Unexpected Nickel Complex Speciation Unlocks Alternative Pathways for the Reactions of Alkyl Halides with dppf-Nickel(0)

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ABSTRACT: The mechanism of the reactions between dppf-Ni0 complexes and alkyl halides has been investigated using kinetic and mechanistic experiments and DFT calculations. The active species is [Ni(κ^2-dppf)(κ^1-dppf)], which undergoes a halide abstraction reaction with alkyl halides and rapidly captures the alkyl radical that is formed. The rates of the reactions of [Ni(COD)(dppf)] with alkyl halides and the yields of prototypical nickel-catalyzed Kumada cross-coupling reactions of alkyl halides are shown to be significantly improved by the addition of free dppf ligand.

1. INTRODUCTION

The coupling of sp^3 centers is a frontier in modern cross-coupling catalysis research^{1,2} and is closely aligned to the drive in areas such as pharmaceutical industry to target sp^3-rich molecules.\(^\text{3,4}\) Due to differences in oxidative addition behavior and the occurrence (and often the dominance) of deleterious side reactions such as β-hydride elimination, couplings of sp^3 centers are typically far more challenging than the palladium-catalyzed sp^2-sp^2 couplings that have become a routine in academia and industry. In order to overcome these synthetic challenges, chemists have looked toward alternative catalyst systems, often based on metals such as iron,\(^\text{5}\) cobalt,\(^\text{6}\) and nickel.\(^\text{7-9}\) Several useful catalytic systems have been disclosed. Practical nickel-catalyzed reductive cross-electrophile couplings have also been developed, which allow sp^3-sp^3 couplings of an aryl halide and an alkyl halide.\(^\text{10}\) However, despite synthetic advances in this field, we require further and deeper mechanistic understanding to underpin future developments.

Mechanistic studies of the reactions of alkyl halides with nickel are relatively few, and many studies of sp^3 couplings (both synthetic and mechanistic) invoke nickel(1) intermediates.\(^\text{11-15}\) Tilley et al. have reported the oxidative addition of methyl iodide to a nickel(1) species, forming a nickel(III) complex.\(^\text{16,17}\) Baird et al. have studied the reactions of alkyl halides with [Ni^0(PPh_3)_4], which occurred via halide abstraction and which generate mixtures of alkane and alkene products, with the latter arising from β-hydride elimination.\(^\text{18}\) Studies were typically carried out by combining Ni^0 and alkyl halide at low temperatures and carefully increasing the temperature and observing NMR spectral changes. Wang et al. explored the reactions of a diphosphinodithio-ligated nickel(0) complex with alkyl halides, which were followed by the addition of NaBPh_4; this led to alkynickel(II) complexes, which degenerated to hydride species via β-hydride elimination.\(^\text{19}\) Diao et al. probed the reactions of [Ni(I)(Ar)- (Xantphos)] with alkyl halides and also proposed a halide abstraction mechanism (Xantphos = 4,5-bis-(diphenylphosphino)-9,9-dimethyl-xanthene).\(^\text{20}\) Jarvo et al. studied the nickel/dppm-mediated synthesis of cyclopropanes from 1,3-dimesylates and uncovered a halide abstraction mechanism involving the initially formed 1,3-diodide (dppm = bis(diphenylphosphino)methane).\(^\text{21}\)

The present study builds on our recent investigations of the oxidative addition of aryl halides to Ni^0\(^\text{22-24}\) and works toward the understanding of reaction mechanisms and structure/reactivity relationships in nickel catalysis (Scheme 1). We work with bidentate phosphate ligands because they exhibit favorable reactivity in cross-coupling reactions;\(^\text{25-29}\) [Ni^0(COD)(dppf)] (1), a thermally stable and readily prepared model Ni^0 complex, has been used for mechanistic studies of nickel catalysis and for catalytic reactions in organic...
synthesis \((\text{dppf} = 1,1’\text{-bis(diphenylphosphino)ferrocene})\).\(^{30}\) This is known to be the catalyst that is formed in reactions where \([\text{Ni(COD)}_2]\) and dppf are combined in situ.\(^{30}\) Our key finding in this study is that the active Ni\(^0\) species must bear two dppf ligands, even though most pre-catalysts with bidentate phosphine ligands have a 1:1 ligand-to-nickel ratio.

