

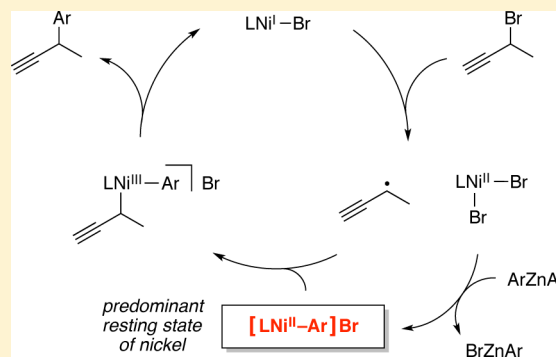
Nickel-Catalyzed Negishi Arylations of Propargylic Bromides: A Mechanistic Investigation

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S Supporting Information

ABSTRACT: Although nickel-catalyzed stereoconvergent couplings of racemic alkyl electrophiles are emerging as a powerful tool in organic chemistry, to date there have been no systematic mechanistic studies of such processes. Herein, we examine the pathway for enantioselective Negishi arylations of secondary propargylic bromides, and we provide evidence for an unanticipated radical chain pathway wherein oxidative addition of the C–Br bond occurs through a bimetallic mechanism. In particular, we have crystallographically characterized a diamagnetic arylnickel(II) complex, $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]\text{BAr}^{\text{F}}_4$, and furnished support for $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$ being the predominant nickel-containing species formed under the catalyzed conditions as well as a key player in the cross-coupling mechanism. On the other hand, our observations do not require a role for an organonickel(I) intermediate (e.g., $(i\text{-Pr-pybox})\text{Ni}^{\text{I}}\text{Ph}$), which has previously been suggested to be an intermediate in nickel-catalyzed cross-couplings, oxidatively adding alkyl electrophiles through a monometallic pathway.

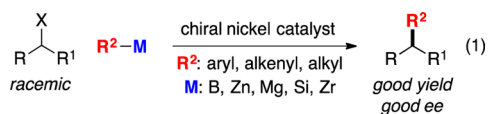


INTRODUCTION

During the past few decades, tremendous progress has been described in the development of transition-metal-catalyzed cross-coupling reactions.¹ Palladium-catalyzed processes have been the primary focus of interest, mechanistic studies of which have established the feasibility of an array of catalytic cycles, the predominant ones involving palladium(0)/(II).

Complexes of nickel, a congener of palladium, have been less thoroughly investigated as catalysts for cross-coupling reactions, although this situation has begun to change in recent years.^{1,2} Correspondingly, the mechanisms of nickel-catalyzed couplings are also less well-studied, and no single pathway has yet been shown to be especially common.³

During the past decade, we have pursued the development of a wide range of nickel-catalyzed cross-couplings of alkyl electrophiles, including stereoconvergent reactions of racemic activated and unactivated alkyl halides (eq 1).^{4,5} We have postulated that



cleavage of the C–X bond may occur via a radical pathway,^{6,7} and Vici⁸ and Phillips⁹ have reported experimental and computational studies, respectively, that are consistent with certain Negishi couplings of unactivated alkyl electrophiles proceeding through a transmetalation-first pathway (Figure 1). Recent mechanistic investigations by Weix (reductive coupling)¹⁰ and Hu (Kumada cross-coupling)¹¹ of nonasymmetric nickel-

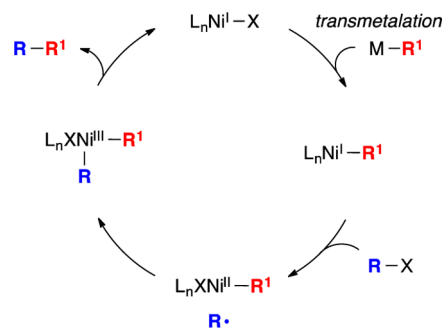


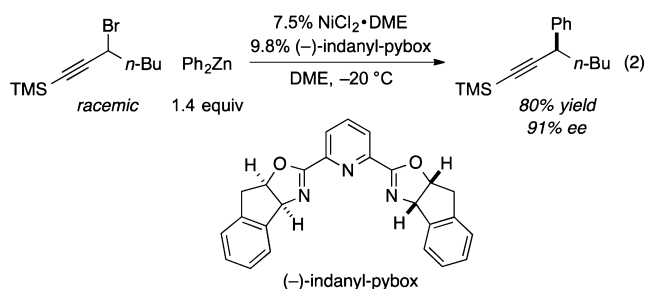
Figure 1. Outline of one of the possible mechanisms for nickel-catalyzed cross-coupling of unactivated alkyl electrophiles: transmetalation before oxidative addition.

catalyzed couplings of unactivated alkyl electrophiles have provided support for diverse reaction pathways.¹²

