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Bis(dialkylphosphino)ferrocene-Ligated Nickel(II) Precatalysts for Suzuki–Miyaura Reactions of Aryl Carbonates

Emily L. Barth[†], Ryan M. Davis[†], Megan Mohadjer Beromi[†], Andrew G. Walden[†], David Balcells[‡], Gary W. Brudvig[†], Amira H. Dardir[†], Nilay Hazari[*,†], Hannah M. C. Lant[†], Brandon Q. Mercado[†], Ian L. Peczak[†]

[†]Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520, United States

[‡]Hylleraas Centre for Quantum Molecular Sciences, Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, N-0315 Oslo, Norway

Abstract

Aryl carbonates, a common protecting group in synthetic organic chemistry, are potentially valuable electrophiles in cross-coupling reactions. Here, after performing a thorough evaluation of different precatalysts, we demonstrate that (dcypf)Ni(2-ethylphenyl)(Br) (dcypf = 1,1-bis-(dicyclohexylphosphino)ferrocene) is an efficient precatalyst for Suzuki-Miyaura reactions using a variety of aryl carbonates as substrates. Mechanistic studies indicate that (dcypf)Ni(2-ethylphenyl)(Br), which contains a bidentate phosphine that binds in a trans geometry, is an effective precatalyst for these reactions for two reasons: (i) it rapidly forms the Ni(O) active species and (ii) it minimizes comproportionation reactions between the Ni(O) active species and both the unactivated Ni(II) precatalyst and on-cycle Ni(II) complexes to form catalytically inactive Ni(I) species. In contrast, the state of the art precatalyst (dppf)Ni(*o*-tolyl)(Cl) (dppf = 1,1-bis(diphenylphosphino)ferrocene), which contains a bidentate phosphine that binds in a cis geometry, forms Ni(I) species during activation and is essentially inactive for aryl carbonate couplings. Although the exact reasons on a molecular level why the dcypf system is more active than the dppf system are unclear, our results indicate that in general Ni catalysts supported by the dcypf ligand will give better performance for catalytic reactions involving substrates which undergo relatively slow oxidative addition, such as aryl carbonates.

Graphical Abstract

Low loadings, mild conditions
EPR spectroscopy identifies off-cycle species
*Decreased formation of inactive Ni^I species results
in more active precatalyst for aryl carbonate coupling*

INTRODUCTION

Pd-catalyzed cross-coupling reactions represent one of the most powerful synthetic methods and, due to their versatility and reliability, have been utilized in numerous commercial processes.[1] In recent years, the significant research effort dedicated to developing more sustainable catalysts for cross-coupling using base metals such as Ni has revealed that there are many reactions which are more effectively facilitated by Ni catalysts in comparison with traditional Pd systems.[2] Perhaps the most notable example is the use of Ni catalysts for a variety of cross-coupling and related reactions involving sp^3-hybridized substrates.[3] However, it has also been demonstrated that Ni catalysts are superior to Pd systems for the coupling of a variety of nontraditional sp^2-hybridized substrates. For example, aryl nitriles,[4] aryl trimethylammonium salts,[5] aryl fluorides,[6] aryl carbamates,[7] aryl esters,[8] and aryl carbonates,[7] which are the focus of this work, are all more effectively coupled using Ni catalysts. Nevertheless, despite the impressive variety of cross-coupling reactions which Ni catalysts can now facilitate, in general the harsh reaction conditions and high catalyst loadings limit the practicality of these reactions. Further, detailed mechanistic studies over several decades led to the current widely used systems for cross-coupling with Pd catalysts, while in the case of most Ni-catalyzed cross-coupling reactions these mechanistic studies still need to be performed.

Aryl carbonates are commonly used as protecting groups in organic chemistry and can be readily prepared from phenols.[9] There are potentially significant benefits in complex molecule synthesis, in terms of the step count and overall efficiency, if practical methods could be developed to use a protecting group such as an aryl carbonate as an electrophile in cross-coupling. The first report of the use of aryl carbonates in cross-coupling was by Garg et al.[7] They performed several Suzuki–Miyaura reactions involving naphthyl carbonates under reaction conditions that utilized 10 mol % of (PCy$_3$)$_2$NiCl$_2$, 4 equiv of boronic acid, and 7.2 equiv of base at 130 °C for 24 h. Subsequently, Kuwano and Shimizu showed that a catalytic system generated in situ from Ni(COD)$_2$ (COD = 1,5-cyclooctadiene) and 1,1-bis(dicyclohexylphosphino)ferrocene (dcypf) could couple a limited number of phenyl carbonates, in addition to a small range of naphthyl carbonates, at 60 °C.[10] However, this system still required high catalyst loadings (10 mol %) and extended reaction times (24–96 h) in order for high yields to be obtained. In related chemistry, Molander et al. reported that a closely related Ni(COD)$_2$/2PCy$_3$·HBF$_4$ system could couple a naphthyl carbonate

electrophile with a potassium aryltrifluoroborate nucleophile at 110 °C with 10 mol % catalyst loading.[11] A conceptually different approach was adopted by Chakraborti and co-workers, who showed that heterobimetallic Ni/Pd nanoclusters could perform Suzuki–Miyaura reactions using aryl carbonates, but high temperatures (100 °C) were required, and the substrate scope was not explored.[12] At this stage, in order to develop practical coupling reactions involving aryl carbonates, improvements are required in the substrate scope, reaction conditions, and catalyst loadings.

Both our group and others have been exploring the use of precatalysts of the type (dppf)Ni(aryl)(X) (dppf = 1,1-bis(diphenylphosphino)ferrocene; X = Cl, Br) for a variety of Suzuki–Miyaura reactions including those involving aryl sulfamate electrophiles.[13] Our results show that these precatalysts give markedly better activity than systems generated in situ from Ni(COD)$_2$ or other "ligandless" Ni precursors, likely because precatalysts increase the amount of Ni in a catalytically active form.[2e,13e] However, despite the increased catalytic efficiency of these precatalysts, they often generate off-cycle Ni(I) species during activation. [13b,c,e] Given the close relationship between aryl sulfamates and aryl carbonates, we hypothesized that the use of well-defined precatalysts of the type (PP)Ni(aryl)(X) (PP = bidentate phosphine ligand) could lead to more active catalysts for reactions with aryl carbonates. Here, we demonstrate that the precatalyst (dcypf)Ni(2-ethylphenyl) (Br) (^{dcypf}**Ni^{II}** $_{(2\text{-ethylph})(Br)}$), which contains a bidentate phosphine ligand that binds in a trans geometry, generates the most active catalyst reported to date for Suzuki–Miyaura reactions involving aryl carbonates (Figure 1). We show that this precatalyst activates rapidly under the reaction conditions and only forms a small amount of inactive Ni(I) species during catalysis, which is likely a reason for its high activity. Our results indicate that judicious selection of the ancillary ligand can limit the formation of Ni(I) species during catalysis and provide fundamental information about ligand selection that may be relevant to the design of improved catalysts for a variety of Ni-catalyzed cross-coupling reactions.

RESULTS AND DISCUSSION

Optimization of a Catalyst System for Aryl Carbonate Coupling.

