

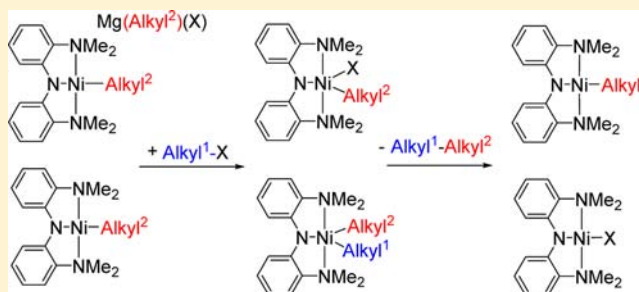
Bimetallic Oxidative Addition Involving Radical Intermediates in Nickel-Catalyzed Alkyl–Alkyl Kumada Coupling Reactions

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S Supporting Information

ABSTRACT: Many nickel-based catalysts have been reported for cross-coupling reactions of nonactivated alkyl halides. The mechanistic understanding of these reactions is still primitive. Here we report a mechanistic study of alkyl–alkyl Kumada coupling catalyzed by a preformed nickel(II) pincer complex ($[(N_2N)Ni-Cl]$). The coupling proceeds through a radical process, involving two nickel centers for the oxidative addition of alkyl halide. The catalysis is second-order in Grignard reagent, first-order in catalyst, and zero-order in alkyl halide. A transient species, $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$, is identified as the key intermediate responsible for the activation of alkyl halide, the formation of which is the turnover-determining step of the catalysis.



1. INTRODUCTION

Cross-coupling reactions of nonactivated alkyl halides are challenging, yet potentially powerful, transformations in organic synthesis.^{1–8} Recent studies show that with judicious choices of metal, ligands, and conditions the normally problematic β -H elimination can be suppressed, and the coupling of nonactivated alkyl halides can be achieved with high yields and selectivity.^{9–20} While significant progress has been made in the development of novel synthetic methods based on these coupling reactions,^{21–34} the mechanistic understanding of such reactions remains limited.^{34–41} In the majority of cases, the active catalysts are unidentified and unknown.⁴² Many reactions are shown to involve radicals, yet how the radicals recombine to give the coupling products is unclear.^{43,44}

Our group recently developed nickel-catalyzed alkyl–alkyl Kumada coupling reactions using preformed nickel pincer complexes as catalysts.^{45–47} The reactions were proposed to occur through the sequence depicted in Figure 1. A nickel(II) halide complex reacts with an alkyl Grignard reagent to make a nickel(II) alkyl complex. The latter reacts with an alkyl halide to give the coupling product and to regenerate the nickel halide complex. This proposed reaction sequence was supported by the following experimental observations: (1) The individual steps of this sequence could be reproduced in stoichiometric reactions. (2) Both the nickel(II) chloride complex ($[(N_2N)Ni-Cl]$, **1**) and the nickel(II) methyl complex ($[(N_2N)Ni-Me]$, **2**) were competent (pre)catalysts. (3) Either a nickel(II) halide complex or a nickel(II) alkyl complex could be isolated in high yields after the completion of the catalysis, depending on the limiting reagent. The activation of alkyl halides was shown to be a radical process, evidenced by experiments using radical-clock substrates and, more unambig-

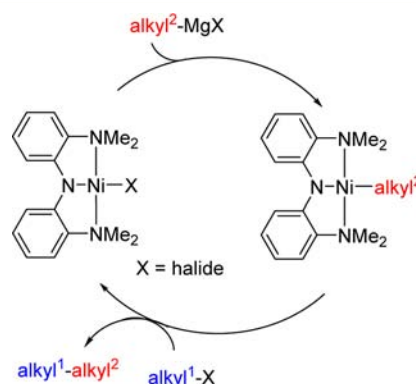


Figure 1. Proposed reaction sequence for alkyl–alkyl Kumada coupling reactions catalyzed by nickel(II) pincer complexes.

uously, by the diastereoselectivity in the coupling of remotely substituted cyclohexyl halides.⁴⁸ The proposed reaction sequence and the individual pieces of mechanistic information, however, do not constitute a concrete catalytic cycle because the following questions remain unaddressed: (1) How are the coupling products formed from the alkyl radicals? (2) Is the proposed reaction sequence kinetically relevant under catalytic conditions? (3) What is the turnover-determining step of the catalysis?

Herein, we describe a mechanistic study of alkyl–alkyl Kumada coupling reactions catalyzed by complex **1**. The study establishes a bimetallic oxidative addition mechanism for the reactions, uncovers a key transient species that is responsible

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for the activation of alkyl halides, and reveals the kinetics of the catalysis.

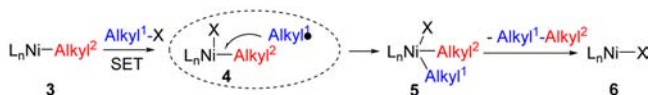
RESULTS AND DISCUSSION

1. From Oxidative Addition to C–C Bond Formation.

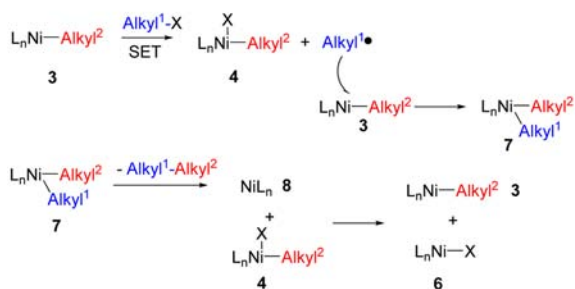
1.1. General Mechanistic Considerations. We first probed the details of the radical process that led to C–C bond formation. Several different radical mechanisms might account for the reaction outcome (Scheme 1). Assuming that a nickel alkyl

Scheme 1. Three Possible Radical Mechanisms for Nickel-Catalyzed Alkyl–Alkyl Kumada Coupling

