# THE DEVELOPMENT OF A RHODIUM-CATALYZED CHEMO- AND STEREOSELECTIVE HYDROAMINATION FOR THE SYNTHESIS OF 1,2-DIAMINES

BY

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THESIS

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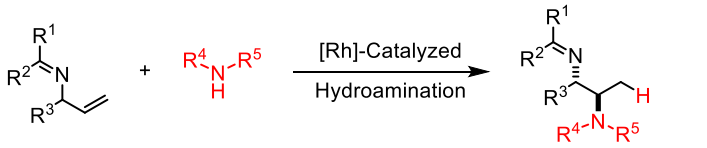
## ABSTRACT

Amines are a prominent functionality found throughout organic molecules, including pharmaceuticals, agrochemicals, organic materials, and organic dyes.[1] However, incorporation of amines into organic frameworks in step and atom economical fashion remains a significant challenge to synthetic chemists.[2–4]

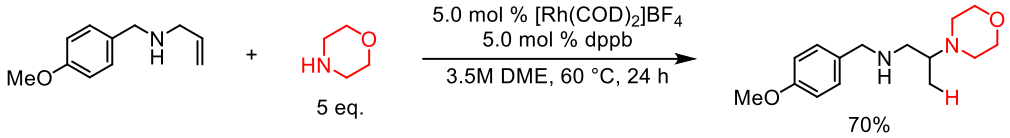
In chapter 1, the importance of a class of compounds, 1,2-diamines is reviewed. Herein, many marketed pharmaceuticals, potential therapeutics, and natural products bearing this motif of interest are discussed. Additionally, 1,2-diamines have been shown as ligands for catalysis. Due to this interest in the 1,2-diamine functionality, some current synthetic methods to access 1,2-diamines will be shown.

Chapter 2 discusses the hypothesis that a Lewis basic functionality could coordinate to a metal center and allow a hydroamination reaction to occur. Hydroamination was seen as a beneficial strategy to synthesize 1,2-diamines as olefins and amines are reacted in an atom-economical fashion. Initial reaction discovery of the rhodium-catalyzed intermolecular hydroamination of *N*-allylimines will be shown as well as reaction development. It was found that modest to high yields and high diastereoselectivities were obtained to synthesize 1,2-diamines with this methodology.

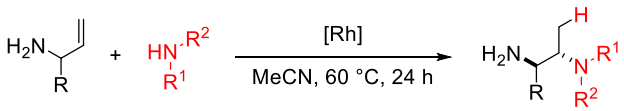



**23 examples**
46-98% yield
$R^3 \neq H$, 11:1 to >20:1 d.r.

Further, reaction development of secondary and primary *N*-allylamines will be discussed. These substrates offer attractive methods toward synthesizing 1,2-diamines by being easy to access. When secondary *N*-allylamines are employed, good yield is obtained for the desired hydroamination reaction.




Excitingly, primary *N*-allylamines were able to be used as substrates for this transformation. This substrate class offered the shortest reaction times and proved to be effective for a wide range of amine nucleophiles.




**22 examples**
45-84% yield
$R \neq H$, 9:1 to >20:1 d.r.

This thesis is dedicated to my wife Chelsea and son James. Over the last 4 years, Chelsea has shown me continuous support in my studies as well as providing encouragement to move forward. In this time, James was born and has provided more joy than I could have imagined. I am beyond excited for everything the future holds and our journeys together.

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# CHAPTER 1

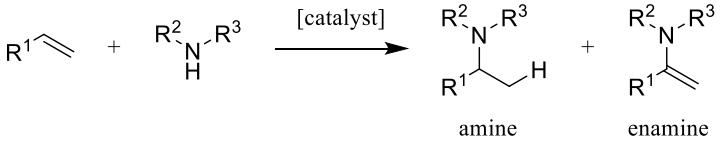
## Importance of 1,2-Diamines as Targets for Reaction Development

### 1.1. Introduction to Our Proposed Reaction

Amines are a prominent functionality found throughout organic molecules, including pharmaceuticals, agrochemicals, organic materials, and organic dyes.[1] However, incorporation of amines into organic frameworks in step and atom economical fashion remains a significant challenge to synthetic chemists.[2–4] Transition metal-mediated hydroamination, the addition of an N–H bond across a C=C bond, is one of the most attractive routes for the generation of C–N bond as it couples two easily accessible functionalities and does not generate any stoichiometric byproducts.[5,6] Although there has been significant research devoted to the development of an efficient and general hydroamination reaction, the current scope of these reactions is fairly limited.

The first major challenge facing the development of a practical hydroamination reaction is that it can afford two isomeric products: the Markovnikov or the anti-Markovnikov product where the new C–N bond is generated at the more or less substituted carbon, respectively. The second significant challenge is that the reactions often generate a mixture of both the hydroamination and the oxidative amination product (Scheme 1).[7–21] A third challenge, as the amines are often much better ligands for the metal, is that the olefin containing substrate is required in moderate to great excess in order to favor association to the metal center.[14–21] These transformations often require intramolecular reaction to take place as well.[7–13] Finally, electronically activated substrates, which can generate π-allyl or π-benzyl intermediates, are often required to react.[14–16,22–27]

**Scheme 1:** General, catalytic hydroamination

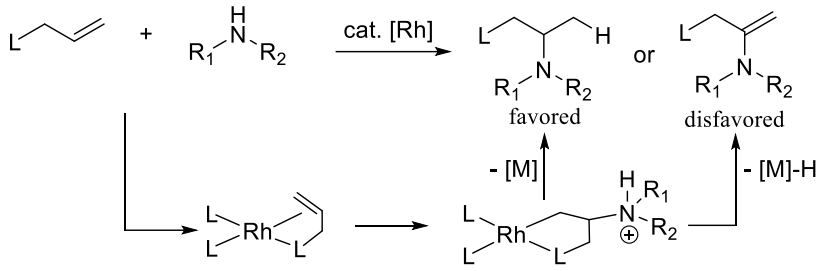



The goal of this project was to develop a Rh-catalyzed hydroamination reaction that does not rely on either an intramolecular reaction or electronically activated olefins to achieve an active and selective catalytic system. Our approach was to employ substrates that have heteroatom groups that can bind to the catalyst and increase the affinity of the olefin to coordinate to the catalyst (Scheme 2). Ideally, this would remove the need to use conjugated or strained substrates. [28–32]

Two mechanisms are proposed throughout the hydroamination literature, an inner-sphere and outer-sphere mechanism.[3,4,19,33,34] In the inner-sphere mechanism, the amine N-H bond undergoes oxidative addition followed by insertion in to the olefin. After reductive elimination or beta-hydride elimination, the amine or enamine product, respectively, is formed. In the outer-sphere mechanism, aminometallation is the

key N-C bond-forming step. Upon the aminometallation, a metallacycle can be generated, directing both the regioselectivity of the nucleophilic attack and helping to prevent ß-hydride elimination (Scheme 2).[35,36] By using an allylimine or allylamine to coordinate to the rhodium (I) catalyst, it was anticipated that an outer-sphere pathway will be operable as seen in Scheme 2.

**Scheme 2:** Proposed hydroamination reaction




Herein, the discovery of such a reaction is discoursed. First, the importance of the products that can be generated, 1,2-diamines, will be discussed. This is followed and brief discussion on ligand scaffolds featuring 1,2-diamines as well as some of the most popular synthetic routes toward 1,2-diamines. This will transition into a brief discussion on late transition metal catalyzed hydroamination as a potentially viable and attractive approach towards forming these products. The choice of rhodium as a metal catalyst, followed by all optimization and reaction development will be shown.

### 1.2. 1,2-Diamines in Pharmaceuticals

Using a hydroamination strategy employing a Lewis-basic directing group, a 1,2-relationship between the Lewis-basic imine or amine and the amine nucleophile will be formed after hydroamination. The proposed hydroamination reaction using allylimines would form aminoimines, which can be reduced to form protected 1,2-diamines. This functionality has found extended use in marketed pharmaceuticals and well as potential therapeutics that are not yet marketed. Cisplatin, a potent anti-cancer compound class, has been widely studied by varying the amine-based ligands of the platinum complex. The method reported herein can be useful towards more streamlined syntheses to these 1,2-diamine moieties, though more studies will be performed to improve substrate scope with respect to internal alkenes and to improve nucleophile scope to encompass primary amines, secondary, acyclic amines, and ammonia. However, nitrogen-containing heterocycles have found prevalence in the U.S. FDA approve pharmaceuticals.[37] Additionally, 84% of the top 200 pharmaceuticals by sales contain at least one nitrogen atom and 59% contain at least one nitrogen heterocycle, highlighting the importance of developing an efficient methods towards their synthesis and incorporation of nitrogen-based functionality into those molecules.[37]

### 1.2.1. Marketed Pharmaceuticals

Few potentially active pharmaceuticals make the journey to clinical trials after initial development in the laboratory. However, the compounds that succeed in clinical trials and make it to the market largely contribute to the success of pharmaceutical companies. The 1,2-diamine moiety has emerged as an important motif in a handful marketed compounds which can be separated into two categories; compounds with substitution vicinal to the amine moieties and compounds bearing the ethylene diamine motif. Marketed compounds with substitution vicinal to one or both of the amines in these pharmaceuticals are underdeveloped. This could be attributed to limited accessibility of these compounds in screening by medicinal chemists. The methodology reported, herein, can be useful in providing access to these new compounds with an overall similar structure.

There are a handful of marketed compounds that could potentially be accessed in the future using the reported rhodium-catalyzed hydroamination (Figure 1). Although the current methodology may not access all of the molecules shown in Figure 1, there is certainly a challenge to access the molecules efficiently. oseltamivir phosphate (**1**) is a marketed anti-influenza compound commonly administered orally. This compound is believed to inhibit neuramidase, an enzyme present in infected cells that allows for the release of the virus throughout the body.[38] Although the molecule bears only three stereocenters on a cyclohexene moiety, methods for accessing the corresponding 1,2-diamine are not well developed and often require multiple steps to access.[39] The industrial synthesis of Tamiflu™ currently involves a 12 step synthesis with an overall yield of 18% (Scheme 3) from (-)-shikimic acid (**13**).[40–42] Because of the high demand of this pharmaceutical and the availability of (-)-shikimic acid to be isolated on large scale from *Illicium verum* (Chinese star anise), alternative approaches have been pursued from readily accessible starting materials.[43–49] The synthesis reported by Trost (Scheme 4) is the shortest synthesis to date, consisting of 8 steps and 30% overall yield from a readily accessible lactone (**14**).[50]

In recent years, Oseltamivir derivatives have been extensively studied yielding two similar pharmaceuticals that are currently marketed. zanamivir (**2**), the first neuraminidase inhibitor commercially developed, is currently marketed by GlaxoSmithKline.[38,39,51] Laninamivir (**3**)[38] has been marketed in Japan and is currently in Phase III clinical trials in the U.S. In light of these 1,2-diamine based anti-viral agents being relatively well received in the market, there have been extensive efforts to understand the binding[52–55] of the compounds to neuraminidase, and many other similar compounds have been shown to be effective toward inhibiting this enzyme.[41,51–57]

Promethazine (**4**), propiomazine, (**5**), and profenamine (**6**) have been available on the market for an extended period of time. Promethazine has been investigated more in-depth compared to propiomazine. Promethazine has been marketed for over 60 years and is often used as a sedative and anti-histamine.[37,58–60] Propiomazine has been used as an anti-histamine and is known to have a binding affinity for $\alpha_2$-

adrenoreceptors.[37,61] However, there are many side-effects associated with these pharmaceuticals including dizziness, sedation, and has anticholinergic properties resulting in recreational use when contained in cough syrup.[62–66] Profenamine also has similar properties as the two former.[67–70]

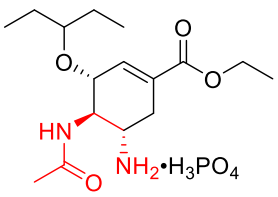
Another 1,2-diamine-containing pharmaceutical is nemonapride (**7**). Nemonapride acts as an antipsychotic for treatment of schizophrenia. The mode of action for nemonapride is as a $D_2$ and $D_3$ receptor antagonist and 5-$HT_{1A}$ receptor agonist.[71–76] One compound used to treat cystic fibrosis, aztreonam (**8**), could be potentially be synthesized using this methodology.[77–82] Lisuride (**9**), an antiparkinson agent, also could be synthesized using this methodology.[83,84] Besifloxacin (**10**), is commonly used as an antibacterial in eyedrops.[85,86] Propiram (**11**) is a μ-opioid receptor agonist that was developed by Bayer.[60,87] Recently taken off of the market, bepridil (**12**), is still being studied as it was once used to treat chest pain.[88–92] Rapid derivatization could lead to a more effective drug candidate with fewer side effects.

Although these 1,2-diamines are limited with respect to the current substrate scope, the 1,2-diamine functionality is very prevalent in pharmaceuticals. However, vicinal substitution is not present in most of the currently marketed pharmaceuticals. Some of this may be attributed to synthetic methods to access these compounds. In a recent review,[93] the methylation effect in medicinal chemistry was discussed. It is observed in many pharmaceuticals and natural products that addition of a methyl group in various locations of a compound can drastically improve favorable interactions with target sites. However, due to synthetic limitations, methyl group substitution adjacent to amines present in 1,2-diamine motifs have not been studied. The reactivity of methylated substrates could be beneficial to drug development. Using the hydroamination methodology described herein, access to methylated substrates on 1,2-diamines can be synthesized.

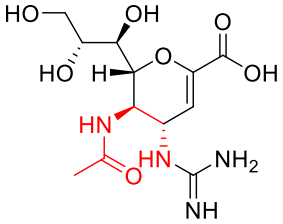
Rhodium-catalyzed hydroamination could be a productive method towards further investigating marketed drug compounds. Although these targets have been approved in various markets, all contain varying levels of side-effects. It would be beneficial towards drug development to have access to targets containing a methyl group where traditional synthetic methods are challenging to employ.

A 1,2-diamine that could be further investigated is metoclopramide (**15**), a dopamine receptor antagonist known to reduce nausea and vomiting.[94–99] Three similar compounds that could be investigated include Procainamide (**16**),[99–103] declopramide (**17**),[99,104–106] and a commercially available antidepressant, moclobemide (**18**). [107–109] All of these compound could be derivatized to include a methyl group at either vicinal position.

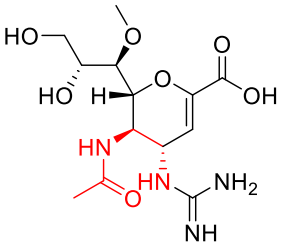
**Figure 1:** Vicinal-substituted 1,2-diamines as medicinal agents



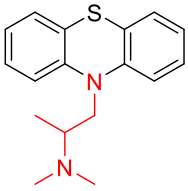
**1**
Oseltamivir
Tamiflu™
Genentech
(antiviral)



**2**
Zanamivir
Relenza™
GlaxoSmithKline
(antiviral)

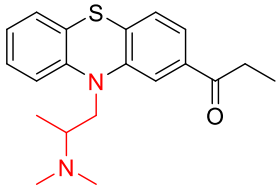


**3**
Laninamivir
Inavir™
Daiichi Sankyo / Biota Pharmaceuticals
(antiviral)



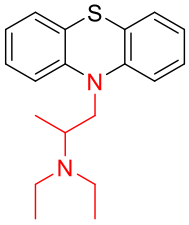
**4**
Promethazine

(antihistamine)



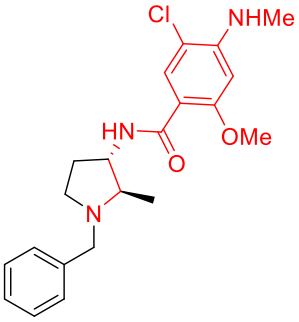
**5**
Propiomazine

(antihistamine)

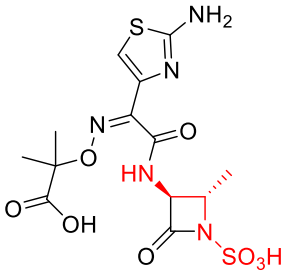


**6**
Profenamine

(antihistamine)

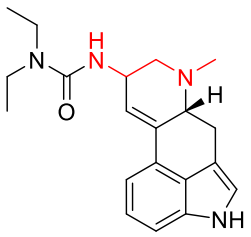


**7**
Nemonapride
Emilace™
Yamanouchi
(antipsychotic)



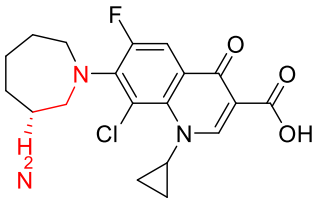
**8**
Aztreonam
Azactam™

(antibiotic)

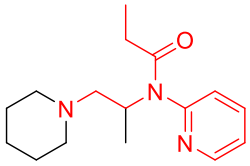


**9**
Lisuride
Dopergin™

(antiparkinson)

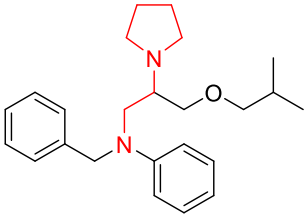


**10**
Besifloxacin
Besivance™
Bausch & Lomb
(antibiotic)



**11**
Propiram

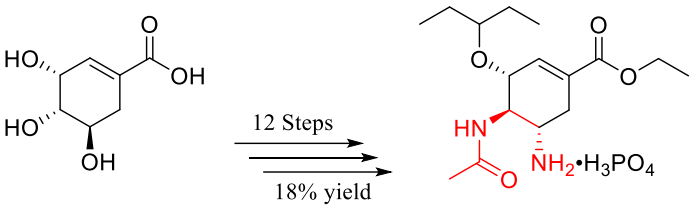
Bayer
(μ-opiod receptor agonist)



**12**
Bepridil
Vascor™

(calcium channel blocker)

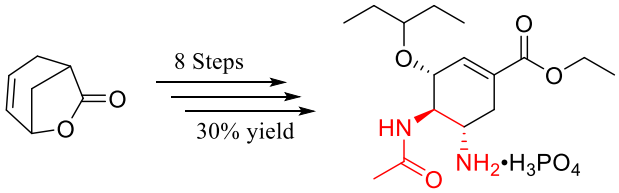
**Scheme 3:** Commercial sythesis of **1**




**13**
(-)-shikimic acid
*Illicium verum*

**1**
Oseltamivir

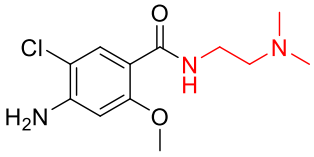
**Scheme 4:** Trost sythesis of **1**



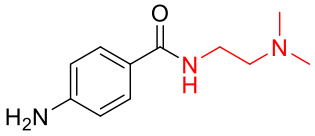

**14**

**1**
Oseltamivir

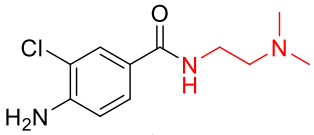
**Figure 2:** Ethylene diamine-derived 1,2-diamines as medicinal agents




**15**
Metoclopramide
Reglen™
Schwarz Pharma
(antiemetic)

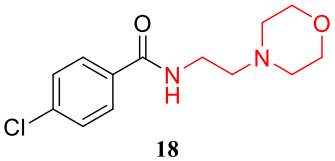



**16**
Procainamide
Pronestyl™
BMS
(antiarrhythmic)




**17**
Declopramide

(antiarrhythmic)



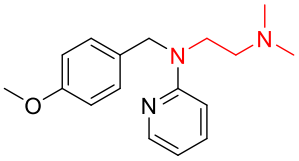

**18**
Moclobemide
Amira™
Hoffmann-La Roche
(antidepressant)

Perhaps the most important discovery with respect to antihistamines was made by Dr. Daniel Bovet who discovered mepyramine (**19**)[59,110–117] and was awarded the 1957 Nobel Prize in physiology or medicine.[118] This shows the importance of this compound though further derivatives have not been explored. This hydroamination methodology would allow for simple derivatives to be investigated. Tripelennamine (**20**) also has similar activity as an antihistamine and is currently marketed by Novartis.[110,111]

Another drug is minaprine (**21**), an anti-depressant bearing the 1,2-diamino moiety, but it was removed from the market, because the drug was believed to cause convulsions.[119–123] It would be interesting to observe reactivity and side effect differences by adding a methyl group next to one of the amine functionalities to observe a methylation effect that could influence solubility, uptake, or binding.[93] Guanethidine (**22**) is an antihypertensive drug often used.[124–126] Zetidoline (**23**) is a dopamine D2 receptor antagonist.[98,127–130] All of these pharmaceuticals would be interesting targets to investigate via the methylation effect and the hydroamination methodology would allow for easy access to these molecules.

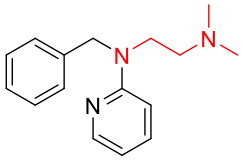
The final compounds that could be further explored include sertindole (**24**), sunitinib (**25**), mitoxantrone (**26**), pixantrone (**27**), diltiazem (**28**), flurazepam (**29**), and ethambutol (**30**). Sertindole is an antipsychotic that could be investigated.[131–135] Sunitinib, an anticancer agent, could be readily derivatized to explore the methylation effect on its anticancer activity and side-effects.[102,136–140] Mitoxantrone[141–146] and, more recently, Pixantrone[142,147–150] have been used to treat certain types of cancer. Diltiazem is a calcium channel blocker which is used to treat hypertension.[151–154] Flurazapam, a sedative, could also be studied in this manner.[155–161] Interestingly, ethambutol,[162–165] an antimycobacterial used to treat tuberculosis, was investigated in this way by adding various substituents to the drug.[166,167] These were evaluated, not by adding substituents internally relative to the 1,2-diamine moiety, but were substituted away from the 1,2-diamine moiety. The rhodium-catalyzed hydroamination would allow a complementary method towards exploring effects of substitution.

**Figure 3:** Ethylene diamine-derived 1,2-diamines as medicinal agents

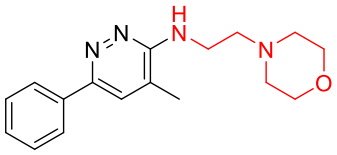


**19**
Mepyramine

(antihistamine)

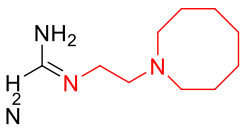


**20**
Tripelennamine
Pyribenzamine™
Novartis
(antihistamine)



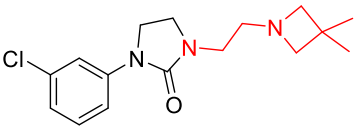
**21**
Minaprine
Brantur™

(antidepressant)

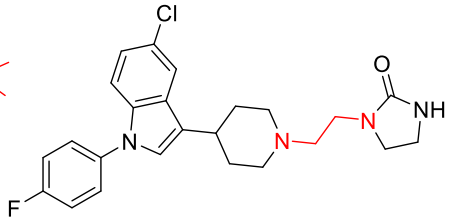


**22**
Guanethidine

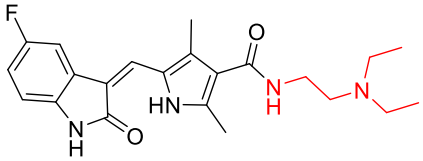
(antihypertensive)



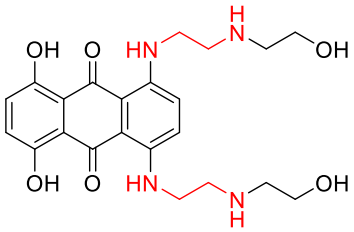
**23**
Zetidoline



**24**
Sertindole

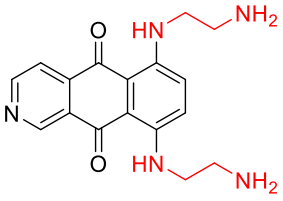


**25**
Sunitinib
Sutent™
Pfizer

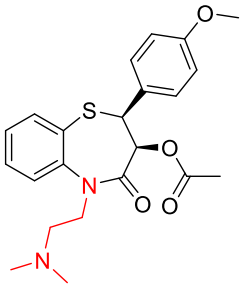


**26**
Mitoxantrone
Novantrone™

(antineoplastic agent)

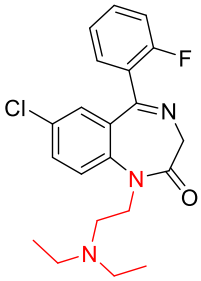


**27**
Pixantrone
Pixuvri™
Novuspharma
(antineoplastic agent)



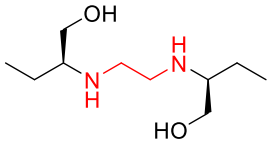
**28**
Diltiazem
Cardizem™

(calcium channel blocker)



**29**
Flurazepam
Dalmane™

(sedative)



**30**
Ethambutol
Myambutol™

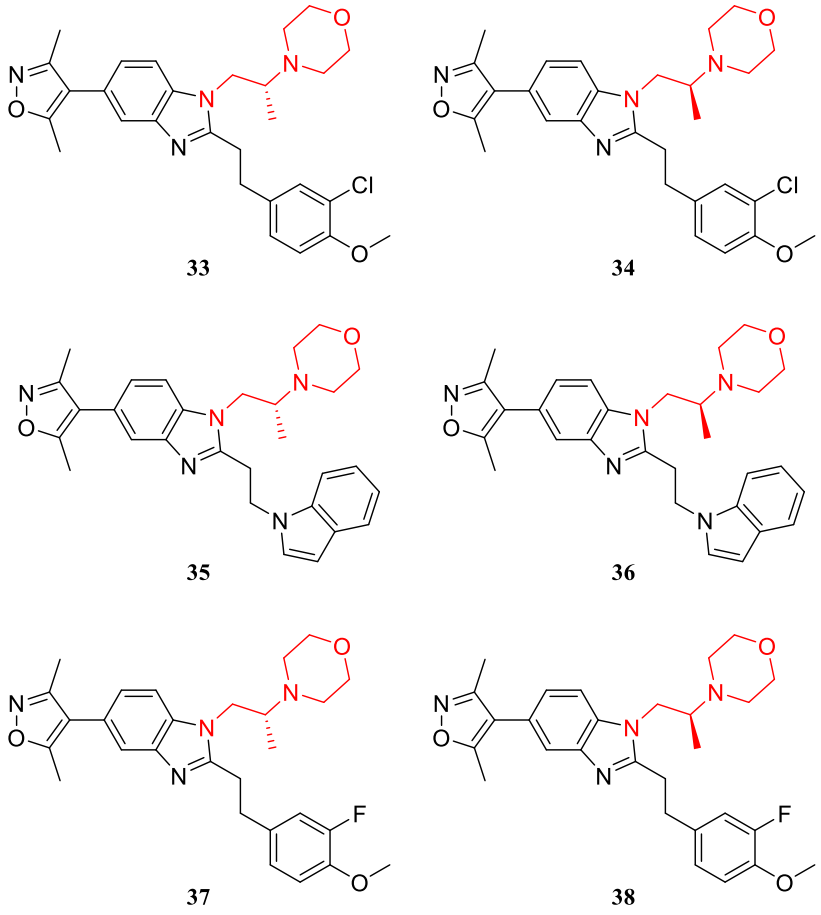
(antimycobacterial)

### 1.2.2. Potential Therapeutics

In addition to marketed pharmaceuticals containing 1,2-diamine functionalities, there are many biologically active compounds that contain 1,2-diamine subunits with vicinal substitution. There are two classes of compounds to be discussed; compounds which could be synthesized using developed rhodium-catalyzed hydroamination of allylamines and nucleophiles that are not yet developed.

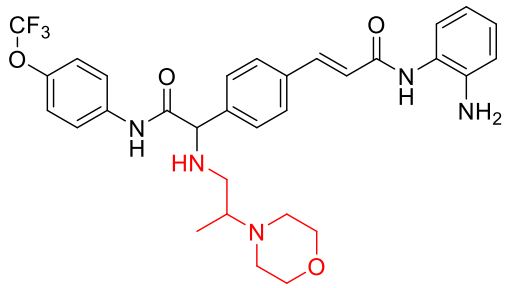
The first class of compounds to be discussed are recent developments with respect to the CBP and p300 bromodomain inhibitors. These bromodomains are involved in post-translational modification and some disorders are related to overactive p53 transcription.[168] Excitingly, highly active inhibitors of these domains were recently developed (Figure 4). The stereochemistry and aromatic substitution was shown to play a vital role and compound **34** emerged as the most potent inhibitor of these domains. Excitingly, the hydroamination methodology herein should allow for rapid derivatization of this compound to explore other nitrogen-containing heterocycles as no additional heterocycles, apart from morpholine, were shown.

**Figure 4:** Inhibitors for *CBP/p300* bromodomains

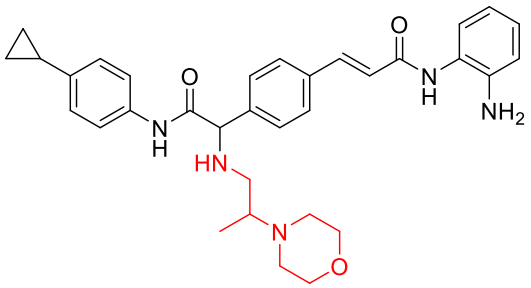


The next class of compounds that could be accessed via hydroamination methodology is the development of 2-aminoanilide histone deacetylase inhibitors. These compounds have been recently explored with respect to anticancer activity, because histone deacetylases are important in post-translational modification.[169] Two representative compounds shown to have inhibitory effects are compound **39** and compound **40** (Figure 5). These were shown to have promising anticancer activity.[169] As these compounds become better understood, hydroamination to form the 1,2-diamine subunit could prove useful in rapid derivatization of the amine functionality.

**Figure 5:** 2-aminoanilide histone deacetylase inhibitors bearing 1,2-diamine moiety




**39**

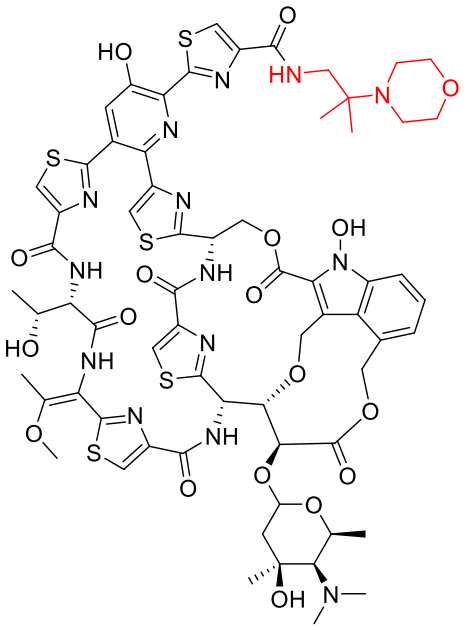



**40**

An interesting class of compounds include those derived from nocathiacins. These antibiotics are isolated from the bacterium *Norcadia* sp. and fungus *Amicolaptosis* sp.[170] Nocathiacins have been shown to have good efficacy against *Staphylococcus aureus*. However, poor water solubility has limited their use in the clinic.[170] This lead to the investigation of developing more water-soluble derived compounds. In an exciting result, several potent analogs were synthesized and one such compound was compound **41** which showed very good activity against three bacterium.[170] It was shown that by adding basic functionality to the nocathiacin, water solubility was increased (Figure 6).

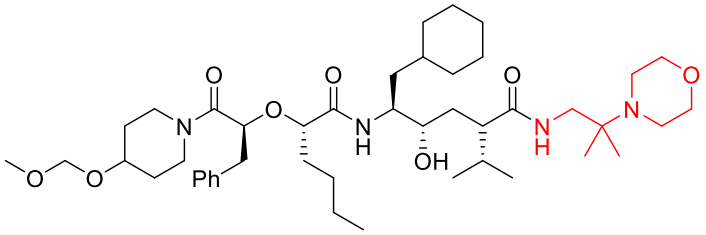
Another class of compounds recently explored include renin inhibitors. The renin-angiotensin system is one of the regulators of blood pressure.[171] Because of his, inhibitors have been developed which can control the release of renin in the system, thereby treating hypertension and heart failure (Figure 7). Compound **42** was shown to be an effective inhibitor by adding the 1,2-diamine moiety to the compound.[172] More recently, compound **43** was found to have similar effects with high binding affinity and higher water solubility.

**Figure 6:** Nocathiacin derivative

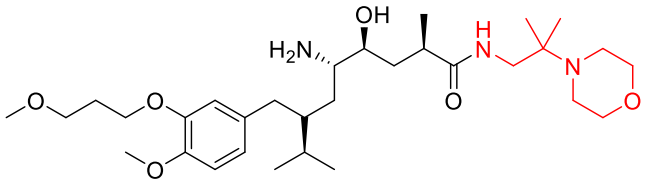


**41**

**Figure 7:** Renin inhibitors



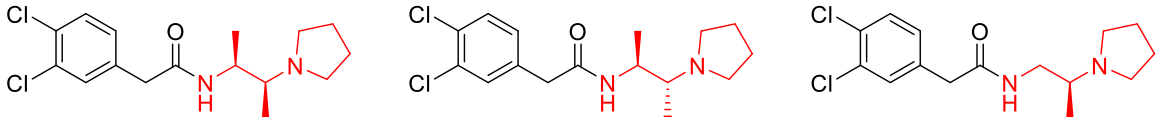
**42**



**43**

An important class of compounds include opioid receptor agonists. In one example, the κ opioid receptor was investigated. This receptor is known to lead to sedation when activated.[173] Three highly active compounds were investigated, among others (Figure 8). Compounds **44-46** showed varying binding and potency with compound **44** being the most effective and compound **45** as the least effective.

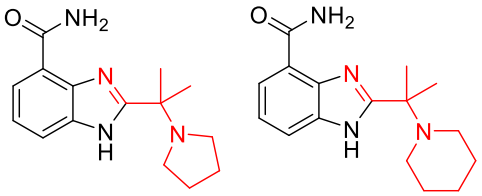
**Figure 8:** κ Opioid receptor agonists



**44** **45** **46**

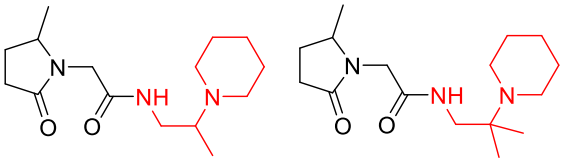
Another class of compounds that are currently being investigated are poly(ADP-ribose) polymerase inhibitors that are useful for cancer therapy and diseases related to inflammation.[174] Interestingly, amines were studied as suitable compounds as represented by compounds **47** and **48** (Figure 9) and **47** is being further investigated. Also, amnesia-reversal compounds have been studied to act against memory loss (Figure 10).[175] Both compounds **49** and **50** showed similar effectiveness at restoring memory. The use of hydroamination methodology in both cases can lead to rapid derivatization of these compounds using different nucleophiles.

**Figure 9:** Poly(ADP-ribose) polymerase inhibitors



**47** **48**

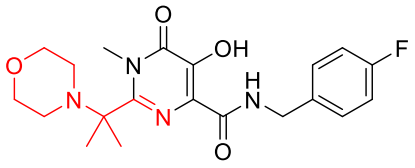
**Figure 10:** Amnesia-reversal activators



**49** **50**

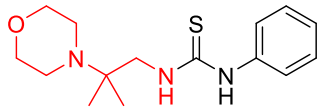
The final three compounds to be discussed are similar in structure but have different medicinal effects. Compound **51** has been shown to have anti-HIV effects by acting as an HIV-integrase inhibitor (Figure 11).[176] Compound **52** has been shown to act as a calcium channel blocker with diltiazem-like (compound **28**) activity for treatment of cardiovascular diseases and was reported as a useful structure due to the limited accessibility of diltiazem-like compounds.[152] Finally, a potent GlyT1 inhibitor, compound **53**, has been shown to be effective at treating schizophrenia by increasing brain glycine levels.[177,178]

**Figure 11:** HIV inhibitor



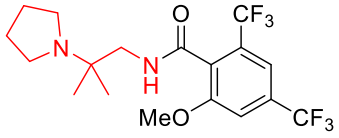
**51**

**Figure 12:** Calcium channel blocker, S046001



**52**

**Figure 13:** GlyT1 inhibitor, GSK1018921

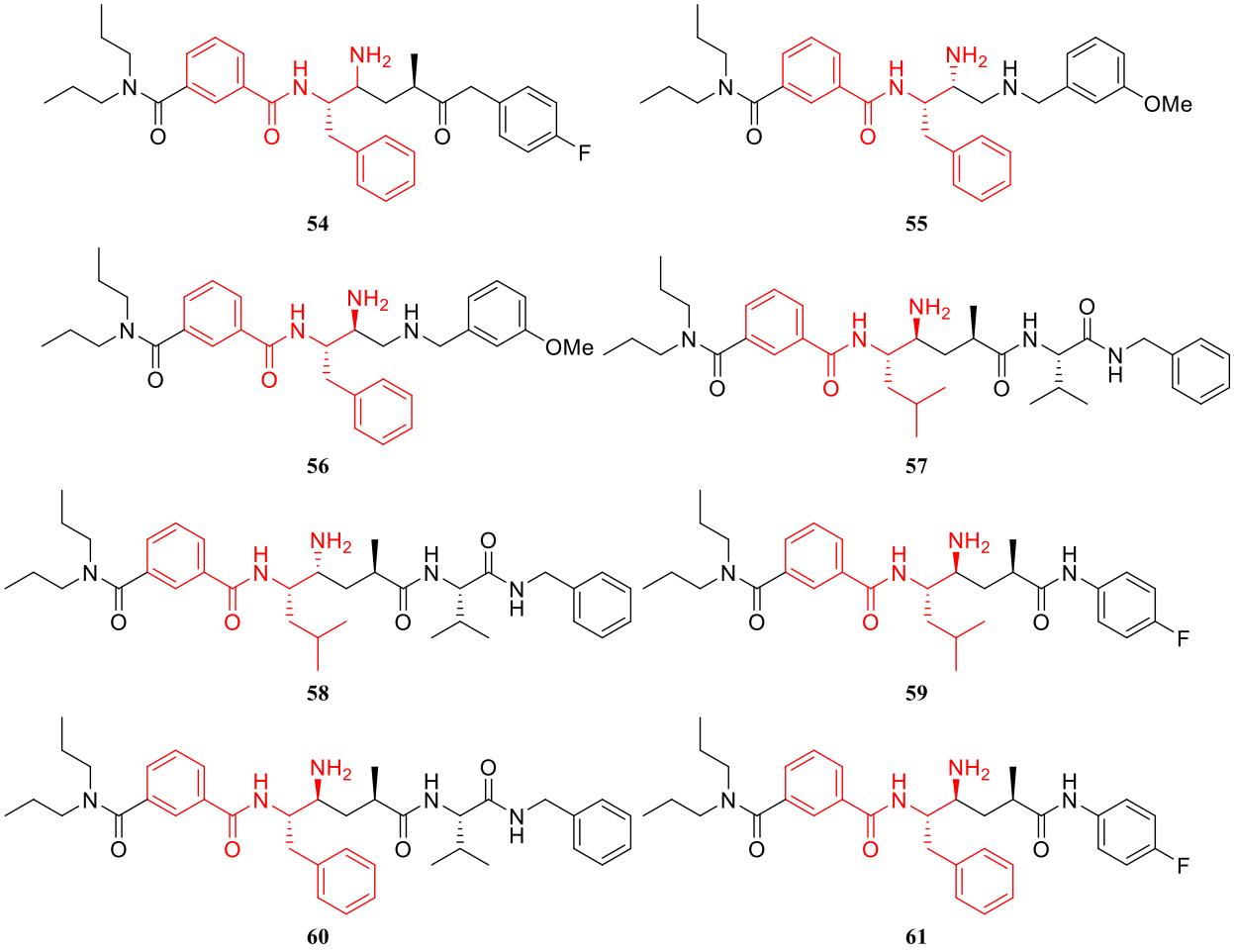


**53**

It is evident that the currently developed hydroamination methodology could be useful in generating screening libraries and as a regio- and chemoselective synthesis towards a variety of biologically active molecules. However, this hydroamination methodology will be further developed to include internal alkenes as well as amides, acyclic, secondary amines, and primary amines to further provide utility towards the synthesis of 1,2-diamines.

