Article

Nickel-Catalyzed N-Arylation of Cyclopropylamine and Related Ammonium Salts with (Hetero)aryl (Pseudo)halides at Room Temperature

Joseph Tassone, Preston M. MacQueen, Christopher M. Lavoie, Michael J Ferguson, Robert McDonald, and Mark Stradiotto

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.7b02014 • Publication Date (Web): 26 Jul 2017

Nickel-Catalyzed *N*-Arylation of Cyclopropylamine and Related Ammonium Salts with (Hetero)aryl (Pseudo)halides at Room Temperature

*Joseph P. Tassone,[1] Preston M. MacQueen,[1] Christopher M. Lavoie,[1] Michael J. Ferguson,[2] Robert McDonald,[2] and Mark Stradiotto[1,]**

[1]Department of Chemistry, Dalhousie University, 6274 Coburg Road, PO Box 15000, Halifax, Nova Scotia, Canada, B3H 4R2

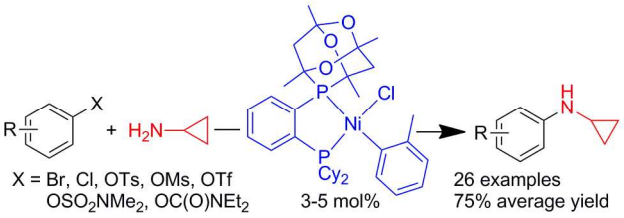
[2]X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2

ABSTRACT. Whereas the metal-catalyzed C(sp^2)-N cross-coupling of cyclopropylamine with aryl electrophiles represents an attractive route to pharmaceutically relevant *N*-arylcyclopropylamines, few catalysts that are capable of effecting such transformations have been identified. Herein, the nickel-catalyzed C(sp^2)-N cross-coupling of cyclopropylamine and related nucleophiles, including ammonium salts, with (hetero)aryl (pseudo)halides is reported for the first time, with the demonstrated scope of reactivity exceeding that displayed by all previously reported catalysts (Pd, Cu, or other). Our preliminary efforts to effect the *N*-arylation of cyclopropylamine with (hetero)aryl chlorides at room temperature by use of (**L**)NiCl(*o*-tolyl) pre-catalysts (**L** = PAd-DalPhos, **C1**; **L** = JosiPhos CyPF-Cy, **C2**) were unsuccessful, despite the established efficacy of **C1** and **C2** in transformations of other primary alkylamines. However, systematic modification of the ancillary ligand (**L**) structure enabled success in such transformations, with crystallographically characterized (**L**)NiCl(*o*-tolyl) pre-catalysts incorporating *o*-phenylene-bridged bisphosphines featuring either phosphatrioxaadamantane and PCy_2 (**L** = **L3**, CyPAd-DalPhos; **C3**), P(*o*-tolyl)$_2$ and P(*t*-Bu)$_2$ (**L** = **L4**; **C4**), or PCy_2 and P(*t*-Bu)$_2$ (**L** = **L5**; **C5**) donor pairings proving to be particularly effective. In employing the air-stable pre-catalyst **C3** in cross-couplings of cyclopropylamine, substituted electrophiles encompassing an unprecedentedly broad range of heteroaryl (pyridine, isoquinoline, quinoline, quinoxaline, pyrimidine, purine, benzothiophene, and benzothiazole) and (pseudo)halide (chloride, bromide, mesylate, tosylate, triflate, sulfamate, and carbamate) structures were employed successfully, in the majority of cases under mild conditions (3 mol% Ni, 25 °C). Preliminary studies also confirmed the ability of **C3** to effect the *N*-arylation of cyclopropanemethylamine hydrochloride and cyclobutylamine hydrochloride under similar conditions. A notable exception in this chemistry was observed specifically in the case of electron-rich aryl chlorides, where the use of

C4 in place of **C3** proved more effective. In keeping with this observation, catalyst inhibition by 4-chloroanisole was observed in the otherwise efficient cross-coupling of cyclopropylamine and 3-chloropyridine when using **C3**. Competition studies involving **C3** revealed a (pseudo)halide reactivity preference (Cl > Br, OTs).

KEYWORDS: nickel, C-N cross-coupling, cyclopropylamine, amination, ligand design

FOR TABLE OF CONTENTS USE ONLY:



1. Introduction

N-Arylcyclopropylamines[1] are an important core structure in several commercially available pharmaceuticals including fluoroquinone antibiotics[2] (e.g. ciprofloxacin) as well as reverse transcriptase inhibitors[3] (e.g. nevirapine), and can serve as effective mechanistic probes in biological[4] and organic[5] reactions. Because cyclopropyl halides are poorly reactive toward nucleophilic substitution by aromatic amines,[6] the development of alternative methods for preparing *N*-arylcyclopropylamines under mild conditions represents an important challenge. The reaction of 1-bromo-1-ethoxycyclopropane or (1-ethoxycyclopropoxy)trimethylsilane with anilines, followed by the reduction of the corresponding hemiaminals,[7] as well as the base-mediated, Smiles rearrangement of 2-aryloxy-*N*-cyclopropylacetamides,[8] each furnish *N*-arylcyclopropylamines, but these approaches employ harsh conditions in two-step procedures. Whereas the application of ubiquitous copper[9] or palladium[10] catalyzed C(sp^2)-N cross-coupling methods employing cyclopropylamine and (hetero)aryl (pseudo)halides as substrates would appear to be well-suited to the assembly of *N*-arylcyclopropylamines, successful examples of such transformations are quite rare (Figure 1). Only a single entry in each of four isolated publications[11] employing copper catalysis with (hetero)aryl bromides and iodides have been disclosed (Figure 1A),[12] and prior to 2016, the scope of such transformations achieved by use of palladium-catalysis was rather limited.[13] Indeed, the first broadly useful palladium-catalyzed *N*-arylation of cyclopropylamine with (hetero)aryl bromides (at room temperature) and chlorides (110 °C) was documented only recently by Colacot and co-workers (Figure 1B).[14]

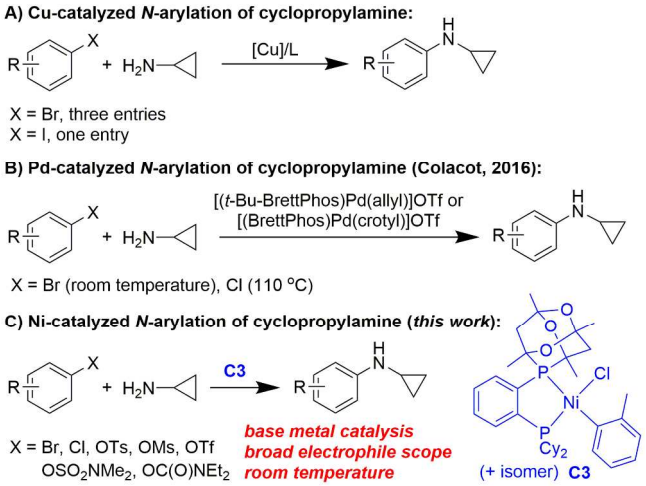
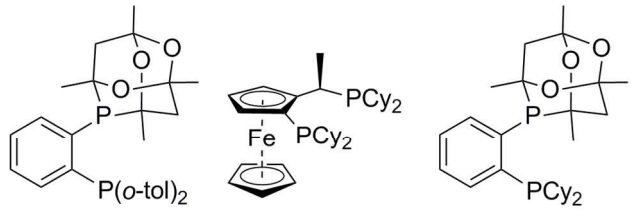


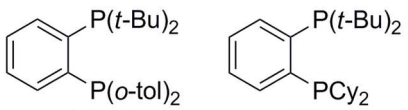
Figure 1. Copper- and palladium-catalyzed *N*-arylation of cyclopropylamine (A and B), as well as the new nickel-catalyzed transformations (C) reported in this work.

Despite the utility of palladium-catalyzed C(sp^2)-N cross-coupling methods, the high cost and low abundance of palladium has prompted the development of related catalytic methodologies employing comparatively inexpensive, Earth-abundant metals.[15] Consequently, nickel-based catalyst systems have emerged as suitable alternatives,[16] exhibiting comparable or superior performance versus palladium-based systems for C(sp^2)-N bond formation, especially in transformations of phenol-derived electrophiles (e.g., sulfonates, sulfamates, and carbamates).[17] However, the growing number of reports of nickel-catalyzed C(sp^2)-N and related cross-couplings has not been met with concomitant effort toward the rational design of ancillary ligands for use specifically with nickel. Indeed, the majority of successful nickel-based catalyst systems for C(sp^2)-N cross-coupling that have been identified to date rely on the 'repurposing' of ligands that were developed and optimized for use with palladium, with little regard to the subtle, yet distinct, characteristics of nickel versus palladium.[18] As part of our effort to address this deficiency, our group recently developed the PAd-DalPhos (**L1**, Chart 1) ancillary ligand for use in nickel-catalyzed C(sp^2)-N bond formation.[19] Whereas electron-rich phosphine ligands are employed almost exclusively in palladium-catalyzed C(sp^2)-N cross-coupling to facilitate

challenging C(sp^2)-X oxidative additions,[10] the sterically demanding design of **L1** was intended primarily to facilitate C(sp^2)-N reductive elimination, given the ease with which nickel can participate in oxidative addition chemistry.[20] Accordingly, the air-stable pre-catalyst (**L1**)NiCl(*o*-tolyl) (**C1**) has been shown to effect the monoarylation of a diverse and challenging set of nitrogen-based nucleophiles, including ammonia, primary alkylamines, anilines, primary amides, and lactams, using (hetero)aryl (pseudo)halides under mild conditions.[19,21]



L1 (PAd-DalPhos) **L2** (CyPF-Cy) **L3** (CyPAd-DalPhos)



L4 **L5**

Chart 1. Ancillary ligands examined in this investigation.

The success of PAd-DalPhos (**L1**) in nickel-catalyzed C(sp^2)-N cross-coupling has prompted us to investigate the application of this and related ancillary ligands in transformations of other challenging amine nucleophiles, with the dual aims of providing useful synthetic advances, and furthering our understanding of the ancillary ligand designs[22] that give rise to superior catalytic performance. Given the lack of effective base metal-catalyzed procedures for the synthesis of *N*-arylcyclopropylamines (*vide supra*), we targeted cyclopropylamine as a candidate for such studies; in particular, we were interested in establishing broadly useful transformations that proceed at room temperature, in light of the low boiling point of cyclopropylamine (49-50 °C).