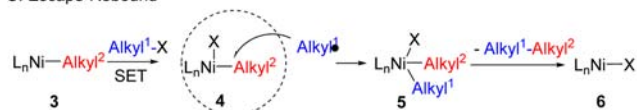
A: Cage-Rebound



B: Bimetallic Oxidative Addition



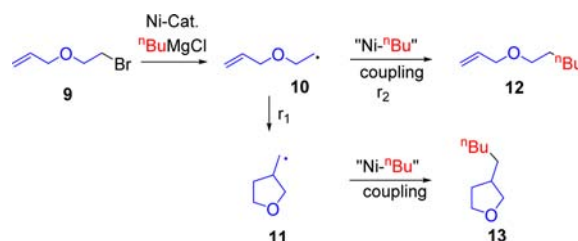
C: Escape-Rebound



species (3) activates alkyl halides, the first step is a single electron transfer (SET) to give an alkyl radical and an oxidized nickel complex (4, nickel(III) or nickel(II) ligand cation). As the reduction potentials of alkyl halides are more negative than the oxidation potential of nickel(II) alkyl complexes, the SET is most likely inner-sphere and takes place through a halide bridge.⁴⁹ In a cage-rebound mechanism (Scheme 1, A), the alkyl radical remains in the solvent cage and recombines with the oxidized nickel complex to give a bis(alkyl) nickel complex (5, formally nickel(IV) but the ligand might be oxidized in place of metal). Reductive elimination from this bis(alkyl) nickel species leads to the coupling product and a nickel(II) halide complex (6). In a bimetallic oxidative addition mechanism (Scheme 1, B),^{50–53} the first SET step is the same. The resulting alkyl radical, however, escapes the solvent cage and recombines with a second molecule of nickel(II) alkyl species to give a formally nickel(III) bis(alkyl) species (7). Reductive elimination from this species leads to the coupling product and a nickel(I) species (8) which is deemed unstable and reacts quickly with 4 to give 3 and 6. A third possibility is the escape-rebound mechanism (Scheme 1, C). Again the first SET step is the same. After the alkyl radical escapes the solvent cage, it might recombine with the oxidized complex (4) to form the bis(alkyl) nickel complex (5). Reductive elimination from this bis(alkyl) nickel species leads to the coupling product and a nickel(II) halide complex (6), just as in the cage-rebound mechanism.

1.2. Exclusion of the Cage-Rebound Mechanism and Confirmation of the Radical Mechanism. To differentiate these three mechanisms, we examined the coupling of substrate 3-(2-bromoethoxy)prop-1-ene (9) with ⁿBuMgCl (Scheme 2).

Scheme 2. Coupling Reactions of a Radical-Clock Substrate



Radical activation of 9 generates the alkyl radical 10, which can undergo a fast intramolecular rearrangement ($k_1 \approx 10^6 \text{ s}^{-1}$) to give another alkyl radical 11.^{54,55} The ensuing reactions, via one of the three mechanisms in Scheme 1, lead to the formation of both linear product 12 and cyclic product 13 (Scheme 2).

The ratio of 12 to 13 can be used as a probe to differentiate the cage-rebound mechanism from the bimetallic oxidative addition and escape-rebound mechanisms.^{54,55} This ratio is a function of r_1/r_2 ; $r_1 = k_1[10]$. In the cage-rebound mechanism, $r_2 = k_2[10]$, as the rate is zero-order with respect to species 4. The ratio r_1/r_2 is then a constant, independent of the catalyst concentration. In the bimetallic mechanism, $r_2 = k_2[10][3]$; in the escape-rebound mechanism, $r_2 = k_2[10][4]$. The ratio r_1/r_2 is then linearly dependent on the concentration of the catalyst.

Figure 2 shows the dependence of the ratio of 12 to 13 on the loading of catalyst under otherwise identical conditions. To

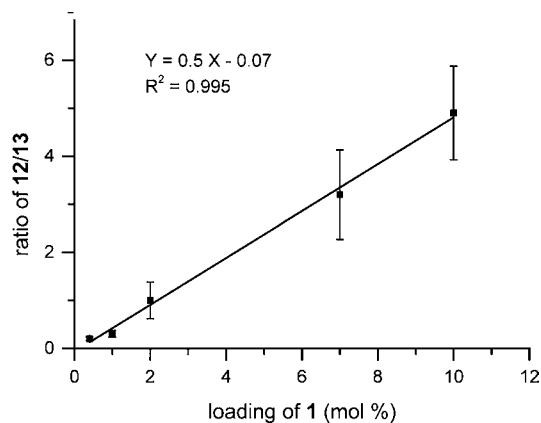


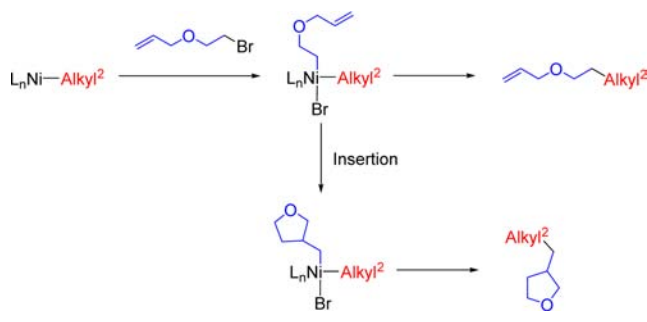
Figure 2. Ratio of 12 to 13 as a function of the loading of catalyst (1) in the coupling reaction of 9 and ⁿBuMgCl. At each loading, four independent trials were conducted to obtain an averaged ratio.

ensure a high yield in this coupling reaction, the Grignard reagent was added slowly. The ratio is first-order in the concentration of the catalyst. The ratio of 12/13 might be influenced by the concentration of Grignard reagent. Thus, this ratio was also determined for reactions in which the Grignard reagent was added at once in the beginning of the reaction.⁵⁶ The coupling yields were lower; however, the same linear dependence of 12/13 on the loading of catalyst (1) was observed (Figure S1, Supporting Information). These results exclude the cage-rebound mechanism.

The coupling of **9** with $^n\text{BuMgCl}$ was also conducted in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).⁵⁶ TEMPO- ^nBu was identified as the major product, from the reaction of TEMPO with $[(\text{N}_2\text{N})\text{Ni}-^n\text{Bu}]$. No trapping of alkyl radical by TEMPO is observed, either because the trapping of the alkyl radical by the nickel catalyst is much faster or because the reaction of TEMPO with $[(\text{N}_2\text{N})\text{Ni}-^n\text{Bu}]$ is much faster than that with the alkyl radical, or both.

