

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

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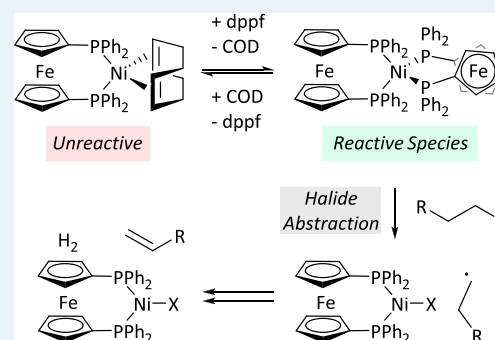


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ABSTRACT: The mechanism of the reactions between dppf-Ni⁰ complexes and alkyl halides has been investigated using kinetic and mechanistic experiments and DFT calculations. The active species is [Ni(κ^2 -dppf)(κ^1 -dppf)], which undergoes a halide abstraction 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.



KEYWORDS: nickel, homogeneous catalysis, cross-coupling, reaction mechanisms, organometallic chemistry

1. INTRODUCTION

The coupling of sp³ 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 sp³-rich molecules.^{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 sp³ centers are typically far more challenging than the palladium-catalyzed sp²-sp² 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,⁵ cobalt,⁶ and nickel.^{7–9} Several useful catalytic systems have been disclosed. Practical nickel-catalyzed reductive cross-electrophile couplings have also been developed, which allow sp³-sp² couplings of an aryl halide and an alkyl halide.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 sp³ couplings (both synthetic and mechanistic) invoke nickel(I) intermediates.^{11–15} Tilley et al. have reported the oxidative addition of methyl iodide to a nickel(I) species, forming a nickel(III) complex.^{16,17} Baird et al. have studied the reactions of alkyl halides with [Ni⁰(PPh₃)₄], which occurred *via* halide abstraction and which generate mixtures of alkane and alkene products, with the latter arising from β -hydride elimination;¹⁸ studies were typically carried out by combining Ni⁰ 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 NaBPh₄; this led to alkylnickel(II) complexes, which degenerated to hydride species *via* β -hydride elimination.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).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-diiodide (dppm = bis(diphenylphosphino)methane).²¹

The present study builds on our recent investigations of the oxidative addition of aryl halides to Ni⁰^{22–26} and works toward the understanding of reaction mechanisms and structure/reactivity relationships in nickel catalysis (Scheme 1). We work with bidentate phosphine ligands because they exhibit favorable reactivity in cross-coupling reactions;^{27–29} [Ni⁰(COD)(dppf)] (**1**), a thermally stable and readily prepared model Ni⁰ complex, has been used for mechanistic studies of nickel catalysis and for catalytic reactions in organic

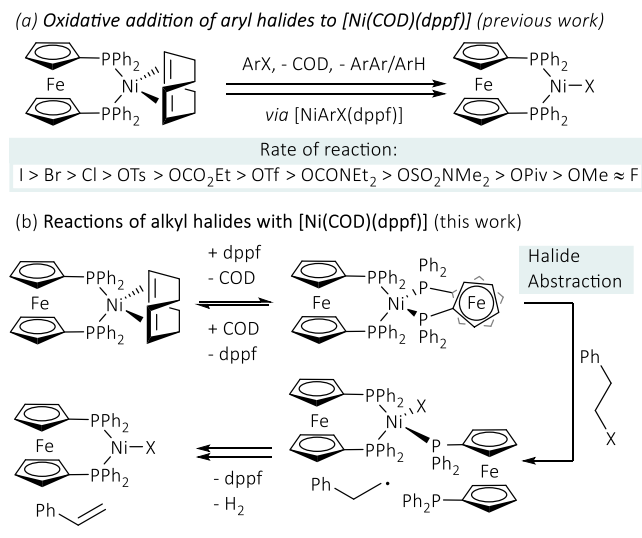
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Scheme 1. (a) Our Previous Work and (b) This Study



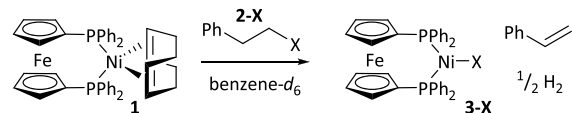
synthesis (dppf = 1,1'-bis(diphenylphosphino)ferrocene).³⁰ This is known to be the catalyst that is formed in reactions where [Ni(COD)₂] and dppf are combined *in situ*.³⁰ Our key finding in this study is that the active Ni⁰ species must bear two dppf ligands, even though most pre-catalysts with bidentate phosphine ligands have a 1:1 ligand-to-nickel ratio.

2. RESULTS AND DISCUSSION

2.1. Kinetic Studies of Reactions with [Ni(COD)(dppf)]

(1). Stoichiometric experiments in which [Ni(COD)(dppf)] (1) was exposed to (2-haloethyl)benzene reagents (2-X) showed that the major products were styrene and [NiX(dppf)] (3-X), as confirmed by GC-FID/GC-MS analysis and EPR spectroscopy, respectively (Scheme 2a);³¹ these Ni^I complexes

Scheme 2. (a) Stoichiometric Reactions, (b) Initial Kinetic Studies Exhibiting a Zero-Order Behavior, (c) Control Experiments, and (d) Kinetic Studies with Added dppf Exhibiting a Pseudo-First-Order Behavior



(a) Products detected:

- EPR spectroscopy
- ¹H NMR spectroscopy
- GC-MS
- GC-FID

(b) Reactions with 15 equiv. 2-X monitored by ³¹P{¹H} NMR spectroscopy

2-Cl	X = Cl	T = 323 K	$k_{\text{obs}} = 0.016(1) \text{ mol L}^{-1} \text{ s}^{-1}$
2-Br	X = Br	T = 303 K	$k_{\text{obs}} = 0.014(1) \text{ mol L}^{-1} \text{ s}^{-1}$
2-I	X = I	T = 293 K	$k_{\text{obs}} = 0.023(1) \text{ mol L}^{-1} \text{ s}^{-1}$

(c) Reactions with 15 equiv. 2-Br monitored by ³¹P{¹H} NMR spectroscopy at 303 K, with 1 equiv. of an additive

Additive: 4-Cl	$k_{\text{obs}} = 0.034 \text{ mol L}^{-1} \text{ s}^{-1}$
Additive: 3-Cl	$k_{\text{obs}} = 0.012(1) \text{ mol L}^{-1} \text{ s}^{-1}$
Additive: dppf	$t_{1/2} \ll 300 \text{ s}$

