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Efficient and General Protocol for the Copper-Free Sonogashira Coupling of Aryl Bromides at Room Temperature

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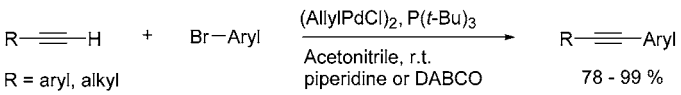
ABSTRACT



A mild and general protocol for the copper-free Sonogashira coupling of aryl bromides with acetylenes has been developed. The use of $(AllylPdCl)_2$ and $P(t\text{-}Bu)_3$ provides the active Pd(0) catalyst that allows subsequent coupling of various alkynes at room temperature with good to excellent yields.

We recently required an efficient and general method to effect the Sonogashira coupling[1] of terminal acetylenes with aryl bromides. We desired conditions that would be practical, amenable to large-scale synthesis and allow for substrate generality. Typical literature procedures for Sonogashira couplings utilize catalytic palladium with a metal cocatalyst and a base.[2] The most widely employed cocatalysts are copper salts, which can suffer from Glaser-type homocoupling of the alkyne.[3] This is a major problem when the supply of acetylene is limited or expensive. In our hands, this was a significant issue that could not be overcome by manipulating the reaction conditions. The use of other metal cocatalysts such as zinc, tin, boron, or aluminum have been developed to address this issue.[4] Unfortunately, most of these procedures require stoichiometric metal, which is a concern in terms of toxicity, cost, and product purity. Additionally, these conditions usually require low temperature and strong bases, which limits the functionality that can be present in the coupling partners.

Sonogashira reactions that do not utilize cocatalysts have been reported.[5] Herrmann and co-workers disclosed a practical procedure that involved utilizing the Fu catalyst (generated from Pd_2dba_3 and $P(t\text{-}Bu)_3$ in a 1:1 ratio) in neat triethylamine.[5c] In our hands, we observed extensive oligomerization of the acetylene when employing these conditions

(1) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470. (b) Takahashi, K.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627−630. (c) For a general review, see: Sonogashira, K. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 5.

(2) For recent advances in Sonogashira coupling, see: (a) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731. (b) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411−1414. (c) Mori, A.; Shimada, T.; Kondo, T.; Sekiguch, A. *Synlett* **2001**, 649−651. (d) Bumagin, N. A.; Sukhomlinova, L. I.; Luzikova, E. V.; Tolstaya, T. P.; Beletsdaya, I. P. *Tetrahedron Lett.* **1996**, *37*, 897−900. (e) Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859−860. (f) Mori, A.; Ahmed, M. S. M.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756−757. (g) Alammi, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114−123. (h) Crisp, G. T.; Turner, P. D.; Stephens, K. A. *J. Organomet. Chem.* **1998**, *570*, 219−224. (i) Negishi, E.; Anastasia, L. *Org. Lett.* **2003**, *5*, 1597−1600. (j) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485−2488. (k) Gelman, D.; Tsvelikhovsky, D.; Molander, G. A.; Blum, J. *J. Org. Chem.* **2002**, *67*, 6287−6290. (l) Yang, C.; Nolan, P. *Organometallics* **2002**, *21*, 1020−1022. (m) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1056−1057. (n) Novak, Z.; Szabo, A.; Repasi, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327−3329. (o) Elangovan, A.; Wang, Y.; Ho, T. *Org. Lett.* **2003**, *5*, 1841−1844. (p) Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571−1574. (q) Choudary, B. M.; Madhi, S.; Chowdari, N. S. *J. Am. Chem. Soc.* **2002**, *124*, 14127−14136. For an analogous Ni-catalyzed Sonogashira, see: (r) Beletskaya, I. P.; Latyshev, G. V.; Tsvetkov, A. V.; Lukashev, N. V. *Tetrahedron Lett.* **2003**, *44*, 5011−5013.

(3) (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 42−424 (b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320−3321. (c) Rossi, R.; Carpita, A.; Begelli, C. *Tetrahedron Lett.* **1985**, *26*, 523−526. (d) Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 4371−4374. (e) For a review of alkyne coupling, see: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632−2657.

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to electron-rich aryl bromides. Slow addition of the acetylene to the reaction mixture minimizes this side reaction, which is in agreement with the observations of Herrmann. More recently, Andrus has described a Pd carbene complex that also catalyzes a copper-free version of this reaction.[5i] Despite these recent advances, there still remained a need for a general protocol that would efficiently broaden the scope of this important reaction. In this manuscript, we disclose the results of a systematic investigation of the copper-free Sonogashira reaction and a general procedure for the coupling of a variety of aryl bromides with terminal acetylenes.

