ORGANOMETALLICS

pubs.acs.org/Organometallics Article

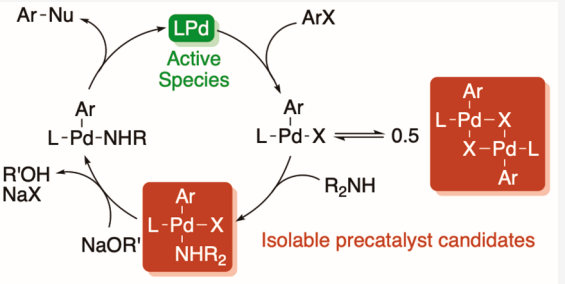
Effect of Aryl Ligand Identity on Catalytic Performance of Trineopentylphosphine Arylpalladium Complexes in *N*-Arylation Reactions

Huaiyuan Hu, Corrie E. Burlas, Sabrina J. Curley, Tomasz Gruchala, Fengrui Qu, and Kevin H. Shaughnessy*

Cite This: https://dx.doi.org/10.1021/acs.organomet.0c00140 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A series of air-stable $[(Np_3P)Pd(Ar)Br]_2$ (Np = neopentyl) and $(Np_3P)Pd(Ar)(amine)Br$ 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 $Pd_2(dba)_3$ and PNp_3. Increasing steric demand of the aryl group on palladium correlates with increased catalyst activity. Reactions catalyzed by $[(Np_3P)Pd(2,6\text{-}Me_2C_6H_3)Br]_2$ occur efficiently at lower temperatures and with similar or higher yields than those using $Pd_2(dba)_3/PNp_3$. The amine adducts give lower reaction rates and conversion to product than the $[(Np_3P)Pd(Ar)Br]_2$ complexes. The lower activity of the amine adducts appears to result from slow base-promoted reductive elimination to generate the catalytically active 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 $Pd(OAc)_2$ or $Pd_2(dba)_3$, under the reaction conditions to generate active catalysts.

For these ligand classes, the active species is an unstable 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 $Pd_2(dba)_3$, but the released dba ligands can act as inhibitors of the catalyst.[6]

In an effort to more efficiently generate the 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 LPd(0) species under catalytic conditions. Successful examples of precatalysts include $(LPd)_2(\mu\text{-cod})$ (**1**),[8] $[((t\text{-}Bu)_3P)Pd(\mu\text{-}X)]_2$ (**2**),[9] (allyl)Pd(L)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 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 $([LPd(Ar)\text{-}X]_n)$, and the amine adduct of the oxidative addition product (Scheme 1).

The $L_2Pd(0)$ 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

Received: February 26, 2020

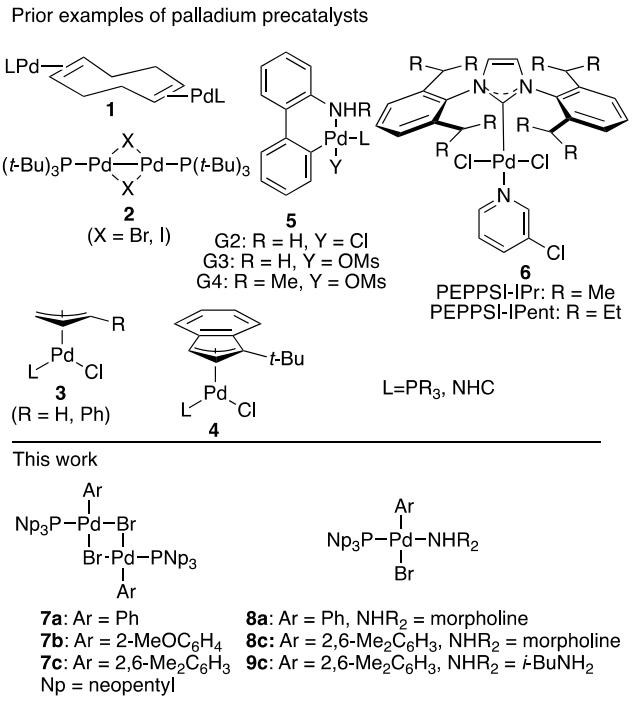
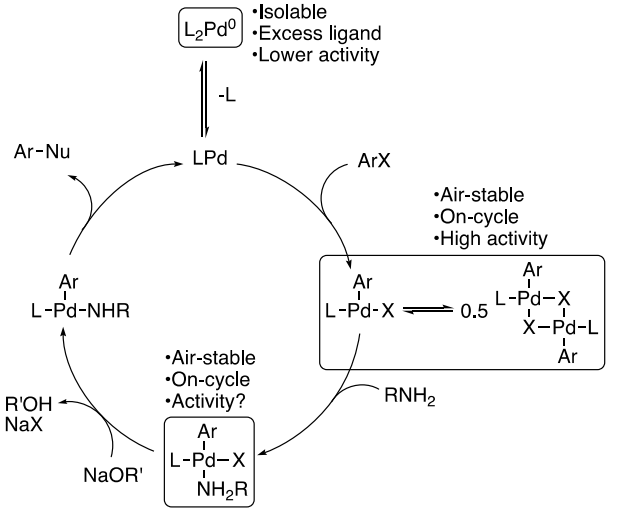


Figure 1. Examples of precatalysts that efficiently generate LPd(0) and the precatalysts studied in this work.

