JOC*Note*

Efficient Copper-Free $PdCl_2(PCy_3)_2$-Catalyzed Sonogashira Coupling of Aryl Chlorides with Terminal Alkynes

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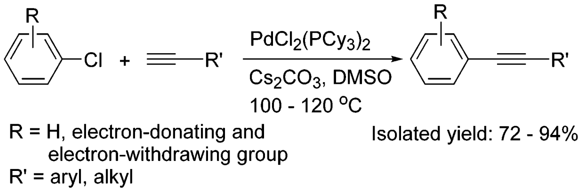
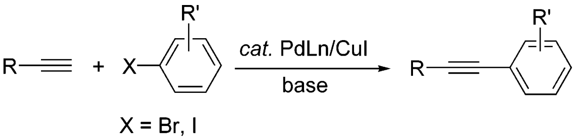
Received December 6, 2005



Under copper-free conditions and with Cs_2CO_3 as a base, $PdCl_2(PCy_3)_2$ showed high catalytic activity for cross-coupling of electron-rich, electron-neutral, and electron-deficient aryl chlorides with a variety of terminal alkynes in DMSO at 100−120 °C affording internal arylated alkynes in good to excellent yields.

Palladium/copper-catalyzed Sonogashira cross-coupling of terminal alkynes with aryl halides has become a powerful method for constructing carbon−carbon bonds leading to the formation of internal arylated alkynes (eq 1).[1] A number of



(1)

efficient catalyst systems have been developed for coupling of aryl bromides or aryl iodides.[2,3] In recent years, although the Sonogashira reaction has been intensively investigated to extend the application generality and simplify the catalyst systems, the reported results focused on the development of copper-free catalyst systems for aryl bromides and aryl iodides.[3] The examples of the efficient palladium catalyst systems for Sonogashira coupling of aryl chlorides are still few.[4] The efficient copper-free palladium catalyst system for Sonogashira coupling of electron-rich, electron-neutral, and electron-poor aryl chlorides was reported by Buchwald and co-workers with $P(Cy)_2Ar$ as ligand.[4b,f] Other catalyst systems showed moderate or high catalytic activity either in the use of activated aryl chlorides[4e] or requiring CuI[4c,d] or $ZnCl_2$[4a] as cocatalyst. Therefore, the purpose of our research work is to develop an effective, copper-free, easily available palladium catalyst for Sonogashira coupling of a wide variety of aryl chlorides. In this Note, we wish to report our preliminary results.

We chose the cross-coupling of chlorobenzene (**1a**) with phenyl acetylene as the model reaction to screen the catalyst and optimize the reaction conditions. First, the catalytic activities of some catalysts such as $NiCl_2$(dppp), $PdCl_2(PPh_3)_2$, $PdCl_2(PPhMe_2)_2$, and $PdCl_2(PCy_3)_2$ were tested in the presence of Cs_2CO_3 at 120 °C in NMP (NMP = *N*-methylpyrrolidone). As shown in Table 1, $NiCl_2$(dppp) and $PdCl_2(PPh_3)_2$ showed no catalytic activity at all and the starting materials were recovered completely (entries 1 and 2), while $PdCl_2(PPhMe_2)_2$ displayed low catalytic activity to give **2a** in 25% GC yield (entry 3). Fortunately, $PdCl_2(PCy_3)_2$, which has more basic and bulky groups of PCy_3, showed moderate catalytic activity (entry 4). These results encouraged us to further optimize the reaction conditions in the presence of $PdCl_2(PCy_3)_2$ by using different bases and solvents, as well as changing the reaction temperature. As can be seen from Table 1, among the bases tested, Cs_2CO_3 was the best chosen. In addition, the use of *p*-xylene, 1,4-dioxane, or DMF to replace NMP as solvent resulted in decreasing the catalytic activity of $PdCl_2(PCy_3)_2$ (entries 8−10). However, in the case of DMSO used as solvent, even at a relative low temperature (100 °C), $PdCl_2(PCy_3)_2$ also showed some catalytic activity, and at 120 °C, **2a** could be obtained in 60% GC yield (entries 11 and 12). More importantly, increase

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[1] Reviews, see: (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46−49. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2017. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

