Sonogashira coupling catalyzed by the Cu(Xantphos)I-Pd(OAc)$_2$ system

Meilin Liu, Mingyan Ye, Yeye Xue, Guodong Yin, Dunjia Wang, Jinkun Huang

PII: S0040-4039(16)30674-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.06.014
Reference: TETL 47741

To appear in: *Tetrahedron Letters*

Received Date: 15 April 2016
Revised Date: 1 June 2016
Accepted Date: 3 June 2016

Please cite this article as: Liu, M., Ye, M., Xue, Y., Yin, G., Wang, D., Huang, J., Sonogashira coupling catalyzed by the Cu(Xantphos)I-Pd(OAc)$_2$ system, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.06.014

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Sonogashira coupling catalyzed by the Cu(Xantphos)I-Pd(OAc)$_2$ system

Meilin Liu, Mingyan Ye, Yeye Xue, Guodong Yin*, Dunjia Wang and Jinkun Huang*

Hubei Collaborative Innovation Center for Rare Metal Chemistry, Hubei Key Laboratory of Pollutant Analysis and Reuse Technology, Hubei Normal University, Huangshi 435002, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

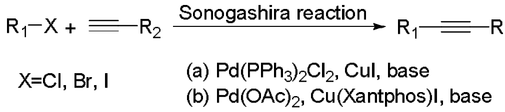
Keywords:
Sonogashira coupling
Alkynylation
Co-catalyst
Copper-phosphine ligand complex

ABSTRACT

An efficient Pd(OAc)$_2$/Cu(Xantphos)I system for Sonogashira coupling is disclosed. Aryl bromides/iodides and electron-poor aryl chlorides were suitable for this reaction. The experimental results suggest that Cu(Xantphos)I plays a unique role in which the phosphine ligand coordinates with copper.

1. Introduction

The Sonogashira cross-coupling reaction[1,2] between aryl halides and terminal alkynes has become a valuable and facile method to prepare substituted alkynes, which are widely employed in synthesis of numerous natural products,[3] bioactive and pharmaceutical molecules,[4] organic materials,[5] and polymers.[6] The reaction is typically performed using a palladium complex as catalyst and copper(I) salt as a co-catalyst under basic conditions (Scheme 1, condition a). Generally, palladium is coordinated with a neutral ligand such as phosphines to form the complex, e.g. Pd(PPh$_3$)$_2$Cl$_2$,[7] Pd(dppe)Cl$_2$,[8] Pd(OAc)$_2$(PPh$_3$)$_2$[9] and Pd(dppp)Cl$_2$.[10] Alternatively, chemists have devoted to develop an impressive variety of effective catalytic palladium system, and this includes the palladium–nitrogen complexes,[11] palladium–N,O complexes,[12] palladium–P,N complexes,[13] palladium–P,O complexes,[14] N-heterocyclic carbene (NHC) palladium complexes,[15] palladacycles[16] and palladium nanoparticles.[17] Although Au(I),[18] Ni(II),[19] Fe(III),[20] Cu(I)[21] and Cu(II)[22] systems sometimes could catalyze this coupling reaction, most of these methods are only effective for aryl iodides or at high temperature. Recently, Hierso reported the [Pd(allyl)Cl]$_2$/copper(I) ferrocenyl tetraphosphine complexes system for Sonogashira coupling reaction at high temperature (120 °C), which was the first example for the phosphine ligand complexation to copper instead of palladium.[23] Recently, we prepared the copper-phosphine ligand complex Cu(Xantphos)I and found a highly efficient palladium/Cu(Xantphos)I co-catalytic system for direct arylation of heteroarenes. The high efficiency is attributed to the unique role of Cu(Xantphos)I.[24] In this paper, we would like to report a novel Pd(OAc)$_2$/Cu(Xantphos)I system for efficient Sonogashira coupling reaction (Scheme 1, condition b).



