

Mechanism of Nickel(II)-Catalyzed C(2)-H Alkynylation of Indoles with Alkynyl Bromide

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Supporting Information

ABSTRACT: The nickel system (THF)₂NiBr₂/phen has recently been shown as an efficient catalyst for the C-H bond alkynylation of diverse heteroarenes with (triisopropylsilyl)alkynyl bromide via monodentate chelation assistance. Herein, we report an extensive mechanistic investigation for the direct alkynylation of indoles involving the well-defined nickel catalyst, which features a coordinative insertion pathway of alkynyl bromide with the Ni(II) catalyst. Catalytic relevant nickel complexes, (phen)NiCl₂ (5), (phen)₂NiCl₂ (6) and [(phen)₃Ni]·NiCl₄ (7) were isolated, and the complexes 6 and 7 were structurally characterized. Welldefined complexes were as competent as the in situ generated catalyst system (THF)₂NiBr₂/phen for the alkynylation of indoles. Various controlled studies and reactivity experiments were performed to understand the probable pathway for the alkynylation reaction. Kinetics analysis highlights that the complex (phen)NiX₂ acts as a precatalyst, and the involvement of substrate indole and LiO^tBu are essential for the generation of the active catalyst. Deuterium labeling



and kinetic studies suggest that the process involving C-H cleavage and carbo-nickelation of indole is a crucial rate influencing step. Reactivity study of various alkynyl compounds with nickel-species highlights a migratory insertion route for the reaction. DFT calculations firmly support the experimental findings and suggest the coordinative insertion pathway of alkynyl bromide rather than oxidative addition toward the nickel(II) center.

INTRODUCTION

Indoles and their derivatives are key structural motifs in natural products, bioactive compounds, marketed drugs, and agrochemicals.¹ Therefore, there exists a strong demand for the efficient synthesis and functionalization of indole derivatives. Particularly, the regioselective alkynylation of indoles via direct C-H bond activation leading to the alkynylated indoles is significant, because of the possibilities of diverse postfunctionalization of the latter compound.² Various transition-metal catalysts have been known for the C-H bond alkynylation of different arenes and heteroarenes, including indoles.³ Specifically, the earth-abundant and inexpensive 3d metals, such as Fe^4 , Co⁵, Ni⁶, Cu⁷ have been successfully employed for the alkynylation of activated azoles and benzamides, and been found to be more beneficial. Shi⁸ and Ackermann⁹ have individually shown the C-2 alkynylation of indoles by cobalt catalysis employing different alkynyl coupling partners. Similarly, Ackermann has demonstrated a versatile approach for the manganese-catalyzed C-2 alkynylation of indoles under mild conditions.¹⁰ Recently, we have demonstrated the alkynylation of indoles and imidazoles with alkynyl bromide using a nickel catalyst, wherein a number of sensitive functional groups are tolerated.11

Although the nickel catalyzed C-H bond alkynylation of arenes and heteroarenes are becoming more developed, detailed mechanistic studies for this method are not well established. Miura has proposed the initial oxidative addition of alkynyl bromide to the nickel(0) species during the alkynylation of azoles,^{6a,b} analogous to the conventional Ni(0)-catalyzed crosscoupling. The oxidative addition is followed by the transmetalation with lithiated azoles, and subsequent reductive elimination of product regenerates the Ni(0) catalyst. Overall, the proposed catalytic process for the alkynylation of azoles follows a Ni(0)/Ni(II) catalytic cycle.^{6a} In contrast, Li^{6e} and Balaraman^{6h} hypothesized that the alkynylation of benzamide proceeds via a Ni(II)/Ni(IV) pathway. It is believed that the sigma donor bidentate directing group stabilizes the nickel in higher oxidation state in such cases. On the other hand, a Ni(I)/Ni(III) redox pathway for the similar alkynylation reaction has been proposed.^{6g,i} All these nickel-catalyzed alkynylation mechanistic proposals, i.e., Ni(0)/Ni(II), Ni(II)/Ni(IV) and Ni(I)/ Ni(III) have been suggested with limited experimental evidence. Recently, we have reported a Ni(II)-catalyzed regioselective

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alkynylation of indoles and speculated a probable reaction pathway.¹¹ Herein, we have provided detailed mechanistic insight for the nickel-catalyzed alkynylation of indoles with alkynyl bromide, which proceeds through the coordinative insertion of the alkynyl functionality without undergoing a redox process. Synthesis and characterization of catalytically relevant nickel complexes, detailed kinetic investigations and controlled reactivity studies have been carried out to obtain more insights. DFT calculations were performed to support the experimental results and to find out the energetically feasible intermediates. An updated and improved mechanistic cycle has been proposed considering all the experimental findings and DFT energy calculations.