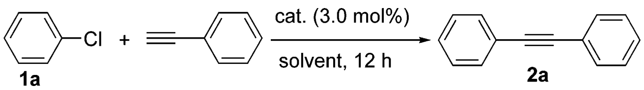
[2] Recent publications: (a) Elangovan, A.; Wang, Y.-H.; Ho, T.-I. *Org. Lett.* **2003**, *5*, 1841−1844. (b) Datta, A.; Plenio, H. *Chem. Commun.* **2003**, 1504−1505. (c) Hillerich, J.; Plenio, H. *Chem. Commun.* **2003**, 3024−3025. (d) Mas-Marza, E.; Segarra, A. M.; Claver, G.; Peris, E.; Fernandez, E. *Tetrahedron Lett.* **2003**, *44*, 6595−6599. (e) Garcia, D.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2004**, *6*, 4175−4178. (f) Wolf, C.; Lerebours, R. *Org. Biomol. Chem.* **2004**, *2*, 2161−2164. (g) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919−7927. (h) Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733−8736. (i) Feuerstein, M.; Doucet, H.; Santelli *Tetrahedron Lett.* **2005**, *46*, 1717−1720. (j) Kollhofer, A.; Plenio, H. *Adv. Synth. Catal.* **2005**, *347*, 1295−1300.

[3] Recent reports on copper-free Sonogashira reactions: (a) Bohm, V. P. M.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, *6*, 3679−3681. (b) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691−1694. (c) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365−9368. (d) Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653−8656. (e) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191−4194. (f) Mery, D.; Heuze, K.; Astruc, D. *Chem. Commun.* **2003**, 1934−1935. (g) Heuze, K.; Mery, D.; Gause, D.; Astruc, D. *Chem. Commun.* **2003**, 2274−2275. (h) Park, S. B.; Alper, H. *Chem. Commun.* **2004**, 1306−1307. (i) Park, S.; Kim, M.; Koo, D. H.; Chang, S. *Adv. Synth. Catal.* **2004**, *346*, 1638−1640. (j) Urganonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752−5755. (k) Cheng, J.; Sun, Y.; Wang, F.; Guo, M.; Xu, J.-H.; Pan, Y.; Zhang, Z. *J. Org. Chem.* **2004**, *69*, 5428−5430. (l) Arques, A.; Aunon, D.; Molina, P. *Tetrahedron Lett.* **2004**, *45*, 4337−4340. (m) Djakovitch, L.; Rollet, P. *Tetrahedron Lett.* **2004**, *45*, 1367−1370. (n) Djakovitch, L.; Rollet, P. *Adv. Synth. Catal.* **2004**, *346*, 1782−1792. (o) Heuze, K.; Mery, D.; Gauss, D.; Blais, J. C.; Astruc, D. *Eur. J. Chem.* **2004**, *10*, 3936−3944. (p) Tyrrell, E.; Al-Saardi, A.; Millet, J. *Synlett* **2005**, 487−488. (q) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391−393.

[4] (a) Eberhard. M. R.; Wang, Z.; Jensen, C. M. *Chem. Commun.* **2002**, 818−819. (b) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993−5996. (c) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056−1058. (d) Novak, Z.; Szabo, A.; Repasi, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327−3329. (e) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 8443−8446. (f) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173−6177.

10.1021/jo0525175 CCC: $33.50

TABLE 1. Palladium-Catalyzed Cross-Coupling of Chlorobenzene with Phenyloacetylene under Different Conditions[a]



entry	catalyst	solvent	base	temp (°C)	yield (%)[b]
1	$NiCl_2(dppp)$[c]	NMP	Cs_2CO_3	120	0
2	$PdCl_2(PPh_3)_2$	NMP	Cs_2CO_3	120	0
3	$PdCl_2(PPhMe_2)_2$	NMP	Cs_2CO_3	120	25
4	$PdCl_2(PCy_3)_2$	NMP	Cs_2CO_3	120	55
5[d]	$PdCl_2(PCy_3)_2$	NMP	Et_3N	120	<5
6	$PdCl_2(PCy_3)_2$	NMP	pyridine	120	<5
7	$PdCl_2(PCy_3)_2$	NMP	Na_3PO_4	120	<5
8	$PdCl_2(PCy_3)_2$	*p*-xylene	Cs_2CO_3	120	<5
9	$PdCl_2(PCy_3)_2$	1,4-dioxane	Cs_2CO_3	120	44
10	$PdCl_2(PCy_3)_2$	DMF	Cs_2CO_3	120	50
11	$PdCl_2(PCy_3)_2$	DMSO	Cs_2CO_3	100	10
12	$PdCl_2(PCy_3)_2$	DMSO	Cs_2CO_3	120	60
13	$PdCl_2(PCy_3)_2$	DMSO	Cs_2CO_3	150	85 (81)