The preceding considerations are only valid if **12** and **13** are indeed produced from radical reactions as suggested in Scheme 2. While compound **9** is widely used as a radical probe, it can also engage in nonradical reactions to give the same products. For example, nucleophilic substitution of alkyl bromide followed by migratory insertion gives a nickel alkyl complex with a hydrofuran side chain, which, after reductive elimination, gives a ring-closed product (Scheme 3). We have several pieces

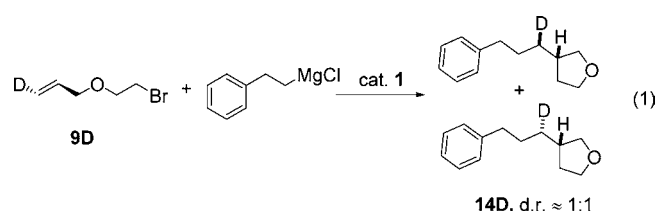
Scheme 3. Nonradical Reaction Sequences That Lead To Ring-Open and Ring-Closed Coupling Products



of circumstantial evidence against this concerted reaction mechanism: (1) The concerted mechanism predicts a zero-order dependence of the ratio of **12** to **13** on the catalyst concentration, whereas a first-order was observed. (2) The diastereoselectivity in alkyl-alkyl coupling reactions of disubstituted cyclohexyl halides confirmed that the coupling reactions occurred via radical intermediates.⁴⁸ (3) We showed earlier that these nickel(II) alkyl complexes do not insert into olefins; rather, olefin exchange reactions took place via β -H elimination.⁵⁷ To further confirm that coupling reactions of compound **9** occur by a radical mechanism as suggested in Scheme 2, we analyzed the reaction outcome of **9D** (the E isomer), where a deuterium is placed at the terminal olefinic position. If a radical mechanism is operating, the insertion of a radical into the exoposition of the olefin gives both R and S stereoisomers; the following coupling steps at the terminal position also give both R and S isomers (Scheme 4, A). Overall, two diastereoisomers are produced. If a concerted mechanism is operating, assuming a syn-insertion and reductive elimination, only one diastereoisomer is produced (Scheme 4, B). Indeed, this method was recently successfully applied to establish a radical mechanism in the copper-catalyzed Ullmann reaction.⁵⁸

The main experimental difficulty encountered was the differentiation of diastereomeric coupling products. Initially we coupled **9D** with $^n\text{BuMgCl}$. The ^2H -NMR spectrum of the product shows only a broad peak and is inconclusive.⁵⁶ The ^{13}C NMR spectrum shows splitting patterns consistent with the presence of two diastereomers; however, the splitting is small and vague (Figure S46, Supporting Information). We then coupled **9D** with phenylethyl-MgCl, hoping that the more rigid phenylethyl group would lead to a bigger differentiation of the

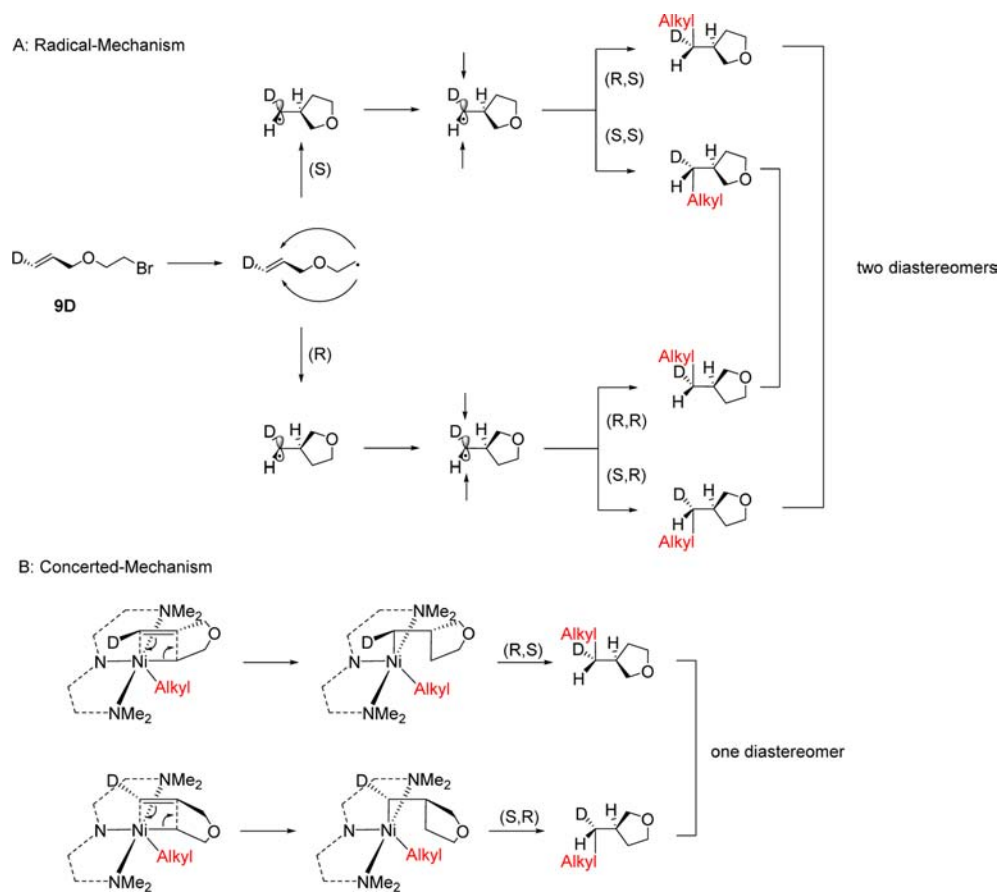
diastereomeric coupling products by ^1H and ^{13}C NMR spectroscopy. This turned out to be successful. The ^1H and ^{13}C NMR spectra of the coupling product, 3-(3-phenylpropyl)-tetrahydrofuran (**14**), were assigned with the help of HMQC and COSY (Figure S43 and S44, Supporting Information).⁵⁶ In both ^1H and ^{13}C NMR spectra, splitting of peaks due to two diastereomers was observed (Figure 3 and Figures S40 and S42, Supporting Information). Thus, the coupling of **9D** with phenylethyl-MgCl gives **14D** with a d.r. of about 1:1, confirming the radical mechanism for this reaction (eq 1).



1.3. Confirmation of the Bimetallic Oxidative Addition Mechanism. The outcome of coupling reactions using the radical-probe substrate **9** excludes the cage-rebound mechanism; it cannot be used to distinguish, however, the bimetallic oxidative addition and the escape-rebound mechanisms (Scheme 1, B and C). In the latter two mechanisms, the nickel species with which the escaped alkyl radical recombines are different. In the bimetallic mechanism, the alkyl radical recombines with the nickel(II) alkyl species (**3**); in the escape-rebound mechanism, the alkyl radical recombines with the oxidized nickel species (**4**). Because of the so-called persistent radical effect,^{59–62} the escape-rebound mechanism can give a high yield in cross-coupling reactions of two radicals, as long as there is a significant difference in the reactivity of the two radicals. In the current case, one can imagine that a nickel-based metalloradical is more stable than an alkyl radical. Therefore, the high efficiency in cross-coupling reactions does not exclude an escape-rebound mechanism a priori.