RESULTS AND DISCUSSION

Synthesis and Characterization of Nickel Complexes. Recently, we have developed a nickel-catalyzed method for the alkynylation of indoles with (triisopropylsilyl)alkynyl bromide, wherein an in situ generated catalyst system (THF)₂NiBr₂/phen [phen = 1,10-phenanthroline] was employed (Scheme 1).¹¹

Scheme 1. Nickel-Catalyzed Alkynylation of 2-Pyridinyl Indole



Further to this, we have found that the well-defined complex $[(phen)_3Ni\cdot NiBr_4]$ (4), obtained from the reaction of (THF)₂NiBr₂ and phen, efficiently catalyzes the reaction under optimized conditions. It is assumed that the complex $[(phen)_3Ni \cdot$ $NiBr_4$ (4) remains in equilibrium with (phen)₂NiBr₂ and (phen)NiBr₂ during the reaction and one of the later species acts as a catalyst for the alkynylation reaction. Notably, even with the different stoichiometric reactions of phen and (THF)₂NiBr₂, the metalation reaction always afforded the mixture of (phen)₂NiBr₂ and (phen)NiBr₂, i.e., the complex composition $[(phen)_3Ni\cdot NiBr_4]$ (4), as evident from the elemental analysis. Unfortunately, the selective isolation of the species (phen)₂NiBr₂ or (phen)NiBr₂ was not successful. To synthesize and identify the differently coordinated nickel complexes, i.e., $(phen)_n NiX_2$ (n = 1 or 2), we have performed various controlled experiments employing the nickel precursor, (DME)NiCl₂. Thus, the reaction of (DME)NiCl₂ with 1.2 equiv of 1,10-phenanthroline in THF afforded complex (phen)NiCl₂ (5) in 91% yield along with 7% of $(phen)_2NiCl_2$ (6) (Scheme 2). However, the reaction of (DME)NiCl₂ with 2.0 equiv of 1,10-phenanthroline yielded (phen)_{1.2}NiCl₂ {mixture of (phen)NiCl₂ and (phen)₂NiCl₂} in 90% yield and a trace amount of $[(phen)_3Ni]\cdot NiCl_4$ (7). The composition of all the compounds 5, 6, and 7 was analyzed by elemental analysis. Furthermore, the structures of complexes 6





and 7 were elucidated by single crystal X-ray diffraction study. The complexes 5, 12 6^{13} and 7^{14} have previously been isolated by different approaches and were analyzed only by elemental analyses.

All the three nickel complexes 5–7 are NMR inactive and hence could not be characterized by ¹H and ¹³C NMR spectroscopy. However, the complexes were crystallized in analytically pure form and characterized by elemental analyses. Furthermore, the molecular structures of two complexes were elucidated by X-ray diffraction studies. The ORTEP diagrams of 6 and 7 are shown in Figures 1 and 2, respectively. Selected



Figure 1. Thermal ellipsoid plot of $(phen)_2NiCl_2$ (6). All hydrogen atoms are omitted for clarity.

bond lengths and bond angles are shown in Table 1. The geometry around the nickel center in the complex **6** is distorted octahedral, wherein the nickel is coordinated by two phenanthroline ligands, and the fifth and sixth coordination sides are occupied by the -Cl ligand. Two phenanthroline rings are almost perpendicular to each other with N(2)–Ni–N(4) and N(1)–Ni–N(3) angles around 85° and 174°, respectively. The bite angle of the phenanthroline ligand is approximately 79°. The Ni–N bond lengths are in the range of 2.08–2.10 Å,



Figure 2. Thermal ellipsoid plot of $[(\text{phen})_3\text{Ni}]\cdot\text{NiCl}_4$ (7). All hydrogen atoms are omitted for clarity.

Table 1. Selected Bond Lengths (Å) and Bond Angles (°) for Complexes 6 and 7

| bond length (Å) | | bond angles (deg) | |
|-----------------|-----------|----------------------|-----------|
| Complex 6 | | | |
| Ni(2)-Cl(1) | 2.2678(6) | N(2)-Ni(1)-N(1) | 80.24(2) |
| Ni(1) - N(2) | 2.0658(6) | N(4)-Ni(1)-N(3) | 78.78(3) |
| Ni(1) - N(4) | 2.0739(6) | N(2)-Ni(1)-N(4) | 171.75(2) |
| Ni(1) - N(1) | 2.0978(6) | Cl(1)-Ni(2)-Cl(4) | 108.81(6) |
| Complex 7 | | | |
| Ni(1)-Cl(1) | 2.418(6) | N(2)-Ni(1)-Cl(1) | 172.5(2) |
| Ni(1)-N(2) | 2.10(6) | N(4) - Ni(1) - Cl(2) | 79.5(3) |
| Ni(1)-N(4) | 2.07 (6) | N(2)-Ni(1)-N(4) | 85.2(2) |
| Ni(1)-N(6) | 2.09(6) | Cl(1)-Ni(1)-Cl(2) | 98.11(6) |

