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A copper- and amine-free Sonogashira reaction employing chlorophosphine as new and efficient ligand

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Abstract

An efficient palladium-catalyzed copper- and amine-free Sonogashira coupling reaction of aryl bromides and chlorides was studied using a sterically hindered monooxychlorophosphine as new ligand. The use of $2 \mod \% Pd(OAc)_2$ in the presence of K_2CO_3 allows the coupling reaction to proceed at mild condition with good to excellent yields. © 2011 Published by Elsevier B.V. on behalf of Chinese Chemical Society.

Keywords: Palladium; Copper-free; Coupling; Sonogashira reaction; Chlorophosphine

Palladium-catalyzed cross-coupling reactions are extremely useful synthetic tools [1,2]. The Sonogashira reaction provides a powerful tool for C–C bond formation, which has been widely applied to natural products, a wide range of industrial intermediates, pharmaceuticals and agrochemicals, and molecular materials for optics and electronics [3,4]. Although a lot of modifications have been reported for the coupling, including phase-transfer reaction conditions and aqueous, and solvent-free, a copper cocatalyst was still needed [5–7]. However, the presence of CuI can induce homocoupling reactions (Glaser-type reaction) of terminal alkynes to diynes in the presence of oxygen. It has been reported that CuI had a deleterious effect on the Sonogashira cross-coupling reaction [8]. Amines, another additive, are not eco-friendly reagent which has bad smell. Though copper-free Sonogashira reaction has been reported, in most case, aryl iodide must be used or high temperature even under MW conditions [9–12]. Several examples have described copper-free methodologies; amines such as piperidine, pyrrolidine and DABCO were still required [13,14]. For these reasons, eliminating the use of copper (I) iodide as cocatalyst and avoiding the use of the amine have been applied to simplify the catalyst system.

Ackermann [15,16] have reported a diaminochlorophosphine as new and high efficient ligand in Suzuki reaction and Buchwald–Hartwig amination and Wolf [17] reported Stille cross-coupling reactions using PXPd (X = Cl) as catalyst. Though chlorophosphine compounds are comparatively unstable in moisture air, they have high activities because oxidative addition of chlorophosphine to low-valent palladium species could give a phosphenium cation which is isolable to *N*-heterocyclic singlet carbenes.

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Results and discussion

Herein we wish to report a new comparatively air-stable monooxychlorophosphine L1 [18] (Scheme 1) as novel and efficient ligand for palladium-catalyzed Sonogashira cross-couplings of aryl bromides and chlorides as our continuous work in coupling reactions.

We first selected 1-bromo-4-methoxybenzene (1a) and phenylacetylene (2a) as substrates and L_{1-3} as ligands (Scheme 2) to develop the Sonogashira reaction in the absence of copper and amine. L2 is commercially available and L3 is Zhang's ligand [19] for copper- and amine-free Sonogashira reaction. The reaction conditions and results were summarized in Table 1.

Treatment of a mixture of 1a (374 mg, 2.0 mmol), 2a (0.24 mL, 2.2 mmol), Pd(OAc)₂ (8.9 mg, 0.04 mmol), L1 (13.6 mg, 0.04 mmol) in 5 mL CH₃CN at 50 °C under N₂ atmosphere for 10 h gave the desired coupling product **3** in 78% isolated yield (Table 1, entry 1). This is good result in the absence of copper salt and amine. We next tested different solvents, bases and ligands under the same conditions. As shown in Table 1, good to excellent yields were obtained for the coupling reaction when using L1 as the ligand and DABCO or K₂CO₃ as base (Table 1, entries 1, 4, 5, 6 and 10). But using Et₃N as base and THF as solvent, the product yield was only 57% in the presence of L1 (Table 1, entry 9). L2 is analog to L1, but only very low product yields were obtained in the presence of organic or inorganic bases (Table 1, entries 2, 7 and 11). The reason maybe the bulk of L2 is smaller than L1 based on the mechanism of the coupling reactions. L3 has been tested in copper- and amine-free Sonogashira reaction in previous study [19] and it was effective in the reaction under our condition but was not the most efficient (Table 1, entries 3, 8 and 12). THF as solvent was better than CH₃CN under our conditions. For example, the yield of product 3 decreased from 93% to 78% when using CH₃CN under the same conditions (Table 1, entries 1 and 10).



Scheme 1. Synthesis of L1.



Scheme 2. Ligands tested in this work.

Table	1					
Effect	of solvents,	bases and	ligands in	the Sonogashira	cross-coupling	reaction.a

Entry	Solvent	Base	Ligand	Yield (%) ^b
1	CH ₃ CN	K ₂ CO ₃	L1	78
2	CH ₃ CN	K_2CO_3	L2	26
3	CH ₃ CN	K ₂ CO ₃	L3	66
4	CH ₃ CN	DABCO	L1	72
5	CH ₃ CN	Et ₃ N	L1	80
6	THF	DABCO	L1	83
7	THF	DABCO	L2	18
8	THF	DABCO	L3	55
9	THF	Et ₃ N	L1	57
10	THF	K ₂ CO ₃	L1	93
11	THF	K_2CO_3	L2	20
12	THF	K ₂ CO ₃	L3	77

^a Pd(OAc)₂ (2.0 mol%), *p*-bromoanisole (2 mmol), phemylacetylene (2.2 mmol) and ligand (2.0 mol%) in 5 mL of the indicated solvent at 50 °C for 10 h.

