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# An Air-Stable Palladium/*N*-Heterocyclic Carbene Complex and Its Reactivity in Aryl Amination

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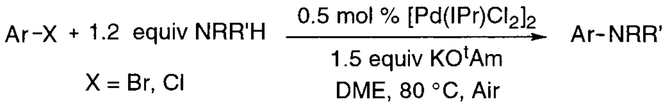
## ABSTRACT



**The synthesis and characterization of $[Pd(IPr)Cl_2]_2$ (1), an air- and moisture-stable complex, is reported. The utilization of 1 as a catalyst for amination of aryl chlorides and bromides with a variety of amine coupling partners under mild conditions is described. The amination reactions with 1 show a remarkable insensitivity to oxygen and water, and thus the amination reactions could be performed in air on the benchtop with undried reagent grade solvents and substrates with small effects on reaction times and conversions.**

Palladium-catalyzed coupling reactions have garnered enormous interest over the past few decades,[1] with great strides achieved in amination of aryl halides.[2] Catalysts based on strongly donating ligands and late transition metals have led to the recent successes in coupling reactions using unactivated aryl chlorides[3] with various transmetalating reagents.[1] Most reported active species are formed in situ from the metal source and (generally) air-sensitive phosphine ligands rather than use of an isolated metal−ligand complex.[4,5] Easily synthesized, highly active, yet air- and “shelf”-stable palladium complexes could be welcome additions to the existing arsenal of cross-coupling catalysts.[6]

*N*-Heterocyclic carbenes (NHC) such as *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) can benefit late metal catalysis systems by virtue of their strong electron-donating properties and their hedge-like steric bulk. The ligand electron-donating nature surely helps promote the aryl halide (or pseudo-halide) oxidative addition, the ligand bulk presumably facilitates the reductive elimination step. Our previous studies on palladium/NHC system revealed the Pd−carbene bond to be robust over time and tolerant of arduous conditions (heat), indicating such a system might not require excess ligand to compensate for ligand−metal bond lability.[7] In studies involving a number of cross-coupling systems, the

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(1) Mitchell, T. N. In *Metal-Catalyzed Cross-Couplings Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science: Mill Valley, CA, 1987. (c) Suzuki, A. In *Metal-Catalyzed Cross-Couplings Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97. (d) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.

(2) See for example: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860.

(3) (a) Wolfe, J. P.; Tomori, H.; Sadighi, Y. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174. (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413 (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 338−3388. (e) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (f) Bei, X.; Guram, A. S.; Turner, H. W.; Weinburg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858. (g) Indolese, A. F. *Tetrahedron Lett* **1997**, *38*, 3513−3516.

(4) For an in situ catalyst generation, see for example: Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327−5333.

(5) Recently palladium tertiary phosphine complexes have been used as catalyst precursors in cross-coupling and related chemistry. See for example: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

(6) For recent reports of defined catalysts for Suzuki coupling, see: (a) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540−1541. (b) Andreu, M. G.; Zapf, A.; Beller, M. *Chem. Commun.* **2000**, 2475−2476.

(7) (a) Huang, J.; Grasa, A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 2053−2055 (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729−7737. (c) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889−9890. (d) Zhang, C.; Huang, J.; Trudell, M. T.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805 (e) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186−190. (f) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 1307−1309. (g) Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 5689−5692. (h) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029−3036.

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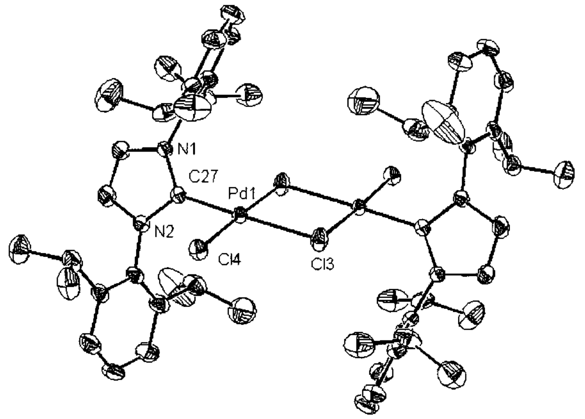
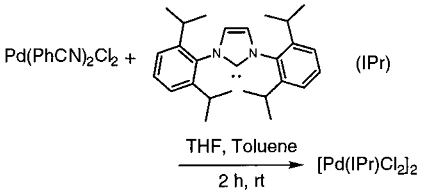


