Microwave-Assisted Copper-Catalyzed Cross-Coupling Reaction of Alkynes with Aryl Iodides and Vinyl Halides

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Abstract: The microwave-assisted, copper-catalyzed coupling of terminal alkynes with aryl iodides and vinyl halides is reported. In general, the reactions are completed in 10–30 min using 2–5 mol% [CuI(xantphos)] as a catalyst to provide the corresponding alkynes and enynes in good to excellent yields. A broad spectrum of aryl iodides, vinyl iodides, and bromides are coupled with aryl- and alkyl alkynes.

Key words: microwaves, copper, cross-coupling, alkynes, aryl iodide

Functional alkynes and enynes are important molecules in organic synthesis and materials science;¹ as such, many methods have been developed for the synthesis of these compounds.^{2–4} Pioneering work reported by Sonogashira employed palladium and a copper cocatalyst for the coupling of alkynes with aryl halides^{1b} and, since this discovery, transition-metal-catalyzed coupling of terminal alkynes with aryl halides and vinyl halides has become an important method for the preparation of alkynes and enynes.^{3,4} More recently, the exclusive use of copper as a catalyst has gained significant attention in the Sonogashira-type reaction owing to the low cost of the copper salts.⁴

Microwave irradiation has been widely applied in organic synthesis^{5,6} due to the high efficiency of this technique. While microwave-promoted Sonogashira-type reactions are known,⁷⁻⁹ such protocols are typically found using Pd/Cu⁷ or Pd⁸ as the catalysts for the coupling of alkynes with aryl halides. Using exclusively copper in the microwave-assisted, copper-catalyzed coupling reaction is known,^{9,10} however, there are some limitations. First, ortho-substituted aryl halides are not involved in these systems.^{9a} Second, the substrates used in these procedures are mainly aryl alkynes.9 Recently, Xie and Wan reported the microwave-assisted coupling of aryl- and alkyl alkynes with aryl iodides.¹⁰ However, some drawbacks remain in these systems. First, high levels of catalyst and ancillary ligand (10 mol% CuI and 20 mol% PPh₃) were required. Second, these systems needed excess phasetransfer reagents. Third, 2.4-3.0 equivalents of alkynes are necessary for these couplings.

Recently, we reported the copper-catalyzed coupling reaction of alkynes with aryl iodides^{4a} and vinyl halides.^{4b}

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Here, we report a general procedure for the microwaveassisted, copper-catalyzed coupling of alkynes with aryl iodides. Aryl and alkyl substrates both reacted smoothly to provide the corresponding alkynes in good to excellent yields.

Initially, iodobenzene and phenylacetylene were selected as model substrates to screen for optimal reaction conditions; the results are summarized in Table 1. A 22% product yield resulted when the reaction was carried out using our previously developed conditions for the coupling of aryl iodides with alkynes under oil bath heating (Table 1, entry 1).^{4a,b} In general, polar solvents have been shown to enhance the efficiency of microwave irradiation.^{7–10} To our delight, a 95% yield was afforded when the solvent was changed to dimethyl sulfoxide (DMSO; Table 1, en-

 Table 1
 Optimization of Microwave-Assisted Copper-Catalyzed

 Coupling of Iodobenzene with Phenylacetylene^a

Ph	+ Ph—I Cul(xa (2 m base, solv 2a MW, 1	ntphos) nol%) ent, 135 °C Ph 10 min 3a	—Ph
Entry	Base	Solvent	Yield (%)
1	Cs ₂ CO ₃	dioxane	22
2	Cs ₂ CO ₃	DMSO	95
3	Cs ₂ CO ₃	DMSO	b
4	Na ₂ CO ₃	DMSO	43
5	K ₃ PO ₄	DMSO	34
6	K ₂ CO ₃	DMSO	71
7	KOt-Bu	DMSO	_
8	Cs ₂ CO ₃	DMF	98
9	Cs ₂ CO ₃	H_2O	63
11	Cs ₂ CO ₃	THF	trace
12	Cs ₂ CO ₃	MeCN	85
13	Cs ₂ CO ₃	NMP	96
14	Cs ₂ CO ₃	DMF	86°

^a Reaction conditions: [CuI(xantphos)] (0.01 mmol, 2 mol%), phenylacetylene (0.75 mmol), iodobenzene (0.5 mmol), base (1.0 mmol), solvent (0.5 mL).

^b No catalyst.