The first class of compounds that could be investigated are β-secretase inhibitors (Figure 14). This class of compounds is important for the treatment of Alzheimer's disease. BACE-1 is known to catalyze the formation of β-amyloid, a major component of neuritic plaques.[179] Excitingly, **54** and **61** were shown to be the most effective inhibitors of β-secretase with all compounds displaying various degrees of potency.[179–181] Although hydroamination of internal alkenes remains a significant challenge, in the future hydroamination could allow to rapid access to these enantiopure derivatives.

**Figure 14:** β-secretase inhibitors




Another important class of compounds are anti-malarial agents. Recently reported are a class of macrolactams bearing a 1,2-diamine moiety (Figure 15).[182–184] Compounds **62-67** were shown to have effective potency against a few different strains of malaria, with **62** being the most effective. However, more screening is needed to ensure greater potency and solubility. Hydroamination off allylamine derivatives could potentially enhance the ability to synthesize derivatives of these compounds.

Similarly, a class of dispiroperoxides have been reported as potential anti-malarial agents (Figure 16).[185] Since the discovery of artemisinin as a potent antimalarial natural product, synthetic derivatives have been investigated. **68** was shown to have activity levels against malaria strains and further generations are being developed to increase potency.[185]

**Figure 15:** Anti-malarial agents

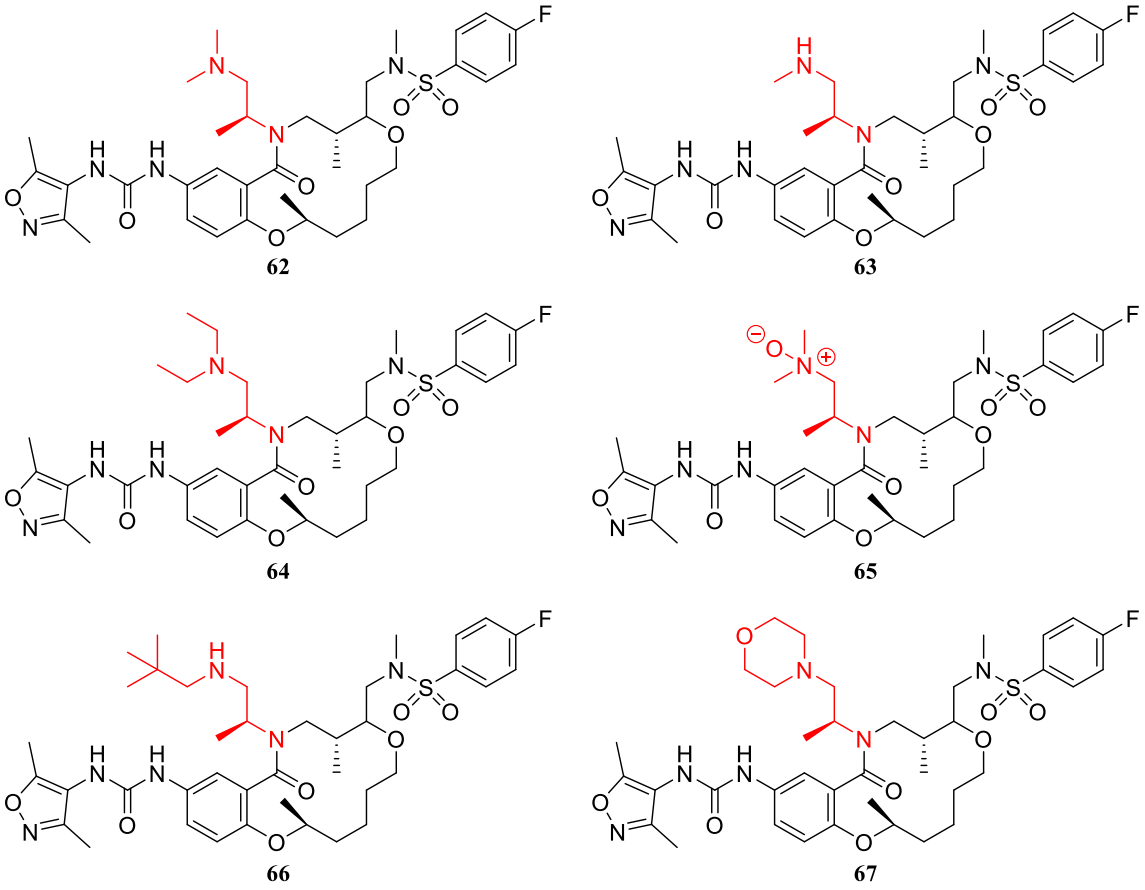
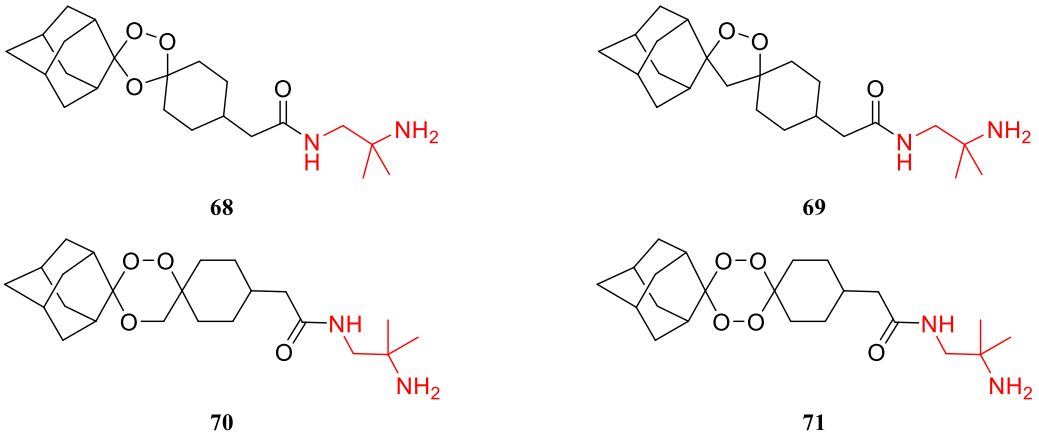


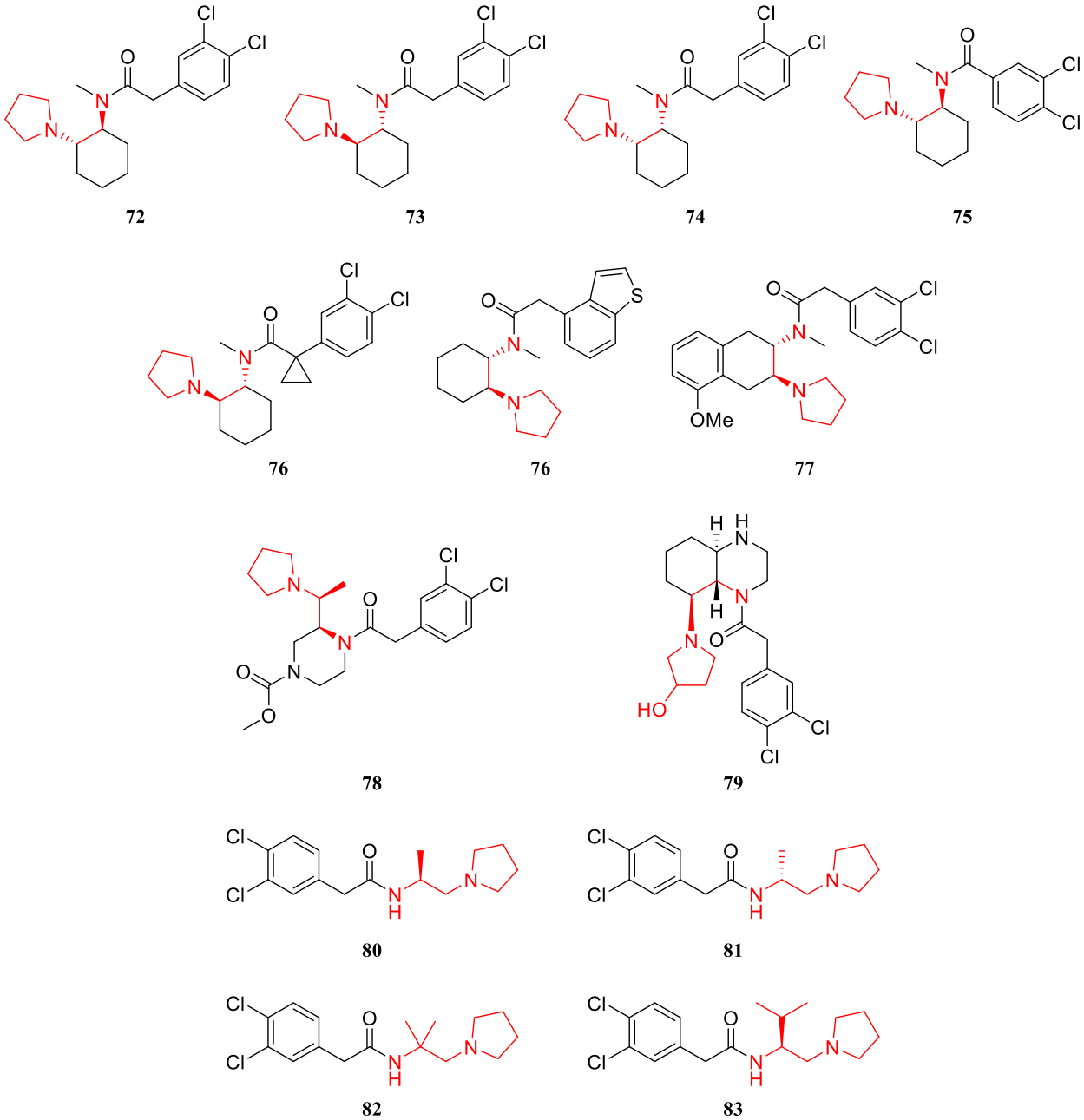

**Figure 16:** Dispiroperoxide anti-malarial agents




An important class of compounds, opioid receptor agonists have also been investigated (Figure 17).[1,173,186–191] Compound **72**, U50,488, represents an early example of a κ-opioid receptor agonist. These compounds are important as they help decrease pain, inflammation, and can induce sedation.[186] Since the discovery of U50,488, similar synthetically derived compounds have been investigated (Figure 18). [1,173,186–

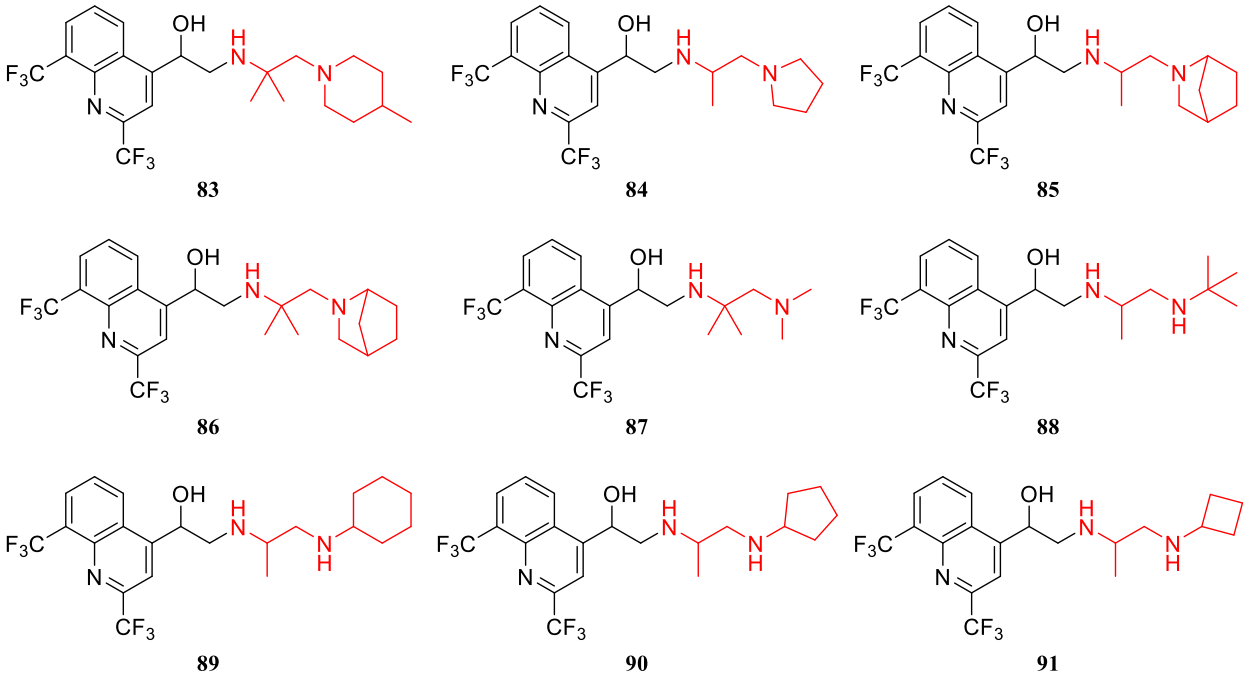
[191] The (+)-enantiomer of U50,488 (**73**) is known to have decreased activity compared to (-)-U50,488 (**72**).[186] Cyclic derivatives (**74-79**)[186,189,190] and linear derivatives (**80-83**)[173] have been investigated. Interestingly, very similar compounds to **72** were shown to be effective as agonists for different opioid receptors; **74** (σ) and **75** (μ).[186] These 1,2-diamine motifs are shown to be important with respect to opioid receptor activity, and the methodology reported herein could potentially be used in the future to aid in developing screening libraries for derivatives of **72**.

**Figure 17:** Opioid receptor agonists



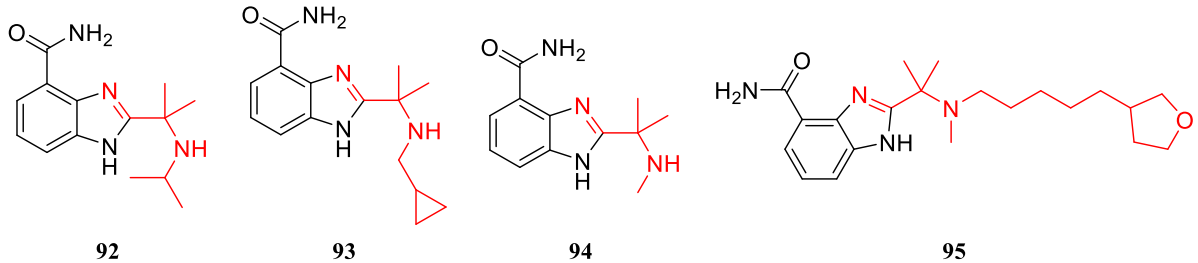
Another type of compound used for treatment of malaria are mefloquine derivatives (Figure 18).[192] A screening library was synthesized and were all shown to have differing potency against malaria. One downside to this diverse library is the exploration of diamine substrate with the methyl group adjacent to the heterocyclic amine. Our methodology would provide a complementary approach towards accessing derivatives of **83-91**.

**Figure 18:** 4-diamino alcohol quinoline derivatives as anti-malarials




Another important class of potential pharmaceuticals are poly(ADP-ribose) polymerase (PARP) inhibitors. PARPs are known to be activated during inflammation events or cancer therapy and enables cancer cells to repair DNA which often leads to mutations contributing to drug resistance.[174] A library of compounds were screened and shown to have varying activities. A representative group of products are shown in Figure 19. Interestingly, **92** showed very promising activity and is being further investigated.

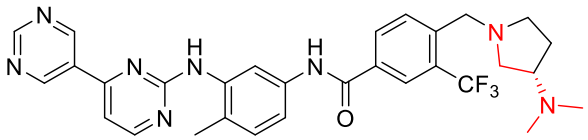
**Figure 19:** Poly(ADP-ribose) polymerase inhibitors




Chronic myeloid leukemia has been studied recently, and it has been shown that a kinase inhibitor (**96**) has increased potency relative to currently marketed compounds.[193] This could lead to decreased mutations

that allow for drug resistance. Hydroamination from a common precursor could lead to the development of a screening library to observe enhanced potency with respect to the 1,2-diamine motif (Figure 20).[193,194]

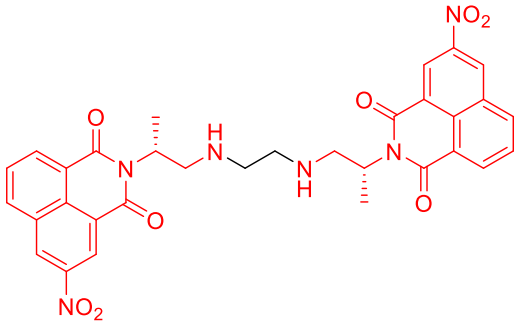
**Figure 20:** Abl/Lyn kinase inhibitor



**96**

A well-studied area of research are anti-cancer drugs that can interact with DNA. Recently, bis-intercolators such as **96** (Figure 21) have been studied with increase affinity to DNA and a longer time for cells to develop drug resistance.[147] Although this compound is unable to be synthesized with current hydroamination methodology, once imides can be used as nucleophiles, this would be able to lead to a useful synthesis of **96**.

**Figure 21:** DNA cross-linking agent



**96**

There are a variety of 1,2-diamine containing compounds that have been explored for biological activity, and a multitude of these compounds could arise from hydroamination of internal alkenes using primary amine, amide, or acyclic secondary amine nucleophiles (Figure 22). Benzodiazepines are known to have a wide variety of biological activity, but **97** and **98** have shown good anticancer activity.[195–197] Mitotic kinesin inhibitor, **99**,[198] renin inhibitor, **100**,[199,200] protein kinase inhibitor, **101**,[201,202] GlyT1 inhibitor, **102**,[203] κ-opioid antagonist, **103**,[188,204] and GlyT1 inhibitor GSK931115, **104**,[205–208] could all be potentially synthesized through hydroamination using internal alkenes with various nucleophiles.

There are also a variety of 1,2-diamine containing compounds that have been explored for biological activity that could arise from hydroamination of terminal alkenes using primary amine, amide, or acyclic secondary amine nucleophiles (Figure 23). Opioid agonists **105** and **106** have been shown to have good activity for the μ-opioid receptor and are dependent on the methyl substituents shown (Figure 23).[209] Also, RNA polymerase inhibitors **107** and **108** were shown to have anticancer activity.[210] Additionally, an MDM2

inhibitor, **109**, has been shown to have anti-tumor activity.[211] All of these could potentially be synthesized using the developed hydroamination methodology.

The final class of compounds to discuss are imaging agents used in the medical field. Cross-linking compounds continue to be studied as compounds that bind to DNA in cancer cells. This can enable easier imaging when coordinated to a radioactive label. Two examples can be seen in Figure 24. Compounds **110** and **111** were shown to be used in low amounts and were reliable for molecular imaging.[212,213]

**Figure 22:** Biologically active compounds that could arise from hydroamination of internal aminoalkenes

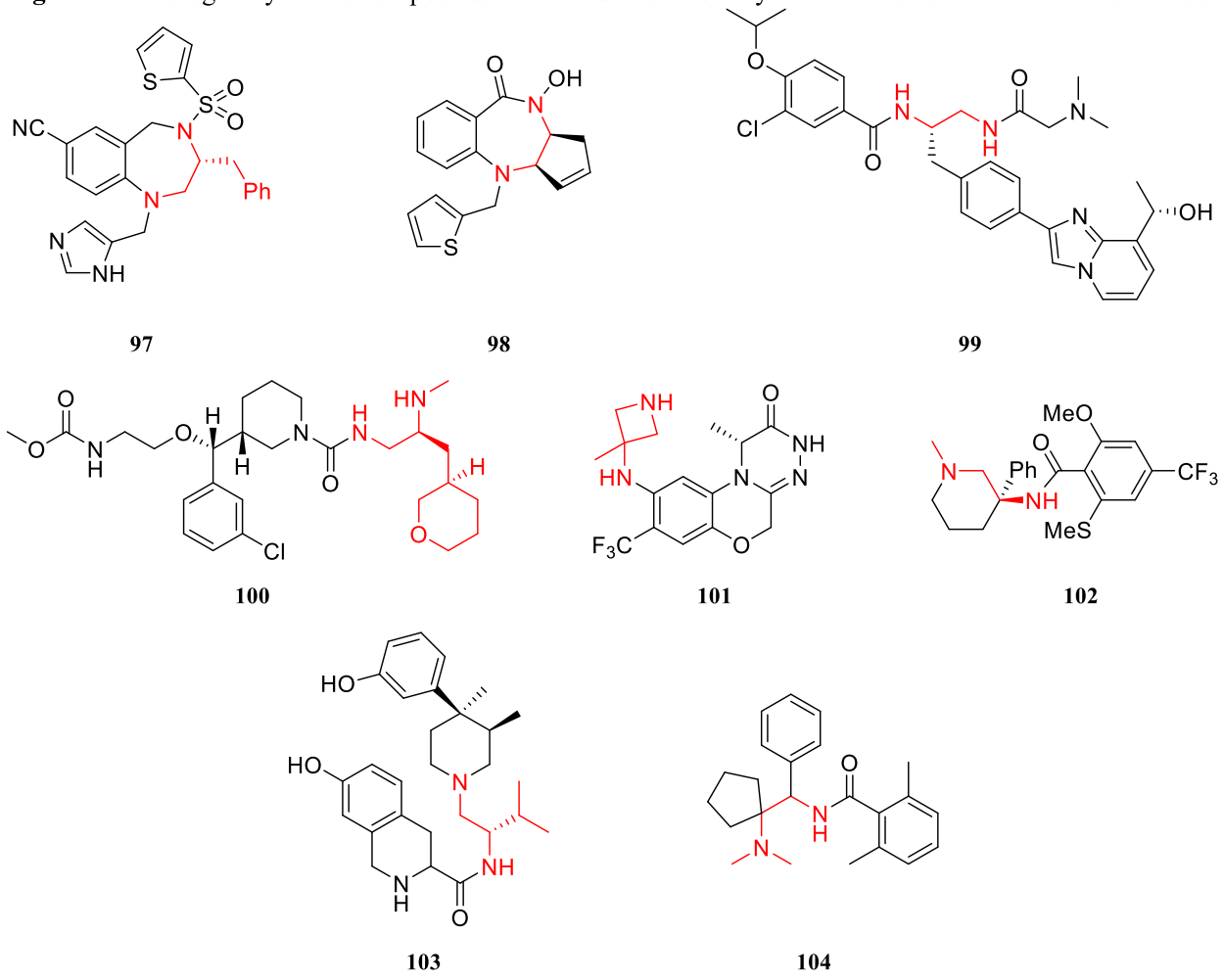
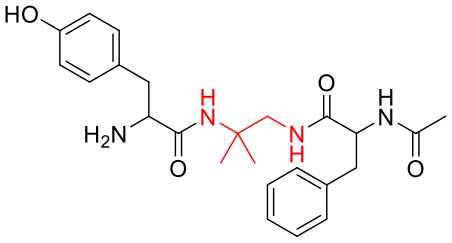
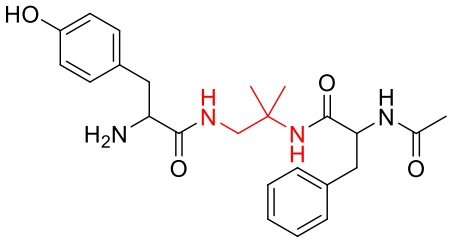


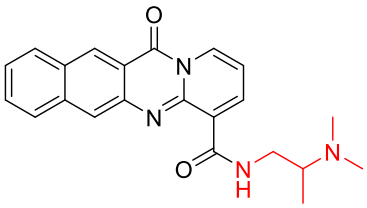
**Figure 23:** Biologically active compounds that could arise from hydroamination of terminal aminoalkenes



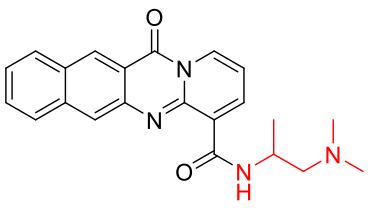
**105**



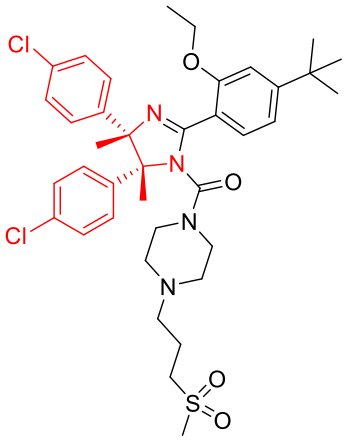
**106**



**107**

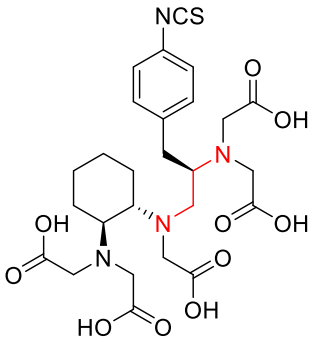


**108**

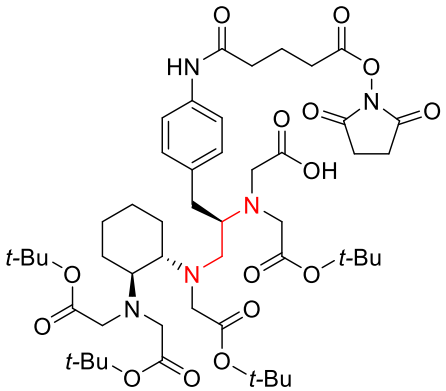


**109**

**Figure 24:** Imaging agents bearing 1,2-diamine motif



**110**



**111**

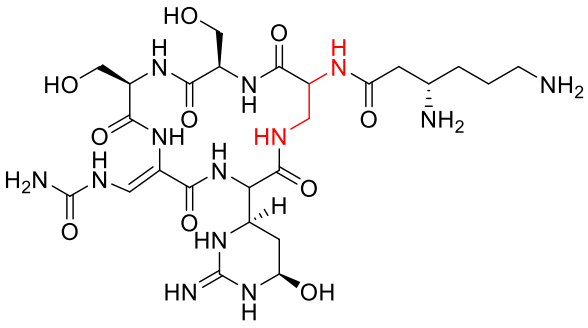
### 1.2.3. Natural Products

Natural products are an important class of compounds for the discovery and application of therapeutic agents. The 1,2-diamine motif can be found in a wide variety of natural product classes, and this motif has been found to have various roles with respect to biological activity. Although the current hydroamination methodology is unable to access these compounds reported herein, future work can be performed to address the nucleophile and alkene scope of the developed rhodium-catalyzed hydroamination. Also, this methodology could allow for the synthesis of unnatural natural products by creating building block that allow for the investigation of the methylation effect in medicinal chemistry.[93]

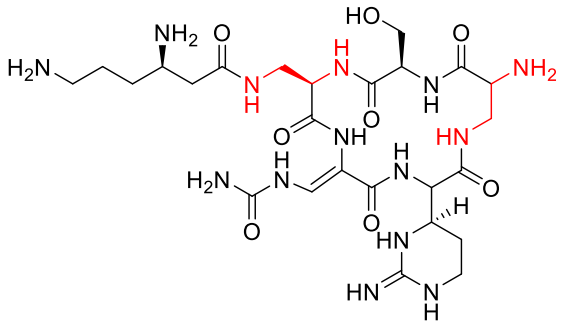
The first class of natural products to discuss are macrocyclic polypeptide natural products (Figure 25). These compounds (**112-119**) all contain a 1,2-diamine moiety. This would allow for the use of this methodology to incorporate this methylated 1,2-diamine building block into the synthesis of these natural products. Viomycin, **112**, is an anti-tuberculosis natural product that is isolated from many different organisms.[214–217] A similar natural product, capreomycin (**113**), has been shown to have similar anti-*Mycobacterium tuberculosis* activity.[214,218–225] GE23077 compounds **114** and **115** have shown to exhibit very good RNA polymerase inhibition in bacterium.[222,226] Cyclocinamide, **116**, has been isolated from marine sponges and has exhibited broad biological activity.[222,227,228] The final two cyclic polypeptides containing the 1,2-diamine moiety are nepadutant (**118**) and laspartomycin C (**119**). Nepadutant is a tachykinin NK-2 receptor antagonist which is being studied as a potential treatment for asthma, bronchial hyperreactivity, and irritable bowel syndrome.[222,229,230] Laspartomycin C is synthesized by bacterium and has shown to exhibit broad antibacterial activity.[222,231–233] It can be seen that these natural products are all important synthetic targets, but due to their complexity, derivatives have rarely been studied. Hydroamination of alkenes could lead to a useful method to explore methylation of these compounds through the synthesis of simpler 1,2-diamine building blocks.

The next set of compound bearing a 1,2-diamine functional group that could be further derivatized can be seen in Figure 26. KMI-684 is a β-secretase inhibitors which is important for the treatment of Alzheimer's disease.[222,234,235] The disulfide bridged *NMe*-Azathiocoraline, **121**, is a DNA-intercalating compound with anti-cancer activity.[222,236–239] Both of these compounds could show significant increase or decrease in activity based on simple methyl-substitution.[93] Additionally, peplomycin, **122**, has shown very good anti-tumor activity by cleaving DNA,[222,240–242] and SCH37137, **123**, has shown antibacterial activity by suppressing microbe growth.[222,243] Finally, dapdiamide A, **124**,[222,244,245] and zwittermycin A, **125**,[222,246–248] have shown broad anti-bacterial activity.

**Figure 25:** Macrocyclic peptide natural products



**112**



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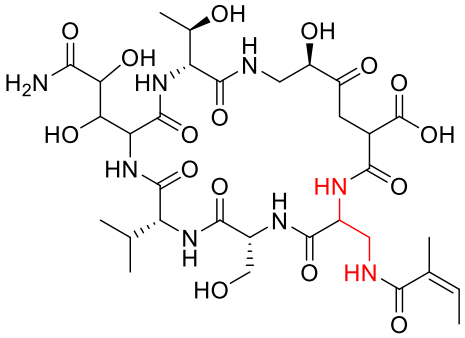

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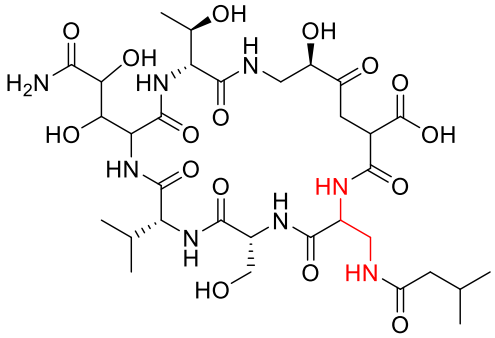

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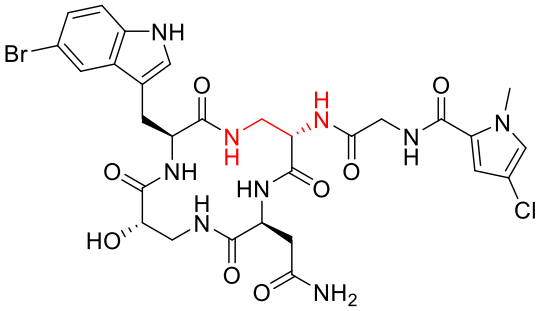

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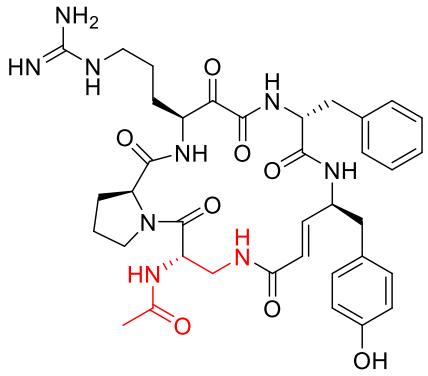
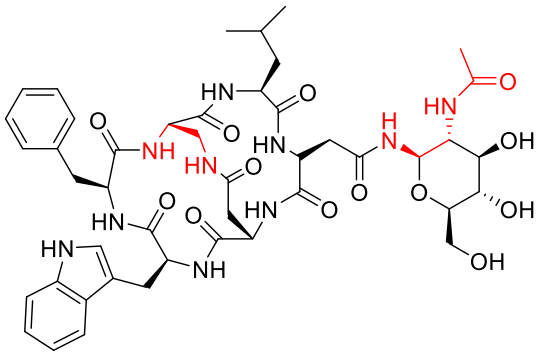


**117**



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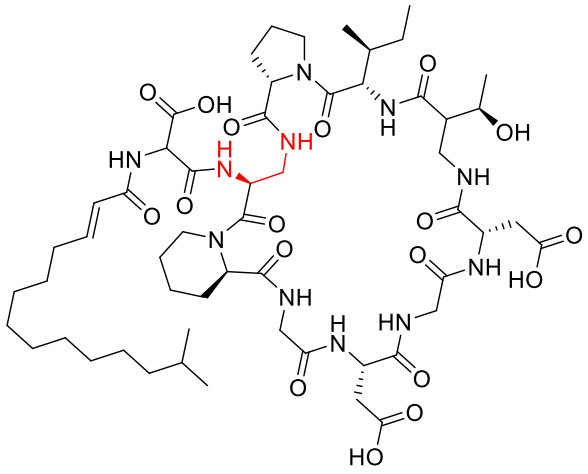
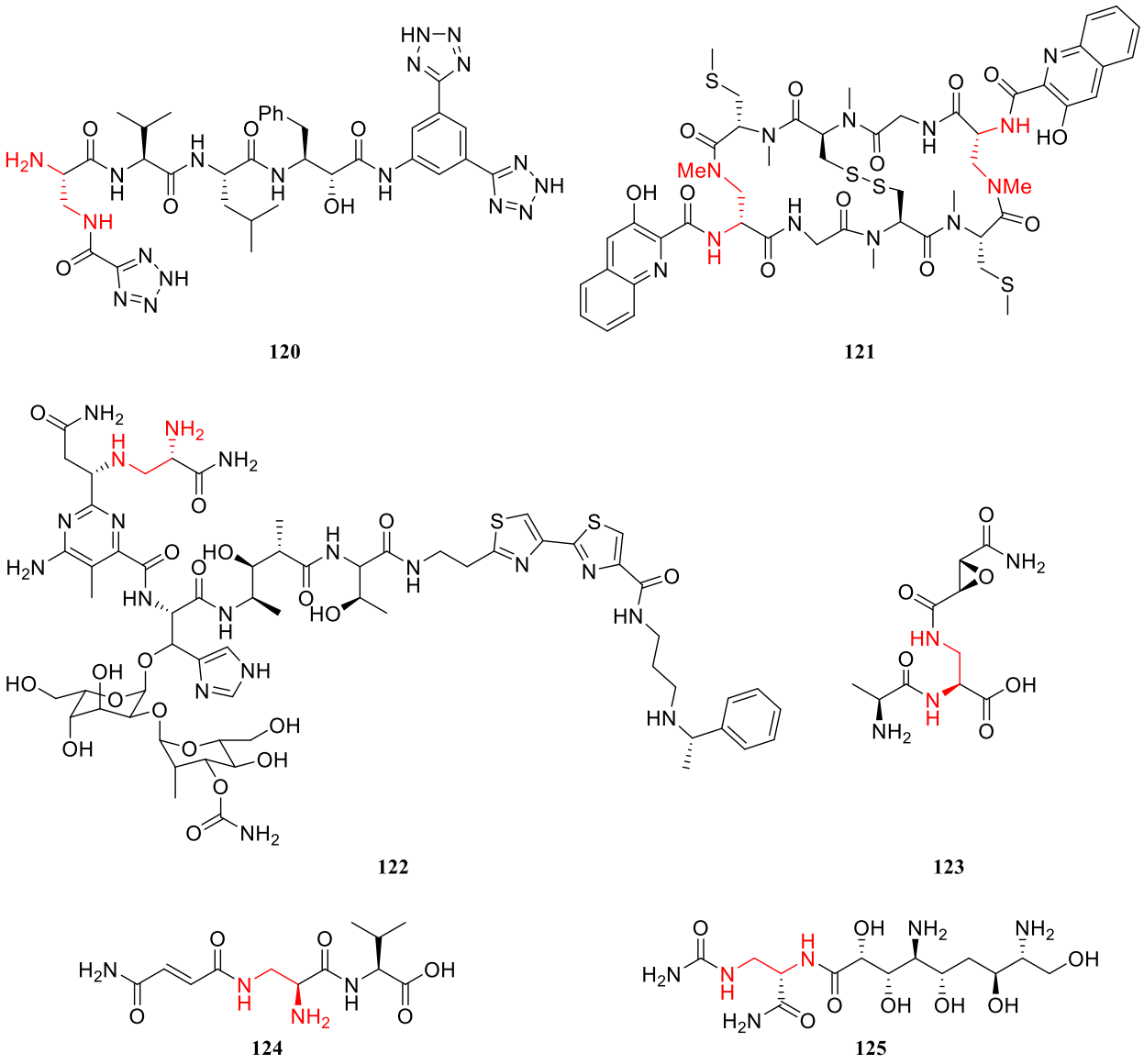


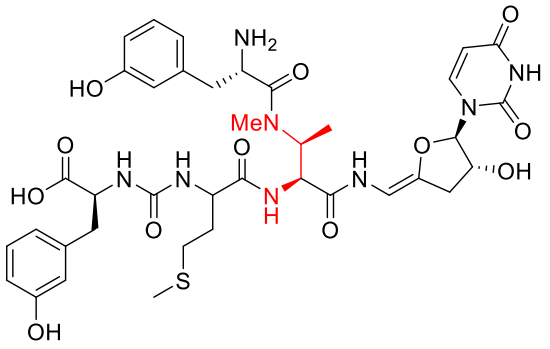
**119**

**Figure 26:** Natural products containing 1,2-diamine motif

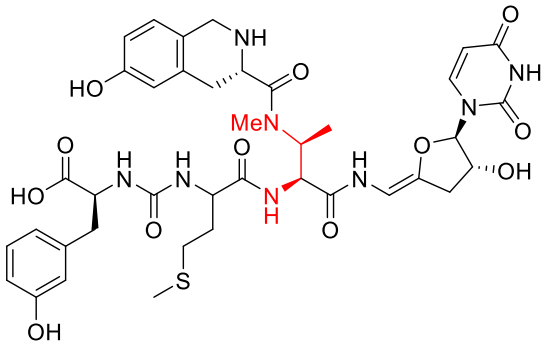



Perhaps the most important class of 1,2-diamine natural products with respect to hydroamination methodology are those bearing a methyl substituent at the same position as one amine functionality (Figure 27).[93] Mureidomycin A, **126**, has been shown to be an effective peptidoglycan biosynthesis inhibitor; acting as a gram-positive anti-bacterial.[222,249,250] Napsamycin A, **127**, has also been shown to have very good anti-bacterial activity.[222,230] Cirratiomycin B, **128**, and lavendomycin, **129**, also have very good antibiotic activity.[222,251] Lastly, the antibiotic, pacidamycin 3 (**130**),[252–256] and the anti-HIV compound, papuamide B (**131**),[222,257–261] could potentially be synthesized using hydroamination methodology.

