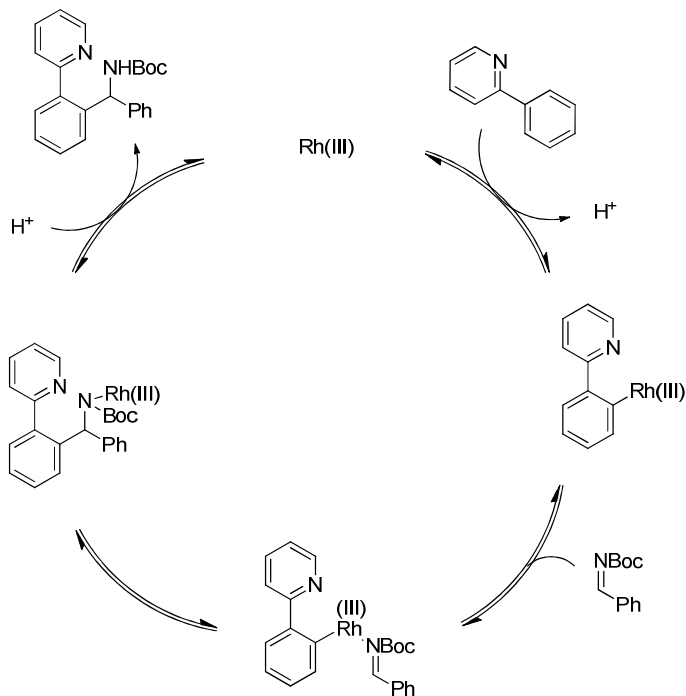
Alkyl *N*-Boc-imines were not effective substrates for this transformation as a result of self-condensation via imine to enamine tautomerization. We therefore explored other protecting groups for alkyl imine substrates. While *N*-diphenylphosphinoyl pentaldimine proved to be unreactive (entry 14), addition to the corresponding *N*-tosyl imine proceeded in good yield (entry 15). This result prompted us to also evaluate the reactivity of an aromatic *N*-tosyl imine substrate, but *N*-tosyl benzaldimine reacted with poor conversion to give the branched amine **5.3v** in only 40% yield (entry 16). We considered that the moderate yield observed might possibly be attributed to the reversibility of arylation of **5.3v**. This reversibility was demonstrated by subjecting purified **5.3v** to the reaction conditions, which resulted in an equilibrium mixture of **5.3v**, 2-phenylpyridine, and *N*-tosyl-benzaldimine (eq 5.1), consistent with the distribution observed in the arylation reaction (Table 5.2, entry 16). Significantly, while β -aryl elimination from aryl carbinols has been reported,¹⁰ to our knowledge, the corresponding transformation for

branched amines has not previously been described. The mechanism for β -aryl elimination between the previously reported carbinols and **5.3v** may be analogous, but further studies are needed. The reversibility of the reaction could be slightly shifted towards product by replacing the *N*-tosyl group with the more electronegative *N*-nosyl¹¹ (entry 17). Notably, reversibility was not observed for the arylation products of aromatic *N*-Boc imines or aliphatic *N*-tosyl pentanaldimine.



A possible mechanism for the arylation reaction could involve initial electrophilic deprotonation of the *ortho*-phenyl C–H bond of 2-phenylpyridine to form an Ar-Rh(III) intermediate (Scheme 5.2).⁸ Coordination of the *N*-Boc-imine would then activate the imine for addition followed by protonolysis to regenerate the catalyst. Alternatively, rhodium could serve as a Lewis acid to activate the imine for electrophilic aromatic substitution (EAS).¹² However, this latter pathway is unlikely given that only the electronically deactivated *ortho* position is functionalized on the electron deficient 2-phenylpyridine. Furthermore, the observation that the reaction is more efficient for electron poor 2-arylpyridines (see Scheme 5.1, **5.3b** vs **5.3c**) is inconsistent with an EAS pathway but supports an electrophilic deprotonation mechanism.

Scheme 5.2. Proposed catalytic cycle



Conclusion

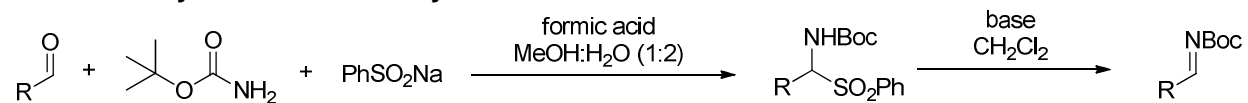
In summary, $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ catalyzes the addition of 2-arylpyridines to *N*-Boc and *N*-sulfonyl imines via C–H bond functionalization to give branched amine products. Many commonly encountered functional groups such as ketones, aldehydes, esters, halides, trifluoromethyl, amides and nitro groups are compatible with the method. Mechanistic studies and the investigation of alternative directing groups will be reported in due course.

Experimental

I. General Methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Substituted 2-phenylarenes were synthesized according to published procedures.^{13,14} Benzene, dichloromethane, and tetrahydrofuran were passed through a column of activated alumina under nitrogen. All reactions of air- and moisture-sensitive materials were carried out using syringe, cannula and/or inert atmosphere box techniques. All glassware was dried overnight at 150 °C or flame-dried under vacuum immediately prior to use. During workup procedures, organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure with a rotary evaporator. Chromatography was performed on Merck 60 230-240 mesh silica gel. NMR chemical shifts are reported in ppm relative to CHCl_3 (7.26 ppm for ^1H , and 77.23 ppm for ^{13}C NMR) or CD_2Cl_2 (5.32 ppm for ^1H , and 53.84 ppm for ^{13}C NMR). IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory or a Nicolet 6700 FT-IR equipped with an attenuated total reflectance accessory, and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. Mass spectra (HRMS) were obtained by the University of California at Berkeley Mass Spectrometry Facility or the Keck Center of Yale University.

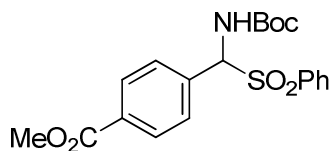
II. Synthesis of Starting Materials

Ila. Synthesis of Sulfonyl Carbamates

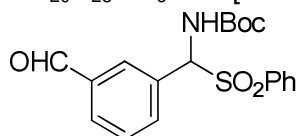


In a 25 mL round bottom flask was combined aldehyde (13.5 mmol, 2 equiv), *tert*-butyl carbamate (0.850 g, 7.25 mmol, 1 equiv), sodium benzenesulfonic acid (2.90 g, 18.1 mmol, 2.5 equiv), formic acid (0.52 mL, 13.5 mmol, 2 equiv), MeOH (8 mL), and water (15 mL). The reaction mixture was stirred at rt for 24 h during which time it becomes heterogeneous. The reaction mixture was filtered and the precipitate was washed with water and Et_2O to yield the sulfonyl carbamate as a white powder.

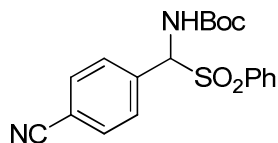
The synthetic procedures and characterization have previously been reported for the following sulfonyl carbamates: *N*-*tert*-butyl((2-methylphenyl)(phenylsulfonyl)methyl)carbamate ($\text{R} = 2\text{-MeC}_6\text{H}_4$),¹⁵ *N*-*tert*-butyl((4-methoxyphenyl)(phenylsulfonyl)methyl)carbamate ($\text{R} = 4\text{-OMeC}_6\text{H}_4$),¹⁵ *N*-*tert*-butyl((2-thienyl)(phenylsulfonyl)methyl)carbamate ($\text{R} = 2\text{-thienyl}$),¹⁵ *N*-*tert*-butyl(4-(trifluoromethyl)phenyl(phenylsulfonyl)methyl)carbamate ($\text{R} = 4\text{-CF}_3\text{C}_6\text{H}_4$),¹⁶ *N*-*tert*-butyl(4-chlorophenyl(phenylsulfonyl)methyl)carbamate ($\text{R} = 4\text{-ClC}_6\text{H}_4$),¹⁷ *N*-*tert*-butyl(2-chlorophenyl(phenylsulfonyl)methyl)carbamate ($\text{R} = 2\text{-ClC}_6\text{H}_4$),¹⁷ *N*-*tert*-butyl *N*-(4-nitrophenyl(phenylsulfonyl)methyl)carbamate ($\text{R} = 4\text{-NO}_2\text{C}_6\text{H}_4$),¹⁶ *N*-*tert*-butyl(4-methylphenyl(phenylsulfonyl)methyl)carbamate ($\text{R} = 4\text{-MeC}_6\text{H}_4$),¹⁷ *N*-*tert*-butylphenyl(phenylsulfonyl)methyl)carbamate ($\text{R} = \text{C}_6\text{H}_5$).¹⁷



