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Efficient Copper-Catalyzed Cross-Coupling Reaction of Alkynes with Aryl Iodides

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A copper-catalyzed cross-coupling reaction of alkynes with aryl iodides is described. The system tolerates a broad range of functional groups and enables the use of sterically demanding substrates with only 1.0–2.5 mol-% of Cu_2O and 1.0–2.5 mol-% of xantphos as the catalyst.

Introduction

Alkynes are important structural motifs utilized in pharmaceutical chemistry,[1] organic synthesis,[2] and materials science.[3] The transition-metal-catalyzed cross-coupling reaction of terminal alkynes with aryl halides represents as a powerful strategy for preparing functionalized alkynes.[4] The Sonogashira reaction employs a Pd/Cu catalyst and is probably the most well-known method for the synthesis of alkynes.[1–4] However, the high cost of palladium may limit its practical applications; thus, it is desirable to search for alternative catalytic systems. The copper-catalyzed cross-coupling reaction of alkynes with aryl halides has gained much attention owing to the low-cost of copper catalysts.[5–12] However, there are still some drawbacks to this approach. First, the combination of 10 mol-% copper salt is generally required[5–12] along with a variety of ligands including PPh_3 (10 mol-%),[5–7] *N*,*N*-dimethylglycine (30 mol-%),[8] ethylene diamine (15 mol-%),[9] 1,4-diazabicyclo-[2.2.2]octane (20 mol-%),[10] pyrimidine (20 mol-%),[11] 1,3-diphenylpropane-1,3-dione (30 mol-%),[12] and others.[13] Recently, less than 1.0 mol-% of copper salt along with 30% of *N*,*N*-dimethylethylenediamine was reported by Bolm et al.[14] Second, alkyl alkynes are typically less reactive than aryl alkynes and some of the methods mentioned above only work with aryl alkynes.[6,7] Third, although the reaction of alkynes with mono-*ortho*-substituted aryl iodides is known,[5–11] to the best of our knowledge, there is no example that employs di-*ortho*-substituted aryl iodides as a coupling partner, as these coupling products are widely utilized in organic synthesis.[1–4] As a result of these limitations, it is desirable to develop an efficient system to overcome such difficulties. Herein we report a catalyst combination consisting of Cu_2O (1.0–2.5 mol-%) and xantphos (**L1**, 1.0–2.5 mol-%), which serves as a powerful catalytic system for coupling terminal alkynes with aryl iodides.

Results and Discussion

To determine the optimal reaction conditions, we used phenylacetylene and iodobenzene as substrates. As shown in Table 1, we examined a series of ligands **L1**–**L6** (Figure 1) and discovered that xantphos (**L1**) was the best choice, affording the desired product nearly quantitatively (Table 1, Entry 1). Interestingly, the electron-rich and sterically hindered ligand **L2** (xantphos-type) shows no activity (Table 1, Entry 2). Likewise, **L3** and **L6** were not effective for this transformation. Ligands **L4** and **L5** showed good activity, yielding the target in 90 and 82% yield, respectively (Table 1, Entries 4 and 5). Among the solvents screened (Table 1, Entries 7–10), dioxane turned out to be the most effective. DMSO and DMF were also suitable for the reaction, resulting in the desired product in 91 and 95% yield, respectively (Table 1, Entries 7 and 9). We studied the effect of base and found that Cs_2CO_3 was the best; other bases such as K_2CO_3, K_3PO_4, and KO*t*Bu (Table 1, Entries 13–15) were found to be unsatisfactory. Furthermore, it was observed that lower catalyst loadings (Table 1, Entry 12), shorter reaction times (Table 1, Entry 19), and lower temperatures (Table 1, Entry 20) diminished the yield of the product. We next investigated the copper sources and found that Cu_2O was superior to CuI, CuO, and $CuCl_2$. The 2:1 ratio of copper to **L1** is better in this system: compare Entry 1 (2:1) with Entries 11 (1:1) and 12 (1:0.5). Assuming that a Cu–xantphos complex is formed,[15] 1 equiv. of Cu is unligated. This situation is not understood at the moment. A low yield of **3a** and the dimerization of phenylacetylene were observed when the reaction was carried out without ligand (Table 1, Entry 21). No desired product was detected in the absence of a catalyst (Table 1, Entry 22). No product was formed when iodobenzene was replaced by bromobenzene (not shown).