To the best of our knowledge, to date there have been no systematic experimental investigations of the mechanism of nickel catalysts that have been employed in enantioselective cross-couplings of alkyl electrophiles, although there has been one computational study.¹³ In this report, we describe our examination of the pathway for a stereoconvergent Negishi arylation of racemic propargylic halides that we reported in 2008, catalyzed by nickel/pybox (eq 2).¹⁴

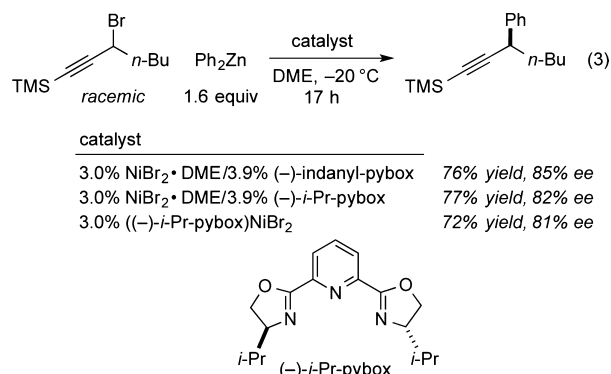
Received: August 24, 2014

Published: November 17, 2014

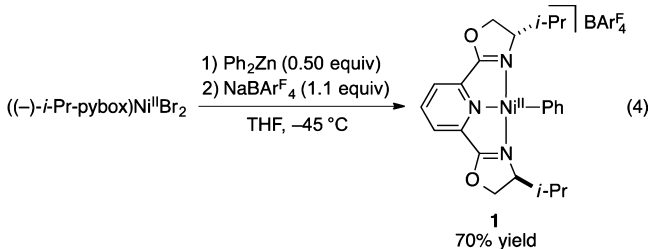


RESULTS AND DISCUSSION

As part of our initial investigation, we attempted to synthesize and structurally characterize a (pybox)Ni^{II}Ph complex, a possible intermediate in the catalytic cycle for cross-couplings of unactivated, as well as potentially for activated, electrophiles (e.g., Figure 1).³ Unfortunately, our efforts with indanyl-pybox as the ligand were unsuccessful. However, by instead employing *i*-Pr-pybox, which furnishes similar yield and ee in a Negishi arylation of a propargylic bromide (eq 3), we were able to achieve our objective.¹⁵



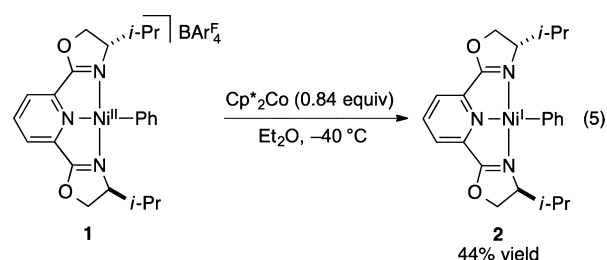
Thus, treatment of ((-)-*i*-Pr-pybox)Ni^{II}Br₂ with Ph₂Zn and then NaBAR₄^F (BAR₄^F = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) provides [((-)-*i*-Pr-pybox)Ni^{II}Ph]BAR₄^F (**1**) in good yield (70%; eq 4). A single-crystal X-ray diffraction study



established that this nickel complex adopts a square-planar geometry, consistent with its formulation as a diamagnetic d⁸ Ni(II) complex (Figure 2, left). Electrochemical analysis of complex **1** reveals two reversible reduction waves, centered at -1.37 and -2.36 V versus Fc/Fc⁺ (0.10 M TBAPF₆ in THF).

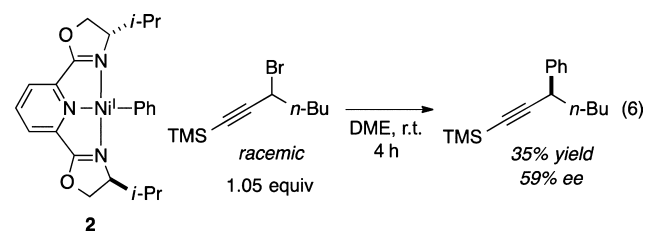
Reduction of [((-)-*i*-Pr-pybox)Ni^{II}Ph]BAR₄^F (**1**) with Cp*₂Co (-1.94 V versus Fc/Fc⁺)¹⁶ provides the desired phenylnickel(I) complex, ((-)-*i*-Pr-pybox)Ni^IPh (**2**; eq 5). The solid-state structure of nickel(I) complex **2** is very similar to that of the nickel(II) cation in [((-)-*i*-Pr-pybox)Ni^{II}Ph]BAR₄^F (**1**; Figure 2).

