High-Activity Catalysts for Suzuki Coupling and Amination Reactions with Deactivated Aryl Chloride Substrates: Importance of the Palladium Source

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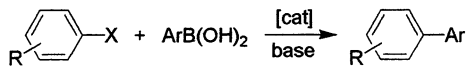
Received October 9, 2002

A range of ortho-metalated catalysts with alkylphosphine ligands of the general formula [Pd(X)(κ^2N,*C*-$C_6H_4CH_2NMe_2$)(PR_3)] have been synthesized, and the crystal structures of five examples (R = Cy, X = TFA, OTf, Cl, I; PR_3 = PCy_2(*o*-biphenyl), X = TFA) have been determined. The crystal structures of two dimeric precursor complexes, [{Pd(μ-TFA)(κ^2N,*C*-$C_6H_4CH_2NMe_2$)}$_2$] and [{Pd(TFA)(κ^2N,*C*-$C_6H_4CH{=}N^iPr$)}$_2$], have also been determined. The application of the phosphine adducts to both Suzuki coupling and Buchwald−Hartwig amination reactions with aryl chloride substrates was examined, and the performance of these catalysts versus conventional palladium sources was evaluated. In general the palladacyclic complexes show considerably enhanced activity. Typically, the best activity is seen with tricyclohexylphosphine adducts in Suzuki coupling and tri-*tert*-butylphosphine analogues in amination reactions. In nearly all the amination reactions performed, small amounts of a second product species were observed, namely 4,6-bis(aryl)-3,4-dihydro-2*H*-[1,4]oxazines. The crystal structure of one example, 4,6-bis(4-methoxyphenyl)-3,4-dihydro-2*H*-[1,4]oxazine, was determined. Studies on the activation of palladacyclic precatalysts in the coupling of morpholine led to the isolation of a morpholine adduct, [Pd(TFA)(κ^2N,*C*-$C_6H_5CH_2NMe_2$){$NH(CH_2CH_2)O$}], which was structurally characterized by X-ray analysis.

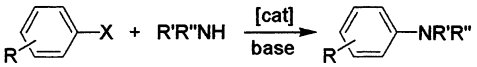
Introduction

Palladium-catalyzed coupling reactions are extremely powerful tools for the synthesis of new carbon−carbon and carbon−heteroatom bonds. The Suzuki coupling reaction (Scheme 1) is a versatile technique for the formation of unsymmetrical biaryls,[1] while the amination of aryl halides (Scheme 2) has emerged as an excellent technique for the synthesis of N-substituted anilines.[2] A major recent focus in coupling chemistry has been on the development of catalysts that are able to activate aryl chloride substrates, since these tend to be cheaper and more readily available than their bromide and iodide counterparts, factors that make them particularly relevant to the industrial sector. Unfortunately the comparatively high C−Cl bond strength makes their activation by oxidative addition comparatively difficult.[3]

Scheme 1. Suzuki Biaryl Coupling Reaction



Scheme 2. Amination of Aryl Halides



While there are now many reports on the use of aryl chlorides in both Suzuki coupling and amination reactions,[4,5] in most cases the catalysts employed need to be used in relatively high loadings. Therefore, the advantages associated with the use of aryl chlorides may be negated by the high cost of the catalyst systems and the need to remove palladium residues from the products down to the ppm level for use in fine chemicals and pharmaceutical applications. Consequently, there is considerable interest in the development of catalysts that can activate aryl chlorides at low loadings. Palladacyclic complexes have played a particular role in this regard. For instance, the complexes **1**−**3** (Chart 1) all show some activity in the Suzuki coupling of aryl chlorides.[6−8] We have recently demonstrated that the complexes **4a** and **5** show very high activity in the Suzuki coupling reaction of both deactivated and acti-

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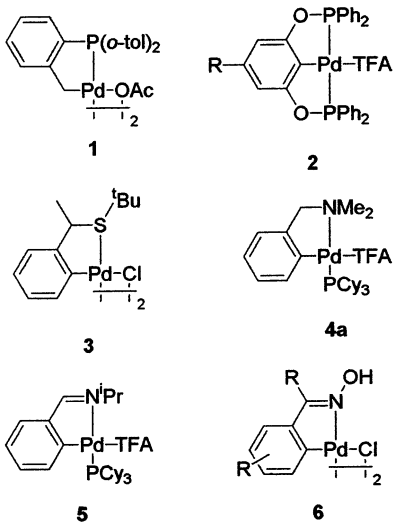
(1) Recent reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(2) For reviews see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(3) For a discussion see: Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

10.1021/om020841+ CCC: $25.00
Publication on Web 02/01/2003

Chart 1

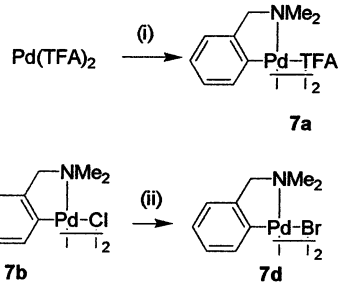


vated aryl chlorides,[4e] while Nájera has shown that the phosphine-free oxime-containing palladacycles **6** show good activity in the presence of water and tetrabutylammonium bromide.[4b,c] We report herein full details of the synthesis of the complexes of the types **4** and **5** and related catalysts and their application to Suzuki coupling and amination reactions. In particular we address the role of the ortho-metalation on catalyst performance. Aspects of this work have been communicated previously.[4e]

Results and Discussion

Synthesis and Characterization of Dimeric Precursor Complexes. We chose to synthesize phosphine adducts of palladacyclic complexes based on ortho-metalated *N*,*N*-dimethylbenzylamine, as we and, later, others have shown that the phosphine-free parent dimers show good activity in coupling reactions with aryl bromide and iodide substrates.[9,10] Similarly good activity has been observed with phosphine-free systems based on ortho-metalated imines and related ligands.[4b,c,11]

Scheme 3[a]



[a] Conditions: (i) $C_6H_5CH_2NMe_2$, THF, 40-70 °C, 1−5 h. (ii) NaBr, acetone, room temperature, 1.5 h.

The new dimeric precursor **7a** was synthesized in 94% yield by heating palladium trifluoroacetate with *N*,*N*-dimethylbenzylamine in THF (Scheme 3). The dimeric complexes [{Pd(μ-X)(κ^2N,*C*-$C_6H_4CH_2NMe_2$)}$_2$] (**7b**, X = Cl; **7c**, X = I) and the imine-containing dimer [{Pd(μ-TFA)(κ^2N,*C*-$C_6H_4CH{=}N^iPr$)}$_2$] (**8**) were prepared as described previously,[12−14] while the complex **7d** (X = Br) was synthesized in 90% yield by the reaction of the complex **7b** with sodium bromide in acetone at room temperature. The ^{1}H NMR spectra of complexes **7a**,**d** were very similar to those reported for the complexes **7b**,**c**.[12,13] The crystal structures of both complexes **7a** and **8** were determined, and the molecules are shown in Figures 1 and 2, while selected data are given in Tables 1 and 2, respectively. When the two structures are compared, it can be seen that, with the exception of the Pd−N bonds, all other bonds to the palladium centers are identical or very close in length. The Pd−N bond of **8** is shorter than that of the analogous bond in **7a**. This may be due to a contribution to the bond by retrodonation into the ortho-metalated imines C=N π^*-LUMO. The Pd···Pd distance in **8** is somewhat shorter than that in **7a**, presumably as a result of lower steric repulsion between the substituents on the N-donor and the ortho-metalated aromatic ring on the opposite half of the molecule. The Pd−C bond lengths of **7a** are essentially the same as those found in the complexes [{Pd(μ-X){κ^2N,*C*-$C_6H_4CH_2NH(CH_2Ph)$}}$_2$] (X = Br, acetate).[15,16] The Pd−N bonds lengths of **7a** are the same as those found for the latter bromide complex but shorter than those in the acetate analogue.[15,16] The Pd−C and Pd−N bonds of complex **8** are very similar to those of the closely related complex [{Pd(μ-TFA)-(κ^2N,*C*-$C_6H_4C(Me){=}N^iPr$)}$_2$].[11a]

(4) For recent examples of Suzuki couplings of aryl chlorides see: (a) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643. (b) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588. (c) Botella, L.; Nájera, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 179. (d) Liu, S.-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408. (e) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540. (f) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (g) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (h) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (i) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (j) Andreu, M. G.; Zapf, A.; Beller, M. *Chem. Commun.* **2000**, 2475. (k) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (l) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (m) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (n) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (o) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797. (p) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P *J. Org. Chem.* **1999**, *64*, 3804. (q) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387.

(5) For examples of aryl chloride amination reactions see: (a) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229. (b) Wolfe, J. P.; Tomori, H.; Sadighi, Y. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (d) Hartwig, J. F.; Kawatsura, M.; Hauk, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (e) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (f) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807. See also ref 4f,g,l,n.

(6) Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed.* **1995**, *34*, 1848.

(7) Bedford, R. B.; Draper, S. M.; Scully, P. N.; Welch, S. L. *New J. Chem.* **2000**, *24*, 745.

(8) Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881.

(9) Albisson, D. A.; Bedford, R. B.; Scully, P. N. *Tetrahedron Lett.* **1998**, *39*, 9793.

(10) Beletskaya, I. P.; Kashin, A. N.; Karlstedt, N. B.; Mitin, A. V.; Cheprakov, A. V.; Kazankov, G. M. *J. Organomet. Chem.* **2001**, *622*, 89.

(11) (a) Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun.* **1999**, 357. (b) Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901. (c) Rocaboy, C.; Gladysz, J. A., *Org. Lett.* **2002**, *4*, 1993.

(12) Pfeffer, M.; Goel, A. B. *Inorg. Synth.* **1989**, *26*, 211.

(13) Maasarani, F; Pfeffer, M.; Le Borgne, G. *Organometallics* **1987**, *6*, 2029.

(14) Bedford, R. B.; Cazin, C. S. J.; Hursthouse, M. B.; Light, M. E.; Pike, K. J.; Wimperis, S. *J. Organomet. Chem.* **2001**, *633*, 173.

(15) Vincete, J.; Saura-Llamas, I.; Turpín, J.; Ramíz de Apellano, M. C.; Jones, P. G. *Organometallics* **1999**, *18*, 2683.

(16) Fuchita, Y.; Yoshinaga, K.; Hanaki, T.; Kawano, H.; Kinoshita-Nagaoka, J. *J. Organomet. Chem.* **1999**, *580*, 273.

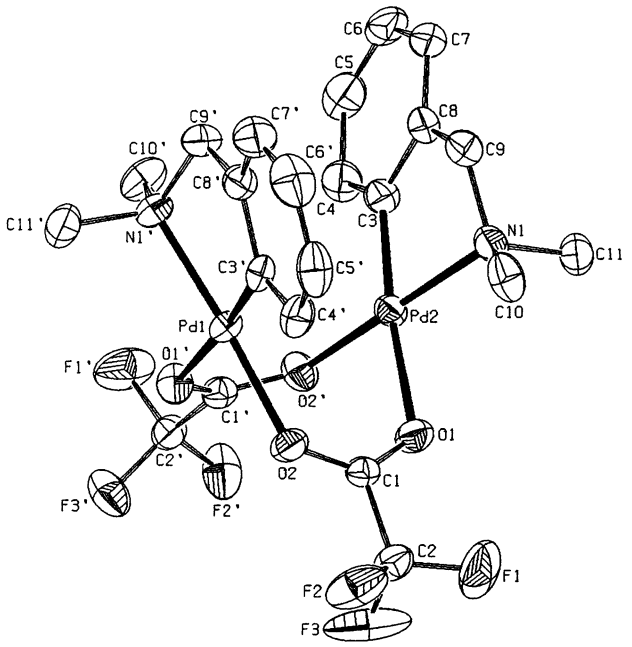


Figure 1. Molecular structure of [{Pd(μ-TFA)(κ^2N,C-C_6H_4-CH_2NMe_2)}$_2$] (**7a**).

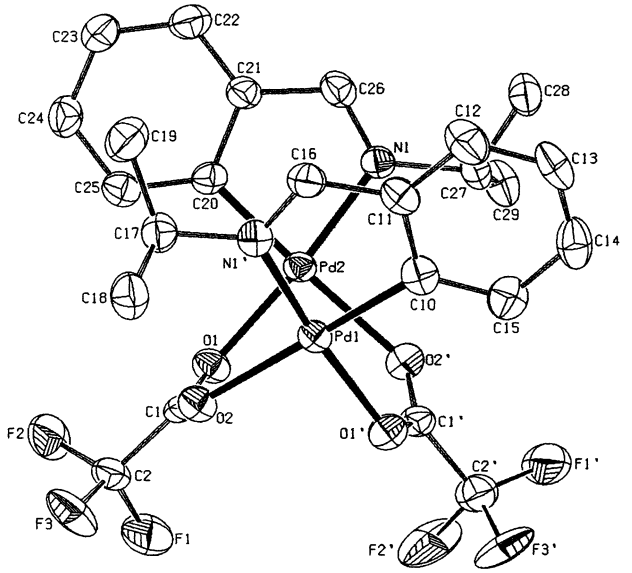


Figure 2. Molecular structure of [{Pd(μ-TFA)(κ^2N,C-$C_6H_4CH{=}N^iPr$)}$_2$] (**8**).