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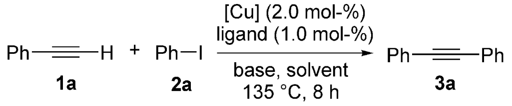
Table 1. Optimization of copper-catalyzed coupling of phenylacetylene with iodobenzene.[a]



Entry	[Cu]	Ligand	Base	Solvent	Yield [%]
1	*Cu_2O*	**L1**	*Cs_2CO_3*	*dioxane*	*99*
2	Cu_2O	**L2**	Cs_2CO_3	dioxane	–
3	Cu_2O	**L3**	Cs_2CO_3	dioxane	8
4	Cu_2O	**L4**	Cs_2CO_3	dioxane	90
5	Cu_2O	**L5**	Cs_2CO_3	dioxane	82
6	Cu_2O	**L6**	Cs_2CO_3	dioxane	12
7	Cu_2O	**L1**	Cs_2CO_3	DMSO	91
8	Cu_2O	**L1**	Cs_2CO_3	NMP	65
9	Cu_2O	**L1**	Cs_2CO_3	DMF	95
10	Cu_2O	**L1**	Cs_2CO_3	DME	88
11[b]	Cu_2O	**L1**	Cs_2CO_3	dioxane	44
12[c]	Cu_2O	**L1**	Cs_2CO_3	dioxane	65
13	Cu_2O	**L1**	K_2CO_3	dioxane	23
14	Cu_2O	**L1**	K_3PO_4	dioxane	34
15	Cu_2O	**L1**	KO*t*Bu	dioxane	19
16[d]	CuI	**L1**	Cs_2CO_3	dioxane	85
17[d]	CuO	**L1**	Cs_2CO_3	dioxane	27
18[d]	$CuCl_2$	**L1**	Cs_2CO_3	dioxane	93
19[e]	Cu_2O	**L1**	Cs_2CO_3	dioxane	76
20[f]	Cu_2O	**L1**	Cs_2CO_3	dioxane	47
21	Cu_2O	–	Cs_2CO_3	dioxane	10
22	–	–	Cs_2CO_3	dioxane	–

[a] Reaction conditions unless otherwise stated: Cu_2O (0.01 mmol, 1.0 mol-%), ligand (0.01 mmol, 1.0 mol-%), phenylacetylene (1.5 mmol), iodobenzene (1.0 mmol), base (2.0 mmol) in solvent (0.5 mL). [b] Cu_2O (0.5 mol-%). [c] Cu_2O (0.5 mol-%), ligand (0.5 mol-%). [d] Copper salt (2.0 mol-%). [e] 6 h. [f] 110 °C.

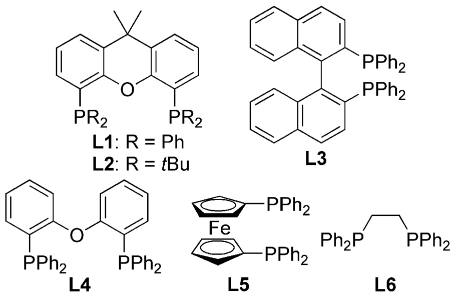
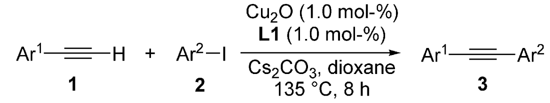


Figure 1. Structures of the ligands **L1**–**L6**.

To explore the scope of this novel system, a series of aryl iodides bearing electron-rich and electron-deficient moieties were tested with aryl alkynes. The functional groups, including enolizable ketones (Table 2, Entries 5 and 12), esters (Table 2, Entries 7 and 20), nitro (Table 2, Entry 8), unprotected amines (Table 2, Entries 2, 11, and 13), chloride (Table 2, Entry 9), bromide (Table 2, Entry 10), and heterocycles (Table 2, Entries 14–16), all tolerated the reaction conditions. Compound **3d** was obtained in 96% when 4-iodoanisole was employed with phenylacetylene. Moreover, it is worthy to note that the sterically demanding di-*ortho* substituted aryl iodide was also suitable as the substrate, as demonstrated in the formation of **3r** in 91% yield through the coupling of 2-ethyl-6-methyliodobenzene with phenylacetylene (Table 2, Entry 19).

