

Effect of Aryl Ligand Identity on Catalytic Performance of Trineopentylphosphine Arylpalladium Complexes in *N*-Arylation Reactions

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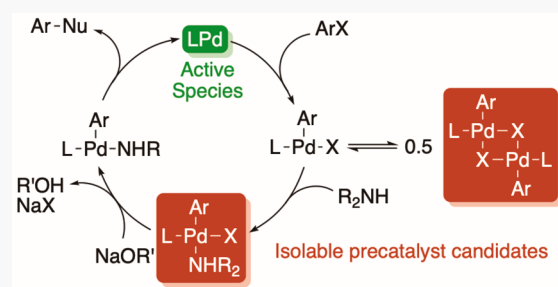
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ABSTRACT: A series of air-stable $[(\text{Np}_3\text{P})\text{Pd}(\text{Ar})\text{Br}]_2$ (Np = neopentyl) and $(\text{Np}_3\text{P})\text{Pd}(\text{Ar})(\text{amine})\text{Br}$ complexes (amine = morpholine and isobutylamine) have been prepared and tested as precatalysts for the coupling of sterically demanding aryl bromides and aniline derivatives. The complexes are more active than the catalyst generated in situ from $\text{Pd}_2(\text{dba})_3$ and PNP_3 . Increasing steric demand of the aryl group on palladium correlates with increased catalyst activity. Reactions catalyzed by $[(\text{Np}_3\text{P})\text{Pd}(2,6\text{-Me}_2\text{C}_6\text{H}_3)\text{Br}]_2$ occur efficiently at lower temperatures and with similar or higher yields than those using $\text{Pd}_2(\text{dba})_3/\text{PNP}_3$. The amine adducts give lower reaction rates and conversion to product than the $[(\text{Np}_3\text{P})\text{Pd}(\text{Ar})\text{Br}]_2$ complexes. The lower activity of the amine adducts appears to result from slow base-promoted reductive elimination to generate the catalytically active $\text{LPd}(0)$ species.



INTRODUCTION

The development of catalysts for C–C and C–heteroatom bond formation through the coupling of aryl halides with nucleophiles has received extensive attention.¹ Early work primarily focused on identifying highly effective ligands, such as trialkylphosphines,² 2-biarylphosphines,³ and *N*-heterocyclic carbenes.⁴ These ligands are typically combined with palladium sources, such as $\text{Pd}(\text{OAc})_2$ or $\text{Pd}_2(\text{dba})_3$, under the reaction conditions to generate active catalysts.

For these ligand classes, the active species is an unstable $\text{LPd}(0)$ species that is highly active toward oxidative addition.⁵ However, forming the catalyst in situ provides limited control over the formation of the active species. In addition, palladium(II) sources must undergo a two-electron reduction to generate the active species. This issue is avoided with $\text{Pd}_2(\text{dba})_3$, but the released dba ligands can act as inhibitors of the catalyst.⁶

In an effort to more efficiently generate the $\text{LPd}(0)$ active species, researchers have worked to develop palladium precatalysts that are primed to form the active species under catalytically relevant conditions.⁷ The optimal precatalyst would have the desired 1:1 L/Pd ratio, be easily prepared and air- and thermally stable, and undergo rapid conversion to the $\text{LPd}(0)$ species under catalytic conditions. Successful examples of precatalysts include $(\text{LPd})_2(\mu\text{-cod})$ (1),⁸ $[(t\text{-Bu})_3\text{P})\text{Pd}(\mu\text{-X})_2]$ (2),⁹ $(\text{allyl})\text{Pd}(\text{L})\text{X}$ (3 and 4),¹⁰ the Buchwald palladacycle precatalysts (5),¹¹ and the PEPPSI complexes (6).^{4b,12} Of these, the palladium(II) precatalysts (3–6) have been most widely used.

Each of the precatalysts in Figure 1 lies off of the catalytic cycle and must undergo one or more steps to generate the catalytically active $\text{LPd}(0)$ species. Catalyst activation can be inefficient, resulting in low activity, off-cycle species. For example, allylpalladium precatalysts (3) are prone to form inactive μ -allylpalladium(I) dimer species.¹³ Alternatively, the catalyst activation may release species that can potentially inhibit the catalyst, such as the carbazole released by the G2 and G3 Buchwald palladacycles (5).^{8a} A precatalyst that is on the catalytic cycle, or in rapid equilibrium with an on-cycle species, would potentially avoid these issues. In considering the catalytic cycle for a Buchwald–Hartwig amine arylation reaction, there are three stable species that are either on the catalytic cycle or are catalytically viable off-cycle resting states: the L_2Pd^0 species, the oxidative addition product $[(\text{LPd}(\text{Ar})\text{-X})_n]$, and the amine adduct of the oxidative addition product (Scheme 1).

The $\text{L}_2\text{Pd}(0)$ species has been extensively used, but suffers from an undesirable 2:1 L:Pd ratio, which can result in decreased catalyst activity.¹⁴ In a mechanistic study of the Pd/ PNP_3 (Np = neopentyl) catalyzed *N*-arylation reaction, we

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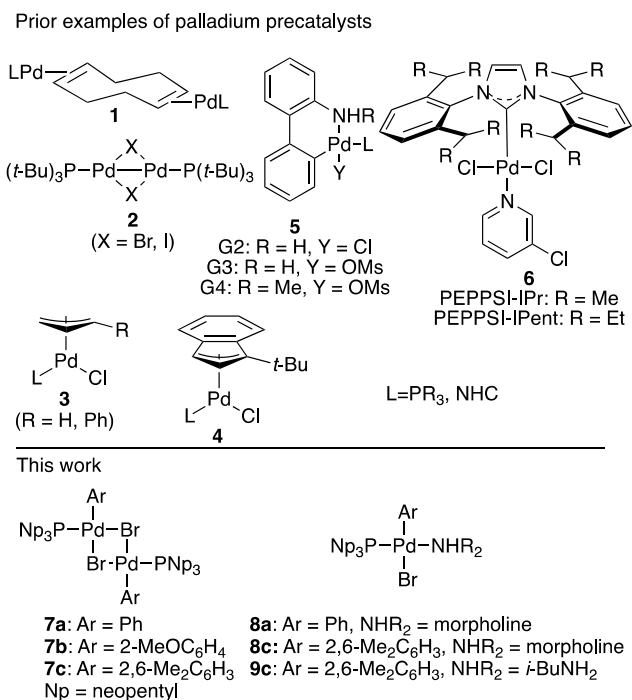
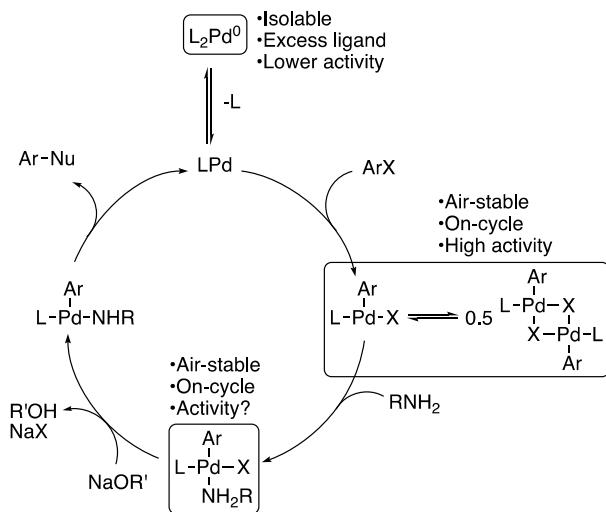


Figure 1. Examples of precatalysts that efficiently generate LPd(0) and the precatalysts studied in this work.