The EPR spectrum of ((-)-*i*-Pr-pybox)Ni^IPh (**2**) displays an approximately axial signal centered at *g* = 2.00 that shows

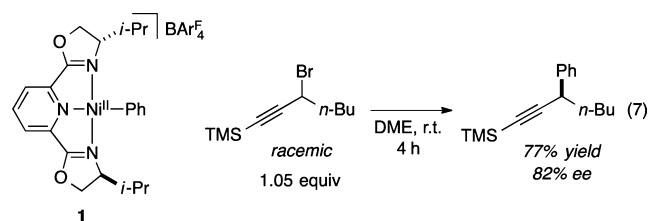


coupling to a single ¹⁴N atom in one *g* component (Figure 3). This is consistent with a largely ligand-centered radical, i.e., a nickel(II) center bound to a singly reduced ligand, a description previously put forward by Vicic to describe the electronic structure of (terpyridine)Ni^IMe.^{8,17,18}

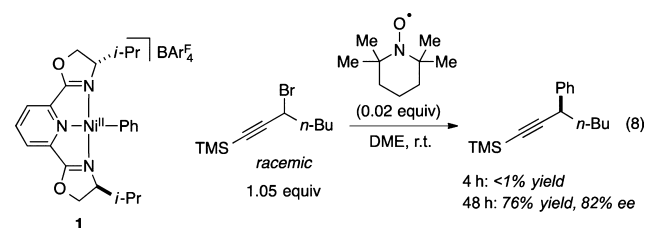
In view of previous reports implicating an organonickel(I) complex as a potential intermediate in cross-coupling reactions of alkyl electrophiles (e.g., Figure 1),³ we examined the reactivity of ((-)-*i*-Pr-pybox)Ni^IPh (**2**) toward a propargylic bromide. Carbon-carbon bond formation does indeed occur, although in modest yield and enantioselectivity (eq 6).



Under the same conditions, the phenylnickel(II) complex, [((-)-*i*-Pr-pybox)Ni^{II}Ph]BAR₄^F (**1**), reacts with the propargylic bromide to furnish the coupling product in substantially higher yield and ee than in the case of the phenylnickel(I) complex (**2**) (eq 7 versus eq 6). The results for the phenylnickel(II) complex are more consistent with the efficiency and the enantioselectivity of the catalyzed process (eq 3).¹⁹



The reaction of the phenylnickel(II) complex (**1**) with the propargylic bromide proceeds at the same rate in the dark as in ambient light, and it is inhibited by a substoichiometric amount of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy). Thus, in the presence of 0.02 equiv of TEMPO, essentially no reaction between the phenylnickel(II) complex and the propargylic bromide is observed after 4 h at room temperature (eq 8), in



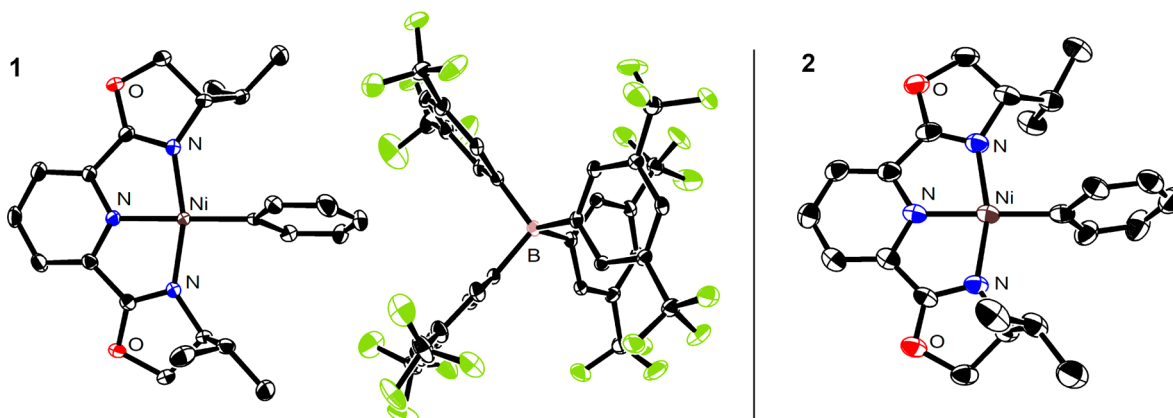


Figure 2. X-ray crystal structures of $[(\text{--})\text{-}i\text{-Pr-pybox}]\text{Ni}^{\text{II}}\text{Ph}]\text{BAR}^{\text{F}}_4$ (**1**; left; Ni–pyridine 1.898(2) Å; Ni–Ph 1.881(3) Å) and $(\text{--})\text{-}i\text{-Pr-pybox}]\text{Ni}^{\text{I}}\text{Ph}$ (**2**; right; Ni–pyridine 1.871(3) Å; Ni–Ph 1.896(3) Å) (ellipsoids are shown at 50% probability, and hydrogens, disordered fluorine atoms, and additional molecules in the asymmetric unit are omitted for clarity).