Scheme 1

2. Results and discussion

On the light of our previous studies in the arylation of heteroarenes catalyzed by the Pd/Cu(Xantphos)I system,[24] we envisioned that the similar system might be effective for the Sonogashira coupling. Initially, we investigated the cross-coupling between 1-bromo-4-methylbenzene (**1a**) and phenylacetylene (**2a**) in the presence of Pd(OAc)$_2$ (1%) and Cu(Xantphos)I (1%) using Cs$_2$CO$_3$ as base in anhydrous DMF at room temperature for 24 h, only trace amount of expected alkynylation product 1-methyl-4-(phenylethynyl)benzene (**3a**) was observed (Table 1, entry 1). The yield of **3a** significantly increased when the temperature was raised to 40 °C (84%, entry 2). While the temperature was further elevated to 60 °C, **3a** was obtained in nearly quantitative yield (98%, entry 3). After screening other typical bases, such as Na$_2$CO$_3$, K$_2$CO$_3$, K$_3$PO$_4$·H$_2$O, NHEt$_2$, NEt$_3$, all of them afforded the yields above 90% except for NEt$_3$ which gave a lower yield of 54% (entries 4–8). The combination of Cu(Xantphos)I with other palladium compounds, e.g. PdCl$_2$, [Pd(allyl)Cl]$_2$ and Pd$_2$(dba)$_3$, the yield was in the range of 38–87% (entries 9–11). When the amount of Pd(OAc)$_2$ or Cu(Xantphos)I was reduced to 0.5% and 0.25%, the coupling resulted in a corresponding lower yield (entries 12–15).

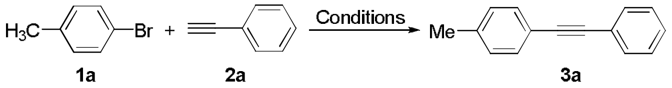
---

*Corresponding author. Tel./fax: +86 0714 6515602; e-mail address: gdyin@hbnu.edu.cn (G. Yin); jxhcm99@qq.com (J. Huang)

Meanwhile, the reaction didn't give the product in the absence of the $Pd(OAc)_2$ (entry 16) and was less effective when no copper(I) salt was employed (entries 17 and 19). Replacement of Cu(Xantphos)I by $Cu(PPh_3)_3Br$ or $Cu(PPh_3)_3I$ also furnished **3a** in a lower yield (entries 21, 22). Cu(Xantphos)Br was also effective for the reaction (entry 23). However, the combination of $Pd(OAc)_2$ and CuI resulted in almost no reaction (<5%, entry 19). Obviously, the addition of Cu(Xantphos)I significantly promotes this coupling reaction (entries 18 and 20).

Table 1

Optimization of the reaction conditions for Sonogashira coupling between 1-bromo-4-methylbenzene and phenylacetylene[a]



Entry	[Pd] (mol%)	[Cu] (mol%)	Base	Yield[b] (%)
1[c]	$Pd(OAc)_2$ (1)	Cu(Xantphos)I[d] (1)	Cs_2CO_3	<5
2	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (1)	Cs_2CO_3	84
3[e]	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (1)	Cs_2CO_3	98 (97[f], 70[g])
4	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (1)	Na_2CO_3	90
5	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (1)	K_2CO_3	96
6	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (1)	$K_3PO_4 \cdot H_2O$	96
7	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (1)	$NHEt_2$	95
8	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (1)	NEt_3	54
9	$PdCl_2$ (1)	Cu(Xantphos)I (1)	Cs_2CO_3	60
10	$[Pd(allyl)Cl]_2$ (1)	Cu(Xantphos)I (1)	Cs_2CO_3	87
11	$Pd_2(dba)_3$[h] (1)	Cu(Xantphos)I(1)	Cs_2CO_3	38
12	$Pd(OAc)_2$ (0.5)	Cu(Xantphos)I(1)	Cs_2CO_3	76
13	$Pd(OAc)_2$ (0.25)	Cu(Xantphos)I (1)	Cs_2CO_3	39
14[i]	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (0.5)	Cs_2CO_3	93
15[i]	$Pd(OAc)_2$ (1)	Cu(Xantphos)I (0.25)	Cs_2CO_3	67
16	—	Cu(Xantphos)I (1)	Cs_2CO_3	0
17	$Pd(OAc)_2$ (1)	—	Cs_2CO_3	<5
18[j]	$Pd(OAc)_2$ (1)	—	Cs_2CO_3	66
19	$Pd(OAc)_2$ (1)	CuI (1)	Cs_2CO_3	<5
20[j]	$Pd(OAc)_2$ (1)	CuI (1)	Cs_2CO_3	87
21	$Pd(OAc)_2$ (1)	$Cu(PPh_3)_3Br$ (1)	Cs_2CO_3	84
22	$Pd(OAc)_2$ (1)	$Cu(PPh_3)_3I$ (1)	Cs_2CO_3	80
23	$Pd(OAc)_2$ (1)	Cu(Xantphos)Br (1)	Cs_2CO_3	94

