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CHINESE Chemical Letters

Chinese Chemical Letters 22 (2011) 1175-1178

www.elsevier.com/locate/cclet

Copper and amine free Sonogashira cross-coupling reaction catalyzed by efficient diphosphane–palladium catalyst

Ting He^a, Lei Lei Wu^a, Xing Li Fu^b, Hai Yan Fu^a, Hua Chen^{a,*}, Rui Xiang Li^a

^a Key lab of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China ^b Guangxi Vocational & Technical Institute of Industry, Nanning 530001, China

> Received 17 February 2011 Available online 18 July 2011

Abstract

The commercially available diphosphane ligand MeO-BIPHEP was first investigated in the palladium-catalyzed Sonogashira reaction in the absence of copper and amine. The coupling of various aryl bromides and aryl chlorides with phenylacetylene gave moderate to excellent yields.

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Keywords: MeO-BIPHEP; Sonogashira reaction; Diphosphane ligand; Palladium complex

The Sonogashira reaction of aryl halides with terminal alkynes is an important tool in the synthesis of organic intermediates, which are mostly encountered within natural products, pharmaceutical products, and molecular materials [1]. This reaction was first reported in 1975, and catalyzed by $(Ph_3P)_2PdCl_2$ together with CuI as co-catalyst [2]. In recent years, various modifications have been improved, including the elimination of CuI, which usually caused the formation of oxidative homocoupling products of terminal alkynes [3], and palladium free catalyst system is also possible [4]. By now, several catalytic systems [5–8] have been reported, and it is undeniable that the most effective catalysts are still palladium–phosphane complexes. For example, phosphanes $P(tBu_3)$ [9], PCy_3 [10], $(1-Ad)_2PBn$ (1-Ad = 1-adamantyl) [11], X-Phos [12] have been successfully applied in this reaction. On the other hand, multidentate phosphane ligands were also reported to improve the stability of catalysts applied in the Sonogashira reaction. For instance, tedicyp [13] was a successful example even in low palladium loading. However, only a few multidentate ligands (di-, tri-, tetradentate or more) have been tested.

In continuation of our work on transition metal diphosphane complexes as catalysts [14], herein is reported a commercially available diphosphane ligand MeO-BIPHEP (Scheme 1) employed in the palladium catalyzed Sonogashira reaction in the absence of copper and amine.

1. Experimental

Unless especially indicated, all experiments were performed under argon atmosphere. All reactants were reagent grade and used as purchased without further purification. Solvents were distilled before use. ¹H NMR and ¹³C NMR spectra were recorded on Bruker AV II-400 MHz in CDCl₃ or DMSO- d_6 .

* Corresponding author.

E-mail address: scuhchen@163.com (H. Chen).

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Scheme 1. MeO-BIPHEP.

An oven-dried Schlenk tube equipped with a stir bar was charged with $PdCl_2$ (0.9 mg, 0.005 mmol), MeO-BIPHEP (4.3 mg, 0.01 mmol), aryl halide (0.5 mmol), alkyne (0.7 mmol), K₂CO₃ (138 mg, 1 mmol) and degassed DMF (2 mL). After stirring for 30 min at room temperature under argon atmosphere, the mixture was heated up until the reaction was completed. The mixture was then quenched with water and extracted with 4×5 mL EtOAc. The combined organic phase was dried over anhydrous MgSO₄. After filtration, the filtrate was concentrated to dryness. The desired product was isolated from the residue by column chromatography using hexane as eluent. The physical and spectral data of all compounds were identical to those previously reported.

2. Results and discussion

During the optimization studies, the effect of solvents on the Sonogashira reaction of bromobenzene with phenylacetylene catalyzed by PdCl₂/MeO-BIPHEP was first investigated in the presence of Et₃N. As shown in Table 1, polar solvents were more appropriate than nonpolar ones. There was no product to be detected using THF or toluene as solvent (Table 1, entries 1 and 2). Moderate yields were obtained in polar solvents (Table 1, entries 3 and 4) in 4 h. A yield of 86% was gained when the reaction time was extended to 24 h in DMF (Table 1, entry 5). When the reaction temperature was increased to 130 °C, the yield was also increased (Table 1, entry 6). Then, K₂CO₃ was tested instead of Et₃N (Table 1, entries 7–10). Inspiringly, a good yield of 92% was given in DMF in 4 h (Table 1, entry 8). A yield of 80% was detected when the reaction temperature dropped from 130 °C to 120 °C (Table 1, entry 10). Other inorganic bases like NaOH and Na₂CO₃ (Table 1, entries 11 and 12) were less efficient than K₂CO₃. Thus, in the following experiments, copper free Sonogashira reaction catalyzed by PdCl₂/MeO-BIPHEP was investigated using K₂CO₃ as the base in DMF.

Table 1 Effect of reaction conditions on the cross-coupling of bromobenzene with phenylacetylene.

Entry	Solvent	Base	Temp. (°C)	Time (h)	Yield (%)
1	THF	Et ₃ N	80	4	Trace
2	Toluene	Et ₃ N	90	4	Trace
3	n-BuOH	Et ₃ N	90	4	44
4	DMF	Et ₃ N	90	4	30
5	DMF	Et ₃ N	90	24	86
6	DMF	Et ₃ N	130	4	76
7	n-BuOH	K_2CO_3	100	4	71
8	DMF	K_2CO_3	130	4	92
9	DMF	K ₂ CO ₃	130	8	98
10	DMF	K_2CO_3	120	4	80
11	DMF	Na ₂ CO ₃	130	4	44
12	DMF	NaOH	130	4	27
13 ^a	DMF	K ₂ CO ₃	130	4	5

Reaction conditions: bromobenzene (0.5 mmol); phenylacetylene (0.7 mmol); PdCl₂ (1% equiv.); MeO-BIPHEP (2% equiv.); solvent (2 mL); Et₃N

(1.5 equiv.); inorganic base (2.0 equiv.); argon protected; GC yield.