Table 1. Selected Bond Lengths or Interatomic Distances (Å) and Angles (deg) for [{Pd(μ-TFA)(κ^2N,C-$C_6H_4CH_2NMe_2$)}$_2$] (7a)

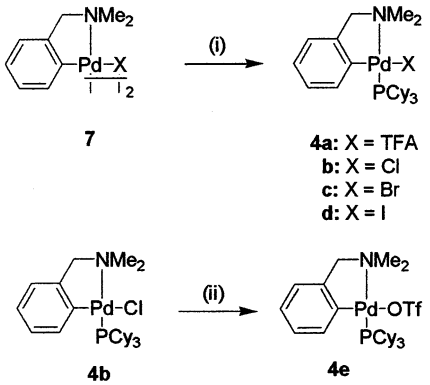
Pd1-C3′	1.954(3)	Pd2−C3	1.960(4)
Pd1−N1′	2.059(3)	Pd2−N1	2.062(3)
Pd1−O1′	2.174(2)	Pd2−O1	2.163(3)
Pd1−O2	2.072(2)	Pd2−O2′	2.064(2)
Pd1···Pd2	3.0588(4)		
C3′−Pd1−N1′	82.73(14)	C3−Pd2−N1	82.16 (14)
C3′−Pd1−O2	92.29(13)	C3−Pd2−O2′	92.77(14)
C3′−Pd1−O1′	174.67(12)	C3−Pd2−O1	174.48(13)
N1′−Pd1−O1′	94.00(11)	N1−Pd2−O1	94.12(12)
N1′−Pd1−O2	171.92(11)	N1−Pd2−O2′	171.93(12)
O1′−Pd1−O2	90.47(10)	O1−Pd2−O2′	90.46(11)

Synthesis and Characterization of Phosphine-Containing Complexes. The reaction of the dimeric complexes **7a**−**d** with 1.1 equiv per palladium of tricyclohexylphosphine in dichloromethane gave the phosphine adducts **4a**−**d** in 36−91% yields (Scheme 4). The triflate-containing complex **4e** was prepared by the metathesis reaction of the chloride complex **4b**, formed in situ, with silver triflate in dichloromethane.

Table 2. Selected Bond Lengths or Interatomic Distances (Å) and Angles (deg) for [{Pd(μ-TFA)(κ^2N,C-$C_6H_4CH{=}N^iPr$)}$_2$] (8)

Pd1−C10	1.964(5)	Pd2−C20	1.960(4)
Pd1−N1′	2.020(3)	Pd2−N1	2.002(3)
Pd1−O1′	2.066(3)	Pd2−O1	2.061(3)
Pd1−O2	2.202(3)	Pd2−O2′	2.182(3)
Pd1···Pd2	2.8996(4)		
C10−Pd1−N1′	81.24(17)	C20−Pd2−N1	81.55(17)
C10−Pd1−O2	179.35(17)	C20−Pd2−O2′	177.59(16)
C10−Pd1−O1′	93.16(16)	C20−Pd2−O1	93.58(15)
N1′−Pd1−O1′	174.38(13)	N1−Pd2−O1	173.27(13)
N1′−Pd1−O2	98.23(13)	N1−Pd2−O2′	96.47(13)
O1′−Pd1−O2	87.38(12)	O1−Pd2−O2′	88.28(12)

Scheme 4[a]



[a] Conditions: (i) 1.1 PCy_3/Pd, CH_2Cl_2, room temperature, 45 min; (ii) AgOTf, CH_2Cl_2, room temperature, 1 h.

The $^{31}P\{^1H\}$ NMR spectra of the complexes **4** each show a single peak in the range 40.4−46.4 ppm. The ^1H NMR spectra of all of the tricyclohexylphosphine adducts **4** show a distinctive multiplet, shifted slightly downfield with respect to the rest of the aromatic protons, corresponding to the proton ortho to the metalated carbon, H-6. The signals corresponding to the methylene bridge of the ortho-metalated dimethylbenzylamine ligand are seen at between 3.91 and 3.98 ppm and are typically broad singlets, except for that of **4e**, which is a doublet with a J_{PH} value of 1.5 Hz. The resonances for the protons of the methyl groups of the ortho-metalated dimethylbenzylamine ligands are seen between 2.57 and 2.76 ppm and are doublets with J_{PH} couplings in the range 2.2−2.5 Hz. A $^1H\{^{31}P\}$ spectrum of **4a** confirmed that the coupling observed was indeed due to a P−H interaction.

The $^{13}C\{^1H\}$ NMR spectra of the complexes **4** show two peaks for quaternary aromatic carbons with phosphorus couplings: **4a**, 147.6 (d, $J_{PC} = 4.5$ Hz), 148.7 ppm (d, $J_{PC} = 1.5$ Hz); **4b**, 148.7 (d, $J_{PC} = 2.3$ Hz), 153.3 ppm (d, $J_{PC} = 1.5$ Hz); **4c**, 148.6 (d, $J_{PC} = 2.3$ Hz), 155.5 (s) ppm; **4d**, 148.7 (d, $J_{PC} = 1.5$ Hz), 159.1 ppm (d, $J_{PC} = 1.5$ Hz); **4e**, 143.6 (d, $J_{PC} = 2.3$ Hz), 148.4 ppm (d, $J_{PC} = 2.3$ Hz). From these data it is apparent that one peak remains constant at 148.55 ± 0.15 ppm with varying "X" ligand, which is assignable as the $C-CH_2$ aromatic carbon with J_{PC} couplings in the range 1.5−2.3 Hz. The position of the second quaternary aromatic peak, which corresponds to the metalated carbon, is dependent on

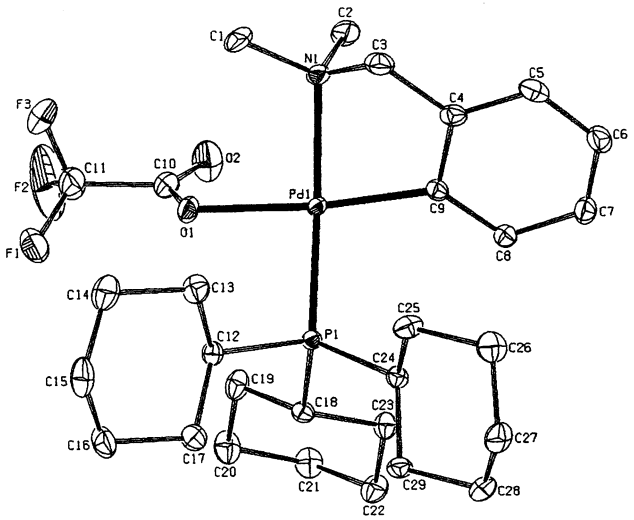


Figure 3. Molecular structure of [Pd(TFA)(κ^2N,C-C_6H_4-CH_2NMe_2)(PCy_3)] (**4a**).

Table 3. Selected Bond Lengths (Å) and Angles (deg) for the Complexes [Pd(X)(κ^2N,C-$C_6H_4CH_2NMe_2$)(PCy_3)] (4a, X = TFA; 4b·$CHCl_3$, X = Cl; 4d, X = I; 4e, X = OTf).

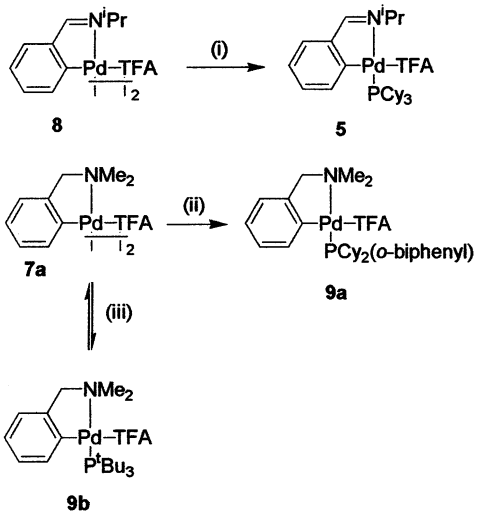
	4a	**4b**·$CHCl_3$	**4d**	**4e**
Pd−P	2.2618(4)	2.2777(7)	2.3203(10)	2.2847(8)
Pd−C	1.9943(17)	2.010(3)	2.104(4)	1.992(3)
Pd−N	2.1672(15)	2.159(2)	2.317(3)	2.145(3)
Pd-X	2.1295(12)	2.4259(7)	2.6814(4)	2.208(2)
C−Pd−N	81.37(7)	81.44(9)	89.59(14)	81.79(13)
C−Pd−P	97.46(5)	99.74(7)	91.78(11)	96.72(10)
N−Pd−X	92.36(5)	91.30(6)	84.34(9)	91.29(10)
P−Pd−X	88.91(4)	89.59(2)	98.38(3)	92.10(7)
C−Pd−X	173.60(6)	166.67(7)	164.52(9)	169.76(12)
N−Pd−P	162.47(5)	168.61(6)	162.03(8)	162.89(8)

the nature of the group trans to it. The TFA and OTf complexes show even greater upfield shift than the chloride, in line with the lower trans influence of oxygen donors. There does not seem to be a discernible pattern for the variation in $^2J_{PC}$ (none to 4.5 Hz). By contrast, the parent dimer **7a** shows two singlets at 141.8 and 147.3 ppm for these two quaternary carbons.

The structures of the tricyclohexylphosphine adducts **4a**,**b**,**d**,**e** were determined by X-ray analysis. The molecular structure of one example (**4a**) is shown in Figure 3, while selected bond lengths and angles for all of the adducts are given in Table 3. In all cases the palladium adopts an approximately square planar configuration in which the PCy_3 ligand is trans to the nitrogen donor. The complex **4b** has a molecule of chloroform hydrogen-bonded to the chloride ligand, with a H···Cl distance of 2.403(6) Å. The Pd−C bond lengths of **4a** (X = TFA) and **4e** (X = OTf) are essentially identical and the same as that reported in [Pd(κ^2N,C-$C_6H_4CH_2NMe_2$)(κ^2P,O-$Ph_2PCH_2CO_2$)].[17] The Pd−C bond length of **4b** (X = Cl) is only marginally longer, but that of **4d** (X = I) is significantly longer. When the Pd−P bond lengths are compared, it can be seen that they fall in the order **4d** > **4e** > **4b** > **4a**, while the Pd−N bond lengths decrease in the order **4d** > **4a** > **4e** ≈ **4b.** Taken together, these data seem to reflect the steric bulk of the X ligand; the larger the X, the further the P and N atoms move away from the palladium center.

(17) Braunstein, P.; Matt, D.; Nobel, D.; Bouaoud, S.-E.; Granjean, D. *J. Organomet. Chem.* **1986**, *301*, 401.

Scheme 5[a]



[a] Conditions: (i) 1.2 PCy_3/Pd, CH_2Cl_2, room temperature, 30 min; (ii) 1.1 PCy_2(*o*-biphenyl)/Pd, CH_2Cl_2, room temperature, 2 h; (iii) 1 P^tBu_3/Pd, CD_2Cl_2, room temperature, 1 h.

A method similar to that used for the synthesis of complexes **4a**−**d** was employed to generate the tricyclohexylphosphine adduct **5** from the ortho-metalated imine complex **8** (Scheme 5). The ^{31}P NMR spectrum of **5** shows a singlet at 39.4 ppm. In addition to the peaks associated with the tricyclohexylphosphine ligand, the ^{1}H NMR spectrum of complex **5** shows a distinct multiplet at 8.07 ppm, downfield of the aromatic signals, corresponding to the benzylidene proton. The methine protons of the ^{i}Pr groups are observed as a multiplet at 3.98 ppm, while the methyl groups are a doublet at 1.36 ppm with a $^3J_{HH}$ value of 6.6 Hz.

The general method for the synthesis of phosphine adducts from the dimer **7a** was applied to the preparation of the 2-(dicyclohexylphosphino)biphenyl and tri-*tert*-butylphosphine adducts **9a**,**b** (Scheme 5).

The ^{31}P{^{1}H} NMR spectrum of complex **9a** shows a broad singlet at 52.8 ppm. The breadth of the signal may indicate that the ligand is reasonably labile. The ^{13}C-{^{1}H} NMR spectrum shows four low-field quaternary aromatic carbons as doublets between 142.3 and 148.5 ppm, two of which correspond to the ortho-metalated ring; the other two are C2 and C1′ of the *o*-biphenyl group. The C1 of the *o*-biphenyl group is seen as a doublet at 125.5 ppm with a 34.3 Hz $^1J_{PC}$ coupling. The ^{1}H NMR spectrum shows the characteristic downfield shift for the proton ortho to the palladium atom observed for the complexes **4**. The protons of the methylene on the ortho-metalated dimethylbenzylamine group are seen as a singlet at 3.97 ppm, while the methyl protons are seen as a doublet at 2.42 ppm with a J_{PH} value of 2.6 Hz. These data are again very similar to those observed for the complexes **4**.

