The Effect of Added Ligands on the Reactions of [Ni(COD)(dppf)] with Alkyl Halides: Halide Abstraction May Be Reversible

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ABSTRACT: The reactions of dppf-nickel(0) with alkyl halides proceed via three-coordinate nickel(0) intermediates of the form [Ni(dppf)(L)]. The effects of the identity of the added ligand (L) on catalyst speciation and the rates of reactions of [Ni(COD)(dppf)] with alkyl halides have been investigated using kinetic experiments and density functional theory calculations. A series of monodentate ligands have been investigated in attempts to identify trends in reactivity. Sterically bulky and electron-donating ligands are found to decrease the reaction rate. It was found that (i) the halide abstraction step is not always irreversible and the subsequent recombination of a nickel(I) complex with an alkyl halide can have a significant effect on the overall rate of the reaction and (ii) some ligands lead to very stable [Ni(dppf)(L)]₂ species. The yields of prototypical (dppf)nicket-catalyzed Kumada cross-coupling reactions of alkyl halides are significantly improved by the addition of free ligands, which provides another important variable to consider when optimizing nickel-catalyzed reactions of alkyl halides.

INTRODUCTION

The importance of molecules that contain a large number of sp³ centers in industries such as pharmaceuticals and agrochemicals is driving much of the reaction discovery and development in the field of nickel catalysis. However, despite recent advances in our mechanistic understanding of nickel catalysis, gaps in this understanding still remain. This is apparent for the case of the reactions of nickel(0) complexes with alkyl halides, which are quite different from the reactions of nickel(0) complexes with sp² organohalides. The reactions of alkyl halides have a greater propensity to involve radical intermediates, and deleterious β-hydride elimination presents further challenges. We have recently focused our attention on the reactions of alkyl halides with nickel(0), with the aim of developing a better understanding of these reactions and thereby underpinning future reaction discovery, development, and understanding.

The outcomes of nickel-catalyzed reactions can be extremely sensitive to the structure(s) of the ligand(s). For example, Liu et al. found that [Ni(COD)₂]/dppf was not a competent catalyst for the cross-coupling of phenyl triflate and aniline but that a modified ligand (1,1′-bis(di(3,5-trifluoromethylphenyl)-phosphino)ferrocene) enabled the reaction to achieve almost quantitative conversion. There are many examples of situations where the mechanisms of nickel-catalyzed reactions can also be very sensitive to the ligand structure. If the nickel-catalyzed Suzuki–Miyaura coupling of benzylic esters is carried out using tricyclohexylphosphine as the ligand, the stereochemistry at the benzylic position is retained; however, the use of SIMes produces the stereoinverted product via a different mechanistic pathway. The size of the NHC ligand in [Ni(NHC)₂] complexes determines whether [Ni(ArX(NHC)₂)] or [NiX-

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The experimental and computational evidence that was gathered supported a mechanism in which \([\text{Ni(Ni(dppf))}_2]\) was in equilibrium with \([\text{Ni(dppf)}_2]^{2+}\) (with the additional dppf being a trace impurity in 1), and \([\text{Ni(k-dppf)}(\text{k}^1\text{-dppf})]\) performed a halide abstraction step to produce \([\text{Ni}(X)(\text{k}^2\text{-dppf})(\text{k}^1\text{-dppf})]\) plus an alkyl radical (Scheme 1a); subsequent dppf dissociation and the recombination of the alkyl radical and nickel(1) complex yielded the formal oxidative addition product \([\text{Ni}(X)(\text{R})(\text{dppf})]\), which underwent rapid \(\beta\)-hydride elimination. The final products were \([\text{Ni}(X)(\text{dppf})]\) (3) and alkene, with no alkane product observed.

The reaction of \([\text{Ni(COD)}(\text{dppf})]\) with alkyl halides relies upon the presence of additional dppf in order to form the three-coordinate species necessary for the halide abstraction step. However, the bidentate nature of dppf means that \([\text{Ni(dppf)}_2]\) is lower in energy than the desired \([\text{Ni(k}^2\text{-dppf})(\text{k}^1\text{-dppf})]\) intermediate. Here, we have examined the use of a range of alternative monodentate ligands and their effects on the rate of stoichiometric and catalytic reactions of alkyl halides (Scheme 1b).

### RESULTS AND DISCUSSION

#### Kinetic Studies of Stoichiometric Reactions with Alternative Ligands

Our previous study\(^{20}\) established that the rate of reaction between \([\text{Ni(COD)}(\text{dppf})]\) (1) and alkyl halides was significantly increased by the addition of free dppf ligands, as this shifted the equilibrium between 1 and \([\text{Ni(dppf)}_2]\) toward the latter species. For this study, a selection of monodentate group 15 ligands were assembled with a diverse range of steric and electronic properties and where the Lewis basic atom was nitrogen, phosphorus, arsenic, or antimony. These were all used as additives in stoichiometric reactions between 1 and (2-bromoethyl)benzene (4-Br) which were monitored by \(^{31}\text{P}\) NMR spectroscopy. All experiments were pseudo-first-order in 1, and the \(^{31}\text{P}\) NMR spectra confirmed that dppf remained bound to the nickel center throughout, with no free dppf ligand detected (\(\delta_p = -17\) ppm). Data were collected at one or two of three temperatures (263, 273, or 293 K) depending on how fast the reaction proceeded; the results for reactions with 15 monodentate ligands, along with previous data for the reaction with added dppf,\(^{20}\) are recorded in Scheme 2. Pseudo-first-order constants are listed in the order of largest to smallest. Data span a ca. 200-fold range of rate constants.

