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Evaluating 1,1′-Bis(phosphino)ferrocene Ancillary Ligand Variants in the Nickel-Catalyzed C–N Cross-Coupling of (Hetero)aryl Chlorides

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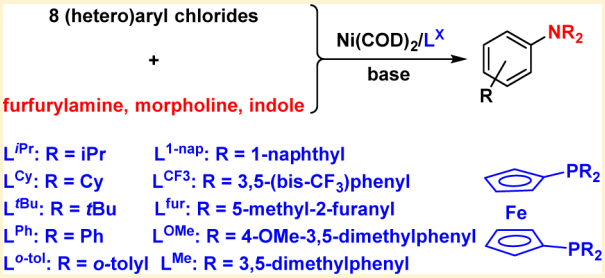
Supporting Information

ABSTRACT: Previous reports in the literature have established the utility of 1,1′-bis(diphenylphosphino)ferrocene (DPPF, L^{Ph}) in the nickel-catalyzed cross-coupling of (hetero)aryl electrophiles with primary or secondary amines. In an effort to evaluate the effect of varying the PR_2-donor groups on catalytic performance in such transformations, a series of 10 structurally varied 1,1′-bis(bis(alkyl/aryl)phosphino)ferrocene ancillary ligands (L^X) were systematically examined in selected competitive test cross-couplings of (hetero)aryl halides with furfurylamine, morpholine, and indole employing $Ni(COD)_2/L^X$ catalyst mixtures. In addition to the excellent performance observed for the parent ligand L^{Ph} in a number of the test transformations explored, selected dialkylphosphino (e.g., DiPPF, L^{iPr}) and meta-disubstituted diarylphosphino variants of L^{Ph} also proved highly effective. In particular, the electron-deficient ligand variant L^{CF3} featuring 3,5-bis(trifluoromethyl)phenyl groups on phosphorus was found to exhibit superior catalytic performance relative to L^{Ph} in most of the test transformations involving the N-arylation of indole. Our efforts to prepare Ni(II) precatalysts of the type (L^X)Ni(*o*-tolyl)Cl, in analogy with known (L^{Ph})Ni(*o*-tolyl)Cl, by employing several literature methods met with mixed results. Whereas (L^{iPr})Ni(*o*-tolyl)Cl was prepared straightforwardly and was crystallographically characterized, the use of L^{CF3} or ligands featuring *tert*-butyl (L^{tBu}), *o*-tolyl ($L^{o\text{-}tol}$), or 4-methoxy-3,5-dimethylphenyl (L^{OMe}) groups on phosphorus under similar conditions resulted in poor conversion to product and/or the formation of poorly soluble materials, highlighting the limitations of this commonly used precatalyst design.



1. INTRODUCTION

The ubiquitous nature of substituted (hetero)anilines, within both biologically active compounds and conjugated materials, provides motivation for the development of efficient catalytic C(sp^2)–N bond-forming protocols.[1] As a complement to Ullmann cross-couplings employing copper,[2] the palladium-catalyzed cross-coupling of NH substrates and (hetero)aryl (pseudo)halides (i.e., Buchwald–Hartwig amination,[3] BHA) has emerged as a broadly useful C(sp^2)–N bond-forming methodology.[4] Collectively, state of the art catalysts for BHA accommodate a broad substrate scope, including, but not restricted to, transformations involving primary and secondary amines and amides, azoles, and ammonia.[4] The successful development of BHA methods can be attributed in part to the design of ancillary ligands[5] that give rise to suitably reactive and selective palladium catalytic species. Whereas tris(*o*-tolyl)-phosphine,[3] racemic 2,2′-bis(diphenylphosphino)-1,1′-bi-naphthyl (*rac*-BINAP),[6] and 1,1′-bis(diphenylphosphino)-ferrocene (DPPF, L^{Ph})[7] were used as ancillary ligands in the early development of BHA, in the ensuing years palladium catalysts supported by more strongly electron donating and sterically demanding ancillary ligands (e.g., biaryl mono-phosphines[8] and N-heterocyclic carbenes[9]) have proven to be particularly effective,[4b,10] especially in combination with less reactive (hetero)aryl chlorides.[11]

Recent efforts to develop base-metal catalysts that offer competitive reactivity profiles versus palladium has contributed to the renaissance in nickel C(sp^2)–N cross-coupling chemistry,[12] due in part to the lower cost, greater natural abundance, and desirable catalytic properties of nickel, including with (hetero)aryl chlorides and phenol-derived electrophiles.[13] The pioneering report on such reactivity by Wolfe and Buchwald[14] documented the cross-coupling of (hetero)aryl chlorides with selected primary or secondary alkyl/aryl amines in the presence of $Ni(COD)_2/L^{Ph}$ mixtures. In the ensuing 20 years, L^{Ph} has remained one of the most effective ligands for use in nickel-catalyzed C(sp^2)–N cross-couplings of secondary alkylamines or anilines (Scheme 1).[15] In keeping with this ancillary ligand design theme, alternatively configured bis(phosphine)-ligated nickel catalysts have also been identified that are particularly effective for the cross-coupling of primary alkylamines,[16] ammonia,[16c,17] primary amides/lactams,[18] and beyond.[19]

In contrast to palladium-catalyzed BHA chemistry, for which overarching ancillary ligand design prerequisites are known (vide supra),[4b] guiding principles for the steric and electronic design of ancillary ligands for use in analogous nickel chemistry

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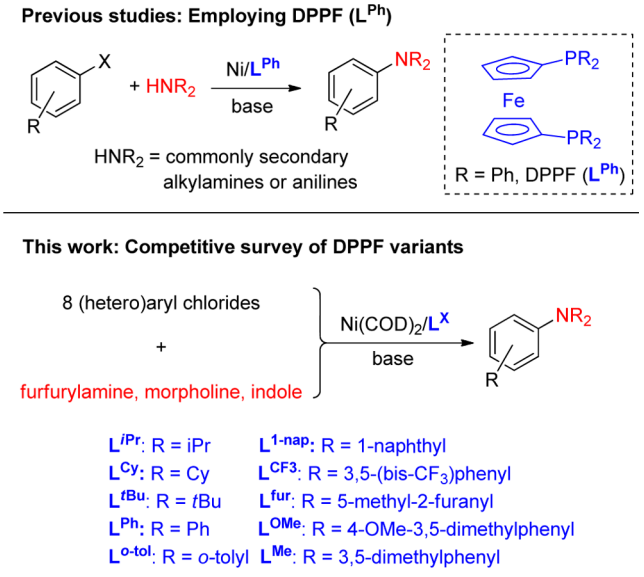
Scheme 1. Prior Nickel-Catalyzed C(sp^2)−N Cross-Coupling Employing DPPF (L^{Ph}) and the Competitive Reactivity Survey Herein



