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PhPAd-DalPhos: Ligand-Enabled, Nickel-Catalyzed Cross-Coupling of (Hetero)aryl Electrophiles with Bulky Primary Alkylamines

Joseph P. Tassone,[a] Emma V. England,[a] Preston M. MacQueen,[a] Michael J. Ferguson,[b] and Mark Stradiotto*,[a]

Abstract: *The base metal-catalyzed C-N cross-coupling of bulky α,α,α-trisubstituted primary alkylamines with (hetero)aryl electrophiles represents a challenging and under-developed class of transformations that is of significant potential utility, including in the synthesis of lipophilic active pharmaceutical ingredients. Herein, we report that a new, air-stable Ni(II) pre-catalyst incorporating the optimized ancillary ligand PhPAd-DalPhos enables such transformations of (hetero)aryl chloride, bromide, and tosylate electrophiles to be carried out for the first time with substrate scope rivalling that achieved using state-of-the-art Pd catalysts, including room temperature cross-couplings of (hetero)aryl chlorides that are unprecedented for any catalyst (Pd, Ni, or other).*

Notwithstanding the utility of the Pd-catalyzed C-N cross-coupling of NH substrates and (hetero)aryl (pseudo)halides (i.e., Buchwald-Hartwig amination, BHA[1]) *en route* to sought-after (hetero)anilines, the use of Ni in place of Pd in such transformations is attractive given the sustainability and cost benefits,[2] as well as in terms of the favorable reactivity of Ni with inexpensive and widely available (hetero)aryl chlorides.[3] The most common approach employed in developing Ni-catalyzed C-N cross-couplings[4] has involved the repurposing of ancillary ligands that work well in BHA, with some well-established bisphosphines[5] (e.g., dppf,[6] BINAP[7]) and *N*-heterocyclic carbenes (e.g., IPr)[8] affording useful reactivity, primarily in transformations of simple primary or secondary aliphatic/aromatic amine coupling partners. However, the comparatively poor performance of premiere BHA ligands,[9] including Buchwald's biarylphosphines,[10] suggests that new ancillary ligands tailored specifically to the properties of Ni may prove advantageous in the quest to address particularly challenging substrate pairings. Despite such promise, ancillary ligand design targeted for use in Ni-catalyzed C-N cross-coupling has remained essentially unexplored.

In 2016 we developed the bulky and modestly electron-donating PAd-DalPhos[11] bisphosphine ligand featuring a phosphaadamantane donor fragment, which we envisioned would work well in promoting rate-limiting C-N reductive elimination within a presumptive Ni(0/II) catalytic cycle.[12] This new and modular design strategy has proven effective, with pre-catalysts incorporating PAd-DalPhos and related variants enabling the Ni-catalyzed monoarylation of ammonia,[11] unhindered primary alkylamines,[11, 13] as well as primary amides and lactams,[14] with a diversity of (hetero)aryl (pseudo)halides. These otherwise challenging Ni-catalyzed C-N cross-couplings using PAd-DalPhos ligands often proceed at room temperature, with demonstrated substrate scope that is commonly competitive with, or superior to, the best Pd catalysts reported to date.

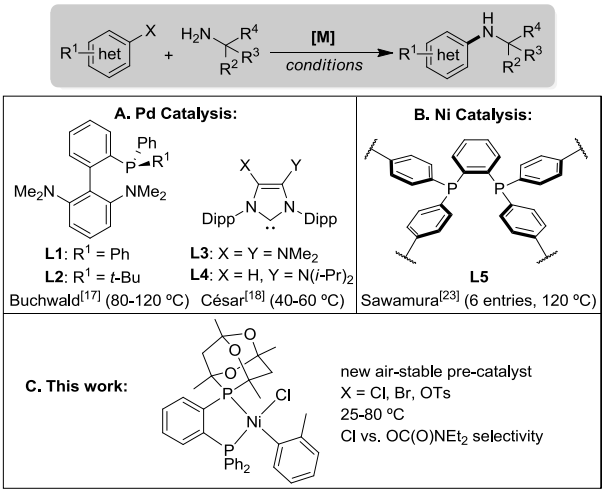

Figure 1. State-of-the-art Pd and Ni catalyst systems for the cross-coupling of bulky, primary amines (A and B), as well as the Ni pre-catalyst system (C) reported in this work. Dipp = 2,6-diisopropylaniline.