In previous work, we established that (dppf)Ni(*o*-tolyl)(Cl) (^{dppf}**Ni^{II}** $_{(o\text{-tol})(Cl)}$) is a highly active precatalyst for Suzuki–Miyaura coupling reactions involving aryl sulfamates.[13c] Given recent results from Nelson and co-workers showing that aryl carbonates undergo oxidative addition to (dppf)Ni^0(COD) (COD = 1,5-cyclooctadiene) only slightly more slowly than aryl sulfamates,[14] we hypothesized that ^{dppf}**Ni^{II}** $_{(o\text{-tol})(Cl)}$ could potentially be a precatalyst for aryl carbonate coupling. However, our initial efforts to use 2.5 mol % of ^{dppf}**Ni^{II}** $_{(o\text{-tol})(Cl)}$ as a precatalyst for the coupling of 2-naphthyl *tert*-butylcarbonate with 4-methoxyphenylboronic acid at 80 °C for 24 h indicated that it was essentially inactive for this transformation (Table 1). One of the major problems in using ^{dppf}**Ni^{II}** $_{(o\text{-tol})(Cl)}$ as a precatalyst for coupling reactions involving aryl sulfamates is that inactive Ni(I) species are formed during catalysis, which is also a potential problem in aryl carbonate coupling.[13c] The proposed pathway for the formation of Ni(I) species involves comproportionation between a Ni(0) and Ni(II) species,[13b,c,15] which DFT calculations suggest is aided by the formation of a dimeric intermediate containing an η^2 interaction between one of the phenyl groups on the

phosphine atoms of dppf and one Ni center.[13c] To address this potential issue, the precatalysts (dippf)Ni(*o*-tolyl)(Cl) (dippf**Ni**II (o-tol)(Cl); dippf = 1,1-bis-(diisopropylphosphino)ferrocene) and (dcypf)Ni(*o*-tolyl)(Cl) (dcypf**Ni**II (o-tol)(Cl)) were synthesized using literature methods.[16] We predicted that the use of these precatalysts containing bis(phosphino)ferrocenyl ligands with aliphatic substituents on the phosphine donors may prevent the formation of a dimeric intermediate with the same type of η^2 interaction between Ni and the ligand that was observed for dppf and as a result could stop the generation of inactive Ni(I) species. Another difference is that the bidentate phosphines have been shown to bind in a trans geometry in dippf**Ni**II(o-tol)(Cl) and dcypf**Ni**II (o-tol)(Cl) in comparison with a cis geometry for dppf**Ni**II (o-tol)(Cl).[16,17] Under the same reaction conditions both dippf**Ni**II (o-tol)(Cl) and dcypf**Ni**II (o-tol)(Cl) are significantly more active for aryl carbonate coupling than dppf**Ni**II (o-tol)(Cl), with dippf**Ni**II (o-tol)(Cl) giving a 61% yield and dcypf**Ni**II (o-tol)(Cl) giving quantitative conversion (Table 1, entries 2 and 3). These initial results represent some of the mildest conditions under which aryl carbonates have been coupled.

Given the promising preliminary results using dcypf**Ni**II (o-tol)(Cl) as a precatalyst, a full optimization of the reaction temperature, time, amount of nucleophile, and catalyst loading for the coupling of 2-naphthyl *tert*-butylcarbonate with 4-methoxyphenylboronic acid was performed (Table 1). Notably, the reaction time can be truncated from 24 h to 4 h without a decrease in yield of cross-coupled product (entry 3 vs entry 4). In fact, at 80 °C, the reaction is almost complete after only 2 h (entry 5). Furthermore, the temperature can be reduced from 80 to 60 °C with no significant loss in catalytic activity at 4 h; however, further reduction of temperature results in a decreased yield (entries 6 and 7). Allowing the reaction to run for 4 h appears to provide an excellent compromise of a short reaction time and a high yield. Varying the amount of boronic acid relative to the aryl carbonate revealed that 1 equiv is sufficient to form the cross-coupled product in moderate yield (entries 8–10), but optimal yields require 2.5 equiv. This represents a decrease from the previously reported conditions requiring 4 equiv.[7] An evaluation of catalyst loading showed that the optimal precatalyst loading is 2.5 mol % (entry 6 vs entries 11–13), which is also reduced from other reports of aryl carbonate coupling where a catalyst is generated in situ rather than using a precatalyst.[10] Interestingly, the reaction is water tolerant, and the addition of 50 equiv of water to the reaction (entries 14 and 15) did not impede catalytic activity. On the basis of this screen, our optimal reaction conditions utilized 2.5 mol % of dcypf**Ni**II (o-tol)(Cl) at 60 °C for 4 h with 2.5 equiv of boronic acid.

Precatalyst performance is typically determined primarily by the nature of the ancillary phosphine ligand and the identity of the aryl ligand, with the halide ligand generally being less important.[13e] Recently, we performed detailed studies exploring how the choice of the aryl group affects catalytic activity for the dppf**Ni**II (aryl)(X) scaffold.[13e] However, as previously described, the dppf ligand binds in a cis geometry; thus, it is not clear if the trends observed for dppf are also relevant to dcypf, which binds in a trans geometry.[16a,17] Additionally, in general, there has been significantly less work exploring Ni precatalysts with a trans geometry; therefore, there is a need for further studies of these systems which have demonstrated improved catalytic activity for some cross-coupling reactions. We

synthesized seven precatalysts of the form $^{dcypf}\textbf{Ni}^{II}$ $_{(aryl)(Br)}$ with different aryl ligands, selected to provide diversity in both electronic and steric properties, through the reaction of $^{dcypf}\textbf{Ni}^{II}$ $_{Br2}$ with the appropriate arylmagnesium bromide reagent (Figure 2).[16a] The choice of bromide as the halide was primarily based on synthetic ease, as there are many more commercially available bromide-containing Grignard reagents in comparison with chloride-containing Grignard reagents, which are also often challenging to prepare. All of the complexes were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and elemental analysis, and in all cases the ^{31}P NMR spectra indicated that the dcypf ligand was bound in a trans geometry, as only a single resonance was present in the spectra. The one exception to this is the $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}OMePh)(Br)}$ precatalyst, which has two resonances in the ^{31}P NMR spectrum due to the presence of two rotamers in a 0.6:1 ratio (see the Supporting Information). Furthermore, the solid-state structure of $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ confirms that the dcypf ligand binds in a trans fashion with a P1–Ni–P2 angle of 145.00(8)° (Table 2). The Ni–C$_{aryl}$ distance in $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ is 1.893(7) Å, which is similar to that observed in $^{dppf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ (1.898(14) and 1.905(14) Å; two molecules are present in the asymmetric unit).[13e] A consequence of the trans geometry of $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ is that it places the aryl ligand trans to the bromide ligand. In contrast, in $^{dppf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ the aryl ligand is trans to one of the phosphine donors of dppf. Due to the stronger trans influence of the aryl ligand, the Ni–Br bond length in $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ (2.4042(11) Å) is approximately 0.08 Å longer than the Ni–Br bond length in $^{dppf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ (2.320(3) and 2.323(2) Å).[13e] Precatalyst activation in Suzuki–Miyaura reactions begins with transmetalation of the bromide ligand with the boronic acid,[13b] and it is possible that the weaker Ni–Br bond in $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ in comparison to its dppf analogue enhances the rate of this process.

All seven of our precatalysts of the type $^{dcypf}\textbf{Ni}^{II}$ $_{(aryl)(Br)}$ were evaluated for the coupling of 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid using the optimized conditions determined in Table 1 (Table 3). To test if there was a halide effect, $^{dcypf}\textbf{Ni}^{II}$ $_{(o\text{-}tol)(Cl)}$ was included in the screen so that it could be directly compared with $^{dcypf}\textbf{Ni}^{II}$ $_{(o\text{-}tol)(Br)}$.[18] When the precatalysts were tested using a catalyst loading of 2.5 mol %, they all performed similarly after 4 h, with the exception of $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}OMePh)(Br)}$ (entry 1), which gave a significantly lower yield of the cross-coupled product. However, at shorter reaction times using 2.5 mol % precatalyst loading (see the Supporting Information) and when the loading was reduced to 1 mol %, significant differences in catalytic activity were observed (Table 3). Interestingly, $^{dcypf}\textbf{Ni}^{II}$ $_{(o\text{-}tol)(Br)}$ gave a yield which was only slightly higher than that observed with $^{dcypf}\textbf{Ni}^{II}$ $_{(o\text{-}tol)(Cl)}$ (entry 2 vs entry 7), which is consistent with our recent studies using related $^{dppf}\textbf{Ni}^{II}$ $_{(o\text{-}tol)(X)}$ (X = Cl, Br) precatalysts in Suzuki–Miyaura reactions using aryl chlorides and aryl sulfamates, where the identity of the halide ligand does not largely affect precatalyst performance.[13e] At 1 mol % loading, there were no major trends in precatalyst performance on the basis of either the steric or electronic properties of the aryl ligand, but $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ operates the most efficiently and is able to produce 73% of cross-coupled product (entry 8). Comparative studies with other substrates also suggest that $^{dcypf\text{-}}\textbf{Ni}^{II}$ $_{(2\text{-}ethylPh)(Br)}$ is the most active precatalyst (see the Supporting Information). On the basis of the low catalyst loading, the relatively low reaction temperature (60 °C), the reduced number of equivalents of boronic acid (2.5 equiv), and the short reaction time (4 h), it is

clear that $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-ethylPh})(Br)}$ generates the most active catalyst system for aryl carbonate coupling reported to date and is an improvement over alternative systems.[7,10–12]

Substrate Scope.

