MECHANISTIC EVALUATION OF THE NICKEL-CATALYZED [2+2+2]-CYCLOADDITION REACTION OF ALKYNES AND NITRILES

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Chapter 1 describes detailed mechanistic studies that were conducted on three discreet Nickel-catalyzed [2+2+2] cycloaddition reactions of diyne and nitriles to afford pyridines. Reaction profiles demonstrated in all cases a heterooxidative coupling mechanism, contrary to other common cycloaddition catalysts.

Through kinetic analysis of the $Ni(IPr)_2$-catalyzed cycloaddition, observed regioisomerism of the products, and stoichiometric reactions, $Ni(IPr)_2$ appears to have catalyzed the cycloaddition by proceeding via a heterooxidative coupling mechanism. Strong coordination and considerable steric bulk of the carbene ligands facilitates selective initial binding of the nitrile, inducing an η^1-$(IPr)_2Ni(NCR)$ catalytic resting state.

Chapter 2 then reports on the reaction of $Ni(COD)_2$, IPr, and nitriles to afford dimeric $[Ni(IPr)RCN]_2$ in high yields. These dimers are catalytically competent in the formation of pyridines from the cycloaddition of diynes and nitriles, wherein the dimeric state was found to be largely preserved throughout the reaction. Observations suggest a mechanism whereby the catalyst is activated by partial dimer-opening followed by binding of exogenous nitrile and subsequent oxidative heterocoupling, leading to pyridine products.

Comparative investigations into the mechanism of the cycloaddition of diynes

and nitriles catalyzed by a complementary $Ni(COD)_2$/Xantphos catalyst are discussed in Chapter 3. Kinetic analysis of two Ni/Xantphos catalysts reveal zeroeth-order in all substrates but catalyst, suggesting a (Xantphos)Ni(diyne) resting state with rate-limiting partial phosphine dissociation.

Chapter 4 then describes the discovery of cyanamides as highly active substrates for cycloaddition with alkynes and diynes. The observed reactivity was further investigated by utilizing a number of cyanamides with diverse functional groups. A variety of bicyclic *N*,*N*-disubstituted-2-aminopyridines were prepared from both terminal- and internal-diynes with cyanamides in a selective manner. Two examples of three-component cycloadditions were conducted and found to be selective and high yielding.

Chapter 5 expands on Chapter 4 illustrating the cross-coupling of alkyl cyanamides with a number of aryl, heteroaryl, and vinyl halide and pseudohalide coupling partners. The synthesis was possible via a modification of reported Pd-catalyzed amidation methods. The reactions proceed selectively under mild conditions with reasonable reaction times in moderate to excellent yields.

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LIST OF ABBREVIATIONS

acac – Acetylacetanato ligand

Ac – Acetyl

Ar – Aryl

ATR – Atenuated total reflectance

BINAP – (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)

Bn – Benzyl

Boc – *tert*-Butyl carboxyl

BPh_3 – Triphenylborane

BrettPhos – 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl

cat. – Catalyst or catalytic

Cp – Cyclopentadienyl ligand

COD – 1,5-cyclooctadiene

C_{sp2} – sp^2-Hybridized carbon

Cy – Cyclohexyl

eq. – Equation

equiv – Equivalents

dba – Dibenzylideneacetone

DFT – Density functional theoryDIBALH – Diisobutylaluminum hydride

DMAD – Dimethyl acetylenedicarboxylate

DMSO – Dimethylsulfoxide

DPPE – 1,2-Bis(diphenylphosphino)ethane

DPPF – 1,1'-Bis(diphenylphosphino)ferrocene

E^+ – Electrophile

Et – Ethyl

Et_2O – Diethyl ether

FT – Fourier transform

GCMS – Gas chromatography/mass spectometry

h – Hours

HMBC – Heteronuclear multiple-bond correlation spectroscopy

HSQC – Heteronuclear single-quantum correlation spectroscopy

IAd – 1,3-di(adamantan-1-yl)imidazol-2-ylidene

I^{t}Bu – 1,3-di-*tert*-butylimidazol-2-ylidene

ICy – 1,3-dicyclohexylimidazol-2-ylidene

IMes – 1,3-dimesitylimidazol-2-ylidene

IPr – 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene

^{i}Pr – isopropyl

IR – Infrared spectroscopy

KO^{t}Bu – Potassium *tert*-butoxide

KHMDS – Potassium bis(trimethylsilyl)amide

k_{obs} – Observed rateL – Ligand

LA – Lewis acid

M – Metal

Me – Methyl

MeCN – Acetonitrile

MeOH – Methanol

MHz – Megahertz

min – Minutes

mol% – Mole percentage

MW – Molecular Weight

NHC – *N*-heterocyclic carbene

NMR – Nuclear magnetic resonance spectroscopy

NOESY – Nuclear Overhauser Effect spectroscopy.

^{n}Pr – *Normal* propyl

^{n}Bu – *Normal* butyl

Nu – Nucleophile

ORTEP – Oak Ridge Thermal Ellipsoid Plot

OTf – Trifluoromethylsulfonate

PCy_3 – Tricyclohexylphosphine

Ph – Phenyl

PhCN – Benzonitrile

phen – 1,10-phenanthroline

PhMe – Toluene

PMB – *para*-Methoxy benzyl

PPh_3 – Triphenylphosphine

$P(^tBu)_3$ – tri-*tert*-butylphosphine

rt – Room temperature

SIPr – 1,3-bis-(2,6-diisopropylphenyl)-4,5 dihydroimidazol-2-ylidene

^{t}AmylOH – *tert*-Amyl alcohol

^{t}Bu – *tertiary* butyl

^{t}Bu – *tert*-Butyl alcohol

^{t}BuXPhos – 2-Di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl

THF – Tetrahydrofuran

TMEDA – *N,N,N',N'*-tetramethyl ethylenediamine

Ts – Tosyl

X – Halogen

Xphos – 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Xantphos – 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthen

ACKNOWLEDGEMENTS

I've always considered myself a lucky person. However, as I look back, luck has had very little to do with my success. I owe everything I have in this world to those who have sculpted me. Interestingly, most of the people who have had the greatest impact are women. First and foremost, I owe my livelihood to my mother. True to form, my mother is my best friend. This is not an innate trait, rather an artifact of having *grown up together,* and it is in the direct observation of my mother overcoming innumerable obstacles, often alone, that I draw all inspiration. Other influential women include my aunt Karen, Jodi Katz, Hiroko Ward, Carol Murphy, Cindy Browder, my love, Jourdan Goode, and of course, my advisor, mentor, and reluctant friend, Janis Louie. I also owe a great debt of gratitude to my grandfather and fellow scientist, Glen Campbell, for instilling an interest of the universe and the opportunity to explore it.

At the University of Utah, I have had the opportunity to work with excellent scientists and some of the greatest friends of my life. In no particular order, I have to thank: Jessica Johnston, Josh Sussman, Tim Lane, Robert DeMille, Dr. Puneet Kumar, Dr. Kainan Zhang, Dr. Rodrigo Cella, Dr. Amber McConnell, Dr. Chris Kareis, and Dr. Tim Cook. I am also sincerely grateful for my excellent graduate committee for patiently pushing me hard to succeed. Finally, thanks to my recurring advisor and longtime friend, Dr. Monte Helm, for all the opportunities he has provided me.

CHAPTER 1

MECHANISTIC EVALUATION OF THE NI(NHC)$_2$-CATALYZED CYCLOADDITION OF ALKYNES AND NITRILES TO AFFORD PYRIDINES*

Abstract

A thorough mechanistic evaluation of the Ni(IPr)$_2$-catalyzed [2+2+2]-cycloaddition of diynes and nitriles was conducted. Through kinetic analysis of these reactions, observed regioselectivities of the products, and stoichiometric reactions, Ni(IPr)$_2$ appears to catalyzed the cycloaddition by proceeding via a heterooxidative coupling mechanism, contrary to other common cycloaddition catalysts. Reaction profiles demonstrated strong dependence in nitrile, resulting in variable nitrile-dependent resting states. Strong coordination and considerable steric bulk of the carbene ligands facilitates selective initial binding of nitrile, forcing a heterocoupling pathway. Following nitrile coordination are a rate-determining hapticity shift and subsequent loss of carbene. Alkyne coordination then leads to heterooxidative coupling, insertion of the pendant alkyne, and reductive elimination to afford pyridine products.

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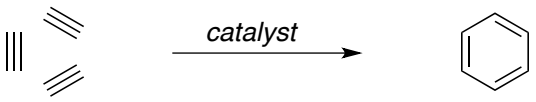
Introduction

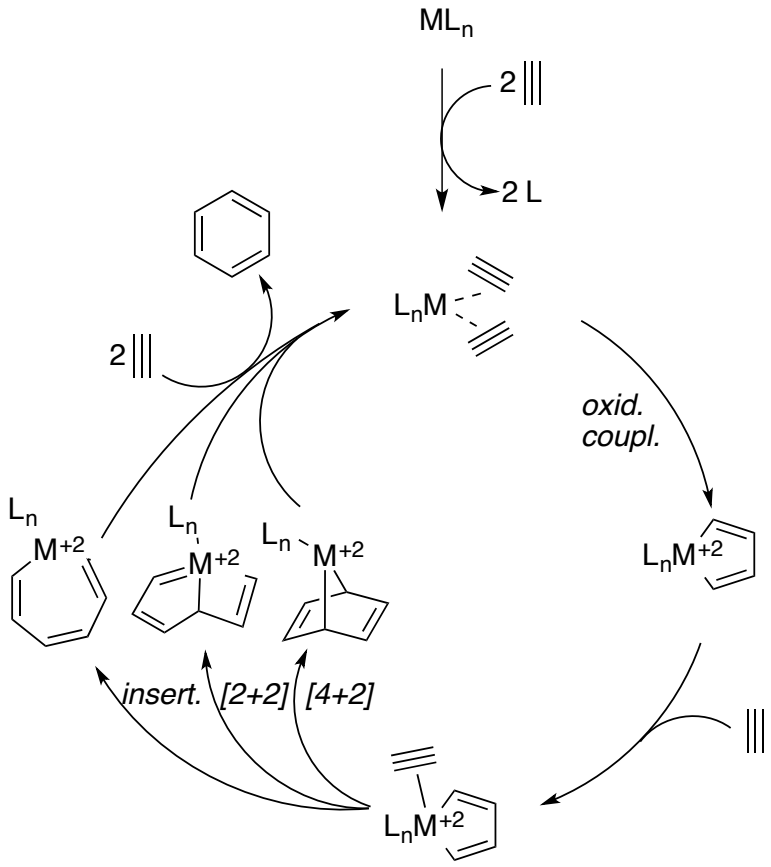
Although thermal [2+2+2]-cycloadditions of alkynes to afford arenes are thermally allowed, the high kinetic barriers and, in particular, the entropic costs of these three component reactions render this approach useless.[1] These problems can be alleviated by the use of a transition metal catalyst by reducing these substantial barriers into accessible steps.



(1.1)

The transition metal-catalyzed cyclotrimerization of three alkynes is easy to envision mechanistically (Scheme 1.1) whereby two alkynes displace labile or hemilabile ligands of a precatalyst bound to a low valent metal center and subsequently undergo 2-electron oxidative coupling. Insertion of another alkyne can then occur in three proposed ways: via alkyne insertion into a M–C bond, formal [2+2]-cycloaddition, or by direct [4+2] cycloaddition. Theoretical studies suggest the latter due to the low barrier of the [4+2] cycloaddition in combination with the symmetry-forbidden reductive elimination from a metallocyclohepatriene, although recent evidence suggests [2+2]-cycloaddition may be operative.[2] Reductive elimination from these proposed metallocycles then afford aryl products and regenerate the catalyst.[3]

Due to the symmetry afforded by using three equivalent alkyne-coupling partners, an analogous mechanistic scenario becomes incomplete when applied to the cocyclization of two alkynes and nitriles. In this situation, two divergent mechanistic pathways are possible: the homocoupling pathway proposed for cyclotrimerization, in which



Scheme 1.1. Proposed Mechanism for the Transition Metal-Catalyzed Cyclotrimerization of Alkynes.

homooxidative coupling of two alkynes occurs, or alternatively, a heterocoupling pathway wherein heterooxidative coupling of one alkyne and a nitrile is invoked. Alkyne cyclotrimerization is generally favored over cocyclization and for this reason, nitriles are generally used in excess (3–10+ equiv) in attempts to circumvent cyclotrimerization of alkynes. Incorporation of more than one nitrile is rarely a concern as transition metal-mediated dimerization and trimerization is generally not thermally or kinetically competent in the presence of alkynes.[4]

The most commonly invoked mechanism for the cocycloaddition of alkynes and nitriles is a homocoupling mechanism (Figure 1.1) wherein metal-mediated homooxidative coupling of two alkynes affords metallocyclopentadiene. Nitrile coordination is proposed to be favored at this stage due to the higher affinity of low-valent metals to more π-acidic alkynes over more σ–donating nitriles and the better Lewis acid/base match of the oxidized M^{+2} and nitriles. This nitrile-bound metallocycle is then followed by insertion of nitrile into the M–C bond, formal [2+2]-cycloaddition, or [4+2]-cycloaddition, with subsequent reductive elimination. The alternative heterocoupling mechanism is less commonly proposed. This route begins with metal-mediated heterooxidative coupling, followed by insertion of the pendant alkyne to generate the insertion or [4+2]-cycloaddition intermediate, which once again reductively eliminates pyridine, reforming the catalyst. To discriminate between these pathways, a number of mechanistic studies have been conducted for a variety of systems (*vide infra*). The most commonly utilized catalysts for the [2+2+2]-cocycloadditions of alkynes and nitriles (and [2+2+2]-cycloadditions in general) are $Cp^xCo^IL_n$ complexes. Seminal works of Yamazaki,[5] Bönneman,[6] and Hardt (at Lonza AG)[7] demonstrated the homogeneous

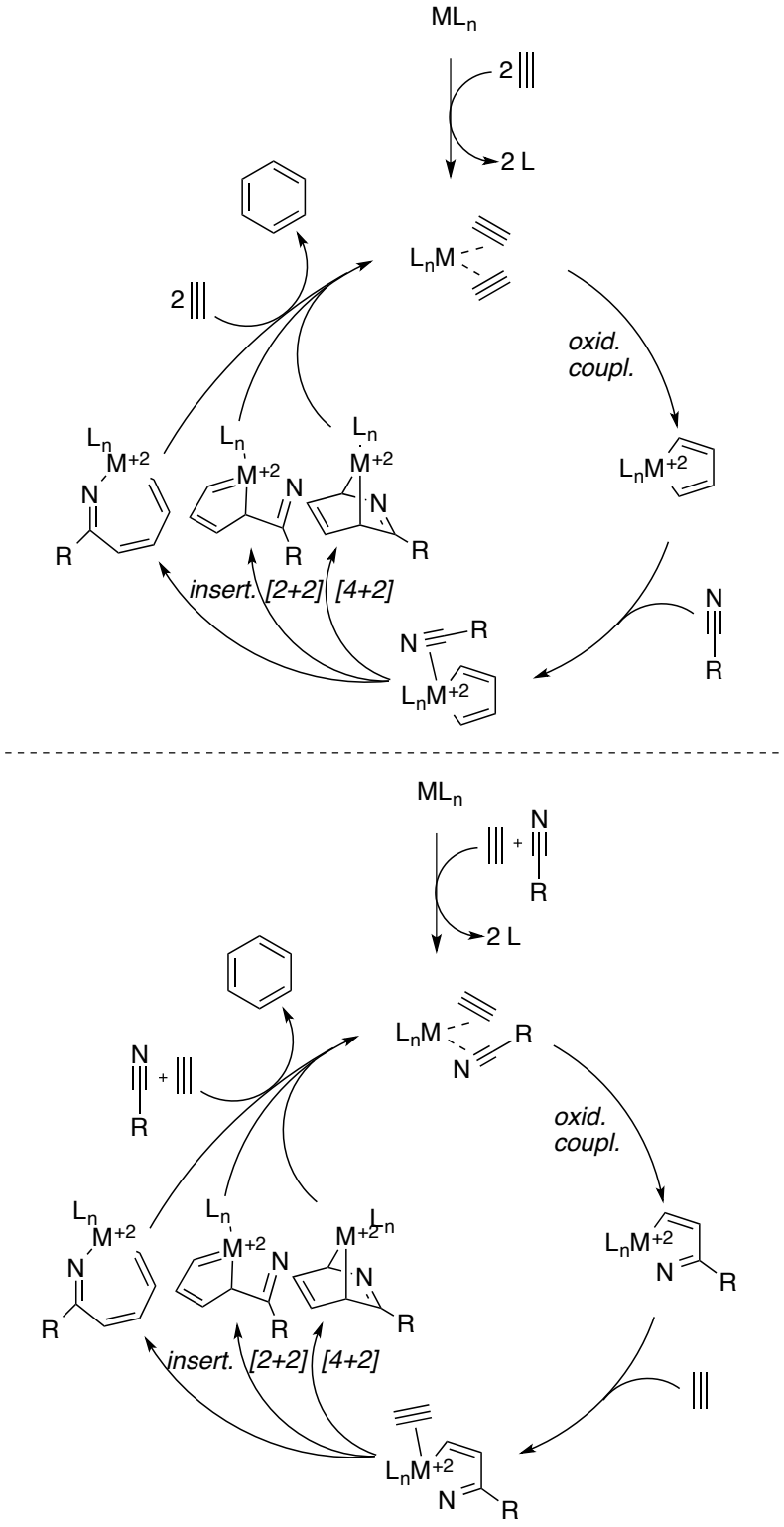
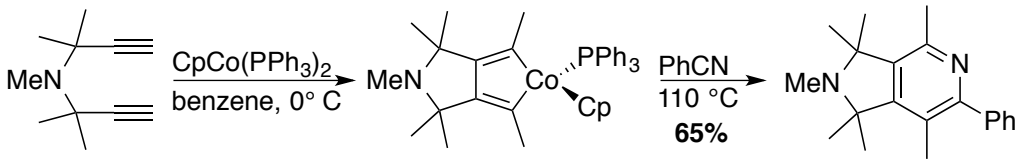


Figure 1.1. Divergent Mechanisms for the Transition Metal-Catalyzed [2+2+2]-Cocycloaddition of Alkynes and Nitriles.

formation of pyridine by subjecting a number of cobaltacene compounds to alkynes in the presence nitriles. The lability of ligand(s) (L) are paramount to the activity of the catalyst. This property, however, also relates to the stability and subsequent handling of the precatalyst. Ligands of choice include ethylene, CO, and COD.[8] Initial mechanistic investigation revealed that in the presence of alkynes and nitriles, Cp^xCoL_n-based catalysts undergo L-dependent ligand substitution to afford $Cp^xCo(alkyne)_2$-complexes. The alkynyl-substituents then oxidatively couple to form cobaltacyclopentadiene intermediates. Cobaltacyclopentadiene complexes have been isolated from the reaction of $CpCoL_n$ and substituted 1,6-heptadiynes[9] and have been shown to form pyridines in high yields upon exposure to nitriles (eq. 1.2).



(1.2)

These observations lend credence to a homocoupling pathway. In unsymmetrical alkynes, the regioselectivity in this intermediate is determined almost entirely by steric factors wherein, to avoid negative steric interactions, at least one alkynyl-substituent is placed α to the Co-atom. When Cp^x is small, 2,5-substitution predominates, whereas when Cp^x is bulky, 2,4-substitution dominates. The nitrile substituent is always placed toward the least-hindered Co–C bond[10] (Figure 1.2).

In addition to the mechanistic proposals derived from observations of the coordination and homooxidative coupling of alkynes and the reactivity of cobaltacyclopentadienes toward nitriles, a number of computational studies, Cobalt-catalyzed [2+2+2]-cocycloadditions of alkynes and nitriles toward nitriles, have been

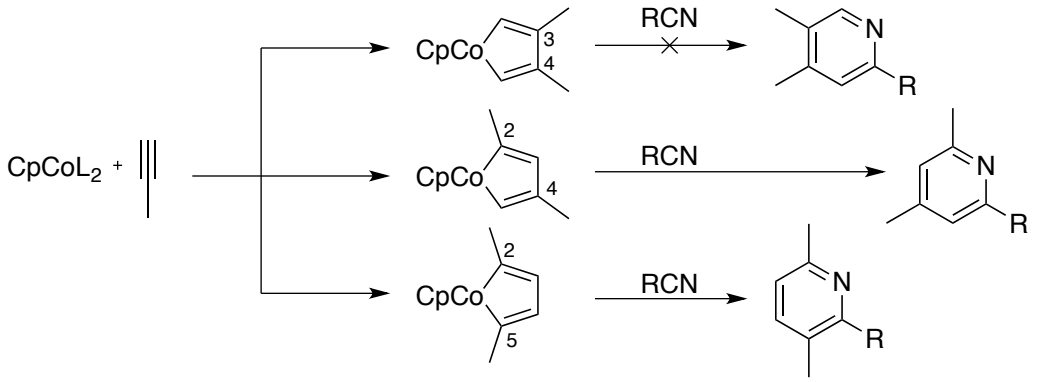


Figure 1.2. Possible Cobaltacyclic Intermediates and their Resultant Pyridine Isomers.

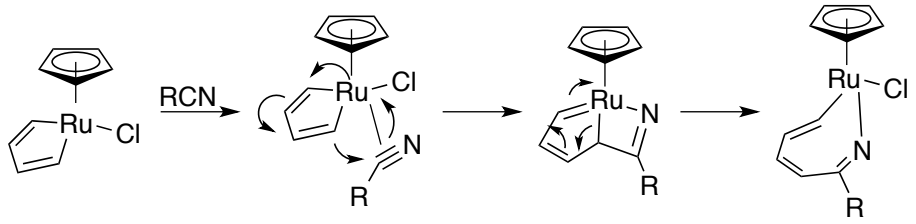
conducted. Kirchner investigated the cocycloaddition of acetylene and HCN catalyzed by CpCo(COD) from both homo- and heterocoupling approaches by means of DFT/B3LYP calculations.[11]

In this study, they describe a mechanistic scenario wherein the COD ligand is substituted by two acetylenes to give a bis-alkyne complex. Oxidative cyclization follows to give a cobaltacyclopentadiene. Hydrogen cyanide binds to cobalt in an η^2 fashion and inserts to give a cobalt–carbene complex indicative of a formal [2+2]-cycloaddition insertion mechanism. Reductive elimination leads to the cobalt–pyridine complex, which in turn is displaced by two acetylene molecules. This stands in stark contrast to the conclusions Koga inferred from a similar study[12] wherein [2+2+2] cycloaddition of acetylene with acetonitrile was also calculated by means of DFT calculations. Homocoupled cobaltacyclopentadiene then reacts with acetonitrile, which undergoes [4+2]-cycloaddition followed by retrocyclative reductive elimination. In the same study, an analogous [2+2]-cycloaddition insertion pathway, such as that proposed by Kircher, was investigated. In this case, a reasonable energetic pathway from the homocoupled metallacycle to the carbene intermediate was not found and was ruled out. However, a

later study by the same authors revealed that the [2+2] insertion mechanism was found to be operative for HCN or CF_3CN. As such, the authors propose that the electronic effect of the nitrile substituent on the frontier orbitals dictates the operative pathway whereby electron-rich nitriles undergo [4+2]-cycloaddition, whereas electron-deficient nitriles undergo insertion.[13] Interestingly, electron-deficient nitriles are generally poor substrates for cycloaddition. The origin of this is believed to be two-fold: the lower donating ability of electron-deficient nitriles to the metal center and sluggish insertion of the nitrile.

Second to cobalt, ruthenium-based cycloadditions are the most commonly used and, as such, well studied mechanistically. In a similar motif to isoelectronic Co^I complexes, the most active Ru^{II} catalysts take the form of $Cp^xRuX(L)$, (where X = halogen) with the most prominent catalyst being Cp*RuCl(COD). Pioneering works of Itoh demonstrated the aptitude of these Ru-catalysts in the cycloaddition of alkynes or diynes and electron-deficient nitriles. The use of alkyl or aryl nitriles resulted in low to zero conversion of nitrile. This limitation was later overcome if the aryl or alkyl substituent bears a coordinating moiety (OR, NR_2, SR, alkynyl, etc.) in close proximity to the nitrile.

Mechanistically, on the basis of density functional theory (DFT) calculations, Itoh and others have reported the novel alkyne cyclotrimerization mechanism, in which the intermediacy of an unprecedented ruthenabicyclo[3.2.0]heptatriene was proposed for the conversion of a ruthenacyclopentadiene-alkyne complex to a seven-membered ruthenacycle complex (eq. 1.3).[14] This mechanism was later proposed to be operative in cobalt-catalyzed cycloadditions by means of DFT calculations (*vide supra*). The intermediacy of a bicyclic carbenoid intermediate was later supported by the isolation of



(1.3)

a relevant iridabicyclo[3.2.0]heptatriene characterized by X-ray crystallography.[15]

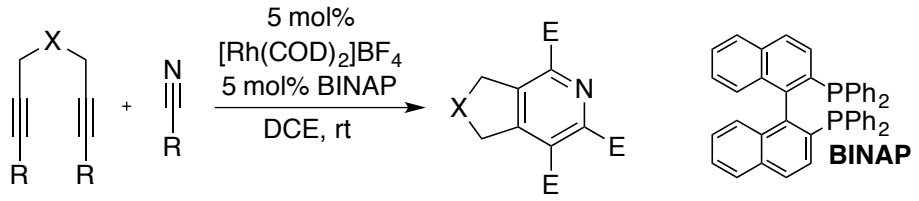
The aforementioned DFT calculations of model reactions showed that the CpRuCl(COD) catalyzed cyclocotrimerization of acetylene with CF_3CN starts with the oxidative cyclization of two acetylene molecules producing a ruthenacyclopentadiene intermediate. The formal [2 + 2] cycloaddition of the ruthenacycle intermediate with the C≡N triple bond gives rise to the azaruthenabicyclo[3.2.0]-heptatriene, and its transformation into the final η^1-pyridine complex takes place via the azaruthenacycloheptatriene complex. The rate-determining step of the overall process was determined as the initial oxidative cyclization of the alkynes. DFT calculations also suggested that the [2 + 2] cycloaddition of the ruthenabicycle intermediate with CF_3CN takes place at the more electron-rich substituent of the ruthenacycle, in accordance with the observed regioselectivity. Interestingly, a *heterocoupling* pathway is proposed for the three-component intermolecular cyclization. This hypothesis was drawn from the observed regiochemistry of the cycloaddition of ethyl cyanoformate and ethyl propiolate.

Of the four possible regioisomers, only the 2,5- 3,5-substituted isomers were formed, which suggest the intermediacy of a ruthenapyrrole intermediate (Scheme 1.2).[16] As with ruthenium, initial investigations of Rh-catalysts followed the motif laid out by cobalt-based systems. Recent DFT studies[11,17] have revealed the mechanism of catalyzed cycloadditions by the CpRh fragment is essentially the same heterocoupling mechanism

described with CpCo as catalyst, but is slightly energetically disfavored (Figure 1.1). The general prevalence of a bicyclic carbenoid intermediate in the cocyclization process is closer to the mechanisms catalyzed by CpRuCl, for which similar intermediates were proposed. The formation of benzene is thermodynamically favored in agreement with the experimental findings in analogy with cobalt-analogues and that an excess of nitrile is required to obtain good yields of pyridine. Unlike cobalt, in the presence of acetonitrile, a nitrile molecule competes with acetylene to coordinate to the rhodacene fragment, perhaps leading to the higher efficiency observed for these systems despite being thermally disfavored versus cobalt-analogues. While highly active, rhodacene-based catalysts have fallen out of favor. With Cp or Cp* metal complexes, modulation of the reactivity of the catalysts is difficult by tuning the steric and electronic effects of the Cp ligand since the introduction of substituents to the Cp ligand can require considerable synthetic operations. Forays into modification of Cp ligands have primarily demonstrated only minor effects. Electron donor substituents on the Cp make the catalyst less able to promote the cocyclization of alkynes and nitriles, whereas electron-withdrawing substituents enhance catalytic activity but diminish regioselectivity.

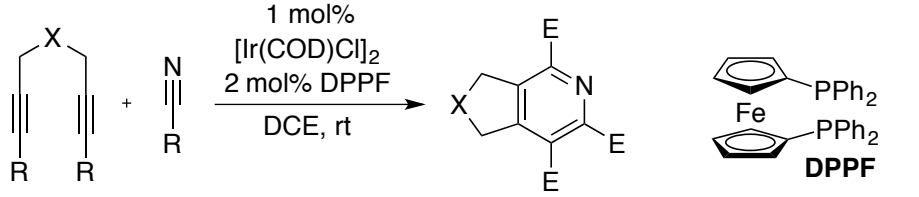
Alternatively, a wide variety of electronically and sterically different phosphines are now commercially available. The catalytic activity can be systematically modulated,both electronically and sterically, by choosing a suitable phosphine ligand, which in turn can selectively tune product chemo-, regio-, and enantioselectivity. In one of the first systems to utilize this property, Tanaka has demonstrated highly efficient cationic Rh^{I}/BINAP catalysts (eq. 1.4).[18] Although well developed synthetically with a broad and diverse substrate scope, mechanistic investigations into these systems are

lacking; however, regioselectivity is indicative of a traditional homocoupling pathway (Scheme 1.3).



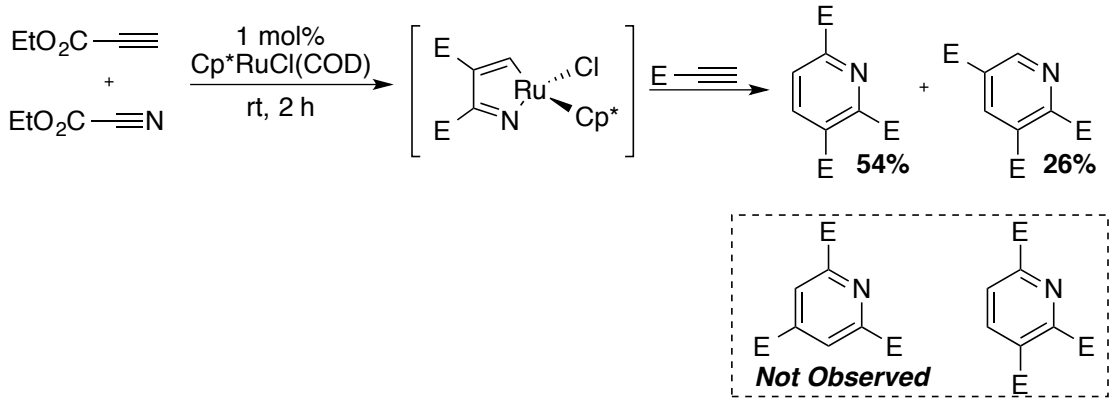
(1.4)

Recently, an outstanding study of the first iridium-catalyzed cycloaddition of diyne and nitriles was reported, building on the work of Tanaka and the well-established field of Iridium-catalyzed cyclotrimerization of alkynes.[19] The use of $[Ir(COD)Cl]_2$ in combination with a chelating phosphine such as DPPF or BINAP was found to be a robust (2 mol% [Ir]) catalyst with a broad substrate scope (eq. 1.5).

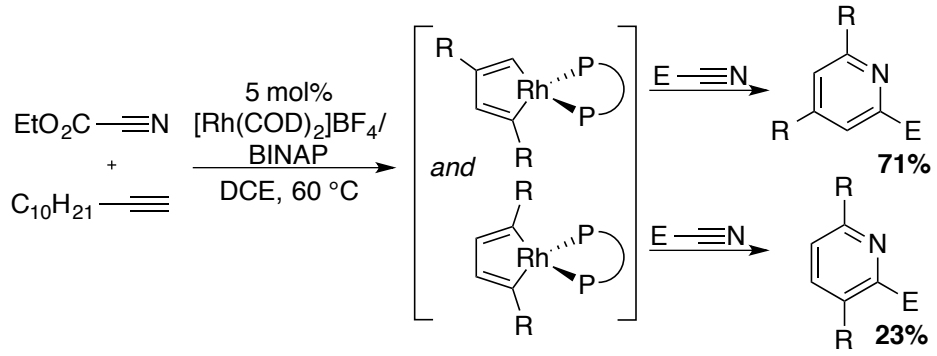


(1.5)

Expanding on models used for the Iridium-catalyzed cyclotrimerization of alkynes, DFT calculations of the reaction pathway were undertaken. Similar to the previously mentioned catalysts, homooxidative coupling of the diyne is operative and rate-limiting. Insertion of nitrile follows suit with rhodium and ruthenium whereby coordination of the nitrile is followed by formal [2+2]-cycloaddition to afford a azametallobicyclo[3.2.0]heptatriene, which reductively eliminates pyridine, reforming the



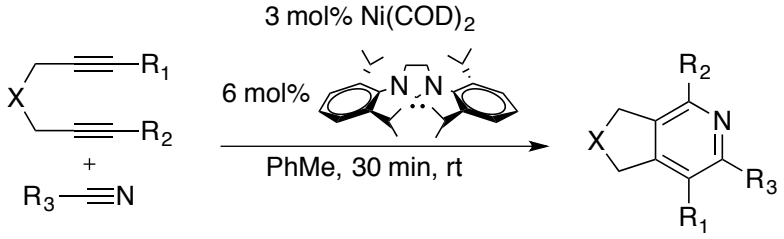
Scheme 1.2. Observed Regiochemistry in the Ruthenium-Catalyzed Cycloaddition of a Nitrile and Terminal Diynes Indicating a Heterocoupling Pathway.



Scheme 1.3. Observed Regiochemistry in the Rhodium-catalyzed Cycloaddition of a Nitrile and Terminal Diynes Indicating a Heterocoupling Pathway.

catalyst.

Through both DFT calculations and thorough regioselectivity studies, nitrile insertion is controlled exclusively by the electronic environment of the *diyne substituents* wherein nitrile insertion will occur at the more electron-rich Ir–C bond. Recently, we have developed the first catalytic system for the nickel-catalyzed cycloaddition of nitrile and alkynes (eq. 1.6).

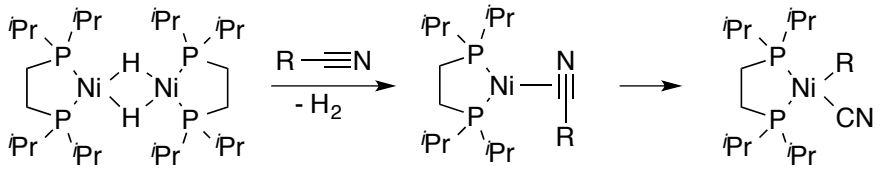


(1.6)

On the surface, the use of nickel as a catalyst is not surprising considering the similarity in reactivity of nickel and other common cycloaddition catalyst metals, which are all members of the extended "platinum-group" of metals. However, upon closer inspection, our discovery that a Ni/NHC (NHC = N-heterocyclic carbene) catalyst couples alkynes and nitriles to afford pyridines is remarkable for a number of reasons. Nickel complexes are traditionally known, like other cycloaddition catalysts, to readily catalyze the trimerization of alkynes,[20] even in the presence of excess nitrile. In addition to alkyne trimerization, surprisingly, nickel-complexes are known to also cause homooligimerization of *nitriles.* In addition to the oligermization of nitriles, nickel-complexes readily undergo oxidative addition of nitrile C−CN bonds.[21] Jones reported that aryl, alkyl, and allyl nitriles undergo facile oxidative addition onto a [Ni(dppe)] fragment generated *in situ* from a dimeric $[Ni(dppe)H]_2$ complex (eq. 1.7). In a more closely related system, $(NHC)_2Ni(NCMe)$ also undergoes oxidative addition to afford

$(NHC)_2Ni(Me)(CN)$, with a considerably higher rate than the reaction reported by Jones (eq. 1.8).[22]

The ability of nickel complexes to cleave C–CN bonds has transitioned from a novelty to a reaction of great synthetic relevance. The cleavage and subsequent rearrangement of allyl nitriles is of particular importance. The nickel-catalyzed isomerization of 2-methyl-3-butenenitrile is one of the key steps of the so-called DuPont process, one of the largest-scale applications of homogeneous transition metal catalysis.



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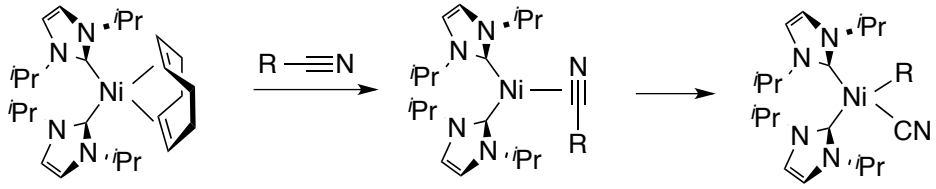
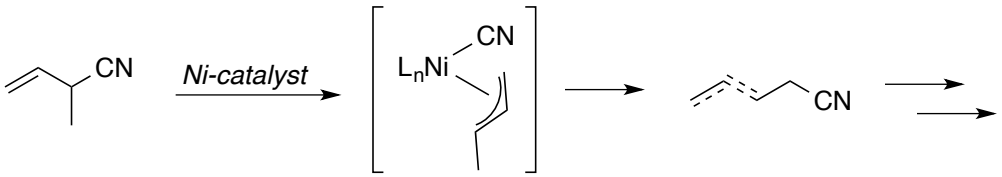


(1.8)

In a two-step process, butadiene is converted to adiponitrile (ADN) by hydrocyanation, wherein 2-methyl-3-butenenitrile is isomerized to 3- and/or 4-pentenenitriles through a η^3-allylnickel intermediate that is generated upon oxidative addition of the allylic C–CN bonds to nickel(0) species (eq. 1.9).[23] Adiponitrile is the precursor for the nylon-6.6 monomer hexamethylenediamine (1,6-diaminohexane); as such, the demand for ADN is therefore almost entirely related to that for nylon- 6.6. In 2005, the global demand was estimated to be about 1.3 million tons, 67% of which was produced by the DuPont process.[24] The problems faced by the possible oxidative addition of nitriles are further exacerbated by downstream reactions of the resultant organonickel

species.



(1.9)

Building upon the seminal work of Jones, the oxidative addition of C−CN has led to powerful carbocyanation of a variety of unsaturated C–C bonds such as alkynes, alkenes, allenes, and 1,3-dienes.[25]

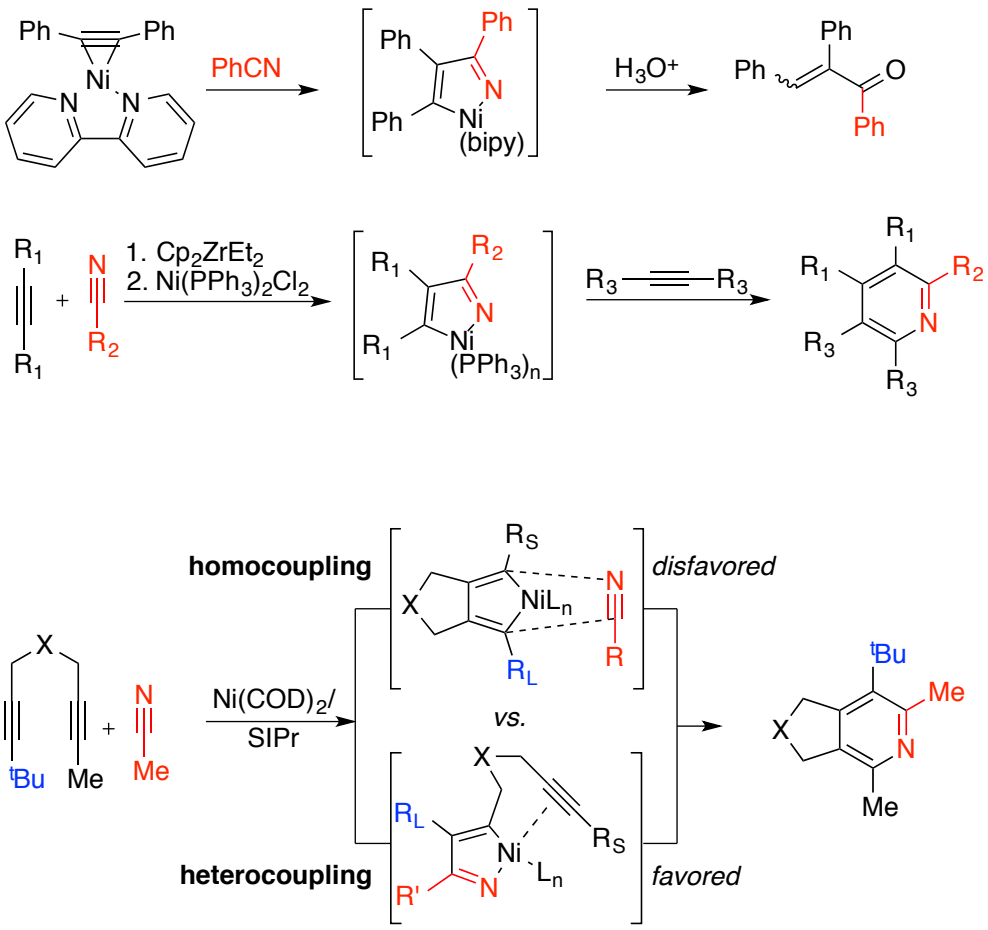
The fact that our Ni/NHC catalyst works (and very well at that) despite these obstacles is merit alone to embark into a mechanistic evaluation. However, this method does have synthetic limitations, namely a substrate scope limited to internal alkynes and fairly simple nitriles. By evaluating the apparently unique mechanistic qualities of our synthetic method, we may be able to overcome these limitations or even discover underlying trends that can lead to the development of new reactions.

In contrast to the previously outlined mechanisms, nickel-mediated pyridine formation appears to follow a different route. Although the oxidative coupling of an alkyne and a nitrile is sluggish at best for nickel,[9] and an isolable azanickelacycle has yet to be discovered (unlike other heteronickelacycles), the resultant azanickelacycles afforded from the oxidative coupling of alkynes and nitriles have been invoked in a number of transformations. Stoichiometric reactions of alkynes and azanickelacycles prepared from transmetallation between an azazirconacycles and $Ni(PPh_3)_2Cl_2$[26] afford highly substituted pyridines, suggesting that heterocoupling between a nitrile and an alkyne, rather than homocoupling of two alkynes, is operative in our method. Further anecdotal evidence of a heterocoupling pathway in our nickel-catalyzed system arises

from the observed regioselectivity of the nickel-catalyzed cycloaddition of unsymmetrical diynes and nitriles, wherein the bulkier substituent is placed adjacent to the nitrile substituent (Scheme 1.4). If a homocoupling pathway were operative, the observed regiochemistry would dictate that insertion of the nitrile would require insertion from the sterically least-accessible face. Alternatively, in order to minimize negative substrate/ligand steric interaction, heterocoupling of the bulky-substituted alkyne with the nitrile would result in the observed regioselectivity. This regioselectivity trend has also been observed in the Ni/NHC-catalyzed coupling of alkynes and aldehydes[27] (as well as isocyanates).[28] Using DFT studies, Montgomery and Houk found that regioselectivity is dictated by the steric contour of NHC ligands and demonstrated that the regioselectivities are directly affected by the shape and orientation of the N-substituents on the ligand.[29]

Results

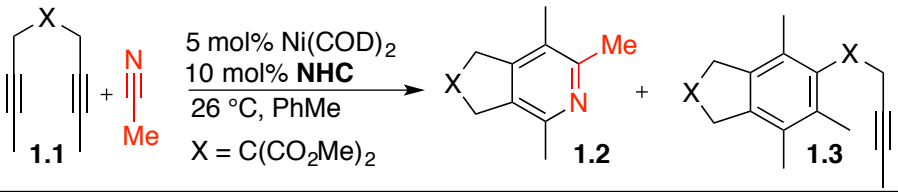
Ligand effects of the Ni(NHC)$_2$-catalyzed [2+2+2] cycloaddition of diyne 1.1 and acetonitrile. The product distribution of the cycloaddition of diyne **1.1** and acetonitrile as a function of the applied NHC ligand are shown in Table 1.1. In the Ni(COD)$_2$-catalyzed reaction without added NHC ligand (entry 1), conversion was low, and the sole product observed was dimerized diyne. Use of bulky *N*-alkyl-substituted carbenes I^{t}Bu[30], ICy,[31] and IAd[32] (entries 2, 3, and 7) afforded only dimerized diyne in 88%, 39%, and 90%, respectively. Bulky *N*-aryl-substituted NHCs such as IPr[33] and SIPr[34] afforded pyridine product exclusively in high yield. In contrast, use of the slightly smaller IMes[35] resulted in the formation of only trace pyridine product and a high yield of dimerized diyne.



Scheme 1.4. Invocations of Heterocoupling Intermediates in Nickel-Mediated Cocycloadditions of Alkynes and Nitriles.

Stoichiometric transmetallation reactions. Takahashi has previously shown that pyridines can be prepared in a stoichiometric protocol by proposed transmetallation from zirconapyrroles to $Ni(PPh_3)_2Cl_2$ followed by nickel-mediated insertion of an exogenous alkyne and reductive elimination. To draw parallels between our catalyst system and these stoichiometric protocols, we subjected complex **1.4**[36] to both zirconapyrrole **1.5** and dissimilar 4-octyne. The reaction afforded unsymmetrical pyridine **1.6** as a single regioisomer[36a] in 64% yield. The reaction of zirconapentadiene **1.7** and **1.4** with MeCN

Table 1.1. Product Ratios with Various NHC Ligands

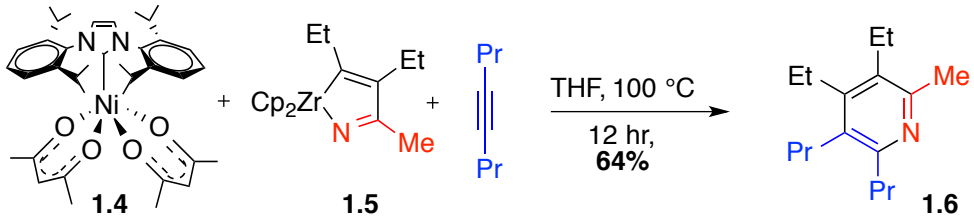


entry	NHC	conv.[a]	yield **1.2**[a]	yield **1.3**[a]
1	none	27%	0%	11%
2	I^{t}Bu	100%	0%	88%
3	ICy	41%	0%	39%
4	IMes	90%	8%	79%
5	IPr[b]	100%	94%[c]	0%
6	SIPr[b]	100%	98%[c]	0%
7	IAd	100%	0%	90%

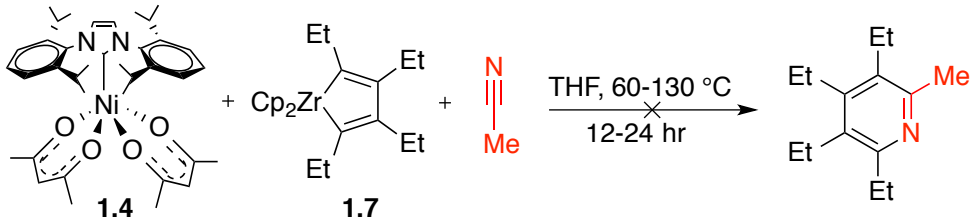
Reaction conditions: Diyne **1.1** (1 equiv, 0.25M), MeCN (1 equiv), 26 °C overnight. $Ni(COD)_2$ and NHC stirred at least 3 h prior to injection. [a]Determined by GC with naphthalene as an internal standard. [b]Diyne **1.1** (1 equiv, 0.05M), MeCN (1.2 equiv), 26 °C overnight. $Ni(COD)_2$ and NHC stirred at least 3 h prior to injection. [c]Determined by ^{1}H-NMR with ferrocene as an internal standard.

failed to produce expected pyridine product (eq. 1.11). The reaction of zirconapentadiene and **1.7** and **1.4** in the presence of diphenylacetylene, however, afforded polysubstituted benzene **1.9** in 72% yield (eq. 1.12). No reaction occurred when heating zirconapentadiene with diphenylacetylene and/or MeCN in the absence of nickel under similar conditions (eq. 1.13). Addition of excess IPr carbene to any of the reaction mixtures had no observable effect.

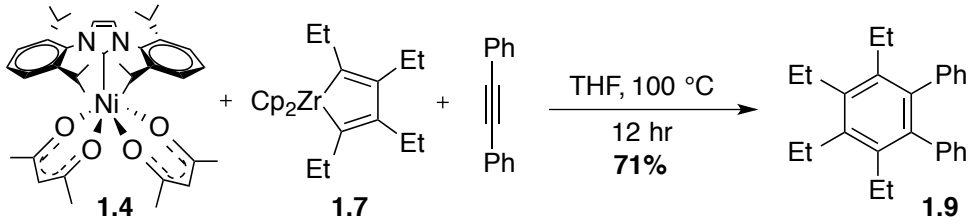
Kinetic analysis of the $Ni(IPr)_2$-catalyzed [2+2+2] cycloaddition of diyne 1.1 and nitriles. In order to avoid complications arising from the equilibrium between $Ni(COD)_2$ and the bulky NHCs (i.e., SIPr and IPr) the complex $Ni(IPr)_2$[37] (**1.10**) was employed as the catalyst in this study. For this study, we selected IPr as the operative ligand for both the ease of ligand preparation over SIPr as well as the easier preparation



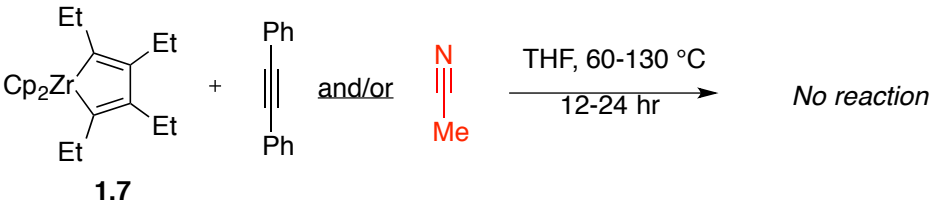
1.4 1.5 1.6 (1.10)



1.4 1.7 (1.11)

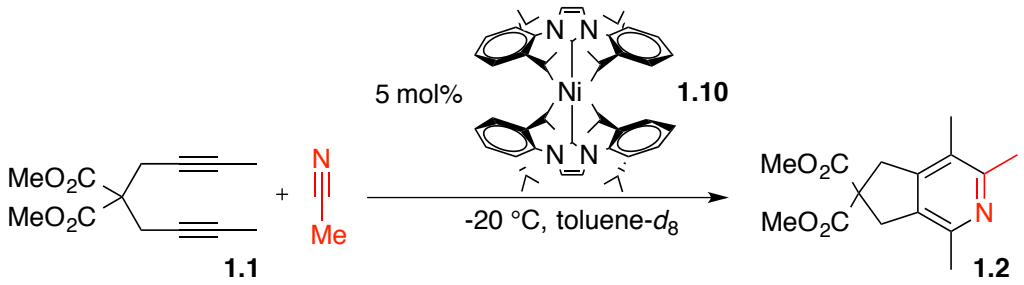


1.4 1.7 1.9 (1.12)



1.7 (1.13)

and apparent stability of $Ni(IPr)_2$ over $Ni(SIPr)_2$. The effect on the overall efficiency of the catalyst was negligible. Using the cycloaddition of diyne **1.1** and MeCN catalyzed by $Ni(IPr)_2$ **1.10** as a model (eq. 1.14), pseudo-first-order kinetic analyses were used to determine the substrate dependence of $Ni(IPr)_2$, diyne, nitrile, and IPr. Excess acetonitrile of at least five equivalents to diyne **1.1** was employed in all measurements. Experimental procedures involved addition of a solution of $Ni(IPr)_2$ in toluene-d_8 via syringe into an NMR tube containing a solution of diyne and nitrile in d^8-toluene, which was cooled to -78 °C prior to the injection.



(1.14)

The NMR tube was then maintained at this temperature until it was inserted into an NMR probe, whose temperature was already set at the desired value. We initially intended to monitor the disappearance of the diyne **1** with time by ^{1}H NMR**.** However, all the resonances of **1.1** overlapped with those of the product pyridine**1.2** ($C\underline{H}_2$ and $CO_2C\underline{H}_3$) or of the Ni(IPr)$_2$ catalyst ($CC\underline{H}_3$).

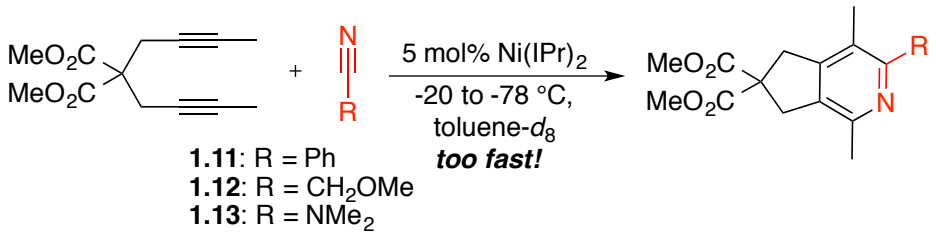
Instead, the reaction rate was calculated based on the rate at which pyridine **1.2** was formed by measurement of the 3-pyridyl methyl resonance. As indicated by ^{1}H NMR, the yields of pyridine **1.2** in all cases were always higher than 90%. At a low catalyst loading of 5 mol%, the error introduced by the resonances of the catalyst into the integration of the two terminally substituted methyl groups of diyne **1.1** ($CC\underline{H}_3$) were insignificant.

As such, determination of the rate through monitoring the disappearance of diyne **1.1** at this catalyst loading was performed and was found to be identical to the rate of formation of pyridine **1.2**. Thus, we were confident that the monitoring the formation of pyridine correlated to the loss of diyne. The concentration of pyridine **1.2** was monitored by ^{1}H NMR spectroscopy and referenced to ferrocene as an internal standard. Optimization of reaction conditions for clear and timely reaction observation resulted in the kinetic measurements being performed at -20 °C, employing 0.05 M diyne **1.1** with

varying amounts of acetonitrile, $Ni(IPr)_2$, and IPr ligand in toluene-d_8.

A linear increase of pyridine **1.2** concentration vs. time was obtained during the course of the reaction, indicating a zero-order dependence of the reaction rate on diyne (Figure 1.3a). Reaction rates remained unchanged with varying amounts of applied IPr (Figure 1.3b). As expected, the reaction rate increased linearly with increased concentration of the catalyst $Ni(IPr)_2$ (**1.10**), demonstrating first-order dependence on catalyst (Figure 1.3c). Surprisingly, reaction rates remained unchanged for various concentrations of MeCN (Figure 1.3d), indicating a zero-order dependence on nitrile and ligand. Observation of the diagnostic IPr backbone protons revealed only what appeared to be a broad $Ni(IPr)_2$ signal and small amounts of free IPr during the course of the reaction.

Upon complete consumption of diyne, facile formation of $[Ni(IPr)MeCN]_2$ was observed. In addition, the rate of $Ni(IPr)_2$-catalyzed reaction is significantly faster than that of the $[Ni(IPr)MeCN]_2$-catalyzed cycloaddition reaction. When an activated nitrile such as benzonitrile **1.11**, methoxyacetonitrile **1.12**, or dimethylcyanamide **1.13** was employed, the reaction was too fast to measure (eq. 1.15).



1.11: R = Ph
1.12: R = CH_2OMe
1.13: R = NMe_2

(1.15)

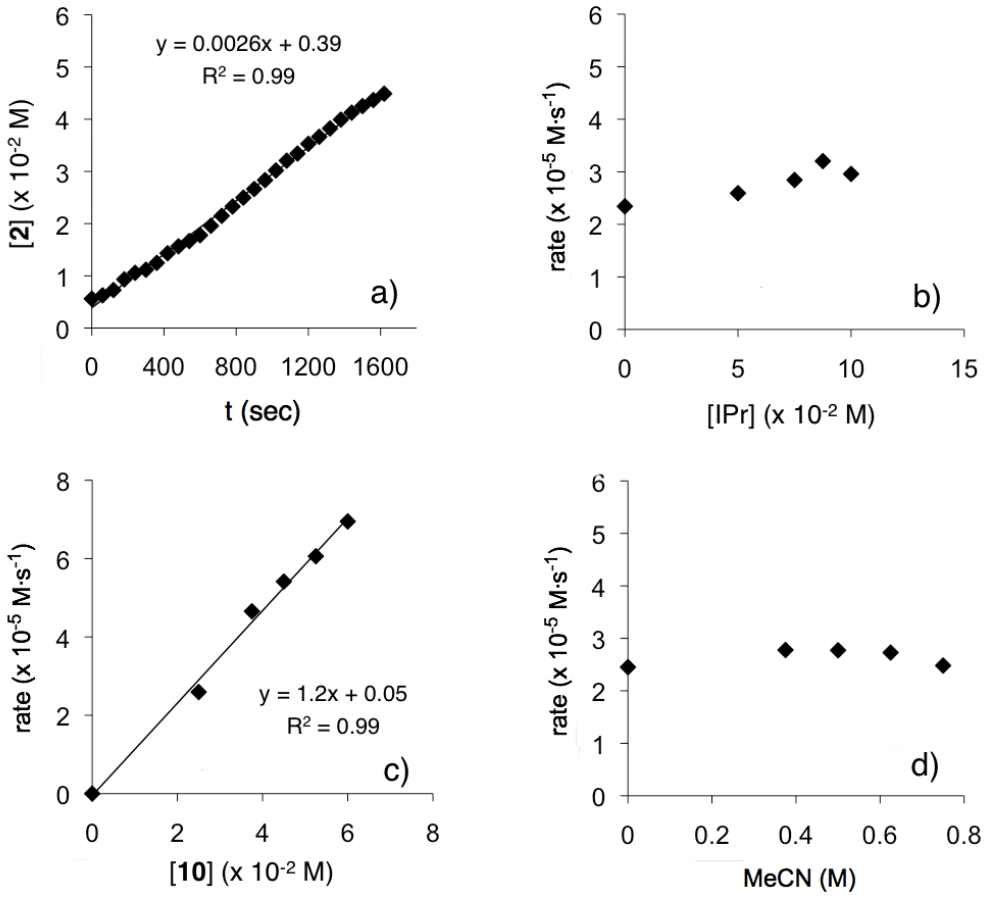
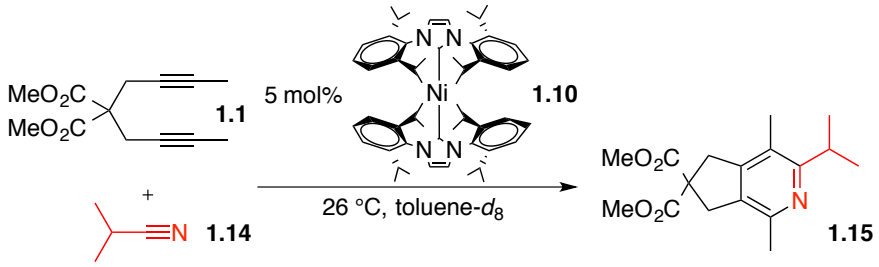


Figure 1.3. Plots of **[1.2]** vs Time, k_{obs} vs [IPr], k_{obs} vs [Ni(IPr)$_2$], and k_{obs} vs [MeCN] for the Cycloaddition of **1.1** and MeCN at -20 °C in C_7D_8.

Attempts at dilution and reduction of catalyst loading were met with inconsistency. The variance in reaction times between nitriles indicated a strong dependence of the reaction rate on the identity of the nitrile studied. The use of more sterically demanding and electron-rich isobutyronitrile **1.14**, however, allowed for comparable measurements of the reaction rate. Reaction conditions were identical to the cycloaddition of MeCN, yet significant rate depression was observed (eq. 1.16). Timely experiments were carried out at 26 °C, versus -20°C required for MeCN. The reaction with and **1.14** once again demonstrated zero-order dependence in diyne and ligand, and first-order dependence in catalyst. Contrary to MeCN, however, the reaction exhibited first-order kinetics in isobutyronitrile (Figure 1.4).



(1.16)

The only carbene species observed by ^{1}H NMR during the kinetic experiment were Ni(IPr)$_2$ and small amounts of free IPr. Investigations into diyne substitution were then undertaken utilizing more sterically demanding diynes **1.16**, **1.17** and **1.18** (eq. 1.17).