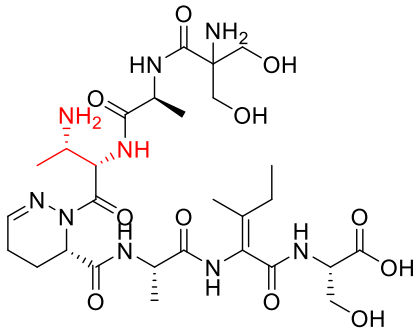
**Figure 27:** Natural products containing methyl-substituted 1,2-diamine motif



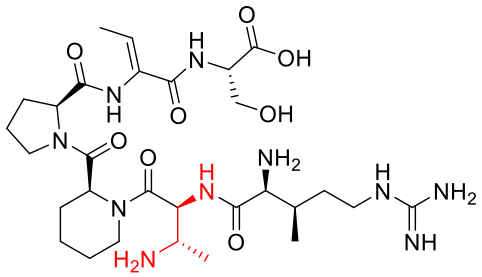
**126**



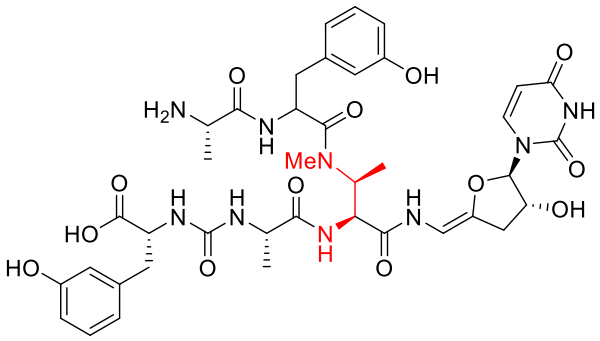
**127**



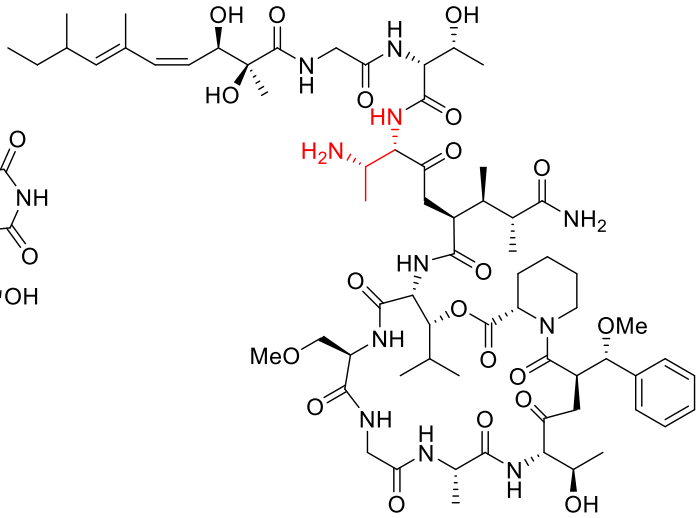
**128**



**129**



**130**

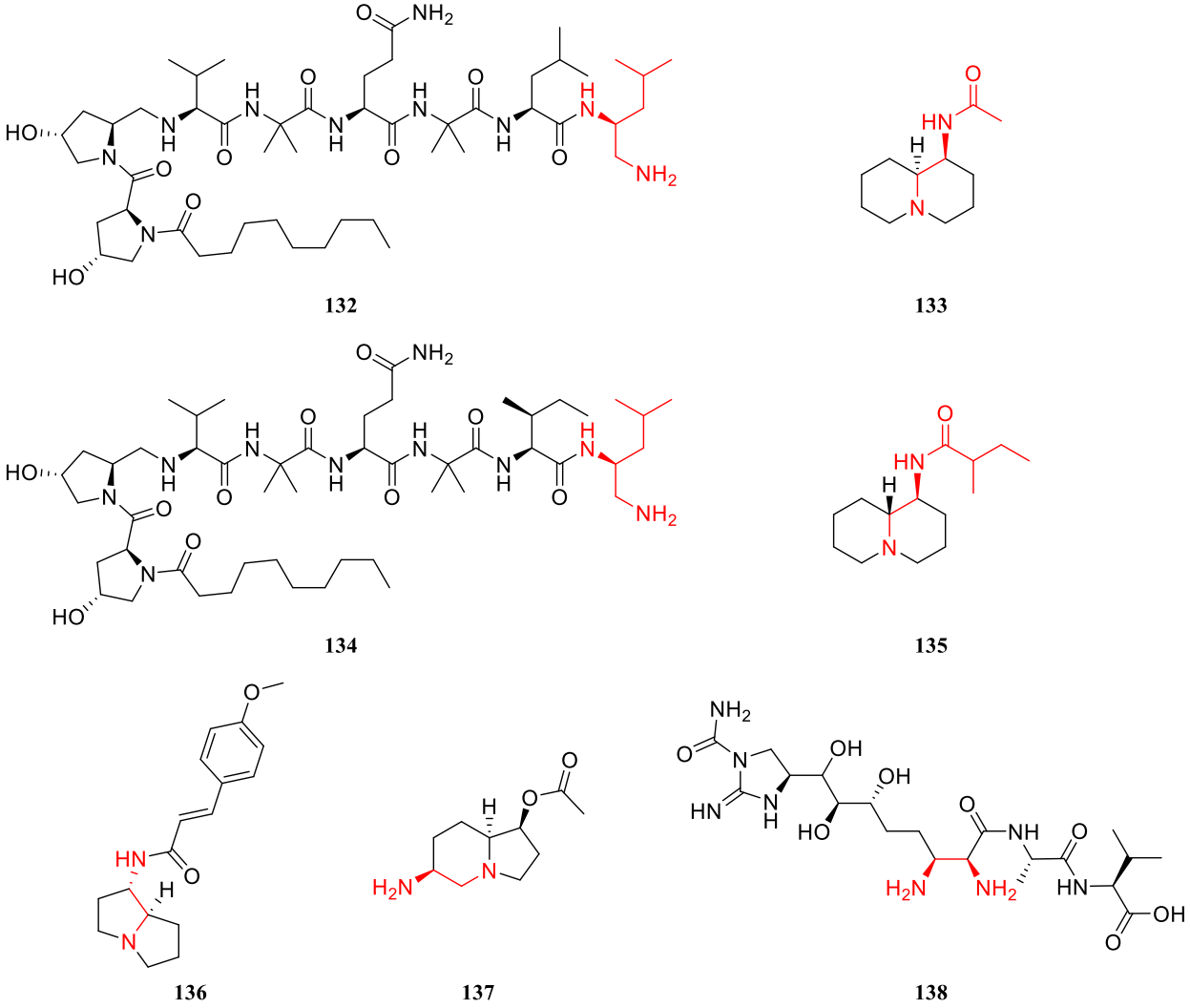


**131**

This hydroamination methodology could also be useful at derivatizing internal alkenes in order to build complexity (Figure 28). Cicadapeptins **132** and **134** were isolated from the Australian cicada and have shown promising antibiotic activity.[262] Epiquinamide, **133**, and laburnamine, **134**,[263] have been shown to possess agonistic activity with respect to nicotinic acetylcholine receptors which are known to be involved in primary functions of the central nervous system. Absouline, **136**, [264–268] and slaframine, **137**,[190,269–273]

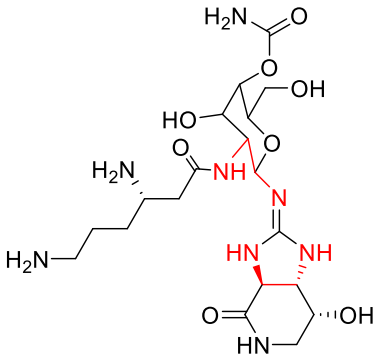
have been shown to possess moderate antiviral activity while guadinomine, **138**, possesses gram-negative antibacterial activity.[274]

**Figure 28:** Natural products that could arise from hydroamination of internal alkenes

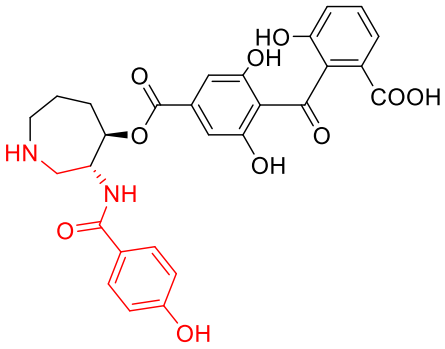



Finally, this hydroamination methodology could potentially be used as a method to synthesize complex, small molecule, natural products. Antibiotic **139**, streptothricin F,[222,275] protein kinase inhibitor **140**, balanol,[190,276–282] anti-cancer compound **141**, agelastatin A,[283–288] and antiproliferative agent **142**, jogyamycin,[289] all possess the 1,2-diamine functionality. However, current hydroamination methodology would not be able to synthesize these compounds.

**Figure 29:** Small molecule natural products containing 1,2-diamine



**139**



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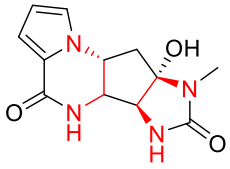
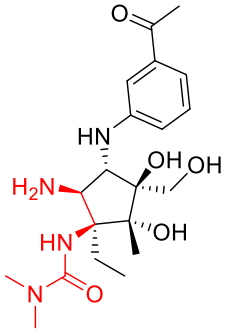


**141**

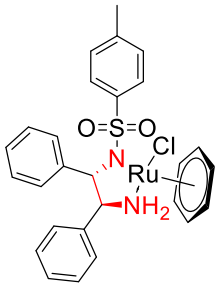


**142**

### 1.3. 1,2-Diamines as Ligand Scaffolds

1,2-Diamines are employed as ligands in a variety of reactions. A beautiful review was published by Buchwald on diamine ligands in copper-catalyzed reactions.[290] Many of the reactions reported have shown usefulness in the pharmaceutical industry for cross-coupling and other reactions. Additionally, Noyori has shown effective ruthenium catalysts for hydrogenation.[291,292] One such catalyst is shown in Figure 30. 1,2-diamines have also been employed in a vast array of iridium-catalyzed hydrogenation and transfer hydrogenation.[293]

**Figure 30:** Noyori hydrogenation catalyst



Perhaps one of the most well-known diamine-derived catalysts is the Jacobsen epoxidation catalyst (Figure 31). This diamine has been utilized in a wide-variety of ways, but few other derivatives of the chiral diamine portion are known.[294–297] Additionally, Grubbs employs a chiral NHC derived from a diamine for metathesis reactions (Figure 32).[298–300]

**Figure 31:** Jacobsen epoxidation catalyst

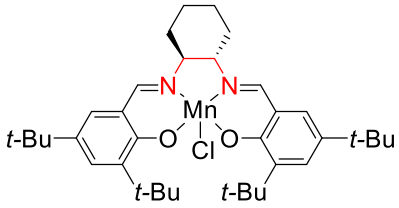
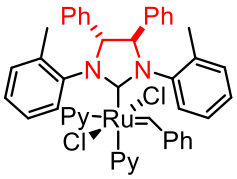
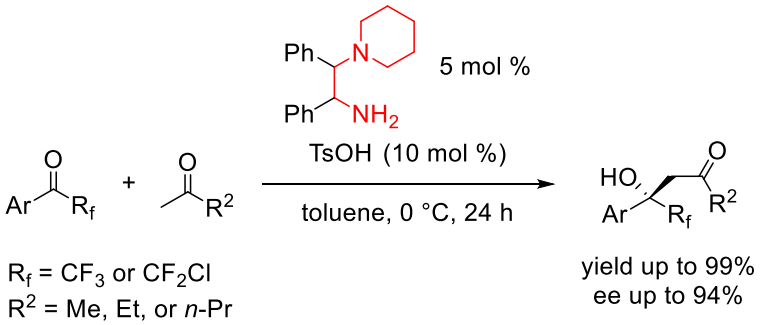



**Figure 32**: Grubbs metathesis catalyst




Lastly, the Song group has developed a chiral ligand which is efficient in the catalytic enantioselective cross-aldol reaction between linear aliphatic ketones and fluorinated ketones (Scheme 5).[301] The authors noted that by fine-tuning the diamine catalyst, a wide range of enantioselectivities were obtained.

**Scheme 5:** Asymmetric aldol reaction




There are many other ligands for catalysis that are not discussed here that contain 1,2-diamine moieties. The hydroamination methodology reported herein would allow the derivatization of some of these ligand scaffolds that could impact both reactivity and enantioselectivity.

### 1.4. Synthesis of 1,2-Diamines

Typically, 1,2-diamines are synthesized in a multi-step fashion. Therefore, it would be desirable to synthesize diamines through reaction with 1,2-dihalides. However, when these reactions are conducted, elimination byproducts are formed preferentially.[190] Hydroamination would be a step and atom-economical approach toward this problem. Traditionally, 1,2-diamines are synthesized through aziridination followed by nucleophilic ring-opening, the Nitro-Mannich reaction, 1,2-diamination of olefins, and Cope-type

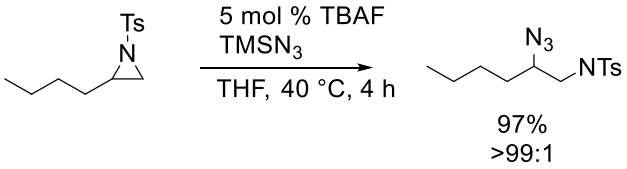
hydroamination. These methods will be discussed among other unique approaches, and the state-of-the-art methods will be discussed in detail.

### 1.4.1. Aziridine Ring-Opening

Nucleophilic addition of amines to aziridine containing molecules has been a known transformation for over 30 years.[302] However, it was noted that the corresponding aziridine could undergo ring-opening in an $S_N2$ fashion or undergo a single-electron transfer mechanism, forming a radical, and producing the opposite regioselectivity.[302] Due to unpredictable regioselectivity, aziridine ring-opening has been well-studied using a variety of nucleophiles. When amine nucleophiles are used, the final product contains a 1,2-diamine. In addition to regioselectivity problems, unprotected aziridines can act as nucleophiles themselves which causes chemists to protect the aziridine before nucleophilic ring-opening.[190] It would be desirable to instead form a 1,2-diamine directly from an olefin. A large portion of work has been dedicated to the stereoselective synthesis of aziridines,[303] but the regioselective opening of aziridines will primarily be discussed in this report.

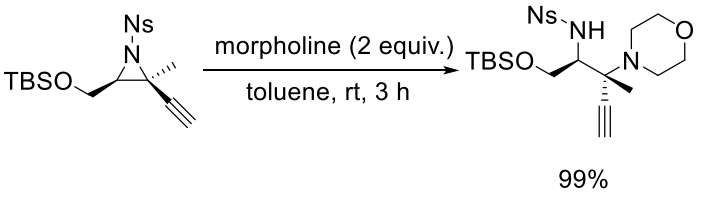
There are two notable examples that exhibit exquisite regioselectivity. First, it was shown that 1,2-diamines could be formed in high selectivities from alkyl aziridines (Scheme 6).[304] Catalyzed by tetrabutylammonium fluoride, this reaction proceeds in high yield with the nucleophile adding to the more substituted position of the aziridine ring. This regioselectivity differs from what would be expected from an $S_N2$-type ring opening.

**Scheme 6:** Aziridine ring-opening using trimethylsilyl compounds




The second example could be considered the state-of-the-art method for synthesizing chiral 1,2-diamines from trisubstituted aziridines (Scheme 7).[305] This method allows for the nucleophile to add to the more sterically hindered position and the opposite regioisomer is not observed. The yields of this reaction were excellent in most cases and secondary and primary amines are tolerated as nucleophiles.

**Scheme 7:** Trisubstituted aziridine ring-opening

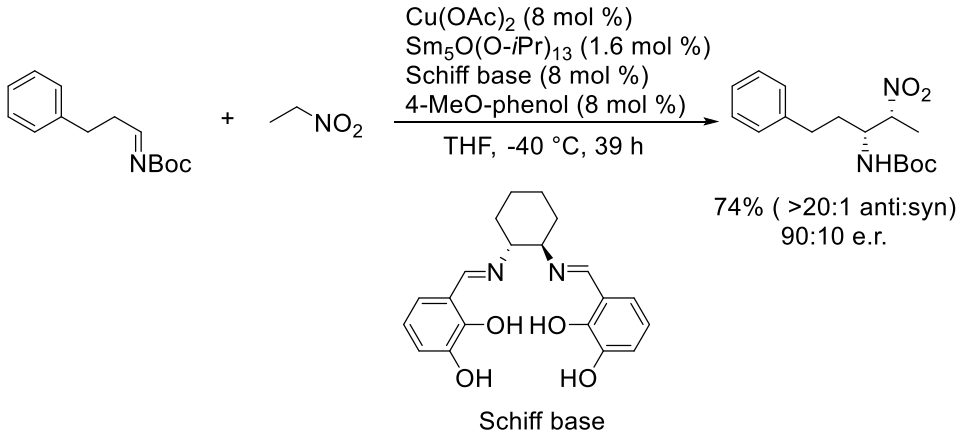


### 1.4.2. Mannich and Nitro-Mannich Reaction

Another powerful approach towards the generation of 1,2-diamines is by the use of the nitro-Mannich (aza-Henry) reaction. This process involves the addition of a nitronate to an imine which generates a new carbon-carbon bond. This process has been very well-studied and has found use in generating differentially protected nitrogen functionalities in different oxidation states.[306,307] This allows for selective transformation of these functional groups. Although widely studied showing a diverse series of transformations, there are two notable examples that will be discussed in this report.

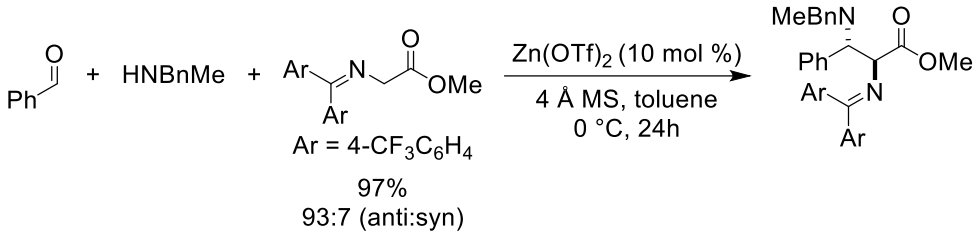
The first example is the development of a *syn*-selective nitro-Mannich reaction (Scheme 8).[73,308] Typically, the nitro-Mannich reaction leads to the *anti* diastereomer.[306] Interestingly, when promoted by a Cu/Sm/dinucleating Schiff base system, the syn diastereomer can be achieved in good to very good enantiomeric ratios. This diastereoselectivity is explained by the coordination of the catalyst to both the Boc-protected amine as well as the nitro-group in the transition state. To further show the reaction's effectiveness, the authors used this methodology to synthesize the antipsychotic agent, nemonapride (**7**).

**Scheme 8:** *Syn*-selective nitro-Mannich reaction




The second example is a Mannich reaction that is a direct three-component reaction that leads to α,β-diamino acid derivatives (Scheme 9).[309] It was shown that a variety of aromatic aldehydes, secondary amines, and iminoesters could be combined in one-pot with a Lewis acid to afford 1,2-aminoimines. These were reduced in order to form the diamine acid derivatives. The yields were excellent in most cases, though aliphatic aldehydes showed diminished yields and selectivities. Work in this area is ongoing to address this limitation.

**Scheme 9:** Lewis-acid catalyzed Mannich reaction

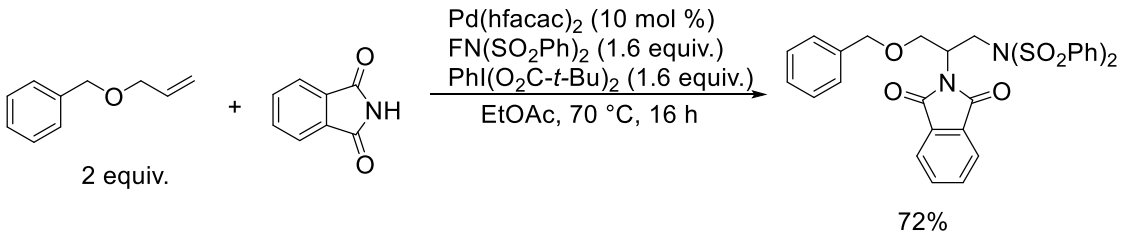



### 1.4.3. Diamination of Olefins

An attractive approach towards the synthesis of 1,2-diamines is through direct diamination of olefins. This has been studied extensively, including the use of transition metal catalysis.[310] The main limitations of this methodology include the use of unactivated terminal olefins and diamination of unactivated internal alkenes. The two methods discussed herein are the most recent and effective examples of diamination.

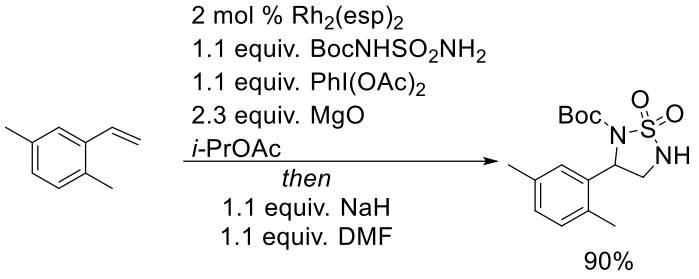
The first to be discussed was able to achieve diamination of unactivated terminal alkenes using palladium catalysis (Scheme 10).[311] Using allylic ethers, it was shown that differentially protected 1,2-diamines could be formed. However, the olefin in this case is required in excess to give moderate yields of the product.

**Scheme 10:** Diamination of unactivated alkene

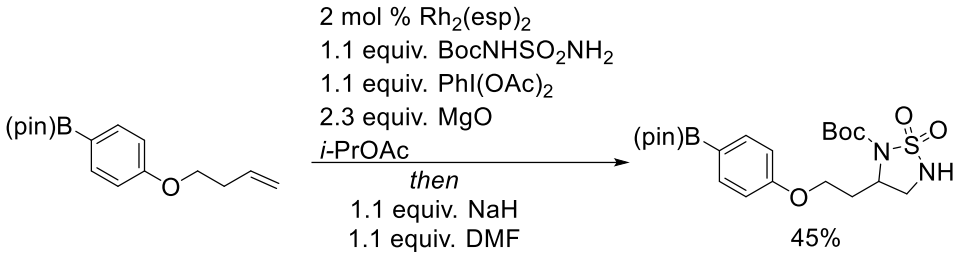



The next example illustrates the current state-of-the-art with respect to diamination reactions. In this rhodium-mediated reaction, an aziridine is formed and is subsequently converted into the corresponding diamine *in situ*.[312] Diamination of styrene derivatives proceeded in very good yields (Scheme 11). However, when aliphatic alkenes were used as the substrate, yield were halved (Scheme 12). Work in this area to further expand the alkene scope as well as making this an enantioselective process are ongoing.

**Scheme 11:** Diamination of substituted styrene derivative



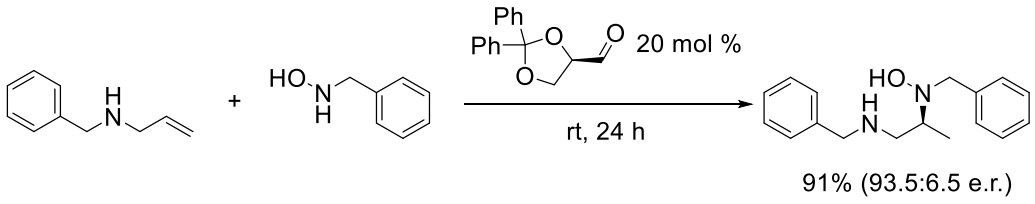

**Scheme 12:** Diamination of unactivated terminal alkene




### 1.4.4. Cope-Type Hydroamination of Olefins

The recently developed Cope-type hydroamination of olefins provides a unique complementary approach toward synthesizing 1,2-diamines. This methodology employs a chiral aldehyde to induce a temporary intramolecular reaction which affords the desired products in very good yields and enantiomeric ratios (Scheme 13).[28,313] This methodology allows access to methyl-substituted 1,2-diamines. However, the reaction appears to be strongly substrate dependent and aldehyde dependent. The rhodium-catalyzed hydroamination reported herein provides a complementary approach towards this methodology by allowing cyclic, secondary amines to be used as nucleophiles and is not as substrate dependent.

**Scheme 13:** Cope-type hydroamination of Bn-protected allylamine



# CHAPTER 2*

## Rhodium-Catalyzed Chemo- and Stereoselective Hydroamination

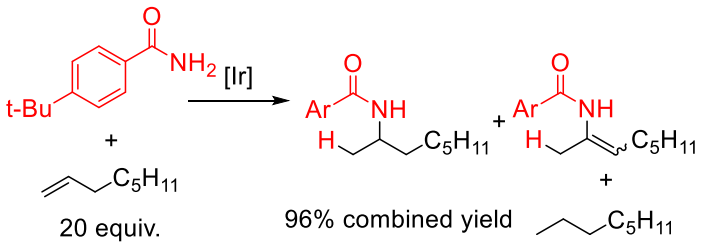
### 2.1. Introduction

As it has been demonstrated, 1,2-diamines and nitrogen-containing compounds in general are very important molecules for a variety of reasons. The direct addition of a nitrogen and hydrogen across an olefin, the hydroamination reaction, would be a desirable was to make these important functionalities. Amines and olefins represent readily accessible starting materials that could be coupled in 100% atom economy. Typically, hydroamination is hindered by high activation barriers due to high electron density of the nucleophile and electrophile components. Because of this, metal-catalyzed approaches toward hydroamination have become popular. Although significant and impressive work has been conducted with a variety of early and late transition metals, rhodium and iridium have shown good reactivity as well as functional group tolerance. Functional group tolerance, was an important consideration when choosing a metal catalyst to perform the Lewis-base directed hydroamination reaction. Rhodium and iridium have been extensively studied in terms of hydroamination and have been shown to perform intermolecular hydroamination on a variety of functionalized substrates at relatively low catalyst loadings.[3,33,314,315] Therefore, our initial investigations began utilizing rhodium and iridium catalysts for this reaction.

#### 2.1.1. Iridium Catalyzed Intermolecular Hydroamination

Coulson demonstrated the first example of homogeneous transition metal-catalyzed hydroamination in 1971 with $RhCl_3•(H_2O)_3$ and $IrCl_3•(H_2O)_3$,; enabling the hydroamination of ethylene with piperidine.[316] Later, Milstein demonstrated an Ir(I) hydroamination of norbornene with aniline.[317] This reaction has been made asymmetric with a variety of strained, bicyclic olefins.[27] Iridium-catalyzed intermolecular hydroamination was given a significant advance in 2012 when Hartwig was able to demonstrate Markovnikov hydroamination of unactivated and unstrained 1-octene with benzamide nucleophiles (Scheme 14).[318] Unfortunately, a 1.4:1 (hydroamination: oxidative amination) ratio was obtained. Importantly, the byproduct from oxidative amination was able to be hydrogenated *in situ* either by $H_2$ balloon or transfer hydrogenation with 2-propanol.

**Scheme 14**: Iridium-catalyzed hydroamination with benzamides



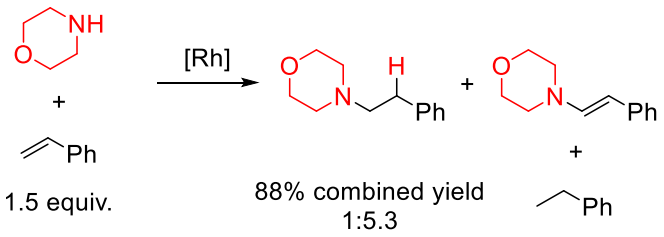

* This section includes previously published material[319]

It is suggested that iridium catalysts, in general, first undergo oxidative addition into the N–H bond of the amine nucleophile. Next, insertion of the olefin takes place followed by either reductive elimination or β-hydride elimination to afford the hydroamination or oxidative amination product, respectively.

### 2.1.2. Rhodium Catalyzed Intermolecular Hydroamination

As previously mentioned, Coulson demonstrated the first example of homogeneous transition metal-catalyzed hydroamination in 1971 with $RhCl_3•(H_2O)_3$ and $IrCl_3•(H_2O)_3$.[316] In a significant advance, Beller was able to demonstrate that $[Rh(COD)]BF_4$ catalyzes the intermolecular hydroamination of styrene with cyclic secondary amine nucleophiles.[14] Perhaps this reaction could be describe more accurately as an oxidative amination reaction as enamine products were preferentially formed over hydroamination products (Scheme 15). However, when utilizing DPEphos as a ligand for this reaction rather than $PPh_3$, Hartwig was able to significantly improve the chemoselectivity in favor of the hydroamination product; though enamine byproducts were still significant.[320]

**Scheme 15**: Anti-Markovnikov hydroamination of styrene




In contrast to the typical iridium hydroamination catalytic cycle, rhodium generally coordinates the desired alkene followed by inner- or outer-sphere nucleophilic attack of the amine nucleophile.[3] Lastly, proton transfer to the rhodium catalyst and reductive elimination or direct protolytic cleavage of the Rh–C bond occurs to form the hydroamination product. Similar to iridium, and other transition metals, β-hydride elimination is a competing pathway.

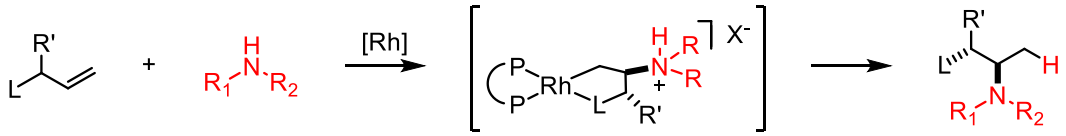
## 2.2. Rhodium-Catalyzed Chemo- and Diastereoselective Hydroamination

Many of the challenges in developing an intermolecular hydroamination have been discussed. Amines are typically better ligands for a metal catalyst than the desired olefinic substrate. To outcompete this binding, excess olefin is employed. Secondly, β-hydride elimination is unable to be avoided in almost all cases, leading to oxidative amination byproducts. Lastly, electronically activated substrates are typically required and are limited to a single class of amine nucleophiles.

In order to combat these challenges, it was envisioned that incorporating a Lewis-basic directing group would alleviate these challenges (Scheme 16). First, the need for moderate to high excess of olefin to outcompete the amine nucleophile can be mitigated through coordination of the Lewis-basic group, bringing the tethered olefin in closer proximity to the metal center. This would increase the relative concentration of olefin to the metal catalyst allowing reactivity to occur. Following formation of a 5-

membered metallocycle post-aminometallation, proton-transfer/reductive elimination or direct protolytic cleavage of the newly formed Rh–C bond can occur to form the desired product. It is expected the formation of the metallocycle would disfavor oxidative amination byproducts arising from β-hydride elimination due to the lack of syn-periplanar hydrogens to eliminate.

**Scheme 16**: Proposed intermolecular hydroamination



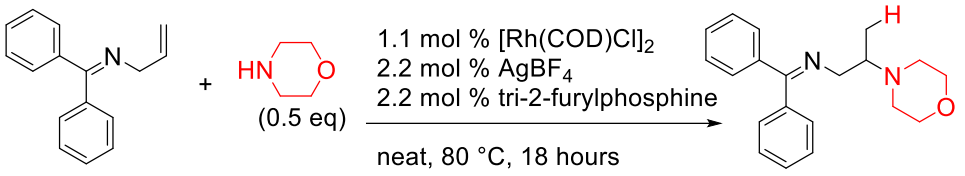

With these potential challenges in hand, imines were chosen as the first directing group to explore. It was hypothesized that primary and secondary allylamine directing groups would bind strong to the rhodium catalyst, perhaps inhibiting reactivity. Imines are themselves well-known ligands for transition metals, so allylimines were first investigated

### 2.2.1. *N*-Allylimine Reaction Discovery and Optimization

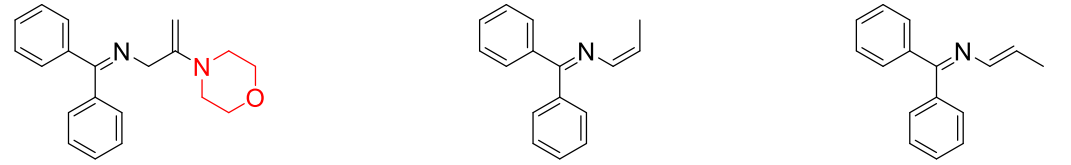
The initial investigation began by using *N*-allylbenzophenone imine (**143**) with 0.5 equivalents of morpholine (**144a**) as the nucleophile. It was hypothesized that the olefin may need to be in excess still based on literature precedence for rhodium and iridium catalyzed hydroamination reactions. When the reaction was conducted, and analyzed by GC-MS, a peak containing a molecular ion and base peak, 308 m/z and 114 m/z, respectively, was observed. This is consistent with hydroamination of *N*-allylbenzophenone imine with morpholine. In this case, no enamine product (**146a**) was observed (Scheme 17). The main byproducts were *(E)*-4-(prop-1-en-1-yl)morpholine (**146e**), benzophenone imine (**146d**), *N*-benzhydryl-1,1-diphenylmethanimine (1**46f**), and isomerization of the starting material to the *cis* and *trans* isomers of 1,1-diphenyl-N-(prop-1-en-1-yl)methanimine (**146b** and **146c**) (Scheme 17). In order to confirm the product, scale-up of the reaction was conducted (Scheme 18). After purification via silica gel chromatography, aminoimine **3a** was isolated in a 44% yield and was confirmed by $^{1}$H-NMR.

As expected, the aminoimine product appeared to slowly decompose when exposed to the silica gel during column chromatography. Because of this decomposition of the imine, future isolations were conducted by first reducing the imine *in situ* with $NaBH_4$ to form the corresponding 1,2-diamine. It was hypothesized that aldimines would be more reactive than their ketimine counterparts due to potential steric interactions with the rhodium (I) metal center. *N*-allyl-1-(4-methoxyphenyl)-methanimine (**147**) was chosen as the substrate of choice. After reduction of the aminoimine product (**148**), the diamine would contain the *p*-methoxybenzyl protecting group.

**Scheme 17:** Initial discovery by GC-MS analysis and reaction byproducts




**143** **144a** **145**
observed by GC-MS



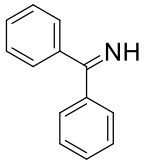
**146a**
not observed by GC-MS



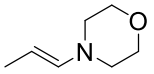
**146b**
observed by GC-MS



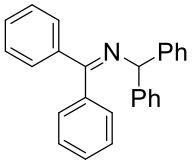
**146c**
observed by GC-MS



**146d**
observed by GC-MS

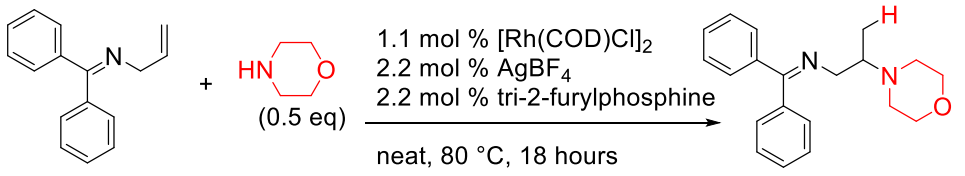


**146e**
observed by GC-MS



**146f**
observed by GC-MS

**Scheme 18:** Isolation of aminoimine **145**



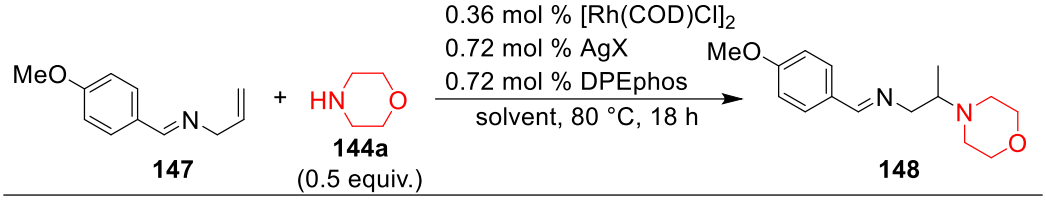

**143** **144a** **145**
44% isolated

The first parameter of our reaction that we chose to investigate was the role of the phosphine ligand. By analyzing the GC-MS traces, initial screens showed a significant increase in yield for the reaction when using DPEphos as the phosphine ligand. We hypothesized that parameters such as solvent, silver salt, nucleophile equivalents, temperature, and time could all depend on the phosphine ligand chosen, I elected to further optimize the reaction using DPEphos while Seth Ensign investigated other phosphine ligands, namely dppb and dppf, in more detail.

The next parameter investigated was the effect of silver salts and solvent used in the reactions. A representation of these screening reactions can be found in Table 1. All iterations of these were conducted and we found that the non-coordinating counter ions were more effective at promoting the desired hydroamination reaction. These silver salts were higher yielding across all solvents, so we chose to continue

with the best silver salts ($AgBF_4$, $AgSO_3CF_3$, and $AgPF_6$) and solvents (1,4-dioxane, acetonitrile, and benzene) as we investigated the equivalents of morpholine used in the hydroamination reaction.

**Table 1:** Select silver salt and solvent screening reactions



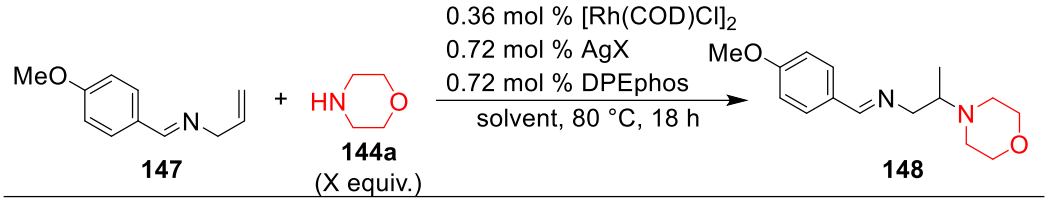

| Silver Salt | Solvent | GC Yield | Silver Salt | Solvent | GC Yield |
|---|---|---|---|---|---|
| **$AgBF_4$** | **1,4-dioxane** | **24** | $AgBF_4$ | DME | 12 |
| **$AgSO_3CF_3$** | **1,4-dioxane** | **33** | $AgSO_3CF_3$ | DME | 8 |
| **$AgPF_6$** | **1,4-dioxane** | **29** | $AgPF_6$ | DME | 8 |
| $AgBF_4$ | benzene | 4 | $AgBF_4$ | THF | 18 |
| $AgSO_3CF_3$ | benzene | 6 | $AgSO_3CF_3$ | THF | 15 |
| $AgPF_6$ | benzene | 1 | $AgPF_6$ | THF | 9 |
| $AgBF_4$ | toluene | 5 | $AgBF_4$ | MeCN | 11 |
| $AgSO_3CF_3$ | toluene | 8 | $AgSO_3CF_3$ | MeCN | 8 |
| $AgPF_6$ | toluene | 8 | $AgPF_6$ | MeCN | 10 |

The third parameter that was investigated was the equivalents of morpholine used in the reaction. Interestingly, when excess morpholine was added to the reaction, the yield was increased (Table 2). The majority of hydroamination reactions require an excess of olefin, as it is less favorable for the olefin to bind to the metal than the amine; the proximal imine makes the olefin-imine substrate a significantly better ligand and therefore it does not need to be used in excess. To the best of our knowledge, this is the first example of a metal-catalyzed hydroamination reaction where the olefin can be used as the limiting reagent.