have not yet been firmly established. To contribute toward this understanding, we became interested in evaluating the performance of structurally varied 1,1′-bis(bis(alkyl/aryl)-phosphino)ferrocene ancillary ligand variants of L^{Ph} in nickel-catalyzed C(sp^2)−N cross-coupling chemistry, owing to the privileged nature of this ligand in such transformations (vide supra). A conceptually related study involving the palladium-catalyzed amination of aryl bromides with selected primary alkylamines appeared nearly 20 years ago;[20] nonetheless, we envisioned that the influence of 1,1′-bis(bis(alkyl/aryl)-phosphino)ferrocene ligation on the performance of nickel in C(sp^2)−N cross-couplings would be distinct from analogous transformations involving palladium, given the differing sizes, electronegativities, and redox properties of these metals.[13c,21] To the best of our knowledge, the comparison of L^{Ph} analogues in nickel-catalyzed C(sp^2)−N cross-couplings is limited to a single report by Stewart and co-workers[15g] involving a relatively small number of DPPF variants in the cross-coupling of 4-chloroanisole and *p*-toluidine. We report herein on the results of our competitive reactivity survey involving 10 variants of L^{Ph} in the nickel-catalyzed C(sp^2)−N cross-coupling of the test nucleophiles furfurylamine, morpholine, and indole in combination with structurally varied (hetero)aryl chlorides (Scheme 1).

2. RESULTS AND DISCUSSION

2.1. Selection of Ancillary Ligand Variants and Test Substrates. While definitive mechanistic data pertaining to nickel-catalyzed C(sp^2)−N cross-couplings employing L^{Ph} and related variants are lacking, we envisioned that the use of relatively electron rich ancillary ligands might promote (hetero)aryl chloride oxidative addition; conversely, relatively electron-poor ancillary ligands may facilitate product-forming C−N reductive elimination. Furthermore, sterically demanding ancillary ligands may enhance catalytic performance both by driving C−N reductive elimination and by discouraging the formation of putative off-cycle $(L^X)_2$Ni-type intermediates.[16a] In this context, and in viewing DPPF (L^{Ph}) as the parent ancillary ligand prototype, we targeted the use of variants featuring the following (Scheme 1): electron-rich alkylphosphines of varying steric bulk (D*i*PPF, L^{iPr}; DCPF, L^{Cy}; DTBPF, L^{tBu}), a relatively electron rich arylphosphine (L^{OMe}); electron-poor arylphosphines (L^{CF3} and HiersoPHOS-3, L^{fur}), an electron-neutral meta-disubstituted arylphosphine (L^{Me}), and bulky ortho-substituted arylphosphines ($L^{o\text{-}tol}$ and $L^{1\text{-}nap}$).

Encouraged by the established utility of L^{Ph} in the nickel-catalyzed C(sp^2)−N cross-coupling of alkylamines, we opted to include furfurylamine and morpholine as test substrates.[14,15] Whereas (NHC)Ni catalysts have proven to be particularly effective in the cross-coupling of a range of (hetero)aryl chlorides and indole derivatives,[19i] the application of L^{Ph}-ligated nickel catalysts in analogous transformations of aryl chlorides is limited to the cross-coupling of 4-chlorobenzotrifluoride and carbazole at 110 °C;[15e] indeed, to the best of our knowledge no examples of nickel-catalyzed indole N-arylation at room temperature are known. In this context, indole was selected as a potentially more challenging nucleophile for our reactivity survey. 1-Chloronaphthalene, 4-chlorobenzonitrile, 3-chloroanisole, and 5-chlorobenzo[*b*]thiophene were employed initially as representative ortho-disubstituted, para-substituted electron poor, meta-disubstituted electron poor, and heterocyclic test electrophiles, respectively. A selection of successful L^X variants was then carried forward in potentially more challenging cross-couplings involving 4-chloroquinaldine (at room temperature), 1-bromo-4-*tert*-butylbenzene, hindered 2-chloro-1,4-dimethylbenzene, and/or electron-rich 4-chloroanisole. Throughout, our focus remained on efficiently identifying L^X variants that afforded high conversion to the target monoarylation product of interest. While for the most part low yields of the target compound were accompanied by substantial quantities of unreacted starting materials, in some cases non-negligible amounts of byproducts possibly arising from hydrodehalogenation, diarylation, and/or aryl transfer from the L^X ligand[20] were observed but were neither identified nor quantified. To expedite our catalytic screen, we opted to employ Ni(COD)$_2$/L^X catalyst mixtures, which mandated the use of inert-atmosphere conditions owing to the air-sensitive nature of Ni(COD)$_2$. While the requirement of inert-atmosphere instrumentation has in the past represented a barrier to the implementation of protocols that make use of Ni(COD)$_2$, Garg and co-workers[22] have recently demonstrated that employing paraffin-coated Ni(COD)$_2$ capsules allows for the use of more simple benchtop techniques.

2.2. Nickel-Catalyzed Monoarylation of Furfurylamine. The relative ability of the L^X ancillary ligand variants in Scheme 1 to promote the nickel-catalyzed monoarylation of furfurylamine was explored initially (Scheme 2). In cross-couplings with 1-chloronaphthalene or 4-chlorobenzonitrile, the use of L^{iPr}, L^{Cy}, L^{Ph}, L^{CF3}, L^{OMe}, or L^{Me} in each case afforded high conversion to the target products **1a,b**. Conversely, the application of L^{tBu}, $L^{o\text{-}tol}$, $L^{1\text{-}nap}$, or L^{fur} in all of the furfurylamine cross-couplings examined gave minimal conversion to product. The superiority of the diarylphosphino variants L^{Ph}, L^{CF3}, L^{OMe}, and L^{Me}, relative to the dialkylphosphino derivatives L^{iPr} and L^{Cy}, was apparent in transformations involving 3-chloroanisole and 5-chlorobenzo[*b*]thiophene leading to **1c,d**. Collectively, these observations suggest that, for the nickel-catalyzed monoarylation of primary alkylamines, a range of electronically diverse L^X variants are competent, including dialkylphosphino (L^{iPr} and L^{Cy}), electron-neutral (L^{Ph} and L^{Me}), electron-poor (L^{CF3}), and electron-rich (L^{OMe}) diarylphosphino derivatives. However, L^X derivatives featuring