(1.17)

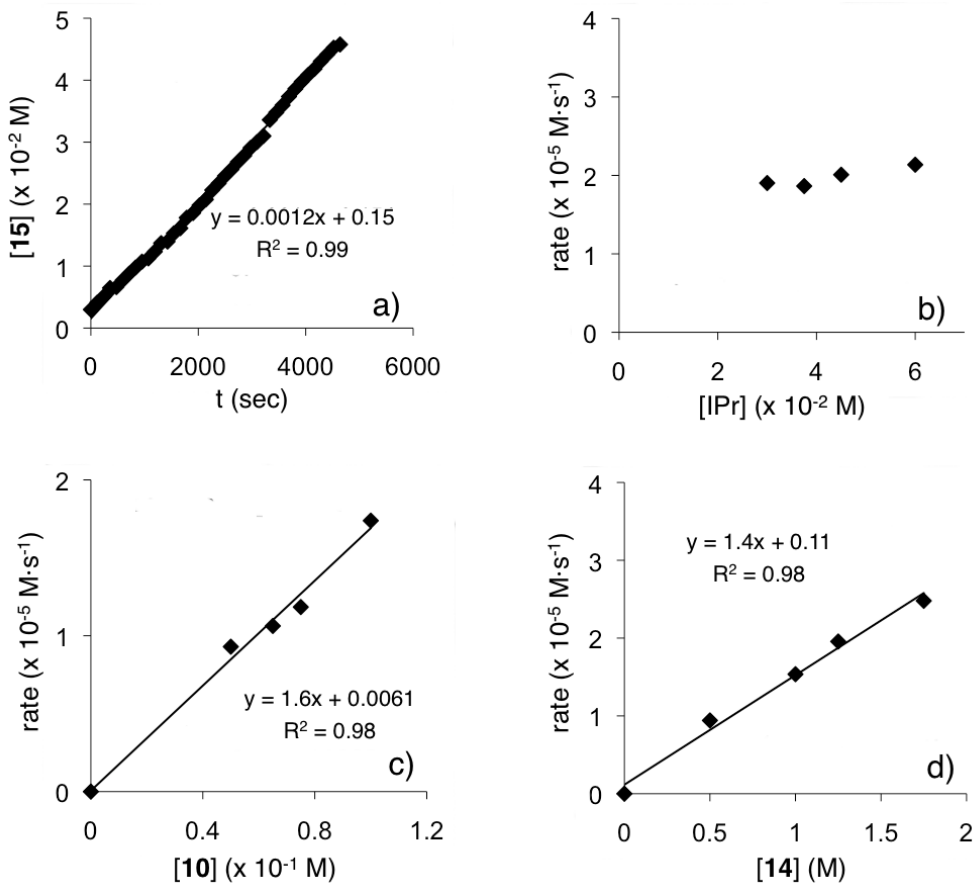


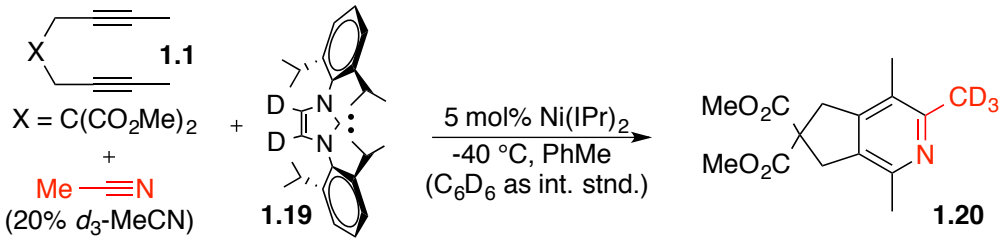
Figure 1.4. Plots of [**1.15**] vs Time, k_{obs} vs [IPr], k_{obs} vs [Ni(IPr)$_2$], and k_{obs} vs [^{i}PrCN] for the Cycloaddition of **1.1** and **1.14** at 26 °C in C_6D_6.

While **1.16** failed to deliver the desire pyridine product, **1.17** and **1.18** resulted in catalyst decomposition

Resting-state observation studies of the Ni(IPr)$_2$-catalyzed [2+2+2] cycloaddition of diyne 1 and MeCN. To better observe any possible nickel species present, we increased the catalyst loading to 30 mol% with concurrent reduction in reaction temperature to -40 °C. Observation of the cycloaddition reaction of isobutyronitrile showed a sharp Ni(IPr)$_2$ resonance, which we believe to be the sole-resting state in this reaction. However, for the cycloaddition of MeCN, the resonance we attribute to Ni(IPr)$_2$ was slightly more broad and the baseline less resolved. We believed this line broadening might correspond to another undetermined nickel species in the latter case. Due to the similarity to the chemical shift observed for Ni(IPr)$_2$ and this possible new species, we believed this may correspond to a tricoordinate Ni(IPr)$_2$X-species. Initial investigations were focused on observing a Ni(IPr)$_2$(nitrile) species. Jones and coworkers found a substantial shift (from 1.95 to 2.42 ppm, in THF-d_8) in the C**H$_3$**CN resonance upon η^2-coordination to a (dippe)Ni[38] residue. We were, however, unable to conclusively observe any new ^{1}H resonance corresponding to an η^2-bound MeCN in the reaction mixture by ^{1}H NMR spectroscopy. Changes in chemical shifts of α-protons in η^1-bound nitriles have been shown to be negligible.[39] We reasoned that lack of observation could be due to the overlap of the bound acetonitrile and an enormous resonance resulting from the use of excess free acetonitrile. In attempts to observe this resting state by eliminating overlap due to resonances from other reaction components, we performed a number of ^{2}H-observed NMR experiments. Our first experiment was in hopes of observing coordinated MeCN by partially labeling the applied MeCN with MeCN-d_3 to avoid the

extremely large resonance observed in the ^{1}H-NMR spectrum.

However, when this experiment was carried out (using C_6D_6 as an internal standard) once again, a broad resonance corresponding to only free MeCN was observed. In our work with Ni(NHC)$_n$-complexes, we have found the electronic environment of the backbone protons of the IPr ligand can be extremely sensitive to coordination environment. To observe the resting state by the nature of the carbene, we employed free IPr-d_2, once again, in conjugation with MeCN-d_3 under similar reaction conditions for ^{2}H-observed NMR experiments. During the course of the reaction we observed only MeCN-d_3 and IPr-d_2; although we did observe Ni(IPr-d_2)$_2$[40] formation from ligand scrambling (eq. 1.18).



(1.18)

We then turned our attention to possible observation of coordinated MeCN by FT IR spectroscopy. Free acetonitrile has a sharp absorption at 2280 cm^{-1} (C≡N stretch), which we felt would be diagnostic upon coordination to nickel. Nickel(II)-complexes of MeCN are common and well studied,[41] yet are irrelevant towards our proposed resting state. Nickel(0)-complexes of MeCN, however, are exceedingly rare, in particular η^1-bound MeCN complexes. However, both benzo-[42] and homobenzylic nitrile[43] η^1-bound nitrile nickel-phosphine complexes have been isolated or inferred in a number of studies. Stretching frequencies for these species are generally reduced by 50-100 cm $^{-1}$ upon η^1-

coordination to Ni^0 versus reduction of 200-500 cm^{-1} for h^2-bound species.[42d, 43]

We carried out *in situ* observation of the model cycloaddition reaction of **1.1** and MeCN via an ATR FT IR immersion probe. We initiated the experiment by cooling a solution of diyne **1.1** in toluene to -78 °C, followed by addition of MeCN. We then added an increased loading of 50 mol% $Ni(IPr)_2$ to help facilitate the observation a nickel intermediate. Due to the significant rate enhancement observed by increasing catalyst loading, we significantly reduced the reaction temperature to slow the reaction progress. Upon warming to -40 °C, we observed growth of a new resonance at 2188 cm^{-1}. This stretch was present for roughly 10 minutes. We believe the observed stretching frequency is indicative of an η^1-bound MeCN-$Ni(IPr)_2$ complex (Figure 1.5). The formation of such a species is supported by the stretching frequency that is in accordance with other η^1-bound nitrile-transition nickel complexes, and a lifetime consistent with ^{1}H-NMR observed reaction times under similar conditions.

Discussion

Consistent with general mechanistic themes in transition metal-catalyzed [2+2+2]-cocycloadditions to form pyridines; we had two straightforward mechanistic proposals (Scheme 1.5). As discussed earlier, the most commonly invoked mechanism for non-nickel catalysts is homocoupling mechanism A, wherein nickel-mediated homooxidative coupling of diyne is then inserted to form an azanickelacycloheptatriene that then reductively eliminates to form pyridine. This route begins with nickel-mediated heterooxidative coupling, followed by insertion of the pendant alkyne to generate the common azanickelacycloheptatriene (or analogous intermediate) intermediate , which

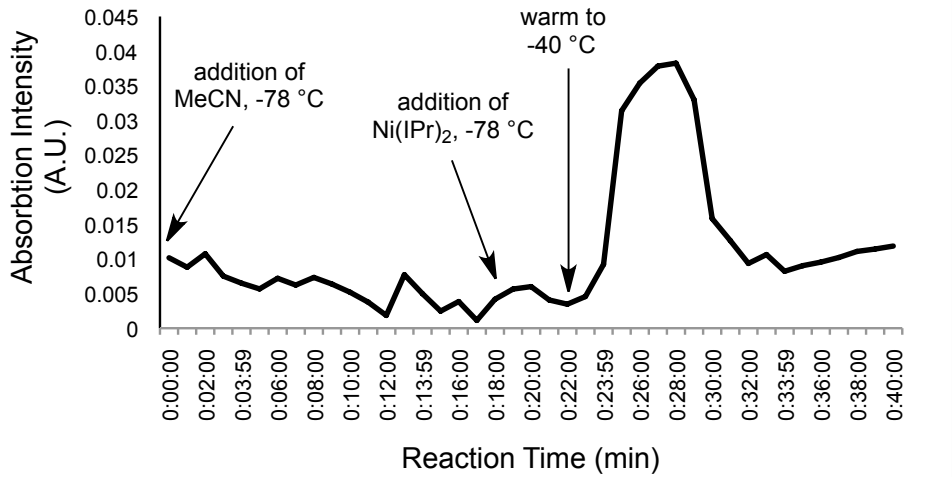
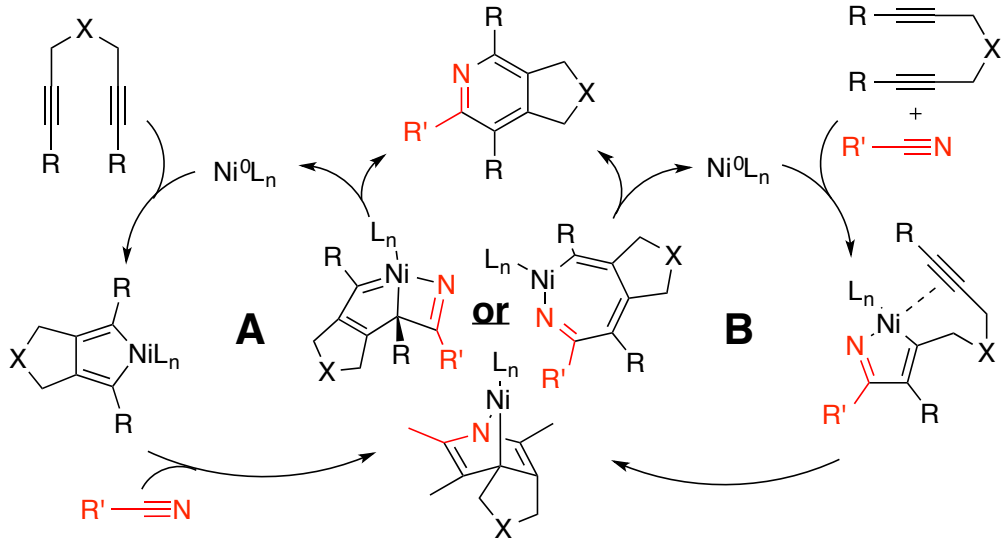


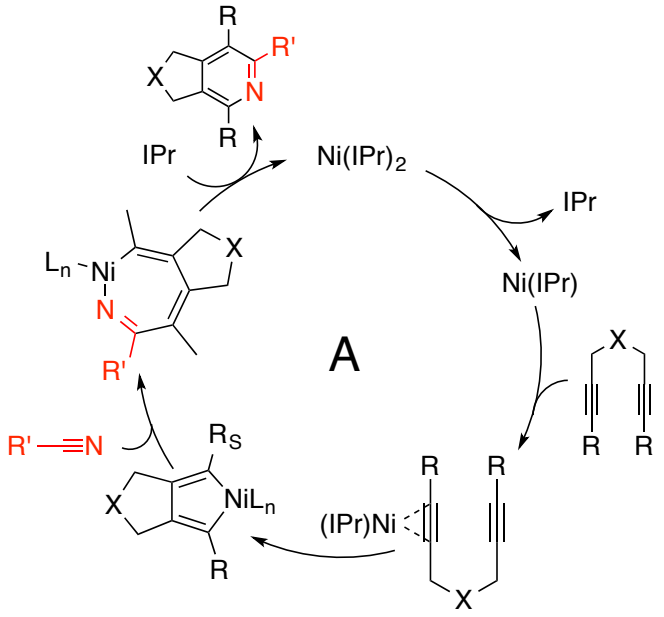
Figure 1.5. Absorption Intensity at 2188 cm^{-1} vs. Reaction Time for the Cycloaddition of **1.1** (1 equiv) and MeCN (5 equiv) Mediated by $Ni(IPr)_2$ (50 mol%).

once again reductively eliminates pyridine, reforming the Ni^0-catalyst. We proposed that the rate behavior of the reaction components could help further differentiate the two reacting pathways A and B depicted in Scheme 1.5. Presumably, oxidative coupling was the rate-limiting step as determined for other transition metal-based catalysts.[44] Pathway **A** should exhibit first-order kinetics in diyne and zero-order in nitrile (Scheme 1.6).

However, as previously illustrated, both the cycloaddition of MeCN or isobutyronitrile are zero-order in diyne. Nevertheless, the lack of order in diyne can be explained if initial ligand-loss is rate-determining, as subsequent steps would be unobservable. In addition, if ligand-loss is irreversible, we would expect zero-order dependence in ligand, consistent with our observations for both isobutyronitrile and MeCN. However, a mechanism involving rate-limiting ligand-loss and subsequent homooxidative coupling of diyne (i.e., mechanism **A**) is inconsistent with our observed rate dependence on the nature of the nitrile.



Scheme 1.5. Possible Mechanistic Pathways for the Nickel-Catalyzed [2+2+2]-Cycloaddition of Diynes and Nitriles.



Scheme 1.6. Proposed Homocoupling Catalytic Pathway.

That is, if ligand-loss is rate-determining, then the nature of the ligand would be inconsequential. Yet, we observed distinct differences in rates between reactions run with MeCN and isobutyronitrile as well as activated nitriles such as benzonitrile and cyanamide. In addition to the change of k_{obs} when modifying the applied nitrile, the *order* in nitrile also changed from zero-to first-order when isobutyronitrile was used. To accommodate for the rate effects of the nitrile in these reactions, nitrile binding would have to be before ligand-loss, which again would result in dependence in nitrile. Taken together, these results suggest a homocoupling pathway is not operative. In addition, the regioselectivity observed in the cycloaddition of MeCN with unsymmetrical diynes also appeals to a hetercoupling pathway, where, in order to minimize considerable negative substrate/ligand steric interaction, heterocoupling of the bulky-substituted alkyne with the nitrile would result in the observed regioisomer (Scheme 1.7). Similar sterics-driven regioselectivity has been observed in other Ni/NHC catalyzed coupling reactions.[45,46,47]

If a homocoupling pathway were operative, the observed regiochemistry would dictate a counterintuitive insertion of the nitrile from the sterically least-accessible face of the nickelacyclopentadiene intermediate. In addition to the regioselectivity that is typically observed in nickel-catalyzed cycloadditions of unsymmetrical diynes, our stoichiometric reactions between zirconacycles and Ni(II) salts also suggest pyridine formation can *only* occur from a nickelacycle intermediate obtained from heterooxdiative coupling.

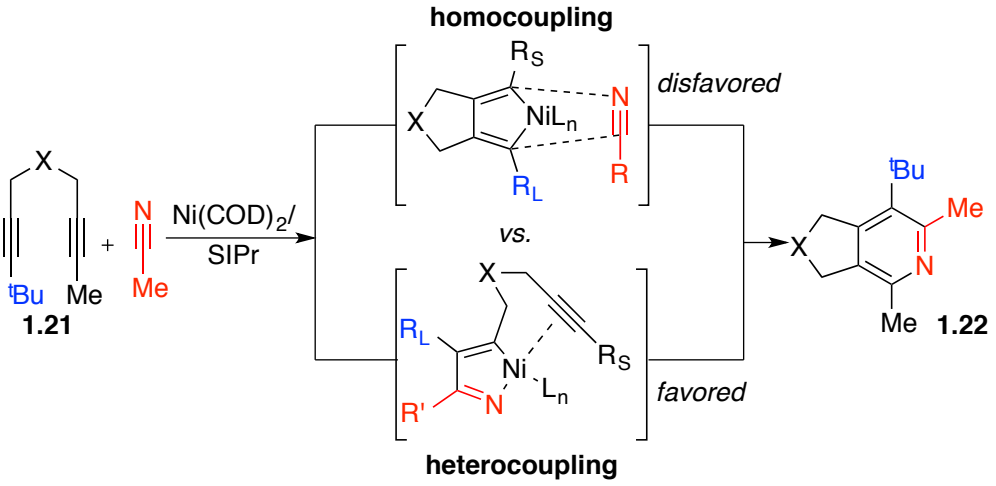
In these stoichiometric reactions (eq. 1.10-1.13), transmetallation from zirconacycles **1.7** and **1.5** to the $(IPr)_nNi^{II}$-fragment affords nickelacycles **1.22** and **1.23**, proposed intermediates in the homocoupling and heterocoupling pathways, respectively

(Scheme 1.8). Subsequent insertion of exogenous nitrile or alkyne then affords common nickelacycloheptatriene, which reductively eliminates to afford pyridine. As reported, pyridine formation only occurred from the reaction of zirconapyrrole **1.5** and 4-octyne in the presence of (IPr)Ni(acac)$_2$ (eq. 1.10).

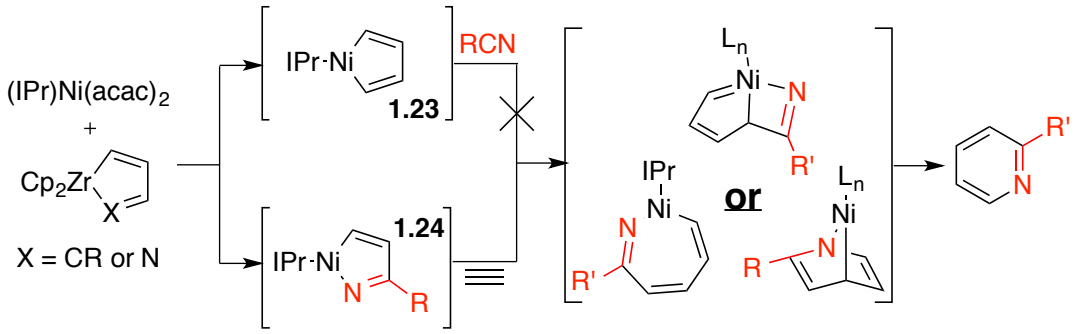
In contrast, the reaction of zirconapyrrole **1.7**, (IPr)Ni(acac)$_2$, and acetonitrile – a reaction that would produce a nickelacycle product of homooxidative coupling – failed to produce any detectable pyridine (eq. 1.11). To verify that transmetallation from zirconacyclopentadiene was occurring, zirconacyclopentadiene **1.7** was reacted with diphenylacetylene and (IPr)Ni(acac)$_2$. This reaction cleanly yielded substituted benzene **1.9** (eq. 1.12). Furthermore, zirconapentadiene **1.7** fails to produce arene products with nitrile and/or alkyne in the absence of nickel. These results support the intermediacy of heterocoupling nickelacycles along the catalytic pathway (Scheme 1.8).

Kinetic analysis. Analysis of the kinetic data for the cycloaddition of diyne and MeCN revealed rate dependence in catalyst only. We believe that this might be indicative of a dissociative pathway with rate-determining irreversible ligand-loss, as the reaction is zero-order in IPr as well (Scheme 1.9). In this scenario, if heterooxidative coupling is involved, ligand-loss would be followed by nitrile-binding.

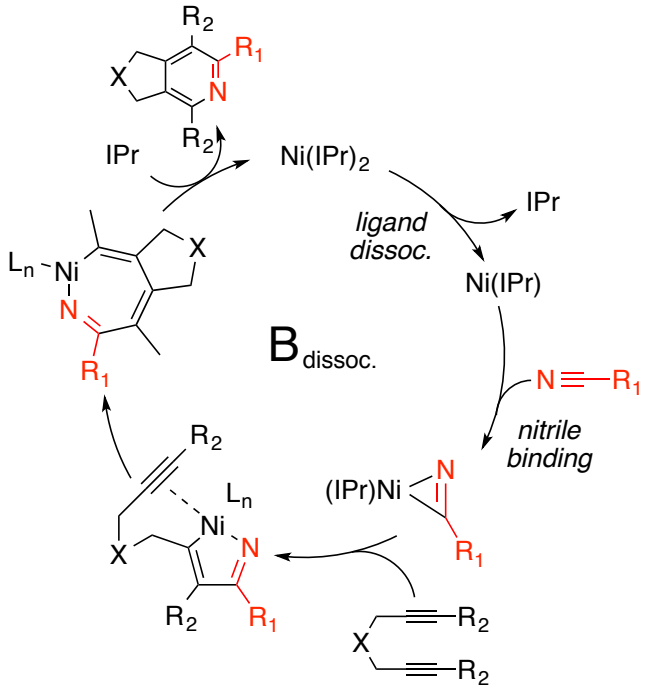
Subsequent, binding of diyne, oxidative heterocoupling, and insertion of the pendant alkyne would afford the common cycloheptatriene nickelacycle. Reductive elimination and IPr coordination would afford pyridine product and regenerate the catalyst. Unfortunately, a heterooxidative coupling mechanism initiated by rate-limiting ligand-loss does not account for the nitrile-dependent rate behavior (PhCN > MeCN >



Scheme 1.7. Proposed Intermediates for the Observed Regiochemistry in the Cycloaddition of Sterically-Biased Diynes and MeCN.



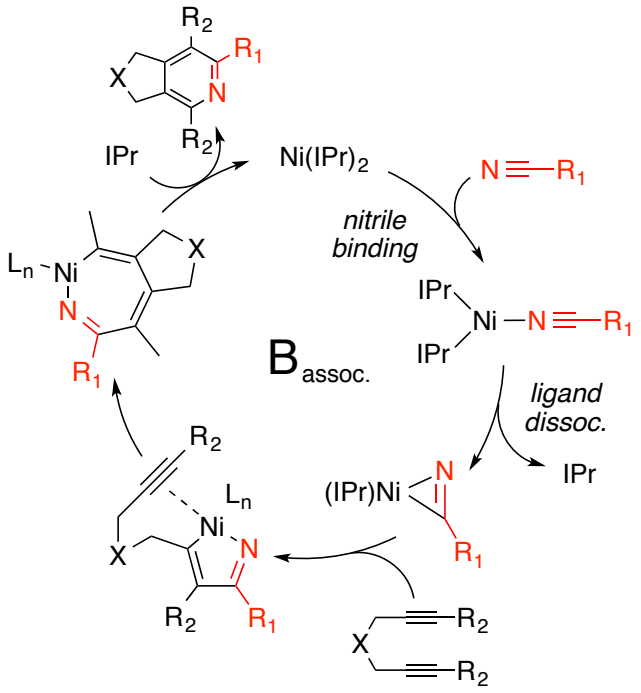
Scheme 1.8. Nickel-Mediated Transmetallitive Routes to Pyridine Formation.



Scheme 1.9. Proposed Catalytic Cycle with Initial Ligand Dissociation.

^{i}PrCN). Recall that k_{obs} changed when modifying the applied nitrile *as well as* the *order* in nitrile changed from zero- to first-order when isobutyronitrile was used. A possible explanation for the first-order dependence of reaction rate on isobutyronitrile is shown in Scheme 1.9. Ligand dissociation from $Ni(IPr)_2$ is followed by rate-determining nitrile binding to Ni(IPr). This pathway predicts a first-order dependence on nitrile and an inverse-order dependence on ligand when the ratio [nitrile]:[ligand] is small and zero-order dependence on both when [nitrile]:[ligand] is large. However, both scenarios are inconsistent with our observation that the reaction was first-order in nitrile and zero-order in ligand.

A more reasonable mechanism, one that invokes nitrile binding *prior* to ligand dissociation, involves coordination of a bulky isobutyronitrile to $Ni(IPr)_2$ to form h^1-$Ni(IPr)_2(^{i}PrCN)$ **1.25** (R = ^{i}Pr*)* as the rate-limiting step (Scheme 1.10).



Scheme 1.10. Proposed Catalytic Cycle with Initial Nitrile Coordination.

Loss of IPr then follows nitrile coordination, allowing for coordination of diyne and the subsequent coupling, insertion, and pyridine forming reductive elimination steps. Such a mechanism would be first-order in catalyst, first-order in nitrile, zero-order in ligand, and zero-order in diyne. Indeed, kinetic analysis of the $Ni(IPr)_2$-catalyzed cycloaddition of ^{i}PrCN displays this rate behavior.

Though the mechanism depicted in Scheme 1.10, with rate-limiting ligand-loss, does not concur with the kinetic data we obtained in the cycloaddition of diyne **1.1** and MeCN where a zero-order dependence in nitrile was observed. An alternative mechanism seems unlikely due to the simple dichotomy between reasonable pathways (e.g., homocoupling versus heterocoupling), and a consistent lack of order in diyne. Thus, to explain the change to zero-order rate behavior of the MeCN without invoking a completely different pathway, we believe our results point to a simple and

straightforward reason. We speculate that a new resting state η^1-Ni(IPr)$_2$(MeCN) (**1.25**, R = Me)**,** versus Ni(IPr)$_2$, exists in the reaction mixture of diyne **1.1** and MeCN.

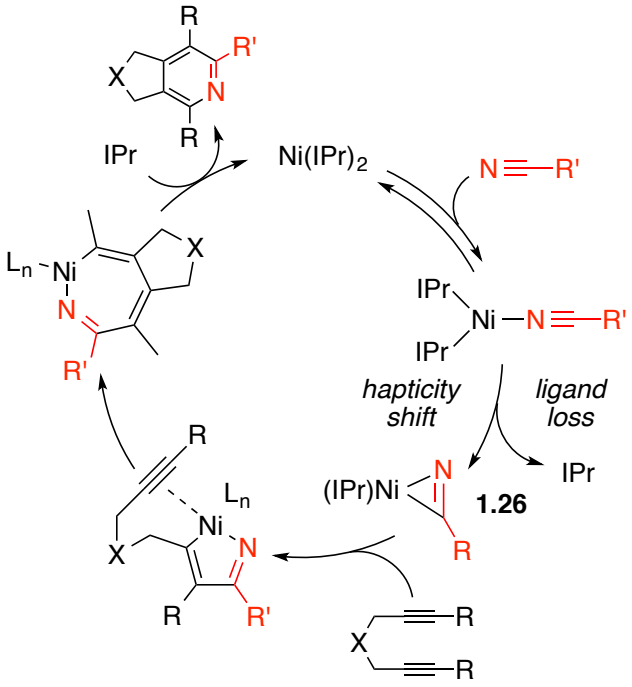
Indeed, our *in situ* IR analysis of the cycloaddition reaction supports the formation of the η^1-Ni(IPr)$_2$(MeCN) (**1.25**, R = Me) resting state (Scheme 1.10) as we observed a new nitrile stretching frequency ~100 cm^{-1} (rather than 200-500 cm^{-1}) less than free MeCN (2188 cm^{-1} versus 2280 cm^{-1}, respectively).

Although nitrile binding is prior to ligand-loss, ligand-loss is still rate-limiting. Such a mechanism, which involves the formation of a new resting-state that includes nitrile, would still display first-order in catalyst, zero-order in ligand, zero-order in nitrile, and zero-order in diyne. Our kinetic analysis of the Ni(IPr)$_2$-catalyzed cycloaddition of MeCN did indeed display this rate behavior. Both mechanistic scenarios account for the observed difference in rate-behavior between MeCN and isobutyronitrile (i.e., zero-order versus first-order, respectively). From a steric standpoint, it is easy to envision slower (hence, rate-determining) nitrile binding for the larger ^{i}PrCN relative to the smaller MeCN. Interestingly, PhCN, methoxyacetonitrile, and dimethylcyanamide all displayed rates that were distinct (and typically faster) than that for MeCN. Although these activated nitriles are larger and poorer σ-donors than MeCN, the difference in rate behavior suggests that unique η^1-Ni(IPr)$_2$(RCN)-type resting states may exist in these cycloadditions as well (*vide infra*).

We believe the hetercoupling pathway is dictated by requisite initial η^1-nitrile coordination and that this coordination is highly reversible. Productive nitrile coordination is then followed by an η^1-η^2 *hapticity shift*, which induces irreversible ligand-loss affording unsaturated nickel species **1.26** (Scheme 1.11). Such a

transformation is easily envisioned when $R_1={}^{i}Pr$, wherein nitrile coordination is sterically hindered. The hindered coordination accounts for both the reduced rate of cycloaddition as well as the observation of $Ni(IPr)_2$ as the apparent resting-state. Furthermore, both the large size and electron-rich nature of the nitrile reduce the rate of hapticity shift. Due to the small size of MeCN, coordination is facile. However, hapticity shift is reduced versus more electron-deficient nitriles (such as benzonitrile, methoxyacetonitrile, and dimethylcyanamide). These combined attributes account for the apparent three-coordinate resting state in this case. We believe the key to productive cocycloaddition lies primarily in the unique properties of the carbene ligand. Historically, a number of organometallic nickel complexes are highly active alkyne trimerization catalysts.[42d,48]

Electronically, $Ni(IPr)_2$ and $Ni(SIPr)_2$ would also fit this motif. Strong σ-donation to a coordinatively unsaturated Ni^0 would allow for facile oxidative homocoupling and subsequent insertion. The donation effect can be easily observed by the application of less sterically demanding carbene ligands to the aforementioned standard reaction conditions (Table 1.1), wherein dimerization is rampant (entries 2-4). Conversely, selective dimerization is observed when IAd is used (entry 7). We believe dimerization arises from the inability of such a sterically demanding carbene to doubly coordinate, effectively exposing the nickel-center for competitive alkyne trimerization. While other NHC carbenes facilitate dimerization, the productivity of our system then attests to steric parameters crucial for the selective binding of nitriles over alkynes with $Ni(IPr)_2$ and $Ni(SIPr)_2$. Selectivity presumably lies in the initial linear coordination motif of nitriles over the exclusive side-coordination required of internal alkynes. The steric “protection”



Scheme 1.11. Proposed Catalytic Cycle of the $Ni(IPr)_2$-Catalyzed [2+2+2]-Cycloaddition of Diynes and Nitriles.

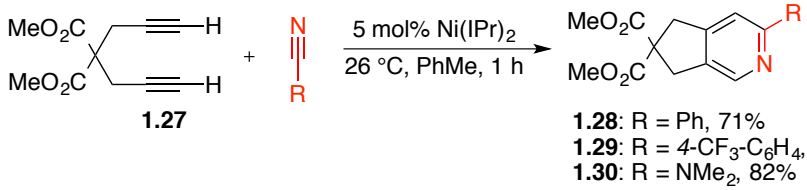
these carbenes provide is further demonstrated by the much slower rate of alkyne dimerization in the absence of nitrile and by the competitive alkyne trimerization when fewer than 2 equivalents of carbene to nickel are used. If only one carbene is coordinated to start, alkyne trimerization is competitive due to the more accessible nickel center.

As observed with sterically less demanding NHC ligands, dimerization of *internal* alkynes is favored. We believe that this may be due to alkyne's ability to reach the metal center with less sterically demanding NHCs .

Terminal alkynes pose an even greater challenge for heterocycle formation as dimerization (i.e., the formation of aromatic by-products) is more facile. Even when IPr or SIPr are employed, the linear steric availability of terminal alkynes may allow for the

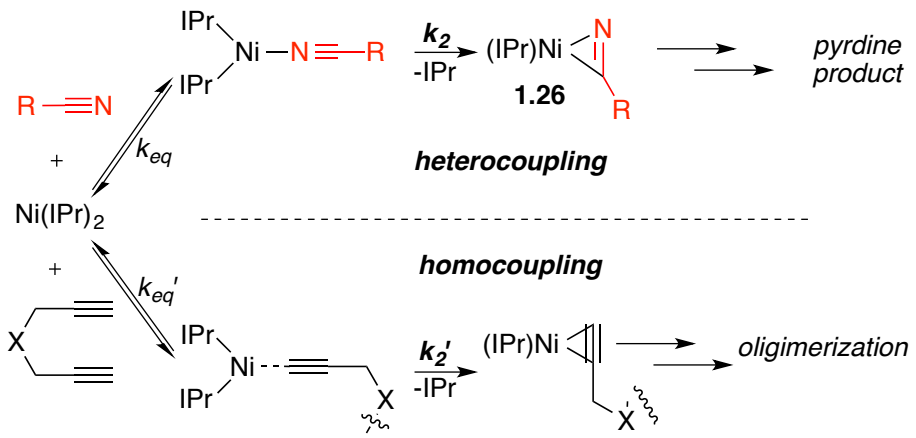
alkyne to approach the metal center to allow a reaction.

The lack of productive cycloaddition of terminal alkynes with alkyl nitriles, with complete conversion of the diyne to unknown (presumably oligimerization) products, illustrates this hypothesis nicely. Therefore, expanding upon the conclusions drawn from our mechanistic analysis, we hypothesized that if initial *linear "binding*" of nitriles and terminal diynes are competitive, the balance between the relative rates of hapticity shift may dictate the operative pathway. For productive cycloaddition, whether by homo- or heterocoupling, side-on coordination is required; and as such, the first species to access the necessary η^1-η^2 hapticity shift will dictate the operative pathway. Our hypothesis is supported by the *first* successful Nickel-catalyzed cycloaddition of a terminal alkyne**.** The key is to use electron deficient nitriles such as PhCN, 4-CF_3-C_6H_4CN, and Me_2NCN (eq. 1.19). When these activated nitriles are employed, good yields of pyridine products (**1.28**-**1.30**) are obtained. In contrast, neither MeCN nor isobutyronitrile afforded pyridine product. When the less active nitriles (i.e., species with a slower rate of hapticity shift), MeCN and ^{i}PrCN, are subjected to cycloaddition conditions with terminal diynes, side reactions of the terminal diyne out-compete heterocoupling through competitive initial end-on binding of the alkyne concomitant with a faster hapticity shift.



(1.19)

However, when more active nitriles with stronger side-on coordination are employed, the nickel catalyst gets sequestered (as **1.26**, Scheme 1.12) and is unable to



Scheme 1.12. Product Distribution as a Function of Competitive Binding of Nitriles and Terminal Alkynes.

follow the homooxidative coupling pathway required for dimerization side-products to form. Thus, activated nitriles are competitive with terminal alkynes and become viable cycloaddition partners.

In summary, a thorough mechanistic study of the Ni(IPr)$_2$-catalyzed [2+2+2]-cycloaddition of alkynes and nitriles has been conducted. Through the observed regiochemistry, stoichiometric reactions, and kinetic evaluation, we believe that the reaction proceeds by a novel heterocoupling pathway. The use of NHC ligands with finely tuned steric properties allows for the initial selective binding of nitriles over alkynes. Electronically, the strong σ-donating nature of the NHC ligands is also crucial for the stabilization of the reactive coordinatively unsaturated Ni^0 resting-state and for facile oxidative heterocoupling.

Ligand-loss and subsequent binding of an exogenous alkyne then follow nitrile binding. Oxidative hetercoupling and insertion of a second alkyne or pendant alkyne (for diynes) leads to a proto-aromatic nickelacyclic cycloheptatriene. Reductive elimination

and NHC coordination then complete the catalytic cycle. The conclusions drawn from our mechanistic analysis lead to the predicted selective cycloaddition of activated nitriles with previously problematic terminal diynes.

Future Work

While we seem to have the mechanism well characterized, continued evaluation is paramount. This endeavor can be pursued in two ways: experimentally and theoretically. Experimentally, we first intend on isolating potential reactive intermediates. This route is in continuation to the stoichiometric transmetallation reaction performed with azazirconacycles and $IPrNi^{II}$ fragments.

We plan on synthesizing proposed homo- and heterocoupling Ni(NHC) intermediates and investigating their insertion behavior with nitriles and alkynes, respectively (Figure 1.6). The synthesis of homocoupled intermediates is easily envisioned, wherein simple transmetallation from dilithio species to $IPrNiX_2$ would afford nickelacyclopentadienes. The dilithio compounds are easily accessible from known Zr-mediated oxidative coupling protocols.[11] The choice of nickel starting material is not so straightforward. Initial investigations with the transmetallation of dilithio diene **1.31** and $IPrNi(acac)_2$ (**1.4**) (eq. 1.20) or IPr_2NiCl_2 (**1.32**) (eq. 1.21) were unsuccessful. In the former case, reaction was apparent, but the characterization of the crude reaction mixture was too messy to interpret and purification was unsuccessful. We believe incomplete transmetallation or a disproportionation resulting in decomposition is occuring. In a related experiment, when $IPrNi(acac)_2$ was exposed to excess (3+ equiv) XMgPh (X = Cl or Br), only monosubstituted product **1.32** was identified with no trace

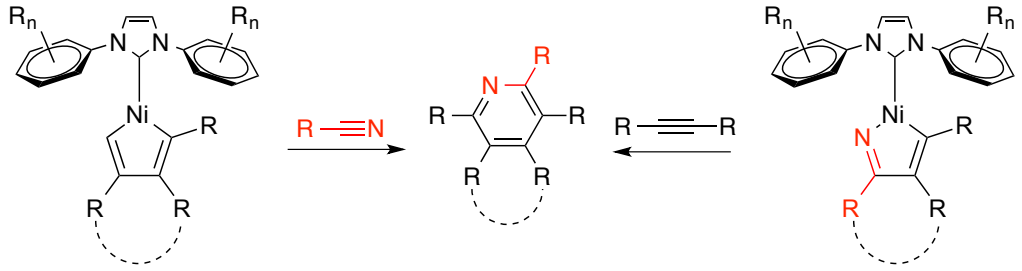
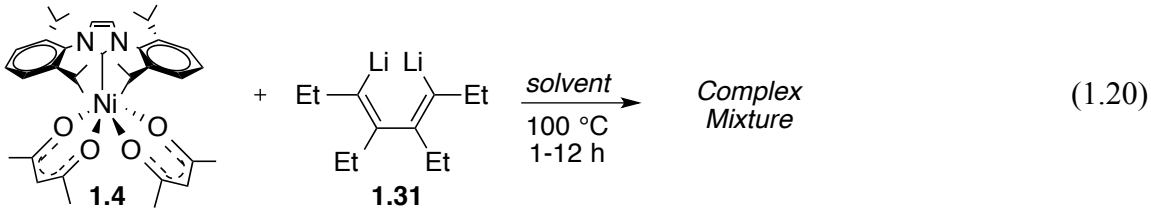
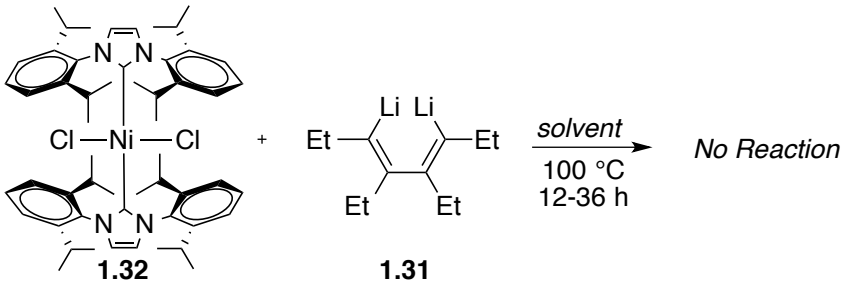


Figure 1.6. Proposed isolation of Reactive Intermediates and Their Insertion behavior.

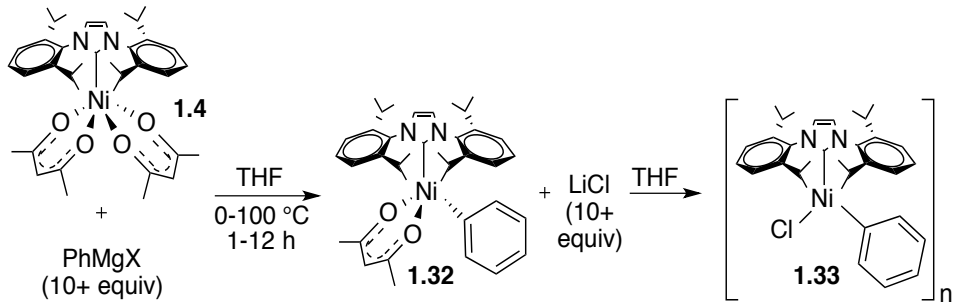


(1.20)



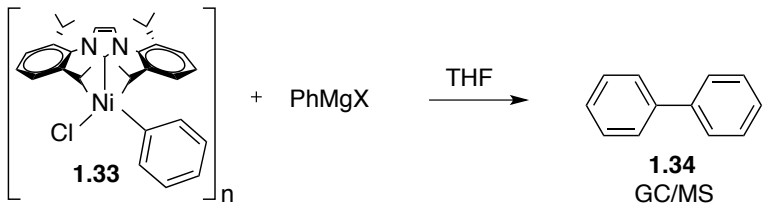
(1.21)

of biphenyl, even upon heating and prolonged reaction times (eq. 1.21).We believe the exclusive monosubstitution is due to such a large ligand environment. For the reaction of IPr_2NiCl_2, the reactants failed to react even upon heating to 100 °C overnight. Once again, we believe this to be a steric effect, in combination with the *trans*-coordination of the Cl-ligands. The reaction mixture changed from yellow-brown to bright green. Upon filtering, crude NMR analysis revealed displacement of the acac-ligand and only minor shifts in the other ^{1}H-resonances (eq. 1.22).



(1.22)

Exposure of this species with BrMgPh resulted in immediate color change to black-yellow, with resultant formation of biphenyl **1.34** (eq. 1.23). No further reactions were pursued. Investigations will also be pursued with $(NHC)NiX_2$-species (NHC = IPr, SIPr or similar; X = halogen) with transmetallation with a dilithio- or other bismetallative compound.

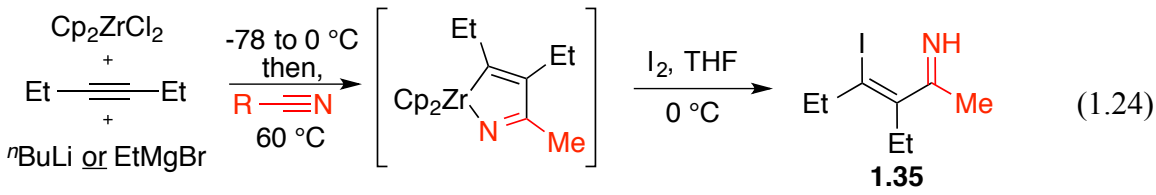


(1.23)

If a nickelacyclopentadiene species is accessed, the next step is simple exposure

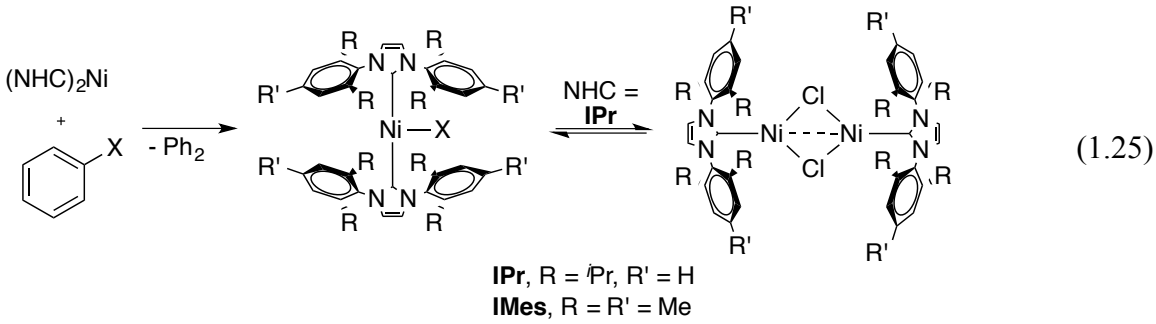
to nitriles. *In situ* monitoring of the reaction would be intriguing regardless of pyridine formation, for simple observation of the nickel-nitrile interaction. If pyridine formation does occur, rate data would be collected for comparison with the results of the alternative heterocoupled nickelapyrrole.

A route to a nickelapyrrole does not appear to be as straightforward as the homocoupled analogue. We proposed that perhaps it may be accessed via oxidative addi tion of an iodinated unsaturated imine **1.35** (eq. 1.24).



(1.24)

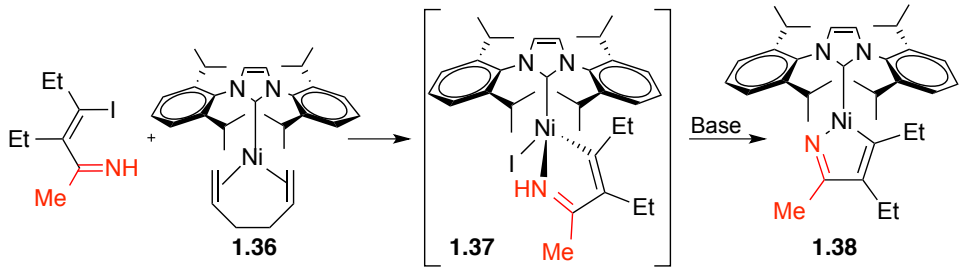
However, we and others have shown that if $Ni(COD)_2$/NHC or isolated $Ni(NHC)_2$ is exposed to aryl halides, the resultant oxidative addition product quickly comproportionates to Ni^{I}(NHC) and biphenyl (eq. 1.25).[49]



(1.25)

Apparently the observed reactivity is dependent on at least two equivalents of carbene to nickel. Considering this, we felt IPrNi(diene) species **1.36**[50] would be an excellent nickel source. We proposed facile oxidative addition of the I-C_{sp2} bond would

afford cyclic 4-coordinate complex **1.37** that upon exposure to base would afford the desired nickelapyrrole **1.38**. (eq. 1.26). While the synthesis of the nickel species was smooth, we were unable to repeat the procedure for the reported synthesis of iodoimines.[51] Once the iodoimine is synthesized, investigations into the oxidative addition/cyclization will follow. As with the homocoupling analogue, this nickelacycle will be exposed to an exogenous alkyne, and the insertion (if at all) behavior investigated.



(1.26)

If the model complexes and subsequent reactions are productive, electronic and steric effects of alkyne and nitriles can be investigated in the appropriate analogues. These investigations will be intriguing to gain some mechanistic insight that was heretofore unobservable in our previous study, namely secondary insertion and reductive elimination. Modulation of the carbene ligand may allow for isolation of the insertion intermediate(s), if the rate of reductive elimination can be successfully minimized. This synthetic methodology may also be applied to phosphine complexes of nickel for comparison of the requisite steps to help further reveal why NHC ligands are so productive while phosphines are not.

As an extension to this study, comparative mechanistic investigations into the cycloaddition of other heteroatomic coupling partners should be conducted, to investigate

an overlying trend of initial heteroatom binding, forcing a hetercoupling pathway.

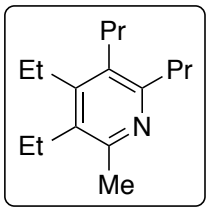
In addition to experimental investigations, theoretical studies are incredibly powerful tools for mechanistic evaluation. Evaluation of our method and proposed mechanism would be incredibly exciting considering the deviation of our mechanism for other transition metal cycloaddition catalysts. We know experimentally that alkyne trimerization is the favored reaction with nickel-NHC catalysts based on our own and previous research, common to all cycloaddition catalysts. However, we concluded that our catalyst is selective because it is forced into heterocoupling pathway by initial nitrile coordination, but we can only speculate as to the mode of pendant-alkyne insertion. In addition, such a study will give us insight into the role the freed carbene has in subsequent steps and what may be occurring after the first turnover. For instance, with only 5 mol% catalyst, we believe that another ligand (nitrile or alkyne, or pyridine?) can plausibly out-compete IPr coordination, which based on our hypothesis, would create a mechanistic deviation. In addition, it would be interesting to see if a homocoupling mechanism for pyridine formation is even feasible and the relative barriers associated with such a reaction.

Experimental

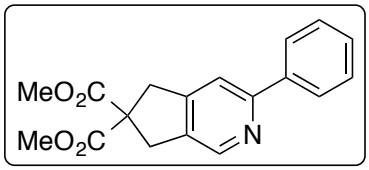
General experimental. All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Toluene and Acetonitrile were dried over neutral alumina under N_2 using a Grubbs type solvent purification system. Benzonitrile was either distilled from CaH_2 prior to use or used from a sure-sealed bottle purchased directly from Sigma-Aldrich.

Methoxyacetonitrile was degassed and distilled from CaH_2 before use. 4-Octyne was purchased from SigmaAldrich and degassed prior to use. Deuterated benzene and chloroform were purchased from Cambridge and used without further purification. Deuterated toluene was purchased from SigmaAldrich and distilled from benzophenone ketyl and passed through dry neutral alumina prior to use. $Ni(COD)_2$ was purchased from Strem and used without further purification. Diynes **1.1**,[52] **1.27**,[52] **1.16**,[53] **1.17**,[54] **1.18**[54] were prepared according to literature procedures. All other reagents were purchased and used without further purification unless otherwise noted. Zirconacycles **1.5** and **1.7**[55] nickel complex **1.4**[56] are known compounds and spectra were matched with reported values. ^{1}H, ^{2}H, and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300, 500, and 75 MHz, respectively, unless otherwise noted. All spectra are referenced to residual solvent peaks. All ^{13}C NMR spectra were proton decoupled. Gas Chromatography was performed using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 minutes; detector temperature: 250 ºC. *In situ* IR measurements were carried out with a Mettler Toledo ReactIR™ iC10, with data collection and analysis carried out with iC IR (version 4.1) software.

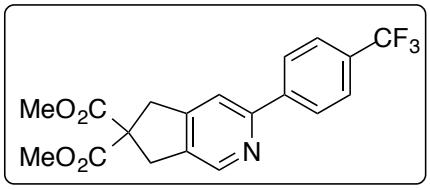
Experimental procedures. Preparation of 3,4-diethyl-2-methyl-5,6-dipropylpyridine, 1.6: in a drybox, zirconacycle **1.5** (50 mg, 0.145 mmol), $(IPr)Ni(acac)_2$ (94 mg, 0.146 mmol), 1,3,5-trimethoxybenzene (24 mg, 0.145 mmol; internal standard), and 4-octyne (24 μL, 0.16 mmol) were weighed into a scintillation vial and dissolved in THF (1 mL). After stirring the reaction for 10 min, the vial was brought out of the drybox and



heated to 50 °C for 12 h. After cooling to rt, the reaction mixture was evaporated to dryness. Comparison of the ^{1}H-NMR ($CDCl_3$) of the reported spectrum[57] and the crude reaction mixture, revealed formation of product **1.6** in 64% NMR yield.

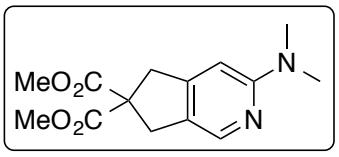


Preparation of dimethyl 3-phenyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate 1.28: diyne **1.1** (20 mg, 0.096 mmol), benzonitrile (1.5 equiv, 15 μL, 0.144 mmol), and 1,3,5-trimethoxybenzene (10 mg, 0.059 mmol; internal standard) were weighed into a scinillation vial in a drybox and dissolved in toluene (1 mL). $Ni(IPr)_2$ (0.05 equiv, 4 mg, 0.0048 mmol) in toluene (1 mL) was then added and the reaction mixture was stirred for 1 h. Upon completion, the vial was brought out of the drybox and the reaction mixture evaporated to dryness. Comparison of the ^{1}H-NMR (CDC_3) of the reported spectrum[58] and the crude reaction mixture, revealed formation of product **1.28** in 76% NMR yield.

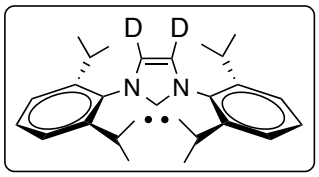


Preparation of dimethyl 3-(4-(trifluoromethyl)phenyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate 1.30: diyne **1.1** (20 mg, 0.096 mmol), 4-CF_3-C_6H_4CN (1.5 equiv, 24.6 mg, 0.144 mmol), and 1,3,5-trimethoxybenzene (10 mg, 0.059 mmol; internal standard) were weighed into a scintillation vial in a drybox and dissolved in toluene (1 mL). $Ni(IPr)_2$ (0.05 equiv, 4 mg, 0.0048 mmol) in toluene (1 mL) was then added and the reaction mixture was stirred for 1 h. Upon completion, the vial was brought out of the drybox and the reaction mixture evaporated to dryness. The crude reaction mixture was purified by column chromatography, eluting with 1:1 Et_2O:pentane to afford 28.8 mg (79% yield) of

the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 2H), 3.70 (s, 2H), 3.81 (s, 6H), 7.64 (s, 1H), 7.74 (d, J = 12 Hz, 2H), 8.08 (d, J = 8 Hz, 2H), and 8.57 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 38.1, 40.4, 53.2, 60.2, 116.79, 122.7, 125.6 (q, $J_{C\text{-}F}$ = 16 Hz), 127.2, 135.6, 142.8, 145.6, 150.7, 154.8, 171.4. IR (neat, cm^{-1}) $\tilde{\nu}$ 3006, 2956, 1735, 1607, and 1274. HRMS (ESI) calc'd for $C_{19}H_{17}F_3NO_4$ $[M+H]^+$ 380.1110, found 380.1114.

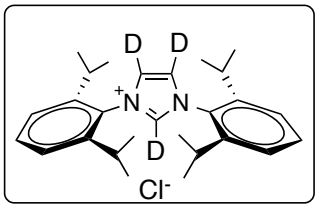


Preparation of dimethyl 3-(dimethylamino)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate 1.30: diyne **1.1** (20 mg, 0.096 mmol), dimethylcyanamide (1.5 equiv, 8 μL, 0.144 mmol), and 1,3,5-trimethoxybenzene (10 mg, 0.059 mmol; internal standard) were weighed into a scinillation vial in a drybox and dissolved in toluene (1 mL). $Ni(IPr)_2$ (0.05 equiv, 4 mg, 0.0048 mmol) in toluene (1 mL) was then added and the reaction mixture was stirred for 1 h. Upon completion, the vial was brought out of the drybox and the reaction mixture evaporated to dryness. Comparison of the ^{1}H-NMR of the reported spectrum[59] and the crude reaction mixture, revealed formation of product **1.30** in 82% yield.



Preparation of IPr·HCl-d_3:[60,6] IPr•HCl (1.5 g, 3.527 mmol) and K_2CO_3 (24.7 mg, 0.179 mmol) were added to a 50 mL roundbottom flask followed by ~ 6 ml D_2O. The reaction mixture was heated at 100 °C under N_2 for 24 h. After allowing the reaction to cool, remaining solvents were removed under reduced pressure. Once dry, the product was washed with hexanes before filtering to collect a white solid (1.35 g, 89 % yield). 100 % deuteration of backbone was observed with roughly 64 % deuteration of 2-position on

imidazole ring. Theoretical yield assumes total deuteration of product. ^{1}H NMR ($CDCl_3$, ppm) δ 10.12 (s, <1H), 7.58 (t, 7.9 Hz, 2H), 7.36 (d, 7.78 Hz, 4H), 2.46 (septet, 6.7 Hz, 4H), 1.30 (d, 6.7 Hz, 12 H), 1.25 (d, 6.9 Hz, 12 H). ^{2}H NMR ($(CD_3)_2SO$, ppm) 3.50, 8.75. ^{13}C NMR ($CDCl_3$, ppm) δ 145.3, 132.4, 130.1, 128.6, 125.0, 29.4, 25.0, 24.0.



Preparation of IPr-d_2 (1.19):[61] a suspension was created by adding 1.05 equiv IPr•HCl-d_3 (397 mg, 0.927 mmol) to 10 mL diethylether in a 20 mL, oven-dried scintillation vial. To this was added 1.0 eq. KHMDS (183 mg, 0.89 mmol), which had been dissolved in 10 mL diethylether. The resulting mixture was stirred for 3 min before being filtered through celite followed by removal of solvent under vacuum. The resulting solid was recrystallized from diethylether to give 149.6 mg of white solid (43 % yield); < 3% proteated IPr remained (backbone position). Theoretical yield assumes total deuteration of product. ^{1}H NMR (C_6D_6, ppm) δ 7.30 (dd, 8.6, 6.7 Hz, 2H) 7.21-7.15 (m, 4H) 6.61 (s, <1H), 2.97 (sept, 6.9 Hz, 4H), 1.30 (d, 6.7 Hz, 12H) 1.19 (d, 6.9 Hz, 12H) ^{2}H NMR (C_6D_6), ppm) 6.58. ^{13}C NMR (C_6D_6, ppm) δ 221.0, 146.7, 139.4, 129.4, 124.1, 29.2, 25.1, 24.0.

^{1}H NMR kinetic studies. In general, the NMR spectrometer was precooled and stabilized at the desired temperature prior to any sample injection. In all kinetic experiments, all noncatalyst solutions and excess solvent were added together and cooled to -40 °C in the freezer in a drybox. Upon cooling, the catalyst solution was injected, and the sample tube was removed from the drybox immediately and placed in a dry ice/acetone bath. The sample tube was then removed from the cooling bath, briefly shaken, loaded into the instrument, and immediately subjected to analysis. Spectra were

collected within 30 sec with delay intervals of 1 min. All samples were analyzed to >90% completion.

Kinetic analysis for the cycloaddition of MeCN. Order in $Ni(IPr)_2$ was determined as follows: stock solution #1 was prepared by dissolution of 59.2 mg (0.251 mmol) of diyne **1.1** and 46.5 mg (0.50 mmol) of ferrocene in toluene-d_8 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 298.6 mg (7.27 mmol) of acetonitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 10.45 mg (0.0125 mmol) of $Ni(IPr)_2$ in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, 21 μL of solution #2, and an appropriate volume of solution #3. An amount of toluene-d_8 was then added to make a total of 0.5 mL solution. Reactions were monitored at -20 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of $Ni(IPr)_2$ (k, [$Ni(IPr)_2$]): 0.0 $M \cdot s^{-1}$, 0.0 M; 2.59×10^{-5} $M \cdot s^{-1}$, 2.5×10^{-6} M; 4.65×10^{-5} $M \cdot s^{-1}$, 3.75×10^{-6} M; 5.41×10^{-5} $M \cdot s^{-}$, 4.5×10^{-6} M; 6.06×10^{-5} $M \cdot s^{-}$, 5.25×10^{-6} M; 6.95×10^{-5} $M \cdot s^{-}$, 6.0×10^{-6} M .

Order in acetonitrile was determined as follows: stock solution #1 was prepared by dissolution of 59.2 mg (0.251 mmol) of diyne **1.1** and 46.5 mg (0.50 mmol) of ferrocene in toluene-d_8 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 298.6 mg (7.27 mmol) of acetonitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 10.45 mg (0.0125 mmol) of $Ni(IPr)_2$ in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of solution #2, and 100 μL of solution #3. An amount of toluene-d_8 was then

added to make a total of 0.5 mL solution. Reactions were monitored at -20 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of acetonitrile (k, [MeCN]): 2.45×10^{-5} $M \cdot s^{-1}$, 2.50×10^{-1} M; 2.78×10^{-5} $M \cdot s^{-1}$, 3.75×10^{-1} M; 2.77×10^{-5} $M \cdot s^{-1}$, 5.0×10^{-1} M; 2.73×10^{-5} $M \cdot s^{-}$, 6.25×10^{-1} M; 2.48×10^{-5} $M \cdot s^{-}$, 7.50×10^{-1} M.

Order in IPr was determined as follows: stock solution #1 was prepared by dissolution of 59.2 mg (0.251 mmol) of diyne **1.1** and 46.5 mg (0.50 mmol) of ferrocene in toluene-d_8 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 298.6 mg (7.27 mmol) of acetonitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 48.6 mg (0.125 mmol) of IPr in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #4 was prepared by dissolution of 10.45 mg (0.0125 mmol) of $Ni(IPr)_2$ in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, 21 μL of solution #2, an appropriate volume of solution #3, and 100 μL of solution #4. An amount of toluene-d_8 was then added to make a total of 0.5 mL solution. Reactions were monitored at -20 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of $Ni(IPr)_2$ (k, [IPr]): 2.65 $M \cdot s^{-1}$, 0.0 M; 2.59×10^{-5} $M \cdot s^{-1}$, 5.0×10^{-3} M; 2.84×10^{-5} $M \cdot s^{-1}$, 7.5×10^{-3} M; 3.31×10^{-5} $M \cdot s^{-}$, 8.75×10^{-3} M; 2.96×10^{-5} $M \cdot s^{-}$, 1.0×10^{-2} M.

Kinetic analysis for the cycloaddition of ^{i}PrCN. Order in $Ni(IPr)_2$ was determined as follows: stock solution #1 was prepared by dissolution of 59.2 mg (0.251 mmol) of diyne **1.1** and 46.5 mg (0.50 mmol) of ferrocene in toluene-d_8 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 200.2 (2.89

mmol) of isobutyronitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 10.45 mg (0.0125 mmol) of $Ni(IPr)_2$ in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, 43 μL of solution #2, and an appropriate volume of solution #3. An amount of toluene-d_8 was then added to make a total of 0.5 mL solution. Reactions were monitored at -20 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of $Ni(IPr)_2$ (k, [$Ni(IPr)_2$]): 0.0 $M \cdot s^{-1}$, 0.0 M; 9.3×10^{-6} $M \cdot s^{-1}$, 5.0×10^{-6} M; 1.06×10^{-5} $M \cdot s^{-1}$, 6.5×10^{-6} M; 1.18×10^{-5} $M \cdot s^{-}$, 7.5×10^{-6} M; 1.74×10^{-6} $M \cdot s^{-}$, 1.0×10^{-5} M.

Order in ^{i}PrCN was determined as follows: stock solution #1 was prepared by dissolution of 59.2 mg (0.251 mmol) of diyne **1.1** and 46.5 mg (0.50 mmol) of ferrocene in toluene-d_8 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 200.2 (2.89 mmol) of isobutyronitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 10.45 mg (0.0125 mmol) of $Ni(IPr)_2$ in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of solution #2, and 100 μL of solution #3. An amount of toluene-d_8 was then added to make a total of 0.5 mL solution. Reactions were monitored at -20 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of acetonitrile (k, [MeCN]): 0.0 $M \cdot s^{-1}$, 0.0 M; 9.42×10^{-6} $M \cdot s^{-1}$, 5.0×10^{-1} M; 1.54×10^{-5} $M \cdot s^{-1}$, 1.0 M; 1.96×10^{-5} $M \cdot s^{-}$, 1.25 M; 2.48×10^{-5} $M \cdot s^{-}$, 1.75 M.

