ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

A Comparative Reactivity Survey of Some Prominent Bisphosphine Nickel(II) Precatalysts in C–N Cross-Coupling

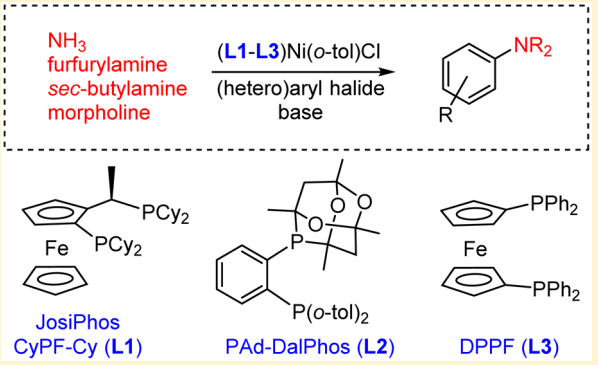
Jillian S. K. Clark,[†] Christopher M. Lavoie,[†] Preston M. MacQueen,[†] Michael J. Ferguson,[‡] and Mark Stradiotto*[,†]

[†]Department of Chemistry, Dalhousie University, 6274 Coburg Road, P.O. Box 15000, Halifax, Nova Scotia B3H 4R2, Canada

[‡]X-ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

Supporting Information

ABSTRACT: The synthesis and characterization of the new air-stable precatalyst (**L1**)Ni(*o*-tol)Cl (**C1**; where **L1** = JosiPhos CyPF-Cy) is reported, along with the results of a comparative reactivity survey involving **C1** and analogous PAd-DalPhos- and DPPF-containing precatalysts (**C2** and **C3**, respectively) in representative nickel-catalyzed C(sp^2)–N cross-coupling reactions. Precatalyst **C1** was found to be competitive with, and in some cases complementary to, **C2** in the monoarylation of ammonia and primary alkylamines with (hetero)aryl chlorides, including in otherwise challenging room temperature transformations. (Pseudo)halide comparison studies involving the cross-coupling of furfurylamine at room temperature revealed that in contrast to **C2** precatalyst **C1** performs less effectively with aryl bromides. Whereas **C3** was found to be ineffective for such transformations, this DPPF-derived precatalyst proved superior to **C1** and **C2** in reactions involving the secondary dialkylamine test substrate morpholine.



1. INTRODUCTION

The palladium-catalyzed cross-coupling of NH substrates and (hetero)aryl (pseudo)halides (i.e., Buchwald–Hartwig amination, BHA) is a well-established C(sp^2)–N bond-forming methodology that is employed widely in the synthesis of biologically active molecules and functional materials.[1] Building on the initial development of such transformations over 20 years ago,[2] state-of-the-art catalyst systems for BHA collectively enable the cross-coupling of a broad spectrum of aryl electrophiles and NH substrates. The remarkable expansion of BHA chemistry can be attributed in large part to the design and application of electron-rich and sterically demanding alkylphosphine and *N*-heterocyclic carbene ancillary ligands[3] that promote the formation of low-coordinate,[4] electron-rich LPd(0) complexes that are predisposed toward otherwise challenging oxidative additions (e.g., X = Cl).[5]

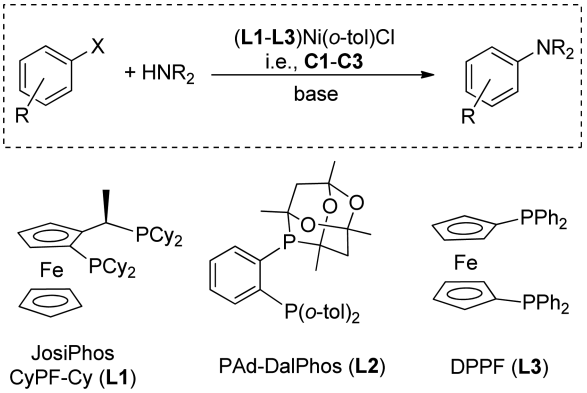
Notwithstanding the utility of BHA chemistry, the cost and relative scarcity of palladium, as well as the desire to access new substrate classes in C(sp^2)–N cross-coupling reactions, provides motivation for the development of base-metal catalysts for such transformations. Nickel-based catalysts are particularly attractive in this regard, especially in light of their ability to promote alternative cross-couplings involving a diversity of phenol-derived electrophiles.[6] In this context it is surprising that the application of nickel-based catalysts in C(sp^2)–N cross-coupling has received comparatively little attention[7] because the first report of such transformations involving aryl chlorides coincided with the early development of BHA methods.[8] Consequently, our understanding of the influence of ancillary ligation on such nickel-catalyzed C(sp^2)–N bond-forming reactions is rather limited. Despite the potential for both single-electron chemistry and Ni(I)/(III)[9] catalytic cycles,[10] recent studies support an active Ni(0)/Ni(II) cycle in C(sp^2)–N[11] (as well as C(sp^2)–S)[12] cross-couplings involving phosphine-ligated nickel species with aryl (pseudo)-halides, in keeping with BHA. However, the smaller atomic radius and lower electronegativity of nickel versus those of palladium, as well as the greater propensity for C(sp^2)–Cl oxidative addition to phosphine-ligated Ni(0) versus Pd(0),[5a,13] suggest that ancillary ligands optimized for use with palladium in BHA are unlikely to be universally effective in related nickel chemistry. In this regard, the systematic evaluation of known and newly identified/developed ancillary ligands sharing a common donor atom motif will serve to illuminate important structure–reactivity trends, thereby directing the evolution of increasingly effective nickel catalysts for use in C(sp^2)–N cross-coupling chemistry.

