

# Nickel-Catalyzed Direct Alkylation of Terminal Alkynes at Room Temperature: A Hemilabile Pincer Ligand Enhances Catalytic Activity

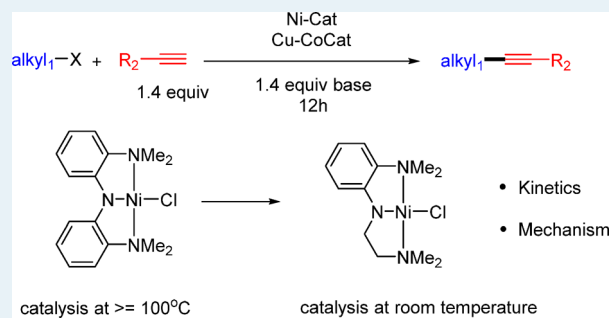
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## Supporting Information

**ABSTRACT:** Direct coupling of alkyl halides with terminal alkynes provides an efficient and streamlined access to alkyl-substituted alkynes, which are important synthetic intermediates, biologically active molecules, and organic materials. However, until now, there have been fewer than a handful of catalytic methods available for this reaction, and detailed mechanistic studies have not been reported. Herein, we describe the design and development of a new nickel pincer complex that catalyzes the direct coupling of primary alkyl halides with terminal alkynes at room temperature. The catalysis has a good substrate scope and high functional group tolerance. Kinetic data suggest that the new pincer ligand is hemilabile, and the dissociation of a labile amine donor is the turnover-determining step of the catalysis. An intermediate Ni-alkynyl species has been isolated and structurally characterized. The reactivity of this species gives insight into the nature of the active species for the activation of alkyl halide.

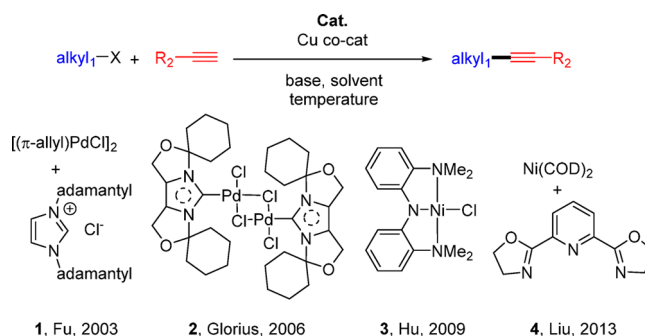
**KEYWORDS:** nickel, Sonogashira coupling, alkynylation, pincer complex, kinetics, alkylation



## 1. INTRODUCTION

Alkynes are ubiquitous synthetic intermediates and precursors to biologically active molecules and organic materials;<sup>1,2</sup> therefore, methods that provide a streamlined access to alkynes are highly desirable. The synthesis of aryl- and alkenyl-substituted alkynes has become routine, largely thanks to the development of Sonogashira coupling of aryl and alkenyl halides with terminal alkynes;<sup>3–6</sup> however, the synthesis of alkyl-substituted alkynes is less straightforward. The traditional method of reacting alkali metal acetylides, in particular lithium acetylides, with alkyl electrophiles has a limited scope, is intolerant to sensitive functional groups, and needs a low temperature. Organometallic coupling reactions of alkynyl halides with metal-alkyl reagents<sup>7,8</sup> or alkyl halides with metal-alkynyl reagents<sup>9–12</sup> are more general and tolerant, but they require the preactivation of alkynes, a reactive organometallic reagent, or both. Compared with these methods, the direct coupling of alkyl halides with terminal alkynes involves fewer steps, is operationally simpler, and often costs less. On the other hand, such coupling is challenging not only because of the general difficulty in the coupling of alkyl electrophiles, but also because of a low concentration of metal alkynyl intermediate in the reaction mixture.

Until now, there are only four metal-ligand combinations that are capable of catalyzing the direct alkylation of terminal alkynes with nonactivated alkyl electrophiles. The groups of Fu<sup>13</sup> and Glorius<sup>14</sup> introduced the first two systems (1 and 2, Figure 1) both of which were based on Pd and a N-heterocyclic carbene ligand. Our group reported the first Ni catalyst for this



**Figure 1.** Reported catalyst systems/precatalysts for direct alkylation of alkynes.

transformation:<sup>15</sup> the catalyst is a nickel pincer complex, Nickamine (3). The group of Liu<sup>16</sup> then developed a system based on Ni(cod)<sub>2</sub> and a pyridine bisoxazoline (Pybox) ligand (4). This system is the most active catalyst to date, and it catalyzes the coupling of both primary and secondary nonactivated alkyl halides at room temperature.

Despite the progress in method development, the mechanism of the coupling of alkyl halides with terminal alkynes remains largely unclear. The catalysis by Nickamine seems appropriate for in-depth mechanistic investigations because the

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catalyst is well-defined. In comparison, the coordination environment of the active catalyst in the Liu system is unidentified.<sup>16</sup> Nevertheless, Nickamine catalyzes the coupling only at an elevated temperature (100–140 °C) which is inconvenient for both synthetic applications and mechanistic study. Herein, we describe the development of a new nickel pincer complex that catalyzed the direct alkylation of terminal alkynes at room temperature. The new catalytic system was subject to a kinetics study, which revealed the hemilabile nature of the new pincer ligand as a key factor for the improved catalytic efficiency. A catalytically relevant Ni alkynyl complex was synthesized and structurally characterized. The reactivity of this Ni alkynyl complex gave important insights into the active species for the activation of alkyl halide.

