

A Copper-Catalyzed Sonogashira Coupling Reaction of Diverse Activated Alkyl Halides with Terminal Alkynes Under Ambient Conditions

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Abstract: We describe a copper-catalyzed Sonogashira coupling reaction of alkyl halides with terminal alkynes under ambient conditions, efficiently providing a versatile tool for the construction of substituted alkynes. A new proline-based N,N,Pligand is utilized to promote the transformation under a mild reaction condition. Diverse alkyl halides, such as primary and secondary (hetero) benzyl chlorides and bromides, secondary and tertiary α -bromo amides and propargylic bromide, are applicable to provide a wide array of alkynes.

Keywords: copper catalysis; Sonogashira coupling reaction; alkyl halides; proline-based N,N,P-ligand; ambient conditions

Alkynes are versatile intermediates and precursors in organic synthesis and structural motifs in many natural products, bioactive molecules and functional materials.^[1] Therefore, the straightforward assembly of alkynes has attracted much interest from organic chemists.^[1] Among numerous strategies for the synthesis of alkynes, transition metal-catalyzed Sonogashira coupling reaction has evolved into one of the most prevalent tools during to the wide substrate scope and broad functional group tolerance.^[2] While the synthesis of aryl/vinyl alkynes from aryl/vinyl (pseudo)halides and terminal alkynes has been well documented utilizing the palladium-copper co-catalysis^[2c,3] or the copper catalysis,^[2d] the synthesis of alkyl alkynes from alkyl halides and terminal alkynes are less developed. Several challenges are associated with this transformation, such as the difficult oxidative addition of alkyl halides and the easily occurring βhydrogen elimination of metal-alkyl intermediates.^[4] Thus, there are only limited reports on the successful Sonogashira reaction of alkyl halides which bear a β hydrogen. In this aspect, the groups of Fu and Glorius have pioneered this field by demonstrating the coupling reaction of such alkyl halides using a palladium/copper cocatalyst and a N-heterocyclic carbene ligand (Scheme 1a).^[4a,5] Later, $Hu^{[6]}$ and $Liu^{[7]}$ independently introduced the nickel/copper-cocatalyzed Sonogashira reaction of such substrates employing pincer and pyridine bisoxazoline ligand in their strategy, respectively (Scheme 1a). Notably, these early Sonogashira reactions require an additional transition metal catalyst (Pd or Ni) along with the copper catalyst. Therefore, the utilization of copper as a sole catalyst in Sonogashira coupling reaction of alkyl halides, a more appealing and economic strategy, represents impressive advance organic an in





$$\begin{array}{c} X \\ R^{1} \\ R^{2} \\ X = Br, I \end{array} \stackrel{+}{\longrightarrow} \begin{array}{c} R^{3} \\ R^$$

(b) Coupling of activated alkyl halides (Cu)



(c) Coupling or alkyl halides (Cu) via heating or hv



(d) This work: coupling of diverse alkyl halides under ambient conditions (Cu)



Scheme 1. Sonogashira coupling of alkyl halides.

synthesis.^[8] Unfortunately, copper also catalyzes the Glaser homocoupling of terminal alkynes^[9] and always leads to lower yields of the desired cross coupling products, further impeding the methodology development.

In this field, two early reports on copper-catalyzed Sonogashira coupling of activated α - and β -haloamides were disclosed by Shi and Nishikata, respectively (Scheme 1b).^[10] To extend the scope of alkyl halides, Lalic and co-workers developed a copper-catalyzed coupling of alkyl iodides, wherein a blue LED had to be used to initiate the reaction (Scheme 1c).^[11] Very recently, Jin and co-workers accomplished a general copper-catalyzed Sonogashira coupling of benzyl bromides with terminal alkynes (Scheme 1c).^[12] In Jin's strategy, only benzyl bromides were applicable and high temperature together with a strong base (LiHMDS) was necessary to reach a good reaction efficiency. Based on these facts, a general and gentle copper-catalyzed Sonogashira coupling of diverse alkyl halides to forge the $C(sp^3)$ –C(sp) bond at ambient conditions is still desirable. Our group has recently realized a radical asymmetric Sonogashira reaction of secondary alkyl halides, during which we found that the use of a chiral cinchona alkaloid-based N,N,Pligand is crucial to the transformation and results in a very mild reaction condition.^[13] As our continuous research interest in developing novel ligands to promote the copper-catalyzed radical reactions,^[13,14] we herein report a copper-catalyzed Sonogashira coupling of alkyl halides with terminal alkynes. One representative feature of this strategy is the utilization of a unique proline-based N,N,P-ligand to promote the reaction under a very mild condition. Diverse alkyl halides are applicable to this transformation, such as primary and

