

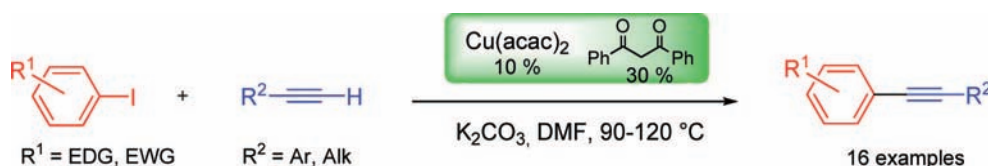
Copper-Catalyzed Sonogashira-Type
Reactions Under Mild Palladium-Free
Conditions

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ABSTRACT



We have developed an inexpensive catalytic system using a readily available copper/ligand combination for the Sonogashira-type cross-coupling of aryl iodides and phenyl- and hexyl-acetylene which affords disubstituted alkynes in good to excellent yields.

After a spectacular resurgence of interest at the turn of this century, Ullmann-type coupling in its catalytic version is becoming a very competitive method for synthesis of aryl–nucleophile bonds with various sources of C-, O-, N-, P-, and S-nucleophiles.¹ Since 2001, we have demonstrated in previous reports² and patents³ that combinations of copper salts and ligands (oximes, Schiff bases, bipyridines, phenanthrolines, diketones, butadienyl phosphines) are

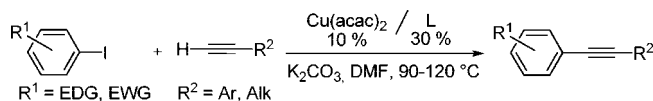
(1) For general reviews on Ullmann-type reaction, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096.

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(3) For patents, see: (a) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. FR 2833947-WO 0353225 (Pr. Nb. Fr 01 16547), **2001**; *Chem. Abstr.* **2003**, *139*, 69290. (b) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Ouali, A. 2840303-WO 03101966 (Pr. Nb. Fr 02 06717), **2002**; *Chem. Abstr.* **2004**, *140*, 16744. (c) Taillefer, M.; Kaddouri, H.; Ouazzani, F. FR 0706826, **2007**. (d) Taillefer, M.; Xia, N. FR 0706827, **2007**.

highly efficient catalytic systems for the formation of aryl–heteroatom bonds such as C–O, C–N, and also C–C bonds. To the best of our knowledge, these methods are often among the mildest ever described in the literature. As part of our goal of developing a “tool box” of copper-based catalysts for cross-coupling reactions, we are very much interested in suitable methods for C–C bond formation between aryl halides and terminal aryl- and alkyl-alkynes to afford the corresponding disubstituted alkynes.⁴ Here we report an efficient catalysis of such reactions with a $\text{Cu}(\text{acac})_2/\beta$ -diketone catalyst in DMF at 90–120 °C using K_2CO_3 as an inexpensive base (Scheme 1).

Scheme 1. Reactions of Aryl Iodides with Terminal Alkynes Catalyzed by a Copper/Ligand Combination



This novel method is economically attractive since, in contrast to almost all of the traditional Pd/Cu-cocatalyzed Sonogashira coupling reactions, it does not use any palladium.⁵

Initially, we chose as a model reaction for method development the coupling of 4'-iodoacetophenone **1** with phenylacetylene **2** where we found that in the absence of supporting ligand L the reaction gave 1,4-diphenylbuta-1,3-diyne **2'** as the only product from homocoupling of **2** through a Glaser-type reaction (Table 1, entry 1).⁶

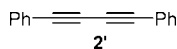
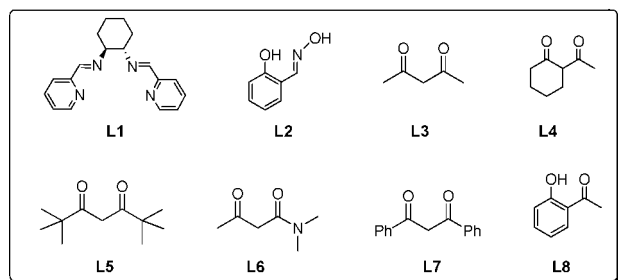
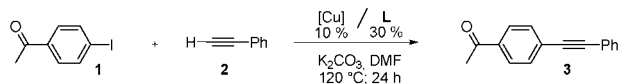


Table 1. Reaction of Phenylacetylene **2** with 4'-Iodoacetophenone **1** Catalyzed by Different Cu/L Combinations