## 2. RESULTS AND DISCUSSION

**2.1. A New Nickel Pincer Catalyst for Direct Alkylation of Alkynes.** The coupling between 1-iodooctane and 1-octyne was used as the test reaction for the optimization of reaction conditions. It was reported that Nickamine catalyzed this reaction efficiently at 100 °C.<sup>15</sup> The reaction was best carried out using 5 mol % **3** as catalyst, 3 mol % of CuI as the cocatalyst, 1.4 equiv of Cs<sub>2</sub>CO<sub>3</sub> as the base, and dioxane as the solvent. The reaction time was 16 h. We found that replacing Cs<sub>2</sub>CO<sub>3</sub> with LiO<sup>t</sup>Bu led to successful coupling at 60 °C (Table S1, Supporting Information); however, the yield of the reaction decreased to only 10% at 50 °C (entry 1, Table 1). The use of

**Table 1. Optimization of Conditions for Ni-Catalyzed Direct Coupling of 1-Iodooctane with 1-Octyne<sup>a</sup>**

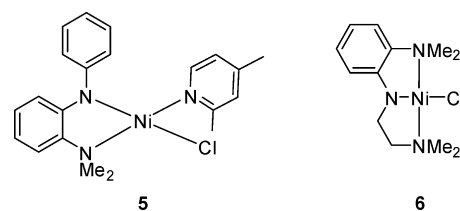
entry	CuI (mol %)	base (1.4 equiv)	solvent	catalyst	temp (°C)	yield (%) <sup>b</sup>
1	9	LiO <sup>t</sup> Bu	dioxane	<b>3</b>	50	10
2	9	LiO <sup>t</sup> Bu	MeCN	<b>3</b>	20	8
3	9	LiO <sup>t</sup> Bu	DMF	<b>3</b>	20	43
4	9	LiO <sup>t</sup> Bu	DMF	<b>5</b>	20	13
5	9	LiO <sup>t</sup> Bu	DMF	<b>6</b>	20	74
6	0	LiO <sup>t</sup> Bu	DMF	<b>6</b>	20	13
7	4.5	LiO <sup>t</sup> Bu	DMF	<b>6</b>	20	74
8	9	Cs <sub>2</sub> CO <sub>3</sub>	DMF	<b>6</b>	20	10

<sup>a</sup>General reaction conditions: 0.5 mmol of 1-iodooctane and other reagents according to Table 1 in 2 mL of solvent. <sup>b</sup>Yields are determined by GC and are relative to alkyl halide.

more-polar solvents, such as acetonitrile (MeCN) or dimethylformamide (DMF), allowed the coupling at room temperature, but the best yield was 43% in DMF (entries 2 and 3, Table 1).

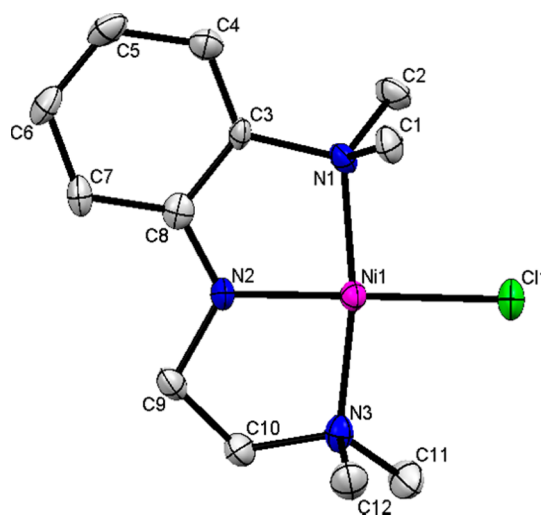
Complex **5** (Figure 2) was previously shown to have improved efficiency for the coupling of secondary alkyl halides with alkyl Grignard reagents;<sup>17</sup> however, the coupling yield was only 15% when **5** was used as catalyst (entry 4, Table 1). At the same time, heterogeneous black particles were observed in the reaction using **5** as catalyst. We suspected that complex **5**, having only a bidentate chelate, was unstable under the reaction conditions and decomposed to nickel particles.

To maintain the stability of the Ni complex while potentially increasing its activity, complex **6** was designed and synthesized. One of the two aryl linkers in the N<sub>2</sub>N ligand of Nickamine was



**Figure 2.** Structural formula for complexes **5** and **6**.

replaced by a simple ethylene linker. The new NNN pincer ligand was expected to be more labile, which rendered the resulting Ni complex more reactive. This ligand and its Ni complex were synthesized in a manner similar to that of the N<sub>2</sub>N ligand and Nickamine.<sup>18</sup> The crystal structure of **6** was determined, showing Ni in the expected square planar ligand environment (Figure 3). The Ni–N and Ni–Cl bond distances in **6** are nearly identical to those in **3**,<sup>19</sup> except that the Ni1–N1 distance is 0.04 Å longer in **6**.



