THE DEVELOPMENT OF DIRECTING GROUP ENABLED HYDROAMINATION STRATEGIES TO ACCESS TO 1,2-, 1,3-, AND 1,4- DIAMINES WITH HIGH LEVELS OF REGIO-, CHEMO-, AND STEREOSELECTIVITY

BY

EVAN PATRICK VANABLE

DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2019

Urbana, Illinois

Doctoral Committee:

Professor Kami L. Hull, Chair
Professor Gregory S. Girolami
Assistant Professor David Sarlah
Professor Steven C. Zimmerman

ABSTRACT

Carbon-nitrogen bonds are found in many societally important molecules, ranging from bulk commodities such as polymers and agrochemicals to fine chemicals, such as pharmaceuticals and therapeutic candidates. Our interest is primarily in the rapid, convergent, synthesis of the latter. The ability to form these bonds in a selective and mild manner from easily accessible starting materials is highly sought after, and has been a major goal of for many transition-metal catalysis groups, including ours. We have chosen to approach this from the vantage of a hydroamination reaction of olefins, as olefins and amines are both readily accessible. This reaction has the potential to be entirely atom-economical, as well as modular. Another advantage, and concomitant challenge, that comes with this strategy, is the ability to form multiple isomers: there are multiple regio- and stereoisomers which can be formed in this transformation, which we have overcome with careful catalyst selection and a directing group strategy.

The synthesis of 1,2-diamines is an efficient manner is an unresolved challenge for organic chemists. The enantioselective synthesis thereof is more challenging yet, and is generally approached through inefficient and step-intensive approaches such as nucleophilic displacement and resolution. We report the mild Rh-catalyzed enantioselective hydroamination of allylamines to afford chiral 1,2-diamines in good yields and excellent enantioselectivities. This transformation is impeccably chemoselective and regioselective, and highly enantioselective. This reaction tolerates a broad scope of secondary cyclic amine nucleophiles, as well as showing that secondary acyclic amine nucleophiles can be used, so long as one substituent is methyl. Future directions for this project include changing the directing group, the nucleophile, and the use of internal allylamines.

The transition-metal catalyzed hydroamination of olefins typically proceeds with Markovnikov selectivity. Overturning this typically requires electronically biased substrates such as conjugated alkenes or the use of elaborate workarounds. Herein we report an approach towards the anti-Markovnikov selective hydroamination of electronically unbiased olefins based on control of the aminometallation through a directing group approach to afford 1,4-diamines which are well represented in neurologically active molecules. We demonstrate the tolerance for secondary cyclic amines, secondary acyclic amines, and a variety of substitution adjacent to the

amine directing group. We have also studied the mechanism of this transformation, and the results are summarized within. Future directions for this project include changing the nucleophile and the directing group to afford different 1,4-motifs.

The hydroamination of electronically unbiased olefins with high regioselectivity has been highly limited. We have evolved our directing group strategy to allow for high levels of regiocontrol when performing the hydroamination of olefins with very little steric or electronic differentiation using aniline nucleophiles. This transformation is catalyzed by an iridium catalyst, and some preliminary mechanistic studies have been performed. In the case of cyclic olefins, high diastereoselectivity is observed. This strategy has multiple interesting future directions, including potential enantioselective hydroamination of internal olefins, use of different nucleophiles, and comprehensive mechanistic studies.

Dedicated to Bailey Jackson, Trish Vanable, and Dave Vanable

For all your love and support.

ACKNOWLEDGEMENTS

Thesis Committee	Assistant Prof. Kami L. Hull Prof. Gregory S. Girolami Assistant Prof. David Sarlah Professor Steven C. Zimmerman
Colleagues	Alexander Beebe William Bell Tiara Brown Travis Buchanan Dr. Seth Ensign Samuel Gockel Dr. Anil. K. Gupta Andrew Ickes Jennifer Kennemur Dr. Daniel Kohler Dr. Gregory Kortman Summer Laffoon Dr. Trang Nguyen Alexander Rago Alexander Veatch Jiachen Wang Lee Weir Dr. Zhao Wu Xujia Zhong
Family and Friends	Dave & Trish Vanable Colleen Vanable Austin Smith Alex Smith The entire Dewey family Sam Williams Andrew Persson Alyssa Adler Michael Schmidt David Kornfilt Siraj Ali Chris Patillo Marlin Sessler
Partner	Bailey Jackson

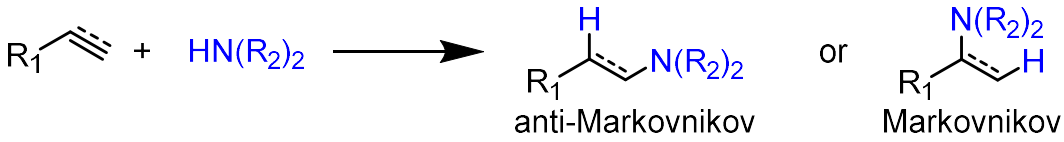
TABLE OF CONTENTS

Chapter 1: Introduction

1.1 Introduction

The introduction of carbon-nitrogen bonds into molecules remains a critical challenge in organic chemistry. Amines are ubiquitous in some of the most commercially important sectors of organic chemistry, especially within medicinal chemistry. 59% of all FDA approved small molecule pharmaceuticals contain at least one nitrogen containing heterocycle, for instance, and there is an average of 2.3 nitrogens per small molecule drug, including those with none.[1] Currently used approaches towards the resolution of this problem typically require sensitive, prefunctionalized, moieties such as alkyl halides, alcohols, and oxygenated leaving groups.[2, 3] These methods are inherently wasteful through their poor atom economy, and also raise issues of accessibility of these prefunctionalized scaffolds or the viability of maintaining their presence during the synthesis of a molecule, especially since they are often base and/or acid sensitive. Transition-metal catalysis offers a uniquely advantageous approach to this problem: hydroamination. The hydroamination of olefins with amines offers a solution to the incorporation of C–N bonds into molecules in a perfectly atom-economical way, with the opportunity to also set a stereocenter, and discriminate between regioisomer of product formation (**scheme 1.1**).

Scheme 1.1: Products accessible through hydroamination

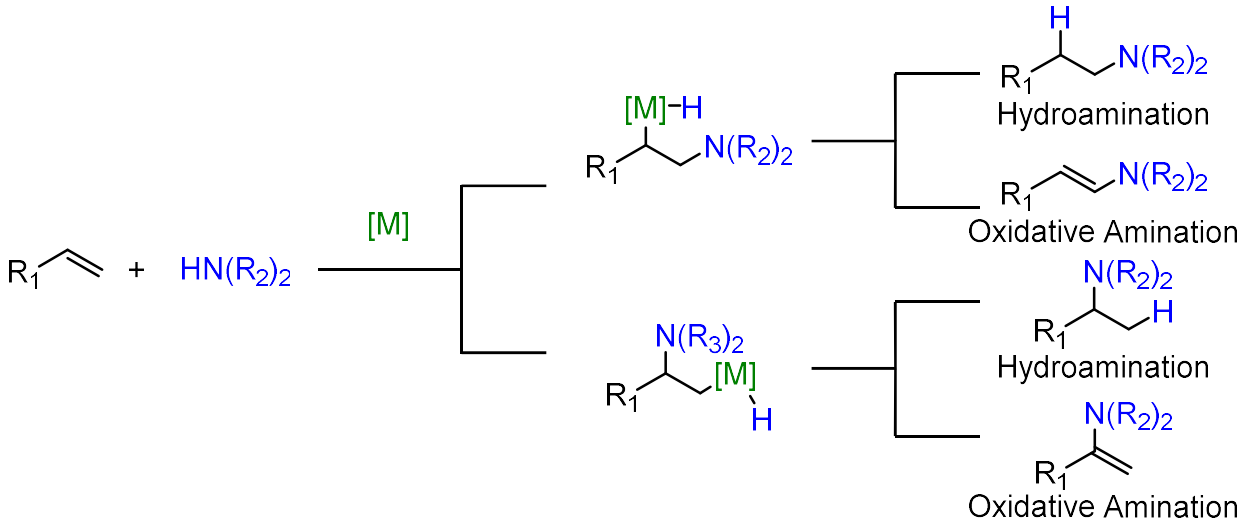


Huge progress has been made since the initial report of transition-metal catalyzed hydroamination in 1971 by Coulson, but there is still much room for improvement.[4-6]

The major challenges opposing the transitional-metal catalyzed hydroamination of olefins are lack of olefin coordination, byproduct formation from a metal alkyl species, and regio- or stereoselectivity.[7-10] Amines are considerably superior ligands than olefins for transition metals, leading to challenges with displacing them with olefins. Unfortunately, without olefin coordination, hydroamination is impossible. Oftentimes this problem is resolved through the use of a significant excess of the olefin reaction partner, or by using protected amines such as amide

or sulfonamides which are more poorly coordinating.[7-10] Another challenge can be the selectivity of the olefin insertion step; whether that be the regiochemistry or stereochemistry of insertion, each is a major challenge. In addition to these problems, once a metal-alkyl is formed there is the potential for β-hydride elimination. This is especially the case for late transition-metals, as they are more stable to protonolysis of the C–M bond. This affords an undesirable oxidative amination product, which decreases yields of the desired product. In some cases, this byproduct can be transformed back to the hydroamination product through transfer hydrogenation.[7]

Scheme 1.2: The pathways to the four products of indiscriminate hydroamination

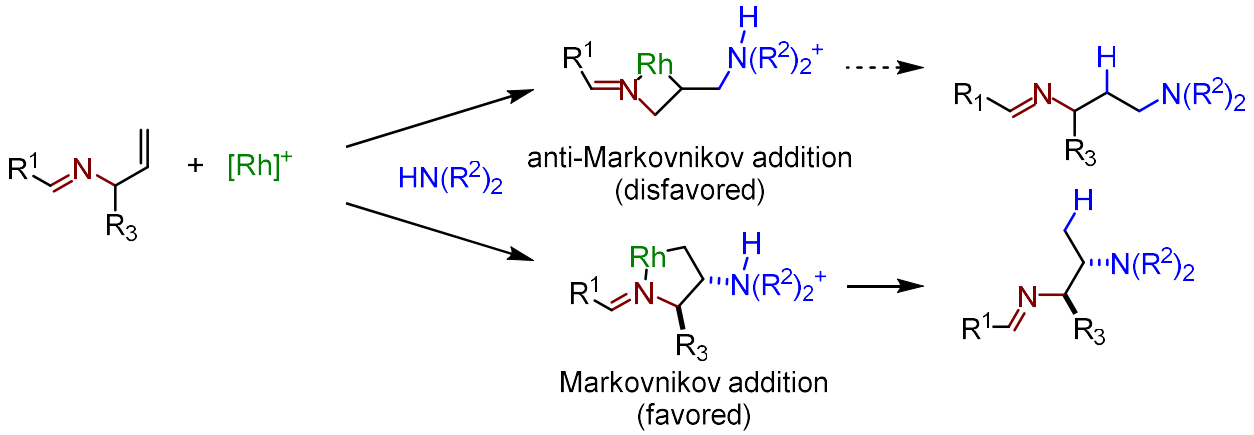


Typically, aliphatic substituted alkenes afford hydroamination and oxidative amination products with markovnikov selectivity (the bottom pathway). This is due to the significant buildup of partial positive charge at the internal carbon upon donation of the π-electrons of the olefin to the metal.[7, 9, 10] Also, this allows for the significantly more sterically encumbered metal center to reside at the less substituted position, with both factors driving the formation of the Markovnikov isomer. This has been overcome using a variety of strategies, including formal hydroamination, two-step work arounds, and the use of radical chemistry, however prior to our work there had been no 2-electron driven catalytic direct anti-Markovnikov hydroamination reactions of alkyl substituted olefins.[6] The recent growth in publications on anti-Markovnikov hydroamination to the extent of using prefunctionalized reagents and taking two-step work arounds shows a strong interest from the community in solving this challenge.

The approach that we have selected to address the challenges presented by both the selective hydroamination of aliphatic alkenes is the use of directing groups. Directing groups have been used to make many transformations more viable: most well known are epoxidations, hydrogenations, and direct C–H functionalizations.[11-21] It is well known that alcohols and carboxylic acids can direct metal catalyzed hydrogenation reactions to an olefin, allowing for hydrogenation from the same face as the directing group with very high selectivities. It has also been shown that a catalyst can hydrogenate considerably more sterically encumbered olefins when directed than when undirected. This effect is attributed to the entropic κ-2 chelation effect.[22] Because of this effect, an olefin which previously would have a low binding affinity for a metal center compared to other ligands in solution can have an increased affinity. In the example of C–H functionalization reactions, it has been shown that a directing group can control precisely which C–H bond will be functionalized in a molecule, with a strong preference for a 5-membered chelate in many instances. This has been shown to allow for many impressive transformations, including but not limited to C–H alkylation, arylation, borylation, and fluorination. This generally conserved preference for a 5-membered ring inspired us to think that it may be possible to use this clearly preferred metallacycle size in order to modify whether the Markovnikov or anti-Markovnikov product is formed, based on the tether length to the directing group.

The ways a directing group would obviate these challenges to hydroamination are not immediately obvious. To clarify, the first effect of using a directing group to alleviate these challenges is the improvement of the effective concentration of the alkene to the metal. This will allow us to reduce the amount of precious olefin required for the transformation. Also, upon the aminometallation step, a metallacyclic intermediate will be formed. This metallacycle should be much more stable to β-hydride elimination than an acyclic M–alkyl, due to being much more restricted conformationally which makes accessing the β-hydrogens less favorable. In addition, if the oxidative amination product is formed, the directing group may direct the reinsertion of the resultant M–H into the olefin, allowing for formation of the desired hydroamination product regardless. Our group has previously worked in this area and developed a hydroamination of N-allyl imines (**scheme 1.3**).

Scheme 1.3: The hydroamination of N-allyl imines



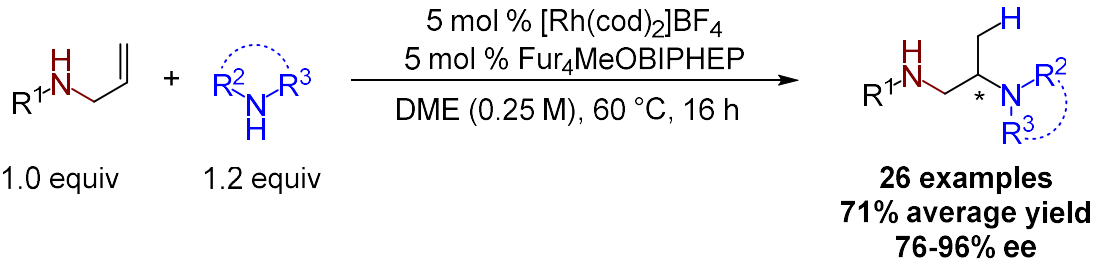
The metallacycle size control may also help control the formation of the desired regioisomer: upon aminometallation two differently sized metallacycles can be afforded, based on directing group and tether length. If there is a significant enough enthalpic preference for once of these metallacycles, the inherent regioselectivity may be enhanced, or overturned, depending on tether length, metal, and ligand environment. In the case of allylic directing groups, the 5-membered metallacycle is clearly less strained than the 4-membered metallacycle, enhancing the natural selectivity for the Markovnikov product.

This directing group strategy is not limited to either of the dominant mechanisms of hydroamination, and we must consider both options for our reactions. The two mechanisms referred to here are the inner-sphere and outer-sphere pathways. The inner-sphere pathway involves the activation of an N–H bond, likely in an oxidative addition manner. This high-valent metal amido species can then undergo a migratory insertion of the olefin into the M–N bond, affording a transient metal–hydride alkyl complex which can undergo reduction elimination to regenerate the catalyst. The outer sphere mechanism is a π-bond activation mechanism in which an olefin coordinates to an electron-deficient metal center. The donation of the π bonding electrons to the metal center results in highly electrophilic carbon centers. An outer sphere nucleophilic attack on this olefin results in a metal-alkyl species with an adjacent ammonium, which then undergoes protonolysis or oxidative proton transfer and reductive elimination to afford the desired hydroamination product. The difference between these is almost completely academic, and is very challenging to distinguish between using experimental methods, and so will be presumed to be the protonolysis for ease of discussion. In this document, we will often assume that alkyl substituted amines undergo an outer-sphere nucleophilic aminometallation

pathway, as this is commonly accepted to be the case with late transition metals.[6, 23, 24] Exceptions to this rule, where pointed to by experimental evidence, will be discussed in detail.

The first project discussed herein will be the asymmetric hydroamination of allylamines with secondary amines to afford chiral 1,2-propylene diamine derivatives. This project is building off the success of our group's first foray into hydroamination, the hydroamination of N-allyl imines using nucleophilic amines (**Scheme 1.4**).

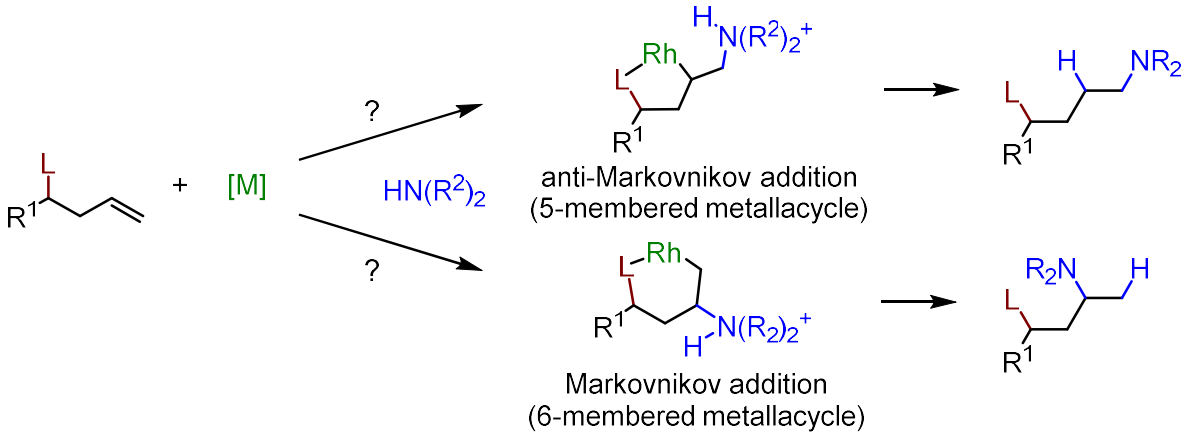
Scheme 1.4: N-allyl amine hydroamination



This project was a collaborative project, with Merck & Co. Inc.. This transformation likely proceeds through a κ-2 substrate-bound complex, outer sphere aminometallation to form a 5-membered metallacycle, and protonolysis to afford the desired product. This transformation proceeds under mild conditions, with nearly stoichiometric reaction partners, and with good to excellent enantioselectivity. These chiral 1,2-propylene diamine derivatives are very interesting products, and very challenging to produce using traditional methods.

The next step to using metallacycle size to assist with controlling the regioselectivity of the reaction was to see if the preference for the 5-membered metallacycle can actually overcome the inherently preferred (Markovnikov) selectivity of the reaction. To do this, we were inspired to synthesis homoallylamine substrates to see if the formation of the 5-membered metallacycle would remain preferred, affording anti-Markovnikov hydroamination and 1,4-diamines (**Scheme 1.5**). As anti-Markovnikov hydroamination was essentially unprecedented at the time through direct metal-catalyzed methods, this appealed to us.

Scheme 1.5: Homoallyl directing groups aminometallation metallacycle depiction



We were able to show that this theory is viable, and that through the correct optimization of ligand and counterion we are able to access fair to excellent selectivities for the anti-Markovnikov product, as well as good yields. This transformation does require more forcing conditions than the previous: higher concentrations, temperatures, and equivalencies of the commercial amine nucleophile reagent. This is understandable, as it requires a much more challenging aminometallation to occur: the bulky metal center must be localized to the more hindered carbon, instead of the less, in the selectivity determining step. Even if this is shown by the product distribution to be more favorable than forming the six-membered metallacycle, it is still inherently higher in energy than forming a 5-membered metallacycle which does not require this additional energetic cost. The mechanism of this transformation has been vigorously studied, with some conclusions obtained and paths towards others considered.

We have also been able to adapt this strategy, through the work of Dr. Seth Ensign, to be able to access the Markovnikov and anti-Markovnikov hydroamination products of homoallylamines to make 1,3 and 1,4 diamines. More recently, my own work has been in the development of the 1,4 diamine selective hydroamination of homoallylamines with internal olefins instead of terminal olefins. The scope and mechanism of this transformation are explored herein, along with ideas for future directions and ways of resolving remaining issues with the transformation.

1.2 References

(1) “Analysis of Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals”, Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57* (24), 10257

(2) Carruthers, W.; Coldham, I. *Modern Methods of Organic Synthesis*, Fourth Ed.; Cambridge University Press: Cambridge, U.K., U.K., 2004.

(3) Lecozotan (SRA-333): A Selective Serotonin 1A Receptor Antagonist That Enhances the Stimulated Release of Glutamate and Acetylcholine in the Hippocampus and Possesses Cognitive-Enhancing Properties” Schechter, L. E.; Smith, D. L.; Rosenzweig-Lipson, S.; Sukoff, S. J.; Dawson, L. A.; Marquis, K.; Jones, D.; Piesla, M.; Andree, T.; Nawoschik, S.; Harder, J. A.; Womack, M. D. Buccafusco, J.; Terry, A. V. Hoebel, B.; Rada, P.; Kelly, M.; Abou-Gharbia, M.; Barrett, J. E. Childers, W. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1274–1289

(4) “Catalytic Addition of Secondary Amines to Ethylene”, Coulson, D.R. Tetrahedron Lett. **1971**, *12*, 429-431

(5) “Hydroamination: Direct Addition of Amines to Alkenes and Alkynes”, Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108* (9), 3795–3892

(6) “Late Transition Metal-Catalyzed Hydroamination and Hydroamidation”, Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem.Rev.* **2015**, *115* (7), 2596–2697.

(7) Iridium-Catalyzed Intermolecular Hydroamination of Unactivated Aliphatic Alkenes with Amides and Sulfonamides”, Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134* (29), 11960-11963

(8) “Iridium-Catalyzed, Intermolecular Hydroamination of Unactivated Alkenes with Indoles”, Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136* (8), 3200-3207

(9) “Asymmetric Intermolecular Hydroamination of Unactivated Alkenes with Simple Amines”, Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2010**, *49* (47), 8984-8987

(10) The First Rhodium-Catalyzed Anti-Markovnikov Hydroamination: Studies on Hydroamination and Oxidative Amination of Aromatic Olefins", Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Muller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999***, 5* (4), 1306-1319

(11) "Substrate-Directable Chemical Reactions", Hoveyda, A. Evans, D. A. Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370

(12) "Regio- and Enantioselective Intermolecular Hydroacylation: Substrate-Directed Addition of Salicylaldehydes to Homoallylic Sulfides", Coulter, M. M. Kou, K. G. M. Galligan, B.; Dong, Vy. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330-16333

(13) "Directed, Regiocontrolled Hydroamination of Unactivated Alkenes via Prtodepalladation". Gurak, J. A. Yang, K. S.; Liu, Z.; Engle, K. M. *J. Am Chem. Soc.* **2016**, *138* (18), 5805-5808

(14) "β,γ-Dicarbofuntionalization of Alkenyl Carbonyl Compounds via Directed Nucleopalladation". Liu, Z.; Zeng, T.; Yang, K. S.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138* (46), 15122-15125. e. "Amide-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes". Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740-1741

(15) "Amide-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes". Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740-1741.**12**

(16) "Practical Intermolecular hydroarylation of Diverse Alkenes via Reductive Heck Coupling". Gurak, J. A.; Engle, K. M. *ACS Catal.* **2018**, *8*, 8987-8992

(17) "Catalytic Intermolecular Carboamination of Unactivated Alkenes via Directed Aminopalladation". Liu, Z.; Wang, Y.; Wang, Z.; Zeng, T.; Liu, P.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139* (32), 11261-11270

(18) Rhodium(I)-Catalyzed Hydrogenation of Olefins. The Documentation of Hydroxyl-Directed Stereochemical Control in Cyclic and Acyclic Systems", Evans. D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106* (13), 3866-3868

(19) “Regio- and Chemoselective Intermolecular Hydroamination of Allyl Imines for the Synthesis of 1,2-Diamines.” Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. *J. Am. Chem. Soc.* **2014**, *136* (32), 11256-11259

(20) “Anti-Markovnikov Hydroamination of Homoallylic Amines”, Ensign, S. C.; Vanable, E. P.; Kortman, G. D.; Hull, K. L. *J. Am. Chem. Soc.* **2015**, *137*, 13748-13751

(21) “Rhodium-Catalyzed Regiodivergent Hydrothiolation of Allyl Amines and Imines”, Kennemur, J. L. Kortman, G. D. Hull, K. L. *J. Am. Chem. Soc.* **2016**, *138* (36), 11914-11919

(22) “Der Chelateffekt”, Schwarzenbach, G. *Helv. Chim. Acta.* **1953**, *35* (7), 2344-2359

(23) “Transition-Metal-Catalyzed Hydroamination Reactions”, Schafer, L. L. Yim, J.C. H.; Yonson, N. *Metal-Catalyzed Cross-Coupling Reactions and More*, *1, 2 and 3*. **2013**, *Chapter 15*

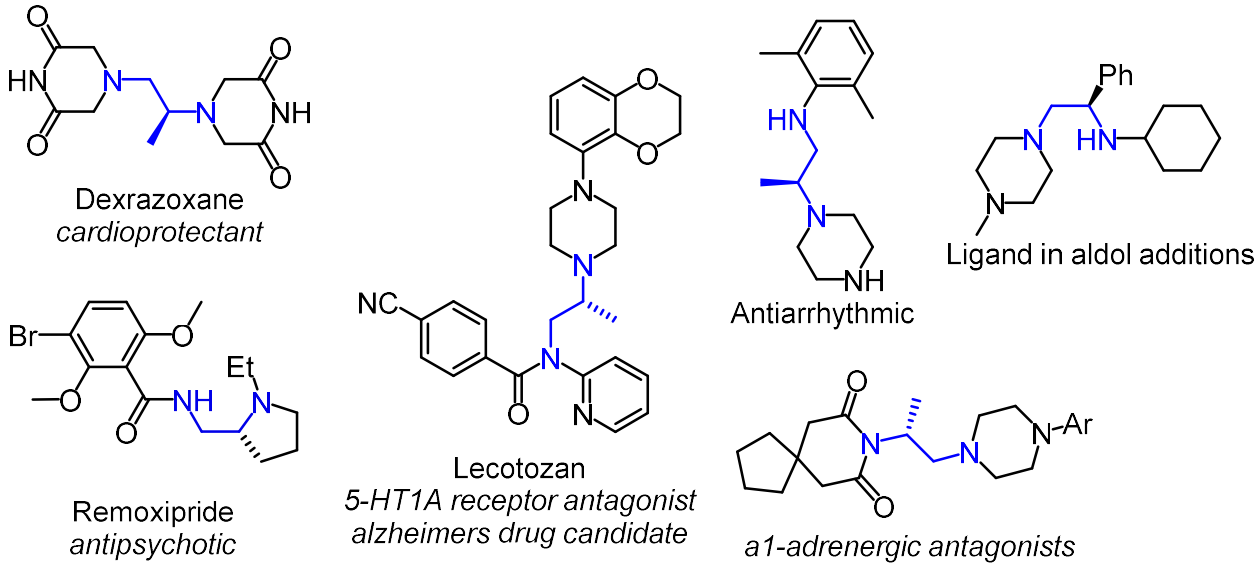
(24) “Recent Advances in Metal Free- and Late Transition Metal-Catalyzed Hydroamination of Unactivated Alkenes”, Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. *Catalysis Science and Technology*, **2015**, *5*, 2017-2037

Chapter 2: Asymmetric Hydroamination of Allylic Amines To Afford Chiral Propylene Diamine Derivatives

2.1 Introduction

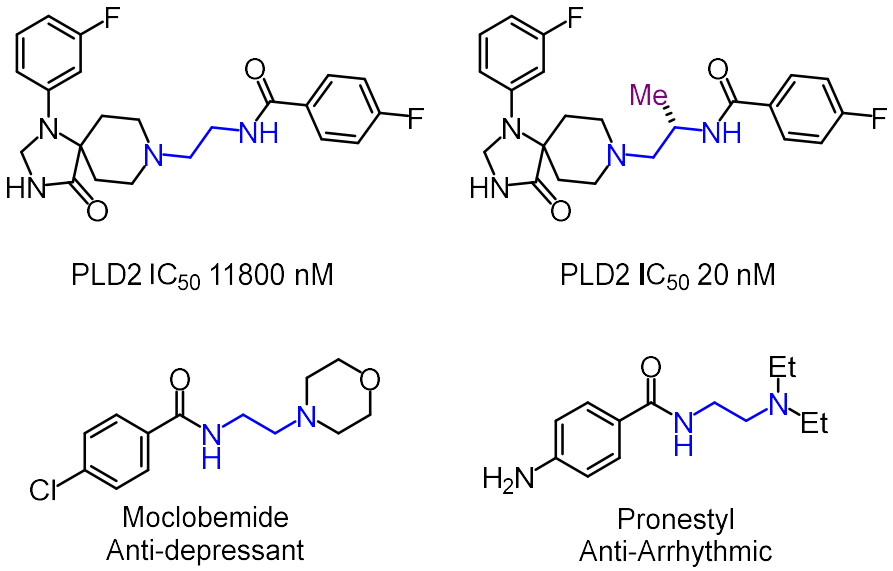
The efficient and versatile synthesis of chiral 1,2-diamines is an unresolved challenge which deleteriously impacts two important fields: chiral ligand synthesis, and biologically active molecule synthesis. This motif is common in these fields (**Figure 2.1**), and there has been a dearth of good methods to form them.[1-3] The main methods used to access these molecules are through invertive displacement of a chiral alcohol derivative,[4] aziridine opening,[5, 6] nitro-mannich reactions,[7, 8] or resolution of racemic mixtures. Unfortunately, these reactions either have inherently poor efficiency, or are hindered by the poor accessibility of chiral aziridines. The development of a novel approach to these compounds which was more efficient and step economical is highly desirable.

Figure 2.1: Some chiral 1,2-diamines which are biologically active or used as ligands



Part of our inspiration is also due to a promising effect in medicinal chemistry: the magic methyl effect.[9] This effect describes a phenomenon where observationally, sometimes the difference between a H and a Me substituent on a molecule affects its binding capability or efficacy to extreme levels, such as a 500 fold factor of binding affinity (**Figure 2.2**).[9]

Figure 2.2: Magic methyl effect example and clinical drugs which may profit from it

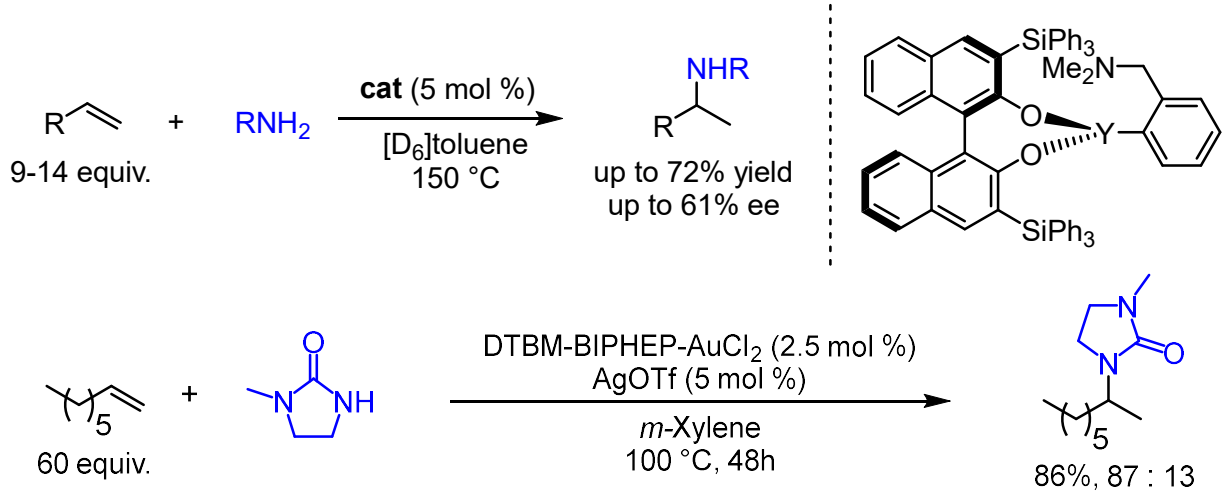


This is generally attributed to changes in the energy landscape for conformational changes in a molecule, although this is still just a working hypothesis. There is now a drive in the community to be able to make net C–H methylated versions of compounds which are biologically interesting. We note that there are a fair amount of ethylene diamine derived molecules in the pharmaceutical literature (such as Moclobemide and Pronestyl, above), and that the ability to access their chiral propylene diamine derivatives would be a boon. We decided that the best approach to this challenge would be to develop a hydroamination reaction of allylamines which could afford enantioenriched 1,2-propylene diamines in a perfectly atom-economical manner. This transformation would start with achiral allylamines, easily obtained from commercially available materials in a single step, and transform them into these value-added materials. Unfortunately, existing enantioselective hydroamination reactions of unactivated olefins are rare and quite limited.[13]

Reports on the enantioselective intermolecular hydroamination of electronically unactivated terminal olefins have developed significantly since the first report by Togni and coworkers, using the strain-activated norbornene as a susbtrate.[10] The two most advanced methods for the direct, enantioselective, hydroamination of non-strained alkyl-substituted olefins (shown below), for instance, afford the products with a maximum of 89.0 : 11.0 er[11] and 79.5 : 20.5 er[12] while using 10 or more equivalents of alkene, and high temperatures (> 100 °C). There have been many more

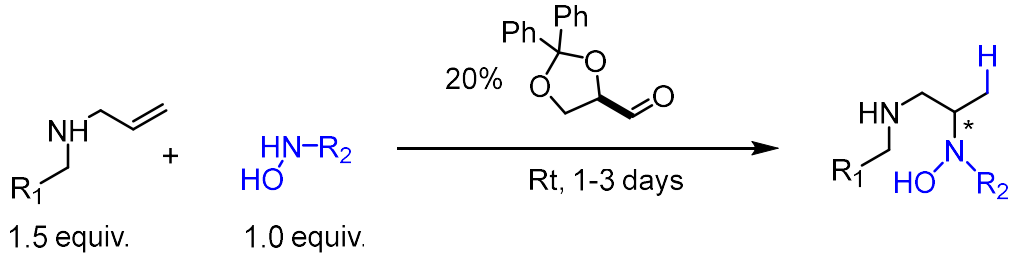
reports on the hydroamination of dienes and styrenes enantioselectively than alkyl substituted olefins, which are not going to be discussed here.[13]

Scheme 2.1: Direct enantioselective hydrogenation methods of terminal olefins



One niche example which is quite similar to our approach is that of the Beauchemin group, which has shown that allylamines can be hydroaminated through a Cope-type process, using a chiral tethering aldehyde catalyst (**Scheme 2.2**).[14] Unfortunately this system is plagued by catalyst racemization in many instances, and affords hydroxylamines instead of amines, introducing an unnecessary deprotection step.[14] This reaction does afford enantioenriched 1,2 diamines from allylamine derivatives, however, making it a close analogue to our reaction.

Scheme 2.2: Beauchemin's Cope-type hydroamination of allylamines

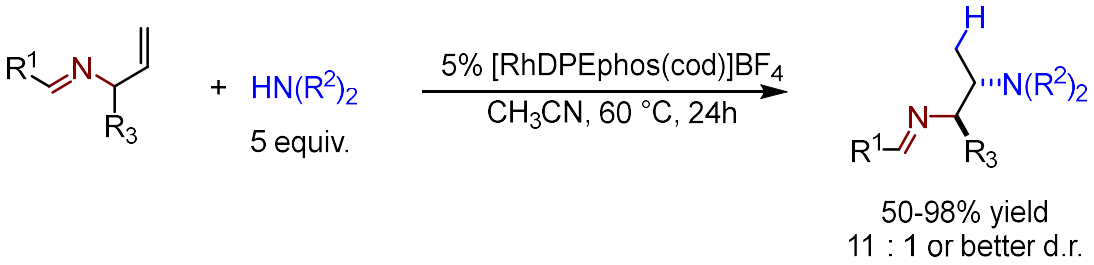


This transformation relies on temporary intramolecularity, the ability to organize the required components into a single molecule prior to the challenging step of hydroamination. The hydroxylamine is then poised to undergo rapid hydroamination to afford an amine N-oxide, which eventually regenerates the hydroxylamine. This strategy has many similarities to a transition-metal catalyzed approach, especially an inner-sphere approach where a metal catalyst

is bound to both an amine and an olefin prior to the amination step. Unfortunately, transition-metal catalyzed hydroamination has proven very difficult to implement.

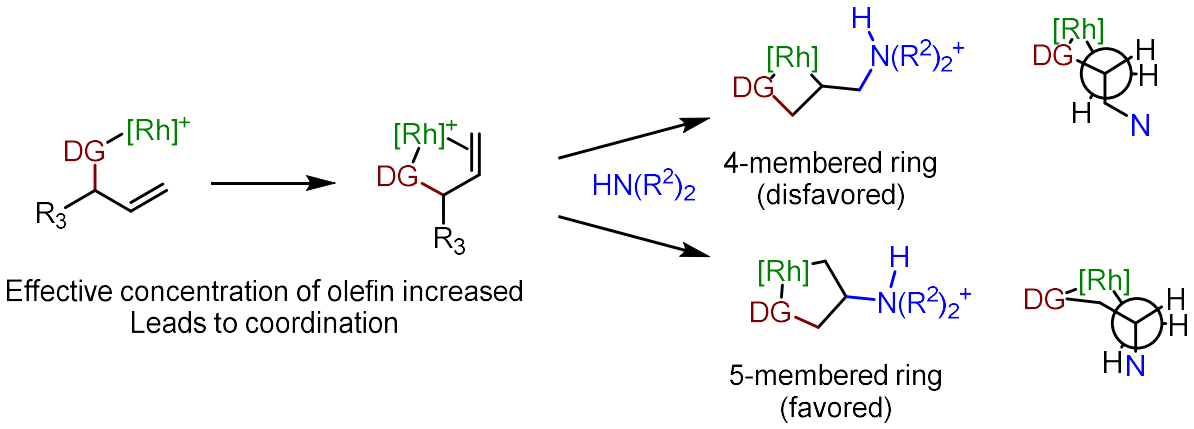
As discussed in **Chapter 1**, the hydroamination of olefins has many associated challenges, foremost among them being the issues of olefin coordination and selectivity against β-hydride elimination.[15-18] To address the existing challenges of transition-metal catalyzed hydroamination we have proposed a directing group approach (*vide infra*). In the case of synthesizing 1,2-propylene diamine derivatives, we have a substrate which inherently includes a directing group, the nitrogen on the 1 position. The other nitrogen can be incorporated through a Markovnikov selective hydroamination of an olefin, starting from the general class of allylamines or N-allyl imines. We have previously shown that the diastereoselective hydroamination of N-allyl imines can be performed, lending credence to the theory that an enantioselective variant could be developed (**Scheme 2.3**).[19]

Scheme 2.3: Imine-directed hydroamination previously published in our group



We hypothesize that the success of this published transformation revolves around the use of the directing group. Being able to use a limiting amount of the precious olefin reagent is likely due to the chelate effect: after the binding of the strong imine ligand, a second coordination is significantly favored. The excellent diastereoselectivity is likely due to the rigid metallacycle formed by the imine, olefin, and metal center prior to the aminometallation step. In addition, the excellent regioselectivity is likely related to the size of metallacycle formed by each insertion: a 4-membered ring would be highly strained compared to the 5-membered metallacycle, and the transition state energies likely reflect that (**Scheme 2.4**)

Scheme 2.4: Effect of the directing group on the hydroamination reaction

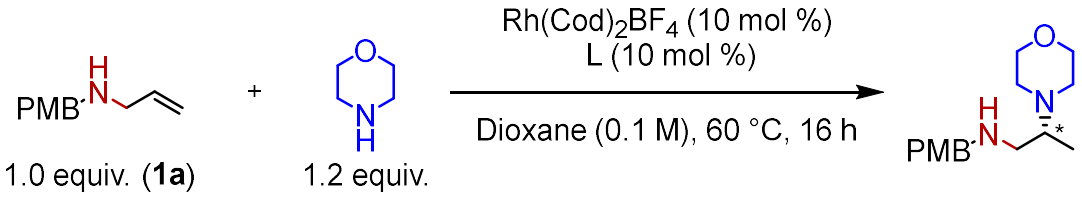


The lack of observed oxidative amination is due to the fact that there are no syn-periplanar β-hydrogens available in the alkyl metallacycle. After the success of this reaction, we attempted to develop an enantioselective variant.

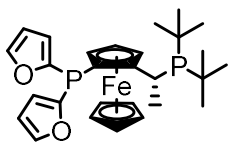
2.2 Initial Discovery

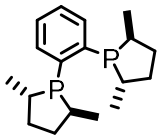
After some initial forays into this area, primarily done on N-allyl imines by Andrew Ickes, it became clear that the development of an enantioselective variant would be both nontrivial, and require large amounts of ligand screening. Despite this, we were still interested in developing the transformation and determined that we needed to find a partner to collaborate with. Thankfully, my colleague Jennifer Kennemur was able to secure a collaboration with Merck & Co. Inc. to do a high-throughput screening of some reactions we wanted to develop, including this one. We were able to screen 288 chiral ligands for the hydroamination of **1a** using their high throughput screening facility, and analyze them for yield and enantiomeric ratio using UHPLC. Summarized below are 13 of those results.

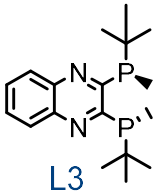
Scheme 2.5: Summary of Ligands Screened for Hydroamination with Yields and E.R.s

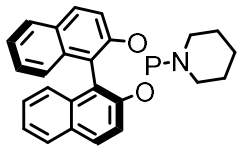


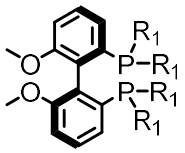
Entry	Ligand	% conversion	er
1	L1	<1%	<1%
2	L2 (S,S)-Me-DUPHOS	11%	0.5:99.5
3	L3, (R) QuinoxP	52%	99.0:1.0
4	L4, (S)-PipPhos	22%	47.0:53.0
5	L5, (R)-p-Tol-MeOBIPHEP	14%	99.5:0.5
6	L6, (R)-2-Furyl-MeOBIPHEP	63%	99.0:1.0
7	L7	33%	87.5:12.5
8	L8	52%	12.5:87.5
9	L9, (S,S)-DIPAMP	32%	63.5:36.5
10	L10, (1S,1'S,2R,2'R)-Duanphos	22%	0.5:99.5
11	L11, (R)-Segphos	<1%	n.d.

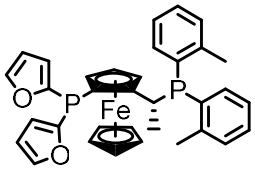

L1

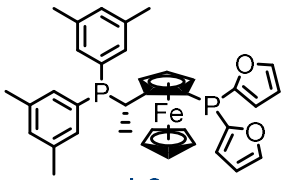

L2

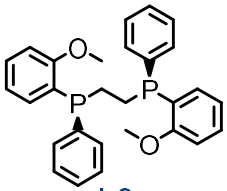

L3

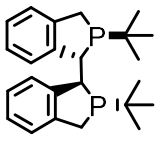

L4

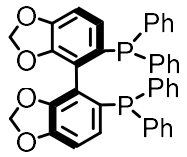

L5: R_1 = p-MeC_6H_4
L6 = 2-Furyl


L7


L8


L9

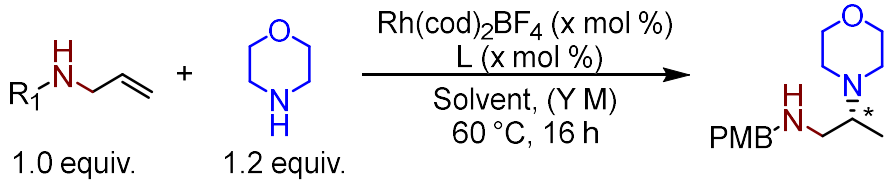

L10


L11: R_1 = Ph

Astonishing us was the fact that only 9 of the 288 ligands formed catalysts which generated >5% product. Also surprising was the fact that very small changes in ligand scaffold resulted in large changes in product yield: for instance the stark contrasts between L5, L6, and L11. L5 and L11 are very similar: L11 is slightly more electron rich at the phosphine center due to having a para-methoxy group in addition to a meta-methoxy group. This small change results in a drop from 14% to <1% yield. Following this trend in the opposite direction, from L5 to L6, where now the furyl substituents are quite electron withdrawing, and slightly smaller than 4-MePh substituents, we can see a dramatic increase in yield from 14% to 63%.[20] We hypothesize that the phosphine must be highly electron withdrawing in order to help the metal center withdraw electron density from the olefin. The more π-philic the olefin, the more prone it will be to an outer sphere attack, which is required for this transformation. We believe that this hypothesis is borne out in the results of this transformation, although more in-depth investigation or computations would be required to prove it.

In order to optimize this reaction, there were only a few parameters to change that didn't invalidate our goals of a highly atom-economical transformation: with a ligand found, really only catalyst loading, solvent, molarity, and temperature needed to be examined. After some screening, summarized in brief below in **Table 2.1**, we developed more optimal conditions.

Table 2.1: Brief summary of optimized hydroamination conditions



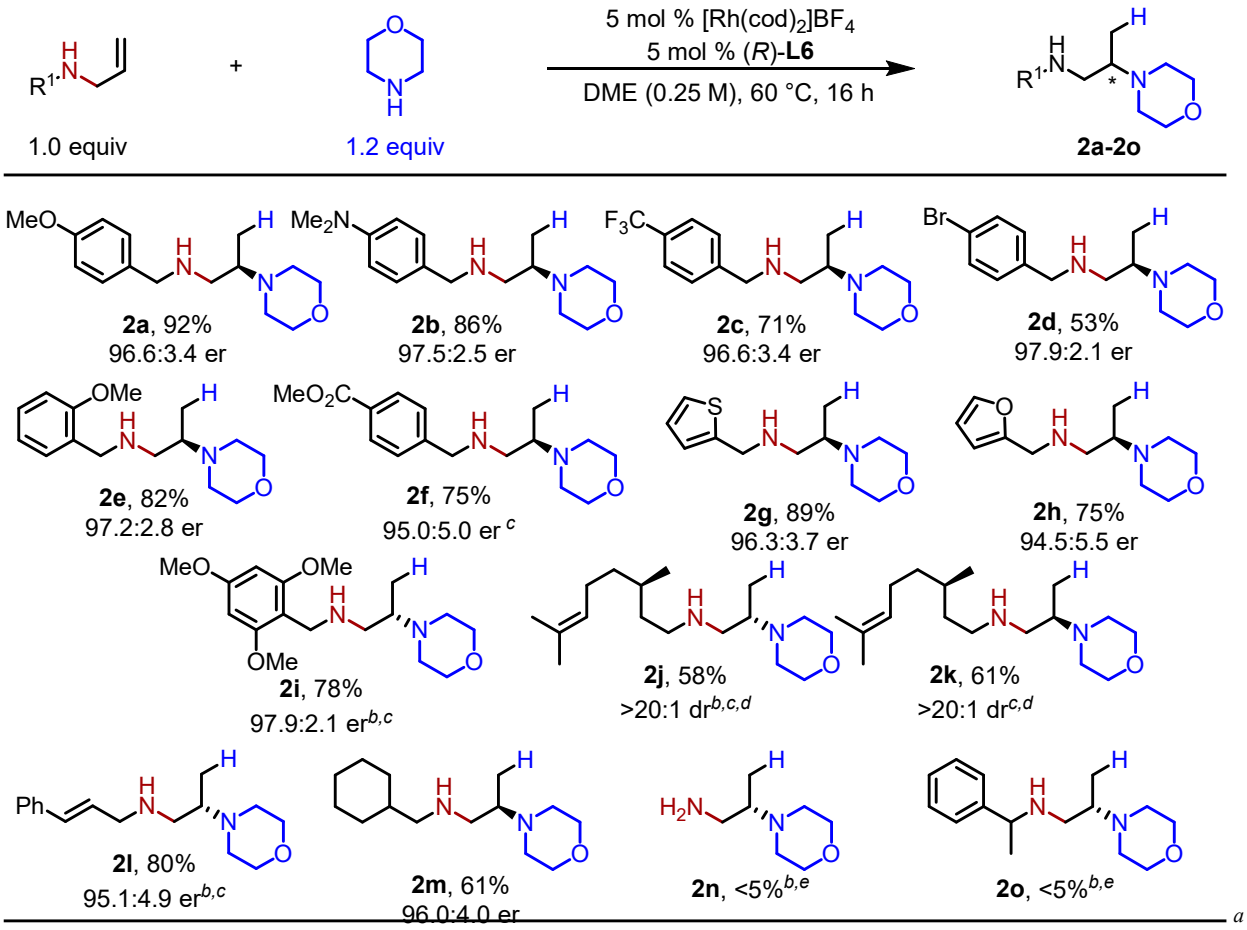
Entry	Solvent	M (Y)	Catalyst (mol %)	Yield	er
1	Dioxane	0.1	10%	51%	99.0 : 1.0
2	Dioxane	1	3%	72%	94.0 : 6.0
3	Dioxane	4	3%	86%	91.0 : 9.0
7	Benzonitrile	1	3%	72%	95.0 : 5.0
9	Dimethoxyethane	1	3%	93%	95.1 : 4.9
10	Dimethoxyethane	0.25	3%	77%	97.0 : 3.0
11	**Dimethoxyethane**	**0.25**	**5%**	**92%**	**97.0 : 3.0**

We found that by increasing the concentration by a factor of 4 (entry 2 to entry 3) with reduced catalyst loading the yield improves, but the enantiomeric excess drops precipitously. In very dilute solutions, albeit with increased catalyst loading, the enantiomeric excess is much higher than either 2 or 3 (entry 1) confirming this trend: increasing molarity decreased the enantiomeric excess. When switching solvents we found that DME, a close cousin to 1,4-dioxane, was a significantly superior solvent, dramatically improving the yield and modestly improving the enantiomeric excess. Further reactions confirmed that by decreasing the concentration and increasing the catalyst loading, the product could be obtained in a 92% isolated yield with 94% ee. These were used as the base conditions, and for examples which performed more poorly, inspiration was taken from the optimization table to try and resolve the issue – either increasing the concentration, the amount of nucleophile, or the catalyst loading if those fail.

2.3 Scope

With these optimized conditions, we were then curious about determining what was tolerated in the reaction. A series of electronically diverse aryl and heteroaryl rings can be incorporated in the substrate with essentially no impact on the enantioselectivity (2a-2i, Table 2.2). This includes interesting heterocycles such as furan and thiophene, as well as as well as arylethers, tertiary amines, aryl bromides (which can be further functionalized), trifluoromethyl groups, and an ester without any amidation observed. Neither a single *ortho*-substituent on the aryl ring or the highly hindered 2,4,6-trimethoxy benzyl results in breakdown of reactivity, although the both require doubling the concentration of the reaction to obtain high conversion. An internal styrenal allylamine can be compared to the terminal allylamine and no reactivity at all was observed: notably this indicates that it is possible to synthesize glycine derivatives using this method and an oxidative cleavage. There is no inherent need to include a π-system on the directing group, this was just most often done for convenience; for example, simple aliphatic substitution, i.e. cyclohexyl, can be employed with little impact on the yield or enantioselectivity, we also note with products 2j and 2k that a stereogenic center on the aliphatic directing group presents no difficulty to enantioinduction; i.e., the favored diastereomer is governed solely by catalyst control.

Table 2.2: Directing group scope for hydroamination of allylamines using 2° cyclic amines

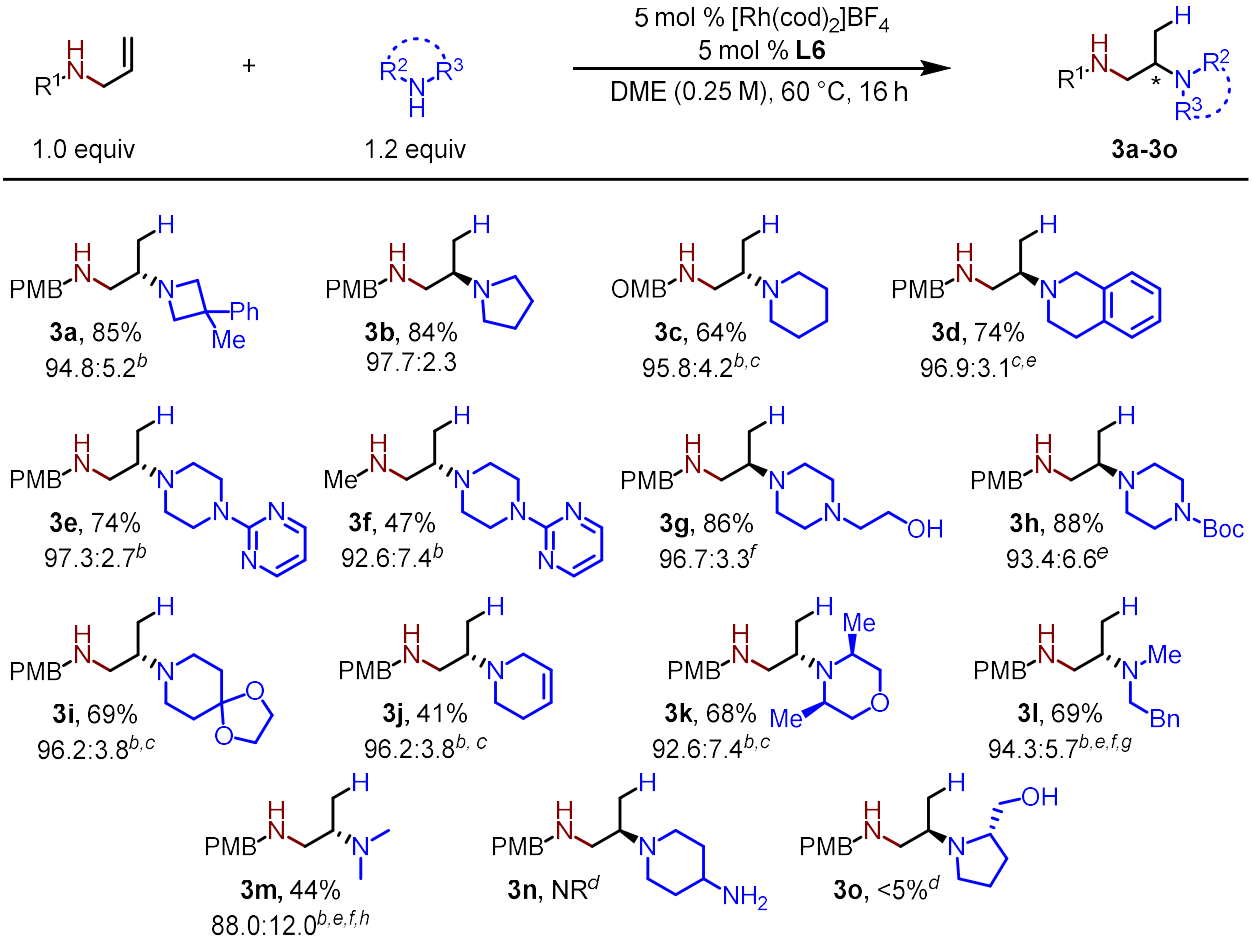


Allyl amine (0.20 mmol), nucleophile (0.24 mmol), $[Rh(cod)_2]BF_4$ (0.010 mmol), *(R)*-**L6** (0.010 mmol), and DME (0.25 M) at 60 °C for 16 h. Isolated yields determined by the average of duplicate runs; Enantiomeric ratio determined by HPLC of the purified product. [b] (*S*)-**L6**. [c] DME (0.50 M). [d] Diastereomeric ratio determined by ^{1}H NMR of the crude reaction mixture. [e] ^{1}H NMR yield determined by comparison to an internal standard.

Unfortunately, using either an α-branched amine or a primary amine as the directing group failed to afford the desired products 2n or 2o, respectively. The scope of nucleophiles that are amenable to this transformation is likewise quite broad (**Table 2.3**). We can use 4-6 membered ring nucleophiles with no significant issue noted for either yield or enantioselectivity (**3a**-**3c**). Unfortunately, azepane (not depicted), affords an unsatisfactory 25% NMR yield of the desired product even with 10 mol % catalyst, likely due to its diminished nucleophilicity.[21] Similarly,

tetrahydroisoquinoline requires doubling the concentration and nucleophile equivalencies to get high yields (**3d**).

Table 2.3: Nucleophile scope for hydroamination of allylamines



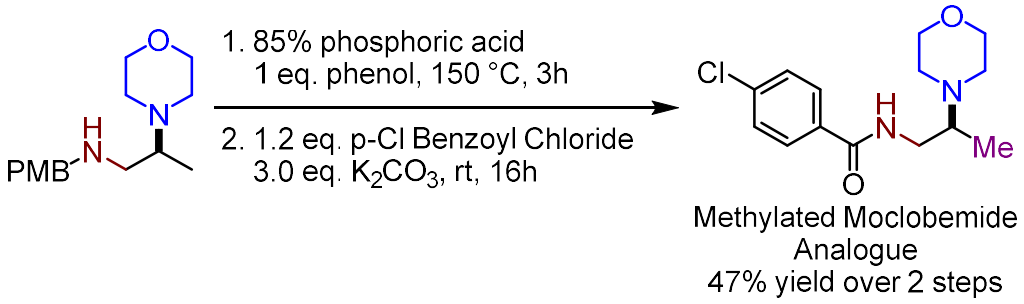
[a] Allyl amine (0.20 mmol), nucleophile (0.24 mmol), $[Rh(cod)_2]BF_4$ (0.010 mmol), *(R)*-**L6** (0.010 mmol), and DME (0.25 M) at 60 °C for 16 h. Isolated yields determined by the average of duplicate runs; Enantiomeric ratio determined by HPLC of the purified product. [b] (*S*)-**L6**. [c] DME (0.50 M) [d] ^{1}H NMR yield determined by comparison to an internal standard. [e] 10 mol % catalyst. [f] 4.8 equiv. nucleophile. [g] DME (1.0 M). [h] 0.38M.

We next investigated more complex and synthetically relevant nucleophiles, beginning with substituted piperazines. The inclusion of a Lewis basic pyrimidine group was tolerated by the reaction. Excitingly, 1-(2-hydroxyethyl)piperazine can be used without protection of the free hydroxyl group, showing a tolerance even for primary aliphatic alcohols (**3g**). 1-Boc-piperazine is an excellent nucleophile and affords **3h** in 88% yield and 93.4:6.6 er. This nucleophile is

especially useful, as the Boc group provides access to a handle for subsequent derivatization of the piperazine. Acetals are also compatible with the reaction conditions, as 1,4-dioxa-8-azaspiro[4,5]decane, a known ammonia surrogate,[22. 23] is an effective nucleophile, affording **3i** in 69% yield with a 96.2:3.85 er. Hindered 3,5-dimethylmorpholine requires a higher reaction concentration to afford a good yield (68%) of the product, although with slightly lower enantiomeric ratio (92.6:7.4) (**3k**). Both N-methylbenzylamine and dimethylamine are effective nucleophiles, with sufficiently forcing conditions. Unfortunately, the hydroamination products were not observed with nucleophiles containing free amines, or which were capable of forming energetically favoritable chelates, such as prolinol. Subjecting the imine derived from p-methoxybenzaldehyde and allylamines to the reaction conditions resulted in low yields and enantiomeric ratios, and therefore these products were not isolated in pure form (< 60% yield, < 85 : 15% er).

We have also endeavored to show that our methodology allows rapid access to the synthetically challenging 1,2-propylene diamine motif by synthesizing a C–H methylated derivative of the clinically used antidepressant Moclobemide. This synthesis shows that our most commonly used PMB directing group can be deprotected in the case of these molecules, and also that this method can be used to access this highly challenging motif in a diversifiable and modular manner. Intriguingly, the use of photochemical or traditional oxidative cleavage methods (DDQ, CAN) methods to deprotect this moiety resulted in decomposition or lack of reaction, resulting in the use of this somewhat exotic deprotection.[24]

Scheme 2.6: Synthesis of methyl-Moclobemide Analogue



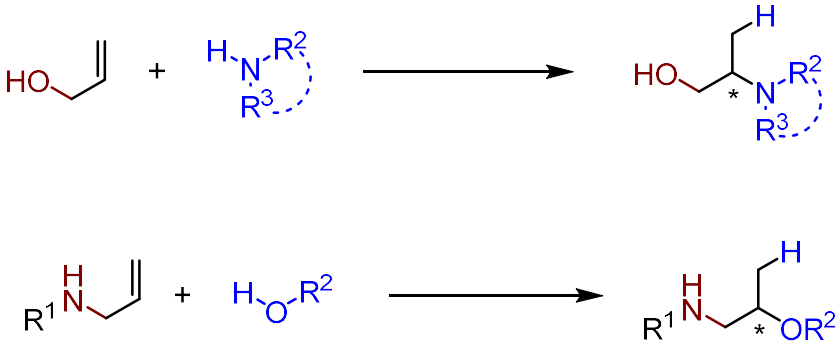
2.4 Summary & Future Directions

Reported herein is the development of a novel direct asymmetric enantioselective hydroamination reaction of allylamines (*vide infra*) which represents a major advance in the field

of hydroamination.[25] The method has a wide scope for substitution of the directing group, and nucleophilic amines that can be utilized, so long as they are sufficiently nucleophilic. Included in this scope is a tolerance for aryl bromides, free alcohols, deprotectable amines, and esters. Also, it is the first general report which can be used to directly make highly desirable enantioenriched 1,2-propylene diamine derivatives with high yields and enantiomeric excess. The reaction likely proceeds through an outer sphere aminometallation which forms a 5-membered metallacycle. The formation of this metallacycle drastically reduces the opportunity for β-hydride elimination, as well as enforcing high selectivity for the regioselectivity of the insertion.

Future work involving this directed strategy has many paths. The most obvious path forward is to utilize the same strategy, with different components (**Scheme 2.7**). An alcohol-directed hydroamination, or an amine-directed hydroetherification are clear potential future directions for this transformation, though it is likely that ligand screening would be necessary in order to obtain high yields of either product. Neither of these products are simple to access, and considering that our interest in these molecules is driven by an interest in biological activity, the ability to make structurally similar and electronically varied molecules is intriguing.

Scheme 2.7: Future directions for directed, chiral hydrofunctionalizations to afford 1,2 moieties

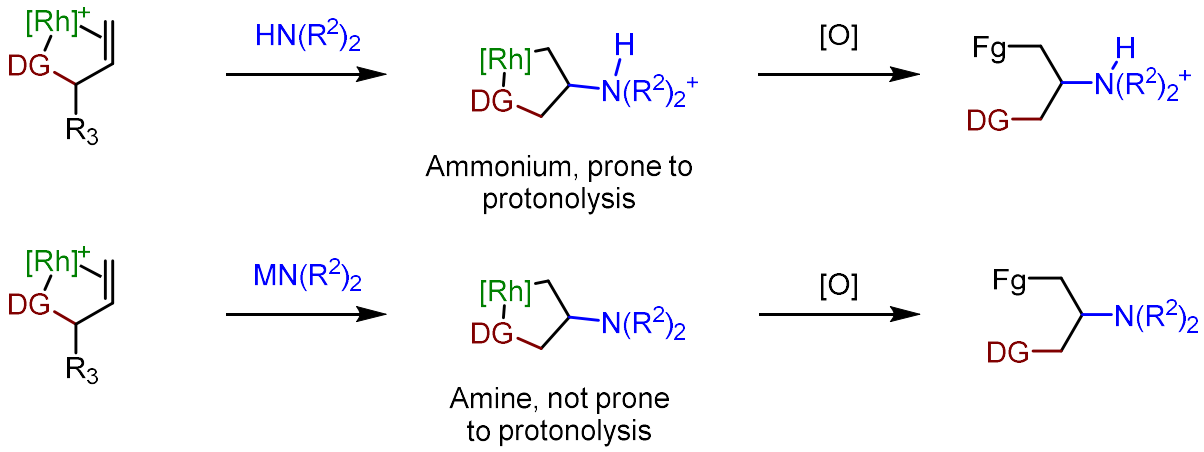


With the suspected mechanism of this transformation, it is very unlikely that we could directly overcome the regioselectivity of the insertion, as the alternative is making a 4-membered metallacycle which is highly strained. For this transformation we would be looking forward to other allylamines substrates. A clear and present challenge which is not addressed by this method currently is extending this method to allylamines which are internal olefins or 1,1-disubstituted olefins, allowing for the formation of enantiomerically enriched 1,2-butylene diamines and beyond, through this same method. The challenge of this transformation, of course, is that

internal alkenes are much worse ligands than terminal olefins. In addition, the metal now must be affixed to a secondary carbon instead of a primary carbon during the aminometallation step, which induces additional strain due to steric constraints, leading to a higher energy and more difficult to access intermediate. As these substrates currently are not compatible with the reaction, we must ask how to rectify this through catalyst design. One possible resolution would be make the metal center even more electrophilic: ligand design could produce a metal which was even more electrophilic than our catalyst. Replacing the methoxy groups of the ligand with CF_3 groups, for instance, would have this effect. Another way to achieve this would be to append CF_3 or other inductively withdrawing group to the furyl rings of the phosphine. This would make it so olefin coordination was more favored electronically, overcoming the energetic cost induced by coordinating. If neither of these approaches worked, it may be necessary to reduce the coordinating ability of the amine by changing it to a less basic amine, such as aniline or amide class nucleophiles.

