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The Discovery of [Ni(NHC)RCN]$_2$ Species and Their Role as Cycloaddition Catalysts for the Formation of Pyridines

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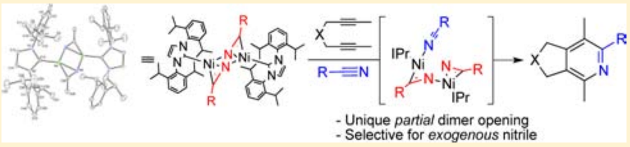
Supporting Information



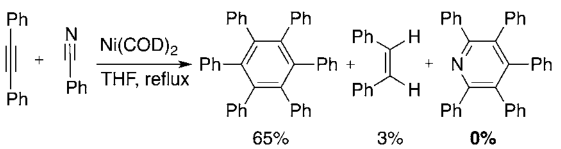
- Unique *partial* dimer opening
- Selective for *exogenous* nitrile

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 dimer-opening followed by binding of exogenous nitrile and subsequent oxidative heterocoupling.

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 Ni,[6] Fe,[7] and Ir[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[6a] is remarkable for a number of reasons: (1) Ni complexes readily catalyze the trimerization of alkynes (even in the presence of excess nitrile, eq 1);[9] (2) Ni complexes readily undergo oxidative addition of R−CN bonds (eq 2);[10] (3) Ni complexes are known to cause homodimerization of nitriles;[9] and, perhaps most intriguingly, (4) Ni complexes catalyze a completely different reaction between alkynes and nitriles, namely, the carbocyanation of alkynes (eq 3).[11] Despite these potential obstacles, the Ni/NHC catalyst efficiently converts a variety of nitriles and diynes into pyridines in generally high yields.



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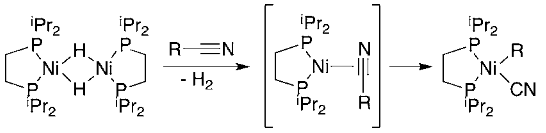

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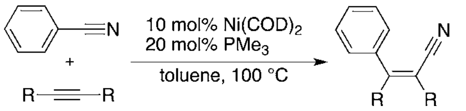

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A cursory look into the possible mechanism of Ni-catalyzed cycloaddition raises even more questions. Of the above-mentioned transition metals, the cobalt-catalyzed mechanistic pathway is the most thoroughly studied and is believed to proceed through a homocoupling pathway, that is, Co undergoes oxidative homocoupling of the two alkynes before inserting the nitrile, with subsequent reductive elimination affording the desired product (Scheme 1).[3,12] While considerably less studied, the reactions catalyzed by Ru and Rh are believed to undergo a similar homocoupling mechanism.[4a,b,5a,12] In contrast, Ni-*mediated* pyridine formation appears to follow a different route. Stoichiometric reactions of alkynes and azanickelacycles (prepared from transmetalation between an azazirconacyclopentenone and Ni(PPh$_3$)$_2$Cl$_2$)[13] afford highly substituted pyridines suggesting that heterocoupling between a nitrile and an alkyne, rather than homocoupling of two alkynes, is the initial step (eq 4). Yet, the oxidative coupling of an alkyne and a nitrile is *sluggish* at best for Ni,[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

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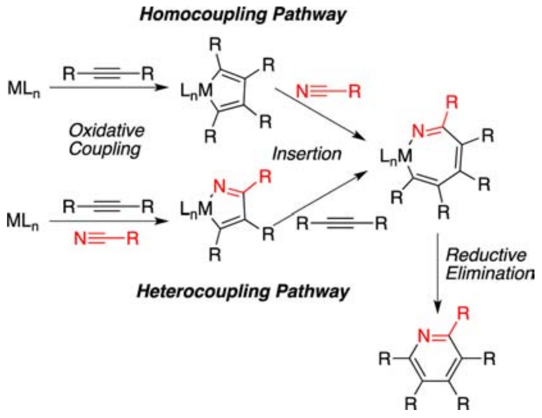
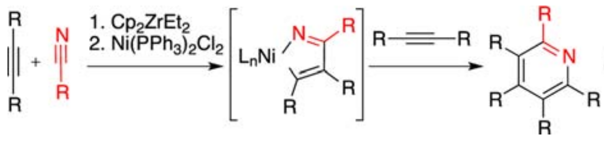
Scheme 1. Divergent Pathways for Alkyne/Nitrile Cycloaddition