To demonstrate the feasibility of the reaction of **3** with an alkyl radical to give the coupling product, we monitored the reaction of $[(\text{N}_2\text{N})\text{Ni}-^n\text{Pr}]$ with an independently generated alkyl radical (Scheme 5). Photolysis of *tert*-butyl-4-phenylbutaneperoxoate yielded the phenylpropyl radical;⁶³ in the presence of $[(\text{N}_2\text{N})\text{Ni}-^n\text{Pr}]$, hexylbenzene was produced in a yield of 13% (relative to $[(\text{N}_2\text{N})\text{Ni}-^n\text{Pr}]$). This result proves that a nickel(II) alkyl complex can react with an alkyl radical to give the cross-coupling product. Thus, the bimetallic oxidative addition mechanism is feasible. As the formally nickel(III) alkyl species **4** cannot yet be isolated, an analogous experiment cannot be conducted to probe the feasibility of the reaction of **4** with an alkyl radical.

Thus, density functional theory (DFT) computations at the M06^{64,65}/def2-TZVP⁶⁶ level were used to compare reaction free energies and transition state barrier heights for the reactions of **3** and **4** with an alkyl (ethyl) radical (full computational details available in the SI).⁵⁶ The DFT-optimized structures of the reactants, products, and the transition state from **4** to **5** are given in Figure 4. The reaction of **3** with an ethyl radical to form **7** is both exergonic (~ -5 kcal/mol) and barrierless (Figure 5). In contrast, the reaction of **4** with an ethyl radical to form **5** is endergonic (~ 4 kcal/mol) and has a large transition state barrier (~ 24 kcal/mol) (Figure 5). It should also be mentioned that the concentration of **3** is much higher than **4** during catalysis. Therefore, the DFT

Scheme 4. Stereochemical Outcomes of Coupling Reactions of 9D^a

^aThe ligand N₂N is simplified for clarity.

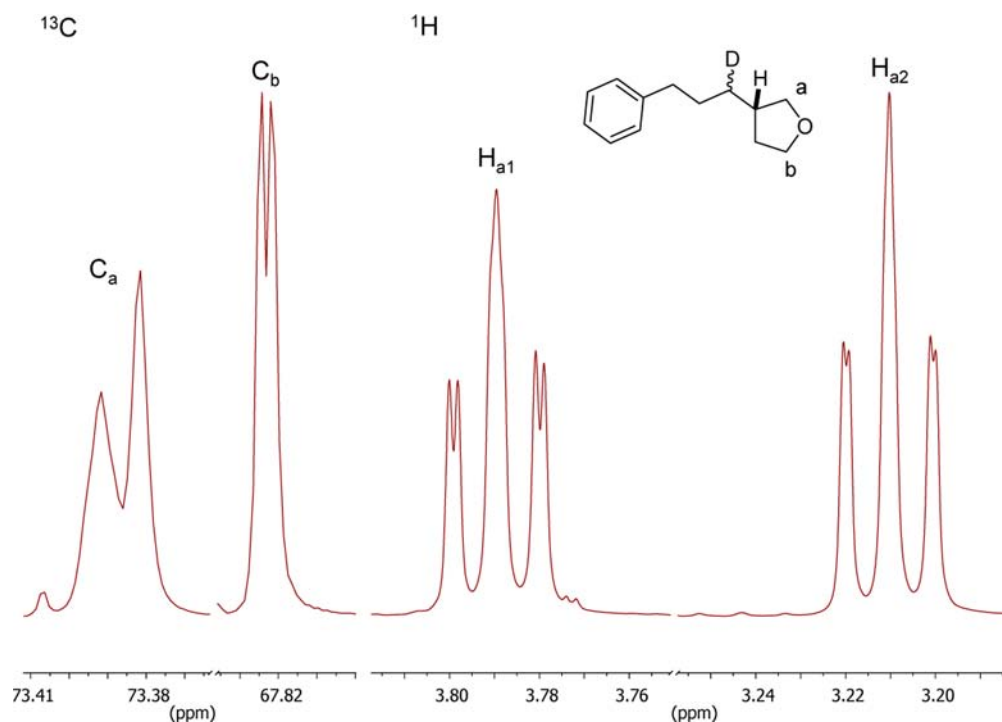


Figure 3. Detection of diastereomers of 14D by ¹³C and ¹H NMR. The splitting of signals for C_a and C_b in the ¹³C spectrum (left) is evident, indicating a pair of diastereomers; likewise, the splitting of signals for each diastereotopic proton H_a is also evident in the ¹H spectrum (right).

Scheme 5. Reaction of an Alkyl Radical with a Nickel(II) Alkyl Complex

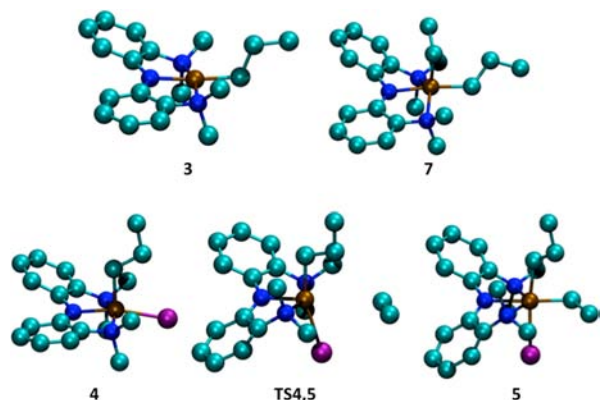
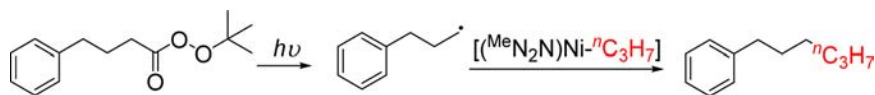


Figure 4. Structures (optimized at the M06/def2-SVP level) of relevant species for the bimetallic oxidative addition and escape-rebound mechanisms.

