Received: 19 October 2014

Revised: 20 January 2015

Accepted: 20 January 2015

Applied Organometallic

Chemistry

Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/aoc.3291

Organophosphate-accelerated coppercatalyzed C(sp²)–C(sp) Sonogashira-type cross couplings

Wei Xu, Bo Yu, Huaming Sun, Guofang Zhang, Weiqiang Zhang* and Ziwei Gao*

A dramatic acceleration in copper-catalyzed Sonogashira-type reactions was observed when an organophosphate was used as additive. The catalyst systems featuring low copper loading (0.5 mol% < Cu < 5 mol%) gave Sonogashira-type products with a broad scope of aromatic and aliphatic terminal alkynes as well as aryl iodides in good to excellent yields. Among the organophosphate/copper catalytic systems, that of 4 mol% Cu(OTf)₂/10 mol% (*R*)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate exhibited the highest catalytic activity. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: Sonogashira coupling; organophosphate; Cu(II) complexes

Introduction

Alkynes are efficient building blocks that can be used as a basic functional group in organic synthesis.^[1-4] Nowadays, Pd/Cuphosphine-catalyzed Sonogashira cross coupling provides a straightforward access to C(sp)–C(sp²) bond formation and the cross-coupling products are widely used as precursors for the synthesis of pharmaceuticals, natural products and organic materials.^[5–8] One of the latest aspects of attention focuses on the efficiency of catalyzed cross coupling of aryl halides with terminal alkynes using copper catalysts,^[9–15] for copper is less toxic and far more economic than palladium. Since Miura and co-workers reported that PPh₃/Cul (10 mol%) catalyzed the Castro reactions of aryl iodides and terminal alkynes in 1993,^[16] there have been reported huge innovations of copper-catalyzed C(sp²)-C(sp) coupling reactions,^[17-19] including those involving Cu(I)/ diamines,^[20-22] Cu(I)/amino acid derivatives,^[23-25] Cu(I)/1,4diazabicyclo[2.2.2]octane,^[26] copper nanoparticles,^[27–29] supported copper complexes^[30–32] and other copper catalytic systems.^[33] Although copper-based catalysts have been proposed as an alternative to palladium-based catalysts for Sonogashira couplings, these catalyst systems generally require high copper loadings (5-20 mol%) to maintain a catalytic cycle. Therefore, it is still highly desirable to develop new copper-based catalytic systems with low copper loadings.

Herein, we report a new copper-based catalyst system featuring low copper loadings (0.5 mol% < Cu < 5 mol%) and organophosphate additives (Fig. 1), by which a number of Cu(I) and Cu(II) compounds are activated for Songashira-type couplings. The combination of an organophosphate and Cu(OTf)₂ (4 mol%) is able to catalyze the cross couplings of terminal alkynes and aryl iodides with good to excellent yields. To the best of our knowledge, a copper-based catalytic system promoting $C(sp^2)$ –C(sp) couplings with copper loadings less than 5 mol% has been rarely reported before.^[11,14,35]

Results and Discussion

We initially elucidated whether the Cul/ L_1 catalytic system is effective for Sonogashira coupling in DMF. The results are listed in Table 1. The effect of solvents was investigated for the Sonogashira coupling reaction of phenylacetylene with iodobenzene at 130 °C under nitrogen (Scheme 1; Table 1, entries 1–7). Various solvents such as dioxane, THF, toluene, DMF, ethanol, acetonitrile and DMSO were tested under similar conditions, but less than 21% products are obtained except when DMSO and DMF are employed as solvent (Table 1, entries 4 and 5). Further screening experiments were conducted using different bases and the best result is obtained when Cs₂CO₃ is employed. Other commonly used inorganic bases such as KOH, KF and K₃PO₄ show no marked effect on the cross-coupling reactions (Table 1, entries 8–11). In addition, very low yields are obtained when organic bases are used (Table 1, entries 12 and 13).

Encouraged by these preliminary results, a number of reaction parameters (Table S1) were evaluated to determine the optimal reaction conditions. It is found that the catalytic activity of Cul/L catalytic system is sensitive to Cu loadings (Table S1, entries 1–8). When 1, 2 and 3 mol% Cul are added, the yields of the products are 43, 62 and 74%, respectively, in the presence of 10 mol% L_1 (Table S1, entries 1–3). To our pleasure, when using 4 mol% Cul the product yield can reach 94% (Table S1, entry 4). However, on

^{*} Correspondence to: Ziwei Gao, Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, 199 South Chang'an Road, Xi'an, China. E-mail: zwgao@snnu.edu.cn

Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, 199 South Chang'an Road, Xi'an, China



Figure 1. Structures of organophosphate ligands: $L_1 = (R)-(-)-1,1'$ binaphthyl-2,2'-diyl hydrogenphosphate; $L_2 = 2$ -ethylhexyl-2-ethylpentyl hydrogenphosphate; $L_3 = 1,2,3$ -propanetriol-1-(dihydrogenphosphate).