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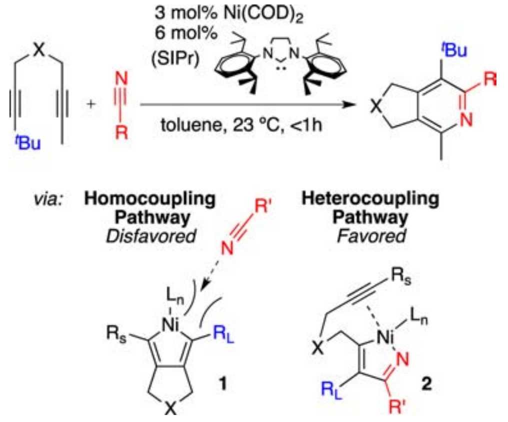
from the observed regioselectivity of the nickel-catalyzed cycloaddition of unsymmetrical diynes and nitriles (Scheme 2).[6] If a homocoupling pathway were operative, the observed regiochemistry would dictate that insertion of the nitrile would require insertion from the sterically least-accessible face of intermediate **1**. 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 (intermediate **2**). 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]

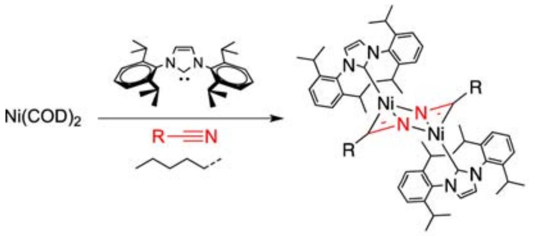
Scheme 2. Observed Regioselectivity in Ni/SIPr Catalyzed Cycloaddition



Given the ambiguity surrounding the success of Ni-catalyzed pyridine formation, we initiated a mechanistic investigation of these cycloaddition reactions of alkynes and nitriles. We discovered 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 Ni 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 ^1H 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 **3a** as a red precipitate in 76% yield (eq 5).



(5)

3a R = Me, 76%
3b R = Ph, 78%
3c R = 4-CF_3-C_6H_4, 69%
3d R = 4-MeO-C_6H_4, 86%
3e R = CH_2OMe, 48%

A single-crystal X-ray structure of **3a** was obtained (Figure 1) wherein **3a** was found to be an unexpected dimeric species in which one nitrile is bound to two Ni 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

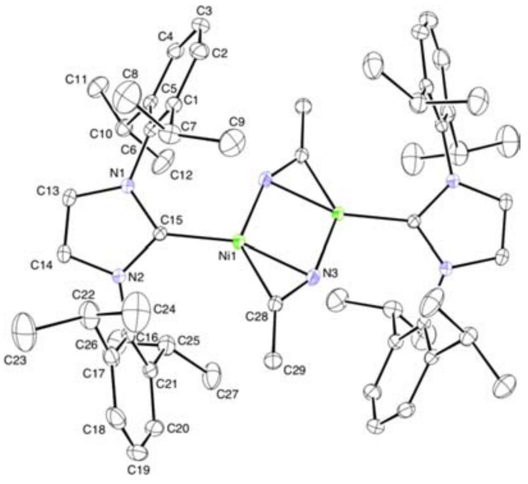


Figure 1. Ortep plot of **3a** at the 30% probability level. Hydrogen atoms omitted for clarity. Pertinent bond lengths include: Ni(1)–C(28): 1.854 Å, Ni(1)–C(15): 1.8677 Å, Ni(1)–N(3): 1.9523 Å, Ni(1)–N(3)_3: 1.9951 Å, N(3)–C(28): 1.226 Å. Pertinant bond angles include: C(28)–Ni(1)–C(15): 120.29°, C(28)–Ni(1)–N(3): 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°.

those of analogous phosphine bound nickel−nitrile complexes.[17b,c] However, the Ni−C15 bond length of **3a** is significantly shortened (1.8677 vs 2.1−2.2 Å) compared to previously reported Ni−NHC bonds.[18] Interestingly, the double hapticity of 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 **3a** exists as a dimer in solution (MW = cald. 978.7; obsd 961.9 ± 100) as well as the solid state. Dimers **3b**−**3e** were prepared in a similar synthetic protocol from the requisite nitrile. The structure of **3c** is shown in Figure 2. Not surprisingly, the Ni−C and N−C bond lengths are similar to those seen in **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.