Scheme 1. General Mechanism for Palladium-Catalyzed *N*-Arylation Showing Potentially Isolable Complexes That Could Serve as Precatalysts



noted that palladium aryl species ($[(\text{PNP}_3)\text{Pd}(\text{Ar})\text{Br}]_2$) were dramatically more active than $\text{Pd}(\text{PNP}_3)_2$ for *N*-arylation reactions.¹⁵ Buchwald reported the use of (AlPhos) $\text{Pd}(\text{Ar})\text{X}$ (X = Br and OTf) precatalysts for the fluorination of aryl bromides.¹⁶ Since these initial reports, $[\text{LPd}(\text{Ar})\text{X}]_n$ complexes have been shown to be significantly more active than catalysts generated in situ or precatalysts 1–6 by a number of groups.¹⁷

The arylpalladium complex ($[\text{LPd}(\text{Ar})\text{X}]_n$) can be a stable 3-coordinate species ($n = 1$) or a halide bridged dimer ($n = 2$) depending on the properties of the ligand, aryl group, and halide.¹⁸ The $[\text{LPd}(\text{Ar})\text{X}]_n$ precatalyst is converted to the active LPd^0 species by reaction with the nucleophilic coupling partner followed by reductive elimination. The halide bridged

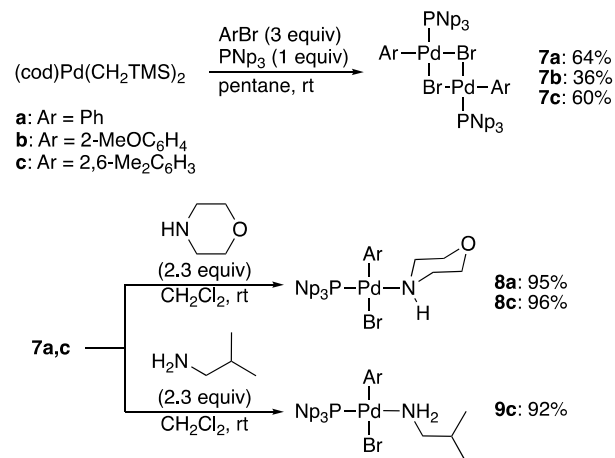
dimer is an off-cycle complex that can readily enter the catalytic cycle through equilibration with the 3-coordinate species or direct dimer cleavage by the nucleophilic reagent (Scheme 1). In the case of C–N coupling reactions, the amine coordinates to the $[\text{LPd}(\text{Ar})\text{X}]_n$ complex to give $\text{LPd}(\text{amine})(\text{Ar})\text{X}$, which is an isolable intermediate. Deprotonation of the amine adduct and reductive elimination generates the LPd^0 species. Therefore, the $\text{LPd}(\text{amine})(\text{Ar})\text{X}$ complex represents another possible stable precatalyst that could be used. The amine adduct would only need to be deprotonated and undergo reductive elimination to generate the LPd^0 active species. This is the activation pathway employed with the Buchwald palladacycle precatalysts (5).^{8a}

Coupling of hindered 2,6-di-*ortho*-substituted aryl halides with hindered amines is often challenging with commonly used ligands, such as tri-*tert*-butylphosphine or S-phos.¹⁹ Successful examples of couplings to give highly hindered diaryl amines have been achieved with *N*-heterocyclic carbene palladium complexes,²⁰ diketiminate palladium complexes,²¹ proazaphosphatane-derived catalysts,²² and iminoproazaphosphatane-phosphine/Pd systems.²³ We have previously shown that trineopentylphosphine-supported catalysts are particularly effective for the coupling of sterically demanding aryl halides.²⁴ Here we report the use of air-stable complexes $[(\text{Np}_3\text{P})\text{Pd}(\text{Ar})\text{Br}]_2$ and $(\text{Np}_3\text{P})\text{Pd}(\text{Ar})(\text{HNR}_2)\text{Br}$ (Np = neopentyl) as catalysts for the coupling of sterically demanding aryl bromides and aniline derivatives. We have explored how the aryl group on palladium affects catalyst performance and the relative activity of the $[(\text{Np}_3\text{P})\text{Pd}(\text{Ar})\text{Br}]_2$ and $(\text{Np}_3\text{P})\text{Pd}(\text{Ar})(\text{HNR}_2)\text{Br}$ complexes as catalyst sources.

RESULTS AND DISCUSSION

Oxidative addition complexes ($[(\text{Np}_3\text{P})\text{Pd}(\text{Ar})\text{Br}]_2$, 7a–c) were synthesized from $(\text{cod})\text{Pd}(\text{CH}_2\text{TMS})_2$ under conditions previously reported by our group (Scheme 2).^{15,25} Complexes

Scheme 2. Synthesis of Trineopentylphosphine Arylpalladium Complexes



7a and 7b can also be made by reacting $\text{Pd}(\text{PNP}_3)_2$ with an excess of the aryl bromide in toluene at 70 °C, but this method does not work to prepare 7c.¹⁵ Complexes 7a–c were stored in air, and no degradation was observed over the course of several months. The aryl groups were chosen to have zero (7a), one (7b), or two (7c) *ortho* substituents. Bromide-bridged dimeric complexes 7a and 7c were converted to amine adducts by

treatment with a secondary amine (morpholine) or a primary amine (isobutylamine) in methylene chloride. Amine adducts **8c** and **9c** were recently reported by us.²⁵ Complex **8a** was prepared in the same way in high yield. X-ray quality crystals of **8a** were obtained (Figure 2), which showed the structure was

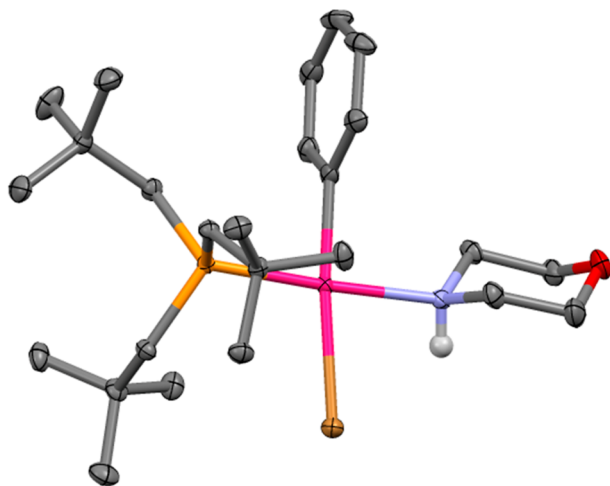
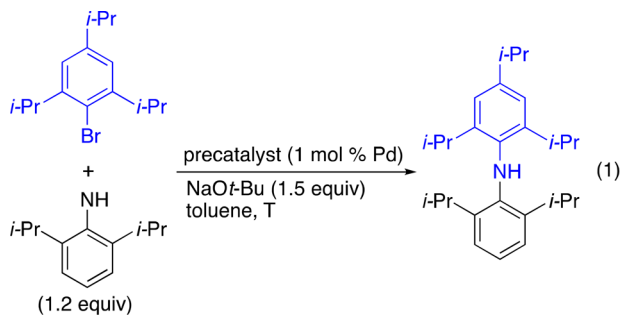


Figure 2. Thermal ellipsoid plot of **8a**. Ellipsoids are drawn at the 50% level and hydrogens with the exception of the N–H hydrogen have been omitted for clarity.

similar to that of **8c**. ¹H NMR analysis confirmed that the amine coordinated as a neutral amine in all cases, rather than as an anionic amido ligand. Complexes **8a**, **8c**, and **9c** are also air-stable solids that show no degradation when stored in ambient conditions over several months.

