THE DEVELOPMENT OF IRON-CATALYZED [2+2+2]

CYCLOADDITIONS TO PRODUCE 6-MEMBERED

NITROGEN HETEROCYCLES

by

Timothy Karl Lane

A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

The University of Utah

December 2015

The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

The dissertation of   **Timothy Karl Lane**

has been approved by the following supervisory committee members:

Janis Louie	, Chair	**March 6, 2015**
		Date Approved
Jon Rainier	, Member	**March 6, 2015**
		Date Approved
Gary Keck	, Member	**March 6, 2015**
		Date Approved
Thomas Richmond	, Member	**March 6, 2015**
		Date Approved
Amy Barrios	, Member	**March 6, 2015**
		Date Approved

and by   **Cynthia Burrows**   , Chair/Dean of the

Department/College/School of   **Chemistry**

and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

One of the greatest challenges in synthetic chemistry is the development of reactions that can efficiently afford target compounds without creating byproducts. One such class of reactions are [2+2+2] cycloadditions. Here, three unsaturated coupling partners are combined to create six-membered rings, often with high regioselectivity, high yield, and no byproducts (i.e., secondary products). To further increase the attractiveness of these reactions, iron, a cheap and abundant catalyst, can be used. However, for the [2+2+2] synthesis of pyridines, a very important class of compounds, iron has traditionally been a very poor catalyst. By tethering unreactive nitriles to the more reactive alkynes, the first general iron-catalyzed [2+2+2] method to synthesize pyridines has been developed. This reactivity was further explored with the cycloaddition of diynes and cyanamides. Cyanamides demonstrated remarkable chemo- and regioselectivity. The three-component cycloaddition of terminal alkynes and a cyanamide could be performed with high yield and complete chemoselectivity. By combining aforementioned strategies of nitrile incorporation, the entirely novel cycloaddition of alkynenitriles and cyanamides has been developed. In this case, iron demonstrated reactivity that few [2+2+2] cycloaddition catalyst exhibited by incorporating multiple nitrogen atoms into the resulting 6-membered ring. Finally, isolation of presumed inorganic and organometallic intermediates provides a preliminary understanding of the mechanistic sequences involved in these iron-catalyzed [2+2+2] cycloadditions.

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 1

A BRIEF INTRODUCTION TO [2+2+2] CYCLOADDITION, IRON

CATALYSIS, AND THE IMPORTANCE OF

SIX-MEMBERED NITROGEN

HETEROCYCLES

Introduction

This chapter will introduce the relevant background in the three general fields in which this research has focused. It will explain the basic mechanistic premise of [2+2+2] cycloadditions to make arenes and pyridines. This section will conclude with regioselectivity challenges that have been largely unaddressed in three-component cyclizations. The next discussion will weigh the benefits of using iron catalysts in place of precious metal catalysts. This will highlight the challenges associated with iron-catalysis and some examples where these challenges have been overcome. Finally the importance of six-membered nitrogen heterocycles and the motivation to create synthetic methods by which they can be synthesized will be addressed. These three general categories will be tied into the one main idea that encompasses this thesis.

[2+2+2] Cycloaddition

The cyclization of three acetylenes into benzene is a highly exothermic, symmetry-allowed transition. However, to overcome the significant energetic barriers,

high temperatures must be employed.[1] The first such thermal cyclization was reported in

1866 by Bertholet, however, this reaction was not further studied for the better part of a

century.[2] In 1948 Walter Reppe described the cyclotrimerization of acetylene by a nickel

catalyst to produce benzene (equation 1).[3] Since this initial report, countless studies have

been undertaken in the field that is generally known as [2+2+2] cycloaddition. A

[2+2+2] cycloaddition is the combination of three unsaturated units, each containing two

atoms, into a 6-membered ring. This atom-economical transformation holds tremendous

synthetic potential which, even after 55 years, continues to attract fervent interest.

Reactions in this field have grown to encompass the synthesis of numerous carbocycles

from various combinations of unsaturated hydrocarbons.[4] Additionally, heteroatoms can

be incorporated into cycloaddition products through the use of nitriles, carbonyls, and

heteroallenes.[5] This discussion will focus on the evolution of metal-catalyzed [2+2+2]

arene and pyridine synthesis.

(1)
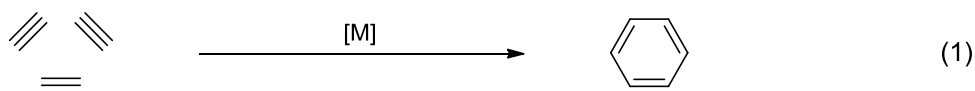
Reppe demonstrated that the kinetic and entropic barriers to [2+2+2]

cycloaddition can be overcome through the use of a transition metal.[3] Subsequent

mechanistic studies have uncovered the integral role played by metals in the

cycloaddition mechanism (Figure 1). When two alkynes coordinate to a low-oxidation-

state metal center, oxidative cyclization occurs. This creates one of two possible

metallacycles, which is dependent on the identity of the metal. The formation of

metallacyclopentadienes (**1** for nickel and cobalt) or metalacyclopentatrienes (**2** for

ruthenium) has been substantiated through computational[6] studies in addition to the

isolation of metallacyclic intermediates.[7] Coordination of a third alkyne will result in one
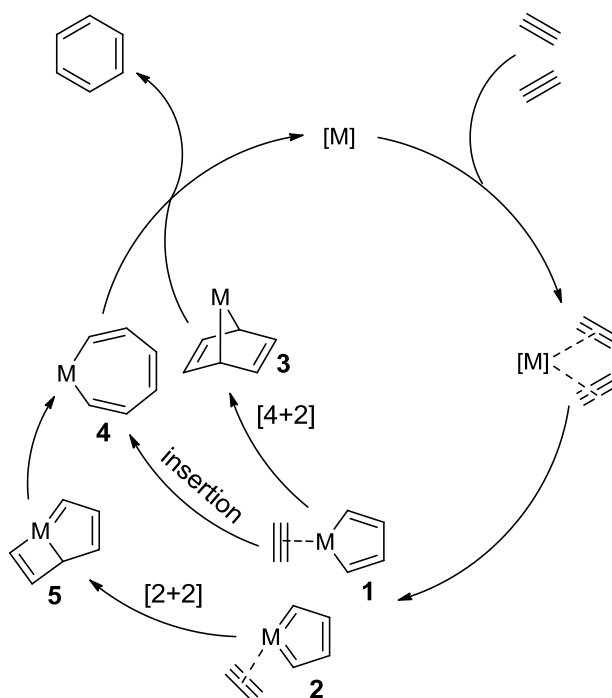
Figure 1. Mechanistic possibilities in metal catalyzed [2+2+2] alkyne cyclotrimerization.

of several possible reactions.[6] The first possibility is a [4+2] cycloaddition, creating a cyclohexadiene bridged by the metal (**3**). Alternatively, the alkyne can insert into the metal-carbon bond, creating a metallacycloheptatriene (**4**). The third possibility involves a [2+2] cycloaddition between the metallacyclopenatriene and the alkyne, creating a metallabicycloheptatriene (**5**). The bicyclic intermediate (**5**) then rearranges to the metallacycloheptatriene (**4**). In any case, reductive elimination occurs creating the benzene product, thus completing the catalytic cycle.

In 1973 Yamazaki reported the first use of a [2+2+2] cycloaddition to synthesize a heterocyclic compound.[8] Here, pyridines were produced from the combination of two acetylenes and one nitrile in the presence of a cobalt catalyst (equation 2). Like Reppe's first reports of [2+2+2] cycloaddition, this report has led to countless subsequent studies which continue to this day.

$$R = Me, Ph, p\text{-tolyl, benzyl}$$

(2)
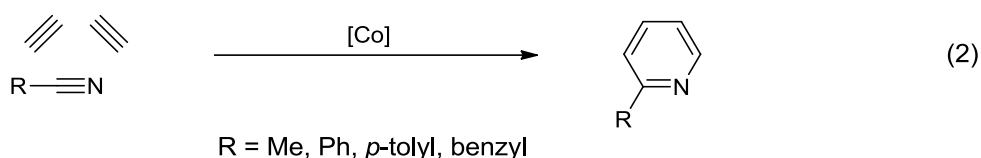
The synthesis of pyridines from alkynes and nitriles by various metals is a well-studied class of reactions.[5] Two alkynes and one nitrile are cyclized in a [2+2+2] fashion which can follow one of two general catalytic cycles closely resembling that of alkyne cyclotrimerization (Figure 2). The first catalytic cycle begins with oxidative cyclization of two alkynes (homocoupling) forming either a metallacyclopentadiene (**6**) or a metallacyclopentatriene (**7**).[9] From here, three insertion intermediates (**8-10**), which are analogous to those of the alkyne trimerization, are possible. The second pathway involves oxidative cyclization of an alkyne and a nitrile (heterocoupling) forming an azametallacyclopentadiene (**11**). Insertion of alkynes into azametallacyclopentadienes has not been extensively studied and therefore only intermediate **9** is drawn.

Today, the [2+2+2] construction of pyridines can be catalyzed by several metals, with cobalt traditionally being the most effective. More recently systems involving ruthenium,[10] rhodium,[11] and iridium[12] have been the subject of several studies. Nickel was initially only useful for the stoichiometric conversion of azazirconacyclopentadienes to pyridines.[13] Over the past decade the Louie group has established nickel/NHC (NHC = N-heterocyclic carbene) and nickel/Xantphos systems that are among the most effective methods of pyridine synthesis.[14]

While conceptually straightforward, the [2+2+2] cyclization of two alkynes and one nitrile are quite challenging. Reactions with unsymmetrical alkynes generally provide mixtures of pyridine regioisomers (equation 3).[15] Additionally, side reactions of

Homocoupling **Heterocoupling**
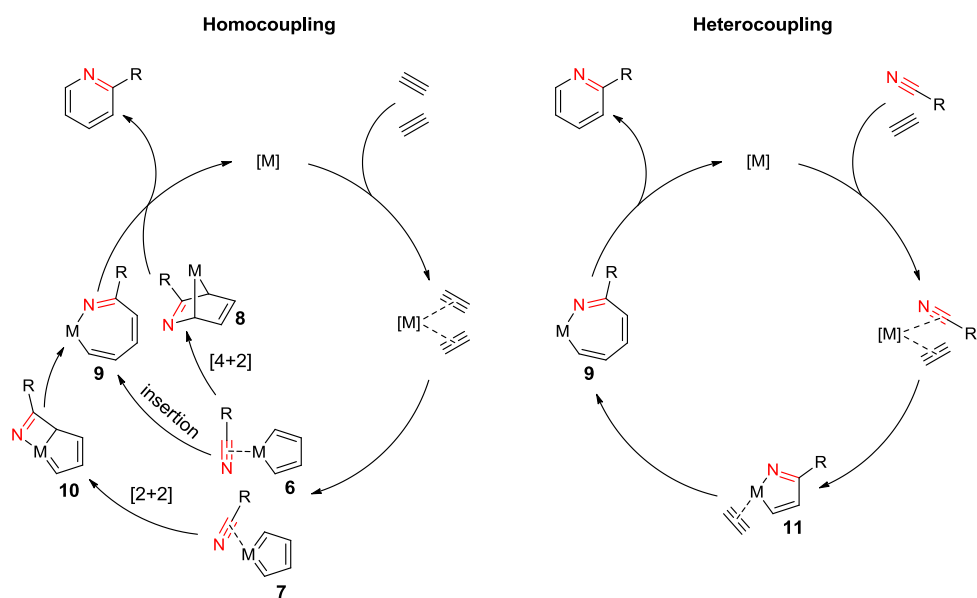
Figure 2. Homocoupling and heterocoupling pathways for the [2+2+2] cycloaddition of alkynes and nitriles.

alkyne cyclotrimerization further complicate the product mixture. These complications are avoided by utilizing symmetrical diyne substrates, which can only afford one pyridine regioisomer (equation 4).[16] Cycloadditions of diynes and nitriles produce bicyclic pyridines with the ring fusion at the 3- and 4-position. To obtain two, 3-ring-fused pyridines, alkynenitrile substrates are used (equation 5).[17] To build tricyclic pyridines in a single step, all three coupling partners are tethered (equation 6).[18]

(3)

(4)

(5)

(6)
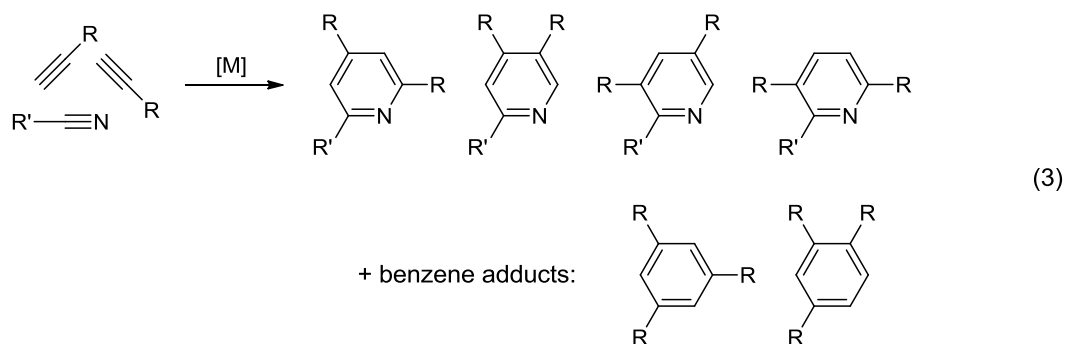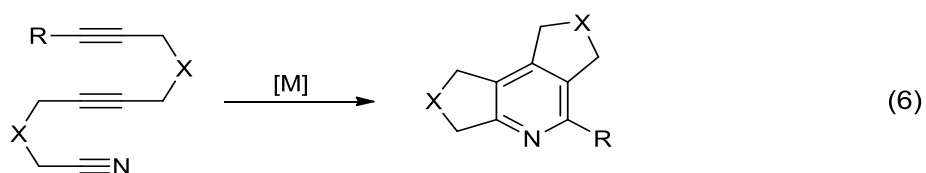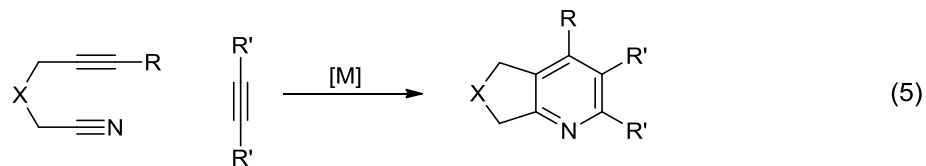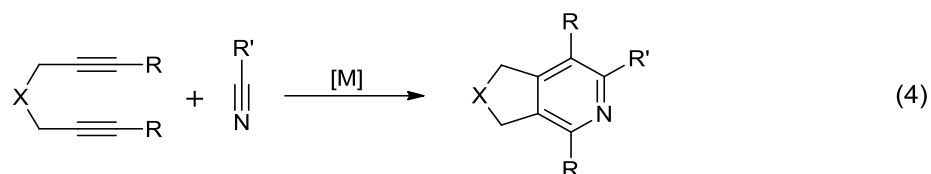
For the synthetic chemist, [2+2+2] cycloadditions provide a highly attractive tool for the atom-economic construction of 6-membered rings. The cyclotrimerization of alkynes has been used as a key step in numerous total syntheses.[19] The key step in the total syntheses of Alcyopterosins I, L, and M by Witulski and co-workers demonstrates the effectiveness of this strategy (Figure 3).[20]

Although less frequently used, the [2+2+2] cycloaddition of two alkynes and a nitrile has also been applied to total syntheses. The natural product (+)–Complanadine A exhibits an interesting bipyridyl structure. In an ambitious approach, the Siegel group created the bipyridyl bridge with two [2+2+2] intermolecular cobalt-mediated cycloadditions (Figure 4).[21]

Ironically, the simplest substrates for [2+2+2] synthesis of pyridines, untethered alkynes and nitriles, provide the greatest challenge for metal-catalyzed [2+2+2] cycloaddition. As mentioned earlier, cycloadditions with unsymmetrical alkynes can lead to the formation of numerous regioisomers (equation 3).[15] Furthermore, terminal alkynes are highly active in [2+2+2] cycloaddition and readily trimerize to substituted arenes
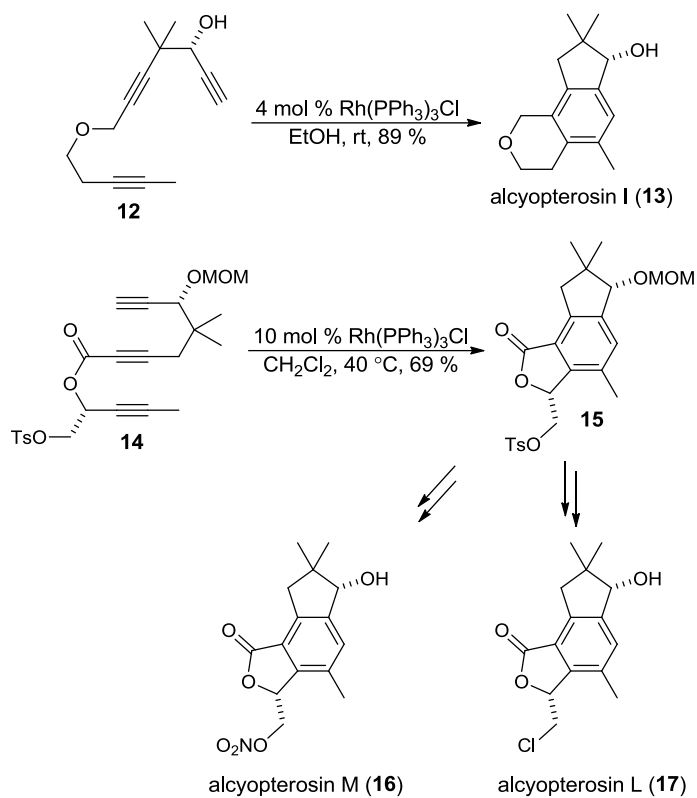
Figure 3. Rhodium-catalyzed [2+2+2] cycloaddition of triynes in the total synthesis of alcyopterosin I, M, and L.
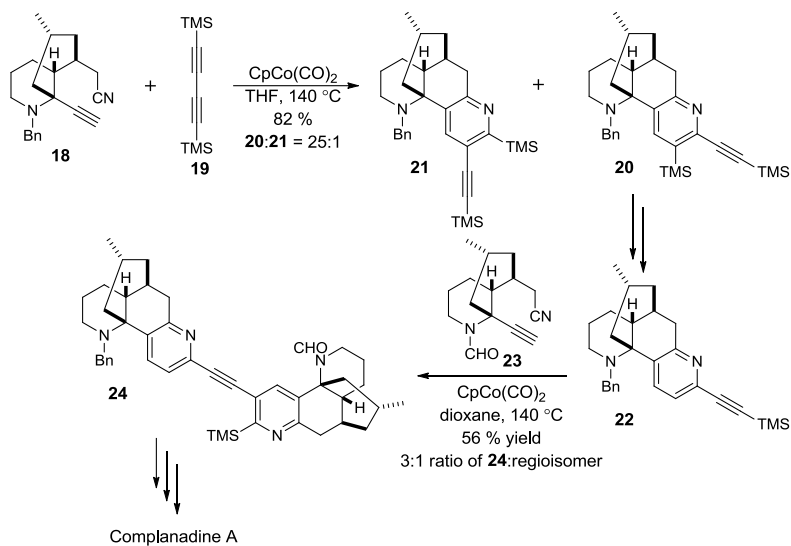

Figure 4. Cobalt-catalyzed [2+2+2] cycloadditions of alkynes and Nitriles used in the total synthesis of Complanadine A.

even in the presence of nitriles.[22] These issues highlight the fact that 3-component [2+2+2] cycloadditions remain underdeveloped. If regioselectivity challenges can be overcome, monocyclic six-membered rings of varying complexity can be synthesized from exceedingly simple starting materials.

The synthetic power of a reaction that creates three new bonds in a single step with high atom efficiency is rare. Currently, [2+2+2] cycloadditions to create substituted benzenes and pyridines are increasingly reliable and synthetically useful reactions. Future work in the field of [2+2+2] cycloaddition will involve improving the regio- and chemoselectivity in three-component reactions.

Iron Catalysis

Nearly every iron-catalysis report starts with the same three points: iron is abundant, cheap, and nontoxic. Iron's abundance is the result of a process called stellar nucleosynthesis.[23] Iron, because of its unique nuclear stability, is the final product of several stages of fusion in supergiant stars. When these massive stars build up enough iron, their core becomes unstable, leading to a supernova. The energy created by this enormous explosion causes various fusion and fission reactions, creating the elements that we know to populate the periodic table. These newly formed elements, along with copious amounts of iron, are spread throughout space. Over time, new stars and planets form from the debris. This is the mechanism by which iron is spread throughout the universe and is the reason for its abundance on earth.

The abundance of iron leads to its low cost and low toxicity. Readily obtained on the earth's crust, billions of tons of iron ore are extracted annually.[24] Such largescale production ensures a low cost relative to precious metals such as Pt, Pd, Au, and so forth. Biological systems are very tolerant of iron because not only has life evolved in its

presence, but most organisms have come to depend on it for basic functions. This point is demonstrated by the prevalence of metalloproteins such as hemoglobin and nitrogenase.[25]

Despite the economic and environmental advantages of iron, precious metals have come to dominate the field of transition metal catalysis. This is because precious metals reliably undergo two-electron processes, while iron tends to undergo difficult-to-control single-electron processes. Furthermore, iron exhibits a remarkably broad range of possible oxidation states as compared to other transition metals. While the 2+ and 3+ oxidation states are most common, reports range from 6+ to 2-.[26] This oxidative indecisiveness leads to the many side reactions, poor selectivity, and generally poor catalytic activity of iron.

The combination of increasing refinement costs, environmental concerns, and ever-decreasing availability has led to the search for alternatives to precious metal catalysis. In the past 20 years interest in iron-catalysis has grown immensely because iron is largely free from the economic, social, and environmental detriments associated with precious metals. With so much attention over the past two decades, systems which overcome the challenges associated with iron-catalysis are now being realized.

A very promising method of controlling iron reactivity is through the use of redox active ligands.[27] Redox active (A.K.A. non-innocent) ligands exhibit HOMOs or LUMOs which are close in energy to their respective bound metal.[28] The result of this energetic compatibility is that the metal center can share, or delocalize electron density onto the ligand. This delocalization creates an exceedingly complicated electronic environment. Despite this complexity, these ligands can impart extraordinary reactivity to the metal they bind. As our understanding of the electronic environments of these

complexes grows, so does the scope and efficiency of the reactions which they catalyze.

In 1998 Brookhart and Gibson independently discovered a class of iron catalysts that could polymerize ethylene with remarkably high turn-over-frequencies (equation 7).[29] The success of this reactivity can be attributed to the tridentate bis(imino)pyridine ligand bound to the iron center. Subsequent studies into the mechanism of this reaction brought to light the unique electronic structure of these complexes. For this reaction, the catalyst is activated by MAO (methylaluminoxane), creating a methylated, cationic complex. The catalytic cycle involves continuous ethylene coordination and insertion, which repeats until a chain-termination event occurs (Figure 5). Traditional chemical intuition and several density functional theory (DFT) studies classify the oxidation state of iron as Fe(II).[30] However, conflicting DFT[31] and spectroscopic[32] studies suggest that the active catalyst may be Fe(III).

$$\text{TOF} = 177 \times 10^{-6}/\text{h}$$

(7)
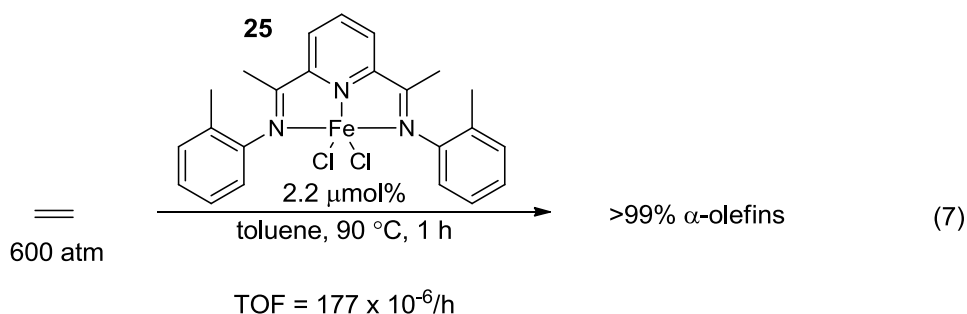
The unique (^{iPr}PDI)Fe(N)$_2$ complex has been synthesized by Chirik and co-workers (PDI = pyridyl diimine).[33] In-depth spectroscopic and computational studies have been performed on this compound, clearly demonstrating the redox activity of bis(imino)pyridine ligands (Figure 6).[34] What at first glance appears to be an Fe(0) complex is actually an Fe(II) coupled to a diradical dianionic ligand. The first signs of an unexpected electronic structure are evident in the x-ray crystal structure of (^{iPr}PDI)Fe(N)$_2$.
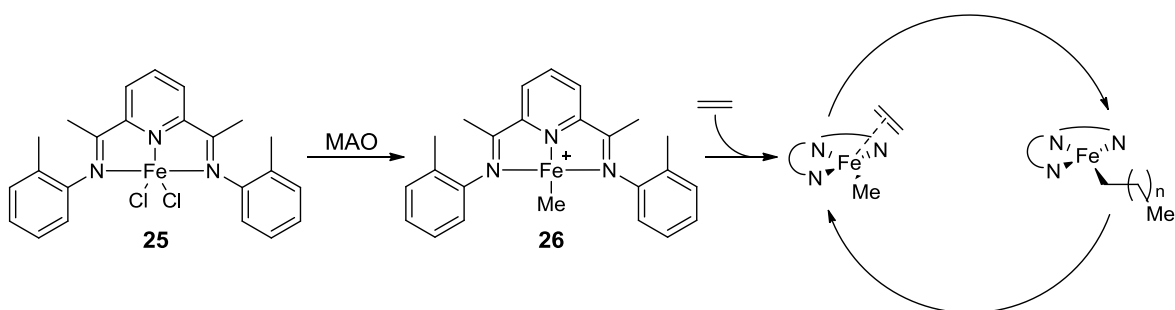
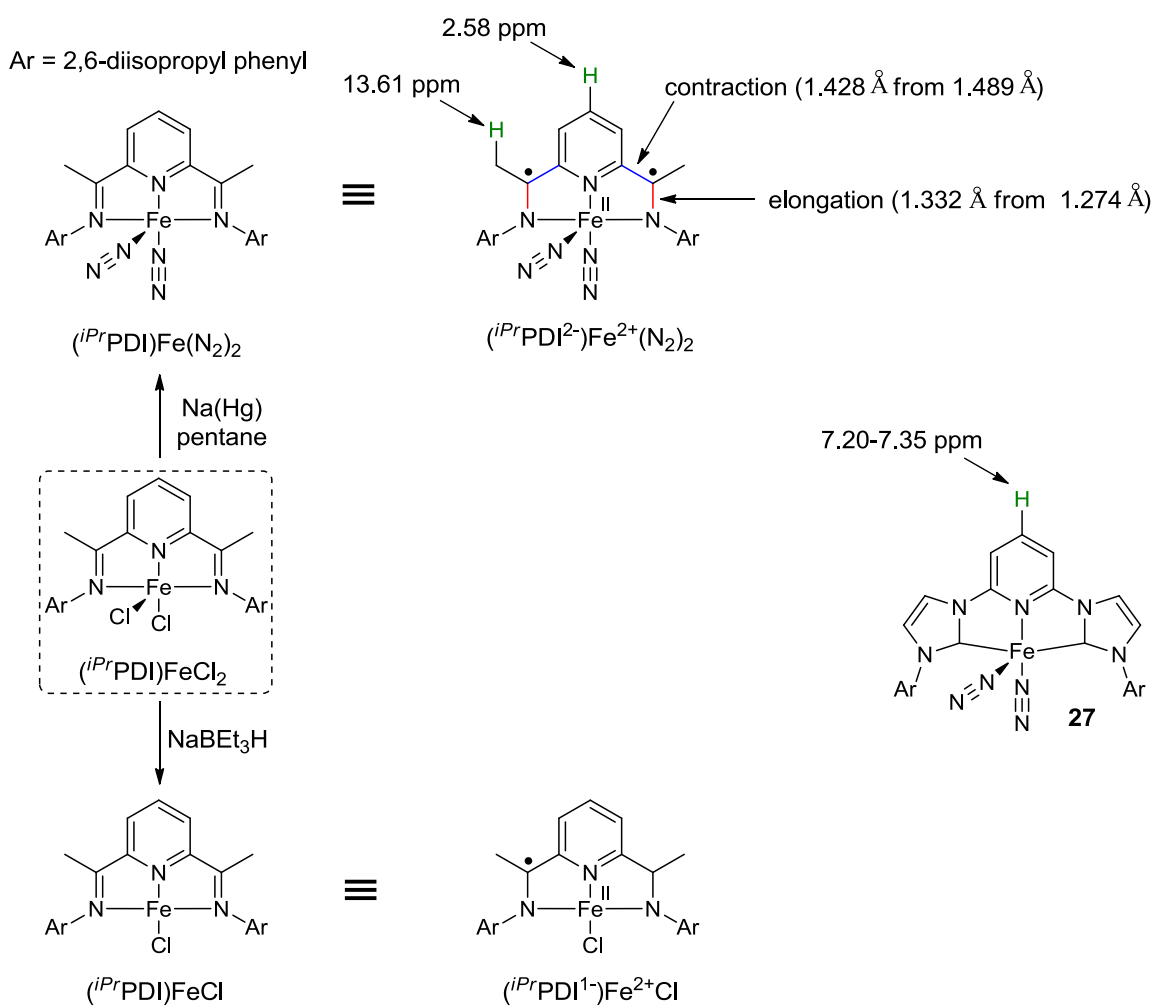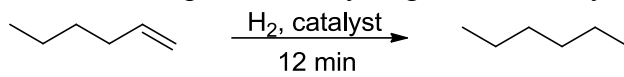**Figure 5**. Generation of ethylene polymerization active catalyst.

**Figure 6**. Electronic structures of iron complexes bearing PDI ligands.

Elongation of the imine bonds and contraction of the C_{imine}-C_{ipso} bonds suggest the presence of a radical centered on the imine carbons. The NMR spectrum of (^{iPr}PDI)Fe(N)$_2$ shows an unusual shift of 13.61 ppm for the imine methyl protons and 2.58 ppm for the *p*-pyridine proton. This is especially unique when comparing to the similar bis(carbene)pyridine iron dinitrogen complex (**27**) prepared by Danopoulos and co-workers.[35] In the dicarbene complex, the *p*-pyridine proton is found in the usual aromatic range of 7.20-7.35 ppm. Mössbauer spectroscopy and SQUID magnetometry in combination with DFT studies further substantiate the diradical dianionic nature of (^{iPr}PDI)Fe(N)$_2$. This study also compared the nonreduced dihalide (^{iPr}PDI)FeCl$_2$ and the single-electron reduced complex (^{iPr}PDI)FeCl with (^{iPr}PDI)Fe(N)$_2$. In each case iron retains its +2 oxidation state. The bis(imino)pyridine ligands maintain an oxidatively stable iron center while still providing a place to store added electrons. In the case of (^{iPr}PDI)Fe(N)$_2$, the ligand appears to promote the two-electron processes necessary to catalyze reactions such as ethylene polymerization. Meanwhile it prevents the one-electron processes that lead to undesirable side products.

The dinitrogen complex and its analogues have demonstrated remarkable catalytic activity in a number of reactions. Olefin hydrogenation by (^{iPr}PDAI)Fe(N)$_2$ exhibited a turnover frequency (TOF) of 1814 mol/h.[33] This result is astounding when compared to the TOF for precious metal hydrogenation catalysts (Table 1). In a second example by Chirik, the antimarkovnikov hydrosilylation of terminal alkenes was carried out with only 0.02 mol% of the dimeric complex [(^{Me}PDI)Fe(N$_2$)]$_2$(μ-N$_2$) (equation 8).[36] In an excellent demonstration of the advantages offered by iron over precious metals, (^{iPr}PDAI)Fe(N)$_2$ was capable of cross-linking hydrido- and vinyl-functionalized silicone polymers at only 500 ppm (equation 9). The resulting cross-linked silicone polymers

Table 1. Comparison of Hydrogenation Catalysts

catalyst	tof (mol/h)
$(^{iPr}PDI)Fe(N_2)_2$	1814
10 % Pd/C	366
$(PPh_3)_3RhCl$	10
$[(COD)Ir(PCy_3)py]PF_6$	75

present a significant challenge for catalyst recovery. While catalyst recovery is necessary

for expensive Pt catalysts, it is less of a concern for inexpensive iron.

$[(^{iPr}PDI)Fe(N_2)](\mu_2–N_2)$

(8)

(9)
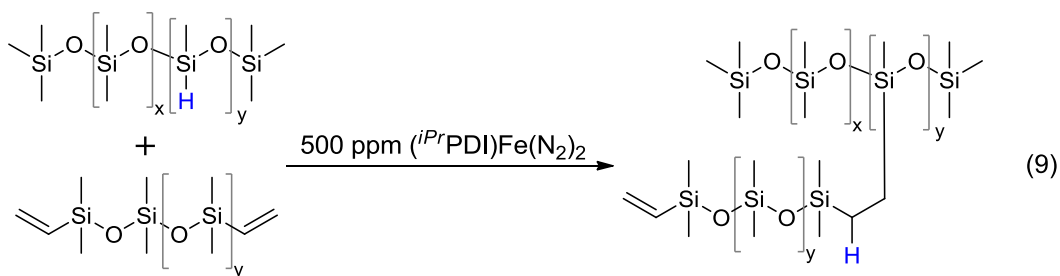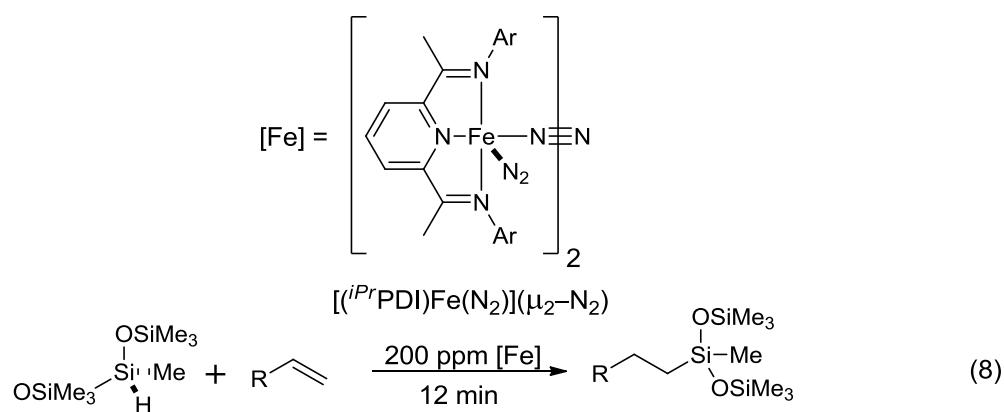
Another highly active iron-catalyzed system has been developed by Ritter and co-

workers for the polymerization of 1,3-dienes (Figure 7).[37] In this system, two different

bidentate imiopyridine ligands can be used with catalyst loadings of only 0.02 mol%.

The first ligand exhibits a tertiary alkyl imine substituent that selectively produces *trans*-

polydienes. Remarkably, replacing the alkyl imine with an aromatic imine substituent

reverses the selectivity to produce *cis*-polydienes in >99:1 (*cis*:*trans*).

The aforementioned examples of iron-catalysts rivalling or outperforming their

respective precious metal counterparts are likely only the beginning of a much larger

trend. As our understanding of redox-active iron complexes continues to advance, so will

the scope of reactions that are efficiently catalyzed by iron.

Six-Membered Nitrogen Heterocyles

Six-membered nitrogen heterocycles represent a class of compounds with several

important applications. The FDA provides information on drug approvals on a monthly

basis.[38] For the past 10 years, 181 small-molecule drugs have been introduced in the US.

Out of these 181 compounds, 50% contain at least one six-membered nitrogen-

containing heterocycle (Figure 8). This demonstrates the tremendous importance that this

class of compounds holds in the pharmaceutical industry. Furthermore, numerous natural

products contain six-membered nitrogen heterocycles such as pyridines, pyrimidines,

piperidines, and so forth.[39] Six-membered nitrogen heterocycles also constitute

numerous inorganic ligands and can be found in organic materials.[40]

Billions of dollars are made annually by the top agrochemical companies.[41]

Research and development in this industry can never cease because pest species are

continuously evolving resistance to these chemicals. A recent example is the appearance

of glyphosate (Round-Up) resistance in weeds. Adding an urgency to these
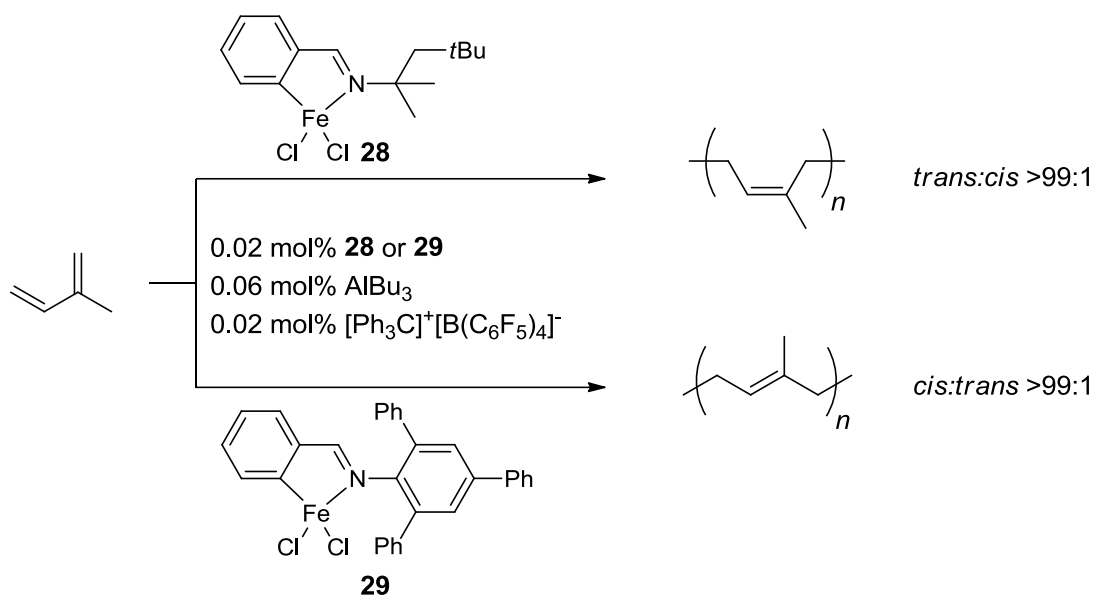
Figure 7. Ligand-dependent selectivity of Ritter's isoprene polymerization catalysts.

pyridines, 25%   Pyrimidines, 22%   piperidines, 20%   piperazines, 9%

Pyrimidones, 7%   pyridones, 6%   pyrazines, 4%   morpholines, 3%

triazines, 2%   pyridazines, 1%   thiazines, 1%   oxazinanes, 1%

Figure 8. Breakdown of six-membered N-heterocycles found in drugs approved by the FDA since January 2004.

complications is the quickly growing world population, which is expected to reach 8 billion by 2024.[42] To avoid a world food crisis it is imperative that high crop yields can be maintained without excessive costs. The chemical industry must be able to supply safe and effective agrochemicals that can be produced at low cost. Several known agrochemicals use 6-membered N-heterocycles (Figure 9).

Organic light emitting diode (OLED) devices are an emerging technology that offer a combination of flexibility, durability and minimal energy consumption. This new technology has very recently achieved commercialization in the form of electronic displays used in devices such as smart phones and televisions. In 2013 this fledgling industry was projected to create $53 million in revenue. That number is projected to increase to $3.4 billion by 2017.[43] Currently, the excessive costs of these products limit their availability to only wealthy customers. For this exponentially growing industry to expand into broader markets, costs must be reduced through improved fabrication methods and more effective production of raw materials.

The raw materials that make OLED technologies special are known as electroluminescent materials. These revolutionary materials often include 6-membered N-heterocycles. Improved methods to produce electrolum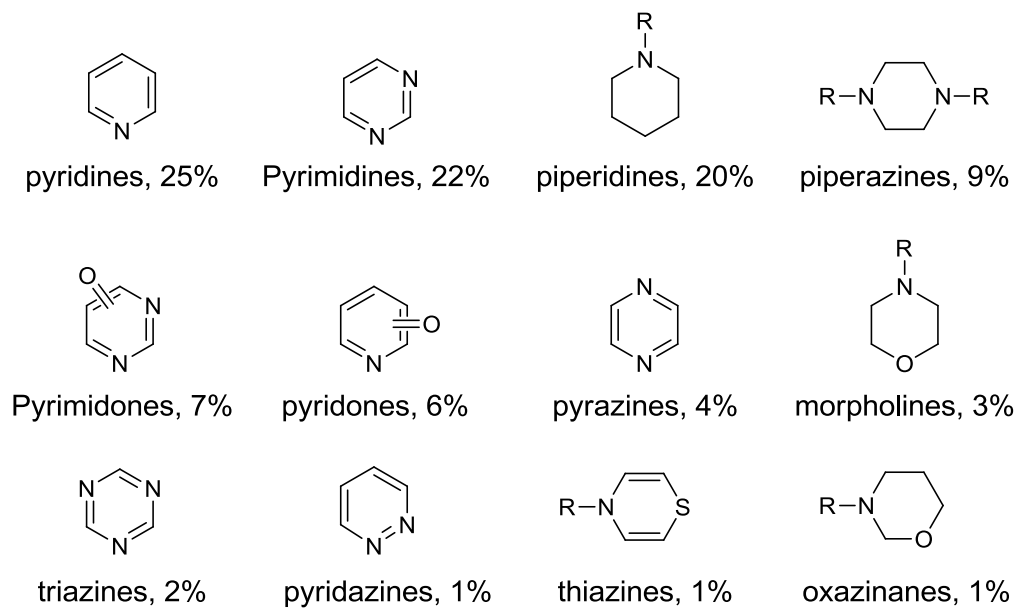inescent N-heterocycles will decrease costs and potentially open up previously unavailable materials for study. Figure 10 highlights a few such compounds.[44]

Concluding Remarks

A major area of study in the Louie group is the development of metal-catalyzed [2+2+2] cycloadditions which produce six-membered nitrogen heterocycles. Atom-efficient [2+2+2] cycloadditions have the potential to produce complex heterocycles from
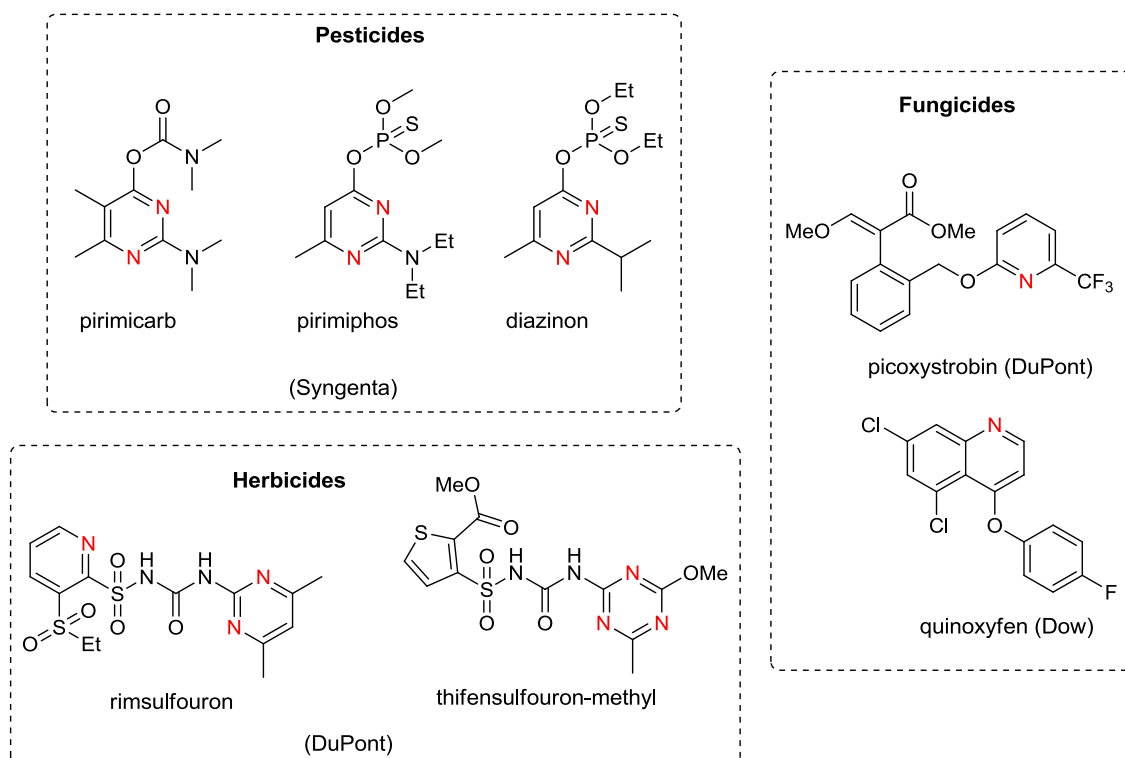
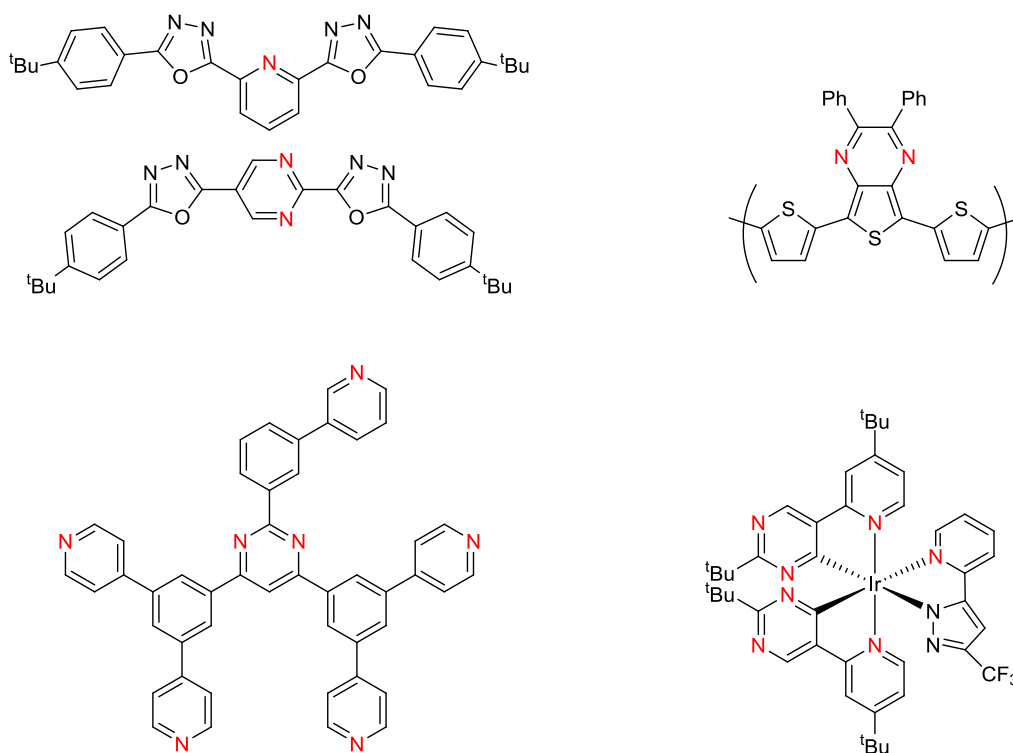**Figure 9**. Chemicals commonly used in the agrochemical industry.