Despite recent advances, metal-catalyzed C-N cross-couplings involving α,α,α-trisubstituted primary alkylamines remains a significant challenge. Such under-developed transformations are appealing as a potential means of introducing large hydrocarbon groups (e.g. adamantyl) into active pharmaceutical ingredients to increase lipophilicity,[15] resulting in changes in absorption or membrane permeability that can positively modulate biological activity.[16] The groups of Buchwald[17] and César[18] have disclosed what are state-of-the-art Pd pre-catalysts incorporating tailored biarylmonophosphines (**L1** and **L2**) or backbone-decorated *N*-heterocyclic carbenes (**L3** or **L4**) for the cross-coupling of (hetero)aryl halides with α,α,α-trisubstituted primary alkylamines (Figure 1A). In each report, ancillary ligand design was crucial in engendering the desired reactivity, giving rise to useful (hetero)aryl electrophile (X = Cl , Br) scope at elevated temperatures (80-120 ºC),[17] or milder reaction temperatures with primarily aryl (not (hetero)aryl) chlorides (40-60 ºC).[18] Examples of analogous Ni-catalyzed transformations are scarce, with reports from the groups of Tu,[19] Montgomery,[20] Baran,[21] and Sawamura[22] each featuring one or two entries whereby *tert*-butylamine and/or 1-adamantylamine is employed, often with modest efficacy, in the context of a broader Ni-catalyzed C-N cross-coupling survey. While Sawamura and

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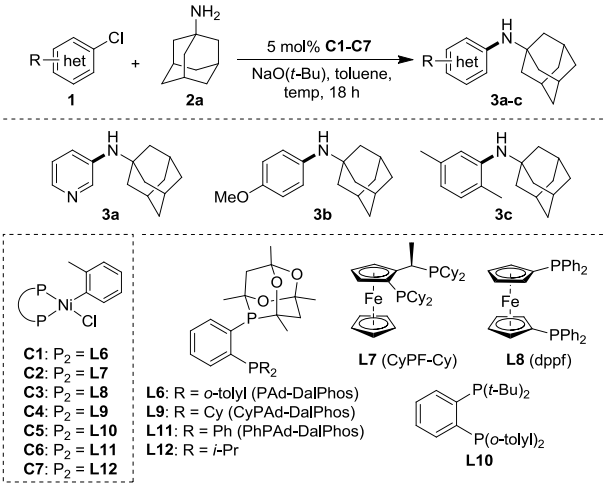
coworkers[23] have developed a polystyrene cross-linked bisphosphine (**L5**) that facilitates C-N cross-couplings of 1-adamantylamine, *tert*-octylamine, and cumylamine with $Ni(cod)_2$, only 4-chlorotoluene or 4-chloroanisole are employed as electrophiles, and elevated temperatures (120 ºC) are required (Figure 1B). In this context, the Ni (or other base metal) catalyzed C-N cross-coupling of α,α,α-trisubstituted primary alkylamines and (hetero)aryl chlorides with synthetically useful substrate scope has yet to be described in the literature. Herein, we report that application of a new, air-stable Ni(II) pre-catalyst incorporating the optimized ancillary ligand PhPAd-DalPhos enables such challenging transformations (Figure 1C), including the first examples of room temperature C-N cross-couplings of α,α,α-trisubstituted primary alkylamines and (hetero)aryl chlorides by use of any catalyst (i.e., Pd, Ni, or other).

