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NITROGENATION OF HYDROCARBONS VIA TRANSITION-METAL AND NON-METAL CATALYSIS

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NITROGENATION OF HYDROCARBONS VIA TRANSITION-METAL AND NON-METAL CATALYSIS

A DISSERTATION APPROVED FOR THE
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

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"One doesn't discover new lands without consenting to lose sight

of the shore for a very long time" - Andre Gide

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ABSTRACT

The overall objective in the Nicholas Group's Amination Project is to develop new methodologies to form C-N bonds via C-H functionalization that utilize transition metal activation of non-polar and otherwise unreactive saturated and unsaturated hydrocarbons. Within this context, several new methodologies have been discovered and developed in the field of amination, and are presented within this document. For example, investigations aimed at the development of a mild allylic amination using nitroaromatics as *N*-source have resulted in a novel sodium borohydride and iron (II) phthalocyanine promoted reaction, the first example of microwave-assisted allylic amination, and a new Fe-Cu co-catalyst system that produces allylamine product in > 98% *N*-selectivity. In addition to allylic amination, we have developed a new iron (II) phthalocyanine catalyzed indolization of arylalkynes and *N*-aryhydroxylamines in order to form parent (NH) indoles efficiently in one-step. Several new indoles as well as some biologically relevant targets have been produced with this method. Finally, we have developed the first non-transition-metal-catalyzed aminosulfonation of hydrocarbons. In addition, we have discovered the first protic acid-catalyzed amidation as well as a novel I_2-catalyzed nitrenoid C-H insertion of benzylic, tertiary, and secondary saturated hydrocarbons. During mechanistic investigations of the iodine-promoted reaction, a novel aminating agent was discovered that is stable at $< 0^{\circ}C$ and efficiently produces aminosulfonated hydrocarbons under remarkably mild conditions.

CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1   Synthesis of Amines in Organic Chemistry

The nitrogen atom is an important fixture in nature, present in a wide variety of natural product families including amino acids, alkaloids, penicillins and porphyrins. It is generally incorporated via condensation reactions with pre-installed oxygen functionality through a biosynthetic pathway.[1] In addition, nitrogen is of key importance in biology due to its flexibility, *i.e.* the ability to carry a positive charge, act as a hydrogen bond donor/acceptor, and possession of pKa values typically in the range of physiological pH. Due to these important factors, nitrogen containing functionalities are also ubiquitous in pharmaceutical drug compounds. In fact, synthetic drugs generally contain more nitrogen than natural products.[2] Finally, nitrogen is essential to material science, as its presence in polymers and dyes can have large effects on their physical, surface, or electronic properties.[3,4]

Due to the abundance and importance of amines and nitrogen-containing heterocycles as synthetic intermediates and end-products, the incorporation of nitrogen-containing functionalities via novel C-N bond forming methodologies has been and continues to be intensely investigated. Classical methods such as reductive carbonyl amination, nucleophilic displacement of a leaving group, or imine alkylation have been firmly established in organic synthesis.[5] Modern amination methods such as allylic amination,[6] hydroamination[7] and diamination[8] of alkenes, Buchwald-

Hartwig C-N coupling,[9,10] and metal-imido "nitrenoid" insertion[11] have emerged as valuable tools due to the advent of transition metal-catalysis and are quickly joining the myriad of classical organic synthetic reactions.

1.2   Classical and Modern Amination Methods

Due to the importance of amines in a variety of fields, amination has been intensely investigated for well over 100 years. During this time, a number of well established, or "classical", methods have been produced. These methods are presented in Figure 1.1 and can be classified into three main areas: reduction (of a nitro or an imine),[12] alkylation (of an imine or amine),[13] and substitution (of an amine with an electrophile).[13] The most common and straightforward route to forming C-N bonds is via direct *N*-alkylation of a primary amine with alkyl halides, though the method is substantially limited by overalkylation, giving rise to mixtures of primary, secondary, tertiary, and quaternary ammonium salts.[13] The most important feature of all classical methods is the requirement of pre-functionalized starting materials including acyl (imine), alkyl halide, alkyl alcohols, and/or nitro units in order to proceed. In addition, the pre-existing group is exchanged for an amine, thus destroying the original functionality and decreasing the atom economy of the reaction relative to a method employing C-H activation.

CLASSICAL AMINATION METHODS

R-NH$_2$ + R'-OH   R-NH$_2$ + X-R'

SUBSTITUTION   Condensation   *N*-Alkylation   ALKYLATION

Nucleophilic
Substitution

R'-NH$_2$ + R-LG ⟶ R—NHR' ⟵ R—N=R'
                    Alkylative Addition
                    to Imine

+ Nu⁻

Reduction
of Nitro   Reduction
                  of Imine

R—N=R' ⟵ O‖R'

R-NO$_2$ REDUCTION   + H⁻   + R-NH$_2$
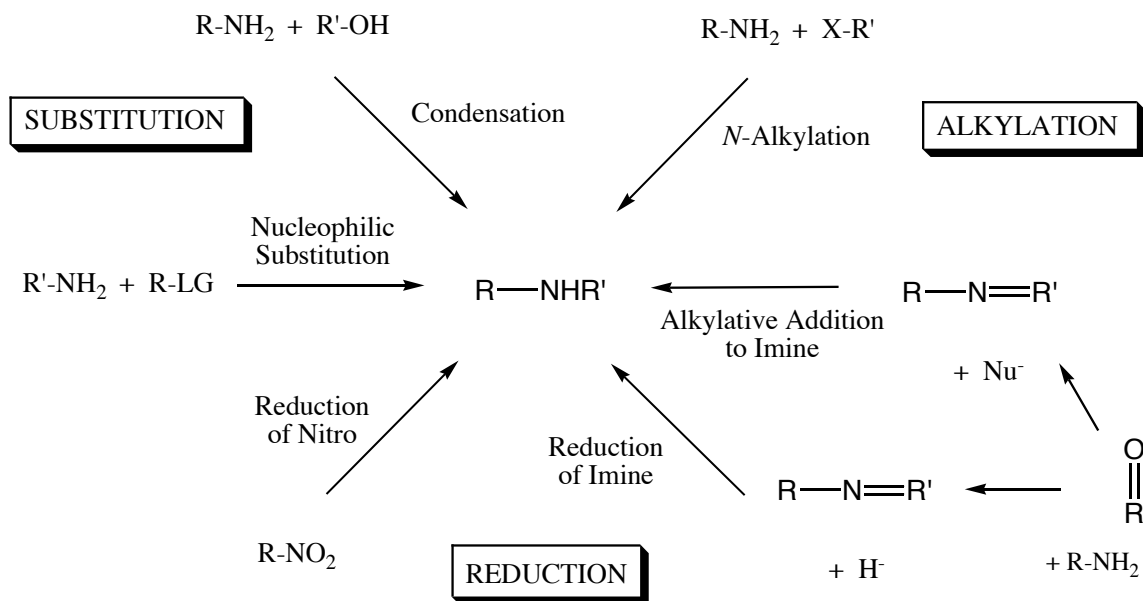
Figure 1.1

Modern amination methods have been developed largely within the last thirty

years and have focused on improving the previous problems in amination of atom

economy, chemo- and regioselectivity, and conservation of functional groups on the

reactive substrates.[14] One class of molecules that has proven quite flexible as a

reactive partner in modern amination methodology is the alkene (Figure 1.2).

Depending upon conditions, *N*-reagent, and catalyst, a number of useful

transformations can occur with alkenes including: hydroamination,[7] aziridination,[15,16]

diamination,[8] and allylic amination.[6] Hydroamination, aziridination, and diamination

all involve the loss of the C-C unsaturation, however allylic amination offers unique

potential with regard to the conservation of a chemical handle for further reactivity.

Allylic amination occurs via two main pathways: the nucleophilic substitution of a π-

allyl complex (which can suffer from regioselectivity issues), and C-H allylic amination occurring via an "ene"-like transfer.[6] Of these methods, the "ene" type allylic amination is more attractive as it is more atom-economical and does not require a pre-functionalized alkene. Progress in the field of allylic amination will be summarized in more detail in Section 1.2.1.

MODERN AMINATION METHODS
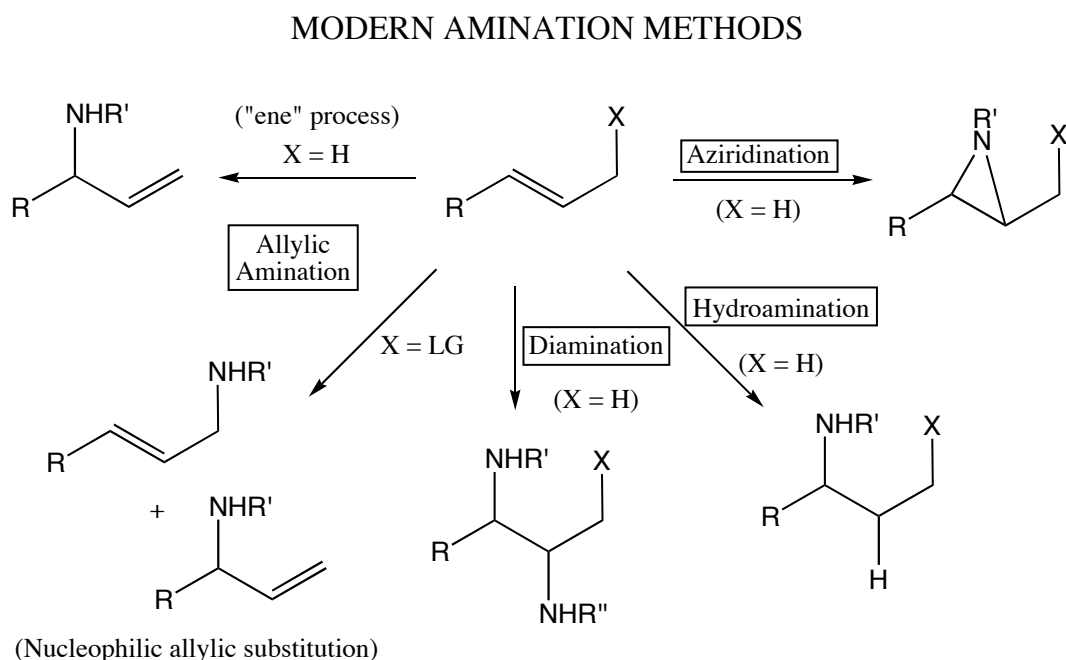
Figure 1.2

In addition to alkenes, another class of molecules that has been intensely investigated recently as effective amination partners are aryl halides used in conjunction with *N*-nucleophiles and palladium or copper catalyst systems, in reactions typically referred to as Buchwald-Hartwig couplings (Figure 1.3).[9,10] Though the direct arylation of amines with aryl halides has been largely successful and has quickly become viewed as a standard synthetic method of amination, the

requirement of pre-functionalized aryl coupling partners presents a potential limitation to that of more recently developed C-H activations of aryl substrates via metal-imido or metal-nitride complexes.

Finally, the most recently developed, and perhaps the amination method with the highest potential, is the direct C-H to C-N bond conversion via nitrenoid insertion (Figure 1.3).[11] Like "ene" process allylic amination reactions, these systems do not result in transformaton (or destruction) of pre-existing functionalities. More importantly, this method also does not require pre-functionalization of the reacting hydrocarbon substrate. The –NR unit insertion via transition metal-catalyzed reactions of nitrenoid precursors will be discussed in more detail in Section 1.2.2.

MOST RECENT MODERN AMINATION METHODS
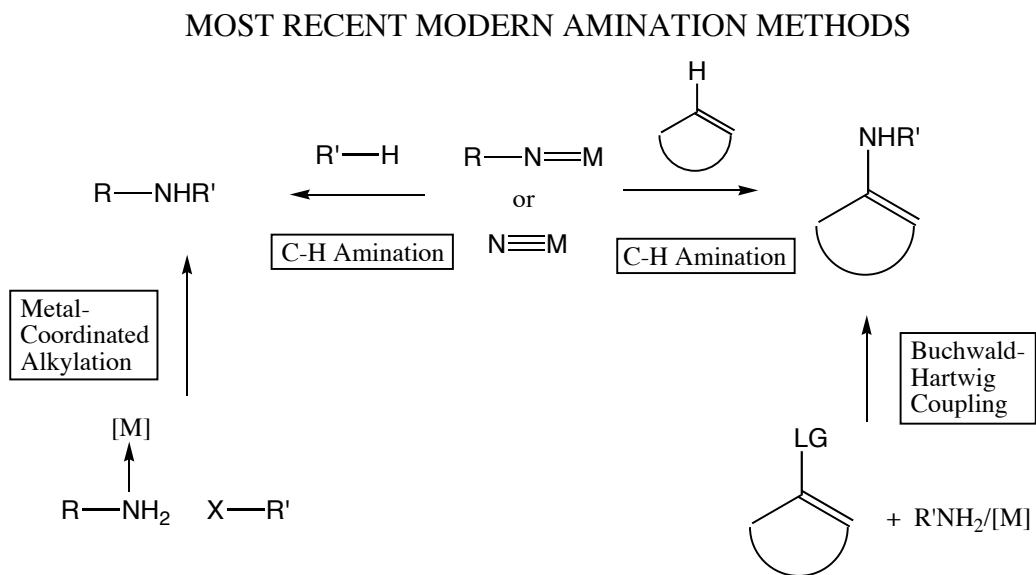
Figure 1.3

1.2.1 Allylic Amination

The allylamine motif represents an important building block in organic chemistry due to the possibility of further functionalization of the double bond. In addition to being important and versatile intermediates, the allylamine fragment can also be encountered intact in many natural products.[6] The two main methods of synthesizing allylamines are shown in Figure 1.2. In the nucleophilic substitution method, a pre-formed allylic leaving group is required. Examples of this type of transformation are shown in Figure 1.4 and include the Mitsunobu reaction (allyl alcohols), Gabriel synthesis (allyl halides), and nucleophilic substitution of a transition-metal π-allyl complex formed from allyl halides or acetates (which can suffer from regioselectivity issues).[6] Though some of these nucleophilic substitution systems can produce high yields and regioselectivities, they all require a pre-functionalized allylic substrate, which detracts from their overall generality and atom economy.

NUCLEOPHILIC ALLYLIC SUBSTITUTION METHODS

Figure 1.4

6
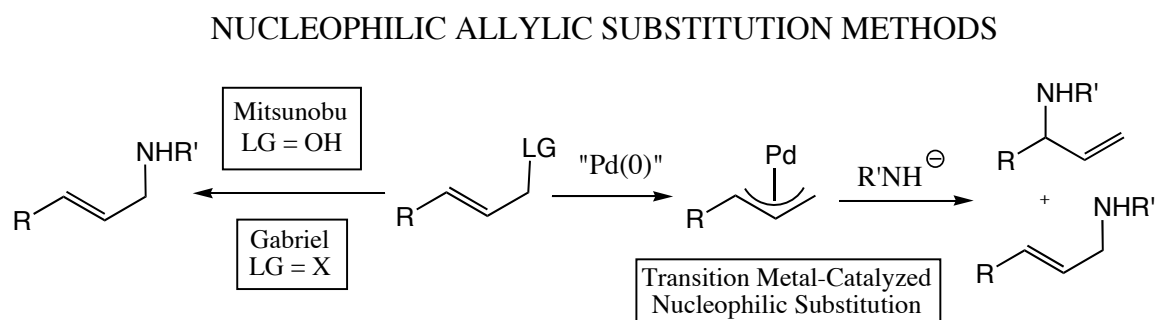
In the second method of allylic amination, a simple allylic unit undergoes C-N bond formation via C-H activation through an "ene"-like process. Several N-transfer reagents have been developed for this type of "N-ene" reaction including nitroso compounds **1,** electron-deficient azo compounds **2**, and diimido complexes of sulfur and selenium **3** (Scheme 1.5).[6,17] The nitroso compounds offer a distinct atom-economical advantage over the diimido and azo reagents as the latter only form one C-N bond from the two reactive nitrogens of the reagent, with the other being cleaved in a separate step to produce the amine.

ALLYLIC AMINATION VIA "ENE" PROCESSES
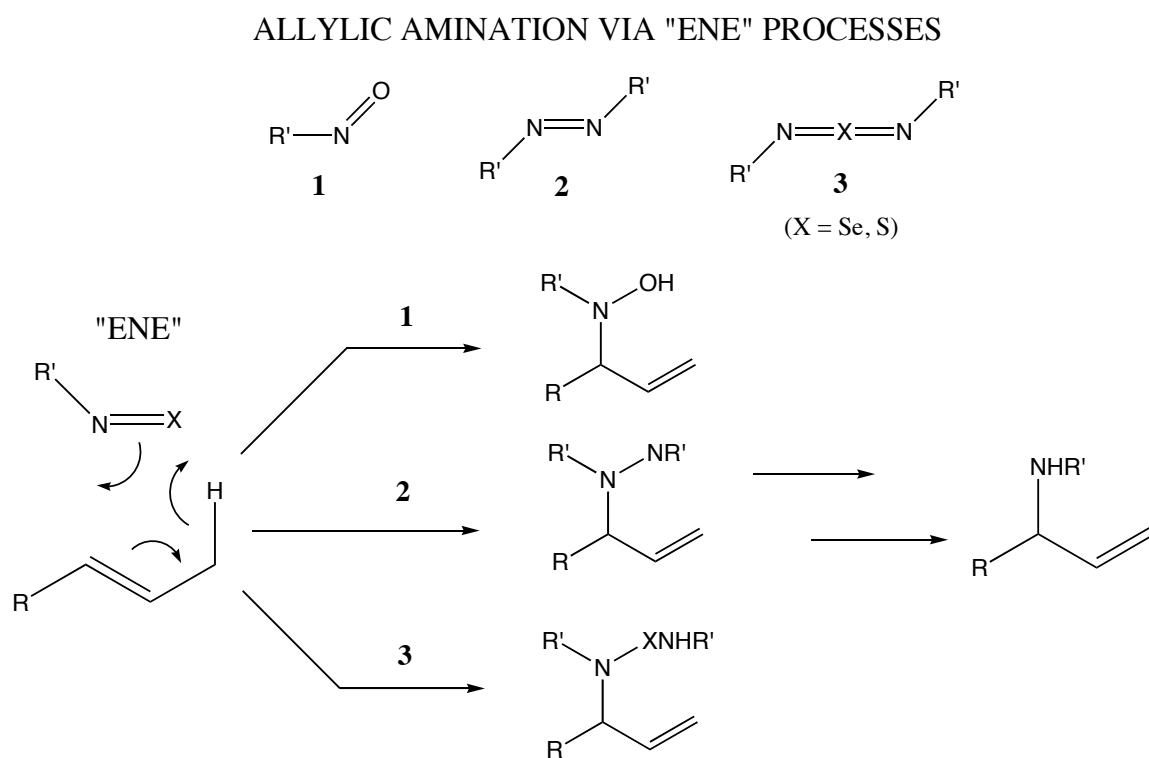
Figure 1.5

Beginning in the early 1990s, the majority of developments in the field of intermolecular allylic C-H activation-amination have been presented by Nicholas and

Srivastava. In their work, molybdenum(VI),[18-20] iron(II,III)[21,22] and copper(I)[23,24] catalysts have promoted C-H amination of simple alkenes with employment of arylhydroxylamines as the *N*-aminating reagent. The arylhydroxylamines are oxidized *in situ* to nitrosoaryls, which can then undergo a nitroso-ene reaction,[17] and the resulting allylic hydroxyamine is reduced *in situ* to regenerate the catalyst and produce the allylamine. Though the amination occurs with high regioselectivity at the less substituted carbon, modest yields with somewhat limited substrate scopes are obtained by employment of an excess of alkene substrate, thus limiting the overall synthetic potential of the method. The arylhydroxylamine systems are described in more detail in Chapter 3, Section 3.1.1. In addition to arylhydroxylamines, catalytic systems employing more stable and commercially available nitroaryl substrates have also been developed by Nicholas and Srivastava.[25] These systems are discussed in detail in Chapter 2, Section 2.1.1. To date, disadvantages of the reductive nitroaryl system include harsh reaction conditions including high temperatures and high CO pressure.

Perhaps a more promising result with regard to the development of a more general reaction has been reported within the last few years by the M. C. White Group. An initial investigation was conducted of an intramolecular palladium-catalyzed allylic C-H activation system in which *N*-tosylcarbamates such as **4** are converted to oxazolidinones **5** with high regioselectivity (Scheme 1.6).[26]
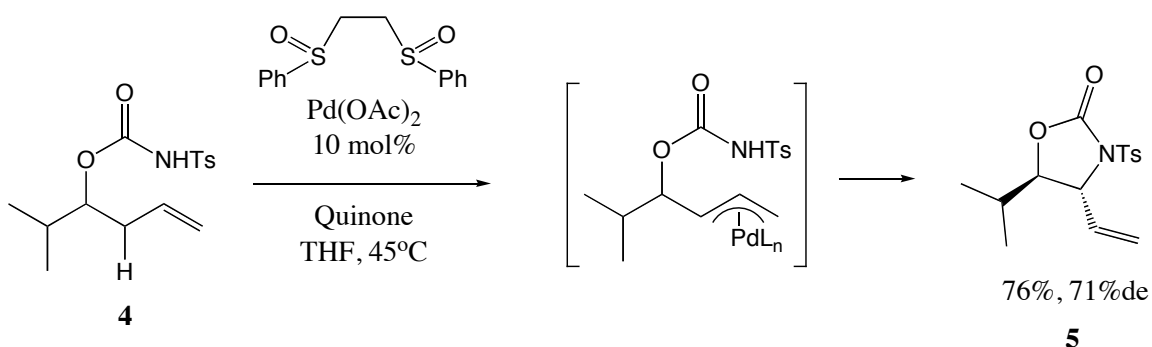
Figure 1.6

Following the intramolecular report, an intermolecular version was designed by Reed and White employing terminal olefins (Figure 1.7).[27] In the reaction, a combination of Pd(OAc)$_2$-bis-sulfoxide and Cr(III) complex transform terminal olefins used in stoichiometric amounts into linear (*E*)-allylic amines with excellent regio- and stereoselectivity (linear: branched amines = >20:1; (*E*) : (*Z*) olefins = >20 : 1). The reaction appears to accommodate a wide range of functionalities, though it appears that the system may be limited to the use of terminal olefins as allylic substrates. In addition, Liu *et al*. have reported an analogous system in which intermolecular allylic amination results are obtained with similar tolerance to functionality and regioselectivity (Scheme 1.7).[28] In this system, Pd(OAc)$_2$ and sodium acetate under an O$_2$ atmosphere facilitate amination of a *N*-tosyl-carbamate in the presence of maleic anhydride. The reaction proceeds with lower efficiency than the Pd-Cr bimetallic system, as three equivalents of alkene or 20 mol% of palladium catalyst are necessary to ensure good yields.

Figure 1.7

1.2.2 Transition Metal-Catalyzed Amidation of Hydrocarbons via Nitrenoid Precursors

Similar to allylic amination methods involving an "ene" process, the ability to directly replace a hydrogen with an amino group via a transition metal-catalyzed nitrenoid transfer is an extremely attractive method of amination as it does not require a pre-functionalized substrate, and generally does not destroy any pre-existing functionality on the reactive molecule. Following the seminal work in the early 1980s on the rhodium-catalyzed intramolecular amidation of hydrocarbons by Breslow[29] and the intermolecular version by Mansuy,[30] a large number of *N*-aminating agents have been developed in conjunction with transition metal-catalysts in order to facilitate efficient C-H bond amination. To date, transition metal-catalysts employed include those of rhodium,[31-40] ruthenium,[41-44] cobalt,[45-47] manganese,[41,42,48,49] silver,[50]

gold,[51] palladium,[52,53] iron,[54] and copper.[55-59] Commonly exploited C-H bonds include those with lower dissociation energies, such as benzylic, allylic, and α-ethereal positions, though reactivity has been demonstrated with a broad variety of higher energy C-H bonds (Figure 1.8). With current methods producing highly regio- and chemoselective C-H insertion reactions, applications of these systems have been steadily increasing and should continue to receive attention in synthetic organic chemistry in the future.

C-H BOND DISSOCIATION ENERGY (kcal/mol)
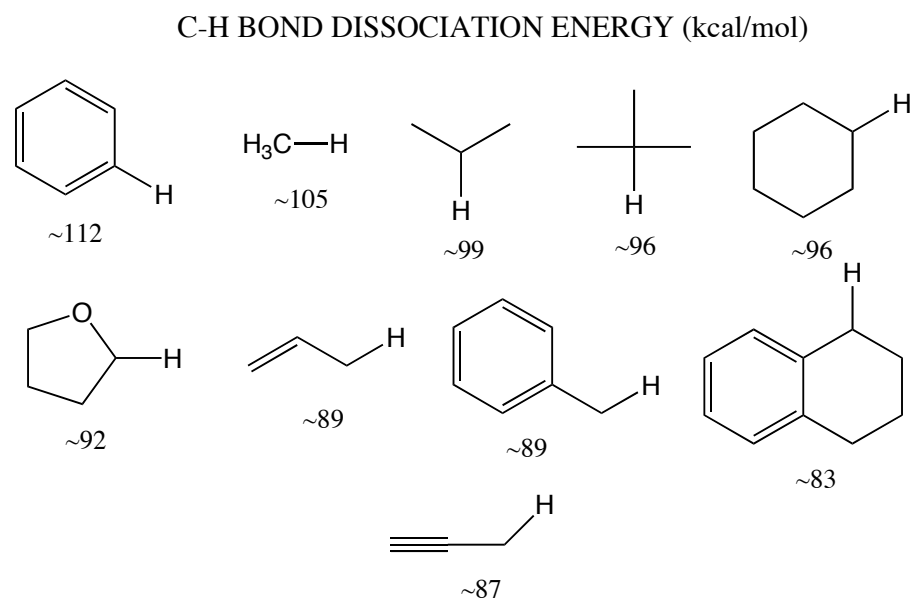
Figure 1.8

1.2.2.1   Common Nitrenoid Precursors

In general, the three main types of aminating agents that are used in conjunction with transition metal-catalysts in direct C-H amination reactions of hydrocarbons are I-N iodonium ylides **10** (commonly referred to as

11

imidoiodinanes),[60] *N*-halogenated amido sodium salts **11** (shown in Figure 1.9 as commercially available chloramine-T), and azides **12**.

10

R^1 = Me PhI=NTs
R^1 = NO$_2$ PhI=NNs

R^2 = Me; X = Cl Chloramine-T
R^2 = H; X = Cl Chloramine-B
R^2 = NO$_2$; X = Cl Chloramine-N
R^2 = Me; X = Br Bromamine-T

11

R^3 = Ts Tosylazide
R^3 = 1-adamantyl
1-Adamantylazide

12
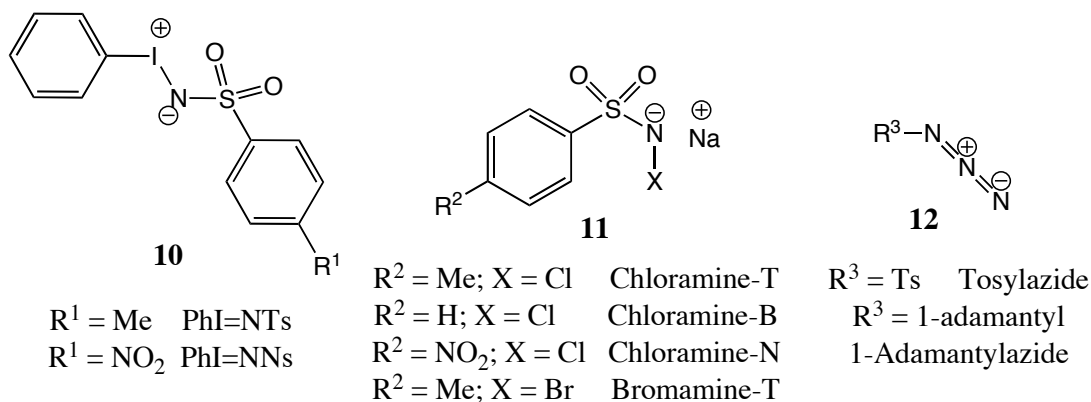
Figure 1.9

To date, the imidoiodinanes have received the majority of attention in C-H insertion reactions due to their higher reactivity and the recently developed method of *in situ* preparation[41] from a combination of commercially available sulfonamide, PhI(OAc)$_2$, and MgO. The first example of an iodonium imide to be synthesized was derived from methanesulfonamide and was reported by Abramovitch in 1974,[61] though many attribute Yamada's 1975 isolation of [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) as the seminal report on imidoiodinanes.[62] Since that time, several varieties of sulfamates, ureas, guanidines, carbamates, and sulfamides have been used in conjunction with hypervalent iodine reagents in the presence of transition metal catalysts to provide intra- and intermolecular C-H functionalization.[11] Though frequently employed, the imidoiodinanes suffer from a number of notable drawbacks, including the

employment of an oxiding agent such as PhI(OAc)$_2$ typically in excess, and the production of toxic iodobenzene as main by-product.[60]

As "greener" alternatives to imidoiodinanes, azides (producing N$_2$ as by-product) and commercially available chloramine-T trihydrate (producing innocuous NaCl as by-product) have also been employed, though in surprisingly relatively few studies given their potential. Along with imidoiodinanes, these *N*-aminating agents were initially employed for aziridination reactions of olefins,[60] but in the last ten years have been shown to be suitable for C-H insertion reactions when employed with transition metal-catalysts.[56,58] More recently, Lebel *et al.* introduced the use of *N*-tosyloxycarbamates (Troc-NH-OTs, **13**), which release a tosylate salt easily removed by aqueous workup (Figure 1.10).[63]

Finally, chiral versions of nitrene precursors have also been developed by Dauban and Dodd and used in stoichiometric amount in conjunction with a chiral rhodium catalyst in order to produce diastereoselective C-H insertions.[36,38] These chiral iminoiodinanes **14** (Figure 1.10) are formed from sulfonimidamides utilizing an *in situ* oxidation via PhI(O$_2$C^{t}Bu)$_2$.
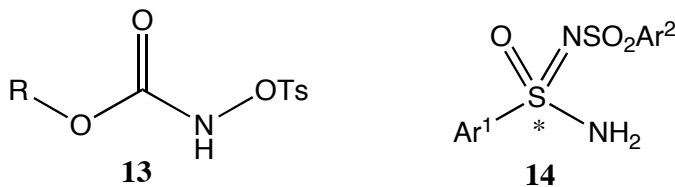
Figure 1.10

1.2.2.2 Transition Metal Nitride Complexes

Nitrenoid precursors are generally believed to form reactive metal-imido complexes *in situ* in the presence of redox-active transition metal-catalysts (Figure 1.11).

$$[M] \ + \ \begin{array}{c} TsNNaCl \\ or \ PhI=NTs \end{array} \longrightarrow \ ^{"}[M=NTs]^{"} \ + \ PhI$$

metal-imido species
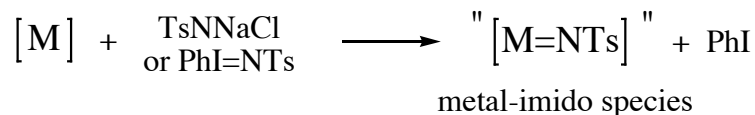
Figure 1.11

Structurally related and potentially similar in reactivity are the more thoroughly characterized and extensively studied transition metal nitride complexes (Figure 1.12). Complexes have been synthesized from a wide variety of high oxidation state transition metals including chromium, manganese, molybdenum, osmium, tantalum, rhenium, vanadium, ruthenium, technetium, and tungsten.[14] Well over 30 different *N*-atom sources have been applied to form metal nitrides as well, due to the lack of a general preparation.[14]

$$L_x \!-\! M \!\equiv\! N$$

Transition-metal nitride species
M = Cr, Mo, Mn, Os, Re, W, Ta, Ru, V, Tc
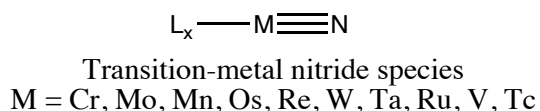
Figure 1.12

The metal-nitride structural motif has been employed in nitrogen-transfer reactions to both inorganic and organic acceptors with several of these complexes, with the most notable examples found in aziridination reactions employing

manganese salen or porphyrin complexes. Asymmetric versions of the aziridination reaction have also been developed utilizing chiral complexes such as **15**[64] (Figure 1.13) resulting in very high ee's (> 90%). The asymmetric amination has additionally been extended to silyl enol ethers resulting in enantioselectivity up to 79% ee.[64] Although nitrido complexes are typically stable and easy to prepare and handle, the current disadvantage lies in the need for stoichiometric amounts of the complex in order for nitrogen transfer to proceed. Much more catalytically relevant are the metal-imido species that can be generated via the use of nitrenoid precursors.

15
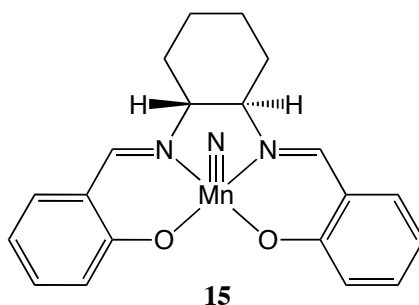
Figure 1.13

1.2.2.3   Intramolecular Transition Metal-Catalyzed Amidation of Hydrocarbons via Nitrenoid Precursors

Generally investigated before or concurrently with respective intermolecular counterparts, several intramolecular systems have been developed using nitrene precursors to induce selective C-H bond amination following Breslow's seminal work in the early 1980s. The first major advance of Breslow's system was reported by Espino and Du Bois in 2004 in which an internal delivery of a formal nitrenoid unit formed *in situ* by the combination of PhI(OAc)$_2$ and MgO in the presence of a

rhodium catalyst resulted in highly regioselective insertion into C-H bonds.[34] It was observed that utilization of $Rh_2(tpa)_4$ (tpa = triphenylacetate) as catalyst resulted in carbamates selectively inserting into the β C-H, and sulfamates into the γ–position (Figure 1.14). Due to electronic effects, the preferred reacting positions are α-ethereal, tertiary, and benzylic sites.
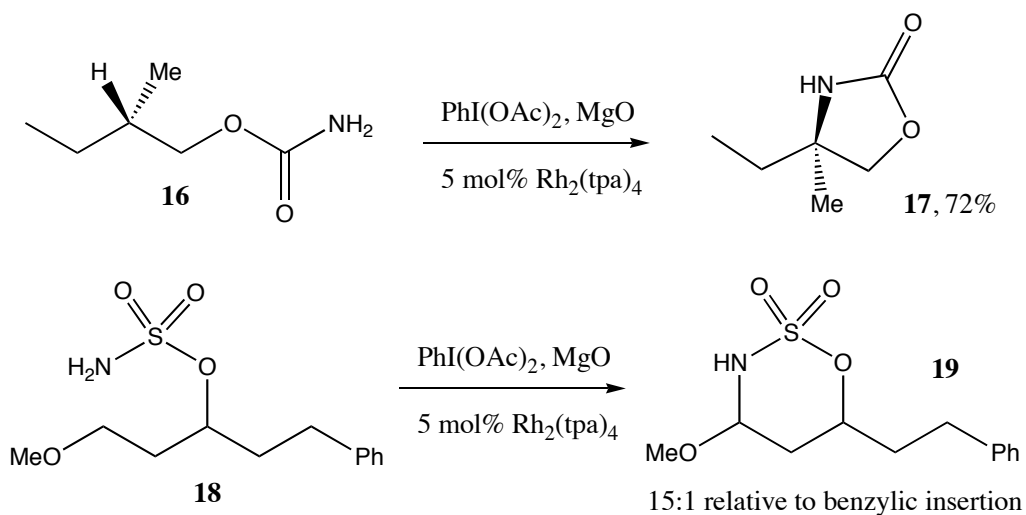
Figure 1.14

Following this initial breakthrough, most advances to improve the reaction scope have come by means of either new catalyst development or the utilization of new nitrene precursors. Due to difficulties arising from catalyst degradation in their previous system, Du Bois *et al.* have designed a more robust catalyst, $Rh_2(esp)_2$ (**22**), from two identical bidentate ligands comprised of *m*-benzenedipropionic acid.[34] This catalyst has allowed for the extension of the substrate scope to include ureas,

guanidines,[65] and sulfamides[66] as well as 1,2-diamines via a sulfamate derived from hydroxylamines of type **20** (Figure 1.15).[67]

Mbs = *p*-methoxybenzenesulfonyl
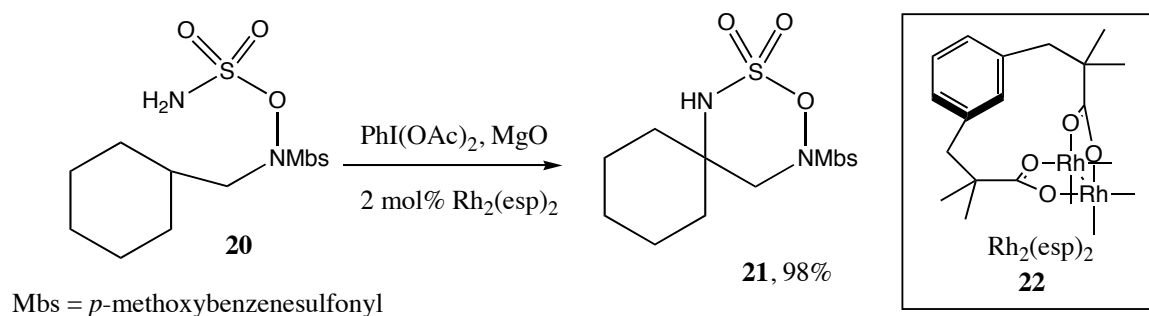
Figure 1.15

In addition to catalyst design, other major advances have arisen from the development and utilization of "greener" nitrene precursors, due to imidoiodinanes release of a stoichiometric amount of iodobenzene. In 2005, Lebel *et al.* introduced the more innocuous Troc-NH-OTs **13**, and results from this rhodium-promoted system are comparable to those derived from hypervalent iodine reagents in regard to chemo- and regioselectivity, yields, and even enantioselectivity when employing a chiral rhodium catalyst.[40,63] In addition, Lebel's Troc-NH-OTs system displays the rare capability of a nitrenoid C-H insertion into a primary position (Figure 1.16, **25**).
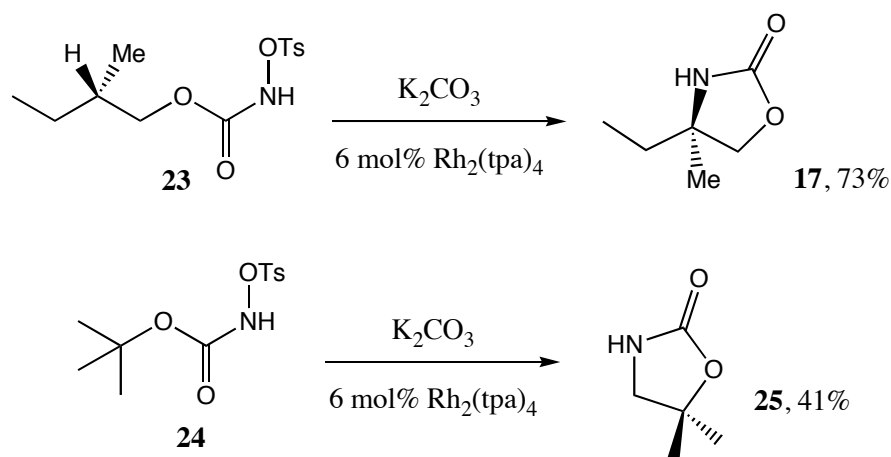
Figure 1.16

The potential for catalytic asymmetric induction has been addressed recently by several groups via the design and employment of various chiral ligands. Most of the success to date has come from rhodium-catalyzed systems, such as Du Bois' $Rh_2(S\text{-nap})_4$, in which an amide-derived Rh^{II} complex **26** was used for the first time in C-H amination resulting in ee's typically in the 60-99% range (Figure 1.17).[68] In addition to the success of Rh^{II} systems, chiral ruthenium porphyrins have induced asymmetric nitrenoid C-H insertions in up to 87% ee.[42] Due to the difficulty of chiral porphyrin preparation, Blakey *et al.* designed a cationic Ru^{II} pybox complex **27** that displayed comparable efficiency to that of the rhodium-catalyzed systems (Figure 1.17).[69] Though success has been found with benzylic and allylic substrates, asymmetric induction has been thus far limited to these positions.

Figure 1.17[11]

PhIO, 2 mol% **26**   87%, **99%ee**   PhIO, 2 mol% **26**
PhI(OCO^{t}Bu)$_2$, 5 mol%   68%, **90%ee**   PhI(OCO^{t}Bu)$_2$, 5 mol%
AgOTf, 5 mol% **27**   AgOTf, 5 mol% **27**

51%, **54%ee**
60%, **89%ee**
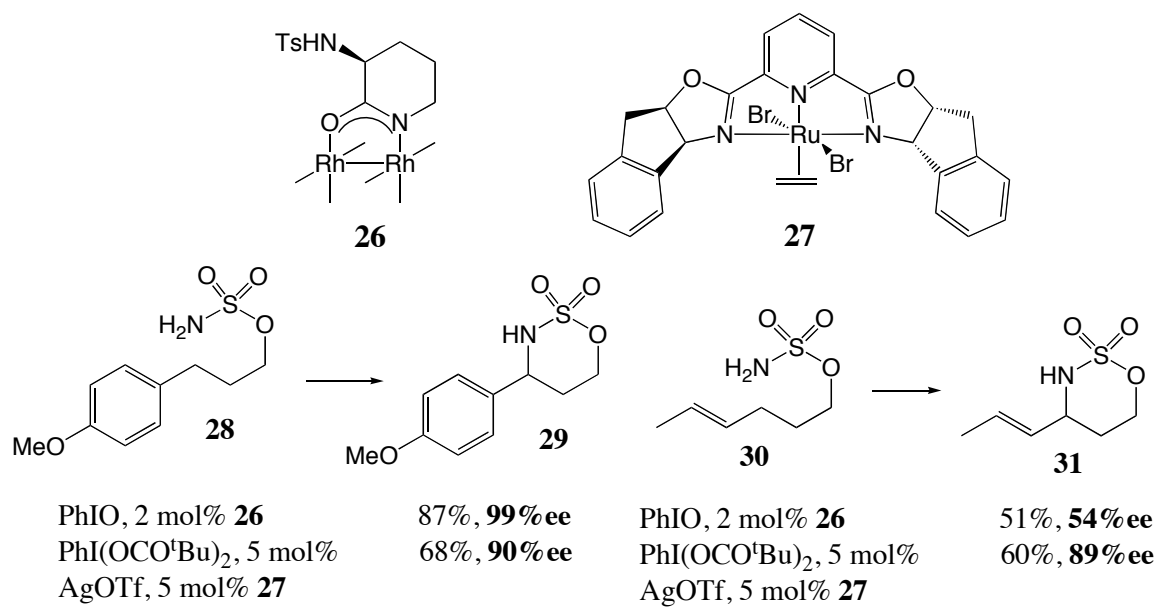
Lastly, several applications of the methodology have recently been employed in the production of simple and complex natural products.[11] These reports serve to illustrate the emergence of intramolecular nitrenoid insertion into C-H bonds as a standard C-N bond forming reaction. As an example of the high regioselectivity that can be attained even on complex substrates, Che's selective functionalization of the deoxoartemisinin motif **32** is shown in Figure 1.18.[70]

19

R = OCONH$_2$
5 mol% Rh$_2$(pfb)$_4$
PhI(OAc)$_2$, MgO

33, 67%

sulfamate

carbamate

32

R = OSO$_2$NH$_2$
5 mol% Rh$_2$(pfb)$_4$
PhI(OAc)$_2$, MgO

34, 87%
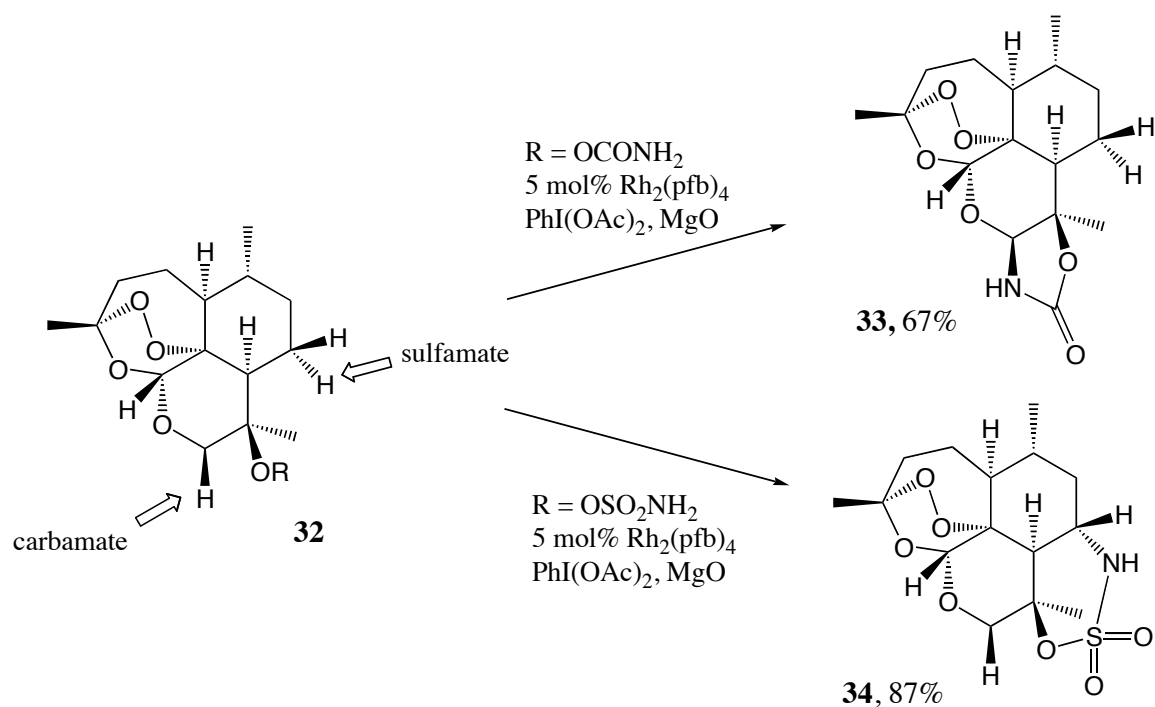
Figure 1.18

1.2.2.4   Intermolecular Benzylic C-H Amidation

Though intramolecular methodologies have displayed excellent chemo- and regioselectivity and even high enantioselectivity when employing chiral ligands, the hydrocarbon substrates require pre-functionalization in order to proceed. Perhaps more desirable, but more challenging, is the intermolecular version of the nitrenoid insertion reaction (Figure 1.19).

Nitrenoid
Precursor

Ar—R

Catalyst

NHR'

Ar—R
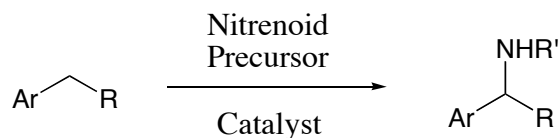
Figure 1.19

Difficulties to overcome regarding the efficiency of these reactions include the lowered regioselective discrimination due to the inability to position the reactive sites in close proximity to each other, and increased formation of over-oxidized by-products.[11] In early examples, these problems were partially overcome by the utilization of substrates in large excess, high temperatures, and/or utilization of more activated C-H bonds, such as electron rich benzylic and allylic positions. Almost every intermolecular system that has been investigated to date displays high reactivity with benzylic substrates. Typically, secondary benzylics are more active than primary or tertiary positions as a compromise of steric and electronic effects. In fact, the functionalization of primary and/or tertiary benzylic substrates is relatively rare and often results in low yields of aminated products. Results from typically employed representative benzylic substrates have been compiled and are summarized in Table 1.1.

In 1997 imidioiodinanes re-emerged as effective aminating agents of C-H bonds in the presence of a transition metal-catalysts when Muller reported the utilization of PhI=NNs and catalytic $Rh_2(OAc)_4$ to aminate a variety of hydrocarbons through what was determined to be an asynchronous concerted mechanism.[31] Several benzylic substrates were employed resulting in moderate-good yields of secondary benzylic amidated products. The system proved ineffective for primary and tertiary benzylic substrates however, resulting in < 10% yields from the reaction with either toluene or cumene.

Another major advance in intermolecular nitrenoid insertion was reported by Che in 2000.[41] In the study, ruthenium and manganese porphyrins were used

catalytically to amidate a variety of hydrocarbons with PhI=NTs, producing high yields up to 86% of benzylic and allylic substrates employed in stoichiometric amount. More importantly, the report marked the first *in situ* formation of the nitrenoid precursor from a variety of commercially available sulfonamides, PhI(OAc)$_2$, and an inorganic base such as NaOH or Na$_2$CO$_3$. The ruthenium- or manganese-promoted amidation using the *in situ* system produced similar results as that with pre-formed PhI=NTs when employed with a set of the same representative hydrocarbons. This procedure would inspire numerous inter- and intramolecular formal nitrene transfers from a wide range of *N*-functionalities, including some that are unstable with hypervalent iodine reagents such as carboxamides.[71]

Among the numerous nitrenoid insertion reactions that have been reported, perhaps the most recognizable system to date (though mainly for the intramolecular version) has been developed by Du Bois.[37] In the intermolecular reaction, an *in situ* method of nitrenoid formation is employed with Tces-NH$_2$ (Tces = trichloroethylsulfamate), slow addition of PhI(O$_2$C^{t}Bu)$_2$, and 2 mol% Rh$_2$(esp)$_2$ **22** at room temperature. Benzylic substrates when used in stoichiometric amount are amidated in moderate-good yields as high as 74%. As of yet, enantioselective induction using a chiral version of the catalyst has been met with limited success with ee's in the 20% range.

Other nitrenoid insertion reactions catalyzed by rhodium include Hashimoto's enantioselective system with PhI=NTs,[33] Davies' *in situ* nitrenoid formation from NsNH$_2$/PhI(OAc)$_2$,[35] Dauban's system which utilizes chiral *N*-substrate **14** in stoichiometric amount to undergo diastereoselective insertions with a chiral catalyst
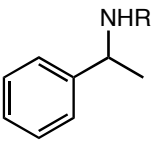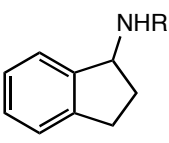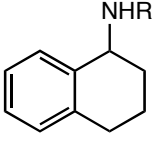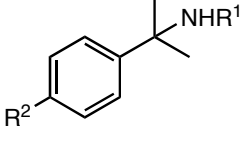
in excellent yields and % de,[36,38] and Lebel's "greener" Troc-NH-OTs system.[40] All display good-excellent regio- and chemoselectivity for a variety of secondary benzylic substrates with yields of typically 60-90%.

While rhodium complexes have been employed most frequently in –NR unit insertion reactions of benzylic hydrocarbons, several other transition metals have been successfully employed with a variety of nitrenoid precursors. Efficient systems employing catalytic amount of copper were reported by both Powell in 2006[57] and Nicholas in 2007.[58] In Powell's Cu(II)-promoted system, sulfonamides are used in conjunction with ^{t}BuOOAc to produce benzylic-substituted products in moderate-good yields, including good yields from electron-deficient substrates. In the "greener" system developed by Bhuyan and Nicholas, dehydrated chloramine-T is employed in conjunction with catalytic amount of inexpensive Cu(I) salts to produce efficient product formation from a variety of primary, secondary, and even tertiary benzylic substrates, though efficiency is lower with electron deficient substrates.

In addition to copper, Co(II) porphyrins have been used with azides by Cenini,[45] and with Bromamine-T by Zhang[47] in "greener" formal nitrenoid insertion reactions of benzylics. Though Cenini's amination is a rare example that employs attractive azide reagents, the system has several drawbacks including low yields due to deleterious by-product formation and the requirement of elevated temperatures (75°C). Zhang's system, reported in 2007, is the only example in which Bromamine-T (Figure 1.2, **11**; typically employed in aziridination reactions) was employed for benzylic C-H insertion. Good yields can be obtained from sterically accessible benzylic C-H positions, though the substrate scope of the reaction is relatively small.

Finally, the He Group has employed more exotic gold and silver catalysts for benzylic amidation, with moderate-good results obtained from the silver-catalyzed system,[50] though the system requires pre-formation of a silver-phenanthroline complex in order to proceed efficiently. The AuCl$_3$-catalyzed reaction of PhI=NNs occurs with low-moderate efficiency for secondary or tertiary benzylic C-H bonds due to a large amount of arene C-H insertion.[51] Lastly, Fe(II) salts were employed with *N*-bromosuccinimide (NBS) and a variety of amides/sulfonamides by Zhao in 2008.[54] Good yields are obtained with a limited range of hydrocarbon substrates at 50°C with the employment of 1.1 equivalents of NBS through what is believed to be an iron-nitrene complex formed *in situ* from *N*-bromosulfonamide (resulting from NBS bromination).

