Pd-Catalyzed C–C Coupling

Efficient Palladium-Catalyzed Coupling of Aryl Chlorides and Tosylates with Terminal Alkynes: Use of a Copper Cocatalyst Inhibits the Reaction**

*Dmitri Gelman and Stephen L. Buchwald**

Aryl alkynes are important intermediates in organic synthesis.[1] Currently, palladium and copper cocatalyzed alkyne synthesis, the Sonogashira reaction, is the most straightforward and powerful method for the construction of $C(sp^2)$–C(sp) bonds. The original protocol[2] has been repeatedly modified and improved to overcome several significant limitations: a) the use of various palladacycles led to catalytic systems with higher turnover numbers,[3] b) copper-free[4] or silver cocatalyzed[5] protocols eliminated the undesired dimerization of terminal alkynes,[6] c) Sonogashira coupling of aryl bromides and iodides at room temperature is now possible.[7] However, unlike other cross-coupling reactions, the use of aryl chlorides as coupling partners for alkyne synthesis, until recently, had remained largely unexplored. Significant progress in this field has recently been made.[4c,8] In particular the work of Plenio and co-workers represents the most general procedure for Sonogashira coupling of aryl chlorides described to date. They used a catalyst derived from bis(adamantyl)benzylphosphane and Na_2PdCl_4/CuI for the coupling of

[*] Prof. S. L. Buchwald, D. Gelman
Department of Chemistry, Room 18–490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

[**] We thank the National Institutes of Health (GM46059) for support of this work. We are grateful to Merck, Pfizer, Lundbeck, Rhodia, and Novartis for additional support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200353015

aryl chlorides with terminal acetylenes. Although excellent yields were obtained for activated chloroarenes at 100 °C, the reactions of electron-neutral and electron-rich substrates were less successful, even at 120 °C. In addition, no examples of the coupling of alkyl acetylenes with *ortho*-substituted aryl chlorides were reported. Clearly, the need for improved catalysts remains. Herein we report the most general and efficient method for the coupling of alkynes with aryl chlorides available so far. In addition, we demonstrate for the first time, that a copper cocatalyst, rather than being beneficial, can lead to complete inhibition of the catalytic activity.

Our work began with the intention of discovering a general catalytic system for the Sonogashira coupling of aryl chlorides, based on a family of bulky, electron-rich *ortho*-biphenylphosphane ligands developed in our laboratories.[9] An important observation was made during our initial experiments: for a catalyst derived from **1** and $[PdCl_2(CH_3CN)_2]$, the presence of a copper cocatalyst has a deleterious effect on the desired transformation. In contrast, in the absence of copper the desired transformation proceeds smoothly. As can be seen from Figure 1, 0.5 mol% of CuI, either added prior to the start of the reaction or one hour after its initiation (~35% conversion), causes suppression of the coupling process.

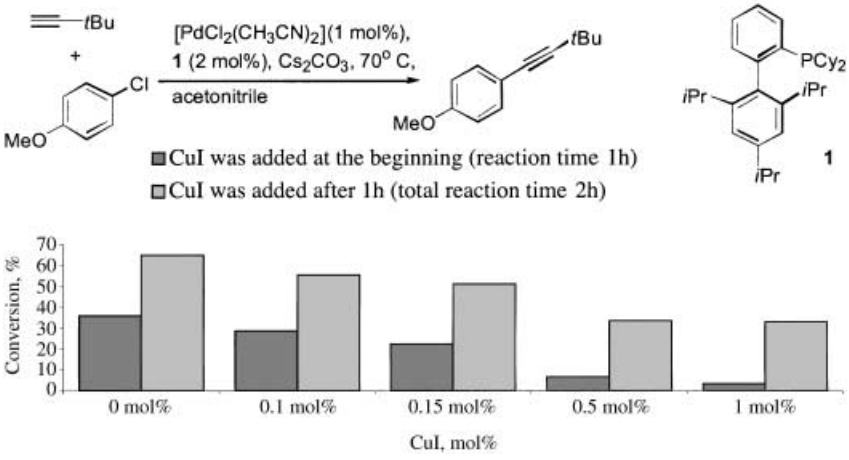
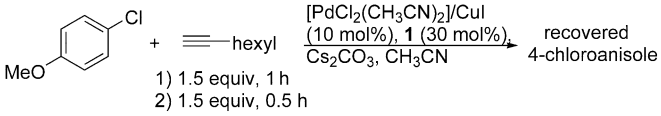


Figure 1. Effect of the copper additive on the efficiency of alkyne coupling of 4-chloroanisole.