Order in IPr was determined as follows: stock solution #1 was prepared by dissolution of 59.2 mg (0.251 mmol) of diyne **1.1** and 46.5 mg (0.50 mmol) of ferrocene

in toluene-d_8 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 200.2 (2.89 mmol) of isobutyronitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 48.6 mg (0.125 mmol) of IPr in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #4 was prepared by dissolution of 10.45 mg (0.0125 mmol) of $Ni(IPr)_2$ in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, 86 μL of solution #2, an appropriate volume of solution #3, and 100 μL of solution #4. An amount of toluene-d_8 was then added to make a total of 0.5 mL solution. Reactions were monitored at -20 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of $Ni(IPr)_2$ (k, [IPr]): 1.98 $M \cdot s^{-1}$, 0.0 M; 1.86×10^{-5} $M \cdot s^{-1}$, 3.75×10^{-2} M; 1.90×10^{-5} $M \cdot s^{-1}$, 3.0×10^{-2} M; 2.14×10^{-5} $M \cdot s^{-}$, 4.5×10^{-2} M; 2.14×10^{-5} $M \cdot s^{-}$, 6.0×10^{-2} M.

^{2}H-observe NMR experiments with MeCN-d_3 and/or IPr-d_2Stock solution #1 was prepared by dissolution of 59.2 mg (0.251 mmol) of diyne **1.1**, 46.5 mg (0.50 mmol) of ferrocene, and 39 mg (0.5 mmol, internal standard) in toluene in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 159.9 mg (3.63 mmol) of in MeCN-d_3 and 149.3 mg (3.63 mmol) of in MeCN toluene in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 48.9 mg (0.125 mmol) of IPr-d_2 in toluene in a 1.00 ± 0.01 mL volumetric flask. Stock solution #4 was prepared by dissolution of 62.7 mg (0.075 mmol) of $Ni(IPr)_2$ in toluene in a 1.00 ± 0.01 mL volumetric flask. Samples for each experiment were prepared by adding 100 μL of solution #1, 86 μL of solution #2, and/or an appropriate volume of solution #3, and 100 μL of solution #4. An amount of toluene-d_8 was then added to make a total of 0.5 mL

solution. Reactions were monitored at -40 ºC.

***In Situ* IR experiments.** To an oven-dried 100 mL tubular Schlenk flask equipped with a magnetic stirbar, was added diyne **1.1** (35.4 mg, 0.15 mmol) in a drybox. Toluene (2.5 mL) was then added, the flask sealed, and removed from the drybox. Under a steady flow of N_2, the immersion probe was then fixed into the flask. The apparatus was then placed into a dry ice/acetone bath and cooled to -78 ºC. Upon cooling, MeCN (39 mL, 0.75 mmol) at was added at -78 ºC and concurrent with data collection. After stirring for *ca*. 18 min, $Ni(IPr)_2$ (60 mg, 0.075 mmol) in toluene (0.5 mL) was added. The reaction was allowed to stir for 4 min then placed into a dry ice/MeCN bath.

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31 ICy = 1,3-dicyclohexylimidazol-2-ylidene

32 IAd = 1,3-di(adamantan-1-yl)imidazol-2-ylidene

33 IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene.

34 SIPr = 1,3-bis-(2,6-diisopropylphenyl)-4,5 dihydroimidazol-2-ylidene

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CHAPTER 2

THE DISCOVERY OF [NI(NHC)RCN]$_2$ SPECIES AND THEIR ROLE AS CYCLOADDITION CATALYSTS FOR THE FORMATION OF PYRIDINES*

Abstract

The reaction of Ni(COD)$_2$, IPr, and nitrile affords dimeric [Ni(IPr)RCN]$_2$ in high yields. X-ray analysis revealed these species display simultaneous η^1- and η^2-nitrile binding modes. These dimers are catalytically competent in the formation of pyridines from the cycloaddition of diynes and nitriles. Kinetic analysis showed the reaction to be first-order in [Ni(IPr)RCN]$_2$, zeroth-order in added IPr, zeroth-order in nitrile, and zeroth-order in diyne. Extensive stoichiometric competition studies were performed, and selective incorporation of the exogenous, not dimer-bound, nitrile was observed. Post cycloaddition, the dimeric state was found to be largely preserved. Nitrile and ligand exchange experiments were performed and found to be inoperative in the catalytic cycle. These observations suggest a mechanism whereby the catalyst is activated by partial

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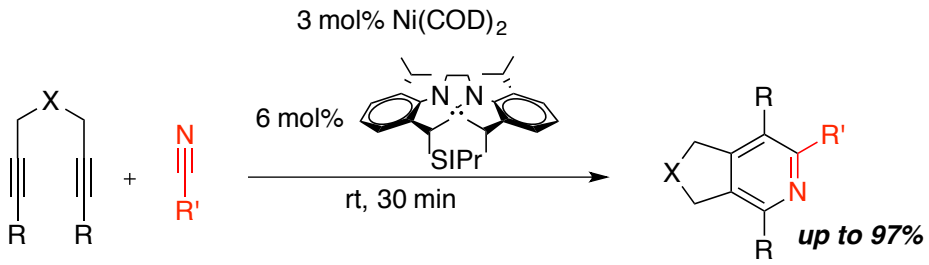
dimer-opening followed by binding of exogenous nitrile and subsequent oxidative heterocoupling leading to pyridine products.

Introduction

Because of the prevalence of pyridine-containing molecules in nearly all aspects of the chemical sciences,[1] the ability to selectively synthesize structurally diverse pyridine-containing molecules is paramount. Transition metal-catalyzed methods to prepare pyridine cores have become a significant synthetic route as they hold the potential to access highly functionalized pyridines in a simplistic and atom-economical fashion.[2] A handful of transition metals have demonstrated the ability to cocyclize alkynes and nitriles to make pyridines catalytically. Specifically, Co,[3] Ru,[4] and Rh[5] have received considerable attention. More recently, we and others have developed new nickel,[6] iron,[7] and iridium[8] complexes that are able to catalyze pyridine formation.

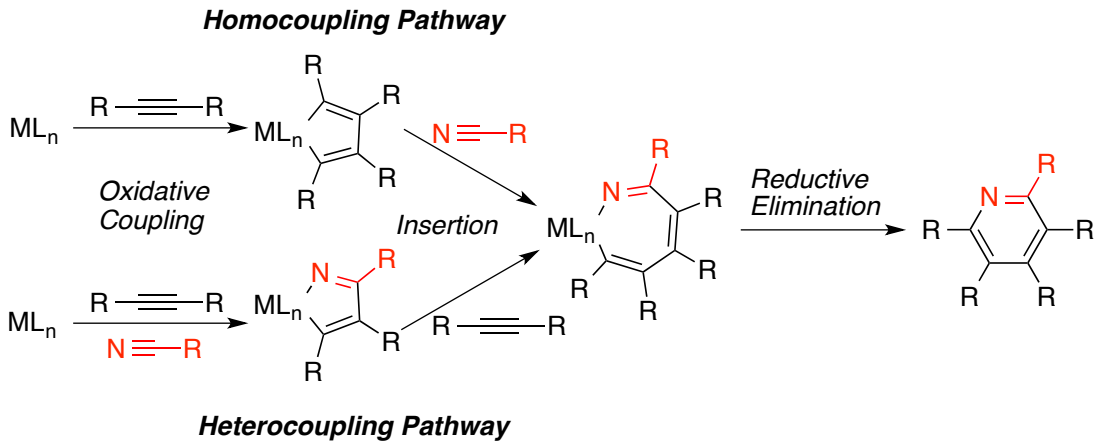
Our discovery that a Ni/NHC (NHC = N-heterocyclic carbene) catalyst couples alkynes and nitriles to afford pyridines (eq. 2.1)[6a] is remarkable for a number of reasons: (1) Nickel complexes readily catalyze the trimerization of alkynes (even in the presence of excess nitrile;[9] (2) nickel complexes readily undergo oxidative addition of R−CN bonds;[10] (3) nickel complexes are known to cause homodimerization of nitriles;[9] and, perhaps most intriguingly; (4) nickel complexes catalyze a completely different reaction between alkynes and nitriles, namely, the carbocyanation of alkynes (see Chapter 1).[11] Despite these potential obstacles, the Ni/NHC catalyst efficiently converts a variety of nitriles and diynes into pyridines in generally high yields. A cursory look into the possible mechanism of nickel-catalyzed cycloaddition raises even more questions. Of the abovementioned transition metals, the cobalt-catalyzed mechanistic pathway is the



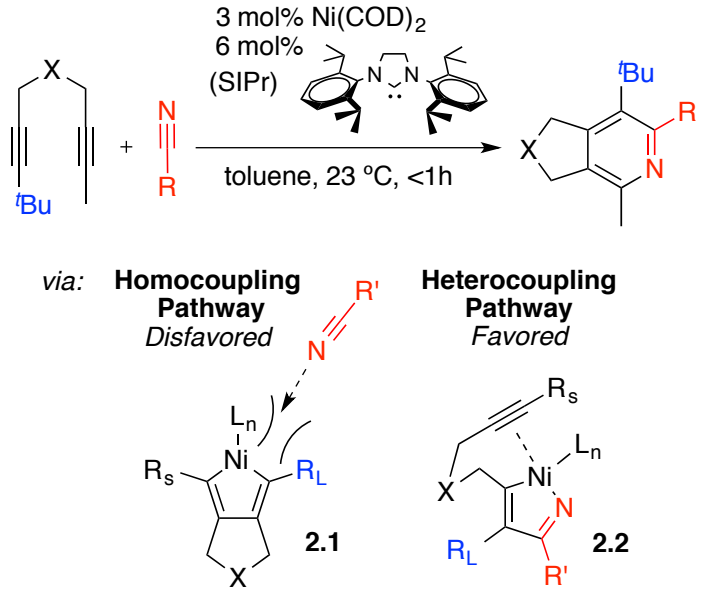
(2.1)

most thoroughly studied and is believed to proceed through a homocoupling pathway, that is, cobalt undergoes oxidative homocoupling of the two alkynes before inserting the nitrile, with subsequent reductive elimination affording the desired product (Scheme 2.1).[3,12]

While considerably less studied, the reactions catalyzed by ruthenium and rhodium are believed to undergo a similar homocoupling mechanism.[4a,4b,5a,12] In contrast, nickel-mediated pyridine formation appears to follow a different route. Stoichiometric reactions of alkynes and azanickelacycles (prepared from transmetallation between an azazirconacyclopentenone and $Ni(PPh_3)_2Cl_2$)[13] afford highly substituted pyridines, suggesting that heterocoupling between a nitrile and an alkyne, rather than homocoupling of two alkynes, is the initial step. Yet, the oxidative coupling of an alkyne and a nitrile is sluggish at best for nickel,[9] and an isolable azanickelacycle has yet to be discovered (unlike other heteronickelacycles). Further anecdotal evidence of an alternate oxidative heterocoupling pathway in the nickel-catalyzed system arises from the observed regioselectivity of the nickel-catalyzed cycloaddition of unsymmetrical diynes and nitriles (Scheme 2.2).[6] If a homocoupling pathway were operative, the observed regiochemistry would dictate that insertion of the nitrile would require insertion from the sterically least- accessible face of intermediate **2.1**. Alternatively, in order to minimize negative substrate/ligand steric interaction, heterocoupling of the bulky-substituted



Scheme 2.1. Divergent Pathways for Alkyne/Nitrile Cycloaddition

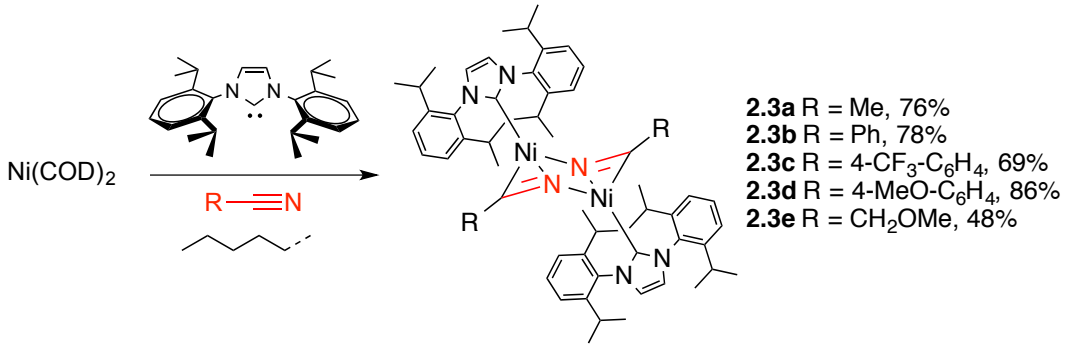


Scheme 2.2. Observed Regioselectivity in Ni/NHC-Catalyzed Cycloaddition

alkyne with the nitrile would result in the observed regioselectivity. This regioselectivity trend has also been observed in the Ni/NHC-catalyzed coupling of alkynes and aldehydes[14] (as well as isocyanates[15]). Using DFT studies, Montgomery and Houk found that regioselectivity is primarily controlled by the steric hindrance at the region of the ligand closest to the alkyne. Analysis of steric contour maps of NHC ligands demonstrated that the regioselectivities are directly affected by the shape and orientation of the *N*-substituents on the ligand.[16] Given the ambiguity surrounding the success of nickel-catalyzed pyridine formation, we initiated a mechanistic investigation of these cycloaddition reactions of alkynes and nitriles. Through kinetic analysis of these reactions, observed regioselectivities of the products, and stoichiometric reactions, $Ni(IPr)_2$ appears to proceed by a heterooxidative coupling mechanism, contrary to other common cycloaddition catalysts. Reaction profiles demonstrated strong dependence in nitrile, resulting in variable nitrile-dependent resting states. Strong coordination and considerable steric bulk of the carbene ligands facilitates selective initial binding of nitrile, forcing a heterocoupling pathway. Following nitrile coordination are a rate-determining hapticity shift and subsequent loss of carbene. Alkyne coordination then leads to heterooxidative coupling, insertion of the pendant alkyne, and reductive elimination to afford pyridine products. Within this mechanistic investigation, we attempted to isolate reactive intermediates along the catalytic pathway. However, what we discovered was an interesting nitrile-bound Ni(NHC) dimer resulting from the stoichiometric reaction between Ni(NHC) complexes and nitrile. Herein, we report the synthesis and characterization of these Nickel dimers and their role in catalytic pyridine formation.

Results

Synthesis of [Ni(IPr)RCN]$_2$ species. The reaction of Ni(COD)$_2$, IPr, and acetonitrile (1:1:1 equiv) in C_6D_6 was observed *in situ* by ^{1}H NMR spectroscopy and revealed clean displacement of the COD ligands by IPr and nitrile to form a new complex (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene). Interestingly, relative intensities of 1H resonances indicated a complex in which the ratio of IPr to acetonitrile was 1:1. A larger scale reaction between equivalent amounts of Ni(COD)$_2$, IPr, and acetonitrile in hexane or pentane at room temperature afforded **2.3a** as a red precipitate in 76% yield (eq. 2.2).



(2.2)

A single-crystal X-ray structure of 3a was obtained (Figure 2.1) wherein **2.3a** was found to be an unexpected dimeric species in which one nitrile is bound to two nickel atoms in both η^1- and η^2- binding modes. Importantly, an N−C bond length of 1.226(3) Å was observed. This, along with a stretching frequency of 1757 cm^{-1}, is indicative of an N−C double bond of an η^2-bound nitrile.[10,17] The Ni−N and Ni−C bond lengths are similar to those of analogous phosphine-bound nickel-nitrile complexes.[17b,c] However, the Ni−C15 bond length of **2.3a** is significantly shortened (1.8677 vs 2.1−2.2 Å) compared previously reported Ni−NHC bonds.[18] Interestingly, the double hapticity of

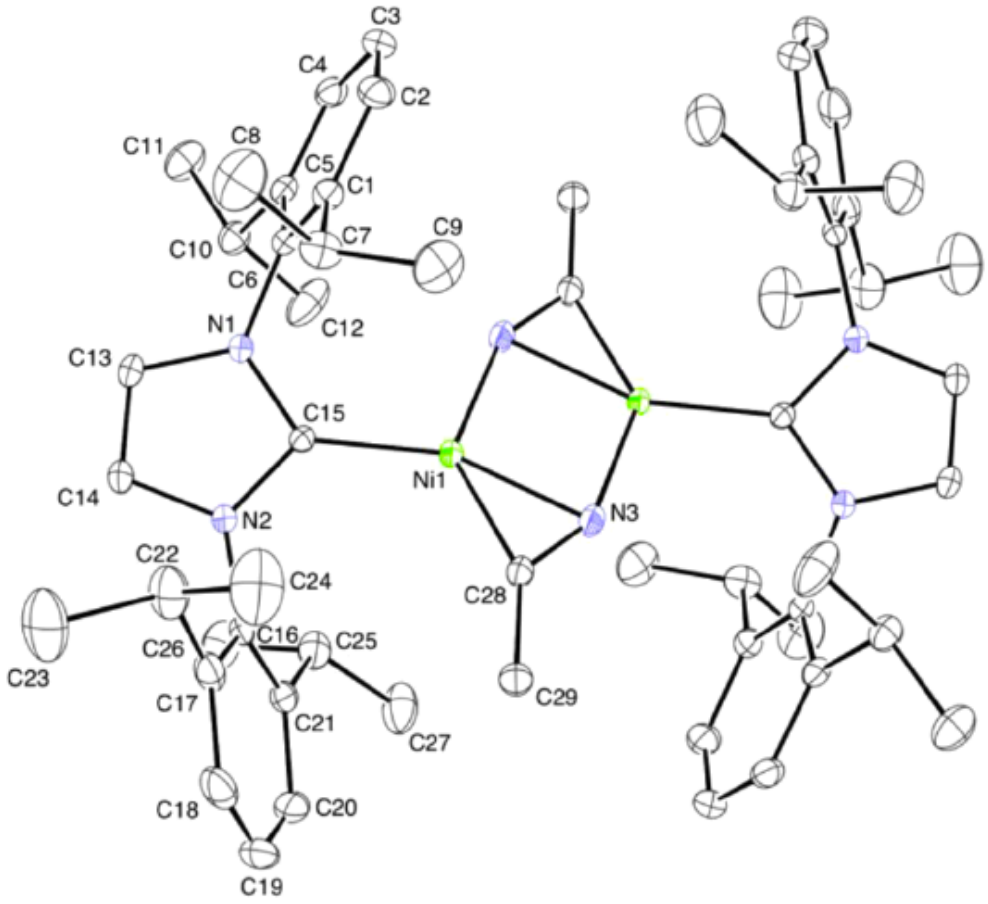
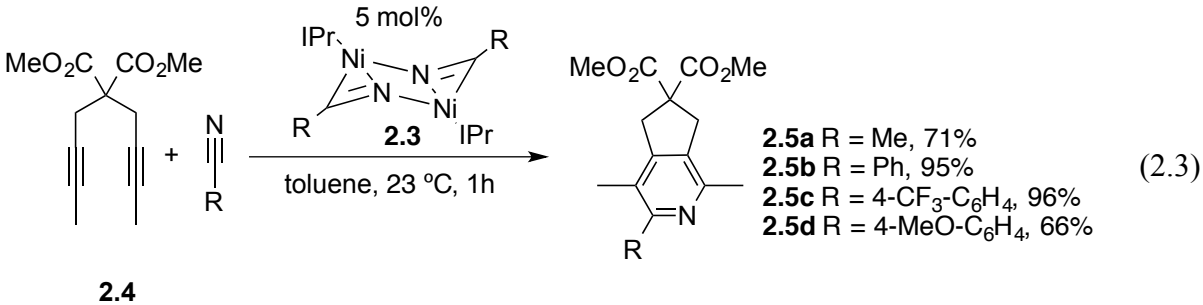


Figure 2.1. ORTEP Plot of **2.3a** at the 30% Probability Level. Hydrogen Atoms Omitted for Clarity. Pertinent Bond Lengths Include: Ni(1)−C(28): 1.854 Å, Ni(1)−C(15): 1.8677 Å, Ni(1)−N(3): 1.9523 Å, Ni(1)−N(3)_3: 1.9951 Å, N(3)−C(28): 1.226 Å. Pertinent Bond Angles Include: C(28)−Ni(1)−C(15): 120.29°, C(28)−Ni(1)−N(3):37.37°, C(15)−Ni(1)−N(3)_3: 132.83°,N(3)−Ni(1)−N(3)_3:95.37°, N(3)−C(28)−C(29): 134.6°.

the nitriles has been observed with only select transition metals[17a] and, to the best of our knowledge, has only been observed for nickel in tetranuclear species.[17] Importantly, Signer analysis[19] confirmed that **2.3a** exists as a dimer in solution (MW = cald. 978.7; obsd 961.9 ± 100) as well as the solid state. Dimers **2.3b**−**2.3e** were prepared in a similar synthetic protocol from the requisite nitrile. The structure of **2.3c** is shown in Figure 2.2. Not surprisingly, the Ni−C and N−C bond lengths are similar to those seen in **2.3a**; only the Ni−N bond was slightly shorter (1.982 vs 1.995 Å). Attempts to form a dimer from isobutyronitrile and other bulky nitriles were unsuccessful and resulted in complex reaction mixtures.

[Ni(IPr)RCN]$_2$-catalyzed [2 + 2+ 2] cycloadditions. When dimers **2.3** were employed as catalysts for the cycloaddition of diynes and nitriles, the expected pyridine products were obtained in good to excellent yields. Specifically, when diyne **2.4** and acetonitrile were subjected to 5 mol % dimer **2.3a**, clean formation of pyridine **2.5a** occurred (eq. 2.3). Similarly, when aryl dimers 3b, 3c, and 3d were used as catalysts with PhCN, 4-$CF_3C_6H_4CN$, and 4-$MeOC_6H_4CN$, respectively, pyridines **2.5b**−**2.5d** were obtained. Importantly, all yields compare favorably to those obtained in our parent $Ni(COD)_2$/SIPr catalyst system (SIPr = 1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene).[6a]



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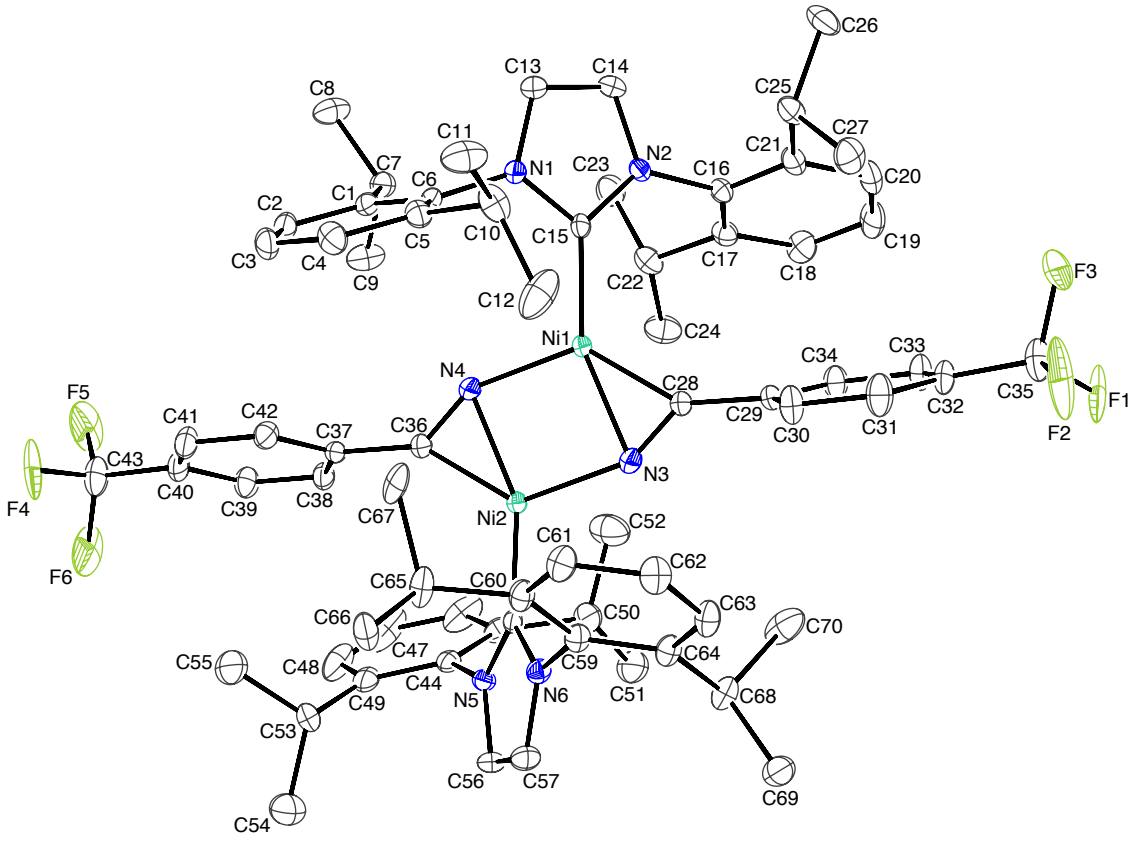


Figure 2.2. Ortep plot of **2.3c**. Hydrogen Atoms are Omitted for Clarity. Pertinent Bond Lengths Include: Ni(1)−C(28): 1.857 Å, Ni(1)−C(15)-1.895 Å, Ni(1)−N(3): 1.974 Å, Ni(1)−N(4): 1.982 Å, N(3)−C(28): 1.223 Å. Pertinent Bond Angles Include: C(28)−Ni(1)−C(15): 119.48°, C(28)−Ni(1)−N(3): 37.08°, C(15)−Ni(1)−N(4): 109.50°, N(3)−Ni(1)−N(4): 93.93°, N(3)−C(28)−C(29): 136.1°.

Stoichiometric [2 + 2+2] cycloadditions. In contrast to the high yields observed in dimer-catalyzed reactions, stoichiometric reactions between equimolar amounts of Nickel dimers and diynes produced pyridines in unexpectedly low yields. However, when free nitrile was added, increased product yields were observed. For example, when 1 equiv of diyne **2.4** was added to dimer **2.3a**, pyridine **2.5a** was formed in 30% yield (eq. 2.4, Table 2.1, entry 1). Yet, when diyne **2.4** (1 equiv) was added to dimer **2.3a** in the presence of MeCN (1 equiv), pyridine **2.5a** was formed in 64% yield. The same phenomenon was observed in reactions with dimer **2.3b** and PhCN (34% vs 91% yield, entry 2), **2.3c** and 4-$CF_3C_6H_4CN$ (35% vs 96%, entry 3), and **2.3d** with 4-$MeOC_6H_4CN$ (31% vs 63% yield, entry 4). Again, all yields obtained in the presence of free nitrile compare favorably to those obtained in our parent $Ni(COD)_2$/SIPr catalyst system.[6]

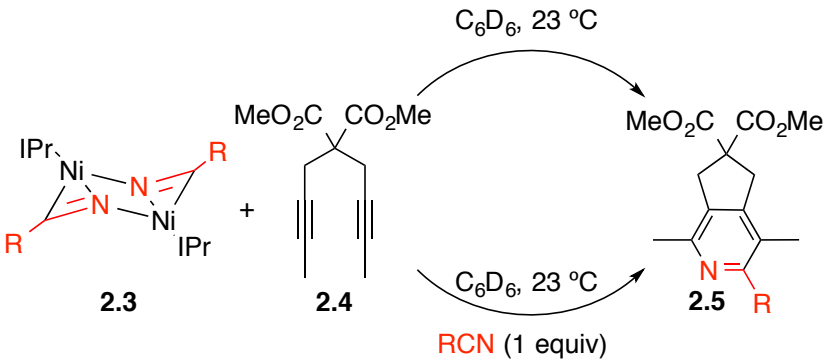
Stoichiometric cross-cycloaddition reactions. The stoichiometric reaction of dimer **2.3a**, diyne **2.4**, and CD_3CN was also performed (eq. 2.5). Surprisingly, the major pyridine product (**2.5ad**) resulted from incorporation of CD_3CN, the exogenous nitrile, rather than the already bound acetonitrile.

Other cross-cycloaddition combinations were evaluated to determine whether preferred incorporation of the exogenous nitrile was a general trend (eq. 2.6). These results are summarized in Table 2.2. Upon examination, the exogenous, rather than the dimer-bound (i.e., endogenous or internal), nitrile was the most widely incorporated into the product. However, it is also worth noting that the dimer-bound nitrile was incorporated into a significant amount of product in some cases. Specifically, when dimer **2.3b** reacted with exogenous MeCN and diyne **2.4**, 45% pyridine product **2.5b**, which incorporates the internal, nickel-bound benzonitrile, was formed (entry 2). Notably, when the exogenous MeCN was supplied in heavy excess (10 equiv), the ratio of products

Table 2.1. Pyridine Yields from Stoichiometric Cycloaddition Reactions

entry	R	yield of **2.5** (no added RCN)	yield of **2.5** (w/ 1 equiv RCN added)
1	**2.5a**, R = Me	30%	64%
2	**2.5b**, R = Ph	34%	91%
3	**2.5c**, R = 4-CF_3-C_6H_4	35%	96%
4	**2.5d**, R = 4-MeO-C_6H_4	31%	63%

[a]Dimer **2.3** (1 equiv), diyne **2.4** (1 equiv), w/ and w/out nitrile, C_6D_6, 23 °C. [b]Yields determined by ^{1}H NMR spectroscopy.



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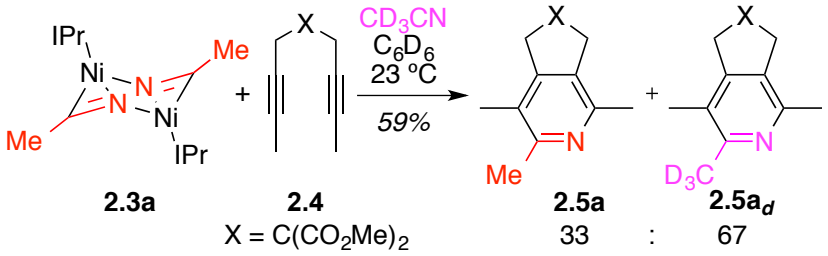

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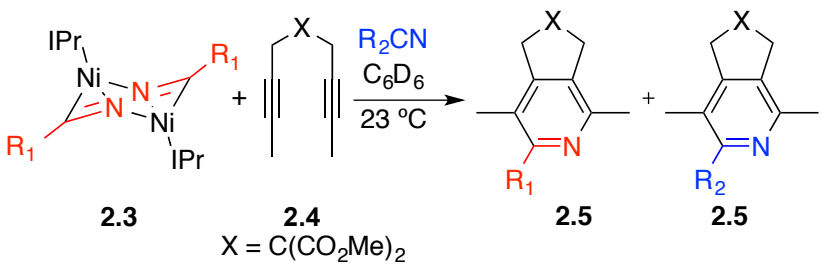


(2.6)

Table 2.2. Pyridine Yields and Product Ratios from Stoichiometric Cross-Cycloaddition Reactions

entry	dimer **2.3**	R_2CN (equiv)	yield of **2.5** (R_1 : R_2)	postreaction dimer species
1	**2.3a**	PhCN (1)	84% (1:27)	**2.3a**
2	**2.3b**	MeCN (1)	74% (1:1.6)	**2.3b**
3	**2.3b**	MeCN (10)	67% (1:2.9)	**2.3b/3a**[c]
4	**2.3b**	4-CF_3-C_6H_4 (1)	93% (1:4.5)	**2.3b/3d**[c]
5	**2.3b**	4-MeO-C_6H_4 (1)	95% (1:4)	**2.3b**
6	**2.3c**	MeCN (1)	63% (1:1.4)	**2.3c**[c]
7	**2.3c**	MeCN (10)	91% (1:1.9)	**2.3c**[c,d]
8	**2.3c**	PhCN (1)	96% (1:4.3)	**2.3c**[c]
9	**2.3d**	MeCN (1)	69% (1:2.1)	**2.3d**
10	**2.3d**	PhCN (1)	99% (1:11)	**2.3d**

[a]Dimer **2.3** (1 equiv), diyne **2.4** (1 equiv), nitrile (1 equiv), C_6D_6, 23 °C. [b]Yields, product ratios, and postreaction dimer species determined by ^{1}H NMR spectroscopy with ferrocene as an internal standard. [c]Traces of unknown Ni species were detected. [d]Complex mixture of Ni products were formed.

changed only slightly (entry 2 vs entry 3, 1:1.6 vs 1:2.9). Similar trends were observed in reactions with other aryl nitrile-bound dimers and exogenous MeCN (entries 6−7 and 9). Conversely, when exogenous PhCN reacted with diyne **2.4** and dimer **2.3a**, PhCN was almost exclusively incorporated into the product (entry 1). The stoichiometric cross-cycloaddition of diyne **2.4** and dimer **2.3b**, which is ligated with PhCN, with electronically dissimilar 4-CF_3-PhCN and 4-MeO-PhCN were also carried out (entries 4 and 5). Surprisingly, the yields and product distributions were nearly identical. That is, in both cases, the exogenous nitrile is preferentially incorporated and afforded a mixture of pyridines in ~95% yield and in a 1:~4 ratio (internal vs exogenous nitrile incorporation). The high yields of pyridines 2.5c−2.5d obtained in these cross-cycloaddition reactions are in stark contrast to the individual catalytic and stoichiometric yields for these respective nitriles (Table 2.1) where pyridine **2.5d** was formed in lower yields (31−63%). In almost

every case where MeCN was used as the exogenous nitrile, overall pyridine yields were modest (compared to those employing only aryl nitriles) and agreed with the pyridine yield from $Ni(COD)_2$/SIPr-catalyzed cycloaddition of **2.4** and MeCN. The one exception to this observation was when 10 equiv of MeCN was used in the reaction with **2.4** and **2.3c**, a considerably higher yield was observed (91%, Table 2.2, entry 7). In addition to lower yields, lower selectivity for the exogenous nitrile was observed when MeCN was used as the exogenous nitrile. Also summarized in Table 2.2, the identity of the dimer at the end of the reaction was predominately the dimer that was initially employed for the reaction.

That is, when dimer **2.3a**, diyne **2.4**, and PhCN were reacted (to form predominately pyridine **2.5b**), only dimer **2.3a** (not dimer **2.3b**, which possesses bound PhCN) was observed after full consumption of both diyne and nitrile (entry 1).

In the cases where MeCN was supplied in heavy excess (10 equiv), significant amounts of other nickel species were present as indicated by unknown resonances in the ^{1}H NMR spectrum (entries 3 and 7). Presumably, these resonances can be attributed to a mixed nickel dimer species (such as **2.3ab**), although attempts to isolate these mixed species thus far have been unsuccessful. Kinetic analysis of the $[Ni(IPr)MeCN]_2$-catalyzed [2+2+2] cycloaddition of diyne **2.4** and MeCN was carried out using the cycloaddition of diyne **2.4** and MeCN catalyzed by dimer **2.3a** as a model. Pseudo-first-order kinetic analyses were used to determine the substrate dependence of dimer, diyne, nitrile, and IPr. All kinetic evaluations were performed via ^{1}H NMR spectroscopy at 0 °C in toluene-d_8 using either ferrocene or 1,3,5-trimethoxybenzene as an internal standard. Clean kinetics revealed the reaction to be first-order in **2.3a** and zeroth-order in **2.4**, MeCN, and IPr (Figure 2.3). When equimolar amounts of **2.3a** and **2.3b** were combined

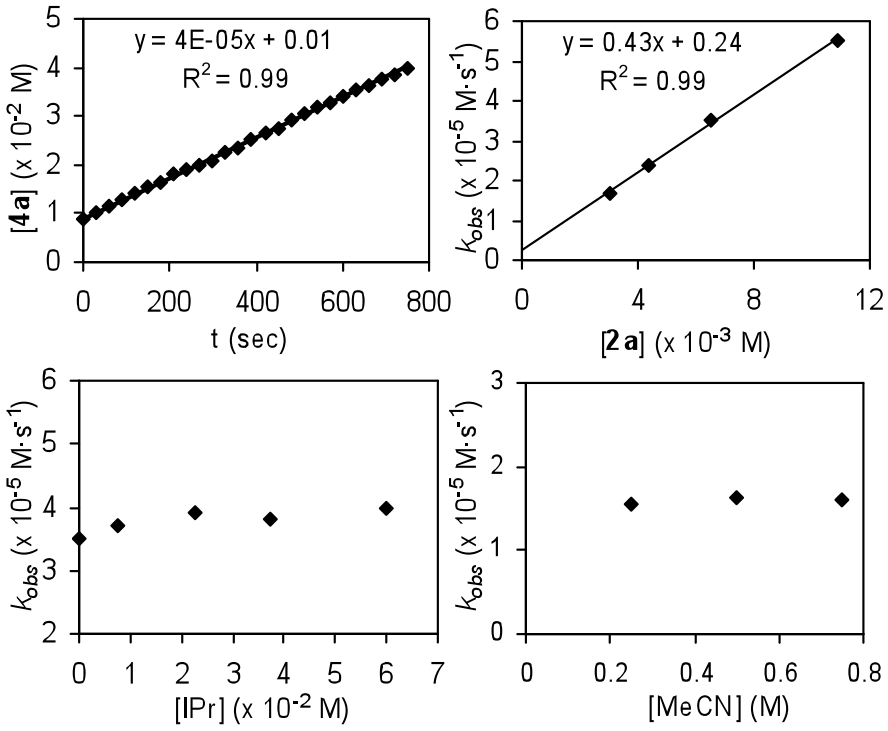
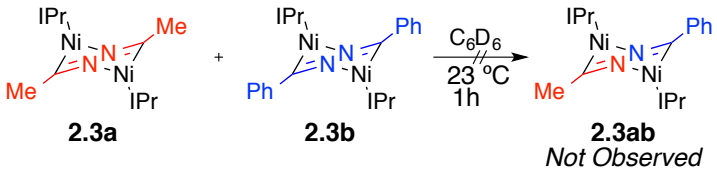


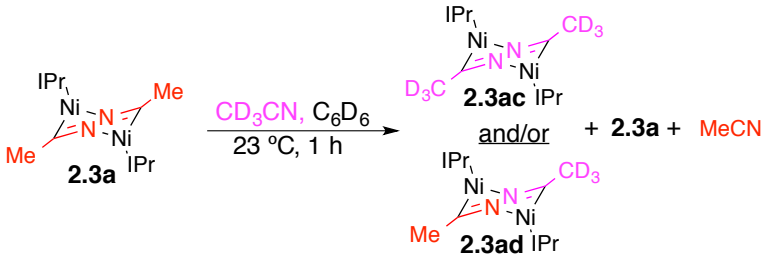
Figure 2.3. Plots of [**2.3a**] vs Time, k_{obs} vs [IPr], and k_{obs} vs [MeCN] for the Cycloaddition of **2.4** at 0 °C in C_7D_8.

in a solution of benzene-d_6 at room temperature, no detectable amount of mixed dimer (i.e., **2.3ab**) was observed after 1 h at room temperature (eq. 2.7).



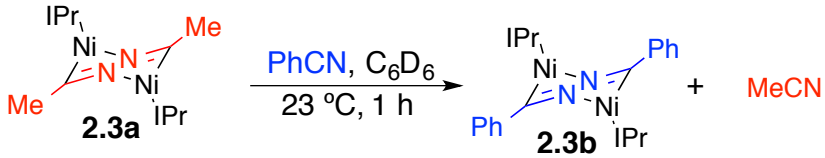
(2.7)

In contrast, a possible mixed-dimer species formed when a sterically- and electronically equivalent nitrile was added to dimer **2.3a** (eq. 2.8). That is, upon exposure of **2.3a** to one equivalent of CD_3CN, 50% consumption of **2.3a** was observed in

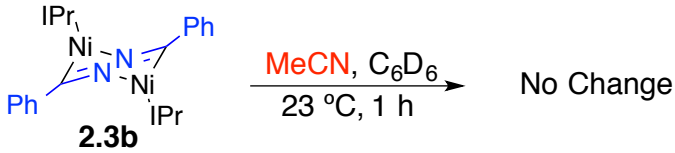


(2.8)

addition to the free, unligated MeCN after 1 h at room temperature.The nature of the deuterated exchange-product (**2.3ac** or **2.3ad**) is unknown. Similar nitrile exchange was observed when the more electrophilic benzonitrile was added to dimer **2.3a** (eq. 2.9). Within minutes, **2.3b**, **2.3a**, and free acetonitrile, along with resonances corresponding to an unknown species (presumably **2.3ab**), were observed by ^{1}H NMR spectroscopy in the reaction of **2.3a** with free benzonitrile at room temperature. Complete exchange occurred in roughly an hour and a half. Conversely, a solution of **2.3b** and acetonitrile exhibited no exchange under the same conditions and the same reaction time scale (eq. 2.10), although a complex mixture was observed after 3 h. Unlike the nitrile exchange reactions, dimers **2.3a** and **2.3b** displayed analogous reactivity toward free IPr ligand. When either **2.3a** or



(2.9)

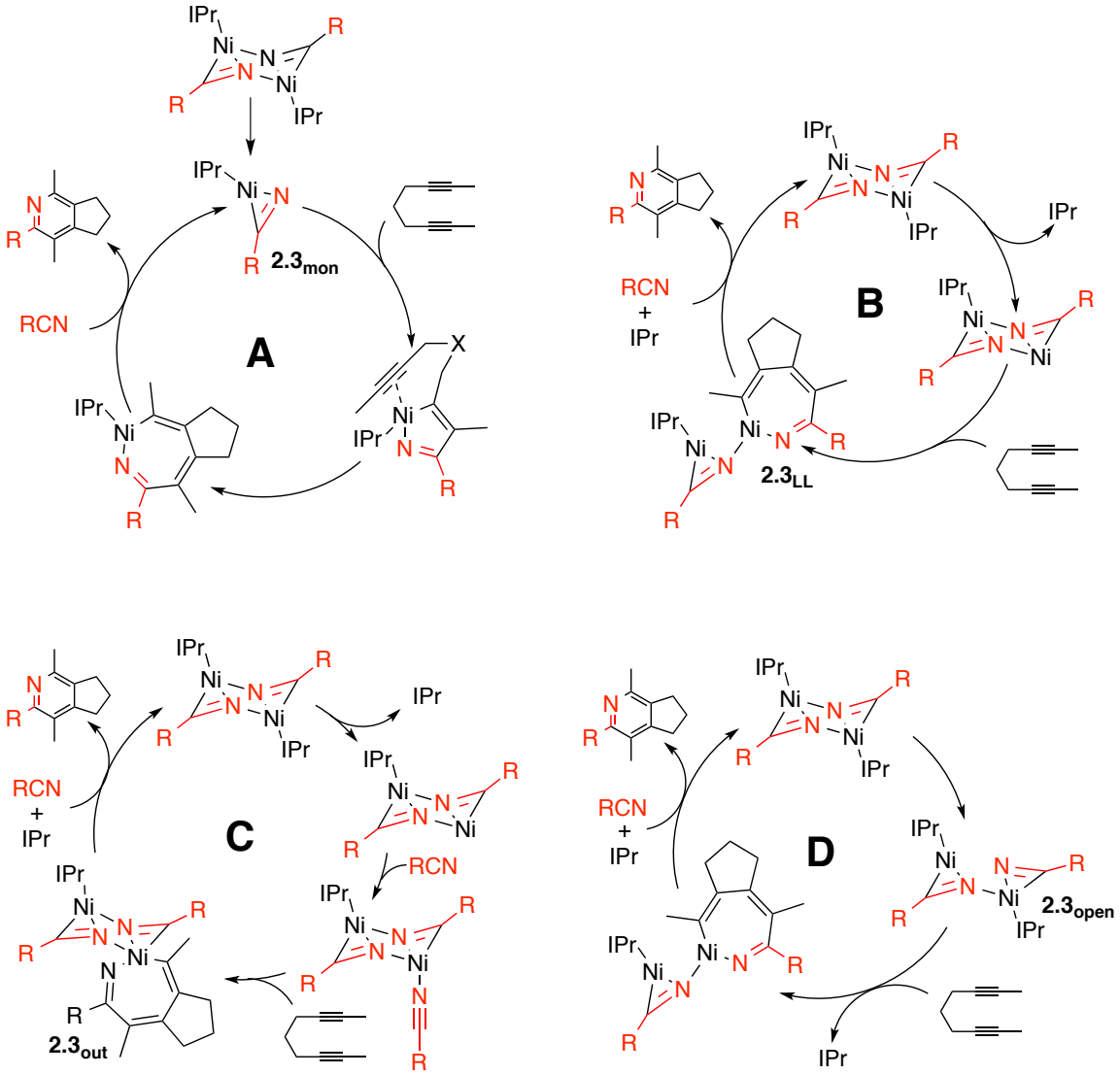


(2.10)

2.3b were exposed to excess IPr-d_2 in C_6D_6 at room temperature, no ligand exchange was observed even after 3 h. Similarly, no ligand exchange was observed in the reaction of dimer **2.3a** or **2.3b**, excess IPr-d_2, and 1 equiv of free nitrile (acetonitrile or benzonitrile, respectively, eq. 2.11). The stoichiometric reaction of **2.3a**, diyne **2.4**, and MeCN was also carried out in the presence of IPr-d_2 (1−5 equiv). Upon completion of the cycloaddition reaction, no ligand exchange was observed (eq. 2.12).

Discussion

At the onset of our research, four reasonable and relatively simplistic mechanisms were proposed (Scheme 2.3). The most straightforward pathway, A, begins with an initial dimer dissociation to an active monomeric form $\mathbf{2.3_{mon}}$. Following dissociation, we envision alkyne binding followed by subsequent oxidative coupling, alkyne insertion, and, finally, reductive elimination. Alternatively, in order to generate an open coordination site, IPr ligand-loss could occur (Scheme 2.3, pathway B or C). Pathway B involves initial alkyne binding followed by partial dimer dissociation and oxidative coupling of the proximal nitrile, thereby generating an open dimeric species $\mathbf{2.3_{LL}}$. Nitrile and/or IPr-facilitated reductive elimination then regenerates the dimer. Pathway C, on the other hand, involves initial nitrile binding subsequent to ligand-loss. This externally bound nitrile (i.e., of an exogenous nitrile) then undergoes oxidative coupling and insertion on the "outside" of the dimer species ($\mathbf{2.3_{out}}$). In an entirely different process, an alternative pathway (pathway D) is initiated by an incomplete dissociation or dimer opening ($\mathbf{2.3_{open}}$). Alkyne binding onto the open dimer followed by IPr loss then leads to oxidative coupling with an internally-bound nitrile. Nitrile/IPr facilitated reductive

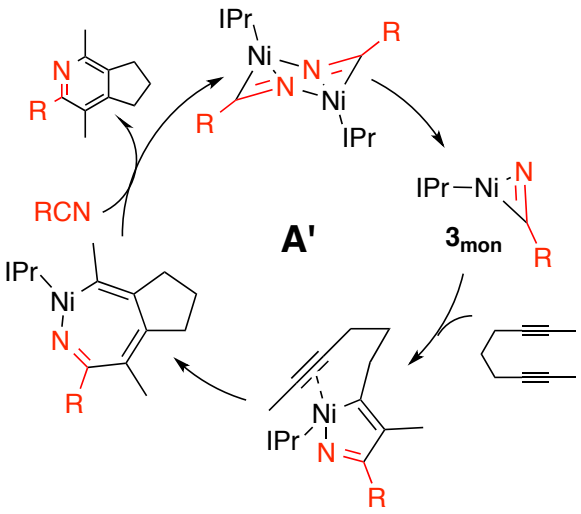


Scheme 2.3. Possible Mechanistic Pathways for $[Ni(IPr)RCN]_2$-Catalyzed Cycloadditions

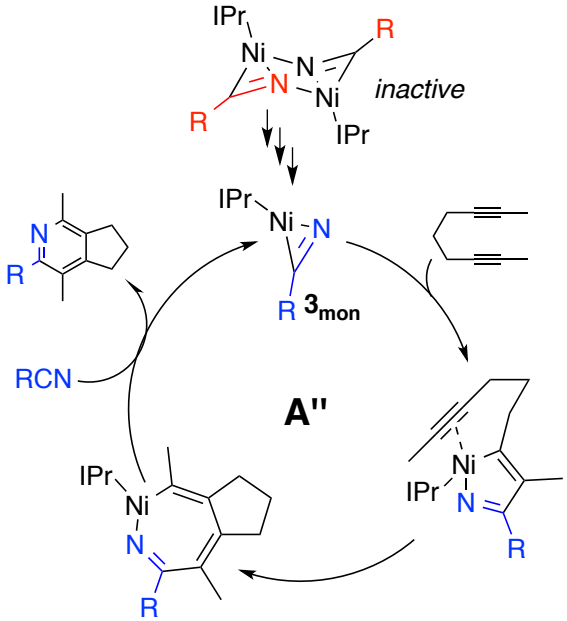
elimination then regenerates the dimer.

Systematic evaluation of the proposed mechanistic pathways. Mechanistically, we initially surmised pathway A was the operative pathway as it is the most simplistic and straightforward. However, the kinetic evaluation of the cycloaddition of 4 and MeCN catalyzed by **2.3a** revealed the rate of cycloaddition depended solely on the concentration of dimer (i.e., a first-order dependence of dimer **2.3a**). These data reveal that the dimer must be on the catalytic pathway (otherwise autocatalytic behavior would be observed). Thus, in a modified pathway A′ (Scheme 2.4), the dimer is the catalyst resting state and dimer dissociation is rate-limiting.

The observed irreversibility may be attributed to the high activity of the monomer (**2.3**$_{\mathbf{mon}}$). However, as seen in the stoichiometric reactions of dimers **2.3a**−**2.3d** with diyne **2.4**, added nitrile is required for optimal yield (Table 2.1). If dissociation were operative, one would expect complete consumption of dimer and high pyridine yields without the need for additional nitrile. In addition, each of these stoichiometric cycloaddition reactions (eq. 2.4), without added nitrile, afforded pyridines in comparable yields despite considerable differences in their reactivity (i.e., **2.3a** < **2.3b**), suggesting that catalyst degradation products that may facilitate homodimerization of diyne **2.4** (at a faster rate than cycloaddition)[20] do not account for the added nitrile requirement. Furthermore, if dimer to monomer dissociation were operative, dimer crossover would be expected, yet no crossover is observed even in trace amounts (eq. 2.7). An alternative possibility that still includes dimer-to-monomer dissociation involves generation of a small amount of catalytically active monomer from catalytically inactive dimer (Pathway A″, Scheme 2.5). At first glance, assuming dimer degradation to monomer **2.3**$_{\mathbf{mon}}$ was first-order and much slower than cycloaddition.



Scheme 2.4. Modified Pathway A'



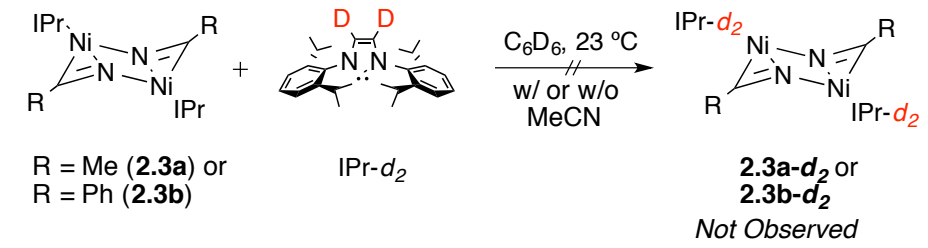
Scheme 2.5. Modified Pathway A''

Such a mechanism would account for: (1) the lack of dimer crossover observed (eq. 2.7), (2) the observed dimer species at the end of the cycloaddition reaction (i.e., the original dimer is almost always observed), and (3) the selective incorporation of the exogenous nitrile. However, several stoichiometric cross-cycloaddition reactions rule out this possibility. For example, the reaction of dimer **2.3b**, diyne **2.4**, and MeCN affords the phenyl-substituted pyridine **2.5b** in 28% yield (Table 2.2, entry 2). To accommodate for this yield, at least 14% of the applied dimer **2.3b** must dissociate to $\mathbf{2.3b_{mon}}$ and react with diyne **2.4** to afford **2.5b**. Once pyridine **2.5b** is formed, the only reactants left are MeCN, and possibly free IPr. As such, dimer **2.3a** or $Ni(IPr)_n$ would be formed in a detectable amount (i.e., ~14%). Yet, upon completion of the reaction, the only carbene species present is from **2.3b**, not **2.3a**; no other species were present. Generally, of the nickel-species present post-reaction, nitrile exchange products that arise through diyne-free nitrile exchange were the only other observed products (eqs 2.9 and 2.10). The cross-cycloaddition of **2.3b** with diyne **2.4** and both 4-CF_3-PhCN and 4-MeO-PhCN (Table 2.2, entries 4 and 5) provides more evidence against a negligible amount of dimer dissociation/degradation product as the active catalyst. Both of these cross-cycloaddition reactions afforded comparable pyridine yields and product ratios (i.e., similar amount of exogenous nitrile incorporation). However, catalytic cycloaddition of 4-CF_3-PhCN is higher yielding than 4-MeOPhCN (eq. 2.3). As such, a small concentration of active $\mathbf{2.3b_{mon}}$ catalyst would have produced higher amounts of **2.5c** than **2.5d**, in agreement with the catalytic reactions, rather than the similar yields observed. A similar phenomenon is observed in the discrepancy between the observed effects of increasing the equivalents of applied nitrile. In the cycloaddition of **2.3b**, **2.4**, and 10 equiv of MeCN (Table 2.2, entry 3), a mild decrease in yield and a 2-fold increase in selectivity

for MeCN were observed. This is contrary to the cycloaddition of **2.3c**, **2.4**, and 10 equiv of MeCN (Table 2.2, entry 7) where a significant increase in yield and only mild increase in selectivity were observed. Lastly, if a negligible amount of dimer **2.3** degrades into an active catalyst (e.g., not necessarily $\mathbf{2.3_{mon}}$), the incorporation of exogenous nitrile would be directly related to the stability of the dimer. That is, faster dimer degradation would result in more exogenous nitrile incorporation. Thus, product ratios would suggest a dimer stability trend of **2.3a** < **2.3d** < **2.3b** ≈ **2.3c** where **2.3a** is the least stable since it incorporates the most exogenous nitrile (Table 2.2). However, qualitative measurement of the decomposition of the dimers displayed the opposite relative stabilities where **2.3a** was the most stable to decomposition. Taken together,our data suggest the dissociative pathway A (or A′ or A'') is not operative.

Just as with pathway A, pathways B and C (Scheme 2.3) are also straightforward to envision. With exclusive first-order dependence in dimer for the cycloaddition reaction, IPr loss must be rate-determining if either pathway B or C were operative. However, when both **2.3a** and **2.3b** were individually treated with IPr-d_2 (eq. 2.11), no ligand exchange was observed. Additionally, no ligand exchange occurred when either **2.3a** or **2.3b** were treated with IPr-d_2 in the presence of the requisite nitrile. Furthermore, no ligand exchange occurred when **2.3a** or **2.3b** were used in the cycloaddition of diyne **2.4** and nitrile in the presence of excess IPr-d_2 (eq. 2.12). As such, the lack of observable ligand exchange in conjunction with our kinetic data rule out pathways B and C.

Given the congested nature of dimers **2.3**, rate-limiting partial dimer opening would allow for subsequent substrate binding and reaction and would agree with our kinetic data. Subsequent to rate-determining dimer opening, a mechanism involving oxidative coupling and insertion of the diyne followed by nitrile-assisted reductive

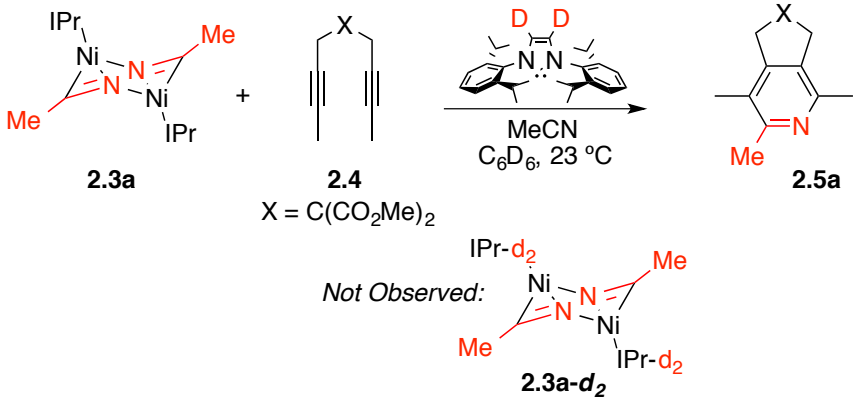


R = Me (**2.3a**) or
R = Ph (**2.3b**)

IPr-d_2

2.3a-d_2 or
2.3b-d_2
Not Observed

(2.11)



2.3a

2.4
X = $C(CO_2Me)_2$

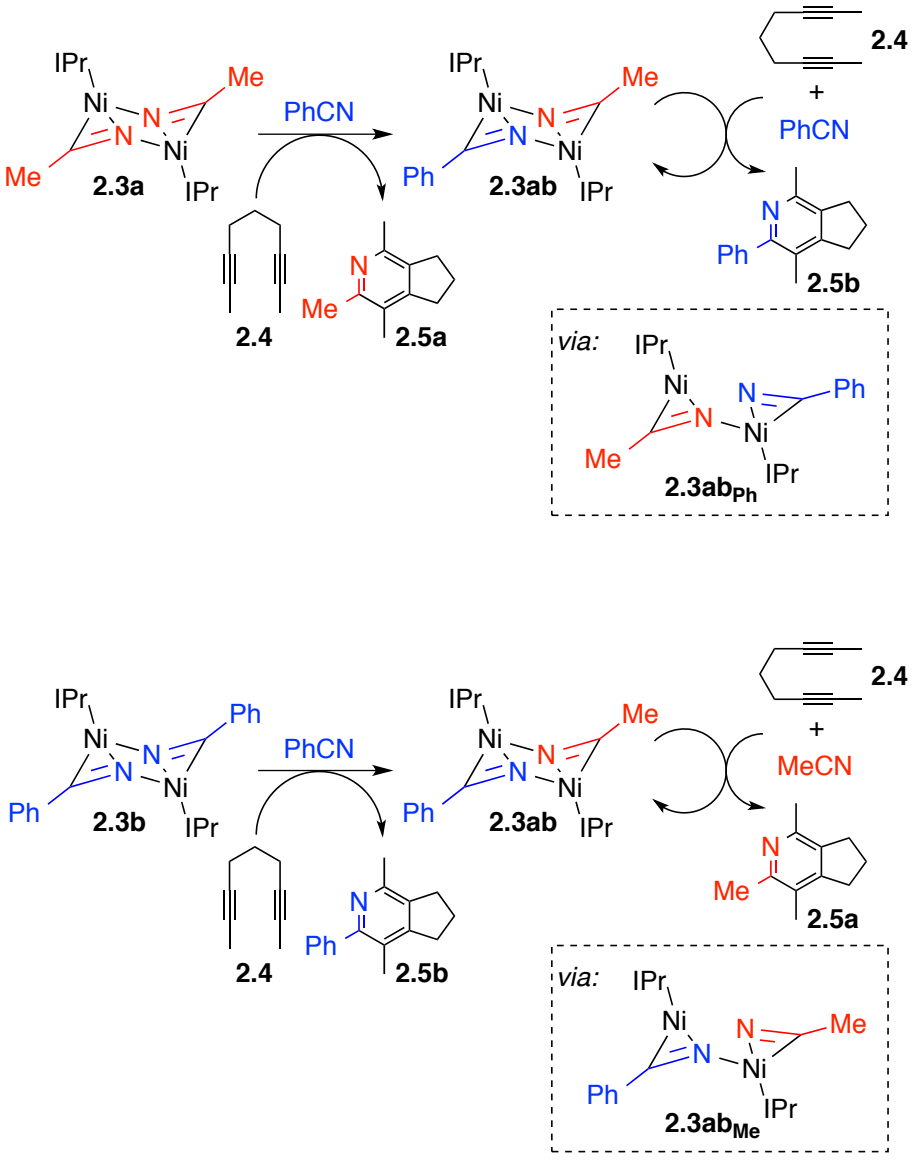
2.5a

Not Observed:

2.3a-d_2

(2.12)

elimination agrees not only with our kinetic data but our stoichiometric analyses, which showed the requirement of added nitrile for high pyridine yield (eq. 2.3). Nevertheless, our stoichiometric cross-cycloaddition reactions rule out pathway D since this pathway would provide pyridine products that incorporate the internally bound nitrile, rather than the exogenous nitrile. For example, in the reaction of MeCN-bound dimer **2.3a**, diyne **2.4**, and PhCN, pyridine **2.5b** (which incorporates exogenous PhCN) is formed almost exclusively. However, in the reaction of PhCN-bound dimer **2.3b**, diyne **2.4**, and MeCN, pyridines **2.5a** (which incorporates exogenous MeCN) and **2.5b** are formed almost equally with a moderate preference for **2.5b** (1:1.6, Table 2.2, entry 2). Furthermore, to account for these product distributions, the reactivity of a mixed dimer intermediate would react one way in the first reaction ($2.3_{\mathbf{abPh}}$) but in the opposite way in the latter reaction (**2.3**$_{\mathbf{abMe}}$, Scheme 2.6). Alternatively, if we were to explain the exclusive



Scheme 2.6. Contradictory Reactivities of **2.3$_{ab}$** Required by Pathway D to Account for Observed Product Ratios.