An even more ambitious project would be to perform an oxidative difunctionalization reaction of the olefin: aminometallation results in an interceptable Rh(I) alkyl species. This species could react with an oxidant, rather than being protonolyzed, affording a product which has new functionality at both of the carbons which were previously an alkene. Difunctionalization reactions are inherently attractive as they are no longer simple functional group exchanges from alkenes to a functional group, they also add a second functional group. The challenge, as with any three component reaction, is side reactivity. Olefins and amines are both readily oxidized by many of the most common oxidants, especially in conjunction with transition-metal catalysts. This side reactivity must be avoided. The desired reactivity will most likely be observed in a reaction using acidic amine nucleophiles in conjunction with base, such that aminometallation occurs from an anionic nitrogen source. This means that protonolysis can be drastically slowed or prevented altogether. This, coupled with an oxidant which is slow to react with both the alkene and the metal-olefin complex, would allow for this transformation. We could envision that this would lead to exciting and dense polar functionalization such as aminoacetoxylation, aminohalogenation, and diamination.

Scheme 2.8: Difunctionalization proposal



2.5 Experimental

Portions of this experimental procedure section are reprinted with permission from "Rhodium-Catalyzed Asymmetric Hydroamination of Allyl Amines" Evan P. Vanable, Jennifer L. Kennemur, Leo A. Joyce, Rebecca T. Ruck, Danielle M. Schultz, Kami L. Hull, Journal of the American Chemical Society, 2019, 141 (2), 739-742. Copyright 2019, American Chemical Society.

General Experimental Procedures: All reactions were carried out in flame-dried (or oven-dried at 140 °C for at least 2 h) glassware under an atmosphere of nitrogen unless otherwise indicated. Nitrogen was dried using a drying tube equipped with Drierite™ unless otherwise noted. Air and moisture sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level < 1.0 ppm). Column chromatography was performed with silica gel from Silicycle (40-63 μm) mixed as a slurry with the eluent, or with basica alumina, 60Å from Acros. Columns were packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on pre-coated glass silica gel plates (by EMD Chemicals Inc.) with F-254 indicator. Visualization was by short wave (254 nm) ultraviolet light, or by staining with ninhydrin, potassium permanganate, or I_2 on silica followed by brief heating on a hot plate or by a heat gun. Distillations were performed using a 3 cm short-path column.

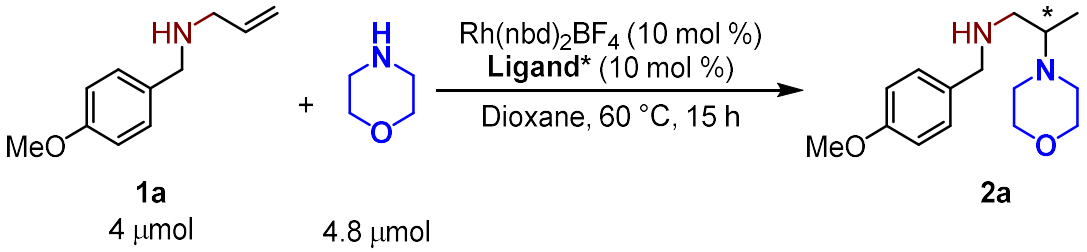
Instrumentation: ^{1}H NMR, ^{13}C NMR, and ^{19}F were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for ^{13}C) a VXR-500 MHz spectrometer, or a Carver-Bruker 500 MHz spectrometer equipped with a cryoprobe. Spectra were referenced using either $CDCl_3$ or

C_6D_6 as solvents (unless otherwise noted) with the residual solvent peak as the internal standard (^{1}H NMR: δ 7.26, ^{13}C NMR: δ 77.36 for $CDCl_3$ and ^{1}H NMR: δ 7.16, ^{13}C NMR: δ 128.62 for C_6D_6). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) p (pentet,) m (multiplet,) and br (broad). Coupling constants, *J*, are reported in Hertz and integration is provided, along with assignments, as indicated. Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). A similar GC with a mass spectrometer was utilized for compound identification in some instances. Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at University of Illinois at Urbana-Champaign.

Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated stainless steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted. All amines and thiols were distilled, degassed, and stored under an atmosphere of nitrogen in glove box before use. Racemic samples were prepared as in Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. "Regio- and Chemoselective Intermolecular Hydroamination of Allyl Imines for the Synthesis of 1,2-Diamines." *J. Am. Chem. Soc.* **2014**, *136* (32), 11256-11259 or by using this method with racemic ligand.

High Throughput Screening Information

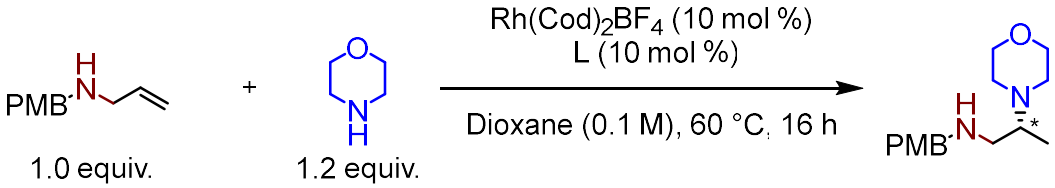
i. General procedure for the high throughput screening of chiral ligands



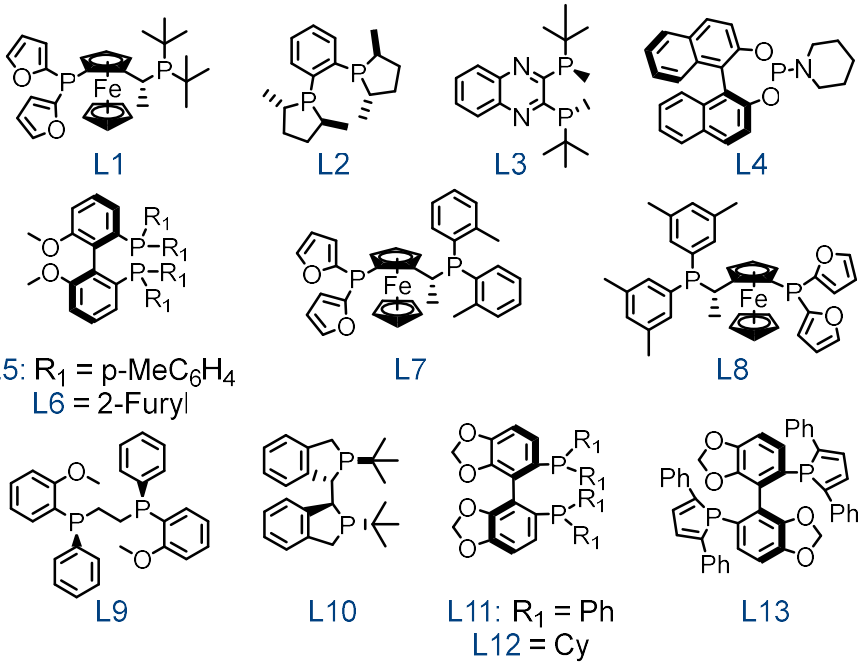
Inside of a N_2 filled glovebox, a stock solution of the rhodium catalyst was prepared by dissolving $Rh(nbd)_2BF_4$ (45 mg, 0.12 mmol) in 1,2-dichloroethane (6 mL) in a 20 mL screw-cap scintillation vial. The reaction was stirred until a clear orange solution was obtained. This stock solution was dosed out into 1.5 mL vials (20 µL per vial) containing pre-weighed chiral ligands in a 96-well reactor plate. The resulting solutions were stirred at 35 °C for 30 minutes after which the 1,2-dichloroethane was removed under reduced pressure. Next, a stock solution of amine **1a** and morpholine was prepared by dissolving amine **1a** (71 mg, 0.4 mmol) and morpholine (42 µL, 0.48 mmol) in 4mL of dioxane. The solution was stirred for one minute. Subsequently, the stock solution was dosed out into each of the 96-well vials (40 µL per vial). The reactions were heated to 60 °C and stirred for 15 hours. After 15 hours, the reactions were cooled to room temperature, diluted with acetonitrile, had internal standard added, and were analyzed by supercritical fluid chromatography (SFC) to probe the enantiomeric excess.

Of the 288 ligands screened (Appendix 1), few afforded significant amounts of product. The ligands which afforded product, or derivatives thereof, are shown below in **Table 2.4**.

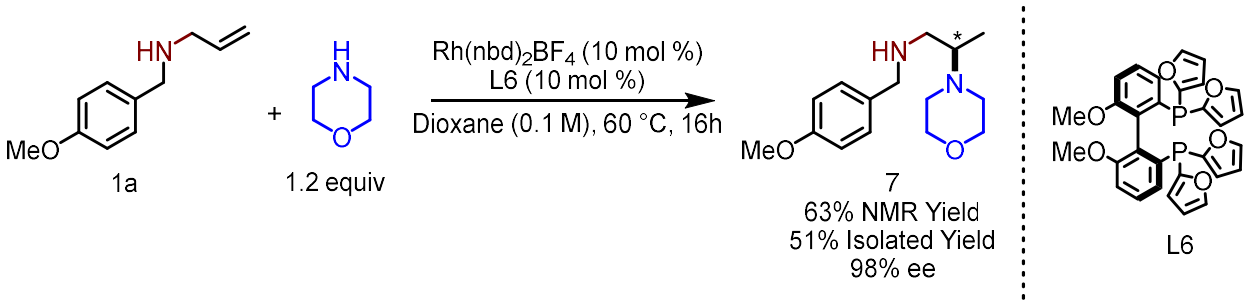
Table 2.4. Representative results from the high-throughput screen



Entry	ligand	% conversion	er
1	L1	<1%	n.d.
2	L2, (S,S)-Me-DUPHOS	11%	0.5:99.5
3	L3, (R) QuinoxP	52%	99.0:1.0
4	L4, (S)-PipPhos	22%	47.0:53.0
5	L5, (R)-*p*-Tol-MeOBIPHEP	14%	99.5:0.5
6	L6, (R)-2-Furyl-MeOBIPHEP	63%	99.0:1.0
7	L7	33%	87.5:12.5
8	L8	52%	12.5:87.5
9	L9, (S,S)-DIPAMP	32%	63.5:36.5
10	L10, (1S,1'S,2R,2'R)-Duanphos	22%	0.5:99.5
11	L11, (R)-Segphos	<1%	n.d.
12	L12, (+)-Cy-Segphos	<1%	n.d.
13	L13, (R)-P-3-Segphos	<1%	n.d.



ii. Isolation of compound 2a



Inside of a glovebox under an inert atmosphere of N_2, $Rh(nbd)_2BF_4$ (7.48 mg, 0.02 mmol) and (S)-OMe-BIPHEP-ligand **12** (10.85 mg, 0.02 mmol) were added to a 4 mL scintillation vial. Subsequently, 2 mL of dioxane were added, followed by amine **1a** (35.4 mg, 0.2 mmol) and morpholine (21.0 µL, 0.24 mmol). The vial was capped and brought out of the glovebox. The reaction was heated to 60 °C and stirred for 16 h. After such time, the reaction was cooled to room temperature. The crude yield of the reaction was determined by ^{1}H NMR using 1-methylnapthalene as an internal standard. Purification by flash column chromatography (1% MeOH, 25% EtAc, 74% hexanes on basic alumina (prepared by adding 5-9 mL of water to 100 mL basic alumina)) yielded **7** as a pale yellow oil (27.1 mg, 51% yield). The ^{1}H NMR spectra matched that found in literature (Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. J. Am. Chem. Soc. 2014, 136, (32), 11256-11259). The enantioselectivity of the reaction was determined by HPLC analysis of the purified 1,2-diamine (vide infra) to be 99 : 1

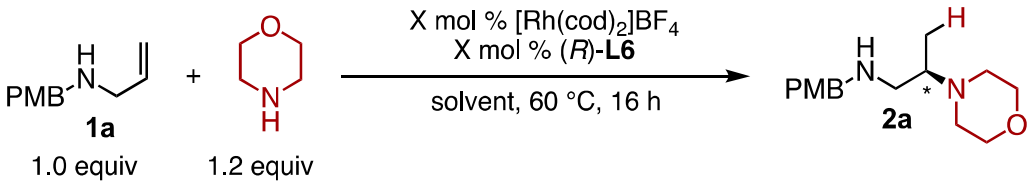
iii: General procedure for the screening of conditions with tetrafuryl-MeO-BIPHEP ligand

Inside of a glovebox under an inert atmosphere of N_2, $Rh(nbd\text{ or }cod)_2BF_4$ (xx mmol) and ligand **6** (xx mmol) were added to 4 mL scintillation vials. Subsequently, solvent was added, followed by amine **1a** (35.4 mg, 0.2 mmol) and morpholine (21.0 µL, 0.24 mmol). The vials were capped with screw cap septa and brought out of the glovebox. The reactions were heated to YY °C and stirred for 16 h. Then the reactions were cooled to room temperature. The crude yield of the reaction was determined by GC using 1-methylnapthalene as an internal standard. Purification by flash column chromatography (1% MeOH, 39% EtAc, 60% hexanes on basic alumina

(prepared by adding 9 mL of water to 100 mL alumina)) yielded **7** as a pale yellow oil. The enantioselectivity of the reaction was determined by HPLC analysis of the purified 1,2-diamine.

C. Reaction Optimization

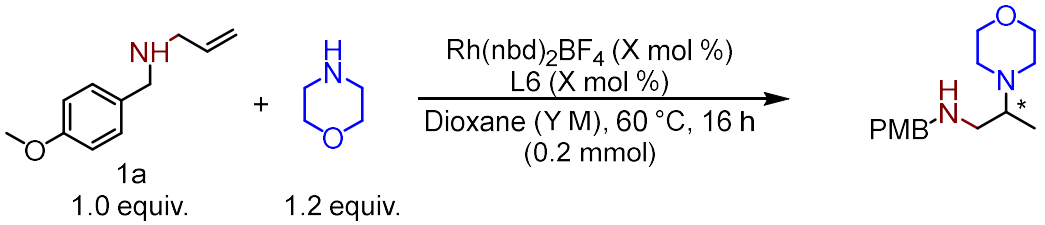
Table 2.5. Summarized reaction optimization



entry	solvent	conc. (M)	X	isolated yield	e.r.
1	Dioxane	0.1	10	51%	99.0:1.0
2	Dioxane	1.0	3	72%	94.2:5.8
3	Dioxane	4.0	3	86%	91.1:8.9
4	$PhCF_3$	1.0	3	96%	93.5:6.5
5	PhCN	1.0	3	72%	94.7:5.3
6	DME	1.0	3	93%	95.1:4.9
7	DME	0.25	3	77%	96.9:3.1
8	DME	0.25	5	92%	96.6:3.4

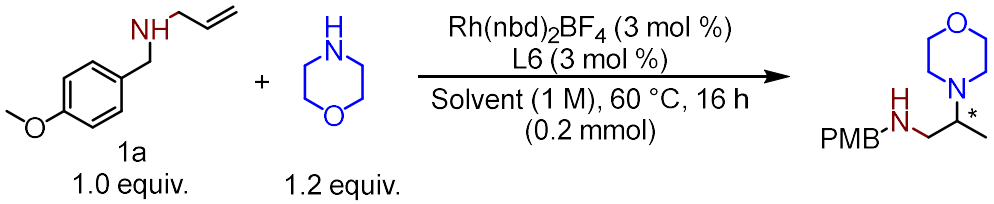
[a]Yields are of the isolated material. Reactions were run on a 0.20 mmol scale with respect to **1a**. [b]Enantiomeric ratios (er) were measured using HPLC analysis after isolation via column chromatography.

Table 2.6. Screening concentration and catalyst loading



entry	cat. loading (%)	Conc. (M)	GC yield (%)	er
1	10	1.0	65	nd
2	5	1.0	79	94.6:5.4
3	3	1.0	72	94.2:5.8
4	1	1.0	41	nd
5	10	4.0	78	nd
6	5	4.0	87	90.5:9.5
7	3	4.0	86	91.1:8.9
8	1	4.0	53	nd

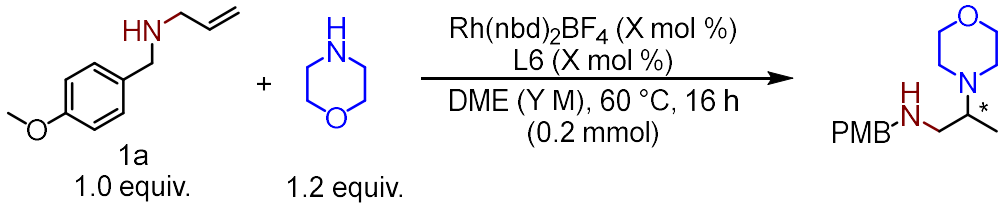
Table 2.7. Solvent study



entry	solvent	GC yield (%)	isolated yield (%)	er
1	Dioxane	112	62%	94.2 : 5.8
2	Hexanes	19	nd	nd
3	Et_2O	50	nd	nd
4	Toluene	90	74	93.8:6.2
5	DME	101	93	95.1:4.9
6	THF	117	82	93.6:6.4
7	Pentanes	120	84	95.1:4.9
8	$PhCF_3$	99	91	93.5:6.5
9	PhCN	73	72	94.7:5.3
10	DCE	26	nd	nd

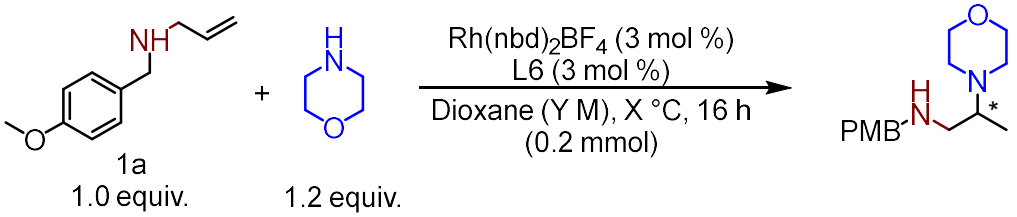
Dioxane affords a higher GC yield, although it is clear that this is due at least in part to some byproduct coming at the same retention time, as the GC yield is over 100%. See THF, pentanes.

Table 2.8. Catalyst loading and concentration study with DME



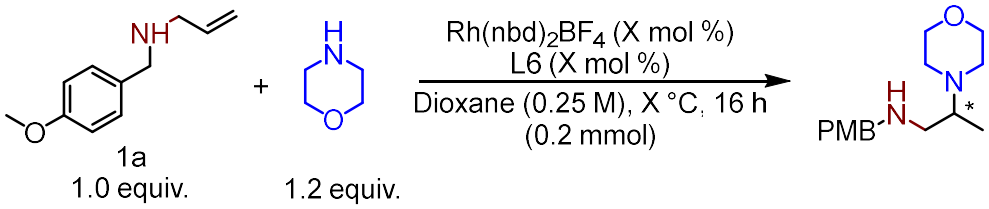
entry	cat. loading (%)	Conc. (M)	GC yield (%)	isolated yield (%)	er
1	1	1	63	nd	nd
2	2	1	102	nd	nd
3	3	1	102	nd	nd
4	1	0.5	55	nd	nd
5	2	0.5	88	nd	nd
6	3	0.5	101	85	95.3:4.7
7	1	0.25	39	nd	nd
8	2	0.25	77	nd	nd
9	3	0.25	91	77	96.9:3.1
10	1	0.1	21	nd	nd
11	2	0.1	54	nd	nd
12	3	0.1	67	58	98.2:1.8

Table 2.9. Temperature and concentration study



entry	Temperature	Conc. (M)	GC yield (%)	isolated yield (%)	er
1	40	1	96	94	92.2:7.8
2	50	1	102	92	92.9:7.1
3	60	1	106	nd	95.1 : 4.9
4	40	0.5	111	91	95.0:5.0
5	50	0.5	108	88	94.8:5.2
6	70	0.5	94	84	95.5 : 4.5
7	80	0.5	77	72	96.0 : 4.0
8	60	0.1	71	nd	96.7:3.3

Table 2.10. Catalyst loading at 0.25 M



entry	mol [Rh] %	mol L* %	isolated yield (%)	er
1	3	3	85	95.6:4.4
2	3	3.6	90	95.6:4.4
3	5	5	92	97.2:2.8
4	5	6	84	97.2:2.8

D. Experimental Procedures, Isolation, and Characterization

Starting Material Synthesis:

Starting materials were prepared as described in our previous report. Imine condensation, followed by borohydride reduction of the crude imine affords the free amine, which is then distilled or columned for purification as in Kennemur, J. L.; Kortman, D. G.; Hull, K. L.; "Rhodium-Catalyzed Regiodivergent Hydrothiolation of Allyl Amines and Imines." *J. Am. Chem. Soc.* **2016**, *138*, (36), 11914-11919.

Hydroamination:

General Procedure 1: Asymmetric Hydroamination

To a 4-mL vial equipped with a stirbar in a glovebox is added 4.1 mg $Rh(cod)_2BF_4$ or 3.7 mg $Rh(nbd)_2BF_4$ (0.010 mmol, 5.0 mol %), 5.4 mg **L6** (2-furyl-MeO-BIPHEP, 0.010 mmol, 5.0 mol %), and 800 µL DME. This is allowed to stir for 2 minutes before the addition of 0.20 mmol of the desired allylamine derivative. This is stirred for a further 2 minutes prior to the addition of 0.24 mmol (1.2 equiv) of the desired nucleophilic secondary amine. The vial is then capped, removed from the glovebox, and heated to 60 °C for 16 hours with a stir rate of approximately 600 rpm. The vial is removed from heat, and allowed to cool. The crude reaction mixture is loaded onto 5 mL celite by transferring with dichloromethane and columned using one of two methods.

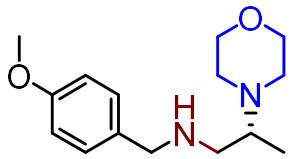
Alumina column chromatography:

1000 mL basic alumina (60Å, Acros**)** and 50 mL water were mixed together for a period of 10 minutes using a metal spatula. The end product should be homogeneous, however, it will significantly heat up and form clumps during this mixing, which will eventually break apart. Approximately 125 mL of this mixture is loaded into a 1 inch diameter column dry, tapped with a cork ring to improve settling, and 150 mL 60:39.25:0.75 ethyl acetate : hexanes : methanol is then run through it until the solvent level approaches the top of the alumina. The eluent which has been passed through the column is returned to the top, and washed through another three times. After this loading process, the dry celite loaded compound is poured on top of the column, and washed down with 10 mL of the eluent. This is then covered with sand, and more of the previously mentioned eluent system is run for fractions, and spotted by TLCs which are developed using UV or ninhydrin stain. Some compounds were more polar and required additional methanol to be added in order to elute. Compounds typically elute across 8-10 18 mL fractions in the range of fractions 8-30.

Silica column chromatography:

40 mL NH_4OH and 1000 mL chloroform are mixed and allowed to settle in a separatory funnel. The chloroform layer is taken, and added to 10 mL methanol to afford the eluent. 125 mL of silica (35-75 μm, Grace Discovery Sciences) and ≈ 250 mL of this eluent are mixed to afford a translucent slurry. This is poured into the column, and loaded in a normal slurry load procedure. The celite-loaded compound is loaded on top, and washed onto the column with 3x8 mL washes of dichloromethane (critical). The column is then run using the eluent, and additional methanol if required. The TLC is developed in an identical way. Compounds typically elute in very narrow bands of 4-8 18 mL fractions, in the range of 22-60.

Nitrogen Substituent Scope



2a

N-(4-methoxybenzyl)-2-morpholinopropan-1-amine (2a):

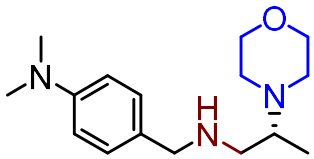
Compound **2a** was prepared under **General Procedure 1** with no deviations ((*R*)-**L6**) and purified by alumina column chromatography**.** The desired compound was obtained as a clear viscous oil in a 92% yield (48.6 mg, 0.184 mmol) with 96.6 : 3.4 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.27 (d*, 8.5 Hz, 2H), 6.83 (d*, 8.6 Hz, 2H), 3.71 (d, 13.1 Hz, 1H), 3.66 (d, 13.1 Hz, 1H), 3.53 (qdd, J = 10.9, 6.1, 3.0 Hz, 4H), 3.32 (s, 3H), 2.58 (dqd, J = 8.5, 6.6, 4.8 Hz, 1H), 2.46 (dd, J = 11.6, 8.5 Hz, 1H), 2.37 (dd, J = 11.6, 4.9 Hz, 1H), 2.24 (ddd, 10.4, 5.8, 2.7 Hz, 2H), 2.21 (dddd, 11.3, 6.2, 3.1, 1.0 Hz, 2H), 1.60 (br s, 1H), 0.73 (d, J = 6.6 Hz, 3H).

* Second order AA'BB' coupling was observed.

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.84, 134.12, 130.10, 114.67, 68.12, 59.61, 55.39, 54.24, 52.26, 49.49, 12.40.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1925



2b

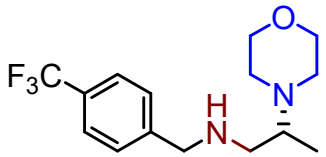
N,N-dimethyl-4-(((2-morpholinopropyl)amino)methyl)aniline (2b):

Compound **2b** was prepared using **General Procedure 1** with no deviations ((*R*)-**L6**) and purified via alumina column chromatography. The desired compound was obtained as a pale yellow oil in 86% yield (47.7 mg, 0.172 mmol) with 97.5 : 2.5 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.35 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 3.80 (d, J = 12.9 Hz, 1H), 3.74 (d, J = 12.9 Hz, 1H), 3.55 (ddd, J = 11.0, 6.2, 3.1 Hz, 2H), 3.50, (ddd, J = 10.9, 6.1, 3.1 Hz, 4H), 2.61 (dqd, J = 8.5, 6.5, 4.9 Hz, 1H) 2.56 – 2.48 (m, 7H), 2.43 (dd, J = 11.5, 4.9 Hz, 1H), 2.25 (ddd, J = 10.5, 5.7, 3.0 Hz, 2H), 2.11 (dddd, J = 11.3, 6.2, 3.1, 1.0 Hz, 2H), 1.93 (s, 1H), 0.75 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 150.79, 130.26, 129.91, 113.67, 68.18, 59.69, 54.54, 52.34, 49.53, 41.08, 12.49.

HRMS (ESI-TOF) m/z: [M+H$^+$] calcd for $C_{16}H_{28}N_3O$, 278.2232; found, 278.2224



2c

2-morpholino-N-(4-(trifluoromethyl)benzyl)propan-1-amine (2c):

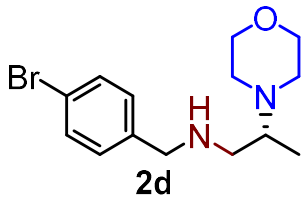
Compound **2c** was prepared under **General Procedure 1** with no deviations ((*R*)-**L6**) and was purified by alumina column chromatography. The desired compound was obtained as a yellow viscous oil in a 71% yield (42.9 mg, 0.142 mmol) with 96.9 : 3.1 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.38 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 3.58 – 3.47 (m, 4H), 3.50, (br S, 2H) 2.51 (dqd, J = 8.6, 6.6, 4.7 Hz, 1H), 2.30 (dd, J = 11.6, 8.6 Hz, 1H), 2.21 (m, 3H), 2.08 (dddd, J = 10.3, 6.2, 3.1, 1.5 Hz, 2H), 1.55 (s, 1H), 0.69 (d, J = 6.6 Hz, 3H).

^{19}F NMR (471 MHz, C_6D6) δ -61.96.

^{13}C NMR (126 MHz, Benzene-d_6) δ 146.25, 129.72, 129.03, 126.42 (q, 270 Hz), 125.47 (q, 3.8 Hz), 68.09, 59.55, 54.00, 52.32, 49.48, 12.27.

HRMS (ESI-TOF) m/z: [M+H$^+$] calcd for $C_{15}H_{22}N_2OF_3$, 303.1684; found, 303.1686



2d

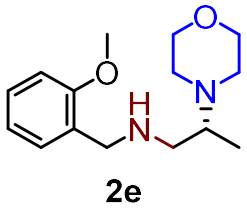
N-(4-bromobenzyl)-2-morpholinopropan-1-amine (2d):

Compound **2d** was generated using **General Procedure 1** without modification ((*R*)-**L6**)and was purified using alumina column chromatography. The compound was obtained in a 53% yield (33.2 mg, 0.106 mmol) with 97.9 : 2.1 er as a pale yellow oil.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.30 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 3.4 (ddd, J = 10.9, 6.2, 3.0 Hz, 2H), 3.49 (ddd, J = 10.9, 6.2, 3.0 Hz, 2H), 3.46 (s, 2H), 2.50 (dqd, J = 8.5, 6.6, 4.8 Hz, 1H), 2.32 (dd, J = 11.6, 8.5 Hz, 1H), 2.26 – 2.17 (m, 3H), 2.08 (dddd, J = 11.3, 6.3, 3.0, 1.0 Hz, 2H), 1.47 – 1.21 (br s, 1H) 0.70 (d, J = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 141.22, 132.21, 130.57, 121.40, 68.11, 59.63, 53.96, 52.35, 49.52, 12.36.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{14}H_{22}N_2OBr$, 313.0915; found, 313.0922



2e

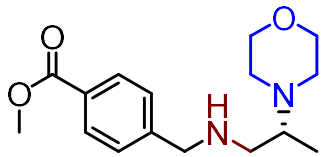
N-(2-methoxybenzyl)-2-morpholinopropan-1-amine (2e):

Compound **2e:** was prepared under **General Procedure 1** with no deviations **((R)-L6)** and was purified by alumina column chromatography. It was obtained as a clear viscous oil in an 82% yield (43.3 mg, 0.164 mmol) with 97.2 : 2.8 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.35 (dd, J = 7.4, 1.7 Hz, 1H), 7.08 (td, J = 7.8, 1.8 Hz, 1H), 6.88 (td, J = 7.4, 1.1 Hz, 1H), 6.52 (dd, J = 8.1, 1.0 Hz, 1H), 4.02 (d, J = 13.8 Hz, 1H), 3.86 (d, J = 13.8 Hz, 1H), 3.55 (ddd, J = 10.9, 6.2, 3.1 Hz, 2H), 3.50 (ddd, J = 10.8, 6.2, 3.0 Hz, 2H), 3.31 (s, 3H), 2.62 (dqd, J = 8.6, 6.6, 4.8 Hz, 1H), 2.51 (dd, J = 11.5, 8.6 Hz, 1H), 2.43 (dd, J = 11.5, 4.8 Hz, 1H), 2.20 (dq, J = 10.8, 2.7 Hz, 1H), 2.07 (dddd, J = 11.2, 6.3, 3.1, 1.0 Hz, 2H), 1.85 (br s, 1H), 0.73 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 158.63, 130.59, 130.13, 128.71, 121.22, 110.92, 68.18, 59.58, 55.37, 52.24, 49.84, 49.41, 12.37.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1911



2f

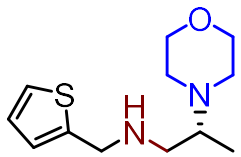
methyl (R)-4-(((2-morpholinopropyl)amino)methyl)benzoate (2f):

Compound **2f** was generated via **General Procedure 1** ((R)-L6) with one half the volume of DME (0.5 M) and purified via SiO_2 column chromatography. The compound was obtained as a pale oil in 75% yield (43.9 mg, 0.150 mmol) with 94.4 : 5.6 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 8.18 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 3.57 (s, 2H), 3.54 – 3.47 (m, 4H), 3.50 (br s, 3H), 2.51 (dqd, J = 8.5, 6.6, 4.8 Hz, 1H), 2.34 (dd, J = 11.6, 8.5 Hz, 1H), 2.28 – 2.18 (m, 3H), 2.08 (dddd, J = 11.2, 6.2, 3.1, 1.0 Hz, 2H), 1.76 – 1.59 (br s, 1H), 0.70 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 167.29, 147.49, 130.61, 130.10, 128.76, 68.10, 59.60, 54.27, 52.33, 52.13, 49.49, 12.33.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{16}H_{25}N_2O_3$, 293.1865; found, 293.1862



2g

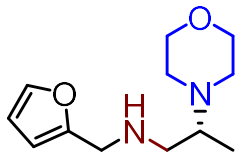
2-morpholino-N-(thiophen-2-ylmethyl)propan-1-amine (2g):

Compound **2g** was prepared under **General Procedure 1** ((*R*)-**L6**) with no deviations and was purified by alumina column chromatography. The desired compound was obtained as a yellow viscous oil in a 89% yield (42.8 mg, 0.178 mmol) with 96.2 : 3.8 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 6.89 (dd, J = 5.0, 1.3 Hz, 1H), 6.81 – 6.78 (m, 1H), 6.76 (dd, J = 5.0, 3.4 Hz, 1H), 3.82 (dd, J = 14.2, 1.0 Hz, 1H), 3.78 (dd, J = 14.2, 1.0 Hz, 1H), 3.54 (ddd, J = 10.9, 6.2, 3.1 Hz, 2H), 3.49 (ddd, J = 10.9, 6.2, 3.1 Hz, 2H), 2.51 (dqd, J = 8.6, 6.6, 4.8 Hz, 1H), 2.42 (dd, J = 11.6, 8.5 Hz, 1H), 2.33 (dd, J = 11.6, 4.8 Hz, 1H), 2.21 (dddd, J = 11.3, 6.1, 3.0, 1.0 Hz, 2H), 2.07 (dddd, J = 11.3, 6.2, 3.1, 1.0 Hz, 2H), 1.61 (s, 1H), 0.69 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 146.50, 127.26, 125.11, 124.99, 68.11, 59.52, 52.13, 49.46, 49.36, 12.29.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{12}H_{21}N_2SO$, 241.1375; found, 241.1385



2h

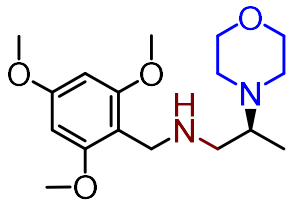
N-(furan-2-ylmethyl)-2-morpholinopropan-1-amine (2h):

Compound **2h** was generated using **General Procedure 1** without modification ((*R*)-**L6**)and purified via alumina column chromatography. It was obtained in a 75% (33.6 mg, 0.150 mmol) yield as a pale yellow oil with 94.5 : 5.5 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.08 (dd, J = 1.8, 0.9 Hz, 1H), 6.08 (dd, J = 3.1, 1.8 Hz, 1H), 6.03 (dd, J = 3.1, 0.9 Hz, 1H), 3.72 (dd, J = 14.7, 0.8 Hz, 1H), 3.61 (dd, J = 14.7, 0.7 Hz, 1H), 3.55 (ddd, J = 11.0, 6.2, 3.1 Hz, 2H), 3.51 (ddd, J = 10.9, 6.2, 3.2 Hz, 2H), 2.52 (dqd, J = 8.8, 6.6, 4.7 Hz, 1H), 2.43 (dd, J = 11.5, 8.7 Hz, 1H), 2.32 (dd, J = 11.4, 4.7 Hz, 2H), 2.20 (ddd, J = 14.0, 4.8, 2.7 Hz, 2H), 2.06 (dddd, J = 11.2, 6.2, 3.1, 1.0 Hz, 2H), 0.69 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 155.95, 142.18, 111.02, 107.33, 68.11, 59.47, 51.88, 49.34, 47.01, 12.25.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{12}H_{21}N_2O_2$, 225.1603; found, 225.1607



2i

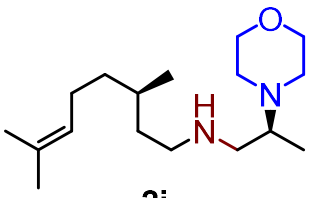
2-morpholino-N-(2,4,6-trimethoxybenzyl)propan-1-amine (2i):

Compound **2i** was prepared using **General Procedure 1** ((*S*)-**L6**) with half the usual amount of DME (0.5M). It was purified via SiO_2 chromatography. The desired compound was obtained in an 78**%** yield (50.6 mg, 0.156 mmol) with 97.8 : 2.2 e.r.

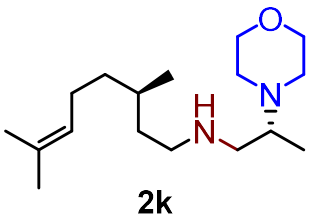
^{1}H NMR (500 MHz, Benzene-d_6) δ 6.09 (s, 2H), 4.25 (d, J = 12.7 Hz, 1H), 4.17 (d, J = 12.7 Hz, 1H), 3.59 (qdd, J = 11.1, 6.3, 3.2 Hz, 2H), 3.54 (ddd, J = 10.7, 6.2, 3.1 Hz, 2H), 3.38 (s, 3H), 3.33 (s, 6H), 2.73 – 2.55 (m, 3H), 2.42 (br s, 1H), 2.27 (ddd, J = 13.8, 4.6, 2.6 Hz, 2H), 2.13 (dddd, J = 11.2, 6.3, 3.0, 1.0 Hz, 2H), 0.82 (d, J = 5.9 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 160.57, 115.29, 111.40, 91.49, 68.28, 59.74, 55.85, 55.42, 52.18, 49.46, 42.36, 12.72.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{17}H_{29}N_2O_4$, 325.2127; found, 325.2122



2j



2k

(R)-3,7-dimethyl-N-((S)-2-morpholinopropyl)oct-6-en-1-amine (2j):

(R)-3,7-dimethyl-N-((R)-2-morpholinopropyl)oct-6-en-1-amine(2k):

2j and **2k w**ere prepared using the general procedure; **2j** was prepared using (*S*)-**L6** and **2k** was prepared using ((*R*)-**L6**). 2j was obtained in a 58% yield (32.8 mg, 0.116 mmol) and 2k was obtained in a 61% (34.5 mg, 0.122 mmol) yield. The DR was observed by ^{1}H NMR to be > 20 : 1.

2j:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.10 (tdd, *J* = 8.5, 3.2, 1.6 Hz, 1H), 3.77 – 3.61 (m, 4H), 2.76 (dtt, *J* = 11.3, 8.3, 5.7 Hz, 1H), 2.69 – 2.51 (m, 5H), 2.48 (ddd, *J* = 11.9, 4.9, 1.5 Hz, 1H), 2.42 (tdd, *J* = 9.5, 3.2, 1.6 Hz, 2H), 1.97 (tp, *J* = 14.5, 7.1, 6.6 Hz, 2H), 1.81 – 1.62 (m, 4H), 1.60 (s, 3H), 1.58 – 1.43 (m, 2H), 1.38 – 1.27 (m, 2H), 1.17 (ddddd, *J* = 13.4, 9.3, 7.4, 5.8, 1.5 Hz, 1H), 0.95 (dd, *J* = 6.6, 1.4 Hz, 3H), 0.91 – 0.87 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 131.50, 125.18, 67.88, 59.12, 52.83, 48.85, 48.32, 37.68, 37.66, 30.95, 26.07, 25.87, 19.85, 18.00, 11.87.

2k:

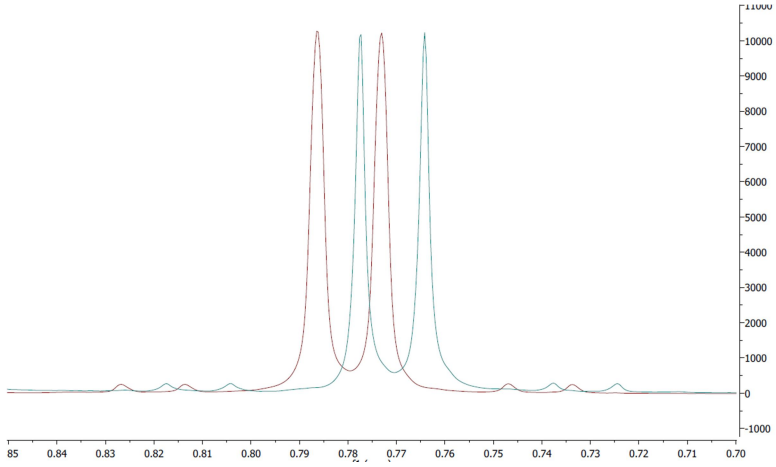
^{1}H NMR 500 MHz, Chloroform-*d*) δ 5.12 – 5.06 (m, 1H), 3.71 (ddd, *J* = 11.2, 6.3, 3.0 Hz, 2H), 3.65 (ddd, *J* = 11.1, 6.3, 3.0 Hz, 2H), 2.75 (dtd, *J* = 13.3, 6.7, 4.6 Hz, 1H), 2.65 – 2.51 (m, 5H),

2.51 – 2.37 (m, 3H), 1.97 (dtq, *J* = 22.0, 14.5, 7.1, 6.6 Hz, 2H), 1.67 (d, *J* = 1.6 Hz, 4H), 1.59 (s, 3H), 1.57 – 1.41 (m, 2H), 1.40 – 1.23 (m, 2H), 1.16 (dddd, *J* = 13.4, 9.7, 7.5, 5.8 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H).

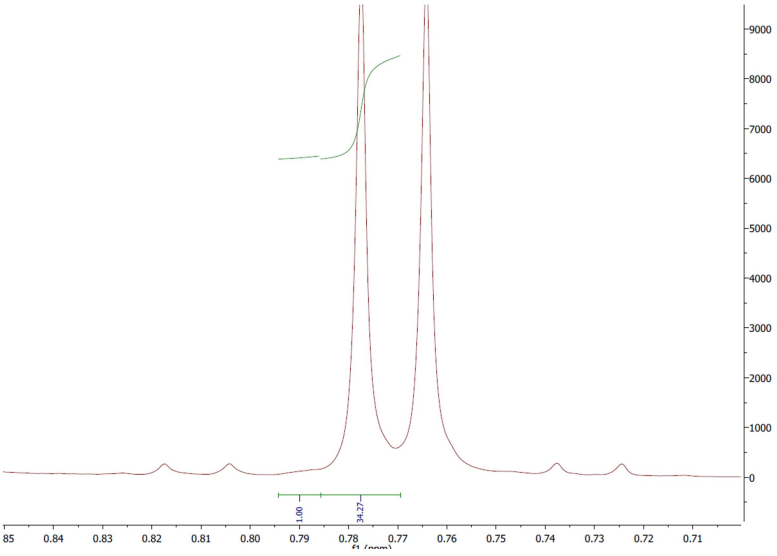
^{13}C NMR (126 MHz, $CDCl_3$) δ 131.48, 125.17, 67.86, 59.04, 52.72, 48.88, 48.24, 37.66, 37.53, 31.02, 26.06, 25.85, 20.02, 17.99, 11.88.

D.R. determination: The proton NMR in benzene-*d6* revealed that the methyl groups had sufficiently different chemical shifts to determine the d.r. by proton NMR to be > 20 : 1

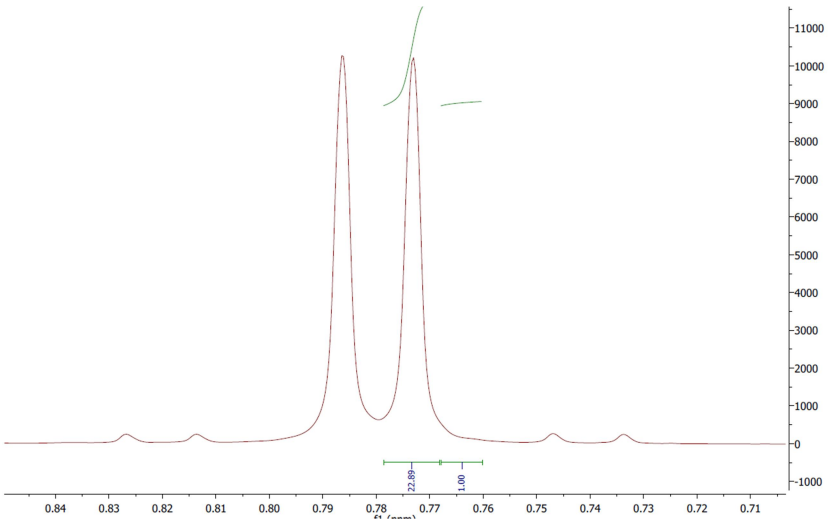
Stacked NMR showing the difference: 2j is in blue



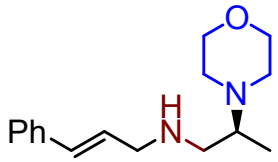
NMR of 2j



NMR of 2k



HRMS (ESI-TOF) *m/z*: [M+H+] calculated for C17H35N2O, 283.2737; found, 283.2749.



2l

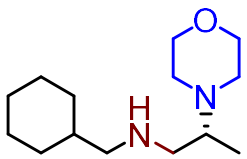
(E)-N-(2-morpholinopropyl)-3-phenylprop-2-en-1-amine (2l):

Compound **2l** was generated using **General Procedure 1** ((*S*)-**L6**) with half the normal quantity of DME (0.5M). It was purified via SiO_2 column chromatography. The compound was obtained as a pale yellow oil in an 80% yield (41.7 mg, 0.160 mmol) with 95.0 : 5.0 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.30 – 7.26 (m, 2H), 7.13 – 7.10 (m, 2H), 7.06 – 7.01 (m, 1H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.1 Hz, 1H), 3.57 (ddd, *J* = 10.9, 6.2, 3.1 Hz, 2H), 3.53 (ddd, *J* = 10.9, 6.2, 3.1 Hz, 2H), 3.29 (dd, *J* = 6.1, 1.6 Hz, 2H), 2.58 (dqd, *J* = 8.3, 6.6, 4.8 Hz, 1H), 2.50 (dd, *J* = 11.5, 8.3 Hz, 1H), 2.39 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.29 (dddd, *J* = 11.4, 6.2, 2.9, 1.1 Hz, 2H), 2.14 (dddd, *J* = 11.2, 6.2, 3.1, 1.0 Hz, 2H), 1.43 – 1.31 (br s, 1H), 0.77 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 138.45, 131.51, 130.49, 129.43, 128.06, 127.20, 68.15, 59.83, 52.85, 52.73, 49.62, 12.53.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{16}H_{25}N_2O$, 261.1967; found, 261.1958



2m

N-(cyclohexylmethyl)-2-morpholinopropan-1-amine (2m):

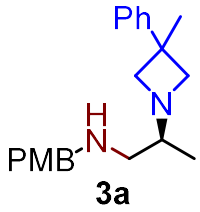
Compound **2m** was prepared under **General procedure 1** ((*R*)-**L6**) with no deviations and was purified by alumina column chromatography. The desired compound was obtained as a clear yellow oil in a 61% yield (29.3 mg, 0.122 mmol) and a 96.0 : 4.0 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 3.59 (ddd, *J* = 10.9, 6.3, 3.0 Hz, 2H), 3.54 (ddd, *J* = 10.9, 6.2, 3.0 Hz, 2H), 2.59 (dqd, *J* = 8.5, 6.6, 4.9 Hz, 1H), 2.50 – 2.35 (m, 4H), 2.31 (dddd, *J* = 11.4, 6.1, 3.0, 1.0, 2H), 2.15 (dddd, *J* = 11.3, 6.3, 3.0, 1.0 Hz, 2H), 1.87 – 1.80 (m, 2H), 1.73 – 1.68 (m, 2H), 1.67 – 1.60 (m, 1H), 1.44 (tdd, *J* = 11.3, 6.7, 3.4 Hz, 2H), 1.28 – 1.09 (m, 3H), 0.94 (qd, *J* = 12.3, 11.9, 3.5 Hz, 2H), 0.78 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 68.22, 59.67, 58.02, 53.67, 49.56, 39.21, 32.51, 27.80, 27.16, 12.50.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{14}H_{29}N_2O$, 241.2280; found, 241.2282

Nucleophile Scope:



3a

N-(4-methoxybenzyl)-2-(3-methyl-3-phenylazetidin-1-yl)propan-1-amine (3a):

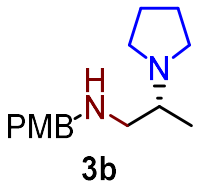
Compound **3a** was prepared via **General Procedure 1** ((*S*)-**L6**) with no deviations. It was purified via alumina column chromatography. The compound was obtained as a colorless viscous oil in an 85% yield (55.2 mg, 0.170 mmol) with 94.8 : 5.2 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.26 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 7.6 Hz, 2H), 7.05 (ddt, J = 7.9, 6.9, 1.3 Hz, 1H), 6.98 (dd, J = 8.3, 1.3 Hz, 2H), 6.84 (d*, J = 8.6 Hz, 2H), 3.66 (br s, 2H), 3.33 (s, 3H), 3.25 – 3.22 (m, 2H), 3.13 (dd, J = 11.7, 6.5 Hz, 2H), 2.53 (dd, J = 11.5, 4.0 Hz, 1H), 2.46 (dd, J = 11.5, 5.7 Hz, 1H), 2.18 (pd, J = 6.2, 4.0 Hz, 1H), 1.55 (s, 3H), 1.32 (br s, 1H), 1.03 (d, J = 6.3 Hz, 3H).

* Second order AA'BB' coupling was observed.

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.81, 150.15, 134.21, 130.05, 129.20, 126.49, 126.03, 114.66, 65.52, 64.94, 63.43, 55.37, 54.70, 53.14, 38.99, 29.85, 16.27. (methylene carbons in nucleophile are diastereotopic through intramolecular H-bonding)

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{21}H_{29}N_2O$, 325.2280; found, 325.2285



3b

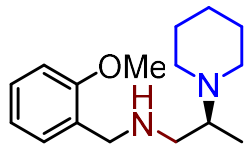
N-(4-methoxybenzyl)-2-(pyrrolidin-1-yl)propan-1-amine (3b):

Compound **3b** was prepared using **General Procedure 1** ((*R*)-**L6**) without modification and was purified via alumina column chromatography. The compound was obtained as a pale yellow oil in an 84% yield (41.7 mg, 0.168 mmol) with 97.7 : 2.3 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.27 (d, J = 7.9 Hz, 2H), 6.82 (d, J = 7.5 Hz, 2H), 3.67 (br s, 2H), 3.32 (s, 3H), 2.62 – 2.58 (m, 2H), 2.56 – 2.49 (m, 1H), 2.39 (dh, J = 4.3, 2.4 Hz, 4H), 1.73 (br s, 1H), 1.55 (ddt, J = 5.0, 4.0, 1.7 Hz, 4H), 1.07 (dd, J = 6.4, 0.8 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.77, 134.30, 130.10, 114.62, 58.44, 55.36, 54.65 (br, 2C), 50.85, 24.50, 16.2f0.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1975



3c

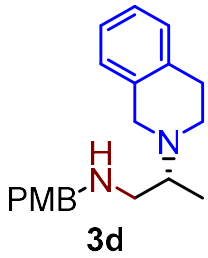
N-(2-methoxybenzyl)-2-(piperidin-1-yl)propan-1-amine (3c):

Compound **3c** was prepared using **General Procedure 1** ((*S*)-**L6**) with half the normal quantity of DME (0.5M). It was isolated via SiO_2 column chromatography in a 64% yield (33.6 mg, 0.128 mmol) with 95.8 : 4.2 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.44 (dd, J = 7.4, 1.8 Hz, 1H), 7.10 (td, J = 7.8, 1.8 Hz, 1H), 6.91 (td, J = 7.4, 1.1 Hz, 1H), 6.56 (dd, J = 8.2, 1.1 Hz, 1H), 4.04 (s, 1H), 3.94 (s, 1H), 3.35 (s, 3H), 2.79 (dqd, J = 9.2, 6.6, 4.8 Hz, 1H), 2.62 (dd, J = 11.4, 9.1 Hz, 1H), 2.46 (dd, J = 11.4, 4.8 Hz, 1H), 2.34 (dddd, J = 10.8, 7.3, 3.4, 1.0 Hz, 2H), 2.16 (ddd, J = 10.9, 7.0, 3.4 Hz, 2H), 2.07 (br s, 1H), 1.50 – 1.35 (m, 4H), 1.29 (p, J = 5.9 Hz, 2H), 0.78 (d, J = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 158.63, 130.59, 130.39, 128.49, 121.23, 110.88, 60.05, 55.38, 53.06, 49.97, 49.84, 27.66, 26.07, 12.04.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{16}H_{27}N_2O$, 263.2123; found, 263.2121



3d

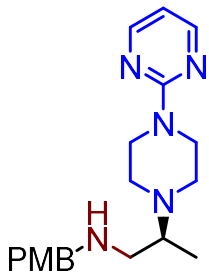
2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(4-methoxybenzyl)propan-1-amine (3d):

Compound **3d** was generated using **General Procedure 1** (*(R)*-**L6**) with half the quantity of DME (0.5M) and twice the quantity of rhodium catalyst and ligand (10 mol % each). The product was purified via alumina column chromatography and was obtained as a pale yellow oil in a 74% yield with 96.9 : 3.1 e.r (this compound was challenging to purify and roughly 10% SM remains. The yield has been corrected for by their relative proton integral and mass ratios).

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.22 (dd, J = 8.2, 1.2 Hz, 2H), 7.07 – 7.02 (m, 2H), 6.97 (dd, J = 5.3, 3.6 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.83 – 6.79 (m, 2H), 3.72 (d, J = 13.3 Hz, 1H), 3.66 (d, J = 13.3 Hz, 1H), 3.57 (d, J = 14.3 Hz, 1H), 3.48 – 3.42 (m, 1H), 3.32 (s, 3H), 2.90 (dqd, J = 9.0, 6.6, 4.6 Hz, 1H), 2.66 (t, J = 5.8 Hz, 2H), 2.59 (dd, J = 11.6, 9.1 Hz, 1H), 2.56 – 2.50 (m, 1H), 2.45 (dd, J = 11.6, 4.7 Hz, 1H), 2.30 (dt, J = 11.7, 6.1 Hz, 1H), 1.99 – 1.55 (br s, 1H), 0.78 (d, J = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 159.78, 136.77, 135.81, 134.19, 130.11, 129.60, 127.53, 126.69, 126.30, 114.64, 59.13, 55.37, 54.15, 52.58, 51.92, 46.24, 31.02, 11.84.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{20}H_{27}N_2O$, 311.2123; found, 311.2126



3e

N-(4-methoxybenzyl)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)propan-1-amine (3e):

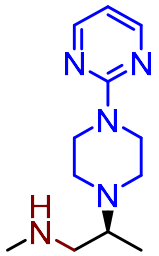
Compound **3e:** was prepared using **General Procedure 1** ((*S*)-**L6**) with no deviations and purified via SiO_2 column chromatography. The compound was obtained as a pale oil in 74% yield (50.5 mg, 0.148 mmol) with 97.3 : 2.7 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 8.11 (d, J = 4.7 Hz, 2H), 7.28 (d*, J = 8.5 Hz, 2H), 6.84 (d*, J = 8.6 Hz, 2H), 5.93 (t, J = 4.7 Hz, 1H), 3.88 (tdt, J = 16.1, 10.1, 3.4 Hz, 4H), 3.71 (d, J = 13.2 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 3.33 (s, 3H), 2.65 (dqd, J = 8.8, 6.6, 4.8 Hz, 1H), 2.46 (dd, J = 11.6, 8.8 Hz, 1H), 2.37 – 2.30 (m, 3H), 2.16 (dddd, J = 11.1, 6.7, 3.4, 1.0 Hz, 2H), 1.79 (br s, 1H), 0.65 (d, J = 6.6 Hz, 3H).

* Second order AA'BB' coupling was observed.

^{13}C NMR (126 MHz, Benzene-d_6) δ 163.00, 159.84, 158.36, 134.31, 130.09, 114.67, 110.33, 59.53, 55.40, 54.26, 52.55, 48.74, 45.08, 12.27.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{19}H_{28}N_5O$, 342.2294; found, 342.2284



3f

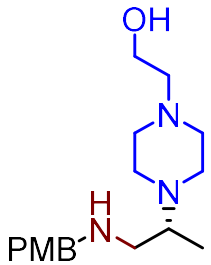
N-methyl-2-(4-(pyrimidin-2-yl)piperazin-1-yl)propan-1-amine (3f):

Compound **3f** was general using **General Procedure 1** ((*S*)-**L6**) with no modifications, and was isolated using SiO_2 column chromatography. The product was obtained in a 47% yield (22.0 mg, 0.094 mmol) as a white powder with 92.6 : 7.4 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 8.11 (d, J = 4.7 Hz, 2H), 5.94 (t, J = 4.7 Hz, 1H), 3.93 (ddd J = 12.8, 6.8, 3.4 Hz, 2H), 3.87 (ddd J = 12.8, 6.8, 3.3 Hz, 2H), 2.62 (dqd, J = 8.6, 6.7, 5.0 Hz, 1H), 2.42 – 2.32 (m, 3H), 2.29 (s, 3H), 2.25 – 2.16 (m, 3H), 1.35 (br s, 1H), 0.67 (d, J = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6) δ 162.97, 158.38, 110.32, 59.36, 55.76, 48.87, 45.10, 37.28, 12.35.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{12}H_{22}N_5$, 236.1875; found, 236.1884



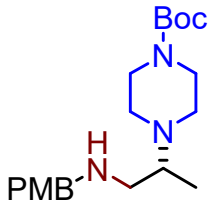
3g

2-(4-(1-((4-methoxybenzyl)amino)propan-2-yl)piperazin-1-yl)ethan-1-ol (3g):

Compound **3g** was prepared using **General Procedure 1** ((*R*)-**L6**) with half the usual amount of DME (0.5M). It was purified via SiO_2 chromatography. The desired compound was obtained in an 86% yield (52.9 mg, 0.172 mmol) with 96.7 : 3.3 e.r.

^{1}H NMR (500 MHz, Benzene-d_6) δ 7.30 (d*, *J* = 8.5 Hz, 2H), 6.85 (d*, *J* = 8.5 Hz, 2H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.69 (d, *J* = 13.1 Hz, 1H), 3.44 (t, *J* = 5.4 Hz, 2H), 3.33 (s, 3H), 2.69 (dqd, *J* = 8.7, 6.6, 4.9 Hz, 1H), 2.50 (dd, *J* = 11.6, 8.7 Hz, 1H), 2.41 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.31 (td, *J* = 8.8, 3.9 Hz, 2H), 2.27 – 2.09 (m, 9H), 1.33 (dd, *J* = 27.6, 7.8 Hz, 1H), 0.77 (d, *J* = 6.7 Hz, 3H).
* Second order AA'BB' coupling was observed.
^{13}C NMR (126 MHz, Benzene-d_6) δ 159.83, 134.29, 130.09, 114.67, 60.42, 59.23, 58.47, 55.38, 54.37, 54.26, 52.70, 30.79, 12.43.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{17}H_{30}N_3O_2$, 308.2338; found, 308.2339



3h

tert-butyl 4-(1-((4-methoxybenzyl)amino)propan-2-yl)piperazine-1-carboxylate (3h):

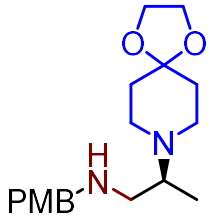
Compound **3h** was prepared using **General Procedure 1** ((*R*)-**L6**) with twice the Rh and ligand quantity (10 mol % each). It was purified via alumina column chromatography. The compound was obtained in a 88% yield (64.0 mg, 0.176 mmol) as a clear viscous oil with 93.4 : 6.6 e.r.

^{1}H NMR (500 MHz, Benzene-d_6): δ 7.25 (d*, *J* = 8.5 Hz, 2H), 6.83 (d*, *J* = 8.6 Hz, 2H), 3.68 (d, *J* = 13.1 Hz, 1H), 3.63 (d, *J* = 13.1 Hz, 1H), 3.32 (m, 7H), 2.59 (dqd, *J* = 8.8, 6.6, 4.9 Hz, 1H), 2.40 (dd, *J* = 11.7, 8.8 Hz, 1H), 2.31 (dd, *J* = 11.7, 5.0 Hz, 1H), 2.17 (dt, *J* = 10.4, 4.6 Hz, 2H), 2.01 (dd, *J* = 10.3, 4.6 Hz, 2H), 1.72 – 1.60 (br s, 1H), 1.47 (s, 9H), 0.62 (d, *J* = 6.6 Hz, 3H).

* Second order AA'BB' coupling was observed.

^{13}C NMR (126 MHz, Benzene-d_6): δ 158.92, 154.23, 133.25, 129.13, 113.74, 78.58, 58.57, 54.45, 53.30, 51.52, 47.67, 28.18, 11.29. Two carbons have coincidental signals.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{20}H_{34}N_3O_3$, 364.2600; found, 364.2599



3i

N-(4-methoxybenzyl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propan-1-amine (3i):

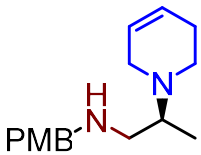
Compound **3i** was prepared according to **General Procedure 1** ((*S*)-**L6**) with half the quantity of DME (0.5M). It was purified via alumina column chromatography. The compound was obtained as a viscous oil in 69% yield (44.2 mg, 0.138 mmol) with 96.2 : 3.8 e.r.

* Second order AA'BB' coupling was observed.

^{1}H NMR (500 MHz, Benzene-d_6): δ 7.27 (d* J = 8.8 Hz, 2H), 6.82 (d*, J = 8.6 Hz, 2H), 3.73 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 13.2 Hz, 1H), 3.51 (s, 4H), 3.32 (s, 3H), 2.82 (dqd, J = 9.1, 6.6, 4.8 Hz, 1H), 2.60 (dddd, J = 11.4, 7.7, 4.1, 1.4 Hz, 2H), 2.53 (dd, J = 11.6, 9.1 Hz, 1H), 2.46 – 2.37 (m, 3H), 1.88 – 1.83 (br s, 1H), 1.81 – 1.68 (m, 4H), 0.79 (d, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6): δ 159.77, 134.42, 130.09, 114.64, 108.42, 64.73, 59.37, 55.38, 54.29, 52.93, 46.82, 36.74, 12.31.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{18}H_{29}N_2O_3$, 321.2178; found, 321.2173



3j

2-(3,6-dihydropyridin-1(2H)-yl)-N-(4-methoxybenzyl)propan-1-amine (3j):

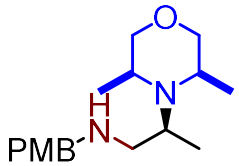
Compound **3j** was prepared via **General Procedure 1** ((*S*)-**L6**) at half the usual amount of DME (0.5M). It was purified via SiO_2 column chromatography. It was obtained as a pale yellow oil in a 41% yield (21.4 mg, 0.082 mmol) with 96.2 : 3.8 e.r. Subsequent attempts to increase the concentration or catalyst loading did not afford significantly more product, likely due to the increased ligation capacity of the nucleophile. Isomerization byproducts were not observed.

^{1}H NMR (500 MHz, Benzene-d_6): δ 7.27 (d*, J = 8.5 Hz, 2H), 6.82 (d*, J = 8.6 Hz, 2H), 5.64 (ddq, J = 9.4, 3.7, 1.8 Hz, 1H), 5.57 (dtt, J = 9.9, 3.3, 1.8 Hz, 1H), 3.71 (d, J = 13.3 Hz, 1H), 3.68 (d, J = 13.0 Hz, 1H), 3.32 (s, 3H), 2.94 (dt, J = 16.2, 2.8 Hz, 1H), 2.88 – 2.76 (m, 2H), 2.56 (dd, J = 11.6, 8.8 Hz, 1H), 2.45 (ddd, J = 20.1, 11.3, 5.2 Hz, 2H), 2.27 (dt, J = 11.2, 5.7 Hz, 1H), 1.98 (tdd, J = 5.4, 3.3, 2.2 Hz, 2H), 1.65 – 1.33 (br s, 1H), 0.78 (d, J = 6.6 Hz, 3H).

* Second order AA'BB' coupling was observed.

^{13}C NMR (126 MHz, Benzene-d_6): δ 159.75, 134.42, 130.08, 127.18, 125.85, 114.62, 59.09, 55.36, 54.36, 52.82, 48.62, 45.47, 27.96, 11.99.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{16}H_{25}N_2O$, 261.1967; found, 261.1977



3k

2-(cis)-3,5-dimethylmorpholino)-N-(4-methoxybenzyl)propan-1-amine (3k):

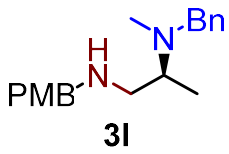
Compound **3k** was prepared according to **General Procedure 1** ((*S*)-**L6**) with half the normal volume of DME (0.5M). It was purified via SiO_2 column chromatography and obtained as a pale yellow oil in a 68% yield (39.5 mg, 0.136 mmol) with 92.6 : 7.4 e.r.

^{1}H NMR (500 MHz, Benzene-d_6): δ 7.27 (d*, *J* = 8.5 Hz, 2H), 6.83 (d*, *J* = 8.5 Hz, 2H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.57 (dqd, *J* = 9.9, 6.4, 2.4 Hz, 1H), 3.50 (dqd, *J* = 9.1, 5.8, 5.4, 1.7 Hz, 1H), 3.33 (s, 3H), 2.66 (dqd, *J* = 8.8, 6.6, 4.7 Hz, 1H), 2.52 (dd, *J* = 11.5, 8.8 Hz, 1H), 2.40 (dd, *J* = 11.5, 4.8 Hz, 1H), 2.23 (ddt, *J* = 10.9, 2.7, 1.7 Hz, 2H), 2.03 (dd, *J* = 11.1, 9.7 Hz, 1H), 1.77 – 1.61 (m, 2H), 1.07 (dd, *J* = 6.3, 2.9 Hz, 6H), 0.75 (d, *J* = 6.6 Hz, 3H).
* Second order AA'BB' coupling was observed.

^{13}C NMR (126 MHz, Benzene-d_6): δ 159.82, 134.31, 130.12, 114.66, **72.89**, **72.87**, 59.29, 58.65, 55.38, 54.26, **52.23, 52.04**, **20.08, 19.94**, 12.22.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{17}H_{29}N_2O_2$, 293.2229; found, 293.2228

The bolded pairs of peaks each arise from the same carbon, and are due to the conformers observed in apolar solution.