The structure of **9a** was confirmed by X-ray analysis. The asymmetric unit contains two distinct molecules and a molecule of diethyl ether. The structure of one of the molecules (molecule A) is shown in Figure 4, while selected data for both molecules are given in Table 4. All of the lengths of the bonds to the palladium fall in the range of those observed for the complexes **4a**,**b**,**d**,**e**,

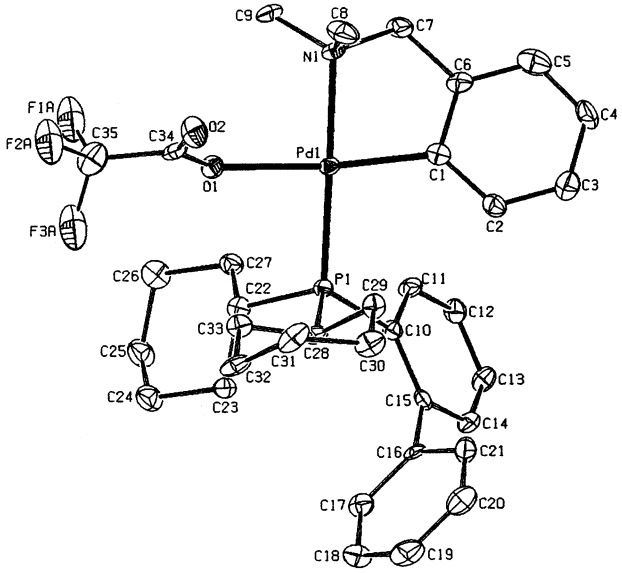


Figure 4. Structure of one of the molecules (molecule A) of the two molecules of [Pd(TFA)(κ^2N,C-$C_6H_4CH_2NMe_2$)-{PCy_2(*o*-biphenyl)}]·0.5Et_2O (**9a**·0.5Et_2O).

Table 4. Selected Bond Lengths (Å) and Angles (deg) for [Pd(TFA)(κ^2N,C-$C_6H_4CH_2NMe_2$)-{PCy_2(*o*-biphenyl)}]·0.5Et_2O (9a·0.5Et_2O)

	molecule	
	A (shown)	B (not shown)
Pd−P	2.2781(11)	2.2792(12)
Pd−C	2.002(5)	2.007(5)
Pd−N	2.134(3)	2.143(4)
Pd−O	2.144(3)	2.136(4)
C−Pd−N	82.4(2)	81.9(2)
C−Pd−P	98.35(14)	98.54(15)
N−Pd−O	91.84(17)	92.76(18)
P−Pd−O	87.35(9)	86.71(10)
C−Pd−O	173.98(17)	174.36(18)
N−Pd−P	177.99(18)	178.9(2)

with the Pd−O bond lengths being directly comparable with that of **4a**. The C−Pd−N and C−Pd−P bond angles again fall in the range for those observed for **4a**,**b**,**d**,**e**, while the N−Pd−O and C−Pd−O angles are comparable with those of **4a**. The P−Pd−O angles in the two molecules of **9a** are slightly more acute than that for **4a**, while the N−Pd−P angles in **9a** are considerably larger than that in **4a**.

The isolation and purification of the tri-*tert*-butylphosphine adduct, **9b**, proved to be problematic. The phosphine ligand is extremely labile, presumably due to its high steric bulk. Even removal of solvents from the product under reduced pressure led to the regeneration of **7a** and the loss of P^tBu_3 by sublimation. However, NMR spectroscopy of a sample prepared in CD_2Cl_2 demonstrated conclusively that it does indeed form at room temperature. The ^{31}P NMR spectrum shows a singlet at 75.8 ppm. The ^1H NMR spectrum shows, in addition to peaks associated with the phosphine ligand, a doublet at 2.42 ppm with a J_{PH} value of 2.6 Hz corresponding to the methyl groups of the ortho-metalated *N*,*N*-dimethylbenzylamine ligand. This is directly comparable with the data for all of the complexes **4**. The methylene peaks for the ortho-metalated ligand are seen as a singlet at 3.97 ppm, again in the range for the analogous peaks of the complexes **4**. As with the complexes **4**, a distinctive multiplet is seen downfield of the other aromatic protons corresponding to the proton ortho to the metalated carbon. The distinctive peaks for the two quaternary aromatic carbons seen in the ^{13}C NMR spectra of the complexes **4** are also seen in the spectrum of **9b**. Thus, a doublet at 148.2 ppm with a 1.9 Hz coupling to phosphorus is assignable as the $C-CH_2$ group of the aromatic ring, while a doublet at 144.4 ppm with a 3.0 Hz coupling to phosphorus corresponds to the metalated carbon. Considered together, the NMR data show that not only does **9a** form but also that its structure and stereochemistry are very similar to those of the complexes **4**.

Catalysis. (a) Suzuki Coupling. We have previously shown that complex **4a** functions as an excellent precatalyst in the coupling of a range of aryl chloride substrates.[4e] Here we wished to compare its activity with other catalyst systems and palladium precursors. To standardize the results, we decided to concentrate primarily on the coupling of 4-chloroanisole with phenylboronic acid, as this is an electronically "challenging" reaction due to the reluctance of the electron-rich aryl chloride to undergo oxidative addition reactions. Three phosphine ligands were chosen for the study: PCy_3, PCy_2(*o*-biphenyl), and P^tBu_3. The last two ligands were chosen as they have proven to be useful in a range of aryl chloride coupling reactions, including the Suzuki reaction.[4h,i,k−n,q,5b,d] The palladium sources investigated in the first instance were palladium acetate, dipalladium tris(dibenzylideneacetone), the dimeric complex **7a**, and its PCy_3 and PCy_2(*o*-biphenyl) adducts **4a** and **9a**. Since the preformed complex **9b** is highly labile and could not be isolated pure, it was not used in the catalytic studies. Instead, the catalyst was formed in situ from **7a** and P^tBu_3. The range of catalyst precursors and ligands chosen allows for the results to be "standardized" with literature examples of their use. The results of these catalytic studies are summarized in Table 5.

The initial reactions were performed using potassium phosphate as the base in toluene at 100 °C (Table 5, entries 1−8), as these conditions were found previously to give good results when palladium acetate and PCy_2(*o*-biphenyl) are used in aryl chloride Suzuki reactions.[4l] However, we found that changing to cesium carbonate in 1,4-dioxane gave much better results with the reported catalyst system, especially at lower catalyst loadings. Therefore, the rest of the Suzuki coupling reactions were performed using this solvent/base combination.

Dipalladium tris(dibenzylideneacetone) proved early on to be a poor palladium precursor (Table 5, entries 1 and 2). This is probably not surprising, in light of Amatore and Jutland's observation that DBA can in fact be a tenacious ligand during coupling reactions and is not as "innocent" a spectator ligand as previously supposed.[18] Therefore, this catalyst system was not examined further. When P^tBu_3 is used as a ligand, there is no advantage in the use of the dimeric palladium precursor **7a** compared with palladium acetate (Table 5, entries 25−28, 31, and 32). With PCy_2(*o*-biphenyl) at lower catalyst concentrations (≤0.1 mol %) there is some

(18) For leading references see: Amatore, C.; Jutland, A.; Thuilliez, *J. Organomet. Chem.* **2002**, *643*−*644*, 416.

Table 5. Investigation into the Suzuki Coupling of 4-Chloroanisole with Phenylboronic Acid with Varying Palladium Sources and Phosphines[a]

entry	Pd source (amt, mol % Pd)	added phosphine (amt, mol %)	base	solvent	conversn (%)[b]
1	$Pd_2(dba)_3$ (1.0)	PCy_2(*o*-biphenyl) (1.0)	K_3PO_4	toluene	3.5
2	$Pd_2(dba)_3$ (1.0)	PCy_2(*o*-biphenyl) (2.0)	K_3PO_4	toluene	8.5
3	$Pd(OAc)_2$ (1.0)	PCy_2(*o*-biphenyl) (1.0)	K_3PO_4	toluene	28.5
4	$Pd(OAc)_2$ (1.0)	PCy_2(*o*-biphenyl) (2.0)	K_3PO_4	toluene	50
5	**7a** (1.0)	PCy_2(*o*-biphenyl) (1.0)	K_3PO_4	toluene	17.5
6	**7a** (1.0)	PCy_2(*o*-biphenyl) (2.0)	K_3PO_4	toluene	39.5
7	**9a** (1.0)		K_3PO_4	toluene	49
8	**4a** (1.0)		K_3PO_4	toluene	15
9	$Pd(OAc)_2$ (1.0)	PCy_2(*o*-biphenyl) (2.0)	Cs_2CO_3	dioxane	100
10	$Pd(OAc)_2$ (0.1)	PCy_2(*o*-biphenyl) (0.2)	Cs_2CO_3	dioxane	77
11	$Pd(OAc)_2$ (0.01)	PCy_2(*o*-biphenyl) (0.02)	Cs_2CO_3	dioxane	40
12	$Pd(OAc)_2$ (0.01)	PCy_2(*o*-biphenyl) (0.01)	Cs_2CO_3	dioxane	15
13	7a (0.1)	PCy_2(*o*-biphenyl) (0.2)	Cs_2CO_3	dioxane	88
14	7a (0.01)	PCy_2(*o*-biphenyl) (0.01)	Cs_2CO_3	dioxane	19.5
15	7a (0.01)	PCy_2(*o*-biphenyl) (0.02)	Cs_2CO_3	dioxane	46.5
16	**9a** (0.01)		Cs_2CO_3	dioxane	45
17	**9a** (0.01)	PCy_2(*o*-biphenyl) (0.01)	Cs_2CO_3	dioxane	64.5
18	**9a** (0.01)	PCy_2(*o*-biphenyl) (0.02)	Cs_2CO_3	dioxane	72
19	**9a** (0.01)	PCy_2(*o*-biphenyl) (0.03)	Cs_2CO_3	dioxane	71
20	**4a** (0.1)		Cs_2CO_3	dioxane	88
21	**4a** (0.01)		Cs_2CO_3	dioxane	71
22	**4a** (0.01)	PCy_3 (0.01)	Cs_2CO_3	dioxane	78
23	**4a** (0.01)	PCy_3 (0.02)	Cs_2CO_3	dioxane	4
24	**4a** (0.01)	PCy_3 (0.03)	Cs_2CO_3	dioxane	2.5
25	**7a** (0.01)	P^tBu_3 (0.01)	Cs_2CO_3	dioxane	19
26	**7a** (0.01)	P^tBu_3 (0.02)	Cs_2CO_3	dioxane	33
27	**7a** (0.01)	P^tBu_3 (0.03)	Cs_2CO_3	dioxane	6
28	**7a** (0.01)	P^tBu_3 (0.04)	Cs_2CO_3	dioxane	4.5
29	$Pd(OAc)_2$ (0.01)	PCy_3 (0.01)	Cs_2CO_3	dioxane	2.5
30	$Pd(OAc)_2$ (0.01)	PCy_3 (0.02)	Cs_2CO_3	dioxane	7
31	$Pd(OAc)_2$ (0.01)	P^tBu_3 (0.01)	Cs_2CO_3	dioxane	19
32	$Pd(OAc)_2$ (0.01)	P^tBu_3 (0.02)	Cs_2CO_3	dioxane	46

[a] Conditions: $MeOC_6H_4$-4-Cl (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), base (2.0 mmol), solvent (3 mL), 100 °C, 2 h. [b] Conversion to 4-methoxybiphenyl, average of two reactions, determined by GC (hexadecane standard).

advantage to using the dimeric precursor **7a** (Table 5; compare entries 10−12 with 13−15); however, this advantage becomes greatly pronounced when tricyclohexylphosphine is employed. Indeed, at 0.01 mol % catalyst loading, tricyclohexylphosphine goes from showing virtually no activity when palladium acetate is used to giving the best catalyst systems. The overall order of activity when the ortho-palladated precursor is used is PCy_3 > PCy_2(*o*-biphenyl) > P^tBu_3. The advantage of using tricyclohexylphosphine is compounded by the fact that it is much cheaper than either PCy_2(*o*-biphenyl) or P^tBu_3 and it is much easier to handle than the latter phosphine. In general we find it is not necessary to use the preformed catalyst **4a**, since the catalyst formed in situ from the dimer **7a** plus 2 equiv of phosphine shows very similar activity. However, catalyst **4a** has the advantage of being air and moisture stable in solution (at least >1 month) as well as in the solid state; thus, handling is facilitated compared with the air-sensitive phosphine.

