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# Effect of Electronic Enrichment of NHCs on the Catalytic Activity of [Pd(NHC)(acac)Cl] in Buchwald–Hartwig Coupling

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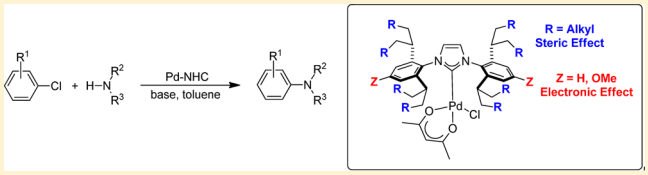
Supporting Information

**ABSTRACT:** A series of [Pd(NHC)(acac)Cl] (NHC = *N*-heterocyclic carbene) complexes have been synthesized and characterized to investigate the electronic and steric effects of NHC ligands in catalysis. Their reactivity in Buchwald–Hartwig coupling has been explored and compared with that of their nonmethoxylated congeners. Combining the optimal steric and electronic properties, [Pd(IHept$^{OMe}$)(acac)Cl] performed excellently in the palladium-catalyzed amination of deactivated aryl chlorides with various anilines.




## INTRODUCTION

Palladium-catalyzed arylamination has become an important and widely employed method for the formation of C–N bonds.[1] Of the different substrates that are available, economically attractive aryl chlorides require special catalyst design for successful coupling, particularly with deactivated or hindered anilines. In addition to the phosphine-based ligands commonly used for this reaction,[2] recent reports have shown that NHC ligands are also efficient catalysts for the Buchwald–Hartwig coupling.[3] Well-defined Pd$^{II}$–NHC precatalysts have the advantages of being air and moisture stable and of introducing the palladium and ligand in the optimal ratio (1:1).[4] Easily synthesized in a one-pot procedure from the NHC·HCl salts, [Pd(NHC)(acac)Cl] complexes are perfect examples of efficient Pd$^{II}$–NHC precatalysts.[5] The catalytic activity of Pd–NHC complexes is directly related to the unique properties of the supporting NHC: their strong $\sigma$-donor character facilitates the oxidative addition of aryl halides, and their steric bulk increases the rate of the reductive elimination.[6] Glorius introduced the concept of "*flexible steric bulk*" to define adaptable ligands that exist in different conformations: one small enough to accept substrates in the coordination sphere of the metal and another one bulky enough to promote monoligation and reductive elimination.[7] As examples, the bulky IPr* (*N*,*N*′-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) reported by Markó and co-workers[8] and further investigated by Nolan[9] and the more flexible IPent (*N*,*N*′-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene), reported by Organ,[3a,10] performed well in the Buchwald–Hartwig arylamination reaction. Recently, we investigated the steric effect of the ITent ligands ("Tent" for "tentacular") and we found that IHept (*N*,*N*′-bis(2,6-di-4-heptylphenyl)imidazol-2-ylidene) exhibited excellent catalytic properties.[11] Moreover, it has been reported, by comparison between [Pd(IPr*)(acac)Cl] (**1**) and [Pd(IPr*$^{OMe}$)(acac)Cl] (**2**), that modification of the electronic properties of the aromatic rings, introduced by the presence of a methoxy group, can increase the efficiency of the catalyst.[12] Interestingly, an optimal combination of steric and electronic effects of substituents appended to the NHC frameworks may improve the performance of NHC ligands in catalysis.[13] In this context, we report the preparation of the conformationally flexible [Pd(ITent$^{OMe}$)(acac)Cl] complexes (Figure 1; **6**–**8**) to examine together the steric and electronic effects of NHC ligands. These precatalysts were tested in the Buchwald–Hartwig arylamination reaction and compared with their