(d) Reactions with 15 equiv. 2-X monitored by ³¹P{¹H} NMR spectroscopy with 0.3 equiv. of dppf as an additive, in benzene-*d*₆ or toluene-*d*₈

X = Cl	T = 313 K (benzene- <i>d</i> ₆)	$k_{\text{obs}} = 8.4(3) \times 10^{-4} \text{ s}^{-1}$
X = Br	T = 283 K (benzene- <i>d</i> ₆)	$k_{\text{obs}} = 1.29(1) \times 10^{-3} \text{ s}^{-1}$
X = I	T = 273 K (toluene- <i>d</i> ₈)	$k_{\text{obs}} = 3.5(2) \times 10^{-3} \text{ s}^{-1}$

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 [Ni(COD)(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 ³¹P{¹H} 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

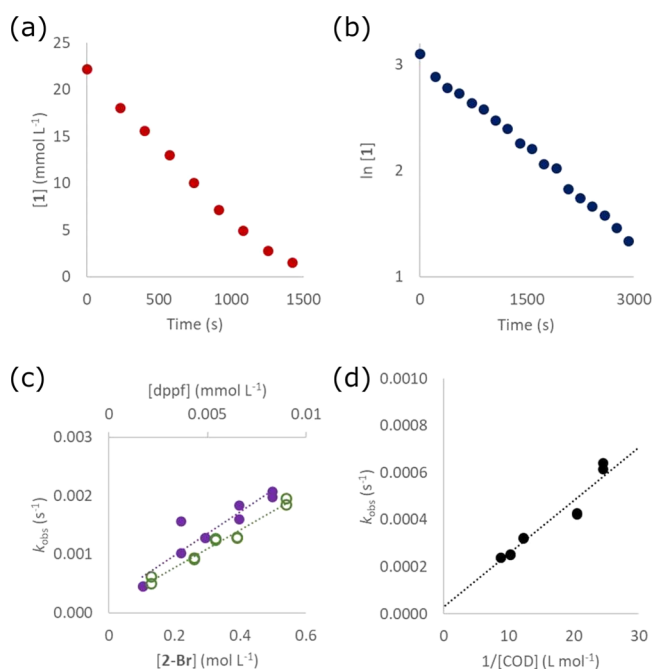


Figure 1. Kinetic data from the reactions of [Ni(COD)(dppf)] (1) (22 mmol L⁻¹) in benzene-*d*₆ at 283 K with 0.33 mol L⁻¹ (2-bromoethyl)benzene (2-Br) (unless otherwise stated): (a) pseudo-zero-order behavior (no added dppf; 303 K); (b) pseudo-first-order behavior (2.2 mmol L⁻¹ dppf; 283 K); (c) first-order in dppf (open green circles) and 2-Br (closed purple circles) (6.6 mmol L⁻¹ dppf for varied [2-Br]); and (d) inhibition by COD (6.6 mmol⁻¹ dppf).

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 [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 [NiCl₂(dppf)] (4-Cl) led to an increase in the rate of reaction, prompting speculation that [NiCl(dppf)] (3-Cl), formed from comproportionation between [Ni(COD)(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 [NiCl₂(dppf)] (4-Cl) by ³¹P{¹H} NMR spectroscopy revealed small quantities of free dppf, thus accounting for its accelerating effect. [Ni(COD)(dppf)] (1) contained approximately 1% of what was assigned as [Ni(dppf)₂] (5) by comparison with literature ³¹P NMR data ($\delta_{\text{P}} = \text{ca. } 15 \text{ ppm}$).³⁴ Complex 1 is prepared from dppf and [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 ($K_{\text{eq}} = 6.8$).

2.3. Kinetic Studies of Reactions with $[\text{Ni}(\text{dppf})_2]$.

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 $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with (2-haloethyl)benzene substrates (**2-X**) (Scheme 2d). The products of these reactions were again styrene and $[\text{NiX}(\text{dppf})]$ (**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* $[\text{Ni}(\text{dppf})]$, but the reactions of alkyl halides proceed *via* $[\text{Ni}(\text{dppf})_2]$ (**5**).

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

$$K_1 = \frac{[\mathbf{5}][\text{COD}]}{[\mathbf{1}][\text{dppf}]}$$

$$[\mathbf{5}] = K_1 \times [\mathbf{1}] \times [\text{dppf}] \times [\text{COD}]^{-1} \quad (1)$$

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

$$\text{rate} = k_2 \times [\mathbf{5}] \times [\mathbf{2-X}] \quad (2)$$

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

$$k_{\text{obs}} = K_1 \times k_2 \times [\mathbf{1}] \times [\mathbf{2-X}] \times [\text{dppf}] \times [\text{COD}]^{-1} \quad (3)$$

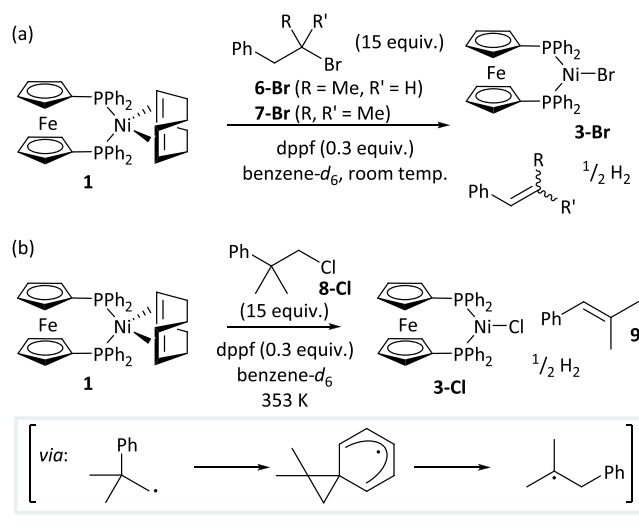
An alternative treatment based on the steady-state approximation leads to the same rate expression (see the Supporting Information).

An Eyring–Polanyi treatment of the reaction between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and 15 equiv of **2-Cl** in the presence of 0.3 equiv of dppf yielded activation parameters (see the Supporting Information); $\Delta S^\ddagger \approx 0$ for the equilibrium between **1** and **5**, and so ΔH^\ddagger is estimated at 26.2 kcal mol⁻¹ and ΔS^\ddagger 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 alkylnickel(II) halide complexes that then undergo β -hydride elimination; however, it is possible that these might form directly from Ni⁰ or through the formation of Ni^I and a radical, which then recombine to form Ni^{II}. 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;³⁶ no 1,4-diphenylbutane or ethylbenzene is detected in any of these reactions.