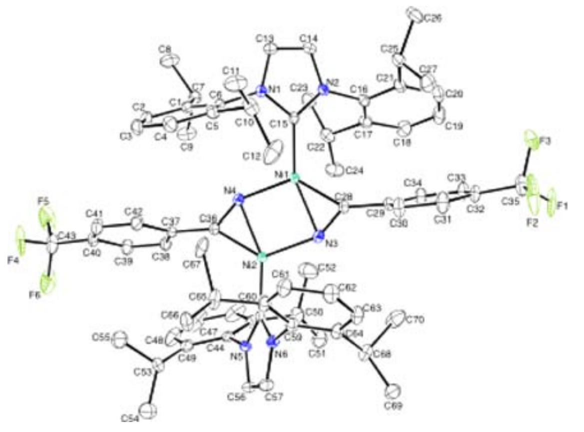
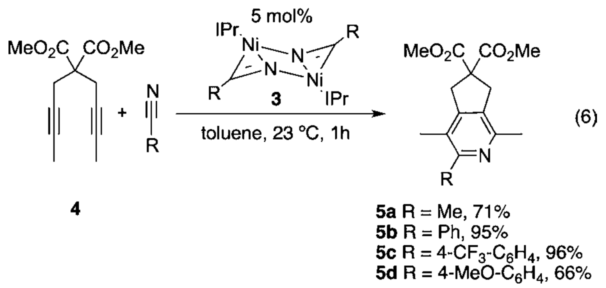


Figure 2. Ortep plot of **3c**. Hydrogen atoms are omitted for clarity.Pertinent bond lengths include: Ni(1)−C(28): 1.857 Å, Ni(1)−C(15)-1.895 Å, Ni(1)−N(3): 1.974 Å, Ni(1)−N(4): 1.982 Å, N(3)−C(28): 1.223 Å. Pertinant bond angles include: C(28)−Ni(1)−C(15): 119.48°, C(28)−Ni(1)−N(3): 37.08°, C(15)−Ni(1)−N(4): 109.50°, N(3)−Ni(1)−N(4): 93.93°, N(3)−C(28)−C(29): 136.1°.

[Ni(IPr)RCN]$_2$-Catalyzed [2 + 2+ 2] Cycloadditions. When dimers **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 **4** and acetonitrile were subjected to 5 mol % dimer **3a**, clean formation of pyridine **5a** occurred (eq 6). 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 **5b**−**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]



(6)

5a R = Me, 71%
5b R = Ph, 95%
5c R = 4-CF_3-C_6H_4, 96%
5d R = 4-MeO-C_6H_4, 66%

Stoichiometric [2 + 2+2] Cycloadditions. In contrast to the high yields observed in dimer catalyzed reactions, stoichiometric reactions between equimolar amounts of Ni 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 **4** was added to dimer **3a**, pyridine **5a** was formed in 30% yield (eq 7, Table 1, entry 1). Yet, when diyne **4** (1 equiv) was added to dimer **3a** in the presence of MeCN (1 equiv), pyridine **5a** was formed in 64% yield. The same phenomenon was observed in reactions with dimer **3b** and PhCN (34% vs 91% yield, entry 2), **3c** and 4-$CF_3C_6H_4CN$ (35% vs 96%, entry 3), and **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]