Amidated Products of Commonly Employed Benzylic Substrates

| 35 | 36 | 37 | 38 |

Entry	System	% yield			
		35	**36**	**37**	**38**
1	PhI=NNs, Rh$_2$(OAc)$_2$ [Muller, 1997]	50	69	57	8
2	Chloramine-T (hydrate), Cu(OTf)$_2$ [Taylor, 1998]	-	-	46	-
3	PhI=NTs, [Ru(TPFPP)(CO)] - (or Mn) [Che, 2000]	34	72	-	-
4	PhI=NTs, Mn(salen) [Katsuki, 2001]	-	70 (43% ee)	67 (77% ee)	
5	PhI=NNs, Rh$_2$(S-TCPTTL)$_4$ [Hashimoto, 2002]	61 (33% ee)	82 (70% ee)	88 (76% ee)	-
6	4-NO$_2$PhN$_3$, [Co(p-ClTPP)] [Cenini, 2003]	25	-	-	53[a]
7	PhI(OCO^{t}Bu)$_2$, **14**, Rh$_2$(S-nttl)$_4$ [Dauban, 2006]	73 (97% de)	88 (99% de)	80 (96% de)	-
8	NsNH$_2$/PhI(OAc)$_2$, Rh$_2$(S-TCPTAD)$_4$ [Davies, 2006]	86 (74% ee)	-	82 (73% ee)	-
9	RNHSO$_2$R', ^{t}BuOOAc, Cu(OTf)$_2$, 1,10-phen [Powell, 2006]	60	-	54	-
10	PhI=NTs, Tp^{Br3}Cu(NCMe) [Perez, 2006]	56	-	-	30[a]
11	PhI=NNs, (AgOTf)/4,7-diphenyl-1,10-phen [He, 2007]	-	68	70	57[b]
12	PhI=NNs, AuCl$_3$ [He, 2007]	-	29	36	-
13	Tces-NH$_2$, PhI(O$_2$C^{t}Bu)$_2$, Rh$_2$(esp)$_2$ [Du Bois, 2007]	72	72	-	-
14	Bromamine-T, Co(TDClPP) [Zhang, 2007]	-	73	66	-
15	Chloramine-T (anhydrous), Cu(CH$_3$CN)$_4$PF$_6$ [Nicholas, 2007]	69	64	-	39[a]
16	R-NH$_2$, NBS, FeCl$_2$ [Zhao, 2008]	64	-	-	-
17	Troc-NH-OTs, K$_2$CO$_3$, Rh$_2$(S-nttl)$_4$ [Lebel, 2008]	71	75	-	-

[a] R^2 = H   [b] R^2 = ^{i}Pr

Table 1.1

1.2.2.5   Intermolecular Allylic C-H Amidation

Several systems (as listed in Table 1.2) have employed a representative olefin to investigate the potential for allylic C-H amination. While some methods such as Muller's produce aziridination products in minor or major amounts with cyclic or linear terminal alkenes,[31] other procedures are highly selective for allylic amination, such as Dauban's rhodium-promoted system,[36,38] and have been employed with a wide variety of cyclic and linear alkenes. In addition to aziridination side-products, other potential by-products are illustrated in the Nicholas chloramine-T/Cu(I) promoted reaction in which allylic amination **42** occurs as major product with cyclohexene **41**, but 1,2-chloroamidated products are seen from 1-octene **44** and cyclohexene (Figure 1.20, **43**, **45**).[58]
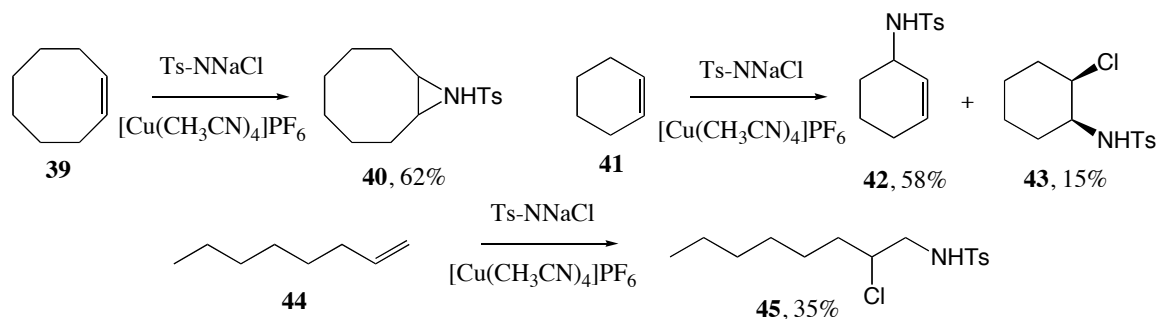
Figure 1.20

Attempts to develop highly enantioselective allylic amination reactions of simple olefins have thus far been met with limited success, with ee's typically ranging from 10-70%.[33,36,48] As of yet, the scope of substrates used in most systems has been largely confined to one or two cyclic alkenes (such as cyclohexene), with the

exception being Dauban's investigation in 2007.[38] As this represents a reaction that retains the C-C unsaturation in the amidated product, it is surprising that more attention has not been paid to a full investigation of allylic C-H functionalization via nitrenoid precursors.

Amidation of a Commonly Employed Allylic Substrate (Cyclohexene)
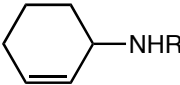
Entry	System	% Yield
1	PhI=NNs, $Rh_2(OAc)_2$ [Muller, 1997]	57
2	Chloramine-T (hydrate), $Cu(OTf)_2$ [Taylor, 1998]	22
3	PhI=NTs, [Ru(TPFPP)(CO)] - (or Mn) [Che, 2000]	86
4	PhI=NTs, Mn(salen) [Katsuki, 2001]	44 (67% ee)
5	PhI=NNs, $Rh_2(S\text{-}TCPTTL)_4$ [Hashimoto, 2002]	54 (19% ee)
6	$PhI(OCO^tBu)_2$, **14**, $Rh_2(S\text{-}nttl)_4$ [Dauban, 2006]	75 (38% ee)
7	$RNHSO_2R'$, ^tBuOOAc, $Cu(OTf)_2$, 1,10-phen [Powell, 2006]	75
8	Chloramine-T (anhydrous), $Cu(CH_3CN)_4PF_6$ [Nicholas, 2007]	58

Table 1.2

1.2.2.6 Intermolecular Saturated Hydrocarbon 3° and 2° (sp^3) C-H Amidation

In attempts to make progress towards one of the "holy grails" of organic chemistry, *i.e.* the selective functionalization of simple alkanes, several
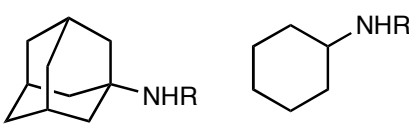
intermolecular catalytic systems employing nitrenoid precursors have utilized simple cyclic and linear saturated alkanes (as summarized in Table 1.3) in addition to benzylic and allylic substrates.

The tertiary sp^3 C-H amidation of adamantane can be accomplished by a variety of methods in good yields,[31,36,40,41,57] though tertiary amidation is almost always accompanied by a minor amount of secondary sp^3 C-H amidation product. An even simpler cyclic alkane that is commonly employed as a representative hydrocarbon is cyclohexane. Muller first reported the amidation of cyclohexane with PhI=NNs/Rh$_2$(OAc)$_4$, though the reaction was performed at elevated temperatures (83°C).[31] In 2003, Perez reported the room temperature amidation of cyclohexane used as solvent in 65% yield by reaction of PhI=NTs with an exotic copper scorpionate complex.[72] The first report of a highly efficient amidation of a range of simple cyclic hydrocarbons was presented by Dauban and Dodd in 2007 using their sulfonimidamide reagent **14**, PhI(O$_2$C^{t}Bu)$_2$, and Rh$_2$[(S)-nttl]$_4$.[38] Yields ranging from 85-96% were obtained from saturated C$_5$-C$_8$ cyclic hydrocarbons when the alkane was used in excess of 5 equivalents. Moderate success was even obtained from a linear alkane, 2-methylbutane, with amidation at the tertiary C-H position occurring in 36% yield.

He's silver-promoted amidation also allowed for extension of substrate scope to include simple cyclic hydrocarbons, though yields were mainly in the 30-40% range.[50] An excellent yield (95%) of cyclohexane amidation **47** is reported by Du Bois' Rh$_2$(esp)$_2$-promoted reaction when cyclohexane is used in 5 equivalents, but efficiency is lowered to 38% when the hydrocarbon is employed in 1 equivalent.[37] In

addition, a 46% yield of amidated product is obtained from 1,4-dimethylcyclohexane exclusively at the tertiary C-H position. Lastly, Lebel reported the amidation of simple saturated hydrocarbons using the Troc-NH-OTs/Rh$_2$[(S)-nttl]$_4$ system.[40] Reactions were conducted at room temperature with 5 equivalents of hydrocarbon substrate producing yields ranging from 50-80%.

Amidation of Commonly Employed Saturated Hydrocarbon Substrates

46   **47**

Entry	System	% Yield	
		46	**47**
1	PhI=NNs, Rh$_2$(OAc)$_2$ [Muller, 1997]	71	30
2	PhI=NTs, [Ru(TPFPP)(CO)] - (or Mn) [Che, 2000]	79	-
3	PhI(OCO^{t}Bu)$_2$, **14**, Rh$_2$(S-nta)$_4$ [Dauban, 2006]	94	85
4	RNHSO$_2$R', ^{t}BuOOAc, Cu(OTf)$_2$, 1,10-phen [Powell, 2006]	56	-
5	PhI=NTs, Tp^{Br3}Cu(NCMe) [Perez, 2006]	-	65
6	PhI=NNs, (AgOTf)/4,7-diphenyl-1,10-phen [He, 2007]	-	40
7	Tces-NH$_2$, PhI(O$_2$C^{t}Bu)$_2$, Rh$_2$(esp)$_2$ [Du Bois, 2007]	-	95
8	Troc-NH-OTs, K$_2$CO$_3$, Rh$_2$(S-nttl)$_4$ [Lebel, 2008]	70	80

Table 1.3

1.2.2.7   Aromatic (sp^2) C-H Amidation

To date, very few examples of arene C-H insertion have been reported utilizing nitrenoid precursors. The systems reported to date suffer from poor yields, exotic catalysts, poor regioselectivity, and/or the stoichiometric use of palladium. A more efficient and economical method is still desirable, as other methods of intermolecular arene C-H bond insertion such as that of Buchwald[73] and Shi[74] employ stoichiometric amounts of Cu as oxidant.

Intramolecular methods of arene C-H amidation via nitrenoid precursors have been developed recently which allow for highly regioselective insertion due to a metal-coordinating scaffold that places the catalyst in close proximity to a specific arene C-H bond. In 2007, Sanford reported the PhI=NTs-mediated amination of benzo[h]quinoline palladacycles **48**.[53] After hydrolytic cleavage with HCl, the C-H aminated product **50** can be isolated in good yields, though the reaction remains stoichiometric in palladium[II] complexes (Figure 1.21).
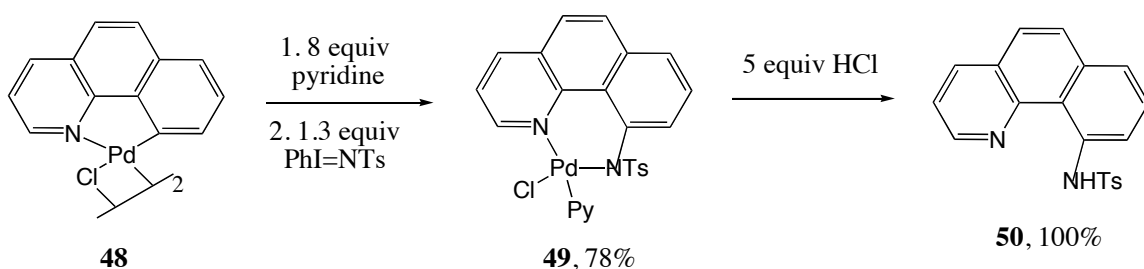
Figure 1.21

Intermolecular arene C-H functionalization via nitrenoid precursors remains an elusive but highly desirable approach to the amination of bulk feed stocks such as

benzene. As early as 2003, Perez reported the amidation of benzene with PhI=NTs (or chloramine-T), and a scorpionate ligand in combination with Cu (I) salts.[72] The reaction at room temperature produces 40% of amidated product, and 80% at 85°C. In addition, amidation of electron-deficient pyridine occurs at the 2-position in 35% yield at 80°C.[56]

Lastly, He reported in 2007 the amination of electron-rich tri-, tetra-, or penta-substituted arenes used in excess with PhI=NNs and catalyzed by AuCl₃.[51] Of particular interest in this system is the preferential amination of aryl C-H bonds over primary or secondary benzylic C-H positions (Figure 1.22; **52**, **54**).
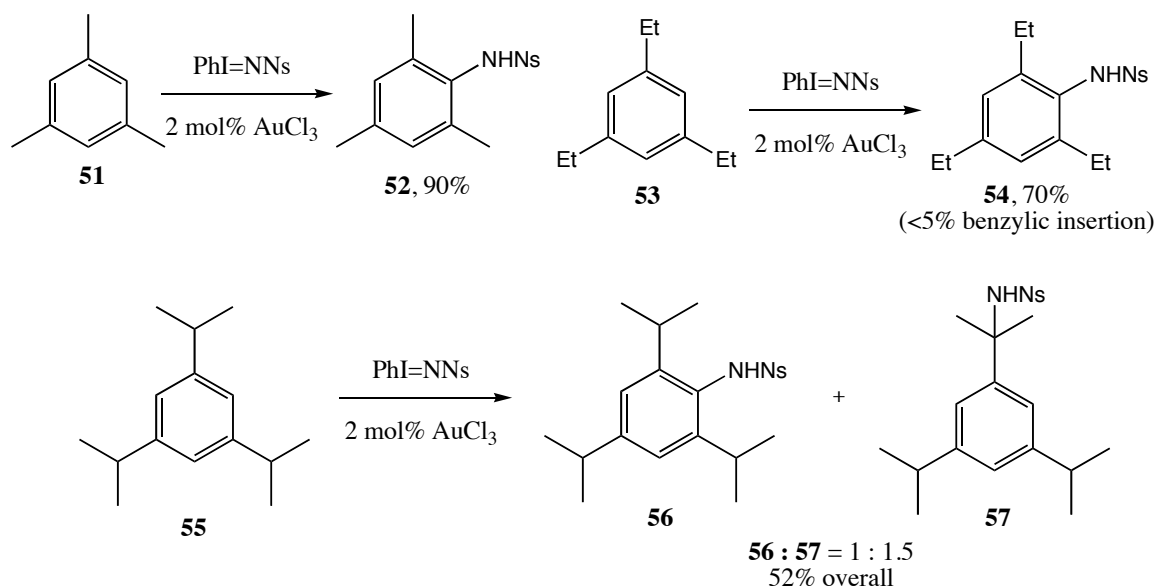
Figure 1.22

1.3 Synthesis of Indoles in Organic Chemistry

In addition to amines, *N*-containing heterocycles are also valuable targets for the design and development of new C-N bond forming methodologies via C-H

activation from unsaturated hydrocarbons. Indoles are an important class of *N*-heterocycle due to their frequent occurrence in natural products and bioactive compounds. As electron-rich heterocycles, indoles are capable of a wide range of bioactivity due mainly to their ability to serve as useful ligands for a wide variety of receptors.[75] A few examples of bioactive indoles are presented in Figure 1.23, the most famous of which is the amino acid tryptophan.

SOME BIOLOGICALLY ACTIVE INDOLES

Indomethacin
Non-steroidal anti-inflammatory agent

Ellipticine
Anti-tumor activity

Yohimbine
α_2-blocker for treating ED

Sumatriptan
Treatment of migraine headaches

Tryptophan

Reserpine
Treatment of mental disorders

Melatonin
Hormone that controls sleep patterns

(+)-Staurosporine
Protein Kinase Inhibitor

Serotonin
Key neurotransmitter in animals
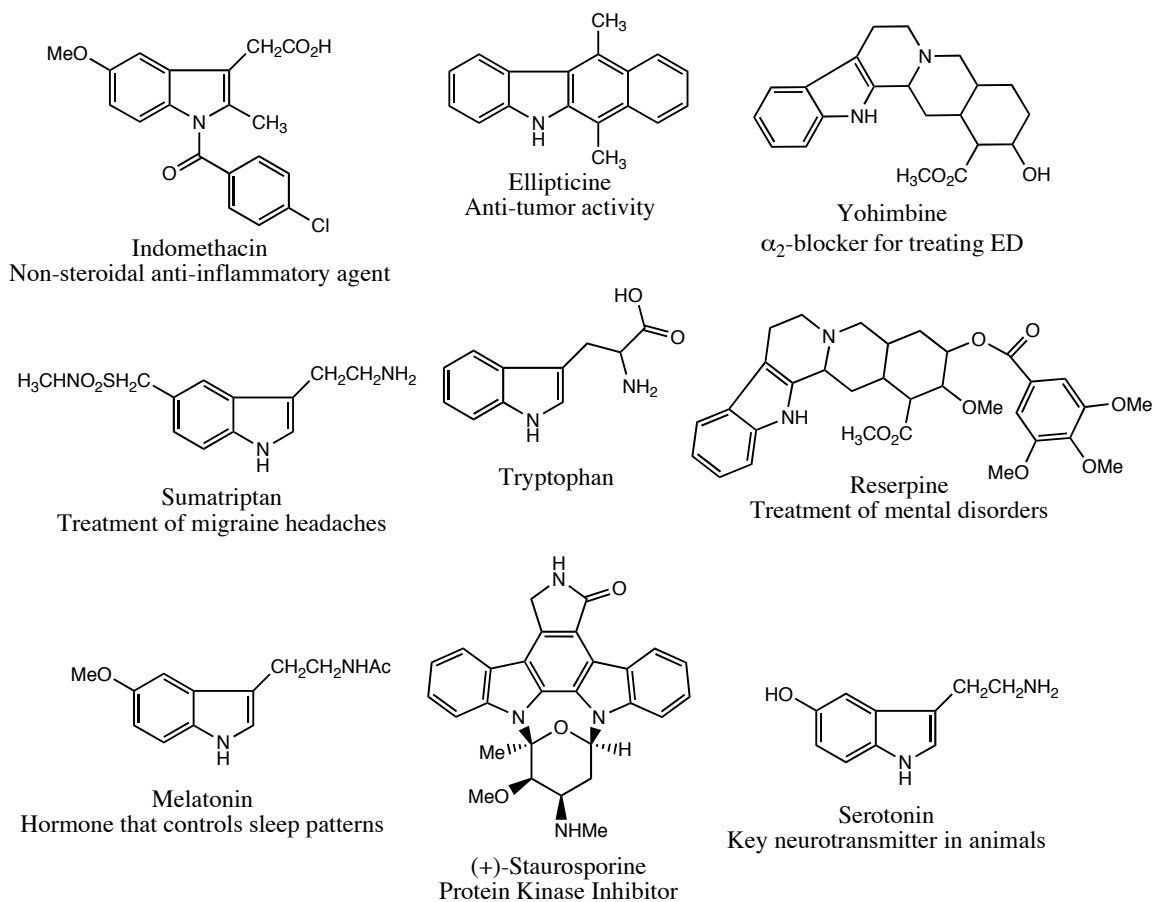
Figure 1.23

The indole framework consists of a benzene ring fused to a pyrrole ring, resulting in a 10 electron aromatic structure. Due to this fact, most synthetic methodologies exploit the resulting aromaticity of the product indole in order to facilitate annulation. Other physical properties of the indole framework include a low basicity (pK_a of the conjugate acid is -2.4) similar to that of pyrrole, due to the compromise of aromaticity.[75] In fact, protonation or oxidation of indole typically occurs at the C-3 instead of the N-1 position. Typically, functionalization of the indole framework is more readily obtained at C-2 and C-3 positions, while selective functionalization of the benzene unit (C-4,5,6,7) is more difficult.[75]
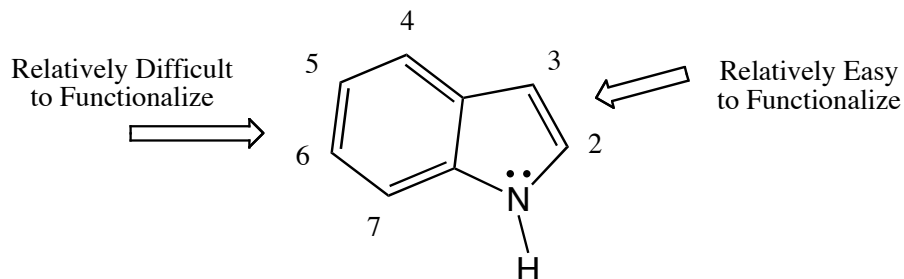
Figure 1.24

1.3.1 Classical and Modern Indolization Methods

Though some indoles occur naturally in coal tar, most complex indoles are produced by synthetic methods.[75] Many methods have been developed for their preparation in a wide variety of annulating approaches which mainly consist of either the formation of the pyrrole unit from an aryl precursor or *vice versa* (Figure 1.25).[75] Despite numerous methodologies, new systems and improvements are still being

sought which employ more accessible starting materials, milder reaction conditions, are functional group tolerant, and achieve improved regioselectivity.

From a pre-existing benzene

From a pre-existing pyrrole

The Most Convergent
Approach
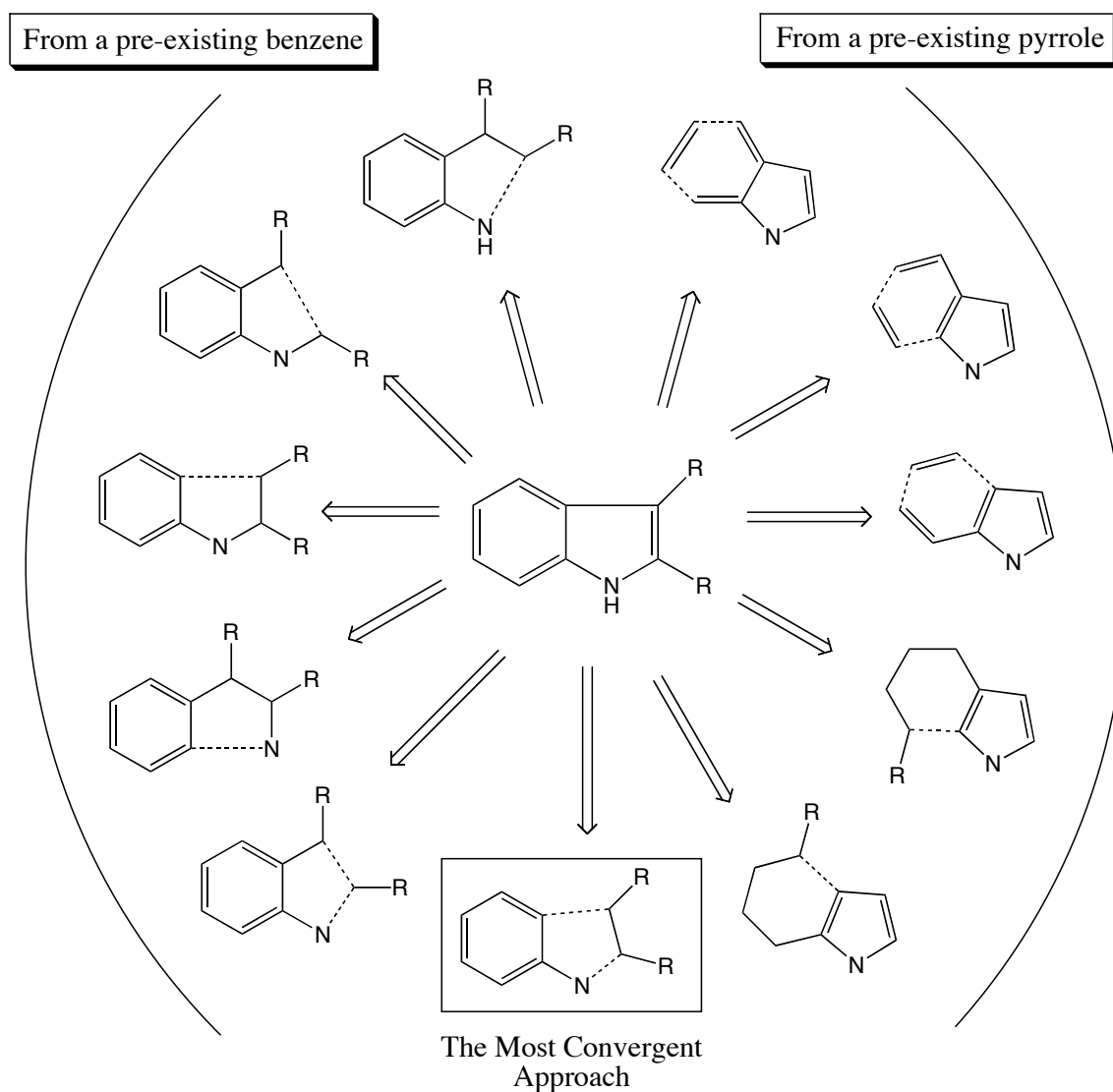
Figure 1.25

The first preparation of indole was reported in 1866,[75] and the Fischer indole synthesis, which is the most versatile and widely used indole forming method, was first reported in 1883.[76] In the Fischer indole synthesis, an arylhydrazone formed

from an aldehyde or ketone cyclizes via a sigmatropic rearrangement *ortho* to the initial hydrazine (Figure 1.27). Indolization is then driven to completion by loss of ammonia and the consequent generation of aromaticity. Potential drawbacks to the method include the use of protic or Lewis acids (which can prohibit certain functionalitites), and the formation of regioisomers from the use of unsymmetrical ketones or substituted aryl hydrazines.

The continued search for a general and efficient annulation method has spawned several transition metal-promoted routes to indoles, though most of these are intramolecular cyclizations requiring an *ortho*-substituted *N*-aromatic substrate.[75] The most widely used and recognized of these methods are related to pathway B shown in Figure 1.26. Variations include an *ortho*-nitro phenylacetylene **61** (with reduction of the nitro to aniline **62** and subsequent annulation), and the Stille and Larock variations in which the *ortho*-alkynyl aniline **62** is formed *in situ* via palladium-mediated insertion into an *ortho*-halogenated aniline such as **63** and **64**.[75] Disadvantages of these methods include the requirement of more highly functionalized *N*-aryl substrates.
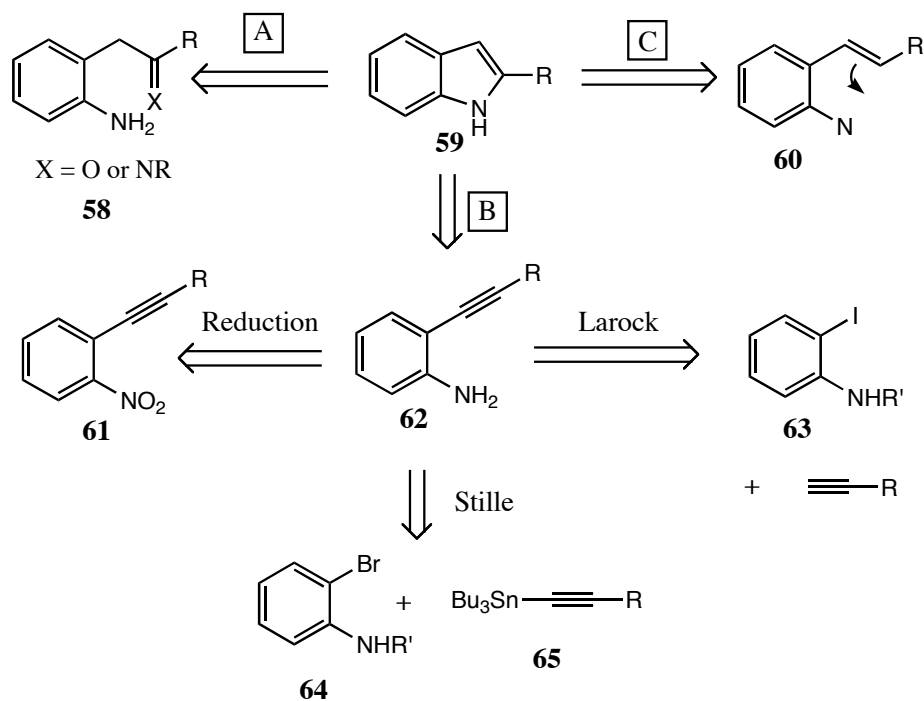
Figure 1.26

1.3.2 Non-Directed Intermolecular Methods

Especially attractive, but relatively rare, are methods which produce indoles by annulation of simple mono-substituted *N*-aromatic precursors in highly convergent and atom-economical methods (as highlighted in Figure 1.25). To date, a wide range of *N*-aryl precursors have been utilized for this type of method including arylhydrazines, -hydroxylamines, -amines, and -chloroamines as well as nitro- and nitrosoaromatics.[75,77,78] The most widely recognized and used of these methods is the Fischer indole synthesis, shown in Figure 1.27 as Path F.
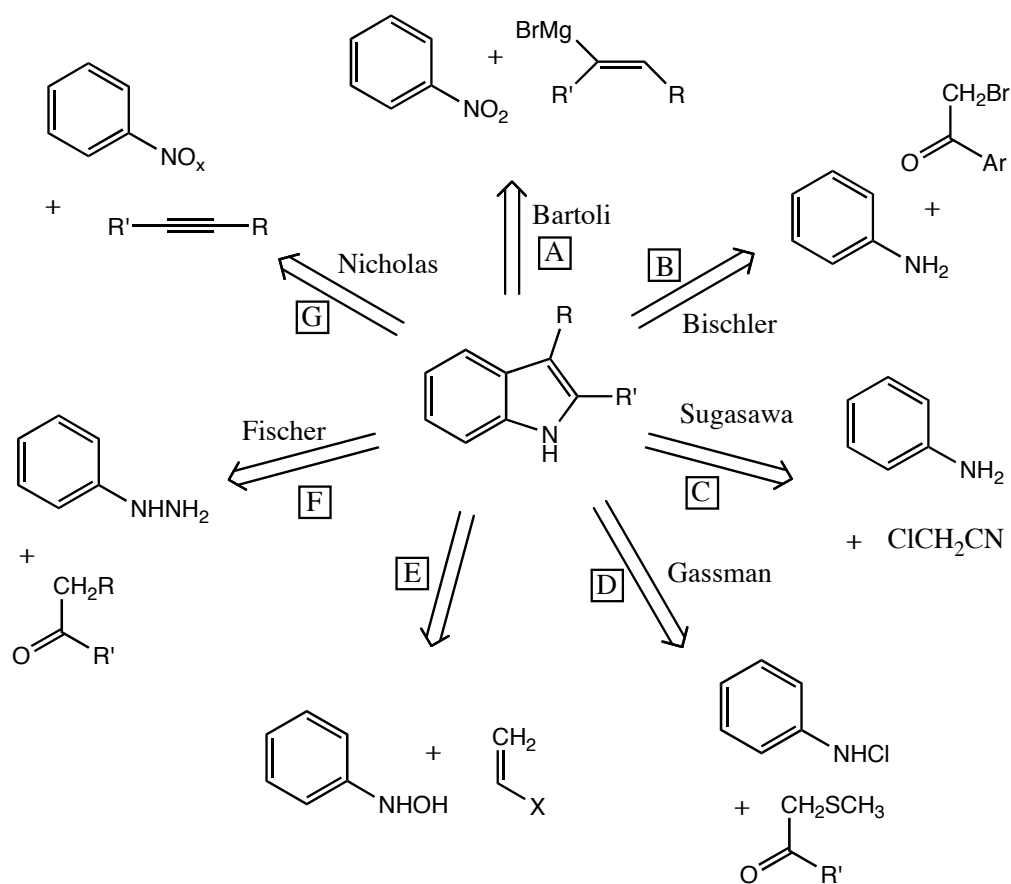
Figure 1.27

In the Bartoli indole synthesis (Path A, Figure 1.27),[79] a nitroaromatic is reacted with three equivalents of vinyl Grignard at low temperatures to produce indole. A unique advantage of the Bartoli reaction lies in the ability of the method to form C-2 and C-3 unsubstituted indoles. Another method that can directly produce indole from widely available nitroaromatics is the iron- or ruthenium-catalyzed Nicholas-Penoni alkyne annulation shown as Pathway G.[77,78] This reaction is discussed in detail in Chapter 3, Section 3.1.2.

In the Bischler synthesis (Path B), α-haloacetophenones are reacted with anilines at 200-250°C to produce indole through the formation of an imine which can

isomerize to an aldimine intermediate, producing the 2-substituted indole.[75] The Sugasawa reaction (Path C) proceeds by conversion of anilines to indoles via BCl$_3$-directed *ortho*-chloroacetylation, and cyclization is completed by reduction with NaBH$_4$.[80] Typically, an additional Lewis acid such as TiCl$_4$ or AlCl$_3$ is needed. Aniline is also employed as *N*-substrate in the Gassman synthesis (Path D).[81] The reaction involves a sigmatropic rearrangement of anilinosulfonium ylides prepared from aniline and a chlorosulfonium salt (or from *N*-chloroanilines and α-thiomethylketones) to form thioindoles that can be desulfurized with Raney nickel. Lastly, the oxygen analogue of the Fischer indole cyclization (arylhydroxylamine) has been shown to readily form indole with vinyl acetate or electrophilic allenes (Path E),[82] but is much less accessible than analogous arylhydrazone.

1.4   Reduction of Aromatic Nitro Groups in Organic Chemistry

Nitroaromatics represent attractive *N*-aminating reagents in C-H activation reactions due to their widespread availability and robust nature. As opposed to amines, the nitro functionality is not nucleophilic or basic, and is tolerant of a wide variety of conditions. Due to their high potential as aminating reagents, the transformation of the nitro group to other functionalities has been investigated for over 100 years.[83] Transformations obtained via nitroaromatic reduction will be grouped into two categories: functionalities arising from C-N bond formation (such as reductive carbonylation or alkylation), and functionalities arising from N-N, N-O, or N-H bond formation (via metal-hydride or acidic reduction). By careful selection of catalysts, conditions, and reagents, transformations can be highly selective for the

formation of a specific product, though in most cases reactions are almost always accompanied by the standard by-products of nitro reduction, such as azo, azoxy, and amino compounds (Figure 1.28).
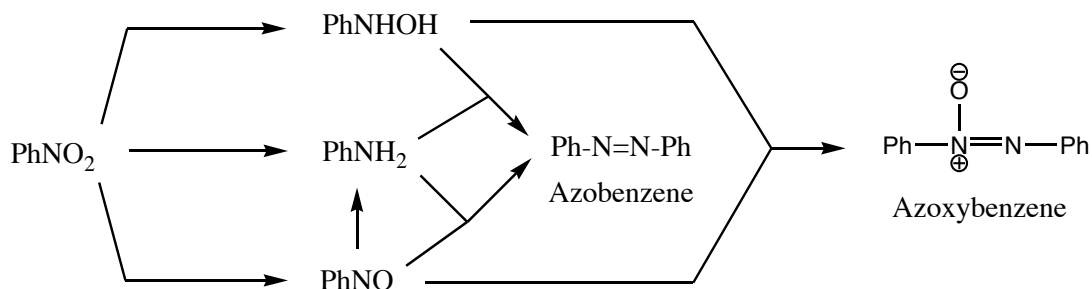
Figure 1.28

As of yet, no method is known to selectively reduce a nitroaromatic to a nitrosoaromatic without the intervention of metal-coordination. This is due to the lower reduction potential of nitroso relative to nitro.[84] While nitroso can be implicated as a transient intermediate in nitro reduction since it can be trapped in some examples,[85,86] it has not been isolated in its free state and thus, is not included as a viable product of nitro reduction.

Carbon monoxide is an important reagent used in the transformation of a wide range of unsaturated functionalities. Although CO is a toxic gas, it remains industrially important due to its low cost, accessibility, and wide range of uses.[83] Along with alkylative methods including the use of Grignard reagents (such as the Bartoli indole synthesis),[12] transition metal-catalyzed carbonylation of nitroaromatics using CO comprises the majority of methods to form C-N bond containing functional

groups.[83] Functional groups that can be produced include isocyanates, carbamates, ureas, and primary-, secondary-, and tertiary amines (Figure 1.29).[12,21,77,83]

METAL-CATALYZED REDUCTIVE CARBONYLATION OF NITROAROMATICS
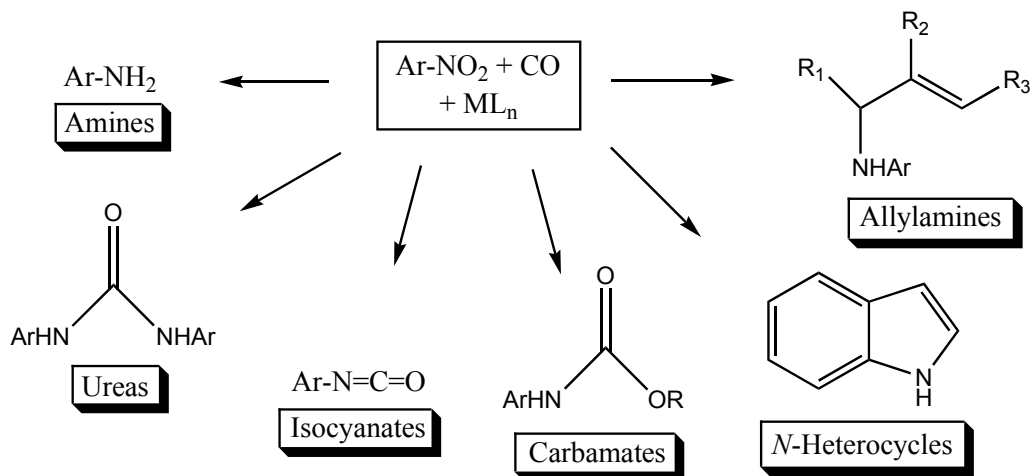
Figure 1.29

Standard by-products such as azo and azoxy compounds are frequently observed in minor amounts. Isocyanates, carbamates, and ureas are important substrates used in the production of herbicides and polyurethanes, and other methods of production typically employ extremely toxic and corrosive phosgene.[83] Lastly, Nicholas and others have shown the ability to form secondary amines or *N*-heterocycles via C-H activation from metal-coordinated *N*-aminating species produced in the reduction of nitroaromatics.[21,77]

In the second and more recognizable category of nitroaromatic reduction, functional groups capable of being produced include aniline, hydroxylamine, azo, hydrazo, and azoxy compounds.[87] Many of these products are formed using similar catalysts and reagents, with selective production being obtained by careful

manipulation of conditions. For example, metal hydrides such as LiAlH$_4$ typically produce azo products,[12] but when a milder metal hydride such as NaBH$_4$ is used in conjunction with a transition-metal phthalocyanine or porphyrin,[12] aniline is produced in major amount.

Classical methods of reduction of nitroaromatics to anilines include:[12,87] catalytic hydrogenation via palladium, platinum, or nickel catalysts, iron in acidic media (Bechamp reduction), sulfides and sulfites, and the employment of a variety of additional metals including tin, titanium, zinc, samarium, selenium, and tellurium. *N*-Arylhydroxylamines are typically produced by reduction with zinc metal in aqueous acidic media,[88] though over reduction to hydrazo compounds can occur when using excess zinc.[89] Additional methods of *N*-arylhydroxylamine production include reduction via NaBH$_4$/Te^o or Se^o,[90,91] hydrazine/Raney nickel,[12] electrolytic conditions,[92] and even baker's yeast.[93] As most arylhydroxylamines are thermally unstable, care in most cases must be given to maintaining low temperatures throughout the typically exothermic reactions.

1.5 Project Objectives

The overall objective in the Nicholas Group's Amination Project is to develop new methodologies to form C-N bonds via C-H functionalization that utilize transition metal activation of non-polar and otherwise unreactive saturated and unsaturated hydrocarbons. In addition, we aim to utilize stable, readily available, inexpensive nitrogen sources for atom-economical, regioselective reactions. Finally, we aim to mechanistically explore these new methodologies in order to understand

the reactivity, and potentially to create more reactive or selective systems for application towards highly desirable target compounds.

Within this context, the three main areas of amination that have been investigated by the author can be separated according to the level of unsaturation of the reacting hydrocarbon (Figure 1.30): nitrenoid C-H insertion (alkanes), allylic amination (alkenes), and indole annulation (alkynes). The three areas will be presented and discussed in the chronological order that they were investigated. In the first, the exploration for a new method of the allylic amination of unfunctionalized olefins via nitroaryl reduction is presented. With an eye to developing milder reaction conditions, new catalysts, additives, and/or stoichiometric reducing agents are explored. The second area of research involves the design and development of a one-pot indolization of arylalkynes and arylhydroxylamines in order to form unprotected (NH) indoles in an efficient and convenient manner. Finally, methods of direct C-N bond formation from saturated alkanes by employment of new catalysts and aminating agents are presented along with mechanistic investigations.

Transition Metal-Catalyzed Allylic Amination of Nitroaromatics and Unfunctionalized **Alkenes**
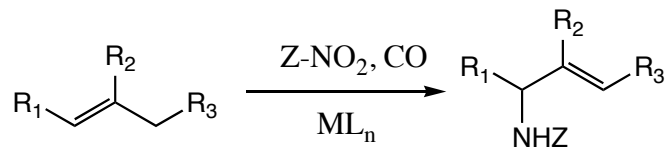
Transition Metal-Catalyzed Annulation to Form Parent (NH) Indoles from Arylhydroxylamines and **Alkynes**
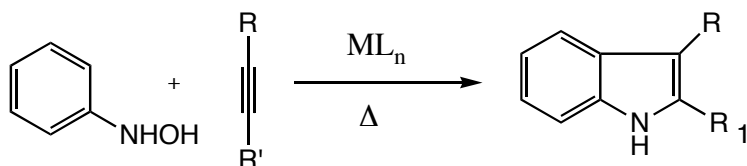
Nitrenoid Precursor C-H Insertion of Saturated Benzylic and Non-Benzylic **Alkanes**
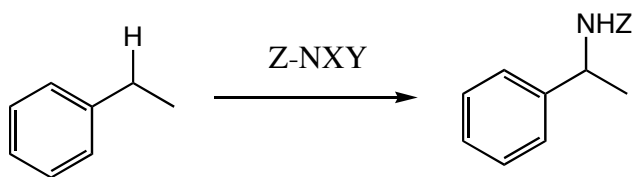
Figure 1.30

CHAPTER 2

SYNTHESIS OF ALLYLIC AMINES VIA NITROARYL REDUCTION: TOWARDS IMPROVED REACTION CONDITIONS

2.1   Introduction and Background

The nitro group represents a very attractive functionality for use as a potential *N*-aminating agent due to its widespread abundance in commercial compounds and robust nature. For this reason, the development of new C-N bond forming methodologies via C-H activation employing nitroaromatics as the *N*-source have been recently investigated in allylic amination reactions, and further improvements are still greatly desired.

Fp-Z = [CpFe(CO)$_2$]$_2$, CpFe(CO)$_2$CH$_2$Ph, [(C$_5$Me$_5$)Fe(CO)$_2$]$_2$
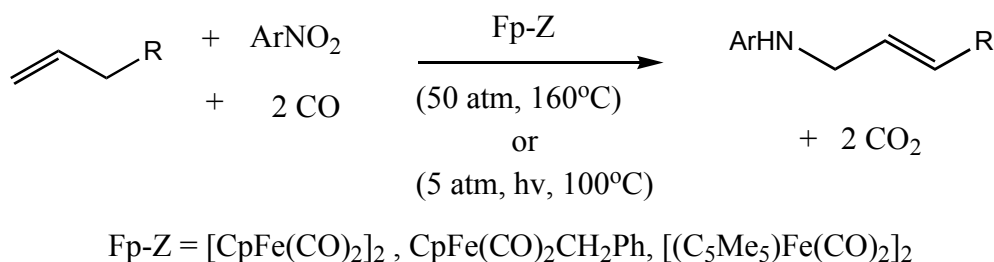
Figure 2.1

To date, the iron/ruthenium-catalyzed deoxygenation and subsequent activation of nitroaromatics towards C-N bond formation (Figure 2.1) requires

relatively harsh conditions such as high pressures (40-60 atm) of toxic carbon monoxide, long reaction times, and high temperatures (>150°).[25,94-97] In order to obtain milder, less energy intensive, and more convenient conditions to allow for general use in a laboratory environment, we aimed to discover a new methodology to complement previous contributions to the field made by the Nicholas and Cenini Groups.[25,94-97] Our investigations focused mainly on the search for new catalysts and/or stoichiometric reducing agents to provide for more reactive and/or selective systems.

2.1.1 Modern Allylic Amination via Nitroaryl Reduction

To date, only two allylic amination systems that employ nitroaryls as the *N*-aminating reagent have been discovered and investigated. Reported by Cenini *et al.* in 1996,[94] the first intermolecular system of allylic amination of an unactivated alkene (cyclohexene **41**, *neat*) by nitroaryls was conducted under reducing conditions of 40 atm CO and 160°C, and catalyzed by $Ru_3(CO)_{12}$ in the presence of DIAN-R **67** (Figure 2.2).
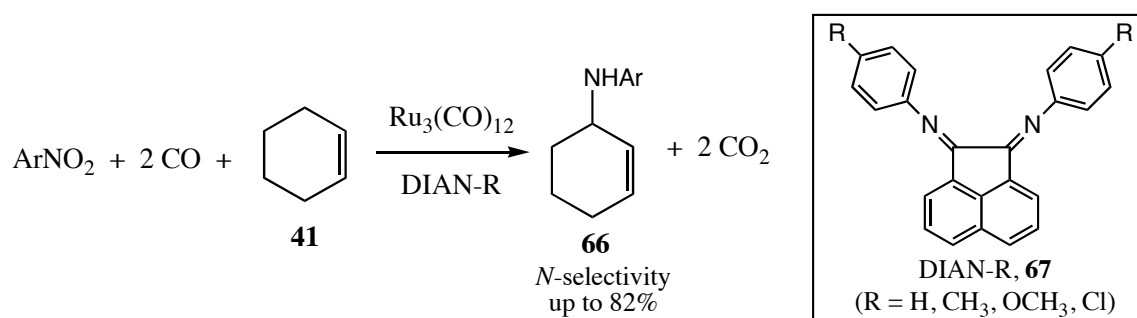
Figure 2.2

In subsequent substrate scope expansion and mechanistic studies,[95] a variety of nitroarenes were employed with best results being obtained from those with electron-withdrawing substituents. In addition, a small sampling of olefins was also tested resulting in moderate allylamine *N*-selectivity (37-57%) and incomplete nitroarene conversion. Finally, it was determined that the amination reaction proceeded through an "on-the-metal" mechanistic pathway involving preliminary coordination of the alkene (**70**), followed by coordination and reduction of the nitroaryl to a ruthenium-oxaziridine (Figure 2.3). Complex **71** could then undergo oxidative addition to the alkene followed by reductive elimination to form the allylamine. By-products could be obtained through reductive pathways in which the alkene was not coordinated to the ruthenium (via Complex **69**), either from complete deoxygenation to the aniline, or by release of a free nitrosoarene to form azo and azoxy compounds.
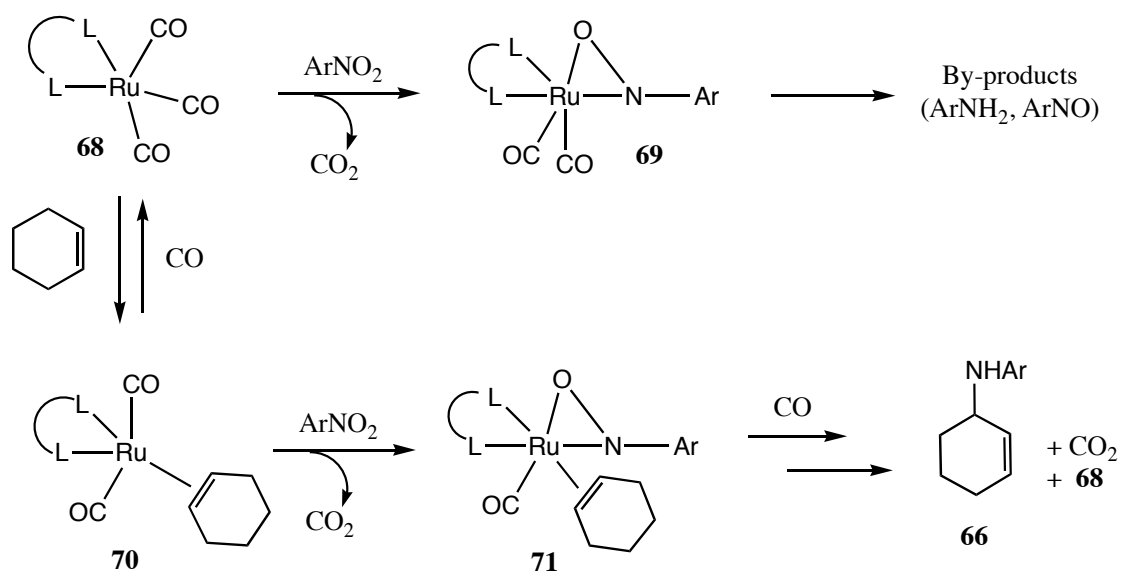
Figure 2.3

In the second system, Nicholas *et al.* describe a more efficient amination that employs nitroaromatics as aminating agents in conjunction with a slight excess of olefin and inexpensive $[CpFe(CO)_2]_2$ as catalyst.[25,97] Though conditions of 50-75 atm CO and 150-180°C are similar to the Cenini reaction, mechanistic differences were observed to verify the iron-catalyzed system as a distinctly unique method. For example, employment of 2,3-dimethylbutadiene **72** as a hetero-Diels-Alder trapping agent was conducted as an experimental test for the intermediacy of nitrosobenzene. In Cenini's system, the hetero-Diels-Alder product **74** was observed,[95] whereas it was not in the iron-catalyzed system[25] (Figure 2.4).
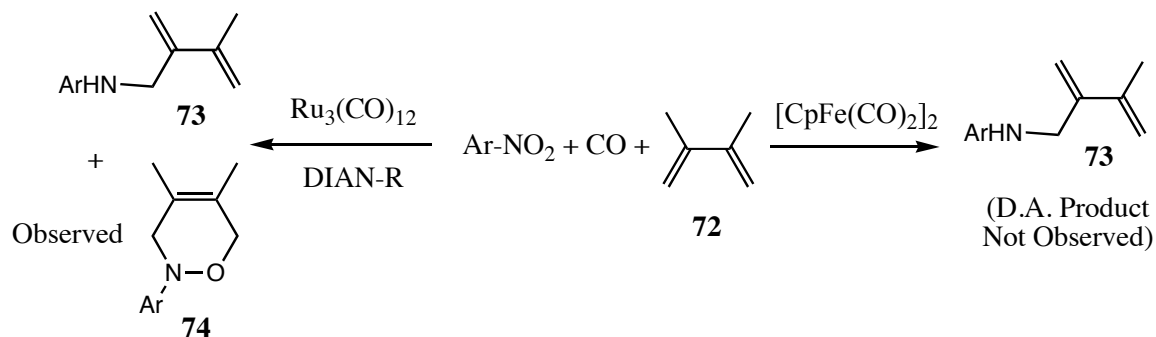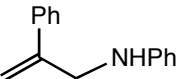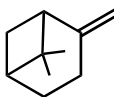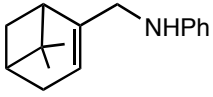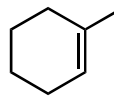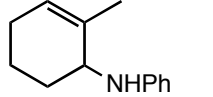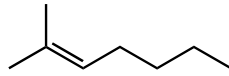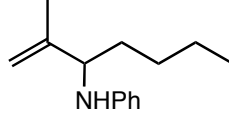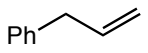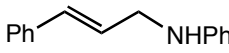
Figure 2.4

Using optimized conditions of 5 mol% $[CpFe(CO)_2]_2$, one equivalent of nitrobenzene, 1.3 equivalents of olefin, 900-1000 psi CO, and heated to 160-180°C in dioxane for 24 hours, a series of representative olefins and nitroarenes were employed (Table 2.1).[25] In all examples, regioselectivity of the reaction resembled that of an "ene" process with the amination occurring at the less substituted olefinic carbon. Electron-withdrawing and –donating groups are tolerated on the nitroarene, though

yields are decreased as compared to unsubstituted nitrobenzene, and substantially

decreased (2% isolated) when an electron-donating substituent is present. Finally, a

photoassisted procedure was developed that allowed for allylic amination of olefins

with nitrobenzene catalyzed by 10 mol% of either $[CpFe(CO)_2]_2$, $[(C_5Me_5)Fe(CO)_2]_2$,

or $[(C_5Me_5)Ru(CO)_2]_2$ to be conducted under 3-6 atm CO at 80-120°C in a glass

Fisher-Porter bottle, with lower yields relative to the high pressure thermal reaction.[96]

Allylic Amination of Nitrobenzene with Various Alkenes
Catalyzed by $[CpFe(CO)_2]_2$[a]

Entry	Alkene	Allylamine	Yield[b]
1			92
2			64
3			27
4			10
5			13

[a] Conditions: 5 mol% catalyst, 1 equiv $PhNO_2$, 1.3 equiv
alkene, CO (900-1000 psi), 160-180°C, dioxane, 24 hours
[b] GC yield calculated using naphthalene as internal standard

Table 2.1[25]

2.2   Results and Discussion

2.2.1 Attempts to Discover Milder Conditions for Nitroaromatic Reduction with Subsequent Allylic Amination

In our attempts to develop milder catalytic conditions for the allylic amination of olefins via nitroaromatic reduction, a large number of heterogeneous and homogeneous catalytic and stoichiometric systems were investigated. Systems that were chosen for investigation had shown the ability in previous reports to either deoxygenate nitro, nitroso, or other loosely related functional groups such as epoxides or carbonyls. Fundamentally, our strategy could be divided into two main areas: employment of systems that produce a metal-coordinated species from nitroaromatic reduction, and utilization of systems that reduce nitroaromatics to azoxy, azo, or aniline compounds. In the first strategic area, allylic amination is envisioned by reaction of a metal-coordinated *N*-species of nitroaryl reduction directly with an olefin, or through a "nitroso-ene" reaction from the forced release of a reactive *N*-species, such as a nitrosoaromatic, from the metal-complex. The second area is comprised mainly of heterogeneous systems in which the trapping of a "free" nitrosoaryl as an intermediate in nitroaryl reduction with an olefin through a "nitroso-ene" reaction is envisioned.