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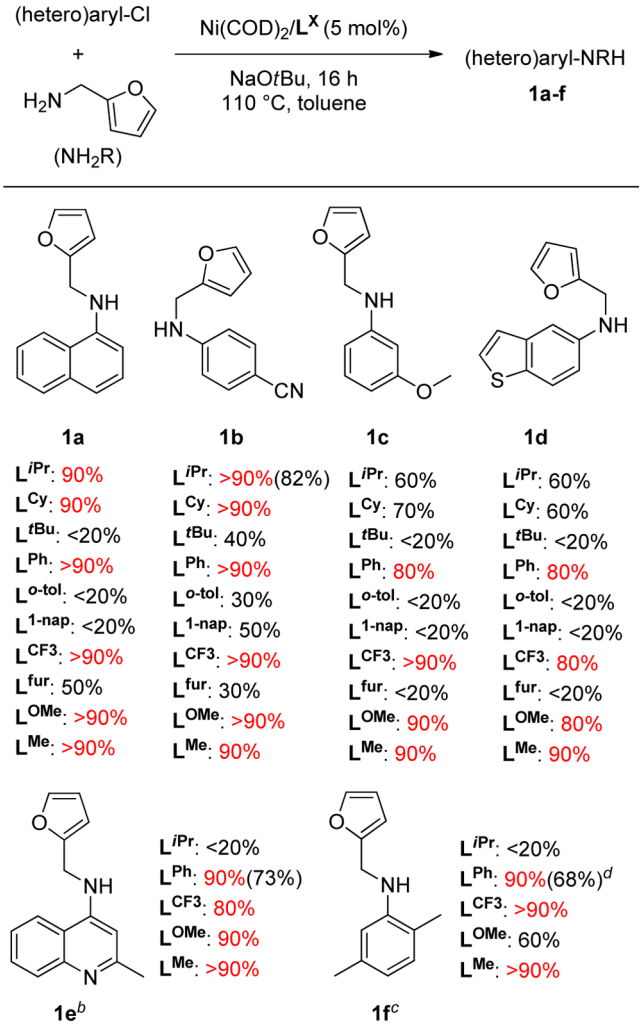
Scheme 2. Comparative Catalytic Screening in the Nickel-Catalyzed Monoarylation of Furfurylamine[a]



[a]Estimated conversion to product after 16 h (unoptimized) on the basis of calibrated GC data, with isolated yields in parentheses (unless otherwise indicated). [b]Conducted at 25 °C. [c]Using 10 mol % Ni/L^X. [d]Calculated yield on the basis of ^{1}H NMR data.

sterically demanding phosphorus donor groups (e.g., L^{tBu}, $L^{o\text{-}tol}$, and $L^{1\text{-}nap}$), are incompatible with such transformations. Similar trends were observed by Stewart and co-workers[15g] in their study of L^{Ph} variants in the nickel-catalyzed cross-coupling of 4-chloroanisole and *p*-toluidine. The poor performance of L^{tBu} and $L^{o\text{-}tol}$ may be related to difficulty in accessing putative (L^X)Ni(aryl)Cl intermediates, in keeping with our inability to synthesize (L^X)Ni(*o*-tolyl)Cl precatalysts derived from these ancillary ligands (see section 2.5).

We then turned our attention to what we envisioned were potentially more challenging nickel-catalyzed cross-couplings of 4-chloroquinaldine (at room temperature), or ortho-disubstituted 2-chloro-1,4-dimethylbenzene, with furfurylamine leading to **1e,f**, employing L^X variants that performed well in the formation of **1a−d** (Scheme 2). Whereas L^{iPr} gave low conversion to products **1e,f**, the arylphosphine derivatives L^{Ph}, L^{CF3}, L^{OMe}, and L^{Me} in general performed well (>80%); modest deviation from this trend was observed in the lower conversion to **1f** (60%) that was achieved by use of L^{OMe}.

To place our observations in the context of some related palladium-catalyzed C(sp^2)−N cross-coupling chemistry involving primary alkylamines, Hamann and Hartwig[20,23] noted that while the use of $L^{o\text{-}tol}$ in place of L^{Ph} in some instances improved selectivity for monoarylation over diarylation, increased hydrodehalogenation also occurred. These workers also established that electronic perturbations arising from arylphosphine substitution in variants of L^{Ph} are less pronounced than in simple monodentate triarylphosphines, in keeping both with the observation that electron-poor (L^{CF3}) and electron-rich (L^{OMe}) diarylphosphino derivatives performed similarly to the parent ligand L^{Ph} in palladium-catalyzed amination chemistry[20] and with our observations with nickel herein. Conversely, whereas the use of L^{tBu} afforded negligible conversion in our survey of nickel-catalyzed cross-couplings of furfurylamine with (hetero)aryl chlorides (Scheme 2), Hamann and Hartwig[23] found L^{tBu} to be highly effective in analogous palladium-catalyzed arylations of primary anilines and alkylamines, as well as secondary cyclic dialkylamines such as morpholine. This latter observation further underscores the concept that the application of ancillary ligands that perform well in palladium-catalyzed BHA chemistry is not a universally effective strategy for the development of effective nickel-catalyzed C(sp^2)−N cross-couplings.[16c,17a]

2.3. Nickel-Catalyzed N-Arylation of Morpholine. Morpholine was employed subsequently, under established literature conditions,[15e] as a prototypical secondary dialkylamine test substrate in our survey of L^X variants in nickel-catalyzed amine arylation (Scheme 3). Whereas in transformations involving 1-chloronaphthalene leading to **2a** the relatively unhindered diarylphosphino derivatives L^{Ph}, L^{CF3}, L^{OMe}, and L^{Me} proved most effective, a much larger collection of the L^X ancillary ligands surveyed performed well in cross-couplings of 4-chlorobenzonitrile leading to **2b**. Indeed, the cross-coupling of morpholine and 4-chlorobenzonitrile represents the only substrate pairing throughout our entire study in which L^{tBu}, $L^{o\text{-}tol}$, and $L^{1\text{-}nap}$ perform in a competitive manner relative to other effective L^X variants. When 3-chloroanisole was used, a different collection of ligands afforded ≥80% conversion to **2c** (L^{iPr}, L^{Cy}, L^{Ph}, and L^{Me}), with L^{CF3} and L^{OMe} proving somewhat less effective. A similar trend was observed in the cross-coupling of 5-chlorobenzo[*b*]thiophene to give **2d**, with the exception that L^{OMe}, but not L^{CF3}, proved competitive with L^{iPr}, L^{Cy}, L^{Ph}, and L^{Me}.

