NOVEL SYNTHETIC ROUTES TO COMPLEX AMINES: THE CATALYTIC

HYDROAMINATION OF ALKYNES AND HYDROIMINATION OF ALLENES

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MASTER OF SCIENCE

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ABSTRACT

Amines are valuable targets for synthesis in contexts of both research and industrial applications. This work proposes two atom-economical methods—hydroamination (HAM) and hydroimination (HIM)—as C-N bond formation strategies. A nickel-(N-heterocyclic carbene) catalyst system was developed to carry out HAM of internal, unactivated alkynes with aryl amines and cyclic secondary amines. It was demonstrated that the Ni-NHC catalyst was capable of promoting both HAM at room temperature and transfer hydrogenation to produce α-branched aryl amines. These two procedures were performed by the same catalyst to demonstrate an elegant 1-pot, multi-transformation protocol. Separately, optimization of a Rh-HIM catalyst system for the combination of monosubstituted allenes and aromatic N-H-ketimine was carried out to favor high conversion of substrates to the linear HIM product rather than [3+2] annulation. Both HAM and HIM C-N bond formation methods were found to be successful and capable of good conversion and selectivity for their respective products.

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank those whose efforts have made possible my success both as a graduate student here at NDSU and as a scientist in the works to follow. When I moved to uncharted territory in Fargo, ND from Hampshire, IL to pursue a new opportunity and way of life, little regard was made to the future stresses and obstacles in the life of a graduate student in a place where I had not yet any friends. I am pleased to say that I was met by the faculty and students of my department as well as the surrounding community warmly and supportively. I find solace in the fact that the fellow scientists I have worked with these past three years were not only professional in their work but also humans capable of sardonic humor and optimism in the face of the seemingly impossible.

I owe much credit to my success here for the opportunities offered by Dr. Zhao. In his group I was able to establish a research space highly conducive to discovery and strongly bearing my own personal affectations. Additionally, my groupmates—Raj, Praveen, Sword, and Sunil— were indispensable. I offer particular respects to Raj for his preliminary achievements in my projects without which this work would not be possible.

The faculty and staff of the chemistry department are also owed much thanks here for keeping the department running effectively no matter the cost. I deeply appreciate that my committee has remained so highly supportive and understanding as teachers and advisors throughout my time here. Amy, Dionna, and Tina have also proved invaluable as generous resources when I was faced with challenges I could not address alone.

DEDICATION

It is not without difficulty to dedicate this work to a sole individual who alone inspired me to continue pursuing my graduate degree for many have assumed that role in my time here. I feel that in total, there have been two people along the way who I have steadily relied upon to confide in and look for hardy example of what it means to be a graduate student when I, all too often, lost perspective. These wonderful souls are Kaitlin Dailey and Eric Serum.

When I first came to NDSU the summer before my enrollment, I felt myself in an abyss of new names and faces, one of which was Eric. His bombastic and sometimes overly charismatic visage invited me to feel maybe I could also find a home in Fargo, ND among people like myself. I would later become roommates with Eric and as a result we have shared many memories and hours of shop-talk together that I will carry with me in the future. While we had many similar interests outside of school, I believe his example of young-person-turned-professional through graduate school was key in making my own similar transformation that much more obtainable.

To Kaitlin I feel a similar gratitude as a fellow grad-student always willing to discuss troubles like a closed stockroom or a broken instrument. However, my career and personal debt to this young woman are far deeper and beyond any means of repayment. If Eric is the force that lured me to Fargo in the first place, Kait is what has stood by and kept me here to complete my path. Through graduate school, we have come to rely on one another as partners fighting the same enemy as we find our place in the world. I can only hope we remain united in such terms as the future pulls us towards new callings and places.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

CHAPTER 1: AN INTRODUCTION TO CATALYTIC HYDROAMINATION AND NICKEL-CATALYZED HYDROAMINATION OF ALKYNES WITH ARYL AMINES

Abstract

α-Branced-aryl-amines are valuable targets for organic synthesis in contexts of both research and industry and elegant methods for their synthesis are of equal value. Classical methods fail to universally accommodate factors of atom-economy, selectivity, reactivity, and functional-group tolerance. Hydroamination (HAM) offers a highly atom-economical approach to synthesis of amines and has been carried out by a variety of highly-active, precious late-transition metals. HAM has also been facilitated with non-precious metals like Fe, Ni, Cu, and Zn. The goal of this work is to provide an alternative to precious-metal HAM of alkynes with aryl amines by modification of Ni using the novel chemistry of N-heterocyclic carbene (NHC) ligands. After optimization of the catalyst system, a variety of HAM-substrate combinations were attempted and isolation strategies were explored and optimized. The Ni-NHC catalyst was also adapted to be used as a one-pot room-temperature-HAM-reduction catalyst to selectively produce α-branched-aryl amines under mild conditions.

Introduction

Among all things carbon that can make and take the essence of life from pharmaceuticals to pesticides, nitrogen has a special place as guest and intermediary between atoms and molecules big and small. From the dozens of different configurations capable between carbon and nitrogen from the simple amine to the elegant xanthine, it is obvious nitrogen holds stakes of great importance across the board. Interestingly the element nitrogen only makes up about 3% of the human body but holds tremendous importance in safeguarding the genetic information which ties the individual to ancestors past and all that implies as deoxyribonucleic acid or DNA.[1]

Nitrogen also constitutes the backbone of proteins which garner the gift of locomotion. Its implications are not limited to the individual organism's components; nitrogen also has far broader impacts on society and culture. The more recent wars in human history—fought with gunpowder—have been driven by the stuff in the form of nitrates. It is speculated the Nazi regime would have fallen far sooner if not for the ingenious work of Fritz Haber and Carl Bosch to fixate ammonia from the air.[2] The pain relief delivered from drugs like morphine and Prozac would not be possible without the masterful synthesis which can incorporate nitrogen to a contrived string of carbon. The egalitarian opportunity to enjoy a lifestyle where synthetic fabrics can enshroud one's person in a meaningful and personalized way owes all credit to the development of synthetic nitrogen-containing polymers like Wallace Carrothers's nylon.[3] With the multitude of advancements through evolution and research, nitrogen plays so many roles now it is difficult to imagine what may come of it in the future. The following body of research presented herein is, in essence, an effort to develop the means to eventually uncover and embrace a part of that future.

From these illustrative prepositions, it is clearly the ability to form bonds to nitrogen bonds that enables synthetic chemistry to create and explore new potentialities for nitrogen-containing molecules. So important is this task, that C-N bond formation comprises a majority of all reactions by process chemistry in top drug companies.[4] Such a large emphasis is not a meager call for innovation and demonstrates that no universal method exists which is both efficient and simple to carry exists for the task of C-N bond formation. When the number of considerations a good synthesis must address, is trying to design an all-encompassing method asking too much? Attributes of selectivity, functional group tolerance, ease of execution, and atom economy, to name a few are all of great importance. On top of these factors, the worldview of both chemists

and their funding sources is evolving to accept and confront the idea that human impact on the environment should probably be minimized in the future. Therefore, material and energy intensive processes should be avoided when possible. This modern imploration has been the driving force for more efficient methods of catalysis to be developed like the research on Rh-catalyzed hydroimination and Ni-catalyzed hydroamination—both efficient C-N bond forming reactions—presented in this work.

Amines & Classical Approaches to Synthesis[5,6]

Amines, the functionality featuring a sigma-bond between sp^3-carbon and sp^3-nitrogen are a "basic" but important subclass within the alkaloids. Simple amines exist in a variety of configurations that vary by their degree of branching—substitution of the N-H bond for a N-C bond (*Figure 1*).
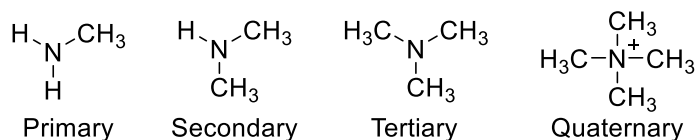
Figure 1: Possible Degrees of N-Methylamine Branching

From these four subtypes, a variety of different substituents can be bonded to the nitrogen center allowing for a limitless array of combinations. However, as the diversity of the amine substituents increases so does the difficulty of their syntheses. Like-substituted amines can be produced from repeated nucleophilic substitution (see *Scheme 1*) with simple binary starting mixtures (one nucleophile, one electrophile). Such synthetic simplicity is not possible when the
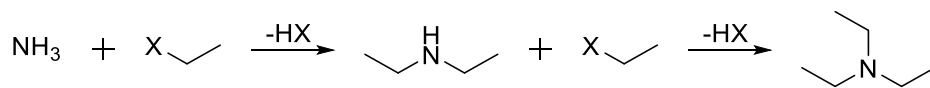
Scheme 1: Synthesis of Triethylamine by Hoffmann Alkylation

desired amine has different substituents. Additionally, amines having aryl substituents offer more difficulties where nucleophilic substitution is not tolerated for aryl electrophiles.

For industrially-prominent amines like N,N-diisopropylethylamine or Hunig's base, similar methods can be used to produce amines with two types of substituents. Amines bearing two or more unlike substituents cannot be synthesized by Hoffmann alkylation or similar additions due to overalkylation since further alkylation enhances N-nucleophiliticy. Overalkylation can be mitigated by a variety of modifications to nitrogen to limit its potency as a nucleophile. The Gabriel and Delepiné synthesis exemplify such means of modification (*Scheme 2*).
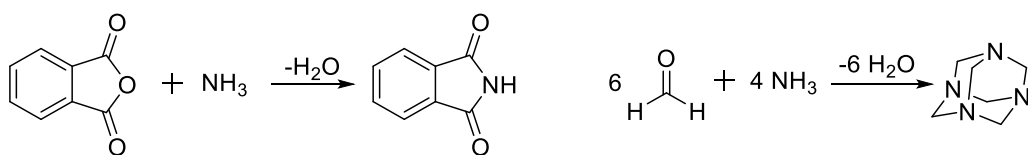
Scheme 2: The Gabriel and Delepiné Modifications to Hoffmann Alkylation

While a majority of classical synthetic routes to amines exploit the inherent nucleophilicity of the nitrogen lone pair, a number of more indirect syntheses exist to produce amines. A representative example of such a method is the reductive amination of carbonyl containing substrates (*Scheme 3*).
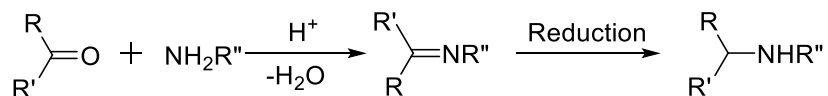
Scheme 3: Reductive Amination of Carbonyl Species

This strategy offers versatility en route to primary and secondary amines by drawing from the diverse pool of readily available Wacker-oxidation-derived aldehydes and ketones. A primary benefit of reductive amination is the lack of byproducts aside from benign water. Another similarly eco-friendly traditional method to produce primary amines indirectly is the Hoffmann rearrangement of amides which proceeds through isocyanate intermediate to eliminate water and carbon dioxide (*Scheme 4*).
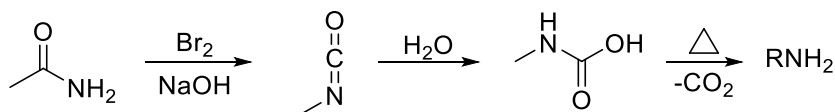
Scheme 4: Hoffman Elimination of Amides to Primary Amines

Secondary amines are veritably the most challenging subtype of simple-substituted amine to synthesize selectively and efficiently since overalkylation cannot be tolerated and any covalent modifications to prevent overalkylation must be wastefully removed later. Tertiary and quaternary amines are more easily arrived at from precursor primary and secondary amines since overalkylation becomes less problematic with decreasing nitrogen nucleophilicity at higher substituencies.

The classical long-standing recipes for amines, as mentioned before are hardy and reliable methods. They are often designed to work on large scale as well which makes them suited to industry. Yet their common drawback is that they are often not atom-economical—generating stoichiometric amounts of byproducts. Without viable on-site applications for these by-products to be harvested and used directly on-site, they are often mere waste. Similarly, even reactions which generate minimal by-product but are not high in selectivity create more unwanted material which must be separated from desired product. To summarize, large-scale methods low in atom-economy and/or selectivity are potentially wasteful and require compensational energy and/or material input. Therefore, methodologies which do not generate large amounts of unusable by-products will be highly desirable for amine synthesis in an eco-friendly way.

Utilizing Catalysis for Generation of Secondary Amines

Catalysis offers a natural solution to wasted reagents by providing an intermediary (the catalyst) that is not used up by the reaction and in some cases decrease the overall energy input to the reaction. A myriad of diverse strategies exist currently for catalytic C-N bond formation

but only a few will be discussed here. Two methodologies which boast extremely high atom-economy are hydrogen-autotransfer (HAT) and hydroamination (HAM) (*Scheme 5*).

Hydrogen Auto-Transfer(HAT):
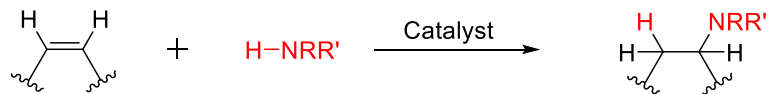
Scheme 5: General Strategy for HAT and HAM

HAT relies on the ability of the catalyst to perform both dehydrogenation and hydrogenation in a reversible fashion.[7] Therefore, the catalyst metal center must have readily accessible (x) and (x-2) oxidation states without a tendency to reach high-oxidation states (>x). The primary benefit of HAT is its ability to employ cheap and abundant classical heterogeneous hydrogenation catalysts like Rainey nickel or copper. In addition, the use of amines and alcohols as the electrophile in place of aldehydes and ketones as pseudo-reductive amination substrates allows HAT to be a very adaptable technique. α-Chiral amines are also potential substrates if slightly more intricate catalysts are used. Grubbs has demonstrated this enantioselectiv HAT-type amination which first employed Wacker oxidation of an alkene followed by asymmetric reduction using a chiral Shvo-type catalyst.[8] The field of asymmetric reductive amination has also independently produced a number of protocols which could be adapted to asymmetric HAT.[9]

The catalysts that make HAT desirable from purchasing standpoint—cheap and abundant—implicate a disadvantage in relation to the original issue of atom economy. The heterogeneous catalysts in some cases can require very high loadings to attain a desired degree of surface interaction. Additionally, significantly high hydrogen-pressure and temperature are

6

needed to encourage the reaction proceed in reasonable length durations and acceptable degrees of conversion.[4] Even though such conditions could be considered inefficient, they are common for many classical industrial syntheses. As such, forcing conditions of high temperature and pressure have been adapted to by industry and chemical manufacturers are equipped to do so easily. As an alternative to the high-loading of heterogeneous catalysis, homogeneous catalysts can often be used at lower loadings. Ruthenium and iridium have shown good potential for this purpose.[10,11]

Another point of HAT which potentially creates issue for HAT amination is the disproportionation that can occur between two primary amines to form a di-substituted secondary amine and ammonia (*Scheme 6*). This issue is usually minimized since dehydrogenation of alcohols (lower pK_a) is generally favored over amines.[12] Subsequent imine formation further enhances that equilibrium. In cases where ammonia production can be encouraged by equilibrium, entropy can drive the selectivity towards disproportionation.

Scheme 6: Self-Disproportionation of Primary Amine[12]

Given that a majority of alcohols, aldehydes, and ketones source from alkenes or alkynes, a method that can utilize the unsaturated carbon functionalities directly would theoretically be superior to HAT. HAM does just that by adding a N-H bond over a C-C unsaturation resulting in a new C-H and C-N bond (*Scheme 7*).

ΔH^o = -52.7 kJ/mol, ΔS^o = -127.3 J/(mol*K), ΔG^o = -14.7
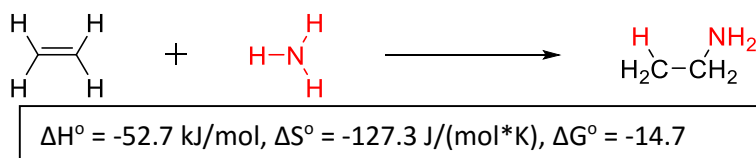
Scheme 7: Thermodynamics of Simple HAM[13]

Generally speaking, the intermolecular HAM is a near-thermo-neutral reaction which is then mostly facilitated by catalysis in a kinetic rather than thermodynamic way. In late transition metals, some thermodynamic assistance is proffered via activation of the C-C unsaturation. This activation is less significant in less electrophilic, electron-rich systems.

Because of the high atom-economy of the HAM process, great interest has been taken in this method of C-N bond formation. While ideally HAM would be a completely efficient process generating no byproducts, it is often not the case in real situations. Many times, the catalyst can engage in other transformations or degradation of starting materials can lead to impurities in the final product. Despite the current limitations of the technology, many reviews on HAM have been generated in recent years for a number of reasons: the high degree of "novelty" to create a niche in the field for combining a particular nitrogen group with a particular unsaturated carbon system (amines with alkynes vs. imines with allenes), the growing interest in catalysis from a green chemistry perspective, and the easing availability of exotic ligands to facilitate the reaction.[14-18] Such great enthusiasm among supplicants in the scientific community has resulted in HAM being made its own sub-field of catalysis chemistry. For the interest of this body of work, a limited analysis of two subcategories of HAM and its practical execution will be the primary focus of the remainder of the background: <u>HAM of alkynes with aryl amines</u> and <u>hydroimination (HIM) of allenes with imines</u>.