Figure 10. Electroluminescent compounds containing 6-membered N-Heterocycles.

simple, inexpensive starting materials. Our aim is to create efficient catalysts to give access to these important molecular scaffolds. The purpose of this work has been to expand this focus to include iron catalysts. The economic and environmental benefits of iron would further enhance the synthetic desirability and efficiency of [2+2+2] cycloaddition reactions. Furthermore, introducing a new metal catalyst to the field opens the door to discovering new reactivity trends and potentially addressing the limitations of previous systems.

References

(1) a) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741-4767. b) Broere, D. L. J.; Ruijter, E. *Synthesis* **2012**, *44*, 2639-2672.

(2) Bertholet, P. E. M. C. R. *Hebd. Seances Acad. Sci.* **1886**, *63*, 515.

(3) Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104-116.

(4) (a) Chopode, P. R.; Louie, J.; *Adv. Synth. Catal.* **2006**, *384*, 2307-2327. (b) Evans, P. A.; Baum, E. W.; Fazal, A. N.; Lai, K. W.; Rovinson, J. E.; Sawyer, J. R. *ARKIVOC*, **2006**, 338-358. (c) Galan, B. R.; Rovis, T. *Angew. Chem. Int. Ed.* **2009**, *49*, 2830-2834. (d) Rajca, A.; Rajca, S.; *Angew. Chem. Int. Ed.* **2009**, *49*, 672-674. (e) Tanaka, K. *Chem.-Asian J.* **2009**, *4*, 508-518.

(5) (a) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787-3801. (b) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085-1094. (c) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149-3159. (d) Tanaka, K. *Heterocycles* **2012**, *85*, 1017-1043. (e) Wang, C.; Wan, B. *Chin. Sci. Bull.* **2012**, *57*, 2338-2351.

(6) (a) Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G.-L. *J. Am. Chem. Soc.* **1999**, *121*, 6055-6067. (b) Kirchner, K.; Calhorda, M. J.; Schmid, r.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721-11729. (c) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143-12160.

(7) (a) Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907-1912. (b) Yamazaki, H.; Wakatsuki, Y. *J. Organomet. Chem.* **1984**, *272*, 251-263. (c) Kawatsura, M.; Yamamoto, M.; Namioka, J.; Kajita, K.; Hirakawa, T.; Itoh, T. *Org. Lett.* **2011**, *13*, 1001-1003. (d) Paneque, M.; Poveda, M. L.; Rendón, N.; Mereiter, K. *J. Am. Chem. Soc.* **2004**, *126*, 1610-1611.

(8) Wakatsuki, Y.; Yamazaki, H. *Tet. Lett.* **1973**, *36*, 3383-3384.

(9) (a) Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. *J. Organomet. Chem.* **2006**, *691*, 4434-4445. (b) Dahy, A. A.; Koga, N. *J. Organomet. Chem.* **2010**, *695*, 2240-2250.

(10) (a) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2001**, 1102-1103. (b) Medina, S.; Domínguez, G.; Pérez-Castells, J. *Org. Lett.* **2012**, *14*, 4982-4985.

(11) (a)Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917-3922 (b) Tanaka, K.; Hara, H.; Nishida, G.; Hirano, M. *Org. Lett.* **2007**, *9*, 1907-1910.

(12) Onodera, G.; Shimizu, Y.; Kimura, J.-n; Kobayashi, J.; Ebihara, Y.; Kondo, K.; Sakata, K.; Takeuchi, R. *J. Am. Chem. Soc.* **2012**, *134*, 10515-10531.

(13) (a) Takahashi, T.; Tsai, F.-Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994-4995. (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059-5067.

(14) (a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030-5031. (b) Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J. *J. Org. Chem.* **2006**, *71*, 5834-5836. (c) Kumar, P.; Prescher, S.; Louie, J. *Angew. Chem. Int. Ed.* **2011**, *123*, 10882-10886.

(15) (a) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Ocuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605-613. (b) Tanaka, K.; Suzuki, N.; Goushi, N. *Eur. J. Org. Chem.* **2006**, 3917-3922.

(16) (a) Wakatsuki, Y.; Yamazaki, H. *Tetrahedron Lett.* **1973**, *36*, 3383-3384. (b) Wakatsuki, Y.; Yamazaki, H. *J. C. S. Chem. Commun.* **1973**, 280.

(17) Moretto, A. F.; Zhang, H.-C.; maryanoff, B. E. *J. Am. Chem. Soc.* **2001**, *123*, 3157-3158. (b) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487-489.

(18) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2007**, *9*, 505-508.

(19) (a) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149-3159. (b) Kotora, M.; Hessler, F.; Eignerová *Eur. J. Org. Chem.* **2012**, 29-42.

(20) Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, *12*, 5644-5647.

(21) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *J. Am. Chem. Soc.* **2010**, *132*, 5924-5925.

(22) (a) Knoch, F.; Kremer, F.; Schmidt, U.; Zenneck, U. *Organometallics* **1996**, *15*, 2713-2719. (b) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 7162-7166. (c) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474-1475. (d) Hilt, G.; Hess,W.; Vogler, T.; Hengst, C. *J. Organomet. Chem.* **2005**, 5170-5181. (e) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2992-2994.

(23) Viola, V. E. *Journal of Chemical Education*, **1990**, *67*, 723-730.

(24) Tuck, C. A.; Virta, R. L. *U.S. Gological Survey Minerals Yearbook–2011* **2013**, 39.1-39.17.

(25) (a) Hemoglobin: Perutz, M. F.; Rossmann, M. G.; Cullis, A. F.; Muirhead, H.; Will, G. *Nature* **1960**, *185*, 416-422. (b) Nitrogenase: Anderson, J. S.; Rittle, J.; Peters, J. C. *Nature* **2013**, *501*, 84-88.

(26) Fe(VI): Wagner, B.; Reinen, D.; Brunold, T. C.; Güdel *Inorg. Chem.* **1995**, *34*, 1934-1942. Fe(V): Kundu, S.; Thompson, J. V. K.; Ryabov, A. D.; Collins, T. J. *J. Am. Chem. Soc.* **2011**, *133*, 18546-18549. Fe(IV): Bigi, J. P.; Harman, W. H.; Lassalle-Kaiser, B.; robles, D. M.; Stich, T. A.; Yano, J.; Britt, R. D.; Chang, C. J. *J. Am. Chem. Soc.* **2012**, *134*, 1536-1542. Fe(I): Zadrozny, J. M.; Xiao, D. J.; Long, J. R.; Atanasov, M.; Neese, F.; Grandjean, F.; Long, G. J. *Inorg. Chem.* **2013**, *52*, 13123-13131. Fe2-: Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364-1367.

(27) Blanchard, S.; Derat, E.; Murr, M. D.-E.; Fensterbank, L.; Malacria, M.; Mouriès-Mansuy, V. *Eur. J. Inorg. Chem.* **2012**, 376-389.

(28) Szilagyi, R. K.; Lim, B. S.; Glaser, T.; Holm, R. H.; Hedman, B.; Hodgson, K. O.; Solomon, E. I. *J. Am. Chem. Soc.* **2003**, *125*, 9158-9169.

(29) a) Small, B. L.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 4049-4050. b) Britovsek, G. J. P.; Givson, V. C.; Kimberley, B. S.; Maddox, P. J.; McTavish, S. J.; Solan, G. A.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1998**, 849-850. c) Small, B. L.; Brookhart, M.; *J. Am. Chem. Soc.* **1998**, *120*, 7143-7144.

(30) Tondreau, A. M.; Milsmann, C.; Patrick, A. D.; Hoyt, H. M.; Lobkovsky, E.; Wieghardt, K.; Chirik, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 15046-15059.

(31) a) Cruz, V. L.; Ramos, J.; Martinez-Salazar, J.; Gutiérrez-Oliva, S.; Toro-Labbé, A. *Organometallics* **2009**, *28*, 5889-5895. b) Raucoules, R.; de Bruin, T.; Adamo, C.; Raybaud, P. *Organometallics* **2011**, *30*, 3911-3914.

(32) Britovsek, G. J. P.; Clentsmith, G. K. B.; Gibson, V. C.; Goodgame, D. M. L.; McTavish, S. J.; Pankhurst, Q. A. *Catal. Commun.* **2002**, *3*, 207-211.

(33) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794-13807.

(34) Bart, S. C.; Chłopek, K.; Bill, E.; Bouwkamp, M. W.; Lobkovsky, E.; Neese, F.; Wieghardt, K.; Chirik, P. J. *J. Am. Chem. Soc.*, **2006**, *128*, 13901-13912.

(35) Danopoulos, A. A.; Wright, J. A.; Motherwell, W. B. *Chem. Commun.* **2004**, 784-786.

(36) Tondreau, A. M.; Atienze, C. C. H.; Weller, K. J.; Nye, S. A.; Lewis, K. M.; Delis, J. G.; Chirik, P. J. *Science*, **2012**, *335*, 567-570.

(37) Raynaud, J.; Wu, J. Y.; Ritter, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 11805-11808.

(38) http://www.accessdata.fda.gov

(39) (a) Kiuru, P.; Yli-Kauhaluoma, J. *Heterocycles in Natural Product Synthesis* **2011**, 267-297. (b)Kumar, V.; Mahajan, M. P. *Heterocycles in Natural Product Synthesis* **2011**, 507-533. (c) Escolano, C.; Amat, M.; Bosh, J. *Chem.–Eur. J.* **2006**, *12*, 8198-8207.

(40) (a) Motoyama, T.; Sasabe, H.; Seino, Y.; Takamatsu, J.; Kido, J. *Chem. Lett.* **2011**, *40*, 306-308. (b) Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M.; Baum, G.; Genske, D. *Angew. Chem., Int. Ed.* **1997**, *36*, 1842-1844.

(41) http://news.agropages.com

(42) www.prg.org

(43) http://www.businesskorea.co.kr

(44) a) Wang, C.; Jung, G.-Y., Batsanov, A. S.; Bryce, M. R.; Petty, M. C. *J. Mater. Chem,* **2002**, *12*, 173. b) Liu, M.; Su, S.-J.; Jung, M.-C.; Qi, Y.; Zhao, W.-M.; Kido, J. *Chem. Mater.* **2012**, *24*, 3817. c) Chang, C.-H.; Wu, Z.-J.; Dhiu, C.-H.; Liang, Y.-H.; Tsai, Y.-S.; Liao, J.-L. Chi, Y.; Hsieh, H.-Y.; Kuo, T.-Y.; Lee, G.-H.; Pan, H.-A.; Chou, P.-T.; Lin, J.-S.; Tseng, M.-R. *ACS Appl. Mater. Interfaces* **2013**, *5*, 7341.

CHAPTER 2

THE IRON-CATALYZED CYCLOADDITION OF ALKYNENITRILES AND

ALKYNES; THE FIRST GENERAL IRON-CATALYZED

METHOD TO PRODUCE PYRIDINES

Introduction

Iron has long been known as an effective catalyst for the [2+2+2]

cyclotrimerization of alkynes, with reports dating back to 1960.[1] This reaction has since

been expanded to regioselective 3-component cyclizations[2] and the intramolecular

cyclization of triynes.[3] These methods are an excellent example of how complex

products can be made in an atom-economical fashion using an inexpensive nontoxic

catalyst.

The iron-catalyzed synthesis of pyridines does not share the same efficiency.

Despite early reports that iron is capable of producing pyridines in a [2+2+2] fashion, few

efforts have been made to develop this into useful methodology. The first report of iron-

catalyzed pyridine synthesis from acetylene and acetonitrile was in 1992 by Zenneck.[4]

Although pyridine production was catalytic, it was significantly overshadowed by

cyclotrimerization of the more reactive acetylene. In an effort to favor the production of

pyridine, Zenneck tested the reactivity of a unique (η^6-phosphinine)Fe(cod) complex

(equation 1).[5] Although turnover numbers (TON) for pyridine production were as high as 160 (mole pyridine/mole catalyst), arenes still dominated the product mixture. Guerchais then demonstrated that pyridines could be produced exclusively from (Cp*)Fe(MeCN)$_3$ in acetonitrile solvent (equation 2).[6] This reaction was not catalytic, however, due to strong η^6-binding of the pyridine product to the iron reagent.
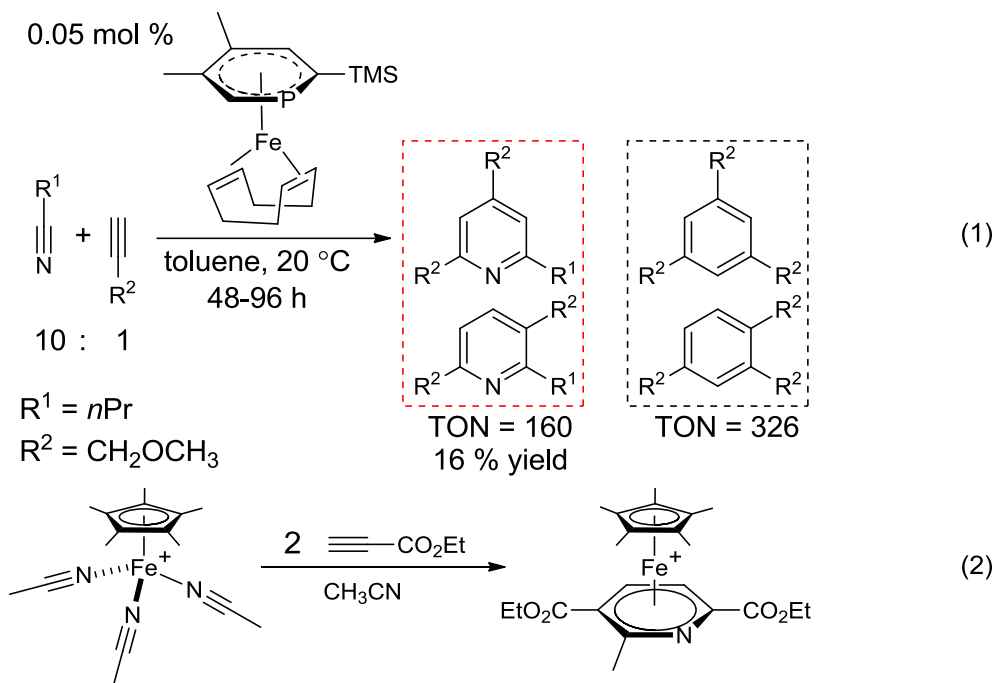
These examples demonstrate the overwhelming reactivity of alkynes as compared to nitriles in iron-mediated [2+2+2] cycloaddition. Guerchais was able to overcome the barrier to nitrile incorporation by utilizing a complex with precoordinated acetonitrile ligands. Additionally, the reaction was carried out in acetonitrile solvent. In this case, both factors seem to increase the local concentration of nitrile around the iron center, leading to exclusive pyridine formation.

We theorized that, if a nitrile could be held in close proximity to the iron center, catalytic pyridine production may be possible. Using a stoichiometric iron reagent with precoordinated nitriles is neither synthetically useful nor efficient. Alternatively a system

which employs a large nitrile:alkyne ratio could improve the selectivity for pyridine products. Such an approach would, however, negate the atom-economy provided by [2+2+2] cycloaddition by leaving unreacted nitrile. Such disadvantages would make reactions requiring elaborate nitriles highly unattractive. A third and more elegant method would be to utilize substrates where the unreactive nitrile is tethered to the more reactive alkyne. Such a substrate should facilitate nitrile incorporation regardless of the metallacyclic intermediate (Figure 11). Thus we set out to develop an iron-catalyzed cycloaddition of alkynenitriles and alkynes.

Discussion

To begin developing this system, a wise approach would be to start with the iron complexes that have previously catalyzed pyridine synthesis. The half-sandwich complex synthesized by Zenneck and co-workers required the addition of iron vapor to a solution of phosphinine and cyclooctadiene (cod). Guerchais' $(Cp^*)Fe(MeCN)_3$ (**3**) complex was available in four synthetic steps and was low yielding. Neither complex offers practical access to an iron catalyst platform on which to begin screening.

In contrast to these problematic catalysts, Okomoto's triyne cyclotrimerization system utilizes readily accessible catalyst systems (equation 3).[3] This method only requires catalytic amounts of an iron salt, a ligand, and zinc dust. Presumably the iron salt coordinates to the ligand *in situ,* then undergoes a two-electron reduction by zinc (equation 4). The authors followed their initial report with a description of the various ligands that are effective for this reaction (Figure 12).[3] If modified, this simple and practical approach could be applied toward the cyclization of alkynenitriles and alkynes.

The initial hit came from the combination of 30 mol% $Fe(OAc)_2$, 40 mol%
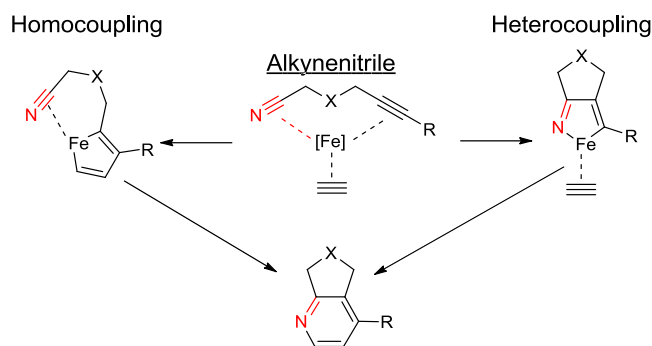
Figure 11. Alkynenitriles will aid nitrile incorporation no matter which catalytic cycle is operative.
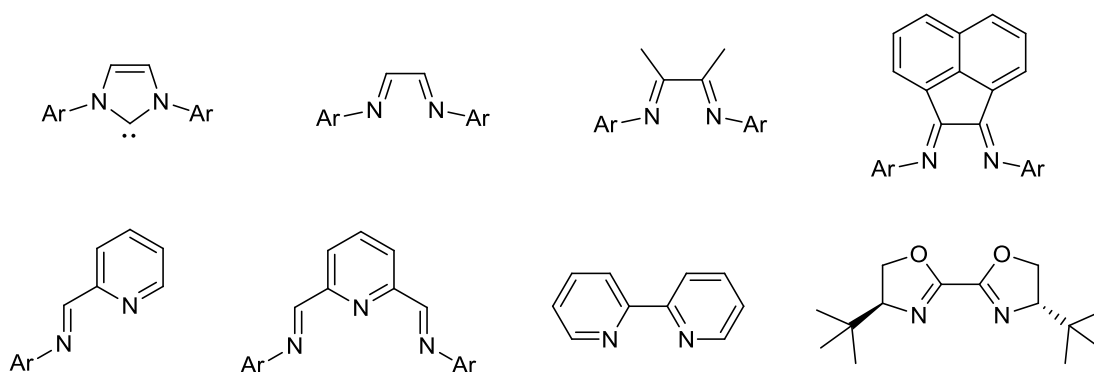
Figure 12. Ligands which effectively catalyzed the cycloaddition of triynes in Okomoto's system.

$$FeX_2 + Ligand \xrightarrow{\quad Zn \quad} (Ligand)Fe^0 \qquad (4)$$
$$\searrow ZnX_2$$
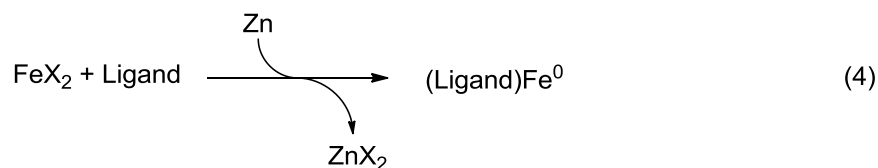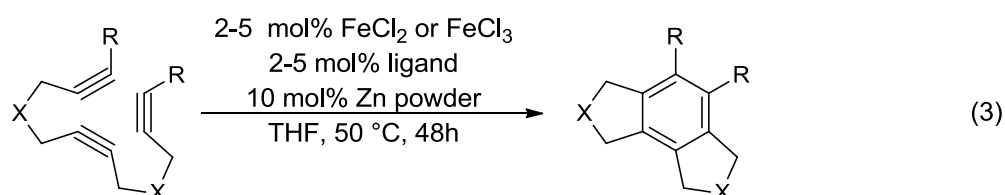
^{Mes}Bisimine ligand (**L4**), and 40 mol% Zn dust in DMA at 80 °C. Despite the

exhaustive optimization of this system, yields never exceeded 47% (GC yield) (Table 2).

The ligands from Okamoto's report were then reassessed in greater depth. While ^{iPr}PDAI

(**L7**) was ineffective, the very similar ^{Mes}PDAI (**L8**) provided significantly improved

activity, affording 84% (GC yield). By fine-tuning the steric and electronic environment

of the ligand, ^{iPr,OBn}PDAI (**L10**) was determined to be optimum the ligand for this reaction. The final optimized conditions utilized 10 mol% Fe(OAc)$_2$, 13 mol% ^{iPr,OBn}PDAI, 20 mol% Zn dust in DMF at 85 °C.

$$\text{(5)}$$
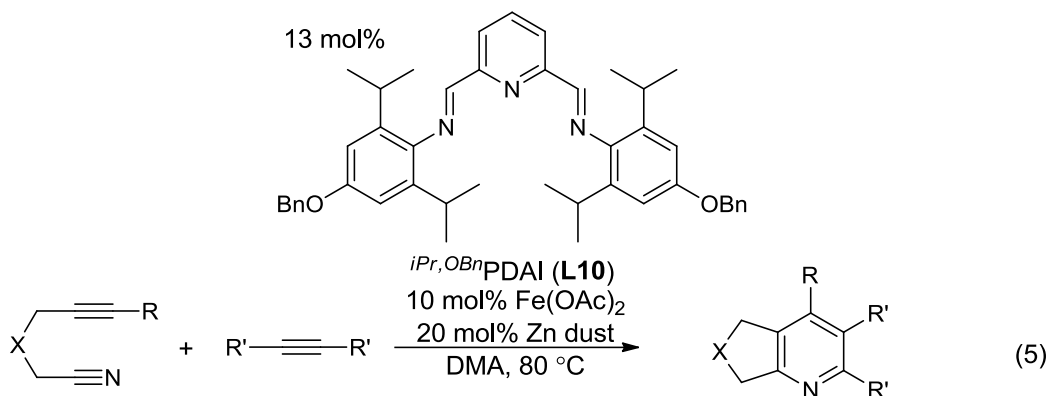
The scope and limitations of this reaction were assessed (Table 3). Substitution of the alkynenitrile-alkyne tolerated both alkyl and aryl substituents (entries 1-3). Despite a propensity to cyclotrimerize into benzene products, the challenging terminal alkyne-containing substrate, **1d**, provided **3d** in 30% yield (entry 4). Remarkably the bulky TMS substituent of **1e** was cyclized in 57% yield, demonstrating a high tolerance for steric bulk at this position (entry 5). Decreasing the bulk of the free alkyne made no significant difference to the yield (entry 6). Diphenyl acetylene (**2c**) was effectively cyclized if two-equivalents were employed (entry 7). Changing the backbone of the alkynenitrile demonstrated varied results. Heteroatom tethers afforded moderate yields of pyridine product (entries 9-11) while the alkyl tether of **1f** was well tolerated, with a 65% yield (entry 8). The aromatic backbone of **1k** can afford an interesting tricyclic pyridine in good yield (entry 13). Finally, increasing the tether length tested the boundaries of this reaction (entry 12). The creation of a 6-6-bicyclic pyridine **3l** could be done in moderate yield, however, longer tethers were unreactive.

Table 2. Ligand Screening

entry	ligand		% conversion	yield^a (%)	entry	ligand		% conversion	yield^a (%)
					5	**L5**	R^1,R^2,R^3 = Me	43	0
					6	**L6**	R^1 = Me, R^2 = iPr, R^3 = H	63	2
					7	**L7**	R^1 = H, R^2 = iPr, R^3 = H	42	0
1	**L1**	R^1,R^2,R^3 = Me	49	10	8	**L8**	R^1 = H, R^2, R^3 = Me	100	84
2	**L2**	R^1 = Me, R^2 = iPr, R^3 = H	3	0	9	**L9**	R^1 = H, R^2 = Me, R^3 = OBn	100	62*
3	**L3**	R^1 = H, R^2, R^3 = Me	36	2	10	**L10**	R^1 = H, R^2 = iPr, R^3 = OBn	100	95*
4	**L4**	R^1 = H, R^2 = iPr, R^3 = H	63	47					

^{a} Yields determined by GC using a naphthalene internal standard

* 20 mol % Fe(OAc)$_2$, 30 mol % ligand, 30 mol % Zn

Table 3. Pyridine Substrate Scope

entry	alkynenitrile		alkyne	time	yield (%)	entry	alkynenitrile		alkyne	time	yield (%)
	E = CO$_2$Me		Bu—≡—Bu			8	X = CH$_2$, R = Ph	**1f**	**2a**	4h	**3h**, 65
1	R = Me	**1a**	**2a**	2h	**3a**, 70	9	X = O, R = Et	**1g**	**2a**	4h	**3i**, 41
2	R = Et	**1b**	**2a**	26h	**3b**, 86	10	X = O, R = Ph	**1h**	**2a**	4h	**3j**, 45
3	R = Ph	**1c**	**2a**	5h	**3c**, 75						
4	R = H	**1d**	**2a**	26h	**3d**, 30	11		**1i**	**2a**	4h	**3k**, 41
5	R = TMS	**1e**	**2a**	6h	**3e**, 57						
6		**1a**	**2b**	6h	**3f**, 71	12		**1j**	**2a**	24h	**3l**, 40^b
7		**1a**	**2c**	5h	**3g**, 54^a	13		**1k**	**2a**	4h	**3m**, 64

^{a} 2 equiv of alkyne. ^{b} 20 mol % catalyst loading, 26 mol % **L10**, 40 mol % Zn

The regioselectivity of unsymmetrical alkynes was also studied (Table 4).

Alkyl/aryl-substituted alkynes demonstrated a moderate selectivity to place the alkyl

substituent next to the pyridine nitrogen atom (entries 1-4, 6). This trend was

exaggerated to a ratio of 4:1 when using an electron-withdrawing substituent (**2f**) on the

aryl group or when using a pyridyl-substituted alkyne (**2g**). The latter likely invokes a

chelation effect to provide its regioselectivity. Interestingly, the larger n-butyl substituent

reversed the regioselectivity in entry 5. This system was unable to differentiate linear

alkyl from methyl substituents (entry 7), however, tert-butyl afforded complete

regioselectivity to place the bulkier substituent adjacent to the pyridine nitrogen atom

(entry 8). The regioisomer identity of **3n** was confirmed by x-ray crystallography (Figure

13).

To identify the structure of the precatalyst, unsuccessful attempts were made to

synthesize (^{iPr,OBn}PDAI)Fe(OAc)$_2$. Instead the similar (^{OBn,iPr} PDAI)FeBr$_2$ proved to be

more readily accessible. This complex could effectively catalyze the reaction along with

the *in situ* zinc reductant (equation 6). The 58% isolated yield of this reaction compares

well with the 54% GC yield of the reaction run with uncoordinated FeBr$_2$. Crystals of

(^{iPr,OBn}PDAI)FeBr$_2$ were grown, however, x-ray crystallographic analysis demonstrated

Table 4. Unsymmetrical alkynes

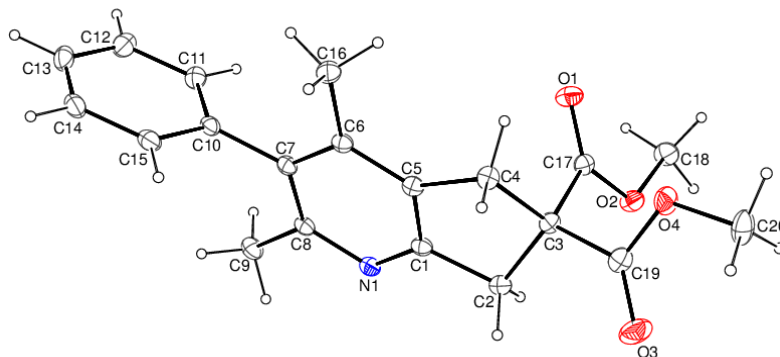| entry		alkyne	time	yield % (**3:3'**)	entry		alkyne	time	yield % (**3:3'**)
		R———R'			5	**2h**	R = Bu R' = Ph	5h	**3r**, 53 (2:3)
1	**2d**	R = Me R' = Ph	6h	**3n**, 69 (1.2:1)	6	**2i**	R = (CH$_2$)$_2$NTsBoc R' = Ph	5h	**3s**, 44 (3:2)
2	**2e**	R = Me R' = p-OMeC$_6$H$_4$	6h	**3o**, 39 (3:2)	7	**2j**	R = Me R' = Bu	24h	**3t**, 62 (1:1)
3	**2f**	R = Me R' = p-CF$_3$C$_6$H$_4$	6h	**3p**, 39 (4:1)	8	**2k**	R = Me R' = ^{t}Bu	6h	**3u**, 26 (0:1)
4	**2g**	R = Me R' = Py	16h	**3q**, 56 (7:3)					

Figure 13. Ortep of **3n**.

significant disorder in the benzyloxy substituents. This analysis did, however confirm the tridentate coordination mode of the complex. Subsequently the analogous methoxy-substituted complex (^{iPr,OMn}PDAI)FeBr$_2$ was synthesized and characterized by x-ray crystallography (Figure 14).

(6)
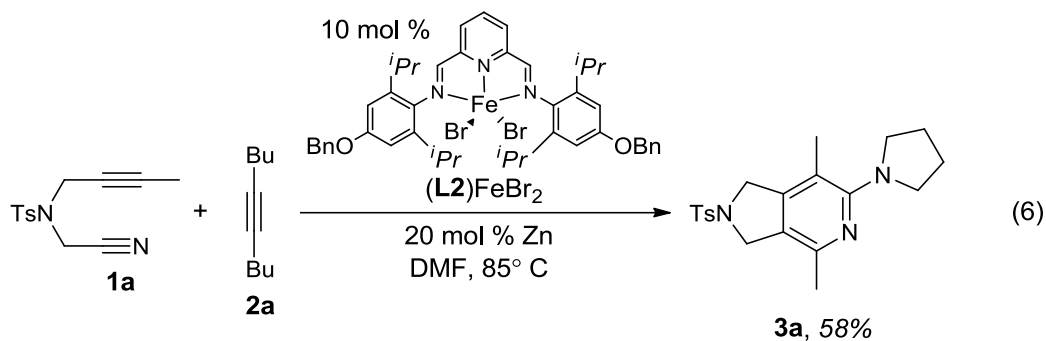
Conclusion

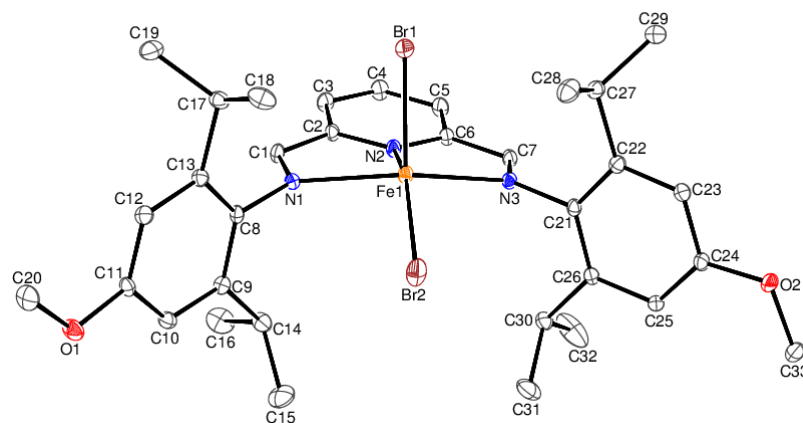**Figure 14**. ORTEP of (^{OMe,iPr}PDAI)FeBr$_2$.

The first general and practical method to synthesize pyridines via iron-catalyzed [2+2+2] cycloaddition has been successfully developed. By tethering the unreactive nitrile to the more reactive alkyne, the obstacle of poor nitrile reactivity was overcome. Furthermore the key to this reaction was the utilization of the dimethoxy-substituted bis(aldimino)pyridine ligand (^{iPr,OBn}PDAI)FeBr$_2$. The oxidative identity of the active catalyst as well as the likely catalytic pathway will be addressed in Chapter 5. Studies to improve and expand the applications of this catalyst system have since been undertaken and are disclosed in the subsequent chapters of this thesis.

Experimental

General experimental. All reactions were conducted under an atmosphere of N$_2$ using standard Schlenk techniques or in a N$_2$, filled glove box, unless otherwise noted. Toluene was dried over neutral alumina under N$_2$ using a Grubbs-type solvent purification system. Dimethyl formamide was purchased from Sigma Aldrich in a sure-seal bottle. THF was freshly distilled from Na/benzophenone. Iron acetate (99.995% purity) was purchased from Sigma Aldrich. Alkynenitriles **1a**, **1b**,[7] **1i**,[8] and **1j**,[9] were prepared by known literature procedures. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz, respectively, unless otherwise noted. All spectra are referenced to residual proteated CHCl$_3$ via a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.26 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, quartet, and quintet, respectively. All ^{13}C NMR spectra are proton decoupled. Gas Chromatography was performed using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 10 ºC/min.; final

temperature: 300 ºC held for 12 minutes; detector temperature: 250 ºC. S2

Ligand syntheses. Ligands **L1-L6**[10] and **L7-L10**[11] were synthesized by the reported methods. Ligands **L11** and **L12** were synthesized as follows:

Step 1 (general procedure). Adapted from the literature procedure.[12] To a stirring mixture of 2,6-substituted aniline and $NaHCO_3$ (3 equiv) in methanol, a solution of iodinemonochloride (1.1 equiv) in CH_2Cl_2 was added dropwise over 1 hour. The reaction was stirred at room temperature for 24 hours. Solids were filtered from the mixture and rinsed with diethyl ether. The filtrate was reduced *in vacuo* to a dark red oil to which a 300 mL solution of saturated sodium thiosulfate was added. The solution was stirred for 10 minutes then extracted with 3 x 200 mL portions of diethyl ether. The organic extracts were dried with Na_2SO_4 and reduced *in vacuo*.

Synthesis of 4-iodo-2,6-dimethylaniline. 4-iodo-2,6-dimethylaniline was prepared using the Step 1 general procedure with 2,6-dimethylaniline (10.0 g, 83 mmol), iodinemonochloride (14.7 g, 91 mmol), and sodium bicarbonate (20.8 g, 248 mmol). The reaction was stirred at room temperature with 115 mL of methanol and 90 mL of dichloromethane to yield 4-iodo-2,6-dimethylaniline (19.2g, 93%) as a dark red oil. Spectral data match the reported values.[13]

Synthesis of 4-iodo-2,6-diisopropylaniline. 4-iodo-2,6-diisopropylaniline was prepared using the Step 1 general procedure with 2,6 diisopropylaniline (10.0 g, 56 mmol), iodinemonochloride (10.1 g, 62 mmol), and sodium bicarbonate (14.2 g, 169 mmol). The reaction was stirred at room temperature with 80 mL of methanol and 60 mL of dichloromethane to yield 4-iodo-2,6-diisopropylaniline (16.8 g, 93%) as a dark red oil. Spectral data match the reported values.[14]

Step 2 (general procedure). Adapted from the literature procedure.[14] In a nitrogen glove box, a 20 mL scintillation vial was filled with CuI (7 mol%) 3,4,7,8-tetramethyl-1,10-phenanthroline (Me$_4$Phen, 14 mol%), Cs$_2$CO$_3$ (2.0 equiv), and 4-iodo-2,6-dialkyl aniline (1.0 equiv). The vial was sealed with a rubber septum, removed from the glove box, then evacuated and backfilled with Argon three times. Toluene was added and the mixture was stirred at 80 °C for 20 minutes. Benzyl alcohol (2.0 equiv) was added and the rubber septum was quickly replaced with a vial cap. The reaction was stirred for 24 hours at 80 °C then cooled to room temperature, filtered through a silica gel plug, and flushed with 150 mL of ethyl acetate. The resulting solution was reduced *in vacuo* and purified using silica gel flash chromatography with 10% ethyl acetate in hexanes.

Synthesis of 4-(benzyloxy)-2,6-dimethylaniline. 4-(benzyloxy)-2,6-dimethylaniline was prepared using the Step 2 general procedure with CuI (57.8 mg, 0.30 mmol), Me$_4$Phen (143.5 mg, 0.61 mmol), cesium carbonate (1.56 g, 8.1 mmol), 4-iodo-2,6-dimethylaniline (1.0 g, 4.0 mmol), and benzyl alcohol (875.3 mg, 8.1 mmol). The reaction was run for 24 hours at 80 °C in 1.9 mL of toluene to yield 4-(benzyloxy)-2,6-dimethylaniline (362.9 mg, 40%) as a blue solid. Mp: 71-73 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 7.48-7.33 (m, 5H), 6.68 (s, 2H), 5.01 (s, 2H), 3.35 (s, 2H), 2.20 (s, 6H). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 151.5, 137.9, 136.9, 128.7, 127.9, 127.7, 123.4, 115.2, 70.9, 18.2. IR (cm-1) 3450, 3375, 3032, 2969, 2908, 2735, 1602, 1489, 1380, 1328, 1298, 1242, 1150, 1054, 856, 738, 698. HRMS (ESI) calcd for C$_{15}$H$_{17}$NO [M+H]+ 228.1388, found 228.1385.

Synthesis of 4-(benzyloxy)-2,6-diisopropylaniline. 4-(benzyloxy)-2,6-

diisopropylaniline was prepared using the Step 2 general procedure with CuI (57.8 mg, 0.30 mmol), Me$_4$Phen (143.5 mg, 0.61 mmol), cesium carbonate (1.56 g, 8.1 mmol), 4-iodo-2,6-diisopropylaniline (1.0 g, 4.0 mmol), and benzyl alcohol (875.3 mg, 8.1 mmol). The reaction was run for 24 hours at 80 °C in 1.9 mL of toluene to yield 4-(benzyloxy)-2,6-diisopropylaniline (948.9 mg, 84%) as a dark red oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.48-7.27 (m, 5H), 6.74 (s, 2H), 3.48 (s, 2H), 3.01- 2.94 (m, 2H), 1.28 (d, J = 6.8, 12H). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 152.4, 138.0, 134.5, 134.4, 128.7, 128.01, 127.96, 110.1, 71.0, 28.4, 22.7. IR (cm-1) 3382, 2960, 1599, 1463, 1347, 1218, 1175, 1100, 1027, 737, 696. HRMS (ESI) calcd for C$_{19}$H$_{26}$NO [M+H]+ 284.2014, found 284.2013.

Step 3 (general procedure). Adapted from the literature procedure.[12] 4-benzyloxy-2,6-dialkyl aniline (2.0 equiv) and 2,6-pyridinedicarboxaldehyde (1.0 equiv) and a catalytic amount of glacial acetic acid were stirred in 100% ethanol overnight at room temperature. The mixture was cooled to 0 °C, filtered, and rinsed with cold 100% ethanol.

Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(4-(benzyloxy)-2,6-dimethylaniline) (L11). Coumpound **L11** was prepared using the Step 3 general procedure with 4-(benzyloxy)-2,6-dimethylaniline (194.6 mg, 0.86 mmol), 2,6-pyridinedicarboxaldehyde (57.8 mg, 0.43 mmol), and 5 drops of glacial acetic acid. The reaction was run at room temperature in 10 mL of 100% ethanol yielding **L11** (108.0 mg, 45.6%) as a yellow solid. Mp: 174-177 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 8.40 (s, 2H), 8.38 (d, J = 8.0 2H), 7.97 (t, J = 7.8, 1H), 7.47-7.33 (m, 10H), 7.76 (s, 4H), 5.06 (s, 4H), 2.20 (s, 12H). ^{13}C NMR (75

MHz, CDCl$_3$): δ (ppm). IR (cm-1) 3087, 2970, 2948, 1602, 1584, 1480, 1455, 1379, 1332, 1312, 1198, 1052, 738, 698. HRMS (ESI) calcd for C$_{37}$H$_{35}$N$_3$O$_2$ [M+H]+ 576.2627, found 576.2633.

Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(4-(benzyloxy)-2,6-diisopropylaniline) (L12).

Coumpound **L12** was prepared using the Step 3 general procedure with 4-(benzyloxy)-2,6-diisopropylaniline (2.35 g, 8.3 mmol), 2,6-pyridinedicarboxaldehyde (599.5 mg, 4.1 mmol), and 10 drops of glacial acetic acid. The reaction was run at room temperature in 10 mL of 100% ethanol to yield **L12** (2.48 g, 85%) as a yellow solid. M.P. 170-173 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 8.40-8.38 (m, 4H), 7.99 (t, J = 8.0, 1H), 7.51-7.28 (m, 10H), 6.83 (s, 4H), 5.08 (s, 4H), 3.07-2.98 (m, 4H), 1.18 (d, J = 7.2, 24H). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 163.4, 156.3, 154.8, 142.4, 139.1, 137.6, 137.5, 128.1, 128.2, 128.0,122.8, 109.9, 70.5, 28.4, 23.7. IR (cm-1) 3391, 2961, 2869, 1637, 1600, 1458, 1326, 1190, 1026, 736. HRMS (ESI) calcd for C$_{45}$H$_{51}$N$_3$O$_2$ [M+H]+ 688.3879, found 688.3882.

Synthesis of dimethyl-2-(cyanomethyl)malonate. To a stirring suspension of NaH (1.8 g, 75.7 mmol) in 150 ml THF was added dimethylmalonate (10 g, 75.7 mmol) under N$_2$ counter-flow. The resulting solution was stirred at room temperature for 1 h, after which time bromoacetonitrile (5.0 g, 42.1 mmol) was added. The mixture was stirred at room temperature for 24 h, at which time the solution was quenched with 100 mL of a saturated NH$_4$Cl solution. The layers were separated and the aqueous layer was extracted with Et$_2$O (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over anhydrous MgSO$_4$, and concentrated *in vacuo*. The resulting crude

yellow oil was purified by flash column chromatography (20% EtOAc/hexanes) to yield

dimethyl-2-(cyanomethyl)malonate (4.1 g, 57%) as a pale yellow oil. ^{1}H NMR (400

MHz, CDCl$_3$) δ (ppm) 3.78 (s, 6H), 3.73 (t, J= 8.8 Hz, 1H), 2.89 (d, J= 7.2 Hz, 2H). [13]C

NMR (100 MHz, CDCl$_3$) δ (ppm) 167, 116.8, 53.5, 47.8, 17.1.

Synthesis of dimethyl 2-(cyanomethyl)-2-(prop-2-yn-1-yl)malonate (1d).

