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Mechanistic Evaluation of the Ni(IPr)₂-Catalyzed Cycloaddition of Alkynes and Nitriles to Afford Pyridines: Evidence for the Formation of a Key η^1 -Ni(IPr)₂(RCN) Intermediate

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Abstract

A detailed 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-catalyzed cycloadditions of diynes and nitriles appear 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 facilitate selective initial binding of nitrile thereby forcing a heterocoupling pathway. In situ IR data suggests the initial binding of the nitrile resides in a rare, η^1 -bound conformation. Following nitrile coordination are a rate-determining hapticity shift of the nitrile and subsequent loss of carbene. Alkyne coordination then leads to heterooxidative coupling, insertion of the pendant alkyne, and reductive elimination to afford pyridine products.

Introduction

Substantial progress has been made in the field of transition metal-catalyzed [2+2+2] cocycloadditions of alkynes and nitrile partners for well over three decades.¹ Owing to the ubiquitous presence of pyridines across all chemical disciplines and applications,² this simple, one step, three-component route to pyridines stands as a powerful strategy. The primary focus of these investigations has been expanding the substrate scope of these reactions, even to the point of their application in complex natural product synthesis.³ In addition to advancing cycloaddition utility, considerable progress has been made in understanding the mechanism of the cycloadditions. The most commonly invoked mechanism for the transition metal-catalyzed cocycloaddition of alkyne and nitriles is a homocoupling mechanism (Scheme 1)⁴ wherein metal-mediated homooxidative coupling of two alkynes affords a metallocyclopentadiene. Nitrile coordination then follows. This nitrile-bound metallocycle is then followed by insertion of nitrile into the M-C bond by traditional M-C bond insertion, formal [2+2]-cycloaddition, or by [4+2]-cycloaddition, with

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subsequent reductive elimination. The alternative heterocoupling pathway, wherein an alkyne and a nitrile undergo oxidative coupling followed by insertion of the secondary alkyne, is rarely invoked.^{4e,f}

We recently developed a mild and efficient nickel-catalyzed cocycloaddition of nitriles and alkynes or diynes that affords a wide range of pyridines (eq 1).⁵ While pleased with the activity of our catalyst, we were surprised by the efficacy of the nickel catalyst since our results contrast the known reactivity of nickel complexes under similar reaction conditions. For example, nickel complexes are known to readily trimerize alkynes in the presence of nitriles.⁶ In addition nickel species are known to activate C-CN bonds⁷ affording nickel complexes that can then undergo alkyne insertion to yield carbocyanation products.⁸ Considering the remarkable cycloaddition behavior, we believed a mechanistic investigation to be paramount.

(1)

Our initial experiments into the investigation of the mechanism of the cycloaddition reaction centered on the isolation of reactive intermediates we believed to be along the catalytic pathway. What we discovered, however, was an entirely unique $[\text{Ni}(\text{IPr})\text{RCN}]_2$ -based catalytic system (Scheme 2).⁹ While initial hypotheses focused on a dimer-to-monomer dissociative pathway, a number of stoichiometric cycloaddition experiments and kinetic analyses instead suggested a cycloaddition mechanism involving partial dimer opening, with no evidence of a dissociative pathway. From a number of competition reactions, ligand exchange experiments, and the resultant nickel species post-cycloaddition, we concluded that following rate-limiting dimer-opening, binding of an exogenous nitrile occurs prior to alkyne binding, thereby dictating a *heterocoupling pathway*. This stands in stark contrast to the mechanistic proposals of other cycloaddition catalysts, which propose an alkyne-homocoupling pathway followed by nitrile incorporation (*vide supra*). While the dimer-catalyzed formation of pyridines appears to have many similarities to the parent $\text{Ni}(\text{NHC})_2$ system, we discovered that the dimer-catalyzed mechanism is a stand alone mechanistic scenario. Herein we report the investigation of the $\text{Ni}(\text{NHC})_2$ -catalyzed [2+2+2] cycloaddition of diynes and nitriles to form pyridines.