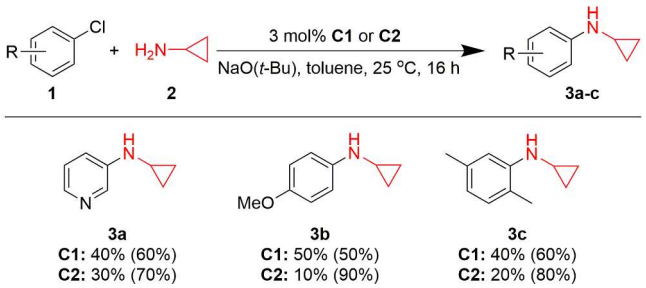
We anticipated two major obstacles that could discourage the successful cross-coupling of cyclopropylamine with (hetero)aryl (pseudo)halides using nickel catalysis. Firstly, the cyclopropylaminyl radical is known to undergo rapid ring opening,[23] which, given the propensity for nickel to engage in radical chemistry,[16b, c] could lead to unwanted side reactions rather than the desired cross-coupled product. Additionally, the nickel-catalyzed ring opening of substituted cyclopropanes is well-documented,[24] further restricting the potential use of cyclopropylamine in this reaction. Notwithstanding such challenges, we anticipated that unwanted reactivity might be circumvented through the application of an appropriately tailored ancillary ligand. Herein, we report the first examples of the nickel-catalyzed *N*-arylation of cyclopropylamine and related nucleophiles including ammonium salts with (hetero)aryl (pseudo)halides, which is enabled by use of the air-stable, nickel pre-catalyst **C3** (Figure 1C) that incorporates the CyPAd-DalPhos ligand (**L3**, Chart 1). Notably, the catalytic performance of **C3** is competitive with the best catalysts known for such transformations, whereby a broad spectrum of substrates is accommodated at room temperature, including the first examples of transformations involving mesylate, tosylate, triflate, sulfamate, and carbamate (hetero)aryl electrophiles.

2. Results and Discussion

2.1. Screening of Pre-Catalysts C1 and C2 in the Nickel-Catalyzed *N*-Arylation of Cyclopropylamine

Pre-catalysts (**L1**)NiCl(*o*-tolyl) (**C1**)[19] and (**L2**)NiCl(*o*-tolyl) (**C2**)[25] were selected for use in a preliminary screen of the nickel-catalyzed *N*-arylation of cyclopropylamine (Scheme 1)[26] employing three challenging (hetero)aryl chlorides, under mild conditions (3 mol% Ni, 25 °C) that had previously proven effective for the cross-coupling of other primary alkylamines (e.g., furfurylamine) with **C1** or **C2**. Notably, in each case only modest conversion to the desired *N*-

(hetero)arylcyclopropylamine (≤ 50% conversion to **3a-c**) was achieved. However, the observation of negligible by-product formation in these test reactions suggested that unwanted side-reactions (e.g., cyclopropane ring-opening, *vide supra*) are not dominant under the reaction conditions employed.



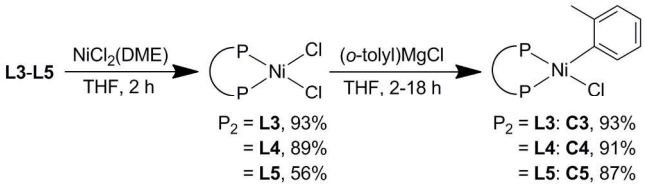
Scheme 1. Pre-catalyst screen of **C1** and **C2** in the nickel-catalyzed *N*-arylation of cyclopropylamine.[a] [a]General conditions: (hetero)aryl chloride (1.0 equiv), cyclopropylamine (1.5 equiv), NaO(*t*-Bu) (1.5 equiv), in toluene. Conversions to product are estimated on the basis of calibrated GC data, reported as % **3a-c** (% **1a-c** remaining).

2.2. Synthesis of Pre-catalysts C3-C5

Encouraged by the clean, though modest, conversion to the desired *N*-(hetero)arylcyclopropylamine (**3a-c**) that was achieved by use of **C1** and **C2** in the nickel-catalyzed *N*-arylation of cyclopropylamine (Scheme 1), we questioned if variants of **C1** and **C2**, incorporating modified ancillary ligands similar to **L1** or **L2**, might promote the desired transformations more effectively. As such, a selection of alternative ancillary ligands featuring pairings of sterically demanding, yet electronically varied, phosphine donor fragments were targeted (**L3**-**L5**, Chart 1). Substitution of the sterically hindered, but relatively electron poor, di-*o*-tolylphosphino donor fragment in **L1** for the similarly bulky, but comparatively more electron-releasing, dicyclohexylphosphino group gives rise to CyPAd-DalPhos (**L3**).[19] Alternatively, replacement of the phosphatrioxaadamantane moiety in **L1** with the more electron-rich and sterically similar[27] di-*tert*-butylphosphino group affords **L4**.[19] Finally, exchange of the phosphatrioxaadamantane cage in **L3** for a di-*tert*-butylphosphino group results in **L5**, whereby

both phosphine donors are bulky and strongly electron-releasing, similar to **L2**. While **L3** and **L4** had previously been synthesized,[19] **L5** had not been prepared prior to this work. Ligand **L5** was prepared via lithiation of (2-bromophenyl)di-*tert*-butylphosphine[28] followed by quenching with $ClPCy_2$. Notably, whereas **L3** and **L4** are air-stable in the solid state, **L5** was found to be air-sensitive, requiring handling under inert atmosphere.

Given the established efficacy of nickel pre-catalysts of the form $L_nNiCl(aryl)$ in cross-coupling applications,[26] including C(sp^2)-N bond formation, we wished to develop (**L**)NiCl(*o*-tolyl) pre-catalysts incorporating **L3**-**L5** in order to assess their catalytic competency in the *N*-arylation of cyclopropylamine. The desired complexes (**L3**)NiCl(*o*-tolyl) (**C3**), (**L4**)NiCl(*o*-tolyl) (**C4**), and (**L5**)NiCl(*o*-tolyl) (**C5**) were prepared in a two-step procedure adapted from the literature (Scheme 2).[19] Combination of each of **L3**-**L5** with $NiCl_2$(DME) (DME = 1,2-dimethoxyethane) in THF afforded the corresponding (**L**)$NiCl_2$ species, the identities of which were confirmed via spectroscopic and microanalytical analysis. Subsequent treatment with *o*-tolylmagnesium chloride in THF afforded after workup **C3**-**C5** as air-stable solids that were structurally characterized, including by use of single-crystal X-ray techniques (Figure 2). In all cases a distorted square planar geometry is observed ($\sum\angle \approx 360°$), and the Ni-P distance *trans* to the aryl group is longer than the analogous distance *trans* to chloride.



Scheme 2. Synthesis of pre-catalysts **C3**-**C5**.

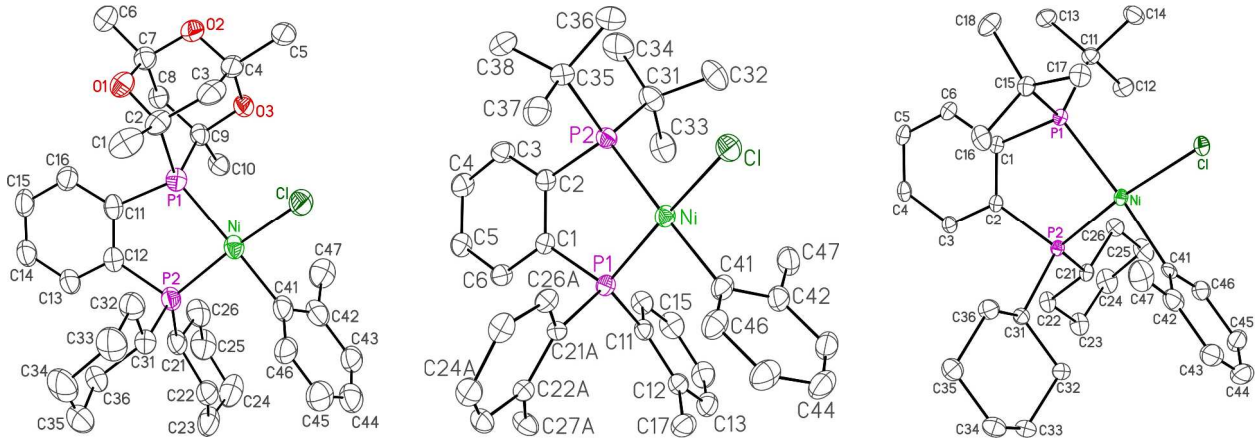


Figure 2. Single-crystal X-ray structures of **C3** (left), **C4** (middle), and **C5** (right), represented with thermal ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected interatomic distances (Å): for **C3** Ni-P1 2.2504(12), Ni-P2 2.1575(11), Ni-Cl 2.2019(11), Ni-C(41) 1.953(4); for **C4** Ni-P1 2.1380(5), Ni-P2 2.2789(5), Ni-Cl 2.2056(6), Ni-C(41) 1.941(2); for **C5** Ni-P1 2.2603(5), Ni-P2 2.1452(5), Ni-Cl 2.2142(5), Ni-C(41) 1.9759(17).