A selection of effective L^X variants were then carried forward and applied in nickel-catalyzed cross-couplings of morpholine with more challenging electrophiles, leading to products **2e−h** (Scheme 3). While in all cases L^{Ph} and/or L^{Me} provided optimal catalytic performance, it worth noting that the hindered and modestly electron rich 2-chloro-1,4-dimethylbenzene proved particularly challenging (≤50% conversion to **2g** for all L^X variants).

2.4. Nickel-Catalyzed N-Arylation of Indole. The nickel-catalyzed N-arylation of indoles and related derivatives continues to represent a particularly challenging transformation.[12] The most broadly effective nickel catalyst for such reactions is (IPr)Ni(styrene)$_2$ (5−10 mol % of Ni, 110 °C), which has been shown to accommodate a range of (hetero)aryl chlorides.[19i] Conversely, the feasibility of conducting such aryl chloride aminations employing L^X ancillary ligands is restricted to a single entry involving the cross-coupling of the unhindered and electronically activated electrophile 4-chlorobenzotrifluoride with carbazole using L^{Ph} at elevated temperatures.[15e] As

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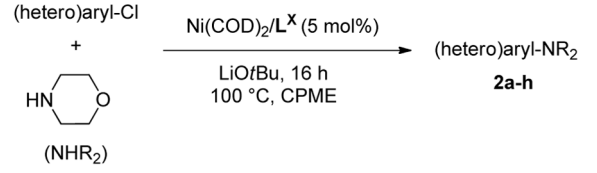
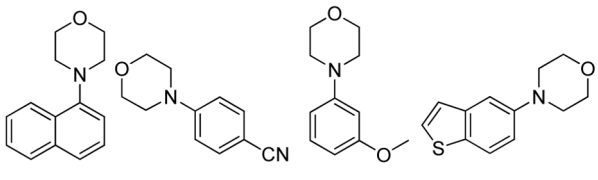
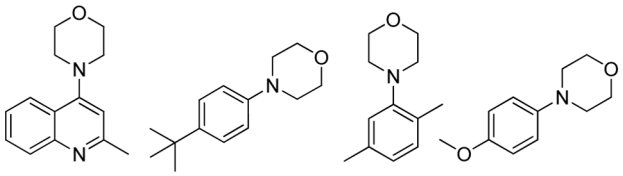
Scheme 3. Comparative Catalytic Screening in the Nickel-Catalyzed N-Arylation of Morpholine[a]





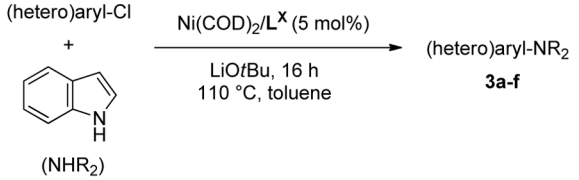
2a	2b	2c	2d
L^{iPr}: 60%	L^{iPr}: >90%	L^{iPr}: 90%	L^{iPr}: >90%
L^{Cy}: 40%	L^{Cy}: >90%	L^{Cy}: 80%	L^{Cy}: >90%
L^{tBu}: <20%	L^{tBu}: 70%	L^{tBu}: <20%	L^{tBu}: <20%
L^{Ph}: >90%(85%)	L^{Ph}: >90%	L^{Ph}: >90%(84%)	L^{Ph}: >90%
$L^{o\text{-}tol}$: <20%	$L^{o\text{-}tol}$: 60%	$L^{o\text{-}tol}$: <20%	$L^{o\text{-}tol}$: <20%
$L^{1\text{-}nap}$: <20%	$L^{1\text{-}nap}$: 80%	$L^{1\text{-}nap}$: <20%	$L^{1\text{-}nap}$: <20%
L^{CF3}: >90%	L^{CF3}: 90%	L^{CF3}: 70%	L^{CF3}: 60%
L^{fur}: <20%	L^{fur}: 40%	L^{fur}: <20%	L^{fur}: <20%
L^{OMe}: 80%	L^{OMe}: 80%	L^{OMe}: 60%	L^{OMe}: >90%
L^{Me}: >90%	L^{Me}: >90%	L^{Me}: >90%	L^{Me}: >90%

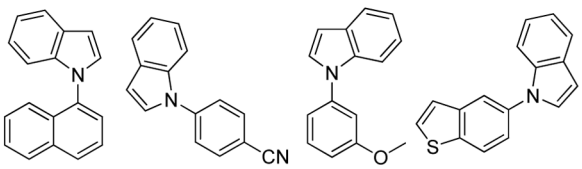


2e[b]	2f[c]	2g	2h
L^{iPr}: 30%	L^{iPr}: <20%	L^{iPr}: <20%	L^{iPr}: 30%
L^{Ph}: 80%(91%)	L^{Ph}: 80%(82%)	L^{Ph}: 40%(16%)	L^{Ph}: 80%(65%)
L^{CF3}: 70%	L^{CF3}: 50%	L^{CF3}: 30%	L^{CF3}: 60%
L^{OMe}: 60%	L^{OMe}: 40%	L^{OMe}: <20%	L^{OMe}: 50%
L^{Me}: 80%	L^{Me}: 60%	L^{Me}: 50%	L^{Me}: 70%

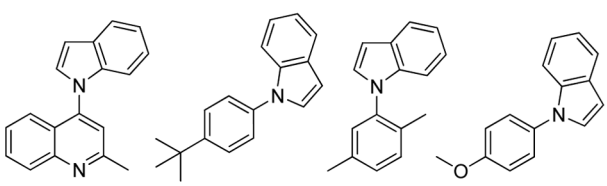
[a]Estimated conversion to product after 16 h (unoptimized) on the basis of calibrated GC data, with isolated yields in parentheses. [b]Conducted at 25 °C. [c]From the aryl bromide.