While varying the tricyclohexylphosphine to palladium ratio from 1:1 to 2:1 does not unduly affect the activity under these conditions, increasing the ratio further is highly deleterious, with essentially a complete loss of activity observed. This can be more easily seen in the plot of P:Pd vs conversion for PCy_3, P^tBu_3, and PCy_2(*o*-biphenyl) shown in Figure 5. The data for PCy_3 and PCy_2(*o*-biphenyl) were obtained by adding the phosphines to the preformed complexes **4a** and **9a**, while the data for P^tBu_3 were obtained by adding the phosphine to the dimeric precursor **7a**. With P^tBu_3 a similar trend is observed to that seen with PCy_3, whereby the addition of more than 2 equiv of phosphine per palladium is highly deleterious, whereas with PCy_2(*o*-biphenyl) there appears to be no diminution in activity.

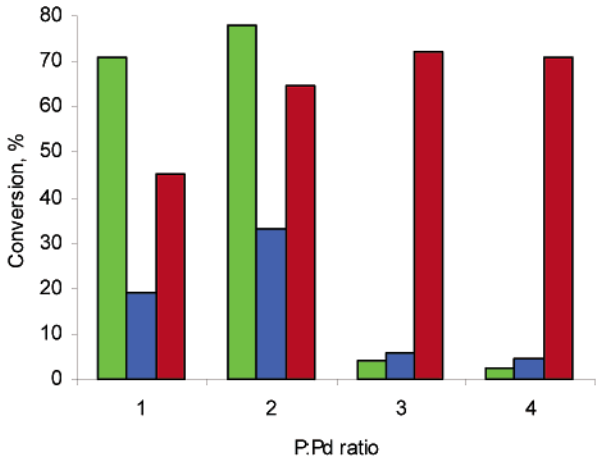


Figure 5. Effect of P:Pd ratio on the performance of the ortho-metalated complexes [Pd(TFA)(κ^2N,C-$C_6H_4CH_2NMe_2$)(PR_3)] in the Suzuki coupling of 4-chloroanisole with phenylboronic acid. PR_3: (green) PCy_3; (blue) P^tBu_3; (red) PCy_2(*o*-biphenyl). Conditions: $MeOC_6H_4$-4-Cl (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), Cs_2CO_3 (2.0 mmol), 1,4-dioxane (3 mL), 100 °C, 2 h.

This tends to imply that the optimum active catalysts, when both tricyclohexylphosphine and tri-*tert*-butylphosphine are used, are low-coordinate and that overcoordination effectively "switches off" the catalysis. Indeed, a recurrent feature of chloride coupling catalysts is the observation that in many cases the active catalysts are

Table 6. Investigation into the Suzuki Coupling of 4-Chloroanisole with Phenylboronic Acid with Various Palladacyclic Precatalysts[a]

entry	catalyst	conversn (%)[b]	entry	catalyst	conversn (%)[b]
1	**4a**	71	4	**4b**	80.5
2	**5**	81	5	**4c**	81.5
3	**4e**	72	6	**4d**	64.5

[a] Conditions: $MeOC_6H_4$-4-Cl (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), Cs_2CO_3 (2.0 mmol), catalyst (0.01 mol % Pd), 1,4-dioxane (3 mL), 100 °C, 2 h. [b] Conversion to 4-methoxybiphenyl, average of two reactions, determined by GC (hexadecane standard).

probably monophosphine complexes.[19] With ligands such as PCy_2(*o*-biphenyl) it is possible that, regardless of the amount of added phosphine, the formation of monophosphine adducts is favored. Such a preference for monocoordination may be due in part to a secondary π-coordination of the aromatic ring to the palladium center.[20] In this scenario excess phosphine would simply act to force any dissociation equilibria back to the formation of complex and thus increase catalyst longevity. In contrast, the use of an excess of a phosphine that can have no secondary interactions may tip the balance in favor of higher coordinate complexes, thus diminishing activity.

Having established that tricyclohexylphosphine shows by far the best activity, provided it is used in conjunction with an appropriate palladium precursor, we decided to investigate the effect of simple structural changes of the ortho-palladated precursor on activity. The results from this study are summarized in Table 6. As can be seen, the ortho-palladated imine complex **5** (entry 2) shows slightly higher activity than the dimethylbenzylamine-containing complex **4a** (entry 1) under the conditions employed here; however, the need to presynthesize the ortho-palladated ligand in this case detracts from its overall appeal. The effect of varying the nature of the anionic coligand, "X", in the ortho-palladated complexes **4** was also investigated (entries 1 and 3−6). While the range of activity varied, the values obtained are not sufficiently disparate to allow detailed interpretation.

The formation of poly-ortho-substituted biaryls by Suzuki coupling is obviously particularly challenging.[20a] To test whether the complex **4a** was able to catalyze such reactions, we briefly investigated its use in the coupling of the sterically hindered substrates 2-chloro-*m*-xylene and 2-tolylboronic acid. When the same conditions as those in Table 5 were used with 0.1 mol % Pd, quantitative conversion was observed. Lowering the catalyst loading to 0.01 mol % Pd gave a 20% conversion, which is equivalent to a TON of 2000.

We have previously found that the coupling of 4-chloroanisole with phenylboronic acid catalyzed by **4a** (0.01 mol % Pd) in 1,4-dioxane with cesium carbonate acting as base can be performed under air with, if anything, a slight increase in activity.[4e] In this case the reaction was set up under air and an oil bubbler was placed on the top of the reflux condenser to provide a closed system. Numerous repetitions of this reaction show it to be highly capricious, with two contrasting outcomes observed: either complete activity or complete inactivity! To examine this phenomenon further, we performed a series of experiments. In the first instance reactions were performed under air, but with a drying tube containing calcium chloride on the top of the condenser. Here we found complete inactivity. Next we examined reactions performed under nitrogen with controlled amounts of water added. The results of this are shown in Figure 6. As can be seen, the added water is deleterious to catalyst performance at all the levels investigated. Since both oxygen and water appear to be separately deleterious, we are unable to account for the fact that sometimes very high activity is observed under aerobic conditions.

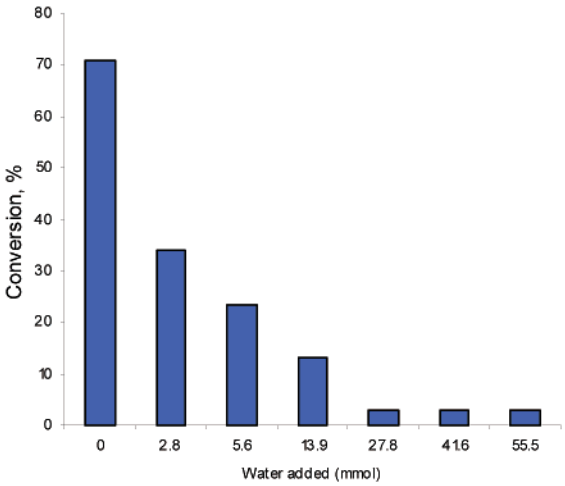


Figure 6. Effect of added water on the coupling of 4-chloroanisole with phenylboronic acid catalyzed by complex **4a**. Conditions: $MeOC_6H_4$-4-Cl (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), Cs_2CO_3 (3.0 mmol), 1,4-dioxane (10 mL), 100 °C, 17 h.

(b) Amination. We again find that the palladium source, in addition to the correct choice of phosphine ligand, can play a pivotal role in Buchwald−Hartwig amination reactions. To illustrate this point, the data in Table 7 show the coupling of 4-chloroanisole with morpholine with a range of palladium precursors and the phosphines used above in the Suzuki coupling as well as the ligand P^tBu_2(*o*-biphenyl).[4m,n,5b] As can be seen, the relative ordering of ligand performance when palladium acetate is used as a precursor is PCy_2(*o*-biphenyl) > P^tBu_2(*o*-biphenyl) > PCy_3 > P^tBu. In all cases, except with PCy_3, changing from palladium acetate to an ortho-metalated palladium source gives an increase in TON of between about 2- and 6.5-fold. The fact that no advantage is seen on changing palladium source when tricyclohexylphosphine is employed (compare entries 5 and 6 with 11 and 12) is a little surprising, since the maximum enhancement in activity in the Suzuki couplings is observed with this ligand. Conversely, the greatest activity enhancement seen in the amination reaction was for P^tBu_3 (compare entries 7 and 8 with 9 and 10), which showed essentially no enhancement in the Suzuki coupling reaction.

In all cases, regardless of phosphine or palladium source, except in the coupling catalyzed by **7a** (0.1 mol

(19) See: Stambuli, J. P.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346 and references therein.

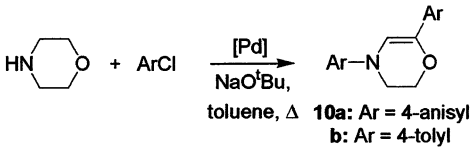
(20) For examples of Pd−aryl π-interactions see: (a) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (b) Kočovský, P.; Vyskočil, S.; Císařovřá, I.; Sejbal, J.; Tišlerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714. (c) Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y.; Miki, M.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 775.

Table 7. Amination of 4-Chloroanisole with Morpholine[a]

entry	Pd source (amt, mol % Pd)	added phosphine (amt, mol %)	conversn (%)[b]	TON
1	$Pd(OAc)_2$ (0.1)	P^tBu_2(*o*-biphenyl) (0.1)	7	70
2	$Pd(OAc)_2$ (0.1)	P^tBu_2(*o*-biphenyl) (0.2)	26	260
3	$Pd(OAc)_2$ (0.1)	PCy_2(*o*-biphenyl) (0.1)	23.5	235
4	$Pd(OAc)_2$ (0.1)	PCy_2(*o*-biphenyl) (0.2)	62.5	625
5	$Pd(OAc)_2$ (0.1)	PCy_3 (0.1)	5.5	55
6	$Pd(OAc)_2$ (0.1)	PCy_3 (0.2)	7	70
7	$Pd(OAc)_2$ (0.1)	P^tBu_3 (0.1)	1	10
8	$Pd(OAc)_2$ (0.1)	P^tBu_3 (0.2)	2	20
9	**7a** (0.1)	P^tBu_3 (0.1)	92	920
10	**7a** (0.05)	P^tBu_3 (0.1)	17	340
11	**7a** (0.05)	PCy_3 (0.1)	3.5	70
12	**4a** (0.5)		25	50
13	**9a** (0.5)		63	126
14	**7a** (0.05)	PCy_2(*o*-biphenyl) (0.1)	41	820
15	**7a** (0.05)	P^tBu_2(*o*-biphenyl) (0.1)	22.5	450

[a] Conditions: $MeOC_6H_4$-4-Cl (1.0 mmol), morpholine (1.26 mmol), NaO^tBu (1.39 mmol), toluene (3 mL), 110 °C, 17 h. [b] Conversion to *N*-(4-methoxyphenyl)morpholine, average of two reactions, determined by GC (hexadecane standard).

Scheme 6. Formation of 4,6-Bis(aryl)-3,4-dihydro-2*H*-[1,4]oxazines from Aryl Halides and Morpholine



% Pd) and 1 equiv of P^tBu_3 (entry 9), we see a substantial (ca. 20−45%) loss of 4-chloroanisole besides that which is incorporated into the coupled product. We suspect that much of this "missing chloride" is lost by a hydrodehalogenation reaction of the substrate. In addition, at least two minor peaks are observed in the GC traces, one of which we have as yet been unable to characterize. The mass spectrum of the other compound is consistent with the formation of 4,6-bis(4-methoxyphenyl)-3,4-dihydro-2*H*-[1,4]oxazine (**10a**) (Scheme 6).[21] We were unable to isolate the new compound cleanly, but careful column chromatography of the product mixture for a reaction between 4-chloroanisole and morpholine gave a small (<4 mg), impure sample of the new compound **10a** in which the major impurity was *N*-(4-methoxyphenyl)morpholine.[22]

The ^1H NMR spectrum of the mixture indicated the presence of an alkenic proton as a broad singlet at 6.44 ppm. The methylene protons are seen as two broad signals at 4.28 and 3.66 ppm, and the methyl groups appear as two broad singlets at 3.82 and 3.80 ppm. A broad multiplet was observed at 7.41 ppm, and a sharper multiplet was seen at 7.18 ppm, each integrated to two protons and assignable as aromatic CH's. An additional peak was observed under the $CDCl_3$ peak, and further aromatic signals may be buried under a large multiplet at 6.90 ppm, which corresponds to the aromatic protons of the *N*-(4-methoxyphenyl)morpholine. The very small amount of **10a** isolated meant that we were unable to obtain full ^{13}C NMR characterization; in particular, we were not able to see any of the quaternary carbons. However, we did observe the appearance of seven of the expected eight aromatic CH's at 113.8, 114.8, 116.5, 123.6, 125.3, 128.2, and 129.0 ppm. The eighth is presumably obscured by one of the signals for the *N*-(4-methoxyphenyl)morpholine's aromatic CHs. The alkenic CH is seen at 106.6 ppm. Two distinct peaks are observed at 55.7 and 55.3 ppm corresponding to the 4-methoxyphenyls' methyl groups. For comparison, the methyl group of *N*-(4-methoxyphenyl)morpholine is seen at 55.6 ppm. Two CH_2 peaks were observed at 64.4 and 53.4 ppm corresponding to the methylenes next to the nitrogen and oxygen atoms, respectively. By comparison, the equivalent peaks in *N*-(4-methoxyphenyl)morpholine are seen at 67.0 and 50.8 ppm. The proposed structure of **10a** was confirmed by X-ray crystallography, and the molecule is shown in Figure 7. Unfortunately crystallographic disorder is present, where the asymmetric unit is half a molecule, with the second half being generated by the symmetry of the space group about the C9−C10 axis causing an overlap of atom types on the N1/C8 and C11/O2 sites. As a result it is not possible to rely on geometric data in the oxazine region of the molecule.