The reactions of secondary and tertiary alkyl halides with $[\text{Ni}(\text{COD})(\text{dppf})]$ (**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

Scheme 3. Experiments to Probe the Involvement of Radicals



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 $[\text{NiBr}(\text{dppf})]$ (**3-Br**), which is darker in color than $[\text{Ni}(\text{COD})(\text{dppf})]$ (**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 β -hydride elimination process, (1-chloro-2-methylpropan-2-yl)benzene (**8-Cl**) was used as the reaction substrate (Scheme 3b). The putative alkylnickel(II) chloride intermediate cannot undergo β -hydride elimination. Instead, 2-methyl-1-phenylprop-1-ene (**9**) was obtained as the organic product. No *tert*-butylbenzene was detected in the reaction mixture. This result is further evidence of radical intermediates; a [1,2]-phenyl shift explains the observation of **9** in the reactions of **8-Cl**.

Attempts to trap a radical intermediate with TEMPO or BHT were unsuccessful (TEMPO = 2,2,6,6-tetramethylpiperidin-1-yl)oxyl; BHT = 2,6-di(*tert*-butyl)-4-methylphenol). TEMPO reacts directly with $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**), while reactions with 1–15 equiv of BHT with respect to **1** yielded no alkane products. The radical intermediate formed is therefore rapidly trapped by the nickel complex—as required to yield the β -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^I.

2.5. Events after Radical Capture and β -Hydride Elimination. The evidence points to a mechanism in which $[\text{Ni}(\text{dppf})_2]$ (**5**) reacts with alkyl halides to form a Ni^I complex and an alkyl radical, which in turn combine to form a Ni^{II} complex that can undergo β -hydride elimination to form styrene. This would also produce $[\text{Ni}(\text{H})(\text{X})(\text{dppf})]$ (**10-X**), which must then form $[\text{NiX}(\text{dppf})]$ (**3-X**), as this is the ultimate product identified by EPR spectroscopy.

Attempts to obtain an authentic sample of $[\text{NiCl}(\text{CH}_2\text{CH}_2\text{Ph})(\text{dppf})]$ (**11-Cl**) by reaction of $[\text{NiCl}_2(\text{dppf})]$ (**4-Cl**) with the appropriate Grignard reagent led only to decomposition products including styrene and ethylbenzene; no Ni^I products were detected by EPR analysis, suggesting that Ni^I in the reactions between Ni⁰ and alkyl halides must arise

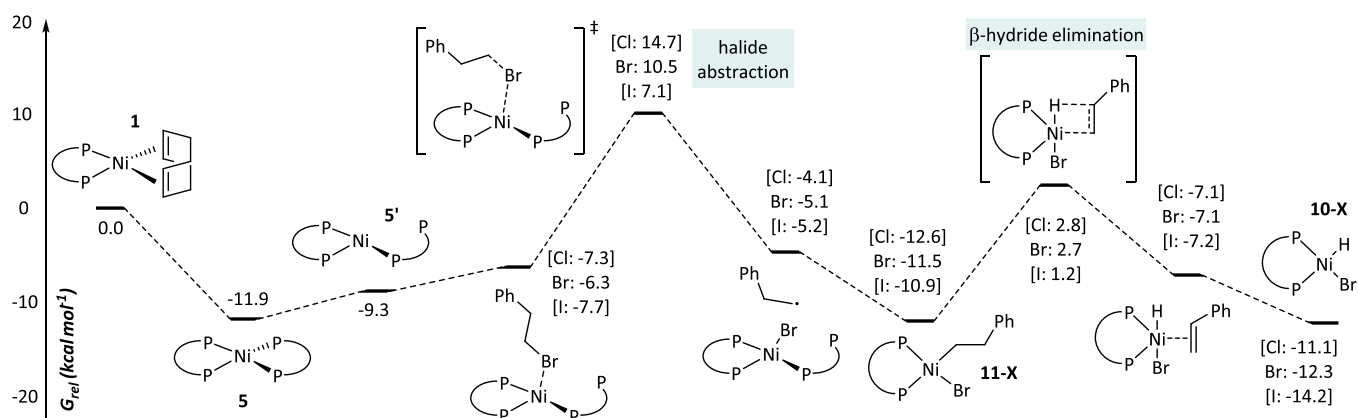


Figure 2. DFT studies of the reaction between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and (2-haloethyl)benzene substrates (**2-X**) via $[\text{Ni}(\text{dppf})_2]$ (**5**). All energies are free energies in kcal mol^{-1} in benzene solution and are quoted relative to complex **1**. The profile 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 $[\text{Ni}(\text{H})(\text{Cl})(\text{dppf})]$ (**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 $[\text{NiX}(\text{dppf})]$ (**3-X**) via comproportionation with Ni^0 . Reactions between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and 1 equiv of **2-X** (in the presence of 0.3 equiv of dppf) were followed by ^1H 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 $[\text{Ni}(\text{COD})(\text{dppf})]$ (**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 $[\text{Ni}(\text{dppf})_2]$ (**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 $[\text{Ni}(\text{dppe})_2]$ (**12**) was prepared⁴³ and exposed to alkyl halides (dppe = 1,2-bis(diphenylphosphino)ethane); this complex is known to be unreactive toward a range of species found in typical cross-coupling reactions³⁵ but is capable of undergoing outer-sphere electron transfer.⁴⁴ The dppe ligand has similar electronic properties to dppf, as judged from the IR spectra of $[\text{Ni}(\text{CO})_2(\text{dppf})]$ (ν_{CO} (DCM) = 2001, 1939 cm^{-1})⁴⁵ and $[\text{Ni}(\text{CO})_2(\text{dppe})]$ (ν_{CO} (CHCl_3) = 2006, 1945 cm^{-1}).⁴⁶ $[\text{Ni}(\text{dppe})_2]$ (**12**) does not undergo reaction with alkyl halides at all. If the reaction proceeded via outer-sphere

electron transfer, then both $[\text{Ni}(\text{dppf})_2]$ (**5**) and $[\text{Ni}(\text{dppe})_2]$ (**12**) should be competent. However, only **5**, which can open a vacant site, undergoes reaction while **12**, which cannot open a vacant site, is inert.