Scheme 4. Comparative Catalytic Screening in the Nickel-Catalyzed N-Arylation of Indole[a]





3a	3b	3c	3d
L^{iPr}: 30%	L^{iPr}: >90%	L^{iPr}: 70%	L^{iPr}: 20%
L^{Cy}: <20%	L^{Cy}: >90%	L^{Cy}: 70%	L^{Cy}: <20%
L^{tBu}: <20%	L^{tBu}: <20%	L^{tBu}: <20%	L^{tBu}: <20%
L^{Ph}: 20%	L^{Ph}: >90%(98%)	L^{Ph}: 80%	L^{Ph}: >90%(92%)
$L^{o\text{-}tol}$: <20%	$L^{o\text{-}tol}$: 30%	$L^{o\text{-}tol}$: <20%	$L^{o\text{-}tol}$: 30%
$L^{1\text{-}nap}$: <20%	$L^{1\text{-}nap}$: 60%	$L^{1\text{-}nap}$: <20%	$L^{1\text{-}nap}$: <20%
L^{CF3}: >90%(80%)	L^{CF3}: >90%	L^{CF3}: >90%	L^{CF3}: >90%
L^{fur}: <20%	L^{fur}: 40%	L^{fur}: <20%	L^{fur}: <20%
L^{OMe}: <20%	L^{OMe}: >90%	L^{OMe}: 50%	L^{OMe}: 90%
L^{Me}: <20%	L^{Me}: >90%	L^{Me}: 50%	L^{Me}: >90%



3e[b]	3f[c,d]	3g[e]	3h
L^{iPr}: <20%	L^{iPr}: 40%	L^{iPr}: <20%	L^{iPr}: 40%
L^{Ph}: 80%(96%)	L^{Ph}: 60%(64%)[f]	L^{Ph}: 60%	L^{Ph}: 30%
L^{CF3}: 40%	L^{CF3}: 60%	L^{CF3}: 90%(67%)	L^{CF3}: >90%(91%)
L^{OMe}: 30%	L^{OMe}: 40%	L^{OMe}: <20%	L^{OMe}: 80%
L^{Me}: <20%	L^{Me}: 50%	L^{Me}: >90%	L^{Me}: <20%

[a]Estimated conversion to product after 16 h (unoptimized) on the basis of calibrated GC data, with isolated yields in parentheses. [b]Conducted at 25 °C. [c]From the aryl bromide. [d]Using 2.5 mol % of Ni/L^X. [e]Using 10 mol % of Ni/L^X. [f]Using 5 mol % of Ni/L^X.

such, we viewed the nickel-catalyzed cross-coupling of indole with sterically and electronically varied (hetero)aryl chlorides leading to **3a–f** as offering an intriguing context in which to compare the catalytic utility of L^X variants (Scheme 4).

The remarkable utility of the electron-poor ancillary ligand L^{CF3} in the nickel-catalyzed N-arylation of indole was apparent in reactions involving 1-chloronaphthalene, whereby only this variant afforded the target product **3a** in high yield. In contrast, cross-couplings employing less challenging 4-chlorobenzonitrile, leading to **3b**, proceeded effectively with several L^X variants, including L^{iPr}, L^{Cy}, L^{Ph}, L^{CF3}, L^{OMe}, and L^{Me}. In keeping with our previous reaction surveys involving furfurylamine and morpholine (vide supra), consistently inferior performance was noted for L^{tBu}, $L^{o\text{-}tol}$, $L^{1\text{-}nap}$, and L^{fur} in each of the indole cross-couplings examined.

Amination of 3-chloroanisole to form **3c** was brought about most successfully by use of L^{CF3}, followed by L^{Ph} and the two dialkylphosphine derivatives L^{iPr} and L^{Cy}; the observation that L^{OMe} and L^{Me} afforded comparatively lower conversion to **3c** was somewhat surprising, given the otherwise competitive nature of these ligands relative to L^{Ph} and L^{CF3} in the formation of **3b**. Formation of **3d**, derived from 5-chlorobenzo[*b*]-thiophene, in ≥90% yield was achieved by use of L^{Ph}, L^{CF3}, L^{OMe}, or L^{Me} exclusively.

We then employed a focused set of ancillary ligands (i.e., L^{iPr}, L^{Ph}, L^{CF3}, L^{OMe}, and L^{Me}) in subsequent reactivity studies involving more challenging transformations of 4-chloroquinaldine, 1-bromo-4-*tert*-butylbenzene, 4-chloroanisole, and 2-chloro-1,4-dimethylbenzene, leading to **3e–h**, respectively. The parent ligand L^{Ph} proved superior in the formation of **3e**; to the best of our knowledge, this transformation represents the first room-temperature N-arylation of indole employing an aryl chloride electrophile by any catalyst (i.e., Cu, Pd, Ni, or other). With the exception of transformations employing L^{CF3} or L^{Me} in the formation of **3g**, and L^{CF3} or L^{OMe} in the formation of **3h**, modest conversion to **3f–h** (≤60%) was achieved throughout. The successful nickel-catalyzed cross-coupling leading to **3g** observed herein warrants further

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commentary. The only analogous C(sp^2)−N cross-coupling reaction leading to **3g** of which we are aware was claimed by Buchwald and co-workers,[24] whereby 2-bromo-1,4-dimethylbenzene was employed in the presence of a $Pd_2(dba)_3$/binaphthylmonophosphine catalyst system (5 mol % of Pd, 120 °C, 87% isolated yield **3g**). In this regard, the first high-yielding formation of **3g** from an aryl chloride by use of $Ni(COD)_2$/L^{CF3} (10 mol % Ni, 110 °C) is noteworthy.

2.5. Attempted Precatalyst Syntheses. Interest in the application of well-characterized $L_nNi(aryl)X$ precatalysts in place of $Ni(COD)_2/L_n$ mixtures arises from the fact that such nickel(II) species are typically air stable and can be reduced directly under catalytic conditions;[25] moreover, the potentially inhibiting effect of COD is also avoided.[26] In the context of our ancillary ligand survey herein, Buchwald and co-workers[15e] have demonstrated that (L^{Ph})Ni(*o*-tolyl)Cl is particularly effective in nickel C(sp^2)−N cross-couplings. In this vein, we sought to prepare new (L^X)Ni(*o*-tolyl)Cl variants so as to compare directly their catalytic abilities. The synthetic methods that we envisioned might be effective in this regard included the following: formation of (L^X)$NiCl_2$ followed by treatment with (*o*-tolyl)MgCl,[25] ligand displacement by L^X starting from (TMEDA)Ni(*o*-tolyl)Cl[15h,19l] or $(PPh_3)_2$Ni(*o*-tolyl)Cl,[15e] and exposure of L^X to $Ni(COD)_2$ followed by addition of 2-chlorotoluene. We were pleased to find that our preliminary attempt employing the first of these methods proved suitable for the synthesis of diamagnetic (L^{iPr})Ni(*o*-tolyl)Cl, which was obtained as an air-stable analytically pure solid. The single-crystal X-ray structure of (L^{iPr})Ni(*o*-tolyl)Cl is presented in Figure 1 and features what is best described as a distorted-