**Figure 1.** ORTEP of **1**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C1(3) 2.4029(9); Pd(1)−C1(4) 2.2715(9); Pd(1)−C(27) 1.9553(3); C1(3)−Pd(1)−C1(4) 91.26(3); C1(3)−Pd(1)−C(27) 178.26(9); C1(4)−Pd(1)−C(4) 90.48(9).

optimum palladium-to-ligand ratio was determined to be 1:1.[8] With this ratio in mind, we examined possible routes leading to complexes where the palladium center was bound by a single NHC ligand.



(1)

One of the initial reactions examined involved the interaction between 1 equiv IPr[9] with $PdCl_2(MeCN)_2$ or $PdCl_2(PhCN)_2$ in THF/toluene (eq 1).[10] The highly nucleophilic carbene readily displaces the nitrile ligands generating the tan-orange $[Pd(IPr)Cl_2]_2$ **1**. Single-crystal X-ray analysis of crystals formed in 1,2-dichloroethane/hexanes under slow cooling revealed **1** to be a dimer, with two terminal and two bridging chlorine atoms, Figure 1. The geometry at the metal centers is distorted square planar with all Pd and chlorine atoms coplanar and the aryl groups of the trans-disposed IPr ligands canted normal to each other.

Although the reaction requires dry solvents under inert atmosphere, the synthetic workup can be performed in air with little or no compromise to yield or purity of product. Complex **1** is soluble in polar to slightly polar solvents and sparingly soluble in hexanes and benzene. It is both air- and moisture-stable and showed no deterioration after storage on the bench for 3 months.

To test its potential utility, complex **1** was used as a catalyst precursor in aryl amination. The amination reactions were performed (under optimized conditions) in DME with potassium *tert*-amylate ($KO^tAm$) as base,[11] as described in eq 2.[12] The palladium loading, 1 mol % (0.5 mol % **1**), is significantly lower than loadings needed in our previously reported studies (2−3 mol %) and is comparable to catalyst loadings used in the best Pd/phosphine systems. [3a,6,13]

$$\text{Ar-X} + 1.2\ \text{equiv NRR}'\text{H} \xrightarrow[80\ ^\circ\text{C, DME}]{\substack{0.5\ \text{mol \%}\ \mathbf{1}\\ 1.5\ \text{equiv KO}^t\text{Am}}} \text{Ar-NRR}' \qquad (2)$$

The role of the base appears crucial in aryl amination systems. We believe the alkoxide base acts as an initiator in the present system, leading to the formation of a palladium-alkoxide species that is subsequently transformed via a mechanism recently proposed by Hartwig.[14]

Results of the amination study using aryl and heteroaryl halides are listed in Table 1. We focused our attention on the more economical and more difficult to activate aryl chlorides, determining some overall steric and reaction condition limitations through reactions with aryl bromides. The reaction of 4-chlorotoluene with aniline proceeds to complete conversion in 40 min at 80 °C and in 1 h at 50 °C (entries 1 and 2, Table 1), whereas we found only moderate conversion was achieved at room temperature (75% in 15 h).

Activated aryl bromides and chlorides completely converted to products in just a few minutes (entries 4 and 5). Electronically deactivated and sterically hindered substrates generally required longer reaction times of up to 3 h (entries 7−9). Both primary amines and secondary anilines are capable coupling partners with aryl chlorides, giving high conversions to products in 2 h at 80 °C. Chloropyridines are fully compatible with this catalyst system and lead to product in short reaction times (entry 10). The potentially very attractive multiple amination approach leading to oligomeric or polymeric material is illustrated by entry 11.[15]

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[8] Herrmann has recently reported a palladium complex bearing two bulky NHC leading to a stable Pd(0) complex. Its reactivity has been investigated in Suzuki−Miyaura cross coupling: Gstöttmayr, C. W. K.; Böhn, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363−1365.

