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Development of an Aryl Amination Catalyst with Broad Scope Guided by Consideration of Catalyst Stability

Scott D. McCann,† Elaine C. Reichert,† Pedro Luis Arrechea, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, MA 02139

Abstract

We have developed a new dialkylbiaryl monophosphine ligand, GPhos, that supports a palladium catalyst capable of promoting carbon–nitrogen cross-coupling reactions between a variety of primary amines and aryl halides; in many cases these reactions can be carried out at room temperature. The reaction development was guided by the idea that the productivity of catalysts employing BrettPhos-like ligands is limited by their lack of stability at room temperature. Specifically, it was hypothesized that primary amine and *N*-heteroaromatic substrates can displace the phosphine ligand, leading to the formation of catalytically dormant palladium complexes that reactivate only upon heating. This notion was supported by the synthesis and kinetic study of a putative off-cycle Pd complex. Consideration of this off-cycle species, together with the identification of substrate classes that are not effectively coupled at room temperature using previous catalysts, led to the design of a new dialkylbiaryl monophosphine ligand. An O*t*-Bu substituent was added *ortho* to the dialkylphosphino group of the ligand framework to increase stability of the most active catalyst conformer. To offset the increased size of this substituent, we also removed the *para i*-Pr group of the non-phosphorous-containing ring, which allowed the catalyst to accommodate binding of even very large α-tertiary primary amine nucleophiles. Compared to previous catalysts, the GPhos-supported catalyst exhibits better reactivity both under ambient conditions and at elevated temperatures. Its use allows for the coupling of a range of amine nucleophiles, including: (1) unhindered, (2) five-membered-ring *N*-heterocycle-containing, and

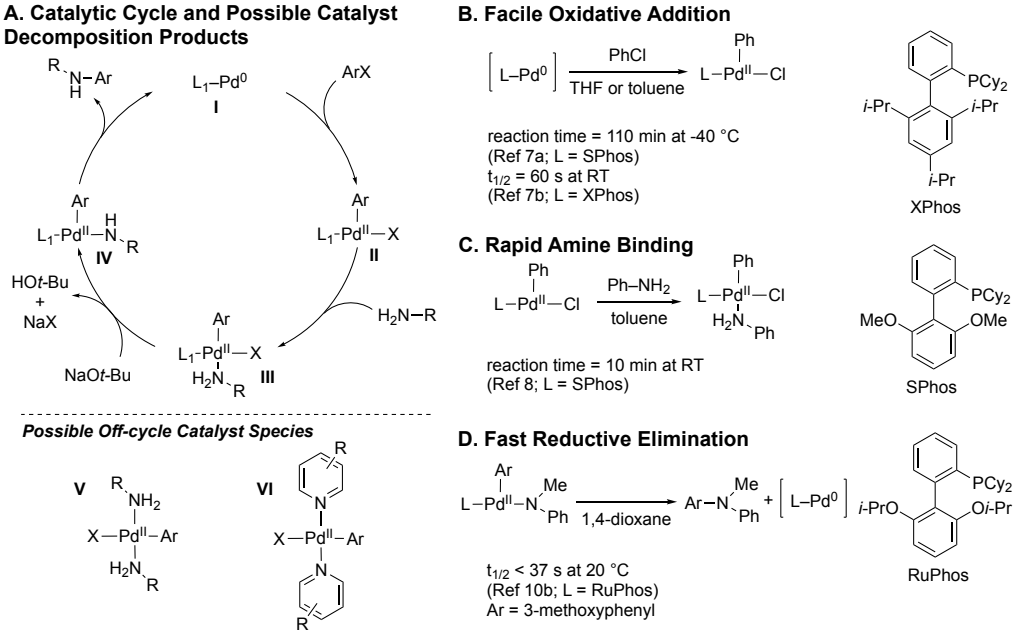
(3) α-tertiary primary amines, each of which previously required a different catalyst to achieve optimal results.

Introduction

The coupling of aryl (pseudo)halide electrophiles with amines to form carbon–nitrogen (C–N) bonds is an important transformation with applications in a variety of fields. In particular, transition-metal-catalyzed aryl amination reactions are one of the most used reaction classes in the synthesis of pharmaceutical candidates.[1,2] Palladium-based catalysts are among the most effective for catalytic aryl amination reactions.[3] We have a longstanding interest in the development of new ligands for palladium-catalyzed C–N bond-forming reactions.[4,5] Specifically, our group has created a variety of dialkylbiaryl monophosphine ligands to support Pd catalysts that are highly active for the coupling of many classes of aryl electrophiles with a broad range of amine nucleophiles.

The mechanism by which palladium catalyzes C–N cross-coupling reactions is well documented (Scheme 1A).[5,6] The elementary steps of these reactions, including oxidative addition (Scheme 1B),[7] amine binding (Scheme 1C),[8] and reductive elimination (Scheme 1D),[9,10] occur at or near ambient temperature using Pd complexes ligated by dialkylbiaryl monophosphines. However, most currently used synthetic protocols that exhibit a broad substrate scope are carried out above room temperature. Many early reports of Pd-catalyzed aryl amination reactions included examples of reactions run at room temperature, but the substrate scopes of these protocols were generally limited and included very few primary aliphatic amine nucleophiles.[5c-e, 11 - 13] By increasing the reaction temperature and developing new ligands, our group has been able to improve both the catalyst reactivity and stability.[4,14-16]

Scheme 1. Mechanistic Hypothesis and Previous Studies of Elementary Steps.



The vast majority of aryl amination reactions that proceed at room temperature use alkoxide bases,[11-13] so we chose to employ NaO*t*-Bu during our reaction development. Based on previous results from our group indicating that amines can displace dialkylbiaryl monophosphine supporting ligands,[17] we anticipated that a key challenge to facilitating a broader scope of C–N coupling reactions at room temperature would be avoiding the production of off-cycle aryl–Pd species such as **V**[18] and **VI**[19] that form through the reaction of on-cycle Pd complexes with excess primary amine or *N*-heterocycle-containing substrates, respectively (Scheme 1A). The formation of both types of Pd complexes (i.e., **V** and **VI**) likely has a negative impact on productive catalytic turnover,[20-22] and minimizing their production could enable more effective catalysis, particularly at room temperature.

Herein, mechanistic studies and ligand design informed the development of a practically useful catalyst that promotes C–N cross-coupling reactions involving a variety of aryl (pseudo)halides

and primary amine nucleophiles. The GPhos-supported catalyst can operate at room temperature in many cases, which allows for a greater tolerance of base-sensitive substrates relative to previous catalyst systems that operate above room temperature, while retaining the desirable qualities of those systems, such as low catalyst loadings and fast reaction kinetics.[23] The catalyst can accommodate sterically hindered aryl halides and amines, which were not successfully coupled by our group's recently developed Pd catalyst system that employs an amine base.[15d,15e] In addition to displaying improved stability and reactivity at room temperature, the GPhos-supported catalyst system shows high activity when heated, enabling the coupling of substrates that do not work well at room temperature. Altogether, the precatalyst based on GPhos can perform the function of catalysts based on three different ligand families: BrettPhos (unhindered primary amines),[14b,c] PhCPhos and (*t*-Bu)PhCPhos (α-tertiary amines),[15a] and EPhos (aryl halides or amines containing five-membered-ring *N*-heterocycles).[15c]