The effectiveness of precatalyst **7c** (0.5 mol %) was compared to the catalyst generated from Pd₂(dba)₃ (0.5 mol %) and PNP₃ (1 mol %) for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisopropylaniline at 60, 36, and 22 °C (Figure 3). At 60 °C, complex **7c** and the Pd₂(dba)₃/PNP₃



gave similar reaction profiles, but complex **7c** gave a higher conversion after 30 min (90 vs 62%). At 36 and 22 °C, the reaction catalyzed by **7c** gave a significantly higher initial rate and overall conversion to product. The reactions catalyzed by the Pd₂(dba)₃/PNP₃ system showed an induction period prior achieving maximum rate at both temperatures. We have previously observed that the displacement of dba by PNP₃ is slow at room temperature.²⁶ Therefore, the concentration of active species early in the reaction is likely much higher using **7c** than with the Pd₂(dba)₃/PNP₃ system, particularly at lower temperature. The dba ligand has also been shown to be an inhibitor in cross-coupling reactions, which leads to slower rates once the active species is formed.⁶

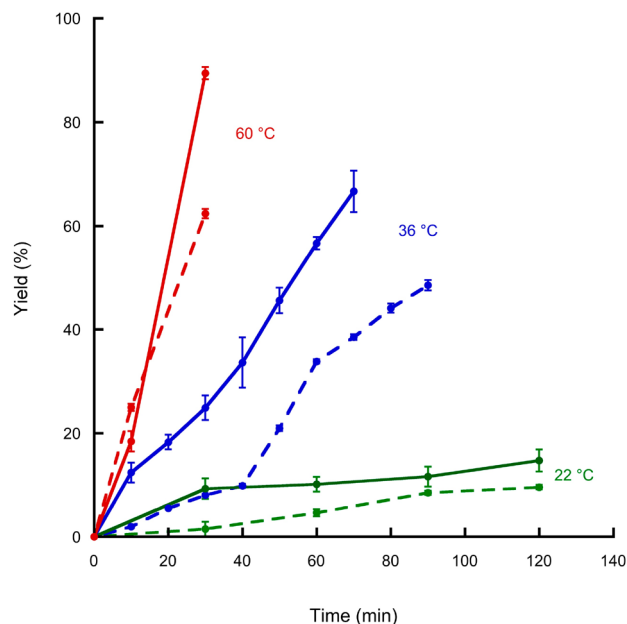


Figure 3. Reaction profiles for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisopropylaniline using precatalysts **7c** (solid line) or Pd₂(dba)₃/PNP₃ (dotted line) as a function of temperature (eq 1). Data points are the average of two independent trials.

The effect of the aryl group on palladium was then tested by comparing the reaction profiles for arylpalladium complexes **7a–c**. At 60 °C, over 90% conversion is obtained after 30 min with precatalysts **7b** and **7c** (Figure 4), with the anisole complex **7b** giving a higher yield and faster rate. In contrast, precatalyst **7a** gave only 65% conversion after 30 min. At 36 °C, the trend was similar. Complexes **7b** and **7c** gave similar reaction profiles (65% yield after 1 h), whereas conversion was

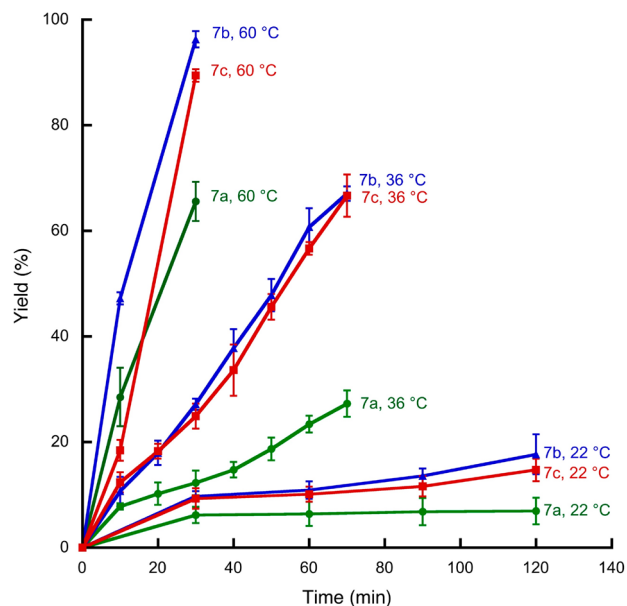


Figure 4. Reaction profiles for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisopropylaniline using precatalysts **7a–c** as a function of temperature (eq 1). Data points are the average of two independent trials.

much slower for the phenyl-substituted complex **7a**. At room temperature all three complexes gave low conversions, but again ortho-substituted complexes **7b** and **7c** gave a higher conversion than **7a**.

Amine adducts **8a,c** and **9c** were then tested under the same conditions as complexes **7a–c** (eq 1). At 60 °C, the palladium complexes with 2,6-dimethylphenyl ligands (**8c** and **9c**) gave significantly higher reaction rates than that of the phenyl complex (**8a**) (Figure 5). The isobutyl amine complex (**9c**)

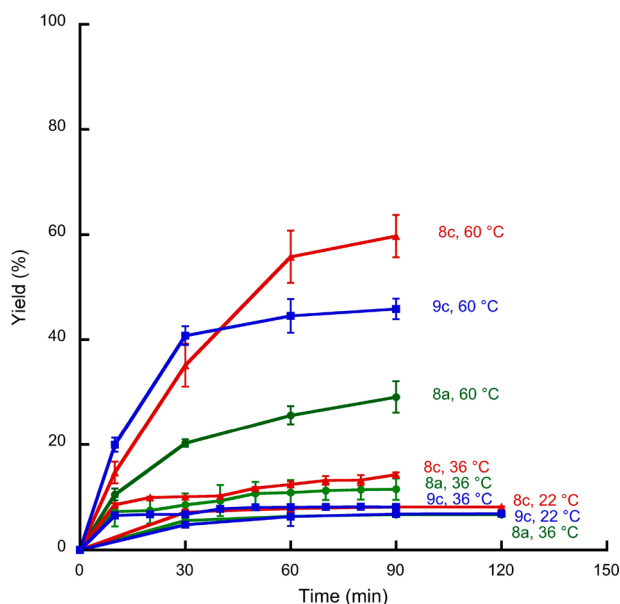


Figure 5. Reaction profiles for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisopropylaniline using precatalysts **8a,c** and **9c** as a function of temperature (eq 1). Data points are the average of two independent trials.

gave a comparable initial rate to the morpholine adduct (**8c**), but it became inactive after about 30 min at about 45% conversion. Morpholine complex **8c** retained activity during the reaction and gave a higher overall conversion (60%). Notably, the rate of conversion and yield of the amine adducts (**8a,c** and **9c**) are significantly lower than for halide-bridged dimers **7a** and **7c** (Figure 6). At 36 and 22 °C, amine adducts **8a,c** and **9c** gave low conversions with catalyst deactivation occurring rapidly.