Given the exceptional activity of $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-ethylPh})(Br)}$ as a precatalyst for the coupling of 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid under our optimized conditions, we explored its activity with other substrates. Initially, the scope for the coupling of 2-naphthyl *tert*-butylcarbonate with different boronic acids was investigated, and most reactions proceeded with good to excellent yields (Figure 3). A lower than expected yield was repeatedly obtained with phenylboronic acid (**1a**), but reactions involving arylboronic acids containing electron-donating substituents, such as 4-methoxyphenylboronic acid (**1b**) and *p*-tolylboronic acid (**1c**), proceeded in high yields. Notably, mono- and diortho substitution on the boronic acid could be tolerated without a change in the optimized reaction conditions (**1d–f**, respectively), and 1- and 2-naphthylboronic acids (**1f,g**) were also coupled in high yield. With electron-deficient boronic acids such as 4-trifluoromethylphenylboronic acid (**1h**) and 3-furanylboronic acid (**1i**), increased amounts of boronic acid (3.5 equiv) and base (6 equiv) and extended reaction times (24 h) were required to obtain good yields. At this stage, the reaction is not compatible with heteroarylboronic acids (see the Supporting Information for more information). The scope of the carbonate electrophile was also examined but proved to be more limited than that of the boronic acid. A 2-naphthyl carbonate with an ester substituent in the 6-position was coupled in good yield (**1j**), but in general we were unable to couple aryl carbonates with electron-donating substituents. When 1-naphthyl *tert*-butylcarbonate was used as a substrate, increased catalyst loading (5 mol %), temperature (80 °C), and reaction time (24 h) were required to give a reasonable yield (**1k**). Presumably, this substrate is more challenging than 2-naphthyl *tert*-butylcarbonate for steric reasons, which makes oxidative addition more difficult. Interestingly, under our more forcing conditions we were able to couple 4-methoxy-1-naphthyl carbonate (**1l**), our only example of an aryl carbonate with an electron-donating group. A phenyl carbonate containing a strongly electron-withdrawing trifluoromethyl group was coupled with modest yield but required even higher temperatures (**1m**) (100 °C). The unsubstituted substrate *tert*-butyl phenyl carbonate was even more difficult to couple and required increased catalyst loading (10 mol %), temperature (130 °C), and reaction time (48 h) and still gave a low yield of product (**1n**). The observed trend that naphthyl carbonates are considerably easier to couple in comparison to phenyl carbonates is consistent with results for a variety of other Ni-catalyzed cross-coupling reactions[1g] and is likely due to the relative ease of oxidative addition of naphthyl-containing substrates in comparison with simple phenyl substrates.

Precatalyst Activation.

In order to understand the high catalytic activity observed using $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-ethylPh})(Br)}$ as a precatalyst, we examined the activation of this system to generate Ni(0) species. Previous studies have implicated Ni(0) as the catalytically active species when analogous dppf-ligated σ-aryl precatalysts are employed in Suzuki–Miyaura reactions involving sp²-hybridized substrates.[13c–e] In this case, we propose that $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-ethylPh})(Br)}$ activates by

transmetalation with arylboronic acid and base, followed by reductive elimination of an organic biaryl activation product to generate a Ni(0) unit that enters catalysis (Figure 4). Quantification of the amount of the biaryl activation product as a function of time provides information about the rate of activation and the amount of Ni(0) that can potentially enter the catalytic cycle. To probe activation, a catalytic reaction was performed between 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid catalyzed by $^{dcypf}\mathbf{Ni^{II}}$ $_{(2\text{-ethylPh})(Br)}$ using the conditions optimized in Table 1. The amount of the activation product, 2-ethyl-4′-methoxybiphenyl, was quantified over the course of the reaction. As indicated by the data shown in Figure 4, the activation of $^{dcypf}\mathbf{Ni^{II}}$ $_{(2\text{-ethylPh})(Br)}$ is extremely rapid; after 5 min, 93% of the precatalyst is activated. However, over the course of the reaction, the observed amount of the biaryl activation product never reaches the expected amount predicted for complete activation of the precatalyst, even though the reaction proceeds in greater than 90% yield. The high efficiency of activation is not exclusive to $^{dcypf}\mathbf{Ni^{II}}$ $_{(2\text{-ethylph})(Br)}$, as a similar experiment conducted with $^{dcypf}\mathbf{Ni^{II}}$ $_{(o\text{-tol})(Br)}$ also indicates approximately 90% activation of the precatalyst. Interestingly, when the chloride congener $^{dcypf}\mathbf{Ni^{II}}$ $_{(o\text{-tol})(Cl)}$ is used, only 80% of the activation byproduct forms, which is consistent with its slower performance in catalysis (see the Supporting Information). The activation of $^{dppf}\mathbf{Ni^{II}}$ $_{(o\text{-tol})(Cl)}$ was also monitored under these conditions (see the Supporting Information). Surprisingly, given its poor activity in catalysis (Table 1), $^{dppf}\mathbf{Ni^{II}}$ $_{(o\text{-tol})(Cl)}$ activated rapidly and after 4 h an 85% yield of the activation byproduct was observed. This likely suggests that the poor performance of $^{dppf}\mathbf{Ni^{II}}$ $_{(o\text{-tol})(Cl)}$ as a precatalyst for aryl carbonate coupling in comparison to $^{dcypf}\mathbf{Ni^{II}}$ $_{(2\text{-ethylPh})(Br)}$ cannot be explained only by differences in activation and that potentially the trans-spanning dcypf ligand is better at promoting the elementary steps, such as oxidative addition, in catalysis than the dppf ligand.

We hypothesized that the slightly less than quantitative yields of activation product during catalysis with $^{dcypf}\mathbf{Ni^{II}}$ $_{(2\text{-ethylPh})(Br)}$ could be due to the formation of Ni(I) species during activation. Specifically, comproportionation between $^{dcypf}\mathbf{Ni^{II}}$ $_{(2\text{-ethylPh})(Br)}$ and the active $^{dcypf}\mathbf{Ni^0}$ species could produce a Ni(I) halide species as well as a Ni(I) aryl species, which would lower the amount of biaryl activation product formed. Comproportionation processes of this type are well precedented in dppf-ligated systems,[13b,c,e,14] and even though the dcypf ligand was selected to prevent the stabilization of the dimeric intermediate proposed in these reactions, this off-cycle reaction may still be able to occur. As opposed to related systems in which well-defined Ni(I) species ligated by ferrocenyl ancillary ligands exist,[13b,c,e,15a] there are no documented examples of Ni(I) species ligated by dcypf. In order to identify if these complexes are formed in catalysis, we synthesized dcypf-supported Ni(I) halide complexes. [19] Comproportionation of $^{dcypf}\mathbf{Ni^0}$ $_{C2H4}$ with $^{dcypf}\mathbf{Ni^{II}}$ $_{Cl2}$ or $^{dcypf}\mathbf{Ni^{II}}$ $_{Br2}$ produces paramagnetic species with solution magnetic moments consistent with $S = 1/2$ species (Figure 5a). Crystallographic characterization of the resulting complexes confirms their identity as $^{dcypf}\mathbf{Ni^I}$ $_{Cl}$ or $^{dcypf}\mathbf{Ni^I}$ $_{Br}$ (Figure 5b). Notably, the dcypf bite angle is contracted by about 40° in the two Ni(I) species in comparison to the Ni(II) species $^{dcypf}\mathbf{Ni^{II}}$ $_{(2\text{-ethylPh})(Br)}$ such that the primary coordination sphere around the nickel center is Y-shaped. These Ni(I) species were also characterized by EPR spectroscopy performed at 77 K to provide a handle with which to compare catalytic mixtures. The EPR spectrum of $^{dcypf}\mathbf{Ni^I}$ $_{Cl}$ (Figure 5b) shows an axial spectrum with *g* values of 2.10 and 2.33, while the spectrum of $^{dcypf}\mathbf{Ni^I}$ $_{Br}$

(Figure 5b) shows a slightly rhombic spectrum with g values of 2.01, 2.12, and 2.33. Additionally, hyperfine splitting consistent with the presence of a bromine nucleus is present in the spectrum of $^{dcypf}\textbf{Ni}^{I}$ $_{Br}$. It is notable that the time required to obtain high yields of $^{dcypf}\textbf{Ni}^{I}$ $_{Cl}$ and $^{dcypf}\textbf{Ni}^{I}$ $_{Br}$ via comproportionation are significantly longer than those required to synthesize the corresponding dppf analogues, suggesting that comproportionation of these species is indeed more difficult.[13c] Analysis of the catalytic activity of both Ni(I) species for the coupling of 2-naphthyl *tert*-butylcarbonate with 4-methoxyphenylboronic acid demonstrates that they operate poorly (Figure 5c). This indicates that if they are formed in catalysis using Ni(II) precatalysts, they are likely inactive species.