2.2.1.1   Metal-Complex Screening

The first system to be tested involved a stoichiometric amount of Fe(salen) complex **77** (Figure 2.5) that has been shown to deoxygenate nitrosoaryls as well as secondary *N*-hydroxylamines under relatively mild conditions.[98] It was not reported,

however, that the Fe(salen) would deoxygenate nitro compounds. Upon preparation of the complex,[99] a series of reactions to test for nitroaryl reduction were conducted by the employment of two equivalents of the Fe(salen) along with nitrobenzene and excess α-methylstyrene in either THF or DMF at temperatures ranging from 22-110°C. No detection (by GC) of *N*-phenylallylamine or nitrobenzene reduction products were observed under any of the reaction conditions.

In somewhat similarly reactive systems reported by Kochi[85] and O'Connor[86], either Ni or Co metal complexes have been shown to stoichiometrically reduce nitrobenzene under mild conditions to form side-on coordinated nitroso-metal complexes (such as **76** and **80**). We aimed to develop a catalytic nitroaryl reduction process from these complexes by attempting to react the coordinated nitrosoaromatic with an olefin. Both systems were initially tested by employment of the reactive metal complex (Figure 2.5, **75**, **79**) in a catalytic amount in the presence of nitrobenzene with a slight excess of α-methylstyrene using benzene as solvent with temperatures ranging from 22-60°C. The *N*-phenylallylamine product was not detected by GC, and little reduction of nitrobenzene was observed by either metal complex.

Complexes Tested for Activity
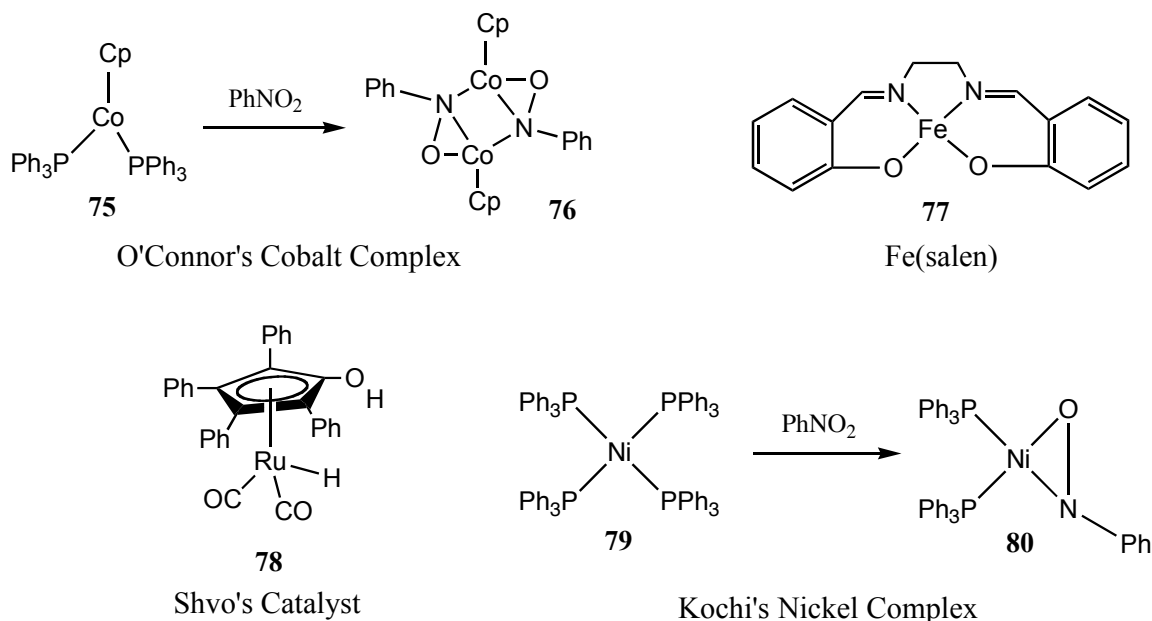
Figure 2.5

The final homogeneous catalyst to be tested was $\{[Ph_4(\eta^5\text{-}C_4CO)]_2H]\}Ru_2(CO)_4(\mu\text{-}H)$, or Shvo's catalyst **78**,[100] shown in Figure 2.5. The ruthenium complex has been shown to hydrogenate a number of functional groups including ketones, though the reduction of nitro groups has not been previously reported. Due to the possession of a metal-hydride and an acidic proton on the complex, reduction of the nitro group was envisioned by which the loss of water could form a nitrosoaromatic (Figure 2.6). Unfortunately, no reduction of nitrobenzene was detected in test reactions using a stoichiometric amount of the ruthenium complex at $22^\circ C$ or at elevated temperatures.
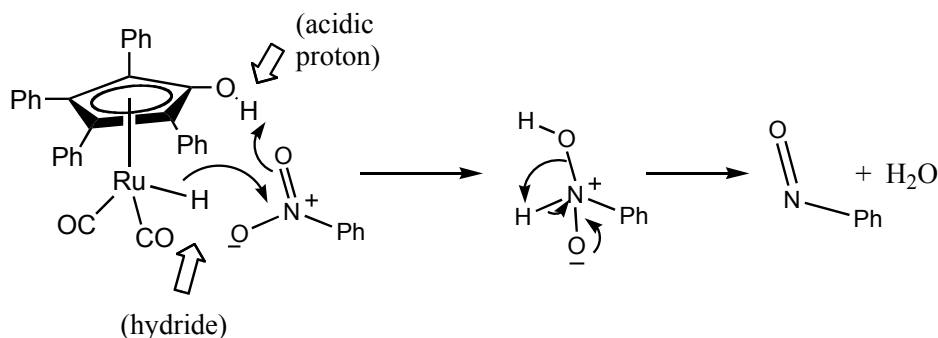
Figure 2.6

2.2.1.2   Heterogeneous System Screening

Numerous reductions or hydrogenations of nitroaromatics are known to generate either azo, azoxy, or aniline products. In attempts to induce the allylic amination of an olefin with "free" nitrosoaromatic formed as a potential intermediate from one of these reductions, a series of stoichiometric or catalytic systems were investigated. In almost all of these systems, a strategy involving an initial one (or two) electron reduction of a nitroaromatic followed by the removal of an oxygen atom to generate free nitroso-aromatic (or hydroxylamine) in the presence of an olefin (which could then undergo an ene reaction) was envisioned. Systems tested that employed milder conditions by utilizing a different stoichiometric reducing agent and/or oxygen acceptor than CO are shown in Table 2.2.

Initial Screening for Allylic Amination by Reduction of Nitrobenzene
in the Presence of α-Methylstyrene[a]

$$Ph\text{-}NO_2 \ + \ Ph\text{—}\overset{}{\underset{}{=}}< \ \xrightarrow{\text{Reducing System}} \ Ph\text{—}\underset{H}{N}\diagup\diagdown\overset{Ph}{=} \ + \ \text{By-products of } PhNO_2 \text{ reduction}$$

(AMS)   **81**
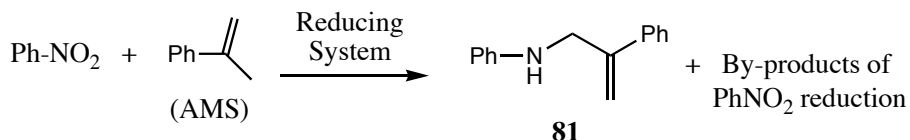
Entry	Equiv PhNO$_2$	Equiv AMS	Reducing Agents	Literature Reference	Observation
1	1.2	2	(Mg, Mn, Zn) + TMSCl	-	Multiple products, dimerization of styrene, no observable **81**
2	1.2	2	(Zn, TiCl$_3$) + TMSCl or HMDS	101 102	No apparent reduction of PhNO$_2$, no observable **81**
3	1	1.3	Na$_2$Te or NaHTe	103	Formation of azoxy- and azobenzene, no observable **81**
4	1	5	Sm^o, TMSBr	104	Formation of azoxy- and azobenzene, no observable **81**
5	1	10	RuCl$_3$, H$_2$O, indoline	105	No observable **81**
6	1	1	Fe(Pc) or Fe(TPP)Cl + NaBH$_4$	106 107	Formation of azoxybenzene AMS dimer, and trace amount of **81**

[a] Procedures are presented in the Experimental Section

Table 2.2

2.2.2 NaBH$_4$/Fe(Pc) Promoted Allylic Amination of α-Methylstyrene by Nitrobenzene

Of the systems tested, some initial success was only exhibited by the Fe(Pc)/NaBH$_4$ reduction of nitrobenzene conducted without the use of CO and at relatively mild temperatures. The overall reaction was originally envisioned as the combination of two known reactions that were both promoted by the same commercially available catalyst, the first step being the selective reduction of

nitrobenzene to PhNHOH with $NaBH_4$,[106] and the second being the allylic amination of PhNHOH and olefins.[6] An initial catalyst screening was conducted of metal salts and complexes that have been reported to undergo at least one of the two previously described reaction steps (Table 2.3).

Initial Screening for the Transition-Metal Catalyzed Reduction of Nitrobenzene with $NaBH_4$ in the Presence of α-Methylstyrene

$$\text{Ph-NO}_2 \ + \ \text{Ph}\diagdown\diagup \ + \ NaBH_4 \ \xrightarrow[\substack{80°C, 24 \text{ hrs} \\ \text{dioxane}}]{\substack{10 \text{ mol}\% \\ \text{catalyst}}} \ \text{Ph-N-}\diagup\diagdown\text{-Ph} \ + \ \text{By-products of PhNO}_2 \text{ reduction}$$

1 equiv   5 equiv   2 equiv   **81**
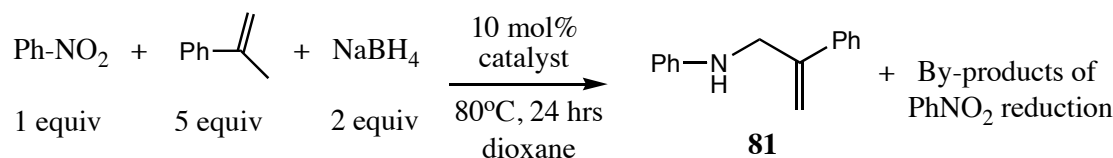
entry	catalyst	GC Detection[a] of **81**	GC Detection[a] of nitro reduction
1	CuCl (anhyd)	ND	Moderate
2	$CuCl_2$ (anhyd)	ND	None
3	$CuCl_2 \cdot 2\,H_2O$	ND	High
4	$Cu(CH_3CN)_4PF_6$	ND	Low
5	$FeCl_2$ (anhyd)	ND	High
6	$FeCl_3$ (anhyd)	ND	Moderate
7	9:1 $FeCl_2/FeCl_3$	ND	Moderate
8	$Fe^{II}(Pc)$	Trace	Low
9	$Fe^{III}(Pc)Cl$	ND	Mod-High
10	$SnCl_2$ (anhyd)	ND	Low
11	$SnCl_2 \cdot 2\,H_2O$	ND	Low[b]
12	$Co^{II}(Pc)$	ND	Moderate
13	$Mn^{III}(Pc)Cl$	ND	Moderate

[a] Confirmed by GC-MS   [b] Significant reduction of AMS

Table 2.3

Upon detection of *N*-phenylallylamine by GC-MS from the reaction catalyzed by Fe(Pc), a screening of solvents was performed including toluene, tetrahydrofuran, dichloromethane, diglyme, diglyme-10% MeOH, and dioxane. No reduction of

nitrobenzene was observed in toluene or dichloromethane likely due to insolubility of NaBH$_4$, and aniline was seen as the main product when diglyme or the diglyme-MeOH solvents were employed. Using refluxing dry tetrahydrofuran, however, produced the *N*-phenylallylamine along with a large amount of what was identified by GC-MS and previous reports[108] as a dimerized hydrocarbon formed from two equivalents of α-methylstyrene (Table 2.4, **82**). The reaction systems as performed in either refluxing dioxane or THF were then investigated further in an attempted optimization.

During the early stages of optimization, it was observed that the reaction performed in refluxing THF was complete in two hours, producing a 5-10% yield of allylamine. The reaction employing refluxing dioxane as solvent produced a 6% yield in 20 hours. Therefore the majority of the optimization process utilized THF due to the more expedient completion of the reactions. Neither increased catalyst loading nor application of techniques such as slow addition of reagents had any positive effect on the reactions either in THF or in dioxane. In addition, additives such as PPh$_3$, *N*-methylimidazole, and Sc(OTf)$_3$ also had no positive effect on the reaction. The reaction performed in dioxane produces large amounts of azoxybenzene **83** in all cases, and the reaction in THF produces large amounts of dimerized α-methylstyrene **82**. Only slight improvements in terms of limiting the aforementioned major products from the initial conditions were observed by the stoichiometric manipulation of the reactions in either THF or dioxane (Table 2.4). The best conditions employing THF as solvent (2 hours refluxing or 5 days at room temperature) produced an approximately 10% yield of allylamine **81** from a 20 equivalents excess of

nitrobenzene, one equivalent AMS, 10 mol% Fe(Pc), and 2 equivalents NaBH₄. In refluxing dioxane, however, it was observed that the azoxybenzene produced as major product could be limited by utilizing conditions of one equivalent of PhNO₂, 10 equivalents of AMS, 10 mol% Fe(Pc), and 2 equivalents NaBH₄, producing the allylamine in 12% yield. Phenylacetylene and 2-methyl-2-heptene were both employed as representative unsaturated hydrocarbons in order to test the generality of the reaction. However, neither reagent resulted in a product of amination.

Optimization Summary of the Allylic Amination of α-Methylstyrene by Nitrobenzene
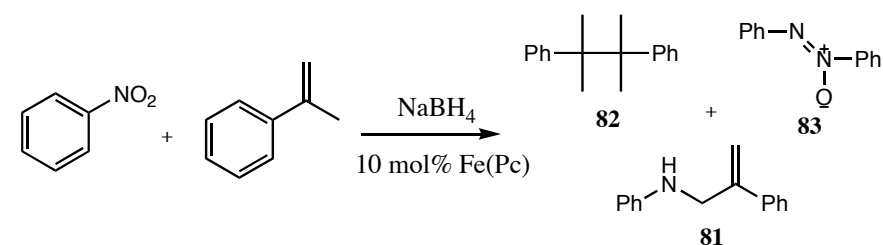
Entry	Equiv PhNO₂	Equiv AMS	Solvent	Time	Product Ratios		
					81	82	83
1	1	1	Dioxane	24 hrs (reflux)	trace	minor	major
2[a]	1	10	Dioxane	24 hrs (reflux)	1 :	1 :	3
3	1	1	THF	2 hrs (reflux)	trace	major	minor
4[a]	20	1	THF	2 hrs (reflux) 5 days (rt)	1 :	4 :	2

[a] Both reactions result in 10-12% yield (GC) of N-phenylallylamine 81

Iron Phthalocyanine
[Fe(Pc)]
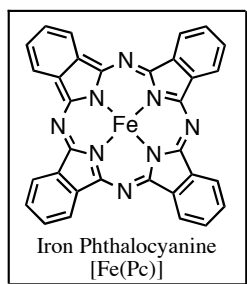
Table 2.4

In attempts to explore the reaction mechanism, known trapping experiments were conducted to attempt to detect either free nitroso or nitrene as intermediates in the reduction of nitrobenzene by NaBH$_4$/Fe(Pc) (Figure 2.7). Employment of 5 equivalents of 2,3-dimethylbutadiene **72** in the reaction conditions resulted in no formation of hetero-Diels-Alder product **74** or allylic amine **73**, thus implicating that a free nirosobenzene is not present in the mechanistic pathway. In addition, employment of 2-phenyl-nitrobenzene **84** did not result in the formation of carbazole **85**, only 2-phenyl-aniline **86** was observed by isolation. Therefore it can be concluded that the reduction of nitrobenzene does not produce a nitrene intermediate species during deoxygenation.
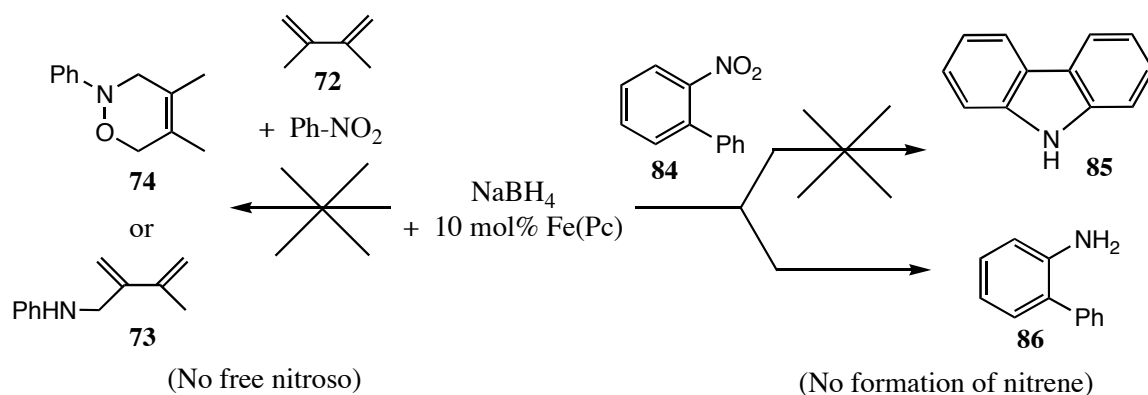
Figure 2.7

Finally, the state of the Fe(Pc) might be circumstantially characterized by the appearance of the dark heterogeneous mixture at various stages in the reaction. Fe^{II}(Pc) is dark blue in solution, and upon addition of NaBH$_4$ and heating, the mixture turns a dark wine red in THF, which is indicative of Fe^{I}(Pc).[109] Finally, upon exposure to air or cooling of the mixture, the color changes to dark green, which is

indicative of $Fe^{III}(Pc)$. Therefore, it is presumed that the $NaBH_4$ acts to initiate the reaction by forming the reduced $Fe^I(Pc)$, which can transfer an electron to the nitrobenzene to form a nitrobenzene anion radical that is subsequently deoxygenated by the catalyst. It is also presumed that the addition of the olefin substrate to the *N*-aminating species occurs on-the-metal in an unknown process, as no free nitrosobenzene could be trapped with known methods.

In summary, the allylic amination of α-methylstyrene via $NaBH_4/Fe(Pc)$ promoted reduction of nitrobenzene in either dioxane or THF produced in all cases *N*-phenylallylamine as a minor product, with unavoidable formation of dimer **82** or azoxybenzene as major products. In addition, the reaction did not appear to be applicable to alkenes or alkynes other than α-methylstyrene. Despite these shortcomings, the reaction as described represents the first example of allylic amination of an olefin employing nitroaromatics as the *N*-aminating reagent without the use of CO in high pressure autoclaves, and performed at temperatures lower than the previously reported 100-180°C. Investigations were discontinued mainly due to the inability to optimize the system to a synthetically useful or general reaction. Though a novel system, the inability to identify the role of the active catalyst in order to more fully understand the reaction also contributed to its abandonment.

2.2.3 Utilization of Conventional Microwave Oven

In addition to efforts made in regard to the development of new catalytic systems of nitroaryl reduction and subsequent allylic amination, attention was also paid to modifying the existing system in order to obtain more convenient reaction

conditions. An approach to conduct reactions outside of high-pressure stainless steel autoclave reactors was envisioned in which conventional microwaves were used in conjunction with thick-walled Teflon screw-top vessels. While procedures are available for the modification of conventional microwaves to allow for the regulation of reaction temperatures,[110] the conventional microwaves that were used in our study were used without any modification. Due to the lack of temperature regulation, a typical reaction procedure involved pulsing with the microwave for 2-4 minutes, upon which the vessel was removed from the microwave, stirred (shaken), and allowed to cool 2-4 minutes. Failure to agitate the mixture or allow the solution to cool could result in plating of the transition metal-catalyst (or free metal) on the vessel wall, which creates an area of supercritical heat that can crack the reaction vessel, resulting in a deafening explosion of the vessel and the microwave oven.

Initial reactions were conducted using an excess of α-methylstyrene, one equivalent of nitrobenzene, and 10 mol% $[CpFe(CO)_2]_2$ (Fp_2) without the use of a solvent or stoichiometric source of CO, though it was quickly observed that a source of CO is needed in order to obtain a catalytic reaction. Stoichiometric sources of CO for use in microwave reactions are known such as $Mo(CO)_6$,[111] though it was deemed economically unacceptable for the allylic amination reaction, considering that a stoichiometric amount of Fp_2 (used in the reaction as a catalyst) is less expensive than $Mo(CO)_6$. Therefore, attempts to utilize inexpensive sources of CO such as CO gas (1-4 atm), formamide,[112] and $Fe(CO)_5$[113] were explored. Some success was obtained using CO gas and/or $Fe(CO)_5$ as stoichiometric CO sources. However, the

employment of formamide was less fruitful due to catalyst poisoning from the production of ammonia.

In attempts to optimize a microwave-assisted reaction, it was observed that reactions generally required 80-120 minutes of microwave heating (in four minute intervals) in order for > 90% conversion of nitrobenzene (Figure 2.8).

Fp2/Fe(CO)5 Microwave-Assisted Production of N-Phenylallylamine

A line graph titled "Fp2/Fe(CO)5 Microwave-Assisted Production of N-Phenylallylamine". The y-axis is labeled "Yield of N-Phenylallylamine" ranging from 0% to 25%. The x-axis is labeled "Time (Minutes)" ranging from 50 to 90. Data points: 7% at ~56 min, 11% at ~72 min, 18% at ~80 min, 21% at ~88 min.
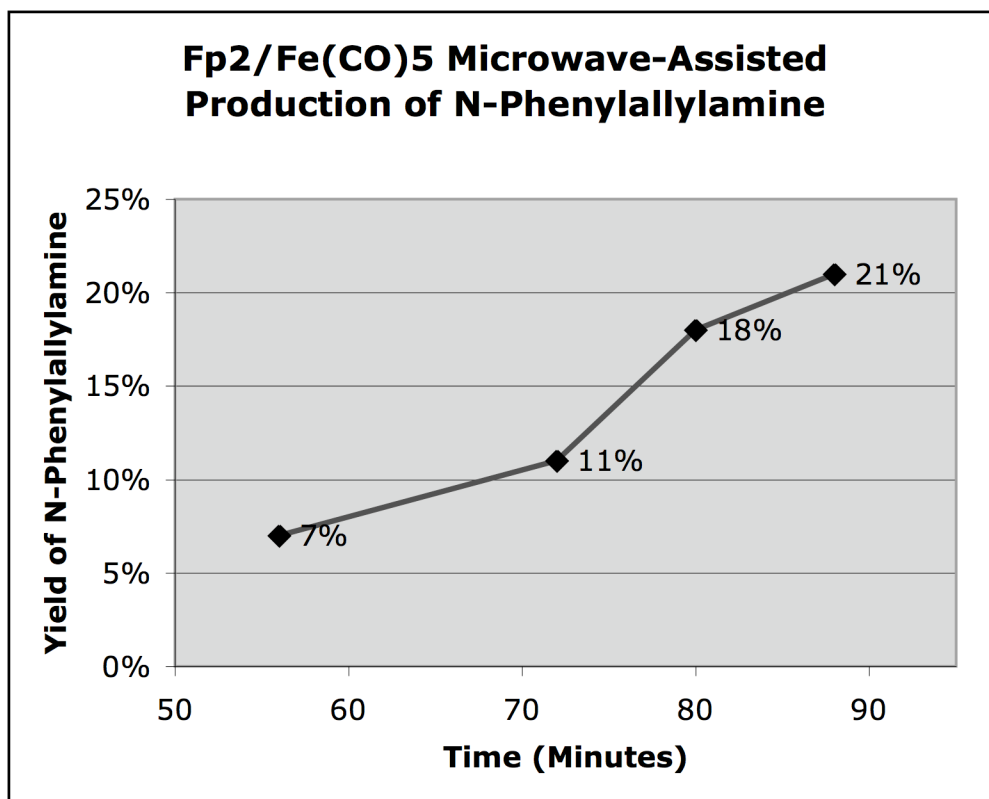
Figure 2.8

It was also observed that lower yields were consistently obtained by employment of benzene as solvent. Best results were obtained by using one equivalent nitrobenzene in 6 equivalents of α-methylstyrene, with one atm CO and/or 1-2 equivalents of $Fe(CO)_5$ and 0.1 equivalents of Fp_2. After microwave heating a total of 80-120

minutes, yields of *N*-phenylallylamine were typically modest (6-21%) as determined by GC. Though a source of CO was deemed necessary for a catalytic reaction, the variation of amounts of Fe(CO)$_5$ or CO seemed to have little effect on product yield (Table 2.5, entries 3-7). Additionally, the allylamine product was consistently accompanied by large amounts of by-products of nitrobenzene reduction including azoxybenzene (10-30%), aniline (10-30%), and azobenzene (5-15%).

Fe-Catalyzed Microwave Assisted Allylic Amination of Nitrobenzene and α-Methylstyrene
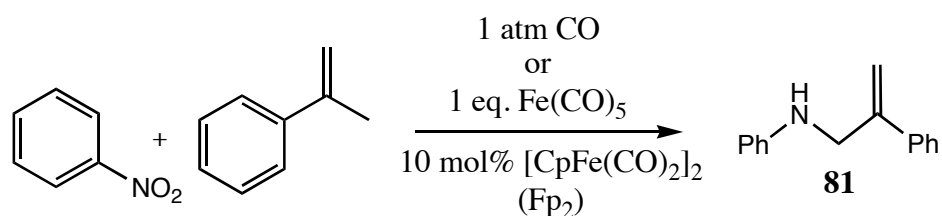
Entry	Amount of CO	Equiv Fe(CO)$_5$	Equiv Fp$_2$	Time (Minutes)	Solvent	GC Yield **81** (%)
1	0	0	1	80	Benzene	8
2	0	10	0.1	120	Benzene	6
3	0	2	0.1	80	neat	19
4	0	1	0.1	80	neat	18
5	0	0.5	0.1	88	neat	15
6	1 atm	1	0.1	88	neat	21
7	2-4 atm	0	0.1	122	neat	17

Table 2.5

With the appearance of a seemingly maximum product yield in the initial optimization attempts, analogous thermal reactions were investigated at 100°C employing Fe(CO)$_5$ as stoichiometric source of CO, and/or lower atmospheric pressure of CO gas (~7 atm). The milder thermal reactions were envisioned to

determine typical product ratios that are observed without the employment of high pressures of CO (50-70 atm) and high temperatures (160-180°C) used in the standard reaction conditions. Upon varying amounts of $[CpFe(CO)_2]_2$ (Fp_2) catalyst, $Fe(CO)_5$, and CO pressure (Table 2.6), it was determined that yields ranging from 19-24% are in fact typical of milder conditions. Additionally, the thermal and microwave-assisted methods produce similar amounts of by-products of nitrobenzene reduction including azoxybenzene (10-30%), aniline (10-30%), and azobenzene (5-15%). Thus, it was determined that while conventional microwave-assisted conditions can provide shorter reaction times as well as a more accessible reaction vessel, reactivity and consequently product yields are not enhanced as compared to the high pressure thermal reaction. Though yields are modest, this system represents the first example of a microwave-assisted allylic amination of an olefin from a nitroaromatic.

Fe-Catalyzed Thermal Allylic Amination of Nitrobenzene and α-Methylstyrene
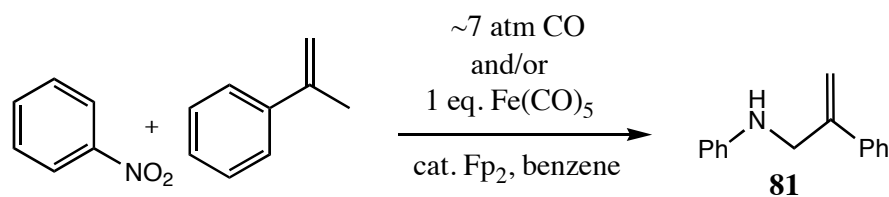
Entry	Amount of CO	Equiv $Fe(CO)_5$	Equiv Fp_2	Time (Hours)	GC Yield 81 (%)
1	0	1	0.1	72	19
2	7 atm	1	0.1	72	22
3	7 atm	1	0	72	trace
4	7 atm	1	0.25	72	23
5	7 atm	0.1	0.1	72	22
6	7 atm	0	0.1	70	24

Table 2.6

2.2.4 Additive Effects: An Fe-Cu Co-Catalyst System

In addition to the use of microwave-assisted conditions in order to develop a milder, more convenient reductive nitroaromatic allylic amination procedure, several additives were also tested with the Fp_2-catalyzed reaction. Among the additives and/or ligands that were initially tested in conjunction with a catalytic amount of Fp_2 at 100^oC and 150 psi (~10 atm) CO were pyridine, bipyridine, triphenylphosphine, phenanthroline, and CuBr. Of these, only CuBr produced an observable positive effect on the reaction. The choice of CuBr as an additive was originally made due to the previously unpublished observation within the Nicholas Group that the addition of halides increased the product selectivity, but decreased the reaction rate. As most common sources of halides such as ammonium halide salts are not stable to prolonged exposure at higher temperatures, CuBr was originally viewed as a potentially thermally innocuous source of halide.

In the standard Fp_2-catalyzed reaction conducted at higher temperatures and pressures of CO, N-selectivity of the allylamine product is typically 60-85% due to the deleterious formation of by-products such as azoxy, azo, and aniline compounds. However, it was observed that addition of a catalytic amount of CuBr increased the N-selectivity of the allylamine product relative to the other observable (by GC) N-containing by-products to levels >98%. An initial co-catalyst screening was conducted of various copper salts and $[CpFe(CO)_2]_2$, $[(C_5Me_5)Fe(CO)_2]_2$, or $[(C_5Me_5)Ru(CO)_2]_2$ complexes (Table 2.7).

Co-Catalyst Screening of Allylic Amination of Nitrobenzene and α-Methylstyrene
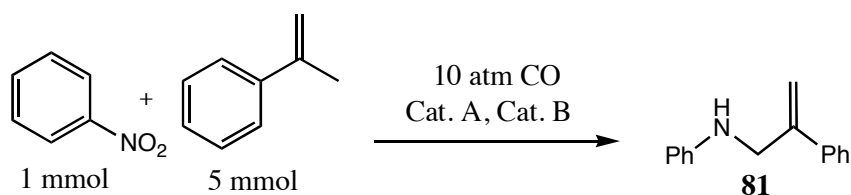
Entry	Catalyst A[a] (mol %)	Catalyst B (mol %)	Solvent	Temp (°C)	Time (hours)	GC Yield **81** (%)	N-Selectivity (%)
1	Fp$_2$ (5)	none	Benzene	160	96	24	64
2	none	CuBr (10)	Benzene	100	72	0	
3	Fp$_2$ (5)	CuBr (5)	Benzene	100	72	19	>98
4	Fp$_2$ (5)	Cu(CH$_3$CN)$_4$PF$_6$ (5)	Benzene	100	45	13	99
5	Fp$_2$ (5)	CuBr$_2$ (5)	Benzene	100	72	0	
6	Fp$_2$ (5)	CuI (5)	Dioxane	100	92	19	98
7	Fp$_2$ (5)	CuBr (5)	Dioxane	100	114	21	94
8	Fp*$_2$ (5)	CuBr (5)	Dioxane	100	114	11	
9	Ru*$_2$ (5)	CuBr (5)	Dioxane	100	114	2	

[a] Fp$_2$ = [CpFe(CO)$_2$]$_2$; Fp*$_2$ = [(C$_5$Me$_5$)Fe(CO)$_2$]$_2$; Ru*$_2$ = [(C$_5$Me$_5$)Ru(CO)$_2$]$_2$

Table 2.7

In the first of two control reactions, an experiment was performed without CuBr (entry 1), and it was observed that a low yield of N-phenylallylamine (24%) is obtained under 10 atm CO and 160°C, with an N-selectivity of only 64%. In the second control reaction, Fp$_2$ was excluded from the reaction (entry 2), resulting in very little reduction of nitrobenzene and no detectable product formation. As these results verified the necessity of both Fp$_2$ and CuBr for production of high N-selectivity (entry 3), the nature of the copper salt was then investigated. To attempt to determine if the counter-anion halide is necessary or responsible for the observed

increase in selectivity, Cu[(CH$_3$CN)$_4$]PF$_6$ was employed as catalyst (entry 4), and high selectivity was still observed, thus implicating a role of Cu^I in the reactive catalytic complex. Employment of CuBr$_2$ in the reaction (entry 5) resulted in reduction of nitrobenzene as well as the olefin, with no observable formation of *N*-phenylallylamine product. Lastly, an additional Cu^I salt (CuI) was employed with similar success (entry 6).

In addition to varying the copper salt catalysts, attempts were also made to improve the efficiency of the reaction by varying the iron (or ruthenium) catalyst complexes. Since it has been shown in previous studies[77,96] that employment of [(C$_5$Me$_5$)Fe(CO)$_2$]$_2$ or [(C$_5$Me$_5$)Ru(CO)$_2$]$_2$ can have positive effects on the efficiency of C-N bond forming reactions via nitroaryl reduction, the aforementioned complexes were employed in conjunction with catalytic amount of CuBr (entries 8-9). Interestingly, the catalysts that were shown to be more effective in previously reported studies produced less efficient results than Fp$_2$ in side-by-side reactions (entries 7-9). This may either be due to electronic effects, as the pentamethyl-cyclopentadienyl ligand would provide more electron donation to the metal, or potentially due to steric effects of the bulkier Cp* ligand that may prevent a potentially reactive Fe-Cu or Ru-Cu complexation.

Using the best results and most convenient catalysts from the catalyst screening, an optimization of stoichiometry and reaction conditions was then performed (Table 2.8). As our initial goals were to develop a milder system employing lower reaction temperatures and CO pressures, a reaction was performed at 75°C and 10 atm CO resulting in little conversion of nitrobenzene to the product

allylamine, even over a period of 6 days (entry 1). The role of reaction temperature at lower CO pressures was further investigated by conducting reactions at 100° and 160^oC (entries 2-3). It was observed that product yield increases as temperature increases, and *N*-selectivity remains high even at higher temperatures. Dioxane was determined to be a better solvent than benzene for the reaction (entries 3-4), and though yields are improved (39%, 96% *N*-selectivity), they still remain modest relative to the high pressure (900-1000 psi CO) conditions.[25] In an attempt to determine if the Fe/Cu co-catalyst system could be applied to high pressure and temperature conditions in order to achieve high yield and high *N*-selectivity, an experiment was conducted at 160^oC and 48 atm CO (entry 5). Strangely, the system actually produced a lower yield (16%) and slightly decreased selectivity. Finally, by employing a larger excess of olefin in the reaction stoichiometry, moderate yields with excellent selectivity were obtained at the lower temperature of 100^oC and 10 atm CO (entry 6). Though modest, this result is in fact comparable to that obtained from the Fp_2-catalyzed (without Cu^I) reaction at higher temperatures and pressures of CO (entry 9).

Optimization of Cu^I/Fp_2-Catalyzed Allylic Amination of Nitrobenzene and α-Methylstyrene
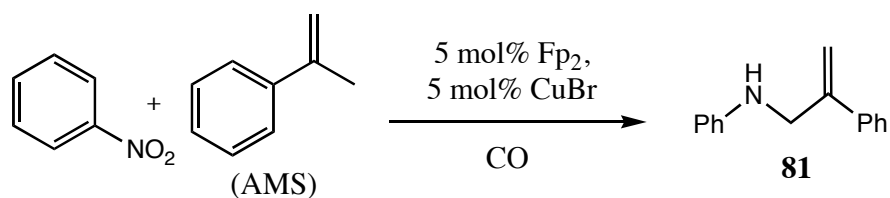
Entry	mmol PhNO$_2$	mmol AMS	Solvent	Temp (°C)	Time (hours)	CO (atm)	GC Yield 81 (%)	N-Selectivity (%)
1	2	10	Dioxane	75	144	10	7	
2	1	5	Benzene	100	72	10	19	>98
3	1	5	Benzene	160	96	10	29	94
4	1	5	Dioxane	160	112	10	39	96
5	1	5	Benzene	160	72	48	16	88
6	1	15	Dioxane	100	92	10	41	97
7[a]	1	15	Dioxane	100	112	10	26	96
8[b]	1	15	Dioxane	100	112	10	8	99
9[c]	2	2.6	Dioxane	160	90	51	47	86

[a] 15 mol% of each catalyst [b] 2 mol% of each catalyst, incomplete nitrobenzene conv.
[c] Reaction conducted without using CuBr as co-catalyst

Table 2.8

With an eye to determining the role of the Cu^I salt in the reaction, attempts were made to spectroscopically detect a potential bi-metallic complex using IR. The IR spectrum of solid $[CpFe(CO)_2]_2$ in KBr has two $\nu(CO)$ peaks at 1934 [corresponding to the terminal (η^1-CO) groups] and 1756, corresponding to the bridging (η^2–CO) groups. In dioxane solution, three $\nu(CO)$ peaks from $[CpFe(CO)_2]_2$ are observed at 1994, 1953, and 1779. Upon heating one equivalent Fp_2 with one equivalent CuBr in dioxane at 100°C under 10 atm CO for 48 hours, an aliquot was

withdrawn from the autoclave reactor via diptube and analyzed by IR. In addition to the known three ν(CO) peaks from [CpFe(CO)$_2$]$_2$ at 1995, 1952, and 1779, a new peak at 2045 was observed. After an additional 24 hours of heating (3 days total), another new ν(CO) peak at 1984 emerged. Thus, after subtraction of the known three ν(CO) peaks from [CpFe(CO)$_2$]$_2$ in dioxane, two new ν(CO) peaks at 2045 and 1984 are observed, likely from the coordination of CuBr in some manner to the Fp$_2$. A number of possible complexes similar in structure to reported species formed from the additions of halides[114] and ligands[115] to Fp$_2$ are envisioned (Figure 2.9). It is difficult to definitively claim that these ν(CO) peaks can be attributed to a possible reactive bimetallic species responsible for the selective formation of allylamine since all IR spectra were obtained after the samples were cooled to room temperature and released to atmospheric pressure of air. For further verification, IR measurement taken under reaction conditions (100°C, 10 atm CO) would be desirable.

Some Possible Bi-metallic Fe/Cu Complexes
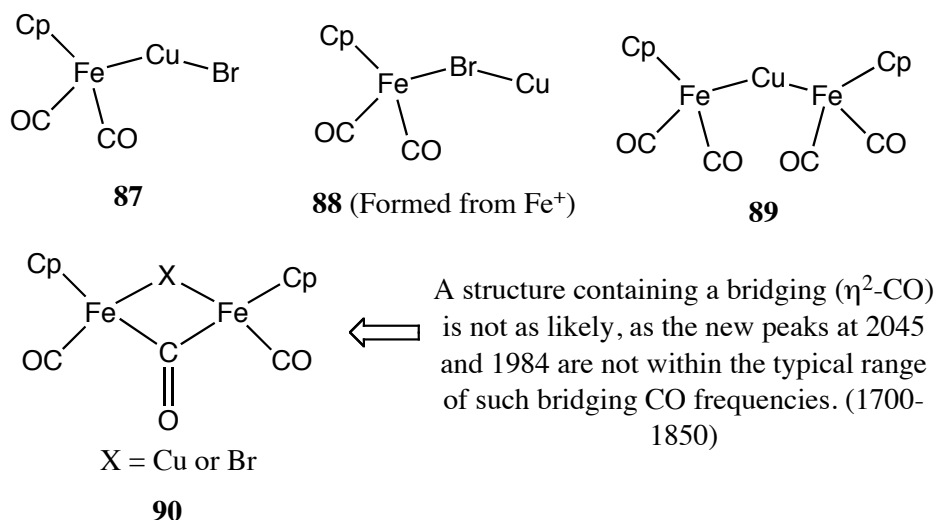
Figure 2.9

Finally, the discrepancy that lies in the mass balance from the reactions in which almost complete nitrobenzene conversion (>95%) is accompanied by excellent *N*-selectivity (>95%), but low product yield (~40%) is of concern. The *N*-selectivity of the product allylamine as it is discussed in this context and in comparison to previous reports only considers the additional *N*-containing by-products that can be detected by GC, including aniline, azobenzene, and azoxybenzene. Other potential by-products that may be responsible for a large portion of the *N*-containing products of nitrobenzene reduction include *N,N*-diphenylurea (as previously reported[25]) and/or polymerized nitrobenzene or polyaniline.[116]

The investigation was discontinued mainly due to the emergence of other more promising systems, which are discussed in the next two chapters. In addition, the optimized reaction in its present form was not considered synthetically useful, though further improvements could be made to the system in order to achieve sufficient product yield (~60%). For example, employment of the alkene substrate as solvent could conceivably increase the yield from 41% to a value similar to that produced by the photoassisted method.[96] Additional attempts to characterize the nitrobenzene by-products as well as the potential bi-metallic complex using MS-ESI would also add to the value of the novel system.

2.3   Summary and Conclusions

In summary, our attempts to develop a new catalytic allylic amination from nitrobenzene without the use of high pressures of CO and high temperatures were met with moderate success in the NaBH$_4$/Fe(Pc) promoted reaction. Though large

amounts of deleterious by-products always accompanied low yields of allylamine product and substrate scope appeared limited to α-methylstyrene, the reaction still represents the first example of a bench-top allylic amination from nitroaromatics without the requirement of stoichiometric CO. In addition, the first microwave-assisted preparation of allylic amines from nitroaromatics was developed by employing either one atm CO, or one equivalent $Fe(CO)_5$ as a stoichiometric CO source. Yields obtained were relatively low (~20%), though the procedure allows for employment of a more widely available reactor as well as shorter reaction times than the previously reported high pressure and temperature system. Finally, a more *N*-selective co-catalytic system was developed by employing CuBr with $[CpFe(CO)_2]_2$ under milder conditions such as 100^0C and 10 atm CO pressure. These conditions are very close to those allowing for the reaction to be conducted in Fisher-Porter vessels, and slight improvements in the allylamine product yield (from 41%) could make this a synthetically applicable system due to the ease of purification of the crude mixtures that are already 95-99% pure due to the high *N*-selectivity of the system. Further attempts to elucidate the role of Cu^I in the catalytic system could also prove fruitful in developing an even more reactive system.

2.4   Experimental

2.4.1 General Considerations

Commercial reagents were purchased from Sigma Aldrich, Strem, Alfa Aesar, or GFS. Fe(salen)[99], Ni(PPh$_3$)$_4$[117], CpCo(PPh$_3$)$_2$[118], {[Ph$_4$(η^5-C$_4$CO)]$_2$H]}Ru$_2$(CO)$_4$(μ-H)[119], and Na$_2$Te[103] were prepared by literature procedures without modification and

each compound was determined pure by comparison to individual known data. Purchased nitrobenzene, 2,3-dimethylbutadiene, 2-methyl-2-heptene, and α-methylstyrene were purified by distillation before use. Products including β-methylene-*N*-phenylbenzene-ethanamine **81**,[120] 1,1'-(1,1,2,2-tetramethyl-1,2-ethanediyl)bis-benzene **82**,[108] azoxybenzene, azobenzene, and aniline are reported compounds, and ^{1}H NMR spectra and GC-MS data were compared to literature data. Toluene, benzene, tetrahydrofuran, and dioxane were distilled prior to use over Na/benzophenone. Dichloromethane and acetonitrile were distilled over CaH_2 before use. All other solvents including those used in chromatography were used without any purification. Visualization of the developed chromatogram was performed under UV light or I_2 stain. ^{1}H NMR spectra were obtained at 300 MHz; NMR spectra were internally referenced to residual protio solvent signals. Mass spectra were acquired either in methanol or acetonitrile solution by ESI, or by GC-MS (EI) dissolved in hexanes. Naphthalene was used as an internal standard for GC yield determinations.

2.4.2 Procedures for Metal-Complex and Heterogeneous System Screening for Milder Methods of Allylic Amination of Nitrobenzene and α-Methylstyrene

Fe(salen) [77]

To a 100 mL round bottom flask was added ~30 mL of THF (or DMF) and magnetic stir bar. Then Fe(salen) (0.195 g, 0.600 mmol), nitrobenzene (30 μL, 0.30 mmol), naphthalene (~30 mg), and α-methylstyrene (390 μL, 3.0 mmol) was added at once.

The reaction mixtures were stirred under argon for 2-4 hours, then heated to reflux up to 24 hours. Samples taken for GC were cooled and diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

Ni(PPh₃)₄ [79]

To a flask in a nitrogen atmosphere glovebox was added freshly prepared Ni(PPh$_3$)$_4$ (0.080 g, 0.072 mmol) and the flask was sealed with a septum. To this was added 5 mL of dry THF and nitrobenzene (29.5 μL, 0.289 mmol) and the reaction was stirred at room temperature under nitrogen for 1 hour. Then α-methylstyrene (39 μL, 0.30 mmol) was added through the septum and the reaction was stirred at room temperature overnight. During this time, aliquats were withdrawn for product detection by GC. The reaction was then heated to ~40°C for an additional 6 hours. Samples taken for GC were cooled and diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

CpCo(PPh₃)₂ [75]

To a flask in a nitrogen atmosphere glovebox was added freshly prepared CpCo(PPh$_3$)$_2$ (0.228 g, 0.351 mmol) and the flask was sealed with a septum. To this was added either 10 mL of dry benzene or acetonitrile, nitrobenzene (110 μL, 1.07 mmol), and α-methylstyrene (787 μL, 5.00 mmol) by oven-dried glass syringe. The reaction was stirred at room temperature under nitrogen for 24 hours. During this

time, aliquots were withdrawn for product detection by GC. The mixture was then heated to 60°C for an additional 18 hours. Samples taken for GC were cooled and diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

{[Ph$_4$(η^5-C$_4$CO)]$_2$H]}Ru$_2$(CO)$_4$(μ-H) [78]

To a flask in a nitrogen atmosphere glovebox was added freshly prepared {[Ph$_4$(η^5-C$_4$CO)]$_2$H]}Ru$_2$(CO)$_4$(μ-H) (0.150 g, 0.138 mmol) and the flask was sealed with a septum. To this was added 25 mL of dry dichloromethane and nitrobenzene (30.0 µL, 0.276 mmol) and the reaction was stirred at room temperature under nitrogen for 20 hours. During which, samples were withdrawn for product detection of nitrobenzene reduction by GC. Then α-methylstyrene (22.0 µL, 0.138 mmol) was added through the septum and the reaction was stirred at room temperature 6 hours, followed by reflux overnight. Samples taken for GC were cooled and diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

(Mg, Mn, Zn) and TMSCl

In individual test tubes, reaction screening was conducted using nitrobenzene (125 µL, 1.22 mmol), α-methylstyrene (316 µL, 2.00 mmol), and 4 mL of dry dioxane. To these separate test tubes was added either Mg°, Mn°, or Zn° (2.44 mmol),

trimethylsilylchloride (190 μL, 1.5 mmol), and in some reactions Cp$_2$TiCl$_2$ (61 mg, 0.24 mmol). The reactions were heated to 75°C under a nitrogen atmosphere for 24 hours and samples taken for GC were cooled and diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

Zn, TiCl$_3$, and TMSCl (or HMDS)

In individual test tubes, reaction screening was conducted using nitrobenzene (125 μL, 1.22 mmol), either α-methylstyrene or 2-methyl-2-heptene (2.0 mmol), and 10 mL of either acetonitrile or DMF. To these separate test tubes was added Zn^o (160.0 mg, 2.440 mmol), either trimethylsilylchloride or hexamethyldisilane (2.5 mmol), and either Cp$_2$TiCl$_2$ or TiCl$_3$ (0.244 mmol). The reactions were stirred at room temperature for 24 hours, then heated to 40°C for an additional 20 hours. Samples taken for GC were cooled and diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

Na$_2$Te or NaHTe

To a flask in a nitrogen atmosphere glovebox was added tellurium powder (0.258 g, 2.00 mmol) and sodium hydride (0.100 g, 4.20 mmol) and the flask was sealed with a septum. To this was added 3.5 mL of DMF and the reaction was heated to 100°C. Upon formation of a pale yellow solution, nitrobenzene (103 μL, 1.00 mmol), and α-methylstyrene (169 μL, 1.30 mmol) were added by oven-dried glass

syringe. The reaction was stirred at reflux overnight. Samples taken for GC were cooled and added to 5-10 mL of saturated NaCl solution, then extracted with diethyl ether and followed by GC injection in order to determine product yields using naphthalene as internal standard.

Sm⁰ and TMSBr

To an oven-dried flask was added 25 mL of dry acetonitrile, trimethylsilylbromide (524 μL, 4.00 mmol), and samarium metal (0.301 g, 2.00 mmol). The mixture was then stirred under N_2 for 5 hours at room temperature. Then nitrobenzene (103 μL, 1.00 mmol) and α-methylstyrene (650 μL, 5.0 mmol) were added by oven-dried glass syringe, upon which the dark green solution turned to a light beige. The reaction was stirred at room temperature overnight. Samples taken for GC were cooled and added to 1-2 mL of saturated NaCl solution, then extracted with diethyl ether and followed by GC injection in order to determine product yields using naphthalene as internal standard.

RuCl₃/H₂O/indoline

To an oven-dried side-arm flask was added 4 mL of dry toluene, RuCl₃ · H₂O (41.5 mg, 0.200 mmol), indoline (336 μL, 3.00 mmol), nitrobenzene (103 μL, 1.00 mmol) and α-methylstyrene (1.57 mL, 10.0 mmol). The flask was then sealed and evacuated under high vacuum two times, and sealed while under vacuum. The reaction was then stirred and heated to reflux overnight. Samples taken for GC were cooled and diluted with hexanes and passed through a small pipette silica gel plug to

remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

2.4.3 Procedure for the NaBH$_4$/Fe(Pc) Promoted Allylic Amination of α-Methylstyrene by Nitrobenzene in Dioxane

To an oven-dried 50 mL round-bottom flask and magnetic stir bar was added iron phthalocyanine [Fe(Pc)] (28.4 mg, 0.050 mmol), naphthalene (~60 mg as internal standard for GC), and sodium borohydride (37.8 mg, 1.00 mmol). The flask was then placed under high vacuum to remove air and purged with argon. Dry dioxane (10 mL) was then added by syringe through a septum on the flask, and the flask was purged with argon again. Then α-methylstyrene (650 μL, 5.0 mmol) was added by an oven-dried glass 1 mL syringe, followed by addition of nitrobenzene (51.7 μL, 0.500 mmol) while stirring. An oven-dried condenser with a septum and argon balloon was then attached to the flask, and the setup was flushed with argon a final time. The reaction mixture (dark blue, then dark green) was then refluxed for 20-24 hours. Samples taken for GC were diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

2.4.4 Procedure for the NaBH$_4$/Fe(Pc) Promoted Allylic Amination of α-Methylstyrene by Nitrobenzene in Tetrahydrofuran

To an oven-dried 50 mL round-bottom flask and magnetic stir bar was added iron phthalocyanine [Fe(Pc)] (28.4 mg, 0.050 mmol), naphthalene (~60 mg as internal standard for GC), and sodium borohydride (37.8 mg, 1.00 mmol). The flask was then placed under high vacuum to remove air and purged with argon. Dry THF (10 mL) was then added by syringe through a septum on the flask, and the flask was purged with argon a second time. Then α-methylstyrene (65 μL, 0.50 mmol) was added by an oven-dried glass 1 mL syringe, followed by addition of nitrobenzene (1.03 mL, 10.0 mmol) while stirring. An oven-dried condenser with a septum and argon balloon was then attached to the flask, and the setup was flushed with argon a final time. The reaction mixture (dark blue, then dark red, and finally dark green) was then refluxed for 2 hours. Samples taken for GC were diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

2.4.5 Mechanistic Test for the Presence of Free Nitrosobenzene as an Intermediate in the NaBH$_4$/Fe(Pc) Promoted Allylic Amination of α-Methylstyrene by Nitrobenzene

The reaction was conducted according to the procedure described in 2.4.2 by employing Fe(Pc) (28.4 mg, 0.050 mmol), naphthalene (56.6 mg, 0.442 mmol), NaBH$_4$ (37.8 mg, 1.00 mmol), nitrobenzene (51.7 μL, 0.500 mmol), 2,3-

dimethylbutadiene (282 μL, 2.50 mmol), and 15 mL dry THF. Product characterization of the crude material was determined by GC-MS and compared to that of a known isolated sample of 4,5-dimethyl-2-phenyl-3,6-dihydro-2H-1,2-oxazine.

