

Speciation and Reactivity of Mono- and Binuclear Ni Intermediates in Aminoquinoline-Directed C–H Arylation and Benzylation

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ABSTRACT: This report describes detailed organometallic studies of the aminoquinoline-directed Ni-catalyzed C–H functionalization of 2,3,4,5-tetrafluoro-*N*-(quinolin-8-yl)benzamide with diaryliodonium reagents. A combination of ^{19}F NMR spectroscopy and X-ray crystallography are used to track and characterize diamagnetic and paramagnetic intermediates throughout this transformation. These provide key insights into both the cyclometalation and oxidative functionalization steps of the catalytic cycle. The reaction conditions (solvent, ligands, base, stoichiometry) play a central role in the observation of a Ni^{II} pre-cyclometalation intermediate as well as in the speciation of the Ni^{II} products of C–H activation. Both mono- and binuclear cyclometalated Ni^{II} species are observed and interconvert, depending on the reaction conditions. Cyclic voltammetry reveals that the $\text{Ni}^{\text{II/III}}$ redox potentials for the cyclometalated intermediates vary by more than 700 mV depending on their coordination environments, and these differences are reflected in their relative reactivity with diaryliodonium oxidants. The oxidative functionalization reaction affords a mixture of arylated and solvent functionalization organic products, depending on the conditions and solvent. For example, conducting the oxidation in toluene leads to preferential formation of the benzylated product. A series of experiments implicate a $\text{Ni}^{\text{II/III/IV}}$ pathway for this transformation.

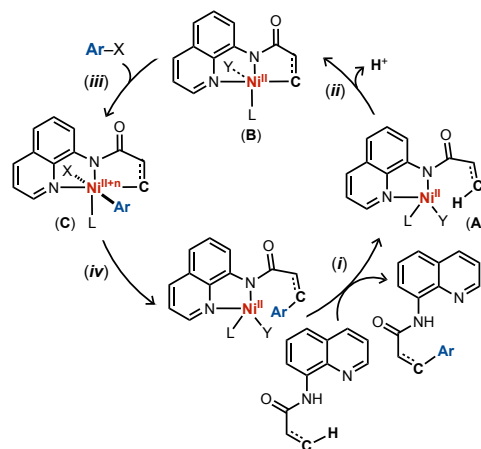
INTRODUCTION

Aminoquinoline (AQ)-directed C–H functionalization has emerged as a powerful approach for the late-stage derivatization of arene and alkane substrates.¹ The AQ directing group was pioneered by Daugulis for palladium-catalyzed C–H arylation² and subsequently other C–C and C–heteroatom coupling reactions. Several years later, analogous transformations were developed using its first-row congener nickel.^{3,4} Intermediates in the palladium-catalyzed transformations have been well-studied and characterized.⁵ In contrast, the details of the structures, oxidation states, and reactivity of Ni intermediates have only begun to emerge.^{6,7,8,9,10}

To date, organometallic investigations of Ni-catalyzed AQ-directed C–H arylation have largely focused on individual steps of the catalytic cycle. For instance, Love and Schafer,⁶ Johnson,⁷ and others⁸ have interrogated C–H activation at Ni^{II} centers to generate NNC pincer intermediate **B** (Scheme 1, steps *i* and *ii*). These studies show the initial formation of Ni^{II} aminoquinoline coordination complexes of general structure **A** (Scheme 1, step *i*). The speciation of these paramagnetic and often fluxional coordination complexes has been shown to vary as a function of stoichiometry, base, and quinoline electronics; furthermore, the formation/reactivity of **A** has been implicated as a key factor in the rate of C–H activation to generate **B** (step *ii*).^{6,7} Despite these advances, the detection and characterization of paramagnetic coordination complexes has largely been limited to what crystallizes from solution, as there are not good

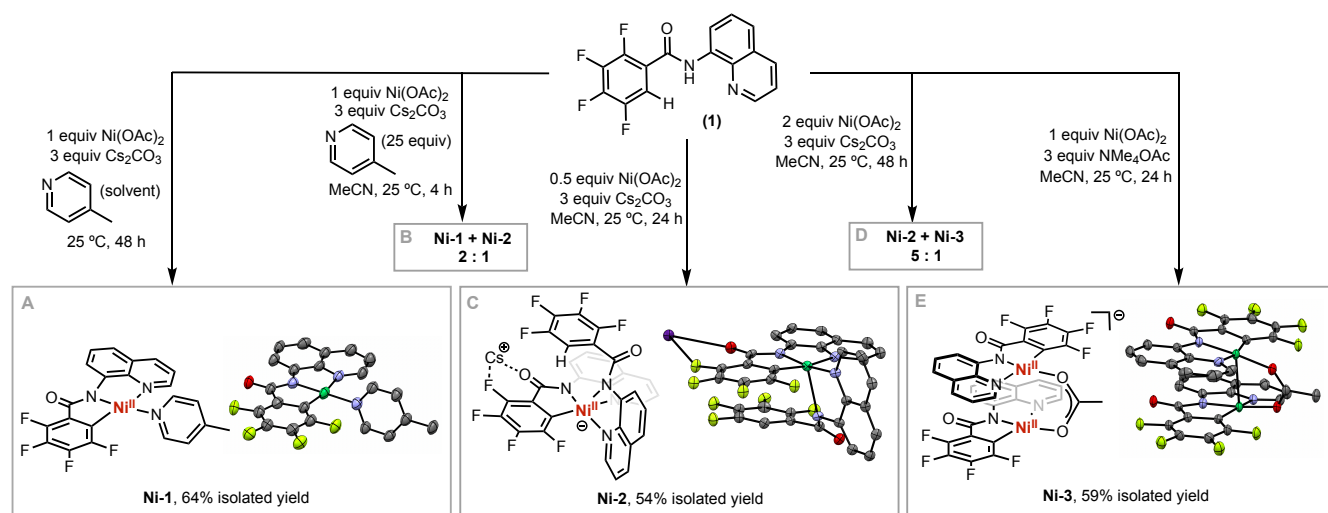
ways to track their formation and evolution *in situ*. Additionally, isolation of the cyclometalated intermediate (**B**) typically requires trapping with an exogenous donor ligand (e.g., phosphine, pyridine, CO) that would not be present during catalysis. As such, the structure and speciation of Ni^{II} intermediate **B** under catalytically relevant conditions remains an open question.

