Efficient and Copper-Free Sonogashira Cross-Coupling Reaction Catalyzed by $Pd(OAc)_2$/Pyrimidines Catalytic System

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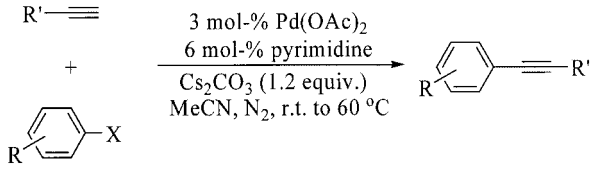
Keywords: Palladium / Cross-coupling reaction / Homogeneous catalysis

An efficient and copper-free catalyst system for Sonogashira cross-coupling reaction is presented. In the presence of 3 mol-% of $Pd(OAc)_2$ and 6 mol-% of 2-aminopyrimidine-4,6-diol, various aryl iodides and bromides can be coupled smoothly with terminal alkynes to afford the corresponding coupled alkynes in moderate to excellent yields under mild conditions.

Introduction

The acetylenic subunit is a commonly found motif in biologically active molecules and a useful building block in organic synthesis. Accordingly, the construction of alkynes remains an active area in organic synthesis. Besides the homocoupling reactions of terminal alkynes, the Pd-catalyzed Sonogashira cross-coupling reaction represents another important method for the formation of alkynes.[1] Generally, the combination of palladium, phosphane and CuI is used as the catalytic system for the reaction.[2–5] However, many phosphane ligands are air-sensitive and expensive.[6] Besides these drawbacks, the other significant limits on their synthetic applications is that the generation of some Cu^I acetylides in situ by the reaction of CuI with alkyne can result in oxidative homocoupling reaction of alkynes readily.[5f,7] For these reasons, the development of an efficient, inexpensive, copper- and phosphane-free catalytic system is still significant. Generally, a number of *N*-heterocyclic compounds is commercially available and these compounds (often pyridines) can directly be used as ligands for palladium catalysts.[2c] Thus, we tested these ligands in palladium-catalyzed cross-coupling reactions. Indeed, we found that pyrimidines were efficient ligands for $Pd(OAc)_2$-catalyzed Sonogashira cross-coupling reaction of aryl halides with terminal alkynes. Here we report our initial results according to Equation (1).



X = I, Br (1)

Results and Discussion

Efficiency of $Pd(OAc)_2$/pyrimidines as the catalytic system for coupling of 1-iodo-4-methoxybenzene (**1a**) with phenylacetylene (**2a**) was first evaluated, and the results are summarized in Table 1. Initially, a series of pyrimidines ($\mathbf{L_1}$–$\mathbf{L_4}$) as ligands were tested (entries 1–5). The results showed that the ligand 2-aminopyrimidine-4,6-diol ($\mathbf{L_1}$) was most effective, and the amount of $\mathbf{L_1}$ also affected the yield to some extent. Without any ligands, treatment of **1a** with **2a**, $Pd(OAc)_2$ and Cs_2CO_3 afforded a low yield of the corresponding cross-coupled product **3** at room temperature (entry 1), whereas the yield of **3** was increased sharply to 80% when 3 mol-% of $\mathbf{L_1}$ was added (entry 2). In the presence of 3 mol-% of $Pd(OAc)_2$ and 6 mol-% of $\mathbf{L_1}$, the yield of **3** was enhanced to 92% (entry 3). Identical results were observed when the amount of $\mathbf{L_1}$ was further increased to 12 mol-% (entry 4). A set of bases, such as Cs_2CO_3, KOAc, K_2CO_3, and Et_3N, were then investigated, and Cs_2CO_3 as the base gave the best results (entries 3 and 8–10). Finally, some solvents including MeCN, acetone and DMF were also examined and MeCN as the solvent provided the highest yield (entries 3, 11, and 12).

As shown in Table 2, the combination of $Pd(OAc)_2$ and 2-aminopyrimidine-4,6-diol ($\mathbf{L_1}$) is an effective catalytic system for the cross-coupling reactions of various aryl halides **1a**–**j** with alkynes **2a**–**e**. In the presence of 3 mol-% of $Pd(OAc)_2$, 6 mol-% of $\mathbf{L_1}$, and 1.2 equiv. of Cs_2CO_3, coupling of a

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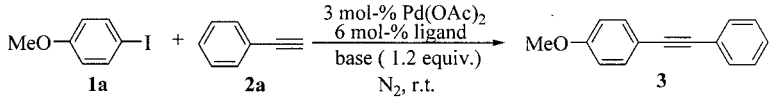
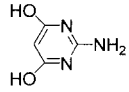
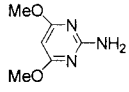
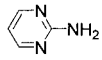
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

  DOI: 10.1002/ejoc.200500519

Table 1. Palladium-catalyzed Sonogashira cross-coupling reaction of 1-iodo-4-methoxybenzene (**1a**) with phenylacetylene (**2a**).[a]



1a **2a** **3**

Entry	Ligand	Base	Time [h]	Yield [%][b]
1	–	Cs_2CO_3	15	38
2[c]	 (**L1**)	Cs_2CO_3	8	80
3	**L1**	Cs_2CO_3	4	92
4[d]	**L1**	Cs_2CO_3	4	91
5	 (**L2**)	Cs_2CO_3	8	78
6	 (**L3**)	Cs_2CO_3	8	72
7	 (**L4**)	Cs_2CO_3	8	41
8	**L1**	K_2CO_3	8	65
9	**L1**	NaOAc	10	40
10	**L1**	Et_3N	9	50
11[e]	**L1**	Cs_2CO_3	12	80
12[f]	**L1**	Cs_2CO_3	6	74