Arylpalladium complex **7c** was applied to the coupling of a range of sterically demanding aryl bromides and amines at 40 °C (Scheme 3). Sterically demanding aryl bromides and amines are challenging substrates for most catalyst systems but are well-tolerated by the PNP_3/Pd system.²⁴ Excellent yields (93–95%) were obtained in the coupling of 2-substituted aryl bromides with 2,6-diisopropylaniline. Less hindered 3- and 4-substituted aryl bromides also gave excellent yields, with the exception of 4-bromobenzonitrile (**11g**, 36%). Nitriles are competitive ligands for palladium and often lead to low yields. Tetra-*ortho*-isopropyl-substituted product **11h** was obtained in 97% yield. In comparison, the $\text{Pd}_2(\text{dba})_3/\text{PNP}_3$ catalyst system gave a similar yield but required that the reaction be run at 80 °C.^{24a} However, 1-bromo-2,6-dimethoxybenzene gave only a 54% yield with 2,6-diisopropylaniline (**10i**). The lower yield is likely due to the increased electron density of the dimethoxyarene. Coupling of 1-bromo-2,6-dimethylbenzene with 2-substituted aniline derivatives also gave high yields

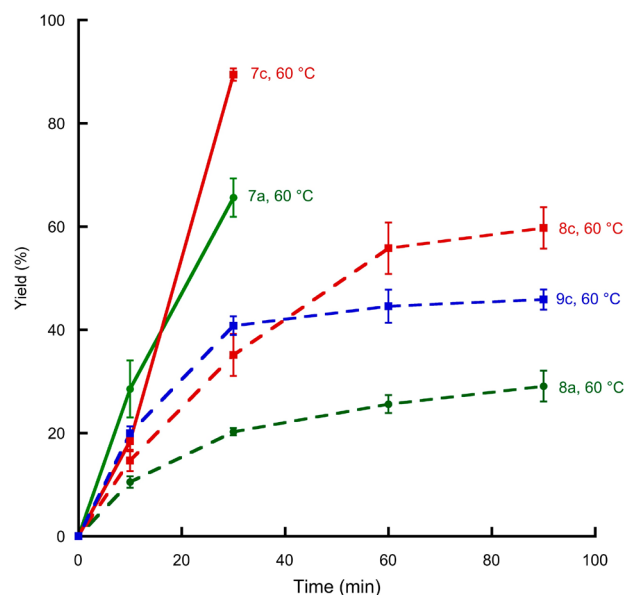


Figure 6. Comparison of aryl palladium precatalysts **7a** and **7c** and their amine adducts (**8a** and **8c**) in the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisopropylaniline (eq 1). Data points are the average of two independent trials.

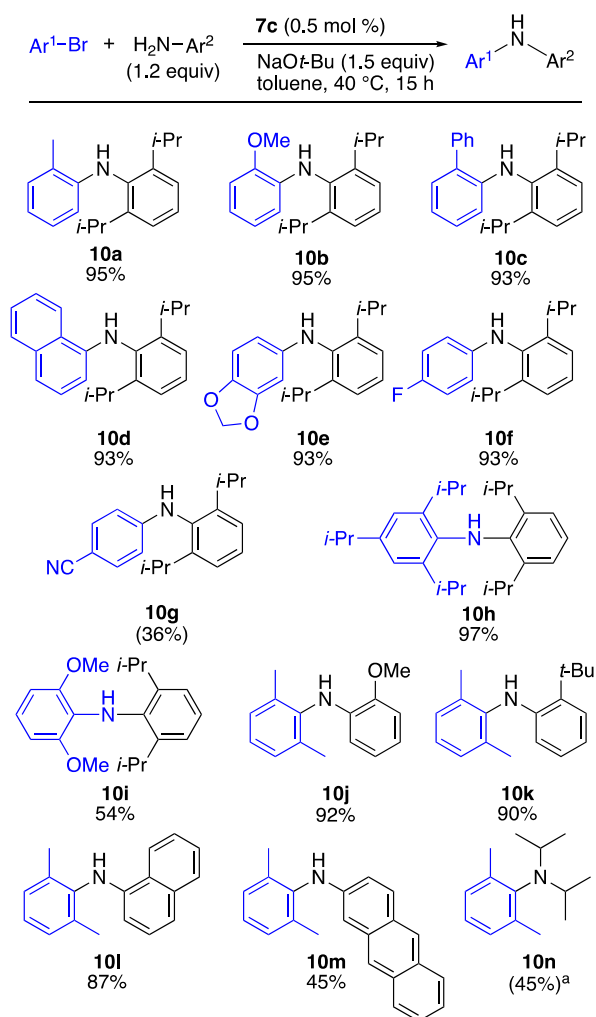
(**10j–l**). Coupling with 2-aminoanthracene gave only a 45% yield.

A modest yield of **10n** (45%) was achieved in the coupling of 1-bromo-2,6-dimethylbenzene with diisopropyl amine at 100 °C. Branched secondary amines represent a significant challenge in amine arylation reactions.²⁷ To our knowledge, this represents the first example of a palladium-catalyzed coupling of a secondary amine having α -carbon branches at both nitrogen substituents with an ortho-substituted aryl halide. The only catalytic coupling reactions to produce these types of hindered *N,N*-dialkylaniline derivatives involve the copper-catalyzed electrophilic amination of organozinc or boron reagents with *O*-benzoyl hydroxylamines.²⁸

Complex **7c** provides comparable or higher reactions yields, while using lower reaction temperatures than the catalyst derived from $\text{Pd}_2(\text{dba})_3/\text{PNP}_3$. The reactions catalyzed by **7c** were accomplished at 40 °C, compared to 80 °C for reactions using a combination of $\text{Pd}_2(\text{dba})_3$ and PNP_3 .^{24a} Precatalyst **7c** gave higher yields in many cases. For example, products **10b** and **10c** were obtained in 86 and 83% yield, respectively, using the catalyst derived in situ from $\text{Pd}_2(\text{dba})_3$ and PNP_3 . In other cases, such as **10d** and **10h**, the yields were the same under both systems, although the in situ catalyst system required higher temperatures to achieve those yields.

Catalyst Activation. Previous mechanistic studies of the Pd/PNP_3 catalyst system have shown that $[(\text{PNP}_3)_2\text{Pd}(\text{Ar})\text{Br}]$ complexes react with aniline in the presence of NaOt-Bu at 80 °C to form $\text{Pd}(\text{PNP}_3)_2$ and ArNHPh within a few minutes (Scheme 1).¹⁵ Because of the fast rate, we have not been able to obtain kinetics for the reaction of complexes **7a–c** with aniline and base. Reductive elimination of aryl bromides has been observed with sterically demanding ligands, such as $\text{P}(t\text{-Bu})_3$.²⁹ We have seen no evidence of this behavior with PNP_3 and think that is unlikely to occur under catalytic conditions.