HAM of Alkynes by Aryl Amines

As previously mentioned, the synthesis of N-substituted aryl amines is limited within the classical methods of synthesis where nucleophilic substitution will not be tolerated by an aryl

electrophile".[6] This hindrance was largely overcome by the research of Buchwald and Hartwig in the development of catalytic cross-coupling aryl-amination (*Scheme 8*).[19,20]
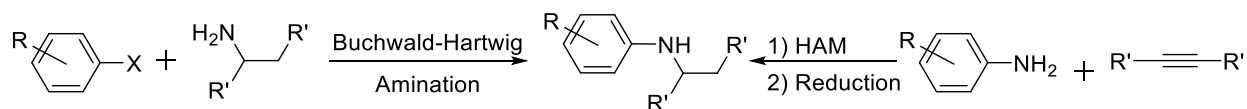
Scheme 8: Synonymous Outcomes of Buchwald-Hartwig Amination and Alkyne HAM

The Buchwald-Hartwig amination requires independent development of a complex aryl-halide substituent followed by coupling to an amine. This methodology mostly vies for greater diversity in the aryl substituent and less versatility is available to the amine coupling-partner as a starting material. To further expand the potential for substitution, HAM of an alkyne offers a potential way to couple the complexity of a Buchwald-Hartwig primary aryl-amine with a di-substituted alkyne. The HAM which uses aryl amines as source reagents can be considered an extension of the Buchwald-Hartwig coupling chemistry. The depth of the catalog of potential alkynes that can be drawn from then remains a separate issue that must conform to available industrial feedstocks or employ preliminary cross-coupling chemistry such as Sonogashira coupling.[21]

Sources of Catalysts for HAM

Because the emphasis of this body of research is in the design of a practical HAM method, development of catalysts which are low cost and abundant is key.[18,22] S-block and main-group elements can be used to promote catalytic C-N bond formation but of transition metals four are of prominence: iron, zinc, copper, and nickel. Additionally beneficial to their use in catalysis catalysis, these four metals are all naturally-occurring prosthetic groups in enzymes and do not require rigorous abscondence when used in pharmaceutical production. Of the four, iron finds the most limited application due to its lower valency and different reactivity. To date, successful use of iron as a HAM catalyst has only been attempted with styrenes and N-activated

amines which signify this chemistry is still in its earliest developmental stages for HAM.[23] Zinc, specifically Zn(OTf)$_2$, has recently seen some rather successful use as a Markovnikov-selective HAM catalyst.[24,25] The activity of Zn in HAM is comparable to early transition-metal Ti-HAM by Ackerman.[26] The superiority of Zn lies in that Zn is a far less oxophilic metal and therefore much easier to handle. In terms of availability, copper is given great interest as a HAM catalyst since Cu(II) precursors are massively abundant and cheap. Cu also has the second smallest redox potential of the four making access towards Cu(0) a relatively facile operation.[27] A Cu-H intermediate is usually the active culprit implicated in Cu-HAM. Very recently, a report outlining the HAM of activated internal alkynes with simple aryl amines by Cu(OTf)$_2$ demonstrated effectiveness of Cu as a low-cost HAM catalyst.[28] This work bears striking resemblance to Zn-HAM and it is no coincidence that their mechanism of action is much the same for their reliance on similar oxidation states. In these reactions, the metal will act like a Lewis acid to polarize the alkyne and thereby make nucleophilic attack by nitrogen more favorable. This explanation is strongly supported by the enhancement of activity going from CuBr$_2$ to Cu(OTf)$_2$ and the system's incompatibility with alkynes absent of strongly electron-withdrawing groups.

With the somewhat meager abilities of Fe, Cu, and Zn to make true Werner-complexes with their HAM intermediates, it would not be expected that Ni, being in the middle of them electronically would differ very greatly. However, it is Ni's unique abilities as a catalyst to both astound and confound the proclaimed master chemist that gives it a special place in this body of work. Having a very modest redox potential from Ni(0) to Ni(II) of 0.25 V/mol, Ni has access to a wide range of oxidation states from (0) to (IV), though (0) and (II) are most common.[29,30] These factors allow nickel to perform a plethora of different transformations in different contexts

(*Figure 2*). Generally with Ni, processes that increase electron-density like oxidative addition are generally favored over electron-density decreasing activities like reductive elimination for Ni.[29]
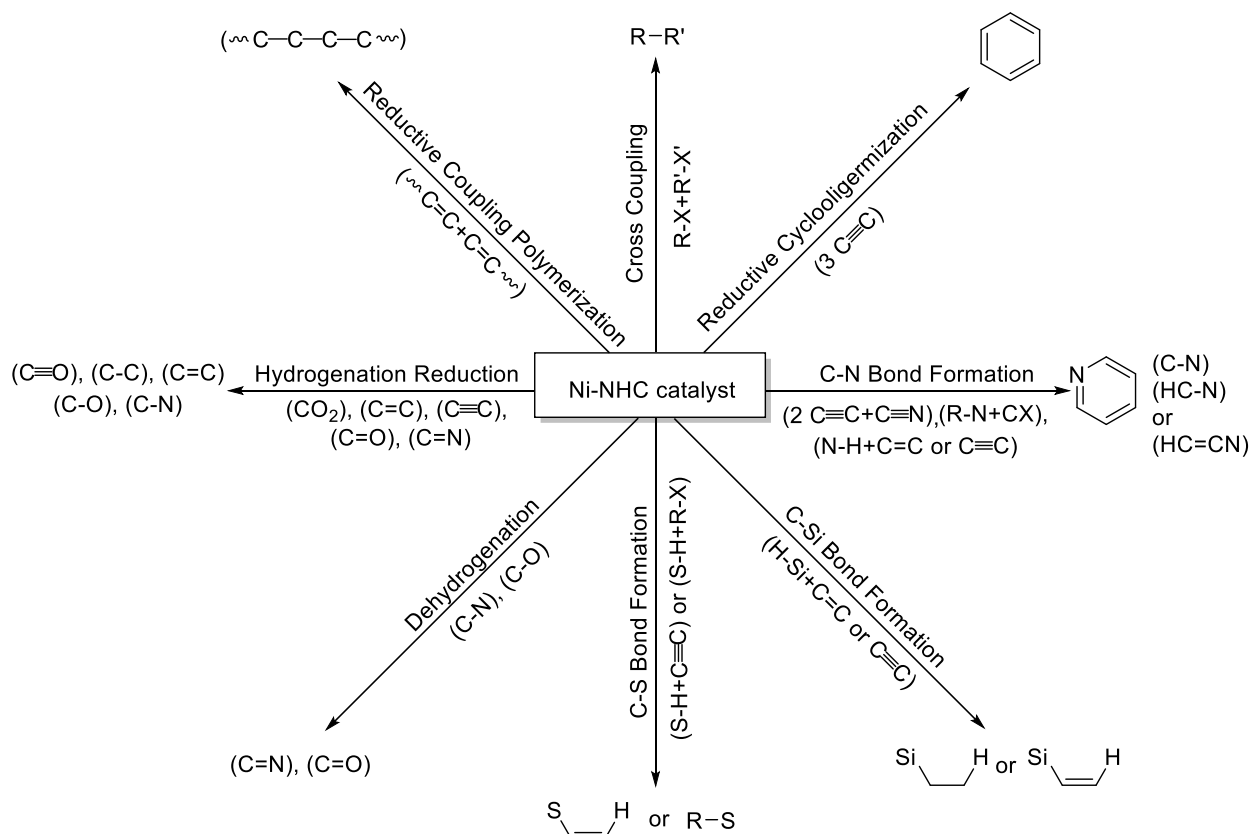
Figure 2: Schematic of Nickel Catalysis[29]

A History of Nickel as Catalyst: Discovery and Applications

Nickel was first isolated in 1751 by Mond in the form of $Ni(CO)_4$ which is a volatile yellow liquid.[30] Nickel was suspected and implicated in a number of "chemical" processes before the work of Mond as *Kupfernickel*—a nickel-copper ore. The 1912 Nobel prize for chemistry was awarded for the discovery of Ni-catalyzed hydrogenation of unsaturated C-C bonds. The interest in nickel, beyond reduction and its incorporation to alloys, did not greatly increase until the 1970's when Kumada and Corriu designed a cross-coupling methodology employing $NiCl_2$, alkyl halide, and Grignard reagent.[31,32] Nickel is also often regarded as an Earth-abundant metal, which purposefully disguises the fact Ni is available only as a small fraction in the easily-mined

11

crust and is only actually "abundant" in context of the material of the entire planet.[30] Lastly, Ni catalysts are is usually also considered to be very cheap due to this "abundance". Again this is a misconception not accounting for the deviation in market prices of bulk nickel compared to commonly used synthesis precursors like $Ni(COD)_2$. According to a simple price comparison made May 3, 2016, the price of Ni-metal was \$4.34/lb and $Ni(COD)_2$ from a commercial supplier was \$34/g or \$15,400/lb. If just the Ni(0) metal in the $Ni(COD)_2$ complex is considered, the price is ~\$73,000/lb. This simple comparison shows that the actual price of Ni(0) is several orders of magnitude more expensive than the encouraging market price of bulk Ni metal. Despite the fact that Pt is around 4,000 more expensive than Ni by bulk-metal prices, the previous cost comparison does not necessarily mean that Ni is always the cost-effective alternative it is touted as.

Despite these somewhat discouraging discussion, this body of research seeks to demonstrate that Ni can be a suitable alternative as a catalyst with proper development to established precious metal catalysts outside of price. While Ni has long been known to possess capacity for hydrogenation like Pd and Pt, it has only recently joined the precious-metal chemical ranks as a prevalent promoter for intermolecular HAM. In the midst of Ni-HAM advancement, Ni has also been discovered to be a suitable replacement for precious metals in other applications like Suzuki cross-coupling.[33] While Ni, may function effectively as a precious-metal doppelgänger, it also has unique abilities. In comparison to precious metals Rh, Ru, Pt, and Pd, Ni has smaller atomic size and more easily engages in reductive coupling chemistry.[34] Such unique behaviors will continue to become more established as Ni catalysis enjoys inevitably increased use in the future.

Development of Free Carbenes Towards Stable Ligands

The carbene, defined as a neutral divalent carbon with six electrons, is a somewhat rare and unusual configuration for carbon, which is normally considered to prefer a four-bond-arrangement to neighboring atoms.[35] The carbene structure was implicated long before its structure was ever elucidated. Work by Geuther and Hermann in 1855 which suggested dichlorocarbene could be synthesized from chloroform was used to explain the reactivity observed in the Reimer-Tiemann orthoformylation (*Scheme 9*).
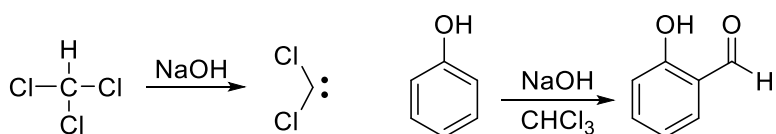
Scheme 9: Reimer-Tiemann Orthoformylation by Dichlorocarbene

With the gradual but reluctant acceptance of the existence of radicals in the 1920's, the notion of a carbene (a di-radical) became less contentious.[35] In the 1950's interest into the exact structure of carbenes became explored as the field of molecular orbital theory was then more established. It became apparent that there were two possible electronic states for the carbene, the "diradical" triplet state and a paired singlet state (*Figure 3*). Eventually, with the initial quantum-mechanic calculations work of Lennard-Jones and Pople and later developments by Duschenne and Burnelle, it was concluded the singlet state was usually the ground state for most carbenes. Zimmerman suggested that the substituents of the carbene carbon will largely affect the differences in stability.
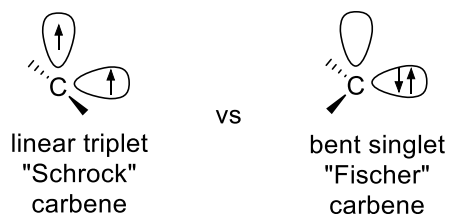

linear triplet
"Schrock"
carbene

vs

bent singlet
"Fischer"
carbene

Figure 3: Differences Geometrically Between Triplet and Singlet Carbene

In 1961, Wanzlick demonstrated that carbenes could be stabilized by α-amino groups.[35] Between 1964 and 1974, Fischer and Schrock independently isolated, respectively, the first singlet-carbene-metal complex and the first triplet-carbene-metal complex. In between these discoveries, Wanzlick applied his stabilization postulate towards synthesizing the first metal-N-heterocyclic carbene (NHC) complex.[36] Twenty years later, Bertrand was able to produce the first stable carbene which could be isolated as a free carbene.[37] However, Bertrand's carbene was not found to promote any useful catalysis so it is Arduengo who is given most of the credit for the synthesis of the reagent-ready, stable NHC ligand and their resulting impact on catalysis.[38] Even though many of the NHC-ligands are relatively stable as free carbenes, it is more favorable to transport and handle them as the imidazolium chloride and deprotonate them *in situ* giving them greater utility as ligands. *Figure 4* represents a summary of these advancements in carbene chemistry.
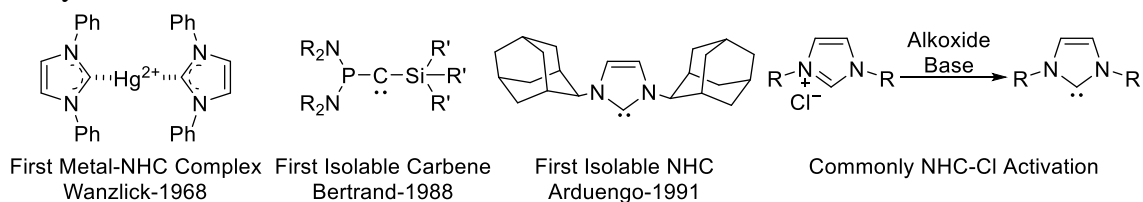

First Metal-NHC Complex   First Isolable Carbene   First Isolable NHC   Commonly NHC-Cl Activation
Wanzlick-1968   Bertrand-1988   Arduengo-1991

Figure 4: A Small Exposition of Development Toward NHC ligands

N-Heterocyclic Carbenes: Useful Reagents

The use of bulky N-heterocyclic carbene (NHC) ligands has recently become a popular strategy since carbenes can provide strong coordination while their bulky peripheral substituents make high degrees of coordination difficult.[35, 39] The combination of the two factors allow the metal center to remain reactive but shielded. This inherent reactivity can be conferred to substrates undergoing catalysis. The bulkiness of the carbene can further serve to assist catalytic reactivity where associative processes occur quickly but dissociation is relatively slower. Therefore, when designing the NHC for catalysis, factors of steric bulk and electron-richness of
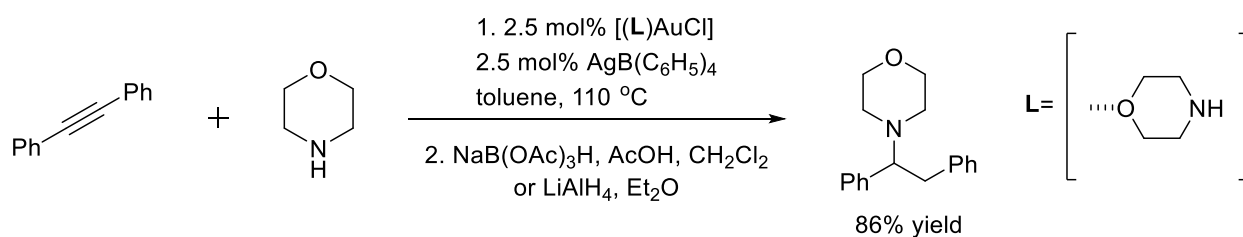
the carbene must be tuned to the reaction mechanism and in some cases to the substrate. Modifications to NHCs can also be performed after metal-complexation has occurred giving more flexibility to the process.[40]

NHC ligands themselves possess a surprising capacity as organocatalysts. NHCs have been used effectively for promoting transesterification and Michael-umpolung chemistry.[39] In most cases, NHC ligands can be used as substitutes for mono-phosphine ligands as seen in many reviews.[34, 35, 41-43] For late-transition-metal HAM of alkynes, NHC ligands are thought to play a more important role than mere coordination. For instance, the HIM precursor $Ni(\sigma^1\text{-IPr})_2$ which is formally a 14 e$^-$ species if only the carbene is bound demonstrates excellent affinity for unactivated internal alkynes.[44] The 14 e$^-$-Ni's tendency towards achieving higher valency to attain 16 or 18 e$^-$ in combination with Ni's natural electropositivity may be the rationale for the complex's ability to activate normally electronically-inert substances toward catalytic transformation. In any case, NHCs offer novelty in ligands both with their unique electronic properties and their ability to be tuned by precise adjustment of the alkaloid ring or its peripheral substituents.

Development of Ni-NHC Complexes as Catalyst for Intermolecular Alkyne HAM

The initial inspiration to use Ni-NHC complexes is not profoundly novel given the current direction of synthesis towards methods which demand more efficient and tuneable catalysts. Additionally, the use of NHCs as ligands by our group is of ongoing interest having previously published examples of catalysis featuring Ru-NHCs and Ni-NHCs.[44,45] It is also fair to say the work is inspired by, and hoped to be an extension in terms of the following works by catalysis with a "group-10"-like metal, the use of NHC ligand, and/or the similarity of substrates.