2. RESULTS AND DISCUSSION

2.1. Kinetic Studies of Reactions with \([\text{Ni(COD)}(\text{dppf})]\) (1). Stoichiometric experiments in which \([\text{Ni(COD)}(\text{dppf})]\) (1) was exposed to (2-haloethyl)benzene reagents (2-X) showed that the major products were styrene and \([\text{NiX(dppf)}]\) (3-X), as confirmed by GC-FID/GC−MS analysis and EPR spectroscopy, respectively (Scheme 2a);\(^{31}\) these NiI complexes have been reported previously.\(^{30,32}\) No ethylbenzene was detected in any of these reactions. Styrene must arise from a β-hydride elimination process. The reactions between \([\text{Ni(COD)}(\text{dppf})]\) (1) and an excess of each of the three alkyl halides (2-X, 15 equiv) in benzene-\(d_6\) solution were monitored over time by \(^{31}\)P\({^1}\)H NMR spectroscopy (Scheme 2b). Surprisingly, these reactions were pseudo-zero order in 1 (Figure 1a) and displayed a saturation behavior in 2-Br. This is in stark contrast to the reactions of 1 with aryl halides, which are pseudo-first order in 1 under the same conditions.\(^{22}\) These results suggested that 1 was not the active species in these reactions.

2.2. Identification of \([\text{Ni(dppf)}_2]\) as the Active Species. Control reactions were conducted with additives to understand what the active species in these reactions might be (Scheme 2c). The addition of \([\text{NiCl}_2(\text{dppf})]\) (4-Cl) led to an increase in the rate of reaction, prompting speculation that \([\text{NiCl(dppf)}]\) (3-Cl), formed from comproportionation between \([\text{Ni(COD)}(\text{dppf})]\) (1) and 4-Cl,\(^{22,30,33}\) might be the active species. However, added 3-Cl did not affect the reaction rate. When an additional dppf ligand was present, there was a significant increase in reaction rate. Further analysis of \([\text{NiCl}_2(\text{dppf})]\) (4-CL) by \(^{31}\)P\({^1}\)H NMR spectroscopy revealed small quantities of free dppf, thus accounting for its accelerating effect. \([\text{Ni(COD)}(\text{dppf})]\) (1) contained approximately 1% of what was assigned as \([\text{Ni(dppf)}_2]\) (5) by comparison with literature \(^{31}\)P NMR data (\(\delta_p \approx 15 \text{ ppm}) .^{34}\) Complex 1 is prepared from dppf and \([\text{Ni(COD)}_2]\), which yields 1 as the major product,\(^{30,35}\) but the presence of 5 appears to be essential for these reactions with alkyl halides.
The equilibrium constant for the formation of 5 from 1 plus dppf was measured ($K_{eq} = 6.8$).

### 2.3. Kinetic Studies of Reactions with [Ni(dppf)$_2$]

Attempts were made to prepare a sample of 5 for kinetic studies but a sufficiently pure sample could not be obtained. Instead, a series of experiments were carried out in which additional dppf was present during the reactions of [Ni-(COD)(dppf)] (1) with (2-haloethyl)benzene substrates (2-X) (Scheme 2d). The products of these reactions were again styrene and [NiX(dppf)] (3-X).

In the presence of added dppf, these kinetic studies showed a pseudo-first-order behavior in 1, were first order in 2-X and dppf, and were inhibited by COD (Figure 1b–d). Notably the reactions of aryl halides with 1 are inhibited by added dppf, as established by control experiments; the reactions of aryl halides therefore proceed via [Ni(dppf)], but the reactions of alkyl halides proceed via [Ni(dppf)$_2$] (5).

A rate expression can be formulated for the reactions of alkyl halides with 1. If an equilibrium between [Ni(COD)(dppf)] (1) plus dppf and [Ni(dppf)$_2$] (5) plus COD is rapidly established then the concentration of 5 can be defined according to eq 1

$$K_1 = [5][COD]/[1][dppf]$$

If the reaction proceeds through a rate-determining reaction between 5 and the alkyl halide (2-X) with rate constant $k_2$ then the reaction rate can be expressed as in eq 2; the expression for [5] can then be substituted to give eq 3

$$rate = k_2 \times [5] \times [2-X]$$

$$rate \approx k_{obs} \times [Ni]_{tot} \text{ where}$$

$$k_{obs} = K_1 \times k_2 \times [1] \times [2-X] \times [dppf] \times [COD]^{-1}$$

An alternative treatment based on the steady-state approximation leads to the same rate expression (see the Supporting Information).