#### Scheme 2. Kinetic Studies of the Reactions between \([\text{Ni(COD)}(\text{dppf})]\) (1) (0.022 mol L\(^{-1}\)) and (2-Bromoethyl)benzene (4-Br) (0.33 mol L\(^{-1}\)) in Toluene-\(d_8\) in the Presence of Various Added Ligands (0.0132 mol L\(^{-1}\))

| Ligand                          | \(k_{rel}\) \(x 10^3\) s\(^{-1}\) | Temperature (K) |
|--------------------------------|-----------------------------------|-----------------|
| \(\text{P(p-C}_6\text{H}_5\text{CF}_3}\) | 2.8(1)                           | 263             | 1.00  |
| \(\text{P(m-C}_6\text{H}_4\text{Me}_3}\) | 2.4(1)                           | 273             | 0.89  |
| \(\text{P(p-C}_6\text{H}_4\text{F}_3}\) | 2.4(1)                           | 293             | 0.89  |
| \(\text{P(p-C}_6\text{H}_4\text{Me}_3}\) | 1.7(1)                           | 263             | 0.63  |
| \(\text{PPh}_3\)                  | 1.40(3)                          |                 | 0.52  |
| \(\text{P(p-C}_6\text{H}_4\text{OMe}_3}\) | 1.5(1)                           |                 | 0.48  |
| \(\text{FePPh}_2\)                | 1.80(6)                          |                 | 0.20  |
| \(\text{P(n-Bu}_3\)\)             | 0.87(1)                          |                 | 0.091 |
| \(\text{dppf}\)                   | 0.50(1)                          |                 | 0.055 |
| \(\text{PM}_{3}\)                 | 3.3(1)                           |                 | 0.030 |
| \(\text{AsPh}_3\)                | 2.7(1)                           |                 | 0.026 |
| \(\text{SbPh}_3\)                | 1.8(1)                           |                 | 0.019 |
| \(\text{PC}_{3}\)                 | 0.94(3)                          |                 | 0.008 |
| \(\text{P(o-C}_6\text{H}_4\text{Me}_3}\) | 0.04(1)                          |                 | 0.004 |
| \(\text{OPPh}_3\)                | 0.45(2)                          |                 | 0.004 |
| \(\text{NE}_3\)                   | 0.45(2)                          |                 | 0.004 |

A series of reactions were carried out with different concentrations of triphenylphosphine, confirming that the reaction is first order in added triphenylphosphine (Figure 1a,b); our previous work noted that the reaction was first order in dppf when this was the added ligand.\(^{20}\)

The use of diphenylphosphinoferrocene (FcPPh\(_2\)) as an additive led to a higher rate of reaction than the corresponding experiment with dppf. This can be rationalized by considering the requirement for (bidentate) dppf to dissociate one phosphine atom from the nickel center to enable the reaction to occur; the binding of a second FcPPh\(_2\) ligand does not benefit from the chelate effect.

It is apparent that neither the steric nor the electronic properties of the ligand dominate the observed effects on reaction rates; The Tolman electronic parameter (TEP) and cone angle data are gathered for some of the ligands deployed in this study (Table 1).\(^{21}\) It was initially anticipated that electron-rich ligands would generate a more reactive nickel(0) complex and therefore accelerate halide abstraction. However, the use of tricyclohexylphosphine leads to a very slow reaction with no conversion after 45 min at 273 K (\(k_{rel} = 0.008\)); reactions in the presence of trimethylphosphine (\(k_{rel} = 0.030\)) or tri(n-butyl)-phosphine (\(k_{rel} = 0.091\)) are faster. The reaction with triphenylphosphine as an additive led to a reaction that was faster still (\(k_{rel} = 0.52\)), despite being less electron-rich.
obtained using σ triarylphosphines (Figure 1d), but in both cases these show L σ (using substituent constants σ substituted triarylphosphines. (d) Hammett plot (using substituent constants σ) for the reactions in the presence of substituted triarylphosphines. (d) Hammett plot (using substituent constants σ).

Table 1. Relative Rate Constants for Selected Reactions where the TEP and Cone Angle Are Known for the Corresponding Ligand

| Ligand               | TEP (cm⁻¹) | Cone angle (°) | %Vbur | krel |
|----------------------|------------|----------------|-------|------|
| P(m-C₆H₄Me)₃        | 2067.2     | 31.4           | 0.89  | 0.61 |
| P(p-C₆H₄Me)₃        | 2071.3     | 31.4           | 0.89  | 0.61 |
| P(p-C₆H₄Me)₃        | 2066.7     | 145            | 31.3  | 0.63 |
| PPh₃                 | 2068.9     | 145            | 31.2  | 0.52 |
| P(p-C₆H₄OMe)₃       | 2066.7     | 145            | 31.3  | 0.48 |
| (n-Bu)₃             | 2060.3     | 132            | 0.91  | 0.61 |
| PMe₃                 | 2064.1     | 118            | 24.0  | 0.030 |
| P(ό-C₆H₄Me)₃       | 2066.6     | 194            | 0.004 | 0.61 |
| P(OPh)₃             | 2085.3     | 128            | 0.004 | 0.61 |

A Hammett plot of log(kobs(X)/kobs(H)) versus σ for a set of five triarylphosphines gave a relatively shallow gradient of ρ = 0.37 (Figure 1c). A slightly better correlation with ρ = 0.24 is obtained using σ parameters for the para-substituted triarylphosphines (Figure 1d), but in both cases these show that the reaction is promoted by electron-poor triarylphosphines. The relatively simple reaction mechanism that we had initially anticipated—i.e., ligand binding, halide abstraction, and ligand dissociation—is too simple to explain the observed trends, and so, we turned to computational chemistry for additional insight.