Scheme 1. General catalytic cycle for nickel-catalyzed AQ-directed C–H arylation



In parallel, work from our group¹⁰ and others^{8,9} has probed the oxidative functionalization of Ni^{II} pincer complex **B**. These studies implicate the accessibility of Ni^{III} and/or Ni^{IV}

Scheme 2. Selective formation of **Ni-1**, **Ni-2**, and **Ni-3** under varying conditions. Experimental and crystallographic details in SI.



intermediates, depending on the oxidant and reaction conditions. For instance, arylation has been shown to proceed from either Ni^{III} (following single-electron redox transmetalation between **B** and a silver(I)–aryl species)⁹ or Ni^{IV} (following the net two-electron oxidative addition of a diaryliodonium reagent).^{10,11} However, questions remain about the detailed mechanism of C–H arylation, including the relationship between the Ni^{II} , Ni^{III} , and Ni^{IV} oxidation states. For instance, it is currently unclear whether Ni^{IV} –aryl intermediates are accessed exclusively via two-electron redox pathways ($\text{Ni}^{\text{II/IV}}$) or whether sequential single electron $\text{Ni}^{\text{II/III/IV}}$ mechanisms¹² are feasible with aryl electrophiles.^{13,14} Furthermore, the connection between the speciation of C–H activation intermediate **B** and its reactivity towards oxidative functionalization has not been established.

We hypothesized that many of these questions could be studied directly by using 2,3,4,5-tetrafluoro-*N*-(quinolin-8-yl)benzamide **1** as a substrate to interrogate organonickel intermediates throughout the $\text{C}(\text{sp}^2)$ –H arylation catalytic cycle. A recent report from our group showed that **1** enables the detection and isolation of related NNC pincer Cu^{II} and Cu^{III} intermediates, which had previously proven elusive.¹⁵ In the Cu system, the fluorine substituents played multiple roles including: (1) serving as ^{19}F NMR spectroscopic handles for detecting and tracking paramagnetic intermediates,¹⁶ (2) lowering the barrier to C–H activation by acidifying the (fluoro)aryl–H bond,¹⁷ and (3) stabilizing σ -aryl–Cu intermediates.¹⁸

In this report, we study the Ni-catalyzed reaction of **1** with diaryliodonium reagents and use ^{19}F NMR spectroscopy and X-ray crystallography to track and quantify diamagnetic and paramagnetic intermediates throughout these transformations. These studies reveal that the reaction conditions (solvent, ligands, base, stoichiometry) play a central role in the speciation of Ni^{II} coordination complexes and cyclometalated products. This speciation, in turn, dramatically impacts reactivity towards oxidative functionalization with diaryliodonium reagents, which occurs via $\text{Ni}^{\text{II/III/IV}}$ pathway. Overall, this work provides detailed insights into multiple steps of the catalytic cycle and informs the development of a Ni-catalyzed C–H benzylation reaction involving diaryliodonium salts and toluene.

RESULTS AND DISCUSSION

Cyclometalation. We initially interrogated the cyclometalation of **1** at $\text{Ni}(\text{OAc})_2$ under a range of different conditions.¹⁹ First, substrate **1** (1 equiv), $\text{Ni}(\text{OAc})_2$ (1 equiv), and Cs_2CO_3 (3 equiv) were combined in 4-methylpyridine, which can serve as both the solvent and an L-type ligand for the cyclometalated product **B**. Monitoring this reaction by ^{19}F NMR spectroscopy revealed clean formation of the diamagnetic 4-methylpyridine-coordinated cyclometalated product **Ni-1** in 72% yield after 48 h at room temperature (Scheme 2A).²⁰ **Ni-1** was isolated in 64% yield by column chromatography on silica gel and was characterized by ^1H , ^{13}C , and ^{19}F NMR spectroscopy, elemental analysis, HRMS, and X-ray crystallography. The solid-state structure of **Ni-1** shows a square planar Ni^{II} center with a Ni–C bond distance of 1.906 Å. This is within 0.02 Å of that in other reported neutral $(\text{NNC}_{\text{Aryl}})\text{Ni}^{\text{II}}$ complexes.^{8,9,10b} Overall, this initial experiment shows that the cyclometalation of **1** at Ni^{II} proceeds under mild conditions.