An Eyring–Polanyi treatment of the reaction between [Ni(COD)(dppf)] (1) and 15 equiv of 2-Cl in the presence of 0.3 equiv of dppf yielded activation parameters (see the Supporting Information); $\Delta S^0 \approx 0$ for the equilibrium between 1 and 5, and so $\Delta H^o$ is estimated at 26.2 kcal mol$^{-1}$ and $\Delta S^0$ at 15 cal K$^{-1}$ mol$^{-1}$. The latter value indicates a decrease in order as the reaction proceeds through the transition state.

### 2.4. Evidence for Radical Intermediates

The formation of styrene in the reactions of (2-haloethyl)benzene substrates requires the intermediacy of alkynickel(II) halide complexes that then undergo $\beta$-hydride elimination; however, it is possible that these might form directly from Ni$^0$ or through the formation of Ni$^1$ and a radical, which then recombine to form Ni$^0$. The direct formation of styrene from an ethylbenzene radical is ruled out because recombination to produce 1,4-diphenylbutane is favored by ca. 7-fold over disproportionation to styrene and ethylbenzene; no 1,4-diphenylbutane or ethylbenzene was detected in any of these reactions.

The reactions of secondary and tertiary alkyl halides with [Ni(COD)(dppf)] (1) (and added dppf) were studied (Scheme 3a). The reactions of (2-bromopropyl)benzene (6-Br) and (2-bromo-2-methylpropyl)benzene (7-Br) were both far too fast to allow the measurement of rate constants. A distinct color change occurred within 30 s of substrate addition at room temperature (ca. 293 K), so $k_{obs}$ is at minimum ca. 0.2 s$^{-1}$ and therefore at least two orders of magnitude faster than for the reaction of 2-Br; the color change is proposed to be due to the formation of [NiBr(dppf)] (3-Br), which is darker in color than [Ni(COD)(dppf)] (1). This significant rate enhancement on moving from primary to secondary and tertiary alkyl halides is consistent with a reaction that generates alkyl radicals.

Reasoning that styrene formation occurs due to a $\beta$-hydride elimination process, (1-chloro-2-methylpropan-2-yl)benzene (8-Cl) was used as the reaction substrate (Scheme 3b). The putative alkynickel(II) chloride intermediate cannot undergo $\beta$-hydride elimination. Instead, 2-methyl-1-phenylprop-1-ene (9) was obtained as the organic product. The putative alkylnickel(II) chloride intermediate was therefore rapidly trapped by the nickel complex—so as to yield the $\beta$-hydride elimination products—more quickly than it can undergo reaction with BHT. Intramolecular rearrangement processes such as the [1,2]-phenyl shift in Scheme 3b, with a rate constant of 500 s$^{-1}$ at 20 °C, $^{37}$ can outpace the capture of the primary alkyl radical by Ni$^0$.

### 2.5. Events after Radical Capture and $\beta$-Hydride Elimination

The evidence points to a mechanism in which [Ni(dppf)$_2$] (5) reacts with alkyl halides to form a Ni$^1$ complex and an alkyl radical, which in turn combine to form a Ni$^0$ complex that can undergo $\beta$-hydride elimination to form styrene. This would also produce [Ni(X)(dppf)] (10-X), which must then form [NiX(dppf)] (3-X), as is the ultimate product identified by EPR spectroscopy.