Results

Ligand Effects of the $\text{Ni}(\text{NHC})_2$ -Catalyzed [2+2+2] Cycloaddition of Diyne 1 and MeCN

The product distribution of the cycloaddition of diyne **1** and acetonitrile as a function of added NHC ligand are shown in Table 1. In the $\text{Ni}(\text{COD})_2$ -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^tBu¹⁰, ICy,¹¹ and IAd¹² (entries 2, 3, and 7) afforded only dimerized diyne in 88%, 39% and 90% respectively. Bulky *N*-aryl-substituted NHCs such as IPr¹³ and SIPr¹⁴ afforded pyridine product exclusively in high yield. In contrast, use of the slightly smaller IMes¹⁵ resulted in the formation of only trace pyridine product and a high yield of dimerized diyne.

Stoichiometric Transmetallation Reactions

Takahashi has previously shown that pyridines can be prepared in a stoichiometric protocol by proposed transmetallation from zirconapyrroles to Ni(PPh₃)₂Cl₂ followed by Ni-mediated insertion of an exogenous alkyne and reductive elimination.¹⁶ To draw parallels between our catalyst system and these stoichiometric protocols we subjected complex **4**¹⁶ to both zirconapyrrole **7** and dissimilar 4-octyne (eq 3). The reaction afforded unsymmetrical pyridine **6** as a single regioisomer^{16a} in 64% yield.¹⁷ The reaction of zirconapentadiene **7** and **4** in the presence of MeCN failed to produce expected pyridine product (eq 4). The reaction of zirconapentadiene **7** and **4** in the presence of diphenylacetylene however afforded polysubstituted benzene **9** in 72% yield¹⁷ (eq 5). No reaction occurred when heating zirconapentadiene **7** with diphenylacetylene and/or MeCN in the absence of nickel under similar conditions (eq 6). Addition of excess IPr carbene to any of the reaction mixtures had no observable effect.

(3)

(4)

(5)

(6)

Kinetic Analysis of the Ni(IPr)₂-Catalyzed [2+2+2] Cycloaddition of Diyne **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),⁵ complex Ni(IPr)₂¹⁸ (**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 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** and MeCN catalyzed by Ni(IPr)₂ **10** as a model (eq 7), 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 5 equivalents to diyne **1** was employed in all measurements. Experimental procedures involved addition of a solution of Ni(IPr)₂ in d⁸-toluene via syringe into an NMR tube containing a solution of diyne and nitrile in d⁸-toluene, which was cooled to -78 °C prior to the injection. 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.

(7)

We initially intended to monitor the disappearance of the diyne **1** with time by ¹H NMR. However, all the resonances of **1** overlapped with those of the product pyridine **2** (CH₂ and CO₂CH₃) or of the Ni(IPr)₂ catalyst (CCH₃). Instead, the reaction rate was calculated based on the rate at which pyridine **2** was formed by measurement of the 3-pyridyl methyl resonance. As indicated by ¹H NMR, the yields of pyridine **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** (CCH₃) were insignificant. As such, determination of the rate through monitoring the disappearance of diyne **1** at this catalyst loading was performed and was found to be identical to the rate of formation of pyridine **2**. Thus, we were confident that monitoring the formation of pyridine correlated to the loss of diyne. The concentration of pyridine **2** was monitored by ¹H 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 $-20\text{ }^{\circ}\text{C}$, employing 0.05 M diyne **1** with varying amounts of acetonitrile, $\text{Ni}(\text{IPr})_2$, and IPr ligand in toluene- d_8 .