The behavior of **C3** and **C4** in solution was more complex than initially anticipated, and warrants further discussion (Figure 3). The solution $^{31}P\{^{1}H\}$ NMR spectrum of bulk (as-prepared, amorphous) **C3** exhibits four pairs of doublets (Figure 3A), corresponding to four distinct species (**C3A**-**C3D**), as confirmed on the basis of ^{31}P-^{31}P COSY data (see Figure S12 in the Supporting Information). Conversely, the solution $^{31}P\{^{1}H\}$ NMR spectrum of crystalline **C3** (Figure 3B) features only two pairs of doublets (~3:1 ratio) – a pattern that is similar to that of **C1**.[19] Given that the crystal structure of **C3** features the nickel-bound *o*-tolyl fragment *trans* to the chiral (racemic) phosphatrioxaadamantane cage (Figure 2), we ascribe the two pairs of doublets observed in Figure 3B as arising from the presence of two Ni-C(aryl) rotational isomers (**C3A** and **C3B**) that differ on the basis of the relative orientation of the methyl group of the nickel-bound *o*-tolyl fragment above or below the square plane of the molecule. The emergence over time of the remaining two sets of doublets (**C3C** and **C3D**) in the solution $^{31}P\{^{1}H\}$ NMR

spectrum of dissolved crystalline **C3** (see Figure S13 in the Supporting Information) suggests that **C3C** and **C3D** are structurally related to **C3A** and **C3B**. On the basis of these collective observations, the proposed identities of **C3A**-**D** are depicted in Figure 3: **C3A** and **C3B** are complexes in which the nickel-bound *o*-tolyl group is *trans* to the phosphatrioxaadamantane cage, while **C3C** and **C3D** are isomeric complexes in which the nickel-bound *o*-tolyl group is *trans* to the PCy_2 moiety. The chiral (racemic) nature of the phosphatrioxaadamantane cage, when paired with the relative orientation of the methyl group of the nickel-bound *o*-tolyl fragment above or below the square plane, arising from hindered Ni-C(aryl) rotation, affords four diastereomers in keeping with the solution $^{31}P\{^1H\}$ NMR spectrum of bulk **C3** (Figure 3A). Variable-temperature solution NMR experiments suggest that **C3A**/**B** to **C3C**/**D** isomerization is slow on the NMR timescale, with only slight changes in the relative $^{31}P\{^1H\}$ NMR peak intensities of **C3A**-**D** observed at elevated temperatures (see Figure S14 in the Supporting Information). This notion is further supported by $^{31}P\{^1H\}$ NMR saturation transfer experiments, in which chemical exchange was not observed between **C3A**/**B** and **C3C**/**D** at room temperature (see Figure S15 in the Supporting Information). Though we did not conduct experiments to determine the mechanism for this isomerization process, the interconversion of **C3A**/**B** to **C3C**/**D** might occur through tetrahedral intermediates, or through dissociation of one phosphine donor atom of **L3** followed by rearrangement and subsequent re-chelation. Notably, only two diastereomers likely arising from rotamers of the nickel-bound *o*-tolyl group are observed in solution for **C1**.[19] At first glance, it is tempting to rationalize the differing ancillary ligand binding selectivity within each of **C1** and **C3** as being attributable to the more closely matched *trans*-directing ability of the dialkylphosphino donor fragments in **C3** (leading to poor selectivity), versus the phosphatrioxaadamantane (superior) and P(*o*-tolyl)$_2$ (inferior) pairing in

C1. However, the somewhat complex solution NMR behavior of **C4** (*vide infra*), featuring P(*o*-tolyl)$_2$ and P(*t*-Bu)$_2$ donors in analogy to **C1**, when contrasted with the observation of a *single* diastereomer in solution for **C5** which features two dialkylphosphino donors similar to **C3**, suggests that the observed equilibrium distribution of isomers in pre-catalysts of this type may result from a complex interplay of factors.

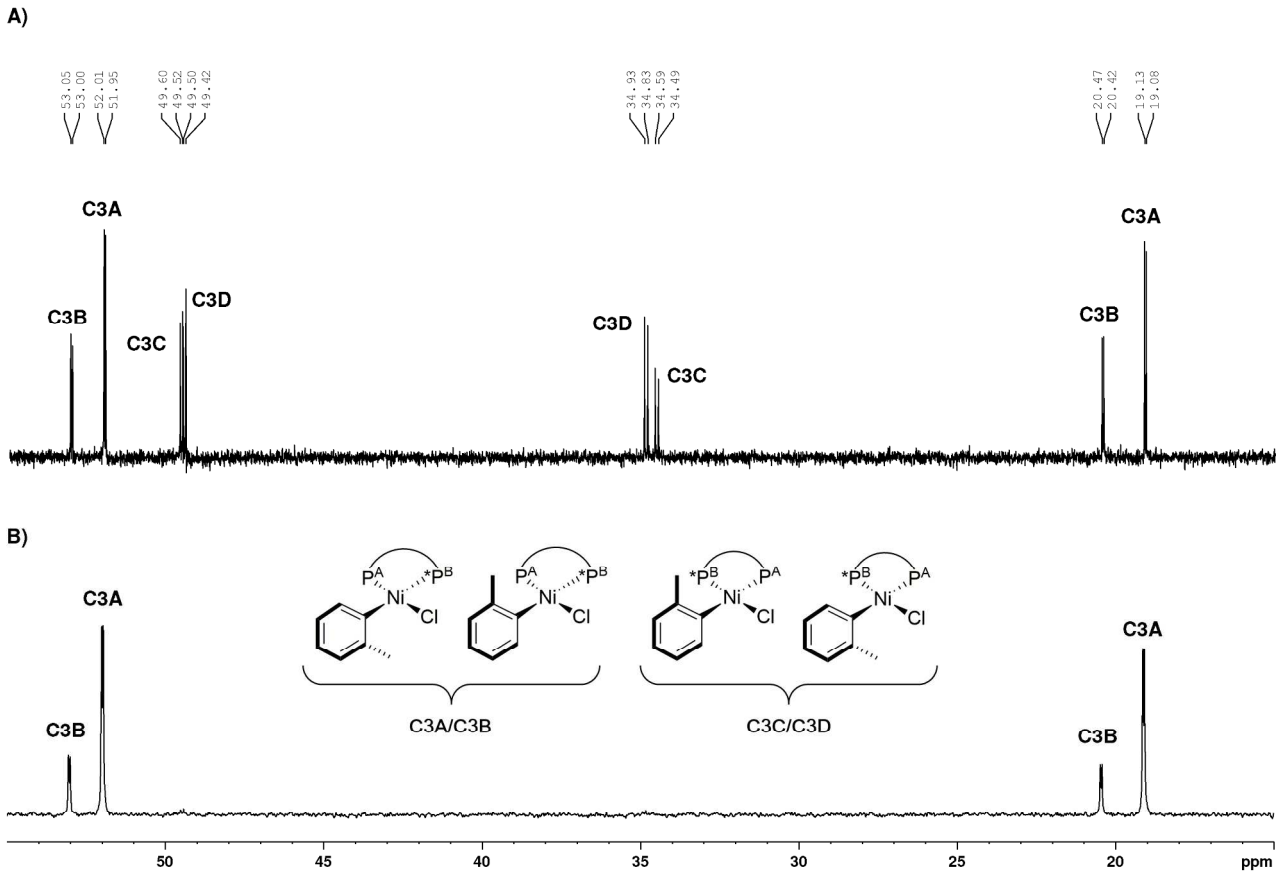


Figure 3. $^{31}P\{^1H\}$ NMR spectrum ($CDCl_3$) of A) bulk and B) recrystallized **C3**, with the proposed four diastereomers **C3A-D** depicted (P^A = PCy_2; $*P^B$ = chiral phosphatrioxaadamantane cage).

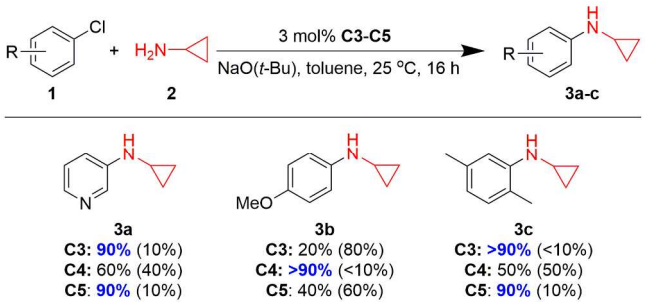
The solution $^{31}P\{^1H\}$ NMR spectrum of **C4** (see Figure S21 in the Supporting Information) exhibits four distinct resonances that exhibit varying degrees of line-broadening. Compound **C4** is distinct from **C3** in that the orientation of the methyl group of the nickel-bound *o*-tolyl fragment above or below the square plane is rendered enantiotopic (rather than

diastereotopic, as in **C3**) in the absence of a secondary chiral element. Variable-temperature solution $^{31}P\{^{1}H\}$ NMR studies of **C4** revealed coalescence to two broad signals at elevated temperatures (see Figure S22 in the Supporting Information). On this basis, we tentatively assign the four $^{31}P\{^{1}H\}$ NMR resonances observed for **C4** as corresponding to two geometric isomers in which the nickel-bound *o*-tolyl group is *trans* to either the P(*o*-tolyl)$_2$ or P(*t*-Bu)$_2$ fragment. However, isomerism arising from hindered rotation involving the P(*o*-tolyl)$_2$ and Ni(*o*-tolyl) moieties, in addition to possible equilibria involving tetrahedral and square planar species,[29] is also likely contributing to the observed line broadening behavior. In keeping with such a scenario, the solution ^{1}H NMR spectrum of (**L4**)$NiCl_2$ is consistent with a C_1-symmetric structure arising from hindered rotation phenomena, whereas a C_S-symmetric structure is evident for (**L5**)$NiCl_2$.

2.3. Screening of Pre-Catalysts C3-C5 in the Nickel-Catalyzed *N*-Arylation of Cyclopropylamine

With the desired new pre-catalysts in hand, we set out to screen **C3**-**C5** for activity in the nickel-catalyzed C(sp^2)-N cross-coupling of cyclopropylamine (3 mol% Ni, 25 °C; Scheme 3), employing the same three challenging (hetero)aryl chlorides for which **C1** and **C2** had performed poorly (Scheme 1). Gratifyingly, both **C3** and **C5** demonstrated excellent performance in two of these test transformations, with almost quantitative conversion being observed when utilizing the heteroaryl or *ortho*-substituted aryl chloride **1a** or **1c** (leading to **3a** and **3c**, respectively). While **C4** performed comparatively poorly in transformations of **1a** or **1c**, this pre-catalyst proved superior to **C3** or **C5** in the test transformation of electron-rich 4-chloroanisole (**1b**) leading to **3b**. Substituting weaker bases such as Cs_2CO_3 or K_3PO_4 for NaO(*t*-Bu) resulted in minimal conversion to the desired product (<5% conversion to **3a** when using **C3**). Furthermore, reducing

the catalyst loading of **C3** below 3 mol% resulted in poorer conversions (e.g., 65% conversion to **3a** at 1 mol% catalyst loading). Given the similar reactivity profile of **C3** and **C5**, we opted to carry forward with **C3** (and where appropriate, **C4**) in subsequent catalytic applications on the basis of the practical consideration that **L3** (unlike **L5**) is not air-sensitive.



