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Cu-Catalyzed Alkynylation of Unactivated C(sp^3)−X Bonds with Terminal Alkynes through Directing Strategy

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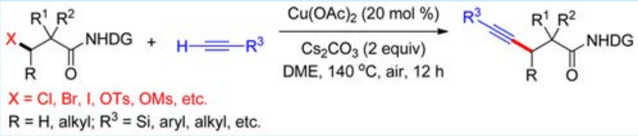
Supporting Information

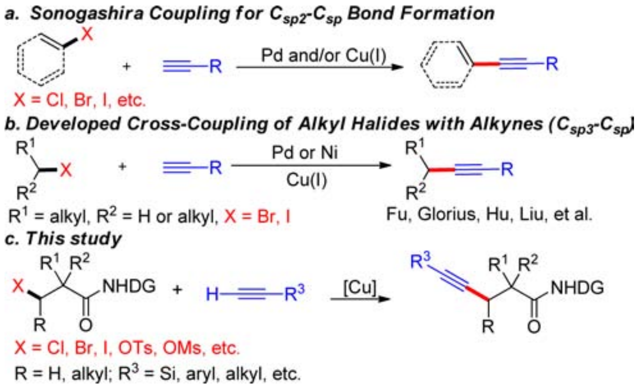


ABSTRACT: In this letter, we report an efficient and concise protocol for Cu-catalyzed cross-coupling of unactivated alkyl halides/peusudohalides with terminal alkynes to afford internal alkynes with the assistance of various amides as directing groups. Different alkyl halides/pseudohalides exhibited excellent reactivities, and the inactivated alkyl chlorides and sulfonates showed better reactivity than bromides/iodides. This is the first successful example to apply alkyl chlorides and sulfonates directly in cross-coupling with terminal alkynes in the absence of any additives. A Cu catalyst was found to be more effective than other transition metal catalysts. This reaction also exhibited a broad substrate scope with respect to terminal alkynes.

Alkynes are fundamental structural motifs in bioactive molecules and materials[1] as well as versatile synthons in synthetic transformations.[2] Continuous attention has been focused toward developing efficient methods to construct internal alkynes, and great achievements have been made in the past several decades.[3] As the most powerful method to construct internal alkynes, Sonogashira coupling between terminal alkynes and aryl/alkenyl halides/pseudo halides exhibited their beauty and power in both academia and industry.[4] In comparison, direct alkynylation of alkyl halides with terminal alkynes have remained challenging for quite a long time. The lag of such coupling reactions has been attributed to the difficulty of organometallic transformations of alkyl halides (including oxidative addition of alkyl halides to low-valent transition metals and reductive elimination of sp^3 C−M species) and the thermodynamic and kinetic instability of alkyl C−M intermediates.[5]

In 2003, the first example of direct alkynylation of primary alkyl bromides and iodides was disclosed by Fu and co-workers.[6] Subsequently, Glorius and co-workers applied more challenging, inactivated secondary alkyl halides for direct alkynylation.[7] With their own developed Ni/pincer ligand-based catalyst, Hu and co-workers also reported direct alkynylation of primary iodides.[8] Very recently, a modified hemilabile pincer ligand made such a coupling take place at room temperature.[9] Liu and co-workers also reported a protocol to carry out the coupling of alkynes with secondary bromides/iodides under mild conditions by using a nickel/Pybox catalyst set in the presence of a copper salt as an additive.[10] Very recently, Li and co-workers reported a study to perform a photopromoted transition-metal-free coupling between alkynes and alkyl iodides in water.[11]

Scheme 1. Cross-Coupling of Terminal Alkynes with Halides


a. Sonogashira Coupling for C_{sp2}-C_{sp} Bond Formation

b. Developed Cross-Coupling of Alkyl Halides with Alkynes (C_{sp3}-C_{sp})

c. This study

Despite the progress that has been made in the cross-coupling of alkyl halides with terminal alkynes (Scheme 1b), challenges still remain: (1) the current catalytic systems are efficient while highly dependent on either Pd or Ni with special ligands. In some cases a copper(I) salt was incorporated as an additive. (2) The substrate scope is limited to primary and secondary bromides/iodides, leaving cheap and easily available chloride and O-based electrophiles unreactive.