**DFT Calculations of the Reaction Mechanism.** Density functional theory (DFT) calculations carried out during our earlier study supported the proposal that the reaction occurs via formation of a three-coordinate nickel(0) complex, halide abstraction to form nickel(I) plus a radical, and recombination of these species to form a nickel(II) complex. The nickel(II) complex is then proposed to undergo β-hydride elimination followed by comproportionation to form [NiX(dppf)] (3), styrene, and hydrogen. For details of the level of theory used in this study please see the Experimental Section. Trimethylamine was used as a conformationally less complicated model for triethylamine; we have previously used trimethylphosphine as a model for triethylphosphine.

The reactions of [Ni(COD)(dppf)] (1) with (2-bromoethyl)benzene (4-Br) in the presence of added ligands were systematically studied. Scheme 3 outlines the mechanism, while Table 2 records the corresponding data and the overall barrier for the halide abstraction transition state versus the lowest energy preceding intermediate. For simplicity, the reactions with the corresponding alkyl chloride and alkyl iodide were not studied here.

In most cases, [Ni(dppf)(L)] had Grel = -0.6 to 1.6 kcal/mol, with the exceptions of trimethylamine (Grel = 14.3 kcal/mol) and triphenylphosphite (Grel = -6.1 kcal/mol). The strong binding of the π-accepting phosphite to the dppf-nickel(0) fragment is not unexpected, given the important role of π-backbonding in the coordination chemistry of organometallic complexes of nickel(0). The steric profile of each coordinated ligand in a selection of the corresponding [Ni(dppf)(L)] complexes was evaluated using the percent buried volume (%Vbur) metric (see the Supporting Information for the full data set). This metric has been widely applied across organometallic chemistry and catalysis. The %Vbur value did not vary as much as was anticipated. For example, tricyclohexyloxiphosphine and triphenylphosphine have %Vbur that vary by less than one unit (31.9 and 31.2, respectively), despite their vastly different cone angles (170° and 145°, respectively). Trimethylphosphine (24.0), triphenylarsine (22.7), and triphenylstibine (27.7) have a lower %Vbur than triarylphosphines (ca. 31) in this environment.

It is possible for two monodentate ligands to coordinate the [Ni(dppf)] fragment in most cases; [Ni(dppf)(PMe₃)] and [Ni(dppf)(P(OPh)₃)] are known species that have been fully characterized using methods including single crystal X-ray diffraction. The possible formation of these species was also

![Figure 1. (a) Kinetic data for the reaction between [Ni(COD)(dppf)] (1) (0.022 mol L⁻¹) and (2-bromoethyl)benzene (4-Br) (0.33 mol L⁻¹) at 263 K in toluene-d₈ in the presence of triphenylphosphine (0.0132 mol L⁻¹). (b) Plot of kobs versus [PPh₃]. (c) Hammett plot (using substituent constants σ) for the reactions in the presence of substituted triarylphosphines. (d) Hammett plot (using substituent constants σ).](image-url)

**Scheme 3. Mechanism for the Reactions of 1 Plus the Added Ligand (L) with (2-Bromoethyl)benzene 4-Br**

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investigated computationally. In the case of trimethylamine and tricyclohexylphosphine, geometry optimization led to the spontaneous decoordination of the second ligand. In all other cases, [Ni(dppf)(L)₂] complexes could be optimized as minima on the free energy surface. For triphenylarsine, triphenylstibene, trimethylphosphine, and triphenylphosphite the binding of a second ligand is very favorable, and so this increases the barrier to halide abstraction by [Ni(dppf)(L)₂]; this explains the rather poor performance of these four ligands in the kinetic experiments. The binding of a second diphenylphosphinoferrocene or triarylphosphine ligand is endergonic by a few kcal/mol.

The next step is the formation of [Ni(BrCH₂CH₂Ph)(dppf)(L)₂], although in many cases the steric environment around nickel precludes short Ni...Br distances. These are typically slightly higher in energy than [Ni(dppf)(L)₂], presumably due to the entropic cost of bringing two molecules together. Halide abstraction takes place subsequently, and forms [NiBr(dppf)(L)] plus an alkyl radical. Our initial treatment of the data assumed facile ligand dissociation and radical recombination to form [NiBr(CH₂CH₂Ph)(dppf)] (S) (G_{rel} = −4.2 kcal/mol) which transpired to be an oversimplification of the reaction mechanism; the events after halide abstraction but before the formation of S will be discussed subsequently.

An initial analysis of the data revealed limited agreement between experimentally determined rate constants and computationally determined halide abstraction barriers. FePPh₃ is a more effective ligand than dppf, and this is reflected in the 1.4 kcal/mol decrease in ΔG°. However, the DFT data for triarylphosphine ligands are at odds with the experimental observations and instead suggest that the reactions with more electron-rich ligands should proceed more quickly.

We next considered the possibility that the halide abstraction is in fact reversible and that a subsequent step in the mechanism might be rate-determining in some or all cases. Experimental evidence suggests that the alkyl radical exists for long enough to undergo unimolecular rearrangement reactions, but the lack of any corresponding alkane or dimerized product suggests that it is captured by the nickel complex relatively quickly. However, the radical might be captured by the formation of a nickel(II) complex (formation of a C–Ni bond) or by the abstraction of the halide from the nickel center (C–X reformation), especially within the relatively crowded environment of the nickel center.