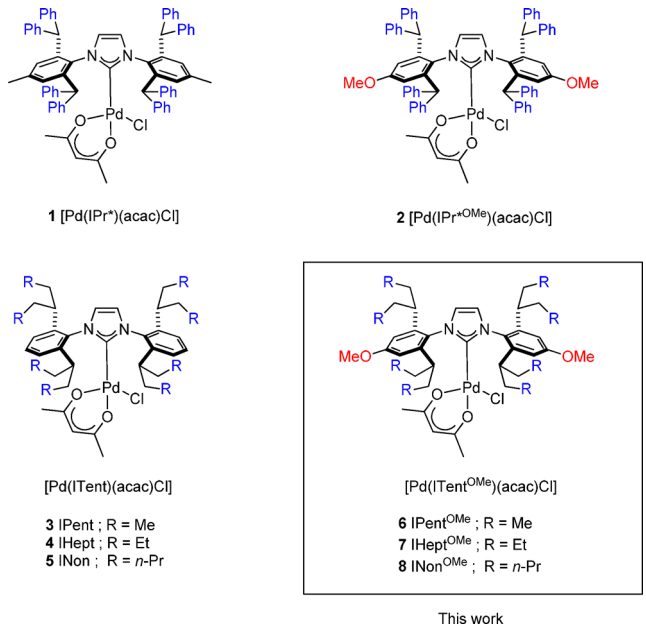



**Figure 1.** Pd(NHC)(acac)Cl precatalysts.

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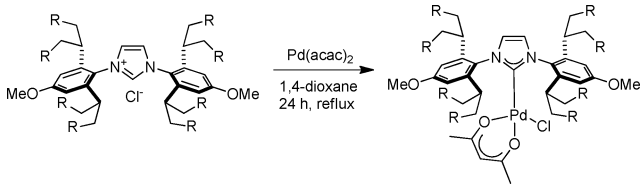
[Pd(ITent)(acac)Cl] analogues (**3**–**5**) to evaluate the influence of the methoxy group.

## RESULTS AND DISCUSSION

By reacting the corresponding ITent$^{OMe}$·HCl[14] salts with $Pd(acac)_2$ in 1,4-dioxane at reflux, as described in the literature,[5] an additional family of palladium precatalysts, [Pd(ITent$^{OMe}$)(acac)Cl], can be easily prepared via a synthetic route that does not require the isolation of the free NHC. The newly prepared [Pd(IPent$^{OMe}$)(acac)Cl] (**6**; IPent$^{OMe}$ = *N*,*N*′-bis(2,6-di-3-pentyl-4-methoxyphenyl)imidazol-2-ylidene), [Pd(IHept$^{OMe}$)(acac)Cl] (**7**; IHept$^{OMe}$ = *N*,*N*′-bis(2,6-di-4-heptyl-4-methoxyphenyl)imidazol-2-ylidene), and [Pd(INon$^{OMe}$)(acac)Cl] (**8**; INon$^{OMe}$ = *N*,*N*′-bis(2,6-di-4-nonyl-4-methoxyphenyl)imidazol-2-ylidene) were obtained as air- and moisture-stable yellow solids in high purity and good yields: respectively 82%, 87%, and 78% (Scheme 1).

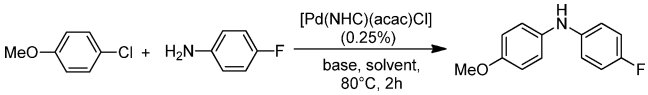
**Scheme 1. Preparation of [Pd(ITent$^{OMe}$)Cl] (6–8)**




The new [Pd(ITent$^{OMe}$)(acac)Cl] complexes **6**–**8** were characterized. Interestingly, $^1$H NMR spectroscopy revealed that the gap between the singlets of the acac methyl groups depends on the length of the R alkyl groups of the NHC ligand: the $^1$H spectrum of **6** exhibited two singlets at 1.61 and 1.78 ppm for the methyl groups of the acac ligand. The $^1$H NMR spectrum of **7** revealed that these singlets were shifted upfield, the first one slightly (1.76 ppm) and the second one more significantly (1.46 ppm). This suggests that, in solution, the magnetic and chemical environment around the metal is directly affected by the length of the R alkyl groups appended to the NHC ligand. Complex **8** exhibited approximately the same gap as **7** (1.48 and 1.76 ppm). This result could be explained by the similar bulk of **7** and **8** in the coordination sphere of the metal. Consequently, the alkyl group of **8** could be partially located further away from the metal center. We have previously observed similar results with the [Pd(ITent)(acac)Cl] series. The gap between the singlets of the acac methyl groups increased with the length of the R alkyl chain (until R = Et): [Pd(IPr)(acac)Cl] (1.82 and 1.84 ppm), **3** (1.53 and 1.73 ppm), **4** (1.40 and 1.77 ppm). In addition, **5** exhibited singlets similar (1.40, 1.75) to those of **4**.[11] It appeared that these observations are general for the ITent and ITent$^{OMe}$ series and were not fortuitous. Such spectroscopic information may help to explain the effect of the NHC bulk on the catalysts in solution and may be correlated with their activity in homogeneous catalysis. Having prepared our new precatalysts, we then investigated their catalytic properties in Buchwald–Hartwtig arylamination. Recent reports identified electron-rich aryl halides and electron-deficient anilines as highly disfavored coupling partners.[9b] For this reason, these challenging substrates were examined with our new acac-bearing catalysts.