3l

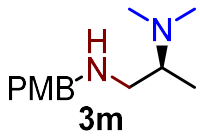
N2-benzyl-N1-(4-methoxybenzyl)-N2-methylpropane-1,2-diamine (3l):

Compound **3l** was prepared via **General Procedure 1** ((*S*)-**L6**) with one quarter the quantity of DME (1.0M), twice the amount of nucleophile (4.8 equiv), and twice the amount of Rh and ligand (10 mol % each). It was purified via alumina column chromatography to afford 69% (41.2 mg, 0.138 mmol) of the desired compound as a clear viscous oil with 94.3 : 5.7 e.r.

^{1}H NMR (500 MHz, Benzene-d_6): δ 7.32 – 7.27 (m, 4H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.12 – 7.07 (m, 1H), 6.83 (dt, *J* = 8.7, 1.5 Hz, 2H), 3.70 (d, *J* = 13.2 Hz, 1H), 3.66 (d, *J* = 13.2 Hz, 1H) , 3.45 (d, *J* = 13.4 Hz, 1H), 3.33 (s, 3H), 3.28 (d, *J* = 13.4 Hz, 1H), 2.91 (dqd, *J* = 9.2, 6.6, 4.8 Hz, 1H), 2.56 (dd, *J* = 11.5, 9.4 Hz, 1H), 2.41 (ddd, *J* = 11.7, 4.9, 1.0 Hz, 1H), 2.21 – 2.04 (br s, 1H), 1.96 (s, 3H), 0.75 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Benzene-d_6): δ 159.79, 141.26, 134.24, 130.13, 129.54, 129.12, 127.67, 114.66, 58.65, 57.99, 55.37, 54.29, 53.36, 36.66, 11.38.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{19}H_{27}N_2O$, 299.2123; found, 299.2114



3m

N1-(4-methoxybenzyl)-N2,N2-dimethylpropane-1,2-diamine (3m):

Compound **3m** was prepared according to **General Procedure 1** ((*S*)-**L6**) with a concentration of 0.384 M. This affords 4.8 equiv (4x normal) of dimethylamine (solution freshly made, concentration determined by proton NMR). Also, 10% catalyst and ligand (double) were utilized. The desired compound was purified via SiO_2 column chromatography in a 44% yield (19.6 mg, 0.088 mmol) with 88.0 : 12.0 e.r.

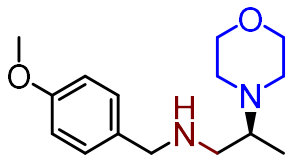
^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.24 (d*, J = 8.5 Hz, 2H), 6.85 (d*, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.76 (d, J = 13.1 Hz, 1H), 3.70 (d, J = 13.1 Hz, 1H), 2.77 (m, 1H), 2.54 (dd, J = 11.8, 8.8 Hz, 1H), 2.46 (dd, J = 11.8, 5.0 Hz, 1H), 2.25 (s, 1H), 2.17 (s, 6H), 0.87 (d, J = 6.6 Hz, 3H).

* Second order AA'BB' coupling was observed.

^{13}C NMR (126 MHz, Chloroform-*d*): δ 158.86, 132.98, 129.66, 114.03, 58.47, 55.60, 53.70, 52.50, 40.43, 10.52.

HRMS (ESI-TOF) *m/z*: [M+H+] calculated for C13H23N2O, 223.1810; found, 223.1821.

Scaleup procedure:

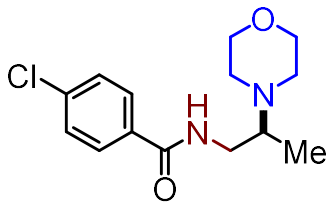


2a

N-(4-methoxybenzyl)-2-morpholinopropan-1-amine:

General procedure 1 was utilized with 2.0 mmol of the starting material, 2.4 mmol of morpholine and 4 mL DME. 2.5 mol % of Rh and the (*S*)-**L6** were utilized (half normal). The reaction was run as normal, and columned as normal (alumina) except using a 2 inch column instead of a 1 inch column and doubling the volumes of eluent and solid phase. The product was obtained in 75% yield (396.6 mg, 1.5 mmol) with 97.0 : 3.0 e.r.

Synthesis of Moclobemide Analogue:



4

(S)-4-chloro-N-(2-morpholinopropyl)benzamide (4):

Compound **2a** (100 mg, 0.38 mmol) and phenol (42.7 mg, 0.45 mmol, 1.2 equiv) were dissolved in phosphoric acid (0.5 mL) and heated to 150 °C in a sealed vial for 3 hours. The resulting suspension was diluted with 10 mL 1M HCl, and extracted with 2 x 10 mL portions of diethyl ether, back-extracting with 5 mL 1M HCl each time. The aqueous was then partitioned with 10 mL DCM, and basified using 6 M NaOH to a pH of 9. (too much basification lead to emulsification issues) The layers were separated, and the aqueous layer extracted with a further 2 x 10 mL portions of dichloromethane. 2.1 equivalents (0.9 mmol) PTSA•H_2O were added, and the crude was stirred overnight. The dichloromethane was removed to afford the crude acid salt. This was then subjected directly to the acid chloride (100 mg, 1.5 equivalents) in 5 mL dichloromethane, with the addition of 3 equivalents K_2CO_3 as base. This was stirred a further 24 hours, after which the K_2CO_3 was removed by filtration, and the crude material was columned. This afforded a 48% yield (52 mg, 0.18 mmol) of the desired compound as a pale yellow foam.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.76 (d*, *J* = 8.5 Hz, 2H), 7.15 (d*, *J* = 8.5 Hz, 2H), 6.78 (s, 1H), 3.62 – 3.48 (m, 5H), 3.08 (ddd, *J* = 13.8, 9.4, 3.3 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.20 (ddd, J = 10.6, 5.8, 2.2 Hz, 2H), 2.02 (dddd, *J* = 11.5, 6.4, 3.1, 1.0 Hz, 2H), 0.69 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 166.43, 137.97, 133.33, 129.21, 128.64, 41.95, 31.94, 23.01, 14.47, 11.69.

HRMS (ESI-TOF) *m/z*: [M+H+] calculated for C14H20N2O2Cl, 283.1213; found, 283.1210.

X-ray crystallography parameters for 2a•$(PTSA)_2$

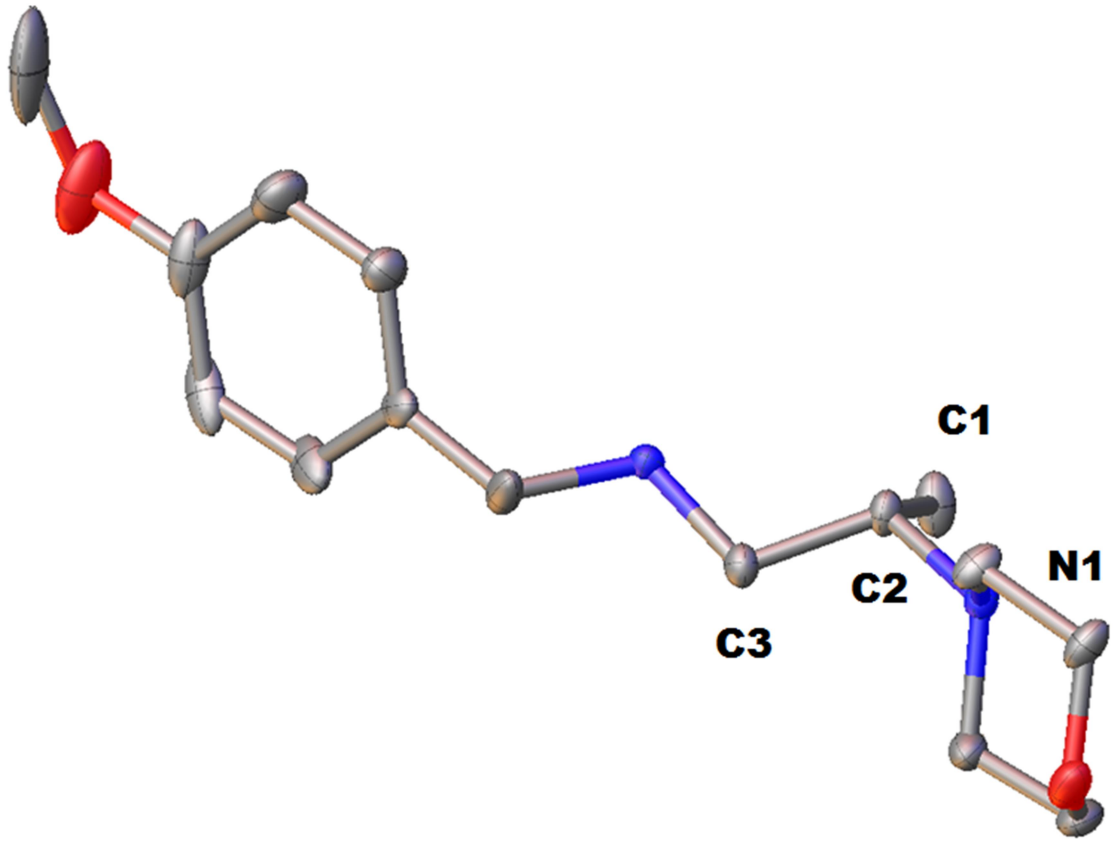
X-Ray Diffraction Techniques: The structure was collected on a Bruker three-circle platform goniometer equipped with an Apex II CCD and an Oxford cyrostream cooling device. Radiation was from a graphite fine focus sealed tube Mo Kα (0.71073 Å) source. A suitable crystal was

mounted on a cryoloop using paratone N oil. The structure was collected at 173 K. Data was collected as a series of φ and/ or ω scans. Data was integrated using SAINT[xx] and scaled with multi-scan absorption correcting using SADABS[xx]. Using Olex2[xxx], the structure was solved with the ShelXT structure solution program using the Intrinsic Phasing method, and refined with the ShelXL refinement package using Least Squares minimization. The methoxy group was disordered over two positions, using standard restraints and constraints. See appendix 2 for CIF details

Table 2.11: X-Ray diffraction details for **2a**•$(PTSA)_2$

Formula:	C48 N12 O17 S4
W:	1217.50
Crystal System:	Triclinic
Space Group:	P1
a (Å):	6.1734(2)
b (Å):	12.3999(4)
c (Å):	20.4254(6)
α (°):	97.203(1)
β (°):	97.059(1)
γ (°):	99.727(1)
Volume ($Å^3$):	1512.23(8)
Calc. ρ (g/cm^3):	1.337
μ (mm^{-1}):	0.492
Crystal Size (mm):	0.091x0.124x0.36
Reflections:	15036
Completeness (to 2θ):	0.999 (28.372)
GOF on F2:	1.052
Flack parameter:	-0.02(2)
Hooft parameter:	-0.01(2)
R1, wR2c [I>2σ(I)]:	0.0413, 0.1007

Figure 2.3: Crystal structure of **2a**•(PTSA)

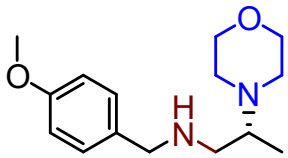


Crystal structure of **2a**•$(PTSA)_2$. Hydrogen atoms, other molecules in unit cell omitted for clarity. Thermal ellipsoids are drawn at 50% probability. The configuration of C2 can be observed clearly.

Crystals were grown from a layered crystallization of the crude reaction of **2a** with 2 equivalents PTSA in ethanol, layered with fresh ethanol and ethyl acetate. After two weeks, X-ray suitable crystals had formed and were mounted in the traditional manner.

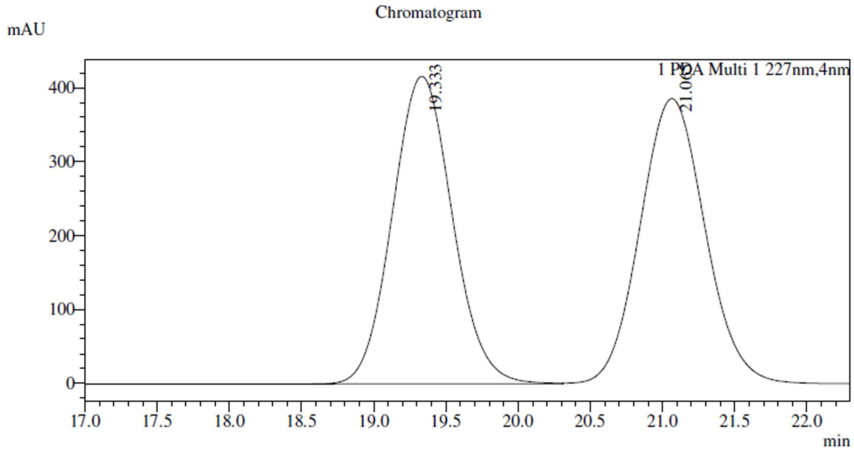
HPLC results for racemic and chiral samples of the isolated compounds

Chiral phase HPLC was performed using a Shimadzu HPLC system at pressures below 1000 psi, using Chiralpak A-D columns. \



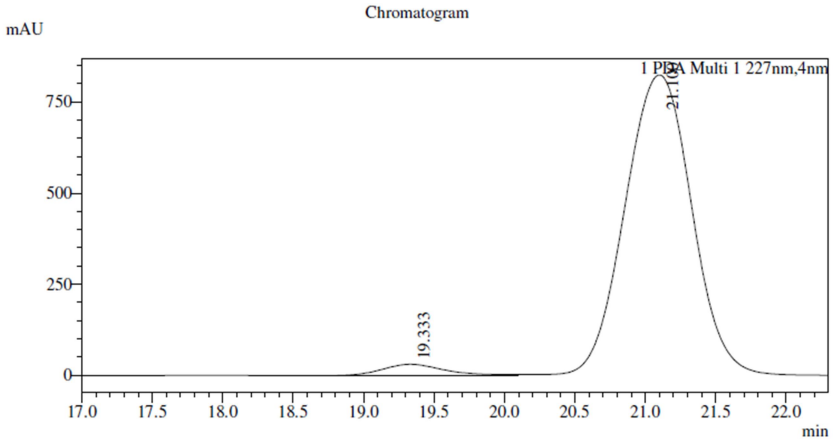
2a

CHIRALPAK® IA-3 94.7 : 5 : 0.2 : 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 227nm

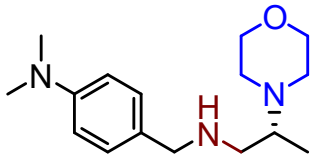
Peak#	Ret. Time	Area	Area%
1	19.333	12041400	49.936
2	21.065	12072215	50.064
Total		24113616	100.000



PDA Ch1 227nm

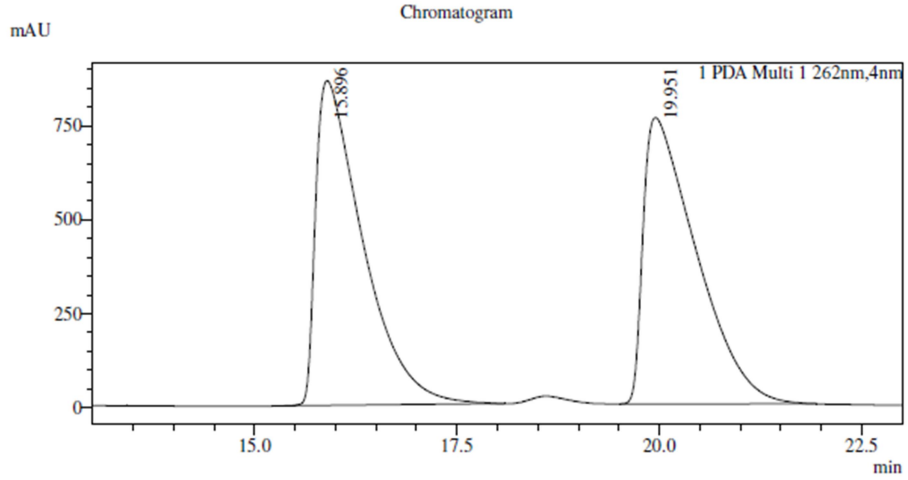
Peak#	Ret. Time	Area	Area%
1	19.333	946025	3.362
2	21.100	27188939	96.638
Total		28134964	100.000

Enantiomeric ratio (average of two runs): 96.6 : 3.4. Ligand enantiomer used: R



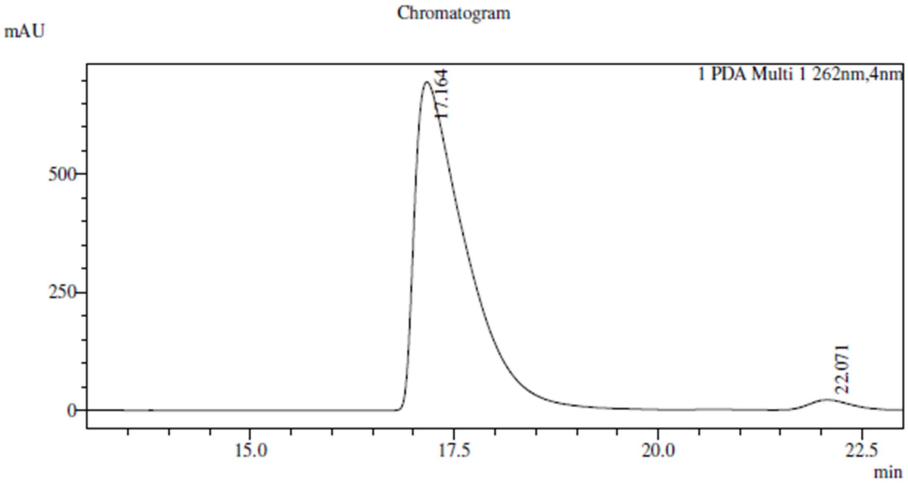
2b

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 262nm

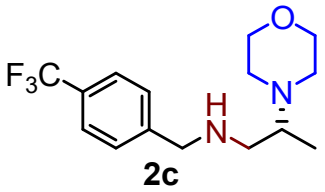
Peak#	Ret. Time	Area	Area%
1	15.896	35059056	50.175
2	19.951	34815146	49.825
Total		69874202	100.000



PDA Ch1 262nm

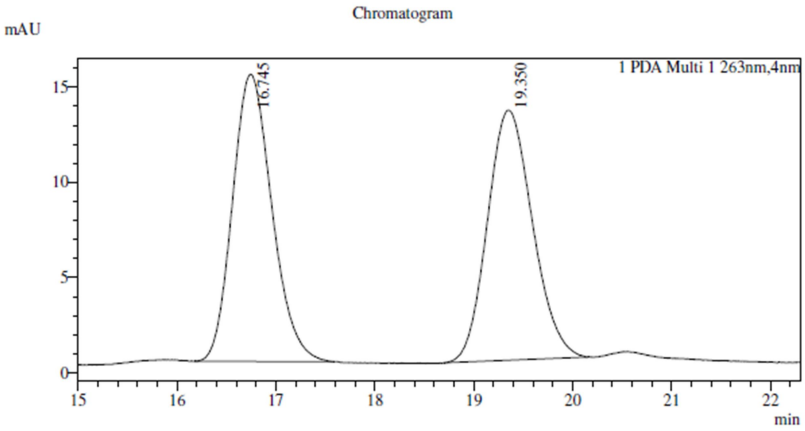
Peak#	Ret. Time	Area	Area%
1	17.164	30726211	97.476
2	22.071	795524	2.524
Total		31521735	100.000

Enantiomeric ratio (average of two runs): 97.5 : 2.5. Ligand enantiomer used: R



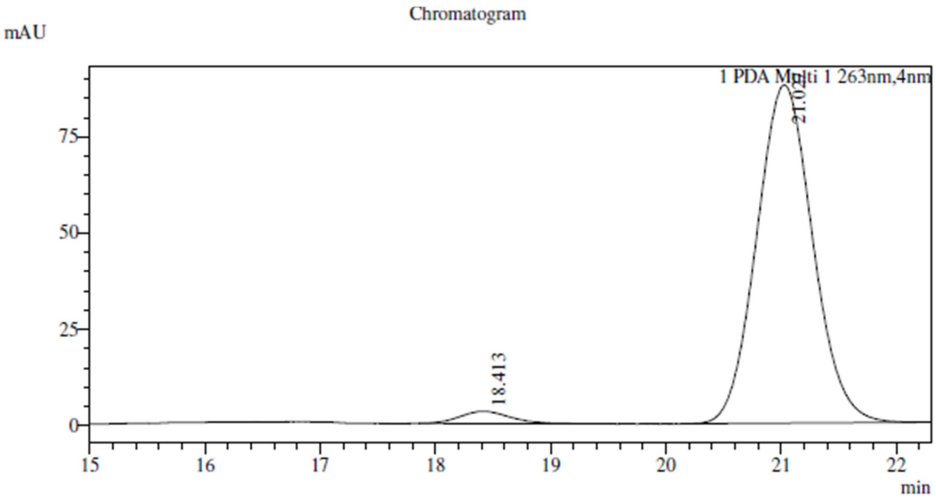
2c

CHIRALPAK® IA-3 97.45 : 2.4 : 0.1: 0.05 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 263nm

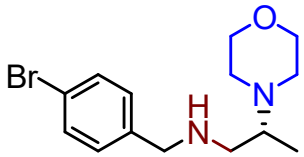
Peak#	Ret. Time	Area	Area%
1	16.745	417747	50.110
2	19.350	415912	49.890
Total		833658	100.000



PDA Ch1 263nm

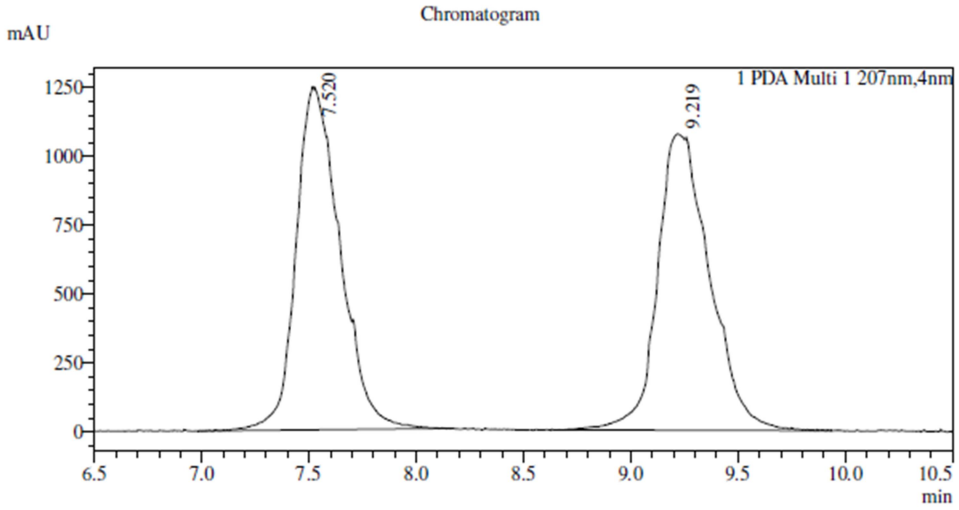
Peak#	Ret. Time	Area	Area%
1	18.413	95520	3.119
2	21.027	2967057	96.881
Total		3062577	100.000

Enantiomeric ratio (average of two runs): 96.6 : 3.4. Ligand enantiomer used: R



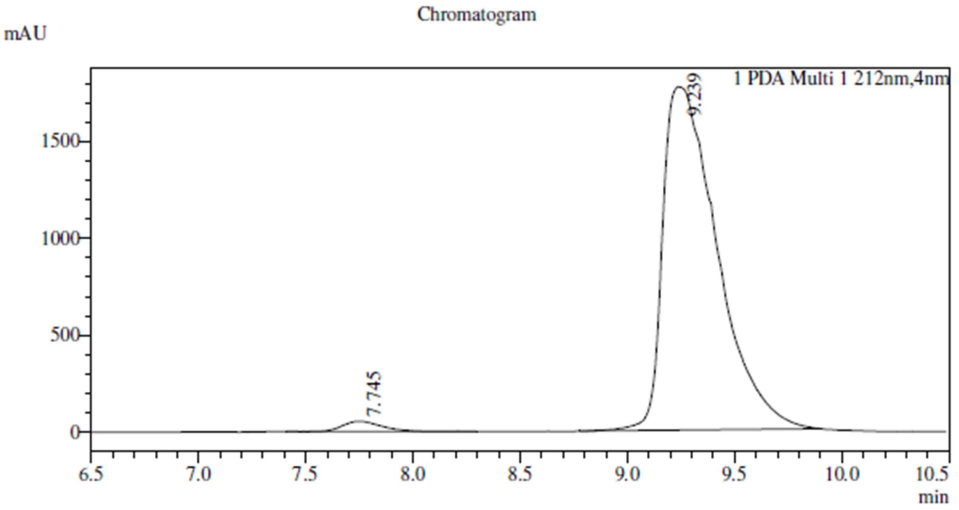
2d

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 207nm

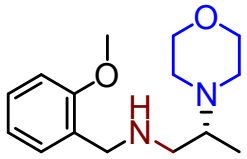
Peak#	Ret. Time	Area	Area%
1	7.520	17803884	49.424
2	9.219	18218571	50.576
Total		36022455	100.000



PDA Ch1 212nm

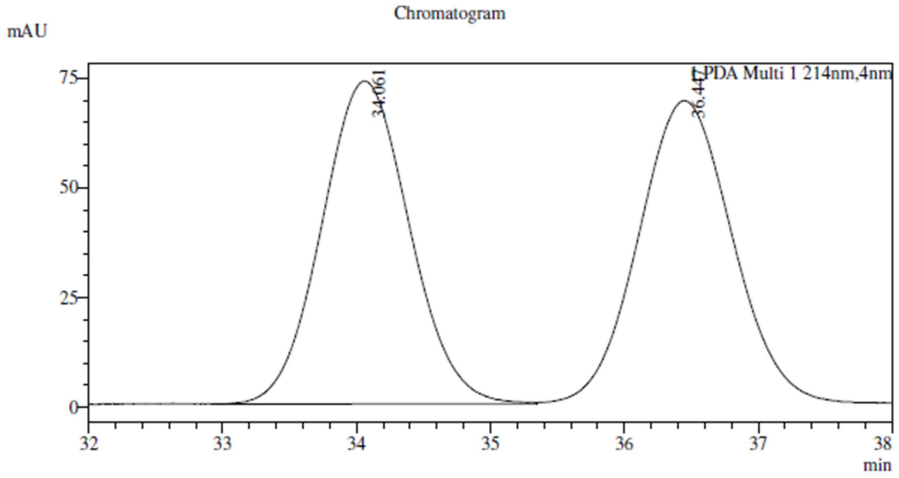
Peak#	Ret. Time	Area	Area%
1	7.745	663382	2.074
2	9.239	31323772	97.926
Total		31987155	100.000

Enantiomeric ratio (average of two runs): 97.9 : 2.1. Ligand enantiomer used: R



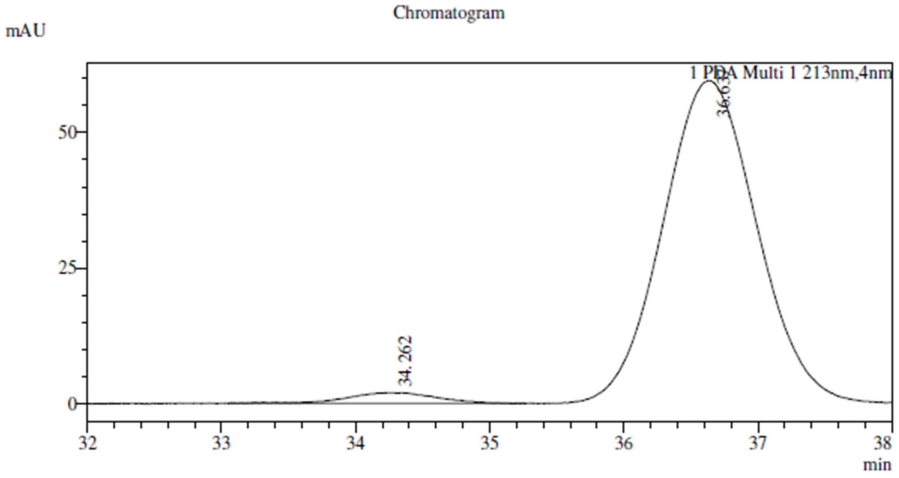
2e

CHIRALPAK® IC-3 94.8 : 4.9 : 0.2: 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 214nm

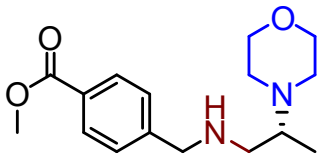
Peak#	Ret. Time	Area	Area%
1	34.061	3354333	49.948
2	36.447	3361312	50.052
Total		6715644	100.000



PDA Ch1 213nm

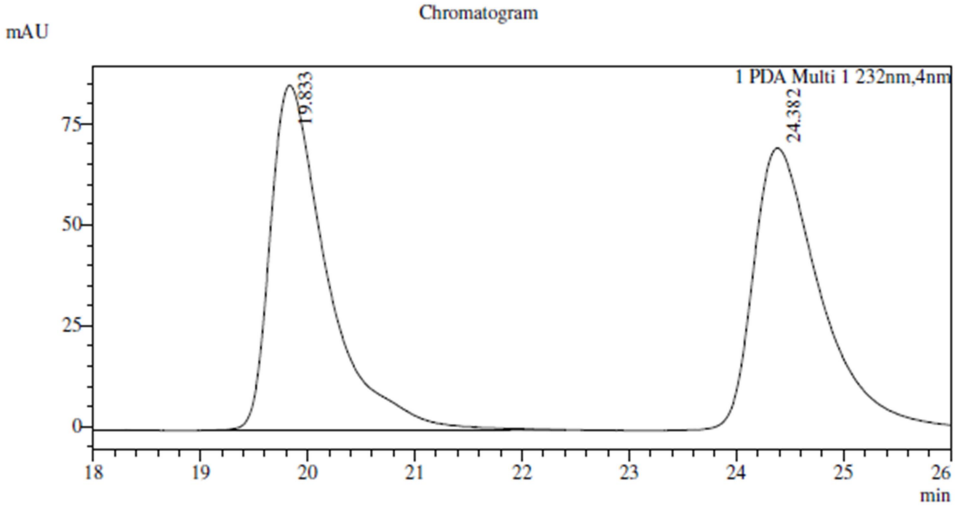
Peak#	Ret. Time	Area	Area%
1	34.262	89477	2.989
2	36.637	2904551	97.011
Total		2994028	100.000

Enantiomeric ratio (average of two runs): 97.2 : 2.8. Ligand enantiomer used: R



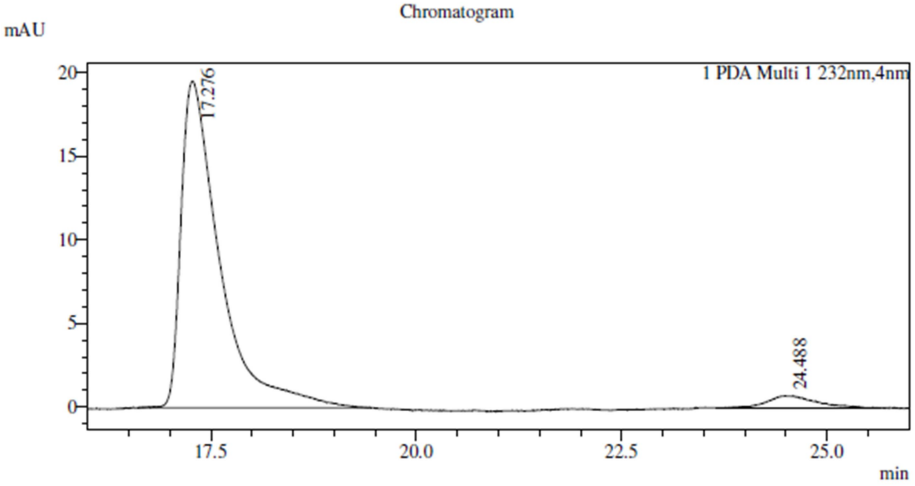
2f

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine 0.8 ml/min



PDA Ch1 232nm

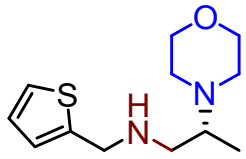
Peak#	Ret. Time	Area	Area%
1	19.833	3147689	50.658
2	24.382	3065965	49.342
Total		6213654	100.000



PDA Ch1 232nm

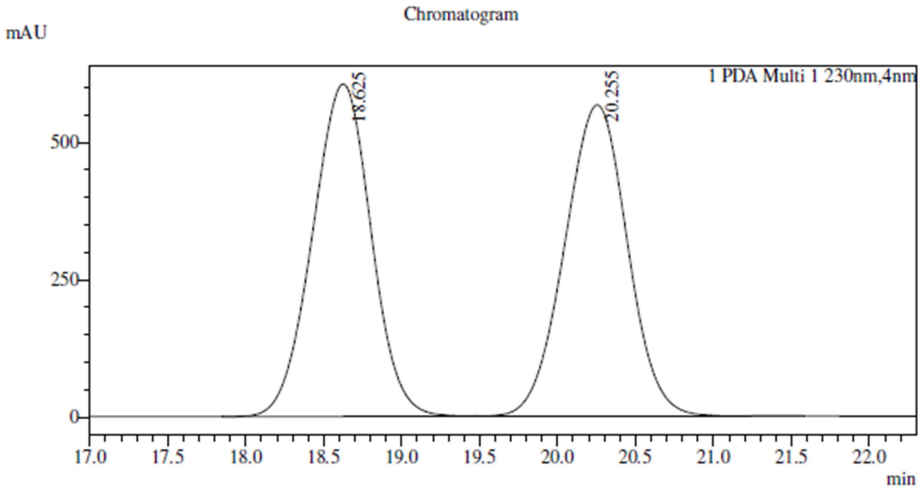
Peak#	Ret. Time	Area	Area%
1	17.276	640118	95.648
2	24.488	29129	4.352
Total		669247	100.000

Enantiomeric ratio (average of two runs): 95.0 : 5.0. Ligand enantiomer used: R



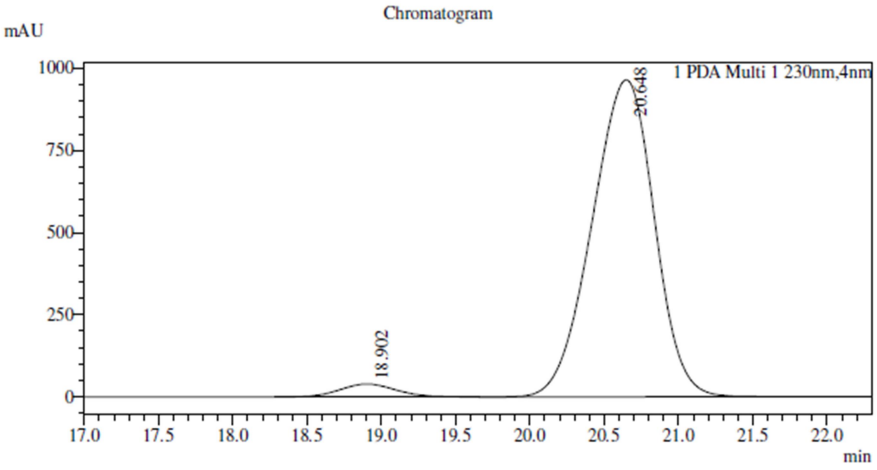
2g

CHIRALPAK® IC-3 94.7 : 5 : 0.2: 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 230nm

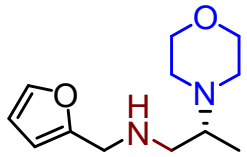
Peak#	Ret. Time	Area	Area%
1	18.625	15822240	49.923
2	20.255	15871257	50.077
Total		31693497	100.000



PDA Ch1 230nm

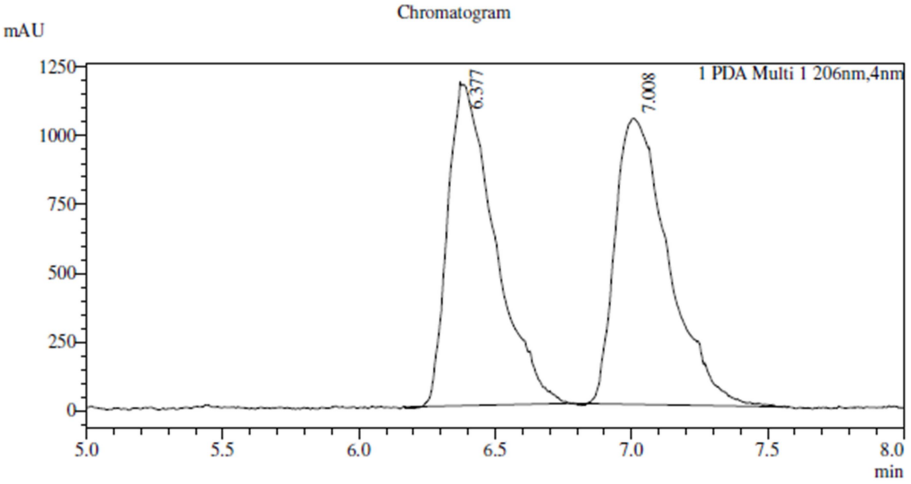
Peak#	Ret. Time	Area	Area%
1	18.902	1033610	3.531
2	20.648	28235492	96.469
Total		29269102	100.000

Enantiomeric ratio (average of two runs): 96.3 : 3.7. Ligand enantiomer used: R



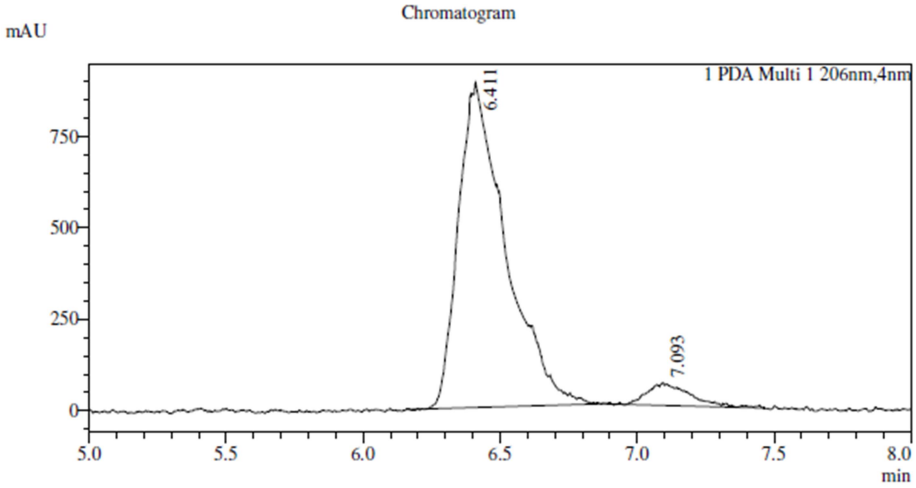
2h

CHIRALPAK® IA-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 206nm

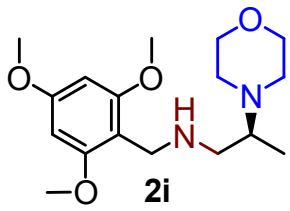
Peak#	Ret. Time	Area	Area%
1	6.377	14082470	49.703
2	7.008	14250820	50.297
Total		28333290	100.000



PDA Ch1 206nm

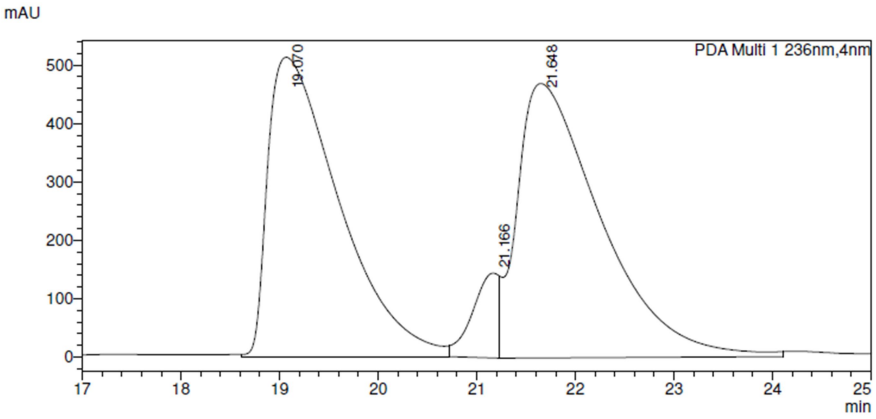
Peak#	Ret. Time	Area	Area%
1	6.411	10693241	94.068
2	7.093	674361	5.932
Total		11367602	100.000

Enantiomeric ratio (average of two runs): 94.5 : 5.5. Ligand enantiomer used: R



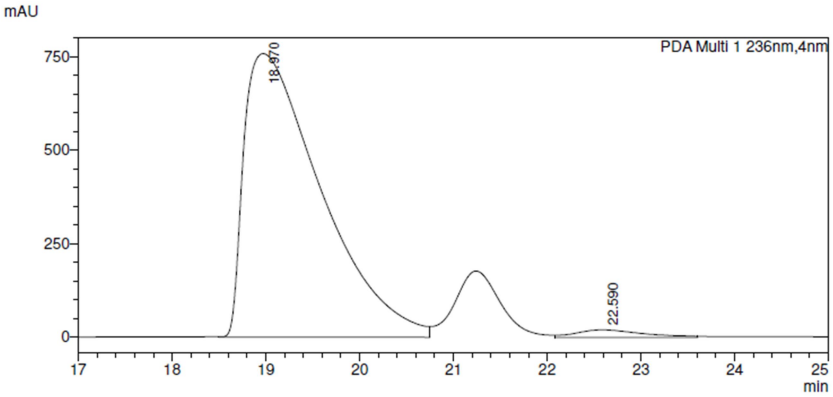
2i

CHIRALPAK® IA-3 95.9 : 3.4 : 0.2: 0.5 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 236nm

Peak#	Ret. Time	Area	Height
1	19.070	25789902	512759
2	21.166	2641762	145353
3	21.648	27829500	470016
Total		56261165	1128129

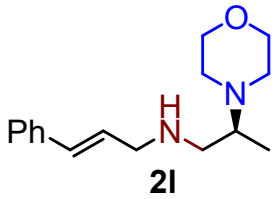


PDA Ch1 236nm

Peak#	Ret. Time	Area	Height
1	18.970	43288615	758468
2	22.590	1023070	20549
Total		44311685	779017

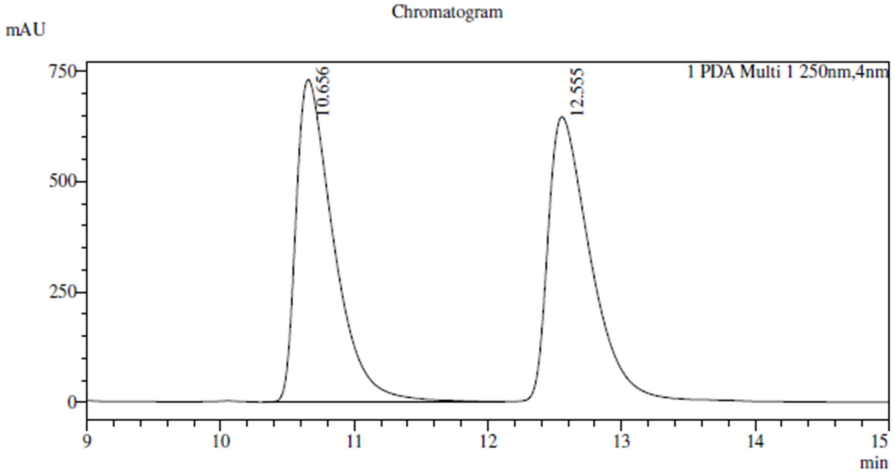
Enantiomeric ratio (average of two runs): 97.9 : 2.1. Ligand enantiomer used: S

Peak at 21.16 is a small amount of remaining starting material.



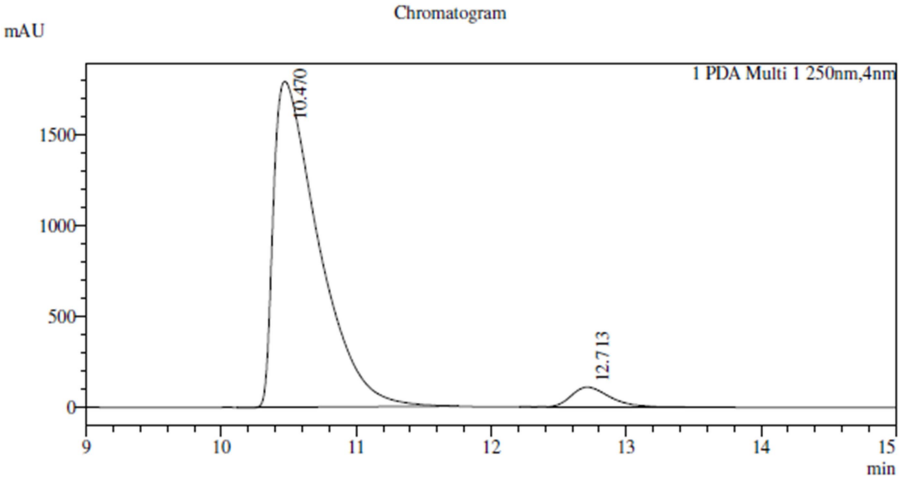
2l

CHIRALPAK® ID-3 94.8 : 4.9 : 0.2: 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 250nm

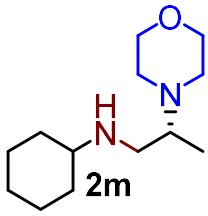
Peak#	Ret. Time	Area	Area%
1	10.656	14354290	49.853
2	12.555	14439070	50.147
Total		28793361	100.000



PDA Ch1 250nm

Peak#	Ret. Time	Area	Area%
1	10.470	41650780	95.002
2	12.713	2191182	4.998
Total		43841962	100.000

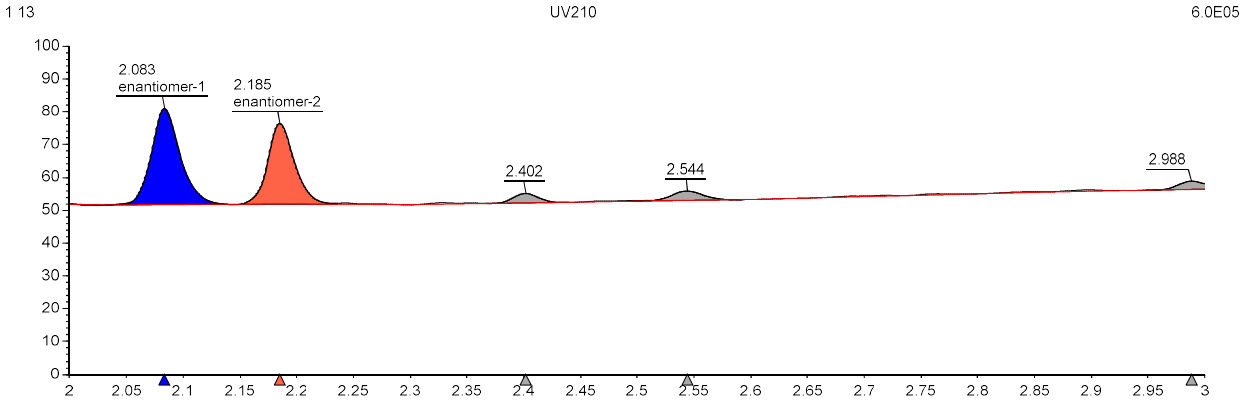
Enantiomeric ratio (average of two runs): 95.1 : 4.9. Ligand enantiomer used: S

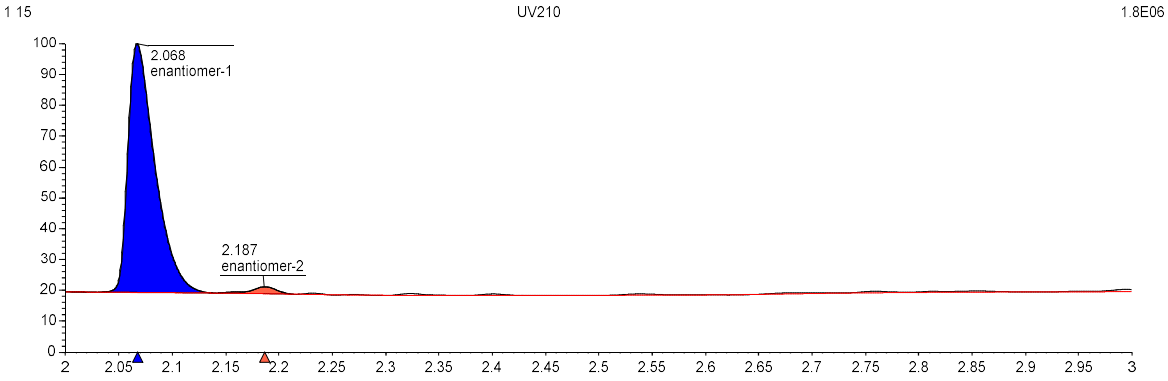


Separated using SFC. Chiralcel OD-3 4.6 x 150 mm, 3 um

CO_2 MPA, MeOH w/ 25 mM IBA MPB,

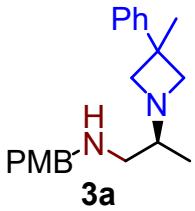
10-30% B (0-3 min), 30% (3-6 min), 40 °C, 3mL/min . Spectra at 210 nm





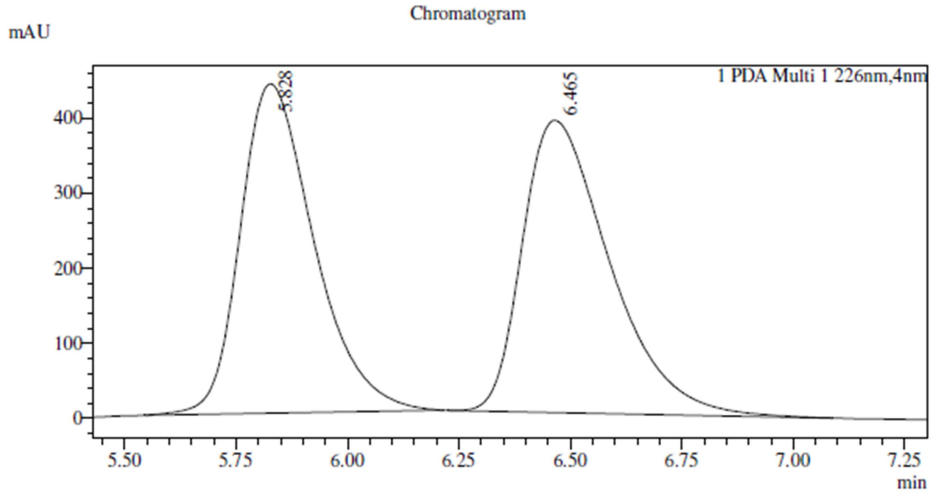
94.5 : 5.5 e.r. and 97.5 : 2.5 respectively. e.r.

Enantiomeric ratio (average of two runs): 96 : 4. Ligand enantiomer used: R



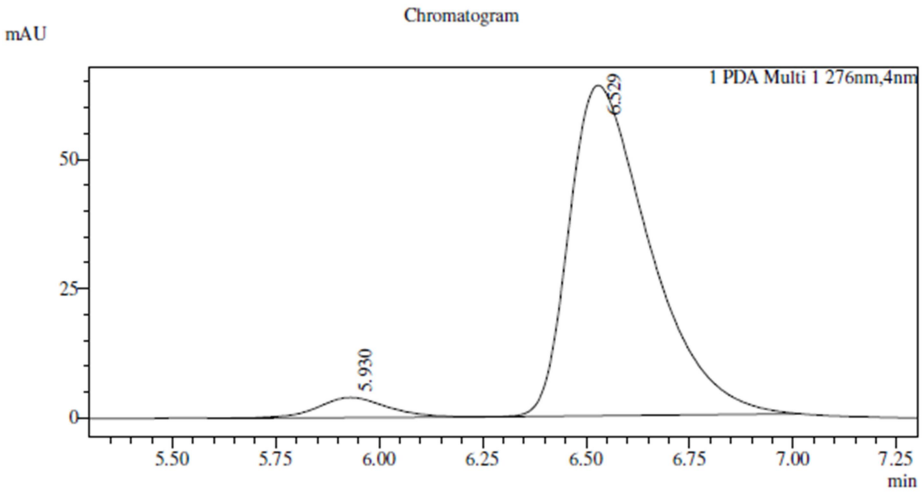
3a

CHIRALPAK® IA-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 226nm

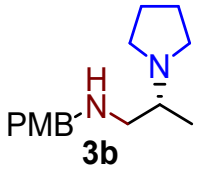
Peak#	Ret. Time	Area	Area%
1	5.828	5048239	48.780
2	6.465	5300669	51.220
Total		10348909	100.000



PDA Ch1 276nm

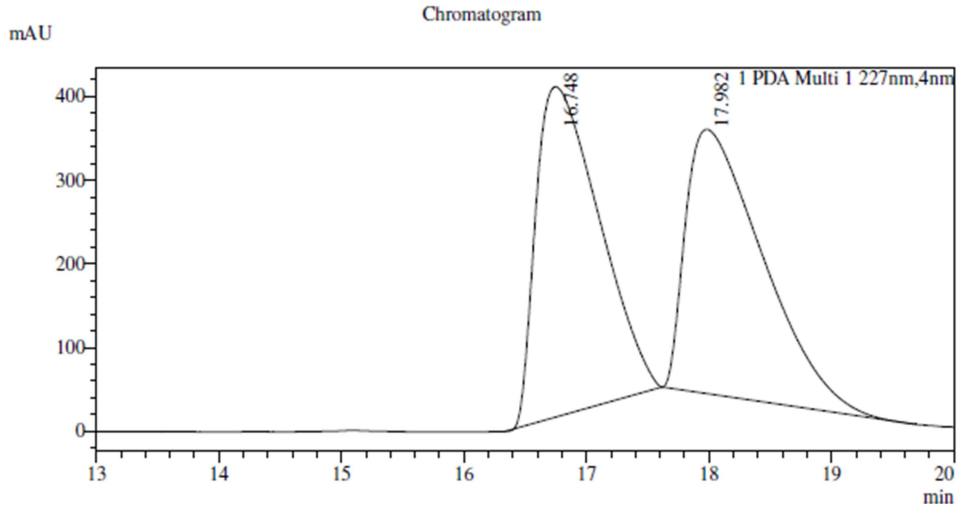
Peak#	Ret. Time	Area	Area%
1	5.930	45322	4.970
2	6.529	866668	95.030
Total		911990	100.000

Enantiomeric ratio (average of two runs): 94.9 : 5.1. Ligand enantiomer used: S



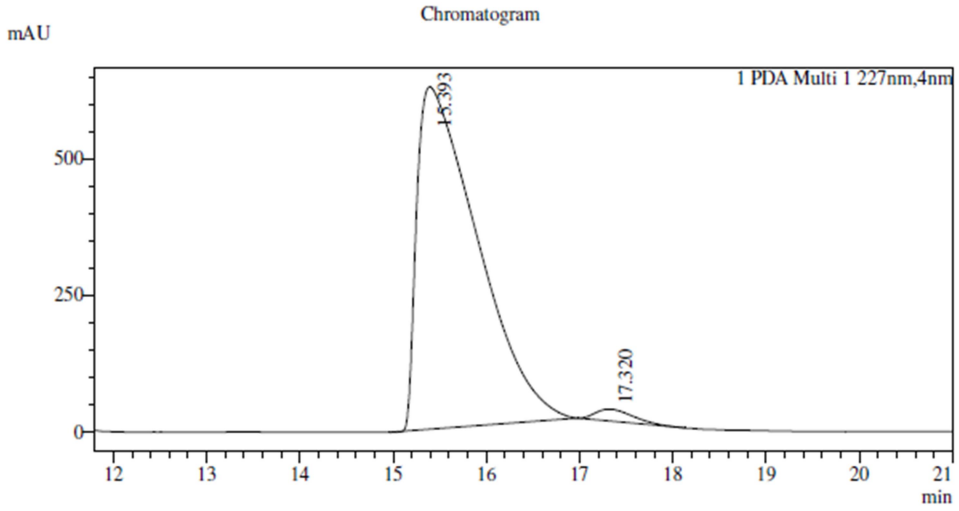
3b

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 227nm

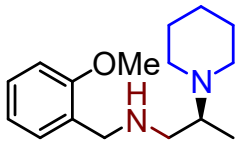
Peak#	Ret. Time	Area	Area%
1	16.748	14119785	50.355
2	17.982	13920714	49.645
Total		28040499	100.000



PDA Ch1 227nm

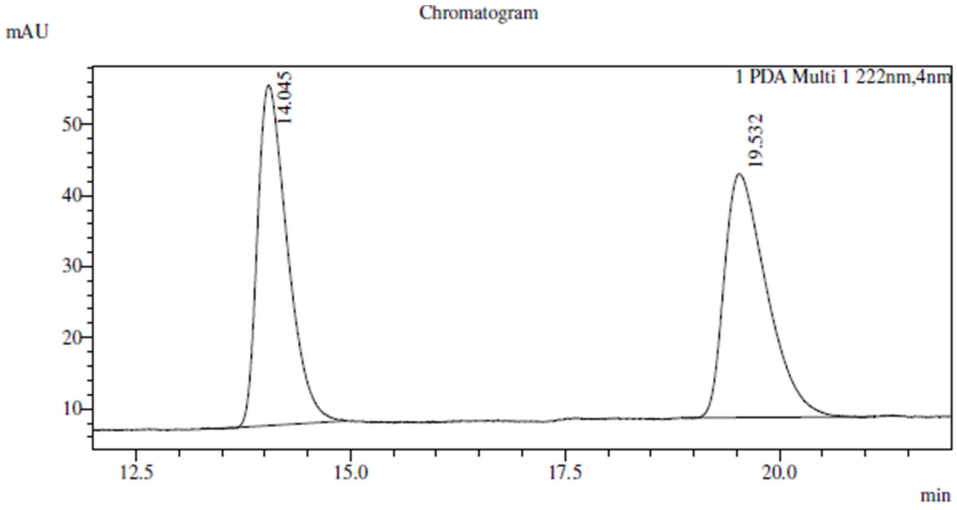
Peak#	Ret. Time	Area	Area%
1	15.393	28311382	97.857
2	17.320	619945	2.143
Total		28931327	100.000

Enantiomeric ratio (average of two runs): 97.9 : 2.1. Ligand enantiomer used: R



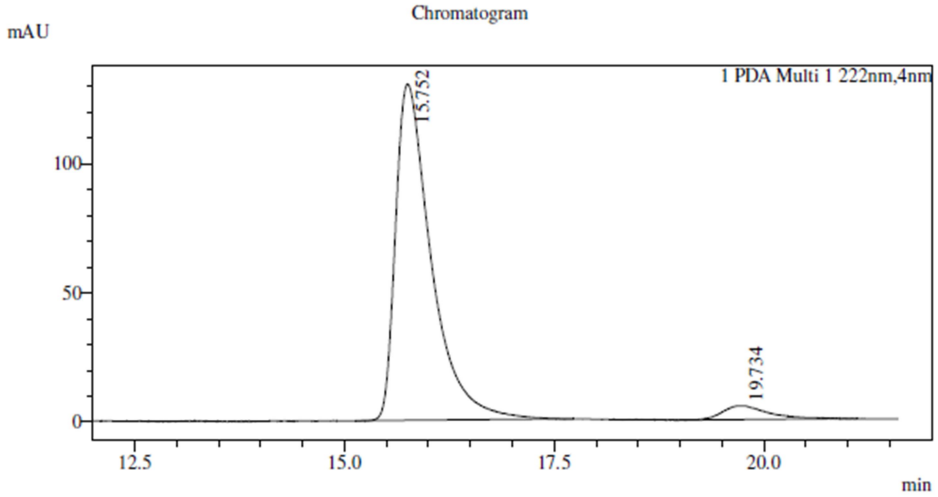
3c

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine 0.8 ml/min



PDA Ch1 222nm

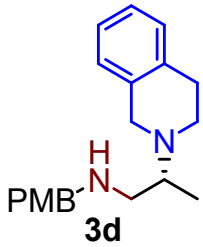
Peak#	Ret. Time	Area	Area%
1	14.045	1161051	49.709
2	19.532	1174638	50.291
Total		2335689	100.000



PDA Ch1 222nm

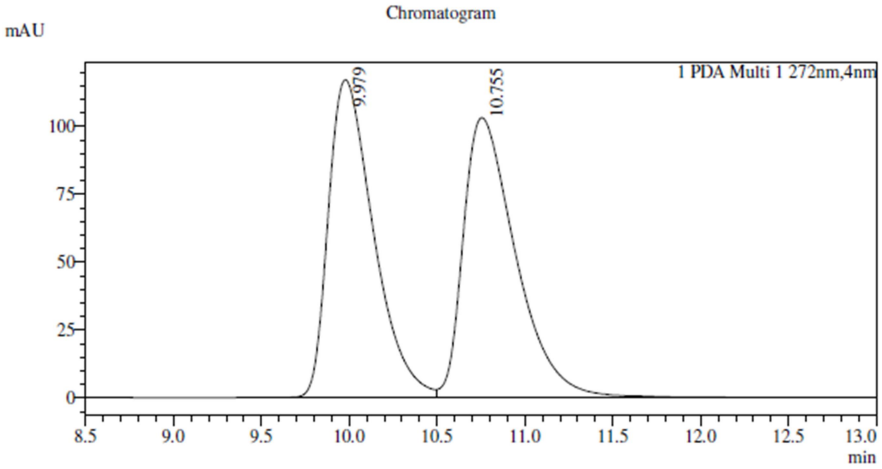
Peak#	Ret. Time	Area	Area%
1	15.752	3860349	95.038
2	19.734	201546	4.962
Total		4061895	100.000

Enantiomeric ratio (average of two runs): 95.8 : 4.2. Ligand enantiomer used: R



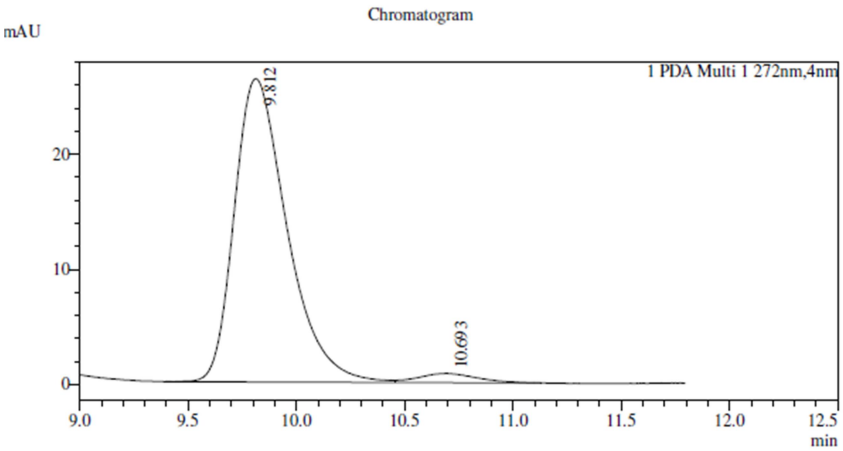
3d

CHIRALPAK® ID-3 94.8 : 4.9 : 0.2: 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 272nm

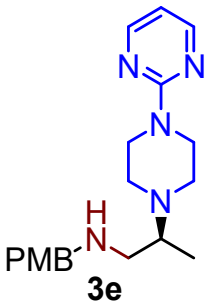
Peak#	Ret. Time	Area	Area%
1	9.979	2092690	49.469
2	10.755	2137631	50.531
Total		4230321	100.000



PDA Ch1 272nm

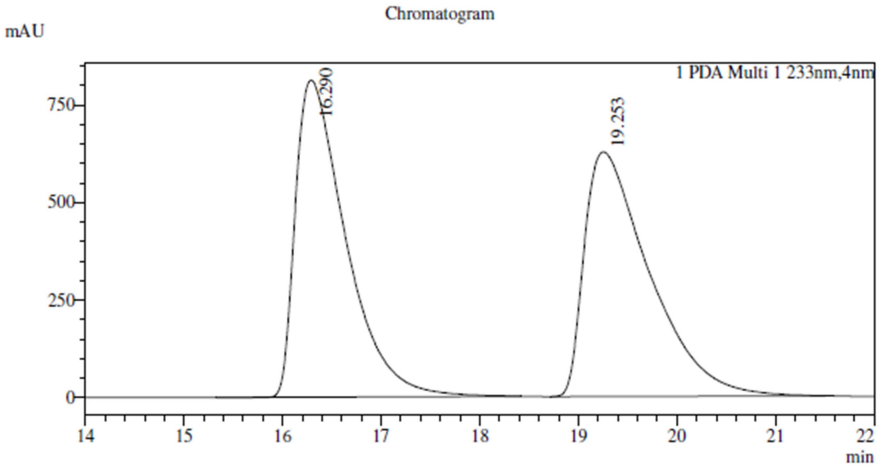
Peak#	Ret. Time	Area	Area%
1	9.812	445030	96.764
2	10.693	14885	3.236
Total		459914	100.000

Enantiomeric ratio (average of two runs): 96.9 : 3.1. Ligand enantiomer used: R



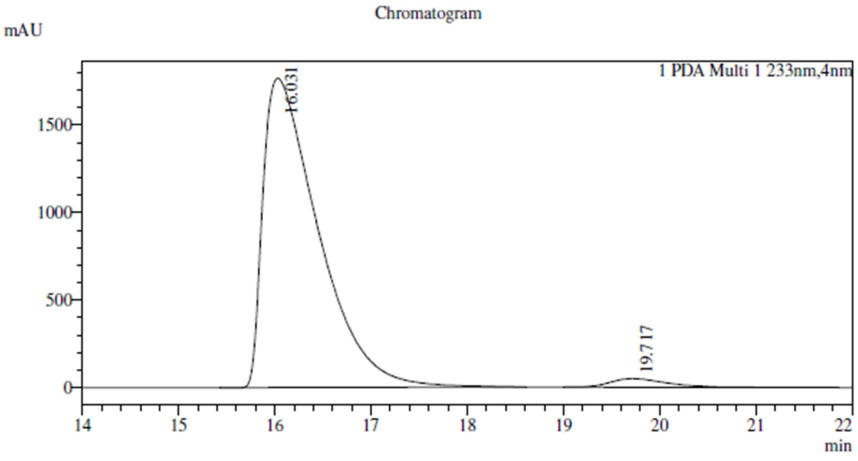
3e

CHIRALPAK® ID-3 94.8 : 4.9 : 0.2: 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 233nm

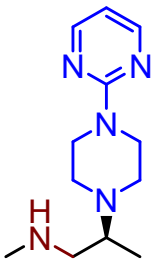
Peak#	Ret. Time	Area	Area%
1	16.290	28846531	50.012
2	19.253	28832935	49.988
Total		57679466	100.000



PDA Ch1 233nm

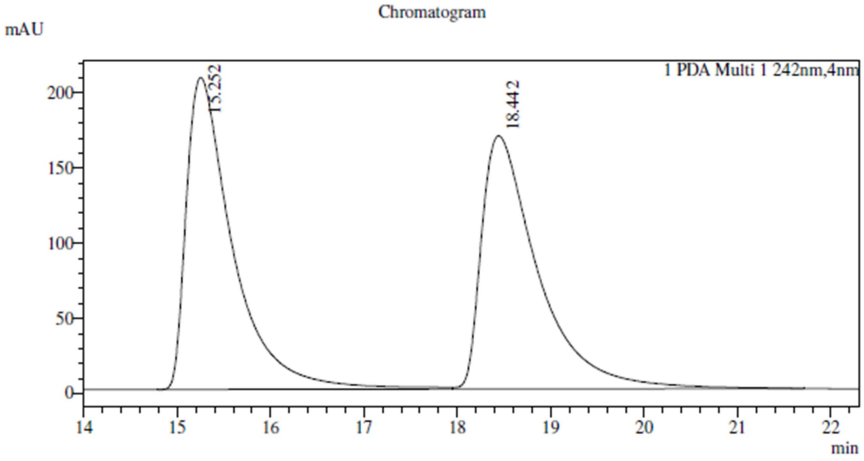
Peak#	Ret. Time	Area	Area%
1	16.031	70611892	97.223
2	19.717	2016992	2.777
Total		72628885	100.000

Enantiomeric ratio (average of two runs): 97.4 : 2.6. Ligand enantiomer used: S



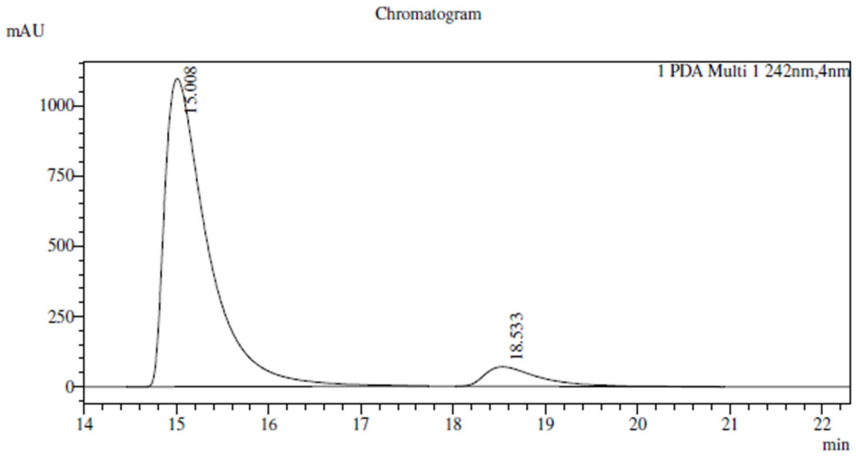
3f

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 242nm

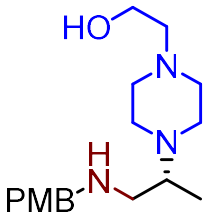
Peak#	Ret. Time	Area	Area%
1	15.252	7211300	50.379
2	18.442	7102673	49.621
Total		14313974	100.000



PDA Ch1 242nm

Peak#	Ret. Time	Area	Area%
1	15.008	35509335	92.613
2	18.533	2832160	7.387
Total		38341496	100.000

Enantiomeric ratio (average of two runs): 92.6 : 7.4. Ligand enantiomer used: S

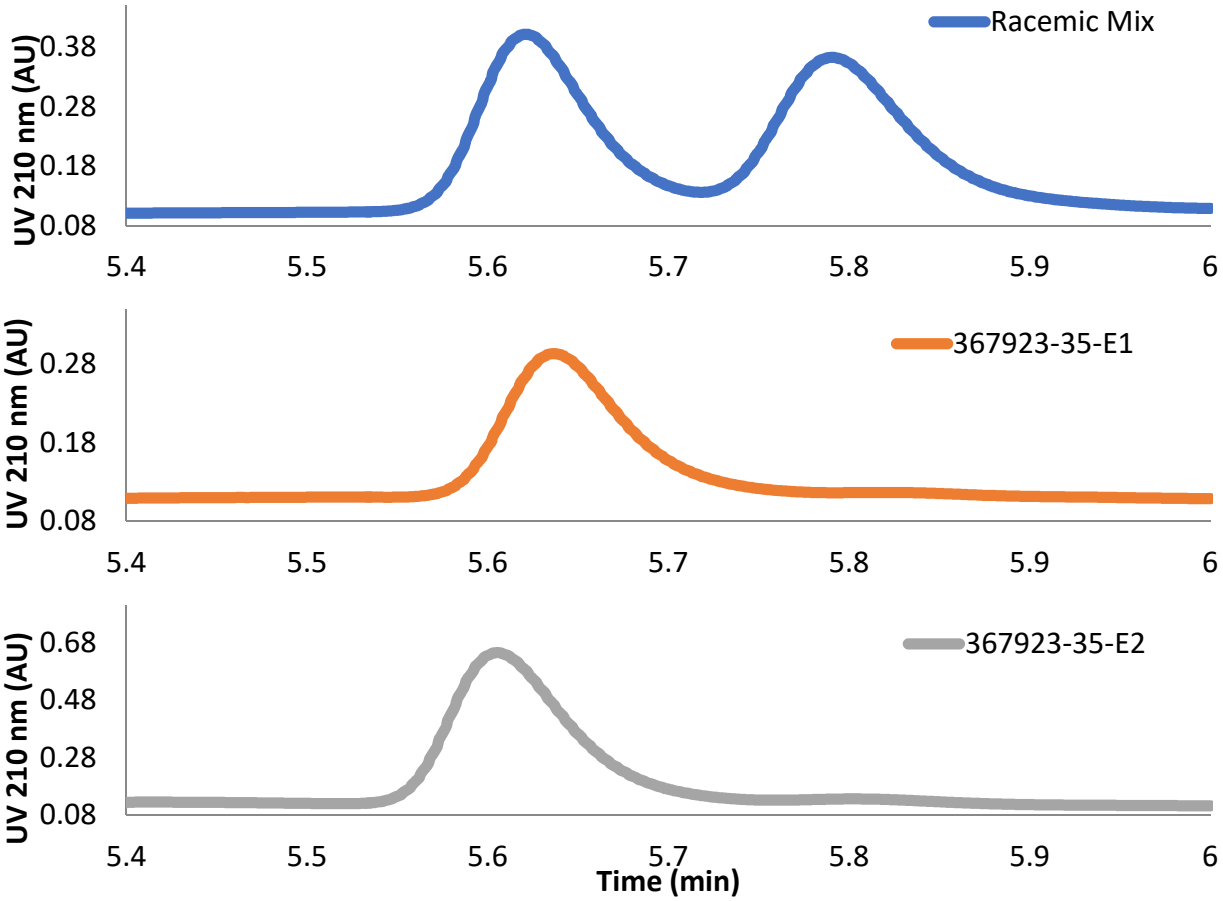


3g

Column: Phenomenex Lux-4 4.6 x 150 mm, 3 um

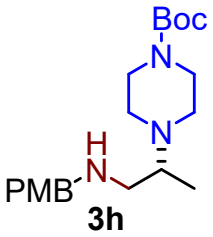
MPA: CO_2 MPB: MeOH w/ 25 mM IBA

10-40% B (0-3 min), 40% (3-6 min), 40 °C, 3 mL/min. Detection at 210 nm.



