A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions: Room-Temperature Suzuki Couplings and Amination of Unactivated Aryl Chlorides

David W. Old, John P. Wolfe, and Stephen L. Buchwald*

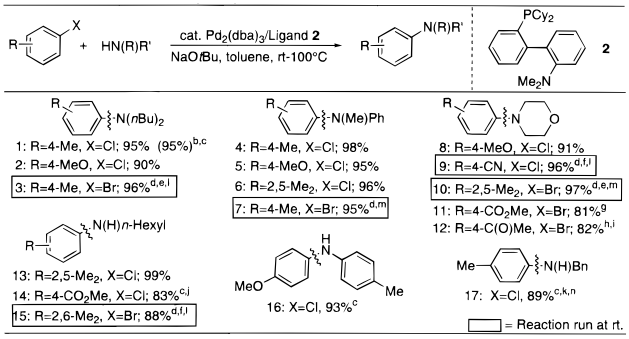
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received June 29, 1998

Palladium-catalyzed C−N bond-forming reactions have evolved into a versatile and efficient synthetic transformation.[1] However, the lack of a general palladium-based catalyst for aryl chloride substitution reactions,[2,3] as well as the elevated reaction temperatures often required, prompted us to search for new, more active ligands.

^{1}H NMR studies in our laboratories of the amination reactions of aryl bromides catalyzed by BINAP/Pd(OAc)$_2$ suggested that oxidative addition was rate limiting.[4] For aryl chlorides, oxidative addition can be anticipated to be even more sluggish. To facilitate this slow step, we began to explore the use of electron-rich phosphine ligands.[2,3c,5a] After some experimentation, we focused our efforts on the preparation of electron-rich bidentate phosphines.[4] We first prepared the known 2,2′-bis(dicyclohexylphosphino)-1,1′-binaphthyl (**1**)[6] and found that **1**/Pd(0) constituted a reasonably effective catalyst for the coupling of pyrrolidine with 4-chlorotoluene. This important result, taken together with our experience with bidentate monophosphines PPF−OMe and PPFA[1b] prompted us to prepare aminophosphine ligand **2** (Table 1).[7] In comparison to **1**, use of ligand **2** is generally superior and significantly expands the scope of palladium-catalyzed aryl chloride transformations. Herein, we demonstrate that the **2**/Pd(0) catalyst system is highly active and allows for the room-temperature amination of aryl bromides and the first example of a room-temperature amination of an aryl chloride. Moreover, this system functions as the first general catalyst for room-temperature Suzuki coupling reactions of aryl chlorides.

Table 1. Catalytic Amination[a] of Aryl Chlorides and Bromides



[a] Reaction conditions: 1.0 equiv of aryl halide, 1,2 equiv of amine, 1.4 equiv of NaO*t*Bu, 0.5 mol % Pd$_2$(dba)$_3$, 1.5 mol % ligand (1.5 L/Pd), toluene (2 mL/mmol halide), 80 °C. Reactions were complete in 11−27 h; reaction times have not been minimized. [b] Reaction run with 0.025 mol % Pd$_2$(dba)$_3$. [c] Reaction run at 100 °C. [d] Reaction run at room temperature in DME solvent. [e] Reaction run with 1.5 mol % Pd$_2$(dba)$_3$. [f] Reaction run with 2.5 mol % Pd$_2$(dba)$_3$. [g] Reaction run using K_3PO_4, DME solvent. [h] Reaction run using Pd(OAc)$_2$, K_3PO_4, DME solvent. [i] One of the two runs only proceeded to 98% conversion. [j] Reaction run with Pd(OAc)$_2$, ligand **1**, Cs_2CO_3 as catalyst, ligand, and base. [k] Using **1** as ligand. [l] [ArBr] = 1 M. [m] [ArBr] = 2 M. [n] 1.5 equiv of benzylamine used.

To demonstrate the efficacy of the **2**/Pd(0) catalyst system, we have prepared several aniline derivatives from aryl chlorides (Table 1, entries 1, 2, 4−6, 8, 9, 13, and 16). Secondary amines give excellent results in the coupling procedure (Table 1, entries 1, 2, 4−6, 8, and 9), and the arylation of a primary aniline can also be accomplished (Table 1, entry 16). Primary alkylamines are efficient coupling partners provided the aryl chloride is substituted at the ortho position (Table 1, entry 13), or through the use of ligand **1** (Table 1, entries 14 and 17). Catalyst levels as low as 0.05 mol % Pd have been achieved in the reaction of chlorotoluene with di-*n*-butylamine (Table 1, entry 1).

Given the high reactivity of this catalyst, we explored the possibility of carrying out room-temperature aminations. We found that both aryl iodides and aryl bromides (Table 1, entries 3, 7, 10, and 15) reacted readily at room temperature when DME was employed as the solvent. The experimentally simple procedure did not require crown ether or other additives.[1c,4] Broadly speaking, the room-temperature amination of aryl bromides displays the same scope as the reactions of aryl chlorides at 80 °C. Aryl bromides containing functional groups sensitive to NaO*t*-Bu could be converted to the corresponding aniline derivative by using K_3PO_4 as the base. In these reactions (Table 1, entries 11 and 12), heating at 80 °C was required due to the decreased basicity and/or solubility of K_3PO_4.