Attempts to obtain an authentic sample of [NiCl$_x$-CH$_2$CH$_2$Ph](dppf)] (11-Cl) by reaction of [NiCl$_2$(dppf)] (4-Cl) with the appropriate Grignard reagent led only to decomposition products including styrene and ethylbenzene; no Ni$^0$ products were detected by EPR analysis, suggesting that Ni$^0$ in the reactions between Ni$^0$ and alkyl halides must arise.
Figure 2. DFT studies of the reaction between \([\text{Ni(COD)(dppf)}]\) (1) and (2-haloethyl)benzene substrates (2-X) via \([\text{Ni(dppf)}]\) (5). All energies are free energies in kcal mol\(^{-1}\) in benzene solution and are quoted relative to complex 1. The profile is drawn for the case of (2-bromoethyl)benzene (2-Br) with energies provided in square brackets for the reactions of (2-chloroethyl)benzene (2-Cl) and (2-iodoethyl)benzene (2-I). The dppf ligand is abbreviated to two linked P atoms for clarity.

through comproportionation and therefore does not form in the absence of Ni\(^0\). The instability of 11-Cl makes any comproportionation pathways between this complex and Ni\(^0\) unlikely. Attempts to prepare \([\text{Ni(H)}(\text{Cl})(\text{dppf})]\) (10-X) by reaction of \([\text{NiCl}_2(\text{dppf})]\) (4-Cl) with various hydride sources did not produce any tractable nickel hydrides and no structurally similar nickel hydrides have been reported in the literature.\(^{38}\)

We propose that putative hydride complex 10-X undergoes decomposition to form \([\text{NiX(dppf)}]\) (3-X) via comproportionation with Ni\(^0\). Reactions between \([\text{Ni(COD)}(\text{dppf})]\) (1) and 1 equiv of 2-X (in the presence of 0.3 equiv of dppf) were followed by \(^1\text{H}\) NMR spectroscopy and showed a signal consistent with that for hydrogen;\(^{39}\) when the sample was placed under a hydrogen atmosphere, the intensity of this signal increased, supporting the assignment. It has been shown using computational techniques that complexes of the form \([\text{NiH}_2(\text{PR}_3)_2]\) exist most favorably as non-classical dihydrogen complexes, suggesting the release of hydrogen from such a species to be facile;\(^{40}\) no such complexes have been experimentally characterized. A sample of \([\text{Ni(COD)}(\text{dppf})]\) (1) placed under a hydrogen atmosphere at room temperature decomposed slightly over the course of several hours, forming free dppf and COD; the analogous experiment with additional dppf formed COD and cyclooctene, with the latter presumably arising from COD hydrogenation by a putative nickel hydride intermediate.\(^{41}\)

2.6. Ruling Out Outer-Sphere Electron Transfer. Two possible mechanisms for the reactions of \([\text{Ni(dppf)}]\)(5) with alkyl halides can lead to the formation of alkyl radicals: outer-sphere electron transfer or halide abstraction.\(^{18,23,24,42}\) These differ in the fact that the latter requires a vacant site for coordination of the substrate prior to halide abstraction. A sample of \([\text{Ni(dppe)}]\)(12) was prepared\(^{43}\) and exposed to alkyl halides (dppe = 1,2-bis(diphenylphosphino)ethane); this complex is known to be unreactive toward a range of species to be facile;\(^{44}\) no such complexes have been experimentally characterized. A sample of \([\text{Ni(COD)}(\text{dppf})]\) (1) placed under a hydrogen atmosphere at room temperature decomposed slightly over the course of several hours, forming free dppf and COD; the analogous experiment with additional dppf formed COD and cyclooctene, with the latter presumably arising from COD hydrogenation by a putative nickel hydride intermediate.\(^{41}\)

Halide abstraction provides an alternative pathway; it is proposed to be the predominant mechanism in this reaction due to the lack of reactivity of \([\text{Ni(dppe)}]\)(5) with alkyl halides (vide supra). The binding of alkyl halides to \(S\) via the halide is endergonic by \(ca. 2\)–\(3\) kcal mol\(^{-1}\), but the halide abstraction transition state is then accessible (19–26 kcal mol\(^{-1}\) from S). Halide abstraction by \([\text{Ni(η}^3\text{-COD)}(\text{dppf})]\) is ruled out based on the experimentally determined first-order behavior in dppf. In addition, computational studies of halide abstraction by \([\text{Ni(dppe)}(\text{η}^3\text{-ethene})]\) (as a model for \([\text{Ni(η}^3\text{-COD)}(\text{dppf})]\)) show that this process is less competent than halide abstraction by \(S\), with a barrier that is 5.7 kcal/mol higher in energy (see the Supporting Information for details).