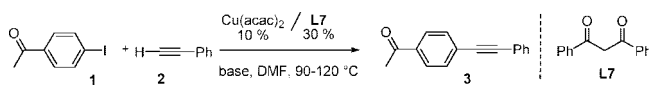
entry	[Cu] ^a	L	3 ^b
1	Cu(acac) ₂	–	0 ^c
2	Cu(acac) ₂	L1	40
3	“	L2	52
4	“	L3	28
5	“	L4	66
6	“	L5	81
7	“	L6	78
8	“	L7	94
9	“	L8	41
10	CuI	L1	36
11	“	L2	47
12	“	L3	10
13	“	L4	50
14	“	L5	70
15	“	L6	65
16	“	L7	80
17	“	L8	>50
18	Cu(OAc) ₂	L1	40
19	“	L2	48
20	“	L3	11
21	“	L4	54
22	“	L5	75
23	“	L6	60
24	“	L7	84
25	“	L8	45\

^a All reactions were performed with: 4'-iodoacetophenone (0.5 mmol), phenylacetylene (0.75 mmol), [Cu] (0.05 mmol), L (0.15 mmol), K₂CO₃ (1 mmol), 1 mL of DMF, 24 h. ^b Yields established by GC-MS with 1,3-dimethoxybenzene as the internal standard. ^c Isolated yield of 1,4-diphenylbuta-1,3-diyne **2'** (resulting from the homocoupling of **2**): 70%.

Then we examined the efficiency of using various copper salts in combination with ligands **L1–L8** and K₂CO₃ at 120 °C. Table 1 demonstrates that ligands **L1–L2**, which are usually highly efficient for C–N and C–O coupling reactions,^{2,3} gave only moderate yields for alkyne C–C cross-

coupling. Similarly, the β-hydroxy ketone **L8** and acetylacetonone **L3** also give disappointing results. On the other hand, other β-diketones such as **L4–L7**⁷ are active for this Sonogashira cross-coupling reaction. Moreover, 1,3-diphenylpropane-1,3-dione **L7** easily appears to be the most efficient of the ligands tried. Moreover, Cu(acac)₂ showed the best activity compared with other copper sources such as CuI and Cu(OAc)₂ (entries 8, 16, and 24). In a second set of experiments (Table 2), we examined the influence of

Table 2. Influence of the Base on the Cross-Coupling between 4'-Iodoacetophenone **1** and Phenylacetylene **2**



entry	base ^a	3 ^b
1	K ₂ CO ₃	94
2	Cs ₂ CO ₃	48
3	K ₃ PO ₄	75
4	NaOH	7
5	pyridine	0
6	K ₂ CO ₃ ^c	96

^a All reactions except entry 6 were performed with: **1** (0.5 mmol), **2** (0.75 mmol), [Cu(acac)₂] (0.05 mmol), **L7** (0.15 mmol), base (1 mmol), 1 mL of DMF, 24 h, 120 °C. ^b Yields established by GC-MS with 1,3-dimethoxybenzene as internal standards. ^c **1** (0.55 mmol), **2** (0.5 mmol), [Cu(acac)₂] (0.05 mmol), **L7** (0.15 mmol), base (1 mmol), 1 mL of DMF, 24 h, 90 °C.

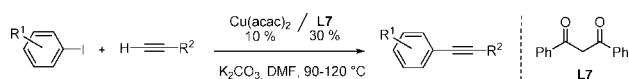
altering the base on the best result from Table 1. This confirms that K₂CO₃ was the best of the bases tried for both yield and selectivity. Protic and organic bases such as NaOH and pyridine were totally inefficient. In addition, the solvents DMF, toluene, acetonitrile (at 80 °C), and dioxane were tried, affording 94, 0, 10, and 5%, respectively, of the desired coupling product **3**.

At this stage in the investigation, we were pleased to have found an efficient system for cross-coupling aryl iodides with terminal alkynes. However, we were also seeking more attractive reaction conditions in terms of elapsed time and temperature.

Further research demonstrated that good yields could be maintained at significantly lower temperatures simply by reversing the reagent in excess (Table 2, entry 6): a slight excess of aryl iodide **1** (1.1 equiv for every 1 equiv of terminal alkyne **2**, instead of the previous ratio of 1:1.5) affords a similar yield of **3** at only 90 °C.