Bisphosphine ligands, including commercially available JosiPhos CyPF-Cy (**L1**),[14] PAd-DalPhos (**L2**),[15] and DPPF (**L3**)[8,16] have proven effective in supporting useful nickel catalysts for C(sp^2)–N cross-coupling chemistry (Scheme 1). Our group,[14] as well as Green and Hartwig,[11c] independently disclosed the first examples of nickel-catalyzed ammonia

Received: August 12, 2016

DOI: 10.1021/acs.organomet.6b00650
Organometallics XXXX, XXX, XXX–XXX

Scheme 1. Nickel-Catalyzed C(sp^2)−N Cross-Coupling Employing C1−C3



monoarylation, in which relatively electron-rich JosiPhos-type ligands were employed at elevated temperatures (≥100 °C); in our report[14] on such chemistry, Ni(COD)$_2$/**L1** catalyst mixtures were used with success in combination with (hetero)aryl bromides, chlorides, and tosylates. Subsequent application of nickel precatalyst (**L2**)Ni(*o*-tol)Cl (**C2**), featuring new and relatively electron-poor bisphosphine **L2**, enabled the first examples of nickel-catalyzed room temperature transformations of primary alkylamines and ammonia in combination with an unprecedented scope of (hetero)aryl electrophiles.[15] Ligand **L3** was employed in the pioneering report on nickel-catalyzed C(sp^2)−N cross-coupling[8] and remains a prominent ligand for such transformations. Notably, Buchwald and co-workers have demonstrated that the **L3**-supported nickel precatalyst (**L3**)Ni(*o*-tol)Cl (**C3**) is effective for cross-couplings of secondary amines and anilines in combination with (hetero)aryl chlorides, sulfamates, mesylates, and triflates.[16] While collectively **L1**−**L3** cover a broad scope of NH substrates, individually the successful application of each of these ancillary ligands in nickel-catalyzed C(sp^2)−N cross-coupling chemistry is demonstrated only for selected substrate classes (*vide supra*). In an effort to learn more about the relative abilities of **L1**−**L3** in nickel-catalyzed C(sp^2)−N cross-couplings, we sought to carry out a head-to-head reactivity comparison employing a representative selection of aryl electrophiles and structurally varied NH substrates. Given the efficacy of catalysts based on either electron-rich ligand **L1** or comparatively electron-poor ligand **L2** in rather challenging nickel-catalyzed ammonia monoarylation chemistry, we were particularly interested in comparing directly the reactivity behavior of structurally analogous nickel precatalysts featuring these electronically divergent ancillary ligand sets; in the case of **L1**, this required preparation of the hitherto unknown precatalyst (**L1**)Ni(*o*-tol)Cl (**C1**). Herein we report on the synthesis and characterization of **C1** and on the results of a comparative reactivity survey of **C1**−**C3** in representative nickel-catalyzed C(sp^2)−N cross-coupling reactions.

2. RESULTS AND DISCUSSION

2.1. Synthesis and Characterization of Precatalyst C1.

From a practical perspective, there is considerable interest in the development of air-stable nickel(II) precatalysts that can be reduced to the requisite nickel(0) species under catalytic conditions, without the required addition of an exogenous reductant. Given the utility of precatalysts of the type L_nNi(aryl)X[17] in this regard, including **C2**[15] and **C3**,[16] we sought to prepare (**L1**)Ni(*o*-tol)Cl (**C1**). Combination of **L1** with NiCl$_2$(DME) to give the putative intermediate (**L1**)NiCl$_2$, followed by treatment with (*o*-tol)MgCl afforded (**L1**)Ni(*o*-tolyl)Cl (**C1**) in 76% overall isolated yield (Figure 1, eq 1).

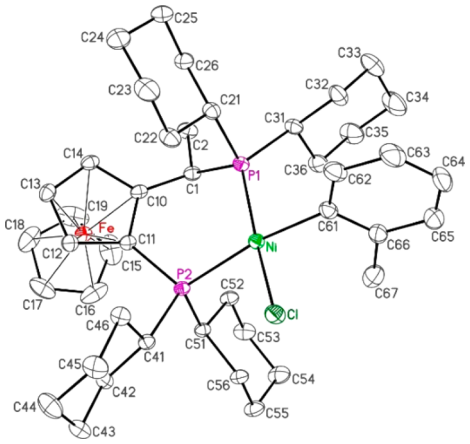


Figure 1. Single-crystal X-ray structure of **C1**, shown with 30% thermal ellipsoids and with hydrogen atoms omitted for clarity. Selected interatomic distances (Å) and angles (deg) for **C1**: Ni−P1 2.1774(8), Ni−P2 2.2721(8), Ni−Cl 2.2078(8), Ni−C(aryl) 1.925(3), P1−Ni−P2 97.84(3), P1−Ni−C(aryl) 89.16(10), P2−Ni−C1 89.54(3), Cl−Ni−C(aryl) 84.34(10).

The diamagnetic, air-stable complex **C1** was characterized by use of NMR spectroscopic and single-crystal X-ray diffraction techniques (Figure 1). The crystal structure of **C1** reveals a distorted square planar geometry at nickel ($\Sigma_{\text{angles at Ni}} \approx 360°$), whereby the κ^2-*P*,*P*-**L1** ligand features chloride *trans* to the trialkylphosphine donor fragment. The *cis*-chelating bisphosphine in **C1** exhibits a P−Ni−P bite angle (~97.8°) that is intermediate between those found in the crystal structures of **C2** (~86.5°)[15] and **C3** (~102.0°).[16]

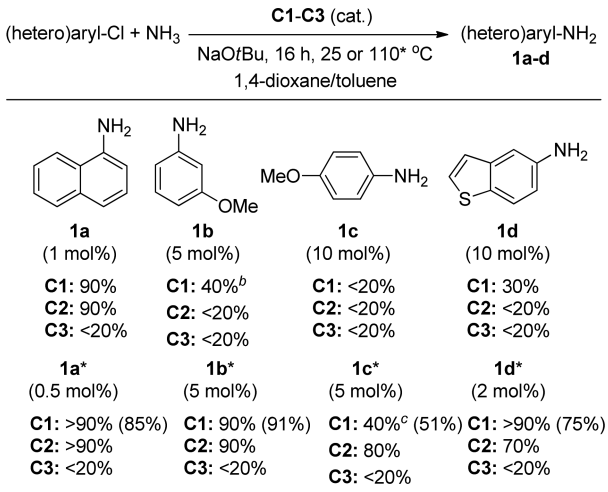
2.2. Nickel-Catalyzed Monoarylation of Ammonia.

