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Communication

Development of a Deactivation-Resistant Dialkylbiarylphosphine Ligand for Pd-Catalyzed Arylation of Secondary Amines

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ABSTRACT: Despite the prevalence of N-heteroarenes in small-molecule pharmaceuticals, Pd-catalyzed C−N cross-coupling reactions of aryl halides and amines containing these rings remain challenging due to their ability to displace the supporting ligand via coordination to the metal center. To address this limitation, we report the development of a highly robust Pd catalyst supported by a new dialkylbiarylphosphine ligand, FPhos. The FPhos-supported catalyst effectively resists N-heteroarene-mediated catalyst deactivation to readily promote C−N coupling between a wide variety of Lewis-basic aryl halides and secondary amines, including densely functionalized pharmaceuticals. Mechanistic and structural investigations, as well as principal component analysis and density functional theory, elucidated two key design features that enable FPhos to overcome the limitations of previous ligands. First, the ligated Pd complex is stabilized through its conformational preference for the O-bound isomer, which likely resists coordination by N-heteroarenes. Second, 3′,5′-disubstitution on the non-phosphorus-containing ring of FPhos creates the ideal steric environment around the Pd center, which facilitates binding by larger secondary amines while mitigating the formation of off-cycle palladacycle species.

Pd-catalyzed C−N cross-coupling of aryl halides with amines, beyond being one of the most frequently used transformations for the preparation of pharmaceutical candidates,[1] is useful for applications across the chemical sciences.[2] While N-heterocycles are present in most FDA-approved small-molecule drugs,[3] reported methods for coupling secondary amines often encounter significant challenges when faced with N-heteroarene-containing substrates. Among the suite of biarylphosphine ligands developed by our group to promote efficient C−N coupling between a variety of substrate classes, RuPhos (**L1**) is considered to be generally optimal for coupling secondary amines.[4] Yet, while RuPhos-supported Pd catalysts can couple non-coordinating substrates efficiently, N-heteroarene-containing substrates necessitate substantially higher catalyst loadings and longer reaction times, even for relatively simple substrates (Scheme 1A).[5] Pd catalysts supported by the JackiePhos/CPhos hybrid ligand (**L2**), designed for coupling α-branched secondary amines, similarly struggle to accommodate coordinating N-heteroarenes.[6]

Several challenges have limited the ability of previously reported ligand systems to couple secondary amines in the presence of coordinating N-heteroarenes (Scheme 1B). Previous studies from our group and others revealed that phosphine ligands can be displaced due to competitive N-heteroarene coordination,[7,8] rendering catalysts supported by smaller ligands, such as RuPhos (**L1**), especially vulnerable to inhibition.[9,10] In contrast, catalysts supported by sterically encumbered ligands, while more resistant to this mode of deactivation, do not allow for efficient binding of larger secondary amines to Pd.[11]

We reasoned that the design of a new ligand with an optimized steric profile could promote efficient coupling of secondary amines in the presence of coordinating N-heteroarenes. We first assessed the performance of previously reported catalysts on two model coupling reactions between N-heteroarene-containing aryl halides and secondary amines (**3b−c**, Table 1). Each catalyst's activity was additionally benchmarked against a representative non-inhibitory substrate combination (**3a**). While **L2** resulted in a higher yield of **3a** compared to **L1**, low yields of N-heteroarene-containing products **3b−c** were observed for both **L1**−**L2**. The GPhos (**L3**)-supported catalyst, originally developed for coupling primary amines,[7] has been shown to resist catalyst deactivation due to coordinating substrates.[9] However, **P3** provided very low yields of **3a−c**, presumably because **L3** is too bulky to accommodate larger secondary amines.[12]