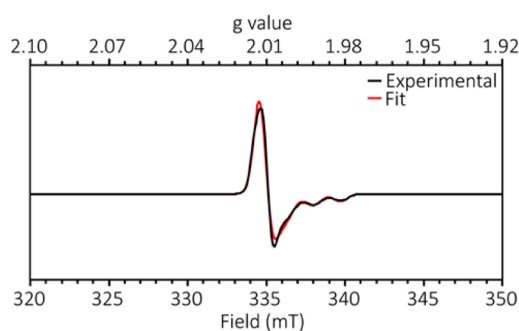


Figure 3. EPR spectrum of $(\text{--})\text{-}i\text{-Pr-pybox}]\text{Ni}^{\text{I}}\text{Ph}$ (**2**; black) and corresponding fit (red). Fit parameters: $g_1 = 2.0067$, $g_2 = 2.0075$, $g_3 = 1.9889$, ^{14}N coupling (MHz) = 0.0205, 0.0124, 47.2047, line width = 0.9929. X-band EPR spectra were collected at 77 K in a toluene glass at $\nu = 9.411$ GHz at 2 mW power and a modulation amplitude of 2 G.

contrast to the TEMPO-free reaction (eq 7); however, after 48 h, the coupling has proceeded to completion, demonstrating a TEMPO-induced induction period (eq 8). Analysis of the reaction mixture by ESI+MS reveals a signal with m/z of 324.27, the expected mass of the product of capture of the propargylic radical by TEMPO.²⁰ These data are consistent with inhibition by TEMPO of a radical chain process that is subject to slow, ongoing initiation, with product formation commencing only after the TEMPO has been consumed (TEMPO reacts with alkyl

radicals with rate constants of $\sim 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ to effect chain termination).^{21,22}

We postulate that an odd-electron nickel(I) complex may be generated slowly at room temperature and serves as an initiator for carbon–carbon bond formation through a radical chain process that includes an overall bimetallic oxidative addition (Figure 4). Accordingly, whereas there is essentially no reaction between phenylnickel(II) complex (**1**) and the propargylic bromide after 4 h in the presence of TEMPO, upon the addition of $(\text{+})\text{-}i\text{-Pr-pybox}]\text{Ni}^{\text{I}}\text{Br}$ (**3**; 0.20 equiv), carbon–carbon bond formation initiates and proceeds to completion within 0.5 h (83% yield, 82% ee; eq 9). Similarly, in the absence of TEMPO, the addition of $(i\text{-Pr-pybox}]\text{Ni}^{\text{I}}\text{Br}$ to a solution of phenylnickel(II) complex (**1**) and the propargylic bromide leads to an enhanced rate of carbon–carbon bond formation.²³

When the nickel(I) complex (**3**) that is employed as the initiator bears the opposite enantiomer of the pybox ligand as compared with the phenylnickel(II) adduct (**1**), there is no change in the ee of the coupling product (eq 9), indicating that the enantioselectivity of the carbon–carbon bond-forming process is determined by the configuration of the pybox ligand bound to the phenylnickel(II) complex.²⁴ This result is consistent with the propagation sequence outlined in Figure 4.

Treatment of a solution of $(i\text{-Pr-pybox}]\text{Ni}^{\text{I}}\text{Br}$ (**3**) with the propargylic bromide (1.0 equiv) leads to immediate bleaching (violet \rightarrow colorless) and the formation of $(i\text{-Pr-pybox}]\text{Ni}^{\text{II}}\text{Br}_2$ (identified by UV–vis spectroscopy) and a mixture of racemic