[a] All of the reactions were carried out with **1a** (1.0 mmol), **2a** (1.2 mmol) and base (2.0 mmol) in anhydrous DMF (5 mL) at 60 °C for 16 h unless otherwise specified.

[b] Yield was determined by GC or NMR after 16 h based on a purified standard.

[c] At room temperature for 24 h.

[d] Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

[e] At 40 °C for 24 h.

[f] Isolated yield.

[g] Toluene was used as the solvent.

[h] dba = *trans*, *trans*-dibenzylideneacetone.

[i] At 60 °C for 24 h.

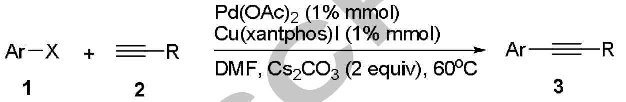
[j] 0.01 mmol Xantphos was added.

With the above optimal condition in hand, a variety of substituted aryl halides were coupled with alkynes, and the results are shown in Table 2. Excellent yields of **3a–l** were obtained regardless of the reactions using electron-neutral (H), -rich (-OMe, $-N(CH_3)_2$, $-NH_2$, -OH) or -poor (-CHO, $-COCH_3$, -COOEt, -CN, $-CF_3$, $-NO_2$) aryl bromides with phenylacetylene (entries 2–12). 1-Bromonaphthalene and heterocyclic bromides (furyl, thienyl and pyridyl) were also suitable for this reaction, affording the corresponding products **3m–q** in 90–96% isolated yields (entries 13–17). Electron-rich or electron-poor substituted phenylacetylenes and aliphatic alkynes also gave **3c**, **3k** and **3r–t** in excellent yields, respectively (entries 18–22). Furthermore, under the above disclosed typical conditions, a variety of aryl bromides and alkynes were coupled to form a structurally diverse products **3u-z** and **3A-C** (entries 23–31).

Next, we were pleased to find that at room temperature, aryl iodides bearing electron-rich or electron-poor groups on the phenyl ring could afford a nearly quantitative yield of **3b, 3c** and **3l** (entries 32–34). Notably, the reactions for electron-poor ($COCH_3$, CN, CF_3) arylchlorides proceed smoothly and gave the corresponding products **3a, 3h** and **3j** in good yields (entries 36–38). However, this novel Pd/Cu co-catalyzed system was so far ineffective for less reactive aryl chlorides. Only 20% GC yield of **3a** was obtained using 1-chloro-4-methylbenzene at 120 °C with high loading of 5% mmol $Pd(OAc)_2$ and Cu(Xantphos)I respectively (entry 35).