While several previously reported 2′,6′-dialkylbiarylphosphine ligands,[4] including BrettPhos (**L10**, Figure 1B)[5,11] and GPhos (**L3**),[7,9] are too hindered to promote efficient coupling of secondary amines, ligands lacking substitution on the non-phosphorus-containing ring are also less effective due to their propensity to form off-cycle palladacycle species via 2′- or 6′-C−H metalation.[13] We hypothesized that 3′,5′-disubstitution, an underexplored scaffold, would provide an ideal steric profile

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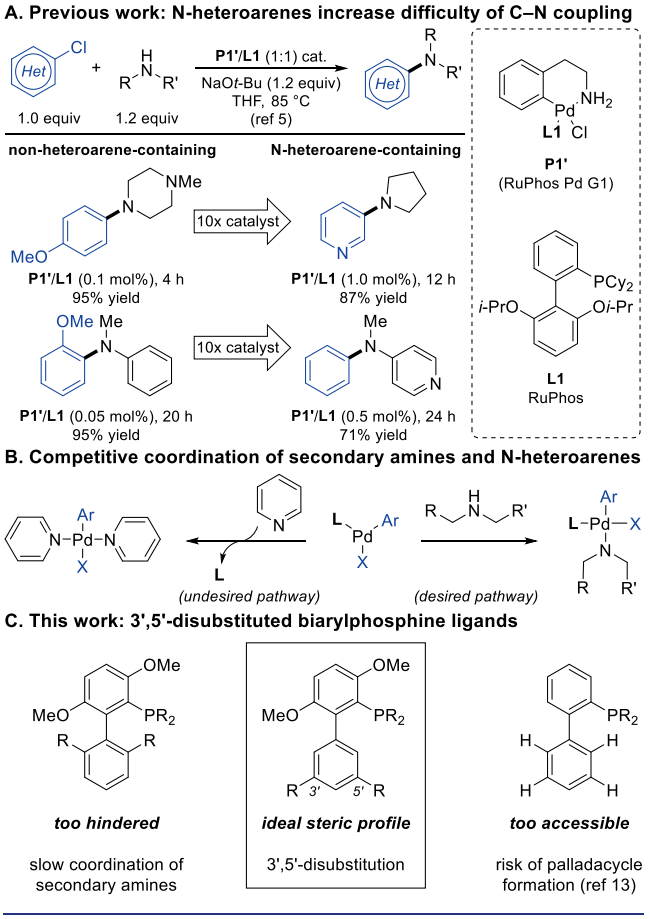
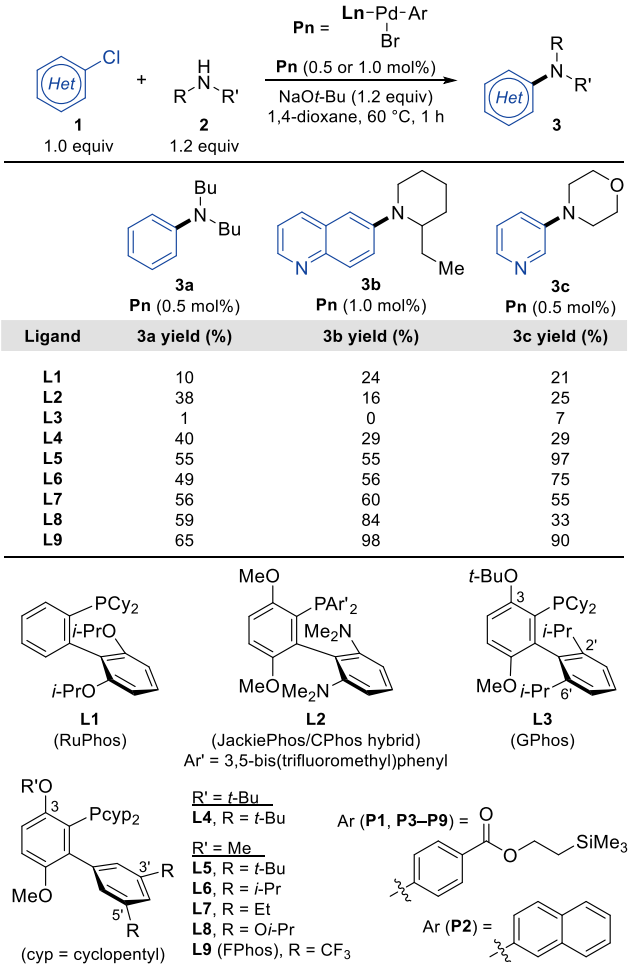
Scheme 1. Challenges of Pd-Catalyzed C−N Coupling of Secondary Amines in the Presence of N-Heteroarenes