Ammonia is one of the most widely produced commodity chemicals and as such represents an attractive synthon in the synthesis of nitrogen-containing organic molecules.[18] However, the selective monoarylation of ammonia with (hetero)aryl electrophiles has proven to be a significant challenge due in part to the fact that for most catalyst systems the sought-after primary (hetero)aniline products are often better substrates than ammonia itself, leading to uncontrolled polyarylation.[19] In this regard, ammonia monoarylation provides a useful testing ground for ancillary ligand design in metal-catalyzed C(sp^2)−N cross-coupling chemistry. Whereas palladium-based catalysts have traditionally offered optimal performance for the cross-coupling of ammonia with (hetero)aryl chlorides,[20] the scope of reactivity exhibited by **C2**, both in terms of the breadth of electrophilic partners and the varied reaction conditions tolerated including room temperature transformations, was found to exceed that achieved by use of any known catalyst system.[15] We previously demonstrated that Ni(COD)$_2$/**L1** mixtures were effective in ammonia monoarylation chemistry conducted at elevated temperatures (*vide supra*); under analogous conditions, the performance of Ni(COD)$_2$/**L3** was found to be comparatively poor.[14] Given the potential for catalyst inhibition by COD,[21] we sought to compare directly the performance of precatalysts **C1**−**C3** in ammonia monoarylation chemistry at both 25 and 110 °C, involving 1-chloronaphthalene, 3-chloroanisole, 4-chloroanisole, and 5-

DOI: 10.1021/acs.organomet.6b00650
Organometallics XXXX, XXX, XXX−XXX

chlorobenzo[*b*]thiophene as representative *ortho*-substituted, electron-poor, electron-rich, and heterocyclic aryl chlorides, respectively (Scheme 2). For these transformations as well as

Scheme 2. Comparative Catalytic Screening of C1−C3 in the Nickel-Catalyzed Monoarylation of Ammonia[a]



[a]Reactions using 0.5 M stock solutions of ammonia in 1,4-dioxane, employing the mol % **C1−C3** as indicated. Conditions: 0.10 M 1-chloronaphthalene and ammonia (25 °C, 3 equiv; 110 °C, 5 equiv), otherwise 0.07 M Ar−Cl and ammonia (7 equiv). Estimated conversion to product after 16 h (unoptimized) is based on GC data, with product yield based on ^{1}H NMR data in parentheses. [b]80% conversion to **1b** employing 10 mol % **C1**. [c]Significant amounts of higher molecular weight byproducts observed.

related cross-couplings involving alternative amine substrates (*vide infra*), somewhat challenging reaction conditions (e.g., low catalyst loading) were intentionally selected in an effort to differentiate the catalytic abilities of **C1−C3**. For the majority of the transformations reported herein, poor product formation was accompanied by low conversion of the electrophile.

The room temperature monoarylation of ammonia employing 1-chloronaphthalene leading to **1a** was readily achieved by use of either **C1** or **C2** (1 mol %, 90%); however, in both cases efforts to reduce the catalyst loading to 0.5 mol % resulted in <20% conversion to **1a** under similar conditions. In monitoring the rate of formation of **1a** in such reactions employing **C1** or **C2** (25 °C, 1 mol %), 50% conversion to **1a** was observed after 20 min with **C2**, whereas 20% conversion was achieved by use of **C1**. After 1 h, 60% conversion to **1a** was achieved with each **C1** and **C2**. While we are hesitant to definitively ascribe mechanistic significance to these limited observations, it appears that **C2** is more easily activated under the specific reaction conditions employed. Notably, **C3** proved ineffective for ammonia monoarylation involving 1-chloronapthalene and the other electrophiles examined in the survey.

Related room temperature reactions involving more challenging test electrophiles leading to **1b−d** were less successful (Scheme 2). In the transformation of relatively electron-poor 3-chloroanisole, 40% conversion to **1b** was achieved by use of **C1** (5 mol %); in doubling the catalyst loading, 80% conversion to **1b** was achieved. Under analogous conditions using **C2** (25 °C, 5 mol %), <20% conversion to **1b** was observed. This trend was retained in the monoarylation of ammonia with electron-poor 4-chlorobenzonitrile under analogous conditions (25 °C, 5 mol % precatalyst); >90% conversion to 4-aminobenzonitrile was achieved with **C1**, whereas poor conversion to 4-aminobenzonitrile was observed when using **C2**, along with the formation of higher molecular weight byproducts.

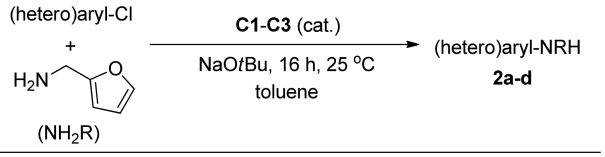
Improved catalytic performance in ammonia monoarylation was observed for **C1** and **C2** at 110 °C, with each of these precatalysts affording synthetically useful conversions to **1a**, **1b**, and **1d**. Divergent performance was noted in reactions involving the relatively electron-rich substrate, 4-chloroanisole, whereby selectivity for conversion to **1c** with **C2** (80%) exceeded that achieved by use of **C1** (40%). Collectively, these results provide preliminary evidence that the catalytic performance of **C1** is competitive with, and in some ways complementary to, **C2** in otherwise challenging ammonia monoarylation chemistry.