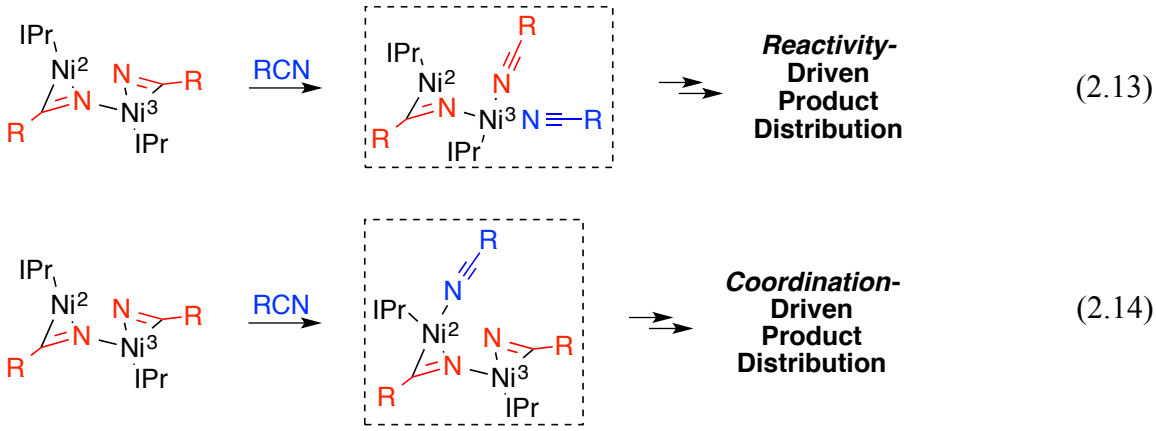
formation of **2.5b** through nitrile exchange, another contradiction would occur. That is, initial nitrile exchange of **2.3a** and PhCN would result in the formation of **2.3b** and MeCN. Yet, reaction of **2.3b** and MeCN (and diyne) afforded a mixture of products rather than almost exclusive formation of **2.5b** (Table 2.2, entry 1).

Our other cross-cycloaddition reactions further highlight this discrepancy. Incorporation of the exogenous nitrile cannot be explained solely through nitrile exchange. If this were true, higher incorporation of 4-CF_3-PhCN relative to 4-MeO-PhCN (since 4-CF_3-PhCN exchanges more readily than 4-MeO-PhCN) would be expected.

Instead, equal ratios of pyridine products are observed when 2.3b, diyne 2.4, and either 4-CF_3-PhCN or 4-MeO-PhCN are reacted (Table 2.1, entries 4 and 5). As such, the last of the initial mechanisms, pathway D, can be ruled out. Although delineating a detailed mechanism of a reaction with an early rate-determining step is difficult, our data suggest a mechanism that does indeed involve partial dimer opening.

However, rather than subsequent reaction with alkyne, nitrile binding immediately follows dimer opening since, regardless of electronic bias, the exogenous nitrile is selectively incorporated. Our kinetic data and all of our stoichiometric reactions suggest a nitrile cycloaddition mechanism past dimer opening that involves the following: 1. Both of the initially bound, endogenous nitriles must remain coordinated to the active catalyst throughout the entire reaction. Upon dimer opening, two unique nickel-coordination environments are formed (eq. 2.13). One is a two-coordinate (Ni_2) and the other three-coordinate (Ni_3). Coordination of the external nitrile to Ni_3 would occur in an η^1-fashion, owing to the congested steric-environment. As such, a hapticity-shift would need to occur in the exogenous nitrile in order for subsequent oxidative

heterocoupling. This is problematic in that selectivity for the exogenous nitrile would then be lost, and product distributions would be dictated by relative reactivities of the different nitriles, which is inconsistent with the observed product ratios. Alternatively, coordination of exogenous nitrile would occur at the less saturated Ni_2 (eq. 2.14). In this case, the internal (i.e., precoordinated) nitrile is in a unique $\eta^{2,1}$-μ-binding motif, which renders it inaccessible and/or unreactive. Thus, the exogenous nitrile remains in a coordination environment distinct from the internal nitrile. At this point, alkyne-binding leads to subsequent cycloaddition with the only reactive nitrile available, namely the exogenous nitrile, thereby resulting in the observed product distribution.

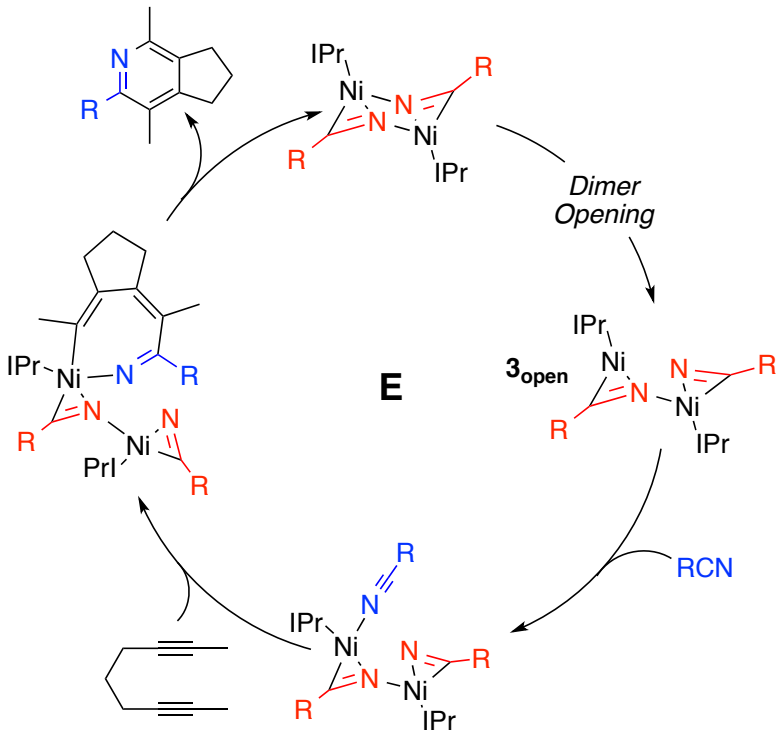


Alternatively, the catalyst maintains a bimetallic (or higher) motif. To accommodate the required continuous coordination of both initially bound, endogenous nitriles, a bimetallic complex is necessary. As previously mentioned, if the dissimilar nitriles ever occupy an equivalent coordination environment, either simultaneously or stepwise, the reactivity would be dictated by the relative reactivities of the nitriles themselves. In this context, if the catalyst split into a monomeric form, all nitrile

coordination-modes, and subsequent product distribution, would be dependent on the individual nitrile reactivities. Only through secondary coordination (aside from direct reaction) could nitrile resolution occur, in this case by effectively tying-up the internal nitrile.

Most likely, there may be competing pathways. Binding of an exogenous nitrile appears to follow dimer opening followed by cycloaddition. To account for the consistent incorporation of the internal nitrile, however, a competing pathway(s) must also be operative. Most likely, this arises through minimal nitrile exchange to facilitate the required coordination chemistry for cycloaddition. Taken together, a mechanism (Pathway E) that includes these requirements is summarized in Scheme 2.1.

In summary, a new class of Ni/RCN/NHC dimers have been isolated and characterized in an investigation of the unique reactivity of Ni/NHC systems with nitriles. These dimers were found to be catalytically competent in the [2 + 2 + 2]-cycloaddition of nitriles and diynes to form pyridines. While initial hypotheses focused on a dimer-to-monomer dissociative pathway, a first-order dependence solely on dimer, lack of dimer-crossover, and poor stoichiometric yields in the absence of free nitrile instead suggest a cycloaddition mechanism involving partial dimer opening as the rate-determining step. Immediate binding of an exogenous nitrile and subsequent reaction with diyne led to pyridine product as deduced from product ratios from competition reactions, ligand exchange reactions, and final outcome of the nickel species post-cycloaddition (Scheme 2.7). Future work on this system will be focused on computational experiments, which may aid in determining the coordination environment of the nickel intermediates that form after the rate-limiting step. In addition, recent success in *in situ* mass spectrometric methods may also help elucidate the structure of some complex intermediates.[21]



Scheme 2.7. Proposed Mechanism of [Ni(IPr)RCN]$_2$-Catalyzed Cycloaddition.

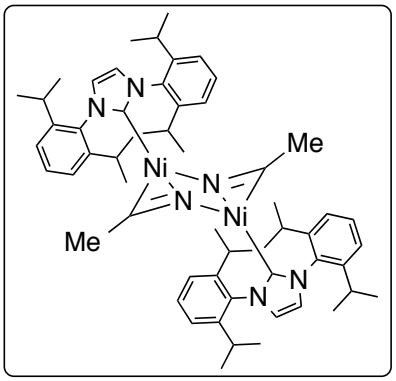
Experimental

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 and acetonitrile were dried over neutral alumina under N_2 using a Grubbs type solvent purification system. Benzonitrile was either distilled from CaH_2 prior to use or used from a sure-sealed bottle purchased directly from Sigma-Aldrich.

Methoxyacetonitrile was degassed but not dried before use. Deuterated solvents were purchased from Cambridge and used without further purification. Ni(COD)$_2$ was purchased from Strem and used without further purification. Diyne **2.4** was prepared according to literature procedures.[22] All other reagents were purchased and used without

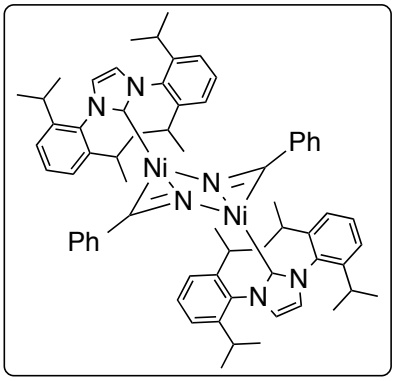
further purification unless otherwise noted.

Products **2.5a**-**2.5d** are known compounds and spectra were matched with reported values.[6a] ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 75 MHz, respectively, unless otherwise noted. All spectra are referenced to residual solvent peaks. 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, in that order. All ^{13}C NMR spectra were proton decoupled. Gas Chromatography was performed using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 minutes; detector temperature: 250 ºC.

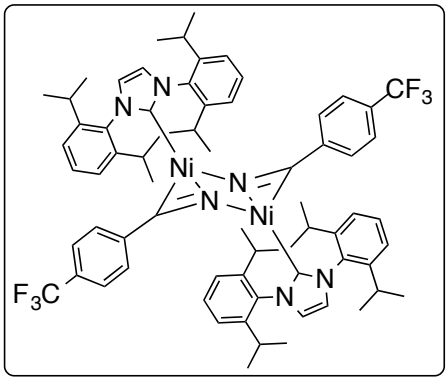


Syntheses of η^2-nitrile-bound nickel complexes. Preparation of $[Ni(MeCN)(IPr)]_2$ (2.3a) is as follows: $Ni(COD)_2$ (163 mg, 0.59 mmol) and IPr (230 mg, 0.59 mmol) was dissolved in hexane (10 mL). After stirring the reaction for 10 min, acetonitrile (24.4 mg, 0.59 mmol) was added. After stirring the reaction for 1 h, the red precipitate was isolated and dried in vacuuo to give **2.3a** (219 mg, 76 %). ^{1}H NMR (THF-d_8, ppm) δ 7.13-7.25 (m, 12H), 6.81 (s, 4H), 3.03 (m, 8H), 1.24 (s, 24H), 1.05 (s, 24H), 0.61 (s, 6H). ^{13}C NMR (THF-d_8, ppm) δ 199.8, 154.5, 146.9, 139.9, 129.2, 124.2, 123.4, 29.1, 24.9, 24.2, 9.0. IR (nujol, cm^{-1}) 1757. Anal. Calcd for $C_{58}H_{78}N_6Ni_2$: C, 71.33; H, 8.05; N, 8.60, found C, 71.17; H, 7.95; N, 8.69.

Preparation of $[Ni(PhCN)(IPr)]_2$ (2.3b) is as follows: $Ni(COD)_2$ (50 mg, 0.18 mmol) and IPr (70 mg, 0.18 mmol) was dissolved in hexane (5 mL). After stirring the reaction for 10 min, benzonitrile (22.2 mg, 0.22 mmol) was added. After stirring the

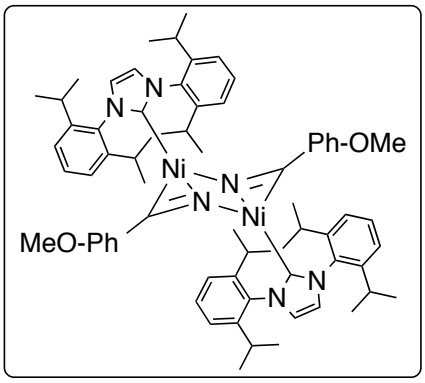


reaction for 1 h, the brown precipitate was collected. Cooling the mother liquor to -40 ºC induced further precipitation. The combined brown solid was dried in vacuuo to give 3b (78mg, 78 %). ^{1}H NMR (THF-d_8, ppm) δ 7.35–7.38 (m, 4H), 7.02–7.16 (m, 22H), 3.11 (m, 8H), 1.00 (d, 6.5Hz, 24H), 0.80 (d, 6.5 Hz, 24H). ^{13}C NMR (THF-d_8, ppm) δ 201.9, 157.7, 145.3, 137.4, 128.3, 127.5, 126.1, 125.9, 123.8, 122.7, 26.8, 24.0, 21.8. IR (nujol, cm^{-1}) 1758. Anal. Calcd for $C_{68}H_{82}N_6Ni_2$: C, 74.19; H, 7.51; N, 7.63, found C, 74.29; H, 7.35; N, 7.36.

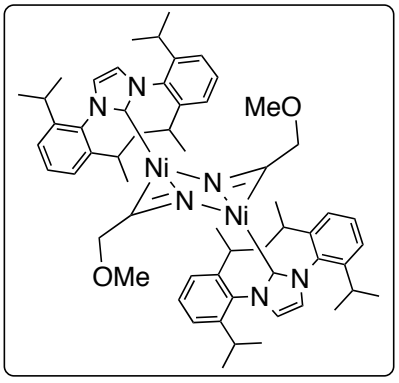


Preparation of [Ni(4-CF_3-C_6H_4CN)IPr]$_2$ (2.3c) is as follows: Ni(COD)$_2$ (55.6 mg, 0.202 mmol) and IPr (77.6 mg, 0.200 mmol) were dissolved in pentane (4 mL). After stirring the reaction for 10-15 min, 4-(triflouromethyl)benzonitrile (34.6 mg, 0.202 mmol), which had been dissolved in 0.5 ml pentane, was added. An additional 0.5 ml pentane was used to ensure complete transfer of nitrile to reaction mixture. After stirring for 1 h, the reaction mixture was cooled to -40 °C and allowed to sit overnight to induce maximum precipitation. The remaining pentane was decanted off and the precipitate dried under vacuuo to give **2.3c** as a very dark solid (84.7 mg, 68.6%). ^{1}H NMR (C_6D_6, ppm) δ 7.33 (d, 4H, 7.9 Hz), 7.17 (t, 4H, 7.7 Hz), 7.04 (d, 8H, 7.7 Hz), 6.77 (d, 4H, 7.9 Hz), 6.41 (s, 4H), 3.12 (sp, 8H, 6.7 Hz), 1.02 (d, 24H, 7.4 Hz), 1.01 (d, 24H, 7.4 Hz). ^{13}C NMR (C_6D_6, ppm) δ 200.7, 158.4, 146.8, 146.3, 138.43, 132.83, 131.1, 129.9, 129.4, 124.9, 124.5, 123.6, 28.8, 25.6, 23.6. IR (nujol, cm^{-1}): 1726, 1609. Anal. Calcd for

$C_{70}H_{80}F_6N_6Ni_2$: C, 67.98; H, 6.52; N, 6.79, found C, 67.93; H, 6.49; N, 6.61.

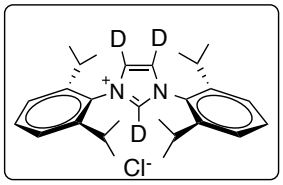


Preparation of [Ni(4-MeO-C_6H_4CN)IPr]$_2$ (2.3d) is as follows: Ni(COD)$_2$ (53.4 mg, 0.194 mmol) and IPr (77.6 mg, 0.200 mmol) were dissolved in pentane (4 mL). After stirring the reaction for 10-15 min, 4-methoxybenzonitrile (26.6 mg, 0.200 mmol), was added in one portion. An additional 0.5 ml pentane was used to ensure complete transfer of nitrile to reaction mixture. Then reaction became turbid after 15 min and an addition 10 mL pentane was added. After stirring for 1 h, the reaction mixture was cooled to -40 °C and allowed to sit overnight to induce maximum precipitation. The remaining pentane was decanted off and the precipitate dried under vacuuo to give **2.3d** as a light brown solid (96.8 mg, 86%).^{1}H NMR (THF-d_8, ppm) δ 7.25–7.30 (m, 8H), 7.08–7.28 (m, 8H), 6.72-6.85 (d, 8.8Hz, 4H), 6.57, (s, 4H), 3.34 (m, 8H), 3.30 (s, 6H), 1.10 (d, 6.5Hz, 24H), 1.05 (d, 6.5 Hz, 24H). ^{13}C NMR (THF-d_8, ppm) δ 204.5, 160.1, 158.6, 146.8, 138.9, 132.8, 131.7, 129.4, 123.8, 118.5, 113.5, 55.0, 28.6, 26.2, 23.9. IR (nujol, cm^{-1}) 1732, 1605.

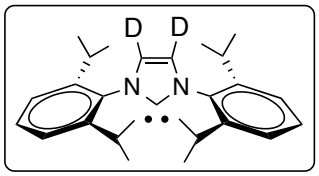


Preparation of [Ni(MeOCH$_2$CN)(IPr)]$_2$ (2.3e) is as follows: Ni(COD)$_2$ (54 mg, 0.20 mmol) and IPr (79 mg, 0.20 mmol) was dissolved in hexane (5 mL). After stirring the reaction for 10 min, methoxyacetonitrile (17.2 mg, 0.24 mmol) was added. After stirring the reaction for 1 h, the solution was cooled down to -40 ºC to induce precipitation. The solid obtained was further recrystallized from pentane at -40 ºC to give **2.3e** as a red solid (49mg, 48 %). ^{1}H NMR (THF-d_8, ppm) δ 7.16-7.28 (m,

12H), 6.38 (s, 4H), 3.16-3.26 (m, 12H), 2.97 (s, 6H), 1.39 (d, 6.9 Hz, 24H), 1.12 (d, 24H, 6.9 Hz). ^{13}C NMR (THF-d_8, ppm) δ 201.9, 157.7, 147.1, 139.5, 129.1, 124.3, 123.7, 62.3, 57.4, 28.9, 25.2, 23.8. IR (nujol, cm^{-1}) 1768, 1739. Anal. Calcd for $C_{60}H_{82}N_6Ni_2O_2$: C, 69.51; H, 7.97; N, 8.11, found C, 69.40; H, 7.94; N, 8.29. S4



Preparation of IPr·HCl-d$_3$[23] is as follows: IPr•HCl (1.5 g, 3.527 mmol) and K_2CO_3 (24.7 mg, 0.179 mmol) were added to a 50 mL roundbottom followed by ~6 ml D_2O. The reaction mixture was heated at 100 °C under N_2 for 24 h. After allowing the reaction to cool, remaining solvents were removed under reduced pressure. Once dry, the product was washed with hexanes before filtering to collect a white solid (1.35 g, 89 % yield). 100 % deuteration of backbone was observed with roughly 64 % deuteration of 2-position on imidazole ring. Theoretical yield assumes total deuteration of product. ^{1}H NMR ($CDCl_3$, ppm) δ 10.12 (s, <1H), 7.58 (t, 7.9 Hz, 2H), 7.36 (d, 7.78 Hz, 4H), 2.46 (septet, 6.7 Hz, 4H), 1.30 (d, 6.7 Hz, 12 H), 1.25 (d, 6.9 Hz, 12 H). ^{2}H NMR ($(CD_3)_2SO$, ppm) 3.50, 8.75. ^{13}C NMR ($CDCl_3$, ppm) δ 145.3, 132.4, 130.1, 128.6, 125.0, 29.4, 25.0, 24.0.



Preparation of IPr-d$_2$[6a] is as follows: A suspension was created by adding 1.05 equiv IPr•HCl-d_3 (397 mg, 0.927 mmol) to 10 mL diethyl ether in a 20 mL, oven-dried scintillation vial. To this was added 1.0 eq. KHMDS (183 mg, 0.89 mmol), which had been dissolved in 10 mL diethyl ether. The resulting mixture was stirred for 3 min before being filtered through celite followed by removal of solvent under vacuum. The resulting solid was recrystallized from diethyl ether to give 149.6 mg of white solid (43 % yield); < 3% proteated IPr remained (backbone position). Theoretical yield assumes total deuteration of product. ^{1}H NMR (C_6D_6, ppm) δ 7.30 (dd, 8.6, 6.7 Hz, 2H) 7.21-7.15 (m,

4H) 6.61 (s, <1H), 2.97 (sept, 6.9 Hz, 4H), 1.30 (d, 6.7 Hz, 12H) 1.19 (d, 6.9 Hz, 12H) ^{2}H NMR (C_6D_6), ppm) 6.58. ^{13}C NMR (C_6D_6, ppm) δ 221.0, 146.7, 139.4, 129.4, 124.1, 29.2, 25.1, 24.0.

A representative [Ni(IPr)RCN]$_2$-catalyzed cycloaddition is as follows: a stock solution of 3a was prepared by dissolving 28.4 mg (0.0290 mmol) in 1 ml toluene. Diyne **2.4** (59.2 mg, 0.251 mmol) was weighed into an oven-dried vial equipped with a magnetic stir bar and dissolved in 4.6 ml of toluene. Acetonitrile (13.1 μL, 0.25 mmol) and the catalyst (**2.3a**) stock solution (431.0 μL, 0.0125 mmol) were sequentially added to the diyne solution via micropipette. The reaction mixture was stirred for 1 h at room temperature before being quenched by exposure to air and acetone. Remaining solvent was removed under vacuum and the pyridine product was purified via flash chromatography (1:1 ethyl acetate to hexanes) to give 49.2 mg **2.5a** (71 % yield).

A representative stoichiometric cycloaddition is as follows: a stock solution of 3a was prepared by dissolving 41.1 mg (0.042 mmol) in 1 ml toluene. Diyne **2.4** (10.2 mg, 0.042 mmol) was weighed into an oven-dried vial equipped with a magnetic stir bar and dissolved in 3.5 ml of toluene. Acetonitrile (2.25 μL, 0.043 mmol) and the catalyst (**2.3a**) stock solution (431 μL, 0.0125 mmol) were sequentially added to the diyne solution via micropipette. The reaction mixture was stirred for 1 hr at room temperature before being quenched by exposure to air and acetone. Remaining solvent was removed under vacuum and the pyridine product was purified via flash chromatography (1:1 ethyl acetate to hexanes) to give 7.5 mg **2.5a** (64 % yield). For cross-cycloaddition, yields reported are NMR yields.

Dimer exchange experiments is as follows: dimer stock solutions: Dimers **2.2a** (27.7 mg, 0.028 mmol) and **2.2b** (14.6 mg, 0.013 mmol) were individually weighed into

separate oven-dried 5 mL vials. Benzene-d_6 (1 mL) was added to each vial and the solutions were stirred for 10-15 min. Benzene-d_6 (267 μL) was added to the NMR tube. The stock solutions of dimer **2.2a** (106 μL, 0.0030 mmol) and dimer **2.2b** (227 μL, 0.0030 mmol) were sequentially added to the NMR tube. The tube was sealed and then shaken and inverted to ensure proper mixing. ^{1}H NMR spectra were taken at 17 min and 29 min after mixing. No significant mixing of dimers was observed at either time point.

Procedures for the kinetic studies of the cycloaddition of MeCN with 4 and catalyst 3a via observation of the reaction progress by 1H NMR spectroscopy. Order in **3a** was determined as follows: Stock solution #1 was prepared by dissolution of 213.2 mg (0.90 mmol) of **2.4** and 115.1 mg (0.68 mmol) of 1,3,5,-trimethoxybenzene (internal standard) in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 298.6 mg (7.27 mmol) of acetonitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 34.8 mg (0.036 mmol) of **2.3a** in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 33 μL of solution #1, 21 μL of solution #2, and an appropriate volume of solution #3. An amount of toluene-d_8 was then added to make a total of 0.6 mL solution. Reactions were monitored by ^{1}H NMR spectroscopy at 0 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of 3a (k_{obs}, [3a]): 1.6×10^{-5} M·s^{-1}, 3.0×10^{-3} M; 2.2×10^{-5} M·s^{-1}, 4.4×10^{-3} M; 3.5×10^{-5} M·s^{-1}, 6.5×10^{-3} M; 5.5×10^{-5} M·s^{-1}, 10.9×10^{-3} M.

Order in acetonitrile was determined as follows: Stock solution #1 was prepared by dissolution of 213.2 mg (0.90 mmol) of **2.4** and 115.1 mg (0.68 mmol) of 1,3,5,-trimethoxybenzene (internal standard) in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 298.6 mg (7.27 mmol) of acetonitrile in

toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 34.8 mg (0.036 mmol) of **2.3a** in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurements were prepared by adding 33 μL of solution #1, 50 μL of solution #3, and an appropriate volume of solution #2. An amount toluene-d_8 was then added to make a total of 0.6 mL solution. Reactions were monitored by ^{1}H NMR spectroscopy at 0 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of acetonitrile (k_{obs}, [MeCN]): 1.7×10^{-5} M·s^{-1}, 0.25 M; 1.7×10^{-5} M·s^{-1}, 0.50 M; 1.7×10^{-5} M·s^{-1}, 0.75 M.

Order in IPr was determined as follows: Stock solution #1 was prepared by dissolution of 213.2 mg (0.90 mmol) of **2.4** and 115.1 mg (0.68 mmol) of 1,3,5,-trimethoxybenzene (internal standard) in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 298.6 mg (7.27 mmol) of acetonitrile in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 34.8 mg (0.036 mmol) of **2.3a** in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #4 was prepared by dissolution of 36.6 mg (0.094 mmol) of IPr in toluene-d_8 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 33 μL of solution #1, 21 μL of solution #2, 108 μL of solution #3, and an appropriate volume of solution #4. An amount of toluene-d_8 was then added to make a total of 0.6 mL solution. Reactions were monitored by ^{1}H NMR spectroscopy at 0 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of IPr (k_{obs}, [IPr]): 3.5×10^{-5} M·s^{-1}, 0.8×10^{-3} M; 3.8×10^{-5} M·s^{-1}, 1.5×10^{-3} M; 3.9×10^{-5} M·s^{-1}, 2.3×10^{-3} M; 3.9×10^{-5} M·s^{-1}, 3.0×10^{-3} M; 4.0×10^{-5} M·s^{-1}, 3.8×10^{-3} M; 3.9×10^{-5} M·s^{-1}, 4.5×10^{-3} M; 3.8×10^{-5} M·s^{-1}, 6.8×10^{-3}

Deuterated IPr exchange reactions. A stock solution was prepared by

dissolution of 19.6 mg (0.0200 mmol) of **2.3a** in benzene-d_6 in a 2.00 ± 0.01 mL volumetric flask. Similarly, a stock solution of deuterated IPr and ferrocene (internal standard) was prepared by dissolution of 80.5 mg (0.206 mmol) IPr-d_2 followed by 10.2 mg (0.0548 mmol) of ferrocene in benzene-d_6 in a 2.00 ± 0.01 mL volumetric flask. A stock solution was prepared by dissolution of 50.0 µL (0.957 mmol) of MeCN in 450 µL of benzene-d_6 in a 5 mL oven-dried vial. Solutions were added to two NMR tubes in the following order: 189 µL and 182.4 µL benzene-d_6 respectively, 117.2 µL IPr-d_2/ferrocene stock solution, 6.3 µL MeCN stock (to second tube only), and finally 294.1 µL dimer **2.2a** stock solution. The NMR tubes were equipped with septa caps before being shaken and inverted to ensure total mixing. Spectra were taken at after 1 h and compared to an NMR sample made of only IPr-d_2/ferrocene stock solution.

Cycloadditions preformed in the presence of IPr-d_2 followed the representative stoichiometric cycloaddition procedure with the addition of IPr-d_2 to the reaction flask prior to the diyne stock solution.

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CHAPTER 3

BRIEF YET FRUITFUL: INITIAL INVESTIGATIONS INTO THE MECHANISM OF THE NI(COD)$_2$/XANTPHOS-CATALYZED [2+2+2]-CYCLOADDITION OF ALKYNES AND NITRILES TO AFFORD PYRIDINES

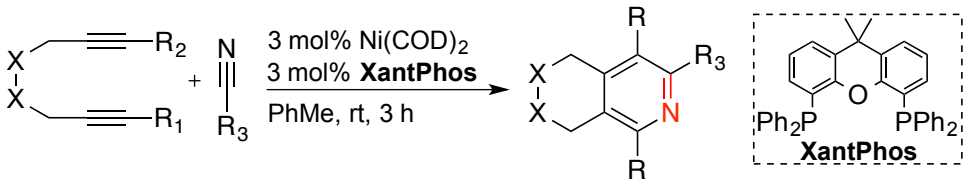
Abstract

Initial investigations into the mechanism of the unprecedented cycloaddition of diynes and nitriles catalyzed by Ni(COD)$_2$/Xantphos was conducted. Our brief, yet fruitful investigations into this mechanism reveal that the reaction proceeds via a heterocoupling pathway consistent with other nickel-based cycloaddition catalysts. Kinetic analysis of two discreet catalysts reveal consistent lack of order in all substrates but catalysts, suggesting a (Xantphos)Ni(diyne) resting state. The kinetic studies also suggest a rate-limiting partial Xantphos dissociation. In the course of this investigation, two intriguing (Xantphos)Ni-complexes were isolated. These complexes will be further investigated both as coordination compounds as well as for their competency as catalysts.

Introduction

As thoroughly discussed in Chapter 1, nickel-based catalysts for the [2+2+2]-cycloaddition of nitriles and diynes are an unexpected success. From our mechanistic

evaluations of both $Ni(NHC)_2$ and $[Ni(IPr)RCN]_2$-catalysts, we concluded that the sterically-large coordination environment in combination with the strong donation properties provided by the carbene ligands were critical for the formation of pyridines. The steric protection afforded by such sterically demanding ligands results in initial coordination of nitriles over alkynes, forcing a heterocoupling pathway. The strong σ–donation of these ligands facilitates the heterooxidative coupling of an alkyne and nitrile, which had been shown previously to be energetically unfavorable for other cycloaddition catalysts.[1] We recently reported that $Ni(COD)_2$ in the presence of Xantphos was an excellent catalyst for the cycloaddition of diynes and nitriles to afford bicyclic pyridines, often out-competing our previously reported $Ni(NHC)_2$-catalysts (eq. 3.1). In as much, we were incredibly surprised by the serendipitous discovery that an unrelated ligand set is also capable in a reaction that we proposed to require such *special constraints* for successful catalysis.



(3.1)

Although there are clear dissimilarities between a chelating arylphosphine and a monodentate carbene, both ligand sets have a considerable steric bulk. Due to the conformationally constrained tricyclic xanthene backbone, the rigidity afforded by Xantphos affords a bite angle of 109-121°. With additional aryl-substituents on the phosphorus atoms, a bite angle this large equates to a cone angle of roughly 250-300° as observed for Pd-, Rh-, and Pt-complexes.[2] While specific cone angles are not reported for

nickel-bound IPr or SIPr, a number of computational studies, particularly on Grubbs-type Ru-IMes fragments, have reported calculated cone angles between 200-240°.[3]

Ligand effects in catalysis were reviewed for the first time by Tolman (Figure 3.1).[4] The review was inspired by the observed effects the donating ability of the phosphine ligands had in catalytic polymerization, hydrogenation, and hydroformylation. Later studies revealed that systematic steric effects are just as important in modulating the activity of catalysts.[5] Tolman later quantified the steric parameters in terms of the cone angle (θ), defined as the apex angle of a cylindrical cone, centered at 2.28 Å from the center of the P atom, which touches the outermost atoms of the model.[4] In this sense, direct comparisons of IPr or SIPr and monodentate phosphines is rather simplistic, and has been reviewed extensively.[6] However, while this steric parameter works well to evaluate monodentate ligand effects, the model is incomplete when applied to bidentate (or higher order) ligands, such as Xantphos. The coordination chemistry of chelating phosphines began as little more than a novelty, but found considerable application in catalysis for use in asymmetric catalytic hydrogenation due to their rigidity,[7] a property previously blamed for their lack of productivity in other catalytic processes.[8] Considerable attempts to quantify the steric and electronic effects have been met with inconsistency or often require costly or otherwise prohibitive computational characterization. Empirically, bidentate phosphines follow similar electronic trends at monodentate ligands, wherein similar phosphine substituent effects affect the donating ability of the individual phosphorous atoms. However, coordination geometry often plays an equal, if not greater, electronic effect. The geometry of chelation has a considerable electronic effect on the metal center as it can strain and distort the ligand field of the

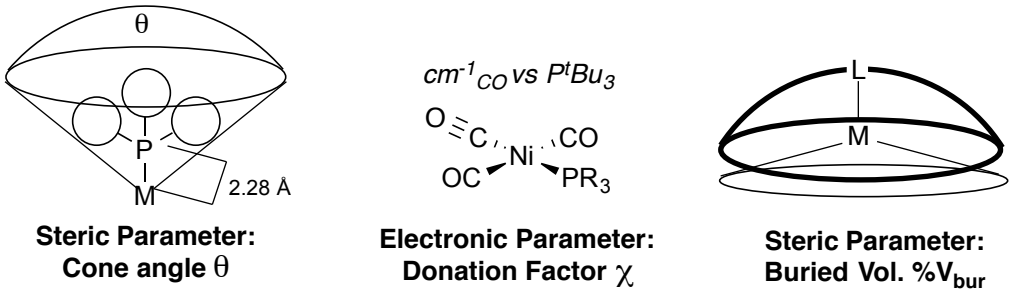


Figure 3.1. Quantitative Ligand Parameters for Monodentate Ligands.

Metal -center away from lower-energy confirmations, leading to a propensity to undergo redox chemistry in order to alleviate this strain.[9] The coordination-based electronic effect can be tied nicely to the steric properties of these ligands. A generalized method for predictive chelational preferences of bidentate ligands, and subsequent steric and electronic parameters was recently developed.[10] The model is based on the natural bite angle and the flexibility range for diphosphine ligands, which can be calculated by simple and cost-effective molecular mechanics calculations. The natural bite angle (β_n) is defined as the preferred chelation angle determined by ligand backbone only and not by metal valence angles. The flexibility range is defined as the accessible range of bite angles within 3 kcal/mol^{-1} of the excess strain energy from the calculated natural bite angle (Figure 3.2). While not originating from a bite angle, conformational constraints also dictate the electronic properties of Ni(NHC)$_2$-catalysts. Unlike arylphosphines that demonstrate both moderate σ-donation and π-back bonding, *N*-Heterocyclic carbene ligands are strong σ-donating ligands that have little to no π-back bonding.[11] However, considering the steric bulk of IPr, SIPr, and IMes, only two ligands can coordinate to a nickel-atom and, in the case of Ni^0, this effect leaves a linear, coordinatively unsaturated,

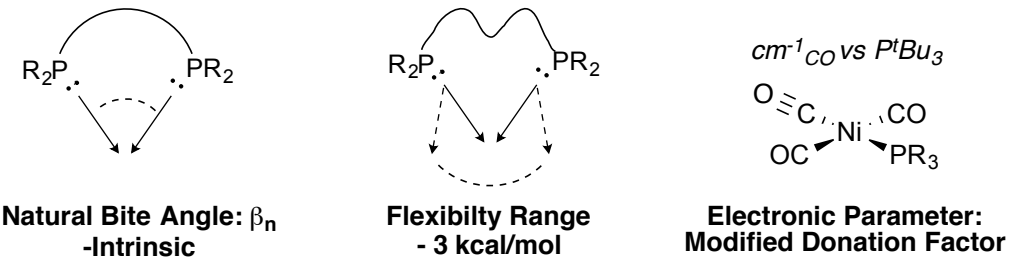


Figure 3.2. Quantitative Ligand Parameters for Chelating Diphosphines.

extremely electron-rich catalyst. In this context, Xantphos is special, even within the family of chelating phosphines. van Leeuwen found that diphosphines with a semirigid xanthene-aromatic backbones would enforce coordination modes between *cis* and *trans* (Figure 3.3).[12] Because of their butterfly-like structure, the donor atoms of xanthene-type ligands are well oriented to form complexes with bite angles of 90°. Mechanistic proposals of Rh-catalyzed hydroformylation suggested that bidentate ligands that would enforce a coordination angle of 100-120° were expected to have a positive effect on the linear-selectivity of the products.[13] The bite angle of Xantphos was found to stabilize traditionally unstable critical trigonal bipyramidal intermediates even at high temperatures, leading to linearly selective catalysts with high turnover.

In addition to its application in hydroformylation reactions, Xantphos and Xantphos-like ligands are well-represented in Pd-catalyzed aryl amination, and nickel-catalyzed hydrocyanation chemistry. The nickel-catalyzed hydrocyanation of butadiene and subsequent isomerization of 2-methyl-3-butenenitrile is one of the key steps of the so-called DuPont process, one of the largest-scale applications of homogeneous transition metal catalysis.[14] Once again, the unique bite angle and dynamic range were critical for

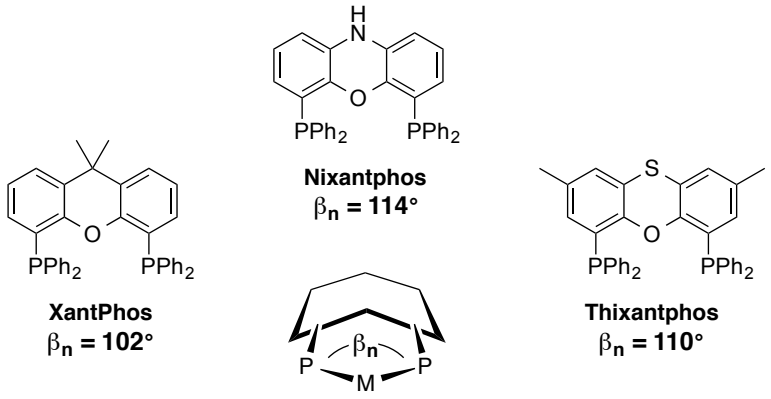


Figure 3.3. Selected Xantphos-type Ligands and General Coordination Mode.

stabilizing previously unstable intermediates and destabilizing stable intermediates.

During our mechanistic evaluations of the $Ni(NHC)_2$-catalyzed cycloaddition of nitriles and diynes, we believed that only the unique properties of the carbene ligands allowed for the selective formation of pyridines dictated by ligand-directed initial nitrile coordination. This hypothesis, however, seems incomplete considering the success we have observed with the $Ni(COD)_2$/Xantphos-catalyzed reaction. Although $Ni(COD)_2$/Xantphos out-competes $Ni(NHC)_2$-catalysts in nearly all competitive cycloadditions, limitations remain, namely the inability of $Ni(COD)_2$/Xantphos to catalyze a cocycloaddition of two alkynes and a nitrile. To investigate the role of Xantphos in these cycloadditions and to compare the two catalytic mechanisms, we decided to pursue a mechanistic evaluation of the $Ni(COD)_2$/Xantphos cycloaddition of diynes and nitriles. By doing so, we hope to build a cohesive picture as to why nickel is such a prolific cycloaddition catalyst and to exploit these findings toward overcoming the substrate limitations.

Results

Initial investigations were directed toward observation of the reaction of $Ni(COD)_2$ and Xantphos in solution. In order to reduce variables in our mechanistic evaluation, we were hopeful of isolating a singular Ni/Xantphos species to test. However, we were skeptical owing to no reports of such a species in such a wealth of literature. True to our hypothesis, upon stirring $Ni(COD)_2$ and Xantphos (1:1) in C_6D_6 for 20 min, the combination of ^{1}H- and ^{31}P-NMR revealed a complex mixture. The ^{1}H-NMR spectrum was fairly inconclusive, as the aromatic region was broad and complex, with only a few identifiable resonances corresponding to small amount of free Xantphos and unligated $Ni(COD)_2$.

The ^{31}P-NMR spectrum was far more conclusive, wherein only three resonances were observable: a small resonance corresponding to free Xantphos, a large multiplet (ddd) indicative of a AA'XX' pattern typical for double coordination of distorted bidentate phosphines (Figure 3.4),[5,15] and smaller downfield singlet we attribute to a Ni(Xantphos)(COD) complex.[16] Variation of the equivalents of Xantphos to $Ni(COD)_2$ always resulted in the presence of all of these species, albeit in variable amounts. When excess Xantphos is used (>1.2 equiv), precipitation of a red insoluble powder was observed. The rate of precipitation qualitatively increased with the relative equivalents of Xantphos used.

Due to insolubility, the powder was not characterized fully but was identified as aggregates of $Ni(Xantphos)_2$ by HRMS. Considering this complex equilibrium, we turned our efforts toward alternate methods to afford a Ni^0(Xantphos) complex. We approached this synthesis in two strategies. First is the synthesis of mixed ligand (Xantphos)NiL_n

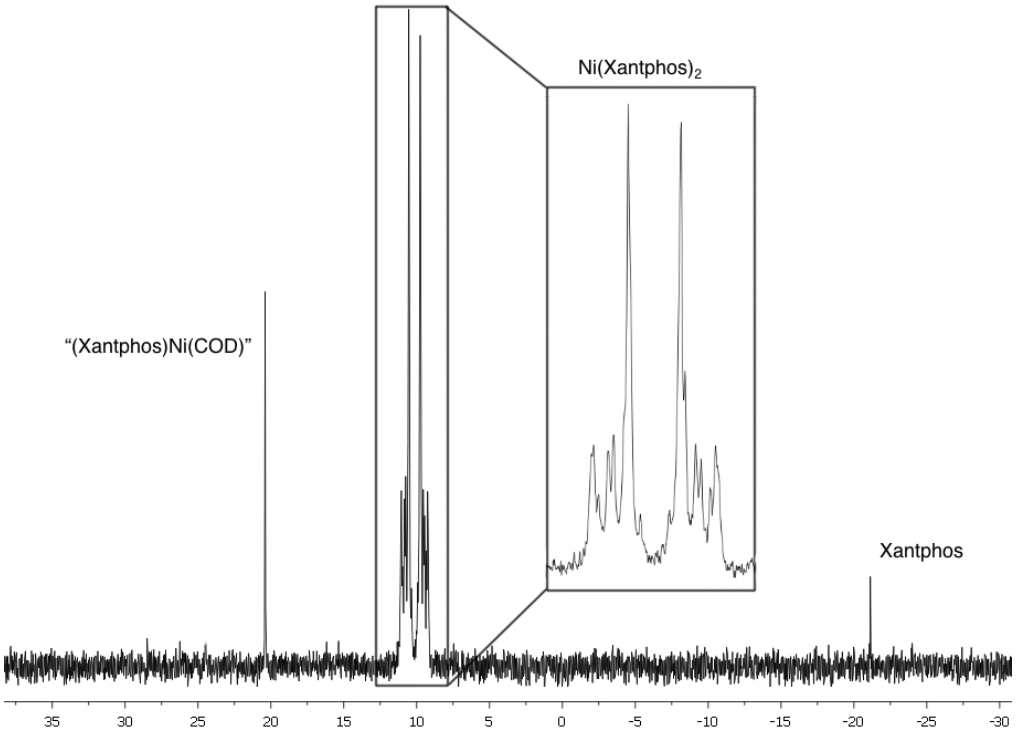


Figure 3.4. ^{31}P-NMR of the 1:1 Mixture of $Ni(COD)_2$ and Xantphos in C_6D_6.

complexes from ligand substitution of (Xantphos)Ni(COD) generated *in situ*. Second was to form (Xantphos)NiL_n complexes from reductive ligation of (Xantphos)NiX_2 complexes.

Ligand substitutions were conducted by simple stirring of $Ni(COD)_2$ (1 equiv), Xantphos (1 equiv), and a supporting ligand in varying amounts (Figure 3.5). We felt that the use of nitrile or alkynes as a supporting ligand may be possible. In the original investigations, we found that, unlike $Ni(NHC)_2$-catalysts, $Ni(COD)_2$/Xantphos does not catalyze the three component cycloaddition of alkynes with nitriles to afford either arene or pyridine products. Due to this observation, we believed we may be able to use alkynes or nitriles as supporting ligands to yield isolable complexes. However, under a number of reaction conditions, we were always met with a red insoluble powder with a red to red-

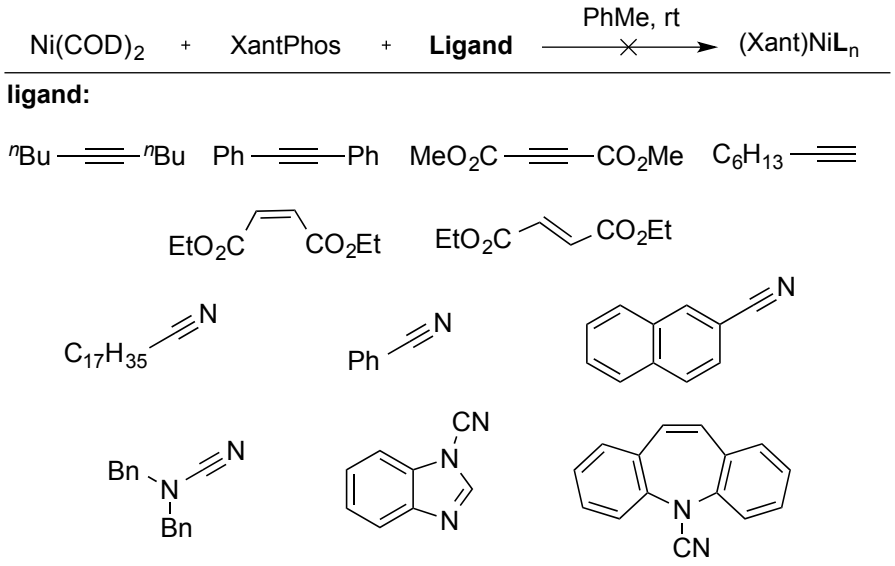


Figure 3.5. Attempted Ligand Substitution to Afford (Xantphos)Ni^0L_n Complexes

brown reaction mixture. Analysis of the crude reaction mixture by ^{31}P-NMR displayed an identical spectrum to the $Ni(COD)_2$/Xantphos mixture or only $Ni(Xantphos)_2$.

In order to avoid the formation of $Ni(Xantphos)_2$, we attempted reductive ligation from $Ni(Xantphos)X_2$ (Table 3.1). Initial investigations utilized NaHg amalgam in the presence of potential supporting ligands such as COD, alkynes, nitriles, etc. These reductions once again were screened with a number of nickel sources, temperatures, solvents, and concentrations. Crude ^{31}P-NMR analysis revealed a lack of any ^{31}P-resonances, or a complex unidentifiable mixture. Believing perhaps Na was too strong of a reductant, we switched to more mild MgHg amalgam. The same screening of reaction conditions as NaHg were conducted, but once again, we were met with dismay. However, when $Ni(Xantphos)Cl_2$ was reduced with MgHg in the presence of COD at room temperature for 2 h, ^{31}P-NMR analysis revealed the formation of a resonance indicative

Table 3.1. Attempted Reductive Ligation of (Xantphos)NiX_2

X	reductant	ligand	result
Cl, Br	NaHg	COD	———
Cl, Br	NaHg	diethyl fumarate	———
Cl, Br	NaHg	Ph—≡—Ph	———
Cl, Br	NaHg	^{n}Bu—≡—^{n}Bu	———
Cl	MgHg	COD	red soln, singluar ^{31}P, unisolable
Cl	MgHg	diethyl fumarate	———
Cl	MgHg	Ph—≡—Ph	———
Cl	MgHg	^{n}Bu—≡—^{n}Bu	———
Br	DIBALH	COD	———
Br	$KHBEt_3$	COD	———
Br	$(TMEDA)MgMe_2$	COD	yellow soln, singluar ^{31}P, unisolable
Br	^{n}BuLi	COD	———
Br	PhLi	COD	———
Br	MeLi	COD	yellow soln, singluar ^{31}P, unisolable
Br	$Li(Naphth)^{\bullet-}$	COD	———

of Ni(Xantphos)(COD). All attempts to isolate this compound only resulted in the formation of $Ni(Xantphos)_2$. The use of organometallic reducing agents such as organolithiates and Grignard reagents was met with similar failures.

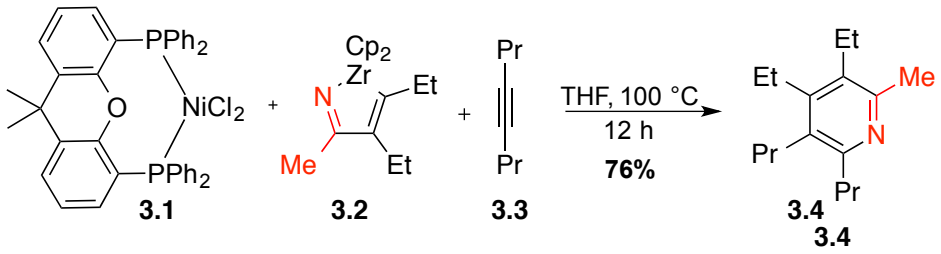
Considering the equilibrium between $Ni(COD)_2$, Xantphos, Ni(Xantphos)(COD), and $Ni(Xantphos)_2$, we were hesitant to pursue kinetic analysis as extraction of usable data would be complex, if at all possible. None-the-less, due to the reasonable reaction times and high yields of the reaction, we felt observation of the reaction would be easy. What we observed was a first-order dependence in catalyst, zero-order in diyne, nitrile, and COD (see experimental section for details).

We also observed a minimal effect on rate when using PhCN and ^{i}PrCN, and unlike $Ni(IPr)_2$, there is no change in order in nitrile. Addition of excess Xantphos

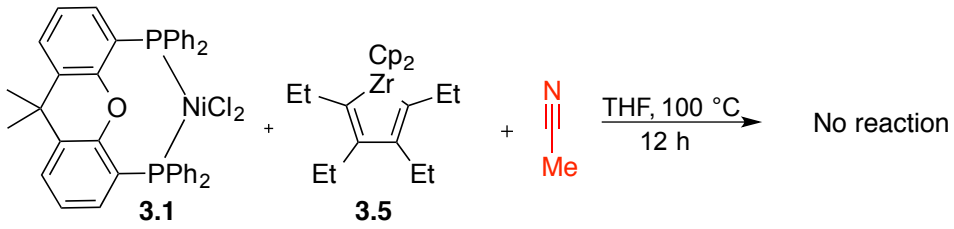
resulted in reaction retardation, without a clear order or consistent reaction behavior. Since we expected large kinetic contributions from the $Ni(COD)_2$/Xantphos equilibrium, we were surprised by lack of order in COD. Sparsely soluble $Ni(Xantphos)_2$ is entirely incompetent as a catalyst. This suggests, not surprisingly, that Ni(Xantphos)(COD) is an active species or active precatalyst, as neither Ni(COD) or $Ni(Xantphos)_2$ is catalytically active. If it is, the equilibrium should be dependent on COD, if not in the precatalytic equilibrium, at least in the subsequent steps.

As mentioned in Chapter 1, Takahashi has previously shown that pyridines can be prepared in a stoichiometric protocol by proposed transmetallation from zirconapyrroles to $Ni(PPh_3)_2Cl_2$ followed by nickel-mediated insertion of an exogenous alkyne and reductive elimination.[17] We saw identical trends with transmetallative reactions between homo- and heterocoupled zirconacycles and $IPrNi(acac)_2$. Once again, to glean insight into the intermediacy of nickelcyclopentadienes and nickelapyrroles, similar stoichiometric protocols were carried out with $(Xantphos)NiCl_2$.

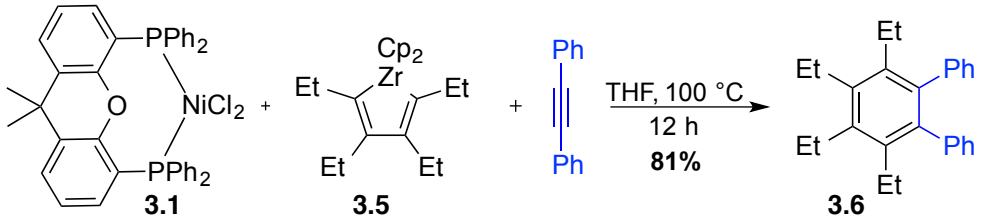
In a similar protocol as $IPrNi(acac)_2$, $(Xantphos)NiCl_2$ (**3.1**) was subjected to zirconapyrrole **3.2** and dissimilar alkyne **3.3** (eq. 3.2). The reaction afforded unsymmetrical pyridine **3.4** as a single regioisomer[36a] in 76% yield. The reaction of zirconapentadiene **3.5** and **3.1** in the presence of MeCN failed to produce expected pyridine product (eq. 3.3). The reaction of **3.5** and **3.1** in the presence of diphenylacetylene, however, afforded polysubstituted benzene **3.6** in 81% yield (eq. 3.4), verifying that transmetallation from zirconacyclopentadiene was occurring, but without subsequent insertion of nitrile. These results suggest, as with the $Ni(IPr)_2$-catalyzed reaction, that a heterocoupling pathway is operative. Due to the low solubility we observe



(3.2)



(3.3)



(3.4)

with Ni(Xantphos)$_n$ complexes and the excellent solubility of the aforementioned zirconcene complexes, isolation of the proposed nickelapyrrole via transmetallation may be feasible. Compounds **3.1** and **3.2** were exposed to the standard transmetallation conditions without exogenous nitrile or alkyne (eq. 3.5). The resultant cloudy red-brown solution was condensed, extracted with pentane, filtered, and redissolved in benzene. Crude NMR analysis was inconclusive. In attempts to isolate the proposed nickelacycle, the crude brown benzene solution was placed in a diffusion chamber with pentane. After two days, the solution turned yellow, with the formation of yellow crystals suitable for X-ray structural analysis. Instead of expected nickelacycle **3.7**, what we isolated was a (Xantphos)Ni^{I}Br complex **3.8** (Figure 3.6).

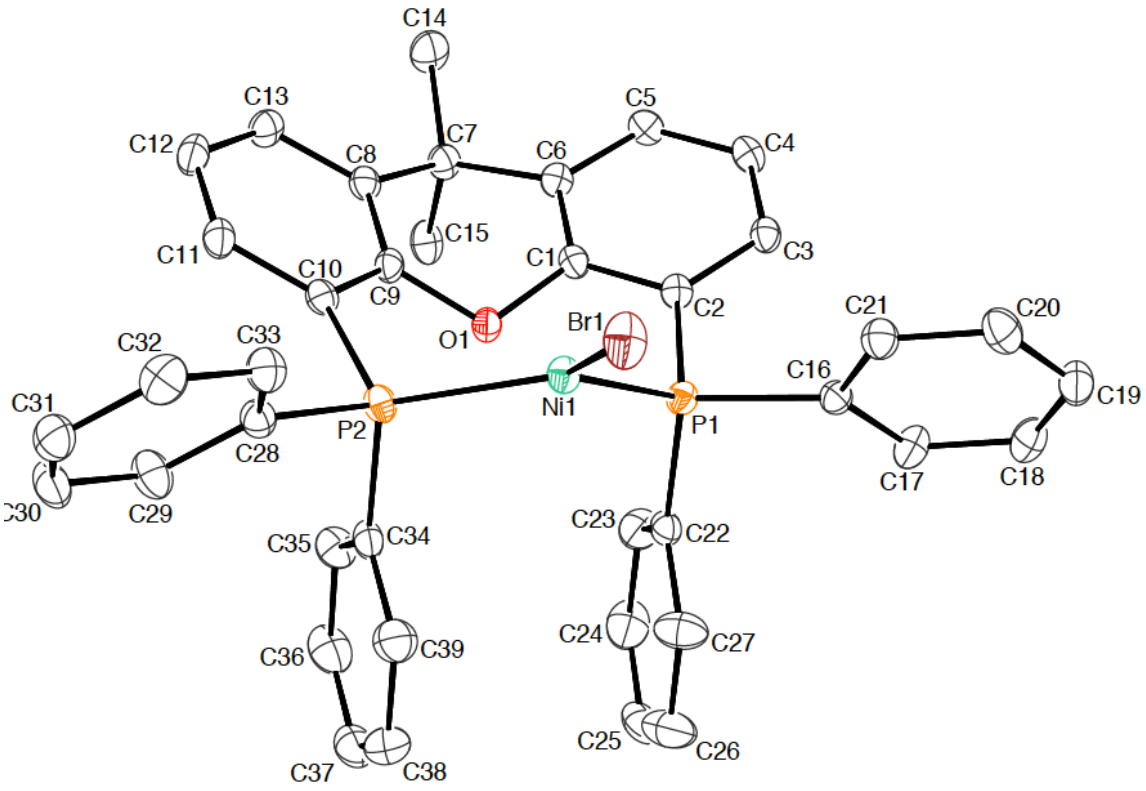
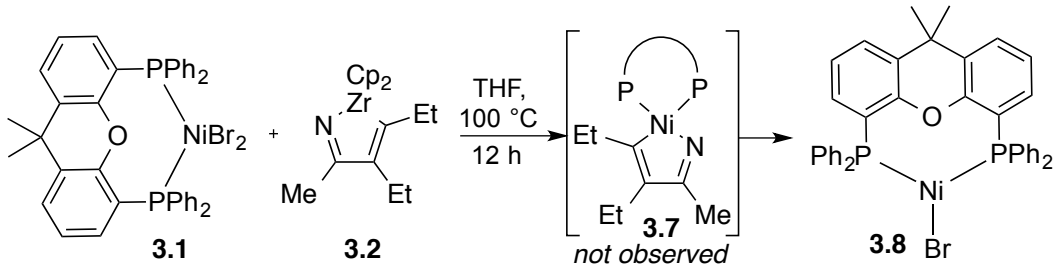


Figure 3.6. ORTEP Plot of (Xantphos)Ni^{I}Br. Selected Bond Lengths: Ni(1)-P(1): 2.260 Å, Ni(1)-P(2): 2.252 Å, Ni(1)-Br(1): 2.304 Å. Ni(1)-O(1) Distance: 3.325 Å. Selected Bond Angles: P(1)-Ni(1)-P(2): 108.719°, P(1)-Ni(1)-Br(1): 125.600°, P(2)-Ni(1)-Br(1): 125.465°.

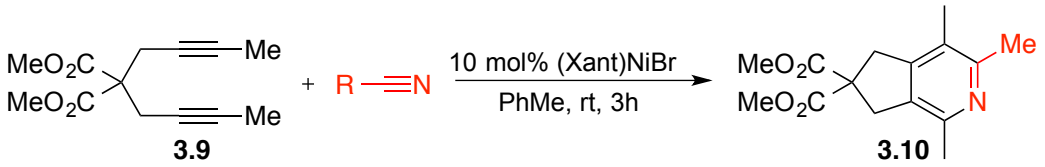


(3.5)

Initially perplexed as to how this species was generated in the reaction, we believe a similar comproportionation mechanism observed in the formation of $(NHC)_2Ni^{I}X$ complexes may be at play.[18]

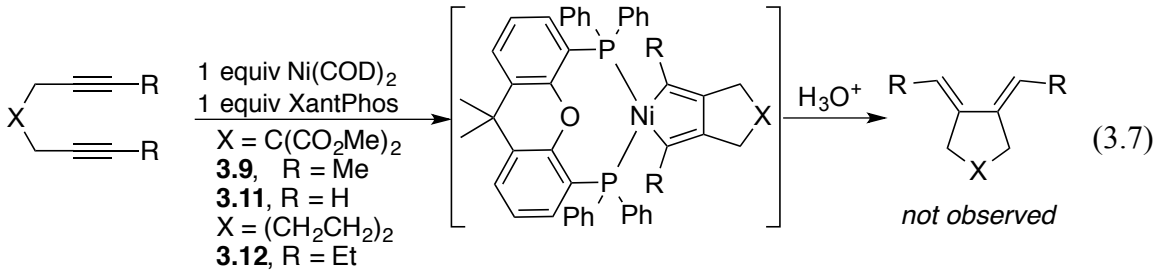
Possible comproportionation was tested by mixing 1 equiv of $Ni(Xantphos)Br_2$ with 1 equiv of a 1:1 solution of $Ni(COD)_2$/Xantphos in THF. The muddy red-brown solution turned dark yellow within 2 h, affording crystals of $(Xantphos)Ni^{I}Br$ upon filtering and cooling.

While divergent from the initial aims of this project, this compound and the mechanism of its formation are deserving of a focused study. The mechanisms of organonickel-catalyzed reactions are often assumed to involve nickel intermediates in the oxidation states of +2 and 0. Although some mechanistic studies have proposed addition/elimination reaction sequences that require the presence of Ni^{1}-Ni^{III} redox cycle,[19] such mechanisms are often difficult to verify, due to the relative scarcity of model complexes in these oxidation states.[20] Inorganic complexes of Ni(I) have considerable precedent,[21] although such simply accessed and monometallic species are rare. Unexpectedly, $(Xantphos)Ni^{I}Br$ catalyzes the cycloaddition of model diyne 3.9 and MeCN (eq. 3.6), albeit in significantly extended reaction times (3 h with 10 mol% Ni^{I}). Mechanistically, this reaction occurs in three generalized scenarios: 1) the compound is impure, with residual Ni^{0}; 2) The dis/comproportionation is reversible, generating Ni^{0} *in situ*; or 3) a true Ni^{I}-Ni^{III} redox cycle. Observation of the $Ni(COD)_2$/Xantphos-mediated stoichiometric reaction of model diyne **3.9** and MeCN by ^{31}P-NMR has led to great insight into the reactivity of our method. During the initial development of the



(3.6)

$Ni(COD)_2$/Xantphos-catalyzed cycloaddition, we observed dimerization of diyne in the absence of nitriles, consistent with other cycloaddition catalysts. Observation by ^{31}P-NMR of a 1:10 mixture of $Ni(COD)_2$/Xantphos and diyne **3.9** revealed the disappearance of the singlet resonance at 19.6 ppm, with the appearance of a new resonance at 17.45, concurrent with a stark color change from dark red to dark brown. Analysis of the reaction mixture after 30 min by GC/MS revealed the incomplete formation of dimerized diyne. Following this result, 1:1 mixture of $Ni(COD)_2$/Xantphos and either diyne **3.9**, **3.11**, or **3.12** was allowed to stir for 15 min, once again changing from red to brown. After 15 min, the crude reaction mixtures were quenched with 1M HCl. We reasoned that since dimerization was fairly slow, we may intercept an oxidative addition product and effectively quench this intermediate with acid affording diene products. However, we only observed minor dimerization and recovered diyne, with no trace of homocoupled diyne (eq. 3.7). We suspected this result was indicative of an (Xantphos)Ni(Diyne) complex. When the 1:1:1 mixture of $Ni(COD)_2$, Xantphos, and diyne **3.9** was taken to dryness, the ^{1}H-NMR was poorly resolved with broad indeterminate resonances. In general, the $Ni(COD)_2$/Xantphos is not a suitable catalyst for the cycloaddition of terminal diynes and nitriles, and even more surprising is that consumption of terminal diyne either with or without the presence of nitrile is minimal. The lack of conversion stands in stark contrast to the $Ni(NHC)_2$ catalysts, which will react with electron-poor nitriles with complete consumption of terminal diyne with or without nitrile.