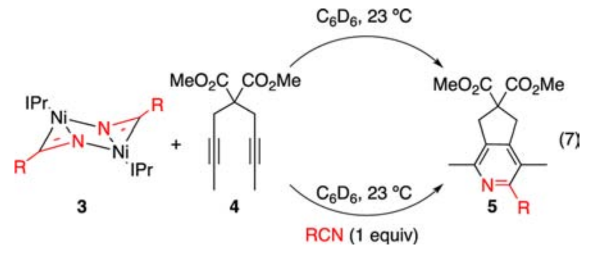


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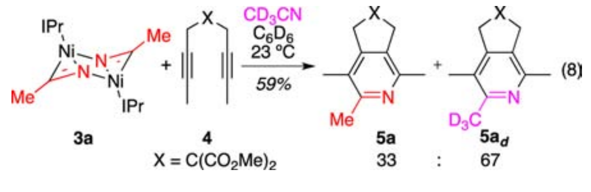
Table 1. Pyridine Yields from Stoichiometric Cycloaddition Reactions[a]

entry	R	yield of 5 (no added RCN)[b]	yield of 5 (w/1 equiv RCN added)[b]
1	**5a**, R = Me	30%	64%
2	**5b**, R = Ph	34%	91%
3	**5c**, R = 4-CF_3-C_6H_4	35%	96%
4	**5d**, R = 4-MeO-C_6H_4	31%	63%

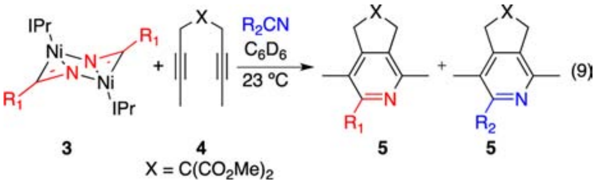
[a] Dimer **3** (1 equiv), diyne **4** (1 equiv), w/and w/out nitrile, C_6D_6, 23 °C. [b] Yields determined by ^1H NMR spectroscopy.

Stoichiometric Cross-Cycloaddition Reactions. The stoichiometric reaction of dimer **3a**, diyne **4**, and CD_3CN was also performed (eq 8). Surprisingly, the major pyridine product (**5a**$_d$) resulted from incorporation of CD_3CN, the *exogenous nitrile*, rather than the already bound acetonitrile.



(8)

Other cross-cycloaddition combinations were evaluated to determine whether preferred incorporation of the *exogenous nitrile* was a general trend (eq 9). These results are summarized



(9)

in Table 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 **3b** reacted with *exogenous* MeCN and diyne **4**, 45% pyridine product **5b**, which incorporates the *internal*, Ni-bound benzonitrile, was formed (entry 2). Notably, when the exogenous MeCN was supplied in heavy excess (10 equiv), the ratio of products 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 **4** and dimer **3a**, PhCN was almost exclusively incorporated into the product (entry 1).

Table 2. Pyridine Yields and Product Ratios from Stoichiometric Cross-Cycloaddition Reactions[a,b]

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

[a] Dimer **3** (1 equiv), diyne **4** (1 equiv), nitrile (1 equiv), C_6D_6, 23 °C. [b] Yields, product ratios, and postreaction dimer species determined by ^1H NMR spectroscopy with ferrocene as an internal standard. [c] Traces of unknown Ni species were detected. [d] Complex mixture of Ni products were formed.

The stoichiometric cross-cycloaddition of diyne **4** and dimer **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 **5c**−**5d** obtained in these cross-cycloaddition reactions are in stark contrast to the individual catalytic and stoichiometric yields for these respective nitriles (eq 7) where pyridine **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 **4** and MeCN. The one exception to this observation was when 10 equiv of MeCN was used in the reaction with **4** and **3c**; a considerably higher yield was observed (91%, 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, 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 **3a**, diyne **4**, and PhCN were reacted (to form predominately pyridine **5b**), only dimer **3a** (not dimer **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 Ni species were present as indicated by unknown resonances in the ^1H NMR spectrum (entries 3 and 7). Presumably, these resonances can be attributed to a mixed Ni dimer species (such as **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 4 and MeCN. Using the cycloaddition of diyne **4** and MeCN catalyzed by dimer **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 ^1H 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 **3a** and zeroth-order in **4**, MeCN, and IPr (Figure 3).