2.4.6 Mechanistic Test for the Formation of Nitrene in the NaBH$_4$/Fe(Pc) Promoted Allylic Amination of α-Methylstyrene by Nitrobenzene

The reaction was conducted according to the procedure described in 2.4.2 by employing Fe(Pc) (56.8 mg, 0.100 mmol), naphthalene (66.7 mg, 0.521 mmol), NaBH$_4$ (75.6 mg, 2.00 mmol), 2-nitrobiphenyl (189 mg, 1.00 mmol), and 25 mL dry THF. Product characterization of the crude mixture was determined by GC-MS, and 2-aminobiphenyl was then isolated by flash chromatography of the residue over silica gel (20% EtOAc/hexane eluant; R$_f$ = 0.55), and characterization by ^{1}H NMR matched reported spectra.

2.4.7 General Procedure for the Microwave-Assisted Allylic Amination of α-Methylstyrene by Nitrobenzene

To a mixture of nitrobenzene (103 μL, 1.00 mmol) and α-methylstyrene (800 μL, 6 mmol) in a thick-walled Teflon screw-top reaction vessel was added [CpFe(CO)$_2$]$_2$ (35.4 mg, 0.100 mmol) and naphthalene (as internal standard, 20-40 mg). To this heterogenous mixture was added either iron pentacarbonyl (132 μL, 1.00 mmol) and/or 1 atmosphere carbon monoxide gas added by bubbling directly into the

mixture for 15 minutes via a balloon connected to a long syringe, through a septum attached to the reaction vial with an additional venting needle – CAUTION – only perform in a fume hood. The vessel was then sealed and placed in a conventional microwave oven and heated in 4-minute intervals, followed each time by 4-5 minutes of cooling and manual agitation of the slurry. Finally, an aliquot was diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates, followed by GC injection in order to determine product yields using naphthalene as internal standard.

2.4.8 General Procedure for the Fp_2/Cu^I Co-Catalyzed Allylic Amination of α-Methylstyrene by Nitrobenzene

To a solution of nitrobenzene (103 µL, 1.00 mmol), α-methylstyrene (670 µL, 5.0 mmol), and dry dioxane (6-8 mL) in the glass liner of a stainless steel autoclave was added $[CpFe(CO)_2]_2$ (16.7 mg, 0.050 mmol), naphthalene (as internal standard, 20-40 mg), and CuBr (7.2 mg, 0.05 mmol). The autoclave was purged three times with CO, then finally charged with 150 psi CO and heated with stirring to $100^{\circ}C$ for 3-4 days. During this time, aliquats were withdrawn via dip tube for GC analysis. Upon observation of complete conversion of the nitrobenzene, the autoclave was cooled and vented in a fume hood. Samples for GC were diluted with hexanes and passed through a small pipette silica gel plug to remove metal precipitates. Yields of N-phenylallylamine and by-products were determined by GC using naphthalene as internal standard.

2.4.9 Procedure for Infrared Characterization of a Potential Fp$_2$/CuBr Complex

To 8 mL of dry dioxane in the glass liner of a stainless steel autoclave was added [CpFe(CO)$_2$]$_2$ (167 mg, 0.500 mmol) and CuBr (72 mg, 0.50 mmol). The autoclave was purged three times with CO, then finally charged with 150 psi CO and heated with stirring to 100°C for 3-4 days. During this time, samples were withdrawn via dip tube and cooled to room temperature for direct IR analysis.

File # 1 : FP2-DIOX

Number of Scans: 16

Comment: Fp2 in dioxane

View Mode: Peaks

3/21/08 8:05 AM Res=8cm-1
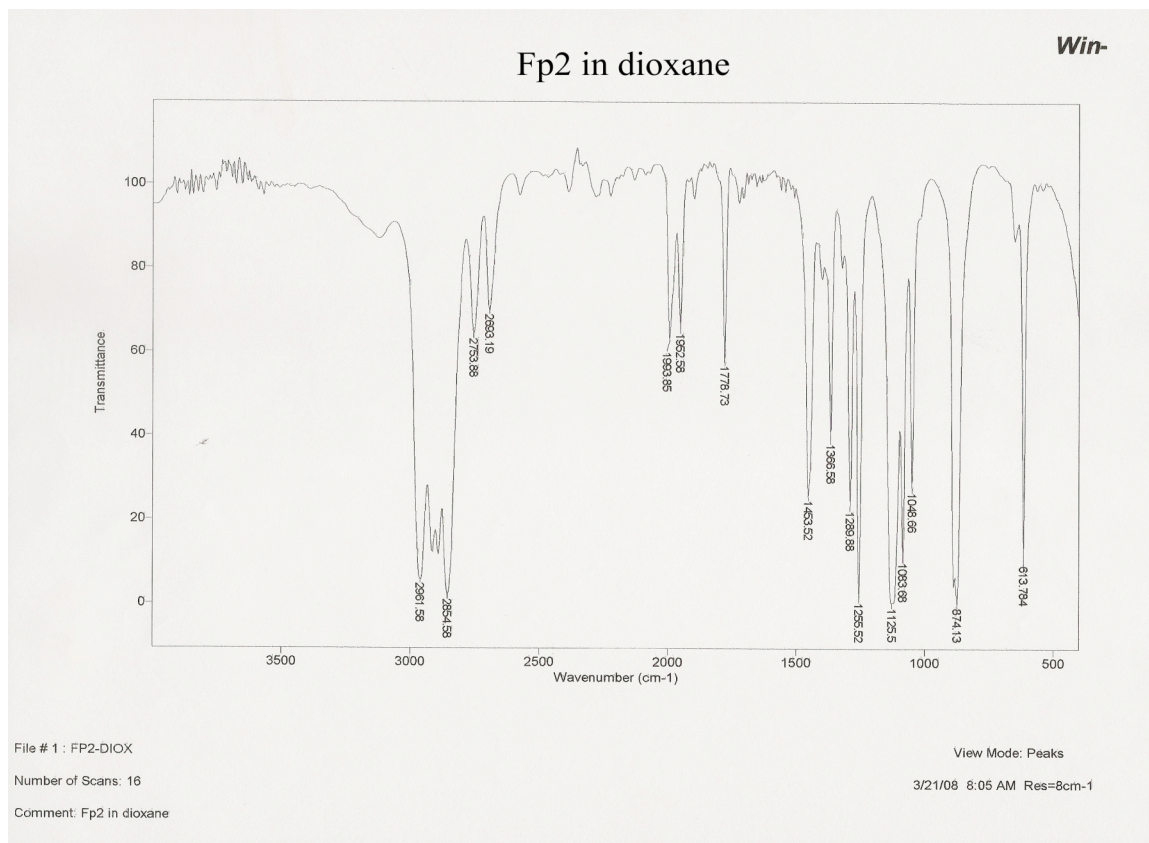
Fp2 and CuBr in dioxane, 2 days

Win-
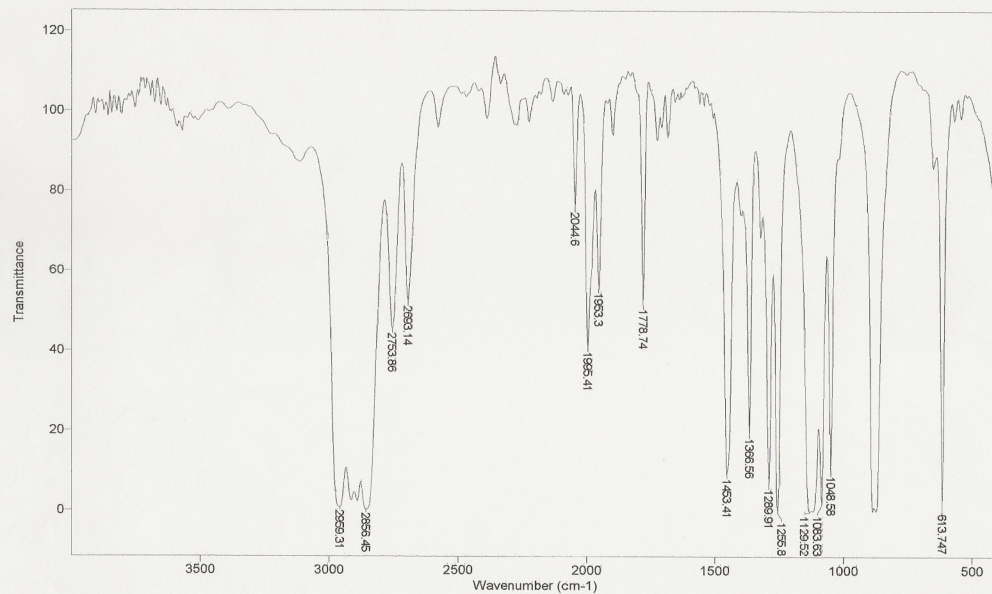
Transmittance vs. Wavenumber (cm-1)

Labeled peaks: 2953.14, 2753.86, 2959.31, 2856.45, 2044.6, 1953.3, 1905.41, 1778.74, 1453.41, 1366.56, 1289.91, 1255.8, 1129.52, 1083.63, 1048.58, 613.747

Fp2 and CuBr in dioxane, 3 days

Win-
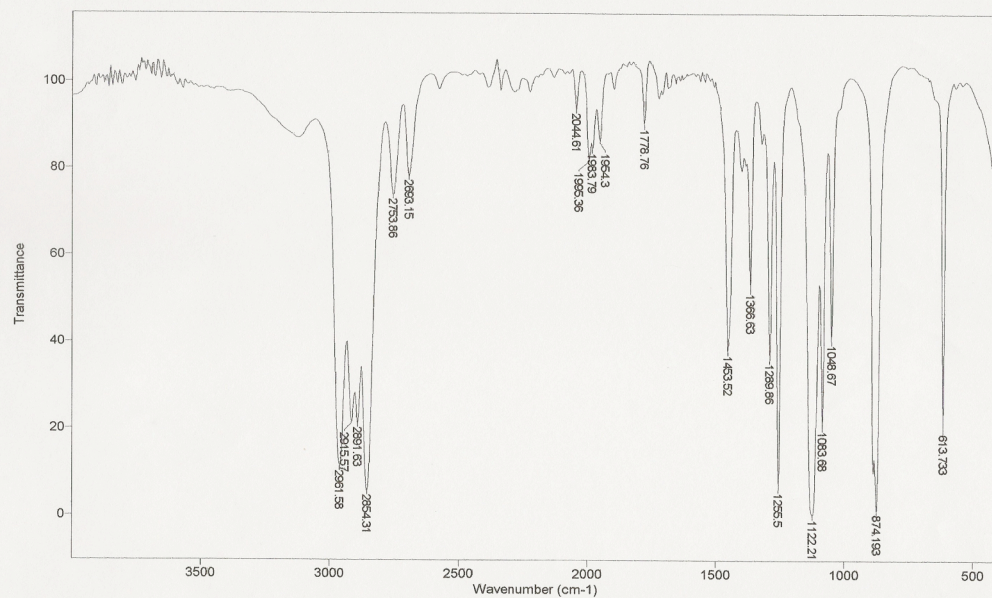
Transmittance vs. Wavenumber (cm-1)

Labeled peaks: 2953.15, 2753.86, 2891.63, 2915.57, 2961.58, 2854.31, 2044.61, 1964.3, 1963.79, 1905.36, 1778.76, 1453.52, 1366.63, 1289.86, 1255.5, 1122.21, 1083.66, 1048.67, 874.193, 613.733

CHAPTER 3

DIRECT SYNTHESIS OF 3-ARYLINDOLES VIA ANNULATION

OF ARYLHYDROXYLAMINES WITH ALKYNES

3.1   Introduction

In addition to the utilization of alkenes to produce allyl amines, the recent discoveries of indole-forming reactions of alkynes with nitro-[77,121] and nitroso[78,122,123]-aromatics (Figure 3.1) has stemmed from the Nicholas Group's ongoing interest in metal-promoted nitrogenation reactions of unsaturated hydrocarbons. The indole skeleton in each of these reactions is formed via a novel thermally driven cycloaddition of a nitrosoarene with an aryl or acyl alkyne.[124] The intermediate labile *N*-hydroxy indole can either be efficiently trapped and isolated as the *N*-methoxy indole[121] or reduced *in situ* in a second step with either CO/[Cp*Ru(CO)$_2$]$_2$ or H$_2$ and Pd/C to the parent (NH) indole.[77,78,121] The one step, metal-catalyzed indolization from nitroarenes ((i) a=2) requires both high temperatures (150-200 ^{o}C) and high pressures of the CO reductant, resulting in modest yields.

i) a=2, CO/[CpRu(CO)$_2$]$_2$, A=H;
   ii) a=1, Δ, A=OH;
iii) a=1, Δ/Me$_2$SO$_4$, A=OMe
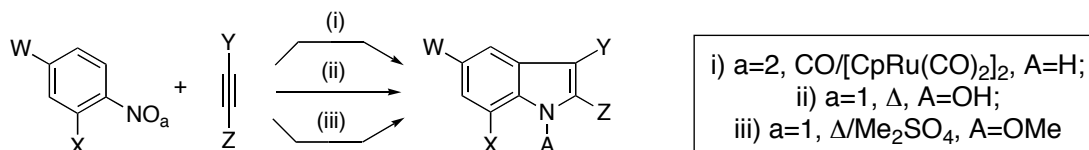
Figure 3.1

In order to broaden the scope of *N*-aromatic precursors from nitro- and nitrosoaryls, arylhydroxylamines were considered attractive candidates due to their ability to be oxidized *in situ* to nitrosoaromatics. In addition, we aimed to develop a more efficient one-step method to produce the parent (NH) indoles that did not require the use of high-pressures of CO and high temperatures (>150^{0}C). Since redox metal-catalyzed allylic aminations of olefins with arylhydroxylamines[6] involve *in situ* hydroxylamine oxidation, ene reaction of the resulting nitrosoarene,[17] and reduction of the allyl hydroxylamine, we envisioned a similar catalytic pathway for alkyne indolization by arylhydroxylamines via nitrosoarene and *N*-hydroxyindole intermediates.

3.1.1 Transition-Metal Catalyzed Allylic Amination of Arylhydroxylamines

The stoichiometric allylic amination of 2-methyl-2-hexene by a molybdooxaziridine was first reported in 1978 by Liebeskind, et al.[125] The d^0 metallooxaziridines **92** were formed by reaction of an arylhydroxylamine with a dioxomolybdenum (VI) complex, or transversely by addition of a nitrosoaryl to an oxomolybdenum (IV) complex. In the initial report, the allylic amination **94** occurred in 55-57% yield without aziridination **93** of the alkene or observation of the allylic hydroxylamine. (Figure 3.2) Formation of the original dioxomolybdenum (VI) complex **95** was observed, prompting the possibility of efficient molybdenum-catalyzed reactions.
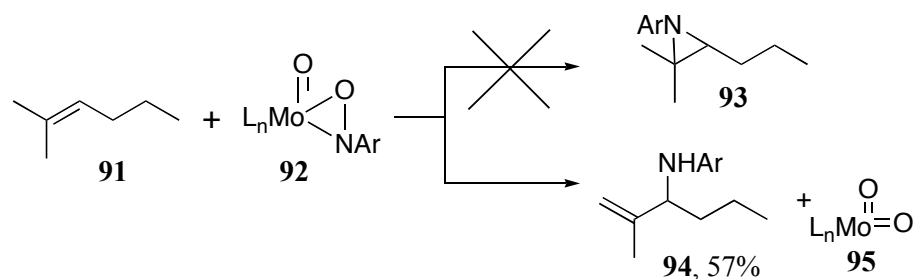
Figure 3.2

The first catalytic investigation of metal-catalyzed allylic amination of arylhydroxylamines was reported by Nicholas in 1992.[18] In the study, the arylhydroxylamine was slowly added to a refluxing dioxane solution of 1-10% dioxomolybdenum (VI) catalyst and an excess of alkene. Moderate yields of representative alkenes were displayed. From mechanistic investigations,[19] it was concluded that the key step of the reaction was a "nitroso-ene" reaction involving the alkene and free nitrosoaryl generated by the molybooxaziridine **96**, evidenced by hetero-Diels-Alder addition of PhNO to 2,3-dimethylbutadiene (Figure 3.3, **74**).
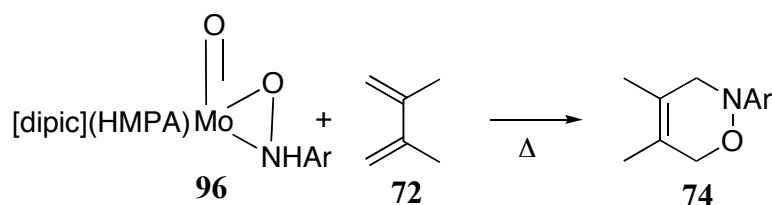
Figure 3.3

In the postulated mechanism (Figure 3.4), the PhNHOH **97** is first oxidized to a coordinated PhNO with concomitant reduction of the molybdenum complex, followed by release of the nitrosobenzene **98** that undergoes the ene reaction. The

intermediate allyl hydroxylamine **100** is then reduced by the oxomolybdenum (IV) species to regenerate the dioxomolybdenum (VI) catalyst, producing the allyl amine **101** with a high degree of regiocontrol.
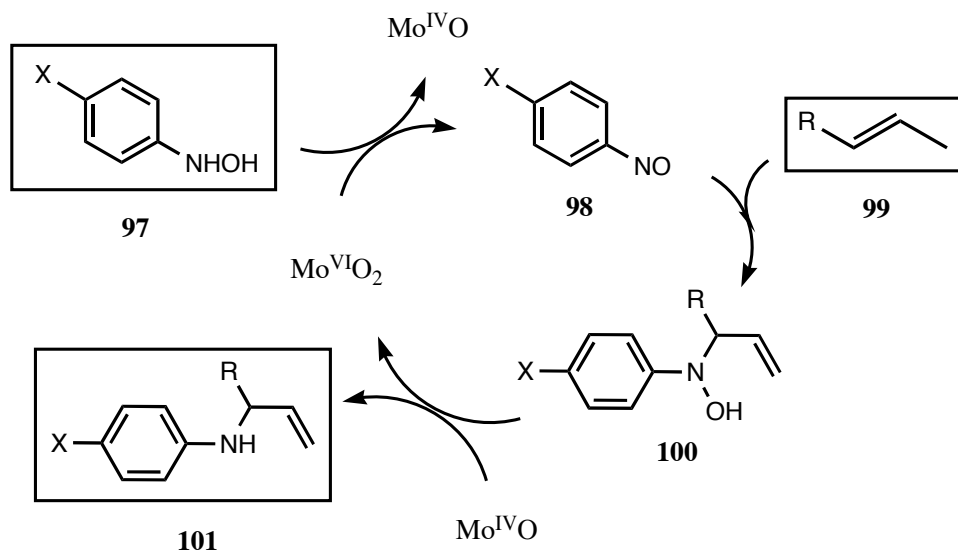
Figure 3.4

In subsequent studies,[20,21,23,126-128] several metal catalysts have been shown to be effective in the allylic amination of various alkenes utilizing arylhydroxylamines (Table 3.1). To date, Fe complexes and salts have displayed higher yields and lower amounts of nitrogen-containing by-products from arylhydroxylamines (such as aniline, azoxybenzene, and azobenzene) than the molybdenum or copper catalysts.

Fe(Pc)
102   **103**   (dipic)MoO$_2$(HMPA) **104**   FeCl$_2$ + FeCl$_3$ (9:1) **105**   [Cu^I(CH$_3$CN)$_4$]PF$_6$ **106**   CuCl$_2$ · 2H$_2$O **107**
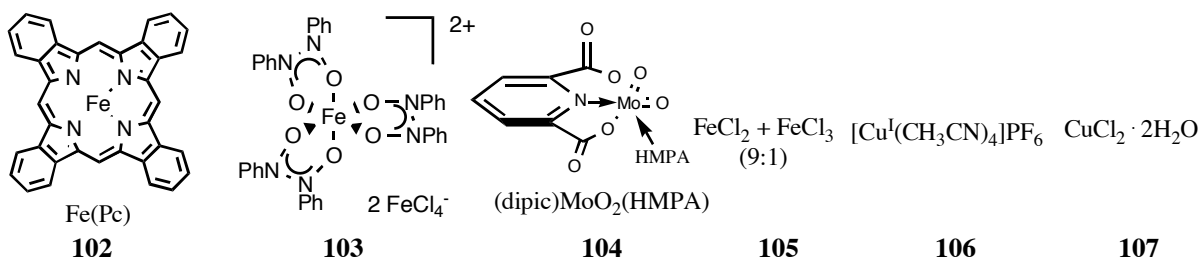
Comparison of the Allylic Amination of Various Alkenes by PhNHOH Catalyzed by **102-107**

Entry	Alkene	Allyl Amine	Catalyst (% yield)					
			102	**103**	**104**	**105**	**106**	**107**
1			76	-	42	41	30	40
2			-	88	52	72	38	-
3			22	-	-	13	10	9
4			30	-	11	22	-	-

Table 3.1 (Compiled from References 6, 24, and 128)

In mechanistic investigations, the molybdenum complexes[19] along with Fe(Pc)[127] were believed to proceed through "off-the-metal" nitroso-ene reactions, while the Fe^{II}/Fe^{III} salts[22] and Cu^I salt systems[24] are believed to be C-nitroso "on-the-metal" processes, as nitroso adduct complexes have been isolated and shown to react with alkenes in each respective case.[129,130]

3.1.2 Nitroso-Alkyne Intermolecular Thermal Annulation

A novel synthetic approach to 3-substituted indoles was discovered by Penoni and Nicholas in 2002 involving the reductive annulation of nitroarenes with alkynes under high pressures of CO and catalytic $[CpFe(CO)_2]_2$, $[(C_5Me_5)Fe(CO)_2]_2$, or $[(C_5Me_5)Ru(CO)_2]_2$.[77] This reaction was a rare example of direct indole formation from a commercially available *N*-aromatic precursor, such as the Fischer-indole synthesis[76] involving the condensation of aromatic hydrazines and ketones. In addition, the transformation did not require *ortho*-substitution of the *N*-aromatic as other commonly employed metal-catalyzed intramolecular cyclizations such as the Larock indole synthesis.[131]

Strategically similar to the Fp_2 or $[Cp*Ru(CO)_2]_2$ catalyzed reductive nitroaromatic allylic amination reaction, the utilization of alkynes under the same reductive conditions was initially anticipated to produce a new route to propargyl-**108** or allenylamines **109**, but in fact produced 3-substituted indoles **110** with a high degree of regioselectivity. The reaction (Figure 3.5) provided modest yields (23-53%) of substituted 3-phenylindoles by employing either $[CpFe(CO)_2]_2$, $[(C_5Me_5)Fe(CO)_2]_2$, or $[(C_5Me_5)Ru(CO)_2]_2$ as catalyst (5 mol%), under CO pressure (dioxane or benzene, 170^0C, 750 psi, 24-120 h).

Figure 3.5

87
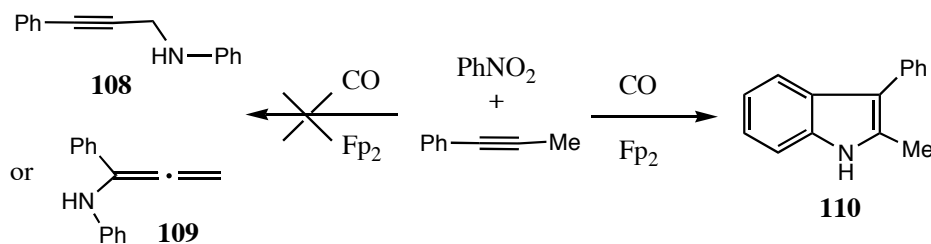
The reaction proceeds well with a slight excess of internal or terminal aryl alkynes, though only a trace of indole was formed from reaction with 2-octyne. Both electron-donating and -withdrawing groups are tolerated on the nitroaromatic substrate, though the reaction proceeds more rapidly with electron-neutral or -deficient species. An unsymmetrical *meta*-substituted nitroarene produced a 3:2 mixture of regioisomers, though the 3-aryl regiospecificity remained intact. Lastly, employment of a nitropyridine substrate led to direct formation of an azaindole in 53% yield, which is of notable importance due to the role of azaindoles as clinical, fluorescent, and metal-complexing agents.[132]

Suspecting the role of either free or complexed nitrosoarenes as intermediates in the reductive nitroaromatic reaction, nitrosoaryls were employed using the same conditions and were found to produce similar yields of the respective indoles.[78] More importantly, a mild, uncatalyzed thermal reaction of nitrosoaromatics and alkynes was shown to produce *N*-hydroxyindoles (Figure 3.6).

i) Δ, A=OH;
ii) Δ/Me$_2$SO$_4$, A=OMe
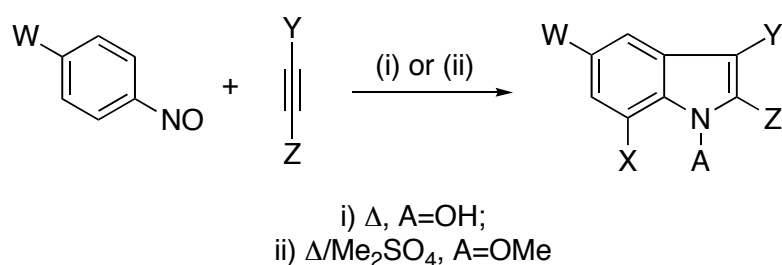
Figure 3.6

Due to the relative instability and difficulty of isolation of these products, *in situ* reduction by means of either hydrogenation under one atm H$_2$ and 10% Pd/C, or 5

atm CO at 80°C and 10 mol% $[(C_5H_5)Ru(CO)_2]_2$ was developed to allow for isolation of the more stable parent (NH) indoles. This modification resulted in improved yields of the parent indoles (29-64%), as well as expansion of alkyne scope to include terminal and internal propiolic esters and the aliphatic 1-octyne. In addition to the aryl alkynes, the acyl- and aliphatic alkynes employed also exhibited highly regioselective 3-substituted indole products.

The efficiency of the thermal ArNO-alkyne reaction was then improved in 2006 by the alkylative trapping of the intermediate *N*-hydroxyindoles with K_2CO_3-Me_2SO_4.[122] The *N*-methoxyindoles which are produced in moderate to excellent yields (41-99%) by the trapping procedure are comparitively very stable and can be easily isolated. The *N*-methoxyindoles can also be reduced to the parent (NH) indole by the same means as that of the *N*-hydroxyindoles in a second step. The effectiveness of this method was illustrated most clearly by the one-step production of 3-carboxy-N-alkoxyindole analogues, which occur naturally in Wasabi phytoalexins.[133]

Most recently, the nitroso-alkyne annulation was applied towards the synthesis of biologically active indoles.[123] Meridianins and their analogues A-G are marine indole alkaloids and have proven to be potent kinase inhibitors (Figure 3.7).[134]

Meridianin A	R_1=OH; R_2=R_3=R_4=H
Meridianin B	R_1=OH; R_2=R_4=H; R_3=Br
Meridianin C	R_1=R_3=R_4=H; R_2=Br
Meridianin D	R_1=R_2=R_4=H; R_3=Br
Meridianin E	R_1=OH; R_2=R_3=H; R_4=Br
Meridianin F	R_1=R_4=H; R_2=R_3=Br
Meridianin G	R_1=R_2=R_3=R_4=H
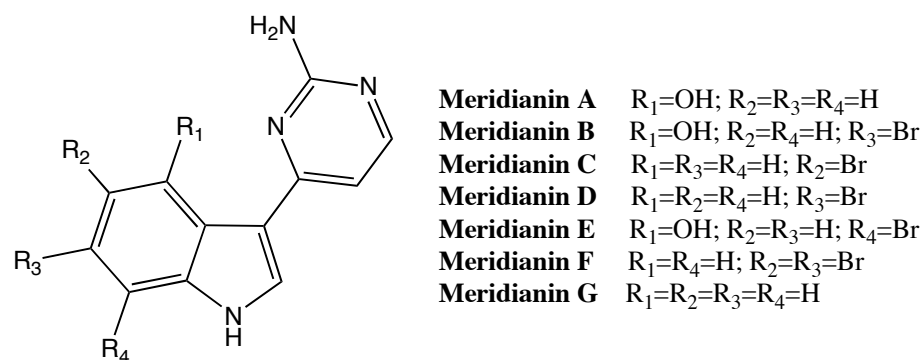
Figure 3.7[123]

Using several nitrosoarenes with 2-chloro-4-ethynylpyrimidine resulted in efficient production (19-71%) of meridianin analogue precursors. The meridianin analogues were also prepared more directly by reaction of nitrosoarenes and 2-amino-4-ethynylpyrimidine, resulting in yields ranging from 28-99%. Of particular interest in this system is the ability to use a 1:1 stoichiometry of ArNO to alkyne, as the product indoles are generally insoluble in the reaction media and can be isolated in some cases without further purification. In addition, only the parent (NH) indoles were isolated as opposed to previous systems in which *N*-hydroxy- or *N*-methoxyindoles were major products. The reasons for the differences in reactivity are presently unknown.

A mechanistic investigation was conducted and reported in 2009 concerning the nature of the uncatalyzed thermal annulation by Penoni, et al.[124] It was concluded through experimental and calculational results that the reaction most likely proceeds through a stepwise mechanism initiated by rate-limiting bond-formation between the terminal alkyne C and the nitrosoaryl N, forming a polar diradical intermediate **111** in conjugation with the alkynyl substituent. This intermediate can then rapidly cyclize to

form a C-C bond and generate a cyclohexadienyl nitroxyl radical **112** which can rapidly tautomerize to form the *N*-hydroxyindole **113** (Figure 3.8).
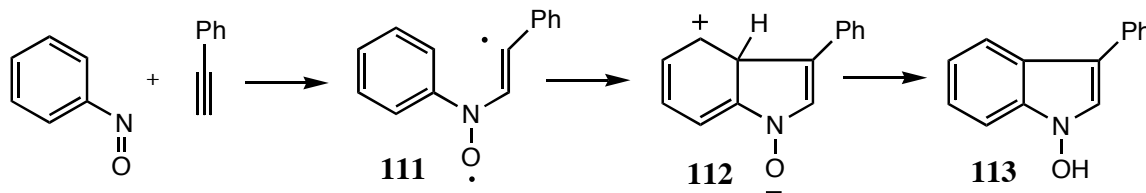
Figure 3.8

3.2 Results and Discussion

The following results described in this chapter have been published in *Tetrahedron*, **2009**, *65*, 3829.

3.2.1 Catalyst Screening and Optimization

Beginning with reaction conditions similar to those previously reported,[122] (20 equiv. alkyne, refluxing benzene) along with 10 mol% Mo(dtc)$_2$O$_2$ and one equiv. PhNHOH, the product indole was detected by GC in <10%. Due to the detection of a large amount of azoxybenzene by GC, it was reasoned that the reaction conditions would benefit from a slow addition of PhNHOH, similar to the Mo-catalyzed allylic amination of alkenes by PhNHOH.[18] Using a syringe pump in order to add 0.5 mmol PhNHOH in 6-7 mL of solvent increased the yield of indole to 51%. Some decomposition of PhNHOH in the syringe at room temperature can be observed by the darkening of the faint yellow solution. During additions of > 8 hours, the decomposition becomes more apparent; therefore it was determined that reactions

should be run with addition times between 5-8 hours. A survey and initial optimization study (Table 3.2) was conducted on the reaction of PhNHOH with excess phenylacetylene in the presence of various redox-active complexes that have been used in the allylic amination of alkenes by PhNHOH (Table 3.1), including $Mo(dtc)_2O_2$, $(dipic)MoO_2(HMPA)$, $FeCl_2/FeCl_3$, $Cu(CH_3CN)_4PF_6$, $CuCl_2 \cdot 2H_2O$ and Fe(Pc) (dtc=N,N-diethyl dithiocarbamate, dipic=2,6-pyridinedicarboxylate, HMPA=hexamethyl phosphortriamide, Pc=phthalocyanine), and solvents (benzene, dioxane, toluene, 1,2-dichloroethane, EtOH, CH_3CN, i-PrOH, t-BuOH, and chlorobenzene).

Transition-metal catalyzed indolization of phenylacetylene
and N-phenylhydroxylamine[a]

entry	solvent	catalyst[b]	yield (%)[c]
1	benzene	$Mo(dtc)_2O_2$	51
2	benzene	$(dipic)MoO_2(HMPA)$	11
3	benzene	9:1 $FeCl_2/FeCl_3$	34[d]
4	benzene	$Cu(CH_3CN)_4PF_6$	15
5	benzene	$CuCl_2 \cdot H_2O$	19
6	benzene	Fe(Pc)	66
7	dioxane	Fe(Pc)	70
8	toluene	Fe(Pc)	84
9	toluene	Fe(Pc)	70[e]

[a] 0.5 mmol phenylhydroxylamine added by syringe pump (7-8 h), 10 mmol phenylacetylene, Ar, reflux. [b] 10 mol% cat. [c] GC yield using naphthalene as internal standard. [d] Anhydrous Fe salts or FeX_n hydrates. [e] 5 mol% Fe(Pc).

Table 3.2

GC, GC-MS and TLC analysis indicated the production of 3-phenylindole with several of these systems with the best results being obtained with inexpensive commercial Fe(Pc) as catalyst. By slowly adding PhNHOH (0.5 mmol in 5-6 mL toluene, 7-8 h) to a refluxing solution of phenylacetylene **114** (10 mmol), 15 mL toluene, and Fe(Pc) (0.05 mmol) an 84% yield of 3-phenylindole **116** (GC) was obtained. Minor products include azoxybenzene (3-10%), azobenzene (0-2%), and aniline (0-15%). As water is formed in the reaction, there was no difference in yield when using either anhydrous $Fe^{II/III}$ salts or $Fe^{II/III}$ salt hydrates.

Using a chemical simplex method[135] an attempt was made to further optimize the reaction conditions. In this method, a set of pre-determined variables are all changed for an individual reaction, as opposed to altering one variable at a time as in a more classical optimization. After an initial set (number of variables plus one), a "simplex" is calculated to determine the next set of conditions. When the "simplex" is not producing a higher yield than what has already been produced, the local maximum, or optimized conditions has been found. In the optimization, temperature and solvent were not considered variables, as a minimum of $70^{o}C$ appears to be necessary to avoid large amounts of azoxybenzene. Variables that were randomly adjusted include: catalyst loading, excess equivalents of alkyne, mL of benzene (optimization was conducted prior to testing in dioxane or toluene) in the reaction pot, and the rate of addition of 0.5 mmol PhNHOH (Table 3.3). It was quickly determined that conditions closest to our initial set was in fact optimized.

Simplex Method Optimization
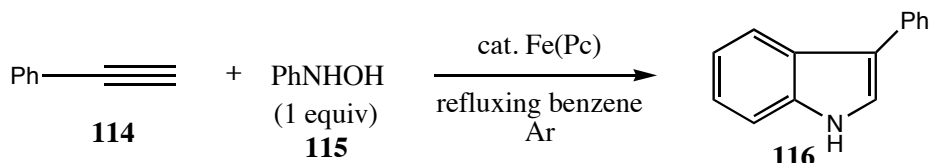
| | Entry | Variables | | | | GC |
		1 (Cat. loading)	2 (Equiv alkyne)	3 (ml solvent)	4 (rate of addn)	Yield
Initial	1	10%	20	9	405 min.	64
	2	2%	25	20	486 min.	42
	3	7%	15	5	568 min.	40
	4	13%	12	9	162 min.	36
	5	5%	5	9	324 min.	42
Simplex 1 →	6	2%	18.8	12	616 min.	57
Simplex 2 →	7	6%	16	11	446 min.	58

Table 3.3

3.2.2 Fe(Pc)-Catalyzed Preparation of Indoles from Phenylacetylene and Various *N*-Arylhydroxylamines

Using the optimized conditions, a series of substituted *N*-arylhydroxylamines were then tested with phenylacetylene in the indolization reaction (Figure 3.9, Table 3.4). During isolation, the parent (NH) indoles are easily recognizable by detection of the characteristic broad N-H ^{1}HNMR singlet typically found between 8.0-9.0 ppm (see experimental section).
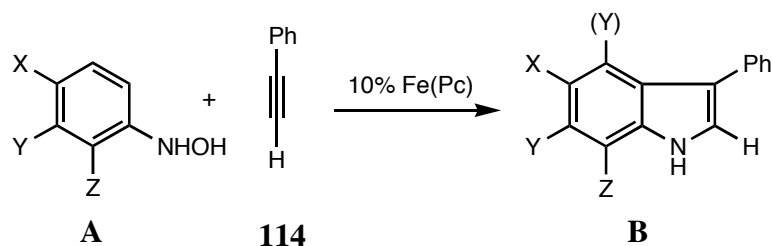
Figure 3.9

Fe(Pc)-catalyzed preparation of indoles from phenylacetylene
and *N*-arylhydroxylamines[a] (Scheme 3.8)

entry	A	X	Y	Z	B	Isolated Yield
1	**115**	H	H	H	**116**	81
2	**117**	Me	H	H	**118**	55
3	**119**	CN	H	H	**120**	55
4	**121**	Cl	H	H	**122**	38
5	**123**	H	H	Me	**124**	45
6	**125**	H	Me	H	**126,127**	47 (4-Me:6-Me = 27:20)
7	**128**	H	CF$_3$	H	**129,130**	65 (4-CF$_3$:6-CF$_3$ = 34:31)
8	**131**	Cl	Cl	H	**132,133**	55 (4,5-Cl:5,6-Cl = 34:21)
9	**134**	H	-C$_4$H$_4$-		**135**	37

[a] 10 mol% Fe(Pc), refluxing toluene, 7-8 h addition of
arylhydroxylamine (procedure in experimental section)

Table 3.4

Arylhydroxylamines with either electron-donating or -withdrawing groups are
effective reaction partners. In fact, there appears to be little preference in reactivity
with regard to the electronic nature of the arylhydroxylamine, as the electron-
donating 4-methyl-phenylhydroxylamine **117** and the electron-withdrawing 4-cyano-
phenylhydroxylamine **119** both produce a 55% yield of the respective indole (entries
2-3, **118**, **120**). In terms of regioselectivity of the alkyne cycloaddition, 3-aryl isomers
are solely detected in all cases. From *meta*-substituted *N*-arylhydroxylamine
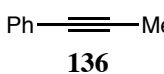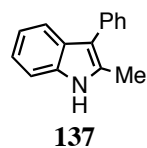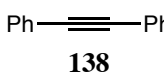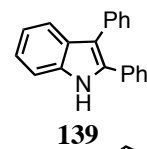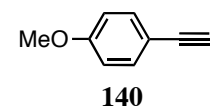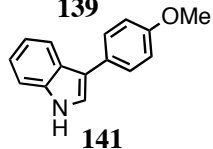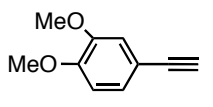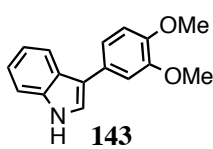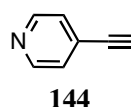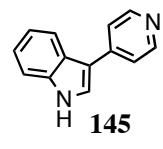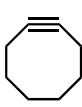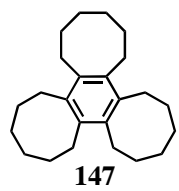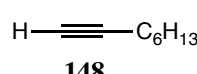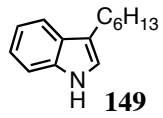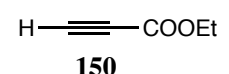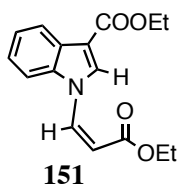
substrates (entries 6-8), mixtures of 4- and 6-substituted indoles were obtained, with the 4-substituted indole slightly favored in each case. Determination of indoles **129** and **130** resulted from comparison to known ^{1}H NMR spectra. In addition, determination of **133** (vs. **132**) resulted from the observation of two singlets that each integrate 1H at 7.99 and 7.55 ppm from the C-4 and C-7 protons (see Experimental Section).   Structural characterization of regioisomers **126** and **127** is currently tentative. A benzoindole **135** (entry 9) was also produced regioselectively from the annulation of phenylacetylene with 1-hydroxylamino-naphthalene **134**. Yields of indoles from the current one-step procedure are comparable (3-15% lower) to those produced by the two-step method from the nitrosoarene *via* the *N*-hydroxyindole and its reduction (H_2/10% Pd/C) to the free indole.[78] In addition, the yields of indoles are also generally increased 20-40% over those produced by the one-step method utilizing nitroaromatics and high CO pressures and temperatures.[77]

3.2.3 Fe(Pc)-Catalyzed Preparation of Indoles from *N*-Phenylhydroxylamine and Various Aryl Alkynes

Due to the unfortunate side-reaction[82] of arylhydroxylamines with ethyl propiolate (Table 3.5, entry 17), our focus shifted towards utilization of aryl alkynes as effective annulating partners. Representative terminal and internal aryl alkynes displayed varying levels of success with good to excellent yields produced from terminal alkynes (Table 3.4, entry 1) and poor to moderate yields from internal alkynes (Table 3.5, entry 10-11). The 2-Me-3-Ph-indole **137** is isolated exclusively from reaction with 1-phenylpropyne **136**, further demonstrating the 3-aryl

regioselectivity of the reaction. A scale-up reaction using 2.0 mmol of PhNHOH and 10 equiv. 3,4-OMe-phenylacetylene **142** resulted in a nearly identical yield (55% **143**, entry 13), with ~98% of the unreacted alkyne recovered. In addition to aryl alkynes, some representative aliphatic alkynes were also attempted (entries 15-16), though previous studies have indicated low reactivity with this class of substrate. An attempt to utilize a cyclic and potentially strained aliphatic alkyne, cyclooctyne **146**, as a substrate in order to generate a precursor to the drug iprindole[136] resulted in cyclotrimerization **147**[137,138] in either refluxing toluene or benzene, with no indole formed. Reaction with 1-octyne **148** either in refluxing toluene or neat resulted in only trace indole formation according to GC-MS. Electron-donating groups on the terminal aryl alkyne are tolerated and appear to result in more efficient product indole formation (Table 3.4 entry 1, Table 3.5 entry 12).

Fe(Pc)-catalyzed preparation[a] of indoles from
alkynes and **115** (*N*-phenylhydroxylamine) (Scheme 3.8)

entry	Alkyne	Major Product	Isolated Yield of Indole
10	Ph—≡—Me **136**	3-Ph, 2-Me indole **137**	25
11	Ph—≡—Ph **138**	3-Ph, 2-Ph indole **139**	--- trace (GC-MS)
12	MeO—C6H4—≡ **140**	3-(4-OMe-phenyl)indole **141**	88
13[c]	MeO, MeO—C6H3—≡ **142**	3-(3,4-diOMe-phenyl)indole **143**	57 (55)[b]
14[d]	4-pyridyl—≡ **144**	3-(4-pyridyl)indole **145**	72
15	cyclooctyne **146**	**147**	>50
16	H—≡—C6H13 **148**	3-C6H13 indole **149**	--- trace (GC-MS)
17	H—≡—COOEt **150**	3-COOEt indole N-vinyl **151**	--- trace (GC-MS)

---

[a] 10 mol% Fe(Pc), refluxing toluene, 7-8 h addition of **115**.
[b] Scale-up reaction: 10 equiv. alkyne, 32 h addition of **115**.
[c] 17 equiv. alkyne, reaction run in dark. [d] No indole detected.

Table 3.5

Several previously untested alkynes were utilized in this study as a result of the affinity for aryl alkynes in the annulation reaction, resulting in new pathways to indoles **143** and **145**. These indoles are otherwise produced by relatively limited synthetic approaches[139-142] that include expensive catalysts or substrates, long reaction times (as much as 30 days), electrochemical conditions, multiple steps, and/or moderate yields. Both indoles appear to present high degrees of bioactivity as indole **143** was recently investigated[143] for antitumor activity, and **145** possesses interesting bioactivity as a Rho-kinase inhibitor[144] as well as inosine monophosphate dehydrogenase inhibitor.[145] Using our new method, the target indole and potentially a wide variety of analogues can be prepared in one step in good yield from inexpensive, readily available substrates and catalyst. It is noteworthy that indole **145** is produced in 72% yield despite employing a potentially *N*-coordinating alkyne in excess.

3.2.4 Mechanistic Investigation

To address the issue of whether the free nitrosoarene was generated in the Fe(Pc)-catalyzed reactions, the trapping experiment shown in Figure 3.10 was conducted. When the PhNHOH/PhC≡CH reaction was conducted in the presence of 2,3-dimethyl-1,3-butadiene **72** (10 equiv. diene, 10 equiv. alkyne), none of the indole **116** was detected, but rather the hetero Diels-Alder product **74**[146] was formed and verified by ^{1}H NMR and GC-MS. This result strongly suggests the intermediacy of PhNO in the Fe(Pc)-catalyzed reaction. Interestingly, when the same experiment is conducted using Fe[II]/Fe[III] salts as catalyst, the same result occurs, i.e. "free" PhNO appears to be the reactive pathway (though this catalyst system is believed to occur

through a *C*-nitroso complex "on-the-metal" pathway in related allylic amination of alkenes[22]).
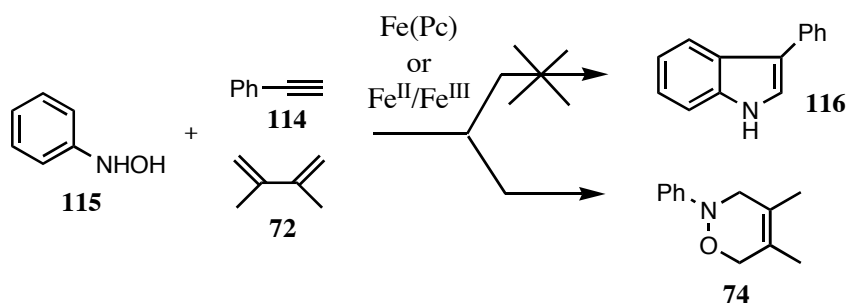
Figure 3.10

The catalytic reaction pathway is thus suggested to proceed via PhNHOH oxidation to PhNO **98** by a Fe^{III}(Pc) species[127] (which can be initially generated from Fe^{II}(Pc) by reduction of some PhNHOH), nitrosoarene/alkyne cycloaddition to the *N*-hydroxyindole **152**, and reduction of the latter to the indole **153** by Fe^{II}(Pc) (Figure 3.11).
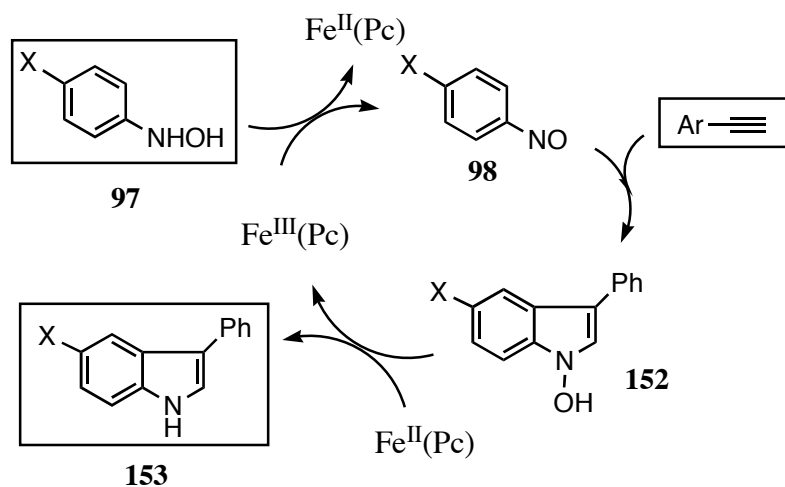
Figure 3.11

3.3   Summary and Conclusions

In summary, we have developed a new metal-catalyzed indolization reaction to produce 3-arylindoles from arylhydroxylamines and alkynes in moderate to excellent yields. In the study, we were able to successfully address the challenge of developing a one-step procedure that utilizes convenient laboratory conditions in order to efficiently produce parent (NH) indoles. Using a method of slow addition, electron-donating and −withdrawing *N*-arylhydroxylamines can be included. A variety of aryl alkynes can serve as effective coupling partners, including one with *N*-coordinating ability, though aliphatic alkynes and propiolic esters were largely unsuccessful. Terminal and internal aryl alkynes can be applied with exceptional regioselectivity to 3-aryl products. Though the alkynes are used in excess (15-20 equiv), in most cases the alkyne could be recovered. Another advantage of the system includes the use of inexpensive commercial catalysts such as Fe(Pc), $Fe^{II/III}$ salts, and $Cu^{I/II}$ salts, as well as easily prepared and inexpensive Mo complexes. The *N*-arylhydroxylamines used are conveniently prepared in one step via reduction of nitroaromatics, and purified by recrystallization. In contrast, the nitrosoaromatics utilized in previous methods are formed in one step *via* oxidation of amines with purification generally by column chromatography. Owing to the technical ease of isolation of the parent (NH) indoles using the present one-step procedure, several previously untested *N*-aromatic substrates and/or alkynes were utilized in this study resulting in new indoles **126**, **127**, **132**, **133**, **135**, **143**, and **145**. Moreover, in this annulation reaction, an *ortho*-substituted arene or activated scaffold is not required, resulting in a highly efficient and convergent generation of the indole skeleton.

3.4   Experimental

3.4.1 General Considerations

Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, or GFS. Nitroaromatics employed in reduction to *N*-arylhydroxylamines were used without any purification. $Mo(dtc)_2O_2$[147] and $(dipic)MoO_2(HMPA)$[125] were prepared by individual literature procedures without modification and each compound was determined pure by comparison to individual known data. All *N*-arylhydroxylamines were stored under argon and kept below $0^\circ C$. Purchased alkynes were purified by distillation before use. Toluene, benzene, and dioxane were distilled prior to use over Na/benzophenone. All other solvents including those used in chromatography were used without any purification. Visualization of the developed chromatogram was performed under UV light or I_2 stain. ^1H NMR spectra were obtained at 300 MHz and ^{13}C NMR spectra at 60 MHz; NMR spectra were internally referenced to residual protio solvent signals. Data for ^1H NMR data are reported as follows: chemical shift (δ shift), multiplicity (br=broad, s=singlet, d=doublet, t=triplet, m=multiplet, dd=doublet of doublets), coupling constant (Hz), integration, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Mass spectra were acquired in methanol or acetonitrile solution by ESI. Naphthalene was used as an internal standard for GC yield determinations.

3.4.2 Preparation of N-Arylhydroxylamines

Phenylhydroxylamine (115)

The title compound was prepared in 58% yield by the reaction of nitrobenzene, zinc powder, and NH_4Cl according to procedure found in literature reference 88. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 2H), 7.01 (m, 3H), 6.45 (br s, 2H).

4-Methyl-phenylhydroxylamine (117)

The title compound was prepared in 50% yield by the reaction of 4-nitrotoluene, zinc powder, and NH_4Cl according to procedure found in literature reference 88. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, 2H), 6.90 (d, 2H), 5.55 (br s, 2H), 2.28 (s, 3H).

4-Cyano-phenylhydroxylamine (119)[148]

The title compound was prepared the reaction of 4-cyano-nitrobenzene, sodium borohydride, and catalytic selenium powder according to procedure found in literature reference 90. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, 2H), 7.01 (m, 3H), 5.23 (d, J=2.4Hz, 1H).

4-Chloro-phenylhydroxylamine (121)

The title compound was prepared in 35% yield by by the reaction of 4-chloro-nitrobenzene, sodium borohydride, and catalytic tellurium powder according to procedure found in literature reference 91. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 2H), 7.15 (s, 1H), 6.85 (d, 2H), 6.74 (s, 1H).

2-Methyl-phenylhydroxylamine (123)

The title compound was prepared in 19% yield by the reaction of 2-nitrotoluene, zinc powder, and NH_4Cl according to procedure found in literature reference 88. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (m, 1H), 7.21 (m, 1H), 7.10 (d, J=3.6 Hz, 1H), 6.90 (t, J=6.6 Hz, 1H), 6.77 (br s, 1H), 5.22 (br s , 1H), 2.18 (s, 3H).