**Figure 3.** Crystal structure of complex **6**. Only one of the two molecules in the asymmetric unit is shown. Hydrogen atoms are omitted for clarity. The thermal ellipsoids are displayed in a 50% probability. Selected lengths (Å) and angles (deg): Ni1–N1, 1.995(3); Ni1–N2, 1.832(3); Ni2–N3, 1.962(4); Ni1–Cl1, 2.2102(11); N1–Ni1–N2, 85.60(14); N2–Ni1–N3, 84.74(13); N3–Ni1–N1, 169.04(13).

To our delight, complex **6** is, indeed, a better catalyst than Nickamine for the reaction in Table 1. At room temperature, a coupling yield of 74% was obtained when **6** was used as the catalyst (entry 5, Table 1). CuI was important for the coupling. Without CuI, the yield was only 13% (entry 6, Table 1). The loading of CuI could be decreased to 4.5 mol % while maintaining the same yield (entry 7, Table 1). For convenience in weighting, a 9 mol % loading of CuI was applied in small-scale reactions. LiO<sup>t</sup>Bu was the best base; use of Cs<sub>2</sub>CO<sub>3</sub> as the base decreased the yield to 10% (entry 8, Table 1). Under the optimized conditions (entry 5 or 7, Table 1), the main side products were 1-*tert*-butoxyoctane and 1-octene. The former was produced by the attack of *tert*-butoxide anion on 1-iodooctane, whereas the latter was produced by base-induced HI elimination of octyl iodide or reductive elimination from a Ni-octyl intermediate. The excess amount of 1-octyne was unreacted.

**2.2. Scope of Direct Alkylation of Alkynes.** The optimized conditions in Table 1 were then applied for the coupling of more elaborate substrates (Table 2). For some

**Table 2. Scope of Direct Alkylation of Alkynes Using 6 as Catalyst<sup>a</sup>**

$$\text{alkyl}_1\text{-X} + \text{R}_2\text{-C}\equiv\text{C} \xrightarrow[\text{DMF, 16h, r.t.}]{\substack{3.5 \text{ mol\% } \mathbf{6} \\ 9 \text{ mol\% CuI} \\ 1.4 \text{ equiv LiOBU}^t}} \text{alkyl}_1\text{-C}\equiv\text{C-R}_2$$

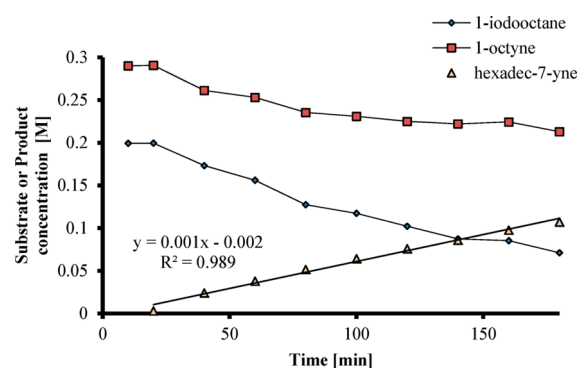
Entry	Alkyl-X	Alkyne	Yield [%]
1	Octyl-I		60 <sup>c</sup> (82) <sup>d</sup>
2	Octyl-I		60 <sup>c</sup> (69) <sup>d</sup>
3	Decyl-I		58 <sup>c</sup>
4	Octyl-I		60 <sup>c</sup>
5	Octyl-I		64 <sup>b</sup>
6	Octyl-I		63 <sup>b</sup>
7	Octyl-Br		60 <sup>c</sup>
8			65 <sup>c</sup>
9			52 <sup>b</sup>
10			50 <sup>c</sup>
11	Octyl-I		65 <sup>c</sup>
12	Octyl-Br		57 <sup>b</sup>
13			60 <sup>c</sup>

<sup>a</sup>For coupling of iodides, no NaI was added; for coupling of bromides, 20 mol % NaI was added. <sup>b</sup>Isolated yields relative to alkyl halide; the reaction was set up using 2 mL DMF for every 0.5 mmol of alkyl halide. <sup>c</sup>Isolated yields relative to alkyl halide; the reaction was set up using 1 mL DMF for every 0.5 mmol of alkyl halide. <sup>d</sup>Calibrated GC yields are shown in parentheses.

substrates, increasing the concentrations of the reactants led to slightly higher yields (about 10%). Alkyl, aryl, and silyl-substituted alkynes could be coupled (entries 1–3, Table 2). The isolated yields of some products were significantly lower than calibrated GC yields (entry 1, Table 2), which was probably due to the difficulty in isolation of these products. Modest to good isolated yields were obtained for the coupling of substrates containing acetal (entry 5, Table 2), amide (entry 6, Table 2), amine (entry 7, Table 2), furan (entry 8, Table 2), ester (entries 9 and 10, Table 2), alkyl chloride (entry 10, Table 2), ketone (entry 11, Table 2), and nitrile (entry 13, Table 2). The conditions could be applied to the coupling of alkyl bromides if 20 mol % of NaI was used for a presumable Br/I exchange (entries 7, 12–13, Table 2). The coupling of alkyl chlorides was not successful, likely because of a more inert C–Cl bond. Unfortunately, the system is not efficient for the

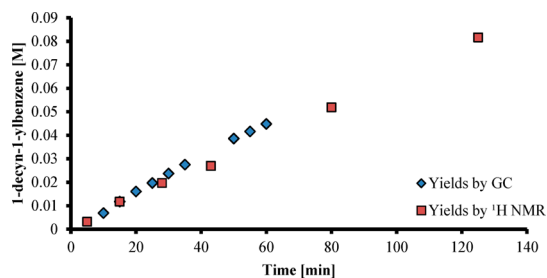
alkylation of secondary alkyl halides, which seems to be a general limitation of the Ni(II) pincer systems. Overall, the scope and yields for the alkynylation of primary alkyl halides are comparable to those catalyzed by the Ni(cod)<sub>2</sub>/Pybox system developed by Liu and co-workers.<sup>16</sup> The current system, therefore, is well suited for an in-depth mechanistic study because of the defined nature of the catalyst and the mild reaction conditions.