Next, catalyst loading was optimized for the reaction. For all of the previous screening reactions, 0.36 mol % was the catalyst loading that chosen of the rhodium (I) dimer. We chose to investigate lowering the catalyst loading to 0.1 mol % while also increasing the catalyst loading to 0.5 mol % and 1.0 mol % using three of the best silver salts from previous optimization (Table 3). Interestingly, by increasing the catalyst loading from 0.25 mol % to 0.50 mol %, yield was increased drastically from 63% to 93%, respectively. Because $AgBF_4$ provided the best yield with fewer equivalents of morpholine at 0.5 mol % catalyst loading, we chose these components as optimal for the hydroamination reaction.

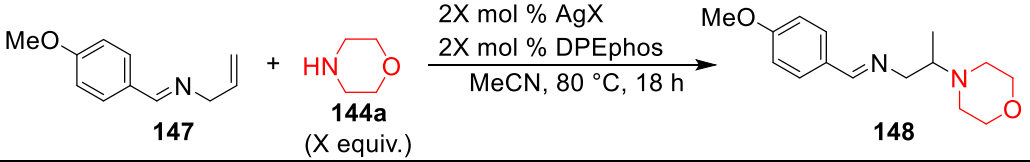
The final parameters that we investigated were time and temperature. Seth Ensign performed the time studies and found that 24 hours was the completion time for the reaction. We then investigated the temperature of the reaction at different equivalents of morpholine (Table 4). We elected to move forward with a temperature of 60 °C and using 3-5 equivalents of morpholine, as it was found to be substrate dependent.

**Table 2:** Select silver salt, solvent, and morpholine equivalent screening reactions



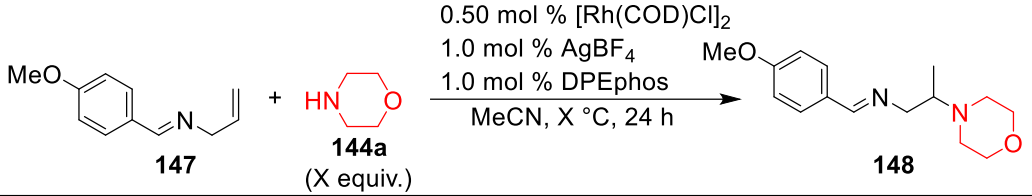

| Silver Salt | Morpholine Equivalents | Solvent | GC Yield | Silver Salt | Morpholine Equivalents | Solvent | GC Yield |
|---|---|---|---|---|---|---|---|
| $AgSO_3CF_3$ | 1 | 1,4-dioxane | 13 | $AgSO_3CF_3$ | 1 | MeCN | 14 |
| $AgSO_3CF_3$ | 4 | 1,4-dioxane | 28 | $AgSO_3CF_3$ | 4 | MeCN | 59 |
| $AgSO_3CF_3$ | 7 | 1,4-dioxane | 39 | $AgSO_3CF_3$ | 7 | MeCN | 76 |
| $AgSO_3CF_3$ | 10 | 1,4-dioxane | 44 | **$AgSO_3CF_3$** | **10** | **MeCN** | **83** |
| $AgPF_6$ | 1 | 1,4-dioxane | 20 | $AgPF_6$ | 1 | MeCN | 13 |
| $AgPF_6$ | 4 | 1,4-dioxane | 42 | $AgPF_6$ | 4 | MeCN | 57 |
| $AgPF_6$ | 7 | 1,4-dioxane | 53 | $AgPF_6$ | 7 | MeCN | 73 |
| $AgPF_6$ | 10 | 1,4-dioxane | 58 | **$AgPF_6$** | **10** | **MeCN** | **80** |
| $AgBF_4$ | 1 | 1,4-dioxane | 21 | $AgBF_4$ | 1 | MeCN | 12 |
| $AgBF_4$ | 4 | 1,4-dioxane | 48 | $AgBF_4$ | 4 | MeCN | 55 |
| $AgBF_4$ | 7 | 1,4-dioxane | 56 | **$AgBF_4$** | **7** | **MeCN** | **62** |
| **$AgBF_4$** | **10** | **1,4-dioxane** | **66** | $AgBF_4$ | 10 | MeCN | 65 |

**Table 3:** Select silver salt and catalyst loading screening reactions




| Silver Salt | Morpholine Equivalents | Catalyst Loading | GC Yield |
|---|---|---|---|
| $AgSO_3CF_3$ | 9 | 0.10 | 31 |
| $AgSO_3CF_3$ | 9 | 0.25 | 65 |
| $AgSO_3CF_3$ | 9 | 0.50 | 93 |
| $AgSO_3CF_3$ | 9 | 1.00 | 91 |
| $AgBF_4$ | 6 | 0.10 | 49 |
| $AgBF_4$ | 6 | 0.25 | 63 |
| **$AgBF_4$** | **6** | **0.50** | **93** |
| $AgBF_4$ | 6 | 1.00 | 91 |
| $AgPF_6$ | 10 | 0.10 | 16 |
| $AgPF_6$ | 10 | 0.25 | 65 |
| $AgPF_6$ | 10 | 0.50 | 95 |
| $AgPF_6$ | 10 | 1.00 | 96 |

**Table 4:** Select temperature and morpholine equivalent screening reactions[a]




| Temperature | Morpholine Equivalents | GC Yield | Temperature | Morpholine Equivalents | GC Yield |
|---|---|---|---|---|---|
| 23 | 6 | 41 | 60 | 1 | 49 |
| 30 | 6 | 52 | 60 | 2 | 76 |
| 40 | 6 | 71 | 60 | 3 | 88 |
| 50 | 6 | 90 | 60 | 4 | 91 |
| **60** | **6** | **97** | **60** | **5** | **92** |
| 70 | 6 | 90 | 60 | 6 | 93 |
| 80 | 6 | 85 | 60 | 7 | 92 |

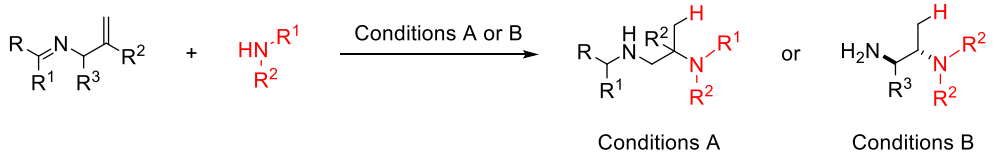
[a] with Seth Ensign

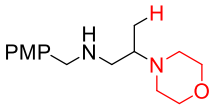
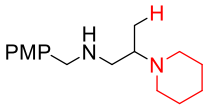
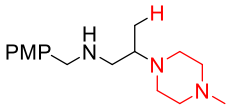
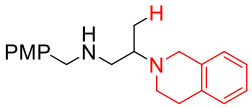
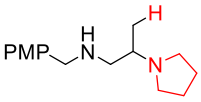
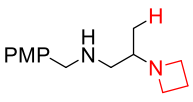
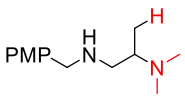
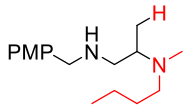
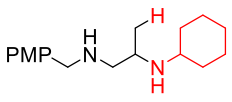
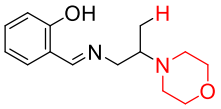
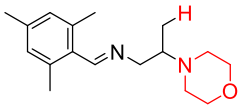
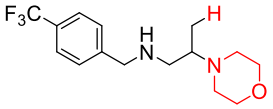
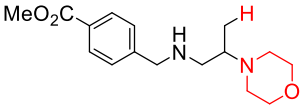
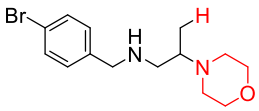
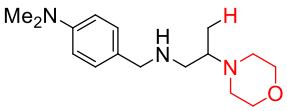
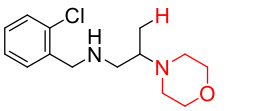
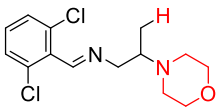
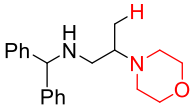
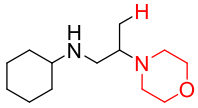
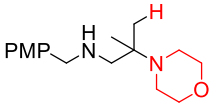
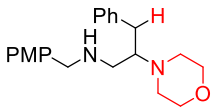
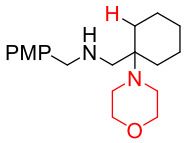
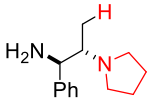
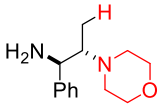
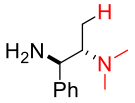
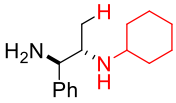
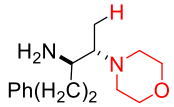
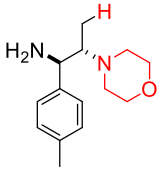
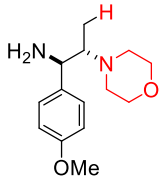
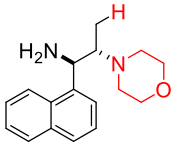
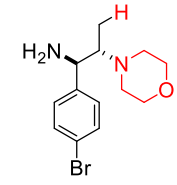
### 2.2.2. *N*-Allylimine Substrate Scope

With the optimized reaction conditions in hand, the scope of the hydroamination reaction was investigated. First, scale-up of the hydroamination of imine 1**47** with morpholine, affords **148** in 92% *in situ* yield. Unsurprisingly, compound **148** is not stable to column chromatography; the imine is rapidly hydrolyzed to 4-methoxybenzaldehyde on silica gel. Therefore, reduction of the imine was conducted with $NaBH_4$ or $LiAlH_4$, in the case of aldimine or ketimine reduction, respectively. Upon purification by column chromatography, **149a** was isolated in 82% yield.

This was a collaborative effort between Seth C. Ensign, Dr. Anil Gupta, and myself. The first that we investigated was the imine substrate scope (Table 5). Seth Ensign found that cyclic, secondary amine nucleophiles performed well under reaction conditions. However the highest yields were obtained by determining the optimal equivalents of nucleophile for each hydroamination reaction. In the case of morpholine, **144a**, 3 equivalents were required for the maximum yield; while only 1.5 equivalents of pyrollidine (**144e**) was required to afford **149e** in 76% isolated yield. Additionally, dimethylamine was able to be employed as the nucleophile is this reaction. However, larger acyclic secondary amine nucleophiles such as *N*-methylbutylamine and primary amines such as cyclohexylamine were much less effective, requiring 5 mol % of the rhodium catalyst.

**Table 5**: Nucleophile and imine for the directed hydroamination



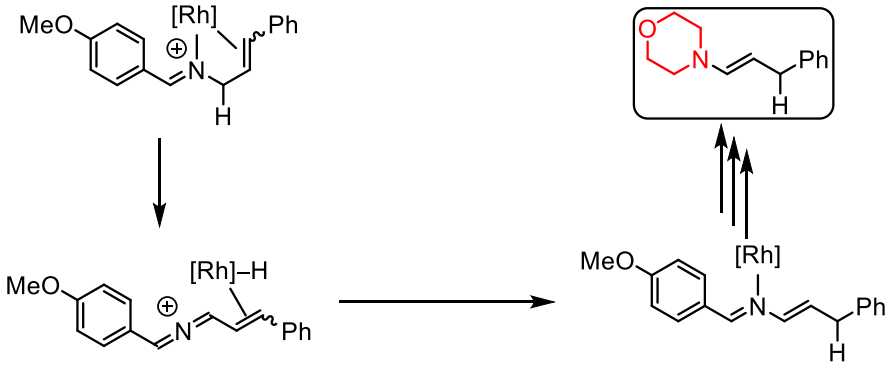

| Conditions A | | | Conditions B |
|---|---|---|---|
|  |  |  |  |
| **149a** 82% | **149b** 87% | **149c** 66% | **149d** 87% |
|  |  |  |  |  |
| **149e** 76% | **149f** 72% | **149g** 73% | **149h** 27% | **149i** 34% |
|  |  |  |  |
| **150** 90% | **151** 98% | **152** 62% | **153** 52% |
|  |  |  |  |
| **154** 76% | **155** 74% | **156** 44% | **157** not observed |
|  |  |  |  |  |
| **158** 40% | **159** 40% | **160** 58% | **161** from trans: < 5% from cis: < 5 % | **162** <5% |
|  |  |  |  |  |
| **163a** 50%, dr = 11:1 | **163b** 79%, dr = 25:1 | **163c** 22%, dr = >20:1 | **163d** 45%, dr = 12:1 | **164** 73%, dr = 16:1 |
|  |  |  |  |  |
| **165**[f] 67%, dr = 23:1 | **166** 80%, dr = 21:1 | **167** 78%, dr = >20:1 | **168** 69%, dr = 25:1 | **169** 62%, dr = >20:1 |

a (i.) 12a-g (1.0 equiv), 1a (5.0 equiv), [(DPEphos)Rh(COD)]BF4 (1.0 mol %), MeCN (4.3 M), 60 °C, 24 h.
(ii.) 10% HCl, 60 °C, 2 h, then KOH. b NMR yield of imine after hydroamination. c Pyrrolidine (1e) (1.0 equiv) used.
d 2.0 mol % [Rh] used. e Combined isolated yield of diastereoisomers after hydrolysis and isolation.
f The minor diastereomer was not observed by either 1H NMR or GC. g The p-tolylimine was used.
a (i.) 12a-g (1.0 equiv), 1a (5.0 equiv), [(DPEphos)Rh(COD)]BF4 (1.0 mol %), MeCN (4.3 M), 60 °C, 24 h. d 2.0 mol % [Rh] used. e Combined isolated yield of diastereoisomers after hydrolysis and isolation. f The p-tolylimine was used.

With Seth Ensign and Dr. Anil Gupta, the scope of the imine was explored next. Although 3.0 equivalents was optimal for the PMP-imine substrate, 5.0 equivalents was found to be the most general across a variety of *N*-allylimines. Electron donating (**149a**, **150**, and **155**) and withdrawing groups (**152**, **153, 154**, and **156**) on the imine were tolerated, although there was a moderate decrease in yield with *p*-$CF_3$- and *p*-$MeO_2C$-substituents. The *o*-phenolic substrate (**150**) and the sterically encumbered mesityl substrate (**151**) react cleanly and quantitatively; the corresponding` amino imines could be obtained after filtration through basic alumina without the need for *in situ* reduction. Bromides, chlorides, and tertiary amines were also well tolerated under the reaction conditions. However, bis-*o*-dichloro substrate did not form any of the desired hydroamination product (**157**) Ketimines were able to be employed (**158** and **159**); however, higher catalyst loadings were required and the products were obtained in only modest yields after reduction.

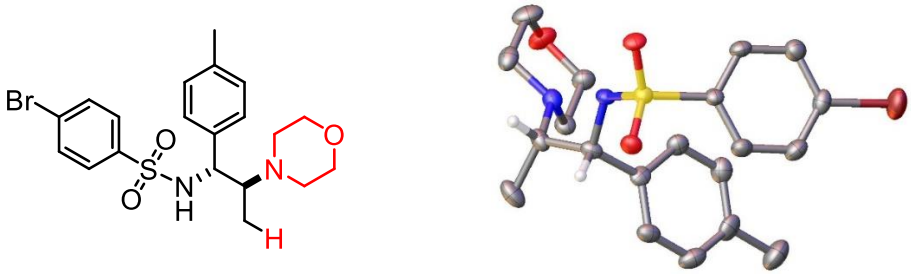
Next, the substitution on the allyl group was modified. The allylimine containing a 1,1-disubstituted olefin was successfully converted to the desired product (**160**). This allows for the formation of a tertiary C–N bond. Unfortunately, *cis*- and *trans*-1,2-disubstituted alkenes did not afford any of the hydroamination products, rather an undesired 1,3-hydride shift occurred to afford an enamine (Scheme 19).[321,322] Additionally, 1,1,2-trisubstituted alkene product **162** was not observed for the directed hydroamination.

**Scheme 19**: Enamine byproduct formation




Next, substitution at the allylic position was explored. Excitingly, the diastereoselectivities observed were all >10:1. Using pyrrolidine, 11:1 d.r. was observed (**163a**), and >20:1 was observed with morpholine (**163b**). When using dimethylamine as the nucleophile, poor yield was obtained with high diastereoselectivity (**163c**). Cyclohexylamine could be employed to form the corresponding 1,2-diamine in modest yield and good diastereoselectivity (**163d**). It was found that these products were all the *anti*-1,2-diamine as confirmed by x-ray diffraction (Figure 33 completed by Dr. Anil Gupta and Gregory Kortman). The relative configurations were confirmed by comparison to the literature using pyrrolidine as the nucleophile with the phenyl-substituted substrate (**163a**).[323]

**Figure 33**: X-ray crystal structure

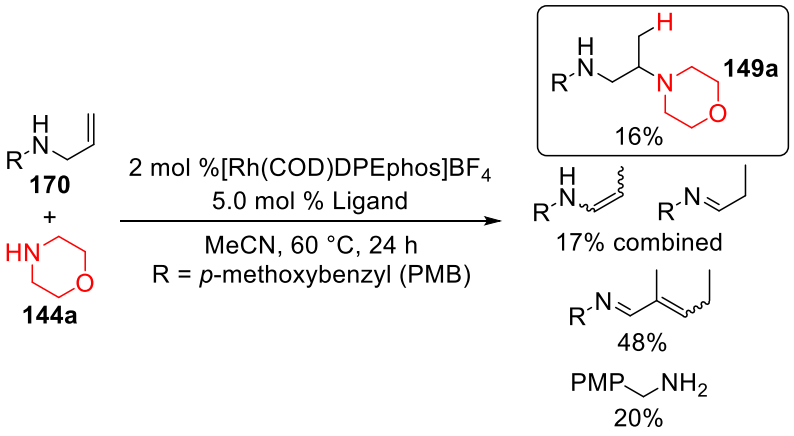



### 2.2.3. Secondary *N*-Allylamine Reaction Discovery and Optimization

Having demonstrated *N*-allylimines can undergo Markovnikov-selective hydroamination, we sought to expand the scope of directing groups for this reaction. The ideal directing group would be one that is easily isolated and allow for the facile formation of 1,2-diamines. As such, we sought to develop conditions that use secondary or and primary amine directing groups.

Initial attempts by Dr. Anil Gupta resulted in poor yields when PMB protected allyl amine **170** and morpholine (**144a**) were employed (Scheme 20). It was observed that the starting material **170** was undergoing a 1,3-hydride shift to afford an enamine and imine under the reaction conditions. Moreover, a major byproduct resulting from the aldol condensation between imine and enamine, was observed.

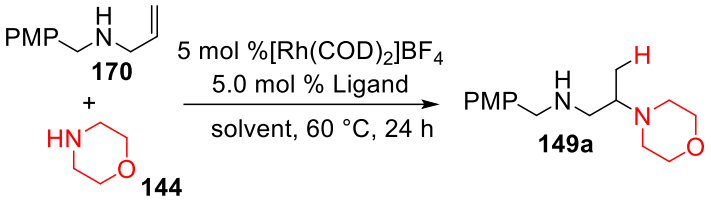
**Scheme 20**: Initial secondary *N*-allylamine hydroamination




The reaction was optimized in order to slow the rate of isomerization relative to the hydroamination reaction and is summarized in Table 6 (performed by Dr. Anil Gupta). The desired product **149a** was initially afforded in only 12% yield (Table 6, entry 1). Changing the ligand provided the most dramatic improvements in the reaction; BINAP facilitated the hydroamination reaction with an NMR yield of 40% (Table 6, entry 2). Increasing the flexibility and decreasing the bite angle lead to significant improvements, as dppp and dppb afford **149a** in 62% and 64%, respectively (Table 6, entries 4 and 5). A further increase in yield to 70% was observed upon using DME as the solvent (Table 6, entry 5). Smaller bite angle ligands

(dppe) and larger bite angle ligands (dpppent and dpph) were much less effective. Compared to the imine reaction, dppb was employed rather than DPEphos, DME was used as a solvent instead of MeCN, and 5% catalyst instead of 1% was sufficient to increase yields and reducing byproduct formation. Excitingly, this hydroamination reaction favors an intermolecular reaction over the corresponding intramolecular 1,3-hydride shift known with tertiary *N*-allylamines.[321,322]

**Table 6**: Secondary allylamine optimization

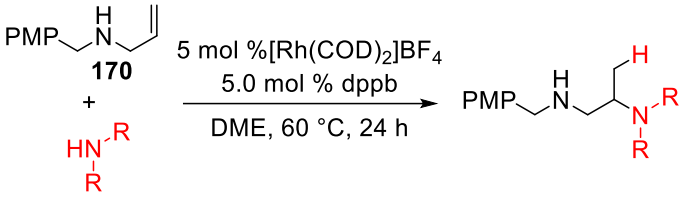



| Entry | [M]-Catalyst | Ligand | Solvent | % NMR Yield[b] |
|---|---|---|---|---|
| 1 | $[Rh(COD)_2]BF_4$ | DPEphos | MeCN | 12 |
| 2 | $[Rh(COD)_2]BF_4$ | BINAP | MeCN | 40 |
| 3 | $[Rh(COD)_2]BF_4$ | dppe | MeCN | 5 |
| 4 | $[Rh(COD)_2]BF_4$ | dppp | MeCN | 62 |
| 5 | $[Rh(COD)_2]BF_4$ | dppb | MeCN | 64 |
| 3 | $[Rh(COD)_2]BF_4$ | dppppent | MeCN | 17 |
| 4 | $[Rh(COD)_2]BF_4$ | dpph | MeCN | 7 |
| 5 | $[Rh(COD)_2]BF_4$ | dppb | DME | 70 |

[a] General reaction conditions: Allylamine, **170** (0.125 mmol, 1.0 eq), nucleophile, **144** (0.625 mmol, 5.0 eq.), 3.5M solvent
[b] % NMR yield determined by using $Ph_3CH$ as an internal standard

While secondary allylic amines are competent substrates for the hydroamination reaction, they remain some of the most difficult. First, 7.0 equiv of the nucleophile generally required to obtain the product in good yields (Table 7). This was demonstrated for a variety of cyclic, secondary amine nucleophiles. Second, these reactions require far higher catalyst loading (5 mol % of catalyst) for the reaction to go to completion in 24 hours (performed by Dr. Anil Gupta) compared to the imine hydroamination.

**Table 7**: Equivalents of nucleophile in the PMB-allylamine hydroamination




| Entry | Amine | Equiv. Amine | % NMR Yield |
|---|---|---|---|
| 1 |  **144** | 1.5 | 17 |
| 2 | | 3 | 33 |
| 3 | | 5 | 55 |
| 4 | | 7 | 77 |

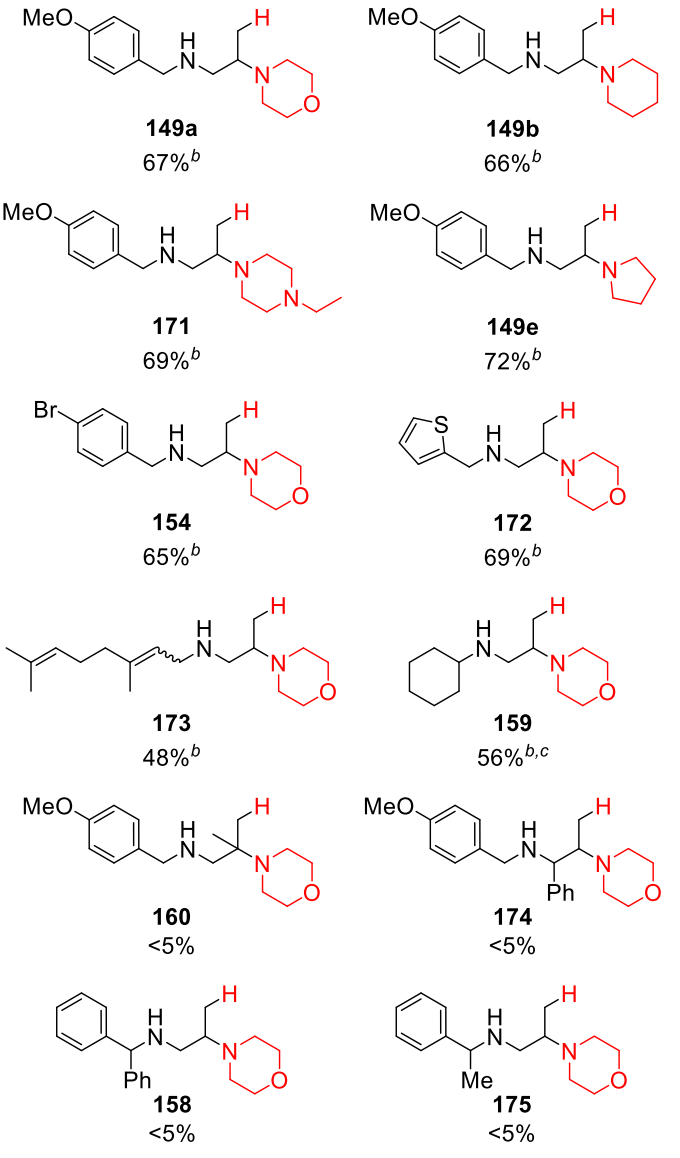
### 2.2.4. Secondary *N*-Allylamine Substrate Scope

In terms of reaction scope, the scope of the amine nucleophile with secondary allylic amines was determined. As shown in Table 8, cyclic secondary amines are incorporated in good yields. Other secondary allylic amines were reactive under the optimized conditions to afford good yields of the 1,2-diamines. Aryl bromides (**154**), thiophene (**172**), geranyl (**173**), and cyclohexyl (**159**) groups were all successfully employed in generating the corresponding 1,2-diamines. 1,1-disubstituted (**160**) and allylic substituted (**174**) substrates were not amenable, as the 1,3-hydride shift dominated. Additionally, mono- and bis-aryl ketones (**158** and **175**) were not tolerated as the 1,3-hydride shift was the major competing reaction. This substitution proximal to the amine directing-group proved to inhibit the desired-reaction from occurring.

### 2.2.5. Primary *N*-Allylamine Reaction Discovery and Optimization

As previously mentioned, cyclohexanamine undergoes imine exchange with the starting material, releasing allyl amine into the solution when the *N*-allylimine is utilized as the substrate. Because of this, it was questioned if allylamine itself is a competent directing group for the hydroamination. Under nearly identical conditions to the imine reaction (increasing catalyst loading from 1 mol % to 2 mol %),

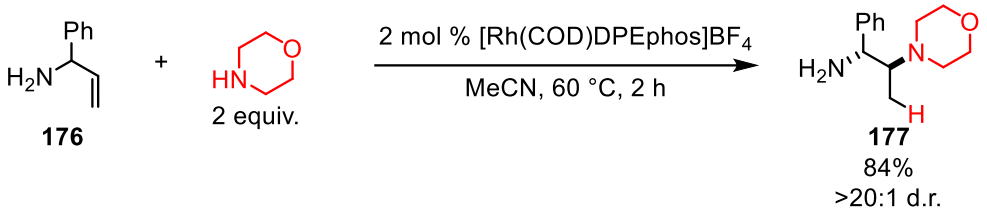
**Table 8**: Substrate scope for secondary *N*-allylamine hydroamination


[a] Allylamine (1.0 equiv), nucelophile (7.0 equiv), $[Rh(COD)_2BF_4]$ (5.0 mol %), DPEphos (5.0 mol %), DME (3.5 M), 60 °C, 24 h. [b] Isolated yield. [c]dppp was used.

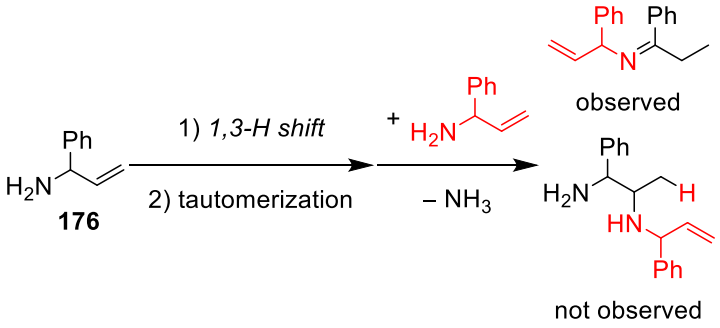
allylamine was able to undergo the hydroamination with morpholine to form desired product **177** (Scheme 21).

**Scheme 21**: Primary allylamine hydroamination




Seeking to develop conditions that allow for lower catalyst and nucleophile loading, we reasoned that primary amines would be the ideal directing groups; these should be significantly less hindered. However, one anticipated challenge was that the substrate could undergo an intermolecular hydroamination with itself. However, this was not observed under standard reaction conditions. A significant amount of the 1,3-hydride shift byproduct was observed instead (Scheme 22). We found that by changing the ligand to DPEphos, and using the optimized conditions for allyl imine substrates, an 87% yield could be obtained in the hydroamination of allylamine with morpholine after 24 hours.

**Scheme 22**: Byproduct formation

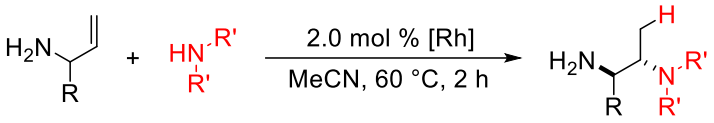


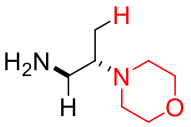
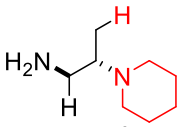
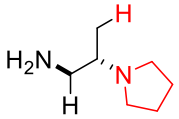
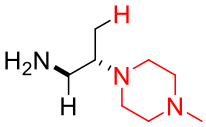
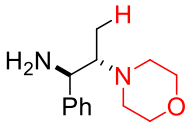
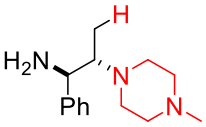
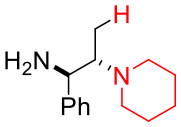
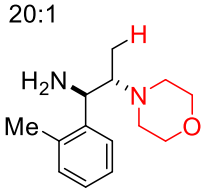
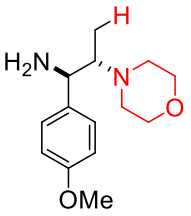
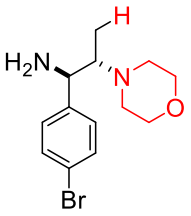
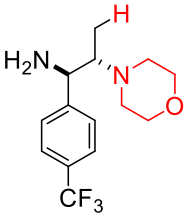
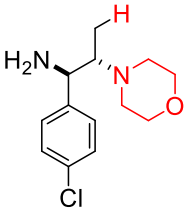
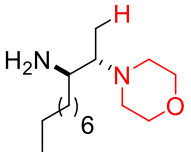
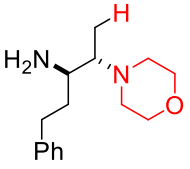

To further optimize, a time study was conducted under the previously optimized conditions; it was found that the reaction was complete after 30 minutes with 5.0 equivalents of morpholine and 2 mol % of the rhodium catalyst. However, upon lowering the equivalents of morpholine from 5.0 to 2.0, the reaction only took 2 hours at 60 °C to reach completion.

### 2.2.6. Primary *N*-Allylamine Substrate Scope

Gratifyingly, high diastereoselectivities were observed when 1-phenylallylamine was employed (**177**). An 84% yield (>20:1 d.r.) was obtained of the desired 1,2-diamine. Similar functional group tolerance to the allyl imine hydroamination was also observed. Aryl bromides (**168**), trifluoromethyl (**179**), methoxy groups (**166**), and chlorides (**180**) were amenable to the reaction in very good yields. Aliphatic substitution showed similar reactivity, but lower diastereoselectivities were obtained (**181**, **164**). When

**Table 9**: Allylamine hydroamination scope



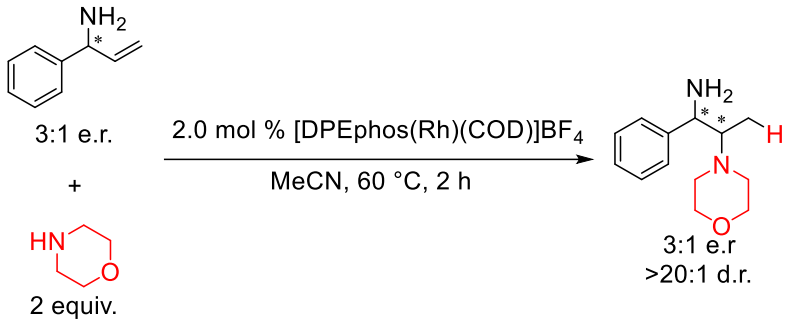

| | | |
|---|---|---|
|  **177a**[d] 72% |  **177b**[d] 60% |  **177c**[d] 45% |
|  **177d**[d] 63% |  **163b** 84%, dr > 20:1 | |
|  **163c**[b] 71%, dr > 20:1 |  **163d**[c] 65%, dr > 20:1 |  **178**[d] 76%, dr > 20:1 |
|  **166**[d,e] 77%, dr = 19:1 |  **168** 77%, dr = >20:1 |  **179** 82%, dr = >20:1 |
|  **180** 68%, dr = >20:1 |  **181**[d,e] 75%, dr = 13:1 |  **164**[d,e] 73%, dr = 13:1 |

[a] Allylamine (1.0 equiv), morpholine (**144a**) (2.0 equiv), $[DPEphosRh(COD)]^+BF_4^-$ (1.0-2.0 mol %), MeCN (4.0 M), 60 °C, 2 h. [b] 4 hours. [c] 8 hours. [d] 24 hours. [e] morpholine (**144a**) (4.0 equiv.)

comparing to those obtained for the allyl imine-directed hydroamination, slightly lower diastereoselectivities were obtained in most cases as exemplified by the phenethyl substituted substrate (**164**) where a 73% isolated yield (16:1 d.r.) was obtained when using the PMP-imine. When using the phenethyl-substituted allyl amine, a 73% isolated yield (13:1 d.r.) was obtained. **Note**: Table 9 was completed with Dr. Anil Gupta.

The allyl amine hydroamination reaction was also investigated using a chiral substrate (Scheme 23). No loss in enantioselectivity was observed after the hydroamination suggesting that isomerization of the starting material does not lead to the desired product.

**Scheme 23**: Hydroamination with enantio-enriched substrate

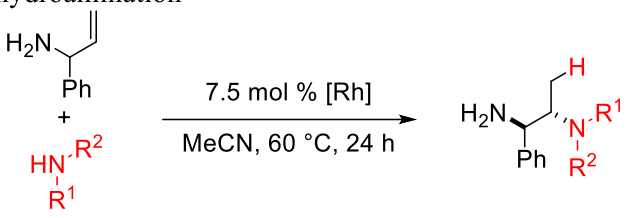


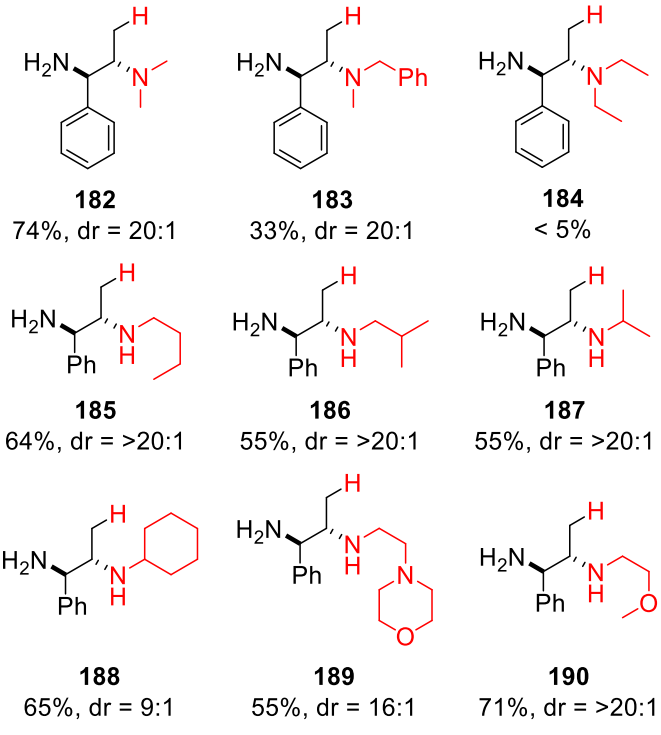

Lastly, in an effort to expand the nucleophile scope for the developed hydroamination reactions, secondary acyclic and primary amine nucleophiles were investigated. Dimethylamine and methylbenzylamine afforded the 1,2-diamine in 74% (**182**) and 33% (**183**) isolated yield, respectively. Dimethylamine was considerably lower yielding (22%) when the allylic substituted imine was employed. Unfortunately, no product is observed when diethylamine is employed under the reaction conditions.

Excitingly, we found that primary amines were also able to undergo the desired hydroamination with primary allylamine directing groups. Our studies began by using cyclohexylamine as the nucleophile. It was found that excess nucleophile was required; 5.0 equivalents of cyclohexylamine was found to be required along with higher catalyst loadings (7.5 mol %) (Table 8, **188**). To our knowledge, this is the first example of an intermolecular hydroamination catalyzed by rhodium that can employ primary aliphatic amine nucleophiles.

Other primary aliphatic amines, butylamine (**185**), *iso*-butylamine (**186**), and isopropylamine (**187**) showed similar reactivity and high diastereoselectivity (>20:1) in most cases. The 1,2-diamine and 1,2-aminoether were effective nucleophiles, affording (**189**) and (**190**) in 55% and 71% yield, respectively. Interestingly, cyclohexanamine gave a 9:1 d.r. which is slightly lower than the 12:1 d.r. when the imine was used as the directing group.

**Table 10**: Nucleophile scope for primary allylamine hydroamination



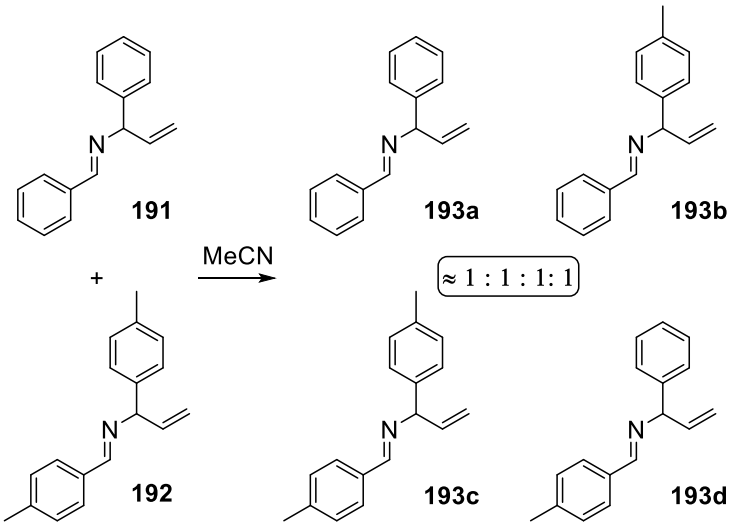




[a] Allylamine (1.0 equiv), nucleophile (4–6.0 equiv), $[DPEphosRh(COD)]^+BF_4^-$ (1.0-2.0 mol %), MeCN (3.8 M), 60 °C, 24 h. [b] Reaction temperature = 40 °C. [c] D.R. determined by the $^1H$ NMR analysis of the crude reaction mixture.