[a] Reactions were carried out with 0.66 mmol of **1a**, 0.6 mmol of phenyl acetylene, 0.7 mmol of base, and 0.02 mmol of catalyst in 0.8 mL of solvent in a sealed tube for 12 h. [b] Yield according to GC based on the amount of phenyl acetylene used. Number in parentheses is isolated yield. [c] DPPP = 1, 3-bis(diphenylphosphino)propane. [d] For 20 h.

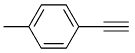
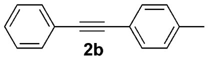
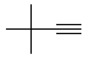
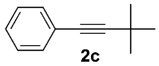
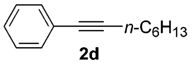
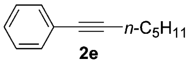
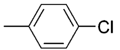
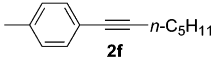
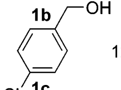
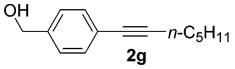
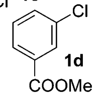
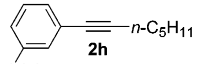
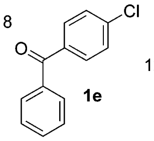
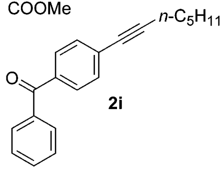
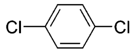
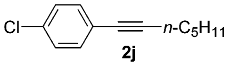
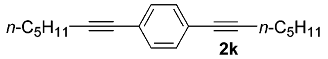
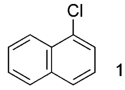
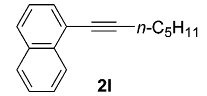
of the reaction temperature could greatly accelerate the reaction to give **2a** in 85% GC yield (entry 13). Therefore, the catalysis system of $PdCl_2(PCy_3)_2/Cs_2CO_3$ in DMSO is considered as an efficient catalyst system for Sonogashira cross-coupling of aryl chlorides.

To assess the scope of the $PdCl_2(PCy_3)_2$-catalyzed Sonogashira reaction, the cross-coupling reactions of **1a** with several terminal alkynes and the unactivated as well as activated aryl chlorides with 1-heptyne have been investigated. The results are concluded in Table 2. *p*-Tolylacetylene showed somewhat low reactivity compared to phenyl acetylene: the cross-coupling with **1a** at 150 °C for 12 h afforded the corresponding product phenyl-*p*-tolyl acetylene **2b** in 77% GC yield (entry 1). Although the cross-coupling of **1a** with phenyl acetylene at 100 °C proceeded slowly (heating for 12 h, 10%), the reactions of **1a** with aliphatic alkynes took place smoothly under this reaction temperature to give the corresponding 1-alkyl-2-phenylacetylene in excellent yields (Table 1, entry 11 vs Table 2, entries 2−4). The electron-rich aryl chlorides 4-chlorotoluene (**1b**) and 4-chlorobenzyl alcohol (**1c**) reacted with 1-heptyne at 120 °C to give the cross-coupling products **2f** and **2g** in near quantitative yields (entries 5 and 6). As expected, under the same reaction conditions, the electron-poor aryl chlorides underwent cross-coupling reaction smoothly. For example, the reactions of methyl 3-chlorobenzoate (**1d**) and 4-chlorobenzophenone (**1e**) with 1-heptyne afforded the desired products in high yields (entries 7 and 8). These results also indicated that a variety of important functional groups such as alcohol, ester, and ketone were tolerated under the present conditions.

When 1,4-dicholorobenzene was employed, the product distribution could be controlled completely by the use of a different ratio of the reactants. Therefore, 1-(4-chlorophenyl)-1-heptyne (**2j**) and 1,4-bis(1-heptynyl)benzene (**2k**) were obtained in good yields (entries 9 and 10).

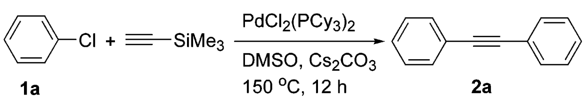
In addition, 1-chloronaphthalene (**1g**) showed reactivity similar to that of phenyl acetylene at 120 °C, affording **2*l*** in 92% GC yield (entry 11).