Further calculations identified transition states for the combination of the alkyl radical with [NiBr(dppf)(L)], where L is trimethylphosphine, tricyclohexylphosphine, or triphenylphosphine. In the case of trimethylphosphine, two transition states were characterized: one with approximately trigonal bipyramidal geometry and one (of lower energy) with distorted square-based pyramidal geometry. For tricyclohexylphosphine and triphenylphosphine pathways only the latter geometry of the transition state was located; attempts to locate trigonal bipyramidal transition states were unsuccessful. Geometry optimizations of structures along the reaction coordinate confirmed that the transition states linked the nickel(I) complex and a square-based pyramidal nickel(II) species.

The barrier to recombination varies considerably depending on the identity of the ligand. For tricyclohexylphosphine, the radical capture transition state is significantly higher in energy than the halide abstraction transition state (31.7 versus 26.3 kcal/mol), which explains the poor performance of this ligand in the stoichiometric reactions. In contrast, the recombination of the radical with the triarylphosphine complex presents no significant barrier.

Figure 2 displays the free energy profiles for the reactions where trimethylphosphine, tricyclohexylphosphine, and triphenylphosphine are used as additives; these illustrate the three types of behavior that are observed in these reactions. These are discussed in turn.

In the case of trimethylphosphine, the formation of [Ni(dppf)(PMe₃)₂] inhibits the reaction because one of the trimethylphosphine ligands must dissociate before halide abstraction can occur, and this carries a significant energetic penalty. Similar behavior is observed for triphenylphosphine, triphenylarsine, and triphenylstibene.

The reaction in the presence of tricyclohexylphosphine suffers from a large barrier to radical recombination with the nickel(I) intermediate. A structure for [Ni(dppf)(PCy₃)₂] could not be obtained because one of the tricyclohexylphosphine ligands dissociated during geometry optimization, and so, the barrier to halide abstraction is reasonable. However, the radical formed...
during halide abstraction (D) faces a smaller barrier to re-form the C−Br bond (26.5 kcal/mol) than to form a C−Ni bond (31.9 kcal/mol), and so the halide abstraction is reversible.

The reaction in which triphenylphosphine is present faces neither of these issues. The coordination of a second phosphine (ΔG = 3.9 kcal/mol) is less favorable than coordination of the substrate (ΔG = 1.1 kcal/mol) and the transition states for C−Br formation and C−Ni formation are close in energy (Grel = 24.6 and 26.4 kcal/mol), respectively.

The “ideal” added ligand for this process is therefore a ligand that coordinates only once but is not sufficiently bulky to interfere with the recombination of the radical with nickel(I).

Relevance to Catalysis. We sought to link our new understanding of the effects of ligands on the halide abstraction step to the outcomes of catalytic reactions of importance to synthetic chemistry. A series of prototypical Kumada−Tamao−Corriu cross-coupling reactions were carried out using (2-haloethyl)benzene substrates (4-Cl, 4-Br, 4-I) to understand the effects of additives on catalytic reactions (Scheme 4). All reactions were catalyzed by 5 mol % [Ni(COD)(dppf)] in the
presence of 5 mol % of an additional ligand; the same conditions were used in our previous study.

These reactions, and reactions closely analogous to these, have previously been carried out using other nickel catalysts and

Figure 3. Product distributions in model Kumada−Tamao−Corriu cross-coupling reactions using different added ligands. Reactions were conducted with three substrates: (a) (2-iodoethyl)benzene, (b) (2-bromoethyl)benzene, and (c) (2-chloroethyl)benzene.
typically at temperatures around room temperature. Catalyst systems include 10 mol % Cp*CH3-PPh2/5 mol % NiCl2, 5 mol % of a nickel pincer complex, 37 2.5 mol % of a dinickel(II)/ tridente nitrogen ligand complex, 38 and 2 mol % of a diphosphinodithio complex of nickel. 39 The topics of nickel-catalyzed alkyl halide cross-coupling reactions 40,41 and nickel-catalyzed Kumada–Tamao–Corriu reactions have been reviewed. 42

The reactions undertaken for this study, like those disclosed previously, 20 produced the expected 1,2-diphenylethylen e product (6), the 1,1-diphenylethylene regioisomer (7), styrene, ethylbenzene, and biphenyl (Figure 3). We have shown previously, through the use of control reactions, that ethylbenzene and biphenyl do not arise from nickel-catalyzed reactions. 20 The regioisomer is likely formed from $\beta$-hydride elimination followed by migratory insertion to generate the added ligand can of course a...20

This added ligand must be noted that a full optimization of this reaction has not been carried out, but the choice of the added ligand represents an important factor that should be considered in these reactions. This added ligand can of course affect steps other than halide abstraction, but an examination of the full catalytic cycle for this reaction is beyond the scope of the present study.

### CONCLUSIONS

This study has established that a range of different added ligands increase the rate of the reaction between \( \text{Ni(COD)(dppf)} \) (1) and a model alkyl bromide (4-Br), with a ca. 200-fold range of rate constants. This is consistent with our current mechanistic model which requires a three-coordinate nickel(0) complex that can abstract the halide atom from the alkyl halide substrate. DFT studies have provided further insight into the reaction, identifying that the rate-determining step in the stoichiometric reactions between 1 and 4-Br can be either the halide abstraction step or the recombination of the alkyl radical with the nickel(I) complex formed during halide abstraction.