Dimethyl-2-(prop-2-yn-1-yl)malonate was prepared by known literature procedure.[15] To

a stirring suspension of NaH (0.21 g, 8.82 mmol) in 50 mL THF was added dimethyl-2-

(prop-2-yn-1-yl)malonate (1.0g, 5.88 mmol) under N$_2$ counter-flow. The resulting

solution was stirred at room temperature for 1 h, after which time bromoacetonitrile (1.0

g, 8.82 mmol) was added. A reflux condenser was attached and the mixture was stirred

at reflux for 8-12 h, at which time GC analysis showed no starting material. The solution

was cooled to room temperature and quenched with 100 mL of a saturated NH$_4$Cl

solution. The layers were separated and the aqueous layer was extracted with Et$_2$O (3 x

100 mL). The combined organics were washed with brine (100 mL), dried over

anhydrous MgSO$_4$, and concentrated *in vacuo*. The resulting crude yellow oil was

purified by flash column chromatography (10% EtOAc/hexanes then 12%

EtOAc/hexanes) to yield **1d** (0.6 g, 49%) as pale yellow oil. [1]H (400 MHz, CDCl$_3$): 3.83

(s, 6H), 3.17 (s, 2H), 3.03 (d, J= 2.8Hz, 2H), 2.13 (t, J= 2.8Hz, 1H). [13]C (100 MHz,

CDCl$_3$) δ (ppm) 168.3, 116.4, 81.0, 71.8, 53.9, 24.2, 22.1, 3.7. IR (cm-1) 3288, 2960,

2253, 1743, 1483, 1327, 1217, 971, 892. HRMS calculated for C$_{10}$H$_{11}$NO$_4$Na 232.0586,

found 232.0592.

Synthesis of dimethyl-2-(cyanomethyl)-2-(3-phenylprop-2-yn-1-yl)malonate

(1c). Pd(PPh$_3$)$_2$Cl$_2$ (28.4 mg, 0.04 mmol) and CuI (27.7 mg, 0.14 mmol) were added to a

solution of **1d** (3.0 g, 14.5 mmol) in Et$_3$N (17 mL). To the mixture was added a solution

of phenyl iodide (1.6 g, 8.1 mmol). The resulting mixture was stirred at 50 °C for 6 h.

The reaction was quenched by the addition of water and extracted with Et$_2$O. The

organic layer was washed with saturated aqueous NH$_4$Cl, and the water layer was

extracted with Et$_2$O. The combined organic layer was washed with brine, dried over

Na$_2$SO$_4$, and concentrated. The residue was purified on a silica gel column

chromatography (10% EtOAc/Hexanes), which furnished **1c** (1.2 g, 52% yield) as a dark

brownish yellow oil. ^{1}H (400 MHz, CDCl$_3$): δ (ppm) 7.34 (m, 5H), 3.85 (s, 6H), 3.25 (s,

2H) 3.22 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 168.1, 132.0, 128.7, 128.5,

122.6, 116.2, 85.2, 82.3, 55.5, 54.0, 24.7, 22.3. IR (cm-1) 2957, 2253, 1743, 1438, 1295,

1215, 1030. HRMS (ESI) calculated for C$_{16}$H$_{15}$NO$_4$Na (M+Na)+ 308.0899, observed

308.0895.

Synthesis of dimethyl 2-(cyanomethyl)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)malonate (1e). To a stirring suspension of NaH (0.12 g, 4.82 mmol) in 30 mL THF

was added dimethyl-2-(cyanomethyl)malonate (0.55 mg, 3.21 mmol) under N$_2$. The

resulting solution was stirred at room temperature for 1 h, after which time (3-bromoprop-1-yn-1-yl)trimethylsilane (0.50 g, 4.82 mmol) was added. A reflux condenser

was attached and the mixture was stirred at reflux for 12 h, at which time GC analysis

showed no starting material. The solution was cooled to room temperature and quenched

with 70 mL of a saturated NH$_4$Cl solution. The layers were separated and the aqueous

layer was extracted with Et$_2$O (3 x 70 mL). The combined organics were washed with

brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*.

The resulting crude yellow oil was purified by flash column chromatography (20%

EtOAc/hexanes) to yield **1e** (0.79 g, 87%) as a colorless solid. Mp: 34-36 °C. ^{1}H NMR

(400 MHz, CDCl$_3$): δ(ppm) 3.82 (s, 6H), 3.14 (s, 2H), 3.03 (s, 2H), 0.15 (s, 9H). ^{13}C

NMR (100 MHz, CDCl$_3$) δ(ppm) 167.9, 116.2, 99.1, 90.5, 55.4, 53.9, 25.4, 22.1, 0.1. IR

(cm-1): 2960, 2902, 2253, 2181, 1746, 1437, 1322, 1294, 1028, 847. HRMS calculated

for C$_{13}$H$_{19}$NO$_4$NaSi 304.0981, found 304.0977.

Synthesis of 2-(pent-2-yn-1-yloxy)acetonitrile (1f). To a stirring suspension of

NaH (0.7 g, 30.9 mmol) in 25 ml THF was added pent-2-yn-1-ol (2.0 g, 23.8 mmol)

under N$_2$ counter-flow in two portions. The resulting solution was stirred at room

temperature for 1 h, after which time bromoacetonitrile (3.7 g, 30.9 mmol) was added.

The reaction mixture was stirred at room temperature for 8-12 h, at which time GC

analysis showed no starting material. The solution was cooled and quenched with 100

mL of a saturated NH$_4$Cl solution. The layers were separated and aqueous layer was

extracted with Et$_2$O (3 x 100 mL). The combined organics were washed with brine (100

mL), dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo*. The resulting crude

yellow oil was purified by flash column chromatography (10% EtOAc/hexanes) to yield

1f (1.2 g, 42%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 4.34 (s, 2H),

4.28 (t, J= 4.4 Hz, 2H), 2.25 (m, 2H), 1.15 (t, J= 7.6 Hz, 3H). ^{13}C NMR (100 MHz,

CDCl$_3$) δ (ppm) 115.9, 91.3, 72.8, 58.9, 54.0, 13.7, 12.5. IR (cm- 1) 2980, 2919, 2292,

1452, 1320, 1140, 1092, 902. HRMS (ESI) calcd for C$_{21}$H$_{24}$NO$_5$ [M+H]+ 124.0762,

found 124.0776.

Synthesis of 2-((3-phenylprop-2-yn-1-yl)oxy)acetonitrile (1g). To a stirring

suspension of NaH (0.3 g, 9.1 mmol) in 50 ml THF was added 3-phenylprop-2-yn-1-ol

(2.0 g, 7.57 mmol) under N$_2$ counter-flow. The resulting solution was stirred at room

temperature for 1 h, after which time bromoacetonitrile (1.1 g, 9.1 mmol) was added.
The mixture was stirred at room temperature for 12 h, at which time GC analysis showed
no starting material. The solution was cooled and quenched with 100 mL of a saturated
NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3
x 100 mL). The combined organics were washed with brine (100 mL), dried over
anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude yellow oil was
purified by flash column chromatography (20% EtOAc/hexanes) to yield **1g** (1.2 g, 92%)
as pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.49 (m, 2H), 7.36 (m, 3H),
4.55 (s, 2H), 4.43 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 132.0, 129.2, 128.6,
121.9, 115.9, 88.8, 82.3, 59.1, 54.3. IR cm-1 3060, 2908, 2857, 2242, 1964, 1598, 1490,
1350, 1249, 1093, 902, 759, 692. HRMS (ESI) calcd for $C_{11}H_{10}NO$ [M+H]+ 172.0762,
found 172.0728.

Synthesis of N-(cyanomethyl)-4-methyl-N-(3-phenylprop-2-yn-1yl)benzenesulfonamide (1h). To a stirring suspension of NaH (0.05 g, 1.9 mmol) in 20
ml THF was added 4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide[16] (0.5 g,
1.7 mmol) under N_2. The resulting solution was stirred at room temperature for 1 h, after
which time bromoacetonitrile (0.2 g, 1.9 mmol) was added. A reflux condenser was
attached and the mixture was stirred at reflux for 12 h, at which time GC analysis showed
no starting material. The solution was cooled to room temperature and quenched with
100 mL of a saturated NH_4Cl solution. The layers were separated and the aqueous layer
was extracted with Et_2O (3 x 100 mL). The combined organics were washed with brine
(100 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting crude
yellow oil was purified by flash column chromatography (30% EtOAc/hexanes) to yield

1h (0.34 g, 60%) as a colorless solid. Mp: 97-99 °C. ^{1}H (400 MHz, CDCl$_3$): δ (ppm)

7.78 (d, J= 8Hz, 2H), 4.28 (t, J= 4.4 Hz, 2H), 2.25 (m, 2H), 1.15 (t, J= 7.6 Hz, 3H). ^{13}C

(100 MHz, CDCl$_3$) δ (ppm) 145.2, 134.3, 131.9, 130.3, 129.2, 128.5, 128.1, 121.8, 113.8,

87.6, 80.1, 38.8, 35.4, 21.8. IR (cm-1) 2958, 2253, 1744, 1438, 1215, 1072, 759. HRMS

(ESI) calculated for C$_{18}$H$_{16}$N$_2$O$_2$NaS (M+Na) 347.0830, observed: 347.0835.

Synthesis of dimethyl-2-(but-2-yn-1-yl)-2-(2-cyanoethyl)malonate (1k). To a

stirring suspension of NaH (0.24 g, 10.1 mmol) in 100 ml THF was added

dimethylmalonate (2.00 g, 15.14 mmol) under N$_2$. The resulting solution was stirred at

room temperature for 1 h, after which time bromopropionitrile (1.35 g, 10.1 mmol) was

added. A reflux condenser was attached and the mixture was stirred at reflux for 12 h, at

which time the solution was cooled to room temperature and quenched with 100 mL of a

saturated NH$_4$Cl solution. The layers were separated and the aqueous layer was extracted

with Et$_2$O (3 x 100 mL). The combined organics were washed with brine (100 mL),

dried over anhydrous MgSO$_4$, and concentrated *in vacuo*. The resulting crude yellow oil

was purified by flash column chromatography (40% EtOAc/hexanes) to yield dimethyl-2-

(2-cyanoethyl)malonate (1.2 g, 64%) as a pale yellow oil. Spectral data were compared

with known literature values.[17]

To a stirring suspension of NaH (0.16 g, 6.5 mmol) in 50 ml THF was added

dimethyl-2-(2-cyanoethyl)malonate (**1g**, 5.4 mmol) under N$_2$. The resulting solution was

stirred at room temperature for 1 h, after which time 1-bromo-2-butyne (0.86 g, 6.5

mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux

for 12 h, at which time the solution was cooled to room temperature and quenched with

50 mL of a saturated NH$_4$Cl solution. The layers were separated and the aqueous layer

was extracted with Et$_2$O (3 x 50 mL). The combined organics were washed with brine

(50 mL), dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo*. The resulting crude

yellow oil was purified by flash column chromatography (40% EtOAc/hexanes) to yield

1k (0.6 g, 50%) as a colorless solid. Mp: 62-63 °C. ^{1}H (400 MHz, CDCl$_3$): δ (ppm) 3.78

(s, 6H), 2.79 (q, J= 2.4, 2.8 Hz, 2H), 2.44 (m, 4H), 1.77 (t, J= 2.4, 2.8 Hz, 3H). ^{13}C NMR

(100 MHz, CDCl$_3$) δ (ppm) 170.0, 119.2, 80.3, 72.4, 56.2, 53.3, 28.9, 24.2, 13.2, 3.7. IR

(cm-1) 2957, 2249, 1736, 1441, 1340, 1209. HRMS C$_{12}$H$_{15}$NO$_4$Na calculated: 260.0899,

observed 260.0898.

Synthesis of tert-butyl(4-phenylbut-3-yn-1-yl)tosylcarbamate (2i). Under N$_2$,

diisopropylazodicarboxylate (1.7 ml, 8.92 mmol, 1.1 equiv) was added to a solution of N-

(tert-butyoxycarbonyl)-p-toluenesulfonamide (2.2 g, 8.1 mmol, 1 equiv),

triphenylphosphine (8.9 g, 1.3 mmol, 1.1 equiv) and 4-phenylbut-3-yn-1-ol[18] (1.3 g, 8.92

mmol, 1.1 equiv) in a dropwise fashion at 0 °C. The reaction mixture was then stirred at

room temperature for 15 h. The solvent was removed under reduced pressure. Hexanes

(100 mL) were added to the resultant yellow mixture and the white precipitate was

filtered. The solid was preabsorbed on silica gel and purified by flash column

chromatography (20% EtOAc and Hexanes) affording the product **2i** as a white solid (3.1

g, 96%). Mp: 98-99 °C. ^{1}H (400 MHz, CDCl$_3$) δ (ppm) 7.84 (d, J= 6.8 Hz, 2H), 7.38 (m,

2H), 7.28 (m, 5H), 4.10 (t, J= 7.2 Hz, 2H), 2.89 (t, J= 8 Hz, 2H), 2.43 (s, 3H), 1.35 (s,

9H). ^{13}C (100 MHz, CDCl$_3$) δ ppm 151.1, 144.4, 137.6, 131.9, 129.5, 128.4, 128.2,

128.1, 123.7, 86.3, 84.7, 82.8, 45.6, 28.1, 21.8, 21.1. IR (in cm-1): 3058, 2980, 2932,

1739, 1598, 1357, 1287, 1162, 970, 846, 693. HRMS (ESI) calculated for m/z

C$_{22}$H$_{25}$NO$_4$NaS (M+Na)+ 422.1402, observed 422.1403.

General Procedure for Cycloaddition. In a nitrogen-filled glove box, a solution of alkynenitrile (>1.0 M in DMF) was added to a vial containing 10 mol% Fe(OAc)2 and 13 mol% **L12**. Additional DMF was added to make the final concentration of cyanoalkyne 0.4 M (accounting for alkyne volume). The mixture was stirred for 10 minutes, then 1 equiv of alkyne and 20 mol% of zinc dust were added. The vial was capped and removed from the glove box then stirred at 85 °C for the indicated period of time. The crude mixture was purified via silica gel flash chromatography.

Synthesis of dimethyl-2,3-dibutyl-4-methyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3a). Compound **3a** was prepared using the general procedure with **1a** (51.3 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)2 (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of N,N-dimethylformamide. The reaction was stirred at 85 °C for 2 hours and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3a** (58.2 mg, 70%) as a viscous, yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 3.75 (s, 6H), 3.70 (s, 2H), 3.64 (s, 2H), 2.72 (t, J = 8 Hz, 2H), 2.56, (t, J = 8 Hz, 2H), 2.19 (s, 3H), 1.62 (m, 2H), 1.42 (m, 2H), 0.93 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 172.4, 159.8, 156.6, 141.6, 123.3, 130.3, 57.7, 53.2, 42.2, 38.1, 35.6, 33.0, 32.5, 28.4, 23.4, 23.3, 15.9, 14.2, 14.1. IR (cm-1) 3476, 2963, 2019, 1736, 1582, 1438, 1380, 1241, 1071, 963, 863, 818, 737. HRMS (ESI) calcd for C$_{21}$H$_{32}$NO$_4$ [M+H]+ 362.2331, found 362.2338.

Synthesis of dimethyl-2,3-dibutyl-4-ethyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3b). Compound **3b** was prepared using the general procedure with **1a** (81.8 mg, 0.23 mmol), **2b** (47.7 mg, 0.35 mmol), Fe(OAc)2 (6.0 mg, 3.5 x 10-2 mmol),

L12 (29.9 mg, 4.5 x 10-2 mmol), and zinc (4.5 mg, 6.9 x 10-2 mmol) in 800 mL of dimethylformamide. The reaction was stirred at 85 °C for 4 hours and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3b** (102.9 mg, 86%) as a viscous, yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 3.75 (s, 6H), 3.63 (s, 2H), 3.51 (s, 2H), 2.76 (q, J = 7.6, 7.6, 7.6 Hz, 2H), 2.62 (q, J = 7.2, 7.2, 7.2 Hz, 2H), 2.20 (s, 3H), 1.24 (t, J = 7.6, 7.6 Hz, 3H), 1.10 (t, J = 7.6, 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 172.3, 160.4, 157.1, 147.4, 131.4, 129.7, 58.1, 53.2, 42.0, 37.5, 42.0, 37.5, 35.5, 33.7, 33.0, 27.9, 23.5, 23.4, 23.3, 14.2, 14.04, 13.98. IR (cm-1) 3476, 2958, 1744, 1580, 1437, 1408, 1378, 1253, 1104, 1070, 964, 905, 865, 736. HRMS (ESI) calcd for C$_{22}$H$_{34}$NO$_4$ [M+H]+ 376.2488, found 376.2497.

Synthesis of dimethyl-2,3-dibutyl-4-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3c). Compound **3c** was prepared using the general procedure with **1c** (98.4 mg, 0.35 mmol), **2a** (47.7 mg, 0.35 mmol), Fe(OAc)2 (6.0 mg, 3.5 x 10-2 mmol), **L12** (29.9 mg, 4.5 x 10-2 mmol), and zinc (4.5 mg, 6.9 x 10-2 mmol) in 800 mL of N,N-dimethylformamide. The reaction was stirred at 85 °C for 4 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3c** (136.6 mg, 75%) as a viscous, yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.42 (t, J = 8Hz, 2H), 7.36 (d, J = 7.2, 1H), 7.17 (d, J = 8 Hz, 2H), 3.71 (s, 6H), 3.22 (s, 2H), 2.78 (t, J = 10 Hz, 2H), 2.41 (t, J = 8 Hz, 2H), 1.70 (q, J = 7.2 Hz, 8 Hz, 2H), 1.46 (sext, J = 7.2 Hz, 7.2 Hz, 2H), 1.28 (q, J = 6.8 Hz, 8 Hz, 2H), 1.15 (q, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 2H), 0.96 (t, J = 7.2, 3H), 0.71 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 172.1, 160.6, 156.9, 146.8, 138.2, 131.6, 129.7, 128.6, 128.2,

127.7, 57.9, 42.3, 38.4, 35.4, 33.2, 32.9, 28.6, 23.3, 22.9, 14.2, 13.7. IR (cm-1) 2956, 2869, 1783, 1576, 1490, 1437, 1273, 1198, 1073, 964, 739. HRMS (ESI) calcd for $C_{26}H_{34}NO_4$ [M+H]+ 424.2488, found 424.2484.

Synthesis of dimethyl 2,3-dibutyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3d). Compound **3d** was prepared using the general procedure with **1d** (32.8 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)2 (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of N,N-dimethylformamide. The reaction was stirred at 85 °C for 26 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3d** (24.0 mg, 30%) as a viscous, yellow oil. ^1H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.23 (s, 1H), 3.76 (s, 6H), 3.65 (s, 2H), 3.54, (s, 2H), 2.76 (t, J = 8 Hz, 2H), 2.56 (t, J =8 Hz, 2H), 1.63 (m, 4H), 1.53 (m, 4H), 1.42 (m, 4H), 0.95 (td, J = 7.2 Hz, 1.2 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 172.2, 159.7, 157.7, 133.8, 133.2, 130.6, 58.4, 53.3, 41.9, 38.5, 35.0, 33.4, 32.6, 32.2, 30.6, 23.3, 22.9, 14.24, 14.17. IR (cm-1) 3286, 2958, 2868, 1737, 1603, 1572, 1437, 1379, 1249, 1072, 969, 853, 654. HRMS (ESI) calcd for $C_{26}H_{34}NO_4$ [M+H]+ 348.2175, found 348.2176.

Synthesis of dimethyl 2,3-dibutyl-4-(trimethylsilyl)-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3e). Compound **3e** was prepared using the general procedure with **1e** (64.7 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)2 (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of N,N-dimethylformamide. The reaction was stirred at 85 °C for 26 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3e** (55.0 mg, 57%) as a viscous, yellow oil. ^1H

NMR (400 MHz, CDCl₃): δ (ppm) 3.75 (s, 6H), 3.60 (s, 4H), 2.72 (t, J = 8 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H, 1.64 (m, 4H), 1.42 (m, 4H), 0.96 (m, 6H), 0.39 (s, 9H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 172.3, 159.3, 156.5, 144.4, 138.8, 136.0, 58.3, 53.2, 41.3, 41.0, 35.4, 35.3, 33.0, 32.2, 29.9, 23.4, 23.3, 14.2, 14.1, 2.4. IR (cm-1) 3476, 2957, 2870, 2179, 1739, 1556, 1436, 1376, 1253, 1200, 1167, 1072, 1049, 965, 877, 843, 762, 695, 633. HRMS (ESI) calcd for $C_{23}H_{38}NO_4$ [M+H]+ 420.2570, found 420.2579.

Synthesis of dimethyl 2,3-diethyl-4-methyl-5H-cyclopenta[b]pyridine-6,6(7H)- dicarboxylate (3f). Compound **3f** was prepared using the general procedure with **1a** (100.0 mg, 0.45 mmol), **2b** (36.8 mg, 0.45 mmol), Fe(OAc)2 (7.8 mg, 4.5 x 10-2 mmol), **L12** (38.8 mg, 5.8 x 10-2 mmol), and zinc (5.9 mg, 9.0 x 10-2 mmol) in 1.0 mL of N,N-dimethylformamide. The reaction was stirred at 85 °C for 6 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3f** (97.0 mg, 71%) as a viscous, yellow oil. ^{1}H NMR (300 MHz, CDCl₃): δ (ppm) 3.77 (s, 6H), 3.65 (s, 2H), 3.52 (s, 2H), 2.78 (q, J = 7.8 Hz, 7.5, Hz, 7.5 Hz, 2H), 2.64 (q, J = 7.5 Hz, 7.5 Hz, 7.5 Hz, 2H), 2.21 (s, 3H), 1.29-1.23 (m, 3H), 1.11 (t, J = 7.5 Hz, 7.5 Hz, 3H). ^{13}C NMR (100 MHz, CDCl₃): δ (ppm) 172.3, 160.6. 156.7, 141.6, 133.4, 130.5, 57.7, 53.2, 42.2, 38.1, 28.7, 21.6, 15.6, 14.9, 14.5. IR (cm-1) 2965, 1737, 1584, 1437, 1377, 1259, 1071, 961, 928, 864, 820, 733. HRMS (ESI) calcd for $C_{17}H_{24}NO_4$ [M+H]+ 306.1705, found 306.1707.

Synthesis of dimethyl-4-methyl-2,3-diphenyl-5H-cyclopenta[b]pyridine-6,6(7H)- dicarboxylate (3g). Compound **3g** was prepared using the general procedure with **1a** (100.0 mg, 0.45 mmol), **2c** (159.7 mg, 0.90 mmol), Fe(OAc)2 (7.8 mg, 4.5 x 10-2 mmol), **L12** (38.8 mg, 5.8 x 10-2 mmol), and zinc (5.9 mg, 9.0 x 10-2 mmol) in 1.1 mL

of N,N-dimethylformamide. The reaction was stirred at 85 °C for 6 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3g** (88.0 mg, 54%) as a viscous, yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 7.27-7.02 (m, 10H), 3.82 (s, 8H), 3.65 (s, 2H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm). IR (cm-1) 3057, 2854, 1737, 1601, 1554, 1495, 1432, 1400, 1266, 1201, 1121, 1073, 908, 862, 819, 797, 771, 736, 701, 574. HRMS (ESI) calcd for C$_{25}$H$_{24}$NO$_4$ [M+H]+ 402.1705, found 402.1700.

Synthesis of 2,3-dibutyl-4-ethyl-5,7-dihydrofuro[3,4-b]pyridine (3h).

Compound **3h** was prepared using the general procedure with **1f** (28.3 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)2 (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of N,Ndimethylformamide. The reaction was stirred at 85 °C for 26 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3h** (24.7 mg, 41%) as a yellow, viscous oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 5.13 (s, 2H), 5.02 (s, 2H), 2.77, (t, J = 8.4 Hz, 8.1 Hz, 2H), 2.64-2.50 (m, 4H), 1.71-1.6 (m, 2H), 1.50-1.41 (m, 6H), 1.15 (t, J = 7.8 Hz, 7.8 Hz, 3H), 1.00-0.929 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 160.9, 156.9, 145.2, 131.6, 128.7, 73.4, 71.9, 35.4, 33.7, 32.8, 27.6, 23.7, 23.4, 23.2, 14.1, 14.02, 13.97. IR (cm-1) 2959, 1768, 1583, 1462, 1406, 1376, 1304, 1186, 1104, 1049, 903, 795, 742. HRMS (ESI) calcd for C$_{17}$H$_{28}$NO [M+H]+ 262.2171, found 262.2173.

Synthesis of 2,3-dibutyl-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (3i).

Compound **3i** was prepared using the general procedure with **1g** (39.4 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)2 (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2

mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of N,Ndimethylformamide. The

reaction was stirred at 85 °C for 4 h and the resulting brown mixture was purified with

silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3i** (37.8 mg,

45%) as a colorless solid. Mp 49-50 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.41 (m,

3H), 7.19 (m, 2H), 5.1 (s, 2H), 4.8 (s, 2H), 2.85 (t, J = 8.0 Hz, 8.0 Hz, 2H), 2.49 (t, J =

8.0 Hz, 8.4 Hz, 2H), 1.74 (m, 2H), 1.45 (sext, J = 7.2 Hz, 7.2 Hz, 7.2 Hz, 2H), 1.34 (m,

2H), 1.18 (sext, J = 7.2, 7.2 Hz, 7.2 Hz, 2H), 0.98 (t, J = 7.6 Hz, 7.6 Hz, 3H), 0.74 (t, J =

7.2 Hz, 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 161.3, 156.9, 144.5, 137.9,

131.9, 129.0, 128.8, 128.1, 128.0, 73.8, 72.6, 35.5, 33.4, 32.9, 28.4, 23.3, 23.0, 14.2, 13.7.

IR (cm-1) 3058, 2957, 1952, 1780, 1581, 1497, 1463, 1399, 1289, 1257, 1181, 1101,

1042, 999, 900, 849, 748, 704, 647. HRMS (ESI) calcd for $C^{21}H^{28}NO$ [M+H]+

310.2171, found 310.2171.

**Synthesis of 2,3-dibutyl-4-phenyl-6-tosyl-6,7-dihydro-5H-pyrrolo[3,4-
b]pyridine (3j).** Compound **3j** was prepared using the general procedure with **1h** (74.6

mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)2 (4.0 mg, 2.3 x 10-2 mmol), **L12**

(20 mg, 3.1 x 10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of

N,Ndimethylformamide. The reaction was stirred at 85 °C for 4 h and the resulting

brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate

in hexanes to yield **3j** (43.5 mg, 41%) as a colorless solid. MP 158-160 °C. ^{1}H NMR

(400 MHz, CDCl$_3$): δ (ppm) 7.71 (d, J= 8Hz, 2H), 7.43 (q, J= 6.0, 7.2, 81.0 Hz, 4H), 7.29

(d, J= 8.4 Hz, 2H), 7.10 (dd, J= 18.4, 0.8 Hz, 2H), 4.63 (s, 2H), 4.28 (s, 2H), 2.78 (t, J=

7.6, 8.4 Hz, 2H), 2.41 (t, J= 10.4, 5.6 Hz, 5H), 1.68 (q, J= 6.8, 8.4, 7.6 Hz, 2H), 1.43

(sext, J= 7.6, 7.2, 7.6, 7.2 Hz, 2H), 1.26 (q, J = 7.2, 8.4, 7.2 Hz, 2H), 0.96 (t, J= 7.2, 7.2,

3H), 0.71 (t, J= 7.2, 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 161.8, 153.3, 145.7, 143.9, 137.2, 134.0, 132.7, 130.0, 129.0, 128.3, 127.9, 127.8, 126.7, 54.5, 52.4, 35.4, 33.2, 32.7, 28.5, 23.2, 23.0, 21.7, 14.2, 13.7. IR (cm-1) 3064, 2957, 2926, 2860, 1725, 1494, 1212, 1097, 1061, 966, 740. HRMS (ESI) calcd for C$_{28}$H$_{35}$N$_2$O$_2$ [M+H]+ 463.2419, found 463.2426.

Synthesis of 2,3-dibutyl-4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (3k). Compound **3k** was prepared using the general procedure with **1i** (38.9 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)$_2$ (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of N,Ndimethylformamide. The reaction was stirred at 85 °C for 4 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3k** (54.3 mg, 65%) as a yellow, viscous oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 7.46-7.39 (m, 3H), 7.19 (dd, J = 1.5 Hz, 6.6 Hz, 1.2 Hz, 2H), 5.09 (s, 2H), 4.84 (s, 2H), 2.85 (t, J = 7.8 Hz, 8.1 Hz, 2H), 2.49 (t, J = 7.5 Hz, 8.4 Hz, 2H), 1.79 (m, 2H), 1.48 (sext, 7.5 Hz, 7.2 Hz, 7.8 Hz, 8.7 Hz, 6.0 Hz, 2H), 1.38-1.12 (m, 6H), 0.98 (t, J = 7.2 Hz, 7.8 Hz, 3H), 0.74 (t, J = 7.2 Hz, 7.5 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 161.6, 159.1, 146.7, 139.0, 133.2, 130.3, 128.5, 128.32, 128.25, 127.3, 35.5, 34.7, 33.3, 33.1, 30.4, 28.6, 23.3, 23.0, 22.9, 14.2, 13.6. IR (cm-1) 3057, 3029, 2959, 1950, 1725, 1573, 1496, 1462, 1393, 1338, 1243, 1178, 1104, 1073, 1028, 964, 916, 846, 739, 703, 619. HRMS (ESI) calcd for C$_{22}$H$_{30}$N [M+H]+ 308.2378, found 308.2384.

2,3-diethyl-4-phenyl-9H-indeno[2,1-b]pyridine (3l). Compound **3l** was prepared using the general procedure with **1j** (50.0 mg, 0.23 mmol), **2b** (18.9 mg, 0.23 mmol), Fe(OAc)$_2$ (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2 mmol), and zinc

(3.0 mg, 4.6 x 10-2 mmol) in 552 mL of N,Ndimethylformamide. The reaction was stirred at 85 °C for 2 h. To the resulting brown mixture, 5 mL of dichloromethane, 5 mL of acetone and 10 mL of 6M HCl was added. The solution was stirred for 2 h. The aqueous layer was extracted with 3 x 25 mL portions of dichloromethane and the organic layer was collected and concentrated *in vacuo*. The resulting greenish-yellow oil was dissolved in minimal dichloromethane and loaded onto a silica plug. The silica plug was then washed with 100 mL of ethyl acetate and the resulting filtrate was discarded. A 100 mL solution of 1% acetic acid in ethyl acetate was passed through the plug which was also discarded. A 100 mL of 1% NEt_3 solution in ethyl acetate was run through the plug, collected, concentrated *in vacuo*, and further purified by column with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3l** (44.2 mg, 64%) as a yellow solid. Mp: 118-122 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.56-7.50 (m, 4H), 7.31 (d, J = 2.0 Hz, 2H), 7.19 (t, J = 7.5 Hz, 8.0 Hz, 1H), 6.15 (d, J = 8.0 Hz, 1H), 3.99 (s, 2H). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 161.4, 159.9, 144.5, 141.8, 140.2, 138.4, 132.9, 131.1, 129.2, 128.6, 128.1, 126.7, 125.1, 122.7, 38.7, 28.8, 22.2, 15.8, 15.0. HRMS (ESI) calcd for $C_{22}H_{22}N$ [M+H]+ 300.1752, found 300.1746.

Synthesis of dimethyl 2,3-dibutyl-4-methyl-7,8-dihydroquinoline-6,6(5H)-dicarboxylate (3m). Compound **3m** was prepared using the general procedure with **1k** (54.6 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), Fe(OAc)$_2$ (4.0 mg, 2.3 x 10-2 mmol), **L12** (20 mg, 3.1 x 10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 533 mL of N,N-dimethylformamide. The reaction was stirred at 85 °C for 24 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3m** (34.5 mg, 40%) as a yellow, viscous oil. ^{1}H NMR (400 MHz,

CDCl$_3$): δ (ppm) 3.74 (s, 6H), 3.12 (s, 2H), 2.86 (t, J= 6.5, 6.5 Hz, 2H), 2.70 (t, J= 8.5,

8.0 Hz, 2H), 2.59 (t, J= 8 Hz, 2H), 2.37 (t, J= 7.0, 6.0 Hz, 2H), 2.19 (s, 3H), 1.62 (m, 2H),

1.44 (m, 6H), 0.96 (m,6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 171.8, 157.4, 150.4,

131.6, 127.7, 124.8, 53.7, 52.8, 35.5, 32.6, 32.3, 32.0, 29.5, 28.5, 27.7, 23.3, 23.1, 14.6,

14.0, 13.8. IR (cm-1) 2957, 2870, 1738, 1665, 1571, 1438, 1332, 1242, 1169, 1084,

1027, 976, 858, 792, 737, 700. HRMS (ESI) calcd for C$_{22}$H$_{34}$NO$_4$ [M+H]+ 376.2488,

found 376.2486.

Synthesis of Dimethyl-2,4-dimethyl-3-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)- dicarboxylate (3n) and dimethyl-3,4-dimethyl-2-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)- dicarboxylate (3n'). Compounds **3n** and **3n'** were

prepared using the general procedure with **1a** (100 mg, 0.45 mmol) and **2e** (52 mg, 0.45

mmol), 10 mol% Fe(OAc)$_2$ (7.80 mg, 4.5x10-2 mmol), 13 mol% of **L12** (39.7 mg,

5.9x10-2 mmol), and zinc (5.9 mg, 9.0 x 10-2 mmol) in N,N-dimethylformamide. After

6 h the crude reaction mixture was purified via flash column chromatography using 100

ml hexanes then 20% ethyl acetate in hexanes to afford **3m** and **3m'** in a 1.2:1.0::**3n:3n'**

as yellowish oils (105.3 mg, 69% yield). **3n**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.41

(d, J = 8.4Hz, 2H), 7.34 (m, 1H), 7.41 (m, 2H), 3.78 (s, 6H), 3.71 (s, 2H), 3.55 (s, 2H),

2.21 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.2, 158.2, 155.5,

141.7, 139.1, 135.5, 130.1, 129.3, 128.8, 127.4, 127.4, 57.8, 53.3, 42.2, 37.8, 23.7, 17.1.

IR (cm-1) 3472, 2954, 1737, 1575, 1437, 1273, 1071, 868, 705. nOe correlation of the

methyl group and the phenyl ring and between the methyl and the methylene on the 5-

membered ring. HRMS (ESI) calcd for C$_{20}$H$_{22}$NO$_4$ [M+H]+ 340.1549, found 340.1552.

3n': ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.41 (d, J= 4Hz, 4H), 7.36 (d, t, J = 4.4Hz, 1H),

3.78 (s, 6H), 3.72 (s, 2H), 3.6 (s, 2H), 2.25 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.2, 158.4, 157.1, 142.8, 141.5, 131.3, 129.3, 128.3, 127.9, 127.7, 57.9, 53.3, 42.2, 37.9, 16.5, 16.4. IR (cm-1) 3055, 2955, 1736, 1575, 1436, 1269, 1073, 738, 703. nOe corelation between the 2 methyl groups and the methyl group with the methylene on the 5-membered ring. HRMS (ESI) calcd for C$_{20}$H$_{22}$NO$_4$ [M+H]+ 340.1549, found 340.1553.

Synthesis of dimethyl-3-(4-methoxyphenyl)-2,4-dimethyl-5H-cyclopenta[b] pyridine-6,6(7H)-dicarboxylate (3o) and dimethyl-2-(4-methoxyphenyl)-3,4-dimethyl-5Hcyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3o'). Compounds **3o** and **3o'** were prepared using the general procedure with **1a** (100 mg, 0.45 mmol) and **2f** (65 mg, 0.45 mmol), 10 mol% Fe(OAc)$_2$ (7.80 mg, 4.5x10-2 mmoles), 13 mol% of **L12** (39.7 mg, 5.9x10-2 mmol), and zinc (5.9 mg, 9.0 x 10-2 mmol) in N,N-dimethylformamide. After 6 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes then 20% ethyl acetate in hexanes and finally 30% ethyl acetate and hexanes to afford **3o** and **3o'** in a 3:2::**3o**:**3o'** as oils (65.2 mg, 39% yield). **3o**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.02 (d, J= 8.8Hz, 2H), 6.96 (d, J= 8.4Hz 2H), 7.41 (m, 2H), 3.86 (s, 3H), 3.79 (s, 6H), 3.72 (s, 2H), 3.55 (s, 2H), 2.23 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.3, 158.9, 158.0, 156.0, 142.3, 135.1, 131.2, 130.5, 130.2, 114.3, 57.9, 55.5, 53.3, 42.2, 37.9, 23.8, 17.2. IR (cm-1): 3053, 2956, 2842, 1736, 1515, 1269, 1246, 1071, 838, 737. nOe corelation between the methyl group and phenyl ring. HRMS (ESI) calcd for C$_{19}$H$_{21}$N$_2$O$_4$ [M+H]+ 370.1654, found 370.1660. **3o'**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.37 (d, J= 8.8Hz, 2H), 6.95 (d, t, J= 8.8Hz, 2H), 3.84 (s, 3H), 3.78 (s, 6H), 3.71 (s, 2H), 3.59 (s, 2H), 2.25 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz,

CDCl$_3$) δ (ppm) 172.3, 159.3, 158.1, 157.1, 142.8, 134.2, 130.9, 130.6, 127.9, 113.8, 58.0, 55.5, 53.3, 42.2, 38.0, 16.6, 16.5. IR (cm-1): 2955, 2840, 1736, 1608, 1437, 1247, 1107, 1071, 839, 765. nOe correation between the two methyl groups and the methylene on the 5-membered ring. HRMS (ESI) calcd for C$_{21}$H$_{24}$NO$_5$ [M+H]+ 370.1654, found 370.1660

Synthesis of dimethyl-2,4-dimethyl-3-(4-(trifluoromethyl)phenyl)-5Hcyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3p) and dimethyl-3,4-dimethyl-2-(4-(trifluoromethyl)phenyl)-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3p').

Compounds **3p** and **3p'** were prepared using the general procedure with **1a** (100 mg, 0.45 mmol) and **2g** (65 mg, 0.45 mmol), 10 mol% Fe(OAc)$_2$ (7.80 mg, 4.5x10-2 mmol), 13 mol% of **L12** (39.7 mg, 5.9x10^{-2} mmol), and zinc (5.9 mg, 9.0 x 10^{-2} mmol) in DMF. After 4 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes then 20% ethyl acetate in hexanes, and finally 30% ethyl acetate in hexanes to afford **3p** and **3p'** in a 4:1::**3p**:**3p'** as yellowish oils (63.7 mg, 39%). **3p**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.02 (d, J= 8.8Hz, 2H), 6.96 (d, J= 8.4Hz 2H), 7.41 (m, 2H), 3.86 (s, 3H), 3.79 (s, 6H), 3.72 (s, 2H), 3.55 (s, 2H), 2.23 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.2, 158.9, 158.0, 156.0, 142.3, 135.1, 131.2, 130.5, 130.2, 114.3, 57.9, 55.5, 53.3, 42.2, 37.9, 23.8, 17.2. IR (cm-1): 2956, 2927, 2856, 1737, 1615, 1438, 1325, 1167, 1126, 1067, 848. nOe correaltion between the methyl and the methylene, and also the methyl group with the phenyl ring. HRMS (ESI) calcd for C$_{21}$H$_{21}$NO$_4$F$_3$ [M+H]+ 408.1423, found 408.1425. **3p'**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.69 (d, J= 8Hz, 2H), 7.25 (d, J= 8Hz, 2H), 3.78 (s, 6H), 3.71 (s, 2H), 3.55 (s, 2H), 2.19 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.1, 159.0, 155.2,

143.1, 141.5, 134.0, 130.3, 130.0, 126.0, 125.9, 57.8, 53.4, 42.3, 37.8, 23.8, 17.1. nOe correlation between the methyl group and the phenyl and also between the 2 methyl groups. IR (CH$_2$Cl$_2$, cm-1): HRMS (ESI) calcd for C^{19}H^{21}N^{2}O^4 [M+H]+ 370.16, found 370.1660

Synthesis of dimethyl-2,4-dimethyl-3-(pyridin-2-yl)-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3q) and dimethyl-3,4-dimethyl-2-(pyridin-2-yl)-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3q'). Compounds **3q** and **3q'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2g** (39.4 mg, 0.22 mmol) with 10 mol% Fe(OAc)$_2$ (3.89 mg, 2.2x10-2 mmol), 13 mol% of **L12** (19.83 mg, 2.9x10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in DMF. After 5 h the crude reaction mixture was purified via flash column chromatography using using 50% EtOAc in hexanes then 2% dichloromethane in methanol, and finally 5% dichloromethane in methanol to afford **3q** and **3q'** in a 7:3::**3q**:**3q'** as yellowish oils (42.7 mg, 56%). **3q**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 8.80 (s, 1H), 7.70 (dt, J= 8Hz. 1.2Hz, 1H), 7.28 (m, 1H), 7.21 (d, J= 7.6 Hz, 1H), 3.77 (s, 6H), 3.70 (s, 2H), 3.54 (s, 2H), 2.22 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.1, 159.2, 158.3, 155.4, 150.1, 141.7, 136.8, 134.2, 130.3, 124.9, 122.4, 58.0, 53.3, 42.2, 37.7, 23.3, 16.7. IR (cm-1): 2954, 2924, 2851, 1736, 1588, 1434, 1274, 1071, 964, 823. nOe corelation between the methyl group and the pyridyl ring and also with the methylene protons on the 5-membered ring. HRMS (ESI) calcd for C$_{19}$H$_{21}$N$_2$O$_4$ [M+H]+ 341.1517, found 341.1511. **3q'**: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.70 (s, 1H), 7.79 (t, J= 7.6Hz, 1H), 7.60 (d, J= 7.6Hz, 1H), 7.28 (m, 1H), 3.78 (s, 6H), 3.73 (s, 2H), 3.61 (s, 2H), 2.26 (d, J= 4Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 172.2, 159.8, 157.3, 156.4,

149.0, 143.4, 136.7, 132.4, 129.0, 124.6, 122.6, 58.1, 53.4, 42.2, 38.0, 16.5, 15.9. IR (cm-1): 2954, 2924, 2853, 1736, 1585, 1436, 1276, 1072, 964. HRMS (ESI) calcd for $C_{19}H_{21}N_2O_4$ [M+H]+ 341.1501, found 341.1505.

Synthesis of dimethyl-2-butyl-4-methyl-3-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3r) and dimethyl-3-butyl-4-methyl-2-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3r'). Compounds **3r** and **3r'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2i** (26.2 mg, 0.22 mmol), 10 mol% Fe(OAc)$_2$ (3.89 mg, 2.2x10-2 mmol), 13 mol% of **L12** (19.83 mg, 2.9x10-2 mmol) catalyst, and zinc (3.0 mg, 4.6 x 10-2 mmol) in DMF. After 16 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes and then 20% EtOAc in hexanes to afford **3r** and **3r'** in a 3:2::**3r**:**3r'** as oils (45.2 mg, 53%). **3r**: ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 7.36 (m, 5H), 3.76 (s, 6H), 3.71 (s, 2H), 3.60 (s, 2H), 2.53 (t, J= 8.4Hz, 2H), 2.29 (s, 3H), 1.35 (s, 2H), 1.21 (sext, J= 7.2 Hz, 2H), 0.77 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.3, 159.0, 156.8, 142.3, 141.8, 132.9, 131.8, 128.9, 128.2, 127.6, 57.8, 53.3, 42.2, 38.1, 32.5, 29.0, 23.0, 16.0, 13.8. IR (cm-1): 2956, 2860, 1737, 1574, 1437, 1273, 1071, 736, 705. HRMS (ESI) calcd for $C_{23}H_{27}NO_4$ [M+H]+ 382.2018, found 382.2022 **3r'**: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.39 (m, 3H), 7.60 (td, J1= 6.8 Hz, J2= 1.6 Hz, J3= 1.2 Hz, 2H) 3.80 (s, 6H), 3.74 (s, 2H), 3.56 (s, 2H), 2.45 (t, J1= 8.4Hz, J2= 7.6 Hz, 2H), 1.91 (s, 3H), 1.76 (sext, J1= 7.6 Hz, J2= 7.2 Hz, J3= 7.2 Hz, 2H), 0.73 (t, J1= 7.6 Hz, J2= 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.2, 159.7, 158.4, 141.9, 139.0, 135.0, 129.9., 129.0, 128.6, 127.4, 57.7, 53.3, 42.4, 38.0, 36.1, 32.6, 22.9, 17.2, 14.0. IR (cm-1): 2956, 2870, 1737, 1436, 1274, 1071, 961, 862, 735, 702. HRMS (ESI) calcd for

$C_{23}H_{28}NO_4$ [M+H]+ 382.2018, found 382.2032.