for coupling secondary amines in the presence of coordinating N-heteroarenes, allowing secondary amines to bind to Pd while simultaneously providing the requisite protection of the 2′- and 6′-positions against metalation (Scheme 1C).[14]

Upon incorporating 3′,5′-di-*tert*-butyl substitution into the **L3** scaffold, the less hindered **L4**[15] accommodated secondary amines more readily than **L3**. However, **L4** did not significantly outperform **L2**, likely due to the remaining large 3-O*t*-Bu group. **L5**, which features a smaller 3-OMe group, provided a marked improvement in the yields of **3a−c** compared to **L1−L4** (Table 1). We therefore set out to identify the structural features of **L5** responsible for its improved reactivity. Decreasing the size of the 3′,5′-substituents (*t*-Bu > *i*-Pr > Et > O*i*-Pr)[16] resulted in lower yields of pyridine-containing **3c**, while yields of **3a−b** remained the same or increased (**L5−L8**). This discrepancy is likely due to the increased accessibility associated with smaller 3′,5′-substituents, which promotes binding of both secondary amines and coordinating N-heteroarenes to Pd. Additionally, we recognized that inductively electron-withdrawing substituents (*t*-Bu < *i*-Pr, Et < O*i*-Pr)[17] may facilitate coupling in the absence of deactivating heteroarenes. Based on these hypotheses, we designed and synthesized FPhos (**L9**), which possesses 3′,5′-bis(trifluoromethyl) substituents that are both large and strongly electron-withdrawing. In accordance with the hypothesized steric and electronic trends, **L9** demonstrated the best reaction performance across all three model coupling reactions (**3a−c**).[18]

Table 1. Ligand Development[a]



Ligand	3a yield (%)	3b yield (%)	3c yield (%)
L1	10	24	21
L2	38	16	25
L3	1	0	7
L4	40	29	29
L5	55	55	97
L6	49	56	75
L7	56	60	55
L8	59	84	33
L9	65	98	90

[a]Reaction conditions: aryl halide (**1**, 0.2 mmol), amine (**2**, 0.24 mmol), NaO*t*-Bu (0.24 mmol), **Pn** (0.5 or 1.0 mol %), 1,4-dioxane (0.2 mL), 60 °C, 1 h. Yields were determined by gas chromatography (GC) of the crude product mixtures, using *n*-dodecane as the internal standard (**3a**), or by ^{1}H NMR spectroscopy of the crude product mixtures, using 1,3,5-trimethoxybenzene as the internal standard (**3b−c**). Ar = 4-(2-(trimethylsilyl)ethyl benzoate) (**P1**, **P3−P9**) or 2-naphthyl (**P2**), cyp = cyclopentyl.[18]

To better understand the superior performance of **L9**, its molecular descriptors were compared against those of monodentate phosphine ligands in the *kraken* organophosphorus(III) descriptor library, a database of >190 conformationally dependent molecular descriptors of 1,558 monodentate phosphine ligands[19] (Figure 1A). Principal component analysis (PCA), a dimensionality reduction technique, was used to project the 190-dimensional data into two, more descriptive principal component dimensions; monophosphines close in PC space exhibit similar molecular features. Structurally similar dialkylbiarylphosphines are grouped in a distinct cluster, with **L9** appearing in a relatively low-density region of the PCA plot, an indication of its unique features. **L9** exhibits a natural bond orbital population of the phosphorus lone pair (NBO_{LP_P}, a descriptor related to σ-donating ability) in the 80th percentile of dialkylbiarylphosphines. However, **L9** is best differentiated from other dialkylbiarylphosphines by its steric profile. **L9** can adopt sterically demanding conformations, as quantified by Ster-