A linear increase of pyridine **2** concentration vs. time was obtained during the course of the reaction, (Figure 1a). Reaction rates remained unchanged with varying amounts of applied IPr (Figure 1b). As expected, the reaction rate increased linearly with increased concentration of the catalyst $\text{Ni}(\text{IPr})_2$ (**10**), demonstrating first-order dependence on catalyst (Figure 1c). Surprisingly, reaction rates remained unchanged for various concentrations of MeCN (Figure 1d), indicating a zero-order dependence on nitrile and ligand. Because we observe first order in catalyst, zeroth order in nitrile and IPr with an overall first order, the reaction must be zeroth order in diyne. If the reaction ordered in diyne, we would observe nonlinear behavior in the reaction profile as diyne was consumed. Observation of the diagnostic IPr backbone protons, revealed only what appeared to be a broad $\text{Ni}(\text{IPr})_2$ signal and small amounts of free IPr during the course of the reaction. Upon complete consumption of diyne, facile formation of $[\text{Ni}(\text{IPr})\text{MeCN}]_2$ was observed.⁹ In addition, the rate of $\text{Ni}(\text{IPr})_2$ -catalyzed reaction is significantly faster than that of the $[\text{Ni}(\text{IPr})\text{MeCN}]_2$ -catalyzed cycloaddition reaction.⁹

(8)

The reaction profile with respect to nitrile was next investigated. When an activated nitrile such as benzonitrile **11**, methoxyacetonitrile **12**, or dimethylcyanamide **13** was employed, the reaction was too fast to measure at a temperature as low as $-78\text{ }^{\circ}\text{C}$ (eq 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.

(9)

The use of more sterically demanding and electron-rich isobutyronitrile **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 9). Timely experiments were carried out at 26 °C, versus -20 °C required for MeCN. The reaction with **1** and **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 2). The only carbene species observed by ^1H NMR during the kinetic experiment were $\text{Ni}(\text{IPr})_2$ and small amounts of free IPr.

Investigations into diyne substitution were then undertaken utilizing more sterically demanding diynes **16**, **17** and **18** (eq 10). While **16** failed to deliver the desired pyridine product, **17** and **18** resulted in catalyst decomposition as indicated by incomplete conversion and irreproducible reaction rates.

(10)

Resting-State Observation Studies of the $\text{Ni}(\text{IPr})_2$ -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 $\text{Ni}(\text{IPr})_2$ resonance, which we believe to be the sole-resting state in this reaction. However for the cycloaddition of MeCN, the resonance we attribute to $\text{Ni}(\text{IPr})_2$ was slightly more broad and the baseline less resolved. We believed this line broadening might correspond to another undetermined Ni species in the latter case. Due to the similarity to the chemical shift observed for $\text{Ni}(\text{IPr})_2$ and this possible new species, we believed this may correspond to a tricoordinate $\text{Ni}(\text{IPr})_2\text{L}$ -species. Initial investigations were focused on observing a $\text{Ni}(\text{IPr})_2$ (nitrile) species. Jones and coworkers found a substantial shift (from 1.95 to 2.42 ppm, in $\text{THF-}d_8$) in the CH_3CN resonance upon η^2 -coordination to a (dippe) $\text{Ni}^{7c,19}$ residue. We were however unable to conclusively observe any new ^1H resonance corresponding to an η^2 -bound MeCN in the reaction mixture by ^1H NMR spectroscopy. Changes in chemical shifts of α -protons in η^1 -bound nitriles have been shown to be negligible.²⁰ 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 ^2H -observed NMR experiments. In our first experiment, we used MeCN that was partially labeled (i.e., 20% $\text{MeCN-}d_3$) and monitored the reaction by ^2H NMR spectroscopy

using C_6D_6 as an internal standard (eq 11). However, only free MeCN was observed. In our study of $[Ni(IPr)RCN]_2$ -catalyzed cycloadditions, we found the electronic environment of the backbone protons of the IPr ligand can be extremely sensitive to coordination environment. To observe the resting state of the catalyst by exploiting the sensitivity of the carbene chemical shift, we employed free $IPr-d_2$ (**20**), once again, in conjugation with $MeCN-d_3$ under similar reaction conditions for 2H -observed NMR experiments (eq 12). During the course of the reaction we observed only $MeCN-d_3$ and $IPr-d_2$; although, we did also observe $Ni(IPr-d_2)_2$ ²¹ formation from ligand scrambling.