EPR spectroscopy was performed to determine if Ni(I) species are formed in a reaction between 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid using $^{dcypf}\textbf{Ni}^{II}$ $_{(2-ethylPh)(Br)}$ as the precatalyst. After 4 h at 60 °C and 2.5 mol % catalyst loading, EPR spectroscopy indicated that approximately 12% of the Ni was in the form of Ni(I) (Figure 6b). Approximately the same amount of paramagnetic material was present after 2 h (see the Supporting Information). In comparison to the authentic EPR spectrum of $^{dcypf}\textbf{Ni}^{I}$ $_{Br}$, the spectrum of the catalytic mixture does not show bromine hyperfine coupling. Instead, the spectrum of the catalytic mixture is axial with a broad feature at $g_{\parallel}$ and a triplet at $g_{\perp}$ corresponding to hyperfine coupling to two slightly inequivalent phosphorus nuclei. This suggests that $^{dcypf}\textbf{Ni}^{II}$ $_{(2-ethylPh)(Br)}$ does not form detectable quantities of $^{dcypf}\textbf{Ni}^{I}$$_{Br}$ during activation. The rapid activation of the precatalyst and the lack of aryl groups on the phosphine donors may prevent this off-cycle reaction from occurring and contribute to the overall efficiency of the precatalyst. However, at this stage the nature of the side process which leads to the slightly less than quantitative yields (93%) of the biaryl activation product when $^{dcypf}\textbf{Ni}^{II}$ $_{(2-ethylPh)(Br)}$ is used as a precatalyst remains unclear.

We propose that the small amount of EPR-active material which was detected both during and after catalysis with $^{dcypf}\textbf{Ni}^{II}$ $_{(2-ethylph)(Br)}$ is generated because the Ni(II) complex formed after oxidative addition of the substrate, $^{dcypf}\textbf{Ni}^{II}$ $_{(2-nap)(carbonate)}$, undergoes comproportionation with the active Ni(0) species (Figure 6a). This is a well-documented process with other substrates for catalysts with dppf ligands.[13c–e,14,15] The Ni(I) species that could form after comproportionation are $^{dcypf}\textbf{Ni}^{I}$$_{(2-naphthalene)}$ and $^{dcypf}\textbf{Ni}^{I}$$_{(carbonate)}$,[20] which would decrease the yield of the catalytic reaction by siphoning the electrophile to an unproductive, off-cycle reaction. To further probe the possibility of comproportionation occurring between the Ni(II) product of oxidative addition and the Ni(0) active species, a Suzuki–Miyaura reaction between the aryl halide 2-bromonaphthalene and 4-methoxyphenylboronic acid catalyzed by $^{dcypf}\textbf{Ni}^{II}$ $_{(o-tol)(Cl)}$ was monitored using EPR spectroscopy. In this case, given that the precatalyst does not contain a bromine ligand, the Ni(I) bromide complex $^{dcypf}\textbf{Ni}^{I}$$_{Br}$ can only form via comproportionation from the Ni(II) product from oxidative addition and the active Ni(0) species. The resulting spectrum (Figure 6c) contains bromine hyperfine splitting and is consistent with the formation of $^{dcypf}\textbf{Ni}^{I}$$_{Br}$ in catalysis. However, the EPR spectrum also contains additional features and line broadening that are not present in the EPR spectrum of authentic $^{dcypf}\textbf{Ni}^{I}$$_{Br}$, which suggests that the observed spectrum is a composite of multiple EPR-active species. We propose that the other species is $^{dcypf}\textbf{Ni}^{I}$$_{(2-naphthalene)}$ (which is likely relatively unstable[13d]), the other expected

product from a comproportionation reaction involving the Ni(II) species from oxidative addition and a Ni(0) species (Figure 6a). Consistent with this interpretation, the EPR spectra from catalysis agree with a simulation that models the data as a linear combination of $^{dcypf}\mathbf{Ni^{I}}_{Br}$ and an unknown species with hyperfine coupling to two phosphorus nuclei. Additionally, we note that our simulation strongly suggests that the other species is not $^{dcypf}\mathbf{Ni^{I}}_{Cl}$, which could be formed if comproportionation was occurring during activation (see the Supporting Information).

To provide further information about why the state of the art precatalyst $^{dppf}\mathbf{Ni^{II}}_{(o\text{-}tol)(Cl)}$ is not active for aryl carbonate coupling, spin-integrated X-band EPR spectroscopy was performed to compare the amount of paramagnetic material produced by $^{dcypf}\mathbf{Ni^{II}}_{(2\text{-}ethylPh)(Br)}$ to that of $^{dppf}\mathbf{Ni^{II}}_{(o\text{-}tol)(Cl)}$. When the reaction between 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid using $^{dppf}\mathbf{Ni^{II}}_{(o\text{-}tol)(Cl)}$ as the precatalyst was monitored using EPR spectroscopy, approximately 22% of the Ni is in an EPR-active form at the end of the reaction, in comparison to only 12% when $^{dcypf}\mathbf{Ni^{II}}_{(2\text{-}ethylph)(Br)}$ is used (Figure 6b). This result suggests that dcypf-supported species are less prone to comproportionation than dppf-supported species and is also consistent with the observation that approximately 85% of $^{dppf}\mathbf{Ni^{II}}_{(o\text{-}tol)(Cl)}$ activates under these conditions. Comparing the EPR spectrum of the catalytic mixture with a simulated EPR spectrum of authentic $^{dppf}\mathbf{Ni^{I}}_{Cl}$ suggests that the catalytic mixture contains multiple EPR-active species, including $^{dppf}\mathbf{Ni^{I}}_{Cl}$, which is presumably formed as a result of comproportionation during precatalyst activation (see the Supporting Information). Additionally, the reaction with $^{dppf}\mathbf{Ni^{II}}_{(o\text{-}tol)(Cl)}$ does produce a small amount of product, and the complexity of the EPR spectrum also suggests that comproportionation occurs between the Ni(II) product from oxidative addition and the Ni(0) active species.[13c] Overall, we propose that, because oxidative addition of aryl carbonates is more difficult than other substrates such as aryl chlorides or aryl sulfmates,[14] the Ni(0) active species has more time to comproportionate with unreacted precatalyst and become inactive. Therefore, a ligand which is less likely to promote comproportionation is expected to give better results in catalysis. This suggests that dcypf-supported precatalysts may generally be more active in catalysis than dppf-supported systems for substrates that do not readily undergo oxidative addition.

CONCLUSIONS

In this work, we have shown that $^{dcypf}\mathbf{Ni^{II}}_{(2\text{-}ethylph)(Br)}$ is a rapidly activating and selective precatalyst for Suzuki–Miyaura reactions involving aryl carbonate electrophiles. It can couple naphthyl carbonates, a limited number of phenyl carbonates, and boronic acids with a variety of steric and electronic properties under milder conditions and lower catalyst loadings in comparison to previously reported systems. Our results suggest that one reason $^{dcypf}\mathbf{Ni^{II}}_{(2\text{-}ethylph)(Br)}$ is a significantly more active precatalyst for Suzuki–Miyaura reactions involving aryl carbonates in comparison with the state of the art $^{dppf}\mathbf{Ni^{II}}_{(o\text{-}tol)(Cl)}$ precatalyst is because it is less likely to form inactive Ni(I) species. At this stage the exact mechanistic reasons $^{dcypf}\mathbf{Ni^{II}}_{(2\text{-}ethylph)(Br)}$ is less likely to form Ni(I) species are unclear. Possible reasons include that it could be (i) an electronic effect related to changing from aryl substituents on the phosphine donors to more donating alkyl substituents, (ii) a steric effect

related to having more bulky cyclohexyl substituents on the phosphine donors as opposed to phenyl substituents, or (iii) a geometric effect related to the fact that dcypf can bind to the metal in a trans geometry whereas dppf binds in a cis geometry. Given the high activity of $^{dcypf}\mathbf{Ni}^{II}$ $_{(2-ethylph)(Br)}$, we suggest that more detailed studies looking at the exact role of the ligand on the elementary reactions and decomposition events in catalysis would be beneficial. In particular, there is a lack of information about how the coordination geometry of bidentate phosphine ligands, cis or trans, affects elementary reactions and more information on the topic would be useful for catalyst design. From a synthetic perspective, we propose that $^{dcypf}\mathbf{Ni}^{II}$ $_{(2-ethylph)(Br)}$ is likely to be a more active catalyst than $^{dppf}\mathbf{Ni}^{II}$ $_{(o-tol)(Cl)}$ for other substrates that undergo slow oxidative addition and intend to test this hypothesis in ongoing studies in our laboratory.