The coupling of 4-chloroanisole with 4-fluoroaniline was chosen as the test reaction for our initial optimization. After an initial base/solvent screening, the use of KO$^t$Am in toluene at 80 °C was found to provide the best conditions, leading to complete conversion of the starting materials with 0.25 mol % of **6**–**8** in 2 h. As the base is also involved in the activation of the catalyst, its choice is crucial. A plausible mechanism involves a chloride/alkoxide anion exchange followed by a rearrangement of the acac moiety and then a reductive elimination step to generate the active Pd species.[3k] Moreover, as in the case of **3**–**5**,[11] the use of more polar solvents appeared to be detrimental to the reaction (Table 1).

**Table 1. Optimization for Amination with 6–8**[a]




| entry | cat. | solvent | base | conversion, %[b] |
|---|---|---|---|---|
| 1 | **6** | toluene | KO$^t$Bu | 91 |
| 2 | **6** | toluene | KO$^t$Am | **100** |
| 3 | **6** | toluene | LiHMDS | 85 |
| 4 | **6** | 1,4-dioxane | KO$^t$Bu | 48 |
| 5 | **6** | 1,4-dioxane | KO$^t$Am | 35 |
| 6 | **6** | 1,4-dioxane | LiHMDS | 18 |
| 7 | **6** | DME[c] | KO$^t$Bu | 40 |
| 8 | **6** | DME | KO$^t$Am | 37 |
| 9 | **6** | DME | LiHMDS | 21 |
| 10 | **6** | DMF | KO$^t$Am | 23 |
| 11 | **7** | toluene | KO$^t$Am | **100** |
| 12 | **8** | toluene | KO$^t$Am | **100** |

[a]Reagents and conditions: ArX (0.5 mmol), Ar'NH$_2$ (0.55 mmol), base (0.55 mmol), solvent (1.0 mL), **6**–**8** (0.25 mol %) . [b]Conversion to coupling product based on starting aryl chloride by GC, average of three runs. [c]DME = dimethoxyethane.

To compare the catalytic properties of **3**–**5**[15] and **6**–**8**, the reaction was performed at lower catalyst loadings. Couplings of 4-chloroanisole with 4-fluoroaniline and 3-trifluoromethylaniline were chosen as benchmark reactions. By employing 0.05 mol % of precatalyst at 80 °C, 70% conversion was obtained with **6**, 98% with **7**, and 86% with **8** (Table 2, entry 1). At 110 °C, the coupling of 4-chloroanisole and 3-trifluoromethylaniline provided the desired products in 53%, 85%, and 76% GC conversions using **6**–**8**, respectively (Table 2, entry 2). It appeared that [Pd(IHept$^{OMe}$)(acac)Cl] (**7**) is the most efficient catalyst in every case. For both benchmark reactions, we previously observed the same trend with the [Pd(ITent)(acac)Cl] precatalysts (Table 2): **4** was more efficient than **3** and slightly more efficient than **5**.[11] The results obtained with [Pd(ITent$^{OMe}$)(acac)Cl] are in agreement with our previous results and confirmed the influential role of the length of the R-alkyl chains. This effect was optimal with the IHept$^{OMe}$ ligand. It appears that in the case of **8** the additional bulk is too far from the coordination sphere of the metal and does not influence the catalytic properties of the complex. We also observed that the activity of each [Pd(ITent$^{OMe}$)(acac)Cl] complex was superior to that of its [Pd(ITent)(acac)Cl] analogues, as observed on a comparison between **1** and **2**.[12] As the gain of activity is general of all the ITent$^{OMe}$ series, these results prove the positive effect of the methoxy group. As the methoxy substituent resides away from the coordination sphere of the metal, the stronger $\sigma$-donor properties of the ITent$^{OMe}$


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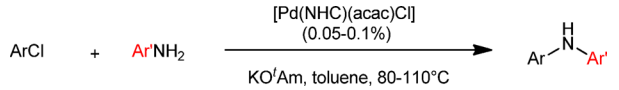
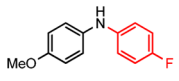
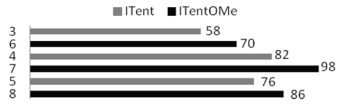
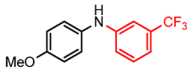
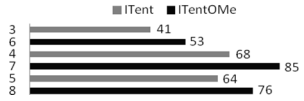
**Table 2. Comparison of [Pd(ITent)(acac)Cl] (3−5) and [Pd(ITent$^{OMe}$)(acac)Cl] (6−8) Precatalysts in Arylamination[a]**




| Entry | Product | GC conversions (%)[d] |
|---|---|---|
| 1[b] |  |  |
| 2[c] |  |  |