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



noted that palladium aryl species ($[(PNp_3)Pd(Ar)Br]_2$) were dramatically more active than $Pd(PNp_3)_2$ for *N*-arylation reactions.[15] Buchwald reported the use of (AlPhos)Pd(Ar)X (X = Br and OTf) precatalysts for the fluorination of aryl bromides.[16] Since these initial reports, $[LPd(Ar)X]_n$ complexes have been shown to be significantly more active than catalysts generated in situ or precatalysts **1**–**6** by a number of groups.[17]

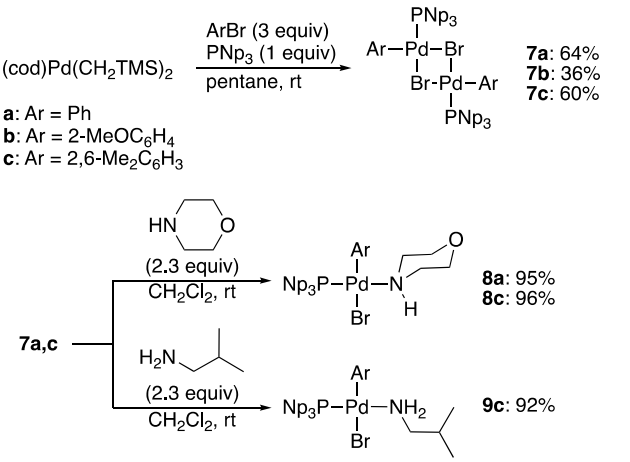
The arylpalladium complex ($[LPd(Ar)X]_n$) can be a stable 3-coordinate species ($n = 1$) or a halide bridged dimer ($n = 2$) depending on the properties of the ligand, aryl group, and halide.[18] The $[LPd(Ar)X]_n$ precatalyst is converted to the active LPd^0 species by reaction with the nucleophilic 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 $[LPd(Ar)X]_n$ complex to give LPd(amine)(Ar)X, which is an isolable intermediate. Deprotonation of the amine adduct and reductive elimination generates the LPd^0 species. Therefore, the LPd(amine)(Ar)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] proazaphosphatrane-derived catalysts,[22] and iminoproazaphosphatrane-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 $[(Np_3P)Pd(Ar)Br]_2$ and $(Np_3P)Pd(Ar)(HNR_2)Br$ (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 $[(Np_3P)Pd(Ar)Br]_2$ and $(Np_3P)Pd(Ar)(HNR_2)Br$ complexes as catalyst sources.

RESULTS AND DISCUSSION

Oxidative addition complexes ($[(Np_3P)Pd(Ar)Br]_2$, **7a**–**c**) were synthesized from $(cod)Pd(CH_2TMS)_2$ 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 $Pd(PNp_3)_2$ 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

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX–XXX

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

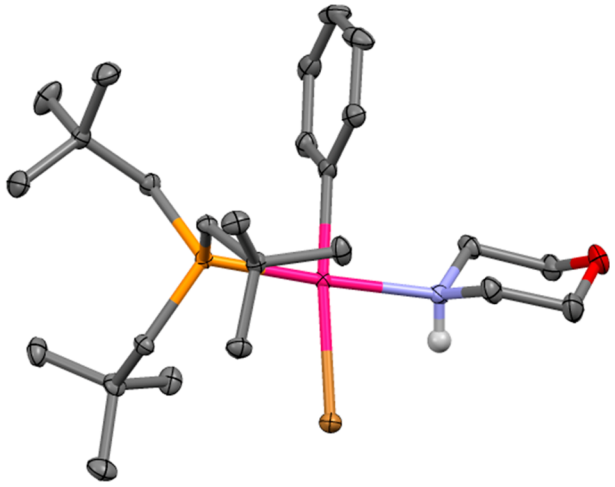
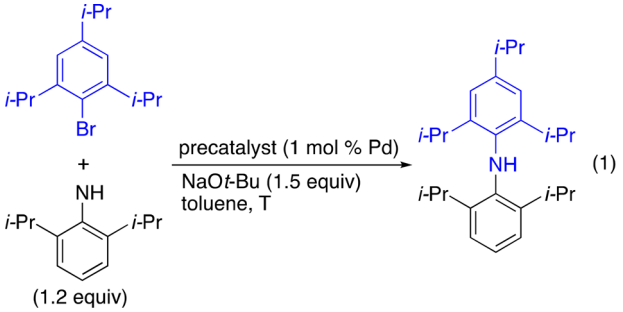


Figure 2. Thermal ellipsoid plot of **8a**. Ellipsoids are drawn at the 50% level and hydrogens with the exception of the N−H hydrogen have been omitted for clarity.

similar to that of **8c**. ^{1}H 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 $Pd_2(dba)_3$ (0.5 mol %) and PNp_3 (1 mol %) for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisoproylaniline at 60, 36, and 22 °C (Figure 3). At 60 °C, complex **7c** and the $Pd_2(dba)_3/PNp_3$



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 $Pd_2(dba)_3/PNp_3$ system showed an induction period prior achieving maximum rate at both temperatures. We have previously observed that the displacement of dba by PNp_3 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 $Pd_2(dba)_3/PNp_3$ 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]

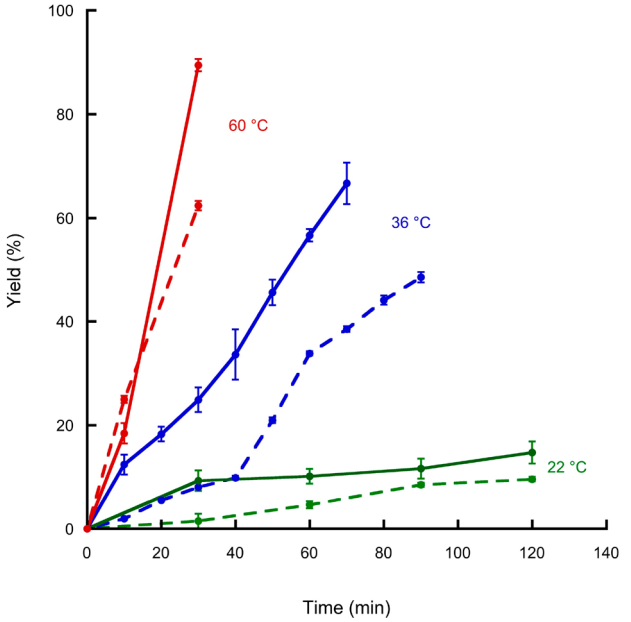


Figure 3. Reaction profiles for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisoproylaniline using precatalysts **7c** (solid line) or $Pd_2(dba)_3/PNp_3$ (dotted line) as a function of temperature (eq 1). Data points are the average of two independent trials.