(11)

(12)

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} ($C\equiv N$ stretch), which we felt would be diagnostic upon coordination to nickel. $Ni(II)$ -complexes of MeCN are common and well studied²² yet are irrelevant to our proposed resting state. In contrast, $Ni(0)$ -complexes of MeCN are exceedingly rare, in particular η^1 -bound MeCN complexes. However, both benzo-²³ and homobenzylic nitrile²⁴ η^1 -bound nitrile nickel-phosphine complexes have been isolated or inferred. Stretching frequencies for these species are generally reduced by $50\text{--}100\text{ cm}^{-1}$ upon η^1 -coordination to Ni^0 versus reduction of $200\text{--}500\text{ cm}^{-1}$ for η^2 -bound species.^{23,24}

We carried out *in situ* observation of the model cycloaddition reaction of **1** and MeCN via an ATR FT IR immersion probe. We initiated the experiment by cooling a solution of diene **1** in toluene to $-78\text{ }^\circ\text{C}$, followed by addition of MeCN. We then added an increased loading of $50\text{ mol\% } Ni(IPr)_2$ to help facilitate the observation of a Ni 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 $-40\text{ }^\circ\text{C}$, we observed growth of a new resonance at 2188 cm^{-1} (Figure 3). 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. 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 ^1H -NMR observed reaction times under similar conditions. No new absorptions were observed in an analogous reaction conducted with isobutyronitrile.

Discussion

Our data shows that the mechanism of $\text{Ni}(\text{IPr})_2$ -catalyzed cycloaddition of diynes and nitriles is distinct from that of the $[\text{Ni}(\text{IPr})\text{RCN}]_2$ -catalyzed system. First and foremost, we discovered that although the $[\text{Ni}(\text{IPr})\text{RCN}]_2$ -catalyzed system is catalytically competent for pyridine formation, the system is *not kinetically competent*. Specifically, the cycloaddition of MeCN and diyne **1** catalyzed by $[\text{Ni}(\text{IPr})\text{MeCN}]_2$, has a k_{obs} of $3.5 \times 10^{-5} \text{ M}\cdot\text{s}^{-1}$ at 0°C whereas the k_{obs} for the $\text{Ni}(\text{IPr})_2$ -catalyzed reaction is $2.5 \times 10^{-5} \text{ M}\cdot\text{s}^{-1}$ at -20°C . Furthermore, the resting state of the catalyst in the $[\text{Ni}(\text{IPr})\text{RCN}]_2$ -catalyzed system appears to be $[\text{Ni}(\text{IPr})\text{RCN}]_2$ itself whereas in $\text{Ni}(\text{IPr})_2$ -catalyzed reactions, $[\text{Ni}(\text{IPr})\text{RCN}]_2$ only forms at the conclusion of pyridine formation. As such, we felt an independent mechanistic analysis of the $\text{Ni}(\text{IPr})_2$ -catalyzed reaction was warranted.

Consistent with general mechanistic themes in transition metal-catalyzed [2+2+2]-cycloadditions to form pyridines, we had two straightforward mechanistic proposals (Scheme 3). The most commonly invoked mechanism for non-nickel catalysts is homocoupling mechanism **A**, wherein Ni-mediated homooxidative coupling of diyne is then inserted to form an azanickelacycloheptatriene that then reductively eliminates to form pyridine. Alternative mechanism **B** is a less commonly proposed heterocoupling pathway and one that we observed with the $[\text{Ni}(\text{IPr})\text{RCN}]_2$ -catalyzed pathway. This route begins with Ni-mediated heterooxidative coupling, followed by insertion of the pendant alkyne to generate the common azanickelacycloheptatriene (or analogous intermediate) intermediate, which 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 3. Presumably, oxidative coupling is rate-limiting, as is observed in other transition metal catalyzed systems;^{4g,25} and a Ni^0L_n species is the actual resting state. Pathway **A** should exhibit first-order kinetics in diyne and zero-order in nitrile. 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., Scheme 3, mechanism **A** and Scheme 4) is inconsistent with our observed rate dependence on the nature of the nitrile. 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.