Scheme 3. Pre-catalyst screen of **C3**-**C5** in the nickel-catalyzed *N*-arylation of cyclopropylamine.[a] [a]General conditions: (hetero)aryl chloride (1.0 equiv), cyclopropylamine (1.5 equiv), NaO(*t*-Bu) (1.5 equiv), in toluene. Conversions to product are estimated on the basis of calibrated GC data, reported as % **3a-c** (% **1a-c** remaining).

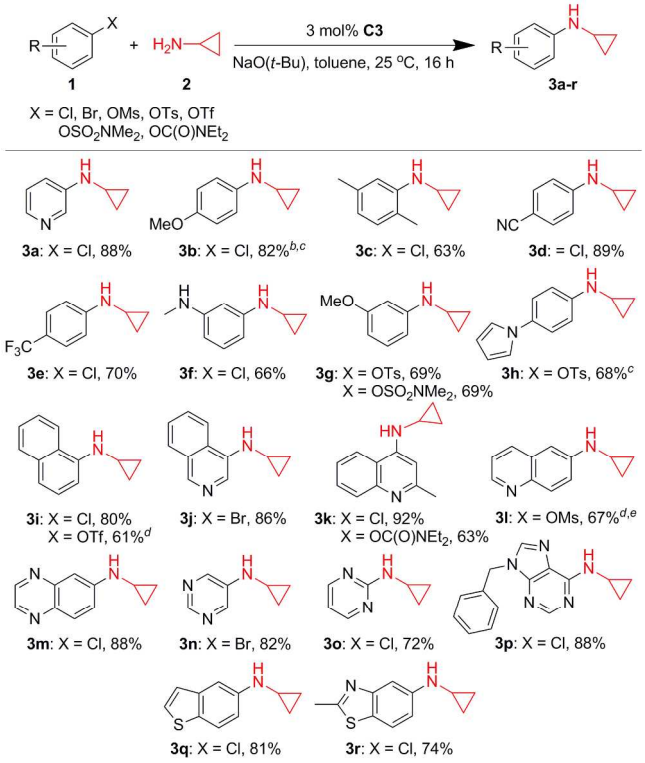
From an ancillary ligand design perspective,[22] the similar performance of **C3** and **C5** in the successful formation of **3a** and **3c** indicates that the phosphatrioxaadamantane and P(*t*-Bu)$_2$ groups are interchangeable in terms of engendering desirable nickel catalysis in these particular transformations. Knowing that the phosphatrioxaadamantane cage is a poorer electron-donor versus P(*t*-Bu)$_2$, but that the two fragments possess a similar steric profile,[27] suggests that the selection of appropriate ancillary ligand sterics, rather than electronics, is a key design consideration in this particular reaction setting. However, such simple conclusions do not translate to the transformation leading to **3b**, whereby poor conversion to product was noted with the PAd-DalPhos (**L1**)-derived pre-catalyst **C1** featuring phosphatrioxaadamantane and P(*o*-tolyl)$_2$ ancillary ligand donor pairings, yet excellent conversion was achieved with the analogous pre-catalyst **C4**, which features P(*t*-Bu)$_2$ in place of the phosphatrioxaadamantane moiety. It is plausible that the successful formation of **3b** by use of **C4** may arise in part from the more

electron-rich nature of **L4** versus **L1**, resulting in more facile C(sp^2)-Cl activation of the electronically deactivated 4-chloroanisole substrate. However, the poor performance of **C2** or **C5** in the formation of **3b**, each featuring strongly electron-releasing phosphine donor fragments, supports the notion that a subtle balance of ancillary ligand steric and electronic properties must be achieved in order to engender desirable performance in nickel-catalyzed C(sp^2)-N cross-coupling of particular nucleophile and electrophile pairings. Indeed, while **L1** and **L2** proved inferior to **L3** and **L4** in the nickel-catalyzed *N*-arylation of cyclopropylamine under examination herein, the inverse trend has been observed for the monoarylation of ammonia.[19, 25a] It must also be recognized that in contrast to the Pd(0)/Pd(II) cycle traversed in palladium-catalyzed C(sp^2)-N cross-coupling, the mechanistic scenario is likely more complex for nickel, whereby the ancillary ligand and substrates employed influence partitioning between Ni(0)/Ni(II) and Ni(I)/Ni(III) reaction manifolds of differing productivity.[30]

2.4. Scope of the Nickel-Catalyzed *N*-Arylation of Cyclopropylamine

We then surveyed the electrophile scope in the C(sp^2)-N cross-coupling of cyclopropylamine using **C3** (Scheme 4). A variety of (hetero)aryl (pseudo)halide coupling partners were successfully employed in this reaction, including those with electron-withdrawing (**3d**-**g**) or *ortho*-substituents (**3c**, **3i**-**k**). Heterocyclic electrophiles were also well-tolerated, including those featuring pyridine (**3a**), isoquinoline (**3j**), quinaldine (**3k**), quinoline (**3l**), quinoxaline (**3m**), pyrimidine (**3n**-**o**), purine (**3p**), benzothiophene (**3q**), or benzothiazole (**3r**) frameworks. In conducting such transformations on an 8.5 mmol scale in (hetero)aryl chloride by use of **C3** (3 mol%), each of **3a** (1.004 g, 88%) and **3d** (1.223 g, 91%) were obtained in excellent yield. However, aryl electrophiles containing carbonyl moieties (e.g., ketone or ester) proved to be ineffective coupling partners. The use of **C3** enabled the *N*-arylation of cyclopropylamine

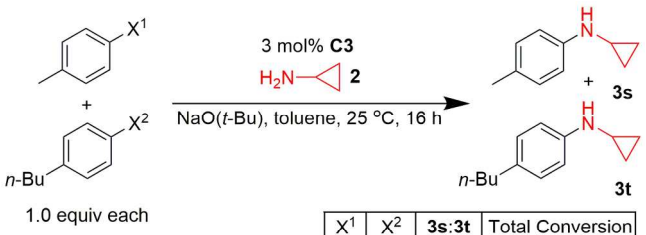
using (hetero)aryl chlorides, bromides, and phenol-derived electrophiles (tosylate, sulfamate, and carbamate) at room temperature (3 mol% **C3**), as well as aryl triflate and aryl mesylate coupling partners, albeit at higher catalyst loadings (5 mol% **C3**) and elevated temperatures (110 °C). Use of **C4** in place of **C3** allowed the coupling of an electron-rich aryl chloride (**3b**) and aryl tosylate (**3h**) at room temperature. Control experiments performed in the absence of nickel showed no conversion to **3d** or **3i**, and only 10% conversion to **3p** (as determined on the basis of GC analysis), highlighting the essential nature of the pre-catalyst in promoting this transformation. Notably, the transformations depicted in Scheme 4 represent the first examples of room temperature C(sp^2)-N cross-couplings of cyclopropylamine employing (hetero)aryl chlorides, as well as the first examples of such cross-couplings involving phenol-derived electrophiles under any conditions. Collectively, the scope of reactivity demonstrated herein can be viewed as exceeding that displayed by all previously reported catalysts (Pd, Cu, or other) for the *N*-arylation of cyclopropylamine.



Scheme 4. Scope of the nickel-catalyzed *N*-arylation of cyclopropylamine.[a] [a]General conditions: (hetero)aryl (pseudo)halide (1.0 equiv), cyclopropylamine (1.5 equiv), NaO(*t*-Bu) (1.5 equiv), in toluene. Isolated yields reported. [b]Isolated as the corresponding *N*-acyl derivative. [c]Conducted using 3 mol% **C4**. [d]Conducted using 5 mol% **C3** and K_3PO_4 (3.0 equiv) at 110 °C. [e]1,4-dioxane used as solvent.

Given that a variety of (hetero)aryl electrophiles proved to be viable coupling partners when using **C3**, we conducted a brief (pseudo)halide competition study with limiting cyclopropylamine to assess the relative preference of this pre-catalyst (Scheme 5). The aryl components of the electrophiles employed in our competition study were purposefully chosen to be sterically and electronically similar in order to minimize any reactivity bias, while still enabling rational analysis of the product mixtures. When an aryl chloride and bromide were used as competing cross-coupling partners, a modest preference for the aryl chloride was observed, with an overall 80% combined conversion to both products (**3s** and **3t**). In the case of the aryl chloride or bromide versus the aryl tosylate, a sizeable preference for the aryl halide was

observed. However, the total conversion to **3s** and **3t** under these conditions was significantly lower (< 50%), suggesting a potential inhibitory effect when the aryl tosylate engages with **C3**. Pre-catalyst **C2** displayed a similar intolerance to certain aryl electrophiles in the cross-coupling primary alkylamines.[25a]

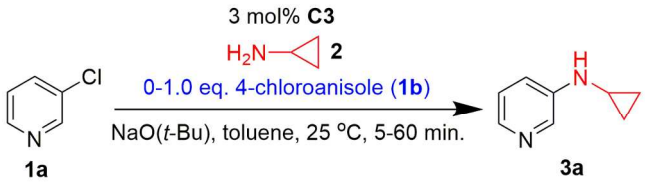


X^1	X^2	**3s**:**3t**	Total Conversion
Cl	Br	2:1	80%
Cl	OTs	4:1	45%
Br	OTs	5:1	25%

Scheme 5. (Pseudo)halide competition study employing **C3**.[a] [a]General conditions: cyclopropylamine (1.5 equiv), NaO(*t*-Bu) (1.5 equiv), in toluene. Reported product distributions and total conversions to **3s** and **3t** were estimated on the basis of calibrated GC data.

In our initial set of screening reactions using **C3** as a pre-catalyst for the room temperature cross-coupling of cyclopropylamine, the amination of 3-chloropyridine (**1a**) proceeded in high conversion to afford **3a** (Scheme 3). Conversely, the analogous cross-coupling using 4-chloroanisole (**1b**) afforded only modest amounts of the target *N*-arylcyclopropylamine (**3b**) along with significant quantities (~80%) of unreacted **1b**. It is plausible that the poor performance of **1b** can be attributed to the inability of catalytic species derived from **C3** to engage in oxidative addition to the rather electron-rich and thus deactivated **1b**, and/or to subsequent catalyst inhibition pathways (e.g., slow transmetallation or reductive elimination; deleterious redox chemistry). In a preliminary examination of such phenomena, the otherwise successful cross-coupling of cyclopropylamine and **1a** to give **3a** by using **C3** was monitored over time in the presence of varying amounts of added **1b** (Scheme 6 and Figure S1 in the Supporting Information). Evaluation of the conversion to **3a** after 40 minutes reaction time

revealed that increasing the concentration of **1b** diminished the ability of **C3** to effect the otherwise facile conversion of **1a** to **3a**, and throughout, negligible amounts of **3b** were detected by use of GC methods. These preliminary observations suggest that **1b** engages with catalytic species derived from **C3** in such a way as to lead to suppression of catalytic activity.