In the pursuit of a Ni catalyst capable of effecting C-N cross-couplings of α,α,α-trisubstituted primary alkylamines, we screened [(**L**)NiCl(*o*-tolyl)][24] pre-catalysts in the *N*-arylation of 1-adamantylamine (**2a**) with three potentially challenging (hetero)aryl chlorides (**1a**-**c**, Table 1) at 110 ºC. Pre-catalysts that had proven effective in cross-couplings of less hindered primary alkylamines with (hetero)aryl chlorides, namely **C1**[11] and **C2**[13a] incorporating parent PAd-DalPhos (**L6**) and JosiPhos CyPF-Cy (**L7**), afforded poor conversion to the target anilines **3a**-**c** (entries 1 and 2). The dppf (**L8**) pre-catalyst **C3** also did not afford significant conversion to the desired products (entry 3), despite effecting the cross-coupling of secondary alkylamines as documented in prior reports.[25] Similarly, although **C4** (featuring CyPAd-DalPhos, **L9**) and **C5** (featuring **L10**) are each known to effect cross-couplings of cyclopropylamine,[13b] only **C4** afforded moderate levels of conversion in the case of **3a** (68%) and **3b** (48%) (entries 4 and 5).

On the basis of this initial screen, we anticipated that the bulk of **2a** might necessitate a less sterically hindered ancillary ligand in order to improve catalytic performance. As such, we sought to examine pre-catalysts containing PAd-DalPhos variants in which the -P(*o*-tolyl)$_2$ group was replaced with a -PPh_2 or -P(*i*-Pr)$_2$ moiety (**L11** and **L12** respectively). While **L11** and **L12** are known,[11] the corresponding [(**L**)NiCl(*o*-tolyl)] pre-catalysts (i.e., **C6** and **C7**) had not been reported and were synthesized herein as air-stable solids using a literature procedure.[11] Pre-catalysts **C6** and **C7** exhibit spectroscopic and solid-state (Figure 2)[26] features similar to those of PAd-DalPhos[11] and CyPAd-DalPhos[13b] [(**L**)NiCl(*o*-tolyl)] pre-catalysts.

In screening **C6** and **C7** in the cross-coupling of **1a**-**c** and **2a** at 110 ºC (Table 1, entries 6 and 7), **C6** afforded suitable conversions to **3a** and **3b**, while only modest conversion to the desired products was achieved using **C7**. In noting that **C6** provided comparable or superior conversion to products versus **C4** in our test reactions at 110 ºC (entries 4 and 7), we examined transformations with **C6** at 80 and 60 ºC (entries 8 and 9). While more mild reaction temperatures afforded improved conversion to **3a** and **3c**, lower conversion to **3b** was noted under these conditions. Additional screening to ascertain the effects of base and solvent (see Tables S3-S9 of the SI for complete optimization details) revealed the reagents and concentrations employed in entry 9 of Table 1 to be generally most effective.

Table 1. Pre-catalyst screening and reaction optimization for the Ni-catalyzed cross-coupling of **1a**-**c** and **2a**.[a]



Entry	Pre-catalyst	Temp [°C]	Yield **3a** [%][b]	Yield **3b** [%][b]	Yield **3c** [%][b]
1	**C1**	110	<5	11	19
2	**C2**	110	<5	<5	<5
3	**C3**	110	<5	<5	<5
4	**C4**	110	68	48	19
5	**C5**	110	<5	8	6
6	**C7**	110	27	27	27
7	**C6**	110	65	83	32
8	**C6**	80	91	66	49
9	**C6**	60	90	49	81

[a] Reaction conditions: pre-catalyst (5 mol%), NaO(*t*-Bu) (1.5 equiv), **1a**-**c** (0.12 mmol, 1.0 equiv), **2a** (1.1 equiv), and toluene (1 mL, [ArCl] = 0.12 M) at the indicated temperature. [b] Conversions to product are estimated on the basis of calibrated GC data.