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

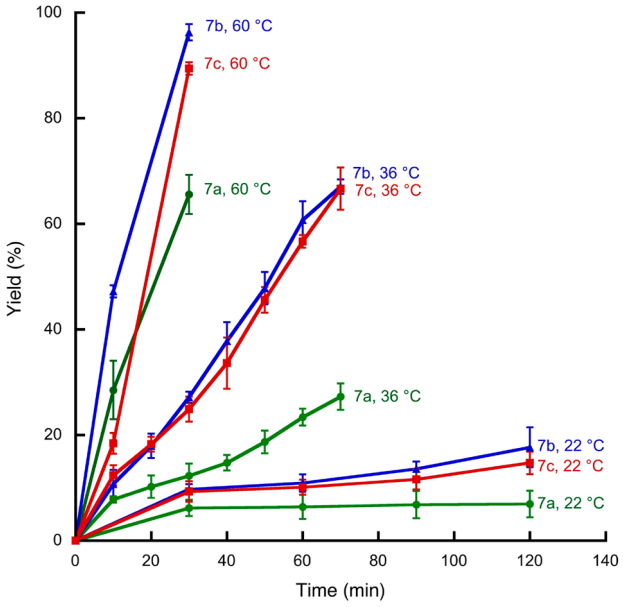


Figure 4. Reaction profiles for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisoproylaniline using precatalysts **7a−c** as a function of temperature (eq 1). Data points are the average of two independent trials.

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX−XXX

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**)

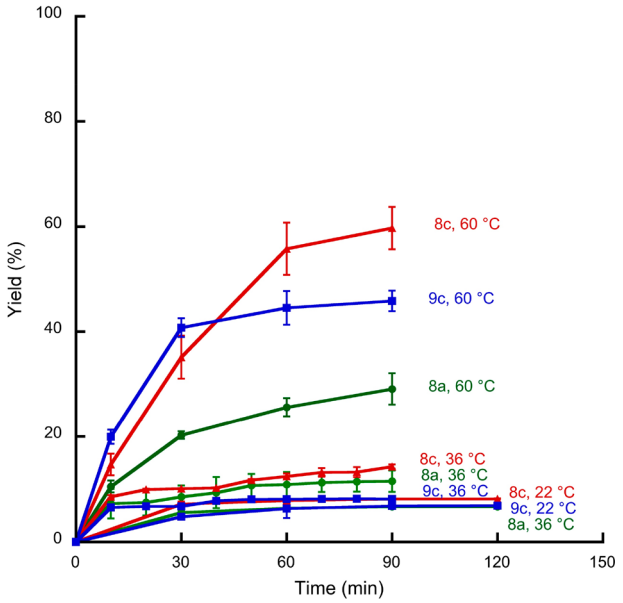


Figure 5. Reaction profiles for the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisoproylaniline using precatalysts **8a,c** and **9c** as a function of temperature (eq 1). Data points are the average of two independent trials.

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 $Pd_2(dba)_3$/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

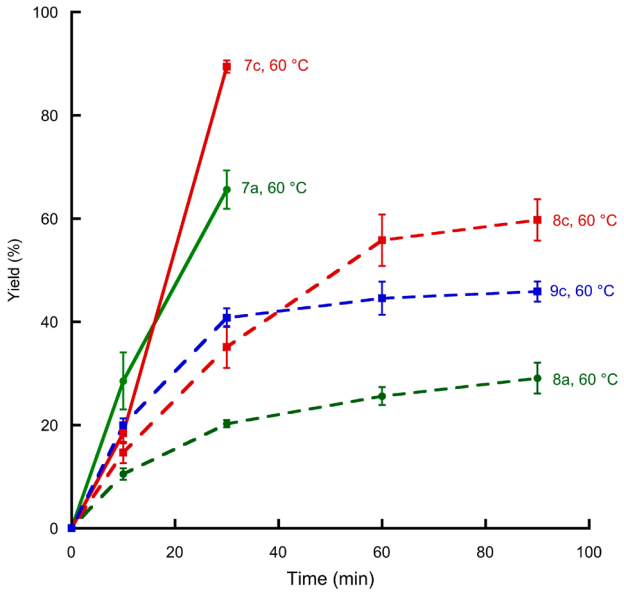


Figure 6. Comparison of aryl palladium precatalysts **7a** and **7c** and their amine adducts (**8a** and **8c**) in the coupling of 1-bromo-2,4,6-triisopropylbenzene and 2,6-diisoproylaniline (eq 1). Data points are the average of two independent trials.

(**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]

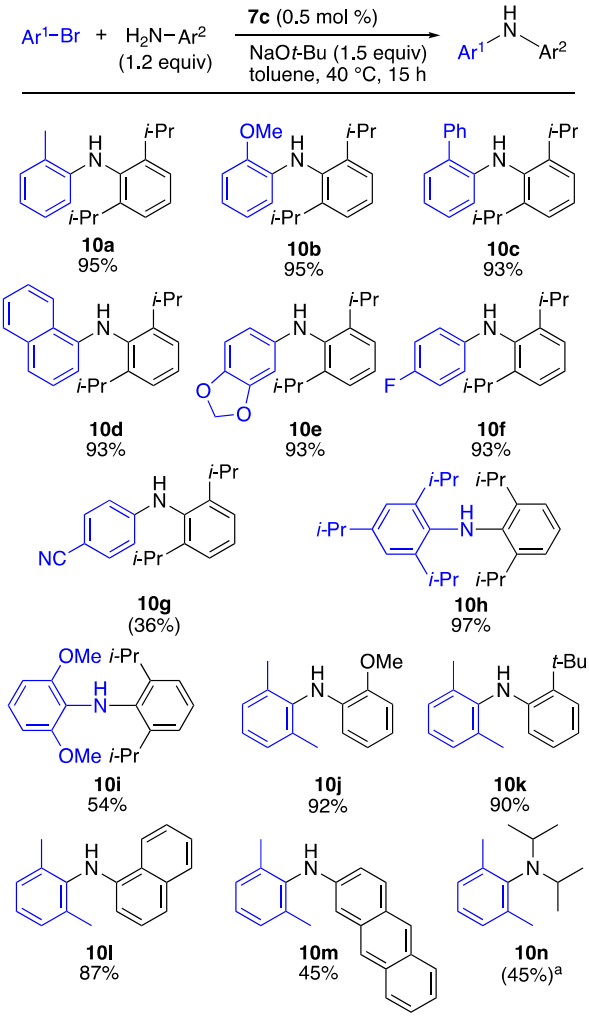
Complex **7c** provides comparable or higher reactions yields, while using lower reaction temperatures than the catalyst derived from $Pd_2(dba)_3$/PNp_3. The reactions catalyzed by **7c** were accomplished at 40 °C, compared to 80 °C for reactions using a combination of $Pd_2(dba)_3$ and PNp_3.[24a] 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 $Pd_2(dba)_3$ 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 [(PNp_3)Pd(Ar)Br] complexes react with aniline in the presence of NaO*t*-Bu at 80 °C to form $Pd(PNp_3)_2$ 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 P(*t*-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 $(PNp_3)Pd^0$ (Scheme 1), the identity of the aryl group