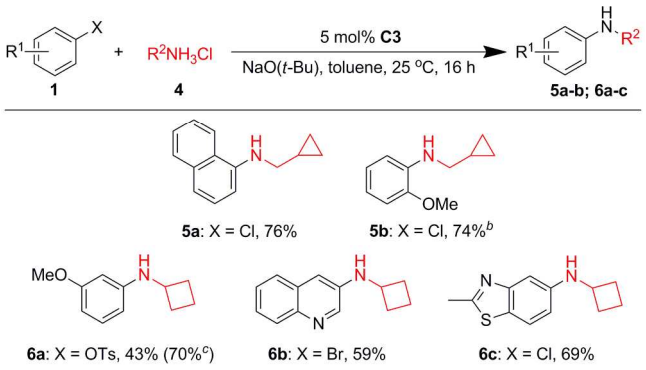
eq. **1b**	Conversion to **3a**[b]
0	85%
0.1	65%
1	50%

Scheme 6. Reaction monitoring of the formation of **3a** using **C3** with varying amounts of **1b**.[a] [a]General conditions: **1a** (1.0 equiv) cyclopropylamine (1.5 equiv), NaO(*t*-Bu) (1.5 equiv), in toluene. Conversion to **3a** determined on the basis of calibrated GC data. [b]After 40 minutes reaction time.

2.5. Nickel-Catalyzed *N*-Arylation of Cyclic Alkyl Ammonium Salts

The utility of **C3** in the nickel-catalyzed *N*-arylation of cyclopropylamine prompted us to explore its application in reactions involving other small, cyclic alkylamines. Like cyclopropylamine, both cyclopropanemethylamine and cyclobutylamine have only seldom been utilized in palladium- and copper-catalyzed C(sp^2)-N bond-forming processes,[31] and analogous nickel-catalyzed transformations were unknown prior to our work herein. Given that both amines are sensitive to air and moisture, we opted to employ the more conveniently handled and commercially available hydrochloride salts of these substrates in our catalytic survey. Notably, the use of alkyl ammonium salts in C(sp^2)-N cross-coupling chemistry is restricted to three reports concerning transformations of methylamine or ethylamine hydrochloride exclusively, employing palladium[32] or nickel[19, 33] catalysis.

Adapting the conditions employed for the *N*-arylation of cyclopropylamine (Scheme 4), we assessed the performance of **C3** in the *N*-arylation of cyclopropanemethylamine hydrochloride and cyclobutylamine hydrochloride with some representative (hetero)aryl (pseudo)halides (Scheme 7). Desired amination products derived from electrophiles featuring *ortho*-substituents (**5a**, as well as **5b** using **C4**), an electron-withdrawing group (**6a**), or heterocyclic frameworks (**6b** and **6c**) were obtained successfully in this reaction, spanning (hetero)aryl chloride, bromide, and tosylate coupling partners. Notably, these transformations represent the first examples of the metal-catalyzed C(sp^2)-N cross-coupling of alkyl ammonium salts at room temperature.



Scheme 7. The nickel-catalyzed *N*-arylation of cyclopropanemethylamine hydrochloride and cyclobutylamine hydrochloride.[a] [a]General conditions: (hetero)aryl (pseudo)halide (1.0 equiv), amine hydrochloride (1.1 equiv), NaO(*t*-Bu) (2.5 equiv), in toluene. Isolated yields reported. [b]Conducted using 5 mol% **C4**. [c]Yield estimated on the basis of calibrated GC data.

3. Conclusion

In summary, we have developed the first nickel-catalyzed C(sp^2)-N cross-couplings of cyclopropylamine, cyclopropanemethylamine hydrochloride, and cyclobutylamine hydrochloride, with an unprecedented scope of (hetero)aryl (pseudo)halides. Subtle electronic modifications in the ancillary ligand framework were shown to be crucial for obtaining a highly effective pre-catalyst for such challenging transformations. In this regard, the reported protocol makes use of the new, air-stable CyPAd-DalPhos pre-catalyst **C3**, in the majority of cases under

mild conditions (3 mol% Ni, 25 °C), with the demonstrated electrophile scope spanning a diverse range of heteroaryl (pyridine, isoquinoline, quinoline, quinoxaline, pyrimidine, purine, benzothiophene, and benzothiazole) and (pseudo)halide (chloride, bromide, mesylate, tosylate, triflate, sulfamate, and carbamate) motifs. Whereas **C3** was found to be less effective in combination with electron-rich aryl chlorides, pre-catalyst **C4**, featuring P(*o*-tolyl)$_2$ and P(*t*-Bu)$_2$ donor pairings, proved to be useful in promoting cross-couplings of these particular substrates. This reactivity trend was found to be consistent with our observation of catalyst inhibition in the otherwise efficient cross-coupling of cyclopropylamine and 3-chloropyridine using **C3**, upon addition of 4-chloroanisole. Competition studies involving **C3** revealed a (pseudo)halide reactivity preference (Cl > Br, OTs). Overall, this report highlights the utility of rationally optimized ancillary ligand design for application in nickel-catalyzed C(sp^2)-N bond formation, as a means of establishing new and synthetically useful base metal-catalyzed amination reactions. Our efforts to apply these and other ancillary ligand design strategies in the development of new nickel-catalyzed transformations will be the focus of future reports.

4. Experimental Section

General Considerations. Unless otherwise indicated, all experimental procedures were conducted in a nitrogen-filled, inert atmosphere glovebox using oven-dried glassware, with work-up procedures carried out on the benchtop in air. Toluene, and pentane used in the synthesis of **L5**, were purged with nitrogen, passed through a double column purification system containing alumina and copper-Q5 reactant, and stored over 4Å molecular sieves in bulbs with Teflon taps prior to use. Diethyl ether, tetrahydrofuran (THF), and 1,4-dioxane were dried over Na/benzophenone, distilled under a nitrogen atmosphere, and stored in bulbs with Teflon taps over 4Å molecular sieves. Dichloromethane (DCM) used in the synthesis of **L5** was purged with

nitrogen, and stored over 4Å molecular sieves in a bulb with a Teflon tap. $C_2D_2Cl_4$ was freeze-pump-thaw degassed three times and stored over 4Å molecular sieves in a bulb with a Teflon tap in the glovebox. K_3PO_4 was dried under vacuum at 180 °C for 24 h, and stored under nitrogen in the glovebox prior to use. (2-bromophenyl)di-*tert*-butylphosphine,[28] **L3**,[19] **L4**,[19] **C1**,[19] **C2**,[25a] 3-methoxyphenyl 4-methylbenzenesulfonate,[34] quinolin-6-yl methanesulfonate,[34] naphthalene-1-yl trifluoromethanesulfonate,[35] 3-methoxyphenyl dimethylsulfamate,[36] 2-methylquinolin-4-yl diethylcarbamate,[25b] and 9-benzyl-6-chloropurine[37] were prepared according to established literature procedures. Otherwise, all other solvents, reagents, and materials were used as received from commercial sources. For **General Procedures A and B**, automated flash chromatography was carried out on a Biotage Isolera One automated flash purification system using 10 g Biotage SNAP KP-SIL (particle size 30-90 μm) or 12 g Silicycle Silia*Sep* (particle size 40–63 μm, 230–400 mesh) silica flash cartridges with a typical gradient of 2-4-2 column volumes and a flow rate of 10 mL/min. For **General Procedure C**, flash chromatography was carried out on silica gel using Silicycle Silia*Flash* 60 silica (particle size 40–63 μm; 230–400 mesh). Unless otherwise indicated, NMR spectra were recorded on a Bruker AV 300 MHz or Bruker AV 500 MHz spectrometer at 300 K, with chemical shifts (in ppm) referenced to residual protio solvent peaks (^1H), deuterated solvent peaks ($^{13}C\{^1H\}$), or external 85% H_3PO_4 ($^{31}P\{^1H\}$). Splitting patterns are indicated as follows: br, broad; app, apparent; s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; dd, doublet of doublets; td, triplet of doublets; m, multiplet, with all coupling constants (*J*) reported in Hertz (Hz). In some cases, fewer than expected carbon resonances were observed despite prolonged acquisition times. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Mass spectra were obtained using ion trap electrospray ionization (ESI) instruments operating in positive mode. Gas chromatography

(GC) data were obtained on an instrument equipped with a SGE BP-5 column (30 m, 0.25 mm i.d.).

Synthesis of di-*tert*-butyl(2-(dicyclohexyl)phosphino)phenyl)phosphine (L5). *All manipulations, including work-up, were performed in an inert atmosphere glovebox*. A glass vial was charged with (2-bromophenyl)di-*tert*-butylphosphine (0.138 g, 0.458 mmol), Et_2O (2 mL), and a magnetic stir bar, and the vial was placed in a –33 °C freezer for 20 min. After this time, the vial was removed from the freezer, magnetic stirring was initiated, and *n*-BuLi (275 μL of a 2.5 M solution in hexanes, 0.687 mmol) was added dropwise to the cooled, stirring solution, yielding a clear yellow solution. The solution was then allowed to stir at room temperature for 30 min., after which time a cold (–33 °C) solution of $ClPCy_2$ (106 μL, 0.481 mmol) in Et_2O (1 mL) was added dropwise to the stirring solution, yielding a cloudy yellow mixture upon complete addition. The mixture was allowed to stir at room temperature for 18 h (unoptimized), after which time DCM (3 mL) was added, and the mixture was filtered through a Celite/silica plug (~1:1), eluting with DCM (2 x 1 mL). The volatiles were removed from the clear, yellow filtrate under reduced pressure yielding a yellow-orange oil, which solidified under vacuum after several hours. The solid residue was then washed with cold (–33 °C) pentane (3 x 1 mL), and was dried under reduced pressure to afford **L5**. Yield: 26.2 mg (14%). Additional **L5** could be isolated by removing the volatiles from the retained pentane washings, washing the resulting yellow solid with cold (–33 °C) pentane (2 x 1 mL), and drying under reduced pressure. Yield: 33.5 mg (17%). Combined Yield: 59.7 (31%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.82-7.81 (m, 1H), 7.54 (br d, J = 5.8 Hz, 1H), 7.33-7.28 (m, 2H), 1.94-1.05 (m, 40H, overlapping Cy and *t*-Bu resonances, with the latter at 1.21, d, J_{PH} = 11.4 Hz). $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 146.3-145.6 (overlapping m), 135.7, 133.1 (d, J_{PC} = 6.9 Hz), 127.8,

126.7, 35.9 (dd, J_{PC} = 17.1, 5.0 Hz), 33.6 (dd, J_{PC} = 26.6, 4.1), 31.1 (d, J_{PC} = 14.7), 30.8 (d, J_{PC} = 16.2 Hz), 29.7 (d, J_{PC} = 9.4 Hz), 27.6-27.5 (overlapping d), 26.6. $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 17.9 (d, J_{PP} = 156.0 Hz), -9.9 (d, J_{PP} = 156.0 Hz). HRMS-ESI (*m/z*): Calc'd for $C_{26}H_{45}P_2$ $[M+H]^+$: 419.2996. Found: 419.2991.