***N*-tert-Butyl(4-methoxycarbonylphenyl)(phenylsulfonyl)methylcarbamate** The synthesis was performed according to the general procedure using 4-methoxycarbonylbenzaldehyde (2.79 g, 17.0 mmol, 2 equiv), *tert*-butyl carbamate (1.02 g, 8.71 mmol, 1 equiv), sodium benzenesulfinic acid (3.55 g, 21.6 mmol, 2.5 equiv), formic acid (0.60 mL, 16 mmol, 2 equiv), MeOH (10 mL), and water (18 mL) yielded the sulfonyl carbamate as a white powder (1.37 g, 3.38 mmol, 39% yield). mp: 176 °C (decomp.). IR (neat): 1726 (s), 1694 (s), 1506 (m), 1505 (m), 1308 (s), 1270 (s), 1248 (m), 1161 (w), 1142 (s), 1104 (m), 1085 (m), 1018 (w), 764 (w), 726 (m), 710 (m), 689 (m) cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.09 (d, *J* = 8.1 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.61 – 7.50 (m, 4H), 6.04 (d, *J* = 10.7 Hz, 1H), 5.97 (d, *J* = 10.6 Hz, 1H), 3.96 (s, 3H), 1.28 (s, 9H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 166.36, 153.50, 136.66, 134.72, 134.19, 131.38, 129.84, 129.48, 129.17, 129.01, 81.48, 73.63, 52.34, 28.01. HRMS (ESI+) Calcd for C₂₀H₂₃NO₆NaS [M+Na]⁺ 428.1138; Found 428.1131.



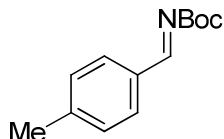
***N*-tert-Butyl(3-carbonylphenyl)(phenylsulfonyl)methylcarbamate** The synthesis was performed according to the general procedure using isophthalaldehyde (1.15 g, 8.57 mmol, 2 equiv), *tert*-butyl carbamate (0.50 g, 4.3 mmol, 1 equiv), sodium benzenesulfinic acid (1.76 g, 10.7 mmol, 2.5 equiv), formic acid (0.3 mL, 8 mmol, 2 equiv), MeOH (5 mL), and water (9 mL). The obtained solid was heated at reflux for 10 min in Et₂O (20 mL) and filtered hot to remove excess isophthalaldehyde. The sulfonyl carbamate was isolated as a white solid (0.67 g, 1.8 mmol, 42% yield). mp: 160 °C (decomp.). IR (neat): 1715 (m), 1688 (s), 1526 (m), 1448 (w), 1307 (m), 1169 (m), 1145 (s), 1084 (m), 800 (m), 715 (m), 686 (s) cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 10.08 (s, 1H), 8.06 – 7.93 (m, 4H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.73 (t, *J* = 7.1 Hz, 1H), 7.69 – 7.58 (m, 3H), 6.09 (d, *J* = 10.5 Hz, 1H), 5.92 (d, *J* = 10.1 Hz, 1H), 1.30 (s, 9H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 191.53, 153.56, 153.40, 136.64, 136.50, 135.07, 134.30, 131.20, 131.01, 129.85, 129.57, 129.31, 81.66, 73.21, 28.03. HRMS (ESI+) Calcd for C₁₉H₂₁NO₅NaS [M+Na]⁺ 398.1033; Found 398.1024.



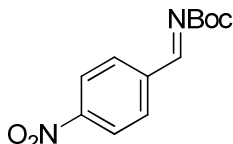
***N*-tert-Butyl(4-cyanophenyl)(phenylsulfonyl)methylcarbamate** The synthesis was performed according to the general procedure using 4-cyanobenzaldehyde (1.19 g, 9.08 mmol, 2 equiv), *tert*-butyl carbamate (0.51 g, 4.3 mmol, 1 equiv), sodium benzenesulfinic acid (1.73 g, 10.5 mmol, 2.5 equiv), formic acid (0.3 mL, 8 mmol, 2 equiv), MeOH (5 mL), and water (9 mL). The obtained solid was heated at reflux for 10 min in Et₂O (20 mL) and filtered hot to remove excess 4-cyanobenzaldehyde. The sulfonyl carbamate was isolated as a white solid (0.665 g, 1.79 mmol, 41% yield). mp: 158 °C (decomp.). IR (neat): 2231 (w), 1695 (m), 1498 (m), 1447 (w), 1305 (m), 1247 (m), 1138 (s), 1078 (m), 797 (m) cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.77 – 7.66 (m, 3H), 7.65 – 7.55 (m, 4H), 6.04 (d, *J* = 10.7 Hz, 1H), 5.95 (d, *J* = 10.5 Hz, 1H), 1.27 (s, 9H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 153.41, 136.35, 135.12, 134.44, 132.34, 129.75, 129.46, 129.30, 118.09, 113.71, 81.76, 73.29, 27.98. HRMS (ESI+) Calcd for C₁₉H₂₀N₂O₄NaS [M+Na]⁺ 395.1036; Found 395.1034.

IIb. General Synthesis Procedure I for the Preparation of Boc-Imines

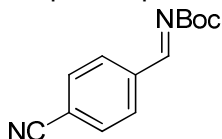
In a typical experiment sulfonyl carbamate (0.5 mmol) was dissolved in CH₂Cl₂ (8 mL) and 1.4 M K₂CO₃ (8 mL) was added. The biphasic solution was stirred vigorously at rt for 4 h. The organic layer was separated and the aqueous layer was washed two times with 10 mL of CH₂Cl₂. The combined organics were concentrated *in vacuo* at rt to yield the Boc-imine.



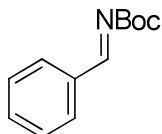
***N*-tert-Butyl-4-methylbenzylidenecarbamate** was synthesized according to the general synthesis procedure I using 1 mmol of sulfonyl carbamate and was obtained as a colorless oil (182 mg, 0.830 mmol, 83% yield). Characterization of this compound has been reported previously.¹⁵



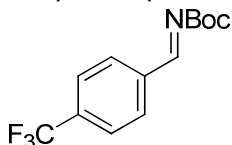
***N*-tert-Butyl-4-nitrobenzylidenecarbamate** was synthesized according to the general synthesis procedure I and was obtained as a white solid (109 mg, 0.437 mmol, 87% yield). Characterization of this compound has been reported previously.¹⁶



***N*-tert-Butyl-4-cyanobenzylidenecarbamate** was synthesized according to the general synthesis procedure I and was obtained as a white solid (73 mg, 0.32 mmol, 63% yield). mp: 85-87 °C. IR (film): 2230, 1698, 1631 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.83 (s, 1H), 8.02 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 1.59 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 166.7, 161.9, 137.7, 132.5, 130.2, 117.9, 116.4, 83.1, 27.8. HRMS (ESI+) Calcd for C₁₃H₁₅N₂O₂ [MH]⁺ 231.1129; Found 231.1128.



***N*-tert-Butyl-benzylidenecarbamate** was synthesized according to the general synthesis procedure I and was obtained as a colorless oil (57 mg, 0.28 mmol, 51% yield). Characterization of this compound has been reported previously.¹⁷

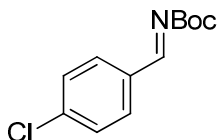


***N*-tert-Butyl-4-(trifluoromethyl)benzylidenecarbamate** was synthesized according to the general synthesis procedure I and was obtained as a white solid (80 mg, 0.30 mmol, 59% yield). Characterization of this compound has been reported previously.¹⁶

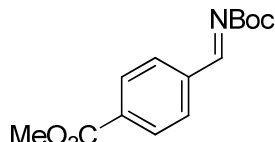
IIc. General Synthesis Procedure II for the Preparation of Boc-Imines II

In a typical experiment the sulfonyl carbamate (0.75 mmol) was dissolved in CH₂Cl₂ (10 mL) and dry Cs₂CO₃ (2.4 g, 7.5 mmol, 10 equiv) was added. The mixture was stirred vigorously

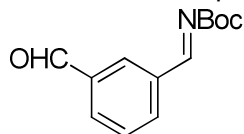
at rt for 1 h. The slurry was filtered and the organic phase concentrated *in vacuo* to afford the desired pure Boc-imine.