If excerpts were taken of the best parts of these works (*schemes 10-12*) it would include the following desired outcome: sturdy and reusable cataly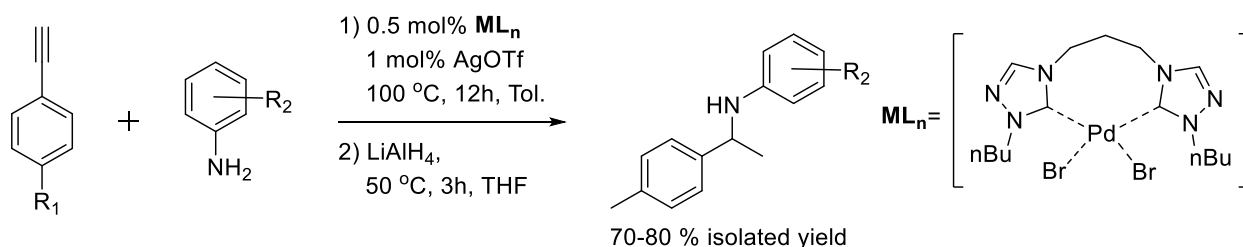sts with tunable NHC ligands capable of performing HAM of unactivated alkynes with aryl amines at low catalyst loading. The Straddioto works (*Scheme 10*) demonstrates that "group-10"-like or group-11 (I) catalysts are capable of performing activation of internal alkynes with electronically balanced substituents.[46] Lavoie demonstrates that slightly-activated terminal aryl-alkynes can undergo Markovnikov-selectivity HAM in in the presence of gold(I)-NHC complex at moderate temperature and catalyst loading (*Scheme 11*).[47] Cao shows that with the proper NHC ligand, very low loading,

1. 2.5 mol% [(**L**)AuCl]
2.5 mol% AgB(C$_6$H$_5$)$_4$
toluene, 110 °C

2. NaB(OAc)$_3$H, AcOH, CH$_2$Cl$_2$
   or LiAlH$_4$, Et$_2$O

86% yield

Scheme 10: Straddioto Gold Internal Alkyne HAM[46]

5 mol % [Au]
10 mol % AgBF$_4$

CD$_3$CN, 70 °C, 20 h

95-99%
HNMR conversion
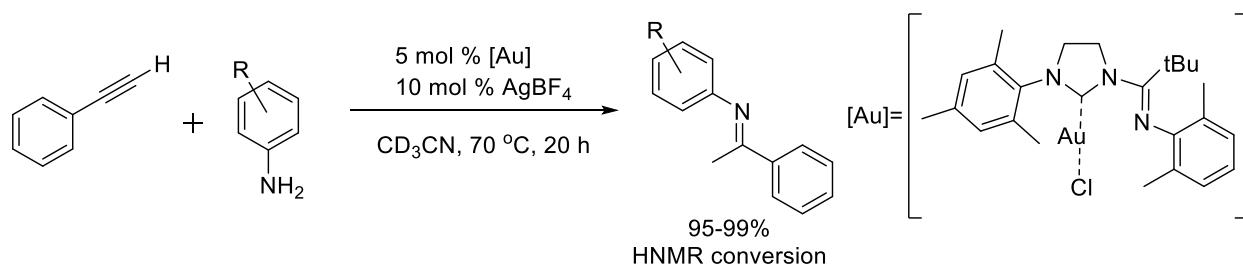
Scheme 11: Lavoie Terminal Alkyne HAM with Au-NHC Complexes[47]

1) 0.5 mol% **ML$_n$**
   1 mol% AgOTf
   100 °C, 12h, Tol.

2) LiAlH$_4$,
   50 °C, 3h, THF

70-80 % isolated yield

Scheme 12: Cao Reusable Pd-NHC Catalyst for Terminal Alkyne HAM[48]

16

group-10 Pd catalysts can be used to facilitate the HAM of substrates similar to Lavoie (*Scheme 12*).[48] While these are all good examples of what can be done with "group-10"-like metals, they use the relatively expensive metals Pd and Au. Can a cheaper substitute be attempted (see *Scheme 13*)?
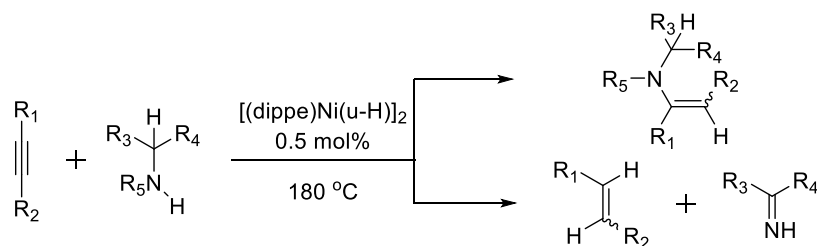
Scheme 13: Initial Report of Ni-HAM of Alkynes by Garcia[49]

In an effort to explore the transfer hydrogenation capacity of Ni for semi-reduction of alkynes to alkenes, the Garcia group found that at low-loadings, Ni is also capable of promoting alkyne HAM.[49] Since the area of intermolecular Ni-HAM was relatively undeveloped at the time, the Garcia group went on to publish the following:
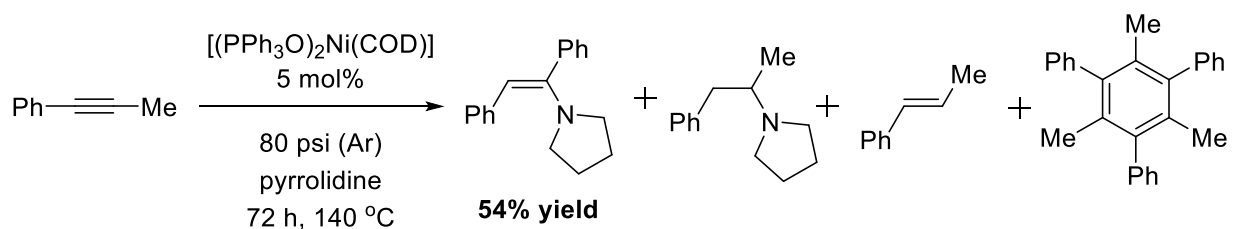
Scheme 14: Garcia Ni-HAM of Unactivated Alkynes[50]

As can be seen, their synthesis was met with some selectivity problems.[49,50] Additionally, the conditions used to obtain the modest yields were decidedly *forcing*. The reactivity and selectivity problems seen in the Garcia work can potentially be overcome if the ideas of the previous expensive-metal catalyst designs are applied to a Ni-catalyst. In terms of investigation design, the goal of this works is to provide a viable and synergistic alternative to the cited works by design of a protocol that will allow for facile HAM of unactivated alkynes using highly-active but affordable Ni-NHC catalysts.

Ni-Transfer Hydrogenation

The ability for nickel to perform such a wide array of reactions (*Figure 2*) can be a bane for complicated systems employing Ni-catalysis or for multi-functional substrates (HAM vs. reduction). However, if properly controlled, this problem can be made advantageous for design of a multi-step one-pot transformation. We envisioned this sort of activity where the Ni(IPr)$_2$ catalyst could perform tandem HAM followed by reduction (*Scheme 15*).

$$RHN-H \quad + \quad \equiv \quad \xrightarrow{\text{HAM}} \quad RHN\diagdown\diagup H \quad \rightleftharpoons \quad RN\diagdown \quad \xrightarrow{\text{Reduction}} \quad RHN\diagdown$$

Scheme 15: Tandem HAM/Reduction
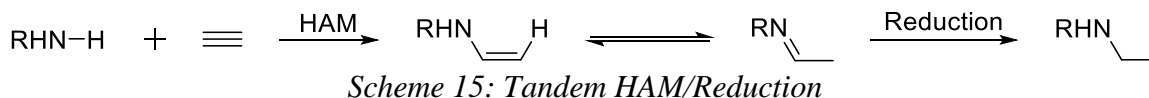
The reduction of double and triple bonds by nickel and molecular hydrogen has been well established early on.[51] Transfer hydrogenation (TH), catalytic dehydrogenation of one molecular-hydrogen-analog moiety followed by hydrogenation of a different moiety, is also a stand-by reaction from about the same time. The first documented transfer hydrogenation between two unlike molecules was discovered by Meerwein and Verley in 1925.[52,53] The use of late-transition-metals as TH catalysts was developed in the 1960's but it was the work of Nolan in 2001 that is of interest to this work.[54,55] In this seminal work of NHC-assisted TH, Nolan utilized a cationic [Ir(COD)(Py)(NHC)]PF$_6$ catalyst and, as in the Meerwein-Ponndorf-Verley reduction, isopropanol was used as the hydrogen-source.[55]

Returning to the HAM work of Garcia (*Scheme 14*), it can be seen that part of the by-product produced (as was the original intent of the research) are reduced alkanes and alkenes from the alkyne and the enamine-HAM product. Reduction of HAM imines/eneamines was also demonstrated by the Zhou group to promote TH of both α-amino-α, β-unsaturated and β-amino-α, β-unsaturated esters which are similar in structure to enamines using Ni-phosphine catalysts.[56] Adaptations from these works of Ni-TH and that of Nolan which improved the TH-potential of Ir using NHC ligand, were used in the design of the following tandem HAM/TH system.

Experimental

General Experimental Procedures and Reagent Procurement

Unless specifically noted, all experimental set-ups were carried out under dry, inert nitrogen atmosphere (<15 ppm H_2O and O_2) either using a glovebox or standard Schlenck techniques. All glassware and other instrumentation were thoroughly dried in an oven or by a dessication chamber. All reaction solvents were obtained from commercial vendors in high-purity anhydrous grade. Chromatography solvents were obtained from bulk solvent supplier EMD or Fischer and were used without further purification. Precatalysts Ni(COD)$_2$ (**1a**), [Rh(COD)$_2$]BF$_4$ (**5a**) and Rh(COE)$_2$Cl$_2$ (**5b**) were obtained from Strem. All phosphine and Josiphos ligands were obtained from Strem except triphenyl phosphine (**7d**) which was obtained from Alfa Aesar. N-heterocyclic free carbene ligands were obtained from Frontier Scientific (~95-97% purity) and stored in the glovebox inert environment. Aniline (**3a**) and morpholine (**3g**) were obtained from Alfa Aesar and were freshly distilled from CaH$_2$ under nitrogen and degassed by the freeze-pump-thaw method. Allenes (**9a-b**) and o-phthalic acid were obtained from Sigma-Aldrich and used directly. All other reagents were obtained from Alfa Aesar and were used without further purification.

TLC plates were visualized under 254 nm ultraviolet light and were further visualized by exposure to either KMnO$_4$ or I$_2$. Solvent removal was generally carried out by vacuum rotary evaporation or under high vacuum utilizing a liquid N$_2$ trap. Chromatographic purification was performed using silica obtained from Sorbtech (60 Åf, 230-300 mesh size) either by flash column chromatography (3-5 psi) or by automated Combiflash separation using a Teledyne Rf 150 instrument. GC analyses were performed with a Shimadzu GC-2010 or Agilent 7890A GC and Agilent 5975C MS. ^{1}H-NMR and ^{13}C-NMR spectra were obtained either on a Varian

400 MHz spectrometer or a Bruker 400 MHz spectrometer. Both ^{1}H-NMR and ^{13}CNMR are reported in parts per million downfield from tetramethylsiline (TMS) standard.

General Optimized Preparation Method for Ni-Hydroamination (HAM) of Alkynes (Method A)

Inside the glovebox, solid Ni(cod)$_2$ (x mol%) and NHC ligand (2.1*(x) mol%) are added to a dried 1-dram screw-top glass vial gravimetrically. To the vial, a magnetic stir bar and appropriate (1-1.5 mL) amount of solvent are added. The mixture is topped loosely with a PTFE-lined phenolic screw cap and allowed to stir briefly (3-5 min). To this mixture, alkyne (1.3 eq) is added gravimetrically, the reaction is stirred briefly to incorporate alkyne, and lastly amine is added (1.0 eq) gravimetrically. The vial is then sealed tightly and removed from the glovebox and is promptly sealed with 3M super 33+ electrical tape. The vial is then hung in a silicone oil or ethylene glycol bath by a copper wire and heated at the appropriate temperature for the appropriate amount of time.

General Procedure for Borane Reduction of Hydroamination Product[57] (Method B)

The crude HAM mixture is transferred by pipette to a celite plug with additional toluene washes and filtered into a vessel charged with 1.33 eq of o-phthalic acid and magnetic stir bar. The celite plug is then washed with a minimal volume of Et$_2$O until celite returns to original color. The vessel is then sealed with a rubber septum and sparged with a flow of N$_2$ via needle for a brief period (3-5 min). Once positive pressure of N$_2$ is established above the mixture, the vessel is cooled to -30 °C and stirred. To the cooled mixture, 1.33 eq of 1.0 M BH$_3$-THF adduct is added via syringe in one volume. The mixture is allowed to stir for 2 h at -30 °C and is then warmed to 0 °C for one hour. After one hour, DI water (~50% total volume) is added and the mixture is stirred an additional 15 minutes.

Work-up is performed by transferring the mixture to a separatory funnel and the organic layer is removed. The aqueous layer is extracted three times with EtOAc (~25% total volume) and is added to the organic layer. The combined organic fractions are then washed once with saturated $NaHCO_3$ and twice with a saturated NaCl solution and then dried over anhydrous $MgSO_4$. The solvent is then removed and the crude mixture is stored under Ar for further use.

General Procedure for Transfer-Hydrogenation Reduction (Method C)

The crude HAM mixture is taken into the glove box after the reaction time has progressed. The vials are charged with 5 mol eq. of a 1:4 *i*-PrOH:benzene solution and resealed. The vials are then taken out of the glovebox and heated for a specified amount of time using a silicone oil or ethylene glycol bath. The solution is then filtered through a celite plug with EtOAc washes. The mixture is then concentrated by rotary evaporation and dried under high vacuum (~5 torr) overnight (8-12 h).

General Procedure for Flash Column Chromatographic Purification (Method D)

The crude mixture is loaded onto dry silica (~5-10 eq by mass) by solvation in EtOAc and rotary evaporation. The chromatography column is prepared by solvating the chosen mass of column-silica in a volume of hexane. This slurry is poured into the column and packed by applied even pressure of 15 psi. The column is equilibrated by three column volumes of hexane. The column is then equilibrated with three column volumes of the starting separation gradient mixture. To the equilibrated column, the crude-loaded-silica is added underneath a layer of sand, and is loaded to the column by addition of small amounts of starting gradient solvent. After loading, the column is filled with solvent and run under 3-5 psi of pressure and the fractions are collected. Product-containing fractions (TLC or GC analysis) are combined and solvent is

removed. The fractions are then dried under high vacuum (~5 torr) and placed in a 40 °C bath under vacuum overnight (8-12 h) to remove trace solvent.

General Procedure for Hydroamination Imine Hydrolysis (Method E)

After hydroamination, the crude mixture was filtered through a celite plug with four 0.5 mL-benzene-washes. To the filtered mixture, 0.5 mL of ~10 %wt HCl/H_2O solution was applied. The acidified solution was stirred at 80 °C for two hours and was then transferred to a separatory funnel. The organic layer was extracted twice with ~10%wt HCl solution. The organic layer was then neutralized with saturated $NaHCO_3$ solution and dried over $CaCl_2$ and $MgSO_4$. The organic mixture was then concentrated by rotary evaporation.

General Procedure for HAM-Alkyne Slow Addition (Method F)

The experimental apparatus was assembled as depicted in *Figure 5*. A KD Scientific syringe pump was connected to the system via Luer-lock PEEK tubing and Hamilton glass syringe sealed with vacuum grease. The apparatus was evacuated and purged with N_2. In the
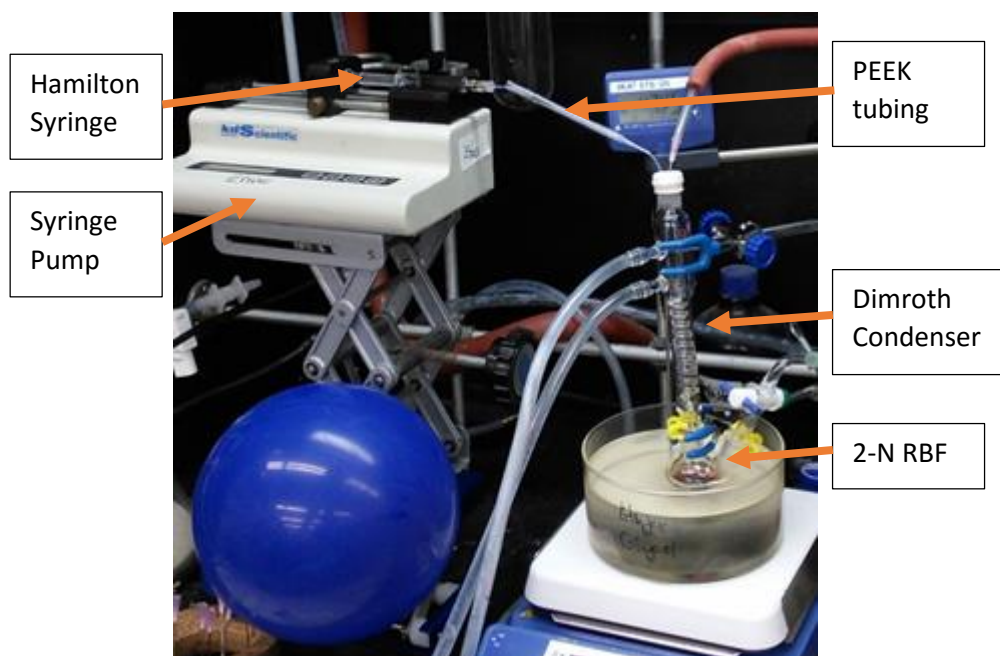

Figure 5: Slow Addition Experimental Apparatus

glovebox, solid Ni(COD)$_2$ (**1a**) and NHC ligand (**2a-d**) and a stir bar and solvent are added to a RB-Schlenck-flask followed by brief stirring (3-5 min). Amine (**3a-g**) is added and the flask is sealed with a rubber septum. In a separate SN flask, an alkyne/solvent solution is prepared in excess to account for transfer loss. Outside the glovebox, liquid reagents are transferred under positive N$_2$ pressure to the apparatus set-up. Heat is applied and the alkyne solution is set to be delivered at a constant rate over the initial 75% of the total reaction time.