**2.3. Kinetics of Direct Alkylation of Alkynes.** The reaction profile of the coupling of 1-iodooctane with 1-octyne was measured by gas chromatography (GC). Figure 4 shows



**Figure 4.** Reaction profile for the coupling of 1-iodooctane with 1-octyne. At the end of this period, the conversion of 1-iodooctane is 72%, the conversion of 1-octyne is 39%, and the yield of hexadec-7-yne is 43%.

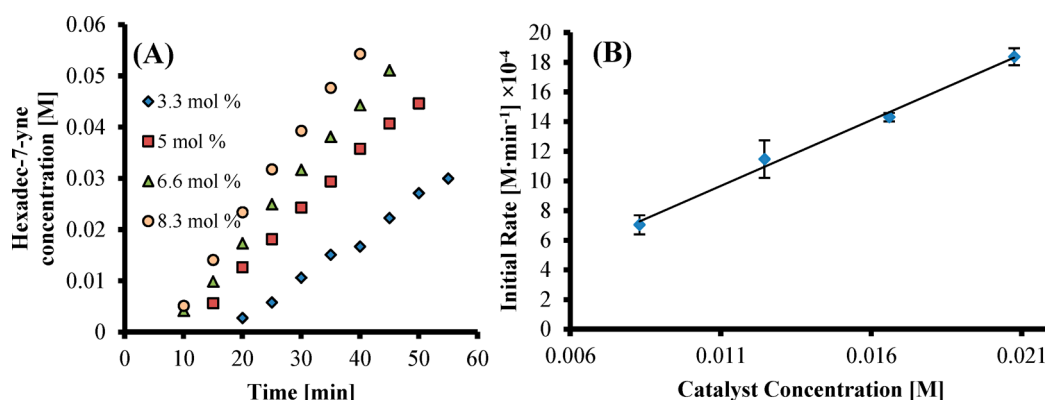
the conversion of reagent and formation of production over a period of 3 h. The formation of product followed a linear line, indicating a constant reaction rate. Because of the detection limit of the FID detector of GC, only the data collected after 20 min could be reliably used. This gave the false impression of an induction period in the reaction profiles produced from GC data; however, following reactions by NMR indicates that there is no induction period. For example, the coupling of 1-iodooctane with phenylacetylene was followed by <sup>1</sup>H NMR in DMF-*d*<sub>7</sub>. The formation of the coupling product from the beginning of the reaction was confirmed by NMR (Figure 5



**Figure 5.** Comparison of time-dependent yields of coupling determined by NMR and GC.

and Figure S2, Supporting Information). Moreover, the yields of the coupling product determined by NMR were identical to the yields determined by GC analysis (Figure 5). For experimental convenience, we chose GC as the analytical tool for further kinetic measurements.

The kinetics of the coupling of 1-iodooctane and 1-octyne was further studied by determining the rates of the coupling reaction using the initial rate approximation. Figure S3 shows



**Figure 6.** (A) Time-dependent yields of coupling at different loadings of catalyst. (B) The dependence of initial reaction rates on the loading of catalyst. The rates were averaged over three independent measurements. The error bar represents the standard deviation of the results from three independent measurements.

the reaction is zeroth-order in the concentration of 1-iodooctane. An equal amount of product was formed after a same reaction time for various concentrations of 1-iodooctane (Figure S3A, Supporting Information). The rates of the reaction are nearly constant at different concentrations of 1-iodooctane (Figure S3B). Figure S4 shows that the reaction is also zeroth order in the concentration of 1-octyne. Figure S5 shows the coupling is independent of the loading of CuI. Figure S6 shows that the rate of coupling is also independent of the loading of LiO<sup>t</sup>Bu. On the other hand, Figure 6 shows that the reaction is first-order in the concentration of catalyst **6**. The reaction profiles are different with different catalyst loadings (Figure 6A), and the reaction rate is first-order with respect to catalyst concentration (Figure 6B).

Therefore, a simple rate law can be drawn for the catalysis (eq 1) that can be used to determine the rate constant ( $k_{\text{cat}}$ ). Table 3 lists the values determined from a different set of experiments. The averaged value is  $1.6 \times 10^{-3} \text{ s}^{-1}$ .

$$\frac{d[\text{P}]}{dt} = k_{\text{cat}}[\mathbf{6}] = k_{\text{OBS}} \rightarrow k_{\text{cat}} = \frac{k_{\text{OBS}}}{[\mathbf{6}]} \quad (1)$$

**Table 3. Rate Constants of Coupling of 1-Iodooctane with 1-Octyne**

set of experiment	$k_{\text{cat}} \text{ (s}^{-1}\text{)}$	error <sup>a</sup> (%)
varying [1-iodooctane]	$1.8 \times 10^{-3}$	10
varying [1-octyne]	$1.8 \times 10^{-3}$	7
varying [CuI]	$1.5 \times 10^{-3}$	10
varying [Catalyst]	$1.5 \times 10^{-3}$	10
overall reaction profile	$1.8 \times 10^{-3}$	16
average	$1.6 \times 10^{-3}$	

<sup>a</sup>The error is calculated as the standard deviation of three independent measurements.