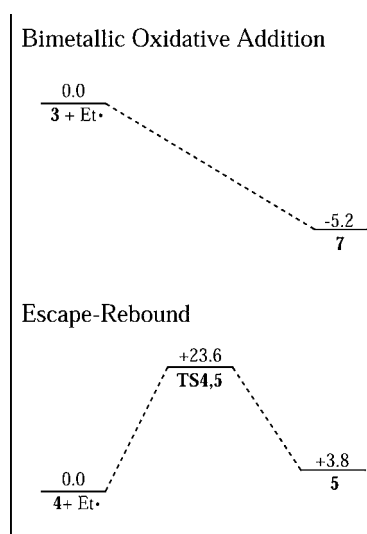


Figure 5. Reaction free energies computed at the M06/def2-TZVP level (in implicit THF solvent with the SMD model⁶⁷) for the bimetallic oxidative addition and escape-rebound mechanism. Values in kcal/mol.

computations unambiguously identify the bimetallic oxidative addition pathway ($3 + \text{Et}\cdot \rightarrow 7$) as the likely mechanism; the escape-rebound mechanism is excluded.

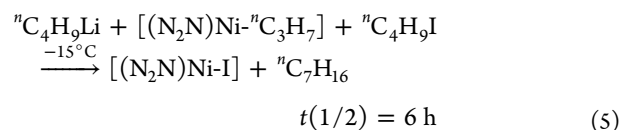
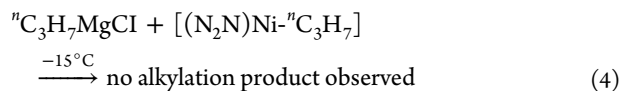
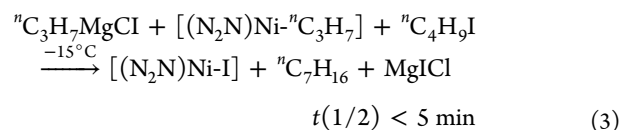
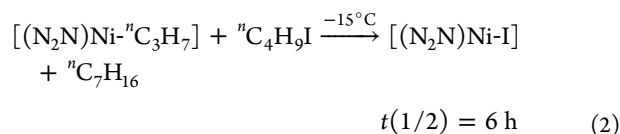
An alternative pathway to the coupling product is the direct reaction of the alkyl radical with an alkyl Grignard reagent, as oxidative coupling of Grignard reagents has been reported.^{68,69} To probe this possibility, photolysis of *tert*-butyl-4-phenylbutaneperoxoate was conducted in the presence of ⁿPrMgCl.⁵⁶ If the photogenerated alkyl radical could couple with ⁿPrMgCl, then hexylbenzene would be generated. However, this product was not detected, suggesting that direct coupling of the alkyl radical with the alkyl Grignard reagent may not be a viable pathway in the catalysis. The diastereoselectivity of alkyl–alkyl coupling reactions of substituted cyclohexyl halides provides further evidence against the direct coupling of the alkyl radical

with alkyl Grignard reagents: different diastereoselectivity was observed for different nickel catalysts,⁴⁸ whereas the same diastereoselectivity is expected for a direct coupling of the alkyl radical with the Grignard reagent.

The preceding results establish the bimetallic oxidative addition mechanism as the major mechanism by which the nickel catalysis occurs. Bimetallic oxidative addition of organic halides involving radical intermediates is rare but does have some precedent. For example, Cr(II),⁵¹ Co(0),⁵² and Fe(II)–ligand diradical⁵⁰ complexes were shown to activate alkyl and aryl halides in stoichiometric reactions through bimetallic oxidative addition. However, this is the first time that convincing evidence is reported for such a mechanism in catalytic cross-coupling reactions. Given the tendency of first-row transition metal complexes to undergo one-electron redox chemistry, this type of mechanism might be prevalent for cross-coupling reactions of nonactivated alkyl halides catalyzed by nickel, cobalt, and iron. Recently, bimetallic oxidative addition and reductive elimination are proposed to occur in preorganized bimetallic Pd and Ni complexes.^{53,70,71} In such “preassociated” bimetallic catalysis, two adjacent metals function together to perform the chemistry. The current bimetallic catalysis differs from those systems in that the oxidative addition involves sequentially two monometallic complexes.

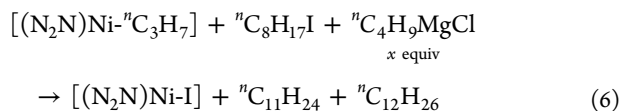
2. Nature of the Active Nickel Alkyl Intermediate.

2.1. Reactivity of Different Nickel Alkyl Species. After the mechanism of oxidative addition and C–C bond formation was established, the nature of the key alkyl species responsible for oxidative addition was probed. Earlier we believed that this species was simply a four-coordinate nickel(II) alkyl species, i.e., $[(\text{N}_2\text{N})\text{Ni-alkyl}^2]$ (**3**). Indeed, a $[(\text{N}_2\text{N})\text{Ni-alkyl}^2]$ complex could react with an alkyl halide to yield a coupling product in high yield. Yet, whether such a reaction would be *kinetically* relevant to the catalysis had not been examined. We studied the reaction of $[(\text{N}_2\text{N})\text{Ni-}^n\text{Pr}]$ with ⁿC₄H₉I under catalytically relevant conditions (THF/DMA as solvent and at –15 °C). The reaction took place smoothly to give $[(\text{N}_2\text{N})\text{Ni-I}]$ and ⁿC₇H₁₆ (eq 2). However, the reaction was significantly slower than the catalysis: the half-life of the reaction was 6 h, whereas the catalysis normally completed within 30 min. The same reaction was, however, much faster in the presence of 1 equiv of ⁿPrMgCl (eq 3). The half-life was less than 5 min, so that the rate of this reaction was compatible to that of the catalysis. These results indicate that the reaction of a $[(\text{N}_2\text{N})\text{Ni-alkyl}^2]$ complex with an alkyl halide is not the major pathway to the formation of the coupling product in the catalysis. Instead, the reaction of $[(\text{N}_2\text{N})\text{Ni-alkyl}^2]$ with alkyl²-MgCl seems to yield a species $[(\text{N}_2\text{N})\text{Ni-alkyl}^2](\text{alkyl}^2\text{-MgCl})$ that reacts much faster with an alkyl halide to give the coupling product. This species is the key alkyl species (**3'**). As no apparent reaction was observed between $[(\text{N}_2\text{N})\text{Ni-alkyl}^2]$ and alkyl²-MgCl (eq 4), **3'** shall be a thermodynamically unstable intermediate. Interestingly, a lithium alkyl reagent, ⁿBuLi, did not accelerate the reaction of $[(\text{N}_2\text{N})\text{Ni-}^n\text{Pr}]$ with ⁿC₄H₉I. The half-life of the reaction was again 6 h (eq 5). Likewise, MgCl₂ did not accelerate the reaction.⁵⁶