Synthesis of (L3)NiCl$_2$. A glass vial was charged with $NiCl_2$(DME) (85.7 mg, 0.390 mmol), **L3** (200.0 mg, 0.409 mmol), THF (2 mL), and a magnetic stir bar. Stirring was initiated, affording initially a clear, dark orange solution. A red-brown precipitate formed after several minutes. The resulting mixture was stirred at room temperature for 2 hours, after which time the solid was collected on a glass filter frit in air and washed with cold (~0 °C) pentane (2 x 2 mL). The remaining solid was then dissolved off the frit using DCM (10 mL), and the clear, dark red solution thus formed was collected. The volatiles were removed from the collected eluent solution under reduced pressure, yielding the target complex as a dark red-brown solid. Yield: 0.224 g (93%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.32 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.68-7.62 (m, 2H), 4.02 (d, *J* = 13.5 Hz, 1H), 2.74-2.65 (m, 3H), 2.53 (d, *J* = 13.4 Hz, 1H), 2.31 (d, *J* = 14.0 Hz, 1H), 2.00-1.93 (m, 1H), 1.87-1.11 (overlapping m, 31H). $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 141.2, 139.0, 134.9, 132.4 (two signals), 131.8, 97.1 (d, J_{PC} = 64.7 Hz), 74.7, 53.6, 41.1, 40.2, 38.5, 37.3, 29.9 (d, J_{PC} = 13.6 Hz), 29.5, 28.9 (d, J_{PC} = 7.9 Hz), 27.6, 27.3-27.1 (m, overlapping signals), 26.8, 26.4, 25.8 (d, J_{PC} = 6.1 Hz). $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 75.8 (br s), 46.4 (br s). Anal. Calc'd. for $C_{28}H_{42}Cl_2NiO_3P_2$: C, 54.40; H, 6.85; N, 0. Found: C, 54.76; H, 6.72; N, <0.5.

Synthesis of (L3)NiCl(*o*-tolyl), **C3**. A glass vial was charged with (**L3**)$NiCl_2$ (150.0 mg, 0.243 mmol), THF (2.5 mL), and a magnetic stir bar, yielding a clear, dark orange solution. Stirring

was initiated, then (*o*-tolyl)MgCl (277 μL of a 0.920 M solution in THF, 0.255 mmol) was added dropwise (~30 s/drop) to the stirring solution over ~1-2 min., yielding a hazy, orange mixture upon complete addition. The mixture was allowed to stir at room temperature for 2 h, after which time the reaction mixture was quenched with MeOH (2 mL) in air. The volatiles were removed from the clear, orange solution under reduced pressure, yielding a pale-orange solid, which was dried under reduced pressure for ~1 h (unoptimized). The solid was then dissolved in DCM (5 mL), cooled to ~0 °C, then filtered through Celite, eluting with cold (~0 °C) DCM (2 x 3 mL). The volatiles were removed from the clear, orange filtrate under reduced pressure yielding the target complex as an orange solid. Yield: 0.153 g (93%). Anal. Calc'd. for $C_{35}H_{49}ClNiO_3P_2$: C, 62.38; H, 7.33; N, 0. Found: C, 62.71; H, 7.47; N, <0.5. A single crystal suitable for X-ray diffraction was obtained by slow evaporation of pentane into a toluene solution of **C3** at ~4 °C. As outlined in the text (Figure 3), complex **C3** (as prepared above) exists as four diastereomers in solution, whereas recrystallized samples, when dissolved in solution, initially feature only two of these diastereomers. Even in the latter case, the solution ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for **C3** are sufficiently complex so as to preclude meaningful assignment, given the C_1-symmetric nature of each diastereomer of **C3**; these and related spectra are provided for reference in the Supporting Information. Bulk **C3**: $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 53.0 (d, J_{PP} = 10.6 Hz), 52.0 (*d*, J_{PP} = 10.5 Hz), 49.55 (d, J_{PP} = 20.3 Hz), 49.47 (d, J_{PP} = 20.6 Hz), 34.9 (d, J_{PP} = 20.8 Hz), 34.5 (d, J_{PP} = 20.3 Hz), 20.4 (d, J_{PP} = 10.6 Hz), 19.1 (d, J_{PP} = 10.5 Hz). Recrystallized **C3**: $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 53.0 (d, J_{PP} = 10.4 Hz), 52.0 (d, J_{PP} = 10.2 Hz), 20.4 (d, J_{PP} = 10.4 Hz), 19.1 (d, J_{PP} = 10.3 Hz). Further spectroscopic experiments conducted on **C3** include: $^{31}P\{^{1}H\}$-$^{31}P\{^{1}H\}$ COSY (Figure S12), time-lapsed $^{31}P\{^{1}H\}$ NMR spectra of recrystallized **C3** (Figure S13), elevated-temperature $^{31}P\{^{1}H\}$ NMR (in

$C_2D_2Cl_4$, Figure S14**)**, and $^{31}P\{^1H\}$ NMR saturation transfer experiments (Figure S15), which are discussed in the Results and Discussion section.

Synthesis of (L4)$NiCl_2$. A glass vial was charged with THF (2.6 mL), $NiCl_2$(DME) (57.8 mg, 0.263 mmol), **L4** (200.0 mg, 0.276 mmol), and a magnetic stir bar, yielding a cloudy, purple mixture. The mixture was then stirred magnetically at room temperature for 2 hours, after which time the purple solid was collected on a glass filter frit in air and washed with cold (~0 °C) pentane (2 x 2 mL). The solid was dissolved off the frit using DCM (15 mL), and was collected. The volatiles were removed from the clear, dark purple solution under reduced pressure, yielding the target complex a dark purple solid. Yield: 0.132 g (89%). ^1H NMR (500.1 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.56-7.53 (m, 1H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.41-7.37 (m, 2H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.24 (s, 1H), 7.21-7.18 (m, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 6.8 Hz, 1H), 6.31 (d, *J* = 6.1 Hz, 1H), 3.62 (br s, 3H), 2.55 (br s, 3H), 1.77 (br s, 9H), 1.30 (br s, 9H). $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 145.6, 142.9, 137.7, 136.0, 135.8, 133.8, 133.3, 132.6, 132.2, 131.94, 131.87, 131.7, 128.5, 126.7, 126.3, 126.0, 41.4, 39.7, 31.8, 31.0, 27.0, 23.9. $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$): δ 126.6 (br s), 90.7 (br s). Anal. Calc'd. for $C_{28}H_{36}Cl_2NiP_2$: C, 59.61; H, 6.43; N, 0. Found: C, 59.76; H, 6.01; N, <0.5.

Synthesis of (L4)NiCl(*o*-tolyl), **C4**. A glass vial was charged with (**L4**)$NiCl_2$ (40.0 mg, 0.0709 mmol), THF (2 mL), and a magnetic stir bar, yielding a cloudy, purple mixture. Stirring was initiated, then (*o*-tolyl)MgCl (92.5 μL of a 0.920 M solution in THF, 0.0851 mmol) was added dropwise (~30 s/drop) to the stirring mixture, affording a clear, brown-orange solution upon complete addition. The solution was then allowed to stir at room temperature for 18 h (unoptimized), after which time the now darker-colored solution was quenched with MeOH (1.5

mL) in air. The volatiles were removed under reduced pressure, yielding a brown-orange solid residue, which was dried further under reduced pressure for ~1 h (unoptimized). DCM (5 mL) was then added, and the cloudy, orange mixture was cooled to ~0 °C, and filtered through Celite, eluting with cold (~0 °C) DCM (3 x 2 mL). The volatiles were removed from the clear, orange-brown filtrate under reduced pressure, yielding a brown-orange solid. The solid was washed with cold (~0 °C) pentane (2 x 1 mL) and dried under reduced pressure to afford the target complex. Yield: 0.040 g (91%). Anal. Calc'd. for $C_{34}H_{43}ClNiP_2$: C, 67.82; H, 6.99; N, 0. Found: C, 67.58; H, 7.04; N, <0.5. A single crystal suitable for X-ray diffraction was obtained by slow evaporation of pentane into a DCM solution of **C4** at ~4 °C. As outlined in the text, complex **C4** exists in solution as two diastereomers, where temperature-dependent line broadening due to hindered rotation and/or dynamic equilibria involving tetrahedral and square planar species, is also apparent. As such, the solution ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for **C4** are sufficiently complex so as to preclude meaningful assignment; these spectra, as well as variable-temperature $^{31}P\{^{1}H\}$ NMR for **C4** (Figure S22), are provided for reference in the Supporting Information. $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 69.9 (s), 66.9 (d, J_{PP} = 8.9 Hz), 55.4 (br s), 49.2 (br s).