Table 2. Cu_2O-catalyzed cross-coupling reaction of aryl alkynes with aryl iodides.[a]

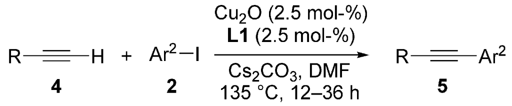


Entry	Ar^1	Ar^2	Yield [%]
1	Ph	$4\text{-}MeC_6H_4I$	98 (**3b**)
2[b]	Ph	$2\text{-}H_2NC_6H_4I$	97 (**3c**)
3[b]	Ph	$4\text{-}MeOC_6H_4I$	96 (**3d**)
4[c]	Ph	$2\text{-}MeOC_6H_4I$	95 (**3e**)
5	Ph	$4\text{-}CH_3COC_6H_4I$	99 (**3f**)
6	Ph	$2\text{-}MeC_6H_4I$	97 (**3g**)
7	Ph	$4\text{-}EtO_2CC_6H_4I$	89 (**3h**)
8	Ph	$4\text{-}O_2NC_6H_4I$	99 (**3i**)
9	Ph	$4\text{-}ClC_6H_4I$	85 (**3j**)
10	Ph	$4\text{-}BrC_6H_4I$	93 (**3k**)
11[b]	Ph	$4\text{-}H_2NC_6H_4I$	95 (**3l**)
12	Ph	$3\text{-}CH_3COC_6H_4I$	99 (**3m**)
13[d]	$3\text{-}H_2NC_6H_4$	PhI	86 (**3n**)
14	Ph	3-iodopyridine	97 (**3o**)
15	Ph	2-iodopyridine	89 (**3p**)
16	Ph	2-iodothiophene	90 (**3q**)
17[b,d]	$4\text{-}MeC_6H_4$	PhI	90 (**3b**)
18[b,d]	$4\text{-}MeOC_6H_4$	PhI	93 (**3d**)
19	Ph	$2\text{-}Et\text{-}6\text{-}MeC_6H_3I$	91 (**3r**)
20	Ph	$3\text{-}MeO_2CC_6H_4I$	82 (**3s**)

[a] Reaction conditions unless otherwise stated: Cu_2O (0.01 mmol, 1.0 mol-%), **L1** (0.01 mmol, 1.0 mol-%), aryl alkyne (1.5 mmol), aryl iodide (1.0 mmol), Cs_2CO_3 (2.0 mmol) in dioxane (0.5 mL). [b] 12 h. [c] 20 h. [d] Aryl alkyne (1.0 mmol), aryl iodide (1.5 mmol).

We turned our attention towards alkyl alkynes, as illustrated in Table 3. When the reaction was carried out by using the conditions for aryl alkynes, **5a** was obtained in only 64% yield. However, a 91% yield of **5a** can be ob-

Table 3. Cu_2O-catalyzed cross-coupling reaction of alkyl alkynes with aryl iodides.[a]

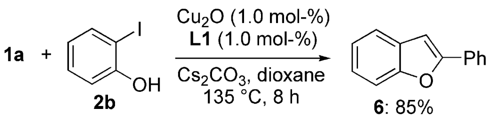


Entry	R	Ar^2	Time [h]	Yield [%]
1	nC_8H_{17}	PhI	24	91:64[b] (**5a**)
2	nC_8H_{17}	$4\text{-}MeC_6H_4I$	24	90 (**5b**)
3	nC_4H_9	PhI	12	99 (**5c**)
4	nC_4H_9	$4\text{-}MeOC_6H_4I$	20	91 (**5d**)
5	nC_8H_{17}	$2\text{-}MeC_6H_4I$	24	98 (**5e**)
6	nC_8H_{17}	$4\text{-}MeOC_6H_4I$	24	93 (**5f**)
7[c]	nC_4H_9	$4\text{-}MeC_6H_4I$	18	80 (**5g**)
8	nC_4H_9	$4\text{-}H_2NC_6H_4I$	24	77 (**5h**)
9	nC_8H_{17}	$2\text{-}Et\text{-}6\text{-}MeC_6H_3I$	24	88 (**5i**)
10	nC_4H_9	$2\text{-}Et\text{-}6\text{-}MeC_6H_3I$	24	93 (**5j**)
11	nC_4H_9	$2\text{-}MeC_6H_4I$	24	97 (**5k**)
12	nC_4H_9	3-iodopyridine	24	85 (**5l**)