secondary benzyl chlorides and bromides, propargylic bromide and secondary and tertiary α -bromo amides to efficiently provide a wide range of alkynes.

We initiated our hypothesis by examining the cross coupling reaction of (1-bromoethyl)benzene (1 a) with phenylacetylene (2 a) in 1,4-dioxane in the presence of 10 mol% CuI and 2 equivalents of Cs_2CO_3 (Table 1). We systematically screened various types of mono-, biand tri-dentate ligands (L1–L9). The results showed that mono- and di-phos ligands provided the desired product in very low yields (entries 1 and 2 in Table 1). The widely used bi-and tri-pyridine ligands were also not ideal ligands to enhance the reactivity (entries 3–7 in Table 1). Screening of the N,N,P-ligand L9 gave rise to

 Table 1. Screening of reaction conditions.



Entry	Cu salt	Ligand	Base	Solvent	Yield
1	CuI	L1	Cs ₂ CO ₃	dioxane	20%
2	CuI	L2	Cs_2CO_3	dioxane	15%
3	CuI	L3	Cs_2CO_3	dioxane	22%
4	CuI	L4	Cs_2CO_3	dioxane	3%
5	CuI	L5	Cs_2CO_3	dioxane	37%
6	CuI	L6	Cs_2CO_3	dioxane	0
7	CuI	L7	Cs_2CO_3	dioxane	7%
8	CuI	L8	Cs_2CO_3	dioxane	22%
9	CuI	L9	Cs_2CO_3	dioxane	81%
10	CuI	L9	Cs_2CO_3	THF	78%
11	CuI	L9	Cs_2CO_3	CH_2Cl_2	0
12	CuI	L9	Cs_2CO_3	Et ₂ O	82%
13	CuI	L9	^t BuOK	Et_2O	0
14	CuI	L9	K_2CO_3	Et_2O	37%
15	CuI	L9	LiOH	Et_2O	0
16	CuOAc	L9	Cs ₂ CO ₃	Et ₂ O	94%
17	CuCN	L9	Cs_2CO_3	Et ₂ O	41%
18	CuOAc	-	Cs_2CO_3	Et ₂ O	0

^[a] All the reactions were conducted on a 0.05 mmol scale.
 ^[b] Yields were determined by ¹H NMR using CH₂Br₂ as an internal standard.



the desired coupling product **3 a** with the best results at ambient conditions (entries 8 and 9 in Table 1). Further screening of the reaction solvent, base and copper salt (entries 10–17 in Table 1) led us to identify the best reaction conditions as follows: the reaction of **1 a** and 1.5 equivalents **2 a** in the presence of 10 mol% CuOAc, 12 mol% L9, 2.0 equivalents of Cs_2CO_3 in Et₂O delivered **3 a** in 94% NMR yield under ambient conditions (entry 16 in Table 1).^[15] The control experiment showed that no product was formed in the absence of L9 (entry 18 in Table 1).

Having established the optimal condition, we next investigated the substrate scope of alkyl halides. As shown in Table 2a, a variety of secondary benzyl bromides can be successfully coupled with phenylacetylene **2a** under the standard conditions to afford the coupling products **3a–3j** in 51–90% yields. Substrates with electron-withdrawing groups, such as the CF₃ group at *para-*, *meta-*, and *ortho*-positions all participated in the cross coupling reaction to provide **3b–3d** in good yields, though the *ortho*-substituted substrates provided a relatively lower yield of product. The cyano group can also be tolerated under the coupling conditions to give rise to **3e** in 73% yield. The halogen (F, Cl, I)-substituted benzyl bromides reacted smoothly to provide the desired products **3f–3i**