2.7. DFT Calculations of a Halide Abstraction Mechanism. The halide abstraction pathway was modeled using DFT calculations.⁴⁷ Pathways via $[\text{Ni}(\text{dppf})_2]$ (**5**) are discussed here; alternative pathways that are ruled out based on experimental evidence are discussed in the Supporting Information. Throughout this manuscript, energies from DFT calculations are quoted as free energies in benzene solvent with respect to $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) unless otherwise stated;⁴⁸ a 1.89 kcal/mol correction is applied to the free energy of each molecule so that the standard state is then 1 mol/L rather than 1 atm.⁴⁹

The formation of $[\text{Ni}(\text{dppf})_2]$ (**5**) from $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) is energetically favorable (Figure 2); $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]$ (**5'**) in which one phosphine is dissociated from the nickel center is slightly higher in energy than **5** (by 2.6 kcal mol^{-1}) so is also a plausible intermediate. DFT calculations overestimate the stability of **5**, compared to experimental data for the equilibrium between **1** and **5**, but qualitatively agree with the fact that the formation of **5** is favorable. Complexes **5** or **5'** might be able to undergo outer-sphere electron transfer to the alkyl halide, and so the barrier for these processes was estimated using Marcus–Hush theory;⁵⁰ the barriers are rather high (26–33 kcal mol^{-1} for **5**; 31–38 kcal mol^{-1} for **5'**; see the Supporting Information).

Halide abstraction provides an alternative pathway; it is proposed to be the predominant mechanism in this reaction due to the lack of reactivity of $[\text{Ni}(\text{dppe})_2]$ with alkyl halides (*vide supra*). The binding of alkyl halides to **5'** 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 **5**).

Halide abstraction by $[\text{Ni}(\eta^2\text{-COD})(\text{dppf})]$ ²¹ is ruled out based on the experimentally determined first-order behavior in dppf. In addition, computational studies of halide abstraction by $[\text{Ni}(\text{dppf})(\eta^2\text{-ethene})]$ (as a model for $[\text{Ni}(\eta^2\text{-COD})(\text{dppf})]$) show that this process is less competent than halide abstraction by **5'**, 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^{I} complex to form an alkylnickel(II) halide species with

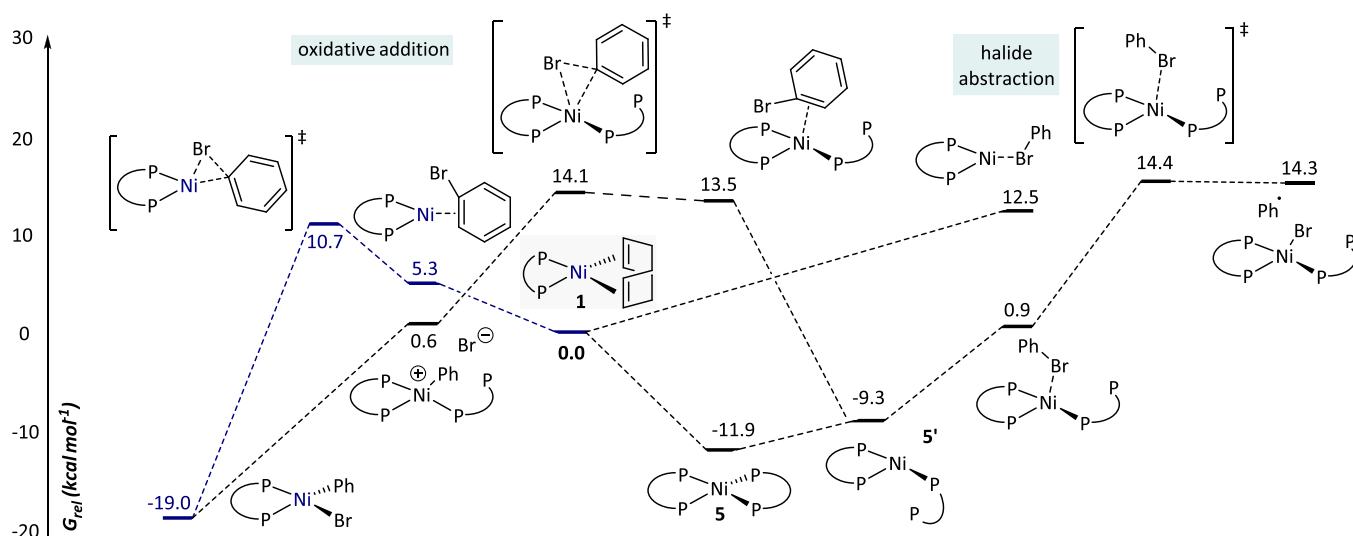
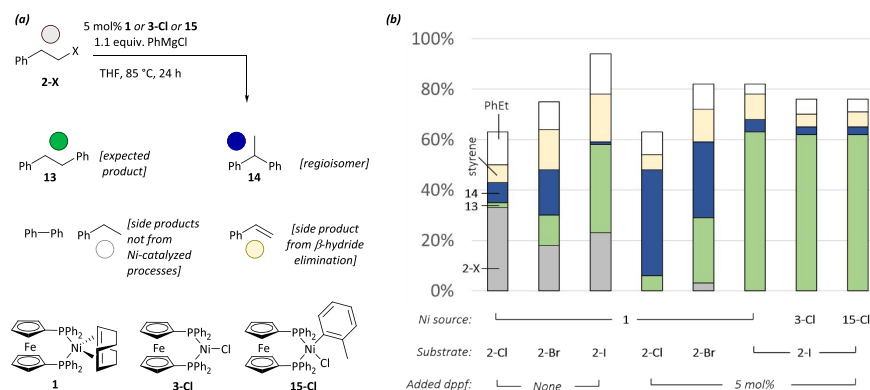


Figure 3. DFT studies of the reaction between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and bromobenzene. All energies are free energies in kcal mol^{-1} in benzene solution and are quoted relative to complex **1**. The dppf ligand is abbreviated to two linked P atoms for clarity.