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX−XXX

Scheme 3. Coupling of Hindered Aryl Bromides and Amines Using Precatalyst 7c[a]

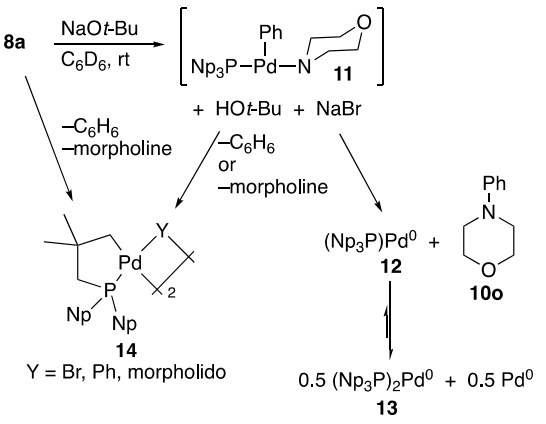


[a]Reaction performed at 100 °C. Reaction times were not optimized. Isolated yields, except for yields in parentheses, which were determined by GC analysis.

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 $(PNp_3)Pd^0$ 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 $(Np_3P)Pd^0$ 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** (Y = Br).[15] Elimination of arene or morpholine could also potentially occur from **11** to give palladacycle **14** (Y = phenyl or morpholido).

Scheme 4. Base Activation of Precatalyst 8a



The reaction of complex **8a** (17 μM) and NaO*t*-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 NaO*t*-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 $(PNp_3)_2Pd$ (**13**) (Figure S43). Complete conversion to $Pd(PNp_3)_2$ 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 NaO*t*-Bu (170 μM) to **8a** (10 μM) showed conversion of **8a** to $Pd(PNp_3)_2$ 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 $(Np_3P)_2Pd(0)$, although a number of unidentified palladium(II) species were present throughout the reaction (Figures S51–S56). After 40 min, 23% conversion to $(Np_3P)_2Pd(0)$ had occurred. After 1 h, the reaction had progressed to 31% conversion. Complex **9c** (16.9 ppm) did not form $(Np_3P)_2Pd(0)$ 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.

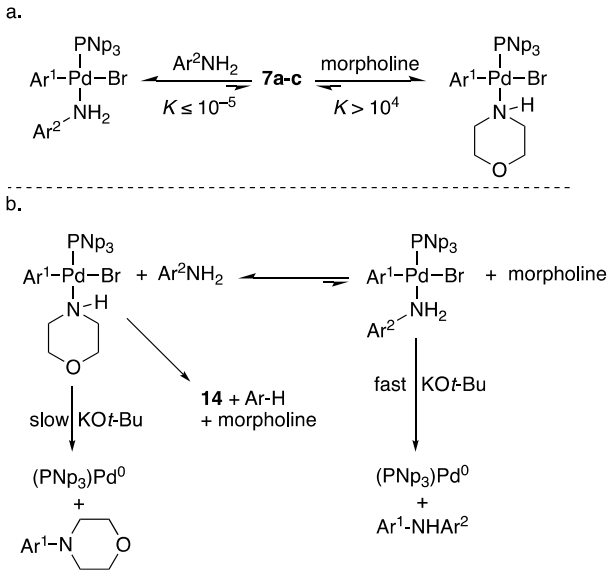
The amine adducts (**8a,c** and **9c**) undergo base-promoted reductive elimination at rates that are slow compared to the catalytic reaction. The observed rates are much slower than those reported for other LPd(Ar)(amine)X complexes.[31] The reason for the slow reductive elimination is unclear, although 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 $[(PNp_3)Pd(Ar)Br]_2$ complexes **7a–c**. In contrast, complexes **8c** and **9c**

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX–XXX

give base-promoted formation of $Pd(PNp_3)_2$ 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 $(PNp_3)Pd(Ar)Br$ fragment than morpholine or isobutyl amine (Scheme 5a). Reaction of $[(PNp_3)Pd(Ar)Br]_2$ 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 $(PNp_3)Pd^0$ 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 $Pd_2(dba)_3$ 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 NaO*t*-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 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] $(cod)Pd(CH_2TMS)_2$,[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 Brüker 500 MHz spectrometer. ^{31}P 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

$[(PNp_3)Pd(C_6H_5)Br]_2$ (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 $(cod)Pd(CH_2TMS)_2$ (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). ^{13}C NMR (125 MHz, C_6D_6, 295 K): δ 152.9, 135.8, 123.4, 108.0, 40.2 (d, J_{C-P} = 20 Hz), 33.5, 32.6. $^{31}P\{^1H\}$ NMR (202.5 MHz, C_6D_6, 295 K): δ 7.9. Elemental analysis: calcd for $C_{42}H_{76}Br_2P_2Pd_2$: C, 49.67; H, 7.54; N, 0. Found: C, 50.56; H, 7.72; N, 0.0.