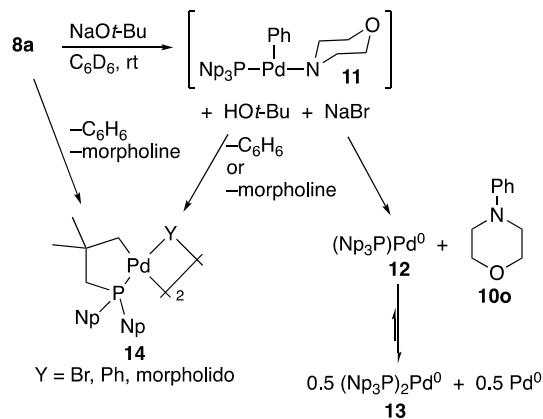
Assuming that complexes **7a–c** initiate the catalytic cycle by reaction with amine and base followed by reductive elimination to $(\text{PNP}_3)_2\text{Pd}^0$ (Scheme 1), the identity of the aryl group

Scheme 3. Coupling of Hindered Aryl Bromides and Amines Using Precatalyst **7c**^a

^aReaction performed at 100 °C. Reaction times were not optimized. Isolated yields, except for yields in parentheses, which were determined by GC analysis.

should not affect the reaction after this initial process. Therefore, differences in the effectiveness of these precatalysts are presumably due to differences in the rate and/or efficiency of generating the $(\text{PNp}_3)\text{Pd}^0$ active species. It is unclear how the identity of the aryl group on palladium affects this process. Amine coordination would be expected to be more favorable with less hindered aryl groups.²⁵ Reductive elimination from **7c** would also be expected to be slower than for **7a** or **7b** due to the increased steric demand of the 2,6-dimethylphenyl ligand.³⁰

The amine adducts would be expected to be deprotonated by base to give a palladium amido intermediate (**11**) that would undergo reductive elimination of the aryl amine to generate the active $(\text{Np}_3\text{P})\text{Pd}^0$ species (**12**, Scheme 4). In the absence of aryl halide, **12** would disproportionate to **13** and Pd^0 . A possible side reaction would be metalation of the PNp_3 ligand in **8a** with elimination of arene and dissociation of morpholine to give palladacycle **14** ($\text{Y} = \text{Br}$).¹⁵ Elimination of arene or morpholine could also potentially occur from **11** to give palladacycle **14** ($\text{Y} = \text{phenyl or morpholido}$).

Scheme 4. Base Activation of Precatalyst **8a**

The reaction of complex **8a** (17 μM) and NaOt-Bu (43 μM) at room temperature in C_6D_6 showed a single resonance at 9.1 ppm in the ^{31}P NMR spectrum after 1 min (Figure S41). This peak does not correspond with the peak for **8a** (7.8 ppm), although the ^1H NMR spectrum is similar to that of **8a** (Figure S40). Notably, the N–H proton is observed in the same place as **8a**, which would suggest the new peak is not the deprotonated amide complex (**11**). The new peak also is not palladacycle **14** (37 ppm). It is possible that the addition of NaOt-Bu results in a shift of the resonance for **8a** due to an increase in the ionic strength of the solution. Alternatively, the new peak may be due to *t*-butoxide displacing bromide in the complex. After 5 min, the peak at 9.1 ppm had partially converted to give a 20% yield of $(\text{PNp}_3)_2\text{Pd}$ (**13**) (Figure S43). Complete conversion to $\text{Pd}(\text{PNp}_3)_2$ occurred after 14 h (Figure S45). The ^1H NMR spectrum shows that the morpholine ligand was completely converted to *N*-phenyl morpholine (Figure S44). Repeating the reaction with a 10:1 ratio of NaOt-Bu (170 μM) to **8a** (10 μM) showed conversion of **8a** to $\text{Pd}(\text{PNp}_3)_2$ over the course of an hour (Figures S46–S50) along with formation of a small amount of palladacycle **14** as a byproduct.

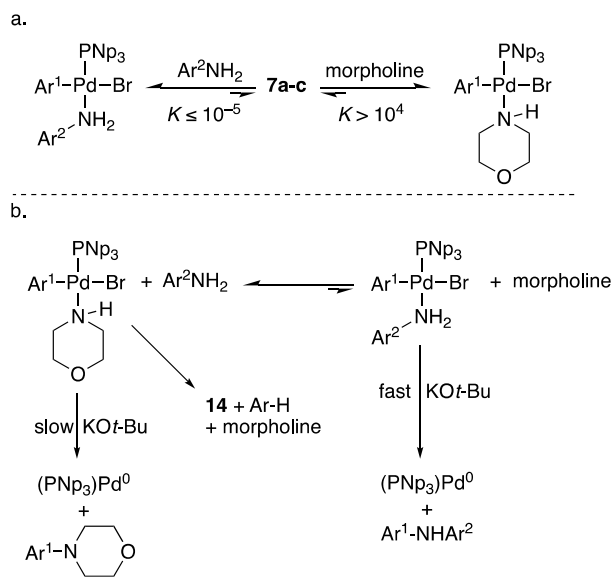
Complex **8c** (12.0 ppm) underwent a similar slow conversion to $(\text{Np}_3\text{P})_2\text{Pd}(0)$, although a number of unidentified palladium(II) species were present throughout the reaction (Figures S51–S56). After 40 min, 23% conversion to $(\text{Np}_3\text{P})_2\text{Pd}(0)$ had occurred. After 1 h, the reaction had progressed to 31% conversion. Complex **9c** (16.9 ppm) did not form $(\text{Np}_3\text{P})_2\text{Pd}(0)$ under these conditions. After 20 min, complex **9c** was completely converted to a new complex with a chemical shift of -6.7 ppm (Figure S57), but no further change occurred over the next 80 min (Figure S58). Attempts to isolate or further characterize the species at -6.7 ppm were unsuccessful.

The amine adducts (**8a,c** and **9c**) undergo base-promoted reductive elimination at rates that are slow compared to the catalytic reaction. The observed rates are much slower than those reported for other $\text{LPd}(\text{Ar})(\text{amine})\text{X}$ complexes.³¹ The reason for the slow reductive elimination is unclear, although it is consistent with the lower coupling efficiency for these complexes compared to the halide-bridged dimers (**7a–c**). However, the reactivity of the amine adducts with base does not correlate with their catalyst performance. Complexes **8c** and **9c** give conversion rates and turnover numbers higher than those of **8a**, although both are less efficient than $[(\text{PNp}_3)\text{Pd}(\text{Ar})\text{Br}]_2$ complexes **7a–c**. In contrast, complexes **8c** and **9c**

give base-promoted formation of $\text{Pd}(\text{PNP}_3)_2$ slower than does **8a**.

The reason for this apparent contradiction is unclear, but it should be noted that under the catalytic conditions the aniline substrate is present in large excess relative to the catalyst species (120 equiv). Aniline binds much more weakly to the $(\text{PNP}_3)\text{Pd}(\text{Ar})\text{Br}$ fragment than morpholine or isobutyl amine (Scheme 5a). Reaction of $[(\text{PNP}_3)\text{Pd}(\text{Ar})\text{Br}]_2$ with 20 equiv of

Scheme 5. Amine Binding Equilibria and Plausible Activation Route to Complexes 7a–c^a



^a(a) Amine binding equilibria and (b) a plausible activation route for amine adduct complexes **8a,c** and **9c**.

aniline results in no observable adduct formation ($K < 10^{-5}$).²⁵ The binding constant would be expected to be even lower for the sterically demanding aniline derivatives used in this study. In contrast, morpholine and isobutylamine react stoichiometrically with **7a–c** to give the amine adduct ($K > 10^4$). Despite the unfavorable equilibrium for displacement of an alkyl amine by aniline, the much larger concentration of aniline may allow for a small equilibrium concentration of the aniline adduct to form. Deprotonation and reductive elimination of the aniline adduct is fast,¹⁵ whereas deprotonation and reductive elimination of amine adducts **8** and **9** is slow. Therefore, displacement of the amine by aniline may be necessary to form the active species (Scheme 5b). This process may compete with formation of catalytically inactive palladacycle **14**. Further mechanistic study of this system is ongoing.