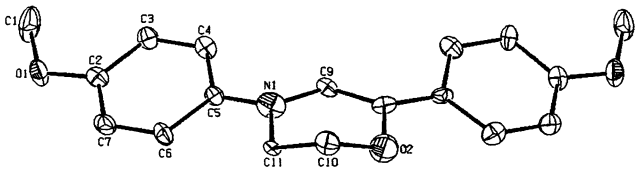


Figure 7. Molecular structure of 4,6-bis(4-methoxyphenyl)-3,4-dihydro-2*H*-[1,4]oxazine (**10a**).

An amination reaction between 4-chlorotoluene and morpholine catalyzed by **4a** at 0.5 mol % catalyst loading gave an isolated yield of 52% of *N*-(4-tolyl)-morpholine, and again the GC-MS spectrum of the product mixture showed a peak with a mass of 265.1, consistent with the presence of a species that could be tentatively assigned as 4,6-bis(4-tolyl)-3,4-dihydro-2*H*-[1,4]oxazine (**10b**).[23] Attempts to isolate and further characterize **10b** have so far proved unsuccessful.

Obviously the formation of compounds of the type **10** requires three processes to occur: (i) an amination reaction, (ii) the formation of a double bond, and (iii) the arylation of the carbon. That the amination occurs first is demonstrated by the fact that when pure *N*-(4-methoxyphenyl)morpholine is treated with 4-chloroanisole in the presence of NaO^tBu and the catalyst **4a**, the formation of small amounts of **10a** is observed by GC-MS.[24] It is probable that the second aryl group is introduced by a Heck reaction on a preformed C−C double bond. The double bond presumably results from the oxidation of the *N*-(4-methoxyphenyl)morpholine, but we do not yet know the precise mechanism by which

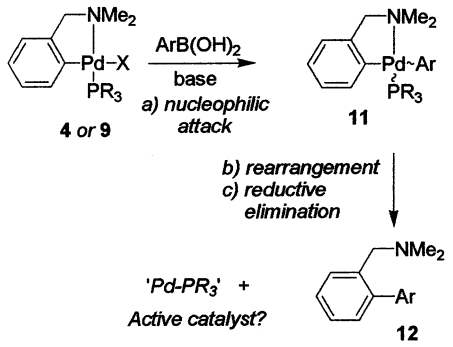
(21) GC-MS (EI) data for **10a**: *m*/z 297.2 (53%) [M^+], 283.2 (3%) [M^+ − Me], 148.7 (20%), 134.1 (100%), 107.1 (18), 92.1 (14%), 77.1 (35%), 64.1 (10%).

(22) Conditions: $MeOC_6H_4$-4-Cl (1.0 mmol), morpholine (1.26 mmol), NaO^tBu (1.39 mmol), **4a** (1.0 mol % Pd), toluene (3 mL), 110 °C, 17 h. Column chromatography (silica, hexane/ethyl acetate/methanol 90:10:2) gave impure **10a** (<4 mg) and *N*-(4-methoxyphenyl)morpholine (0.099 g, 51%).

(23) Conditions: MeC_6H_4-4-Cl (1.0 mmol), morpholine (1.26 mmol), NaO^tBu (1.39 mmol), **4a** (0.5 mol % Pd), toluene (3 mL), 110 °C, 17 h. Yield of *N*-(4-tolyl)morpholine: 52%. GC-MS (EI) data for compound tentatively assigned as **10b**: *m*/z 265.1 (74%) [M^+], 174.0 (8%), 132.9 (19%), 117.9 (100%), 90.9 (90%), 65.0 (57%).

(24) Conditions: *N*-(4-methoxyphenyl)morpholine (1.15 mmol), 4-chloroanisole (1.31 mmol), NaO^tBu (5.75 mmol), **4a** (2.0 mol % Pd), toluene (3 mL), 110 °C, 17 h.

Scheme 7. Possible Mechanism for the Formation of Active Catalysts from the Precatalysts 4 and 9



this occurs. Further studies on this novel reaction are ongoing in our group.

Mechanistic Considerations. (a) Suzuki Coupling. From the above catalytic studies it seems apparent that the source of palladium can play at least as important a role as the nature of the phosphine ligand in aryl chloride coupling reactions. Additionally it appears that palladacyclic complexes make excellent catalyst precursors. What, therefore, is the role of the ortho-metalation and why does it lead to such high activity in catalysis? To address these questions, we performed the following mechanistic studies.

It seems highly unlikely that a Pd(II)/Pd(IV) catalytic cycle operates when complexes of the type [Pd(X)(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)(PR_3)] are used as precatalysts, particularly when 4-chloroanisole, which is comparatively resistant to oxidative addition reactions, is used as the substrate. Indeed, we see no reaction of complex **4a** with either aryl chlorides or considerably more reactive aryl bromides in the absence of boronic acids under the conditions used in the catalytic reactions. It is far more likely that the active catalysts formed from such precursors are low-coordinate palladium(0) monophosphine species. Monocoordinate phosphine complexes have been implicated previously as catalysts in coupling. Indeed, Hartwig recently isolated and structurally characterized monophosphine adducts of the type [Pd(X)(Ar)(P^tBu_3)], formed by oxidative addition of aryl halides to palladium(0) precursors in the presence of phosphine.[19] The isolated complexes react smoothly with a range of coupling partners to generate coupled organic products.

Zerovalent monophosphine species may conceivably be formed from the palladacyclic catalysts **4** and **9** by the process outlined in Scheme 7, which involves (a) nucleophilic attack of the aryl boronic acid at the metal center,[25] (b) rearrangement, and (c) reductive elimination of the aryl and the metalated *N*,*N*-dimethylbenzylamine functions from the putative intermediates **11**. We have previously demonstrated that such an activation process is likely to be operative in the Suzuki coupling of aryl bromides catalyzed by imine dimers of the type **5** and their triphenylphosphine adducts.[14] However, the previous study was performed under stoichiometric conditions. GC and GC-MS analysis of a reaction mixture for the coupling of 4-chloroanisole with phenylboronic acid catalyzed by 1.0 mol % of **4a** at 60 °C showed the presence of substantial amounts of *N*,*N*-dimethyl-(2-phenyl)benzylamine (**12a**; ~63% yield, based on **4a**), indicating that such a process almost certainly occurs under catalytic conditions.[26] Compound **12a** could also be prepared, for comparison purposes, by the reaction of dimethylamine with 2-phenylbenzyl bromide. A related ring-opening process of a palladacyclic catalyst has been reported in the Stille coupling of aryl bromides catalyzed by complex **1**,[27] while the formation of palladium(0) catalysts from Pd(II) N-donor palladacycles has been implicated in coupling reactions.[14,28]

In effect the ortho-metalated ligand plays a "sacrificial" role, and the palladacycle therefore acts as a precatalyst that is able to deliver essentially all of the catalyst into the catalytic manifold early on in the process, where, by definition, the highest rate of catalysis occurs. As it is a simple molecular activation pathway, the process would deliver large amounts of relatively uniform active catalyst species in a "clean' manner. The de-ortho-metalated N-donor ligands, such as **12a**, are relatively labile ligands on palladium(II) and very poor ligands for Pd(0) and are therefore not expected to compete effectively with the incoming substrates, unlike, for instance, DBA.[18] In addition, the liberated N-donor ligands will act as a base and will be "mopped-up" by the arylboronic acid during the course of the reaction, preventing them from reversibly coordinating to the palladium centers.

Induction times of up to 1 h have been noted previously when using **4a** as a catalyst in Suzuki couplings of aryl chlorides.[29] This is followed by rapid catalysis for about 30 min and then fast catalyst decomposition, with no further activity noted after 2 h. If the model is correct, then it may be anticipated that the induction process would be influenced by changing the leaving group "X". Unfortunately, attempts to prove this by following the reaction catalyzed by **4d** over time have been repeatedly unsuccessful, with no activity observed. We are not able to explain why careful sampling of this system should lead to such a major disruption in catalytic activity compared with the catalyst **4a.**

(b) Amination Reactions. Since the complexes **4** show no tendency to react with aryl chlorides, we instead investigated their reactions with morpholine. ^{31}P and ^1H NMR spectra of a solution of **4a** and 1.3 equiv of morpholine in d_8-toluene at room temperature showed no apparent reaction. Heating a toluene solution of **4a** with 1.3 equiv of morpholine again showed no reaction. However, when **9b** is formed in situ in toluene and then reacted with 1.25 equiv of morpholine at room temperature, then P^tBu_3 is liberated and a new complex results which contains no phosphine ligands. The new complex, **13**, can be more conveniently prepared by the reaction of dimer **7a** with 1.25 equiv of morpholine per palladium center (Scheme 8).

The ^1H NMR spectrum of **13** shows a large downfield shift of ca. 2.9 ppm for the proton corresponding to the N−H compared with morpholine and four environments

(25) This process is sometimes referred to as "transmetalation".

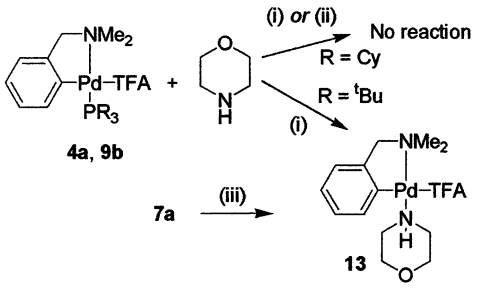
(26) Conditions: $MeOC_6H_4$-4-Cl (2.0 mmol), $PhB(OH)_2$ (3.0 mmol), Cs_2CO_3 (6.0 mmol), **4a** (1.0 mol % Pd), 1,4-dioxane (20 mL), 60 °C, 17 h. Conversion to 4-methoxybiphenyl determined as 97% by GC (hexadecane standard).

(27) Louie, J.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2359.

(28) Nowotny, M.; Hanefeld, U.; van Koningsveld, H.; Maschmeyer, T. *Chem. Commun.* **2000**, 1877.

(29) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4120.

Scheme 8[a]



[a] Conditions: (i) toluene, room temperature; (ii) toluene, Δ; (iii) morpholine, toluene, room temperature.

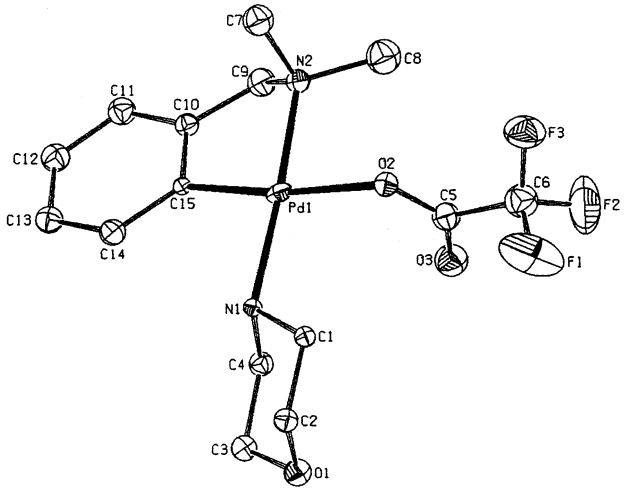


Figure 8. Structure of one (molecule A) of the two molecules of [Pd(TFA)(κ^2N,C-$C_6H_5CH_2NMe_2$){NH(CH_2-CH_2)O}] (**13**).