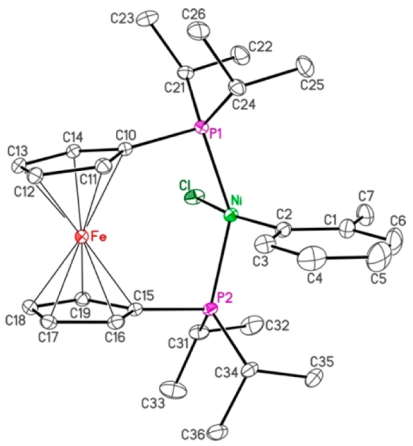

Figure 1. Single-crystal X-ray structure of (L^{iPr})Ni(*o*-tolyl)Cl, shown with 30% thermal ellipsoids and with hydrogen atoms omitted for clarity. Selected interatomic distances (Å) and angles (deg): Ni−P1 2.1888(4), Ni−P2 2.1927(4), Ni−Cl 2.2462(4), Ni−C(aryl) 1.8993(13),; P1−Ni−P2 144.863(16), P1−Ni−C(aryl) 91.99(4), P2−Ni−Cl 90.57(4), Cl−Ni−C(aryl) 166.54(4).

square-planar geometry, involving a trans-spanning L^{iPr} ligand; the trans coordination of L^{iPr} is consistent with the observation of a single ^{31}P NMR resonance. Whereas the structural features of (L^{iPr})Ni(*o*-tolyl)Cl mirror those in (L^{Cy})Ni(*o*-tolyl)Cl,[25] (L^{Ph})Ni(*o*-tolyl)Cl[15e] features cis-ligated bis(phosphine) ligation. Unfortunately, we were unsuccessful in preparing analogous complexes featuring L^{tBu} and $L^{o\text{-}tol}$, despite exhaustive efforts employing the synthetic protocols outlined above. Our inability to synthesize (L^X)Ni(*o*-tolyl)Cl complexes of L^{tBu} and $L^{o\text{-}tol}$, and their poor performance in our catalytic survey (vide supra), may arise due to the poor ligating properties of these sterically demanding ligands with nickel and/or their inability to support putative (L^X)Ni^0 species that undergo oxidative addition of (hetero)aryl chlorides. The problematic nature of preparing alternative (bisphosphine)Ni(*o*-tolyl)Cl complexes featuring sterically demanding P(*o*-tolyl)$_2$ or P(*t*Bu)$_2$ donor fragments has been described.[25]

Difficulties were also encountered in our efforts to prepare (L^X)Ni(*o*-tolyl)Cl precatalysts using L^{CF3} or L^{OMe}. Our most promising, albeit low-yielding (<30%), results were obtained by treatment of L^{CF3} with (TMEDA)Ni(*o*-tolyl)Cl or via formation of the putative intermediate (L^{OMe})$NiCl_2$ followed by exposure to (*o*-tolyl)MgCl. In both cases, yellow-orange solids were obtained that proved competent in a selection of the C(sp^2)−N cross-couplings presented herein. Nonetheless, the remarkably poor solubility of these presumed (L^X)Ni(*o*-tolyl)Cl complexes derived from L^{CF3} or L^{OMe} in a range of solvents thwarted our efforts to properly characterize these materials.

3. CONCLUSIONS

In summary, our comparative reactivity survey involving 10 structurally varied 1,1′-bis(bis(alkyl/aryl)phosphino)ferrocene ancillary ligands (L^X) in the nickel-catalyzed C(sp^2)−N cross-coupling of furfurylamine, morpholine, or indole with various (hetero)aryl halides using $Ni(COD)_2$ revealed some informative structure−reactivity trends. Whereas ortho-disubstituted diarylphosphino ($L^{o\text{-}tol}$ and $L^{1\text{-}nap}$), sterically demanding dialkylphosphino (L^{tBu}), and difuranylphosphino (L^{fur}) variants proved ineffective, the parent ligand L^{Ph}, less sterically demanding dialkylphosphino (L^{iPr} and L^{Cy}), and meta-disubstituted diarylphosphino (L^{CF3}, L^{OMe}, and L^{Me}) ancillary ligands proved competent in several of the test reactions employed. Particularly challenging cross-couplings such as the room-temperature amination of 4-chloroquinaldine, or reactions involving ortho-disubstituted electrophiles revealed the superiority of the diarylphosphino ancillary ligand subclass (L^{Ph}, L^{CF3}, L^{OMe}, and L^{Me}); in the case of indole N-arylation, the electron-poor variant L^{CF3} proved particularly effective. The comparable catalytic performance of L^{Ph}, L^{CF3}, and L^{OMe} in several of the nickel-catalyzed C(sp^2)−N cross-couplings examined herein suggests that any electronic perturbations arising from arylphosphine substitution do not markedly influence the behavior of nickel in this chemistry, in keeping with prior observations in related metal-catalyzed aminations. However, the poor performance of L^{tBu} in the nickel-catalyzed transformations reported herein contrasts the outstanding ability of this ancillary ligand in enabling palladium-catalyzed arylations of primary anilines and alkylamines, highlighting the sometimes divergent ancillary ligand preferences of nickel and palladium in C(sp^2)−N cross-couplings.

Whereas the synthesis of (L^{Ph})Ni(*o*-tolyl)Cl and related nickel(II) compounds has been described previously in the literature, our efforts to prepare analogous L^X ancillary ligand derivatives met with limited success. Whereas (L^{iPr})Ni(*o*-tolyl)Cl was prepared straightforwardly and crystallographically characterized, the use of L^{CF3}, L^{tBu}, $L^{o\text{-}tol}$, or L^{OMe} under similar conditions resulted in poor conversion to product and/or the formation of highly insoluble materials. Notwithstanding the utility of $L_nNi(aryl)X$ precatalysts, these results bring to light practical limitations of this design strategy.