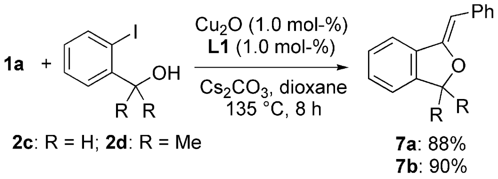
[a] Conditions unless otherwise stated: Cu_2O (0.025 mmol, 2.5 mol-%), **L1** (0.025 mmol, 2.5 mol-%), alkyl alkyne (1.5 mmol), aryl iodide (1.0 mmol), Cs_2CO_3 (2.0 mmol) in DMF (0.5 mL). [b] Cu_2O (1.0 mol-%), **L1** (1.0 mol-%). [c] 1-Hexyne (1.0 mmol), 4-iodotoluene (1.5 mmol).

tained when the reaction was performed under the catalyst combination of Cu_2O (2.5 mol-%)/**L1** (2.5 mol-%) in DMF (Table 3, Entry 1). A variety of aryl iodides were coupled smoothly with alkyl alkynes to give products **5a–l** in good to excellent yields based on this catalytic system. 4-Iodoanisole was coupled smoothly to afford **5d** and **5f** in excellent yields (Table 3, Entries 4 and 6). Free amine (Table 3, Entry 8) and pyridine moieties (Table 3, Entry 12) were also tolerated during the catalysis. Furthermore, sterically demanding substrates did not hamper the efficiency of the reaction, as seen for products **5i** and **5j**, which were obtained in 88 and 93% yield, respectively (Table 3, Entries 9 and 10).

When the reaction was carried out with **1a** and **2b**, product **6** was obtained in 85% yield [Equation (1)].[10,16] Products **7a** and **7b** can be selectively synthesized in excellent yields through 5-*exo*-*dig* cyclization[17] in one pot [Equation (2)].



(1)



(2)

Conclusions

In conclusion, we have demonstrated that the combination of Cu_2O (1.0–2.5 mol-%) with xantphos (1.0–2.5 mol-%) serves as a powerful catalytic system for the cross-coupling reaction of terminal alkynes with aryl iodides. A variety of functional groups such as enolizable ketones, esters, nitro groups, unprotected amines, chlorides, bromides, and heterocycles were all tolerated by the reaction conditions explored. Moreover, the highly sterically demanding substrate di-*ortho*-substituted aryl iodide was also shown to be a good coupling partner to give the alkynes in good to excellent yields.

Experimental Section

Representative Procedure: A sealable vial equipped with a magnetic stir bar was charged with Cs_2CO_3 (652 mg, 2.0 mmol), Cu_2O (1.43 mg, 0.01 mmol), and **L1** (5.79 mg, 0.01 mmol) under a nitrogen atmosphere. The aperture of the vial was then covered with a rubber septum. Under a nitrogen atmosphere, phenylacetylene (**1a**; 0.167 mL, 1.5 mmol), iodobenzene (**2a**; 0.11 mL, 1.0 mmol), and dioxane (0.5 mL) were added by syringe. The septum was then replaced by a screw cap containing a Teflon-coated septum, and the reaction vessel was placed in an oil bath at 135 °C. After stirring at this temperature for 8 h, the heterogeneous mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The resulting solution was filtered through a pad of silica gel then washed with ethyl acetate (20 mL) and concentrated to give the crude material, which was then purified by column chromatography (SiO_2, hexane) to yield **3a**.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^1H and ^{13}C NMR spectra of the new compounds.

Acknowledgments

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