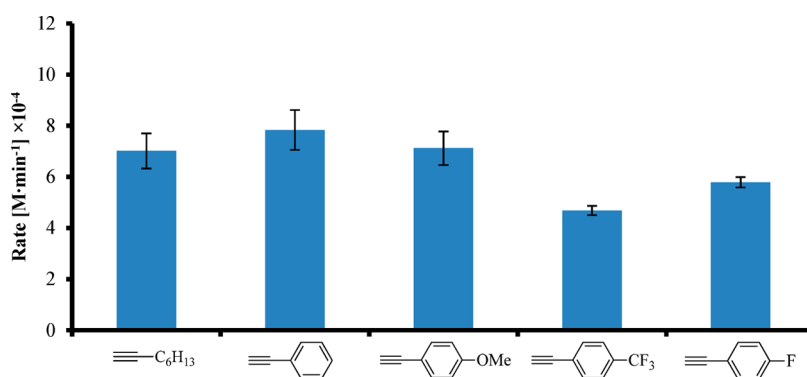
To probe possible catalyst deactivation, a reaction progress analysis<sup>20</sup> at the same excess conditions was performed for the coupling of 1-iodooctane and the 1-octyne (Figure S7). The reaction rates are nearly identical for three runs with the same excess, precluding significant catalyst deactivation. In addition, the catalytic system was subject to a recycling experiment. After a catalytic run of the coupling between 1-iodooctane and 1-octyne (yield = 80%), new samples of the same substrates and base, but neither the Ni catalyst nor Cu cocatalyst, were added to the reaction mixture. The coupling proceeded again to give

the product in 80% yield (Scheme S1). This result again suggests that there was no significant catalyst deactivation.

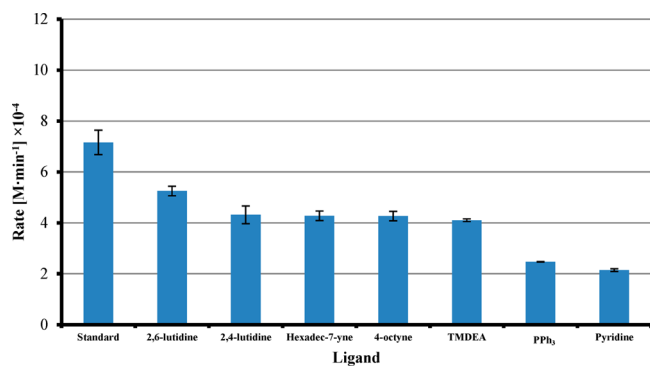
**2.4. Turnover-Determining Step.** The kinetic studies show that the catalysis is zeroth-order in CuI, LiO<sup>t</sup>Bu, alkyl halide, and alkyne and first-order in the catalyst. One possible explanation is that reductive elimination is the turnover-determining step. If this is true, the reaction rate should be influenced by the electronic properties of the substrates.<sup>21</sup> Thus, the reaction rates of the coupling of 1-iodooctane with substituted phenylacetylenes were measured.<sup>22</sup> These rates are compared with the rate of the coupling of 1-iodooctane with 1-octyne (Figure 7). The rates of the coupling of 1-octyne, phenylacetylene, and 4-ethynylanisol are similar despite difference in the electronics. With electron-withdrawing CF<sub>3</sub> and F groups, the rates decrease. These results suggest reductive elimination is not likely the turnover determining step because reductive elimination would favor more electron-poor substrates.

A possible turnover-determining step that does not involve either substrate or Cu is an intramolecular rearrangement of the catalyst. Judging from the ligands of complex **6**, we suspected that exchange of the flexible ethylenylamine nitrogen by another ligand from the Ni center was likely during catalysis. The dissociation of the nitrogen will create an open coordination site necessary for the coupling reaction. If the dissociation is the slowest step, then the catalysis would depend on only Ni, not any other reagent. The different catalytic efficiencies of complexes **3**, **5**, and **6** provide circumstantial evidence for this hypothesis. Complex **3** has a more rigid pincer ligand, so dissociation of an amine donor would be more difficult, especially at room temperature. Complex **5** has a more labile lutidine ligand, and its dissociation is more facile; however, the favorable ligand dissociation also makes the complex unstable. Complex **6** has the best catalytic activity, which might be a result of having a stable “pincer” form and a hemilabile amine ligand. To further support this hypothesis, the coupling reaction of 1-iodooctane and 1-octyne was conducted in the presence of 30 mol % coordinating ligands. Figure 8 shows that the rates of the coupling were decreased in the presence of these ligands. Among pyridine derivatives, the least bulky ligand pyridine slowed down the reaction the most. The less bulky 2,4-lutidine slowed down less, and the most bulky 2,6-lutidine slowed down the least. This result is consistent with the inhibition of catalytically active, amine-decoordinated nickel species by the exogenous ligands. The coupling was also slowed





**Figure 7.** Comparison of coupling rates when different alkynes are used as coupling partners; the rates were averaged over three independent measurements. The error bar represents the standard deviation of the results from independent measurements.