Our first goal is to incorporate cheap and easily available alkyl chlorides as electrophiles in such a cross-coupling. To challenge this problem, we intended a search for other strategic approaches for cross-coupling between alkyl halides/peusudohalides and terminal alkynes different from the current

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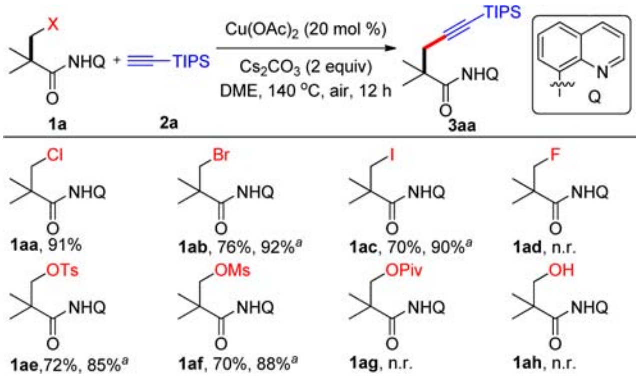
methods. As we know, a directing strategy has been well applied to activate the "inert" C−H,[12] C−O,[13] C−C,[14] and other bonds. We considered that it would be a possible strategy to apply for the cross-coupling of inactive aliphatic C−Cl bonds with terminal alkynes. After systematic investigations, we herein demonstrate the first successful example of direct alkynylation of unactivated alkyl chlorides as well as other halides/peusodohalides with various terminal alkynes.

Indeed, the bidentated directing groups have exhibited their power in transition-metal-catalyzed C−H functionalizations.[12] Inspired by this idea, we chose alkyl chloride **1aa** by introducing the 8-quinonyl amide[15] as a directing group to test our design (Table S1). Initial screenings were carried out to test the coupling between **1aa** and ethynyltriisopropylsilane **2a** in the presence of different transition-metal catalysts and Cs_2CO_3 as base (entries 1−5). $Cu(OAc)_2$ gave the desired product **3aa** in excellent yield in 1,2-dimethoxyethane (DME) as solvent at 140 °C under air (entry 1), while other transition-metal catalysts completely failed to promote this coupling. In previous reports, the iodide was required to activate the chloride through S_N2 substitution to generate iodide *in situ* to promote the coupling.[8] In our case, no other additives were required to promote the reaction. Further screening indicated that other copper salts also showed credible catalytic activity to some extent, while $Cu(OAc)_2$ exhibited better performance (cf. entry 1 to entries 6−11). Screening of the bases and solvents gave the best combination with Cs_2CO_3 as a base in DME (entries 12−17). The amount of $Cu(OAc)_2$ was essential, and 20 mol % gave the best results (cf. entry 1 to entries 18−20). Obviously, in the absence of $Cu(OAc)_2$, the coupling did not take place, while the cyclic butyl amide was afforded through intramolecular nucleophilic cyclization (entry 20). A lower temperature decreased the efficacy (entries 21−23). Decreasing the amount of Cs_2CO_3 (entry 24) or shortening the reaction time (entry 25) also led to lower yields. Notably, the reaction conducted under an inert atmosphere of N_2 also proceeded well and gave a 95% NMR yield (entry 26). This result excluded the potential roles of dioxygen (O_2) in this catalytic cycle.

With the optimal reaction conditions in hand, different leaving groups were investigated for such an alkynylation with the same scaffold (Scheme 2). Besides the chloride **1aa**, the bromide (**1ab**) and iodide (**1ac**) also showed credible reactivity toward this alkynylation. The chloride showed much better performance under the same conditions. To approach the better yields of **1ab** and **1ac**, a stoichiometric amount of $Cu(OAc)_2$ was required to obtain the comparable efficacy compared to **1aa** with 1,2-dichloroethane (DCE) as a solvent. These phenomena might imply a completely different catalytic pathway from the traditional cross-coupling between alkynes and organohalides. Unfortunately, the fluoride (**1ad**) failed, with complete recovery of the starting materials. Notably, the tosylate (**1ae**) and mesylate (**1af**) were also workable, and their reactivity was comparable with the corresponding bromide (**1ab**) and iodide (**1ac**). Similarly, the yields from those sulfonates can also be enhanced by adding a stoichiometric amount of $Cu(OAc)_2$ and running the reactions in DCE to suppress side reactions. Understandably, both the corresponding pivalate (**1ag**) and precursor alcohol (**1ah**) were not suitable because of their reduced leaving ability.

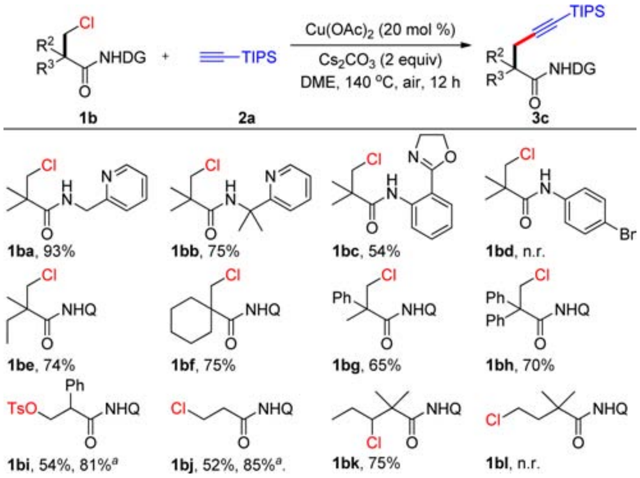
Scheme 2. Substrate Scope of Alkyl Halides



[a] The reaction was conducted in DCE with stoichiometric $Cu(OAc)_2$ loading.