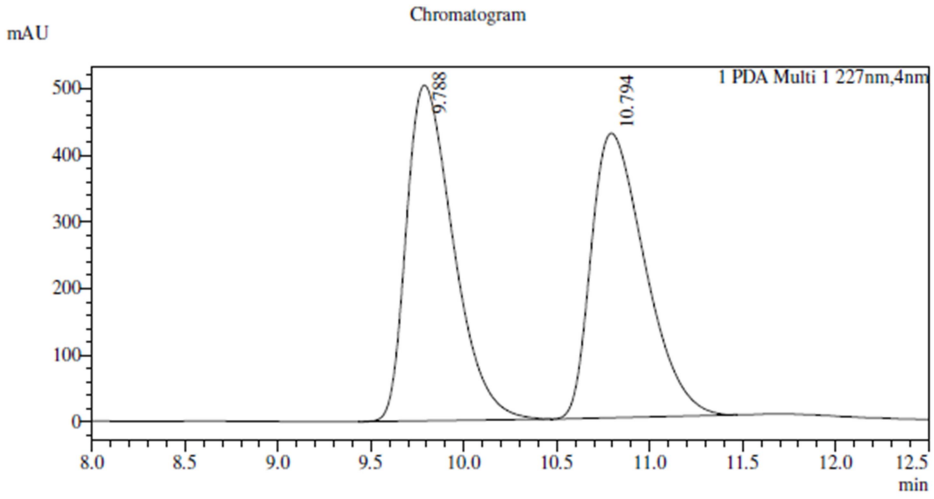
ER: 97.8 : 2.2, 96.5 : 3.5

Enantiomeric ratio (average of two runs): 96.7 : 3.3. Ligand enantiomer used: R



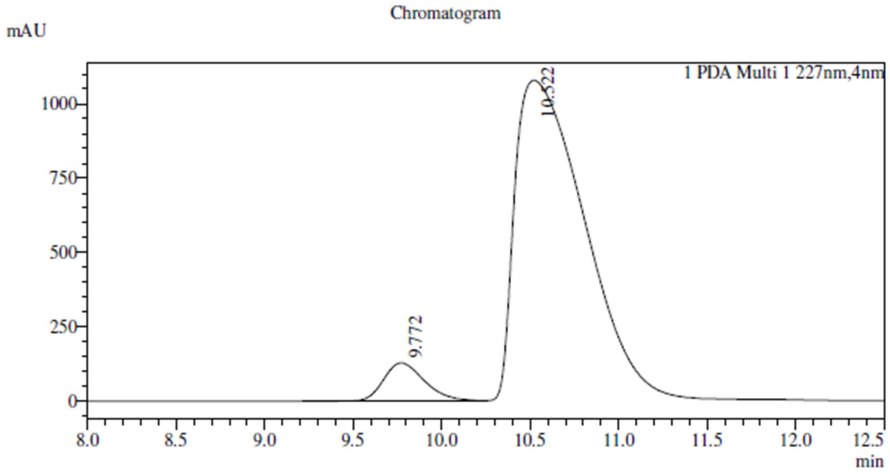
3h

CHIRALPAK® ID-3 94.8 : 4.9 : 0.2: 0.1 hexanes : ethanol : trifluoroacetic acid : diethylamine



PDA Ch1 227nm

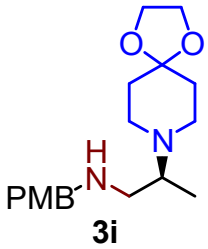
Peak#	Ret. Time	Area	Area%
1	9.788	8835522	50.716
2	10.794	8586052	49.284
Total		17421574	100.000



PDA Ch1 227nm

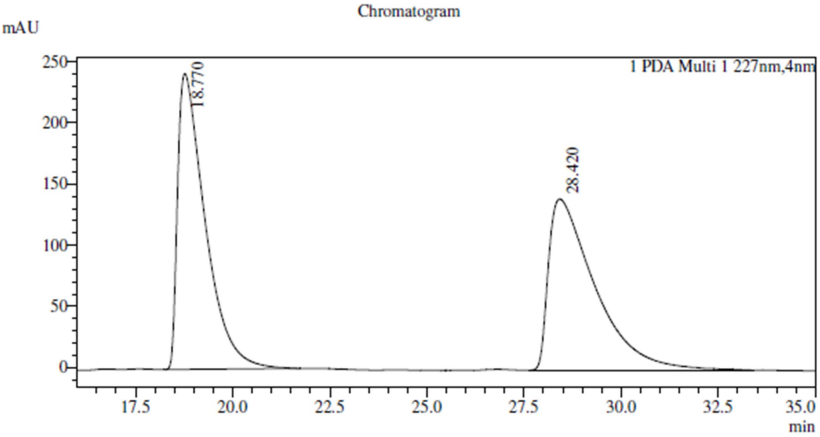
Peak#	Ret. Time	Area	Area%
1	9.772	2104437	6.551
2	10.522	30017034	93.449
Total		32121471	100.000

Enantiomeric ratio (average of two runs): 93.4 : 6.6. Ligand enantiomer used: R



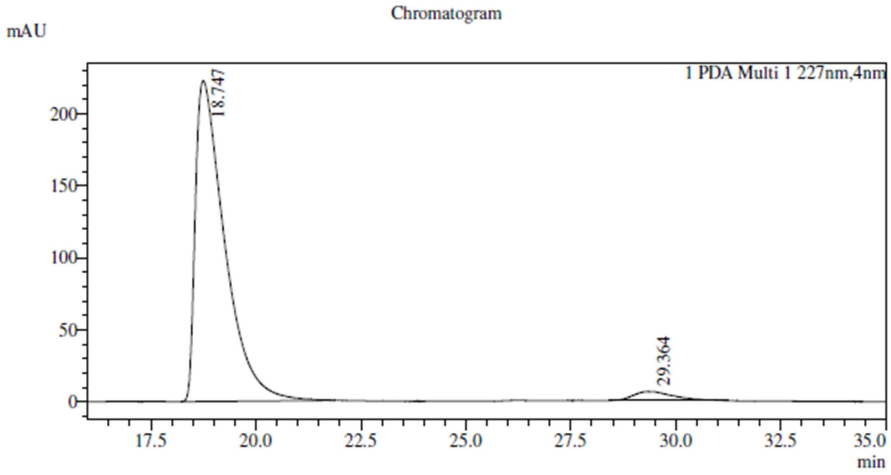
3i

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 227nm

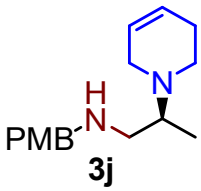
Peak#	Ret. Time	Area	Area%
1	18.770	11920289	50.605
2	28.420	11635456	49.395
Total		23555745	100.000



PDA Ch1 227nm

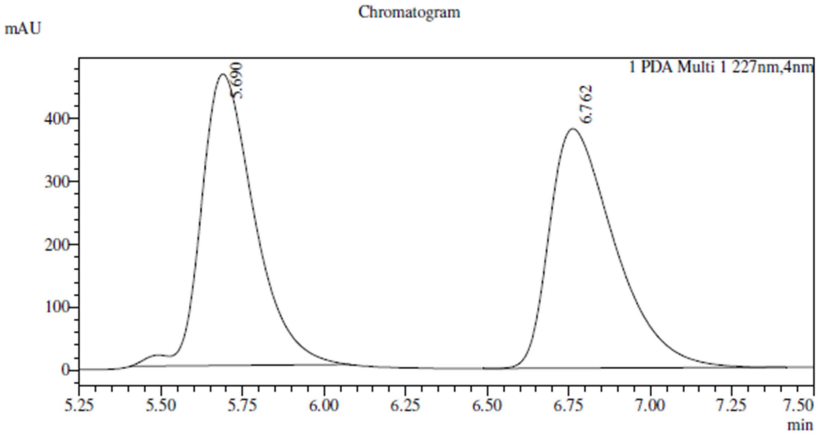
Peak#	Ret. Time	Area	Area%
1	18.747	10835011	96.249
2	29.364	422229	3.751
Total		11257241	100.000

Enantiomeric ratio (average of two runs): 96.4 : 3.6. Ligand enantiomer used: S



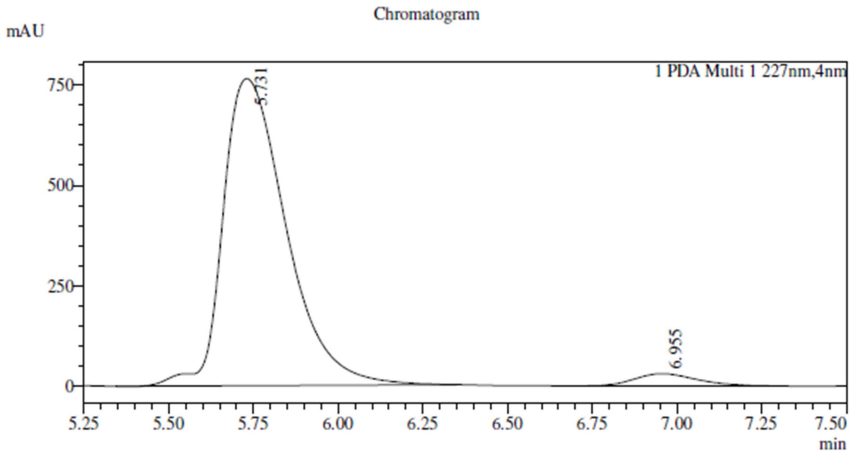
3j

CHIRALPAK® IA-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 227nm

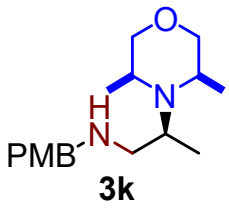
Peak#	Ret. Time	Area	Area%
1	5.690	5261099	49.673
2	6.762	5330450	50.327
Total		10591549	100.000



PDA Ch1 227nm

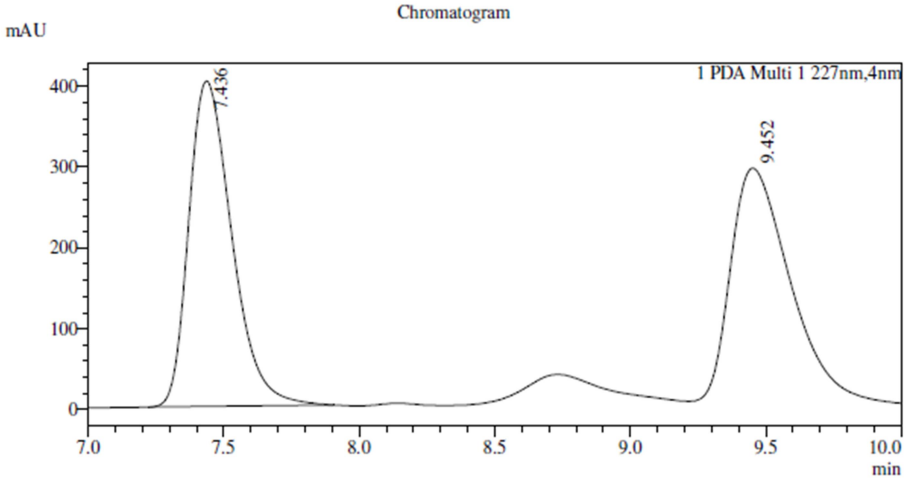
Peak#	Ret. Time	Area	Area%
1	5.731	9902885	96.247
2	6.955	386124	3.753
Total		10289009	100.000

Enantiomeric ratio (average of two runs): 96.2 : 3.8. Ligand enantiomer used: S



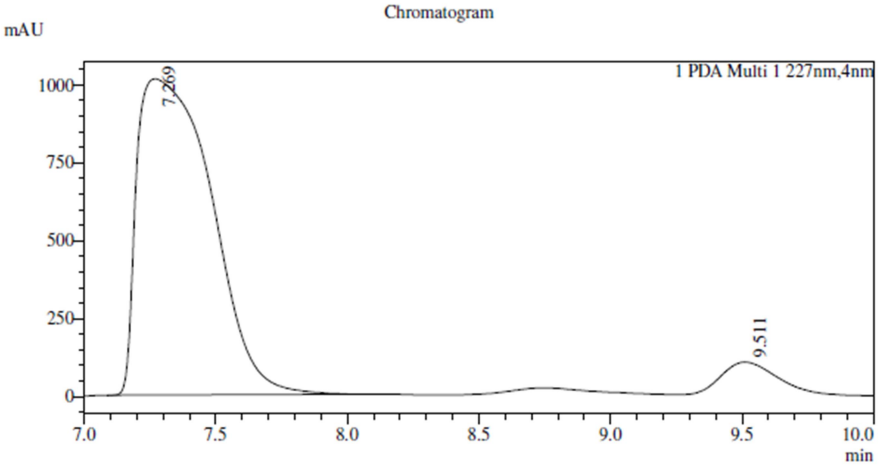
3k

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 227nm

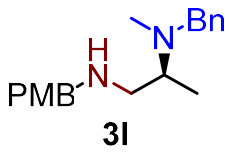
Peak#	Ret. Time	Area	Area%
1	7.436	4458184	50.106
2	9.452	4439296	49.894
Total		8897480	100.000



PDA Ch1 227nm

Peak#	Ret. Time	Area	Area%
1	7.269	20067180	92.601
2	9.511	1603323	7.399
Total		21670503	100.000

Enantiomeric ratio (average of two runs): 92.6 : 7.4. Ligand enantiomer used: S

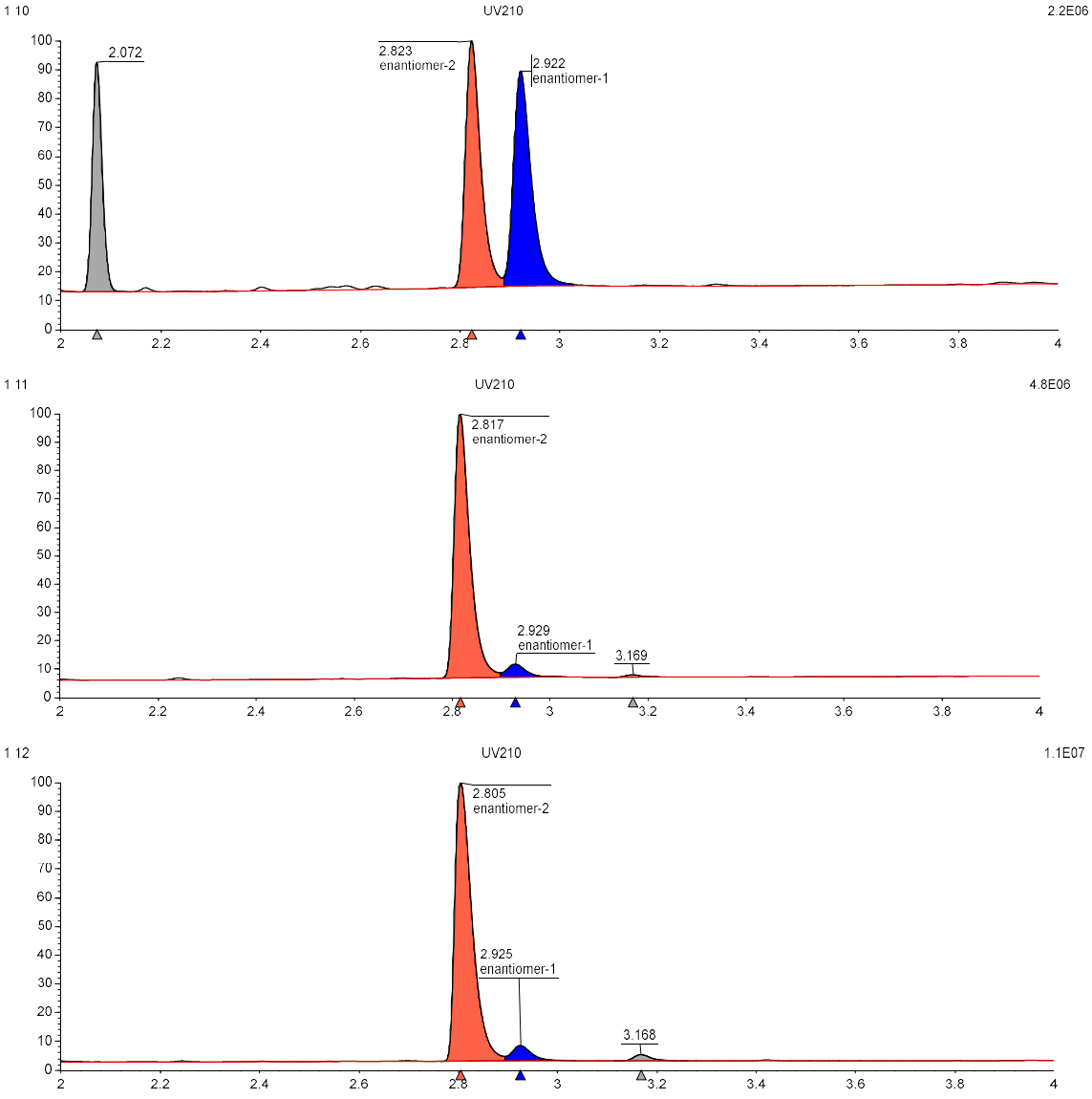


3l

Chiralcel OD-3 4.6 x 150 mm, 3 um

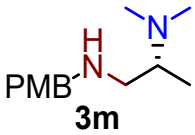
MPA: CO_2 MPB: MeOH w/ 25 mM IBA

10-30% B (0-3 min), 30% (3-6 min), 40 °C, 3 mL/min. Detection at 210 nm.



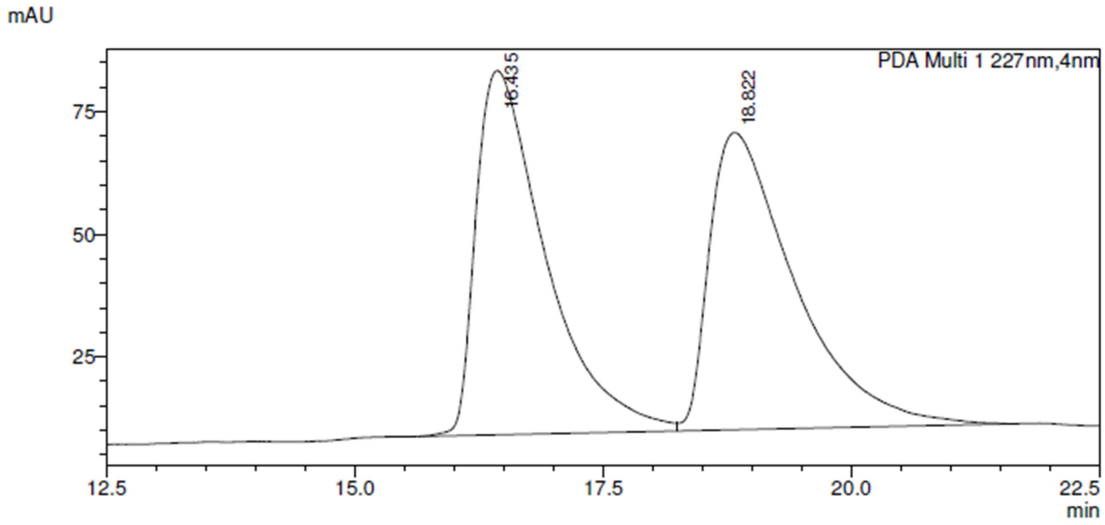
ER: 94.4 : 5.6, 94.1 : 5.9, 94.3

Enantiomeric ratio (average of two runs): 94.3 : 5.7. Ligand enantiomer used: S



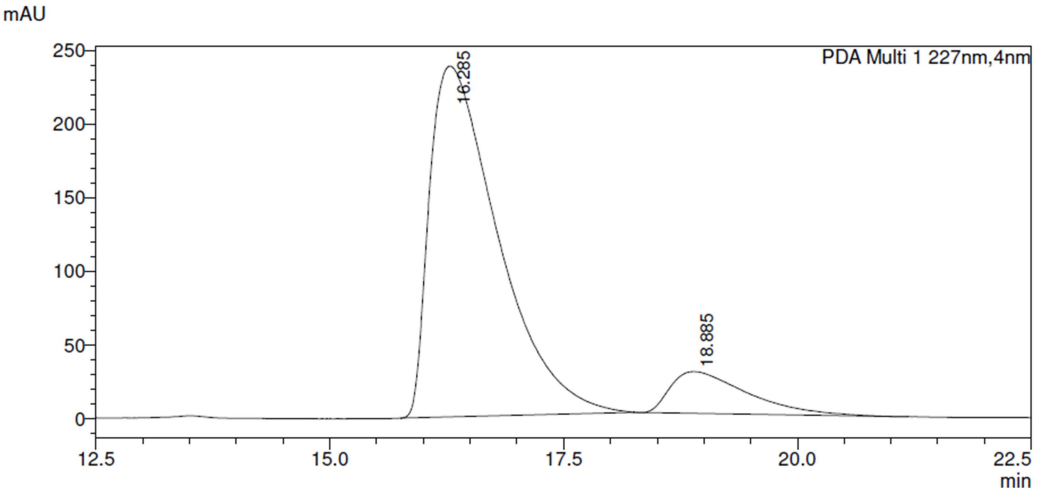
3m

CHIRALPAK® ID-3 94.7 : 4.9 : 0.3: 0.1 hexanes : ethanol : acetic acid : diethylamine



PDA Ch1 227nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	16.435	3633491	74306	0.000	49.972
2	18.822	3637602	60603	0.000	50.028
Total		7271094	134909		100.000



PDA Ch1 227nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	16.285	12154153	238122	0.000	88.209
2	18.885	1624701	28366	0.000	11.791
Total		13778855	266488		100.000

Enantiomeric ratio (average of two runs): 88.0 : 12.0 . Ligand enantiomer used: S

2.6 References

(1) “Chiral Tertiary Diamines in Asymmetric Synthesis,” Kizirian, J-C. *Chem. Rev.* **2008**, *108*, 140-205

(2) “Vicinal Diamino Functionalities as Privileged Structural Elements in Biologically Active Compounds and Exploitation of their Synthetic Chemistry.” Kotti, S. R. S. S., Timmons, C.; Li, Guigen. *Chem. Bio. & Drug Design*, **2006**, *67*, 101-114

(3) “The Chemistry of Vicinal Diamines,” Lucet, D.; LeGall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580-2627

(4) “Lecozotan (SRA-333): A Selective Serotonin 1A Receptor Antagonist That Enhances the Stimulated Release of Glutamate and Acetylcholine in the Hippocampus and Possesses Cognitive-Enhancing Properties” Schechter, L. E.; Smith, D. L.; Rosenzweig-Lipson, S.; Sukoff, S. J.; Dawson, L. A.; Marquis, K.; Jones, D.; Piesla, M.; Andree, T.; Nawoschik, S.; Harder, J. A.; Womack, M. D. Buccafusco, J.; Terry, A. V. Hoebel, B.; Rada, P.; Kelly, M.; Abou-Gharbia, M.; Barrett, J. E. Childers, W. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1274–1289

(5) “A Novel Synthesis of Unsymmetric 1,2-Diamines from N-substituted 2-Methylaziridines” Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2531-2533

(6) “Nucleophilic Ring Opening Reactions of Aziridines” Akhtar, R.; Naqvi, S. A. R.; Zahoor, A. F.; Saleem, S. *Mol. Divers*¸ **2018**, *22*, 447-501

(7) “Heterobimetallic Transition Metal/Rare Earth Metal Bifunctional Catalysis: A Cu/Sm/Schiff Base Complex for *Syn*-Selective Catalytic Asymmetric Nitro-Mannich Reaction.” Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925

(8) “Highly *anti*-Selective Asymmetric Nitro-Mannich Reactions Catalyzed by Bifunctional Amine-Thiourea-Bearing Multiple Hydrogen Bonding Donors. Wang, C-J.; Dong, X-Q.; Zhang, Z-H.; Xue, Z-Y.; Teng, H-L. *J. Am. Chem. Soc.* **2008**, *130*, 8606-8607

(9) “Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation reactions" Schönherr, H.; Cernak, T. *Angew. Chem. Int. Ed*. **2013**, *52*, 12256-12267

(10) “The [IrCl(diphosphine)]$_2$/Fluoride System. Developing Catalytic Asymmetric Olefin Hydroamination”, Dorta, R.; Egli, P.; Zü rcher, F.; Togni, A. *J. Am. Chem. Soc*. **1997**, *119*, 10857

(11) “Intermolecular Hydroamination of Ethylene and 1-Alkenes with Cyclic Ureas

Catalyzed by Achiral and Chiral Gold(I) Complexes,” Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2009**, *131*, 5372-5373

(12) “Asymmetric Intermolecular Hydroamination of Unactivated Alkenes with Simple Amines”, Reznichenko, A.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem. Int. Ed*. **2010**, *49*, 8984-8987.

(13) “Late Transition Metal-Catalyzed Hydraomination and Hydroamidation”, Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem.Rev.* **2015**, *115* (7), 2596–2697.

(14) “Highly Enantioselective Intermolecular Hydroamination of Allylic Amines with Chiral Aldehydes as Tethering Catalysts” MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. *Chem. Eur. J*. **2013**, *19*, 2597-2601.

(15) Iridium-Catalyzed Intermolecular Hydroamination of Unactivated Aliphatic Alkenes with Amides and Sulfonamides”, Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134* (29), 11960-11963

(16) “Iridium-Catalyzed, Intermolecular Hydroamination of Unactivated Alkenes with Indoles”, Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136* (8), 3200-3207

(17) “Asymmetric Intermolecular Hydroamination of Unactivated Alkenes with Simple Amines”, Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2010**, *49* (47), 8984-8987

(18) The First Rhodium-Catalyzed Anti-Markovnikov Hydroamination: Studies on Hydroamination and Oxidative Amination of Aromatic Olefins”, Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Muller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999***, 5* (4), 1306-1319

(19) “Regio- and Chemoselective Intermolecular Hydroamination of Allyl Imines for the Synthesis of 1,2-Diamines.” Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. *J. Am. Chem. Soc.* **2014**, *136* (32), 11256-11259

(20) “2-Furyl Phosphines as Ligands for Transition-Metal-Mediated Organic Synthesis.” Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997−1030.

(21) “Nucleophilicities of Primary and Secondary Amines in Water”, Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2006**, *72*, 3679-3688.

(22)” . Asymmetric Diastereoselective Conjugate Additions of Lithium Amides to Chiral Naphthyloxazolines Leading to Novel .beta.-Amino Acids”, Shimano, M.; Meyers, A. I *J. Org. Chem.* **1995**, *60*, 7445-7455

(23) “One-Pot Synthesis of α- Amino Acids through Carboxylation of Ammonium Ylides with CO2 Followed by Alkyl Migration”, Mita, T.; Sugawara, M.; Sato, Y. *J. Org. Chem.* **2016,** *81,* 5236-5243.

(24) “Synthesis of a-Dehydrobiotin”, Field, G. F.; Zally, W. J.; Sternbach, L. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3853−3857

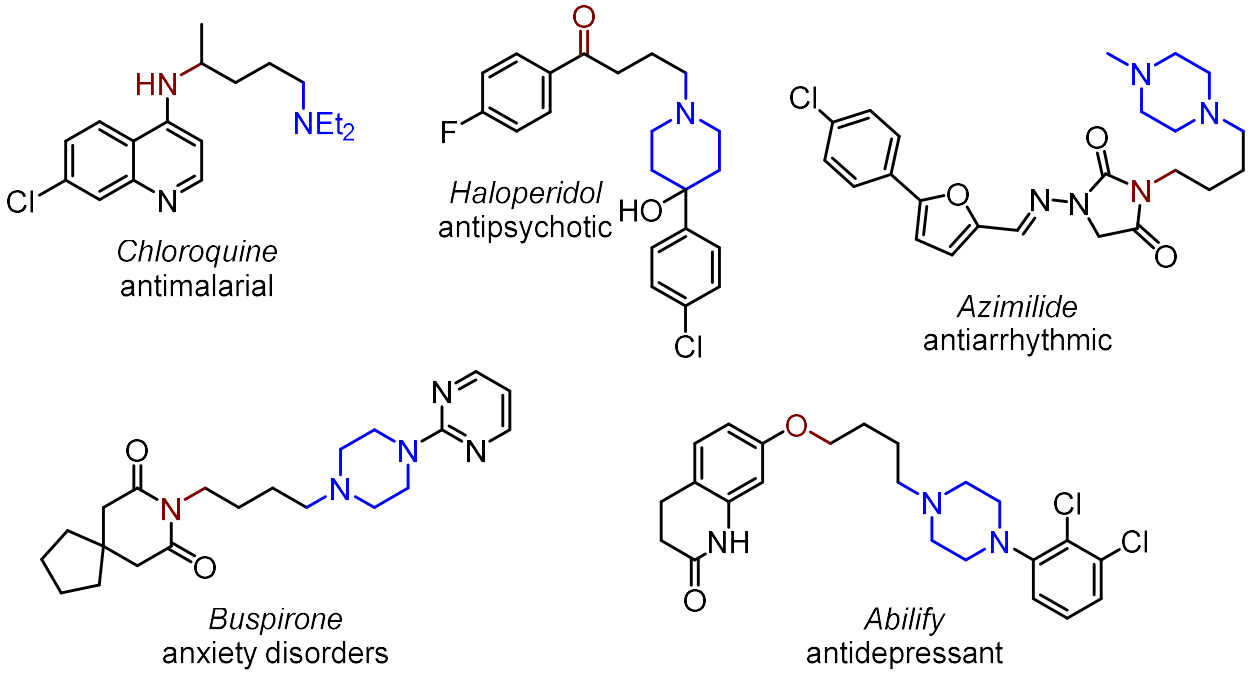
(25) “Rhodium-Catalyzed Asymmetric Hydroamination of Allyl Amines”, Vanable, E. P. Kennemur, J. L.; Joyce, L. A.; Ruck, R. T.; Schultz, D. M.; Hull, K. L. *J. Am.Chem. Soc.* **2019**, *141*, 739-742

Chapter 3: Anti-Markovnikov Hydroamination of Homoallylamines to Afford 1,4-Diamines and Further Work on Homoallyl Directing Groups

3.1 Introduction

Transition metal catalyzed hydroamination, by and large, affords the Markovnikov product with some notable exceptions: primarily with conjugated alkene substrates or by using indirect hydroamination methods.[1-7] Of course, there are times when linear amines, instead of branched amines, may be the desired product. This is particularly the case when considering molecules which have important biological activity. Many classic antidepressants and anti-anxiety medications fall under the class of γ-butyrophenones, for instance, where there is a 1,4 relationship between a ketone and the linear amine, mimicking dopamine to receptors in the brain.[11] This 1,4 relationship intrigued us, and further investigated led us to realize that 1,4 diamines are also fairly common (serotonin, for instance), as well as 1,4 amino alcohols, in the pharmaceutical literature (**Figure 3.1**). These compounds are often made through reductive amination or S_N2 reactions, involving the use of preoxidized functionality that is prone to side reactions and byproducts. The importance of these compounds, of course, begs the question of how can we make these compounds in a new and efficient way. As with many amine-containing motifs this lends itself to the perfectly atom-economical hydroamination of an olefin.

Figure 3.1: Pharmaceuticals containing a 1,4 motif with an amine and a polar directing group

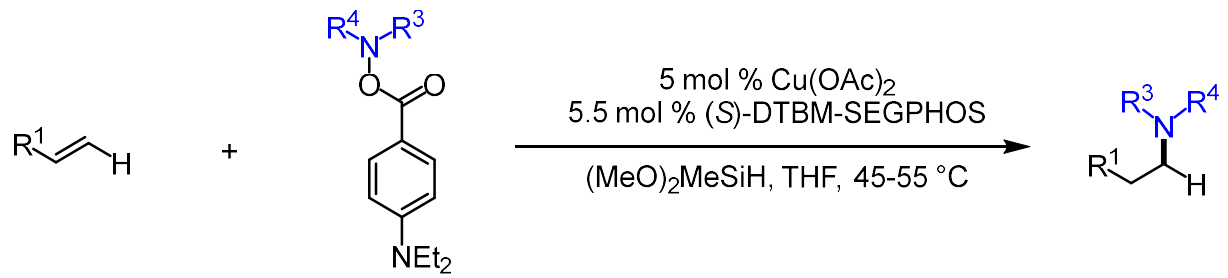


For this hydroamination, we again envisioned using a directing group approach to resolve the traditional regioselectivity and reactivity issues. As these compounds have been selected with this criterion in mind, the potential directing group has been shown in red, and the amine nucleophile in blue. Clearly this approach would be effective to form the C–N bond - but only if we could overturn the traditional selectivity for the Markovnikov product. To obtain these products, this inherent bias must be understood and overcome.

This selectivity is driven by two synergistic driving forces. First, the metal center is very bulky, due to its atomic radius and ligands, so putting it at the terminal position minimizes any steric strain incurred in the aminometallation step. The second driving force is electronic in nature: the internal carbon is able to stabilize significantly more positive charge than the terminal carbon when the olefin donates some of its π-electron density to the metal center. This partial positive charge makes the internal carbon much more electrophilic than the terminal carbon, more attractive to the nucleophile, and drives functionalization at that position. This is not to say that all alkene hydroaminations afford Markovnikov products: for instance, often with styrenes and dienes the anti-Markovnikov product can be formed, due to the stabilization of the afforded metal-benzyl or allyl complex.[1-7]

There are three major approaches towards resolving the issue of anti-Markovnikov selective hydroamination for alkyl substituted olefins, all of which skirt the issue of reversing the selectivity of aminometallation by avoiding that mechanism altogether. The most obvious is the recent work in copper-catalyzed indirect hydroamination pioneered by the Lalic group and made popular by the Buchwald group.[12-18] This elegant approach utilizes a Cu-H derived from a silane source, undergoes an insertion putting the copper at the expected terminal position, and is then aminated by a benzoyl hydroxylamine derivative. An example is shown below in **Scheme 3.1**.

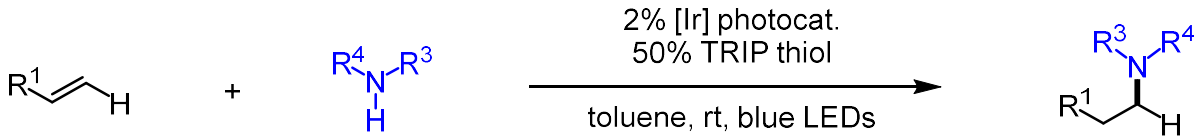
Scheme 3.1: Copper-catalyzed indirect hydroamination of alkenes



This strategy of approach will be referred to as indirect hydroamination for the duration of this document. The synthesis of the benzoyl N-hydroxylamines is a significant challenge which limits the utility of this strategy. Furthermore, this strategy is inherently less atom-economical – the benzoyl group, the components of synthesizing it, and the waste from the silane group are all unavoidable and inefficient. As these are inherent to the strategy, there is no means to avoid them at this time, meaning that this approach will always be wasteful.

A second approach to work around this problem is to use radical chemistry. There have been multiple reports of this in the past,[19, 20] however the most elegant approach to this problem was reported shortly after we finished working in this area, though it would be remiss to not mention it here.[21] This approach uses light and a photocatalyst to generate an amine radical cation which is highly electrophilic and is rapidly attacked by an olefin. The terminal carbon attacks to afford a new C–N bond and a relatively stable secondary radical, which drives the selectivity. This then abstracts a hydrogen atom from a proton shuttle, affording the hydroamination product.[21] This method is an elegant approach to this problem, although certainly there are motifs which will not tolerate the presence of amine radical cations and alkyl radicals including weak C–H bonds and Michael acceptors as a couple of examples (**Scheme 3.2**).

Scheme 3.2: Photocatalyst induced anti-Markovnikov reaction through a radical pathway

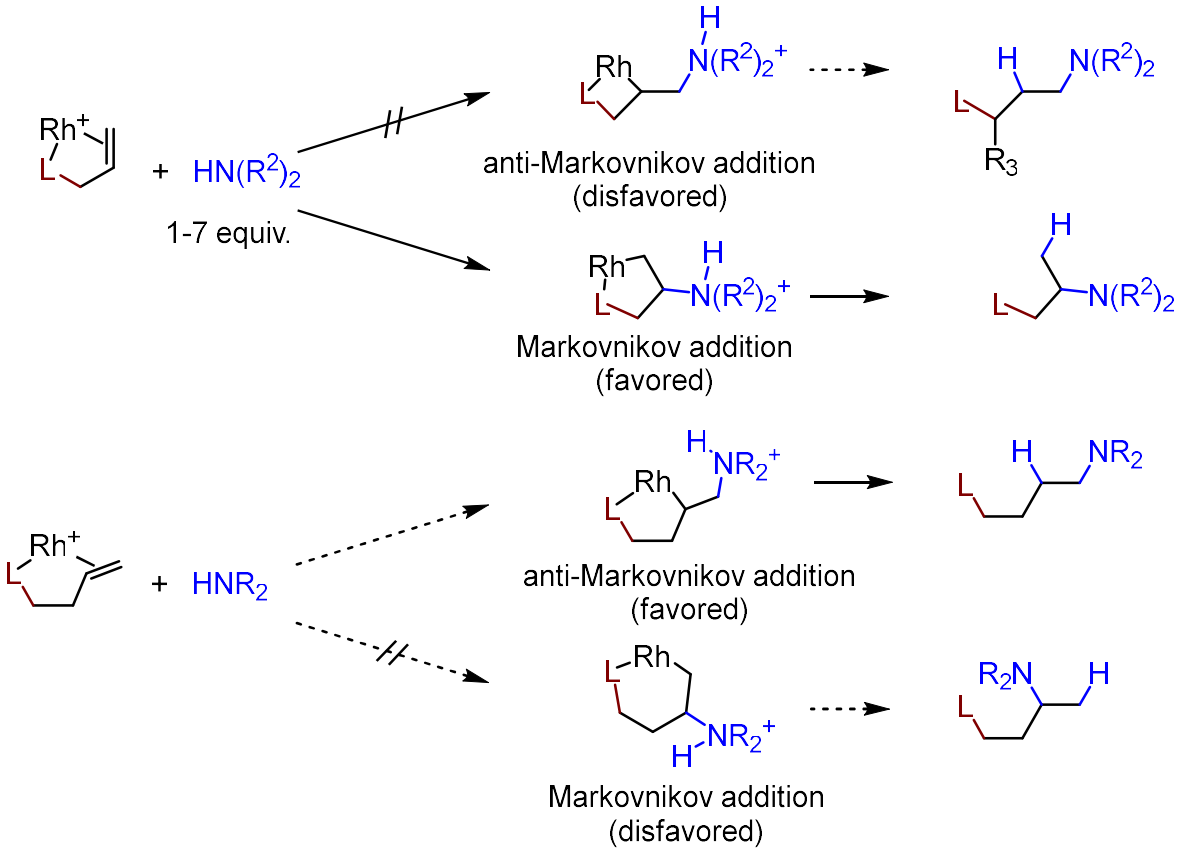


This approach, again, does not resolve the challenge we have taken on: how to get aminometallation to occur to place the metal on the internal carbon. In some other ways, this approach is equal or superior to transition-metal catalyzed hydroamination, although the amount of TRIP thiol used is absurdly high for an expensive catalyst.

The third approach is the general umbrella of multistep reactions to afford amines: hydrozirconation followed by amination or anti-Markovnikov Wacker followed by reductive amination are the two main ones. These approaches are both inefficient and do not resolve the desired challenge, and will therefore not be discussed here other than this brief mention.[3, 4]

In order to overcome the challenges discussed herein, and resolve the problem of transition-catalyzed direct anti-Markovnikov intermolecular hydroamination, we opted to turn towards a strategy we had previously been exploring in our group. Our work on imine and amine-directed hydroamination has been discussed herein, along with how it assists in resolving the challenges of olefin coordination, product selectivity, and perhaps regioselectivity. [22-24] This approach has been validated in terms of assisting with reactivity and chemoselectivity of hydroamination, but we wanted to see if it is truly affecting the regioselectivity – considering that it is only hypothesized, not proven, to be enhancing the existing regioselectivity in those cases. By changing the tether length to the directing group from allyl to homoallyl, instead of having the option of forming a 4-membered or 5-membered metallacycle upon aminometallation, now the choice leading to the two different regioisomers is between a 5- and a 6-membered metallacycle (**Scheme 3.1**) which should have a smaller energy difference.

Scheme 3.3: Showing how different tether lengths affect metallacycles upon aminometallation

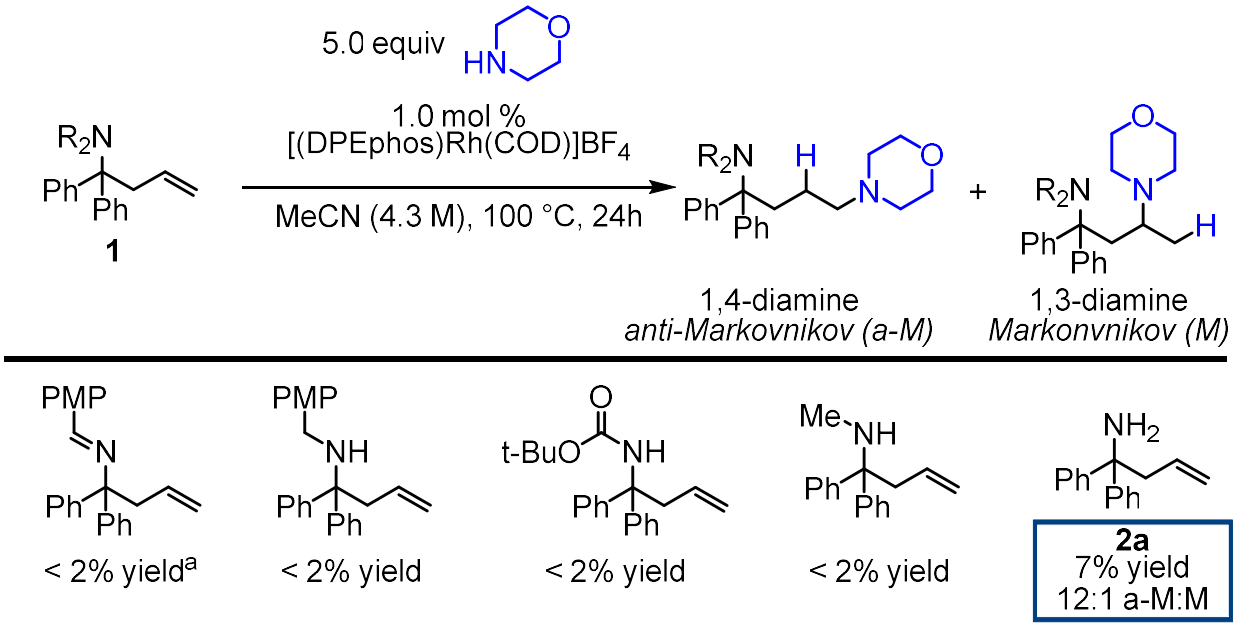


Our hypothesis was that as the 5-membered metallacycle may be lower in energy than the 6-, accompanied by the transition states leading to each, so that we may be able to overcome this inherent selectivity through this enthalpic preference to resolve the challenge of anti-Markovnikov aminometallation. This hypothesis tracks well with some literature observations: when selecting between transition-metal containing ring sizes, such as through C-H activation, the 5-membered metallacycle is often heavily preferred.[25-27] Of course, this effect would be ligand and metal dependent, but we considered it an excellent starting hypothesis.

3.2 Initial Development & Scope

With our initial investigations we employed α,α-diphenyl homoallylamine derivatives, as we wanted to utilize the Thorpe-Ingold effect to encourage olefin coordination.[28] We synthesized a variety of different homoallylamine derivatives including a N-homoallyl imine, primary amine, secondary amine, and a Boc protected amine to subject to the reaction conditions in order to determine which of these was the optimal directing group for the transformation.

Scheme 3.4: Initial testing of different directing groups for this transformation

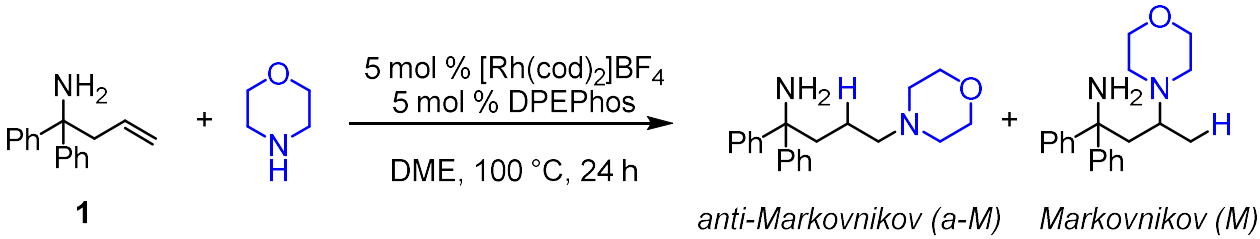


In situ yield determined by gas chromatography relative to an internal standard, a-M:M determined by gas chromatography. [a]An aza-cope rearrangement yielded *N*-(1-(4-methoxyphenyl)but-3-ene-1-yl)-1,1-diphenylmethanimine.

Excitingly, compound **2a** is produced in a 12 : 1 ratio of isomers, favoring the regioisomer we desired, with a 7% yield. This validates our hypothesis that the 5-membered metallacycle is

preferred over the six, leading to the anti-Markovnikov product. We increased the catalyst loading from this initial hit, and performed a solvent screen to find a better solvent for this transformation.

Table 3.1: Initial solvent screening on anti-Markovnikov hydroamination[a]

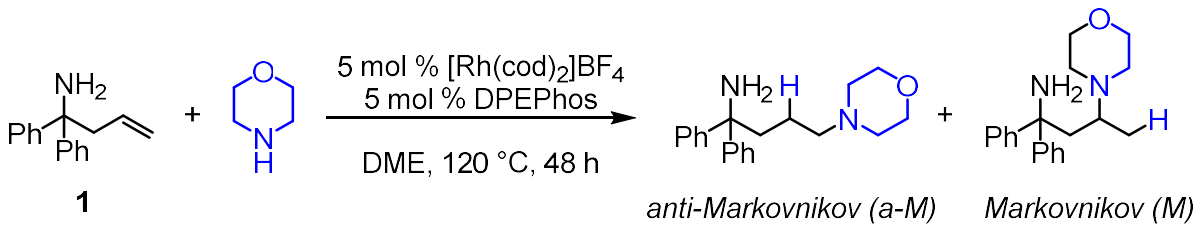


Solvent	GC Yield (%)[b]	Selectivity (a-M:M)[c]
DME	92	45:1
MeCN	66	20:1
p-Dioxane	92	39:1
PhMe	88	41:1
THF	90	42:1

[a] 1.0 equiv. **1**, 5.0 equiv. morpholine, 1 M. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography.

We found that the catalyst increase had a dramatic effect on the yield of the reaction, and with a solvent switch to dimethoxyethane, an excellent 92% yield with 45 : 1 selectivity for the desired product was observed. We next turned to investigating similar ligands, and checked if complete conversion was possible at a higher temperature. Some of the results from this screening are shown below.

Table 3.2: Initial ligand screening on anti-Markovnikov hydroamination[a]

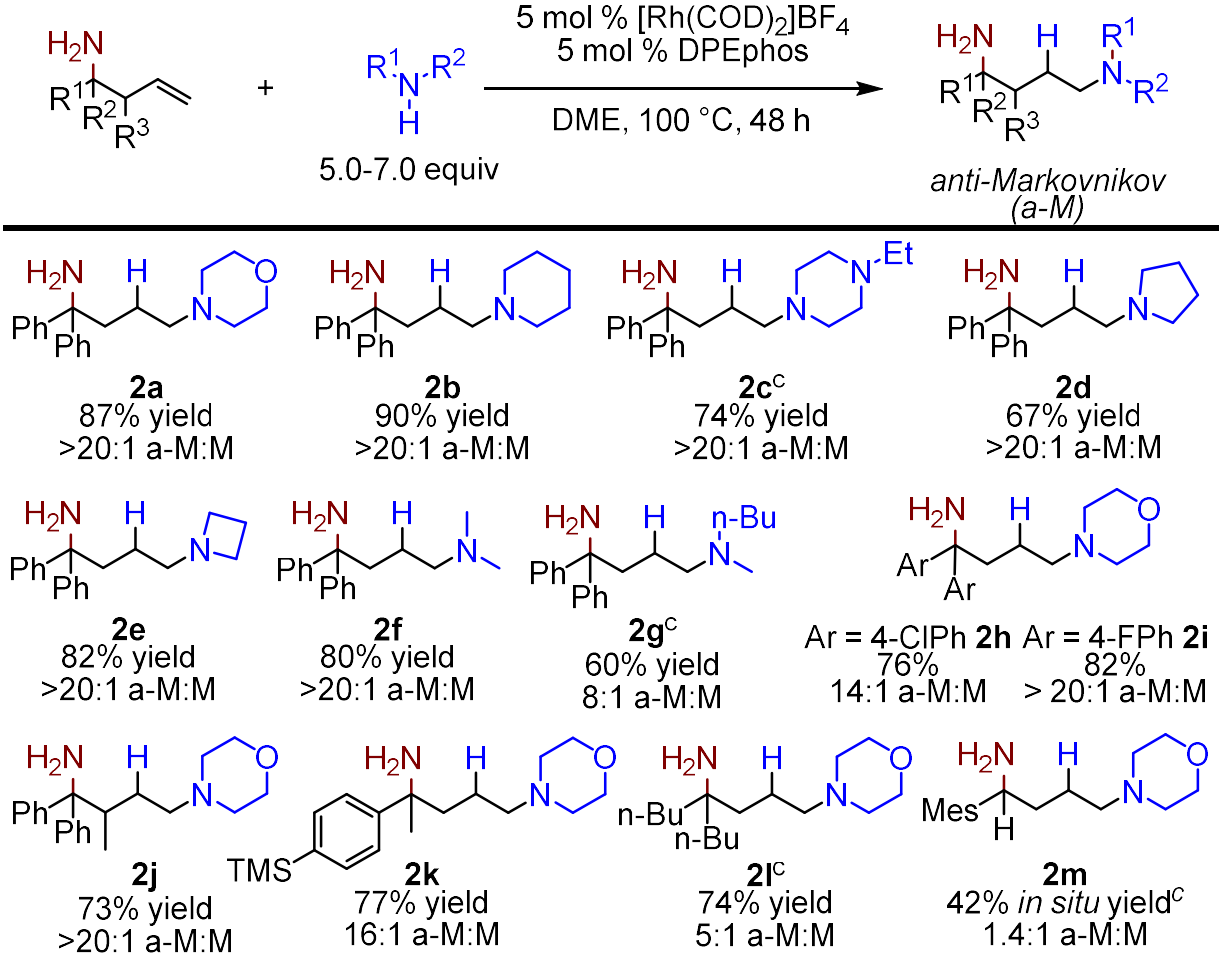


Phosphine	GC Yield (%)[b]	Selectivity (a-M:M)[c]
DPEphos	88	45 : 1
dppe	9.2	69 : 1
dppp	16	48 : 1
dppb	17	31 : 1
dpppent	22	27 : 1

[a] 1.0 equiv. **1**, 5.0 equiv. morpholine, 1 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography.

The omitted ligands gave significantly worse yields than the ones shown here. We can see that DPEphos is unique in affording high yields of the product, but many ligands afford the product with the desired selectivity. It is unclear why this ligand is unique in its high yield, although some information about the complexes formed with these ligands will be discussed herein (*vide supra*). The identity of the counterion marginally affected the yield and selectivity of this transformation in this stage.

Table 3.3: α-disubstituted substrates demonstrating the generality of this reaction[a]

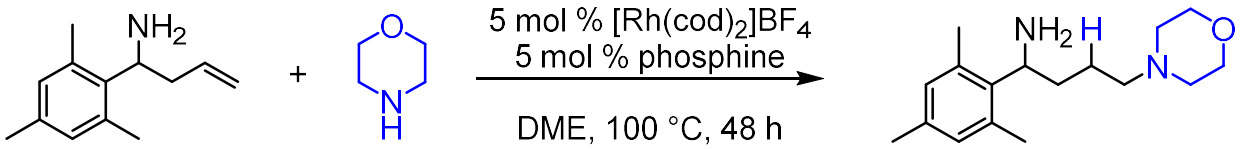


[a] 1.0 equiv. **1**, 5.0 equiv. nucleophile, 1 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] 120 °C.

The scope of the transformation for nucleophiles and α-disubstituted homoallylamine substrates, is broad. 4-, 5-, and 6- membered ring nucleophiles can be utilized including azetidine, pyrrolidine, piperidine, morpholine, and piperazine moieties (2a-2e). In addition, dimethylamine and methyl butylamine can be utilized as nucleophiles, showing that secondary acyclic amines can also be utilized in this transformation (2f, 2g). This is limited to amines where one substituent is methyl, and also does not include amines such as methyl *tert*-butylamine which are highly hindered. Further, different aryl substitutents can be utilized, including chloro and fluoro and trimethylsilyl groups (2h, 2i, 2k). One substituent can also be as small as methyl, although this results in a slightly reduced ratio of products. In addition a β-methyl substituent can be

utilized (2j). Also, both adjacent substituents can be alkyl, as seen in 2l, which has 2 butyl substituents, although this affords a reduced 5 : 1 ratio of regioisomers. Additionally, when an α-monosubstituted substrate was subjected to the reaction conditions with a change to 120 °C, a poor ratio of regioisomers (1.4 : 1) and yield were observed. This limitation did not sit well with us, and we wanted to overcome it. This led us to going back to optimization to see if we could find conditions which tolerated this class of substrates, making the reaction more general.

Table 3.4: Phosphine screening on α-mesityl substrate to increase a-M : M ratio[a]



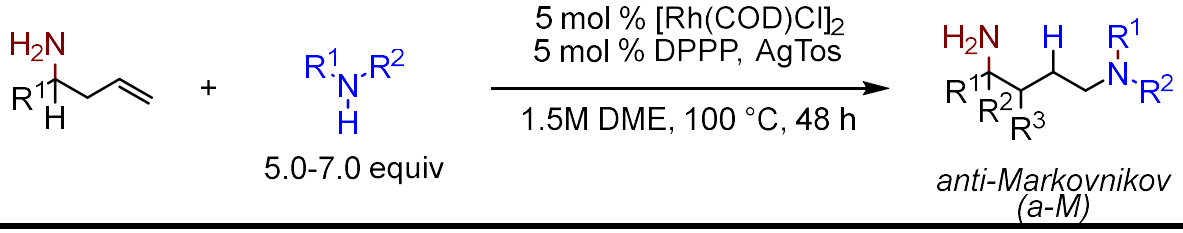
anti-Markovnikov (a-M)

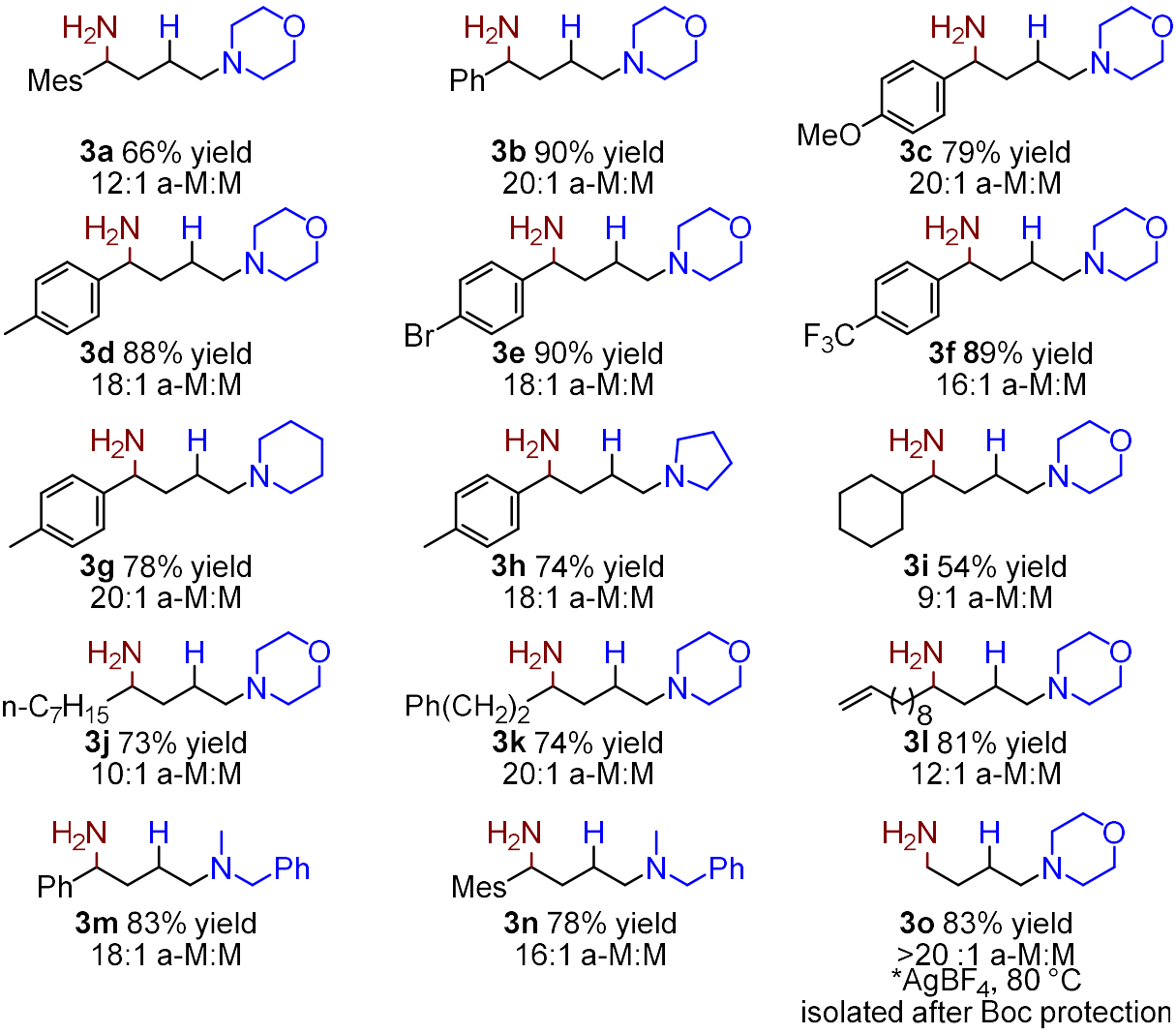
Phosphine	GC Yield (%)[b]	Selectivity (a-M:M)[c]
dppm	<5	1.7 : 1
dppe	<5	2.7 : 1
dppp	68	14 : 1
dppb	41	5.2 : 1
dppf	<5	2.2 : 1
DPEphos	<5	1.2 : 1

[a] 1.0 equiv. **2a**, 5.0 equiv. morpholine, 1.5 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography.