[9] The synthesis of IPr·HCl has been reported.[7c] The ligand precursor (IPr·HCl) can be deprotonated by use of a strong base; see for example: Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49−54.

[10] **Synthesis of 1.** A 50-mL Schlenk flask was charged with 1.00 g (2.61 mmol) of $Pd(PhCN)_2Cl_2$, 10 mL of dry THF, and 10 mL of dry toluene. In a separate flask 1.00 g (2.57 mmol) of IPr was dissolved in 15 mL of THF. The IPr solution was transferred to the $Pd(PhCN)_2Cl_2$ solution via cannula, and the mixture was stirred for 2 h at room temperature during which time the solution changed color to cloudy dark red-orange. The reaction mixture was filtered through Celite, and 60% of the solvent was removed in vacuo. Hexanes were added with stirring until a persistent precipitate formed (20 mL). The product was collected on a frit and dried in vacuo, yielding a tan-orange powder in 83%.

[11] Other alkoxide bases function well on the test reaction: $KO^tBu$ leads to the desired product in 78% yield in 1.5 h, as does $NaO^tBu$ (75% in 1.5 h). The increased solubility of the amylate base in DME may be responsible for the increased reactivity.

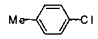
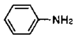
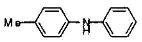
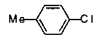
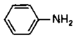
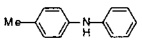
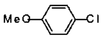
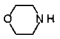
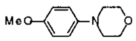
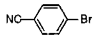
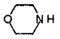
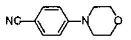
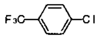
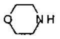
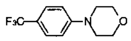
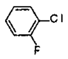
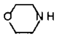
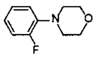
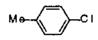
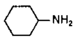
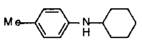
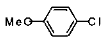
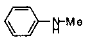
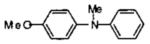
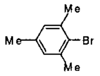
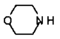
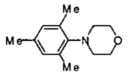
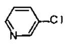
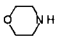
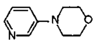
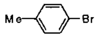
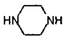
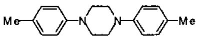
[12] For these reactions a stock solution of **1** and $KO^tAm$ in DME were made and used over the course of several days' experiments without apparent loss in activity.

[13] Hartwig, J. F.; Kawatsura, M.; Hauk, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

[14] Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905−12906.

[15] See for example: Zhang, X.-X.; Sadighi, J. P.; Mackewitz, T. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7606−7607.

**Table 1.** Air-Free Aryl Amination Catalyzed by **1**[a]

| entry | ArX | amine | product | time, h | T, °C | yield[b] |
|---|---|---|---|---|---|---|
| 1 |  |  |  | 0.6 | 80 | 100(86) |
| 2 |  |  |  | 1 | 50 | 98(84) |
| 3 |  |  |  | 1 | 50 | 99(79) |
| 4 |  |  |  | 0.1 | 80 | 100(83) |
| 5 |  |  |  | 0.25 | 80 | 100(97) |
| 6 |  |  |  | 1 | 80 | 78(58) |
| 7 |  |  |  | 2 | 80 | 95(92) |
| 8 |  |  |  | 2 | 80 | 98(88) |
| 9 |  |  |  | 3 | 80 | 78(71) |
| 10 |  |  |  | 1 | 80 | 100(84) |
| 11 |  |  |  | 0.8 | 80 | 100(89) |