Supplementary Material

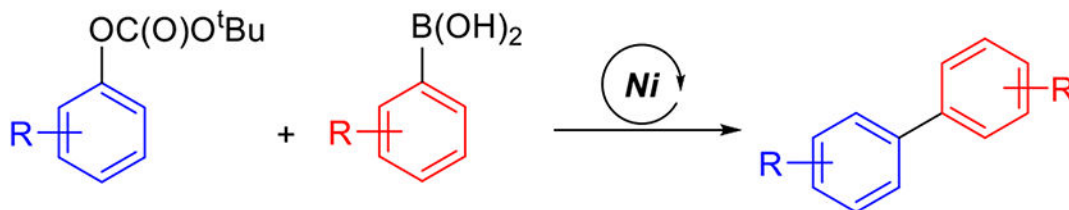Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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(18). As part of this work, we also prepared the iodo compound $^{dcypf}\mathbf{Ni}^{II}$$_{(o-tol)(I)}$. As described in the Supporting Information, this gave inferior catalytic activity for the coupling of 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid under our standard conditions compared with $^{dcypf}\mathbf{Ni}^{II}$$_{(o-tol)(Br)}$. As a consequence, this compound was not studied further.

(19). The other product from comproportionation is a Ni(I) aryl complex. Species of this nature are known to be highly unstable at room temperature (see ref 13d), and as a consequence we did not attempt to prepare a dcypf-supported Ni(I) aryl complex as part of this work.