$[(PNp_3)Pd(2\text{-}MeOC_6H_4)Br]_2$ (7b). Trineopentylphosphine (100 mg, 0.410 mmol), 2-bromoanisole (160 μL, 1.285 mmol), $(cod)Pd(CH_2TMS)_2$ (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). ^{13}C NMR (125 MHz, C_6D_6, 295 K): δ 162.1 (d, J_{C-P} = 12.5 Hz), 141.4, 138.2 (d, J_{C-P} = 13.8 Hz), 126.0, 122.4 (d, J_{C-P} = 3.75 Hz), 112.4 (d, J_{C-P} = 25 Hz), 56.5 (d, J_{C-P} = 11.3 Hz), 41.3 (brs), 34.7, 34.0. $^{31}P\{^1H\}$ NMR (202.5 MHz, C_6D_6, 295 K): δ 11.21,

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX−XXX

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_3)Pd(morpholine)(Ph)Br (8a). The target compound was prepared according to the reported synthesis of **8c**.[25] $[(PNp_3)Pd(C_6H_5)Br]_2$ (**7a**, 67.6 mg, 0.067 mmol) was dissolved in methylene chloride (8 mL) under nitrogen. Morpholine (13.0 μL, 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. ^{1}H NMR (500 MHz, C_6D_6, 295 K): δ 7.56 (d, J = 8.8 Hz, 2 H), 7.07(t, J = 7.4 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.53 (brs, 1H), 3.11 (d, J = 11.3 Hz, 2H), 2.60 (m, 6H), 1.99 (d, J = 9.9 Hz, 6H), 1.30(s, 27H). ^{13}C NMR (125 MHz, C_6D_6, 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. ^{31}P{^{1}H} NMR (202.5 MHz, C_6D_6, 295 K): δ 7.8. Elemental analysis: calcd for $C_{25}H_{47}BrNOPPd$: 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 ShelXT[35] structure solution program using Intrinsic Phasing and refined with ShelXL[36] refinement package using Least Squares minimization using either Olex2[34] or ShelXle[37] 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. NaO*t*-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 μL, 1.00 mmol) and 2,6-diisopropylaniline (226 μL, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as brown oil (254 mg, 95%). ^{1}H NMR (500 MHz, CD_3CN): 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). ^{13}C NMR (125 MHz, CD_3CN): 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 $C_{24}H_{27}N$ (M^+) 267.1987. Found 267.1984.

*N-(2-Methoxyphenyl)-2,6-diisopropylaniline (**10b**).*[19a] Using the general procedure, 2-bromoanisole (125 μL, 1.00 mmol) and 2,6-diisopropylaniline (226 μL, 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%). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{19}H_{25}NO$ (M^+) 283.1936. Found 283.1940.

*N-(2,6-Diisopropylphenyl)-[1,1′-biphenyl]-2-amine (**10c**).*[24a] Using the general procedure, 2-bromobiphenyl (172 μL, 1.00 mmol) and 2,6-diisopropylaniline (226 μL, 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%). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{24}H_{27}N$ (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 μL, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as a white solid (282 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{22}H_{25}N$ (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 μL, 1.00 mmol) and 2,6-diisopropylaniline (226.3 μL, 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%). ^{1}H NMR (500 MHz, CD_3CN): 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). ^{13}C NMR (125 MHz, CD_3CN): 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 $C_{19}H_{23}NO_2$ (M^+) 297.1729. Found 297.1725.

*N-(4-Fluorophenyl)-2,6-diisopropylaniline (**10f**).* Using the general procedure, 1-bromo-4-fluorobenzene (109.9 μL, 1.00 mmol) and 2,6-diisopropylaniline (226 μL, 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, CD_3CN): 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). ^{13}C NMR (125 MHz, CD_3CN): 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 $C_{18}H_{22}FN$ (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 μL, 1.00 mmol) and 2,6-diisopropylaniline (226 μL, 1.20 mmol) were coupled using 0.5 mol % **7c** at 40 °C to give the product as clear, colorless crystals (341 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{24}H_{27}N$ (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 μL, 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%). ^{1}H NMR (500 MHz, CD_3CN): δ 7.15 (m, 1H), 7.10 (d, J = 7.9 H, 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). ^{13}C NMR (125 MHz, CD_3CN): 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 $C_{20}H_{27}NO_2$ (M^+) 313.2042. Found 313.2038.

*N-(2-Methoxyphenyl)-2,6-dimethylaniline (**10j**).*[40] Using the general procedure, 2-bromo-*m*-xylene (133 μL, 1.00 mmol) and *o*-anisidine (135 μL, 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%). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{15}H_{17}NO$ (M^+) 227.1310. Found 227.1307.

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

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX−XXX

NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{18}H_{23}N$ (M^+) 253.1830. Found 253.1837.

*N-(2,6-Dimethylphenyl)naphthalen-1-amine (**10l**).*[41] Using the general procedure, 2-bromo-*m*-xylene (133 μL, 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%). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{18}H_{17}N$ (M^+) 247.1361. Found 247.1360.

*N-(2,6-Dimethylphenyl)anthracen-2-amine (**10m**).* Using the general procedure, 2-bromo-*m*-xylene (133 μL, 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%). ^{1}H NMR (500 MHz, CD_3CN): 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). ^{13}C NMR (126 MHz, CD_3CN): 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 $C_{22}H_{19}N$ (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.

■ AUTHOR INFORMATION

Corresponding Author

Kevin H. Shaughnessy − *Department of Chemistry & Biochemistry, The University of Alabama, Tuscaloosa, Alabama 35487, United States;* orcid.org/0000-0002-1375-5563; Email: kshaughn@ua.edu

Authors

Huaiyuan Hu − *Department of Chemistry & Biochemistry, The University of Alabama, Tuscaloosa, Alabama 35487, United States*

Corrie E. Burlas − *Department of Chemistry & Biochemistry, The University of Alabama, Tuscaloosa, Alabama 35487, United States*

Sabrina J. Curley − *Department of Chemistry & Biochemistry, The University of Alabama, Tuscaloosa, Alabama 35487, United States*

Tomasz Gruchala − *Department of Chemistry & Biochemistry, The University of Alabama, Tuscaloosa, Alabama 35487, United States*

Fengrui Qu − *Department of Chemistry & Biochemistry, The University of Alabama, Tuscaloosa, Alabama 35487, United States;* orcid.org/0000-0002-9975-2573

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.organomet.0c00140

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

H.H. acknowledges support of his postdoctoral associate position from the College of Arts & Sciences, The University of Alabama. The structure of **8a** was obtained on an X-ray diffractometer purchased with support from NSF (CHE MRI 1828078). Johnson-Matthey is acknowledged for donation of palladium salts.