(3.7)

Observation by ^{31}P-NMR of the stoichiometric cycloaddition of terminal diyne **3.11** and MeCN mediated by Ni(COD)$_2$/Xantphos shows similar consumption of the resonance at 19.6 with an appearance of a resonance at 17.6 ppm.

Another surprising difference between our Ni(NHC)$_2$ and Ni(COD)$_2$/Xantphos catalytic systems is the inability of Ni(COD)$_2$/Xantphos to catalyzed the three component cycloaddition of alkynes and nitriles. Investigations revealed that there appears to be catalyst deactivation, due to lack of formation of any organic product: pyridine, arene, or otherwise; regardless of alkyne or nitrile used. As such, we observed the separate stoichiometric reactions of Ni(COD)$_2$/Xantphos with 3-hexyne and MeCN. No change was observed in the ^{31}P-NMR spectrum of the reaction mixture upon addition of 1-3 equiv of either alkyne or nitrile, even after 2 h. However, upon addition of 1 equiv of *both* nitrile and alkyne, we saw a gradual decrease in the resonances attributed to Ni(Xantphos)$_2$, Ni(Xantphos)(COD), and free Xantphos with a steady increase of a singlet resonance at 17.7 ppm. After roughly 30 min, only the new resonance remained, with a color change from dark red to yellow. The reaction mixture was then taken to dryness and ^{1}H-NMR revealed formation of a 1:1 mixture of Xantphos to hexyne (eq. 3.8). Single crystal X-ray structural analysis (Figure 3.7) of this compound revealed a

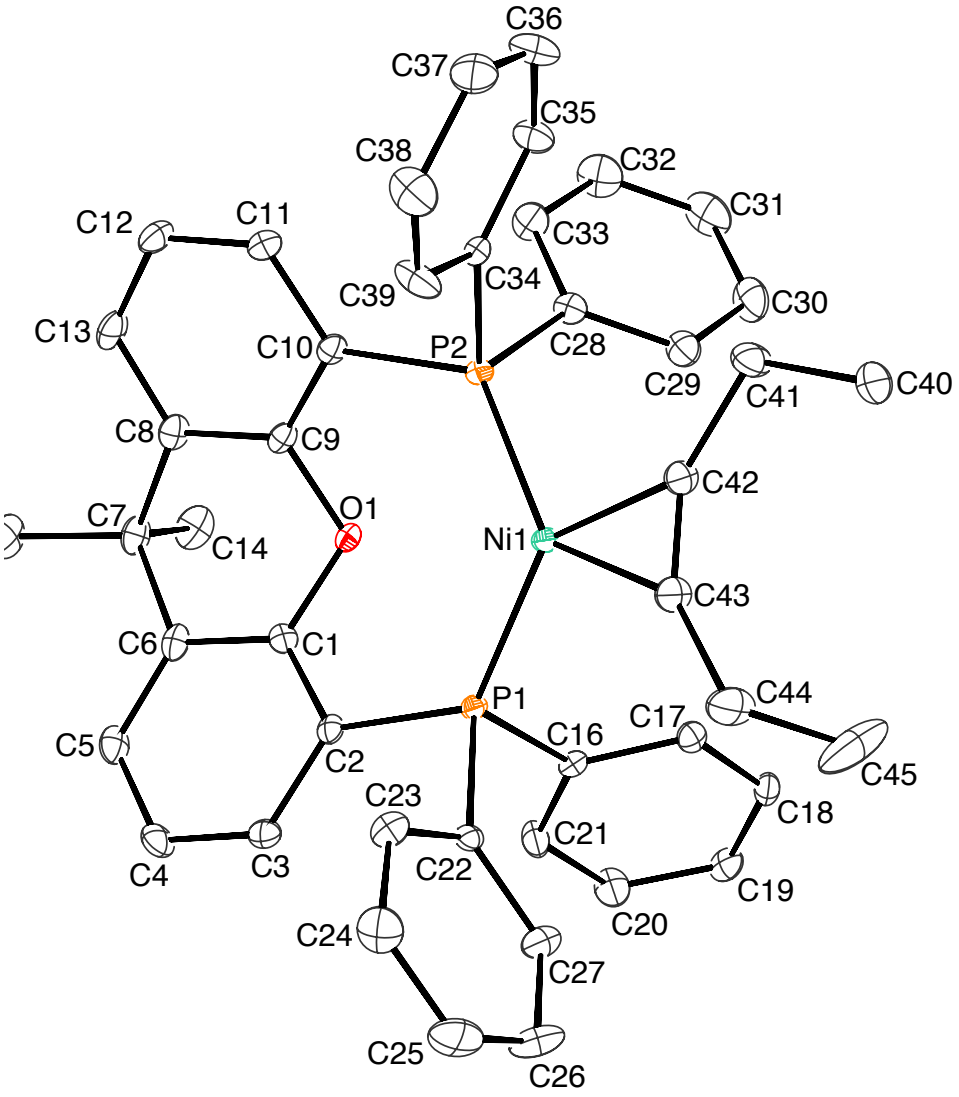
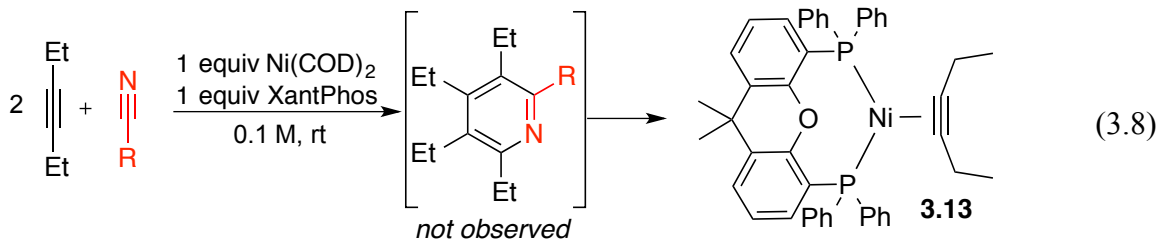


Figure 3.7. ORTEP Plot of (Xantphos)Ni^0(3-hexyne). Selected Bond Angles: Ni(1)-P(1): 2.173 Å, Ni(1)-P(2): 2.176 Å, Ni(1)-C(42): 1.905 Å, Ni(1)-C(43): 1.894 Å, C(41)-C(42): 1.502 Å, C(43)-C(44): 1.497 Å. Ni(1)-O(1) Distance: 3.392 Å. Selected Bond Angles: P(1)-Ni(1)-P(2): 118.922°, P(1)-Ni(1)-C(43): 99.084°, P(2)-Ni(1)-C(42): 103.030°, C(41)-C(42)-C(43): 144.207°, C(42)-C(43)-C(44): 145.618°.

pseudo square planar (Xantphos)Ni(hexyne) complex **3.13**. The bonding motif is similar to other nickel-alkyne complexes with chelating phosphines.[22]



(3.8)

As far as we can tell, complex **3.13** is the first isolated monochelate Ni^0/Xantphos complex reported. As such, we have plans to apply this synthetic method toward the isolation of other (Xantphos-like)Ni(alkyne) complexes and subsequently test these compounds in a number of Ni^0/Xantphos-catalyzed (or Xantphos-like) reactions, including hydrocyanation,[23] alkylcyanation,[24] and cross-coupling reactions (Figure 3.8).[25]

We also intend to use this compound to prepare a number of mixed ligand Ni^0/Xantphos complexes that may also catalyze these reactions. While interesting enough from a coordination chemistry perspective, the possibility of discreet, isolable Ni^0 precursors can have substantial application in mechanistic analysis of Ni(Xantphos) catalyzed reactions. The lack of isolable species has made conclusive mechanistic analysis of the aforementioned reactions difficult. This is of particular importance to hydrocyanation of alkenes, a multibillion dollar process (*vide supra*). With an isolated and stable Ni^0(Xantphos)-species in hand, we refocused our investigation toward kinetic analysis of the cycloaddition reaction. Initial tests revealed (Xantphos)Ni(hexyne) to be a competent catalyst with a nearly quantitative yield in the cycloaddition of our model diyne **3.9** and MeCN (eq. 3.9). Interestingly, the reaction mixture retains the bright

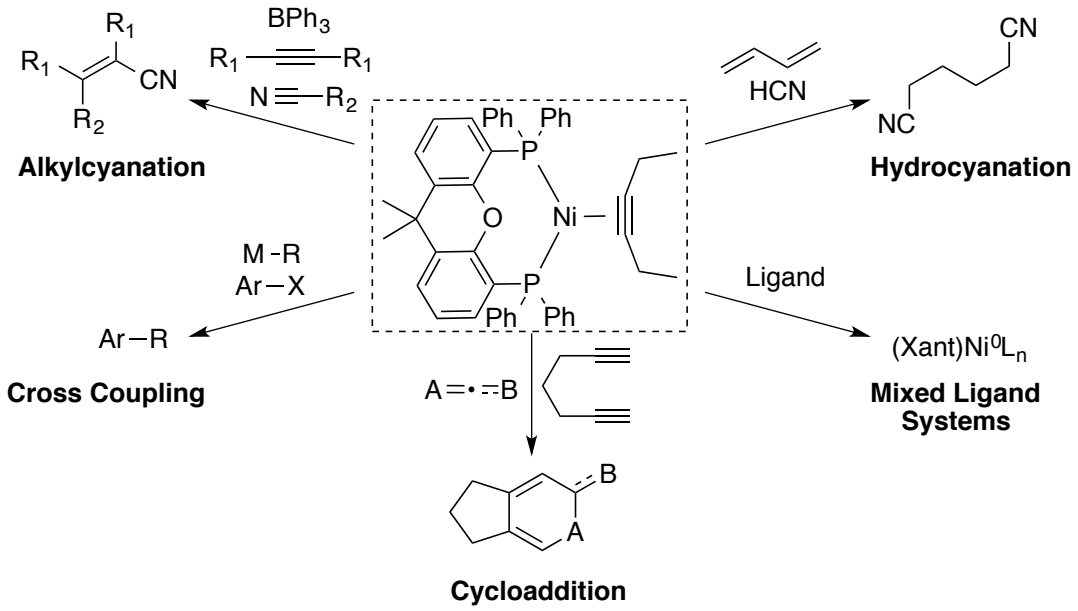


Figure 3.8. Potential Applications of (Xant)Ni(Hexyne).

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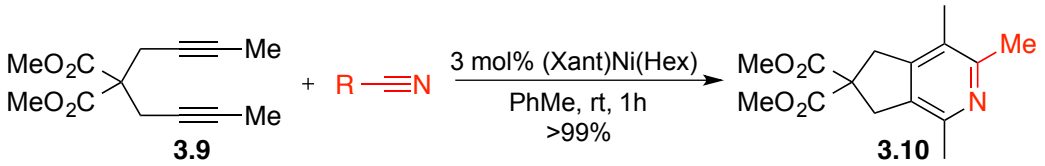


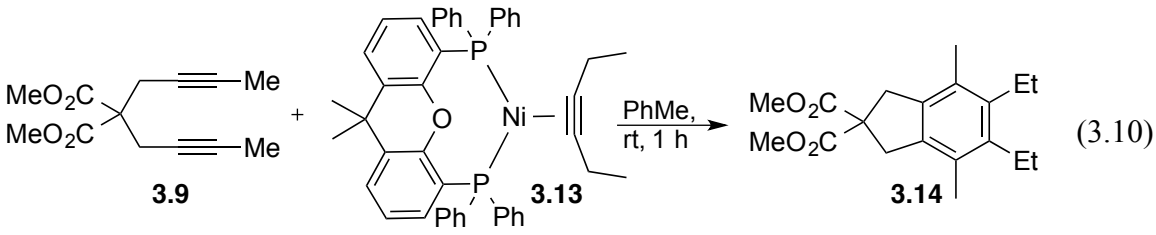
(3.9)

yellow color of the catalyst during reaction, versus the bright red to brown color change observed in the identical cycloaddition using the *in situ* generated catalyst. We immediately embarked on a kinetic evaluation of the (Xantphos)Ni(hexyne)-catalyzed cycloaddition of model diyne and nitriles. Once again, however, we observe only first-order dependence in catalyst and zeroth-order in diyne, nitrile, and hexyne.

The reaction is moderately faster than using the *in situ* generated catalyst, which may arise from moderate amounts of nickel tied up as Ni(Xantphos)$_2$ in the *in situ* method. Once again, we observe only minor rate variation when using PhCN or ^{i}PrCN, with no change in order of nitrile. Addition of excess Xantphos stops the reaction within

minutes, concurrent with a stark yellow to red color change. The lack of reaction in the presence of Xantphos suggests the formation of an inactive Ni(Xantphos)$_2$ species. The lack of order in all substrates but catalyst, once again, is surprising. Stoichiometric reactions of the (Xantphos)Ni(hexyne) complex with diyne and MeCN show no reaction of hexyne with either diyne or nitrile.

The stoichiometric reactions of the (Xantphos)Ni(hexyne) complex with diyne alone, however, affords bicyclic arene **3.14** as the major product with trace amounts of dimerized diyne (eq. 3.10). While still in its infancy, this investigation lends some insight into the mechanism of the (Xantphos)Ni^0-catalyze cycloaddition of diynes and nitriles.



(3.10)

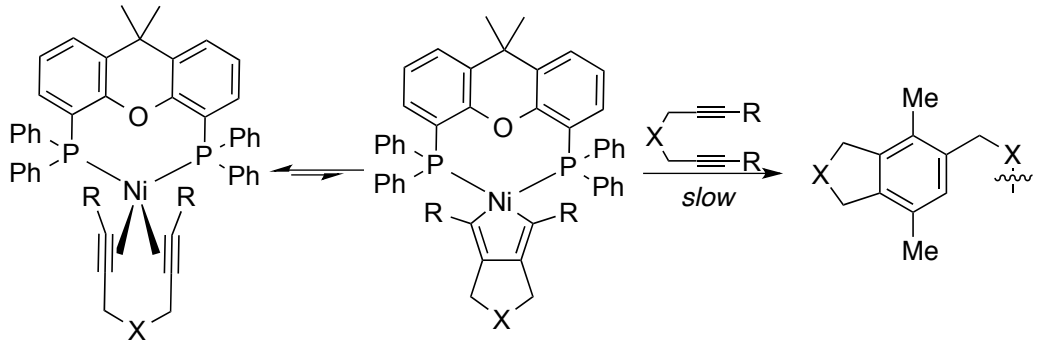
As observed in the mechanistic studies of the Ni(IPr)$_2$-catalyzed cycloaddition of diynes and nitriles outlined in Chapter 1, stoichiometric transmetallation reactions from L$_n$Ni^{II}-fragments suggest a heterocoupling pathway is operative. This is shown in eq. 3.1 wherein (Xantphos)NiCl$_2$ was subjected to zirconapyrrole **3.2** and alkyne **3.3** affording pyridine product. The reaction of zirconapentadiene **3.5** and **3.1** in the presence of MeCN failed to produce expected pyridine product (eq. 3.2); however, formation of arene **3.6** (eq. 3.4) verified that transmetallation from zirconacyclopentadiene was occurring.

Reactions utilizing either the *in situ* generated catalyst or (Xantphos)Ni(hexyne) demonstrated reaction order in catalyst alone; as such, a resting state of (Xantphos)Ni(COD) or (Xantphos)Ni(hexyne) seems unlikely. In this regard, a resting

state with an alkyne- or nitrile-bound (Xantphos)Ni^0 fragment is probably operative, although ^{31}P-NMR observation of either nickel species in the presence of nitrile displayed no reaction. The lack of a nickel-nitrile resting state is further supported by the synthesis of (Xantphos)Ni(hexyne) where in the presence of nitriles and alkyne, the (Xantphos)Ni^0 fragment will select for the alkyne. Observation of the substoichiometric reaction of diyne **3.9** by ^{31}P-NMR revealed the loss of the resonance assigned to (Xantphos)Ni(COD) with the formation of a new nickel-intermediate. Initial observations of the stoichiometric cycloaddition of diyne **3.9** and MeCN by ^{31}P-NMR displayed only the multiplet assigned to Ni(Xantphos)$_2$. This observation, however, may be a result of observation of the post-reaction solution without gaining insight into the mechanism as it happens. Future variable temperature NMR experiments are pending to validate this hypothesis.

At this point, we can infer from the stoichiometric transmetallation reactions that nitrile insertion into the homocoupled intermediate will not occur. Considering the lack of reactivity of **3.5** nickelapentadiene with nitrile, and kinetically incompetent tertiary alkyne insertion, we can infer that this nickelacycle is possibly the actual resting state with rate-limiting retro-coupling allowing for latter nitrile incorporation. However, the aforementioned quenching experiments of the stoichiometric reaction of Ni(COD)$_2$/Xantphos with diynes with acid revealed no oxidative coupling products, and only trace amounts of dimerized diyne. This result suggests that coordination of the diyne to nickel is fast (qualitatively verified by fast color change of the reaction mixture) however that insertion of a second equivalent of diyne is slow. The lack of observable oxidative coupling products after quenching suggests that when oxidative homocoupling

occurs, it is short lived. This equilibrium is further supported by ^{1}H-NMR observation of the stoichiometric reaction of Ni(COD)$_2$/Xantphos with diynes. Recall that the stoichiometric reaction of Ni(COD)$_2$/Xantphos with diynes only affords trace quantities of dimerized diyne; however, the ^{1}H-NMR analysis revealed broad, poorly resolved resonances. nickel(0) has a full shell, and as such, compounds thereof are NMR active regardless of geometries. However, Ni^{II} complexes of Xantphos often occur as high-spin tetrahedral complexes that are spectroscopicly ill-defined or even NMR opaque.[26] The broad resonances observed may be due to a net paramagnetic moment originating from the equilibrium of a Ni^0 and tetrahedral Ni^{II} oxidative coupling product (eq. 3.11).



(3.11)

Variable temperature NMR experiments may allow for thermal resolution of a Ni^0-alkyne complex. An interesting corollary to this is the lack of reaction of (Xantphos)Ni with *two* equivalents of alkyne. The lack of reaction may lead credence to the Ni^0-Ni^{II} diyne complex equilibrium, wherein the reversible oxidative coupling of two alkynes is generally disfavored, most likely owing to the steric properties of the ligand. However, when a diyne is used, the local concentration of secondary alkyne is higher, resulting in a kinetic chelate-like (η^4)-diyne complex. The relatively longer lifetime facilitates the otherwise disfavored oxidative homocoupling. The lack of reaction of terminal diynes may also be derived by this behavior. Lacking a terminal substituent, the

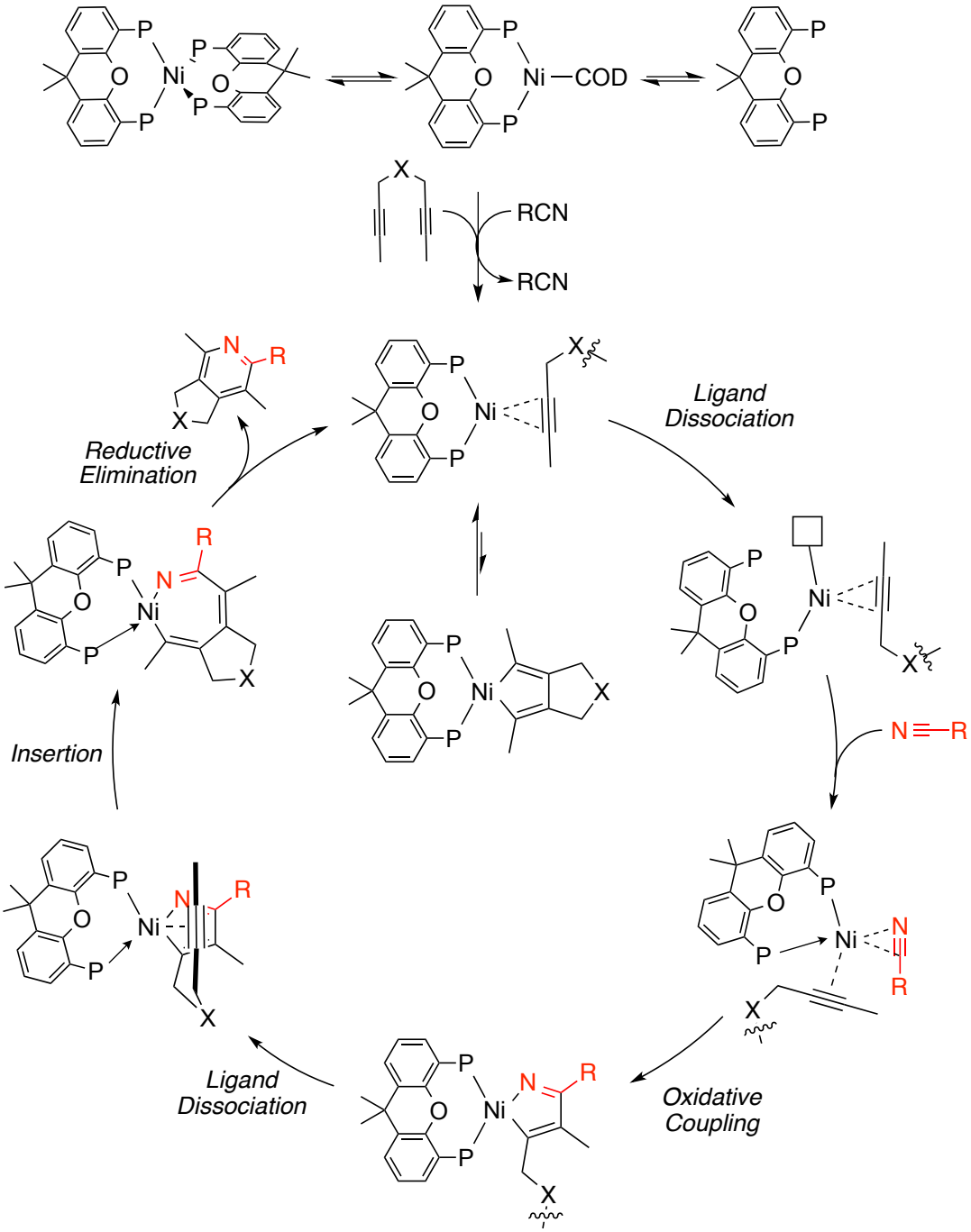
oxidative coupling of terminal diynes may lead to a more stable (and ultimately unreactive) nickelacyclopentadiene, creating a catalytic well.

Working with the hypothesis that a (Xantphos)Ni(diyne) species is the resting state, in order to maintain the reaction order, rate-limiting oxidative homocoupling or partial ligand dissociation will then occur (Scheme 3.1). Following ligand dissociation, nitrile binding into the open coordination location then leads to oxidative heterocoupling. Insertion of the pendant alkyne, likely with another partial ligand dissociation, leads to nickelacycloheptatriene (or analogous insertion product).

This intermediate then reductively eliminates with assistance from the large bite-angle of Xantphos. We assume that diyne dimerization is possible, just kinetically slow. This includes the assumption that the homocoupled- heterocoupled-, and (Xantphos)Ni^0(diyne) intermediates are in equilibrium. Due the combined effect, we believe insertion into the heterocoupled intermediate is the only productive pathway.

While the aforementioned mechanistic scenario is a reasonable *preliminary* hypothesis, a number of mechanistic questions remain, for instance, investigations into the mechanism by which terminal alkynes deactivate the catalyst except for when utilized in the presence of cyanamides. Additional investigations into the role the nitrile plays in reaction rate (regardless how slight) should also be conducted, as this mechanism does not account for such behavior.

These investigations will most likely involve full kinetic analysis for various nitriles, as was required in the mechanistic study of the $Ni(IPr)_2$-catalyzed cycloaddition. The lack of stoichiometric reactions of $Ni(COD)_2$/Xantphos with diynes alludes to the possibility of isolating a (Xantphos)Ni(diyne)-complex; however, the Ni^0-Ni^{II}



Scheme 3.1. Preliminary Catalytic Cycle for the $Ni(COD)_2$/Xantphos-Catalyzed Cycloaddition of Nitriles and Diynes

equilibrium alluded to earlier may require modification of the Xantphos ligand to isolate a singular species. Along these lines, we are currently in the process of modifying the aryl substituents of the Xantphos ligand.

Our working hypothesis would suggest that reducing the nucleophilicity of the phosphines should speed up the reaction by facilitating partial ligand dissociation. However, reducing the donating abilities of the phosphines may slow oxidative coupling and could even induce a change in mechanism. The reported overriding effects of the *structure* of Xantphos-like ligands suggests that modulating the electronics of the ligand will most likely not induce a deviation in mechanism.

In accordance with the large volume of literature on the topic, we have confirmed that Xantphos is a special ligand. We intend to add to the wealth of unique mechanistic scenarios induced by such a ligand by further investigating the mechanism of the unprecedented cycloaddition of diynes and nitriles catalyzed by (Xantphos)Ni^0 complexes.

Our brief, yet fruitful, investigations into this mechanism reveal that the reaction proceeds via a heterocoupling pathway that appears to be unique to nickel-based cycloaddition catalysts. Kinetic analysis of two discreet catalysts reveal consistent lack of order in all substrates but catalysts, suggesting a (Xantphos)Ni(diyne) resting state. The kinetic studies also suggest a rate-limiting partial Xantphos dissociation. Brief qualitative experimentation revealed that $Ni(COD)_2$/Xantphos is also a competent catalysts for the cycloaddition of isocyanates, ketones, and aldehydes. Further investigations into the reactions as well as any mechanistic relevance to the project at hand will also be investigated.

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 and Acetonitrile were dried over neutral alumina under N_2 using a Grubbs type solvent purification system. Benzonitrile was either distilled from CaH_2 prior to use or used from a sure-sealed bottle purchased directly from Sigma-Aldrich. 3-hexyne was purchased from SigmaAldrich and degassed prior to use. Deuterated benzene and chloroform were purchased from Cambridge and used without further purification. $Ni(COD)_2$ and XantPhos were purchased from Strem and used without further purification. Diyne **3.9**,[1] (XantPhos)$NiCl_2$,[26] (XantPhos)$NiBr_2$,[26] and zirconacycles **3.2** and **3.5**[5] are known compounds and were prepared according to literature procedures. All other reagents were purchased and used without further purification unless otherwise noted. ^1H, ^{31}P, and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300, 400, or 500 MHz. All spectra are referenced to residual solvent peaks. All ^{13}C NMR spectra were proton decoupled. Gas Chromatography was performed using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 min; detector temperature: 250 ºC.

Experimental procedures. The general procedure for the reduction of (XantPhos)NiX_2 compounds is as follows: In a drybox, Na metal (2-10 equiv) was weighed in a 20 mL scintillation vial. To this vial was then added liquid Hg (5 wt% Na), then carefully shaken to ensure dissolution of the Na. To this vial was then added an appropriate amount of solvent (0.005-.01 M) and a Teflon coated magnetic stirbar. At this stage, if the reaction were cooled, the biphasic solution was capped and placed in a -40 ºC

freezer for 1 h. Concurrently, (XantPhos)NiX_2 was weight into a separate 5 mL vial and was suspended/dissolved in the appropriate solvent. The nickel solution/suspension was then added slowly to the stirring NaHg solution. Analysis of the reaction progress/outcome was conducted by ^{31}P-NMR via removal of a ~0.5 mL aliquot of the reaction solution followed by filtration through a small pad of silica directly into the NMR tube.

Preparation of 3,4-diethyl-2-methyl-5,6-dipropylpyridine, (**3.4**) is as follows: In a drybox, zirconacycle **3.2** (50 mg, 0.145 mmol), (XantPhos)$NiBr_2$ (115.6 mg, 0.145 mmol), 1,3,5-trimethoxybenzene (24 mg, 0.145 mmol; internal standard), and 4-octyne (24 μL, 0.16 mmol) were weighed into a scintillation vial and dissolved in THF (1 mL). After stirring the reaction for 10 min, the vial was brought out of the drybox and heated to 50 °C for 12 h. After cooling to rt, the reaction mixture was evaporated to dryness. Comparison of the ^{1}H-NMR ($CDCl_3$) of the reported spectrum[7] and the crude reaction mixture, revealed formation of product **6** in 76% NMR yield.

Preparation of 3',4',5',6'-tetraethyl-1,1':2',1''-terphenyl, (**3.6**) is as follows: In a drybox, zirconacycle **3.5** (50 mg, 0.130 mmol), (XantPhos)$NiBr_2$ (104 mg, 0.130 mmol), 1,3,5-trimethoxybenzene (24 mg, 0.145 mmol; internal standard), and diphenylacetylene (26 mg, 0.145 mmol) were weighed into a scintillation vial and dissolved in THF (1 mL). After stirring the reaction for 10 min, the vial was brought out of the drybox and heated to 50 °C for 12 h. After cooling to rt, the reaction mixture was evaporated to dryness. ^{1}H-NMR ($CDCl_3$) revealed complete consumption of zirconacycle **7**. The crude residue was filtered through a short silica pad, eluting with benzene and the crude residue was evaporated to dryness. Comparison of the resultant methyl peaks in the crude ^{1}H-

NMR ($CDCl_3$; 1.21 (t)) with the internal standard revealed formation of product **3.6** in 81% NMR yield. HRMS (ESI) calc'd for $C_{26}H_{30}$ $[M+H]^+$ 343.2426, found 343.2431.

Preparation of ((9,9-dimethyl-9H-xanthene-4,5-diyl) bis(diphenylphosphan-ato))nickel^{I} bromide, (XantPhos)Ni^{I}Br (**3.8**). In a drybox, zirconacycle **3.2** (50 mg, 0.145 mmol) and (XantPhos)$NiBr_2$ (115.6 mg, 0.145 mmol) were weighed into a 5 mL scintillation vial and dissolved in THF (2 mL). After stirring the reaction for 10 min, the vial was brought out of the drybox and heated to 100 °C for 12 h. After cooling to rt, the reaction mixture was evaporated to dryness. The crude brown/red residue was taken up in 2 x 1 mL of benzene and filtered through a short pad of silica into a 5 mL scintillation vial. The vial was then placed in a diffusion chamber loaded with pentane. The title compound was isolated as a few small yellow crystals, suitable for X-ray crystallographic analysis.

Formation by comproportionation is as follows: In a drybox, $Ni(COD)_2$ (19 mg, 0.07 mmol) and Xantphos (40 mg, 0.07 mmol) were weighed into a 5 mL scintillation vial equipped with a Teflon coated stirbar and subsequently dissolved in 3 mL of THF. Concurrently, (XantPhos)$NiBr_2$ (50 mg, 0.07 mmol) was weighed into a separate 20 mL scintillation vial, into which the $Ni(COD)_2$/Xantphos solution was added with an additional 1 mL of THF to ensure complete transfer. The resultant brown suspension was then brought out of the drybox and heated at 50 °C for roughly 10 min, resulting in a homogeneous yellow/green solution. The vial was then returned to the drybox, and the contained solution passed through a short pad of silica. The eluent was then placed in a -40 °C freezer overnight, resulting in the formation of aggregations of blocky yellow crystals. The unit cell of these crystals match that of (XantPhos)Ni^{I}Br. Further

characterization is underway.

Preparation of (η^2-3-hexynyl-(9,9-dimethyl-9H-xanthene-4,5-diyl) bis(diphen ylphosphanato))nickel^{I} bromide, (XantPhos)Ni^0(3-hexyne) (**3.13**): In a drybox, Ni(COD)$_2$ (100 mg, 0.363 mmol) and Xantphos (210.4 mg, 0.363 mmol) were weighed into a 20 mL scintillation vial equipped with a Teflon coated stirbar and subsequently dissolved in 12 mL of benzene. After stirring for 10 min, PhCN (75 μL, 0.726 mmol) followed by 3-hexyne (83 μL, 0.726 mmol) were added to the stirring Ni(COD)$_2$/Xantphos solution and stirred at rt for 3 h. The resultant yellow solution was then reduced in volume by about half, being sure to maintain homogeneity, followed by the addition 5 mL of pentane. This solution was then placed in a -40 °C freezer overnight, resulting in the formation of aggregations of needle-like crystals. These crystals were filtered off and dried to yield 198.5 mg (76% yield) of the title compound. A secondary recrystallization from benzene/pentane afforded another 30 mg (87.5% total yield) of the title compound. Crystals suitable for X-ray crystallographic analysis can be prepared by slow diffusion of pentane into a benzene solution of the complex. ^{1}H NMR (300 MHz, C_6D_6) δ 1.12 (t, J = 5.4 Hz 6H), 1.29 (s, 6H), 3.81 (q, J = 5.4 Hz, 4H), 6.75-6.82 (m, 4H), 6.92-7.14 (m, 14H), 7.81 (br s, 8H) ppm. ^{31}P NMR (300 MHz, C_6D_6) 17.97 ppm.

Cycloaddition of Diyne **3.9** and MeCN Catalyzed by (XantPhos)Ni^0(3-hexyne) was carried out as follows: In a drybox, (XantPhos)Ni^0(3-hexyne) (8 mg, 0.011 mmol, 3 mol%) was weighed into a 5 mL scintillation vial and subsequently dissolve in 1 mL PhMe. Into a separate 5 mL vial was weighed diyne **3.9** (50 mg, 0.211 mmol) and 1,3,5-trimethoxybenzene (36 mg, 0.211 mmol; internal standard), followed by the addition of MeCN (17 μL, 0.34 mmol), a Teflon coated magnetic stirbar, and 1 mL PhMe. This

solution was allowed to stir for 1-2 min to ensure dissolution of the diyne and internal standard. To this stirring solution was added the catalyst solution in one portion. The combined solution was allowed to stir for 1 h then removed from the drybox and brought to dryness on a rotary evaporator. Analysis of the crude reaction mixture by ^{1}H-NMR revealed to quantitative formation of pyridine **3.10**.

^{1}H NMR kinetic studies. In all kinetic experiments, all noncatalyst solutions and excess solvent were added together in an NMR tube in a drybox. The catalyst solution was injected, and the sample tube was capped and removed from the drybox and immediately brought to a 400 MHz NMR spectrometer. The sample tube was then briefly shaken, loaded into the instrument, and immediately subjected to analysis. Spectra were collected within 30 sec of catalyst injection. Spectra were collected over 18 sec with delay intervals of 1 min. All samples were analyzed to >90% completion.

Kinetic analysis for the cycloaddition of nitriles and diyne 3.9 catalyzed by Ni(COD)$_2$/Xantphos. Order in nickel was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9**, 261.2 μL (5 mmol) of acetonitrile, and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 10.0 mg (0.036 mmol) of Ni(COD)$_2$, and 20.8 mg (0.036 mmol) of Xantphos in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1 and an appropriate volume of solution #2. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of Ni(COD)$_2$/XANTPHOS (k, [Ni(COD)$_2$/XANTPHOS]): 0.0 $M \cdot s^{-1}$, 0.0 M; 8.95×10^{-6}

$M \cdot s^{-1}$, 1.5×10^{-6} M; 1.34×10^{-5} $M \cdot s^{-1}$, 3.00×10^{-6} M; 2.06×10^{-5} $M \cdot s^{-}$, 5.00×10^{-6} M; 3.02×10^{-5} $M \cdot s^{-}$, 7.00×10^{-6} M (see Figure 3.9).

Order in acetonitrile was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9** and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 261.2 μL (5 mmol) of acetonitrile in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask.

Stock solution #3 was prepared by dissolution of 10.0 mg (0.036 mmol) of $Ni(COD)_2$, and 20.8 mg (0.036 mmol) of Xantphos in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of solution #2, and 139 μL of solution #3. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of acetonitrile (k, [MeCN]): 1.41×10^{-5} $M \cdot s^{-1}$, 4.0×10^{-1} M; 1.46×10^{-5} $M \cdot s^{-1}$, 5.0×10^{-1} M; 1.37×10^{-5} $M \cdot s^{-1}$, 7.0×10^{-1} M; 1.40×10^{-5} $M \cdot s^{-}$, 1.0 M; 1.39×10^{-5} $M \cdot s^{-}$, 1.2 M (see Figure 3.10).

Order in COD was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9**, 261.2 μL (5 mmol) of acetonitrile, and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 61.5 μL (0.5 mmol) of 1,5-cyclooctadiene (COD) in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 10.0 mg (0.036 mmol) of $Ni(COD)_2$, and 20.8 mg (0.036 mmol) of Xantphos in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate

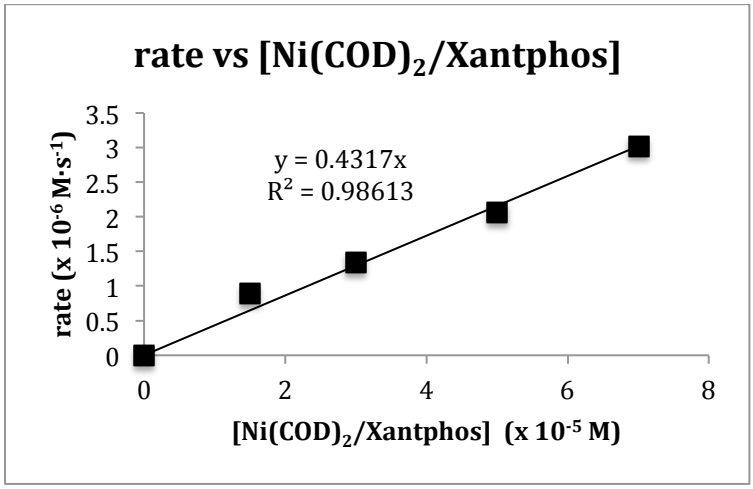


Figure 3.9. Rate Versus Catalyst Concentration.

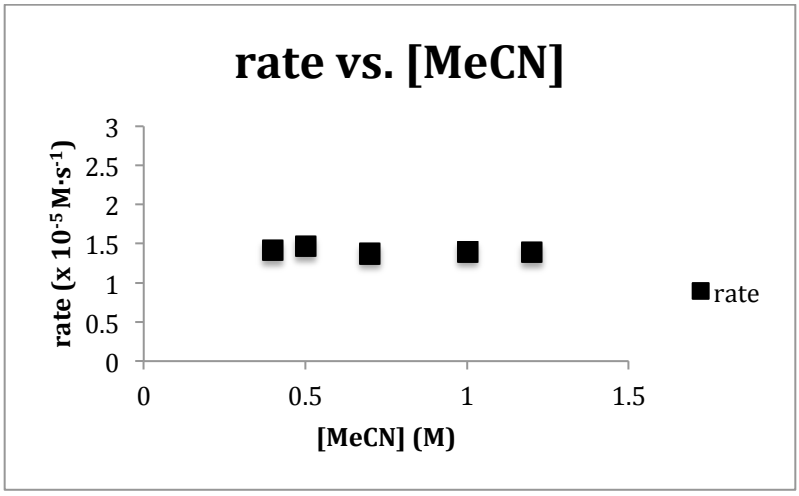


Figure 3.10. Rate Versus Acetonitrile Concentration.

measurement were prepared by adding 100 μL of solution #1, and an appropriate volume of solution #2, and 139 μL of solution #4. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of COD (*k*, [COD]): 1.41 $M \cdot s^{-1}$, 0.0 M; 1.31×10^{-5} $M \cdot s^{-1}$, 2.5×10^{-3} M; 1.32×10^{-5} $M \cdot s^{-1}$, 5.0×10^{-3} M; 1.46×10^{-5} $M \cdot s^{-}$, 1.0×10^{-2} M; 1.32×10^{-5} $M \cdot s^{-}$, 2.0×10^{-2} M (see Figure 3.11).

Kinetic analysis for the cycloaddition of ^{i}PrCN and PhCN. Order in PhCN was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9** and 91.6 mg (1 mmol) of Fc in C_6D_6 in a 2.00 ± 0.01 mL vol. flask.

Stock solution #2 was prepared by dissolution of 10.0 mg (0.036 mmol) of $Ni(COD)_2$, and 20.8 mg (0.036 mmol) of Xantphos in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, and an appropriate volume of PhCN, 139 μL of solution #3. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of PhCN (*k*, [PhCN]): 1.63×10^{-5} $M \cdot s^{-1}$, 5.0×10^{-1} M; 1.67×10^{-5} $M \cdot s^{-1}$, 1.0 M.

Order in ^{i}PrCN was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9** and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 10.0 mg (0.036 mmol) of $Ni(COD)_2$, and 20.8 mg (0.036 mmol) of Xantphos in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of ^{i}PrCN, and 139 μL of solution

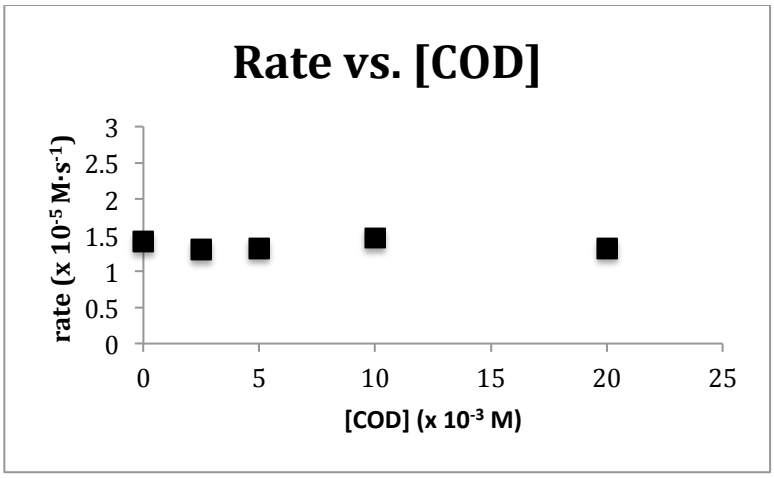


Figure 3.11. Rate Versus COD Concentration.

#3. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of ^{i}PrCN (k, [MeCN]): 1.15×10^{-5} M·s^{-1}, 5.0×10^{-1} M; 1.17×10^{-5} M·s^{-1}, 1.0 M (see Figure 3.12).

Kinetic analysis for the cycloaddition of nitriles and diyne 3.9 catalyzed by (Xantphos)Ni^0(3-hexyne). Order in nickel was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9**, 261.2 μL (5 mmol) of acetonitrile, and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 14.4 mg (0.036 mmol) of (Xantphos)Ni^0(3-hexyne) in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1 and an appropriate volume of solution #2. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-

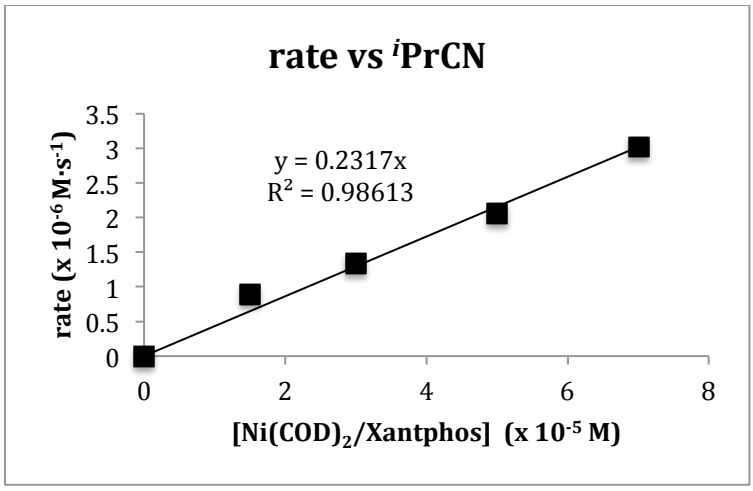


Figure 3.12. Rate Versus ^{i}PrCN Concentration.

first-order rate constants were obtained at different concentrations of (Xant)Ni(Hex) (*k*, [(Xant)Ni(Hex))$_2$]): 0.0 M·s^{-1}, 0.0 M; 1.75 × 10^{-5} M·s^{-1}, 1.75 × 10^{-6} M; 2.84 × 10^{-5} M·s^{-1}, 2.50 × 10^{-6} M; 4.13 × 10^{-5} M·s^{-}, 3.50 × 10^{-6} M; 5.32 × 10^{-5} M·s^{-}, 5.00 × 10^{-6} M (see Figure 3.13).

Order in 3-hexyne was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9**, 261.2 μL (5 mmol) of acetonitrile, and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask.

Stock solution #2 was prepared by dissolution of 28.5 μL (0.25 mmol) of 3-hexyne in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 14.4 mg (0.036 mmol) of (Xantphos)Ni^0(3-hexyne) in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of solution #2, and 125 μL of solution #3. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reaction

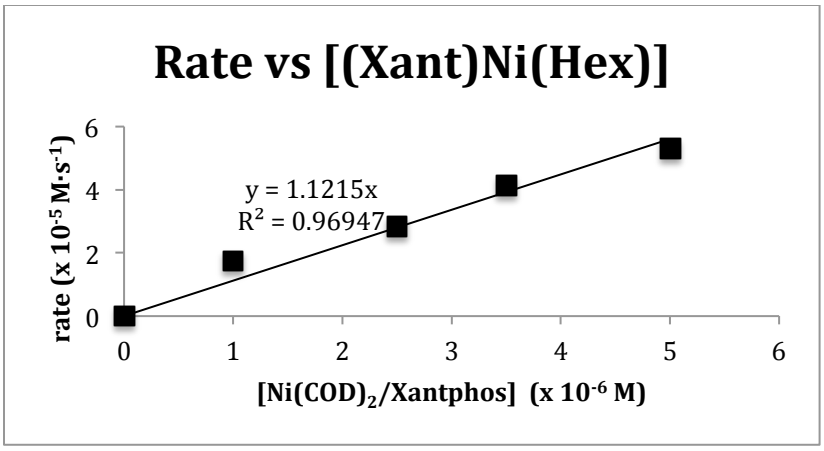


Figure 3.13. Rate Versus Catalyst Concentration.

were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of 3-hexyne (*k*, [3-hexyne]): 2.84×10^{-5} M·s^{-1}, 0.0 M; 2.66×10^{-5} M·s^{-1}, 2.5×10^{-3} M; 2.89×10^{-5} M·s^{-1}, 5.0×10^{-3} M.

Kinetic analysis for the cycloaddition of MeCN, PhCN, and ^{i}PrCN. Order in Acetonitrile was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9** and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 261.2 μL (5 mmol) of acetonitrile in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Stock solution #3 was prepared by dissolution of 14.4 mg (0.036 mmol) of (Xantphos)Ni^0(3-hexyne) in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of solution #2, and 125 μL of solution #3. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate

constants were obtained at different concentrations of acetonitrile (*k*, [MeCN]): 2.84×10^{-5} $M \cdot s^{-1}$, 5.0×10^{-1} M; 2.78×10^{-5} $M \cdot s^{-1}$, 1.0 M. Order in PhCN was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9** and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 14.4 mg (0.036 mmol) of (Xantphos)Ni^0(3-hexyne) in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of PhCN, and 125 μL of solution #3. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of PhCN (*k*, [PhCN]): 3.28×10^{-5} $M \cdot s^{-1}$, 5.00×10^{-1} M; 3.32×10^{-5} $M \cdot s^{-1}$, 1.00 M.

Order in ^{i}PrCN was determined out as follows: stock solution #1 was prepared by dissolution of 236.3 mg (1 mmol) of diyne **3.9** and 91.6 mg (1 mmol) of ferrocene in C_6D_6 in a 2.00 ± 0.01 mL volumetric flask. Stock solution #2 was prepared by dissolution of 14.4 mg (0.036 mmol) of (Xantphos)Ni^0(3-hexyne) in C_6D_6 in a 1.00 ± 0.01 mL volumetric flask. Samples for each rate measurement were prepared by adding 100 μL of solution #1, an appropriate volume of ^{i}PrCN, and 139 μL of solution #3. An amount of C_6D_6 was then added to make a total of 0.5 mL solution (0.1M). Reactions were monitored at 26 ºC. The following pseudo-first-order rate constants were obtained at different concentrations of ^{i}PrCN (*k*, [^{i}PrCN]): 2.01×10^{-5} $M \cdot s^{-1}$, 5.0×10^{-1} M; 2.11×10^{-5} $M \cdot s^{-1}$, 1.0 M.

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CHAPTER 4

NICKEL-CATALYZED CYCLOADDITION OF ALKYNES AND DIYNES WITH CYANAMIDES[‡]

Abstract

The nickel-catalyzed [2+2+2] cycloaddition of alkynes and diynes with cyanamides was investigated. The reactions proceeded at room temperature with low catalyst loading to afford 2-aminopyridines in good to excellent yields. A variety of bicyclic *N*,*N*-disubstituted-2-aminopyridines were prepared from both terminal- and internal-diynes with cyanamides in a selective manner. The fully intermolecular version employing 3-hexyne and *N*-cyanopyrrolidine also afforded the desired pentasubstituted *N*,*N*-disubstituted-2-aminopyridine in good yield. The intermolecular version employing 1-pentyne and *N*-cyanopyrrolidine also afforded the desired *N*,*N*-disubstituted-2-aminopyridine in good yield, as a single regioisomer. A number of cyanamides with diverse functional group tolerance were employed.

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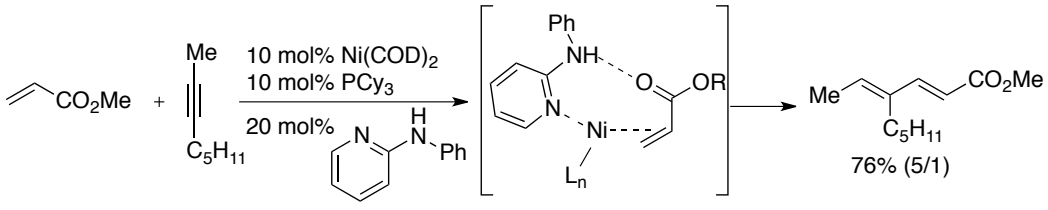
Introduction

Pyridine containing molecules are ubiquitous in nearly all aspects of the chemical sciences. Within this context lies considerable interest in pyridines containing more than one heteroatom. These pyridines allow for further elaboration toward a plethora of heterocyclic products.[1] More specifically, and the focus of this endeavor, are 2-aminopyridines. These attractive synthetic targets have found utility in many aspects of chemistry. For instance, they are often used as organometallic ligands.[2] Horie and coworkers have demonstrated an excellent example of the unique abilities of 2-aminopyridinyl ligands. In this study, they report the necessity of 2-aminopyridines as coligand for the selective nickel-catalyzed codimerization of alkynes and acrylates. The effect of the 2-aminopyridine on the selectivity of the coupling is believed to arise from the ability of the 2-aminopyridine to both coordinate to the nickel center as well as to selectively bind the acrylate prior to the alkyne (eq. 4.1).[3]



(4.1)

In addition to organometallic ligands, 2-aminopyridines can be strong chromophores,[4] and are very well-represented intermediates in biologically active molecules.[5] In an exciting application of both of these properties, 2-aminopyridine antihistamines have been utilized as selective fluorophores for biological study. Among the most commonly used H_1 antihistamines, only tripelennamine and mepyramine have had their native fluorescence rigorously studied (Figure 4.1).

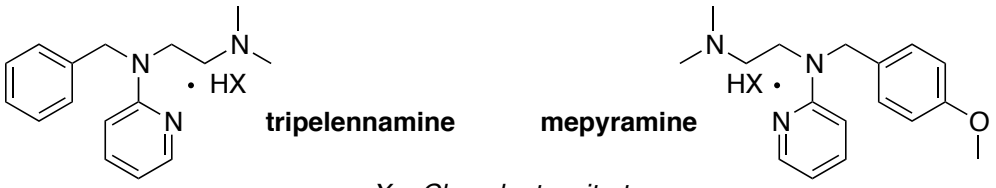


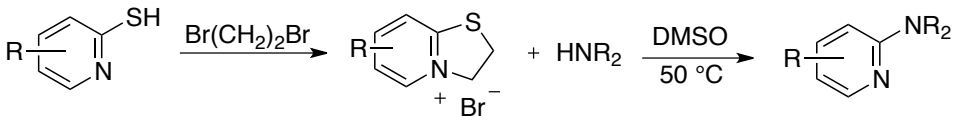
Figure 4.1. Fluorescent 2-Amniopyridine Containing H_1-Antihistamines Utilized in the Design of Better Antihistamines.

They have the advantage that they can be selectively excited in the presence of protein, since they absorb at longer wavelengths (>300 nm) than nearly all natural residues.[6] As such, they have found utility in H_1 binding assays with hopes of developing better antihistamines.[7]

A variety of methods for the synthesis of 2-aminopyridines currently exist, all with their own benefits and limitations. Traditionally, 2-aminopyridine was synthesized by direct amination of pyridines from $NaNH_2/NH_3$, known as the Chichibabin Reaction.[8] While yields are generally high, the requisite harsh conditions limit the substrate-scope. In addition, the requisite use of $NaNH_2/NH_3$ limits the scope of the amine functionality provided. Buchwald-Hartwig aminations[9] are one of the most common methods and are renowned for their functional-group tolerance; as such, fully functionalized pyridines can be easily aminated. While powerful and diverse, problems can arise from the necessary halogenation/pseudohalogneation of substituted pyridines, either with synthetic incompatibility of functional groups, or by lack of compatibility of an aryl-halide with pyridine pre-amination elaboration. Reaction optimization (e.g., ligand/Pd-source screening) often leads to considerable costs.

In the same vein, Goldberg-like coupling may provide a more cost-effective

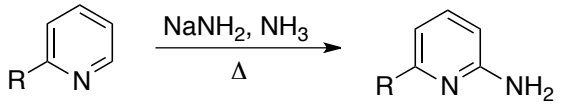
route.[10] The same issue of the need for halogenation and substrate compatibility may subvert the apparent utility. Many modern Goldberg-type reactions require the use of amine ligands in excess, which may competitively add into the requisite aryl halide. These reactions generally require high reaction temperatures and extended reaction times. Nucleophilic aromatic substitution of pyridines is one of the most common synthetic strategies. This route follows a similar mechanistic scheme as the Chichibabin reaction but with the use of better leaving-groups than hydride. Of these leaving-group-substituted pyridines, halopyridines[11] are the most commonly used (see Figure 4.2). Alternatively, sulfur-based leaving-groups[12] or pyridyl nitrogen activation[13] can be used. In an interesting combination of these two strategies, alkylation of 2-mercaptopyridine with 1,2-dibromoethane affords a cyclic dihydrothiazolopyridinium salt that can serve as a precursor of 2-aminopyridines (eq. 4.2).[14]



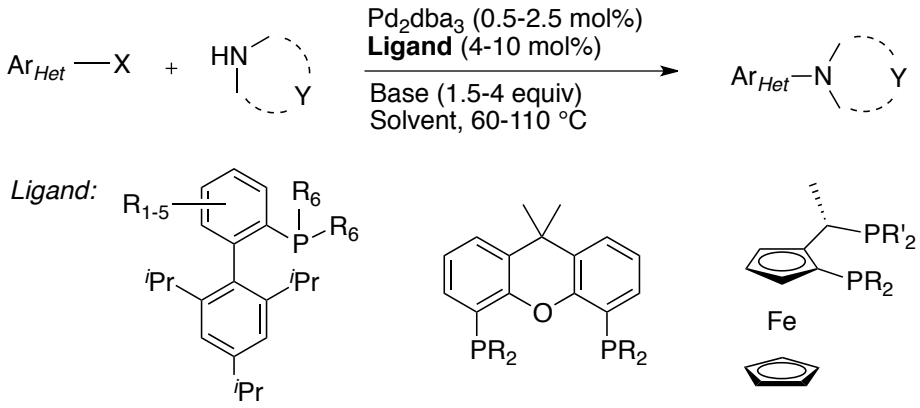
(4.2)

Like Buckwald-Hartwig and Goldberg couplings, compatibility issues may arise from the halogenation/activation of the required pyridine. In addition to the inherent limitations within the amination method, in all the above-mentioned reaction types, the nontrivial synthesis of substituted pyridines may be a hindrance. Additional synthetic limitations are associated polysubstitued pyridines to use in addition- or coupling-reactions. This can be addressed by integrating both the pyridine substitution and 2-amino functionality by selective annulation of simply synthesized starting materials. This

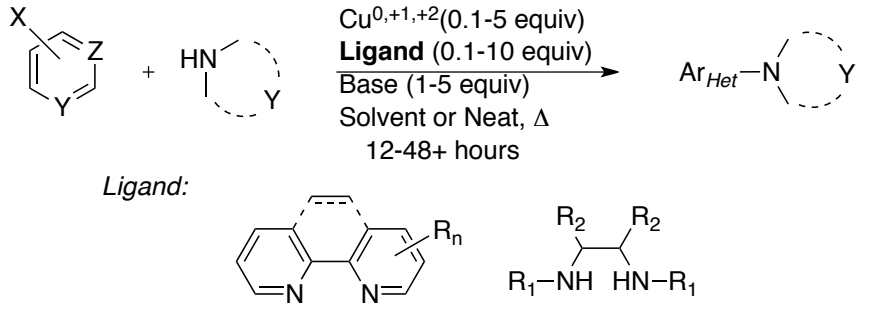
Chichibabin Reaction



Buchwald-Hartwig Amination



Goldberg-type Amination



S_NAr Aminations

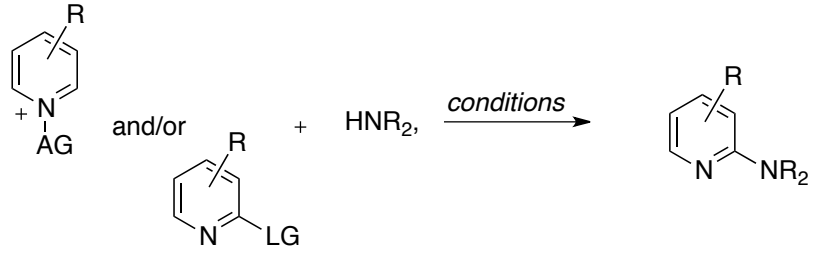
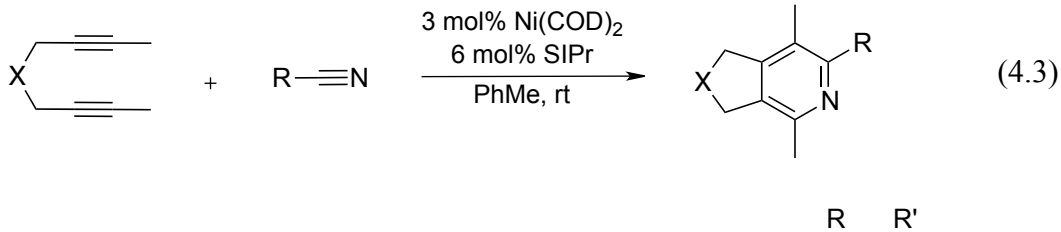


Figure 4.2. Common Methods for the Synthesis of 2-Aminopyridines

method is realized in multicomponent condensation,[15] and Diels-Alder reactions.[16] While intricate substitution patterns are possible with this method, the molecular architectures are limited due to necessary functionalities required for productive condensation (Figure 4.3).

As a compliment to existing methods, an easily envisioned route is via [2+2+2]-cycloaddition of simple alkynes and cyanamides. This method has the potential to incorporate complex substitution on the pyridine concurrent with providing a 2-amino functionality.

The metal-catalyzed [2+2+2] cycloaddition of alkynes and nitriles utilizing a variety of transition metals has rich and extensive history and continues to be a highly studied field.[17,18] Due to the recent success our group reported the mild and efficient nickel-catalyzed [2+2+2]-cycloaddition of alkynes and nitriles to generate pyridines (eq. 4.3),[19] we felt cyanamides as a coupling partner would be a practical extension of this methodology to afford 2-aminopyridines (eq. 4.4).