Studies of a prototypical Kumada–Tamao–Corriu reaction have established that the choice of ligand has relatively little effect for the reactions of 4-I but that the reactions in the absence of an added ligand give poor outcomes. The outcomes of the reactions of 4-Br and 4-Cl show a more complicated dependence on the structure of the added ligand, but this certainly presents a useful vector for the optimization of these types of cross-coupling reactions.

Further studies of the complex reactions between nickel(0) and alkyl halides and of the related catalytic cross-coupling reactions are currently underway within our laboratories.

The raw data underpinning the experimental parts of this study can be downloaded from the University of Strathclyde Knowledgebase at  http://dx.doi.org/10.15129/10523ca4-2c98-4d77-8575-06d97ba66621. Computational chemistry data underpinning this study can be accessed via the ioChemBD data repository 43 at  http://dx.doi.org/10.19061/iochem-bd-1-208.

### EXPERIMENTAL SECTION

**Materials.** Anhydrous toluene, THF, and hexane were obtained from an Inert Technologies PureSolv apparatus (<10 ppm water by Karl-Fischer titration). Any manipulations of air-sensitive nickel complexes were carried out under argon using Schlenk techniques or in a glovebox. Substrates used for kinetic experiments and cross-coupling reactions were obtained from commercial sources and used as supplied. The synthesis of FePPh3 and some of the reaction side products are detailed below; characterization data for the remaining products can be found in our previous paper. 20 \[ \text{Ni(COD)} \] (96% purity) was purchased from Alfa Aesar and stored at –35 °C in a glovebox freezer. 1,1′-Bis(diphenylphosphino)ferrocene was purchased from Fluorochem and stored in a glovebox. \[ \text{Ni(COD)(dppf)} \] was prepared according to the literature method. 19 Deuterated solvents were obtained from commercial sources and dried overnight on 4 Å molecular sieves before use.

**Analysis.** NMR spectroscopy was performed using Bruker AV3–400 (liquid nitrogen cryoprobe), Bruker AV3–400 Nano (BBO-z-ATMA probe), or Bruker AVIII-600 (BBO-z-ATMA) instruments. All kinetic experiments were performed using the latter instrument. 1H NMR spectra are referenced to residual solvent signals, 13C{1H} NMR spectra are referenced to the deuterated solvent signal, and 31P{1H} NMR spectra are externally referenced. 44 Chemical shifts are given in ppm and coupling constants in Hertz. Gas chromatography–mass spectrometry (GC–MS) analyses were carried out using an Agilent 7890A gas chromatograph fitted with a RESTEK-Rxi-5Sil column (30 m × 0.32 mm I.D. × 0.25 μm) connected to an Agilent 5975C MSD running in an EI mode. GC-FID analyses were carried out using an Agilent 7890A gas chromatograph fitted with an Agilent HPS column (30 m × 0.25 mm I.D. × 0.25 μm).

**1,4-Diphenylbutylane.** 1,4-Diphenyl-1,3-butadiene (1 g, 4.8 mmol) was added to a flask with Pd/C (0.1 g, 10 wt %), which was then sealed with a septum and evacuated and backfilled with nitrogen. Propan-2-ol (20 mL) was added and the flask was evacuated and backfilled again. A balloon of hydrogen was attached to the flask via a needle. The reaction was stirred at room temperature for 24 h. The balloon was inflated, the Pd/C was filtered off, and the solvent was removed under reduced pressure to give 1,3-diphenylbutane as a white solid (0.7 g, 73%). \[ 1H \text{NMR (400 MHz, CDCl}_3\text{)}: \delta 7.17 (dt, 4H, J_H-H = 7.0, ArCH}_3\text{), 2.67 (t, 4H, J_H-H = 7.1, ArCH}_2\text{CH}_3\text{), 7.19–7.22 (m, 6H, aryl C-H), 7.28–7.32 (m, 4H, aryl C-H).}\] 13C{1H} NMR (101 MHz, CDCl3): δ 30.6, 35.3, 125.1, 127.8, 127.9, 142.2. GC–MS (C9H18) m/z: 210.2. NMR data are consistent with the literature. 45
2,3-Diphenylbutane. Benzil (2 g, 9.5 mmol) was dissolved in anhydrous THF (20 mL) under a nitrogen atmosphere. MeMgCl (12.6 mL, 3 M in THF, 37.8 mmol) was added dropwise and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched (HCl, 1 M, 100 mL) and extracted with DCM (3 × 20 mL). The organic layers were combined, dried over MgSO₄, and concentrated to give 2,3-diphenylbutane-2,3-diol which was used in the next step without purification. Following a literature preparation,23,24 2,3-diphenylbutane-2,3-diol (1.5 g) was dissolved in hexamethylphosphoramidte (20 mL) and stirred at room temperature for 2 h. The mixture was then heated at reflux for 90 min. After cooling, Et₂O (25 mL) was added and the reaction mixture was washed with water (100 mL). The aqueous layer was extracted with Et₂O (15 mL). The combined organic layers were then washed with water (2 × 50 mL) and brine (25 mL), dried over MgSO₄, and concentrated to give brown/red oil. Column chromatography on silica gel (petroleum ether) gave 2,3-diphenylbutane-1,3-diene as a white solid. 2,3-Diphenylbutane-1,3-diene (150 mg) was added to a RBF with Pd/C (15 mg, 10 wt %), which was sealed with a septum and evacuated and backfilled with hydrogen. A balloon was removed, the Pd/C was filtered, and concentrated to give brown/red oil. Propan-2-ol (20 mL) was added and the flask was evacuated and backfilled again. A balloon of hydrogen was attached to the flask via a needle. The reaction was then stirred at room temperature for 24 h. The balloon was removed, the Pd/C was filtered off and the solvent was removed under reduced pressure to give 2,3-diphenylbutene (95 mg, 5% over three steps) as a white solid. 1 H NMR (400 MHz, CDCl₃): δ 1.05 (dd, 6H, 3 J = 2.2, 6.7), 1.31 (dd, 4H, 3 J = 1.9, 6.7), 2.80–2.84 (m, 2H), 2.93–3.00 (m, 1.5H), 7.02–7.04 (m, 2.5H), 7.09–7.14 (m, 1.3H), 7.17–7.26 (m, 8.2H), 7.32–7.36 (m, 3.8H). 13C{1H} NMR (101 MHz, CDCl₃): δ 17.4, 20.5, 45.9, 46.8, 125.2, 125.5, 127.1, 127.2, 127.3, 127.8, 145.9. GC–MS (C₁₆H₁₈) m/z: 210.2. NMR data are consistent with the literature.47