Table 1. Cul/L1-catalyzed Sonogashira cross coupling ^a								
Entry	Cu	Solvent	Base	Yield (%) ^b				
1	Cul	Toluene	K ₂ CO ₃	18				
2	Cul	THF	K ₂ CO ₃	0				
3	Cul	1,4-Dioxane	K ₂ CO ₃	12				
4	Cul	DMF	K ₂ CO ₃	69				
5	Cul	DMSO	K ₂ CO ₃	74				
6	Cul	Acetonitrile	K ₂ CO ₃	11				
7	Cul	Ethanol	K ₂ CO ₃	21				
8	Cul	DMSO	K ₃ PO ₄	40				
9	Cul	DMSO	KF	10				
10	Cul	DMSO	КОН	13				
11	Cul	DMSO	Cs ₂ CO ₃	78				
12	Cul	DMSO	Pyridine	12				
13	Cul	DMSO	Et_3N	16				
^a Reaction conditions: Cul (99.995%, 2.0 mol%), L_1 (10 mol%), solvent (3.0 mL), base (1 mmol), aryl iodide (1 mmol, 112 µl), alkyne (1								

mmol, 109.8 μl), 130 °C, stirred in nitrogen, 12 h. ^bGC yield based on alkyne.

increasing Cul to 10, 20 and 30 mol% the product yields fall to 45, 44 and 42%, respectively (Table S1, entries 6–8). According to the literature, the ligand concentration has a major impact on coppercatalyzed cross-coupling reactions.^[35] Therefore, we further investigated the concentration effect of L_1 in the coupling reaction. Cul (4 mol% Cu)-catalyzed cross-coupling reaction was conducted using 1–30 mol% L_1 (Table S1, entries 9–16). The screening results



Scheme 1. Cul-catalyzed cross coupling of aryl iodide and alkyne.

Scheme 2. Copper salt-catalyzed cross coupling of aryl iodide and alkyne.

Table 2.reaction ^a	Effect of copper salts of	n the Sonogashira	a cross-coupling
Entry	Copper salt	Ligand	Yield (%) ^b
1	Cul	L ₁	91
2	Cul	L ₂	58
3	Cul	L ₃	43
4	CuCl	L ₁	42
5	CuBr	L ₁	51
6	Cu ₂ O	L ₁	63
7	Cu(OTf) ₂	L ₁	96
8	Cu(OAc) ₂	L ₁	40
9	CuO	L ₁	46
10	Cu(acac) ₂	L ₁	81

^aReaction conditions: Cu (4 mol%), Cs₂CO₃ (99.995%, 1.0 mmol, 0.3259 g), L (10 mol%), 4-iodoanisole (1 mmol, 0.2410 g), phenylacetylene (1 mmol, 109.8 μ l), DMSO (3.0 mL), 130 °C, 12 h. ^{b1}H NMR yields.



Scheme 3. Cu(OTf)₂-catalyzed cross coupling of aryl iodides and alkynes.

show that with less than 10 mol% L_1 , the product yields are no more than 60% (Table S1, entries 9–13). When L_1 is increased to 10 mol%, the yield increases markedly to 94%. However, higher concentration (15–30 mol%) of L_1 does not promote the cross-coupling reaction further.

We next investigated the effects of the ligands and copper salts in order to further optimize reaction conditions. The cross coupling of phenylacetylene and 1-iodo-4-methoxybenzene in DMSO (Scheme 2) was conducted as a model reaction. The product yield using Cul/L₁ catalytic system is 91%, much higher than that using L₂ and L₃ (Table 2, entries 1–3). The high efficiency of L₁ indicates that this aromatic phosphate ligand preferentially stabilizes the catalytically active Cu(I) species compared to its aliphatic analogue L₂, whilst L₃ is a multi-dentate hard donor ligand that inhibits the formation of Cu(I) by chelating Cu(II) pre-catalyst. Furthermore, seven commercial Cu(I) and Cu(II) salts were assessed in the coupling reactions. Other commonly used Cu(II) salts such as CuO, Cu(OAc)₂ and Cu(acac)₂ also accelerate the cross-coupling reaction (Table 2, entries 7–10). Among them, Cu(OTf)₂ gives the highest yield of 96% (Table 2, entry 7).