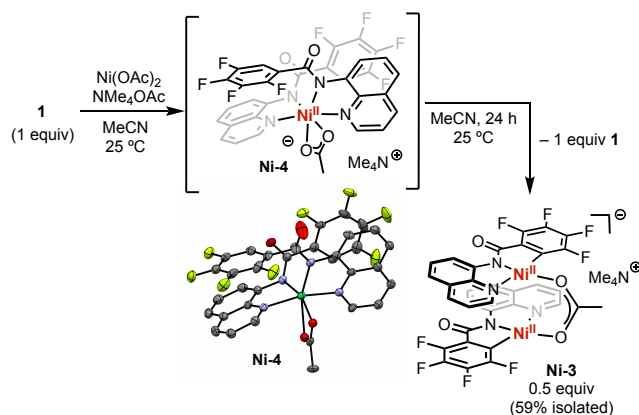
Pyridine ligands are typically not present during C–H functionalization catalysis; thus, to mimic more catalytically relevant conditions, we next examined the analogous reaction in MeCN with smaller quantities of 4-methylpyridine. Using 25 equiv of 4-methylpyridine led to a 2 : 1 mixture of **Ni-1** and a second cyclometalated product (**Ni-2**) after 4 h at 25 °C (Scheme 2B). Lowering the amount of 4-methylpyridine led to corresponding decreases in the **Ni-1** to **Ni-2** ratio, suggesting that **Ni-2** does not contain the pyridine as a supporting ligand. Indeed, excluding 4-methylpyridine under otherwise identical conditions afforded **Ni-2** in 48% yield as the sole detectable Ni-containing product.²¹ Upon adjusting the reaction stoichiometry to 0.5 equiv of $\text{Ni}(\text{OAc})_2$ and 1 equiv of **1**, **Ni-2** was isolated in 54% yield (Scheme 2C). Characterization by X-ray crystallography revealed that **Ni-2** is a 5-coordinate anionic complex ($\tau = 0.07$) bearing one cyclometalated ligand and one aminoquinoline bound as an N–N donor.²² A Cs cation balances the charge, and in the solid state the Cs^+ has close contacts with the C=O ($\text{Cs} \cdots \text{O} = 2.938$ Å) and *ortho*-fluorine ($\text{Cs} \cdots \text{F} = 3.012$ Å) of the cyclometalated aminoquinoline. The Ni–C bond length of 1.916 Å is 0.01 Å longer than that of the neutral analogue **Ni-1**. Notably, Huang isolated a neutral Ni^{III} complex with an analogous coordination environment using *N*-(quinolin-8-yl)benzamide as the AQ substrate.^{8b}

Finally, changing the $\text{Ni}(\text{OAc})_2$: **1** stoichiometry to $\geq 1 : 1$ resulted in the formation of a third cyclometalated product, **Ni-3**. For instance, the reaction of 2 equiv of $\text{Ni}(\text{OAc})_2$ with 1 equiv **1** afforded a 5 : 1 mixture of **Ni-2** : **Ni-3** after 48 h at 25 °C (Scheme 2D). Adjusting the stoichiometry to a 3 : 1 ratio of **Ni** : **1** and lowering the overall concentration produced **Ni-3** as the sole detectable product in 52% yield. Characterization of the tetramethylammonium salt of **Ni-3** by X-ray crystallography showed that this is a binuclear monoanionic structure, with an acetate ligand bridging two square planar NNC-coordinated nickelacycles. Related Pd^{23} and Ni^{24} acetate-bridged complexes have been well-studied in the C–H functionalization of substrates bearing monodentate directing groups (e.g., 2-phenylpyridine, benzo[h]quinoline). However, to our knowledge, this is the first analogue with a bidentate AQ directing group.¹ The X-ray structure of **Ni-3** reveals an average Ni–C bond length of 1.896 Å, which is 0.01 Å shorter than that in the neutral monomeric complex **Ni-1**. The Ni–Ni distance is 2.926 Å, which is significantly longer (by 0.1 to 0.3 Å) than the metal-metal distances observed in related acetate-bridged complexes of both Ni^{II} ²⁴ and Pd^{II} ²³.

Based on the structure of **Ni-3**, we hypothesized that this complex could also be formed using an acetate base instead of Cs_2CO_3 . Indeed, a higher yield of 68% of **Ni-3** was observed by ^{19}F NMR spectroscopy with tetramethylammonium acetate (NMe_4OAc) as the base under otherwise identical conditions. Ultimately, the optimal route to **Ni-3** involved the use of 1 equiv of **1**, 1 equiv of $\text{Ni}(\text{OAc})_2$, and 3 equiv of NMe_4OAc in MeCN at 25 °C (Scheme 2E). This reaction afforded quantitative yield of **Ni-3** by ^{19}F NMR spectroscopy, and the product was isolated in 59% yield and characterized by ^1H , ^{13}C , and ^{19}F NMR, elemental analysis, and HRMS.