Next, the reaction of $[(N_2N)Ni-{}^n Pr]$ with ${}^n C_8H_{17}I$ was examined in the presence of ${}^n BuMgCl$ (Table 1). Both $C_{11}H_{24}$

Table 1. Crossover Experiments of Stoichiometric Cross-Coupling Reactions^a



entry	equiv of C_4H_9MgCl	conversion of $C_8H_{17}I$ (%)	yield of $C_{11}H_{24}$ (%)	yield of $C_{12}H_{26}$ (%)
1	1	100	58	34
2	0.7	100	60	30
3	0.5	98	64	23
4	0.3	74	53	5

^aSee the Supporting Information for experimental details; yields were determined by GC analysis and are relative to $C_8H_{17}I$; results are averaged over three independent trials and are for reactions in which the Grignard reagents were added last.

and $C_{12}H_{26}$ were produced, originating from the coupling of $C_8H_{17}I$ with ${}^n Pr$ and ${}^n Bu$ fragments, respectively. However, the selectivity for the coupling with the ${}^n Pr$ fragment was higher. For example, when 1 equiv of ${}^n BuMgCl$ was present, $C_{11}H_{24}$ and $C_{12}H_{26}$ were produced in a ratio of 1.7:1, and when 0.3 equiv of ${}^n BuMgCl$ was present, $C_{11}H_{24}$ and $C_{12}H_{26}$ were produced in a ratio of 12:1. On the other hand, coupling of the two nucleophiles (which would give C_7H_{16} as the product) was negligible. If $[(N_2N)Ni-{}^n Pr]$ was premixed with ${}^n BuMgCl$ before reacting with ${}^n C_8H_{17}I$, coupling of ${}^n Pr$ with C_8H_{17} was still dominant (Figure S7, Supporting Information). Furthermore, reaction of $[(N_2N)Ni-{}^n Pr]$ and $MeMgCl$ was monitored by NMR, but no exchange of alkyl ligand was observed.⁵⁶ These results suggest that formation of both $C_{11}H_{24}$ and $C_{12}H_{26}$ in Table 1 does not originate from a fast alkyl exchange reaction of $[(N_2N)Ni-{}^n Pr]$ and ${}^n BuMgCl$. The selectivity for coupling of ${}^n Pr$ fragment implies that the two alkyl groups in $[(N_2N)Ni-{}^n Pr]({}^n BuMgCl)$, the presumed active species for eq 6 in Table 1, are inequivalent and nonexchangeable.

2.2. Kinetics of Catalysis. The acceleration of the reaction between $[(N_2N)Ni-alkyl^2]$ and $alkyl^1-X$ by an alkyl Grignard reagent prompted us to determine the rate order of the catalysis with respect to the Grignard reagent. Thus, the rates of the

coupling of 2-phenylethylbromide with ${}^n BuMgCl$ (4 mol % **1** as catalyst) were measured using the initial rate approximation. Figure 6A depicts the dependence of the reaction rate on the concentration of ${}^n BuMgCl$. The rate order is approximately two.

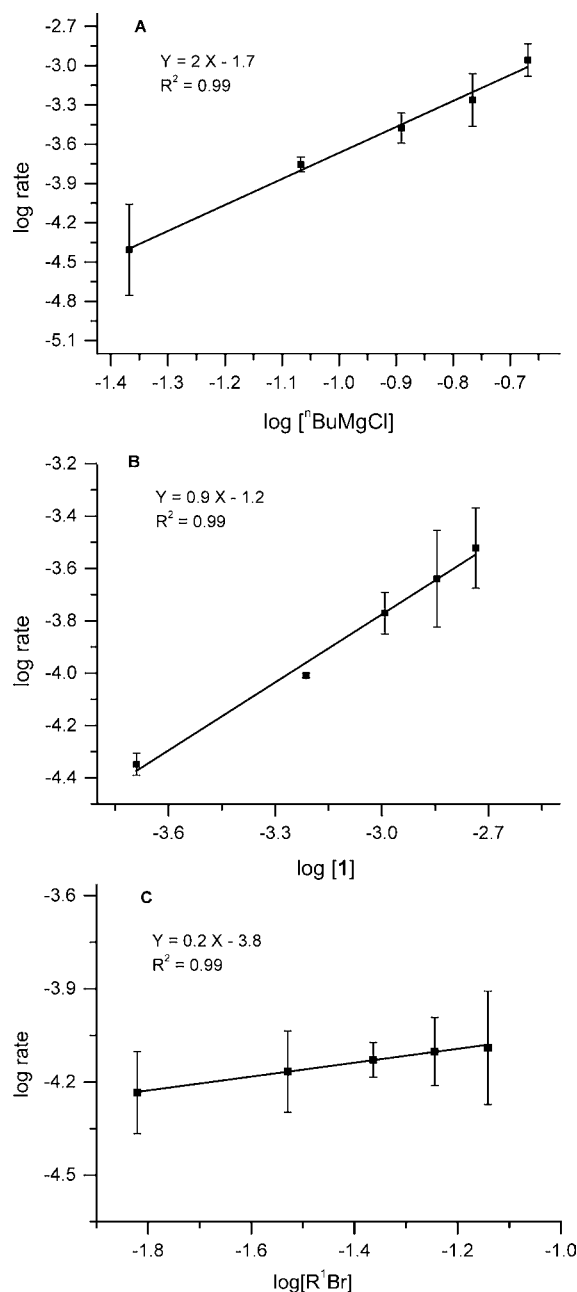


Figure 6. Rate orders of Grignard reagent (A), catalyst (B), and alkyl halide (C). At each loading, three independent trials were conducted to obtain an averaged value. The slopes of log rate vs log reagent are the rate order.