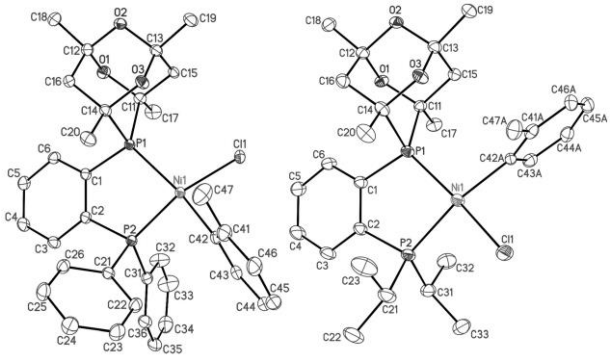
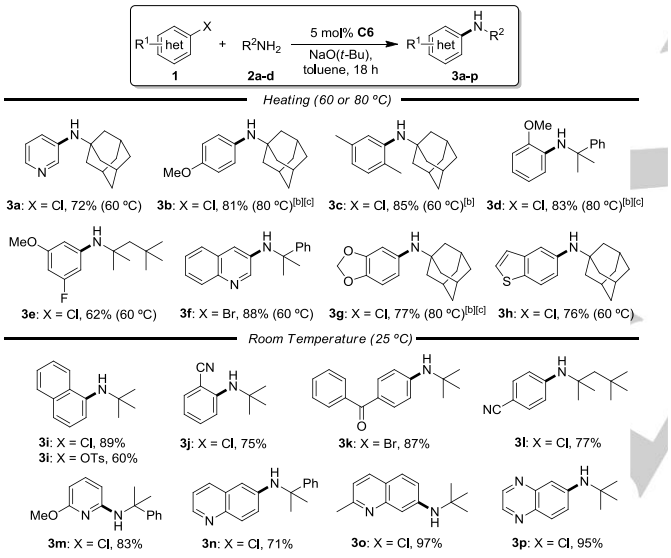


Figure 2. Single-crystal X-ray structures of **C6** (left) and **C7** (right; major orientation of disordered tolyl group shown), each represented with thermal ellipsoids at the 30% probability level. All hydrogen atoms, and the CH_2Cl_2 solvent molecule for **C7**, omitted for clarity. Selected interatomic distances (Å): for **C6**, Ni–P1 2.2471(5), Ni-P2 2.1185(5), Ni-Cl1 2.2071(5), Ni–C42 1.9356(19); for **C7**, Ni–P1 2.1661(8), Ni–P2 2.2047(8), Ni–Cl1 2.1986(9), Ni–C42A 1.943(4).

Having identified **C6** as a promising pre-catalyst for the Ni-catalyzed C-N cross-coupling of α,α,α-trisubstituted primary alkylamines with (hetero)aryl chlorides, we then surveyed the reaction scope (Scheme 1). (Hetero)aryl electrophiles featuring electron-donating (**3b,d**), electron-withdrawing (**3e**,**j**-**l**) (e.g., ether, fluoro, nitrile, and ketone functional groups), or *ortho*-substitution (**3c-d**,**i-j**) were successfully employed. Cross-couplings employing heteroaryl halides containing pyridine (**3a,m**), quinoline (**3f**,**n**), benzodioxole (**3g**), benzothiophene (**3h**),