■ REFERENCES

(1) (a) Gildner, P. G.; Colacot, T. J. Reactions of the 21st Century: Two Decades of Innovative Catalyst Design for Palladium-Catalyzed Cross-Couplings. *Organometallics* **2015**, *34*, 5497−5508. (b) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564−12649. (c) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. *Chem. Rev.* **2018**, *118*, 2249−2295. (d) Campeau, L.-C.; Hazari, N. Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future. *Organometallics* **2019**, *38*, 3−35. (e) Hartwig, J. F.; Shaughnessy, K. H.; Shekhar, S.; Green, R. A. Palladium-Catalyzed Amination of Aryl Halides. In *Organic Reactions*; Denmark, S. E., Ed.; John Wiley & Sons: Hoboken, NJ, 2019; Vol. *100*, pp 853−958.

(2) (a) Fleckenstein, C. A.; Plenio, H. Sterically Demanding Trialkylphosphines for Palladium-Catalyzed Cross Coupling Reactions—Alternatives to P*t*Bu$_3$. *Chem. Soc. Rev.* **2010**, *39*, 694−711. (b) Shaughnessy, K. H. Monodentate Trialkylphosphines: Privileged Ligands in Metal-Catalyzed Cross-Coupling Reactions. *Curr. Org. Chem.* **2020**, *24*, 231−264.

(3) (a) Surry, D. S.; Buchwald, S. L. Diamine Ligands in Copper-Catalyzed Reactions. *Chem. Sci.* **2010**, *1*, 13−21. (b) Surry, D. S.; Buchwald, S. L. Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide. *Chem. Sci.* **2011**, *2*, 27−50. (c) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. Biaryl Monophosphine Ligands in Palladium-Catalyzed C−N Coupling: An Updated User's Guide. *Tetrahedron* **2019**, *75*, 4199−4211.

(4) (a) Fortman, G. C.; Nolan, S. P. *N*-Heterocyclic Carbene (NHC) Ligands and Palladium in Homogeneous Cross-Coupling Catalysis: a Perfect Union. *Chem. Soc. Rev.* **2011**, *40*, 5151−5169. (b) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. The Development of Bulky Palladium NHC Complexes for the Most-Challenging Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314−3332. (c) Valente, C.; Pompeo, M.; Sayah, M.; Organ, M. G. Carbon−Heteroatom Coupling Using Pd-PEPPSI Complexes. *Org. Process Res. Dev.* **2014**, *18*, 180−190. (d) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N-C/O-C Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589−2599.

(5) (a) Christmann, U.; Vilar, R. Monoligated Palladium Species as Catalysts in Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2005**, *44*, 366−374. (b) Ortiz, D.; Blug, M.; Le Goff, X. F.; Le Floch, P.; Mézailles, N.; Maître, P. Mechanistic Investigation of the Generation of a Palladium(0) Catalyst from a Palladium(II) Allyl Complex: A Combined Experimental and DFT Study. *Organometallics* **2012**, *31*, 5975−5978. (c) Zheng, Q.; Liu, Y.; Chen, Q.; Hu, M.; Helmy, R.; Sherer, E. C.; Welch, C. J.; Chen, H. Capture of Reactive