and both the Ni–Cl bond lengths are around 2.41 Å. The molecular structure of complex 7 has two different nickel centers; one is coordinated through three phenanthroline ligands in an octahedral fashion, and the other nickel center is NiCl₄ with a tetrahedral geometry. All three phenanthroline rings are almost perpendicular to each other with the *trans* N–Ni(1)–N bond angles in the range of 168.5–170.3°. The N–Ni(1)–N bite angles of phenanthroline moieties are in between 79.2° and 80.1°. All the six Ni(1)–N bond lengths are in the range of 2.07 to 2.10 Å. The Cl–Ni(2)–Cl bond angles are in the range of 106.28(7)° to 114.54(7)°, which indicates the distorted tetrahedral geometry around the nickel.

Alkynylation of Indole Using Isolated Nickel Complexes. To know the competency of isolated nickel complexes as catalysts for the alkynylation of indoles, the complexes (phen)NiCl₂ (5), (phen)₂NiCl₂ (6) and $[(phen)_3Ni] \cdot NiCl_4$ or $[(phen)_{1.5}NiCl_2]$ (7) were employed for the alkynylation of indoles with alkynyl bromide under the standard catalytic conditions. All three complexes 5–7 were as competent as the in situ generated catalyst (THF)₂NiBr₂/phen or the catalyst $[(phen)_3Ni] \cdot NiBr_4$ (4) for the alkynylation reaction (Scheme 3). Hence, complex 4 or (THF)₂NiBr₂/phen was employed as a catalyst for the mechanistic study of the alkynylation reaction.

Kinetics Analysis of the Alkynylation Reaction. In order to know the effect of reaction components on the alkynylation, the rate orders of the alkynylation reaction with various reaction components were determined by the initial rate method. First, the rate order of the alkynylation reaction on substrate (pyridin-2-yl)-1*H*-indole (1) was determined by measuring the initial rates of the alkynylation at different initial concentrations of **1**. In a standard kinetic experiment (rate measurement),



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a Teflon screw cap tube was charged with catalyst 4 (0.0044 g, 0.009 mmol, 0.009 M), alkynyl bromide 2 (0.45 mmol, 0.45 M), LiO^tBu (0.60 mmol), mesitylene (0.22 mmol, 0.22 M, internal standard) and 1-(pyridin-2-yl)-1H-indole 1 (0.058 g, 0.30 mmol, 0.30 M), and toluene (0.97 mL) was added to make the total volume to 1.0 mL. The tube containing the reaction mixture was heated at 150 °C in a preheated oil bath and progress of the alkynylation was monitored by gas chromatography (GC) at regular intervals. The data was collected after the exclusion of the induction period (30-60 min). The final data was obtained by averaging the results of two independent experiments for the reaction. The rate of the reaction was then calculated by plotting concentration of product versus time (min), wherein the slope represents the reaction rate. Similarly, the rate of alkynylation was measured using different initial concentrations (0.6, 0.9, 1.2 M) of indole 1 (see Table S1 and Figure S1 in the Supporting Information for details). As shown in Figure S1 in the Supporting Information, the rate of the alkynylation reaction increases upon the increased initial concentrations of 1. A slope of 1.15 was obtained from the plot of log(rate) versus log(conc. 1), suggesting a fractional and complex rate order on substrate 1 (Figure 3). This finding highlights a significant and



diverse role of substrate 1 in the alkynylation. The rate of the alkynylation reaction was almost similar to different initial concentrations of alkynyl bromide, highlighting a zeroeth order behavior with respect to the concentration of alkynyl bromide (Figure S2 in the Supporting Information). Similarly, the rate of the alkynylation was independent of the concentration of LiO^tBu and was zeroeth order with respect to LiO^tBu