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4. EXPERIMENTAL SECTION

4.1. General Considerations. All reactions were assembled inside a nitrogen-filled inert-atmosphere glovebox and were worked up in air using benchtop procedures. When used within the glovebox, toluene, hexanes, pentane, and dichloromethane were deoxygenated by sparging with nitrogen gas followed by passage through an mBraun double column solvent purification system packed with alumina and copper-Q5 reactant. Anhydrous cyclopentyl methyl ether (CPME) was sparged with nitrogen gas and was stored over 4 Å molecular sieves for 24 h prior to use. Tetrahydrofuran and diethyl ether were dried over Na/benzophenone followed by distillation under an atmosphere of nitrogen gas. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. With the exception of bis(3,5-dimethyl-4-methoxyphenyl)chlorophosphine, which was prepared as per literature methods,[27] all chlorophosphines as well as L^{Ph}, L^{iPr}, L^{Cy}, L^{tBu}, and L^{fur} were obtained from Strem Chemicals. The known ligands $L^{o\text{-}tol}$,[20] L^{CF3},[20] and $L^{1\text{-}nap}$,[28] were synthesized in a manner analogous to that described below for L^{OMe} and L^{Me}, via quenching of dilithiated ferrocene prepared in situ using literature methods[28] with 2 equiv of the appropriate $ClPR_2$ reagent, employing modified literature protocols.[20] All other chemicals were obtained from commercial suppliers and were used as received. GC data were obtained on an instrument equipped with a SGE BP-5 column (30 m, 0.25 mm i.d.). Flash column chromatography was carried out using Silicycle Siliaflash 60 silica (particle size 40−63 μm; 230−400 mesh). ^{1}H NMR (500 and 300 MHz), $^{13}C\{^1H\}$ NMR (125.8 and 75.5 MHz), and $^{31}P\{^1H\}$ NMR (202.5 and 121.4 MHz) spectra were recorded at 300 K in $CDCl_3$ with chemical shifts expressed in parts per million (ppm). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode.

4.2. Synthesis of 1,1′-(Bis(bis(3,5-dimethyl-4-methoxyphenyl))phosphino)ferrocene (L^{OMe}). Within a glovebox, a vial containing a magnetic stir bar was charged with ferrocene (167 mg, 0.9 mmol), tetramethylethylenediamine (283 μL, 1.89 mmol), and hexanes (3.74 mL), and magnetic stirring was initiated. To the vial was added dropwise *n*-butyllithium (2.5 M in hexanes, 756 μL, 1.89 mmol), and the resulting mixture was stirred at ambient temperature for 12 h. In a separate vial, bis(3,5-dimethyl-4-methoxyphenyl)-chlorophosphine (637 mg, 1.89 mmol) was treated with tetrahydrofuran (1.2 mL); we found this chlorophosphine to be poorly soluble in this and other common solvents. Both the chlorophosphine mixture and the dilithioferrocene mixture were cooled to −33 °C. To the stirring dilithioferrocene mixture was added the chlorophosphine mixture dropwise, and the resulting mixture was then stirred until full consumption of the chlorophosphine was confirmed on the basis of $^{31}P\{^1H\}$ NMR data obtained from a reaction aliquot (ca. 2 h). The reaction mixture was then concentrated in vacuo and purified by flash column chromatography on silica gel using a gradient eluent: starting with hexanes (∼200 mL), 49/1 hexanes/ethyl acetate (∼200 mL), 24/1 hexanes/ethyl acetate (∼400 mL) and finishing with 15.7/1 hexanes/ethyl acetate. The product was isolated in 30% yield (210 mg, 0.27 mmol) as a light orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97−6.96 (m, 8H), 4.20 (m, 4H), 4.03 (m, 4H), 3.71 (s, 12H), 2.22 (s, 24H). $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 157.6, 134.1 (d, J = 20.1 Hz), 135.5, 130.7, 130.6, 73.6 (d, J = 13.8 Hz), 72.3, 59.8, 16.3. $^{31}P\{^1H\}$ NMR (202.5 MHz; $CDCl_3$): δ −19.1. HRMS: m/z ESI$^+$ found 787.2763 $[M + H]^+$, calculated for $C_{46}H_{53}FeO_4P_2$ 787.2769.

4.3. Synthesis of 1,1′-(Bis(3,5-dimethylphenyl)phosphino)-ferrocene (L^{Me}). A protocol directly analogous to that described for the synthesis of L^{OMe} was employed, using ferrocene (148 mg, 0.85 mmol), tetramethylethylenediamine (268 μL, 1.79 mmol), *n*-butyllithium (2.5 M in hexanes, 714 μL, 1.79 mmol), and bis(3,5-dimethylphenyl)chlorophosphine (494 mg, 1.79 mmol). The reaction mixture was then concentrated in vacuo and purified by flash column chromatography on silica gel using a gradient eluent: starting with hexanes (∼200 mL), 99/1 hexanes/ethyl acetate (∼200 mL), 49/1 hexanes/ethyl acetate (∼200 mL), 32.3/1 hexanes/ethyl acetate (∼200 mL), and finishing with 24/1 hexanes/ethyl acetate. The product was isolated in 35% yield (221 mg, 0.30 mmol) as a light orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97−6.94 (m, 12H), 4.27−4.26 (m, 4H), 4.04−4.03 (m, 4H), 2.27 (s, 24H). $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 138.7 (d, J = 7.6 Hz), 137.8 (d, J = 6.3 Hz), 131.7, 131.5, 130.7, 74.0 (d, J = 13.8 Hz), 72.8, 21.8. $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$): δ −16.9. HRMS: m/z ESI$^+$ found 667.2340 $[M + H]^+$, calculated for $C_{42}H_{45}FeP_2$ 667.2346.