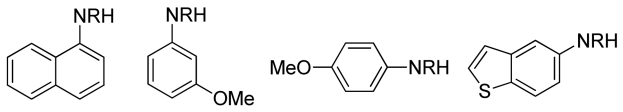
2.3. Nickel-Catalyzed Monoarylation of Primary and Secondary (Di)alkylamines. The selective monoarylation of primary alkylamines with (hetero)aryl (pseudo)halides remains a relatively challenging class of transformations in nickel-catalyzed C(sp^2)−N cross-coupling chemistry.[7] Notwithstanding two isolated entries involving the arylation of *n*-hexylamine with aryl chlorides by use of Ni(COD)$_2$/**L3** catalyst mixtures at 110 °C that are present in Wolfe and Buchwald's[8] pioneering paper, the first broadly useful nickel precatalyst for the selective monoarylation of primary alkylamines, (*rac*-BINAP)Ni(η^2-NC-Ph), was disclosed in 2014 by Hartwig and co-workers.[11b] Use of this (*rac*-BINAP)Ni(0) precatalyst enabled the cross-coupling of a range of functionalized primary alkylamines with (hetero)aryl chlorides and bromides under relatively mild conditions (1−4 mol % Ni; 50−80 °C). Stewart and co-workers[22] subsequently reported on analogous transformations employing (*rac*-BINAP)Ni(P(OPh)$_3$)$_2$ as a precatalyst. We have demonstrated that **C2** is a superlative precatalyst for such transformations that promotes the cross-coupling of a broad spectrum of electron-rich and -poor (hetero)aryl (pseudo)-halides with linear and branched primary alkylamines, including the first examples of nickel-catalyzed room temperature transformations of this type.[15] Encouraged by the efficacy of **C1** in nickel-catalyzed ammonia monoarylation (Scheme 2), we initiated a reactivity comparison of **C1−C3** in the cross-coupling of furfurylamine or *sec*-butylamine with 1-chloronaphthalene, 3-chloroanisole, 4-chloroanisole, or 5-chlorobenzo[*b*]-thiophene.

Whereas each of **C1−C3** proved effective as a precatalyst for the monoarylation of furfurylamine and 1-chloronaphthalene under mild conditions (25 °C, 0.5 mol %) leading to **2a**, related transformations involving the other electrophiles proved challenging for **C3** (Scheme 3). Conversely, under the screening conditions employed each of **C1** and **C2** provided useful levels of conversion to the target monoarylation products **2b−d** at room temperature, with slightly higher conversions to the target aniline achieved in each transformation by use of **C2**. The efficacy of **C1** and **C2** as precatalysts in the monoarylation of ammonia (Scheme 2) and primary alkylamine furfurylamine (Scheme 3) prompted us to examine the relative preference of these precatalysts for such substrates within a competition scenario (Scheme 4). Interestingly, in cross-couplings employing equal amounts of ammonia and methylamine with limiting amounts of 1-chloronaphthalene (25 °C, 5 mol %), **C1** exhibited a marked preference for ammonia monoarylation leading to **1a**, whereas preferential monoarylation of methylamine leading to **2e** was achieved by use of **C2**. The observed **1a**/**2e** selectivity drops to 2:1 (for **C1**) and 1:2 (for **C2**) for

DOI: 10.1021/acs.organomet.6b00650
Organometallics XXXX, XXX, XXX−XXX

Scheme 3. Comparative Catalytic Screening of C1−C3 in the Nickel-Catalyzed Monoarylation of Furfurylamine[a]

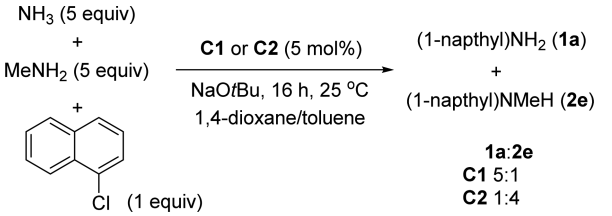




2a (0.5 mol%)	2b (0.5 mol%)	2c (5 mol%)	2d (1 mol%)
C1: 90%	**C1:** 50%	**C1:** 80%	**C1:** 70%
C2: 90%	**C2:** 70% (78%)	**C2:** 90% (90%)	**C2:** 80% (75%)
C3: 80% (62%)	**C3:** <20%	**C3:** <20%	**C3:** <20%

[a]Reactions: 1.1 equiv of furfurylamine; 0.16 M 5-chlorobenzo[*b*]-thiophene, otherwise 0.24 M Ar−Cl; mol % **C1−C3** as indicated. Estimated conversion to product after 16 h (unoptimized) is based on GC data, with isolated yields in parentheses.

Scheme 4. Competitive Monoarylation of Ammonia and Methylamine with 1-Chloronaphthalene Using C1 and C2[a]



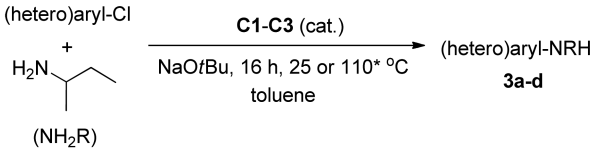
[a]Estimated product ratio is based on GC data; full conversion of the aryl chloride observed.

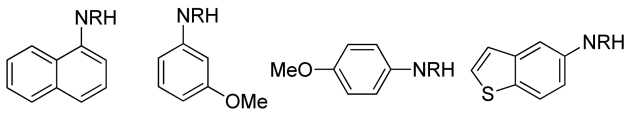
analogous reactions conducted at 110 °C. While it is plausible to conclude that the less electron-donating nature of PAd-DalPhos (**L2**) versus that of CyPF-Cy (**L1**) gives rise to reactive nickel intermediates that favor binding and turnover of more basic amines (e.g., methylamine over ammonia), the scenario is likely more nuanced; for example, the contribution of steric differences between **L1** and **L2** on the observed selectivity outlined in Scheme 4 is also likely to be important.