General Analysis by Gas Chromatography

Samples prepared for gas chromatography were diluted with MeOH or EtOAc (0.5-1.0%). The samples were either taken in the glovebox when the sample needed to remain air-free or in atmospheric conditions when no further reaction was required. A common aliquot of internal standard was added from a stock solution automatically by the GC autosampler. GC conversions were determined by area under peaks relative to dodecane internal standard. Standard FID response curves were generated for internal standard, starting materials, and product (serial dilution of crude mixture) by serial dilution and triplicate measurement. Determination of selectivity in GC optimization was determined by arbitrary degree of amplification of desired product peak area to remaining starting material peak area after normalization by internal standard.

$$Selectivity\ \alpha\ \frac{normalized\ product\ peak\ area}{normalized\ limiting\ reagent}$$

Results and Discussion

Control Experiments of HAM System

—See *Figures 6-9*—

Reactions were prepared according to general preparation method (Method A) with the following conditions: uncatalyzed (*Figure 7*), just Ni(COD)$_2$ (*Figure 8*), just IPr (*Figure 9*). The

23

model substrates aniline and diphenyl acetylene do not appear to react under thermal conditions alone as compared to the chromatogram for a successful model system. As suspected, a catalyst intermediary is required to promote the hydroamination reaction. Additionally it was discovered that Ni(COD)$_2$ in absence of IPr-NHC ligand (**2c**) will still promote the [2+2+2] oligomerization of diphenyl acetylene (2a). This result is verified by comparison to the product of a separate synthesis of hexaphenyl benzene by a previously reported method.[58] This trimerization product is observed in all reactions as such there is intentional *excess* alkyne to overcome this by-product formation. The 2:1 coupling by-product that can be seen at 14.7 min in *Figure 6* was never isolated but was further analyzed by GC/MS to be the addition of one aniline, two diphenyl acetylene and a hydrogen equivalent (93+2*178+2=451) (for potential mechanism see *Scheme 16*). It seems that the appearance of this by-product is concurrent with the appearance of the HAM product and is more prevalent at higher initial alkyne concentrations. It is likely the result of aniline interrupting the [2+2+2] oligomerization process:
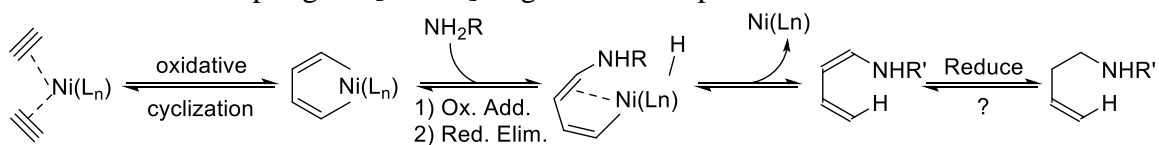
Scheme 16: Possible 2:1 Coupling Byproduct Formation Mechanism

Before optimization was performed on the system, the conditions originally used to undertake this work are represented in *Scheme 17*. The experimental results of manipulation to that system follow in *Figures 10*-16.
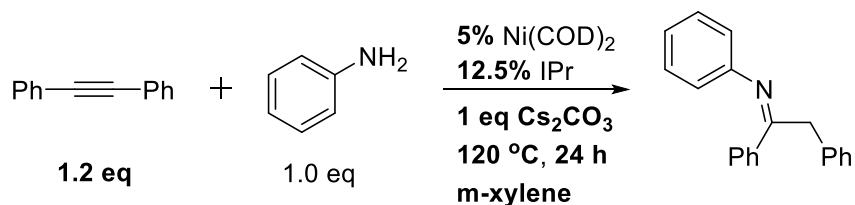
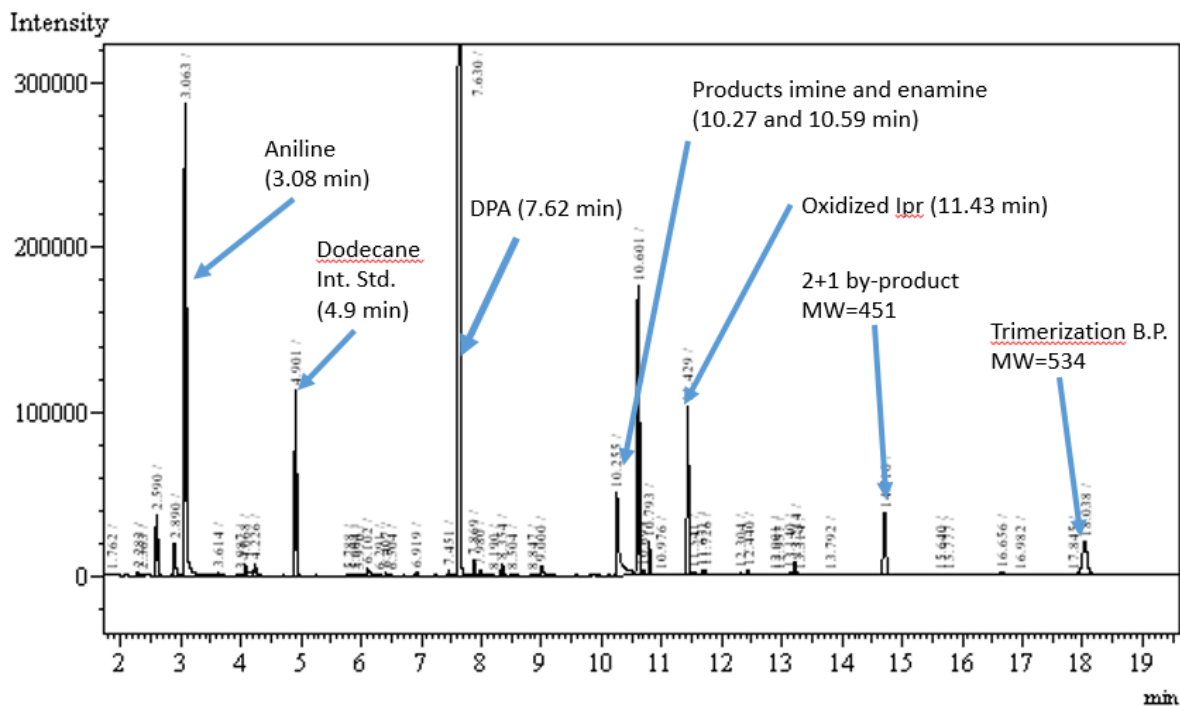*Scheme 17: Original HAM-System of Diphenyl Acetylene with Aniline*

24

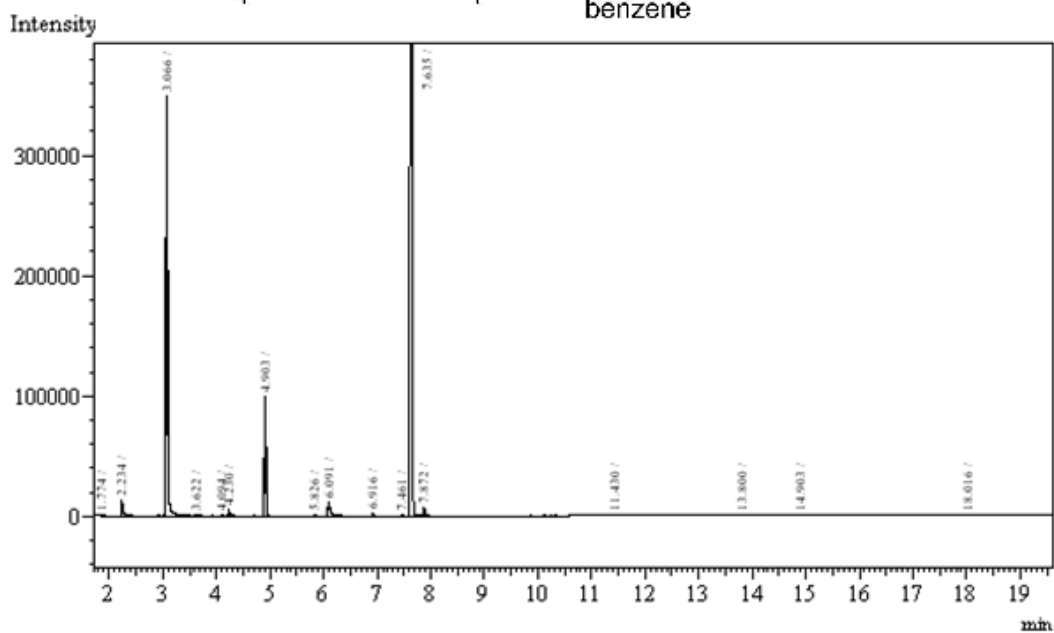*Figure 6: Sample Chromatogram of HAM of Diphenyl Acetylene with Aniline*
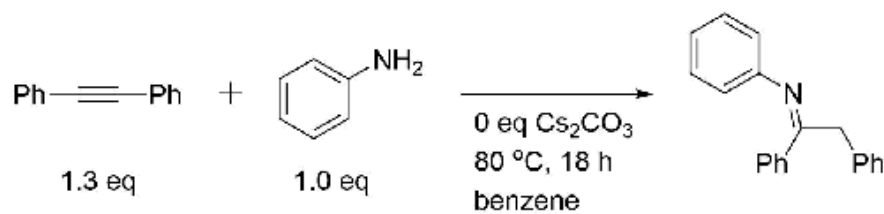

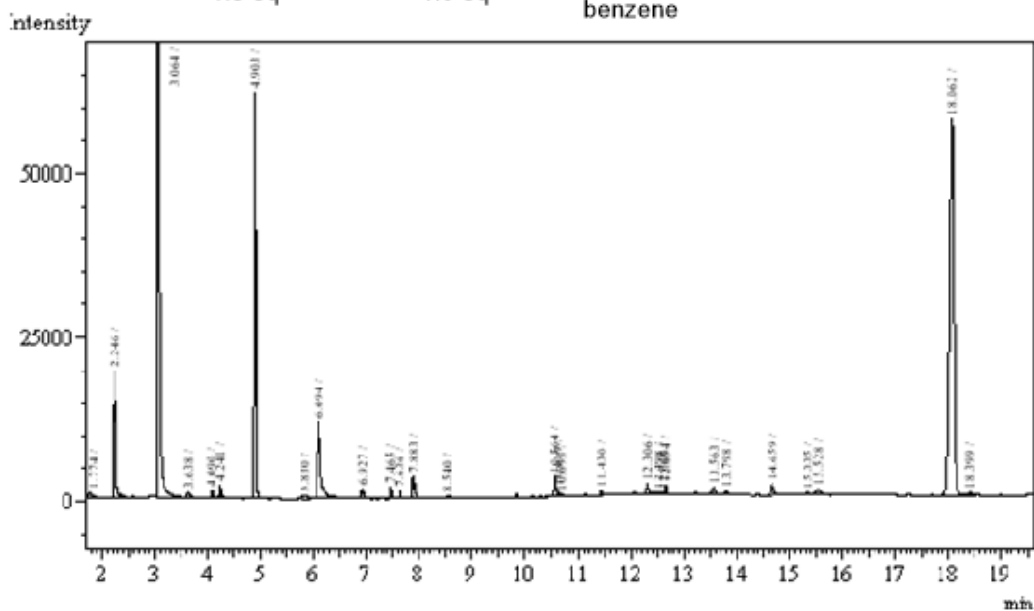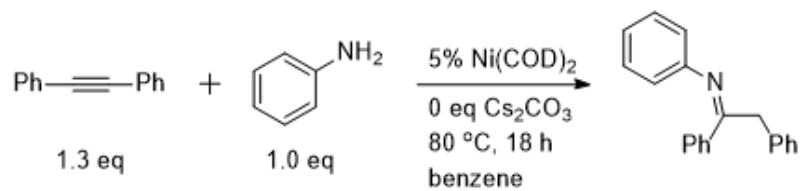*Figure 7: Uncatalyzed Thermal Reaction of Diphenyl Acetylene with Aniline*

25

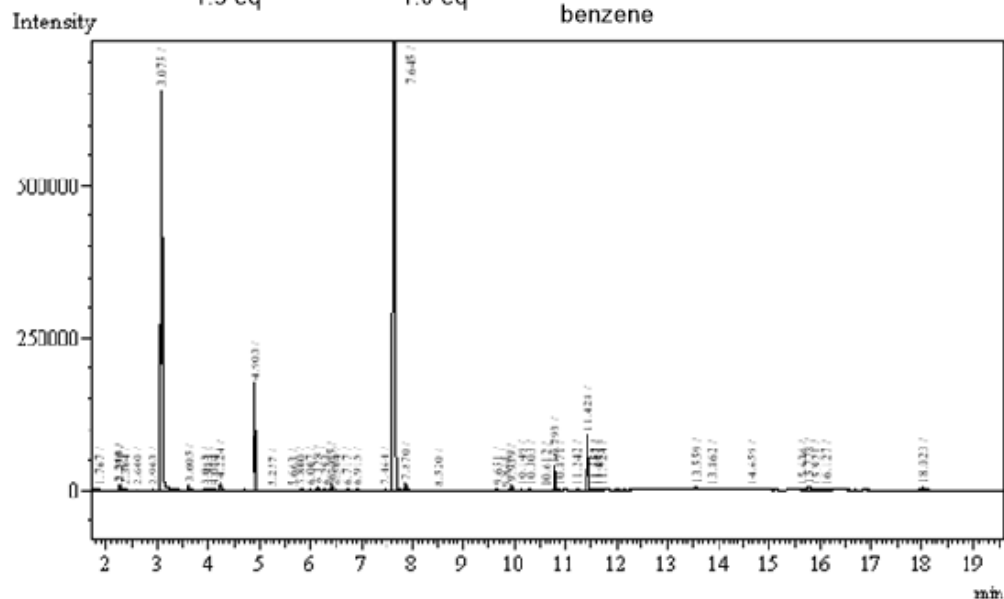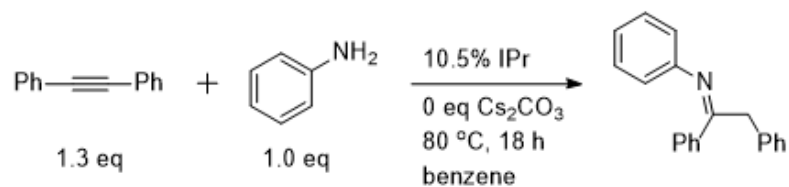*Figure 8: Ni(COD)₂-Catalyzed Reaction of Diphenyl Acetylene with Aniline*

Figure 9: IPr-Catalyzed Reaction of Diphenyl Acetylene with Aniline

26

HAM Reaction Optimization

Optimization of the hydroamination system was performed using the most basic

substrates aryl-amine aniline (**3a**) and the bi-aryl internal alkyne diphenyl acetylene (**4a**) with

Ni(COD)₂ (**1a**) and N,N'-(2,6-Diisopropylphenyl)dihydroimidazol-2-ylidene (IPr) (**2c**). The goal

of studying the parent system was to establish the following:

1. Attempt to find a set of conditions requiring minimal catalyst material input for optimal

    conversion of a model substrate

2. Using these findings, ease the extrapolation to new optimal conditions for new substrates

3. Explore new substrate combinations as research requires

4. Attempt to minimize side-product formation which may be negatively affecting yield

These optimization studies were conducted after several attempts to perform HAM under a

previous set of conditions which was not allowing significant progress on this body of research.

Success following optimization has been remarkably enhanced based on these results. The

following scheme represents the results of a variety of manipulations to the following reaction

conditions (the conditions changed are bolded:
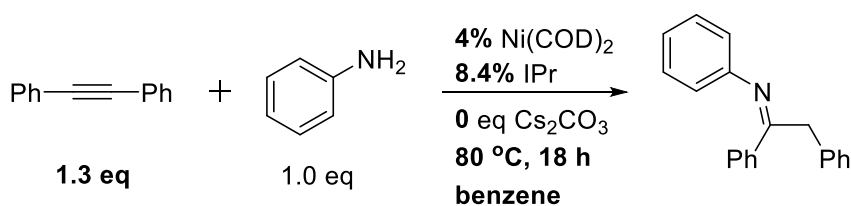
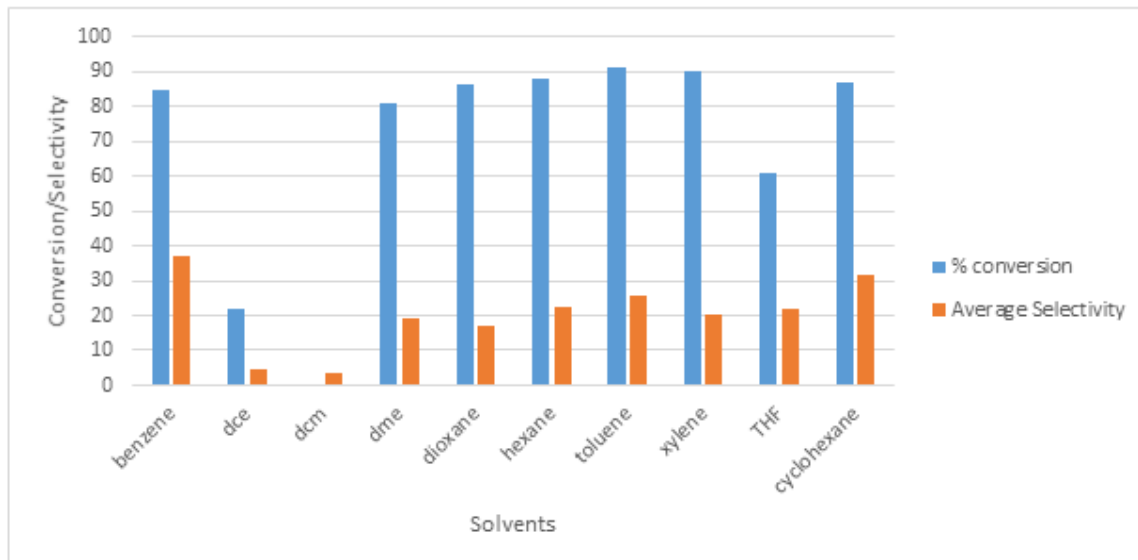*Scheme 18: Results of HAM Optimization*
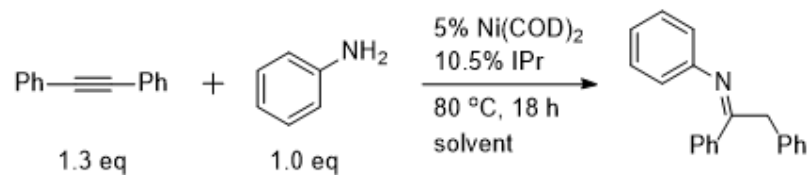
Figure 10: Solvent Optimization

The solvents were tested in a 65 °C reaction (to accommodate lower boiling points) and little preference for simple hydrocarbon solvents was found. Benzene and cyclohexane gave the highest selectivity for the desired product while giving similar levels of conversion. In addition to benzene being the more economic choice of the two, solubility in benzene was the main reason for its selection as choice as reaction solvent. Concerns for health effects of benzene compared to cyclohexane may opt for the other.