Synthesis of dimethyl 2-(2-(N-(tert-butoxycarbonyl)-4-methylphenylsulfonamido)ethyl-4-methyl-3-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3s), and dimethyl 3-(2-(N-(tert-butoxycarbonyl)-4-methylphenylsulfonamido)ethyl)-4-methyl-2-phenyl-5Hcyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3s'). Compounds **3s** and **3s'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol), **2i** (26.2 mg, 0.22 mmol), 10 mol% Fe(OAc)$_2$ (3.89 mg, 2.2x10-2 mmol), 13 mol% of **L12** (19.83 mg, 2.9x10-2 mmol) catalyst, and zinc (3.0 mg, 4.6 x 10-2 mmol) in DMF. After 16 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes, then 20% EtOAc in hexanes and finally 40% EtOAc in hexanes to afford **3s** and **3s'** in a 3:2::**3s**:**3s'** as yellowish oils (61.8 mg, 44%). **3s**: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.52 (d, J= 8.4 Hz, 2H), 7.44 (m, 4H), 7.39 (m, 1H), 7.21 (d, J= 8.14 Hz, 2H), 3.80 (s, 6H), 3.74 (s, 2H), 3.61 (s, 2H), 3.03 (t, J= 8.4, 8.0 Hz, 2H), 2.42 (d, J= 8.4 Hz, 6H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.2, 160.0, 158.0, 151.0, 144.3, 143.6, 141.3, 137.5, 132.1, 129.4, 129.1, 128.6, 128.2, 128.1, 127.9, 84.6, 57.8, 53.4, 46.1, 42.3, 38.1, 30.1, 28.1, 21.8, 16.3. nOe correlation between the methyl group and the phenyl ring and also the methyl group and the methylene protons on the 5-membered ring. IR (cm-1): 2956, 1734, 1575, 1437, 1400, 1278, 1159, 1090, 969, 736. HRMS (ESI) calcd for $C_{33}H_{38}N_2O_8SNa$ [M+Na]+ 645.2247, found 645.2264. **3s'**: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.61(d, J=8.4 Hz, 2H), 7.45 (t, J=7.2 Hz, 2H), 7.39 (d, J=7.2 Hz, 2H), 7.20 (d, J=7.6, 2H), 7.13 (d, J=7.6 Hz, 2H), 4.12 (t, J=7.6 Hz, 2H), 3.80 (s, 6H), 3.72 (s, 2H), 3.57 (s, 2H), 2.86 (t, J= 7.2 Hz, 2H), 2.41 (s, 3H), 1.92 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100

MHz, CDCl$_3$) δ (ppm) 172.3, 158.7, 155.6, 151.0, 144.0, 141.7, 138.5, 137.7, 135.6, 130.4, 129.6, 129.2, 128.9, 128.1, 127.5, 84.0, 57.8, 53.3, 46.8, 42.2, 37.9, 35.8, 28.0, 21.8, 17.2. nOe corelation between the methylene on the side chain with the phenyl and also the methyl group. IR (cm-1): 2956, 1734, 1596, 1439, 1400, 1277, 1159, 1088, 970, 735. HRMS (ESI) calcd for C$_{33}$H$_{38}$N$_2$O$_8$SNa [M+Na]+ 645.2247, found 645.2254.

Synthesis of dimethyl-3-butyl-2,4-dimethyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3t) and dimethyl-2-butyl-3,4-dimethyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3t'). Compounds **3t** and **3t'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2j** (28.9 mg, 0.22 mmol), 10 mol% Fe(OAc)$_2$ (3.89 mg, 2.2x10-2 mmol) and 13 mol% of **L12** (19.83 mg, 2.9x10-2 mmol), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 0.53 ml DMF. After 16 h the crude reaction mixture was purified via flash column chromatography using 100 mL hexanes, then 20% EtOAc in hexanes and finally 30% EtOAc in hexanes to afford **3t** and **3t'** in a 1:1::**3t**:**3t'** as oils (44.3 mg, 62%). **3t**: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.76 (s, 3H), 3.63 (s, 2H), 3.51 (s, 2H), 2.57 (t, J= 8Hz, 2H), 2.50 (s, 3H), 2.20 (s, 3H), 1.42 9m, 4H), 0.96 (t, J= 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.3, 156.4, 155.7, 141.4, 133.0, 130.6, 57.9, 53.3, 42.2, 38.1, 31.6, 28.9, 23.3, 22.8, 15.8, 14.1. IR (cm-1) 2956, 2869, 1737, 1586, 1437, 1274, 1070, 961, 736. nOe correlation between the methyl group and the butyl group and also the methyl group with the methylene protons on the 5-membered ring. HRMS (ESI) calcd for C$_{18}$H$_{26}$NO$_4$ [M+H]+ 320.1862, found 320.1867. **3t'**: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.76 (s, 6H), 3.65 (s, 2H), 3.52 (s, 2H), 2.76 (t, J= 8.4 , 8.0Hz, 2H), 2.17 (d, J= 3.6 Hz, 6H), 1.60 (m, 2H), 1.43 (sextet, J= 7.6, 7.2, 2H), 0.94 (t, J= 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm)

172.3, 159.8, 156.5, 142.0, 130.1, 127.6, 57.9, 53.3, 42.2, 38.0, 36.5, 32.0, 23.2, 16.5, 14.5, 14.2. IR (cm-1) 2956, 1737, 1583, 1436, 1378, 1273, 1199, 1163, 1103, 1071, 962, 863, 735. nOe correation between the methylene of the butyl group and the methyl group. HRMS (ESI) calcd for $C_{18}H_{25}NO_4$ [M+H]+ 320.1862, found 320.1866.

Synthesis of dimethyl-2-(tert-butyl)-3,4-dimethyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3u). Compound **3u** was prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2j** (28.9 mg, 0.22 mmol), 10 mol% Fe(OAc)$_2$ (3.89 mg, 2.2x10-2mmoles), 13 mol% of **L12** (19.83 mg, 2.9x10-2mmoles), and zinc (3.0 mg, 4.6 x 10-2 mmol) in 0.53 ml DMF. After 16h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes, then 20% EtOAc in hexanes and finally 30% EtOAc in hexanes to afford 3u as a single product as an oil (44.3 mg, 26%). **3u**: ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 3.78 (s, 6H), 3.66 (s, 2H), 3.53 (s, 2H), 2.35 (s, 2H), 2.16 (s, 3H), 1.43 (s, 12H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.5, 165.0, 155.2, 142.9, 129.7, 128.7, 128.0, 57.7, 53.2, 42.4, 38.8, 38.1, 30.6, 24.4, 23.7, 22.7, 17.1, 16.7. nOe correlation between the 2 methyl groups and one methyl group with the t-butyl group. IR (cm-1): 2956, 2900, 1731, 1638, 1438, 1273, 1199, 1071, 961, 737, 701. HRMS (ESI) calcd for $C_{18}H_{26}NO_4$ [M+H]+ 320.1862, found 320.1861.

Synthesis of (L12)FeBr$_2$. The FeBr$_2$ and **L12** complex was prepared by a previously reported method[19] using FeBr$_2$ (20 mg, 9.2 x10-2 mmol) **L12** (61.8 mg, 9.2 x10-2 mmol) in THF in the glove box. The reaction mixture was stirred for 3 h and then filtered over celite. Removal of THF *in vacuo* afforded the complex as a dark green solid. ^{1}H NMR (300 MHz, CD$_2$Cl$_2$) (All peaks appeared broad) δ (ppm) 59.5 (2H), 14.02 (4H), 7.55 (17H), 0.34 (28H), 3.62 (s, 2H), 3.52 (s, 2H), 3.49 (s, 2H), 2.42 (s, 3H).

Crystals were grown by slow diffusion of diethyl ether from dichloromethane. Based on the preliminary crystal structure analysis, we found that the iron is coordinated to the 3 nitrogens of **L12**. The crystal system is triclinic A= 8.8401 Å, B= 9.9680 Å, C= 27.2923 Å, α= 90.91°, β= 94.59°, γ= 113.99°. Unit cell volume = 2194.98 Å³, Space group = P1̄. Disorder in the p-substituted benzyloxy region was also observed.

Compound **3a** was prepared using **1a** (51.3 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), (**L12**)FeBr$_2$ complex (20.3 mg, 2.3x 10-2 mmol), and zinc (30 mg, 4.6x10-2 mmol) in 533 mL of N,N-dimethyl formamide. The reaction was stirred at 85 °C for 2 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% EtOAc in hexanes to yield **3a** (48 mg, 58%) as a viscous, yellow oil (characterization reported above).

References

(1) Hübel, W.; Hoogzand, C. *Chem. Ber.* **1960**, 103-115.

(2) Liu, Y.; Yan, X.; Yang, N.; Xi, C. *Catal. Commun.* **2011**, *12*, 489-492.

(3) (a) Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065-3067. (b) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, 3129-3136.

(4) Schmidt, U.; Zenneck, U. *J. Organomet. Chem.* **1992**, 187-190.

(5) Knoch, F.; Kremer, F.; Schmidt, U.; Zenneck, U. *Organometallics* **1996**, *15*, 2713-2719.

(6) Ferré, K.; Toupet, L.; Guerchais, V. *Organometallics* **2002**, *21*, 2578-2580.

(7) Miura, T.; Nakazawa. H.; Murakami, M. *Chem. Commun.* **2005**, 2855-2856.

(8) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642-13643.

(9) Shen, H.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 11473-11480.

(10) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, *691*, 3129-

3136.

(11) Britovsek, G. J. P.; Bruce, M.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; Mastroianni, S.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Stroemberg, S.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728-8740.

(12) Degnan, A. P.; Chaturvedula, P. V.; Conway, C. M.; Cook, D. A.; Davis, C. D.; Denton, R.; Han, X.; Macci, R.; Mathias, N. R.; Moench, P.; Pin, S. S.; Ren, S. X.; Schartman, R.; Signor, L. J.; Thalody, G.; Widmann, K. A.; Xu, C.; Macor, J. E.; Dubowchik, G. M. *J. Med. Chem.* **2008**, *51*, 4858-4861.

(13) Knox, J. R.; Toia, R. F.; Casida, J. E. *J. Aric. Food Chem.* **1992**, *40*, 909-913.

(14) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284-286.

(15) Tekavac, T.; Louie, J. *J. Org. Chem.* **2008**, *73*, 2641-2648.

(16) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2000**, 3007-3011.

(17) Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. *J. Mol. Catal. A: Chem.* **2008**, *292*, 44-48.

(18) Mori, S.; Yanase, T.; Aoyagi, S.; Monguchi, Y.; Maegawa, T.; Sajiki, H. *Eur. Chem. J.* **2008**, *14*, 6994-6999.

(19) Small, B. L.; Brookhart, M.; Bennett, A. M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4049-4050.

CHAPTER 3

THE IRON-CATALYZED CYCLOADDITION OF DIYNES AND CYANAMIDES

Reproduced in part with permission from *J. Org. Chem.* **2012**, *77*, 7555-7563.
Copyright (2012) American Chemical Society.

Introduction

The first general iron-catalyzed method for pyridine synthesis was recently

developed in the Louie Lab.[1] In this initial report, the strong tendency for iron to

cyclotrimerize alkynes was overcome using alkynenitrile substrates along with a unique

bis(aldimino)pyridine ligand (**L1**) (equation 1).[2] Shortly after this report, Wan and co-

workers published an iron-catalyzed synthesis of pyridines from diynes and nitriles

(equation 2).[3] Unfortunately, relatively high catalyst loadings were required in both

systems. In addition, these systems either gave pyridines in moderate yields (former) or

required 10 to 20 molar equivalents of nitrile (latter).[4] Although these reports are an

important step forward, an efficacious iron-catalyzed route to pyridines that utilizes low

catalyst loading yet affords high yield of pyridine remains scarce.

$$(1)$$

$$\underset{\substack{\\ \\ 10\text{ - }20\text{ equiv}}}{X\ \diagdown\diagup\diagup R \ + \ \overset{R'}{\underset{N}{\mid\mid\mid}}} \xrightarrow[\substack{20\text{ mol\% dppp}\\ 20\text{ mol\% Zn, THF, rt}}]{10\text{ mol\% FeI}_2} X \diagdown\diagup\overset{R}{\underset{N}{\diagup}}R' \qquad (2)$$
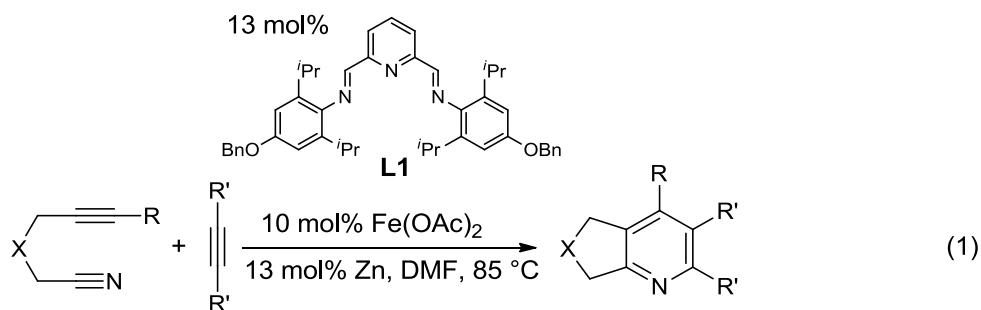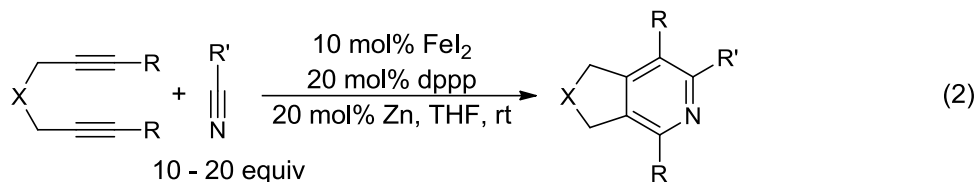
Attempts to react unactivated nitriles with diynes using the Louie system afforded only traces of pyridine products. Reactions with electron-deficient nitriles were also unsuccessful.[5] Recent work with cyanamides suggested that they could be suitable partners in Fe-catalyzed cycloaddition chemistry, as they appeared to be more reactive in Ni-catalyzed cycloadditions.[6] Thus, 2-aminopyridines could potentially be prepared by our iron bisiminopyridine catalyst without requiring a large excess of cyanamide or having to tether the cyanamide to an alkyne.

Variations on the 2-aminopyridine core have been studied extensively due to their potential as medicinally useful compounds.[7] 2-Aminopyridines are also a central structural motif in α-carboline natural products[8] as well as in a variety chromophores,[9] pharmacophores,[10] OLED's,[11] and inorganic ligands.[12] These broadly applicable compounds are commonly synthesized by Buchwald-Hartwig-type aminations,[13] nucleophilic aromatic substitutions,[14] and multicomponent condensations.[15] Such methods are useful for the creation of simple 2-aminopyridines, but more complex substitution patterns require additional synthetic manipulations. For more complex aminopyridines, Co, Ni, Rh, and Ti, catalysts and a photocatalytic system have all been used to mediate [2+2+2] cycloadditions.[16] However, in most of these studies (i.e., Rh and Ti), only a single example of a [2+2+2] cycloaddition with a cyanamide was demonstrated. In an effort to improve the conditions and expand the scope of these reactions, the Louie lab recently developed a Ni/NHC-catalyzed system for the [2+2+2]

formation of 2-aminopyridines from diynes and cyanamides.[6] Although this system was

high yielding and regioselective, the low-cost and environmentally-benign nature of iron

compares favorably to nickel. Additionally, highly reactive cyanamides present an

opportunity to improve on iron-catalyzed pyridine formation. This chapter outlines the

successful development of an iron catalyst for the cycloaddition of diynes and

cyanamides to afford 2-aminopyridines.

Results and Discussion

The first attempt to make 2-aminopyridine **3a** from diyne **1a** and 2 equivalents of

cyanamide **2a** using the original catalyst system (10 mol% Fe(OAc)$_2$, 13 mol% Zn and 13

mol% **L1** in DMF) afforded 2-aminopyridine **3a** in 69% isolated yield at 85 °C (equation

3). Furthermore, the use of a simpler ligand (**L2**) led to an increase in isolated yield

(85%).[17] Further optimization led to conditions employing 5 mol% catalyst loading of

inexpensive FeCl$_2$, 10 mol% Zn and 10 mol% **L2** in benzene over 4 h at room

temperature. Evaluation of other ligands (N-heterocyclic carbenes, phosphines, and

pyridyl diimines provided no product.[18]
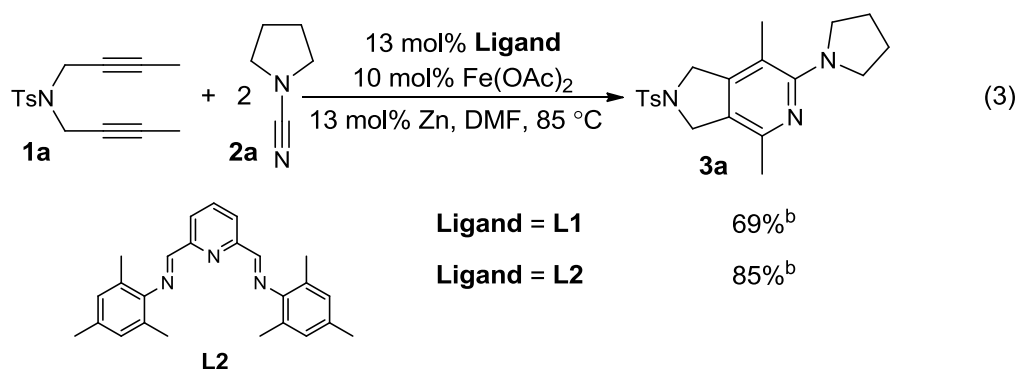
Unfortunately, the mild conditions that worked for the model substrates (i.e., **1a**

and **2a**) were not amenable to other diynes. Although increasing the reaction temperature

to 70 °C led to good reactivity of the substrates, diyne dimerization accounted for as much as half of substrate conversion. An excess of cyanamide (10 equiv) led to no reactivity suggesting that cyanamide binding outcompetes alkyne binding at high concentrations. Gratifyingly, slow addition of diyne over the course of 3 h solved this problem and provided a general method for coupling a variety of diynes. Slow addition of the diyne also allowed us to decrease the cyanamide:diyne ratio to 1.2:1 with no deleterious effects on the yield.

Control studies were performed to establish the necessity of iron in this catalytic system. Importantly, removing any part of the catalytic system renders the reaction ineffective. Additionally, (**L2**)FeBr$_2$ (Figure 15) was independently synthesized and used directly as an all-in-one catalyst precursor to provide a 97% NMR yield (equation 4). That is, the combination of (**L2**)FeBr$_2$ and Zn dust provided a catalytically competent system. The comparable activity of (**L2**)FeBr$_2$ indicates that the active catalyst is bound to a single ligand. The use of a 1:2 ratio of FeCl$_2$:**L2** is only necessary to increase the rate of complexation of the iron salt to the ligand. No reaction occurred in the absence of zinc dust.[19]
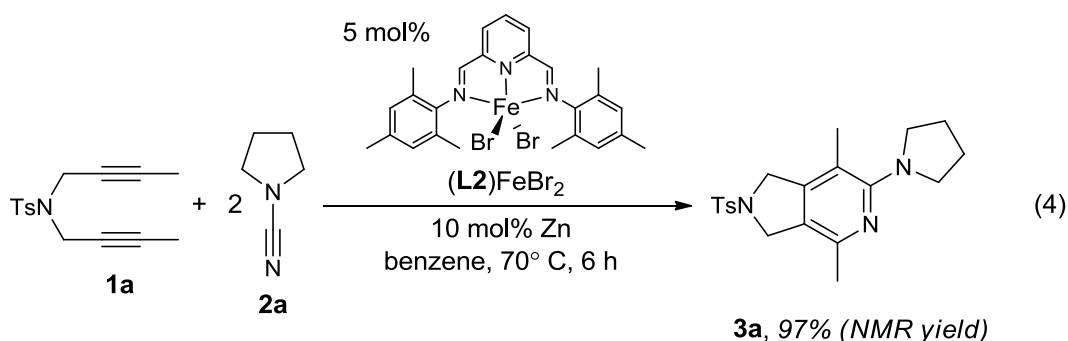
A broad range of diynes and cyanamides were successfully converted to their respective 2-aminopyridines (Table 5). The protected nitrogen backbone diyne **1a** and
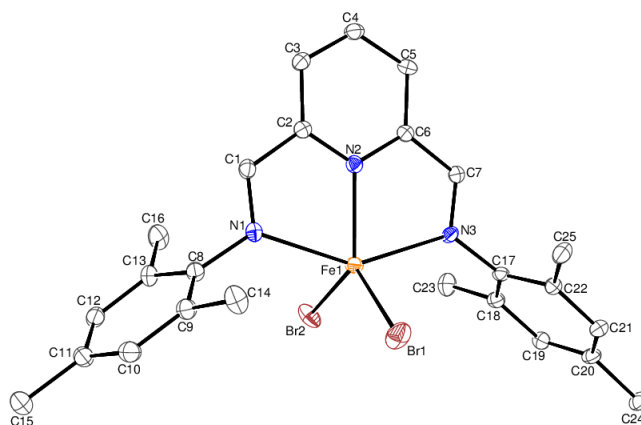
Figure 15. Ortep of (**L2**)FeBr$_2$.

Table 5. 2-Aminopyridine Substrate Scope
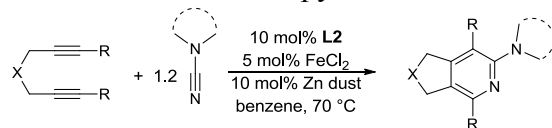
entry	substrate[a]	cyanamide	product	yield	entry	substrate[a]	cyanamide	product	yield
1	**1a**	**2a**	**3a**	93			X = C(CO$_2$Me)$_2$		
2	**1b**, R = Me	**2a**	**3b**	90	9	**1b**	**2b**, R^1 = R^2 = Me	**3i**	97
3	**1c**, R = H	**2a**	**3c**	65	10	**1b**	**2c**, R^1 = R^2 = Et	**3j**	35
4	**1d**, R = Ph	**2a**	**3d**	NR	11	**1b**	**2d**, R^1 = Me, R^2 = Ph	**3k**	70
5	**1e**, R = TMS	**2a**	**3e**	NR					
6[b]	**1f**	**2a**	**3f**	84	12	**1b**	**2e**	**3l**	95
7[c]	**1g**	**2a**	**3g**	84	13[e]	**1b**	**2f**	**3m**	67
8	**1h**	**2a**	**3h**	80	14	**1b**	**2g**	**3n**	69

malonate backbone diyne **1b** both afforded products (**3a** and **3b**) in excellent yield

(entries 1-2). The challenging terminal diyne **1c** provided **3c** in good yield (entry 3).

However, other difficult substrates such as phenyl and TMS-substituted diynes (**1d** and

1e respectively, entries 4-5) were unreactive. The lack of Thorpe-Ingold effect in

substrates **1f** and **1g** did not affect cycloaddition, as products **3f** and **3g** were both

obtained in 84% yield (entries 6-7). Notably, entries 1 and 6 demonstrate that heteroatom

tethers, which were problematic in the previous iron systems,[1,3] are well tolerated by this

system. Diyne **1h** successfully provided the 6,6-bicyclic pyridine (**3h**) in good yield

(entry 8). High yields of 2-aminopyridine were obtained with methyl-phenyl (**2d**) and

dimethyl (**2b**)-substituted cyanamide substrates (entries 9 and 11). Cycloaddition of

diethyl cyanamide **2c** afforded a lower yield of product, suggesting a poor tolerance

toward sterically bulky cyanamides (entry 10). Cyclic cyanamides N-cyanopiperidine

(**2e**) and N-cyanomorpholine (**2f**) reacted readily (entries 12-13). In contrast to the

apparent negative effect of cyanamide sterics in entry 10, the large dibenzazepinyl

cyanamide provided **3n** in good yield (entry 14). This result compares well with the 19%

yield afforded by cobalt.[16] Attempts to react (dimethylamino)acetonitrile with diyne **1b**

were unsuccessful, which may indicate that the inherent electronic structure of

cyanamides, not a chelation effect, is the source of their high reactivity in this system.[20]

To demonstrate the synthetic utility of this methodology, entry 1 was repeated on a 1

mmol scale, leading to a comparable yield of 94% (equation 5).

For future synthetic application, an understanding of the regioselectivity of

unsymmetrical coupling partners is paramount. Diynes **1i-k** were evaluated under the

(5)
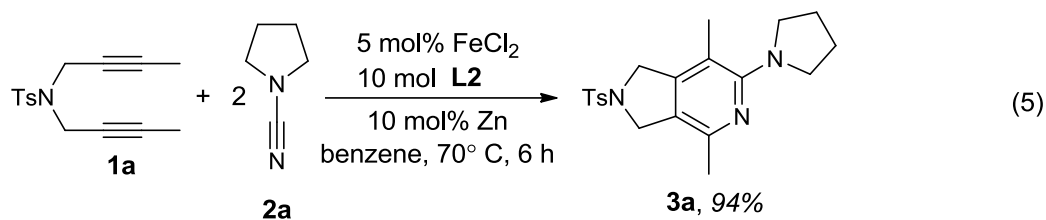
1 mmol scale

optimized conditions and the results are summarized in Table 6. In each of these cases,

good yields of 2-aminopyridine products were obtained. What is surprising, however, is

that each of the reactions shows a strong preference to place the larger substituent

proximal to the pyridine nitrogen. For example, the cycloaddition of H, Me-substituted

diyne **1i**, and cyanamide **2b** provided an 85:15 ratio of **3o** and **3o'** in 72% combined yield

(entry 1). A similar product ratio was obtained in the cycloaddition of a bulkier diyne

(**1j**, entry 2) as well as aryl/alkyl diyne (**1k**, entry 3). These regioselectivity trends nicely

Table 6. Unsymmetrical diynes
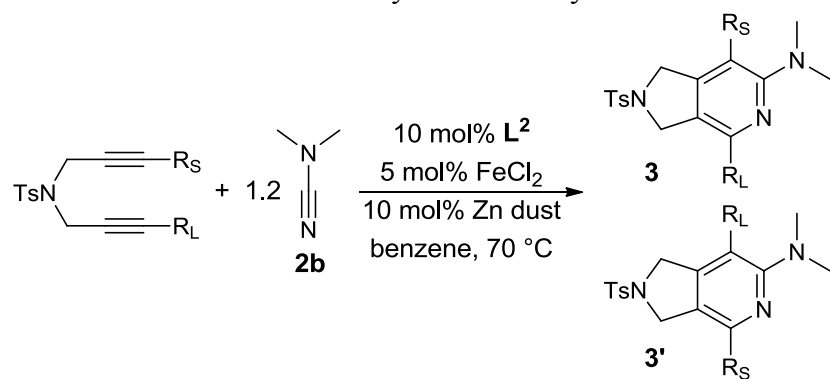
entry	substrate	product	yield[a] (**3:3'**)[b]
1	**1i**, R_S = H, R_L = Me	**3o**	72 (85:15)
2	**1j**, R_S = Me, R_L = ^tBu	**3p**	80 (86:14)
3	**1k**, R_S = Me, R_L = Ph	**3q**	67 (88:12)

[a]Yields reported as a combination of both regioisomers.
[b]Product ratios determined by ^{1}H NMR.

complement the nickel-catalyzed systems where the larger substituent is placed at the 3-position of the 2-aminopyridine ring.[6] Additionally, this Fe-catalyzed method is milder than the cobalt-catalyzed system, which is primarily limited to terminal alkynes.[16] Notably, the regioselectivity is the reverse of that observed in the previous Fe-catalyzed system involving diynes and nitriles, wherein the larger alkyne substituent was placed ortho- to the nitrile substituent.[3] To verify that this trend is a result of the catalyst and not the type of nitrile, diyne **1k** was reacted with dimethyl cyanamide **2b** under the catalyst developed by Wan and co-workers (equation 6).

$$(6)$$
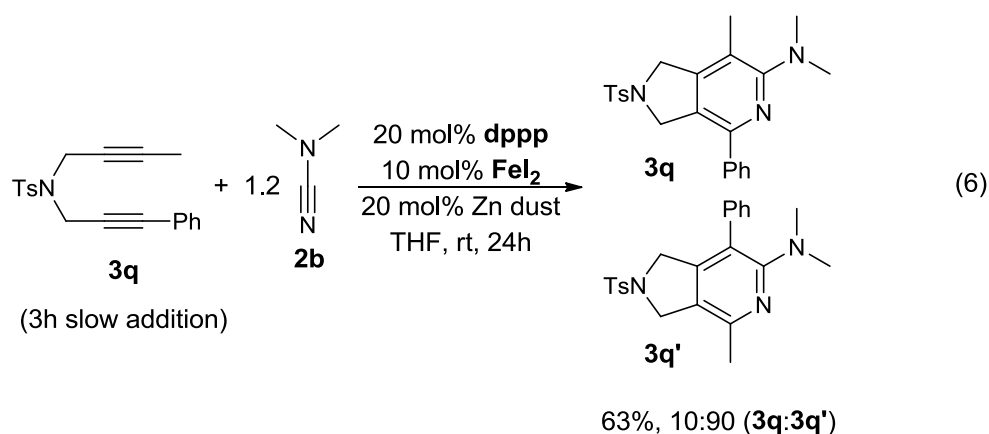
63%, 10:90 (**3q:3q'**)

The FeI$_2$/dppp system provided the product in a 63% combined yield but with **3q'** as the major regioisomer in a 10:90 (**3q**, **3q'**) ratio. This represents opposite regioselectivity compared to the Louie system. The regioisomers of these reactions were identified through the use of 2-D NOESY, HMBC, and HMQC NMR experiments. An x-ray quality crystal of **3q'** was grown, verifying the regioselectivity trends established by NMR (Figure 16).

The fully intermolecular [2+2+2] cycloaddition of alkynes and nitriles to form pyridines is a challenging reaction. To date, intermolecular reactions with cyanamides are limited to cobalt catalysts, and these systems provide a mixture of products when
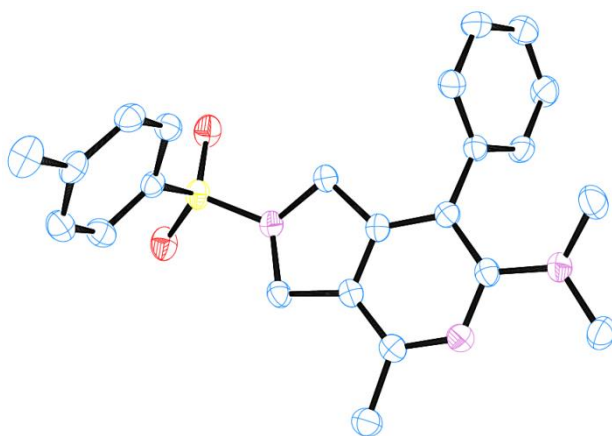
Figure 16. Ortep of **3q'**.

using unsymmetrical internal alkynes.[21] Furthermore, no reports of [2+2+2]

cycloadditions involving aryl acetylenes and cyanamides exist, to our knowledge.

Terminal aryl acetylenes are particularly challenging substrates since these tend to

undergo rapid oligomerization to provide unwanted side products.[22] Despite this

potential pitfall, as well as the possibility of forming multiple regioisomers, the reaction

of two equivalents of alkyne **4a** and one equivalent of cyanamide **2b** afforded **5a** as a

single regioisomer in 90% yield (equation 7).

(7)
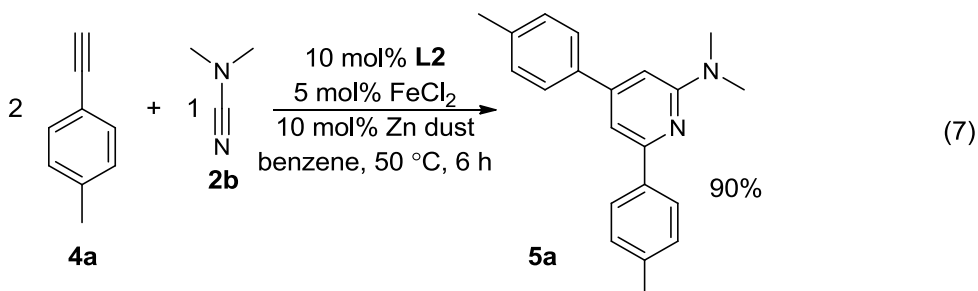
This mild and efficient route to 2-amino-4,6-aryl pyridines may provide an

alternative to multistep syntheses of biologically active compounds.[23] Furthermore, this

reaction overcomes the greatest obstacle present in [2+2+2] cycloaddition. That is, the

regioselective three-component cyclization of unsymmetrical alkynes with a nitrile. This

finding will be studied further by the Louie group with the aim to develop a new method

to regioselectively produce monocyclic 2-aminopyridines from simple alkynes and cyanamides. This project holds the promise to provide simple and efficient access to a variety of substituted pyridines that would otherwise require multiple synthetic manipulations. Additionally, the products of these reactions can be used as building block chemicals. Recent work has demonstrated that aryl amines are a useful synthetic handle. The amine can be easily converted to an ammonium salt, which can then allow for cross-coupling reactions.[24]

The contrast in regioselectivity between our $FeCl_2$/**L2** system and the FeI_2/dppp system is a rare example of ligand-dependent regioselectivity in metal-catalyzed [2+2+2] pyridine formation.[25] The regioselectivity observed in the Louie Fe system mirrors that observed in Co-catalyzed protocols. As such, this preliminarily suggests that the **L2**/Fe-catalyzed cycloaddition of cyanamides may follow a similar mechanism to that of the well-established mechanism for Co-catalyzed pyridine formation.[26] Following *in situ* ligand coordination and reduction by zinc, a reduced Fe catalyst binds the diyne and facilitates oxidative coupling of the two alkyne units to form a ferracyclopentadiene (Figure 17). Insertion of cyanamide and reductive elimination subsequently afford the pyridine product. Interestingly, the FeI_2/dppp catalyst system, which follows the regioselectivity patterns of nickel, has been proposed to undergo a mechanism involving initial oxidative coupling between an alkyne and a nitrile instead.[3] This is in agreement with the proposed mechanism for nickel-catalyzed pyridine formation.[27] The regioselectivity results of this study, combined with what is known about cobalt and nickel systems, may indicate that iron is capable of following either mechanistic pathway and is dependent on ligand choice.
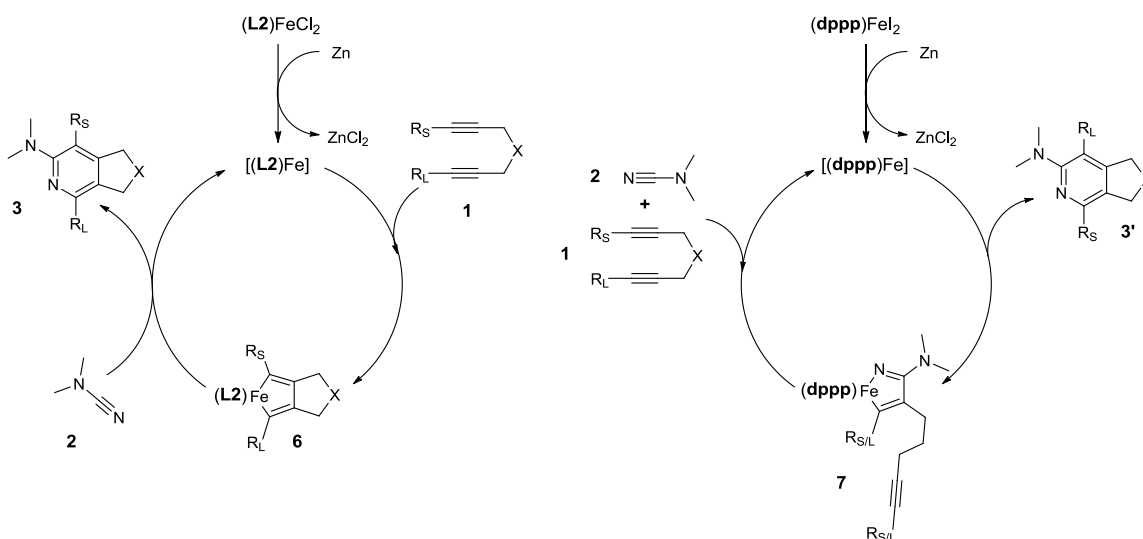
Figure 17. Mechanistic hypothesis.

Conclusions

The iron-catalyzed [2+2+2] cycloaddition of alkynes and cyanamides is a high-yielding, atom-efficient and regioselective method to obtain 2-aminopyridines. Iron catalyzed pyridine synthesis is no longer limited by alkynenitrile substrates or large excesses of nitrile. The ability to use cheap and inexpensive $FeCl_2$ in only 5 mol% adds further to the overall efficiency of this system. Differences in regioselectivity trends between the Louie and Wan iron catalyst systems raise interesting mechanistic questions. Studies into the mechanism of the Louie system have begun and are discussed in Chapter 5. The surprisingly effective 3-component cyclization that is catalyzed by this method opens the door to an exciting new avenue of study. This reaction will be optimized and developed into a practical route to access monocyclic 2-aminopyridines. Finally the Louie iron catalyst system has now been demonstrated as a versatile cyclotrimerization tool. More reactions should be explored using this catalyst system. One such reaction is discussed in the next chapter.

Experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Benzene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. Iron Chloride (99.95% purity) was purchased from Alfa Aesar. Diynes **1a**,[28] **1b-c**,[29] **1d**,[30] **1e**,[31] **1f**,[32] **1g**,[33] **1h**,[34] **1i**,[35] and **1j-k**[36] were prepared from known literature procedures. Liquid cyanamides were degassed using three sequential freeze-pump-thaw cycles. Slow addition of diyne was performed using a syringe pump and a disposable 1 mL syringe with a 6 inch, stainless steel, 24 gauge needle. The needle was dried overnight at 160 °C and was fitted to the syringe while hot. The syringe/needle joint was then wrapped tightly with Teflon tape.

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, td, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet of doublets, triplet, quartet, and quintet, respectively. All ^{13}C NMR spectra were proton-decoupled. The infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 10 ºC/min.; final temperature: 300 ºC held for 12 minutes; detector temperature: 250 ºC.

General Procedure for the Cycloaddition. In a nitrogen-filled glove box, 5 mol% FeCl$_2$, 10 mol% **L2** and benzene were added to a vial. The mixture was stirred for

10 to 15 minutes, at which time 1.2 equivalents of cyanamide and 10 mol% Zn dust were added. The vial was then capped with a Teflon-lined septum screw cap and removed from the glove box. The vial was stirred in a 70 °C oil bath, and a solution of diyne in benzene was slowly added to the vial over 3 hours (unless otherwise noted) via syringe pump. The final concentration of the diyne after addition was 0.4 M.

Purification Procedure A. For 2-aminopyridines with an $R_f > 0.3$ (20% ethyl acetate in hexanes) **L2** ($R_f = 0.51$, 20% ethyl acetate in hexanes) may co-elute with and contaminate the final product. This method was devised to avoid this issue. Once the reaction was complete, as determined by GC, the crude mixture was stirred in aqueous HCl for 10 minutes to protonate the 2-aminopyridine product. The aqueous layer was collected and the organic layer was further extracted with 4 x 15 mL portions of aqueous HCl. The aqueous extracts were collected, then a saturated aqueous $NaHCO_3$ solution was carefully added until the pH >7, causing the product to precipitate. The aqueous layer was then extracted with 3 x 25 mL portions of diethyl ether. The organic extracts were collected, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude product was then purified via silica gel flash chromatography.

Purification Procedure B. For 2-aminopyridines with $R_f < 0.3$ (20% ethyl acetate in hexanes). Once the reaction was complete, as determined by GC, the crude mixture was purified via flash silica gel chromatography. The product often contained unreacted cyanamide at this point, so the product was stirred in aqueous HCl for 10 minutes. The aqueous layer was collected and the organic layer was further extracted with 4 x 15 mL portions of aqueous HCl. The aqueous extracts were collected, then a saturated aqueous $NaHCO_3$ solution was carefully added until the pH >7, causing the

product to precipitate. The aqueous layer was then extracted with 3 x 25 mL portions of diethyl ether. The organic extracts were collected, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*.

Synthesis of 4,7-dimethyl-6-(pyrrolidin-1-yl)-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (3a). Compound **3a** was prepared using the general procedure with **2a** (42 mg, 4.4 x 10^{-1} mmol), $FeCl_2$ (2.3 mg, 1.8 x 10^{-2} mmol), **L2** (13.4 mg, 3.6 x 10^{-2} mmol), and zinc (2.4 mg, 3.6 x 10^{-2} mmol) in 418 μL of benzene. Diyne **1a** (100 mg, 3.6 x 10^{-1} mmol), dissolved in 490 μL benzene was added over 3 h at 70 °C. The reaction was stirred an additional 1 h for a total reaction time of 4 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B, with silica gel flash chromatography using 10% ethyl acetate in hexanes followed by an acid/base extraction with 3M HCl to yield **3a** (126 mg, 93%) as a white solid. R_f = 0.19 (20% ethyl acetate in hexanes). ^1H and ^{13}C NMR spectral data were compared with known literature values.[6]

Synthesis of dimethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (3b). Compound **3b** was prepared using the general procedure with **2a** (49 mg, 5.1 x 10^{-1} mmol), $FeCl_2$ (2.7 mg, 2.1 x 10^{-2} mmol), **L2** (16 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 560 μL of benzene. Diyne **3b** (100 mg, 4.2 x 10^{-1} mmol), dissolved in 498 μL benzene, was added over 3 h at 70 °C. The reaction mixture was stirred for an additional 3 h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B, with silica gel flash chromatography using 20% ethyl acetate in hexanes followed by an acid/base extraction with 1M HCl to yield **3b**

(127 mg, 90%) as a yellowish solid. $R_f = 0.27$ (20% ethyl acetate in hexanes). [1]H and

^{13}C NMR spectral data were compared with known literature values.[6]

Synthesis of dimethyl 3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (3c). Compound **3c** was prepared using the general procedure with **2a** (55

mg, 5.7×10^{-1} mmol), FeCl$_2$ (3.0 mg, 2.4×10^{-2} mmol), **L2** (18 mg, 4.8×10^{-2} mmol), and

zinc (3.1 mg, 4.8×10^{-2} mmol) in 194 μL of benzene. Diyne **1c** (99 mg, 4.8×10^{-1}

mmol), dissolved in 1 mL benzene, was added over 3 h at 70 °C. The reaction was

stirred at 70 °C for an additional 15 h for a total reaction time of 18 h. After the reaction

was complete (reaction monitored by GC), the product was isolated as described in

Purification Procedure B, with silica gel flash chromatography using 2% methanol in

dichloromethane followed by an acid/base extraction with 1M HCl to yield **3c** (94 mg,

65%) as a white solid. $R_f = 0.01$ (20% ethyl acetate in hexanes). ^{1}H and ^{13}C NMR

spectral data were compared with known literature values.[6]

Synthesis of 4,7-diethyl-6-(pyrrolidin-1-yl)-1,3-dihydrofuro[3,4-c]pyridine

(3f). Compound **3f** was prepared using the general procedure with **2a** (36 mg, 3.8×10^{-1}

mmol), FeCl$_2$ (2.0 mg, 1.6×10^{-2} mmol), **L2** (12 mg, 3.2×10^{-2} mmol), and zinc (2.1 mg,

3.2×10^{-2} mmol) in 0.292 μL of benzene. Diyne **1f** (47 mg, 3.2×10^{-1} mmol), dissolved

in 497 μL benzene, was added over 5 h at 70 °C. The reaction was stirred an additional 1

h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by

GC), the product was isolated as described in Purification Procedure A, with an acid/base

extraction using 1M HCl then silica gel flash chromatography using 5% ethyl acetate in

hexanes (500 mL), then 10% ethyl acetate in hexanes (500 mL) to yield **3f** (65 mg, 84%)

as a yellow oil. $R_f = 0.52$ (20% ethyl acetate in hexanes). [1]H (300 MHz, CDCl$_3$): δ

(ppm) 1.14 (t, J = 7.7 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H), 1.93 (quint, J = 3.3 Hz, 4H),

2.51-2.60 (m, 4H), 3.52 (quint, J = 3.2 Hz, 4H), 5.05 (s, 4H). ^{13}C (75 MHz, CDCl$_3$) δ

(ppm) 158.0, 150.3, 149.8, 122.9, 116.2, 72.8, 72.4, 50.3, 29.2, 25.8, 23.0, 13.8, 12.5. IR

(cm^{-1}): 2966, 2932, 2869, 1761, 1600, 1428, 1381, 1343, 1311, 1228, 1143, 1053, 906,

783. HRMS (ESI, TOF) calcd for C$_{15}$H$_{23}$N$_2$O [M+H]$^+$ 247.1810, found 247.1814.

Synthesis of 1,4-dimethyl-3-(pyrrolidin-1-yl)-6,7-dihydro-5H-

cyclopenta[c]pyridine (3g). Compound **3g** was prepared using the general procedure

with **2a** (55 mg, 5.7 x 10^{-1} mmol), FeCl$_2$ (3.0 mg, 2.4 x 10^{-2} mmol), **L2** (18 mg, 4.8 x 10^{-2}

mmol), and zinc (3.1 mg, 4.8 x 10^{-2} mmol) in 429 μL of benzene. Diyne **1g** (57 mg, 4.8 x

10^{-1} mmol), dissolved in 765 μL benzene, was added over 5 h at 70 °C. The reaction was

stirred an additional 2 h for a total reaction time of 7 h. After the reaction was complete

(reaction monitored by GC), the product was isolated as described in Purification

Procedure A, with an acid/base extraction using 1M HCl then silica gel flash

chromatography using 5% ethyl acetate in hexanes (500 mL), then 10% ethyl acetate in

hexanes (500 ml) to yield **3g** (86 mg, 84%) as a yellow oil. R_f = 0.49 (20% ethyl acetate

in hexanes). ^{1}H (300 MHz, CDCl$_3$): δ (ppm) 1.89-1.92 (m, 4H), 2.06, (quint, J = 7.4 Hz,

2H), 2.17 (s, 4H), 2.33 (s, 3H), 2.80 (t, J = 7.5 Hz, 4H), 3.44 (t, J = 6.5 Hz, 4H). ^{13}C (75

MHz, CDCl$_3$) δ (ppm) 154.5, 147.4, 129.1, 129.0, 114.3, 50.4, 32.3, 30.6, 25.6, 24.8,

22.0, 16.0. IR (cm^{-1}): 2953, 2868, 1595, 1425, 1347, 1204, 1137, 1063, 938, 858, 756.