While monitoring the formation of **Ni-3** under the optimal conditions, we observed a paramagnetic intermediate (**Ni-4**) with a diagnostic set of three broad ^{19}F NMR signals between -170 and -140 ppm. **Ni-4** appeared after 10 min at 25 °C and slowly decayed over the course of 24 h, with concomitant formation of **Ni-3**. Recrystallization of a solution containing a mixture of **Ni-3** and **Ni-4** from MeCN/ Et_2O , afforded two distinct types of crystals: orange crystals of **Ni-3** and green crystals of **Ni-4**. X-ray crystallographic characterization of the green crystals showed a mononuclear pseudo-octahedral Ni^{II} coordination complex, featuring two equivalents of N–N bound **1** along with a κ_2 -acetate ligand (Scheme 3).

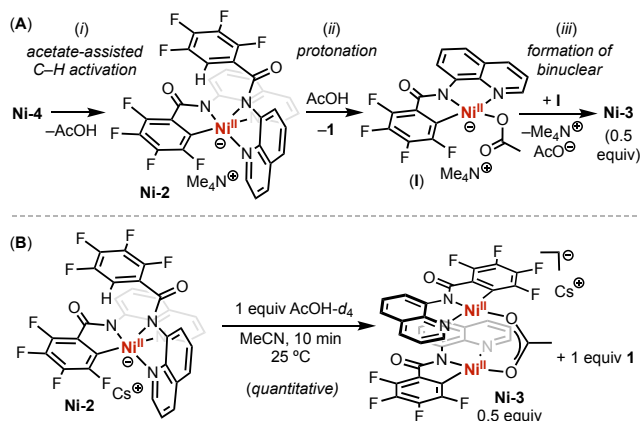
Scheme 3. **Ni-4** is an intermediate en route to **Ni-3**



^aConditions: 1 equiv $\text{Ni}(\text{OAc})_2$, 1 equiv **1**, 3 equiv NMe_4OAc in MeCN at 25 °C.

Intermediate **Ni-4** appears poised to undergo acetate-assisted $\text{C}(\text{sp}^2)\text{--H}$ activation to form the mononuclear cyclometalated product **Ni-2** along with 1 equiv of AcOH (Scheme 4A, step *i*). However, **Ni-2** was not detected by ^{19}F NMR spectroscopy during the conversion of **Ni-4** to **Ni-3**. This observation led us to hypothesize that the AcOH by-product might be reacting rapidly with **Ni-2** to protonate the bidentate AQ ligand, releasing **1** and generating a transient mononuclear intermediate (**I**, Scheme 4A, step *ii*). Reaction with a second equiv of intermediate **I** would then form 0.5 equiv of **Ni-3** along with 1 equiv of NMe_4OAc (Scheme 4A, step *iii*). To evaluate the feasibility of this proposed sequence, we subjected an isolated sample of **Ni-2** to 1 equiv of AcOH- d_4 . As shown in Scheme 4B, this led to rapid (≤ 10 min) and quantitative formation of **Ni-3** and **1**, consistent with the pathway outlined in Scheme 4A.

Scheme 4. (A) Proposed pathway from **Ni-4** to **Ni-3** (via intermediacy of **Ni-2**). (B) Reaction of **Ni-2** with 1 equiv of AcOH- d_4



Overall, these studies demonstrate the accessibility of both mono- and binuclear nickelacycles under typical C–H functionalization reaction conditions. These complexes differ in charge, nuclearity, and coordination environment, and their distribution is highly sensitive to changes in conditions, such as reaction solvent, acid/base, and stoichiometry. For instance, the anionic mononuclear complex **Ni-2** (which contains a second N–N bound AQ ligand) forms selectively in the presence of a relatively strong base (Cs_2CO_3) and an excess of substrate **1** relative to $[\text{Ni}]$. This combination of base and stoichiometry represent the typical conditions for Ni-catalyzed C–H functionalization reactions.⁴ However, binuclear complex **Ni-3** (which contains a bridging acetate and a single AQ ligand per Ni center) is also readily accessible. It forms rapidly from **Ni-2** upon the addition of 1 equiv of AcOH. Furthermore, it is generated selectively via the reaction of **1** with an excess of $\text{Ni}(\text{OAc})_2$ in the presence of an acetate base. These results thus provide insights into how to favor the formation of **Ni-2** versus **Ni-3** in catalysis.

We also detect a pre-cyclometalation intermediate (**Ni-4**), bearing two N–N bound aminoquinoline ligands along with a bidentate acetate. **Ni-4** closely resembles an anionic octahedral $(\text{N–N})_3\text{Ni}^{\text{II}}$ complex that was recently isolated by Love and Schafer.^{6a} Their work (as well as several other recent reports)^{7,32} proposes that productive cyclometalation occurs from a neutral square planar $(\text{N–N})\text{Ni}^{\text{II}}(\text{OAc})$ intermediate, thus requiring dissociation of two AQ ligands and coordination of a carboxylate. In contrast, our results suggest that C–H activation at a bis-AQ complex like **Ni-4** should also be considered as an alternative pathway to cyclometalated product **Ni-2**.