Results and Discussion

Development of New Catalysts for Room Temperature Aryl Amination Reactions

Initial testing of catalytic reactions indicated that couplings of *ortho*-substituted aryl bromide electrophiles with primary amines were especially challenging for catalysts based on BrettPhos (**L1**) and EPhos (**L2**) at room temperature[24,25] (see Supporting Information). As noted in the Introduction, we hypothesized that catalyst deactivation is a key factor in the lack of general success for Pd-catalyzed C–N coupling reactions carried out at room temperature. An alternative explanation is that the catalyst is stable, but rate of the productive C–N coupling reaction is slow at room temperature. To differentiate between these two possibilities, reaction calorimetry was used to monitor the progress of the reaction of 2-bromo-1,4-dimethylbenzene and *n*-propylamine (Figure 1A). Catalysts based on BrettPhos (**L1**) and EPhos (**L2**) are among the most active

catalysts that our group has developed for the arylation of primary amines, so the oxidative addition complex (OAC) precatalysts bearing these ligands (**OA1**, **OA2**) were tested initially.[26] In both cases, these catalysts produced small amounts of the C–N coupled product (<10%), but the catalyst activity decreased within the first 10–30 min of the reaction. Additionally, after 1 h of reaction time, free BrettPhos or EPhos was the only detectable phosphorus-containing species in the ^{31}P NMR spectrum (Figure 1B, see Supporting Information for analogous data for the reaction using **OA2**). These results are in agreement with the hypothesis that sequestration of the palladium as a non-phosphine-ligated complex is a cause of catalyst deactivation and the resulting low yields for the reactions carried out at room temperature using **OA1** and **OA2**. However, because the **OA1**- and **OA2**-derived catalysts showed activity in the first few minutes of the reactions at room temperature, we anticipated that high yields of the C–N coupled product could be achieved with a catalyst that was more stable toward deactivation under these conditions.

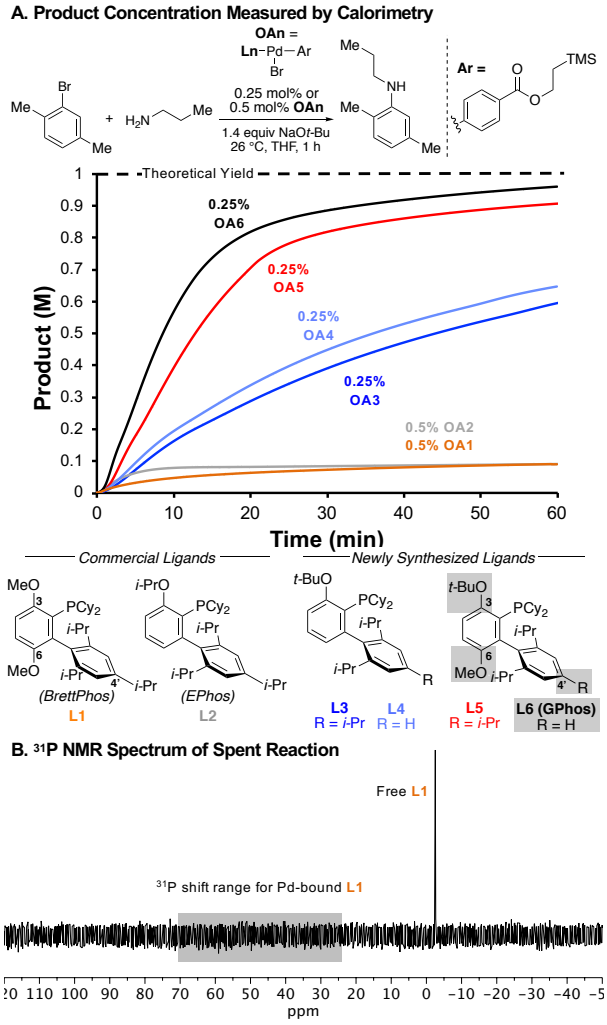


Figure 1. (A) Comparison of reaction time courses as measured by reaction calorimetry for the reaction shown with catalysts **OA1**–**OA6** (Ar = 4-(2-(trimethylsilyl)ethyl benzoate)). (B) ^{31}P NMR spectrum of the reaction employing **OA1** as the precatalyst after 1 h. Reaction conditions: 1.0 mmol 2-bromo-1,4-dimethylbenzene, 1.4 mmol *n*-propylamine, 1.4 mmol NaO*t*-Bu, 0.1 mmol *n*-dodecane (internal standard), 2.5 or 5.0 μmol **OAn** in THF (1.0 M [2-bromo-1,4-dimethylbenzene]) maintained at 26.0 °C in OmniCal calorimeter. Note: **OA1** refers to precatalyst with **L1**, **OA2** to that with **L2**, etc. Reaction GC conversions for each catalyst: **OA1** = 9%, **OA2** = 9%, **OA3** = 60%, **OA4** = 65%, **OA5** = 90%, **OA6** = 96%.

A key difference between EPhos and BrettPhos is the O*i*-Pr substituent at the 3-position in EPhos (vs. OMe in BrettPhos), which was designed to greatly favor the *C*-bound conformation of the OAC (Figure 2A).[15c] Because the *O*-bound isomer exhibits slower reductive elimination[10a] and can thus behave as an off-cycle Pd reservoir,[15c] we hypothesized that adding a larger substituent at the 3-position of the ligand framework could impart additional stability onto the resulting catalyst

by further favoring the *C*-bound isomer relative to the *O*-bound isomer. In accord with this hypothesis, changing the C3-substituent from O*i*-Pr (**OA2**) to O*t*-Bu (**OA3**, **OA4**) significantly decreased the rate of catalyst deactivation relative to the productive reaction rate, although the reaction still failed to reach full conversion within 1 h (Figure 1A). When the 6-OMe group that is present in BrettPhos, but not EPhos, was added to the ligand framework containing the O*t*-Bu substituent (**OA5**, **OA6**), the amination process was fast enough relative to catalyst deactivation to nearly reach completion within 1 h. The progression from **OA1** and **OA2** to the most active catalyst, **OA6**, shows the benefit of improving the ratio of the rate of productive reaction to that of catalyst deactivation. Consideration of catalyst stability is less often an explicit focus of aryl amination catalyst development efforts, but it appears to be an important metric in C–N cross-coupling reactions.