The monoarylation of the more sterically demanding *sec*-butylamine was examined subsequently (Scheme 5). Precatalyst **C2** proved effective in the cross-coupling of 1-chloronaphthalene leading to **3a** (80%) at room temperature; under analogous conditions, the performance of each of **C1** (40%) and **C3** (20%) was inferior. Whereas related room temperature transformations involving 3-chloroanisole, 4-chloroanisole, and 5-chlorobenzo[*b*]thiophene leading to **3b−d** also proved feasible with **C1** and **C2**, it is apparent that the cross-coupling of *sec*-butylamine with 4-chloroanisole to give **3c** is challenging in comparison to reactions involving less-hindered furfurylamine (Scheme 3). Efforts to improve catalytic performance by conducting reactions at 110 °C, albeit at lower loadings of **C1−C3**, met with some success, with the improved formation of **3a** and **3c** by use of **C1** being notable.

The cross-coupling of morpholine and either 4-chlorobenzonitrile or 5-chlorobenzo[*b*]thiophene by use of **C1−C3** leading to **4a** or **4b** was examined in an effort to briefly compare the abilities of these precatalysts in the *N*-arylation of a prototypical secondary dialkylamine (Scheme 6). The reaction conditions

Scheme 5. Comparative Catalytic Screening of C1−C3 in the Nickel-Catalyzed Monoarylation of *sec*-Butylamine[a]

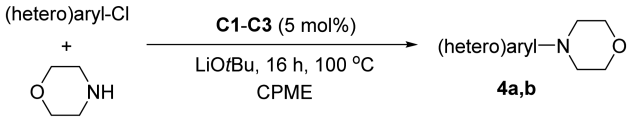


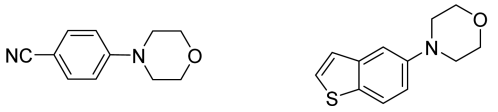


3a (2 mol%)	3b (5 mol%)	3c (10 mol%)	3d (5 mol%)
C1: 40%	**C1:** 70%	**C1:** 40%	**C1:** 70%
C2: 80% (70%)	**C2:** 60%	**C2:** 40%	**C2:** 80% (61%)
C3: 20%	**C3:** <20%	**C3:** <20%	**C3:** <20%
3a* (1 mol%)	**3b*** (2 mol%)	**3c*** (5 mol%)	**3d*** (2 mol%)
C1: 70%	**C1:** 70% (64%)	**C1:** 70% (59%)	**C1:** 30%
C2: 60%	**C2:** 80%	**C2:** 40%	**C2:** 60%
C3: <20%	**C3:** <20%	**C3:** <20%	**C3:** <20%

[a]Reaction conditions: 1.1 equiv of *sec*-butylamine; at 25 °C, 0.16 M 1-chloronaphthalene, otherwise 0.12 M Ar−Cl; at 110 °C, 0.32 M 1-chloronaphthalene or 0.12 M 4-chloroanisole, otherwise 0.24 M Ar−Cl; mol % **C1−C3** as indicated. Estimated conversion to product after 16 h (unoptimized) is based on GC data, with isolated yields in parentheses.

Scheme 6. Comparative Catalytic Screening of C1−C3 in the Nickel-Catalyzed *N*-Arylation of Morpholine[a]





4a	4b
C1: 60%	**C1:** <20%
C2: <20%	**C2:** <20%
C3: >90% (94%)	**C3:** >90% (72%)

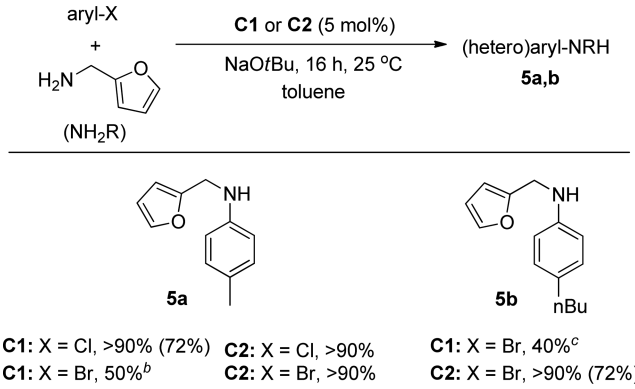
[a]Reactions using morpholine (1.5 equiv), LiO*t*-Bu (1.5 equiv), and 0.5 M in ArCl in CPME. Estimated conversion to product after 16 h (unoptimized) is based on GC data, with isolated yields in parentheses.

employed were based on those described by Buchwald and coworkers[16] in their report pertaining to the use of **C3** in related cross-couplings. Moderate conversion to **4a** (60%) was achieved by use of **C1**; otherwise, **C1** and **C2** proved ineffective in such transformations. Conversely, the use of **C3** enabled high (>90%) conversion to **4a** and **4b** under analogous conditions, in keeping with the literature.[16]

2.4. Aryl (Pseudo)halide Selectivity Involving C1 and C2. In an effort to learn more about the electrophile tolerance and selectivity preferences of **C1** and **C2** beyond the (hetero)aryl chlorides examined thus far, we turned our attention to the room temperature cross-coupling of furfurylamine and aryl bromides (Scheme 7). Whereas high conversion to the target aniline **5a** was achieved when using **C1** or **C2** in

DOI: 10.1021/acs.organomet.6b00650
Organometallics XXXX, XXX, XXX−XXX

Scheme 7. Halide Compatibility in the Arylation of Furfurylamine Using C1 and C2 at Room Temperature[a]

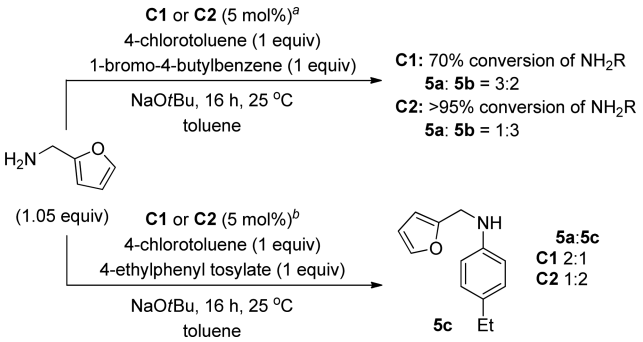


[a]Estimated conversion to product after 16 h (unoptimized) is based on GC data, with isolated yields in parentheses. [b]Significant quantities of starting material remaining. [c]Significant quantities of byproducts detected.

combination with 4-chlorotoluene, comparatively poor catalytic performance was displayed by **C1** in analogous reactions employing 4-bromotoluene. This trend was retained in analogous cross-couplings employing 1-bromo-4-butylbenzene, leading to **5b**. Whereas modest conversion to **5b** (40%) occurred by use of **C1**, clean conversion to **5b** (>90%) was achieved with **C2** under analogous conditions.