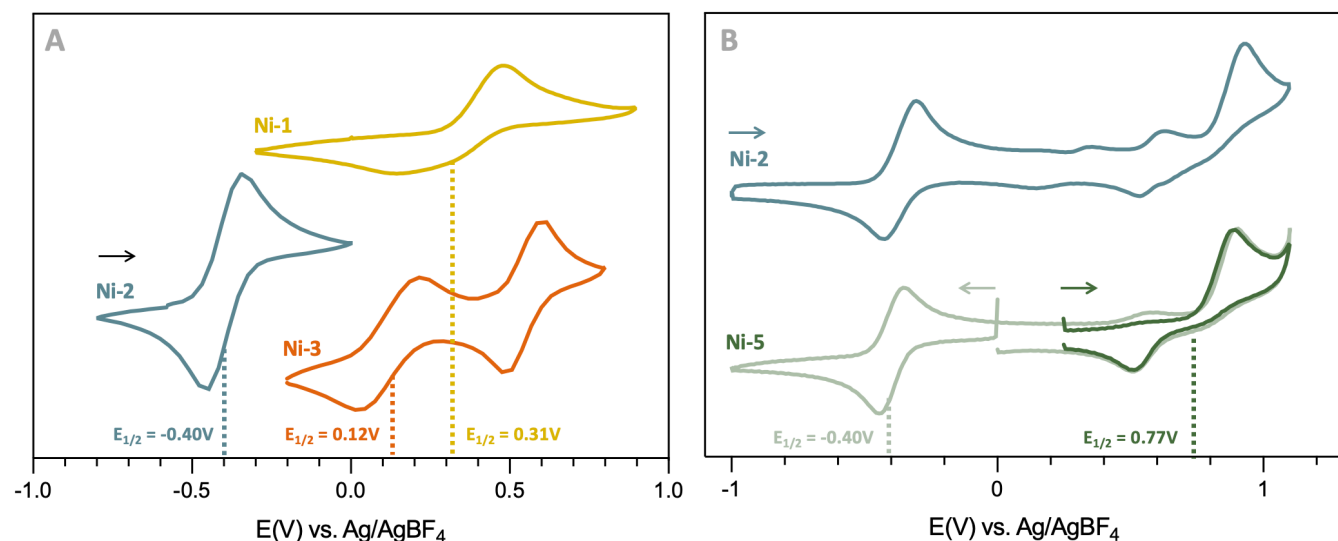
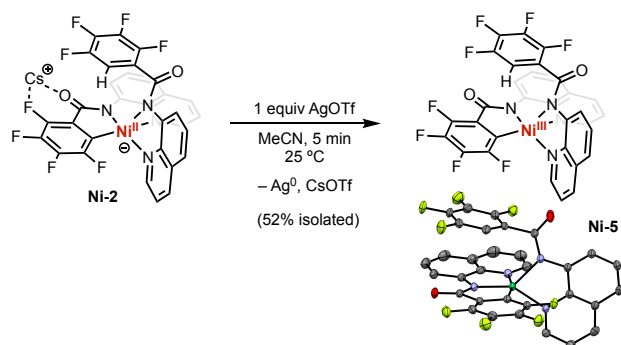


Figure 1. Cyclic voltammetry data for isolated nickelacycles. Conditions: 4–6 mM solution of [Ni] in 0.1 M NBu₄PF₆ in CH₃CN; scan rate of 100 mV/s. (A) Stacked CV traces for **Ni-1** (yellow), **Ni-2** (blue), and **Ni-3** (orange), scanning oxidatively. (B) Stacked CV trace of **Ni-2** scanning oxidatively (blue) and CV traces of **Ni-5** scanning both oxidatively (dark green) and reductively (light green).

Oxidative functionalization. Cyclic voltammograms (CVs) of **Ni-1**, **Ni-2**, and **Ni-3** were obtained in MeCN/NBu₄PF₆ at a scan rate of 100 mV/s and are shown in Figure 1. The neutral complex **Ni-1** shows a quasi-reversible Ni^{II/III} couple with $E_{1/2} = +0.31$ V versus Ag/Ag⁺. The Ni^{II/III} couple for anionic **Ni-2** is more than 700 mV lower ($E_{1/2} = -0.40$ V versus Ag/Ag⁺). This is comparable to that of the Cu^{II} analogue, which shows a Cu^{II/III} couple with $E_{1/2} = -0.58$ V vs Ag/Ag⁺.¹⁵ Finally, the anionic binuclear complex shows discrete oxidations for the two Ni^{II} centers, with $E_{1/2} = +0.12$ V and $+0.55$ V vs Ag/Ag⁺. For complexes **Ni-1** (Figure S18) and **Ni-2** (Figure 1B, top), an additional irreversible peak is observed at $\geq +0.8$ V, likely associated with the Ni^{III/IV} couple (Figure 1B, top).³ Overall, these data indicate that **Ni-2** undergoes single-electron oxidation to Ni^{III} at much lower potentials than **Ni-1** or **Ni-3**.

