ORGANIC LETTERS

2000
Vol. 2, No. 12
1729−1731

$Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$: A Versatile Catalyst for Sonogashira Reactions of Aryl Bromides at Room Temperature

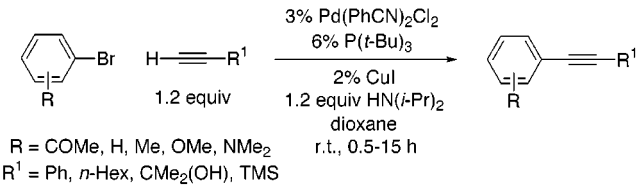
Thomas Hundertmark, Adam F. Littke, Stephen L. Buchwald,* and Gregory C. Fu*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

sbuchwal@mit.edu; gcf@mit.edu

Received April 5, 2000

ABSTRACT



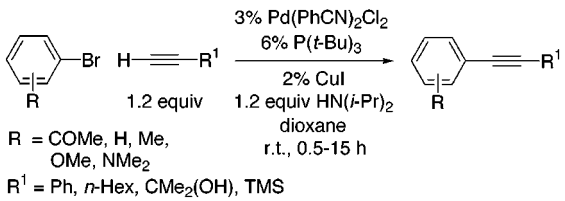
$Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$ serves as an efficient and a versatile catalyst for room-temperature Sonogashira reactions of aryl bromides.

The Sonogashira coupling reaction of terminal acetylenes with aryl and vinyl halides provides a powerful method for synthesizing conjugated alkynes, an important class of molecules that have found application in diverse areas ranging from natural product chemistry to materials science.[1,2] With respect to the organic halide, the following order of reactivity has been observed: vinyl iodide ≈ vinyl bromide > aryl iodide > vinyl chloride ≫ aryl bromide.[2]

For aryl bromides, the least reactive of the commonly employed organic halides, efficient Sonogashira coupling typically requires heating to ∼80 °C.[2] Obviously, reactions that proceed at room temperature have significant practical advantages relative to those that require elevated temperatures. To the best of our knowledge, however, the only descriptions of room-temperature Sonogashira couplings of unactivated aryl bromides are the reports of Sinou (three examples)[3] and Villemin (two examples).[4]

We and others have recently demonstrated that palladium catalysts that incorporate bulky, electron-rich phosphines can display unusually high reactivity in a wide range of coupling processes.[5−8] To date, however, there have been no reports of applications of these ligands to the Sonogashira reaction. In this Letter, we establish that one such ligand, $P(t\text{-}Bu)_3$, does indeed furnish a highly active catalyst for Sonogashira couplings, providing a mild, efficient, and general method for effecting reactions of aryl bromides at room temperature (Scheme 1).

Scheme 1



For our optimization studies, we chose to focus on the Sonogashira coupling of 4-bromoanisole, an electron-rich and

(1) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. (b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253−257. (c) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259−263.

(2) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (b) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: Berlin, 1998; Chapter 10. (c) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127−160. (d) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.4.

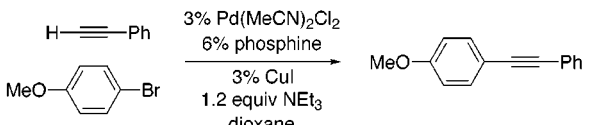
(3) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* **1996**, *31*, 5527−5530.

(4) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255−1261.

10.1021/ol0058947 CCC: $19.00
Published on Web 05/18/2000

therefore relatively unreactive aryl bromide, as our test substrate. As shown in Scheme 2, we have found that, among

Scheme 2

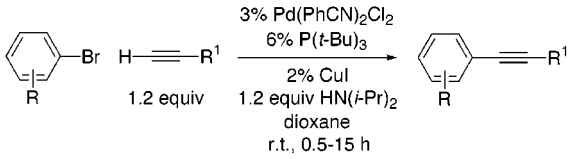


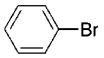
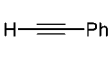
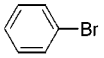
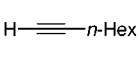
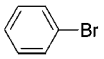
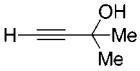
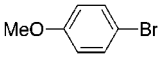
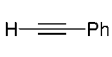
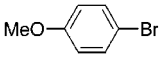
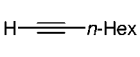
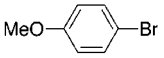
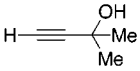
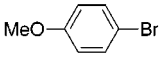
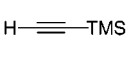
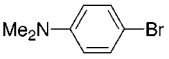
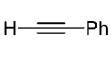
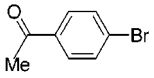
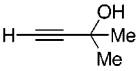
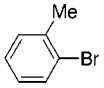
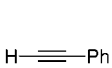
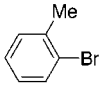
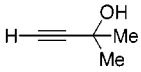
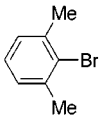
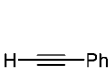
phosphine	*% yield (GC)*
PPh_3	<2
P(*o*-tolyl)$_3$	<2
dppf	<2
PCy_3	<2
P(*t*-Bu)$_3$	96

the five ligands that are illustrated, P(*t*-Bu)$_3$[9] is uniquely effective in accomplishing the palladium-catalyzed Sonogashira reaction at room temperature—triarylphosphines, as well as sterically demanding and electron-rich PCy_3, furnish essentially none of the desired coupling product.[10] Additional optimization experiments have revealed that replacement of $Pd(MeCN)_2Cl_2/NEt_3$ with $Pd(PhCN)_2Cl_2/HN(i\text{-}Pr)_2$ leads to a modest enhancement in reactivity.[11]

By use of these conditions, we can catalyze the Sonogashira coupling of a wide variety of aryl bromides and terminal acetylenes at room temperature (Table 1).[12] Thus, bromobenzene reacts with an array of alkynes in good to excellent yields (entries 1−3). As illustrated in entries 4−7, less reactive 4-bromoanisole also couples with high ef-

Table 1. Room-Temperature Sonogashira Couplings Catalyzed by $Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$



Entry	Aryl Bromide	Alkyne	Yield (%)[a]
1			94
2			70
3			91
4			94
5			93
6			95
7			90
8			94
9			95
10			94
11			84
12			63

[a]Isolated yield, average of two runs.