Scheme 4. (a) Prototypical Kumada–Tamao–Corriu Reactions and (b) Reaction Outcomes^a



^aThe quantity of biphenyl is not plotted.

the concomitant loss of a dppf ligand (Figure 2). The resulting complex $[\text{Ni}(\text{CH}_2\text{CH}_2\text{Ph})(\text{X})(\text{dppf})]$ (**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 $[\text{Ni}(\text{H})(\text{X})(\text{dppf})(\eta^2\text{-styrene})]$, which can then dissociate styrene to form $[\text{Ni}(\text{H})(\text{X})(\text{dppf})]$ (**10-X**). We have not modeled the subsequent processes but propose that **10-X** undergoes comproportionation with Ni^0 present in the reactions to form $[\text{NiX}(\text{dppf})]$ (**3-X**) and $[\text{Ni}(\text{H})\text{dppf}]$. The latter complex could undergo disproportionation to Ni^0 and $[\text{Ni}(\text{H})_2(\text{dppf})]$, 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 $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) proceeds *via* an intermediate η^2 -complex, presents a modest barrier of 10.7 kcal/mol (from **1**), and is exergonic. We were unable to locate a corresponding halide abstraction transition state, but this would be preceded by $[\text{Ni}(\text{dppf})(\text{BrPh})]$ ($G_{\text{rel}} = 12.5$ kcal/mol), in which bromobenzene ligates the nickel center *via* a bromine lone pair. This structure is higher in energy than the oxidative addition transition state by 1.8 kcal/mol. Two pathways were also considered for reactions *via*

$[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]$ (**5'**): direct oxidative addition, which has previously been modeled for $[\text{Ni}(\text{PR}_3)_3]$ complexes ($\text{PR}_3 = \text{PMe}_3, \text{PMe}_2\text{Ph}, \text{PMePh}_2, \text{and PPh}_3$),²³ and halide abstraction. Oxidative addition would require the formation of an intermediate η^2 -complex that is very high in energy ($G_{\text{rel}} = 13.5$ kcal/mol) followed by a transition state that is higher in energy still ($G_{\text{rel}} = 14.1$ kcal/mol). Halide abstraction would proceed through $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})(\text{BrPh})]$ ($G_{\text{rel}} = 0.9$ kcal/mol), leading to a halide abstraction transition state that is even higher in energy ($G_{\text{rel}} = 14.4$ kcal/mol). These data establish that **1** will react with bromobenzene through oxidative addition to a dppf-Ni(0) species; the formation of $[\text{Ni}(\text{dppf})_2]$ as a low-energy off-cycle species would impede this reaction by increasing the barrier to oxidative addition, consistent with the observed rate decrease when dppf is added to the reaction of aryl bromides with **1**.

2.8. Relevance to Catalysis. The results discussed above allow new insights into steps that can proceed under cross-coupling reaction conditions. It is important to link these to an understanding of synthetically relevant catalytic reactions. This is especially important given the significant interest in the synthesis of sp^3 -rich molecules for medicinal chemistry and other applications, especially in fields such as pharmaceuticals and agrochemicals.^{3,4} The prototypical cross-coupling reac-

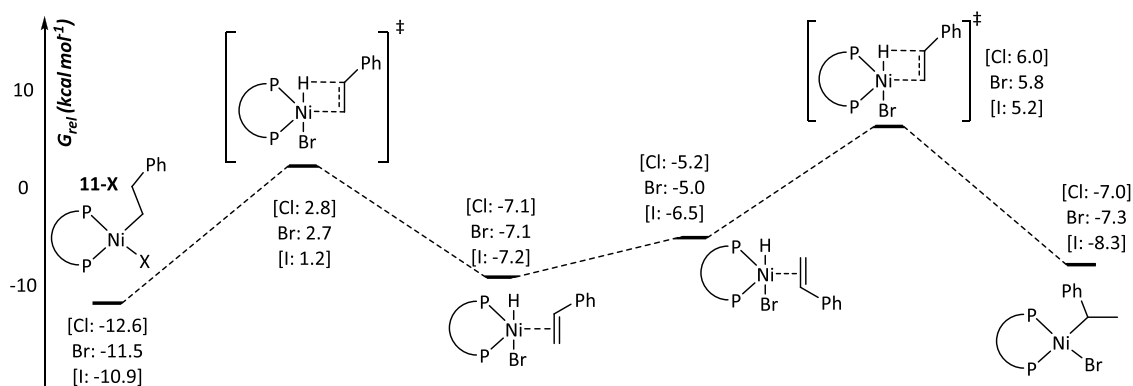
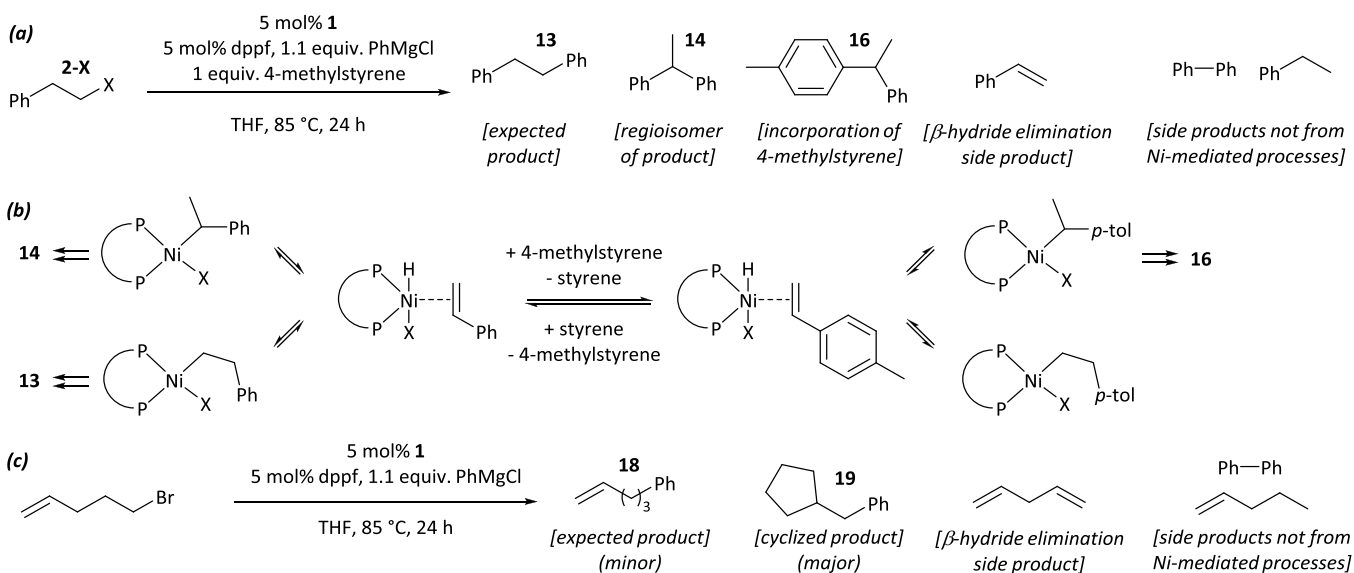


Figure 4. DFT calculations of the migratory insertion pathway to form the regioisomeric alkylnickel(II) halide species implicated in the formation of 14.