Scheme 5. Single electron oxidation with AgOTf



Complexes **Ni-1** and **Ni-3** showed no reaction with AgOTf over 1 h at room temperature.²⁵ This is fully consistent with their Ni^{II/III} redox potentials, which are greater than 0 V vs Ag/Ag⁺. In contrast, the treatment of **Ni-2** (formed *in situ*) with 1 equiv of AgOTf resulted in a nearly instantaneous color change from brown to green along with the precipitation of Ag⁰. Monitoring this reaction by ¹⁹F NMR spectroscopy showed the clean and quantitative formation of a paramagnetic product with three broad resonances. This Ni^{III} complex, **Ni-5**, was isolated in 52% yield as a dark green solid (Scheme 5). **Ni-5** was

characterized by single crystal X-ray diffraction, which shows a distorted trigonal bipyramidal Ni^{III} complex ($\tau = 0.38$) with a Ni–C bond length of 1.930 Å. This is ~ 0.01 Å shorter than that of the unfluorinated analogue of **Ni-5** reported by Huang.^{8b} The Ni^{III}–C distance in **Ni-4** is only slightly longer (by 0.0014 Å) than that in the anionic Ni^{II} precursor **Ni-2**.

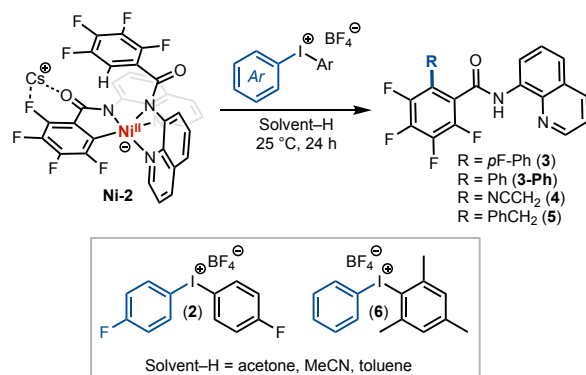
Minimal ($\leq 6\%$) reaction was observed when **Ni-5** was heated for 24 h at 60 °C in MeCN in the absence of an oxidant. This is in marked contrast to the Cu^{III} analogue,¹⁵ which undergoes a second C–H activation at Cu^{III} and subsequent C(sp²)–C(sp²) bond-formation to generate the oxidatively coupled dimer. However, we note that the CV of **Ni-5** (Figure 1B, bottom) shows a quasi-reversible oxidation peak at $+0.77$ V that matches the second redox event observed in the CV of **Ni-2** (Figure 1B). This implicates the feasibility of a second single-electron oxidation of **Ni-5** to generate a cationic Ni^{IV} complex that is expected to be more reactive towards bond-forming reactions. Notably, Ackermann reported that the corresponding unfluorinated Ni^{III} complex shows a similar quasi reversible oxidation at $+0.50$ V vs. Fc/Fc⁺ and assigned this as a Ni^{III/IV} redox couple.^{8a} Furthermore, he showed that electrochemical oxidation to Ni^{IV} in the presence of nucleophiles leads to rapid C(sp²)–nucleophile coupling to release functionalized products.

We next examined the reaction of the cyclometalated Ni^{II} complexes **Ni-1**, **Ni-2**, and **Ni-3** with diaryliodonium oxidant **2**. Diaryliodonium salts have previously been employed as arylation reagents in Ni-catalyzed AQ-directed C–H functionalization reactions.¹¹ Furthermore, our group recently reported that **2** effects the net two-electron oxidation of a related Ni^{II} pincer complex to form a Ni^{IV}–aryl intermediate.^{10a} This Ni^{IV} species then undergoes C–C bond-forming reductive elimination to release an arylated product.^{10a,26}

Neither **Ni-1** nor **Ni-3** showed any reaction with diaryliodonium salt **2** at room temperature in acetone-*d*₆.²⁷ In contrast, under otherwise analogous conditions, **Ni-2** reacted with **2** to afford the C–H arylation product **3** in 52% yield after an acid work up to decomplex the organic product from Ni (Table 1, entry 1). Unexpectedly, when the solvent was changed to

MeCN or toluene, products derived from solvent functionalization were formed competitively. For instance, in MeCN the reaction of **Ni-2** with **2** afforded 24% of nitrile **4** along with the arylated product **3** (in 47% yield). The $-\text{CH}_2\text{CN}$ group derives from C–H functionalization of the solvent, which could occur by either a polar (α -deprotonation) or radical (H-atom abstraction) pathway. The lack of a similar product in acetone (whose pK_a is ~ 20 versus 25 for MeCN) suggests the latter. Consistent with this proposal, moving to toluene (which has homolytically weak benzylic C–H bonds) led to benzylated **5** as the major product (in 37% yield) along with 7% of **3**.²⁸ Changing the iodonium reagent from **2** to **6** resulted in an increase in the yield of **5** to 54%. These results suggest that the use of oxidant **2** or **6** in toluene could be effective for the selective Ni-catalyzed C–H benzylation of substrate **1** (*vide infra*).