Diphenylphosphinoferrocene. This was prepared according to a literature procedure.48 Ferrocene (1.9 g, 0.01 mol) and aluminum chloride (1.3 g, 0.01 mol) were dissolved in hexane (20 mL). Chlorodiphenylphosphine was added and the solution was heated at reflux for 16 h. The hexane was decanted and solids were extracted with fresh hexane (50 mL). This was repeated with water (50 mL). The hexane and water were discarded, and the remaining solids were extracted with hot toluene (50 mL). The toluene was dried over MgSO₄, and concentrated to dryness. The residue was extracted with hexane (100 mL) and this was concentrated to yield 7.41 (d, J = 1.8 Hz), 4.39 (d, J = 1.8 Hz), 4.78 (s, 1H), 6.70 (d, J = 1.8 Hz), 7.30–7.32 (m, 8H). 13C{1H} NMR (101 MHz, CDCl₃): δ 14.9, 28.0, 47.7, 68.6, 70.2, 125.2, 125.5, 127.1, 127.2, 127.3, 127.8, 145.9. GC–MS (C₁₆H₁₈N) m/z: 210.2. NMR data are consistent with the literature.47

Kinetic Experiments. Kinetic data were obtained using the same methodology that has been deployed previously, by monitoring the decay of the concentration of [Ni(COD)(dppf)] over time by 31P{1H} NMR spectroscopy.19,20,24 For a typical experiment, in an anhydrous THF (1 mL) was added followed by phenylmagnesium chloride (0.28 mmol, 1.1 equiv). The vial was then heated (with rapid stirring) to 85 °C. When at the desired temperature, any liquid additives and the aryl halide (0.25 mmol) were added via a microsyringe. The reactions were stirred at 85 °C for 24 h, then cooled to room temperature, and pierced with a needle. Each vial was opened, an accurately known amount of benzene was added, and a sample was taken for GC-FID analysis. All reactions were performed in duplicate; average conversions are reported in the paper, and the result of each individual cross-coupling reaction is tabulated in the Supporting Information. The gas chromatography-flame ionization detector was calibrated for each substrate and product using authentic samples of each compound.

Computational Methodology. DFT calculations were carried out using Gaussian16 Rev. A.03.95 DLPNO-CCSD(T) calculations60–65 were carried out using Orca 4.2.1.53,54 Geometry optimizations were carried out without symmetry constraints using the 31LYP functional53–55 with the Grimme D3 empirical dispersion correction.59 The LANL2TZ(f) pseudopotential/ECP was used for nickel and iron, while LANL2DZ(d,p) was used for bromine, arsenic, and antimony.60–62 The 6-31G(d) basis set was used for all other atoms. Frequency calculations verified the nature of stationary points. Transition states were checked using IRC calculations or by optimizing structures along the reaction coordinate. The energies of all structures were refined using single point calculations with the M06 functional,63 the LANL2DZ(d,p) pseudopotential/ECP on antimony, and the 6-31+G(d,p) basis set on all other atoms. Solvation was included for the single point calculations using the SMD model (in benzene).64 This level of theory was decided upon by benchmarking calculations for the formation of [Ni(dppf)₂] plus COD from [Ni(COD)(dppf)] plus dppf: ΔG (experiment) = −1.2 kcal/mol; ΔG (DLPNO-CCSD(T)/cc-pVTZ) = −1.6 kcal/mol; ΔG (M06/6-31+G(d,p)) = −1.5 kcal/mol (see the Supporting Information for full details). A correction of +1.89 kcal/mol was applied to the free energy of each species to consider a 1 mol/L reference state for the calculations rather than the ideal gas concentration.65 Yamaguchi’s approach was used to correct the electronic energies of open shell singlets for triplet contamination.66 The images of DFT-derived structures in Figure 2 were prepared using CYLView 2.0.67

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organometallics.c00280.