The cross coupling of arylacetylenes with aryl iodides (Scheme 3) containing electron-donating groups (*p*-OMe or *m*-CH₃) gives isolated yields of 76 to 96% (Table 3, entries 1, 2, 9, 10, 13, 14, 22). When aryl iodides with electron-withdrawn groups (*o*-CF₃, *m*-NO₂ or *p*-NO₂) are used, the product yields decrease dramatically and even no cross-coupling product is isolated in the case of *p*-nitroiodobenzene as substrate (Table 3, entries 3, 7, 19–21, 23, 24). When 1-octyne is employed instead of phenylacetylene, lower yields (0–60%) are obtained (Table 3, entries 5–8). When phenylacetylene and *p*-ethylphenylacetylene are involved in the coupling reaction, good to excellent yields are obtained (Table 3, entries 10, 13, 17). However, for aliphatic alkynes coupled with iodobenzenes, only *p*-OMe- and *m*-CH₃-substituted iodobenzes give moderate yields (50–78%; Table 3, entries 5, 6, 11, 12, 16), and *o*-CF₃-substituted iodobenzene gives almost no coupling

Entry	R ₁	R ₂	Yield (%) ^b	Entry	R ₁	R ₂	Yield (%) ^b
1	<i>p</i> -OMe	C ₆ H ₅	96	13	<i>m</i> -CH₃	$p-C_2H_5C_6H_5$	80
2	m-CH ₃	C_6H_5	83	14	<i>m</i> -CH₃	<i>n</i> -C ₅ H ₁₃ C ₆ H ₅	76
3	o-CF ₃	C_6H_5	74	15	<i>m</i> -CH₃	n-C ₄ H ₉	_
4	Н	C_6H_5	90	16	<i>m</i> -CH₃	<i>n</i> -C ₅ H ₁₁	50
5	<i>p</i> -OMe	<i>n</i> -C ₆ H ₁₃	60	17	o-CF ₃	$p-C_2H_5C_6H_5$	82
6	m-CH ₃	<i>n</i> -C ₆ H ₁₃	52	18	o-CF ₃	p-CH ₃ C ₆ H ₅	74
7	o-CF ₃	<i>n</i> -C ₆ H ₁₃	—	19	o-CF ₃	n-C ₄ H ₉	—
8	p-NO ₂	<i>n</i> -C ₆ H ₁₃	—	20	o-CF ₃	<i>n</i> -C ₅ H ₁₁	—
9	<i>p</i> -OMe	C_6H_5	85	21	o-CF ₃	$n-C_5H_{13}C_6H_5$	83
10	<i>p</i> -OMe	p-CH ₃ C ₆ H ₅	90	22	<i>m</i> -CH ₃	$n-C_5H_{13}C_6H_5$	78
11	<i>p</i> -OMe	n-C ₄ H ₉	73	23	m-NO ₂	<i>n</i> -C ₅ H ₁₃	60
12	<i>p</i> -OMe	<i>n</i> -C₅H ₁₁	68	24	p-NO ₂	$p-CH_3C_6H_5$	54

^aReaction conditions: Cu(OTf)₂ (99.995%, 4 mol%), Cs₂CO₃ (1 mmol, 0.3259 g), aryl iodide (1 mmol), alkyne (1 mmol), 130 °C, 16 h. L₁ (10 mol%), DMSO (2.5 mL). ^bIsolated yields.

reaction in this case (Table 3, Entries 19, 20). Therefore, it can be concluded that in the presence of $Cu(OTf)_2/L_1$, iodobenzenes with electron-donating groups and arylalkynes are beneficial to the coupling reaction, but iodobenzenes containing an electron-withdrawing group and aliphatic alkynes decrease the coupling product yield.

Conclusions

We have established an efficient catalytic system for coppercatalyzed Sonogashira cross coupling using $Cu(OTf)_2/L_1$ ($L_1 = (R)$ -(–)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate). This system is effective for cross coupling of both aliphatic and aromatic terminal alkynes under low copper loading (4 mol%) conditions. The coupling reaction is compatible with a broad scope of functional groups and affords products in good to excellent yields.

Experimental

All reactions were carried out using a standard Shlenck line. All halides and alkynes were purchased from Aldrich and Alfa Aesar. Cul (99.995%) was purchased from Aldrich. NMR spectra were measured in $CDCl_3$ with a Bruker AVANCE 400 NMR spectrometer (400 MHz) with tetramethylsilane as an internal reference.

Typical Procedure with Cu(OTf)₂/L₁ System for Cross-Coupling Reactions of Aryl Halides with Terminal Alkynes

A mixture of aryl halide (1.0 mmol), alkyne (1.0 mmol), Cu (4 mol %), L_1 (10 mol %) and Cs₂CO₃ (1 mmol) was stirred at 130°C for 12 h. After the reaction was finished, diethyl ether was poured into the mixture, then washed with water, extracted with diethyl ether, dried with anhydrous Na₂SO₄ and evaporated under vacuum. The residue was purified using flash column chromatography (hexane or hexane–ethyl acetate) to afford the desired coupled product.