This screening revealed that certain phosphines which did not work well for the α-disubstituted now are optimal for these substrates, giving good yields and high selectivities. The selectivity numbers varied with daily measurements due to GC inconsistencies – 14 : 1 one day could be remeasured as 9 : 1 the next, but within a set of GC runs they are comparable. It is interesting that these phosphines now function better with the less hindered α-monosubstituted homoallylamines. Again, the relationship of ligand and substrate will be discussed further *vide supra*. We next endeavored to show that this scope is also broad.

Table 3.5: α-mono and unsubstituted substrates demonstrating the generality of this reaction[a]





[a] 1.0 equiv. SM **1**, 1-7 equiv. nucleophile, 1.5 M DME.

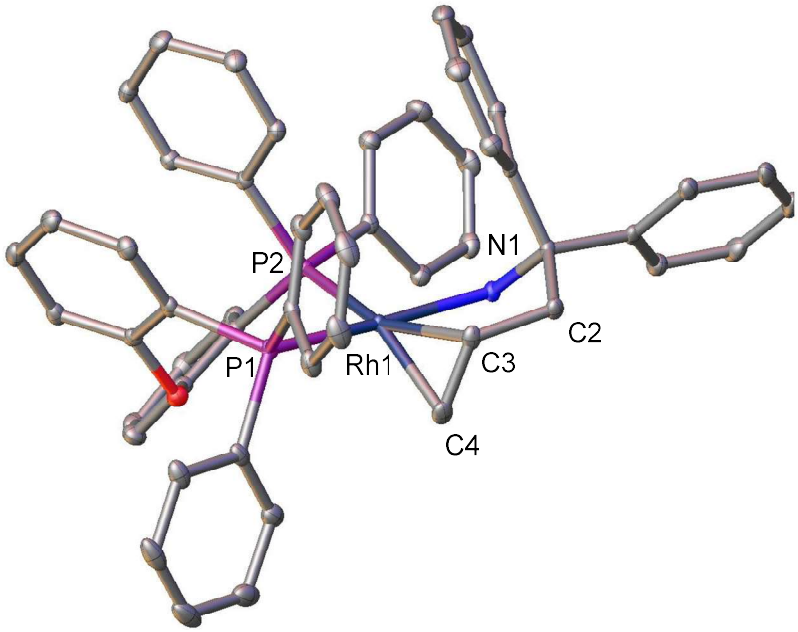
We were gratified to discover that the use of a variety of α-monosubstituted homoallylamine substrates is tolerated. Electronically and sterically differentiated aryl rings including methoxy groups, trifluoromethyl groups, and bromide groups are all tolerated with very small differences in yield and regioselectivity (3a-3g). The substitutent does not have to be aryl: there is no requirement for a π-stacking interaction. For instance, alkyl substitutents such as septyl,

phenethyl, and 8-nonenyl groups are all tolerated with good yields and regioisomeric ratios (3i-3l). In addition, homoallylamine itself can be used, with good yields and selectivity, although mysteriously this required switching back to the BF_4 counterion – <5% yield is observed with the tosylate counterion.

3.3 Probing the Mechanism

This scope is generally quite broad: many classes of 1,4-diamines can be produced efficiently through this transformation. The next thing we were interested in looking into was the mechanism of this transformation, and any information that could be gleaned about whether the selectivity really was driven by a metallacycle size preference in the insertion step. The first experiment we performed was to subject the catalyst to stoichiometric quantitites of the reaction ingredients, upon which a stable bisphosphine complex was observed, but was difficult to characterize and purify, as there were multiple other minor complexes in solution. This same complex is observed, but without that challenge, upon subjection of $Rh(cod)_2BF_4$ to a slightly superstoichiometric quantity of alpha-diphenylhomoallylamine followed by precipitation with an antisolvent. This complex has been characterized by ^{1}H, ^{13}C, ^{31}P NMR and X-ray crystallography. The crystal structure is shown below, with protons, solvent molecule, and counterion omitted. The rhodium is clearly square planar as expected, with a slight distortion (94.745°) to accommodate the ligand's preference for a wide bite angle. The aminoolefin coordination resembles a chair structure, and is clearly set up well for an aminometallation event with little rearrangement to give the branched M-alkyl. It is possible that an approach to the internal carbon is hindered by the projection of steric bulk from the ligand and substrate, but this has not been investigated computationally. There is also a very slight tetrahedral distortion, but nothing worth truly noting.

Figure 3.2: Crystal structure of substrate-bound catalyst with some bond distances and angles included



	Bond (Å)		Angle (°)
Rh1-N1	2.1457(12)	P1-Rh1-P2	94.745(14)
Rh1-C3	2.2662(14)	C3-Rh1-C4	35.56(5)
Rh1-C4	2.2369(14)	C2-C3-C4	121.42(14)
C3-C4	1.375(2)	C4-C3-Rh1	71.06(9)

The proton NMR of this compound has the alkene protons shifted dramatically upfield, which confirms the olefin coordination and slight metallacyclopropane character. This species is also catalytically competent, with no induction period noted (the catalyst components individually do have a short induction period). This, along with its ease of formation under simulated catalytic conditions, implies to us that this species is forming in the reaction, and may even be the resting state. We wanted to further study the mechanism of this transformation, so we turned to kinetics to obtain answers.

Figure 3.3: Select kinetic data for the hydroamination of alpha-phenyl homoallylamine

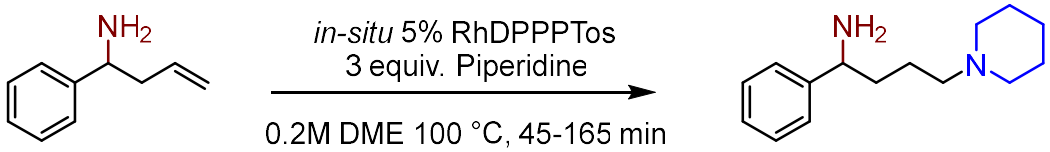
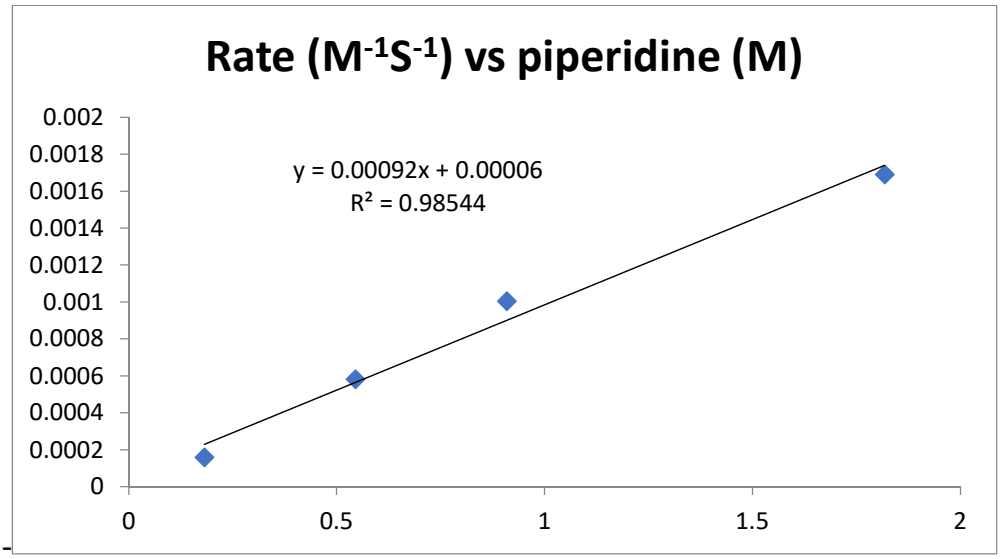


Figure 3.3 (cont.)



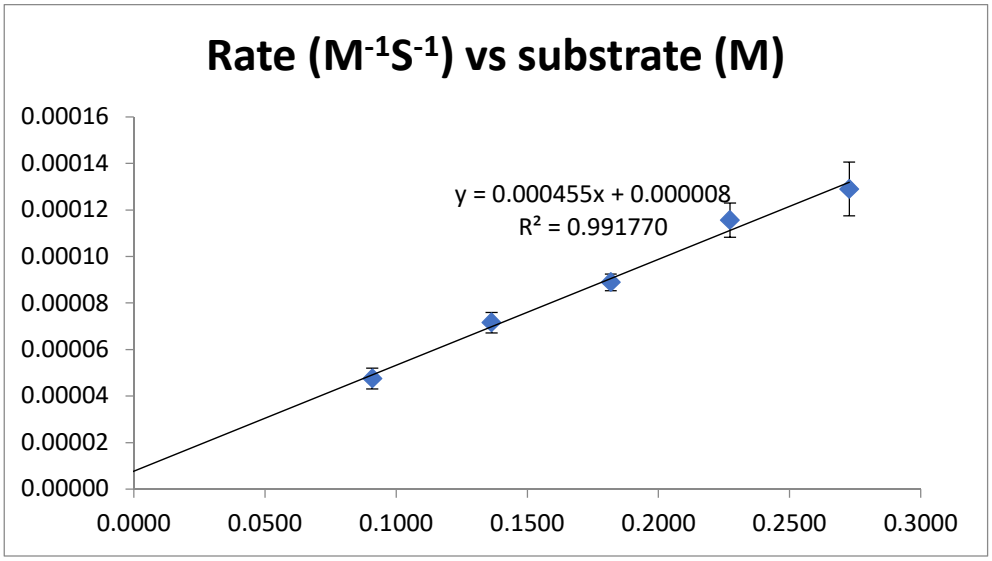
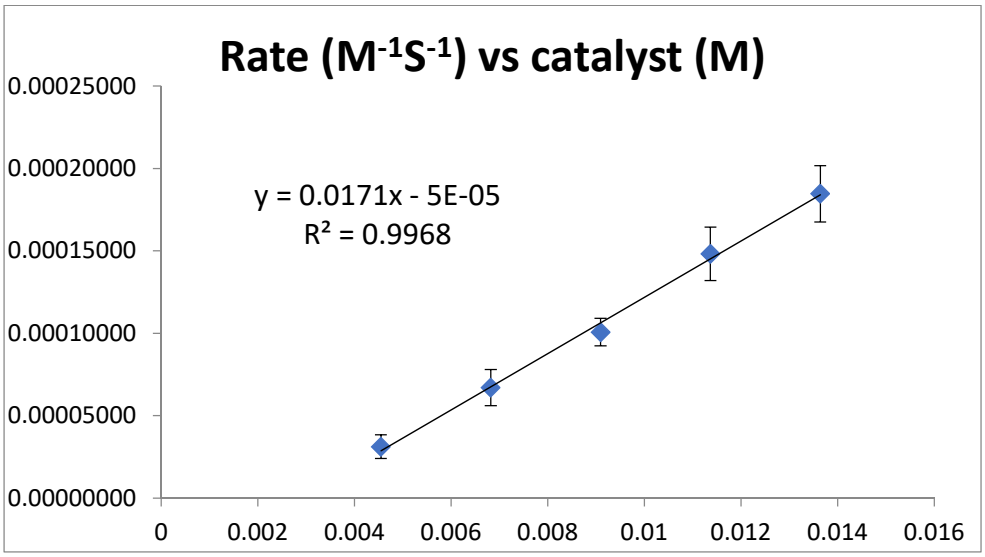
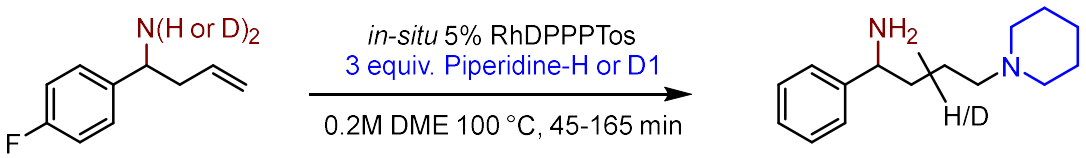


Figure 3.3 (cont)

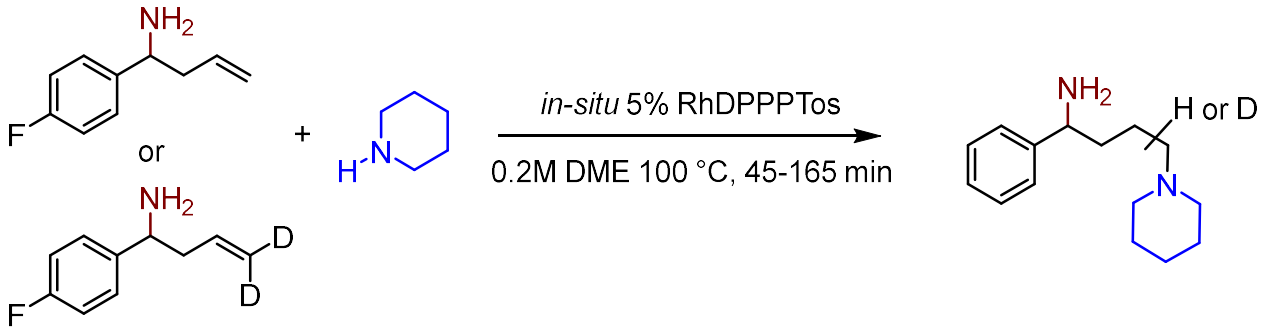


It was observed that the reaction rate was affected in a first order manner by the concentration of metal catalyst, substrate, and amine. This indicated to us that aminometallation was plausibly rate limiting, as the rate law includes the amine. It also excluded metal-metal dimers, and supported the theory that we do not form a significant amount of the complex where an NH_2 from two separate aminooolefins are bound to the metal center. Oddly, the trendline for catalyst concentration does not intersect 0, 0. The reason for this is unclear. We were curious as to whether there was a primary kinetic isotope effect, so we performed a separate vial competition experiment to determine if there was one. A primary kinetic isotope (k_H/k_D) of 3.2 ± 0.1 was observed. This implicates that the rate limiting step for this transformation would be at or after the stage in which the N-H or D bond was cleaved. This limits the options for rate determining steps to either oxidative addition to an amine, aminometallation after that fact, or net protonolysis of the C-Rh bond after aminometallation. We rejected the oxidative addition proposal as that would be unprecepdented for these catalysts in this situation. In order to probe this, we next did a secondary kinetic isotope effect study.

Scheme 3.5: Primary kinetic isotope experiment using α-phenylhomoallylamine



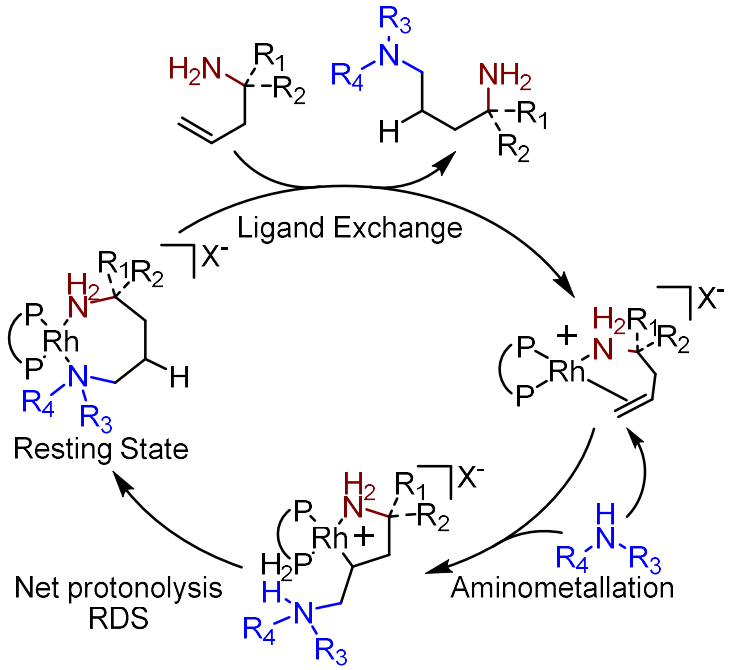
Scheme 3.5 (cont.)



average of 1.5 deuterons

Our secondary kinetioc isotope effect study revealed a k_H/k_D of 0.88 ± .05 uncorrected for the number of deuterons. This implicates that during or before the rate determining step, the carbon substituted by protons or deuterons changes from sp^2 to sp^3 hybridization. This clearly indicates that either aminometallation or protonolysis must be rate limiting. We have not been able to determine if this is through a direct protonolytic cleavage, or proton transfer to the rhodium followed by reductive elimination, although there is little practical difference between the two. A proposed catalytic cycle fitting this evidence is shown below (**figure 3.4**).

Figure 3.4: Proposed Catalytic Cycle



We also attempted to determine the origin of ligand effect in selectivity and reactivity, using stoichiometrically generated aminoolefin complexes. We were able to generate 4

[Rh(bisphosphine)aminoolefin]BF_4 complexes and characterize them crystallographically: the α-diphenylhomoallylamine (DPHAA) complexes with both DPE and DPPP, and the α-monophenylhomoallylamine (MPHAA) complexes with both DPE and DPPP as the phosphine. Unfortunately the tosylate complexes were less stable and less readily crystallized, so those structures were not obtained. These complexes showed one major difference and some more subtle differences. Both MPHAA complexes had the aminoolefin metallacycle in a boat-like conformation (left two), while the DPHAA complexes have a chair-like conformation (right two) (**figure 3.5**).The top structures are the DPEphos structures, and the bottom two are the DPPP structures. The structures are shown from the viewpoint opposite the Rh-P bond, completely occluding that arm of the bisphosphine, such that distortions in the geometry can be more readily seen. We can see that the two MPHAA structures have the terminal carbon of the olefin directly in the square plane of the metal, while both of the DPHAA structures have some distortion. This may be related to the increased bite angle and lower flexibility of the DPEphos compared to DPPP forcing some distortion of the plane: 94.7 and 96.6 ° are observed in the DPEphos cases, while 91.7 and 89.2 ° are observed for the DPPP complexes (DPHAA and MPHAA respectively)

Figure 3.5: Crystal structure views (many atoms and ions omitted for clarity) along with selected bond and angle tables from these structures

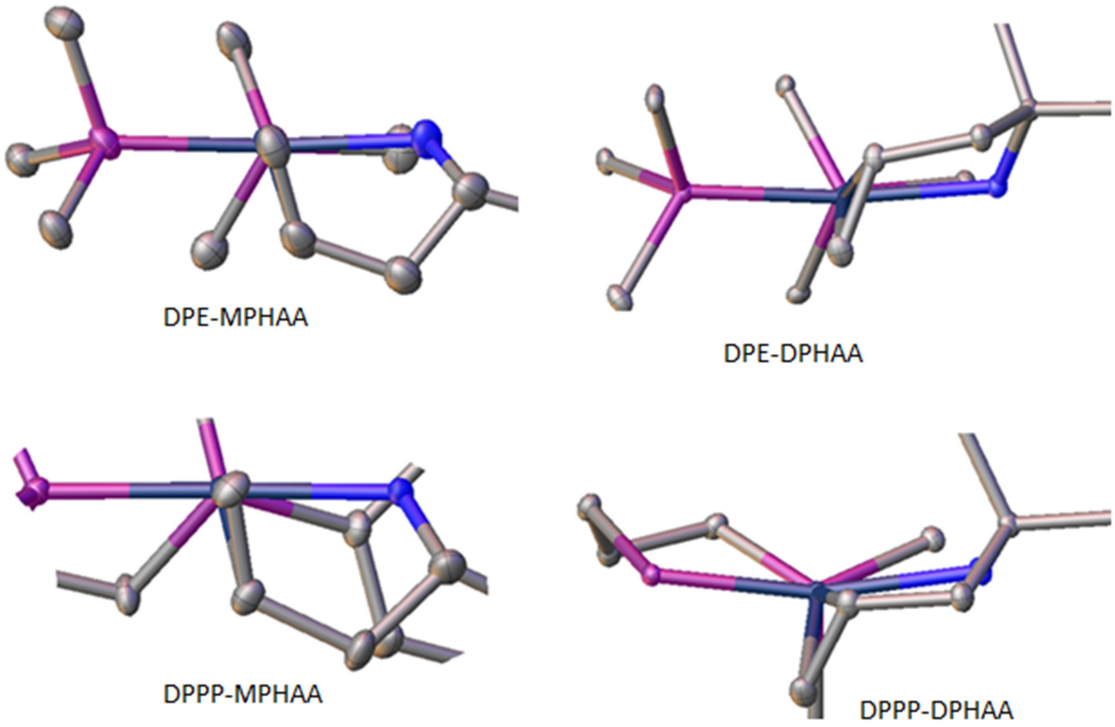


Figure 3.5 (cont.)

DPE-DPHAA	Bond (Å)		Angle (°)
Rh1-N1	2.145	P1-Rh1-P2	**94.745**
Rh1-C3	**2.2662**	C3-Rh1-C4	35.56
Rh1-C4	**2.2369**	C2-C3-C4	121.42
C3-C4	1.375	C4-C3-Rh1	71.06
		DB-Rh1-P2	**174.599**

DPE-MPHAA	Bond (Å)		Angle (°)
Rh1-N1	2.150	P1-Rh1-P2	**96.562**
Rh1-C3	2.203	C3-Rh1-C4	36.570
Rh1-C4	2.214	C2-C3-C4	124.617
C3-C4	1.386	C4-C3-Rh1	72.146
		DB-Rh1-P2	**160.729**

DPPP-DPHAA	Bond (Å)		Angle (°)
Rh1-N1	2.165	P1-Rh1-P2	**91.661**
Rh1-C3	**2.262**	C3-Rh1-C4	35.814
Rh1-C4	**2.230**	C2-C3-C4	121.115
C3-C4	1.382	C4-C3-Rh1	70.813
		DB-Rh1-P2	**160.075**

DPPP-MPHAA	Bond (Å)		Angle (°)
Rh1-N1	2.145	P1-Rh1-P2	89.232
Rh1-C3	2.200	C3-Rh1-C4	36.562
Rh1-C4	2.239	C2-C3-C4	125.136
C3-C4	1.393	C4-C3-Rh1	73.224
		DB-Rh1-P2	161.337

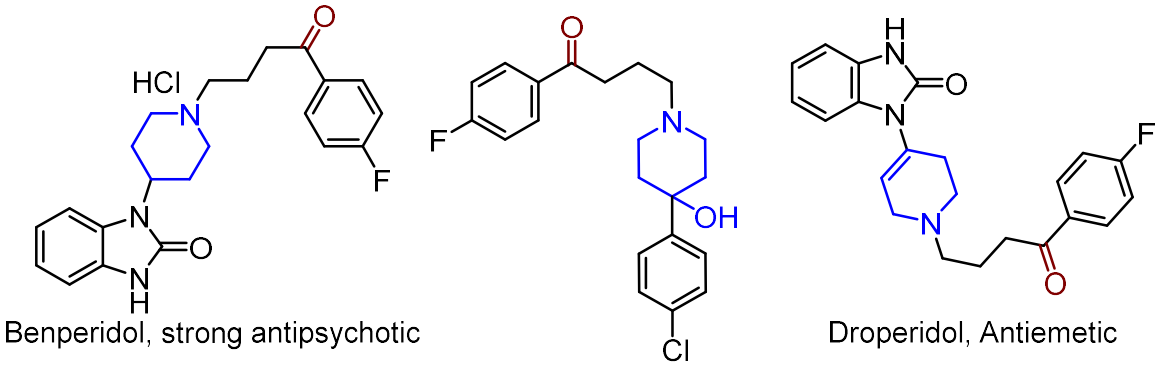
Our attempts to analyze these structures for other clues have provided us little additional information. The selectivity determining factors for the MPHAA cases are likely to be different than the DPHAA ones anyway, due to the different conformations each metallacycle selects. We are interested in continuing this work through studying the mechanism through computation, although that is outside our group's expertise. The selectivity for the DPHAA substrates may partially arise from the fact that the internal carbon is very close to the reactive plane: there is very little reorganization required for formation of the 5-membered metallacycle. This is merely hypothesis at this juncture, which requires computational confirmation.

3.4 Attempts Towards the Hydroamination of Homoallylic Alcohols

One future direction of this work is the expansion to different directing groups, or nucleophilic groups. I have done some preliminary work in this area, which is being followed up

on by An Ho in the Hull lab. The directing group which held the most appeal for us was the use of alcohol or ketone directing groups to directly access the γ-aminobutyrophenone class of drugs which are commonly used as antidepressants and antipsychotics (**figure 3.6**). Before we entered this area, we assessed the challenges that may restrict the use of this strategy with homoallyl alcohols.

Figure 3.6: Some of the most commonly used butyrophenone drugs inspiring this method

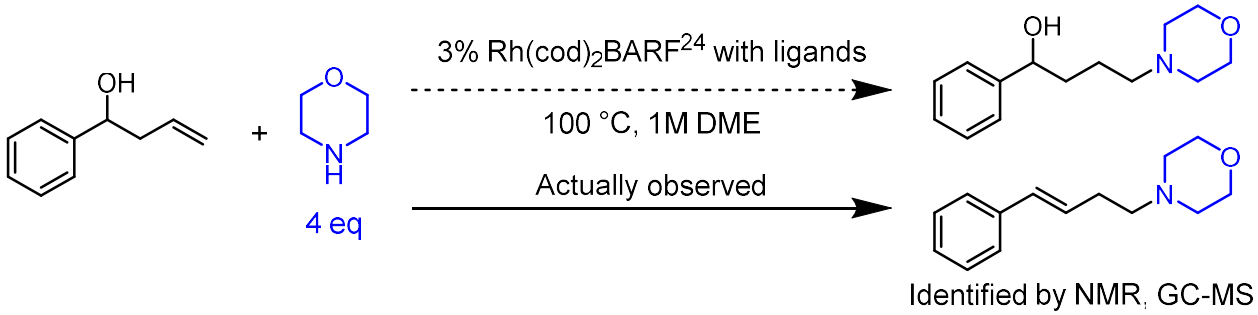


The first obvious challenge is the fact that the alcohol is a much worse ligand for the metal than an amine, such as the secondary cyclic amine nucleophiles we are using in this transformation. This means that the alkoxyolefin will have much less binding affinity to the metal, and may find itself outcompeted by the amine nucleophiles for binding sites on the metal, leading to the typical problem of hydroamination: the olefin has to compete with the amine to bind, but isn't reactive unless it is bound. The second challenge is that alkenes distal to alcohols have a significant enthalpic drive to isomerize to the resultant ketone, and the absence of a strong directing group makes it easier for a catalyst to isomerize the olefin, as it is not bound in a tight metallacycle. Thermal and metal-catalyzed dehydration reactions are a serious concern as well, which would afford an energetically favored 1,3-diene – these are a much larger problem with more electronegative alcohols as leaving groups than amines.

We first attempted simply trying $Rh(cod)_2BF_4$ and $Rh(cod)_2BARF_{24}$ with a variety of monodentate and bidentate phosphine ligands, forming catalysts *in situ* and subjecting α-phenylhomoallylalcohol to them at 100 °C with 4 equivalents of morpholine (**scheme 3.6**). We observed in most of these cases little conversion, or conversion to unidentified materials (GC-MS) but that also in many cases we observed a 100 m/z fragment, corresponding to

methylenemorpholine, which we had previously found highly indicative of anti-Markovnikov hydroamination. This hope, unfortunately, was not the desired product, as we were able to demonstrate through genuine reaction with phenylbutadiene that this was the elimination-hydroamination product shown below in **scheme 3.6.**

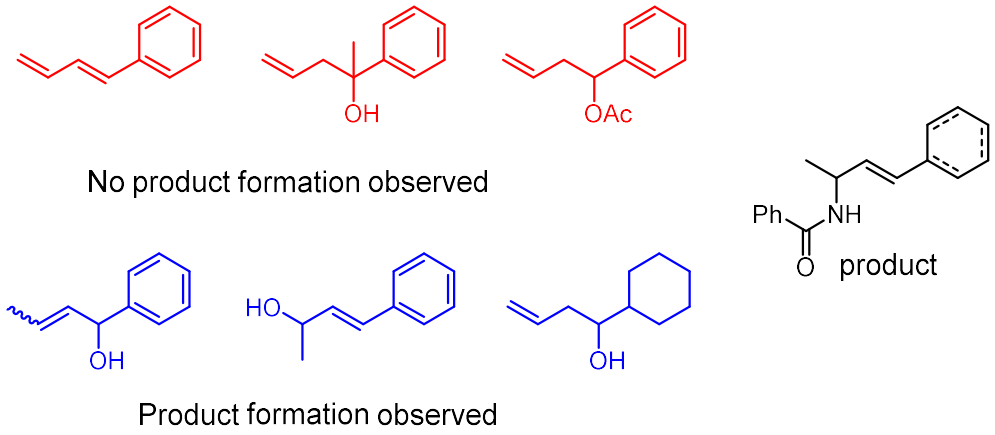
Scheme 3.6: First attempts at hydroamination of homoallylic alcohols



This quickly became the biggest obstacle to effecting this transformation. Even if the α-substituent was changed to cyclohexyl, the elimination still occurred. (These were identified by the formation of olefin peaks at approximately 6.5 ppm and 6.3 ppm for the styrenal product). Unfortunately, this was the realization of one of our expected challenges: fast dehydration followed by facile diene hydroamination. The selectivity is anti-Markovnikov because of the stability of the π-allyl species formed upon aminometallation to afford this regioisomer. Numerous attempts were made to resolve this issue, and a standard screening approach was developed: for a variety of transition-metal sources, including $CuOTf(CH_3CN)_4$, $CuCl_2$, $Fe(OAc)_3$, $CoCl_2$, $PdCl_2$, Ru(P-cymene)Cl, $[Ir(cod)Cl]_2$, Ni(cod)Cl, and $[Rh(cod)Cl]_2$, 6 sets of conditions were attempted. Morpholine, aniline, and p-toluenesulfonamide were used as nucleophiles, a range of 13 selected primarily bidentate phosphine ligands were used, and the reactions were run with and without the presence of silver tetrafluoroborate. In addition, the rhodium screens were run with and without the presence of weak bases, PPh_2Cl, and $P(OPh)_3$ as attempts to improve the directing capability or reduce the elimination capability of the homoallyl alcohol. Essentially all of these screens afforded products of little interest to us. One exception is that in some cases with benzamide we were able to form the diene hydroamination product, but as the markovnikov isomer. This was potentially interesting to us, as it suggested that we were perhaps going through an allylic amination process instead of a hydroamination process. We were able to show that the reaction does not occur through diene hydroamination through subjecting the genuine diene to the reaction conditions, furthering this hypothesis. Also

supporting this hypothesis, α-disubstituted homoallyl alcohols do not afford any product, indicating that it is not hydroamination followed by elimination (**figure 3.7**).

Figure 3.7: Allylic amination substrates subjected to test reaction mechanism

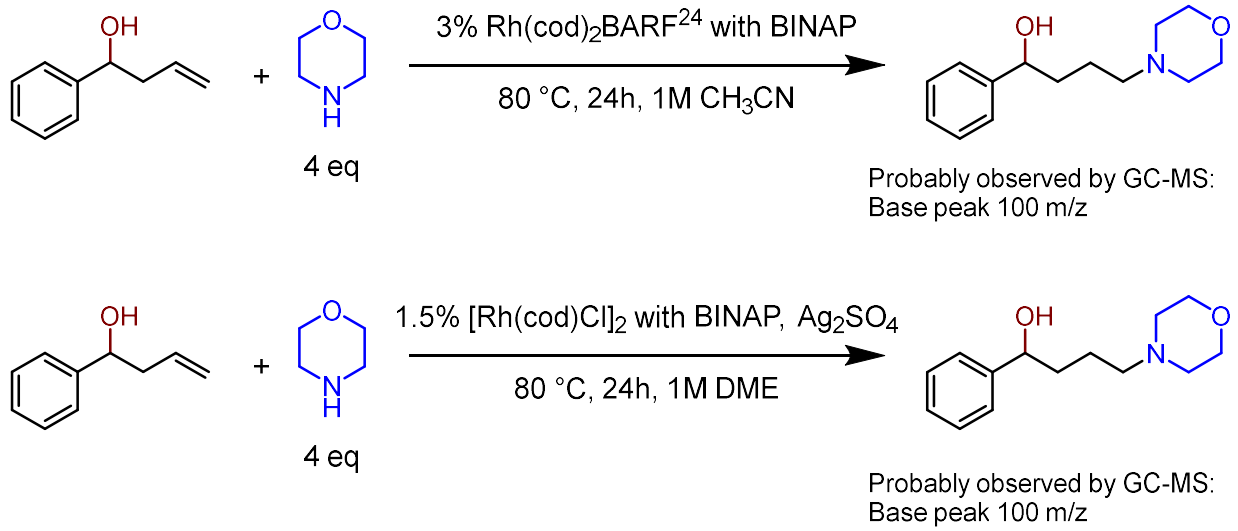


When subjecting an enantiomerically enriched homoallylic alcohol to these reaction conditions, the product was observed to be racemic. This made us consider that the reaction may not be enantiosepecific, and therefore controllable through a chiral ligand. This would be highly unusual for a nonterminal M-allyl species.[29-33] 6 chiral ligands from varied ligand classes (bidentate phosphines) were used as the ligand for this transformation, and all afforded a flat 50-50 e.r. and yields ranging from 20-60%. Without further inspiration, we declined further pursuit of this project, as the racemic product formation was determined to be insufficiently interesting. If this challenge could be overcome and the reaction could be developed to be either enantiospecific, or enantioconvergent and controlled by a chiral ligand, this would be a truly powerful transformation. Investigations in this area should be contingent on having a larger library of ligands to screen, especially chiral ones. If another high throughput screening collaboration was available, this would be a good contender for it.

After we set this venture aside, we returned with some more ideas about the directed hydroamination of homoallyl alcohols project. We considered the possibility that the solvent or the counterion of the metal was causing the issues with the transformation, despite being ideal for the homoallylamines. We selected some ligands which seemed privileged for forming hydroamination products for us in the past (BINAP, DPEphos, DPPP, DPPB), and screened them with the $BARF_{24}$ counterion and a variety of eight solvents, as well as with DME and a 10

different silver salts to provide different counterions. Of these reactions, two afforded promising initial results for the anti-Markovnikov selective hydroamination of homoallyl alcohols (**Scheme 3.7**).

Scheme 3.7: Conditions which afford promising GC-MS peaks



These are promising results because they appear with retention times very similar to the amine-directed product, they have the expected fragment (100 m/z) and are clearly not the diene hydroamination, as we know the retention time of that compound. To date, an authentic standard of the product has not been synthesized, so this identity has not been confirmed. An Ho in the Hull Lab is continuing work on this project, as this is a highly desired transformation. Hopefully this initial success allows a good starting point for developing this transformation.

3.5 Conclusion & Other Future Directions

The development of an efficient and facile method for the anti-Markovnikov hydroamination of homoallylamines has been presented. This transformation has a broad substrate scope, and generates interested 1,4-diamine products. Two exploratory probes into similar transformations are also described herein: the anti-Markovnikov hydroamination of homoallylic alcohols and the allylic amination of allyl and homoallyl alcohols. These are not the only possible future direction for this transformation – just the one with the most promising initial results. Much as with the allylamine hydroamination project, there are a fair number of clear future directions. Internal olefin hydroamination, oxidative difunctionalization, catalyst controlled regioselectivity, and the use of further different directing groups and nucleophiles are all clear directions.

The homoallyl alcohol hydroamination project (*vide infra*) is a perfect example of changing the directing group, and why that would be beneficial. Those compounds are a facile oxidation away from the desired butyrophenone moiety, but it would be beneficial to be able to use ketones directly in the transformation. So far this has not been realized in our hands, and there is considerable room to explore. Only one preliminary screen has been run in this area and it appeared that the olefin isomerized into conjugation, followed by Michael addition, to afford the net Markovnikov selective hydroamination product in all cases. Also, amine or alcohol directed hydroetherification, especially with anti-Markovnikov selectivity, would be a very interesting transformation: instead of changing the directing group, this would be changing the nucleophile. One of the advantages to developing these future directions would be to drastically increase the modularity of this transformation – from two or three classes of starting materials, very rapidly a diverse library of structurally similar but highly electronically varied compounds could be accessed.

Oxidative difunctionalization reactions are traditionally limited because of the short lifespan of a M-alkyl species. These species are prone to other reactions, primarily β-hydride elimination or protonolysis. One approach to these difunctionalization reactions has been shown by Keary Engle & coworkers, the use of a strong directing group to stabilize the M-alkyl such that it is long lived enough for oxidation.[34] Our directing group is not as strong a directing group as theirs, as it only forms a κ-2 chelate instead of a κ-3 chelate, but is also not as limited. Developing similar transformations based on our amination reactions would be appealing including aminohydroxylation, aminoacetoxylation, aminofluorination, and diamination. One challenge we may face in using this approach is that an amine or alcohol directing group is oxidation prone, and so is the nucleophilic amine. This could lead to side reactivity of the starting material or nucleophile with the oxidant, which would lead to unfortunate byproducts and low yields. I have done a bit of initial exploration in this area, all of which has been prevented by this challenge (hypervalent iodine oxidants, N-fluoro oxidants, oxygen, and peroxides, with Rh catalysts, all lead to oxidation of the substrate, nucleophile, or both.) Also, the addition of trapping alkenes or alkynes such as styrene and phenylacetylene afforded none of the carboamination product. Because of this, we believe this direction is likely to be challenging, and would be a significant undertaking to move towards.

Presented in **Chapters 2 & 3** has been the ability to use a direct group to control the regioselectivity of a transformation based on the metallacycle formed upon aminometallation. This approach, while powerful, is inherently lacking the ability to make certain motifs: for instance, 1,3-diamines can be synthesized from neither allylamines nor homoallylamines using this approach, despite the fact that it would be the normal aminometallation regioselectivity for a homoallylamine. We have hypothesized that since changes in ligand resulted in dramatic erosion of selectivity to 1.5:1 in the case of some homoallylamines, that catalyst design may be able to overcome this completely and afford the 1,3 product selectively over the 1,4. Dr. Seth Ensign worked to develop this method in our lab, and has been able to develop Rh-catalyzed conditions which afford the Markovnikov product with homoallylamines and aniline nucleophiles, and Ir-catalyzed conditions which afford the anti-Markovnikov product with the same substrates and nucleophiles. This method also provided promising initial results towards the hydroamination of internal olefins, which I have finished developing into a method for the hydroamination of homoallylamines with internal olefins (discussed in **Chapter 4**).

The hydroamination of internal alkenes is the most interesting of these directions for us, as this approach may lead to solving a currently unsolvable problem: the regioselective hydroamination of olefins which are essentially electronically and sterically undifferentiated. The metallacycle size control approach that has been used in this transformation would be an excellent approach for this problem. Also, the directing group approach allows a possibility of overcoming the traditional problem: if terminal olefins are worse ligands than amines, internal olefins are by necessity even worse ligands. This means that the hydroamination of internal olefins directly with amines is very challenging, as the equilibria favor the olefin coordinated species even less – especially in the absence of a directing group. **Chapter 4** will discuss this challenge, and our progress towards resolving it in detail.

3.6 Supporting Information

This experimental procedure section is reprinted with permission from Ensign, S. C.; Vanable, E. P.; Kortman, G. D.; Hull, K. L. *J. Am. Chem. Soc.* **2015**, *137*, 13748-13751. Copyright 2015 American Chemical Society.

General Experimental Procedures: All reactions were carried out in flame-dried (or oven-dried at 140 °C for at least 2 h) glassware under an atmosphere of nitrogen unless otherwise indicated. Nitrogen was dried using a drying tube equipped with Drierite™ unless otherwise noted. Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level ~ 0.1 ppm). Column chromatography was performed with silica gel from Grace Davison Discovery Sciences (35-75 μm) mixed as a slurry with the eluent and columns were packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on precoated glass silica gel plates (by EMD Chemicals Inc.) with F-254 indicator. Visualization was either by short wave (254 nm) ultraviolet light, or by staining with either ninhydrin or potassium permanganate followed by brief heating on a hot plate or by a heat gun. Distillations were performed using a 3 cm short-path column under reduced pressure or by using a Hickman still at ambient pressure.

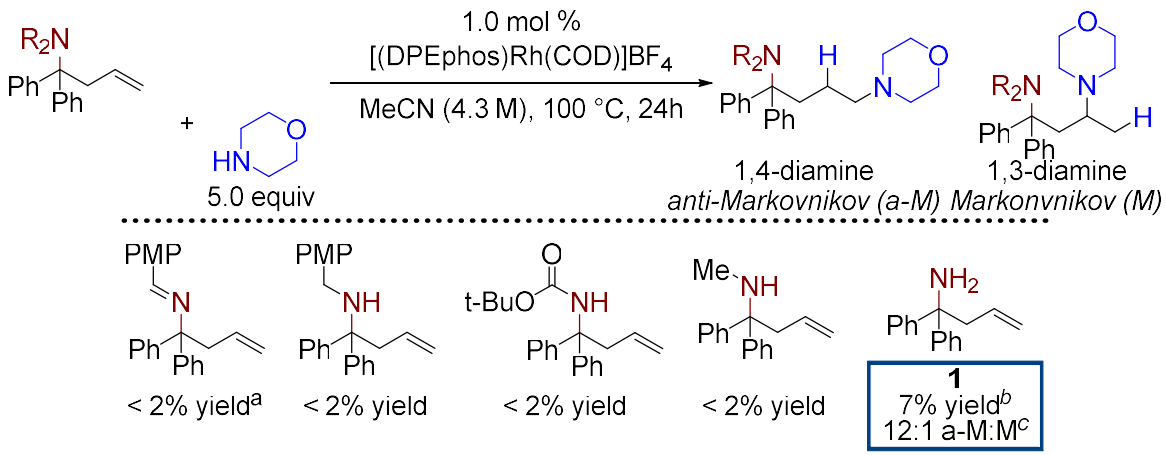
Instrumentation: ^{1}H NMR and ^{13}C NMR were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for ^{13}C) or a VXR-500 MHz spectrometer. Spectra were referenced using either $CDCl_3$ or C_6D_6 as solvents (unless otherwise noted) with the residual solvent peak as the internal standard (^{1}H NMR: δ 7.26 ppm, ^{13}C NMR: δ 77.36 ppm for $CDCl_3$ and ^{1}H NMR: δ 7.15 ppm, ^{13}C NMR: δ 128.62 ppm for C_6D_6). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) p (pentet,) m (multiplet,) and br (broad). Coupling constants, *J*, are reported in Hertz and integration is provided, along with assignments, as indicated. Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at University of Illinois at Urbana-Champaign. The glove box, MBraun LABmaster sp, was maintained under nitrogen atmosphere. Melting points were recorded on a Barnstead Thermolyne Mel-Temp® capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer using KBr salt plates.

Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade),

1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated stainless steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted. All amines (excluding homoallyl amine and dimethylamine) were distilled and degassed by the freeze-pump-thaw method and were stored under an atmosphere of nitrogen in glove box before use. Homoallylamine was obtained from Alfa Aesar and used as received**.** Dimethylamine solution was obtained from TCI and degassed by freezing, placing under vacuum, and refilling with nitrogen before thawing three times.

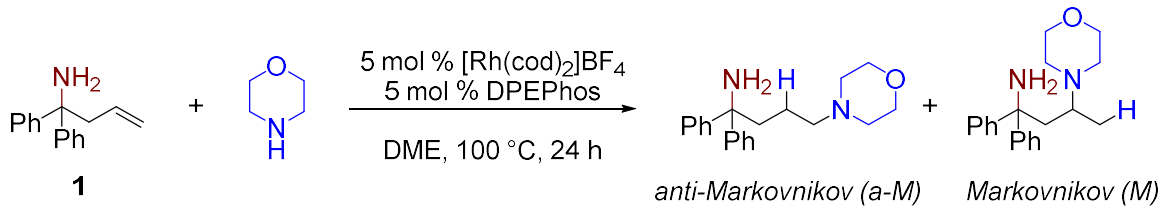
B. Select Optimization

Table 3.6. Directing group screen



In situ yield determined by gas chromatography relative to an internal standard, a-M:M determined by gas chromatography. [a]An aza-cope rearrangement yielded *N*-(1-(4-methoxyphenyl)but-3-ene-1-yl)-1,1-diphenylmethanimine. [b] yield determined by comparison to standard using gas chromatography. [c] ratio determined by gas chromatography.

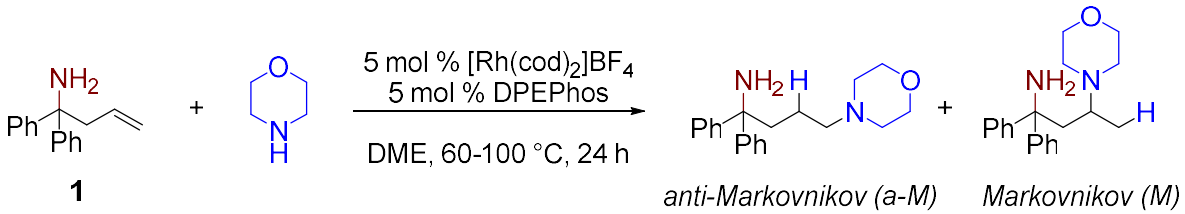
Table 3.7. Solvent screen[a]



Solvent	GC Yield (%)[b]	Selectivity (a-M:M)[c]
DME	92	45:1
MeCN	66	20:1
p-Dioxane	92	39:1
PhMe	88	41:1
THF	90	42:1

[a] 1.0 equiv. **1**, 5.0 equiv. morpholine, 1 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography.

Table 3.8. Temperature and time screen[a]



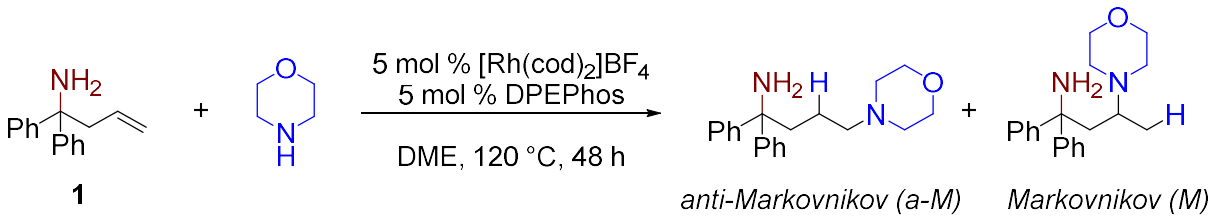
Temperature (°C)	Time (h)	GC Yield (%)[b]	Selectivity (a-M:M)[c]
40	12	3.5	31 : 1
	24	5.3	>20 : 1
	36	10	>20 : 1
	48	6.8	>20 : 1
80	12	74	63 : 1
	24	84	71 : 1

Table 3.8 (cont)

	36	96	75 : 1
	48	98	78 : 1
100	12	92	43 : 1
	24	-	42 : 1
	36	95	44 : 1
	48	95	47 : 1
120	12	84	25 : 1
	24	78	26 : 1
	36	88	26 : 1
	48	88	27 : 1

[a] 1.0 equiv. **1**, 5.0 equiv. morpholine, 1 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography.

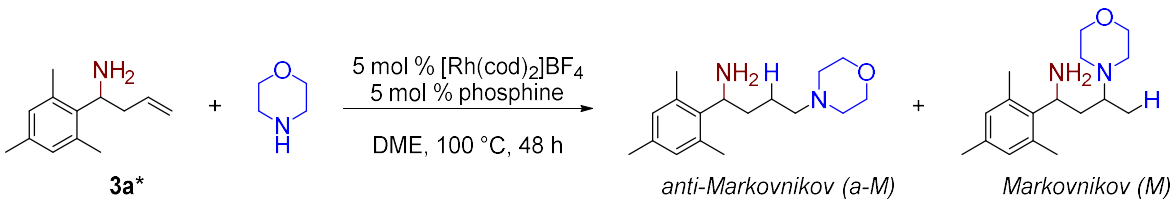
Table 3.9. Phosphine ligand screen[a]



Phosphine	**GC Yield (%)[b]**	**Selectivity (a-M:M)[c]**	**Bite Angle (°)**
DPEphos	88	45 : 1	108[d]
dppe	9.2	69 : 1	85[d]
dppp	16	48 : 1	95[d]
dppb	17	31 : 1	99[d]
dpppent	22	27 : 1	101[e]

[a] 1.0 equiv. **1**, 5.0 equiv. morpholine, 1 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography. [d] *Acc. Chem. Res.* **2011,** *34,* 895. [e] *J. Chem. Soc. Dalton Trans.,* **1999**, 1519.

Table 3.10. Phosphine ligand screen[a]

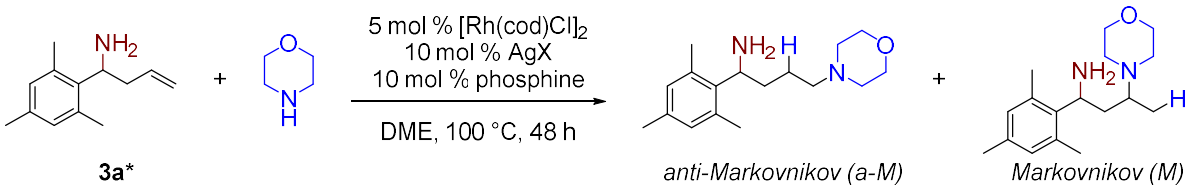


3a* *anti-Markovnikov (a-M)* *Markovnikov (M)*

Phosphine	GC Yield (%)[b]	Selectivity (a-M:M)[c,d]
dppm	<5	1.7 : 1
dppe	<5	2.7 : 1
dppp	68	14 : 1
dppb	41	5.2 : 1
dppf	<5	2.2 : 1
DPEphos	<5	1.2 : 1

[a] 1.0 equiv. **3a***, 5.0 equiv. morpholine, 1.5 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography. [d] See reference 28.

Table 3.11. Silver salt screen[a]



3a* *anti-Markovnikov (a-M)* *Markovnikov (M)*

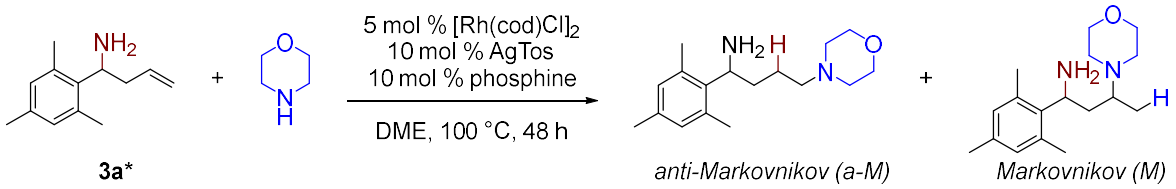
Silver Salt	GC Yield (%)[b]	Selectivity (a-M:M)[c]
AgTFA	55	10 : 1
$AgSbF_6$	66	9.0 : 1
$AgPF_6$	66	7.5 : 1
$AgBF_4$	70	8.9 : 1

Table 3.11 (cont)

AgOTs	69	12 : 1
AgOMs	59	10 : 1

[a] 1.0 equiv. **3a***, 5.0 equiv. morpholine, 1.5 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography.

Table 3.12. Morpholine equivalents screen

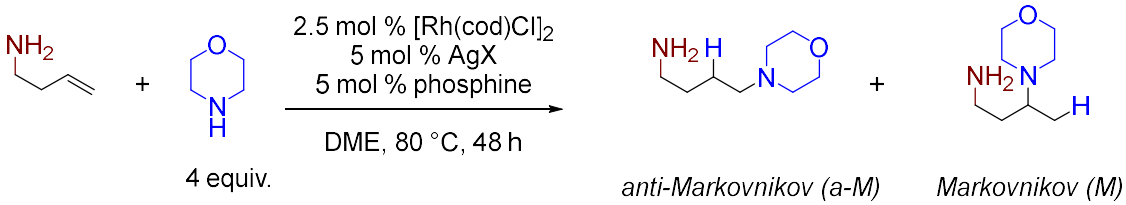


3a* *anti-Markovnikov (a-M)* *Markovnikov (M)*

Morpholine Equivalents	**GC Yield (%)**[b]	**Selectivity (a-M:M)**[c]
2	67	46 : 1
3	67	54 : 1
5	86	37 : 1
7	92	27 : 1

[a] 1.0 equiv. **3a***, 1.5 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] a-M:M determined by gas chromatography.

Table 3.13. Silver salt & phosphine screens for homoallylamine

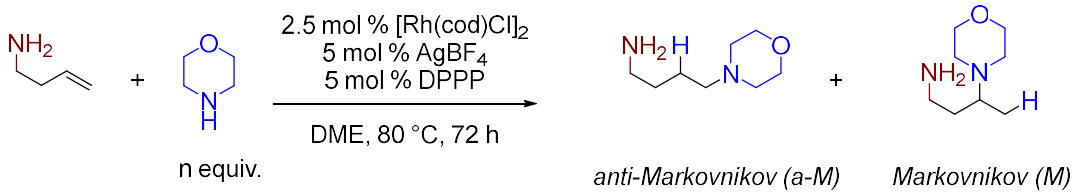


In situ yield determined by gas chromatography relative to an internal standard.

a-M:M determined by gas chromatography.

Phosphine	$AgBF_4$	$AgNO_2$	$AgSbF_6$
PPh_3	0.00	0.00	0.00
Dppe	0.00	0.00	0.00
Dppp	49.39	0.00	24.62
Dppb	7.07	0.00	0.45
Dpppent	0.37	0.62	0.00
DPEPhos	0.00	1.58	0.45

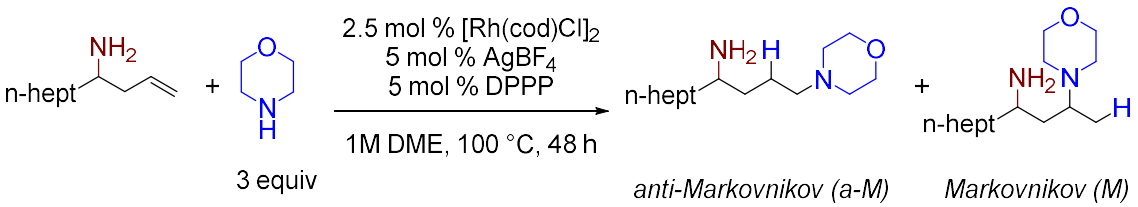
Table 3.14. Nucleophile equivalent screen for homoallylamine



Morpholine Equivalents	GC Yield (%)[a]	Selectivity (a-M:M)[b]
1	46	44 : 1
2	44	21 : 1
3	67	26 : 1
5	77	21 : 1
7	77	27 : 1

. [a] *In situ* yield determined by gas chromatography relative to an internal standard. [b] a-M:M determined by gas chromatography.

Table 3.15: Factors affecting the a-M:M ratio

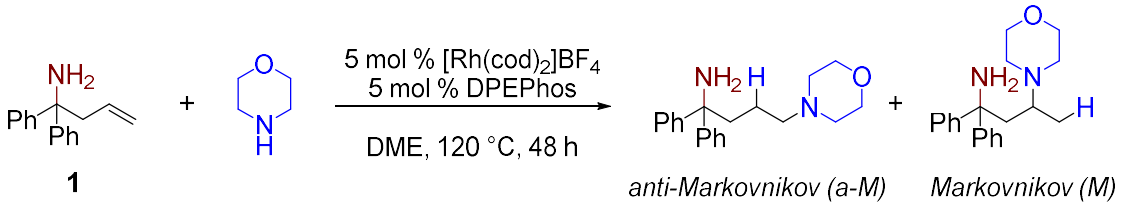


Modification	Conversion	Selectivity (a-M:M)[a]
None	Full	10 : 1
10% DPPP	Full	14.3 : 1
0.5M	Full	12 : 1
Prestirred catalyst components	Full	16.6 : 1
10% DPPP prestirred catalyst components	Full	17.4 : 1

[a] a-M:M determined by gas chromatography.

C. Control Experiments[a]

Table 3.16: Control experiments for Rh, Air sensitivity, and ligand requirement

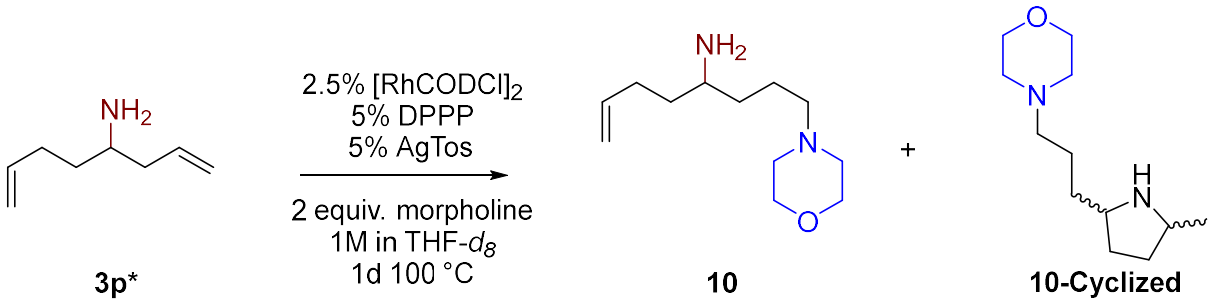


Trial	Variations from Standard Conditions	Yield (%)[b]
A	--	95[b]
B	Before heating open to air for 30 seconds at rt and stir.	3.2[b]
C	Schlenk flask (1 mmol scale.)	91[c]
D	No [Rh] catalyst added.	<1[b]
E	No DPEphos added.	4.1[b]

[a] 1.0 equiv. **1**, 5.0 equiv. morpholine, 1 M DME. [b] *In situ* yield determined by gas chromatography relative to an internal standard. [c] Isolated Yield.

D. Internal Competition Studies:

Competition Experiments:



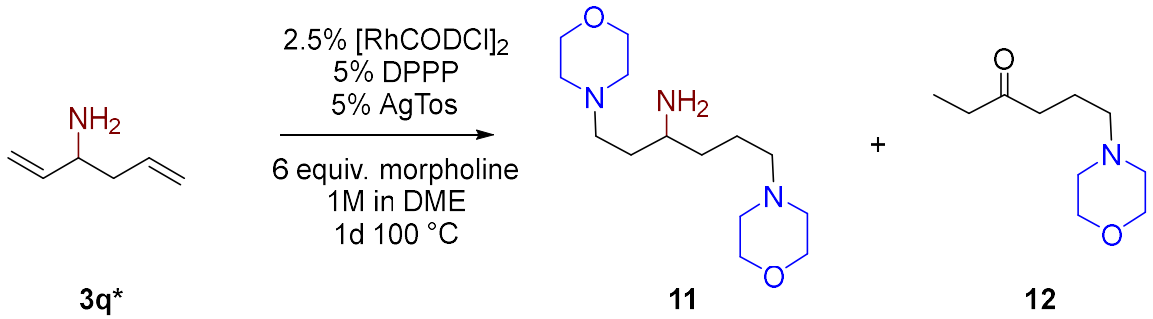
1-morpholinooct-7-en-4-amine

Prepared using general procedure **C** (*vide infra*) using: octa-1,7-dien-4-amine (**3p***) (31.6 mg, 0.25 mmol, 1.0 equiv) and morpholine ($0.43*10^2$ µL, 0.5 mmol, 2 equiv). The reaction was run at 80 °C for 24 h. The reaction volume was 0.3 mL THF-d_8.

Analysis of the crude reaction mixture by gas chromatography failed to separate the 1,4 diamine : 1,3 diamine. The minor diastereomer was not observed in the crude NMR. An NMR yield was obtained through addition of triphenylmethane as standard, showing a 36% yield of the desired product (identified through COSY, proton NMR, and GC-MS). The alkyl peaks consistently integrated higher than the vinyl peaks by 20-30% despite increasing d1 and all attempts at column chromatography. This was attributed to some formation of 4-(3-(5-methylpyrrolidin-2-yl)propyl)morpholine (cyclization of the primary amine onto the olefin) after hydroamination, which would have very similar chemical shifts. The remaining mass balance could not be identified.

R_f = 0.23(20% MeOH : 80% CH_2Cl_2).

^{1}H NMR: See spectrum for details.



3q* **11** **12**

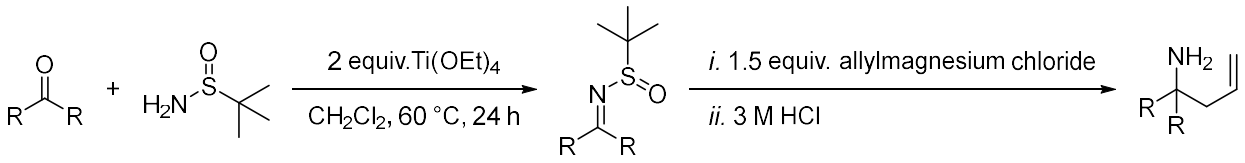
1,6-dimorpholinohexan-3-amine

Diene **3q*** (48 mg, 0.5 mmol, 1 equiv.) morpholine (259 uL, 3.0 mmol, 6 equiv.) $[Rh(cod)Cl]_2$ (6.16 mg, 0.0125 mmol, 2.5 mol%) AgOTs (6.98 mg, 0.025 mmol, 5 mol%) dppp (10.3 mg, 0.0250 mmol, 5 mol%) 24 h at 100 C. Difunctionalized product **11** obtained in 34% yield (45.7 mg.) 4.2:1 d.r.; 13:1 a-M:M; Rf = 0.31 (1:4 MeOH:DCM.) Ketone **12** was obtained in 16% yield (15.0 mg) as a yellow liquid.

^{1}H NMR (500 MHz, C_6D_6) δ 3.71 – 3.48 (m, 8H), 2.62 (ddd, *J* = 8.9, 5.6, 3.6 Hz, 1H), 2.32 – 2.15 (m, 10H), 2.12 – 1.98 (m, 1H), 1.97 – 1.67 (m, 1H), 1.62 – 1.53 (m, 2H), 1.54 – 1.44 (m, 1H), 1.43 – 1.32 (m, 1H), 1.23 – 1.13 (m, 1H), 0.89 (s, 2H), 0.79 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ 67.56, 67.18, 64.54, 59.37, 54.20, 52.28, 50.57, 33.00, 23.84, 9.38.

General Procedure for Substrate Synthesis I:



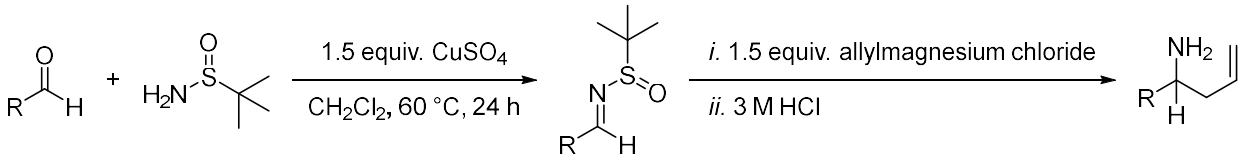
Ketone (x mmol, 1 equiv.), tert-butanesulfinamide (0.121g/mmol aldehyde, x mmol, 1 equiv.), titanium ethoxide (0.210 mL/mmol aldehyde, 2x mmol, 2 equiv.), CH_2Cl_2 (1mL/mmol aldehyde) were added to a 40 mL scintillation vial equipped with stir bar. The vial was sealed with a Teflon cap and heated to 60 °C for 24 h. After 24 h, the reaction vial was cooled to room temperature and quenched with 5 mL brine. The resulting slurry was filtered through celite and filter was washed 3 x 50 mL CH_2Cl_2. The filtrate was collected, dried with $MgSO_4$, filtered, and solvent was removed *in vacuo.* The crude reaction mixture was used without further purification.

To an oven dried 100 mL Schlenk flask equipped with stir bar and under N_2 was added the crude imine product. Dry THF (1 mL/mmol) was then added to the Schlenk flask and the mixture was cooled to 0 °C. Allylmagnesium chloride (1.76 mL/1mmol of 1.7 M solution, 1.5x mmol, 1.5 equiv.) was added dropwise, the resulting mixture was warmed to room temperature, and stirred overnight.

The mixture was cooled to 0 °C and quenched with the dropwise addition of ~15 mL 3 M HCl. The contents of the Schlenk flask were warmed to room temperature and stirred for 2 hours. The crude solution was then basified to pH=12 with 5 M NaOH, the slurry was filtered and the solid was washed with 3 x 75 mL $CHCl_3$. The organic layers were combined and washed with 2 x 75 mL 5 M NaOH. The organic layers were dried with $MgSO_4$, filtered, and solvent was removed

in vacuo. Purification of the crude homoallyl amine by column chromatography afforded pure homoallyl amine.