The dependence of the rate of the coupling reaction on the concentration of catalyst and alkyl halide was also determined. The catalysis is approximately first-order in catalyst (**1**) and zero-order in alkyl halide (Figure 6B and C). Both results are consistent with the scenario that the formation of **3'** is turnover-determining. The zero-order dependence on alkyl

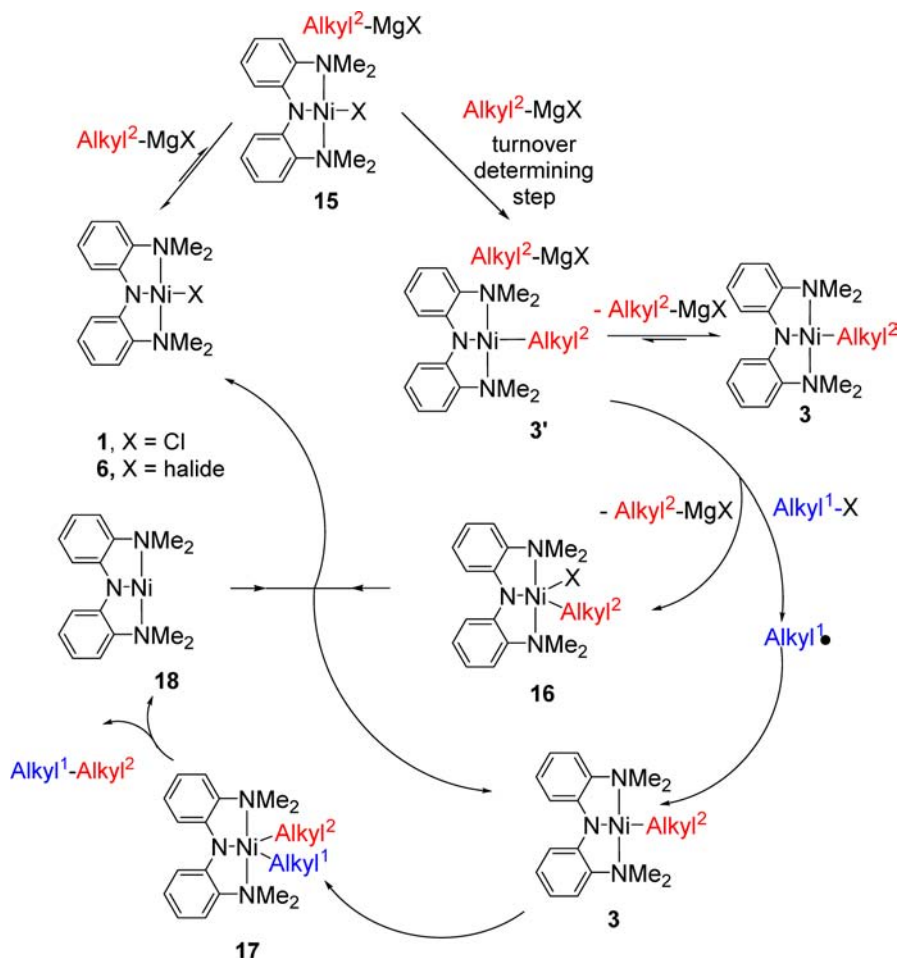
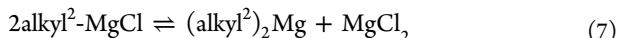


Figure 7. Proposed catalytic cycle of alkyl–alkyl Kumada coupling catalyzed by 1.

halide indicates that the activation of alkyl halide occurs after the transmetalation step in the catalytic cycle.

A scenario that might explain the observed second-order in Grignard reagent is that $\text{alkyl}^2\text{-MgCl}$ coexists with $(\text{alkyl}^2)_2\text{Mg}$ in solution through the Schlenk equilibrium (eq 7).



If $(\text{alkyl}^2)_2\text{Mg}$ is the real transmetalation reagent and the transmetalation step is turnover-determining, a second-order dependence on $\text{alkyl}^2\text{-MgCl}$ is expected. To test this hypothesis, the coupling of 2-phenylethylbromide with $(^t\text{Bu})_2\text{Mg}$ was studied. The yield of this coupling reaction was below 10% after 90 s and 25% after 50 min. These yields were significantly lower than those of the coupling of 2-phenylethylbromide with $^t\text{BuMgCl}$ (40% after 90 s and 77% after 50 min). Furthermore, a significant amount of the homocoupling product, $^t\text{C}_8\text{H}_{18}$, could be detected only when $(^t\text{Bu})_2\text{Mg}$ was used as the coupling partner.

The above experiment alone does not exclude the critical involvement of Schlenk equilibrium, as MgCl_2 was not present in the reaction mixture. The coupling of 2-phenylethylbromide with $(^t\text{Bu})_2\text{Mg}$ was then conducted in the presence of MgCl_2 , yet a similar reaction profile was observed.⁵⁶ Furthermore, the coupling of 2-phenylethylbromide with $^t\text{BuMgCl}$ was also conducted in the presence of MgCl_2 ; again the reaction profile remained similar.⁵⁶ If $(\text{alkyl}^2)_2\text{Mg}$ or other higher-order alkylmagnesium species in equilibrium with $\text{alkyl}^2\text{-MgCl}$ are

the true transmetalation reagent, one expects an influence of MgCl_2 in the reaction. The lack of such an influence suggests that the Schlenk equilibrium is not responsible for the observed rate order in Grignard reagent.

An alternative scenario that might lead to a second-order in Grignard reagent is the following: $[(\text{N}_2\text{N})\text{Ni-Cl}]$ is in equilibrium with $[(\text{N}_2\text{N})\text{Ni-Cl}](\text{alkyl}^2\text{-MgCl})$ (15); the latter undergoes a turnover-determining alkylation step with $\text{alkyl}^2\text{-MgCl}$ to form $[(\text{N}_2\text{N})\text{Ni-alkyl}^2](\text{alkyl}^2\text{-MgCl})$ (3'). If the pre-equilibrium disfavors $[(\text{N}_2\text{N})\text{Ni-Cl}](\text{alkyl}^2\text{-MgCl})$, then a second-order in $\text{alkyl}^2\text{-MgCl}$ is to be observed. A variant of this scenario is that $[(\text{N}_2\text{N})\text{Ni-Cl}]$ first reacts with 1 equiv of $\text{alkyl}^2\text{-MgCl}$ to give $[(\text{N}_2\text{N})\text{Ni-alkyl}^2]$, which further reacts with another equiv of $\text{alkyl}^2\text{-MgCl}$ to give 3'. To reach a second-order in $\text{alkyl}^2\text{-MgCl}$, the first transmetalation reaction needs to be a fast pre-equilibrium favoring the starting reagents. However, the reaction of $[(\text{N}_2\text{N})\text{Ni-X}]$ with $\text{alkyl}^2\text{-MgCl}$ to form $[(\text{N}_2\text{N})\text{Ni-alkyl}^2]$ and MgClX was previously found to favor the products.^{45,46} Therefore, this variant is ruled out by the kinetics of the catalysis.