TABLE 2. Palladium-Catalyzed Cross-Coupling of Aryl Chlorides with Terminal Alkynes[a]

entry	aryl-Cl	temp(°C)	alkyne	product	yield (%)[b]
1	**1a**	150		 **2b**	77(74)
2	**1a**	100		 **2c**	85(76)
3	**1a**	100	n-C_6H_{13}—≡	 **2d**	99(93)
4	**1a**	100	n-C_5H_{11}—≡	 **2e**	99(94)
5	 **1b**	120	n-C_5H_{11}—≡	 **2f**	99(93)
6	 **1c**	120	n-C_5H_{11}—≡	 **2g**	86(72)
7	 **1d**	120	n-C_5H_{11}—≡	 **2h**	91(84)
8	 **1e**	120	n-C_5H_{11}—≡	 **2i**	99(89)
9	 **1f**	120	n-C_5H_{11}—≡	 **2j**	84(78)
10[c]	**1f**	120	n-C_5H_{11}—≡	 **2k**	75(73)
11	 **1g**	120	n-C_5H_{11}—≡	 **2l**	92(85)

[a] Reactions were carried out with 0.66 mmol of aryl chloride, 0.6 mmol of alkynes, 0.7 mmol of Cs_2CO_3, and 0.02 mmol of $PdCl_2(PCy_3)_2$ in 0.8 mL of DMSO in a sealed tube for 12 h. [b] Yield according to GC based on the amount of alkyne used. Numbers in parentheses are isolated yields. [c] Aryl chlorde:alkyne = 1:3 molar ratio.

It should be noted that under the same conditions, the reaction of **1a** with trimethylsilyl acetylene afforded diphenyl acetylene (**2a**) as the major product (46% GC yield, based on the amount of phenyl acetylene used). The corresponding Sonogashira coupling product of 1-phenyl-2-(trimethylsilyl)acetylene was determined in very low yield (<10%) (eq 2). These results indicated that the present catalyst system also displayed the high catalytic activity to catalyze the cross-coupling reaction of **1a** with 1-phenyl-2-(trimethylsilyl) acetylene via activation of C−Si.[5]



(2)

In summary, we developed a practical and efficient $PdCl_2(PCy_3)_2$-catalyzed sonogashira coupling of aryl chlorides with

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(5) Examples of palladium-catalyzed Sonogashira-type coupling of aryl halides with 1-aryl-2-(trimethylsilyl)acetylene have been reported, see: Sorense, U. S.; Pombo-Villar, E. *Tetrahedron* **2005**, *61*, 2697−2703 and references therein.

terminal alkynes. The advantages of this catalytic procedure include (1) omission of a copper cocatalyst, (2) ready availability and easily handling of catalyst, and (3) the high catalytic activity for not only electron-poor aryl chlorides but also electron-rich aryl chlorides under mild and convenient conditions.

Experimental Section

Typical experimental procedure for cross-coupling of chlorobenzene (1a) with phenyl acetylene to afford diphenyl acetylene (2a) (Table 1, entry 13): A mixture of chlorobenzene (**1a**) (75.0 mg, 0.66 mmol), phenyl acetylene (61.5 mg, 0.6 mmol), Cs_2CO_3 (230.0 mg, 0.7 mmol), $PdCl_2(PCy_3)_2$ (15.4 mg, 0.02 mmol), and DMSO (0.8 mL) under nitrogen in a sealed tube was heated with stirring at 120 °C for 12 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 to 1.5 mL and octadecane (45 mg, 0.18 mmol) was added as internal standard for GC analysis. After GC and GCMS analyses, removing the solvents and volatiles under vacuum, the residue was then subjected to preparative TLC isolation (silica, eluted with cyclohexane). **2a** was obtained (85.5 mg, 0.48 mmol, 80%) as a white solid. The results of GC analysis of the reaction mixture revealed that **2a** was formed in 85% yield.

A larger scale reaction (3.3 mmol) of **1a** or **1g** with 1-heptyne (3.0 mmol) afforded a similar isolated yield of **2e** (93%) or **2*l*** (87%) as described in Table 2.

Acknowledgment. This project (20573061) was supported by the National Natural Science Foundation of China.

Supporting Information Available: General method, characterization data, and charts of ^{1}H, ^{13}C NMR for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0525175