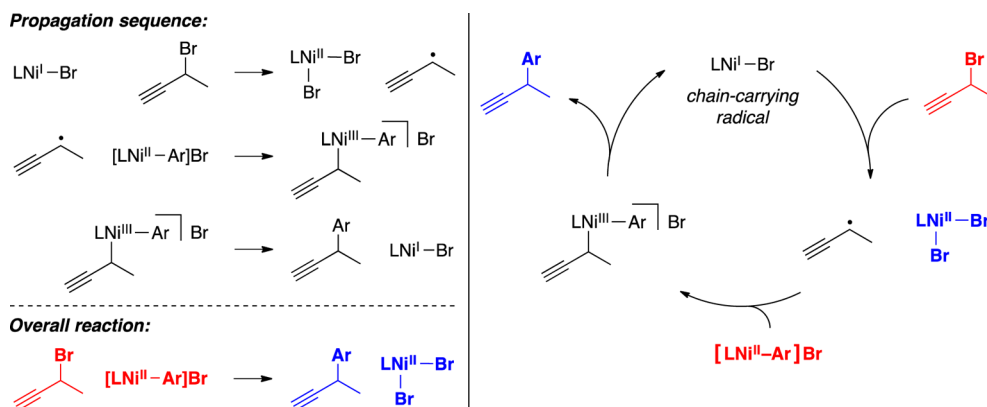
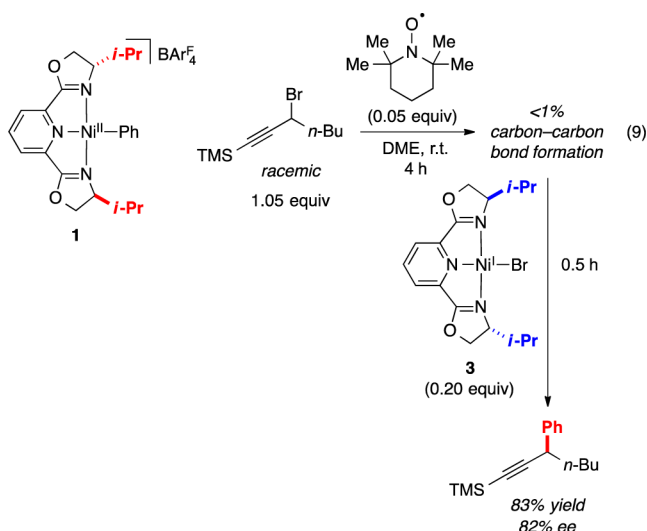


Figure 4. Two representations of a possible radical chain mechanism for the arylation of a propargylic bromide by an arylnickel(II) complex ($L = \text{pybox}$).



and achiral products derived from homocoupling of the propargylic radical, observations consistent with the first step of the suggested propagation sequence (Figure 4). Analysis of this reaction by UV–vis spectroscopy indicates that the second-order rate constant for the halogen-atom abstraction is $>10^4 \text{ M}^{-1} \text{ s}^{-1}$ in DME at -20°C . No intermediates are observed by UV–vis or by EPR spectroscopy.

We hypothesize that, in the presence of an arynickel(II) complex, e.g., $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]\text{Br}$,²⁵ the propargylic radical is captured to form $[(i\text{-Pr-pybox})\text{Ni}^{\text{III}}\text{Ph}(\text{propargyl})]\text{Br}$, which can reductively eliminate to afford the coupling product and the chain-carrying $(i\text{-Pr-pybox})\text{Ni}^{\text{I}}\text{Br}$ radical (Figure 4). When the stoichiometric carbon–carbon bond-forming process depicted in eq 7 is monitored by EPR spectroscopy, essentially no signal is observed, suggesting that the postulated nickel(I) and nickel(III) intermediates in the chain-carrying steps are not present in significant quantities. Consistent with that conclusion, when the coupling illustrated in Figure 5 is monitored by ^{19}F NMR spectroscopy, the consumption of the arynickel(II) starting material correlates directly with the formation of the coupling product, and no intermediates are observed.

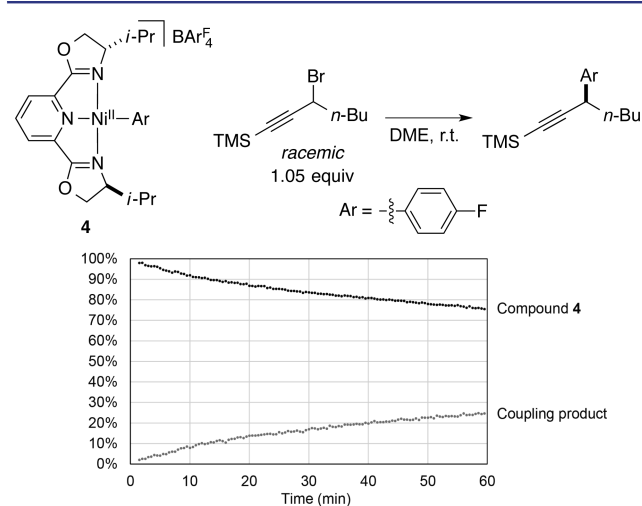


Figure 5. Progress of a stoichiometric arylation of a propargylic bromide: No evidence for the accumulation of an intermediate (monitored by ^{19}F NMR spectroscopy).