Table 2

Sonogashira reactions of aryl halides and alkynes catalyzed by $Pd(OAc)_2$/Cu(Xantphos)I[a]



Entry	X	Ar	R	Product	Yield[b] (%)
1	Br	$4\text{-}MeC_6H_4$	C_6H_5	**3a**	97
2	Br	C_6H_5	C_6H_5	**3b**	98
3	Br	$4\text{-}MeOC_6H_4$	C_6H_5	**3c**	96
4	Br	$4\text{-}N(CH_3)_2C_6H_4$	C_6H_5	**3d**	92
5	Br	$4\text{-}NH_2C_6H_4$	C_6H_5	**3e**	91
6	Br	$4\text{-}OHC_6H_4$	C_6H_5	**3f**	85
7	Br	$4\text{-}CHOC_6H_4$	C_6H_5	**3g**	93
8	Br	$4\text{-}COCH_3C_6H_4$	C_6H_5	**3h**	94
9	Br	$4\text{-}COOEtC_6H_4$	C_6H_5	**3i**	84
10	Br	$4\text{-}CNC_6H_4$	C_6H_5	**3j**	89
11	Br	$4\text{-}CF_3C_6H_4$	C_6H_5	**3k**	95
12	Br	$4\text{-}NO_2C_6H_4$	C_6H_5	**3l**	94
13	Br	1-naphthyl	C_6H_5	**3m**	91
14	Br	3-furyl	C_6H_5	**3n**	96
15	Br	2-thienyl	C_6H_5	**3o**	92
16	Br	2-pyridyl	C_6H_5	**3p**	94
17	Br	3-pyridyl	C_6H_5	**3q**	90
18	Br	C_6H_5	$4\text{-}MeOC_6H_4$	**3c**	92
19	Br	C_6H_5	$4\text{-}n\text{-}C_3H_7C_6H_4$	**3r**	95
20	Br	C_6H_5	$4\text{-}CF_3C_6H_4$	**3k**	97
21	Br	C_6H_5	$n\text{-}C_6H_{13}$	**3s**	94
22	Br	C_6H_5	$CH(OH)CH_3$	**3t**	90
23	Br	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$	**3u**	93
24	Br	$4\text{-}N(CH_3)_2C_6H_4$	$4\text{-}MeOC_6H_4$	**3v**	89
25	Br	$4\text{-}NO_2C_6H_4$	$4\text{-}MeOC_6H_4$	**3w**	96
26	Br	1-naphthyl	$4\text{-}MeOC_6H_4$	**3x**	92
27	Br	3-pyridyl	$4\text{-}MeOC_6H_4$	**3y**	93
28	Br	$4\text{-}COCH_3C_6H_4$	$4\text{-}CF_3C_6H_4$	**3z**	90
29	Br	$4\text{-}MeOC_6H_4$	$n\text{-}C_6H_{13}$	**3A**	95
30	Br	$4\text{-}CF_3C_6H_4$	$n\text{-}C_6H_{13}$	**3B**	92
31	Br	3-pyridyl	$n\text{-}C_6H_{13}$	**3C**	90
32	I	C_6H_5	C_6H_5	**3b**	98[c]
33	I	$4\text{-}MeOC_6H_4$	C_6H_5	**3c**	95[c]
34	I	$4\text{-}NO_2C_6H_4$	C_6H_5	**3l**	97[c]
35	Cl	$4\text{-}MeC_6H_4$	C_6H_5	**3a**	20[d]
36	Cl	$4\text{-}COCH_3C_6H_4$	C_6H_5	**3h**	91[d]
37	Cl	$4\text{-}CNC_6H_4$	C_6H_5	**3j**	89[d]
38	Cl	$4\text{-}CF_3C_6H_4$	C_6H_5	**3k**	93[d]

[a] All of the reactions were carried out with **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (0.01 mmol), Cu(Xantphos)I (0.01 mmol), Cs_2CO_3 (2.0 mmol) in anhydrous DMF (5 mL) at 60 °C for 16 h unless otherwise specified.

[b] Isolated yields.

[c] At room temperature.