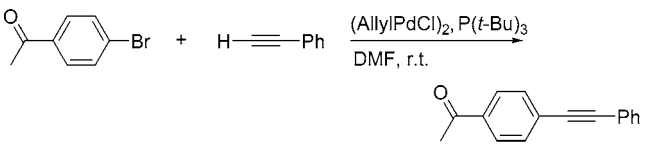
Initial results revealed that $Pd[P(t\text{-}Bu)_3]_2$[6] and 2 equiv of amine base in DMF afforded coupled products at room temperature with activated aryl bromides. Due to the thermal instability of the isolated palladium complex,[7] we required a robust method for the in situ formation of the active catalyst. We were pleased to find that we could obtain the same catalytic activity as the isolated Pd complex with a solution of $(AllylPdCl)_2$ and $P(t\text{-}Bu)_3$ in a 1:2 ratio of Pd to phosphine.

Utilizing a DMF solution of catalyst prepared in this manner, we next examined the effect of base in the model coupling of phenylacetylene with bromoacetophenone in DMF. Several bases ranging from primary to tertiary amines afforded excellent yields (entries 2−6 and 9−10). Reaction rates were noted to increase with more hindered bases such as *tert*-butylamine and tetramethyl piperidine (entry 1 vs 2 and entry 3 vs 4). Employing Herrmann's conditions (entries 7 and 8), we observed decomposition of the phenylacetylene[8] before all of the aryl halide was consumed. DABCO and quinuclidine afforded the fastest reaction rates, with complete conversion in 1.5 and 0.5 h, respectively. Cesium carbonate also resulted in rapid conversion and good yield (entry 16). We were also pleased to discover that the reaction proceeds in excellent conversion in a variety of solvents ranging from nonpolar toluene to amide solvents and even in an alcoholic solvent such as ethanol.

Next, we chose to investigate the coupling of a variety of terminal acetylenes with aryl bromides in acetonitrile[9] (Table 2).[10] Electron-deficient aryl bromides coupled with good to excellent yields with both aryl and alkyl acetylenes (entries 1−5). We were also able to couple bromobenzene and even bromoanisole with aryl and alkyl acetylenes using DABCO[11] (entries 6−9). Sterically demanding 2-bromoxylene coupled with phenylacetylene in excellent yield (entry 10). In addition, heterocyclic compounds such as 3-bromopyridine and 3-bromothiophene coupled with phenylacetylene in good yield (entry 11 and 13). Notably, 3-bromopyridine-*N*-oxide coupled in excellent yield without reduction to the pyridine (entry 12). We have also investigated the coupling of activated aryl chlorides and observed that the reaction can proceed at 80 °C with slow addition of the acetylene (entry 14). Decomposition of the alkyne is currently a limitation of the methodology for coupling of aryl chlorides.

With a viable protocol in hand, we turned our attention toward the mechanism of this reaction. Although the copper-

Table 1. Base-Dependent Conversion in the Copper-Free Sonogashira Coupling of Phenylacetylene and Bromoacetophenone[a]



entry	base	time[b]	yield (%)[c]
1	Bu-NH_2	46 h	51
2	*t*-Bu-NH_2	9 h	95
3	piperidine	7 h	99
4	tetramethyl piperidine	4 h	99
5	morpholine	8 h	99
6	$(i\text{-pr})_2NH$	3 h	99
7	$(i\text{-pr})_2EtN$	4 h	30
8	Et_3N	5 h	79
9	DABCO	1.5 h	99
10	quinuclidine	0.5 h	99
11	tetramethyl guanidine	5 days	85
12	DBU	24 h	0
15	HMDS	24 h	49
16	Cs_2CO_3	2 h	90

[a] All reactions were run in 0.92 M DMF with 1 equiv of aryl halide, 1.1 equiv of acetylene, 2.5 mol % $(AllylPdCl)_2$, 10 mol % phosphine, and 2 equiv of base. [b] Complete consumption of aryl halide by HPLC. [c] HPLC assay yield.

(4) (a) For recent reviews on alkyne cross-coupling, see: (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46−49. (b) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566−1568. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2017.

(5) (a) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403−6406. (b) Nguefack, J.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* **1996**, *37*, 5527−5530. (c) Herrmann, W. A.; Bohm Volker, P. W. *Eur. J. Org. Chem.* **2000**, *22*, 3679−3681. (d) Ryu, I.; Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M. *Org. Lett.* **2002**, *4*, 1691−1694. (e) Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, *12*, 1976−1982. (f) Alonso, D.; Najera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365−9368. (g) Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. P. *Tetrahedron Lett.* **2002**, *43*, 6673−6676. (h) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71−74. (i) Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, *ASAP*.