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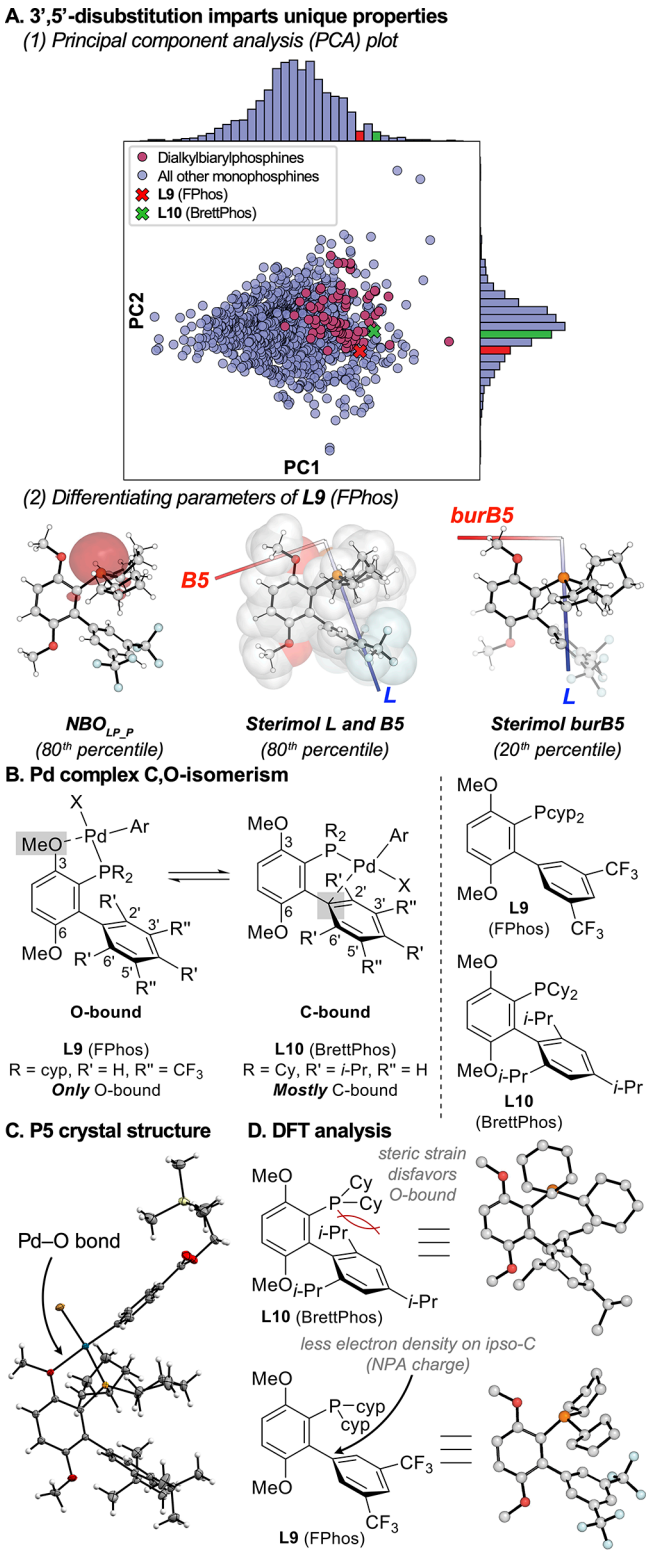