On the basis of these observations for stoichiometric coupling reactions of arynickel complexes with a propargylic bromide, we propose a pathway for nickel/pybox-catalyzed Negishi arylations (Figure 6; through the use of UV–vis spectroscopy, we have

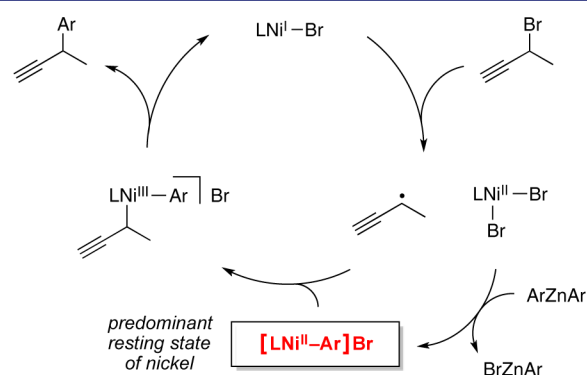


Figure 6. A possible catalytic cycle for the nickel/pybox-catalyzed Negishi arylation of a propargylic bromide. For the sake of simplicity, all elementary steps are illustrated as being irreversible.

established that $(i\text{-Pr-pybox})\text{Ni}^{\text{I}}\text{Br}$ reacts much more rapidly with a propargylic bromide than with Ph_2Zn). The mechanism builds upon the radical chain process depicted in Figure 4, but, rather than employing $[\text{LNi}^{\text{II}}\text{Ar}]\text{Br}$ as a preformed stoichiometric arylating agent, $[\text{LNi}^{\text{II}}\text{Ar}]\text{Br}$ is produced continuously in situ through the reaction of ArZnAr with $\text{LNi}^{\text{I}}\text{Br}_2$, which is a product of the chain reaction.²⁶

With the aid of UV–vis spectroscopy and ESI mass spectrometry, we have obtained data that support the viability of this key process to regenerate $[\text{LNi}^{\text{II}}\text{Ar}]^+$. Thus, reaction of $(i\text{-Pr-pybox})\text{Ni}^{\text{I}}\text{Br}_2$ with Ph_2Zn leads to a UV–vis spectrum that is consistent with independently synthesized $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$ (with BAR_4^{F} as the counterion; Figure 7) and to a mass spectrum in which the major component has $m/z = 436.1$, again consistent with $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$ (positive-ion mode; Figure 8).

In order for the proposed catalyzed pathway (Figure 6) to lead to efficient cross-coupling, during the reaction the concentration of $[\text{LNi}^{\text{II}}\text{Ar}]\text{Br}$ should be substantially higher than that of the

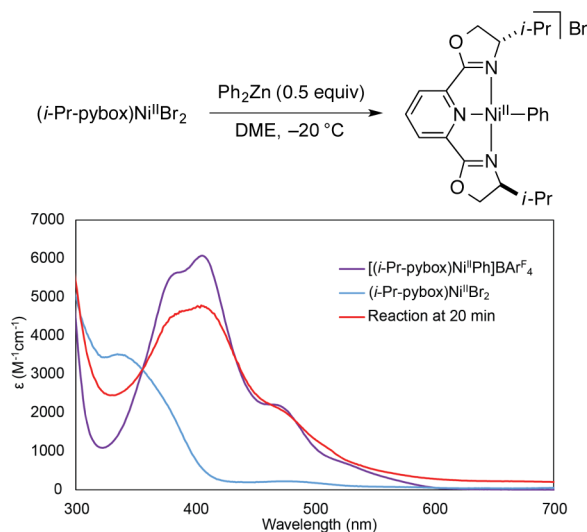


Figure 7. Analysis via UV–vis spectroscopy of the reaction of $(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Br}_2$ with Ph_2Zn to form $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$.

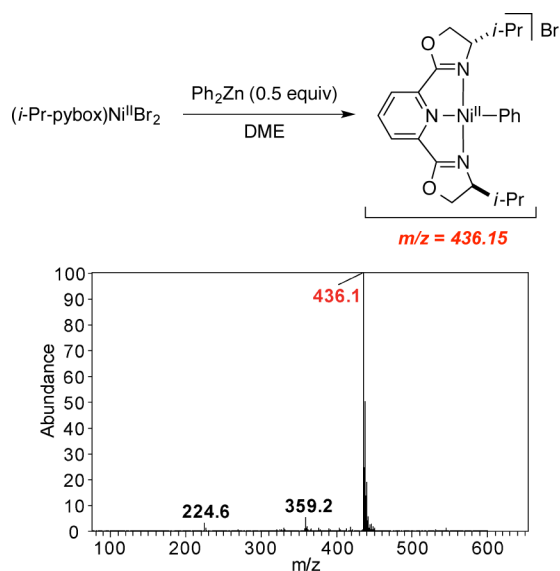


Figure 8. Analysis via ESI-MS (positive-ion mode) of the reaction of $(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Br}_2$ with Ph_2Zn to form $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$.

propargylic radical; otherwise, homocoupling of the propargylic radical could occur to a significant extent. To gain insight into the identity of the resting state of nickel during a coupling process, we have employed ^{19}F NMR spectroscopy to investigate the Negishi cross-coupling depicted in Figure 9. With the aid of an