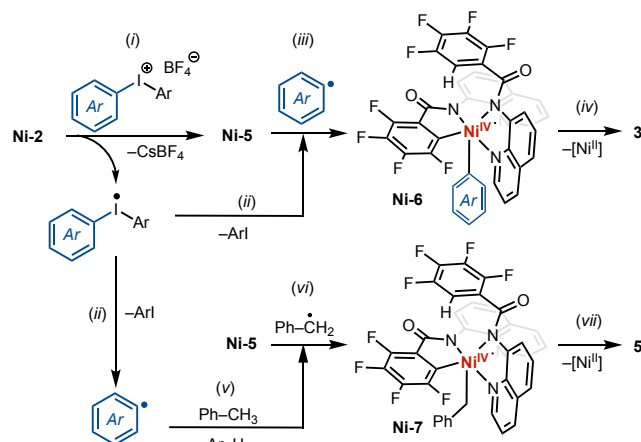
Table 1. Reactivity of Ni^{II} complex **Ni-2** with diaryliodonium oxidants^a



entry	$[\text{Ar}_2\text{I}]^+$	solvent	%3	%4	%5
1 ^a	2	acetone	52	---	---
2 ^a	2	MeCN	47	23	---
3 ^a	2	toluene	7	---	31
4 ^b	6	toluene	6	---	54

^aUsing **2** as oxidant (affords product **3**). ^bUsing **6** as oxidant (affords product **3-Ph**). Following oxidation, an acidic work-up was used to decomplex organic products from Ni. See SI for details.

Scheme 6. Proposed pathway for the oxidative functionalization of **Ni-4** with Ar_2I^+



The results in Table 2 implicate radical intermediates in the oxidation of **Ni-2** with diaryliodonium oxidants, and a pathway consistent with these data is outlined in Scheme 6. It begins with a single electron transfer (SET) from the Ni^{II} starting material **Ni-2** to the diaryliodonium reagent, generating the Ni^{III} complex **Ni-5** along with Ar_2I^+ (step *i*). This electron transfer is likely facilitated by ion pairing between the anionic Ni^{II} complex and cationic oxidant.²⁹ Next, the Ar_2I^+ product fragments to form ArI and $\text{Ar}^{\bullet}$ (step *ii*), a well-documented and rapid pathway for these species.³⁰ Addition of $\text{Ar}^{\bullet}$ to **Ni-5** then forms Ni^{IV} – Ar complex **Ni-6** (step *iii*). Importantly, our group has previously shown the feasibility of $\text{Ar}^{\bullet}$ addition to Ni^{III} complexes in other contexts.¹² Finally, C(sp^2)–C(sp^2) bond-forming reductive elimination from **Ni-6** releases product **3**.^{10a}

This pathway diverges in the presence of solvents with relatively weak C–H bonds (e.g., toluene). Here, the $\text{Ar}^{\bullet}$ formed in step *ii* competitively abstracts a benzylic hydrogen atom from toluene, producing ArH along with $\text{PhCH}_2^{\bullet}$ (step *v*). The benzyl radical then adds to Ni^{III} , generating benzyl Ni^{IV} intermediate **Ni-7** (step *vi*), followed by reductive elimination to release **5**. Notably, related $\text{Ni}^{\text{II/III/IV}}$ pathways have been proposed for AQ-directed C–H alkylation reactions with alkyl iodides as oxidants¹⁴ but have rarely been invoked with aryl electrophiles.¹³

To experimentally evaluate the viability of this pathway, we studied the reactions of **Ni-5** (isolated independently via the procedure in Scheme 5) with $\text{Ar}^{\bullet}$ in acetone, MeCN, and toluene.³¹ For these studies, $\text{Ar}^{\bullet}$ was generated *in situ* by the treatment of ArN_2BF_4 (**7**) with ferrocene (Fc).¹² Controls show that **Ni-5** does not react with either ArN_2BF_4 or Fc independently. However, combining **7**, Fc, and **Ni-5** in acetone- d_6 at 25 °C yielded **3** in 19% yield (Table 2, entry 1). The analogous reaction between **Ni-5** and **7**/Fc was next conducted in MeCN and in toluene. This afforded **4** and **5** as the major products in 41% and 38% yield, respectively (Table 2, entries 2 and 3). Only 8% of the C–H arylation product was observed in MeCN, while none was detected in toluene.