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

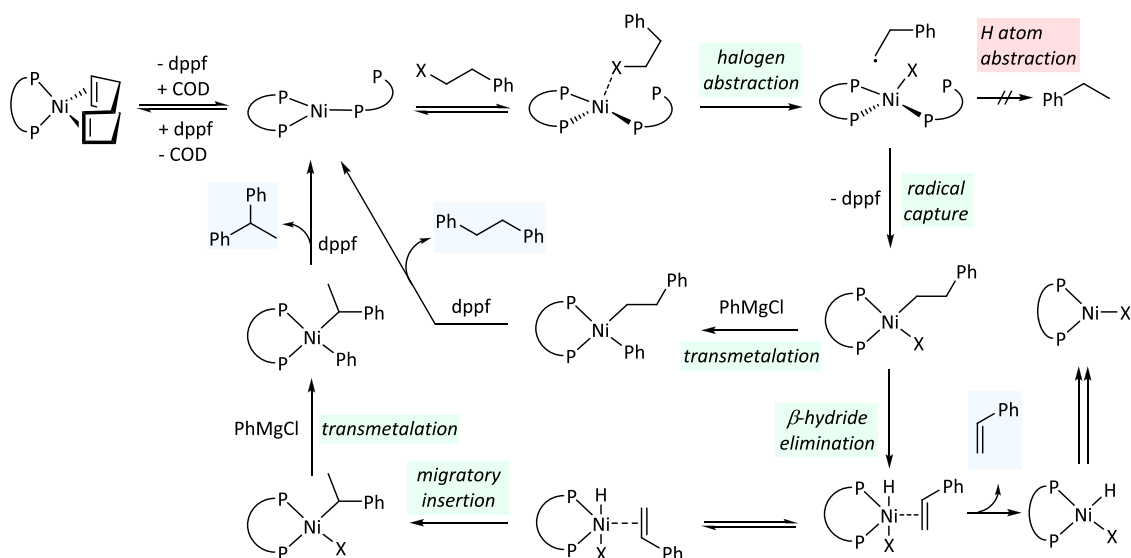


tions of (2-haloethyl)benzene substrates (2-X) with phenylmagnesium chloride were selected (Scheme 4a). These produced 1,2-diphenylethane (13), regioisomeric side product 1,1-diphenylethane (14), styrene, biphenyl, and ethylbenzene. Control reactions without a catalyst showed that the latter two products do not arise *via* nickel-catalyzed processes. Complexes [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. Ni^I complexes such as 3-Cl form Ni^I-aryl species upon reaction with Grignard reagents, and so they can serve as Ni⁰ 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 β -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 β -hydride elimination from [Ni(CH₂CH₂Ph)(X)(dppf)] (11-X) followed by reinsertion to form the regioisomeric alkylnickel(II) halide species [Ni(CH(Me)Ph)(X)(dppf)] (an overall “ β -hydrogen 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 kcal 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

Scheme 6. Processes Occurring during the Kumada Coupling Reactions of (2-Haloethyl)benzene Substrates (2-X) with PhMgCl, Catalyzed by $[\text{Ni}(\text{COD})(\text{dppf})]$ (1) in the Presence of Additional dppf^a



^aThe dppf ligand is simplified to two linked P atoms for clarity.

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 ($k = 1.8 \times 10^5 \text{ s}^{-1}$ at 20 °C)³⁷ followed by capture by Ni^{I} . 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- Ni^0 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 $[\text{Ni}(\text{dppf})_2]$ (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 Ni^{I} species and a radical; these then recombine to form a Ni^{II} species. Some alkyl radicals, such as those derived from alkyl halides without β -hydrogens, can undergo rearrangement reactions before capture by Ni^{I} . The lack of reactivity of Ni^{I} complexes

bearing alternative bidentate phosphine ligands, which more readily form $[\text{Ni}(\text{L})_2]$ complexes, such as $[\text{Ni}(\text{dppe})_2]$ (12), shows that it is necessary to generate a vacant site for the reaction to occur.

3.2. The Fate of the Ni^{II} Intermediate. The Ni^{II} 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 regioisomer of the alkylnickel(II) species; this is also able to undergo transmetalation and reductive elimination, leading to a side product. The putative nickel hydride complex $[\text{Ni}(\text{H})(\text{X})(\text{dppf})]$ (10-X) formed from β -hydride elimination then undergoes comproportionation with Ni^0 to form $[\text{Ni}(\text{X})(\text{dppf})]$ (3-X) and (ultimately) hydrogen.

This study provides insights into the activation of $\text{sp}^3 \text{ C-X}$ 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 Ni^0 , 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 repository⁵⁴ at <http://dx.doi.org/10.19061/iochem-bd-1-182>.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.0c02514>.

Synthetic procedures and characterization data for organometallic compounds; procedures for/data from kinetic studies; procedures for/data from cross-coupling reactions; computational details; and Cartesian coordinates and energies for all structures (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Lucas, E. L.; Jarvo, E. R. Stereospecific and stereoconvergent cross-couplings between alkyl electrophiles. *Nat. Rev. Chem.* **2017**, *1*, 0065.
- (2) Choi, J.; Fu, G. C. Transition metal-catalyzed alkyl-alkyl bond formation: Another dimension in cross-coupling chemistry. *Science* **2017**, *356*, eaaf7230.
- (3) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752–6756.
- (4) Lovering, F. Escape from Flatland 2: complexity and promiscuity. *MedChemComm* **2013**, *4*, 515–519.

(5) Bauer, I.; Knölker, H.-J. Iron catalysis in organic synthesis. *Chem. Rev.* **2015**, *115*, 3170–3387.

(6) Cahiez, G.; Moyeux, A. Cobalt-Catalyzed Cross-Coupling Reactions. *Chem. Rev.* **2010**, *110*, 1435–1462.

(7) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299–309.

(8) Phapale, V. B.; Guisán-Ceinos, M.; Buñuel, E.; Cárdenas, D. J. Nickel-Catalyzed Cross-Coupling of Alkyl Zinc Halides for the Formation of C(sp²)-C(sp³) Bonds: Scope and Mechanism. *Chem. – Eur. J.* **2009**, *15*, 12681–12688.

(9) Ananikov, V. P. Nickel: The “Spirited Horse” of Transition Metal Catalysis. *ACS Catal.* **2015**, *5*, 1964–1971.

(10) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp² Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767–1775.