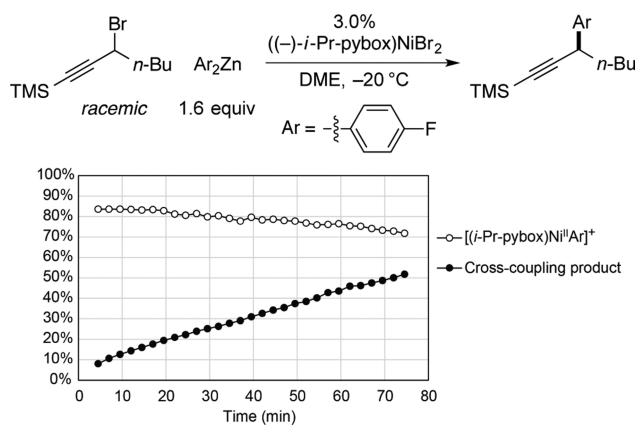


Figure 9. Analysis via ^{19}F NMR spectroscopy of a catalyzed Negishi reaction in progress: (○) $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ar}]^+$ as a percentage of all nickel that is present; (●) yield of cross-coupling product.

internal standard, we have determined that, within 4 min, >80% of the nickel that was originally present has been transformed into $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}(4\text{-fluorophenyl})]^+$ (−121 ppm; as expected, the intensity of this signal is dependent on the loading of nickel). The structural assignment is based on comparison with the ^{19}F NMR chemical shift of independently prepared $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}(4\text{-fluorophenyl})]\text{BAR}^{\text{F}_4}$ (−120 ppm).

Similarly, the results of an investigation that employed UV–vis spectroscopy to monitor a catalyzed Negishi arylation are consistent with the rapid formation of $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$ (Figure 10). Furthermore, when this catalytic process was analyzed by EPR spectroscopy, it was found to be essentially EPR silent, which is consistent with most of the nickel being in the form of $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$.²⁷

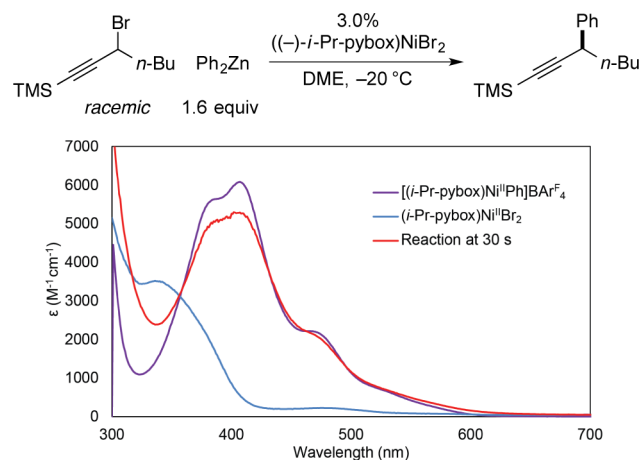


Figure 10. Analysis via UV–vis spectroscopy of a catalyzed Negishi reaction in progress: blue: $(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Br}_2$; red: cross-coupling reaction in progress; purple: $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]\text{BAR}^{\text{F}_4}$.

In a preliminary study, when the propargylic bromide included an olefin suitably positioned to trap the putative propargylic radical through a 5-exo-trig cyclization, we observed more acyclic product at higher catalyst loading, consistent with escape of the radical from the solvent cage and coupling with a different nickel complex to complete an overall bimetallic pathway for oxidative addition. We reported a similar trend in our recent report on catalytic asymmetric Negishi arylations of α -bromosulfonamides.^{4c}

Finally, we have examined the impact of TEMPO (4.5%) on a nickel-catalyzed Negishi arylation (3.0% catalyst loading; Figure 11). During the first ~60 min, essentially no carbon–carbon

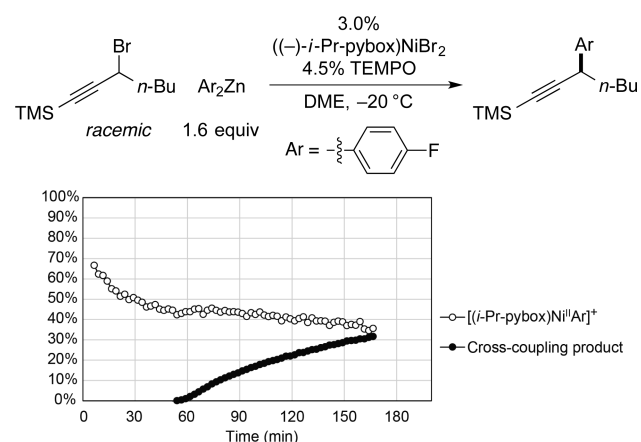


Figure 11. Analysis via ^{19}F NMR spectroscopy of a catalyzed Negishi reaction in progress, in the presence of TEMPO: (○) $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ar}]^+$ as a percentage of all nickel that is present; (●) yield of cross-coupling product.

bond formation is observed, and some of the $[(i\text{-Pr-pybox})\text{Ni}^{\text{II}}\text{Ph}]^+$ is consumed (but less than the amount of added TEMPO). Then, presumably due to depletion of the TEMPO, the cross-coupling proceeds at a substantial rate.