The competitive preference of **C1** and **C2** for chloride versus bromide or tosylate electrophiles in room temperature cross-couplings employing limiting furfurylamine was examined subsequently (Scheme 8). In keeping with challenging aryl

Scheme 8. (Pseudo)halide Competition in the Arylation of Furfurylamine Using C1 and C2 at Room Temperature



[a]Estimated conversion to product after 16 h (unoptimized) is based on ^{1}H NMR data. [b]Estimated conversion to products after 16 h (unoptimized) is based on GC data.

bromide reactivity involving **C1**, incomplete conversion of furfurylamine was observed, accompanied by a modest preference for uptake of the aryl chloride. Conversely, complete consumption of the amine occurred when using **C2**, with the aryl bromide being the preferred electrophile. In analogous competitions involving 4-chlorotoluene and 4-ethylphenyl tosylate, modest and inverted electrophile selectivity was exhibited by **C1** and **C2**.

3. CONCLUSIONS

Our comparative catalytic survey of **C1**−**C3** in selected representative nickel-catalyzed C(sp^2)−N cross-coupling reactions establishes the new air-stable precatalyst **C1** as being competitive with, and in some cases complementary to, **C2** in challenging transformations including the room-temperature monoarylation of ammonia and primary alkylamines with (hetero)aryl chlorides. Although **C3** proved ineffective for such transformations, this DPPF-based precatalyst was found to be superior to **C1** and **C2** in combination with the secondary dialkylamine test substrate, morpholine. The comparable reactivity of **C1** and **C2** in the monoarylation of ammonia and primary alkylamines is intriguing in light of the differing electronic characteristics of the ligand sets features in these precatalysts, with **C1** featuring much more electron-rich phosphorus donor groups relative to those in **C2**; the comparatively poor performance of **C3** with such substrates suggests that significant steric demand is a prerequisite for successful ancillary ligands in these difficult cross-coupling applications. Notwithstanding the generally similar reactivity profiles exhibited by **C1** and **C2**, competition experiments revealed a differing preference for ammonia versus methylamine monoarylation, with **C1** favoring ammonia monoarylation. Furthermore, (pseudo)halide comparison studies at room temperature revealed that **C1** is less effective than **C2** in transformations of aryl bromides. In the absence of additional data, we are unable to comment definitively regarding the manner in which the structurally varied ancillary ligand structures featured in **C1**−**C3** give rise to the differences observed herein with regard to substrate compatibility. Nonetheless, in the context of bisphosphine ligation it is evident that **C1**−**C3** represent a complementary and useful set of precatalysts for use in addressing a broad spectrum of NH nucleophiles in nickel-catalyzed C(sp^2)−N cross-coupling chemistry. Given the potentially important role of ancillary ligand design in promoting elementary catalytic steps, as well as in controlling desired oxidation states of derived catalytic intermediates, we are continuing to pursue the development of new and effective bisphosphine ancillary ligand motifs for use in nickel-catalyzed C(sp^2)−N cross-coupling and beyond. We will report on this work in due course.

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, 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 CPME was degassed via three freeze−pump−thaw cycles 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. 4-Ethylphenyl tosylate,[23] **2e**,[15] **C2**,[15] and **C3**[16] were prepared using literature procedures, and **L1** was purchased from Strem Chemicals. 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). Unless stated, ^{1}H NMR (500 and 300 MHz), ^{13}C{^{1}H} NMR (125.8 and 75.5 MHz), and ^{31}P{^{1}H} 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,

DOI: 10.1021/acs.organomet.6b00650
Organometallics XXXX, XXX, XXX−XXX

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 C1. On the basis of a literature protocol,[15] within an inert atmosphere glovebox a vial containing a magnetic stir bar was charged with $NiCl_2$(DME) (0.095 g, 0.43 mmol) and **L1** (0.25 g, 0.41 mmol). To the solid mixture was added THF (2 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 cold pentane (4 °C, 2 mL) thereby generating a precipitate. The solid was isolated via suction filtration, washed with cold pentane (4 °C; 5 × 2 mL), and dried *in vacuo* to afford the presumptive intermediate product (**L1**)$NiCl_2$ as a dark purple solid (0.29 g, 97%) that was used without further purification. Within an inert atmosphere glovebox, the isolated (**L1**)$NiCl_2$ (0.29 g, 0.40 mmol) was transferred to a vial containing a magnetic stir bar, followed by the addition of THF (3 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; 0.48 mL); the mixture was allowed to warm 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 (4 °C; 1 mL) and cold pentane (4 °C; 2 mL) thereby generating a precipitate. The solid was isolated via suction filtration and washed with cold methanol (4 °C; 4 × 1 mL) followed by cold pentane (4 °C; 5 × 2 mL). The resulting material was dried *in vacuo* to afford desired product **C1** as an orange solid (0.25 g, 78%). A single crystal suitable for X-ray diffraction was obtained via vapor diffusion of diethyl ether into a dichloromethane solution of **C1**. The NMR spectra of **C1** exhibit broadened signals at 300 K, potentially arising due to restricted rotation about the Ni−C bond, as observed for **C2**.[15] ^{1}H NMR (300 K, 500 MHz, $CDCl_3$, δ) 6.95 (s, 1H, ArH), 6.84 (s, 1H, ArH), 6.73 (m, 2H, ArH), 4.81 (s, 1H, Cp−P), 4.51 (s, 1H, Cp−P), 4.44 (s, 1H, Cp−P), 4.25 (s, 5H, C_5H_5), 3.23−3.03 (m, 6H, CH_3 and CH), 2.42−0.96 (m, 46H, CH_2 and CH), 0.32−0.30 (m, 1H, CH); ^{13}C{^{1}H} NMR (300 K, 125.8 MHz, $CDCl_3$, δ) 144.6 (br m), 135.7 (br m), 128.0, 123.9, 122.2, 93.7 (br m), 73.0, 70.5 (br m), 69.2, 68.7, 68.4, 38.5 (d, J_{CP} = 15.1 Hz), 34.3 (br m), 32.0 (br m), 31.3, 30.5, 29.9 (m), 28.7−26.0 (overlapping m), 16.1; ^{31}P{^{1}H} NMR (300 K, 202.5 MHz, $CDCl_3$, δ) 47.3 (br m), 7.9 (apparent d, J_{PP} = 34.4 Hz); ^{31}P{^{1}H} NMR (200 K, 121.4 MHz, $CDCl_3$, δ) 46.9 (d, J_{PP} = 34.0 Hz), 7.3 (d, J_{PP} = 34.0 Hz). Anal. Calcd for $C_{43}H_{63}Cl_1Fe_1Ni_1P_2$: C, 65.22; H, 8.02; N, 0. Found: C, 64.84; H, 7.93; N, <0.3.