Subsequently, different directing groups with an amide linker, which are generally used in C−H functionalization, were introduced to test their reactivity for this alkynylation (Scheme 3). Both picolylamine (**1ba**)[16] and 2-(pyridine-2-yl) isopropyl amine (PIP amine) (**1bb**)[17] showed good reactivity, while the simple **1ba** showed much better performance. Only a moderate yield was obtained with the Oxa directing group (**1bc**),[18] which might be attributed to the less stable 6/5 intermediate. Predictably, the monodentated anilide (**1bd**) did not work, showing the key chelating factor of the directing group. Further investigations were focused to test the different aliphatic carboxylic acid derivatives.

Scheme 3. Substrate Scope of Aliphatic Amides

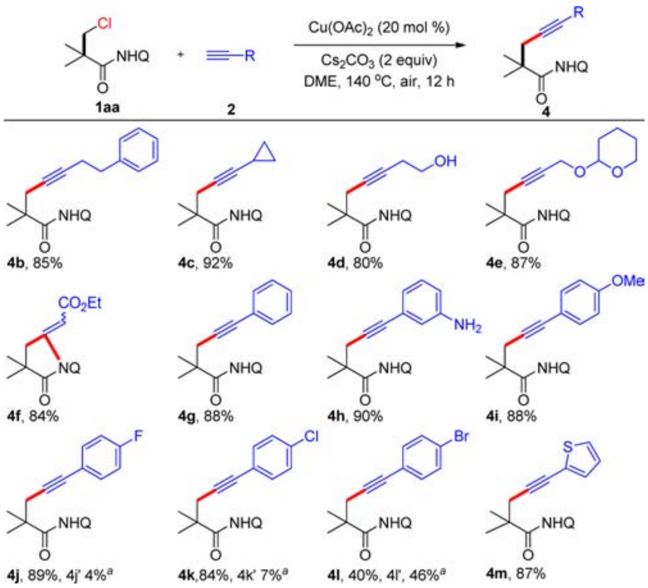


[a] Loading 1 equiv of $Cu(OAc)_2$, in DCE.

First of all, the alkyl or phenyl substituted aliphatic acids in the absence of β-H were tested (**1be**−**1bh**). Alkyl substituents gave good yields of the desired products, despite whether the linear (**1be**) or cyclic (**1bf**) substituents were used. Mono- or diphenyl-substituted substrates (**1bg**−**1bh**) were also suitable, leaving the aromatic C−H bonds unreacted. Besides, both mono- or un-α-substituted aliphatic tosylates and chlorides in the presence of β-H (**1bi** and **1bj**) could also provide such an alkynylation with high efficiency. Notably, high efficiency could only be obtained in a stoichiometric amount of $Cu(OAc)_2$ for all these amides containing α-H. Those substrates highly extended the potential application of these methods. To explore the substrate scope further, we tested a secondary chloride. This substrate (**1bk**) also showed credible reactivity in this transformation. Unfortunately, γ-chloro amide (**1bl**) was not suitable for this transformation, showing the importance of the link length between the chloride and amide, which might fundamentally affect the configuration of the Cu intermediate.

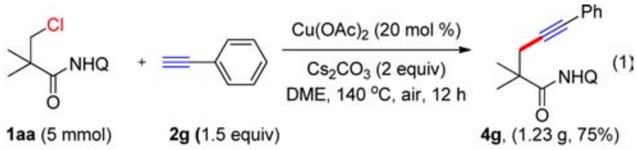
The scope of terminal alkynes was further investigated (Scheme 4). Linear (**2b**) or cyclic (**2c**) aliphatic alkynes showed great reactivity. Both alcohol (**2d**) and the relatively sensitive ketal (**2e**) survived well. However, for propynoic ester (**2f**), a cascade alkynylation and Michael addition occurred to give the cyclic product **4f**. To explore the substrate scope further, we tested different aryl acetylenes. Phenyl acetylenes, equipped with electron-donating (**2h**, **2i**) or electron-withdrawing substituents (**2j–l**), were all coupled with **1aa** to give the corresponding alkynes in excellent yields. Various active groups, including NH_2 (**2h**), and halides (**2j–l**) were compatible, which can be used for further elaborations. Interestingly, phenyl acetylenes containing electron-donating groups only gave the desired alkynylated product. While bearing electron-withdrawing halides at the para-position, cascade Michael addition products were observed. When 4-Br phenyl acetylene (**2l**) was used, the Michael addition product was found as the main product. Moreover, 2-thienyl acetylene (**2m**) could be coupled with **1aa** to give **4m** in 87% yield.