(11) Lin, C. Y.; Power, P. P. Complexes of Ni(i): a “rare” oxidation state of growing importance. *Chem. Soc. Rev.* **2017**, *46*, 5347–5399.

(12) Vechorkin, O.; Hu, X. Nickel-Catalyzed Cross-Coupling of Non-activated and Functionalized Alkyl Halides with Alkyl Grignard Reagents. *Angew. Chem., Int. Ed.* **2009**, *48*, 2937–2940.

(13) Dudnik, A. S.; Fu, G. C. Nickel-Catalyzed Coupling Reactions of Alkyl Electrophiles, Including Unactivated Tertiary Halides, To Generate Carbon–Boron Bonds. *J. Am. Chem. Soc.* **2012**, *134*, 10693–10697.

(14) Zultanski, S. L.; Fu, G. C. Nickel-Catalyzed Carbon–Carbon Bond-Forming Reactions of Unactivated Tertiary Alkyl Halides: Suzuki Arylations. *J. Am. Chem. Soc.* **2013**, *135*, 624–627.

(15) Csok, Z.; Vechorkin, O.; Harkins, S. B.; Scopelliti, R.; Hu, X. Nickel Complexes of a Pincer NN₂ Ligand: Multiple Carbon–Chloride Activation of CH₂Cl₂ and CHCl₃ Leads to Selective Carbon–Carbon Bond Formation. *J. Am. Chem. Soc.* **2008**, *130*, 8156–8157.

(16) Lipschutz, M. I.; Yang, X.; Chatterjee, R.; Tilley, T. D. A Structurally Rigid Bis(amido) Ligand Framework in Low-Coordinate Ni(I), Ni(II), and Ni(III) Analogues Provides Access to a Ni(III) Methyl Complex via Oxidative Addition. *J. Am. Chem. Soc.* **2013**, *135*, 15298–15301.

(17) Lipschutz, M. I.; Tilley, T. D. Carbon–Carbon Cross-Coupling Reactions Catalyzed by a Two-Coordinate Nickel(II)–Bis(amido) Complex via Observable NiI, NiII, and NiIII Intermediates. *Angew. Chem., Int. Ed.* **2014**, *53*, 7290–7294.

(18) Kehoe, R.; Mahadevan, M.; Manzoor, A.; McMurray, G.; Wienefeld, P.; Baird, M. C.; Budzelaar, P. H. M. Reactions of the Ni(0) Compound Ni(PPh₃)₄ with Unactivated Alkyl Halides: Oxidative Addition Reactions Involving Radical Processes and Nickel(I) Intermediates. *Organometallics* **2018**, *37*, 2450–2467.

(19) Zhang, A.; Wang, C.; Lai, X.; Zhai, X.; Pang, M.; Tung, C.-H.; Wang, W. Reactivity of the diphosphinodithio ligated nickel(0) complex toward alkyl halides and resultant nickel(i) and nickel(ii)–alkyl complexes. *Dalton Trans.* **2018**, *47*, 15757–15764.

(20) Diccianni, J. B.; Katigbak, J.; Hu, C.; Diao, T. Mechanistic Characterization of (Xantphos) Ni (I)-Mediated Alkyl Bromide Activation: Oxidative Addition, Electron Transfer, or Halogen-Atom Abstraction. *J. Am. Chem. Soc.* **2019**, *141*, 1788–1796.

(21) Sanford, A. B.; Thane, T. A.; McGinnis, T. M.; Chen, P.-P.; Hong, X.; Jarvo, E. R. Nickel-Catalyzed Alkyl–Alkyl Cross-Electrophile Coupling Reaction of 1,3-Dimesylates for the Synthesis of Alkylcyclopropanes. *J. Am. Chem. Soc.* **2020**, *142*, 5017–5023.

(22) Bajo, S.; Laidlaw, G.; Kennedy, A. R.; Sproules, S.; Nelson, D. J. Oxidative Addition of Aryl Electrophiles to a Prototypical Nickel(0) Complex: Mechanism and Structure/Reactivity Relationships. *Organometallics* **2017**, *36*, 1662–1672.

(23) Funes-Ardoiz, I.; Nelson, D. J.; Maseras, F. Halide Abstraction Competes with Oxidative Addition in the Reactions of Aryl Halides with [Ni(PMenPh(3–n))₄]. *Chem. – Eur. J.* **2017**, *23*, 16728–16733.

(24) Nelson, D. J.; Maseras, F. Steric effects determine the mechanisms of reactions between bis(N-heterocyclic carbene)-nickel(0) complexes and aryl halides. *Chem. Commun.* **2018**, *54*, 10646–10649.