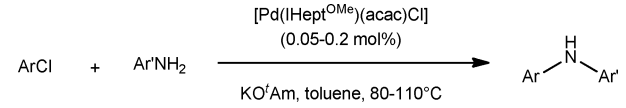
[a]Reagents and conditions: ArX (0.5 mmol), Ar'NH$_2$ (0.55 mmol), KO$^t$Am (0.55 mmol), toluene (1.0 mL). [b]**3−8** 0.05 mol %, 80 °C, 3 h;. [c]**3−8** 0.1 mol %, 110 °C, 6 h. [d]Conversion to coupling product based on starting aryl chloride by GC, average of three runs.

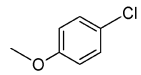
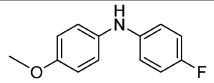
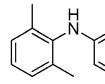
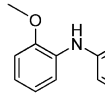
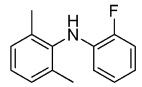
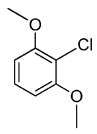
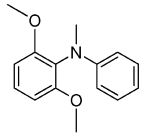
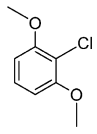
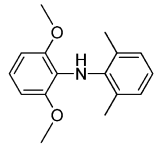
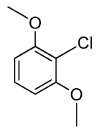
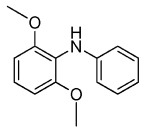
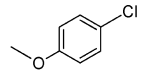
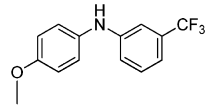
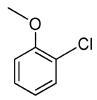
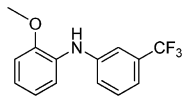
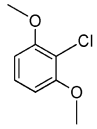
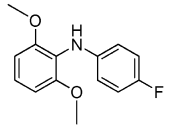
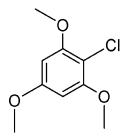
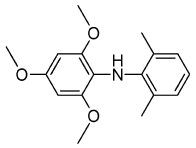
ligand in comparison with ITent ligand could explain the difference in the catalytic activity observed. This extra $\sigma$ donation could offer greater stabilization of the Pd$^0$−NHC complex.[3a,16] [Pd(IHept$^{OMe}$)(acac)Cl] (**7**) combined the optimal length of the alkyl chain and the presence of the methoxy group and gave the best results for C−N coupling.

[Pd(IHept$^{OMe}$)(acac)Cl] (**7**) was selected as the precatalyst to explore the scope of the arylamination reaction. The scope of the reaction was explored with the previously optimized conditions, using 0.05−0.2 mol % of **7** in toluene at 80 °C or at reflux in the presence of KO$^t$Am. The system displayed excellent catalytic activity for the coupling of various substrates. Good yields are obtained with electron-poor anilines and electron-rich aryl chlorides, which are reported to be challenging coupling partners (Table 3, entries 1−4 and 8−10).[10] The system appeared unaffected by the presence of substituents in the *ortho* position of the aryl chlorides: couplings of 2-chloroanisole and 4-chloroanisole with 4-fluoroaniline gave very similar results (Table 3, entries 1 and 3). Similar results are observed for the coupling of 2-chloroanisole or 4-chloroanisole with 3-trifluoromethylaniline (Table 3, entries 8 and 9). Moreover, very good yields were obtained with sterically hindered substrates (Table 3, entries 4, 6, and 11). The increased conformational flexibility of IHept$^{OMe}$ may allow it to better accommodate sterically hindered substrates in the coordination sphere of the metal center.[7,17] In all cases, the product of biarylation is never observed, attesting that this catalytic system is selective for the monoarylation of ArNH$_2$. Finally, various anilines were successfully coupled with deactivated 1,3-dimethoxychlorobenzene (Table 3, entries 5, 6, and 9) and, for the first time, with very deactivated 1,3,5-trimethoxychlorobenzene at low catalyst loading (Table 3, entry 11), attesting to the high reactivity of **7**.