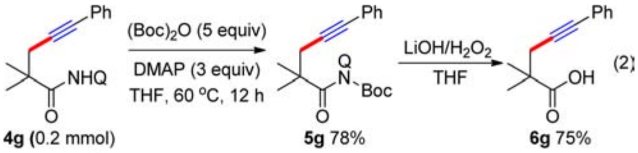
Scheme 4. Substrate Scope of Alkynyl Reagent

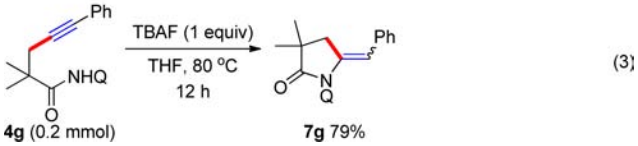


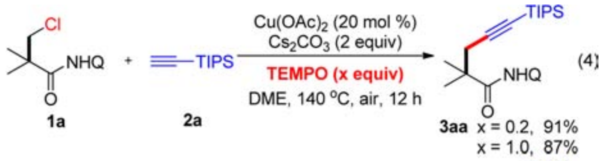
[a]Isolated yield of Michael addition product.

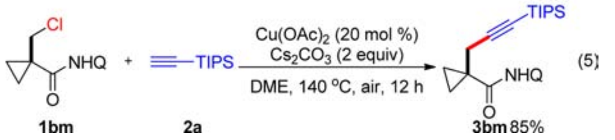
To highlight our method for synthetic application, we scaled this alkynylation to gram scale, and the product **4g** was isolated in 75% yield (eq 1). According to the reference,[3q] the amide group was first protected with a Boc group to obtain compound **5g**, which could be simply hydrolyzed to access β-alkynylated acid **6g** under the simple and mild conditions (eq 2). Finally, the products could be transformed into different substituted pyrrolinones under mild conditions, expending the potential applications of this development (eq 3).







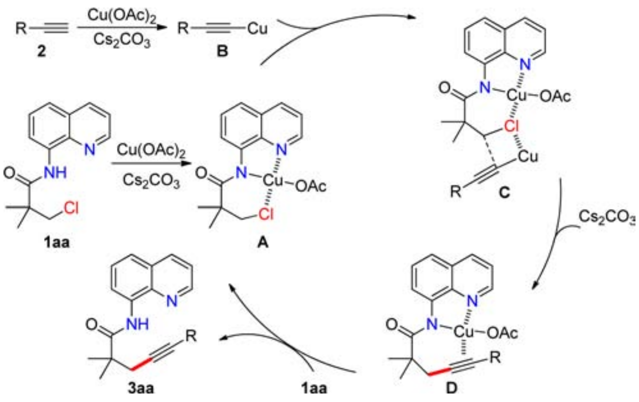




To unveil the reaction pathway, preliminary mechanistic studies were conducted. By adding different amounts of TEMPO as a radical scavenger, the reaction ran smoothly (eq 4). To gain further information on the mechanism, the cyclopropyl substrate (**1bm**) was also workable with the cyclopropyl group untouched (eq 5), since the cyclopropyl group was usually used as a radical clock. Moreover, as we observed, both tosylates and mesylates were workable in this transformation, which was generally difficult in generating a radical. This result ruled out the possible radical pathway.

Based on current results and preliminary mechanistic studies and previous reports,[19] we propose a plausible catalytic cycle (Scheme 5). $Cu(OAc)_2$ may serve as a Lewis acid to realize this reaction.

Scheme 5. Plausible Catalytic Cycle



Initially, under the assistance of Cs_2CO_3, the starting material **1aa** reacts with $Cu(OAc)_2$ to afford the intermediate **A**. Subsequently, the *in situ* generated copper alkynyl intermediate **B** interacts with species **A** to afford intermediate **C**, which can be converted to intermediate **D** through nucleophilic substitution. Finally, intermediate **D** releases the alkynylated product **3aa** via ligand exchange with **1aa** and regenerates **A** to fulfill the catalytic cycle.

In summary, we developed an efficient and concise protocol for direct alkynylation of aliphatic organohalides with terminal alkynes via Cu-catalysis by introducing a directing strategy. This method exhibits a broad substrate scope with respect to both terminal alkynes and alkyl halides, and even tosylates and mesylates. Indeed, this is the first successful protocol for alkynylation of alkyl chlorides in the absence of any additives. Such a coupling prefers alkyl chlorides over other halides/peusudohalides. Preliminary mechanistic studies ruled out a radical pathway. Our next challenge is to extend the reaction to more sterically hindered tertiary organohalides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00289.

Experimental details, spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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