HRMS (ESI, TOF) calcd for C$_{14}$H$_{21}$N$_2$ [M+H]$^+$ 217.1705, found 217.1709.

Synthesis of tetraethyl-1,4-dimethyl-3-(pyrrolidin-1-yl)isoquinoline-

6,6,7,7(5H,8H)-tetracarboxylate (3h). Compound **3h** was prepared using the general

procedure with **2a** (18 mg, 1.9 x 10^{-1} mmol), FeCl$_2$ (1.0 mg, 0.8 x 10^{-2} mmol), **L2** (5.8

mg, 1.5 x 10^{-2} mmol), and zinc (1.0 mg, 1.5 x 10^{-2} mmol) in 100 μL of benzene. Diyne

1h (67 mg, 1.6 x 10^{-1} mmol) dissolved in 300 μL benzene was added over 3 h at 70 °C.

The reaction mixture was stirred an additional 3 h for a total reaction time of 6 h. After

the reaction was complete (reaction monitored by GC), the crude product was isolated

with only silica gel flash chromatography (no acid/base extraction) using 10% ethyl

acetate in hexanes (200 mL), then 15% ethyl acetate in hexanes (400 mL) to yield **3h** (65

mg, 80%) as a yellow oil. R_f = 0.19 (20% ethyl acetate in hexanes). ^{1}H (400 MHz,

CDCl$_3$): δ (ppm) 1.23 (td, J_1 = 3.2, J_2 = 3.2, J_3 = 3.2 Hz, 12H), 1.86-1.92 (m, 4H), 2.12

(s, 3H), 2.34 (s, 3H), 3.30 (s, 2H), 3.36 (m, 6H), 4.13-4.25 (m, 8H). ^{13}C (100 MHz,

CDCl$_3$) δ (ppm) 170.2, 170.1, 157.9, 150.2, 141.7, 118.2, 115.8, 62.2, 62.0, 61.9, 57.4,

57.1, 50.4, 33.1, 31.8, 25.5, 22.3, 14.8, 13.9. IR (cm^{-1}): 2981, 2937, 2871, 2361, 1735,

1571, 1429, 1367, 1326, 1270, 1241, 1202, 1096, 1052, 942, 864, 784, 703, 650, 614,

580. HRMS (ESI, TOF) calculated for C$_{28}$H$_{27}$N$_2$O$_4$ 455.1971, found 455.1969.

Synthesis of dimethyl 3-(dimethylamino)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (3i). Compound **3i** was prepared using

the general procedure B with **2b** (20 mg, 2.8 x 10^{-1} mmol), FeCl$_2$ (1.5 mg, 1.2 x 10^{-2}

mmol), **L2** (8.8 mg, 2.4 x 10^{-2} mmol), and zinc (1.6 mg, 2.4 x 10^{-2} mmol) in 103 μL of

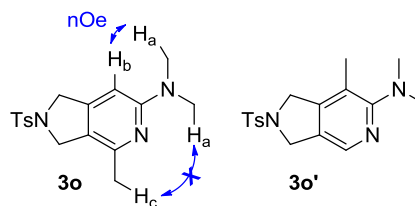benzene. Diyne **1b** (56 mg, 2.4 x 10^{-1} mmol) dissolved in 489 μL benzene was added

over 3 h at 70 °C. The reaction mixture was stirred an additional 2 h for a total reaction

time of 5 h. After the reaction was complete (reaction monitored by GC), the product

was isolated as described in Purification Procedure B, with silica gel flash

chromatography using 5% ethyl acetate in hexanes (500 mL), then 10% ethyl acetate in

hexanes (500 mL), then 20% ethyl acetate in hexanes (500 mL), followed by an acid/base

extraction with 1M HCl to yield **3i** (71 mg, 97%) as a yellow oil. $R_f = 0.27$. ^{1}H and ^{13}C NMR spectral data were compared with known literature values.[6]

Synthesis of dimethyl-3-(diethylamino)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (3j). Compound **3j** was prepared using the general procedure with **2c** (22 mg, 2.8×10^{-1} mmol), FeCl$_2$ (1.5 mg, 1.2×10^{-2} mmol), **L2** (8.8 mg, 2.4×10^{-2} mmol), and zinc (1.6 mg, 2.4×10^{-2} mmol) in 103 μL of benzene. Diyne **1b** (56 mg, 2.4×10^{-1} mmol) dissolved in 489 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B, with silica gel flash chromatography using 10% ethyl acetate in hexanes, followed by an acid/base extraction with 1M HCl to yield **3j** (28 mg, 35%) as a yellow oil. $R_f = 0.27$ (20% ethyl acetate in hexanes). ^{1}H and ^{13}C NMR spectral data were compared with known literature values.[6]

Synthesis of dimethyl 1,4-dimethyl-3-(methyl(phenyl)amino)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (3k). Compound **3k** was prepared using the general procedure with **2d** (22 mg, 1.8×10^{-1} mmol), FeCl$_2$ (1.0 mg, 7.5×10^{-2} mmol), **L2** (5.5 mg, 1.5×10^{-2} mmol), and zinc (1.0 mg, 1.5×10^{-2} mmol) in 65 μL of benzene. Diyne **1b** (35 mg, 1.5×10^{-1} mmol) dissolved in 310 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B, with silica gel flash chromatography using 5% ethyl acetate in hexanes (250 mL), then 10% ethyl acetate in hexanes (250 mL), 20% ethyl acetate in hexanes (500 mL), followed by an acid/base extraction with 1M HCl to

yield **3k** (39 mg, 70%) as a yellowish oil. R_f = 0.16 (20% ethyl acetate in hexanes). [1]H

and ^{13}C NMR spectral data were compared with known literature values.[6]

Synthesis of dimethyl-1,4-dimethyl-3-(piperidin-1-yl)-5H-cyclopenta[c]-pyridine-6,6-(7H)-dicarboxylate (3l). Compound **3l** was prepared using the general

procedure B with **2e** (31 mg, 2.8 x 10^{-1} mmol), FeCl$_2$ (1.5 mg, 1.2 x 10^{-2} mmol), **L2** (8.8

mg, 2.4 x 10^{-2} mmol), and zinc (1.6 mg, 2.4 x 10^{-2} mmol) in 121 μL of benzene. Diyne

1b (56 mg, 2.4 x 10^{-1} mmol) dissolved in 471 μL benzene was added over 3 h at 70 °C.

The reaction mixture was stirred an additional 2 h for a total reaction time of 5 h. After

the reaction was complete (reaction monitored by GC), the product was isolated as

described in Purification Procedure B, with silica gel flash chromatography using 5%

ethyl acetate in hexanes (250 mL), then 10% ethyl acetate in hexanes (250 mL), and 20%

ethyl acetate and hexanes (250 mL), followed by an acid/base extraction with 1M HCl to

yield **3l** (78 mg, 97%) as a yellowish oil. R_f = 0.27 (20% ethyl acetate in hexanes). [1]H

(400 MHz, CDCl$_3$): δ (ppm) 1.58 (q, J = 7.2 Hz, 2H) 1.68 (quint, J = 6 Hz, 4H), 2.14 (s,

3H), 2.33 (s, 3H), 3.0 (t, J = 4.8 Hz, 4H), 3.48 (s, 2H), 3.50 (s, 2H), 3.77 (s, 6H). [13]C

(100 MHz, CDCl$_3$) δ (ppm) 172.3, 161.8, 150.2, 148.3, 127.6, 118.3, 59.7, 53.3, 51.7,

40.1, 38.9, 26.6, 24.9, 21.9, 14.5. IR (cm^{-1}): 2930, 2851, 1738, 1586, 1432, 1371, 1266,

1199, 1163, 1114, 1062, 1028, 963, 858, 610. HRMS (ESI, TOF) calcd for $C_{19}H_{27}N_2O_4$

[M+H][+] 347.1971, found 347.1980.

Synthesis of dimethyl-1,4-dimethyl-3-morpholino-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (3m). Compound **3m** was prepared using the general procedure

B with **2f** (48 mg, 4.7 x 10^{-1} mmol), FeCl$_2$ (2.7 mg, 2.1 x 10^{-2} mmol), **L2** (16 mg, 4.2 x

10[-2] mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 200 μL of benzene. Diyne **2b** (50 mg,

2.1 x 10^{-1} mmol) dissolved in 400 μL benzene was added over 3 h at 70 °C. The reaction mixture was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure A, with an acid/base extraction using 1M HCl, then silica gel flash chromatography using 20% ethyl acetate in hexanes (200 mL), then 30% ethyl acetate in hexanes (400 mL) to yield **3m** (49 mg, 67%) as a yellowish oil. $R_f = 0.38$ (20% ethyl acetate in hexanes). ^{1}H and ^{13}C NMR spectral data were compared with known literature values.[6]

Synthesis of dimethyl-3-(5H-dibenzo[b,f]azepin-5-yl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (3n). Compound **3n** was prepared using the general procedure with **2g** (83 mg, 4.7 x 10^{-1} mmol), FeCl$_2$ (2.68 mg, 2.1 x 10^{-2} mmol), **L2** (15.6 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 121 μL of benzene. Diyne **1b** (50 mg, 2.1 x 10^{-1} mmol), dissolved in 471 μL benzene, was added over 3 h at 70 °C. The reaction mixture was stirred an additional 19 h for a total reaction time of 22 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B, with silica gel flash chromatography using 10% ethyl acetate in hexanes followed by an acid/base extraction with 1M HCl to yield **3n** (133 mg, 69%) as a red oil. $R_f = 0.29$ (20% ethyl acetate in hexanes). ^{1}H (400 MHz, CDCl$_3$): δ (ppm) 1.78 (s, 3H), 2.44 (s, 3H), 3.44 (s, 2H), 3.54 (s, 2H), 3.75 (s, 6H), 6.85 (s, 2H), 7.07 (dt, J = 7.2 Hz, 0.8 Hz, 2H), 7.16 (dd, J = 8 Hz, 1.6 Hz, 2H), 7.22 (dd, J = 8 Hz, 1.6 Hz, 2H), 7.71 (dd, J = 8 Hz, 0.8 Hz, 2H). ^{13}C (100 MHz, CDCl$_3$) δ (ppm) 172.2, 156.1, 151.7, 148.4, 148.1, 135.1, 132.4, 129.6, 128.8, 127.3, 124.7, 120.4, 59.8, 53.3, 40.3, 39.0, 22.1, 14.9. IR (cm^{-1}): 3020, 2953, 2923, 2854, 2361,

1737, 1589, 1482, 1432, 1340, 1266, 1200, 1163, 1113, 1060, 950, 922, 865, 794, 767, 735, 662, 559. HRMS (ESI, TOF) calcd for $C_{28}H_{27}N_2O_4$ [M+H]$^+$ 455.1971, found 455.1982.

Synthesis of N,N,4-trimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-amine (3o).

Compounds **3o** and **3o'** were prepared using the general procedure with **2b** (13 mg, 1.9 x 10^{-1} mmol), FeCl$_2$ (1.0 mg, 7.9 x 10^{-2} mmol), **L2** (5.8 mg, 1.6 x 10^{-2} mmol), and zinc (1.0 mg, 1.6 x 10^{-2} mmol) in 93 μL of benzene. Diyne **1i** (41 mg, 1.6 x 10^{-1} mmol), dissolved in 303 μL benzene, was added over 3 h at 70 °C. The reaction was stirred an additional 5 h for a total reaction time of 8 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B, with silica gel flash chromatography using 20% ethyl acetate in hexanes, followed by an acid/base extraction with 3M HCl to yield **3o** and **3o'** (38 mg, 72%, 85:15) as a white solid. R_f = 0.11 (20% ethyl acetate in hexanes). **3o**: ^{1}H (400 MHz, CDCl$_3$): δ (ppm) 2.26 (s, 3H), 2.42 (s, 3H), 3.02 (s, 6H), 4.45 (s, 2H), 4.51 (s, 2H), 6.12 (s, 1H), 7.32 (d, J = 8, 2H), 7.77 (d, J = 8, 2H). ^{13}C (100 MHz, CDCl$_3$) δ (ppm) 159.4, 150.6, 147.2, 143.9, 134.0, 130.0, 118.2, 96.4, 53.9, 51.9, 38.4, 22.3, 21.7. MP 176 °C. 2-D NOESY (500 MHz, CDCl$_3$): H$_b$ (6.12 ppm) correlates to H$_a$ (4.51 ppm). H$_c$ (2.56 ppm) shows no correlation to H$_a$. IR (cm^{-1}): 2918, 2849, 1614, 1579, 1503, 1408, 1342, 1309, 1159, 1099, 815, 669, 579, 543. HRMS (ESI, TOF) calcd for $C_{17}H_{22}N_3O_2S$ [M+H]$^+$ 332.1433, found 332.1433.

Synthesis of 4-(tert-butyl)-N,N,7-trimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-amine (3p). Compounds **3p** and **3p'** were prepared using the

general procedure with **2b** (13 mg, 1.9 x 10^{-1} mmol),

FeCl$_2$ (1.0 mg, 7.9 x 10^{-2} mmol), **L2** (5.8 mg, 1.6 x 10^{-2} mmol), and zinc (1.0 mg, 1.6 x 10^{-2} mmol) in 59 μL

of benzene. Diyne **1j** (50 mg, 1.6 x 10^{-1} mmol),
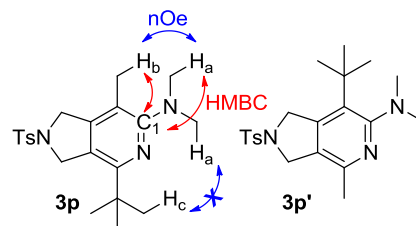
dissolved in 336 μL benzene, was added over 3 h at 70 °C. The reaction was stirred an

additional 3 h for a total reaction time of 6 h. After the reaction was complete (reaction

monitored by GC), the product was isolated as described in Purification Procedure B,

with silica gel flash chromatography using 10% ethyl acetate in hexanes, followed by an

acid/base extraction with 3M HCl to yield **3p** and **3p'** (49 mg, 80%, 88:12) as a white

solid. R$_f$ = 0.27 (20% ethyl acetate in hexanes). **3p**: ^{1}H (500 MHz, CDCl$_3$): δ (ppm) 1.29

(s, 9H), 2.10 (s, 3H), 2.42 (s, 3H), 2.79 (s, 6H), 4.24 (s, 2H), 2.74 (s, 2H), 7.34 (d, J = 8

Hz, 2H), 7.80 (d, J = 8 Hz, 2H). ^{13}C (125 MHz, CDCl$_3$) δ (ppm) 160.2, 157.6, 148.0,

143.9, 134.0, 123.1, 127.8, 121.0, 114.6, 53.6, 52.3, 42.3, 38.6, 29.5, 21.7, 14.9. MP 101

°C. 2-D NOESY (800 MHz, CDCl$_3$): H$_a$ (2.84 ppm) correlates to H$_b$ (2.09 ppm). H$_c$

(1.28 ppm) does not correlate to H$_a$. HMBC (800 MHz, CDCl$_3$): C$_1$ (161.1 ppm) couples

with H$_a$ (2.84 ppm) and H$_b$ (2.09 ppm).   IR (cm^{-1}): 3633, 2954, 2866, 2792, 2361, 1726,

1599, 1566, 1478, 1453, 1416, 1392, 1351, 1315, 1251, 1204, 1165, 1099, 1066, 955,

930, 816, 772, 737, 711, 665, 607, 570, 548, 513. HRMS (ESI, TOF) calcd for

C$_{21}$H$_{30}$N$_3$O$_2$S [M+H]$^+$ 388.2059, found 388.2069.

Synthesis of N,N,7-trimethyl-4-phenyl-2-

tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-

amine (3q). Compounds **3q** and **3q'** were prepared
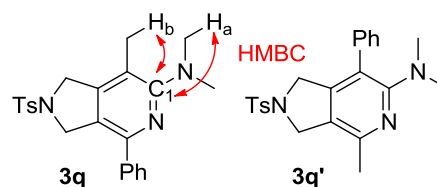
using the general procedure with **2b** (13 mg, 1.9 x 10^{-1} mmol), FeCl$_2$ (1.0 mg, 7.9 x 10^{-2}

mmol), **L2** (5.8 mg, 1.6 x 10^{-2} mmol), and zinc (1.0 mg, 1.6 x 10^{-2} mmol) in 93 µL of benzene. Diyne **1k** (53 mg, 1.6 x 10^{-1} mmol), dissolved in 302 µL benzene, was added over 3 h at 70 °C. The reaction was stirred an additional 3 h for a total reaction time of 6 h. After the reaction was complete (reaction monitored by GC), the product was isolated as described in Purification Procedure B, with silica gel flash chromatography using 10% ethyl acetate in hexanes followed by an acid/base extraction with 3M HCl to yield **3q** and **3q'** (43 mg, 67%, 86:14) as a white solid. R$_f$ = 0.14 (20% ethyl acetate in hexanes). **3q**: ^{1}H (400 MHz, CDCl$_3$): δ (ppm) 2.18 (s, 3H), 2.42 (s, 3H), 2.87 (s, 6H), 4.53 (s, 2H), 4.82 (s, 2H), 7.28-7.47 (m, 5H), 7.76 (dd, J = 6.5, 7.5 Hz, 4H). ^{13}C (125 MHz, CDCl$_3$) δ (ppm) 161.9, 148.2, 147.1, 144.0, 139.4, 134.0, 130.1, 128.8, 128.7, 127.9, 127.8, 122.5, 116.9, 53.7, 52.9, 42.2, 21.7, 15.3. HMBC (800 MHz, CDCl$_3$): C$_1$ (165.2 ppm) couples with H$_a$(2.86 ppm) and H$_b$ (2.17 ppm). MP 176 °C. IR (cm^{-1}): 2924, 2854, 2361, 1733, 1595, 1491, 1458, 1400, 1349, 1161, 1098, 1065, 913, 816, 753, 703, 673, 614, 581, 548. HRMS (ESI, TOF) calcd for C$_{23}$H$_{26}$N$_3$O$_2$S [M+H]$^+$ 408.1746, found 408.1752. A crystal of **3q'** suitable for x-ray analysis was grown by slow evaporation from an ether solution (see supporting information).

Synthesis of N,N-dimethyl-4,6-di-p-tolylpyridin-2-amine (5a). Compound **5a** was prepared using the general procedure with **2b** (22 mg, 3.2 x 10^{-1} mmol), FeCl$_2$ (2.0 mg, 1.6 x 10^{-2} mmol), **L2** (11.7 mg, 3.2 x 10^{-2} mmol), and zinc (2.1 mg, 3.2 x 10^{-2} mmol) in 108 µL of benzene. 4-ethynyltoluene (73 mg, 6.3 x 10^{-1} mmol), dissolved in 287 µL benzene was added over 3 h at 50 °C. The reaction was stirred an additional 2 h for a total reaction time of 5 h. After the reaction was complete (reaction
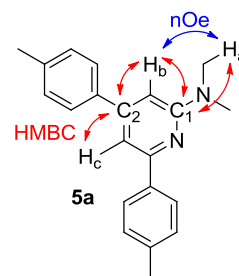
monitored by GC), the product was isolated as described in Purification Procedure A, with an acid/base extraction using 1M HCl then silica gel flash chromatography using 5% ethyl acetate in hexanes (500 mL to yield **5a** (86 mg, 90%) as a white solid. $R_f = 0.57$ (20% ethyl acetate in hexanes). ^{1}H-NMR (500 MHz, CD$_2$Cl$_2$) δ (ppm) 2.41 (d, $J = 4.0$ Hz, 6H), 3.20 (s, 6H), 6.67 (s, 1H), 7.24 (s, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 2H), 7.56 (d, $J = 8.5$ Hz, 2H), 8.0 (d, $J = 7.0$ Hz, 2H) . ^{13}C (125 MHz, CDCl$_3$) δ (ppm) 159.9, 155.8, 150.7, 138.51, 138.48, 137.8, 137.7, 129.7, 129.3, 127.2, 127.0, 107.1, 102.2, 38.3, 21.5, 21.4. 2-D NOESY (800 MHz, CDCl$_3$): H$_a$ (3.24 ppm) correlates with H$_b$ (6.66 ppm). HMBC (800 MHz, CDCl$_3$): C$_1$ (159.6 ppm) couples with H$_a$ (3.24 ppm) and H$_b$ (6.66 ppm). C$_2$ (137.6 ppm) couples with H$_b$ (6.66 ppm) and H$_c$ (7.30 ppm). MP 99 °C. IR (cm^{-1}): 3026, 2920, 1599, 1543, 1511, 1416, 1401, 1250, 1181, 1114, 986, 836, 807, 602, 559. HRMS (ESI, TOF) calcd for C$_{21}$H$_{23}$N$_2$ [M+H]$^+$ 303.1861, found 303.1864.

Ligand Synthesis. L1,[1] **L2**,[37] and **L4**[30] were synthesized according to the literature methods.

Synthesis of 4-(methoxy)-2,6-dimethylaniline 4-(methoxy)-2,6-dimethylaniline was prepared using a similar literature procedure.[31] In a nitrogen-filled glove box, a 20 mL scintillation vial was filled with CuI (353.8 mg, 1.86 mmol) 3,4,7,8-tetramethyl-1,10-phenanthroline (877.4 mg, 3.71 mmol), Cs$_2$CO$_3$ (21.5g, 111.4 mmol), and 4-iodo-2,6-dimethyl aniline[1] (9.17 g, 37.1 mmol). The vial was sealed with a rubber septum, removed from the glove box, then evacuated and backfilled with Argon three times. Toluene (14 mL) was added and the mixture was stirred at 80 °C for 20 minutes. Methanol (3.6 mg, 111.4 mmol) was added and the rubber septum was
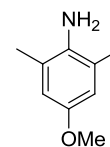
quickly replaced with a vial cap. The reaction was stirred for 24 h at 80 °C then cooled to room temperature, filtered through a silica gel plug, and flushed with 150 mL of ethyl acetate. The resulting solution was reduced *in vacuo* and purified via silica gel flash chromatography with 10% ethyl acetate in hexanes to yield **4-(methoxy)-2,6-dimethylaniline** (3.90 g, 51%) as a blue solid. $R_f = 0.12$ (20% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.20 (s, 6H), 3.23 (s, 2H), 3.75 (s, 3H), 6.58 (s, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ (ppm) 152.23, 134.61, 123.4, 114.1, 55.9, 18.2. MP 38 °C. IR (cm^{-1}): 3449, 3371, 1923, 2835, 1604, 1490, 1378, 1328, 1300, 1243, 1192, 1150, 1064, 949, 854, 728, 599. HRMS (ESI, TOF) calcd for C$_9$H$_{14}$NO [M+H]$^+$ 152.1075, found 152.1083.

Synthesis of 4-(methoxy)-2,6-diisopropylaniline 4-(methoxy)-2,6-diisopropylaniline was prepared using a similar literature procedure.[38] In a nitrogen-filled glove box, a 20 mL scintillation vial was filled with CuI (91.9 mg, 0.48 mmol) 3,4,7,8-tetramethyl-1,10-phenanthroline (228 mg, 0.95 mmol), Cs$_2$CO$_3$ (5.58 g, 28.9 mmol), and 4-iodo-2,6-diisopropyl aniline[1] (2.93 g, 9.65 mmol). The vial was sealed with a rubber septum, removed from the glove box, then evacuated and backfilled with Argon three times. Toluene (5 mL) was added and the mixture was stirred at 80 °C for 20 minutes. Methanol (869 mg, 28.9 mmol) was added and the rubber septum was quickly replaced with a vial cap. The reaction was stirred for 24 h at 80 °C then cooled to room temperature, filtered through a silica gel plug, and flushed with 150 mL of ethyl acetate. The resulting solution was reduced *in vacuo* and purified via silica gel flash chromatography with 10% ethyl acetate in hexanes to yield **4-(methoxy)-2,6-diisopropylaniline** (1.83 g, 91%) as a blue oil. $R_f = 0.28$ (20% ethyl
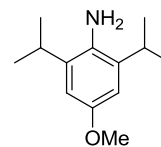
acetate in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 1.32 (d, J = 6.5 Hz, 12H), 3.01 (quint J = 7.5 Hz, 2H), 3.50 (s, 2H), 3.82 (s, 3H), 6.70 (s, 2H). ^{13}C NMR (125 MHz, CDCl$_3$): δ (ppm) 152.9, 134.4, 134.0, 108.8, 55.7, 28.3, 22.6. IR (cm^{-1}): 3459, 3382, 2961, 2871, 2832, 2361, 1600, 1466, 1435, 1383, 1348, 1311, 1242, 1219, 1172, 1123, 1103, 1042, 939, 865, 760, 669. HRMS (ESI, TOF) calcd for C$_{13}$H$_{22}$NO [M+H]$^+$ 208.1701, found 208.1700.

Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(4-methoxy-2,6-dimethylaniline) (L3). L3 was prepared from the

L3

similar literature procedure[37] with 4-methoxy-2,6-methyl aniline (1.54 g, 10.2 mmol) and 2,6-pyridinedicarboxaldehyde (673 mg, 4.98 mmol) and 10 drops of glacial acetic acid in 15 mL 100% ethanol. The reaction was stirred overnight at room temperature. The mixture was then cooled to 0 °C, filtered and rinsed with cold 100% ethanol to yield **L3** (1.9 g, 95%) as a yellow solid. R$_f$ = 0.37 (20% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 2.21, (s, 12H), 3.81 (s, 6H), 6.67 (s, 4H), 7.97 (t, J = 7.8 Hz, 1H), 8.37-8.40 (m, 4H). ^{13}C NMR (75 MHz, CDCl$_3$): δ (ppm) 163.4, 156.4, 154.8, 143.9, 137.4, 128.8, 122.8, 113.7, 55.53, 19.0. MP 190 °C. IR (cm^{-1}): 3044, 2924, 2863, 2300, 1608, 1545, 1518, 1491, 1459, 1421, 1388, 1263, 1226, 1157, 1034, 996, 948, 879, 818, 736, 638, 573, 516. HRMS (ESI, TOF) calcd for C$_{25}$H$_{28}$N$_3$O$_2$ [M+H]$^+$ 402.2182, found 402.2189.

Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene))bis(4-(benzyloxy)-2,6-diisopropylaniline) (L5). L5 was prepared from the

L5
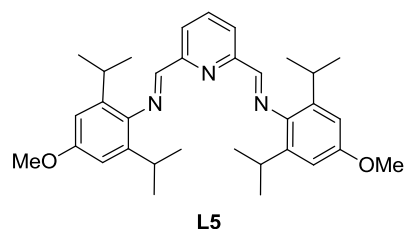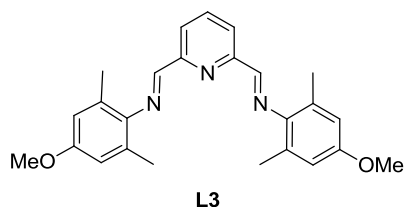
similar literature procedure,[37] with 4-methoxy-2,6-diisoproply aniline (807 mg, 3.89 mmol) and 2,6-pyridinedicarboxaldehyde (263 mg, 1.95 mmol) and 5 drops of glacial acetic acid in 5 mL 100% ethanol. The reaction was stirred overnight at room temperature. The mixture was then cooled to 0 °C, filtered, and rinsed with cold 100% ethanol to yield **L3** (891 mg, 89%) as a yellow solid. $R_f = 0.61$ (20% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 1.20 (d, $J = 6.7$ Hz, 24H), 3.03 (quint, $J = 6.9$ Hz, 4H), 3.85 (s, 6H), 6.74 (s, 4H), 7.99 (t, $J = 7.8$ Hz, 1H), 8.36-8.40 (m, 4H). ^{13}C NMR (125 MHz, CDCl$_3$): δ (ppm) 163.4, 157.0, 154.7, 142.1, 139.1, 137.5, 122.8, 108.8, 55.5, 28.4, 23.7. MP 181 °C. IR (cm^{-1}): 3046, 2961, 2871, 2836, 1638, 1601, 1582, 1462, 1383, 1327, 1289, 1238, 1198, 1169, 1125, 1107, 1076, 1039, 990, 942, 866, 763, 739, 625, 526. HRMS (ESI, TOF) calcd for C$_{33}$H$_{44}$N$_3$O$_2$ [M+H]$^+$ 514.3434, found 5143.3441.

Synthesis of (L2)FeBr$_2$. Adapted from the literature procedure.[18] In a nitrogen-filled glove box, **L2** (109 mg, 5.1 x 10^{-1} mmol), FeBr$_2$ (111 mg, 5.1 x 10^{-1} mmol), and 3.0 mL of THF were combined in a vial and stirred at room temperature overnight. Pentane was added to the mixture, creating a green precipitate. This green solid was filtered and rinsed with pentane then dried *in vacuo*, yiedling a dark green solid (299.3 mg, >99%). A crystal suitable for x-ray analysis was grown from slow diffusion of pentane into a solution of **(L2)FeBr$_2$** in THF. Elemental Analysis calculated: C, 51.31 H, 4.65 N, 7.18 found: C, 51.59 H, 4.88 N, 7.19.
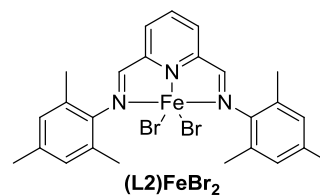
References

(1) D'Souza, B., R.; Lane, T. K., Louie, J. *Org. Lett.* **2011**, *13*, 2936-2939.

(2) Selected examples of iron catalyzed alkyne cyclotrimerization: (a) tom Dieck, H.; Diercks, R. *Angew. Chem. Int. Ed.* **1983**, *22*, 1138-1146. (b) Breschi, C.; Piparo, L.; Pertici, P.; Caporusso, A. M.; Vitulli, G. *J. Organomet. Chem.* **2000**, *607*, 57-63. (c) Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065-3067. (d) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, *691*, 3129-3136. (e) Liu, Y.; Yan, X.; Yang, N.; Xi, C. *Catal. Commun.* **2011**, *12*, 489-492.

(3) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 7162-7166.

(4) The large excess of nitrile presumably favors pyridine formation over diyne dimerization.

(5) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2001**, 1102-1103.

(6) (a) Stolley, R. M.; Maczka, M. T.; Louie, J. *Eur. J. Org. Chem.* **2011**, 3815-3824. (b) Kumar, P.; Prescher, S.; Louie, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 10694-10698.

(7) (a) Kamal, A.; Reddy, J. S.; Ramaiah, M. J.; Dastagiri, D.; Bharathi, E. V.; Sagar, M. V. P.; Pushpavalli, S. N. C. V. L.; Ray, P.; Pal-Bhadra, M. Med. *Chem. Commun.* **2010**, *8*, 355-360. (b) Hilton, S.; Naud, S.; Caldwell, J. J.; Boxall, K.; Burns, S.; Anderson, V. E.; Antoni, L.; Allen, C. E.; Pearl, L. H.; Oliver, A. W.; Aherne, G. W.; Garrett, M. D.; Collins, I. *Bioorg. Med. Chem.* **2010**, *18*, 707-718. (c) Garcin, E. D.; Arvai, A. S.; Rosenfeld, R. J.; Kroeger, M. D.; Crane, B. R.; Andersson, G.; Andrews, G.; Hamley, P. J.; Mallinder, P. R.; Nicholls, D. J.; St-Gallay, S. A.; Tinker, A. C.; Gensmantel, N. P.; Mete, A.; Cheshire, D. R.; Connolly, S.; Stuehr, D. J.; Aberg, A.; Wallace, A. V.; Tainer, J. A.; Getzoff, E. D. *Nature Chem. Biol.* **2008**, *4*, 700-707. (d) Takahashi, Y.; Furukawa, K.; Ishibashi, M.; Kozutsumi, D.; Ishiyama, H.; Kobayashi, J.; Ohizumi, Y. *Eur. J. Pharmacol., Mol. Pharmacol. Sect*, **1995**, *288*, 285-293. (e) Peczyska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. *J. Med. Chem.* **1994**, *37*, 3503-3510.

(8) (a) Kim, J.; Shin-ya, S.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431-3434. (b) Alajarin, M.; Molina, P.; Vidal, A. *J. Nat. Prod.* **1997**, *60*, 747-748.

(9) Toshiki, M.; Cheon, J.; Tsuchiya, G.; Araki, K. *J. Chem. Soc. Perkin Trans. 2* **2002**, 862-865.

(10) Burchak, O. N.; Mugherli, L.; Ostuni, M.; Lacapere, J. J.; Balakirev, M. Y. *J. Am. Chem. Soc.* **2011**, *133*, 10058-10061.

(11) Motoyama, T.; Sasabe, H.; Seino, Y.; Takamatsu, J.; Kido, J. *Chem. Lett.* **2011**, *40*,

306-308.

(12) Horie, H.; Koyama, I.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2011**, *47*, 2658-2660.

(13) (a) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109-4112. (b) Maiti, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 17423-17429.

(14) (a) Thomas, S.; Roberts, S.; Pasumansky, L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2003**, *5*, 3867-3870. (b) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2010**, *12*, 5254-5257.

(15) (a) Salem, M. A. I.; Madkour, H. M. F; Soliman, E. S. A.; Mahmoud, N. F. H. *Heterocycles* **2000**, *53*, 1129. (b) Teague, S. J. *J. Org. Chem.* **2008**, *73*, 9765-9766.

(16) Cobalt: (a) Heller, B.; Reihsig, J.; Schulz, W.; Oehme, G. *Appl. Organomet. Chem.* **1993**, *7*, 641-646. (b) Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131-3133. (c) Boñaga, L. V. R.; Zhang, H.-C.; Maryanoff, B. E. *Chem. Commun.* **2004**, 2394-2395. (d) Hapke, M.; Kral, K.; Fischer, C.; Spannenberg, A.; Gutnov, A.; Redkin, D.; Heller, B. *J. Org. Chem.* **2010**, *75*, 3993-4003. (e) Garcia, P.; Evanno, Y.; Gorge, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* **2011**, *13*, 2030-2033. (f) Garcia, P.; Evanno, Y.; Gorge, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Chem. Eur. J.* **2012**, *18*, 4337-4344. Nickel: (g) Bönnemann, H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 248-262. (h) Rhodium: Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917-3922. Titanium: (i) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774-7780. Photocatalytically: (j) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414-4412.

(17) Additional PDAI class ligands were screened and are included in the Supporting Information.

(18) Studies involving iron bis(imino)pyridine and bis(aldimino)pyridine complexes: (a) Bart, S. C.; Chłopek, K.; Bill, E.; Bouwkamp, M. W. Lobkovsky, E.; Neese, F.; Weighardt, K.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13901-13912. (b) Russell, S. K.; Milsmann, C.; Lobkovsky, E.; Weyhermüller, T.; Chirik, P. *J. Inorg. Chem.* **2011**, *50*, 3159-3169.

(19) See Supplementary Information for details of control experiments.

(20) (a) Yamamoto, Y.; Kinpara, K.; Nishiyama, H.; Itoh, K. *Adv. Synth. Catal.* **2005**, *347*, 1913-1916. (b) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. Eur. J.* **2006**, *12*, 5618-5631.

(21) Cobalt: (a) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-H.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414-4422. (b) Heller,

B.; Reihsig, J.; Schulz, W.; Oehme, G. *Appl. Organomet. Chem.* **1993**, *7*, 641-646. (c) Pietro, D.; Ingrosso, G.; Lucherini, A.; Vanacore, D. *J. Mol. Catal.* **1987**, *41*, 261-270. Rhodium: (d) Cioni, P; Civersi, P. Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 337-357.

(22) Liu, Y.; Yan, X.; Yang, N.; Xi, C. *Cat. Commun.* **2011**, *12*, 489-492.

(23) Henke, B. R.; Drewry, D. H.; Jones, S. A.; Stewart, E. L.; Weaver, S. L.; Wiethe, R. W. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1939-1942.

(24) (a) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046-6047. (b) Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 4388-4391. (c) Xie, L.-G.; Want, Z.-X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4901-4904.

(25) Hyster, T. K.; rovis, T. *Chem. Commun.* **2011**, *47*, 11846-11848.

(26) (a) H. Yamazaki, Y. Wakatsuki, *Tetrahedron Lett.* **1973**, *14*, 3383-3384. (b) Bönnemann, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248-262. (c) Diercks, R.; Eaton, B. E.; Gürtzgen, S.; Jalisatgi, S.; Matsger, A. J.; Radde, R. H.; Vollhardt, K. P. C. *J. Am Chem. Soc.* **1998**, *120*, 8247-8248. (d) Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. *J. Organomet. Chem.* **2006**, *691*, 4434-4445. (e) Dahy, A. A.; Yamada, K.; Koga, N. *Organometallics* **2009**, *28*, 3636-3649. (f) Dahy, A. A.; Koga, N. *J. Organomet. Chem.* **2010**, *695*, 2240-2250.

(27) (a) Takahashi, T.; Tsai, F. Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994-4995; (b) Takahashi, T.; Tsai, F. Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059-5067; (c) Eisch, J. J.; Ma, X.; Han, K. I.; Gitua, J. N.; Kruger, C. *Eur. J. Inorg. Chem.* **2001**, 77-88. (d) Stolley, R. M.; Duong, H. A.; Thomas, D. R.; Louie, J. *J. Am. Chem. Soc.* **2012**, *134*, 15154-15162. (e) Stolley, R. M.; Duong, H. A.; Louie, J. *Organometallics*, **2013**, *32*, 4952-4960.

(28) Nishida, M.; Shiga, H.; Mori, M. *J. Org. Chem.* **1998**, *63*, 8606-8608.

(29) Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1215-1217.

(30) Hu, Y.; Sun, Y.; Hu, J.; Zhu, T.; Yu, T.; Zhao, Q. *Chem. Asian J.* **2011**, *6*, 797-800.

(31) Ishizaki, M.; Hoshino, O. *Tetrahedron* **2000**, *56*, 8813-8819.

(32) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586-4587.

(33) Han, Y.; Harlan, J.; Stoessel, P.; Frost, B. J.; Norton, J. R.; Miller, S.; Bridgewater, B.; Xu, Q. *Inorg. Chem.* **2001**, *40*, 2942-2952.

(34) Tekavec, T. N.; Louie, J. *J. Org. Chem.* **2008**, *73*, 2641-2648.

(35) Apte, S.; Radetich, B.; Shin, S.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 4053-4056.

(36) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516-11517.

(37) Britovsek, G. J. P.; Bruce, M.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; Mastroianni, S.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Stroemberg, S.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728-8740.

(38) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284-286.

CHAPTER 4

THE IRON-CATALYZED CONSTRUCTION OF 2-AMINOPYRIMIDINES FROM

ALKYNENITRILES AND CYANAMIDES

Introduction

The domain of [2+2+2] cycloaddition is poised to enter a new step in its

evolution. Cyclic compounds with multiple heteroatoms constitute a vast collection of

molecules attracting considerable interest. Such motifs are prevalent in pharmaceuticals,

natural products, and other biologically active compounds, as well as in polymers and

supramolecules.[1] Despite such importance, the use of highly efficient [2+2+2]

cycloadditions for the construction of these compounds has received little attention. Such

a reaction requires the incorporation of two heteroatom coupling partners to one

hydrocarbon coupling partner. However, the latter substrates are typically more reactive

in cycloaddition and lead to products that exclude the less reactive heteroatom coupling

partner.[2]   For example, the combination of alkynes and excess nitriles in the presence of

a variety of [2+2+2] cycloaddition catalysts affords either pyridines or substituted

benzenes, or a mixture thereof.[3]   Even when employing nitrile as a solvent, incorporation

of multiple nitrogen atoms is typically not observed.[4]   Despite this significant obstacle,

limited examples demonstrate that strategies to access cyclic compounds with multiple

heteroatoms are possible. The first example by Hoberg involved the cycloaddition of an alkyne and two isocyanates in the presence of stoichiometric Ni(0), producing a pyrimidine dione.[5] The Louie lab revisited this reactivity and successfully developed the first catalytic [2+2+2] route to pyrimidine diones.[6] This work was later followed up by Kondo and co-workers.[7] A more recent example by Obora utilizes a niobium Lewis acid to afford pyrimidines from an alkyne and two nitriles (equation 1).[8] While this method is regioselective, it requires an excess of $NbCl_5$ that must be added in six portions over the course of the reaction. Yields in this system are moderate and substrates are limited to aromatic nitriles. The niobium reagent likely acts as a Lewis acid, invoking a nucleophilic attack of the nitrile nitrogen onto a Nb coordinated alkyne. Such a scarcity of examples in this area led us to seek a new metal-catalyzed [2+2+2] cycloaddition method for the creation of cyclic compounds with two heteroatoms.

$$R^1 \!\!\equiv\!\! R^2 \; + \; 2 \; Ar \!\!\equiv\!\! N \; \xrightarrow{NbCl_5} \qquad\qquad (1)$$
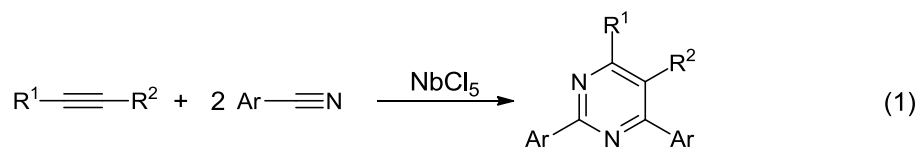
Research by the Louie lab has demonstrated that cyanamides perform exceptionally well in nickel- and iron-catalyzed cycloadditions with diynes (equation 2).[9,10] Furthermore, utilizing alkynenitriles aids in the incorporation of nitrogen into cycloaddition products when using an iron catalyst.[11] This chapter describes the development of a novel Fe-catalyzed cycloaddition reaction between alkynenitriles and cyanamides to provide 2-aminopyrimidines, a class of compounds with rich biological activity (equation 3).[12,13]
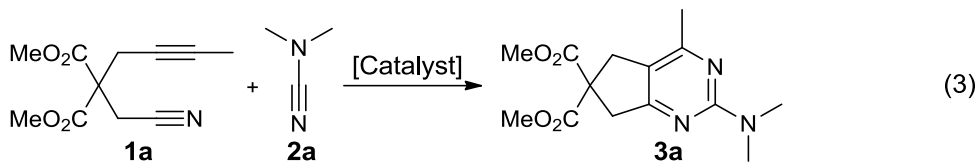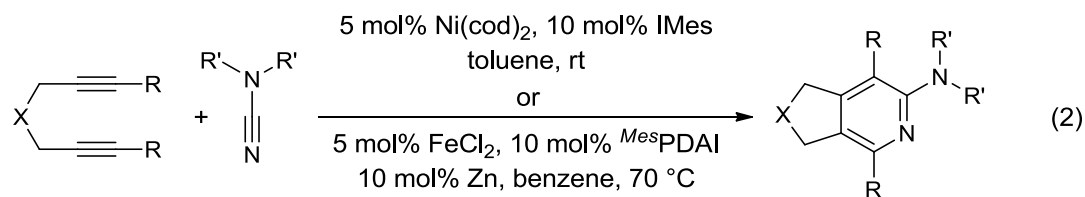
Results and Discussion

This study was begun by applying alkynenitrile **1a** and cyanamide **2a** to various [2+2+2] transition metal catalysts under their previously developed conditions (Table 7).[14] Rhodium, cobalt, nickel, and ruthenium catalysts (entries 1-7) were ineffective while iridium (entry 8) only afforded a trace of **3a**, as detected by GCMS. Additionally, niobium, gold, silver, and copper reagents provided no products (entries 9-13). FeI_2/dppp was ineffective (entries 14 and 15). However, the previously discussed $Fe(OAc)_2$/[p-OMe,iPr]PDAI system[11] provided a trace of 2-aminopyrimidine (entries 16). Curiously, our $FeCl_2$/[Mes]PDAI catalyst (entry 17) under the conditions used to produce 2-aminopyridines[10] afforded 2-aminopyimidine **3a** in 16% NMR yield.