(20). As part of this work, we attempted to prepare an authentic sample of $^{dcypf}\mathbf{Ni}^{I}$$_{(carbonate)}$ through the oxidative addition of 0.5 equiv of 2-naphthyl *tert*-butylcarbonate to dcypf-ligated Ni(0) sources. Unfortunately, we were unable to detect any clear signals for $^{dcypf}\mathbf{Ni}^{I}$$_{(carbonate)}$ using EPR spectroscopy. We propose that this is probably due to the instability of $^{dcypf}\mathbf{Ni}^{I}$$_{(carbonate)}$.
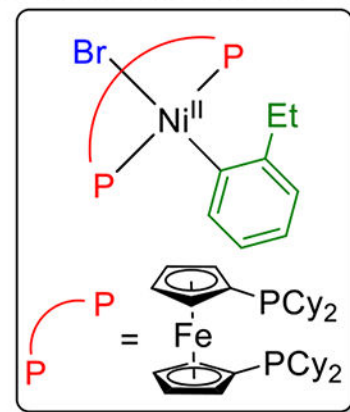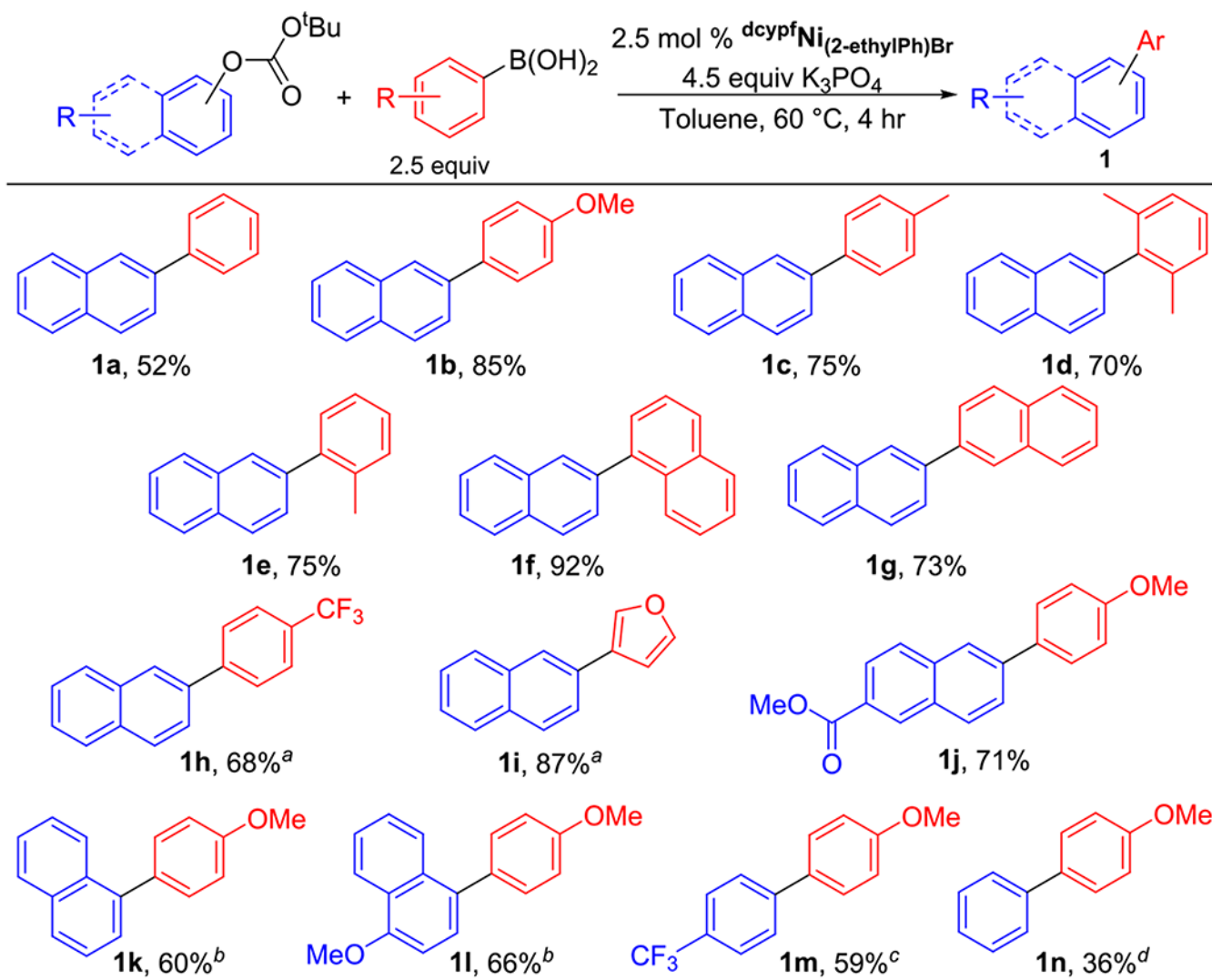
Figure 1.
Comparison between previous and current work exploring Ni-catalyzed Suzuki–Miyaura reactions involving aryl carbonates.
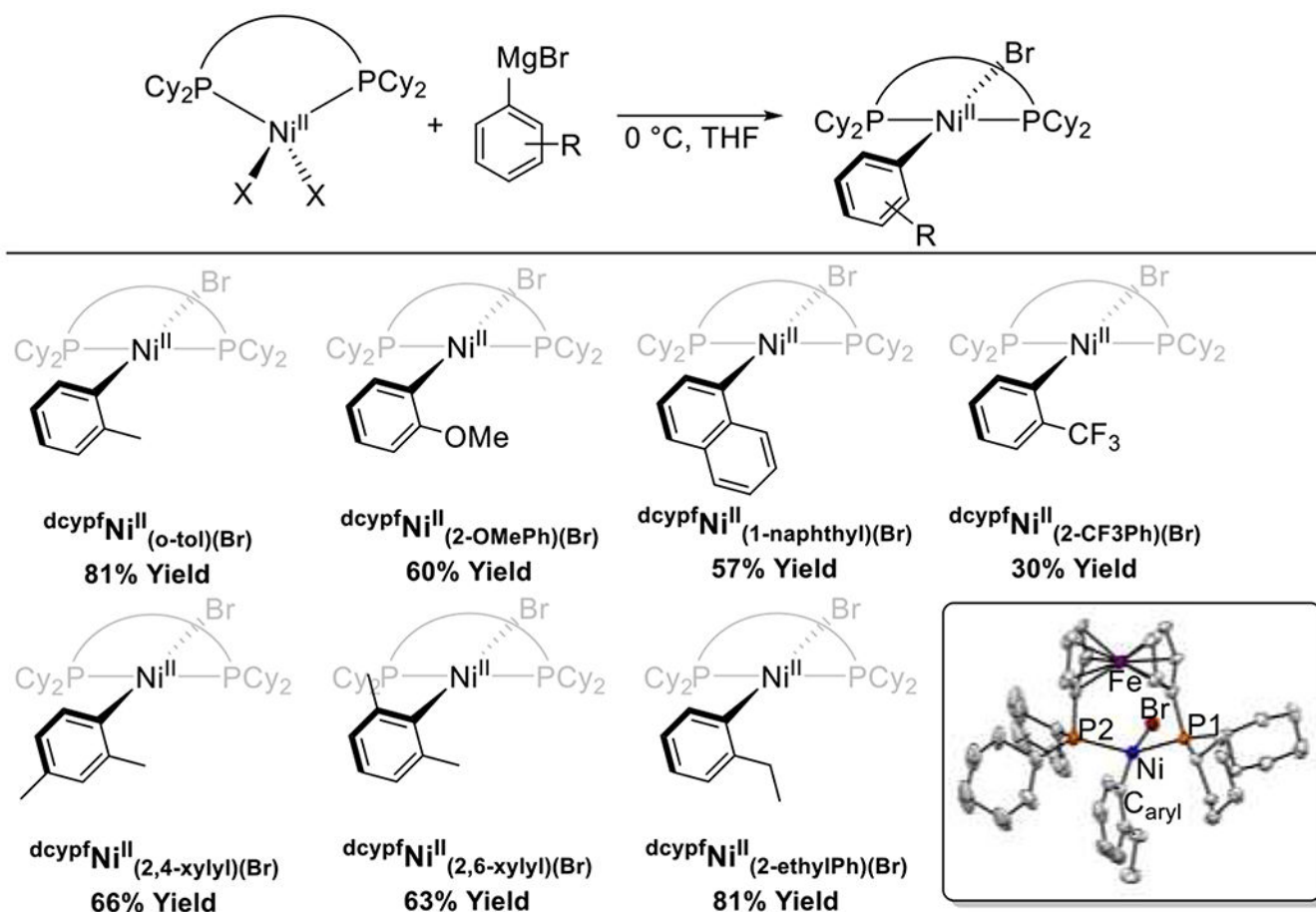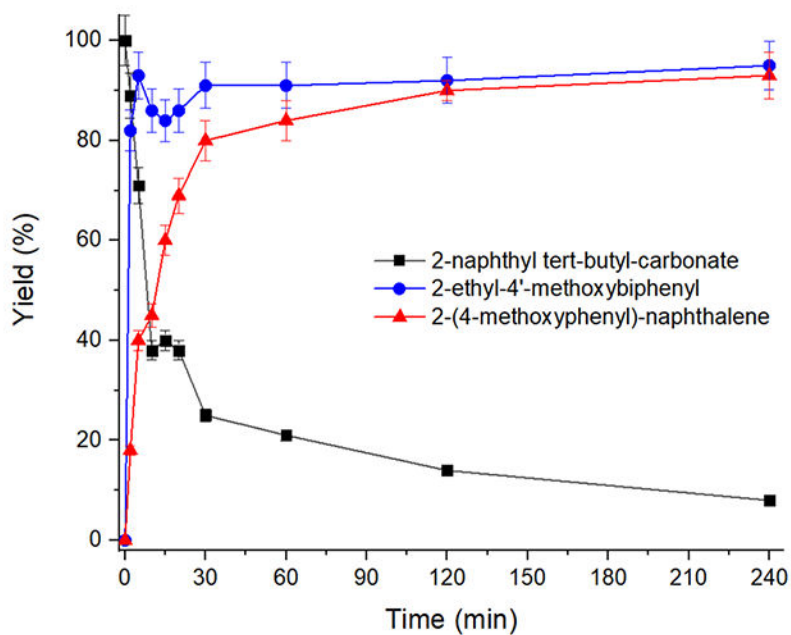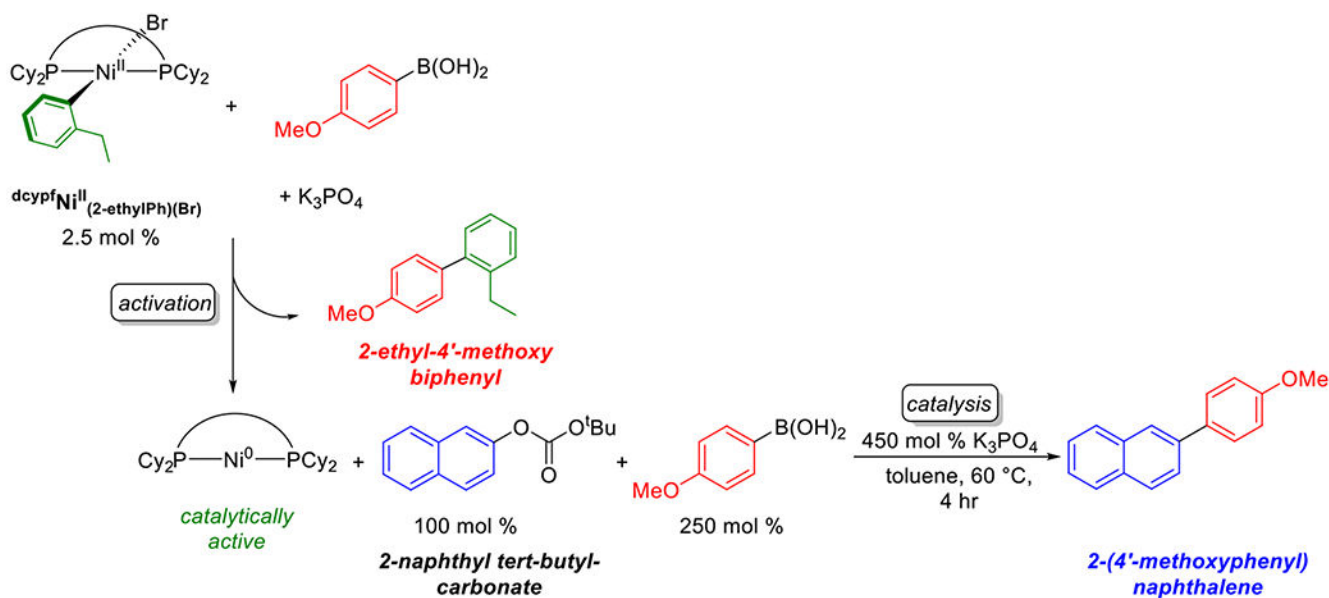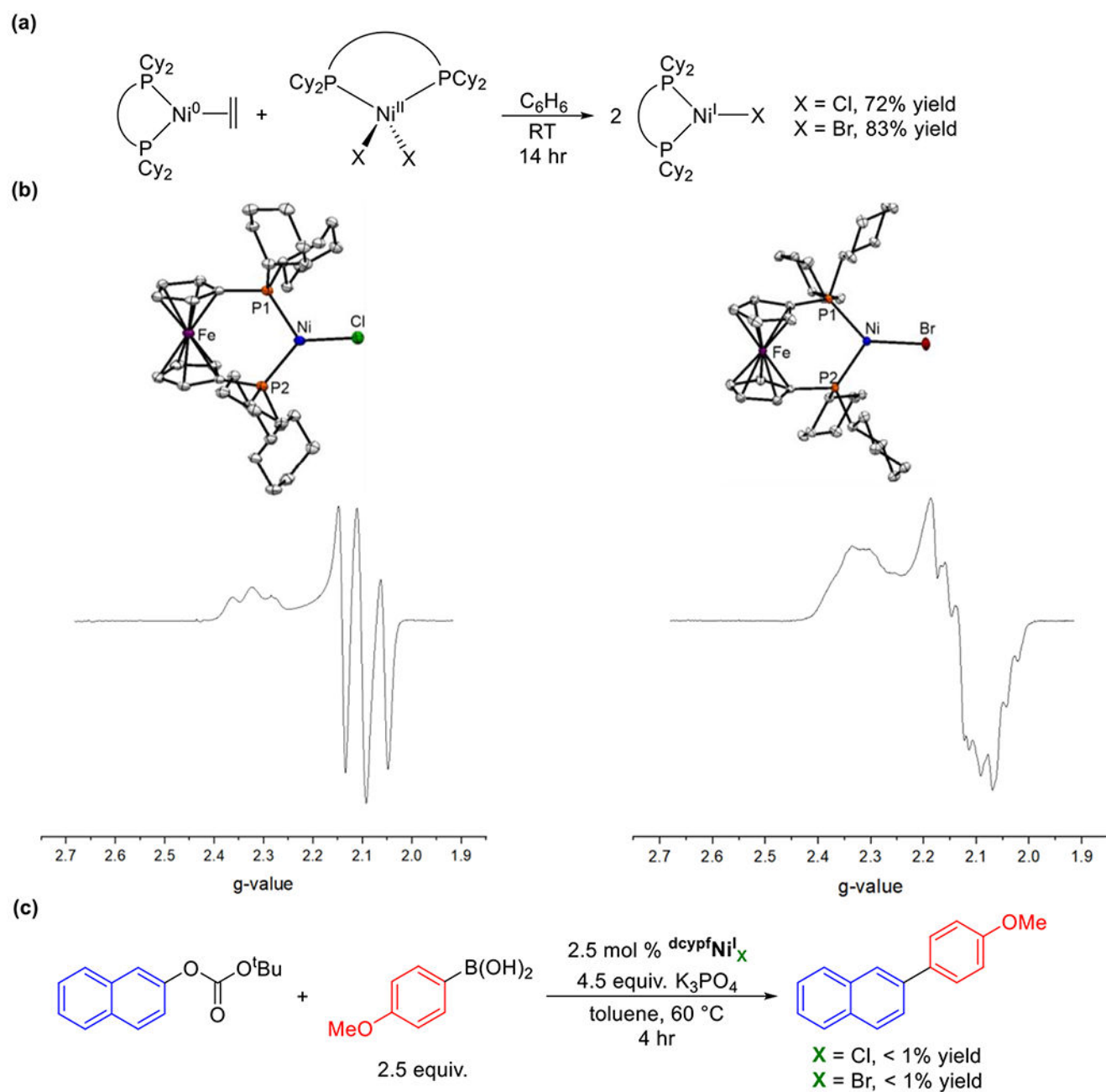
Figure 2.