We also investigated the efficiency of our catalyst with more nucleophilic amines. Nonactivated aryl chlorides were successfully coupled with *N*-methylaniline at low catalytic loading (as low as 50 ppm of **7**), and remarkable catalyst productivity (turnover number up to 18000) was observed (Table 4, entries 2 and 3). These results are comparable with results obtained with the most efficient Pd/phosphine systems for similar substrates.[18]

**Table 3. Scope of the Buchwald−Hartwig Arylamination with [Pd(IHept$^{OMe}$)(acac)Cl] (7)[a]**




| Entry | ArCl | Product | Pd (%) | Yield |
|---|---|---|---|---|
| 1 |  |  | 0.05 | 95 |
| 2 |  |  | 0.05 | 91 |
| 3 |  |  | 0.05 | 96 |
| 4 |  |  | 0.1 | 92 |
| 5 |  |  | 0.1 | 87 |
| 6 |  |  | 0.1 | 79 |
| 7 |  |  | 0.1 | 74 |
| 8 |  |  | 0.2 | 91[c] |
| 9 |  |  | 0.2 | 88[c] |
| 10 |  |  | 0.2 | 90[c] |
| 11 |  |  | 0.2 | 83[c] |

[a]Reagents and conditions: ArX (0.5 mmol), Ar'NH$_2$ (0.55 mmol), KO$^t$Am (0.55 mmol), **7** (x mol %), toluene (1.0 mL), 80 °C, 3 h. [b]Isolated yields after chromatography on silica gel, average of two runs. [c]110 °C, 6 h.

## CONCLUSION

The new [Pd(ITent$^{OMe}$)(acac)Cl] complexes were obtained as well-defined air- and moisture-stable precatalysts in good yields.


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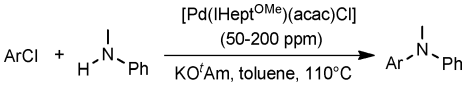
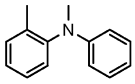
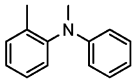
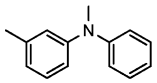
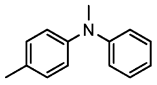
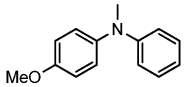
**Table 4. Arylamination with Low Catalytic Loadings**




| Entry | Product | Pd (ppm) | Yield (%)[b] | TON |
|---|---|---|---|---|
| 1 |  | - | 0 | |
| 2 |  | 50 | 91 | 18200 |
| 3 |  | 50 | 93 | 18600 |
| 4 |  | 100 | 84 | 8400 |
| 5 |  | 200 | 83 | 4150 |

[a]Reagents and conditions: ArCl (0.5 mmol), Ar'$NH_2$ (0.55 mmol), KO$^t$Am (0.55 mmol), **7** (x ppm), toluene (1.0 mL), 110 °C. [b]Isolated yields after chromatography on silica gel, average of two runs.

They proved to be superior to their [Pd(ITent)(acac)Cl] analogues. The study confirmed that the "flexible steric bulk" concept is essential in securing high catalytic activity with Pd–NHC complexes and this effect is greatest with [Pd(IHept$^{OMe}$)(acac)Cl]. Combining optimal steric and electronic properties, [Pd(IHept$^{OMe}$)(acac)Cl] exhibited excellent catalytic activity in Buchwald–Hartwig coupling reactions with various substrates, even the most deactivated. Moreover, excellent productivity (TON > 18000) was also observed with nucleophilic anilines. This study will help to identify which characteristics are crucial for the design of future *N*-heterocyclic carbene ligands in palladium catalysis.

## EXPERIMENTAL SECTION

**Procedure for the Synthesis of [Pd(IPent$^{OMe}$)(acac)Cl].** In a Schlenk flask equipped with a magnetic stirring bar were added IPent$^{OMe}$·HCl (223 mg, 0.37 mmol) and $Pd(acac)_2$ (85 mg, 0.28 mmol) in dry 1,4-dioxane (6 mL) under an atmosphere of nitrogen. The reaction mixture was refluxed for 40 h. After this time, dioxane was evaporated and the crude product was dissolved in pentane. The solution was filtered on a pad of silica covered with Celite, and the pad was eluted with pentane. After evaporation of the solvent and drying under high vacuum, the desired complex was obtained as a yellow powder (184 mg, 82%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.01 (s, 2H), 6.73 (s, 4H), 5.04 (s, 1H), 3.86 (s, 6H), 2.66 (m, 4H), 2.11 (m, 4H), 1.78 (s, 3H), 1.61 (s, 3H), 1.75–1.40 (m, 12H), 0.97 (t, $J$ = 7.3 Hz, 12H), 0.75 (t, $J$ = 7.4 Hz, 12H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 186.1, 183.6, 159.5, 154.8, 145.5, 130.2, 125.2, 110.4, 99.7, 55.2, 41.5, 28.5, 27.4, 27.1, 26.7, 26.0, 12.4, 11.5. Anal. Calcd for $C_{42}H_{63}ClN_2O_4Pd$: C, 62.91; H, 7.92; N, 3.49. Found: C, 62.84; H, 8.03; N, 3.53.