4.3. General Procedure for the Monoarylation of Ammonia with Aryl Chlorides (GP1). Precatalyst **C1**, **C2**, or **C3** (0.01−0.10 equiv), NaO*t*-Bu (2.0 equiv), aryl chloride (1.0 equiv), and toluene (0.06−0.1 M in aryl chloride) were added to a screw-capped vial containing a magnetic stir bar, followed by the addition of ammonia (0.5 M in 1,4-dioxane, 3.0−7.0 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 cooling to room temperature, reactions were monitored using both TLC and GC methods. The product was isolated or analyzed by using one of the described workup methods A−C.

4.4. General Procedure for the Monoarylation of Primary Amines with Aryl (Pseudo)halides (GP2). Precatalyst **C1**, **C2**, or **C3** (0.01−0.10 equiv), NaO*t*-Bu (2.0 equiv), and aryl (pseudo)halide (1.0 equiv), and toluene (0.12−0.32 M in aryl (pseudo)halide) were added to a screw-capped vial containing a magnetic stir bar, followed by the addition of primary amine (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 cooling to room temperature, reactions were monitored using both TLC and GC methods. The product was isolated or analyzed by using one of the described workup methods A−C.

4.5. General Procedure for the *N*-Arylation of Morpholine with Aryl Chlorides (GP3). Precatalyst **C1**, **C2**, or **C3** (0.05 equiv), LiO*t*-Bu (1.5 equiv), aryl chloride (1.0 equiv), and cyclopentyl methyl ether (0.5 M in aryl chloride) were added to 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 100 °C for 16 h. After cooling to room temperature, reactions were monitored using both TLC and GC methods. The product was isolated or analyzed by using one of the described workup methods A−C.

4.6. Procedure for Aryl (Pseudo)halide Competition Studies (GP4). Precatalyst **C1** or **C2** (0.006 mmol, 0.05 equiv), furfurylamine (46.4 μL, 0.525 mmol, 1.05 equiv), NaO*t*-Bu (96.1 mg, 1.0 mmol, 2.0 equiv), 4-chlorotoluene (59.1 μL, 0.5 mmol, 1.0 equiv), and 1-butyl-4-bromobenzene or 4-ethylphenyl tosylate (0.5 mmol, 1.0 equiv) were added to a screw-capped vial containing a magnetic stir bar, followed by the addition of toluene (4.2 mL). 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 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (ca. 30 mL), washed with brine (3 × ca. 30 mL), and the organic layer dried over sodium sulfate. The resultant mixture was adsorbed onto silica gel to form a dry pack and eluted with hexanes (200 mL) on a silica plug to remove the residual starting materials. The product was then eluted through the dry pack with ethyl acetate (200 mL), the eluent collected, and the solvent removed *in vacuo* via rotary evaporation. Where NMR analysis was employed, ferrocene was subsequently added to the dry reaction mixture as an internal standard (18.6 mg, 0.1 mmol, 0.2 equiv), and the reaction mixture was taken up in $CDCl_3$ (3 mL). A drop of D_2O was added to the sample to eliminate the exchangeable NH proton peak in the spectrum. The resultant solution was subjected to NMR analysis.

4.7. Procedure for the Monitoring of Reaction Progress via NMR Analysis (GP5). Precatalyst **C1** or **C2** (0.006 mmol, 0.01 equiv), 0.5 M ammonia in 1,4-dioxane (3.6 mL, 1.8 mmol, 3.0 equiv), NaO*t*-Bu (115.3 mg, 1.2 mmol, 2.0 equiv), and 1-chloronaphthalene (81.7 μL, 0.6 mmol, 1.0 equiv) were added to a screw-capped vial containing a magnetic stir bar, followed by the addition of toluene (2.4 mL). The procedure was repeated individually eight times, one for each designated time interval. The vials were sealed with caps containing PTFE septa, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to 25 °C. Each reaction vial was removed from the heating block after incremental time intervals of 15 min, diluted with ethyl acetate (ca. 30 mL), washed with brine (3 × ca. 30 mL), and the organic layer dried over sodium sulfate. The solvent was removed *in vacuo* via rotary evaporation and dodecane subsequently added to the dry reaction mixture as an internal standard (13.6 μL, 0.06 mmol, 0.1 equiv), and the reaction mixture was taken up in $CDCl_3$ (3 mL). The resultant solution was subjected to NMR analysis.