Figure 1. (A) Top: Principal component analysis (PCA) plot of 1,545 monophosphine ligands from the *kraken* database. Histograms on the plot axes indicate the relative density of monophosphines across the plot. Bins containing **L9** and **L10** are colored red and green, respectively. Bottom: Parameters that differentiate **L9** from other dialkylbiarylphosphines include NBO_{LP_P}, Sterimol length (L) and maximum width (B5), and buried Sterimol maximum width (burB5, measured within a 5.5 Å sphere). (B) C,O-isomerism observed for 3-OMe biarylphosphine-supported oxidative addition complexes. (C) X-ray crystal structure of **P5** indicating the conformational preference for the O-bound isomer. Atomic displacement parameter plot drawn at 50% probability level. Color scheme: H, white; C, gray; O, red; Si, yellow; P, orange; Br, brown; Pd, blue. (D) DFT analysis (PBE0/def2-TZVP//PBE/6-31+G(d,p)) indicates that 3′,5′-disubstituted biarylphosphine ligands favor the O-bound isomer due to a combination of decreased steric interactions with phosphine alkyl substituents and less electron density on the ipso-C. Natural population analysis (NPA) charges: **P9** = −0.07, **P10** = −0.15.

imol[20] length (L) and maximum width (B5) parameters, both of which are in the 80th percentile relative to both dialkylbiarylphosphines and the broader *kraken* library. Yet this same ligand allows for relatively high accessibility proximal to Pd, as measured by its *buried* maximum width parameter (buried Sterimol B5), which adopts one of the smallest values (20th percentile) among dialkylbiarylphosphines. These paradoxical steric properties, which arise from the ligand's 3′,5′-disubstitution pattern, are advantageous: from a global perspective, **L9** behaves like a large ligand, resisting catalyst deactivation due to N-heteroarene coordination, but it has the conformational flexibility to adopt a much smaller steric profile when necessary, allowing larger secondary amines to bind to Pd.

While nearly all catalysts based on previously reported biarylphosphine ligands exhibit a reversible π-interaction between Pd and the ipso-C of the non-phosphorus-containing ring (C-bound, Figure 1B), the lowered ipso-C electron density in 3′,5′-disubstituted ligands **L5**–**L9** results in the first reported example of a unique structural feature in which Pd is instead predominantly bound to the 3-OMe on the phosphorus-containing ring (O-bound). Previously, the O-bound isomer was observed only as a minor conformer for 2′,6′-disubstituted biarylphosphine ligands bearing 3-OMe substitution, such as BrettPhos (**L10**).[11] Additionally, only crystal structures of C-bound biarylphosphine oxidative addition complexes were reported.[11] However, the nearly exclusive preference for the O-bound isomer in **P5**–**P9** enabled us to crystallize O-bound **P5**, providing the first reported crystal structure of an O-bound biarylphosphine oxidative addition complex (Figure 1C).[21] Density functional theory (DFT) calculations indicated a significant difference between the Pd–C_{ipso} distances in the C-bound isomers of **P9** (2.66 Å) and **P10** (2.58 Å), a result of the less negative natural population charge on the ipso-C in **P9** (−0.07) compared to **P10** (−0.15) (Figure 1D). Additionally, DFT suggested that 2′,6′-disubstitution (**L10**) introduces costly steric interactions between the phosphine alkyl substituents and the non-phosphorus-containing ring, disfavoring the O-bound isomer, whereas 3′,5′-disubstitution minimizes this steric penalty.