Synthesis of multiple dcypf-ligated precatalysts containing different aryl ligands examined in this study. Inset: ORTEP of dcypfNiII (2-ethylPh)(Br) with thermal ellipsoids shown at 50% probability. Hydrogen atoms and solvent of crystallization have been removed for clarity.
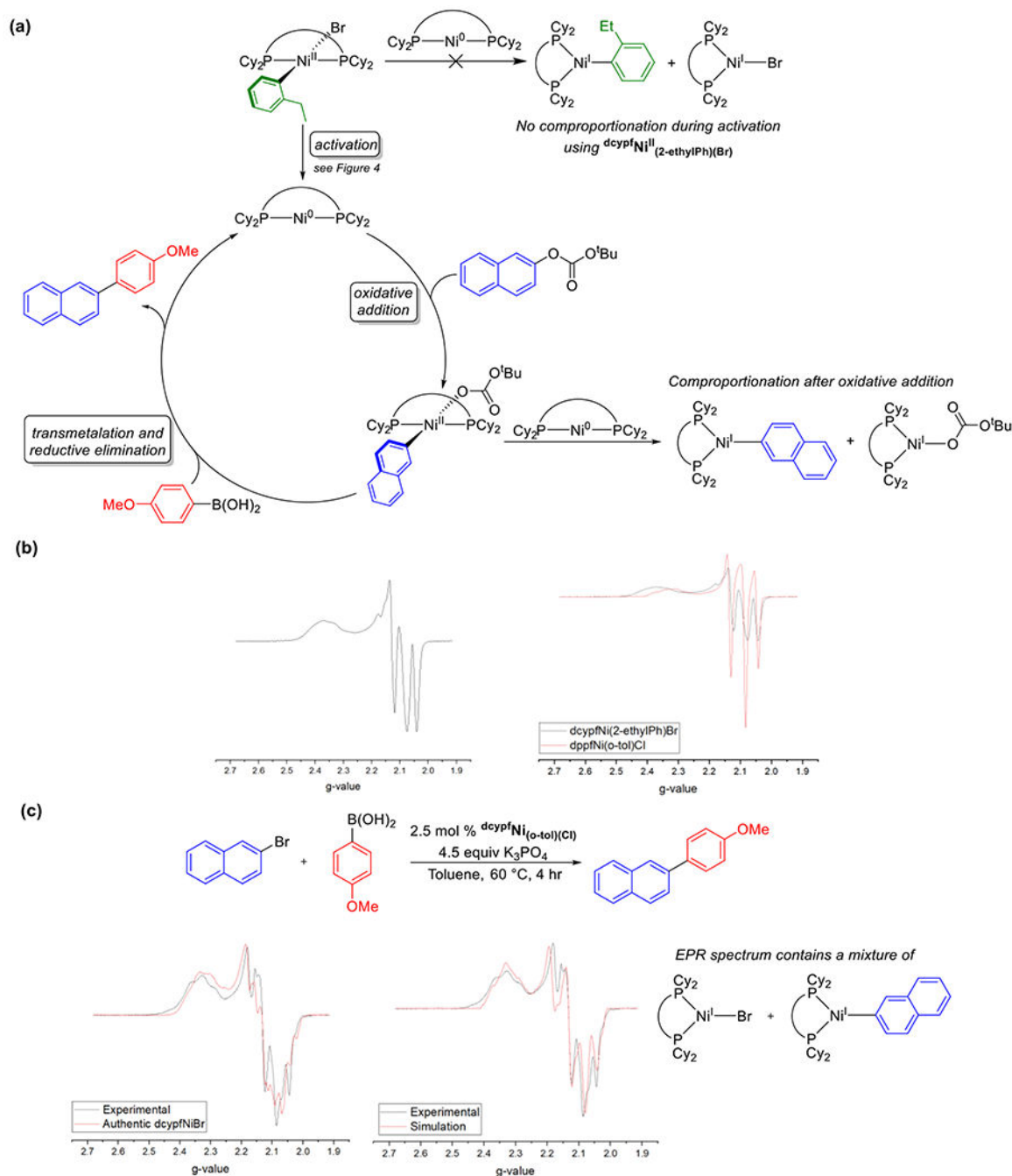
Figure 3.
Isolated yields for Suzuki–Miyaura reactions involving aryl carbonates and a variety of boronic acids catalyzed by ^{dcypf}Ni^{II} $_{(2\text{-ethylPh})(Br)}$. Yields are the average of at least two runs. Legend to reaction conditions: (*a*) 3.5 equiv of boronic acid, 6 equiv of K$_3$PO$_4$, and 6 h of reaction time; (*b*) 5 mol % loading, 3.5 equiv of boronic acid, 6 equiv of K$_3$PO$_4$, 80 °C, and 24 h of reaction time; (*c*) 5 mol % loading, 3.5 equiv of boronic acid, 6 equiv of K$_3$PO$_4$, 100 °C, and 24 h of reaction time; (*d*) 10 mol % loading, 5 equiv of boronic acid, 8 equiv of K$_3$PO$_4$, 130 °C, and 48 h of reaction time.