3-Methyl-phenylhydroxylamine (125)

The title compound was prepared in 10% yield by the reaction of 3-nitrotoluene, zinc powder, and NH_4Cl according to procedure found in literature reference 88. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.16 (t, J=10.2 Hz, 1H), 6.80-6.72 (m, 2H), 6.70 (br s, 1H), 5.08 (s, 1H), 2.30 (s, 3H).

3-Trifluoromethyl-phenylhydroxylamine (128)[149]

The title compound was prepared in 18% yield by the reaction of 3-nitro-trifluorotoluene, zinc powder, and NH_4Cl according to procedure found in literature reference 88. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.36 (t, J=8.1 Hz, 1H), 7.20 (d, J=7.5 Hz, 1H), 7.05 (d, J=8.4 Hz, 1H), 6.83 (br s, 1H), 5.18 (s, 1H).

3,4-Dichloro-phenylhydroxylamine (131)[150]

The title compound was prepared in 43% yield by the reaction of 3,4-dichloro-nitrobenzene, zinc powder, and NH_4Cl according to procedure found in literature reference 88. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, J=8.7 Hz, 1H), 7.12 (d, J=2.1

Hz, 1H), 6.80-6.72 (m, 2H), 5.12 (d, J=2.4 Hz, 1H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 149.5, 133.1, 130.7, 125.1, 116.2, 113.8.

N-1-Naphthyl-hydroxylamine (134)[151]

The title compound was prepared by the reaction of 1-nitronaphthalene, zinc powder, and NH$_4$Cl according to procedure found in literature reference 88. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.85-7.80 (m, 1H), 7.77-7.70 (m, 1H), 7.50-7.32 (m, 6H), 5.14 (s, 1H).

3.4.3 Preparation of Alkynes

1-Phenylpropyne (136)[152]

The title compound was prepared in 40% yield from phenylacetylene, potassium *tert*-butoxide, and methyl iodide according to procedure found in literature reference 152. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.48-7.02 (m, 5H), 1.97 (s, 3H).

3,4-Dimethoxyphenylacetylene (142)[153]

First, 1,1-dibromo-2-(3,4-dimethoxyphenyl)ethane was prepared in 58% yield from triphenylphosphine, carbon tetrabromide, and 3,4-dimethoxybenzaldehyde according to procedure found in literature reference 153. The title compound was then prepared in 76% yield (44% overall) from 1,1-dibromo-2-(3,4-dimethoxyphenyl)ethane and ^{n}BuLi according to the procedure found in reference 153. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.08 (d, J=8.4 Hz, 1H), 6.97 (s, 1H), 6.80 (d, J=8.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.98 (s, 1H).

4-Ethynylpyridine (144)[154]

The title compound was prepared from 4-bromopyridine hydrochloride, triethylamine, trimethylsilylacetylene, and catalytic $PdCl_2(PPh_3)_2$, CuI, and triphenylphosphine according to procedure found in literature reference 154. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.59 (d, J=6.3 Hz, 2H), 7.32 (d, J=6.3 Hz, 2H), 3.27 (s, 1H).

Cyclooctyne (146)[155-156]

First, 1-bromocyclooctene was prepared in 60% yield from 1,2-dibromooctane, morpholine, and DMSO according to procedure Method A found in literature reference 156. Then the title compound was prepared in 64% yield (38% overall) from 1-bromocyclooctene and lithium diisopropylamide according to the procedure found in literature reference 155. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.19 (m, 4H), 1.88 (m, 4H), 1.61 (m, 4H).

3.4.4 General Procedure for the Preparation of 3-Arylindoles

A mixture of 0.050 mmol Fe(Pc), 10.0 mmol alkyne and 15 mL toluene was stirred at reflux under argon and to this was added 0.500 mmol of the *N*-arylhydroxylamine in 5-6 mL toluene by syringe pump (7-8 h). After the addition was complete, reflux was continued overnight (8-12 h). After cooling, the mixture was evaporated to a solid under vacuum. Flash chromatography of the residue over silica gel (20% EtOAc/hexane eluant) afforded the indole products, typically as solids.

3-Phenylindole (116)[78]

Indole **116** was prepared according to the general procedure from *N*-phenylhydroxylamine and phenylacetylene to provide the title compound as a white solid (78.2 mg, 0.405 mmol) in 81% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.22 (br s, 1H, NH), 7.96 (d, *J*=7.8 Hz, 1H), 7.70 (d, *J*=8.1 Hz, 2H), 7.43 (t, *J*=8.4 Hz, 3H), 7.38 (d, *J*=2.1 Hz, 1H), 7.30 (m, 1H), 7.20 (m, 2H); GC-MS (EI) 193 (M$^+$)

5-Methyl-3-phenylindole (118)[121]

Indole **118** was prepared according to the general procedure from 4-methyl-N-phenylhydroxylamine (55.7 mg, 0.45 mmol) dissolved in 6 mL toluene, Fe(Pc) (25.5 mg, 0.045 mmol), phenylacetylene (0.918 g, 9 mmol), and toluene (15 mL) to provide the title compound as a solid (51.3 mg, 0.248 mmol) in 55% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.13 (br s, 1H, NH), 7.74 (s, 1H), 7.67 (d, *J*=7.2 Hz, 2H), 7.43 (t, *J*=7.2 Hz, 2H), 7.30 (m, 3H), 7.08 (dd, *J*=8.4 Hz, *J*=1.5 Hz, 1H), 2.49 (s, 3H); GC-MS (EI) 207 (M$^+$)

5-Cyano-3-phenylindole (120)[77]

Indole **120** was prepared according to the general procedure from 4-cyano-phenylhydroxylamine (72 mg, 0.50 mmol) dissolved in 6 mL dioxane, Fe(Pc) (28 mg, 0.050 mmol), phenyl acetylene (1.1 mL, 10 mmol), and dioxane (15 mL) to provide the title compound (60.1 mg, 0.276 mmol) in 55% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.63 (br s, 1H, NH), 8.28 (s, 1H), 7.62 (d, *J*=6.6 Hz, 2H), 7.50 (m, 5H), 7.38 (t, *J*=7.5 Hz, 1H); LRMS (ESI) 241 (M + Na$^+$)

5-Chloro-3-phenylindole (122)[78]

Indole **122** was prepared according to the general procedure from 4-chloro-N-phenylhydroxylamine and phenylacetylene to provide the title compound as a solid (43 mg, 0.190 mmol) in 38% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.26 (br s, 1H, NH), 7.90 (s, 1H), 7.62 (d, J=7.2 Hz, 2H), 7.43 (t, J=7.8 Hz, 2H), 7.33 (m, 2H), 7.20 (m, 2H), 7.20; GC-MS (EI) 227 (M[+])

7-Methyl-3-phenylindole (124)[157]

Indole **124** was prepared according to the general procedure from 2-methyl-N-phenylhydroxylamine and phenylacetylene to provide the title compound as a solid (46.7 mg, 0.225 mmol) in 45% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.17 (br s, 1H, NH), 7.78 (d, J=7.2 Hz, 1H), 7.64 (d, J=8.1 Hz, 2H), 7.41 (t, J=8.1 Hz, 2H), 7.38 (d, J=2.4 Hz, 1H), 7.28 (d, J=7.2 Hz, 1H), 7.08 (m, 2H), 2.52 (s, 3H); GC-MS (EI) 207 (M[+])

4-Methyl-3-phenylindole (126)

Indole **126** was prepared according to the general procedure from 3-methyl-N-phenylhydroxylamine (61.5 mg, 0.50 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide the title compound as a tan solid (28 mg, 0.135 mmol) in 27% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.13 (br s, 1H, NH), 7.84 (d, J=8.4 Hz, 1H), 7.68 (dd, J=8.1 and 0.9 Hz, 2H), 7.45 (t, J=6.6 Hz, 2H), 7.29 (m, 3H), 7.05 (dd, J=8.4 and 1.2 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 137.3, 135.9, 132.5, 128.9, 127.6, 126.1,

123.8, 122.3, 121.3, 119.7, 118.4, 111.5, 21.9; HRMS (ESI) calculated for $C_{15}NH_{13}$

(M+H$^+$) requires m/z 208.1126, found m/z 208.1186.
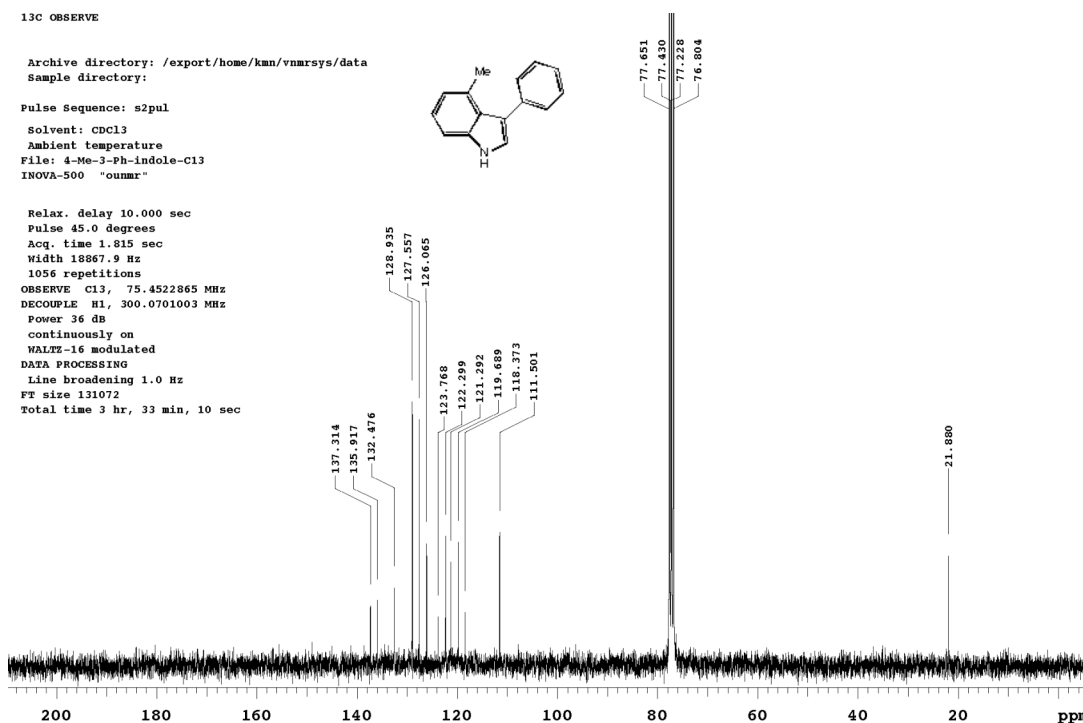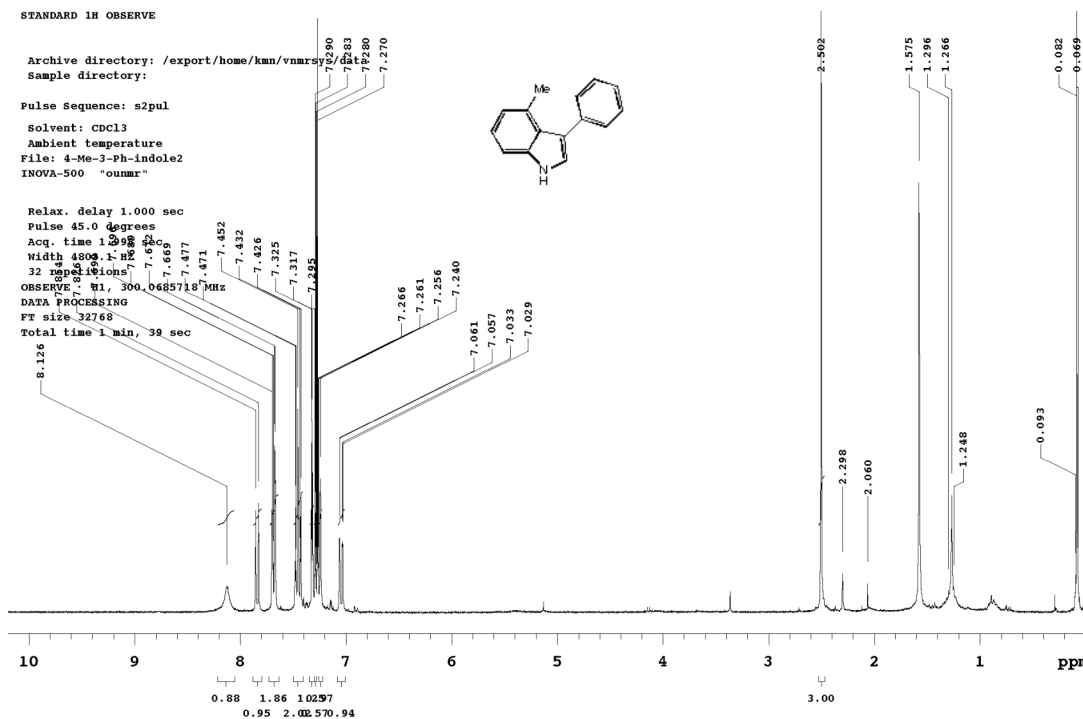
6-Methyl-3-phenylindole (127)

Indole **127** was prepared according to the general procedure from 3-methyl-N-phenylhydroxylamine (61.5 mg, 0.5 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide the title compound as an orange solid (21 mg, 0.101 mmol) in 20% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.19 (br s, 1H, NH), 7.47-7.23 (m, 6H) 7.14 (t, J=4.8 Hz, 2H), 6.89 (dd, J=6.9 and 0.9 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 137.2, 136.4, 131.5, 130.9, 127.8, 126.6, 125.4, 123.1, 122.6, 121.8, 119.9, 109.2, 21.0; LRMS (EI) *m/z* 207.

13C OBSERVE

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 6-Me-3-Ph-indole-C13
INOVA-500 "ounmr"

Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18867.9 Hz
3548 repetitions
OBSERVE C13, 75.4522868 MHz
DECOUPLE H1, 300.0701003 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 11 hr, 56 min, 14 sec

4-Trifluoromethyl-3-phenylindole (129)[77]

Indole **129** was prepared according to the general procedure from 3-trifluoromethyl-N-phenylhydroxylamine and phenylacetylene to provide the title compound as a solid (44.9 mg, 0.170 mmol) in 34% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.46 (br s, 1H, NH), 7.60 (d, J=8.4 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.38 (m, 5H), 7.25 (d, J=7.8 Hz, 1H), 7.21 (m, 1H); GC-MS (EI) 261 (M$^+$)

6-Trifluoromethyl-3-phenylindole (130)[77]

Indole **130** was prepared according to the general procedure from 3-trifluoromethy-N-phenylhydroxylamine and phenylacetylene to provide the title compound as a solid (40.0 mg, 0.155 mmol) in 31% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.46 (br s, 1H, NH), 8.01 (d, J=8.7 Hz, 1H), 7.73 (s, 1H), 7.64 (d, J=7.8 Hz, 2H), 7.46 (m, 4H), 7.36 (t, J=7.5 Hz, 1H); MS (ESI) 284 (M + Na$^+$)

4,5-Dichloro-3-phenylindole (132)

Indole **132** was prepared according to the general procedure from 3,4-dichloro-N-phenylhydroxylamine (89 mg, 0.5 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide the title compound as a beige solid (44.3 mg, 0.169 mmol) in 34% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.23 (br s, 1H, NH), 7.40 (dd, J=7.8 and 1.8 Hz, 2H), 7.34-7.27 (m, 3H), 7.23-7.16 (m, 2H), 7.11 (d, J=2.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 135.6, 134.8, 131.2, 127.6, 126.9, 125.6, 124.9, 124.7, 124.6, 124.1, 119.7, 110.9; HRMS (ESI) calculated for C$_{14}$NCl$_2$H$_9$ (M+Na$^+$) requires m/z 284.0010, found m/z 284.0034.

13C OBSERVE

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 4-5-Cl-3-Ph-indole-C13
INOVA-500 "ounmr"

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18867.9 Hz
1552 repetitions
OBSERVE C13, 75.4522868 MHz
DECOUPLE H1, 300.0701003 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 4 min, 57 sec
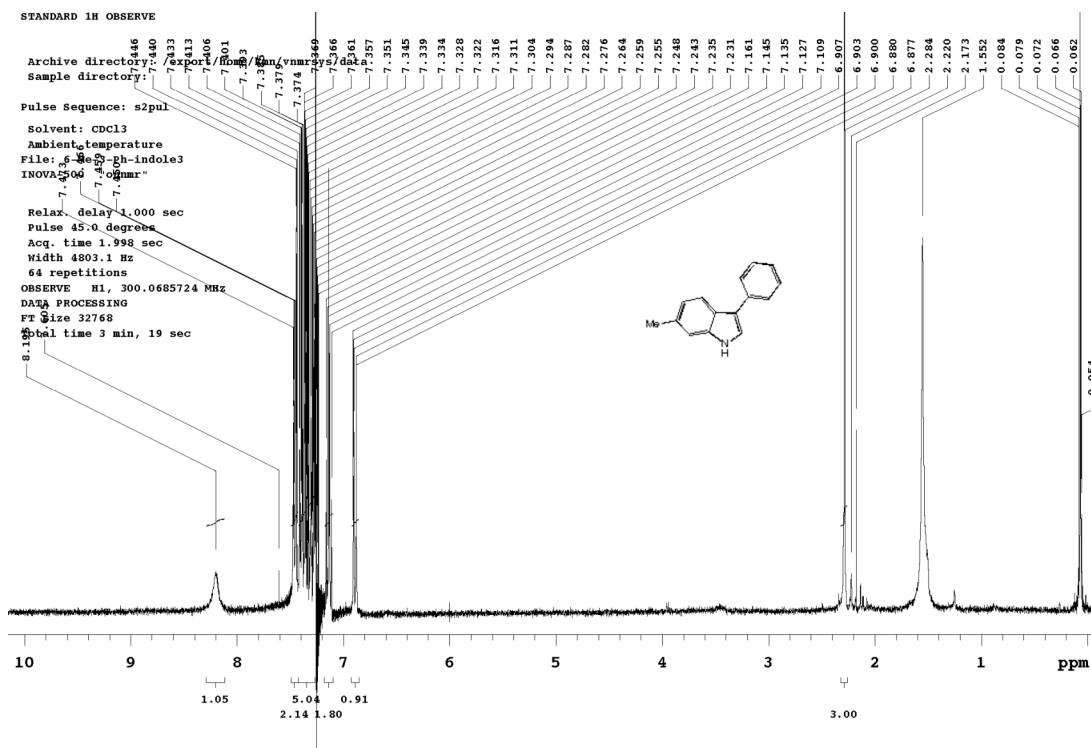

5,6-Dichloro-3-phenylindole (133)

Indole **133** was prepared according to the general procedure from 3,4-dichloro-N-phenylhydroxylamine (89 mg, 0.5 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide the title compound as a white solid (28 mg, 0.107 mmol) in 21% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.26 (br s, 1H, NH), 7.99 (s, 1H), 7.61 (dd, J=8.3 and 1.2 Hz, 2H), 7.55 (s, 1H), 7.47 (t, J=7.2 Hz, 2H), 7.40 (d, J=2.7 Hz, 1H), 7.33 (t, J=7.2 Hz, 1H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 135.5, 134.5, 129.2, 127.6, 126.8, 126.5, 125.8, 124.7, 123.6, 121.1, 118.5, 113.0; LRMS (EI) *m/z* 261, 263.

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 5-6-Cl-3-Ph-indole2
INOVA-500 "ounmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4803.1 Hz
32 repetitions
OBSERVE   H1, 300.0685712 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

8.258

7.554
7.498
7.492
7.474
7.470
7.453
7.448
7.442
7.401
7.392
7.363
7.358
7.355
7.341
7.334
7.327
7.323
7.315
7.310
7.305
7.286
7.283
7.281
7.279
7.276
7.274
7.270

7.266
7.264
7.261
7.259
7.257
7.254
7.252
7.247

1.564
1.528
1.506

0.077

1.07   1.00   2.24 15 30   1.18 27

13C OBSERVE

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 5-6-Cl-3-Ph-indole-C13
INOVA-500 "ounmr"

Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18867.9 Hz
1056 repetitions
OBSERVE C13, 75.4522868 MHz
DECOUPLE H1, 300.0701093 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 33 min, 10 sec

135.521
134.490
129.864
128.633
127.798

126.466
125.787
124.695
123.604

121.086

118.476

113.004

77.651
77.434
77.228
76.804

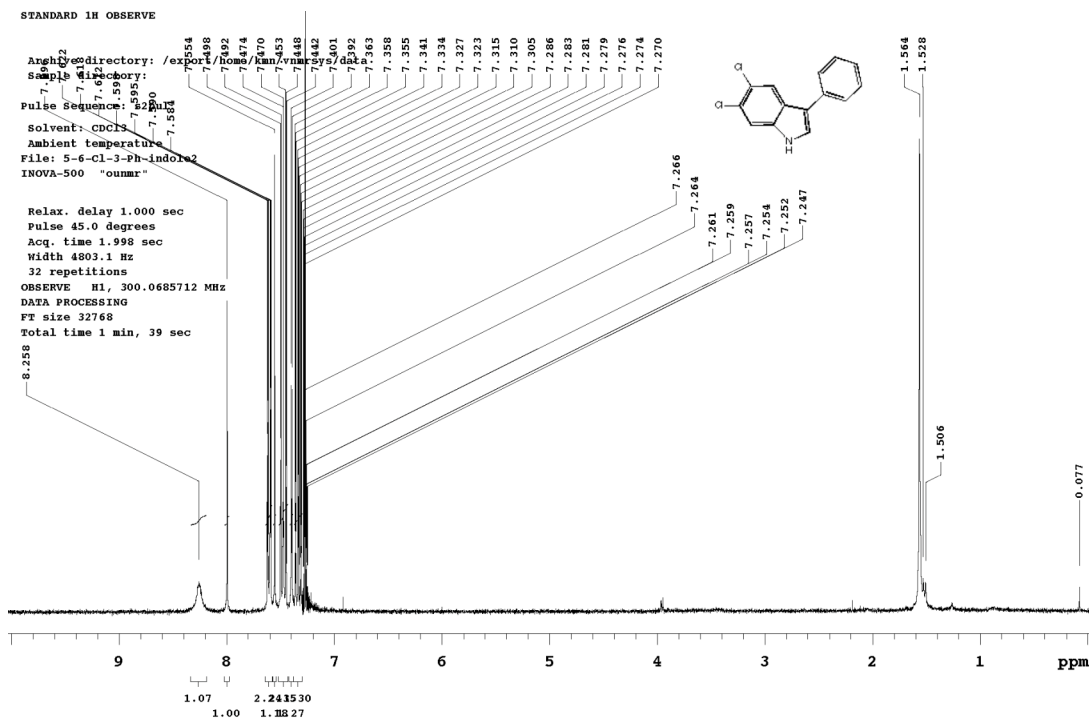### 3-Phenyl-benz[g]indole (135)

Indole **135** was prepared according to the general procedure from N-1-naphthyl-hydroxylamine (79.5 mg, 0.5 mmol) dissolved in 6 mL toluene, Fe(Pc) (28 mg, 0.05 mmol), phenyl acetylene (1.1 mL, 10 mmol), and toluene (15 mL) to provide the title compound as a gray solid (45 mg, 0.185 mmol) in 37% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.97 (br s, 1H, NH), 8.06-7.96 (m, 3H), 7.74 (d, J=8.4 Hz, 2H), 7.60-7.44 (m, 6H), 7.34 (t, J=7.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 135.5, 131.3, 130.5, 128.9, 128.8, 127.8, 126.2, 125.6, 124.2, 121.8, 121.6, 121.2, 120.3, 119.8, 119.6, 119.3; HRMS (ESI) calculated for C$_{18}$NH$_{13}$ (M+Na$^+$) requires m/z 266.0946, found m/z 266.0996.

```
13C OBSERVE

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: naphthyl-indole-C13
INOVA-500  "ounmr"

Relax. delay 5.000 sec
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18867.9 Hz
5988 repetitions
OBSERVE  C13,  75.4523025 MHz
DECOUPLE  H1, 300.0701003 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 11 hr, 49 min, 50 sec
```

2-Methyl-3-phenylindole (137)[78]

Indole **137** was prepared according to the general procedure from N-phenylhydroxylamine and 1-phenylpropyne to provide the title compound as an oily red solid (25.6 mg, 0.125 mmol) in 25% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.96 (br s, 1H, NH), 7.68 (d, J=8.1 Hz, 1H), 7.50 (m, 4H), 7.32 (m, 2H), 7.15 (m, 2H), 2.52 (s, 3H); GC-MS (EI) 207 (M$^+$)

2,3-Diphenylindole (139)[158]

Indole **139** was prepared according to the general procedure from N-phenylhydroxylamine and 1,3-diphenylacetylene to provide the title compound (not isolated) in trace yield: GC-MS (EI) 269 (M$^+$)

3-(4-Methoxyphenyl)indole (141)[159]

Indole **141** was prepared according to the general procedure from N-phenylhydroxylamine and 4-methoxy-phenylacetylene to provide the title compound as a white solid (98 mg, 0.440 mmol) in 88% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.19 (br s, 1H, NH), 7.90 (d, J=8.1 Hz, 1H), 7.60 (d, J=9.0 Hz, 2H), 7.43 (d, J=8.4 Hz, 1H), 7.20 (m, 3H), 7.01 (d, J=9.0 Hz, 2H), 3.86 (s, 3H); GC-MS (EI) 223 (M$^+$)

3-(3,4-Dimethoxyphenyl)indole (143)

Indole **143** was prepared according to the general procedure from N-phenylhydroxylamine (30 mg, 0.27 mmol) dissolved in 5 mL toluene, Fe(Pc) (17 mg, 0.03 mmol), 3,4-dimethoxy-phenylacetylene (0.972 g, 6 mmol), and toluene (10 mL) to provide the title compound as a yellow solid (38.6 mg, 0.153 mmol) in 57% yield: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.23 (br s, 1H, NH), 7.92 (d, J=7.8 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.34 (d, J=2.4 Hz, 1H), 7.30-7.18 (m, 4H), 6.99 (d, J=8.1 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 149.3, 147.7, 136.8, 128.6, 126.1, 122.6, 121.5, 120.4, 119.9, 119.8, 118.4, 111.8, 111.6, 111.3, 56.2, 56.1; HRMS (ESI) calculated for C$_{16}$O$_2$NH$_{15}$ (M+Na$^+$) requires m/z 276.1000, found m/z 276.0898.

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 3-m-p-OMe-Ph-indole2
INOVA-500 "ounmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4803.1 Hz
32 repetitions
OBSERVE H1, 300.0685712 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

8.270
8.267
8.264
8.262
8.259
8.257
8.247
7.240
7.232
7.229
7.224
7.219
7.207
7.341
7.333
7.296
7.292
7.276
7.183
7.179
7.003
6.976
3.968
3.951
1.568
0.080

10 9 8 7 6 5 4 3 2 1 ppm

0.98   0.94 27 1.09
1.00   1.0155   6.45

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 3-m-p-OMe-Ph-indole-C13
INOVA-500 "ounmr"

Relax. delay 10.000 sec
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18867.9 Hz
904 repetitions
OBSERVE C13, 75.4522882 MHz
DECOUPLE H1, 300.0701003 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 2 min, 31 sec

149.299
147.735
136.765
128.637
126.050
122.581
121.471
120.406
119.937
119.861
118.415
111.844
111.607
111.264
77.651
77.228
76.804
56.199
56.130

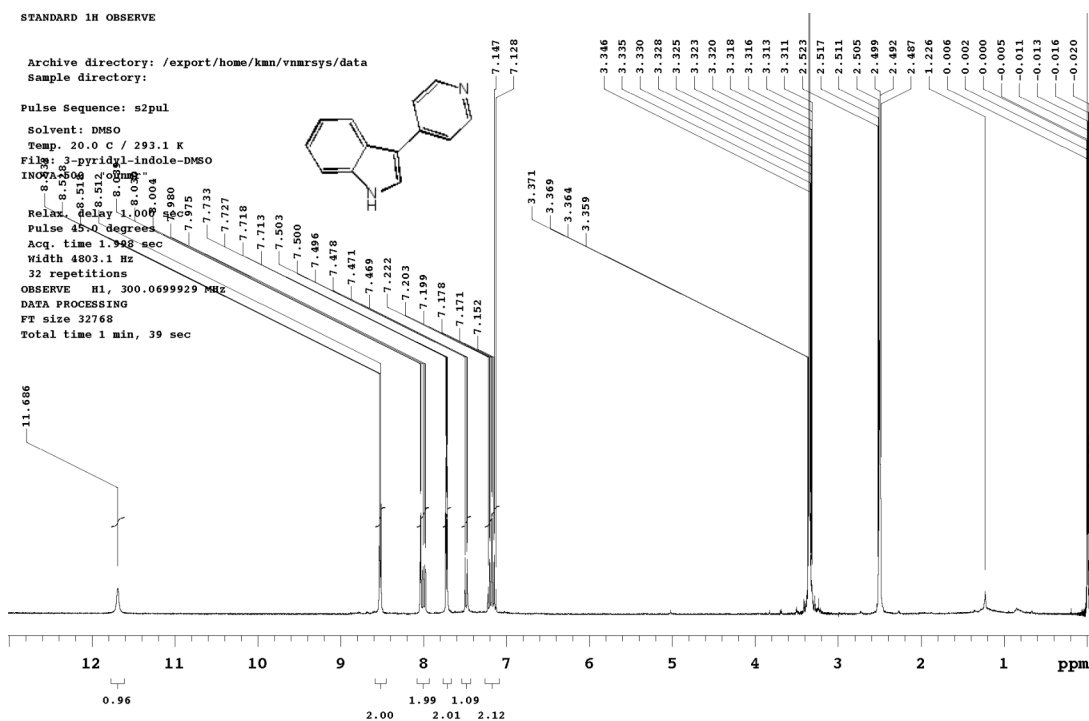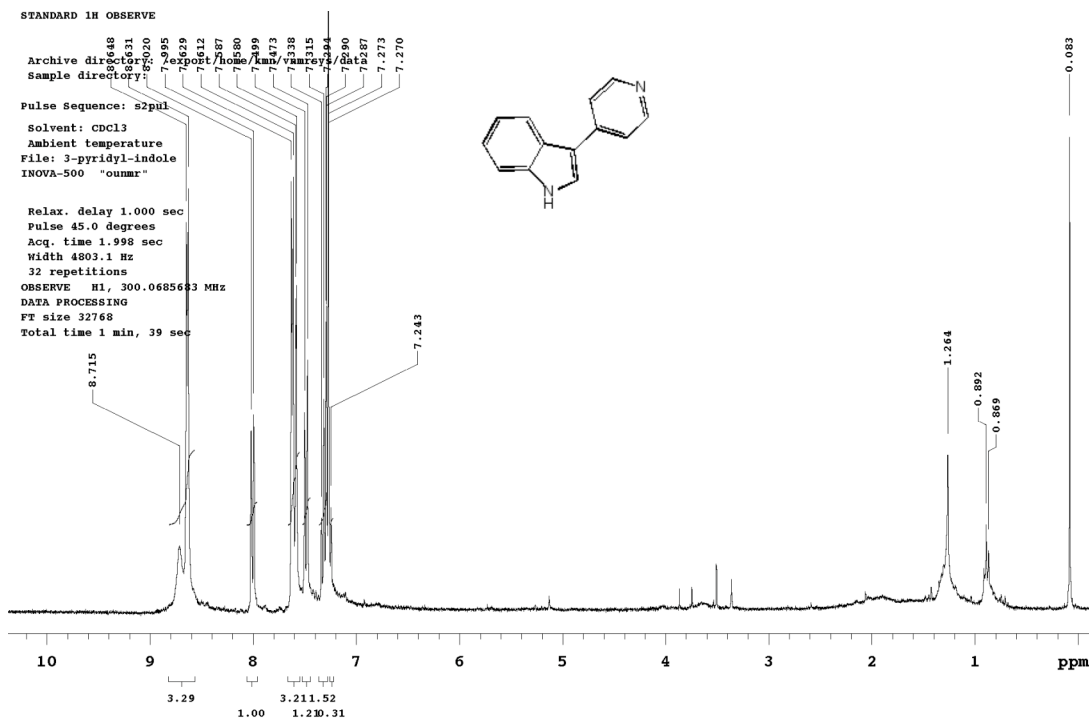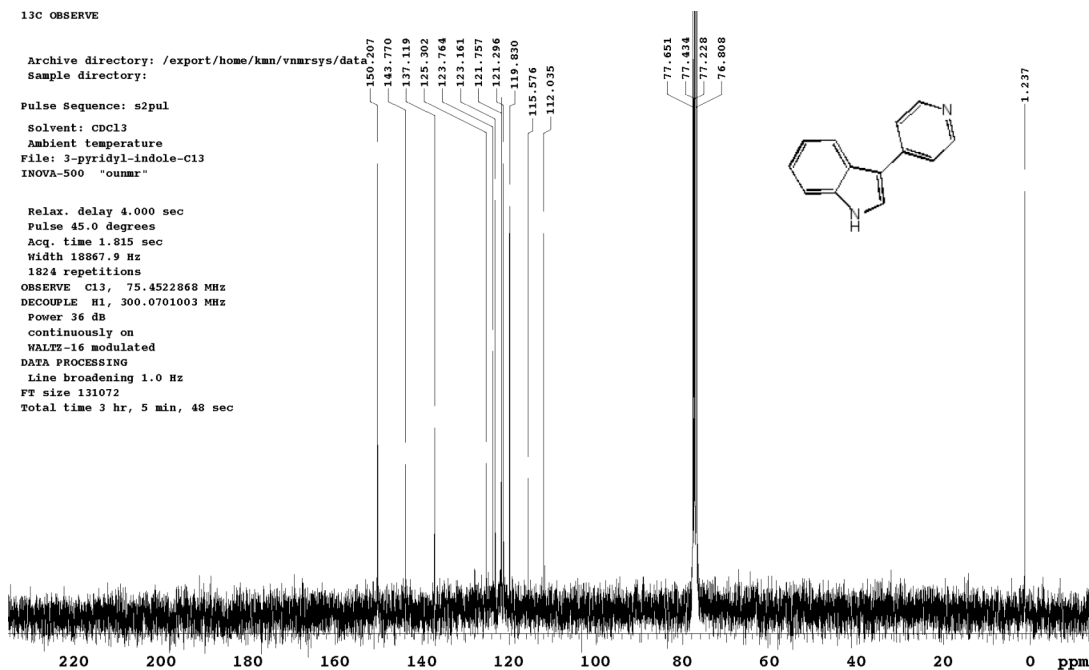200 180 160 140 120 100 80 60 40 20 ppm

118

Scale-up reaction for indole (143)

Indole **143** was prepared by four sequential 7-8 hour additions (~30 hours total) of N-phenylhydroxylamine (4 portions of 50 mg, 0.45 mmol, 200 mg and 1.8 mmol total) dissolved in 6 mL toluene each, Fe(Pc) (113 mg, 0.2 mmol), 3,4-dimethoxy-phenylacetylene (3.24 g, 20 mmol), and toluene (35 mL) followed by additional 8 hours reflux to provide the title compound as a yellow solid (249 mg, 0.984 mmol) in 55% yield. 3.085 g (19.04 mmol) of unreacted alkyne was recovered from column chromatography isolation.

3-(4-Pyridyl)indole (145)

Indole **145** was prepared according to the general procedure (with protection from light during reaction) from N-phenylhydroxylamine (33 mg, 0.3 mmol) dissolved in 5 mL toluene, Fe(Pc) (17 mg, 0.03 mmol), 4-ethynylpyridine (525 mg, 5.1 mmol), and toluene (10 mL) to provide the title compound as a greenish-white solid (41.8 mg, 0.215 mmol) in 72% yield (isolated from preparative TLC using EtOAc): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.72 (br s, 1H, NH), 8.64 (d, J=5.1 Hz, 2H), 8.01 (d, J=7.5 Hz, 1H), 7.63-7.58 (m, 3H), 7.48 (d, J=7.8 Hz, 1H) 7.34-7.24 (m, 2H); ^{1}H NMR (DMSO, 300 MHz) δ 11.69 (s, 1H, NH), 8.53 (d, J=4.5 Hz, 2H), 8.03 (d, J=2.7 Hz, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.77 (d, J=4.5 Hz, 2H) 7.48 (d, J=7.8 Hz, 1H), 7.18 (m, 2H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 150.2, 143.8, 137.1, 125.3, 123.8, 123.2, 121.8, 121.3, 119.8, 115.6, 112.0; HRMS (ESI) calculated for C$_{13}$N$_2$H$_{10}$ (M+H$^+$) requires *m/z* 195.0922, found *m/z* 195.0902, HRMS (ESI) calculated for C$_{13}$N$_2$H$_{10}$ (M+Na$^+$) requires *m/z* 217.0742, found *m/z* 217.0727.

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 3-pyridyl-indole
INOVA-500 "ounmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4803.1 Hz
32 repetitions
OBSERVE   H1, 300.0685633 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

8.715
7.243
1.264
0.892
0.869
0.083

10   9   8   7   6   5   4   3   2   1   ppm

3.29
1.00   1.210.31
3.211.52

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 20.0 C / 293.1 K
File: 3-pyridyl-indole-DMSO
INOVA-500 "ounmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4803.1 Hz
32 repetitions
OBSERVE   H1, 300.0699929 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 39 sec

11.686
7.147
7.128
3.371
3.369
3.364
3.359
3.346
3.335
3.330
3.328
3.325
3.323
3.320
3.318
3.316
3.313
3.311
2.523
2.517
2.511
2.505
2.499
2.492
2.487
1.226
0.006
0.002
0.000
-0.005
-0.011
-0.013
-0.016
-0.020
-0.022

12   11   10   9   8   7   6   5   4   3   2   1   ppm

0.96
2.00
1.99   1.09
2.01   2.12

120

13C OBSERVE

Archive directory: /export/home/kmn/vnmrsys/data
Sample directory:

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
File: 3-pyridyl-indole-C13
INOVA-500 "ounmr"

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 1.815 sec
Width 18867.9 Hz
1824 repetitions
OBSERVE C13, 75.4522868 MHz
DECOUPLE H1, 300.0701003 MHz
Power 36 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 3 hr, 5 min, 48 sec

3-Hexylindole (149)[160]

Indole **149** was prepared according to the general procedure from N-phenylhydroxylamine and 1-octyne to provide the title compound (not isolated) in trace yield: GC-MS (EI) 201 (M$^+$)

1H-Indole-3-carboxylic acid, 1-(3-ethoxy-3-oxo-1-propen-1-yl)-, ethyl ester (151)

Indole **151** was prepared according to the general procedure from N-phenylhydroxylamine and ethyl propiolate to provide the title compound (not isolated) in trace yield: GC-MS (EI) 287 (M$^+$)

Octadecahydrobenzotriscyclooctene (147)[161]

^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.86 (m, 12H), 1.64 (m, 12H), 1.38 (m, 12H); ^{13}C NMR (CDCl$_3$, 300 MHz) δ 136.7, 31.5, 28.3, 27.0.

3.4.5 Nitrosoarene Trapping Experiment

A mixture of 0.05 mmol Fe(Pc), 5 mmol phenyl acetylene, 5 mmol 2,3-dimethyl-1,3-butadiene, and 15 mL benzene was stirred at reflux under argon and to this was added 0.50 mmol of the *N*-aryl hydroxylamine in 5-6 mL benzene by syringe pump (7-8 h). After the addition was complete, reflux was continued overnight (8-12 h). After cooling, the mixture was evaporated to a solid under vacuum. No indole was detected by GC or by isolation.

4,5-Dimethyl-2-phenyl-3,6-dihydro-2H-1,2-oxazine (74)[146]

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.20 (dt, *J*=7.5 Hz, *J*=1.5 Hz, 2H), 6.74 (t, *J*=7.5 Hz, 1H), 6.63 (d, *J*=7.5 Hz, 2H), 4.20 (s, 2H), 3.75 (s, 2H), 1.83 (s, 6H).

CHAPTER 4

NON-TRANSITION METAL CATALYZED INTERMOLECULAR AMINOSULFONATION OF HYDROCARBONS BY IMIDOIODINANES

4.1   Introduction

The direct and selective nitrenoid insertion into a C-H bond is an attractive method of amination because it does not require another functional group to be present or installed on a hydrocarbon substrate prior to the amine forming step. Over the last ten years, numerous transition metal-catalyzed methods have been discovered and investigated involving efficient and regioselective nitrenoid insertion processes (described in Section 1.3.2). These systems generally utilize one or more of a variety of nitrenoid precursors. Intrigued by the potential of an atom-economical, direct amination of C-H bonds, the Nicholas Group began an investigation in 2007 using dehydrated commercially available chloramine-T hydrate[58] (summarized in section 1.3.2.2).

Upon completion of the study of Cu^I-promoted amidation of benzylic C-H bonds by anhydrous chloramine-T, focus turned to developing a more reactive system in order to amidate C-H bonds beyond the range of benzylic or ethereal substrates. Several representative hydrocarbons were marked as targets (Figure 4.1), including those containing unactivated tertiary sp^3, secondary sp^3, sp^2, and/or propargylic C-H

bonds. In order to accomplish this goal, we aimed to discover and investigate new transition metal (or non-metal) catalysts, and/or new nitrenoid precursor aminating agents, preferably air stable and prepared from inexpensive and readily available starting materials. In addition, we also aimed to gain mechanistic insight into a nitrenoid insertion reaction, as details concerning the reactive nature of many of these processes are currently lacking.
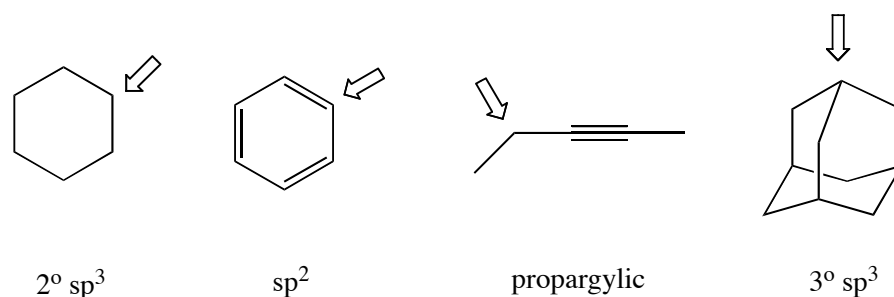

| 2° sp³ | sp² | propargylic | 3° sp³ |

Figure 4.1

4.1.1 Mechanistic Studies of Intermolecular Transition Metal-Catalyzed Aminosulfonation of Hydrocarbons

In contrast to the large number of systems that have been discovered and developed for amidation of hydrocarbons promoted by transition metals (section 1.3.2), relatively few mechanistic studies on the intermolecular C-H insertions have been reported. Mechanistic probes typically employed in these studies have been kinetic isotope effects, Hammett substituent effect studies, radical clocks, and regio- and stereochemical test substrates.

The first system to be fully explored mechanistically was reported in 1997 by the Muller Group.[31] A series of mechanistic probes were conducted and the results

were consistent with a direct nitrenoid insertion mechanism. In order to differentiate a one-step direct insertion pathway from a potential two-step (radical or cationic) mechanistic pathway, a series of radical clock (cyclopropyl containing) substrates (**154**, **155**, **156**) of increasing rate of ring opening were tested (Figure 4.2). In all examples, the ring-opened product that would result from a radical pathway could not be detected.
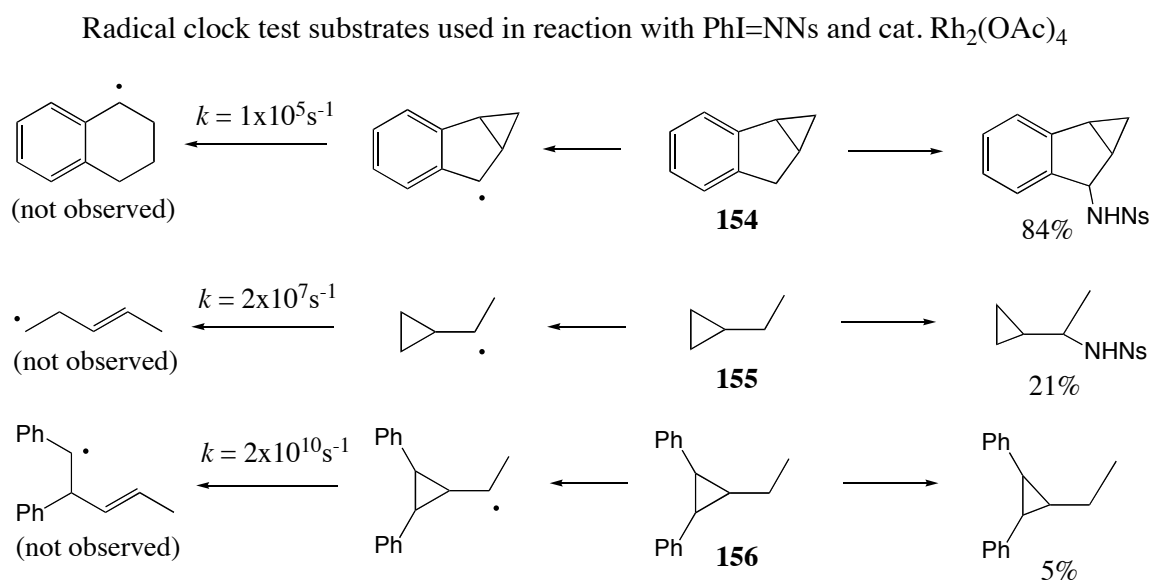
Radical clock test substrates used in reaction with PhI=NNs and cat. $Rh_2(OAc)_4$

Figure 4.2[31]

As further validation of a direct insertion mechanism, (*R*)-2-phenylbutane **157** was utilized as a stereochemical test substrate with PhI=NNs in the $Rh_2(OAc)_4$-promoted amidation reaction, producing only (*S*)-*N*-(l-Methyl-1-phenylpropyl)-4-nitrobenzenesulfonamide **158**, demonstrating retention of configuration in the insertion (Figure 4.3).
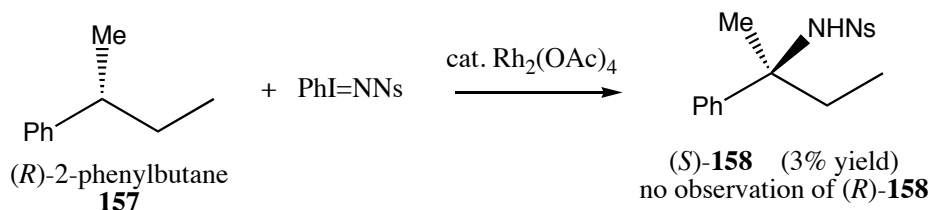
Figure 4.3[31]

In addition, a Hammett plot for sulfonamidation of 4-substituted ethylbenzene substrates with PhI=NNs/[Rh$_2$(OAc)$_4$] resulted in a ρ-value of -0.898 when plotted using σ$^+$ parameters, indicating a slightly (+) charged transition state. Finally, a kinetic isotope effect was determined by reaction of PhI=NNs/[Rh$_2$(OAc)$_4$] with (1,3-D$_2$)-adamantane, which was chosen as a substrate due to its high product formation at a tertiary C-H bond. The intramolecular kinetic isotope effect was then determined to be a primary isotope effect with a value of 3.5 after correction for 100% D-content.[162]

The first report of a hydrocarbon amidating system that involved a radical intermediate pathway was investigated by the Che Group in 1999.[163] Though the focus of the investigation was on the aziridination of alkenes with [Ru^{VI}(TPP)(NTs)$_2$] complexes, the C-H amidation of representative benzylic and saturated 2° and 3° C-H bonds was also performed and the reaction was mechanistically studied. As evidence of a radical pathway, a k_H/k_D of 11 was determined, identical with that obtained in the oxidation of C-H bonds by Ru^{VI} porphyrins via radical intermediates. In addition, a Hammett analysis of *p*-substituted ethylbenzene substrates gave evidence of promotion of the reaction by both electron-donating and –withdrawing groups. When the relative reactivity data (log k_R) was plotted against TE (total effect) parameters

calculated by Wu specifically for radical intermediates,[164] a ρ_{TE}. value of +0.62 was obtained with exceptional linearity ($r^2 = 0.99$).

In a mechanistic study performed by Ragaini et al. in 2003 on the Co(TPP)-promoted C-H insertion of aryl azides,[45] similar data to that of Che's study was obtained, resulting in the interpretation of the reaction proceeding through a carboradical intermediate pathway. A high kinetic isotope effect value of 14 was obtained, potentially elevated due to the high temperature of the reaction, or by a quantum mechanical tunneling effect.[165] In addition, a Hammett analysis was conducted and reactivity data was plotted against a radical parameter set (σ_{JJ}) with addition of small polar effect (σ), and a ρ_{JJ} value of +1.248 and ρ of +0.10 was obtained with good linearity (0.9887). When the same TE parameters used by Che were employed, lower linearity was observed.

In 2007, Fiori and Du Bois reported a mechanistic study of the intermolecular amidation of 3° and benzylic C-H bonds.[37] In Du Bois' system, trichloroethylsulfamate (TcesNH$_2$) is oxidized *in situ* by PhI(O$_2$C^{t}Bu)$_2$ and C-H insertion is promoted by 2 mol% Rh$_2$(esp)$_2$. To attempt to differentiate a stepwise versus a concerted mechanistic pathway, a cyclopropyl clock substrate **159** was used in the standard reaction conditions, resulting in no observed ring-opening (Figure 4.4). In addition, stereochemical tests were also performed and the retention of configuration that was observed is indicative of a direct, concerted, insertion mechanism (Figure 4.4). Lastly, the electronic nature of the transition state was assessed by Hammett analysis through competition experiments with *p*-substituted

ethylbenzene substrates (plotted versus σ^+). A ρ-value of -0.73 was obtained, indicating small cationic charge development in the transition state.
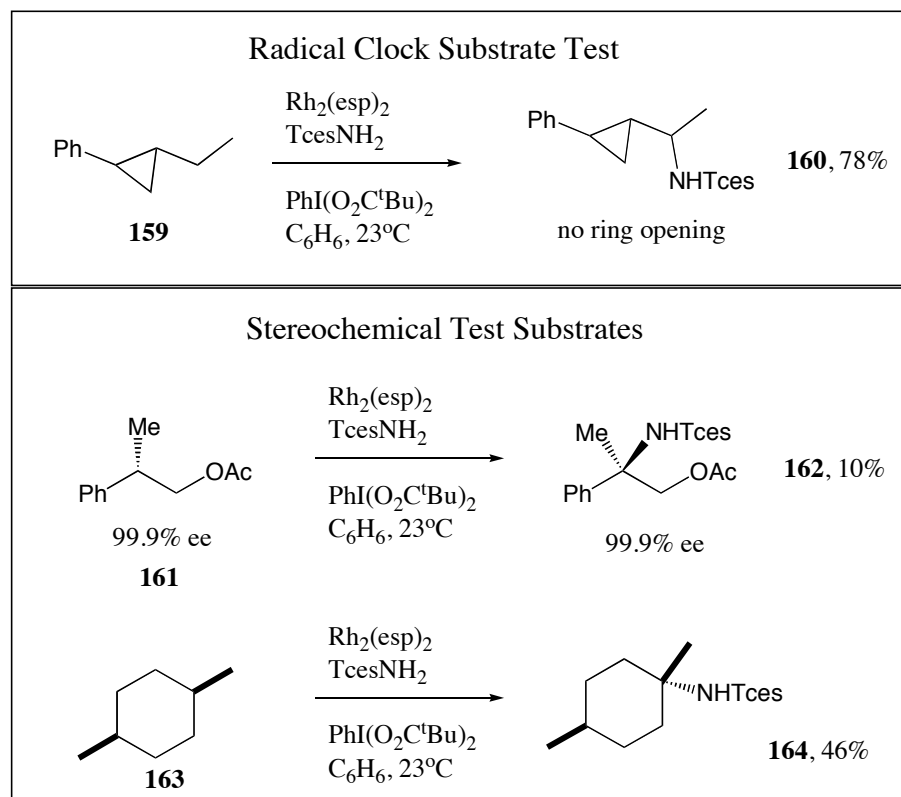

Figure 4.4[37]

In a chemoselective test using a substrate possessing both benzylic and 3° C-H bonds, the benzylic C-H was favored 7 : 1 in the intermolecular amidation, as opposed to the intramolecular reaction which favored the 3° C-H bond in a ratio 7 : 1 (Figure 4.5). This disparity in chemoselectivity is somewhat puzzling as both reactions (intra- and intermolecular) were shown to proceed through asynchronous concerted mechanistic pathways. It was therefore reasoned that the selectivity is a function of the rate in

which the oxidant is trapped by the substrate (two benzylic C-H bonds to one tertiary

C-H) versus the rate at which it decomposes through non-productive pathways.
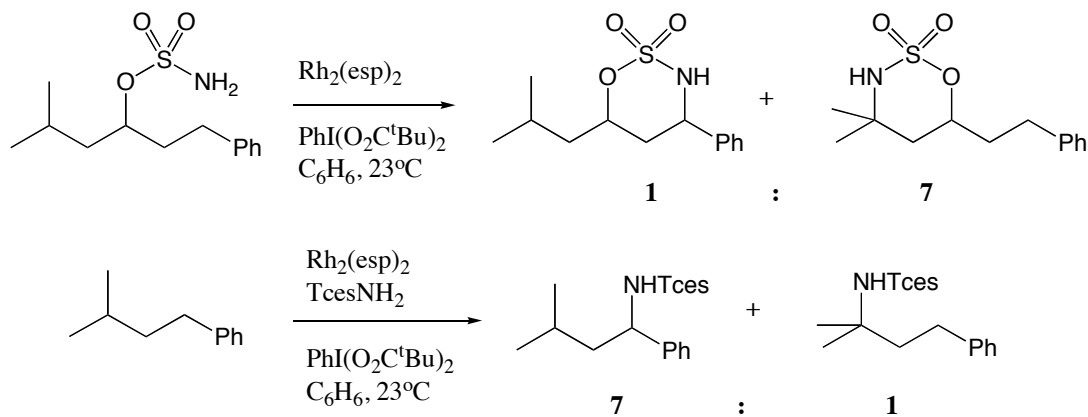
Figure 4.5[37]

The most recently published study occurred in 2008 when Huard and Lebel

reported a mechanistic study of the $Rh_2(tpa)_4$-promoted TrocNH-OTs amidation of 3°

and 2° sp^3, as well as benzylic C-H bonds.[40] Using the same stereochemical test

substrate as Du Bois (**163**, Figure 4.5) resulted in retention of configuration of the

Troc-protected amine (45% yield). In a radical clock experiment utilizing substrate

159, no ring-opening products accompanied the 51% yield of Troc-protected amine.