Kinetic data, computational data (methods and energies), and data regarding the outcomes of catalytic reactions (PDF)

Coordinates of the structures modeled using DFT calculations (XYZ)

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Notes
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ABBREVIATIONS

DPPF 1,1′-bis(diphenylphosphino)ferrocene;
SIMes 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
NHC N-heterocyclic carbene

REFERENCES

(1) 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.
(2) Lovering, F. Escape from Flatland 2: complexity and promiscuity. MedChemComm 2013, 4, 515–539.
(3) Diccianni, J.; Lin, Q.; Tao, T. Mechanisms of Nickel-Catalyzed Coupling Reactions and Applications in Alkene Functionalization. Acc. Chem. Res. 2020, 53, 906–919.
(4) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp2 Halides with Alkyl Electrophiles. Acc. Chem. Res. 2015, 48, 1767–1775.
(5) Greaves, M. E.; Johnson Humphrey, E. L. B.; Nelson, D. J. Reactions of nickel(0) with organochlorides, organobromides, and organoiodides: mechanisms and structure/reactivity relationships. Catal. Sci. Technol. 2021, 11, 2980–2996.
(6) Liu, R. Y.; Dennis, J. M.; Buchwald, S. L. The Quest for the Ideal Base: Rational Design of a Nickel Precatalyst Enables Mild, Homogeneous C–N Cross-Coupling. J. Am. Chem. Soc. 2020, 142, 4500–4507.
(7) Zhang, S.-Q.; Taylor, B. L. H.; Ji, C.-L.; Gao, Y.; Harris, M. R.; Hanna, L. E.; Jarvo, E. R.; Houk, K. N.; Houk, X. Mechanism and Origins of Ligand-Controlled Stereoselectivity of Ni-Catalyzed Suzuki–Miyaura Coupling with Benzyllic Esters: A Computational Study. J. Am. Chem. Soc. 2017, 139, 12994–13005.
(8) Zhang, K.; Conda-Sheridan, M.; Cooke, S. R.; Louie, J. N-Heterocyclic Carbene Bound Nickel(I) Complexes and Their Roles in Catalysis. Organometallics 2011, 30, 2546–2552.
(9) 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.
(10) Kalvet, I.; Guo, Q.; Tizzard, G. J.; Schoenebeck, F. When Weaker Can Be Tougher: The Role of Oxidation State (I) in P- vs Ni-Ligand-Derived Ni-Catalyzed Trifluoromethylation of Aryl Halides. ACS Catal. 2017, 7, 2126–2132.
(11) Hong, X.; Liang, Y.; Houk, K. N. Mechanisms and Origins of Switchable Chemoselectivity of Ni-Catalyzed C(aryl)–O and C-(acyl)–O Activation of Aryl Esters with Phosphine Ligands. J. Am. Chem. Soc. 2014, 136, 2017–2025.
(12) Enz, E. D.; Russell, J. E. A.; Hooker, L. V.; Neufeldt, S. R. Small Phosphine Ligands Enable Selective Oxidative Addition of Ar−O over Ar−Cl Bonds at Nickel(0). J. Am. Chem. Soc. 2020, 142, 15454–15463.
(13) Bajo, S.; Laidlaw, G.; Kennedy, A. R.; Sproules, S.; Nelson, D. J. Oxidative Addition of Ar Electrophiles to a Prototypical Nickel(0) Complex: Mechanism and Structure/Reactivity Relationships. Organometallics 2017, 36, 1662–1672.
(14) Manzoor, A.; Wienefeld, P.; Baird, M. C.; Budzelaar, P. H. M. Catalysis of Cross-Coupling and Homocoupling Reactions of Aryl Halides Utilizing Ni(0), Ni(I), and Ni(II) Precursors; Ni(0) Compounds as the Probable Catalytic Species but Ni(I) Compounds as Intermediates and Products. Organometallics 2017, 36, 3508–3519.
(15) Tsou, T. T.; Kochi, J. K. Mechanism of oxidative addition. Reaction of nickel(0) complexes with aromatic halides. J. Am. Chem. Soc. 1979, 101, 6319–6332.
(16) Pérez-García, P. M.; Daru, A.; Scheerder, A. R.; Lutz, M.; Harvey, J. N.; Moret, M.-E. Oxidative Addition of Ar Halides to a Triphospih nickel(0) Center to Form Pentacoordinate Ni(II) Aryl Species. Organometallics 2020, 39, 1139–1144.
(17) Pérez-García, P. M.; Moret, M.-E. Mechanistic Studies of the Oxidative Addition of Ar Halides to Ni(0) Centers Bearing Phosphine Ligands. CHIMIA International Journal for Chemistry 2020, 74, 495–498.
(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) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. Fundamental Studies and Development of Nickel-Catalyzed Trifluoromethylation of Aryl Chlorides: Active Catalytic Species and Key Roles of Ligand and Traceless MeCN Additive Revealed. J. Am. Chem. Soc. 2015, 137, 4164–4172.
(20) Greaves, M. E.; Ronson, T. O.; Lloyd-Jones, G. C.; Maseras, F.; Sproules, S.; Nelson, D. J. Unexpected Nickel Complex Speciation Unlocks Alternative Pathways for the Reactions of Alkyl Halides with dppb-Nickel(0). ACS Catal. 2020, 10, 10717–10725.
(21) Tolman, C. A. Steric effects of phosphorus ligands in organometallic chemistry and homogeneous catalysis. Chem. Rev. 1977, 77, 313–348.
(22) Hansch, C.; Leo, A.; Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. Chem. Rev. 1991, 91, 165–195.
(23) We note that triphenylphosphine lies quite far off the line of best fit in each case. These reactions were repeated with freshly recrystallized triphenylphosphine but this did not affect the reaction rate.
(24) All six ligands are plotted on the graph, but p-F and m-Me have the same substituent constant and so these are superimposed.
(25) Funes-Ardoiz, I.; Nelson, D. J.; Maseras, F. Halide Abstraction from Aryl Chlorides Competes with Oxidative Addition in the Reactions of Ar Halides with [Ni(PMePh3)3]4+. Chem. – Eur. J. 2017, 23, 16728–16733.
(26) Desnoyer, A. N.; He, W.; Behyan, S.; Chiu, W.; Love, J. A.; Kenneppohl, P. The Importance of Ligand-Induced Backdonation in the Stabilization of Square Planar d10 Nickel pi-Complexes. Chemistry 2019, 25, 5259–5268.
(27) He, W.; Kenneppohl, P. Direct experimental evaluation of ligand-induced backboning in nickel metallaacyclic complexes. Faraday Discuss. 2019, 220, 133–143.
(28) 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.