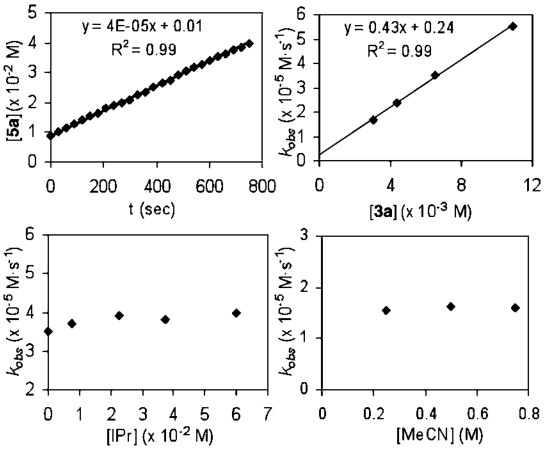
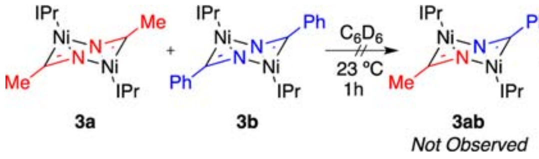


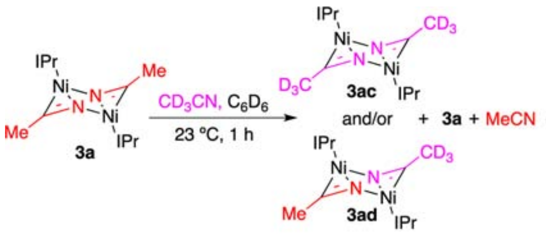
Figure 3. Plots of [**3a**] vs time, k_{obs} vs [IPr], and k_{obs} vs [MeCN] for the cycloaddition of **4** at 0 °C in C_7D_8.

Dimer Crossover and Ligand Exchange Experiments. When equimolar amounts of **3a** and **3b** were combined in a solution of benzene-d_6 at room temperature, no detectable amount of mixed dimer (i.e., **3ab**)[13] was observed after 1 h at room temperature (eq 10).[14]



(10)

In contrast, a possible mixed-dimer species formed when a sterically- and electronically equivalent nitrile was added to dimer **3a** (eq 11). That is, upon exposure of **3a** to one equivalent of CD_3CN, 50% consumption of **3a** was observed in addition to the free, unligated MeCN after 1 h at room temperature. The nature of the deuterated exchange-product (**3ac** or **3ad**) is unknown. Similar nitrile exchange was observed when the more electrophilic benzonitrile was added to dimer **3a** (eq 12). Within minutes, **3b**, **3a**, and free acetonitrile, along with resonances corresponding to an unknown species (presumably **3ab**), were observed by ^1H NMR spectroscopy in the reaction of **3a** with free benzonitrile at room temperature. Complete exchange occurred in roughly an hour



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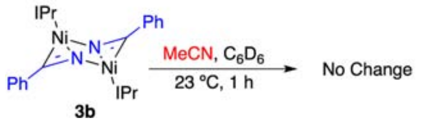
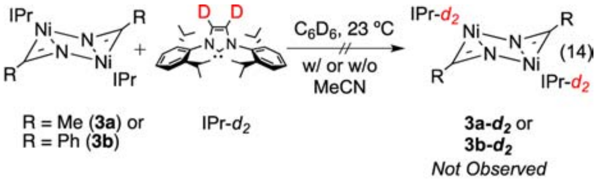


(13)

and a half. Conversely, a solution of **3b** and acetonitrile exhibited no exchange under the same conditions and the same reaction time scale (eq 13), although a complex mixture was observed after 3 h.

Unlike the nitrile exchange reactions, dimers **3a** and **3b** displayed analogous reactivity toward free IPr ligand. When either **3a** or **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 **3a** or **3b**, excess IPr-d_2, and 1 equiv of free nitrile (acetonitrile or benzonitrile, respectively, eq 14). The stoichiometric reaction of **3a**, diyne **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 15).