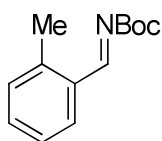
***N*-tert-Butyl-4-chlorobenzylidenecarbamate** was synthesized according to the general synthesis procedure II using of 0.37 mmol sulfonyl carbamate and was obtained as a white solid (54 mg, 0.225 mmol, 72% yield). Characterization of this compound has been reported previously.¹⁷



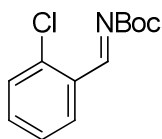
***N*-tert-Butyl-4-methoxycarbonylbenzylidenecarbamate** was synthesized according to the general synthesis procedure II and was obtained as a white solid (129 mg, 0.430 mmol, 55% yield). Characterization of this compound has been reported previously.¹⁸



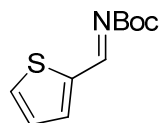
***N*-tert-Butyl-3-carboxylbenzylidenecarbamate** was synthesized according to the general synthesis procedure II and was obtained as a colorless oil (90 mg, 0.39 mmol, 50% yield). IR (neat): 1699 (s), 1633 (m), 1603 (w), 1368 (m), 1240 (s), 1138 (s), 984 (w), 851 (w), 802 (w), 682 (m) cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ 10.08 (s, 1H, CHO), 8.92 (s, 1H, CHN), 8.47 – 8.34 (m, 1H), 8.25 – 8.14 (m, 1H), 8.09 (dt, $J = 7.7, 1.4$ Hz, 1H), 7.66 (t, $J = 7.7$ Hz, 1H), 1.60 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3) δ 191.18, 167.78, 162.12, 136.96, 135.29, 135.10, 133.41, 131.51, 129.71, 82.84, 27.93. HRMS (ESI+) Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 256.0944; Found 256.0946.



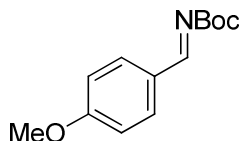
***N*-tert-Butyl-2-methylbenzylidenecarbamate** was synthesized according to the general synthesis procedure II using 0.29 mmol of sulfonyl carbamate and was obtained as a colorless oil (11 mg, 0.050 mmol, 17% yield). Characterization of this compound has been reported previously.¹⁵



***N*-tert-Butyl-2-chlorobenzylidenecarbamate** was synthesized according to the general synthesis procedure II using 0.6 mmol of the sulfonyl carbamate and was obtained as a colorless oil (132 mg, 0.551 mmol, 92% yield). Characterization of this compound has been reported previously.¹⁷

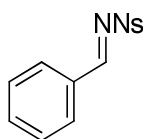


***N*-tert-Butyl-(thiophen-2-ylmethylene)carbamate** was synthesized according to the general synthesis procedure II using 0.58 mmol of the sulfonyl carbamate and was obtained as a slightly orange solid (112 mg, 0.530 mmol, 92% yield). Characterization of this compound has been reported previously.¹⁵

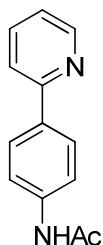


***N*-tert-Butyl-4-methoxybenzylidenecarbamate** was synthesized according to the general synthesis procedure II using 0.99 mmol of the sulfonyl carbamate and was obtained as a white solid (87 mg, 0.38 mmol, 37% yield). Characterization of this compound has been reported previously.¹⁷

IId. Synthesis of Other Starting Materials.



***N*-Benzylidene-4-nitrobenzenesulfonamide.** In a 50 mL round flask equipped with a magnetic stir bar, FeCl₃ (15 mg, 0.092 mmol, 0.04 equiv) was dissolved in EtOH (25 mL) and 4-nitrobenzenesulfonamide (506 mg, 2.50 mmol, 1 equiv) and freshly distilled benzaldehyde (0.51 mL, 5.0 mmol, 2 equiv) were subsequently added. The solution was stirred vigorously at rt for 16 h. All volatiles were then removed *in vacuo* and the resulting solid was crystallized from hot AcOEt/hexanes (1:3). The product was obtained as an off-white powder (360 mg, 1.24 mmol, 50%). Characterization of this compound has been reported previously.¹⁹

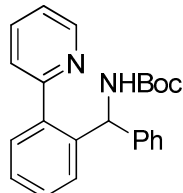


***N*-(4-(pyridin-2-yl)phenyl)acetamide.** In a 10 mL round bottom flask was combined 4-(pyridin-2-yl)aniline¹³ (200 mg, 1.18 mmol, 1 equiv), K₂CO₃ (490 mg, 3.5 mmol, 3 equiv), and CH₂Cl₂ (5 mL). A solution of acetyl chloride in dichloromethane (1 M, 1.7 mL, 1.7 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred at rt for 20 h. The reaction was quenched with sat. NaHCO₃ and the resulting mixture was extracted 3 x with CH₂Cl₂. The combined organics were concentrated and purified by chromatography (1:1 hex:EtOAc) to yield a yellow solid (220 mg, 1.03 mmol, 88% yield) mp: 130-132 °C. IR (film): 3249, 1664, 1590, 1532, 1466 cm⁻¹. ¹H NMR (400 MHz, C₆D₆): δ 8.71-8.64 (m, 1H), 8.53 (d, *J* = 4.5 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.62-7.57 (m, 1H), 7.57-7.51 (m, 3H), 7.11-7.05 (m, 1H), 1.99 (s, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 169.2, 156.9, 149.4, 139.2, 136.9, 134.9, 127.5, 121.9, 120.3, 120.0, 24.4. HRMS (ESI+) Calcd for C₁₃H₁₃N₂O [MH]⁺ 213.1028; Found 213.1023.

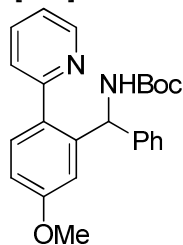
III. General Procedure for C–H Activation Experiments Monitored by NMR. In a nitrogen-filled inert atmosphere box, in a vial was combined [Cp*RhCl₂]₂, AgSbF₆, 2-phenylpyridine, *tert*-butyl benzylidenecarbamate, 2,6-dimethoxytoluene and solvent (0.5 mL). The reaction mixture was transferred to thin-walled NMR tube. The tube was fitted with a Cajon adapter, frozen with liquid nitrogen, and flame-sealed under vacuum. The tube was then placed in an oil bath set to the desired temperature. Periodically, the tube was removed from the bath,

cooled to room temperature, and analyzed by $^1\text{H-NMR}$ spectroscopy to monitor the progress of the reaction based on integration relative to 2,6-dimethoxytoluene as an internal standard. All optimization reactions were carried out via this procedure by varying temperature, ligand, and catalyst loading

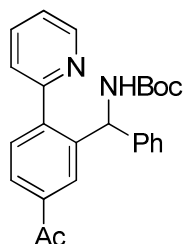
IV. Rh(III) Catalyzed Hydroarylation of Imines



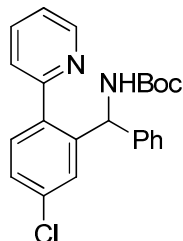
***N*-tert-Butyl (phenyl(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3a).** To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (15.5 mg, 0.0250 mmol, 0.1 equiv), AgSbF_6 (34.3 mg, 0.100 mmol, 0.4 equiv), 2-phenylpyridine (77.5 mg, 0.500 mmol, 2 equiv), *tert*-butyl benzylidene carbamate (51 mg, 0.25 mmol, 1 equiv), and CH_2Cl_2 (2.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (73.8 mg, 0.205 mmol, 82% yield) mp: 146-148 °C. IR (film): 3253, 1690 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.27 (m, 1H), 7.49-7.36 (m, 2H), 7.36-7.19 (m, 3H), 7.07-6.99 (m, 1H), 6.99-6.85 (m, 4H), 6.85-6.75 (m, 2H), 6.72-6.59 (m, 1H), 6.13 (d, $J = 8.5$ Hz, 1H), 1.36 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 160.0, 155.4, 148.4, 142.2, 141.2, 140.6, 136.5, 130.9, 130.1, 128.9, 127.8, 127.7, 126.4, 126.3, 124.3, 121.9, 79.3, 57.2, 28.6. HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{MH}]^+$ 361.1916; Found 361.1909.