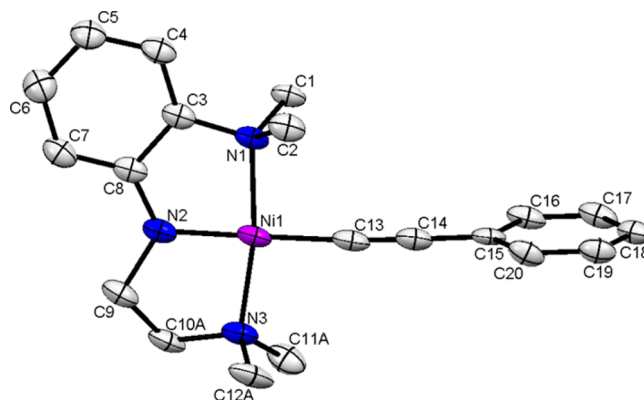
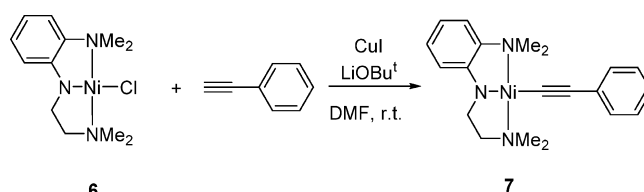
**Figure 8.** Comparison of coupling rates in the presence of different exogenous ligands. Conditions: 5 mg of complex **6** (0.016 mmol, 3.5 mol %), 9 mg of CuI (0.047 mmol, 9 mol %), 56 mg of LiO<sup>t</sup>Bu (0.7 mmol), 90 μL of 1-iodooctane (0.5 mmol), 30 mol % of the exogenous ligand, and 60 μL of decane (0.31 mmol, internal standard) were placed in a vial and 2 mL of DMF were added; 100 μL of 1-octyne (0.7 mmol) was added under magnetic stirring to the reaction mixture to start the coupling process.

down in the presence of internal alkynes, such as hexadec-7-yne and 4-octyne, which suggests that product inhibition might occur to some degree. However, product inhibition has little effect on the kinetic data that were collected at the early or middle stage of catalysis.

**2.5. Active Species for Alkylation.** The literature suggests that organometallic Ni complexes are responsible for the oxidative addition of alkyl halides in a large number of Ni-catalyzed cross-coupling reactions of alkyl halides.<sup>9,19,23–29</sup> For the reactions described here, a ligated Ni-alkynyl species might be proposed as the active intermediate. To take advantage of the well-defined nature of catalyst **6**, we attempted to identify and isolate such an intermediate.

When complex **6** was treated with equal amounts of CuI, LiO<sup>t</sup>Bu, and phenylacetylene in DMF at room temperature, a NNN-Ni-phenylacetylide complex **7** was formed as the only detectable metal-containing product (Scheme 1), with an isolated yield of 60%. Complex **7** was independently synthesized by treating complex **6** with phenylethynylmagnesium bromide. The structure of **7** was determined by X-ray crystallography (Figure 9). The replacement of Cl with phenylacetylide leads to no significant change in the structural parameters of the Ni-NNN fragment (compare Figures 3 and 9). The Ni–N2 bond distance is identical in complexes **6** and **7**. This is surprising, considering the different trans-influence property of Cl and acetylide. A possible explanation is that the

**Scheme 1. Synthesis of Ni-Acetylide Complex 7 under Catalytically Relevant Conditions**

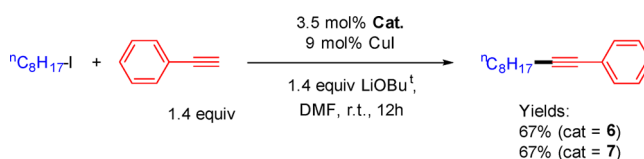


**Figure 9.** Crystal structure of complex **7**. Hydrogen atoms are omitted for clarity. The thermal ellipsoids are displayed in a 50% probability. Selected lengths (Å) and angles (deg): Ni1–N1, 1.965(3); Ni1–N2, 1.832(3); Ni2–N3, 1.958(3); Ni1–Cl3, 1.876(5); C13–C14, 1.219(6); N1–Ni1–N2, 85.39(13); N2–Ni1–N3, 85.13(14); N3–Ni1–N1, 170.52(14); N2–Ni1–C13, 179.22(14); Ni–C13–C14, 175.8(3).