In a similar Hammett analysis to that of Muller and Du Bois, a ρ-value of -0.47 was

obtained, indicating even smaller cationic charge development in the transition state

in comparison to previous studies. Lastly, a competition experiment between

cyclohexane and deuterated cyclohexane was performed to study the kinetic isotope

effect of the C-H insertion step, resulting in a primary isotope effect of ~5. Overall,

these data suggested a concerted asynchronous transition state similar to that of the

other Rh-catalyzed systems of Muller and Du Bois. Comparable results of the reported systems are summarized in Table 4.1.

	$Rh_2(esp)_2$, $TcesNH_2$, $PhI(O_2C^tBu)_2$ C_6H_6, 23°C **(Du Bois)**	$Rh_2(OAc)_4$, $PhI=NNs$, 23°C **(Muller)**	$Rh_2(tpa)_4$, $TrocNH-OTs$, K_2CO_3 23°C **(Lebel)**	$[Rh^{VI}(TPP)(NTs)_2]$ 23°C **(Che)**	$Co^{II}(TPP)$, ArN_3, 75°C **(Cenini)**
Hammett Analysis	$\rho = -0.73$ (σ^+)	$\rho = -0.90$ (σ^+)	$\rho = -0.47$ (σ^+)	$\rho = +0.62$ (TE$^-$)	$\rho_{JJ.} = +1.25$, $\rho = 0.10$ ($\sigma_{JJ.}$, σ)
Radical Clock	No Opening	No Opening	No Opening	ND[a]	ND[a]
Stereochemical Tests	Retention	Retention	Retention	ND[a]	ND[a]
Kinetic Isotope Effect	ND[a]	3.5	5	11	14
Mechanism	Asynch Concert	Asynch Concert	Asynch Concert	Radical	Radical

[a] ND = Not Determined

Table 4.1 (Compiled from References 31,37,40,45,163)

Most recently, in soon-to-be published results that have been generated in the Nicholas Group concurrently to results that will be discussed within this chapter, the Cu^I-promoted amidation of benzylic hydrocarbons in the presence of diimine ligands has been shown to occur through a radical (stepwise) pathway. In a mechanistic study that was accompanied by computational results from a collaboration of Prof. Nicholas and Prof. K. Houk, a kinetic isotope effect of 4.6 was experimentally obtained. In addition, utilization of a benzylic radical clock substrate **165** resulted in observance of a ring-opened product **167**, consistent with a radical process (Figure 4.6). Finally, in a stereochemical test with substrate **168**, C-H insertion occurred without retention of

configuration, further support for the calculational results that suggest a triplet radical pathway is lowest in energy.
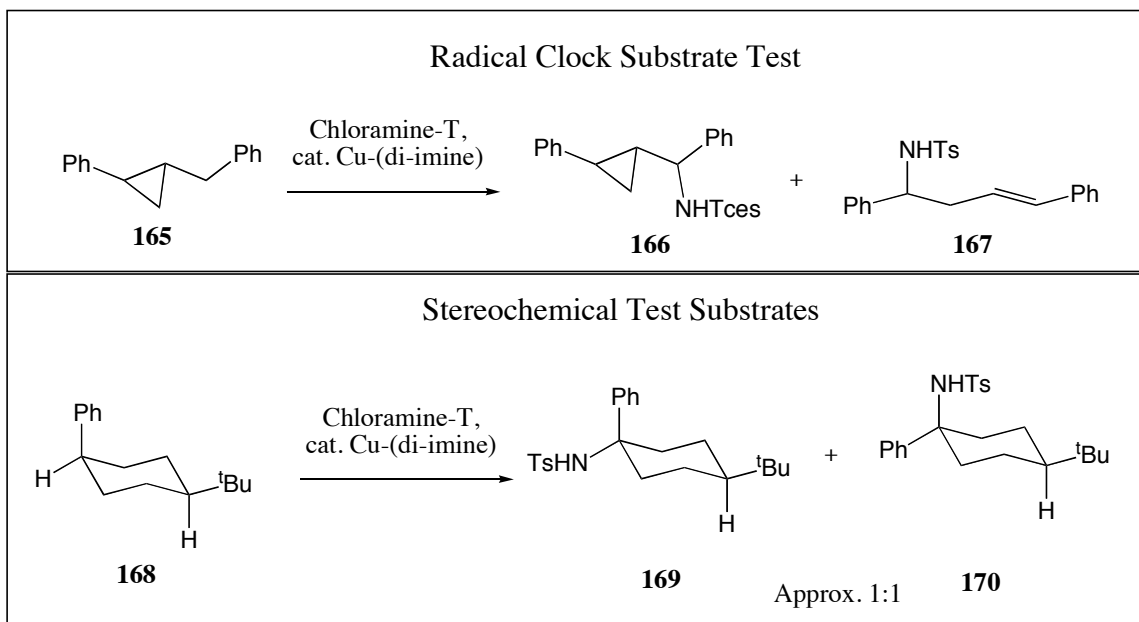

Figure 4.6

4.1.2 Non-Metal Catalyzed Amidation of Hydrocarbons

Over the last ten years, amidation of hydrocarbons via nitrenoid precursors by transition metal promoted systems has received a large amount of attention. However, apart from investigations performed in the Nicholas Group, only one other example of transition-metal-free intermolecular amination by means other than generation of a free nitrene[166] is known. In a study that was being conducted concurrently to that being presented within this chapter, Fan et al. report the amination of secondary benzylic hydrocarbons by various sulfonamides and PhI(OAc)$_2$ that is promoted not by transition metals, but by one equivalent of I$_2$.[167] In the report, amination of ethylbenzene with TsNH$_2$/PhI(OAc)$_2$ was initially observed in low yield in the

presence of I$_2$ (Figure 4.7). A control reaction was performed of ethylbenzene/PhI=NTs and I$_2$ under the same conditions, and curiously, no amination was observed.
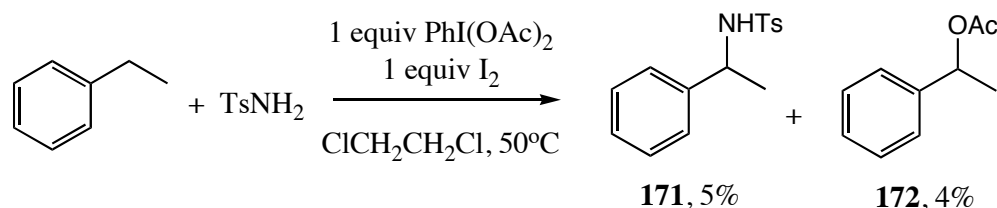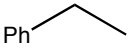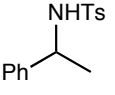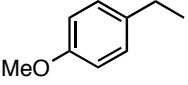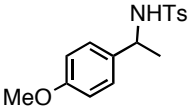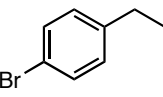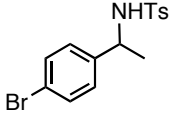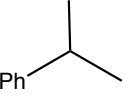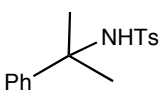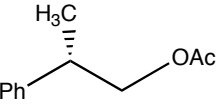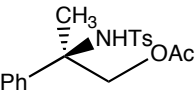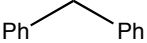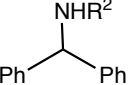

Figure 4.7

Intrigued by the potential of the reaction and in order to inhibit undesired acetoxylation, an optimization of the conditions was conducted with ethylbenzene and TsNH$_2$ in which the best results were obtained by employing 3 equivalents of PhI(OAc)$_2$, 0.5 equivalents of I$_2$, and no solvent (48 hrs, 50°C). Acetoxylated by-product was observed in all cases in yield ranging from 2-98%. It is noteworthy that using the same conditions at room temperature, the reaction proceeded sluggishly, only producing an 8% yield of aminosulfonated ethylbenzene.

With an optimized set of conditions, the substrate scope was explored with a range of benzylic hydrocarbons and sulfonamides and is summarized in Table 4.2.

Amidation Reaction of Benzylic Substrates with Sulfonamides[a]

$$\text{Ar} \diagup \text{R}^1 + \text{R}^2\text{NH}_2 \quad \xrightarrow[\substack{50^\circ C}]{\substack{3 \text{ equiv PhI(OAc)}_2 \\ 1 \text{ equiv I}_2}} \quad \underset{\text{Ar}}{\overset{\text{NHR}^2}{\diagup}} \text{R}^1$$

Entry	Substrate	Product		Isol. % Yield
1	Ph (ethyl)	Ph—CH(NHTs)CH₃		95
2	MeO-C₆H₄-ethyl	MeO-C₆H₄-CH(NHTs)CH₃		88
3	Br-C₆H₄-ethyl	Br-C₆H₄-CH(NHTs)CH₃		92
4	PhCH₃	PhCH₂NHTs		45
5	Ph-C(CH₃)₂H (isopropyl)	Ph-C(CH₃)₂-NHTs		0
6	H₃C, Ph, OAc (chiral)	CH₃, Ph, NHTs, OAc		0
7	Ph—CH₂—Ph	Ph—CH(NHR²)—Ph	R²= Ts	98
8			R²= 4-ClC₆H₄SO₂	97
9			R²= PhSO₂	96
10			R²= CH₃SO₂	98
11			R²= t-BuSO₂	75

[a] Reaction conditions: benzylic substrate (3.0 mmol), TsNH₂ (0.3 mmol), PhI(OAc)₂ (0.9 mmol), I₂ (0.15 mmol), 50°C, 48-56 h.

Table 4.2[167]

Moderate to excellent yields are obtained from secondary benzylic substrates, however, the primary benzylic C-H containing toluene was amidated in moderate yield (entry 4), and tertiary benzylic substrates were unreactive (entries 5 and 6). Hydrocarbons without a benzylic C-H such as hexene and cyclohexane resulted in

complicated reactions and no detection of amidated products. Mechanistically, it was tentatively postulated that a sulfonamidyl radical **174** generated from the combination of sulfonamide and acetyl hypoiodite is the reactive intermediate (Figure 4.8).
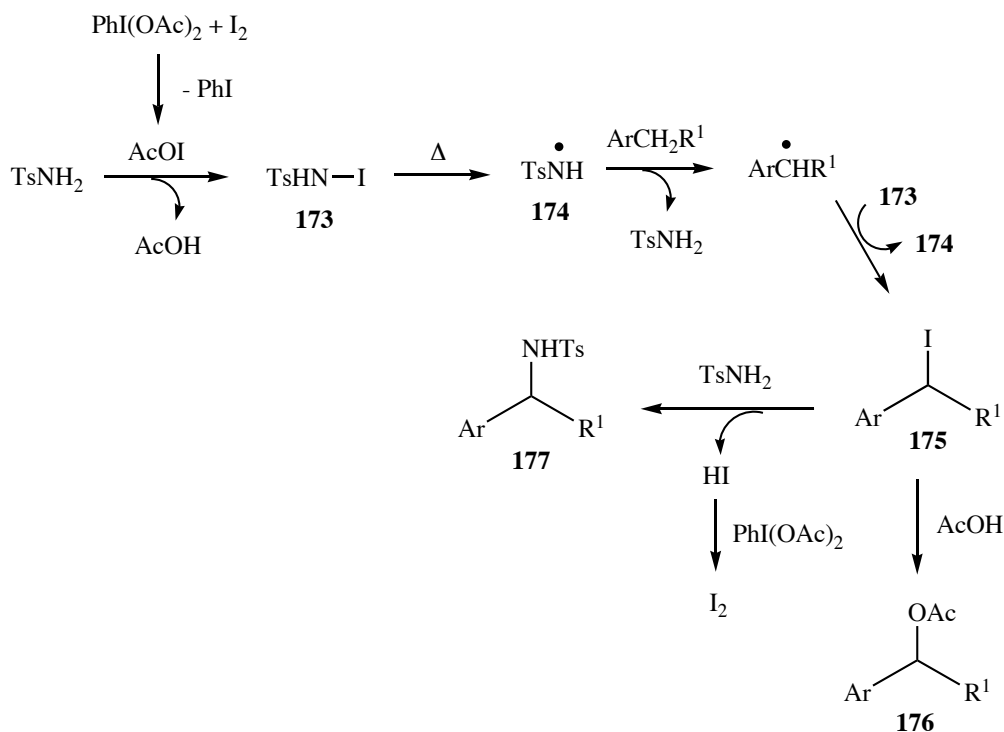

Figure 4.8[167]

4.2   Zinc Halide Catalyzed Aminosulfonation of Hydrocarbons

The following results described in this section have been published as Kalita, B.; Lamar, A. A.; Nicholas, K. M. *Chem. Commun.*, **2008**, 4291.

4.2.1 Catalyst Survey and Optimization

In the search for new transition metal catalysts to effect direct benzylic amidation via nitrenoid precursors, Dr. Biswajit Kalita, a post-doctoral fellow in the

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Nicholas Group, performed a catalyst survey with an array of transition and non-transition metal catalysts. Using the chloramine-T and Cu^I catalyzed amidation reaction[58] previously reported by Bhuyan and Nicholas as inspiration, isoelectronic but presumably redox-inactive Zn^{II} salts were tested. To the Nicholas Group's surprise and satisfaction, the reaction between anhydrous chloramine-T and ethylbenzene (1.2:1) was catalyzed by 15 mol% ZnBr$_2$ (CH$_3$CN, 70°C, 12 hr) producing the benzylic sulfonamide in 25% yield with TsNH$_2$ as major by-product (Figure 4.9).

The reaction conditions were then optimized by Dr. Kalita using 4-ethylanisole as a test substrate in conjunction with a survey of *N*-reagents, group 12 salts, solvents, temperature and stoichiometry. Interestingly, Zn^{II} halides, CdCl$_2$, and HgCl$_2$ all promoted amidation, but Zn(OTf)$_2$ and neutral bromide ion sources such as Bu$_4$N$^+$Br$^-$ and NaBr were all ineffective. The best conditions were found to produce 71% isolated yield of benzylic sulfonamide by utilizing 2-3 equivalents of PhI=NTs, 15 mol% ZnBr$_2$, oven dried (110°C) 4Å molecular sieves in benzene at rt (24-30 hr) or at 50°C (12 hr).
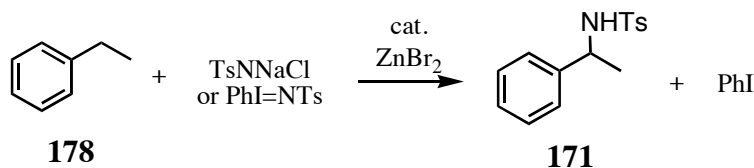

Figure 4.9

Though product yields of representative benzylic hydrocarbons using this Zn^{II} catalyzed method are not as high as in a variety of transition metal-catalyzed methods

(Section 1.3.2), this system represents an important breakthrough in the perceived nature of the active amidating species in reactions utilizing "nitrenoid" precursors. To date, the active aminating species in transition metal-catalyzed amidations is still unknown, but it has been often perceived to be a "metal-netrenoid" **179** formed from redox transformations of the transition metal complexes with the nitrene precursor reagent (Figure 4.10). This catalytic Zn^{II} system thus represented the first example of hydrocarbon C-H amidations catalyzed by non-transition metal (redox-inactive) salts.
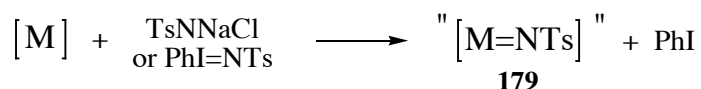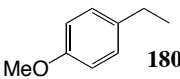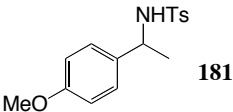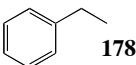
$$[M] \ + \ \begin{array}{c} TsNNaCl \\ or\ PhI=NTs \end{array} \longrightarrow \ {}''[M=NTs]{}'' \ + \ PhI$$

<div align="center">179</div>
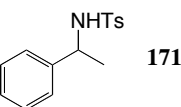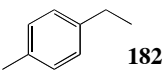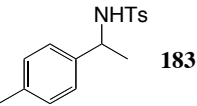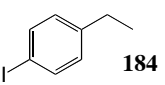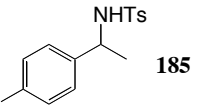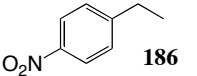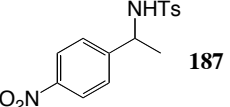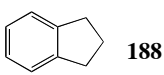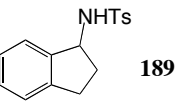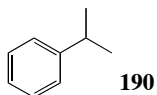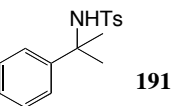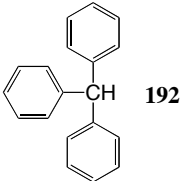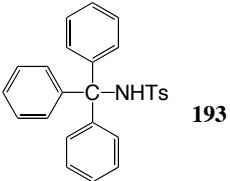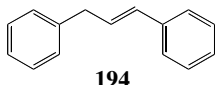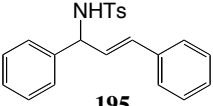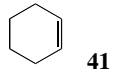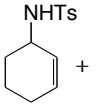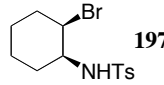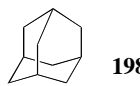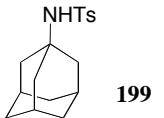
<div align="center">Figure 4.10</div>

4.2.2 Representative Scope

Utilizing the optimized conditions, a survey of the reactions with other hydrocarbon substrates was conducted by Dr. Kalita (Table 4.3).

ZnII Catalyzed Aminosulfonation of Representative Hydrocarbons

Entry	Substrate	Product	Temp. (°C)	Yield[a] (conv)[b]
1	**180**	**181**	RT	71 (81)
2	**178**	**171**	RT	40
			50	48 (75)
3	**182**	**183**	50	52 (75)
4	**184**	**185**	50	42 (50)
5	**186**	**187**	50	10
6	**188**	**189**	50	41
7	**190**	**191**	50	38
8	**192**	**193**	50	38
9	**194**	**195**	50	28
10	**41**	**196** + **197**	50	50 (40,10)
11	**198**	**199**	50	22

[a] % isolated yield; [b] % conversion of hydrocarbon substrate

Table 4.3

Secondary benzylic substrates are moderately effective and highly regioselective as reactants (Table 4.3, entries 1-6), though complete conversion of the limiting hydrocarbon reagent is not always observed. Substrates with p-electron-donating substituents (entries 1 and 3) tend to produce higher yields and conversions along with faster reaction times than the p-electron-withdrawing substrates (entries 4 and 5). As a display of the regioselectivity of the Zn-promoted system, 4-ethyltoluene **182** produced only secondary benzylic amidation **183**, though the substrate also contains primary benzylic C-H bonds (entry 3). The main by-product in all cases was $TsNH_2$, and the observed amount of by-product increased in reactions utilizing less efficient substrates such as entry 5. Hydrocarbon substrates **190** and **192** containing tertiary benzylic C-H bonds were also amidated with moderate efficiency (38%, entries 7 and 8). No observed dehydrogenation of cumene **190** was observed in this system, as opposed to the Cu^I-catalyzed chloramine-T reaction.[58]

In addition to benzylic substrates, the Zn^{II}-catalyzed system was shown to aminate a small sample of representative alkenes. Allylic substrates such as cyclohexene **41** and 1,3-diphenylpropene **194** primarily undergo allylic amination as opposed to aziridination across the double bond, which is often seen in transition metal-catalyzed reactions. Most interestingly, the system was capable of amidating the tertiary C-H bond of adamantane **198** in 22% yield, a substrate that had proven unsuccessful in the Cu^I-promoted amidation reaction. Unfortunately, when benzene and cyclohexane were tested as substrates, no amidated products could be observed.

4.3   Results and Discussion

The following results described in this section have been published as Kalita, B.; Lamar, A. A.; Nicholas, K. M. *Chem. Commun.*, **2008**, 4291.

4.3.1 Optimization Utilizing Hydrous Conditions

Due to the large undesired formation of $TsNH_2$, an investigation was undertaken to improve the reaction efficiency, gain mechanistic insight, and determine the source of the by-product. Suspecting the unintentional incorporation of water into the PhI=NTs reagent (which is prepared by precipitation out of water), the reaction of ethylbenzene, PhI=NTs, and catalytic $ZnBr_2$ in benzene was tested using rigorously dried 4Å molecular sieves (heating in conventional microwave oven followed by immediate placement *in vacuo*). To our great surprise, the reaction only produced a trace amount of the ethylbenzene sulfonamide product by GC (Figure 4.11). The same result occurred when the reaction was conducted under anhydrous conditions without the use of any 4Å molecular sieves. However, when the reaction was performed using either oven dried 4Å molecular sieves, or with addition of one equivalent of H_2O to an anhydrous reaction (without molecular sieves), the aminosulfonated product could be detected in 15-20% yield.

Figure 4.11

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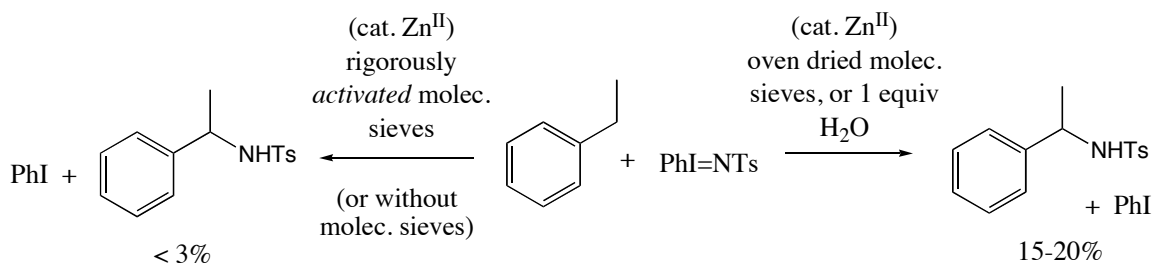
From these experimental results, it was concluded that the reaction actually *required* water, and that the oven dried (110°C) 4Å molecular sieves were in fact providing the necessary amount of water for product formation under Dr. Kalita's optimized conditions. With this knowledge, we then set out to re-optimize the reaction conditions using ethylbenzene, PhI=NTs, and catalytic $ZnBr_2$ to allow for a more reproducible system that incorporated the necessary water in a more controllable fashion (Table 4.4).

Re-Optimization of Benzylic Amidation of Ethylbenzene
with PhI=NTs and Catalytic Hydrous-ZnX_2[a]

Entry	PhI=NTs (equiv)	Ethylbenzene (equiv)	0.15 equiv Catalyst	H_2O (equiv)	GC % Yield
1	1[b]	1	$ZnBr_2$	2	17
2	2[b]	1	$ZnBr_2$	2	20
3	2	1	$ZnBr_2$	1	26
4	2[b]	1	$ZnBr_2$	0.5	17
5	2[b]	1	$ZnBr_2$	0.2	13
6	2	1	$ZnCl_2$	1	12
7	2	1	ZnI_2	1	36
8	1	10	$ZnBr_2$	0.2	20
9	1	10	$ZnBr_2$	1	45
10	1	10	ZnI_2	1	27

[a] 50-55°C in benzene, 12 hrs [b] Added in two portions with second addition occurring after ~5 hrs.

Table 4.4

Upon completion, it was found that a 45% yield of aminosulfonated ethylbenzene (comparable to the 48% yield obtained using 2-3 equivalents of PhI=NTs and oven dried molecular sieves) could be obtained from a more economical use of PhI=NTs (1 : 10 iodinane-hydrocarbon), 15 mol% $ZnBr_2$, and 1 equivalent water in benzene (50°C, 12 hr). Using these conditions, 4-ethylanisole was aminosulfonated in 54% yield, and amidation of adamantane was improved from 22% (previous conditions) to 32%.

4.3.2 Mechanistic Investigation

As part of Dr. Kalita's initial investigation into the active aminating agent in the Zn-promoted aminosulfonation, the reaction of $ZnBr_2$ with PhI=NTs in benzene (in the absence of a benzylic substrate) was conducted at 20-50°C in order to probe for the existence of free nitrene in the system. Free TsN: is itself known to produce azepine **201** and/or PhNHTs **200** by undergoing C-H insertion and/or addition reactions with benzene[168-172] (Figure 4.12). Neither of the trapping products were observed, supporting the argument against the presence of free nitrene in the system.
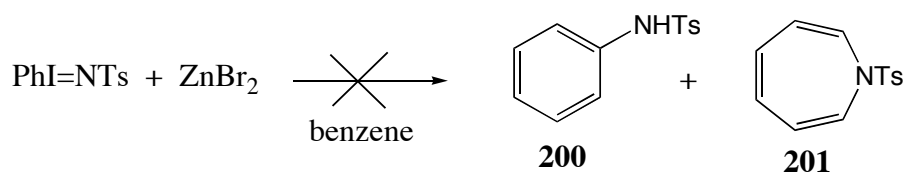
Figure 4.12

In addition to Dr. Kalita's investigation, an experiment was conducted in which a commonly employed radical reaction inhibitor, *p*-methoxyphenol, was added to the reaction medium resulting in almost complete inhibition of the hydrous $ZnBr_2$-PhI=NTs amidation of ethylbenzene, a result suggestive of a radical process.[173] A potential mechanistic pathway is shown in Figure 4.13.
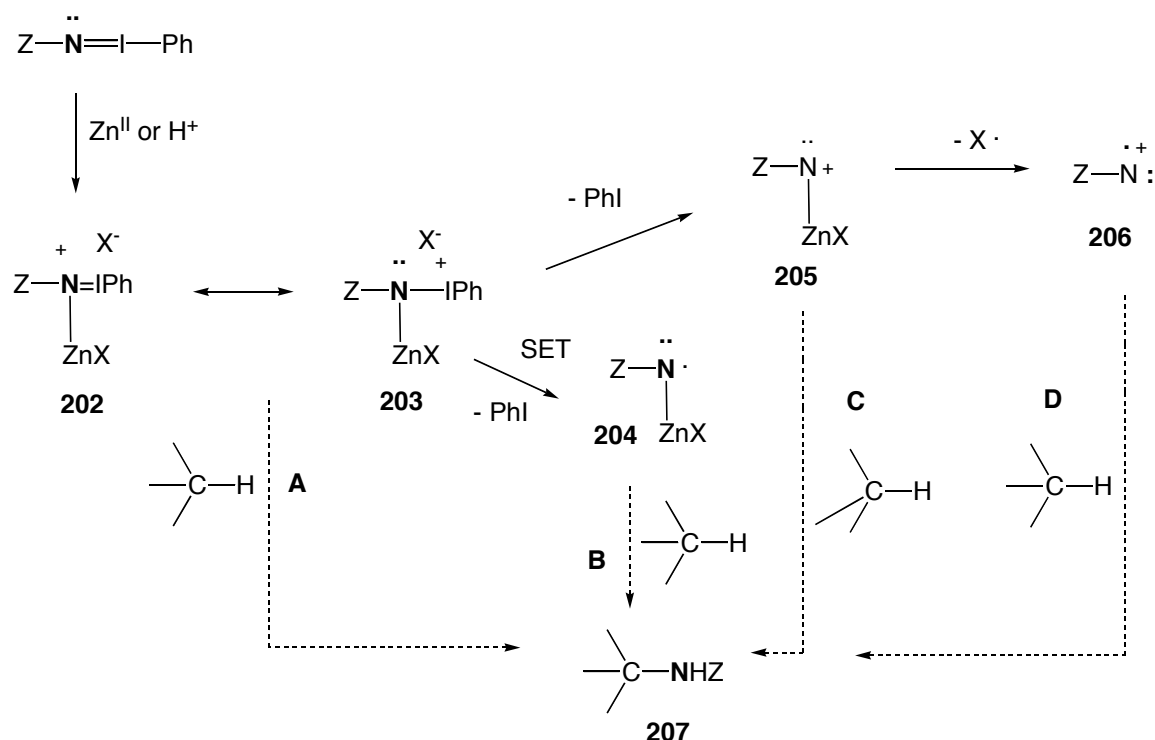
Figure 4.13

Association of the imido-iodinane with Zn^{2+} or H^+ could produce an electrophilic species **202** that attacks the substrate C-H, effecting insertion in a stepwise or concerted fashion (path A). Alternatively, internal electron transfer from the counter-anion (shown as a halide) in **202** and loss of PhI would generate *N*-radical **204** which could undergo C-H insertion (path B). Elimination of PhI from **202** would produce

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nitrenium ion **205** that could also insert to form the amine (path C). Finally, iodine atom dissociation from **205** would form nitrene radical cation **206** which could undergo C-H insertion (path D).

4.3.3 Acid-Catalyzed Amidation of Benzylic Hydrocarbons

Due to the ability of Zn^{II}-H_2O-containing systems to be acidic (Figure 4.14), a survey of protic acids of varying pKa value was conducted in the amidation of ethylbenzene by PhI=NTs (Table 4.5).

$$ZnBr_2 + 2H_2O \rightleftharpoons Zn(OH)_2 + 2HBr$$
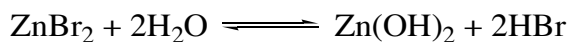
Figure 4.14

In each example, one equivalent of water was either added as needed or existed in the composition of the concentrated acid being employed. In addition, the acids were all utilized in catalytic amount (15-20 mol%). Yields range from trace amount of product (entry 1) up to 32% by employment of hydriodic acid (entry 10). It is of interest that the trend of anionic halide in the Zn^{II} salt catalyzed reactions mirror that seen in the protic acid-catalyzed reactions; i.e., the yield of product increased in the order Cl⁻ < Br⁻ < I⁻. Thus, these results represent the first example of protic acid-catalyzed C-H amidation of a hydrocarbon.

Protic Acid-Catalyzed Benzylic Amidation of Ethylbenzene
with PhI=NTs[a]

Entry	Acid (0.15 equiv)	GC % Yield
1	H_3CCOOH	trace
2	Tartaric	6
3	H_3PO_4	7
4	F_3CCOOH	8
5	HNO_3	5
6	H_2SO_4	9
7	HCl	14
8	HBr/H_2O	10
9	HBr/ H_3CCOOH	19
10	HI	32

[a] 10 equiv. ethylbenzene, 50ºC in benzene, 12 hrs

Table 4.5

4.4   Iodine Catalyzed Aminosulfonation of Hydrocarbons – Results and Discussion

4.4.1 Survey and Optimization

In keeping with our initial goal of expanding the amination substrate scope beyond benzylic and allylic hydrocarbons, we turned our attention toward improving the modest results using the saturated adamantane that were obtained in the hydrous zinc halide-catalyzed aminosulfonation reaction. Viewing adamantane as a

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representative 3° sp³ C-H bond possessing substrate, we envisioned the possibility of an efficient optimization by utilizing Bronsted-Lowry acid catalysis due to the technical ease of the reactions. In our initial catalyst screening using adamantane, we observed yields of **208** comparable to the hydrous zinc-catalyzed system using a catalytic amount of aqueous hydriodic acid (Table 4.6, Entries 1-7). Similar results to those obtained at 45°C were observed at room temperature using HI as catalyst, but the yield was not improved by raising the temperature to 70°C (entries 4-6). Slightly better yields were obtained by using anhydrous CH₂Cl₂ instead of benzene (entries 2 and 4). In addition to HI, hydrous InI₃ appeared to be a more efficient catalyst than ZnBr₂, resulting in a 49% yield (Table 4.6, Entry 8). Due to the color change over the course of the reaction from red to yellow and finally back to dark red, a possible role of trace amounts of free I₂ acting as the catalytic species in the HI and InI₃ systems was suspected. Iodine itself (20 mol %) was then tested as a catalyst (Entry 9). To our surprise and satisfaction, the reaction resulted in an improved yield (55%) of **208** with the inexpensive and easy to handle iodine. Though the reaction proceeds with only 5 mol% I₂, optimum yield was obtained using 20 mol% as catalyst (entries 9-11).

Catalyst screening and initial optimization of the aminosulfonation of adamantane
with imido-iodinanes

Entry	Equiv. Adamantane	1 Equiv. PhI=NZ	Temp. (°C)	Equiv. Catalyst	Solvent	Time (hours)	Yield (%) 208
1	10	Z=Ts	55	0.2 HI (aq)	Benzene	12	28[a]
2	5	Z=Ts	45	0.2 HI (aq)	Benzene	12	20[a]
3	5	Z=Ts	45	0.2 HI (aq)	CH_3CN	12	trace
4	5	Z=Ts	45	0.2 HI (aq)	CH_2Cl_2	12	34[a]
5	5	Z=Ts	RT	0.2 HI (aq)	CH_2Cl_2	12	31[b]
6	5	Z=Ts	70[c]	0.2 HI (aq)	CH_2Cl_2	12	23[b]
7	5	Z=Ts	50	0.15 $ZnBr_2$[d]	Benzene	12	32[a]
8	5	Z=Ts	45	0.15 InI_3[d]	CH_2Cl_2	12	49[b]
9	5	Z=Ts	45	0.2 I_2	CH_2Cl_2	8	55[b]
10	5	Z=Ts	45	0.05 I_2	CH_2Cl_2	8	34[b]
11	5	Z=Ts	45	0.5 I_2	CH_2Cl_2	8	45[b]
12	1	Z=Ts[e]	45	0.2 I_2	CH_2Cl_2	8	82[b]
13	5	Z=Ts	RT	0.2 I_2	CH_2Cl_2	2	63[a], 66[b]
14	5	Z=Ns	RT	0.2 I_2	CH_2Cl_2	2	97[a]
15	5	Z=Ns	RT	0.2 I_2	wet CH_2Cl_2	2	97[b], 86[b,f]

(a) Isolated yield   (b) Calculated by GC using naphthalene as internal standard   (c) Sealed tube
(d) Plus 1 equiv. H_2O (e) 2 equiv.   (f) Open to air
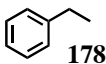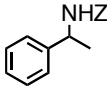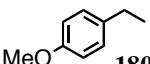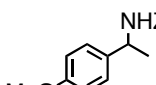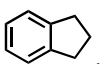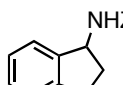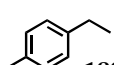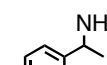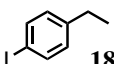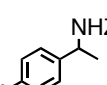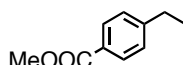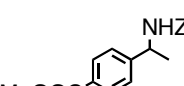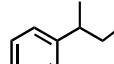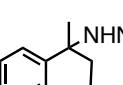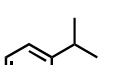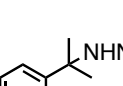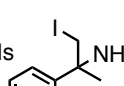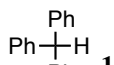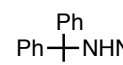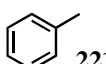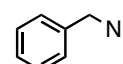
Table 4.6

After optimization of reaction time, temperature, solvent, and stoichiometry, it

was determined that the most efficient conditions were as follows: 5 equiv.

hydrocarbon (good yields can also be obtained using hydrocarbon as limiting reagent – entry 12), one equiv. imidoiodinane added all at once, 0.2 equiv. I$_2$, room temperature under argon for 2 hours. Using PhI=NNs as the aminating agent, a nearly quantitative yield of **208** was isolated (entry 14). This appears to be the most efficient one-step formation of a precursor to the antiviral drug amantadine[174] using an imidoiodinane (see Section 1.3.2.4). The reaction is highly regioselective for the tertiary C-H of adamantane with no 2° C-H aminated product detected, in contrast to some transition-metal-catalyzed systems in which ratios of 3-15 : 1 of 3° : 2° aminated products is exhibited.[31,40,57] An additional interesting feature of the reaction is that it does not require anhydrous solvents or anaerobic conditions (Table 4.6, Entry 15).

4.4.2 Substrate Scope

With a general procedure in hand, the scope of the iodine catalyzed aminosulfonation reaction was investigated and the results are summarized in Tables 4.7 and 4.8. In addition to an excellent isolated yield obtained using adamantane, benzylic substrates generally gave moderate to excellent yields with formation of sulfonamide as main by-product (Table 4.7). In almost all cases of benzylic substrates, the I$_2$-catalyzed system appears to be more efficient than our previously reported Zn-catalyzed system.[175]

I$_2$-Catalyzed Aminosulfonation of Representative Benzylic Hydrocarbons[a]

Entry	PhI=NZ	Substrate	Product		Isolated Yield (%)
1	Z = Ts Z = Ns	178	NHZ	**171** = Ts **209** = Ns	78 73
2	Z = Ts Z = Ns	180	NHZ	**181** = Ts **210** = Ns	91 80
3	Z = Ts Z = Ns	188	NHZ	**189** = Ts **211** = Ns	72 60
4	Z = Ns	182	NHZ	**212**	50
5	Z = Ns	184	NHZ	**213**	57
6	Z = Ns	214	NHZ	**215**	6
7	Z = Ns	216	NHNs	**217**	24
8	Z = Ns	190	NHNs + NHNs	**218** + **219**	218 = 40 219 = 14
9	Z = Ns	192	NHNs	**220**	24
10	Z = Ns	221	NHZ	**222**	13

(a) 5 equiv. hydrocarbon, 1 equiv. PhI=NZ, 0.2 equiv. I$_2$, CH$_2$Cl$_2$, Ar, rt, 2-6 hrs
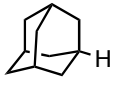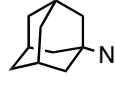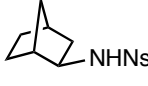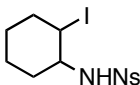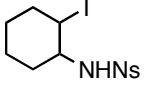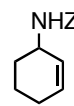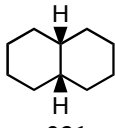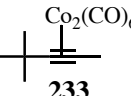
Table 4.7

Substrates with electron-donating as well as −withdrawing groups are reactive with 2° benzylics, though the reaction is distinctly more efficient for electron rich

substrates (entries 1-6). Using PhI=NTs as substrate generally produced slightly more efficient 2° benzylic C-H amidation than PhI=NNs. However, PhI=NTs either produced complex mixtures or little reaction with 1° and 3° benzylic C-H bonds, such as toluene **221** and cumene **190**. The utilization of PhI=NNs with the aforementioned benzylic hydrocarbons did, however, result in amidated products, albeit in modest yields (entries 8 and 10). The amidation of toluene, having a primary benzylic C-H bond, gave a low yield (Table 4.7, Entry 10, **222**), but a number of representative 3° benzylic substrates proved more reactive employing PhI=NNs as the amidating agent (entries 7-9). Modest yields were obtained of the tertiary C-H amidated products **217**, **218**, and **220** as well as the 1,2-difunctionalized product **219** (14%) derived from cumene, which was not produced in the Zn-catalyzed system. This provides a rare example of 1,2-difunctionalization of C-H bonds in an unactivated saturated hydrocarbon,[176-178] and the first example of this reactivity to occur *via* imidoiodinanes. The chemo- and regioselectivity for the present I_2-catalyzed reactions appear to be similar to their Zn-catalyzed counterparts, as 2° benzylic C-H bonds are selectively amidated over 1°, as is shown in the reaction with 4-ethyltoluene (Table 4.7, entry 5). Also, 3° C-H bonds are selectively amidated in the presence of 2° and 1° (entries 7 and 8), leading to an overall trend of $3^o > 2^o > 1^o$.

Similar to 1° and 3° benzylics, other saturated hydrocarbons such as cyclohexane **226** and norbornane **224** produced complex mixtures or little reactivity when PhI=NTs was employed. By utilizing PhI=NNs, however, amidated products were obtained in low yields (Table 4.8). A single isomer, identified by comparison to known ^{1}H NMR data as the 2-*exo* derivative **225**, was isolated from the amidation of

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norbornane **224** (Table 4.8, entry 2). Similar to Muller's Rh-catalyzed system,[31] no reaction is observed at the bridgehead of norbornane, but occurs exclusively at the C(2) position. The reaction with cyclohexane provided another example of novel 1,2-difunctionalization, *i.e.* the iodoamidated derivative **227**, potentially the result of initial dehydrogenation via alkyl radical disproportionation or carbocation deprotonation to an intermediate alkene.[179] The variable and curious specificity of these reactions towards different saturated hydrocarbons (e.g. entries 1, 2, 3) is further highlighted by the absence of appreciable mono-amidation product in the reaction with cis-decalin **231** or *endo*-tetrahydro-dicyclopentadiene **230** (entries 5 and 6).

Table 4.8

A small number of representative unsaturated hydrocarbons were also tested

in the reaction (entries 4, 7-9). Using cyclohexene **41** as a representative alkene, the

reaction produced an inseparable (by chromatography) ~1:1 mixture of allylic amination product (**196** or **229**) and the corresponding 1,2-iodoamidated product (**227** or **228**) as determined by ^{1}H NMR, but without detectable formation of an aziridine (entry 4). In an attempt to functionalize the propargyl position of 4,4-dimethylpentyne **232**, PhIN=Ns was used at both room temperature and refluxing temperatures, resulting in no discernable aminosulfonated products. In an attempt to further activate the propargyl position by complexation with dicobalt hexacarbonyl, **233** was utilized as substrate. Upon addition of I_2 at room temperature, gas evolution could be observed, presumably from production of CO due to decomposition of the complex. Upon addition of PhI=NNs, bubbling intensified and the reaction mixture became a dark reddish brown, and no amidation of the alkyne could be observed. Finally, benzene, either in CH_2Cl_2 or neat, did not lead to any insertion products at room temperature or reflux with either of the imidoiodinane reagents.

4.4.3 Mechanistic Investigation

In addition to the negative result from the "free" nitrene test conducted by employment of benzene as substrate, further efforts to explore the reaction mechanistic pathway and especially to gain insight into the nature of the active aminating agent were made. Due to the higher reactivity of PhI=NNs with 3° benzylic and/or non-benzylic C-H bonds, PhI=NNs was primarily used in mechanistic investigations.

4.4.3.1 Kinetic Isotope Effect

Due to the high reactivity of the system with adamantane, the same intramolecular kinetic isotope effect experiment as in Muller's study was envisioned. 1,3-d_2-Adamantane **235** was prepared from 1,3-dibromoadamantane and LiAlD$_4$ and determined by ^{1}H NMR integration to be 98.4% D$_2$-enriched (see Experimental Section). A 2 : 1 ratio of 1,3-d_2-adamantane to PhI=NNs was allowed to react to completion resulting in a 55% yield of sulfonamidated product. After redissolving the isolated product in MeOH multiple times (to exchange a potential ND for NH), MS-ESI was employed to determine the D$_2$-D$_1$ ratio, resulting in a preliminary experimental k_H/k_D value of 2.51. After calculational correction as outlined by Meunier[162] due to the biased ratio of [D$_2$-D$_1$]-adamantane starting material, a value of 2.68 was obtained (Figure 4.15). Using similar conditions with PhI=NTs gave a 52% isolated yield of sulfonamidated products **236** and **237** and a preliminary experimental k_H/k_D value of 4.55. After calculational correction, a value of 5.12 was obtained. Both results are indicative of a primary isotope effect, with the C-H (D) bond breaking involved in the rate limiting step. The values are also similar to the KIE value of 3.5 that was obtained on the same substrate by Muller[31] in the PhI=NNs/Rh$_2$(OAc)$_4$-promoted reaction. The larger value obtained for PhI=NTs could indicate that the bond breaking step has a more symmetrical transition state than that for PhI=NNs.

Intramolecular Kinetic Isotope Effect
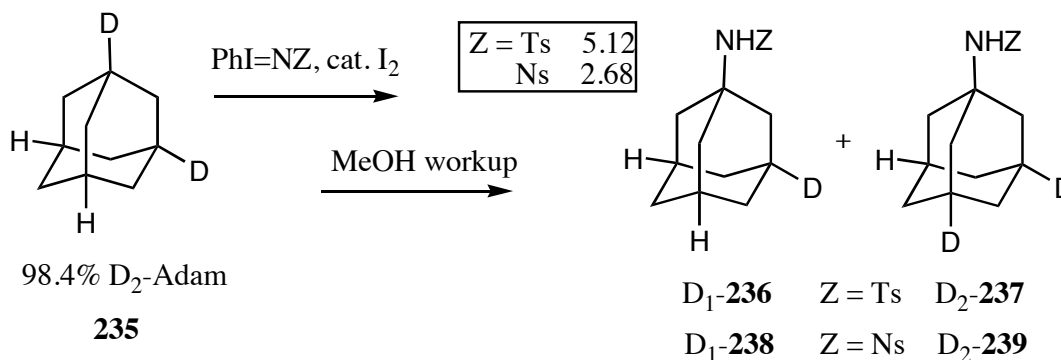
Figure 4.15

4.4.3.2 Hammett Competition Experiment

The electronic nature of the transition state was investigated by a series of competition experiments of ethylbenzene and various *p*-substituted-ethylbenzene substrates. In the experiments, 5 equivalents of both ethylbenzene and a *p*-substituted-ethylbenzene substrate was reacted with one equivalent of PhI=NNs and 20 mol% I_2 at room temperature and allowed to proceed to completion. The ratio of aminosulfonated products was then determined by GC integration. A moderate preference for electron-rich substrates is exhibited by the reaction. Using the same Hammett parameters as Du Bois and Lebel (σ^+) resulted in a ρ-value with poor linearity. In addition, the radical parameters employed by Cenini and Che also resulted in poor linearity. Finally, it was determined that the best linear fit ($R^2 = 0.976$) was achieved by utilization of standard σ_P parameters, producing a ρ-value of -2.77, indicating a considerable cationic charge development in a transition state (Figure 4.16).