(6) Purchased from Strem Chemicals. For use of $Pd[P(t\text{-}Bu)_3]_2$ in palladium cross-coupling reactions, see: (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348. (b) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.(c) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(7) Gray/brown discoloration of catalyst over time was observed when stored in the glovebox or in the freezer.

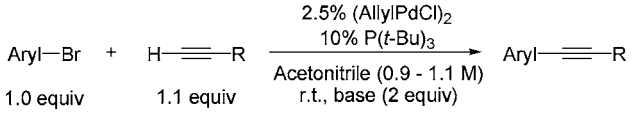
(8) Attempts to identify the product of acetylene decomposition by HPLC, ^1H, and ^{13}C NMR revealed only poorly resolved polymeric material.

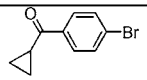
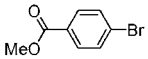
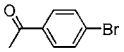
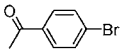
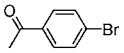
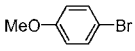
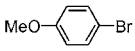
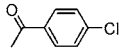
(9) Due to convenient workup, we chose acetonitrile in preference to DMF to continue our investigation.

(10) **Typical Procedure** (Table 2, entry 2). Methyl 4-bromobonzoate (0.46 g, 2.12 mmol) and $(AllylPdCl)_2$ (0.019 g, 0.053 mmol) was added to a dry Schlenk tube and sealed with a rubber septum. The vessel was degassed then backfilled with nitrogen in three repetitions followed by addition of acetonitrile (2.5 mL). Then, $P(t\text{-}Bu)_3$ (0.64 mL of a 10 wt % solution in hexanes, 0.21 mmol), phenylacetylene (0.26 mL, 2.33 mmol), and piperidine (0.42 mL, 4.24 mmol) were added in that order via a syringe to the stirred reaction mixture. During the reaction, the precipitation of piperidine bromide salt was observed. After completion of reaction, as determined by complete HPLC consumption of aryl halide, EtOAc (10 mL) and water (5 mL) were added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of EtOAc. The organic layers were combined and then washed with brine, dried with sodium sulfate, and concentrated. Purification by flash chromatography (95:5 hexanes/EtOAc) furnished the desired product (0.46 g, 92%) as a solid.

(11) Prolonged reaction times (2 days) and incomplete conversion (∼90%) was observed when using piperidine as the base.

Table 2. Copper-Free Sonogashira Coupling of Various Aryl Bromides with Aryl and Alkyl Acetylenes

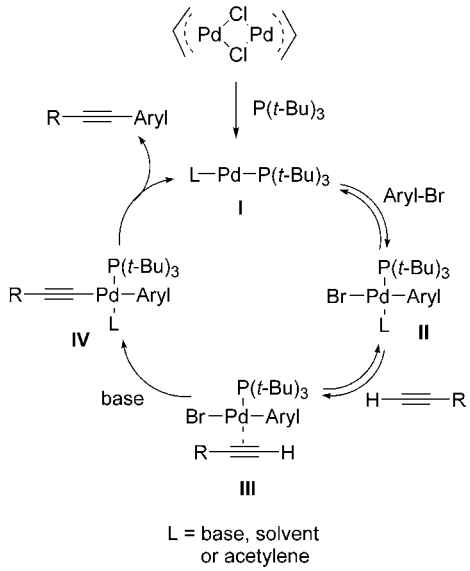


entry	aryl	R	base	time (h)[a]	yield (%)[b]
1			piperidine	16	71
2			piperidine	23	92
3			piperidine	9	96
4			piperidine	48	80
5		*n*-Hex-	DABCO	15	78
6			DABCO	15	99
7			DABCO	20	96
8[c]			DABCO	11	82
9[c]			DABCO	11	92
10			DABCO	18	88
11			piperidine	48	84
12			piperidine	35	96
13			DABCO	16	96
14[d]			piperidine	24	50

[a] Complete consumption of aryl halide by HPLC. [b] Isolated yield of product with ≥98% purity. [c] Performed with 1.4 equiv of acetylene. [d] Performed with 2 equiv of acetylene in DMAc at 80 °C.

catalyzed Sonogashira has been investigated,[12] the mechanism of the copper-free variant has not been described.

Scheme 1. Proposed Catalytic Cycle of Copper-Free Sonogashira Coupling



Drawing from the literature, we envisioned the following catalytic cycle (Scheme 1).

The cycle is proposed to initiate by the generation of palladium complex **I** followed by oxidative addition with the aryl bromide to complex **II**. Then, ligand dissociation followed by complexation with acetylene leads to complex **III** with subsequent deprotonation to provide intermediate **IV**. This species undergoes isomerization followed by reductive elimination to provide product and turn over the catalytic cycle.