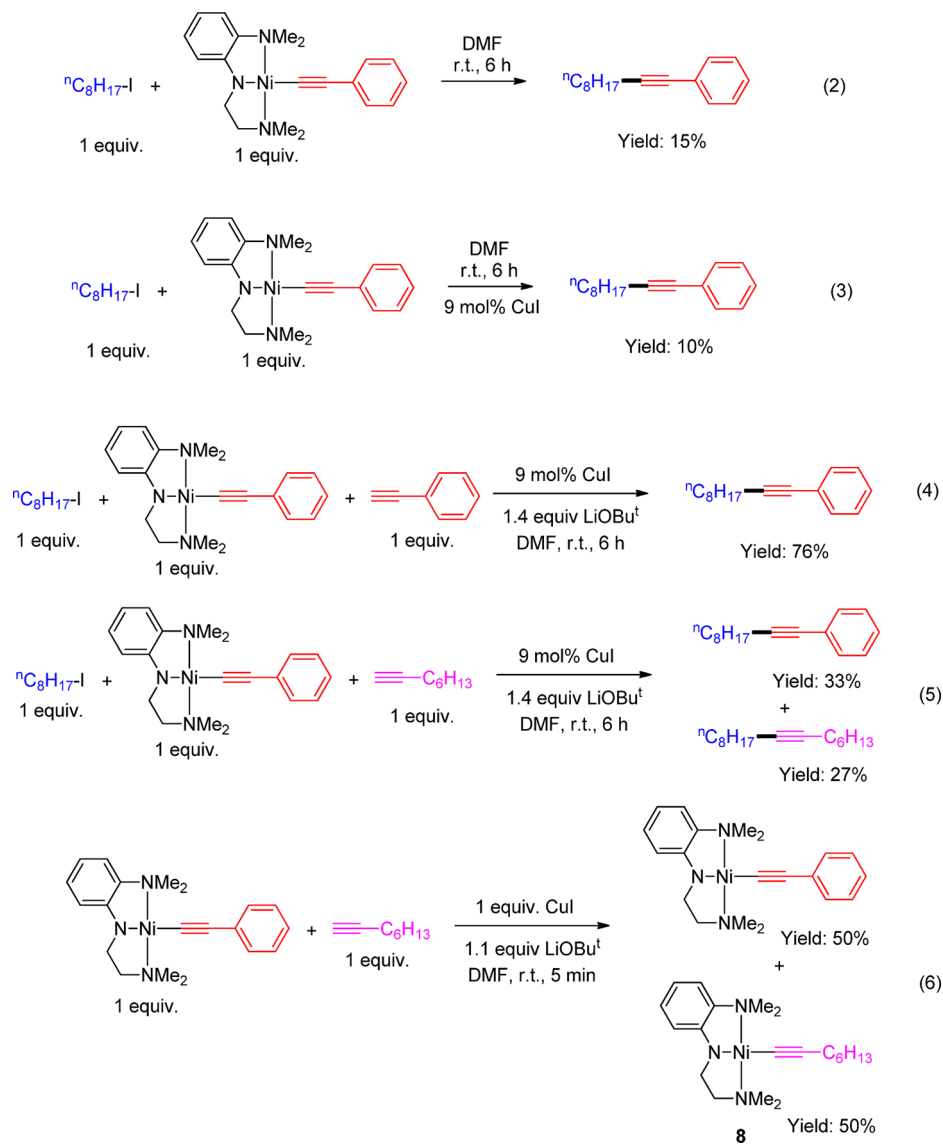
Ni–N2 distance is dictated by the structure of the pincer ligands. The overall structure of **7** is also similar to that of an analogous nickel pincer alkynyl complex.<sup>9</sup>

Complex **7** had the same efficiency as complex **6** for the coupling of 1-iodooctane with phenylacetylene (Scheme 2). Furthermore, the reaction profile of the coupling using **7** as the

**Scheme 2. Comparison of Catalytic Efficiency of Complexes 6 and 7**



Scheme 3. Reactivity of Nickel Alkynyl Complex 7

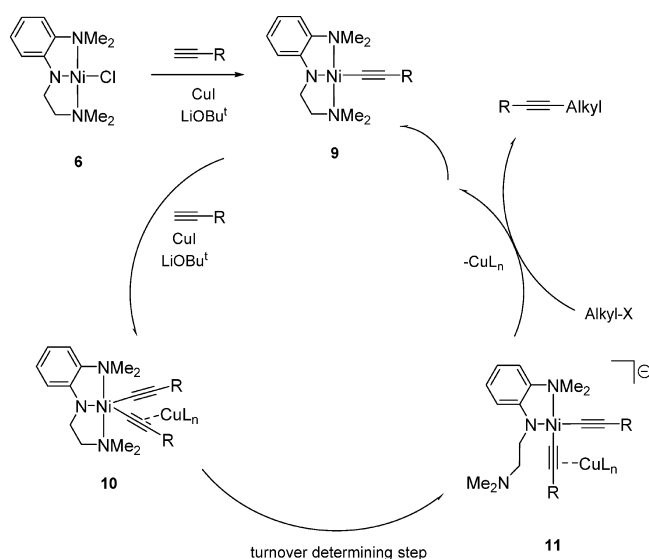


precatalyst is identical to the reaction profile of the coupling using **6** as the precatalyst (Supporting Information). The reactivity of **7** toward alkyl iodide was probed. Under catalytically relevant conditions (room temperature in DMF), **7** reacted with 1-iodooctane to give the coupling product, 1-decyn-1-ylbenzene. However, after 6 h, the yield was only 15%, much lower than that of catalysis (eq 2, Scheme 3). When 9 mol % CuI was added to this reaction, the yield was again only 10% (eq 3, Scheme 3). However, if this reaction was carried out in the presence of 1 equiv of phenylacetylene and 9 mol % of CuI, then after 6 h, the coupling yield was 76%, which was similar to that of catalysis (eq 4, Scheme 3). When eq 4 was conducted without LiO<sup>t</sup>Bu or phenylacetylene, no product was formed. When it was conducted without CuI, a reduced yield of 43% was obtained. These results suggested that complex **7** needs to be activated by an acetylide species to form a Ni bis(acetylide) complex, which was the species that reacted with alkyl halide in the catalysis. Copper acetylide was more efficient than lithium acetylide for the formation of the bis(acetylide) complex. When 1 equiv of 1-iodooctane, **7**, and 1-octyne was mixed together with 9 mol % of CuI and 1.4 equiv of LiO<sup>t</sup>Bu,