Interestingly the inclusion of copper compounds (copper(I) chloride, copper phenylacetylide, copper(II) bis(isobutyrate)), in either the +1 or +2 oxidation state, suppresses the desired transformation. By monitoring the reaction, we discovered that in all reactions that included a copper cocatalyst complete consumption of the starting alkyne takes place by a competitive process, presumably oligomerization. For example, an experiment performed in the presence of 10 mol% of a catalyst derived from **1** and $[PdCl_2(CH_3CN)_2]$ and 10 mol% of CuI showed complete conversion of the 1-octyne after 1 h. An additional injected portion of the alkyne was consumed as well, yet almost no coupling product was observed (Scheme 1).

After further experimentation it was discovered, that if the alkyne is added slowly in a reaction that used CuI/



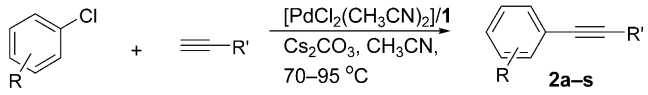
Scheme 1.

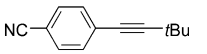
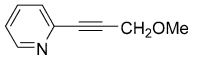
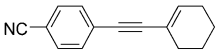
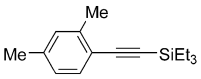
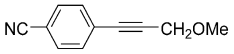
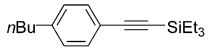
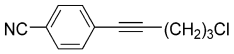
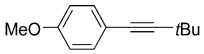
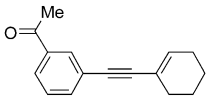
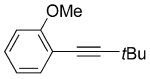
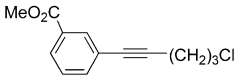
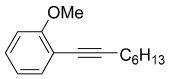
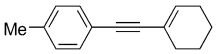
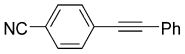
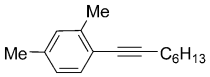
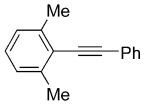
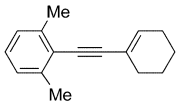
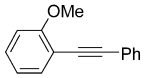
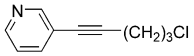
$[PdCl_2(CH_3CN)_2]$/**1**, the side reaction is suppressed and the coupling product cleanly forms. This indicates that no irreversible poisoning of the $[PdCl_2(CH_3CN)_2]$/**1** catalyst with copper takes place and that a lower concentration of the acetylene slows down the rate of oligomerization.

These findings led us to the discovery of a new protocol for the palladium-catalyzed coupling of alkynes with aryl chlorides. The reaction conditions employed (1 mol% of $[PdCl_2(CH_3CN)_2]$, 3 mol% of **1**, 1.3 equivalents of the terminal alkyne, and 2.6 equivalents of Cs_2CO_3 in acetonitrile at 70–90 °C) typically provided very fast and selective transformation of aryl chlorides to the desired product (Table 1). The choice of the solvent as well as of the base was important for the success of the reaction described here: only moderately polar aprotic solvents (acetonitrile, dioxane), in combination with inorganic bases (Cs_2CO_3, K_3PO_4) proved to be useful. In contrast to these observations, no critical role of the precatalyst was detected, although the best results were obtained with $[PdCl_2(CH_3CN)_2]$ or $PdCl_2$ (**2g**, Table 1). The catalyst derived from $[PdCl_2(CH_3CN)_2]$ and **1** was found to promote a high-yielding coupling even when used at 0.1 mol% loading. This corresponds to a turnover number of about 890 (**2a**, Table 1).

As illustrated by Table 1, the reactions of electron-deficient aryl chlorides could be carried out at 70 °C. The transformation with electron-neutral and electron-rich aryl chlorides necessitated a reaction temperature of 90 °C. The coupling of aryl acetylenes required that the alkyne be added over 2 h (**2q–s**, Table 1), otherwise incomplete conversion of the aryl chlorides and nonproductive consumption of the alkynes again takes place. The present method was found to be relatively insensitive to the steric hindrance of the starting aryl chloride. For example, 2-chloro-*m*-xylene was converted to the corresponding acetylene in excellent yield (**2r** Table 1). This is also the first demonstration of the coupling of an *ortho*-substituted aryl chloride with an alkyl acetylene. Good functional group compatibility and wide scope of alkynes highlight the new method. Functionalized as well as unfunctionalized alkynes can be successfully coupled with a variety of aryl and heteroaryl chlorides to yield the corresponding disubstituted acetylenes. While we found that the use of trimethylsilyl-protected acetylenes was inefficient due to the significant desilylation of the product that takes place under our reaction conditions, the use of triethylsilylacetylene was a suitable surrogate (**2l**, **m**, Table 1). Noteworthy is that aryl tosylates, which, to the

Table 1: Coupling of aryl chlorides with terminal alkynes catalyzed by $[PdCl_2(CH_3CN)_2]$/**1**.