The radical formed by halide abstraction recombines with the Ni\(^1\) complex to form an alkynickel(II) halide species with
the concomitant loss of a dppf ligand (Figure 2). The resulting complex [Ni(CH2CH2Ph)(X)(dppf)] (11-X) is known to be unstable (vide supra), and so a bimolecular comproportionation pathway for this species is ruled out. Instead, β-hydride elimination forms [Ni(H)(X)(dppf)(η2-styrene)], which can then dissociate styrene to form [Ni(H)(X)(dppf)] (10-X). We have not modeled the subsequent processes but propose that 10-X undergoes comproportionation with Ni0 present in the reactions to form [NiX(dppf)] (3-X) and [Ni(H)dppf]. The latter complex could undergo disproportionation to Ni0 and [Ni(H)2(dppf)], which would then reductively eliminate hydrogen.

We have studied the corresponding reactions with an aryl halide (bromobenzene) to understand why these proceed more slowly in the presence of added dppf (Figure 3). The oxidative addition of bromobenzene to [Ni(COD)(dppf)] (1) proceeds via an intermediate η2-complex, presents a modest barrier of 10.7 kcal/mol (from 1), and is exergonic. We were unable to locate the subsequent processes but propose that 10-X undergoes comproportionation with Ni0 present in the reactions to form [NiX(dppf)] (3-X) and [Ni(H)dppf]. The latter complex could undergo disproportionation to Ni0 and [Ni(H)2(dppf)], which would then reductively eliminate hydrogen.

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tions of (2-haloethyl)benzene substrates (2-X) with phenyle
magnesium chloride were selected (Scheme 4a). These
produced 1,2-diphenylethane (13), regioisomeric side product
1,1-diphenylethane (14), styrene, biphenyl, and ethylbenzene.
Control reactions without a catalyst showed that the latter two
products do not arise via nickel-catalyzed processes. Com-
plexes [Ni(COD)(dppf)] (1), [NiCl(o-tol)(dppf)] (15-Cl),
and [NiCl(dppf)] (3-Cl) were deployed as catalysts (Scheme
4b).51 Reactions catalyzed by 1 but without an additional
phosphine ligand yield very poor results in catalysis, with
incomplete conversion of 2-X and low yields of product 13
and side product 14. The addition of 5 mol % dppf significantly
improved reaction outcomes, enabling full (or close to full)
conversion of 2-X. Reactions catalyzed by [Ni(COD)(dppf)]
(1), [NiCl(dppf)] (3-Cl), and [NiCl(o-tol)(dppf)] (15-Cl)
with 5 mol % of added dppf converged on the same reaction
outcome. This suggests that they proceed via a common
pathway, despite the different pre-catalyst oxidation states.
NiI complexes such as 3-Cl form NiI-aryl species upon reaction
with Grignard reagents, and so they can serve as NiI sources
for catalysis.22,52 Complex 15-Cl undergoes transmetalation
with Grignard reagents followed by reductive elimination to
form Ni0.22,33

2.9. Reactions Involve Both Radical Intermediates
and \( \beta \)-Hydride Elimination. The analysis of the side
products in catalytic reactions gives additional information
about plausible reaction pathways. Side product 14 (1,1-
diphenylethane) could be generated by \( \beta \)-hydride elimination
from [Ni(CH2CH2Ph)(X)(dppf)] (11-X) followed by re-
insertion to form the regioisomeric alkylnickel(II) halide
species [Ni(CH(Me)(Ph))(X)(dppf)] (an overall “\( \beta \)-hydro-
gen transfer” process) and subsequent transmetalation and
reductive elimination; the plausibility of this pathway is
supported by DFT calculations (Figure 4), which indicate
relatively low barriers of ca. 16–19 kcal mol\(^{-1}\) from 11-X to
the highest energy transition state on the pathway, and lead to
isomeric alkylnickel(II) halide species that are only ca. 4–6
cal mol\(^{-1}\) higher in energy. Consistent with this proposal,
when a prototypical Kumada reaction was carried out in the
presence of a 4-methylstyrene additive, 1-(4-methylphenyl)-1-
phenylethane (16) was also observed (Scheme 5a). We note
that nickel-catalyzed migratory Suzuki–Miyaura cross-coupling
reactions have been developed by Yin and co-workers53 and

Figure 4. DFT calculations of the migratory insertion pathway to form the regioisomeric alkylnickel(II) halide species implicated in the formation
of 14.