(29) Poater, A.; Cosenza, B.; Correa, A.; Giudice, S.; Ragone, F.; Scaro, V.; Cavallo, L. SambVca: A Web Application for the Calculation of the Buried Volume of N-Heterocyclic Carbene Ligands. *Eur. J. Inorg. Chem.* 2009, 2009, 1759–1766.

(30) Falivene, L.; Credendino, R.; Poater, A.; Petta, A.; Serra, L.; Oliva, R.; Scaro, V.; Cavallo, L. SambVca 2: A Web Tool for Analyzing Catalytic Pockets with Topographic Steric Maps. *Organometallics* 2016, 35, 2286–2293.

(31) Falivene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scaro, V.; Cavallo, L. Towards the online computer-aided design of catalytic pockets. *Nat. Chem.* 2019, 11, 872–879.

(32) Clavier, H.; Nolan, S. P. Percent buried volume for phosphate and N-heterocyclic carbene ligands: steric properties in organometallic chemistry. *Chem. Commun.* 2010, 46, 841–861.

(33) Gomez-Suarez, A.; Nelson, D. J.; Nolan, S. P. Quantifying and understanding the steric properties of N-heterocyclic carbenes. *Chem. Commun.* 2017, 53, 2650–2660.

(34) Liu, N.; Li, X.; Wang, Z.; Sun, H. Synthesis, structure and DFT study of dinuclear iron, cobalt and nickel complexes with cyclopentadienyl-metal moieties. *Dalton Trans.* 2011, 40, 6886–6892.

(35) Kampmann, S. S.; Sobolev, A. N.; Koutsantios, G. A.; Stewart, S. G. Stable Nickel(0) Phosphites as Catalysts for C5-cyclopentadienyl-metal moieties. *Chem. Commun.* 2014, 42, 4726–4728.

(36) Vechorkin, O.; Proust, V.; Hu, X. Functional Group Tolerant Kumada–Corriu–Tamao Coupling of Nonactivated Alkyl Halides with Aryl and Heteroaryl Nucleophiles: Catalysis by a Nickel Pincer Complex Permits the Functionalization of Functionalized Grignard Reagents. *J. Am. Chem. Soc.* 2009, 131, 9756–9766.

(37) Xue, F.; Zhao, J.; Hor, T. S. A. Cross-coupling of alkyl halides with aryl or alkyl Grignards catalyzed by dinuclear Ni(ii) complexes containing functionalized triopodal amine-pyrazolyl ligands. *Dalton Trans.* 2013, 42, 5150–5158.

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

(39) Netherton, M. R.; Fu, G. C. Nickel-Catalyzed Cross-Couplings of Unactivated Alkyl Halides and Pseudohalides with Organometallic Compounds. *Adv. Synth. Catal.* 2004, 346, 1525–1532.

(40) Hu, X. Nickel-catalyzed cross coupling of non-activated alkyl halides: a mechanistic perspective. *Chem. Sci.* 2011, 2, 1867–1886.

(41) Fache, F.; Pelotier, B.; Piva, O., Grignard Reagents and Transition Metal Catalysts. In 2. Grignard Reagents and Nickel, Janine, C., Ed. De Gruyter: 2016; pp 61–113.

(42) Álvarez-Moreno, M.; de Graaf, C.; López, N.; Maseras, F.; Poblet, J.; Bo, C. Managing the Computational Chemistry Big Data Problem: The ioChem-DB Platform. *J. Chem. Inf. Model.* 2015, 55, 95–103.

(43) Fulmur, G. R.; Miller, A. J. M.; Sheriff, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercau, 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.

(44) Liu, G.-B.; Zhao, H.-Y.; Dai, L.; Thiermann, T.; Tashiro, H.; Tashiro, M. Raney Ni-Al alloy-mediated reduction of benzils in water. *J. Chem. Res.* 2009, 2009, 579–581.

(45) Wagner, R. A.; Brinker, U. H. A Novel and Facile Synthesis of 2,3-Diphenylbuta-1,3-diene. *Synthesis 2001*, 2001, 0376–0378.

(46) Prinsell, M. R.; Everson, D. A.; Weiss, D. J. Nickel-catalyzed, sodium iodide-promoted reductive dimerization of alkyl halides, alkyl pseudohalides, and aliphatic acetates. *Chem. Commun.* 2010, 46, 5743–5745.
(65) 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.

(66) Yamaguchi, K.; Jensen, F.; Dorigo, A.; Houk, K. N. A spin correction procedure for unrestricted Hartree-Fock and Møller-Plesset wavefunctions for singlet diradicals and polyradicals. *Chem. Phys. Lett.* **1988**, *149*, 537−542.

(67) Legault, C. Y., CYLview20, Université de Sherbrooke, 2020, [http://www.cylview.org](http://www.cylview.org).