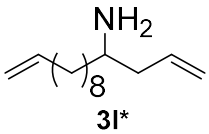
General Procedure for Substrate Synthesis II:



Aldehyde (x mmol, 1 equiv.), tert-butanesulfinamide (0.121 g/mmol aldehyde, x mmol, 1 equiv.), anhydrous copper sulfate (0.160 g/mmol aldehyde, 1.5x mmol, 1.5 equiv.), and 1 mL CH_2Cl_2 /mmol aldehyde were added to a 40 mL scintillation vial equipped with stir bar. The vial was sealed with a Teflon cap and heated to 60 °C for 24 h. After 24 h, the reaction vial was cooled to room temperature, filtered through celite, and solvent was removed *in vacuo.* The crude reaction mixture was used without further purification.

To an oven dried 100 mL Schlenk flask equipped with stir bar and under N_2 was added the crude imine product. Dry THF (15 mL) was then added to the Schlenk flask and the mixture was cooled to 0 °C. Allylmagnesium chloride (1.76 mL/mmol aldehyde of 1.7 M solution, 1.5x mmol, 1.5 equiv.) was added dropwise, the resulting mixture was warmed to room temperature, and stirred overnight.

The mixture was cooled to 0 °C and quenched with the dropwise addition of ~15 mL 3 M HCl. The contents of the Schlenk flask were warmed to room temperature and stirred for 2 hours. The crude solution was then basified to pH=12 with 5 M NaOH, the slurry was filtered and the solid was washed with 3 x 75 mL $CHCl_3$. The organic layers were combined and washed with 2 x 75 mL 5 M NaOH. The organic layers were dried with $MgSO_4$, filtered, and solvent was removed *in vacuo.* Purification of the crude homoallyl amine by silica gel afforded pure homoallyl amine.



3l*

tetradeca-1,13-dien-4-amine

Prepared according to standard procedure **(II)** with the following modifications: 4.0 mL 10-undecylenic aldehyde (20 mmol, 1 eq) was used, and 20 mL allylmagnesium chloride solution (1.7 M, 34 mmol, 1.7 eq) was added to the stirring solution of the crude sulfonimine dropwise at -78 °C. After quenching, deprotection, workup, and a column per the standard procedure (150 mL SiO_2, 5 cm column, packed, loaded, and eluted using 2% MeOH/ 98% DCM) the crude oil was distilled to remove further impurities. The compound distilled at 177.8-185.6 °C at 1 torr, and crystallized upon standing to afford **3l*** (1.43g, 5.72 mmol, 28.6% yield) as a white crystalline solid (mp 50.0-52.1 °C).

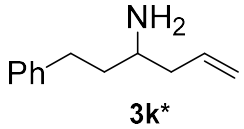
R_f = 0.39 (1 : 9 MeOH : DCM)

^{1}H NMR (C_6D_6, 500 MHz) δ 8.66 (br s, 2H), 5.89-5.73 (m, 2H), 5.19-5.11 (m, 2H), 5.05 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.01-4.96 (m, 1H), 2.95 (p, *J* = 6.4 Hz, 1H) ppm

^{13}C NMR (C_6D_6 126 MHz) δ 139.81, 115.14, 67.82, 60.03, 54.84, 52.10, 39.67, 37.03, 34.81, 30.90, 30.70, 30.53, 30.14, 29.94, 27.23, 24.25 ppm.

IR (salt plate) 3406 (w, br), 3077 (m, br), 2980 (s, br), 2927 (s, br), 2853 (s, s), 1639 (m, s), 1602 (m, s) cm^{-1}

HRMS (ESI-TOF) *m/z:* [M + H^+] calculated for $C_{14}H_{27}N$, 210.2222; found, 210.2228



3k*

1-phenylhex-5-en-3-amine

Prepared according to standard procedure **(CuSO4)** with the following modifications: 2.54 mL trans-cinnamaldehyde (20 mmol, 1 eq) was used, and 20 mL allylmagnesium chloride solution (1.7 M, 34 mmol, 1.7 eq) was added to the stirring solution of the crude sulfonimine dropwise at -78 °C. After quenching, workup, and a column per the standard procedure (150 mL SiO_2, 5 cm

column, packed, loaded, and eluted using 30% Et_2O / 70% DCM and a flush of 10% MeOH / 90% DCM) to afford **3k*** (0.972g, 5.54 mmol, 27.7% yield) as a pale yellow oil.

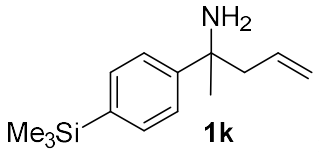
R_f = 0.42 (1 : 9 MeOH : DCM)

^{1}H NMR (C_6D_6, 500 MHz) 7.14 – 6.98 (m, 5H), 5.56 (dddd, *J* = 16.1, 11.0, 7.8, 6.6 Hz, 1H), 5.56 (dddd, *J* = 16.1, 11.0, 7.8, 6.6 Hz, 1H), 2.56 (ddd, *J* = 13.6, 10.1, 5.4 Hz, 1H), 2.51 – 2.39 (m, 2H), 1.98 – 1.89 (m, 1H), 1.80 – 1.70 (m, 1H), 1.50 (dddd, *J* = 13.4, 10.1, 6.5, 4.5 Hz, 1H), 1.39 – 1.27 (m, 1H), 1.05 – 0.91 (br s, 2H) ppm

^{13}C NMR (C_6D_6 126 MHz) δ 143.44, 136.88, 129.34, 129.23, 126.60, 117.57, 50.95, 43.91, 40.28, 33.47.

IR (salt plate) 3370 (w, br), 3290 (w, br), 3062 (m, s), 3026 (s, s), 3000 (m, s), 2957 (m, s), 2921 (s, br), 2856 (s, br), 1639 (m, s), 1603 (m, s), 1495 (s, s), 1454 (s, s), 1438 (m, s) cm^{-1}

HRMS (ESI-TOF) *m/z:* [M + H^+] calculated for $C_{12}H_{17}N$, 176.1439; found, 176.1445



1k

2-(4-(trimethylsilyl)phenyl)pent-4-en-2-amine

Ref: http://pubs.acs.org/doi/pdf/10.1021/jo01083a605

Prepared using reference above:

To a 250 mL round-bottom flask equipped with a stirbar was dispensed 25g (125 mmol) para-bromoacetophenone, 7.2 mL ethylene glycol (125 mmol), 100 mg para-toluenesulfonic acid, and 125 mL benzene. This was then equipped with a Dean-Stark trap, and refluxed for 26 hours. The benzene was then removed *in-vacuo* and the product removed from the para-toluenesulfonic acid

via distillation (0.1 torr, 90-100 °C) to afford 27 grams (88% yield) of predominantly 2-(4-Bromophenyl)-2-methyl-l,3-dioxolane which was used without further purification.

In a 2-necked roundbottom flask equipped with a reflux condenser and a septum 0.255g (1.05 equiv) magnesium turnings were suspended in 10 mL dry tetrahydrofuran. 2.431g (1 eq) of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane was dissolved in 5 mL of dry tetrahydrofuran. The flask was heated to reflux, and at reflux the dioxolane solution was added dropwise over the course of 10 minutes. The reaction was then refluxed for 2 hours, cooled to room temperature, and 1.27 mL (1 eq) TMSCl was added dropwise. This was stirred for 12 hours, then transferred dropwise into a stirring ice-cold solution of 50% 3M HCl in THF and stirred to room temperature for 18 hours. GC-MS analysis showed little remaining acetal, and the reaction was extracted with 3x30 mL Et_2O, dried using $MgSO_4$, filtered, and concentrated *in-vacuo*. The crude material was used without further purification.

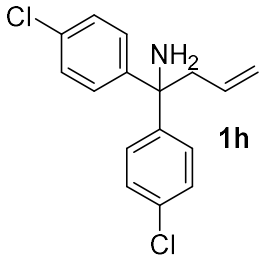
This material was then subjected to the usual aldehyde -> homoallylamine procedure, and was purified via column chromatography (5 cm column, 150 mL SiO_2, packed and loaded using 1% MeOH / 99% DCM, eluted with 1% MeOH / DCM to 3 % MeOH / DCM) to afford **1k** (596 mgs, 2.72 mmol, 27.2% yield) as a pale yellow oil

R_f = 0.47 (1 : 9 MeOH : DCM)

^{1}H NMR (C_6D_6, 500 MHz) δ 7.52 – 7.44 (m, 4H), 5.55 (dddd, *J* = 17.0, 10.2, 8.0, 6.7 Hz, 1H), 5.00 – 4.89 (m, 2H), 2.45 (ddt, *J* = 13.6, 6.8, 1.3 Hz, 1H), 2.25 (ddt, *J* = 13.5, 8.0, 0.8 Hz, 1H), 1.28 (s, 3H), 1.19 (s, 2H), 0.24 (s, 9H) ppm

^{13}C NMR (C_6D_6 125 MHz) δ 150.74, 138.13, 135.65, 134.12, 125.90, 118.72, 55.17, 50.57, 31.79, -0.36 ppm
IR (salt plate) 3369 (w, br), 3292 (w, br), 3073 (m, s), 3013 (m, s), 2957 (s, br), 2926 (m, br), 1639 (w, s), 1599 (m, s), 1248 (s, s), 839 (s, br) cm^{-1}

HRMS (ESI-TOF) *m/z:* [M + H^+] calculated for $C_{14}H_{23}NSi$: 234.1678; found, 234.1678



1,1-bis(4-chlorophenyl)3-buten-1-amine

To an oven-dried 250 mL 3-necked round-bottom flask equipped with a septum, reflux condenser, stirbar, and gas dispersion tube was added 5.00 grams (20 mmol, 1 eq) 4,4' dichlorobenzophenone. The flask was cycled between vacuum and nitrogen three times before it was charged with 90 mL dry, air free THF. The flask was then cooled to 0°, and 3.56 mL (1.8 equivalents, 32.4 mmol) freshly distilled $TiCl_4$ was added dropwise through the septum. (Caution: vigorous reaction). This was then stirred for 15 minutes at 0 °C. Ammonia was bubbled through the gas dispersion tube for 20 minutes slowly into the 0 °C reaction. (Caution: A precipitate forms which can clog the dispersion tube). The color rapidly changed between yellow, green, and brown. The septum and gas dispersion tube were replaced with glass stoppers, and the reaction allowed to stir at room temperature for 48 hours. The reaction was then cooled to 0 °C, and 47 ml (4 eq) 1.7M allylmagnesium chloride in THF solution was cannulated in over 15 minutes (Caution: Significant amounts of gas is evolved during this step.) The reaction was stirred at room temperature for another 24 hours, when another 1 equivalent (11.5 mL) of allylmagnesium chloride in THF was added at room temperature and the reaction allowed to stir an additional 24 hours. The reaction was quenched by the slow addition of 70 mL saturated Na_2CO_3 solution. This was stirred for 30 minutes, filtered through Celite, and rinsed with 4 100 mL portions of ethyl acetate. The mixture was then transferred to a separatory funnel, and the organic layer extracted using 2 x 150 mL deionized water. The organic layers were dried with $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude homoallylamine was purified via column chromatography (7 cm column, 300 mL SiO_2, packed and loaded using 100% dichloromethane, eluted using 100% dichloromethane to 2% MeOH / 98% dichloromethane) to afford **1h** (3.68g, 12.6 mmol, 63% yield) as a pale yellow oil

R_f = 0.88 (1 : 9 MeOH : DCM)

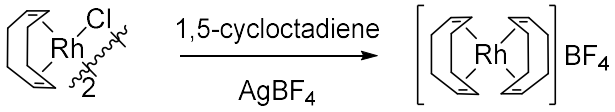
^{1}H NMR ($CHCl_3$, 500 MHz): δ 7.30 (d, *J* = 9.1 Hz, 4H), 7.26 (d, *J* = 9.1 Hz, 4H), 5.47 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.16 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.13 (td, *J* = 10.1, 1.1 Hz, 1H), 1.95 (d, *J* = 7.1 Hz, 2H) ppm

^{13}C NMR (C_6D_6, 126 MHz): 147.41, 134.48, 133.14, 129.02, 128.97, 119.96, 60.19, 48.07.

IR (salt plate) 3373 (w, br), 3309 (w, br), 3076 (m, br), 3032 (w, s), 3007 (w, s), 2978 (m, s), 2929 (m, br), 1661 (m, br), 1638 (m, s), 1590 (s, s), 1489 (s, br), 1441 (m, s) cm^{-1}

Catalyst Synthesis

$[Rh(COD)]_2BF_4$

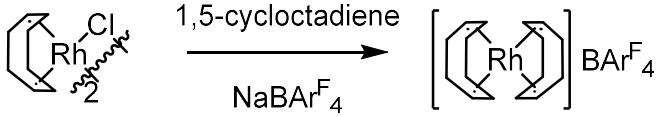


$[Rh(cod)Cl]_2$ (990 mg, 2.0 mmol, 1.0 equiv) and silver tetrafluoroborate ($9.0*10^2$ mg, 4.6 mmol, 2.3 equiv) were added to a 100 mL Schlenk flask. The flask was capped with a rubber septa placed under N2. The solids were dissolved in 15 mL CH_2Cl_2 that was added through the septa. 1,5-cyclooctadiene (740 µL, 6.0 mmol, 3.0 equiv) was then added via the septa. The Schlenk flask contents were stirred for 20 minutes and the contents were then filtered through celite under air. The celite was washed with 2 x 20 mL THF and the organic layer was reduced to approximantly 8 mL *in vacuo*. The precipitated solid was collected by filtration, wash with 2 x 5 mL THF and 2 x 5 mL diethyl ether, and dried under vacuum to obtain the product in 55% yield ($9.0*10^2$ mg, 2.2 mmol.)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (s, 8H), 2.68 – 2.55 (m, 8H), 2.55 – 2.42 (m, 8H) ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -153.64 ppm.

$[Rh(COD)]_2BAr_4^F$



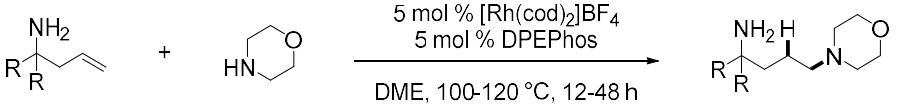
To a 50 mL oven dried schlenk flask was added $[Rh(cod)Cl]_2$ (490 mg, 1.0 mmol, 1.0 equivalents), sodium tetrakis-3,5-bistrifluoromethylphenyl borate (1.8 g, 2.0 mmol, 2.0 equiv), and 20 mL dichloromethane in a nitrogen filled glovebox. This was sealed with a septum, removed, placed under nitrogen on a Schlenk line, and 1,5-cyclooctadiene (370 μL, 3.0 mmol, 3.0 equivalents) were added. The dark orange suspension was stirred for 20 minutes, transferred to a round bottom flask with 20 mL dichloromethane and 20 mL hexanes, the solvent removed by rotary evaporation until the solid had clearly precipitated from solution, and then the burnt orange solid purified via filtration and 3x20 mL washes of hexanes to afford 2.1 g (1.8 mmol, 89% yield) of $[Rh(COD)_2]BAr_4^F$.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 8H), 7.54 (s, 4H), 5.11 (s, 8H), 2.43 (s, 16H) ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -62.75 (s) ppm.

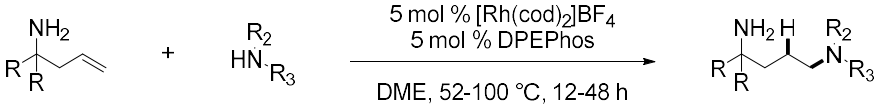
Experimental Procedure, Isolation, and Characterization

General Procedure for Hydroamination A:



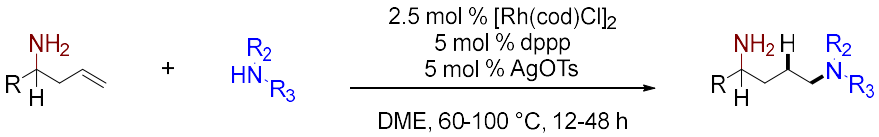
$[Rh(COD)_2]BF_4$ (10. mg, 0.025 mmol, 5.0 mol %), DPEphos (14 mg, 0.025 mmol, 5.0 mol %), DME (330 μL), and homoallyl amine (0.50 mmol, 1.0 equiv) were added to a 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (0.5-3.5 mmol, 1-7 equiv). The resulting solution was sealed with Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 120 °C. After 48 h, the reaction vial was cooled to room temperature and excess morpholine was removed *in vacuo* at 60 °C. Purification of the crude diamine by silica gel afforded pure diamine.

General Procedure for Hydroamination B:

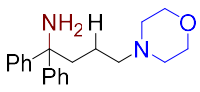


[Rh(COD) $_2$] BAr_4^F (30. mg, 0.025 mmol, 5.0 mol %), DPEphos (27 mg, 0.050 mmol, 10. mol %), DME (330 µL), and homoallyl amine (0.5 mmol, 1.0 equiv) were added to a 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added amine nucleophile (0.5-3.5 mmol, 1-7 equiv). The resulting solution was sealed with Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 100 °C. After 48 h, the reaction vial was cooled to room temperature and excess amine was removed *in vacuo* at 60 °C. Purification of the crude diamine by silica gel chromatography afforded pure diamine.

General Procedure for Hydroamination C:



[Rh(cod)Cl]$_2$ (6.2 mg, 0.013 mmol, 2.5 mol %), dppp (10. mg, 0.025 mmol, 5.0 mol %), silver *para*-toluenesulfonamide (7.0 mg, 0.025 mmol, 5.0 mol %), DME (330 µL) and homoallyl amine (0.50 mmol, 1.0 equiv) were added to an 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added amine nucleophile (0.50-3.5 mmol, 1.0-7.0 equiv). The resulting solution was sealed with Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 100 °C. After 48 h, the reaction vial was cooled to room temperature and excess amine nucleophile was removed *in vacuo* at 60 °C. Purification of the crude diamine by silica gel chromatography afforded pure diamine.



2a

4-morpholino-1,1-diphenylbutan-1-amine (2a):

Prepared using general procedure **A** using: 1,1-diphenyl-but-3-en-1-amine (**1**) (110 mg, 0.51 mmol, 1.0 equiv) and morpholine (220 µL, 2.5 mmol, 5.0 equiv). The reaction was run at 100 °C for 12 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **2a** (140 mg, 0.44 mmol, 87% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

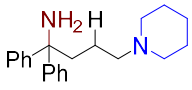
R_f = 0.33 (10% MeOH : 90% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 7.3 Hz, 4H), 7.28 (t, J = 7.7 Hz, 4H), 7.23 – 7.16 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 4.7 Hz, 4H), 2.39 – 2.21 (m, 8H), 1.80 (br s, 2H), 1.47 – 1.35 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 148.95, 128.33, 126.78, 126.54, 67.20, 61.19, 59.41, 53.94, 40.36, 21.53 ppm.

IR (salt plate): 3368 (w, br), 3299 (w, br), 3084 (w, s), 3057 (m, s), 3022 (m, s), 2954 (s, br), 2854 (s, s) 2807 (s, s), 2765 (m, s), 1676 (w, br), 1598 (m, s), 1492 (m, s), 1446 (s, s), 1119 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{20}H_{27}N_2O$, 311.2123; found, 311.2126.



2b

1,1-diphenyl-4-(piperidin-1-yl)butan-1-amine (2b):

Prepared using general procedure **B** using: 1,1-diphenyl-but-3-en-1-amine (**1**) (110 mg, 0.50 mmol, 1.0 equiv) and piperidine (250 μL, 2.5 mmol, 5.0 equiv). The reaction was run at 100 °C for 12 h.

Analysis of the crude reaction mixture by gas chromatography determined a >20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **2b** (140 mg, 0.45 mmol, 90.% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

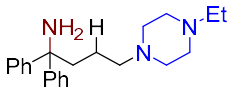
R_f = 0.14 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.1 Hz, 4H), 7.30 – 7.22 (m, 4H), 7.17 (t, J = 7.2 Hz, 2H), 2.26 (t, J = 7.6 Hz, 6H), 2.23 – 2.14 (m, 2H), 1.77 (br s, 2H), 1.52 (p, J = 5.5 Hz, 4H), 1.45 – 1.32 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.07, 128.30, 126.82, 126.47, 61.21, 59.93, 54.87, 40.77, 26.23, 24.74, 21.99 ppm.

IR (salt plate): 3369 (w, br), 3298 (w, br), 3084 (w, s), 3057 (m, s), 3022 (m, s), 2933 (s, br), 2852 (m, s), 2799 (m, s), 2762 (m, br), 1669 (w, br), 1598 (m, s), 1492 (m, s), 1467 (m, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{21}H_{29}N_2$, 309.2331; found, 309.2331.



2c

4-(4-ethylpiperazin-1-yl)-1,1-diphenylbutan-1-amine (2c):

Prepared using general procedure **B** using: 1,1-diphenyl-but-3-en-1-amine (**1**) (110 mg, 0.50 mmol, 1.0 equiv) and 1-ethyl piperazine (320 µL, 2.5 mmol, 5.0 equiv). The reaction was run at 80 °C for 72 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **2c** (130 mg, 0.37 mmol, 74% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

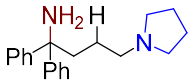
R_f = 0.14 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, J = 8.3, 1.1 Hz, 4H), 7.31 – 7.24 (m, 4H), 7.18 (t, J = 7.3 Hz, 2H), 2.62 – 2.25 (m, 12H), 2.25 – 2.18 (m, 2H), 1.87 (br s, 2H), 1.45 – 1.31 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.10, 128.38, 126.87, 126.56, 61.26, 59.15, 53.48, 53.13, 52.64, 40.65, 21.97, 12.29 ppm.

IR (salt plate): 3366 (w, br), 3290 (w, br), 3084 (w, s), 3057 (m, s), 3023 (m, s), 2966 (s, s), 2944 (s, br), 2875 (m, s), 2810 (s, br), 2770 (s, s), 1674 (w, br), 1598 (m, s), 1492 (m, s), 1465 (m, s), 1446 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{22}H_{32}N_3$, 338.2596; found, 338.2595.



2d

1,1-diphenyl-4-(pyrrolidin-1-yl)butan-1-amine (2d):

Prepared using general procedure **B** using: 1,1-diphenyl-but-3-en-1-amine (**1**) (110 mg, 0.50 mmol, 1.0 equiv) and pyrrolidine (120 µL, 1.5 mmol, 3.0 equiv). The reaction was run at 60 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **2d** ($1.0*10^2$ mg, 0.34 mmol, 67% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

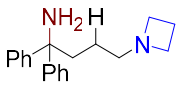
R_f = 0.12 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 8.3 Hz, 4H), 7.32 – 7.25 (m, 4H), 7.23 – 7.16 (m, 2H), 2.51 – 2.37 (m, 6H), 2.31 – 2.19 (m, 2H), 2.04 (br s, 2H), 1.80 – 1.71 (m, 4H), 1.45 (tt, J = 8.9, 6.0 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.07, 128.36, 126.88, 126.54, 61.26, 57.06, 54.47, 40.77, 24.09, 23.70 ppm.

IR (salt plate): 3366 (w, br), 3297 (w, br), 3084 (m, s), 3057 (m, s), 3023 (m, s), 2956 (s, br), 2874 (s, s), 2786 (s, br), 1598 (m, s), 1492 (m, s), 1459 (m, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{20}H_{27}N_2$, 295.2174; found, 295.2173.



2e

4-(azetidin-1-yl)-1,1-diphenylbutan-1-amine (2e):

Prepared using general procedure **B** using: 1,1-diphenyl-but-3-en-1-amine (**1**) (110 mg, 0.50 mmol, 1.0 equiv) and azetidine (170 µL, 2.5 mmol, 5.0 equiv). The reaction was run at 52 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **2e** (120 mg, 0.41 mmol, 82% yield of the major isomer, average of two runs) as a beige crystalline solid (m.p. 61-64 °C).

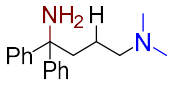
R_f = 0.07 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 7.4 Hz, 4H), 7.12 (t, J = 7.7 Hz, 4H), 7.02 (t, J = 7.3 Hz, 2H), 2.92 (t, J = 6.8 Hz, 4H), 2.25 – 2.14 (m, 4H), 1.78 (p, J = 6.9 Hz, 2H), 1.52 (br s, 2H), 1.33 – 1.13 (m, 2H) ppm.

^{13}C NMR (125 MHz, C_6D_6): δ 150.47, 128.81, 127.68, 126.86, 61.57, 60.96, 55.83, 41.22, 23.18, 18.52 ppm.

IR (salt plate): 3364 (w, br), 3288 (w, br), 3084 (w, s), 3057 (m, s), 3022 (m, s), 2994 (m, s), 2953 (s, s), 2926 (s, s), 2870 (m, s), 2816 (s, br), 1597 (m, br), 1492 (m, s), 1445 (m, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{19}H_{25}N_2$, 281.2018; found, 281.2011.



2f

***N*^{4},*N*^{4}-dimethyl-1,1-diphenylbutane-1,4-diamine (2f):**

Prepared using general procedure **B** using: 1,1-diphenylbut-3-en-1-amine (**1**) (91 mg, 0.41 mmol, 1 equiv) and dimethylamine (2 mL at 2.0 M solution in THF, 4.0 mmol, 10. equiv). The reaction was run at 120 °C for 48 h. This reaction was run in a 15 mL heavy-walled schlenk tube behind a blast shield. Efforts to scale this reaction under general conditions were unreliable as the septa of

the vial often failed. **Reactions under pressure can be a significant hazard if appropriate safety precautions, such as a blast shield, are not taken**.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 10% MeOH : 2.5% sat. NH_4OH : 87.5% $CHCl_3$ as the eluent) to afford **2f** (88 mg, 0.33 mmol, 80.% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

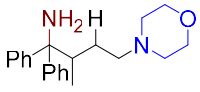
R_f = 0.08 (1:4 MeOH/DCM)

^{1}H NMR (C_6D_6, 500 MHz): δ 7.37 (dd, J = 8.4, 1.2 Hz, 4H), 7.12 (t, J = 7.85 Hz, 4H), 7.02 (tt, J = 7.3, 1.1 Hz, 2H), 2.21 – 2.15 (m, 2H), 2.10 (t, J = 6.7 Hz, 2H), 2.02 (s, 6H), 1.46 – 1.10 (m, 4H) ppm.

^{13}C NMR (C_6D_6 125 MHz): δ 150.47, 128.80, 127.67, 126.88, 61.54, 60.70, 46.10, 41.02, 23.31 ppm.

IR (salt plate): 3367 (w, br), 3300 (w, br), 3084 (w, s), 3058 (m, s), 3022 (m, s), 2942 (s, br), 2856 (m, s), 2814 (s, s), 2765 (s, br), 2719 (w, s) 1598 (m, s), 1492 (m, s), 1456 (m, s), 1446 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{18}H_{25}N_2$: 269.2018; found, 269.2019.



2j

2-methyl-4-morpholino-1,1-diphenylbutan-1-amine (2j):

Prepared using general procedure **A** using: 2-methyl-1,1-diphenylbut-3-en-1-amine (140 mg, 0.61 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 5.8 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **2j** (140 mg, 0.44 mmol, 73% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

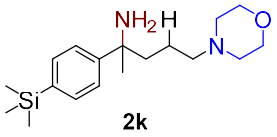
R_f = 0.53 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 7.8 Hz, 2H), 7.25 (t, J = 8.1 Hz, 4H), 7.14 (t, J = 7.3 Hz, 2H), 3.70 (t, J = 4.7 Hz, 4H), 2.82 – 2.69 (m, 1H), 2.43-2.28 (m, 6H), 1.76 – 1.48 (m, 3H), 1.17 – 1.01 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 148.02, 147.93, 128.24, 128.23, 126.73, 126.61, 126.21, 126.10, 67.22, 64.41, 57.81, 54.14, 38.23, 29.00, 15.04 ppm.

IR (salt plate): 3384 (w, br), 3317 (w, br), 3084 (w, s), 3056 (m, s), 3030 (m, s), 3021 (m, s), 2957 (s, br), 2854 (s, s), 2807 (s, s), 2766 (m, s), 1597 (m, s), 1491 (m, s), 1447 (s, s), 1118 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [$M+H^+$] calculated for $C_{21}H_{29}N_2O$, 325.2280; found, 325.2278.



2k

5-morpholino-2-(4-(trimethylsilyl)phenyl)pentan-2-amine (2k):

Prepared using general procedure **A** using: 2-(4-(trimethylsilyl)phenyl)pent-4-en-2-amine (**2k***) (120 mg, 0.52 mmol, 1.0 equiv) and morpholine (260 µL, 3.0 mmol, 6.0equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 16:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography

(using 70 mL of silica in a 3 cm diameter column, with 1% sat. NH_4OH : 99% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% sat. NH_4OH : 99% $CHCl_3$ as the eluent) to afford **2k** (130 mg, 0.40 mmol, 77% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

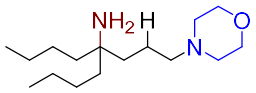
R_f = 0.09 (1:9 MeOH/DCM)

^{1}H NMR (C_6D_6, 500 MHz): δ 7.52 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 3.56 (t, J = 4.5 Hz, 4H), 2.06 (t, J = 4.5 Hz, 4H), 2.02 (td, J = 7.3, 1.4 Hz, 2H), 1.74 (ddd, J = 13.6, 11.8, 4.5 Hz, 1H), 1.57 (ddd, J = 13.5, 11.8, 4.7 Hz, 1H), 1.37-1.27 (m, 4H), 1.19 (tdd, J = 11.7, 9.0, 6.0 Hz, 3H), 0.23 (s, 9H) ppm.

^{13}C NMR (C_6D_6 126 MHz): δ 150.81, 138.10, 134.12, 125.89, 67.73, 60.01, 55.50, 54.67, 43.56, 32.77, 22.43, -0.38 ppm.

IR (salt plate): 3364 (w, br), 3291 (w, br), 3068 (m, s), 3013 (m, s), 2955 (s, br) 2854 (s, s,), 2806 (s, s), 2764 (s, s), 1684 (m, s), 1599 (m, s),1248 (s, s), 1119 (s, s), 840 (br s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{18}H_{33}N_2OSi$: 321.2362; found, 321.2361.



2l

5-(3-morpholinopropyl)nonan-5-amine (2l):

Prepared using general procedure **A** using: 5-allylnonan-5-amine (74 mg, 0.40 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 7.0 equiv). The reaction was run at 120 °C for 72 h.

Analysis of the crude reaction mixture by gas chromatography determined a 5:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **2l** (81 mg, 0.30 mmol, 74% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

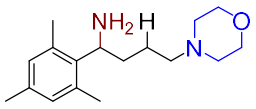
R_f = 0.11 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (t, J = 4.6 Hz, 4H), 2.45 (br s, 4H), 2.35 – 2.26 (m, 2H), 1.51 – 1.41 (m, 2H), 1.37 – 1.17 (m, 16H), 0.90 (t, J = 7.1 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 67.29, 60.07, 54.15, 53.30, 40.30, 38.10, 26.01, 23.73, 21.05, 14.45 ppm.

IR (salt plate): 3360 (w, br), 3284 (w, br), 2956 (s, br), 2931 (s, br), 2858 (s, s), 2807 (m, s), 2764 (m, s), 1560 (w, br), 1119 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{35}N_2O$, 271.2754; found, 271.2749.



3a

1-mesityl-4-morpholinobutan-1-amine (3a):

Prepared using general procedure **C** using: 1-mesitylbut-3-en-1-amine (**3a***) (94 mg, 0.50 mmol, 1.0 equiv) and morpholine (3.0*10^2 μL, 3.5 mmol, 7.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 12:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3a** (91 mg, 0.33 mmol, 66% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

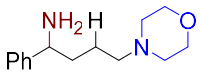
R_f = 0.10 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2H), 4.38 (t, J = 7.5 Hz, 1H), 3.69 (t, J = 4.7 Hz, 4H), 2.39 (m, 10H), 2.33 (dd, J = 8.2, 6.8 Hz, 2H), 2.23 (s, 3H), 1.88 – 1.76 (m, 2H), 1.72 – 1.54 (m, 3H), 1.44 – 1.27 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.77, 136.09, 135.95, 130.4, 67.23, 59.13, 53.98, 52.07, 34.48, 24.60, 21.44, 20.88 ppm.

IR (salt plate): 3369 (w, br), 3300 (w, br), 2955 (s, br), 2923 (s, br), 2856 (s, br), 2808 (s, br), 1676 (m, br), 1611 (m, s), 1456 (m, br), 1118 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{17}H_{29}N_2O$, 277.2280; found, 277.2284.



3b

4-morpholino-1-phenylbutan-1-amine (3b):

Prepared using general procedure **C** using: 1-phenylbut-3-en-1-amine (**3b***) (74 mg, 0.50 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ μL, 3.5 mmol, 7.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 15:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3b** (110 mg, 0.45 mmol, 90.% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

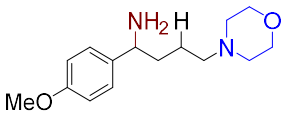
R_f = 0.16 (15% MeOH : 85% CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H), 3.89 (t, J = 6.9 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 2.38 (br s, 4H), 2.31 (t, J = 7.6 Hz, 2H), 1.77 – 1.60 (m, 2H), 1.58-1.45 (m, 3H), 1.45 – 1.30 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 146.68, 128.68, 127.16, 126.51, 67.20, 59.12, 56.48, 53.94, 37.60, 23.80 ppm.

IR (salt plate): 3368 (w, br), 3297 (w, br), 3060 (w, s), 3025 (m, s), 2940 (s, br), 2853 (s, s), 2807 (s, s), 1602 (m, s), 1492 (m, s), 1118 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1814.



3c

1-(4-methoxyphenyl)-4-morpholinobutan-1-amine (3c):

Prepared using general procedure **C** using: 1-(4-methoxyphenyl)but-3-en-1-amine (**3c***) (89 mg, 0.50 mmol, 1.0 equiv) and morpholine (130 µL, 1.5 mmol, 3.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 18:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3c** ($1.0*10^2$ mg, 0.39 mmol, 79% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

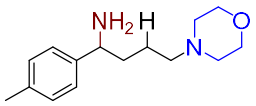
R_f = 0.25 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.85 (t, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.68 (t, J = 4.7 Hz, 4H), 2.38 (br s, 4H), 2.30 (dd, J = 8.3, 6.9 Hz, 2H), 1.66 (ddt, J = 17.8, 12.9, 7.1 Hz, 2H), 1.59 – 1.44 (m, 3H), 1.43 – 1.30 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.81, 138.77, 127.57, 114.06, 67.24, 59.18, 55.90, 55.56, 53.99, 37.70, 23.88 ppm.

IR (salt plate): 3367 (w, br), 3293 (w, br), 2938 (s, br), 2853 (s, br), 2808 (s, s), 2687 (m, s), 1610 (s, s), 1584 (m, s), 1505 (s, s), 1458 (m, br), 1249 (s, br) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1905.



3d

4-morpholino-1-(*p*-tolyl)butan-1-amine:

Prepared using general procedure **C** using: 1-*p*-tolylbut-3-en-1-amine (**3d***) (80 mg, 0.50 mmol, 1.0 equiv) and morpholine ($1.3*10^2$ µL, 1.5 mmol, 3.0 equiv). The reaction was run at 100 °C for 48 h.

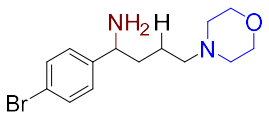
Analysis of the crude reaction mixture by gas chromatography determined a 18 : 1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3d** (108.3 mg, 0.44 mmol, 88% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.15(15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 3.85 (t, *J* = 6.9 Hz, 1H), 3.68 (t, *J* = 4.7 Hz, 4H), 2.40 – 2.35 (m, 4H), 2.32 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.78 – 1.60 (m, 4H), 1.58 – 1.44 (m, 1H), 1.45 – 1.29 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.27, 136.30, 128.97, 126.02, 66.80, 58.74, 55.75, 53.55, 37.18, 23.44, 20.88.

HRMS (ESI-TOF) m/z: [M+H^+] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1971.



3e

1-(4-bromophenyl)-4-morpholinobutan-1-amine (3e):

Prepared using general procedure **C** using: 1-(4-bromophenyl)but-3-en-1-amine (**3d***) (110 mg, 0.50 mmol, 1.0 equiv) and morpholine (130 µL, 1.5 mmol, 3.0 equiv). The reaction was run at 60 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 18:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **3d** (140 mg, 0.45 mmol, 90% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

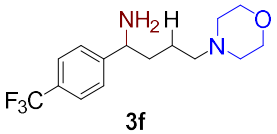
R_f = 0.20 (15% MeOH : 85% CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 3.87 (t, J = 6.8 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 2.37 (m, 4H), 2.30 (t, J = 7.5 Hz, 2H), 1.73 – 1.56 (m, 2H), 1.56 – 1.43 (m, 3H), 1.41 – 1.30 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.56, 131.63, 128.29, 120.68, 67.09, 58.94, 55.82, 53.87, 37.49, 23.58 ppm.

IR (salt plate): 3368 (w, br), 3294 (w, br), 2940 (s, br), 2853 (s, s), 2808 (s, s), 2765 (m, s), 1589 (m, s), 1486 (m, s), 1457 (m, s) cm $^{-1}$.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{22}BrN_2O$, 313.0916; found, 313.0915.



3f

4-morpholino-1-(4-(trifluoromethyl)phenyl)butan-1-amine (3f):

Prepared using general procedure **C** using: 1-(4-(trifluoromethyl)phenyl)but-3-en-1-amine (**3f***) (120 mg, 0.53 mmol, 1.0 equiv) and morpholine (130 µL, 1.5 mmol, 3.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 16:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **3f** (140 mg, 0.47 mmol, 89% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

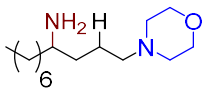
R_f = 0.51 (5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 3.98 (t, J = 6.8 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 2.38 (br s, 4H), 2.31 (t, J = 7.5 Hz, 2H), 1.76 – 1.61 (m, 2H), 1.52 (m, 3H), 1.42-1.32 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.7, 129.6 (q, J = 32.4 Hz), 126.99, 125.68 (q, $^2J_{CF}$ = 3.8 Hz), 124.48 (q, $^1J_{CF}$ = 272 Hz), 67.22, 59.04, 56.17, 54.00, 37.62, 23.67 ppm.

IR (salt plate): 3372 (w, br), 3299 (w, br), 2942 (s, br), 2856 (s, s), 2810 (s, s), 2688 (w, s), 1619 (s, s), 1457 (m, s), 1420 (m, s), 1163 (s, br), 1115 (s, br) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{22}N_2OF_3$, 303.1684; found, 303.1673.



3j

1-morpholinoundecan-4-amine (3j):

Prepared using general procedure **C** using: undec-1-en-4-amine (**3j***) (85 mg, 0.50 mmol, 1.0 equiv) and morpholine (130 µL, 1.5 mmol, 3.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 10:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3j** (94 mg, 0.37 mmol, 73% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

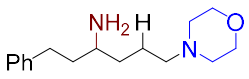
R_f = 0.14 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (t, J = 5.1 Hz, 4H), 2.69 (tdd, J = 7.6, 4.7, 4.2 Hz, 1H), 2.44 (br s, 4H), 2.32 (ddt, J = 8.3, 6.4, 1.8 Hz, 2H), 1.65 – 1.33 (m, 6H), 1.33 – 1.20 (m, 10H), 1.11 (br s, 2H), 0.87 (t, J = 6.2 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 67.20, 59.43, 53.99, 51.36, 38.37, 36.09, 32.04, 29.96, 29.51, 26.37, 23.44, 22.85, 14.30 ppm.

IR (salt plate): 3373 (w, br), 3292 (w, br), 2956 (m, br), 2924 (m, br), 2853 (m, s), 2807 (m, s), 1458 (m, br), 1119 (m, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{33}N_2O_2$, 257.2593; found, 257.2597.



3k

6-Morpholino-1-phenylhexan-3-amine (3k):

Prepared using general procedure **C** using: 1-phenylhex-5-en-3-amine (**3k***) (53 mg, 0.30 mmol, 1.0 equiv) and morpholine ($1.0*10^2$ μL, 1.2 mmol, 4.0 equiv) with the exception that the reaction was run at a 1.0 M in DME. The reaction was run at 60 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a >20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 10% MeOH : 2.5% sat. NH_4OH : 87.5% $CHCl_3$ as the eluent) to afford **3k** (59 mg, 0.23 mmol, 74% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

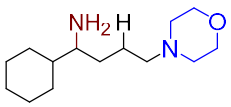
R_f = 0.10 (1 : 9 MeOH : DCM).

^{1}H NMR (C_6D_6, 500 MHz): δ 7.15 (m, 5H), 3.62 (t, *J* = 4.75 Hz, 4H), 2.64 (ddd, *J* = 13.6, 9.9, 5.4 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.17 (m, 4H), 2.09 (t, *J* = 7.10 Hz, 2H), 1.59 (dddd, *J* = 14.10, 9.95, 6.60, 4.41 Hz, 1H), 1.35 (m, 4H), 1.11 (m, 1H) 0.74 (br s, 2H) ppm.

^{13}C NMR (C_6D_6 125 MHz): δ 143.50, 129.34, 129.26, 126.63, 67.79, 59.88, 54.79, 51.41, 41.11, 36.96, 33.49, 24.06 ppm.

IR (salt plate): 3351 (w, br), 3299 (w, br), 3059 (m, s), 3025 (m, s), 2934 (s, br) 2854 (s, s), 2808 (s, s), 1602 (m, s), 1496 (m, s), 1454 (s, s), 1117 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{27}N_2O$: found: 263.2123; found, 263.2128.



3i

1-cyclohexyl-4-morpholinobutan-1-amine (3i):

Prepared using general procedure **C** using: 1-cyclohexylbut-3-en-1-amine (**3i***) (120 mg, 0.76 mmol, 1.0 equiv) and morpholine ($3.0*10^2$ µL, 3.5 mmol, 4.6 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 9:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3i** (99 mg, 0.41 mmol, 54% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

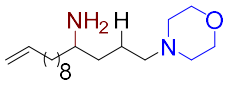
R_f = 0.15 (15% MeOH : 85% CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.71 (t, J = 4.7 Hz, 4H), 2.49 (dt, J = 8.8, 4.4 Hz, 1H), 2.43 (br s, 4H), 2.38 – 2.27 (m, 2H), 1.79 – 1.56 (m, 6H), 1.52 - 1.41 (m, 2H), 1.28 – 0.93 (m, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 67.10, 59.39, 56.11, 53.91, 43.89, 32.71, 29.90, 27.90, 26.78, 26.70, 26.54, 23.75 ppm.

IR (salt plate): 3377 (w, br), 3310 (w, br), 2924 (s, br), 2851 (s, s), 2806 (s, s), 2765 (m, s), 1610 (m, br), 1119 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{14}H_{29}N_2O$, 241.2280; found, 241.2281.



3l

1-morpholinotetradec-13-en-4-amine (3l):

Prepared using a *modified* general procedure **C** using: tetradeca-1,13-dien-4-amine (**3l***) (64 mg, 0.30 mmol, 1.0 equiv) and morpholine ($4.0*10^1$ µL, 0.5 mmol, 1.5 equiv), 1 M in DME (0.3 mL). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 12:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 3% MeOH : 2.5% sat. NH_4OH : 94.5% $CHCl_3$ as the eluent) to afford **3l** (74 mg, 0.27 mmol, 81% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

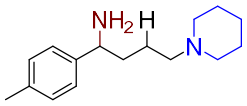
R_f = 0.10 (1 : 9 MeOH : DCM).

^{1}H NMR (C_6D_6, 500 MHz): 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.05 (m, 1H), 5.00 (m, *J* = 10.2, 1.1 Hz, 1H), 3.63 (t, J = 5.2, 4.4 Hz, 4H), 2.55 (tt, J = 7.7, 4.1 Hz, 1H), 2.21 (t, J = 4.1 Hz, 4H), 2.15 (t, J = 7.1 Hz, 2H), 2.00 (qt, J = 7.3, 7.1, 6.8, 1.3 Hz, 2H), 1.52 (m, 1H), 1.46 – 1.10 (m, 17H), 0.73 (br s, 2H) ppm.

^{13}C NMR (C_6D_6 125 MHz): δ 139.81, 115.14, 67.82, 60.03, 54.84, 52.10, 39.67, 37.03, 34.81, 30.90, 30.70, 30.53, 30.14, 29.94, 27.23, 24.25 ppm.

IR (salt plate): 3375 (w, br), 3296 (w, br), 3075 (w, br), 2925 (s, br), 2853 (s, s), 2808 (m, s), 1640 (w, s), 1119 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{18}H_{37}N_2O$: 297.2906; found, 297.2911.



3g

4-(piperidin-1-yl)-1-(*p*-tolyl)butan-1-amine:

Prepared using general procedure **C** using: 1-(*p*-tolylbut-3-en-1-amine (**3g***) (81 mg, 0.50 mmol, 1.0 equiv) and piperidine (1*10^2 µL, 1.0 mmol, 2.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a > 20 : 1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography

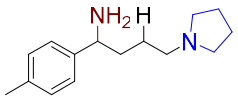
(using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3g** (97.1 mg, 0.39 mmol, 78% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.21 (15% MeOH : 85% CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (s, 2H), 4.38 (t, J = 7.5 Hz, 1H), 3.69 (t, J = 4.7 Hz, 4H), 2.39 (m, 10H), 2.33 (dd, J = 8.2, 6.8 Hz, 2H), 2.23 (s, 3H), 1.88 – 1.76 (m, 2H), 1.72 – 1.54 (m, 3H), 1.44 – 1.27 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.77, 136.09, 135.95, 130.4, 67.23, 59.13, 53.98, 52.07, 34.48, 24.60, 21.44, 20.88 ppm.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{16}H_{27}N_2$, 247.2174; found, 247.2168.



3h

4-(pyrrolidin-1-yl)-1-(*p*-tolyl)butan-1-amine:

Prepared using general procedure **C** using: 1-(*p*-tolylbut-3-en-1-amine (**3h***) (80 mg, 0.50 mmol, 1.0 equiv) and pyrrolidine ($0.5*10^2$ µL, 1.0 mmol, 1.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 18:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$

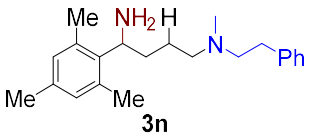
to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3h** (85.8 mg, 0.37 mmol, 74% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.24 (20% MeOH : 80% CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.85 (t, *J* = 6.8 Hz, 1H), 2.51 – 2.38 (m, 6H), 2.32 (s, 3H), 1.85 – 1.62 (m, 8H), 1.55 (dddd, *J* = 15.6, 7.5, 5.0, 2.2 Hz, 1H), 1.42 (dddd, *J* = 16.6, 9.3, 6.9, 4.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.39, 136.26, 128.96, 126.07, 56.31, 55.81, 54.05, 37.54, 26.04, 23.26, 20.92.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{15}H_{25}N_2$, 233.2018; found, 233.2027.



3n

1-mesityl-*N*^{4}-methyl-*N*^{4}-phenethylbutane-1,4-diamine (**3n**):

Prepared using general procedure **C** using: 1-mesityl-3-buten-1-amine (**3n***) (95 mg, 0.50 mmol, 1.0 equiv) and *N*-methyl-2-phenylethan-1-amine (510 µL, 3.5 mmol, 7.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 18:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat. NH_4OH : 90% $CHCl_3$ as the eluent) to afford **3n** (140 mg, 0.42 mmol, 83% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

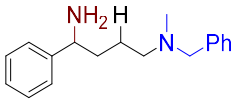
Rf=0.28 (10 : 5 : 85 MeOH : sat. NH_4OH : $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 6.81 (s, 2H), 4.37 (t, J = 7.4 Hz, 1H), 2.77 – 2.72 (m, 2H), 2.61 – 2.54 (m, 2H), 2.49 – 2.33 (m, 8H), 2.28 (s, 3H), 2.24 (s, 3H), 1.88 – 1.72 (m, 2H), 1.67 – 1.46 (m, 3H), 1.45 – 1.29 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 140.39, 138.37, 136.10, 135.50, 128.52, 128.16 (2C), 125.75, 59.46, 57.48, 51.75, 42.01, 34.19, 33.68, 25.09, 21.10, 20.52 ppm.

IR (salt plate): 3369 (w, br), 3289 (w, br), 3085 (m, s), 3061 (m, s), 3053 (s, s), 2945 (s, br), 2961 (s, br), 2789 (s, br), 1610 (m, s), 1495 (m, s), 1453 (s, br) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{22}H_{32}N_2$, 325.2644; found, 325.2641.



3m

N1-benzyl-N1-methyl-4-phenylbutane-1,4-diamine (**3m**):

Prepared using general procedure **C** using: 1-phenyl-3-buten-1-amine (**3m***) (294.4 mg, 2.0 mmol, 1.0 equiv) and *N*-methylbenzylamine (1.8 mL, 14 mmol, 7.0 equiv). The reaction was run at 100 °C for 48 h.

Analysis of the crude reaction mixture by gas chromatography determined a 16:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 4% sat. NH_4OH : 96% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 4% sat. NH_4OH : 96% $CHCl_3$ to 4% MeOH : 4% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **3m** (417.2 mg, 1.55 mmol, 78% yield of the major isomer, average of two runs) as a viscous pale yellow oil after subjecting the material to high vacuum at 40° C for 1 hour.

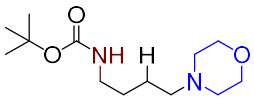
R*f* = 0.39 (15 : 85 MeOH : CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6): δ 7.35 – 7.32 (m, 2H), 7.25 – 7.22 (m, 2H), 7.18 (ddd, *J* = 7.9, 6.8, 1.6 Hz, 4H), 7.12 – 7.07 (m, 2H), 3.64 (t, *J* = 6.8 Hz, 1H), 3.30 (s, 2H), 2.21 (ddd, *J* = 7.4, 6.5, 2.0 Hz, 2H), 2.01 (s, 2H), 1.64 – 1.50 (m, 2H), 1.49 – 1.41 (m, 1H), 1.39 – 1.31 (m, 1H), 0.95 (s, 2H) ppm

^{13}C NMR (125 MHz, $CDCl_3$): δ 146.84, 139.46, 129.27, 128.70, 128.42, 127.15, 127.12, 126.59, 62.62, 57.48, 56.43, 42.45, 37.60, 24.65.

IR (salt plate): 3365 (m, br), 3083 (m, s), 3061 (m, s), 3026 (m, s) 2940 (s, br), 2840 (s, br), 2788 (s, br), 1702 (m, br), 1493 (m, s) cm^{-1}.

HRMS (ESI-TOF) m/z: $[M+H^+]$ calculated for $C_{18}H_{24}N_2$, 269.2018; found, 269.2017.



3o

***tert*-butyl (4-morpholinobutyl)carbamate (3o)**:

$[Rh(COD)Cl]_2$ (6.2 mg, 0.013 mmol, 2.5 mol %), dppp (10. mg, 0.025 mmol, 5.0 mol %), silver tetrafluoroborate (4.9 mg, 0.025 mmol, 5.0 mol %), DME (330 µL) and homoallyl amine (**5**) (46,µL 0.49 mmol, 1.0 equiv) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (220 µL, 2.5 mmol, 5.0 equiv). The resulting solution was sealed with-Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 80 °C. After 48 h, the reaction vial was cooled to room temperature.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The vial was opened to air and di-tert-butyl dicarbonate (547 µL, 2.5 mmol, 5 equiv) was added dropwise while vigorous bubbling occurred. The mixture was stirred at room temperature for 15 minutes, excess solvent was removed *en vacuo,* and the dark brown oil was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and 1% MeOH : 5% sat. NH_4OH : 94% $CHCl_3$ as the eluent) to afford **3o**

($1.0*10^2$ mg, 0.40 mmol, 83% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

Rf = 0.17 (1 : 5 : 94 MeOH : sat. NH_4OH : $CHCl_3$).

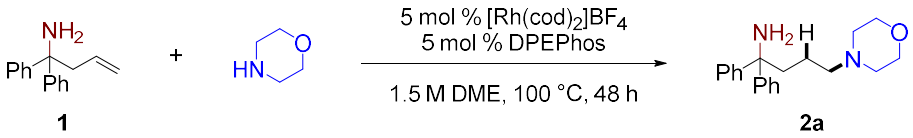
^1H NMR (500 MHz, $CDCl_3$): δ 5.31 (s, 1H), 3.73 (t, J = 4.7 Hz, 4H), 3.13 (d, J = 6.7 Hz, 2H), 2.44 (br s, 4H), 2.39 – 2.31 (m, 2H), 1.59 – 1.51 (m, 4H), 1.45 (s, 9H) ppm.

^{13}C NMR (125 MHz, C_6D_6): δ 155.92, 78.13, 66.96, 58.52, 53.93, 40.74, 28.57, 28.09, 24.15.

IR (salt plate): 3435 (w, br), 3355 (m, br), 3237 (w, br), 2968 (s, br), 2934 (s, br), 2858 (m, s), 2810 (m, s), 2280 (m, s), 1715 (s, br), 1508 (s, br), 1119 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [$M+H^+$] calculated for $C_{13}H_{26}N_2O_3$, 259.2022; found, 259.2021.

H. Scale-up Procedure

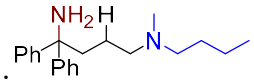


[Rh(COD) $_2$] BF_4 ($1.0x10^2$ mg, 0.025 mmol, 5.0 mol %), DPEphos (140 mg, 0.025 mmol, 5.0 mol %), DME (3.5 mL), and homoallyl amine (1.1 g, 5.1 mmol, 1.0 equiv) were added to an oven-dried 20 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (2.2 mL, 25 mmol, 5.0 equiv). The resulting solution was sealed with Teflon-lined cap, removed from glove box, and allowed to stir for 48 h at 100 °C. After 48 h, the reaction vial was cooled to room temperature and morpholine was removed *in vacuo* at 60 °C.

Analysis of the crude reaction mixture by gas chromatography determined a > 20:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 400 mL of silica, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 15 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 5% MeOH : 5% sat.

NH_4OH : 90% $CHCl_3$ as the eluent) to afford **2a** (1.4 g, 4.63 mmol, 92% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

The product isolated is identical with previous characterization.



N^4-butyl-N^4-methyl-1,1-diphenylbutane-1,4-diamine

Prepared using general procedure **A** using: 1,1-diphenylbut-3-en-1-amine (22 mg, 0.097 mmol, 1.0 equiv) and N-methyl-1-butylamine (120 µL, 1.0 mmol, 10. equiv). The reaction was run at 100 °C for 96 h in toluene instead of dimethoxyethane.

Analysis of the crude reaction mixture by gas chromatography determined a 8:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 40 mL of silica in a 3 cm diameter column, with 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 1% MeOH : 2.5% sat. NH_4OH : 96.5% $CHCl_3$ to 5% MeOH : 2.5% sat. NH_4OH : 92.5% $CHCl_3$ as the eluent) to afford diamine (18 mg, 0.059 mmol, 61% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

R_f = 0.43 in 20% MeOH/DCM.

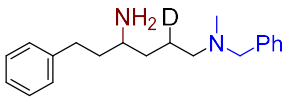
^{1}H NMR (C_6D_6, 500 MHz): δ 7.38 (d, J = 7.4 Hz, 4H), 7.13 (t, J = 7.8 Hz, 4H), 7.03 (t, J = 7.0 Hz, 2H), 2.24 – 2.15 (m, 6H), 2.03 (s, 3H), 1.45 – 1.22 (m, 8H), 0.88 (t, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (C_6D_6 125 MHz): δ 150.52, 128.81, 127.69, 126.89, 61.62, 59.07, 58.50, 42.73, 41.16, 30.65, 23.15, 21.55, 14.93 ppm.

IR (salt plate): 3371 (w, br), 3303 (w, br), 3085 (w, s), 3058 (m, s), 3023 (m, s), 2955 (s, s), 2932 (s, s), 2861 (m, s), 2787 (m, br), 1598 (m, s), 1492 (m, s), 1446 (s, s) cm^{-1}.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{21}H_{31}N_2$: 311.2487; found, 311.2487

I. Deuterium Incorporation Experiment



8-d

N^1-benzyl-N^1-methyl-6-phenylhexane-2-*d*-1,4-diamine:

Prepared using general procedure **C** using: 1-phenylhex-5-en-3-amine-d_2 (**7**) (89 mg, 0.50 mmol, 1.0 equiv) and methylbenzylamine-d_1 ($3.25*10^2$ µL, 1.0 mmol, 5.0 equiv). The reaction was run at 100 °C for 48 h.

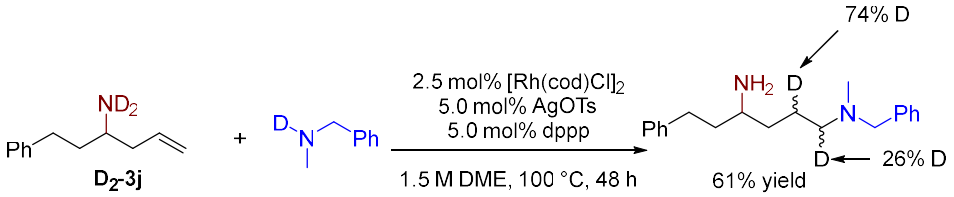
Analysis of the crude reaction mixture by gas chromatography determined a 19:1 ratio of the 1,4 diamine : 1,3 diamine. The crude reaction mixture was purified by column chromatography (using 125 mL of silica in a 4.5 cm diameter column, with 5% sat. NH_4OH : 95% $CHCl_3$, loading the sample with 3 x 5 mL aliquots of dichloromethane, and using 5% sat. NH_4OH : 95% $CHCl_3$ to 3% MeOH : 5% sat. NH_4OH : 92% $CHCl_3$ as the eluent) to afford **8-d** (90.8 mg, 0.31mmol, 61% yield of the major isomer, average of two runs) as a viscous pale yellow oil.

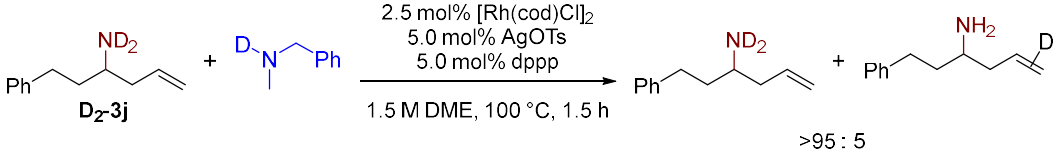
R_f = 0.38 (20% MeOH : 80% CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.37 (d, *J* = 6.7 Hz, 2H), 7.27 – 7.04 (m, 8H), 3.35 (s, 2H), 2.68 – 2.47 (m, 2H), 2.46 (tt, *J* = 8.4, 4.0 Hz, 1H), 2.23 (d, *J* = 7.0 Hz, 2H), 2.08 (s, 3H), 1.58 (ddt, *J* = 14.5, 6.5, 3.2 Hz, 1H), 1.48 (dddd, *J* = 12.6, 10.3, 7.6, 5.3 Hz, 2H), 1.38 (dddd, *J* = 13.5, 10.0, 8.2, 5.5 Hz, 1H), 1.29 (dtd, *J* = 12.9, 7.8, 6.1, 3.5 Hz, 1H), 1.11 (dtt, *J* = 10.4, 7.9, 4.9 Hz, 1H), 0.73 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.28, 139.08, 128.94, 128.28, 128.26, 128.10, 126.80, 125.65, 62.30, 57.35, 50.69, 42.17, 39.80, 35.65, 32.53, 23.52 (t, *J*=19.2 Hz).

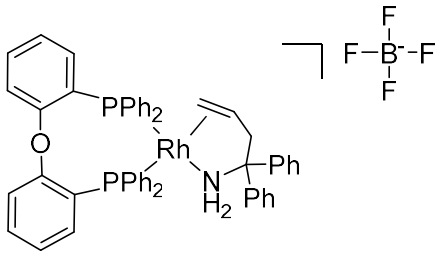
HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for $C_{20}H_{28}DN_2$, 298.2394; found, 298.2397.





Subjecting **D_2-3j** to reaction conditions with *N*-methyl-1-phenylmethanamine-*d* gave **8-d** with deuterium incorporation at both the 3- and 4-position of the substrate in a 74:26 ratio and 61% yield after 48 hours. Subjecting **D_2-3j** to the same conditions gave less than 5% deuterium incorporation (unobserved by deuterium NMR) into the olefin of the starting material after 1.5 h.

J: Homoallyl Complex Synthesis, Characterization, and Crystal Structure



9

[RhDPEphos(α,αdiphenylhomoallylamine)]tetrafluoroborate:

37 mg (0.075 mmol, 0.5 eq) $[RhCODCl]_2$, 80 mg DPEphos (0.15 mmol, 1 eq), and 29 mg $AgBF_4$ (0.15 mmol,1 eq) were stirred at room temperature for 15 minutes to afford a yellow suspension. To this suspension was added 75 mg α,α-diphenylhomoallylamine (0.33 mmol, 2.1 eq), and the vial was sealed and heated to 80°C for 45 minutes. This was brought to room temperature and filtered under nitrogen and washed with 7x2 mL THF, 2x15 mL hexanes to afford a burnt orange solid. This was washed through the filter using 3x5 mL into a tared vial. Upon removal of the solvent through application of high-vacuum 101 mg (0.106 mmol, 71% yield) of **9** was obtained as a burnt-orange powder.

A suitable crystal was obtained through layered crystallization from THF and hexanes

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.69 (ddd, *J* = 10.3, 5.2, 2.0 Hz, 2H), 7.63 (dt, *J* = 4.4, 2.2 Hz, 3H), 7.48 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.42 – 7.33 (m, 7H), 7.33 – 7.24 (m, 8H), 7.21 – 7.11 (m, 3H), 7.05 – 6.85 (m, 10H), 6.83 – 6.72 (m, 4H), 4.54 (d, *J* = 13.0 Hz, 1H), 4.36 (q, *J* = 4.1, 2.8 Hz, 1H), 3.72 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.41 (dt, *J* = 13.8, 6.9 Hz, 1H), 3.05 (dp, *J* = 9.2, 2.4 Hz, 1H), 2.51 (d, *J* = 6.9 Hz, 1H), 2.31 (ddd, *J* = 14.2, 6.9, 2.6 Hz, 1H) ppm

^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.13 (dd, *J* = 50.3, 8.0 Hz), 145.52 (d, *J* = 3.0 Hz), 143.76, 134.77 (dd, *J* = 109.4, 11.4 Hz), 134.14 – 133.23 (m), 132.51, 132.44 (br s), 132.22, 131.93, 131.59, 131.38, 130.71 – 130.50 (m), 130.20 (d, *J* = 11.0 Hz), 129.38 (dd, *J* = 48.2, 9.7 Hz), 129.30, 128.69, 128.45, 128.34 (d, *J* = 10.0 Hz), 127.41, 125.94 (d, *J* = 7.0 Hz), 125.23 – 124.94 (m), 124.78 (d, *J* = 6.3 Hz), 124.59 (m), 123.79 (dd, *J* = 69.7, 43.0 Hz), 122.11 (m), 121.28 (m), 83.74 (m)**, 74.42 (br s)**, 73.50 (dd, *J* = 5.7, 1.9 Hz), 42.83 ppm.

^{31}P NMR (202 MHz, CD_2Cl_2) δ 36.89 (dd, J = 153.5, 41.1 Hz), 12.41 (dd, J = 168.6, 41.1 Hz)

*Much of the coupling in the carbon NMR was poorly resolved into broad carbon signals, likely due to limited rotational freedom on the NMR timescale. Coupling constants are reported where they are clear. See spectrum for more details.

X-ray crystallography parameters and select bond lengths and angles for 9

X-Ray Diffraction Techniques: The structure was collected on a Bruker three-circle platform goniometer equipped with an Apex II CCD and an Oxford cyrostream cooling device. Radiation was from a graphite fine focus sealed tube Mo Kα (0.71073 Å) source. A suitable crystal was mounted on a cryoloop using paratone N oil. The structure was collected at 173 K. Data was collected as a series of φ and/ or ω scans. Data was integrated using SAINT and scaled with either numerical or multi-scan absorption correcting using SADABS[35, 36]. Using Olex2[35, 36], the structure was solved with the XS[35, 36] structure solution program using the Patterson method and refined with the XL[35, 36] refinement package using Least Squares minimization. The BF_4 anion was disordered and modeled over two positions.