### 2.2.7. Mechanistic Studies

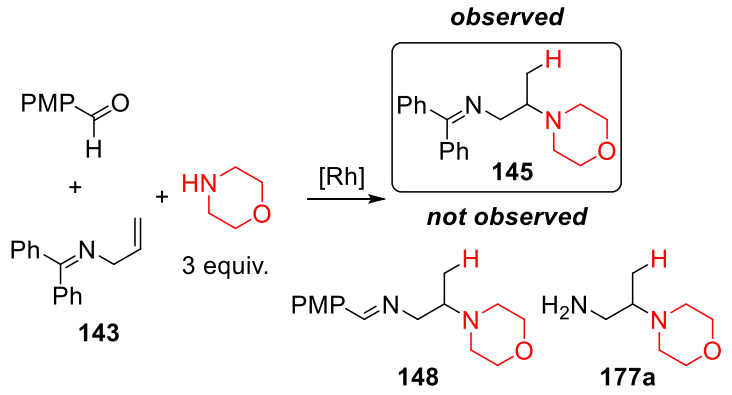
With the discovery of allylamine derivatives as competent functional groups for the hydroamination, it was questioned if the imine directing group was undergoing exchange, releasing allylamine into solution through reaction with morpholine. Our method of study was to perform cross-over experiments using different imine directing groups. We observed that imines **191** and **192** readily exchange with stirring in MeCN, without addition of nucleophile or catalyst to give a statistical mixture of products **193a**, **193b**, **193c**, and **193d**. This suggests that it is possible for the corresponding allylamine to be exchanged (Scheme 24).

**Scheme 24**: Imine exchange experiment

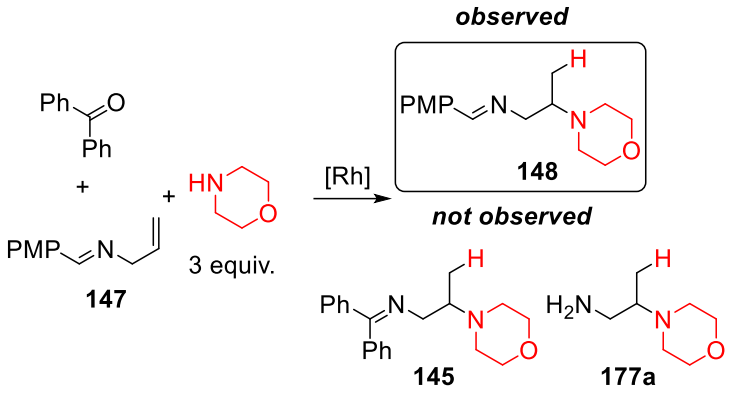



Ketimines are more stable than aldimines. Therefore, in the presence of both a ketone and an aldehyde, imine formation should selectively occur with the aldehyde. If labializing the allyl amine from the imine is required prior to the Rh-catalyzed hydroamination reaction, then when ketamine **143** is subjected to the hydroamination conditions in the presence of added aldehyde, the aldimine product should be formed selectively. However, when ketimine **143** was subjected to the hydroamination conditions in the presence of 4-methoxybenzaldehyde, **145** was the only hydroamination product observed (Scheme 25). Further, when aldimine **147** was used as the substrate, no exchange was observed with the addition of benzophenone (Scheme 26). Combined, these experiments indicate that *N*-allyl imines can undergo the hydroamination, but does not preclude the fact that *N*-allyl amines may also be undergoing the hydroamination reaction simultaneously when aldimines are employed while ketimines undergo the hydroamination reaction directly.

**Scheme 25**: Ketimine exchange experiment



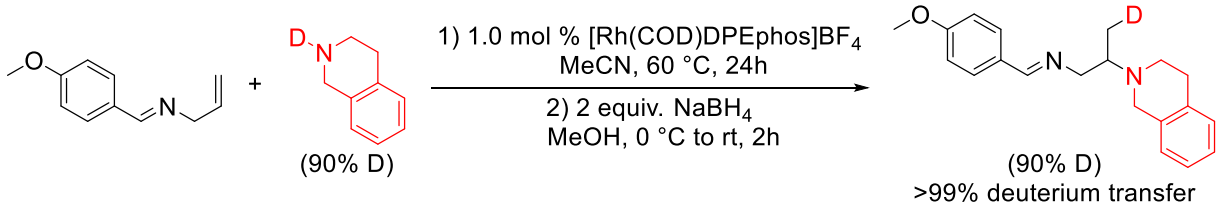
**Scheme 26**: Aldimine exchange experiment




These two experiments suggest that when the ketimine is employed under reaction conditions, the imine is in fact the directing group for the hydroamination reaction. In the case of aldimines, it cannot be ruled out that allylamine is the directing group for the reaction through an exchange reaction.

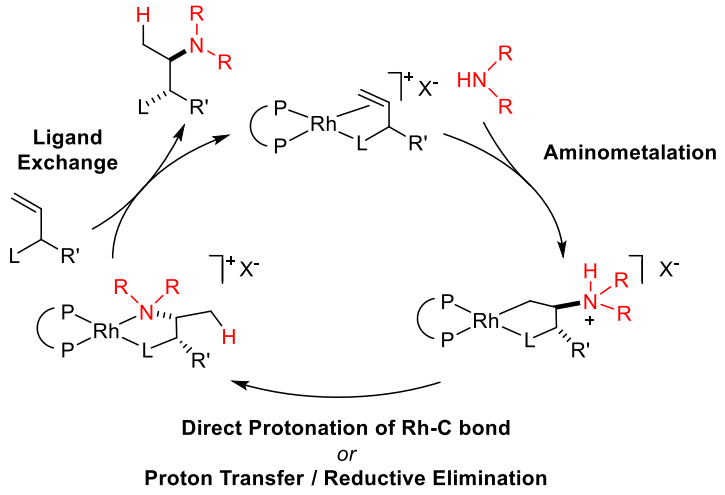
Next, preliminary mechanistic data was obtained by Dr. Anil Gupta by using deuterated tetrahydroisoquinoline as the nucleophile in the imine reaction. The deuterium was exclusively transferred to the terminal position of the olefin. This suggests that β-hydride elimination-reinsertion from the metallacyclic intermediate is slow relative to C–D bond formation (Scheme 27).

**Scheme 27**: Deuterium incorporation study




Based on literature precedence[3,324,325] and our deuterium incorporation study, the following catalytic cycle (Figure 34): 1) the allylimine coordinates to the rhodium (I) catalyst, 2) the cyclic secondary amine nucleophile undergoes an outer-sphere aminometallation, 3) Then, proton transfer to generated a Rh-H followed by reductive elimination or direct protolytic cleavage generates the product-bound metallacycle, and 4) Ligand exchange re-enters the catalytic cycle. The metallacyclic intermediate is proposed to form during the reaction; therefore, it was hypothesized that aminometallation would lead to a highly diastereoselective reaction due to strain built up in the transition-state.

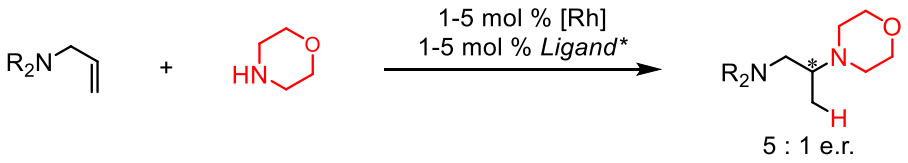
**Figure 34**: Proposed catalytic cycle




## 2.3. Conclusions and Outlook

A highly regio-, chemo-, and diastereoselective intermolecular, rhodium-catalyzed hydroamination reaction has been realized. This represents significant progress in intermolecular hydroamination reactions where the direct addition of N–H across an olefin is possible. Allylimines, secondary allylamines, and primary allylamines proved to be excellent directing groups for this reaction in high diastereoselectivities. Additionally, the nucleophile scope was significantly improved by utilizing secondary cyclic, secondary acyclic, and primary amine nucleophiles, representing one of the only hydroamination reactions that enable the use of such nucleophiles broadly. A better understanding of the reaction mechanism via several mechanistic experiments is currently being pursued. Additionally, it would be extremely useful to enable an asymmetric version of this reaction. Currently, the best result has been a 5:1 enantiomeric ratio and is being pursued further in the Hull lab (Scheme 28).

**Scheme 28**: Enantioselective hydroamination



# CHAPTER 3*

## Experimental

### 3.1. General Information

**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) with a column mixed as a slurry with the eluent and was packed, rinsed, and run under air pressure. Alternatively, automated columns were performed using a Teledyne ISCO system, employing either Biotage® SNAP Dry Load cartridges (loaded under suction with Davisil Chromatographic Silica Media 35-70 micron mesh), ValueBrand Silica Flash Chromatography Columns purchased from Practichem, or end capped cyano RediSep®Rf Gold columns (20-40 micron mesh) purchased from Teledyne Isco. Samples were eluted using a flow rate of 18–40 mL/min, with detection by UV (254 nm or 280 nm). 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 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 77.00 ppm for $CDCl_3$ and $^{1}$H NMR: δ 7.15 ppm, $^{13}$C NMR: δ 128.60 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. Analysis by Gas Chromatography-Mass Spectrometry (GC-MS) was performed using a Shimadzu GC-2010 Plus Gas chromatograph fitted with a Shimadzu GCMS-QP2010 SE mass spectrometer using electron impact (EI) ionization after analytes traveled through a SHRXI–5MS- 30m x 0.25 mm x 0.25 μm column using a helium carrier gas. Data are reported in the form of m/z (intensity relative to base peak = 100). 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

* This section includes previously published material[319]

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 Thomas Hoover capillary melting point apparatus and are uncorrected.

**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, and were stored over 4 Å molecular sieves under an atmosphere of nitrogen in glove box before use. Allylamine **10** was obtained from Aldrich Chemical Co., Inc. and used as received. All liquid aldehydes were distilled prior to use, and ketones, benzophenone and cyclohexanone, were used as received.

### 3.2. Experimental Procedures of Chapters 2.2.1 and 2.2.2

#### A. General Procedure for Screening Reactions with no stock solutions

In the glove box, to a 4 mL scintillation vial fitted with a magnetic stir bar was added $[Rh(COD)Cl]_2$ (1.0 equiv.), followed by the silver salt (2.0 equiv.) and phosphine ligand (2.0 equiv.). Dry solvents were added next followed by the imine substrate. Lastly, morpholine as well as 1-methylnapthalene (10 μL, 0.071 mmol) were added, and the vial was capped with Teflon-sealed cap. This was taken outside of the glove box and heated to the desired temperature overnight.

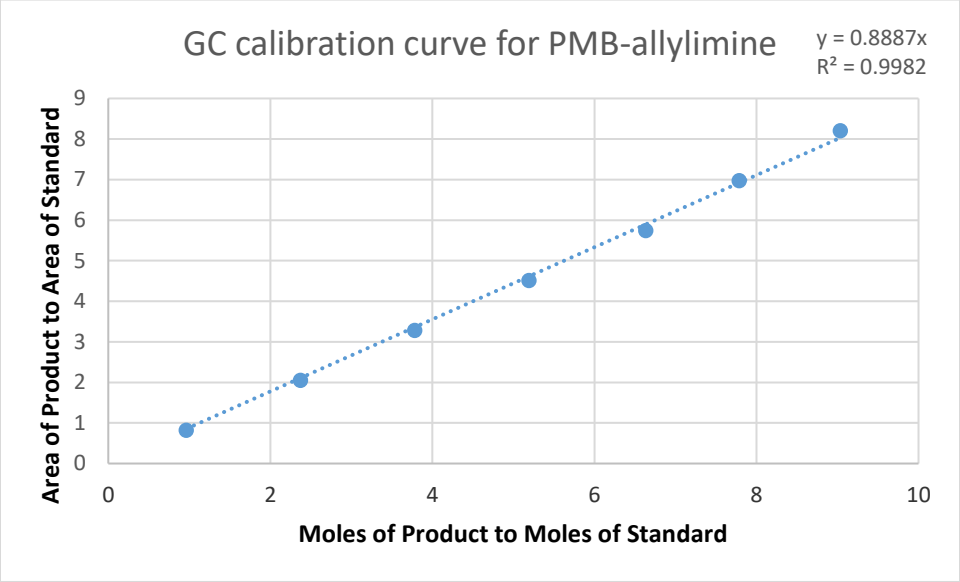
#### B. General Procedure for Screening Reactions with stock solutions

In the glove box, if *n* equivalents of each substance is needed for the desired amount of screens, *n+1* equivalents were used in each case. In a 20 mL scintillation vial fitted with a magnetic stir bar was added $[Rh(COD)Cl]_2$ (1.0 equiv.), followed by the silver salt (2.0 equiv.) and phosphine ligand (2.0 equiv.). Dry solvents were added next followed by the imine substrate. This was stirred for 15 minutes, dissolving all of the rhodium catalyst while precipitating the silver salt. Next, morpholine as well as 1-methylnapthalene were added and was aliquatted equally (total volume/*n+1)* into 4 mL scintillation vials fitted with magnetic stir bars. If drying agents were used, they were added at this stage as well as any base. The vials were capped with Teflon-sealed caps, were taken out of the glove box, and were heated overnight.

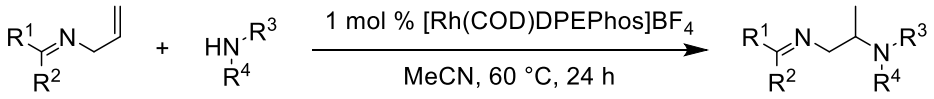
**Calibration Curve for *(E)-N-allyl-1-(4-methoxyphenyl)methanimine* (148)**

Screening reactions were diluted and stirred in 4M HCl (2 mL) after removing morpholine on high vacuum for 3 hours. The resulting aqueous layer was washed with $CH_2Cl_2$. The aqueous layer was basified with NaOH pellets and was washed with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and rotary evaporated to yield the hydrolyzed 1,2-diamine (0.144g, 1.00 mmol). To this was added *p*-methoxybenzaldehyde (135 mg, 1.00 mmol, 1.0 equiv.) to yield imine (**148**) as a yellow oil and was used for the calibration curve.1-methylnapthalene was used as the standard for all screens. The data for the curve can be seen below.

$^1$H-NMR (400 MHz; Benzene): δ 8.01 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 3.73 (ddd, *J* = 11.4, 4.9, 1.3 Hz, 1H), 3.63 (t, *J* = 4.6 Hz, 4H), 3.38 (ddd, *J* = 11.4, 7.8, 1.3 Hz, 1H), 3.22 (s, 3H), 2.90-2.81 (m, 1H), 2.43 (q, *J* = 3.7 Hz, 4H), 1.06 (d, *J* = 6.7 Hz, 3H) ppm.




**C. General Allyl Imine Hydroamination Procedure A:**

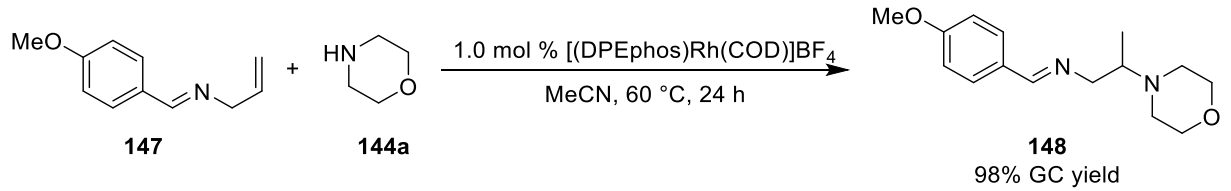



[(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine (259 µL, 1.50 mmol, 1.00 equiv.), amine nucleophile, and dry $CH_3CN$ (350 µL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. The resulting solution was allowed to stir for 24 h at 60 °C. In an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined,

dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude diamine. Purification by silica gel chromatography (125 mL silica, 3% $NH_4OH$ : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine.

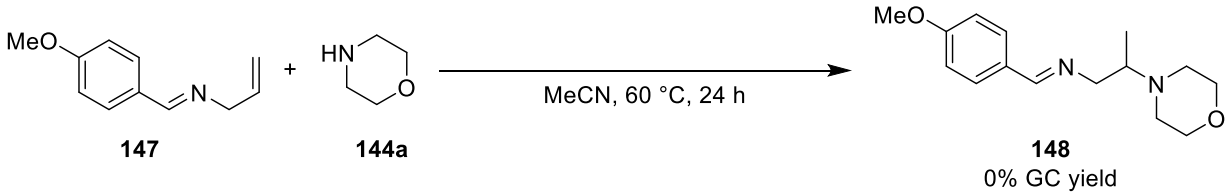
### D. Control Experiments and Optimization

Under the optimized reaction conditions, in the presence of $[(DPEphos)Rh(COD)]BF_4$ **148** is afforded in 98% GC yield.



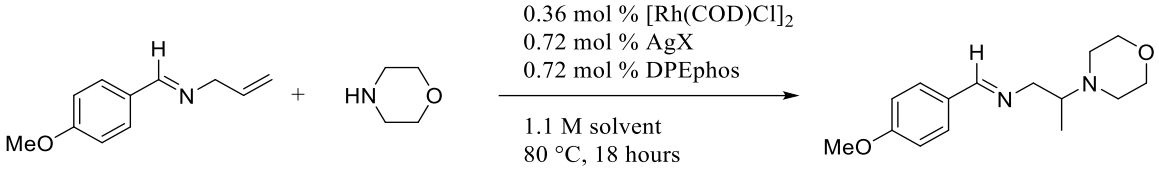

**147** **144a** **148**
98% GC yield

Under the optimized reaction conditions, in the absence of $[(DPEphos)Rh(COD)]BF_4$ **148** is afforded in 0% GC yield; no reaction is observed by GC.



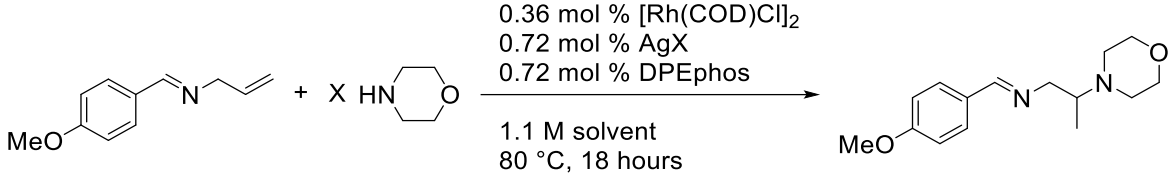

**147** **144a** **148**
0% GC yield

**Table 11: Silver salt screens in various solvents**




| Silver Salt | Solvent | Yield | Silver Salt | Solvent | Yield |
|---|---|---|---|---|---|
| $AgBF_4$ | neat | 26 | $AgSO_3CF_3$ | Toluene | 8 |
| AgOAc | neat | 6 | $AgPF_6$ | Toluene | 8 |
| AgF | neat | 8 | AgTFA | Toluene | 1 |
| $AgSbF_6$ | neat | 23 | $AgSO_3CH_3$ | Toluene | 2 |
| $AgSO_3CF_3$ | neat | 18 | $AgSO_3C_7H_7$ | Toluene | 4 |
| $AgPF_6$ | neat | 19 | $AgBF_4$ | DME | 12 |
| AgTFA | neat | 27 | $AgSbF_6$ | DME | 10 |
| $AgSO_3CH_3$ | neat | 29 | $AgSO_3CF_3$ | DME | 8 |
| $AgSO_3C_7H_7$ | neat | 24 | $AgPF_6$ | DME | 8 |
| $AgBF_4$ | 1,4-Dioxane | 24 | AgTFA | DME | 2 |
| AgOAc | 1,4-Dioxane | 3 | $AgSO_3CH_3$ | DME | 2 |
| AgF | 1,4-Dioxane | 1 | $AgSO_3C_7H_7$ | DME | 2 |
| $AgSbF_6$ | 1,4-Dioxane | 28 | $AgBF_4$ | THF | 18 |
| $AgSO_3CF_3$ | 1,4-Dioxane | 33 | $AgSbF_6$ | THF | 10 |
| $AgPF_6$ | 1,4-Dioxane | 29 | $AgSO_3CF_3$ | THF | 15 |
| AgTFA | 1,4-Dioxane | 18 | $AgPF_6$ | THF | 9 |
| $AgSO_3CH_3$ | 1,4-Dioxane | 19 | AgTFA | THF | 2 |
| $AgSO_3C_7H_7$ | 1,4-Dioxane | 14 | $AgSO_3CH_3$ | THF | 5 |
| $AgBF_4$ | Benzene | 4 | $AgSO_3C_7H_7$ | THF | 2 |
| $AgSbF_6$ | Benzene | 5 | $AgBF_4$ | Acetonitrile | 11 |
| $AgSO_3CF_3$ | Benzene | 6 | $AgSbF_6$ | Acetonitrile | 12 |
| $AgPF_6$ | Benzene | 1 | $AgSO_3CF_3$ | Acetonitrile | 8 |
| AgTFA | Benzene | 2 | $AgPF_6$ | Acetonitrile | 10 |
| $AgSO_3CH_3$ | Benzene | 4 | AgTFA | Acetonitrile | 4 |
| $AgSO_3C_7H_7$ | Benzene | 3 | $AgSO_3CH_3$ | Acetonitrile | 3 |
| $AgBF_4$ | Toluene | 5 | $AgSO_3C_7H_7$ | Acetonitrile | 4 |
| $AgSbF_6$ | Toluene | 7 | | | |

**Table 12: Morpholine equivalency screens with various silver salts and solvents**

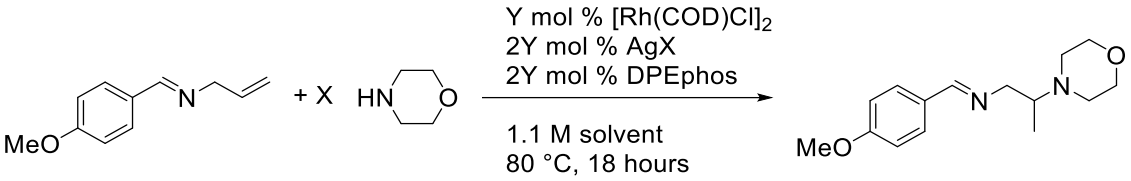



| Silver Salt | Morpholine Equiv | Solvent | Yield |
|---|---|---|---|
| $AgSO_3CF_3$ | 1 | 1,4-Dioxane | 18 |
| $AgSO_3CF_3$ | 2 | 1,4-Dioxane | 28 |
| $AgSO_3CF_3$ | 3 | 1,4-Dioxane | 40 |
| $AgSO_3CF_3$ | 4 | 1,4-Dioxane | 42 |
| $AgSO_3CF_3$ | 5 | 1,4-Dioxane | 36 |
| $AgSO_3CF_3$ | 10 | 1,4-Dioxane | 26 |
| $AgPF_6$ | 1 | 1,4-Dioxane | 22 |
| $AgPF_6$ | 2 | 1,4-Dioxane | 32 |
| $AgPF_6$ | 3 | 1,4-Dioxane | 42 |
| $AgPF_6$ | 4 | 1,4-Dioxane | 43 |
| $AgPF_6$ | 5 | 1,4-Dioxane | 24 |
| $AgPF_6$ | 10 | 1,4-Dioxane | 43 |
| $AgSbF_6$ | 1 | 1,4-Dioxane | 22 |
| $AgSbF_6$ | 2 | 1,4-Dioxane | 16 |
| $AgSbF_6$ | 3 | 1,4-Dioxane | 40 |
| $AgSbF_6$ | 4 | 1,4-Dioxane | 45 |
| $AgSbF_6$ | 5 | 1,4-Dioxane | 41 |
| $AgSbF_6$ | 10 | 1,4-Dioxane | 45 |
| $AgBF_4$ | 1 | 1,4-Dioxane | 24 |
| $AgBF_4$ | 2 | 1,4-Dioxane | 34 |
| $AgBF_4$ | 3 | 1,4-Dioxane | 42 |
| $AgBF_4$ | 4 | 1,4-Dioxane | 42 |
| $AgBF_4$ | 5 | 1,4-Dioxane | 54 |
| $AgBF_4$ | 10 | 1,4-Dioxane | 13 |
| $AgBF_4$ | 1 | DME | 18 |
| $AgBF_4$ | 2 | DME | nd |
| $AgBF_4$ | 3 | DME | 39 |
| $AgBF_4$ | 4 | DME | 46 |

**Table 12 (cont.):**

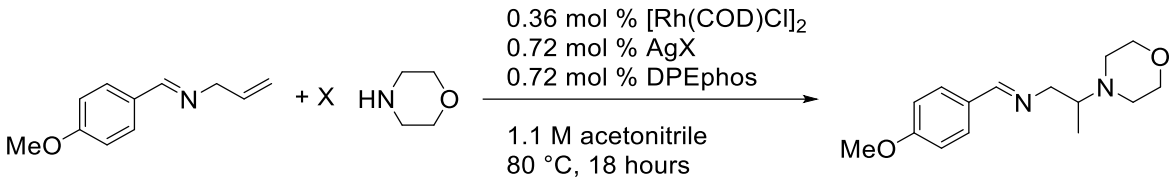
| Silver Salt | Morpholine Equiv | Solvent | Yield |
|---|---|---|---|
| $AgBF_4$ | 5 | DME | 44 |
| $AgBF_4$ | 10 | DME | 42 |
| $AgBF_4$ | 1 | THF | 17 |
| $AgBF_4$ | 2 | THF | 30 |
| $AgBF_4$ | 3 | THF | 34 |
| $AgBF_4$ | 4 | THF | 41 |
| $AgBF_4$ | 5 | THF | 44 |
| $AgBF_4$ | 10 | THF | 45 |
| $AgSbF_6$ | 1 | Acetonitrile | 13 |
| $AgSbF_6$ | 2 | Acetonitrile | 33 |
| $AgSbF_6$ | 3 | Acetonitrile | 45 |
| $AgSbF_6$ | 4 | Acetonitrile | 52 |
| $AgSbF_6$ | 5 | Acetonitrile | 52 |
| $AgSbF_6$ | 10 | Acetonitrile | 49 |
| $AgSO_3CF_3$ | 10 | Benzene | 64 |
| $AgPF_6$ | 10 | Toluene | 51 |
| $AgSbF_6$ | 10 | DME | 44 |
| $AgSO_3CF_3$ | 10 | THF | 63 |
| $AgBF_4$ | 10 | Acetonitrile | 49 |
| $AgPF_6$ | 10 | Acetonitrile | 54 |

**Table 13: Catalyst loading screens with various silver salts, solvents, and equivalents of morpholine**



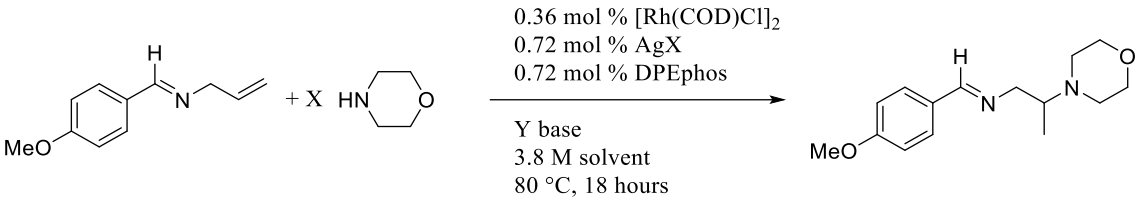

| Silver Salt | Morpholine Equiv | Catalyst Loading | Solvent | Yield |
|---|---|---|---|---|
| $AgSO_3CF_3$ | 3 | 0.25 | 1,4-Dioxane | 24 |
| $AgSO_3CF_3$ | 3 | 0.50 | 1,4-Dioxane | 29 |
| $AgSO_3CF_3$ | 3 | 1.00 | 1,4-Dioxane | 55 |
| $AgSO_3CF_3$ | 3 | 1.50 | 1,4-Dioxane | 61 |
| $AgSO_3CF_3$ | 3 | 2.00 | 1,4-Dioxane | 68 |
| $AgBF_4$ | 5 | 0.25 | 1,4-Dioxane | 10 |
| $AgBF_4$ | 5 | 0.50 | 1,4-Dioxane | 35 |
| $AgBF_4$ | 5 | 1.00 | 1,4-Dioxane | 63 |
| $AgBF_4$ | 5 | 1.50 | 1,4-Dioxane | 68 |
| $AgBF_4$ | 5 | 2.00 | 1,4-Dioxane | 66 |
| $AgBF_4$ | 4 | 0.25 | DME | 12 |
| $AgBF_4$ | 4 | 0.50 | DME | 47 |
| $AgBF_4$ | 4 | 1.00 | DME | 65 |
| $AgBF_4$ | 4 | 1.50 | DME | 72 |
| $AgBF_4$ | 4 | 2.00 | DME | 71 |
| $AgSbF_6$ | 4 | 0.25 | Acetonitrile | 30 |
| $AgSbF_6$ | 4 | 0.50 | Acetonitrile | 44 |
| $AgSbF_6$ | 4 | 1.00 | Acetonitrile | 65 |
| $AgSbF_6$ | 4 | 1.50 | Acetonitrile | 69 |
| $AgSbF_6$ | 4 | 2.00 | Acetonitrile | 65 |

**Table 14: Concentration screens with various silver salts and equivalents of morpholine using a stock solution**




| Silver Salt | Morpholine Equiv | Concentration (M) | Yield |
|---|---|---|---|
| $AgBF_4$ | 6 | 3.8 | 84 |
| $AgBF_4$ | 6 | 1.9 | 78 |
| $AgBF_4$ | 6 | 1.3 | 72 |
| $AgBF_4$ | 6 | 0.95 | 67 |
| $AgBF_4$ | 6 | 0.76 | 64 |
| $AgBF_4$ | 6 | 0.63 | 59 |
| $AgSO_3CF_3$ | 9 | 3.8 | 80 |
| $AgSO_3CF_3$ | 9 | 1.9 | 75 |
| $AgSO_3CF_3$ | 9 | 1.3 | 73 |
| $AgSO_3CF_3$ | 9 | 0.95 | 51 |
| $AgSO_3CF_3$ | 9 | 0.76 | 66 |
| $AgSO_3CF_3$ | 9 | 0.63 | 58 |
| $AgPF_6$ | 10 | 3.8 | 75 |
| $AgPF_6$ | 10 | 1.9 | 73 |
| $AgPF_6$ | 10 | 1.3 | 70 |
| $AgPF_6$ | 10 | 0.95 | 67 |
| $AgPF_6$ | 10 | 0.76 | 68 |
| $AgPF_6$ | 10 | 0.63 | 61 |
| $AgSbF_6$ | 8 | 3.8 | 76 |
| $AgSbF_6$ | 8 | 1.9 | 74 |
| $AgSbF_6$ | 8 | 1.3 | 66 |
| $AgSbF_6$ | 8 | 0.95 | 66 |
| $AgSbF_6$ | 8 | 0.76 | 61 |
| $AgSbF_6$ | 8 | 0.63 | 58 |

**Table 15: Screens with base and silver salts and equivalents of morpholine**




| Silver Salt | Morpholine Equiv | Base | Base Equiv | Solvent | Yield |
|---|---|---|---|---|---|
| $AgBF_4$ | 8 | $Et_3N$ | 1 | 1,4-Dioxane | 68 |
| $AgBF_4$ | 8 | $Et_3N$ | 0.1 | 1,4-Dioxane | 77 |
| $AgBF_4$ | 8 | $Na_2CO_3$ | 1 | 1,4-Dioxane | 82 |
| $AgBF_4$ | 8 | $Na_2CO_3$ | 0.1 | 1,4-Dioxane | 79 |
| $AgBF_4$ | 8 | $K_2CO_3$ | 1 | 1,4-Dioxane | 14 |
| $AgBF_4$ | 8 | $K_2CO_3$ | 0.1 | 1,4-Dioxane | 72 |
| $AgBF_4$ | 8 | $Cs_2CO_3$ | 1 | 1,4-Dioxane | 1 |
| $AgBF_4$ | 8 | $Cs_2CO_3$ | 0.1 | 1,4-Dioxane | 0 |
| $AgBF_4$ | 8 | none | none | 1,4-Dioxane | 76 |
| $AgSO_3CF_3$ | 8 | $Et_3N$ | 1 | 1,4-Dioxane | 72 |
| $AgSO_3CF_3$ | 8 | $Et_3N$ | 0.1 | 1,4-Dioxane | 76 |
| $AgSO_3CF_3$ | 8 | $Na_2CO_3$ | 1 | 1,4-Dioxane | 83 |
| $AgSO_3CF_3$ | 8 | $Na_2CO_3$ | 0.1 | 1,4-Dioxane | 80 |
| $AgSO_3CF_3$ | 8 | $K_2CO_3$ | 1 | 1,4-Dioxane | 60 |
| $AgSO_3CF_3$ | 8 | $K_2CO_3$ | 0.1 | 1,4-Dioxane | 80 |
| $AgSO_3CF_3$ | 8 | $Cs_2CO_3$ | 1 | 1,4-Dioxane | 4 |
| $AgSO_3CF_3$ | 8 | $Cs_2CO_3$ | 0.1 | 1,4-Dioxane | 19 |
| $AgSO_3CF_3$ | 8 | none | none | 1,4-Dioxane | 76 |
| $AgPF_6$ | 6 | $Et_3N$ | 1 | 1,4-Dioxane | 66 |
| $AgPF_6$ | 6 | $Et_3N$ | 0.1 | 1,4-Dioxane | 65 |
| $AgPF_6$ | 6 | $Na_2CO_3$ | 1 | 1,4-Dioxane | 69 |
| $AgPF_6$ | 6 | $Na_2CO_3$ | 0.1 | 1,4-Dioxane | 66 |
| $AgPF_6$ | 6 | $K_2CO_3$ | 1 | 1,4-Dioxane | 60 |
| $AgPF_6$ | 6 | $K_2CO_3$ | 0.1 | 1,4-Dioxane | 70 |
| $AgPF_6$ | 6 | $Cs_2CO_3$ | 1 | 1,4-Dioxane | 1 |
| $AgPF_6$ | 6 | $Cs_2CO_3$ | 0.1 | 1,4-Dioxane | 11 |
| $AgPF_6$ | 6 | none | none | 1,4-Dioxane | 62 |

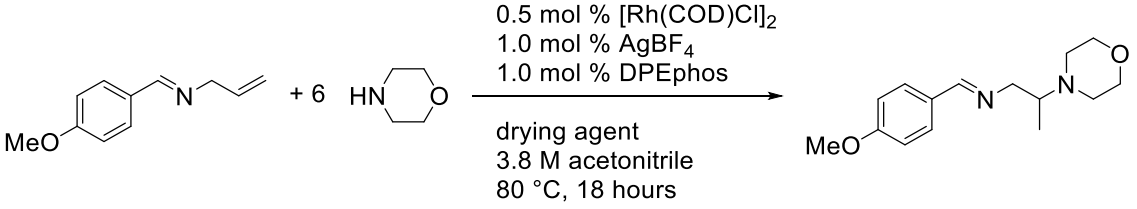
**Table 15 (cont.):**

| Silver Salt | Morpholine Equiv | Base | Base Equiv | Solvent | Yield |
|---|---|---|---|---|---|
| $AgSbF_6$ | 6 | $Et_3N$ | 1 | 1,4-Dioxane | 57 |
| $AgSbF_6$ | 6 | $Et_3N$ | 0.1 | 1,4-Dioxane | 61 |
| $AgSbF_6$ | 6 | $Na_2CO_3$ | 1 | 1,4-Dioxane | 54 |
| $AgSbF_6$ | 6 | $Na_2CO_3$ | 0.1 | 1,4-Dioxane | 58 |
| $AgSbF_6$ | 6 | $K_2CO_3$ | 1 | 1,4-Dioxane | 58 |
| $AgSbF_6$ | 6 | $K_2CO_3$ | 0.1 | 1,4-Dioxane | 58 |
| $AgSbF_6$ | 6 | $Cs_2CO_3$ | 1 | 1,4-Dioxane | 0 |
| $AgSbF_6$ | 6 | $Cs_2CO_3$ | 0.1 | 1,4-Dioxane | 27 |
| $AgSbF_6$ | 6 | none | none | 1,4-Dioxane | 60 |
| $AgBF_4$ | 6 | $Et_3N$ | 1 | Acetonitrile | 80 |
| $AgBF_4$ | 6 | $Et_3N$ | 0.1 | Acetonitrile | 79 |
| $AgBF_4$ | 6 | $Na_2CO_3$ | 1 | Acetonitrile | 87 |
| $AgBF_4$ | 6 | $Na_2CO_3$ | 0.1 | Acetonitrile | 81 |
| $AgBF_4$ | 6 | $K_2CO_3$ | 1 | Acetonitrile | n/a |
| $AgBF_4$ | 6 | $K_2CO_3$ | 0.1 | Acetonitrile | 0 |
| $AgBF_4$ | 6 | $Cs_2CO_3$ | 1 | Acetonitrile | 58 |
| $AgBF_4$ | 6 | $Cs_2CO_3$ | 0.1 | Acetonitrile | 2 |
| $AgBF_4$ | 6 | none | none | Acetonitrile | 73 |
| $AgSO_3CF_3$ | 9 | $Et_3N$ | 1 | Acetonitrile | 80 |
| $AgSO_3CF_3$ | 9 | $Et_3N$ | 0.1 | Acetonitrile | 77 |
| $AgSO_3CF_3$ | 9 | $Na_2CO_3$ | 1 | Acetonitrile | 81 |
| $AgSO_3CF_3$ | 9 | $Na_2CO_3$ | 0.1 | Acetonitrile | 80 |
| $AgSO_3CF_3$ | 9 | $K_2CO_3$ | 1 | Acetonitrile | 55 |
| $AgSO_3CF_3$ | 9 | $K_2CO_3$ | 0.1 | Acetonitrile | 78 |
| $AgSO_3CF_3$ | 9 | $Cs_2CO_3$ | 1 | Acetonitrile | 1 |
| $AgSO_3CF_3$ | 9 | $Cs_2CO_3$ | 0.1 | Acetonitrile | 10 |
| $AgSO_3CF_3$ | 9 | none | none | Acetonitrile | 74 |
| $AgPF_6$ | 10 | $Et_3N$ | 1 | Acetonitrile | 75 |
| $AgPF_6$ | 10 | $Et_3N$ | 0.1 | Acetonitrile | 75 |
| $AgPF_6$ | 10 | $Na_2CO_3$ | 1 | Acetonitrile | 75 |
| $AgPF_6$ | 10 | $Na_2CO_3$ | 0.1 | Acetonitrile | 76 |
| $AgPF_6$ | 10 | $K_2CO_3$ | 1 | Acetonitrile | 39 |

**Table 15 (cont.):**

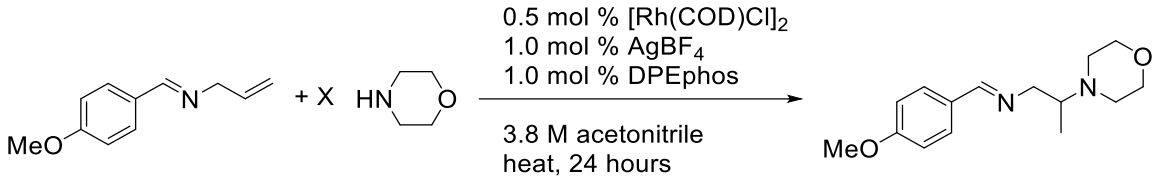
| Silver Salt | Morpholine Equiv | Base | Base Equiv | Solvent | Yield |
|---|---|---|---|---|---|
| $AgPF_6$ | 10 | $K_2CO_3$ | 0.1 | Acetonitrile | 70 |
| $AgPF_6$ | 10 | $Cs_2CO_3$ | 1 | Acetonitrile | 2 |
| $AgPF_6$ | 10 | $Cs_2CO_3$ | 0.1 | Acetonitrile | 9 |
| $AgPF_6$ | 10 | none | none | Acetonitrile | 78 |
| $AgSbF_6$ | 8 | $Et_3N$ | 1 | Acetonitrile | 75 |
| $AgSbF_6$ | 8 | $Et_3N$ | 0.1 | Acetonitrile | 76 |
| $AgSbF_6$ | 8 | $Na_2CO_3$ | 1 | Acetonitrile | 76 |
| $AgSbF_6$ | 8 | $Na_2CO_3$ | 0.1 | Acetonitrile | 78 |
| $AgSbF_6$ | 8 | $K_2CO_3$ | 1 | Acetonitrile | 69 |
| $AgSbF_6$ | 8 | $K_2CO_3$ | 0.1 | Acetonitrile | 75 |
| $AgSbF_6$ | 8 | $Cs_2CO_3$ | 1 | Acetonitrile | 1 |
| $AgSbF_6$ | 8 | $Cs_2CO_3$ | 0.1 | Acetonitrile | 28 |

**Table 16: Screens with various drying agents**




| Drying Agent | Yield |
|---|---|
| 3 Å Mol. Powder | 88 |
| 4 Å Mol. Powder | 88 |
| 5 Å Mol. Powder | 90 |
| 4 Å Mol. Sieves | 85 |
| $MgSO_4$ | 86 |
| none | 88 |

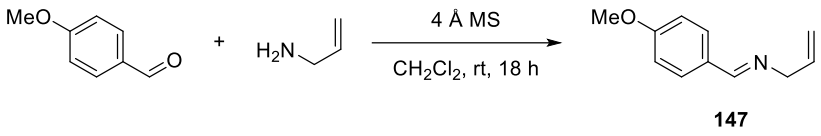
**Table 17: Temperature screens with different equivalents of morpholine**




| Temperature | Morpholine Equiv | Yield |
|---|---|---|
| rt | 1 | 28 |
| rt | 2 | 39 |
| rt | 3 | 46 |
| rt | 4 | 37 |
| 30 | 1 | 33 |
| 30 | 2 | 47 |
| 30 | 3 | 55 |
| 30 | 4 | 50 |
| 40 | 1 | 19 |
| 40 | 2 | 42 |
| 40 | 3 | 55 |
| 40 | 4 | 67 |
| 50 | 1 | 47 |
| 50 | 2 | 71 |
| 50 | 3 | 83 |
| 50 | 4 | 83 |
| 60 | 1 | 47 |
| 60 | 2 | 73 |
| 60 | 3 | 85 |
| 60 | 4 | 88 |
| 70 | 1 | 39 |
| 70 | 2 | 70 |
| 70 | 3 | 79 |
| 70 | 4 | 84 |
| 80 | 1 | 29 |
| 80 | 2 | 65 |
| 80 | 3 | 78 |
| 80 | 4 | 79 |

## E. Experimental Procedure, Isolation, and Characterization

**Note**: All allyl imines were prepared according to the published literature procedure[319] analogous to the synthesis of **147** below.