- (25) Cooper, A. K.; Burton, P. M.; Nelson, D. J. Nickel versus Palladium in Cross-Coupling Catalysis: On the Role of Substrate Coordination to Zerovalent Metal Complexes. *Synthesis* **2020**, *52*, 565–573.
- (26) Cooper, A. K.; Leonard, D. K.; Bajo, S.; Burton, P. M.; Nelson, D. J. Aldehydes and ketones influence reactivity and selectivity in nickel-catalysed Suzuki–Miyaura reactions. *Chem. Sci.* **2020**, *11*, 1905–1911.
- (27) Lavoie, C. M.; Stradiotto, M. Bisphosphines: A Prominent Ancillary Ligand Class for Application in Nickel-Catalyzed C–N Cross-Coupling. *ACS Catal.* **2018**, *8*, 7228–7250.
- (28) Barth, E. L.; Davis, R. M.; Mohadjer Beromi, M.; Walden, A. G.; Balcells, D.; Brudvig, G. W.; Dardir, A. H.; Hazari, N.; Lant, H. M. C.; Mercado, B. Q.; Peczak, I. L. Bis(dialkylphosphino)ferrocene-Ligated Nickel(II) Precatalysts for Suzuki–Miyaura Reactions of Aryl Carbonates. *Organometallics* **2019**, *38*, 3377–3387.
- (29) Mohadjer Beromi, M.; Nova, A.; Balcells, D.; Brasacchio, A. M.; Brudvig, G. W.; Guard, L. M.; Hazari, N.; Vinyard, D. J. Mechanistic Study of an Improved Ni Precatalyst for Suzuki–Miyaura Reactions of Aryl Sulfamates: Understanding the Role of Ni(I) Species. *J. Am. Chem. Soc.* **2017**, *139*, 922–936.
- (30) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. Fundamental Studies and Development of Nickel-Catalyzed Trifluoromethylthiolation of Aryl Chlorides: Active Catalytic Species and Key Roles of Ligand and Traceless MeCN Additive Revealed. *J. Am. Chem. Soc.* **2015**, *137*, 4164–4172.
- (31) Authentic samples of styrene, ethylbenzene, and [NiX(dppf)] were used to calibrate the relevant analyses.
- (32) Kalvet, I.; Guo, Q.; Tizzard, G. J.; Schoenebeck, F. When Weaker Can Be Tougher: The Role of Oxidation State (I) in P- vs N-Ligand-Derived Ni-Catalyzed Trifluoromethylthiolation of Aryl Halides. *ACS Catal.* **2017**, *7*, 2126–2132.
- (33) Guard, L. M.; Mohadjer Beromi, M.; Brudvig, G. W.; Hazari, N.; Vinyard, D. J. Comparison of dppf-Supported Nickel Precatalysts for the Suzuki–Miyaura Reaction: The Observation and Activity of Nickel(I). *Angew. Chem., Int. Ed.* **2015**, *54*, 13352–13356.
- (34) Pilloni, G.; Toffoletti, A.; Bandoli, G.; Longato, B. Homoleptic Complexes of Cobalt(0) and Nickel(0,I) with 1,1'-Bis(diphenylphosphino)ferrocene (dppf): Synthesis and Characterization. *Inorg. Chem.* **2006**, *45*, 10321–10328.
- (35) Clevenger, A. L.; Stolley, R. M.; Staudaher, N. D.; Al, N.; Rheingold, A. L.; Vanderlinden, R. T.; Louie, J. Comprehensive Study of the Reactions Between Chelating Phosphines and Ni(cod)₂. *Organometallics* **2018**, *37*, 3259–3268.
- (36) Sheldon, R. A.; Kochi, J. K. Pair production and cage reactions of alkyl radicals in solution. *J. Am. Chem. Soc.* **1970**, *92*, 4395–4404.
- (37) Newcomb, M. Radical Kinetics and Clocks. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; John Wiley & Sons, 2012, p. 9.
- (38) Eberhardt, N. A.; Guan, H. Nickel Hydride Complexes. *Chem. Rev.* **2016**, *116*, 8373–8426.
- (39) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176–2179.
- (40) Flener Lovitt, C.; Frenking, G.; Girolami, G. S. Donor–Acceptor Properties of Bidentate Phosphines. DFT Study of Nickel Carbonyls and Molecular Dihydrogen Complexes. *Organometallics* **2012**, *31*, 4122–4132.
- (41) Hoshimoto, Y.; Hayashi, Y.; Suzuki, H.; Ohashi, M.; Ogoshi, S. One-Pot, Single-Step, and Gram-Scale Synthesis of Mononuclear [(η⁶-arene)Ni(N-heterocyclic carbene)] Complexes: Useful Precursors of the Ni⁰–NHC Unit. *Organometallics* **2014**, *33*, 1276–1282.
- (42) de Aguirre, A.; Funes-Ardoiz, I.; Maseras, F. Four Oxidation States in a Single Photoredox Nickel-Based Catalytic Cycle: A Computational Study. *Angew. Chem., Int. Ed.* **2019**, *58*, 3898–3902.
- (43) Cundy, C. S. Tetrakis(triethylphosphine)nickel(0) and related complexes. *J. Organomet. Chem.* **1974**, *69*, 305–310.
- (44) Elson, I. H.; Morrell, D. G.; Kochi, J. K. Electron transfer from d10 species: A possible initiation for free radical pathways in oxidative additions. *J. Organomet. Chem.* **1975**, *84*, C7–C10.
- (45) Ringenberg, M. R.; Döttinger, F. Anodic Mechanism of 1,1'-Bis(diphenylphosphino)ferrocenedicarbonylnickel Determined by Low-Temperature Spectroelectrochemistry. *Eur. J. Inorg. Chem.* **2019**, *2019*, 2430–2435.
- (46) Van Hecke, G. R.; Horrocks, W. D., Jr. Approximate Force Constants for Tetrahedral Metal Carbonyls and Nitrosyls. *Inorg. Chem.* **1966**, *5*, 1960–1968.
- (47) All calculations were carried out in Gaussian16 using the B3LYP functional with Grimme's D3 dispersive corrections. Optimization was carried out without symmetry corrections or solvation, with the LANL2TZ(f) basis set on Ni and Fe, the LANL2DZ(dp) basis set on Br and I, and the 6-31G(d) basis set on all other atoms. Frequency calculations were used to verify the nature of stationary points. Potential energies were refined using single-point calculations in benzene solvent (SMD) and with the 6-311+G(d,p) basis set on all atoms except I. Full details and coordinates for all structures can be found in the [Supporting Information](#).
- (48) Optimization was carried out in the gas phase because attempts to optimize some of these structures in solvent using PCM or SMD methods were unsuccessful. Some structures could be optimized in solvent, but this made rather little difference to the energetics of the relevant steps. See the [Supporting Information](#) for more details.
- (49) Harvey, J. N.; Himo, F.; Maseras, F.; Perrin, L. Scope and Challenge of Computational Methods for Studying Mechanism and Reactivity in Homogeneous Catalysis. *ACS Catal.* **2019**, *9*, 6803–6813.
- (50) de Aguirre, A.; Funes-Ardoiz, I.; Maseras, F. Computational Characterization of Single-Electron Transfer Steps in Water Oxidation Inorganics. *Inorganics* **2019**, *7*, 32.
- (51) Reaction outcomes were determined using GC-FID analysis with an internal standard, which was calibrated using authentic samples of all products. See the [Supporting Information](#) for full details and reaction data.
- (52) Mohadjer Beromi, M.; Banerjee, G.; Brudvig, G. W.; Hazari, N.; Mercado, B. Q. Nickel(I) Aryl Species: Synthesis, Properties, and Catalytic Activity. *ACS Catal.* **2018**, *8*, 2526–2533.
- (53) Li, Y.; Luo, Y.; Peng, L.; Li, Y.; Zhao, B.; Wang, W.; Pang, H.; Deng, Y.; Bai, R.; Lan, Y.; Yin, G. Reaction scope and mechanistic insights of nickel-catalyzed migratory Suzuki–Miyaura cross-coupling. *Nat. Commun.* **2020**, *11*, 417.
- (54) Alvarez-Moreno, M.; de Graaf, C.; López, N.; Maseras, F.; Poblet, J. M.; Bo, C. Managing the Computational Chemistry Big Data Problem: The ioChem-BD Platform. *J. Chem. Inf. Model.* **2015**, *55*, 95–103.