CONCLUSIONS

This study represents the first systematic mechanistic investigation of a nickel-based catalyst that has been employed in stereoconvergent cross-couplings of racemic alkyl electrophiles. Specifically, we have applied a wide array of tools to elucidate the

pathway for the enantioselective Negishi arylation of propargylic bromides, examining both stoichiometric and catalyzed processes. Our observations are consistent with a radical chain mechanism, wherein the C–Br bond is cleaved during an overall bimetallic oxidative addition that transiently generates a propargylic radical (which can account for the observed stereoconvergence), as well as a series of nickel(I)/(II)/(III) intermediates. Independent synthesis of an arylnickel(II) complex, combined with spectroscopic analysis of stoichiometric reactions and of cross-couplings in progress, supports the postulate that it is the predominant resting state of nickel during a catalyzed process and that it is the species that couples with the propargylic radical. Our pathway differs from those that have been proposed in recent studies of other nickel-catalyzed cross-couplings, serving as another reminder that the use of different ligands, coupling partners, and conditions can be expected to result in substantial divergences in reaction mechanism. Future investigations will explore similarities and differences between this Negishi arylation of propargylic bromides and other nickel-catalyzed processes developed in our laboratory.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Institute of General Medical Sciences of the National Institutes of Health (R01-GM62871 to G.C.F. and Ruth L. Kirschstein National Research Service Award F32-GM105295 to N.D.S.). We thank Trixia M. Buscagan (preliminary results), Dr. Ivory Hills (preliminary results), Dr. Angel J. Di Bilio (EPR), Lawrence M. Henling (X-ray crystallography), Prof. Jonas C. Peters (discussions and equipment), Dr. Christopher Uyeda (electrochemistry), and Dr. David VanderVelde (NMR). We acknowledge the Gordon and Betty Moore Foundation, the Beckman Institute, and the Sanofi–Aventis Bioengineering Research Program at Caltech for their support of the Molecular Observatory at Caltech. The SSRL is supported by the Department of Energy's Office of Biological and Environmental Research as well as by the National Institutes of Health.

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(18) For leading references on the use of redox-active ligands in catalysis, see: (a) Luca, O. R.; Crabtree, R. H. *Chem. Soc. Rev.* **2013**, *42*, 1440–1459. (b) Praneeth, V. K. K.; Ringenberg, M. R.; Ward, T. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 10228–10234. (c) Lyaskovskyy, V.; de Bruin, B. *ACS Catal.* **2012**, *2*, 270–279.

(19) When the propargylic bromide was replaced with the corresponding propargylic xanthate, similar yield and ee were observed (eq 7).

(20) Calculated for C₁₉H₃₇NOSi + H⁺: 324.2717, observed: 324.2724.

(21) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151–1176.

(22) Treatment of a solution of (*i*-Pr-pybox)Ni^IBr (3) with TEMPO leads to immediate bleaching (violet → colorless).

(23) (*i*-Pr-pybox)Ni^IBr is not the only species that can function as an initiator. The addition of a one-electron reductant (e.g., Cp*₂Co or tetrakis(dimethylamino)ethylene (TDAE)) can also lead to initiation.

(24) The Ni(I)/(II) oxidation potentials of (*i*-Pr-pybox)Ni^IBr and (*i*-Pr-pybox)Ni^IPh are –1.19 and –1.37 V, respectively, indicating that, at redox equilibrium, (*i*-Pr-pybox)Ni^IBr can reduce [(*i*-Pr-pybox)Ni^{II}Ph]BAr₄^F to only a small extent.

(25) We have crystallographically characterized (*i*-Pr-pybox)Ni^{II}Br₂, which is a high-spin, five-coordinate nickel complex. In contrast, our available data (UV–vis, EPR, and NMR spectroscopy as well as reactivity) are consistent with [(*i*-Pr-pybox)Ni^{II}Ph]Br being a low-spin, four-coordinate nickel complex.

(26) For the sake of simplicity, bromide is depicted as the counteranion, although zincate salts may also be present under the catalyzed reaction conditions.

(27) We have conducted a set of corresponding studies wherein “ArZnEt” (ref 14), rather than Ar₂Zn, was employed as the nucleophile, and we have observed similar behavior.