Evidence for a Heterocoupling Pathway

Regioselective cycloaddition products

In addition to previous studies into [Ni(IPr)RCN]-catalyzed cocycloadditions of alkynes and nitriles, the regioselectivity observed in the cycloaddition of MeCN with unsymmetrical diyne **21** also appeals to a heterocoupling pathway.⁵ In order to minimize considerable and negative substrate/ligand steric interaction, heterocoupling of the bulky-substituted alkyne with the nitrile would result in the observed regioisomer. Similar sterics-driven regioselectivity has been observed in other Ni/NHC catalyzed coupling reactions.^{26,27,28} 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 (Scheme 5).

Stoichiometric Reactions

In addition to the regioselectivity that is typically observed in Ni-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 heterooxidative coupling. In these stoichiometric reactions (eq 3-6), transmetallation from zirconacycles **7** and **5** to the (IPr)_nNi^{II}-fragment affords nickelacycles **22** and **23**, proposed intermediates in the homocoupling and heterocoupling pathways, respectively (Scheme 6). 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 **5** and 4-octyne in the presence of (IPr)Ni(acac)₂ (eq 3). In contrast, the reaction of zirconapyrrole **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 4). To verify that transmetallation from zirconacyclopentadiene was occurring, zirconacyclopentadiene **7** was reacted with diphenylacetylene and (IPr)Ni(acac)₂. This reaction cleanly yielded substituted benzene **9**. Furthermore, zirconapentadiene **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.

Kinetic Analysis

Analysis of the kinetic data for the cycloaddition of diyne and MeCN revealed rate dependence in catalyst only. We initially believed 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. 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 ($\text{PhCN} > \text{MeCN} > \text{PrCN}$).

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 7. Ligand dissociation from $\text{Ni}(\text{IPr})_2$ is followed by rate-determining nitrile binding to $\text{Ni}(\text{IPr})$. This pathway predicts a first-order dependence on nitrile and an inverse-order dependence on ligand when the ratio $[\text{nitrile}]:[\text{ligand}]$ is small and zero-order dependence on both when $[\text{nitrile}]:[\text{ligand}]$ 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 associative coordination of a bulky isobutyronitrile to $\text{Ni}(\text{IPr})_2$ to form $\eta^1\text{-Ni}(\text{IPr})_2(\text{PrCN})$ **25** ($\text{R} = i\text{Pr}$) as the rate-limiting step (Scheme 8). 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 $\text{Ni}(\text{IPr})_2$ -catalyzed cycloaddition of PrCN displays this rate behavior.

Though the mechanism depicted in Scheme 8, with rate-limiting ligand loss, does not concur with the kinetic data we obtained in the cycloaddition of diyne **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 $\eta^1\text{-Ni}(\text{IPr})_2(\text{MeCN})$ (**25**, $\text{R} = \text{Me}$), versus $\text{Ni}(\text{IPr})_2$ exists in the reaction mixture of diyne **1** and MeCN. Indeed, our in situ IR analysis of the cycloaddition reaction supports the formation of the $\eta^1\text{-Ni}(\text{IPr})_2(\text{MeCN})$ (**25**, $\text{R} = \text{Me}$) resting state (Scheme 8) as we observed a new nitrile stretching frequency $\sim 100\text{ cm}^{-1}$ (rather than $200\text{-}500\text{ cm}^{-1}$) less than free MeCN (Figure 3; 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 $\text{Ni}(\text{IPr})_2$ -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 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 heterocoupling 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 **26** (Scheme 9). A Michaelis-Menten like scenario affords rate equation 13. Such a transformation is easily envisioned when R₁=*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 resulting in simple rate equation 14. While attempts to monitor the reaction profiles of more activated nitriles were futile, the effect of this hapticity shift can be observed in the significant rate enhancement for electron-deficient nitriles.