Using **2**/Pd(0), the amination of an aryl chloride (albeit an activated one) at room temperature could also be achieved for the first time.[8] Thus, the coupling of *p*-chlorobenzonitrile and morpholine was catalyzed by 2.5 mol % Pd$_2$(dba)$_3$, 7.5 mol % **2**, and NaO*t*-Bu in DME at room temperature to provide the corresponding aniline derivative in 96% yield (Table 1, entry 9).

In light of the high reactivity of this new catalyst system in amination reactions, we proceeded to examine its utility in several different Pd-catalyzed C−C bond-forming reactions. Pd-catalyzed Suzuki coupling reactions[9] of aryl chlorides are usually inefficient if the aryl halide does not contain electron-withdrawing substituents.[5a−f] While nickel catalysts are more effective at promoting Suzuki coupling reactions of unactivated aryl chlorides,

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(2) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

(3) For existing protocols for the amination of aryl chlorides, see ref 4 and: (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058. (b) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301−309. (c) Reddy, N. P.; Tanaka, M. *Tetrahedon Lett.* **1997**, *38*, 4807−4810. (d) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (e) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370.

(4) Hartwig and Hamann have recently reported similar NMR experiments. They have also shown that electron-rich bidentate bis-phosphines can be used for the Pd-catalyzed amination of aryl chlorides and room-temperature aminations of aryl bromides and iodides: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370.

(5) (a) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575−5578. (b) Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848−1849. (c) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437−14450. (d) Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273−2276. (e) Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985−3988. (f) Cornils, B. *Org. Process Res. Dev.* **1998**, *2*, 121−127. (g) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513−3516. (h) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024−8030.

(6) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2309−2322.

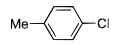
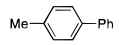
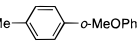
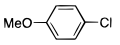
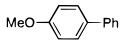
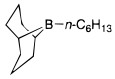
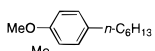
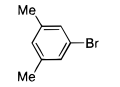
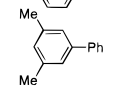
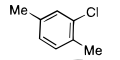
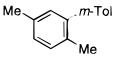
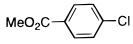
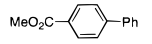
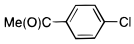
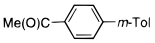
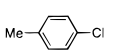
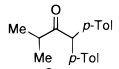
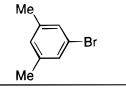
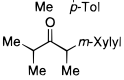
(7) (a) Ligand **2** was prepared in three steps from *N*,*N*-dimethyl-2-bromoaniline. It is obtained as a crystalline solid and is stored and handled in the air without any special precautions. (b) See Supporting Information for complete experimental details.

(8) Control experiments conducted in the absence of palladium afforded no coupled products after 24 h at room temperature.

(9) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2.

S0002-7863(98)02250-1 CCC: $15.00
Published on Web 09/09/1998

Table 2. Suzuki Coupling[a] and Ketone Arylation

Entry	Halide	Coupling Partner	Temp	mol% Pd	Yield	Product
1		$PhB(OH)_2$	100	0.5	96[b]	
2			rt	2.0	94	
3		*o*-$MeOPhB(OH)_2$	100	1.0	94[c]	
4		$PhB(OH)_2$	100	0.5	93[b]	
5			rt	2.0	92	
6			50	2.0	88[c]	
7		$PhB(OH)_2$	rt	1.0	92	
8		*m*-$TolB(OH)_2$	rt	2.0	94	
9		$PhB(OH)_2$	rt	2.0	90	
10		*m*-$TolB(OH)_2$	rt	2.0	92	
11			80	3.0	79[d]	
12			rt	3.0	82[e]	

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boron reagent, 3.0 equiv of CsF, 0.5−2.0 mol % $Pd(OAc)_2$, 0.75−3.0 mol % **2** (1.5 L/Pd), dioxane (3 mL/mmol halide). Reactions were complete in 19−30 h; reaction times have not been minimized. [b] 2.0 equiv of K_3PO_4 used in place of CsF. [c] One of two runs only proceeded to 98% conversion. [d] $Pd_2(dba)_3$, NaO*t*Bu used as catalyst, base. [e] $Pd_2(dba)_3$, NaHMDS used as catalyst, base.

sterically hindered substrates are often problematic.[5g,h] Furthermore, examples of Suzuki coupling reactions that proceed at room temperature are rare[10] and often require stoichiometric amounts of highly toxic thallium hydroxide.[10b,c] To the best of our knowledge, no examples of room-temperature Suzuki couplings of an aryl chloride have been reported.

Suzuki coupling reactions of both aryl bromides and aryl chlorides proceed in high yield at room temperature using the **2**/Pd(0) catalyst system and CsF[11] in dioxane solvent (Table 2, entries 2, 5, and 7−10).[7b,12] These conditions allow for the coupling of both electron-rich and electron-deficient aryl chlorides and tolerate the presence of base-sensitive functional groups. An aryl−alkyl coupling reaction of an aryl chloride using an alkylboron reagent generated in situ from 1-hexene and 9-BBN[13] was achieved at 50 °C. Suzuki coupling reactions of electron-rich aryl chlorides could also be carried out using inexpensive K_3PO_4 with only 0.5 mol % palladium catalyst, although temperatures of 100 °C were required.