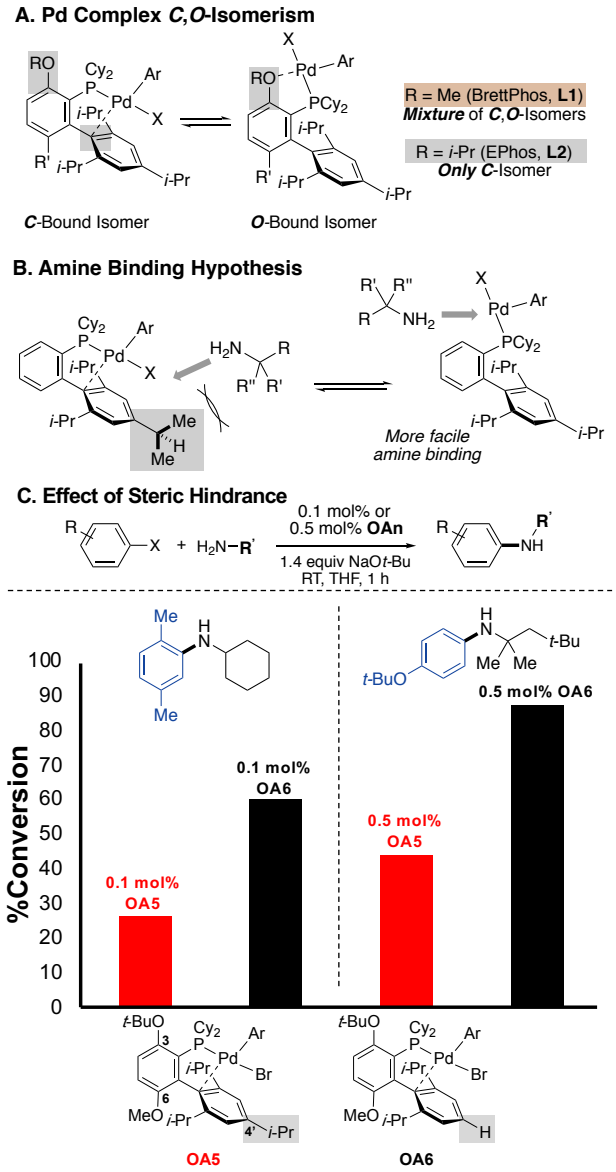


Figure 2. (A) *C*,*O*-isomerism observed in some dialkylbiaryl monophosphine-based OACs. A bulkier R group decreases the relative population of the *O*-bound isomer. (B) Amine binding mode previously proposed for XPhos-supported OAC.[27] (C) Comparison of the performance of precatalysts (**OA5**, **OA6**; Ar = 4-(2-(trimethylsilyl)ethyl benzoate)) for the coupling of α-branched primary amines. Reaction conditions: 0.4 mmol 2-bromo-1,4-dimethylbenzene or 1-(*tert*-butoxy)-4-chlorobenzene, 0.56 mmol cyclohexylamine or *tert*-octylamine, 0.56 mmol NaO*t*-Bu, 0.04 mmol *n*-dodecane (internal standard), 0.4 or 2.0 μmol **OAn** in 0.2 mL THF at RT.

We next sought to examine each catalyst's reactivity with different aryl halides and amines, with a particular emphasis on bulkier α-branched primary amines. It has previously been suggested that amine binding and/or deprotonation may occur when the Pd is positioned away from the

sterically hindered triisopropyl aryl fragment of the ligand (Figure 2B).[27] Such an amine binding mechanism is unlikely with catalysts supported by ligands **L2**–**L6**, which force their corresponding OACs (**OA2**–**OA6**) into the *C*-bound conformation. However, we hypothesized that the catalyst's activity might be increased in coupling reactions involving more hindered α-branched amines if the 4'-*i*-Pr group were removed to reduce the steric hindrance associated with the transition states for amine binding and/or deprotonation. This modification proved critical for enabling the coupling of some α-branched primary amines. For example, **OA6** is significantly more effective than **OA5** for coupling reactions involving cyclohexylamine or *tert*-octyl amine nucleophiles (Figure 2C). Overall, employing **OA6** provided the best combination of catalyst stability and substrate scope of the catalysts tested,[28] likely because it merges the most important features of ligands used in previous catalytic systems (Figure 3): a large substituent *ortho* to the dialkylphosphino group (*cf.* EPhos) to stabilize the catalyst, an electron-donating methoxy group in the 6-position (*cf.* BrettPhos) to improve the reaction rate, and a hydrogen as the 4'-substituent (*cf.* PhCPhos, (*t*-Bu)PhCPhos) to enable the binding of sterically demanding amine nucleophiles.

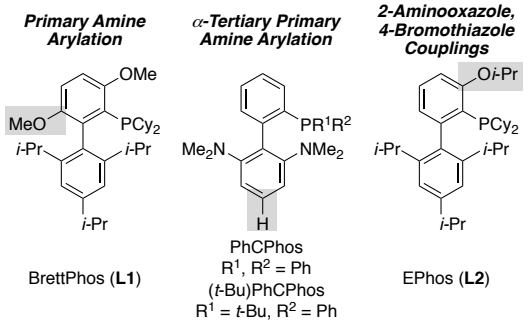


Figure 3. Common dialkylbiaryl monophosphine ligands used to support Pd catalysts for the arylation of different types of primary amine nucleophiles. Key ligand features are highlighted.

Assessment of C–N Coupling Catalysis at Higher Temperatures

Although catalysts based on BrettPhos (**L1**) often do not produce C–N coupled product in high yield at room temperature, they are effective catalysts at higher temperatures.[14b,c] To reconcile the difference in catalyst performance between reactions carried out at room temperature and those that are heated, several mechanistic experiments were performed using **L1**-based catalysts. The studies were initiated by collecting reaction time course data for a model amination reaction similar to the one used for the ligand development described above (*cf.* Figure 1). Two identical series of reactions were allowed to proceed for 1 h at room temperature, during which time they each produced approximately 20% yield of coupled product (Figure 4). Subsequently, one series of reactions was allowed to continue at room temperature for up to 24 hours. During this extended reaction period, minimal additional product was formed, consistent with the result shown in Figure 1A. The other series of reactions was heated to 90 °C after the first hour of reaction time at room temperature. In this case, a quantitative yield of product was formed after ~7 h (~6 h at 90 °C). These results, taken together with the results in Figure 1, indicate that C–N coupling promoted by the **L1**-supported OAC can occur readily at room temperature, but when the L–Pd complex deactivates and only free **L1** is observed in solution (Figure 1B), the reaction mixture must be heated to facilitate productive C–N coupling. The need for heating after dissociation of the phosphine ligand suggests that the re-entry of off-cycle species (e.g., **V**/**VI**, Scheme 1A) is an elementary step that necessitates higher reaction temperature in many catalytic protocols.

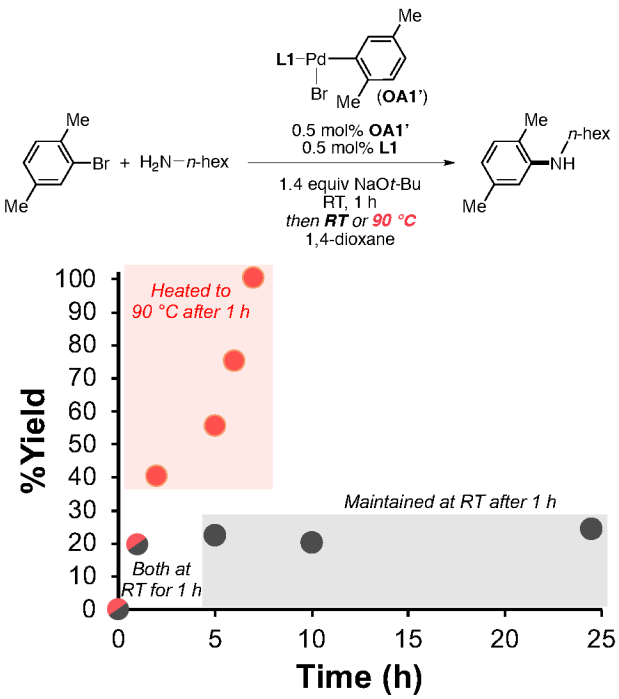


Figure 4. Assessment of unheated and heated **OA1'**-catalyzed aryl amination. Reaction conditions: 0.5 mmol 2-bromo-1,4-dimethylbenzene, 0.7 mmol *n*-hexylamine, 0.7 mmol NaO*t*-Bu, 0.05 mmol *n*-dodecane (internal standard), 2.5 µmol **OA1',** 2.5 µmol **L1** in 0.5 mL 1,4-dioxane at RT (1 h time point) followed by RT (gray box) or 90 °C (red box). Calibrated GC yields. See Supporting Information for full details.