Acknowledgments

This work was supported by the 111 Project (B14041), National Natural Science Foundation of China (21171112, 21271124, 21371112), Fundamental Doctoral Fund of Ministry of Education of China (20120202120005), Natural Science Basic Research Plan in Shaanxi Province of China (2012JM2006) and Shaanxi Innovative Team of Key Science and Technology (2013KCT-17).

References

- [1] M. Meldal, C. W. Tornøe, Chem. Rev. 2008, 108, 2952.
- [2] G. Evano, N. Blanchard, M. Toumi, Chem. Rev. 2008, 108, 3054.
- [3] F. Amblard, J. H. Cho, R. F. Schinazi, Chem. Rev. 2009, 109, 4207.
- [4] R. Chinchilla, C. Nájera, *Chem. Rev.* **2014**, *114*, 1783.
- [5] J. Magano, J. R. Dunetz, Chem. Rev. 2011, 111, 2177.
- [6] K. Sonogashira, Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH, Weinheim, 2004.
- [7] R. R. Tykwinski, Angew. Chem. Int. Ed. 2003, 42, 1566.
- [8] K. Sonogashira, Organopalladium Chemistry for Organic Synthesis, Wiley-Interscience, New York, 2002.
- [9] C. X. Lin, J. F. Zhu, Q. S. Li, L. H. Ao, Y. J. Jin, F. B. Xu, F. Z. Hu, Y. F. Yuan, Appl. Organometal. Chem. 2014, 28, 298.
- [10] J. P. Wan, S. Cao, Y. F. Jing, *Appl. Organometal. Chem.* **2014**, *28*, 631.
- [11] L. H. Zou, A. J. Johansson, E. Zuidema, C. Bolm, *Chem. Eur. J.* **2013**, *19*, 8144.
- [12] T. Y. Li, X. M. Qu, G. L. Xie, J. C. Mao, Chem. Asian J. 2011, 6, 1325.
- [13] A. Tlili, F. Monnier, M. Taillefer, *Chem. Eur. J.* **2010**, *16*, 12299.
- [14] P. F. Larsson, C. Bolm, P. O. Norrby, *Chem. Eur. J.* **2010**, *16*, 13613.
- [15] J. T. Guan, G. A. Yu, L. Chen, T. Q. Weng, J. J. Yuan, S. H. Liu, Appl. Organometal. Chem. 2009, 23, 75.
- [16] K. Okuro, M. Furuune, M. Enna, M. Miura, M. Nomura, J. Org. Chem. **1993**, *58*, 4716.
- [17] F. Monnier, M. Taillefer, Top. Organometal. Chem. 2013, 46, 173.
- [18] R. Chinchilla, C. Nájera, Chem. Soc. Rev. 2011, 40, 5084.
- [19] D. S. Surry, S. L. Buchwald, Chem. Sci. 2010, 1, 13.
- [20] Z. J. Liu, J. P. Vors, E. R. F. Gesing, C. Bolm, Green Chem. 2011, 13, 42.
- [21] K. G. Thakur, E. A. Jaseer, A. B. Naidu, G. Sekar, *Tetrahedron Lett.* 2009, 50, 2865.
- [22] A. Correa, C. Bolm, Adv. Synth. Catal. 2007, 349, 2673.
- [23] D. Maiti, S. L. Buchwald, J. Org. Chem. 2010, 75, 1791.
- [24] F. Liu, D. W. Ma, J. Org. Chem. 2007, 72, 4844.
- [25] Q. Cai, B. Zou, D. W. Ma, Angew. Chem. Int. Ed. 2006, 45, 1276.
- [26] J. C. Mao, J. Guo, S. J. Ji, J. Mol. Catal. A 2008, 284, 85.
- [27] J. H. Kou, A. Saha, C. Bennett-Stamper, R. S. Varma, Chem. Commun. 2012, 48, 5862.
- [28] B. X. Tang, F. Wang, J. H. Li, Y. X. Xie, M. B. Zhang, J. Org. Chem. 2007, 72, 6294.
- [29] M. B. Thathagar, J. Beckers, G. Rothenberg, Green Chem. 2004, 6, 215.
- [30] D. Saha, T. Chatterjee, M. Mukherjee, B. C. Ranu, J. Org. Chem. 2012, 77, 9379.
- [31] Z. L. Wang, L. Wang, P. H. Li, Synthesis 2008, 1367.

- [32] A. Biffis, E. Scattolin, N. Ravasio, F. Zaccheria, Tetrahedron Lett. 2007, 48, 8761.
- [33] A. Sagadevan, K. C. Hwang, Adv. Synth. Catal. 2012, 354, 3421.
- [34] P. F. Larsson, A. Correa, M. Carril, P. O. Norrby, C. Bolm, *Angew. Chem. Int. Ed.* **2009**, *48*, 5691.
- [35] E. Zuidema, C. Bolm, Chem. Eur. J. 2010, 16, 4181.

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