[a] Unless otherwise indicated, the reaction conditions were as follows: **1a** (1 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (3.0 mol-%), ligand (6.0 mol-%), base (1.2 equiv.), and MeCN (4 mL) under N_2 at room temperature. [b] Isolated yield. [c] Ligand (3 mol-%). [d] Ligand (12 mol-%). [e] DMF (4 mL) instead of MeCN. [f] Acetone (4 mL) instead of MeCN.

number of aryl iodides **1a**–**f** with alkynes **2a**–**c** efficiently yields the corresponding alkynes **4**–**11** in good yields (entries 1–8). For example, when 1-iodo-4-nitrobenzene (**1b**) is coupled with alkynes **2a**–**c** the corresponding products **5**–**7** are obtained in yields of 100%, 95%, and 82%, respectively (entries 2–4). The results indicate that the efficiency of the $Pd(OAc)_2$/**L1** catalytic system for the reactions of aryl bromides **1g**–**j** is decreased to some extent, and both higher reaction temperature and prolonged reaction time are required (entries 9–16). For example, treatment of 1-bromo-4-nitrobenzene (**1g**) with alkynes **1a**, **1b**, **1d**, or **1e** gives moderate to good yields of the corresponding products after 20 h at 60 °C (entries 9–12), whereas the deactivated iodide **1f** is consumed completely within 9 h at room temperature (82% yield, entry 8). Unfortunately, the coupling of aryl chlorides **1k** and **1l** with **2a**, respectively, was unsuccessful (entries 17 and 18).

Conclusions

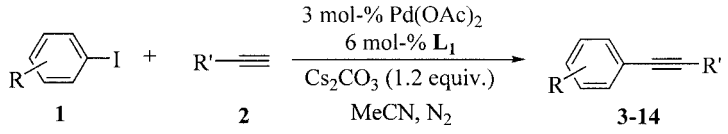
In summary, we have developed an efficient $Pd(OAc)_2$/2-aminopyrimidine-4,6-diol catalytic system for the Sonogashira cross-coupling reaction. In the presence of $Pd(OAc)_2$ and 2-aminopyrimidine-4,6-diol, the reactions of a number of aryl iodides and bromides with terminal alkynes were carried out efficiently to afford the desired products in moderate to excellent yields under mild conditions. Further efforts to extend the application of this catalytic system and this protocol in organic synthesis are underway in our laboratory.

Experimental Section

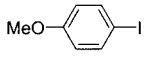
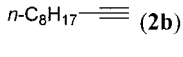
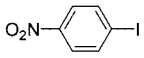
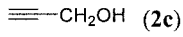
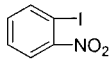
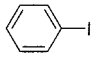
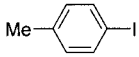
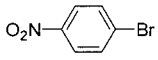
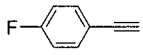
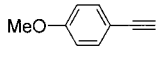
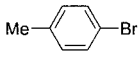
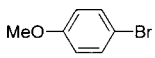
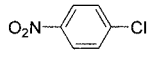
General Remarks: ^1H and ^{13}C NMR spectra were recorded on an INOVA-400 (Varian) spectrometers and a Bruker AMX-300 spectrometers with the use of $CDCl_3$ as the solvent. All reagents were directly used as obtained commercially. All products **3**–**14** are known,[3–5] and their analytical data and spectra (^1H and ^{13}C NMR) are available as Supporting Information (see also the footnote on the first page of this article).

Typical Experimental Procedure for the $Pd(OAc)_2$/L_1-Catalyzed Sonogashira Cross-Coupling Reaction: A mixture of aryl halide **1** (1.0 mmol), alkyne **2** (1.2 mmol), $Pd(OAc)_2$ (3.0 mol-%), 2-aminopyrimidine-4,6-diol (**L1**, 6.0 mol-%), Cs_2CO_3 (1.2 equiv.), and MeCN (4 mL) was stirred under N_2 at the indicated reaction temperature for desired time until complete consumption of starting material as monitored by TLC. After the mixture was filtered and

Table 2. Palladium-catalyzed Sonogashira coupling reaction in the presence of 2-aminopyrimidine-4,6-diol ($\mathbf{L_1}$).[a]



1 2 3-14

Entry	ArX	Alkyne	Time [h]	Yield [%][b]	
1	 (**1a**)	 (**2b**)	7	87	**4**
2	 (**1b**)	 (**2a**)	5	100	**5**
3	**1b**	(**2b**)	5	95	**6**
4	**1b**	 (**2c**)	9	82	**7**
5	 (**1c**)	**2a**	6	95	**8**
6	 (**1d**)	**2a**	6	98	**9**
7	 (**1e**)	**2a**	6	92	**10**
8	 (**1f**)	**2a**	9	82	**11**
9[c]	 (**1g**)	**2a**	20	95	**5**
10[c]	**1g**	**2b**	21	65	**6**
11[c]	**1g**	 (**2d**)	21	88	**12**
12[c]	**1g**	 (**2e**)	24	81	**13**
13[c]	 (**1h**)	**2a**	18	80	**9**
14[c]	 (**1i**)	**2a**	24	60	**10**
15[c]	(**1i**)	**2b**	24	63	**14**
16[c]	 (**1j**)	**2a**	21	72	**3**
17[c]	 (**1k**)	**2a**	24	10	**5**
18[c]	 (**1l**)	**2a**	24	trace	**9**

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (1 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (3.0 mol-%), $\mathbf{L_1}$ (6.0 mol-%), Cs_2CO_3 (1.2 equiv.), and MeCN (4 mL) at room temperature under N_2. [b] Isolated yield. [c] At 60 °C.

evaporated, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the coupled products **3**–**14**.

Acknowledgments

We thank the National Natural Science Foundation of China (No. 20202002) for financial support.

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Received July 13, 2005
Published Online: September 1, 2005