Figure 11: Temperature Optimization

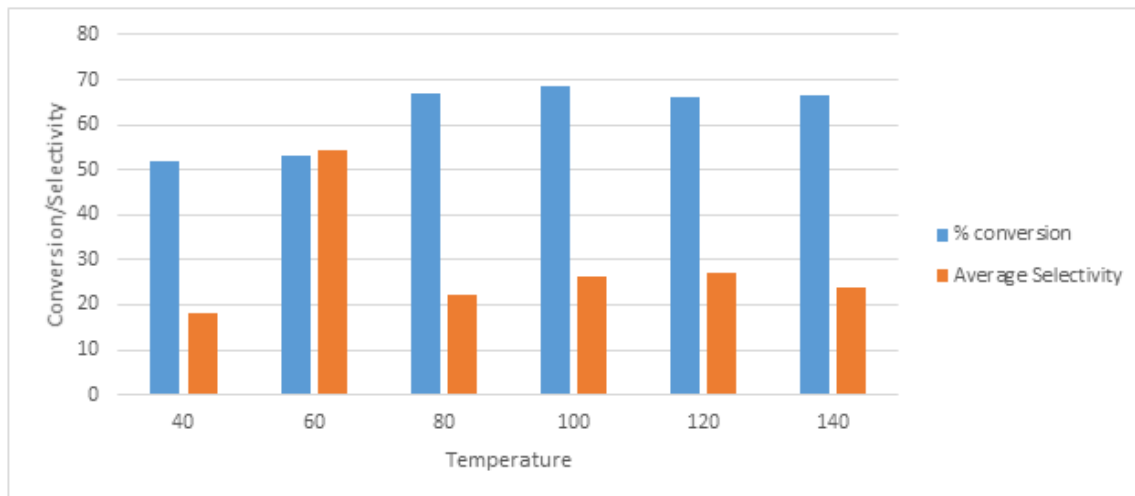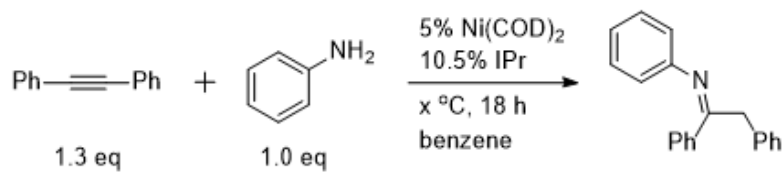The effect of reaction temperature was investigated and found that at 80 °C and above, the conversion reaches a maximum level. Since standard the boiling point of benzene is 80.1 °C, heating about this temperature would be impractical. The high degree of selectivity observed for 60 °C is a result of an outlier with irregular concentration.
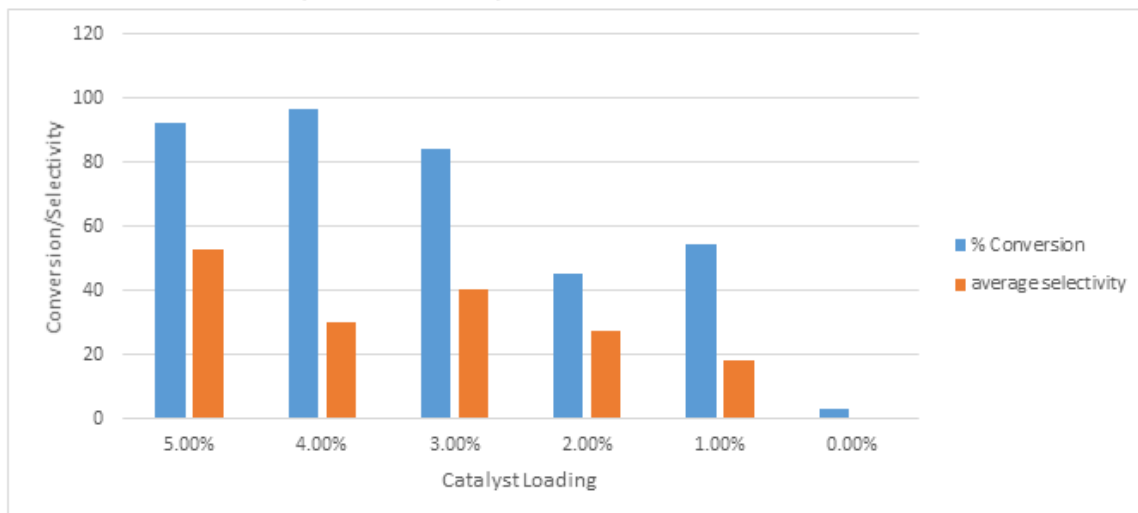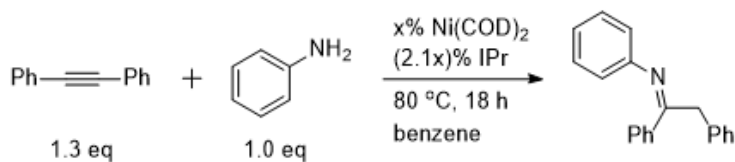
Figure 12: Catalyst Loading Optimization

These results demonstrate that the conversion suffers greatly going below 3% loading. An average turnover-number (TON) for the $Ni(IPr)_2$ precatalyst, based on these results, appears to be between 20 and 25. Since the reactions must be carried out in a practical amount of time that will avoid any catalyst decomposition that may occur at extended intervals, an optimal loading of 4% $Ni(COD)_2$ was chosen. A consideration should be made to the sensitivity of the balance and the operator when measuring minute quantities of catalyst (<3% loading, 0-3 mg) small deviations can significantly alter the results. Such may have been the case in the investigations of lower catalyst loadings here.
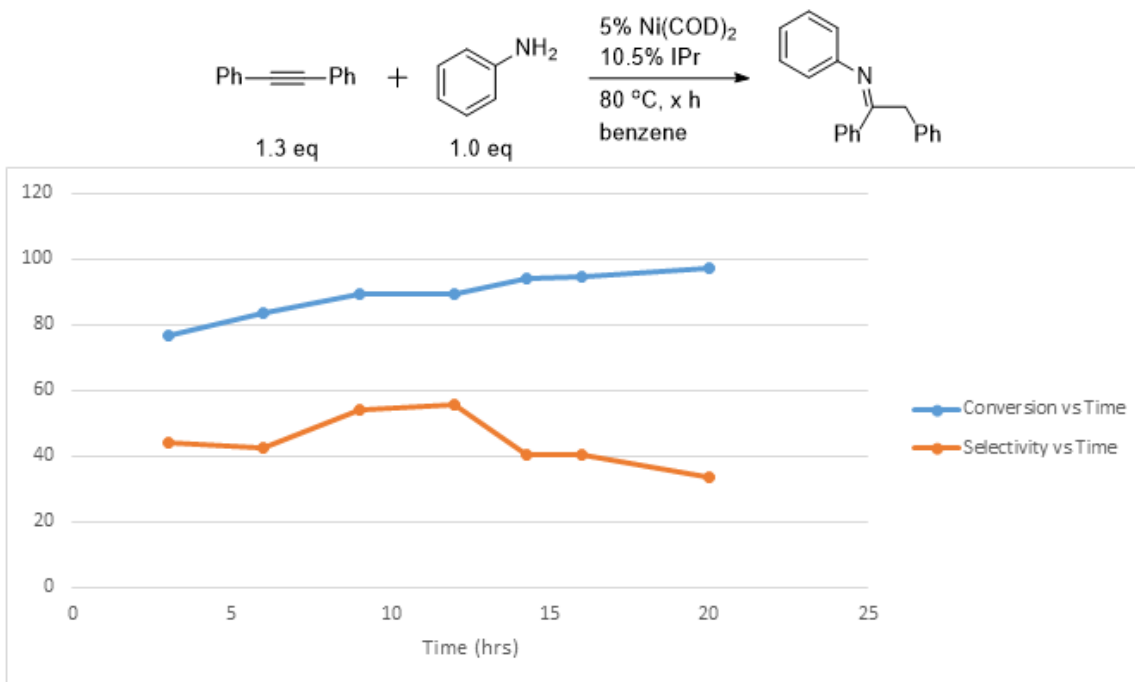
Figure 13: Reaction Time Optimization

After several attempts of this experiment (summer power outages), a composite of several trials demonstrate that conversion occurs at a fairly linear rate while selectivity diminishes as aniline concentration goes down. This change in trend can be attributed to the increase in productivity of the alkyne oligomerization side-reaction which will prevail in cases of low aniline concentration. It is desirable to continue along the conversion trend until completion despite sacrificing excess alkyne if added in batch.
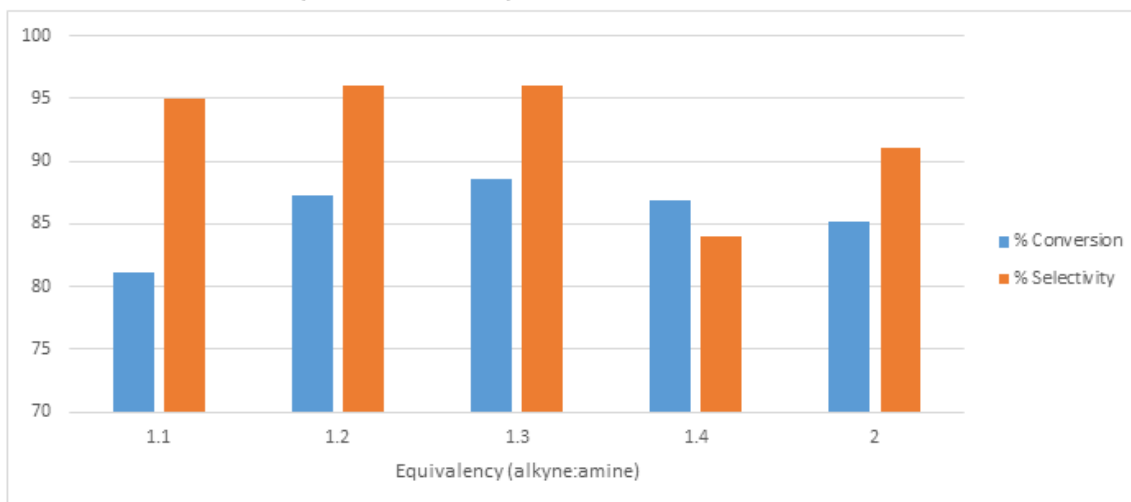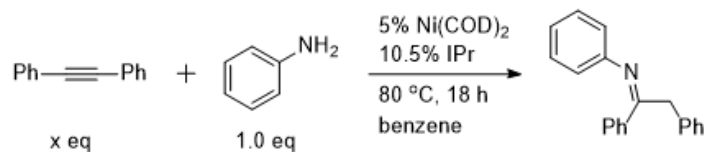
Figure 14: Equivalency Optimization (Alkyne:Amine)

The equivalency optimization uses a different metric for its degree of selectivity where the % selectivity here refers to the percentage of the area that the desired product takes of (product+2:1 coupling byproduct+[2+2+2]byproduct). This change in metric was necessary since the standard internal dodecane standard was not added properly. The conversion and selectivity reach a maximum at 1.3 equivalents of alkyne to amine. The change in selectivity, and thereby conversion, is rationalized by the preference for the catalyst to perform reductive coupling when encountering higher concentrations of alkyne as the equivalency is increased. Since the alkyne has more potential for by-product formation than the amine, no studies were conducted where the alkyne was the limiting reagent.

To determine the effects of Cs_2CO_3 on the system the reaction sequences (I-VII) in *Figure 15* were carried out. Similar conversions were observed for conditions I and II which suggests Cs_2CO_3 doesn't directly play a role in the HAM reaction. It was also thought that Cs_2CO_3 may be able to preserve the catalyst for further reactions (conditions III and IV). These two conditions only showed partial reduction and HAM respectively which does not support that Cs_2CO_3 is an efficacious catalyst preservative. Lastly, conditions V, VI, and VII all gave similar conversion which supports two premises: Cs_2CO_3 is also not required for transfer hydrogenation and the addition of $Ni(COD)_2$ is required to promote the transfer hydrogenation when elevated HAM temperatures are used.

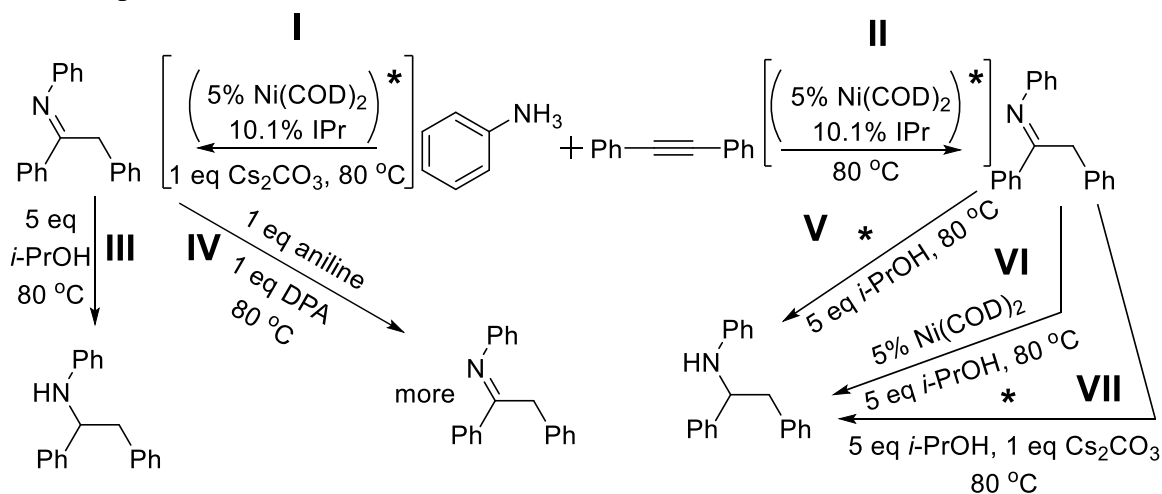*Figure 15: Effect of Cs₂CO₃ on HAM and Transfer Hydrogenation*

The results of the optimization studies are summarized by *Scheme 18*. These conditions were used as a basis for future studies to expand the substrate scope of the system. However, in substrates with lower reactivity than these parent compounds, conditions were altered to make the reaction more favorable by using higher loading and/or longer reaction times.

Ligand Choice and Optimization

N,N'-(2,6-Diisopropylphenyl) dihydroimidazol-2-ylidene (Ipr)	N,N'-(2,6-Diisopropylphenyl) tetrahydroimidazol-2-ylidene (sat Ipr)	N,N'-(2,4,6-Trimethyl) dihydroimidazol-2-ylidene (IMes)	N,N'-(2,4,6-Trimethyl) tetrahydroimidazol-2-ylidene (sat iMes)
100% conversion	**No conversion**	**No conversion**	**No conversion**
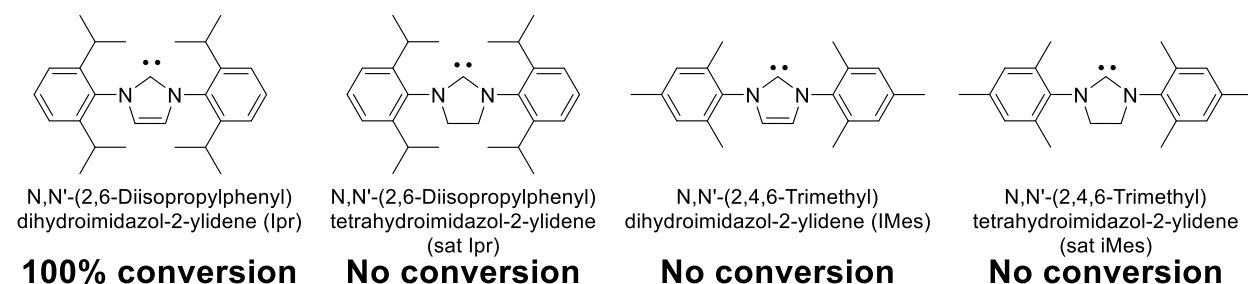
Figure 16: NHC-Ligands Screened in Optimization

The investigation into potential ligands with which to carry out this reaction was in a word cursory. Since NHC chemistry is blossoming so fruitfully, many variations of NHC ligands are available commercially. The decision not to explore further was made mostly because IPr seemed at the time of this research to be an effective choice. Having explored the catalyst system further has revealed some potential short-comings which may be attributed to ligand choice. In certain scenarios, the HAM reaction becomes impractically ineffective or is not permitted. Such outcomes where substrate reactivity is inherently low towards the HAM reaction, a more active catalyst would be required. Additionally, increased catalyst activity could permit significantly lower loadings for substrates already successfully demonstrated to perform HAM. However, it is also quite possible that other NHC ligand alternatives to IPr could produce no conversion as seen in *Figure 16*.

Selected HAM Products

—see Appendix A for chemical structures and Appendix B for NMR spectra—
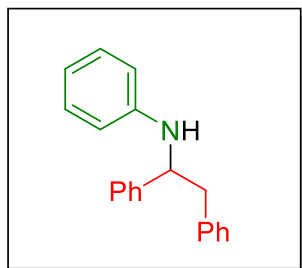
N-(1,2-Diphenylethyl)aniline (**5a**): Prepared from aniline (**3a**) and diphenyl acetylene (**4a**) using general methods for preparation (Method A) and reduction (Method 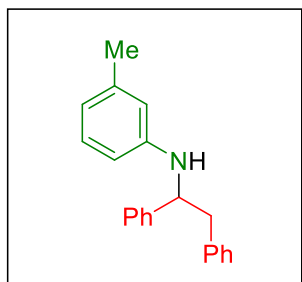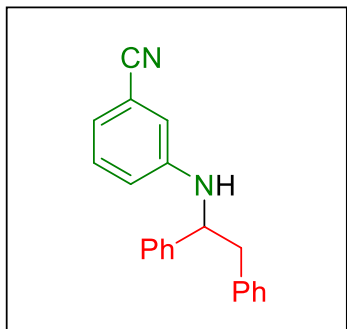B). Chromatography was performed on Combiflash (EtOAC: Hex) or flash column chromatography (Method D) (3.75% Et$_2$O:Hex to (5% EtOAc): (1% MeOH):(94% Hex)) and obtained (**5a**) as a viscous yellow oil (C.F.-50%: 440 mg, H.C.-50%: 440 mg) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.5-6.6 (Ar, 15H) 4.7 (dd, J = 8.2, 5.7 Hz, 1H), 4.3 (s, 1H) 3.5 – 2.8 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.4, 143.6, 137.8, 129.3, 129.2, 128.7, 128.7, 127.2, 126.8, 126.6, 117.6, 113.8, 59.3, 45.3.