In our studies of the Pd/PNP_3 system, we observed that coupling reactions of aniline occurred with slower rates and lower conversion than when 2,6-diisopropylaniline was used as the amine nucleophile.¹⁵ We proposed that aniline promoted the conversion of the active palladium catalyst to inactive palladacycle **14** at a faster rate than the more hindered aniline substrates. Reactions catalyzed by alkylamine adducts **8a,c** and **9c** show catalyst deactivation occurring within 30–60 min. The more basic alkyl amine may facilitate palladacycle formation in competition with the formation of the $(\text{PNP}_3)\text{Pd}^0$ active species, ultimately resulting in catalyst deactivation. Further studies to understand this process are ongoing.

CONCLUSIONS

Trineopentylphosphine arylpalladium halide complexes have been shown to be effective catalysts for the coupling of sterically hindered aryl bromides and anilines. Aryl palladium complex **7c** shows an increased coupling rate compared to the catalyst generated in situ from $\text{Pd}_2(\text{dba})_3$ and PNP_3 . The coupling rate shows a positive correlation between the steric demand of the palladium-bound aryl group and the coupling rate. Mono- and di-ortho-substituted arylpalladium complexes **7b** and **7c** give higher rates and overall conversion than the phenylpalladium complex (**7a**). Amine adducts give slower reaction rates than the halide-bridge dimer precatalysts (**7a–c**). Analysis of the reaction of the amine adducts with NaOt-Bu show that the base-promoted reductive elimination is unexpectedly slow for these complexes. This result suggests that deprotonation and reductive elimination of the alkyl amine adducts occurs more slowly than the reaction of complexes **7a–c** with aniline and base to generate the $\text{LPd}(0)$ active species. Thermodynamically disfavored displacement of the amine by the aniline substrate may be required to activate the amine adducts. This work shows that the structure of the palladium-bound aryl group does have a measurable effect on catalyst performance.

EXPERIMENTAL SECTION

General Procedures and Materials. Reagents were purchased from commercial suppliers and used as received, except as noted. Toluene was refluxed over sodium for an hour and freshly distilled before use. Pentane was dried over CaH_2 , distilled, and degassed by three freeze–pump–thaw cycles prior to use. PNP_3 ,³² $(\text{cod})\text{Pd}(\text{CH}_2\text{TMS})_2$,³³ **7c**,¹⁵ **8c**,²⁵ and **9c**²⁵ were prepared following reported methods. Reactions were conducted under nitrogen using double-manifold inert-atmosphere techniques, unless noted otherwise. All the GC samples were measured using a Shimadzu GC-2014 Gas Chromatograph using a 10 °C/min increasing rate from 150 to 250 °C. NMR spectra were obtained on a Bruker 500 MHz spectrometer. ³¹P NMR spectra were acquired under gated decoupling mode at fixed scans through the length of experiment with the aid of an automated data collection program.

$[(\text{PNP}_3)\text{Pd}(\text{C}_6\text{H}_5)\text{Br}]_2$ (7a**).** The target complex was prepared according to the reported synthesis of **7c**.¹⁵ Trineopentylphosphine (120 mg, 0.492 mmol) and bromobenzene (153.9 μL , 1.476 mmol) were combined in 12 mL of pentane in a two neck flask under N_2 protection. Freshly made $(\text{cod})\text{Pd}(\text{CH}_2\text{TMS})_2$ (190 mg, 0.488 mmol) was added under N_2 counter flow. The reagent mixture was stirred at 22 °C for 14 h. The resulting mixture was concentrated to about 1 mL. The gray solids were filtered and washed with pentane. The gray solids were collected and dissolved in 5 mL of methylene chloride and filtered through Celite. The filtrate was collected, and the volatiles were removed to provide an air-stable white solid (160 mg, 64%). ¹H NMR (500 MHz, C_6D_6 , 295 K): δ 7.72 (br, 2H), 7.06 (br, 2H), 6.91 (br, 1H), 1.72 (d, $J = 10.5$ Hz, 6H), 1.22 (brs, 27H). ¹³C NMR (125 MHz, C_6D_6 , 295 K): δ 152.9, 135.8, 123.4, 108.0, 40.2 (d, $J_{\text{C-P}} = 20$ Hz), 33.5, 32.6. ³¹P{¹H} NMR (202.5 MHz, C_6D_6 , 295 K): δ 7.9. Elemental analysis: calcd for $\text{C}_{42}\text{H}_{76}\text{Br}_2\text{P}_2$: C, 49.67; H, 7.54; N, 0. Found: C, 50.56; H, 7.72; N, 0.0.

$[(\text{PNP}_3)\text{Pd}(2\text{-MeOC}_6\text{H}_4)\text{Br}]_2$ (7b**).** Trineopentylphosphine (100 mg, 0.410 mmol), 2-bromoanisole (160 μL , 1.285 mmol), $(\text{cod})\text{Pd}(\text{CH}_2\text{TMS})_2$ (160 mg, 0.411 mmol), and pentane were reacted by the same method as **7a** to give an air-stable yellow solid (80 mg, 36%). ¹H NMR (500 MHz, C_6D_6 , 295 K): δ 7.79 (br, 1H), 6.99 (m, 1H), 6.89 (m, 1H), 6.49 (d, $J = 8.2$ Hz, 1H), 3.98 (s, 3H), 1.76 (brs, 6H), 1.29 (br, 27H). ¹³C NMR (125 MHz, C_6D_6 , 295 K): δ 162.1 (d, $J_{\text{C-P}} = 12.5$ Hz), 141.4, 138.2 (d, $J_{\text{C-P}} = 13.8$ Hz), 126.0, 122.4 (d, $J_{\text{C-P}} = 3.75$ Hz), 112.4 (d, $J_{\text{C-P}} = 25$ Hz), 56.5 (d, $J_{\text{C-P}} = 11.3$ Hz), 41.3 (brs), 34.7, 34.0. ³¹P{¹H} NMR (202.5 MHz, C_6D_6 , 295 K): δ 11.21,

11.17, 9.75, 9.69 (stereoisomeric mixture: 1:1:0.2:0.2). Elemental analysis: calcd for $C_{44}H_{80}Br_2O_2P_2Pd_2$: C, 49.13; H, 7.50; N, 0. Found: C, 48.93; H, 7.53; N, 0.0.

(PNP)₃Pd(morpholine)(Ph)Br (8a). The target compound was prepared according to the reported synthesis of **8c**.²⁵ [(PNP)₃Pd-(C₆H₅)Br]₂ (**7a**, 67.6 mg, 0.067 mmol) was dissolved in methylene chloride (8 mL) under nitrogen. Morpholine (13.0 μ L, 0.150 mmol) was added into the solution. After stirring for 1 h, the volatiles were removed to provide an air-stable white solid (75 mg, 95%) that was analytically pure. ¹H NMR (500 MHz, C₆D₆, 295 K): δ 7.56 (d, J = 8.8 Hz, 2 H), 7.07 (t, J = 7.4 Hz, 2 H), 6.98 (t, J = 7.2 Hz, 1 H), 3.53 (brs, 1 H), 3.11 (d, J = 11.3 Hz, 2 H), 2.60 (m, 6 H), 1.99 (d, J = 9.9 Hz, 6 H), 1.30 (s, 27 H). ¹³C NMR (125 MHz, C₆D₆, 295 K): δ 158.0, 135.2, 123.8, 67.7, 48.7, 40.5 (d, J_{C-P} = 23.8 Hz), 33.6, 32.8. ³¹P{¹H} NMR (202.5 MHz, C₆D₆, 295 K): δ 7.8. Elemental analysis: calcd for C₂₅H₄₇BrNOPPd: C, 50.47; H, 7.96; N, 2.35. Found: C, 50.57; H, 7.96; N, 2.33.