Table 3.17. X-ray diffraction experimental details for **9**[a,b]

Formula	$C_{52}H_{45}NOP_2Rh,C_4H_8O, BF_4$
W	1023.65
Crystal system	Triclinic
Space group (Z)	P-1 (2)
a (Å)	10.5541(6)
b (Å)	10.8702(6)
c (Å)	21.4812(10)
α (°)	88.2639(19)
β (°)	84.3786(18)
γ (°)	73.4287(19)
Volume ($Å^3$)	2350.7(2)
Calc. ρ (g/cm^3)	1.446
μ (mm^{-1})	0.492
Crystal Size (mm)	0.14x0.119x0.117
Reflections	10430
Completeness	0.999
(to 2θ)	(27.159)
GOF on F^2	1.075
R1, wR2[c]	0.0233, 0.0610
[I>2σ(I)]	

[a] λ = 0.71073 Å; [b] T=173 K; [c] $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

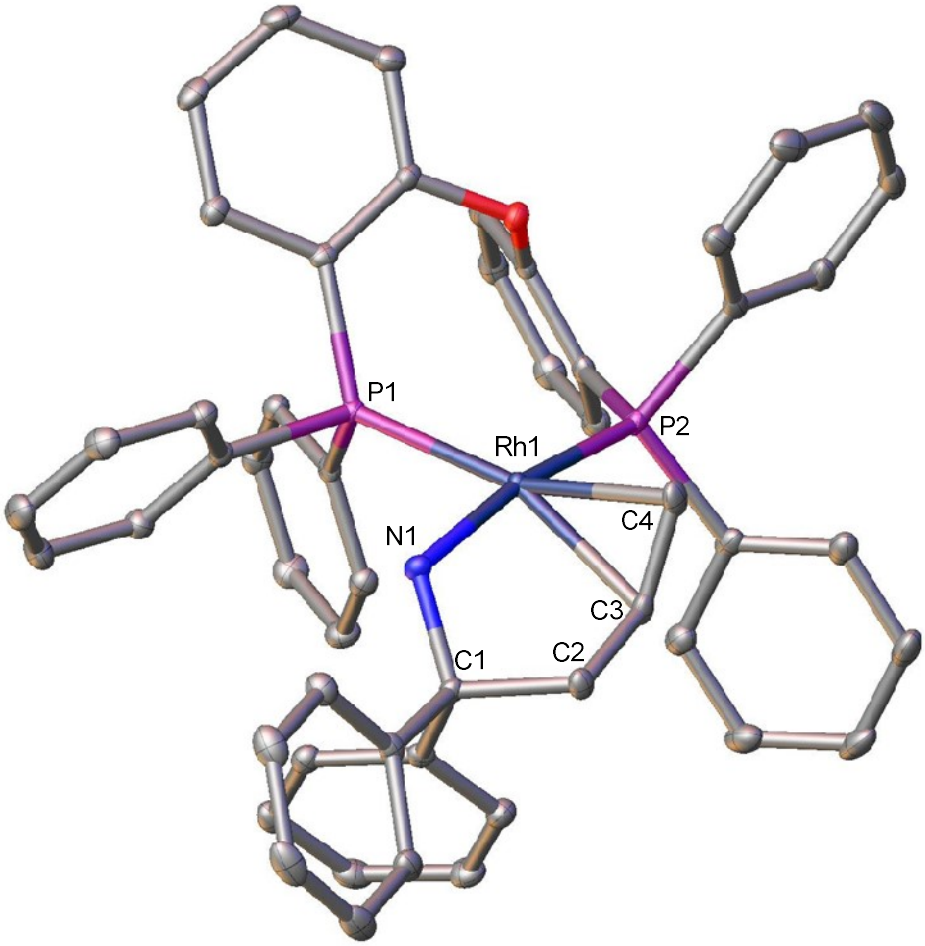
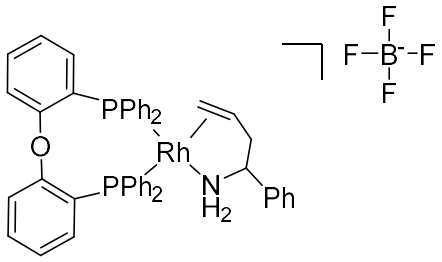


Figure 3.8. Crystal structure of **9** with select atoms labeled. Hydrogen atoms, a molecule of THF and the BF_4 anion are omitted for clarity, and thermal ellipsoids are drawn at 50% probability

Table 3.18. Select bond lengths and angles for **9**

Bond (Å)		Angle (°)	
Rh1-N1	2.1457(12)	P1-Rh1-P2	94.745(14)
Rh1-C3	2.2662(14)	C3-Rh1-C4	35.56(5)
Rh1-C4	2.2369(14)	Rh1-C4-C3	73.38(8)
C3-C4	1.375(2)	C4-C3-Rh1	71.06(9)
		N1-Rh1-C3	76.52(5)
		N1-Rh1-C4	91.09(5)
		C2-C3-C4	121.42(14)

Other Homoallyl Complex Synthesis, Characterization, and Crystal Structures



10

[RhDPEphos(α,phenylhomoallylamine)]tetrafluoroborate:

18.7 mg (0.038 mmol, 0.5 eq) $[RhCODCl]_2$, 40 mg DPEphos (0.075 mmol, 1 eq), and 14.5 mg $AgBF_4$ (0.075 mmol,1 eq) were stirred at room temperature for 15 minutes to afford a yellow suspension. To this suspension was added 40 mg α-phenylhomoallylamine (0.165 mmol, 2.1 eq), and the vial was sealed and heated to 60°C overnight. This was brought to room temperature and filtered under nitrogen and washed with 7x2 mL THF, 2x15 mL hexanes to afford a burnt orange solid. This mixture of species was then directly subjected to crystallization, affording single crystals when dissolved in DCM, and layered with hexanes after a period of two weeks.

Compound was characterized solely through crystallography and crude phosphorous NMR

^{31}P NMR (202 MHz, CD_2Cl_2) δ 14.04 (d, J = 146.2 Hz), 12.40 (dd, J = 168.4, 41.0 Hz)

X-ray crystallography parameters and select bond lengths and angles for 10:

X-Ray Diffraction Techniques: The structure was collected on a Bruker three-circle platform goniometer equipped with an Apex II CCD and an Oxford cyrostream cooling device. Radiation was from a graphite fine focus sealed tube Mo Kα (0.71073 Å) source. A suitable crystal was mounted on a cryoloop using paratone N oil. The structure was collected at 100 K. Data was collected as a series of φ and/ or ω scans. Data was integrated using SAINT and scaled with either numerical or multi-scan absorption correcting using SADABS[35, 36,] Using Olex2[35, 36], the structure was solved with the XS structure solution program using the Patterson method and refined with the XL[35, 36] refinement package using Least Squares minimization. The BF_4 anion was disordered and modeled over two positions.

Table 3.19. X-ray diffraction experimental details for **10**[a,b]

Formula	$C_{53}H_{56}BF_4NOP_2RhCl_2$
W	1045.54
Crystal system	Triclinic
Space group (Z)	P-1 (2)
a (Å)	9.4174(4)
b (Å)	11.7603(5)
c (Å)	22.2103(9)
α (°)	101.1698(16)
β (°)	92.5618(17)
γ (°)	109.2534(15)
Volume ($Å^3$)	2262.55(17)
Calc. ρ (g/cm^3)	0.767
μ (mm^{-1})	0.31
Crystal Size (mm)	0.219*0.349*0.742
Reflections	119396
Completeness (to 2θ)	0.999 (56.71)
GOF on F^2	1.105
R1, wR2[c] [I>2σ(I)]	0.0903, 0.2560,

Figure 3.9. Crystal structure of **10** with select atoms labeled. Hydrogen atoms, a molecule of DCM and the BF_4 anion are omitted for clarity. Thermal ellipsoids are drawn at 50% probability

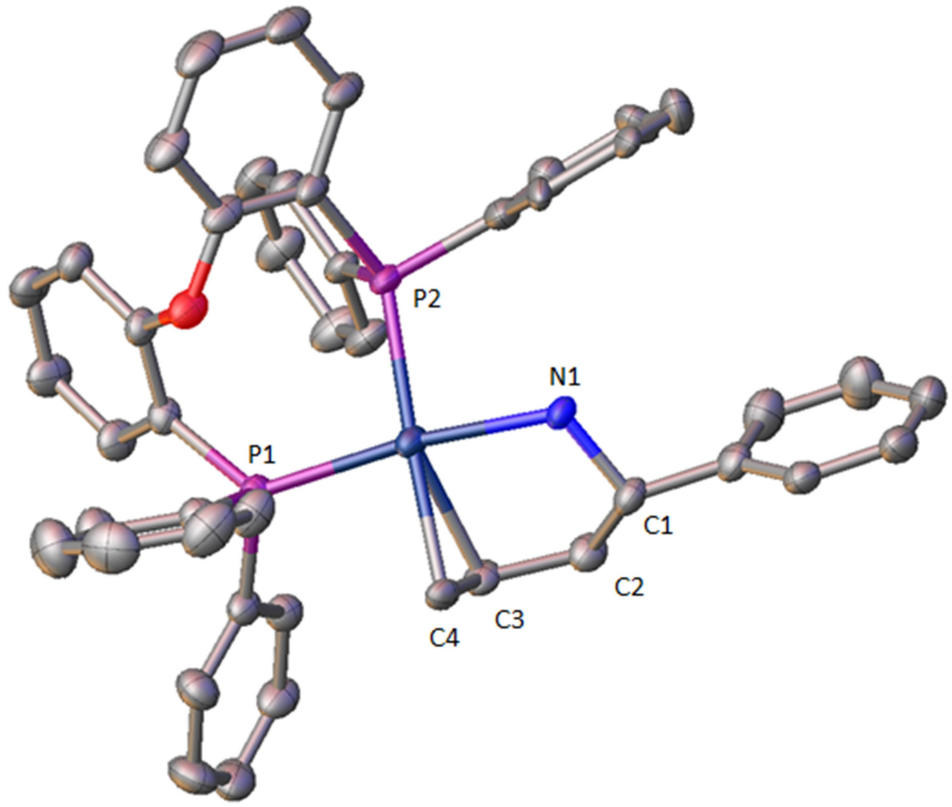
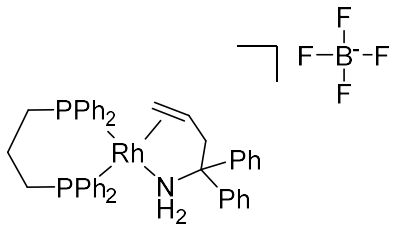


Table 3.20. Select bond lengths and angles for **10**

Bond (Å)		Angle (°)	
Rh1-N1	2.016(5)	P1-Rh1-P2	96.55(5)
Rh1-C3	2.201(5)	C3-Rh1-C4	36.5(2)
Rh1-C4	2.210(5)	N1-Rh1-C3	78.81(18)
C3-C4	1.314(7)	N1-Rh1-C4	85.98(19)
		C2-C3-C4	124.6(5)



11

[RhDPPP(α,α-diphenylhomoallylamine)]tetrafluoroborate

This was prepared in an analogous manner to 9. The crystallization was performed by a layered crystallization between DCM and hexanes, in a 1 : 5 ratio. This compound was only characterized by X-ray crystallography because it appeared to decay rapidly in the solvents it was soluble in (CD_2Cl_2 and CH_3CN)

X-ray crystallography parameters and select bond lengths and angles for 11

X-Ray Diffraction Techniques: The structure was collected on a Bruker three-circle platform goniometer equipped with an Apex II CCD and an Oxford cyrostream cooling device. Radiation was from a graphite fine focus sealed tube Mo Kα (0.71073 Å) source. A suitable crystal was mounted on a cryoloop using paratone N oil. The structure was collected at 100 K. Data was collected as a series of φ and/ or ω scans. Data was integrated using SAINT and scaled with either numerical or multi-scan absorption correcting using SADABS[35, 36,] Using Olex2[35, 36], the structure was solved with the XS structure solution program using the Patterson method and refined with the XL[35, 36] refinement package using Least Squares minimization. The BF_4 anion was disordered and modeled over two positions.

Table 3.21. X-ray diffraction experimental details for **11**[a,b]

Formula	$C_{43}H_{43}BF_4NP_2Rh$
W	3301.77
Crystal system	monoclinic
Space group (Z)	P21/c
a (Å)	19.1167(9)
b (Å)	10.0173(5)
c (Å)	19.7796(9)
α (°)	90
β (°)	90.5265(18)
γ (°)	90
Volume (Å^3)	3787.6(3)
Calc. ρ (g/cm^3)	1.448
μ (mm^{-1})	0.59
Crystal Size (mm)	0.277x0.368x0.461
Reflections	105883
Completeness	0.999
(to 2θ)	56.68
GOF on F^2	1.128
R1, wR2[c]	0.0245, 0.0597
[I>2σ(I)]	

Figure 3.10. Crystal structure of **11** with select atoms labeled. Hydrogen atoms and the BF_4 anion are omitted for clarity, and thermal ellipsoids are drawn at 50% probability

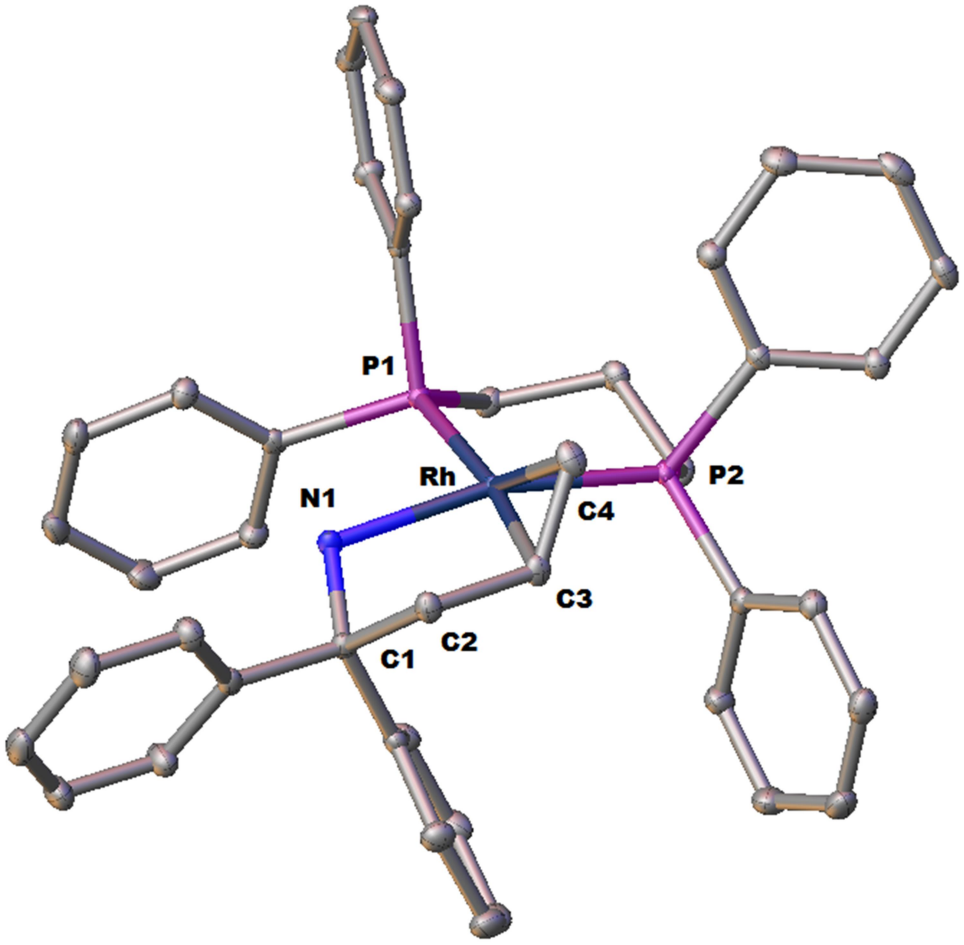
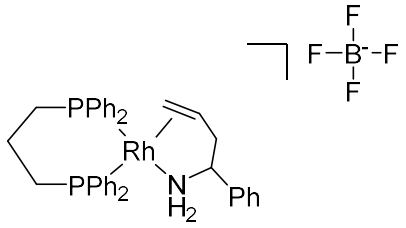


Table 3.22. Select bond lengths and angles for **11**

Bond (Å)		Angle (°)	
Rh1-N1	2.1456(12)	P1-Rh1-P2	91.663(16)
Rh1-C3	2.2623(14)	C3-Rh1-C4	35.81(6)
Rh1-C4	2.2300(15)	N1-Rh1-C3	78.28(5)
C3-C4	1.382(2)	N1-Rh1-C4	97.67(5)
		C2-C3-C4	121.12(14)



12

[RhDPPP(α,α-diphenylhomoallylamine)]tetrafluoroborate

This was prepared in an analogous manner to 10. The crystallization was performed by a layered crystallization between DCM and hexanes, in a 1 : 5 ratio. This compound characterized by X-ray crystallography as well as modestly purified proton and phosphorous NMR.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 4.47 (dt, J = 13.4, 2.4 Hz, 1H), 4.34 (td, J = 6.9, 2.7 Hz, 1H), 3.53 (dd, J = 11.2, 4.2 Hz, 1H), 3.43 (dq, J = 28.3, 7.0 Hz, 1H), 3.14 - 3.03 (m, 1H), 2.59 – 2.48 (m, 1H), 2.30 (ddd, J = 14.3, 7.1, 2.6 Hz, 1H)

Only the alkyl peaks have been shown as the aryl region is simply a mess of overlapping protons.

^{31}P NMR (202 MHz, CD_2Cl_2), δ 36.90 (dd, J = 154.1, 41.2 Hz), 12.40 (dd, J = 168.2, 41.0 Hz)

X-ray crystallography parameters and select bond lengths and angles for 12

X-Ray Diffraction Techniques: The structure was collected on a Bruker three-circle platform goniometer equipped with an Apex II CCD and an Oxford cyrostream cooling device. Radiation was from a graphite fine focus sealed tube Mo Kα (0.71073 Å) source. A suitable crystal was mounted on a cryoloop using paratone N oil. The structure was collected at 100 K. Data was collected as a series of φ and/ or ω scans. Data was integrated using SAINT and scaled with either numerical or multi-scan absorption correcting using SADABS[35, 36,] Using Olex2[35, 36], the structure was solved with the XS structure solution program using the Patterson method and refined with the XL[35, 36] refinement package using Least Squares minimization. The BF_4 anion was disordered and modeled over two positions.

Table 3.23. X-ray diffraction experimental details for **12**[a,b]

Formula	$C_{37}H_{39}BF_4NP_2Rh$
W	5996.13
Crystal system	Cubic
Space group (Z)	Pca21
a (Å)	18.1987(10)
b (Å)	15.1776(8)
c (Å)	24.9713(12)
α (°)	90
β (°)	90
γ (°)	90
Volume ($Å^3$)	6897.4(6)
Calc. ρ (g/cm^3)	1.444
μ (mm^{-1})	0.64
Crystal Size (mm)	0.082x0.173x0.292
Reflections	181918
Completeness	0.999
(to 2θ)	50.78
GOF on F^2	1.113
R1, wR2[c] [I>2σ(I)]	0.0349, 0.0865
Flack	0.011(6)

Figure 3.11. Crystal structure of **12** with select atoms labeled. Hydrogen atoms and the BF_4 anion are omitted for clarity, and thermal ellipsoids are drawn at 50% probability

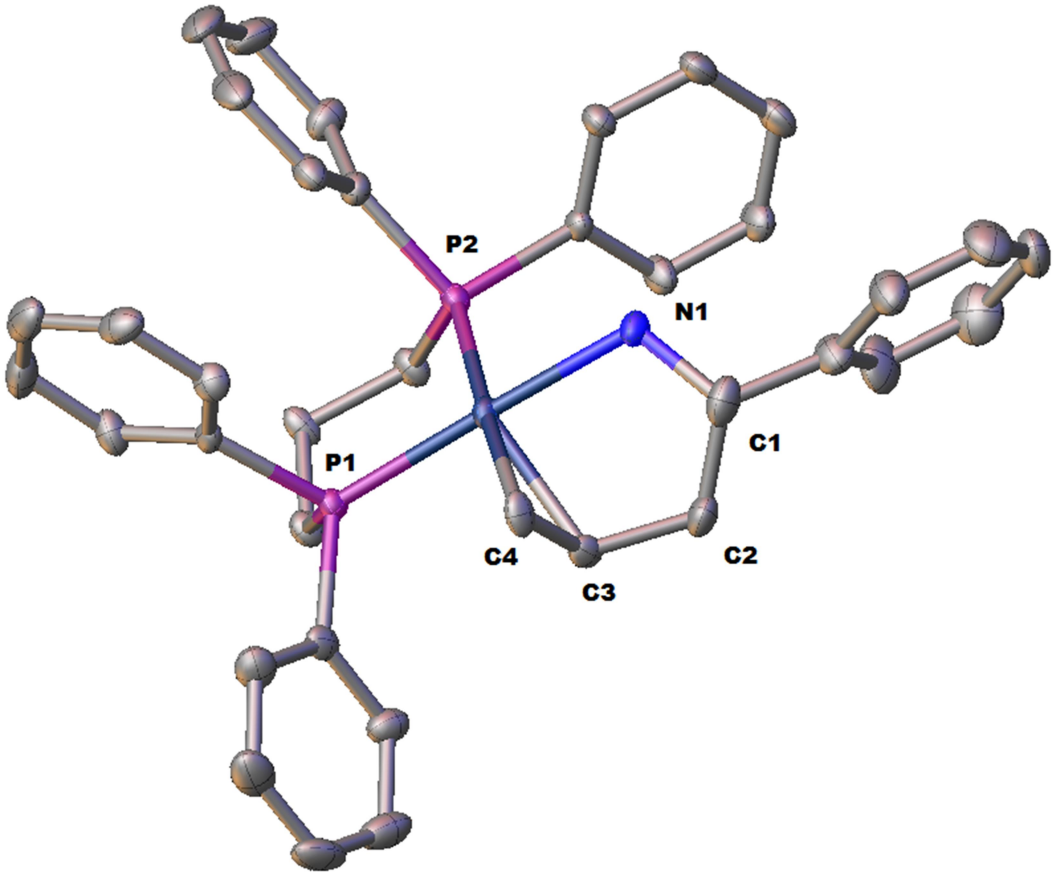


Table 3.24. Select bond Lengths and Angles for **12**

Bond (Å)		Angle (°)	
Rh1-N1	2.142(5)	P1-Rh1-P2	89.22(6)
Rh1-C3	2.202(6)	C3-Rh1-C4	36.4(2)
Rh1-C4	2.234(6)	N1-Rh1-C3	80.4(2)
C3-C4	1.387(8)	N1-Rh1-C4	85.9(2)
		C2-C3-C4	125.1(6)

Procedures for the Exploration of Hydroamination of Homoallylic Alcohols

1-phenyl-but-3-en-1-ol

3.11g (30 mmol, 1 eq) benzaldehyde dissolved in 20 mL THF under nitrogen. To this was added 20 mL 1.7 M allyl Grignard (34 mmol) at 0°. This was stirred up to room temperature overnight, and quenched with 5 mL NH_4Cl (sat'd) solution after 10 hours carefully. To this was added 50 mL 1M HCl, until the suspended particles dissolved. This was extracted using 3x50 mL ethyl acetate, dried, filtered, and the solvent removed. The crude oil was columned to afford 60% of the desired product.

^{1}H NMR (499 MHz, Chloroform-*d*) δ 7.37 – 7.35 (m, 4H), 7.31 – 7.27 (m, 1H), 5.82 (dddd, *J* = 16.9, 10.2, 7.6, 6.6 Hz, 1H), 5.21 – 5.12 (m, 2H), 4.75 (dd, *J* = 7.8, 5.1 Hz, 1H), 2.55 – 2.50 (m, 2H), 2.00 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.79, 134.40, 128.35, 127.48, 125.75, 118.37, 73.22, 43.79.

1-phenyl-butadiene

750 uL methyl iodide (12 mmol) was added to 10 mmol PPh_3 in 30 mL THF dropwise with stirring. This was refluxed for two hours, filtered, washed with xylenes, and dried on high vacuum overnight. To this was added 1.8g KOtBu, cooled to 0°, and 20 mL THF added. This was stirred for 1 hour to allow formation of the ylide, and 1 mL (8 mmol) *trans*-cinnamaldehyde was added to the reaction in 30 mL of THF slowly. This was warmed to RT slowly, quenched with the addition of water after 6 hours, extracted with ethyl acetate, rotovapped, and columned to afford 120 mg (10%) of the desired product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.38 (m, 4H), 7.25 – 7.21 (m, 2H), 6.79 (ddd, *J* = 15.8, 10.6, 0.9 Hz, 2H), 6.51 (td, *J* = 16.9, 10.3 Hz, 2H), 5.34 (dd, *J* = 16.9, 0.9 Hz, 1H), 5.18 (dd, *J* = 10.0, 0.9 Hz, 1H).

2-phenyl-pent-4-en-2-ol

20 mmol (2.33 mL, 1 eq) acetophenone in 20 mL THF was cooled to -78 °C and added to a stirring solution of 1.7M allyl Grignard (20 mL, 1.7 eq) at -78 °C dropwise over five minutes. The ice bath was removed after 10 minutes, and the reaction stirred at room temperature for three hours. This was then quenched using 20 mL 3M HCl and extracted using 3x50 mL diethyl ether. The combined organics were dried, filtered, rotovapped, and purified via column chromatography to afford 55% of the desired product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.51 – 7.46 (m, 2H), 7.39 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.31 – 7.26 (m, 1H), 5.66 (dddd, *J* = 16.8, 10.2, 8.3, 6.4 Hz, 1H), 5.25 – 5.11 (m, 2H), 2.84 – 2.66 (m, 1H), 2.61 – 2.49 (m, 1H), 1.99 (s, 1H), 1.60 (s, 4H).

1-phenyl-but-2-en-1-ol (cis + trans)

1.46 grams (60 mmol, 2 eq) magnesium in 30 mL THF had 1.03 mL 1-bromopropene in 30 mL THF added to it dropwise at reflux. This was refluxed 2 hours, cooled to -78°C, and 1 mL benzaldehyde (10 mmol, 0.33 eq) added to it dropwise. This was stirred to room temperature over 12 hours, quenched with 40 mL 2M HCl, the aqueous and organic decanted away from residual magnesium, and extractions (3x100 mL ether) were performed. The combined organics were dried, filtered, and concentrated. The crude oil was columned, to afford roughly 70% (by Benzaldehyde) product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 – 7.19 (m, 5H), 6.51 (dd, *J* = 15.8, 14.3 Hz, 1H), 6.27 – 6.05 (m, 1H), 4.28 – 4.14 (m, 1H), 1.38 – 1.29 (m, 6H)

4-morpholino-butyrophenone

1 mmol phenyl cyclopropyl ketone, 4 mmol morpholine, 0.05 mmol sodium barf, and 1 mL toluene were heated to 150 ’C for 1 day. Rotovapped, added 10 mL ether, and 2 mmol LAH portionwise at 0°. This was stirred for 1 hour, then quenched with 1 mL NaOH (1M), 1 mL water, 1 mL ethyl acetate, and the gum extracted with 5 portions of ethyl acetate. This was rotovapped, and shown to be mostly product and used as a comparative standard.

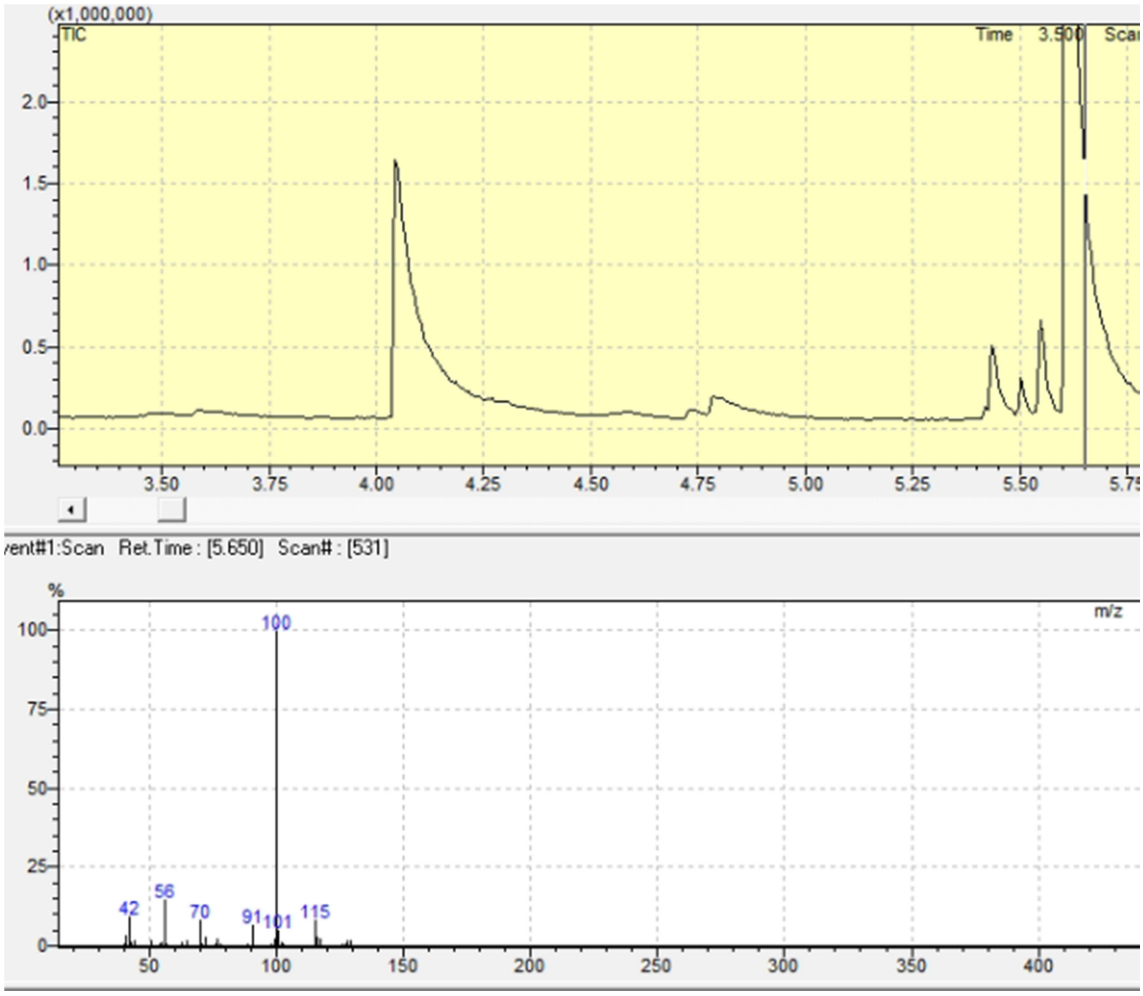
Screening procedure for 1-phenylbut-3-en-1-ol reactions

0.003 mmol of metal source (1.5 if dimeric) was weighed into a 4 mL vial under nitrogen. To this was added 0.006 mmol phosphine (PPh_3, tri-2-furylphosphine, tribenzylphosphine, tricyclohexylphosphine, dimethylphenylphosphine) or 0.003 mmol phosphine (BINAP, DPPP, DPEphos, 1-(Diphenylphospino)-2-(diphenylarsino)ethane, DPPF, BIPY, tbu-DavePhos) or no ligand was added. To this was added 0.003 mmol AgTos or Ag Triflate. To this was added 50 uL solvent (dioxane, toluene, or acetonitrile) and the reactions were stirred for five minutes. In the instances where base was utilized, 0.02 mmol base were added at this point. A stock solution of substrate was made (0.1 mmol of the substrate in 85 microliters of solvent) and 100 microliters of this solution (0.1 mmol) of the substrate was added to each vial using a multipipetter. The vials were allowed to stir an additional five minutes, then 2 equivalents of morpholine (0.2 mmol, 17 microliters) was added to each, and they were sealed. The vials were then heated to 110 °C unless otherwise stated, and stirred for 18-24 hours. The vials were then removed from heat, diluted with approximately 2 mL ethyl acetate, and roughly 100-200 microliters were sampled for gas chromatography. Samples which showed significant area peaks past the starting material's retention time were moved to the GC-MS and sometimes ESI-MS.

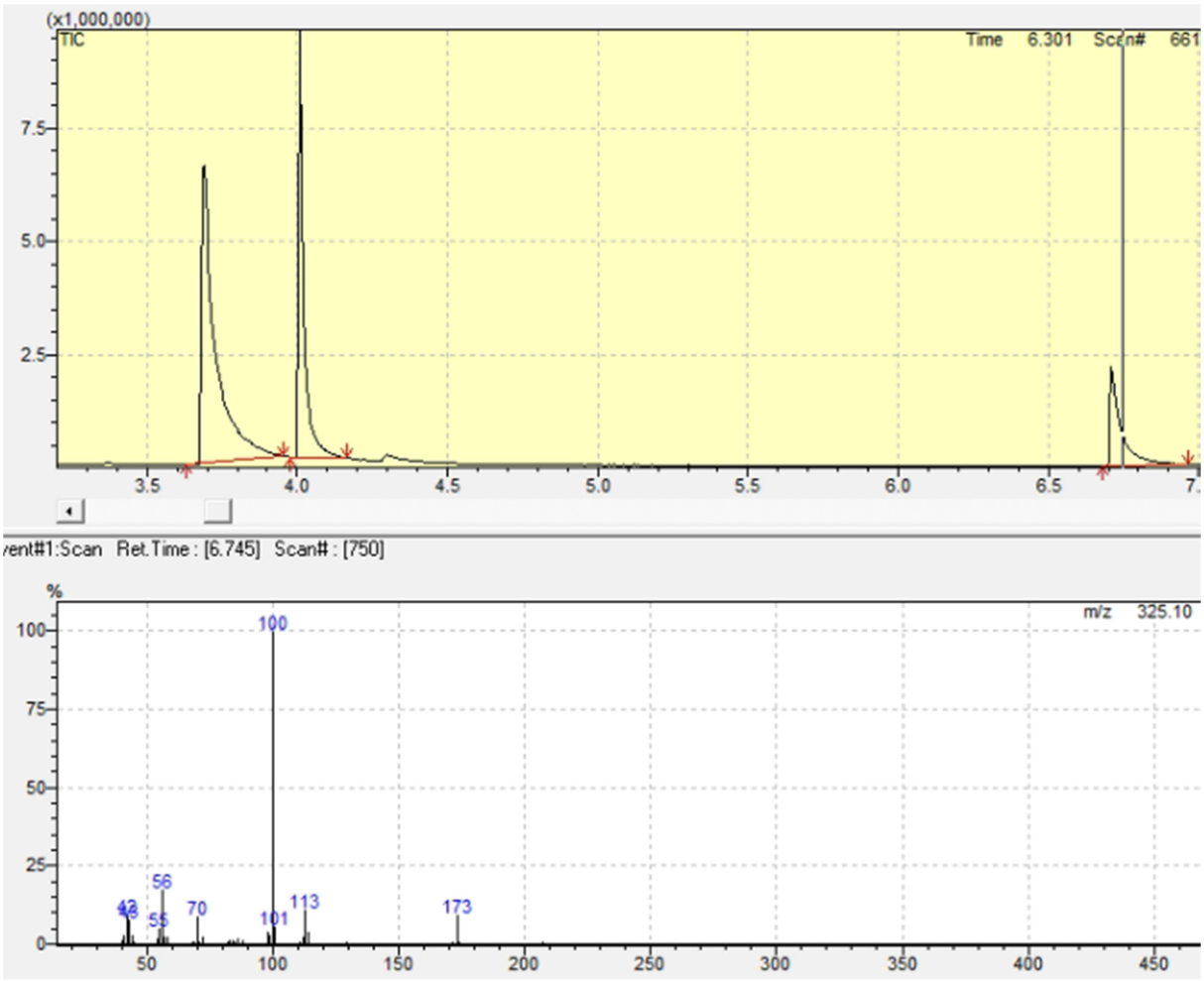
In addition to the alcohol, the acetate protected alcohol, mom protected alcohol, benzyl protected alcohol, TMS protected alcohol, corresponding amide (N towards alkyl chain), and ketone were subjected to reaction conditions without the formation of the desired product.

Metal sources screened:

$[RhCodCl]_2$ – with and without Cs_2CO_3 in CH_3CN, Dioxane, and Toluene, also aniline, ptoluenesulfonamide in all three solvents. RhCodClImes, $[RhCp^*Cl_2]_2$, $[IrCodCl]_2$, $IrCodP(Cy)_3PyrPF_6$. $RuCl_2$*p*-cymene, $NiBr_2$*Diglyme – with and without Cs_2CO_3 in CH_3CN, Dioxane, and Toluene, with aniline, morpholine, and p-toluenesulfonamide, $PdCl_2*(CH_3CN)_2$ - in CH_3CN, Dioxane, and Toluene, with aniline, morpholine, and p-toluenesulfonamide, $CoCl_2$, in CH_3CN, Dioxane, and Toluene, $CuCl_2$, $CuOAc_2$, and CuOTf*benzene, all in DME with morpholine, $FeCl_2$, $FeOTf_2$, $FeAcAc_2$, all in DME with morpholine,

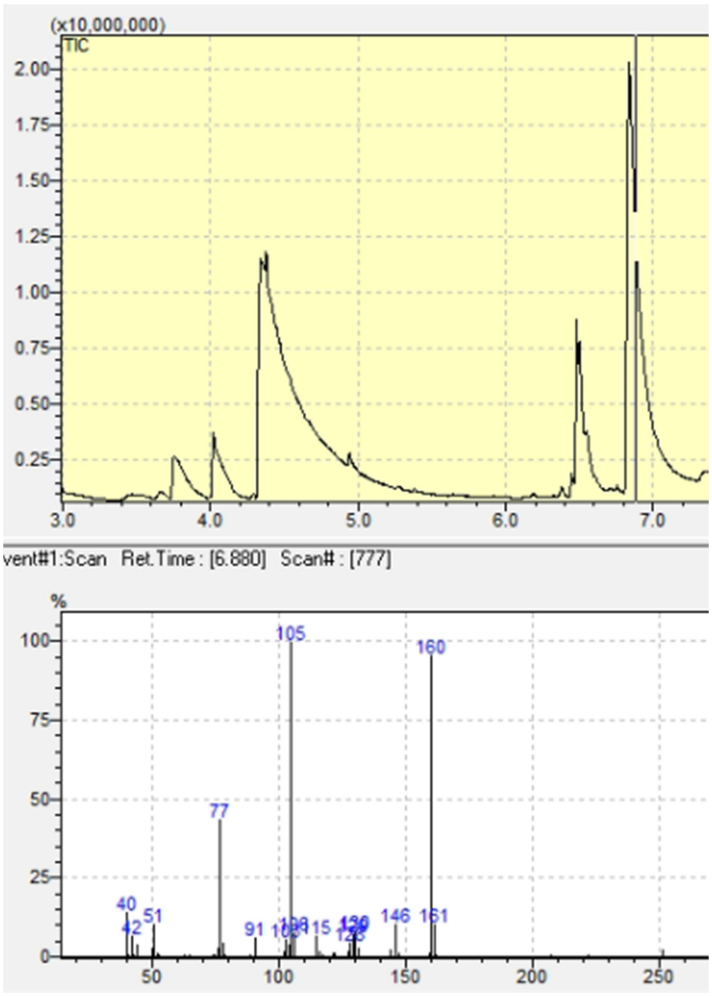


Representative GC-MS of the dehydration-hydroaminaition product, the fragmentation and RT of the product are identical when subjecting 1-phenylhomoallylalcohol and 1-phenylbutadiene to the reaction conditions.



Representative GC-MS of theorized hydroamination product – this trace is from reaction with $Rh(cod)_2BARF_{24}$, BINAP, 100 uL acetonitrile, and 4 equivalents of morpholine.

Procedures for the Exploration of Allylic Amination of Homoallylic Alcohols



Representative crude GC-MS of the allylic amination product of homoallyl alcohols – confirmed by the presence of the mass ion (251) and the NMR (styrenal olefin peaks at 6.5, 6.25 ppm)

This specific reaction is run with 1.5% $[Rh(cod)Cl]_2$, 6% PPh_3, 3% AgTos, 3 eq. Benzamide, at 100 °C, 24 hours 1M in toluene.

3.7 References

(1) "Intermolecular Hydroamination of 1,3-Dienes to Generate Homoallylic Amines", Yang, X.; Lu, A.; Dong, Vy. M. *J. Am. Chem. Soc.* **2017**, *139*, 14049-14052

(2) "Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer", Zhu, Q.; Graff, D. E. Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 741-747

(3) "One-Pot Anti-Markovnikov Hydroamination of Unactivated Alkenes by Hydrozirconation and Amination", Strom, A. E.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8909-8914

(4) "Formal Anti-Markovnikov Hydroamination of Terminal Olefins", Bronner, S. M.; Grubbs, R. H. *Chem. Sci.* **2014**, *5*, 101-106

(5) "Anti-Markovnikov Hydroaminations of Styrene Catalyzed by palladium (II) N-Heterocyclic Carbene Complexes under Conventional and Microwave Heating", Gok, Y.; Yigit, B.; Celikal, O. O.; Yigit, M. *Transition Metal Chemistry,* **2018,** *43*, 591-596

(6) "Ruthenium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes", Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702-2703

(7) "Late Transition Metal-Catalyzed Hydraomination and Hydroamidation", Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem.Rev.* **2015**, *115* (7), 2596–2697.

(8) "Identification of a Butyrophenone Analog as a Potential Atypical Antipsychotic Agent: 4-[4-[4-Chlorophenyl)-1,4-diazepan-1-yl]-1-(4-fluorophenyl)butan-1-one", Ablordeppey, S. Y.; Altundas, R.; Bricker, B.; Zhu, X. Y.; Kumar, E. V. K. S.; Jackson, T.; Khan, A.; Roth, B. L. *Bioorganic & Medicinal Chemistry*, **2008**, *16* (15), 7291-7301

(9) "Chapter 20 - Use of Sedatives, Analgesics, and Neuromuscular Blockers." *Critical Care Medicine,* 3rd ed. Murray, M. J.; Oyen, L. J. Browne, W. T. **2008**, pp 327-342.

(10) "Chapter 123 – Sedation and Analgesia." *Pediatric Critical Care*, 4th ed. Heard, C. M. B.; Fletcher, J. E. **2011**, 1654-1681

(11) "Forty Years of Antipsychotic Drug Research – from Haloperidol to Paliperidone – with Dr. Paul Janssen", Awouters, F. H.; Lewi, P. J. *Arzneimittelforschung*, **2007,** *57* (10), 625-632

(12) “Copper Hydride-Catalyzed Hydroamination of Alkenes and Alkynes”, Pirnot, M. T.; Wang, Y, Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55* (1), 48-57

(13) “Synthesis of Tertiary Alkyl Amines from Terminal Alkenes: Copper-Catalyzed Amination of Alkyl Boranes”, Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134* (15), 6571–6574.

(14) “Copper-Catalyzed Intermolecular Regioselective Hydroamination of Styrenes with Polymethylhydrosiloxane and Hydroxylamines”, Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830–10834.

(15) “Mechanistic Studies Lead to Dramatically Improved Reaction Conditions for the Cu-Catalyzed Asymmetric Hydroamination of Olefins”, Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137* (46), 14812-14818.

(16) “Computational Explorations of Mechanisms and Ligand-Directed Selectivities of Copper-Catalyzed Ullmann-Type Reactions”, Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132* (17), 6205–6213.

(17) “Asymmetric Copper Hydride-Catalyzed Markovnikov Hydrosilylation of Vinylarenes and Vinyl Heterocycles”, Gribble, M. W.; Pirnot, M. T.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139* (6), 2192-2195.

(18) “Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes”, Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135* (42), 15746–15749.

(19) “Radical Transfer Hydroamination of Olefins with N-aminated Dihydropyridines”, Chou, C.; Guin, J.; Muck-Lichtenfeld, C.; Grimme, S.; Studer, A. *Chem – Asian J.* **2011**, *6*, 1197-1209

(20) “Anti-Markovnikov Hydroamination of Alkenes Catalyzed by an Organic Photoredox System”, Nguyen, T. M.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135* (26), 9588-9581

(21) “Catalytic Intermolecular Hydroaminations of Unactivated Olefins with Secondary Alkyl Amines”, Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science*, **2017**, *355 (*6326), 727-730

(22) “Regio- and Chemoselective Intermolecular Hydroamination of Allyl Imines for the Synthesis of 1,2-diamines”, Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. *J. Am. Chem. Soc.* **2014**, *136* (32), 11256-11259

(23) “Rhodium-Catalyzed Regiodivergent Hydrothiolation of Allyl Amines and Imines”, Kennemur, J. L.; Kortman, G. D.; Hull, K. L. *J. Am. Chem. Soc.* **2016**, *138* (36), 11914-11919

(24) “Rhodium-Catalyzed Asymmetric Hydroamination of Allyl Amines”, Vanable, E. P.; Kennemur, J. L.; Joyce, L. A.; Ruck, R. T.; Schultz, D. M.; Hull, K. L. *J. Am. Chem. Soc.* **2019**, *141* (2), 739-742

(25) “Conformational Studies of Metal Chelates. I. Intra-Ring Strain in Five- and Six-membered Chelate Rings”, DeHayes, L. J.; Busch, D. H. *Inorg. Chem.* **1973**, *12*, (7) 1505-1513

(26) “Alkyne Insertion Into Cyclometallated Pyrazole and Imine Complexes of Iridium, Rhodium, and Ruthenium; Relevance to Catalytic Formation of Carbo- and Heterocycles”, Boutadla, Y.; Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Jones, R. C.; Singh, K. *Dalton Transactions*, **2010**, *39*, 10447-10457.

(27) *“*Palladium-Catalyzed Oxygenation of Unactivated sp^3 C–H Bonds”, Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126* (31), 9542-9543.

(28) “CXIX. – The Formation and Stability of *spiro*-compounds. Part I. *spiro*-Compounds from Cyclohexane” Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080-1106

(29) “Iridium-Catalyzed Enantioselective Fluorination of Racemic, Secondary allylic Trichloracetimidates”, Zhang, Q.; Stockdale, D. P.; Mixdorf, J. C.; Topczewski, J. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2015**, *137* (37), pp 11912–11915

(30) “Enantioselective Iridium-Catalyzed Allylic Amination of Ammonia and Convenient Ammonia Surrogates”, Pouy, M. J. Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Organic Letters*, **2007**, *9*, 3949

(31) “A Simple Iridium Catalyst with a Single Resolved Stereocenter For Enantioselective Allylic Amination. Catalyst Selection from Mechanistic Analysis”, Leitner, A.; Shekhar, S.; Pouy, M. J. Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506

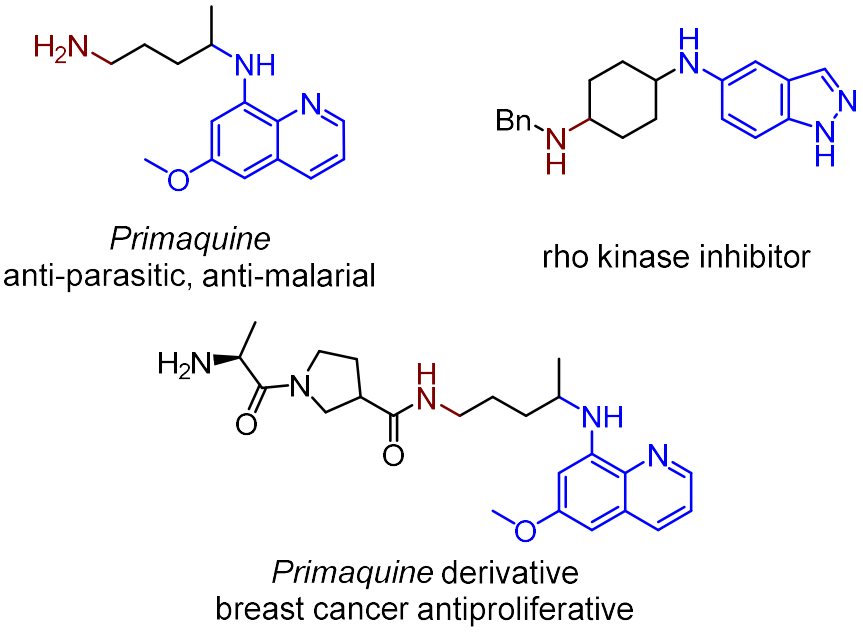
(32) “Direct Enantioselective Iridium-Catalyzed Allylic Amination of Racemic Allylic Alcohols”, Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3470
(33) “Stereospecific Substitution of Allylic Alcohols To Give Optically Active Primary Allylic Amines: Unique Reactivity of a (p, alkene) Ir Complex Modulated by Iodide”, Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917
(34) “Directed Palladium(II)-Catalyzed Intermolecular Aminohydroxylation of Alkenes using a Mild Oxidation System”, Zeng, T.; Liu, Z.; Schmidt, M. A.; Eastgate, M. D.; Engle, K. M. *Org. Lett.* **2018**, *20* (13), 3853-3857 and similar work of theirs in this area
(35) “OLEX2: A Complete Structure Solution, Refinement and Analysis Program”, Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K. Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339-341
(36) “A Short History of SHELX”, Sheldrick, G. M. *Acta Cryst.* **2008**, A*64*, 112-122

Chapter 4: Regioselective Hydroamination of Internal Olefins Through a Directing Group Strategy to Afford 1,4-Diamines

4.1 Introduction

The functionalization of internal olefins with sterically and electronically similar substituents has been a clear challenge for transition-metal methodologies for a long time. This is due to some clear challenges: low binding affinity of internal olefins to metals, slower migratory insertion, and the ease of isomerization of olefins through transition-metal catalysis. These challenges are exacerbated for internal olefin hydroamination, as each of those is already a major challenge for hydroamination reactions.[1-7] Also, the challenge of regioselectivity is much more obtrusive as there is no longer a significant steric or electronic difference in the aminometallation step. Despite these challenges, the development of a hydroamination reaction of internal olefins is highly valued, as it will allow access to 1,3 or 1,4-diamines. In addition, these products would be similar to the products of **Chapter 3**, but with an added methyl. As the "magic methyl" effect has been discussed (*vide infra*),[8] more commentary on the value of such a thing is not necessary.

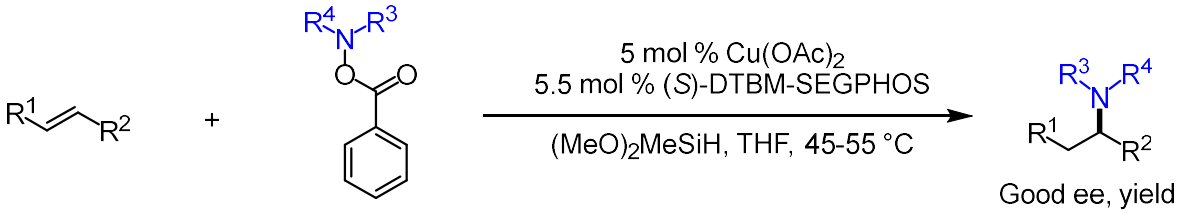
Figure 4.1: Molecules with biological effects containing a branched 1,4-diamine



There are currently two dominant methods of intermolecular hydroamination of unactivated internal olefins with amines,[9] although both are indirect methods, with concomitant waste production. The first one to be published was by the Buchwald group, in 2015.[10] This approach

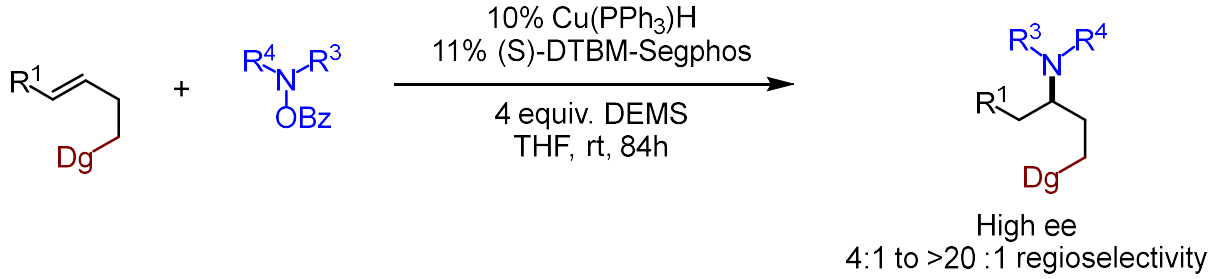
utilizes the Cu-H chemistry discussed in **Scheme 4.1**, the use of a silane to produce a copper hydride, which inserts into the olefin, and the resulting Cu-alkyl is then aminated by an electrophilic amine, with all the waste inherent to this approach (**Scheme 4.1**). This method is also inherently limited to the use of either symmetric or highly sterically differentiated amines; for instance when the two substituents on the olefin are *tert*-butyl and ethyl, only an 85:15 regioisomeric ratio is observed. Other, related, reports from the Buchwald group show similar methods for differing starting materials: all with either these limitations, or with some effect designed into the starting material to assist in differentiation during the regioselectivity determining step.[11, 12] As has been discussed, this approach is also inherently limited by the need to form the benzoylamine derivatives, as well as the high amount of byproducts generated in the reactions.

Scheme 4.1: Copper-catalyzed indirect intermolecular hydroamination of internal alkenes



This approach still relies on the inherent differentiation of the substrate, mostly through steric effects. This does not allow for the general hydroamination of internal olefins lacking steric or π-conjugation differentiation. The only currently published method with that claim to fame is the hydroamination of olefins containing a homoallyl electronic directing group published by the Hartwig group in 2016.[13] This approach uses olefins which have highly electron withdrawing groups located in the homoallyl position (protected alcohols and amines) which create an olefin which is effectively more electrophilic at the further position. This affords a single regioisomer upon Cu-H insertion, which is maintained in the product. This is somewhat similar to our proposal in one major way: the directing group is affecting the selectivity of the reaction.

Scheme 4.2: electronically directed formal hydroamination of internal olefins



It has been shown that this transformation does not involve direct coordination of the directing group to the metal complex, as the stereochemistry of the product when using a cyclic olefin with a tethered directing group has an anti- and not cis relationship between the directing group and the amine. This approach is indeed a good step in the right direction for directed hydroamination reactions, although it is still utilizing atom inefficient indirect hydroamination methods. This also affords a 1,3 relationship between the directing group (which can be a tosylamine) and the amine, whereas our approach would afford the 1,4 diamine selectively.

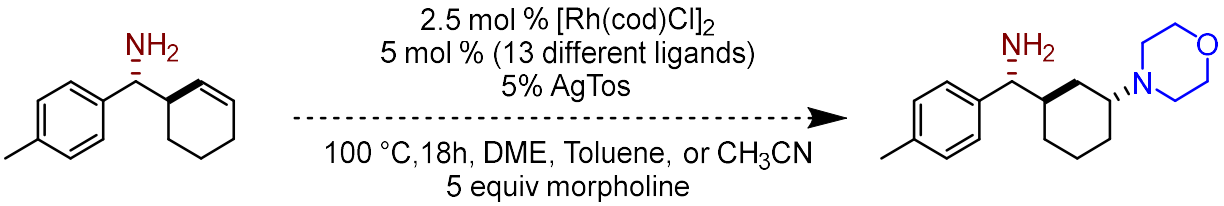
Our goal was to approach this problem through our directing group strategy, where the stability of the transition states leading to the differently sized metallacycles is the guiding principle governing selectivity. This is essentially an expansion of the work in **Chapter 3**, with more difficult aminometallation and olefin coordination issues to overcome. This directing group olefin functionalization strategy has also been borne out in other systems, such as those published by the Dong group, the Takacs groups, and the Engle group, with limited examples of internal olefins.[14-19] We have shown that this allows for the formation of anti-Markovnikov products from terminal olefins, meaning that this strategy can access branched metal-alkyl species, which is sufficiently stable to not undergo side reactivity before protonolysis. Also, the ability to form this product when there is a significant steric difference between the insertion sites, and still obtaining the product derived from insertion of the metal to the more hindered site, means that we anticipate impeccable regioselectivity. This strategy has also, in our experience, resolved the issue of oxidative amination smoothly, leading us to believe this will continue. Also, the stoichiometry of the reactions we use show that the directing group truly is having a powerful effect on the coordination of the olefin: we are using stoichiometric or superstoichiometric quantities of nucleophile, and still observing reactivity, as opposed to the traditional paradigm of an order of magnitude more olefin than amine for direct hydroaminations. We believe that this

approach therefore is the most likely of all approaches to be able to resolve the issue of direct intermolecular hydroamination of internal olefins.

4.2 Adapting Our Approach

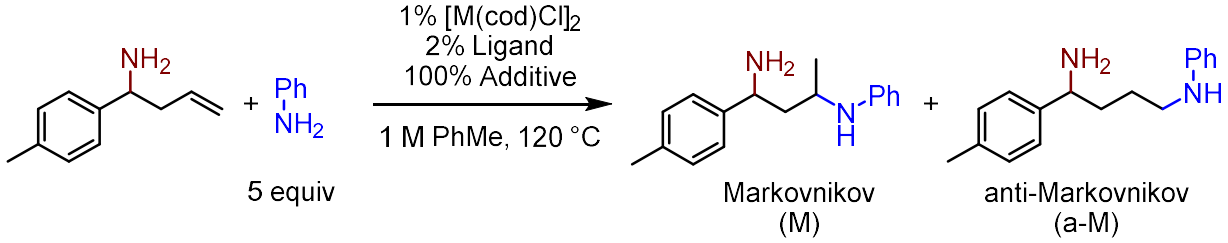
Our initial attempts to adapt the work in **Chapter 3** to internal homoallylamine substrates was met with failure: a variety of ligands afforded at best trace product under our typical reaction conditions (**scheme 4.3**). We did a small amount of other screening on this, but hypothesized that what we needed was either a less strong ligand as a nucleophile, or a different metal. Concurrent with this work was some work on adapting the strategy in **Chapter 3** to the use of aniline nucleophiles, and developing a regiodivergent strategy to access the 1,3 or 1,4 diamine from homoallylamine starting materials.

Scheme 4.3: Initial screening on internal olefins



Initial work on this regiodivergent project had not been done in a vacuum: Our group has published in this area previously: a regiodivergent hydrothiolation of allylamines and imines by Dr. Greg Kortman and Jennifer Kennemur. Dr. Seth Ensign performed initial experiments to show the viability of this regioselective hydroamination reaction of terminal homoallylamines using anilines as nucleophiles, and developed the methodology (unpublished work). This strategy is the realization of a future direction discussed in Chapter 3, the access of two different products from the same starting material (table 4.1). Intriguingly, this work required using different transition-metals to switch the selectivity.

Table 4.1: Regiodivergent hydroamination reaction optimization and conditions

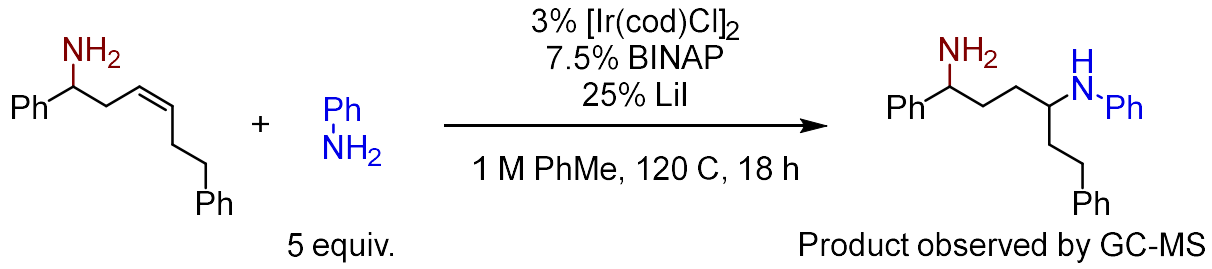


Entry	Ligand	Additive	Combined GC Yield (%)	M:a-M
1	DPEphos	none	4	5.6:1
2	DPEphos	LiBr	20	10.0:1
3	DPEphos	LiI	27	7.4:1
4	DPEphos	$LiBF_4$	16	4.4:1
5	DPEphos	MgF_2	2	3.9:1
6	DPEphos	$MgCl_2$	75	7.1:1
7	DPEphos	$MgBr_2$	61	3.0:1
8	DPEphos	MgI_2	5.8	9.5:1
9	DPEphos	$Mg(OTf)_2$	21	4.6:1
10	dppe	$MgCl_2$	<2	n/a
11	dppp	$MgCl_2$	77	1:1.7
12	dppb	$MgCl_2$	73	1.8:1
13	dpppent	$MgCl_2$	23	2.3:1
14	BINAP	$MgCl_2$	48	1:1.8

This reaction is able to selectively form either the Markovnikov or the anti-Markovnikov product with fairly high levels of selectivity for either isomer of the product (7.8 : 1 or 1 : 8.1) through simply switching the in-situ catalyst and additives for the reaction. This impressive switch is true for a broad range of substrates and nucleophiles, and there were some interesting trends observed which give a hint to the mechanism: the use of electron rich anilines enhances the formation of the anti-Markovnikov product under both conditions (eroding selectivity, or improving, depending on which conditions are in use.) The reverse is also observed: the use of electron-poor nucleophiles enhances the formation of the Markovnikov product. This is in line with the idea that more nucleophilic amines may attack at the less electrophilic, but also less

hindered, carbon more readily than their less nucleophilic counterparts, which require stronger activation of the internal carbon. Also, if an electron deficient aniline or anilido is a ligand to the metal center, we can envision that the internal carbon would be rendered more electrophilic than the instance in which the anilido were electron rich. This project will not be discussed further here, as it is Dr. Ensign's work. Dr. Ensign applied these conditions, albeit slightly modified, to the hydroamination of an internal olefin substrate, and was excited to find initial results for its hydroamination (**scheme 4.4**).

Scheme 4.4: Internal olefin onitial hit

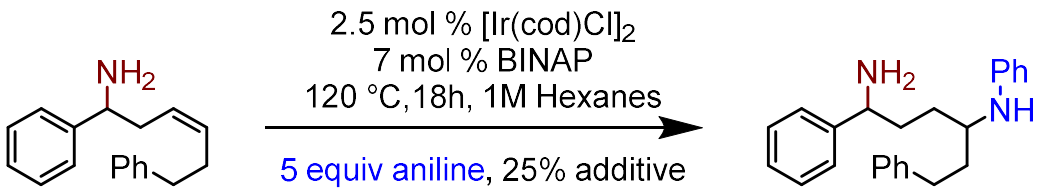


This is where I began work in this area, trying to take the initial hit and optimize it into productive conditions. I found that these conditions afforded a 0.15 p/std in my hands, which when I obtained an NMR yield was roughly a 12% yield. At this stage it was difficult to determine the diastereomeric ratio, or if the product was produced with high regioselectivity, due to messy crude nmrs and an inability to purify the product when it was such a small component of the reaction.

4.3 Initial Optimization Screening

The first thing I considered to optimize to improve the yield of this reaction was the identity of the additive. Since the additive had proved critical in Seth's experience, I thought that it might be important here, and screened a variety of ligands with a variety of anion and cation softness centered around LiI, the previously optimized additive for 1,4-diamine formation. Clearly both cation and anion are important: ZnI_2 performs admirably, and CaI_2 affords essentially no product, which is mirrored with ZnI_2 and $ZnBr_2$.

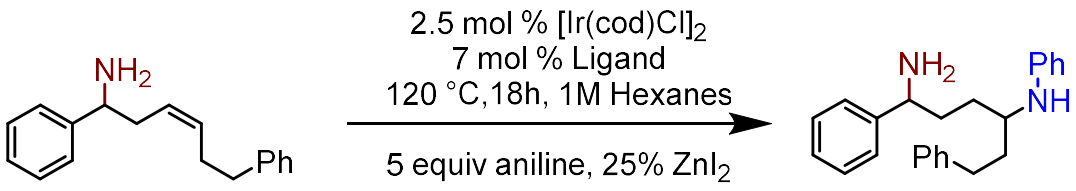
Table 4.2: Additive screen for internal olefin hydroamination



Additive:	p/std
CaI_2	0.01
None	0.00
$CaBr_2$	0.02
$ZnBr_2$	0.04
CsI	0.07
$MgBr_2(Et_2O)$	0.08
KBr	0.08
KI	0.09
NaI	0.10
$SrCl_2$	0.10
$Mg(NO3)_2$	0.11
$LiNO_3$	0.13
$Ca(NO3)_2$	0.14
LiI	**0.15**
ZnI_2	**0.18**
K_2SO_4	**0.18**

This screen demonstrated to us that the identity of the additive was already close to ideal, and that only small advances could be made in this area. We found it very interesting that many additives function, but that the reaction shows no detectable product without an additive. The solvent was switched to hexanes for this screen, as it had been determined to have no impact on the yield and slightly reduced starting material consumption. We hypothesize that it mostly serves to wash material down the walls of the vial, as we are considerably above its boiling point, and that the reaction is essentially neat in aniline. A ligand screen was our next step to attempt to improve the catalyst (**table 4.3**).

Table 4.3: Ligand screen for internal olefin hydroamination

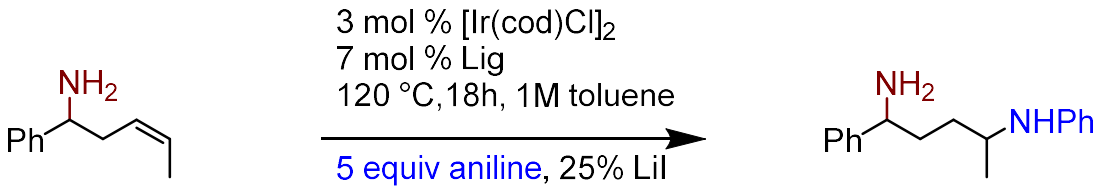


Ligand:	p/std
PPh_3	0.00
Bn_3P	0.00
BIPY	0.00
BINAP	**0.10**
*t*BuDavePhos	0.00
DPPF	0.00
Bis(diphenylarsino)ethane	0.00
DPPM	0.00
DPPE	0.00
DPPP	0.00
DPPB	0.00
DPPPent	0.00
DPPH	0.00
DPE	0.00
Fur_4MeO-Biphep	0.03
MeO-Biphep	0.10
GarPhos	**0.20**
SegPhos	0.12
H8-BINAP	0.12
DIOP	0.04
SDP	0.08
Tol-BINAP	**0.29**

These results clearly showed that *Tol*-BINAP is a superior ligand for this transformation, but that it wouldn't be enough to get the yields to satisfactory levels – this is still only approximately a 25% yield. At this point (with other screening omitted) we were somewhat discouraged by our

progress, and attempted to determine if this was simply a poor substrate for the reaction. We synthesized the methyl capped substrate instead of the phenethyl capped substrate, and subjected it to similar conditions and ligand experiments.