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(Figure S3 in the Supporting Information). Next, the reaction rate was determined with different loadings of catalyst 4. A slope of 0.46 was obtained from the plot of log(rate) versus log(conc. cat 4), suggesting that the reaction is fractional order with catalyst 4 (Figure S4 in the Supporting Information). In consideration of the involvement of catalyst 4 in multiple steps during the alkynylation, the observed fractional rate order appears to be logical. Such a scenario highlights that more than one step has comparable energy barriers during the multisteps involvement of the nickel catalyst. This is also consistent with the DFT energy calculations (vide infra for discussion). Notably, upon increasing the concentrations of catalyst 4, indole 1 or LiO^tBu, the induction periods were drastically reduced (see Figures S1, S3 and S4 in the Supporting Information for details), which strongly supports our previous observation that the active catalyst generation involves precatalyst 4, substrate 1 and LiO^tBu, and that the C-H nickelation could be very crucial.¹

It is interesting to note that the electronics on the 2-py-indole substrate has no influence on the rate of the alkynylation reaction,¹¹ thus, ruling out an electrophilic type C–H activation. Furthermore, the rate of alkynylation was measured employing the 3,4,7,8-tetramethyl-phenanthroline/(THF)₂NiBr₂ catalyst system (see Figure S6 in the Supporting Information). The reaction rate was found to be much slower (1.7×10^{-4} M min⁻¹) compared to the rate employing the (THF)₂NiBr₂/phen system (1.9×10^{-3} M min⁻¹). This indicates that the C–H nickelation could be a function of the electrophilicity on the nickel center and that the electrophilic nickel center favors the alkynylation reaction.

Our previous experimental findings suggested that the complex 4 catalyzed alkynylation reaction does not involve a radical manifold and the substrate indole is essential for the generation of an active nickel catalyst.¹¹ Furthermore, the kinetic isotope effect (KIE) value was determined to be 3.6. The high KIE value along with the positive and fractional rate order on indole 1, strongly suggests that the C-H bond cleavage and carbo-nickelation is one of the rate influencing steps in the alkynylation reaction. This was further supported by the DFT energy calculations (vide infra for discussion), wherein a high barrier was observed for the C-H nickelation step complementing the significant influence of indole substrate 1 on the rate of the alkynylation. Although the observed zeroeth order dependence on base is not consistent with the proposed turnover influencing step, we believe that the reaction is apparent zero order dependence on LiO^tBu under pseudo-first-order conditions

Controlled Reactivity Study. Experimental studies indicated that neither the isolated complex $[(phen)_3Ni\cdot NiBr_4]$ (4) nor a Ni(0)-species is the active catalyst during alkynylation reaction, as the induction period was observed employing these catalyst systems.¹¹ Further, we have found that the generation of the active catalyst involves the indole 1 and LiO^tBu. Looking at the reaction components, we have hypothesized that a nickelacycle species, formed by the reaction of (THF)₂NiBr₂/ phen with indole 1, could be the active catalyst during the reaction. In that regard, in order to detect the presumed nickelacycle species, a stoichiometric reaction of (THF)₂NiBr₂/phen and 1 was performed in the presence of LiO^tBu in toluene- d_8 (Scheme 4). The reaction mixture was heated for 3 h and the ¹H NMR analysis was carried out. The ¹H NMR does not show any detectable nickel containing species; instead the formation of self-coupled dimerized product, 1,1'-di(pyridin-2-yl)-1H,1'H-2,2'-biindole (8)

Scheme 4. Reactivity of $(THF)_2NiBr_2/phen with (Pyridin-2-yl)-1H-indole (1)$



was observed. The hypothesized nickelacycle species could be paramagnetic in nature. Interestingly, the same reaction in the presence of alkynyl bromide 2 afforded the alkynylated product 3 in quantitative yield and did not produce the self-dimerized product 8. We believe that the dimerized product 8 produced via the intermediates A and E in the absence of the coupling partner 2 (Scheme 4). However, in the presence of alkynyl bromide 2, the presumed intermediate A led to the productive alkynylation reaction resulting in the formation of 3. Several attempts to isolate the probable nickelacycle species A were unsuccessful, and the reaction always ended up with the dimerized product 8 in the absence of alkynyl bromide 2. Additionally, a reaction of indole 1 with alkynyl bromide 2 employing 50 mol % of (THF)₂NiBr₂/phen did not produce the detectable dimerized product 8. All these results emphasize that the intermediacy of Ni(0) as an active catalyst is very unlikely. The feasibility of the intermediate species A and further reaction with alkynyl bromide is demonstrated by DFT calculations (vide infra for discussion). Considering the positive and fractional rate order of alkynylation reaction with substrate 1, we believe that both the intermediates A and E generate concurrently (Scheme 4) and react with alkynyl bromide to afford the desired alkynylated product. This probability has been considered and investigated by DFT calculations.