Exhaustive optimization was carried out by myself and Minh Nguyen (Table 8). Expensive and highly toxic benzene was replaced with toluene at the outset of optimization. Initially $Fe(OAc)_2$ was identified as the optimum iron source (entry 3); however, subsequent optimization with $Fe(OAc)_2$ was unproductive. Attention was then turned to FeI_2 (entry 4), which allowed for significant improvements. Decreasing concentration (entry 5), increasing cyanamide loading to 3 equivalents, and ensuing ligand optimization (Figure 18) led to sound improvements in yields. Phosphine, amine,

Table 7. Survey of cycloaddition catalysts and reagents

Entry	Substrates (equiv)	Conditions[a]	% yield 3a[b]
1	**1a** (1), **2a** (2)	5 mol % Rh(cod)$_2$BF$_4$/BINAP	-
2	**1a** (1), **2a** (5)	15 mol % CoCp(CO)$_2$	-
3	**1a** (1), **2a** (3)	10 mol % CoCl$_2$, 10 mol % dppe, 20 mol % Zn	-
4	**1a** (1), **2a** (1.5)	10 mol % Ni(cod)$_2$, 20 mol % SIPr	-
5	**1a** (1), **2a** (1.5)	10 mol % Ni(cod)$_2$, 20 mol % IMes	-
6	**1a** (1), **2a** (1.5)	10 mol % Ni(cod)$_2$, 10 mol % Xantphos	-
7	**1a** (1), **2a** (3)	2 mol % [Ir(cod)Cl]$_2$, 4 mol % DPPF	trace
8	**1a** (1), **2a** (3)	1.2 equiv NbCl$_5$	-
9	**1a** (1), **2a** (3)	5 mol % Ph$_3$PAuOPOF$_2$	-
10	**1a** (1), **2a** (3)	5 mol % AuCl$_3$, 1.1 equiv MsOH	-
11	**1a** (1), **2a** (3)	5 mol % AuPEt$_3$Cl, 5 mol % AgSbF$_6$	-
12	**1a** (1), **2a** (3)	10 mol % AgOTf, 10 mol % CuBr	-
13	**1a** (1), **2a** (3)	20 mol % FeI$_2$, 20 mol % dppp, 20 mol % Zn	-
14	**1a** (1), **2a** (3)	20 mol % FeI$_2$, 20 mol % dppp, 20 mol % Zn, 20 mol % ZnI$_2$	-
15	**1a** (1), **2a** (2)	20 mol % Fe(OAc)$_2$, 40 mol % Zn,, 26 mol % $^{p\text{-}OMe,\ iPr}$PDAI^m	trace
16	**1a** (1), **2a** (2)	10 mol % FeCl$_2$, 20 mol % ^{Mes}PDAI, 20 mol % Zn	16[c]

Table 8. Optimization

Entry	**1a:2a**	FeX$_2$ (mol %)	Ligand (mol %)	Concentration [**1a**] (M)	temp (°C)	% yield[b]
1	1:2	FeCl$_2$ (10)	^{Mes}PDAI (20)	0.4	70	9
2	1:2	FeBr$_2$ (10)	^{Mes}PDAI (20)	0.4	70	10
3	1:2	Fe(OAc)$_2$ (10)	^{Mes}PDAI (20)	0.4	70	23
4	1:2	FeI$_2$ (10)	^{Mes}PDAI (20)	0.4	70	12
5	1:2	FeI$_2$ (10)	^{Mes}PDAI (20)	0.1	70	40
6	1:3	FeI$_2$ (10)	^{iPr}PDI (20)	0.1	70	4
7	1:3	FeI$_2$ (10)	^{Me}PDAI (20)	0.1	70	13
8	1:3	FeI$_2$ (10)	$^{p\text{-}OMe,\ Me}$PDAI (20)	0.1	70	-
9	1:3	FeI$_2$ (10)	^{Ph}PDAI (20)	0.1	70	-
10	1:3	FeI$_2$ (10)	^{tBu}PDAI (20)	0.1	70	-
11	1:3	FeI$_2$ (10)	^{Et}PDAI (20)	0.1	70	47
12	1:3	FeI$_2$ (10)	$^{p\text{-}OMe,\ iPr}$PDAI (20)	0.1	70	25
13	1:3	FeI$_2$ (10)	$^{p\text{-}CF3,\ iPr}$PDAI (20)	0.1	70	70
14	1:3	FeI$_2$ (10)	^{iPr}PDAI (20)	0.1	70	72
15	1:3	FeI$_2$ (10)	^{iPr}PDAI (20)	0.1	40	>99
16[c]	1:3	FeI$_2$ (5)	^{iPr}PDAI (10)	0.1	40	98
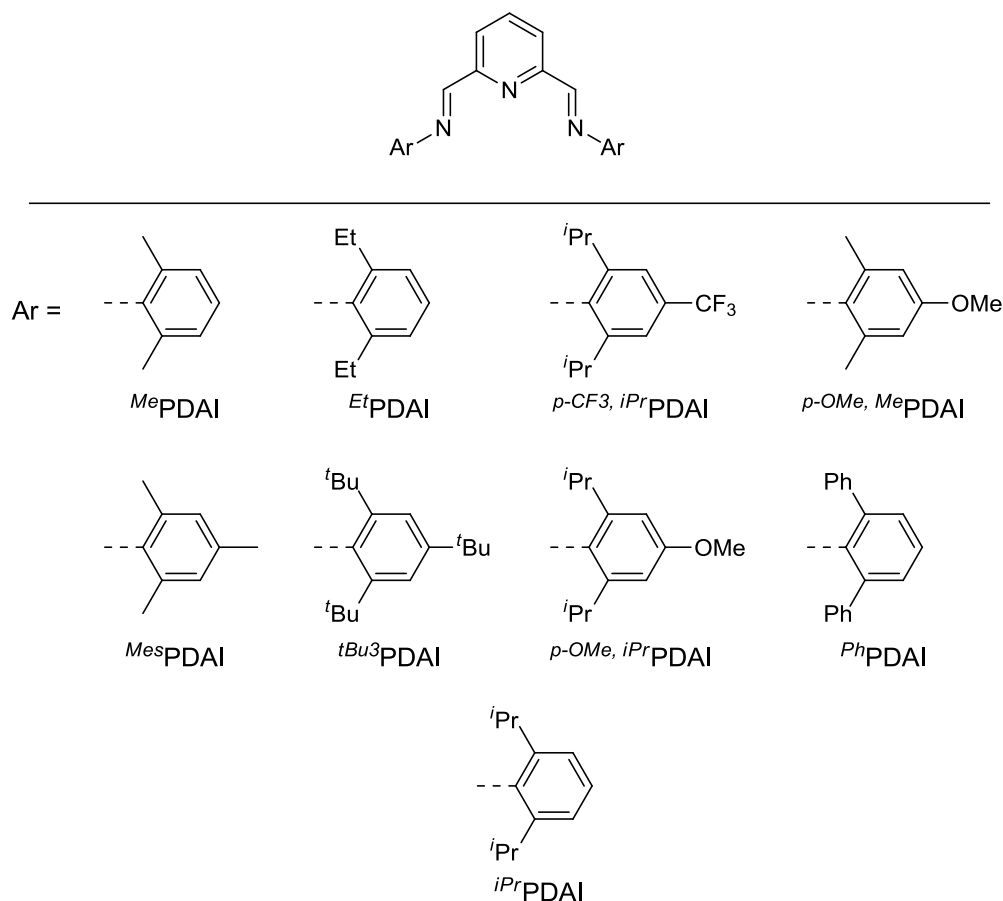
Figure 18. Ligands.

carbene, and bisimine ligands were ineffective, while PDI ligands could only afford traces of product. Decreasing the temperature to 40 °C and increasing Zn dust loading to 30 mol% allowed for catalyst loading to be reduced to 5 mol% (entry 16). The need to increase Zn loading suggests that, at lower concentrations, the reduction of iron pre-catalyst by Zn is perhaps more difficult, leading to the necessity for higher loading. The final conditions utilize a 1:3 ratio of alkynenitrile with 5 mol% FeI₂, 10 mol% ^{iPr}PDAI, and 30 mol% Zn dust in toluene at 40 °C (equation 4).

(4)
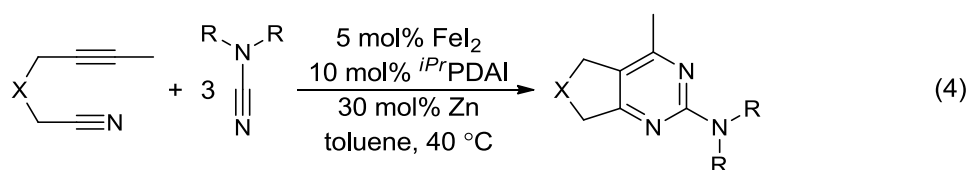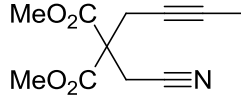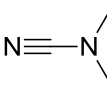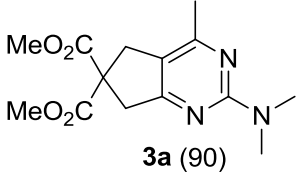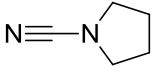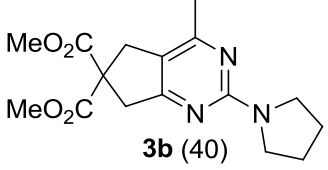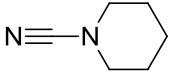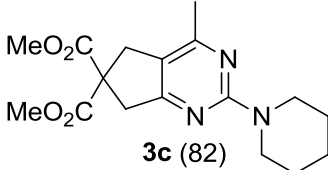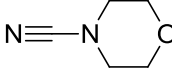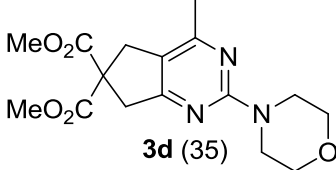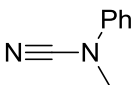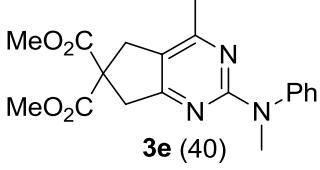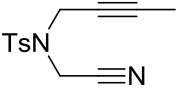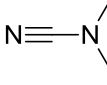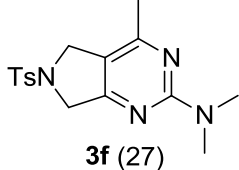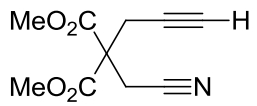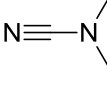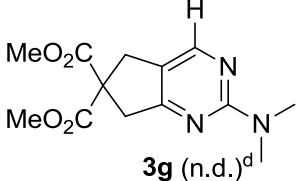
The final optimized conditions were applied to various combinations of substrates (Table 9). Model substrates **1a** and **2a** afforded **3a** in 90% yield in 12 h (entry 1, Figure 19); however, other substrates required extended reaction times. Cyclic cyanamides were incorporated, providing **3b**, **3c**, and **3d** in 40, 82, and 35% yields, respectively (entry 2-4). Me/Ph cyanamide **2e** provided **3e** in 40% yield over 3 days.

Under the standard conditions **1b** was unreactive, however, in the presence of 30 mol% ZnI_2, **3f** was obtained in 27% yield. While ZnI_2 is known to aid in cobalt catalysis by stabilizing transient Co(I) species,[15] its effect in iron-catalyzed reactions is still unclear.[2,16] Applying ZnI_2 to all reactions involving **1a** resulted in increased reaction times and decreased yields. This inconsistent activity of ZnI_2 has been observed in a previous study.[14i] Finally, the challenging terminal alkyne **1c** failed to react under these conditions (entry 7). Efforts to replace the cyanamide substrate with an unactivated nitrile, such as benzonitrile, were ineffective. Also ineffective were 3-component cyclizations of 4-ethynyl toluene with either 2 equivalents of free nitrile (such as benzonitrile) or cyanamides (such as **2a**). Although yields are modest in many cases, this work demonstrates that bicyclic 2-aminopyrimidines with complex substitution patterns can be prepared through iron-catalyzed cycloaddition chemistry. In some cases, however, yields are high, indicating that this system could be synthetically useful if optimization is done on a case-by-case basis.

Conclusions

""""""""""""This work has led to the first catalytic [2+2+2] cycloaddition to produce aromatic diazaheterocycles. What is especially remarkable is that iron, which has traditionally been an inefficient cycloaddition catalyst for nitrile incorporation, can now incorporate

Table 9. 2-Aminopyrimidine Substrate Scope

Entry	Alkynenitrile	Cyanamide	time[b]	Product (% yield)
1	**1a**	**2a**	8 h	**3a** (90)
2	**1a**	**2b**	48 h	**3b** (40)
3	**1a**	**2c**	36 h	**3c** (82)
4	**1a**	**2d**	72 h	**3d** (35)
5	**1a**	**2e**	72 h	**3e** (40)
6[c]	**1b**	**2a**	48 h	**3f** (27)
7	**1c**	**2a**	8 h	**3g** (n.d.)[d]

Figure 19. Ortep of **3a**.

multiple nitriles into aromatic products. Furthermore, traditionally more efficient

catalysts were ineffective toward this strategy of 2-aminopyrimidine synthesis. By

testing the boundaries of these PDAI/iron catalyst systems, the reactivity of [2+2+2]

cycloaddition has been expanded to include the synthesis of 2-aminopyrimidines.

Despite exhaustive optimization for this reaction, yields remained generally low. A

mechanistic study of these iron systems could provide the insight necessary to improve

and expand this methodology. The preliminary mechanistic study will be discussed in

the next chapter.

Experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk

techniques or in a nitrogen-filled glove box unless otherwise noted. Benzene and toluene

were dried over neutral alumina under N_2 using a Grubbs-type solvent purification

system. Iron Chloride (99.95% purity) was purchased from Alfa Aesar. Iron(II) Bromide

(98%), Iron(II) Iodide (anhydrous beads, ≥99.99%), and Iron(II) Acetate (≥99.99%)

were purchased from Sigma Aldrich. Alkynenitrile **1a** was prepared from the literature

procedure and was purified by column chromatrography and recrystallization as

described below.[17] Alkynenitrile **1c** was prepared according to the literature procedure.[11]

Cyanamides **2a-d** were purchased from Sigma Aldrich and were distilled then degassed

using three sequential freeze-pump-thaw cycles. Cyanamide **2e** was prepared from the literature procedure.[9] Zinc dust was purchased from Sigma Aldrich and activated with HCl according to the literature procedure.[18]

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 75 MHz, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, td, t, q, quint, and sext stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet of doublets, triplet, quartet, quintet, and sextet respectively. All ^{13}C NMR spectra were proton-decoupled. The infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 10 ºC/min.; final temperature: 300 ºC held for 12 minutes; detector temperature: 250 ºC.

General Procedure for the Cycloaddition. In a nitrogen-filled glove box, 5 mol% FeI$_2$ beads were added to the reaction vial. The beads were thoroughly crushed into a fine powder to ensure complexation with ligand. 10 mol% ^{iPr}**PDAI** and toluene was added to a vial and the mixture was stirred for 1 hour. At this time additional toluene, a toluene solution of alkynenitrile, 30 mol% Zn dust, and 3 equivalents of cyanamide were added. The vial was then capped, removed from the glove box and stirred in a 40 °C oil bath. After completion as monitored by GC, the crude mixture was purified by silica gel flash chromatography.
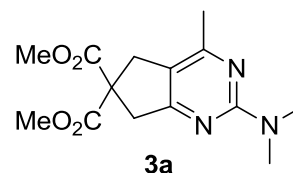
Synthesis of dimethyl 2-(dimethylamino)-4-methyl-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3a). Compound **3a** was prepared using the general procedure with FeI$_2$ (6.9 mg, 2.2 x 10^{-2} mmol) and ^{iPr}**PDAI** (16.6 mg, 4.5 x 10^{-2} mmol), which were stirred in 1 mL of toluene for 1 hour. 2.5 mL of toluene, alkynenitrile **1a** (100 mg, 4.5 x 10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3 x 10^{-1} mmol), and **2a** (100 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 12 h. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25% ethyl acetate in hexanes to yield **3a** (119 mg, 90%) as a white solid. R$_f$ = 0.38 (25% ethyl acetate in hexanes). MP 100.5-102 ^{O}C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.75 (s, 6H), 3.47 (s, 2H), 3.39 (s, 2H), 3.15 (s, 6H), 2.25 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.1, 169.9, 163.1, 162.3, 116.4, 57.4, 53.3, 42.1, 37.4, 36.2, 22.12. IR (cm^{-1}): 2950, 2852, 1729, 1602, 1440, 1281, 1154, 871. HRMS (ESI) m/z calcd for C$_{14}$H$_{20}$N$_3$O$_4$ [M + H]$^+$ 294.1454, found 294.1455.

Synthesis of dimethyl 4-methyl-2-(pyrrolidin-1-yl)-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3b). Compound **3b** was prepared using the general procedure with FeI$_2$ (6.9 mg, 2.2 x 10^{-2} mmol) and ^{iPr}**PDAI** (16.6 mg, 4.5 x 10^{-2} mmol), which were stirred in 1 mL of toluene for 1 h. 2.5 mL of toluene, alkynenitrile **1a** (100 mg, 4.5 x 10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3 x 10^{-1} mmol), and **2b** (129 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 72 h. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25% ethyl acetate in hexanes to yield **3b** (57 mg, 40%) as a white solid. R$_f$ = 0.14 (25% ethyl acetate in hexanes). m.p. 134-135 °C. ^{1}H NMR (CDCl$_3$, 300
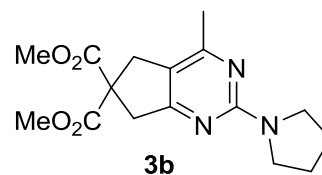
MHz) δ 3.75 (s, 6H), 3.54 (t, J = 6.0, 4H), 3.49 (s, 2H), 3.40 (s, 2H), 2.26 (s, 3H), 1.94 (t, J = 6.0, 4H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.1, 169.9, 162.5, 161.3, 116.4, 57.4, 53.3, 47.0, 42.1, 36.3, 25.7, 22.2. IR (cm^{-1}): 2954, 2869, 2360, 1737, 1600, 1515, 1271, 1198, 1165, 883. HRMS (ESI) m/z calcd for C$_{16}$H$_{22}$N$_3$O$_4$ [M + H]$^+$ 320.1610, found 320.1610.
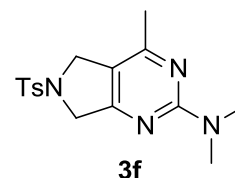
Synthesis of dimethyl 4-methyl-2-(piperidin-1-yl)-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3c).
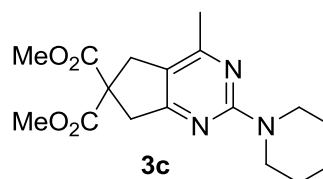
3c

Compound **3c** was prepared using the general procedure with FeI$_2$ (6.9 mg, 2.2 x 10^{-2} mmol) and ^{iPr}PDAI (16.6 mg, 4.5 x 10^{-2} mmol), which were stirred in 1 mL of toluene for 1 h. 2.5 mL of toluene, alkynenitrile **1a** (100 mg, 4.5 x 10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3 x 10^{-1} mmol), and **2c** (148 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 48 h. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25% ethyl acetate in hexanes to yield **3c** (123 mg, 82%) as a clear oil. R$_f$ = 0.50 (25% ethyl acetate in hexanes). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.75 (m, 10H), 3.44 (s, 2H), 3.38 (s, 2H), 2.24 (s, 3H), 1.62 (m, 6H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.1, 170.0, 162.6, 162.4, 116.7, 57.4, 53.3, 45.2, 42.1, 36.2, 30.5, 26.03, 25.1, 22.24. IR (cm^{-1}): 2932, 2852, 1737, 1600, 1566, 1462, 1443, 1361, 1291, 870. HRMS (ESI) m/z calcd for C$_{17}$H$_{24}$N$_3$O$_4$ [M + H]$^+$ 334.1767, found 334.1772.

Synthesis of dimethyl 4-methyl-2-morpholino-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3d). Compound **3d** was prepared using the general

3d
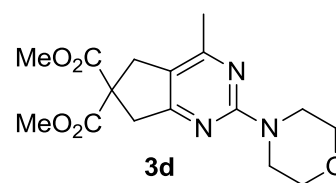
procedure with FeI$_2$ (6.9 mg, 2.2 x 10^{-2} mmol) and ^{iPr}PDAI (16.6 mg, 4.5 x 10^{-2} mmol) which were stirred in 1 mL of toluene for 1 h. 2.5 mL of toluene, alkynenitrile **1a** (100

mg, 4.5 x 10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3 x 10^{-1} mmol) and **2d** (129 mg, 1.34 x 10^{-1} mmol), were added and the reaction was stirred at 40 °C for 96 h. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25% ethyl acetate in hexanes to yield **3d** (57 mg, 38%) as a white solid. R_f = 0.19 (25% ethyl acetate in hexanes). m.p. 104-106 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.76 (m, 12H), 3.47 (s, 2H), 3.41 (s, 2H), 2.26 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 175.1,, 172.0, 170.2, 162.6, 118.1, 67.1, 57.4, 53.4, 44.8, 42.0, 36.2, 22.2. IR (cm^{-1}): 2954, 1792, 1735, 1689, 1559, 1436, 1361, 1203. HRMS (ESI) m/z calcd for C$_{16}$H$_{22}$N$_3$O$_5$ [M + H]$^+$ 336.1559, found 336.1562.

Synthesis of dimethyl 4-methyl-2-(methyl(phenyl)amino)-5H-cyclopenta[d]pyrimidine-6,6(7H)-dicarboxylate (3e). Compound **3e** was prepared using
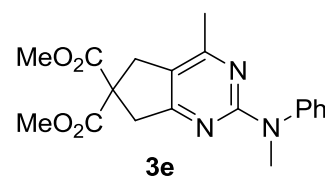
the general procedure with FeI$_2$ (6.9 mg, 2.2 x 10^{-2} mmol) and ^{iPr}**PDAI** (16.6 mg, 4.5 x 10^{-2} mmol), which were stirred in 1 mL of toluene for 1 h. 2.5 mL of toluene, alkynenitrile **1a** (100 mg, 4.5 x 10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (8.8 mg, 1.3 x 10^{-1} mmol), and **2e** (178 mg, 1.34 mmol) were added and the reaction was stirred at 40 °C for 96 h. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 25% ethyl acetate in hexanes to yield **3e** (64 mg, 40%) as a yellow oil. R_f = 0.49 (25% ethyl acetate in hexanes). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30-7.38 (m, 3H),, 7.13-7.18 (m, 2H) 3.75 (s, 6H), 3.52 (s, 3H), 3.48 (s, 2H), 3.42 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.0, 170.0, 162.4, 146.2, 128.9, 126.3, 125.0, 118.7, 57.4, 53.4, 42.1, 39.0, 36.2, 22.2. IR (cm^{-1}): 2954, 2927, 1736, 1603, 1589, 1388, 1271, 1204, 862. HRMS (ESI) m/z calcd for
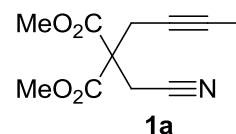
$C_{19}H_{22}N_3O_4$ $[M + H]^+$ 356.1610, found 356.1613.

Synthesis of N,N,4-trimethyl-6-tosyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine (3f). Compound **3f** was prepared using the general procedure with FeI$_2$ (5.9 mg, 1.9 x 10^{-2} mmol) and

3f

^{iPr}**PDAI** (17.3 mg, 3.8 x 10^{-2} mmol), which were stirred in 1 mL of toluene for 1 h. 1.8 mL of toluene, alkynenitrile **1b** (100 mg, 3.0 x 10^{-1} mmol) dissolved in 1 mL of toluene, zinc dust (5.9 mg, 9.0 x 10^{-2} mmol) and **2a** (63.1 mg, 9.0 x 10^{-1} mmol) were added and the reaction was stirred at 40 °C for 96 h. After the reaction was complete (monitored by GC), the product was isolated using silica gel flash chromatography with 10% ethyl acetate in hexanes to yield **3e** (34 mg, 27%) as a white solid. R_f = 0.12 (20% ethyl acetate in hexanes). MP none, decomposed at 177 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.76 (dd, J_1 = 9.0, J_2 = 3.0, 2H), 7.32 (dd, J_1 = 9.0, J_2 = 3.0, 2H), 4.46 (s, 2H), 4.40 (s, 2H), 3.13 (s, 6H), 2.41 (s, 2.41), 2.22 (d, J = 3.0). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 166.1, 161.6, 133.8, 130.1, 127.8, 113.4, 54.0, 50.8, 37.4, 22.3, 21.8. IR (cm^{-1}): 2916.8, 2858.0, 160.7, 1573.4, 1538.3, 1395.6, 1342.3, 1330.7, 1156.7, 1095.3, 1067.6, 820.3, 783.4. HRMS (ESI) m/z calcd for $C_{16}H_{20}N_4NaO_2S$ $[M + Na]^+$ 355.1205, found 355.1208.

Substrate Synthesis dimethyl 2-(but-2-yn-1-yl)-2-(cyanomethyl)malonate (1a)[17]**.** Under nitrogen atmosphere, a

1a

round bottom and stir bar was charged with NaH (1.32g, 54.9 mmol) and THF (40 mL) at 0°C. A solution of dimethyl 2-(but-2-yn-1-yl)malonate (7.22g, 39.2 mmol) in 20 mL of THF was added slowly to the NaH solution at 0°C. The reaction was stirred and warmed to room temperature over 30 min. Then bromoacetonitrile (6.58g, 54.9 mmol) in 20 mL of THF was slowly added to the mixture.

The reaction was stirred at room temperature for 1 h and refluxed for another 4 days at 50°C. The reaction was quenched with saturated NH_4Cl, extracted with diethyl ether (3 x 150 mL). The solvent was removed from the extraction by reduced vacuum and purified by flask chromatography (2L 10%, 1L 25% EtOac/hexanes) to afford the product as a pale yellow oil (8.4g, 96%). The product was further purified by recrystallization. The yellow oil was dissolved in 10 mL of toluene which was layered with pentane. This mixture was stored overnight at -40°C, which afforded a white solid. MP 31.5-32.5 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 6H), 3.11 (s, 2H), 2.94 (s, 2H), 1.2 (s, 3H).

N-(but-2-yn-1-yl)-N-(cyanomethyl)-4-methylbenzenesulfonamide (1b). A 50 mL round-bottom flask was charged with 561.3 mg (2.14 mmol) of triphenyl phosphine, 456.0 mg (2.04 mmol) of N-(cyanomethyl)-4-methylbenzenesulfonamide,[19] approximately 10 mL of anhydrous THF, and 150.0 mg (2.814 mmol) of 2-butyne-1-ol. The reaction was cooled to 0 °C. Next 432.7 mg (2.14 mmol) of Diisopropyl azodicarboxylate was added dropwise over 15 minutes. The reaction was stirred for 48 h, concentrated, and isolated by flash column chromatography using 100 mL of each of 5%, 10%, 15%, 20%, 25%, and 30% of ethyl acetate in hexanes. Evaporation of eluent yielded a clear yellow oil, which was further purified by recrystallization in layered pentane over toluene to obtain 385 mg (72% yield) of the white solid title compound with melting point 60-61 °C. R_f = .23 (20% ethyl acetate in hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ = 7.74 (d, J = 8.5, 2H), 7.36 (d, J = 8.5, 2H), 4.31 (s, 2H), 4.07 (s, 2H), 2.44 (s, 3H), 1.70 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 145.0, 134.1, 130.1, 128.0, 113.8, 84.1, 70.3, 38.2, 35.0, 21.8, 3.6 ppm. IR (cm^{-1}): 3032.96, 2984.53, 2923.11, 2854.27, 2360.66, 2329.90,
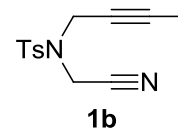
2243.38, 1597.68, 1494.33, 1441.26, 1355.44, 1165.82, 1073.74, 909.05, 889.03, 816.30 cm^{-1}. HRMS (EI) calcd. For $C_{13}H_{14}N_2O_2S$ [M + Na]$^+$ 285.0674; found 285.0679.

Ligand Synthesis. [Me]PDAI, [Mes]PDAI,[20] [p-OMe,Me]PDAI,[10] [Et]PDAI, [iPr]PDAI,[20] and [p-OMe,iPr]PDAI[10] were synthesized according to the literature methods.

Synthesis of *tert*-butyl (4-iodo-2,6-diisopropylphenyl)carbamate. A round-bottom flask was charged with 4-iodo-2,6-disiopropylaniline[11] (1.55 g, 5.10 mmol), di-*tert*-butyl dicarbonate (1.23 g, 5.61 mmol), and stir bar, and dissolved in ethanol (1.5mL). The reaction was stirred at 30 ^{O}C for 3 days. The resulting mixture was stirred with 1M HCl (~1 mL) and extracted with ether (3 x 25 mL). The organic fraction was removed *in vacuo* to yield ***tert*-butyl (4-iodo-2,6-diisopropylphenyl)carbamate** as orange solid (2g, 97%). MP 120-124 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.43 (s, 2H), 5.73, (s, 1H) 3.12 (m, 2H), 1.52 (s, 9H), 1.18 (d, 12H). ^{13}C (CDCl$_3$, 75 MHz) δ 149.6, 133.1, 94.6, 85.4, 80.3, 28.8, 28.5, 27.6, 23.6. IR (cm^{-1}): 3229, 3102, 2965, 2931, 2871, 1811, 1699, 1569, 1366, 1119. HRMS (ESI) m/z calcd for $C_{17}H_{26}INO_2Na$ [M + Na]$^+$ 426.0906, found 426.0914.
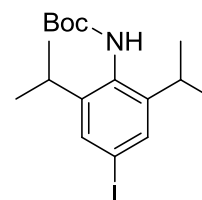
Synthesis of 2,6-diisopropyl-4-(trifluoromethyl)aniline: **2,6-diisopropyl-4-(trifluoromethyl)aniline** was prepared using a similar literature procedure.[21] In a glove box, a three-neck 250 mL round-bottom flask containing a stir bar was charged with *tert*-butyl (4-iodo-2,6-diisopropylphenyl)carbamate (0.89 g, 2.20 mmol), copper iodide (2.48 g, 13.01 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.09g, 0.11 mmol), dissolved in DMF (31 mL). To this mixture, a
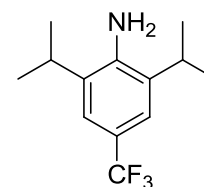
solution of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.5 g, 13.01 mmol) in DMF (5 mL) was added. The reaction was stirred at 100 $^{\circ}$C with a reflux condenser outside the glove box for 2 days under N_2. The reaction was cooled to room temperature and diluted with CH_2Cl_2 (15 mL), filtered through a small plug of celite, affording a dark brown solution which was then washed with water (2 x 100 mL), 50% saturated aqueous NaCl (100 mL), and brine (100 mL). The solution was dried over sodium sulfate, filtered through celite, concentrated *in vacuo*, purified by silica gel flash chromatography (10% EtOAc/hexanes) to afford deprotected **2,6-diisopropyl-4-(trifluoromethyl)aniline** (0.38 g, 50%) as an orange oil. This product contained unknown impurities but was successfully carried through to the next step (*p-CF3,ipr***PDAI**). ^{1}H NMR (CDCl₃, 300 MHz) δ 7.26 (s, 2H), 2.91 (quint, *J* = 7.5, 2H), 1.29 (d, 12H).

Synthesis of (*N,N'E,N,N'E*)-*N,N'*-(pyridine-2,6-diylbis(methanylylidene))bis(2,6-diisopropyl-4-(trifluoromethyl)aniline) (*p-CF3,iPr*PDAI): *p-CF3,iPr***PDAI** was prepared from the similar literature procedure[20] with 2,6-diisopropyl-4-(trifluoromethyl)aniline (0.19 g, 0.81 mmol) and 2,6-pyridinedicarboxaldehyde (0.5 g, 0.369 mmol) and ~10 drops of glacial acetic acid in 3 mL 100% ethanol. The reaction was stirred for 3 days at room temperature. The mixture was then cooled to 0 °C, filtered, and rinsed with cold 100% ethanol to yield *p-CF3,iPr***PDAI** (1.53 g, 70%) as a yellow solid. MP 185-188 $^{\circ}$C. ^{1}H NMR (CDCl₃, 300 MHz) δ 8.41 (d, *J* = 9.0, 1H), 8.35 (s, 2H),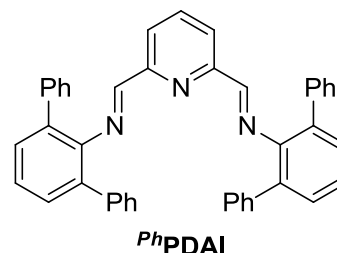 8.05 (t, *J* =9.0, 1H), 7.41 (s, 4H), 2.99 (q, *J* = 6.0, 4H), 1.21 (d, 12H). ^{13}C NMR (CDCl₃, 75 MHz) δ 163.1, 154.3, 151.0, 138.0, 127.1,
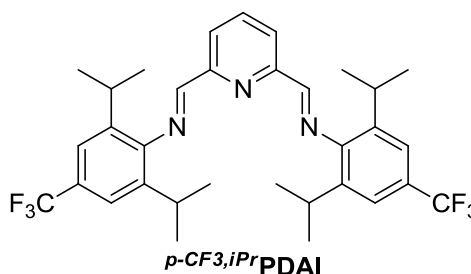
126.6, 123.3, 120.3, 29.9, 28.4, 23.4. IR (cm⁻¹): 2962, 2917, 2869, 2849, 1704, 1646, 1298, 1149, 1116, 845. HRMS (ESI) m/z calcd for $C_{33}H_{38}N_3F_6$ [M + H]⁺ 590.2970, found 590.2972.

Synthesis of (N',N'''E,N',N'''E)-N',N'''-(pyridine-2,6-diylbis(methanylylidene))bis(([1,1':3',1''-terphenyl]-2'-amine)) (_Ph_PDAI). _Ph_PDAI was prepared from the simil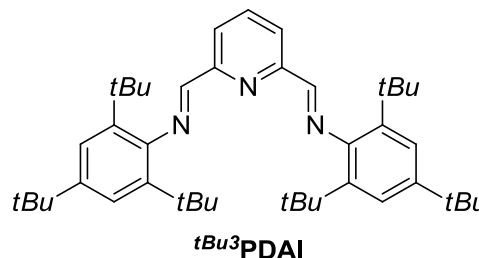ar literature procedure[20] with 2,4-diphenyl aniline (250 mg, 1.02 mmol)l, 2,6-pyridinedicarboxaldehyde (67.2 mg, 5.0 x 10⁻¹ mmol) and ~5 drops of glacial acetic acid in 5 mL 100% ethanol. The reaction was stirred overnight at room temperature. The mixture was then cooled to 0 °C, filtered, and rinsed with cold 100% ethanol to yield _Ph_**PDAI** (165 mg, 56%) as a yellow solid. MP 249 °C. ¹H NMR (CDCl₃, 500 MHz) δ 7.87 (s, 2H), 7.81 (d J = 9Hz, 2H), 7.58 (t, J = 9 Hz, 1H), 7.38-7.35 (m, 12H), 7.29-7.15 (m, 14H). ¹³C NMR (CDCl₃, 75 MHz) δ 165.0, 154.1, 147.8, 139.9. 137.0, 133.4, 128.1, 125.2, 122.5. IR (cm⁻¹): 3056, 3027, 2886, 3261, 1598, 1584, 1458, 1441, 1413, 1332, 1265, 1196, 1072, 1028, 992, 967, 917. HRMS (ESI) m/z calcd for $C_{33}H_{38}N_3F_6$ [M + H]⁺ 590.2596, found 590.2592.

Synthesis of (N,N'E,N,N'E)-N,N'-(pyridine-2,6-diylbis(methanylylidene)) bis(2,4,6-tri-tert-butylaniline) (_tBu3_PDAI).

tBu3**PDAI** was prepared from the similar literature procedure[20] with 2,4,6-tri _tert_-butyl aniline (429 mg, 1.65 mmol), 2,6-pyridinedicarboxaldehyde (109 mg, 8.0 x 10⁻¹ mmol) and ~10 drops of glacial acetic acid in 10 mL 100% ethanol. The reaction was stirred overnight at room temperature. The

mixture was then cooled to 0 °C, filtered, and rinsed with cold 100% ethanol to yield

^{tBu3}**PDAI** (339 mg, 59%) as a yellow solid. MP 284-286 °C. ^{1}H NMR (CDCl$_3$, 300

MHz) δ 8.41 (d, J = 1.5 Hz, 2H), 8.29 (s, 2H), 8.06 (t, J = 1.5 Hz, 1H), 7.38 (s, 4H), 1.37

(s, 18H), 1.35 (s, 36H) . ^{13}C NMR (CDCl$_3$, 75 MHz) δ 163.1, 154.6, 149.6, 144.7, 138.1,

137.7, 122.9, 122.0, 98.8, 36.1, 35.0, 31.2. IR (cm^{-1}): 2961, 2870, 2360, 1735, 1645,

1567, 1455, 14427, 1392, 1269, 1213, 1118, 878, 812. HRMS (ESI) m/z calcd for

C$_{33}$H$_{38}$N$_3$F$_6$ [M + H]$^+$ 644.4920, found 644.4918.

References

(1) (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084-3213. (b) Hanan, G. S.; Volkmer, D.; Schubert, U. S.; Lehn, J.-M.; Baum, G.; Genske, D. *Angew. Chem., Int. Ed.* **1997**, *36*, 1842-1844.

(2) Liu, Y.; Yan, X.; Yang, N.; Xi, C. *Catal. Commun.* **2011**, *12*, 489-492.

(3) (a) Pillai, S. M.; Ohnishi, R.; Ichikawa, M. *J. Chem. Soc., Chem. Commun.* **1990**, 246-247. (b) Costa, M.; Dias,F. S.; Chiusoli, G. P.; Gazzola, G. L. *J. Organomet. Chem.* **1995**, 47-53. (c) Knoch, F.; Kremer, F.; Schmidt, U.; Zenneck, U. *Organometallics* **1996**, *15*, 2713-2719. (d) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 7162-7166.

(4) (a) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474-1475. (b) Hilt, G.; Hess,W.; Vogler, T.; Hengst, C. *J. Organomet. Chem.* **2005**, 5170-5181. (c) Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun.* **2008**, 2992-2994.

(5) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, 359-364.

(6) Duong, H. A.; Louie, J. *Tetrahedron* **2006**, *62*, 7552-7559.

(7) Kondo, T.; Nomura, M.; Y. Ura, Y.; Wada, K.; Mitsudo, T. *Tetrahedron Lett.* **2006**, *47*, 7107-7111.

(8) Satoh, Y.; Yasuda, K.; Obora, Y. *Organometallics* **2012**, *31*, 5235-5238.

(9) (a) Stolley, R. M.; Maczka, M. T.; Louie, J. *Eur. J. Org. Chem.* **2011**, 3815-3824. (b) Kumar, P.;Prescher, S.; Louie, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10694-10886.

(10) Lane, T. K.; D'Souza, B. R.; Louie, J. *J. Org. Chem.* **2012**, *77*, 7555-7563.

(11) D'Souza, B. R.; Lane, T. K.; Louie, J. *Org. Lett.* **2011**, *13*, 2936-2939.

(12) Reviews: (a) Koroleva, E. F.; Gusak, K. N.; Ignatovich, Z. V. *Russ. Chem. Rev.* **2010**, *79*, 655-681. (b) Hill, M. D.; Movassaghi, M. *Chem.–Eur. J.* **2008**, *14*, 6836-6844. (c) von Angerer, S. *Sci. Synth.* **2004**, section 16.2, p. 379; (d) R. I. Christopherson, R. I.; Lyonsk, S. D.; Wilson, P. K. *Acc. Chem. Res.* **2002**, *35*, 961-971.

(13) (a) Anand, N.; Singh, P.; Sharma, A.; Tiwari, S.; Singh, V.; Singh, D. K.; Srivastava, K. K.; Singh, B. N.; Tripathi, R. P. *Bioorg. Med. Chem.* **2012**, *20*, 5150-5163. (b) Han, Y. T.; Choi, G.-I.; Son, D.; Kim, N.-J.; Yun, H.; Lee, Chang, S. D. J.; Hong,H.-S.; Kim, H.; Ha, H.-J.; Kim, Y.-H.; Park, H.-J.; Lee, J.; Suh, Y.-G. *J. Med. Chem.* **2012**, *55*, 9120-9135. (c) Giridhar, R.; Tamboli, R. S.; Ramajayam, R.; Prajapati, D. G.; Yadav, M. R. *Eur. J. Med. Chem.* **2012**, *50*, 428-432. (d) Lebar, M. D.; Hahn, K. N.; Mutka, T.; Maignan, P.: McClintock, J. B.; Amsler, C. D.; van Olphen, A.; Kyle, D. E.; Baker, B. J. *Bioorg. Med. Chem.* **2011**, *19*, 5756-5762. (e) Perl, N. R.; Ide, N. D.; Prajapati, S.; Perfect, H. H.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 1802-1803. (f) Lin, Y.-L.; Huang, R.-L. *J. Nat. Prod.* **1997**, *60*, 982-985.

(14) (a) <u>Rh</u> (Table 1, entry 1): Tanaka,K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917-3922. (b) For $CpCo(CO)_2$ (entry 2) Boñaga,L. V. R.; Zhang, H.-C.; Maryanoff, B. E. *Chem. Commun.* **2004**, 2394-2395. (c) $CoCl_2$ (entry 3): Sugiyama, Y.-K.; Okamoto, S. *Synthesis* **2011**, 2247-2254. (d) Ni (entries 4–6): see ref. 9; (f) Ir (entry 7): Onodera, G.; Shimizu, Y.; Kimura, J.; Kobayashi, J.; Evihara, Y.;Kondo, K.; Sakata, K.; Takeuchi, R. *J. Am. Chem. Soc.* **2012**, *134*, 10515-10531. (g) $NbCl_5$ (entry 8): see ref. 8; (h) $Ph_3AuOPOF_2$ (entry 9): Kim, S. M.; Park, J. H.; Chung, Y. K. *Chem. Commun.* **2011**, *47*, 6719-6721. (i) $AuCl_3$ (entry 10): Xiao, Y.; Zhang, L. *Org. Lett.* **2012**, *14*, 4662-4665. (j) $AuPEt_3Cl/AgSbF_6$ (entry 11): Fernandez-Garcia, J. M.; Fernandez-Rodriguez, M. Á; Aguilar, E. *Org. Lett.* **2011**, *13*, 5172-5175. (k) AgOTf/CuBr (entry 12): Li, S.; Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 4312-4315. (l) FeI_2/dppp: (entry 13) see ref. 3; (entry 14) Wang, C.; Wang, D.; Xu, F.; Pan, B.; Wan, B. *J. Org. Chem.* **2013**, *78*, 3065-3072; (m) $Fe(OAc)_2$/$^{p\text{-}OMe,iPr}$PDAI (entry 16) see ref. 11; (n) $FeCl_2$/^{Mes}PDAI (entry 17) see ref. 10.

(15) Seka, S.; Buriez, O.; Périchon, J. *Chem.–Eur. J.* **2003**, *9*, 3597-3603.

(16) Wang, C.; Wang, D.; Xu, F.; Pan B.; Wan, B. *J. Org. Chem.*, **2013**, *78*, 3065-3072.

(17) Miura, T.; Nakazawa, H.; Murakami, M. *Chem. Commun.* **2005**, 2855-2865.

(18) Bandgar, B. P.; Chavare, S. N.; Pandit, S. S. *J. Chin. Chem. Soc.* **2005**, *52*, 125-128.

(19) Lorand, L.; Rule, N. G.; Ong, H. H.; Furlanetto, R.; Jacobsen, A.; Downey, J.; Öner, N.; Bruner-Lorand, J. *Biochemistry*, **1968**, *7*, 1214-1223.

(20) Britovsek, G. J. P.; Bruce, M.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; Mastroianni, S.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Stroemberg, S.; White,

A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728-8740.

(21) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122-3123.

CHAPTER 5

THE STUDY OF CATALYTIC INTERMEDIATES GENERATED IN IRON-
CATALYZED [2+2+2] PYRIDINE FORMATION

Introduction

The previously introduced iron-catalyzed [2+2+2] cycloaddition methods to produce pyridines, 2-aminopyridines, and 2-aminopyrimidines represent a significant advancement in the field of cycloaddition catalysis. The traditionally poor catalytic activity of iron in this field was overcome by implementing factors that encourage the incorporation of nitriles into the cycloaddition product. Nitrile incorporation was made possible by using alkynenitrile substrates (equation 1)[1] or through the use of highly reactive cyanamides (equation 2).[2] The combination of these two factors results in an entirely novel cycloaddition to afford 2-aminopyrimidines (equation 3).[3] The key to developing these systems was the discovery that bis(aldimino)pyridine (PDAI) ligands enable effective cycloaddition (Figure 20).
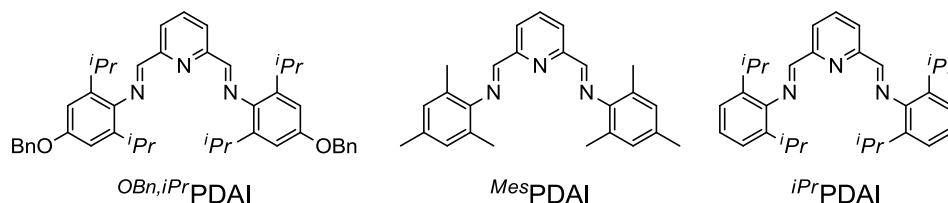
Figure 20. PDAI ligands.