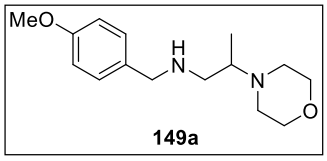

**147**

**(E)-*N*-allyl-1-(4-methoxyphenyl)methanimine, 147**: *p*-Anisaldehyde (30 mL, 250 mmol, 1.0 equiv.), 4 Å MS (10.0 g, beads) and dry $CH_2Cl_2$ (100 mL) were added to a 500 mL round bottom flask with a stir bar followed by allylamine (27 mL, 370 mmol, 1.5 equiv.). The reaction mixture was placed under $N_2$ and stirred at room temperature for 24 h. It was filtered through Celite, washing with $CH_2Cl_2$ (120 mL). The filtrate was washed with water (200 mL × 2) and brine (200 mL × 1). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give imine **147** as a pale yellow oil in 84% yield (36 g, 210 mmol). The imine was used without further purification.

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.92 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.04 (ddt, *J* = 17.1, 10.2, 5.5 Hz, 1H), 5.23 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.04 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.17 – 3.93 (m, 2H), 3.22 (s, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 161.87, 160.47, 136.96, 129.95, 129.90, 115.17, 114.10, 63.57, 54.70 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{11}H_{14}NO$, 176.1075; found: 176.1074.




**149a**

**N-(4-methoxybenzyl)-2-morpholinopropan-1-amine, 149a:** [(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine **147** (259 µL, 1.50 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 µL) 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, **144a** (390 µL, 4.5 mmol, 3.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149a** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% $NH_4OH$ : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing

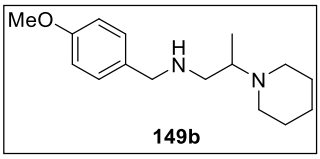
aqueous layer, and adding methanol) afforded pure diamine **149a** as a pale yellow oil in 82% yield (323 mg, 1.22 mmol).

$R_f$ = 0.55 (1:9 $NH_4OH/CHCl_3$).

$^1H$ NMR ($C_6D_6$, 500 MHz): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.66 (d, *J* = 12.9 Hz, 1H), 3.64 (d, *J* = 13.1 Hz, 1H), 3.49 (qdd, *J* = 11.3, 6.4, 3.3 Hz, 4H), 3.29 (s, 3H), 2.54 (dqd, *J* = 8.3, 6.6, 4.9 Hz, 1H), 2.43 (dd, *J* = 11.6, 8.4 Hz, 1H), 2.33 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.21 (ddd, *J* = 10.5, 6.5, 3.5 Hz, 2H), 2.07 (ddd, *J* = 10.6, 6.6, 3.6 Hz, 2H) 1.55 (br s, 1H), 0.70 (d, *J* = 6.4 Hz, 3H) ppm.

$^{13}C$ NMR ($C_6D_6$, 125 MHz): δ 159.0, 133.5, 129.3, 113.9, 67.4, 58.9, 54.7, 53.6, 51.6, 48.8, 11.7 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1906.



**149b**

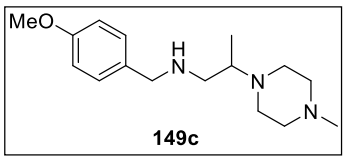
***N*-(4-methoxybenzyl)-2-(piperidin-1-yl)propan-1-amine, 149b:** [(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine **147** (259 μL, 1.50 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added piperidine (185 μL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149b** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% $NH_4OH$ : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149b** as a pale yellow oil in 87% yield (340 mg, 1.3 mmol).

$R_f$ = 0.63 (1:9 $NH_4OH/CHCl_3$).

$^1H$ NMR ($C_6D_6$, 500 MHz): δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.0 Hz, 1H), 3.28 (s, 3H), 2.77-2.70 (dqd, *J* = 9.2, 6.6, 4.7, 1H), 2.52 (dd, *J* = 11.3, 9.4 Hz, 1H), 2.39 (dd, *J* = 11.4, 4.8 Hz, 1H), 2.33 (ddd, *J* = 10.8, 7.3, 3.4 Hz, 2H), 2.14 (t, *J* = 7.1 Hz, 2H), 1.86 (s, 1H), 1.44-1.37 (m, 4H), 1.29-1.22 (m, 2H), 0.74 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}C$ NMR ($C_6D_6$, 125 MHz): δ 159.0, 133.7, 129.4, 113.9, 59.2, 54.7, 53.6, 52.2, 49.3, 26.9, 25.3, 11.3 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{27}N_2O$, 263.2123; found, 263.2130.



149c

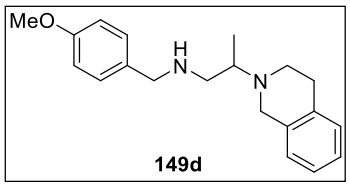
**N-(4-methoxybenzyl)-2-(4-methylpiperazin-1-yl)propan-1-amine, 149c:** [(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine **147** (259 μL, 1.50 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added 1-methylpiperazine (749 μL, 6.75 mmol, 4.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To the vial was added *p*-anisaldehyde (91 μL, 0.75 mmol, 0.50 equiv.) and the mixture was stirred for 2 hours. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149c** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% $NH_4OH$ : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149c** as a pale yellow oil in 66% yield (274 mg, 0.988 mmol).

$R_f$ = 0.42 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.70 (d, *J* = 13.1 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.29 (s, 3H), 2.70 (dqd, *J* = 8.7, 6.7, 4.8 Hz, 1H), 2.49 (dd, *J* = 11.6, 8.8 Hz, 1H), 2.46-2.42 (m, 2H), 2.39 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.30-2.15 (m, 6H), 2.08 (s, 3H), 1.76 (s, 1H), 0.76 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 159.0, 133.7, 129.3, 113.9, 58.5, 55.9, 54.7, 54.7, 53.6, 52.1, 46.2, 11.7 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{28}N_3O$, 278.2232; found, 278.2228.



149d

**2-(3,4-dihydroisoquinolin-2(1H)-yl)-N-(4-methoxybenzyl)propan-1-amine, 149d:** [(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine **147** (259 μL, 1.50 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added tetrahydroisoquinoline (951 μL, 7.50 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL)

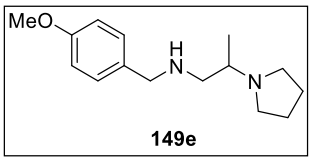
and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149d** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 2% $NH_4OH$ : 2% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149d** as a pale yellow oil in 87% yield (404 mg, 1.30 mmol).

$R_f$ = 0.60 (1:9 MeOH/$CH_2Cl_2$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.20 (d, *J* = 8.7 Hz, 2H), 7.01 (dd, *J* = 5.5, 3.5 Hz, 2H), 6.94 (dd, *J* = 5.3, 3.6 Hz, 1H), 6.84 (dd, *J* = 5.2, 3.7 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 3.69 (d, *J* = 13.3 Hz, 1H), 3.65 (d, *J* = 13.3 Hz, 1H), 3.55 (d, *J* = 14.7 Hz, 1H), 3.43 (d, *J* = 14.6 Hz, 1H), 3.31 (s, 3H), 2.91-2.84 (m, 1H), 2.64 (t, *J* = 5.7 Hz, 2H), 2.58 (dd, *J* = 11.6, 9.0 Hz, 1H), 2.53 (dt, *J* = 11.1, 5.5 Hz, 1H), 2.43 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.29 (dt, *J* = 11.4, 5.8 Hz, 1H), 1.86-1.85 (br s, 1H), 0.77 (d, *J*=6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 159.00, 136.06, 135.09, 133.62, 129.36, 127.71, 126.81, 125.96, 125.58, 113.89, 58.48, 54.65, 53.53, 52.00, 51.21, 45.51, 30.31, 11.15 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{20}H_{27}N_2O$, 311.2123; found, 311.2125.



**149e**

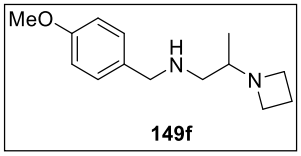
***N*-(4-methoxybenzyl)-2-(pyrrolidin-1-yl)propan-1-amine, 149e:** [(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine **147** (259 μL, 1.50 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added pyrrolidine (185 μL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149e** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 3% $NH_4OH$ : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149e** as a pale yellow oil in 76% yield (282 mg, 1.14 mmol).

$R_f$ = 0.61 (1:9 $NH_4OH$/$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.66 (s, 2H), 3.32 (s, 3H), 2.60-2.54 (m, 2H), 2.49 (dq, *J* = 11.6, 5.8 Hz, 1H), 2.38-2.35 (m, 4H), 1.72 (br s, 1H), 1.53 (m, 4H), 1.04 (d, *J* = 6.4 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 158.99, 133.62, 129.30, 113.85, 57.74, 54.64, 54.01, 53.92, 50.15, 23.80, 15.53 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1960.



**149f**

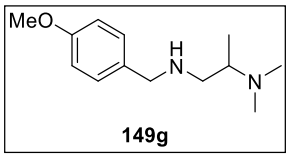
**2-(azetidin-1-yl)-N-(4-methoxybenzyl)propan-1-amine, 149f:** [(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine **147** (259 μL, 1.50 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added azetidine (152 μL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (57 mg, 2.3 mmol, 1.5 equiv) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149f** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 4% $NH_4OH$ : 4% MeOH : 92% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149f** as a pale yellow oil in 72% yield (253 mg, 1.08 mmol).

$R_f$ = 0.53 (1:9 MeOH/$CH_2Cl_2$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.26 – 7.18 (m, 2H), 6.85 – 6.75 (m, 2H), 3.62 (s, 2H), 3.31 (s, 3H), 3.15 – 2.75 (m, 4H), 2.44 (qd, *J* = 11.4, 4.7 Hz, 2H), 2.26 – 2.05 (m, 1H), 1.71 (p, *J* = 6.8 Hz, 2H), 1.30 (s, 1H), 0.98 (d, *J* = 6.3 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 159.01, 133.55, 129.28, 113.87, 62.83, 54.62, 54.00, 53.51, 52.19, 17.23, 15.21 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1811.



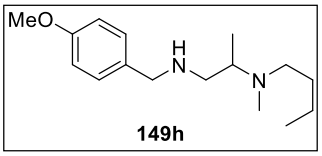
149g

**$N^1$-(4-methoxybenzyl)-$N^2$,$N^2$-dimethylpropane-1,2-diamine, 149g**: [(DPEphos)Rh(COD)]$BF_4$ (15 mg, 0.018 mmol, 5.0 mol %) and imine **147** (70 mg, 0.40 mmol, 1.00 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 dimethylamine (1 mL, 1 mmol, 2.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (15 mg, 0.6 mmol, 1.5 equiv) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149g** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 4% $NH_4OH$ : 4% MeOH : 92% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149g** as a pale yellow oil in 73% yield (32.5 mg, 0.15 mmol).

$^1$H NMR (499 MHz, Chloroform-*d*) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.79 – 3.69 (m, 2H), 2.85 – 2.73 (m, 1H), 2.55 (dd, *J* = 11.7, 8.9 Hz, 1H), 2.46 (dd, *J* = 11.8, 5.0 Hz, 1H), 2.19 (d, *J* = 2.8 Hz, 6H), 0.89 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, $CDCl_3$) δ 158.74, 133.04, 129.53, 113.92, 58.42, 55.48, 53.66, 52.52, 40.35, 10.44 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_{13}H_{22}N_2O$, 223.1810; found, 223.1821.



149h

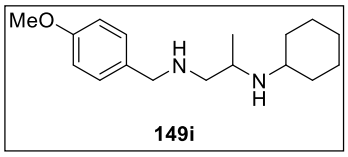
**$N^2$-butyl-$N^1$-(4-methoxybenzyl)-$N^2$-methylpropane-1,2-diamine, 149h**: [(DPEphos)Rh(COD)]$BF_4$ (15 mg, 0.018 mmol, 5.0 mol %), imine **147** (70 mg, 0.40 mmol, 1.00 equiv.) and dry $CH_3CN$ (100 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added methylbutylamine (174 mg, 2 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (15 mg, 0.6 mmol, 1.5 equiv) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford

crude **149h** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 4% $NH_4OH$ : 4% MeOH : 92% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149h** as a pale yellow oil in 27% yield (28.5 mg, 0.11 mmol).

$^1$H NMR (500 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.78 – 3.65 (m, 2H), 2.94 – 2.82 (m, 1H), 2.53 (dd, *J* = 11.5, 9.7 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.39 – 2.34 (m, 1H), 2.25 (ddd, *J* = 12.4, 8.4, 5.7 Hz, 1H), 2.10 (s, 3H), 1.45 – 1.35 (m, 2H), 1.33 – 1.25 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H).

$^{13}$C NMR (126 MHz, $CDCl_3$) δ 129.48, 129.39, 114.02, 110.00, 57.64, 55.47, 53.61, 53.10, 52.68, 36.44, 30.82, 20.75, 14.21, 10.75.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{28}N_2O$, 265.2280; found, 265.2280.



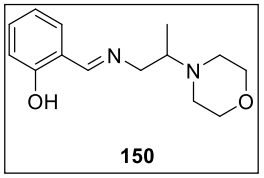
**149i**

**$N^2$-cyclohexyl-$N^1$-(4-methoxybenzyl)propane-1,2-diamine, 149i**: [(DPEphos)Rh(COD)]$BF_4$ (15 mg, 0.018 mmol, 5.0 mol %), imine **147** (70 mg, 0.40 mmol, 1.00 equiv.) and dry $CH_3CN$ (100 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added cyclohexylamine (200 mg, 2.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (15 mg, 0.6 mmol, 1.5 equiv) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **149i** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 4% $NH_4OH$ : 4% MeOH : 92% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **149i** as a pale yellow oil in 34% yield (38 mg, 0.14 mmol).

$^1$H NMR (499 MHz, Benzene-$d_6$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.62 (d, *J* = 1.9 Hz, 1H), 3.30 (s, 3H), 2.83 – 2.72 (m, 1H), 2.53 – 2.39 (m, 3H), 2.34 (dd, *J* = 11.3, 7.9 Hz, 1H), 1.85 (d, *J* = 12.1 Hz, 2H), 1.74 (d, *J* = 13.6 Hz, 1H), 1.63 (d, *J* = 9.6 Hz, 4H), 1.48 (dd, *J* = 8.5, 3.3 Hz, 3H), 1.24 – 1.01 (m, 9H), 0.94 (d, *J* = 6.3 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 158.97, 133.97, 129.24, 113.91, 56.11, 54.68, 53.65, 50.66, 49.58, 35.25, 33.78, 26.55, 25.00, 19.87 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{28}N_2O$, 277.2280; found, 277.2290.



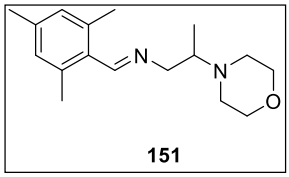
150

**(E)-2-(((2-morpholinopropyl)imino)methyl)phenol, 150:** [(DPEphos)Rh(COD)]$BF_4$ (9.5 mg, 0.011 mmol, 5.0 mol %), imine (36 mg, 0.22 mmol, 1.0 equiv.) and dry $CH_3CN$ (60 μL) 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 (98 μL, 1.1 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. This mixture was concentrated *in vacuo* to afford a crude oil. This was run through a short column of basic alumina (eluent 90% hexane : 10% ethyl acetate followed by 100% ethyl acetate). The resulting solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 2 h at 40 °C to afford pure imine **150** as a clear yellow oil in 90% yield (50 mg, 0.20 mmol). In one case where the imine was not pure, automated column chromatography was performed to using a 5.5 g cyano column received from Teledyne ISCO using hexane as the eluent.

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.78 (s, 1H), 7.13-7.06 (m, 2H), 6.97 (dd, *J* = 7.6, 1.6, 1H), 6.72 (td, *J* = 7.3, 1.3, 1H), 3.57-3.51 (m, 4H), 3.24 (ddd, *J* = 12.0, 5.8, 1.1, 1H), 3.01 (ddd, *J* = 11.9, 7.1, 1.1, 1H), 2.43 (sextet, *J* = 6.5, 1H), 2.24-2.17 (m, 4H), 0.78 (d, *J* = 6.7, 3H), -0.34 (s, 1H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 165.7, 162.1, 132.5, 131.4, 119.4, 118.6, 117.6, 67.5, 62.1, 60.0, 49.6, 13.3 ppm.

HRMS (EI-TOF) *m/z*: [M$^+$] calculated for $C_{14}H_{20}N_2O_2$, 248.1525; found, 248.1521.



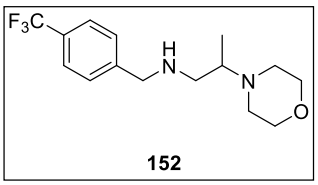
151

**(E)-1-mesityl-N-(2-morpholinopropyl)methanimine, 151:** [(DPEphos)Rh(COD)]$BF_4$ (8.4 mg, 0.010 mmol, 1.0 mol %), imine (180 mg, 0.96 mmol, 1.0 equiv.) and dry $CH_3CN$ (260 μL) 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 (430 μL, 5.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. This mixture was concentrated *in vacuo* to afford a crude oil. This was run through a short column of basic alumina (eluent 90% hexane : 10% ethyl acetate followed by 100% ethyl acetate). The resulting solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 2 h at 60 °C to afford pure imine **151** as a clear yellow oil in 90% yield (237 mg, 0.862 mmol).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 8.43 (s, 1H), 6.74 (s, 2H), 2.79 (sextet, J = 6.2, 1H), 2.43 (s, 6H), 2.38 (t, J = 4.6, 4H), 2.11 (s, 3H), 1.02 (d, J = 6.7, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 161.0, 138.6, 137.9, 131.6, 129.9, 67.7, 66.0, 60.5, 49.9, 21.21, 21.17, 13.8 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{27}N_2O$, 275.2123; found, 275.2120.



152

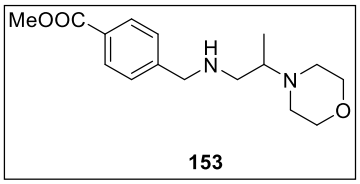
**2-morpholino-N-(4-(trifluoromethyl)benzyl)propan-1-amine, 152:** [(DPEphos)Rh(COD)]$BF_4$ (5.7 mg, 0.0068 mmol, 1.0 mol %), imine (146 mg, 0.683 mmol, 1.00 equiv.) and dry $CH_3CN$ (180 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (296 μL, 3.42 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (39 mg, 1.0 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **152** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 1% $NH_4OH$ : 99% $CHCl_3$ to 1% $NH_4OH$ : 1% MeOH : 98% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **152** as a pale yellow oil in a 62% yield (127 mg, 0.420 mmol).

$R_f$ = 0.50 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.40 (d, *J* = 8.0, 2H), 7.20 (d, *J* = 7.9, 2H), 3.56-3.47 (m, 6H), 2.52 (dq, *J* = 13.2, 6.6, 1H), 2.33 (dd, *J* = 11.6, 8.6, 1H), 2.24 (dd, *J* = 11.3, 4.4, 3H), 2.11 (ddd, *J* = 10.5, 6.5, 3.5, 2H), 1.85 (s, 1H), 0.72 (d, *J* = 6.6, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 145.99, 129.18 (q, $J^{CF}$ = 32.1), 128.46, 125.40 (q, $J^{CF}$ = 3.8), 125.17 (q, $J^{CF}$ = 271.5), 67.55, 59.09, 53.50, 51.92, 48.99, 11.74 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{22}N_2OF_3$, 303.1684; found, 303.1670.



153

**4-(((2-morpholinopropyl)amino)methyl)benzoate, 153:** [(DPEphos)Rh(COD)]$BF_4$ (8.1 mg, 0.0097 mmol, 1.0 mol %), imine (178 mg, 0.967 mmol, 1.00 equiv.) and dry $CH_3CN$ (254 μL) 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 (418 μL, 4.84 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (55 mg, 1.5 mmol, 1.5 equiv) and MeOH (3 mL). The flask containing the reducing agent was brought to 0 °C and the solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and was washed with saturated $NaHCO_3$ (15 mL). The organic layer was

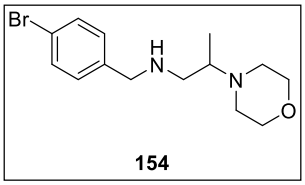
separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **153** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 2% $NH_4OH$ : 98% $CHCl_3$ to 2% $NH_4OH$ : 2% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **153** as a pale yellow oil in 52% yield (132 mg, 0.451 mmol).

$R_f$ = 0.67 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 8.14 (d, *J* = 8.2, 2H), 7.29 (d, *J* = 8.1, 2H), 3.59 (s, 2H), 3.56-3.47 (m, 7H), 2.55-2.49 (m, 1H), 2.35 (dd, *J* = 11.6, 8.5, 1H), 2.23 (ddd, *J* = 18.7, 8.9, 4.1, 3H), 2.09 (ddd, *J* = 10.6, 6.5, 3.5, 2H), 1.92 (s, 1H), 0.71 (d, *J* = 6.6, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 166.7, 147.0, 130.0, 129.5, 128.2, 67.5, 59.1, 53.7, 51.8, 51.6, 48.9, 11.8 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{25}N_2O_3$, 293.1865; found, 293.1858.



**154**

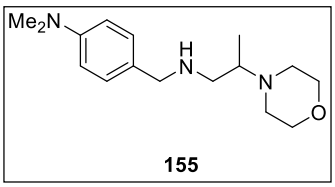
***N*-(4-bromobenzyl)-2-morpholinopropan-1-amine, 154:** [(DPEphos)Rh(COD)]$BF_4$ (7.1 mg, 0.0085 mmol, 1.0 mol %), imine (191 mg, 0.850 mmol, 1.00 equiv.) and dry $CH_3CN$ (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (370 μL, 4.25 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (48 mg, 1.3 mmol, 1.5 equiv) and MeOH (3 mL). The flask containing the reducing agent was brought to 0 °C and the solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature and stirred for 2 h and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **154** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 3% $NH_4OH$ : 97% $CHCl_3$ to 6% $NH_4OH$ : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, and removing aqueous layer) afforded pure diamine **154** as a clear oil in 76% yield (202 mg, 0.646 mmol).

$R_f$ = 0.50 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.30 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 3.52 (ddd, *J* = 14.9, 6.3, 3.1 Hz, 4H), 3.46 (s, 2H), 2.50 (ddd, *J* = 8.6, 6.6, 4.8 Hz, 1H), 2.31 (dd, *J* = 11.6, 8.5 Hz, 1H), 2.26-2.17 (m, 3H), 2.07 (ddd, *J* = 11.2, 6.2, 3.1 Hz, 2H), 1.63 (s, 1H), 0.70 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 139.65, 131.36, 129.72, 120.53, 67.41, 58.66, 53.17, 51.21, 48.39, 11.44 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{22}BrN_2$, 313.0916; found, 313.0908.



**155**

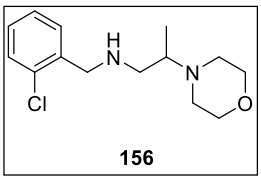
***N*,*N*-dimethyl-4-(((2-morpholinopropyl)amino)methyl)aniline, 155:** [(DPEphos)Rh(COD)]$BF_4$ (7.2 mg, 0.0086 mmol, 1.0 mol %), imine (160 mg, 0.850 mmol, 1.00 equiv.) and dry $CH_3CN$ (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added morpholine (370 μL, 4.25 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (48 mg, 1.3 mmol, 1.5 equiv.) and MeOH (3 mL) and cooled to 0 °C. The aminoimine solution was added dropwise to the $NaBH_4$ solution. The vial was washed with MeOH (2.5 mL) and transferred to the flask. The reaction was brought to room temperature and stirred for 2 h. The resulting mixture was concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **155** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 3% $NH_4OH$ : 97% $CHCl_3$ to 6% $NH_4OH$ : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$ and removing aqueous layer) afforded pure diamine **155** as a clear oil in 74% yield (174 mg, 0.629 mmol).

$R_f$ = 0.33 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.34 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 3.79 (d, *J* = 12.9 Hz, 1H), 3.74 (d, *J* = 13.0 Hz, 1H), 3.53 (dtd, *J* = 13.9, 10.8, 5.4 Hz, 4H), 2.66-2.55 (m, 1H), 2.54-2.50 (m, 1H), 2.53 (s, 6H), 2.42 (dd, *J* = 11.5, 4.8 Hz, 1H), 2.29-2.21 (m, 2H), 2.15-2.07 (m, 2H), 1.80 (s, 1H), 0.75 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 149.70, 128.96, 128.61, 112.61, 67.45, 58.62, 53.27, 51.03, 48.32, 40.75, 11.41 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{28}N_3O$, 278.2232; found, 278.2234.



**156**

**N-(2-chlorobenzyl)-2-morpholinopropan-1-amine, 156**: [(DPEphos)Rh(COD)]$BF_4$ (36 mg, 0.043 mmol, 5.0 mol %), imine (153 mg, 0.85 mmol, 1.00 equiv.) and dry $CH_3CN$ (254 μL) 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 (368 μL, 4.3 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C.

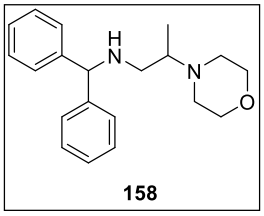
To an oven-dried 25 mL round bottom flask was added $NaBH_4$ (55 mg, 1.5 mmol, 1.5 equiv) and MeOH (3 mL). The flask containing the reducing agent was brought to 0 °C and the solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (2.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (20 mL) and was washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **156** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 2% $NH_4OH$ : 98% $CHCl_3$ to 2% $NH_4OH$ : 2% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **156** as a pale yellow oil in 44% yield (132 mg, 0.451 mmol).

$R_f$ = 0.63 (1:9 $NH_4OH/CHCl_3$)

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.35 (dd, J = 7.6, 1.6, 1H), 7.19 (dd, J = 7.9, 1.2, 1H), 6.93 (td, J = 7.5, 1.2, 1H), 6.80 (td, J = 7.7, 1.7, 1H), 3.87 (d, J = 14.3, 1H), 3.79 (d, J = 14.4, 1H), 3.58-3.50 (m, 4H), 2.55 (dqd, J = 8.7, 6.6, 4.7, 1H), 2.39 (dd, J = 11.6, 8.7, 1H), 2.31 (dd, J = 11.6, 4.7, 1H), 2.22-2.18 (m, 2H), 2.06 (ddd, J = 10.6, 6.3, 3.8, 2H), 2.00 (s, 1H), 0.70 (d, J = 6.6, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 138.0, 133.9, 130.5, 129.6, 128.4, 126.8, 67.5, 58.7, 51.6, 51.2, 48.4, 11.5 ppm.

HRMS (ESI-TOF) m/z: [M+H+] calcd for $C_{14}H_{22}N_2OCl$, 269.1421; found, 269.1416.



158

***N*-benzhydryl-2-morpholinopropan-1-amine, 158:** [(DPEphos)Rh(COD)]$BF_4$ (42 mg, 0.050 mmol, 5.0 mol %), imine (221 mg, 1.00 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 μL) 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 (216 μL, 2.50 mmol, 2.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL Schlenk flask under $N_2$ was added $LiAlH_4$ (76 mg, 2.0 mmol, 2.0 equiv) and THF (5 mL) and cooled to 0 °C. The solution of the aminoimine in THF was added dropwise, *via* syringe through septa. The reaction was brought to room temperature, stirred for 2 h, and then quenched with 1 M NaOH (5 mL). The residue was dissolved with $CHCl_3$ (20 mL) and washed with 1 M NaOH (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **158** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 1% $NH_4OH$ : 99% $CHCl_3$ v/v prepared by

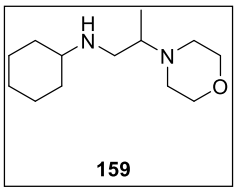
extracting saturated $NH_4OH$ with $CHCl_3$ and removing aqueous layer) afforded pure diamine **158** as a pale yellow oil in 40% yield (137 mg, 0.600 mmol).

$R_f$ = 0.70 (1:9 MeOH/$CH_2Cl_2$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 2H), 7.13 – 7.10 (m, 2H), 7.03 (dt, *J* = 14.8, 7.3 Hz, 2H), 4.72 (s, 1H), 3.44 (dddd, *J* = 19.9, 10.5, 6.9, 3.1 Hz, 4H), 2.56 (h, *J* = 6.7 Hz, 1H), 2.41 (d, *J* = 6.7 Hz, 2H), 2.17 (ddd, *J* = 10.3, 4.8, 2.0 Hz, 2H), 2.03 (ddd, *J* = 11.3, 6.1, 3.2 Hz, 2H), 1.33 (br s, 1H), 0.65 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 144.64, 144.33, 128.71, 128.64, 127.59 (2C, coincident peaks), 127.22, 127.12, 67.71, 67.69, 59.00, 50.87, 48.66, 11.85 ppm.

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



**159**

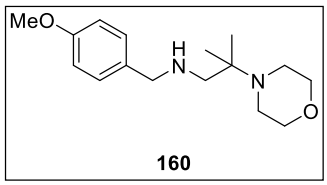
***N*-(2-morpholinopropyl)cyclohexanamine, 159:** [(DPEphos)Rh(COD)]$BF_4$ (13 mg, 0.015 mmol, 1.0 mol %), imine (259 μL, 1.50 mmol, 1.00 equiv.) and dry $CH_3CN$ (350 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (194 μL, 2.25 mmol, 1.50 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 25 mL Schlenk flask was added $LiAlH_4$ (114 mg, 3.00 mmol, 2.00 equiv.) and THF (5 mL) and cooled to 0 °C. The solution of the aminoimine in THF was added dropwise, *via* syringe through septa. The reaction was brought to room temperature, stirred for 2 h, and then quenched with 5 mL 1 M NaOH. The residue was dissolved with $CHCl_3$ (20 mL) and washed with 1 M NaOH (15 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **159** as a yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 1% saturated $NH_4OH$ : 98% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$ and then removing aqueous layer) afforded pure diamine **159** as a pale yellow oil in 44% yield (137 mg, 0.600 mmol).

$R_f$ = 0.37 (1:9 MeOH/$CH_2Cl_2$).

$^1$H NMR ($C_6D_6$, 400 MHz): δ 3.51 (dddd, *J* = 13.9, 10.8, 7.0, 3.9 Hz, 4H), 2.52 (h, *J* = 6.6 Hz, 1H), 2.39 (d, *J* = 6.6 Hz, 2H), 2.33 – 2.20 (m, 2H), 2.08 (dddd, *J* = 9.6, 6.1, 3.6, 1.0 Hz, 2H), 1.86 – 1.69 (m, 3H), 1.63 (dq, *J* = 11.3, 4.2 Hz, 2H), 1.48 (dd, *J* = 11.9, 4.5 Hz, 1H), 1.31 – 0.95 (m, 5H), 0.73 (d, *J* = 6.5 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 171.66, 137.48, 114.00, 52.78, 39.94, 28.54, 27.82, 26.95, 26.14 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{13}H_{27}N_2O$, 227.2123; found 227.2122.



160

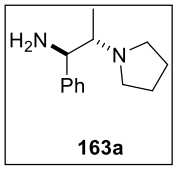
**(E)-1-(4-methoxyphenyl)-N-(2-methyl-2-morpholinopropyl) methanimine, 160**: $[(DPEphos)Rh(COD)]BF_4$ (12 mg, 0.015 mmol, 5.0 mol %), imine (54.5 mg, 0.288 mmol, 1.00 equiv.) and dry $CH_3CN$ (77 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (126 μL, 1.46 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. To an oven-dried 10 mL round bottom flask was added $NaBH_4$ (17 mg, 0.44 mmol, 1.5 equiv.) and MeOH (0.5 mL). The flask containing the reducing agent was brought to 0 °C and the solution of the aminoimine in MeOH was added dropwise, washing the vial with MeOH (0.5 mL). The reaction was brought to room temperature, stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (10 mL) and was washed with saturated $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (15 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude **160** as a yellow oil. Purification of the crude diamine by silica gel chromatography (33 mm × 6 mm column, 2% $NH_4OH$ : 98% $CHCl_3$ to 2% $NH_4OH$ : 2% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **160** as a clear oil in 58% yield (46 mg, 0.17 mmol).

$R_f$ = 0.53 (1:9 $NH_4OH/CHCl_3$).

$^1H$ NMR ($C_6D_6$, 500 MHz): δ 7.25 (d, *J* = 8.6, 2H), 6.82 (d, *J* = 8.6, 2H), 3.67 (s, 2H), 3.54 (t, *J* = 4.6, 4H), 3.33 (s, 3H), 2.35 (s, 2H), 2.19 (t, *J* = 4.6, 4H), 0.90 (s, 6H) ppm.

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 159.1, 133.4, 129.4, 113.9, 67.8, 56.7, 56.0, 54.6, 53.7, 45.9, 21.7 ppm.

HRMS (ESI-TOF) *m/z*: $[M+H^+]$ calculated for $C_{16}H_{27}N_2O_2$, 279.2073; found, 279.2075.



163a

**1-phenyl-2-(pyrrolidin-1-yl)propan-1-amine, 163a:** $[(DPEphos)Rh(COD)]BF_4$ (3.4 mg, 0.0040 mmol, 2.0 mol %), imine (50 mg, 0.20 mmol, 1.0 equiv.) and dry $CH_3CN$ (53 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added pyrrolidine (17 μL, 0.20 mmol, 1.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solution was concentrated *in vacuo* followed by the addition of 10% aqueous HCl (2 mL). The vial was capped and stirred at 60 °C for 2 h. The solution was transferred to a separatory funnel. The reaction vial was rinsed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (10 mm Hg) for 0.5 h to afford the crude

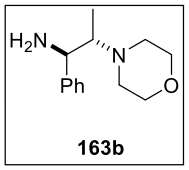
diamine **163a** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (4 g, MeOH : 1% $NH_4OH$ / $CHCl_3$ = 0 : 100 to 5 : 95 as gradient afforded pure diamine **163a** as a yellow oil in 50% yield (20 mg, 0.10 mmol).

$R_f$ = 0.17 (1:9 MeOH/$CH_2Cl_2$).

$^1$H NMR ($CDCl_3$, 500 MHz): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 4.39 (d, *J* = 3.1 Hz, 1H), 2.72 – 2.61 (m, 4H), 2.38 (qd, *J* = 6.5, 3.1 Hz, 1H), 1.85 – 1.78 (m, 4H), 1.69 (s, 2H), 0.85 (d, *J* = 6.5 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 143.79, 128.00, 126.80, 126.44, 66.22, 56.44, 52.32, 23.47, 11.78 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{13}H_{21}N_2$, 205.1705; found, 205.1702.



163b

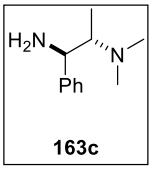
**2-morpholino-1-phenylpropan-1-amine, 163b:** [(DPEphos)Rh(COD)]$BF_4$ (3.0 mg, 0.0036 mmol, 1.0 mol %), imine (100 mg, 0.36 mmol, 1.0 equiv.) and dry $CH_3CN$ (95 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (155 μL, 1.79 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solution was then concentrated *in vacuo* followed by the addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **163b** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (4 g, MeOH : 1% $NH_4OH$ / $CHCl_3$ = 0 : 100 to 10 : 90 as gradient) afforded pure diamine **163b** as a clear oil in 79% yield (61 mg, 0.28 mmol).

$R_f$ = 0.48 (1:9 $NH_4OH$/$CHCl_3$).

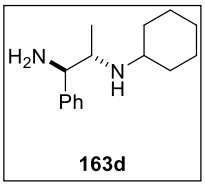
$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.32 (d, *J* = 7.4, 2H), 7.23 (t, *J* = 7.6, 2H), 7.13 (t, *J* = 7.3, 1H), 3.94 (d, *J* = 4.4, 1H), 3.52 (t, *J* = 4.4, 4H), 2.30-2.26 (m, 1H), 2.23 (t, *J* = 4.5, 4H), 1.34 (s, 2H), 0.78 (d, *J* = 6.7, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 165.7, 162.1, 132.5, 131.4, 119.4, 118.6, 117.6, 67.5, 62.1, 60.0, 49.6, 13.3 ppm.

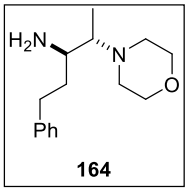
HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{13}H_{21}N_2O$, 221.1654; found, 221.1651.




**(1R,2S)-$N^2$,$N^2$-dimethyl-1-phenylpropane-1,2-diamine, 163c**: [(DPEphos)Rh(COD)]$BF_4$ (15.0 mg, 0.018 mmol, 5.0 mol %) and imine (100 mg, 0.36 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 dimethylamine solution (1 mL, 1.0 mmol, 2.5 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solution was then concentrated *in vacuo* followed by the addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **163c** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (4 g, MeOH : 1% $NH_4OH$ / $CHCl_3$ = 0 : 100 to 10 : 90 as gradient) afforded pure diamine **163c** as a clear oil in 22% yield (15.6 mg, 0.088 mmol).