Product Ratios		
X = OMe	5.4 : 1	H
Me	2 : 1	H
I	1 : 2.8	H
CO$_2$Me	1 : ~25	H

$y = -2.7725x - 0.0529$

$R^2 = 0.9759$
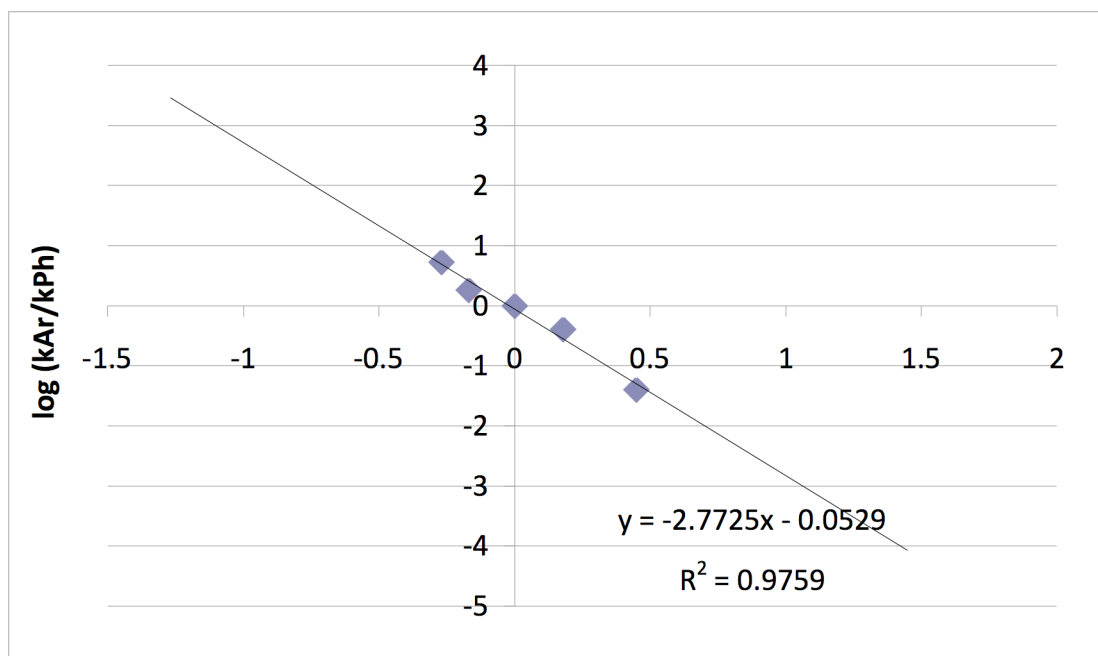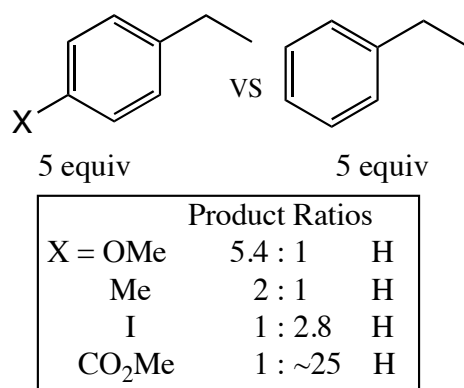
Figure 4.16

4.4.3.3   Radical Clock Substrate Experiment

Due to the ambiguity of the Hammett and KIE results with regard to differentiating a concerted (one-step) insertion versus a two-step radical or cationic producing pathway, a radical clock substrate was employed using standard conditions. [(2-Phenylcyclopropyl)methyl]-benzene **165** was selected as the radical clock substrate due to the presence of a reactive 2° benzylic C-H bond, as well as for

ease of preparation. Upon reaction with PhI=NNs and I_2, pyrrolidine **241** was isolated in 14% yield (69% relative to I_2) without the isolation of any other aminosulfonated products (Figure 4.17). The product **241** was identified by comparison to known pyrrolidine compounds very similar in structure (substituting -Ns for –Ts).[180] In addition, NOESY ^{1}H NMR experiments were conducted in order to determine stereochemistry by correlation of proton signals on the pyrrolidine ring (see Experimental Section). At this time, it appears to be evidence of a two-step process, either by hydrogen or hydride abstraction, as both the benzyl radical and benzyl cation that could form would result in a ring-opened product. The resulting alkenyl sulfonamide could then add as nucleophile in the presence of I_2 (via an iodonium intermediate).[180] No evidence has been found in the literature in support of an iodine assisted intramolecular nucleophilic opening of a cyclopropyl unit, though it cannot be definitively ruled out at this time.
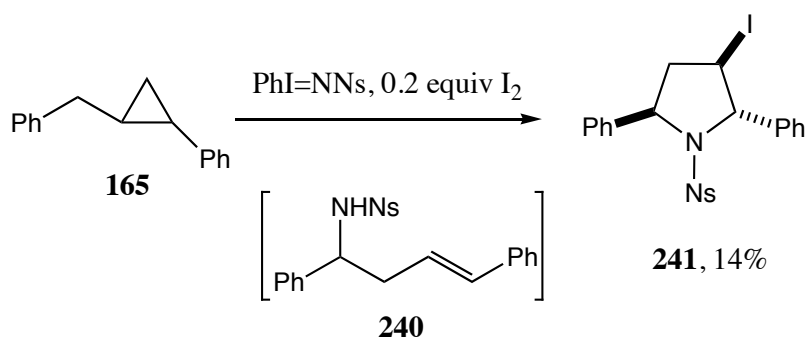
Figure 4.17

4.4.3.4 Stereochemical Tests

In order to determine if the reaction is proceeding through a concerted (one-step) or stepwise insertion pathway, *cis*-**168** was envisioned as a benzylic

stereochemical test substrate. There was some initial concern as to whether or not the potential formation of an alkene (as is seen with another tertiary benzylic, cumene) could add difficulty to the interpretation of potential results. Upon completion of the reaction of PhI=NNs, 20 mol% I$_2$, and [*cis*-4-(*tert*-butyl)cyclohexyl]-benzene **168**, there did appear to be some formation of alkene as we had feared. However, a more interesting result was obtained by the isolation of only one isomer of amidated benzylic product (Scheme 4.16). This seemed to imply that the reaction is in fact a one-step, or concerted, process despite the indirect mechanistic evidence to the contrary (such as the formation of alkene and ring-opened radical clock). To attempt to verify this result the [*trans*-4-(*tert*-butyl)cyclohexyl]-benzene **244** substrate was employed under the same conditions, but no reaction was found to occur, either at room temperature or heated to 40°C (Figure 4.18). The lack of reactivity of the axial benzylic C-H of the *trans*-**244** could be due to steric hindrance of the approaching aminating species, whereas the equatorial benzylic C-H of the *cis*-**168** is more accommodating.
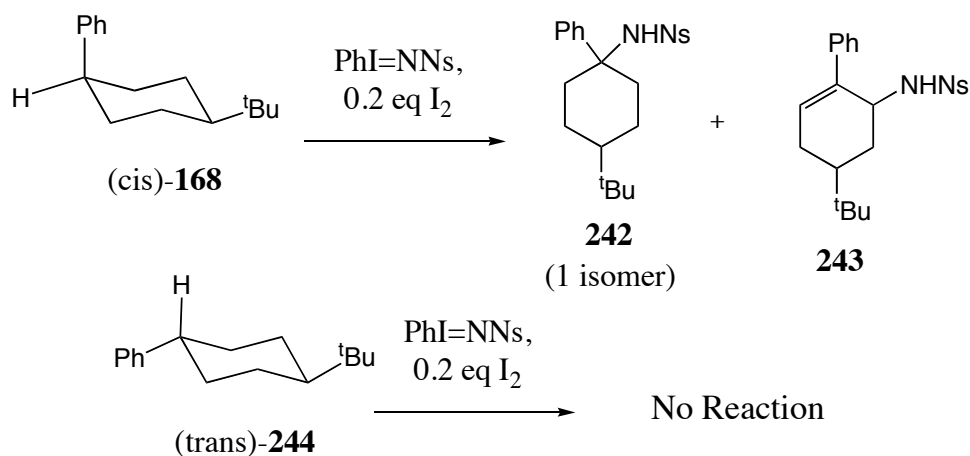
Figure 4.18

An additional stereochemical test to verify this finding could be conducted using an enantiopure substrate of another tertiary benzylic hydrocarbon that has demonstrated sufficient effectiveness using the present reaction conditions. After observing a 24% yield of 3° aminosulfonated product **217** from a reaction using racemic 2-butylbenzene as substrate without an appreciable amount of 1,2-difunctionalized product, the same stereochemical test employed by Muller using enantiopure (R)-2-butylbenzene **157** was envisioned (Figure 4.19). Preparation of **157** for use as an additional stereochemical test substrate is in progress.
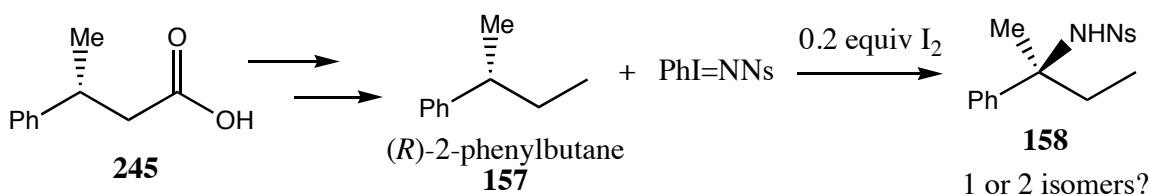
Figure 4.19

4.4.3.5   Isolation of an Active Aminating Agent

In addition to attempting to discern the mechanistic pathway, identification of the active aminating agent was also desired. Using ^{1}H NMR as a tool to gain information into the effect of iodine on the imidoiodinane reagent, a series of experiments was performed in which the addition of reagents was separated in distinct stages (Figure 4.20). First, PhI=NNs was stirred alone at room temperature in CD$_2$Cl$_2$, and the ^{1}H NMR analysis of the mixture indicated a very low solubility of the imidoiodinane reagent. Upon addition of I$_2$ to the insoluble slurry, the mixture slowly became a dark red heterogenous solution containing a pinkish orange

insoluble powder. After 15 minutes, ^{1}H NMR analysis of the solution clearly showed the appearance of iodobenzene, and very little else. To this mixture was added one equivalent of adamantane, and the mixture was allowed to stir for 15 minutes. During this time, the insoluble powder became more soluble, and the solution became more homogenous dark red. ^{1}H NMR analysis showed the emergence of aminosulfonated adamantane product as well as NsNH$_2$. After ~2 hours, an ^{1}H NMR spectrum of the now completely homogenous dark red solution showed a roughly 2 : 1 ratio of aminosulfonated adamantane product to NsNH$_2$. From this experimental series, we can determine that the I$_2$ acts to form an insoluble (in CH$_2$Cl$_2$) powder via decomposition and/or complexation of the imidoiodinane reagent with release of PhI prior to amination of C-H bonds.
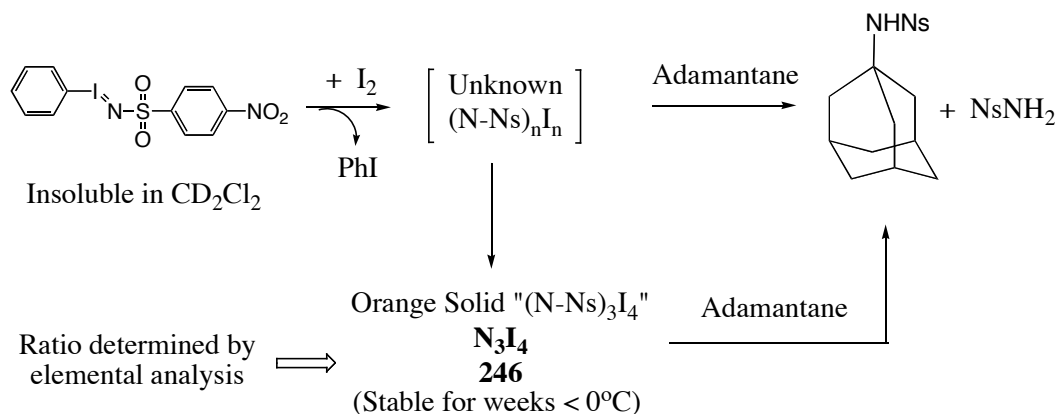
Figure 4.20

Having determined that iodine acts to form the active aminating agent *in situ* by release of PhI from the imidoiodinane reagent, attempts were made to structurally characterize the insoluble powder that forms upon addition of iodine to PhI=NNs. The solid is easily prepared and stable when stored < 0°C. It can be dissolved in

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DMSO, and ^{1}H NMR analysis in this solvent only displays two doublets in the aromatic region with no indication of an NH peak. When the solid itself was added to adamantane in CD$_2$Cl$_2$, ^{1}H NMR analysis indicated the formation of roughly a 5 : 2 ratio of aminosulfonated adamantane product to NsNH$_2$ (Figure 4.20). It was observed that upon stirring of the solid with adamantane, the solution became a dark red, indicative of I$_2$. In order to determine if iodine was complexed with the –NNs unit, a UV-Vis determination of the presence of free I$_2$ was conducted. In a UV-Vis cuvette, the orange solid was added to adamantane in CH$_2$Cl$_2$ and absorbances were measured every 5 minutes (Figure 4.21).
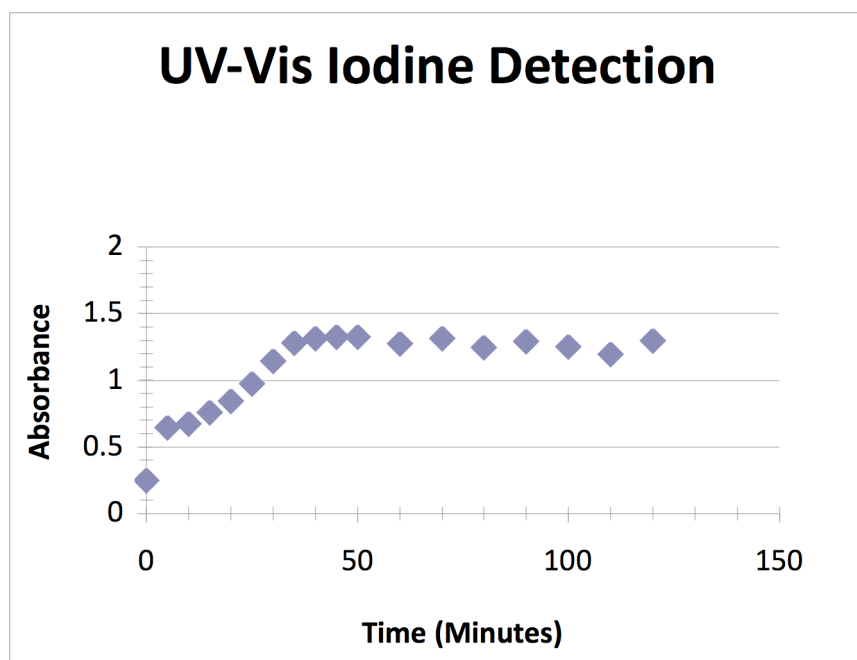
Figure 4.21

The absorbance at 504 λ-max of iodine increases from 0.25 to 1.33 in 40 minutes. From this we can determine that the liberation of approximately 1.35 mg of iodine from 5.0 mg of the orange solid is complete at ~40 minutes, though this does not

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necessarily indicate that the amidation reaction is complete at this time. In addition, it provides evidence in support of a complexed iodine-NNs structure, and represents a distinctly new, isolable, and air-stable nitrogenation agent that will react with C-H bonds at room temperature within minutes and produces only NsNH$_2$ and I$_2$ as by-products. Unsuccessful in our attempts to acquire MS-ESI data on the solid, we turned to elemental analysis for structural information. From results of the analysis, a 3 : 4 ratio of –NNs to I was determined. Attempts to crystallize the solid are underway, but as of yet, the structure remains unknown. Potential structures that could be envisioned must satisfy the ratio of –NNs to I determined by elemental analysis in addition to the observation of only two aromatic doublets in the ^{1}H NMR spectrum. Thus, known coumpounds such as *N,N*-di-iodosulfonamide can be excluded. A possible structure, **246**, is shown in Figure 4.22. As of yet, no literature precedent for such a structure is known.

A Possible Structure of **246**
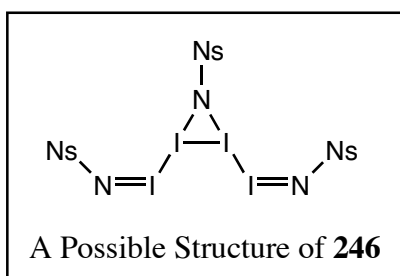
Figure 4.22

4.4.3.6   Mechanistic Summary

In summary, a clearer picture of the reaction mechanistic pathway can be drawn due to several experimental findings (Figure 4.23). It appears that the role of

iodine in the reaction is to promote *in situ* formation of the reactive $(N-Ns)_3I_4$ solid by cleavage of PhI from the imidoiodinane (Path A). This reactive species can then effect C-H insertion by either a one-step (Path B) or two-step process (Paths D and E) with the C-H bond breakage occurring in the rate-limiting step (Path C), as is evinced by a primary kinetic isotope effect. The two-step process could occur either through a fast rebound mechanism of a radical or cation with **247** (Path D), or from the addition to a second equivalent of **246** (Path E). The formation of free nitrene is not observed in the system. In addition, a considerable cationic charge development in a transition state or intermediate is observed by a ρ-value of -2.77 obtained by Hammett competition experiments. Finally, the differentiation between a one-step or two-step process is still somewhat ambiguous. Indirect evidence such as the formation of an alkene and the ring-opened pyrrolidine product from a radical clock substrate indicate a two-step process involving the abstraction of a hydrogen or hydride from the hydrocarbon, followed by C-N bond formation. The stereochemical result, however, indicates a concerted, or one-step process by the isolation of only one isomer **242**, though alkene is formed likely from a two-step process in the same reaction. Most likely is that the reaction can operate through either a one-step or two-step process, and the electronic effects of the hydrocarbon substrate play a role in determining which is dominant.

PhI=NZ

I_2

A

PhI

"(N-Ns)$_3$I$_4$"

246

R_3C——H

C

$R_3C \cdot$ or R_3C+
+
$[(N-Ns)_3I_4H]$
247

$R_3C \cdot$ or R_3C+

------→ alkene

F

G

radical clock
substrate

ring-opening

B

R_3C——H

"one-step"

D

E
246

R_3C——NHNs
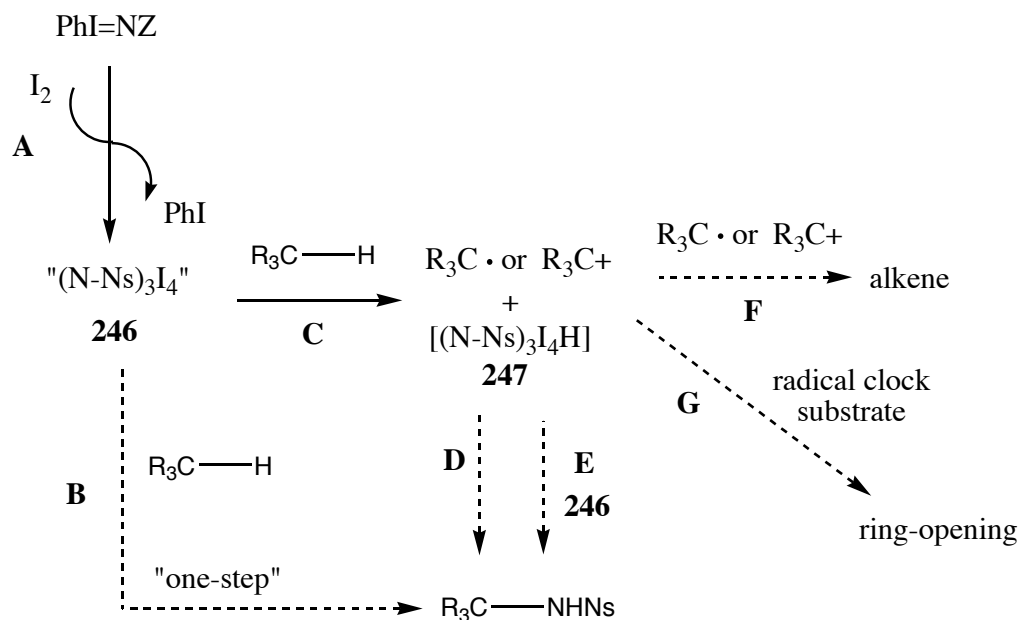
Figure 4.23

4.5   Summary and Conclusions

In summary, the first non-transition metal as well as the first non-metal catalyzed amidation of benzylic and simple saturated hydrocarbons has been developed. In the PhI=NTs/zinc-catalyzed system, it was discovered that water is needed in the reaction in order to facilitate a zinc-aquo or acid-catalyzed reaction. Moderate to good yields were obtained from a variety of benzylic substrates, as well as a saturated sp^3 C-H containing hydrocarbon, adamantane, by employment of an excess of the inexpensive hydrocarbon substrate. Even the simple employment of protic acids was shown to catalyze amidation of benzylic hydrocarbons with the best results being produced by 20 mol% of hydriodic acid.

In addition, we have found that 1°, 2°, and 3° benzylic substrates along with some saturated and unsaturated hydrocarbons can be amino-functionalized by

reaction of PhI=NZ catalyzed by inexpensive I_2. The resulting system is an operationally simple reaction conducted under very mild conditions that includes the employment of wet solvents at room temperature. Good to excellent yields of amidated products are obtained from secondary benzylic C-H containing substrates, with moderate-poor yields resulting from tertiary and primary benzylics. A number of saturated hydrocarbons also proved reactive, including the highest reported yield of a precursor to amantidine being obtained from the reaction of adamantane and PhI=NNs catalyzed by 20 mol% I_2. In addition, the first examples of 1,2-functionalization of unactivated C-H bonds in a single reaction using imido-iodinanes as aminating agents have been observed.

Mechanistic investigations of the I_2-catalyzed system have resulted in the isolation of a new and stable aminating reagent that can directly insert into benzylic and tertiary C-H bonds while only producing innocuous I_2 as by-product, as opposed to the production of toxic iodobenzene from employment of imidoiodinanes. In addition, mechanistic results such as the generation of alkenes from saturated hydrocarbons, formation of a pyrrolidine product from the radical clock experiment, and the detection of a relatively large ρ-value of -2.77 from a Hammett competition experiment, indicate a highly reactive two-step process in which hydrogen or hydride is abstracted and C-N bond formation quickly follows. The stereochemical result in which only one isomer was produced (indicating a concerted insertion) remains mysterious along with the nature of the solid aminating agent, though attempts to crystallize the compound may result in a more definitive elucidation.

4.6   Experimental

4.6.1 General Considerations

Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, or TCI America. Hydrocarbons used in production of aminosulfonated compounds were used without any purification. Compounds *cis*-**168** and *trans*-**244** were prepared within the Nicholas Group by reported procedure and were determined pure by comparison to known data.[181] Toluene and benzene were distilled prior to use over Na/benzophenone. Dichloromethane, acetonitrile, and dichloroethane were all distilled prior to use over CaH_2. All other solvents including those used in chromatography were used without any purification. Visualization of the developed chromatogram was performed under UV light or I_2 stain. ^{1}H NMR spectra were obtained at 300 MHz and ^{13}C NMR spectra at 75 MHz. NMR spectra were internally referenced to residual protio solvent signals. Data for ^{1}H NMR data are reported as follows: chemical shift (δ shift), multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets), coupling constant (Hz), integration, and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Mass spectra were acquired in methanol or CH_2Cl_2 solution by ESI. Naphthalene was used as an internal standard for GC yield determinations.

4.6.2 Preparation of Starting Materials

[{(*p*-Toluene)sulfonyl}imino]phenyliodinane (PhI=NTs)[62,182]

Method A: The title compound was prepared from PhI(OAc)$_2$, TsNH$_2$, and KOH in a MeOH solution and crystallized from H$_2$O without modification according to the procedure found in Reference 62.

Method B: The title compound was prepared from PhI(OAc)$_2$, TsNH$_2$, and KOH in a MeOH solution (with the temperature never rising >10°C) without modification according to the procedure found in Reference 182.

^{1}H NMR (DMSO-*d*-6, 300 MHz) δ 7.69 (d, 2H), 7.43 (m, 3H), 7.28 (t, 2H), 7.05 (d, 2H), 2.25 (s, 3H).

[{(4-Nitrophenyl)sulfonyl}imino]phenyliodinane (PhI=NNs)[183]

The title compound was prepared from PhI(OAc)$_2$, NsNH$_2$, and KOH in methanol and crystallized from H$_2$O without modification according to the procedure found in Reference 183. ^{1}H NMR (DMSO-*d*-6, 300 MHz) δ 8.04 (d, *J*=8.7 Hz, 2H), 7.74 (m, 4H), 7.42 (t, *J*=6.9 Hz, 1H), 7.24 (m, 2H).

Methyl 4-ethylbenzoate (214)[184]

The title compound was prepared in nearly quantitative yield from a mixture of 4-ethylbenzoic acid (1.00 g, 6.66 mmol), Fe$_2$(SO$_4$)$_3$ · 5H$_2$O (80 mg, 0.2 mmol), and 6 μL of conc. sulfuric acid stirred at room temperature overnight in MeOH (12.5 mL).

Solvent was removed *in vacuo* to yield the title compound as a colorless oil. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.89 (dd, *J*=4.5 Hz, *J*=1.2 Hz, 2H), 7.19 (dd, *J*=4.5 Hz, *J*=1.2 Hz, 2H), 3.83 (s, 3H), 2.63 (q, *J*=5.7 Hz, 2H), 1.19 (t, *J*=5.7 Hz, 3H).

(1,3-D$_2$) Tricyclo[3.3.1.1^{3,7}]decane (235)[31,162]

The title compound was prepared in nearly quantitative yield from 1,3-dibromo-adamantane (450 mg, 1.3 mmol), LiAlD$_4$ (56.3 mg, 1.31 mmol), [n]Bu$_3$SnCl (141 μL, 0.450 mmol), and 7 mL diethyl ether without modification according to procedure found in Reference 162. Deuterium enrichment of the product was determined by ^{1}H NMR integration by comparison to adamantane. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.88 (br m, 2H), 1.74 (d, *J*=3.3 Hz, 12H).

[(2-Phenylcyclopropyl)methyl]-benzene (165)[185]

First, *trans*-1,3-diphenylpropene was prepared in 68% yield from phenylacetaldehyde (6.04 g, 50.2 mmol) and KOH pellets (3.00 g, 53.4 mmol) in 20 mL ethanol without modification using a procedure found in Reference 186. Then, the title compound was prepared from *trans*-1,3-diphenylpropene (1.94 g, 10.0 mmol), Et$_2$Zn in hexanes (33.3 mL of 0.6M solution, 20.0 mmol), trifluoroacetic acid (1.54 mL, 20.0 mmol), and diiodomethane (1.61 mL, 20.0 mmol) in CH$_2$Cl$_2$ according to procedure found in Reference 187. After failed separation of the cyclopropane product and the *trans*-1,3-diphenylpropene by flash chromatography, the inseparable mixture was added to a 40% aq. NaOH solution containing [t]BuOH and excess KMnO$_4$. The mixture was stirred at room temperature overnight and the crude mixture was extracted with

diethyl ether, hexanes, then diethyl ether again and solvent was removed. The crude product was then passed through a short silica plug using hexanes as eluant to remove a brown impurity and after removal of solvent, the cyclopropyl product was pure by ^{1}H NMR without further distillation or chromatography necessary. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28-6.96 (m, 10H), 2.80-2.58 (m, 2H), 1.72 (m, 1H), 1.26 (m, 1H), 0.88 (m, 2H). GCMS (EI) 208 (M$^+$)

Hexacarbonyl[μ-{(2,3-η : 2,3-η)-4,4-dimethyl-2-pentyne}]dicobalt (Co-Co) (233)

The title compound was prepared from 4,4-dimethyl-2-pentyne (200 μL, 1.5 mmol) and dicobalt octacarbonyl (1.3 g, 3.0 mmol) in 10 mL CH$_2$Cl$_2$ following a procedure found in Reference 188. The mixture was stirred 30 minutes at room temperature, then solvent was removed. The solid was dissolved in hexanes and filtered with a basic alumina plug. The solution was then filtered through a silica plug and the solvent was removed. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.69 (s, 3H), 1.29 (s, 9H). – shifted from 1.78 and 1.19 –

STANDARD 1H OBSERVE

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Pulse Sequence: s2pul

Operator: kmn
INOVA-500 "ounmrB"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.998 sec
Width 4803.1 Hz
8 repetitions
OBSERVE   H1, 300.0685724 MHz
DATA PROCESSING
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Total time 0 min 25 sec

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3.00   9.21
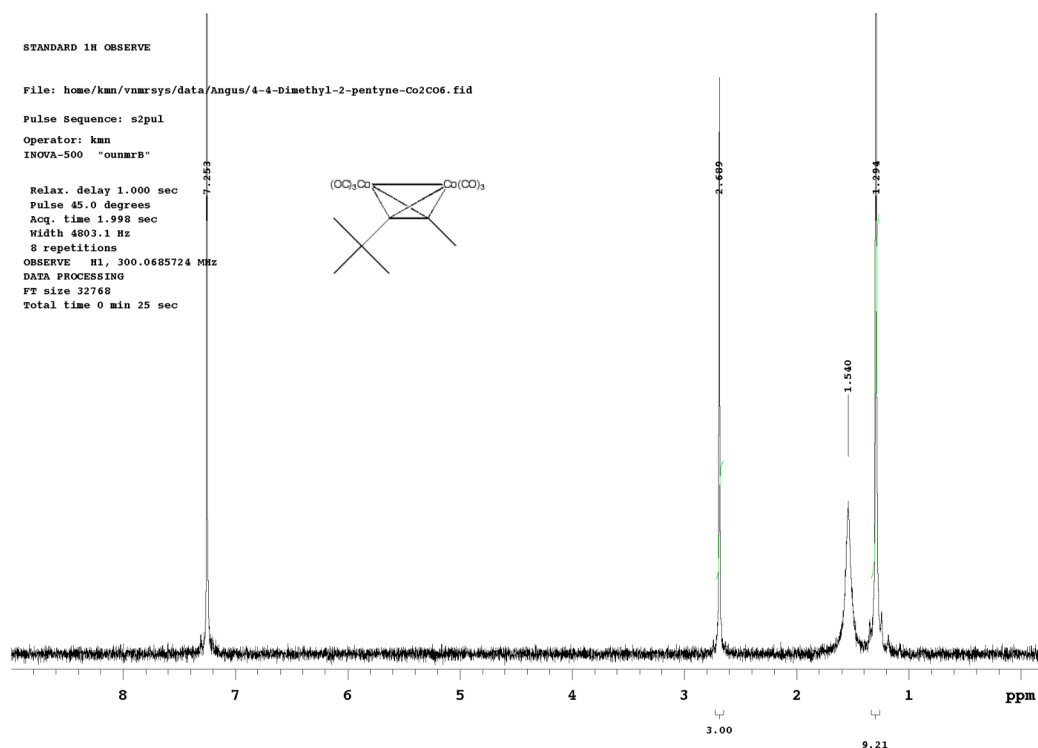
4.6.3 General Procedure for the Zinc-Catalyzed Aminosulfonation of Hydrocarbons Using Oven-Dried 4Å Molecular Sieves

To an oven-dried Schlenk tube (or a test tube) under N₂ was transferred anhydrous ZnBr2 (15-20 mol% of the substrate) and 2 mL of dry benzene. To this was added TsN=IPh (1.0 mmol), oven dried (110°C) 4 Å molecular sieves, hydrocarbon substrate (0.50 mmol), and another 3 mL of dry benzene by syringe. The suspension was stirred at room temperature (or at 50°C, Table 4.3) under N₂. Another 0.5 mmol of TsN=IPh was added to the reaction mixture under N₂ atmosphere after 5-6 h and stirring was continued for 6-24 additional hours during which the reaction mixture became almost homogenous and the color changed into dark brown. When TLC analysis indicated no further conversion, the reaction mixture was filtered

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through filter paper, washed with $CHCl_3$ (~15-20 ml) and the solvent removed by rotary evaporation. The crude residue was then purified by flash column chromatography or preparative thin layer chromatography by elution with ethyl acetate/petroleum ether mixtures.

4.6.4 General Procedure for the Hydrous Zinc-Catalyzed Aminosulfonation of Hydrocarbons

To an oven-dried test tube under N_2 was transferred anhydrous $ZnBr_2$ (15-20 mol% of the substrate) and 1 mL of dry benzene. To this was added TsN=IPh (0.50 mmol) all at once, hydrocarbon substrate (5.0 mmol), 1 equivalent H_2O (~9.0 μL) and another 2-3 mL of dry benzene by syringe. The suspension was stirred at $50^{\circ}C$ under argon overnight. When TLC analysis indicated no further conversion, the reaction mixture was filtered through filter paper, washed with $CHCl_3$ (~15-20 ml) and the solvent removed by rotary evaporation. The crude residue was then purified by flash column chromatography or preparative thin layer chromatography by elution with ethyl acetate/hexane mixtures.

[4-Methyl-*N*-(1-phenylethyl)-benzenesulfonamide] (171)[175]

The title compound was prepared in 45% yield by the general procedure (Method B) from ethylbenzene, PhI=NTs (prepared by Method B), $ZnBr_2$, and 1 equivalent H_2O in benzene at $50^{\circ}C$. ^1H NMR (CDCl$_3$, 300 MHz) δ 7.60 (d, *J*=7.5 Hz, 2H), 7.18 (m, 5H), 7.09 (m, 2H), 4.96 (d, *J*=6.6 Hz, 1H, NH), 4.45 (m, *J*=7.2 Hz, 1H), 2.37 (s, 3H), 1.41 (d, *J*=6.9 Hz, 3H). LRMS (ESI) 298 (M + Na$^+$).

_N_-[1-(4-Methoxyphenyl)ethyl]-4-methyl-benzenesulfonamide (181)[175]

The title compound was prepared in 54% yield by the general procedure (Method B)

from 4-ethylanisole, PhI=NTs (prepared by Method B), $ZnBr_2$, and 1 equivalent H_2O

in benzene at 50°C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.63 (dd, J=8.4 Hz, J=1.6 Hz, 2H),

7.21 (d, J=7.8 Hz, 2H), 7.01 (d, J=7.8 Hz, 2H), 6.73 (dd, J=9.0 Hz, J=2.7 Hz, 2H),

4.58 (m, 1H, NH), 4.42 (m, J=7.2 Hz, 1H), 3.77 (s, 3H). 2.41 (s, 3H), 1.42 (d, J=6.9

Hz, 3H). LRMS (ESI) 328 (M + Na$^+$).

_N_-Adamantan-1-yl-4-methyl-benzenesulfonamide (199)[175]

The title compound was prepared in 32% yield by the general procedure (Method B)

from adamantane, PhI=NTs (prepared by Method B), $ZnBr_2$, and 1 equivalent H_2O in

benzene at 50°C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.78 (d, J=8.1 Hz, 2H), 7.26 (d,

J=7.5 Hz, 2H), 4.64 (s, 1H, NH), 2.41 (s, 3H), 1.99 (br s, 3H), 1.77 (d, J=3.0 Hz, 6H),

1.57 (m, 6H). GCMS (EI) 305 (M$^+$).

4.6.5 Radical Inhibition Experiment with _p_-Methoxyphenol

To an oven-dried test tube under N_2 was transferred anhydrous $ZnBr_2$ (16.9

mg, 0.075 mmol) and 1.0 mL of dry benzene. To this was added TsN=IPh (187 mg,

0.50 mmol) all at once, ethylbenzene (620 μL, 5.0 mmol), 1.0 equivalent H_2O (9 μL,

0.5 mmol), naphthalene (10.0 mg, 1.28 mmol), _p_-methoxyphenol (62 mg, 0.5 mmol),

and another 2-3 mL of dry benzene by syringe. The suspension was stirred at 55°C

under argon. Samples were taken for GC yield determination at one hour, 5 hrs, and

~18 hrs. The yield of the aminosulfonated ethyl benzene product was determined by GC using naphthalene as internal standard to be 1% at each time period.

4.6.6 General Procedure for the Acid-Catalyzed Aminosulfonation of Ethylbenzene

To an oven-dried test tube under N_2 was transferred 1 mL of dry benzene. To this was added TsN=IPh (187 mg, 0.50 mmol) all at once, ethylbenzene (620 μL, 5.0 mmol), concentrated acid (0.05 mmol), the remainder of 1 equivalent H_2O, naphthalene (4.8-5.7 mg), and another 2-3 mL of dry benzene by syringe. The suspension was stirred at 55°C under argon overnight. Samples were taken for GC yield determination at ~14 hrs.

4.6.7 General Procedure for the Iodine-Catalyzed Aminosulfonation of Hydrocarbons

To a mixture of 1.25 mmol hydrocarbon, 0.050 mmol I_2, and 1-2 mL CH_2Cl_2 was added 0.250 mmol PhI=NZ (Z=Ts, Ns) all at once. The reaction vessel was then flushed with argon and stirred at room temperature 2-6 hours. Upon completion of the reaction, solvent was removed under vacuum and the crude mixture was isolated via flash chromatography over silica gel with CH_2Cl_2 as eluant (R_f of product typically 0.3-0.5), affording the amidated products, typically as solids.

N-Adamantan-1-yl-4-methyl-benzenesulfonamide (199)[175]

The title compound was prepared in 63% yield by the general procedure from adamantane, PhI=NTs (prepared by Method A), and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl_3, 300 MHz) δ 7.78 (d, J=8.1 Hz, 2H), 7.26 (d, J=7.5 Hz, 2H), 4.64 (s, 1H, NH), 2.41 (s, 3H), 1.99 (br s, 3H), 1.77 (d, J=3.0 Hz, 6H), 1.57 (m, 6H). GCMS (EI) 305 (M$^+$).

N-Adamantan-1-yl-4-nitro-benzenesulfonamide (223)[31]

The title compound was prepared in 97% yield by the general procedure from adamantane, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl_3, 300 MHz) δ 8.29 (dd, J=6.9 Hz, J=1.9 Hz, 2H), 8.02 (d, J=7.6 Hz, J=8.1 Hz, J=2.1 Hz, 2H), 4.79 (s, 1H, NH), 1.96 (br s, 3H), 1.73 (d, J=2.7 Hz, 6H), 1.54 (m, 6H). LRMS (ESI) 359 (M + Na$^+$).

[4-Methyl-N-(1-phenylethyl)-benzenesulfonamide] (171)[175]

The title compound was prepared in 78% yield by the general procedure from ethylbenzene, PhI=NTs (prepared by Method A), and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl_3, 300 MHz) δ 7.60 (d, J=7.5 Hz, 2H), 7.18 (m, 5H), 7.09 (m, 2H), 4.96 (d, J=6.6 Hz, 1H, NH), 4.45 (m, J=7.2 Hz, 1H), 2.37 (s, 3H), 1.41 (d, J=6.9 Hz, 3H). LRMS (ESI) 298 (M + Na$^+$).

[4-Nitro-*N*-(1-phenylethyl)-benzenesulfonamide] (209)[31]

The title compound was prepared in 73% yield by the general procedure from ethylbenzene, PhI=NNs, and I$_2$ in CH$_2$Cl$_2$ at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.06 (dd, *J*=6.9 Hz, *J*=1.8 Hz, 2H), 7.70 (d, *J*=6.3 Hz, *J*=2.4 Hz, 2H), 7.08 (m, 3H), 6.96 (m, 2H), 5.19 (d, *J*=7.2 Hz, 1H, NH), 4.53 (m, *J*=6.9 Hz, 1H), 1.41 (d, *J*=7.2 Hz, 3H). LRMS (ESI) 329 (M + Na$^+$).

N-[1-(4-Methoxyphenyl)ethyl]-4-methyl-benzenesulfonamide (181)[175]

The title compound was prepared in 91% yield by the general procedure from 4-ethylanisole, PhI=NTs (prepared by Method A), and I$_2$ in CH$_2$Cl$_2$ at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.63 (dd, *J*=8.4 Hz, *J*=1.6 Hz, 2H), 7.21 (d, *J*=7.8 Hz, 2H), 7.01 (d, *J*=7.8 Hz, 2H), 6.73 (dd, *J*=9.0 Hz, *J*=2.7 Hz, 2H), 4.58 (m, 1H, NH), 4.42 (m, *J*=7.2 Hz, 1H), 3.77 (s, 3H). 2.41 (s, 3H), 1.42 (d, *J*=6.9 Hz, 3H). LRMS (ESI) 328 (M + Na$^+$).

N-[1-(4-Methoxyphenyl)ethyl]-4-nitro-benzenesulfonamide (210)[31]

The title compound was prepared in 80% yield by the general procedure from 4-ethylanisole, PhI=NNs, and I$_2$ in CH$_2$Cl$_2$ at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.12 (d, *J*=9.0 Hz, 2H), 7.76 (d, *J*=8.7 Hz, 2H), 6.93 (d, *J*=8.1 Hz, 2H), 6.62 (d, *J*=8.4 Hz, 2H), 5.18 (d, *J*=6.3 Hz, 1H, NH), 4.52 (m, *J*=6.7 Hz, 1H), 3.96 (s, 3H). 1.43 (d, *J*=7.2 Hz, 3H). LRMS (ESI) 359 (M + Na$^+$).

N-Indan-1-yl-4-methyl-benzenesulfonamide (189)[175]

The title compound was prepared in 72% yield by the general procedure from indan, PhI=NTs (prepared by Method A), and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.83 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H), 7.13 (m, 4H), 4.80 (m, 2H), 2.90 (m, 1H), 2.76 (m, 1H), 2.45 (s, 3H). 2.30 (m, 1H), 1.76 (m, 1H). LRMS (ESI) 310 (M + Na^{+}).

N-Indan-1-yl-4-nitro-benzenesulfonamide (211)[31]

The title compound was prepared in 60% yield by the general procedure from indan, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.34 (dd, J=8.7 Hz, J=2.4 Hz, 2H), 8.05 (d, J=8.7 Hz, J=2.4 Hz, 2H), 7.18 (m, 4H), 4.84 (m, 2H), 2.85 (m, 1H), 2.71 (m, 1H), 2.31 (m, 1H). 1.71 (m, 1H). LRMS (ESI) 341 (M + Na^{+}).

4-Methyl-N-(1-p-nitrophenyl-ethyl)-benzenesulfonamide (212)[31]

The title compound was prepared in 50% yield by the general procedure from 4-ethyltoluene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.06 (d, J=9.0 Hz, 2H), 7.70 (d, J=8.1 Hz, 2H), 6.86 (m, 4H), 5.12 (d, J=7.2 Hz, 1H, NH), 4.48 (m, J=7.2 Hz, 1H), 2.17 (s, 3H), 1.39 (d, J=7.5 Hz, 3H). LRMS (ESI) 343 (M + Na^{+}).

4-Nitro-N-[1-(4-Iodo-phenyl)-ethyl]-benzenesulfonamide (213)

The title compound (white solid) was prepared in 57% yield by the general procedure from 4-iodo-ethylbenzene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. m.p. 192-194 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.13 (dd, 2H, J=8.1 and 1.8 Hz), 7.73 (dd, 2H, J=7.8 and 2.4 Hz), 7.43 (dd, 2H, J=6.6 and 1.8 Hz), 6.76 (dd, 2H, J=6.6 and 1.8 Hz), 4.85 (d, 1H, J=6.3 Hz), 4.51-4.46 (m, 1H), 1.38 (d, 3H, J=6.9 Hz). ^{13}C NMR (CDCl$_3$ 75 MHz) δ 146.4, 140.6, 137.7, 128.2, 124.1, 110.0, 93.4, 53.7, 23.4. HRMS (ESI) calculated for $C_{14}IN_2SO_4H_{13}$ (M+Na$^+$) requires m/z 454.9538, found m/z 454.9560.

STANDARD PROTON PARAMETERS

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WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 11 hr, 24 min

4-Nitro-*N*-(1-methyl-1-phenyl-ethyl)-benzenesulfonamide (218)[31]

The title compound was prepared in 40% yield by the general procedure from cumene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, *J*=8.1 Hz, 2H), 7.67 (d, *J*=8.1 Hz, 2H), 7.20 (dd, *J*=8.1 Hz, *J*=2.4 Hz, 2H), 7.12 (m, 3H), 5.30 (s, 1H, NH), 1.70 (s, 6H). LRMS (ESI) 343 (M + Na$^+$).

4-Nitro-*N*-(1-methyl-1-phenyl-2-iodoethyl)-benzenesulfonamide (219)

The title compound (tan solid) was prepared in 14% yield by the general procedure from cumene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. m.p. 133-135 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, 2H, *J*=9.3 Hz), 7.69 (d, 2H, *J*=9.0 Hz), 7.19-7.13 (m, 5H), 5.29 (s, 1H), 3.78 (d, 1H, *J*=10.8 Hz), 3.52 (d, 1H, *J*=10.5 Hz), 1.76 (s, 3H). ^{13}C NMR ($CDCl_3$ 75 MHz) δ 152.3, 150.2, 142.0, 131.2, 131.0, 129.0, 127.1, 126.6, 62.9, 29.9, 23.1.   HRMS (ESI) calculated for $C_{15}IN_2SO_4H_{15}$ (M+Na$^+$) requires *m/z* 468.9695, found *m/z* 468.9667.

Sample: hydroxyrouge
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Operator: kmn

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16 repetitions
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DATA PROCESSING
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Total time 0 min 45 sec

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7.154
7.138
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0.000

2.00
2.00
4.93
1.04
1.14
1.17
3.30

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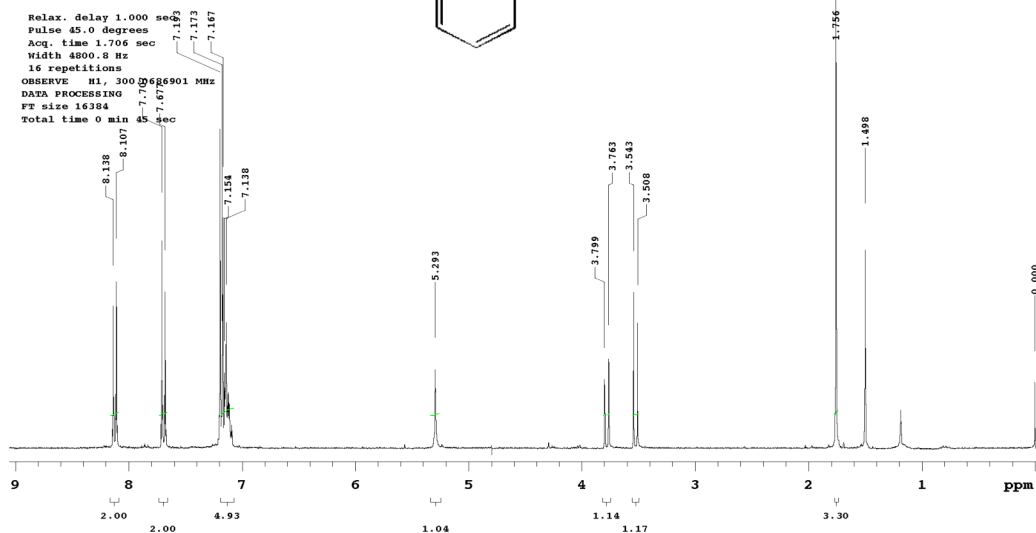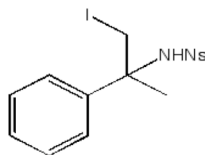
STANDARD PROTON PARAMETERS

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Operator: kmn

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DECOUPLE H1, 300.0702244 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 12 hr, 37 min

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142.030
131.163
130.950
128.965
127.119
126.584
80.109
79.880
79.682
79.255
78.980
62.939
29.925
23.057

180   160   140   120   100   80   60   40   20   ppm

178
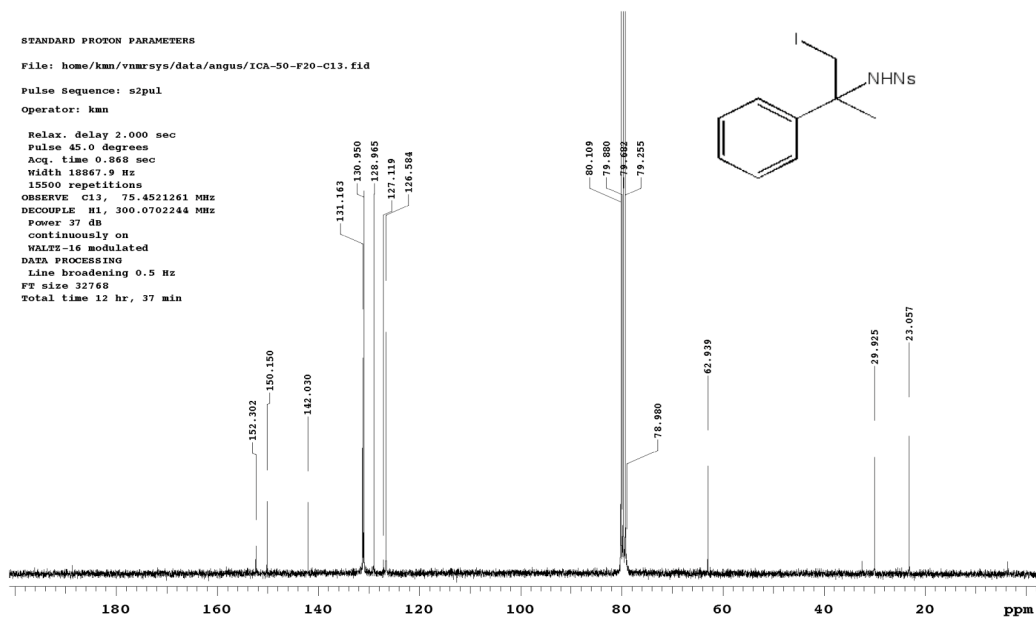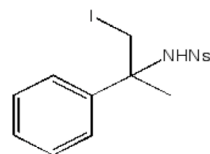
<u>*N*-(1-Methyl-1-phenylpropyl)-4-nitrobenzenesulfonamide (217)[31]</u>

The title compound was prepared in 24% yield by the general procedure from 2-butylbenzene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, *J*=8.4 Hz, 2H), 7.59 (dd, *J*=6.6 Hz, *J*=1.8 Hz, 2H), 7.04 (m, 5H), 5.11 (s, 1H, NH), 1.89 (m, 2H), 1.63 (s, 3H), 0.68 (t, *J*=7.5 Hz, 3H). LRMS (ESI) 357 (M + Na$^+$).

<u>Methyl-[4-{1-(4-nitrophenyl)sulfonylimino}ethyl]-benzoate (215)</u>

The title compound was prepared in 6% yield by the general procedure from methyl-4-ethylbenzoate, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J*=7.8 Hz, 2H), 7.88 (m, 5H), 7.43 (d, *J*=8.4 Hz, 2H), 5.73 (q, *J*=7.8 Hz, 1H), 3.91 (s, 3H), 1.69 (d, *J*=6.9 Hz, 3H).
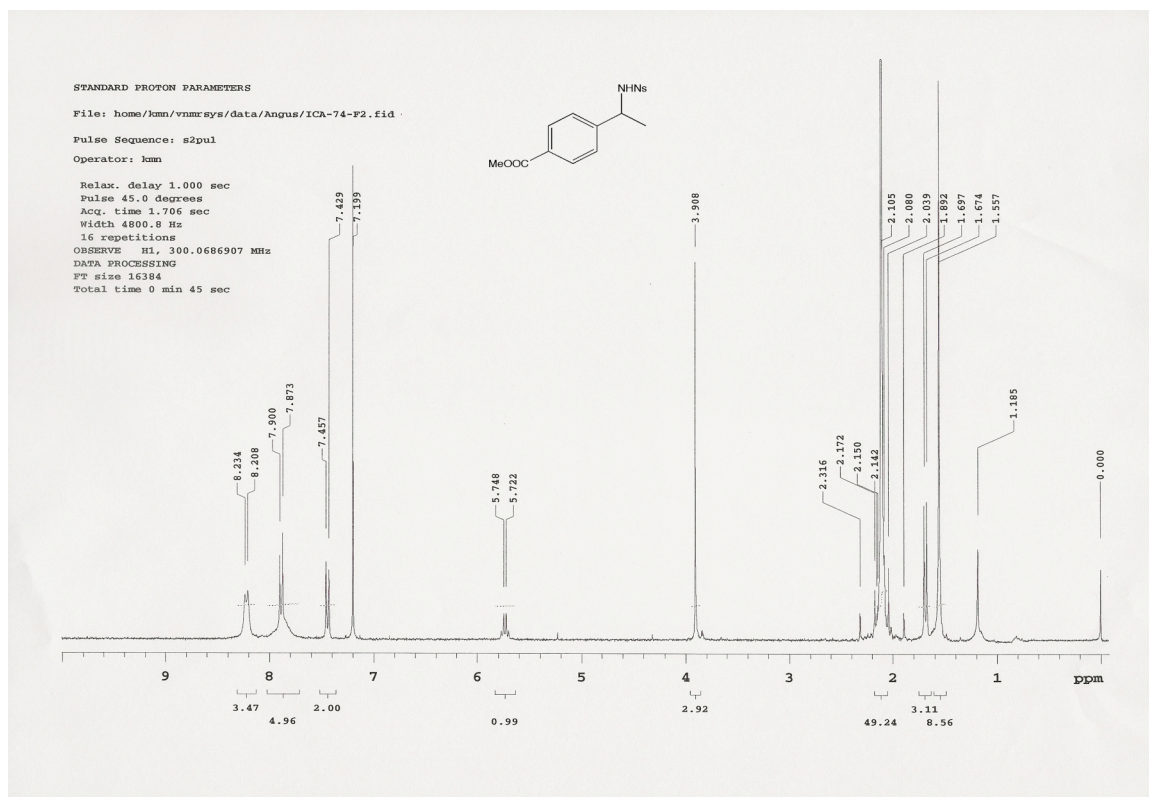
<u>**4-Nitro-*N*-(phenylmethyl)benzenesulfonamide (222)**</u>[31]

The title compound was prepared in 13% yield by the general procedure from dry toluene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.25 (dd, *J*=7.2 Hz, *J*=1.8 Hz, 2H), 7.93 (dd, *J*=7.2 Hz, *J*=1.8 Hz, 2H), 7.20 (m, 3H), 7.10 (m, 2H), 4.87 (br t, 1H, NH), 4.17 (d, *J*=6.3 Hz, 2H). LRMS (ESI) 315 (M + Na$^+$).

<u>**4-Nitro-*N*-trityl-benzenesulfonamide (220)**</u>

The title compound was prepared in 24% yield by the general procedure from triphenylmethane, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.73 (d, *J*=8.1 Hz, 2H), 7.51 (t, *J*=6.9 Hz, 1H), 7.40 (t, *J*=7.5 Hz, 2H), 7.20 (m, 14H), 2.76 (s, 1H, NH).
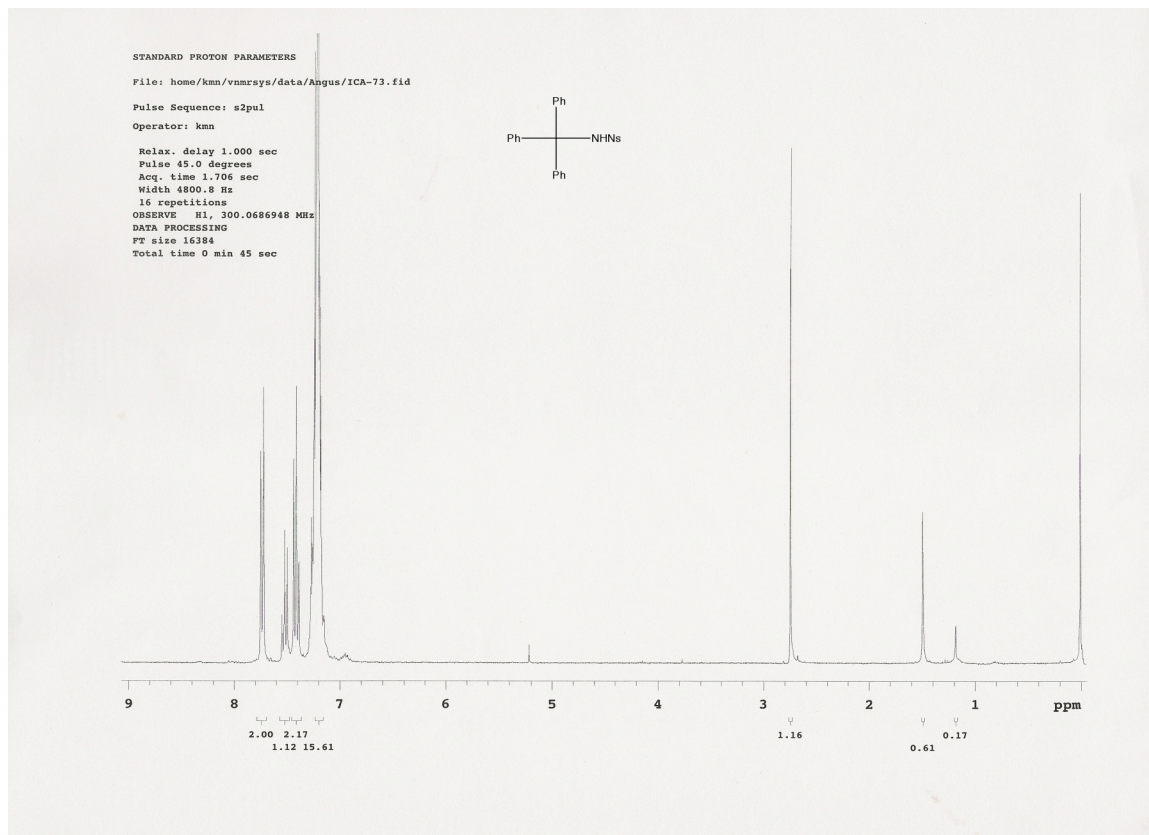
_N_-(Bicyclo[2.2.1]hept-2-exo-yl)-4-nitrobenzenesulfonamide (225)[31]

The title compound was prepared in 20% yield by the general procedure from norbornane, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (d, _J_=8.7 Hz, 2H), 7.99 (d, _J_=8.4 Hz, 2H), 4.51 (d, _J_=7.5 Hz, 1H, NH), 3.16 (dt, _J_=7.5 Hz, _J_=3.0 Hz, 1H), 2.17 (br s, 1H), 2.04 (br s, 1H), 1.59 (m, 1H), 1.45-0.99 (m, 7H). LRMS (ESI) 319 (M + Na^+).