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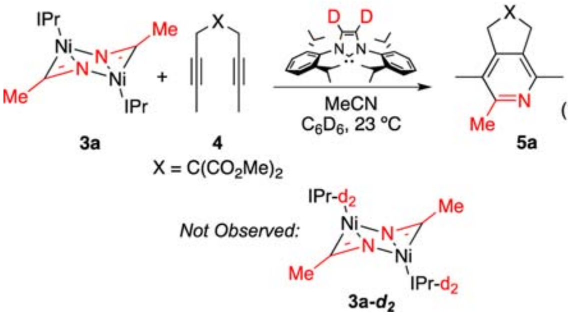
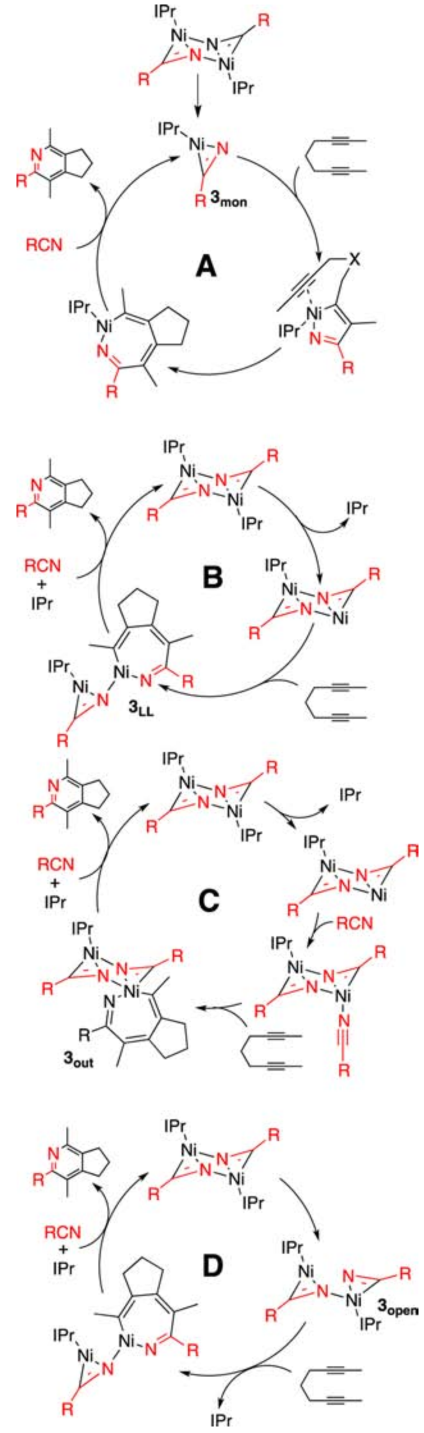


(15)

DISCUSSION

At the onset of our research, four reasonable and relatively simplistic mechanisms were proposed (Scheme 3). The most straightforward pathway, **A**, begins with an initial dimer dissociation to an active monomeric form 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 could occur (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 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

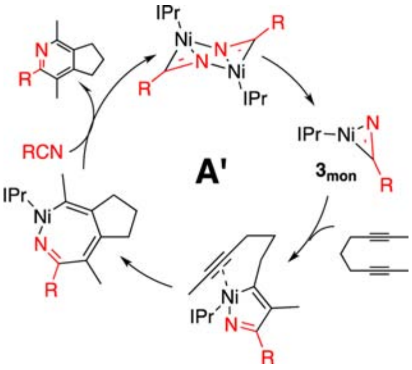
Scheme 3. Possible Mechanistic Pathways for [Ni(IPr)RCN]$_2$-Catalyzed Cycloadditions



species (3_{out}). In an entirely different process, an alternative pathway (pathway **D**) is initiated by an incomplete dissociation or dimer opening (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 elimination then regenerates the dimer.

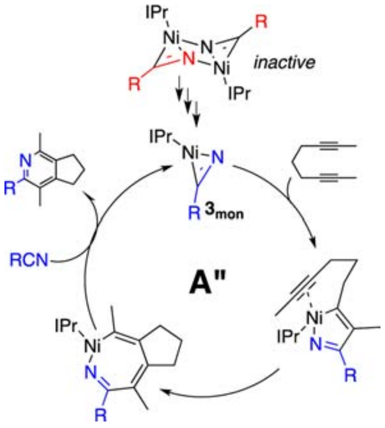
Systematic Evaluation of the Proposed Mechanistic Pathways. *Pathway A.* Mechanistically, we initially surmised pathway **A** was the operative pathway as it is the most simplistic and straightforward. However, the kinetic evaluation of the cycloaddition of **4** and MeCN catalyzed by **3a** revealed the rate of cycloaddition depended solely on the concentration of dimer (i.e., a first-order dependence of dimer **3a**). This data reveals that the dimer must be on the catalytic pathway (otherwise autocatalytic behavior would be observed). Thus, in a modified pathway **A′** (Scheme 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 ($\mathbf{3}_{mon}$). However, as seen in the stoichiometric reactions of dimers **3a**−**3d** with diyne **4**, added nitrile is required for optimal yield (Table 1, eq 7). 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 (without added nitrile, eq 7) afforded pyridines in comparable yields despite considerable differences in their reactivity (i.e., **3a** < **3b**) suggesting that catalyst degradation products that may facilitate homodimerization of diyne **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 cross over is observed even in trace amounts (eq 10).