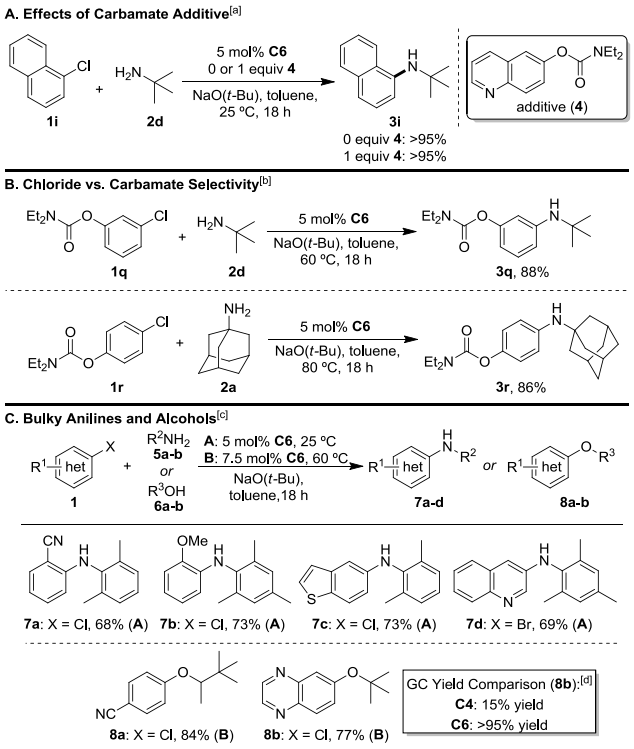
10.1002/anie.201812862

quinaldine (**3o**), and quinoxaline (**3p**) cores also proceeded efficiently. Several sterically hindered, primary alkylamines could be used, including 1-adamantylamine (**3a**-**c**,**g**-**h**), cumylamine (**3d,f**,**m**-**n**), *tert*-octylamine (**3e**,**l**), and *tert*-butylamine (**3i**-**k**,**o**-**p**); however, triphenylmethylamine proved unreactive under analogous conditions. Our reported chemistry was shown to function on gram-scale, with 1.049 g (95%) of **3p** being produced on a 5.5 mmol scale. While the majority of the transformations featured in Scheme 1 focused on the use of synthetically appealing (hetero)aryl chlorides, test cross-couplings involving (hetero)aryl bromides (**3f**,**k**) and an aryl tosylate (**3i**) also proved successful. However, a range of other phenol-derived electrophiles (e.g. triflates, mesylates, or carbamates) were not suitable coupling partners under analogous conditions. While uncatalyzed S_NAr chemistry seemed feasible in the formation of **3a**, **3l**, **3m**, or **3p**, <5% conversion (GC) to product was observed in these transformations in the absence of **C6**. Notably, the first room temperature C-N cross-couplings of α,α,α-trisubstituted primary alkylamines with (hetero)aryl chlorides employing any catalyst (Pd, Ni, or other) was achieved with a diverse set of electrophiles (**3i**-**p**) when using **C6**.



Scheme 1. Scope of the Ni-catalyzed C-N cross-coupling of α,α,α-trisubstituted primary alkylamines with (hetero)aryl electrophiles using **C6**.[a] [a] Reaction conditions: **C6** (5 mol%), NaO(*t*-Bu) (1.5 equiv), **1** (0.5 mmol, 1.0 equiv), **2a-d** (1.1 or 3.0 equiv), and toluene (4.17 mL, [ArX] = 0.12 M). Isolated yields reported. [b] **C6** (6 mol%). [c] Toluene (2.08 mL, [ArCl] = 0.24 M).

Given that phenol-derived electrophiles such as (hetero)aryl carbamates were unsuccessful coupling partners under our optimized reaction conditions, we investigated whether these were simply unreactive with catalytic intermediates derived from **C6**, or if such substrates serve as catalyst poisons (Scheme 2A). Addition of one equivalent of quinolin-6-yl diethylcarbamate (**4**) to the otherwise successful (Scheme 1) room temperature cross-coupling of 1-chloronaphthalene and *tert*-butylamine using **C6** did not hinder conversion to product **3i**, suggesting that (hetero)aryl carbamates do not inhibit catalysis. We exploited this reactivity pattern in chemoselective cross-couplings of **1q** and **1r**, whereby the aryl chloride group reacted preferentially with α,α,α-trisubstituted primary alkylamines when using **C6**, even at elevated temperatures (Scheme 2B). Such chemoselectivity may prove useful in sequential transformations, with **C6** effecting (hetero)aryl chloride C-N cross-coupling with an α,α,α-trisubstituted primary alkylamine in the presence of a carbamate functionality, followed by directed metalation[27] or the introduction of a second nucleophile in a subsequent cross-coupling reaction[28] involving the carbamate moiety.