Considering our inability to detect a dimagnetic nickel species, we have considered an odd electron species as the active catalyst and investigated a probable Ni(I)/Ni(III) process. It should be noted that the standard alkynylation reaction in the presence of radical inhibitors TEMPO or galvinoxyl is unaffected and produced quantitative yield of alkynylated indole.¹¹ Although TEMPO or galvinoxyl are known to quench organic radicals, it has been shown that Ni(I) species can react with TEMPO to generate TEMPO-bound Ni(II) species, which would not allow a Ni(I)/Ni(III) process.¹⁵ These findings suggest that the Ni(I) species does not exist during the reaction to proceed the catalysis via a Ni(I)/Ni(III) pathway. This probability has also been verified by DFT calculations. The inability to observe any diamagnetic nickel species is most likely due to the tetrahedral geometry of the (phen)Ni(II) species, which might be paramagnetic in behavior.^{12a}

Probing Reactivity of Alkynyl-Species with Nickel. We further probed the reactivity pattern of alkynyl bromide with the nickel catalyst. To know the reactivity of the terminal



Figure 4. Free energy profile for the Ni(II)-catalyzed alkynylation of indoles. The free energy values are given in kcal/mol. 1 = 1-(pyridin-2-yl)-1*H*-indole, 2 = (triisopropylsilyl)ethynyl bromide.

alkyne as well as an internal alkyne, the catalytic reactions were performed employing (triisopropylsilyl)acetylene and bis-(trimethylsilyl)acetylene as coupling partners under standard catalytic conditions. Unfortunately, both the terminal as well as internal alkynes were not capable of affording the alkynylated indole. Hence, we have performed stoichiometric reactions to identify any nickel vinylic species. Thus, the reaction of complex 4 with indole 1 and (triisopropylsilyl)acetylene was carried out in the presence of LiO^tBu for 1 h, and MALDI-TOF analysis was performed for the reaction mixture. MALDI shows peak at m/z = 513.42, which correspond to the intermediate $(phen)Ni(2-py-indolyl)Br + H^+ (A + H)^+$. Unfortunately, we could not observe the nickel vinylic species. Notably, the (triisopropylsilyl)ethynyl chloride reacted efficiently under the standard catalytic conditions to afford the alkynylated product in 83% yield. Furthermore, the rate of the alkynylation reaction employing (triisopropylsilyl)ethynyl chloride is comparable with that observed using (triisopropylsilyl)ethynyl bromide $(2.4 \times 10^{-3} \text{ M min}^{-1} \text{ and } 1.8 \times 10^{-3} \text{ M min}^{-1} \text{ with}$ alkynyl chloride and alkynyl bromide, respectively; see Figure S5 in the Supporting Information). These observations suggest that the reaction of alkynyl bromide with nickel is less likely to occur via oxidative addition, because the rate of alkynylation is

expected to be slower with alkynyl chloride than with alkynyl bromide if the reaction proceeds via the oxidative addition approach. This supports our assumption that the reaction of alkynyl-species with nickel most likely occurs via a migratory insertion pathway. This finding is further supported by DFT calculations.

Quantum Chemical Calculations. Full quantum chemical calculations were performed with density functional theory (DFT) at the PBE/TZVP level of theory in order to understand the mechanism of the Ni(II)-catalyzed C-H bond alkynylation of indole. The reaction first proceeds through C-H bond activation of substrate 1 with (phen)NiBr₂ to form a five-coordinated nickelacycle intermediate A via the sixmembered transition state TS-1 (Figure 4). The energy barrier for this process is found to be 22.2 kcal/mol. Upon checking the possible coordination of indole 1 to the nickel catalyst as a separate step, the substrate indole 1 drifted away from the Ni(II) center in all the geometries optimized. Hence, the coordination of indole to the Ni(II) catalyst as an independent step is unlikely. DFT calculations show that the five coordinated nickelacycle intermediate A has energy -12.2 kcal/mol, which appears to be thermodynamically stable. A cationic fourcoordinate nickel species (phen)Ni(2-py indolyl)]⁺Br⁻ is



Figure 5. Free energy profile for the activation of the C-H bond by the Ni(II) catalyst. The values are given in kcal/mol.