^b Isolated yield.

Table 2

 $Pd(OAc)_2$ -catalyzed Sonogashira cross-coupling of aryl halides (1) with alkynes (2)^a.



Entry	ArX	R	Time (h)	Products	Yield (%) ^b
1	4-BrC ₆ H ₄ OMe/1a	H/ 2a	10	3	93
2	$4-BrC_6H_4Me/1b$	Н	10	4	90
3	$2-BrC_6H_4Me/1c$	Н	10	5	87
4	1-Bromonaphthalene/1d	Н	8	6	94
5	$BrC_6H_5/1e$	Н	8	7	90
6	4-BrC ₆ H ₄ CHO/1f	Н	8	8	91
7	4-BrC ₆ H ₄ COCH ₃ /1g	Н	8	9	84
8	2-Bromomesitylene/1h	Н	10	10	72
9	2-Bromopyridine/1i	Н	8	11	89
10	3-Bromopyridine/1j	Н	8	12	93
11	$BrC_6H_5/1e$	CHO/2b	8	8	85
12	$2-BrC_6H_4Me/1c$	СНО	10	13	76
13	ClC ₆ H ₅ /1k	Н	18	7	46 ^c
14	4-ClC ₆ H ₄ COCH ₃ /11	Н	18	9	52 ^c
15	ClC ₆ H ₅ /1k	СНО	18	8	38°
16	$4-ClC_6H_4C_6H_5/1m$	CHO	18	16	Trace ^c

^a Reaction conditions: ArX (2.0 mmol), aryl alkynes (2.2 mmol), K₂CO₃ (4.0 mmol), Pd(OAc)₂ (0.04 mmol), L1 (0.04 mmol), THF (5 mL), 50 °C, 8–18 h.

^b Isolated yield.

 $^{\rm c}\,$ At 90 $^{\circ}{\rm C}.$

Under the optimized reaction conditions, the coupling reactions between a variety of aryl bromides (1a-1j) and chlorides (1k-1m) and two aryl alkynes (2a-2b) were carried out and the results were summarized in Table 2. As shown in Table 2, both electron-poor and electron-rich aryl bromides (1a-1j) were efficiently coupled with phenylacetylene (2a) and 4-ethynylbenzaldehyde (2b) to give products in excellent yields (72-94%). For aryl bromides which have *ortho* substituent groups such as 2-bromotoluene (1c) and 2-bromomesitylene (1h), 72% and 87% product yields were obtained respectively (Table 2, entries 3 and 8). This indicated that the *ortho* group in the aryl bromides had little effect in the reaction under our conditions. On one hand, for aryl bromides, there was no great difference in product yield between



Scheme 3. Probable mechanism.

those electron-deficient and elecron-rich substrates (Table 2, entries 1, 2 and entries 6, 7). On the other hand, for aryl alkynes, it could be observed obviously that the same aryl bromides coupled with phenylacetylene (**2a**) could obtain a little higher yield than those they coupled with 4-ethynyl-benzaldehyde (**2b**) (Table 2, entries 2, 3, 5, 8, 11 and 12). For example, treatment of 2-bromotoluene (**1c**) with alkynes **2a** and **2b** gave 87% and 76% isolated yields (Table 2, entries 3 and 12). The heterocyclic bromides 3-bromopyridine (**1i**) and 2-bromopyridine (**1j**) were likewise converted smoothly to the coupled products with phenylacetylene (**2a**) in 89% and 93% yields respectively (Table 2, entries 9 and 10). According to our earlier report, ligand **L1** was efficient in the Suzuki–Miyaura cross-coupling reaction of aryl chlorides (Table 2, entries 13–15). Treatment of chlorobenzene (**1k**) with **2a** and **2b** could only produced coupled products **7** and **8** in 46% and 38% yields (Table 2, entries 13 and 15). A little higher yield (52%) could be obtained when using more activated 4-chloroacetophenone (**1l**) as substrate coupled with **2a** (Table 2, entry 14). However, when using inactivated 4-chlorobiphenyl (**1m**) and inactivated alkyne **2b** as substrates at the same time, almost no product could be produced (Table 2, entry 16). The reason that L1 was not efficient for Sonogashira reaction of aryl chlorides was not clear.

The use of phosphenium ions as ligands for transition metals has also been investigated [20], but its application in cross-coupling reaction had few reports. We tried to explain its high efficiency in cross-coupling reactions. A working mechanism as outlined in Scheme 3 was proposed on the basis of the earlier report [20]. As shown in Scheme 3, we considered that the intermediate (1') was real ligand coordinated with palladium. Phosphenium ion which lack electrons is isoelectronic analog to *N*-heterocyclic carbene, so its electron-rich property make the Pd-P bond very strong and stabilize the metal. This could make the step I (oxidative step) more easier. The large bulk of intermediate (1') might play key roles in the Sonogashira cross-coupling reactions.

Conclusion

In summary, we have developed an efficient, copper- and amine-free Sonogashira cross-coupling reaction using novel and air-stable chlorophosphine as ligand. A variety of aryl bromides including electron-deficient and electronrich bromides were reacted with aryl alkynes smoothly in good yields under mild conditions. Several aryl chlorides were tested under the conditions and gave the middle yields.

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