The dominance of the O-bound isomer presumably provides **P9** with an advantage for coupling secondary amines, protecting Pd against coordinative deactivation by N-heteroarenes.[22] Although O-bound catalysts were previously deemed undesirable for the coupling of primary amines, as they exhibit slower reductive elimination than C-bound catalysts,[23,24] this drawback is less relevant for larger secondary amines, which reductively eliminate more readily.[25] A similarly fluid boundary between reaction inhibition and deactivation resistance was previously demonstrated with carbazole, an additive known to both inhibit C–N coupling[6,26] and help

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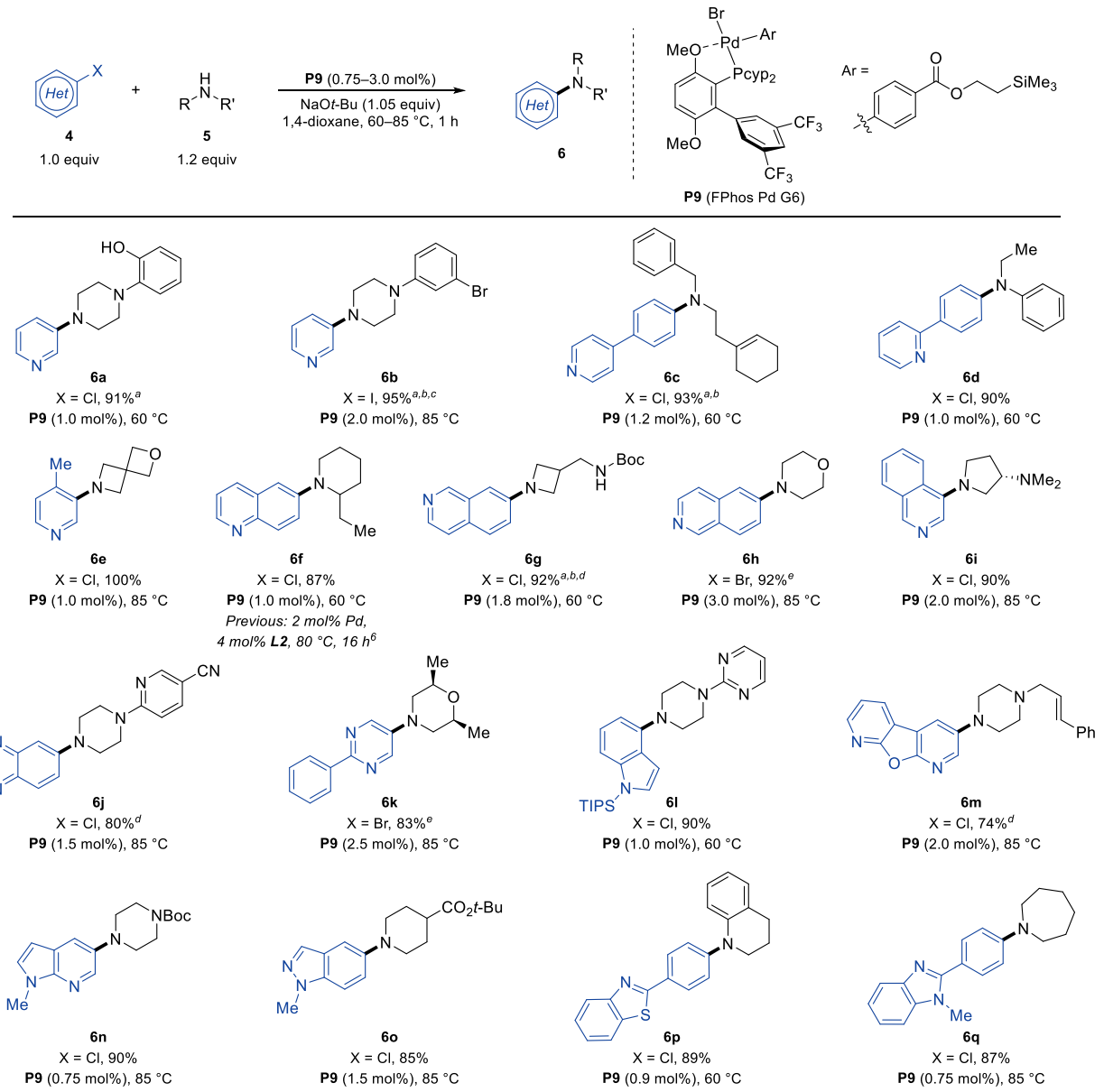