thermodynamically unstable by 5.7 kcal/mol with respect to species A (see Figure S8 in the Supporting Information) and is therefore unlikely to be formed. Next, the approach of substrate 2 to intermediate A would lead to the formation of **B** by the π -coordination of **2** to the Ni(II) center. The formation of B occurs through TS-2, with the breaking of pyridinyl nitrogen-nickel bond and the formation of the nickel-alkynyl bromide π -bond concurrently. The energy barrier for this step is 17.1 kcal/mol. The reaction of intermediate B has two possibilities: either it can convert (i) into intermediate C or (ii) into intermediate D by oxidative addition. The intermediate B can convert to C' via the three-membered transition state TS-3, with the breaking of the Ni-C bond and the formation of C-C bond occurring simultaneously. The intermediate C can generate from C' via the transition state TS-4 with a barrier of 4.8 kcal/mol. The formation of the final coupled product 3 takes place from intermediate C via a four-membered transition state TS-5, with the breaking of the Ni-C and C-Br bonds and the formation of the Ni-Br bond with the surmounting energy barrier of 4.2 kcal/mol. The observed free energy profile, particularly the high barrier for the C-H nickelation process, is consistent with the experimental findings, wherein a significant influence of the substrate indole 1 on the reaction rate as well as a high kinetic isotope effect $(k_{\rm H}/k_{\rm D} = 3.6)^{11}$ was observed.

We further investigated the alternative reaction possibility of the involvement of alkynyl bromide during the alkynylation. The intermediate **B** might convert into **D** via the oxidative addition of alkynyl bromide through the three-membered transition state **TS-3'**. For this step, the energy barrier is 33.0 kcal/mol. The formation of product 3 from **D** takes place via **TS-4'**. The calculations suggest that the formation of **C** has a lower barrier than the formation of **D**, and hence the coordinative insertion path would be more favorable than the oxidative addition path (Figure 4). This observation is also consistent with the experimental findings that the alkynyl chloride reacted slightly faster than the alkynyl bromide during the alkynylation reaction. To better understand the orientation of the bromide with regards to the Ni and $Si^{i}Pr_{3}$ groups, the 3-D pictures of **TS-3**, **C**, **TS-4**, **C**' and **TS-5** have also been provided in Figure 4.

Further, we have probed the possible formation of Ni(I) during the catalytic reaction by DFT calculations. We have performed DFT calculations in the presence as well as in the absence of LiO^{t}Bu . From the calculations, it was observed that the formation of the Ni(I) species is energetically unfavorable (see Figure S7 in the Supporting Information for details). These calculations suggest that the formation of the paramagnetic Ni(I) species is unlikely to proceed the catalytic reaction via a Ni(I)/Ni(III) process, which is in agreement with the experimental observations.

Since indole 1 significantly influences the rate of the alkynylation reaction, and the self-coupled product 8 was observed in the controlled reaction, we believe that the indole is involved in the generation of the active catalyst, which would then initiate the catalytic process. In this regard, we have investigated one more possibility for C-H activation on indole by the Ni(II) catalyst (Figure 5). In this proposal, the C–H activation of indole 1 occurs at the presumed active nickel species A, leading to the formation of intermediate E. The energy barrier for this process is 15.5 kcal/mol. The reaction of E with the alkynyl bromide 2 resulted in the formation of the intermediate G via the coordinative insertion path with a barrier of 21.9 kcal/mol. Though the C-H activation of indole 1 at species A is more facile than the same at $(phen)NiBr_{v}$ the overall barrier for the formation of the alkyne inserted species G is reasonably high (28.4 kcal/mol). Hence, C–H activation and alkyne insertion by this approach could be a minor path. We have also checked the oxidative addition pathway of **2** with intermediate E, but here, the resulted intermediate H was found to be less stable than intermediate G by 7.2 kcal/mol

(ΔE) (Scheme 5). Since the coordinative insertion of the alkynyl bromide **2** with intermediate **A** is lower in barrier (22.2 kcal/mol,

Scheme 5. Electronic Energy for the Intermediate G and Intermediate H



Figure 4) than the overall barrier for the formation of G via species E (28.4 kcal/mol, Figure 5), we assume that the species A would be the crucial intermediate during the alkynylation, and alkynyl bromide 2 would react in a facile manner with A via the coordinative insertion pathway. However, alkynylation through a minor pathway via the coordinative insertion of 2 with intermediate E can also occur.