Scheme 4. Modified Pathway A′



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 5). At first glance, assuming dimer degradation to monomer $\mathbf{3}_{mon}$ was first order and *much slower* than cycloaddition, such a mechanism would account for (1) the lack of dimer crossover observed (eq 10), (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 **3b**, diyne **4**, and MeCN affords the phenyl-substituted pyridine **5b** in 28% yield (Table 2, entry 2). To accommodate this yield, at least 14% of the applied dimer **3b** must dissociate to $\mathbf{3b}_{mon}$ and react with diyne **4** to afford **5b**. Once pyridine **5b** is formed, the only reactants left are MeCN, and possibly free IPr. As such, dimer **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 **3b**, not **3a**; no other species were present. Generally, of the Ni-species present postreaction, nitrile exchange products that arise through diyne-free nitrile exchange were the only other observed products (eq 12 and 13).

Scheme 5. Modified Pathway A″



The cross-cycloaddition of **3b** with diyne **4** and both 4-CF$_3$-PhCN and 4-MeO-PhCN (Table 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-MeO-PhCN (eq 6). As such, a small concentration of active $\mathbf{3b}_{mon}$ catalyst would have produced higher amounts of **5c** than **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 **3b**, **4**, and 10 equiv of MeCN (Table 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 **3c**, **4**, and 10 equiv of MeCN (Table 2, entry 7) where a significant increase in yield and only mild increase in selectivity were observed.

Lastly, if a negligible amount of dimer **3** degrades into an active catalyst (e.g., not necessarily $\mathbf{3}_{mon}$), 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 **3a** < **3d** < **3b** ≈ **3c** where **3a** is the least stable since it incorporates the most exogenous nitrile (Table 2). However, qualitative measurement of the decomposition of the dimers displayed the *opposite* relative stabilities (**3a** ≫ **3d** > **3b** ≈ **3c**) where **3a** was the most stable to decomposition.

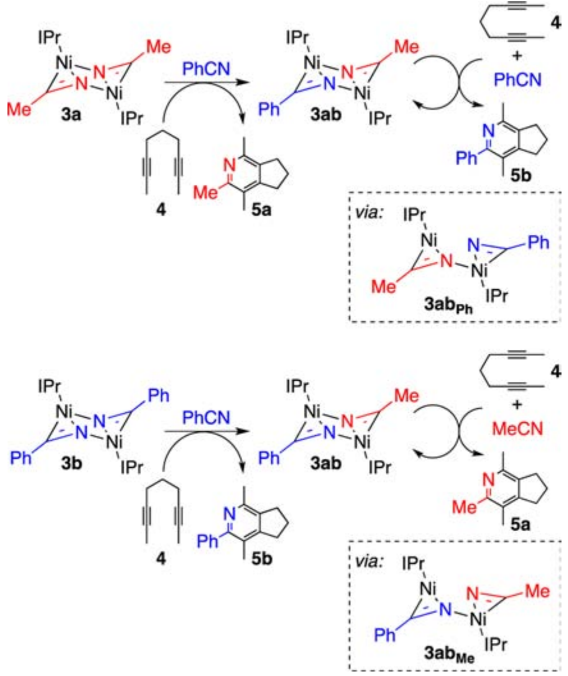
Taken together, our data suggest the dissociative pathway **A** (or **A′**) is not operative.