**(1R,2S)-$N^2$-cyclohexyl-1-phenylpropane-1,2-diamine**, **163d:** [(DPEphos)Rh(COD)]$BF_4$ (15.0 mg, 0.018 mmol, 5.0 mol %), imine (100 mg, 0.36 mmol, 1.0 equiv.) and dry $CH_3CN$ (95 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added cyclohexylamine (200 μL, 2 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solution was then concentrated *in vacuo* followed by the addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **163d** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (4 g, MeOH : 1% $NH_4OH$ / $CHCl_3$ = 0 : 100 to 10 : 90 as gradient) afforded pure diamine **163d** as a clear oil in 45% yield (41.5 mg, 0.18 mmol).



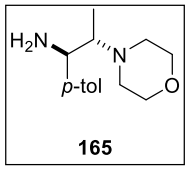

**4-morpholino-1-phenylpentan-3-amine, 164:** [(DPEphos)Rh(COD)]$BF_4$ (8 mg, 0.01 mmol, 1 mol %), imine (267 μL, 1.00 mmol, 1.00 equiv.) and dry $CH_3CN$ (300 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (431 μL, 5.00 mmol, 5.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solvent was reduced under reduced pressure. 3 M HCl (5 mL) was then added to the scintillation and the diphasic solution was vigorously stirred for 18 hours. The organic layer was discarded and the aqueous layer was basified with 5 M NaOH until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (75 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude diamine **164** as yellow oil. Purification of the crude diamine by silica gel chromatography (125 mL silica, 2% MeOH : 2% $NH_4OH$: 96% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **164** as a pale yellow oil in 73% yield (119 mg, 0.731 mmol).

$R_f$ = 0.40 (1:9 MeOH/$CH_2Cl_2$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.19 – 7.14 (m, 3H), 7.09 – 7.03 (m, 2H), 3.57 – 3.46 (m, 4H), 2.72 (ddd, *J* = 13.6, 9.8, 5.2 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.14 (tq, *J* = 10.8, 6.1, 4.9 Hz, 4H), 1.86 (p, *J* = 6.5 Hz, 1H), 1.79 (dddd, *J* = 13.3, 10.1, 7.0, 3.3 Hz, 1H), 1.40 (dddd, *J* = 13.8, 9.7, 8.7, 5.2 Hz, 1H), 0.72 (d, *J* = 6.6 Hz, 5H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 142.65, 128.60, 128.59, 126.00, 67.70, 64.20, 51.77, 50.60, 37.04, 33.17, 9.73 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1963.




**2-morpholino-1-(p-tolyl)propan-1-amine, 165:** [(DPEphos)Rh(COD)]$BF_4$ (5.5 mg, 0.0066 mmol, 2.0 mol %), imine (82 mg, 0.33 mmol, 1.0 equiv.) and dry $CH_3CN$ (87 μL) 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 (140 μL, 1.6 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solution was then concentrated *in vacuo* followed by the addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **165** as yellow oil. Purification of the crude diamine by automated silica

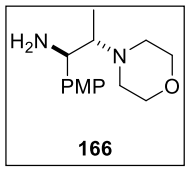
gel chromatography (4 g, MeOH : 1% $NH_4OH$ / $CHCl_3$ = 0 : 100 to 18 : 82 as gradient) afforded pure diamine **165** as a clear oil in 67% yield (52 mg, 0.22 mmol).

$R_f$ = 0.40 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500MHz): δ 7.27 (d, *J* = 8.0, 2H), 7.08 (d, *J* = 7.8, 2H), 3.96 (d, *J* = 4.3, 1H), 3.54 (dd, *J* = 5.0, 2.9, 4H), 2.30 (qd, *J* = 6.7, 4.4, 1H), 2.25 (t, *J* = 4.6, 4H), 2.19 (s, 3H), 1.22 (s, 2H), 0.82 (d, *J* = 6.7, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 142.3, 136.0, 129.0, 127.4, 67.6, 66.0, 55.6, 51.3, 21.1, 10.1 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1812.



166

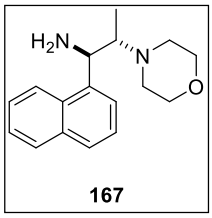
**1-(4-methoxyphenyl)-2-morpholinopropan-1-amine, 166:** [(DPEphos)Rh(COD)]$BF_4$ (4.5 mg, 0.0054 mmol, 2.0 mol %), imine (77 mg, 0.27 mmol, 1.0 equiv.) and dry $CH_3CN$ (72 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added morpholine (120 μL, 1.4 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solution was then concentrated *in vacuo* followed by the addition of 10% aqueous HCl (2 mL) while stirring at room temperature. This was capped and heated to 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was washed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was washed with $CHCl_3$ (50 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine **166** as yellow oil. Purification of the crude diamine by automated silica gel chromatography (24 g, MeOH : 1% $NH_4OH$ / $CHCl_3$ = 0 : 100 to 10 : 90 as gradient) afforded pure diamine **166** as a clear oil in 80% yield (54 mg, 0.22 mmol).

$R_f$ = 0.48 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.26 (d, *J* = 8.3, 2H), 6.88 (d, *J* = 8.7, 2H), 3.94 (d, *J* = 4.4, 1H), 3.54 (t, *J* = 4.5, 4H), 3.37 (s, 3H), 2.30-2.25 (m, 5H), 1.19 (s, 2H), 0.83 (d, *J* = 6.7, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 128.34, 159.03, 137.3, 113.8, 67.6, 66.0, 55.4, 54.8, 51.3, 10.1 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O_2$, 251.1760; found, 251.1759.



167

**2-morpholino-1-(naphthalen-1-yl)propan-1-amine, 167:** [(DPEphos)Rh(COD)]$BF_4$ (3.4 mg, 0.0040 mmol, 2.0 mol %), imine (60 mg, 0.20 mmol, 1.0 equiv.) and dry $CH_3CN$ (53 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added morpholine (88 μL, 1.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir

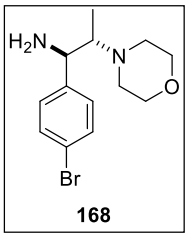
for 24 h at 60 °C. The solution was then concentrated *in vacuo* followed by the addition of 10% aqueous HCl (2 mL). The vial was capped and stirred at 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was rinsed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (10 mm Hg) for 0.5 h to afford the pure diamine **167** as an off white solid in 78% yield (42 mg, 0.16 mmol).

m.p. 103–105 °C.

$^1$H NMR ($C_6D_6$, 500 MHz): δ 8.06 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.39 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 2H), 7.30 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 4.93 (d, *J* = 3.5 Hz, 1H), 3.54 (q, *J* = 4.2 Hz, 4H), 2.60 (qd, *J* = 6.6, 3.5 Hz, 1H), 2.34 (t, *J* = 4.5 Hz, 4H), 1.17 (s, 2H), 0.77 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ 141.21, 135.12, 132.33, 130.07, 128.11, 126.40, 126.35, 126.03, 125.73, 124.01, 68.17, 64.20, 51.95, 51.87, 10.84 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{23}N_2O$, 271.1810; found, 270.1803.



168

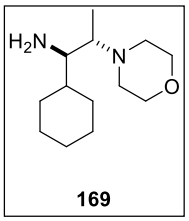
**1-(4-bromophenyl)-2-morpholinopropan-1-amine, 168:** [(DPEphos)Rh(COD)]$BF_4$ (2.5 mg, 0.0030 mmol, 1.0 mol %), imine (100 mg, 0.30 mmol, 1.0 equiv.) and dry $CH_3CN$ (80 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was then added morpholine (79 μL, 0.90 mmol, 3.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. The solution was then concentrated *in vacuo* followed by the addition of 10% aqueous HCl (3 mL). The vial was then capped and stirred at 60 °C for 2 h. The solution was then transferred to a separatory funnel. The reaction vial was rinsed with 10% aqueous HCl (1 mL) followed by $CHCl_3$ (4 mL). The aqueous layer was washed with $CHCl_3$ (10 mL × 3) and was then basified using KOH pellets until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (50 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (10 mm Hg) for 0.5 h to afford the pure diamine **168** as an off white solid in 69% yield (62 mg, 0.21 mmol).

m.p. 63–65 °C.

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.33 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 3.69 (d, *J* = 4.6 Hz, 1H), 3.48 (t, *J* = 5.0 Hz, 4H), 2.15 (td, *J* = 4.2, 1.9 Hz, 4H), 2.09 (qd, *J* = 6.7, 4.6 Hz, 1H), 0.95 (s, 2H), 0.67 (d, *J* = 6.7 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 144.96, 131.86, 129.75, 121.09, 68.03, 66.20, 56.00, 51.64, 10.53 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{13}H_{20}N_2OBr$, 299.0759; found, 299.0761.




**1-cyclohexyl-2-morpholinopropan-1-amine, 169:** [(DPEphos)Rh(COD)]$BF_4$ (8 mg, 0.01 mmol, 1 mol %), imine (257 mg, 1.00 mmol, 1.00 equiv.) and dry $CH_3CN$ (300 μL) 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 (604 μL, 7.00 mmol, 7.00 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. Subjection of the crude aminoimine to silica gel chromatography (125 mL silica, 1% MeOH : 1% $NH_4OH$ : 98% $CHCl_3$ to 2% MeOH : 2% $NH_4OH$ : 96% $CHCl_3$ gradient v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded 1,2-diamine **169** as a pale yellow oil in 58% yield (141 mg, 1.08 mmol).

$R_f$ = 0.53 (1:9 MeOH/$CH_2Cl_2$).

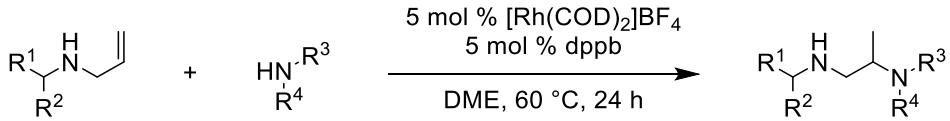
$^1$H NMR ($C_6D_6$, 500 MHz): δ 3.67 – 3.43 (m, 4H), 2.35 (t, *J* = 5.8 Hz, 1H), 2.20 (tq, *J* = 11.4, 6.4, 5.4 Hz, 4H), 2.07 (p, *J* = 6.5 Hz, 1H), 1.69 (td, *J* = 25.1, 23.3, 13.1 Hz, 4H), 1.42 (d, *J* = 9.0 Hz, 2H), 1.29 – 1.05 (m, 3H), 1.01 – 0.84 (m, 2H), 0.82 (d, *J* = 6.6 Hz, 5H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 67.49, 61.10, 56.73, 50.30, 40.43, 30.27, 28.24, 27.03, 26.86, 26.70, 9.60 ppm.

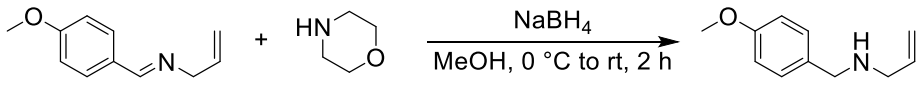
HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{13}H_{27}N_2O$, 227.2123; found, 227.2121.

### 3.3. Experimental Procedures of Chapters 2.2.3 and 2.2.4

**General Secondary Allyl Amine Hydroamination Procedure A:**




[Rh(COD)$_2$BF$_4$] (10 mg, 0.025 mmol, 5.0 mol %), dppb (11 mg, 0.025 mmol, 5.0 mol %), allyl amine (0.50 mmol, 1.00 equiv.), amine nucleophile (2.5 mmol, 5.0 equiv., freshly distilled) and dry DME (144 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude 1,2-diamine as a yellow oil. Purification of the crude diamine by silica gel chromatography (75 mL silica, 3% $NH_4OH$ : 3% MeOH : 94% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine.



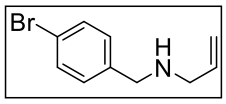

**170**

***N*-(4-methoxyphenyl)prop-2-en-1-amine, 170**: The imine (2.6 mL, 15 mmol, 1.0 equiv.) was added to a 250 mL round bottom flask (precooled at 0 °C) containing MeOH (50 mL). The resulting solution was stirred for 10 min followed by the portion-wise addition of $NaBH_4$ (851.2 mg, 22.5 mmol, 1.5 equiv.) at 0 °C. It was then stirred overnight at room temperature and then concentrated *in vacuo*. The residue was dissolved with $CHCl_3$ (50 mL) and was washed with saturated $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 mL × 3). All organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated *in vacuo* followed by drying under high vacuum (1 mm Hg) for 15 min to afford crude **170** as a yellow oil. Purification of the crude amine by distillation afforded pure amine **170** as a clear oil in 90% yield (2.39 g, 13.5 mmol).

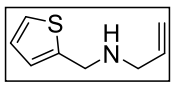
$^1$H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.93 (ddt, *J* = 17.2, 10.2, 6.0 Hz, 1H), 5.19 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.10 (dq, *J* = 10.3, 1.5 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 2H), 3.26 (dt, *J* = 5.9, 1.5 Hz, 2H), 1.25 (s, 1H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 158.46, 136.76, 132.31, 129.20, 115.74, 113.60, 55.08, 52.55, 51.58 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for C11H16NO, 178.1232; found: 178.1230.



***N*-(4-bromophenyl)prop-2-en-1-amine:** Amine was prepared according to the published literature procedure.[326]

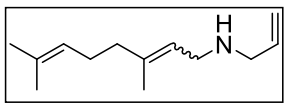


**N-(thiophen-2-ylmethyl)prop-2-en-1-amine:** Amine was prepared according to the synthesis of **170**.

$^1$H NMR (400 MHz, Benzene-$d_6$) δ 6.88 (dt, *J* = 5.1, 1.2 Hz, 1H), 6.79 – 6.68 (m, 2H), 5.74 (ddtd, *J* = 17.1, 10.2, 5.9, 1.0 Hz, 1H), 5.06 (ddt, *J* = 17.2, 2.8, 1.2 Hz, 1H), 4.97 (ddq, *J* = 10.1, 2.4, 1.3 Hz, 1H), 3.65 (s, 3H), 2.99 (d, *J* = 5.9 Hz, 2H) ppm.

$^{13}$C NMR (126 MHz, Benzene-$d_6$) δ 145.25, 137.35, 126.64, 124.63, 124.46, 115.59, 51.64, 47.97 ppm.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_8H_{12}NS$ 153.0612; found 153.0611.



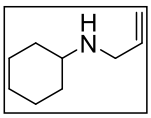
**N-allyl-3,7-dimethylocta-2,6-dien-1-amine, 3aa.** Amine was prepared according to the synthesis of **170** and is reported as a mixture of diastereomers. $R_f$ = 0.24 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) $^1$H NMR (500 MHz, Benzene-$d_6$) δ 5.88 (ddtd, *J* = 17.0, 10.3, 5.8, 2.9 Hz, 1H), 5.37 – 5.29 (m, 1H), 5.16 (dddt, *J* = 14.6, 5.9, 3.9, 1.7 Hz, 2H), 5.01 (dq, *J* = 10.2, 1.6 Hz, 1H), 3.19

– 3.14 (m, 2H), 3.12 (tt, *J* = 5.7, 1.5 Hz, 2H), 2.13 (q, *J* = 7.1 Hz, 1H), 2.09 – 2.00 (m, 3H), 1.68 – 1.62 (m, 5H), 1.54 (d, *J* = 6.0 Hz, 5H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): $^{13}$C NMR (126 MHz, Benzene) δ 138.23, 138.20, 137.15, 136.93, 131.57, 131.28, 125.29, 124.81, 124.73, 124.41, 115.06, 52.38, 52.23, 47.04, 46.95, 40.11, 32.49, 27.12, 27.03, 25.90, 23.58, 17.78, 17.72, 16.34 ppm.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{13}H_{24}N$ 194.1909; found 194.1913.

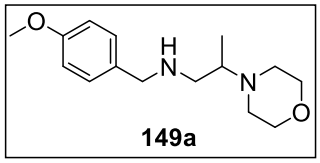


**N-allylcyclohexanamine:** Amine was prepared according to the synthesis of **170.**

$^1$H NMR ($C_6D_6$, 500 MHz) $^1$H NMR (500 MHz, Benzene-$d_6$) δ 5.91 (ddtd, *J* = 16.0, 10.3, 5.8, 1.0 Hz, 1H), 5.18 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.05 – 4.98 (m, 1H), 3.21 – 3.10 (m, 2H), 2.32 (ddd, *J* = 13.4, 9.8, 3.5 Hz, 1H), 1.74 (d, *J* = 10.3 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.52 – 1.46 (m, 1H), 1.14 (dq, *J* = 19.9, 11.4 Hz, 4H), 1.01 (q, *J* = 9.5, 8.9 Hz, 2H), 0.53 (s, 1H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): $^{13}$C NMR (126 MHz, Benzene) δ 138.72, 114.67, 56.27, 49.91, 33.98, 26.71, 25.25 ppm.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_9H_{18}N$ 140.1439; found 140.1436.



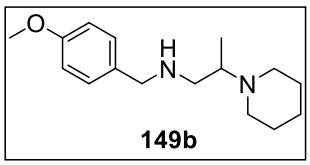

***N*-(4-methoxybenzyl)-2-morpholinopropan-1-amine, 149a:** The general secondary allyl amine hydroamination procedure A was followed using allyl amine **170** (89 mg, 0.50 mmol, 1.00 equiv.) and morpholine (219 μL, 2.5 mmol, 5.0 equiv., freshly distilled). Diamine **149a** was isolated as a pale yellow oil in 70% yield (93 mg, 0.35 mmol).

$R_f$ = 0.56 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.70 (d, *J* = 13.1 Hz, 1H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.52 (dddd, *J* = 19.9, 10.7, 6.1, 3.0 Hz, 4H), 3.34 (s, 3H), 2.58 (dqd, *J* = 8.7, 6.6, 4.8 Hz, 1H), 2.45 (dd, *J* = 11.6, 8.4 Hz, 1H), 2.36 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.28 – 2.16 (m, 3H), 2.10 (ddd, *J* = 11.2, 6.1, 3.1 Hz, 2H), 0.73 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 159.25, 133.54, 129.55, 114.09, 67.56, 59.02, 54.83, 53.68, 51.68, 48.90, 11.82 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2O_2$, 265.1916; found, 265.1913.




***N*-(4-methoxybenzyl)-2-(piperidin-1-yl)propan-1-amine, 149b:** The general secondary allyl amine hydroamination procedure A was followed using allyl amine **170** (89 mg, 0.50 mmol, 1.00 equiv.) and piperidine (247

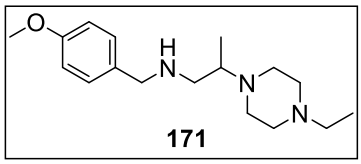
μL, 2.5 mmol, 5.0 equiv., freshly distilled). Diamine **149b** was isolated as a pale yellow oil in 55% yield (72 mg, 0.28 mmol).

$R_f$ = 0.60 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.32 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.72 (d, *J* = 13.1 Hz, 1H), 3.33 (s, 3H), 2.82 – 2.72 (m, 1H), 2.60 – 2.53 (m, 1H), 2.43 (ddd, *J* = 11.5, 4.9, 1.0 Hz, 1H), 2.38 (ddd, *J* = 10.9, 7.2, 3.4 Hz, 2H), 2.24 – 2.12 (m, 2H), 1.77 (brs, 1H), 1.53 – 1.36 (m, 4H), 1.30 (p, *J* = 6.0 Hz, 2H), 0.78 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 159.17, 133.84, 129.53, 114.05, 59.37, 54.82, 53.80, 52.30, 49.44, 27.08, 25.46, 11.42 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{16}H_{27}N_2O$, 263.2123; found, 263.2119.



**171**

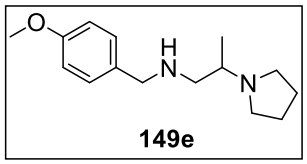
**N-(4-methoxybenzyl)-2-(4-ethylpiperazin-1-yl)propan-1-amine, 171:** The general secondary allyl amine hydroamination procedure B was followed using allyl amine **170** (89 mg, 0.50 mmol, 1.00 equiv.) and 1-ethylpiperazine (318 μL, 2.5 mmol, 5.0 equiv., freshly distilled). Diamine **171** was isolated as yellow oil in 77% yield (112 mg, 0.39 mmol).

$R_f$ = 0.28 (1:8 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.32 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.33 (s, 3H), 2.78 (dqd, *J* = 8.9, 6.6, 4.8 Hz, 1H), 2.60 – 2.41 (m, 5H), 2.41 – 2.28 (m, 6H), 2.24 (qd, *J* = 7.2, 0.9 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 159.26, 133.41, 129.65, 114.08, 58.55, 54.81, 53.82, 53.64, 52.61, 51.96, 12.68, 11.80 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{17}H_{30}N_3O$, 292.2389; found, 292.2384.



**149e**

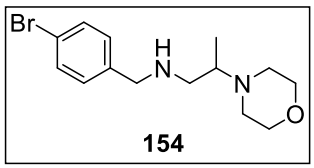
***N*-(4-methoxybenzyl)-2-(pyrrolidin-1-yl)propan-1-amine, 149e:** The general secondary allyl amine hydroamination procedure A was followed using allyl amine **170** (89 mg, 0.50 mmol, 1.00 equiv.) and pyrrolidine (208 μL, 2.5 mmol, 5.0 equiv., freshly distilled). Diamine **149e** was isolated as a pale yellow oil in 80% yield (99 mg, 0.4 mmol).

$R_f$ = 0.62 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.72 (s, 2H), 3.32 (s, 3H), 2.66-2.51 (m, 3H), 2.43-2.36 (m, 4H), 2.18 (br s, 1H), 1.59-1.53 (m, 4H), 1.08 (d, *J* = 6.4 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 159.22, 133.58, 129.59, 114.05, 57.82, 54.79, 54.02, 53.99, 50.27, 23.93, 15.61 ppm.

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



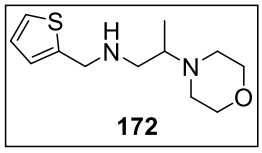
154

**N-(4-bromobenzyl)-2-morpholinopropan-1-amine, 154:** The general secondary allyl amine hydroamination procedure A was followed using substrate (41 mg, 0.2 mmol, 1.00 equiv.) and morpholine (121 μL, 1.4 mmol, 7.0 equiv., freshly distilled). Diamine **154** was isolated as a pale yellow oil in 58% yield (33 mg, 0.11 mmol).

$R_f$ = 0.40 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.31 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 3.55 (ddd, *J* = 9.3, 6.2, 2.9 Hz, 2H), 3.50 (ddd, *J* = 10.8, 6.2, 2.9 Hz, 2H), 3.46 (s, 2H), 2.51 (dqd, *J* = 8.6, 6.6, 4.7 Hz, 1H), 2.32 (dd, *J* = 11.6, 8.5 Hz, 1H), 2.26 – 2.18 (m, 3H), 2.08 (ddd, *J* = 11.1, 6.2, 3.0 Hz, 2H), 1.55 (s, 1H), 0.71 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 140.65, 131.65, 130.02, 120.83, 67.54, 59.05, 53.38, 51.76, 48.88, 11.79 ppm.



172

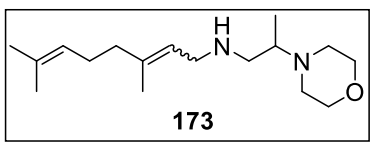
**2-morpholino-N-(thiophen-2-ylmethyl)propan-1-amine, 172:** The general secondary allyl amine hydroamination procedure A was followed using substrate (46 mg, 0.30 mmol, 1.00 equiv.) and morpholine (180 μL, 2.1 mmol, 7.0 equiv., freshly distilled). Diamine **172** was isolated as a pale yellow oil in 76% yield (55 mg, 0.23 mmol).

$R_f$ = 0.37 (1:9 $NH_4OH/CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) $^1$H NMR (500 MHz, Benzene-$d_6$) δ 6.90 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.82 – 6.79 (m, 1H), 6.77 (dd, *J* = 5.0, 3.4 Hz, 1H), 3.81 (dd, *J* = 2.9, 0.8 Hz, 2H), 3.53 (dddd, *J* = 20.3, 10.9, 7.0, 3.1 Hz, 4H), 2.52 (dqd, *J* = 8.5, 6.6, 4.9 Hz, 1H), 2.43 (dd, *J* = 11.5, 8.5 Hz, 1H), 2.34 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.22 (ddd, *J* = 9.4, 5.9, 2.9 Hz, 2H), 2.07 (ddd, *J* = 10.4, 5.8, 3.1 Hz, 2H), 0.70 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 146.00, 128.34, 126.70, 124.53, 67.55, 58.97, 51.60, 48.90, 48.84, 11.74 ppm.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{12}H_{21}N_2OS$ 241.1375; found 241.1372.



173

**3,7-dimethyl-N-(2-morpholinopropyl)octa-2,6-dien-1-amine, 173:** The general secondary allyl amine hydroamination procedure A was followed using substrate (76 mg, 0.40 mmol, 1.00 equiv.) and

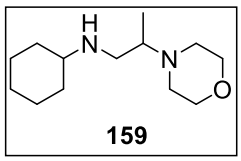
morpholine (242 μL, 2.8 mmol, 7.0 equiv., freshly distilled). Diamine **173** was isolated as a pale yellow oil in 48% yield (52 mg, 0.19 mmol) as a mixture of diastereomers.

$R_f$ = 0.24 (1:9 $NH_4OH/CHCl_3$).

$^1H$ NMR ($C_6D_6$, 500 MHz) $^1H$ NMR (500 MHz, Benzene-$d_6$) δ 5.48 (t, *J* = 6.6 Hz, 1H), 5.26 – 5.17 (m, 1H), 3.57 (ddtd, *J* = 14.1, 10.8, 8.0, 7.1, 3.1 Hz, 4H), 3.31 – 3.24 (m, 2H), 2.60 (dq, *J* = 12.8, 6.5 Hz, 1H), 2.54 (ddd, *J* = 11.5, 8.3, 5.2 Hz, 1H), 2.42 (dt, *J* = 11.5, 4.4 Hz, 1H), 2.32 (ddd, *J* = 9.3, 5.9, 2.8 Hz, 2H), 2.20 – 2.12 (m, 5H), 2.09 – 2.04 (m, 1H), 1.70 – 1.61 (m, 7H), 1.55 (d, *J* = 10.1 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H) ppm.

$^{13}C$ NMR ($C_6D_6$, 125 MHz): $^{13}C$ NMR (126 MHz, Benzene) δ 137.09, 136.87, 131.57, 131.32, 125.65, 124.76, 124.74, 67.61, 59.19, 52.50, 52.36, 49.09, 47.77, 47.67, 40.10, 32.55, 27.26, 27.03, 25.89, 23.61, 17.78, 16.37, 12.04 ppm.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{17}H_{33}N_2O$ 281.2593; found 281.2594.



159

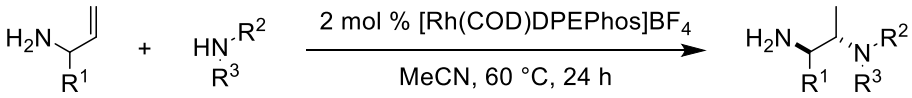
**N-(2-morpholinopropyl)cyclohexanamine, 159:** The general secondary allyl amine hydroamination procedure A was followed using dppp instead of dppb and using substrate (89 mg, 0.50 mmol, 1.00 equiv.) and morpholine (219 μL, 2.5 mmol, 5.0 equiv., freshly distilled). Diamine **159** was isolated as a pale yellow oil in 70% yield (93 mg, 0.35 mmol).

$^1H$ NMR ($C_6D_6$, 500 MHz) $^1H$ NMR (499 MHz, Benzene-$d_6$) δ 3.58 (dtq, *J* = 17.0, 6.2, 3.1 Hz, 4H), 2.58 (dq, *J* = 13.2, 6.5 Hz, 1H), 2.51 – 2.42 (m, 2H), 2.34 (dtd, *J* = 19.6, 7.8, 5.9, 3.3 Hz, 3H), 2.16 (ddd, *J* = 10.4, 6.0, 3.0 Hz, 2H), 1.88 (d, *J* = 11.9 Hz, 1H), 1.81 (d, *J* = 12.2 Hz, 1H), 1.70 (ddd, *J* = 16.9, 8.6, 5.0 Hz, 2H), 1.58 – 1.51 (m, 1H), 1.29 – 1.11 (m, 6H), 0.80 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}C$ NMR ($C_6D_6$, 125 MHz): δ 67.65, 59.28, 57.28, 49.96, 48.92, 34.14, 26.75, 25.34, 25.25, 11.96 ppm.

### 3.4. Experimental Procedures of Chapters 2.2.5 and 2.2.6

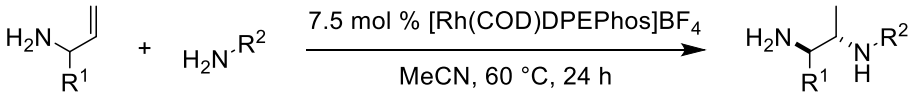
**General Primary Allyl Amine Hydroamination Procedure A:**



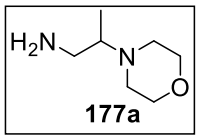

[(DPEphos)Rh(COD)]$BF_4$ (8.4 mg, 0.01 mmol, 2.0 mol %), allylamine substrate (0.50 mmol, 1.0 equiv.), amine nucleophile (3.0 mmol, 3.0 equiv.), and dry $CH_3CN$ (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. The resulting solution was allowed to stir for 2 h at 60 °C. The reaction vial was cooled to room temperature and was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford the crude diamine as yellow oil. The diamine was further dissolved in $CHCl_3$ (10 mL). 6 M HCl was then added to the flask until a pH ~1 was obtained. The organic

layer was then discarded and the aqueous layer was washed with $CHCl_3$ (20 mL × 3). The final aqueous layer was basified with 3 M NaOH until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (30 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford pure diamine.

**General Primary Allyl Amine Hydroamination Procedure B:**




[(DPEphos)Rh(COD)]$BF_4$ (25 mg, 0.030 mmol, 7.5 mol %), allylamine substrate (54 mg, 0.40 mmol, 1.0 equiv.), and dry $CH_3CN$ (100 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added primary amine nucleophile (2.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature. Purification of the crude diamine by silica gel chromatography (10 g silica, 100% $CHCl_3$ to 3% $NH_4OH$ : 1% MeOH: 96% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded the pure diamine after drying under high vacuum (0.05 mm Hg) at 60 °C for 1 h.




**2-morpholinopropan-1-amine, 177a:** [(DPEphos)Rh(COD)]$BF_4$ (14.2 mg, 0.017 mmol, 2.0 mol %), allylamine (64 μL, 0.85 mmol, 1.00 equiv.) and dry $CH_3CN$ (223 μL) 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 (446 μL, 5.1 mmol, 6.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (15 mm Hg) for 10 min to afford crude **8a** as a yellow oil. Purification of the crude diamine by silica gel chromatography (3 X 9 $cm^2$, $NH_4OH$ : $CHCl_3$ (1:20 then 1:15 then 1:6 followed by 1:3) v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:20 $NH_4OH$ : $CHCl_3$ as eluent) afforded pure diamine **177a** as a pale yellow oil in 20% yield (25 mg, 0.17 mmol) after drying under high vacuum (15 mm Hg) for 10 min. A second column of the remained residue (came down the column as mixture of diamine, morpholine and some unknown impurities from the first column) with same conditions gave another batch of diamine **177a** in 25% yield (31 mg, 0.21 mmol). The remaining mixture contained diamine **177a** and morpholine which was kept under high vacuum (15 mm Hg) for 10 min to afford the third batch of diamine **177a** in 27% yield (33 mg, 0.23 mmol). A total of 72% yield (89 mg, 0.61 mmol) of diamine **177a** was obtained. The time slot for keeping the diamine **177a** under the vacuum at 15 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst

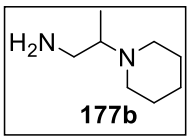
resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.

$R_f$ = 0.34 (1:2 $NH_4OH/CHCl_3$).

$^1H$ NMR ($CDCl_3$, 500 MHz): δ 3.73 – 3.59 (m, 4H), 2.67 – 2.59 (m, 1H), 2.59 – 2.42 (m, 4H), 2.42 – 2.34 (m, 2H), 1.52 (s, 2H), 0.91 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 67.39, 61.62, 48.61, 44.22, 11.40 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_7H_{17}N_2O$, 145.1341; found, 145.1337.



**177b**

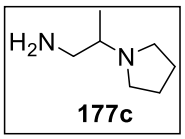
**2-(piperidin-1)propan-1-amine, 177b:** [(DPEphos)Rh(COD)]$BF_4$ (14.2 mg, 0.017 mmol, 2.0 mol %), allylamine (64 μL, 0.85 mmol, 1.00 equiv.) and dry $CH_3CN$ (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added piperidine (504 μL, 5.1 mmol, 6.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (25 mm Hg) for 10 min to afford crude **177b** as a yellow oil. Purification of the crude diamine by silica gel chromatography (3 X 9 $cm^2$, $NH_4OH$ : $CHCl_3$ (1:20 then 1:15 then 1:6 followed by 1:3) v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:20 $NH_4OH$ : $CHCl_3$ as eluent) afforded pure diamine **177b** as a pale yellow oil in 23% yield (28 mg, 0.20 mmol) after drying under high vacuum (15 mm Hg) for 10 min. A second column of the remained residue (came down the column as mixture of diamine, piperidine and some unknown impurities from the first column) with same conditions gave another batch of diamine **177b** in 22% yield (27 mg, 0.19 mmol). The remaining mixture contained diamine **177b** and piperidine which was kept under high vacuum (25 mm Hg) for 10 min to afford the third batch of diamine **177b** in 15% yield (18 mg, 0.13 mmol). A total of 60% yield (73 mg, 0.52 mmol) of diamine **177b** was obtained. The time slot for keeping the diamine **177b** under the vacuum at 25 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.

$R_f$ = 0.31 (1:2 $NH_4OH/CHCl_3$).

$^1H$ NMR ($CDCl_3$, 500 MHz): δ 2.65 (dd, *J* = 11.8, 8.1 Hz, 1H), 2.57 – 2.43 (m, 4H), 2.31 (ddd, *J* = 11.2, 7.2, 3.5 Hz, 2H), 1.66 – 1.45 (m, 6H), 1.41 (q, *J* = 5.9 Hz, 2H), 0.88 (d, *J* = 6.3 Hz, 3H) ppm.

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ 62.02, 49.30, 44.69, 26.60, 24.98, 11.12 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_8H_{19}N_2$, 143.1548; found, 143.1546.



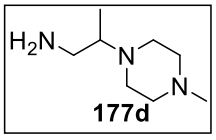

**2-(pyrrolidin-1-yl)propan-1-amine, 177c:** [(DPEphos)Rh(COD)]$BF_4$ (14.2 mg, 0.017 mmol, 2.0 mol %), allylamine (64 μL, 0.85 mmol, 1.00 equiv.) and dry $CH_3CN$ (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added pyrrolidine (284μL, 3.4 mmol, 4.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (15 mm Hg) for 10 min to afford crude **8e** as a yellow oil. Purification of the crude diamine by silica gel chromatography (3 X 9 $cm^2$, $NH_4OH$ : $CHCl_3$ (1:10 followed by 1:8) v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:10 $NH_4OH$ : $CHCl_3$ as eluent) afforded pure diamine **177c** as a pale yellow oil in 37% yield (40 mg, 0.31 mmol) after drying under high vacuum (15 mm Hg) for 10 min. The remaining mixture contained diamine **177c** and pyrrolidine which was kept under high vacuum (15 mm Hg) for 10 min to afford the second batch of diamine **177c** in 8% yield (9 mg, 0.07 mmol). A total of 45% yield (49 mg, 0.38 mmol) of diamine **177c** was obtained. The time slot for keeping the diamine **177c** under the vacuum at 15 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.

$R_f$ = 0.22 (1:2 $NH_4OH/CHCl_3$).

$^1$H NMR ($CDCl_3$, 500 MHz): δ 2.73 (d, *J* = 5.1 Hz, 2H), 2.56 (td, *J* = 5.4, 4.1, 2.6 Hz, 4H), 2.31 (dtd, *J* = 11.5, 6.4, 5.0 Hz, 1H), 1.82 – 1.70 (m, 4H), 1.64 (s, 2H), 1.09 (d, *J* = 6.5 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 60.86, 51.01, 46.49, 23.40, 15.57 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_8H_{17}N_2$, 129.1392; found, 129.1388.




**2-(4-methylpiperazin-1-yl)propan-1-amine, 177d:** [(DPEphos)Rh(COD)]$BF_4$ (14.2 mg, 0.017 mmol, 2.0 mol %), allylamine (64 μL, 0.85 mmol, 1.00 equiv.) and dry $CH_3CN$ (223 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added *N*-methylpiperazine (377μL, 3.4 mmol, 4.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature and concentrated *in vacuo* followed by drying under high vacuum (8 mm Hg) for 10 min to afford crude **177d** as a yellow oil. Purification of the crude diamine by silica gel chromatography (3 X 9 $cm^2$, $NH_4OH$ : $CHCl_3$ (1:20 then 1:15 then 1:6 followed by 1:3) v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol; the column was set up using 1:20 $NH_4OH$ : $CHCl_3$ as eluent) afforded pure diamine **177d** as a pale yellow oil in 35% yield (48 mg, 0.30 mmol) after drying under high vacuum (8 mm Hg) for 10 min. A second column of the remained residue (came down the column as mixture of diamine, *N*-methylpiperazine and some unknown impurities from

the first column) with same conditions gave another batch of diamine **177d** in 22% yield (29 mg, 0.19 mmol). The remaining mixture contained diamine **177d** and *N*-methylpiperazine which was kept under high vacuum (8 mm Hg) for 10 min to afford the third batch of diamine **177d** in 6% yield (8 mg, 0.05 mmol). A total of 63% yield (85 mg, 0.54 mmol) of diamine **177d** was obtained. The time slot for keeping the diamine **177d** under the vacuum at 8 mm Hg is very crucial so that no product is lost to high vacuum. The same reaction is done with 1 mol% of catalyst resulted in no significant difference in yield. Also, an acid-base extraction prior to column does not alter the yield.

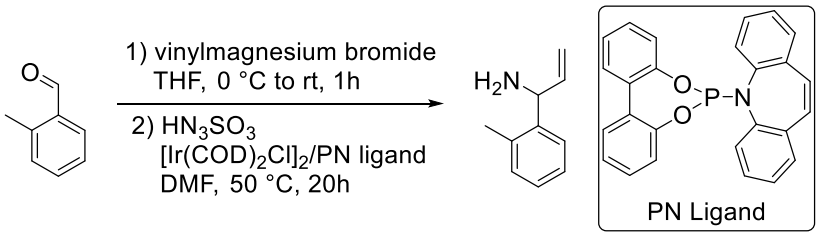
$R_f$ = 0.22 (1:2 $NH_4OH/CHCl_3$).

$^1$H NMR ($CDCl_3$, 500 MHz): δ 2.71 – 2.48 (m, 5H), 2.51 – 2.30 (m, 6H), 2.26 (s, 5H), 0.92 (d, *J* = 6.3 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 60.91, 55.57, 55.46, 46.04, 44.23, 29.66, 11.38 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_8H_{20}N_3$, 158.1657; found, 158.1650.