Table 8. Selected Bond Lengths (Å) and Angles (deg) for the Two Molecules of [Pd(TFA)(κ^2N,C-$C_6H_4CH_2NMe_2$)-{NH(CH_2CH_2)$_2$O}] (13)

	molecule	
	A (shown)	B (not shown)
Pd−C	1.998(12)	1.992(12)
Pd−N_a (benzylamine)	2.073(10)	2.095(9)
Pd−N_b (morpholine)	2.101(9)	2.106(10)
Pd−O	2.173(8)	2.144(8)
C−Pd−N_a	81.6(4)	81.7(4)
C−Pd−N_b	93.4(4)	92.7(4)
C−Pd−O	172.7(4)	173.3(4)
N_a−Pd−N_b	174.8(4)	174.5(4)
N_a−Pd−O	91.2(3)	91.7(3)
N_b−Pd−O	93.8(3)	93.8(3)

for the morpholine methylene protons compared with only two observed in the free amine. The structure of complex **13** was determined by single-crystal X-ray analysis. There are two molecules in the asymmetric unit, one of which (molecule A) is shown in Figure 8, while selected data for both molecules are given in Table 8. The Pd−C bond lengths for the two molecules are essentially the same as those for **4a**, and the Pd−O bond lengths are also very close. The major difference in comparable bond lengths is seen for the Pd−N(benzylamine) bonds of the two molecules compared with those of **4a**, with the latter being substantially longer.

Obviously complex **13** represents a likely candidate for catalyst activation. However, attempts to identify organic products from its thermal decomposition in the presence of sodium *tert*-butoxide have, as yet, proved inconclusive.

Given that there is no reaction between **4a** and morpholine and that catalyst activation may occur via the initial coordination of the morpholine to the palladium center, then it is possible that the poor activity observed with the PCy_3-containing complex may be, in part, due to effective competition between the phosphine and the substrate, preventing catalyst activation.

Conclusions

In conclusion, we have found that the performance of catalysts in the Suzuki coupling and amination reactions of deactivated aryl chlorides is dependent not only on the nature of the phosphines employed but also strongly on the choice of palladium source. Ortho-palladated amine and imine complexes typically show enhanced activity compared with "classical" precursors such as palladium acetate and [Pd_2(dba)$_3$]. It seems likely that the ortho-metalated ligands play a sacrificial role in the activation of the catalysts and that the true active catalysts are low-coordinate palladium(0) monophosphine adducts. During the course of studies on the amination of aryl chlorides we have identified new byproducts, namely the 4,6-bis(aryl)-3,4-dihydro-2*H*-[1,4]oxazines **10a**,**b**, which require three sequential palladium-mediated transformations to occur during their formation. GC-MS analysis of a range of experiments show such species to be present in almost all reactions, regardless of palladium source or phosphine. We are currently investigating the possibility of optimizing conditions for this new transformation and exploiting it in the synthesis of a range of compounds.

Experimental Section

General Methods. Unless otherwise stated, all reactions were carried out under nitrogen using standard Schlenk techniques. Catalytic reactions were performed on a Radleys Carousel Reactor. This consists of 12 ca. 45 mL tubes which are fitted with screw-on Teflon caps that are equipped with valves for the introduction of inert gas and septa for the introduction of reagents. The 12 reaction tubes sit in 2 stacked aluminum blocks; the lower one fits on a heater−stirrer and can be maintained at a constant temperature with a thermostat, while the upper block has water circulating which cools the top of the tubes, allowing reactions to be performed at reflux temperature.

THF, toluene, petroleum ether (40−60), 1,4-dioxane, and diethyl ether were dried over Na/benzophenone and freshly distilled prior to use. Dichloromethane and $CDCl_3$ were distilled from CaH_2, and ethanol was dried over molecular sieves (4 Å) and degassed before use. All other chemicals were used as received. The complexes **7b**,**c** and **8** and the imine *N*-benzylideneisopropylamine were prepared according to literature methods.[12−14,30] GC analyses were performed on a Varian 3800 GC fitted with a WCOT fused silica 25 m column, and data were recorded on a Star workstation. GC-MS measurements were performed on a ThermoQuest Trace spectrometer fitted with a 15 m Restek RTX-5MS column, operating in EI mode. HRMS measurements were run on a Micromass GCT spectrometer operating in CI mode.

(30) Mélot, J.-M.; Texier-Boullet, F.; Foucaud, A. *Synthesis* **1998**, 558.

Synthesis of Complexes. Preparation of [{Pd(μ−TFA)-(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)}$_2$] (7a). *N*,*N*-Dimethylbenzylamine (2.00 mL, 13.38 mmol) and Pd(TFA)$_2$ (4.046 g, 12.18 mmol) were stirred in THF (130 mL) at 40−70 °C for 1−5 h until a dark green coloration appeared. The solution was filtered though Celite and concentrated on a rotary evaporator, leading to the precipitation of the product. Recrystallization from tetrahydrofuran/ethanol gave the product as a yellow solid. Yield: 4.046 g (94%). ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3 H, CH_3), 2.87 (s, 3 H, CH_3), 3.17 (d, ^2J(HH) = 14.05 Hz, 1 H, NCH), 3.62 (d, ^2J(HH) = 14.05 Hz, 1 H, NCH), 6.91 (m, 3 H, ortho-metalated ring), 7.05 (m, 1 H, ortho-metalated ring).^{13}C{^{1}H} NMR (CD_2Cl_2): δ 51.5 (s, CH_3), 53.2 (s, CH_3), 72.6 (s, CH_2), 116.0 (q, ^1J(CF) = 287.8 Hz, CF_3), 122.2 (s, CH, ortho-metalated ring), 125.6 (s, CH, ortho-metalated ring), 125.75 (s, CH, ortho-metalated ring), 131.3 (s, CH, ortho-metalated ring), 141.8 (s, C, ortho-metalated ring), 147.3 (s, C, ortho-metalated ring), 165.6 (q, ^2J(CF) = 37.7 Hz, *C*CF_3). Anal. Calcd for $C_{22}H_{24}F_6N_2O_4Pd_2$: C, 37.4; H, 3.4; N, 4.0. Found: C, 37.2; H, 3.3; N, 3.8.

Preparation of [{Pd(μ-TFA)(κ^2*N*,*C*-C_6H_4CH=N^{i}Pr)}$_2$] (8). A solution of *N*-benzylideneisopropylamine (1.316 g, 8.93 mmol) and Pd(TFA)$_2$ (2.125 g, 6.39 mmol) in THF (80 mL) was stirred at 50 °C for 20 min, cooled to room temperature, and then filtered through Celite. The solvent was removed on a rotary evaporator, and the residue was recrystallized from dichloromethane/ethanol to give the title product as a green solid. Yield: 1.762 g (75%). ^{1}H NMR ($CDCl_3$): δ 0.71 (d, ^3J(HH) = 6.6 Hz, 3 H, CH_3), 1.25 (d, ^3J(HH) = 6.6 Hz, 3H, CH_3), 3.31 (m, 1 H, C*H*CH_3), 6.93 (m, 1 H, ortho-metalated ring), 7.09 (m, 3 H, ortho-metalated ring), 7.40 (s, 1 H, N=CH). Anal. Calcd for $C_{24}H_{24}F_6N_2O_4Pd_2$: C, 39.4; H, 3.3; N, 3.8. Found: C, 39.25; H, 3.2; N, 3.7.

Preparation of [{Pd(μ-Br)(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)}$_2$] (7d). Complex **7b** (0.460 g, 1.67 mmol) and sodium bromide (0.343 g, 3.33 mmol) were stirred in acetone (40 mL) for 1.5 h. The solvent was removed in vacuo, and dichloromethane was added (40 mL). Filtration through Celite and removal of the solvent in vacuo gave the title complex as a yellow solid. Yield: 0.480 g (90%). ^{1}H NMR ($CDCl_3$): δ 2.87 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.98 (br s, 2H, CH_2), 6.79−7.06 (m, 3H, ortho-metalated ring), 7.36 (m, 1H, ortho-metalated ring). Anal. Calcd for $C_{18}H_{24}Br_2N_2Pd$: C, 33.7; H, 3.8; N, 4.4. Found: C, 33.6; H, 3.6; N, 4.0.

Preparation of [Pd(TFA)(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)(PCy_3)] (4a). A solution of complex **7a** (4.046 g, 5.72 mmol) and tricyclohexylphosphine (3.626 g, 12.93 mmol) in dichloromethane (50 mL) was stirred at room temperature for 45 min and concentrated to about 10 mL on a rotary evaporator, and EtOH (15 mL) was added. Further concentration gave a precipitate that was collected by filtration, washed with cold ethanol (3 × 10 mL), and then recrystallized from dichloromethane/ethanol to give the title complex as a colorless solid. Yield: 6.600 g (91%). ^{1}H NMR ($CDCl_3$): δ 1.22 (m, 9H, PCy_3), 1.72 (m, 21H, PCy_3), 2.21 (m, 3 H, PCy_3), 2.57 (d, J(PH) = 2.2 Hz, 6 H, CH_3), 3.92 (br s, 2 H, CH_2), 6.92 (m, 3 H, ortho-metalated ring), 7.11 (m, 1 H, H-6 ortho-metalated ring). ^{31}P-{^{1}H} NMR ($CDCl_3$): δ 41.3 (s, PCy_3). ^{13}C{^{1}H} NMR (CD_2Cl_2): δ 26.8 (br s, CH_2, PCy_3), 28.0 (d, J(PC) = 11.3 Hz, CH_2, PCy_3), 30.2 (s, CH_2, PCy_3), 32.2 (d, ^1J(PC) = 21.85 Hz, CH, PCy_3), 49.1 (d, ^3J(PC) = 2.3 Hz, CH_3), 72.4 (d, ^3J(PC) = 3.0 Hz, *C*H_2N), 117.2 (q, ^1J(CF) = 293.1 Hz, CF_3), 123.3 (br s, CH, ortho-metalated ring), 124.1 (s, CH, ortho-metalated ring), 125.8 (d, J = 3.8 Hz, CH, ortho-metalated ring), 137.0 (d, J(PC) = 6.0 Hz, CH ortho-metalated ring), 147.6 (d, J(PC) = 4.5 Hz, Pd−C), 148.7 (d, J(PC) = 1.5 Hz, *C*CH_2 ortho-metalated ring), 161.4 (q, ^2J(CF) = 34.7 Hz), *C*CF_3). Anal. Calcd for $C_{29}H_{45}F_3NO_2PPd$: C, 54.9; H, 7.15; N, 2.2. Found: C, 54.6; H, 7.2; N, 2.0.

Preparation of [Pd(Cl)(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)(PCy_3)] (4b). This was prepared from complex **7b** (0.399 g, 0.720 mmol) using a scaled-down version of the method employed for the synthesis of complex **4a** to give complex **4b** as a pale yellow solid. Yield: 0.291 g (36%). ^{1}H NMR ($CDCl_3$): δ 1.19 (m, 9H, PCy_3), 1.69 (m, 15H, PCy_3), 2.00 (m, 6H, PCy_3), 2.42 (m, 3 H, PCy_3), 2.62 (d, J(PH) = 2.5 Hz, 6 H, CH_3), 3.94 (br s, 2 H, CH_2), 6.92 (m, 3 H, Me ortho-metalated ring), 7.21 (m, 1 H, H-6 ortho-metalated ring). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 43.4 (s, PCy_3). ^{13}C{^{1}H} NMR (CD_2Cl_2): δ 26.8 (d, J(PC) = 1.5 Hz, CH_2, PCy_3), 28.0 (d, J(PC) = 10.5 Hz, CH_2, PCy_3), 30.55 (s, CH_2, PCy_3), 34.6 (d, ^1J(PC) = 21.85 Hz, CH, PCy_3), 49.8 (d, ^3J(PC) = 2.3 Hz, CH_3), 73.4 (d, ^3J(PC) = 3.1 Hz, *C*H_2N), 122.9 (s, CH, ortho-metalated ring), 123.75 (s, CH, ortho-metalated ring), 125.5 (d, J = 3.8 Hz, CH, ortho-metalated ring), 136.7 (d, J(PC) = 6.0 Hz, CH, ortho-metalated ring), 148.7 (d, J(PC) = 2.3 Hz, *C*CH_2, ortho-metalated ring), 153.3 (d, J(PC) = 1.5 Hz, Pd−C). Anal. Calcd for $C_{27}H_{45}ClNPPd$: C, 58.3; H, 8.15; N, 2.5. Found: C, 58.6; H, 8.3; N, 2.3.