To probe whether putative off-cycle Pd complexes similar to **V** (Scheme 1A), formed via displacement of the supporting ligand, can serve as competent catalyst precursors, complex **A** (Figure 5) was prepared.[29] When the reaction mixture containing the model coupling partners was heated to 90 °C in the presence of 0.5 mol% **A** as the Pd source and 1.0 mol% **L1** (to match the amount of catalyst and ligand used in Figure 4), a high yield of product was observed after 24 hours (Figure 5). When our new ligand, **L6**, was used in place of **L1** (in combination with **A**), the reaction was complete within 1 h at 90 °C. This result indicates that **L6** promotes a higher population of active catalyst (*cf.* **I**–**IV**, Scheme 1A) relative to **A** (*cf.* **V**, Scheme 1A) than **L1**, and/or the population of Pd that enters the productive cycle is significantly more active when supported by **L6** than with **L1**. At room temperature, the **L6**-based catalyst showed the highest

ratio for the rate of the productive reaction relative to the rate of catalyst deactivation. We suspect that the same structural features of **L6** that led to this high ratio at room temperature are also responsible for the higher reactivity of the **L6**-based catalyst relative to the **L1**-based catalyst observed at 90 °C using **A** as the catalyst precursor. Reactions with **A** and **L1** (or **L6**) that were performed at room temperature did not yield any desired product. The notion that non-phosphine-ligated off-cycle Pd species, such as **A**, may recombine with free ligand to form on-cycle catalysts when heated is consistent with the beneficial effect of added equivalents of dialkylbiaryl monophosphine ligand in many Pd-catalyzed C–N cross-coupling reactions.[4]

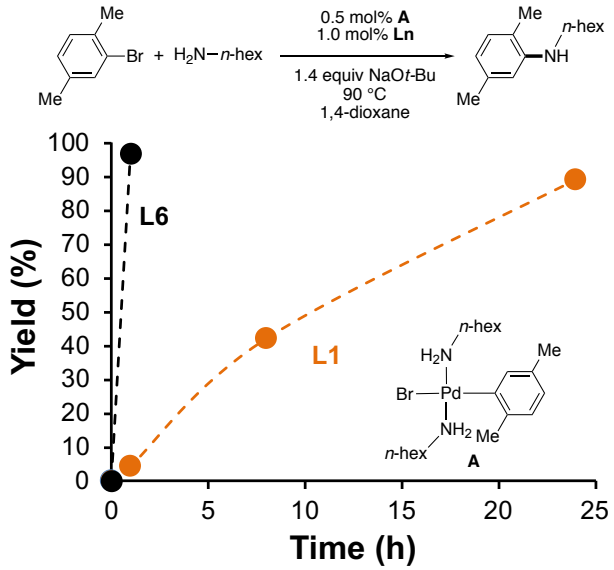


Figure 5. Reaction time course using **A** as a precatalyst. Reaction conditions: 0.5 mmol 2-bromo-1,4-dimethylbenzene, 0.7 mmol *n*-hexylamine, 0.7 mmol NaO*t*-Bu, 0.05 mmol *n*-dodecane (internal standard), 2.5 µmol **A**, 5.0 µmol **L1** or **L6** in 0.5 mL 1,4-dioxane at 90 °C. Calibrated GC yields. See Supporting Information for full details. Dashed lines are intended to guide the eye and do not reflect a kinetic fit.

Only a small amount of free **L1** was observed when excess *n*-hexylamine was stirred with **OA1'** at room temperature for 1 h, suggesting that displacement of **L1** occurs from an intermediate other than an OAC (*cf.* **II**/**III**, Scheme 1). This contrasts with previous studies in which it was

observed that the addition of excess primary amine to P(*o*-tol)$_3$- or P*t*-Bu$_3$-ligated Pd OACs (*cf.* **II**, Scheme 1) resulted in the formation of phosphine-free compounds analogous to **A**.[18] Additionally, Hartwig observed a similar bis(amine) Ni complex when a (BINAP)Ni(Ar)Cl species was treated with an excess of primary amine.[30] Although **A** catalyzed C–N bond formation in the presence of **L1** when heated (Figure 5), related bis(amine)Pd(Ar)Br and bis(amine)Ni(Ar)Cl complexes do not always catalyze aryl amination reactions. For example, the combination of P(*o*-tol)$_3$ and bis(amine)Pd(Ar)Br complexes did not form an active catalyst.[18a] Further, the aforementioned Ni-based bis(amine) complex could not promote stoichiometric C–N coupling when heated in the presence of BINAP supporting ligand.[30] These collective observations suggest that complexes such as **A** are relevant in many primary amine arylation reactions, and the facility with which they re-enter the productive catalytic cycle depends on both the metal (e.g., Pd or Ni) and the supporting ligand.

Scope of Room Temperature C–N Coupling Reactions using OA6 as the Precatalyst

The use of precatalyst **OA6**[31,32] enabled the room temperature coupling of aryl (pseudo)halides with a variety of primary aliphatic amine and aniline coupling partners with low catalyst loadings and short reaction times (typically 1 h).[24] *Ortho*-substituted aryl chlorides (**3k**, **3p**) and aryl bromides (**3a**, **3l**) were coupled efficiently, even though these are difficult classes of electrophiles for catalysts ligated with BrettPhos (**L1**) and EPhos (**L2**) when the reactions are run at room temperature (see Supporting Information). An unhindered aryl iodide (**3b**) was coupled in high yield, which is noteworthy because aryl iodide electrophiles often show reduced reaction rates relative to aryl bromides.[33] Finally, an unhindered aryl triflate was readily coupled with an aniline (**3c**). In some cases, heat release was noted in the first several minutes of the reactions,[24,25] but in only one instance was the reaction negatively affected by this exotherm: on 1.0 mmol scale, a

decreased product yield was observed for **3c** when the reaction vial was not submerged in a room temperature water bath, a modification that was not needed when the coupling was carried out on 0.2 mmol scale.[34]

Aryl halides or amines containing a free primary alcohol (**3d**, **3t**),[35] secondary amine (**3n**, **3r**), or amide (**3c**, **3o**) functional group gave high yields, and several *N*-heterocycle-containing aryl halides and amines are featured as substrates. Despite the high reactivity of the **OA6** catalyst, several chemoselective reactions were achieved. For example, methyl 4-bromobenzoate was selectively coupled in the presence of an aryl chloride (**3e**). Additionally, 4-aminopiperidine was coupled predominantly at the primary amino group (**3n**). For the reaction of aryl bromide **1e**, NaOMe was used as the base to avoid competitive transesterification.[36] Reduction of the aryl halide to the arene was not observed,[37] although a small amount of aryl methyl ether was observed when the crude reaction mixture was analyzed using ^{1}H NMR (~5%).

Procedures using **OA6** were able to efficiently couple sterically hindered primary amines under room temperature conditions, an advantage of this method relative to our group's previous work using soluble amine bases, which could not accommodate α-tertiary amines or *ortho*-substituted anilines.[15d] For example, the reaction of 2-chloropyrazine and *tert*-octylamine occurred under much milder conditions than those formerly required (**3f**).[15a,38] In addition to hindered aliphatic amines, *ortho*-substituted anilines (**3g**, **3h**, **3i**) could be coupled in high yield, though in the cases of an extremely hindered aniline (**3h**) or a hindered electron-deficient aniline (**3i**), a longer reaction time was required (24 h). Electron-deficient anilines (**3e**, **3i**, **3j**, **3k**, **3o**, **3p**, **3t**) were efficiently converted to product under the coupling conditions, including fluorinated anilines (**3i**, **3j**), which have been described as challenging nucleophiles in Pd-catalyzed coupling reactions.[39] Some of the electron-deficient anilines (**3i**, **3o**, **3p**) performed best when NaOPh was used in place of NaO*t*-Bu

as the base, perhaps because these anilines are sufficiently acidic to be deprotonated prior to binding to the Pd catalyst (*cf.* **III**, Scheme 1A) or because of their instability in the presence of strong base.[40] Several potentially base-sensitive functional groups were also accommodated,[41] including an *N*-trifluoroethylaniline (**3l**),[42] nitrile (**3p**), and several substrates containing acidic C–H bonds (**3m**, **3n**, **3o**).