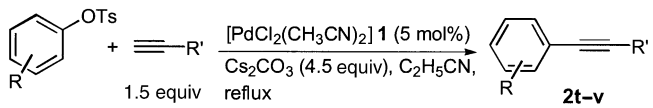


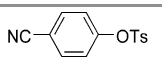
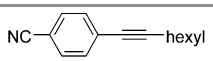
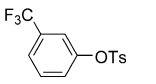
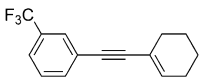
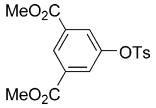
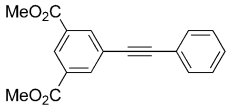
	Compound	Conditions temp. [°C]	time [h]	Yield[a] [%]		Compound	Conditions temp. [°C]	time [h]	Yield[a] [%]
2a[b]		70	9	89	**2k**		90	1.5	79
2b		70	1.5	93	**2l**		90	2	85
2c		70	1.5	94	**2m**		90	2.5	77
2d		70	2	84	**2n**		70	3	87
2e		70	1.5	94	**2o**		90	1.5	93
2f		70	2	92	**2p**		90	2	93
2g		90	4	82	**2q**[c]		82	2.5	93
2h		90	2	90	**2r**[c]		97	2.5	88
2i		90	2	92	**2s**[c]		97	3	95
2j		90	3	85					

[a] Yield of isolated product is the average of two runs. [b] The reaction was performed by using 0.1 mol% of the catalyst. [c] The alkyne was added slowly over the course of the reaction.

best of our knowledge[10] have never been reported as coupling partners in Sonogashira processes, react under similar conditions (**2t**–**v**, Table 2). For these substrates slow addition of an alkyne is necessary to obtain a high yield of the desired product.

Table 2: Coupling of aryl tosylates with terminal alkynes catalyzed by $[PdCl_2(CH_3CN)_2]$/**1**.



Entry	ArOTs	Product	Yield [%][a]
2t			73
2u			78
2v			62

[a] Yield of isolated product is the average of two runs.

In summary, we have developed a general protocol for the palladium-catalyzed coupling of aryl chlorides and alkynes. The new protocol requires less catalyst, lower temperature, and has greater generality than those previously reported. We have also demonstrated for the first time that the Sonogashira coupling of aryl tosylates is possible. Moreover, we have uncovered an unexpected phenomenon: the addition of a copper cocatalyst can inhibit product formation in the coupling reaction of aryl chlorides with terminal alkynes. An important ramification of our finding that the presence of a copper cocatalyst can lead to a decrease in yield in a Sonogashira process is that, particularly in the case of highly active catalysts, screening for new catalyst systems needs to be carried out both in the presence and absence of added copper.

Experimental Section

General procedure for preparation of compounds **2a**–**p**: An oven-dried Schlenk tube was evacuated and backfilled with argon (the cycle was performed twice) and then charged under a positive pressure of argon with $[PdCl_2(CH_3CN)_2]$ (1.2 mg, 4.62 μmol, 1 mol%), **1** (6.6 mg, 14 μmol, 3 mol%), Cs_2CO_3 (391 mg, 1.20 mmol), followed by anhydrous acetonitrile (924 μL) and the aryl chloride (0.462 mmol). The slightly yellow suspension was stirred for 25 min. Then the alkyne (0.6 mmol) was injected, the Schlenk tube was sealed with a Teflon

valve, and the reaction mixture was stirred at the desired temperature for the indicated period of time. The resulting suspension was allowed to reach room temperature, diluted with water (3 mL), and extracted with diethyl ether (4 × 4 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.