Preparation of [Pd(Br)(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)(PCy_3)] (4c). This was prepared from complex **7d** (0.326 g, 0.510 mmol) using a scaled-down version of the method employed for the synthesis of complex **4a** to give complex **4c** as a yellow solid. Yield: 0.314 g (51%). ^{1}H NMR ($CDCl_3$): δ 1.18 (m, 9H, PCy_3), 1.70 (m, 15H, PCy_3), 2.01 (m, 6H, PCy_3), 2.42 (m, 3 H, PCy_3), 2.67 (d, J(PH) = 2.45 Hz, 6 H, CH_3), 3.95 (br s, 2 H, CH_2), 6.93 (m, 3 H, ortho-metalated ring), 7.21 (m, 1 H, H-6 ortho-metalated ring). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 44.6 (s, PCy_3). ^{13}C-{^{1}H} NMR (CD_2Cl_2): δ 26.8 (d, J = 1.5 Hz, CH_2, PCy_3), 28.0 (d, J(PC) = 10.5 Hz, CH_2, PCy_3), 30.7 (br s, CH_2, PCy_3), 35.6 (d, ^1J(PC) = 21.85 Hz, CH, PCy_3), 50.3 (d, ^3J(PC) = 2.3 Hz, CH_3), 73.5 (d, ^3J(PC) = 2.3 Hz, CH_2N), 123.0 (s, CH, ortho-metalated ring), 123.9 (s, CH, ortho-metalated ring), 125.65 (d, J = 4.5 Hz, CH, ortho-metalated ring), 136.45 (d, J(PC) = 6.0 Hz, CH, ortho-metalated ring), 148.6 (d, J(PC) = 2.3 Hz, *C*CH_2, ortho-metalated ring), 155.5 (s, Pd−C). Anal. Calcd for $C_{27}H_{45}BrNPPd$: C, 54.0; H, 7.55; N, 2.3. Found: C, 54.0; H, 7.9; N, 2.1.

Preparation of [Pd(I)(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)(PCy_3)] (4d). This was prepared from complex **7c** (0.490 g, 0.670 mmol) using a scaled-down version of the method employed for the synthesis of complex **4a** to give complex **4d** as a yellow solid. Yield: 0.657 g (76%). ^{1}H NMR ($CDCl_3$): δ 1.18 (m, 9H, PCy_3), 1.71 (m, 15H, PCy_3), 2.04 (m, 6H, PCy_3), 2.43 (m, 3 H, PCy_3), 2.76 (d, J(PH) = 2.45 Hz, 6 H, CH_3), 3.98 (br s, 2 H, CH_2), 6.92 (m, 3 H, ortho-metalated ring), 7.20 (m, 1 H, H-6 ortho-metalated ring). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 46.4 (s, PCy_3). ^{13}C-{^{1}H} NMR (CD_2Cl_2): δ 26.7 (br s, CH_2, PCy_3), 27.95 (d, J(PC) = 11.3 Hz, CH_2, PCy_3), 31.0 (s, CH_2, PCy_3), 36.9 (d, ^1J(PC) = 21.85 Hz, CH, PCy_3), 51.4 (d, ^3J(PC) = 1.5 Hz, CH_3), 73.4 (d, ^3J(PC) = 2.3 Hz, CH_2N), 123.1 (s, CH, ortho-metalated ring), 124.0 (s, CH, ortho-metalated ring), 125.7 (d, J = 4.5 Hz), CH ortho-metalated ring), 136.0 (d, J(PC) = 6.8 Hz, CH, ortho-metalated ring), 148.7 (d, J(PC) = 1.5 Hz, *C*CH_2, ortho-metalated ring), 159.1 (d, J(PC) = 1.5 Hz, Pd−C). Anal. Calcd for $C_{27}H_{45}INPPd$: C, 50.05; H, 7.0; N, 2.2. Found: C, 50.4; H, 7.25; N, 1.8.

Preparation of [Pd(OTf)(κ^2*N*,*C*-$C_6H_4CH_2NMe_2$)(PCy_3)] (4e). A mixture of complex **7b** (0.245 g, 0.44 mmol) and tricyclohexylphosphine (0.274 g, 0.98 mmol) in dichloromethane (40 mL) was stirred at room temperature for 2.5 h, after which time it was transferred to a flask containing silver trifluoromethanesulfonate (0.228 g, 0.89 mmol). The resultant mixture was stirred at room temperature for 1 h with the exclusion of light and then filtered through Celite. Petroleum ether (10 mL) was added, and the solution was concentrated in vacuo to about 5 mL. The resultant precipitate was collected by filtration, washed with petroleum ether (3 × 10 mL), and recrystallized from dichloromethane/petroleum ether to give the title complex as a colorless solid. Yield: 0.214 g (36%). ^{1}H NMR (CD_2Cl_2): δ 1.24 (m, 9H, PCy_3), 1.73 (m, 15H, PCy_3), 2.03 (m, 6H, PCy_3), 2.24 (m, 3 H, PCy_3), 2.69 (d, J(PH) = 2.6 Hz, 6 H, CH_3), 3.94 (d, J(PH) = 1.5 Hz, 2 H, CH_2), 6.96 (m, 3 H, ortho-metalated ring), 7.13 (m, 1 H, H-6 ortho-metalated

ring). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 42.85 (s, PCy_3). $^{19}F\{^1H\}$ NMR (CD_2Cl_2): δ −78.4 (s, OTf). $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 26.7 (d, J(PC) = 1.5 Hz, CH_2, PCy_3), 27.9 (d, J(PC) = 10.6 Hz, CH_2, PCy_3), 30.6 (s, CH_2, PCy_3), 34.1 (d, ^1J(PC) = 21.1 Hz, CH PCy_3), 49.3 (d, ^3J(PC) = 2.3 Hz, CH_3), 72.1 (d, J(PC) = 3.0 Hz, CH_2N), 120.4 (q, ^1J(CF) = 319.5 Hz, CF_3), 123.6 (s, CH, ortho-metalated ring), 124.8 (s, CH, ortho-metalated ring), 126.3 (d, J = 4.5 Hz, CH, ortho-metalated ring), 136.7 (d, J(PC) = 6.8 Hz, CH, ortho-metalated ring), 143.6 (d, J(PC) = 2.3 Hz, Pd−C),148.4 (d, J(PC) = 2.3 Hz, CCH_2, ortho-metalated ring). Anal. Calcd for $C_{28}H_{45}F_3NO_3PPdS$: C, 50.2; H, 6.8; N, 2.1. Found: C, 49.9; H, 6.8; N, 2.0.

Preparation of [Pd(TFA)(κ^2N,C-$C_6H_4CH{=}N^iPr$)(PCy_3)] (5). A mixture of complex **8** (0.096 g, 0.13 mmol) and tricyclohexylphosphine (0.091 g, 0.32 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 30 min. The resultant solution was filtered through Celite, ethanol (40 mL) was added, the solution was concentrated to ca. 5 mL on a rotary evaporator, hexane (20 mL) was added, and the solution was oncentrated to induce precipitation. The resultant precipitate was collected by filtration and then recrystallized from CH_2Cl_2/EtOH to give the title complex as a colorless solid. Yield: 0.076 g (45%). ^1H NMR ($CDCl_3$): δ 1.28 (m, 6 H, PCy_3), 1.36 (d, ^3J(HH) = 6.6 Hz, 6 H, CH_3), 1.70 (m, 12 H, PCy_3), 1.83 (m, 6 H, PCy_3), 2.01 (m, 6 H, PCy_3), 2.30 (m, 3 H, PCy_3), 3.98 (m, 1 H, C*H*Me_2), 7.05 (m, 2 H, ortho-metalated ring), 7.18 (m, 1 H, ortho-metalated ring), 7.27 (m, 1 H, ortho-metalated ring), 8.07 (m, 1 H, N=CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 39.35 (s, PCy_3). Anal. Calcd for $C_{30}H_{45}F_3NO_2PPd$: C, 55.8; H, 7.0; N, 2.2. Found: C, 55.2; H, 7.1; N, 1.95. This analysis was repeated on several samples after multiple recrystallizations, but better data could not be obtained.

Preparation of [Pd(TFA)(κ^2N,C-$C_6H_4CH_2NMe_2$){PCy_2-(*o*-biphenyl)}] (9a). Complex **7a** (0.182 g, 0.26 mmol) and 2-(dicyclohexylphosphino)biphenyl (0.198 g, 0.56 mmol) were stirred in dichloromethane (30 mL) at room temperature for 2 h. The solution was concentrated to 5 mL, and diethyl ether (15 mL) was added. Further concentration led to the precipitation of the product. The supernatant solution was removed with a syringe, and the solid was washed with diethyl ether (2 × 10 mL) and then recrystallized from CH_2Cl_2/Et_2O to give the title compound as a colorless solid. Yield: 0.165 g (49%). ^1H NMR ($CDCl_3$): δ 1.00 (m, 2H, PCy_2), 1.12 (m, 4H, PCy_2), 1.34 (m, 4H, PCy_2), 1.61 (m, 4H, PCy_2), 1.69 (m, 2H, PCy_2), 1.93 (m, 6H, PCy_2), 2.64 (d, J(PH) = 2.3 Hz, 6 H, CH_3), 3.87 (br s, 2 H, CH_2), 6.28 (m, 1H, H-6 of ortho-metalated ring), 6.51 (ddd, ^3J(H5H4) = 7.3 Hz, ^3J(H5H6) = 7.6 Hz, ^4J(H5H3) = 1.5 Hz, 1H, H-5 of ortho-metalated ring), 6.83 (ddd, ^3J(H4H3) = 7.3 Hz, ^3J(H4H5) = 7.3 Hz, ^4J(H4H6) = 0.9 Hz, 1H, H-4 of ortho-metalated ring), 6.89 (dd, ^3J(H3H4) = 7.3 Hz, ^4J(H3H5) = 1.5 Hz, 1H, H-3 of ortho-metalated ring), 7.17 (ddd, J = 1.3 Hz, J = 3.4 Hz, J = 7.6 Hz, 1H, biphenyl), 7.24 (tt, J = 1.2 Hz, J = 7.6 Hz, 1H, biphenyl), 7.38 (m, 4H, biphenyl), 7.52 (m, 2H, biphenyl), 7.79 (ddd, J = 0.8 Hz, J = 7.9 Hz, J = 11.3 Hz, 1H, biphenyl) $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 52.75 (br s, PCy_2(*o*-biphenyl). $^{13}C\{^1H\}$ NMR (CD_2Cl_2), δ 26.4 (d, J(PC) = 1.5 Hz, CH_2, PCy_2), 27.25 (d, J(PC) = 12.4 Hz, CH_2, PCy_2), 27.6 (d, J(PC) = 11.7 Hz, CH_2, PCy_2), 29.7 (s, CH_2, PCy_2), 31.4 (s, CH_2, PCy_2), 34.1 (d, ^1J(PC) = 22.2 Hz, PCH), 49.6 (d, J(PC) = 2.3 Hz, CH_3, NMe_2), 71.8 (d, J(PC) = 3.0 Hz, CH_2N), 117.1 (q, ^1J(CF) = 293.1 Hz, CF_3), 122.7 (s, CH, aromatic), 123.95 (s, CH, aromatic), 124.7 (d, J(PC) = 4.5 Hz, CH, aromatic), 125.5 (d, J(PC) = 34.3 Hz, C, aromatic), 126.3 (d, J(PC) = 10.9 Hz, CH, aromatic), 128.0 (s, CH, aromatic), 128.2 (s, CH, aromatic), 129.8 (d, J(PC) = 2.7 Hz, CH, aromatic), 130.0 (s, CH, aromatic), 132.6 (d, J(PC) = 6.8 Hz, CH, aromatic), 136.9 (d, J(PC) = 14.3 Hz, CH, aromatic), 137.9 (d, J(PC) = 8.7 Hz, CH, aromatic), 142.3 (d, J(PC) = 2.6 Hz, C, aromatic), 145.0 (d, J(PC) = 1.9 Hz, C, aromatic), 147.5 (d, J(PC) = 4.1 Hz, C, aromatic), 148.5 (d, J(PC) = 2.3 Hz, C, aromatic), 161.3 (q, ^2J(CF) = 34.7 Hz, CCF_3). Anal. Calcd for $C_{35}H_{43}F_3NO_2PPd$: C, 59.7; H, 6.2; N, 2.0. Found: C, 59.4; H, 6.4; N, 1.8.

Preparation of [Pd(TFA)(κ^2N,C-$C_6H_4CH_2NMe_2$)(P^tBu_3)] (9b). In a glovebox, an NMR tube was charged with the dimer **7a** (0.142 g, 0.20 mmol), P^tBu_3 (0.081 g, 0.40 mmol), and CD_2Cl_2 (0.8 mL). The ^1H, ^{31}P, and ^{13}C NMR spectra were then recorded. The high lability of the phosphine prevented the isolation of pure **9b**. ^1H NMR (CD_2Cl_2): δ 1.53 (d, ^3J(PH) = 12.5 Hz, 27H, ^{t}Bu), 2.42 (d, J(PH) = 2.6 Hz, 6H, NCH_3), 3.97 (s, 2H, CH_2N), 6.85 (m, 1H, CH ortho-metalated ring), 6.91−7.01 (m, 2H, ortho-metalated ring), 7.42 (dd, ^4J(HH) = 3.8 Hz, ^3J(HH) = 7.9 Hz, 1H, ortho-metalated ring). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 75.8 (s, P^tBu_3). $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 32.9 (d, ^2J(PC) = 3.4 Hz, CH_3, ^{t}Bu), 40.3 (d, ^1J(PC) = 7.9 Hz, CMe_3), 48.9 (d, ^3J(PC) = 2.2 Hz, $N(CH_3)_2$), 73.5 (d, ^3J(PC) = 2.3 Hz, CH_2N), 117.2 (q, ^1J(CF) = 272.7 Hz, CF_3), 124.1 (s, CH, ortho-metalated ring), 124.3 (s, CH, ortho-metalated ring), 125.0 (d, J(PC) = 3.8 Hz, CH, ortho-metalated ring), 138.25 (d, J(PC) = 6.4 Hz, CH, ortho-metalated ring), 144.4 (d, J(PC) = 3.0 Hz, Pd−C), 148.2 (d, J(PC) = 1.9 Hz, CCH_2, ortho-metalated ring), 161.2 (q, ^2J(CF) = 34.7 Hz, C, C−CF_3).