We desired evidence about the formation of active catalyst generated by the in situ protocol. Although this procedure has been previously employed,[13] details of the active catalyst have not been described. We decided to probe the catalyst formation utilizing NMR spectroscopy. Upon mixing $(AllylPdCl)_2$ and phosphine in a 1:2 ratio of Pd/phosphine in CD_3CN,[14] we observed the immediate precipitation of a white solid, which was identified as the $Pd[P(t\text{-}Bu)_3]_2$ complex[15] (Scheme 2). In the yellow supernatant solution was observed the allylphosphonium salt[16] **3** and free $P(t\text{-}Bu)_3$ by ^{31}P NMR. Therefore, we rationalize that initially the phos-

(12) For mechanism of the copper-catalyzed Sonogashira coupling, see: (a) Osakada, K.; Sakata, R.; Yamamoto, T. *Organometallics* **1997**, *16*, 5354−5364. (b) Espinet, P.; Fornies, J.; Martinez, F.; Sotes, M.; Lalinde, E.; Moreno, M. T.; Ruiz, A.; Welch, A. J. *J. Organomet. Chem.* **1991**, *403*, 253−267.

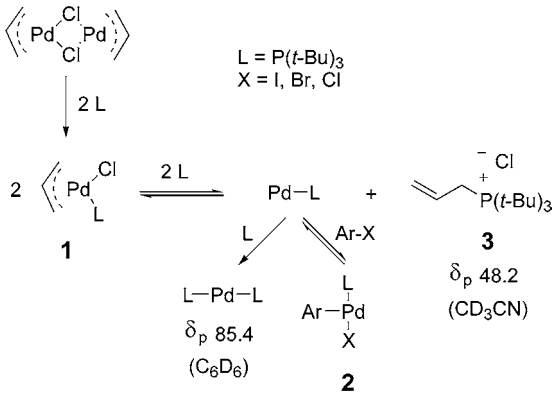
(13) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495−1498.

(14) In a glovebox $P(t\text{-}Bu)_3HBF_4$ (17.7 mg, 0.060 mmol), $(AllylPdCl)_2$ (5.6 mg, 0.015 mmol), and DABCO (7.0 mg, 0.060 mmol) were charged to a dry NMR tube followed by addition of CD_3CN (0.6 mL). The solution immediately turned yellow with the precipitation of a white solid. The NMR tube was then sealed and removed from the glovebox.

(15) Both ^1H and ^{31}P NMR matched the commercially purchased material from Strem Chemicals. $Pd[P(t\text{-}Bu)_3]_2$ is not soluble in acetonitrile or DMF but has high solubility in toluene and benzene.

(16) Allychloride and $P(t\text{-}Bu)_3$ react in acetonitrile to make allylphosphonium chloride only at elevated temperatures. No reaction is observed at room temperature. This suggests that the formation of allylphosphonium chloride in the reaction comes from a *π-allyl* Pd species that is more activated for nucleophilic attack by the phosphine.

Scheme 2. Active Palladium Catalyst Formation



phine reacts with the $(AllylPdCl)_2$ to form the monophosphine Pd(II) species **1** that further reacts with another phosphine to form allylphosphonium chloride and the active Pd-L catalyst.[17] In the presence of an aryl halide, oxidative insertion provides the monophosphine Ar−Pd(II)−X complex **2** (Scheme 2).

We have conducted preliminary kinetic experiments on bromoacetophenone and phenylacetylene using DABCO and observed a rate dependence on the concentration of aryl halide, acetylene, and base.[18] Since a rate dependence on aryl bromide is observed, we conclude that the resting state of the catalyst is not complex **II** but rather a low-valent Pd(0) coordination complex such as **I**. Also, since it has been shown that oxidative insertion and ligand dissociation are reversible pathways,[19] we propose that the rate-limiting step in the catalytic cycle is formation of the σ bound Pd(II) acetylide complex **IV**. We are currently continuing to investigate the mechanism of this reaction.

In conclusion, we have developed a practical and mild copper-free Sonogashira coupling of aryl bromides at room temperature. The reaction proceeds in excellent yield with activated and electron-rich aryl bromides with aromatic and aliphatic acetylenes. Current work is focused on extending the scope to aryl chlorides and further probing the mechanism of this important reaction.

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Supporting Information Available: Experimental procedures for products in Table 2 and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Pd-L species has been rationalized by Fu, Hartwig, Buchwald, and others as the active species in many coupling reactions.

(18) See Supporting Information for full details.

(19) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232−1233.