Figure 4.
Yields of cross-coupled and activation products as a function of reaction time for the Suzuki–Miyaura reaction of 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid catalyzed by dcypfNi^{II} (2-ethylPh)(Br). The error in yields is approximately ±5%.

Figure 5.
(a) Synthesis of dcypf-ligated Ni(I) halides via comproportionation. (b) Solid-state structures and X-band EPR spectra taken at 77 K of $^{dcypf}\mathbf{Ni^I}_{Cl}$ and $^{dcypf}\mathbf{Ni^I}_{Br}$. ORTEP are shown with thermal ellipsoids at 50% probability. Hydrogen atoms and solvent of crystallization have been removed for clarity. (c) Suzuki–Miyaura reaction using $^{dcypf}\mathbf{Ni^I}_{Cl}$ and $^{dcypf}\mathbf{Ni^I}_{Br}$ as precatalysts.

Figure 6.
(a) The abbreviated catalytic cycle, showing comproportionation pathways during activation and oxidative addition. (b) X-band EPR spectrum following the reaction of 2-naphthyl *tert*-butylcarbonate and 4-methoxyphenylboronic acid catalyzed by $^{dcypf}\textbf{Ni}^{II}$ $_{(2\text{-ethylPh})(Br)}$ (left), which is overlaid with the spectrum of the same reaction catalyzed by $^{dppf}\textbf{Ni}^{II}$ $_{(o\text{-tol})(Cl)}$ (right). (c) X-band EPR spectrum following the reaction of 2-bromonaphthalene and 4-methoxyphenylboronic acid catalyzed by $^{dcypf}\textbf{Ni}^{II}$ $_{(o\text{-tolyl})(Cl)}$ overlaid with the spectrum of

authentic $^{dcypf}\mathbf{Ni^I}_{Br}$ (left) and the spectrum of the catalytic mixture overlaid with a simulated spectrum (right).
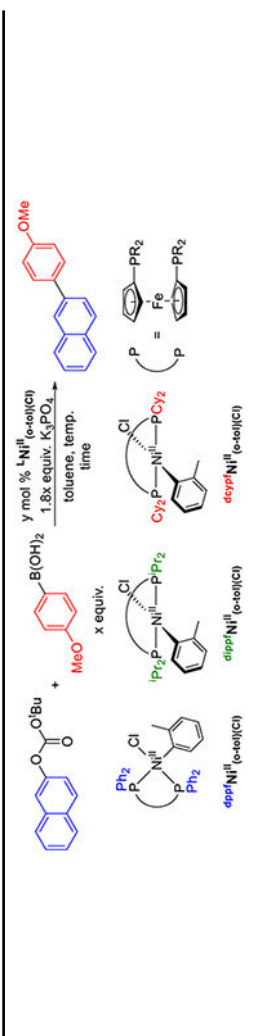
Table 1.

Optimization of the Suzuki–Miyaura Reaction between 2-Naphthyl *tert*-Butylcarbonate and 4-Methoxyphenylboronic Acid Using ^{L}Ni^{II} (o-tol)(Cl) (L = dppf, dippf, dcypf) as Precatalysts[a]

entry	ligand	temp (°C)	time (h)	boronic acid (equiv)	catalyst loading (mol %)	water (equiv)	yield (%)
1	dppf	80	24	2.5	2.5	0	5
2	dippf	80	24	2.5	2.5	0	61
3	dcypf	80	24	2.5	2.5	0	>99
4	dcypf	80	4	2.5	2.5	0	>99
5	dcypf	80	2	2.5	2.5	0	90
6	dcypf	60	4	2.5	2.5	0	92
7	dcypf	40	4	2.5	2.5	0	31
8	dcypf	60	4	1	2.5	0	64
9	dcypf	60	4	1.5	2.5	0	74
10	dcypf	60	4	2	2.5	0	87
11	dcypf	60	4	2.5	0.5	0	31[b]
12	dcypf	60	4	2.5	1	0	57[b]
13	dcypf	60	4	2.5	2	0	74[b]
14	dcypf	60	4	2.5	2.5	50	91
15	dcypf	60	4	2.5	1.0	50	59

[a] Reaction conditions: 2-naphthyl *tert*-butylcarbonate (0.133 mmol), 4-methoxyphenylboronic acid (0.133 mmol), naphthalene internal standard (0.0665 mmol, 0.5 equiv), toluene (1 mL). Yields were determined by GC and are reported as the average of at least two trials. equiv relative to boronic acid), K₃PO₄ (1.8 equiv; 0.200 mmol, 1.5 equiv; 0.266 mmol, 2 equiv; 0.333 mmol, 2.5 equiv), K₃PO₄ (1.8

[b] The reaction went to completion after 12 h of reaction time; however, the reactions at 0.5 and 1.0 mol % did not reach completion even after 24 h.
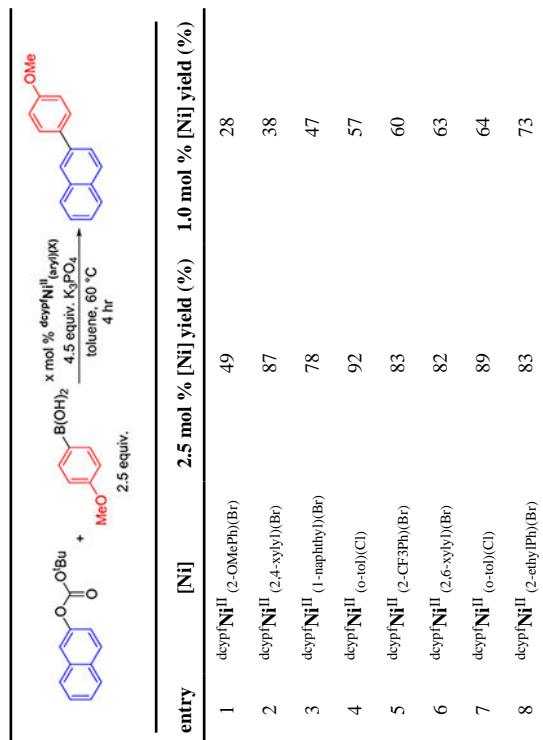
Table 2.

Comparison of Selected Bond Lengths and Angles of dcypfNi^{II} (2-ethylPh)(Br) and dppfNi^{II} (2-ethylPh)(Br)

complex	Ni–Br (Å)	Ni–P1, Ni–P2 (Å)	Ni–C$_{aryl}$ (Å)	P1–Ni–P2 (deg)	Br–Ni–C$_{aryl}$ (deg)	P1–Ni–C$_{aryl}$, P2–Ni–C$_{aryl}$ (deg)
dcypfNi^{II} (2-ethylPh)(Br)	2.4042(11)	2.1843(19)	1.893(7)	145.00(8)	161.1(2)	92.4(2)
		2.1877(18)				92.1(2)
dppfNi^{II} (2-ethylPh)(Br) [a]	2.320(3)	2.151(4), 2.281(4)	1.898(14)	101.63(16)	85.6(4)	83.9(4), 169.4(4)
	2.323(2)	2.133(4), 2.278(4)	1.905(14)	102.43(16)	86.1(4)	84.8(5), 169.2(4)

[a] Data obtained from ref 13e. Two sets of geometric parameters are included because there are two independent molecules in the unit cell.

Table 3.

GC Yields for the Coupling of 2-Naphthyl *tert*-Butylcarbonate and 4-Methoxyphenylboronic Acid Using Precatalysts of the Type $^{dcypf}[Ni]^{II}$(aryl)(X) [a]

entry	[Ni]	2.5 mol % [Ni] yield (%)	1.0 mol % [Ni] yield (%)
1	^{dcypf}[**Ni**]^{II}(2-OMePh)(Br)	49	28
2	^{dcypf}[**Ni**]^{II}(2,4-xylyl)(Br)	87	38
3	^{dcypf}[**Ni**]^{II}(1-naphthyl)(Br)	78	47
4	^{dcypf}[**Ni**]^{II}(o-tol)(Cl)	92	57
5	^{dcypf}[**Ni**]^{II}(2-CF3Ph)(Br)	83	60
6	^{dcypf}[**Ni**]^{II}(2,6-xylyl)(Br)	82	63
7	^{dcypf}[**Ni**]^{II}(o-tol)(Cl)	89	64
8	^{dcypf}[**Ni**]^{II}(2-ethylPh)(Br)	83	73

[a] Reaction conditions: 2-naphthyl *tert*-butylcarbonate (0.133 mmol), 4-methoxyphenylboronic acid (0.333 mmol, 2.5 equiv), K3PO4 (0.599 mmol, 4.5 equiv), naphthalene internal standard (0.0665 mmol, 0.5 equiv), toluene (1 mL). Yields were determined by GC and are reported as the average of at least two trials.