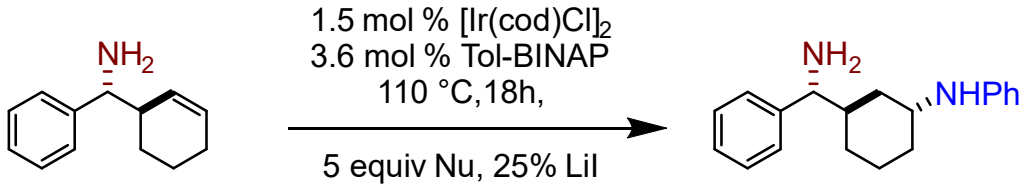
Table 4.4: Ligand screen on methyl capped substrate



Ligand:	p/std
GarPhos	0.57
SDP	0.32
BINAP	0.11
Tol-BINAP	**0.65** (69% NMR)

Tol-BINAP again affords significantly higher yields than every other ligand, and intriguingly, dramatically more than BINAP does. This effect is not well understood, though we believe it is related to an effect observed by Dong and coworkers.[21, 22] These improved p/std ratios, which correlate to much higher yields, are highly encouraging and show a reaction which is now synthetically viable. Also, for the first time, we were able to clearly determine the diastereomeric ratio of the product in the crude from the reaction. Unfortunately, this d.r. is roughly 1.5 : 1 and seems to be ligand independent (± 0.2). It is also olefin geometry independent, with the same d.r. and predominant diastereomer observed with the E olefin, although the Z olefin is much more reactive than the E olefin (20% nmr yield). This potentially implicates the racemization of one stereocenter, as the same stereoisomer is preferred. In order to see if this problem can be resolved, we attempted the subjection of a cyclic alkene to the reaction, in order to determine if the d.r. is vastly improved or whether the catalyst is racemizing one of the centers through β-hydride elimination and reinsertion. We were able to synthesize, with high levels of d.r., a cyclohexenyl internal alkene homoallylamine and subject it to the reaction conditions.

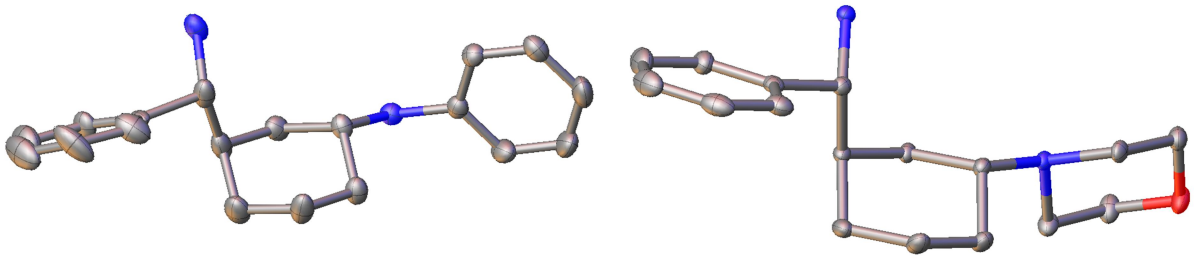
Table 4.5: Preliminary condition screen on cyclohexenyl substrate



	Entry	p1/std	p2/std
As shown	1	0.63	0.62
std, 66 uL aniline	2	0.50	0.78
neat (75 uL an)	3	0.06	**0.83**
morph – std, 40 uL	4	0.35	0.24
morph – neat, 60 uL	5	0.11	**0.49**

We have determined that p2 is the product shown in the scheme, and that p1 appears to be a diastereomer, either generated from a different mechanism of aminometallation or through the erosion of the benzylic stereocenter. We did this by synthesizing the 1,3 products through genuine synthesis, and observing different retention times and fragmentation patterns by GC-MS. Intriguingly, the use of morpholine as a nucleophile in this transformation is also tolerated, and has also been shown through crystallography to afford the same product. Getting the same relative configuration of the diastereomer supports the hypothesis that they are both going through the same mechanism.

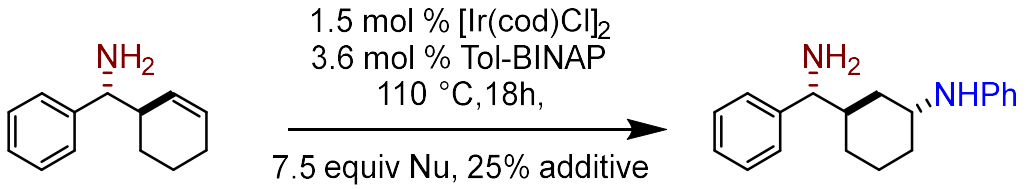
Figure 4.2: **2g*Armstrong's Acid** and **2l*2PTSA**, hydrogen atoms, solvent molecules, and anions omitted for clarity. Thermal ellipsoids shown at 50% probability



This is the first clear hint of the mechanism of this transformation, and supports the hypothesis that the aniline is undergoing a rare outer-sphere aminometallation as opposed to the more standard oxidative addition-migratory insertion pathway for electron deficient amines.

We went on to investigate different additives for this transformation, and while the results included some GC inconsistencies, we did find an additive which dramatically reduced the amount of p1 observed, while maintaining and enhancing the formation of p2, our desired product (**table 4.6**).

Table 4.6: Additive screen on cyclohexenyl substrate



Additive	Product/Std	Product/Byproduct	(SM+Decomp)/
KBr	0.25	0.46	1.41
CaI_2	0.44	1.22	1.39
$LiNO_3$	0.80	9.71	1.40
$MgSO_4$	0.27	1.39	1.78
$Ca(NO_3)_2$	0.43	2.99	1.42
KI	0.63	3.09	1.53
NaI	0.77	6.38	1.30
$CaBr_2$	0.19	1.10	1.90
$Mg(NO_3)_2$	**0.95**	**28.17**	**1.05**
CsI	0.62	4.59	1.45
Li_2SO_4	0.25	1.34	1.77
$MgBr_2$	0.29	1.60	1.73
$ZnBr_2$	**1.04**	**10.87**	0.89
K_2SO_4	0.26	1.44	1.81
ZnI_2	0.95	4.24	0.92
LiI	0.92	3.54	0.98
no additive			1.22

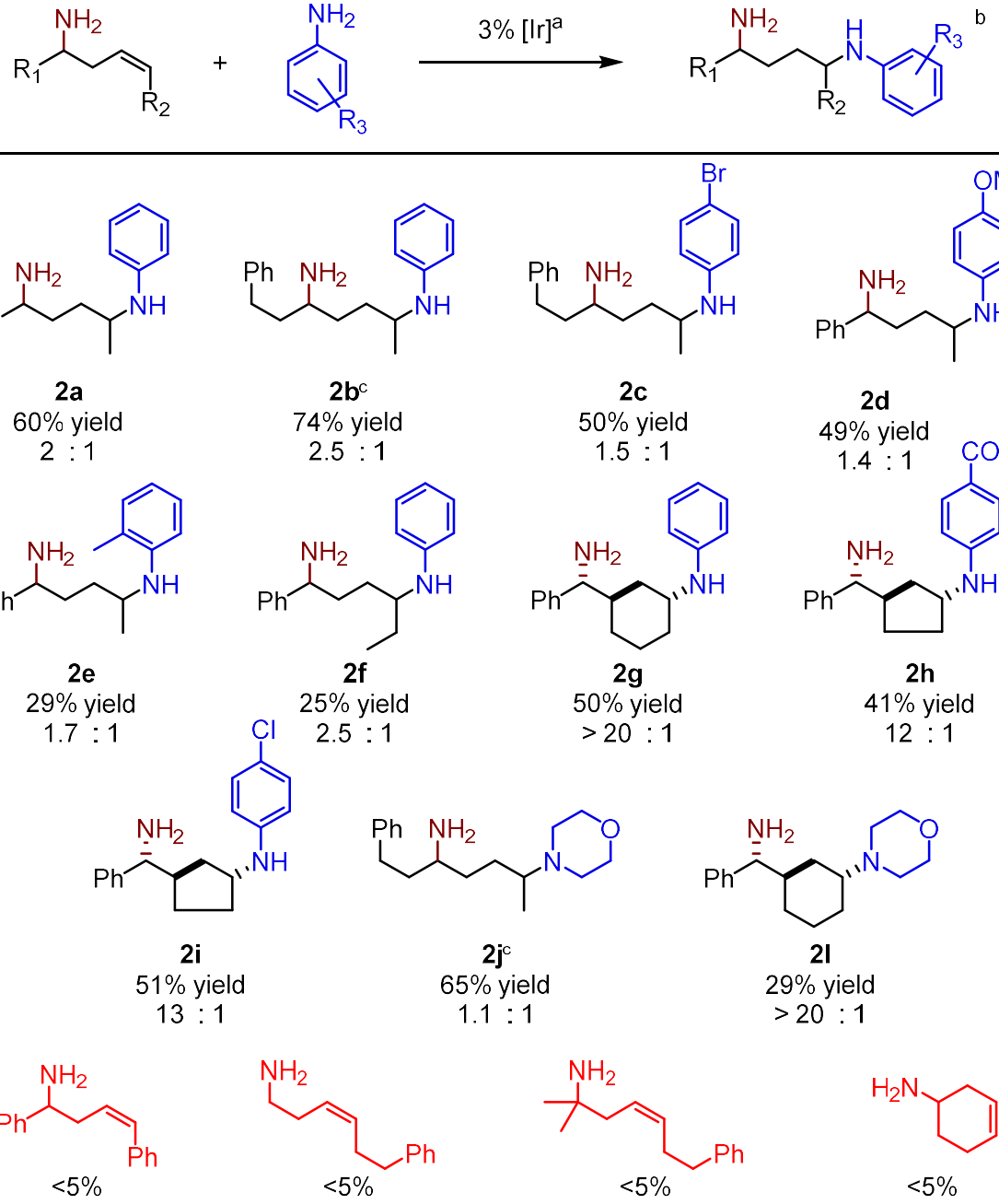
We observed again that the absence of an additive results in no product formation, and even results in significant starting material decomposition (to byproducts which have yet to be identified). The sm/std ratio for the starting material at the beginning of the reaction is roughly 2.10, so about 40% of the starting material decomposes under these conditions. Magnesium nitrate and zinc bromide proved to be the best additives for this reaction for the combination of percent yield and product selectivity, and after some screening (not shown here) it was determined that magnesium nitrate was the superior additive. These conditions were then tested on the linear alkenes, and found to be similar or superior, and were adopted for all substrates. Unfortunately, these changes did not result in an improvement in the diastereomeric ratios observed in the products from linear alkenes, and neither did further additive screening.

4.4 Substrate Scope & Observations

With these conditions in hand we moved forward to test these conditions with a variety of substrates and nucleophiles in order to determine the scope of this transformation. We were especially curious with regards to whether the diastereomeric ratio would be nucleophile dependent, as well as whether it was possible to use significantly different nucleophiles and directing groups in the transformation. Much of our initial exploration focused on methyl capped Z-olefins or cyclic olefins, as they function the best in this transformation. We were able to determine that amines with α-aryl and alkyl groups to the directing group both function well, and in fact the ones with α-alkyl groups (**2b, 2c**) afford slightly superior yields, but with essentially unchanged diastereoselectivity. The use of electron deficient (**2c**) and electron rich anilines (**2d**) is tolerated, and even the presence of an aryl bromide (**2c**) has only a mildly deleterious effect on the yield of the reaction. We also examined the use of a hindered amine, 2-methyl aniline. This aniline functions as a nucleophile; however, the yield is significantly decreased (**2e**). The same is true for making the olefin more hindered, such as an ethyl-capped olefin (**2f**). A propyl-capped olefin has a further reduced yield, with an NMR yield of only 15% indicating a clear limitation for this transformation. All of these products were obtained with a 1.4:1 to 2.5:1 ratio of diastereomers, indicating that the process is essentially unaffected by the starting olefin, and the amine nucleophile. Since we suspect this process goes through an outer-sphere nucleophilic attack, this likely indicates that the aminoolefin complex binds with little discrimination as to which prodiastereomeric face of the olefin is presented. When subjecting cyclic olefins to this process, we see much higher d.r, only slight erosion if any from the d.r. of the starting materials

(~20 : 1 for the cyclohexenyl, ~14 : 1 for the cylopentenyl). This also allowed us to confirm the major diastereomer through crystallography of the Armstrong's acid or *p*-toluenesulfonic acid salts of the products. Subjecting morpholine to the reaction conditions with either a linear or cyclic internal homoallylamine leads to the formation of the desired product, and in the cyclic case, it is even observed as the same diastereomer as the product with aniline as has been discussed (*vide infra*). In none of these cases is a significant amount of the 1,3 or 1,5 isomer observed. In addition, when a bishomoallylamine is subjected to these reaction conditions we do not observe cyclization, but we observe instead a different product with a mass indicative of hydroamination (as yet unidentified), indicating that this is not simply isomerization-hydroamination. Enantioenriched samples of the starting materials for **2a** and **2g** were subjected to the reaction conditions with chiral ligand with essentially no change (yield, or selectivity) observed.

Table 4.7: Substrate scope of the internal olefin hydroamination

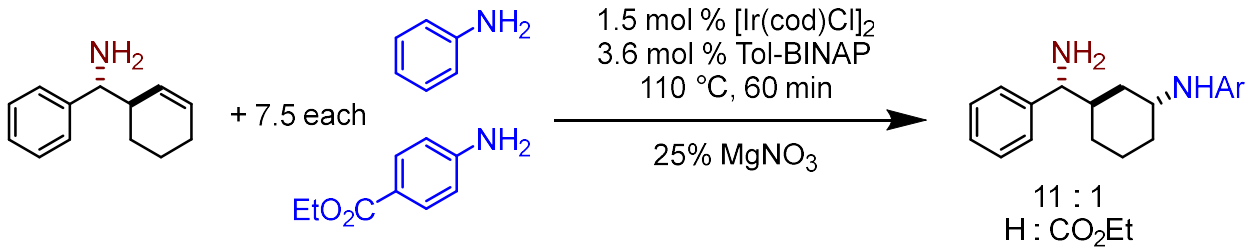


[a] 1.5% $[Ir(cod)Cl]_2$, 3.6% *tol*-BINAP, 25% $MgNO_3$, 7.5 equiv. nucleophile, 100 °C, 16h
[b] Yield and d.r. determined by the mass and NMR of the pure sample, respectively. [c] 90 °C

We were curious to determine something more about the mechanism of this transformation, as this method of aminometallation was unexpected. This inspired us to devise experiments to

verify this mechanism. A drastic effect was observed when performing a competition experiment between an electron neutral and electron deficient amine (**Scheme 4.5**).

Scheme 4.5: Competition experiment



An 11:1 ratio of products is observed, indicating that the electron deficient aniline reacts 10 times slower than aniline does which supports that aminometallation is either rate determining or before the rate determining step. When this experiment was run as a separate vial rates experiment, the trend held, although with slightly lower magnitude: the reaction with aniline happened 3.6 times faster than the reaction with 4-carboxyethyl aniline. We also determined in a separate vial rate experiment that there is a notable (1.46) KH/KD observed. Given the diastereomer of the product, the knowledge that electron deficient anilines are very slow in the reaction, and this KH/KD, it seems likely that the resting state of the catalyst is an aminoolefin or product-bound complex, the selectivity determining step is the outer-sphere aminometallation, and that the rate determining step is during the net protonolysis of the C–Ir bond, giving rise to the KH/KD. Each of the alternatives, such as rate limiting oxidative addition or migratory insertion, fails to coherently fit all the available data. Unless the mechanism is significantly different for cyclic and acyclic internal olefins, the origin of the poor d.r. in the acyclic olefin case must be, as was previously discussed, a poor differentiation of the prodiastereomeric faces of the olefin binding to the metal center.We can imagine, looking at the crystal structures in **Chapter 3** that an aminoolefin complex may have a preference for either a boat, or a chair-like coordinate mode. These two modes lead to two different diastereomers of the product, and the lack of energetic difference between the two is likely driving the poor selectivity.

4.5 Summary, Limitations, and Future Directions

The development of a hydroamination of internal olefins has been presented. This reaction stitches together weakly basic anilines and olefins with remarkable levels of regioselectivity, and in the case of cyclic olefins, also diastereoselectivity. This transformation is remarkable, as it

currently the only highly regioselective direct intermolecular hydroamination process of unstrained internal alkenes known. Despite the clear limitation in terms of substrates that can be utilized, this represents a major advance. This transformation also has been shown to go through a very unusual mechanism for a late-transition metal promoted hydroamination using electron deficient amines.

Currently this transformation, as a synthetically useful reaction, is mostly limited to the production of 1,4 diamines where one amine is directly connected to a ring, and the other is an exocyclic carbinamine. The ability to form this motif, containing three stereocenters, with high levels of fidelity is incredibly challenging using normal methods. In fact, we have not been able to generate the other diastereomers of this compound efficiently in the lab using any other method. The use of this transformation is considerably more limited in the systems with acyclic olefins, due to the issue of the low diastereoselectivity. However, for instances where the stereocenter is not important (such as when it will later be removed), this is an effective way of forming the product. It also leaves room for a very important future direction.

This method, while a strong start, also has significant room for improvement. There are some clear places that could be improved in this transformation, as well as future directions which could be developed. A minor issue with this transformation is that the yields are not impeccable. We did note, as we were developing it, that there was a very large difference in yield (0.11 p/std vs 0.65 p/std) switching from BINAP to *Tol*-BINAP. We would hypothesize that with a larger library of available BINAP derivatives, or the time to synthesize them, this transformation could be dramatically improved. This would also allow for investigation of what is causing this effect, which is an interesting topic of its own right. Connected deeply to this is issue of diastereoselectivity: we would hope that by changing the 3,3' substituents of the BINAP, or using 2,6 disubstituted aryl rings as the substituents on the phosphines, we may be able to peturb the coordination of the olefin, and obtain primarily one diastereomer. The use of enantioenriched starting materials currently leads to a mixture of diastereomers, even using chiral ligand, but in the future if we cannot develop a highly diastereoselective method, the development of an enantioselective hydroamination of enantioenriched homoallylamines would allow access to the desired diastereomerically enriched products, and allow for catalyst control of the two diastereomers being formed.

A common thread for the future directions of each of these directed transformations (**Chapters 2, 3, 4**) is that the directing group strategy should be able to control multiple hydrofunctionalizations and use multiple directing groups, allowing the use of many directing groups to direct the functionalization of a variety of allyl and homoallyl internal olefins, in this case. This would allow the synthesis of a variety of compounds with a 1,4-relationship between two polar groups, with high levels of regio- and diastereo-control. This, of course, would be something like alcohol directed hydroamination, or amine directed hydroalkoxylation. The development of these would not be without their challenges, but would be worthwhile goals nonetheless, and elevate this method from an initial foray into a field into a body of work.

4.6 Experimental Procedures

General Information

General Experimental Procedures:

Unless otherwise specified, all reactions to synthesize homoallylic amines with air sensitive reagents (Grignards, etc.) were carried out in flame-dried glassware under an atmosphere of nitrogen; mildly air sensitive reactions (such as those involving $Ti(OEt)_4$ were not setup in flame-dried glassware. All hydroamination reactions were, and should be, setup under inert atmosphere; while the precatalysts, ligands, amines, and alkenes are all relatively air stable, the active catalyst is not. Nitrogen was dried by passing through drying tube equipped with Drierite. Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen levle ~ 1.0 ppm) or using standard Schlenk technique. Column chromatography was performed with silica gel from Grace Division Discovery Sciences (35-75 μm mesh); all columns were slurry packed. Analytical thin-layer chromatography (TLC) was performed on precoated glass silica gel plates purchased from EMD Chemicals Inc. and visualized with either short wave (254 nm) ultraviolet light or by staining with $KMnO_4$ and briefly heating. Distillations were performed using a 3 cm short-path column under reduced pressure.

Instrumentation: 1H, 13C, and 19F NMR were recorded using a Varian Unity 400 or 500 MHz (100 or 125 MHz respectively for 13 C) or a VXR-500 MHz spectrometer. Spectra were referenced to residual solvent using either CDCl3 (1H NMR: δ7.26 ppm, 13C NMR: δ 77.36

ppm) or C6D6 (1H NMR: δ7.15 ppm and 13C NMR: δ 128.60 ppm). Chemical shifts are reported in part per million and the multiplicity is as indicated: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). Coupling constant values are designated by *J* and are reported in Hertz. Integration of the products is provided. Analysis of products and starting materials by Gas Chromatography (GC) where indicated is performed using a Shimadzu GC-2010 Plus Gas Chromatograph equipped with SHRXI-MS-15 m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and Flame Ionization Detector (FID). GC yields are given relative to diphenylmethane as an internal standard unless otherwise indicated. Gas Chromatogrpahy-Mass Spectrometry (GC-MS) analysis is perfrmed using a Shimadzu GC-2010 Plus Gas chromatograph equipped with Shimadzu GCMS-QP2010 SE mass spectrometer. Analyte is separated by way of a SHRXI-5MS- 30 m x 0.25 mm x 0.25 μm column using helium carrier gas; identification of the analyte is assisted by electron impact ionization. High Resolution-Mass Spectrometry (HR-MS) is performed in the Department of Chemistry at the University of Illinois at Urbana-Champaign. All air sensitive reactions involving the hydroamination reaction, unless otherwise indicated, were setup with the aid of a glove box maintained under nitrogen atmosphere.

Materials:

Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated Stainless Steel columns while following manufacture's recommendations for solvent preparation and dispensation unless otherwise noted. All amines (excluding allyl amine) were distilled and degassed by the freeze-pump-thaw method before use. Allylamine was obtained from Aldrich Chemical Co., Inc. and used as received. All liquid aldehydes and amines were freshly distilled prior to use.

General Procedure A: Synthesis of linear internal olefins

1. 3-amino-1-propanol derivatives (1 equiv) were protected by adding di-*tert*-butyl-dicarbonate (1.03 equiv) to a biphasic mixture of deionized water (3 mL/mmol sm) and DCM (1 mL/mmol sm). This was stirred for 1-24 hours, extracted twice with 30 mL dichloromethane, dried over brine and magnesium sulfate, and the solvent was removed *in vacuo*. These products were taken to the next step without further purification.

2. The protected material was oxidized using typical swern oxidation conditions. An oven dried flask was placed under N_2, and to it was added 2 mL dichloromethane/mmol sm. This was chilled to -78 °C, and had 1.5 equiv oxalyl chloride added to it. 2.0 equiv. dimethylsulfoxide (mixed 1:1 with dichloromethane to prevent freezing in the syringe) was added to this dropwise over five minutes. The solution was stirred for fifteen minutes at this temperature, and then a dichloromethane solution (2 mL/mmol) of the Boc amine was added to the solution over ten minutes. This was stirred a further 30 minutes, and 5 equiv. trimethylamine was added to the reaction. The reaction was allowed to warm to room temperature for 3h or overnight, quenched with 2 mL/mmol of saturated ammonium chloride solution and 1 mL/mmol of deionized water. The mixture was extracted twice with 40 mL dichloromethane, dried with sodium sulfate, and the solvent removed *in vacuo*. The aldehydes produced were mostly stable to column chromatography, however, generally they were used without further purification (Purified yields ranged from 60-80% over 2 steps, and purification was not found to improve yields for further reactions.

3. The resulting aldehydes were then subjected to a Z-selective wittig olefination. An oven dried flask was charged with 2.2 equiv of the corresponding triphenylphosphonium bromide or iodide salt, cycled to a nitrogen atmosphere and chilled to 0 °C. To this was added 3 mL dry THF/mmol aldehyde, and 2.1 equiv KHMDS in toluene (0.7M solution) slowly, producing bright red or orange suspensions. This was allowed to stir for 1-2 hours at this temperature. The aldehyde was dissolved in THF (2 mL/mmol) and added dropwise to the ylide solution . The reaction was

allowed to warm up to rt overnight, and quenched (allowing it to stir longer resulted in no further product formation, and in some cases degradation) using 2mL/mmol sm saturated ammonium chloride solution. The resulting suspension was extracted twice with 50 mL diethyl ether, loaded onto celite, and columned using 25% ethyl acetate in hexanes. These columns generally did not remove all of the impurities, however, the goal was to remove most of the phosphine oxide and phosphine byproducts. These reactions consistently produced >5 : 1 Z olefin, although with modest yields (30-50%).

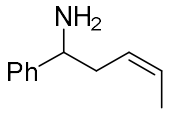
4. The Boc group was then removed to reveal the free internal Z-homoallylamine. This was accomplished by dissolving the starting olefin in 1.5 mL/mmol dichloromethane, and chilling it to 0 °C. TFA was added (5 equiv.) dropwise, usually inducing a stark color change. This was stirred at rt for 1.5 hours, and then chilled, 1.5 mL/mmol sm deionized water added, 1.2 mL/mmol sm 5M NaOH added slowly, and a basic pH confirmed using pH test strips. This was extracted with 3x 10 mL dichloromethane, dried using sodium sulfate, and the solvent removed *in vacuo.* These products could be purified using distillation under reduced pressure (0.2-1 torr) to afford the pure Z-homoallylamines with yields ranging from 25-70%. Distillation was found to have a significant impact on the performance in the hydroamination reaction, and leave behind significant amounts of insoluble materials, so all products were vacuum distilled after column chromatography.

General Procedure B: Synthesis of Cyclic Internal Olefins

1.0 equiv of benzaldehyde had 1.05 equiv LiHMDS in THF added to it at 0 °C. This was warmed to rt overnight, rotovapped, and distilled (55 °C, 0.4 torr) to afford benzaldehyde trimethylsilyl imine (61%).

The trimethylsilyl imine was cycled to nitrogen, and dissolved in 8 mL/mmol diethyl ether, and 1.5 equiv titanium isopropoxide (neat) was added in a slow dropwise fashion. This was stirred 5 minutes, and chilled to -78 °C. To this was added slowly 3 equiv. cyclopentylmagnesium

chloride in thf. This was stirred for 10 minutes, moved to a -40 °C bath, and stirred an additional 1 hour at that temperature. This solution was chilled to -78 °C, and then 1.3 equiv of the corresponding lithium alkoxide of an allylic alcohol was added to it (2-cyclopenten-1-ol or 2-cyclohexen-1-ol) in 5 mL/mmol alkoxide of THF. This was allowed to warm to rt and stir over the course of two days. This was quenched with 5 mL/mmol saturated sodium bicarbonate solution, stirred vigorously for 1h, and filtered through a pad of celite using sodium bicarbonate and diethyl ether to rinse. This was extracted with 3x 50 mL portions of diethyl ether, dried over sodium sulfate, and concentrated *in vacuo*. The free amine was produced in > 20 : 1 d.r. and distilled under reduced pressure to afford the pure product. Yields were 50-65%. Distillation was found to leave behind significant amounts of solids, even if column chromatography was performed, and significantly improved yields in the reaction as well as decreasing viscosity of the liquids.



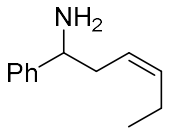
1a

E:Z ratio approximately 1 : 5

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 (qd, *J* = 8.3, 4.0 Hz, 4H), 7.26 – 7.21 (m, 1H), 5.63 – 5.54 (m, 1H), 5.43 – 5.34 (m, 1H), 3.97 (dd, *J* = 7.7, 5.9 Hz, 1H), 2.49 – 2.35 (m, 2H), 1.62 – 1.57 (m, 3H), 1.52 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.46, 128.70, 127.25, 127.23, 127.00, 126.65, 56.34, 37.51, 13.34.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C11H16N = 162.1283; found mass = 162.1385.



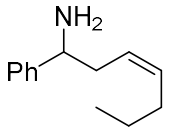
1f

E:Z ratio approximately 1 : 5,

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.30 (m, 4H), 7.26 – 7.21 (m, 1H), 5.62 – 5.52 (m, 1H), 5.38 (dtdd, *J* = 12.8, 6.7, 3.5, 1.7 Hz, 1H), 3.97 (dd, *J* = 7.7, 5.9 Hz, 1H), 1.60 (dq, *J* = 6.6, 0.9 Hz, 3H), 1.57 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.46, 128.70, 127.25, 127.23, 127.00, 126.65, 56.34, 37.51, 13.34.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C12H18N = 176.1439; found mass = 176.1440.



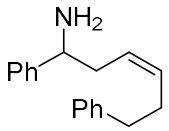
1p

E:Z could not be quantitatively determined by proton NMR.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.30 (m, 4H), 7.24 (ddt, *J* = 6.6, 5.2, 1.9 Hz, 1H), 5.53 – 5.46 (m, 1H), 5.39 – 5.32 (m, 1H), 3.96 (dd, *J* = 7.6, 6.0 Hz, 1H), 2.48 – 2.34 (m, *J* = 6.9 Hz, 2H), 2.00 (qt, *J* = 7.3, 1.9 Hz, 2H), 1.51 (s, 2H), 1.34 (tq, *J* = 13.4, 6.7, 6.0 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.50, 132.94, 128.69, 127.23, 126.66, 126.42, 56.46, 37.93, 29.83, 23.10, 14.14.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C13H20N = 190.1596; found mass = 190.1594.



1q

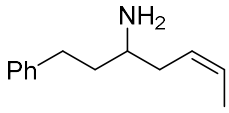
E:Z ratio could not be quantitatively determined by proton NMR. Appears to be > 10 : 1

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.16 (m, 10H), 5.54 (dtt, *J* = 10.8, 7.3, 1.7 Hz, 1H), 5.43 – 5.35 (m, 1H), 3.89 (t, *J* = 6.8 Hz, 1H), 2.65 – 2.59 (m, 2H), 2.41 – 2.32 (m, 4H), 1.49 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.36, 142.24, 131.79, 128.84, 128.70*, 128.60, 127.10, 126.65, 126.15, 56.33, 37.88, 36.11, 29.67.

*2 carbons

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H22N = 252.1752; found mass = 252.1753.



1b

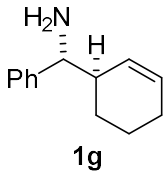
E:Z ratio could not be quantitatively determined by proton NMR. Carbon suggests at least 10 : 1

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.22 – 7.14 (m, 3H), 5.61 (dtdd, *J* = 9.4, 6.8, 6.0, 1.5 Hz, 1H), 5.41 (dddt, *J* = 11.4, 8.5, 5.0, 1.8 Hz, 1H), 2.85 – 2.79 (m, 1H), 2.80 – 2.72 (m, 1H), 2.65 (ddd, *J* = 13.7, 10.2, 6.1 Hz, 1H), 2.24 – 2.16 (m, 1H), 2.16 – 2.07 (m, 1H),

1.78 (dddd, *J* = 15.1, 7.2, 6.1, 4.9 Hz, 1H), 1.65 (m, 1H), 1.64 (dq, *J* = 7.6, 1.1 Hz, 3H), 1.41 (s, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.66, 128.71, 128.70, 127.49, 126.82, 126.10, 51.38, 39.72, 35.82, 33.09, 13.44.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C13H20N = 190.1596; found mass = 190.1597.



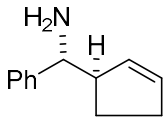
1g

d.r. > 20 : 1

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 5.85 (s, 2H), 3.77 (d, *J* = 7.3 Hz, 1H), 2.38 (dddd, *J* = 10.8, 8.4, 5.7, 2.2 Hz, 1H), 2.00 (ddt, *J* = 8.6, 4.7, 2.1 Hz, 2H), 1.72 (dtd, *J* = 13.9, 6.7, 5.6, 3.9 Hz, 1H), 1.51 (tdd, *J* = 10.1, 7.0, 3.1 Hz, 4H), 1.35 – 1.25 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.82, 129.82, 128.58, 128.10, 127.13, 127.09, 60.70, 43.35, 27.23, 25.67, 21.83.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C13H18N = 188.1439; found mass = 188.1445.



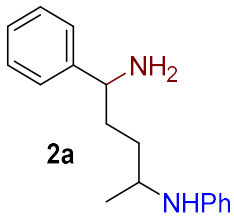
1h

d.r. ~ 14 : 1

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.35 – 7.30 (m, 4H), 7.24 (dtd, *J* = 8.5, 4.4, 2.2 Hz, 1H), 5.88 (dq, *J* = 5.5, 2.2 Hz, 1H), 5.82 – 5.78 (m, 1H), 3.75 (dd, *J* = 7.3, 1.1 Hz, 1H), 3.05 – 2.97 (m, 1H), 2.38 – 2.19 (m, 2H), 1.87 – 1.75 (m, 1H), 1.55 (dddd, *J* = 13.2, 9.1, 6.5, 5.3 Hz, 1H), 1.50 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.15, 133.51, 131.63, 128.59, 127.12, 127.08, 60.89, 54.11, 32.52, 27.55.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C12H16N = 174.1283; found mass = 174.1277.



2a

N4,1-diphenylpentane-1,4-diamine

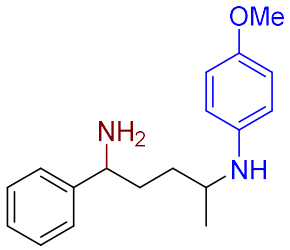
This product (60%, 0.12 mmol) was isolated as a 1.5 : 1 mixture of diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 7.16 (t, *J* = 7.8 Hz, 2H), 6.68 (td, *J* = 7.4, 1.4 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 2H), 3.90 (t, *J* = 6.9 Hz, 1H), 3.51 –

3.42 (m, 1H), 2.1 – 1.65 (br s, 3H) 1.91 – 1.73 (m, 1H), 1.70 – 1.60 (m, 1H), 1.59 – 1.43 (m, 1H), 1.42 – 1.31 (m, 1H), 1.17 (d, J = 6.4, 2.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.86, 146.62, 129.59, 128.86, 127.35, 126.62, 117.18, 113.40, 56.71, 48.83, 36.33, 34.33, 21.16.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H23N2 = 255.1861; found mass = 255.1864.



2d

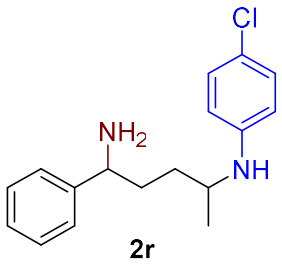
N4-(4-methoxyphenyl)-1-phenylpentane-1,4-diamine

This product (49%, 0.098 mmol) was isolated as a mixture of 2.1 : 1 diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 (ddt, J = 14.6, 8.3, 4.1 Hz, 4H), 7.26 – 7.20 (m, 1H), 6.75 (d, J = 8.9 Hz, 2), 6.50 (d, J = 8.9 Hz, 2H), 3.88 (t, J = 6.9 Hz, 1H), 3.74 (t, J = 1.2 Hz, 3H), 3.39 – 3.30 (m, 1H), 2.27 (br s, 2H), 1.87 – 1.69 (m, 2H), 1.65 – 1.55 (m, 1H), 1.55 – 1.38 (m, 1H), 1.36 – 1.27 (m, 1H), 1.15 – 1.09 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.17, 146.39, 142.08, 128.85, 127.37, 126.64, 115.27, 115.02, 56.70, 56.16, 49.88, 36.20, 34.31, 21.17.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2O = 285.1967; found mass = 285.1965.



2r

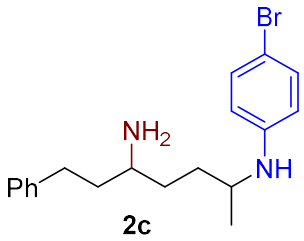
N4-(4-chlorophenyl)-1-phenylpentane-1,4-diamine

This product (29%, 0.058 mmol) was isolated as a mixture of diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 – 7.57 (m, 5H), 7.42 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 3.78 – 3.68 (m, 1H), 2.88 (br s, 3H), 2.23 – 2.05 (m, 2H), 2.01 – 1.83 (m, 1H), 1.82 – 1.65 (m, 1H), 1.48 (dd, *J* = 6.5, 1.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.42, 146.19, 129.39, 128.93, 127.50, 126.62, 121.63, 114.44, 56.64, 49.02, 36.00, 34.09, 21.02.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H22N2Cl = 289.1472; found mass = 289.1476.



2c

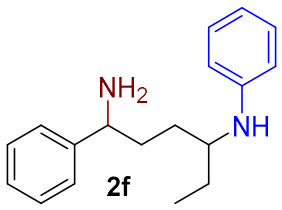
N2-(4-bromophenyl)-7-phenylheptane-2,5-diamine

This product (50%%, 0.10 mmol) was isolated as a 1.6 : 1 mixture of diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 2H), 7.24 – 7.15 (m, 5H), 6.48 – 6.38 (m, 2H), 3.40 (hept, *J* = 7.2, 6.7 Hz, 1H), 2.73 (dtd, *J* = 16.5, 8.7, 7.6, 3.4 Hz, 2H), 2.62 (ddd, *J* = 13.6, 10.0, 6.3 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.67 – 1.31 (m, 5H), 1.17 (dd, *J* = 6.3, 1.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.90, 142.44, 132.27, 128.73, 126.14, 114.93, 114.91, 108.55, 51.22, 49.04, 40.22, 34.60, 33.72, 33.65, 32.84, 21.10.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C19H26N2Br = 361.1279; found mass = 361.1274



2f

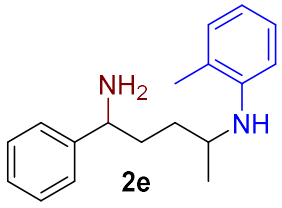
N4,1-diphenylhexane-1,4-diamine

This product (25%, 0.050 mmol) was isolated as a mixture of diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.24 (m, 5H), 7.15 (t, *J* = 7.8 Hz, 2H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 2H), 3.90 (t, *J* = 7.1 Hz, 1H), 3.28 (p, *J* = 6.1 Hz, 1H), 2.84 (br s, 3H), 1.90 – 1.69 (m, 2H), 1.68 – 1.41 (m, 3H), 1.39 – 1.29 (m, 1H), 0.89 (td, *J* = 7.5, 4.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.01, 145.36, 129.26, 128.58, 127.20, 126.34, 116.62, 112.91, 56.32, 54.04, 35.37, 31.18, 27.33, 10.00.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2 = 269.2018; found mass = 269.2019



2e

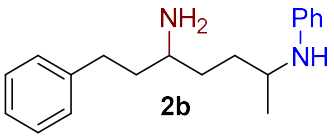
1-phenyl-N4-(o-tolyl)pentane-1,4-diamine

This product (29%, 0.058 mmol) was isolated as a mixture of diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.30 (m, 4H), 7.28 – 7.25 (m, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.63 (t, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 3.97 – 3.89 (m, 1H), 3.57 – 3.47 (m, 1H), 2.73 (s, 2H), 2.11 (s, 3H), 1.92 – 1.75 (m, 2H), 1.73 – 1.63 (m, 1H), 1.63 – 1.44 (m, 1H), 1.41 – 1.33 (m, 1H), 1.19 (dd, *J* = 6.3, 1.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.67, 130.57, 128.96, 127.58, 127.43, 126.72, 122.03, 116.67, 110.39, 110.33, 56.65, 48.61, 35.86, 34.29, 21.32, 17.95.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H25N2 = 269.2018; found mass = 269.2017



2b

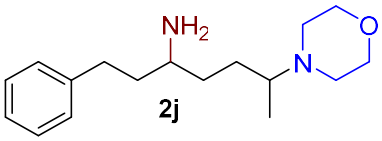
N2,7-diphenylheptane-2,5-diamine

This product (74%, 0.15 mmol) was isolated at 90 °C as a mixture of diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.29 (m, 2H), 7.24 – 7.15 (m, 5H), 6.69 (t, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 2H), 3.48 (h, *J* = 6.1 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.69 – 2.60 (m, 1H), 2.39 – 1.93 (m, 3H), 1.78 (ddt, *J* = 14.0, 10.6, 5.5 Hz, 1H), 1.73 – 1.27 (m, 5H), 1.21 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.93, 142.48, 129.65, 128.74, 128.68, 126.15, 117.24, 113.44, 51.30, 49.03, 40.08, 34.61, 33.89, 32.89, 21.31.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C19H27N2 = 283.2174; found mass = 283.2163



2j

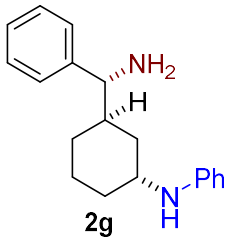
6-morpholino-1-phenylheptan-3-amine

This product (65%, 0.13 mmol) was isolated at 90 °C as a mixture of diastereomers, with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 3.81 – 3.65 (m, 4H), 2.82 – 2.71 (m, 2H), 2.70 – 2.60 (m, 1H), 2.60 – 2.53 (m, 2H), 2.49 (ddt, *J* = 16.5, 11.1, 5.8 Hz, 4H), 2.16 – 2.02 (br s, 2H), 1.85 – 1.73 (m, 1H), 1.64 (ddt, *J* = 18.2, 13.7, 7.1 Hz, 1H), 1.55 (ttt, *J* = 13.2, 5.0, 2.6 Hz, 1H), 1.44 – 1.28 (m, 2H), 1.01 (dd, *J* = 6.6, 1.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.55, 128.73, 128.68, 126.14, 67.72, 59.84, 51.38, 49.14, 40.07, 35.29, 32.95, 30.24, 14.50.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H29N2 = 277.2280; found mass = 277.2267



2g (racemic)

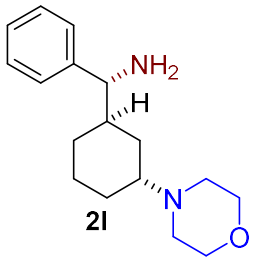
N-((1R,3R)-3-((R)-amino(phenyl)methyl)cyclohexyl)aniline

This product (50%, 0.10 mmol) was isolated as a mixture of diastereomers with predominantly the shown diastereomer (>20 : 1), with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.32 (m, 2H), 7.32 – 7.24 (m, 3H), 7.19 (t, *J* = 7.4 Hz, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.3 Hz, 2H), 3.82 – 3.76 (m, 1H), 3.69 (d, *J* = 7.9 Hz, 1H), 2.10 (dd, *J* = 13.3, 4.0 Hz, 1H), 1.85 (tdt, *J* = 11.3, 7.6, 3.6 Hz, 1H), 1.81 – 1.74 (m, 1H), 1.73 – 1.40 (m, 8H), 1.01 – 0.89 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.35, 145.02, 129.30, 128.31, 127.10, 127.04, 116.83, 113.03, 60.81, 47.50, 39.78, 33.99, 30.19, 28.89, 20.43.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C19H25N2 = 281.2013; found mass = 281.2018



2l

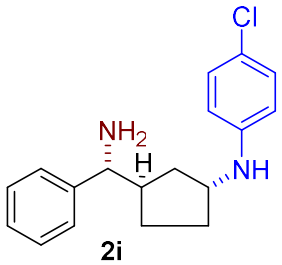
(3-morpholinocyclohexyl)(phenyl)methanamine

This product (29%, 0.058 mmol) was isolated as a mixture of diastereomers with predominantly the shown diastereomer (>20 :1selectivity), with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.26 (m, 4H), 7.23 (td, *J* = 6.9, 1.8 Hz, 1H), 3.74 – 3.67 (m, 4H), 2.43 (qt, *J* = 11.1, 4.6 Hz, 4H), 2.34 (dt, *J* = 5.9, 2.9 Hz, 1H), 2.05 – 1.89 (m, 2H), 1.77 – 1.65 (m, 1H), 1.64 – 1.49 (m, 4H), 1.44 (ddt, *J* = 13.2, 6.6, 3.1 Hz, 2H), 1.38 (dtd, *J* = 12.0, 6.7, 6.2, 3.3 Hz, 2H), 1.08 – 0.96 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.98, 128.59, 127.21, 127.18, 67.71, 60.03, 59.20, 50.69, 39.75, 30.97, 29.83, 28.65, 20.78.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C17H2N2O = 275.2123; found mass = 275.2117



2i

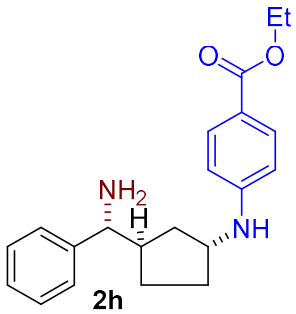
N-(3-(amino(phenyl)methyl)cyclopentyl)-4-chloroaniline

This product (51%, 0.10 mmol) was isolated as a mixture of diastereomers with predominantly the shown diastereomer (13 :1 selectivity), with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.31 (m, 3H), 7.30 – 7.23 (m, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 3.84 (qd, *J* = 6.7, 3.7 Hz, 1H), 3.69 (d, *J* = 8.9 Hz, 1H), 2.72 – 2.29 (m, 4H), 2.13 (dddd, *J* = 12.7, 8.8, 6.7, 3.6 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.51 (dtd, *J* = 11.1, 7.4, 3.4 Hz, 1H), 1.41 (dtd, *J* = 13.2, 8.2, 5.5 Hz, 1H), 1.31 – 1.18 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.59, 145.64, 129.31, 128.78, 127.51, 127.09, 121.90, 114.51, 114.40, 61.80, 54.58, 46.60, 37.91, 33.78, 29.17.

HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C18H22N2Cl = 301.1472; found mass = 301.1465



2h

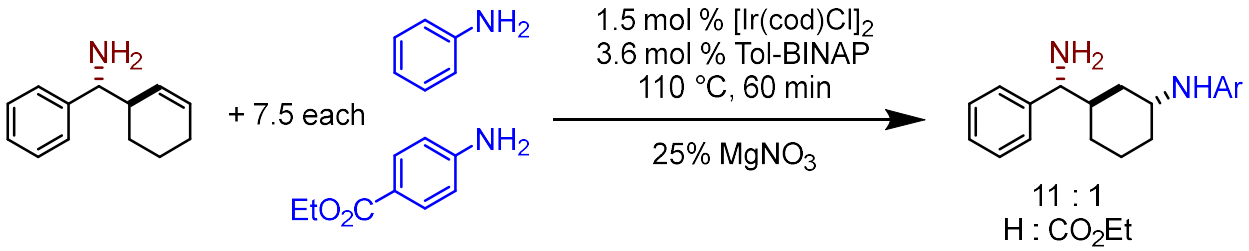
ethyl 4-(((1R,3R)-3-((R)-amino(phenyl)methyl)cyclopentyl)amino)benzoate

This product (41%, 0.082 mmol) was isolated as a mixture of diastereomers with predominantly the shown diastereomer (12 :1 selectivity), with > 20 : 1 selectivity over the 1,3 and 1,5 diamine product

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.7 Hz, 2H), 7.39 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 6.54 (d, *J* = 8.7 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.94 (qd, *J* = 6.7, 4.0 Hz, 1H), 3.71 (d, *J* = 8.9 Hz, 1H), 2.44 – 2.32 (m, 1H), 2.21 – 1.86 (m, 5H), 1.53 (dtd, *J* = 10.6, 7.2, 3.1 Hz, 1H), 1.44 (ddt, *J* = 13.4, 8.0, 4.2 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.31 – 1.23 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.22, 151.61, 145.56, 131.78, 128.80, 127.55, 127.08, 118.72, 112.11, 61.73, 60.47, 54.09, 46.61, 37.92, 33.75, 29.10, 14.80.

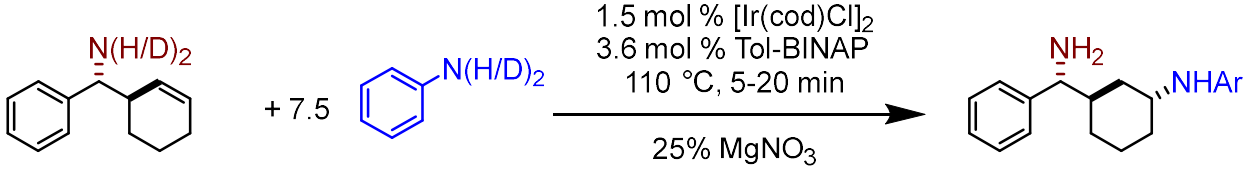
HR-MS (ESI-TOF) *m/z*: [M+H+] calculated for C21H27N2O2 = 339.2073; found mass = 339.2071



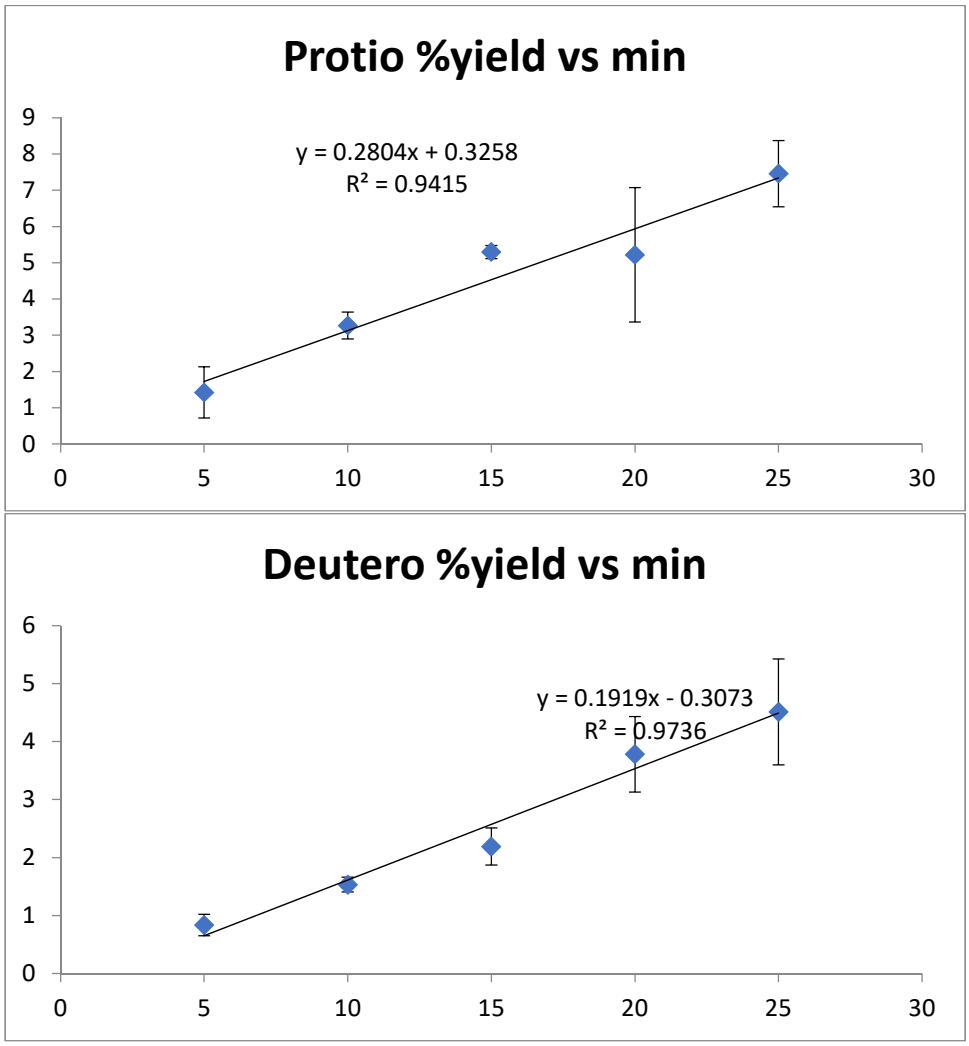
Procedure for competition experiment:

2.05 mg $[Ir(cod)Cl]_2$ (0.003 mmol), 4.8 mg *Tol*-BINAP (0.0072 mmol), and 7.2 mg $MgNO_3$ were added to a flame dried vial equipped with a stirbar. To this was added 37 mg of **1g** (0.2 mmol) and 7.5 equivalents each aniline and 4-(carboxyethyl) aniline. This was removed from the glovebox, and heated to 110 °C for 1 hour. After this, the vial was cooled to room temperature, diluted with 2 mL chloroform, had 10 µL 1-methylnaphthalene added to it, and was injected on the GC for quantitation. Comparison with standard curves showed an 11:1 ratio of the *para*-H product to the *para*-CO_2Et product.

Procedure for the KIE experiment:



Vials were prepared for these experiments using stock solutions of the catalyst and additive, and then drying in a vacuum dessicator overnight. To these vials were then added 0.1 mmol of **2g** or *D*2-**2g**, and 0.75 mmol aniline or aniline d2. This dramatically reduced the induction time of the reaction and allowed for surety when comparing data. All vials used were prepared from the same stock solution, and dried for the same period, levelling some uncertainty effects for small measurements. A KH/KD of 1.46 was measured using the average of 2 runs each for the proteo and deutero kinetics. These points are % yield numbers based on the average of two experiments with three replicate measurements each.



Crystallography

X-ray quality crystals were obtained for ## through mixing 0.1 mmol ## and 0.1 mmol Armstrong's Acid in 1 mL ethanol for 30 minutes at room temperature, then taking a small portion of this and layering it with fresh ethanol and EtOAc as an antisolvent, and waiting for 2 weeks for suitable crystals to form.

X-ray crystallography parameters and select bond lengths and angles for 2g*Armstrong's Acid:

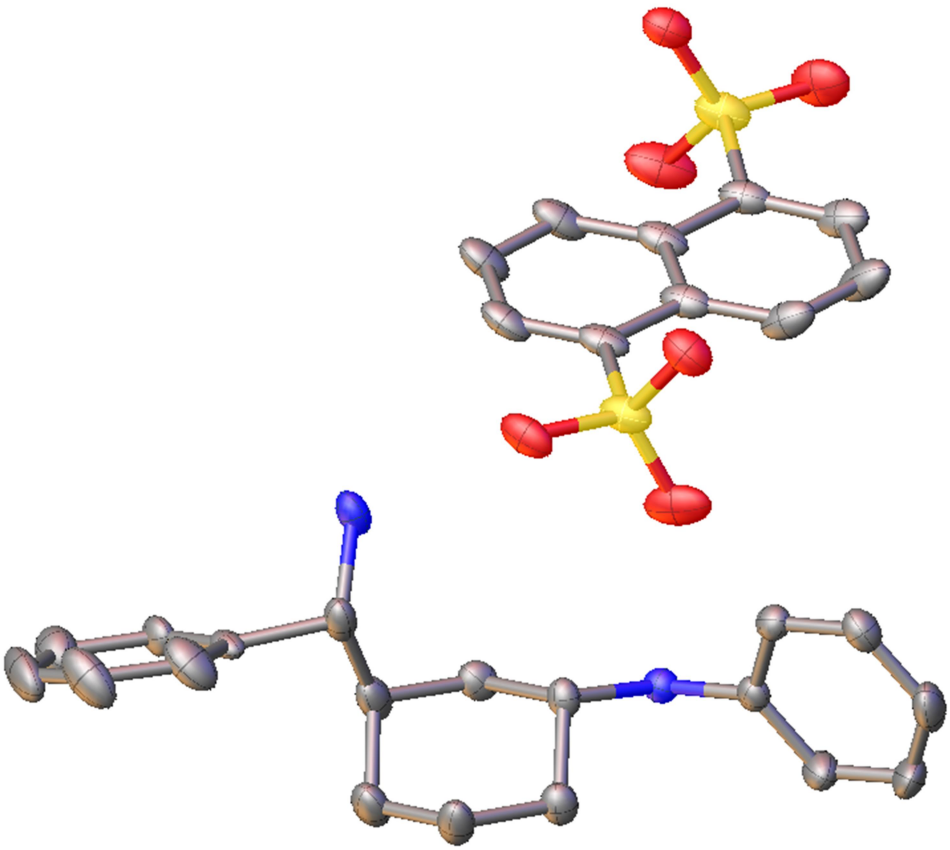
X-Ray Diffraction Techniques: The structure was collected on a Bruker three-circle platform goniometer equipped with an Apex II CCD and an Oxford cyrostream cooling device. Radiation was from a graphite fine focus sealed tube Mo Kα (0.71073 Å) source. A suitable crystal was mounted on a cryoloop using paratone N oil. The structure was collected at 100 K. Data was collected as a series of φ and/ or ω scans. Data was integrated using SAINT and scaled with either numerical or multi-scan absorption correcting using SADABS. Using Olex2, the structure was solved with the XS structure solution program using the Patterson method and refined with the XL refinement package using Least Squares minimization.

Table 4.8. X-ray diffraction experimental details for **2g*Armstrong's Acid**[a,b]

Formula	$C_{160}H_{128}N_8O_{32}S_8$
W	2931.26
Crystal system	Monoclinic
Space group (Z)	$P2_1/C$
a (Å)	15.6273(6)
b (Å)	11.1454(4)
c (Å)	21.3411(8)
α (°)	90°
β (°)	104.896(2)°
γ (°)	90°
Volume (Å^3)	3592.1(2)
Calc. ρ (g/cm^3)	1.355
μ (mm^{-1})	0.21
Crystal Size (mm)	0.104x0.119x0.322
Reflections	74455
Completeness (to 2θ)	1.0 (50.79)
GOF on F^2	1.122
R1, wR2[c] [I>2σ(I)]	0.0529, 0.1797

[a] λ = 0.71073 Å; [b] T=100 K; [c] $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

Figure 4.3. Crystal structure of **2g*Armstrong's Acid** with select atoms labeled. Hydrogen atoms have been omitted, one thing to note is that both amines are protonated. Thermal ellipsoids are drawn at 50% probability



X-ray quality crystals were obtained for ## through mixing 0.2 mmol ## and 0.42 mmol p-toluene sulfonic acid (monohydrate) in 1 mL ethanol for 30 minutes at room temperature, then taking a small portion of this and layering it with fresh ethanol and diethyl ether as an antisolvent, and waiting for 2 weeks for suitable crystals to form.

X-ray crystallography parameters and select bond lengths and angles for 2l*2ptsa:

X-Ray Diffraction Techniques: The structure was collected on a Bruker three-circle platform goniometer equipped with an Apex II CCD and an Oxford cyrostream cooling device. Radiation was from a graphite fine focus sealed tube Mo Kα (0.71073 Å) source. A suitable crystal was mounted on a cryoloop using paratone N oil. The structure was collected at 100 K. Data was collected as a series of φ and/ or ω scans. Data was integrated using SAINT and scaled with

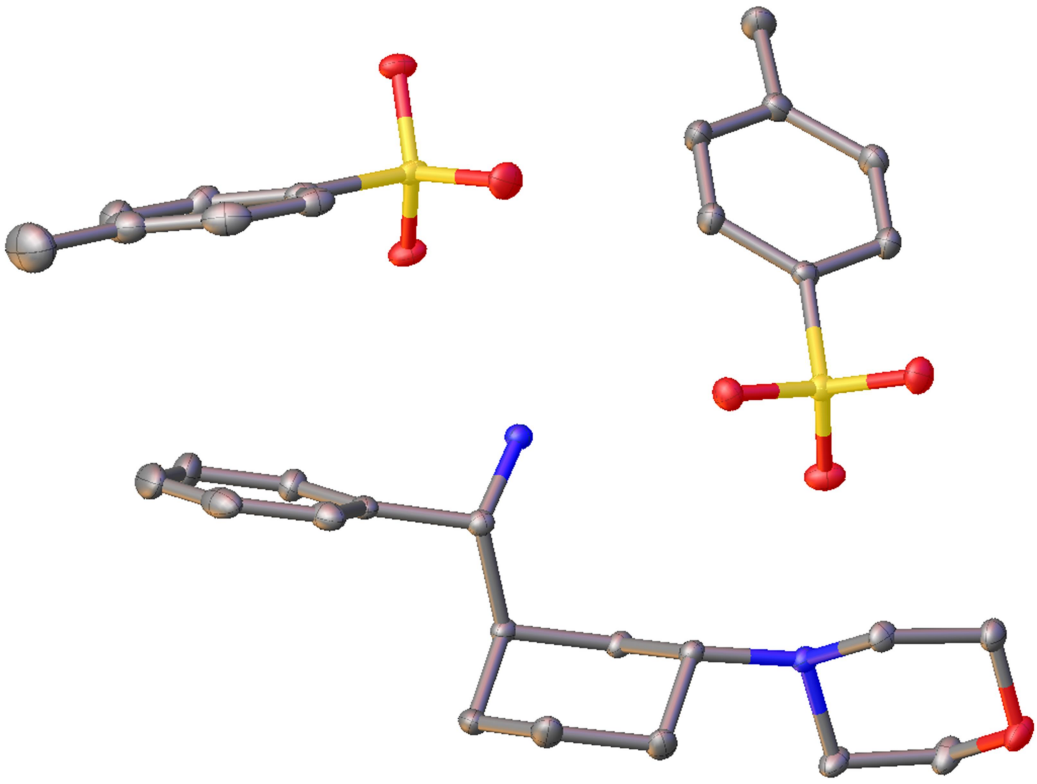
either numerical or multi-scan absorption correcting using SADABS. Using Olex2, the structure was solved with the XS structure solution program using the Patterson method and refined with the XL refinement package using Least Squares minimization.

Table 4.9: X-ray diffraction experimental details for **2l* 2 PTSA**[a,b]

Formula	$C_{31}H_{42}N_2O_7S_2$
W	2475.13
Crystal system	Cubic
Space group (Z)	$P2_12_12_1$
a (Å)	11.1123(4)
b (Å)	11.2096(4)
c (Å)	24.9678(9)
α (°)	90°
β (°)	90°
γ (°)	90°
Volume (Å^3)	3110.1(0)
Calc. ρ (g/cm^3)	1.322
μ (mm^{-1})	0.22
Crystal Size (mm)	0.15x0.475x0.529
Reflections	77911
Completeness	1.0
(to 2θ)	(56.61)
GOF on F^2	1.035
R1, wR2[c]	0.0275, 0.0737
[I>2σ(I)]	

[a] λ = 0.71073 Å; [b] T=100 K; [c] $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

Figure 4.4: Crystal structure of **2l*2 PTSA** with select atoms labeled. Hydrogen atoms have been omitted, one thing to note is that both amines are protonated. Thermal ellipsoids are drawn at 50% probability



4.7 References

(1) “Catalytic Addition of Secondary Amines to Ethylene”, Coulson, D.R. Tetrahedron Lett. **1971**, *12*, 429-431

(2) “Hydroamination: Direct Addition of Amines to Alkenes and Alkynes”, Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108* (9), 3795–3892

(3) “Late Transition Metal-Catalyzed Hydraomination and Hydroamidation”, Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem.Rev.* **2015**, *115* (7), 2596–2697.

(4) Iridium-Catalyzed Intermolecular Hydroamination of Unactivated Aliphatic Alkenes with Amides and Sulfonamides”, Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134* (29), 11960-11963

(5) “Iridium-Catalyzed, Intermolecular Hydroamination of Unactivated Alkenes with Indoles”, Sevov, C. S.; Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136* (8), 3200-3207

(6) “Asymmetric Intermolecular Hydroamination of Unactivated Alkenes with Simple Amines”, Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2010**, *49* (47), 8984-8987

(7) The First Rhodium-Catalyzed Anti-Markovnikov Hydroamination: Studies on Hydroamination and Oxidative Amination of Aromatic Olefins”, Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Muller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999***, 5* (4), 1306-1319

(8) “Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation reactions" Schönherr, H.; Cernak, T. *Angew. Chem. Int. Ed*. **2013**, *52*, 12256-12267

(9) Excluding work on norbornenes and styrenes, as these are particularly privileged substrates for hydroamination

(10) “Catalytic Asymmetric Hydroamination of Unactivated Internal Olefins to Aliphatic Amines.” Yang, Y.; Shi, S.; Niu, D.; Liu, P.; Buchwald, S. L. *Science*, **2015**, *349* (6243), 62-66

(11) “Enantioselective Synthesis of α-aminosilanes by Copper-Catalyzed Hydroamination of Vinylsilanes”. Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1638-1641

(12) “Design of Modified Amine Transfer Reagents Allows the Synthesis of α-Chiral Secondary Amines via CuH-Catalyzed Hydroamination*”.* Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9716-9721

(13) “Regioselective, Asymmetric Formal Hydroamination of Unactivated Internal Alkenes”. Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 776-780

(14) “First-Row Late Transition Metals for Catalytic Alkene Hydrofunctionalisation: Recent Advances in C-N, C-O and C-P Bond Formation”. Bezzenine-Lafollee, S.; Gil, R.; Prim, D.; Hannedouche, J. *Molecules*, **2017**, *22*, 1901-1930.

(15) “Regio- and Enantioseslective Intermolecular Hydroacylation: Substrate-Directed Addition of Salicylaldehydes to Homoallylic Sulfides”, Coulter, M. M. Kou, K. G. M. Galligan, B.; Dong, Vy. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330-16333.

(16)“Directed, Regiocontrolled Hydroamination of Unactivated Alkenes via Protodepalladation”. Gurak, J. A. Yang, K. S.; Liu, Z.; Engle, K. M. *J. Am Chem. Soc.* **2016**, *138* (18), 5805-5808.

(17) “β,γ-Dicarbofuntionalization of Alkenyl Carbonyl Compounds via Directed Nucleopalladation”. Liu, Z.; Zeng, T.; Yang, K. S.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138* (46), 15122-15125.

(18) “Amide-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes”. Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740-1741.

(18) “Practical Intermolecular hydroarylation of Diverse Alkenes via Reductive Heck Coupling”. Gurak, J. A.; Engle, K. M. *ACS Catal.* **2018**, *8*, 8987-8992.

(19) “Catalytic Intermolecular Carboamination of Unactivated Alkenes via Directed Aminopalladation”. Liu, Z.; Wang, Y.; Wang, Z.; Zeng, T.; Liu, P.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139* (32), 11261-11270

(20) “Rhodium-Catalyzed Regiodivergent Hydrothiolation of Allyl Amines and Imines”, Kennemur, J. L.; Kortman, G. D.; Hull, K. L. *J. Am. Chem. Soc.* **2016**, *138* (36), 11914-11919

(21) “Catalytic Hydrothiolation: Regio- and Enantioselective Coupling of Thiols and Dienes”, Yang, X. H.; Davison, R. T.; Dong, V. M. *J. Am. Chem. Soc.* **2018**, *140* (33), 10443-10446

(22) “Rhodium-Catalyzed Enantioselective Cycloizomerization to Cyclohexenes Bearing Quaternary Carbon Centers”, Park, J. W.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2016**, *138*, 3310-3313