Synthesis of (L5)$NiCl_2$. A glass vial was charged with $NiCl_2$(DME) (30.0 mg, 0.137 mmol), **L5** (60.0 mg, 0.143 mmol), THF (1.5 mL), and a magnetic stir bar. Stirring was initiated, yielding a cloudy, red-orange mixture after several minutes. The mixture was allowed to stir at room temperature for 2 h, after which time the mixture was filtered onto a glass filter frit in air, and the collected orange solid was washed with cold (~0 °C) pentane (2 x 1 mL). The solid was washed off the frit using DCM (10 mL), and the volatiles were removed from the slightly hazy, red-orange filtrate yielding an orange solid residue. The solid residue was dissolved in a minimal amount of DCM and filtered through a short Celite plug. The volatiles were removed from the

clear, red filtrate yielding the target complex as an orange solid. Yield 0.044 g (56%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 7.95 (br d, J = 6.7 Hz, 1H), 7.70 (br d, J = 6.3 Hz, 1H), 7.61-7.57 (m, 2H), 2.64-2.57 (overlapping m, 4H), 1.86-1.77 (overlapping m, 8H), 1.70-1.67 (m, 2H), 1.63 (d, J_{PH} = 13.1 Hz, 18H), 1.57 (br s, 2H), 1.36-1.18 (overlapping m, 6H). ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 135.0, 132.2, 131.2, 130.7, 39.6 (d, J_{PC} = 13.2 Hz), 38.4 (d, J_{PC} = 26.7 Hz), 31.8, 30.7, 29.6, 27.5, 26.0. ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$): δ 91.9 (br s), 64.4 (br s). Anal. Calc'd. for $C_{26}H_{44}Cl_2NiP_2$: C, 56.97; H, 8.09; N, 0. Found: C, 56.69; H, 7.83; N, <0.5.

Synthesis of (L5)NiCl(*o*-tolyl), **C5**. A glass vial was charged with (**L5**)$NiCl_2$ (35.0 mg, 0.0638 mmol), THF (1 mL), and a magnetic stir bar, yielding a cloudy, red-orange mixture. Stirring was initiated and (*o*-tolyl)MgCl (72.9 μL of a 0.920 M solution in THF, 0.0670 mmol) was then added dropwise (~30 s/drop) to the stirring solution, yielding a clear, orange solution upon complete addition. After several minutes, a yellow precipitate formed. The resulting cloudy, yellow mixture was then stirred at room temperature for 18 h (unoptimized), after which time the reaction was quenched with MeOH (2 mL) in air. The volatiles were removed under reduced pressure, yielding a yellow solid residue, which was dried further under vacuum for ~1.5 h. To the residue was added DCM (5 mL), and the hazy, yellow mixture was cooled to ~0 °C, and filtered through Celite, eluting with cold (~0 °C) DCM (2 x 3 mL). The volatiles were removed from the clear, orange-yellow filtrate, yielding the target complex as an orange-yellow solid. Yield: 0.034 g (87%). A single crystal suitable for X-ray diffraction was obtained by slow evaporation of a THF solution of **C5** at room temperature. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 8.05-8.03 (m, 1H), 7.66-7.64 (m, 1H), 7.55-7.52 (m, 2H), 7.27-7.25 (overlapping m with $CHCl_3$, 1H), 6.87-6.85 (m, 1H), 6.79-6.75 (m, 2H), 3.13-3.11 (m, 1H), 3.05 (s, 3H), 2.65-2.58 (m, 1H), 2.22-2.14 (m, 1H), 1.86-1.77 (m, 3H), 1.72-1.69 (m, 2H), 1.64-1.58 (m, 10H), 1.53-1.49 (m,

14H), 1.43-1.40 (m, 1H), 1.20-1.00 (m, 6H), 0.41-0.33 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 144.1, 142.1, 135.4, 135.1 (d, J_{PC} = 12.1 Hz), 131.5 (d, J_{PC} = 14.3 Hz), 130.2, 129.6, 127.9, 124.3, 122.5, 37.5 (d, J_{PC} = 7.9 Hz), 37.1, 36.9, 33.8, 33.6, 32.1, 34.8 (d, J_{PC} = 4.2 Hz), 31.1 (d, J_{PC} = 4.4 Hz), 28.5, 27.7-27.5 (overlapping d), 26.3, 26.1 (d, J_{PC} = 11.4 Hz). $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ 69.3 (d, J_{PP} = 15.5 Hz), 49.0 (d, J_{PP} = 15.3 Hz). Anal. Calc'd. for $C_{33}H_{51}ClNiP_2$: C, 65.64; H, 8.51; N, 0. Found: C, 65.27; H, 8.24; N, <0.5.

General Procedure for Pre-catalyst Screening. In a nitrogen-filled glovebox, pre-catalyst (0.0036 mmol, 3 mol%), NaO(*t*-Bu) (17.3 mg, 0.18 mmol, 1.5 equiv), (hetero)aryl chloride (0.12 mmol, 1.0 equiv), toluene (1 mL), and cyclopropylamine (12.5 μL, 0.18 mmol, 1.5 equiv) were consecutively added to a 1 dram, screw-capped vial, followed by a magnetic stir bar. The vial was then sealed with a cap containing a PTFE septum and the reaction mixture was allowed to stir at room temperature for 16 h (unoptimized). After this time, the vial was removed from the glovebox, and an aliquot of the reaction mixture was filtered through a short Celite/silica plug, diluted with EtOAc (~1.5 mL), and subjected to GC analysis.

General Procedure for the *N*-Arylation of Cyclopropylamine Using (Hetero)aryl (Pseudo)halides at Room Temperature (GPA). In a nitrogen-filled glovebox, pre-catalyst (3 mol%), NaO(*t*-Bu) (1.5 equiv), (hetero)aryl (pseudo)halide (1.0 equiv), toluene, and cyclopropylamine (1.5 equiv) were consecutively added to a 4 dram, screw-capped vial, followed by a magnetic stir bar. The vial was then sealed with a cap containing a PTFE septum and the reaction mixture was allowed to stir at room temperature for 16 h (unoptimized). After this time, the vial was removed from the glovebox, and the crude reaction mixture was diluted with EtOAc or DCM (10 mL) and filtered through Celite, eluting with additional solvent (2 x 10

mL). The volatiles were removed from the filtrate under reduced pressure, and the resulting residue was purified by use of automated flash chromatography.

General Procedure for the *N*-Arylation of Cyclopropylamine Using (Hetero)aryl (Pseudo)halides at Elevated Temperatures (GPB). In a nitrogen-filled glovebox, **C3** (25.2 mg, 0.0375 mmol, 5 mol%), K_3PO_4 (3.0 equiv), (hetero)aryl (pseudo)halide (1.0 equiv), 1,4-dioxane or toluene, and cyclopropylamine (1.5 equiv) were consecutively added to a 4 dram, screw-capped vial, followed by a magnetic stir bar. The vial was then sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled, aluminum heating block set to 110 °C. The mixture was stirred this temperature for 16 h (unoptimized), after which time the vial was removed from the heat source and allowed to cool to room temperature. The crude reaction mixture was then diluted with DCM (10 mL) and filtered through Celite, eluting with additional DCM (2 x 10 mL). The volatiles were removed from the filtrate under reduced pressure, and the resulting residue was purified by use of automated flash chromatography.

General Procedure for the *N*-Arylation of Small Cyclic Ammonium Salts Using Aryl (Pseudo)halides (GPC). In a nitrogen-filled glovebox, pre-catalyst (5 mol%), NaO(*t*-Bu) (2.5 equiv), solid (hetero)aryl (pseudo)halide (1.0 equiv), amine hydrochloride (1.1 equiv), and toluene were consecutively added to a 4 dram, screw-capped vial, followed by a magnetic stir bar. Liquid (hetero)aryl (pseudo)halides were added after the amine hydrochloride. The vial was then sealed with a cap containing a PTFE septum and allowed to stir at room temperature for 16 h (unoptimized). After this time, the vial was removed from the glovebox, and the crude reaction mixture was diluted with EtOAc or DCM (10 mL) and filtered through Celite, eluting with

additional solvent (2 x 10 mL). The volatiles were removed from the filtrate under reduced pressure and the resulting residue was purified by use of flash chromatography on silica gel.

General Procedure for the (Pseudo)halide Competition Studies. In a nitrogen-filled glovebox, **C3** (2.4 mg, 0.0036 mmol, 3 mol%), NaO(*t*-Bu) (17.3 mg, 0.18 mmol, 1.5 equiv), aryl halide 1 (1.0 equiv), aryl (pseudo)halide 2 (1.0 equiv), toluene (1 mL), and cyclopropylamine (12.5 μL, 0.18 mmol, 1.5 equiv) were consecutively added to a 1 dram, screw-capped vial, followed by a magnetic stir bar. The vial was then sealed with a cap containing a PTFE septum and the reaction mixture was allowed to stir at room temperature for 16 h (unoptimized). After this time, the vial was removed from the glovebox, and a 367 μL aliquot of the reaction mixture was filtered through a short Celite/silica plug, diluted with EtOAc (~1.5 mL), and subjected to GC analysis.

Reaction Monitoring of the Nickel-Catalyzed *N*-Arylation of Cyclopropylamine. In a nitrogen-filled glovebox, **C3** (10.1 mg, 0.015 mmol, 5 mol%), NaO(*t*-Bu) (72.1 mg, 0.75 mmol, 1.5 equiv), 3-chloropyridine (47.5 μL, 0.5 mmol, 1.0 equiv), and toluene (4.17 mL) were consecutively added to a 4 dram, screw-capped vial, followed by a magnetic stir bar. 4-Chloroanisole (100 μL of a 0.5 M solution in toluene, 0.05 mmol, 10 mol% *or* 61.2 μL, 0.5 mmol, 1.0 equiv) was also added at this time, as appropriate. Finally, cyclopropylamine (52.0 μL, 0.75 mmol, 1.5 equiv) was added, and the vial was sealed with a cap containing a PTFE septum. The reaction was allowed to stir at room temperature for the indicated time, at which point 100 μL aliquots of the reaction mixture were taken, diluted with EtOAc, filtered through a short Celite/silica plug, and analyzed by use of GC methods employing dodecane as an internal standard.

Large-scale Synthesis of 3a. In a nitrogen-filled glovebox, an oven-dried 100 mL round-bottom flask was charged with **C3** (171.8 mg, 0.255 mmol), NaO(*t*-Bu) (1.225 g, 12.75 mmol), 3-chloropyridine (808 μL, 8.5 mmol), toluene (70 mL), and cyclopropylamine (883 μL, 12.75 mmol), followed by a magnetic stir bar. The flask was sealed with a rubber septum, and the reaction mixture was allowed to stir at room temperature for 16 h (unoptimized). After this time, the mixture was diluted with DCM (120 mL) in air, and filtered through Celite, eluting with additional DCM (2 x 100 mL). The filtrate was concentrated to ~20 mL under reduced pressure, and the resulting brown/orange mixture was purified by automated flash chromatography (100 g Biotage SNAP KP-SIL cartridge, 50-100% EtOAc in hexanes, 40 mL/min flow rate), affording the title compound as a white solid (1.004 g, 88%).