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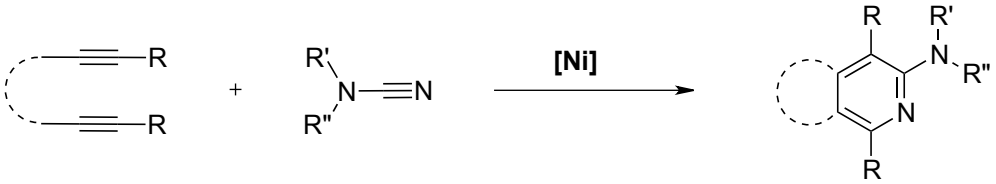


(4.4)

Although studies of cycloadditions of alkynes and nitriles are expansive, independent studies of analogous cyanamides are few. Seminal works of Bönnemann briefly demonstrate the cycloaddition of acetylene and cyanamide utilizing a unique η^6-

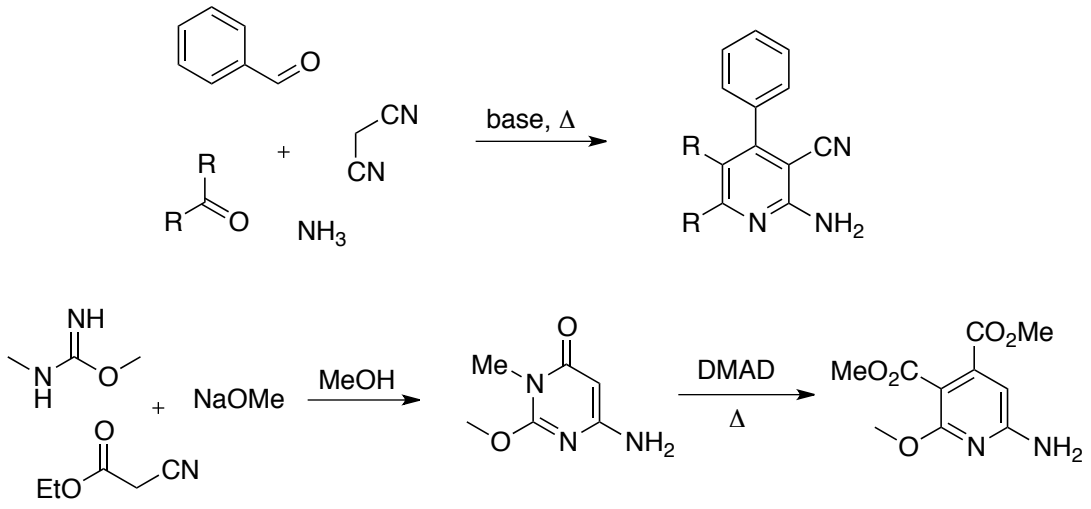
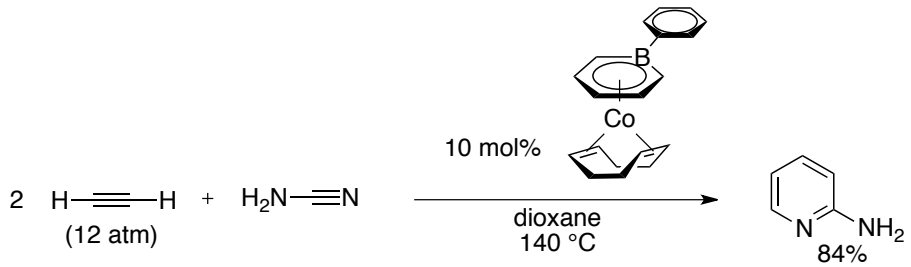
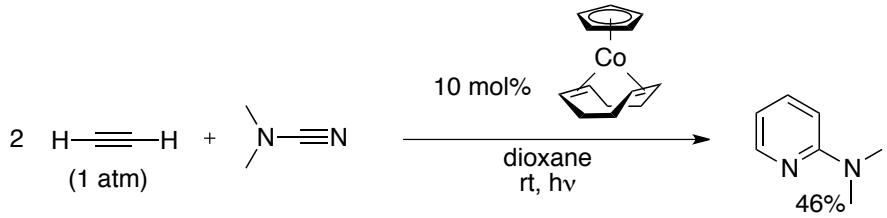


Figure 4.3. Condensation/Diels-Alder routes toward 2-aminopyridines

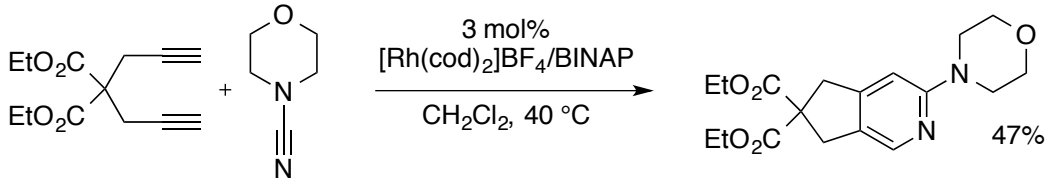
boranato cobalt catalyst at high temperature and pressure (eq. 4.5).Heller and coworkers, accomplished the CpCo(COD)-catalyzed cycloaddition of dimethylcyanamide and acetylene as a single example, affording a moderate 46% yield (eq. 4.6).[20] Maryanoff and coworkers performed a more focused study demonstrating the efficacy of the cycloaddition of diynes with cyanamides using $CpCo(CO)_2$ as a catalyst (Figure 4.4).[21] Recently, Tanaka and coworkers developed a cationic Rh^I(COD)/BINAP cycloaddition catalyst that facilitated the [2+2+2] cycloaddition of malonate-derived diyne and *N*-cyanomorpholine as a single example in 47% (eq. 4.7).[22]



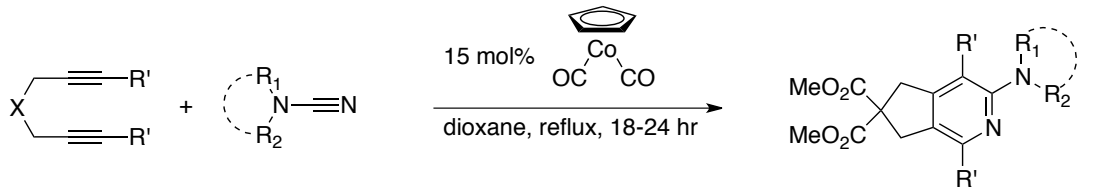
(4.5)



(4.6)



(4.7)



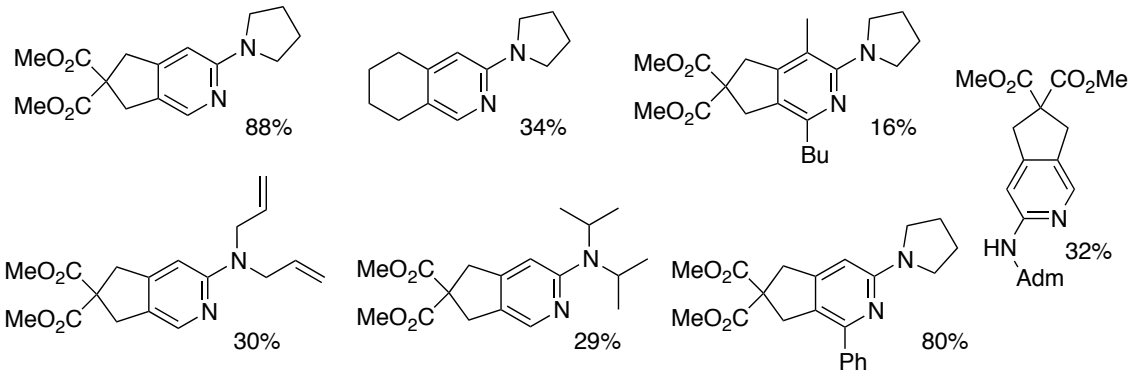
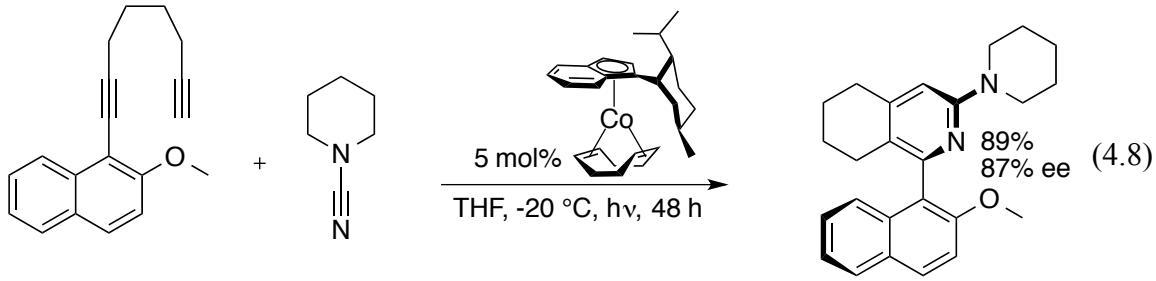


Figure 4.4 Selected Substrate Scope from Maryanoff's Conditions for the Cycloaddition of Diynes and Cyanamides with $CpCo(CO)_2$.

Heller and coworkers utilized a chiral cobalt catalyst to synthesize a variety of chiral 1-aryl-5,6,7,8-tetrahydroquinolines from aryl-substituted diynes and nitriles. This system was also amenable to the cycloaddition of aryl-substituted diynes and piperidine-1-carbonitrile as a single example in an excellent yield (eq. 4.8).[23]

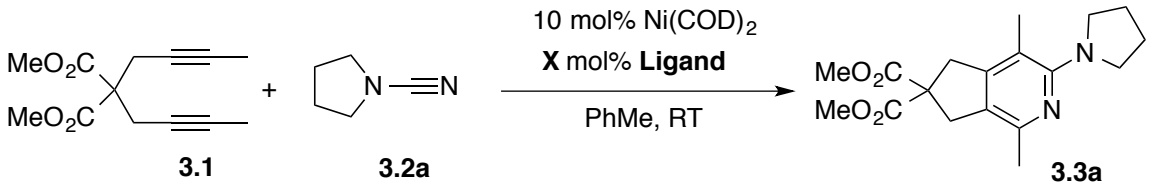


(4.8)

Results and Discussion

Diyne **4.1** and *N*-cyanopyrrolidine (**4.2a**) were chosen as model substrates due to our familiarity and simplicity of **4.1** as well as the ease of handling, and commercial availability of **4.2a**. Initial investigations focused on catalyst screening with $Ni(COD)_2$ as an Ni^0 source in combination with a variety of ligands: phosphines, phosphites, amines, and N-heterocyclic carbenes (Table 4.1). We expected NHCs to be the optimal ligands based on the unexpected success of *N,N*-dimethylcyanamide in the cycloaddition with terminal diynes. Considering the success we observed in the cycloadditions of diynes and cyanamides in Chapter 1, in combination with the aforementioned prevalence of 2-aminopyridines, we pursued an advanced substrate scope. Product **4.3a** was detected with most of the ligands tested, which is a significant deviation from the results of Nickel-catalyzed cycloaddition reactions of simple nitriles for which only select NHC ligands afforded appreciable amounts of pyridine products.[19] The highest yields were obtained

Table 4.1. Ligand Screen for the Attempted Nickel-Catalyzed [2+2+2] Cycloaddition of **4.1** and **4.2a**.

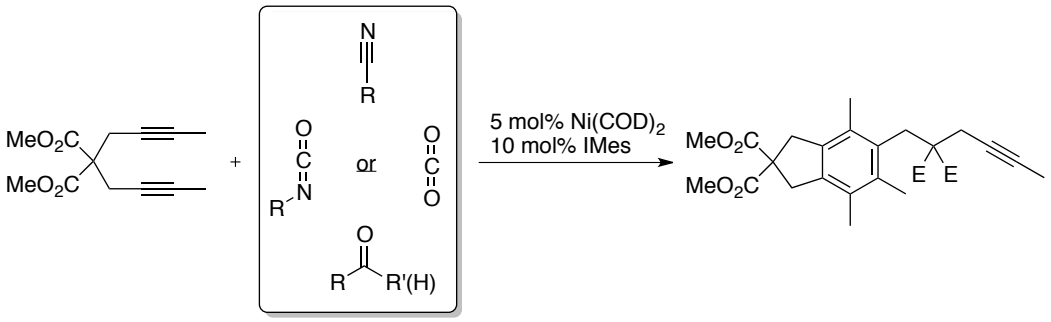


3.1 **3.2a** **3.3a**

Entry	Ligand (mol%)	Conv. (%)[a]	Yield[a]
1	IPr (20)	83	78
2	SIPr (20)	100	98
3	IMes (20)	100	98
4	$P(tBu)_3$ (20)	91	45
5	$P(Cy)_3$ (20)	100	81
6	PPh_3 (20)	80	25
7	DPPE (10)	47	17
8	BINAP (10)	13	6
9	DPPF (10)	11	6
10	$P(OPh)_3$ (20)	6	0
11	$P(OiPr)_3$ (20)	86	11
12	TMEDA (10)	65	0
12	None	91	0

Reaction conditions: 0.1M diyne **3.1**, 0.1M cyanamide **3.2a**, 10% $Ni(COD)_2$, ligand, PhMe 3 h.[a]GC conversion and yields relative to naphthalene as an internal standard

when either IMes or SIPr was employed as the ligand. The efficacy of the $Ni(COD)_2$/IMes catalyst is particularly surprising as this catalyst system typically produces significant amounts of dimerized diyne as a side-product in previous heterocumulene cocycloadditions (eq. 4.9).[19-21]



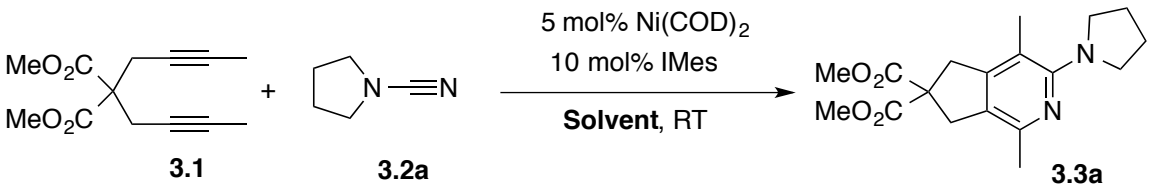
(4.9)

Brief optimization showed that a 1:1 diyne/cyanamide ratio was ideal. In addition, catalyst loading could be reduced to 5 mol-% $Ni(COD)_2$ and 10 mol% IMes or SIPr without loss of yield. A 2:1 ratio of ligand to nickel is critical for productive cocycloaddition.

A variety of solvents were screened for the $Ni(COD)_2$/IMes-catalyzed cycloaddition of diyne **4.1** and cyanamide **4.2a** (Table 4.2). Excellent yields were obtained in pentane, 1,4-dioxane, and toluene. Toluene was chosen for use in further cycloaddition reactions, due to the price and toxicity associated with dioxane and also because many substrates are only moderately soluble in pentane.

With the optimized conditions in hand, we examined the reactions of a range of diyne and cyanamide substrates with varying electronic and steric properties (Table 4.3). In addition to the model cyanamide **4.2a**, other dialkylcyanamides readily underwent cyclization, affording excellent yields. The yields appear to decrease with increasing

Table 4.2. Solvent Screen for the Cycloaddition of **4.1** and **4.2a**



3.1 **3.2a** **3.3a**

Entry	Solvent	Conv. (%)[a]	Yield[a]
1	THF	83	78
2	Et_2O	100	98
3	Benzene	100	98
4	Pentane	91	45
5	1,4-dioxane	100	81
6	Toluene	80	25

Reaction conditions: 0.1M diyne, 0.1M cyanamide, 5% $Ni(COD)_2$, 10 mol% IMes, solvent, 30 min.
[a]GC conversion and yields relative to naphthalene as an internal standard

Table 4.3. Substrate Scope for the $Ni(COD)_2$/IMes-Catalyzed Cycloaddition of Diynes and Cyanamides.

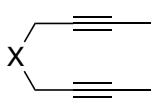
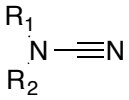
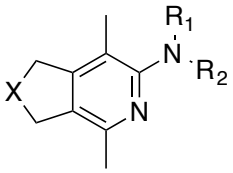
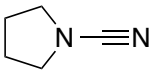
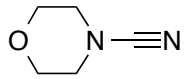
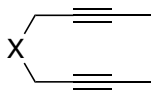
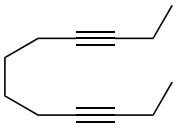
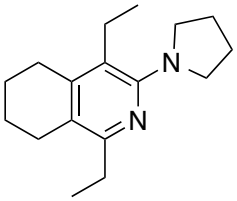
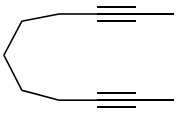
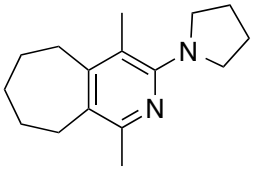
Entry	Diyne	Cyanamide	Product (% Yield)[a]
	 X = $C(CO_2Me)_2$		
1	**3.1**	**3.2a** 	**3.3,** 93%
2	**3.1**	**3.2b** $R_1 = R_2 = Me$	**3.4**, 99%
3	**3.1**	**3.2c** $R_1 = R_2 = Et$	**3.5**, 93%
4	**3.1**	**3.2d** $R_1 = R_2 = n$Pr	**3.6**, 89%
5	**3.1**	**3.2f** 	**3.7**, 97%
6	**3.1**	**3.2g** R_1 = Me, R_2 = PMB	**3.8**, 87%
7	**3.1**	**3.2h** $R_1 = R_2$ = Bn	**3.9**, 88%
8	**3.1**	**3.2i** $R_1 = n$Bu, R_2 = Boc	**3.10**, 82%
9	**3.1**	**3.2j** $R_1 = n$Bu, R_2 = Ac	**3.11**, 87%
10	**3.1**	**3.2m** $R_1 = n$Bu, $R_2 = CH_2CO_2Me$	**3.12**, 81%
11	**3.1**	**3.2p** R_1 = Me, R_2 = Ph	**3.13**, 90%
			
12	**3.14** X = NTs	**2a**	**3.15**, 84%
13	**3.16** X = O	**2a**	**3.17**, 94%

Table 4.3. Continued

Entry	Diyne	Cyanamide	Product (% Yield)[a]
14	 **3.18**	**2a**	 **3.19**, 92%
15	 **3.20**	**2a**	 **3.20**, 76%

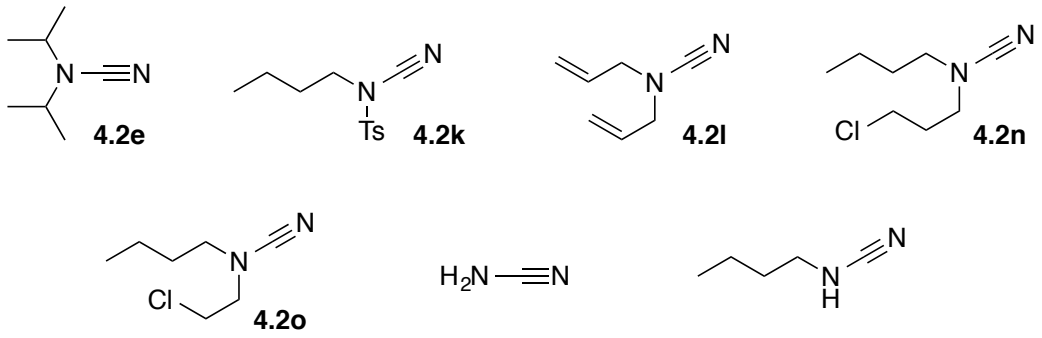
Reaction Conditions: 0.1M diyne, 0.1M cyanamide, 5% $Ni(COD)_2$, 10% IMes, PhMe, rt, 30 min. [a]Isolated yields (average of at least two runs).

steric bulk: Me (**4.4**) > Et (**4.5**) > Pr (**4.6**; Entries 2–4).

Considering the bulk of the carbenes, this result is not surprising. The effect the steric bulk of cyanamides has on the yield of cycloaddition is further highlighted by the complete inactivity of diisopropylcyanamide (**4.2e**) toward cycloaddition. The heterocyclic cyanamide *N*-cyanomorpholine (**4.2f**, Entry 5) was an excellent substrate, affording product **4.7** in 97% yield. Free amine is incompatible with our catalyst system as seen by the lack of reaction of free cyanamide and *N*-butylcyanamide. The incompatibility can be easily accounted for by the relative acidity of the cyanamide N-H bond and the presence of highly basic free carbene. In addition to alkyl substituents, a variety of amine-protected cyanamides were evaluated. These include methyl-*p*-methoxybenzylcyanamide (**4.2g**), dibenzylcyanamide (**4.2h**), as well as carbonyl-protected cyanamides such as *N*-(*tert*-butoxycarbonyl)- *N*-butylcyanamide (**4.2i**), and *N*-butyl-*N*-cyanoacetamide (**4.2j**; Entries 6–9). Notable unreactive protected cyanamides are *N*-tosylated butylcyanamide (**4.2k**) and diallylcyanamide (**4.2l**; Figure 4.5).

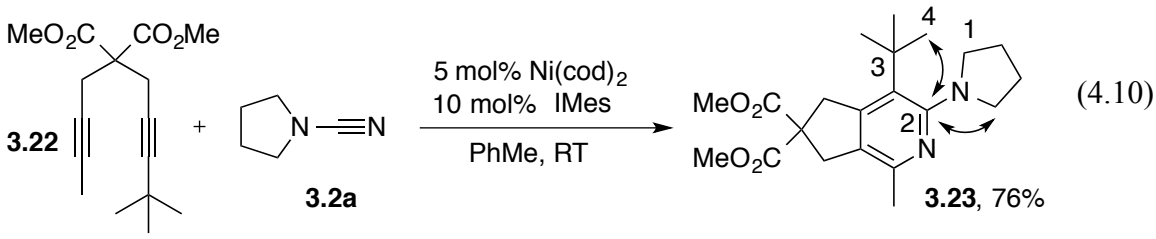
Note, *N*-tosylamines have been, for the most part, troublesome in many of our previous cycloaddition reactions.[19,24-27] It is unclear in this case whether the steric bulk or the reactivity of the *N*-tosyl moiety deactivates the catalyst. Diallylcyanamide was also employed but was also found to deactivate the catalyst. Cyanamides containing pendant functional groups [methyl 2-(*N*-butylcyanamido)acetate (**4.2m**), *N*-butyl-*N*-(3-chloropropyl)cyanamide (**4.2n**), and *N*-butyl-*N*-(3-chloroethyl) cyanamide (**4.2o**)] were also evaluated and gave mixed results. Both chlorinated cyanamides **4.2n** and **4.2o** readily deactivated the catalyst as no conversion was observed in these reactions. Cyanamide **4.2m** afforded amino pyridine **4.12** in 81% yield as a sensitive aminopyridine

Figure 4.5. Cyanamides Incompatible with Cycloaddition Conditions



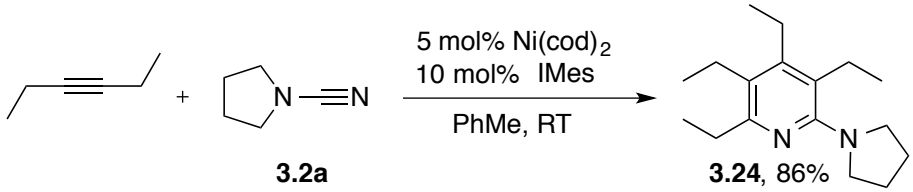
that required immediate purification by column chromatography to be performed in a darkened room (Entry 10). Arylcyanamides are also good substrates with cyanamide **4.2p** affording aminopyridine **4.13** in excellent yield (Entry 11). Various diynes were subjected to the reaction conditions with model cyanamide **4.2a** and afforded excellent yields. For example, internal *N*-protected amines (**4.14**) and ethers (**4.16**) as well as linear diyne **4.18** all reacted well under our conditions (Entries 12–14, respectively). Notably, diyne **4.20** readily reacted to afford an aminopyridine appended to a seven-membered ring in 76% yield despite the lack of Thorpe–Ingold assistance in the substrate (Entry 15). The regioselectivity of the reaction was investigated by treating diyne **4.22** and cyanamide **4.2a** under the optimized reaction conditions; aminopyridine **4.23** was obtained as a single regioisomer in 76% yield (eq. 4.10).[28] The structure of **4.23** was assigned through complementary HMQC and HMBC NMR experiments, with the regiochemistry being determined by exclusive correlations between C-2 and protons located on C-4 and C-1. The regioselectivity is identical to that observed in the cycloaddition of diynes and simple nitriles.

We also investigated the synthesis of *N*,*N*-disubstituted 2-aminopyridines by the



(4.10)

cycloaddition of an untethered alkyne (eq. 4.11). Subjecting 3-hexyne (2 equiv.) and *N*-cyanopyrrolidine (**4.2a**) to the optimized conditions afforded 2-aminopyridine **4.24** in 86% yield.

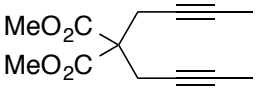
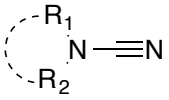
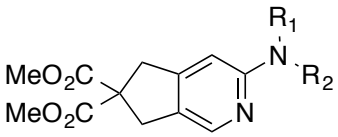


(4.11)

Terminal diynes, a challenging substrate for the parent nickel-catalyzed nitrile cycloaddition reaction,[19] were also evaluated as potential substrates (Table 4.4) Initially, the $Ni(COD)_2$/IMes-catalyzed reaction between diyne **4.25** and cyanamide **4.2a** only yielded trace amounts of the desired product in an otherwise unidentifiable reaction mixture. However, when IMes was substituted for SIPr, the reaction was effective and generated aminopyridine **4.26** in 80% yield. Interestingly, unlike internal diynes, the cycloaddition of terminal diynes and cyanamides using $Ni(COD)_2$/SIPr did not occur in 1,4-dioxane. The use of dioxane did lead to full conversion; however, no identifiable products were formed nor were any by-products isolated from the complex reaction mixture. Thus, cycloaddition reactions using $Ni(COD)_2$/SIPr were carried out exclusively in toluene.

Under these revised conditions, terminal diyne **4.25** was amenable to reaction

Table 4.4. Substrate Scope of the Cycloaddition of Cyanamides and Terminal Diyne **4.25**.

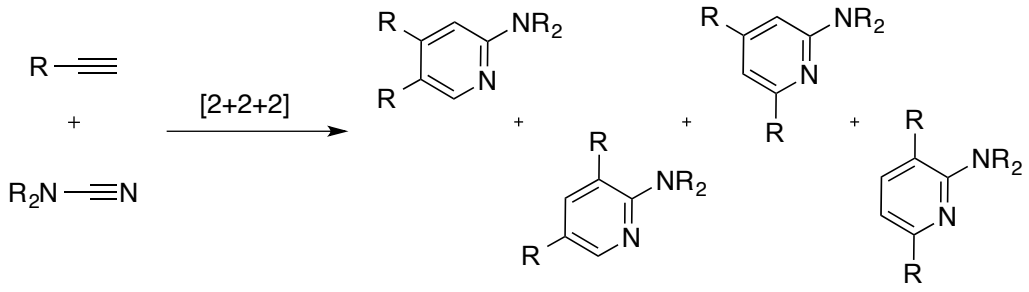
Entry	Diyne	Cyanamide	Product (% Yield)[a]
			
1	**3.25**	**3.2a**	**3.26**, 80%
2	**3.25**	**3.2e**	**3.27**, 86%
3	**3.25**	**3.2h**	**3.28**, 82%
4	**3.25**	**3.2i**	**3.29**, 93%
5	**3.25**	**3.2j**	**3.30**, n.r.[b]
6	**3.25**	**3.2k**	**3.31**, n.r.[b]
7	**3.25**	**3.2k**	**3.32**, 83%

Reaction Conditions: 0.1M diyne, 0.1M cyanamide, PhMe, 5% $Ni(COD)_2$, 10% SIPr, rt, 60 min [a]Isolated yields (average of at least two runs). [b]No reaction.

with most of the previously tested cyanamides **(**Table 4.4). Alkyl substituted cyanamides work well, illustrated by cyanamides **4.2a** and **4.2f** affording products **4.26** and **4.27** in 80 and 86% yields, respectively (Entries 1 and 2). Terminal diyne **4.25** weas also compatible with *N*-Boc- (**4.2i**) and *N*-acylprotected (**4.2j**) cyanamides, with yields comparable to cycloadditions utilizing internal diynes (Entries 3 and 4). No reaction, however, was observed with diyne **4.25** and either PMB-protected cyanamide **4.2g** nor ester-functionalized cyanamide **4.2m** (Entries 5 and 6). In addition to the alkylcyanamides, phenyl-substituted cyanamide **4.2p** is an excellent substrate affording **4.32** in good yield (Entry 7).

Considering the success we had with terminal diynes as well as 3-component cycloaddition, we felt investigations into the three component cycloaddition of terminal alkynes with cyanamides was worth pursuing. Prior to running any experiment, simple

analysis reveals a number of regioisomers are possible when employing unsymmetrical alkynes in cocycloadditions (eq. 4.12). The results of prior cycloaddition studies with both nitriles and terminal alkynes demonstrate this well.



(4.12)

Cobalt catalysts are notorious for their lack of selectivity even when using a large excess of an activated nitrile. The lack of selectivity can be overridden by use of a sterically bulky alkyne, favoring the 2,4,6-trisubstituted pyridine (eq. 4.13).[29] Similar issues of selectivity are apparent in other iron- (eq. 4.14),[30] Rh- (eq. 4.15),[31] and ruthenium-based (eq. 4.16)[32] cycloaddition catalysts. Regioselectivity trends are metal-dependent. With the general issues of selectivity, we were extremely surprised to find that the cycloaddition of **4.2a** with 1-pentyne (**4.33**) catalyzed by $Ni(COD)_2$/SIPr under standard conditions afforded aminopyridine **4.34** as a single diastereomer (determined by GC/MS) in 68% isolated yield (eq. 4.17). The regiochemistry was determined by NOESY, HMBC, and HMQC NMR experiments. Intriguingly, this regioisomer is rarely observed in the aforementioned regioselectivity studies with other metal catalysts.

The regiochemistry observed in **4.34** lends some insight into the mechanism of this reaction. If a homocoupling pathway is first considered, analogous to previous Co-mediated pathways, three intermediates are possible (Figure 4.6). Considering the

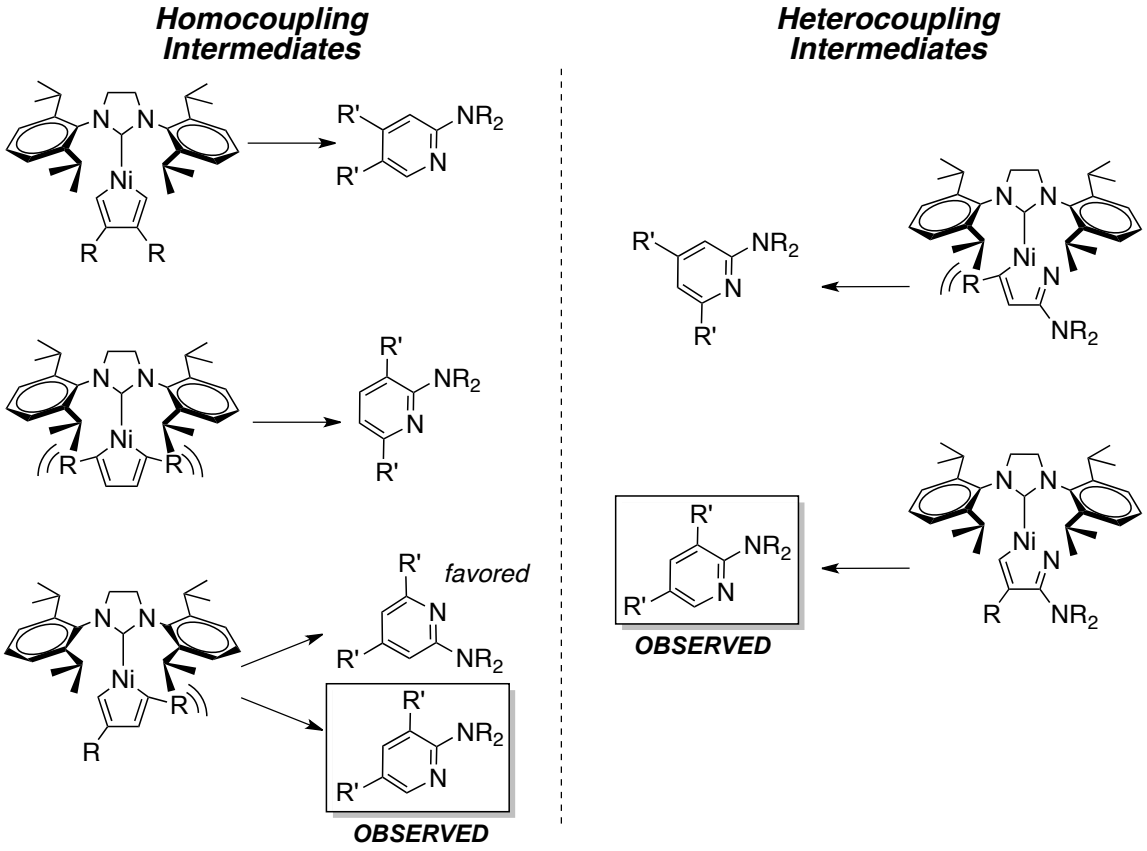
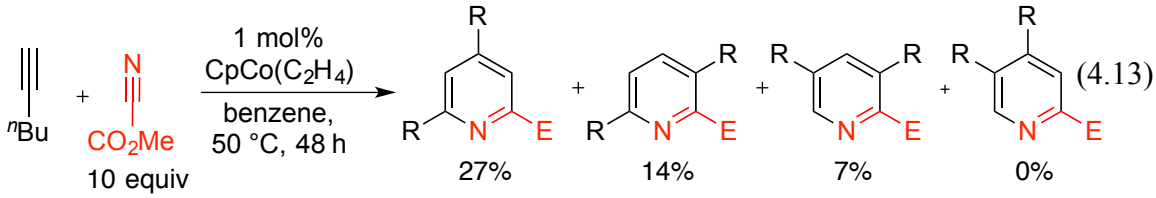
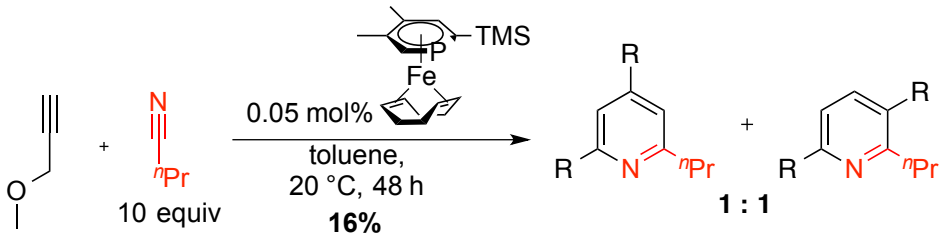


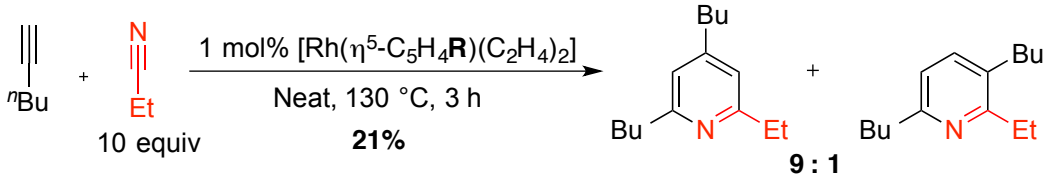
Figure 4.6. Possible Reactive Intermediates on the Catalytic Cycle Based Upon the Observed Selectivity in the Cycloaddition of Cyanamide **3.2a** and 1-Pentyne.



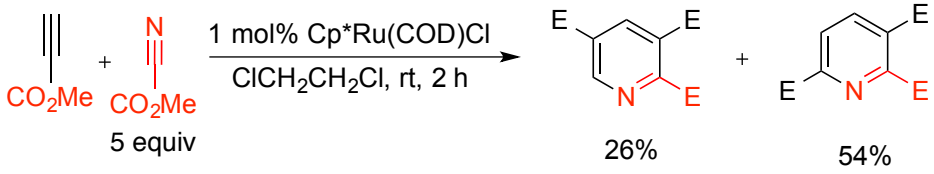
(4.13)



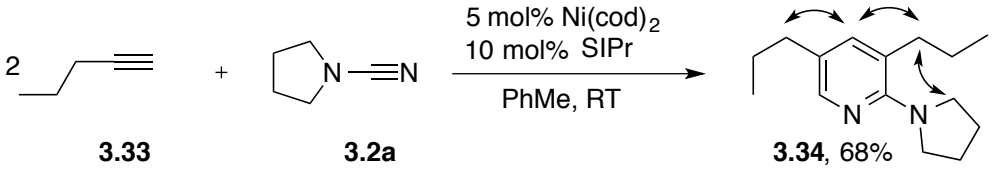
(4.14)



(4.15)



(4.16)



(4.17)

observed regiochemistry, symmetric intermediates **4.35** and **4.36** would be disfavored, as the downstream products are not observed.In the case of unsymmetrical intermediate **4.37** insertion of cyanamide would need to occur from the more-hindered side of the nickelacyclic intermediate. However, the more substituted side is more electron-rich and as such, acts as a better nucleophile in the subsequent insertion of cyanamide. However, the considerable steric bulk of SIPr deems this unlikely.

Alternatively, if heterocoupling intermediate **4.38** is invoked, in order to minimize negative substrate/ligand steric interaction, heterocoupling of the bulky-substituted alkyne with the nitrile would result in the observed regioselectivity. This regioselectivity trend has also been observed in the Ni/NHC-catalyzed coupling of alkynes and aldehydes[26,27] as well as alkynes and isocyanates.[33] Using DFT studies, Montgomery and Houk found that regioselectivity is primarily controlled by the steric hindrance at the region of the ligand closest to the alkyne.

Analysis of steric contour maps of NHC ligands demonstrated that the regioselectivities are directly affected by the shape and orientation of the *N*-substituents on the ligand.[34] These results suggest that, like the parent cycloaddition of simple nitriles, a heterocoupling pathway is operative.

Previously, we developed a method that generates the active Ni^0/NHC catalyst *in situ* from air-stable, readily available precursors.[35] The method employed $Ni(acac)_2$ as a nickel source, an appropriate NHC·HCl or HBF_4 salt, and *n*BuLi as a simultaneous reductant and base. We found this *in situ* method was also effective for the [2+2+2] cycloaddition reactions of diynes and cyanamides. When diyne **4.1** and cyanamide **4.2a** were treated with a stirred solution of $Ni(acac)_2$, IMes·HCl, and *n*BuLi, aminopyridine

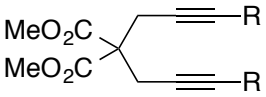
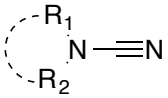
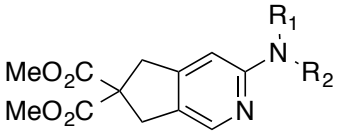
4.3 was obtained in 80% yield. Furthermore, a variety of aminopyridines were obtained in this fashion with yields comparable to the yields obtained in the initial substrate scope experiments (Table 4.5, Entries 1–5). *In situ* cycloaddition using terminal diyne **4.25** and cyanamide **4.2a** was also successful when IMes·HCl was replaced by SIPr·HBF_4. Further cyanamides were tested with diyne **4.25** affording mixed results. The reactions with both cyanamides **4.2a** and **4.2p** went to completion and gave good yields, whereas the Boc (**4.2i**) and acyl (**4.2j**) cyanamides gave modest yields of 50% and 30% with 20% and 32% recovered diyne, respectively (Entries 6–9).

We have demonstrated that diynes undergo [2+2+2] cycloaddition reactions with cyanamides in the presence of an Ni–carbene catalyst to generate *N*,*N*-disubstituted 2-aminopyridines. The method is effective for the cycloaddition of internal as well as terminal diynes with a variety of cyanamides, affording good to excellent yields. *N*,*N*-Disubstituted 2-aminopyridines were also obtained when using an *in situ* generated Ni–carbene catalyst prepared from air-stable, commercially available sources.

Future Work

Considering the effect of the enhanced reactivity of cyanamides over simple nitriles in the Ni/NHC system, development of new (as well as utilization of existing) catalytic systems to modulate the selectivity of the products is underway. Immediate work is now being focused on the successful and selective cocycloaddition of terminal alkynes and cyanamides. Initial results using Ru- and Fe-based systems reveal similar levels of selectivity, however, affording different regioisomers (3,6- and 4,6-substitution, respectively) than the 3,5-substitution observed in our Nickel-catalyzed system

Table 4.5. Yields from *In Situ* Generated Ni–Carbene Catalyst.

Entry	Diyne	Cyanamide	Product (% Yield)[a]
			
1	**3.1**	**3.2a**	**3.3**, 80%[b]
2	**3.1**	**3.2e**	**3.10**, 70%[b]
3	**3.1**	**3.2h**	**3.11**, 79%[b]
4	**3.1**	**3.2i**	**3.12**, 78%[b]
5	**3.1**	**3.2j**	**3.13**, 85%[b]
6	**3.25**	**3.2k**	**3.26**, 75%[c]
7	**3.25**	**3.2k**	**3.28**, 50%[c] (20% rsm[d])
8	**3.25**	**3.2k**	**3.29**, 30%[c] (32% rsm[d])
9	**3.25**	**3.2k**	**3.30**, 80%[c]

[a]Isolated yields (average of at least two runs).[b]Reaction Conditions: 0.1M diyne, 0.1M cyanamide, PhMe, 5 mol% $Ni(acac)_2$, 10 mol% IMes·HCl, 25 mol% *n*BuLi, rt, 60 min. [c]Reaction Conditions: 0.1M diyne, 0.1M cyanamide, PhMe, 5 mol% $Ni(acac)_2$, 10 mol% SIPr·HCl, 25 mol% *n*BuLi, rt, 60 min.
[d]recovered starting material.

(see Figure 4.7). In addition to synthesizing 3,5-substituted 2-aminopyridines, current efforts are focused on applying cleavable diynes[36] to access 4,5-substituted products. Selective cycloaddition has potential to be a considerably powerful method if functional groups whose later chemistries can be dictated by their location on the 2-aminopyridine as in cross-coupling. One such functional group would be boronic esters, which can be easily converted to other functional groups, particularly by cross-coupling methods. The position of ring substitution has a dramatic effect of the reactivity of the resultant arylboronic esters and may allow for unsymmetrical polysubstitution on the amino pyridine core. In addition, amino pyridines themselves are capable cross-coupling substrates upon alkylation.[37] This property could be incredibly usful for the generation of may pharmacophores and monomers for plastics.

Due to the enhanced reactivity observed for cyanamides toward cycloaddition, we attempted to isolate a Ni/NHC/cyanamide complex to observe both the binding mode of cyanamides to nickel and the subsequent reactivity of the resultant complexes. To isolate such a complex, similar strategies to the synthesis of $[Ni(IPr)RCN]_2$-complexes were undertaken. Namely, one equivalent each of $Ni(COD)_2$, IPr and commercially available dibenz[b,f]azepine-5-carbonitrile were stirred together in benzene to yield a brown solid upon drying (eq 4.18).

We chose such a large cyanamide to hopefully disfavor dimer formation that was observed for nitriles. Considering the wealth of aromatic resonances of the ligand and cyanamide, NMR analysis was inconclusive. In attempts to gain some insight into the coordination behavior, we attempted crystallization for X-ray crystallographic structural analysis. During crystallization from slow diffusion of pentane into benzene, the solution

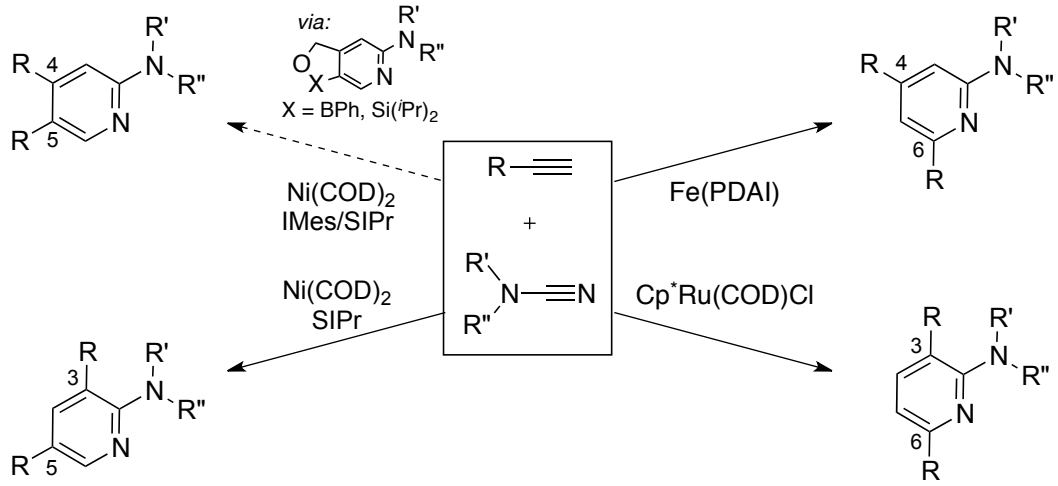
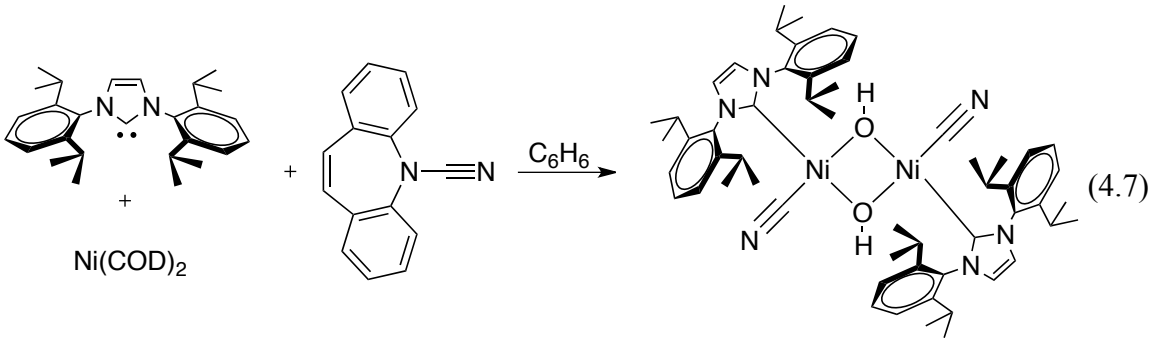


Figure 4.7. Strategy for Catalyst-Directed Regioselective Formation of Disubstituted 2-Aminopridines.



(4.7)

gradually changed from brown to yellow, and from this yellow solution, a single yellow crystal suitable for X-ray analysis was isolated. Surprisingly, what we found was a $[Ni(IPr)CN\text{-}\mu_2\text{-}OH]_2$ dimeric species (Figure 4.8). While this unfortunately pointed towards contamination in our solvent purification system, we were pleased by the ramifications of this discovery. Namely, traditional hydration of cyanamides leads to urea and isourea byproducts by nucleophilic attack of water into the nitrile, not via N-CN cleavage.[38] In fact, direct N-CN cleavage of cyanamides is exceedingly rare. We were only able to find one report of N-CN cleavage wherein a $CpM(CO)(SiEt_3)$ complex (M = Fe or Mo) facilitated the cleavage of cyanamides via silyl-transfer to the nitrile-nitrogen followed by oxidative addition of the resultant *N*-silylated η^2-amidino ligand to afford an amido-isonitrile piano-stool complex. Turnover is facilitated with excess silane (Figure 4.9).[39,40]

First steps toward understanding the formation of $[Ni(IPr)CN\text{-}\mu_2\text{-}OH]_2$ is to find a reproducible synthetic route, something of which has been heretofore unexplored. The mechanism of formation may afford insight into unimagined cyanamide reactivity. Simple mechanistic musings allude to a possible similar mechanism observed with the aforementioned $CpM(CO)(SiEt_3)$ complexes, whereby water may be acidic enough to activate the cyanamide N-CN bond. Along these lines, investigation of the effect other Brønstead and/or Lewis acids will be conducted, similar to those employed in studies of the Nickel-mediated oxidative cleavage of nitriles.[41] In addition, perhaps the cyanamide oxidative addition is not mediated by water, and $[Ni(IPr)CN\text{-}\mu_2\text{-}OH]_2$ is rather a product of ligand exchange. In this case, the role of cyanamide oxidative addition in regard to cycloaddition needs to be conducted. As such, comparative rate behavior will be

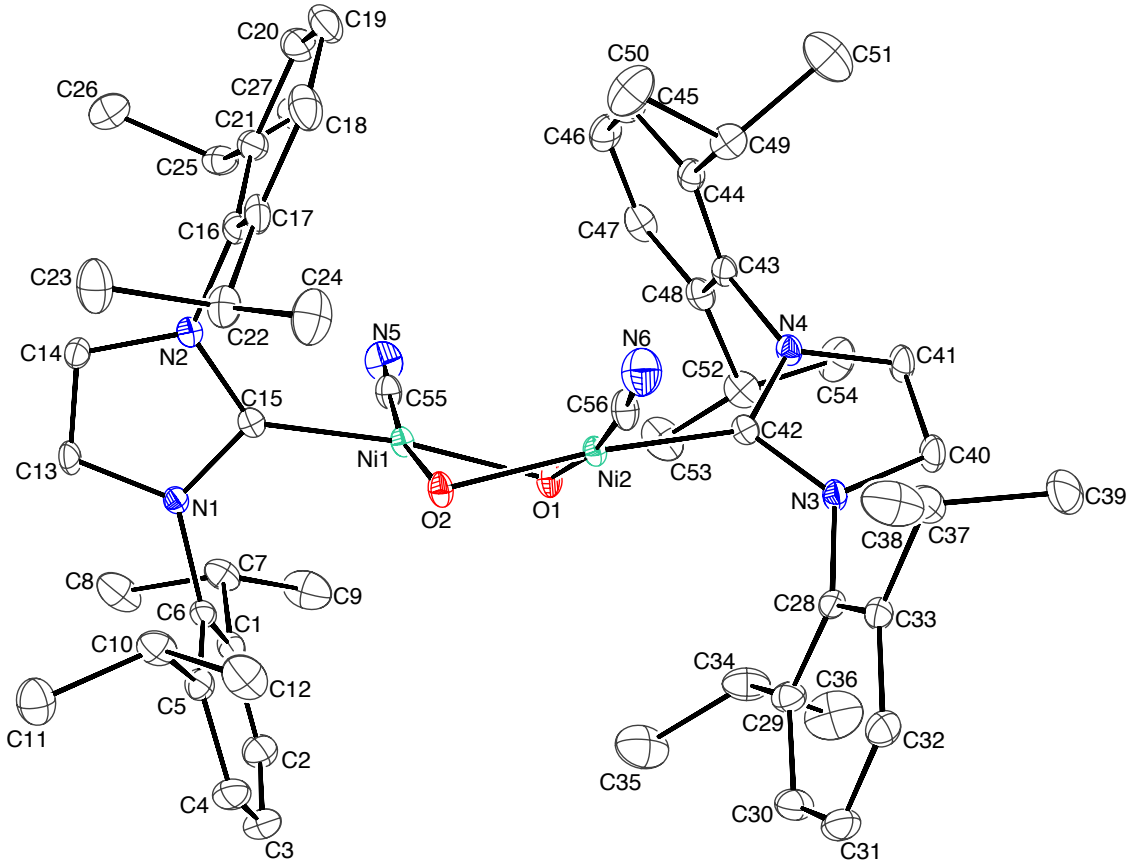


Figure 4.8. ORTEP Plot of [Ni(IPr)CN-μ_2-OH]$_2$. Selected Bond Lengths: Ni(1)-C(55): 1.837 Å, Ni(1)-O(1): 1.892 Å,Ni(1)-O(2): 1.870 Å, Ni(1)-C(15): 1.865 Å, Ni(2)-C(56): 1.834 Å, Ni(2)-O(1): 1.883 Å, Ni(2)-O(2): 1.886 Å, Ni(2)-C(42): 1.865 Å; Ni(1)-Ni(2) distance: 2.753 Å. Selected Bond Angles: Ni(1)-O(1)-Ni(2): 94.250°, Ni(1)-O(1)-Ni(2): 993.624°, O(1)-Ni(1)-O(2): 79.347°, O(1)-Ni(1)-O(2): 79.183°.

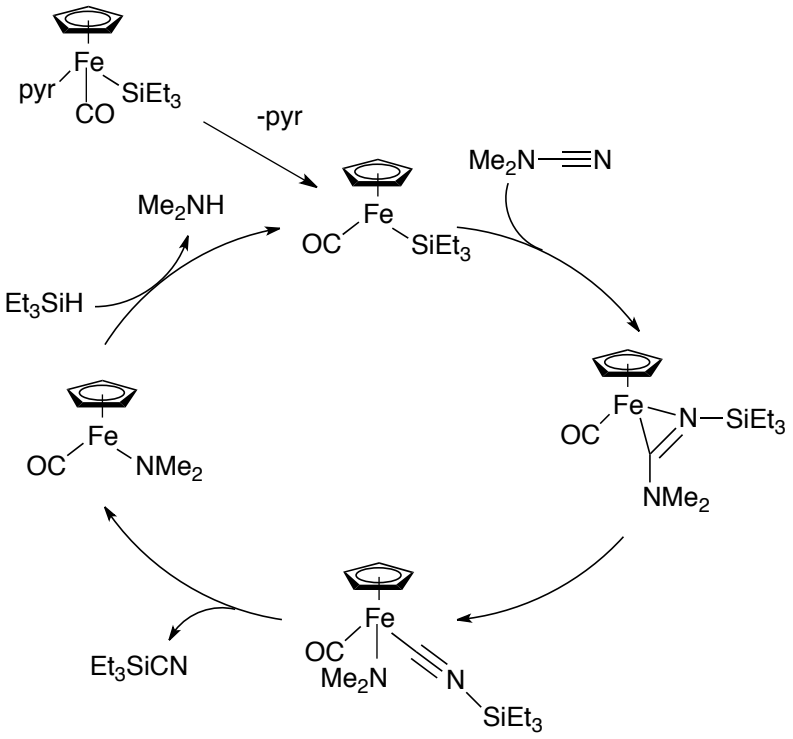


Figure 4.9. Mechanism for the Fe-Catalyzed Cleavage of Cyanamide N-CN Bonds.

investigated.

In addition to studying the mechanism of cyanamide N-CN bond cleavage, utilization of the oxidative addition products will be explored., with hopes that cyanamide cleavage products will exhibit similar behavior as nitrile C-CN cleavage products such as nickel-catalyzed carbocyanation (Figure 4.10).[42] However, in this capacity, nickel-mediated C-N bond forming reactions are unexplored. The development of this methodology can be envisioned in two major capacities: 1) formation of the μ-hydroxo moiety is necessary, or 2) other Lewis acids (if even necessary) can be used. In the former case, this hydroxyl ligand may be a handle for transmetallation with boronic acids/esters or other oxophilic transmetallating agents; however, in this capacity, methods for effective turnover for a catalytic system may be insurmountable. In the latter case,

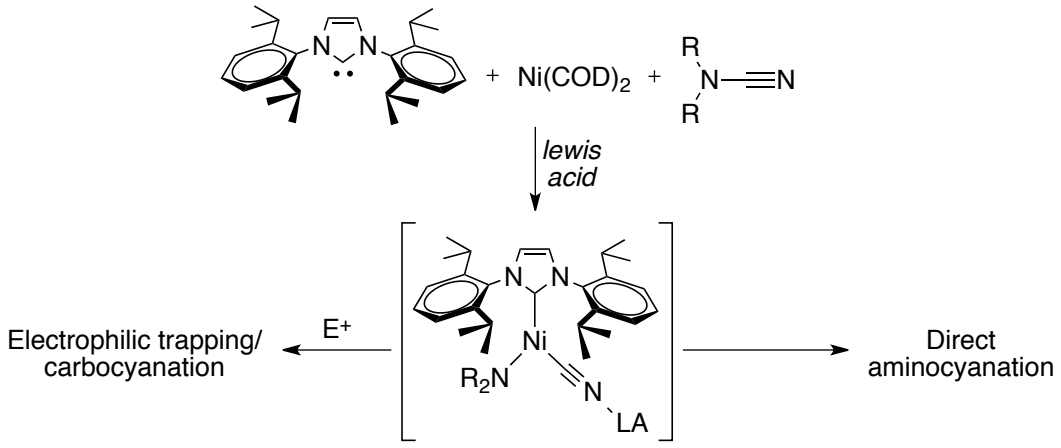


Figure 4.10. Potential Exploitation of Novel Cyanamide N-CN Bond Activation.

two *productive* outcomes may be possible. One, insertion/elimination of both the cyanide and amine occur to form aminocyanation products with any variety of unsaturated C-C bond systems.

Nickel-cyanides are suitable for insertion/elimination reactions with unsaturated C-C bonds and the products of which are versatile building blocks. Two, cyanide insertion occurs, however amine elimination is not possible. In this case, once again, the amine may be a handle for transmetallation, particularly with boronic acids/esters. Alternatively, amine insertion into electrophilic agents such as DMAD, ketenes, CO_2, or CO may lead to more reactive Ni–CC bonds,[43] effectively incorporating both pieces of the oxidatively cleaved cyanamide into organic products.

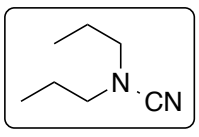
Experimental Section

General experimental. Ligands 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine (IPr), 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidine (SIPr), and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidine (IMes) were prepared according to literature

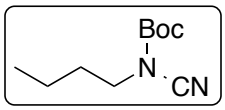
procedures.[44,45] The diynes dimethyl 2,2-bis(but-2-ynyl)malonate (**4.1**),[46] dimethyl 2,2-bis(prop-2-yn-1-yl)malonate (**4.25**),[47] *N*,*N*-bis(but-2-ynyl)-*p*-toluenesulfonamide (**4.14**),[47] 1-(but-2-ynyloxy)but-2-yne (**4.16**),[48] and dimethyl 2-(but-2-ynyl)-2-(4,4-dimethylpent-2-ynyl)malonate (**4.22**)[48] were also prepared according to literature procedures. *N*-Butylcyanamide was also prepared by literature procedures.[49] The diynes 3,9-dodecadiyne (**4.18**) and 2,9-undecadiyne (**4.20**) were purchased from GFS and Lancaster chemical companies, respectively, and distilled from CaH_2 before use. Bis(1,5-cyclooctadiene)nickel(0), $Ni(COD)_2$, was purchased from the Strem chemical company and used without further purification. All other reagents were purchased from commercial sources and used without further purification. All liquid reagents were degassed prior to use by the freeze-pump-thaw method. All reactions were preformed in a nitrogen-filled glove box or under nitrogen using standard Schlenk techniques unless otherwise noted. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 MHz unless otherwise noted.

All spectra are referenced to residual solvent peaks. All ^{13}C NMR spectra were proton decoupled. Gas Chromatography was performed using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 min; detector temperature: 250 ºC. IR spectra were recorded on a Bruker Tensor 27 spectrometer. HRMS analyses were performed at the University of Utah Mass Spectrometry facility.

Experimental procedures. *N,N*-dipropylcyanamide (**4.2d**) was prepared as follows: to a stirring solution of 1.4 g BrCN (13.3 mmol, 0.6 equiv) dissolved in 50 mL of a 1:1 diethyl ether (Et_2O):THF solution was

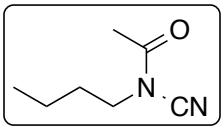


added 3 mL (21.9 mmol, 1.0 equiv) of dipropylamine dropwise over 10 min. The solution was stirred at ambient temperature for 3 h, at which time 10 mL of hexanes was added and followed by an additional 10 min of stirring. The solution was then filtered over a pad of celite and washed with 3x50 mL of H_2O and 2x50 mL of brine. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated to yield 1.35 g of **2d** as a colorless oil: yield 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H), 1.59 (q, J = 7.5 Hz, 2H), and 2.87 (t, J = 7.0 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 10.92, 20.9, 53.1, and 117.8. IR (neat, cm^{-1}) $\tilde{\nu}$ 2968, 2878, 2208, 1462, and 1090. HRMS (ESI) calc'd for $C_7H_{15}N_2$ $[M+H]^+$ 127.1230, found 127.1230.

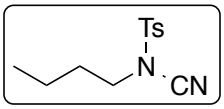


N-butyl-N-(tert-butoxycarbonyl)cyanamide (**4.2i**) was prepared as follows: to a stirring suspension of 217 mg NaH (9.1 mmol, 1.2 equiv) in 75 mL of THF was added 740 mg *N*-butylcyanamide (7.6 mmol, 1 equiv) in 5 mL Et_2O at 0 °C. The solution was warmed to ambient temperature, at which time 1.9 mL of di-*tert*-butyl dicarbonate (8.3 mmol, 1.1 equiv) was added. The solution was stirred for 1 h, at which time 1 mL of H_2O was added dropwise followed by the addition of 10 mL of Et_2O. The crude reaction mixture was poured over 50 mL of a 1:1 mixture of brine and water then extracted with 3x15 mL of Et_2O. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluting with CH_2Cl_2 to afford 1.41 g of the title compound as a colorless oil: yield 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.38 (q, J = 7.5 Hz, 2H), 1.51 (s, 9H), 1.66 (dt, J_1 = 7.0, J_2 = 7.5, 2H), and 3.46 (t, J = 7.5, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.7, 19.5, 27.9, 29.9, 47.6, 85.4, 109.8, and 151.2. IR (neat, cm^{-1}) $\tilde{\nu}$ 2966, 2361, 2241, 1748, 1461, and 1152. HRMS (ESI) calc'd for

$C_{10}H_{19}N_2O_2$ $[M+H]^+$ 199.1441, found 199.1441.

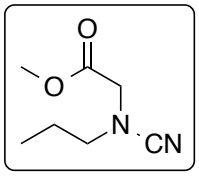


N-butyl-N-cyanoacetamide (**4.2j**) was prepared as follows: to a suspension of 230 mg NaH (9.4 mmol, 1.2 equiv) in 25 mL of THF was added 770 mg *N*-butylcyanamide (7.9 mmol, 1 equiv) in 5 mL of Et_2O at 0 °C. The solution was warmed to ambient temperature, at which time 0.617 mL of acetyl chloride (8.6 mmol, 1.1 equiv) was added. The solution was stirred for 1 h, at which time 1 mL of H_2O was added dropwise followed by the addition of 10 mL of Et_2O. The crude reaction mixture was poured over 50 mL of a 1:1 mixture of brine and water then extracted with 3x15 mL Et_2O. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluting with CH_2Cl_2 to afford 1.07 g of the title compound as a colorless volatile oil: yield 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 3H), 1.35 (q, J = 7.5, 2H), 1.64 (dt, J_1 = 7.0, J_2 = 7.5, 2H), 2.38 (s, 3H) and 3.54 (t, J = 7.5, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.6, 19.6, 22.3, 29.7, 45.9, 111.1, and 169.4. IR (neat, cm^{-1}) $\ddot{v}$ 2963, 2875, 2361, 2233, 1730, 1373, and 1244. HRMS (ESI) calc'd for $C_7H_{13}N_2O$ $[M+H]^+$ 141.1022, found 141.1023.