Crystallographic Structure Determination of 8a. A suitable crystal of **8a** was selected and mounted on a Mitgen cryoloop in a random orientation on a XtaLAB Synergy R, DW system, HyPix diffractometer. The crystal was kept at 101(2) K during data collection. Using Olex2,³⁴ the structure was solved with the ShelXT³⁵ structure solution program using Intrinsic Phasing and refined with ShelXL³⁶ refinement package using Least Squares minimization using either Olex2³⁴ or ShelXle³⁷ or both.

General Procedure for Buchwald–Hartwig Amination. The palladium precatalyst (0.5 mol %) was measured into a 5 mL screw-capped vial in air. The vial with a stirring bar was placed into a nitrogen-filled glovebox. NaOt-Bu (1.5 equiv) was added to the vial. The vial was sealed with a Teflon septum and taken out of the glovebox. The aryl halide (1 mmol), arylamine (1.2 equiv), and 4 mL of toluene were added, and the reaction was placed in an oil bath preheated to 40 °C. After the reaction had reached completion as judged by GC; the reaction mixture was dissolved in ethyl acetate and filtered through a plug of silica gel. After drying, the crude reaction mixture was purified by flash chromatography on silica gel (0.5–10% EtOAc/hexane) to obtain pure product.

N-(2-Tolyl)-2,6-diisopropylaniline (10a).³⁸ Using the general procedure, 2-bromotoluene (120 μ L, 1.00 mmol) and 2,6-diisopropylaniline (226 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as brown oil (254 mg, 95%). ¹H NMR (500 MHz, CD₃CN): δ 7.26 (m, 3H), 7.09 (d, J = 7.0 Hz, 1H), 6.87 (t, J = 7.4 Hz, 1H), 6.57 (t, J = 7.1 Hz, 1H), 5.93 (d, J = 8.0 Hz, 1H), 5.46 (s, 1H), 3.10 (sept, J = 3.10 Hz, 2H), 2.30 (s, 3H), 1.16 (dd, J = 35.5, 6.5 Hz, 12H). ¹³C NMR (125 MHz, CD₃CN): δ 148.8, 147.5, 136.8, 131.1, 128.2, 127.6, 124.7, 122.4, 118.3, 111.6, 29.0, 24.7, 23.4, 18.0. HRMS: m/z calcd for C₂₄H₂₇N (M⁺) 267.1987. Found 267.1984.

N-(2-Methoxyphenyl)-2,6-diisopropylaniline (10b).^{19a} Using the general procedure, 2-bromoanisole (125 μ L, 1.00 mmol) and 2,6-diisopropylaniline (226 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a clear, colorless oil (269 mg, 95%). ¹H NMR (500 MHz, CDCl₃): δ 7.42–7.45 (m, 1H), 7.37–7.38 (m, 2H), 6.99 (dd, J = 7.6, 1.1 Hz, 1H), 6.80–6.89 (m, 2H), 6.29 (dd, J = 7.6, 1.6 Hz, 1H), 5.80 (s, 1H), 4.75 (s, 3H), 3.34 (sept, J = 6.8 Hz, 2H), 1.30 (d, J = 6.9 Hz, 12H). ¹³C NMR (125 MHz, CDCl₃): δ 147.8, 146.2, 138.1, 135.6, 127.3, 123.9, 121.3, 117.0, 111.2, 110.0, 55.8, 28.4, 24.1. HRMS: m/z calcd for C₁₉H₂₅NO (M⁺) 283.1936. Found 283.1940.

N-(2,6-Diisopropylphenyl)-[1,1'-biphenyl]-2-amine (10c).^{24a} Using the general procedure, 2-bromobiphenyl (172 μ L, 1.00 mmol) and 2,6-diisopropylaniline (226 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a white solid (234.5 mg, 93%). ¹H NMR (500 MHz, CDCl₃): δ 7.75 (d, J = 7.4 Hz, 2H), 7.65 (t, J = 7.6 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.42–7.45 (m, 1H), 7.33–7.38 (m, 3H), 7.23 (dt, J = 7.8, 1.0 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 5.42 (s, 1H), 3.63 (sept, J = 6.6 Hz, 2H), 1.34 (d, J = 6.9 Hz, 6H), 1.25 (d, J = 6.8 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 147.6, 145.0, 139.7, 135.7, 130.3, 129.5, 129.2,

128.7, 127.6, 127.4, 127.2, 124.0, 117.6, 111.6, 28.6, 24.7, 23.1. HRMS: m/z calcd for C₂₄H₂₇N (M⁺) 329.2144. Found 329.2147.

N-(2,6-Diisopropylphenyl)naphthalen-1-amine (10d).^{24a} Using the general procedure, 1-bromonaphthalene (207 mg, 1.00 mmol) and 2,6-diisopropylaniline (226 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a white solid (282 mg, 93%). ¹H NMR (500 MHz, CDCl₃): δ 8.22–8.24 (m, 1H), 8.00–8.01 (m, 1H), 7.64–7.68 (m, 2H), 7.48–7.51 (m, 1H), 7.42–7.44 (m, 3H), 7.35 (t, J = 7.8 Hz, 1H), 6.37 (d, J = 7.5 Hz, 1H), 5.90 (s, 1H), 3.34 (sept, J = 6.8 Hz, 2H), 1.36 (d, J = 6.9 Hz, 6H), 1.27 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 147.2, 143.6, 135.8, 134.7, 129.0, 127.4, 126.8, 126.0, 125.2, 124.2, 123.5, 120.2, 118.3, 107.2, 28.4, 25.0, 23.4. HRMS: m/z calcd for C₂₂H₂₅N (M⁺) 303.1987. Found 303.1982.

N-(2,6-Diisopropylphenyl)benzo[d][1,3]dioxol-5-amine (10e). Using the general procedure, 1-bromo-3,4-(methylenedioxy)benzene (120.4 μ L, 1.00 mmol) and 2,6-diisopropylaniline (226.3 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a light yellow solid (276.3 mg, 93%). ¹H NMR (500 MHz, CD₃CN): δ 7.23 (m, 3H), 6.59 (d, J = 8.1 Hz, 1H), 6.10 (d, J = 5 Hz, 1H), 5.80 (s, 2H), 5.78 (d, J = 5.8 Hz, 1H), 5.75 (s, 1H), 3.17 (m, 2H), 1.12 (d, J = 6.5 Hz, 12H). ¹³C NMR (125 MHz, CD₃CN): δ 149.4, 148.7, 145.7, 140.2, 137.0, 128.1, 124.8, 118.3, 109.4, 104.9, 101.6, 96.3, 28.9, 24.1. HRMS: m/z calcd for C₁₉H₂₃NO₂ (M⁺) 297.1729. Found 297.1725.