$$rate_{iPrCN} = \frac{k_2 k_1}{k_{-1} + k_2} [Ni(IPr)_2] [iPrCN] \quad (13)$$

$$rate_{MeCN} = k_2 [25] \quad (14)$$

We believe the key to productive co-cycloaddition lies primarily in the unique properties of the carbene ligand. Historically, a number of organometallic nickel complexes are highly active alkyne trimerization catalysts.^{23d,29} Electronically, Ni(IPr)₂ and Ni(SIPr)₂ would also fit this motif. Strong σ -donation to a coordinatively unsaturated Ni⁰ 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), 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 Ni-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” 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

avored. 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 Ni-catalyzed cycloaddition of a terminal alkyne. The key is to use electron deficient nitriles such as PhCN, 4-CF₃-C₆H₄CN, and Me₂NCN (eq 13). When these activated nitriles are employed, good yields of pyridine products (**28-30**) 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 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. However, when more active nitriles with stronger side-on coordination are employed, the nickel catalyst gets sequestered (as **26**, Scheme 10) and are unable to 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.

(13)

Conclusion

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 Ni⁰ resting-state and for facile oxidative heterocoupling. Ligand

loss and subsequent binding of an exogenous alkyne then follow nitrile binding. Oxidative heterocoupling 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene
14. SIPr = 1,3-bis-(2,6-diisopropylphenyl)-4,5 dihydroimidazol-2-ylidene
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Figure 1. Plots of [2] vs time, k_{obs} vs [IPr], k_{obs} vs [10], and k_{obs} vs [MeCN] for the Ni(IPr)₂-catalyzed cycloaddition of 1 and MeCN at -20 °C in C₇D₈

Figure 2.

Plots of $[15]$ vs time, k_{obs} vs $[IPr]$, k_{obs} vs $[10]$, and k_{obs} vs $[14]$ for the Ni(IPr)₂-catalyzed cycloaddition of **1** and **14** at 26 °C in C₇D₈.

Figure 3.

Absorption intensity at 2188 cm⁻¹ vs. reaction time for the cycloaddition of **1** (1 equiv) and MeCN (5 equiv) mediated by Ni(IPr)₂ (50 mol%).

Scheme 1.

Commonly Proposed Homocoupling mechanism for the [2+2+2]-cycloaddition of Nitrile and Alkynes.

Scheme 2. Proposed Catalytic Cycle for the $[\text{Ni}(\text{IPr})\text{RCN}]_2$ -Catalyzed Cycloaddition of Diyne and Nitriles

Scheme 3. Possible Catalytic Pathways for the Ni-Catalyzed [2+2+2]-Cycloaddition of Diynes and Nitriles

Scheme 4. Homocoupling Catalytic Pathway

Scheme 5.

Proposed Intermediates for the Observed Regiochemistry.

Scheme 6. Nickel-Mediated Transmetalative Routes to Pyridine Formation

Scheme 7.
Proposed Catalytic Cycle with Initial Nitrile Coordination.

Scheme 8.
Proposed Catalytic Cycle with Initial Nitrile Coordination.

Scheme 9. Proposed Catalytic Cycle of the $\text{Ni}(\text{IPr})_2$ -Catalyzed [2+2+2]-Cycloaddition of Diynes and Nitriles

Scheme 10. Product distribution as a function of competitive binding of nitriles and terminal alkynes

Table 1
Product Ratios with Various NHC ligands

(2)

entry	NHC	conv. ^b	yield 2 ^b	yield 3 ^b
1	none	27%	0%	11%
2	I ^t Bu	100%	0%	88%
3	ICy	41%	0%	39%
4	IMes	90%	8%	79%
5	IPr ^c	100%	94% ^d	0%
6	SIPr ^c	100%	98% ^d	0%
7	lAd	100%	0%	90%

^a Diyne **1** (1 equiv, 0.25M), MeCN (1 equiv), 26°C overnight. Ni(COD)_2 and NHC stirred at least 3 h prior to injection.

^b Determined by GC with naphthalene as an internal standard.

^c Diyne **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.

^d Determined by ^1H NMR with ferrocene as an internal standard.