Figure 2. Isolated yields reported as the average of two runs. Reaction conditions: aryl halide (**4**, 0.5 mmol), amine (**5**, 0.6 mmol), NaO*t*-Bu (0.525 mmol), **P9** (0.75−3.0 mol %), 1,4-dioxane (0.5 mL), 60−85 °C, 1 h. Legend: [a]NaO*t*-Bu (2.25 equiv). [b]Amine hydrochloride salt (1.2 equiv). [c]1,4-Dioxane (2.5 mL). [d]1,4-Dioxane (1.25 mL). [e]6 h.

prevent catalyst deactivation by coordinating to the Pd oxidative addition complex.[27]

The FPhos-supported catalyst **P9** enabled facile cross-coupling of a broad scope of N-heteroarene-containing aryl halides and secondary amines in good-to-excellent yields with relatively low catalyst loadings (Figure 2). A variety of N-heteroarenes were investigated, including pyridine[28] (**4a−e**, **5j**), quinoline (**4f**), isoquinoline (**4g−i**), quinoxaline (**4j**), pyrimidine (**4k**, **5l**), azabenzofuran (**4m**), azaindole (**4n**), indazole (**4o**), benzothiazole (**4p**), and benzimidazole (**4q**). Halide substitution was tolerated both on non-heteroarene rings and at unactivated positions on heteroarene rings.[29] In addition to coupling readily available[30] and medicinally prevalent[31] aryl chlorides, **P9** promoted efficient coupling of aryl bromides (**4h**, **4k**) and the selective amination of an aryl iodide (**4b**) in the presence of an aryl bromide. Ortho-substituted aryl halides (**4e**, **4i**, **4l**) were coupled effectively, as **L9** allows for coordination of secondary amines to hindered oxidative addition complexes.

Cyclic amines were readily coupled, including four- (**5e**, **5g**), five- (**5i**), six- (**5a−b**, **5f**, **5h**, **5j−p**), and seven-membered rings (**5q**). *α*-Branched secondary amines were arylated efficiently (**5f**, **5p**), despite the difficulty of coupling such hindered substrates in the presence of coordinating N-heteroarenes.[6] Product **6f** was synthesized using less Pd (2-fold) and ligand (4-fold) with a significantly shorter reaction time (1 h vs 16 h) than a previous report from our group using an **L2**-supported catalyst.[6] In addition to aliphatic amines, both cyclic (**5p**) and acyclic anilines (**5d**) were coupled successfully. The mild reaction conditions also tolerated potentially problematic functional groups, including an unprotected phenol (**5a**), an acidic carbamate (**5g**), and an electrophilic nitrile (**5j**).[32]

To further demonstrate the versatility of catalyst **P9**, coupling reactions were performed on a variety of complex

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pharmaceuticals (Figure 3). While C−N cross-coupling reactions of complex substrates are frequently unsuccessful