^a Ligand free.

Table 2	
Coupling of aryl halides	with phenylacetylene.
	PdCl ₂ /MeO-BIPHEP

	=	$\xrightarrow{\text{DMF}, K_2\text{CO}_3} \qquad \qquad$							
\smile	+ Aryl halide								
Entry	ArX	[L]/[Pd]	Time (h)	Yield (%)	Entry	ArX	[L]/[Pd]	Time (h)	Yield (%)
1	4-BrC ₆ H ₄ Me	2	20	97	13	3, 5-Ditrifluoromethyl	2	20	81
2	2-BrC ₆ H ₄ Me	1	4	96		-Bromobenzene			
3	2-BrC ₆ H ₄ Me	2	20	96	14	4-BrC ₆ H ₄ COOH	2	20	98
4	3-BrC ₆ H ₄ OMe	2	20	98	15	3-Bromoquinoline	2	20	96
5	4-BrC ₆ H ₄ OMe	2	20	97	16	5-Bromopyrimidine	2	20	72
6	4-BrC ₆ H ₄ COMe	2	12	96	17	4-ClC ₆ H ₄ NO ₂	2	24	82
7	3-BrC ₆ H ₄ COMe	2	12	92	18	3-ClC ₆ H ₄ NO ₂	2	24	71
8	4-BrC ₆ H ₄ CN	2	8	96	19	2-ClC ₆ H ₄ NO ₂	2	24	9
9	2-BrC ₆ H ₄ NO ₂	2	20	20	20	2-ClC ₆ H ₄ NO ₂	1	24	70
10	2-BrC ₆ H ₄ NO ₂	1	20	88	21	4-ClC ₆ H ₄ COMe	2	24	60
11	4-BrC ₆ H ₄ NO ₂	2	8	95	22	4-ClC ₆ H ₄ CN	2	24	78
12	4-BrC ₆ H ₄ CF ₃	2	20	97	23	4-ClC ₆ H ₄ CF ₃	2	24	50

Reaction conditions: aryl halides (0.5 mmol); phenylacetylene (0.7 mmol); $PdCl_2$ (1% equiv.); K_2CO_3 (2 equiv.); DMF (2 mL); 130 °C; argon protected; isolated yield; average of two runs; $[L]/[Pd] = [MeO-BIPHEP]/[PdCl_2]$.

Based on the optimal conditions obtained, various substrates were then examined. As shown in Table 2, both activated and unactivated aryl bromides gave the desired products in good to excellent yields, even with crowded *ortho*-substituted substrates. For example, 88% yield was obtained for 1-bromo-2-nitrobenzene (Table 2, entry 10). And for more hindered substrate 3, 5-ditrifluoromethylbromo-benzene, the reaction still gave a good yield of 81% (Table 2, entry 13). In addition, the reaction of heteroaromatic bromides such as 3-bromoquinoline and 5-bromopyrimidine also gave desired products in good yields of 96% and 72% (Table 2, entries 15 and 16). As far as we know, this was the first successful example in the Sonogashira reaction of heteroaromatic bromides catalyzed by palladium–diphosphane complex [15,16]. Entries of 17–23 represented the coupling of aryl chlorides with phenylacetylene could also work well in the presence of PdCl₂/MeO-BIPHEP. A yield of 82% was obtained in the case of *p*-chloronitrobenzene (Table 2, entry 17). Other activated aryl chlorides still gave moderate yields, which was significantly improved than previously reported palladium–diphosphane catalyst [16]. However, the coupling of unactivated aryl chlorides in this system is still a challenging topic.

Interesting phenomena were observed in the reaction of *ortho*-substituted aryl halides. At first, unsatisfied results were obtained with *o*-bromonitrobenzene (Table 2, entry 9). According to the mechanism of palladium catalyzed Sonogashira reaction [3], the oxidative addition of aryl halides to the palladium complex here might be blocked because of the steric hindrance of *ortho*-substituted groups. Thus the ratio of MeO-BIPHEP was reduced to 1% equiv. in order to accelerate the oxidative addition of aryl halides on Pd active species. To our expectation, the reaction of *o*-bromonitrobenzene with phenylacetylene (Table 2, entry 10) was significantly accelerated. In addition, a better yield of *o*-bromotoluene (Table 2, entry 2) and *o*-chloronitrobenzene (Table 2, entry 20) were also obtained in the presence of 1% equiv. of MeO-BIPHEP. However, the activity of the catalyst under this condition obviously decreased in the case of *meta*- and *para*-substituted aryl halides (not shown). We suppose that in the reaction of *ortho*-substituted aryl halides, steric hindrance is a main influence factor; therefore the reaction rate is effectively improved by the decrease of ligand. In the case of *meta*- and *para*-substituted aryl halides, the stability of catalyst complex is more important, thus the ratio of PdCl₂/MeO-BIPHEP is adjusted to 1/2 to maintain the stability of catalyst.

3. Conclusions

In summary, an efficient catalytic system of PdCl₂/MeO-BIPHEP was developed for the copper and amine free Sonogashira reaction. A number of aryl bromides, heteroaryl bromides and aryl chlorides with phenylacetylene were carried out efficiently to afford the desired products in moderate to excellent yields. Various functional groups were

tolerated under these conditions. Further efforts on the application of this catalyst system in organic synthesis are underway in our laboratory.

Acknowledgment

We thank Analytical and Testing Center of Sichuan University for the support of characterization.

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