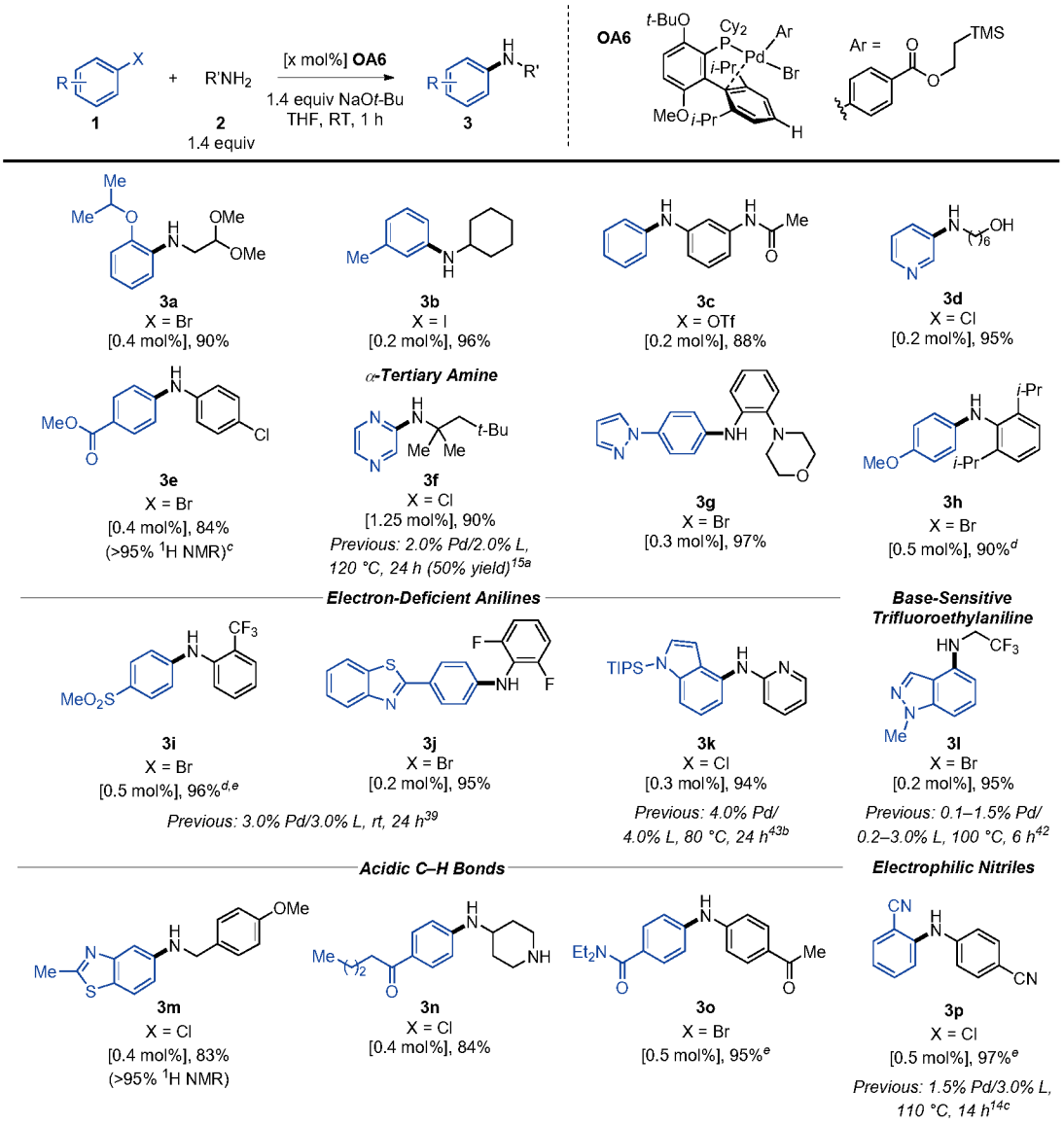


Figure 6. Substrate scope of the room temperature aryl amination protocol.[a,b]
[a]Isolated yields are reported as the average of two runs. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] **OA6**, THF (0.5 mL), RT, 1 h. [b]Previous conditions refer to previously published conditions for the same or similar coupling

reactions. Pd = Pd loading, L = total ligand loading. [c]1.4 equiv NaOMe, 45 min reaction time. [d]24 h. [e]1.4 equiv NaOPh.

In several cases, we compared our conditions to those used for similar or identical coupling reactions that were previously reported. For example, reactions involving fluorinated anilines **3i** and **3j** were formed using less catalyst (6–15-fold) and, in the case of **3j**, shorter reaction time (1 h vs. 24 h) while still operating at room temperature,[39] even though the anilines we employed are either more electron-deficient or more sterically hindered than those in the previous study. Compound **3p** was previously prepared by our group using a BrettPhos-based catalyst.[14c] Under our new conditions, we were able to simultaneously reduce the amount of catalyst (by 3-fold), temperature (RT vs. 110 °C), and reaction time (1 h vs. 14 h), highlighting the improved reactivity of **OA6**. Finally, the room temperature conditions allowed for the use of NaO*t*-Bu to prepare **3l**. Previously published conditions heated the reaction mixture to 100 °C in the presence of a weaker base, KOPh, necessitating longer reaction times (6 h), but our room temperature conditions using NaO*t*-Bu resulted in full conversion to product within 1 h, while maintaining a catalyst loading similar to that employed in the previous report.[42]

In some instances, poisoning or slowing of reactions has been observed with *N*-heterocycle-containing aryl halide or amine substrates. For example, 2-aminopyridine can function as a ligand for Pd(II). Still, **3k** was formed efficiently at room temperature in 1 h, even though similar coupling processes previously required heating (80–100 °C) with more catalyst (1.7–13-fold) for longer reaction times (24–30 h).[43] Finally, **3f** had been previously prepared using our PhCPhos-based catalyst.[15a] Now we are able to use a shorter reaction time (1 h vs. 24 h) at a lower temperature (RT vs. 120 °C), while still using less catalyst. The faster rate of C–N bond formation (i.e., shorter reaction time) and lower temperature avoid the formation of the ArO*t*-Bu side product, which was

competitively produced under the previous reaction conditions, resulting in a lower yield than that observed here (90% vs. 50%). It is possible that such a significant improvement is observed for this reaction because the large O*t*-Bu group on the ligand "protects" the catalyst from degradation by the pyrazine, while the removal of the *i*-Pr group in the ligand's 4'-position still allows for binding of the sterically demanding *tert*-octylamine nucleophile.