Catalysis. Preparation of Stock Catalyst and Phosphine Solutions. In a glovebox, volumetric flasks (10 mL, class A) were charged with the palladium source (0.50 mol % or 1.00 mol %, based on the amount of aryl chloride to be used in reactions) or with the phosphine (1.00 mol % or 2.00 mol %) and the appropriate solvent (i.e. the solvent used for the catalytic run) was added to obtain 10 mL solutions. When necessary, further dilutions were performed in order to obtain the appropriate catalyst amount in 1.00 mL of solvent.

General Procedure for the Suzuki Reaction. In a glovebox, a Radleys tube was charged with the appropriate aryl chloride (1.0 mmol), boronic acid (1.5 mmol), base (2.0 mmol), and solvent (1 or 2 mL, to obtain a total volume of 3 mL after addition of catalyst/phosphine solution(s)). Then the freshly prepared stock solutions (see above) of phosphine (1.00 mL) and/or complex (1.00 mL) were added. The reaction mixture was heated at 100 °C for 2 h, cooled in an ice bath for 5 min, and then HCl(aq) (5 mL, 2.3 M) was added to quench the reaction. The aqueous layer was extracted with toluene (30 mL) and CH_2Cl_2 (30 mL). The combined organic extracts were dried over $MgSO_4$, and the solution was filtered through Celite. The solvent was removed on a rotary evaporator. The residue was dissolved in toluene (4 mL), hexadecane (internal standard, 0.034 M in toluene, 1.00 mL) was added, and the mixture was analyzed by GC. Isolation and purification of coupled products from representative reactions by column chromatography (silica, hexane/ethyl acetate) gave the products with satisfactory microanalyses and with spectroscopic data consistent with genuine examples in yields no more than 5−11% lower than the conversions determined by GC.

General Procedure for the Buchwald−Hartwig Amination Reaction. NaO^tBu (0.134 g, 1.39 mmol), 4-chloroanisole (0.12 mL, 1.0 mmol), and morpholine (0.11 mL, 1.26 mmol) were added to an oven-dried Radleys tube, which was then flushed with nitrogen. Then freshly prepared stock solutions (see above) of phosphine (1.00 mL) and/or complex (1.00 mL) and the necessary amount of toluene to bring the total solvent volume to 3 mL were added. The reaction mixture was then heated to reflux temperature for 17 h. The solution was cooled to 50 °C, quenched with HCl(aq) (5 mL, 2.3 M), and basified with NaOH(aq) (5 mL, 5 M). The aqueous layer was extracted with toluene (2 × 30 mL), the combined organic extracts were dried over $MgSO_4$, the solution was filtered through Celite, and the solvent was removed on a rotary evaporator. The residue was dissolved in toluene (9 mL), hexadecane (internal standard, 0.068 M in toluene, 1.00 mL) was added, and the mixture was analyzed by GC. Isolation of the products of selected couplings by column chromatography (silica, hexane/ethyl acetate/methanol 90:10:2) gave microanalytically pure

Table 9. Crystal Data for the Complexes 7a, 8, 4a, 4b·$CHCl_3$, 4d, 4e, 9a·0.5Et_2O, 10a, and 13

	7a	**8**	**4a**	**4b**·$CHCl_3$	**4d**	**4e**	**9a**·0.5Et_2O	**10a**	**13**
empirical formula	$C_{22}H_{24}F_6N_2O_4Pd$	$C_{24}H_{24}F_6N_2O_4Pd_2$	$C_{29}H_{45}F_3NO_2PPd$	$C_{28}H_{46}Cl_4NPPd$	$C_{27}H_{45}INPPd$	$C_{28}H_{45}F_3NO_3PPdS$	$C_{74}H_{96}F_6N_2O_5P_2Pd_2$	$C_{18}H_{19}NO_3$	$C_{15}H_{20}F_3N_2O_3Pd$
fw	707.23	731.25	634.03	675.83	647.91	670.08	1482.27	297.34	439.73
cryst syst, space group	orthorhombic, $P2_12_12_1$	orthorhombic, $P2_12_12_1$	monoclinic, $P2_1/c$	monoclinic, $P2_1/n$	monoclinic, $P2_1/n$	monoclinic, $P2_1$	monoclinic, $P2_1$	orthorhombic, $Cmc2_1$	monoclinic, $P2_1/c$
a, Å	10.05000(10)	11.0425(2)	14.7341(2)	11.6996(2)	10.5363(2)	9.2892(2)	11.05970(10)	30.742(2)	9.3727(9)
b, Å	14.6781(2)	15.4028(3)	11.2352(2)	15.5253(2)	15.0361(3)	9.6862(2)	19.3488(3)	7.4158(4)	19.1440(15)
c, Å	17.2111(3)	16.0274(4)	19.3377(3)	16.7499(3)	17.3668(3)	16.7860(6	16.9257(3)	6.4650(3)	20.2492(19)
α, deg	90	90	90	90	90	90	90	90	90
β, deg	90	90	111.8780(10)	91.353010)	99.7760(10)	92.1110(10)	99.2200(10)	90	101.41
γ, deg	90	90	90	90	90	90	90	90	90
V, Å^3	2538.89(6)	2726.03(10)	2970.62(8)	3041.60(8)	2711.38(9)	1509.33(7)	3575.17(9)	1473.86(14)	3561.5(6)
Z; calcd density, Mg m^{-3}	4; 1.850	4; 1.782	4; 1.418	4; 1.476	4; 1.587	2; 1.474	2; 1.377	4; 1.340	8; 1.640
abs coeff, mm^{-1}	1.491	1.392	0.723	1.033	1.897	0.785	0.613	0.091	1.086
cryst size, mm^3	0.20 × 0.15 × 0.10	0.20 × 0.15 × 0.10	0.25 × 0.25 × 0.20	0.14 × 0.10 × 0.08	0.10 × 0.08 × 0.05	0.28 × 0.05 × 0.02	0.36 × 0.18 × 0.12	0.15 × 0.10 × 0.03	0.32 × 0.01 × 0.005
θ_{max}, deg	26.00	25.50	27.48	25.03	27.50	27.50	25.03	25.03	23.03
no. of rflns collected/ unique	11 995/4909	15 811/5039	17 439/6656	25 311/5321	35 615/5499	11 588/6436	20 230/10 061	3095/1257	9643/2323
R_{int}	0.0395	0.0557	0.0349	0.0728	0.0924	0.0348	0.0486	0.0804	0.0537
final *R* indices ($I > 2\sigma(I)$) R1, wR2	0.0267, 0.0708	0.0296, 0.0671	0.0284, 0.0714	0.0310, 0.0677	0.0385, 0.0951	0.0341, 0.0734	0.0366, 0.0829	0.0475, 0.1189	0.0535, 0.1097
R indices (all data) R1, wR2	0.0276, 0.0713	0.0343, 0.0688	0.0322, 0.0745	0.0457, 0.0728	0.0513, 0.1026	0.0420, 0.0772	0.0437, 0.0858	0.0538, 0.1251	0.0682, 0.1147
ρ_{max}, ρ_{min}, e Å^{-3}	0.584, −0.685	0.673, −0.526	0.509, −1.097	0.516, −0.623	1.100, −1.264	0.801, −0.762	0.807, −0.573	0.285, −0.204	0.546, −0.643

samples of the coupled products with spectroscopic data consistent with genuine samples in yields no more than ca. 7−12% lower than the conversions determined by GC.

Mechanistic Studies. Preparation of *N*,*N*-Dimethyl(2-phenyl)benzylamine (12a). A solution of 2-phenylbenzyl bromide (1.9 mL, 10.40 mmol) and aqueous dimethylamine (25−30% w/v, 10 mL) in ethanol (13 mL) was heated at reflux temperature for 4 h, cooled, and acidified to pH 1 with HCl(aq). The solution was concentrated on a rotary evaporator to ca. 15 mL and then basified to pH 14 with NaOH(aq). The aqueous phase was extracted with diethyl ether (3 × 20 mL), and the combined organic phase was washed with saturated NaCl(aq) (3 × 30 mL) and water (3 × 30 mL) and then dried ($MgSO_4$). The solution was filtered through Celite, and the solvent was removed on a rotary evaporator. Pentane (10 mL) was added, the solution was filtered through Celite, and the solvent was removed on a rotary evaporator to give the title compound as a yellow oil. Yield: 1.080 g (49%). ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 6H, CH_3), 3.39 (s, 2H, CH_2), 7.24−7.45 (complex overlapping multiplets, 8H, aromatic), 7.58 (br, d of m, $J_{HH} \approx 7$ Hz, 1H, aromatic). HRMS (CI): $[M]^+$ calcd for $C_{15}H_{17}N$ 211.1361, found 211.1364.

Preparation of [Pd(TFA)(κ^2*N*,*C*-$C_6H_5CH_2NMe_2$){NH-(CH_2CH_2)O}] (13). Complex **7a** (0.386 g, 0.55 mmol) and morpholine (0.12 mL, 1.38 mmol) were stirred in toluene (20 mL) for 15 min at room temperature. The solvent was removed in vacuo, and the residue was recrystallized from toluene to give the title product as a colorless solid. Yield: 0.377 g (79%). ^{1}H NMR (CD_2Cl_2): δ 2.66 (s, 6H, CH_3), 3.15 (br d, J(HH) = 13.6 Hz, 2H, (CH_2)$_2$NH), 3.38 (m, 2H, (CH_2)$_2$NH), 3.63 (ddd, J(HH) = 12.25 Hz, J(HH) = 2.4 Hz, 2H, (CH_2)$_2$O), 3.85 (dd, J(HH) = 12.25 Hz, J(HH) = 3.5 Hz, 2H, (CH_2)$_2$O), 3.89 (s, 2H, CH_2NMe_2), 4.67 (br t, 1H, NH), 6.91 (m, 1H, ortho-metalated ring), 7.00−7.10 (m, 3H, ortho-metalated ring). ^{13}C{^{1}H} NMR (CD_2Cl_2): δ 50.4 (s, CH_2, (CH_2)$_2$NH), 51.2 (s, NMe_2), 68.3 (s, (CH_2)$_2$O), 72.9 (s, CH_2NMe_2), 117.1 (q, ^1J(CF) = 292.0 Hz, CF_3), 122.6 (s, CH, ortho-metalated ring), 125.1 (s, CH, ortho-metalated ring), 125.6 (s, CH, ortho-metalated ring), 130.3 (s, CH, ortho-metalated ring), 142.5 (s, C, ortho-metalated ring), 148.6 (s, C, ortho-metalated ring), 162.8 (q, ^2J(CF) = 35.3 Hz, CCF_3). Anal. Calcd for $C_{15}H_{20}F_3N_2O_3Pd$: C, 41.0; H, 4.6; N, 6.4%. Found: C, 40.6; H, 4.7; N, 6.1.

X-ray Structure Determinations. All data were collected on a Bruker-Nonius KappaCCD area detector diffractometer at 120 K with Mo Kα radiation (λ = 0.710 73 Å) produced by a Bruker-Nonius FR591 rotating anode generator. The structures were solved by direct methods and refined by full-matrix least squares using the SHELX-97 suite of programs.[31] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were refined isotropically in geometric positions using the riding model. Data were corrected for absorption by comparison of equivalent reflections using the program SORTAV.[32] All figures were prepared using the program PLATON.[33] Crystallographic data for the complexes **7a**, **8**, **4a**, **4b**·$CHCl_3$, **4d**, **4e**, **9a**·0.5Et_2O, **10a**, and **13** are given in Table 9. Full details of the crystallographic analyses are given in the Supporting Information as CIF files.

Acknowledgment. We thank the University of Exeter for funding (bursary for C.S.J.C.) and Johnson Matthey for the loan of palladium salts.

Supporting Information Available: Full details of the crystallographic analyses as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

OM020841+

(31) Sheldrick, G. M. SHELX-97; University of Göttingen, Göttingen, Germany, 1997.
(32) Blessing, R. H. *J. Appl. Crystallogr.* **1997**, *30*, 421−429.
(33) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C34.