(1)

(2)

(3)
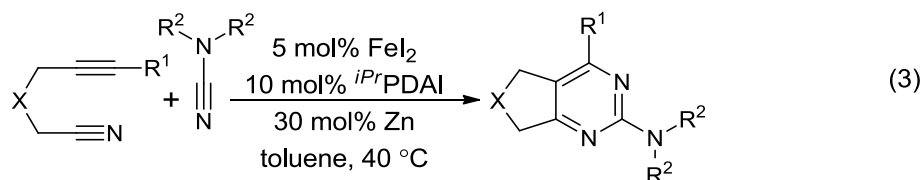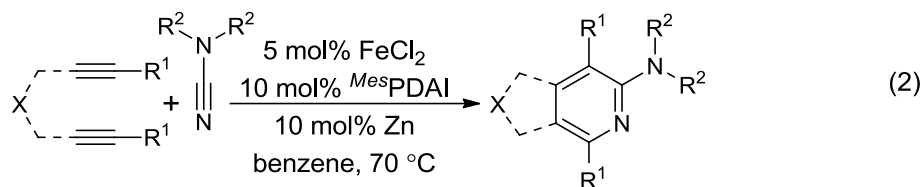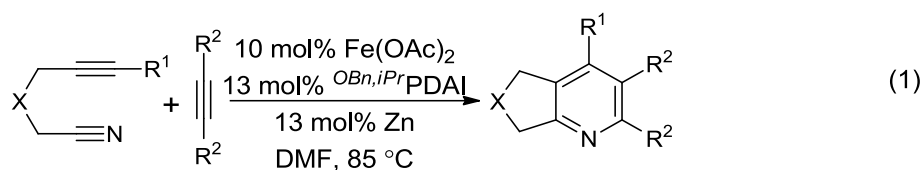
The generality of these iron-catalyzed cycloaddition systems, coupled with their unique reactivity trends, drive us to seek an understanding of the underlying mechanistic pathway. Such an understanding will not only provide reasoning for observed trends, but may highlight new avenues of study. The primary questions about these systems include:

1) What is the oxidative identity of the active catalyst?

2) What is the operative catalytic pathway; homocoupling or heterocoupling?

3) Why are cyanamides more reactive than nitriles toward iron-catalyzed cycloaddition?

Identifying the Oxidation State of the Active Catalyst

Reactions with precatalyst complexes indicate that the active catalyst is bound to a single ligand. The active catalyst has been assumed to be generated *in situ* when an Fe(II) salt coordinates to the ligand and undergoes a two-electron reduction by zinc Figure 21). Another presumption has been that the resulting Zn(II) is a spectator playing no part in the catalytic cycle. To test these hypotheses it is necessary to obtain a well-defined, reduced iron species and study its catalytic activity. Fortunately Chirik and co-
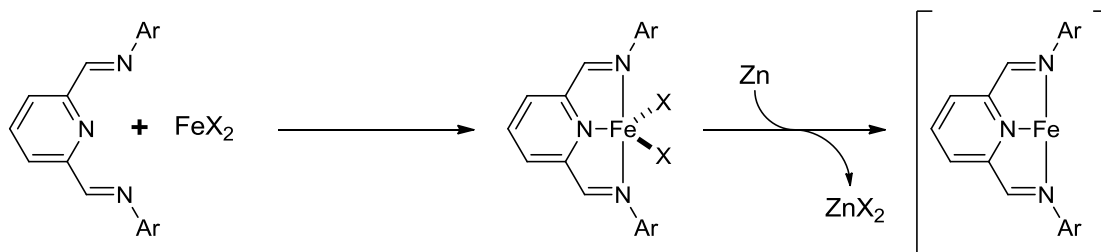
Figure 21. Ligand coordination and reduction to provide active catalyst.

workers have already studied several such complexes in depth.

As discussed earlier, bis(imino)pyridine (PDI) ligands have demonstrated excellent activity in ethylene polymerization, hydrogenation, and hydrosilylation reactions.[4] Curiously, the nearly identical bis(aldimino)pyridine (PDAI) ligands have exhibited rather low activity toward these reactions. In an effort to understand these reactivity differences, Chirik synthesized a series of two-electron reduced (^{iPr}PDAI)Fe(L) compounds and closely examined their electronic structures.[5] This inquiry revealed that (^{iPr}PDAI)Fe(L) and (PDI)Fe(L) complexes are nearly identical electronically. As with PDI complexes, two-electron reduced (PDAI)Fe(L) complexes retain a formal Fe(II) oxidation state, with the additional electrons residing on the ligand (Figure 22). The authors concluded that the difference in reactivity trends is perhaps due to the increased flexibility in the pincer arms of the aldimine ligands as compared to the ketimine derivatives.

The low-valent complex (^{iPr}PDAI)Fe(η^4-C$_4$H$_6$) (**1**) has been synthesized which, in a qualitative preliminary study, effected partial conversion (~50% GC yield) of **6** in the reaction of alkynenitrile **4** and alkyne **5** (equation 4). This result demonstrates that the two-electron reduced **1** can catalyze the cycloaddition between **4** and **5**. When a similar reaction is attempted using an *in situ* generated catalyst with the ^{iPr}PDAI ligand, no

$(^{iPr}PDAI)Fe(\eta^4\text{-}C_4H_6)$ (**1**) $(^{iPr}PDAI)Fe(\eta^6\text{-}C_6H_6)$ (**2**) $(^{iPr}PDAI)Fe(DMAP)$ (**3**)

diradical, dianionic ligand   diradical, dianionic ligand
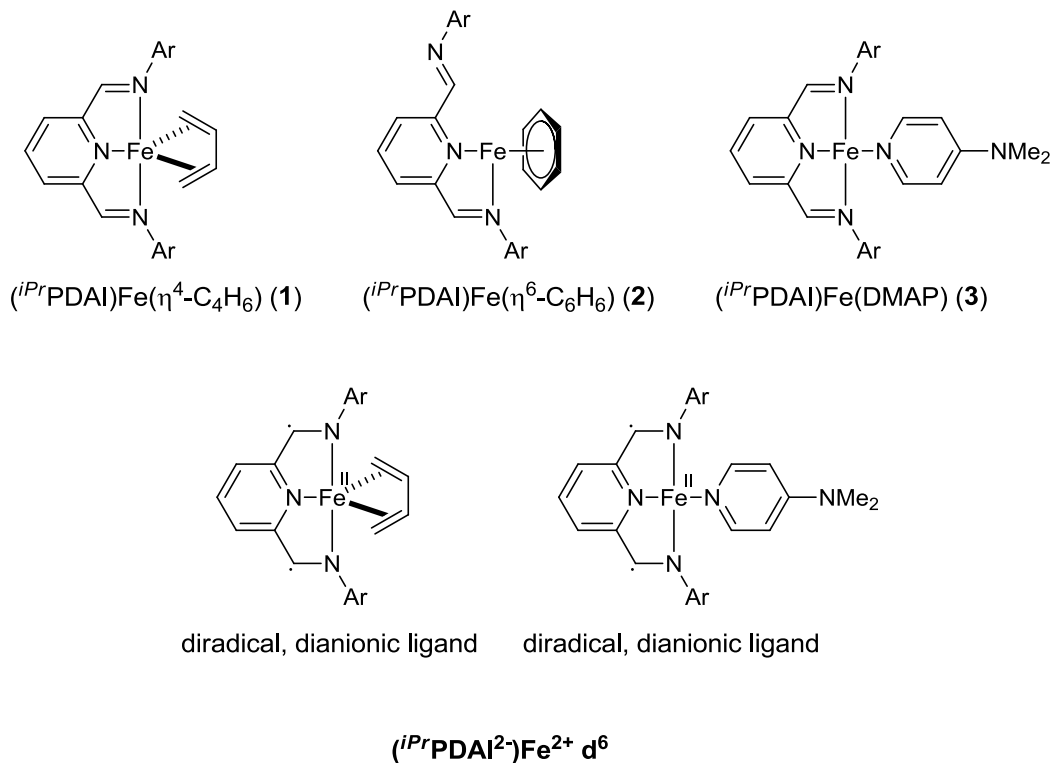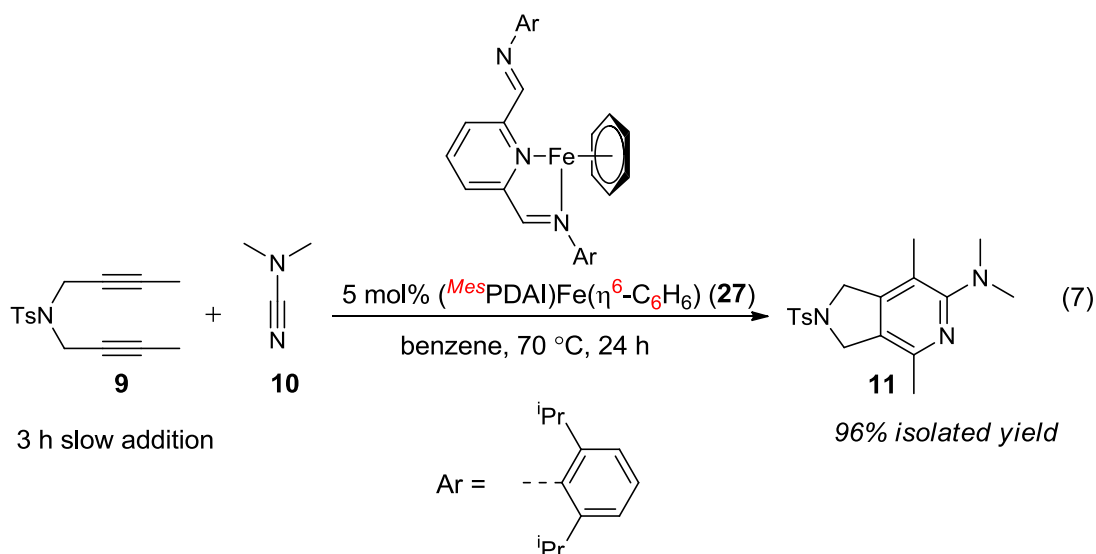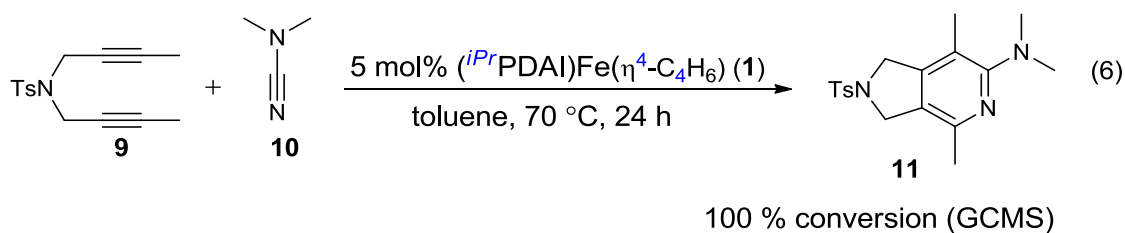
$(^{iPr}PDAI^{2-})Fe^{2+}$ d^6

Figure 22. Two-electron reduction of $(PDAI)Fe^{II}$ leads to a diradical dianionic ligand coordinated to Fe^{II}.

products are detected (equation 5 and Chapter 2, Table 2). Despite the fact that the

^{iPr}PDAI ligand has been proven to be effective for this type of cycloaddition (equation 4),

it does not even produce traces of product in equation 5. Based on the logic presented in

Figure 21, the *in situ* reduced catalyst should be similar to **1** (without the butadiene

ligand). This may be an indication that the combination of Fe(II) salts, PDAI ligand, and

Zn in the presence of unsaturated substrates does not generate exclusively $(PDAI^{2-})Fe^{2+}$

species. These alternative complexes will not only detract from the amount of active

catalyst but may also hinder the desired reactivity. Future tests of this hypothesis must
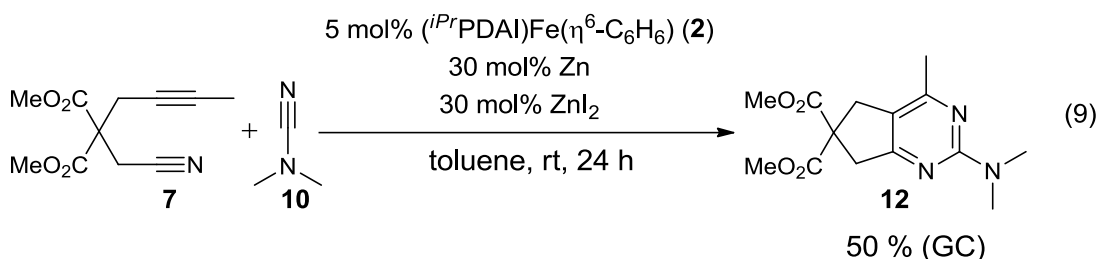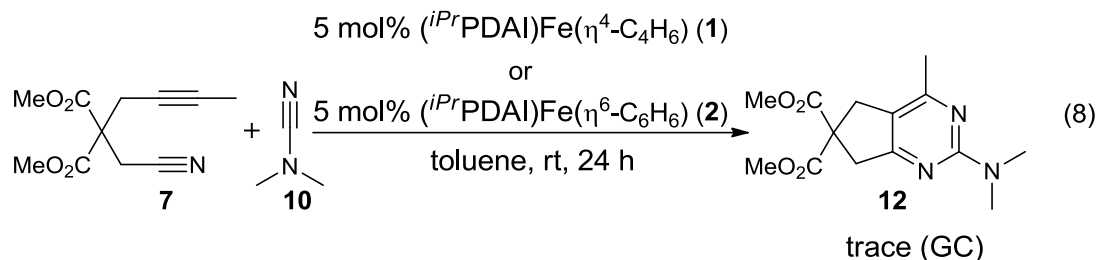
use identical substrates and solvents.

$$\text{(4)}$$

$$\text{(5)}$$
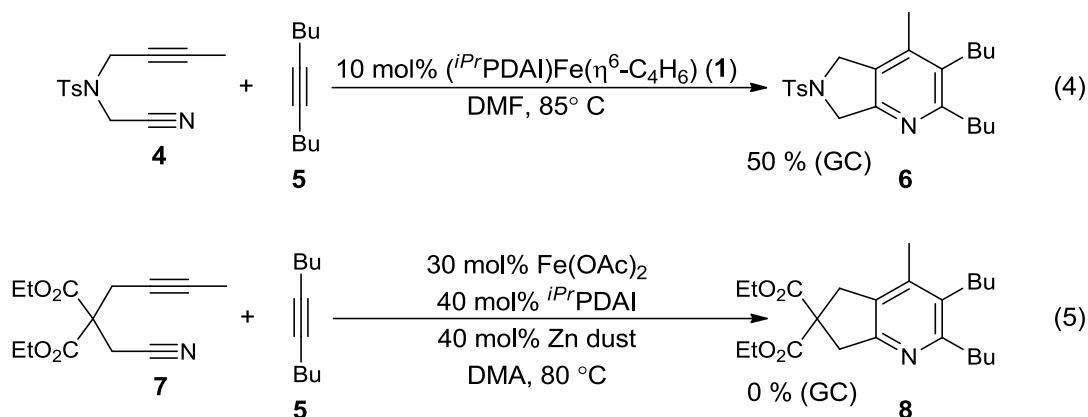
The increased reactivity of $(^{iPr}\text{PDAI})\text{Fe}(\eta^4\text{-}C_4H_6)$ (**1**) may indicate that the *in situ* combination of Fe(OAc)_2, PDAI ligand, and Zn does not completely convert into the active species. Incomplete reduction could be caused by shielding of the iron center by the counter ions (halides, acetates, and so forth.). Alternatively, if the reaction between Zn^0 metal and Fe(II) is biphasic (a possibility if the zinc dust is not dissolving), the reduction of iron may be incomplete. When the iron reacts with the Zn^0 surface, it may leave a protective Zn(II) layer, preventing further reaction with the zinc particle.
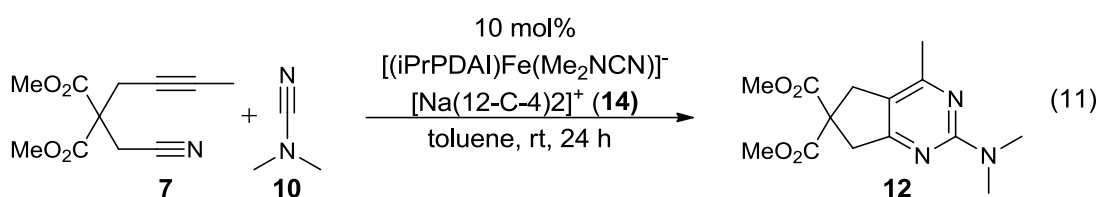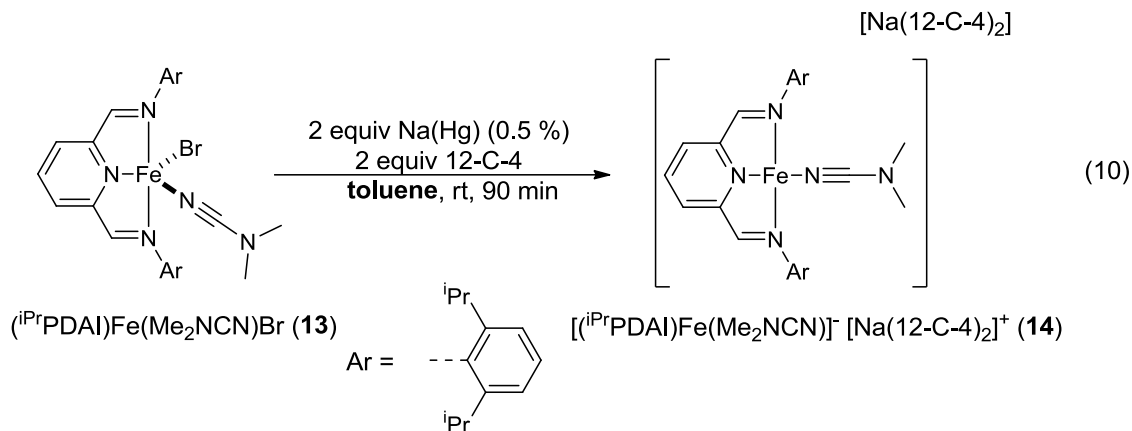
For the cycloaddition of diyne and cyanamide **9** and **10**, a catalytic amount of $(^{iPr}\text{PDAI})\text{Fe}(\eta^4\text{-}C_4H_6)$ (**1**) led to full conversion into **11** in 24 hours (equation 6). As before, this demonstrates that the active catalyst for this system is also a two-electron reduced complex. Efforts to synthesize $(^{Mes}\text{PDAI})\text{Fe}(\eta^4\text{-}C_4H_6)$ have been unsuccessful. The similar $(^{Mes}\text{PDAI})\text{Fe}(\eta^4\text{-}C_6H_6)$ (**27**) has been made, although NMR indicates paramagnetic impurities. Nevertheless, this compound demonstrates high catalytic competency in the cycloaddition of diynes and cyanamides, providing a 96% yield of **11** (equation 7).

$$5 \text{ mol\% } (^{iPr}\text{PDAI})\text{Fe}(\eta^4\text{-C}_4\text{H}_6) \text{ (1)}$$
$$\text{toluene, 70 °C, 24 h}$$

(6)

100 % conversion (GCMS)

$$5 \text{ mol\% } (^{Mes}\text{PDAI})\text{Fe}(\eta^6\text{-C}_6\text{H}_6) \text{ (27)}$$
$$\text{benzene, 70 °C, 24 h}$$

(7)

3 h slow addition

96% isolated yield

Ar =

The oxidative identity of the active catalyst in the reaction of alkynenitriles and cyanamides is not as easily determined. Reactions with $(^{iPr}\text{PDAI})\text{Fe}(\eta^4\text{-C}_4\text{H}_6)$ (1) or $(^{iPr}\text{PDAI})\text{Fe}(\eta^4\text{-C}_6\text{H}_6)$ (2) provide only traces of product after 24 hours (equation 8). Adding Zn or ZnI_2 to the reaction does not alter this result. Curiously the combination of both Zn and ZnI_2 with $(^{iPr}\text{PDAI})\text{Fe}(\eta^4\text{-C}_6\text{H}_6)$ (2) lead to a 50% (GC) yield (equation 9). Two potential scenarios exist which can rationalize this result. First, both zinc and iron play a role in the catalytic cycle. Second, the active catalyst is the result of further reduction of the iron complex. The latter hypothesis is supported by the need for a larger amount (30 mol%) of Zn when generating the catalyst *in situ*. The resulting anionic species would require a counter ion, which could be provided by a cationic zinc species.

$$5 \text{ mol\% } (^{iPr}PDAI)Fe(\eta^4\text{-}C_4H_6) \textbf{ (1)}$$

(8)

trace (GC)

$$5 \text{ mol\% } (^{iPr}PDAI)Fe(\eta^6\text{-}C_6H_6) \textbf{ (2)}$$
$$30 \text{ mol\% Zn}$$
$$30 \text{ mol\% ZnI}_2$$

(9)

50 % (GC)

To test this second scenario, a technique used to make anionic tris(phosphino)borane/iron complexes (used as N_2 fixation catalysts) was applied.[6] Reducing $(^{iPr}PDAI)Fe(Me_2NCN)Br$ (**13**) (*vide infra*) with excess sodium amalgam in the presence of two equivalents of [12-crown-4] would theoretically generate $(^{iPr}PDAI)Fe(Me_2NCN)^-$ [12-crown-4]$_2$•Na^+ (**14**) (equation 10). Importantly, we have verified that $(^{iPr}PDAI)Fe(Me_2NCN)Br$ does not catalyze the cycloaddition of alkynenitriles and cyanamides. Although it is not yet characterized, the reaction produces a brown product which crystalizes from THF. Hopefully future group members will successfully grow x-ray-quality crystals of this potentially interesting complex. Despite these efforts, a concrete understanding of the identity of the active catalyst remains elusive. A 20 mol% catalyst loading of **14** only produced traces of 2-aminopyrimidine product (equation 11).

$[Na(12\text{-}C\text{-}4)_2]$

$(^{iPr}PDAI)Fe(Me_2NCN)Br$ (**13**)

Ar =

$[(^{iPr}PDAI)Fe(Me_2NCN)]^-[Na(12\text{-}C\text{-}4)_2]^+$ (**14**)

(10)

7   10   12 (11)

The above studies, combined with the information available from Chirik's

research, indicate that in two of the three catalytic systems, the active catalyst is a d^6

Fe(II) center bound to diradical dianionic PDAI ligand. The third system (alkynenitriles

+ cyanamides) may operate by a completely different catalytic pathway, perhaps

involving zinc or utilizing an iron species of unknown electronic identity.

Attempts to Isolate Metallacyclic Intermediates

To determine the catalytic cycle employed in iron-catalyzed [2+2+2] pyridine

formation (homocoupling or heterocoupling, Figure 23), attempts were made to isolate

metallacyclic intermediates. The regioselectivity of reactions between metallacycles and

cyanamides should indicate which pathway is operative. The cobalt-type homocoupling

pathway tends to place the pyridine nitrogen adjacent to the larger alkyne substituent

(when using unsymmetrical diynes, Chapter 3), while the nickel-type heterocoupling

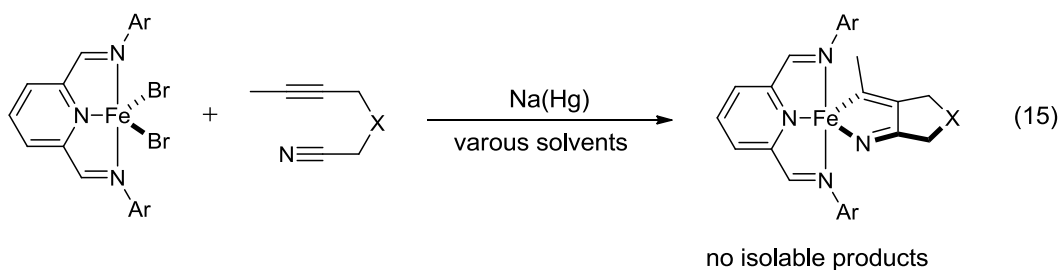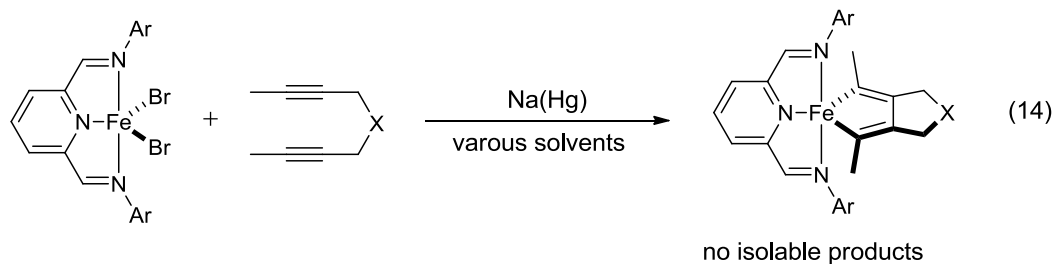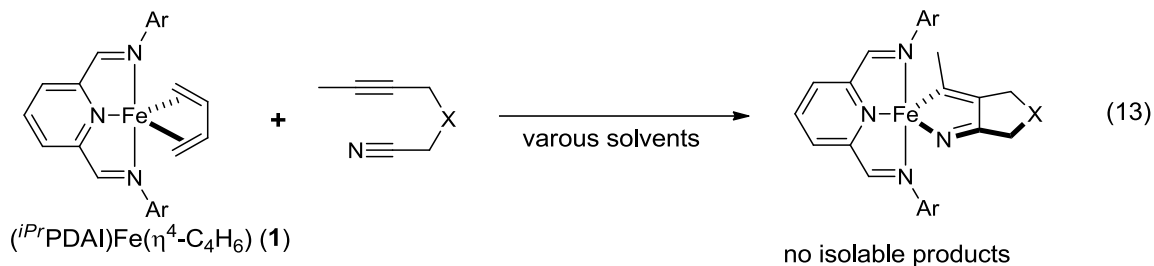pathway has the opposite preference. The previously proposed hypothesis is that the
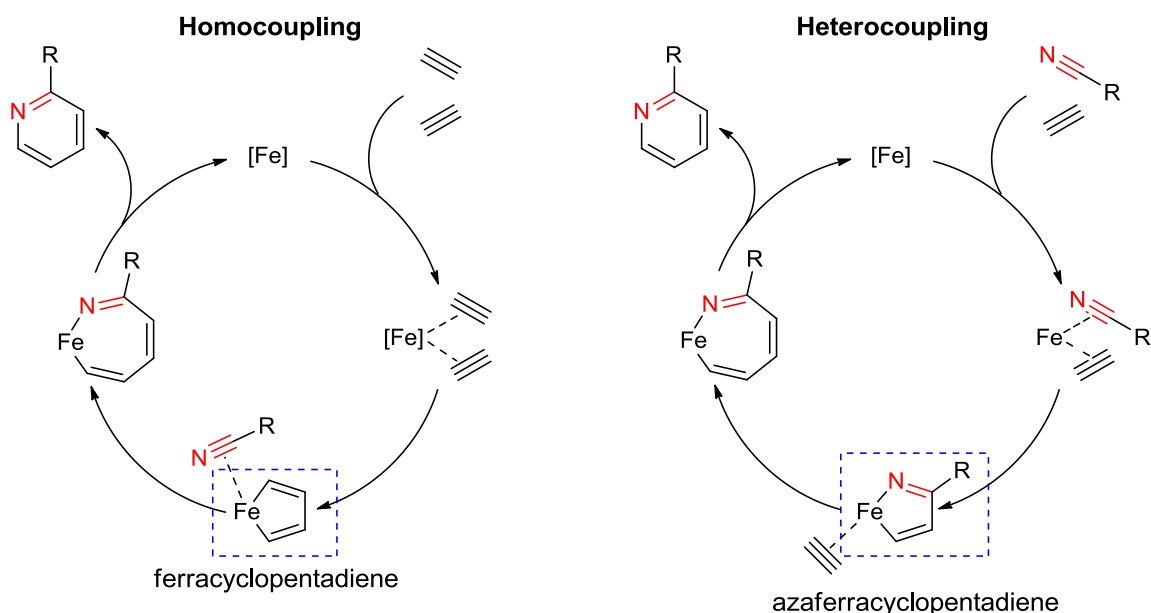
Figure 23. Homocoupling and heterocoupling mechanistic pathways possible in iron-catalyzed cycloaddition of alkynes and nitriles.

Louie iron catalysts utilize the metallacyclopentadiene intermediates similar to cobalt[7], and not the azametallacyclopentadiene pathway employed by nickel.[8]

Several attempts to isolate metallacycles from diynes or alkynenitriles were carried out. Addition of these substrates to $(PDAI^{2-})Fe^{2+}$ complexes led to mixtures which did not afford any isolable products (equations 12, 13). Reduction of (PDAI)FeBr$_2$ complexes in the presence of these substrates were equally unsuccessful (equations 14, 15).

(12)

$(^{iPr}PDAI)Fe(\eta^4\text{-}C_4H_6)$ (**1**)

varous solvents

no isolable products

$(^{iPr}PDAI)Fe(\eta^4-C_4H_6)$ (**1**)

varous solvents

(13)

no isolable products

Na(Hg)
varous solvents

(14)

no isolable products

Na(Hg)
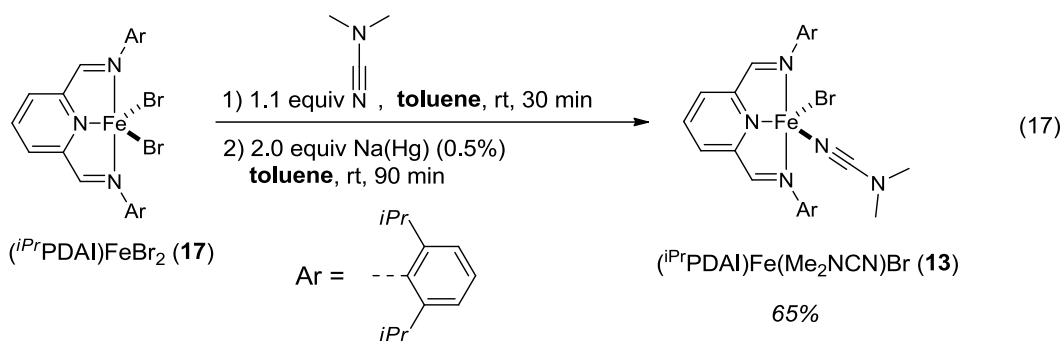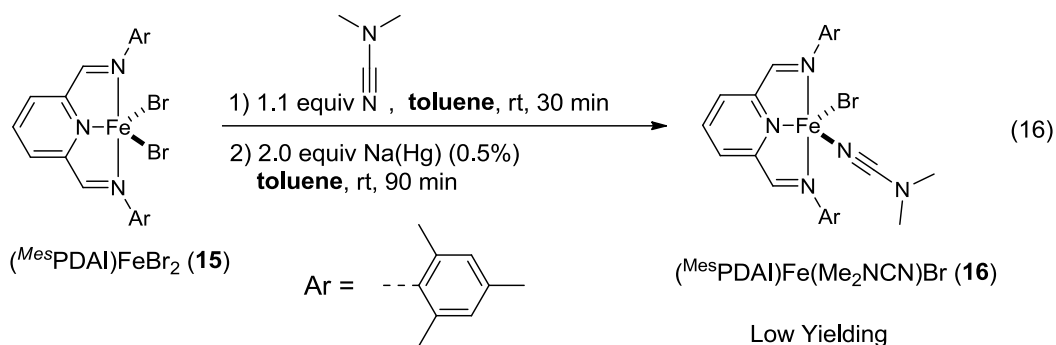varous solvents

(15)

no isolable products
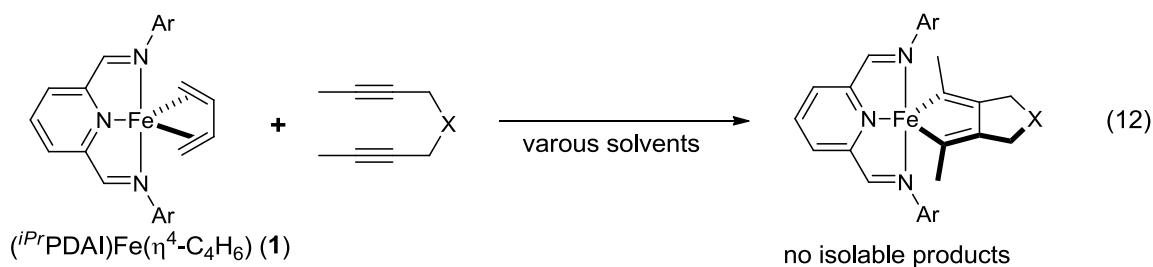
When reactions with cyanamides are carried out (equations 2, 3), cyanamide is added last, initiating an immediate change from a green suspension to a dark green solution. This may indicate that formation of a cyanamide complex initiates the catalytic cycle (Figure 24). If cyanamide does coordinate to the iron prior to oxidative cyclization, an azaferracyclopentadiene is likely to follow, debunking the initial homocoupling hypothesis. To test this hypothesis, attempts were made to isolate iron-cyanamide complexes.

The first successfully isolated cyanamide complex was the trigonal bipyramidal $(^{Mes}PDAI)Fe(Me_2NCN)Br$ (**16**). This compound is the result of coordination of cyanamide and a one-electron reduction of $(^{Mes}PDAI)FeBr_2$ **15** (equation 16). High-

quality crystals of compound **16** were grown and characterized by x-ray crystallography

(Figure 25). Due to low yields of **16**, however, the analogous compound **13** was prepared

and used for further studies (equation 17).

$$(^{Mes}PDAI)FeBr_2 \ (\mathbf{15}) \qquad Ar = \qquad (^{Mes}PDAI)Fe(Me_2NCN)Br \ (\mathbf{16})$$

Low Yielding

(16)

$$(^{iPr}PDAI)FeBr_2 \ (\mathbf{17}) \qquad Ar = \qquad (^{iPr}PDAI)Fe(Me_2NCN)Br \ (\mathbf{13})$$

65%

(17)

In the absence of a reductant, compound **13** would not catalyze the cycloaddition

of diynes and cyanamides (equation 18). This result is consistent with the hypothesis that

the active catalyst results from two-electron reduction. However, in the presence of a

zinc reductant, compound **13** affords 2-aminopyridine, effectively indicating that

metallacycle formation should be possible if a second electron is supplied to the complex
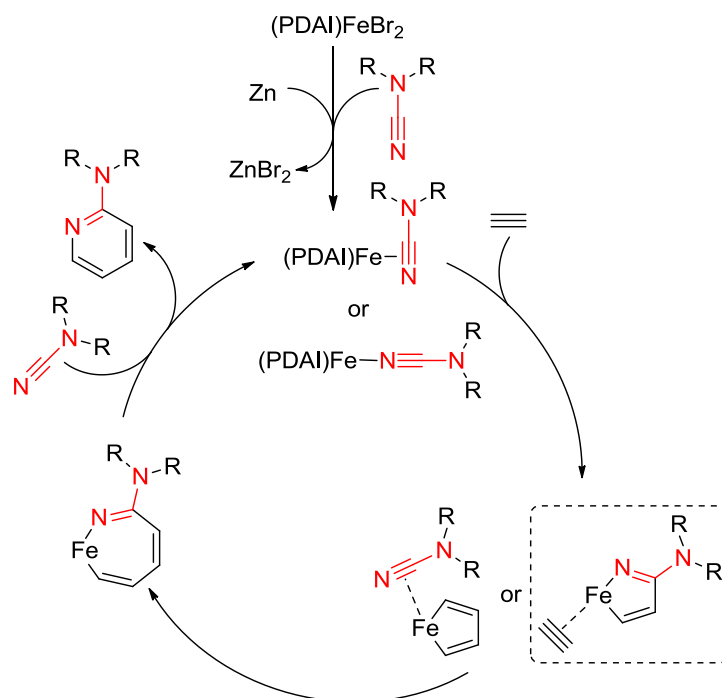
(equation 19).

$$\text{5 mol\% } (^{iPr}PDAI)Fe(Me_2NCN)Br \ (\mathbf{13})$$

toluene, rt, 24 h

NO REACTION

(18)
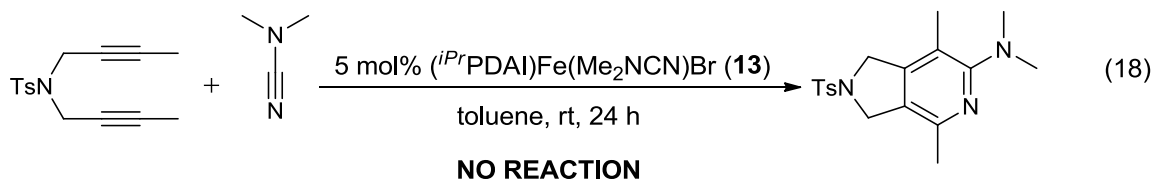
Figure 24. Heterocoupling pathway is likely if cyanamide coordination initiates catalytic cycle.
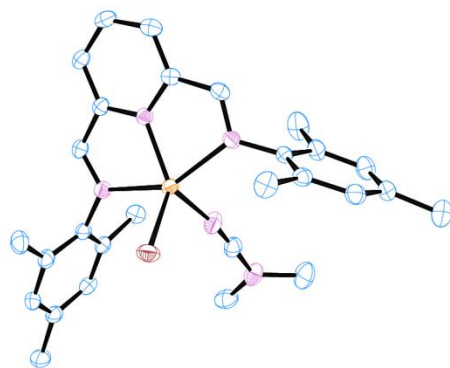
Figure 25. Ortep of (^{Mes}PDAI)Fe(Me$_2$NCN)Br (**16**).
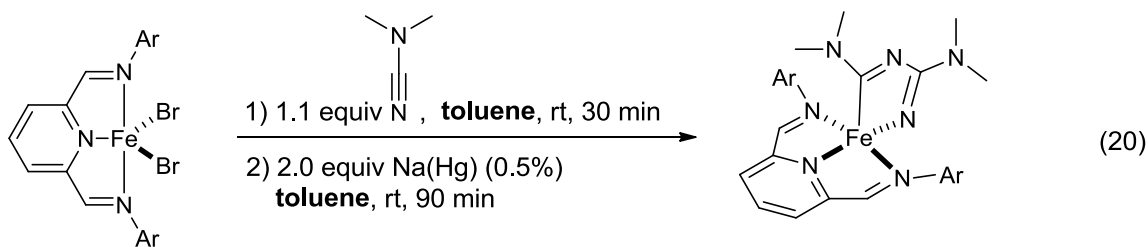
(19)

Full Conversion (GC)
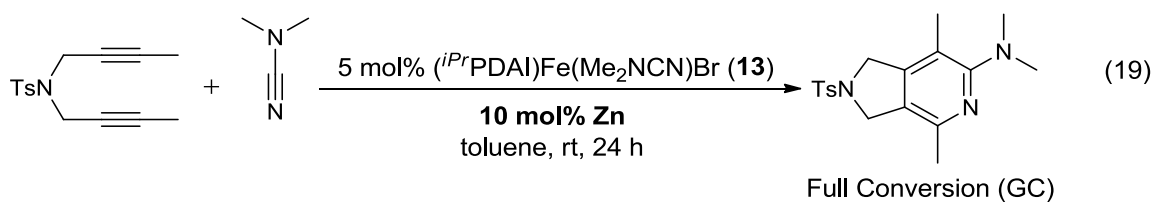
If $(^{iPr}\text{PDAI})\text{FeBr}_2$ (**17**) is reduced in the same manner as before but in diethyl

ether, the diazaferracyclopentadiene $(^{iPr}\text{PDAI})\text{Fe}(\text{Me}_2\text{NCN})_2$ (**18**) is obtained (equation

20, Figure 26A). This unprecedented metallacycle is the result of oxidative cyclization

(20)

$(^{iPr}\text{PDAI})\text{FeBr}_2$ (**15**)   Ar = 2,6-diisopropyl phenyl $(^{iPr}\text{PDAI})\text{Fe}(\text{Me}_2\text{NCN})_2$ (**18**)

$(^{OMe,iPr}\text{PDAI})\text{FeBr}_2$ (**19**) Ar = 4-methoxy-2,6-diisopropyl $(^{OMe,iPr}\text{PDAI})\text{Fe}(\text{Me}_2\text{NCN})_2$ (**20**)
phenyl
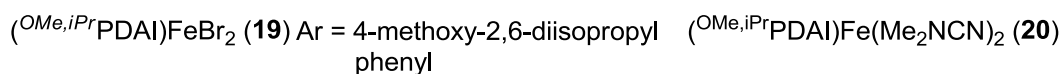
of two cyanamides and exhibits a distorted square pyramidal geometry. A related study

by Chirik involved the oxidative cyclization of diynes or enynes with $(^{iPr}\text{PDI})\text{Fe}(\text{N}_2)_2$

(Chapter 1).[9] In this work, the resulting metallacycles were structurally and

electronically characterized. These ferracyclopentadiene products exhibited the same

distorted square pyramidal geometry as $(^{iPr}\text{PDAI})\text{Fe}(\text{Me}_2\text{NCN})_2$ (**18**). Based on various

bond length data, computational studies, and several spectroscopic analyses, the

metallacycles were determined to be an Fe(III) species bound to a radical anionic ligand

(Figure 27).

Comparison of bond lengths between $(^{iPr}\text{PDAI})\text{Fe}(\text{Me}_2\text{NCN})_2$ (**18**) and Chirik's

ferracyclopentadiene demonstrate remarkable similarities. Most notably, the ligand

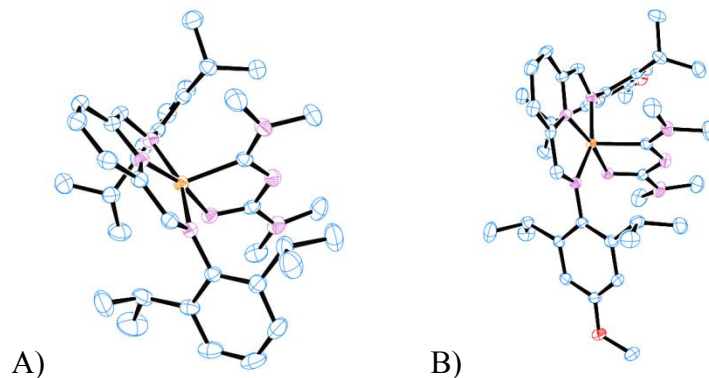imine bond lengths of **18** and Chirik's **21** have elongated as compared to that of **15**,

Figure 26. A) Ortep of (^{iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**18**). B) Ortep of (^{iPr,OMe}PDAI)Fe(Me$_2$NCN)$_2$ (**20**).
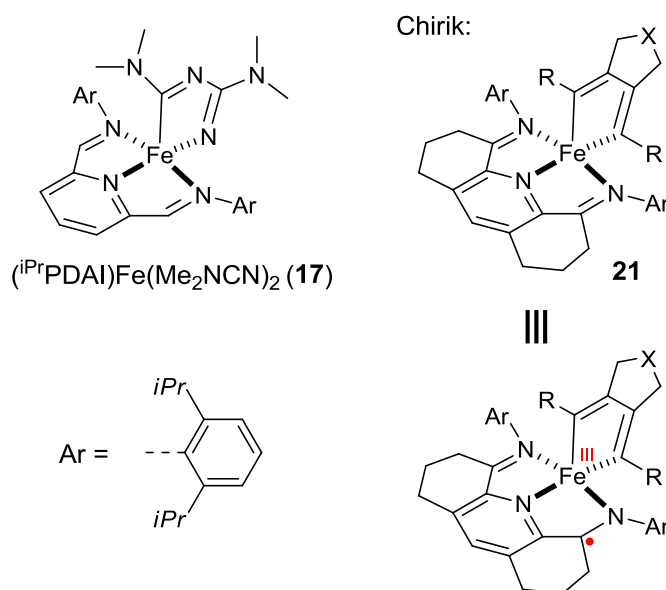

Figure 27. (^{iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**18**) demonstrates similar geometry and bond distances to Chirik's metallacycle **21**.

suggesting a partial double-bond characteristic. This is indicative of a single-electron reduction of the ligand, with the additional electron residing primarily on the imines of the ligand.[9] Based on this comparison we can conclude that (^{iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**18**) is also an Fe(III) species bound to a radical anionic ligand (Table 10). To further supportthis conclusion, future studies will involve Mössbauer spectroscopy and SQUID magnetometry. The analogous methoxy-substituted diazametallacycle

Table 10. Relevant bond length data of various (PDAI)Fe complexes
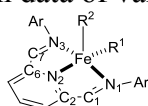
Compound	Bond Lenth: Fe-N$_1$	Fe-N$_3$	Fe-N$_2$	Fe-R$_1$	Fe-R$_2$	N$_1$-C$_1$	N$_3$-C$_7$	C$_1$-C$_2$	C$_6$-C$_7$	N$_2$-C$_2$	N$_1$-Ar
(^{Mes}PDAI)FeBr$_2$ (**15**)	2.338(3)	2.338(3)	2.089(3)	N/A	N/A	1.283(5)	1.283(5)	1.471(6)	1.463(5)	1.343(5)	1.443(5)
(^{OMe,iPr}PDAI)FeBr$_2$ (**19**)	2.223(2)	2.223(2)	2.058(2)	N/A	N/A	1.280(3)	1.284(3)	1.460(4)	1.467(3)	1.349(3)	1.441(3)
(^{Mes}PDAI)Fe(Me$_2$NCN)Br (**16**)	2.2332	2.2332	2.0072	2.036(2)	N/A	1.297(3)	1.301(3)	1.433(3)	1.434(3)	1.367(3)	1.423(3)
(^{iPr}PDAI)Fe(η^4-C$_4$H$_6$) (**1**)	1.973	1.973	1.852	N/A	N/A	1.328	1.333	1.411	1.401	1.366	1.443
(^{iPr}PDAI)Fe(DMAP) (**3**)	1.917	1.889	1.833	1.985	N/A	1.349	1.343	1.406	1.405	1.381	1.435
(^{iPr}PDAI)Fe(Me$_2$NCN) (**26**)	1.885(3)	1.889(3)	1.827(3)	1.888(3)	N/A	1.349(4)	1.349(4)	1.408(5)	1.412(5)	1.388(4)	1.438(5)
(^{iPr}PDAI)Fe(PhCN)$_2$ (**22**)	1.9113	1.9068	1.8436	1.8706	1.9435	1.343(3)	1.343(3)	1.413(3)	1.413(3)	1.381(3)	1.448(3)
(^{iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**18**)	1.9350	1.9149	1.8313	1.9684	1.9956	1.334(2)	1.334(2)	1.416(2)	1.407(3)	1.383(2)	1.442(2)
(^{OMe,iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**20**)	1.913(2)	1.936(2)	1.830(2)	1.974(2)	1.993(4)	1.339(3)	1.339(3)	1.416(4)	1.408(4)	1.381(3)	1.445(3)
21	2.073(2)	2.069(2)	1.862(5)	1.996(6)	2.004(5)	1.327(7)	1.327(8)	1.424(6)	1.427(7)	N/A	N/A

(^{iPr,OMe}PDAI)Fe(Me$_2$NCN)$_2$ was also synthesized and an x-ray crystal structure was elucidated (Figure 26B). Comparison of bond lengths between the two metallacycles demonstrates virtually no change (Table 10), suggesting that the methoxy substituent does not affect the electronic structure.