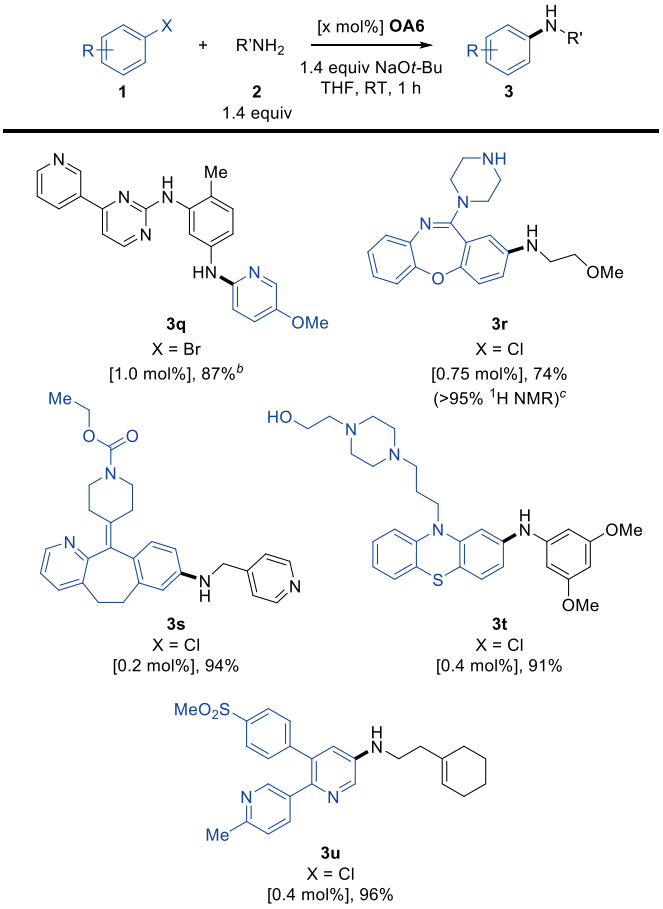


Figure 7. Scope of the room temperature aryl amination of drug-like substrates.[a]
[a]Isolated yields are reported as the average of two runs. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] **OA6**, THF (0.5 mL), RT, 1 h. [b]1.2 mmol aryl halide, 1.0 mmol amine. [c]Reaction conditions: aryl halide (0.5 mmol), amine (0.7 mmol), NaO*t*-Bu (0.7 mmol), 0.75 mol% **OA6**, THF (0.25 mL), RT, 1 h.

We next examined **OA6** in the reactions of more complex substrates under our room temperature conditions. C–N cross-coupling reactions involving pharmaceutical derivatives

possessing multiple functional groups have been shown to exhibit a high failure rate.[44] The **OA6**-based catalyst system enabled the coupling of several high-complexity molecules while generally allowing for low catalyst loadings and short reaction times. These included the arylation of a pyridine- and pyrimidine-containing aniline (**2q**), which is a fragment of the anti-Leukemia drug Gleevec, to form **3q**. Additionally, several aryl halide-containing pharmaceuticals bearing multiple functional groups, such as amoxapine (**1r**), loratadine (**1s**), perphenazine (**1t**), and etoricoxib (**1u**), were efficiently transformed to the C–N coupled product.

Scope of C–N Coupling Reactions using OA6 Catalyst with Heating

As noted in the Introduction, most broad-scope protocols for Pd-catalyzed aryl amination are carried out above room temperature. We endeavored to compare the effectiveness of **OA6** to that of previous catalysts under such conditions, and to examine whether reactions that were unsuccessful at room temperature using **OA6** would work with heating.[45] First, we examined several coupling reactions that were successful at room temperature, and that did not contain functional groups that would be problematic at 90 °C, to probe the general performance of the **OA6** catalyst when heated (Figure 8). Although these exact products (**3a**, **3d**, **3k**, **3o**) have not been previously prepared using catalysts supported by dialkylbiaryl monophosphine ligands, the amount of **OA6** used for these reactions is at or below the levels previously reported by our group for the simplest coupling reactions involving primary aliphatic amines.[14b,c]

In addition to the coupling reactions repeated from Figure 6, we evaluated reactions that were previously reported by our group with other ligands. For example, under the conditions employed for **3aa**, the amount of catalyst (decreased 10-fold) and reaction time (1 h vs. 20 h) were both substantially improved relative to those with a BrettPhos-based catalyst.[14c] Additionally, **OA6** performed much better than PhCPhos- or (*t*-Bu)PhCPhos-based catalysts for coupling reactions

involving α-tertiary primary amines,[15a] consistent with our observation at room temperature (*cf.* Figure 6, **3f**). Compounds **3bb**, **3cc**, and **3dd** were prepared using **OA6** with less catalyst (4–5-fold) and shorter reaction times (1 h vs. 6–24 h) than the previous report.[15a]

Certain reactions involving five-membered-ring *N*-heterocyclic substrates were not effective at room temperature. For example, **3ee** and **3ff** gave no yield at room temperature.[46] Despite these difficulties under room temperature conditions, at higher temperatures the GPhos-based **OA6** precatalyst enabled the coupling reactions that formed **3ee** and **3ff** with less catalyst (3–4-fold) than our group's previously reported EPhos (**L2**)-based catalyst, under otherwise identical conditions.[15c, 47] Additionally, imidazole-containing amines gave low product yields at room temperature, which could be improved in some cases upon using heated reaction conditions (see Supporting Information for details). Although these coupling reactions are quite different than the model reaction in Figure 1, we suspect that the improved reactivity of **OA6** relative to the EPhos-based catalyst for these reactions is due to the improved stability of the catalyst toward deactivation by *N*-heterocyclic substrates.

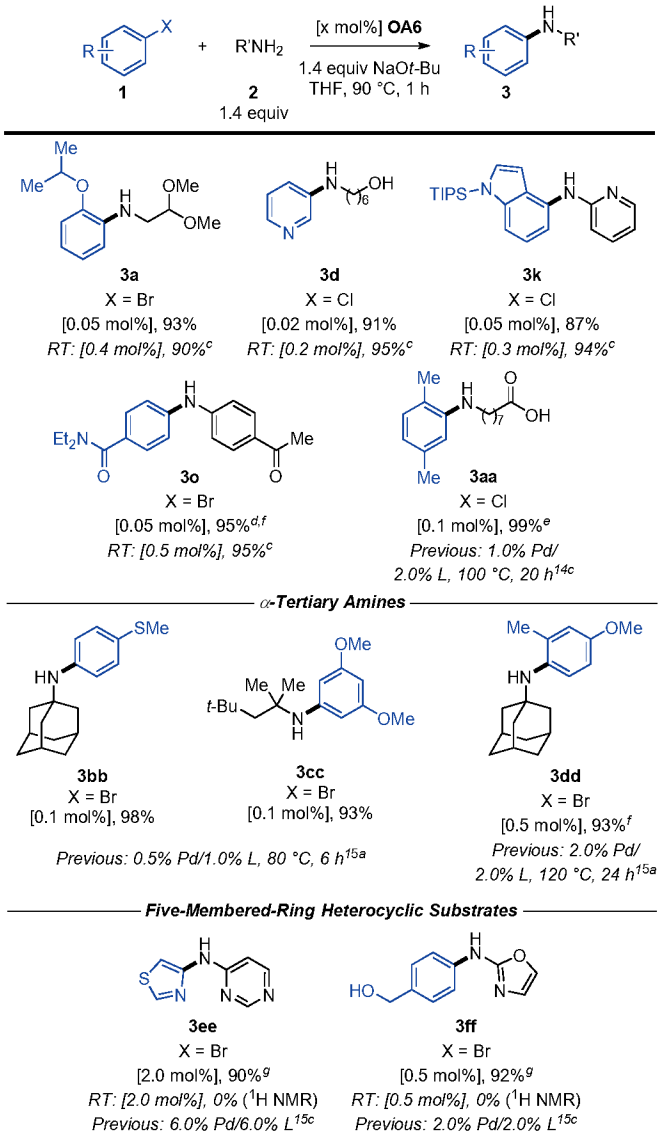
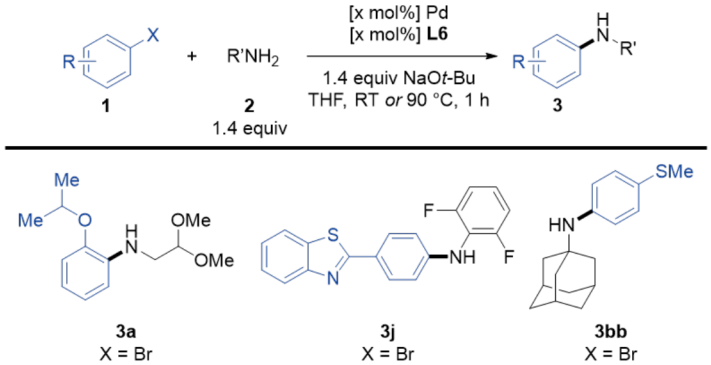


Figure 8. Scope of the aryl amination with heating[a,b]

[a]Isolated yields are reported as the average of two runs. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] **OA6**, THF (0.5 mL), 90 °C, 1 h. [b]Previous conditions refer to previously published conditions for the same or similar coupling reactions. Pd = Pd loading, L = total ligand loading. [c]RT results from Figure 6. [d]1.4 equiv NaOPh. [e]2.4 mmol NaO*t*-Bu, 2.5 mL THF. [f]75 °C. [g]Reaction conditions: aryl halide (1.0 mmol), amine (1.2 mmol), NaOPh (1.2 mmol), [x mol%] **OA6**, 2-MeTHF (4 mL), 100 °C, 3 h.