Scheme 2. A. Exploring the effect of a carbamate additive on the Ni-catalyzed cross-coupling of 1-chloronaphthalene and *tert*-butylamine. B. Chemoselective cross-coupling reactions. C. Ni-catalyzed cross-coupling of (hetero)aryl halides with other bulky nucleophiles. [a] Reaction conditions: **C6** (5 mol%), NaO(*t*-Bu) (1.5 equiv), **1i** (0.12 mmol, 1.0 equiv), **2d** (3.0 equiv), and toluene (1 mL, [ArCl] = 0.12 M). Conversion to **3i** determined on the basis of calibrated GC data. [b] Reaction conditions: **C6** (5 mol%), NaO(*t*-Bu) (1.5 equiv), **1q-r** (0.5 mmol, 1.0 equiv), **2a,d** (1.1 or 3.0 equiv), and toluene (4.17 mL, [ArCl] = 0.12 M) at the indicated temperature. Isolated yields reported. [c] Reaction conditions: NaO(*t*-Bu) (1.5 equiv), **1** (0.5 mmol, 1.0 equiv), **5a-b** (1.1 equiv), and toluene (4.17 mL, [ArCl] = 0.12 M). Isolated yields reported. [d] Conversion to **8b** determined on the basis of calibrated GC data.

We briefly explored the scope of other bulky nucleophiles employing **C6**, beginning with hindered primary anilines (Scheme 2C). In such test transformations, electron-rich, electron-poor, *ortho*-substituted, and heteroaryl electrophiles were C-N cross-coupled successfully, including variants featuring benzothiophene (**7c**) or quinoline (**7d**) motifs. Although these transformations involving 2,6-dimethyl substituted anilines (**7a**-**d**) proceeded efficiently at room temperature, the more hindered 2,6-diisopropylaniline was not a suitable nucleophile, even at 110 ºC. Challenging Ni-catalyzed C-O cross-couplings involving the sterically hindered primary alcohols 3,3-dimethyl-2-butanol and *tert*-butanol (affording **8a** and **8b**) proceeded efficiently under mild conditions (60 ºC) when using **C6**. The only previous report of

such transformations involving (hetero)aryl chlorides was recently published by our group,[29] whereby **C4** was used as a pre-catalyst at 110 ºC. The superiority of **C6** (>95%) over **C4** (15%) in C-O cross-couplings at 60 ºC (Scheme 2C) leading to **8b** suggests that **C6** might hold promise in effecting other demanding catalytic transformations under mild conditions.

In conclusion, we have developed a new Ni pre-catalyst (**C6**) containing an optimized ancillary ligand PhPAd-DalPhos (**L11**) that enables the cross-coupling of α,α,α-trisubstituted primary alkylamines and related hindered nucleophiles with (hetero)aryl electrophiles, including chemoselective transformations. In addition to representing the first Ni-catalyzed C-N cross-couplings of this type whereby the substrate scope is competitive with that achieved by use of state-of-the-art Pd catalysts, the use of **C6** allows for unprecedented room temperature C-N cross-couplings of α,α,α-trisubstituted primary alkylamines and (hetero)aryl chlorides to be achieved. We envision that the application of tailored PAd-DalPhos ancillary ligands will continue to prove effective in solving outstanding problems in base metal catalysis, and will report on our studies in this context in due course.

Acknowledgements

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Keywords: amination • bisphosphines • cross-coupling • ligand design • nickel

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Entry for the Table of Contents

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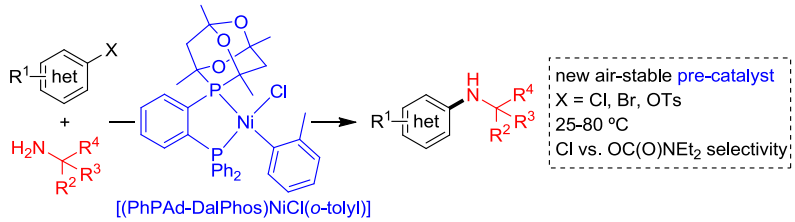

[(PhPAd-DalPhos)NiCl(*o*-tolyl)]

The incredible bulk: A new nickel(II) pre-catalyst featuring the PhPAd-DalPhos ancillary ligand has been shown to be effective for the challenging cross-coupling of sterically hindered primary alkylamines and (hetero)aryl halides under mild conditions.

*Joseph P. Tassone, Emma V. England, Preston M. MacQueen, Michael J. Ferguson, and Mark Stradiotto**

Page No. – Page No.

PhPAd-DalPhos: Ligand-Enabled, Nickel-Catalyzed Cross-Coupling of (Hetero)aryl Electrophiles with Bulky Primary Alkylamines