Scheme 5. (a) Reactions in the Presence of a 4-Methylstyrene Additive, (b) Proposed Pathway for the Incorporation of 4-
Methylstyrene into Cross-Coupling Products via Migratory Insertion into a Nickel Hydride Intermediate, and (c) Cross-
Coupling Reactions with 6-Bromohex-1-ene

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reactions have been developed by Yin and co-workers53 and
that our reactions share some mechanistic features with such reactions, specifically the formation and recombination of an alkyl radical and the transposition of the nickel center along an alkyl chain. We propose that this results from migratory insertion into a nickel hydride intermediate followed by transmetalation and reductive elimination (Scheme 5b). While the secondary alkylnickel(II) complexes are higher in energy than the corresponding primary alkylnickel(II) complexes (11-X), subsequent events in the Kumada cross-coupling reaction such as transmetalation and reductive elimination may have different barriers that depend on the isomer of the alkyl ligand and the identity of the halide; this will be explored in more detail in a subsequent study.

Cross-coupling reactions were carried out using substrates that can act as radical traps. (Chloromethyl)cyclopropane underwent a nucleophilic substitution reaction with the dppf ligand. The reactions of 6-bromohex-1-ene (17-Br) were more informative and led to (phenylmethyl)cyclopentane (19) as the major product, along with 6-phenylhex-1-ene (18) and side products biphenyl, hexa-1,5-diene, and hex-1-ene (Scheme 5c).

Product 19 is proposed to arise from the cyclization of the intermediate primary radical (k = 1.8 × 10^5 s^-1 at 20 °C)^37 followed by capture by NiI. This provides further evidence of the intermediacy of radical species in these reactions.

3. CONCLUSIONS

We have conducted a thorough study of the reactions of alkyl halides with dppf-Ni0 complexes. Scheme 6 outlines the mechanism for this process that is supported by experimental and DFT studies. The key points from this study are as follows.

3.1. The Nature and Reactivity of the Active Catalyst. Reactions proceed through [Ni(dppf)2] (5), which bears two dppf ligands, in contrast to the reactions of aryl halides that proceed through complexes with one dppf ligand. The key mechanistic event is halide abstraction to form a NiI species and a radical; these then recombine to form a NiII species. Some alkyl radicals, such as those derived from alkyl halides without β-hydrogens, can undergo rearrangement reactions before capture by NiI. The lack of reactivity of Ni0 complexes bearing alternative bidentate phosphine ligands, which more readily form [Ni(L)2] complexes, such as [Ni(dppe)2] (12), shows that it is necessary to generate a vacant site for the reaction to occur.

3.2. The Fate of the NiII Intermediate. The NiII intermediate thus formed can undergo either transmetalation during a cross-coupling cycle or β-hydride elimination to form styrene. Re-insertion of styrene is proposed to lead to a regiosomer of the alkynickel(II) species; this is also able to undergo transmetalation and reductive elimination, leading to a side product. The putative nickel hydride complex [Ni(H)X(dppf)] (10-X) formed from β-hydride elimination then undergoes comproportionation with Ni0 to form [Ni(X)(dppf)] (3-X) and (ultimately) hydrogen.

This study provides insights into the activation of sp3 C–X bonds for cross-coupling reactions, as part of our ongoing program to interrogate and understand reaction mechanisms in nickel catalysis, with the aim of exploiting this understanding for catalyst and reaction design. Further mechanistic studies of oxidative addition to Ni0, and how these depend on the ligand and substrate structure, are currently underway in our laboratory.

The raw data underpinning this study can be downloaded from the University of Strathclyde Knowledgebase at http://dx.doi.org/10.15129/7ec1bd50-bdaf-4225-b300-10f875f1f4ae. Computational data underpinning this study can be accessed via the ioChem-BD data repository^54 at http://dx.doi.org/10.19061/iochem-bd-1-182.
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Notes
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