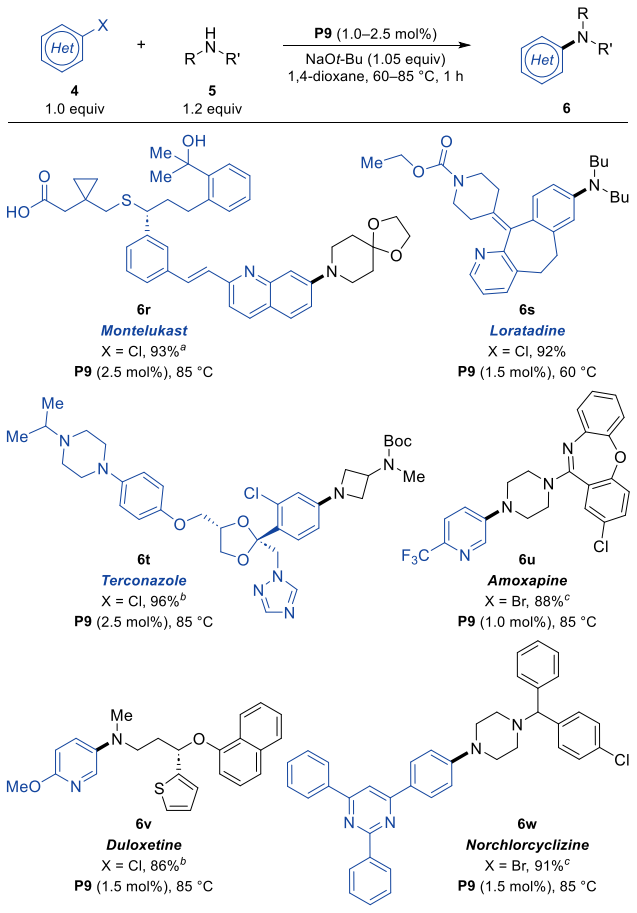

Figure 3. Isolated yields reported as the average of two runs. Reaction conditions: aryl halide (**4**, 0.5 mmol), amine (**5**, 0.6 mmol), NaO*t*-Bu (0.525 mmol), **P9** (1.0−2.5 mol %), 1,4-dioxane (0.5 mL), 60−85 °C, 1 h. Legend: [a]NaO*t*-Bu (2.05 equiv), 1,4-dioxane (1.25 mL). [b]Amine hydrochloride salt (1.2 equiv), NaO*t*-Bu (2.25 equiv), 1,4-dioxane (1.25 mL). [c]6 h.

with previously reported catalyst systems,[33] densely functionalized pharmaceuticals, including aryl chlorides (**4r−t**) and secondary amines (**5u−w**), were effectively coupled using relatively low catalyst loadings. Coordinating N-heteroarenes, including quinoline (**4r**), pyridine (**4s**, **4u−v**), 1,2,4-triazole (**4t**), and pyrimidine (**4w**), were readily accommodated. Even in complex contexts, aryl bromides **4u** and **4w** were aminated selectively in the presence of aryl chlorides. Acidic functional groups were also well-tolerated, including an unprotected alcohol and a carboxylic acid (**4r**).

In summary, we have developed a new biarylphosphine ligand, FPhos (**L9**), which supports a highly reactive and deactivation-resistant Pd catalyst capable of efficiently coupling secondary amines in the presence of coordinating N-heteroarenes. The robustness of **P9** arises from two novel structural features: (1) the preferred O-bound conformation of the FPhos-supported Pd complex resists catalyst deactivation by protecting Pd against N-heteroarene coordination, and (2) 3′,5′-disubstitution on the non-phosphorus-containing ring creates a unique steric environment around Pd, allowing for effective coupling of larger secondary amines. Together, these features enable FPhos to efficiently couple a broad scope of N-heteroarene-containing aryl halides and secondary amines, including complex pharmaceuticals. We anticipate that the potent reactivity induced by these new features will motivate further development of rationally designed catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c09667.

Experimental procedures, NMR spectral data, and computational details (PDF)

Accession Codes

CCDC 2371332 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

Any opinions, findings, conclusions, or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the NIH or NSF.

The authors declare the following competing financial interest(s): MIT has patents on ligands that are described in this manuscript, from which S.L.B. and former coworkers receive royalty payments.

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(21) See the Supporting Information for ^{1}H NMR spectroscopic analysis of **P5**−**P9**, which indicates that these oxidative addition complexes are all predominantly O-bound. The C-bound isomer was not observed by NMR or by X-ray crystallography.

(22) The FPhos (**L9**)-supported catalyst is more resistant to inhibition by coordinating N-heteroarene additives than the RuPhos (**L1**)-supported catalyst. See the Supporting Information for details.

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