Next, we explored the breadth of application of this new method. By using the conditions optimized on the model reaction, we were able to apply this new method to a broad range of targets, including terminal aryl- and alkylacetylenes and also aryl iodides substituted by electron-withdrawing and electron-donating groups (Table 3). Aryl iodides activated by electron-withdrawing groups are coupled with terminal alkynes at 90 °C (entries 1–8) in good to excellent yields, while iodobenzene and aryl iodides deactivated by donating substituents require higher temperatures around 120 °C

Table 3. Coupling Products from Aryl Iodides with Aryl- and Alkyl-alkynes



entry	<i>t</i> (°C)	R ¹	R ²	time / h (Yields / %) ^b	products
1	90	4-COMe	Ph	24 (95)	
2	90	4-COMe	Hex	30 (86)	
3	90	4-CN	Ph	24 (96)	
4	90	4-CN	Hex	30 (85)	
5	90	4-NO ₂	Ph	28 (91)	
6	90	4-NO ₂	Hex	30 (83)	
7	90	4-CO ₂ Me	Ph	30 (89)	
8	90	4-CO ₂ Me	Hex	30 (80)	
9	120	H	Ph	36 (85)	
10	120	H	Hex	36 (90)	
11	120	4-Me	Ph	40 (63)	
12	120	4-Me	Hex	40 (70)	
13	120	4-OMe	Ph	40 (70)	
14	120	4-OMe	Hex	40 (65)	

^a Reaction conditions for entries 1–14: aryl iodides (2.2 mmol), phenylacetylene or hexyne (2 mmol), [Cu(acac)₂] (0.2 mmol), L7 (0.6 mmol), base (4 mmol), 4 mL of DMF. ^b Isolated yields.

(entries 9–14) to afford the desired products in moderate to excellent yields. With the exception of work reported by Ma,^{4d} ours is the only efficient system under such mild conditions (90–120 °C) compared to the harsher conditions of 130–150 °C employed by other groups.^{4a-c,e-j}

Concerning the mechanism, it is worth noting that in copper-catalyzed Ullmann arylations few studies have been performed.^{2b,c,8} In our case, we can only present a working mechanism for this palladium-free Sonogashira reaction (Figure 1).^{4a,g} On the basis of previous studies, it seems reasonable to propose copper(I) as a catalytic species (**1**), with a ligand of diketone type coordinated to the metal. In a first step, in the presence of base, the coordination/deprotonation of the alkyne could then give a copper(I)–acetylide

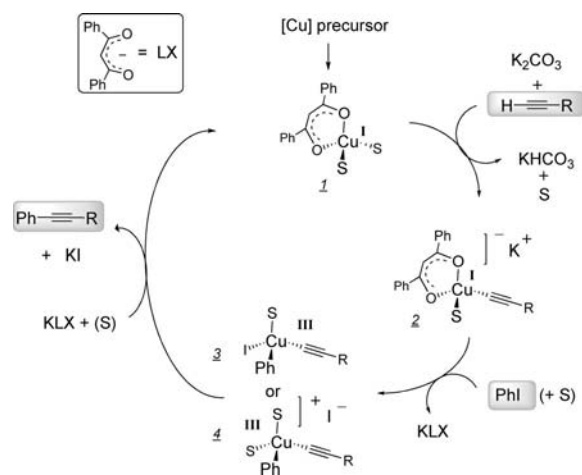


Figure 1. Possible working mechanism for the palladium-free Sonogashira reaction.

intermediate (**2**). The latter would react by oxidative addition with the aromatic halide to form a four-coordinated copper(III) complex from which the cross-coupling product is expelled and the catalytic active species is reformed by reductive elimination. Note that the copper(III) intermediate could be of neutral (**3**) or cationic (**4**) type.

Thus, we have discovered a mild and efficient catalysis of Sonogashira-type reactions using an easily handled Cu/ligand combination. This method is applicable to a wide range of variously substituted aryl iodides for coupling to both alkyl- and aryl-substituted terminal alkynes. This novel catalytic system is tolerant, versatile, and significantly less expensive than “traditional” Pd–Cu-catalyzed

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(6) For a review on acetylenic coupling, see: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

(7) Diketones used as a ligand in Ullmann-catalyzed reaction were successfully described in C–N formation. See: (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (b) de Lange, B.; Lambers-Verstappen, M. H.; Schmieder-van de Vondervoort, L.; Sereinig, N.; de Rijk, R.; de Vries, A. M.; de Vries, J. G. *Synlett* **2006**, 3105. Diketones were also used as ligands in Ullmann-type reactions for the formation of C–O and C–C bonds. (c) Taillefer, M.; Xia, N.; Ouali, A. US 2006/018334 and PCT 001836, 2007. (d) Xia, N.; Taillefer, M. US patent 60996830, 2007. (e) Taillefer, M.; Xia, N. *Chem. Eur. J.* **2008**, DOI: 10/1002/chem.200800436.

(8) (a) Streiter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120. (b) Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546. (c) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190.

cross-coupling of terminal alkynes with aryl iodides and may be able to displace the original Sonogashira method entirely.

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Supporting Information Available: A general synthetic procedure and complete characterization and NMR spectra for products **3–14**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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