Finally, we investigated the use of several common alternative Pd sources (with free **L6**) as catalyst precursors, to compare their performance to **OA6** (Figure 9). Of these, only [Pd(cinnamyl)Cl]$_2$/**L6** formed an active catalyst at room temperature (**3a**, **3j**). This combination

performed as well as **OA6** for the reaction of 2,6-difluoroaniline to provide **3j**, but gave a lower yield for the coupling of an *ortho*-substituted bromoarene with a primary aliphatic amine (**3a**). Using Pd_2dba_3/**L6** at room temperature resulted in no yield of **3j**. The $Pd(OAc)_2$/**L6** catalyst system required heating in the presence of water to form an active catalyst,[48] which could then catalyze the formation of **3j** at room temperature, albeit with a lower yield than reactions with **OA6** or $[Pd(cinnamyl)Cl]_2$/**L6**. At 90 °C, all of the Pd sources tested were capable of producing significant amounts of **3bb**, though the $Pd(OAc)_2$-based catalyst system performed significantly better with the water activation protocol.[48] While in some cases the reaction yields using these alternative Pd sources were comparable to those obtained using **OA6**, none equaled the overall effectiveness of **OA6** as a precatalyst. From the perspective of convenience, the use of a one-component precatalyst (containing both ligand and Pd) has advantages on small scale. For larger scale reactions, a variety of Pd precursors can be used with **L6**.



Pd source	**3a** [0.4 mol%] Pd RT	**3j** [0.2 mol%] Pd RT	**3bb** [0.1 mol%] Pd 90 °C
OA6[b]	90%	95%	98%
$[Pd(cinnamyl)Cl]_2$	47%	>95%	>95%
Pd_2dba_3	-	0%	88%
$Pd(OAc)_2$[c]	-	0%	32%
$Pd(OAc)_2$[d]	-	55%	85%

Figure 9. A comparison of reactions employing OA6 and other, commonly employed, Pd sources.[a]

[a]Yields determined by ^{1}H NMR. Standard reaction conditions: aryl halide (1.0 mmol), amine (1.4 mmol), NaO*t*-Bu (1.4 mmol), [x mol%] Pd, [x mol%] **L6** (Pd:**L6** = 1:1), THF (0.5 mL), RT *or* 90

°C, 1 h. [b]Results from Figure 6 (**3a**, **3j**) and Figure 8 (**3bb**). [c]Reaction conditions: aryl halide (0.4 mmol), amine (0.56 mmol), NaO*t*-Bu (0.56 mmol), [x mol%] $Pd(OAc)_2$, [2x mol%] **L6** (Pd:**L6** = 1:2), THF (0.2 mL), RT *or* 90 °C, 1 h. [d]Pd:**L6** = 1:2. Using water preactivation protocol.[48]

Conclusions

Guided by a combination of mechanistic analysis and ligand design, we developed a new dialkylbiaryl monophosphine ligand, GPhos (**L6**), that supports a palladium catalyst capable of promoting highly efficient coupling between a variety of aryl halide and primary amine coupling partners. The **OA6** catalyst system derived from GPhos enabled room temperature C–N coupling reactions with substantially more complex substrates than had previously been reported, with high levels of efficiency, both in terms of catalyst required and reaction time. Certain coupling reactions involving five-membered-ring *N*-heterocycle-containing substrates required heating, but when heated these reactions proceeded in excellent yield. Overall, the new catalyst system promotes the coupling of a wider range of amines than our group's previously described biarylphosphine-supported systems with equal or greater efficiency. We identified and synthesized a bis(amine)Pd–aryl complex (**A**), a putative off-cycle catalyst species.[29] This complex was not capable of entering the catalytic cycle at room temperature but was found to be a competent catalyst precursor at 90 °C, which is a temperature typical of many Pd-catalyzed C–N coupling protocols. When heated with **A** as the Pd source, the GPhos-based catalyst exhibited a much faster reaction rate than the corresponding BrettPhos-based catalyst. We believe the greater efficiency of the new catalyst at room temperature compared to previously developed dialkylbiaryl monophosphine-based catalysts arises because the new catalyst exhibits an improved ratio of the rate of productive on-cycle catalytic steps relative to that of detrimental catalyst deactivation. At elevated temperatures, the increased reactivity arises from a combination of this improved ratio with accessible activation of off-cycle species back into the productive cycle.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and additional kinetic data.

AUTHOR INFORMATION

Corresponding Author

*sbuchwal@mit.edu

Author Contributions

†S.D.M. and E.C.R. contributed equally.

Notes

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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23. The cost of reactor time and labor associated with carrying out chemical reactions is of particular importance in process chemistry applications. For example, see: Zhang, T. Y. Process Chemistry: The Science, Business, Logic, and Logistics. *Chem. Rev.* **2006**, *106*, 2583–2595.

24. The reactions performed in the OmniCal calorimeter were maintained at 26.0 °C using an external cooling bath (See Supporting Information for details). All other reactions were run under ambient conditions unless otherwise noted (i.e., no heating or cooling bath unless otherwise noted). In many cases, heat evolution was noted upon initiation of the cross-coupling reactions. This phenomenon was previously noted in another C–N cross-coupling protocol that was nominally carried out at room temperature, and likely plays a role in other aryl amination reactions that are effective without heating. See reference 13b.

25. Yang, Q.; Babij, N. R.; Good, S. Potential Safety Hazards Associated with Pd-Catalyzed Cross-Coupling Reactions. *Org. Process Res. Dev.* **2019**, *23*, 2608–2626.

26. (a) The OAC precatalyst was chosen for the mechanistic studies because an analogous OAC is an on-cycle species, which removes the possibility of slow catalyst activation leading to failed reactions at room temperature (seen for sources such as $Pd(OAc)_2$), and it also minimizes the potential for the kinetics of activation to be convoluted with the kinetics of the catalytic cycle (i.e., all of the catalyst is active immediately). (b) The aryl group (Ar = 4-(2-(trimethylsilyl)ethyl benzoate)) on the OAC precatalysts was chosen so that, if necessary, the Ar–NHR byproduct of catalyst activation could be transformed to the carboxylate (upon addition of TBAF) and separated from the desired product by an aqueous wash. See reference 31a.

27. Barder, T. E.; Buchwald, S. L. Insights into Amine Binding to Biaryl Phosphine Palladium Oxidative Addition Complexes and Reductive Elimination from Biaryl Phosphine Arylpalladium Amido Complexes via Density Functional Theory. *J. Am. Chem. Soc.* **2007**, *129*, 12003–12010.

28. Precatalyst **OA6** enabled the broadest scope of coupling reactions, but **OA2**–**OA5** are effective catalysts for a subset of the coupling reactions tested (see Supporting Information Figures S1–S6).