N-(4-Fluorophenyl)-2,6-diisopropylaniline (10f). Using the general procedure, 1-bromo-4-fluorobenzene (109.9 μ L, 1.00 mmol) and 2,6-diisopropylaniline (226 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a red brown oil (251.3 mg, 93%). ¹H NMR (500 MHz, CD₃CN): δ 7.24 (m, 3H), 6.87 (t, J = 8.6 Hz, 2H), 6.39 (m, 2H), 5.89 (s, 1H), 3.15 (d, J = 6.9 Hz, 2H), 1.11 (d, J = 6.7 Hz, 12H). ¹³C NMR (125 MHz, CD₃CN): δ 157.3, 148.8, 146.4, 136.6, 128.3, 124.8, 116.4 (d, J_{C-F} = 22.5 Hz), 114.21 (d, J_{C-F} = 7.5 Hz), 29.0, 24.0. HRMS: m/z calcd for C₁₈H₂₂FN (M⁺) 271.1736. Found 271.1733.

N-(2,6-Diisopropylphenyl)-2,4,6-triisopropylaniline (10h).³⁹ Using the general procedure, 1-bromo-2,4,6-triisopropylbenzene (253 μ L, 1.00 mmol) and 2,6-diisopropylaniline (226 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as clear, colorless crystals (341 mg, 97%). ¹H NMR (500 MHz, CDCl₃): δ 7.27 (d, J = 7.6 Hz, 2H), 7.15–7.18 (m, 3H), 4.99 (s, 1H), 3.24–3.38 (m, 4H), 3.07 (sept, J = 6.7 Hz, 1H), 1.45 (dd, J = 6.9, 0.8 Hz, 6H), 1.45 (d, J = 7.1 Hz, 12H), 1.39 (d, J = 7.1 Hz, 12H). ¹³C NMR (125 MHz, CDCl₃): δ 143.8, 141.9, 141.2, 140.1, 138.3, 124.0, 122.3, 121.8, 34.2, 28.1, 27.9, 24.5, 23.9, 23.8. HRMS: m/z calcd for C₂₄H₂₇N (M⁺) 379.3239. Found 379.3241.

N-(2,6-Diisopropylphenyl)-2,6-dimethoxyaniline (10i). Using the general procedure, 1,3-dimethoxy-2-bromobenzene (217.06 mg, 1.00 mmol) and 2,6-diisopropylaniline (226.3 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a brown oil (168.4 mg, 54%). ¹H NMR (500 MHz, CD₃CN): δ 7.15 (m, 1H), 7.10 (d, J = 7.9 Hz, 2H), 6.68 (m, 1H), 6.58 (d, J = 8.3 Hz, 2H), 5.54 (s, 1H), 3.56 (s, 6H), 3.33 (sept, J = 6.8 Hz, 2H), 1.09 (d, J = 6.9 Hz, 12H). ¹³C NMR (125 MHz, CD₃CN): δ 149.4, 148.0, 140.6, 129.2, 128.9, 126.7, 123.3, 118.3, 107.0, 56.8, 28.9, 23.8. HRMS: m/z calcd for C₂₀H₂₇NO₂ (M⁺) 313.2042. Found 313.2038.

N-(2-Methoxyphenyl)-2,6-dimethylaniline (10j).⁴⁰ Using the general procedure, 2-bromo-*m*-xylene (133 μ L, 1.00 mmol) and *o*-anisidine (135 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a white solid (209.1 mg, 92%). ¹H NMR (500 MHz, CDCl₃): δ 7.22–7.23 (m, 2H), 7.16–7.19 (m, 1H), 6.96 (dd, J = 7.4, 1.8 Hz, 1H), 6.80–6.85 (m, 2H), 6.25 (dd, J = 7.5, 2.1 Hz, 1H), 5.76 (s, 1H), 4.03 (s, 3H), 2.32 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 146.9, 138.6, 136.3, 136.2, 128.6, 125.9, 121.3, 117.4, 111.2, 110.0, 55.8, 18.4. HRMS: m/z calcd for C₁₅H₁₇NO (M⁺) 227.1310. Found 227.1307.

N-(2-tert-Butylphenyl)-2,6-dimethylaniline (10k).^{24a} Using the general procedure, 2-bromo-*m*-xylene (133 μ L, 1.00 mmol) and 2-*tert*-butylaniline (187 μ L, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a white solid (228 mg, 90%). ¹H

NMR (500 MHz, CDCl₃): δ 7.49 (dd, J = 7.8, 1.4 Hz, 1H), 7.27–7.29 (m, 2H), 7.20–7.23 (m, 1H), 7.09–7.12 (m, 1H), 6.91 (dt, J = 8.2, 1.1 Hz, 1H), 6.39 (dd, J = 8.0, 1.1 Hz, 1H), 5.49 (s, 1H), 2.34 (s, 6H), 1.72 (s, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 144.1, 139.2, 135.3, 134.2, 128.8, 127.1, 126.6, 125.4, 118.7, 114.0, 34.7, 30.1, 18.8. HRMS: m/z calcd for C₁₈H₂₃N (M⁺) 253.1830. Found 253.1837.

N-(2,6-Dimethylphenyl)naphthalen-1-amine (10l).⁴¹ Using the general procedure, 2-bromo-*m*-xylene (133 μ L, 1.00 mmol) and 1-naphthylamine (172 mg, 1.20 mmol) were coupled using 0.5 mol % 7c at 40 °C to give the product as a white solid (215 mg, 87%). ¹H NMR (500 MHz, CDCl₃): δ 8.20–8.22 (m, 1H), 8.00–8.01 (m, 1H), 7.64–7.68 (m, 2H), 7.47 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.33–7.35 (m, 2H), 7.27–7.30 (m, 1H), 6.43 (d, J = 7.5 Hz, 1H), 5.84 (s, 1H), 2.37 (s, 6H). ¹³C NMR (125 MHz, CDCl₃): δ 141.4, 138.9, 135.4, 134.8, 128.9, 128.8, 126.7, 126.0, 125.7, 125.2, 124.2, 120.5, 119.0, 107.4, 18.3. HRMS: m/z calcd for C₁₈H₁₇N (M⁺) 247.1361. Found 247.1360.

N-(2,6-Dimethylphenyl)anthracen-2-amine (10m). Using the general procedure, 2-bromo-*m*-xylene (133 μ L, 1.00 mmol) and 2-aminoanthracene (232 mg, 1.20 mmol) were coupled using 0.5 mol % 7c at 40 °C to give the product as an earth gray powder (134 mg, 45%). ¹H NMR (500 MHz, CD₃CN): δ 8.30 (s, 1H), 7.96 (s, 1H), 7.91 (t, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.35 (dt, J = 14.7, 6.9 Hz, 2H), 7.19 (m, 4H), 6.42 (s, 1H), 6.32 (s, 1H), 2.23 (s, 6H). ¹³C NMR (126 MHz, CD₃CN): δ 145.1, 139.1, 137.2, 134.60, 133.3, 130.5, 130.4, 129.5, 129.1, 128.6, 128.2, 127.19, 127.0, 126.4, 124.6, 123.2, 121.0, 103.0, 18.4. HRMS: m/z calcd for C₂₂H₁₉N (M⁺) 297.1517. Found 297.1514.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.organomet.0c00140>.

NMR spectra of isolated compounds, NMR spectra from catalyst activation studies (PDF)

Accession Codes

CCDC 1983639 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

The authors declare no competing financial interest.

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