both 1-decyn-1-ylbenzene and hexadec-7-yn were formed in similar yields, with an overall coupling yield of 60% (eq 5, Scheme 3). This result showed that the acetylide fragments from complex **7** and 1-octyne could be coupled in a similar probability.

To verify whether the phenylacetylide ligand in complex **7** could be exchanged by a different acetylide ligand ligated on Cu under catalytically relevant conditions, **7** was reacted with 1 equiv of 1-octyne in the presence of 1 equiv of CuI and LiO<sup>t</sup>Bu. A new nickel complex (**8**) was formed, and it was present in a roughly 1:1 ratio to complex **7** in the reaction mixture (eq 6, Scheme 3). Complex **8** could be tentatively assigned to the Ni octynyl complex. This result indicates that the acetylide ligand on Ni is exchangeable during catalysis, which explains the outcome of eq 5. The exchange reaction likely proceeds via the Ni bis(acetylide) intermediate. Altogether, the outcomes of reactions 2–6 provide indirect support for the formation of a Ni bis(acetylide) complex, possibly connected to a Cu(I) ion, as the active species for alkylation in the catalysis.

**2.6. Tentative Catalytic Cycle.** On the basis of the above results, a tentative catalytic cycle can be drawn (Figure 10).



**Figure 10.** A simplified catalytic cycle highlighting the mechanistic information obtained from this study.

Catalyst **6** is first transformed to the alkyne complex **9**. A further alkyne coordination on **9** gives a Ni bis(alkynyl) complex **10** in which an alkyne ligand is possibly coordinated to a Cu(I) ion. It is possible that the Cu-alkynyl moiety is coordinated to an amine donor of the pincer ligand rather than the Ni-center (not drawn). Recently, Ni–Cu bimetallic alkyne complexes in which Cu binds to the alkyne  $\pi$ -system were isolated as intermediates in Ni-catalyzed Sonogashira coupling of a vinyl iodide.<sup>30</sup> Complex **10** then undergoes a rate-determining decoordination of the labile amine donor to give a more active intermediate **11**. The Cu ion likely remains coordinated to one of the nitrogen donors of the pincer ligand because the reaction is zeroth-order on Cu. Reaction of **11** with alkyl halide then leads to the coupling product and regenerates complex **9**. Because activation of alkyl halide and reductive elimination occur after the turnover-determining step, the kinetic data do not provide information on these reactions. When the coupling was conducted in the presence of 1 equiv of the radical inhibitor, TEMPO, the yield decreased to 5%, suggesting the involvement of radical intermediates. A similar effect of TEMPO was observed in cross coupling reactions of alkyl halides catalyzed by complex **3**. Our recent studies show that for the latter reactions, the activation of alkyl halides proceeds via an alkyl radical in a bimetallic oxidative addition mechanism.<sup>28,29</sup> On the basis of the similarity of catalysts and reactions, we propose that activation of alkyl halides in the current catalysis has an analogous radical mechanism.

The coupling reaction was monitored by NMR in an attempt to detect the resting state of the catalysis. Diamagnetic species **6**, **9**, and **11** were not detected, ruling them out as the resting states. The dominating Ni species is paramagnetic, and because of interference of signals from other species present in the catalysis mixture, its identification by NMR is impossible. The formation of a paramagnetic resting state, on the other hand, is consistent with **10** being the resting state because this 5-coordinate species is expected to be paramagnetic.

### 3. CONCLUSION

A new Ni pincer complex has been developed for the direct alkylation of alkynes. This complex catalyzes the coupling of

primary alkyl iodides and bromides with terminal alkynes at room temperature and with good scope and group tolerance. The mild reaction conditions and the well-defined nature of the catalyst have facilitated the first in-depth mechanistic study of this type of reaction. Kinetic measurements confirm the hemilabile nature of the new pincer ligand. The decoordination of an amine donor from a catalytic intermediate leads to the species that activates alkyl halides. Results of kinetics and inhibition studies are consistent with this decoordination step being the turnover-determining step of the catalysis. A catalytically relevant Ni-alkynyl complex has been isolated and structurally characterized. This species is both chemically and kinetically competent for the catalytic process. The reactivity of this Ni-alkynyl species suggests a yet undetected Ni bis(alkynyl) species as the essential species to activate alkyl halide. The two alkyne ligands in this species are exchangeable. The work provides significant mechanistic insights into the direct coupling of alkyl halides and alkynes, which is an efficient and versatile method for the synthesis of alkyl-substituted alkynes.

### ■ ASSOCIATED CONTENT

#### Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/cs501502u.

Experimental details and characterization data (PDF, CIF, CIF)

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#### Notes

The authors declare no competing financial interest.

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