Probable Catalytic Cycle. On the basis of the experimental results and DFT calculations, and our earlier observations,¹¹ we have depicted more authentic catalytic cycles for the nickel-catalyzed alkynylation of indole with alkynyl bromide (Figure 6). The (phen)NiBr₂ species enters the catalytic cycle and reacts with 1-(pyridin-2-yl)-1*H*-indole (1) in the rate

influencing step to form the active nickelacylce species **A**. The coordination of alkynyl bromide **2** with intermediate **A** will generate the nickel complex **B** (Figure 6, Path I). Migratory insertion of alkynyl bromide in the Ni(II)–C bond would produce the complex **C**. The DFT calculations support the formation of complex **C**. Complex **C** upon β -bromide elimination would afford the alkynylated product **3** and regenerate the Ni(II) catalyst.⁹ DFT studies suggest that the alkynylation would follow the coordinative insertion pathway rather than the oxidative addition of alkynyl bromide to complex **A**, and are consistent with the experimental findings. The induction period might be necessary for the generation of species **A**, because such an induction period was absent when the mixture of catalyst **4**, indole **1** and LiO^tBu was heated before the addition of alkynyl bromide.

Alternatively, as a minor path, the complex A can act as an active catalyst and facilitate the C–H activation on indole 1 to generate species E (Figure 6, Path II). Coordinative insertion of alkynyl bromide 2 to the intermediate E would afford species G. The complex G, upon β -bromide elimination would produce the alkynylated product 3 and regenerate the active catalyst A. Though there exist a number of reports on the C–H bond alkynylation reaction, most of them have proposed an oxidative addition pathway for the reaction of alkynyl bromide with Ni(II), with limited experimental inputs. However, here we have explicitly demonstrated that the reaction of alkynyl bromide with the Ni(II) species proceeds via the coordinative insertion approach.

CONCLUSION

We have uncovered in detail the mechanism for the nickelcatalyzed alkynylation of indole with alkynyl bromide. Some catalytically competent nickel-complexes were synthesized and structurally characterized. Kinetics, controlled reactivity studies, and DFT energy calculations highlight that the alkynylation of indole follows a coordinative insertion path of alkynyl



Figure 6. Plausible updated catalytic cycles for nickel-catalyzed alkynylation reaction.

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bromide involving the rate influencing C–H activation on indole. The fractional positive rate order of the alkynylation reaction with indole substrate and the involvement of indole in the formation of the active catalyst have provided clear mechanistic insights. The C–H activation of indole at the nickelacycle species (phen)Ni(2-py indolyl)Br (A) appears to be more facile than the same at the (phen)NiBr₂ center; however, the overall process for the alkynylation via the former approach seems less likely. Considering all the experimental findings and DFT calculations, we have drawn two catalytic cycles for the nickel-catalyzed alkynylation of indole with alkynyl bromide that proceed through the coordinative insertion of alkynyl bromide into the Ni(II)–C bond and do not involve a redox pathway.

EXPERIMENTAL SECTION

General Experimental Considerations. All manipulations were conducted under an argon atmosphere either in a glovebox or using standard Schlenk techniques in predried glasswares. The catalytic reactions were performed in flame-dried reaction vessels with Teflon screw cap. Solvents were dried over Na/benzophenone or CaH2 and distilled prier to use. Liquid reagents were flushed with argon before use. The compounds $(THF)_2 NiBr_2 = 16^{16} (2-pyridinyl) - indole^{17}$ synthesized according to the previously described procedures. Alkynyl bromide (2) was synthesized according to literature procedures.¹⁸ All other chemicals were obtained from commercial sources and were used without further purification. High-resolution mass spectroscopy (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Melting point was measured on Büchi 540 capillary melting point apparatus; values are uncorrected. NMR (¹H and ¹³C) spectra were recorded at 400 or 500 (¹H), 100 or 125 {¹³C, DEPT (distortionless enhancement by polarization transfer)}, respectively on Bruker AV 400 and AV 500 spectrometers in CDCl₃ solutions, if not otherwise specified; chemical shifts (δ) are given in ppm. The ¹H and ¹³C NMR spectra are referenced to residual solvent signals (CDCl₃: δ H = 7.26 ppm, δ C = 77.2 ppm).

Procedure for Synthesis of (phen), NiCl₂ Complexes. (phen)-NiCl₂ (5) and (phen)₂NiCl₂ (6). A Schlenk flask was charged with (DME)NiCl₂ (0.30 g, 1.365 mmol) and 1,10-phenanthroline (0.295 g, 1.638 mmol), and THF (15 mL) was added to it. The reaction mixture was stirred at room temperature for 12 h, during which a light blue precipitate was formed. The reaction mixture was filtered, and the light blue solid was washed with THF (30 mL) to remove unreacted 1,10-phenanthroline. The blue solid was further washed with CH₃CN (4 \times 15 mL), and the solid was dried under vacuum to obtain an analytical pure compound of (phen)NiCl₂ (5). The combined acetonitrile solution was concentrated and kept at low temperature to obtain a crystalline compound of $(phen)_2 NiCl_2$ (6). Yield: 0.38 g, 91% (5) and 0.05 g, 7% (6). Anal. Calcd for C₁₂H₈Cl₂N₂Ni (5): C, 46.52; H, 2.60; N, 9.04. Found: C, 46.91; H, 2.67; N, 9.05. Anal. Calcd for $C_{24}H_{16}Cl_2N_4Ni$ (6): C, 58.83; H, 3.29; N, 11.43. Found: C, 59.01; H, 3.35; N, 11.65.