_N_-Cyclohex-2-enyl-4-nitrobenzenesulfonamide (229)[31]

The title compound was prepared as an inseparable mixture with **227** in 24% total yield (in a 3 : 2 ratio of **229/227** as determined by ^{1}H NMR analysis) by the general procedure from cyclohexene, PhI=NNs, and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31* (d, 2H), 8.31 (d, 2H), 8.02* (d, 2H), 8.02 (d, 2H), 5.78* (m, 1H), 5.28* (m, 1H), 4.80 (d, _J_=7.5 Hz, 1H), 4.61* (d, _J_=6.6 Hz, 1H), 3.82* (m, 1H), 3.81 (m, 1H), 3.20 (m, 1H), 2.42-2.20 (m, 2H), 2.00-1.83 (m, 1H), 1.95* (m, 2H), 1.78* (m, 1H), 1.75 (m, 1H), 1.50* (m, 3H), 1.48 (m, 1H), 1.40-1.10 (m, 3H). (NOTE – peaks marked * correspond to **229**)

_N_-Cyclohex-2-enyl-4-methyl-benzenesulfonamide (196)[175]

The title compound was prepared as an inseparable mixture with **228** in 39% total yield (in a 1 : 1 ratio of **196/228** as determined by ^{1}HNMR) by the general procedure from cyclohexene, PhI=NTs (prepared by Method A), and I_2 in CH_2Cl_2 at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72* (d, 2H), 7.70 (d, 2H), 7.24* (d, 2H), 7.21 (d, 2H), 5.69* (m, 1H), 5.28* (m, 1H), 4.87 (d, _J_=6.3 Hz, 1H, NH), 4.54*

(d, *J*=9.9 Hz, 1H, NH), 3.90 (m, 1H), 3.75* (m, 1H), 3.19 (m, 1H), 2.39* (s, 3H), 2.39 (s, 3H), 2.21 (m, 2H), 1.90* (m, 2H), 1.88-1.20 (m, 6H), 1.71* (m, 1H), 1.52* (m, 3H). (NOTE – peaks marked * correspond to **196**)

N-(2-Iodo-cyclohexyl)-4-nitro-benzenesulfonamide (227)

The title compound (white solid) was prepared in 17% yield by the general procedure from cyclohexane, PhI=NNs, and I_2 in DCE at 75°C. m.p. 177-180 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.31 (d, 2H, *J*=9.0 Hz), 8.02 (d, 2H, *J*=9.9 Hz), 4.73 (d, 1H, *J*=10.2 Hz), 3.84-3.75 (dt, 1H, *J*=10.8 and 3.9 Hz), 3.25-3.16 (m, 1H), 2.42-2.20 (m, 2H), 2.00-1.83 (m, 1H), 1.79-1.70 (m, 1H), 1.48 (m, 1H), 1.40-1.10 (m, 3H). ^{13}C NMR (CD$_2$Cl$_2$ 75 MHz) δ 148.7, 131.4, 127.0, 126.9, 63.1, 42.0, 37.6, 37.2, 30.0, 26.9. HRMS (ESI) calculated for $C_{12}IN_2SO_4H_{15}$ (M+Na$^+$) requires *m/z* 432.9695, found *m/z* 432.9696. It remains difficult to definitively state whether the vicinal substitution is *cis* or *trans*. Observed coupling values could be within the range of either, and no additional investigation was conducted.

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16 repetitions
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DATA PROCESSING
FT size 16384
Total time 0 min 45 sec

Pulse Sequence: s2pul

Operator: kmn

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
13000 repetitions
OBSERVE C13, 75.4522709 MHz
DECOUPLE H1, 300.0708005 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 10 hr, 35 min

183

4.6.8 General Procedures for the Mechanistic Experiments

Kinetic Isotope Experiment

To a mixture of 1,3-d_2-adamantane **235** (40.0 mg, 0.290 mmol), iodine (7.4 mg, 0.029 mmol), and 1-1.5 mL of anhydrous CH_2Cl_2 was added PhI=NZ (Z = Ns, 59 mg; Z = Ts, 54 mg; 0.145 mmol) under argon at room temperature and stirred overnight. Upon completion of the reaction, solvent was removed under vacuum and the crude mixture was isolated via flash chromatography over silica gel with CH_2Cl_2 as eluant. The isolated white solid was then dissolved in MeOH and the solvent removed via rotary evaporator a series of five times. The solid was then analyzed by MS-ESI, and the theoretical natural abundance isotopic contribution of pure D_1-Ad-NHZ (as calculated by Dr. Foster) was subtracted from the overall abundance of D_2-Ad-NHZ.
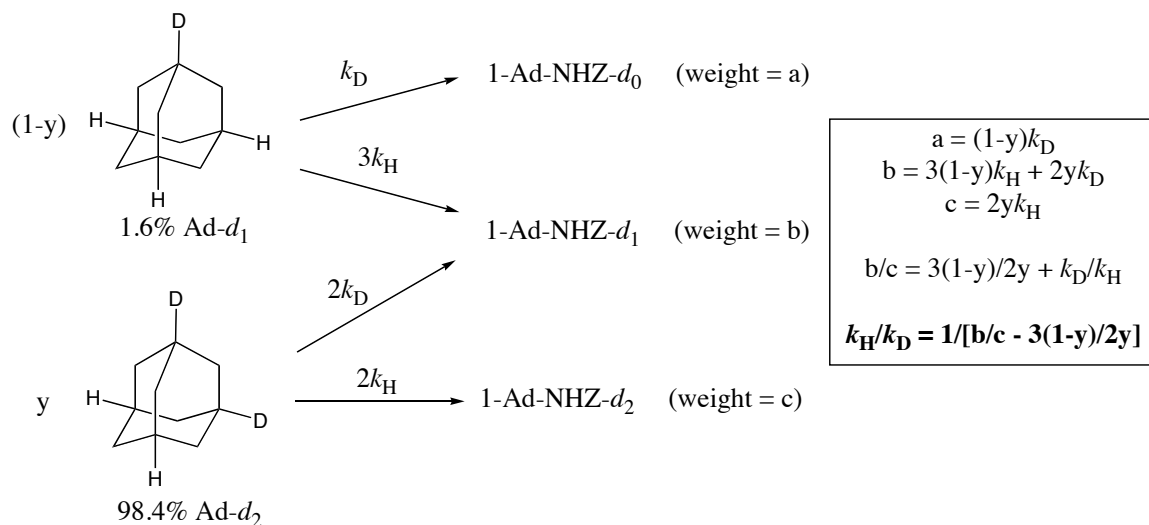
Figure 4.24[162]

[D$_1$-D$_2$]-236,237 (Ts)

MS-ESI observed abundances: D_1-**236** [329 (M + Na$^+$)] = 8930. Theoretical isotopic natural abundance contribution of D_1-**236** to D_2-**237** = 20.49% (1829.8). D_2-**237** [330

184

(M + Na$^+$)] = 42500 (40670 after subtraction of natural contribution). k_H/k_D = D$_2$/D$_1$ =

40670/8930 = 4.55   (82% D$_2$-**237**, 18% D$_1$-**236)**

Calculational correction: k_H/k_D = 1/[(8930/40670) – 3(0.016)/2(0.984)] = 5.123

[D$_1$-D$_2$]-**238,239** (Ns)

MS-ESI observed abundances: D$_1$-**238** [360 (M + Na$^+$)] = 3590. Theoretical isotopic

natural abundance contribution of D$_1$-**238** to D$_2$-**239** = 19.77% (709.7). D$_2$-**239** [361

(M + Na$^+$)] = 9730 (9021 after subtraction of natural contribution). k_H/k_D = D$_2$/D$_1$ =

9021/3590 = 2.51   (72% D$_2$-**239**, 28% D$_1$-**238)**

Calculational correction: k_H/k_D = 1/[(3590/9021) – 3(0.016)/2(0.984)] = 2.68

Hammett Analysis via Competition Experiments of Ethylbenzene versus

p-Substituted Ethylbenzene Substrates

To a mixture of 1.25 mmol *p*-substituted ethylbenzene, 1.25 mmol

ethylbenzene, 0.050 mmol I$_2$, and 1-2 mL CH$_2$Cl$_2$ was added 0.250 mmol PhI=NNs

all at once. The reaction vessel was then flushed with argon and stirred overnight.

Upon completion of the reaction, samples were taken for GC yield determination. The

ratio of aminosulfonated products was determined by GC using previously

determined mass ratios of both products as well as using naphthalene as internal

standard.

<u>Radical Clock Substrate Test Reaction</u>

To a mixture of [(2-phenylcyclopropyl)methyl]-benzene (131 mg, 0.625 mmol), iodine (6.8 mg, 0.025 mmol), and 1-2 mL CH_2Cl_2 was added PhI=NNs (51.0 mg, 0.125 mmol) all at once. The reaction vessel was then flushed with argon and stirred at room temperature overnight. Upon completion of the reaction, solvent was removed under vacuum and the crude mixture was isolated via preparatory TLC with CH_2Cl_2 as eluant, affording the pyrrolidine product as a white solid in 14% yield (or 69% relative to I_2) without observation of any other amidated products.

<u>3-Iodo-2,5-diphenyl-1-nosylpyrrolidine (241)</u>

^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.91 (dd, J=11.1 Hz, J=2.4 Hz, 2H), 7.30 (m, 9H), 7.16 (m, 3H), 5.41 (d, J=2.4 Hz, 1H), 5.22 (dd, J=9.3 Hz, J=5.4 Hz, 1H), 4.36 (dt, J=7.2 Hz, J=7.8 Hz, J=4.5 Hz, 1H), 3.19 (m, 1H), 2.50 (dt, J=20.7 Hz, J=5.4 Hz, J=4.5 Hz, 1H). ^{13}C NMR (CDCl$_3$ 75 MHz) δ 164.7, 149.1, 146.7, 138.8, 138.6, 129.3, 128.9, 128.6, 128.3, 128.1, 126.8, 123.3, 77.8. 65.5, 45.5, 24.5. HRMS (ESI) calculated for C$_{22}$IN$_2$SO$_4$H$_{19}$ (M+Na$^+$) requires *m/z* 557.0008, found *m/z* 556.9981. In the NOESY spectrum of **241**, cross-peaks were observed between H-**A**/H-**E**, H-**D**/H-**B**, and H-**E**/H-**C**.

KEY NOESY INTERACTIONS
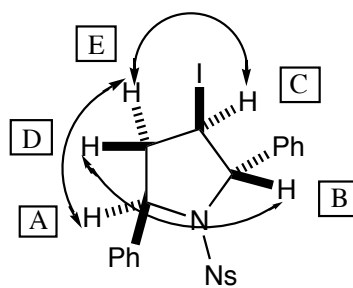
241

Figure 4.25
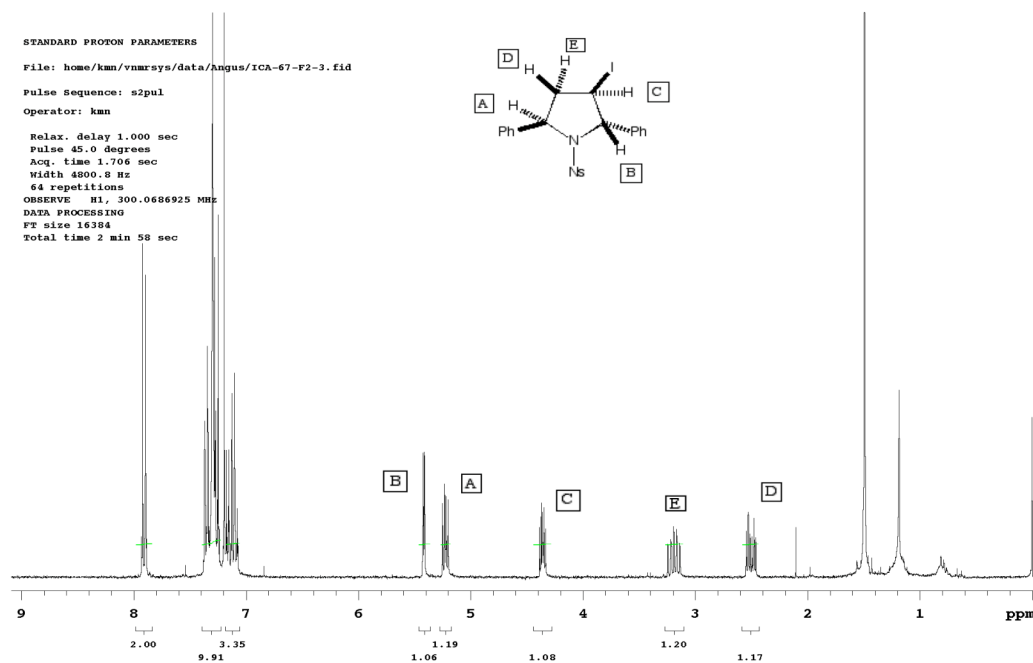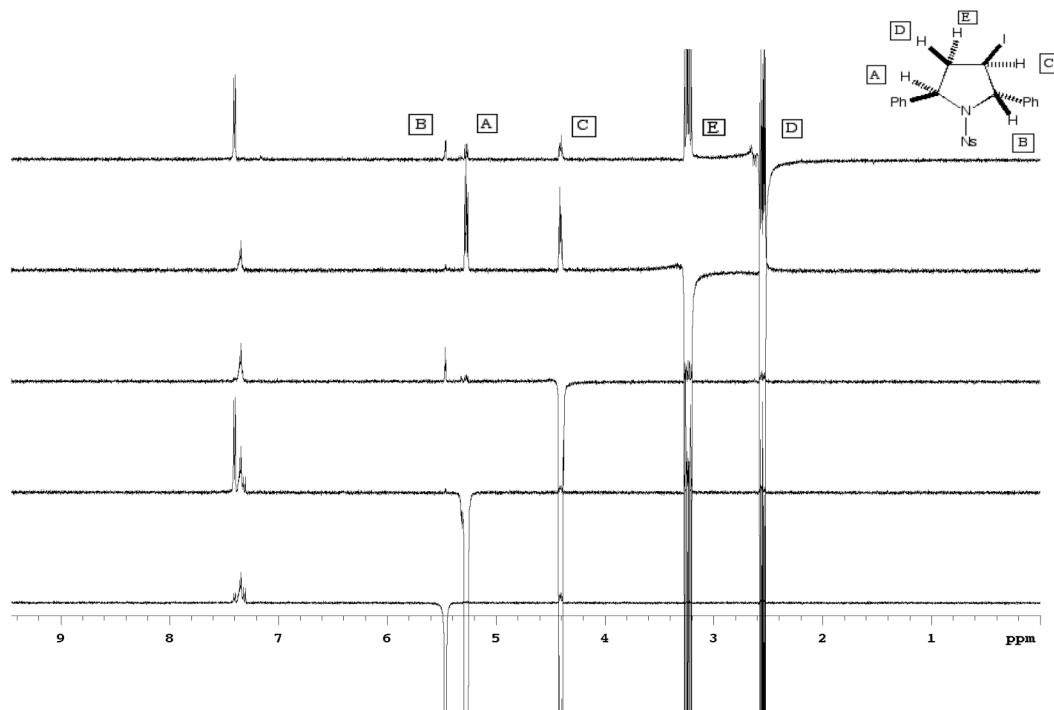
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  Selective band center: 5.30 (ppm); width: 31.4 (Hz)
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DATA PROCESSING
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STANDARD PROTON PARAMETERS

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Pulse Sequence: s2pul

Operator: kmn

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13000 repetitions
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DECOUPLE H1, 300.0702244 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 14 hr, 39 min

189

Stereochemical Test of *cis*-**168** with PhI=NNs

To a mixture of [*cis*-4-(*tert*-butyl)cyclohexyl]-benzene **168** (135 mg, 0.625 mmol), iodine (6.8 mg, 0.025 mmol), and 1-2 mL CH_2Cl_2 was added PhI=NNs (50.5 mg, 0.125 mmol) all at once. The reaction vessel was then flushed with argon and stirred at room temperature overnight. Upon completion of the reaction, solvent was removed under vacuum and the crude mixture was isolated via preparatory TLC with CH_2Cl_2 as eluant, affording the aminosulfonated product **242** as a white solid in 15% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.91 (d, *J*=6.0 Hz, 2H), 7.33 (d, *J*=6.0 Hz, 2H), 7.11 (d, *J*=6.0 Hz, 2H), 6.99 (m, 3H), 4.82 (s, 1H, NH), 2.76 (d, *J*=8.4 Hz, 2H), 1.75 (t, *J*=5.6 Hz, 2H), 1.59 (d, *J*=10.2 Hz, 2H), 1.04 (m, 1H), 0.84 (m, 3H), 0.64 (s, 9H). ^{13}C NMR (CDCl$_3$ 75 MHz) δ 149.0, 147.7, 137.5, 128.2, 128.1, 127.8, 127.6, 123.4, 61.0, 47.5, 38.3, 32.2, 27.4, 23.7. LRMS (ESI) 471 (M + Na$^+$).
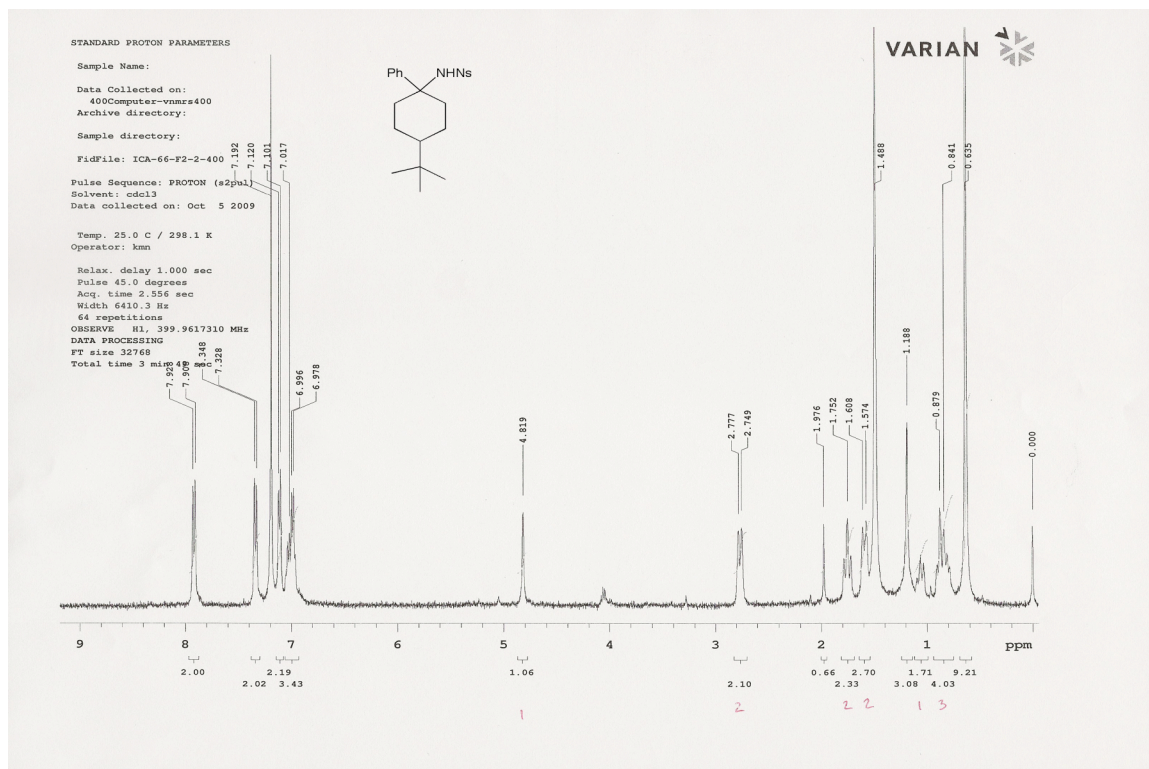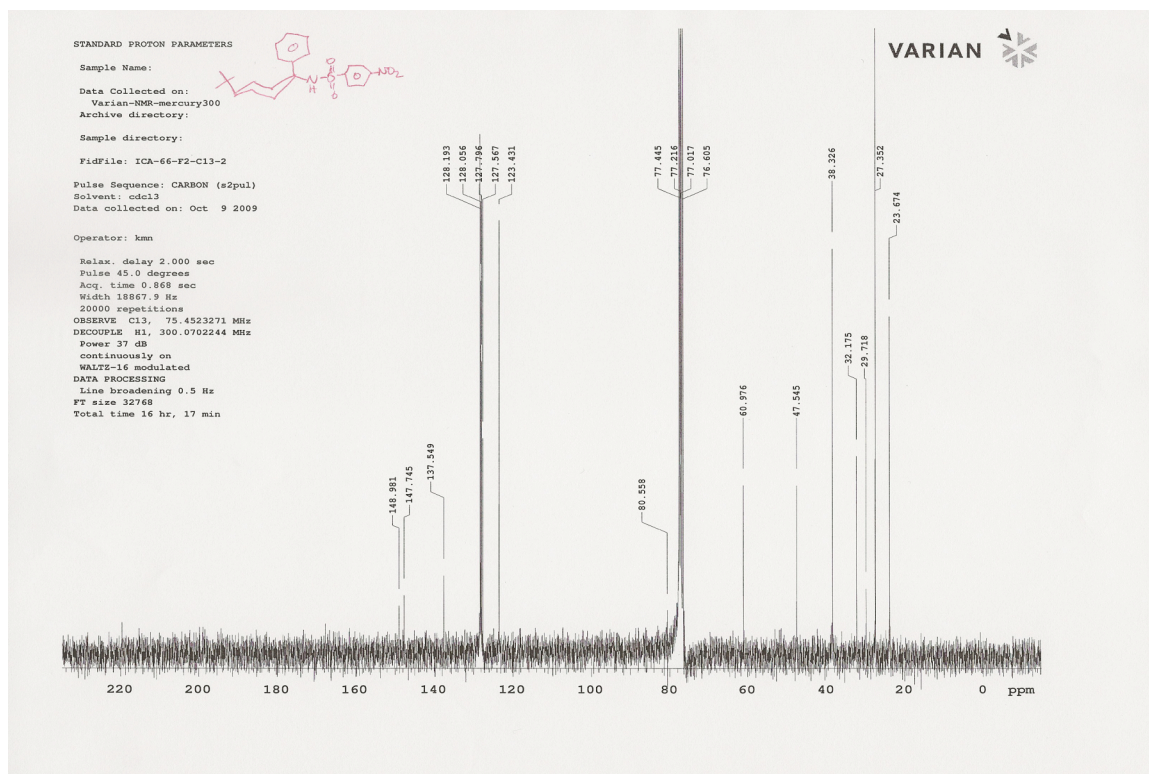
¹H NMR Experiment for Isolation of Solid (N-Ns)₃I₄

To a vial containing 1.5 mL of CD$_2$Cl$_2$ was added PhI=NNs (20 mg, 0.05 mmol), and the insoluble slurry was stirred 15 minutes at room temperature in the air before the entire sample was subjected to ¹H NMR analysis (labeled ICA-80-1). Iodine (12.6 mg, 0.050 mmol) was then added and the mixture was stirred in air an additional 15 minutes before ¹H NMR analysis (labeled ICA-80-2). To the reaction mixture was then added adamantane (6.3 mg, 0.050 mmol) and the mixture was stirred 15 minutes at room temperature in air before a ¹H NMR spectra was obtained (labeled ICA-80-3). After stirring the mixture an additional 1.5 hrs, another ¹H NMR spectrum was obtained (labeled ICA-80-4), and finally after allowing the reaction to stir overnight, an ¹H NMR spectrum was obtained and labeled ICA-80-5.

STANDARD PROTON PARAMETERS

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Operator: kmn

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Width 4800.8 Hz
64 repetitions
OBSERVE   H1, 300.0692462 MHz
DATA PROCESSING
FT size 16384
Total time 2 min 58 sec

ICA-80-1 (PhI=NNs)

STANDARD PROTON PARAMETERS

File: home/kmn/vnmrsys/data/Angus/ICA-80-2.fid

Pulse Sequence: s2pul

Operator: kmn

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4800.8 Hz
64 repetitions
OBSERVE   H1, 300.0692462 MHz
DATA PROCESSING
FT size 16384
Total time 2 min 58 sec

ICA -80-2 (PhI=NNs + Iodine)

STANDARD PROTON PARAMETERS

File: home/kmn/vnmrsys/data/Angus/ICA-80-3.fid

Pulse Sequence: s2pul

Operator: kmn

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4800.8 Hz
64 repetitions
OBSERVE   H1, 300.0692462 MHz
DATA PROCESSING
FT size 16384
Total time 2 min 58 sec

ICA-80-3 (PhI=NNs, Iodine,
Adamantane, 15 minutes)

STANDARD PROTON PARAMETERS

File: home/kmn/vnmrsys/data/Angus/ICA-80-4.fid

Pulse Sequence: s2pul

Operator: kmn

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.706 sec
Width 4800.8 Hz
64 repetitions
OBSERVE   H1, 300.0692462 MHz
DATA PROCESSING
FT size 16384
Total time 2 min 58 sec

ICA-80-4 (PhI=NNs, Iodine,
Adamantane, 1.5 hours)

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ICA-80-5 (PhI=NNs, Iodine, Adamantane, overnight)

Isolation of Solid (N-Ns)$_3$I$_4$

To a heterogeneous mixture of PhI=NNs (100 mg, 0.25 mmol) in 3-4 mL CH$_2$Cl$_2$ was added iodine (63 mg, 0.25 mmol) and the mixture was stirred at room temperature in air 15 minutes. The dark orange precipitate was then filtered in air and rinsed three times with CH$_2$Cl$_2$ to remove any residual PhI and/or I$_2$. The solid (~65 mg) was then dried *in vacuo* and flushed with argon before storage < 0°C. ^{1}H NMR (DMSO-*d*-6, 300 MHz) δ 8.47 (dd, *J*=7.8 Hz, *J*=2.4 Hz, 2H), 8.15 (dd, *J*=7.8 Hz, *J*=1.8 Hz, 2H). Elemental Analysis: 16.0% C, 5.93% N, 0.99% H, 36.10% I; 1.49 : 1 ratio of N to I; ratios of 4I, 6N, 18C, 12H.

Reaction of Solid (N-Ns)₃I₄ with Adamantane

To adamantane (8.4 mg) in 1.5 mL CD_2Cl_2 was added 7.8 mg of orange solid (N-Ns)₃I₄ and the heterogeneous mixture was stirred at room temperature in air 2 hours. The mixture became a dark red homogeneous solution and ¹H NMR analysis was performed directly on the crude solution (labeled ICA-82-1).

ICA-82-1 (Orange Solid + Adamantane)
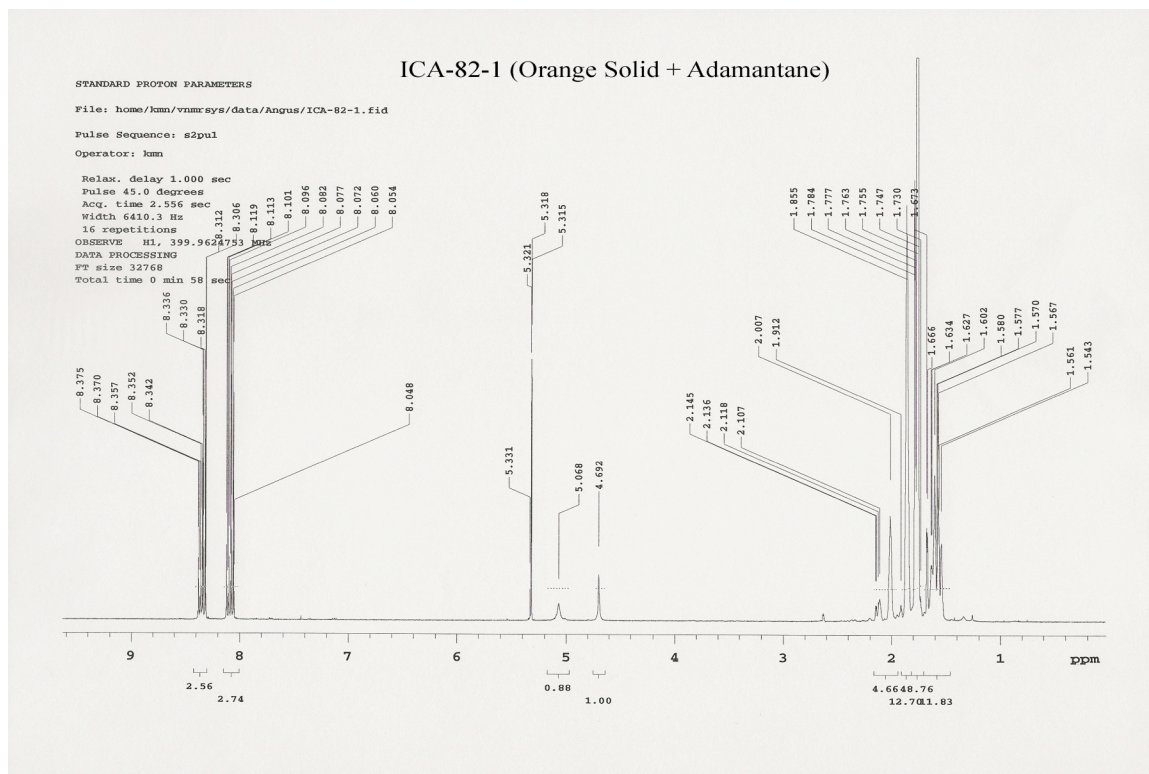
Procedure for UV-Vis Detection of Iodine from Reaction of Adamantane with Solid (N-Ns)₃I₄

To a quartz UV-Vis cuvette was added 5.4 mg of adamantane, 3-4 mL of wet CH_2Cl_2, and 5.0 mg of orange solid (N-Ns)₃I₄. Absorbance (at 504.2 λ-max) was measured at time 0 minutes, then the mixture was stirred in air at room temperature. Absorbance was measured every 5 minutes, and solvent was added as needed (due to evaporation) to maintain a full cuvette.

CHAPTER 5

PROJECT SUMMARY AND FUTURE PLANS

5.1   Project Summary

As a result of our investigations into the discovery of new methodologies to form C-N bonds from transition metal-catalyzed C-H activation of hydrocarbons, we were able to successfully contribute to three areas of our overall project, *i.e.* milder allylic amination using nitroaromatics, *N*-containing heterocycle formation, and the direct amination of saturated hydrocarbons via nitrenoid precursors. Several of the developments made in these areas could additionally serve as platforms for further investigation and application within the context of the overall research project.

Our attempts to develop a new catalytic allylic amination from nitrobenzene without the use of high pressures of CO and high temperatures were met with moderate success. Initially discovered by screening a number of heterogeous and homogeneous catalysts, the $NaBH_4$/Fe(Pc) promoted reaction represents the first example of a mild bench-top allylic amination from nitroaromatics without the requirement of stoichiometric CO (Figure 5.1). The allylic amination of α-methylstyrene resulted in low yields of the desired product (10-15%) and was consistently accompanied by large amounts of deleterious by-products. Though inefficient, the reaction remains novel and further investigation into the nature of the active catalyst could result in a synthetically useful reaction.

Mild NaBH$_4$/Fe(Pc) Promoted Allylic Amination of α-Methylstyrene by Nitrobenzene
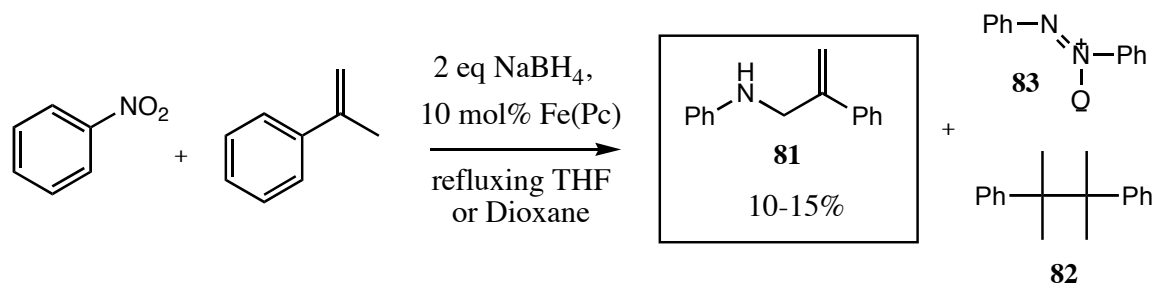
Figure 5.1

In addition to the development of new catalytic methods of nitroaromatic reductive allylic amination, attempts to improve the conditions of the current high pressure and temperature system were also met with success. For example, the first microwave-assisted procedure for allylic amination from nitroaromatics was developed by employing either one atm CO, or one equivalent Fe(CO)$_5$ as stoichiometric CO source (Figure 5.2). Yields obtained were relatively low (~20%), however, the procedure is performed in a more widely available reactor and requires shorter reaction times than the previously reported high pressure and temperature system.

Fe-Catalyzed Microwave Assisted Allylic Amination of Nitrobenzene and α-Methylstyrene
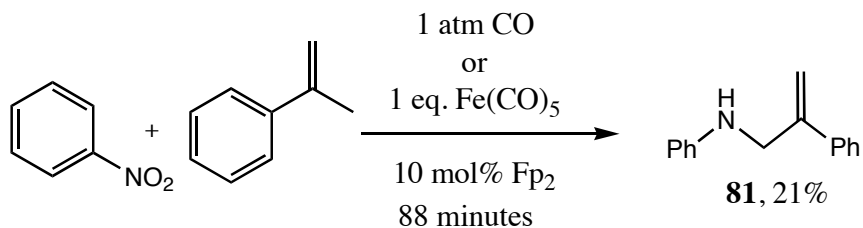
Figure 5.2

In addition, a more *N*-selective co-catalytic system was developed by employing CuBr with [CpFe(CO)$_2$]$_2$ under milder conditions such as 100^0C and 10 atm CO pressure (Figure 5.3). These conditions enable the reaction to be conducted in Fisher-Porter glass vessels, and slight improvements in the allylamine product yield (from 41%) could make this a synthetically useful system due to the ease of purification from the high *N*-selectivity of the system. Further attempts to elucidate the role of Cu^I in the catalytic system could also prove fruitful in developing an even more reactive system.

Cu^I/Fp$_2$-Catalyzed Allylic Amination of Nitrobenzene and α-Methylstyrene
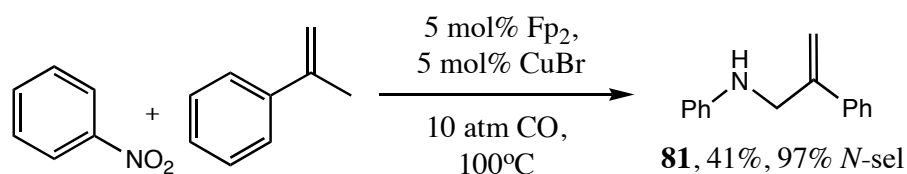
Figure 5.3

In regard to our aim to investigate new methodologies of *N*-containing heterocycle formation, we have developed a new metal-catalyzed indolization reaction to produce 3-arylindoles from aryl hydroxylamines and alkynes in moderate to excellent yields (Figure 5.4). In the study, we were able to successfully address the challenge of developing a one-step procedure that utilizes convenient laboratory conditions in order to efficiently produce parent (NH) indoles. Using a procedure of slow addition of the aminating reagent, electron-donating and –withdrawing *N*-aryl hydroxylamines are both effective in the reaction. The *N*-aryl hydroxylamines used

are conveniently prepared in one step via reduction of nitroaromatics, and purified by recrystallization. In contrast, the nitrosoaromatics utilized in previous methods are formed in one step via oxidation of amines with purification generally by column chromatography. A variety of aryl alkynes can serve as effective coupling partners, including one with *N*-coordinating ability (4-ethynylpyridine), though aliphatic alkynes and propiolic esters were largely unsuccessful. Terminal and internal aryl alkynes can be converted with exceptional regioselectivity to 3-aryl products. Though the alkynes are used in excess (15-20 equiv), in most cases the alkyne could be almost completely recovered.

Fe(Pc)-Catalyzed Parent (NH) Indole Formation from
N-Arylhydroxylamines and Aryl Alkynes

16 examples
25-88% isolated
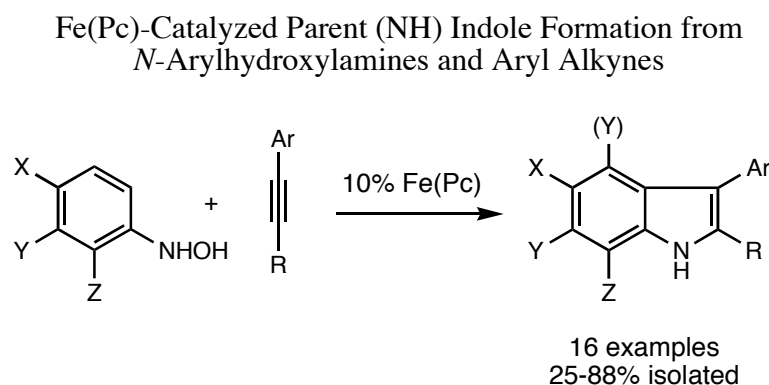
Figure 5.4

Another advantage of the system includes the use of inexpensive commercial catalysts such as Fe(Pc), $Fe^{II/III}$ salts, and $Cu^{I/II}$ salts, as well as easily prepared and inexpensive Mo^{VI} complexes. Owing to the technical ease of isolation of the parent (NH) indoles using the present one-step procedure, several previously untested *N*-aromatic substrates and/or alkynes were utilized in this study resulting in several new indoles. Moreover, in this annulation reaction, an *ortho*-substituted arene or activated

scaffold is not required, resulting in a highly efficient and convergent generation of the indole skeleton.

Finally, in our exploration of new methodologies for direct C-H insertion employing nitrenoid precursors, we were able to discover multiple novel systems. For example, the first non-transition metal as well as the first non-metal catalyzed amidation of benzylic and simple saturated hydrocarbons has been developed (Figure 5.5). In the PhI=NTs/zinc-catalyzed system, it was discovered that water is necessary in the reaction in order to facilitate a zinc-aquo or acid-catalyzed reaction. Moderate to good yields were obtained from a variety of benzylic substrates, as well as a saturated sp^3 C-H containing hydrocarbon, adamantane, by employment of an excess of the inexpensive hydrocarbon substrate. In addition to a zinc-aquo catalyzed reaction, the first example of the simple employment of protic acids was shown to catalyze amidation of ethylbenzene in as high as 32% (un-optimized) by 0.2 equivalents of hydriodic acid.

Zn^{II}-aquo or Acid-Catalyzed Aminosulfonation of Benzylic and 3º Hydrocarbons with Imidoiodinanes
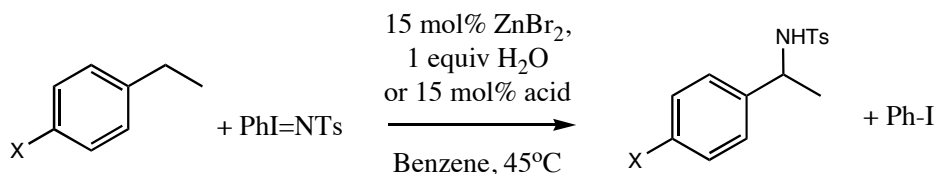
Figure 5.5

Our initial investigation into non-transition metal-catalyzed amidation then led us to develop an improved system. In our subsequent exploration, we have found that

1°, 2°, and 3° benzylic substrates along with some saturated and unsaturated hydrocarbons can be amino-functionalized by reaction of PhI=NZ catalyzed by inexpensive I_2 (Figure 5.6). The resulting system is an operationally simple reaction conducted under very mild conditions that includes the employment of wet solvents at room temperature. Good to excellent yields of amidated products are obtained from secondary benzylic C-H containing substrates, with moderate-poor yields resulting from tertiary and primary benzylics. A number of saturated hydrocarbons also proved reactive, including the highest reported yield of a precursor to amantidine being obtained from the reaction of adamantane and PhI=NNs catalyzed by 20 mol% I_2. In addition, the first examples of 1,2-functionalization of unactivated C-H bonds in a single reaction using imido-iodinanes as aminating agents have been observed.

I_2-Catalyzed Aminosulfonation of Benzylic, 3°, and 2° Saturated
Hydrocarbons with Imidoiodinanes
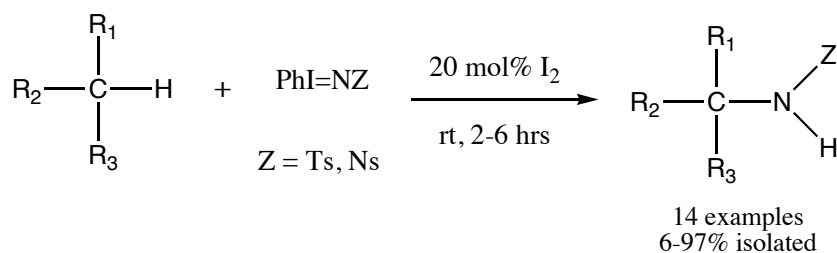
Figure 5.6

Mechanistic investigations of the I_2-catalyzed system have resulted in the isolation of a new and stable aminating reagent that can directly insert into benzylic and tertiary C-H bonds. In addition, mechanistic results such as the generation of alkenes from saturated hydrocarbons, formation of a pyrrolidine product from the

radical clock experiment, and the detection of a relatively large ρ-value of -2.77 from a Hammett competition experiment, indicate a highly reactive two-step process in which hydrogen or hydride is abstracted and C-N bond formation quickly follows. The stereochemical result in which only one isomer was produced (indicating a concerted insertion) remains mysterious along with the nature of the solid aminating agent, though attempts to crystallize the compound may result in a more definitive elucidation.

5.2 Future Directions

In the context of the overall Nicholas Group Amination Project goals, there are several areas of research remaining that could be identified as high priority. Investigations in the future could in fact be divided into two groups; more challenging problems such as catalyst design or methodology discovery (higher risk, higher reward), and lower risk studies such as the extension or improvement of our previously discovered methodologies into new areas and/or applications. In addition, future plans within each of the three areas of the project (allylic amination, indole formation, and nitrenoid insertion) are envisioned and will be discussed in a general sense.

5.2.1 Allylic Amination via Nitroaromatic Reduction

With the re-emergence of interest in allylic amination via C-H activation in the last few years (M. C. White's bi-metallic system), more advances in the field may potentially come to light in the near future. In that time, it is the author's opinion that

the most significant contribution that could be made still lies in the use of nitroaromatics as *N*-aminating agents in an intermolecular reaction. In order to overcome the harsh conditions associated with reduction of the nitro compound, a new or different strategy than that which is described in Chapter 2 is needed. A more in-depth investigation into either the $Ni(PPh_3)_4$[85] or $CpCo(PPh_3)_2$[86] complexes that are known to produce a metallo-oxaziridine from the stoichiometric reduction of a nitroaromatic at ambient temperatures is desired. A more complete study of the reactivity of the nitroso-coordinated metal complexes with olefins or nucleophiles under various conditions (thermal, photoassisted) or modification of the $Ni(PPh_3)_4$ or $CpCo(PPh_3)_2$ complexes may lead eventually to a new and mild catalytic system (Figure 5.7).
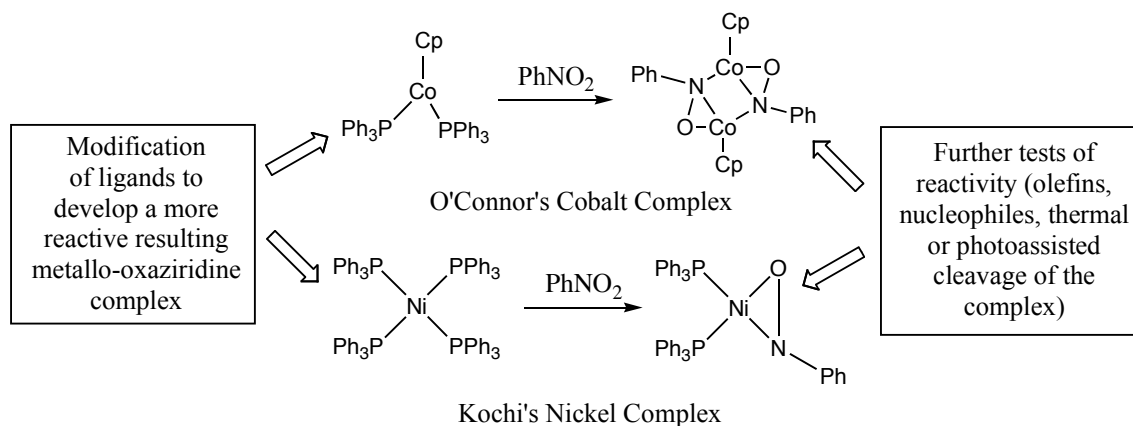
Figure 5.7

In addition, the design of a new catalyst for nitroaromatic reduction is also envisioned. The currently employed $[CpFe(CO)_2]_2$ catalyst is particularly attractive as it is commercially available, however, modification of the Cp ligand for electronic or steric effects must be done synthetically since a variety of Cp dimers are not available

commercially. More desirable would be a metal complex in which adjustments towards the aforementioned effects could be easily made. For this purpose the synthesis of a series of novel tris-pyrazolylborate metal dimers[189] or $TpM(CO)_n$ complexes[190] for use as catalysts in the allylic amination from nitroaromatics reaction would be ideal (Figure 5.8). Replacing the Cp unit for Tp should allow for a tunable ligand system that could potentially be employed to reduce the conditions from $160^{\circ}C$ and 700 psi of CO to a level that can be employed on a common bench top.
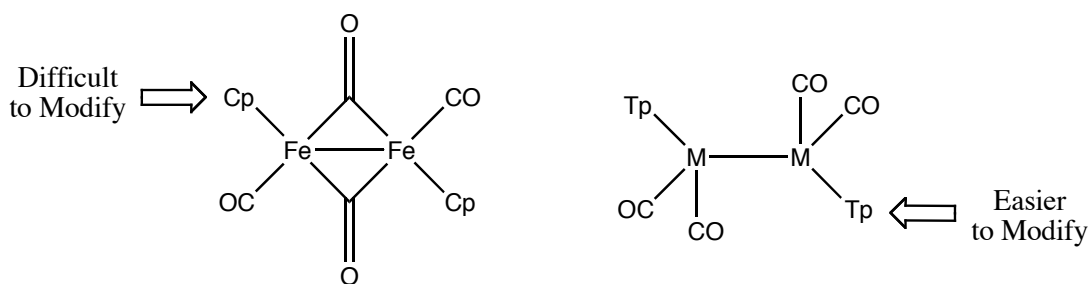
Figure 5.8

5.2.2 Indole Formation

The thermal nitroso/alkyne intermolecular annulation that has been discovered and investigated within the last eight years in the Nicholas Group is particularly attractive as a highly convergent reaction. The reaction employs relatively simple reagents that do not require additional *ortho*-functionalization of the *N*-aryl substrate, which is commonly found in transition metal-catalyzed methods. Though several improvements to the efficiency of the reaction have been developed, the system currently has limitations in regard to the range of alkynes that can be used. It has been shown through mechanistic calculations that a vinyl radical is present in the

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mechanism.[124] To date, the reaction has mainly only been shown to be effective with either acyl or aryl alkynes (both substituents are known to help stabilize vinyl radicals). Therefore, the use of transition metals to help stabilize the radical character of the intermediate may allow for a much wider range of alkyne to be employed, and potentially reduce the required reaction conditions from 80°C (Figure 5.9).

R = aryl, COR   "Stabilized" Approach
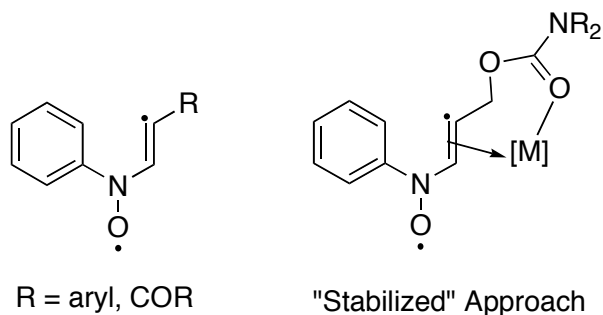
Figure 5.9

In addition to attempts to improve the reaction, further application of the current system towards natural products or other indole-containing frameworks, such as indolocarbazoles, could be a fruitful area of investigation. The synthesis of carbazoles is an area of increasing intensity as the framework is found in numerous natural products, photochromic, and biologically active compounds.[191] Currently, an efficient strategy to produce unsymmetrical indolocarbazoles is lacking. Employing our current indole-forming methods, the production of unsymmetrical carbazoles as well as other frameworks could be envisioned and investigated (Figure 5.10).

Unsymmetrical Bisindoles

$R_2 = OMe, H$
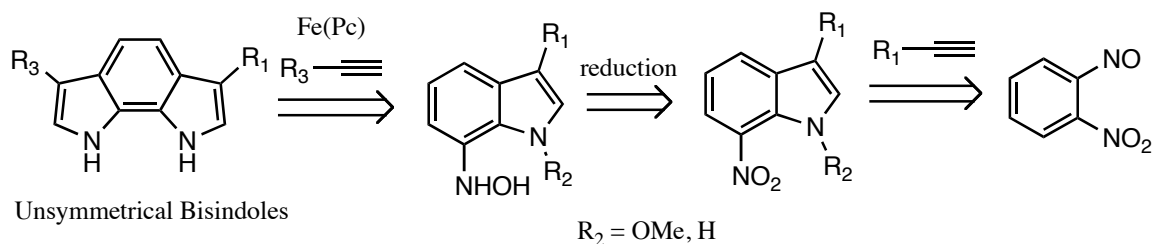
Figure 5.10

5.2.3 Nitrenoid C-H Insertion

While the inter- and intramolecular insertion of nitrenoid precursors into benzylic C-H bonds has been shown to be a very valuable addition to amination methodology over the last ten years, several aspects of the generality of the transformation are still lacking. For example, chemo- and regioselective amination of aryl C-H bonds (such as in benzene) is still without an efficient catalytic method (see Chapter 1.2.2.7). To overcome this challenge, investigations employing an intramolecular directing group on an aryl substrate may serve to facilitate amidation and provide incremental advances towards discovery of a more reactive system (Figure 5.11). Another area requiring more attention is the functionalization of simple cyclic or linear alkanes (Chapter 1.2.2.6). In order to address this issue, the discovery and/or development of new, more reactive aminating reagents will most likely lead to the most significant advances.

X = Any Metal-Coordinating
Heteroatom
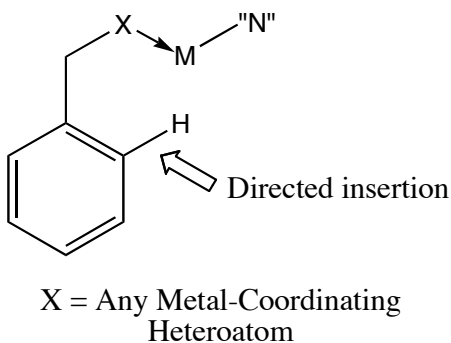
Figure 5.11

The design of new aminating reagents should focus on the production of stable, electron-deficient, and "greener" substrates from commercially available sources. To date, very little attention has been given to the employment of azides in the nitrenoid precursor insertion reactions. Though potentially explosive, azides provide a "greener" approach to the transformation, and with the correct design could produce highly reactive N-sources. In addition, the development of a catalytic nitrido aminating system would be very interesting. Currently, the nitrido-metal complexes have only been shown to perform aziridination or C-H insertion reactions stoichiometrically. The systems remain intriguing due to the possible methods of production of the nitrido-metal complexes, which can include employment of ammonia as the stoichiometric N-source. Potentially with the design of a more reactive metal complex, the development of a catalytic system could be within reach.

As extensions of our recently discovered methodologies within the Nicholas Group, several studies could be envisioned in order to develop more reactive systems, or to apply the current processes towards compounds of interest. For example, the chemo- and regioselective application of an intermolecular C-H insertion method to a

complex molecule in the synthesis of a natural product or analogue thereof has yet to be demonstrated as opposed to the numerous examples of the intramolecular version. By selection of the right complex molecule, this application should be able to be effectively illustrated. Another area deserving a more complete investigation lies within the chemoselectivity discrepancies of nitrenoid precursor reactivity with olefins (which can result in aziridination, allylic amination, or halo-amination). An effective study could lead to the development of a highly desirable more chemospecific catalytic method of allylic amination via C-H activation. In addition, the development of an enantioselective allylic amination is also attractive, though challenging, as current reported methods only provide low-moderate ee's (see Chapter 1.2.2.5).

Finally, to further investigate the recently developed I_2-catalyzed amidation of hydrocarbons by imidoiodinanes, attempts could be made to elucidate the structure of the solid aminating agent in order to develop a more reactive species. Potential advances could also be made by the simple exploration of mixed halogens (such as I-Br, I-Cl, etc.) instead of I_2, different imidoiodinanes, or system additives in conjunction with representative hydrocarbons.

CHAPTER 6

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