Pathways B and C. Just as with pathway **A**, pathways **B** and **C** 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 **3a** and **3b** were individually treated with IPr-d_2 (eq 14), no ligand exchange was observed. Additionally, no ligand exchange occurred when either **3a** or **3b** were treated with IPr-d_2 in the presence of the requisite nitrile. Furthermore, no ligand exchange occurred when **3a** or **3b** were used in the cycloaddition of diyne **4** and nitrile in the presence of excess IPr-d_2 (eq 15). As such, the lack of observable ligand exchange in conjunction with our kinetic data rule out pathways **B** and **C**.

*Pathway **D**.* Given the congested nature of dimers **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 elimination agrees with not only with our kinetic data but our stoichiometric analyses which showed the requirement of added nitrile for high pyridine yield (eq 6). 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 **3a**, diyne **4**, and PhCN, pyridine **5b** (which incorporates *exogenous* PhCN) is formed almost exclusively. However, in the reaction of PhCN-bound dimer **3b**, diyne **4**, and MeCN, pyridines **5a** (which incorporates *exogenous* MeCN) and **5b** are formed in almost equally with a moderate preference for **5b** (1:1.6, Table 2, entry 2). Furthermore, to account for these product distributions, the reactivity of a mixed dimer intermediate (**3ab**) would react one way in the first reaction (**3ab**$_{\mathbf{Ph}}$) but in the opposite way in the latter reaction (**3ab**$_{\mathbf{Me}}$, Scheme 6).

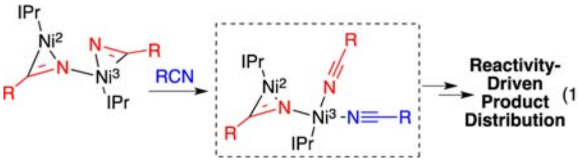
Alternatively, if we were to explain the exclusive formation of **5b** through nitrile exchange, another contradiction would occur. That is, initial nitrile exchange of **3a** and PhCN would result in the formation of **3b** and MeCN. Yet, reaction of **3b** and MeCN (and diyne) afforded a mixture of products rather than almost exclusive formation of **5b** (Table 2, entry 1). Our other cross-cycloaddition reactions further highlight this discrepancy. If incorporation of the *exogenous* nitrile were explained solely through nitrile exchange, a 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 **3b**, diyne **4**, and either 4-CF$_3$-PhCN or 4-MeO-PhCN are reacted (Table 1, entries 4 and 5). As such, the last of the initial mechanisms, pathway **D**, can be ruled out.

Scheme 6. Contradictory Reactivities of 3ab Required by Pathway D to Account for Observed Product Ratios



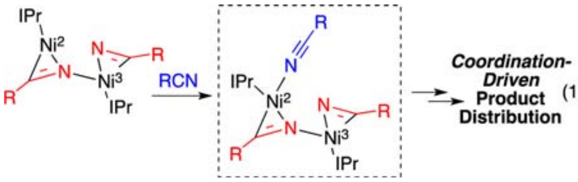
*Pathway **E**.* Although delineating a detailed mechanism of a reaction with an early rate-determining step is difficult, our data suggest a mechanism that does indeed involve partial dimer opening. However, rather than subsequent reaction with alkyne, nitrile binding *immediately follows* dimer opening since, regardless of electronic bias, the exogenous nitrile is selectively incorporated. Our kinetic data and all of our stoichiometric reactions suggests 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 Ni-coordination environments are formed (eq 16). 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.



(16)

Alternatively, coordination of exogenous nitrile would occur at the less saturated Ni^2 (eq 17). 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.



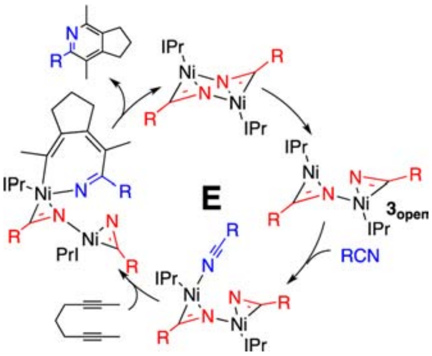
(17)

2. 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.

3. 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 7.

Scheme 7. Proposed Mechanism of [Ni(IPr)RCN]$_2$-Catalyzed Cycloaddition



In summary, a new class of Ni/nitrile/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. Future work on this system will be focused on computational experiments, which may aid in determining the coordination environment of the Ni 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]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details, spectral data, and X-ray data for **3a** and **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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