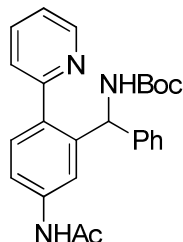
***N*-tert-Butyl ((5-methoxy-2-(pyridin-2-yl)phenyl)(phenyl)methyl)carbamate (5.3b).** To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (9.3 mg, 0.015 mmol, 0.1 equiv), AgSbF_6 (20.6 mg, 0.060 mmol, 0.4 equiv), 2-(4-methoxyphenyl)pyridine (55.5 mg, 0.300 mmol, 2 equiv), *tert*-butylbenzylidenecarbamate (31 mg, 0.15 mmol, 1 equiv), and CH_2Cl_2 (1.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (37 mg, 0.095 mmol, 63% yield) mp: 135-137 °C. IR (film): 3335, 1703 cm^{-1} . $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.46 (d, $J = 4.3$ Hz, 1H), 7.43-7.36 (m, 1H), 7.26-7.15 (m, 1H), 7.04-6.97 (m, 2 H), 6.97-6.87 (m, 4H), 6.87-6.80 (m, 3H), 6.80-6.73 (m, 1H), 6.11 (d, $J = 8.6$ Hz, 1H), 3.78 (s, 3H), 1.39 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 158.8, 154.3, 147.2, 141.5, 140.8, 135.3, 132.0, 131.2, 127.2, 126.6, 125.1, 123.1, 120.3, 114.7, 113.3, 111.5, 78.2, 56.3, 54.4, 27.5. HRMS (ESI+) Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{MH}]^+$ 391.2022; Found 391.2003.



***N*-tert-Butyl ((5-acetyl-2-(pyridin-2-yl)phenyl)(phenyl)methyl)carbamate (5.3c).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (15.5 mg, 0.0250 mmol, 0.1 equiv), AgSbF₆ (34.3 mg, 0.100 mmol, 0.4 equiv), 1-(4-(pyridin-2-yl)phenyl)ethanone (106 mg, 0.500 mmol, 2 equiv), *tert*-butyl benzylidenecarbamate (51 mg, 0.25 mmol, 1 equiv), and CH₂Cl₂ (2.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (2:1 hex:EtOAc) to yield a white solid (87 mg, 0.22 mmol, 87% yield) mp: 47-49 °C. IR (film): 3350, 1690, 1681 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.50 (d, *J* = 4.3 Hz, 1H), 8.08-8.02 (m, 1H), 7.88 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 7.07 (dd, *J* = 6.9, 5.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.97-6.89 (m, 3H), 6.75 (m, 2H), 6.55-6.49 (m, 1H), 6.23 (d, *J* = 8.7 Hz, 1H), 2.57 (s, 3H), 1.38 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 197.7, 158.7, 155.1, 148.5, 144.7, 141.6, 141.4, 137.0, 136.5, 131.2, 129.2, 127.9, 127.4, 126.5, 126.3, 124.1, 122.3, 79.5, 56.8, 28.4, 26.8. HRMS (ESI+) Calcd for C₂₅H₂₇N₂O₃ [MH]⁺ 403.2022; Found 403.2006.

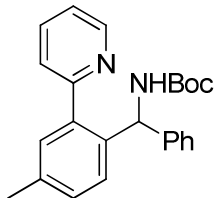


***N*-tert-Butyl ((5-chloro-2-(pyridin-2-yl)phenyl)(phenyl)methyl)carbamate (5.3d).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (9.3 mg, 0.015 mmol, 0.1 equiv), AgSbF₆ (20.6 mg, 0.060 mmol, 0.4 equiv), 2-(4-chlorophenyl)pyridine (57 mg, 0.30 mmol, 2 equiv), *tert*-butyl benzylidenecarbamate (31 mg, 0.15 mmol, 1 equiv), and CH₂Cl₂ (1.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (30 mg, 0.075 mmol, 50% yield) mp: 145-147 °C. IR (film): 3347, 1703, 1500, 1020 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.49 (d, *J* = 4.7 Hz, 1H), 7.48-7.41 (m, 2H), 7.28 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.21-7.17 (m, 1H), 7.07-7.03 (m, 1H), 7.00-6.93 (m, 4H), 6.85-6.78 (m, 2H), 6.49-6.38 (m, 1H), 6.14 (d, *J* = 8.1 Hz, 1H), 1.38 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 159.0, 155.5, 148.9, 143.1, 141.6, 139.1, 136.8, 134.9, 132.4, 129.8, 128.2, 127.9, 126.8, 126.6, 124.5, 122.3, 79.8, 56.9, 28.8. HRMS (ESI+) Calcd for C₂₃H₂₄ClN₂O₂ [MH]⁺ 395.1526; Found 395.1507.

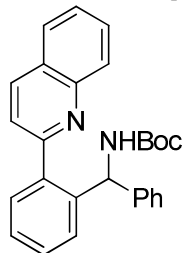


***N*-tert-Butyl ((5-acetamido-2-(pyridin-2-yl)phenyl)(phenyl)methyl)carbamate (5.3e).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (15.5 mg, 0.0250 mmol, 0.1 equiv), AgSbF₆

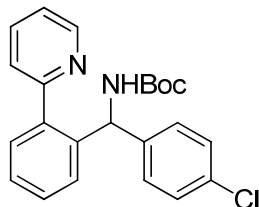
(34.3 mg, 0.100 mmol, 0.4 equiv), *N*-(4-(pyridin-2-yl)phenyl)acetamide (106 mg, 0.500 mmol, 2 equiv), *tert*-butyl benzylidenecarbamate (51 mg, 0.25 mmol, 1 equiv), and CH₂Cl₂ (2.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (1:2 hex:EtOAc) to yield a white solid (70 mg, 0.17 mmol, 67% yield) mp: 127-130 °C. IR (film): 3281, 1690, 1671 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.45 (d, *J* = 4.5 Hz, 1H), 8.29-8.25 (m, 1H), 7.71-7.74 (m, 1H), 7.44-7.36 (m, 1H), 7.31-7.25 (m, 1H), 7.19-7.15 (m, 1H), 7.04-6.98 (m, 1H), 6.98-6.83 (m, 5H), 6.83-6.74 (m, 2H), 6.08 (d, *J* = 8.5 Hz, 1H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 169.0, 159.3, 155.5, 148.2, 141.6, 141.3, 138.6, 136.5, 135.8, 131.7, 127.7, 126.3, 126.2, 124.2, 121.6, 120.8, 119.2, 79.4, 57.0, 28.5, 24.4. HRMS (ESI+) Calcd for C₂₅H₂₈N₃O₃ [MH]⁺ 418.2131; Found 418.2125.



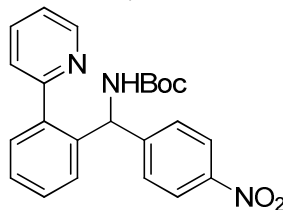
***N*-tert-Butyl ((4-methyl-2-(pyridin-2-yl)phenyl)(phenyl)methyl)carbamate (5.3f).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (9.3 mg, 0.015 mmol, 0.1 equiv), AgSbF₆ (20.6 mg, 0.060 mmol, 0.4 equiv), 2-(*m*-tolyl)pyridine (50.7 mg, 0.300 mmol, 2 equiv), *tert*-butyl benzylidenecarbamate (31 mg, 0.15 mmol, 1 equiv), and CH₂Cl₂ (1.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (50 mg, 0.13 mmol, 89% yield) mp: 53-56 °C. IR (film): 3312, 1697 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.52-8.42 (m, 1H), 7.47-7.35 (m, 1H), 7.35-7.22 (m, 1H), 7.15-7.10 (m, 1H), 7.10-6.76 (m, 8H), 6.76-6.54 (m, 1H), 6.07 (d, *J* = 8.3 Hz, 1H), 2.29 (s, 3H), 1.37 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 160.3, 155.6, 148.8, 142.7, 140.7, 138.5, 137.7, 136.7, 132.0, 130.3, 129.8, 128.1, 126.6, 126.5, 124.6, 122.1, 79.5, 57.2, 28.9, 21.4. HRMS (ESI+) Calcd for C₂₄H₂₇N₂O₂ [MH]⁺ 375.2073; Found 375.2066.