[d] $Pd(OAc)_2$ (0.05 mmol) and Cu(Xantphos)I (0.05 mmol) were employed at 120 °C for 12 h.

In summary, we have disclosed a mild and efficient Sonogashira coupling reactions catalyzed by the $Pd(OAc)_2$/Cu(Xantphos)I system. This is an interesting catalytic system in which the phosphine ligand coordinates with copper instead of the commonly accepted palladium. The novel catalytic system has been demonstrated to be suitable for a broad range of substrates. Further applications to other substrates as well additional data on the reaction mechanism will be reported in due course.

Acknowledgments

We gratefully acknowledge support from the National Natural Science Foundation of China (21542009) and the Educational Commission of Hubei Province (D20142501).

Supplementary data

Supplementary data related to this article can be found, in the online version at:

References and notes

1. (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084; (c) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783; (d) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.
2. Bakherad, M. *Appl. Organometal. Chem.* **2013**, *27*, 125.
3. (a) Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, 2689; (b) Wang, D.; Gao, S. H. *Org. Chem. Front.* **2014**, *1*, 556.
4. King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205.
5. Prathapan, S.; Johnson, T. E.; Lindsey, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 7519.
6. Pautzsch, T.; Klemm, E. *Macromolecules* **2002**, *35*, 1569.
7. (a) Bai, X. Y.; Chen, X. Y.; Barnes, C.; Dias, J. R.; Sandreczki, T. C. *Tetrahedron* **2013**, *69*, 1105; (b) Huang, H.; Liu, H.; Jiang, H. L.; Chen, K. X. *J. Org. Chem.* **2008**, *73*, 6037; (c) Liang, Y.; Xie, Y. X.; Li, J. H. *J. Org. Chem.* **2006**, *71*, 379.
8. Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8169.
9. Cacchi, S.; Morera, E.; Ortar, G. *Synthesis* **1986**, 320.
10. Fairlamb, I. J. S.; Bäuerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, 632.
11. (a) Nájera, C.; Gil-Molto, J.; Karlström, S.; Falvello, L. R. *Org. Lett.* **2003**, *5*, 1451; (b) Gil-Moltó, J.; Karlström, S.; Nájera, C. *Tetrahedron* **2005**, *61*, 12168; (c) Lee, D. H.; Lee, Y. H.; Harrowfield, J. M.; Lee, I. M.; Lee, H. I.; Lim, W. T.; Kim, Y.; Jin, M. J. *Tetrahedron* **2009**, *65*, 1630; (d) Li, F. W.; Hor, T. S. A. *Adv. Synth. Catal.* **2008**, *350*, 2391; (e) Feng, Z. J.; Yu, S. Y.; Shang, Y. J. *Appl. Organomet. Chem.* **2008**, *22*, 577.
12. Mi, X.; Huang, M. M.; Feng, Y. J.; Wu, Y. J. *Synlett* **2012**, *23*, 1257.
13. Arques, A.; Auñon, D.; Molina, P. *Tetrahedron Lett.* **2004**, *45*, 4337.
14. Nishide, K.; Liang, H.; Ito, S.; Yoshifuji, M. J. *J. Organomet. Chem.* **2005**, *690*, 4809.
15. (a) Dhudshia, B.; Thadani, A. N. *Chem. Commun.* **2006**, 668; (b) Roy, S.; Plenio, H. *Adv. Synth. Catal.* **2010**, *352*, 1014; (c) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642; (d) Gallop, C. W. D.; Chen, M. T.; Navarro, O. *Org. Lett.* **2014**, *16*, 3724; (e) Zanardi, A.; Mata, J. A.; Peris, E. *Organometallics* **2009**, *28*, 4335.
16. (a) Hu, H.; Yang, F.; Wu, Y. J. *J. Org. Chem.* **2013**, *78*, 10506; (b) Buxaderas, E.; Alonso, D. A.; Nájera, C. *Eur. J. Org. Chem.* **2013**, 5864.
17. (a) Ye, C. F.; Xiao, J. C.; Twamley, B.; LaLonde, A. D.; Norton, M. G.; Shreeve, J. M. *Eur. J. Org. Chem.* **2007**, 5095; (b) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127; (c) Son, S. U.; Jang, Y.; Park, J.; Na, H. B.; Park, H. M.; Yun, H. J.; Lee, J.; Hyeon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5026; (d) Isfahani, A. L.; Mohammadpoor-Baltork, I.; Mirkhani, V.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S. *Eur. J. Org. Chem.* **2014**, 5603.
18. (a) González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1536; (b) Lauterbach, T.; Livendahl, M.; Rosellón, A.; Espinet, P.; Echavarren, A. M. *Org. Lett.* **2010**, *12*, 3006.
19. (a) Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 12078; (b) Gallego, D.; Brück, A.; Irran, E.; Meier, F.; Kaupp, M.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 15617.
20. (a) Firouzabadi, H.; Iranpoor, N.; Gholinejad, M.; Hoseini, J. *Adv. Synth. Catal.* **2011**, *353*, 125; b) Sawant, D. N.; Tambade, P. J.; Wagh, Y. S.; Bhanage, B. M. *Tetrahedron Lett.* **2010**, *51*, 2758; (c) Carril, M.; Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *48*, 4862.
21. (a) Santandrea, J.; Bédard, A. C.; Collins, S. K. *Org. Lett.* **2014**, *16*, 3892; (b) Lin, C. H.; Wang, Y. J.; Lee, C. F. *Eur. J. Org. Chem.* **2010**, 4368.
22. Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203.
23. (a) Baupérin, M.; Job, A.; Cattey, H.; Royer, S.; Meunier, P.; Hierso, J. C. *Organometallics* **2010**, *29*, 2815; (b) Beaupérin, M.; Fayad, E.; Amardeil, R.; Cattey, H.; Richard, P.; Brandès, S.; Meunier, P.; Hierso, J. C. *Organometallics* **2008**, *27*, 1506; (c) Trivedi, M.; Singh, G.; Kumar, A.; Rath, N. P. *Dalton Trans.* **2014**, *43*, 13620.
24. (a) Huang, J. K.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674; (b) Huang, J.; Wang, X.; Chan, J. *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries* (Eds. by Dunn, P. J.; Hii, K. K.; Krische, M. J.; Williams, M. T.), Wiley-VCH, Weinheim, **2013**.