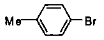
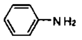
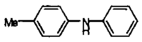
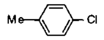
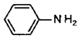
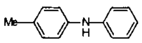
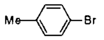
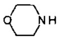
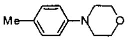
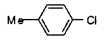
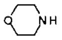
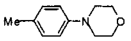
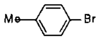
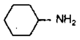
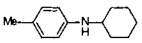
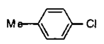
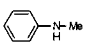
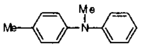
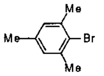
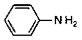
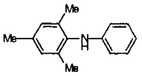
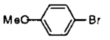
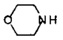
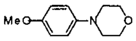
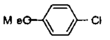
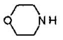
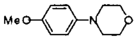
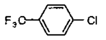
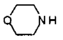
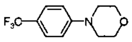
[a] Reaction conditions: 1 mmol of ArX; 1.2 mmol of NHRR′; 4 mL of DME (0.25 M in ArX); 1.5 equiv of KO$^t$Am; 0.5 mol % **1**. [b] GC conversion (isolated yield); average of two runs.

Dehalogenation of ArX was only a minor side reaction in all cases (<2%) with the exception of entry 6, where the fluorobenzene/product ratio was 22:78 as determined by GC analysis.

Suprisingly, aryl triflates were not active amine coupling partners in the present system, nor were base-sensitive substrates. Substitution of Cs$_2$CO$_3$ or K$_3$PO$_4$ for KO$^t$Am to address the latter limitation led to rapid formation of palladium black during the course of reactions. Indoles were inert to coupling in the present system; even at elevated temperatures coupling of indoles with aryl bromides did not occur.

A remarkable aspect of aryl amination utilizing **1** is the tolerance of these reactions to both air and moisture. As evidence of the robust nature of **1**, we were able to perform the amination reactions loaded on the benchtop in reagent grade solvent (stored on the bench without measures to exclude air or water) under air (Table 2).[16] There have only recently been reports of Pd-catalyzed coupling under similar conditions.[17,18] In the present system many substrate pairs reacted on par with those of the air-free system (entries 2 and 3). Some reactions involving aryl chlorides have diminished activity when conducted in air (e.g., entry 9). Lowering the catalyst loading to as little as 0.05 mol % of **1** led to only moderate activity (50% conversion after 12 h) when 4-chlorotoluene was reacted with morpholine.

**Table 2.** Aryl Amination Reactions Catalyzed by **1** under Aerobic Conditions[a]

| entry | ArX | amine | product | time, h | yield[b] |
|---|---|---|---|---|---|
| 1 |  |  |  | 0.3 | 100(84) |
| 2 |  |  |  | 1.3 | 100(81) |
| 3 |  |  |  | 0.1 | 100(88) |
| 4 |  |  |  | 0.5 | 99(87) |
| 5 |  |  |  | 0.6 | 97(94) |
| 6 |  |  |  | 1.5 | 100(85) |
| 7 |  |  |  | 4.0 | 99(92) |
| 8 |  |  |  | 0.5 | 100(89) |
| 9 |  |  |  | 4.0 | 66(58)[c] |
| 10 |  |  |  | 0.5 | 100(95) |

[a] Reaction conditions: 1 mmol of ArX; 1.2 mmol of NHRR′; 4 mL of DME (0.25 M in ArX); 1.5 equiv of KO$^t$Am; 0.5 mol % **1**. [b] GC conversion (isolated yield); average of two runs. [c] No further conversion after 4 h.

In summary, we report the synthesis and aryl amination reactivity of an air-stable NHC−palladium dichloride dimer (**1**). This complex shows good catalytic activity and can be used under aerobic conditions in some cases. Investigations focusing on the reactivity profile of **1** and related palladium complexes, their efficacy as catalysts in cross-coupling reactions, and mechanistic elucidation of these reactions are ongoing in our laboratories.

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**Supporting Information Available:** Experimental details for the synthesis of **1**, catalysis protocol, and product isolation are provided, as are crystallographic data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Aerobic conditions: 50-mL scintillation vials were charged with **1** and KO$^t$Am in the glovebox. On the bench DME, ArX, and amine (used as received) were added to the open vials. The vials were capped to prevent evaporation and suspended in an 80 °C oil bath for the duration of the reaction.

(17) (a) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677−8681. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584.

(18) Hartwig has reported[3a] a procedure involving the loading of catalyst and base in air followed by a purging of the reaction flask prior to carrying out aryl amination under N$_2$ without deleterious effects.