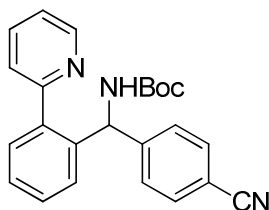
***N*-tert-Butyl (phenyl(2-(quinolin-2-yl)phenyl)methyl)carbamate (5.3g).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (9.3 mg, 0.015 mmol, 0.1 equiv), AgSbF₆ (20.6 mg, 0.060 mmol, 0.4 equiv), 2-phenylquinoline (61.5 mg, 0.300 mmol, 2 equiv), *tert*-butyl benzylidenecarbamate (31 mg, 0.15 mmol, 1 equiv), and CH₂Cl₂ (1.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (46 mg, 0.11 mmol, 75% yield) mp: 61-63 °C. IR (film): 3286, 1704, 1487 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, *J* = 8.8 Hz, 1H), 7.86-7.81 (m, 1H), 7.71-7.63 (m, 3H), 7.58-7.53 (m, 1H), 7.49-7.44 (m, 1H), 7.42-7.36 (m, 1H), 7.36-7.30 (m, 2H), 7.02-6.96 (m, 1H), 6.95-6.80 (m, 1H), 6.80-6.62 (m, 4H), 6.1 (d, *J* = 8.8 Hz, 1H), 1.41 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 160.5, 155.8, 147.0, 142.5, 142.2, 141.1, 136.9, 131.5, 131.1, 130.3, 129.3, 128.1, 127.9, 127.8, 127.0, 126.9, 126.3, 126.2, 126.1, 122.5, 79.4, 58.4, 28.9. HRMS (ESI+) Calcd for C₂₇H₂₇N₂O₂ [MH]⁺ 411.2073; Found 411.2061.



***N*-tert-Butyl ((4-chlorophenyl)(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3h).** To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (3.3 mg, 0.0053 mmol, 0.1 equiv), AgSbF_6 (6.8 mg, 0.020 mmol, 0.4 equiv), 2-phenylpyridine (15.4 mg, 0.0992 mmol, 2 equiv), 2,4-dimethoxytoluene (15.4 mg, 0.101 mmol, 2 equiv) *N*-tert-butyl-4-chlorobenzylidenecarbamate (12.8 mg, 0.0530 mmol, 1 equiv), and CH_2Cl_2 (0.5 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C_6D_6 . The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oil bath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield a white solid (16.0 mg, 0.0410 mmol, 77% yield) mp: 60 °C. IR (neat): 1699 (s), 1588 (w), 1488 (s), 1365 (m), 1247 (m), 1163 (s), 1090 (m), 1043 (w), 1014 (s), 752 (s) cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ 8.56 (s, 1H), 7.51 (m, 2H), 7.44 (td, 1H, $J = 7.5, 1.5$ Hz), 7.41 (td, 1H, $J = 7.2, 1.5$ Hz), 7.33 (m, 1H), 7.16 (d, $J = 5.3$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 6.99 (d, $J = 7.7$ Hz, 2H), 6.95 (d, $J = 8.1$ Hz, 1H), 6.86 (d, $J = 7.6$ Hz, 2H), 6.15 (d, $J = 7.6$ Hz, 1H, *CH*NBoc), 1.46 (s, 9H, *CMe*₃). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3) δ 159.88, 155.39, 148.34, 140.92, 140.73, 140.46, 136.72, 131.92, 131.12, 130.39, 128.99, 128.00, 127.82, 127.41, 124.31, 122.05, 79.49 (*Ar*₂CHN), 57.04 (*CMe*₃), 28.61 (*CMe*₃). HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_2\text{Cl}$ $[\text{MH}]^+$ 395.1521; Found 395.1530.

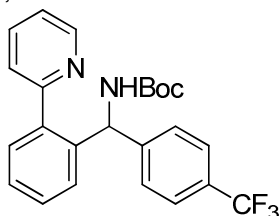


***N*-tert-Butyl ((4-nitrophenyl)(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3i).** To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (15.5 mg, 0.0250 mmol, 0.1 equiv), AgSbF_6 (34.3 mg, 0.100 mmol, 0.4 equiv), 2-phenylpyridine (77.5 mg, 0.500 mmol, 2 equiv), *tert*-butyl 4-nitrobenzylidenecarbamate (62.5 mg, 0.250 mmol, 1 equiv), and CH_2Cl_2 (2.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (78 mg, 0.19 mmol, 77% yield) mp: 51-53 °C. IR (film): 3306, 1701, 1514 1342 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 8.55 (d, $J = 4.4$ Hz, 1H), 7.85 (d, $J = 8.1$ Hz, 2H), 7.60-7.53 (m, 1H), 7.53-7.39 (m, 3H), 7.39-7.29 (m, 2H), 7.16-7.05 (m, 3H), 7.05-6.98 (m, 1H), 6.25 (d, $J = 9.1$ Hz, 1H), 1.48 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 159.5, 155.4, 150.2, 148.1, 146.1, 140.0, 139.8, 136.9, 131.3, 131.0, 121.1, 128.3, 126.7, 124.2, 122.6, 122.1, 79.7, 57.7, 28.4. HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_4$ $[\text{MH}]^+$ 406.1762; Found 406.1768.

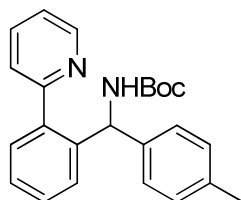


***N*-tert-Butyl ((4-cyanophenyl)(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3j).** To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (25.5 mg, 0.0413 mmol, 0.1 equiv), AgSbF_6 (56.7

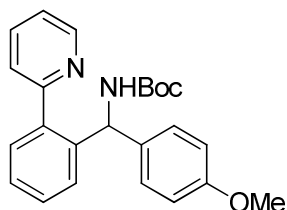
mg, 0.165 mmol, 0.4 equiv), 2-phenylpyridine (128 mg, 0.826 mmol, 2 equiv), *tert*-butyl 4-cyanobenzylidenecarbamate (95.0 mg, 0.413 mmol, 1 equiv), and CH₂Cl₂ (4.1 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (3:1 hex:EtOAc) to yield a white solid (85 mg, 0.21 mmol, 50% yield) mp: 55-57 °C. IR (film): 3299, 2226, 1695, 1472 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.53 (d, *J* = 4.4 Hz, 1H), 7.56-7.47 (m, 2H), 7.47-7.39 (m, 2H), 7.36-7.31 (m, 1H), 7.31-7.24 (m, 3H), 7.14-7.09 (m, 1H), 7.06-7.01 (m, 2H), 7.01-6.96 (m, 1H), 6.21 (d, *J* = 8.2 Hz), 1.47 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 159.5, 155.3, 148.1, 148.0, 140.1, 140.0, 136.7, 131.3, 131.2, 131.0, 129.1, 128.3, 126.6, 124.1, 122.0, 118.9, 109.7, 79.6, 57.7, 28.5. HRMS (ESI+) Calcd for C₂₄H₂₄N₃O₂ [MH]⁺ 386.1864; Found 386.1866.