As the catalysis is second-order in Grignard reagents, the transmetalation reaction should also be second-order in Grignard reagent. To verify this, the reaction of $[(\text{N}_2\text{N})\text{Ni-Cl}]$ with EtMgCl was followed by dip-probe UV–vis spectroscopy. Indeed, this reaction had an order of ca. 1.7 in Grignard reagent (Figure S14, Supporting Information).⁵⁶ The result is consistent with that obtained from catalytic reactions.

In intermediates **3'** and **15**, the amide and amine donors of the pincer N_2N ligand are possible binding sites for Mg^{2+} . This is reasonable as we reported previously that the N_2N -Mg complex could be formed in a small amount by reaction of $[(N_2N)Ni-Cl]$ with an alkyl Grignard reagent.⁴⁶ As tetramethylethylenediamine (TMEDA) is a good binder for Mg^{2+} , we monitored the coupling of 2-phenylethylbromide with $nBuMgCl$ in the presence of TMEDA.⁵⁶ It turned out that TMEDA significantly slowed down the catalytic coupling reaction. We speculate that TMEDA competes with one or more nitrogen donors in the N_2N ligand for binding of Mg^{2+} , thereby slowing the transmetalation reaction. If this is the case, then we can propose that $(alkyl^2-MgCl)$ is associated with the nickel complex through a nitrogen donor of the ligand in **3'** and **15**. In this way, the two $alkyl^2$ ligands in $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$ (**3'**) are different, which is consistent with their inability to exchange with one another (see above). On the other hand, TMEDA can influence the reaction in other ways, for example, by changing the nature of the Grignard reagents or by influencing the Schlenk equilibrium. It is important to recognize that the $alkyl^2-MgCl$ component in **3'** and **15** might bind to nickel via a halide or alkyl bridge as well.

2.3. Catalytic Cycle. A catalytic cycle for the nickel-catalyzed alkyl-alkyl Kumada coupling can be proposed based upon the aforementioned results and discussion (Figure 7). Catalyst **1** first reacts with $alkyl^2-MgCl$ to form $[(N_2N)Ni-Cl](alkyl^2-MgCl)$ (**15**) in a pre-equilibrium; reaction of **15** with another equivalent of $alkyl^2-MgCl$ gives the key intermediate $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$ (**3'**). The latter is in equilibrium with $[(N_2N)Ni-alkyl^2]$ (**3**), which is thermodynamically more stable but less reactive toward alkyl halide. Intermediate **3'** reacts with $alkyl^1-X$ through an inner sphere SET to give the $alkyl^1\bullet$ radical and a one-electron oxidized complex $[(N_2N)Ni(X)(alkyl^2)]$ (**16**). At this point $alkyl^2-MgCl$ might have left the nickel complex. The $alkyl^1\bullet$ radical then escapes from the solvent cage and reacts with a second molecule of $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$ (**3'**) or $[(N_2N)Ni-alkyl^2]$ (**3**) to give $[(N_2N)Ni(alkyl^2)(alkyl^1)]$ (**17**) (for simplicity, only reaction with **3** is drawn in Figure 7). Reductive elimination from **17** gives $alkyl^2-alkyl^1$ as the coupling product and a formally nickel(I) species $[(N_2N)Ni]$ (**18**) as an unstable intermediate. Species **18** reacts with the formally nickel(III) species **16** to give $[(N_2N)Ni-X]$ (**6**) and $[(N_2N)Ni-alkyl^2]$ (**3**), both of which can re-enter the catalytic cycle.

The catalytic cycle in Figure 7 reinforces the notion that the two alkyl ligands in intermediate **3'** are inequivalent. When **3'** activates an alkyl halide, it is oxidized to a formally nickel(III) complex. If there are two identical alkyl ligands in **3'**, they will undergo reductive elimination to give the product of $alkyl^2-alkyl^2$ homocoupling. Such a product, however, was not observed.

The role of $[(N_2N)Ni-alkyl^2]$ (**3**) warrants some comments. **3** is a stable species that can be isolated from the reaction mixture and is catalytically competent. The kinetics of the catalysis indicates that it is not the key species for the activation of alkyl halide; thus, **3** can be considered as a dormant species in the catalytic cycle. Equations 2 and 4 show **3** can be transformed into the active species **3'** by alkylation with a Grignard reagent. The binding of Mg^{2+} by **3** seems essential for this alkylation reaction: if $nBuMgCl$ is replaced by $nBuLi$, an equally active species is no longer generated (eq 5).

The resting state of the catalysis, according to the kinetic data in Figure 6 and the catalytic cycle in Figure 7, is the nickel(II)

halide complex (**1** or **6**). To support this hypothesis, the coupling of octyl-I with $EtMgCl$ was monitored by UV-vis spectroscopy.⁵⁶ The absorption spectra of nickel(II) halide and ethyl complexes are significantly different in the visible region⁴⁶ so that their concentrations can be determined by analysis of the spectra. It is found that a significant amount (ca. 60%) of nickel-containing species during catalysis (at partial conversions) was $[(N_2N)Ni-Cl]$.⁵⁶ This result is consistent with $[(N_2N)Ni-X]$ being the resting state.⁷² $[(N_2N)Ni-Et]$ was also present, consistent with its role as the dormant species.

CONCLUSION

In conclusion, a bimetallic oxidative addition mechanism involving radical intermediates has been revealed for alkyl-alkyl Kumada cross-coupling reactions catalyzed by the nickel(II) pincer complex **1**. The oxidative addition of alkyl halide involves two nickel centers, and the highest formal oxidation state of nickel in the intermediates is +3.⁷³⁻⁷⁵ The catalysis is second-order in Grignard reagent, first-order in catalyst, and zero-order in alkyl halide. The key intermediate species for the activation of alkyl halide is the complex $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$; the formation of this species is the turnover-determining step of the catalysis. One or more nitrogen donors in the pincer N_2N ligand is proposed to assist the catalysis in binding to the Mg^{2+} ion in the Grignard reagents. To the best of our knowledge, this is the first time that a bimetallic radical mechanism has been established for nickel-catalyzed cross-coupling reactions of alkyl halides. While the study is specific to the reactions catalyzed by **1** and its derivatives, a similar mechanism might be operating in many other systems known to involve radical processes. The work significantly enhances the current understanding of these challenging, yet potentially useful, chemical transformations.

ASSOCIATED CONTENT

Supporting Information

Experimental and computational details and 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.

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