The reduction of (^{iPr}PDAI)FeBr$_2$ in the presence of benzonitrile provides an interesting comparison between cyanamide and nitrile reactivity (equation 21). Instead of
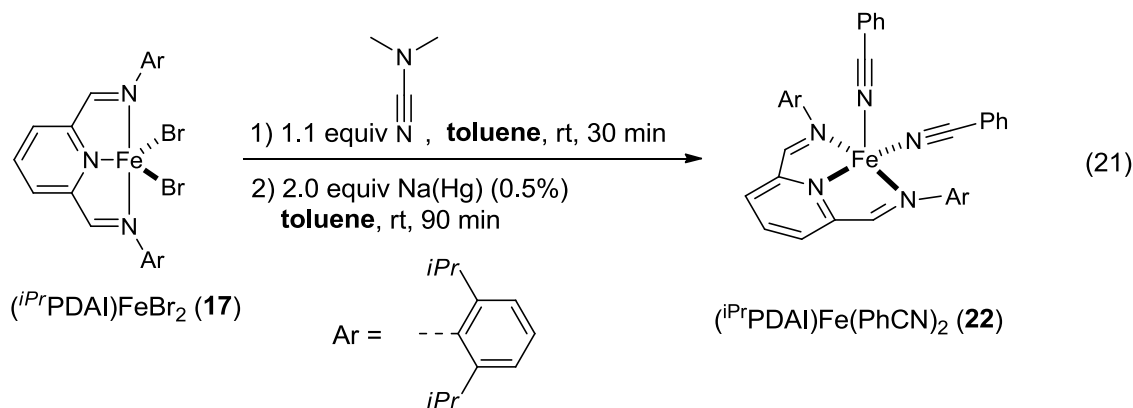
forming a diazametallacycle, both nitriles coordinate in an end-on fashion (^{iPr}PDAI)Fe(PhCN)$_2$ (**22**) (Figure 28). Although it has not oxidatively cyclized, it exhibits the same distorted square pyramidal geometry as the metallacyclic complexes.
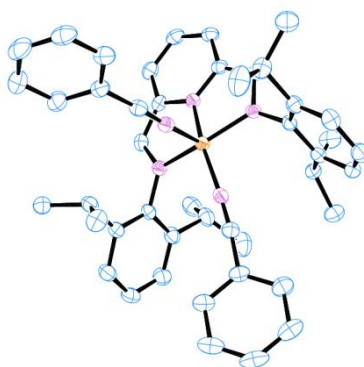
Figure 28. Ortep of (^{iPr}PDAI)Fe(PhCN)$_2$ (**22**).

Bond lengths on the ligand (imine elongation) are consistent with those of a one-electron

reduced ligand coordinated to Fe(II) (Table 10). The Fe-nitrile bond lengths present an

interesting picture. The axial Fe-N bond length is 1.8706 Å, while the equatorial nitrile is

longer at 1.9435 Å. This indicates that the second electron is mostly localized on the

axial nitrile.

In an attempt to isolate an azaferracyclopentadiene, compound **13** was stirred with

alkyne **23** in the presence of two equivalents of a sodium amalgam reductant (Figure 29).

The reaction quickly turns from green to brown. From the dried crude mixture is a brown

product which can be extracted with pentane. When this brown solid is subjected to

another equivalent of alkyne, an exothermic reaction occurs and a 2-aminopyridine

product, **25**, is detected by GCMS. The 2,4,6-subsitution pattern of **25** is easily separated

and differentiated from its other regioisomers by GCMS. This GCMS match suggests

that not only has the cycloaddition occurred, but with the same regioselectivity observed

previously (chapter 3, equation 7). The fact that this product was obtained by a 2-step

alkyne addition to **13** suggests that an azametallacyclopentadiene, **24**, was formed in the

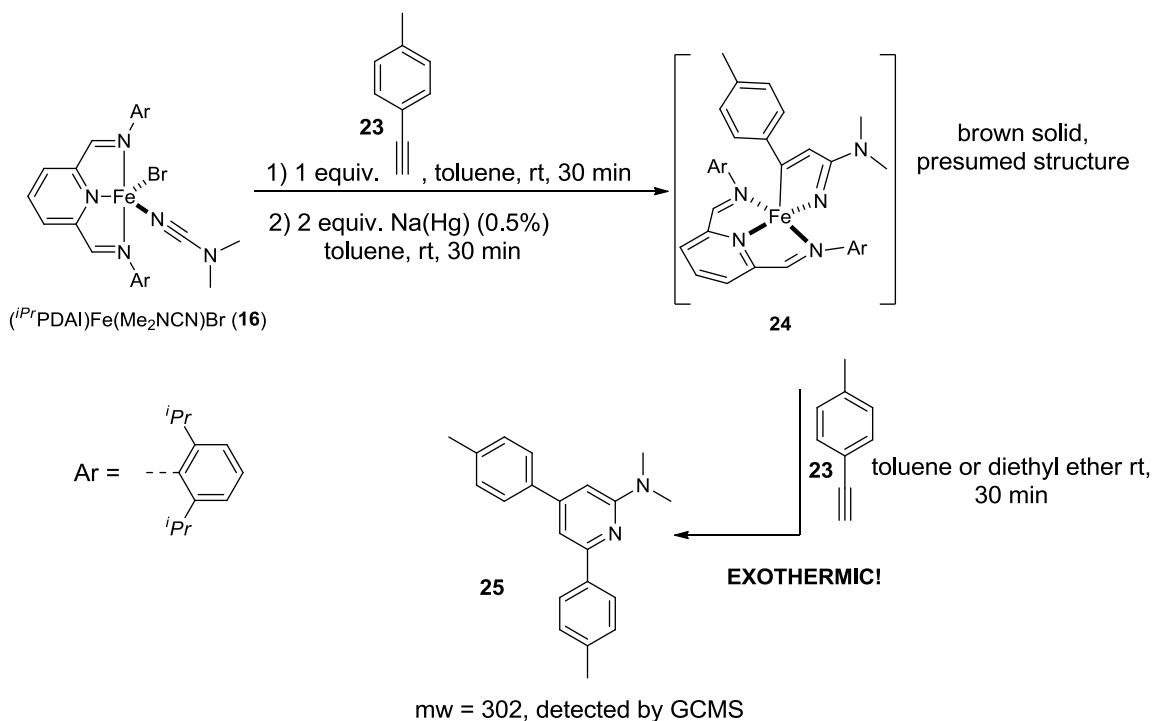first addition and that the second alkyne is inserted and reductively eliminated, leading to

Figure 29. Synthesis of **25** via azaferracyclopentadiene **24**.

25. Remarkably, this reaction is so exothermic that addition of neat alkyne to a diethyl ether solution of **24** causes the ether to boil. Computational studies of metallacyclopentadienes show that the transformation from metallacycle to metal-bound pyridine is significantly exothermic.[10] The matching regioselectivity and the observable release of energy strongly suggest the presence of an azaferracyclopentadiene intermediate.

Attempts to crystalize metallacycle **24** have been unsuccessful thus far. However, an ether solution of this crude mixture has provided an x-ray-quality crystal of (^{iPr}PDAI)Fe(Me$_2$NCN) **26** (Figure 30). Presumably, **26** is created when **13** undergoes a one-electron reduction but fails to coordinate and oxidatively cyclize an alkyne. Compound **26** is of significant interest to this study because we believe it is the active catalyst and precursor to the oxidative cyclization intermediate (Figure 29). Attempts to
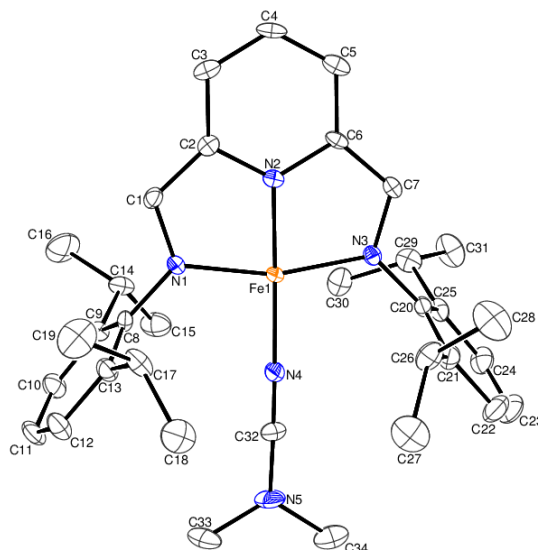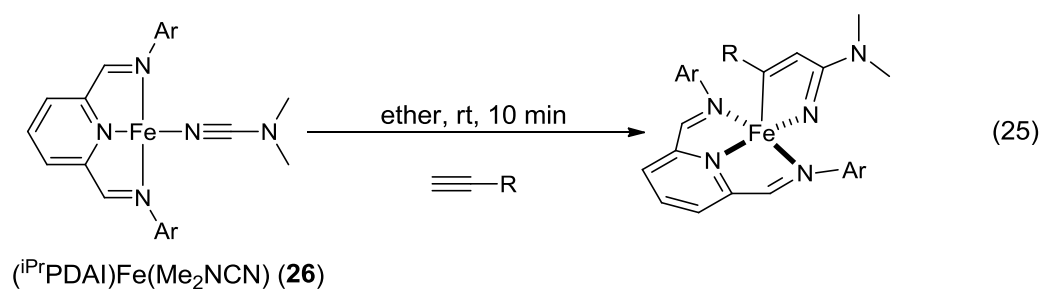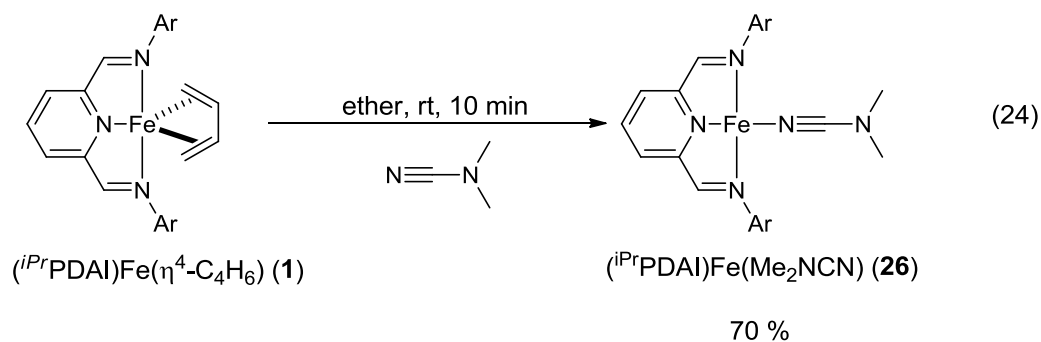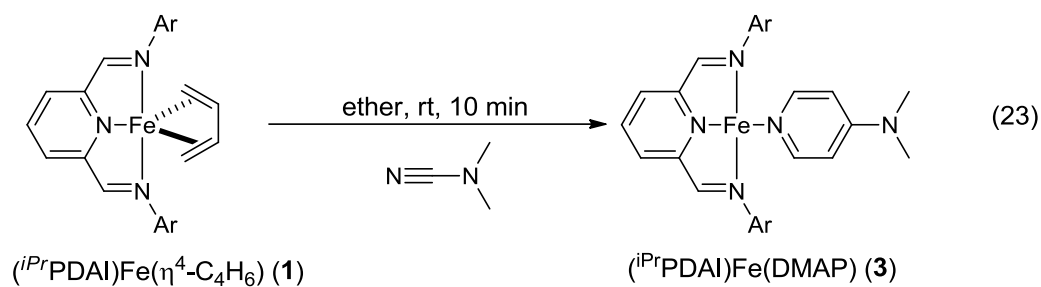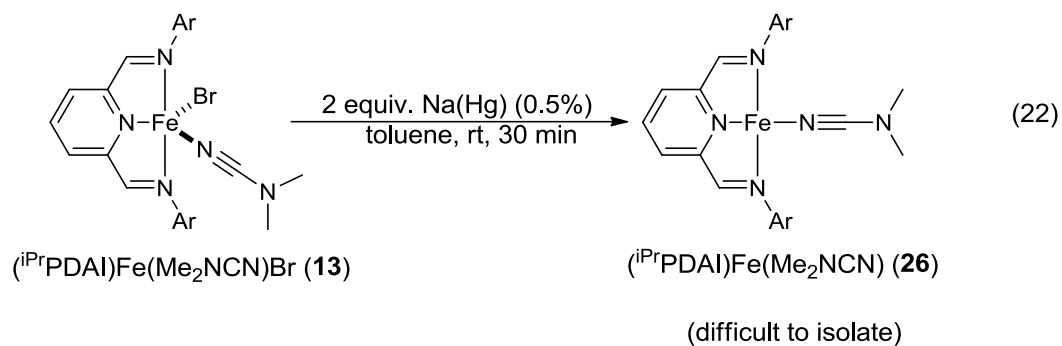
Figure 30. Ortep of (^{iPr}PDAI)Fe(Me$_2$NCN) (**26**).

cleanly produce **26** from **13** have proven unsuccessful (equation 22). Chirik has

synthesized a similar square planar complex **3** from **1** (equation 23).[5] Analogously,

useful quantities of **26** should be available from **1** (equation 24). The reaction of **1** with

dimethyl cyanamide produces a compound with the same brown color as **26**. The NMR

of the product obtained from this reaction differs from that of **1** and exhibits broad peaks

that fall in the range expected for **26**. However, to validate the identity of this product, it

will be necessary to grow a crystal and compare the unit cell with that of the previously

determined **26**. Once verified, useful amounts of compound **26** will allow for more

comprehensive reactivity studies. We hope that addition of an alkyne to **26** will cleanly

provide the oxidative cyclization intermediates that we are seeking (equation 24).

(^{iPr}PDAI)Fe(Me$_2$NCN)Br (**13**)　　　　(^{iPr}PDAI)Fe(Me$_2$NCN) (**26**)

(22)

(difficult to isolate)

(^{iPr}PDAI)Fe(η^4-C$_4$H$_6$) (**1**)　　　　(^{iPr}PDAI)Fe(DMAP) (**3**)

(23)

(^{iPr}PDAI)Fe(η^4-C$_4$H$_6$) (**1**)　　　　(^{iPr}PDAI)Fe(Me$_2$NCN) (**26**)

(24)

70 %

(^{iPr}PDAI)Fe(Me$_2$NCN) (**26**)

(25)

Analysis of (^{iPr}PDAI)Fe(Me$_2$NCN) – Cyanamides vs Nitriles

The x-ray crystal structure of **26** exhibits ligand bond lengths which are

remarkably similar to the analogous compound **3** previously prepared by Chirik (Table

10).[5] Particularly, the imine bond lengths (1.349 Å for both) are significantly elongated while the C_{imine}-C_{ipso} bond lengths have contracted to 1.408 Å and 1.406 Å, respectively. Compound **3** was determined to be a d^6 Fe(II) center coordinated to a dianionic diradical ligand (Figure 31). Operating under the assumption that **26** is also a d^6 Fe(II) center coordinated to a dianionic diradical ligand, we can qualitatively predict its electronic structure. A square planar complex with C_2v symmetry will adopt one of two possible crystal-field-splitting environments (Figure 32). The relative energy of the d_z^2 orbital will depend on the ligand environment and could possibly be above or below the d_{xy} orbital. For a d^6 metal, the HOMO will be either the d_{xy} or d_z^2 orbital. For **26**, if d_{xy} is the HOMO, this orbital will be unavailable to react because it is blocked by the ligands (Figure 32 B). However, d_z^2 will be perpendicular to the ligand plane, making it available to react with outside LUMOs such as the π^* orbital of an alkyne (Figure 32 A). In order for **26** to be the active catalyst, the d_z^2 orbital must be available to react.

Of further interest is the cyanamide coordinated to the iron center in **26**. Surprisingly, the dimethyl amino substituent of the cyanamide exhibits a planar geometry (Figure 33 A). The planar amine can only result from significant resonance donation of the amine lone pair into the nitrile, creating a carbodiimide-like structure (Figure 33 B). This resonance structure is not available to regular nitriles (such as acetonitrile) and provides insight into the increased reactivity of cyanamides over nitriles. The partial carbodiimide nature of the bound cyanamide may allow for an alternative nonlinear coordination mode. Additionally, the partial negative charge on N_1 may increase the overall electron density of the iron center.

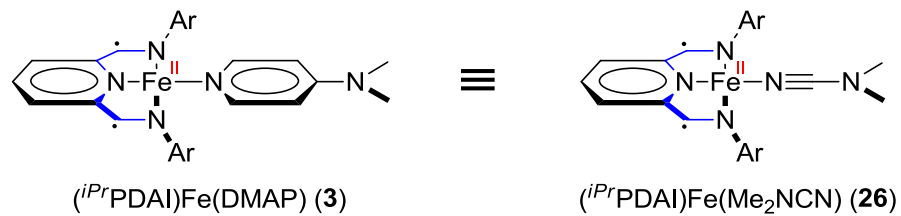When comparing (^{iPr}PDAI)Fe(Me$_2$NCN) (**26**) with metallacyclic

Figure 31. Comparison of (^{iPr}PDAI)Fe(DMAP) (**3**) and (^{iPr}PDAI)Fe(Me$_2$NCN) (**26**).
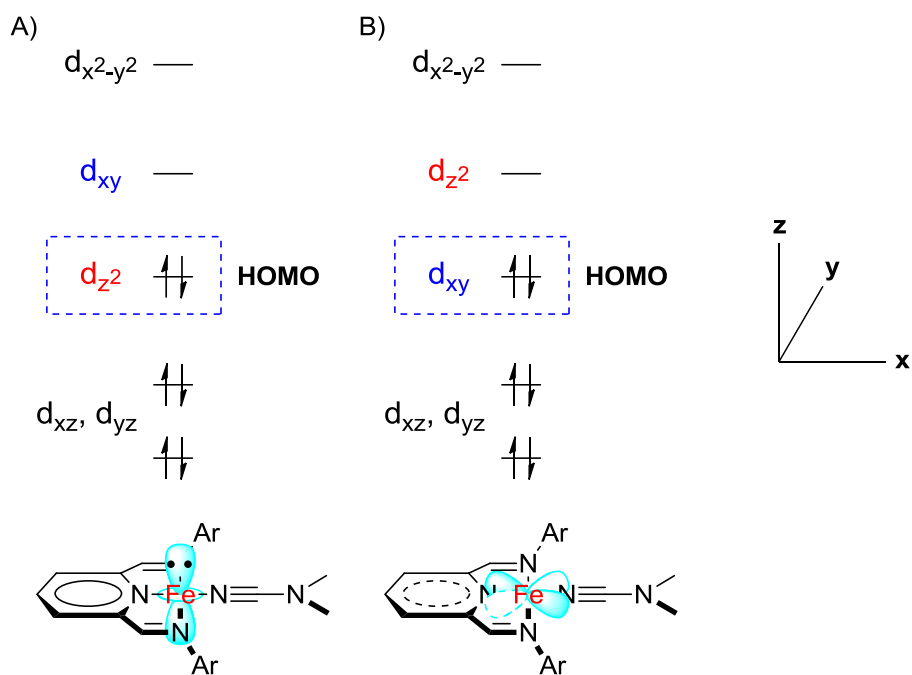

Figure 32. Possible crystal field splittings for a d^6 square planar complex with C$_2$v symmetry.
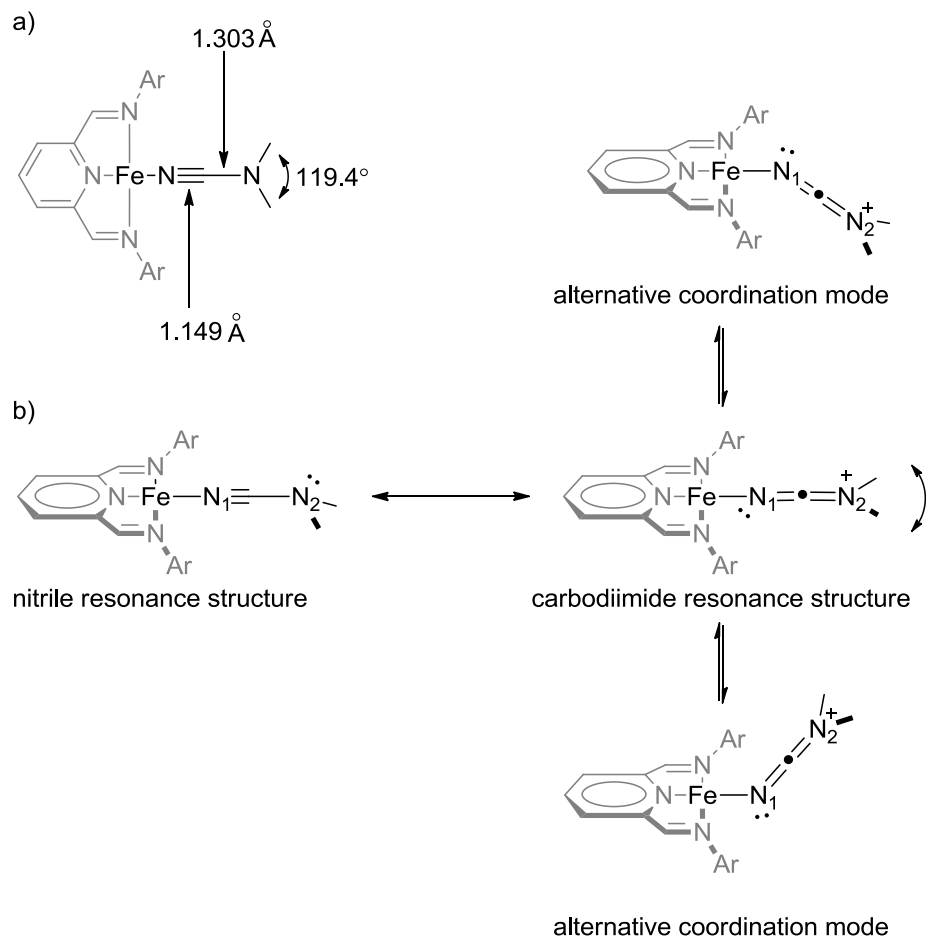
Figure 33. a) Cyanamide bond lengths and amine geometry of (^{iPr}PDAI)Fe(Me$_2$NCN) (**26**). b) Resonance structures of **26** based on the planar geometry of the cyanamide amine.

(^{iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**18**) , the (^{iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**18**) appears to have formed when a cyanamide coordinated to the open face of (^{iPr}PDAI)Fe(Me$_2$NCN) (**26**) (Figure 34 A). When oxidative cyclization occurs, the cyanamides do not change position in relation to the metal center. We can envision the same transformation occurring between (^{iPr}PDAI)Fe(Me$_2$NCN) (**26**) and an alkyne. This deviates from the traditionally accepted oxidative cyclization of two η^2-bound coupling partners (Figure 34 B). To substantiate this theory, further analysis of (^{iPr}PDAI)Fe(Me$_2$NCN) (**26**) will be necessary.

Figure 35 depicts the reaction between the nitrile-type resonance structure of

A) Newly propsed mechanism of cyclization

(^{iPr}PDAI)Fe(Me$_2$NCN) (**26**)

(^{iPr}PDAI)Fe(Me$_2$NCN)$_2$ (**18**)

(^{iPr}PDAI)Fe(Me$_2$NCN) (**26**)

B) Traditional cyclization mechanism

(^{iPr}PDAI)Fe(Me$_2$NCN) (**26**)

Figure 34. Cyclization from A) end-on coordinated cyanamide or B) η^2-bound cyanamide.

increased overlap

Figure 35. In-depth look at the formation of an azaferracyclopentadiene from an η^1-bound cyanamide complex.

(^{iPr}PDAI)Fe(Me$_2$NCN) (26) and an alkyne. Here alkyne coordination will lead to electron donation from the d$_z^2$ orbital of iron to the alkyne π* orbital (Figure 35 A). Filling the alkyne π* orbital will set in motion electron movement that breaks the alkyne triple bond, leading, momentarily, to a filled p-orbital at the C$_2$-position of the alkyne. This filled p-orbital can then donate electrons to the π* orbital of the cyanamide, leading to cyclization. While explained here in a step-wise fashion, a concerted movement of electrons is also reasonable. In Figure 35 B, the same reaction occurs, but with the carbodiimide resonance structure of 26. For the cases presented in Figure 35 A and B, the distance between C$_2$ and C$_3$ appears to be large enough that orbital overlap will be poor. The distance from the iron center to C$_3$ is 3.037 Å, while the average alkyne bond distance is only 1.20 Å (Figure 36). The distance appears to be great enough that the alkyne π* orbitals will be unable to overlap with both the Fe d$_z^2$ orbital and the C$_3$ π* orbital. This poor overlap would suggest that cyclization occurs from the traditional η^2-bound coordination modes, however, one more possibility remains. The angled coordination mode available from the carbodiimide resonance structure in Figure 35 C
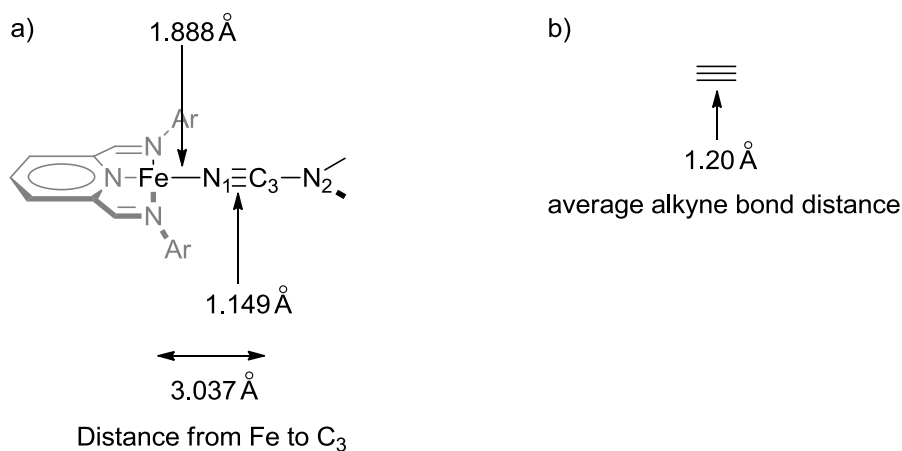

Figure 36. The 1.2 Å length of an alkyne is likely not enough to bridge the distance from Fe to C$_3$.

allows for increased overlap of the π^* orbitals of C_2 and C_3. Therefore the increased reactivity of cyanamides could be due to the existence of a carbodiimide-like resonance structure which can subsequently adopt a bent coordination mode.

Conclusions

By synthesizing and studying various bis(aldimino)pyridine iron complexes, we have begun to understand the mechanistic pathway in iron-catalyzed [2+2+2] cycloadditions of alkynes and cyanamides. The active catalyst is likely a d^6 Fe(II) bound to a two-electron reduced ligand. This unique structure imparts a Lewis acidic property to the iron center while simultaneously providing the two electrons necessary for oxidative cyclization. The Lewis acidic nature of the iron in this context likely attracts nitriles to coordinate in an end-on fashion, initiating a heterocoupling catalytic cycle. Square planar (^{iPr}PDAI)Fe(Me$_2$NCN) exhibits a coordinatively open d_z^2 HOMO, which can readily coordinate and donate electrons into a second coupling partner, leading to oxidative cyclization. The cyclization with an end-bound cyanamide is possible due to the carbodiimide-like resonance structure of the coordinated cyanamide. This resonance structure suggests it may be possible for the cyanamide to adopt a bent coordination mode, making the cyclization possible.

The completion of this project will fall to Nathan Spahn and Shantel Leithead. The isolation and characterization of an azametallacyclopentadiene intermediate from (^{iPr}PDAI)Fe(Me$_2$NCN) is of paramount importance for demonstrating the above mentioned theories. Additionally, further DFT calculations should be performed to substantiate the identity of the HOMO of (^{iPr}PDAI)Fe(Me$_2$NCN) and to compare the energies of bent and linear coordination modes of the cyanamide. A DFT study

comparing the oxidative cyclization of η^2- and η^1- bound cyanamides will shed further light on the true nature of this important catalytic step.

Experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques, or in a nitrogen-filled glove box, unless otherwise noted. Toluene, diethyl ether, pentane, and THF were dried over neutral alumina under N_2 using a Grubbs-type solvent purification system. Iron Chloride (99.95% purity) was purchased from Alfa Aesar. Compounds **1**, **3**,[5] and **15**, **17**[2] were prepared from known literature procedures. Liquid cyanamides were distilled then degassed using three sequential freeze-pump-thaw cycles and stored under N_2. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz, unless otherwise noted. The abbreviations s, d, dd, dt, dq, td, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet of doublets, triplet, quartet, and quintet, respectively. All ^{13}C NMR spectra were proton-decoupled. Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 10 ºC/min.; final temperature: 300 ºC held for 12 minutes; detector temperature: 250 ºC.

(^{iPr}PDAI)Fe(Me₂NCN)Br (13). In a round-bottom flask, (^{iPr}PDAI)FeBr₂ (**17**) (1.02g, 1.52 mmol) and dimethyl cyanamide (116.9 mg, 1.68 mmol) were stirred in 50 mL of toluene for 30 minutes at room temperature. Meanwhile a separate vial with sodium (69.7 mg, 3.03 mmol) and mercury
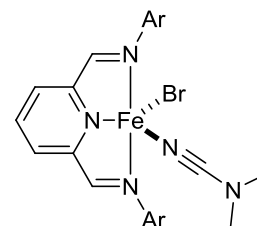

Ar = 2,6-diisopropyl phenyl

(14.0g, 69.8 mmol) in 5 mL of toluene was stirred for 30 minutes. After 30 minutes the

Na(Hg) mixture was added to **17** and dimethyl cyanamide, and the reaction was stirred

for 30 minutes. At this time the reaction was passed through a plug of celite and rinsed

with 20 mL diethyl ether. The solvent was removed and the resulting green solid was

rinsed with 3 x 5 mol portions of pentane. The pentane was discarded, yielding 651 mg

of (^{iPr}PDAI)FeBr$_2$ (**13**) (*65% yield*).

(^{iPr}PDAI)Fe(Me$_2$NCN)$^-$ [Na(12-C-4)]$^+$ (14).

[Na(12-C-4)$_2$] +

Ar = 2,6-diisopropyl phenyl

In a 1.5 dram vial, sodium (7.8 mg, 0.33 mmol) and

mercury (1.6g, 7.7 mmol) were stirred in 2 mL of

toluene. After 30 mintues the Na(Hg) mixture was

added to a solution of (^{iPr}PDAI)FeBr$_2$ (**17**) (100 mg,
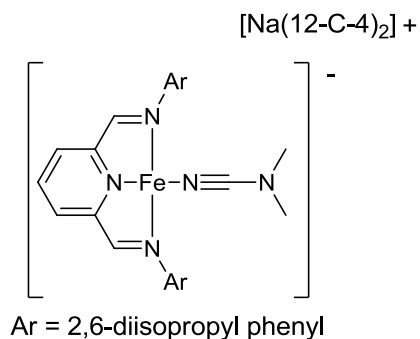
0.15 mmol) and 12-C-4 (53.5 mg, 0.30 mmol) in 15 mL of toluene and stirred for 90

minutes. The resulting brown mixture was passed through a plug of celite and rinsed

with 20 mL of THF. The solvent was removed and the resulting green solid was rinsed

with 3 x 2 mol portions of pentane then 3 x 2 mL portions of diethyl ether. The

remaining brown solid was dissolved in 5 mL of THF, passed through celite, and stored

at -40°C. Crystals had formed from this solution but were not of high enough quality for

x-ray analysis. The mother liquor was dried and the remaining reddish brown solid was

stored under N$_2$ at room temperature. A % yield was not obtained.

(^{Mes}PDAI)Fe(Me$_2$NCN)Br (16). In a 1.5 dram vial,

(^{Mes}PDAI)FeBr$_2$ (**15**) (50 mg, 0.086 mmol) and dimethyl

cyanamide (6.3 mg, 0.090 mmol) were stirred in 2 mL of toluene

for 30 minutes at room temperature. Meanwhile a separate vial

Ar = *Mes*
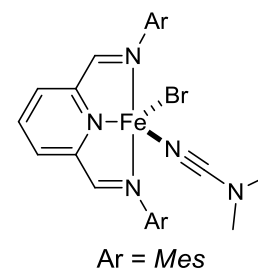
with sodium (4.3 mg, 0.19 mmol) and mercury (874 mg, 4.4 mmol) in 1 mL of toluene

was stirred for 30 minutes. After 30 mintues the Na(Hg) mixture was added to **15** and

dimethyl cyanamide and the reaction was stirred for 30 minutes. At this time the reaction

was passed through a plug of celite and rinsed with 5 mL diethyl ether. The solvent was

removed and the resulting green solid was rinsed with 2 x 1 mL portions of pentane

which was discarded. The remaining green solid was dissolved in 2 mL of diethyl ether,

passed through pentane, and stored at -40°C. Large green crystals formed which were of

high enough quality for x-ray analysis. A yield was not determined. Elemental Analysis

calculated: C, 58.45; H, 5.78; N, 12.17; found: C, 57.91; H, 5.82; N, 11.85.
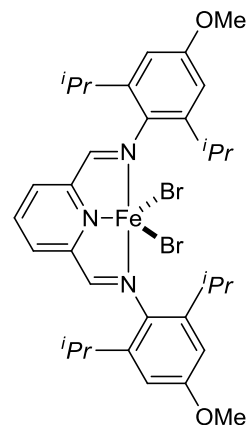
      (^{iPr}**PDAI)Fe(Me₂NCN)₂ (18).** In a 20 mL

scintillation vial, (^{iPr}PDAI)FeBr₂ (**17**) (500 mg,

0.747 mmol) and dimethyl cyanamide (157 mg,

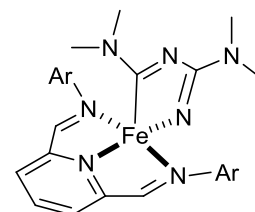2.24 mmol) were stirred in 15 mL of diethyl ether
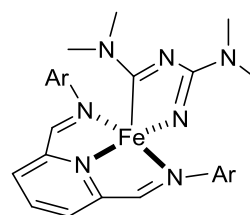
Ar = 2,6-diisopropyl-4-methoxy phenyl

for 30 minutes at room temperature. Meanwhile a separate vial with sodium (37.8 mg,

1.64 mmol) and mercury (7.6 g, 38 mmol) in 5 mL of diethyl ether was stirred for 30

minutes. At this time the Na(Hg) mixture was added to **16** and dimethyl cyanamide, and

the reaction was stirred for 30 minutes. The brown mixture reaction was passed through

a plug of celite and rinsed with 20 mL diethyl ether. The solvent was removed and the

resulting dark brown solid was stirred with 20 mL of pentane. The pentane solution was

passed through celite and stored at -40°C. (^{iPr}PDAI)Fe(Me₂NCN)₂ (**18**) crystalized with

one molecule of pentane, yielding 67.7mg (*14% yield*). These crystals were analyzed by

x-ray crystallography. Elemental Analysis calculated: C, 68.40; H, 7.91; N, 15.09;

found: C, 68.65; H, 8.15; N, 15.04.

(^{OMe,iPr}PDAI)FeBr$_2$ (19). In a round-bottom flask, ^{OMe,iPr}PDAI^3 (101 mg, 0.20 mmol) and FeBr$_2$ (43 mg, 0.20 mmol) were stirred in 2 mL of THF for 24 h. Additional THF was added until the green product was dissolved, then the solution was passed through celite, removing a brown impurity. Pentane was added until the product precipitated and the green/brown product was collected, yielding 63 mg (*74% yield*).

(^{OMe,iPr}PDAI)Fe(Me$_2$NCN)$_2$ (20). In a 20 mL scintillation vial, (^{iPr}PDAI)FeBr$_2$ (**17**) (500 mg, 0.747 mmol) and dimethyl cyanamide (157 mg, 2.24 mmol) were stirred in

Ar = 2,6-diisopropyl phenyl

15 mL of diethyl ether for 30 minutes at room temperature. Meanwhile a separate vial with sodium (37.8 mg, 1.64 mmol) and mercury (7.6 g, 38 mmol) in 5 mL of diethyl ether was stirred for 30 minutes. At this time the Na(Hg) mixture was added to **17** and dimethyl cyanamide, and the reaction was stirred for 30 minutes. The brown mixture reaction was passed through a plug of celite and rinsed with 20 mL diethyl ether. The solvent was removed and the resulting dark brown solid was stirred with 20 mL of pentane. The pentane solution was passed through celite and stored at -40°C. Crystals resulting from this solution were analyzed by x-ray crystallography.

(^{iPr}PDAI)Fe(PhCN)$_2$ (22). In a 25 mL round-bottom flask, (^{iPr}PDAI)FeBr$_2$ (**17**) (50 mg, 0.075 mmol) and benzonitrile (8.5 mg, 0.082 mmol) were stirred in 5 mL of toluene for 30 minutes at room temperature. Meanwhile a separate vial with sodium (3.4 mg, 0.15 mmol) and mercury (690 mg, 3.4 mmol) in 2 mL
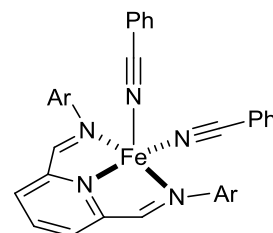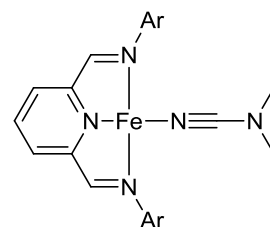
Ar = 2,6-diisopropyl phenyl

of diethyl ether was stirred for 30 minutes. At this time the Na(Hg) mixture was added to

17 and benzonitrile and the reaction was stirred for 30 minutes. The brown mixture

reaction was passed through a plug of celite and rinsed with 10 mL diethyl ether. The

solvent was removed and the resulting dark brown solid was stirred with 10 mL of

pentane for 2 minutes. The pentane solution was passed through celite and stored at -

40°C. Crystals resulting from this solution were analyzed by x-ray crystallography.

Metallacycle (24) and (^{iPr}PDAI)Fe(Me₂NCN) (26).

In a 25 mL round bottom flask, (^{iPr}PDAI)Fe(Me₂NCN)Br **(13)**

(40 mg, 0.075 mmol) and 4-ethynyl toluene (8.5 mg, 0.067

mmol) were stirred in 5 mL of toluene for 30 minutes at room

Ar = 2,6-diisopropyl phenyl

temperature. Meanwhile a separate vial with sodium (2.8 mg, 0.12 mmol) and mercury

(559 mg, 2.8 mmol) in 2 mL of diethyl ether was stirred for 30 minutes. At this time the

Na(Hg) mixture was added to **13** and 4-ethynyl toluene, and the reaction was stirred for

30 minutes. The brown mixture reaction was passed through a plug of celite and rinsed

with 20 mL diethyl ether. The solvent was removed, and the resulting dark brown solid

was stirred with 5 mL of pentane for 2 minutes. The pentane solution was passed

through celite and solvent was removed, yielding what is presumed to be **(24)**. ¹H NMR

was too convoluted to provide any useful information. After treatment with pentane, a

brown solid remained. This was stirred with 2 mL of diethyl ether for 2 minutes and the

resulting brown solution was passed through celite and stored in the freezer. A mixture

of low-quality green crystals and a small amount of high-quality brown crystals were

obtained from this solution. X-ray analysis of the brown crystals showed the structure of

(^{iPr}PDAI)Fe(Me₂NCN) **(26)**.

(^{Mes}PDAI)Fe(η^6-C$_6$-H$_6$) (27). Sodium (31 mg, 1.3 mmol) was stirred with mercury (6.2 g, 31 mmol) in 4 mL of diethyl ether for 30 minutes. The amalgam mixture was added to a suspension of (^{Mes}PDAI)FeBr$_2$ (**15**) in 10 mL of benzene and the reaction was stirred for 16 hours. The brown mixture was passed through celite and rinsed with 10 mL of pentane. Solvent was removed, yielding 141 mg of (^{Mes}PDAI)Fe(η^6-C$_6$-H$_6$) (**27**) (*55% yield*).
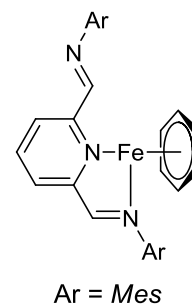
(^{Mes}PDAI)Fe(η^6-C$_6$-H$_6$) (**27**) (4.6 mg, 0.0091 mmol) was dissolved in 109 µL of benzene and pyrrolidine-1-carbonitrile (21 mg, 0.22 mmol) was added in a 1.5 dram vial which was capped with a septum cap. A separate solution, containing N,N-di(but-2-yn-1-yl)-4-methylbenzenesulfonamide in 323 µL of benzene, was added to a syringe. The diyne solution was slowly added via syringe pump to the stirring mixture of **27** and cyanamide at 70 °C over 3 h. After 6 h the product was purified as described in Chapter 3, yielding 65 mg of 4,7-dimethyl-6-(pyrrolidin-1-yl)-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (*96% yield*).

<div align="center">References</div>

(1) D'Souza, B. R.; Lane, T. K.; Louie, J. *Org. Lett.* **2011**, *13*, 2936-2939.

(2) Lane, T. K.; D'Souza, B. R.; Louie, J. *J. Org. Chem.* **2012**, *77*, 7555-7563.

(3) Lane, T. K.; Nguyen, M. H.; D'Souza, B. R.; Spahn, N. A.; Louie, J. *Chem. Commun.* **2013**, *49*, 7735-7737.

(4) a) Small, B. L.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 4049-4050. b) Britovsek, G. J. P.; Givson, V. C.; Kimberley, B. S.; Maddox, P. J.; McTavish, S. J.; Solan, G. A.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1998**, 849-850. c) Small, B. L.; Brookhart, M.; *J. Am. Chem. Soc.* **1998**, *120*, 7143-7144. (b) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794-13807. (c) Tondreau, A. M.; Atienze, C. C. H.; Weller, K. J.; Nye, S. A.; Lewis, K. M.; Delis, J. G.; Chirik, P. J.

Science, **2012**, *335*, 567-570.

(5) Russell, S. K.; Milsmann, C.; Lobkovsky, E.; Weyhermüller, T.; Chirik, P. J. *Inorg. Chem.*, **2011**, *50*, 359-3169.

(6) Anderson, J. J; Rittle, J.; Peters, J. C. *Nature* **2013**, *501*, 84-88.

(7) Co metallacycle papers

(8) (a) Takahashi, T.; Tsai, F. Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994-4995; (b) Takahashi, T.; Tsai, F. Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059-5067; (c) Eisch, J. J.; Ma, X.; Han, K. I.; Gitua, J. N.; Kruger, C. *Eur. J. Inorg. Chem.* **2001**, 77-88. (d) Stolley, R. M.; Duong, H. A.; Thomas, D. R.; Louie, J. *J. Am. Chem. Soc.* **2012**, *134*, 15154-15162. (e) Stolley, R. M.; Duong, H. A.; Louie, J. *Organometallics*, **2013**, *32*, 4952-4960.

(9) Hoyt, J. M.; Sylvester, K. T.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 4862-4877.

(10) (a) Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. *J. Organomet. Chem.* **2006**, *691*, 4434-4445. (b) Dahy, A. R. A.; Yamada, K.; Koga, N. *Organometallics* **2009**, *28*, 3636-3649. (c) Dahy, A. R. A.; Koga, N. *J. Organomet. Chem.* **2010**, *695*, 2240-2250.