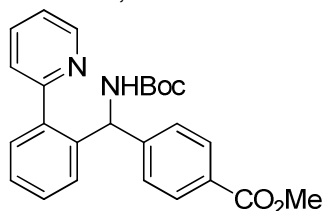
***N*-tert-Butyl ((2-(pyridin-2-yl)phenyl)(4-(trifluoromethyl)phenyl)methyl)carbamate (5.3k).** To a vial in a glovebox was combined [Cp**RhCl*₂]₂ (13.6 mg, 0.022 mmol, 0.1 equiv), AgSbF₆ (30.2 mg, 0.088 mmol, 0.4 equiv), 2-phenylpyridine (68 mg, 0.44 mmol, 2 equiv), *tert*-butyl 4-(trifluoromethyl)benzylidenecarbamate (60 mg, 0.22 mmol, 1 equiv), and CH₂Cl₂ (2.2 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (89 mg, 0.21 mmol, 95% yield) mp: 52-54 °C. IR (film): 3260, 1693, 1325 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.55 (d, *J* = 4.9 Hz, 1H), 7.56-7.37 (m, 4H), 7.35-7.29 (m, 1H), 7.26-7.22 (d, 2H), 7.14-7.08 (m, 1H), 7.08-6.94 (m, 4H), 6.3 (d, *J* = 9.4 Hz, 1H), 9.25 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 159.7, 155.3, 148.1, 146.4, 140.4, 140.3, 136.6, 131.0, 130.7, 128.9, 128.4, 128.3 (q, *J*_{C-F} = 31.1 Hz), 126.3, 124.5 (q, *J*_{C-F} = 3.1 Hz), 124.2, 124.1 (q, *J*_{C-F} = 270.2 Hz), 121.9, 79.5, 57.4, 28.5. ¹⁹F NMR (375 Mhz, CDCl₃): δ -61.7 HRMS (ESI+) Calcd for C₂₄H₂₄F₃N₂O₂ [MH]⁺ 429.1785; Found 429.1790.



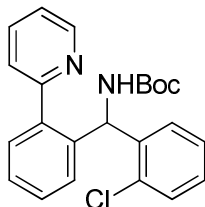
***N*-tert-Butyl ((2-(pyridin-2-yl)phenyl)(p-tolyl)methyl)carbamate (5.3l).** To a vial in a glovebox was combined [Cp**RhCl*₂]₂ (15.5 mg, 0.0250 mmol, 0.1 equiv), AgSbF₆ (34.3 mg, 0.100 mmol, 0.4 equiv), 2-phenylpyridine (77.5 mg, 0.499 mmol, 2 equiv), *tert*-butyl 4-methylbenzylidenecarbamate (54.8 mg, 0.250 mmol, 1 equiv), and CH₂Cl₂ (2.5 mL). The reaction mixture was transferred to a 5 mL Schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (65 mg, 0.18 mmol, 70% yield) mp: 49-51 °C. IR (film): 3299, 1696, 1472 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.58 (d, *J* = 4.5 Hz, 1H), 7.58-7.50 (m, 1H), 7.50-7.30 (m, 4 H), 7.18-7.09 (m, 2H), 6.92-6.72 (m, 4 H), 6.53-6.34 (m, 1H), 6.16 (d, *J* = 8.3 Hz, 1H), 2.19 (s, 3H), 1.44 (s, 9H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 159.7, 155.1, 148.4, 140.9, 140.3, 139.1, 136.2, 135.7, 130.7, 129.4, 128.7, 128.4, 127.5, 126.2, 124.2, 121.7, 79.1, 56.5, 28.4, 20.9. HRMS (ESI+) Calcd for C₂₃H₂₇N₂O₂ [MH]⁺ 375.2068; Found 375.2076



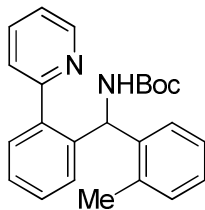
***N*-tert-Butyl((4-methoxyphenyl)(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3m).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (3.0 mg, 0.005 mmol, 0.1 equiv), AgSbF₆ (3.7 mg, 0.011 mmol, 0.2 equiv), 2-phenylpyridine (15.5 mg, 0.100 mmol, 2 equiv), 2,4-dimethoxytoluene (15.4 mg, 0.101 mmol, 2 equiv) a solution of *N*-tert-butyl-4-methoxybenzylidenecarbamate in CH₂Cl₂ (0.13 mL, 0.42 M, 0.055 mmol, 1 equiv), and CH₂Cl₂ (0.5 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C₆D₆. The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oil bath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield a white solid (15.1 mg, 0.039 mmol, 70% yield). mp: 50 °C. IR (neat): 2160 (m, broad), 2027 (m, broad), 1698 (s), 1586 (w), 1508 (m), 1468 (w), 1364 (m), 1245 (s), 1161 (s), 1025 (m), 752 (s) cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 8.61 (s, 1H), 7.57 (t, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 6.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.35 (s, 1H), 7.16 (s, 1H), 7.13 (m, 1H), 6.85 (m, 2H), 6.61 (m, 2H), 6.53 (m, 1H), 6.18 (d, *J* = 8.0 Hz, 1H, *CHN*Boc), 3.72 (s, 3H, *OMe*), 1.47 and 1.48 (rotamers of *CMe*₃, 9H, coalescence at 323K). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 159.83, 157.94, 155.13, 148.41, 141.04, 140.42, 136.34, 134.36, 130.76, 129.29, 128.66, 127.47, 124.17, 121.75, 113.95, 113.22, 79.27 (*Ar*₂*CHN*), 56.37 (*CMe*₃), 55.21 (*OMe*), 28.47 and 28.24 (rotamers of *CMe*₃, coalescence at 323 K). HRMS (ESI+) Calcd for C₂₄H₂₇N₂O₃ [MH]⁺ 391.2016; Found 391.2030.



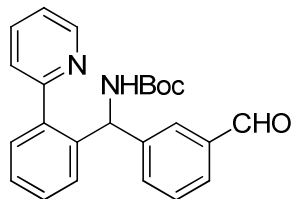
***N*-tert-Butyl ((4-methylbenzoato)(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3n).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (3.6 mg, 0.006 mmol, 0.1 equiv), AgSbF₆ (8.5 mg, 0.025 mmol, 0.5 equiv), 2-phenylpyridine (15.4 mg, 0.099 mmol, 2 equiv), 2,4-dimethoxytoluene (15.4 mg, 0.101 mmol, 2 equiv) *N*-tert-butyl-4-methoxycarbonylbenzylidenecarbamate (13.2 mg, 0.050 mmol, 1 equiv), and CH₂Cl₂ (0.5 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C₆D₆. The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oil bath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield a white solid (14.6 mg, 0.035 mmol, 70% yield). mp: 71 °C. IR (neat): 1705 (s), 1610 (w), 1470 (m), 1365 (w), 1276 (s), 1161 (s), 1103 (m), 1043 (w), 1017 (m), 753 (s) cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J* = 4.2 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 6.9 Hz, 1H), 7.54 – 7.43 (m, 3H), 7.38 (d, *J* = 7.1 Hz, 1H), 7.22 – 7.11 (m, 2H), 7.03 (m, 2H), 6.27 (d, *J* = 9.0 Hz, 1H, *CHN*Boc), 3.88 (s, 3H, *CO*₂*Me*), 1.51 (s, 9H, *CMe*₃). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 167.01, 159.73, 155.40, 148.17, 147.68, 140.57, 140.51, 140.33, 136.67, 131.14, 131.09, 130.80, 128.95, 128.02, 125.99, 124.21, 121.98, 79.65 (*Ar*₂*CHN*), 57.62 (*CMe*₃), 51.98 (*OMe*), 28.51 (*CMe*₃). HRMS (ESI+) Calcd for C₂₅H₂₇N₂O₄ [MH]⁺ 419.1965; Found 419.1969.