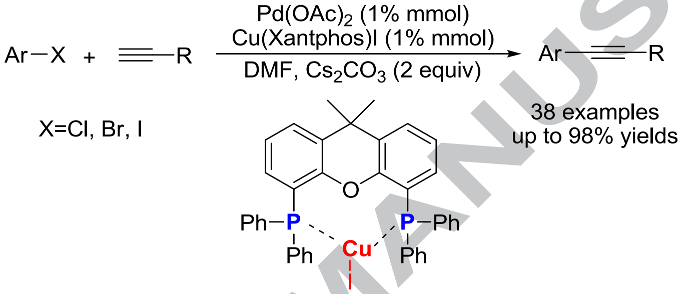
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Sonogashira coupling catalyzed by the Cu(Xantphos)I-Pd(OAc)$_2$ system

Leave this area blank for abstract info.

Meilin Liu, Mingyan Ye, Yeye Xue, Guodong Yin*,
Dunjia Wang and Jinkun Huang*
Hubei Collaborative Innovation Center for Rare Metal Chemistry, Hubei Key Laboratory of Pollutant Analysis and Reuse Technology, Hubei Normal University, Huangshi 435002, China



Research highlights

- A novel Pd(OAc)$_2$/Cu(Xantphos)I system for efficient Sonogashira coupling reaction is disclosed.
- This is an interesting catalytic system in which the phosphine ligand coordinates with copper.
- Cu(Xantphos)I plays a unique role in this coupling reaction.