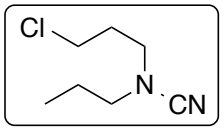


N-butyl-N-cyano-4-methylbenzenesulfonamide (**4.2k**) was prepared as follows: to a suspension of 356 mg NaH (14.8 mmol, 1.2 equiv) in 50 mL of THF was added 1.21g *N*-butylcyanamide (12.3 mmol, 1 equiv) in 5 mL Et_2O at 0 °C. The solution was warmed to ambient temperature, at which time 2.9 g of *p*-toluenesulfonyl chloride (14.8 mmol, 1.2 equiv) dissolved in 5 mL THF was added. The solution was stirred for 4 h, at which time 1 mL of H_2O was added dropwise followed by the addition of 10 mL of Et_2O. The crude reaction mixture was poured over 50 mL of a 1:1 mixture of brine and water then extracted with 3x15 mL Et_2O. The

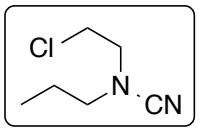
organic phase was then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluting with CH_2Cl_2 to afford 1.3 g of the title compound as a viscous colorless oil: yield 97%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3H), 1.29 (q, J = 7.5, 2H), 1.59 (dt, J_1 = 7.0, J_2 = 7.5, 2H), 2.44 (s, 3H), 3.33 (t, J = 7.5, 2H), 7.38 (d, J = 8.0, 2H), and 7.78 (d, J = 8.5, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.3, 19.1, 21.7, 29.6, 49.8, 108.5, 127.7, 130.4, 133.5, and 146.5. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2963, 2875, 2230, 1380, and 1173. HRMS (ESI) calc'd for $C_{12}H_{17}N_2O_2S$ $[M+H]^+$ 253.1005, found 253.1006.



Methyl 2-(N-butylcyanamido)acetate (**4.2m**) was prepared as follows: to a suspension of 295 mg NaH (12.3 mmol, 1.2 equiv) in 50 mL of THF was added 1.01 g *N*-butylcyanamide (10.3 mmol, 1 equiv) in 5 mL Et_2O at 0°C. The solution was warmed to ambient temperature, at which time 1.0 mL of methyl 2-bromoacetate (11 mmol, 1.1 equiv) was added. The solution was stirred for 3 h, at which time 1 mL of H_2O was added dropwise followed by 10 mL of Et_2O. The crude reaction mixture was poured over 50 mL of a 1:1 mixture of brine and water, and extracted with 3x15 mL Et_2O. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluting with CH_2Cl_2 to afford 1.53 g of the title compound as a pale yellow oil: yield 88%. ^{1}H NMR (400 MHz, C_6D_6) δ 0.59 (t, J = 7.2 Hz, 3H), 0.98 (q, J = 7.2, 2H), 1.21 (dt, J_1 = 7.5, J_2 = 7.5, 2H), 2.63 (t, J = 7.2, 2H), 3.19 (s, 2H) and 3.23 (s, 3H). ^{13}C NMR (400 MHz, C_6D_6) δ 13.9, 20.1, 30.1, 52.1, 52.2, 52.6, 117.0, and 168.9. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2960, 2875, 2360, 2216, 1752, and 1217. HRMS (ESI) calc'd for $C_8H_{15}N_2O_2$ $[M+H]^+$ 171.1128, found 171.1128.

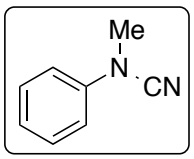


N-butyl-N-(3-chloropropyl)cyanamide (**4.2n**) was prepared as follows: to a suspension of 250 mg NaH (9.9 mmol, 1.2 equiv) in 50 mL of THF was added 805 mg *N*-butylcyanamide (8.2 mmol, 1 equiv) in 5 mL Et_2O at 0 °C. The solution was warmed to ambient temperature, at which time 2.45 mL of 1-bromo-3-chloropropane (24.7 mmol, 3 equiv) was added. The solution was heated to reflux and stirred overnight. The solution was cooled to ambient temperature then quenched with 1 mL of H_2O followed by the addition of 10 mL of Et_2O. The crude reaction mixture was poured over 50 mL of a 1:1 mixture of brine and water then extracted with 3x15 mL Et_2O. Then organic phase was then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography eluting with CH_2Cl_2 to afford 1.3 g of the title compound as a colorless oil: yield 91%. ^{1}H NMR (400 MHz, C_6D_6) δ 0.59 (t, J = 7.2 Hz, 3H), 0.93 (q, J = 7.2, 2H), 1.15 (dt, J_1 = 7.2, J_2 = 7.6, 2H), 1.48 (m, 2H), 2.30 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 6.8 Hz, 2H), and 3.04 (t, J = 6.2 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.99, 20.1, 30.1, 30.8, 41.9, 48.7, 51.9, 117.0. IR (neat, cm^{-1}) $\tilde{\nu}$ 2961, 2874, 2361, 2208, and 1459. HRMS (ESI) calc'd for $C_8H_{16}ClN_2$ $[M+H]^+$ 175.0997, found 175.0997.



N-butyl-N-(2-chloroethyl)cyanamide (**4.2o**) was prepared as follows: to a stirring suspension of 400 mg NaH (16.8 mmol, 1.5 equiv) in 20 mL 1:1 THF/dichloroethane was added dropwise 1.1 g *N*-butylcyanamide (11.2 mmol, 1.0 equiv) in 5 mL THF. The solution was stirred for 15 min at ambient temperature then brought to reflux for 8 h. The solution was cooled to room temperature, quenched with 5 mL MeOH, then poured into 100 mL H_2O. The suspension was extracted with 3x15 mL CH_2Cl_2. The combined organic phase was dried over anhydrous

Na_2SO_4, concentrated, and purified by column chromatography eluting with CH_2Cl_2 affording 1.38 g of **2o** as a pale yellow oil: yield 77%. ^{1}H NMR (500 MHz, C_6D_6) δ 0.68 (t, J = 7.5 Hz, 3H), 0.97 (q, J = 7.5, 2H), 1.18 (dt, J_1 = 7.0, J_2 = 7.5, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.42 (t, J = 6.2 Hz, 3H), and 2.92 (t, J = 6.2 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.6, 19.5, 29.8, 40.9, 51.7, 53.1, and 116.8. IR (neat, cm^{-1}) $\tilde{\nu}$ 2962, 2874, 2210, 1461, and 1106. HRMS (ESI) calc'd for $C_7H_{13}N_2$ $[M+H]^+$ 161.0840, found 161.0841.



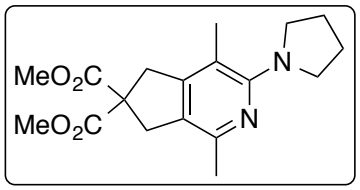
N-methyl-N-phenylcyanamide (**4.2p**) was prepared as follows: to a solution of cyanogen bromide (1 g, 9.4 mmol, 0.6 equiv) in 25 mL of 1:1 Et_2O:THF was added 1.7 mL *N*-methylaniline (15.6 mmol, 1 equiv) at ambient temperature. The solution was then stirred overnight, at which time 5 mL of hexane was added and the solution was stirred for an additional 10 min. The solution was then filtered over a pad of Celite, and the filtrate was washed with 4 x 25 mL of H_2O and 2 x 25 mL of brine. The organic phase was dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with 1:1 ethyl acetate/hexane to afford 2.19 g of the title compound as a colorless solid: yield 82%. Mp 28-30 °C. ^{1}H NMR (300 MHz, C_6D_6) δ 2.21 (s, 3H), 6.96 (m, 2H), 6.76 (m, 1H), 6.7 (m, 2H). ^{13}C NMR (300 MHz, C_6D_6) δ 36.2, 115.1, 123.3, 129.9, 141.4. IR (neat, cm^{-1}) $\tilde{\nu}$ 2361, 2223, 1600, and 1114. HRMS (ESI) calc'd for $C_8H_9N_2$ $[M+H]^+$ 133.0760, found 133.0760.

General co-cycloaddition procedure for internal diynes (A). In a nitrogen-filled glove box, 10 mg (.036 mmol, 0.05 eq.) $Ni(COD)_2$ and 11.1 (.072 mmol, 0.1 eq.) IMes were dissolved in 1 mL of toluene and stirred for 4 h. Separately, 0.72 mmol (1 eq.)

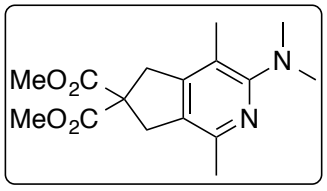
diyne and 0.72 mmol (1 eq.) cyanamide were dissolved in 6.27 mL of toluene. To the diyne/cyanamide solution was added the $Ni(COD)_2$/IMes solution and the combined solution was stirred for 30 min at ambient temperature, taken out of the glove box, concentrated, and then purified via flash column chromatography to afford the aminopyridine product.

General co-cycloaddition procedure for terminal diynes (B). In a nitrogen-filled glove box, 10 mg (.036 mmol, 0.05 eq.) $Ni(COD)_2$ and 14.2 (.072 mmol, 0.1 eq.) SIPr were dissolved in 1 mL of toluene and stirred for 4 h. Seperately, 0.72 mmol (1 eq.) of diyne and 0.72 mmol (1 eq.) of cyanamide were dissolved in 6.27 mL of toluene. To the diyne/cyanamide solution was added the $Ni(COD)_2$/SIPr solution and the and the combined solution was stirred for 1 h at ambient temperature, taken out of the glove box, concentrated, and then purified via flash column chromatography to afford the aminopyridine product.

***In situ* cycloaddition procedure.** In a nitrogen-filled glove box, 5.3 mg (0.02 mmol) $Ni(acac)_2$ and either 14.1 mg (0.04 mmol) IMes·HCl or 19.8 mg (0.04 mmol) SIPr·HBF_4 were suspended in 1.5 mL pentane. To this was added 45 mL (0.103 mmol) of a 2.5 M solution of ^{n}BuLi in hexanes. The resultant suspension was stirred for 10 min at room temperature. Concurrently, 0.41 mmol of diyne and 0.41 mmol of cyanamide were weighed into an oven-dried vial equipped with a stir-bar, and dissolved with 3 mL of toluene. The catalyst solution was then added to the toluene solution, and the reaction vessel was sealed and the solution stirred for 1 h at room temperature. The reaction was quenched by addition of 5 drops of MeOH. The solution was then concentrated and purified by column chromatography.

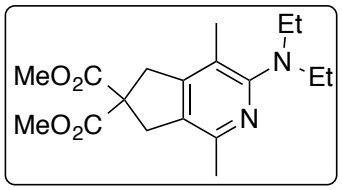


Dimethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**4.3**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 42.7 μL (0.42 mmol) of cyanamide **4.2a** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 130.7 mg of the title compound as a white solid: yield 93%. Mp 85-87 °C. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.885 (m, 4H), 2.162 (s, 3H), 2.30 (s, 3H), 3.440 (m, 4H), 3.475 (s, 2H), 3.483 (s, 2H) and 3.763 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.9, 21.9, 25.7, 38.7, 40.2, 50.3, 53.2, 60.0, 113.5, 124.7, 147.5, 150.3, 159.1, 172.4. IR (neat, cm^{-1}) $\tilde{\nu}$ 2955, 2870, 2211, 1738, 1600, 1430. HRMS (ESI) calc'd for $C_{18}H_{25}N_2O_4$ $[M+H]^+$ 333.1809, found 333.1808.

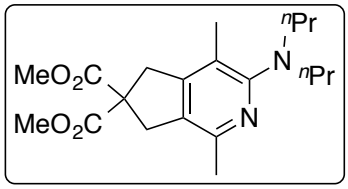


Dimethyl 3-(dimethylamino)-1,4-dimethyl-5H-cyclopenta [c] pyridine-6,6(7H)-dicarboxylate (**4.4**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 34.2 μL (0.42 mmol) of cyanamide **4.2b** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 129.5 mg of the title compound as a white solid: yield 99%. Mp 63-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H), 2.78 (s, 6H), 3.49 (s, 2H), 3.50 (s, 2H) and 3.77 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ15.0, 21.8, 38.8, 40.1, 42.5, 53.3, 59.9, 117.2, 127.3, 147.9, 150.4, and 172.3. IR (neat, cm^{-1}) $\tilde{\nu}$ 2953, 2360, 1735, 1588, 1442, and 1277. HRMS (ESI) calc'd for $C_{16}H_{23}N_2O_4$ $[M+H]^+$ 307.1652, found 307.1652.

Dimethyl 3-(diethylamino)-1,4-dimethyl-5H-cyclopenta [c] pyridine-6,6(7H)-



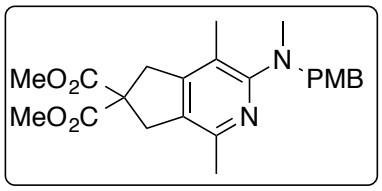
dicarboxylate (**4.5**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 42.7 μL (0.42 mmol) of cyanamide **2c** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 135.8 mg the title compound as a colorless oil: yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.0 Hz, 6H), 2.11 (s, 3H), 2.30 (s, 3H), 3.09 (q, J = 7.0, 4H), 3.48 (s, 2H), 3.49 (s, 2H) and 3.74 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.4, 14.6, 21.7, 38.8, 40.1, 45.7, 53.0, 59.7, 119.3, 127.3, 147.8, 149.9, 160.3 and 172.2. IR (neat, cm^{-1}) $\ddot{v}$ 2967, 2361, 1738, 1588, 1433, and 1264. HRMS (ESI) calc'd for $C_{18}H_{27}N_2O_4$ $[M+H]^+$ 335.1965, found 335.1968.



Dimethyl 3-(dipropylamino)-1,4-dimethyl-5H-cyclopenta [c]pyridine-6,6(7H)-dicarboxylate (**4.6**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 53.5 mg (0.42 mmol) of cyanamide **4.2d** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 136.4 mg the title compound as a colorless oil: yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.839 (t, J = 7.3 Hz, 6H), 1.24 (m, 4H), 2.13 (s, 3H), 2.32 (s, 3H), 3.02 (t, J = 7.2, 4H), 3.49 (s, 2H), 3.50 (s, 2H) and 3.77 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.9, 14.7, 21.4, 21.9, 38.9, 40.2, 53.3, 53.9, 59.8, 119.2, 127.3, 147.9, 150.1, 160.8, and 172.4. IR (neat, cm^{-1}) $\ddot{v}$ 2956, 2872, 1739, 1589, 1433, and 1267. HRMS (ESI) calc'd for $C_{20}H_{31}N_2O_4$ $[M+H]^+$ 363.2278, found 363.2279.

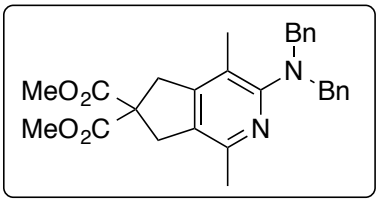
Dimethyl 1,4-dimethyl-3-morpholino-5H-cyclopenta [c] pyridine-6,6(7H)-

dicarboxylate (**4.7**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 42.8 μL (0.42 mmol) of cyanamide **4.2f** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 142.9 mg of the title compound as a white solid: yield 97%. Mp 82-83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.34 (s, 3H), 3.08 (t, J = 4.6 Hz, 4H), 3.49 (s, 2H), 3.51 (s, 2H), 3.77 (s, 6H) and 3.84 (t, J = 4.4 Hz, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.5, 21.8, 38.8, 40.1, 50.8, 53.3, 59.9, 67.5, 117.9, 128.4, 148.6, 150.5, 160.3, and 172.2. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2955, 2848, 2361, 1737, 1588, 1431, and 1259. HRMS (ESI) calc'd for $C_{18}H_{25}N_2O_5$ $[M+H]^+$ 349.1758, found 349.1757.

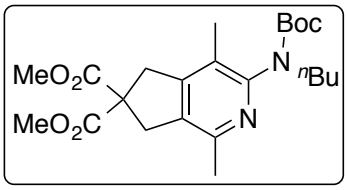


Dimethyl 3-((4-methoxybenzyl)(methyl)amino)-1,4-dimethyl- 5H-cyclopenta [c] pyridine -6,6 (7H)-dicarboxylate (**4.8**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **1** and 74.6 mg (0.42 mmol) of cyanamide **4.2g** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 151.9 mg of the title compound as a viscous colorless oil: yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.41 (s, 3H), 2.71 (s, 3H), 3.57 (s, 2H), 3.58 (s, 2H), 3.82 (s, 6H), 3.84 (s, 3H), 6.92 (d, J = 8.5 Hz, 2H), and 7.37 (d, J = 8.6 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.7, 21.7, 38.7, 39.6, 40.0, 53.1, 55.3, 57.7, 59.8, 113.7, 117.8, 127.6, 129.3, 131.9, 148.0, 150.3, and 172.1. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2953, 2838, 1737, 1588, 1512, 1436, and 1246. HRMS (ESI) calc'd for $C_{23}H_{29}N_2O_5$ $[M+H]^+$ 413.2071, found 413.2069.

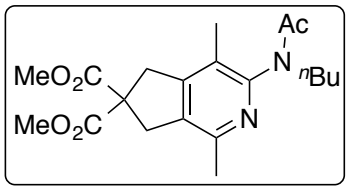
Dimethyl 3-(dibenzylamino)-1,4-dimethyl- 5H-cyclopenta [c] pyridine-6,6(7H)-



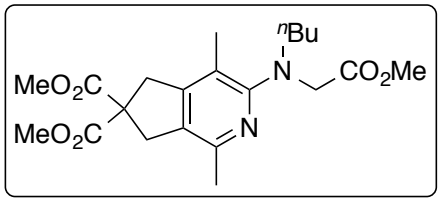
dicarboxylate (**4.9**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 94.1 mg (0.42 mmol) of cyanamide **4.2h** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 170.8 mg of the title compound as a viscous colorless oil: yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.36 (s, 3H), 3.55 (s, 2H), 3.55 (s, 2H), 3.82 (s, 6H), 4.31 (s, 3H), 7.24 (t, J = 7.0, 2H), 7.32 (t, J = 7.2, 4H), 7.38 (d, J = 7.2, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.6, 21.7, 38.8, 40.1, 53.2, 55.4, 59.8, 118.9, 126.8, 128.2, 128.3, 128.6, 139.9, 148.2,150.5, 159.9, and 172.2. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 3029, 2952, 2360, 1737, 1591, 1434, and 1267. HRMS (ESI) calc'd for $C_{28}H_{31}N_2O_4$ $[M+H]^+$ 459.2278, found 459.2282.



Dimethyl 3-((ter-butoxycarbonyl) (butyl)amino)-1,4 dimethyl-5H-cyclopenta [c]pyridine-6,6(7H)-dicarboxylate (**4.10**) General procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 87.2 mg (0.44 mmol) of cyanamide **4.2i** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 149.7 mg of the title compound as a colorless solid: yield 82%. Mp 64-66 °C. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 60 °C) δ 0.85 (t, J = 7.4 Hz, 3H), 1.28 (m, 2H), 1.38 (s, 9H), 1.62 (br s, 2H) 2.11 (s, 3H), 2.21 (s, 3H), 3.37 (s, 6H), 3.45 (s, 2H), 3.51 (s, 2H), and 3.88 (br s, 2H). ^{13}C NMR (400 MHz, $C_6D_5CD_3$, 60 °C) δ 14.1, 14.8, 20.4, 21.5, 30.4, 38.6, 40.0, 51.4, 52.0, 52.7, 53.1, 59.8, 116.6, 127.2, 147.4, 150.6, 159.1, 172.1, and 172.7. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2955, 2361, 1738, 1595, 1434, and 1271. HRMS (ESI) calc'd for $C_{23}H_{35}N_2O_6$ $[M+H]^+$ 435.2490, found 435.2497.

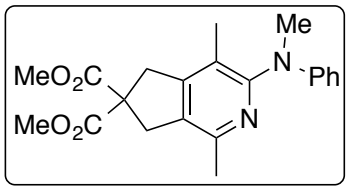


Dimethyl 3-(N-butylacetamido)- 1,4-dimethyl- 5H-cyclo penta [c] pyridine-6,6(7H)-dicarboxylate (**4.11**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 63.1 mg (0.45 mmol) of cyanamide **4.2j** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 5% MeOH:CH_2CH_2 to afford 137.5 mg of the title compound as a colorless yellow viscous oil: yield 87%. ^{1}H NMR (400 MHz, $C_6D_5CD_3$, 60 °C) δ 0.81 (m, 3H), 2.11 (br s, 2H), 1.59 (br s, 2H), 1.66 (s, 3H), 1.87 (s, 3H), 2.20 (s, 3H), 3.35 (s, 6H), 3.44 (s, 4H), 4.03 (br s, 1H). ^{13}C NMR (400 MHz, $C_6D_5CD_3$, 60 °C) δ 13.4, 13.9, 20.5, 21.4, 22.0, 30.4, 38.9, 39.9, 47.4, 52.7, 59.7, 123.9, 133.8, 137.4, 150.9, 151.5, 153.5, 168.9, and 171.3. IR (neat, cm^{-1}) *ῡ* 2955, 2361, 1738, 1595, 1434, and 1271. HRMS (ESI) calc'd for $C_{20}H_{29}N_2O_5$ $[M+H]^+$ 377.2071, found 377.2072.

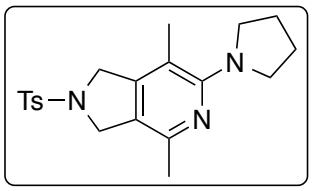


Dimethyl 3-(butyl(2-methoxy-2-oxoethyl)amino)-1,4-dimethyl- 5H -cyclopenta[c] pyridine-6,6(7H)-dicarboxylate (**4.12**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 73 mg (0.43 mmol) of cyanamide **4.2m** dissolved in 3.6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 138.3 mg of the title compound as a viscous colorless oil: yield 81% (*Note: the title compound is light sensitive and chromatography was preformed in a dimly lit room. The green degradation products were not isolated.)* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.27 (m, 3H), 1.55 (m, 2H), 2.15 (s, 3H), 2.23 (s, 3H), 3.15 (t, *J* = 7.8, 2H), 3.45 (s, 2H), 3.46 (s, 2H), 3.65 (s, 3H), 3.73 (s, 6H), and 3.91 (s,

2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.1, 14.8, 20.4, 21.5, 30.4, 38.6, 40.0, 51.4, 52.0, 52.7, 53.1, 59.8, 116.6, 127.2, 147.4, 150.6, 159.1, 172.1, and 172.7. IR (neat, cm^{-1}) *ῡ* 2955, 2361, 1738, 1595, 1434, and 1271. HRMS (ESI) calc'd for $C_{21}H_{31}N_2O_6$ $[M+H]^+$ 407.2177, found 407.2186.

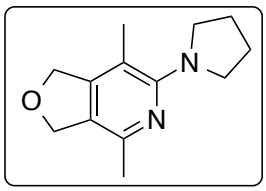


Dimethyl 1,4- dimethyl- 3- (methyl (phenyl) amino)-5H-cyclopenta [c] pyridine -6,6(7H)-dicarboxylate (**4.13**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.42 mmol) of diyne **4.1** and 55.5 mg (0.42 mmol) of cyanamide **4.2p** dissolved in 3.0 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 139 mg of the title compound as a colorless waxy oil: yield 90%. ^{1}H NMR (500 MHz, $C_6D_5CD_3$) δ 1.77 (s, 3H), 2.29 (s, 3H), 3.33 (s, 3H), 3.34 (s, 6H), 3.46 (s, 2H), 3.53 (s, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), and 7.03 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.5, 21.6, 38.9, 39.8, 39.8, 39.9, 52.4, 59.9, 117.9, 119.9, 120.9, 129.2, 129.9, 137.4, 149.8, 149.9, 150.7, 157.1, 171.6. IR (neat, cm^{-1}) *ῡ* 2956, 1737, 1592, 1436, and 1265. HRMS (ESI) calc'd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$ 369.1809, found 369.1810.

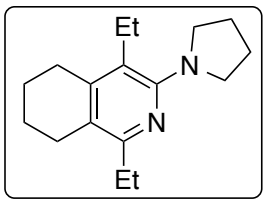


4,7-Dimethyl -6- (pyrrolidin-1-yl) -2- tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (**4.15**) was prepared as follows: general procedure (**A**) was used with 100 mg (0.36 mmol) of diyne **4.14** and 36.6 μL (0.36 mmol) of cyanamide **4.2a** dissolved in 3.0 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 2:1 hexanes:ethyl acetate to afford 113.3 mg of the title compound as a white solid: yield 84%. Mp 110-112 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88 (m, 4H), 2.09 (s,

3H), 2.23 (s, 3H), 2.42 (s, 3H), 3.44 (m, 4H), 4.50 (s, 4H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.9, 21.7, 21.8, 25.8, 50.3, 52.6, 53.6, 111.4, 120.8, 127.7, 130.1, 134.1, 143.9, 146.5, 146.7, and 159.2. IR (neat, cm^{-1}) *ῡ* 2963, 2875, 2230, 1380, and 1173. HRMS (ESI) calc'd for $C_{20}H_{26}N_3O_2S$ $[M+H]^+$ 372.1740, found 372.1749.

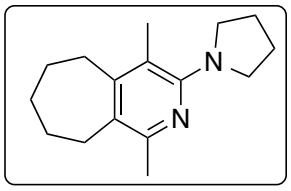


4,7-Dimethyl-6-(pyrrolidin-1-yl)-1 ,3-dihydrofuro [3,4-*c*]pyridine (**4.17**) was prepared as follows: general procedure (**A**) was used with 103.4 mg (0.85 mmol) of diyne **4.16** and 85.3 μL (0.85 mmol) of cyanamide **4.2a** dissolved in 7.2 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 2:1 hexanes:ethyl acetate to afford the 174.3 mg of the title compound as a colorless oil: yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (m, 4H), 2.13 (s, 1H), 2.27 (s, 3H), 3.49 (m, 4H), 4.99(s, 2H), and 5.02 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.1, 21.9, 25.7, 50.2, 72.8, 73.2, 110.3, 123.7, 145.1, 149.9, and 159.1. IR (neat, cm^{-1}) *ῡ* 2960, 2865, 2361, 1591, 1430.5, 1345, and 1060. HRMS (ESI) calc'd for $C_{13}H_{19}N_2O$ $[M+H]^+$ 219.1492, found 219.1493.

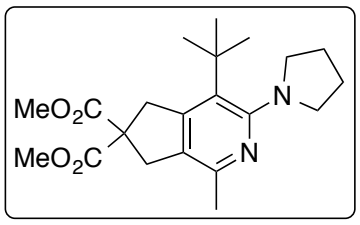


1,4-Diethyl-3- (pyrrolidin-1-yl)-5,6,7,8- tetrahydro isoquinoline (**4.19**) was prepared as follows: general procedure (**A**) was used with 107 mg (0.66 mmol) of diyne **4.18** and 66.5 μL (0.66 mmol) of cyanamide **4.2a** dissolved in 5.2 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 156.6 mg of the title compound as a colorless viscous oil: yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.5 Hz, 3H), 1.31 (t, *J* = 7.5 Hz, 3H), 1.81 (m, 4H), 1.95 (m, 4H), 2.69 (m, 8H), and 3.47 (m, 4H). ^{13}C NMR (400 MHz,

$CDCl_3$) δ 12.3, 13.8, 20.5, 23.0, 23.1, 25.6, 25.8, 26.9, 27.6, 51.1, 122.2, 123.1, 145.5, 155.4, and 157.2. IR (neat, cm^{-1}) $\tilde{\nu}$ 2931, 2866, 2361, 1739, 1563, and 1416. HRMS (ESI) calc'd for $C_{17}H_{27}N_2$ $[M+H]^+$ 259.2169, found 259. 2170.

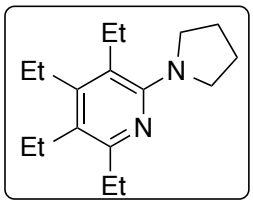


1,4-Dimethyl -3- (pyrrolidin-1-yl) -6,7,8,9 -tetrahydro-5H-cyclohepta[c]pyridine (**4.20**) was prepared as follows: general procedure (**A**) was used with 104 mg (0.70 mmol) of diyne **4.22** and 71 μL (0.70 mmol) of cyanamide **4.2a** dissolved in 6 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes-ethyl acetate to afford 130.3 mg of the title compound as a colorless viscous oil: yield 76%. ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (m, 4H), 1.81 (m, 2H), 1.89 (m, 4H), 2.17 (s, 3H), 2.42 (s, 3H), 2.75 (m, 4H), and 3.38 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.7, 23.1, 25.5, 26.8, 27.6, 29.2, 30.1, 32.2, 50.4, 116.1, 128.5, 148.9, 152.3, and 158.2. IR (neat, cm^{-1}) $\tilde{\nu}$ 2920, 2853, 1570, and 1420. HRMS (ESI) calc'd for $C_{16}H_{25}N_2$ $[M+H]^+$ 245.2012, found 245.2014.

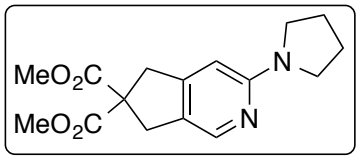


Dimethyl 4-(tert-butyl)-1-methyl-3-(pyrrolidin-1-yl)-5H-cyclopenta [c] pyridine -6,6 (7H)-dicarboxylate (**4.23**) was prepared as follows: general procedure (**A**) was used with 70 mg (0.30 mmol) of diyne **4.22** and 31.0 μL (0.30 mmol) of cyanamide **4.2a** in 3.0 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 85.4 mg of the title compound as a colorless viscous oil: yield 76%. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.88 (m, 4H), 2.18 (s, 3H), 3.42 (s, 2H), 3.48 (m, 4H), 3.68 (s, 2H), and 3.75 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.7, 25.7, 29.34, 29.55, 38.4,

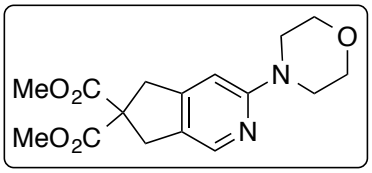
39.2, 40.5, 50.2, 53.2, 60.5, 112.6, 122.3, 151.5, 157.2, 157.8, and 172.3. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2959, 1739, 1704, 1612, 1569, 1480, 1389, 1275, and 1141. HRMS (ESI) calc'd for $C_{21}H_{31}N_2O_4$ $[M+H]^+$ 375.2278, found 375.2284.



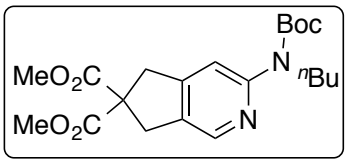
2,3,4,5-Tetraethyl-6-(pyrrolidin-1-yl)pyridine (**4.24**) was prepared as follows: general procedure (**A**) was used with 75 mL (0.66 mmol) of 3-hexyne and 33.3 μL (0.33 mmol) of cyanamide **4.2a** dissolved in 7.0 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes-ethyl acetate to afford 74 mg of the title compound as a waxy colorless oil: yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (m, 9H), 1.31 (t, J = 7.5 Hz, 3H), 1.91 (m, 4H), 2.67 (m, 8H), 3.45 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.5, 14.7, 15.58, 15.61, 20.9, 21.1, 22.0, 25.7, 27.9, 50.8, 122.8, 126.5, 150.3, 155.3, and 157. 5. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2966, 2871, 1562, and 1416. HRMS (ESI) calc'd for $C_{17}H_{29}N_2$ $[M+H]^+$ 261.2325, found 261.2328.



Dimethyl 3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**4.26**) was prepared as follows: general procedure (**B**) was used with 100 mg (0.48 mmol) of diyne **4.25** and 48.4 μL (0.48 mmol) of cyanamide **4.2a** dissolved in 4.1 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 3:1 hexanes:ethyl acetate to afford 116.8 mg of the title compound as a light yellow solid: yield 80%. Mp 98-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (m, 4H), 3.38 (m, 4H), 3.45 (s, 4H), 3.71 (s, 6H), 6.20 (s, 1H), and 7.92 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.6, 37.5, 40.5, 46.9, 53.1, 60.7, 101.8, 123.2, 143.1, 151.0, 157.0, and 171.9. Melting point and spectra match known values.[32]

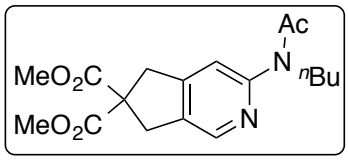


Dimethyl 3-morpholino-5H-cyclopenta[c] pyridine-6,6 (7H)-dicarboxylate (**4.27**) was prepared as follows: general procedure (**B**) was used with 100 mg (0.48 mmol) of diyne **4.25** and 48.5 μL (0.48 mmol) of cyanamide **4.2f** dissolved in 4.1 mL of toluene. The remaining residue was purified via flash column chromatography eluting with CH_2Cl_2 to afford 132.2 mg of the title compound as a lightly yellow wax: yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (t, J = 4.8 Hz, 4H), 3.49 (s, 4H), 3.74 (s, 6H), 3.79 (t, J = 4.7 Hz, 4H), 6.51 (s, 1H), and 8.01 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 37.6, 40.6, 46.3, 53.2, 60.7, 66.9, 102.8, 126.32, 143.1, 151.7, 159.5, and 171.8. Spectra match known values.[32]

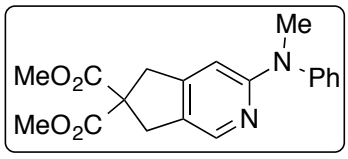


Dimethyl 3-((tert-butoxycarbonyl) (butyl)amino)-5H-cyclopenta [c]pyridine-6,6(7H)-dicarboxylate (**4.28**) was prepared as follows: general procedure (**B**) was used with 100 mg (0.48 mmol) of diyne **4.25** and 96 mg (0.48 mmol) of cyanamide **4.2i** dissolved in 4.1 mL of toluene. The remaining residue was purified via flash column chromatography eluting with dichloromethane to afford 160.7 mg of the title compound as a lightly yellow viscous oil: yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 3H), 1.27 (q, J = 7.5 Hz, 3H), 1.48 (s, 9H), 1.54 (m, 2H), 3.55 (s, 2H), 3.56 (s, 2H), 3.74 (s, 6H), 3.86 (t, J = 7.5, 2H), 7.42 (s, 1H), and 8.17 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9, 20.2, 28.5, 31.2, 37.8, 40.4, 47.1, 53.3, 60.6, 80.8, 116.1, 132.3, 143.0, 150.9, 153.8, 154.6, and 171.6. IR (neat, cm^{-1}) $\tilde{\upsilon}$ 2959, 1739, 1704, 1390, 1276, and 1142. HRMS (ESI) calc'd for $C_{21}H_{31}N_2O_6[M+H]^+$ 407.2177, found 407.2189.

Dimethyl 3-(N-butylacetamido)-5H-cyclopenta [c]pyridine -6,6(7H)-



dicarboxylate (**4.29**) was prepared as follows: general procedure (**B**) was used with 100 mg (0.48 mmol) of diyne **4.25** and 67 mg (0.48 mmol) of cyanamide **4.2j** dissolved in 4.1 mL of toluene. The remaining residue was purified via flash column chromatography eluting with dichloromethane to afford 155.5 mg of the title compound as a lightly yellow viscous oil: yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 3H), 1.27 (q, J = 7.5, 2H), 1.47 (m, 2H), 1.93 (br s, 3H), 3.61 (s, 4H), 3.76 (br s, 8H), 7.04 (s, 1H), and 8.30 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9, 20.2, 23.2, 30.5, 37.9, 40.4, 48.4, 53.4, 60.4, 117.7, 128.7,135.1, 144.7, 152.5, 154.7, 170.2, and 171.4 IR (neat, cm^{-1}) *ϋ* 2955, 2361, 1738, 1595, 1434, and 1271. HRMS (ESI) calc'd for $C_{18}H_{25}N_2O_5[M+H]^+$ 349.1758, found 349.1760.



Dimethyl 3-(methyl(phenyl)amino)-5H-cyclopenta [c] pyridine-6,6(7H)-dicarboxylate (**4.32**) was prepared as follows: general procedure (**B**) was used with 100 mg (0.48 mmol) of diyne **4.25** and 63.5 mg (0.48 mmol) of cyanamide **4.2p** dissolved in 4.1 mL of toluene. The remaining residue was purified via flash column chromatography eluting with 1:2 hexanes:ethyl acetate to afford 135.5 mg of the title compound as a lightly yellow viscous oil: yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.43 (s, 3H), 3.48 (s, 3H), 3.71 (s, 6H), 6.41 (s, 1H), 7.19 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 7.4 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), and 8.04 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 37.5, 38.9, 40.4, 53.2, 60.6, 104.8, 125.3, 125.7, 126.3, 129.8, 142.8, 147.2, 150.8, 158.5, and 171.9. IR (neat, cm^{-1}) *ϋ* 3005, 2953, 2370, 1736, 1617, 1491, 1393, and 1268. HRMS (ESI) calc'd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$ 341.1496, found 341.1496.

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CHAPTER 5

PALLADIUM-CATALYIZED ARYLATION OF CYANAMIDES

Abstract

The cross-coupling of alkyl cyanamides with a number of aryl, heteroaryl, and vinyl halide and pseudohalide coupling partners has been developed via a modification of Pd-catalyzed amidation methods. The reactions proceed selectively under mild conditions with reasonable reaction times in moderate to excellent yields.

Introduction

Incredible progress has been made in metal-catalyzed cross-coupling methods culminating with the recent awarding of a Nobel Prize. In addition to C-C bond forming reactions, the progress in C-N cross-coupling has come a long way since Ullman discovered copper-mediated *ipso*-substitution of aryl halides in 1901. While considerable progress has been made in Cu-mediated (and catalyzed) methods, the utility of systems is often limited by harsh reaction conditions, often excessive use of copper, high reaction temperatures temperatures, and extended reaction times. Although well-developed in terms of application,[1,2] mechanistically, these reactions are generally ill-defined with many mechanistic scenarios proposed to be at play, even within a singular protocol.

Aside from modifications on stoichiometric Cu-mediated (i.e., Goldberg) reactions (Figure 5.1), considerable progress has been made in Pd-catalyzed C-N cross-coupling. Building on the Pd-catalyzed cross-coupling arylhalides and organostannanes (Kosugi-Migita-Stille coupling), Migita demonstrated the first Pd-catalyzed C-N cross-coupling reaction, albeit with a very limited scope.[3] This reaction remained unexplored for nearly 10 years when Hartwig and coworkers investigated the mechanism in detail.[4] As a sign of things to come, Buchwald published shortly after a new report modifying Migita's initial protocol, expanding the scope of the catalytic aryl amination.[5] A year later, both groups publish protocols for the tin-free aryl amination of aryl halides and single-handedly elevate carbon-heteroatom cross-coupling to the field it is today (Figure 5.2).

Under a number of catalytic protocols, the reaction is amenable with nearly any arylhalide and pseudohalide, with sterically hindered arylhaildes and amines, with 1°, 2°, or 3° amines, ammonia, heteroaryl partners, and is mild enough for application in natural product synthesis.[6] These protocols have proven to be extremely diverse and have been extended to other C-N coupling partners such as amides, amidines, iminines, ureas, and hydrazones. As such, we were surprised to find that to the best of our knowledge, cyanamides have never been the subject of a cross-coupling study.

Cyanamides are highly versatile N-C-N components for a number of organic transformations in the synthesis of amidines, and in the synthesis of a number of heterocycles[7] (Figure 5.3) Cyanamides are a currently under investigation in a number of biological and medicinal arenas. Cyanamides are an efficient bioisostere of both $-N_3$ and -OH groups.[8] Bioisosteres modulate biological activity by virtue of subtle differences in

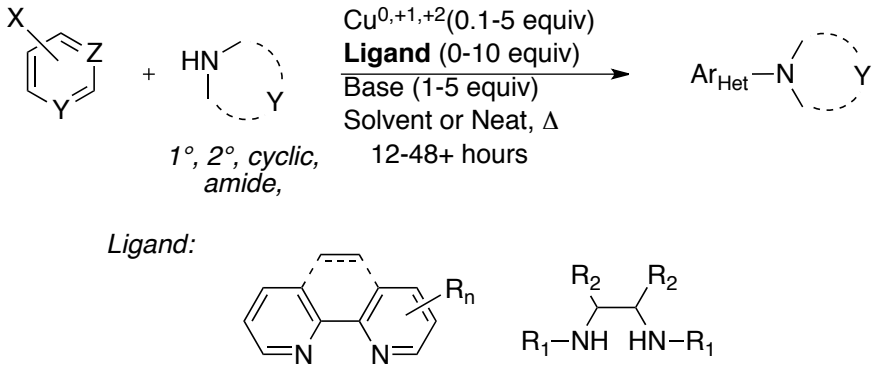
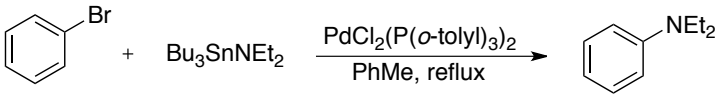
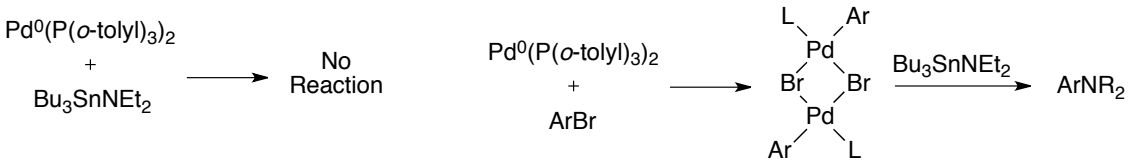


Figure 5.1. Goldberg-Type Aryl Amination with Copper.

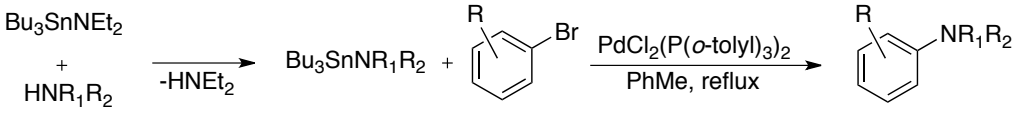
Migita - 1983, Initial Reports



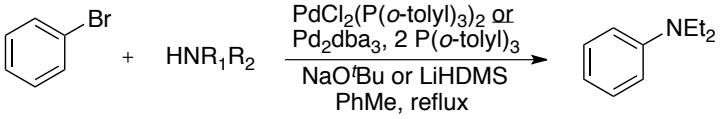
Hartwig - 1994, Mechanistic investigation



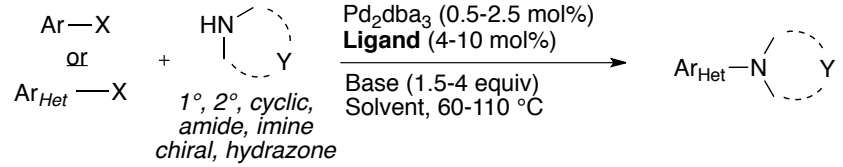
Buchwald - 1994, Substrate Expansion



Buchwald + Hartwig - 1995, Tin-Free Coupling



Buchwald + Hartwig - 1996-Present, Considerable Ligand Effects



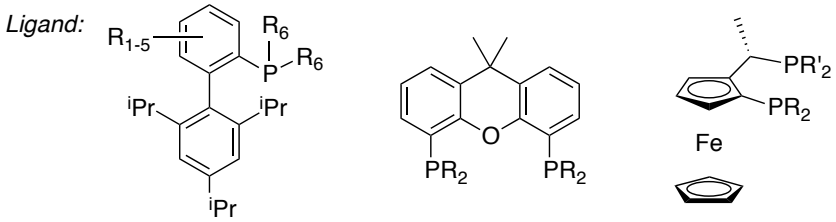


Figure 5.2. Development of Pd-catalyzed C-N Cross-Coupling

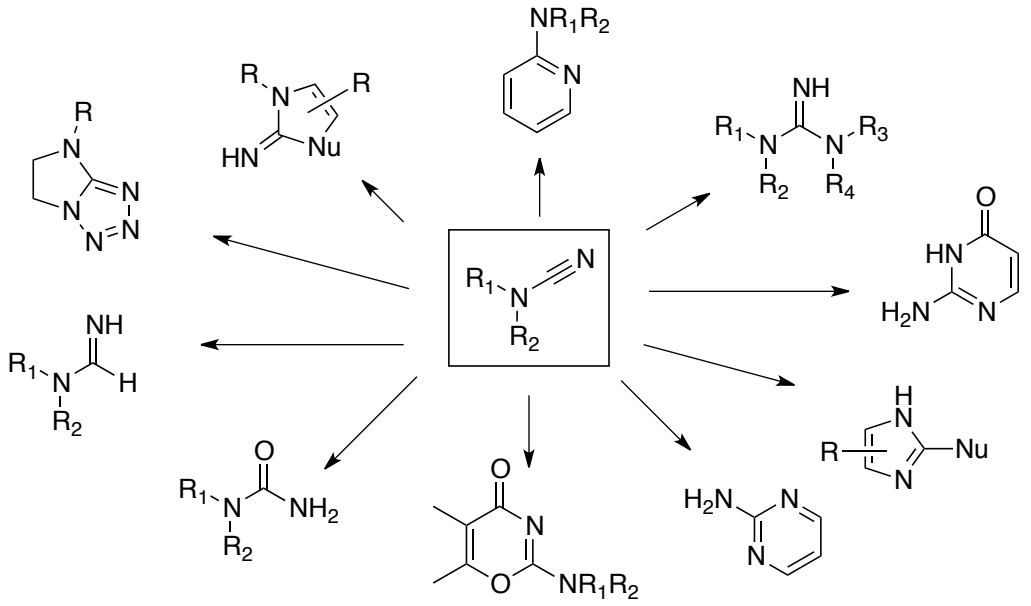


Figure 5.3. Diverse Molecular Architectures Available from Reactions of Cyanamides.

physical and chemical properties and define some of the essential requirements of the pharmacophores. This is illustrated in the synthesis of antiherpes (HSV-1 and HSV-2) uracil nucleosides wherein substitution of a cyanamide moiety displayed broader potency than the azido- or hydroxyl-analogue.[9] In addition to application in library diversification as a bioisostere, cyanamides have been utilized as "warheads" in a number of drug leads for covalent enzyme inhibition.[10] This strategy was found to be particularly powerful in the potent inhibition of cathespsins by cyanopyrrolidinyl compounds.[11] Cathespsins are group of proteolytic enzymes involved in many physiological processes and proposed to play important roles in a number of pathological conditions such as Alzheimer's disease and multiple sclerosis.[12] Cyanamides have also been found to be potent anticancer agents. In a recent structure-activity relationship (SAR) study, a cyanamide derivative of the SMART (SMART = 4-substituted methoxybenzoyl-aryl-thiazole)[13] scaffold was found to

be a potent tubulin inhibitor in a number of human melanoma and prostate cancer cells lines.[14] Cyanamide-containing radioisotope-labeled compounds have been utilized in a number of neurological diagnostic techniques such as positron emission tomography (PET). Glutamate activation of the N-methyl-D-aspartate (NMDA) receptor subtype is thought to mediate important physiological and pathological processes, including memory formation and excitotoxicity (Figure 5.4).[15] As such, compounds for the selective and non-competitive binding of this receptor has garner much attention. Radio-labeled cyanamide CNS5161 was found to be an excellent ligand for this receptor and has found application in PET visualization of brain tissues with high expression of this receptors.[16] Even simple cyanamide (H_2NCN) itself is under investigation as an alcohol deterrent agent, and as such, pro-drugs for its applications are also being investigated.[17]

While a number of methods to synthesize cyanamides exist, methods for the formation of unsymmetrical aryl/alkyl and aryl/aryl cyanamides are sparse, particularly with electron-deficient aryl substituents. Common methods for the preparation of cyanamides include simple substitution of cyanogen bromide or electrophilic hetercocyclic cyanating agents.[18] However, the reduced nucleophilicity of aryl or diaryl amines (particularly with electron-withdrawing groups) can lead to reduced yields. Second to electrophilic cyanation of amines with cyanogen bromide, the Von Braun reaction[19] is most commonly used.

This method requires trisubstituted amines, with the use of a labile leaving group, such as *p*-methoxylbenzyl, for efficient transformation (eq. 5.1). While convenient, synthesis of a suitable homo- or heterodiarylamines can be cumbersome and atom-inefficient.

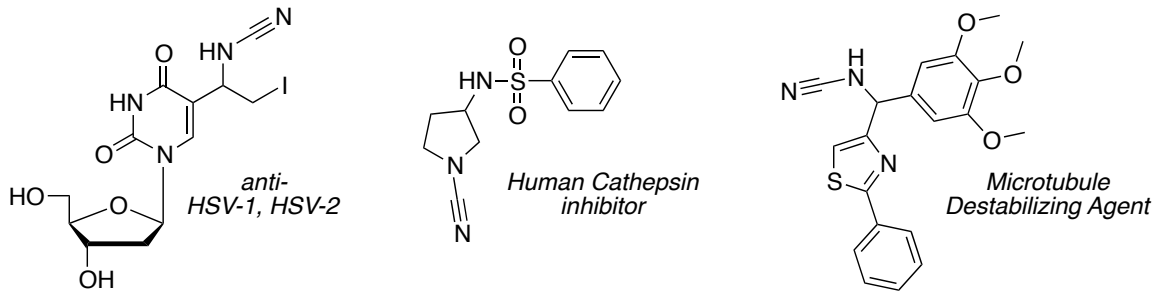
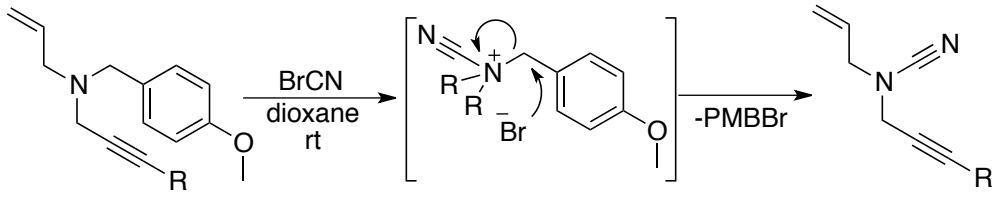


Figure 5.4. Biologically Active Cyanamide-Containing Compounds



(5.1)

As an alternative, more-direct, approach we believed a mild and efficient cross-coupling method might be utilized to greatly expand the inventory of available arylcyanamides.

Containing both nucleophilic and electrophilic sites within the same molecule, cyanamides have a unique reactivity, which may be a hindrance for a metal-catalyzed arylation. The basicity of the amino nitrogen is strongly reduced due to the conjugation of its lone pair with the C-N triple bond. This has been analyzed by DFT calculations of a variety of substituted nitriles and cyanamides.[20]

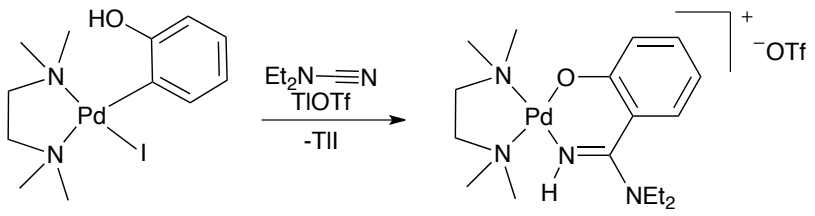
As such, cyanamides exist as both an N-cyanoamine and diimide tautomers (Scheme 5.1), while the N-cyanoamine form dominates; in a few reactions (e.g., silylation, protonation, metal coordination, etc.), the diimide form appears to dominate.[7] Unlike alkylnitriles, cyanamides are prone to thermal trimerization, with trimerization much more facile for monosubstituted cyanamides. In addition to heat, trimerization

occurs in both Lewis acidic and basic conditions to form melamine and isomelamine derivatives (Scheme 5.2).[21]

Cyanamides have a rich history of metal coordination that has been the subject of reviews.[7,22] In monometallic complexes, cyanamides behave as monodentate ligands η^1-bound through the terminal nitrile nitrogen atom, whereas unsubstituted cyanamide behaves as an η^2- or η^3- ligand (Figure 5.5).

This motif is maintained in anionic monosubstituted cyanamide complexes in monometallic complexes. Due to multiple coordination sites, cyanamides are often found in coordination polymers, and polymetallic complexes and clusters.[23] The syntheses of cyanamide complexes with neutral cyanamides follow the coordination reactions of other nitriles; however, anionic cyanamides are generally too weak for nucleophilic halide displacement and often require transmetallation from silver or thallium salts. The rich coordination of chemistry of cyanamides has primarily been directed towards materials (coordination polymers) for a number of applications, or towards utilizing the photophysical properties of cyanamide complexes. Considering the wealth of coordination chemistry, we were surprised to find a lack of reported organometallic transformations of cyanamides.

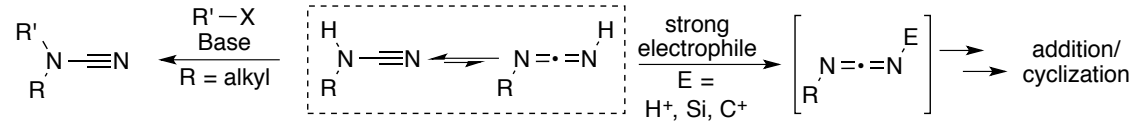
Disconcertingly a rencent report has demonstrated insertion behaviorof cyanamides in the carbopallidationof cyanamides with 2-hydroxy- and 2-aminoarylpallaidum(II) complexes (eq 5.2).



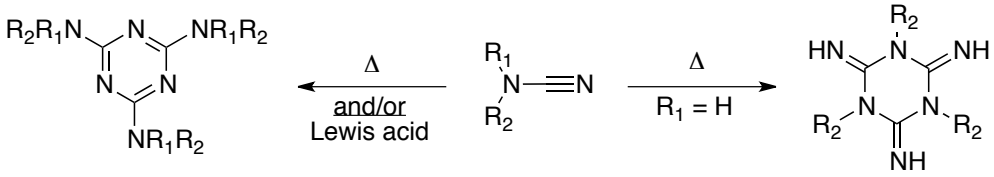
(5.2)

Tertiary Cyanamide

Secondary Cyanamide



Scheme 5.1. Cyanamide Tautomerization



Scheme 5.2. Cyanamide Cyclotrimerization

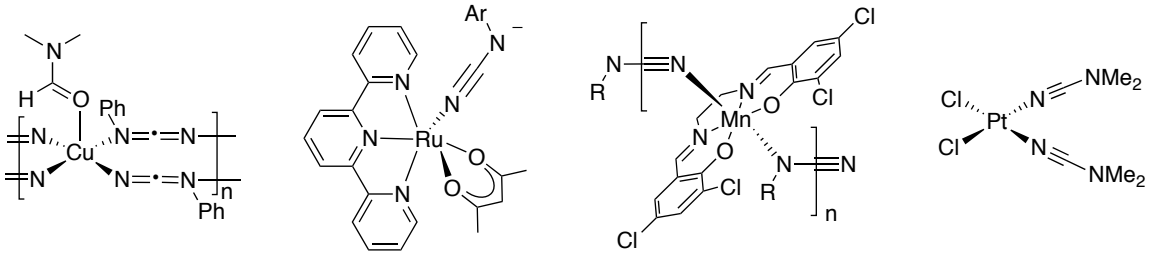


Figure 5.5. Coordination Compounds of Cyanamides

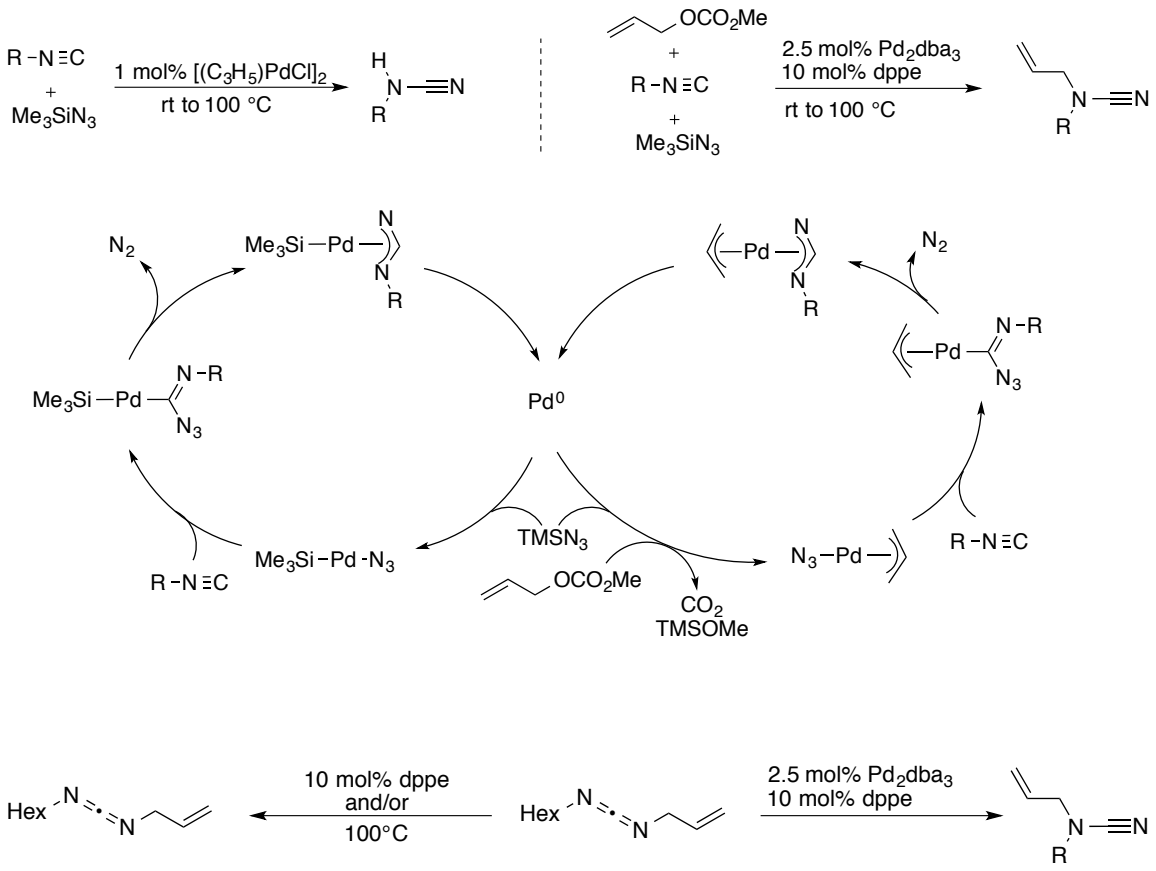
While not a transformation of cyanamide, the Pd-catalyzed *formation* of cyanamides from isonitriles and trimethylsilylzaide provides powerful insights toward the realization of our hypothesis (Scheme 5.4). The reaction begins with oxidative addition of $TMSN_3$ followed by insertion of an isonitrile into the Pd-N bond. This complex then undergoes a denitrogenative Curtius-like rearrangement, to afford a proposed azaallylpalladium species. This species then undergoes reductive elimination to afford silyl cyanamides, which hydrolyze on workup to afford monosubstituted cyanamides. This method has been extended to a three-component reaction with allylcarbonates to afford substituted allylcyanamides.

These results provide a critical insight: that reductive elimination of a cyanamide is possible, and that it favors cyanamide versus carbodiimide formation. While the authors propose that a carbodiimide complex forms, it tautomerizes to a productive cyanamide complex. Strong support for this interesting isomerization was obtained by subjecting allylhexylcarbodiimide under the reaction conditions whereby the allyl cyanamide was obtained in 88% yield.

As a control when allylcarbodiimide was heated in toluene both alone and with ligand, no reaction took place.[24]

As such, we hypothesized that perhaps Pd-catalyzed aryl *amidation* (considering the electronic similarities of amides and cyanamides) conditions may be mild enough to facilitate coupling. Herein, we report a general Pd-catalyzed method for the cross-coupling of alkyl cyanamides with a number of aryl, heteroaryl, and vinyl halides as well as pseudohalides.

Initial investigations focused on the Pd-catalyzed cross-coupling of butyl



Scheme 5.4. Pd-Catalyzed Formation of Cyanamides from Isonitriles

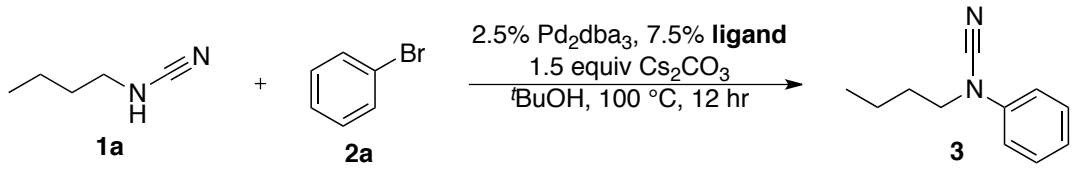
cyanamide (**5.1a**) and bromobenzene (**5.2a**, Table 5.1). Our survey of phosphine ligands revealed that the use of ^{t}BuXPhos[25] resulted in full conversion of bromobenzene and formation of the desired product (**5.3**) in 55% yield.