Monophosphine-Ligated Palladium(0) Intermediates by Mass Spectrometry. *J. Am. Chem. Soc.* **2015**, *137*, 14035−14038.
(6) (a) Amatore, C.; Jutand, A. Role of dba in the Reactivity of Palladium(0) Complexes Generated in Situ from Mixtures of $Pd(dba)_2$ and Phosphines. *Coord. Chem. Rev.* **1998**, *178*−*180*, 511−528. (b) Fairlamb, I. J. S. π-Acidic Alkene Ligand Effects in Pd-Catalysed Cross-Coupling Processes: Exploiting the Interaction of Dibenzylidene Acetone (dba) and Related Ligands with Pd(0) and Pd(II). *Org. Biomol. Chem.* **2008**, *6*, 3645−3656.
(7) (a) Hazari, N.; Melvin, P. R.; Beromi, M. M. Well-Defined Nickel and Palladium Precatalysts for Cross-Coupling. *Nat. Rev. Chem.* **2017**, *1*, 0025. (b) Shaughnessy, K. H. Development of Palladium Precatalysts that Efficiently Generate LPd(0) Active Species. *Isr. J. Chem.* **2020**, *60*, 180−194.
(8) (a) Lee, H. G.; Milner, P. J.; Buchwald, S. L. An Improved Catalyst System for the Pd-Catalyzed Fluorination of (Hetero)Aryl Triflates. *Org. Lett.* **2013**, *15*, 5602−5605. (b) Lee, H. G.; Milner, P. J.; Buchwald, S. L. Pd-Catalyzed Nucleophilic Fluorination of Aryl Bromides. *J. Am. Chem. Soc.* **2014**, *136*, 3792−3795.
(9) (a) Aufiero, M.; Scattolin, T.; Proutière, F.; Schoenebeck, F. Air-Stable Dinuclear Iodine-Bridged Pd(I) Complex - Catalyst, Precursor, or Parasite? The Additive Decides. Systematic Nucleophile-Activity Study and Application as Precatalyst in Cross- Coupling. *Organometallics* **2015**, *34*, 5191−5195. (b) Bonney, K. J.; Proutiere, F.; Schoenebeck, F. Dinuclear Pd(I) Complexes—Solely Precatalysts? Demonstration of Direct Reactivity of a Pd(I) Dimer With an Aryl Iodide. *Chem. Sci.* **2013**, *4*, 4434−4439. (c) Proutière, F.; Aufiero, M.; Schoenebeck, F. Reactivity and Stability of Dinuclear Pd(I) Complexes: Studies on the Active Catalytic Species, Insights into Precatalyst Activation and Deactivation, and Application in Highly Selective Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2012**, *134*, 606−612.
(10) (a) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. Design of a Versatile and Improved Precatalyst Scaffold for Palladium-Catalyzed Cross-Coupling: $(\eta^3$-1-*t*-Bu-indenyl$)_2(\mu$-Cl$)_2$Pd$_2$. *ACS Catal.* **2015**, *5*, 3680−3688. (b) Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M. Insight into the Efficiency of Cinnamyl-Supported Precatalysts for the Suzuki−Miyaura Reaction: Observation of Pd(I) Dimers with Bridging Allyl Ligands During Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 7300−7316. (c) Johansson Seechurn, C. C. C.; Parisel, S. L.; Colacot, T. J. Air-Stable Pd(R-allyl)LCl (L= Q-Phos, P(t-Bu)$_3$, etc.) Systems for C−C/N Couplings: Insight into the Structure−Activity Relationship and Catalyst Activation Pathway. *J. Org. Chem.* **2011**, *76*, 7918−7932. (d) Marion, N.; Nolan, S. P. Well-Defined N-Heterocyclic Carbenes-Palladium(II) Precatalysts for Cross-Coupling Reactions. *Acc. Chem. Res.* **2008**, *41*, 1440−1449.
(11) (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. A New Class of Easily Activated Palldium Precatalysts for Facile C−N Cross-Coupling Reactions and the Low Temperature Oxidative Addition of Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 6686−6687. (b) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and Preparation of New Palladium Precatalysts for C-C and C-N Cross-Coupling Reactions. *Chem. Sci.* **2013**, *4*, 916−920.
(12) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of N-Heterocyclic Carbene as Catalysts for Cross-Coupling Reactions—a Synthetic Chemist's Perspective. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768−2813.
(13) Melvin, P. R.; Balcells, D.; Hazari, N.; Nova, A. Understanding Precatalyst Activation in Cross-Coupling Reactions: Alcohol Facilitated Reduction from Pd(II) to Pd(0) in Precatalysts of the Type $(\eta^3$-allyl)Pd(L)(Cl) and $(\eta^3$-indenyl)Pd(L)(Cl. *ACS Catal.* **2015**, *5*, 5596−5606.
(14) (a) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. Scope and Mechanism of Palladium-Catalyzed Amination of Five-Membered Heterocyclic Halides. *J. Org. Chem.* **2003**, *68*, 2861−2873. (b) Littke, A. F.; Dai, C.; Fu, G. C. Versatile catalysts for the Suzuki cross-coupling of arylboronic acids with aryl and vinyl halides and triflates under mild conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.
(15) Hu, H.; Qu, F.; Gerlach, D. L.; Shaughnessy, K. H. Mechanistic Study of the Role of Substrate Steric Effects and Aniline Inhibition on the Bis(trineopentylphosphine)palladium(0)-Catalyzed Arylation of Aniline Derivatives. *ACS Catal.* **2017**, *7*, 2516−2527.
(16) 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.
(17) (a) 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. (b) Malapit, C. A.; Bour, J. R.; Laursen, S. R.; Sanford, M. S. Mechanism and Scope of Nickel-Catalyzed Decarbonylative Borylation of Carboxylic Acid Fluorides. *J. Am. Chem. Soc.* **2019**, *141*, 17322−17330. (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. (d) Tang, S.-Q.; Bricard, J.; Schmitt, M.; Bihel, F. Fukuyama Cross-Coupling Approach to Isoprekinamycin: Discovery of the Highly Active and Bench-Stable Palladium Precatalyst POxAP. *Org. Lett.* **2019**, *21*, 844−848.
(18) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. Synthesis, structure, theoretical studies, and ligand exchange reactions of monomeric, T-shaped arylpalladium(II) halide complexes with an additional, weak agostic interaction. *J. Am. Chem. Soc.* **2004**, *126*, 1184−1194.
(19) (a) Ehrentraut, A.; Zapf, A.; Beller, M. A New Improved Catalysts for the Palladium Catalyzed Amination of Aryl Chlorides. *J. Mol. Catal. A: Chem.* **2002**, *182*−*183*, 515−523. (b) Rodriguez, S.; Qu, B.; Haddad, N.; Reeves, D. C.; Tang, W.; Lee, H.; Krishnamurthy, D.; Senanayake, C. H. Oxaphosphole-Based Monophosphorus Ligands for Palladium-Catalyzed Amination Reactions. *Adv. Synth. Catal.* **2011**, *353*, 533−537.
(20) (a) Chartoire, A.; Frogneux, X.; Boreux, A.; Slawin, A. M. Z.; Nolan, S. P. [Pd(IPr*)(3-Cl-pyridinyl)Cl$_2$]: A Novel and Efficient PEPPSI Precatalyst. *Organometallics* **2012**, *31*, 6947−6951. (b) Meiries, S.; Chartoire, A.; Slawin, A. M. Z.; Nolan, S. P. [Pd(IPr*)-(acac)Cl]: An easily synthesized, bulky precatalyst for C-N bond formation. *Organometallics* **2012**, *31*, 3402−3409. (c) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. Pd-catalyzed aryl amination mediated by well defined, N-heterocyclic carbene (NHC)-Pd precatalysts, PEPPSI. *Chem. - Eur. J.* **2008**, *14*, 2443−2452. (d) Tu, T.; Fang, W.; Jiang, J. A highly efficient precatalyst for amination of aryl chlorides: synthesis, structure and application of a robust acenaphthoimidazolylidene palladium complex. *Chem. Commun.* **2011**, *47*, 12358−12360. (e) Zhu, L.; Ye, Y.-M.; Shao, L.-X. Well-defined NHC−Pd(II)−Im (NHC = N-heterocyclic carbene; Im = 1-methylimidazole) complex catalyzed C−N coupling of primary amines with aryl chlorides. *Tetrahedron* **2012**, *68*, 2414−2420.
(21) Lee, D.-H.; Taher, A.; Hossain, S.; Jin, M.-J. An efficient and general method for the Heck and Buchwald-Hartwig coupling reactions of aryl chlorides. *Org. Lett.* **2011**, *13*, 5540−5543.
(22) Urgaonkar, S.; Verkade, J. G. Scope and limitations of $Pd_2(dba)_3$/P(*i*-BuNCH$_2$CH$_2$)$_3$N-catalyzed Buchwald-Hartwig amination reactions of aryl chlorides. *J. Org. Chem.* **2004**, *69*, 9135−9142.
(23) Reddy, C. V.; Kingston, J. V.; Verkade, J. G. *t*-Bu)$_2$PN = P(*i*-BuNCH$_2$CH$_2$)$_3$N: new efficient ligand for palladium-catalyzed C−N couplings of aryl and heteroaryl bromides and chlorides and for vinyl bromides at room temperature. *J. Org. Chem.* **2008**, *73*, 3047−3062.
(24) (a) Raders, S. M.; Moore, J. N.; Parks, J. K.; Miller, A. D.; Leißing, T. M.; Kelley, S. P.; Rogers, R. D.; Shaughnessy, K. H. Trineopentylphosphine: A Conformationally Flexible Ligand for the Coupling of Sterically Demanding Substrates in the Buchwald-Hartwig Amination and Suzuki-Miyaura Reaction. *J. Org. Chem.* **2013**, *78*, 4649−4664. (b) Raders, S. M.; Jones, J. M.; Semmes, J. G.; Kelley, S. P.; Rogers, R. D.; Shaughnessy, K. H. Di-*tert*-Butylneopentylphosphine (DTBNpP): An Efficient Ligand in the Palladium-Catalyzed α-Arylation of Ketones. *Eur. J. Org. Chem.* **2014**, *2014*, 7395−7404.