^c [CuI(xantphos)] (0.005 mmol, 1.0 mol%)

try 2). No product was observed when the reaction was carried out in the absence of catalyst (Table 1, entry 3). We then studied the effect of base on the reaction (Table 1, entries 4–7), and the results showed that Cs_2CO_3 was optimal for this transformation. Other solvents were examined (Table 1, entries 8-13) and N,N-dimethylformamide (DMF) was found to be superior, giving the product in 98% isolated yield (Table 1, entry 8). Lower catalyst

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loadings resulted in diminished yield of the desired target (Table 1, entry 14).

In order to explore the scope of the system, a variety of aryl alkynes were reacted with aryl iodides (Table 2, entries 1–12). Functional groups such as free amines (Table 2, entries 2 and 11), chloro (Table 2, entries 4 and 12), bromo (Table 2, entry 5), and sulfur-containing heterocycles (Table 2, entries 6 and 7) were all tolerated under the

 Table 2
 Microwave-Assisted Copper-Catalyzed Coupling of Alkynes with Aryl Iodides^a

·	Cul(xantphos) (2–5 mol%) Cs ₂ CO ₃ , DMF	—					
$H \longrightarrow Ar = Ar = 1 = 135 ^{\circ}C, MW, 10-30 ^{o}min = 3$							
Entry	R	2	Product	Yield (%) ^b			
1	Ph	4-MeC ₆ H ₄ I	3b	99			
2	Ph	$4-H_2NC_6H_4I$	3c	99°			
3	Ph	4-MeOC ₆ H ₄ I	3d	70			
4	Ph	4-ClC ₆ H ₄ I	3e	82			
5	Ph	$4-BrC_6H_4I$	3f	87			
6	Ph	2-iodothiophene	3g	53 ^d			
7	Ph	3-iodopyridine	3h	97			
8	$4-MeC_6H_4$	PhI	3i	87°			
9	$4-MeOC_6H_4$	PhI	3j	67			
10	$4-F_3CC_6H_4$	PhI	3k	99°			
11	$3-H_2NC_6H_4$	PhI	31	76			
12	3-ClC ₆ H ₄	PhI	3m	99			
13	<i>n</i> -Bu	PhI	3n	75°			
14	<i>n</i> -Bu	4-MeOC ₆ H ₄ I	30	75			
15	<i>n</i> -Bu	$4-H_2NC_6H_4I$	3p	99			
16	<i>n</i> -Bu	2-Et-6-MeC ₆ H ₃ I	3q	34°			
17	<i>n</i> -Bu	4-MeC ₆ H ₄ I	3r	76			
18	<i>n</i> -Bu	3-iodopyridine	3s	74			
19	<i>n</i> -Bu	2-MeC ₆ H ₄ I	3t	63°			
20	<i>n</i> -Bu	$4-BrC_6H_4I$	3u	78			
21	<i>n</i> -C ₈ H ₁₇	PhI	3v	90			
22	<i>n</i> -C ₈ H ₁₇	4-MeOC ₆ H ₄ I	3w	80			
23	<i>n</i> -C ₈ H ₁₇	4-MeC ₆ H ₄ I	3x	87			
24	<i>n</i> -C ₈ H ₁₇	2-MeC ₆ H ₄ I	3у	42°			

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^a Reaction conditions: [CuI(xantphos)] (0.01 mmol, 2 mol% for entries 1–12; 0.025 mmol, 5 mol% for entries 13–24), alkyne (0.75 mmol), aryl iodide (0.5 mmol), base (1.0 mmol), DMF (0.5 mL), 10 min. ^b Isolated yield.

° 30 min.

^d [CuI(xantphos)] (0.025 mmol, 5 mol%), 10 min.

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reaction conditions. In general, alkyl alkynes were more problematic than aryl alkynes for the copper-catalyzed Sonogashira-type reaction.^{4a} Good yields were obtained when the reactions were carried out using 5 mol% catalyst (Table 2, entries 13–24). Functional group tolerance was evident in cases in which the substrate contained an unprotected amine (Table 2, entry 2), a bromine (Table 2, entry 5), or when nitrogen-containing heterocycles were used. More importantly, the sterically demanding 2-iodotoluene could also be used as a coupling partner to provide the products in moderate yields (Table 2, entries 19 and 24), and a 34% isolated yield was obtained when the reaction was carried out with 2-ethyl-6-methyliodobenzene (Table 2, entry 16).