4.4. Synthesis of (L^{iPr})Ni(*o*-tolyl)Cl. Within a glovebox, a vial containing a magnetic stir bar was charged with $NiCl_2$(DME) (0.088 g, 0.4 mmol) and 1,1′-(bis(diisopropylphenyl)phosphino)ferrocene (0.176 g, 0.42 mmol). To the solid mixture was added tetrahydrofuran (4 mL), and the resulting heterogeneous mixture was stirred magnetically at room temperature for 2 h. The reaction vial was removed from the glovebox, and in air the reaction mixture was treated with pentane (4 mL), thereby generating a precipitate. The solid was isolated via suction filtration, washed with pentane (5 × 2 mL), and dried in vacuo to afford the presumptive intermediate product (D*i*PPF)$NiCl_2$ as a dark green solid (0.18 g, 0.34 mmol, 83%), which was used without further purification. Within an inert-atmosphere glovebox, the isolated (D*i*PPF)$NiCl_2$ (0.18 g, 0.34 mmol) was transferred to a vial containing a magnetic stir bar, followed by the addition of THF (3.4 mL). The resultant heterogeneous mixture was cooled to −30 °C for 0.5 h, followed by the addition of precooled (*o*-tol)MgCl (−30 °C, 1.0 M in THF; 0.41 mL); the mixture was warmed to room temperature under the influence of magnetic stirring. After 4 h, the reaction vial was removed from the glovebox, and in air the reaction mixture was treated with cold methanol (∼ −90 °C; 0.5 mL) and cold pentane (∼−90 °C; 2 mL), thereby generating a precipitate. The solid was isolated via suction filtration and washed with cold methanol (∼−90 °C; 4 × 1 mL) followed by cold pentane (∼−90 °C; 5 × 2 mL). The resulting material was dried in vacuo to afford the product as a dark red-orange solid (0.12 g, 0.2 mmol, 57%). A single crystal suitable for X-ray diffraction was obtained via vapor diffusion of diethyl ether into a dichloromethane solution of the target complex. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.17 (m, 1H), 6.74−6.70 (m, 3H), 4.64−4.36 (m, 8H), 3.61 (s, 3H), 3.09 (m, 2H), 1.69 (m, 2H), 1.50−1.48 (m, 6H), 1.10−0.97 (m, 12H), 0.38−0.36 (m, 6H). $^{13}C\{^1H\}$ NMR (125.8 MHz; $CDCl_3$; quaternary carbons not observed despite prolonged acquisition times): δ 136.0, 125.9, 124.0, 122.0, 72.8, 71.7, 70.8, 69.7, 27.0, 25.1−24.9 (overlapping), 24.0, 21.1, 19.6, 17.5. $^{31}P\{^1H\}$ NMR (202.5 MHz; $CDCl_3$): δ 0.26 (s). Anal. Calcd for $C_{29}H_{43}Cl_1Fe_1Ni_1P_2$: C, 57.71; H, 7.18; N, 0. Found: C, 57.33; H, 6.80; N, <0.5.

4.5. General Procedure for the Monoarylation of Furfurylamine with Aryl Halides (GP1). Within a glovebox, bis(cyclooctadiene)nickel(0) (0.05 equiv), L^X (0.05 equiv), NaO*t*Bu (2.0 equiv), aryl halide (1.0 equiv), and toluene (0.12 M of aryl halide) were placed in a screw-capped vial containing a magnetic stir bar, followed by the addition of furfurylamine (1.1 equiv). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to either 25 or 110 °C for 16 h. After the mixtures were cooled to room temperature, reactions were monitored using both TLC and calibrated GC methods. The product was isolated or analyzed by using Workup Method A or Workup Method B.

4.6. General Procedure for the Arylation of Morpholine with Aryl Halides (GP2). Within a glovebox, bis(cyclooctadiene)nickel(0) (0.05 equiv), L^X (0.05 equiv), LiO*t*Bu (1.5 equiv), aryl halide (1.0 equiv), and cyclopentyl methyl ether (0.5 M of aryl halide) were placed in a screw-capped vial containing a magnetic stir bar, followed by the addition of morpholine (1.5 equiv). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to 25 or 100 °C for 16 h. After the mixtures were cooled to room temperature, reactions were monitored using both TLC and calibrated GC methods. The product was isolated or analyzed by using Workup Method A or Workup Method B.

4.7. General Procedure for the Arylation of Indole with Aryl halides (GP3). Within a glovebox, bis(cyclooctadiene)nickel(0) (0.05 equiv), L^X (0.05 equiv), LiO*t*Bu (1.5 equiv), aryl halide (1.0 equiv),

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and toluene (0.12 M of aryl halide) were placed in a screw-capped vial containing a magnetic stir bar, followed by the addition of indole (1.1 equiv). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to 25 or 110 °C for 16 h. After the mixtures were cooled to room temperature, reactions were monitored using both TLC and calibrated GC methods. The product was isolated or analyzed by using Workup Method A or Workup Method B.

4.8. Workup Method A (Purification by Chromatography). Following GP1, GP2, or GP3 (employing between 0.6 and 1.0 mmol of aryl halide), after it was cooled to room temperature, the reaction mixture was diluted with ethyl acetate (ca. 30 mL) and washed with brine (3 × ca. 30 mL) and the organic layer was dried over sodium sulfate. The solvent was removed in vacuo, and the compound was purified by flash column chromatography on silica gel.

4.9. Workup Method B (Procedure for the Preparation of GC Samples). Following GP1, GP2, or GP3 (employing 0.12 mmol of aryl halide), after it was cooled to room temperature, the reaction mixture was diluted using ethyl acetate and was passed through a Kimwipe filter containing a Celite/silica gel pad into a GC vial. Calibrated GC estimates are given by comparison to authentic samples.

4.10. Workup Method C (Procedure for the Preparation of NMR Yield Samples). Following GP2 or GP3 (employing 0.5 mmol of aryl chloride), after it was cooled to room temperature, the reaction mixture was diluted with ethyl acetate (ca. 30 mL) and washed with brine (3 × ca. 30 mL) and the organic layer was dried over sodium sulfate. The solvent was removed in vacuo, followed by the addition of the internal standard (dodecane or ferrocene, 10–20 mol %) in the vial containing the product mixture. The resultant mixture was taken up in $CDCl_3$ and was then analyzed by use of NMR spectroscopy.

4.11. Crystallographic Solution and Refinement Details. Crystallographic data for (L^{iPr})Ni(*o*-tolyl)Cl were obtained at −100 °C on a Bruker D8/APEX II CCD diffractometer equipped with a CCD area detector using Cu Kα (α = 1.54178 Å) (microfocus source) radiation employing a sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer. Data reduction, correction for Lorentz–polarization, and absorption correction (Gaussian integration; face indexed) were each performed. Structure solution by using intrinsic phasing was carried out, followed by least-squares refinement on F^2. All non-hydrogen atoms were refined with anisotropic displacement parameters, while all hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters on the basis of the isotropic displacement parameter of the attached atom. Crystallographic data are available from the Cambridge Structural Database as file CCDC 1519106.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00885.

Characterization data and NMR spectra for new DPPF ligand variants and catalytic reaction products (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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