29. It is possible that **A** is not the final catalyst deactivation product but is rather an intermediate in the catalyst deactivation pathway, particularly because Pd/amine complexes are known to form dimeric μ-amido species under basic conditions. See reference 6c and: Driver, M. S.; Hartwig, J. F. Energetics and Mechanism of Alkylamine N–H Bond Cleavage by Palladium Hydroxides: N–H Activation by Unusual Acid-Base Chemistry. *Organometallics* **1997**, *16*, 5706–5715.

30. Ge, S.; Green, R. A.; Hartwig, J. F. Controlling First-Row Catalysts: Amination of Aryl and Heteroaryl Chlorides and Bromides with Primary Aliphatic Amines Catalyzed by a BINAP-Ligated Single-Component Ni(0) Complex. *J. Am. Chem. Soc.* **2014**, *136*, 1617–1627.

31. For use of oxidative addition complexes as precatalysts in C–N, C–C, C–F, and C–S cross-coupling reactions, see: (a) Ingoglia, B. T.; Buchwald, S. L. Oxidative Addition Complexes as Precatalysts for Cross-Coupling Reactions Requiring Extremely Bulky Biarylphosphine Ligands. *Org. Lett.* **2017**, *19*, 2853–2856. (b) Chen, L.; Francis, H.; Carrow, B. P. An "On-Cycle" Precatalyst Enables Room-Temperature Polyfluoroarylation Using Sensitive Boronic Acids. *ACS Catal.* **2018**, *8*, 2989–2994. (c) Xu, J.; Liu, R. Y.; Yeung, C. S.; Buchwald, S. L. Monophosphine Ligands Promote Pd-Catalyzed C−S Cross-Coupling Reactions at Room Temperature with Soluble Bases. *ACS Catal.* **2019**, *9*, 6461–6466.

32. The G3 precatalyst based on **L6** performed slightly worse than the corresponding oxidative addition complex. See Supporting Information Figure S7 for details.

33. Fors, B. P.; Davis, N. R.; Buchwald, S. L. An Efficient Process for Pd-Catalyzed C–N Cross-Coupling Reactions of Aryl Iodides: Insight Into Controlling Factors. *J. Am. Chem. Soc.* **2009**, *131*, 5766–5768.

34. NaO*t*-Bu is known to cleave triflates at elevated temperatures. Hartwig was able to minimize triflate cleavage at high temperature with slow addition of the aryl triflate. (a) Louie, J.; Driver. M. S.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Triflates and Importance of Triflate Addition Rate. *J. Org. Chem.* **1997**, *62*, 1268–1273. (b) Wolfe, J. P.; Buchwald, S. L. Palladium-Catalyzed Amination of Aryl Triflates. *J. Org. Chem.* **1997**, *62*, 1264–1267.

35. Substrates containing secondary or tertiary benzylic alcohols underwent competitive dehydration reactions to form the corresponding styrene derivatives. See Supporting Information Figure S8.

36. Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repič, O.; Blacklock, T. J. *β*-Hydrogen-Containing Sodium Alkoxides as Suitable Bases in Palladium-Catalyzed Aminations of Aryl Halides. *J. Org. Chem.* **2000**, *65*, 2612–2614.

37. Zask, A.; Helquist, P. Palladium hydrides in organic synthesis. Reduction of aryl halides by sodium methoxide catalyzed by tetrakis(triphenylphosphine)palladium. *J. Org. Chem.* **1978**, *43*, 1619–1620.

38. For a recent nickel catalyst capable of performing the arylation of α-tertiary amines, see: Tassone, J. P.; England, E. V.; MacQueen, P. M.; Ferguson, M. J.; Stradiotto, M. PhPAd-DalPhos: Ligand-Enabled, Nickel-Catalyzed Cross-Coupling of (Hetero)aryl Electrophiles with Bulky Primary Alkylamines. *Angew. Chem., Int. Ed*. **2019**, *58*, 2485–2489.

39. Pompeo, M.; Farmer, J. L.; Froese, R. D. J.; Organ, M. G. Room-Temperature Amination of Deactivated Aniline and Aryl Halide Partners with Carbonate Base Using a Pd-PEPPSI-IPent^{Cl}- *o*-Picoline Catalyst. *Angew. Chem., Int. Ed.* **2014**, *53*, 3223–3226.

40. The **OA6** catalyst system is also compatible with carbonate bases. See Figure S8 in the Supporting Information.

41. For an example of NaO*t*-Bu reacting with a base-sensitive substrate at elevated temperature, see: Sperry, J. B.; Wiglesworth, K. E. P.; Edmonds, I.; Fiore, P.; Boyles, D. C.; Damon, D. B.; Dorow, R. L.; Chekler, E. L. P.; Langille, J.; Coe, J. W. Kiloscale Buchwald−Hartwig

Amination: Optimized Coupling of Base-Sensitive 6-Bromoisoquinoline-1-carbonitrile with (*S*)-3-Amino-2-methylpropan-1-ol. *Org. Process Res. Dev.* **2014**, *18*, 1752–1758.

42. Brusoe, A. T.; Hartwig, J. F. Palladium-Catalyzed Arylation of Fluoroalkylamines. *J. Am. Chem. Soc.* **2015**, *137*, 8460–8468.

43. (a) Sheng, Q.; Ogata, T.; Hartwig, J. F. Highly Reactive, General and Long-Lived Catalysts for Palladium-Catalyzed Amination of Heteroaryl and Aryl Chlorides, Bromides, and Iodides: Scope and Structure–Activity Relationships. *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596. (b) Khadra, A.; Mayer, S.; Organ, M. G. Pd-PEPPSI-IPent^{Cl}: A Useful Catalyst for the Coupling of 2-Aminopyridine Derivatives. *Chem.–Eur. J.* **2017**, *23*, 3206–3212.

44. (a) Kutchukian, P. S.; Dropinski, J. F.; Dykstra, K. D.; Li, B.; DiRocco, D. A.; Streckfuss, E. C.; Campeau, L.-C.; Cernak, T.; Vachal, P.; Daavies, I. W.; Krska, S. W.; Dreher, S. D. Chemistry informer libraries: a chemoinformatics enabled approach to evaluate and advance synthetic methods. *Chem. Sci.* **2016**, *7*, 2604–2613. (b) Lin, S.; Dikler, S.; Blincoe, W. D.; Ferguson, R. D.; Sheridan, R. P.; Peng, Z.; Conway, D. V.; Zawatzky, K.; Wang, H.; Cernak, T.; Davies, I. W.; DiRocco, D. A.; Sheng, H.; Welch, C. J.; Dreher, S. D. Mapping the dark space of chemical reactions with extended nanomole synthesis and MALDI-TOF MS. *Science* **2018**, *361*, eaar6236. (c) Uehling, M. R.; King, R. P.; Krska, S. W.; Cernak, T.; Buchwald, S. L. Pharmaceutical diversification via palladium oxidative addition complexes. *Science* **2019**, *363*, 405–408.

45. Heating reactions above the boiling point of the solvent may not be appropriate for reactions run on larger scales.

46. See Figure S8 in the Supporting Information for additional problematic coupling reactions.

47. For a recent nickel catalyst capable of performing the arylation of 2-aminooxazole and 2-aminothiazole, see: Clark, J. S. K.; Ferguson, M. J.; McDonald, R.; Stradiotto, M. PAd2-DalPhos Enables the Nickel-Catalyzed C-N Cross-Coupling of Primary Heteroarylamines and (Hetero)aryl Chlorides. *Angew. Chem., Int. Ed.* **2019**, *58*, 6391–6395.

48. Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. Water-Mediated Catalyst Preactivation: An Efficient Protocol for C−N Cross-Coupling Reactions. *Org. Lett.* **2008**, *10*, 3505–3508.

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