N-(1,2-Diphenylethyl)-3-methylaniline (**5b**): Prepared from *m*-toluidine (**3b**) and diphenyl acetylene (**4a**) using general methods for preparation (Method A) and reduction (Method B). Benzyl phenyl ketone was synthesized from hydroamination imine by standard hydrolysis procedure (Method E). Chromatography was performed on Combiflash (EtOAC: Hex) and obtained (**5b**) as a viscous yellow oil (>95% yield, 269 mg). Flash column chromatography (Method D) was used to isolate benzyl phenyl ketone (isocratic 7% EtOAC:Hex) as a white solid (75%: 22 mg). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.5-6.4 (Ar, 14H), 4.7 (dd, J = 8.2, 5.7 Hz, 1H), 4.2 (s, 1H), 3.5 – 2.9 (m, 2H), 2.3 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.4, 143.7, 138.8, 137.9, 129.3, 129.0, 128.7, 128.6, 127.1, 126.8, 126.6, 118.6, 114.6, 110.7, 59.3, 45.3, 21.7.

N-(1,2-Diphenylethyl)-3-cyanoaniline (**5c**): Prepared from 3-aminobenzonitrile (**3c**) and diphenyl acetylene (**4a**) using general methods for preparation (Method A) and reduction (Method B). Chromatography was performed on Combiflash (EtOAC: Hex) or flash column chromatography (Method D) (3.75% Et$_2$O:Hex to (5% EtOAc): (1% MeOH):(94% Hex)) and obtained (**5c**) as yellow/white solid (C.F.->95%: 716 mg, H.C.-62%: 269 mg) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.4- 6.7 (Ar, 14H), 4.6 (dt, $J = 8.3$, 5.2 Hz, 1H), (d, $J = 4.9$ Hz, 1H), 3.3 – 3.0 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.5, 142.1, 137.1, 129.7, 129.2, 128.8, 128.7, 127.5, 127.0, 126.3, 121.0, 119.4, 117.9, 116.0, 112.7, 59.0, 45.0.

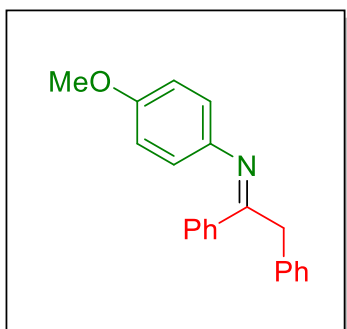N-(4-Methoxyphenyl)-1,2-diphenylethanimine (**5d**): Prepared from *p*-anisidine (**3d**) and diphenyl acetylene (**4a**) using general methods for preparation (Method A) where benzene was substituted for benzene-D$_6$. HNMR scans of the reaction at 0 h and 24 h show full conversion of amine peak δ 2.7 (broad s, 2H) to a benzylic peak δ 4.0 (sharp s, 2H). (100% HNMR conversion).
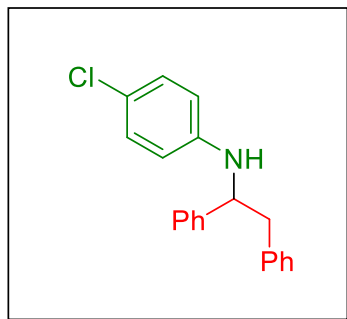
N-(4-Chlorophenyl)-1,2-diphenylethanimine (**5e**): Prepared from *p*-chloroaniline (**3e**) and diphenyl acetylene (**4a**) using standard methods for preparation (Method A) and reduction (Method B). Flash column chromatography (Method D) (5% EtOAc:Hex to 40% EtOAc:Hex) was used to obtain (**5e**) as a yellow oil

(42% yield, 211 mg). ^{1}H NMR (400 MHz, CDCl₃) δ 7.3-7.0 (Ar, 14H),

4.6 (dd, *J* = 8.2, 5.7 Hz, 1H), 4.1 (s, 1H), 3.2 – 3.0 (m, 2H). ^{13}C NMR (101 MHz, CDCl₃)

δ 146.0, 143.1, 137.6, 129.4, 129.1, 128.9, 128.8, 127.5, 127.1, 126.6, 122.4, 115.0, 59.5, 45.3.
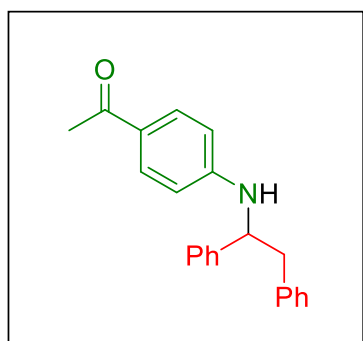
N-(1,2-Diphenylethyl)-4-aminoacetophenone (**5f**): Prepared 4-aminoacetophenone (**3f**) and diphenyl acetylene (**4a**) using general methods for preparation (Method A) followed by standard transfer-hydrogenation reduction (Method C). Flash column chromatography (Method D) was performed by Jian Wang to

obtain (**5f**) as a yellow oil (23% yield). ^{1}H NMR (400 MHz, CDCl₃) δ 7.8-6.5 (Ar, 14H),

4.8 (d, *J* = 5.4 Hz, 1H), 4.8, 4.7 (dt, *J* = 7.9, 5.7 Hz, 1H), 3.2 (dd, *J* = 14.0, 5.9 Hz, 1H),

3.1 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.5 (s, 3H). ^{13}C NMR (101 MHz, CDCl₃) δ 196.4, 151.2, 142.3,

137.2, 130.6, 130.6, 129.2, 128.8, 128.7, 127.4, 126.9, 126.4, 112.5, 58.7, 44.8, 26.0.
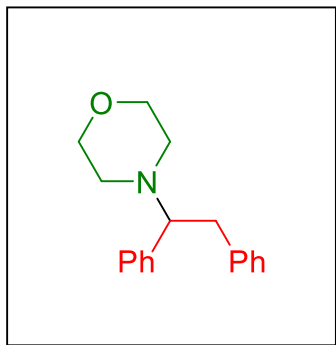
1-(N-Morpholino)-1,2-diphenylethane (**5g**): Prepared from morpholine (**3g**) and diphenyl acetylene (**4a**) using general methods for preparation (Method A) and reduction (Method B). Chromatography was performed on Combiflash (EtOAC: Hex) or flash column chromatography (Method D) (3.75% Et$_2$O:Hex to 3% EtOAc:Hex to 7.5% MeOH:EtOAC) and obtained (9g) as golden oil (C.F.-69 %: 317 mg, H.C.-22%: 122 mg). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.2-6.9 (Ar, 10H), 3.68 (dd, J = 4.7, 4.7 Hz, 4H), 3.5 (dd, J = 9.4, 5.2 Hz, 1H), 3.3 (dd, J = 13.2, 5.2 Hz, 1H), 2.9 (dd, J = 13.2, 9.4 Hz, 1H), 2.6-2.4 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.0, 139.5, 129.6, 129.0, 128.1, 128.1, 127.3, 126.0, 72.7, 67.5, 66.0, 52.2, 51.5, 39.5.

R=Bu,R'=Ph-Major (7:1)
R=Ph,R'=Bu-Minor (1:7)
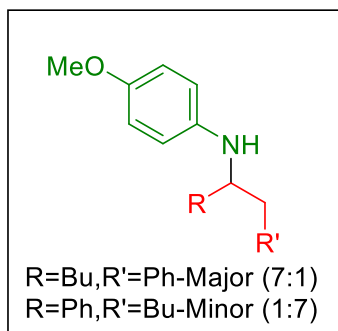
N-(1-butyl-2-phenylethyl)-4-methoxyaniline (**5h**): Prepared from *p*-anisidine (**3d**) and 1-phenyl-1-hexyne (**4b**). This substrate was prepared via slow addition modification of the general preparation (Method E) and reduction (Method B). (**5h** and **5h'**) were obtained by flash column chromatography (Method D) (1% Et$_2$O:Hex to 10% Et$_2$O:Hex) as a yellow oil (28% yield, 370 mg). The major and minor product were not separated (^{1}H NMR ratio). Major: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.3-6.4 (Ar, 9H), 3.6 (s, 2H), 3.5 (tt, J = 6.6, 4.8 Hz, 2H), 3.3 (broad s, 1H), 2.9-2.7 (m, 2H), 1.5-1.2 (m, 7H), 0.9 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 152.1, 142.2, 139.1, 129.9, 128.5, 126.4, 115.4, 114.9, 56.1, 55.0, 40.4, 34.1, 28.7, 23.0, 14.4.

Difficulties Encountered in Substrate Scope Expansion

Many attempts were made in this research to expand the substrate scope of the HAM reaction. Technical issues aside, the variety of substrates that can be used in this catalyst system is currently highly exclusive. It was found that only special cyclic secondary amines like morpholine are tolerated whereas substrates like N-ethylaniline and diallyl amine show no conversion. Additionally, the degree of electronegative substituents in aryl amines has an upper limit as the highly electron-deficient 3,4,5-trifluoroaniline and 4-(trifluoromethyl)aniline showed nearly zero conversion even with higher catalyst loadings. A good explanation for why secondary and highly electron-deficient amines are not successful substrates may be their role as a nucleophile in the catalysis cycle is not being fulfilled. It was also found that aliphatic amines such as N-hexylamine, benzylamine, and 2-phenylethylamine are ineffective as HAM substrates. An explanation for this behavior would not necessarily call into question these substrates' inherent nucleophilicity but rather their potential to undergo a different nickel-mediated reaction (*Scheme 19*).

Scheme 19: Alkylation of Amines with Amines[12]
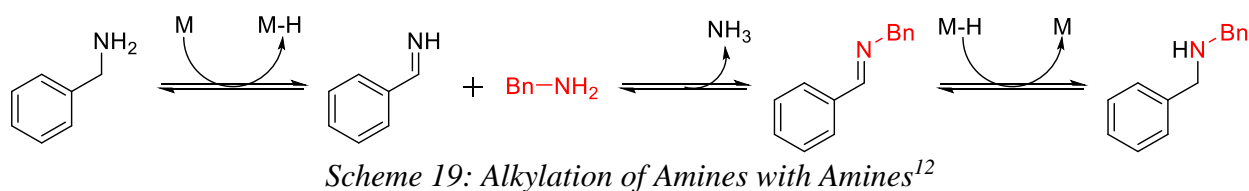
This type of reactivity would generate secondary amines which could then result in incompatible nucleophiles for HAM described here. A third type of intolerance for substrates bearing acidic protons (*p*-aminophenol and *p*-aminobenzoic acid) was observed. Such incompatibility is not uncommon where oxidative addition of the O-H bond is not favorable to produce a HAM-inactive Ni(II) species.

An entirely different issue of reactivity affronts the lack of successful alkyne substrates in this study. The alkyne-nickel reaction towards cyclo-oligomerization is a significant problem it

seems for any alkyne. However, this problem becomes so prevalent in aryl-alkyl, alkyl-alkyl, or terminal alkynes that no HAM activity is observed over oligomerization using bulk-addition-HAM (Method A). This problem can be surmounted via slow addition HAM techniques (Method E) as described for the successful transformation of mixed 1-phenyl-1-hexyne. However, increasing the technical difficulty of an already technically-challenging system (namely isolation), does not seem a reasonable solution for practicality. Therefore, with limited time and desire for a better solution, no further exploration beyond two alkyne substrates was undertaken.

Attempts to Quantify Yield via ^{1}H NMR

It was the overarching goal of this research to create a procedure of chemical transformation that is both hardy and reliable while remaining technically simplified requiring as little man-power as possible. Since a majority of the time spent working on this project was in the isolation and purification step, alternative means of quantifying the yield of the HAM reaction were explored. One such means was yield calculated from ^{1}H NMR of the crude HAM mixture. In principle, to calculate such a yield, resolution of three separate signals must be possible: an unreactive internal standard proton signal, a starting material signal, and a unique signal for the product. Because the substrate was limited to alkynes and amines with a majority of aromatic signals, no protons in this region could be used for ^{1}H NMR yield. The most seemingly reliable signals going from amine to HAM product would be the N-H protons in amine and the benzylic protons in product (*Scheme 20*).
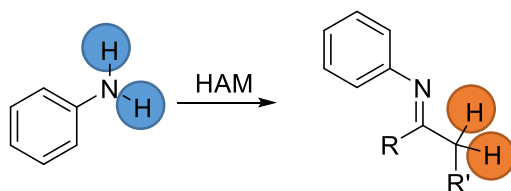
Scheme 20: ^{1}H NMR Distinct Protons in HAM

Such behavior was observed for the amine *p*-methoxyaniline which has a good methoxy-"handle" to integrate signals against to confirm their identity (*Figure 17*). The results of this experiment seem to clearly indicate that the original amine has fully converted to the HAM product with full depletion of amine peak at 2.63 ppm and concurrent appearance of the benzylic peak for 2H at 3.30 ppm. However, such a generalization does not account for byproducts formed in this complex situation that may not be resolved by this depiction. Therefore, this method using these parameters alone does not quantify conversion to product for amine but rather more general conversion to any outcome. Further studies found this method to be even more unreliable where the internal standard does not always integrate for the same ratio with a chemically-"anchored" signal which should remain constant throughout the reaction. Lastly, the most convincing reason for abandoning ^{1}H NMR is that even if the conversion can be verified to being directed to one product, the results do not conclusively prove the product structure since a
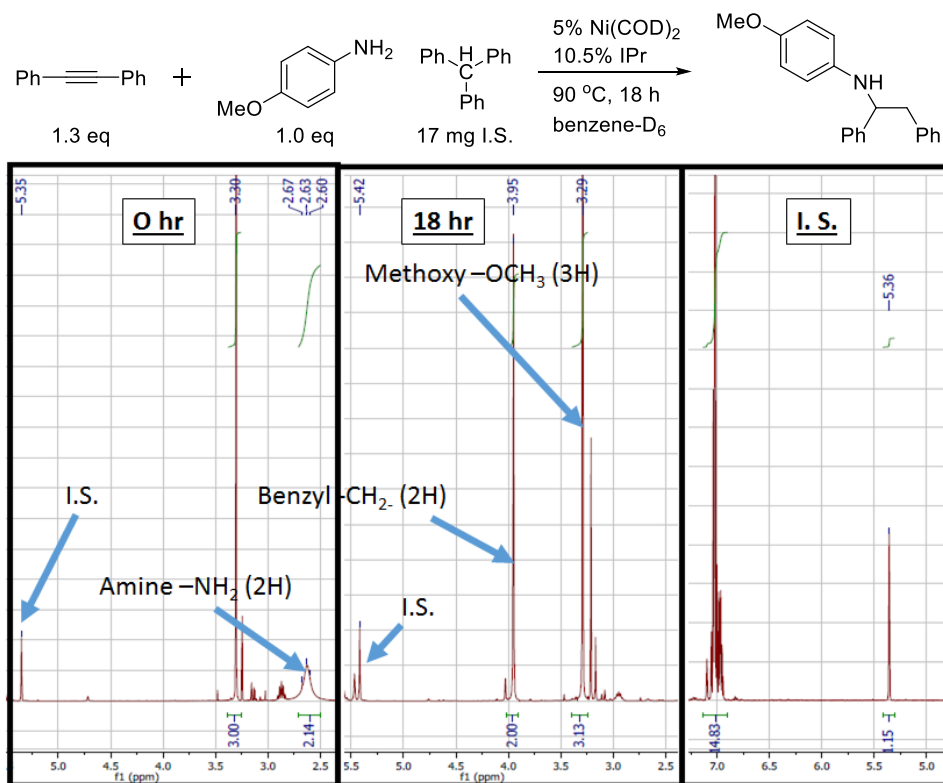

Figure 17: ^{1}H NMR Yield of p-Methoxyaniline and DPA

majority of the spectrum will remain unresolved. This problem can be overcome if reliable

standards can be obtained of the predicted products but many of the structures are too exotic to

be obtained commercially.

A simple method to procure such reliable standards would be by their independent

synthesis using a reliable amination method like reductive-amination of carbonyls which should

be commercially available in most cases. Again this kind of activity would be a diversion away

from the central goal of the project and would be frivolous given that chromatographic isolation

is possible.

Conclusion

A summary of the work in Ni-HAM can be made with the system represented in

Scheme 21. This scheme demonstrates the ability for the Ni-NHC catalyst to be both multi-

functional and reusable. The step-wise series of developments were required for this system

include: initial screening of a progenitor system, optimization of the system, expansion of its

substrate scope, and final adaptation to a room-temperature tandem HAM-reduction sequence.

Of course, with each bit of the journey to *Scheme 21* was the incremental process of

troubleshooting one issue only to find another. Isolation still seems to be at an unsatisfying

compromise requiring the use of large (80-120:1 silica:product) flash chromatography columns

which also use large amounts (3-4 L) of organic solvents that are typically thrown away as well

as plenty of a skilled researcher's available time and concentration. The substrate scope was able

to be extended to a handful of different products and remains viable for further inclusions. It was
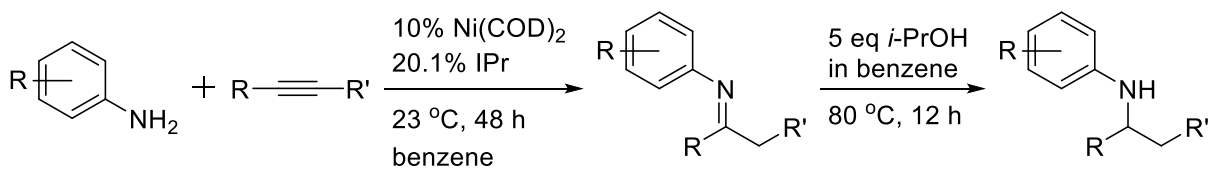
Scheme 21: Optimized One-Pot RT-HAM

found that many aryl primary amines and internal alkynes will be tolerated while non-cyclic secondary and primary aliphatic amines will not. No foreseeable limit exists for the alkyne substrate scope as long as proper handling such as slow addition is employed.