***N*-tert-Butyl((2-chlorophenyl)(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3o).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (3.0 mg, 0.005 mmol, 0.1 equiv), AgSbF₆ (4.8 mg, 0.014 mmol, 0.2 equiv), 2-phenylpyridine (16.1 mg, 0.104 mmol, 2 equiv), 2,4-dimethoxytoluene (15.8 mg, 0.104 mmol, 2 equiv) a solution of *N*-tert-butyl-2-chlorobenzylidenecarbamate in CH₂Cl₂ (0.25 mL, 0.20 M, 0.05 mmol, 1 equiv), and CH₂Cl₂ (0.45 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C₆D₆. The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oil bath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield a white solid (17.7 mg, 0.047 mmol, 76% yield). mp: 82 °C. IR (neat): 1697 (s), 1468 (m), 1364 (m), 1255 (m), 1160 (s), 1017 (m), 749 (s) cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 8.67 (s, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.39 (m, 3H), 7.35 - 7.30 (m, 2H), 7.26 - 7.23 (m, 1H), 7.21 (d, *J* = 5.5 Hz, 1H), 7.17 (s, 1H), 7.10 (m, 2H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.85 (s, 1H), 1.47 and 1.48 (rotamers of CMe₃, 9H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 154.56, 148.94, 140.77, 139.44, 138.60, 136.46, 133.14, 130.45, 129.62, 129.15, 128.22, 128.53, 128.12, 127.87, 127.74, 126.26, 123.79, 121.98, 79.50 (Ar₂CHN), 54.65 (CMe₃), 28.41 and 28.33 (rotamers of CMe₃). HRMS (ESI+) Calcd for C₂₃H₂₃N₂O₂Cl [MH]⁺: 395.1521; Found 395.1527.

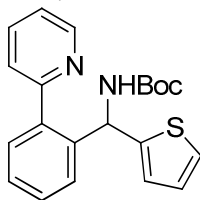


***N*-tert-Butyl((2-methylphenyl)(2-(pyridin-2-yl)phenyl)methyl)carbamate (5.3p).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (3.1 mg, 0.005 mmol, 0.1 equiv), AgSbF₆ (3.8 mg, 0.011 mmol, 0.2 equiv), 2-phenylpyridine (16.7 mg, 0.108 mmol, 2 equiv), 2,4-dimethoxytoluene (15.4 mg, 0.101 mmol, 2 equiv) a solution of *N*-tert-butyl-2-methylbenzylidenecarbamate in CH₂Cl₂ (0.17 mL, 0.30 M, 0.051 mmol, 1 equiv), and CH₂Cl₂ (0.5 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C₆D₆. The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oil bath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield a white solid (17.7 mg, 0.047 mmol, 92% yield). mp: 55 °C. IR (neat): 1696 (s), 1485 (m), 1426 (w), 1364 (m), 1250 (m), 1162 (s), 1017 (m), 751 (s) cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, *J* = 4.1 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.47 - 7.31 (m, 4H), 7.21 (m, 2H), 7.04 (m, 4H), 6.33 (d, *J* = 7.8 Hz, 1H, CHNHBoc), 5.55 (d, *J* = 7.4 Hz, 1H, NHBoc), 2.01 (s, 3H, ArMe), 1.54 - 1.37 (rotamers, 9H, CMe₃). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 154.51, 149.07, 140.72, 140.11, 139.55, 136.26, 135.78, 130.37, 130.32, 128.55, 128.38, 127.50, 126.84, 126.08, 125.56, 124.26, 123.75, 121.88, 79.30 (Ar₂CHN), 53.61 (CMe₃), 28.44 and 28.26 (rotamers CMe₃), 19.43 (ArMe). HRMS (ESI+) Calcd for C₂₄H₂₇N₂O₂ [MH]⁺ 375.2067; Found 375.2072.

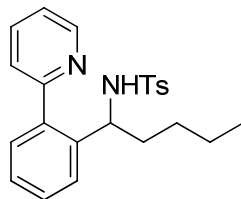


***N*-tert-Butyl ((3-carboxylphenyl)(2-pyridin-2-yl)phenyl)methylcarbamate (5.3q).**

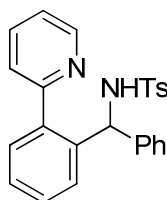
To a vial in a glovebox was combined [Cp*RhCl₂]₂ (3.5 mg, 0.006 mmol, 0.1 equiv), AgSbF₆ (7.7 mg, 0.022 mmol, 0.4 equiv), 2-phenylpyridine (15.5 mg, 0.100 mmol, 2 equiv), 2,4-dimethoxytoluene (15.4 mg, 0.101 mmol, 2 equiv) *N*-tert-butyl-3-carboxylbenzylidenecarbamate (14.5 mg, 0.062 mmol, 1 equiv), and CH₂Cl₂ (0.5 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C₆D₆. The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oil bath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield a white solid (16.9 mg, 0.050 mmol, 81% yield). mp: 52 °C. IR (neat): 1694 (s), 1488 (m), 1365 (w), 1246 (m), 1157 (s), 1044 (w), 1018 (m), 794 (m), 752 (s) cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 9.79 (s, 1H, ArCHO), 8.56 (d, *J* = 4.8 Hz, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.49 (d, *J* = 6.6 Hz, 1H), 7.47 – 7.39 (m, 4H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.23 – 7.14 (m, 3H), 7.11 – 7.06 (m, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.25 (d, *J* = 8.9 Hz, 1H), 1.48 (bs, 9H, CMe₃). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 192.24 (ArCHO), 159.78, 155.40, 148.17, 143.56, 140.49, 140.27, 136.58, 135.75, 132.36, 131.11, 130.75, 129.01, 128.29, 128.06, 127.61, 127.01, 124.09, 121.89, 79.52 (Ar₂CHN), 57.39 (CMe₃), 28.48 (CMe₃). HRMS (ESI+) Calcd for C₂₄H₂₅N₂O₃ [MH]⁺ 389.1860; Found 389.1866.



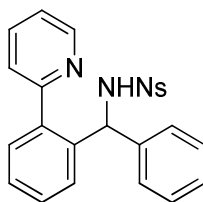
***N*-tert-Butyl(thiophene-2-yl)(2-pyridin-2-yl)phenyl)methylcarbamate (5.3r).** To a vial in a glovebox was combined [Cp*RhCl₂]₂ (3.3 mg, 0.005 mmol, 0.1 equiv), AgSbF₆ (9.0 mg, 0.026 mmol, 0.5 equiv), 2-phenylpyridine (15.8 mg, 0.102 mmol, 1 equiv), 2,4-dimethoxytoluene (15.5 mg, 0.102 mmol, 1 equiv) a solution of *N*-tert-butyl-(thiophen-2-ylmethylene)carbamate in CH₂Cl₂ (0.30 mL, 0.27 M, 0.08 mmol, 1 equiv), and CH₂Cl₂ (0.40 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C₆D₆. The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oil bath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield an orange solid (21.1 mg, 0.057 mmol, 71% yield). mp: 110 °C. IR (neat): 1694 (s), 1470 (s), 1364 (m), 1246 (m), 1160 (s), 1043 (w), 1014 (m), 751 (s), 694 (s) cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 8.58 (d, *J* = 4.1 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.55 (d, *J* = 6.7 Hz, 1H), 7.47 – 7.34 (m, 3H), 7.24 – 7.18 (m, 1H), 7.14 (dd, *J* = 6.0, 1H), 6.95 (m, 2H), 6.65 (s, 1H), 6.42 (s, 1H), 6.37 (d, *J* = 8.5 Hz, 1H), 1.46 (bs, 9H, CMe₃). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 159.71, 155.03, 148.47, 147.32, 140.42, 136.53, 130.98, 129.31, 128.85, 128.03, 126.26, 124.48, 124.30, 124.22, 123.97, 121.82, 79.45 (Ar₂CHN), 54.11 (CMe₃), 28.47 and 28.34 (rotamers of CMe₃). HRMS (ESI+) Calcd for C₂₁H₂₃N₂O₂S [MH]⁺ : 367.1475; Found 367.1480.