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX−XXX

(25) Hu, H.; Vasiliu, M.; Stein, T. H.; Qu, F.; Gerlach, D. L.; Dixon, D. A.; Shaughnessy, K. H. Synthesis, Structural Characterization, and Coordination Chemistry of (Trineopentylphosphine)palladium(aryl)-bromide Dimer Complexes ($[(Np_3P)Pd(Ar)Br]_2$). *Inorg. Chem.* **2019**, *58*, 13299−13313.
(26) Hill, L. L. Investigations of Cross Coupling Reactions: Synthesis and Scope of New Neopentyl Phosphine Ligands and Pre-Formed Palladium Catalysts. PhD Thesis, The University of Alabama, Tuscaloosa, AL, 2009.
(27) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. Design of New Ligands for the Palladium-Catalyzed Arylation of α-Branched Secondary Amines. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259−8262.
(28) (a) Berman, A. M.; Johnson, J. B. Copper-Catalyzed Eectrophilic Amination of Functionalized Diarylzinc Reagents. *J. Org. Chem.* **2005**, *70*, 364−366. (b) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. Synthesis of Hindered Anilines: Copper-Catalyzed Electrophilic Amination of Aryl Boronic Esters. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953−3956.
(29) (a) Roy, A. H.; Hartwig, J. F. Reductive elimination of aryl halides from palladium(II). *J. Am. Chem. Soc.* **2001**, *123*, 1232−1233. (b) Roy, A. H.; Hartwig, J. F. Directly Observed Reductive Elimination of Aryl Halides from Monomeric Arylpalladium(II) Halide Complexes. *J. Am. Chem. Soc.* **2003**, *125*, 13944−13945.
(30) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. Carbon-Sulfur Bond-Forming Reductive Elimination Involving sp-, sp^2-, and sp^3-Hybridized Carbon. Mechanism, Steric Effects, and Electronic Effects on Sulfide Formation. *J. Am. Chem. Soc.* **1998**, *120*, 9205−9219.
(31) (a) Louie, J.; Paul, F.; Hartwig, J. F. Catalysis with Platinum-Group Alkylamido Complexes. The Active Palladium Amide in Catalytic Aryl Halide Aminations as Deduced from Kinetic Data and Independent Generation. *Organometallics* **1996**, *15*, 2794−2805. (b) Hartwig, J. F. Carbon-Heteroatom Bond-Forming Reductive Elimination of Amines, Ethers, and Sulfides. *Acc. Chem. Res.* **1998**, *31*, 852−860.
(32) King, R. B.; Cloyd, J. C., Jr.; Reimann, R. H. Poly(Tertiary Phosphines and Arsines). XIII. Some Neopentyl Poly(Tertiary Phosphines). *J. Org. Chem.* **1976**, *41*, 972−977.
(33) Pan, Y.; Young, G. B. Syntheses and Spectroscopic Characteristics of Dialkylpalladium(II) Complexes; $PdR_2(cod)$ as Precursors for Derivatives with *N*- or *P*-Donor Ligands. *J. Organomet. Chem.* **1999**, *577*, 257−264.
(34) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Crystallogr.* **2009**, *42*, 339−341.
(35) Sheldrick, G. M. SHELXT − Integrated Space-Group and Crystal- Structure Determination. *Acta Crystallogr., Sect. A: Found. Adv.* **2015**, *71*, 3−8.
(36) Sheldrick, G. M. Crystal Structure Refinement with ShelXL. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3−8.
(37) Hübschle, C. B.; Sheldrick, G. M.; Dittrich, B. ShelXle: a Qt Graphical User Interface for SHELXL. *J. Appl. Crystallogr.* **2011**, *44*, 1281−1284.
(38) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. (IPr)Pd(acac)Cl: An Easily Synthesized Efficient, and Versatile Precatalyst for C-N and C-C Bond Formation. *J. Org. Chem.* **2006**, *71*, 3816−3821.
(39) Ishihara, K.; Nakagawa, S.; Sakakura, A. Bulky Diarylammonium Arenesulfonates as Selective Esterification Catalysts. *J. Am. Chem. Soc.* **2005**, *127*, 4168−4169.
(40) Li, J.; Cui, M.; Yu, A.; Wu, Y. Carbene Adduct of Cyclopalladated Ferrocenylimine as an Efficient Catalyst for the Amination of Aryl Chlorides. *J. Organomet. Chem.* **2007**, *692*, 3732−3742.
(41) Gao, C.-Y.; Yang, L.-M. Nickel-Catalyzed Amination of Aryl Tosylates. *J. Org. Chem.* **2008**, *73*, 1624−1627.

https://dx.doi.org/10.1021/acs.organomet.0c00140
Organometallics XXXX, XXX, XXX−XXX