Though only trivial amounts of effort were taken to address the catalytic activity of the system by directly altering the catalyst, a final loading of 4% seems a satisfactory first attempt using two commercially available components—Ni(COD)$_2$ and free-carbene IPr NHC ligand. Cursory studies investigating the ability of the catalyst to perform multiple rounds of HAM with several additions of substrate, show potential for such hardiness. The ligand optimization studies found on/off activity for the species tested and suggest no reactivity trend that might be able to predict a more active NHC-ligand.

# CHAPTER 2: RHODIUM-CATALYZED HYDROIMINATION OF ALLENES

Abstract

Allyl amines are an important subclass of amines that are amenable to a wide berth of further functionalization. The hydroimination (HIM) of allenes produces 2-aza-1,4-dienes which upon hydrolysis offer a direct route to allyl amines with easily-controlled substitutions. Rh has been found to react imines and allenes to generate either [3+2] annulation products or linear HIM products. The work presented here demonstrates the optimization of a Rh-phosphine catalyst for the selective HIM of allenes by aryl N-H ketimines. The results obtained from optimization were found to match results that were published independently in the progress of the research. Brevity is presented for lack of reasonable impetus to continue the research beyond initial phase.

Introduction

Allyl Amines from Allenes and Imines

Allyl amines are a privileged subcategory of amines which offer a unique functionality and are highly amenable to further modifications (*Scheme 22*). These amines prove difficult substrates to arrive at selectively by classical substitution and rearrangement methods due to the simple allyl system's lack of 1,3-substitution selectivity. Therefore, an indirect method which can install the amine functionality by alternate means which produce an allyl system indirectly seems a viable solution. HAM of allenes with a nitrogen source would demonstrate this.
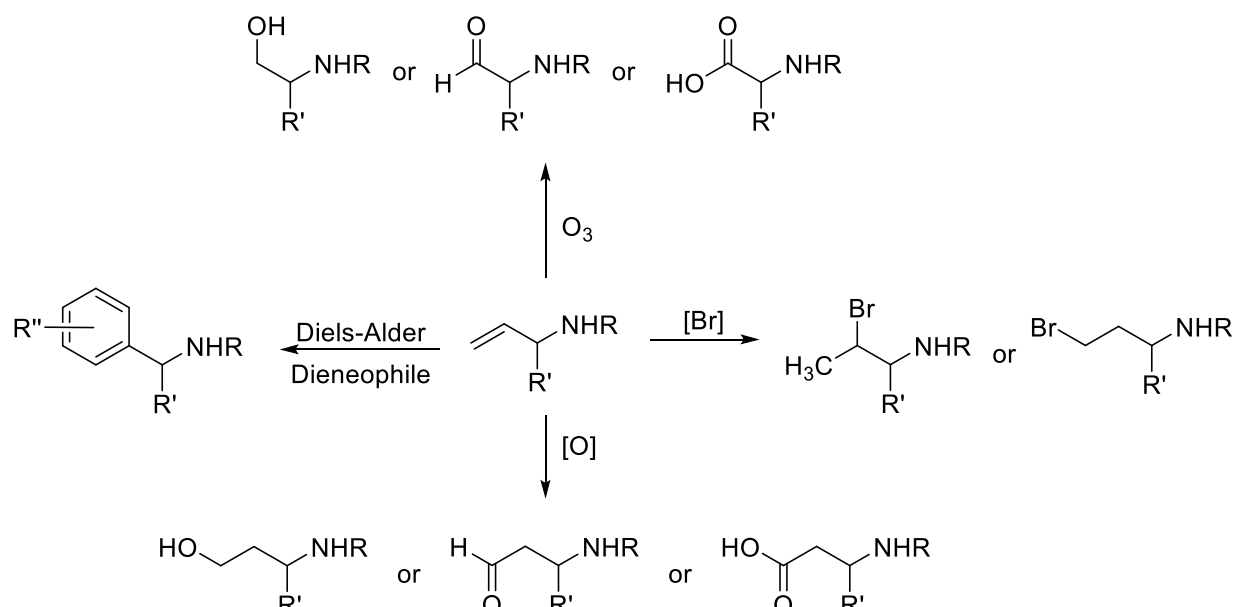
Scheme 22: Potential Allyl Modifications of Allyl Amines[5]

Allenes are another distinguished functionality consisting of a class of unsaturated carbon systems. Their reactivity is predictably between that of the alkene and alkyne in most cases, but their unique orthogonal and linear π-systems also infer for some exclusively unique reactivities.[59] Another facet of allene distinction is their unusual axial m and p chirality. Asymmetric syntheses for allenes with conferred axial chirality is a fairly underdeveloped area of synthesis despite the explosive growth in catalysis using them as substrates. The Doering-Moore-Skattebøl rearrangement of alkenes after addition by a dihalocarbene is a classical route to racemic allenes. Other routes can include rearrangement of alkene and alkyne π-systems into the allene functionality. In recent years, as catalysis finds more abundant uses for allenes, the community in turn has generated a near equal abundance of possible allene synthesis protocol.[60,61] Despite many innovative attempts, no universal and simple method exists for their synthesis especially in an asymmetric fashion. As a result, allenes are currently expensive substrates to buy and are limited in their commercial availability.

Previous works by our group on imine chemistry for Rh-catalyzed [3+2] annulation of alkynes revealed that linear HIM products (2-aza-1,3-dienes) are capable of being synthesized with proper ligand selection (*Scheme 23*).[62]
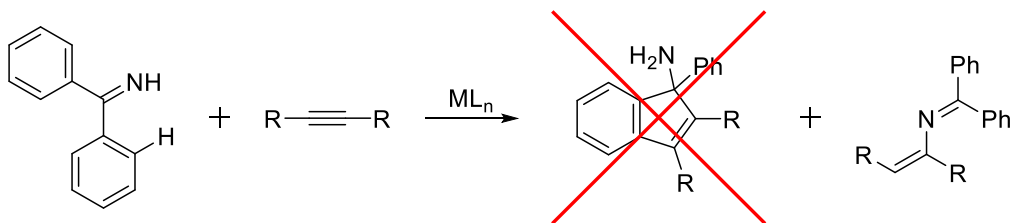
Scheme 23: Discovery of Imine HIM of Alkyne[62]

With the availability of tools to perform this reaction on a different substrate, the allene, Rh-catalyzed HIM of allenes seemed a natural choice for as potential avenue of research. Since HIM of allenes has previously been reported in other groups' efforts, a high degree of success was expected.[63,64] The HIM product, a 2-aza-1,4-diene has good potential for conversion to valuable allyl amine by hydrolysis. It is of interest to note the Cramer group was able to achieve selectivity for the [3+2] annulation product. The system presented here is similar to the Cramer-published system (*Scheme 24*).[65]
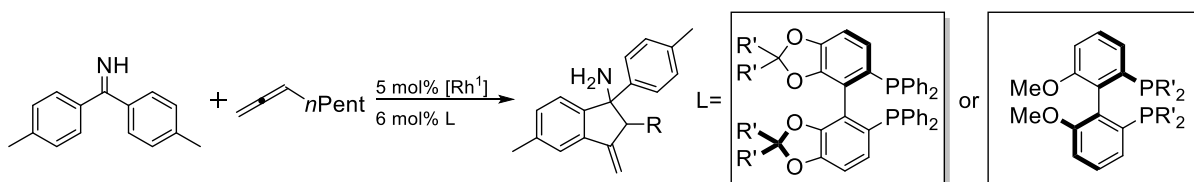
Scheme 24: Cramer [3+2] Annulation by Imine and Allene[65]

The research presented here is a summary of initial-stage discovery and optimization for the Rh-phosphine HIM system. Similar results were arrived at by the Breit group described in a recent publication (*Scheme 25*).[65]
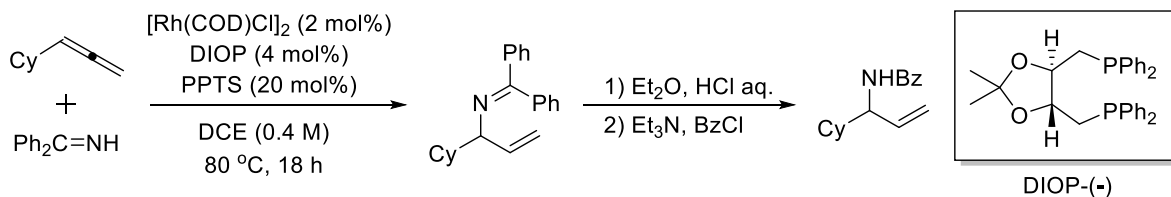
Scheme 25: Breit HIM of Allenes with Imines[66]

The conditions attained independently lead to a similar initial conclusion of that presented here. Breit's research proceeded to develop a system that successfully produces the N-protected allyl amine from a diverse group of substrates which this research originally was intended to develop.

Experimental

—Refer to general experimentation parameters described in **CHAPTER 1-Experimental**—

General Small Scale HIM

Inside the glovebox, solid Rh-precursor ([Rh(COE)Cl]$_2$ or [Rh(COD)$_2$]BF$_4$) (x mol%) and phosphine ligand (2.1*(Rh mol%) mol%) are added to a dried 1-dram screw-top glass vial gravimetrically. To the vial, a magnetic stir bar and appropriate (1-1.5 mL) amount of solvent are added. The mixture is topped loosely with a PTFE-lined phenolic screw cap and allowed to stir briefly (3-5 min). To this mixture, imine (1.0 eq) is added gravimetrically, the reaction is stirred briefly to incorporate imine, and lastly allene is added (1.5 eq) gravimetrically. The vial is then sealed tightly and removed from the glovebox and is promptly sealed with 3M super 33+ electrical tape. The vial is then hung in a silicone oil or ethylene glycol bath by a copper wire and heated at the appropriate temperature for the appropriate amount of time.

Results and Discussion

Initial investigations of the Rh-catalyzed HIM were carried out using GC/MS analysis (*Figure 22*). Having established by the retention pattern of the chromatogram using mass spectrometry, further analysis was carried out by GC to obtain peak area conversions. Conversions presented herein were determined by simple peak area to peak area comparisons normalized by an internal standard's peak area. This simplified method of analysis does not claim to have the rigor of a full study and as such, the results presented will be minimal. The

reaction conditions were never fully optimized beyond selection of an optimal temperature

(*Figure 18),* an appropriate ligand (*Figure 19*), and a feasible solvent (*Figure 20*), and a Rh-

precatalyst (*Figure 21*). The conditions settled upon are presented in *Scheme 26*.
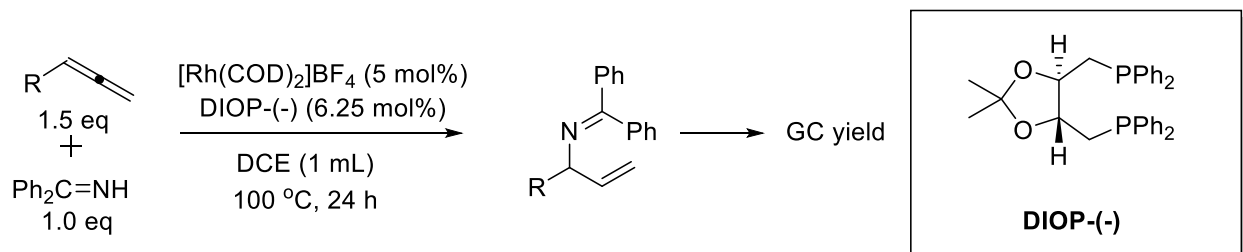
Scheme 26: Optimized Rh-HIM System

Preliminary optimization (not involving a complete GC analysis with replicates) was

conducted to determine a functional catalyst loading and reaction temperature (*Figure 18*).
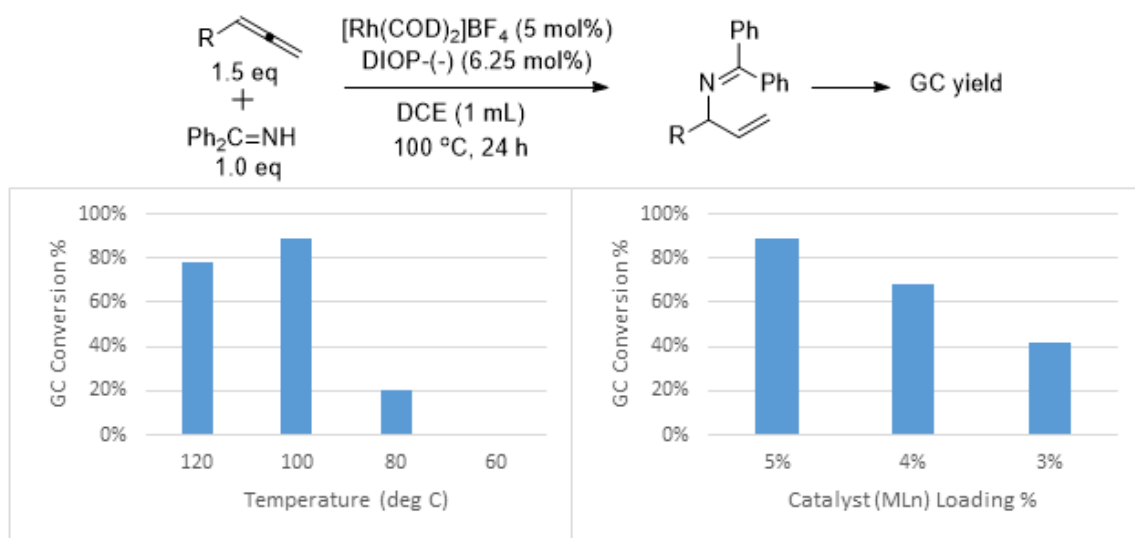
Figure 18: Temperature and Catalyst Loading Optimization

The results of the preliminary screening found that the reaction requires a temperature of

approximately 100 °C. Significant decreases in reactivity were observed below this temperature

indicating either catalyst activation or hydroimination is a thermally-assisted process.

Additionally, it appears that catalyst loadings below 5% will be impractical necessitating either

this relatively large amounts of Rh or the development of a more active catalyst.
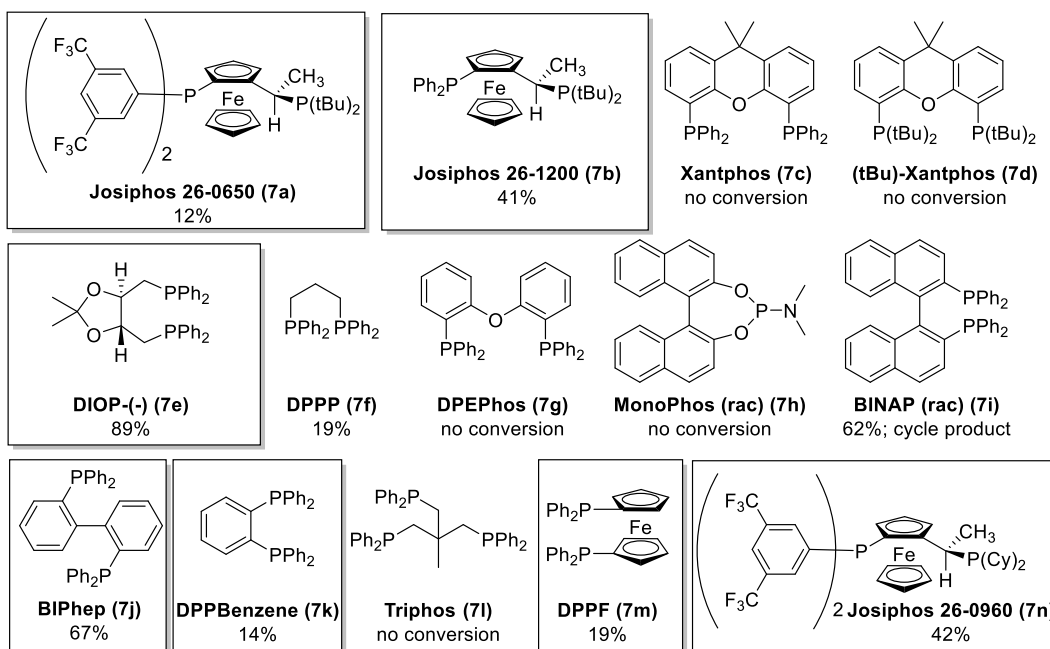
Figure 19: Ligands Screened in HIM Optimization

Significant efforts were made to discover a ligand that was capable of promoting HIM

reaction over [3+2] annulation while utilizing both commercially procurable and economically

viable reagents. Selection of reagents of good priced is made difficult where chiral control is

desired due to the cost of enantiomerically pure substance production. Fortunately, it was found

that the DIOP bis-phosphine ligand is capable of promoting the HIM reaction while satisfying

other factors far more than the exotic Josiphos ligands originally found to select for HIM.

BINAP, another affordable source of chirality, was discovered to give good conversion but the

[3+2] annulation was effected instead of HIM (*Scheme 27*).
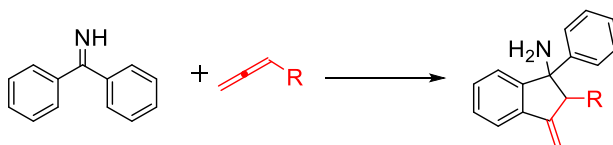
Scheme 27: [3+2] Imine and Allene Annulation

The synthesis of the 1-amino-1-phenyl-3-methyleneindane species was confirmed by GC.