4-Methyl-N-(1-(2-(pyridin-2-yl)phenyl)pentyl)benzenesulfonamide (5.3u). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (6.5 mg, 0.011 mmol, 0.1 equiv), AgSbF_6 (8.9 mg, 0.026 mmol, 0.3 equiv), 2-phenylpyridine (14.8 mg, 0.0953 mmol, 1 equiv), 2,4-dimethoxytoluene (14.6 mg, 0.0959 mmol, 1 equiv), 4-methyl-N-pentylidenebenzenesulfonamide⁸ and CH_2Cl_2 (0.70 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C_6D_6 . The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oilbath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (75:25 hexanes:EtOAc) to yield a white solid (26.4 mg, 0.069 mmol, 72% yield). mp: 105 °C. IR (neat): 3060 (w), 1588 (9w), 1469 (m), 1323 (s), 1157 (s), 1147 (s), 1092 (s), 1053 (m), 997 (w), 951 (m), 754 (s), 658 (s) cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 8.72 (d, $J = 4.1$ Hz, 1H), 8.37 (s, 1H), 7.84 (td, $J = 7.7, 1.8$ Hz, 1H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 7.9$ Hz, 1H), 7.38 – 7.33 (m, 1H), 7.26 – 7.16 (m, 2H), 7.04 – 6.95 (m, 3H), 6.83 (d, $J = 7.4$ Hz, 1H), 4.33 (ddd, $J = 7.7$ Hz, 1H, $\text{ArCH}(\text{NHTs})\text{Bu}$), 2.31 (s, 3H), 1.48 – 1.34 (m, 1H), 1.23 – 1.10 (m, 2H, CH_2Pr), 1.11 – 0.98 (m, 2H, CH_2Et), 1.00 – 0.84 (m, 1H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.68 (t, $J = 7.1$ Hz, 3H, CH_2CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3) δ 160.61, 148.29, 142.21, 139.53, 138.82, 138.69, 137.65, 131.48, 130.41, 129.04, 128.37, 127.30, 127.03, 124.82, 122.46, 59.59 ($n\text{BuCHNTs}$), 35.17 (CH_2Pr), 28.69 (CH_2Et), 22.14 (Ar-Me), 21.49 (CH_2Me), 13.87 (CH_2Me). HRMS (ESI+) Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ $[\text{MH}]^+$: 395.1788; Found 395.1786.



4-Methyl-N-(phenyl(2-(pyridin-2-yl)phenyl)methyl)benzenesulfonamide (5.3v). To a vial in a glovebox was combined $[\text{Cp}^*\text{RhCl}_2]_2$ (15.5 mg, 0.0250 mmol, 0.1 equiv), AgSbF_6 (34.3 mg, 0.100 mmol, 0.4 equiv), 2-phenylpyridine (39 mg, 0.25 mmol, 1 equiv), *N*-benzylidene-4-methylbenzenesulfonamide (65 mg, 0.25 mmol, 1 equiv), and CH_2Cl_2 (2.5 mL). The reaction was transferred to a 5 mL schlenk tube, removed from the glovebox, and heated at 75 °C for 20 h. Reaction was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (5:1 hex:EtOAc) to yield a white solid (42 mg, 0.10 mmol, 40% yield) mp: 152-154 °C. IR (film): 3260, 1330, 1148, 1048 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 8.78 (d, $J = 10.5$ Hz, 1H), 8.45 (d, $J = 4.6$ Hz, 1H), 7.54 (d, $J = 7.9$ Hz, 2H), 7.42-7.33 (m, 1H), 7.23-7.10 (m, 2H), 7.06-6.90 (m, 5H), 6.90-6.78 (m, 6H), 5.63 (d, $J = 9.9$ Hz, 1H), 2.25 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 159.8, 147.5, 142.3, 140.7, 139.9, 139.4, 138.7, 137.0, 131.4, 131.1, 129.1, 128.1, 127.7, 127.3, 126.9, 126.2, 125.9, 124.4, 121.9, 61.4, 21.4. HRMS (ESI+) Calcd for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ $[\text{MH}]^+$ 415.1480; Found 415.1478.



4-Nitro-*N*-(phenyl-(2-(pyridin-2-yl)phenyl)methyl)benzenesulfonamide (5.3w). To a vial in a glovebox was combined [Cp*RhCl₂]₂ (1.6 mg, 0.003 mmol, 0.05 equiv), AgSbF₆ (5.0 mg, 0.015 mmol, 0.3 equiv), 2-phenylpyridine (15.8 mg, 0.102 mmol, 2 equiv), 2,4-dimethoxytoluene (15.5 mg, 0.102 mmol, 2 equiv), 4-nitro-*N*-benzylidenebenzenesulfonamide, and CH₂Cl₂ (0.60 mL). The slurry was transferred to an NMR tube equipped with a sealed capillary containing C₆D₆. The tube was closed with a Cajon adapter, removed from the glovebox, flame sealed and then placed into an oilbath preheated to 75 °C for 20 h. The reaction mixture was then cooled to rt, concentrated *in vacuo*, and purified by chromatography (85:15 hexanes:EtOAc) to yield a white solid (16.6 mg, 0.028 mmol, 51% yield). mp: 130 °C. IR (neat): 2160 (m, broad), 2028 (m, broad), 1526 (s), 1347 (s), 1301 (m), 1162 (s), 1091 (m), 1027 (w), 854 (m) 794 (w), 745 (s), 734 (s), 697 (m), 685 (s) cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 9.74 (d, *J* = 7.5 Hz, 1H), 8.55 (d, *J* = 4.8 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.52 (td, *J* = 7.7, 1.6 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.16 – 7.12 (m, 1H), 7.07 (td, *J* = 7.4, 1.5 Hz, 1H), 7.04 – 7.01 (m, 1H), 7.00 – 6.95 (m, 6H), 5.77 (d, *J* = 6.5 Hz, 1H). ¹³C{¹H} NMR (151 MHz, CDCl₃) δ 159.59, 149.31, 147.70, 147.35, 139.74, 139.24, 139.18, 137.44, 131.91, 131.20, 128.30, 128.29, 128.05, 127.52, 126.53, 125.75, 124.79, 123.63, 122.24, 62.17. HRMS (ESI+) Calcd for C₂₄H₂₀N₃O₄S [MH]⁺: 446.116; Found 446.1167.

References

- (1) (a) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094-5115; (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624-655; (c) Karimi, B.; Behzadnia, H.; Elhamifar, D.; Akhavan, P. F.; Esfahani, F. K.; Zamani, A. *Synthesis* **2010**, *9*, 1399-1427; (d) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212-11222; (e) Wang, X.; Zhou, L.; Lu, W. *Curr. Org. Chem.* **2010**, *14*, 289.
- (2) (a) Fukumoto, Y.; Sawada, K.; Hagihara, M.; Chatani, N.; Murai, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2779-2781; (b) Kuninobu, Y.; Nishina, Y.; Takeuchi, T.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6518-6520.
- (3) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302-2303.
- (4) (a) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141-5143; (b) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498-13499.
- (5) (a) Aydin, J.; Conrad, C. S.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 5175-5178; (b) Aydin, J.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 2881-2884; (c) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650-3651.
- (6) (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169-196; (b) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535-1553.
- (7) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147-1169.
- (8) (a) Davies, D. L.; Al-Duajj, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132-4138; (b) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414-12419; (c) Li, L.; Jiao, Y.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2010**, *29*, 4593-4605.
- (9) (a) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982-9983; (b) Schipper, D. J.; Hutchinson, M.; Fagnou, J. *J. Am. Chem. Soc.* **2010**, *132*, 6910-6911; (c) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475.
- (10) (a) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587-5588; (b) Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* **2003**, *5*, 2997-2999; (c) Nishimura, T.; Katoh, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4937-4939; (d) Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14158-14159; (e) Terao, Y.; Wakui, H.; Nomoto, M.;

- Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236-5243; (f) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 3124-3125.
- (11) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353-359.
- (12) (a) Gong, Y.; Kato, K.; Kimoto, H. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2637-2645; (b) Johannsen, M. *Chem. Commun.* **1999**, 2233-2234; (c) Poulsen, T. B.; Jorgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903-2915; (d) Saaby, S.; Fang, X.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114-4116; (e) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858-2859; (f) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804-11805.
- (13) Kim, S. H.; Rieke, R. D. *Tetrahedron Lett.* **2009**, *50*, 6985-6988.
- (14) Kim, S. H.; Rieke, R. D. *Tetrahedron Lett.* **2009**, *50*, 5329-5331.
- (15) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965.
- (16) Gizecki, P.; Ait Youcef, R.; Poulard, C.; Dhal, R.; Dujardin, G. *Tetrahedron Lett.* **2004**, *45*, 9589-9592.
- (17) Rampalacos, C.; Wulff, W. D. *Adv. Synth. & Catal.* **2008**, *350*, 1785-1790.
- (18) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; Lopez, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117-120.
- (19) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. & Catal.* **2005**, *347*, 1701-1708.