Large-scale Synthesis of 3d. In a nitrogen-filled glovebox, an oven-dried 100 mL round-bottom flask was charged with **C3** (171.8 mg, 0.255 mmol), NaO(*t*-Bu) (1.225 g, 12.75 mmol), 4-chlorobenzonitrile (1.169 g, 8.5 mmol), toluene (70 mL), and cyclopropylamine (883 μL, 12.75 mmol), followed by a magnetic stir bar. The flask was sealed with a rubber septum, and the reaction mixture was allowed to stir at room temperature for 16 h (unoptimized). After this time, the mixture was diluted with EtOAc (120 mL) in air, and filtered through Celite, eluting with additional EtOAc (2 x 100 mL). The filtrate was concentrated to ~20 mL under reduced pressure, and the resulting orange solution was purified by automated flash chromatography (100 g Biotage SNAP KP-SIL cartridge, 0-5% EtOAc in hexanes, 25-60 mL/min flow rate), affording the title compound as an off-white solid (1.223 g, 91%).

AUTHOR INFORMATION

Corresponding Author

*Email: mark.stradiotto@dal.ca

Author Contributions

The manuscript was written through contributions of J.P.T. and M.S. All authors have given approval to the final version of the manuscript.

Funding Sources

Operational funding for this work was provided by the Natural Sciences and Engineering Research Council of Canada (Discovery Grant RGPIN-2014-4807 and I2I Grant I2IPJ/485197-2015).

Notes

The authors declare the following competing financial interest(s): Dalhousie University has filed patents on **L1**, **L3**, **C1**, and **C3** used in this work, from which royalty payments may be derived.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge at the ACS Publications website.

Complete crystallographic solution and refinement details, compound characterization data, and NMR spectra (PDF)

Deposited crystallographic data for **C3** (CCDC 1553430), **C4** (CCDC 1553431), **C5** (CCDC 1553432)

ACKNOWLEDGMENTS

We are grateful to the Natural Sciences and Engineering Research Council of Canada (Discovery and I2I Grants for M.S.; CGS-D for P.M.Q. and C.M.L), the Government of Canada (Vanier CGS for J.P.T.), the Killam Trusts, and Dalhousie University for their support of this work. Cytec (Solvay) is thanked for the generous donation of the phosphatrioxaadamantane used herein. We also 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) Salaün, J. Cyclopropane Derivatives and their Diverse Biological Activities. In *Small Ring Compounds in Organic Synthesis VI*, de Meijere, A., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 2000; pp 1-67; (b) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625-1647; (c) Reichelt, A.; Martin, S. F. *Acc. Chem. Res.* **2006**, *39*, 433-442.

2. Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432-2506.

3. Mandala, D.; Thompson, W. A.; Watts, P. *Tetrahedron* **2016**, *72*, 3389-3420.

4. (a) Silverman, R. B. *Acc. Chem. Res.* **1995**, *28*, 335-342; (b) Shaffer, C. L.; Harriman, S.; Koen, Y. M.; Hanzlik, R. P. *J. Am. Chem. Soc.* **2002**, *124*, 8268-8274; (c) Cerny, M. A.; Hanzlik, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 3346-3354.

5. (a) Loeppky, R. N.; Singh, S. P.; Elomari, S.; Hastings, R.; Theiss, T. E. *J. Am. Chem. Soc.* **1998**, *120*, 5193-5202; (b) Loeppky, R. N.; Elomari, S. *J. Org. Chem.* **2000**, *65*, 96-103.

6. Brown, H. C.; Fletcher, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212-221.

7. (a) Kang, J.; Kim, K. S. *J. Chem. Soc., Chem. Commun.* **1987**, 897-898; (b) Yoshida, Y.; Umezu, K.; Hamada, Y.; Atsumi, N.; Tabuchi, F. *Synlett* **2003**, 2139-2142.

8. Arava, V. R.; Bandatmakuru, S. R. *Synthesis* **2013**, *45*, 1039-1044.

9. Monnier, F.; Taillefer, M. *Top. Organomet. Chem.* **2013**, *46*, 173-204.

10. Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564-12649.

11. (a) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435-4443; (b) Liu, Z.-J.; Vors, J.-P.; Gesing, E. R. F.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 3158-3162; (c) Xie, R.; Fu, H.; Ling, Y. *Chem. Commun.* **2011**, *47*, 8976-8978; (d) Wang, Y.; Ling, J.; Zhang, Y.; Zhang, A.; Yao, Q. *Eur. J. Org. Chem.* **2015**, *2015*, 4153-4161.

12. (a) For the copper-promoted *N*-cyclopropylation of anilines and amines by cyclopropylboronic acid, see: Benard, S.; Neuville, L.; Zhu, J. *Chem. Commun.* **2010**, *46*, 3393-3395; (b) For the direct *N*-cyclopropylation of cyclic amides and azoles employing a cyclopropylbismuth reagent, see: Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, *129*, 44-45.

13. (a) Cui, W.; Loeppky, R. N. *Tetrahedron* **2001**, *57*, 2953-2956; (b) Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 222-226; (c) Nguyen, T. H.; Morris, S. A.; Zheng, N. *Adv. Synth. Catal.* **2014**, *356*, 2831-2837; (d) Nguyen, T. H.; Maity, S.; Zheng, N. *Beilstein J. Org. Chem.* **2014**, *10*, 975-980.

14. Gildner, P. G.; DeAngelis, A.; Colacot, T. J. *Org. Lett.* **2016**, *18*, 1442-1445.

15. Bullock, R. M., *Catalysis Without Precious Metals*. Wiley-VCH: Weinheim, Germany, 2010, 1-276.

16. (a) 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; (b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299-309; (c) Ananikov, V. P. *ACS Catal.* **2015**, *5*, 1964-1971.

17. (a) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29-39; (b) Marín, M.; Rama, R. J.; Nicasio, M. C. *Chem. Rec.* **2016**, *16*, 1819-1832; (c) Ritleng, V.; Henrion, M.; Chetcuti, M. J. *ACS Catal.* **2016**, *6*, 890-906.

18. For an elegant example of systematic phosphine-ligand parameterization/optimization leading to enhanced performance in Ni-catalysed Suzuki cross-coupling, see: Wu, K.; Doyle, A. G. *Nat. Chem.* **2017**, *9*, 779-784.

19. 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.

20. Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047-1062.

21. Lavoie, C. M.; MacQueen, P. M.; Stradiotto, M. *Chem. Eur. J.* **2016**, *22*, 18752-18755.

22. Stradiotto, M.; Lundgren, R. J., *Ligand Design in Metal Chemistry: Reactivity and Catalysis*. John Wiley & Sons: Hoboken, NJ, 2016, 1-405.

23. Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, *22*, 347-359.

24. (a) Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 4677-4679; (b) Taniguchi, H.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 11298-11299; (c) Ogata, K.; Shimada, D.; Furuya, S.; Fukuzawa, S.-i. *Org. Lett.* **2013**, *15*, 1182-1185; (d) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79*, 3030-3039; (e) Hori, H.; Arai, S.; Nishida, A. *Adv. Synth. Catal.* **2017**, *359*, 1170-1176.

25. (a) Clark, J. S. K.; Lavoie, C. M.; MacQueen, P. M.; Ferguson, M. J.; Stradiotto, M. *Organometallics* **2016**, *35*, 3248-3254; (b) MacQueen, P. M.; Stradiotto, M. *Synlett* **2017**, doi: 10.1055/s-0036-1590819.

26. For a recent review documenting the benefits of employing L_nNiCl(*o*-tolyl) and related pre-catalysts in nickel cross-couplings, see: Hazari, N.; Melvin, P. R.; Beromi, M. M. *Nat. Rev. Chem.* **2017**, *1*, 0025.

27. Pringle, P. G.; Smith, M. B. Phosphatrioxa-adamantane Ligands. In *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*, Kamer, P. C. J.; van Leeuwen, P. W. N. M., Eds. John Wiley & Sons Ltd.: 2012; pp 391-404.

28. Li, Y.-H.; Zhang, Y.; Ding, X.-H. *Inorg. Chem. Commun.* **2011**, *14*, 1306-1310.

29. (a) Coussmak, C.; Hutchinson, M. H.; Sutton, L. E.; Mellor, J. R.; Venanzi, L. M. *J. Chem. Soc.* **1961**, 2705-2713; (b) Browning, M. C.; Venanzi, L. M.; Morgan, D. J.; Mellor, J. R.; Pratt, S. A. J.; Sutton, L. E. *J. Chem. Soc.* **1962**, 693-703; (c) Garton, G.; Henn, D. E.; Venanzi, L. M.; Powell, H. M. *J. Chem. Soc.* **1963**, 3625-3629.

30. Lavoie, C. M.; McDonald, R.; Johnson, E. R.; Stradiotto, M. *Adv. Synth. Catal.* **2017**, *359*, *in press*, DOI 10.1002/adsc.201700672.

31. (a) Yang, C.-T.; Fu, Y.; Huang, Y.-B.; Yi, J.; Guo, Q.-X.; Liu, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 7398-7401; (b) Henderson, J. L.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 4442-4445; (c) Henderson, J. L.; McDermott, S. M.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 4438-4441; (d) Huang, Y.-B.; Yang, C.-T.; Yi, J.; Deng, X.-J.; Fu, Y.; Liu, L. *J. Org. Chem.* **2011**, *76*, 800-810; (e) Wang, J.; Zheng, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 11424-11427.

32. Green, R. A.; Hartwig, J. F. *Org. Lett.* **2014**, *16*, 4388-4391.

33. Green, R. A.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2015**, *54*, 3768-3772.

34. 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.

35. Kwong, F. Y.; Lai, C. W.; Yu, M.; Tian, Y.; Chan, K. S. *Tetrahedron* **2003**, *59*, 10295-10305.

36. Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748-17749.

37. Gundersen, L.-L.; Bakkestuen, A. K.; Aasen, A. J.; Øverås, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743-9756.