(5) For pioneering studies, see the following references. (a) Carbonylation: Huser, M.; Youinou, M.-T.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1386-1388. Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742−8744. (b) Dechlorination: Ben-David, Y.; Gozin, M.; Portnoy, M.; Milstein, D. *J. Mol. Catal.* **1992**, *73*, 173−180.

(6) (a) Coupling of vinyl- or arylsilanes: Gouda, K.-i.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232−7233. (b) Amine arylation: Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807−4810. Nishiyama, M.;Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237−1240. (c) Suzuki reaction: Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575−5578. Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985−3988. Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858. (d) Heck reaction: Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123-2132. (e) Ketone arylation: Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478. (f) Alkoxide arylation: Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837−8840. (g) Amidocarbonylation: Kim, J. S.; Sen, A. *J. Mol. Catal. A* **1999**, *143*, 197−201.

(7) (a) Suzuki reaction and amine arylation: Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Alkoxide arylation: Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378. (c) Ketone arylation: Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.

(8) (a) Suzuki reaction: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (b) Heck reaction: Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (c) Stille reaction: Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 2411−2413.

(9) For a pioneering study of the use of P(*t*-Bu)$_3$ in palladium-catalyzed coupling reactions, see: Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620.

(10) Notes: (a) For the triarylphosphines and for PCy_3, essentially no reaction is observed even after 24 h at room temperature (≤ 5% yield). (b) Preliminary experiments with recently reported biaryl dialkyl phosphines indicate that catalysts derived from these ligands, while useful at ∼50 °C, are inefficient at room temperature. The origins of these differences in reactivity are being investigated in our laboratories.

(11) Notes: (a) $Pd_2(dba)_3$ provides a slightly less active catalyst. (b) Toluene and THF may be used in place of dioxane. (c) Couplings proceed extremely slowly in the absence of CuI.

(12) **General procedure:** $Pd(PhCN)_2Cl_2$ (11.5 mg, 0.030 mmol) and CuI (3.8 mg, 0.020 mmol; stored under argon or nitrogen) are added to a dry, 4-mL septum-capped vial, which is then sparged with argon and charged with dioxane (1.0 mL; Aldrich Sure/Seal anhydrous/99.8%). P(*t*-Bu)$_3$ (250 μL of a 0.25 M solution in dioxane; 0.062 mmol; P(*t*-Bu)$_3$ is sold by Strem Chemicals in a Sure/Seal bottle as a 10 wt % solution in hexane), $HN(i\text{-}Pr)_2$ (170 μL, 1.20 mol; Aldrich Sure/Seal 99.5%), the aryl bromide (1.00 mmol), and the alkyne (1.20 mmol) are added via syringe to the stirred reaction mixture. During the reaction, which is followed by TLC or by GC, precipitation of $[H_2N(i\text{-}Pr)_2]Br$ is observed. After the aryl bromide has been consumed, the reaction mixture is diluted with EtOAc (5 mL), filtered through a small pad of silica gel (with EtOAc rinsings), concentrated, and purified by flash chromatography.

ficiency. Even very electron-rich 4-bromo-*N*,*N*-dimethylaniline reacts cleanly at room temperature (entry 8). The coupling of 4′-bromoacetophenone that is depicted in entry 9 establishes that ketones are compatible with the reaction conditions. Finally, $Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$ can even effect Sonogashira couplings of hindered aryl bromides at room temperature (entries 10−12).

Because the goal of this study has been to establish a truly general protocol for room-temperature Sonogashira couplings of aryl bromides, we have applied an identical experimental procedure to all of the reactions that are illustrated in Table 1[12]—i.e., the reactions have not been individually optimized (e.g., with respect to catalyst loading). We have briefly addressed the issue of whether a lower catalyst loading may be employed, and we have found that it may—thus, 4-bromoanisole cleanly couples with phenylacetylene in the presence of just 0.5% $Pd(PhCN)_2Cl_2$/1.0% $P(t\text{-}Bu)_3$ (reaction time: 22 h; 99% isolated yield ⟹ ∼200 turnovers).

In summary, we have determined that $Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$ serves as an efficient and a versatile catalyst for Sonogashira reactions of aryl bromides, accomplishing a wide range of couplings at room temperature. We believe that this system compares favorably with other catalyst systems that have been reported for this process. This study provides further evidence of the usefulness of bulky, electron-rich phosphines in palladium-catalyzed coupling reactions.

Acknowledgment. For support, T.H. thanks the Deutsche Forschungsgemeinschaft (research fellowship), A.F.L. thanks the Natural Sciences and Engineering Research Council of Canada (predoctoral fellowship), S.L.B. thanks the National Institutes of Health (GM34917), Pfizer, and Merck, and G.C.F. thanks Bristol-Myers Squibb, Merck, Novartis, Pfizer, and Pharmacia & Upjohn.

Supporting Information Available: An experimental procedure, as well as ^1H NMR data and literature references for the products illustrated in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0058947