(phen)_nNiCl₂ and [(phen)₃Ni]NiCl₄ (7). A Schlenk flask was charged with (DME)NiCl₂ (0.50 g, 2.275 mmol) and 1,10-phenanthroline (1.03 g, 5.689 mmol), and THF (20 mL) was added to it. The reaction mixture was stirred at room temperature for 12 h, during which a light green precipitate was formed. The reaction mixture was filtered, and the light green solid was washed with THF (30 mL) to remove unreacted 1,10-phenanthroline. The light green solid was further washed with CH_3CN (4 × 15 mL), and the solid was dried under vacuum to obtain a mixture of compounds (phen)_{1.2}NiCl₂ [mixture of (phen)NiCl₂ and (phen)₂NiCl₂]. The combined acetronitrile solution was concentrated and kept at low temperature to obtain a crystalline compound of [(phen)₃Ni]NiCl₄ (7). Yield: 0.71 g, 90% for $(phen)_{1.2}NiCl_2$ and 0.055 g, 6% for $[(phen)_3Ni]NiCl_4$ (or $(phen)_{1.5}NiCl_2$; 7). Anal. Calcd for $C_{14,4}H_{9,6}Cl_2N_{2,4}Ni$ [(phen)_{1,2}NiCl₂]: C, 50.01; H, 2.80; N, 9.72. Found: C, 50.40; H, 2.87; N, 9.85. Anal. Calcd for C₁₈H₁₂Cl₂N₃Ni

[(phen)₃Ni]NiCl₄ (7): C, 54.06; H, 3.02; N, 10.51. Found: C, 54.31; H, 3.09; N, 10.67.

General Procedure for Kinetic Experiment. To a Teflon-screw capped tube equipped with magnetic stir bar was introduced catalyst 4 (0.0044 g, 0.009 mmol), LiO'Bu (0.048 g, 0.60 mmol), alkynyl bromide 2 (0.117 g, 0.45 mmol) and 1-(pyridin-2-yl)-1H-indole 1 (0.058 g, 0.304 mmol, 0.30 M), and toluene (required amount) was added to make the total volume 1.0 mL. To the reaction mixture mesitylene (0.030 mL, 0.215 mmol) was added as an internal standard. The reaction mixture was then stirred at 150 °C in a preheated oil bath. At regular intervals, the reaction vessel was cooled to ambient temperature, introduced to the glovebox and an aliquot of the sample was withdrawn to the GC vial. The sample was diluted with toluene/acetone and subjected to GC analysis. The concentration of the product 3 obtained in each sample was determined with respect to the internal standard mesitylene. The data of the concentration of the product vs time (min) plot was drawn with Origin Pro 8. For the reaction rate, the data were fitted linear (excluding induction period) with Origin Pro 8, and the rate was determined by initial rate method with different time intervals. The slope of the linear fitting represents the reaction rate. The order of the reaction was then determined by plotting the log(rate) vs log(conc. component) for a particular component.

Computational Details. All the calculations in this study have been performed with density functional theory (DFT), with the aid of the Turbomole 7.1 suite of programs,¹⁹ using the PBE functional.²⁰ The TZVP²¹ basis set has been employed. The resolution of identity (RI),²² along with the multipole accelerated resolution of identity $(marij)^{23}$ approximations have been employed for an accurate and efficient treatment of the electronic Coulomb term in the DFT calculations. Solvent correction was incorporated with optimization calculations using the COSMO model,²⁴ with toluene ($\varepsilon = 2.38$) as the solvent. The values reported are ΔG values, with zero-point energy corrections, internal energy and entropic contributions included through frequency calculations on the optimized minima with the temperature taken to be 298.15 K. Harmonic frequency calculations were performed for all stationary points to confirm them as local minima or transition state structures. For all the Ni(II) and Ni(IV) species considered, the DFT studies have been performed for the singlet state, whereas for Ni(I) and Ni(III) the DFT studies have been performed for the doublet spin state.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00177.

Detailed experimental procedures, analytical data for compounds, kinetic plots (PDF) Additional data (XYZ)

Accession Codes

CCDC 1832266–1832267 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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