**Procedure for the Synthesis of [Pd(IHept$^{OMe}$)(acac)Cl].** In a Schlenk flask equipped with a magnetic stirring bar were added IHept$^{OMe}$·HCl (193 mg, 0.27 mmol) and $Pd(acac)_2$ (62 mg, 0.2 mmol) in dry 1,4-dioxane (5 mL) under an atmosphere of nitrogen. The reaction mixture was refluxed for 40 h. After this time, dioxane was evaporated and the crude product was dissolved in pentane. The solution was filtered on a pad of silica covered with Celite, and the pad was eluted with pentane. After evaporation of the solvent and drying under high vacuum, the desired complex was obtained as a yellow powder (159 mg, 87%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.96 (s, 2H), 6.70 (s, 4H), 4.99 (s, 1H), 3.84 (s, 6H), 2.76 (m, 4H), 2.10 (m, 4H), 1.76 (s, 3H), 1.46 (s, 3H), 1.68–1.04 (m, 28H), 0.79 (t, $J$ = 7.1 Hz, 24H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 186.0, 183.6, 159.5, 154.5, 146.0, 130.0, 125.1, 110.1, 99.6, 52.3, 39.7, 39.6, 38.5, 26.5, 25.7, 21.3, 20.8, 14.7. Anal. Calcd for $C_{50}H_{79}ClN_2O_4Pd$: C, 65.70; H, 8.71; Cl, N, 3.06. Found: C, 65.64; H, 8.80; N, 3.15.

**Procedure for the Synthesis of [Pd(INon$^{OMe}$)(acac)Cl].** In a Schlenk flask equipped with a magnetic stirring bar were added INon$^{OMe}$·HCl (221 mg, 0.27 mmol) and $Pd(acac)_2$ (62 mg, 0.2 mmol) in dry 1,4-dioxane (5 mL) under an atmosphere of nitrogen. The reaction mixture was refluxed for 40 h. After this time, dioxane was evaporated and the crude product was dissolved in pentane. The solution was filtered on a pad of silica covered with Celite, and the pad was eluted with pentane. After evaporation of the solvent and drying under high vacuum, the desired complex was obtained as a yellow powder (160 mg, 78%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.96 (s, 2H), 6.72 (s, 4H), 5.00 (s,1H), 3.86 (s, 6H), 2.76 (m, 4H), 2.13 (m, 4H), 1.76 (s, 3H), 1.48 (s, 3H), 1.68–1.10 (m, 44H), 0.83 (m, 24H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 185.9, 183.4, 159.5, 154.4, 146.0, 130.0, 124.9, 110.0, 99.7, 55.3, 39.7, 37.0, 36.0, 30.4, 29.8, 26.6, 25.8, 23.5, 23.4, 14.2, 14.0. Anal. Calcd for $C_{58}H_{95}ClN_2O_4Pd$: C, 67.88; H, 9.33; N, 2.73. Found: C, 67.72; H, 9.46; N, 2.88.

**General Procedure for Buchwald–Hartwig Cross Coupling of Aryl Halides with Anilines.** In a glovebox, a glass vial equipped with a stirring bar was charged with KO$^t$Am (0.55 mmol) and sealed with a screw cap fitted with a septum. The vial was then loaded with the neat aniline (0.55 mmol) and the aryl halide (0.50 mmol) outside the glovebox. Finally, a premade solution of the precatalyst in anhydrous solvent (prepared in the glovebox) was injected at room temperature under argon and the reaction mixture was stirred and heated until completion, as indicated by GC. Then, water was added to the reaction mixture, the organic layer was extracted with $Et_2O$ and dried over magnesium sulfate, and the solvent was evaporated in vacuo. The product was purified by flash chromatography on silica gel.

## ASSOCIATED CONTENT

### Supporting Information

Text and figures giving detailed procedures for the amination reactions and NMR spectra for complexes **6**–**8** and cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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