The results were compared to samples produced using methods from the Cramer group.[64] The

chromatogram retention time for the [3+2] product was similar to the desired linear HIM product

but was different enough to be resolved in cases where both products were formed.

| **benzene** | **toluene** | **m-xylene** | **THF** | **DCE** | **1,4 dioxane** | **DME** |
| cyclization | cyclization | cyclization | no rxn | 78% | cycle | cycle |

Figure 20: HIM Solvents Tested During Optimization

Of the seven solvents screened, all but 1,2-dichloroethane (DCE) gave the undesired
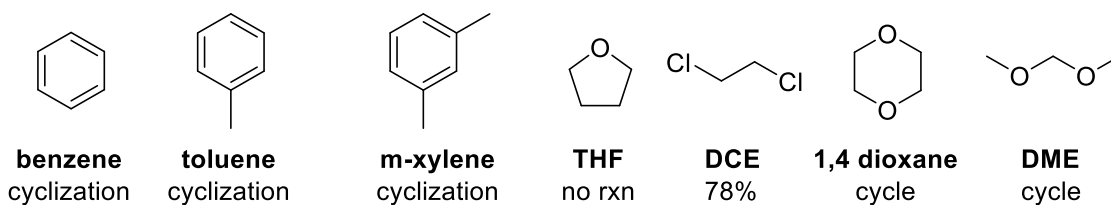
[3+2] indane cyclization product. DCE appears to have a special place with this reaction since it

was also the solvent the Breit group chose as their optimized solvent for the same reaction.

The last facet for optimization in this reaction was the choice of Rh precursor. Of two

possibilities—[Rh(COE)]$_2$Cl$_2$ and [Rh(COD)$_2$]BF$_4$—the latter was found to possess superior

catalytic activity. This is likely since the activation for monomeric species is more easily

performed than for dimeric species which may also suggest to the preliminary thermal-assistance

requirement of this reaction. The Rh sources were tested with the two best-performing ligands:

DIOP-(-) (7e) and **6a**: 68% and **6b**: 89%

Josiphos 26-1200 (7b) and **6a**: 26% and **6b**: 65%

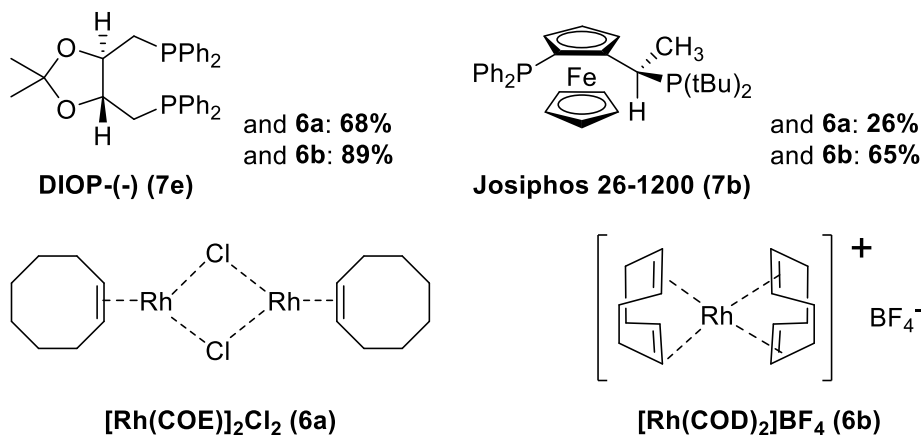**[Rh(COE)]$_2$Cl$_2$ (6a)**   **[Rh(COD)$_2$]BF$_4$ (6b)**

Figure 21: Rh Precursor Optimization

The isolation of the 2-aza-1,4-butadiene HIM product was attempted multiple times with

varying conditions. Each attempt was met with failure suggesting the unmodified HIM product is

elusive to direct isolation. Methods which utilize chromatographic separation appear

50

unsuccessful because instability on silica under normal conditions. Modifications which eliminate any harshness (alumina stationary phase, low polarity gradients, pH control by added base) are arduous and impractical to carry out precisely. N-protection was another option that was not explored for similar reasons. Ultimately, no successful isolation was ever achieved for the parent system.

Normally, optimization would be followed by substrate screening. Since only two allene substrates were available at the onset of this project, the substrate scope for this reaction is severely limited (*Scheme 28*). Also, before procuring prohibitively expensive allene substrates, it is first necessary to ensure the efficacy of a HIM system for production of isolable allyl amine products. However, without a broad sample of substrates to try, little can be said for predicting reactions. These conflicting points left research progress with a significant morass.
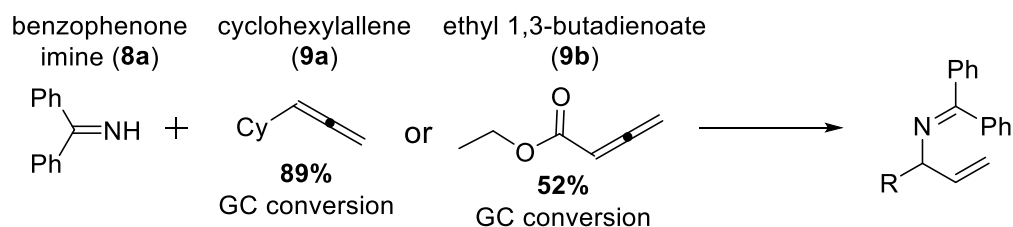
Scheme 28: HIM Substrates Tested

Without isolated product in hand to conclusively confirm HIM, it is needless to discuss the degree of GC conversion. GC conversion alone places this evidence of the HIM reaction occurring on speculative ground. Efforts were made into a third allene's procuration was attempted (*Scheme 29*), but the published method for synthesis of benzyl allene from benzyl magnesium bromide and propargyl bromide was ineffective demonstrating the high degree of allene synthesis difficulty.
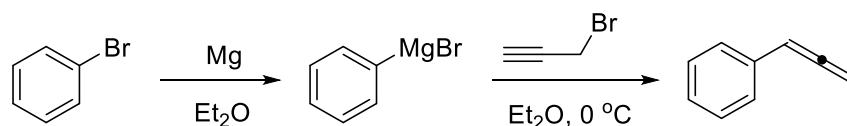
Scheme 29: Synthesis of Benzyl Allene from Phenyl Bromide[67]
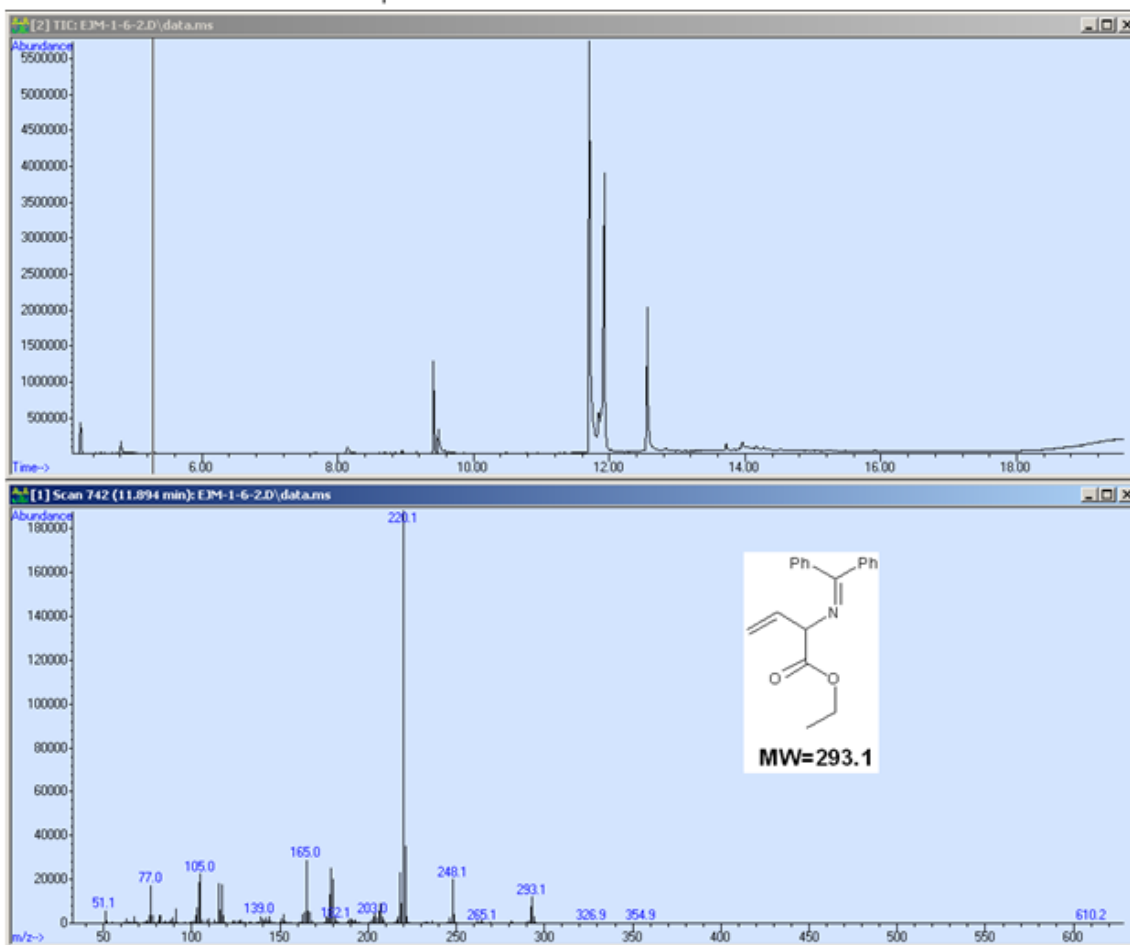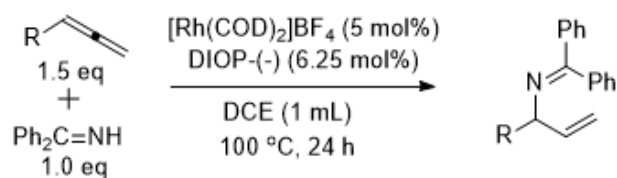
Figure 22: GC/MS Chromatogram of Ethyl 2,3-butadienoate and Benzophenone Imine HIM

Conclusion

From this body of research, a system capable of producing 1,4-azadienes from biaryl-ketimines and substituted allenes was established using a monomeric cationic Rh(I) precursor [Rh(COD)$_2$]BF$_4$ and chiral bisphosphine ligand—2,3-*O*-isopropylidene-2,3-dihydro-1,4-bis(diphenylphosphino)butane (DIOP). The system was optimized to the extent allowed by its limited exploration for factors of catalyst/ligand selection, temperature, solvent choice, and catalyst loading. The results of these findings helped design a catalyst system that appears

52

capable of good conversion for a subcategory of imines and allenes to desired HIM product(s). A method to easily isolate the amines produced by this system was never achieved. Furthermore, it is unknown by these results alone, how versatile this catalyst system will prove when applied to a wider variety of substrates. Inferred chirality in HIM products from chiral DIOP was never investigated. It seems reasonable these results would suggest the remainder of the body of evidence compiled by Breit in their more extensive investigation.

CHAPTER 3: FUTURE WORKS

The HIM of allenes, as presented in this body of work, has demonstrated that the valuable functionality of the allyl amine can be arrived at by novel C-N bond formation strategies. Since these targets are valuable for their synthetic utility, research into more efficient methods for their preparation should continue to be undertaken. Further development of the presented Rh-HIM system would not be of direct value in a novel or exploratory sense in regards to the Breit paper.[66] However, manipulation and improvement of the system may result in greater potential for efficient transformation as in the presented Ni-HAM research. Development of non-precious catalysts for substitution into the Rh-HIM system would be a logical next step in this area of research.

The results compiled by the Ni-HAM project have made for an exciting new avenue of discovery by an eco-friendly method to produce novel N-alkylated anilines. It is hoped this method may be adopted in the future to overcome barriers to synthesis of such novel amines by insufficiencies of established methods.

However, the HAM catalyst activity still fails to meet industrial standards of TON exceeding 1000 and TOF exceeding 200 h^{-1}.[22] Development of more activity catalysts will be a future requirement. This goal may be achieved either through better mechanistic understanding which allows for more careful implementation or different components for catalyst assembly (ligands or Ni-precursors). It is possible the ideal ligand choice will not be available commercially and additional novel synthesis will be required.

The scope of viable alkyne substrates remains unexplored but the groundwork established by this research to do so should ease the difficulty of this task. Additionally, this method is not a wholly modular tool for general secondary aryl amine synthesis since the β-position of the amine

will be limited to a single substituent by alkyne geometry. Furthermore, the Ni-HAM does not appear conducive to amines outside of the aniline family but this intolerance may only be limited by current catalyst activity.

The major focus of future efforts in Ni-HAM should be on the room-temperature HAM and tandem transfer-hydrogenation. The ability to perform the HAM followed by reduction at low temperature greatly decreases overall energy and material input. This area holds the most value to industrial and fine chemical synthesis since it also accords to motivation to utilize more efficient and green chemistry. Instrumentation which will make the operation simpler, especially where slow addition technique is required, should be developed to make the research progress more quickly as currently the process is quite labor intensive.

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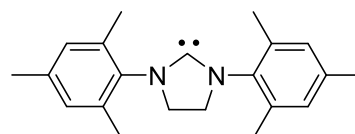
APPENDIX A: HYDROAMINATION SUBSTRATE STRUCTURES

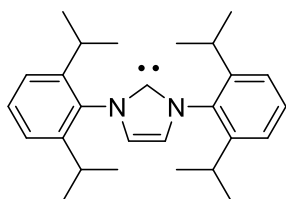## Ni and Carbene Ligands(1a,2a-d):
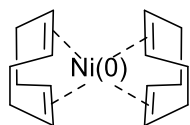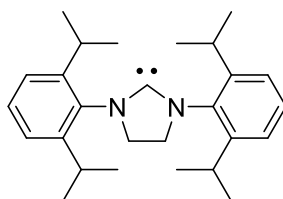
bis(1,5-cyclooctadiene)nickel(0)
(**1a**)
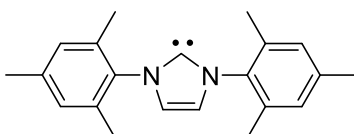
N,N'-(2,4,6-Trimethyl)
dihydroimidazol-2-ylidene (IMes)
(**2a**)

N,N'-(2,4,6-Trimethyl)
tetrahydroimidazol-2-ylidene
(sat IMes) (**2b**)

N,N'-(2,6-Diisopropylphenyl)
dihydroimidazol-2-ylidene (IPr)
(**2c**)

N,N'-(2,6-Diisopropylphenyl)
tetrahydroimidazol-2-ylidene
(sat IPr) (**2d**)

Amines(3a-g):
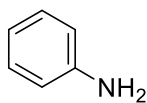
Aniline (**3a**)
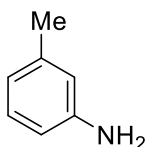
m-toluidine (**3b**)
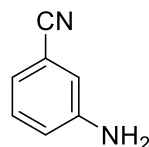
3-aminobenzonitrile
(**3c**)
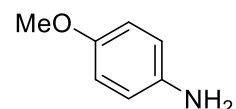
p-anisidine (**3d**)
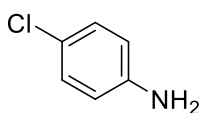
p-chloroaniline
(**3e**)
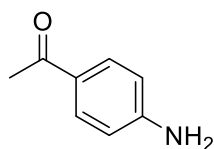
4'-aminoacetophenone
(**3f**)

morpholine (**3g**)

Alkynes (4a-b)
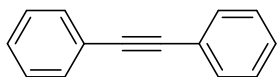
diphenylacetylene (**4a**)

1-phenyl-1-hexyne (**4b**)

EJM-1-131-2.1.fid
EJM-1-131-2

EJM-1-131-2.2.fid
EJM-1-131-2

45.28
59.34
113.77
117.62
126.59
126.84
127.19
128.66
128.70
129.16
129.34
137.81
143.55
147.40

62

EJM-1-85-3a 2nd spot m-toluidine.1.fid
EJM-1-85-3a 2nd spot m-toluidine

EIM-1-85-3a 2nd spot m-toluidine.2.fid
EIM-1-85-3a 2nd spot m-toluidine

64

Ph

NH

Ph

CN

3.03
3.05
3.07
3.09
3.18
3.19
3.22
3.23
4.40
4.42
4.59
4.61
4.62
4.62
4.63
4.64
6.67
6.67
6.67
6.68
7.37
7.39

15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
11.0
11.5

f1 (ppm)

0.99
1.00
0.97
0.99
1.94
1.09
11.03

EJM-1-85-1a 2nd spot 3-aminobenzonitrile.1.fid
EJM-1-85-1a 2nd spot 3-aminobenzonitrile

15000
10000
5000
0

4.40
4.42
4.59
4.61
4.62
4.62
4.63
4.64

0.97
0.99

4.3
4.4
4.5
4.6
4.7
4.8

f1 (ppm)

15000
10000
5000
0

3.03
3.05
3.07
3.09
3.18
3.19
3.22
3.23

0.99
1.00

2.9
3.0
3.1
3.2
3.3
3.4

f1 (ppm)

65

EJM-1-85-1a 2nd spot 3-aminobenzonitrile.2.fid
EJM-1-85-1a 2nd spot 3-aminobenzonitrile

66

EJM-1-139-9th15-13C
C220PPM

45.29
59.50
114.95
122.35
126.61
127.05
127.46
128.82
128.88
129.06
129.39
137.64
143.10
146.00

126.61
127.05
127.46
128.82
128.88
129.06
129.39

68

W125P-carbon.1.fid

26.02
44.78
58.72
112.47
126.40
126.95
127.44
128.66
128.76
129.22
130.58
137.16
142.30
151.20
196.3

126.40
126.95
127.44
128.66
128.76
129.22
130.58
130.59

f1 (ppm)

EJM-1-137-13Cα
C220PPM

39.50

51.50
52.23

65.98
67.47
72.69

126.00
127.31
128.11
128.11
128.96
129.61

139.46
139.96

126.00

127.31

128.11
128.11

128.96

129.61

EJM-1-147-tube-1H
H12PPM

R=Bu,R'=Ph-Major (88%)
R=Ph,R'=Bu-Minor (12%)

Major (88%)
Minor (12%)

R=Bu,R'=Ph-Major (88%)
R=Ph,R'=Bu-Minor (12%)

MeO

NH

R

R'

14.40

23.04
28.65
34.07
40.42

54.95
56.06

114.88
115.35

126.41
128.54
129.86

139.06
142.21

152.08

f1 (ppm)

114.88
115.35
126.41
128.54
129.86

f1 (ppm)