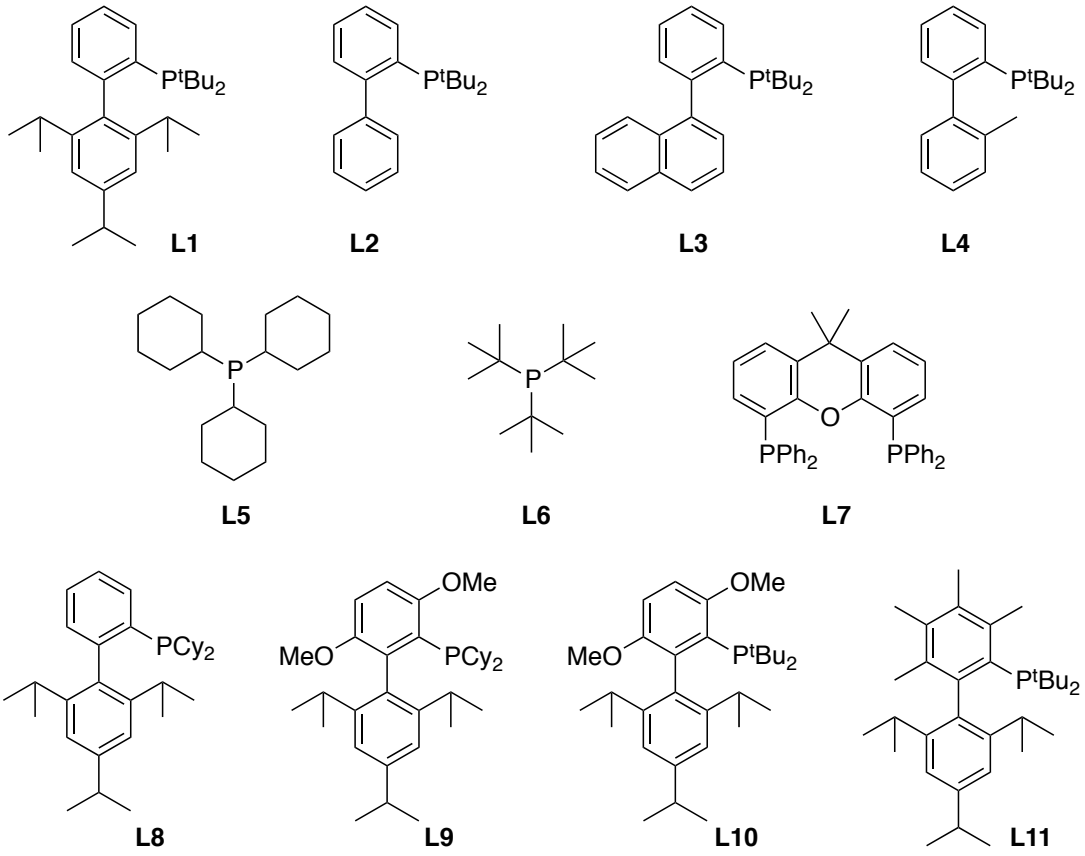
Interestingly, XPhos,[25] BrettPhos,[26] and XantPhos[27] ligands, which are all more effective than ^{t}BuXPhos in analogous Pd-catalyzed amidation reactions, notably gave incomplete conversion of starting material but also afforded only trace amounts of the desired cross-coupling product (**5.3**).

Further evaluation of the reaction conditions led to the following optimized conditions: cyanamide (1.1 equiv), aryl halide (1 equiv), Cs_2CO_3 (1.5 equiv), Pd_2dba_3[28] (2.5 mol%), and ^{t}BuXPhos (7.5 mol%) in ^{t}AmylOH. $Pd(OAc)_2$ (5 mol%), instead of Pd_2dba_3, is not a competent precatalyst. However, when $PhB(OH)_2$ (10 mol%) is added as a sacrificial reductant, cross-coupling does occur, although yields are slightly lower than when Pd_2dba_3 is employed. Although we require 5 mol% palladium in our system, versus 1 mol% or less palladium for aryl amidations utilizing similar conditions, we were surprised by both the final reaction time and temperature of this optimized method.

Previous studies on aryl amidation generally required reaction temperatures of roughly 100 °C, with reaction times of 12-24 h, whereas our reaction requires 60 °C for only 3 h. Our cross-coupling conditions are amenable with a number of substituted aryl bromides, triflates, and iodides (Table 5.2). Furthermore, the order of reactivity follows ArBr > ArOTf > ArI (entries 1, 2, 5-8). Reactions with aryl chlorides resulted in minimal (<10%) conversion (entries 3-4). Selective coupling can be obtained as seen in the reaction of butyl cyanamide (**5.1a**) with 1-bromo-4-fluoro-benzene, which leads to formation of N-butyl-N-(4-fluorophenyl)cyanamide (**5.7**, entry 9).

Table 5.1. Ligand Screen for the Pd-Catalyzed Cross-Coupling of Butylcyanamide and Bromobenzene.

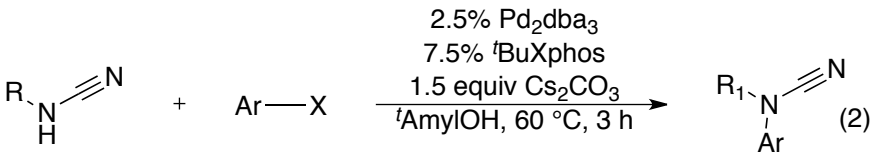


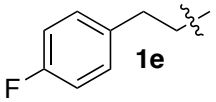
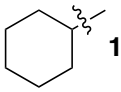
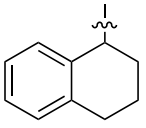


ligand	L1	L2	L3	L4	L5[b]	L6[b]	L7	L8	L9	L10	L11	no L
conversion[a] (%)	**100**	27	24	27	3	29	74	35	59	70	92	12
yield[a] (%)	**55**[c]	d	d	d	0	0	24	d	d	0	d	0

Reaction conditions: **1a** (0.25M in ^{t}BuOH), **2a** (1 equiv), Cs_2CO_3 (1.5 equiv), Pd_2dba_3 (2.5 mol%) ligand, (7.5 mol%) 100 °C, 12 h. [a]Determined by GC using naphthalene as an internal standard. [b]10 mol% ligand used. [c]isolated yield. [d]Trace product detected.

Table 5.2. Substrate Scope for the Pd-Catalyzed Cross-Coupling of Cyanamides and Arylhalides.



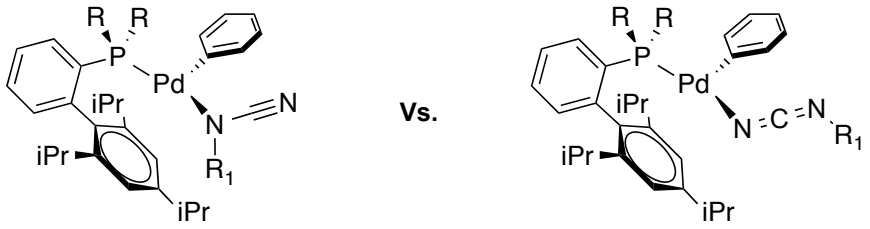
entry	R	Ar	X	yield (%)[a]
1	**1a**	Ph, **2a**	Br	**3**, 76
2	**1a**	Ph, **2a**	I	**3**, 67
3	**1a**	Ph, **2a**	Cl	**3** (NR)
4	**1a**	*p*-Cl-C_6H_4, **2b**	Br	**4**, 77
5	**1a**	*p*-Me-C_6H_4, **2c**	Br	**5**, 77
6	**1a**	*p*-Me-C_6H_4, **2c**	I	**5**, 63
7	**1a**	*p*-Me-C_6H_4, **2c**	OTf	**5**, 74
8	**1a**	*p*-^{t}Bu-C_6H_4, **2d**	Br	**6**, 77
9	**1a**	*p*-F-C_6H_4, **2e**	Br	**7**, 65
10	**1a**	*p*-CF_3-C_6H_4, **2f**	Br	**8**, 92
11	**1a**	*p*-CN-C_6H_4, **2g**	Br	**9**, 82
12	**1a**	*m*-Ac-C_6H_4, **2h**	Br	**10**, 79
13	**1a**	*p*-OMe-C_6H_4, **2i**	Br	**11**, 63[b]
14	**1a**	*p*-Me_2N-C_6H_4, **2j**	Br	**12**, 66[b]
15	**1a**	2,4,6-Me-C_6H_4, **2k**	Br	**13** (NR)
16	^{t}Bu, **1b**	**2f**	Br	**14**, 49
17	Bn, **1c**	**2f**	Br	**15**, 89
18	 **1e**	**2f**	Br	**16**, 84
19	 **1f**	2-pyridyl, **2l**	Br	**17**, 96
20	 **1g**	**2f**	Br	**18** (NR)

Reaction conditions: cyanamide (1.1 equiv), aryl hailde (1 equiv), Cs_2CO_3 (1.5 equiv), Pd_2dba_3 (2.5 mol%), ligand, (7.5 mol%) 60 °C, 3 h. [a]all yields are average isolated yields of reactions run in at least duplicate. [b]Pd_2dba_3 (3.5 mol%), ligand, (10.5 mol%) 60 °C, 6 h.

While the conditions are effective with most aryl halides screened, yields are generally higher with activated (i.e., electron-deficient) aryl halides (entries 10-12).

For reactions with electron-rich aryl halides, yields are generally depressed, and extended reaction times and higher catalyst loadings are required (entries 13-14). Other alkyl cyanamides, such as benzyl- and cyclohexylcyanamide, are also excellent substrates (entries 18 and 20, respectively). However, bulky *tert*-butyl cyanamide leads to decreased yields (entry 17). Negative steric effects are further observed in the lack of reaction between both *o*-bromotoluene and mesityl bromide with **5.1a** (entries 15-16). This is further illustrated in the attempted coupling of tetrahydronaphthylcyanamide **5.1g** and the previously productive arylhalide **5.2f** (entry 21). Bulky coupling substrates in combination with the large ^{t}BuXPhos ligand may force unproductive diimide coordination, effectively killing the catalyst (Scheme 5.5). Heterocycles were also found to be viable substrates. Coupling of 3-bromopyridine occurred smoothly, leading to 20 in excellent yield (Figure 5.6). Previous attempts to achieve cyanated 2-aminopyridines with cyanogen bromide or *N*-cyanoimidazole led to presumed cyanation at the pyridine nitrogen, followed by rapid decomposition.

As such, we were delighted to find coupling of 2-bromopyridine with butyl cyanamide proceeded to afford **5.21** in excellent yield. Free amines are amenable to reaction conditions if conformationally restrained from nucleophilic addition into the nitrile, as seen in the coupling of 5-bromoindole (Figure 5.6). In addition, cyanamides react preferentially in the presence of amides, as seen in the coupling between the exclusive coupling of 4-bromobenzamide and butyl cyanamide (eq. 5.3). The coupling of vinyl bromides and vinyl triflates afforded rare vinyl cyanamides.[29]



Scheme 5.5. Cyanamide Versus Carbodiimide Coordination Modes

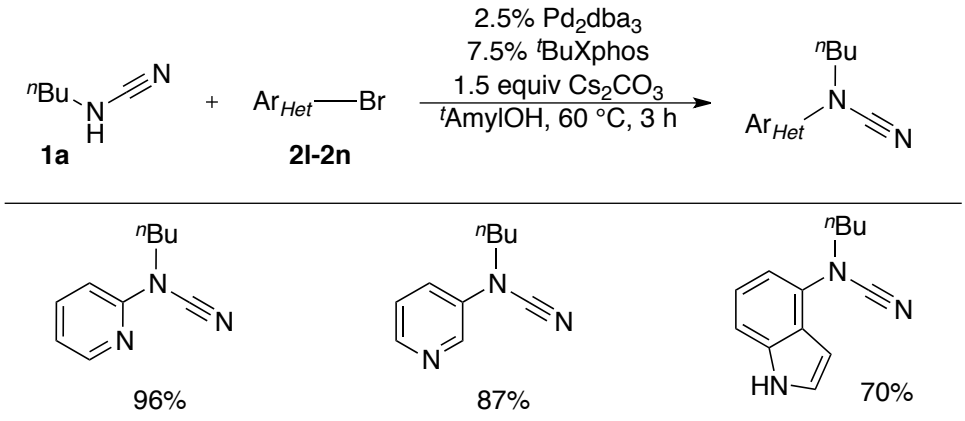
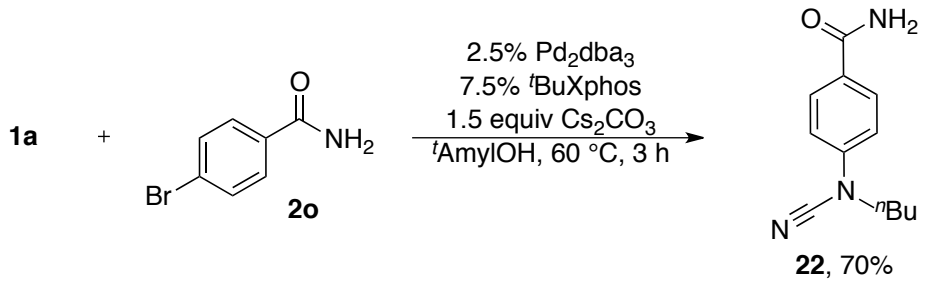
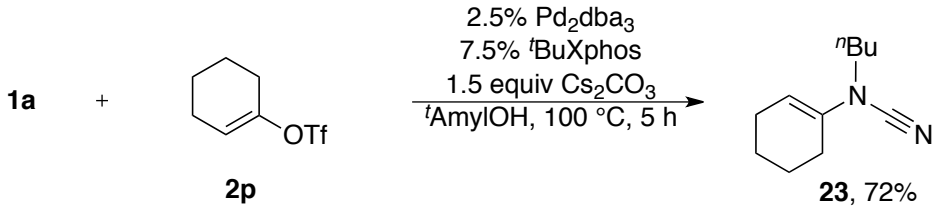


Figure 5.6. Cross-Coupling of Heterocyclic Aryl Halides and Butylcyanamide.

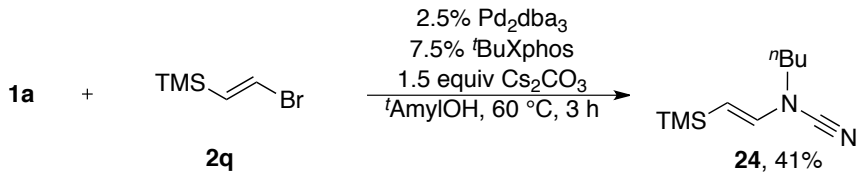


(5.3)

While productive vinylcyanamides are formed in decreased yields (eqs 5.4 and 5.5). Attempts to couple phenylcyanamide with any aryl halide were unsuccessful.

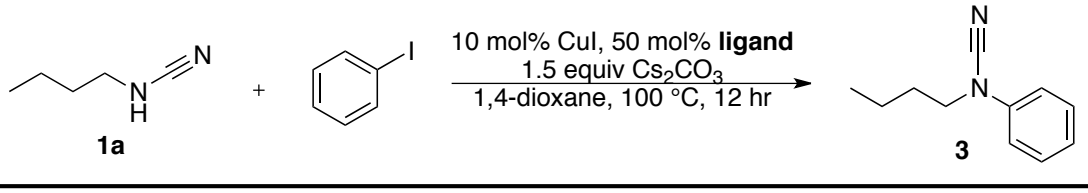


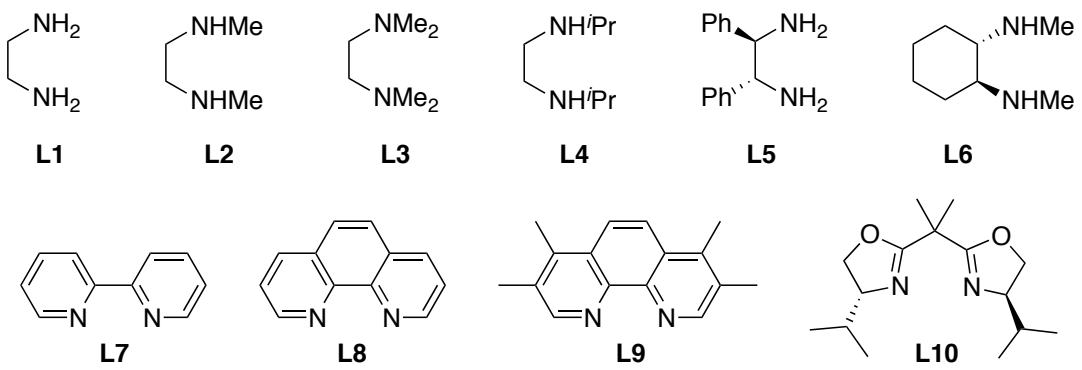
(5.4)



(5.5)

As a compliment to this Pd-catalyzed method, we also attempted to catalyze the arylation of cyanamides with copper. Once again, we hypothesized that previously developed Cu-catalyze aryl amidation would be a beneficial starting point. As such, we initially screened a number of substituted ethylenediamine ligands with the coupling of butyl cyanamide (**5.1a**) and iodobenzene under reported conditions (Figure 5.7).[30] Consistent with the observations made in Cu-catalyzed aryl amidation, *N*,*N*'-monosubstituted ethylenediamine ligands were the most productive. Neither disubstituted nor unsubstituted ethylenediamines provided coupling product. Surprisingly, (*rac*)-*trans*-





ligand	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	no L
conversion[a] (%)	30	100	13	65	100	100	74	44	58	24	100
yield[a] (%)	b	65	0	12	62	b	b	b	b	0	0

Reaction conditions: **1a** (1.0M in dioxane), **2a** (1 equiv), Cs_2CO_3 (1.5 equiv), CuI (10 mol%) ligand, (7.5 mol%) 100 °C, 12 h. [a]Determined by GC using naphthalene as an internal standard. [b]Trace product detected.

Figure 5.7. Ligand Screen for the Cu-Catalyzed Cross-Coupling of Butylcyanamide and Iodobenzene.

N,*N*'-dimethylcyclohexane-1,2-diamine, the ligand of choice for amidation reactions, only provided only trace product. Bulky, *N*,*N*'-diisopropylethylenediamine only provided trace product.

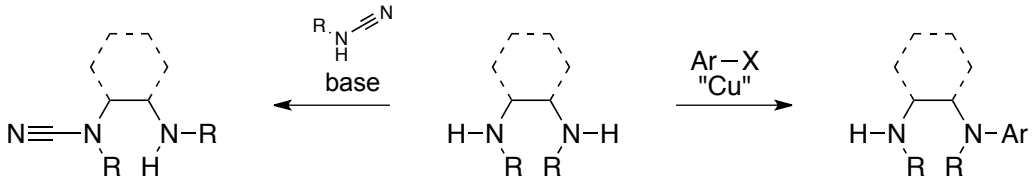
While yields for *N*,*N*'-dimethylethylenediamine and (*rac*)-*trans*-*N*,*N*'-dimethyl-1,2-diphenylethane-1,2-diamine were nearly identical, *N*,*N*'-dimethylethylenediamine was chosen as ligand of choice from a cost and simplicity stand-point. Although yields were moderate, conversion was high. The mass balance was identified in three side products; an isomelamine cyanamide trimerization side product, biphenyl, and modified

ligand. This product arises from competitive transcyanation from butylcyanamide followed by amine arylation (Scheme 5.6). Exclusive formation of these two products was found if K_3PO_4 or K_2HPO_4 were used as the base. Upon switching to Cs_2CO_3, formation of isomelamine was significantly reduced. Ligand modification remained (Scheme 5.7). Ligand loading was then screened in attempts to avoid this ligand modification. We found that at least 4 equivalents of ligand to copper are required for substantial product formation. Unfortunately, ligand modification persisted. Considering the broad applicability of the Pd-catalyzed method, further progress into developing the Cu-catalyzed method was abandoned.

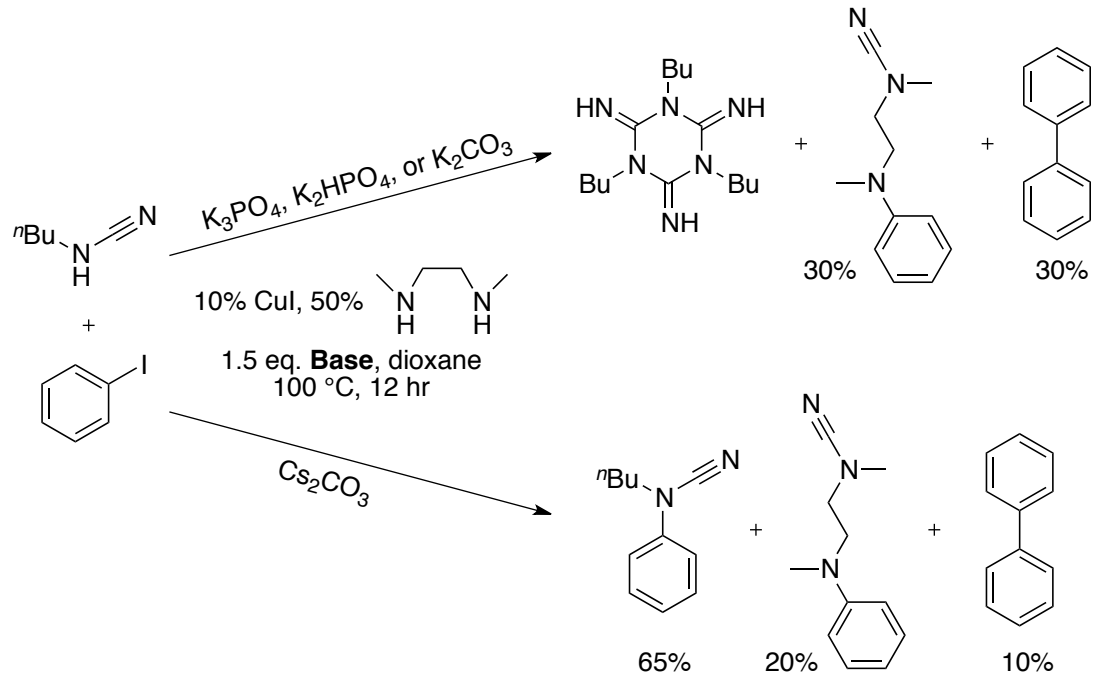
In conclusion, we have developed a mild and efficient method for the Pd-catalyzed arylation of alkyl cyanamides. The reaction is amenable to electron donating and-withdrawing aryl halides as well as heteroaryl halides and pseudohalides. In addition, vinyl halides are also able to be cross-coupled with cyanamides to yield vinyl cyanamides in moderate yields.

Future Work

Clear issues exist in this cross-coupling. Primarily is the inability to couple aryl halides and aryl cyanamides to afford diarylcyanamides. In a number of attempts to couple arylcyanamides, we observed complete conversion of both starting materials; however, we were unable to trace the mass balance. We believe that most likely the coupling is successful, considering the complete conversion of arylhalide but lack of any biphenyl or alkoxylated aryl products. Perhaps the instability of such an electron-deficient diaryl cyanamide may be leading to oligimerization products. The lack of



Scheme 5.6. Origin of Modified Ligand Isolated from the Reaction Mixture of the Cu-Catalyzed Cross-Coupling of Butylcyanamide and Iodobenzene.



Scheme 5.7. Product Distribution in the Cu-Catalyzed Cross-Coupling of Butylcyanamide and Iodobenzene.

known diarylcyanamides, the initial inspiration for this investigation, may attest to this reactivity. In order to address this observation and to reconcile the lack of known diaryl cyanamides, investigations into the synthesis of these species could be investigated.

While seemingly simplistic in scope, investigations into the specific synthesis and careful exploration into side products may contribute to the fundamental chemistries of cyanamides and find practical application in biomedical application as previously mentioned, or in polymer and materials chemistry as extrapolated from the apparent ease of oligimerization and the utility of mealamine, isomelamine, and other urethane-like compounds in polymer chemistry.

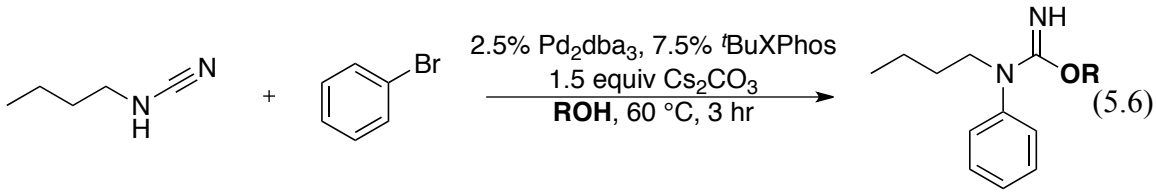
Recent success in increasing the reactivity of Pd-catalysts utilizing the XPhos family of ligands has been accomplished by forming a heteropalladacyclic precatalyst.[31] This strategy allowed for significant improvements over the catalyst formed *in situ* from a Pd^0 source and free ligand in terms of loading, sterically hindered substrates, and less reactive arylhalides and pseudohalides. Along these lines, formation of a Pd-cyanamide complex and its bonding behavior will be a worthwhile pursuit. The coupling of cyanamides with aryl halides is considerably more facile than either amines or amides. The use of higher catalyst loading is just to accommodate/out-compete for the facile oligimerization of cyanamides in basic media. Considering how well the reaction works with the reduced nucleophilicity and multiple bonding motifs of cyanamides, and the need for a singular ligand investigation, should be conducted to answer these interesting mechanistic questions. In doing so, we may overcome the limited substrate scope, and increase yields all around. Investigations into the halide displacement can be carried out in this context as well. Considering the number of possible bonding interactions between

cyanamides and the palladium center will be of interest from both a structural and synthetic inorganic standpoint and how this translates into the observed increased reactivity of cyanamides over amines and amides. In addition to the cyanamide-palladium interaction, the XPhos family of ligands has recently been shown to have unexpected reactivity under other cross-coupling reactions.[32] Formation of complexes of other XPhos-type ligands may also lend insight into the apparent selectivity of only *t*BuXPhos in these reaction conditions. This further supports the need of investigations into the behavior of these complexes under our reaction conditions.

The oligimerization of cyanamides is not limited to only arylcyanamides and appears to be the major reason why relatively high catalyst loadings are required for efficient catalysis. Investigations into the rate of oligimerization under modified conditions (e.g.; differing base, solvent, additives) may afford insight into ways to avoid this problematic side reaction.

The relative stability and cost of aryl chlorides over other aryl halides and pseudohalides make them the arylhalide of choice. The limitation afforded by the incompatibility of aryl chlorides in this method appears minimal, but limits it practical application in larger scale application. The origins of this incompatibility are unknown. However, aryl chlorides have generally been poorer substrates for cross-coupling in general, particularly when Pd_2dba_3 is used. Due to the low conversion in this system, either the oxidative addition or halosubstitution steps are slow. The reduction in rate of turnover may lead to high levels of cyanamide trimerization, and/or catalyst poisoning by an as of yet unknown process. Once again, utilization of palladacyclic precatalysts may allow for the use of aryl chlorides.

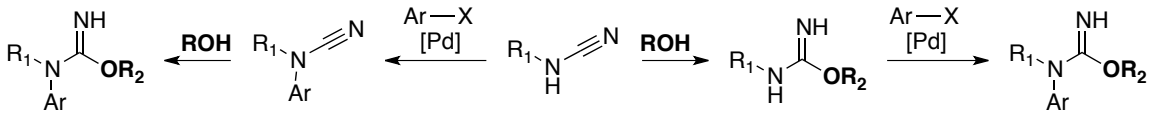
In the course of this investigation, we became quite familiar with the reactivity trends of cyanamides. One such reaction was observed while screening solvents for this reaction. We observed that the use of primary or secondary alcohols leads exclusively to isourea products in high yield (eq. 5.6). These products demonstrate that the cross-coupling is facile; however, whether it is the cyanamide or isourea residue is unclear.



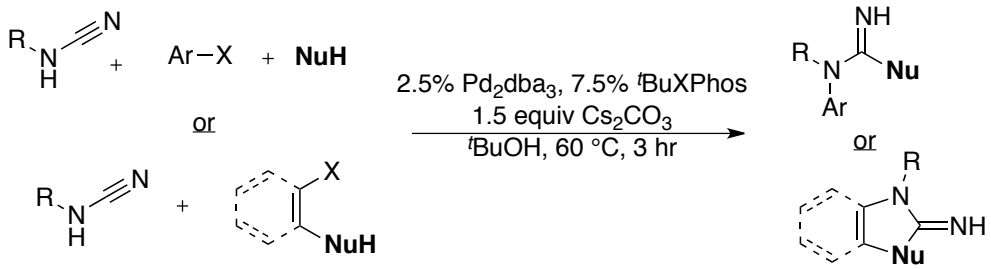
(5.6)

The active substrate can be easily identified by subjecting a prepared monosubstituted isourea to the reaction conditions (Scheme 5.8) Regardless of the mechanism at play, isoureas are a well-studied and highly utilized class of compounds.

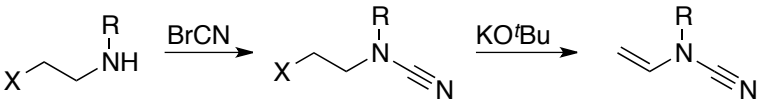
Isoureas have diverse biological activity, and are also utilized in a number of reaction types, primarily in the synthesis of heterocycles.[33] This observation may also lead to the introduction of heteroatomic nucleophiles, such as amines, in either an inter- or intramolecular addition to form guanidines or polyheteroatomic functionalities. As a simple test case, 2-bromoaniline derivatives could be coupled with simple alkyl cyanamides to form benzoimidazole or benzoimidazolimines. Alternatively, a disubstituted amine may be added into a standard reaction to form polysubstituted guanidines (eq. 5.7). Exploration into the underexplored chemistry of vinylcyanamides should be pursued as well. We believe the lack of synthetic application of the species is primarily due to the limited scope provided the traditional synthetic method of preparation (eq. 5.8).[29]



Scheme 5.8. Possible Origins of Isourea Products Isolated from the Cross-Coupling of Cyanamides and Aryl Halides.



(5.7)



(5.8)

The first step in expanding this chemistry is to optimize the reaction conditions specifically for vinylhalides. Included in this would be, as previously mentioned, developing strategies for the utilization of vinylchlorides. In terms of the development of new methods, the orientation of the unsaturated bonds (with additional orientation available by tapping into the carbodiimide tautomeric form) alludes to utilization in a number of cycloaddition reactions. An easily envisioned transformation would be the [*3*,*3*]-sigmatropic rearrangement of allylvinyl cyanamide to β,δ-unsaturated *N*-cyanoaldimine. However, allyl cyanamide was incompatible with these reaction conditions. The lack of synthetic utility of allylcyanamides in our method in itself may provide an opportunity for the development of an additional expansion of our method. Considering the three-component reaction to synthesize cyanamides from isonitriles (*vide supra*),2[8] we believe it may be capable of generating allylvinyl cyanamides from cyanamide, allylcarbonates, and vinylhalides by a similar mechanism. Additional reaction of an induced carbodiimide tautomeric form could be performed, including [4+2]-cycloadditions (Figure 5.8).

Considering the unique property of cyanamides wherein they have both nucleophilic and electrophilic species, a single pot aza-Michael addition/cyclization protocol may also allow for the synthesis of additional heterocycles, with the possibility for asymmetric synthesis with a suitable catalyst.

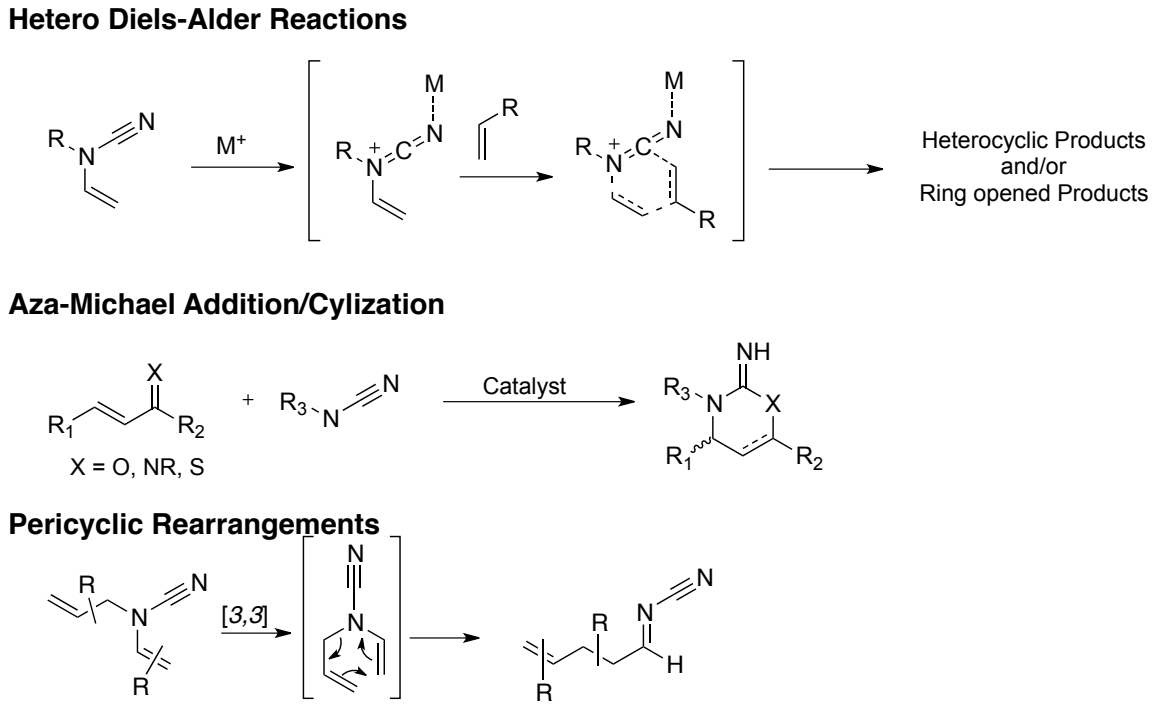


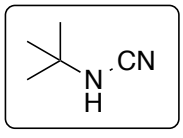
Figure 5.8. Possible Synthetic Utilization of Vinyl Cyanamides

Experimental Section

General experimental. Unless otherwise specified, all reactions were conducted in oven-dried glassware equipped with a Teflon-coated stirbar under a nitrogen atmosphere. Reported reaction temperatures refer to the measured external reaction temperatures in which the reaction was immersed. Diethylether, pentane, and dichloromethane degassed by thorough nitrogen sparge followed by passage through an activated alumina column using a Grubbs type solvent purification system. Dry *tert*-amyl alcohol was purchased from Sigma Aldrich in a sure-seal® bottle and used as received. Tetrahydrofuran was freshly distilled from Na/benzophenone. Biarylphosphines (**L2-L4**), tricyclohexylphoshine, dipalladium trisbenzylideneacetone (Pd_2dba_3), and palladium acetate were purchased from Strem chemical company and used as received. Tri-*tert*-

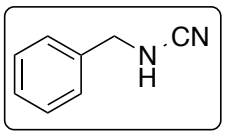
buylphosphine, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), triphenylborane and cesium carbonate were purchased from Sigma-Aldrich chemical company and used as received. All prepared liquid cyanamides were degassed by thorough nitrogen sparge prior to use in coupling reactions. All ^{1}H and ^{13}C nuclear magnetic resonance spectra of pure compounds were acquired on a 400 MHz Varian Inova spectrometer unless otherwise noted. All spectra are referenced to residual proteated $CHCl_3$ via a singlet at 7.26 ppm for ^{1}H and to the center-line of a triplet at 77.23 ppm for ^{13}C. All ^{13}C NMR spectra are proton decoupled. Gas chromatography was performed using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 10 °C/min.; final temperature: 300 °C held for 12 min; detector temperature: 250 °C.

General procedure for synthesis of alkyl cyanamides. Requisite amine (1 equiv) was added to a solution of cyanogen bromide (0.6 equiv.) dissolved in dry Et_2O/THF (1:1) (0.5M) at 0 °C. The solution was then stirred for 3 h. Solids were then filtered off through a pad of celite, and the filtrate was washed with H_2O and brine. The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue then passed through a pad of silica eluting with CH_2Cl_2 to afford pure title compound unless otherwise noted. *CAUTION: cyanogen bromide is toxic, handle in a ventilation hood. Care should be taken during both set up and work up of cyanation reactions.*

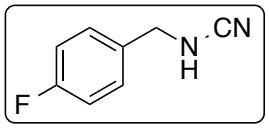


N-(tert-butyl)cyanamide (**5.1b**) was prepared using cyanamide synthesis general procedure with *tert*-butylamine (4.29 mL, 40.8 mmol) and cyanogen bromide (2.59 g, 24.4 mmol). Residue was purified by flash column

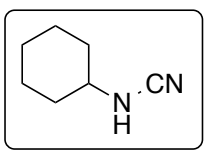
chromatography eluting with 4:1 Et_2O:pentane to afford 1.28 g (64%) of the title compound as a colorless oil. ^1H NMR ($CDCl_3$): δ = 1.21 (s, 9H), 4.21 (br s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.7, 52.8, 115.5 ppm. IR (neat): ῡ = 3199, 2975, 2212, 1442, 1396, 1209, 896 cm^{-1}. Spectra match reported values.[34]



N-benzylcyanamide (**5.1c**) was prepared using cyanamide synthesis general procedure with benzylamine (3.31 mL, 30.3 mmol) and cyanogen bromide (1.92 g, 18.2 mmol). Residue was purified by flash column chromatography eluting with CH_2Cl_2 to afford 1.29 g (64%) of the title compound as a white solid. Mp: 45-47 °C. ^1H NMR ($CDCl_3$): δ = 3.86 (br s, 1H), 4.23 (d, *J* = 6.0 Hz, 2H), 7.27-7.42 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ = 50.4, 116.1, 127.9, 128.6, 129.1, 136.2 ppm. IR (neat): ῡ = 3262, 2217, 1435, 748, 703 cm^{-1}. Spectra match reported values.[34]

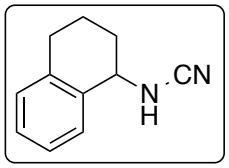


N-(4-fluorophenethyl)cyanamide (**5.1e**) was prepared using cyanamide synthesis general procedure with 2-(4-fluorophenyl)ethanamine (3.21 mL, 24.4 mmol) and cyanogen bromide (1.55g, 14.6 mmol). Residue was purified by flash column chromatography eluting with 3% MeOH in CH_2Cl_2 to afford 0.74 g (37%) of a yellow oil. ^1H NMR ($CDCl_3$): δ = 2.87 (t, *J* = 6.9 Hz, 2H), 3.28 (q, *J* = 6.3 Hz, 2H), 3.76 (br s, 1H), 6.98-7.03 (m, 2H), 7.14-7.19 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.9, 47.0, 115.5, 116.5, 130.3, 133.1, 163.3 ppm. (neat): ῡ = 3212, 2933, 2223, 1603, 1511, 1158, 827, 533 cm^{-1}. HRMS (ESI): calcd. for $C_9H_9FN_2$



Cyclohexylcyanamide (**5.1f**) was prepared using cyanamide synthesis general procedure with cyclohexylamine (1.83 mL, 13.3

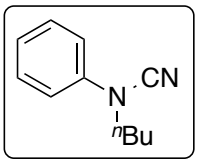
mmol) and cyanogen bromide (0.85 g, 8.0 mmol) affording 0.86 g (86%) of the title compound as a pale yellow oil. Spectra match reported values.[34]



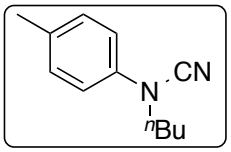
N-(1,2,3,4-tetrahydronaphthalen-1-yl)cyanamide (**5.1g**) was prepared using cyanamide synthesis general procedure with 1,2,3,4-tetrahydronaphthalen-1-amine (3.28 mL, 23.4 mmol) and cyanogen bromide (1.48 g, 14.0 mmol). Residue was purified by flash column chromatography eluting with CH_2Cl_2 to afford 1.01 g (50%) of the title compound as a pale yellow solid. Mp: 98-99 °C ^{1}H NMR ($CDCl_3$): δ = 1.86-1.95 (m, 2H), 2.04-2.11 (m, 2H), 2.75-2.87 (m, 2H), 3.59 (br s, 1H), 4.45 (q, *J* = 5.1 Hz, 1H), 7.10-7.21 (m, 1H), 7.22-7.26 (m, 2H), 7.36-7.39 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.7, 29.1, 29.8, 54.6, 115.3, 126.7, 128.6, 129.1, 129.7, 134.3, 137.8 ppm. IR (neat): ῡ = 3179, 2936, 2215, 1450, 1162, 774 cm^{-1}. Spectra match reported values.[35]

General procedure for Pd-catalyzed coupling. In a nitrogen-filled glove box: Pd_2dba_3 (0.025 equiv), *t*BuXPhos (0.075 equiv), and Cs_2CO_3 (1.5 equiv) were weighed sequentially into an oven-dried scintillation vial equipped with a Teflon-coated stirbar. *tert*-Amyl alcohol (0.5M) was added and solution was stirred for 5 min, at which time arylhalide (1.0 equiv) and cyanamide (1.1 equiv) were added. The vial was then sealed with an airtight cap, removed from the glove box, immersed in an oil bath set to the required temperature, and stirred for 3-5 h. After cooling to rt, the vial was opened to air and CH_2Cl_2 was added. The resultant solution was then filtered through a short pad of celite. The filtrate was then concentrated *in vacuuo* and residue was purified by flash column chromatography.

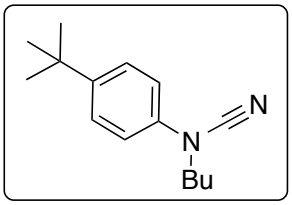
N-butyl-N-phenylcyanamide (**5.3**) was prepared following the cross-coupling



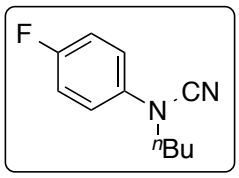
general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), bromobenzene (105.3 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:4 Et_2O:pentane to afford 132.4 mg (76%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.2 Hz, 3 H), 1.39 (q, *J* = 7.2 Hz, 2 H,), 1.81 (quint, *J* = 7.6 Hz, 2H), 3.58 (t, *J* = 7.2 Hz, 2 H), 7.11 (m, 3 H), 7.34 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.6, 49.4, 113.8, 116.0, 123.6, 129.8, 140.2 ppm. IR (neat): ῡ = 2961, 2874, 2218, 1380, 1598, 1499, 752 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}N_2$ [M + H]+ 175.1235; found175.1236.



N-butyl-N-(p-tolyl)cyanamide (**5.5**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 4-bromotoluene (123.0 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:4 Et_2O:pentane to afford 144.9 mg (77%) of the title compound as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.2 Hz, 3 H), 1.49 (q, *J* = 7.2 Hz, 2 H,), 1.78 S4 (quint, *J* = 7.6 Hz, 2H), 2.30 (s, 3 H), 3.53 (t, *J* = 7.2 Hz, 2 H), 6.95 (d, *J* = 7.8 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 13.8, 19.9, 20.7, 29.6, 49.4, 114.2, 116.1, 130.2, 133.2, 137.7 ppm. IR (neat): ῡ = 2961, 2929, 2871, 2217, 1514, 809 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{17}N_2$ [M + H]+ 189.1392; found 189.1391.

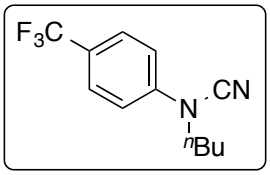


N-butyl-N-(4-(tert-butyl)phenyl)cyanamide (**5.6**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 1-bromo-4-*tert*-butylbenzene (173.3 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:5 Et_2O:pentane to afford 177.2 mg (77%) of the title compound as a viscous clear colorless oil. ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.6 Hz, 3 H), 1.31 (s, 9 H), 1.47 (q, *J* = 7.2 Hz, 2 H), 1.78 (quint, *J* = 7.6 Hz, 2H), 3.56 (t, *J* = 7.2 Hz, 2 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 7.37 (d, *J* = 9.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 20.0, 29.7, 31.6, 34.5, 49.7, 114.2, 115.9, 126.7, 137.7, 146.7 ppm. IR (neat): ῡ = 2962, 2872, 2218, 1611, 1515, 1365, 1197, 827 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{23}N_2$ [M + H]+ 231.1861; found 231.1860.

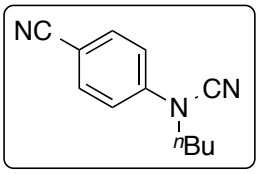


N-butyl-N-(4-fluorophenyl)cyanamide (**5.7**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol), followed by *tert*-amyl alcohol (2 mL), 1-bromo-4-fluorobenzene (109.9 μL, 1 mmol) and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:5 Et_2O:pentane to afford 125.0 mg (65%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3 H), 1.46 (q, *J* = 7.2 Hz, 2 H), 1.79 (quint, *J* = 7.2 Hz, 2H), 3.54 (t, *J* = 7.2 Hz, 2 H), 7.06 (d, *J* = 2.0 Hz, 2 H), 7.08 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.6, 50.1, 114.0, 116.5, 116.7, 117.9, 118.0, 136.5 (d, $J_{C\text{-}F}$ =

10.8 Hz), 158.1 ppm. IR (neat): ῡ = 2962, 2875, 2361, 2219, 1510, 1232, 827 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{14}FN_2$ [M + H]+ 193.1141; found 193.1139.

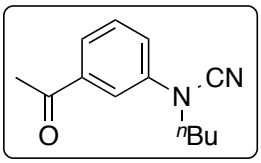


N-butyl-N-(4-(trifluoromethyl)phenyl)cyanamide (**5.8**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 4-bromobenzotrifluoride (139.8 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:4 Et_2O:pentane to afford 222.7 mg (92%) of the title compound as a clear colorless oil. ^{1}H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.2 Hz, 3 H), 1.49 (q, *J* = 7.6 Hz, 2 H), 1.84 (quint, *J* = 7.6 Hz, 2H), 3.67 (t, *J* = 7.6 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.5 49.4, 112.6, 115.7, 125.5, 127.2 (q, $J_{C\text{-}F}$ = 15.2 Hz), 143.3 ppm. IR (neat): ῡ = 2965, 2877, 2361, 2224, 1619, 1521, 1331, 1121, 833 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{14}F_3N_2$ [M + H]+ 243.1109; found 243.1108.

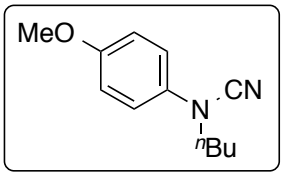


N-butyl-N-(4-cyanophenyl)cyanamide (**5.9**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol), followed by *tert*-amyl alcohol (2 mL), 4-bromobenzonitrile (182.0 mg, 1 mmol) and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:2 Et_2O:pentane to afford 163.3 mg (82%) of the title compound as a colorless crystalline solid, mp = 59-61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ

= 1.03 (t, *J* = 7.2 Hz, 3 H), 1.49 (q, *J* = 7.6 Hz, 2 H), 1.84 (quint, *J* = 7.6 Hz, 2H), 3.63 (t, *J* = 7.6 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.4, 49.4, 106.9, 111.9, 115.8, 118.6, 134.1, 144.1 ppm. IR (neat): ῡ = 2963, 2875, 2230, 1380, 1173 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{14}N_2$ [M + H]+ 200.1188; found 200.1187.

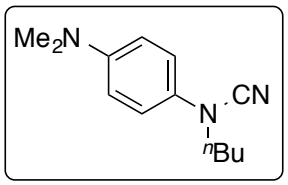


N-(3-acetylphenyl)-N-butylcyanamide (**5.10**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 3-bromoacetophenone (131.8 µL, 1 mmol), and butylcyanamido (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:4 Et_2O:pentane to afford 170.7 mg (79%) of the title compound as a clear colorless oil. ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3 H), 1.48 (q, *J* = 7.2 Hz, 2 H), 1.82 (quint, *J* = 7.6 Hz, 2H), 2.60 (s, 3 H), 3.62 (t, *J* = 7.6 Hz, 2 H), 7.37 (dd, *J* = 8.0, 2.8 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.65 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 26.9, 29.6, 49.4, 113.2, 114.6, 120.7, 123.8, 130. 2, 138.6, 140.9, and 197.4 ppm. IR (neat): ῡ = 2962, 2874, 2361, 2215, 1511, 1284, 1036, 825 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{17}N_2O$ [M + H]+ 217.1341; found 217.1343.

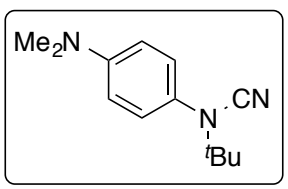


N-butyl-N-(4-methoxyphenyl)cyanamide (**5.11**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (32.06 mg, 0.035 mmol), ^{t}BuXPhos (47.7 mg, 0.10 mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 4-bromoanisole (125.5 µL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The

reaction was carried out at 100 °C for 5 h. Residue was purified by flash column chromatography eluting with 1:4 Et_2O:pentane to afford 128.6 mg (63%) of the title compound as a clear pale pink oil. ^1H NMR ($CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H), 1.45 (q, *J* = 7.2 Hz, 2 H), 1.78 (quint, *J* = 7.6 Hz, 2H), 3.52 (t, *J* = 7.6 Hz, 2 H), 3.79 (s, 3 H), 6.91 (d, *J* = 9.2, 2.8 Hz, 2 H), 7.07 (d, *J* = 9.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.7, 50.3, 55.8, 114.8, 115.1, 118.3, 133.7, 156.4 ppm. IR (neat) ῡ = 2960, 2874, 2361, 2115, 1511, 1284, 1036, 825 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{17}N_2O$ [M + H]+ 205.1341; found 205.1338.

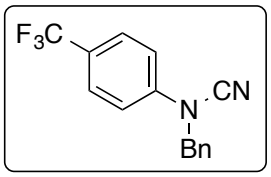


N-butyl-N-(4-(dimethylamino)phenyl)cyanamide (**5.12**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (32.06 mg, 0.035 mmol), ^{t}BuXPhos (47.7 mg, 0.10 mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 4-bromo-*N*,*N*-dimethylaniline (200.1 mg, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 100 °C for 5 h. Residue was purified by flash column chromatography eluting with 1:2 Et_2O:pentane to afford 143.3 mg (66%) of the title compound as a yellow viscous oil. ^1H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H), 1.45 (q, *J* = 7.6 Hz, 2 H), 1.75 (quint, *J* = 7.6 Hz, 2H), 2.92 (s, 6 Hz), 3.49 (t, *J* = 7.2 Hz, 2 H), 6.73 (d, *J* = 9.2, 2 H), 7.04 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 19.9, 29.8, 41.1, 50.7, 113.8, 115.5, 118.9, 130.3, 148.0 ppm. IR (neat): ῡ = 2960, 2873, 2802, 2361, 2212, 1519, 1459 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{20}N_3$ [M + H]+ 218.1657; found 218.1656.



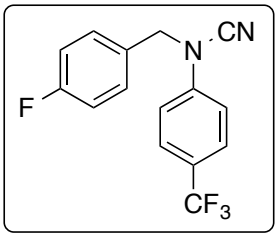
N-(tert-butyl)-N-(4-(trifluoromethyl)phenyl)cyanamide (**15.5**) was prepared following the cross-coupling general

procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 1-bromo-4 (trifluoromethyl)benzene (0.14 μL, 1 mmol), *tert*-Butylcyanamide (147.2 mg, 1.5 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:4 Et_2O:pentane to afford 134.9 (49%) the title compound as a yellow semisolid. ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 9H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.7, 58.1, 120.5, 122.5, 123.5, 126.7 (q, *J* = 15 Hz), 145.1 ppm. IR (neat): ῡ = 2976, 2131, 1613, 1522, 1325, 1166, 843, 595 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{13}F_3N_2$ [M + H]+ 243.1109; found 243.1111

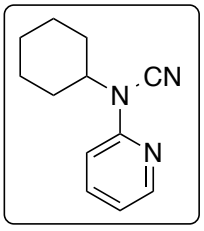


N-benzyl-N-(4-(trifluoromethyl)phenyl)cyanamide (**5.16**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 1-bromo-4-(trifluoromethyl)benzene (0.14 μL, 1 mmol), and *N*-benzylcyanamide (198.1 mg, 1.5 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:4 Et_2O:pentane to afford 246.3 mg (89%) of the title compound as a red solid. Mp: 98-100 °C. ^{1}H NMR ($CDCl_3$): δ = 4.86 (s, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.36 (m, 5H), 7.61 (d, *J* = 0.9 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ = 53.8, 112.9, 127.1 (q, $J_{C\text{-}F}$ = 15.3 Hz), 127.4, 128.5, 128.9, 129.4, 133.5, 142.8, 143.5 ppm. IR (neat): ῡ = 2214, 1618 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{12}F_3N_2$ [M + H]+ 277.0953; found 277.0957.

N-(4-fluorophenethyl)-N-(4-(trifluoromethyl) phenyl) cyana mide (**5.17**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025



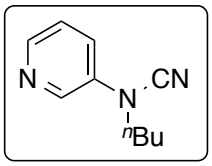
mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 4-bromobenzotrifluoride (139.8 µL, 1 mmol), and *N*-(4-fluorophenethyl)cyanamide (**5.1e**) (180.5 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:2 Et_2O:pentane to afford 258.9 mg (84%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.11 (t, *J* = 7.6 Hz, 2 H), 3.85 (t, *J* = 7.6 Hz, 2 H), 7.02 (dd, *J* = 8.8 Hz, 2 H), 7.15-7.22 (m, 4 H), 7.62 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = ppm. 13C NMR ($CDCl_3$): δ = 33.0, 51.0, 112.4, 115.8, 115.9 116.2, 127.3 (q, $J_{C\text{-}F}$ = 15.2 Hz), 130.5, 130.6, 132.3 (d, $J_{C\text{-}F}$ = 12.8 Hz), 142.9, 161.1, 163.5 ppm. IR (neat): ῡ = 2224, 1618, 1512, 1330, 1120, 1073, 831 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{12}F_4N_2$ [M + H]+ 309.1015; found 309.1018.



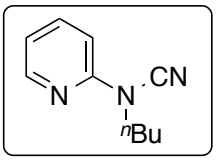
N-cyclohexyl-N-(pyridin-2-yl)cyanamide (**5.18**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 2-bromopyridine (95.2 µL, 1 mmol), and cyclohexylcyanamide (**5.1f**) (136.5 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with CH_2Cl_2 to afford 168.1 mg (96%) of the title compound as a clear colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.23 (m, 2 H), 1.37-1.66 (m, 4 H), 1.89 (br d, *J* = 13.2 Hz, 2H), 2.03 (br d, *J* = 10.4 Hz, 2 H), 4.41 (m, 1 H), 6.96 (ddd, *J* = 6.0, 3.6, 0.8; 1 H), 7.18 (dt, *J* = 6.4, 0.8; 1 H) 7.67 (ddd, *J* = 7.2, 6.0, 1.6; 1 H), 8.30 (ddd, *J* = 4.4, 1.6, 0.8; 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.4, 25.6, 31.1, 54.3, 111.04,

111.8, 118.6, 138.8, 148.2, 152.2 ppm. IR (neat): ῡ = 2934, 2858, 2221, 1591, 1472, 1433, 1288, 772 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}N_3$ [M + H]+ 202.1344; found 202.1340.

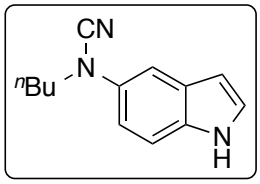
N-butyl-N-(pyridin-3-yl)cyanamide (**5.20**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 3-bromopyridine (95.2 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with CH_2Cl_2 to afford 152.3 mg (87%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.6 Hz, 3 H), 1.49 (q, *J* = 7.6 Hz, 2 H), 1.83 (quint, *J* = 7.6 Hz, 2H), 3.60 (t, *J* = 7.2 Hz, 2 H), 7.31 (dd, *J* = 8.4, 4.4; 1 H), 7.46 (ddd, *J* = 8.4, 3.6, 1.6; 1 H), 8.36 (dd, *J* = 4.8, 1.2; 1 H), 8.46 (d, *J* = 2.8, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.5, 49.5, 112.6, 123.5, 124.1, 136.9, 137.8, 145.1 ppm. IR (neat): ῡ = 2961, 2873, 2361, 2220, 1581, 1484, 800 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}N_3$ [M + H]+ 176.1188; found 176.1184.



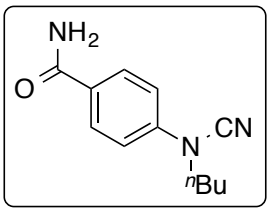
N-butyl-N-(pyridin-2-yl)cyanamide (**5.21**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 2-bromopyridine (95.2 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1% MeOH in CH_2Cl_2 to afford 168.1 mg (96%) of the title compound as a clear colorless oil.



^{1}H NMR ($CDCl_3$): δ = 0.97 (t, *J* = 7.6 Hz, 3 H), 1.45 (q, *J* = 7.6 Hz, 2 H), 1.83 (quint, *J* = 7.6 Hz, 2H), 3.85 (t, *J* = 7.2 Hz, 2 H), 7.03 (ddd, *J* = 6.0, 3.6, 0.8; 1 H), 7.20 (dt, *J* = 6.4, 0.8; 1 H) 7.60 (ddd, *J* = 7.2, 6.0, 1.6; 1 H), 8.11 (ddd, *J* = 4.4, 1.6, 0.8; 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.6, 49.4, 112.8, 115.5, 128.4, 129.4, 143.5, 168.2 ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 19.9, 29.9, 47.1, 110.4, 113.1, 118.6, 138.8, 148.3, 152.4 ppm. IR (neat): ῡ = 2960, 2872, 2223, 1592, 1475, 1433, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{14}N_3$ [M + H]+ 176.1188; found 176.1186.

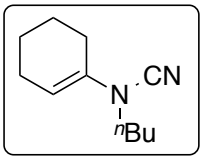


N-butyl-N-(1H-indol-5-yl)cyanamide (**5.22)** was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 5-bromoindole (196.1 mg, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 100 °C for 5 h. Residue was purified by flash column chromatography eluting with 1% MeOH in CH_2Cl_2 to afford 149.2 mg (70%) of the title compound as an off-white microcrystalline solid, Mp 63-64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.6 Hz, 3 H), 1.49 (q, *J* = 7.6 Hz, 2 H), 1.83 (quint, *J* = 7.6 Hz, 2H), 3.61 (t, *J* = 7.2 Hz, 2 H), 6.53 (s, 1 H), 7.09 (dd, *J* = 8.4, 1.8; 1 H), 7.27 (t, *J* = 2.4 , 1 H), 7.42 (m, 2 H), 8.35 (br s, 1H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 13.8, 19.9, 29.8, 50.9, 102.7, 109.1, 112.2, 113.4, 115.8, 126.1, 128.6, 133.1, 133.5 ppm. IR (neat): ῡ = 3302 (br), 2958, 2875, 2215, 1581, 1462 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{16}N_3$ [M + H]+ 214.1344; found 214.1346.

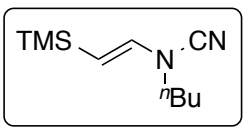


4-(N-butylcyanamido)benzamide (**5.23**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and

Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 4- bromobenzamide (200.0 mg, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1% MeOH in CH_2Cl_2 to afford 152.0 mg (70%) of the title compound white solid, mp 173°-175° (decomp). ^{1}H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.6 Hz, 3 H), 1.49 (q, *J* = 7.6 Hz, 2 H), 1.84 (quint, *J* = 7.6 Hz, 2H), 3.63 (t, *J* = 7.6 Hz, 2 H), 5.51-6.12 (br s, 2 H), 7.18 (d, *J* = 8.8, 2 H), 7.86 (d, *J* = 9.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 19.9, 29.6, 49.4, 112.8, 115.5, 128.4, 129.4, 143.5, 168.2 ppm. IR (neat): ῡ = 3414, 3134 (br), 2973, 2223, 1592, 1475, 1433, 773 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{16}N_3$ [M + H]+ 218.1293; found 218.1294.



N-butyl-N-(cyclohex-1-en-1-yl)cyanamide (**5.24**) was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), 1-cyclohexenyl trifluoromethanesulfonate (174.4 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 100 °C for 5 h. Residue was purified by flash column chromatography eluting with 1:10 Et_2O:pentane to afford 128.4 mg (72%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H), 1.41 (q, *J* = 7.6 Hz, 2 H), 1.55 (m, 4 H), 1.71 (m, 2H), 2.08 (m, 2H), 2.23 (m, 2 H), 5.04 (t, *J* = 4.0, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 20.1, 22.1, 22.7, 24.1, 26.3, 29.6, 48.4, 105.8, 114.7, 135.2 ppm. IR (neat): ῡ = 2934, 2870, 2212, 1666, 1202 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_9N_2$ [M + H]+ 179.1548; found 179.1547.



(E)-N-butyl-N-(2-(trimethylsilyl)vinyl)cyanamide (**5.25**)

was prepared following the cross-coupling general procedure with: Pd_2dba_3 (22.9 mg, 0.025 mmol), ^{t}BuXPhos (31.8 mg, 0.075mmol), and Cs_2CO_3 (488.7 mg, 1.5 mmol) followed by *tert*-amyl alcohol (2 mL), (*E*)-(2-bromovinyl)trimethylsilane (107.3 μL, 1 mmol), and butylcyanamide (107.8 mg, 1.1 mmol). The reaction was carried out at 60 °C for 3 h. Residue was purified by flash column chromatography eluting with 1:10 Et_2O:pentane to afford 80.4 mg (41%) of the title compound as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 9 H), 0.96 (t, *J* = 7.2, 3 H), 1.41 (q, *J* = 7.6 Hz, 2 H), 1.69 (quint, *J* = 7.6 Hz, 2H), 3.27 (t, *J* = 7.6 Hz, 2 H), 5.03 (d, *J* = 16.5, 1 H), 5.89 (d, *J* = 16.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 0.76, 13.8, 19.8, 30.1, 50.1, 105. 9, 113.6, 138.3 ppm. IR (neat): ῡ = 2958, 2220, 1607, 1249, 867, 841 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{21}N_2Si$ [M + H]+ 197.1474; found 197.1476.

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