The **2**/Pd(0) catalyst system was also effective for the Pd-catalyzed α-arylation of ketones[14] at room temperature using NaHMDS as base (Table 2, entry 12). Interestingly, while the BINAP catalyst system was selective at promoting the monoarylation of methyl ketones, **2**/Pd was selective for the diarylation of methyl ketones (Table 2, entry 11). This may be due to the decreased steric bulk of **2** relative to BINAP.[15]

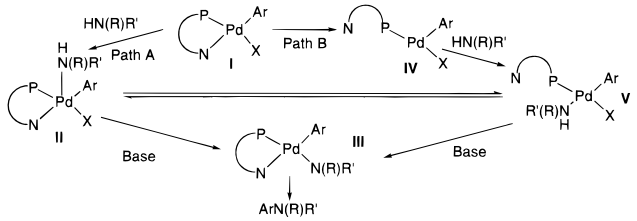


Figure 1.

While the precise mechanistic details of the reactions promoted by the **2**/Pd(0) catalyst system remain unknown, we believe that the overall catalytic cycle for the amination reaction is similar to that postulated for the BINAP/Pd-catalyzed amination of aryl bromides.[1a] However, in reactions catalyzed by **2**/Pd, there may be different pathways available for the amine coordination/deprotonation step. Our current view of the course of the reaction involves binding of the amine to four-coordinate complex **I**, followed by deprotonation of the resulting five-coordinate complex **II** to give **III** (Figure 1, path A). Alternatively, coordination of the amine substrate may occur after initial dissociation of the dimethylamino moiety of the ligand, followed by nucleophilic attack of the amine substrate on three-coordinate[16b] complex **IV** to give **V**. Deprotonation of **V** is followed by rapid recomplexation of the ligand amine group to give **III** (Figure 1, path B).[16] If path B is operative, the recomplexation of the amine is presumably fast relative to β-hydride elimination since little or no reduced side product is observed. This notion is supported by the fact that Cy_2PPh was not an effective ligand for any of these Pd-catalyzed processes;[7b,12] amination reactions conducted with electron-rich monodentate phosphines as ligands such as Cy_3P or Cy_2PPh demonstrated that reduction via β-hydride elimination can be a significant problem without a chelating group on the ligand. The relatively small size of the amine group in **2** allows for the efficient coupling of both cyclic and acyclic secondary amines.[1b] That **2**/Pd(0) can be employed in an amination procedure at the 0.05 mol % level (Table 1, entry 1) suggests that the dimethylamino group also contributes to the stability of the catalyst.

Of special importance is that the results presented herein indicate that the reactions of aryl chlorides in Pd-catalyzed processes need not be limited by the rate of the oxidative addition step.[2] Efforts to design catalysts that maintain this high activity for oxidative addition, but in which the rates of other processes (e.g., transmetalation, reductive elimination, migratory insertion) are enhanced, are currently underway in our laboratories.

Acknowledgment. We thank Amgen, the National Science Foundation, and the National Cancer Institute (Training Grant NCI CI T32CA09112) for financial support. Additional unrestricted support from Pfizer, Merck, and Novartis and fellowships from the Division of Organic Chemistry of the ACS sponsored by Schering-Plough and from Boehringer-Ingelheim are gratefully acknowledged. We also thank Dr. Michael Palucki for his contribution which ultimately led to the preparation of ligand **2**. We also thank Professors John F. Hartwig and Greg Fu for sharing related results on aromatic amination and Suzuki coupling processes, respectively, prior to publication.

Supporting Information Available: Complete experimental procedures and characterization data for all new compounds (13 pages, print/PDF). See any current masthead page for ordering and Internet access instructions. See any current masthead page for ordering information and Web access instructions.

JA982250+

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(11) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

(12) Control experiments conducted using dicyclohexylphenylphosphine in place of **2** gave low conversions and low yields of products.[7b]

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(15) Other Pd-catalyzed cross couplings of aryl chlorides were surveyed using this catalyst. Stille couplings, Sonogashira couplings, and cross-couplings of aryl halides with organozinc reagents gave no detectable products. The Heck arylation of styrene gave some conversion to product at 110 °C.

(16) (a) It is also possible that reductive elimination occurs from a three-coordinate intermediate[1f] formed by deprotonation of **V**. (b) There is precedent for the dissociation of one phosphine of a chelating bis-phosphine.[1f] (c) In reactions that employ NaO*t*-Bu as base, it is possible that complexes shown in Figure 1 may contain X = O*t*Bu: Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110. In reactions that employ Cs_2CO_3 or K_3PO_4 as base, it is unlikely that carbonate or phosphate complexes form due to the low solubility and low nucleophilicity of Cs_2CO_3 and K_3PO_4 relative to NaO*t*-Bu.