General procedure for preparation of compounds **2q–s**: An oven-dried two-necked flask, equipped with reflux condenser, gas inlet/outlet, and rubber stopper, was evacuated and backfilled with argon (the cycle was performed twice) and then charged under a positive pressure of argon with $[PdCl_2(CH_3CN)_2]$ (5.9 mg, 22.7 μmol, 1 mol%), **1** (32.5 mg, 68.2 μmol, 3 mol%), Cs_2CO_3 (1.63 g, 4.99 mmol), followed by anhydrous acetonitrile (for **2q**) or propionitrile (for **2r**,**s**) (4.5 mL) and the aryl chloride (2.27 mmol). The slightly yellow suspension was stirred for 25 min at room temperature. Then the reaction mixture was heated to reflux and the alkyne (0.6 mmol) was injected slowly over the course of reaction (2 h) by means of a syringe pump. The reaction mixture was stirred for additional 30 min after the addition was complete and the resulting suspension was allowed to reach room temperature, diluted with water (3 mL), and extracted with diethyl ether (4 × 4 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.

General procedure for coupling of aryl tosylates with terminal acetylenes (**2t–v**): An oven-dried two-necked flask, equipped with reflux condenser, gas inlet/outlet, and rubber stopper, was evacuated and backfilled with argon (the cycle was performed twice) and then charged under a positive pressure of argon with $[PdCl_2(CH_3CN)_2]$ (7.7 mg, 29.6 μmol, 5 mol%), **1** (42.4 mg, 89 μmol, 15 mol%), Cs_2CO_3 (0.87 g, 2.66 mmol), followed by propionitrile (1.8 mL) and the aryl tosylate (0.59 mmol). The slightly yellow suspension was stirred for 25 min at room temperature. (The efficient stirring of the reaction mixture and a high purity of the starting tosylate are important for the transformation to be successful.) Then the reaction mixture was heated to the reflux temperature and the alkyne (0.88 mmol diluted with 1 mL of propionitrile) was injected slowly over the course of reaction (8 h) by means of a syringe pump. The reaction mixture was stirred for additional 2 h after the addition was complete and the resulting suspension was allowed to reach room temperature, diluted with water (3 mL), and extracted with diethyl ether (4 × 4 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.

Received: October 3, 2003 [Z53015]

Keywords: alkynes · aryl chlorides · C–C coupling · cross-coupling · palladium

[1] a) K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, Weinheim, **1996**, pp. 582–586; b) L. Brandsma, S. F. Vasilevsky, H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer, Berlin, **1998**, pp. 179–225; c) J. Tour, *Acc. Chem. Res.* **2000**, *33*, 791.

[2] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467.

[3] a) W. A. Herrmann, V. P. W. Böhm, C. P. Reisinger, *J. Organomet. Chem.* **1998**, *576*, 23; b) D. A. Alonso, C. Najera, M. C. Pacheco, *Org. Lett.* **2000**, *2*, 1283; c) D. A. Alonso, C. Najera, M. C. Pacheco, *Tetrahedron Lett.* **2002**, *43*, 9365.

[4] a) M. Pal, K. Parasuraman, S. Gupta, K. R. Yeleswarapu, *Synlett* **2002**, *14*, 1976; b) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* **2002**, *4*, 1691; c) D. Méry, K. Heuze, D. Astruc, *Chem. Commun.* **2003**, 1934.

[5] A. Mori, J. Kawashima, T. Shimada, M. Suguro, K. Hirabayshi, Y. Nishihara, *Org. Lett.* **2000**, *2*, 2935.

[6] P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.

[7] a) V. P. W. Böhm, W. A. Herrmann, *Eur. J. Org. Chem.* **2000**, 3679; b) T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Org. Lett.* **2002**, *4*, 1729.

[8] a) M. R. Eberhard, Z. Wang, C. M. Jensen, *Chem. Commun.* **2002**, 818.b) B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2002**, *124*, 14127; c) A. Kollhofer, T. Pullmann, H. Plenio, *Angew. Chem.* **2003**, *115*, 1086; *Angew. Chem. Int. Ed.* **2003**, *42*, 1056; d) J. W. Faller, R. G. Kultyshev, J. Parr, *Tetrahedron Lett.* **2003**, *44*, 451.

[9] a) H. Tomori, J. M. Fox, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 5334; b) S. Kuwabe, K. E. Torraca, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 12202; c) J. Yin, M. P. Rainka, X.-X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162; d) T. Hamada, A. Chieffi, J. Ahman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261; e) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.

[10] Activated vinyl tosylates have been used previously for Sonogashira reaction: see, for example: X. Fu, S. Zhang, J. Yin, D. P. Schumacher, *Tetrahedron Lett.* **2002**, *43*, 6673.