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

4.9. Workup Method B (Procedure for the Preparation of Samples for NMR Quantification). Following **GP1** (employing between 0.48 and 0.5 mmol aryl chloride), after cooling to room temperature, the reaction mixture was diluted with ethyl acetate (ca. 30 mL), washed with brine (3 × ca. 30 mL), and the organic layer dried over sodium sulfate. The solvent was removed *in vacuo*, followed by the addition of the internal standard (dodecane or ferrocene, 10−20 mol %) to the vial containing the product mixture. The resultant mixture was taken up in $CDCl_3$ (3 mL) and then subjected to NMR spectroscopic analysis. In select cases where the resultant aniline was volatile and thus subject to evaporation *in vacuo*, the reaction mixture was not dried exhaustively, resulting in residual solvent impurity peaks in the NMR spectra.

DOI: 10.1021/acs.organomet.6b00650
Organometallics XXXX, XXX, XXX−XXX

4.10. Workup Method C (Procedure for the Preparation of Samples for GC Analysis). Following **GP1**, **GP2**, or **GP3** (employing between 0.12 and 0.48 mmol aryl (pseudo)halide), the reaction mixture was diluted using ethyl acetate (1 mL) and in turn passed through a Pasteur pipet filter containing Celite and silica gel. The eluent was collected and subjected to GC analysis with comparison to authentic materials.

4.11. Crystallographic Solution and Refinement Details. Crystallographic data for **C1** were obtained at 193(2) K on a Bruker D8/APEX II CCD diffractometer equipped with a CCD area detector using graphite-monochromated Mo Kα (α = 0.71073 Å) 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 based on the isotropic displacement parameter of the attached atom.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00650.

Complete experimental details, characterization data, and NMR spectra (PDF)

Crystallographic data for **C1** (CCDC 1496592) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mark.stradiotto@dal.ca.

Notes

The authors declare the following competing financial interest(s): Dalhousie University has filed patents on **L2** and **C2** used in this work, from which royalty payments may be derived.

■ ACKNOWLEDGMENTS

We are grateful to the Natural Sciences and Engineering Research Council of Canada (Discovery Grant RGPIN-2014-04807 and I2I Grant I2IPJ/485197-2015) and Dalhousie University for their support of this work. We thank Dr. Michael Lumsden (NMR-3, Dalhousie) for ongoing technical assistance in the acquisition of NMR data and Mr. Xiao Feng (Maritime Mass Spectrometry Laboratories, Dalhousie) for technical assistance in the acquisition of mass spectrometric data.

■ REFERENCES

(1) (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361.

(2) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609−3612.

(3) (a) Lemen, G. S.; Wolfe, J. P. *Top. Organomet. Chem.* **2012**, *46*, 1−54. (b) Stradiotto, M.; Lundgren, R. J. *Ligand Design in Metal Chemistry: Reactivity and Catalysis*; John Wiley & Sons: Hoboken, NJ, 2016.

(4) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374.

(5) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(6) (a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346−1416. (c) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29−39. (d) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299−309.

(7) For a review of nickel-catalyzed C(sp^2)−N cross-coupling chemistry prior to 2016, see Marin, M.; Rama, R. J.; Nicasio, M. C. *Chem. Rec.* **2016**, *16*, 1819−1832.

(8) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058.

(9) For an example in Suzuki−Miyaura chemistry, see Guard, L. M.; Mohadjer Beromi, M.; Brudvig, G. W.; Hazari, N.; Vinyard, D. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 13352−13356.

(10) Ananikov, V. P. *ACS Catal.* **2015**, *5*, 1964−1971.

(11) (a) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Nathel, N. F. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766−1771. (b) Ge, S.; Green, R. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 1617−1627. (c) Green, R. A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 3768−3772.

(12) Yin, G. Y.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc.* **2015**, *137*, 4164−4172.

(13) (a) Hidai, M.; Kashiwagi, T.; Ikeuchi, T.; Uchida, Y. *J. Organomet. Chem.* **1971**, *30*, 279−282. (b) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1981**, *208*, 103−113.

(14) Borzenko, A.; Rotta-Loria, N. L.; MacQueen, P. M.; Lavoie, C. M.; McDonald, R.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 3773−3777.

(15) Lavoie, C. M.; MacQueen, P. M.; Rotta-Loria, N. L.; Sawatzky, R. S.; Borzenko, A.; Chisholm, A. J.; Hargreaves, B. K. V.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *Nat. Commun.* **2016**, *7*, 11073.

(16) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220−223.

(17) For the synthesis and crystallographic characterization of related precatalyst complexes, see Standley, E. A.; Smith, S. J.; Muller, P.; Jamison, T. F. *Organometallics* **2014**, *33*, 2012−2018.

(18) (a) Appl, M. *Ammonia: Principles and Industrial Practice*; Wiley-VCH: Weinheim, 1999. (b) Schranck, J.; Rotzler, J. *Org. Process Res. Dev.* **2015**, *19*, 1936−1943.

(19) Klinkenberg, J. L.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 86−95.

(20) Stradiotto, M. Ancillary ligand design in the development of palladium catalysts for challenging selective monoarylation reactions. In *New Trends in Cross-Coupling: Theory and Application*; Colacot, T. J., Ed.; Royal Society of Chemistry: Cambridge, U.K., 2014; pp 228−253.

(21) Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585−1592.

(22) Kampmann, S. S.; Skelton, B. W.; Wild, D. A.; Koutsantonis, G. A.; Stewart, S. G. *Eur. J. Org. Chem.* **2015**, *2015*, 5995−6004.

(23) (a) Oliverio, M.; Costanzo, P.; Paonessa, R.; Nardi, M.; Procopio, A. *RSC Adv.* **2013**, *3*, 2548−2552. (b) Wilson, D. A.; Wilson, C. J.; Moldoveanu, C.; Resmerita, A. M.; Corcoran, P.; Hoang, L. M.; Rosen, B. M.; Percec, V. *J. Am. Chem. Soc.* **2010**, *132*, 1800−1801.

DOI: 10.1021/acs.organomet.6b00650
Organometallics XXXX, XXX, XXX−XXX