Table 2. Reactivity of **Ni-5** with $\text{Ar}^{\bullet}$ in different solvents

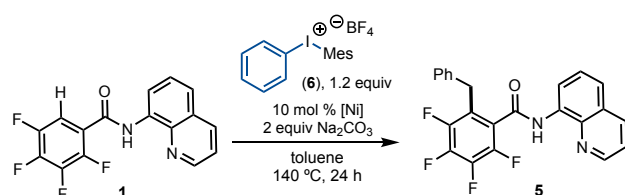
entry	solvent	%3	%4	%5
1	acetone	19	---	---
2	MeCN	8	41	---
3	toluene	<1	---	38

Overall, these experiments support the viability of steps *iii*–*vii* of the pathway in Scheme 6. Furthermore, the results in Table 2 provide a framework for leveraging hydrogen atom transfer with $\text{Ar}^{\bullet}$ to install different functional groups in AQ-directed C–H functionalization reactions. As mentioned above, this $\text{Ni}^{\text{II/III/IV}}$ pathway is unusual for AQ-directed C–H functionalization with aryl electrophiles, which are generally proposed to participate in two-electron oxidative addition at Ni^{II} . For

instance, a 2017 computational paper by Liu and coworkers³² suggested that radical oxidation pathways are disfavored in cases where unstable Ar[•] would be formed. While this is likely the case in reactions of aryl halides (which are not strong one-electron oxidants),³³ the current work shows that aryl radicals are viable intermediates when using an oxidant and Ni^{II} precursor that are electronically well-matched for SET.

Translation to catalysis. A final set of studies focused on translating insights from these stoichiometric organometallic experiments to the catalytic AQ-directed C(sp²)-H functionalization of substrate **1**. Based on the results in Schemes 5 and 6, we hypothesized that conducting the Ni-catalyzed reaction of **1** with a diaryliodonium salt in toluene would enable oxidative coupling with solvent to afford benzylated product **5**.³⁴ This catalytic transformation was evaluated using 10 mol % of different Ni^{II} catalysts using with **6** as the oxidant, and a carbonate salt as the base. Iodonium **6** was selected because it afforded the highest yield of and chemoselectivity for the benzylation product in Table 1 (compare entries 3 to 4). Carbonate bases were selected based on the results in Schemes 2-4 showing that these strong bases favor speciation of Ni as **Ni-2**, which is most reactive towards SET with the oxidant.

Table 3.³⁵ Ni-catalyzed reaction of **1** with **6** in toluene to form benzylated product **5**



entry	[Ni]	base	% 5
1	Ni(OTf) ₂	Na ₂ CO ₃	41
2	Ni(OTf) ₂	NaHCO ₃	45
3	Ni-2	Na ₂ CO ₃	55
4	Ni-3	Na ₂ CO ₃	45
5	Ni(OTf) ₂	NaOAc	3
6	Ni-2	NaOAc	23
7	Ni-3	NaOAc	14

As shown in Table 3, the combination of 10 mol % Ni(OTf)₂,¹⁹ 1 equiv of **1**, 1.2 equiv of **6**, and 2 equiv of Na₂CO₃ afforded the benzylated product in 41% yield (entry 1).³⁶ Importantly, this catalytic reaction (and all the rest of the examples in Table 3) was highly chemoselective, and <1% of the corresponding arylated product **3-Ph** was detected. **Ni-2** and **Ni-3** were also competent catalysts with Na₂CO₃ as a base, affording

5 in 55% and 45% yield, respectively. This latter result was initially surprising based in the low reactivity of **Ni-3** with **2** at room temperature.²⁷ However, ¹⁹F NMR studies show that **Ni-3** partially converts to **Ni-2** upon the addition of an excess of carbonate base (see SI, p. S25), which is likely responsible for much of the observed catalytic activity. Consistent with this proposal, the use of NaOAc as a base (which favors speciation as **Ni-3**) led to significantly lower reactivity with all three catalysts (entries 6-8).

CONCLUSION

In summary, this report leverages fluoroaryl substrate **1** to detect and study key intermediates in aminoquinoline-directed C-H activation and functionalization at Ni. A series of Ni^{II}, Ni^{III}, and Ni^{IV} intermediates are isolated or implicated in the reaction of **1** with Ni(OAc)₂ and subsequent functionalization of the cyclometalated Ni products with diaryliodonium oxidants. These studies implicate a Ni^{II/III/IV} pathway involving Ar[•] intermediates for this transformation. The Ar[•] can react to form arylated products or with solvent (acetonitrile, toluene) to form solvent functionalization products. Ultimately, insights from these stoichiometric organometallic reactions were leveraged to achieve a Ni-catalyzed C-H benzylation reaction using diaryliodonium salts in toluene. We anticipate that further study of organometallic Ni intermediates derived from **1** will provide deeper insights into the mechanisms of established Ni-catalyzed transformations as well as serve as a platform for new reaction discovery and optimization.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Procedure details and characterization data (PDF)

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- ²⁰ The carbonate base was not necessary to promote the formation of **Ni-1** but did lead to a significantly higher yield of this complex. For example, under the conditions in Scheme 2A but without added Cs₂CO₃, **Ni-1** was formed in 27% yield after 48 h.
- ²¹ Ligand **1** is poorly soluble in MeCN, so the conversion/mass balance could not be established via ¹⁹F NMR spectroscopic analysis of the crude reaction mixture.
- ²² This structure is very similar to that isolated from the reaction of **1** with Cu(OAc)₂ and Cs₂CO₃ [ref. 15].

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TOC Graphic:

