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[(CyPF-^{t}Bu)PdCl$_2$]: An Air-Stable, One-Component, Highly Efficient Catalyst for Amination of Heteroaryl and Aryl Halides

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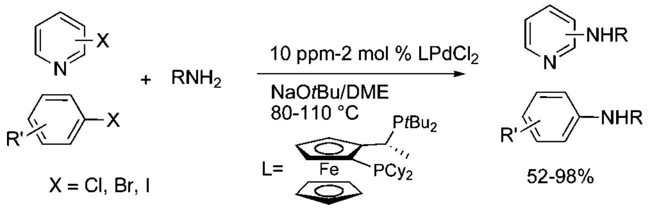
ABSTRACT



An air- and moisture-stable palladium catalyst, [(CyPF-^{t}Bu)PdCl$_2$] (1), for coupling of heteroaryl chlorides, bromides, and iodides with a variety of primary amines is described. Most of these reactions occurred in high yield with 0.001−0.05 mol % catalyst loading. The reactions tolerated a wide range of functional groups.

The palladium-catalyzed amination of aryl halides has emerged as a powerful tool for the synthesis of substituted anilines.[1] However, catalyst loadings for this transformation have been high enough (>0.1 mol %) to limit its use for the coupling of amines to produce less expensive intermediates and to produce commodity building blocks.[2] In 2005, we reported that the combination of Pd(OAc)$_2$ and the Josiphos ligand CyPF-^{t}Bu catalyzed, for the first time, the coupling of primary amines with heteroaryl halides with extremely low catalyst loadings (5.0−100 ppm).[3] This discovery increased the utility of palladium-catalyzed carbon−nitrogen coupling processes in an industrial setting.

These reactions would be made even more practical if a stable, single-component catalyst precursor could be used. When low loadings of palladium and ligand are used separately, the rate of complexation is slow. Thus, mixing of the metal and ligand in solution must be conducted at higher concentrations prior to addition of solvent and reagents. Moreover, the complex formed from the Josiphos ligand and Pd(OAc)$_2$ has a limited stability in solution and as a solid.

These observations led us to study C−N coupling reactions initiated with precatalysts bearing a single CyPF-^{t}Bu ligand per palladium that are more stable than the adduct of this with Pd(OAc)$_2$. Herein, we report that the air- and moisture-stable palladium complex [(CyPF-^{t}Bu)PdCl$_2$] (**1**) in the absence of any additional ligand is a convenient and highly active catalyst precursor for the amination of heteroaryl and aryl halides that

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(1) (a) Hartwig, J. F.; Shekhar, S.; Shen, Q.; Barrios-Landeros, F. In *Chemistry of Anilines*; Rappoport, Z., Ed.; John Wiley & Sons Ltd.: Chichester, UK, 2007; Vol. 1, p 455. (b) Hartwig, J. F. In *Modern Arene Chemistry*; Austruc, C., Ed.; Wiley-VCH: Weinheim, 2002; p 107. (c) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negoshi, E., Ed.; Wiley-Intescience: New York, 2002; p 1051. (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (e) Belfield, A. J.; Brown, G. R.; Foubister, A. J.; Ratcliffe, P. D. *Tetrahedron* **1999**, *55*, 13285. (f) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(2) (a) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (b) King, A. O.; Yasuda, N. In *Organometallics in Process Chemistry*; Larsen, R. D., Ed.; Springer: Berlin, 2004; p 205.

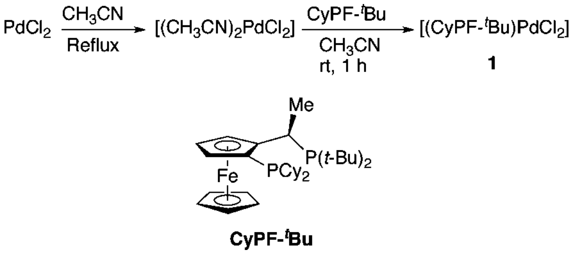
(3) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371.

10.1021/ol801615u CCC: $40.75

alleviates the need to generate the metal−ligand complex in situ prior to the amination process.

[(CyPF-^{t}Bu)PdCl$_2$] **1** was synthesized as shown in Scheme 1 by mixing CyPF-^{t}Bu with PdCl$_2$(CH$_3$CN)$_2$[4] as a slurry in CH$_3$CN at room temperature under nitrogen. Crystalline product was obtained by layering a THF solution of the crude product with hexanes. Dichloride **1** is soluble in THF, CH$_2$Cl$_2$ and toluene and slightly soluble in DME. It is stable to both air and moisture and did not deteriorate after storage on the bench for three months, as determined by ^{1}H NMR and ^{31}P NMR spectroscopy.

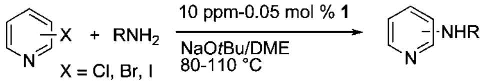
Scheme 1



To evaluate the potential of **1** as a catalyst for the amination of heteroaryl halides, we studied the prototype reaction of 3-chloropyridine[5] with octylamine in the presence of sodium *tert*-butoxide as base and 0.005 mol % of **1** in DME at 110 °C. This reaction was complete after 24 h and formed *N*-octyl-3-aminopyridine in 88% isolated yield. The reaction occurred at a similar rate and in a similar yield when conducted with 0.005 mol % Pd(OAc)$_2$/CyPF-^{t}Bu. Reactions conducted with NaO-^{t}Bu as base were fast and occurred in high yield, while reactions conducted with the weaker base K$_3$PO$_4$ required higher loading (1.0 mol %) and longer time (36 h) for full conversion. Reactions in toluene with NaO-^{t}Bu as base were slightly slower than those in DME, while reactions in THF and 1,4-dioxane were much slower.

Tables 1 and 2 summarize the coupling of heteroaryl and aryl chlorides, bromides, and iodides with primary alkylamines, catalyzed by dichloride **1**. In general, the rates for amination of aryl bromides were slightly faster than those for amination of aryl chlorides. The rates for amination of aryl iodides were markedly slower than those for amination of either aryl chlorides or bromides. Consequently, the catalyst loadings for reactions of aryl iodides were 5−10 times higher than those for reactions of aryl chlorides and bromides, but reactions of aryl iodides still occurred with much greater efficiency than with catalysts reported previously containing other ligands.[6]

Table 1. Coupling of Heteroaryl Halides with Primaryl Alkylamines Using (CyPF-^{t}Bu)PdCl$_2$ **1**[a]



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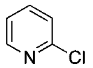
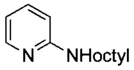
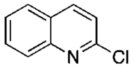
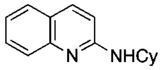
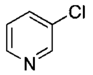
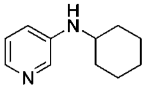
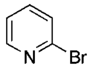
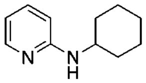
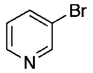
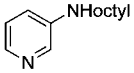
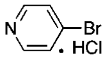
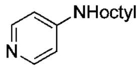
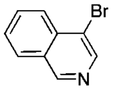
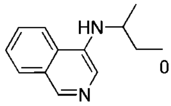
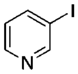
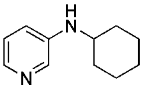
1			0.001	110 °C, 24 h	92
2			0.01	110 °C, 24 h	85
3			0.05	100 °C, 24 h	88
4			0.005	80 °C, 36 h	86
5			0.005	100 °C, 36 h	74
6[c]			0.005	110 °C, 12 h	87
7			0.05	100 °C, 30 h	88
8			0.05	100 °C, 24 h	96
9			0.05	110 °C, 24 h	70

[a] Reactions conducted with specified mol % of **1**, 1 mmol of ArX, 1.2 equiv of amine, and 1.4 equiv of NaO-^{t}Bu in 1 mL of DME. [b] Isolated yield. [c] Reaction with 7.90 g of 3-bromopyridine (50.0 mmol).

Reactions of primary alkylamines with a variety of heteroaryl chlorides, bromides, and iodides occurred in high yield with catalyst loadings between 0.001−0.05 mol % (Table 1). These loadings are 1 or 2 orders of magnitude lower than those reported previously for the reactions of aryl chlorides with primary amines in the presence of catalysts based on other ligands.[7,8] These loadings are just as low as those with the combination of Pd(OAc)$_2$ and the Josiphos ligand. For example, reaction of 3-bromopyridine with octylamine occurred in 74% yield with only 0.005 mol % of catalyst. Of course, these reactions can be conducted without a drybox.

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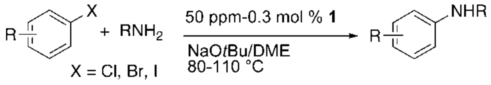
(4) Schlosser, M. *Organometallics in Synthesis: A Manual*, 2nd ed.; John Wiley & Sons, Ltd.: Chichester, 2002.

(5) (a) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861. (b) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481. (c) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (d) Maes, B. U. W.; Loones, K. T. J.; Lemiere, G. L. F.; Dommisse, R. A. *Synlett* **2003**, 1822. (e) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* **2003**, *5*, 4373. (f) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (g) Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611.

(6) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (c) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560. (d) Parrot, I.; Ritter, G.; Wermuth, C. G.; Hibert, M. *Synlett* **2002**, 1123.

(7) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (d) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (e) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (f) Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416. (g) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229. (h) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (i) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (j) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983.

Table 2. Coupling of Aryl Halides with Primary Alkylamines Using (CyPF-^{t}Bu)PdCl$_2$ **1**[a]



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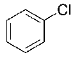
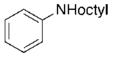
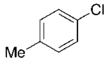
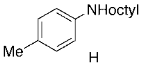
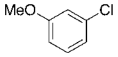
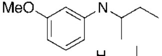
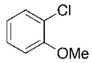
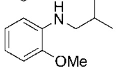
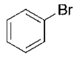
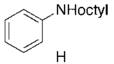
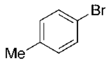
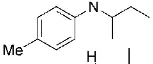
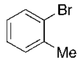
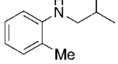
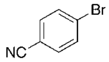
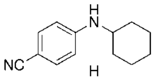
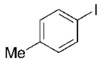
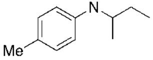
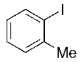
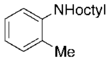
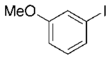
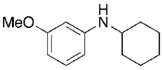
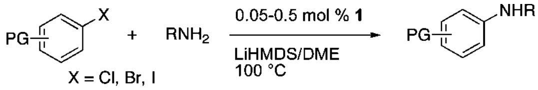
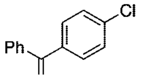
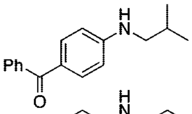
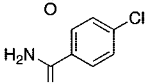
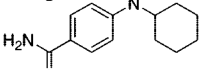
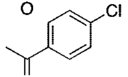
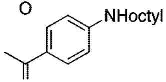
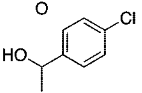
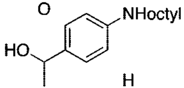
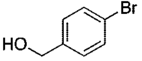
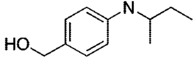
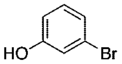
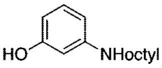
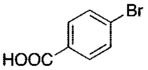
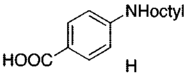
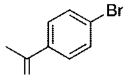
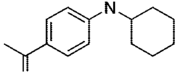
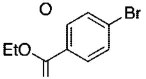
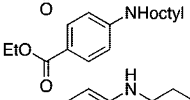
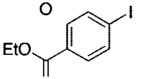
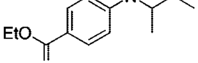
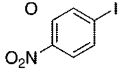
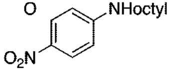
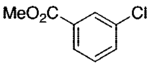
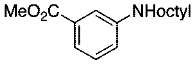
1			0.005	110 °C, 36 h	98
2			0.05	110 °C, 30 h	96
3			0.05	110 °C, 24 h	75
4			0.05	110 °C, 24 h	98
5			0.005	110 °C, 36 h	66
6			0.05	110 °C, 24 h	81
7			0.05	110 °C, 24 h	98
8			0.005	80 °C, 36 h	59
9			0.3	110 °C, 36 h	82
10			0.05	110 °C, 30 h	98
11			0.05	110 °C, 36 h	96

[a] Reactions conducted with specified mol % of **1**, 1 mmol of ArX, 1.2 equiv of amine, and 1.4 equiv of NaO-^{t}Bu in 1 mL of DME. [b] Isolated yield.

Table 3. Amination of Functionalized Aryl Halides with Primary Alkylamine Using (CyPF-^{t}Bu)PdCl$_2$ **1**[a]



entry	halide	product	catalyst loading (%)	conditions	yield (%)[b]
1			0.05	100 °C 48 h	84
2			0.5	100 °C 36 h	52
3[c]			0.5	110 °C 24 h	67
4			0.5	100 °C 24 h	77
5			0.5	100 °C 24 h	69
6			0.05	100 °C 24 h	84
7			0.05	100 °C 24h	78
8[c]			1.0	110 °C 24 h	75
9[c]			0.5	110 °C 24 h	88
10[c]			2.0	110 °C 48h	71
11[c]			1.0	110 °C 24 h	85
12[c]			1.0	110 °C 24 h	89

[a] Reactions conducted with specified mol % of **1**, 1 mmol of ArX, 1.2 equiv of amine, and 2.4 equiv of LiN(SiMe$_3$)$_2$ in 1 mL of DME. [b] Isolated yield. [c] Using K$_3$PO$_4$ as the base.

The same process conducted on an 8.0 g scale using Schlenk methods formed the product in a comparable 87% yield.

Reactions of aryl chlorides, bromides, and iodides with primary alkylamines occurred in high yield with low catalyst loading without changing the reaction conditions from that of entry 3 in Table 1. These results are summarized in Table 2. Electron-poor, electron-neutral, and electron-rich aryl halides reacted with a variety of primary alkylamines with 0.005−0.05 mol % of catalyst. For instance, in the presence of only 0.05 mol % of the catalyst, the reaction of *sec*-butylamine with 3-chloroanisole and 4-bromotoluene occurred in 75% and 81% yields, respectively (Table 2, entries 3 and 6). However, the coupling of an electron-rich aryl iodide with an α-branched primary alkylamine required a slightly higher loading (0.3 mol %) to proceed to completion (Table 2, entry 9). Typically, reactions of more hindered α-branched primary alkylamines were slower and required higher loadings than those of linear primary amines. However, reactions of these amines with aryl chlorides and bromides still occurred with just 0.05 mol % of catalyst and with aryl iodides with 0.3 mol % of catalyst.

This catalyst is not only highly reactive for coupling of primary amines, it is highly selective for monoarylation. No products from diarylation of amines were observed by GC/MS for any of the reactions in Tables 1 or 2.

The use of NaO-^{t}Bu as base in catalytic amination reactions can be incompatable with certain functional groups. However, the use of 2 equiv of lithium bis(trimethylsilyl)amide (LiN(TMS)$_2$) as base[9,10] greatly improves the functional group compatibility of these reactions. Reactions of aryl halides containing protic functional groups,[10,11] including a free alcohol, phenol, carboxylic acid, amide, and protected amine, are summarized in Table 3. These reactions occurred in high yield in the presence of 0.05−0.5 mol % of complex **1** and

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(8) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

(9) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

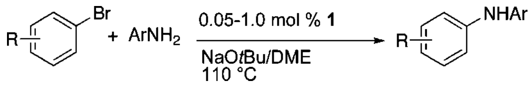
(10) (a) Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885. (b) Urgaonkar, S.; Verkade, J. G. *Adv. Synth. Catal.* **2004**, *346*, 611.

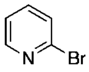
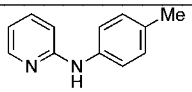
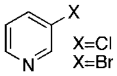
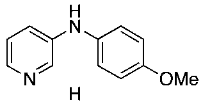
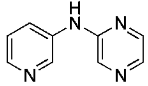
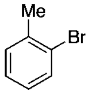
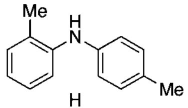
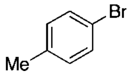
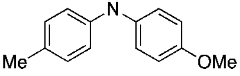
(11) (a) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (c) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.

LiN(TMS)$_2$[10] as the base (Table 3, entries 2−7). Reactions of aryl chlorides, bromides, and iodides bearing carboalkoxy and nitro groups, as well as acyl groups containing enolizable hydrogens, occurred in higher yields when using K$_3$PO$_4$ as base, instead of LiN(TMS)$_2$ (Table 3, entries 8−11).[10,11] In these reactions, higher loadings of the catalyst and higher temperatures were required for full conversion, due to the decreased basicity and/or solubility of K$_3$PO$_4$.

Reactions of primary arylamines are summarized in Table 4. These reactions were slower than the reactions of primary alkylamines. Nevertheless, high yields of coupled product from reactions of heteroaryl and aryl chlorides and bromides with electron rich arylamines were obtained using only 0.05−0.1 mol % catalyst (Table 4, entries 1−3, 5−6). Reactions of electron-deficient primary heteroarylamines were slower and required higher catalyst loadings than the reactions of primary arylamines. For example, the reaction of 2-aminopyrazine with the unactivated 3-chloropyridine ccurred in high yield, but required 1 mol % of catalyst at 110 °C (Table 4, entry 4).

Table 4. Coupling of Heteroaryl and Aryl Halides with Primary Arylamines Using (CyPF-^{t}Bu)PdCl$_2$ **1**[a]

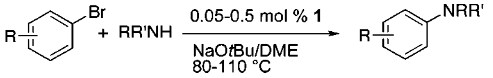


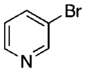
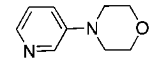
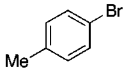
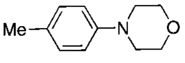
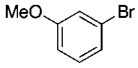
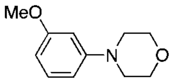
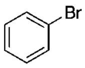
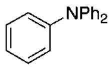
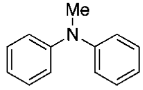
entry	halides	product	catalyst loading (%)	conditions	yield (%)[b]
1			0.05	110 °C, 24 h	92
2			0.1	110 °C, 36 h	89
3			0.05	110 °C, 24 h	83
4			1.0	110 °C, 24 h	86
5			0.05	110 °C, 48 h	95
6			0.05	110 °C, 48 h	98

[a] Reactions conducted with specified mol % of **1**, 1 mmol of ArX, 1.2 equiv of amine, and 1.4 equiv of NaO-^{t}Bu in 1 mL of DME. [b] Isolated yield.

Dichloride complex **1** was less effective as a catalyst for reactions of secondary amines[8,12] with heteroaryl and aryl halides. Reactions were slower and substantial amounts of hydrodehalogenation product were observed. Only a limited number of combinations of secondary amines and aryl halides reacted in high yield at low catalyst loading. These data are summarized in Table 5. For instance, the cyclic secondary amine morpholine reacted with 3- bromoanisole in the presence of 0.05 mol % catalyst to give the desired products in 89% yield (Table 5, entry 3).

Table 5. Coupling of Heteroaryl and Aryl Bromides with Secondary Amines Using (CyPF-^{t}Bu)PdCl$_2$ **1**[a]



entry	halide	product	catalyst loading (%)	conditions	yield (%)[b]
1			0.5	110 °C, 20 h	76
2			0.5	110 °C, 48 h	90
3			0.05	110 °C, 48 h	89
4			0.5	110 °C, 20 h	81
5			0.05	110 °C, 48 h	69

[a] Reactions conducted with specified mol % of **1**, 1 mmol of ArX, 1.2 equiv of amine, and 1.4 equiv of NaO-^{t}Bu in 1 mL of DME. [b] Isolated yield.

In summary, we have shown that the palladium complex [(CyPF-^{t}Bu)PdCl$_2$] (**1**) is a general, highly efficient catalyst for the coupling of heteroaryl and aryl chlorides, bromides, and iodides with primary nitrogen nucleophiles. Reactions catalyzed by [(CyPF-^{t}Bu)PdCl$_2$] occur with 0.001−0.05 mol % of catalyst, and these catalyst loadings are, in most cases, 2 orders of magnitude lower than those of analogous couplings by catalysts containing other ligands. These data are similar to those obtained with the combinatinon CyPF-^{t}Bu and Pd(OAc)$_2$ without the need to first bind the ligand to the metal precursor. The process exhibits a broad scope and a high tolerance for functional groups, such as cyano, keto, free carboxylate, amido, carboalkoxy, aromatic, and aliphatic hydroxyl and amino functional groups.

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Note Added after ASAP Publication. Tables 1 and 2 were corrected on August 27, 2008.

Supporting Information Available: All experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (b) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem.—Eur. J.* **2006**, *12*, 5142. (c) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (d) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816 .