We then turned our attention to the coupling of vinyl halides with alkynes, as illustrated in Table 3. A variety of vinyl iodides reacted with alkynes, giving the corresponding enynes in good to excellent yield. Interestingly, 1-(2bromovinyl)benzene could also be used as a substrate for this system, giving the enynes in good yields (Table 3, entries 11 and 12).

In summary, we have demonstrated that [CuI(xantphos)] is an active catalyst for the microwave-assisted coupling reaction of alkynes with aryl iodides, vinyl iodides and bromides, giving the corresponding internal alkynes and enynes in good to excellent yields.

All products are known compounds, with spectral data agreeing with literature values. See the Supporting Information for details.

Microwave-Assisted Copper-Catalyzed Coupling of Iodobenzene with Phenylacetylene; General Procedure for Table 1

A sealable vial equipped with a magnetic stir bar was charged with base (1.0 mmol) and [CuI(xantphos)] (7.7 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**; 0.083 mL, 0.75 mmol), iodobenzene (**2a**; 0.056 mL, 0.5 mmol) and solvent (0.5 mL) were added by using a syringe. The septum was then replaced by a screw-cap containing a Teflon-coated septum, and the reaction vessel was placed under microwave irradiation at 135 °C. After stirring at this temperature for 10 min, the heterogeneous mixture was cooled to r.t. and diluted with EtOAc (20 mL). The resulting solution was filtered through a pad of silica gel then washed with EtOAc (20 mL) and concentrated to give the crude material, which was then purified by column chromatography (SiO₂, hexane) to yield **3a**.

Microwave-Assisted Copper-Catalyzed Coupling of Alkynes with Aryl Iodides; General Procedure for Table 2

A sealable vial equipped with a magnetic stir bar was charged with Cs_2CO_3 (325 mg, 1.0 mmol) and [CuI(xantphos)] (7.69 mg, 0.01 mmol for aryl alkyne; 19.23 mg, 0.025 mmol for alkyl alkyne) under a nitrogen atmosphere. The aperture of the vial was then covered with a rubber septum. Under a nitrogen atmosphere, aryl or alkyl alkyne (1; 0.75 mmol), aryl iodide (2; 0.5 mmol) and DMF (0.5 mL) were added by using a syringe. The septum was then replaced by a screw-cap containing a Teflon-coated septum, and the reaction vessel was placed under microwave irradiation at 135 °C. After stirring at this temperature for 10–30 min, the heterogeneous mixture was cooled to r.t. and diluted with EtOAc (20 mL). The resulting solution was filtered through a pad of silica gel then washed with EtOAc (20 mL) and concentrated to give the crude material, which was then purified by column chromatography (SiO₂, hexane or hexane–EtOAc) to yield alkyne **3**.

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 Table 3
 Microwave-Assisted Copper-Catalyzed Coupling of Alkynes with Vinyl Halides^a



^a Reaction conditions: [CuI(xantphos)] (0.01 mmol, 2 mol% for aryl alkyne; 0.025 mmol, 5 mol% for alkyl alkyne), alkyne (0.75 mmol), vinyl iodide or bromide (0.5 mmol), Cs_2CO_3 (1.0 mmol), DMF (0.5 mL), 30 min.

^b Reaction time: 1 h.

Microwave-Assisted Copper-Catalyzed Coupling of Alkynes with Vinyl Halides; General Procedure for Table 3

A 4-mL scalable vial equipped with a magnetic stir bar was charged with Cs_2CO_3 (325 mg, 1 mmol) and [CuI(xantphos)] (7.69 mg, 0.01 mmol for aryl alkyne; 19.23 mg, 0.025 mmol for alkyl alkyne) under a nitrogen atmosphere. The aperture of the vial was then covered with a rubber septum. Under a nitrogen atmosphere, alkenyl halide (4; 0.5 mmol), aryl or alkyl alkyne (2; 0.75 mmol), and DMF (0.5

mL) were added by using a syringe. The septum was then replaced by a screw-cap containing a Teflon-coated septum, and the reaction vessel was placed under microwave irradiation at 135 °C. After stirring at this temperature for 30–60 min, the heterogeneous mixture was cooled to r.t. The resulting solution was filtered through a pad of silica gel then washed with EtOAc (20 mL) and concentrated to give the crude material, which was then purified by column chromatography (SiO₂, hexane) to yield **5**.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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