Table 2. Substrate scope of alkyl halides.^[a]



^[a] Reaction conditions: 1 (0.50 mmol), 2 a (0.75 mmol), CuOAc (10 mol%), L9 (12 mol%), and Cs_2CO_3 (1.0 mmol) in Et₂O (2.0 mL). The yield is isolated.

in good yields. The electron-donating group on the phenyl ring is also compatible with the standard conditions to deliver **3***i* in 83% yield. In addition, the 1- and 2-naphthyl bromides both underwent the cross coupling reaction smoothly to afford 3k and 3l in 65% and 78% yield, respectively. The aliphatic chain of benzyl bromides is not limited to methyl group, as can be viewed by the formation of **3 m** and **3 n**. The alkyl bromide containing a heterocycle, such as benzo[b]furan, worked well to provide 30 in 60% yield. Moreover, the primary and tertiary bromides were also suitable to deliver the coupling products **3p** and **3q**. More significantly, the coupling reaction is also applicable to other type of alkyl bromides. As such, the α -bromo amide coupled successfully with phenylacetylene under the standard conditions to generate the α -alkynylated amide **3r** in 56% yield. The propargylic bromide underwent the coupling reaction smoothly to afford the target product 3s in 64% yield. Moreover, the benzyl chloride was also amenable to the reaction to afford **3a** in a comparable yield with the bromide counterpart (Table 2b).

Encouraged by the above results, we then switched our attention to the terminal alkynes (Table 3). As such, substrates bearing diverse substituents on the phenyl ring of alkynes reacted well to give the products 3t-3w in good yields. Besides, heteroaryl alkynes were also applicable to the standard coupling conditions, which can be proved by the formation of 3x from the reaction of thiophene-type alkynes. Notably, aliphatic alkynes were also tolerable to generate 3y and 3z, albeit with relatively low yields.

To gain some insight into the reaction mechanism, we carried out the control experiments (Scheme 2a). The reaction of 1 a and 2 a was completely inhibited by the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy





^[a] Reaction conditions: **1 a** (0.50 mmol), **2** (0.75 mmol), CuOAc (10 mol%), **L9** (12 mol%), and Cs_2CO_3 (1.0 mmol) in Et₂O (2.0 mL). The yield is isolated.

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Scheme 2. Mechanistic investigation and plausible mechanism.

(TEMPO) or *p*-benzoquinone. Furthermore, the enantioenriched **1a** delivered the alkyne **3a** with very low ee under the standard conditions (Table 2b). These results suggested that radical intermediates might be involved in the process. Based on the experimental results and previous reports,^[13,16] we proposed a plausible mechanism as depicted in Scheme 2c. A single electron transfer process occurred between the *in situ* generated copper(I) acetylide complex and alkyl halides **1** to generate the copper(II) complex **II** and the alkyl radical intermediates **III**. The subsequent coupling of the complex **II** and **III** provided the coupling products **3** and regenerated the Cu¹L complex for next catalytic cycle.

In conclusion, we have developed a mild coppercatalyzed Sonogashira reaction of alkyl halides and terminal alkynes. Owing to the utilization of a novel proline-based N,N,P-ligand, the cross coupling reaction is accomplished under ambient conditions. A wide range of alkyl halides, such as primary and secondary (hetero)benzyl chlorides and bromides, secondary and tertiary α -bromo amides and propargylic bromide were suitable to the strategy, thus providing diverse alkynes in good efficiency. Mechanistic study revealed that the reaction might proceed via a free radical process.

Experimental Section

General Procedure for Sonogashira coupling of all substrates: To a 10-mL Schlenk tube was added CuOAc (6.0 mg, 0.05 mmol), L9 (23 mg, 0.06 mmol), Cs₂CO₃ (325 mg, 1.0 mmol), and anhydrous Et_2O (2.0 mL). Alkyl halide 1 (0.50 mmol) and alkyne 2 (0.75 mmol) were sequentially added into the mixture. The reaction mixture was stirred at room temperature for 20 h. After completion of the reaction, the precipitate was filtered off and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with petro ether to afford **3**.

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