Amines for the synthesis of **163b**, **166, 168,** and **164** were made using reported procedure.[319] The syntheses of allylamines for the preparation of 1,2-diamines **178**, **179**, **180**, and **181** are given below:




**1-(*o*-tolyl)prop-2-en-1-ol:** To a flame dried 500 mL roundbottom flask charged with stir bar was added *o*-tolualdehyde (2.3 mL, 20 mmol, 1.00 equiv.) in dry THF (100 mL). The flask was placed under nitrogen and cooled to 0 °C. Vinylmagnesium bromide (40 mL, 40 mmol, 2.0 equiv., 1 M solution) was added drop-wise to the flask. The round bottom was warmed to room temperature and stirred for 1 hour. The reaction contents were quenched with the addition of saturated $NH_4Cl$ (75 mL). The organic layer was removed and the aqueous layer was extracted with $Et_2O$ (75 mL × 3 mL). The organic layers were then combined and washed with brine (75 mL × 1), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (20% ethyl acetate: 80% hexanes) gave the product as a colorless oil in 83% yield (2.46 g, 16.6 mmol).

$^1$H NMR ($CDCl_3$, 400 MHz) δ 7.46 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.25 – 7.14 (m, 3H), 6.04 (ddd, *J* = 17.3, 10.3, 5.7 Hz, 1H), 5.42 (dt, *J* = 5.7, 1.5 Hz, 1H), 5.32 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.21 (dt, *J* = 10.3, 1.4 Hz, 1H), 2.36 (s, 3H), 1.88 (s, 1H) ppm.

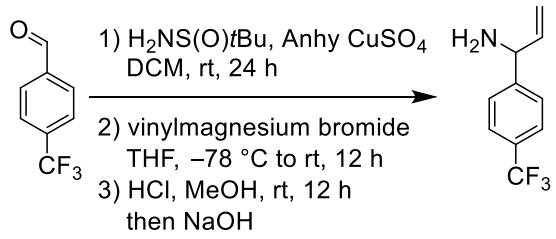
**1-(*o*-tolyl)prop-2-en-1-amine:** To an oven dried 50 mL Schlenk flask charged with stir bar was added $[Ir(cod)_2Cl]_2$ (100 mg, 0.15 mmol, 1.5 mol %), PN ligand (122 mg, 0.3 mmol, 3.0 mol %) in a glove box.

The Schlenk flask was capped with a rubber septum, removed from glove box, and placed under nitrogen. Dry DMF (20 mL) was added via syringe through the septum. The Schlenk flask contents were stirred for 15 minutes. The alcohol (1.48 g, 10 mmol, 1.00 equiv.) was then added via syringe through the septum. The septum was removed, sulfamic acid (971 mg, 10 mmol, 1.00 equiv.) was added under positive flow of nitrogen, and the septum was replaced on the flask. The contents were stirred 20 h at 50 °C. DMF was removed under reduced pressure and the viscous residue was quenched with $NaHCO_3$ (75 mL) and $CH_2Cl_2$ (75 mL) was added. This was stirred for 30 minutes at 50 °C. The organic layer was removed and the aqueous layer extracted with $CH_2Cl_2$ (50 mL × 3). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The reaction mixture was further dissolved in $CHCl_3$ (10 mL). To the reaction mixture was then added 6M HCl dropwise until a pH ~1 was obtained. The organic layer was separated. The aqueous layer was washed with $CHCl_3$ (20 mL × 3) and was then basified using NaOH (2 M) until a pH ~12 was obtained. The aqueous layer was extracted with $CHCl_3$ (60 mL × 3). All organic layers were then combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* followed by drying under high vacuum (10 mm Hg) for 1 h to afford the amine as a yellow viscous oil in 50% yield (736 mg, 5.0 mmol).

$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, *J* = 7.2 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.18 – 7.14 (m, 2H), 6.01 (ddd, *J* = 17.2, 10.3, 5.8 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.13 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.75 (dt, *J* = 5.8, 1.6 Hz, 1H), 2.38 (s, 3H), 1.80 (s, 2H) ppm.

$^{13}$C NMR ($CDCl_3$, 125 MHz): δ 142.08, 141.35, 135.19, 130.34, 126.76, 126.21, 125.53, 113.63, 54.03, 19.09 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{10}H_{14}N$, 148.1126; found, 148.1119.




**1-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine**: To an oven dried 100 mL round bottom flask charged with stir bar was added 2-methylpropane-2-sulfinamide (2.42 g, 20 mmol), anhydrous $CuSO_4$ (7.02 g, 44 mmol, 2.2 equiv.) and dry $CH_2Cl_2$ (40 mL). To this suspension was added 4-(trifluoromethyl)benzaldehyde (3 mL, 22 mmol, 1.1 equiv.) and the resulting mixture was stirred at room temperature for 24 h. After 24 h, it was filtered through Celite, washed with $CH_2Cl_2$ (80 mL). The filtrate was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude imine as a yellow solid. Purification of the crude imine by silica gel chromatography (75 mL silica, 70% $CH_2Cl_2$ : 30% Hexanes) afforded pure

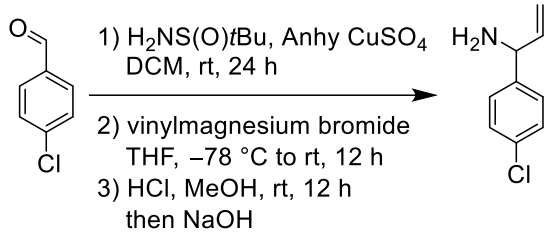
imine as a white solid in 79% yield (4.38 g, 15.8 mmol). To an oven dried 100 mL round bottom flask charged with stir bar was added (*E*)-2-methyl-*N*-(4-(trifluoromethyl)benzylidene)propane-2-sulfinamide (2.77 g, 10 mmol) and dry THF (40 mL). The flask was then cooled to –78 °C using dry ice-acetone bath. To this cooled stirring solution, vinyl Grignard (30 mL, 30 mmol, 3 equiv., 1 M in THF) was added drop-wise via syringe through the septum. During addition, a precipitate was observed. The flask was stirred at –78 °C for 1 h and was gradually warmed to room temperature followed by stirring overnight. After 12 h, the flask was cooled to 0 °C and then the reaction was quenched by the drop-wise addition of saturated $NH_4Cl$. The organic layer was separated and the aqueous layer was extracted with ether (50 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h. The resulting crude material was dissolved in MeOH (35 mL). To this solution was passed freshly generated dry HCl gas until the color of the solution turns black (~1.5 h). The resulting solution was stirred at room temperature for 12 h. The solution containing the amine salt was then concentrated *in vacuo* followed by addition of $CHCl_3$ (20 mL). The crude amine salt was basified with 3 M NaOH until a pH ~12 was obtained. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford pure amine as colorless oil in 70% yield (1.41g, 7 mmol).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 5.96 (ddd, *J* = 16.8, 10.2, 6.3 Hz, 1H), 5.24 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.12 (dt, *J* = 10.2, 1.3 Hz, 1H), 4.56 (d, *J* = 6.2 Hz, 1H), 1.55 (s, 2H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 148.27, 141.45, 129.21 (q, $^2J_{CF}$ = 32.4 Hz), 126.93, 125.33 (q, $^3J_{CF}$ = 3.8 Hz), 124.13 (d, $^1J_{CF}$ = 271.9 Hz), 114.38, 58.01 ppm.

$^{19}$F NMR ($C_6D_6$, 470 MHz) δ –62.81ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{10}H_{11}NF_3$, 202.0844; found, 202.0838.



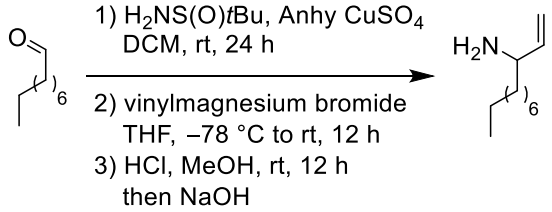

**1-(4-chlorophenyl)prop-2-en-1-amine**: To an oven dried 100 mL round bottom flask charged with stir bar was added 2-methylpropane-2-sulfinamide (6.7 g, 55 mmol, 1.1 equiv.), anhydrous $CuSO_4$ (17.6 g, 110 mmol, 2.2 equiv.) and dry $CH_2Cl_2$ (80 mL). To this suspension was added 4-(chloro)benzaldehyde (7.0 g,

50 mmol, 1.0 equiv.) and the resulting mixture was stirred at room temperature for 24 h. After 24 h, it was filtered through Celite, washed with $CH_2Cl_2$ (80 mL). The filtrate was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude imine as a yellow solid. Purification of the crude imine by silica gel chromatography (75 mL silica, 70% $CH_2Cl_2$ : 30% Hexanes) afforded pure imine as a white solid in 64% yield (7.8 g, 32 mmol). To an oven dried 100 mL round bottom flask charged with stir bar was added (*E*)-N-(4-chlorobenzylidene)-2-methylpropane-2-sulfinamide (7.8 g, 32 mmol) and dry THF (32 mL). The flask was then cooled to 0 °C. To this cooled stirring solution, vinyl Grignard (48 mL, 48 mmol, 1.5 equiv., 1 M in THF) was added drop-wise via syringe through the septum. During addition, a precipitate was observed. The flask was gradually warmed to room temperature followed by stirring overnight. After 12 h, the flask was cooled to 0 °C and then the reaction was quenched by the drop-wise addition of saturated $NH_4Cl$. The organic layer was separated and the aqueous layer was extracted with ether (50 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h. The resulting crude material was dissolved in MeOH (35 mL). To this solution was added 12M HCl (35 mL). The resulting solution was stirred at room temperature for 12 h. The solution was washed with $CHCl_3$ (50 mL × 3). The aqueous layer was basified with 3 M NaOH until a pH ~12 was obtained. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford pure amine **9f** as colorless oil in 52% yield (2.76g, 16.5 mmol).

$^1$H NMR ($C_6D_6$, 500 MHz): δ $^1$H NMR (500 MHz, Benzene-$d_6$) δ 7.12 (d, $J$ = 8.4 Hz, 2H), 6.99 (d, $J$ = 8.6 Hz, 2H), 5.80 – 5.66 (m, 1H), 5.02 (d, $J$ = 17.1 Hz, 1H), 4.89 (d, $J$ = 10.2 Hz, 1H), 4.06 (d, $J$ = 6.2 Hz, 1H), 0.84 (s, 2H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ. $^{13}$C NMR (126 MHz, Benzene) δ 143.64, 142.72, 132.86, 128.71, 128.54, 113.49, 58.03 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_9H_{11}NCl$, 168.0580; found, 168.0578.



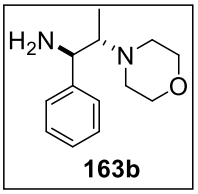

**undec-1-en-3-amine**: To an oven dried 100 mL round bottom flask charged with stir bar was added 2-methylpropane-2-sulfinamide (2.42 g, 20 mmol), anhydrous $CuSO_4$ (7.02 g, 44 mmol, 2.2 equiv.) and dry

$CH_2Cl_2$ (40 mL). To this suspension was added nonanal (3.8 mL, 22 mmol, 1.1 equiv.) and the resulting mixture was stirred at room temperature for 24 h. After 24 h, it was filtered through Celite, washed with $CH_2Cl_2$ (80 mL). The filtrate was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford crude imine as a colorless oil. Purification of the crude imine by silica gel chromatography (75 mL silica, 70% $CH_2Cl_2$ : 30% Hexanes) afforded pure imine as a colorless oil in 87% yield (4.27 g, 17.4 mmol). To an oven dried 100 mL round bottom flask charged with stir bar was added (*E*)-2-methyl-*N*-nonylidenepropane-2-sulfinamide (1.96 g, 8 mmol) and dry THF (40 mL). The flask was then cooled to –78 °C using dry ice-acetone bath. To this cooled stirring solution, vinyl Grignard (30 mL, 30 mmol, 3 equiv., 1 M in THF) was added drop-wise via syringe through the septum. During addition, a precipitate was observed. The flask was stirred at –78 °C for 1 h and was gradually warmed to room temperature followed by stirring overnight. After 12 h, the flask was cooled to 0 °C and then the reaction was quenched by the drop-wise addition of saturated $NH_4Cl$. The organic layer was separated and the aqueous layer was extracted with ether (50 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h. The resulting crude material was dissolved in MeOH (35 mL). To this solution was passed freshly generated dry HCl gas until the color of the solution turns black (~1.5 h). The resulting solution was stirred at room temperature for 12 h. The solution containing the amine salt was then concentrated *in vacuo* followed by addition of $CHCl_3$ (20 mL). The crude amine salt was basified with 3 M NaOH until a pH ~12 was obtained. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 mL × 3). The organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated *in vacuo* followed by drying under high vacuum (0.05 mm Hg) for 1 h to afford pure amine as colorless oil in 82% yield (1.11 g, 6.56 mmol).

$^1$H NMR ($CDCl_3$, 400 MHz) δ 5.77 (ddd, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.09 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.26 (q, *J* = 6.6 Hz, 1H), 1.46 – 1.06 (m, 16H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): δ 143.67, 113.09, 54.52, 37.63, 31.87, 29.63, 29.55, 29.27, 26.07, 22.66, 14.11 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{11}H_{24}N$, 170.1909; found, 170.1909.



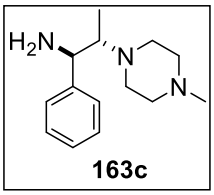
**163b**

**2-morpholino-1-phenylpropan-1-amine, 163b:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (67 mg, 0.50 mmol, 1.00 equiv.) and morpholine (87 μL, 1.0 mmol, 2.0 equiv., freshly distilled). Diamine **163b** was isolated as a pale yellow oil in 84% yield (93 mg, 0.42 mmol).

$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.39 – 7.28 (m, 4H), 7.25 – 7.20 (m, 1H), 4.16 (d, *J* = 4.4 Hz, 1H), 3.66 (ddd, *J* = 5.4, 3.7, 1.4 Hz, 4H), 2.63 (qd, *J* = 6.8, 4.4 Hz, 1H), 2.51 (tq, *J* = 11.3, 5.7, 4.7 Hz, 4H), 2.47 (brs, 2H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 145.29, 128.25, 127.41, 126.79, 67.53, 65.89, 55.87, 51.19, 10.10 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{13}H_{21}N_2O$, 221.1654; found, 221.1645.



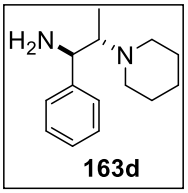
**163c**

**2-morpholino-1-phenylpropan-1-amine, 163c:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (55 mg, 0.40 mmol, 1.00 equiv.) and *N*-methylpiperazine (120 μL, 1.2 mmol, 3.0 equiv., freshly distilled) and was run for 4 hours. Diamine **163c** was isolated as a pale yellow oil in 65% yield (59 mg, 0.25 mmol).

$^1$H NMR ($CDCl_3$, 500 MHz) $^1$H NMR (500 MHz, Benzene-$d_6$) δ 7.33 (d, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 4.01 (d, *J* = 4.4 Hz, 1H), 2.50 – 2.38 (m, 5H), 2.24 (s, 4H), 2.11 (s, 3H), 1.32 (s, 2H), 0.85 (d, *J* = 6.7 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ $^{13}$C NMR (126 MHz, Benzene) δ 145.60, 128.19, 127.47, 126.69, 65.53, 56.40, 56.14, 50.56, 46.31, 10.49 ppm.

HRMS (EI-TOF) *m/z*: [M] calculated for $C_{14}H_{24}N_3$ 234.1970; found 234.1968.



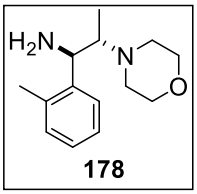
**163d**

**2-morpholino-1-phenylpropan-1-amine, 163d:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (53 mg, 0.40 mmol, 1.00 equiv.) and piperidine (37 μL, 0.44 mmol, 1.1 equiv., freshly distilled) and was run for 8 hours. Diamine **163d** was isolated as a pale yellow oil in 57% yield (48 mg, 0.22 mmol).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.26 (d, *J* = 6.9 Hz, 2H), 7.13 – 6.97 (m, 3H), 3.87 (d, *J* = 4.2 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.33 – 2.18 (m, 4H), 1.28 (d, *J* = 57.9 Hz, 10H), 0.84 (d, *J* = 6.4 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 145.93, 127.95, 127.27, 126.44, 66.04, 57.19, 51.45, 26.88, 25.12, 10.23 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2$, 219.1861; found, 219.1854.



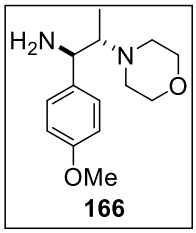
**178**

**2-morpholino-1-(*o*-tolyl)propan-1-amine, 178:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (113 mg, 0.85 mmol, 1.00 equiv.) and morpholine (223 μL, 1.2 mmol, 3.0 equiv., freshly distilled) and was run for 24 hours. Diamine **178** was isolated as a pale yellow oil in 75% yield (149 mg, 0.64 mmol).

$^1$H NMR ($C_6D_6$, 500MHz) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.10 (td, *J* = 7.4, 1.4 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 4.26 (d, *J* = 3.8 Hz, 1H), 3.54 (t, *J* = 4.6 Hz, 4H), 2.27 (dq, *J* = 12.2, 3.8, 2.9 Hz, 5H), 2.14 (s, 3H), 1.08 (s, 2H), 0.85 (d, *J* = 6.7 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 142.94, 134.98, 130.51, 127.75, 126.67, 126.13, 67.60, 63.14, 51.79, 51.29, 19.47, 10.06 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O$, 235.1810; found, 235.1806.



**166**

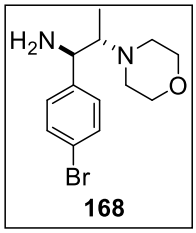
**1-(4-methoxyphenyl)-2-morpholinopropan-1-amine, 166:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (82 mg, 0.50 mmol, 1.00 equiv.) and morpholine (175 μL, 2.0 mmol, 4.0 equiv., freshly distilled) and was run for 24 hours. Diamine **166** was isolated as an off white solid in 80% yield (100 mg, 0.40 mmol).

m.p. 63–65 °C.

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.27 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 3.95 (d, *J* = 4.1 Hz, 1H), 3.55 (dd, *J* = 5.6, 3.8 Hz, 4H), 3.36 (s, 3H), 2.35 – 2.20 (m, 5H), 1.37 (s, 2H), 0.84 (d, *J* = 6.7 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 159.04, 137.03, 128.37, 113.78, 67.58, 65.96, 55.34, 54.82, 51.29, 10.16 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{14}H_{23}N_2O_2$, 251.1760; found, 251.1754.



**168**

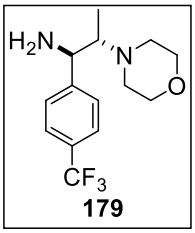
**1-(4-bromophenyl)-2-morpholinopropan-1-amine, 168:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (106 mg, 0.50 mmol, 1.00 equiv.) and morpholine (87 μL, 1.0 mmol, 2.0 equiv., freshly distilled). Diamine **168** was isolated as an off white solid in 80% yield (120 mg, 0.40 mmol).

m.p. 64–66 °C.

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.35 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.70 (d, *J* = 4.6 Hz, 1H), 3.57 – 3.41 (m, 4H), 2.16 (dd, *J* = 6.0, 3.6 Hz, 4H), 2.09 (qd, *J* = 6.7, 4.6 Hz, 1H), 0.96 (s, 2H), 0.68 (d, *J* = 6.7 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 500 MHz) δ 144.33, 131.30, 129.19, 120.55, 67.46, 65.60, 55.34, 51.08, 9.97 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{13}H_{20}N_2OBr$, 299.0759; found, 299.0755.



**179**

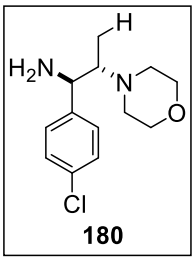
**1-(4-(trifluoromethyl)phenyl)-2-morpholinopropan-1-amine, 179:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (64 mg, 0.32 mmol, 1.00 equiv.) and morpholine (56 μL, 0.64 mmol, 2.0 equiv., freshly distilled). Diamine **179** was isolated as a clear oil in 91% yield (84 mg, 0.29 mmol).

$^1$H NMR ($C_6D_6$, 500 MHz): δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 3.75 (d, *J* = 4.7 Hz, 1H), 3.48 (t, *J* = 4.6 Hz, 4H), 2.21 – 2.08 (m, 5H), 1.10 – 0.92 (m, 2H), 0.66 (d, *J* = 6.7 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 149.63, 128.95 (q, $^2J_{CF}$ = 32.1 Hz), 125.25 (d, $^1J_{CF}$ = 271.7 Hz), 125.07 (q, $^3J_{CF}$ = 3.8 Hz), 67.42, 65.59, 55.65, 51.00, 9.91 ppm.

$^{19}$F NMR ($C_6D_6$, 470 MHz) δ –62.23 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{14}H_{20}N_2OF_3$, 289.1528; found, 289.1524.

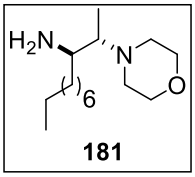


**180**

**1-(4-chlorophenyl)-2-morpholinopropan-1-amine, 180:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (64 mg, 0.38 mmol, 1.00 equiv.) and morpholine (70 μL, 0.8 mmol, 2.0 equiv., freshly distilled). Diamine **180** was isolated as a clear oil in 81% yield (78 mg, 0.31 mmol).

$^1$H NMR (500 MHz, Benzene-$d_6$) δ 7.19 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 2H), 3.74 (d, *J* = 4.6 Hz, 1H), 3.52 – 3.47 (m, 4H), 2.17 (dd, *J* = 5.4, 3.1 Hz, 4H), 2.15 – 2.09 (m, 1H), 1.06 (s, 2H), 0.69 (d, *J* = 6.7 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 143.89, 132.37, 128.81, 128.33, 67.46, 65.67, 55.33, 51.07, 9.98 ppm.



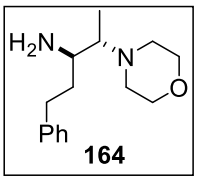
**181**

**2-morpholinoundecan-3-amine, 181:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (85 mg, 0.50 mmol, 1.00 equiv.) and morpholine (175 μL, 2.0 mmol, 4.0 equiv., freshly distilled) and was run for 24 hours. (175 μL, 2.0 mmol, 4.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. Diamine **181** was isolated as a clear oil in 80% yield (103 mg, 0.40 mmol).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 3.59 (ddd, *J* = 5.3, 3.9, 2.5 Hz, 4H), 2.68 (ddd, *J* = 8.2, 5.2, 3.0 Hz, 1H), 2.27 (tq, *J* = 11.0, 6.3, 5.0 Hz, 4H), 1.96 (qd, *J* = 6.6, 5.2 Hz, 1H), 1.48 (dd, *J* = 7.5, 3.0 Hz, 2H), 1.40 – 1.26 (m, 11H), 1.21 (dt, *J* = 10.0, 8.2 Hz, 1H), 0.97 – 0.88 (m, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.77(s, 2H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz): δ 67.62, 64.37, 52.18, 50.80, 35.42, 32.39, 30.45, 30.18, 29.87, 27.05, 23.17, 14.42, 9.52 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calcd for $C_{15}H_{33}N_2O$, 257.2593; found, 257.2595.




**4-morpholino-1-phenylpentan-3-amine, 164:** The general primary allyl amine hydroamination procedure A was followed using allyl amine substrate (81 mg, 0.50 mmol, 1.00 equiv.) and morpholine (175 μL, 2.0 mmol, 4.0 equiv., freshly distilled) and was run for 24 hours. Diamine **164** was isolated as a clear oil in 75% yield (93 mg, 0.38 mmol).

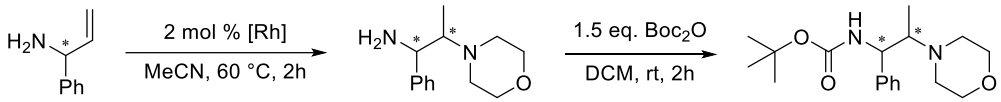
$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.22 – 7.17 (m, 4H), 7.12 – 7.07 (m, 1H), 3.60 – 3.48 (m, 4H), 2.75 (ddd, *J* = 13.6, 9.8, 5.1 Hz, 1H), 2.60 – 2.51 (m, 2H), 2.16 (dtdd, *J* = 15.4, 11.2, 7.2, 3.5 Hz, 4H), 1.89 (dt, *J* = 13.1, 6.5 Hz, 1H), 1.82 (dddd, *J* = 13.3, 10.2, 7.1, 3.3 Hz, 1H), 1.42 (dddd, *J* = 13.7, 9.5, 8.8, 5.1 Hz, 1H), 0.75 (d, *J* = 6.6 Hz, 3H) ppm.

$^{13}$C NMR ($C_6D_6$, 125 MHz) δ 143.14, 128.83, 128.69, 126.08, 67.58, 64.51, 51.79, 50.52, 37.27, 33.14, 9.40 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2O$, 249.1967; found, 249.1969.

**Determining the Enantiospecificity of the Hydroamination reaction:**

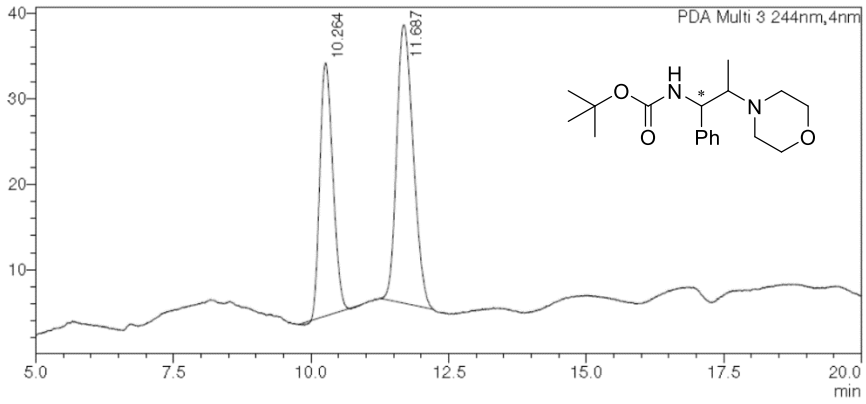
Racemic 1-phenylprop-2-en-1-amine was synthesized according to the above procedure. Enantioenriched substrate was synthesized using the general procedure for the synthesis of primary amines with (S)-2-methylpropane-2-sulfinamide in a 1:3 enantiomeric ratio.[326]



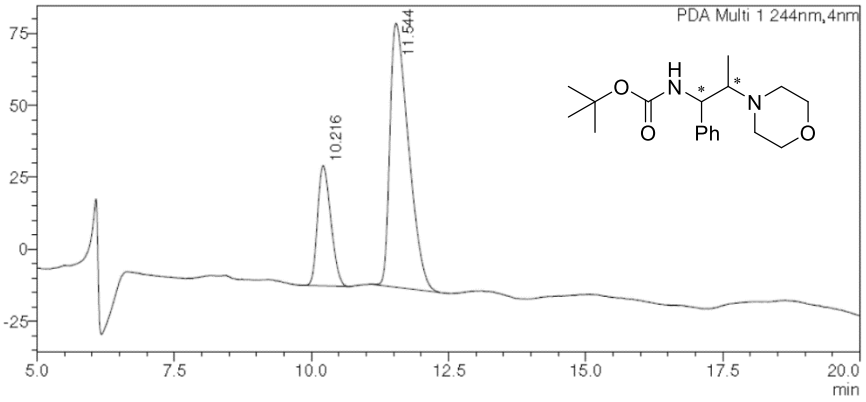

The enantiomeric ratio of the corresponding hydroamination product was determined by chiral HPLC of the BOC-protected products. Racemic and enantioenriched products were synthesized according to the general allylamine hydroamination procedure A. After isolation, 1,2-diamines **163b** and **163b*** were subjected to BOC-protection conditions. The 1,2-diamine substrate (49 mg, 0.224 mmol, 1.0 equiv.) was dissolved in DCM (225 μL, 1M). $Boc_2O$ (73 mg, 0.45 mmol, 1.5 equiv.) was added dropwise and stirred at room temperature for 2 hours. The enantiomeric ratio of both products was determined by chiral HPLC (IC-3 column, 3% IPA in hexanes (99:1 hexanes: $Et_2NH$), λ = 254 nm, flow rate = 1.00 mL/min).

$^1$H NMR ($CDCl_3$, 500 MHz) δ 7.30 (d, *J* = 7.3 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 3H), 5.46 (s, 1H), 4.78 (s, 1H), 3.64 (s, 4H), 2.82 – 2.72 (m, 1H), 2.47 (s, 4H), 1.44 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H) ppm.

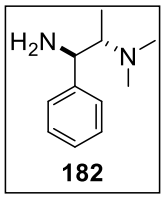
$^{13}$C NMR ($CDCl_3$, 126 MHz) δ 155.71, 141.07, 128.33, 127.17, 127.10, 79.74, 67.54, 63.89, 56.35, 50.92, 28.65, 11.16 ppm.




| $t_r$ (min) | Area (%) |
|---|---|
| 10.264 | 41.574 |
| 11.687 | 58.426 |




| $t_r$ (min) | Area (%) |
|---|---|
| 10.216 | 24.487 |
| 11.544 | 75.513 |


182

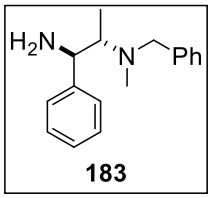
**$N^2$,$N^2$-dimethyl-1-phenylpropane-1,2-diamine, 182:** [(DPEphos)Rh(COD)]$BF_4$ (8.5 mg, 0.010 mmol, 5.0 mol %) and amine substrate (27 mg, 0.20 mmol, 1.0 equiv.) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added *N*,*N*-dimethylamine (1.0 mL, 1.4M in THF, 1.4 mmol, 7.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature. The reaction mixture was then concentrated *in vacuo* to afford the crude diamine **182** as yellow oil. Purification of the crude diamine by silica gel chromatography (10 g silica, 100% $CHCl_3$ to 3% $NH_4OH$ : 1% MeOH : 96% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **182** as a pale yellow oil in 80% yield (30 mg, 0.17 mmol).

$R_f$ = 0.12 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.34 (d, J = 7.7 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 4.00 (d, J = 4.8 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.07 (s, 6H), 1.47 (s, 2H), 0.86 (d, J = 6.6 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 145.55, 128.27, 127.45, 126.73, 66.32, 56.81, 42.90, 10.23 ppm.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C11H19N2, 179.1548; found, 179.1546.



183

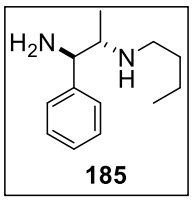
**(1R,2S)-$N^2$-benzyl-$N^2$-methyl-1-phenylpropane-1,2-diamine, 183:** [(DPEphos)Rh(COD)]$BF_4$ (8.5 mg, 0.010 mmol, 5.0 mol %), amine substrate (54 mg, 0.40 mmol, 1.0 equiv.), and dry $CH_3CN$ (100 μL) were added to an oven-dried 4 mL vial equipped with a stir bar in the glove box. To the reaction mixture was added *N*-methyl-*N*-benzylamine (242 mg, 2.0 mmol, 5.0 equiv.). The resulting solution was allowed to stir for 24 h at 60 °C. After 24 h, the reaction vial was cooled to room temperature. The reaction mixture was then concentrated *in vacuo* to afford the crude diamine **183** as yellow oil. Purification of the crude diamine by silica gel chromatography (10 g silica, 100% $CHCl_3$ to 3% $NH_4OH$ : 97% $CHCl_3$ to 3% $NH_4OH$ : 3% MeOH: 97% $CHCl_3$ v/v prepared by extracting saturated $NH_4OH$ with $CHCl_3$, removing aqueous layer, and adding methanol) afforded pure diamine **183** as a pale yellow oil in 31% yield (32 mg, 0.13 mmol).

$R_f$ = 0.35 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.22 (d, J = 6.8 Hz, 4H), 7.14 (d, J = 8.3 Hz, 8H), 7.11 – 7.04 (m, 4H), 3.77 (d, J = 6.9 Hz, 1H), 3.41 (d, J = 13.6 Hz, 1H), 3.34 (d, J = 13.6 Hz, 1H), 2.67 (p, J = 6.7 Hz, 1H), 1.98 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, $CDCl_3$) δ 145.38, 140.15, 128.63, 128.19, 128.16, 127.16, 126.76, 126.74, 63.87, 59.10, 58.72, 37.90, 10.02 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_{17}H_{23}N_2$, 255.1861; found, 255.1862.



185

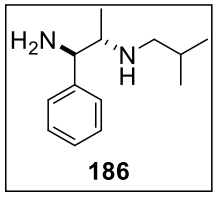
**$N^2$-butyl-1-phenylpropane-1,2-diamine, 185:** The general primary allyl amine hydroamination procedure B was followed using allyl amine substrate (54 mg, 0.40 mmol, 1.0 equiv.) and *N*-butylamine (146 mg, 2.0 mmol, 5.0 equiv.). Diamine **185** was isolated as a pale yellow oil in 67% yield (57 mg, 0.28 mmol).

$R_f$ = 0.20 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.34 (d, J = 7.6 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.93 (d, J = 4.1 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.51 (dt, J = 11.2, 7.0 Hz, 1H), 2.44 (dt, J = 11.2, 7.0 Hz, 1H), 1.44 – 1.30 (m, 8H), 1.27 – 1.21 (m, 2H), 0.88 – 0.83 (m, 6H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 144.90, 128.31, 127.63, 126.91, 59.51, 58.57, 47.59, 33.09, 20.87, 15.34, 14.30 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_{13}H_{23}N_2$, 207.1861; found, 207.1871.



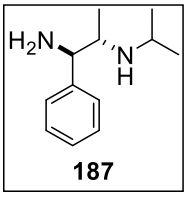

**$N^2$-isobutyl-1-phenylpropane-1,2-diamine, 186:** The general primary allyl amine hydroamination procedure B was followed using allyl amine substrate (54 mg, 0.40 mmol, 1.0 equiv.) and *N*-isobutylamine (146 mg, 2.0 mmol, 5.0 equiv.). Diamine **186** was isolated as a pale yellow oil in 58% yield (49 mg, 0.24 mmol).

$R_f$ = 0.20 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.34 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.86 (d, J = 4.3 Hz, 1H), 2.73 – 2.67 (m, 1H), 2.34 (dd, J = 11.2, 6.5 Hz, 1H), 2.25 (dd, J = 11.2, 6.8 Hz, 1H), 1.51 (dp, J = 13.3, 6.6 Hz, 1H), 1.10 (s, 3H), 0.88 – 0.82 (m, 9H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 144.89, 128.31, 127.61, 126.92, 59.55, 58.57, 55.98, 29.23, 20.91, 15.44 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_{13}H_{23}N_2$, 207.1861; found, 207.1871.



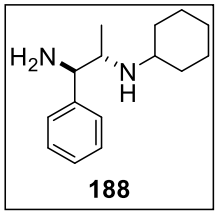

**$N^2$-isopropyl-1-phenylpropane-1,2-diamine, 187:** The general primary allyl amine hydroamination procedure B was followed using allyl amine substrate (54 mg, 0.40 mmol, 1.0 equiv.), and *N*-isopropylamine (120 mg, 2.0 mmol, 5.0 equiv.). Diamine **187** was isolated as a pale yellow oil in 60% yield (47 mg, 0.24 mmol).

$R_f$ = 0.13 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.31 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.81 (d, J = 4.0 Hz, 1H), 2.85 (qd, J = 6.4, 4.2 Hz, 1H), 2.71 (hept, J = 6.2 Hz, 1H), 0.98 (s, 3H), 0.92 (d, J = 6.2 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 144.00, 128.37, 127.56, 127.03, 58.37, 55.93, 46.22, 23.21, 22.69, 14.84 ppm.

HRMS (ESI-TOF) *m/z*: [M+$H^+$] calculated for $C_{12}H_{21}N_2$, 193.1705; found, 193.1710.



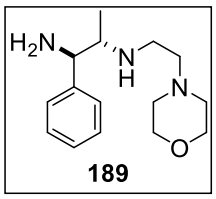

**$N^2$-cyclohexyl-1-phenylpropane-1,2-diamine, 188:** The general primary allyl amine hydroamination procedure B was followed using allyl amine substrate (54 mg, 0.40 mmol, 1.0 equiv.) and *N*-cyclohexylamine (200 mg, 2.0 mmol, 5.0 equiv.). Diamine **188** was isolated as a pale yellow oil in 66% yield (62 mg, 0.27 mmol).

$R_f$ = 0.12 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.34 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 3.89 (d, J = 4.0 Hz, 1H), 2.94 (qd, J = 6.4, 4.2 Hz, 1H), 2.43 (tt, J = 10.0, 3.7 Hz, 1H), 1.85 – 1.45 (m, 13H), 1.20 – 1.04 (m, 5H), 1.02 – 0.90 (m, 4H), 0.85 (d, J = 6.5 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 144.84, 128.28, 127.65, 126.89, 59.08, 55.60, 53.94, 34.56, 34.23, 26.61, 25.47, 25.33, 15.89 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{25}N_2$, 233.2018; found, 233.2013.



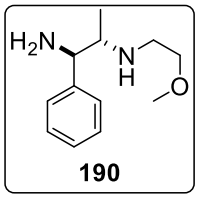

**N$^2$-(2-morpholinoethyl)-1-phenylpropane-1,2-diamine, 189:** The general primary allyl amine hydroamination procedure B was followed using allyl amine substrate (54 mg, 0.40 mmol, 1.0 equiv.) and 2-morpholinoethylamine (260 mg, 2.0 mmol, 5.0 equiv.). Diamine **189** was isolated as a pale yellow oil in 58% yield (62 mg, 0.24 mmol).

$R_f$ = 0.28 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.33 (d, J = 7.2 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 3.82 (d, J = 5.0 Hz, 1H), 3.47 (q, J = 4.1 Hz, 4H), 2.73 – 2.65 (m, 1H), 2.57 – 2.50 (m, 1H), 2.44 (ddd, J = 11.7, 6.8, 5.3 Hz, 1H), 2.28 – 2.14 (m, 3H), 2.07 (t, J = 4.4 Hz, 4H), 1.43 (s, 3H), 0.95 (d, J = 6.4 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 144.96, 128.39, 127.66, 127.04, 67.11, 59.96, 59.28, 58.60, 53.90, 44.33, 15.75 ppm.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{15}H_{26}N_3O$, 264.2076; found, 264.2084.




**N$^2$-(2-methoxyethyl)-1-phenylpropane-1,2-diamine, 190:** The general primary allyl amine hydroamination procedure B was followed using allyl amine substrate (54 mg, 0.40 mmol, 1.0 equiv.) and 2-methoxyethylamine (150 mg, 2.0 mmol, 5.0 equiv.). Diamine **190** was isolated as a pale yellow oil in 70% yield (59 mg, 0.28 mmol).

$R_f$ = 0.13 (1:9 $NH_4OH$ /$CHCl_3$).

$^1$H NMR ($C_6D_6$, 500 MHz) δ 7.33 (d, J = 7.2 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 3.87 (d, J = 4.1 Hz, 1H), 3.25 (t, J = 5.3 Hz, 2H), 3.06 (s, 3H), 2.77 – 2.66 (m, 2H), 2.61 (dt, J = 12.0, 5.2 Hz, 1H), 1.27 (s, 3H), 0.85 (d, J = 6.4 Hz, 3H) ppm.

$^{13}$C NMR (126 MHz, Benzene) δ 144.75, 128.28, 127.61, 126.87, 72.66, 59.39, 58.47, 58.45, 47.49, 14.95.

HRMS (ESI-TOF) *m/z*: [M+H$^+$] calculated for $C_{12}H_{21}N_2O$, 209.1654; found, 209.1660.

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