

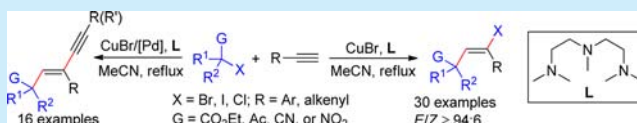
# Copper-Catalyzed *trans*-Carbohalogenation of Terminal Alkynes with Functionalized Tertiary Alkyl Halides

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**S** Supporting Information

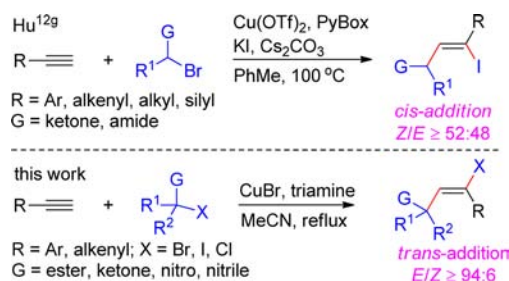
**ABSTRACT:** A highly *trans*-selective Cu-catalyzed carbohalogenation including carbobromination, carboiodination, and carbochlorination of terminal alkynes with activated tertiary alkyl halides has been realized, providing quaternary-carbon-containing alkenyl halides in good yields with excellent regio- and stereoselectivity. Meanwhile, an unprecedented alkyne *trans*-carboalkynylation process has been achieved via the tandem *trans*-carbohalogenation/Sonogashira coupling reaction, which furnishes highly functionalized 1,3-enynes in a single chemical transformation.



Alkenyl halides are important building blocks in organic chemistry because of the wide application in transition-metal-catalyzed cross-coupling reactions. Hence, the development of facile methods allowing rapid construction of these motifs has attracted immense interest. In particular, the catalytic addition of C–X (X = halogen) bonds to acetylenes, simultaneously forming C(sp<sup>2</sup>)–X and C(sp<sup>2</sup>)–C bonds in a single operation, is particularly attractive to synthetic chemists due to its high step- and atom-economy. In this respect, a range of alkyne carbohalogenation reactions have been developed, including chloroesterification,<sup>1</sup> chloroacetylation,<sup>2</sup> bromoalkynylation,<sup>3</sup> bromocyanation,<sup>4</sup> bromoarylation,<sup>5</sup> and haloallylation.<sup>6,7</sup> Despite these advances, there are still some significant challenges to be overcome. First, the aforementioned methods usually rely on the insertion of C–C triple bonds, therefore leading to *cis*-carbohalogenation products, and the *trans*-addition of C–X bonds to alkynes is still highly desirable.<sup>8</sup> Second, the previous reports are mainly restricted to the transformation of activated organohalides, such as C(sp<sup>2</sup>)–X and C(sp)<sup>2</sup>–X bonds, whereas the alkyne carbohalogenation with alkyl halides, especially the functionalized tertiary substrates, remains largely unexplored.

Recently, Cu-catalyzed atom-transfer radical addition (ATRA),<sup>9</sup> atom-transfer radical polymerization (ATRP),<sup>10</sup> and related processes<sup>11</sup> have stood out as appealing methods for addition of alkyl C–X bonds across C–C double bonds. In contrast, less progress has been made in the ATRA of alkyl halides onto alkynes,<sup>11c,d,12</sup> mainly because of the difficulty in controlling the regio- and stereoselectivity. Very recently, Hu<sup>12g</sup> reported an elegant Cu-catalyzed *cis*-selective carboiodination of terminal acetylenes with functionalized alkyl iodides, generated in situ by treating alkyl bromides with KI (Scheme 1). However, the reaction with a reversed stereoselectivity has not been achieved. Pursuing our recent interest in the *trans*-addition of alkynes,<sup>13</sup> we report here a Cu-catalyzed highly *trans*-selective carbohalogenation, including carbobromination, carboiodination, and carbochlorination, of terminal alkynes with tertiary alkyl halides activated by ester, ketone, nitrile, or nitro groups. This

## Scheme 1. Cu-Catalyzed Intermolecular ATRA of Functionalized Alkyl Halides to Alkynes

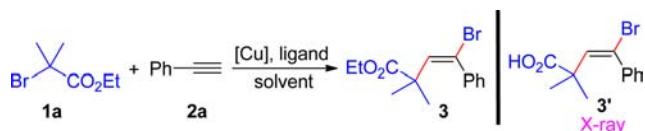


reaction produces highly functionalized products and may find broad utility given the prevalence of alkenyl halides as well as quaternary carbon centers in organic synthesis. Moreover, a rare *trans*-carboalkynylation<sup>14</sup> of C–C triple bonds has been realized via the tandem *trans*-carbohalogenation/Sonogashira coupling reaction, giving a facile entry to polysubstituted 1,3-enynes in a single synthetic step.

At first, the reaction was carried out with commercially available ethyl 2-bromo-2-methylpropanoate (**1a**) and phenylacetylene (**2a**) in MeCN with 30 mol % of 1,10-phenanthroline (**L1**) as the ligand (Table 1). Using 10 mol % of CuBr as the catalyst, alkenyl bromide **3** was obtained in 72% yield as a 94:6 mixture of *E/Z* isomers, and no improvement was observed by replacing CuBr with either CuI or CuCl (entries 1–3). In contrast, CuCl<sub>2</sub> and CuBr<sub>2</sub> were not effective at all (entries 4 and 5). Meanwhile, the ligand has a significant influence on the reaction outcome. Triamine ligand **L4** was found to be the most suitable choice, giving **3** in 85% yield with >97% *E*-selectivity, although tetraamine **L5** also worked well for this transformation (entries 8 and 9).<sup>9c,e</sup> The regio- and stereochemistry of this reaction was determined by NOE measurements and further

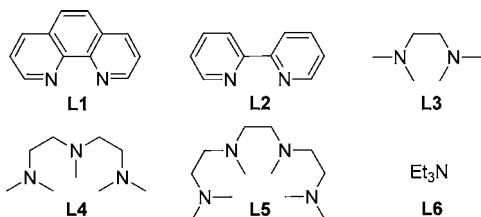
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Table 1. Optimization of the Reaction Conditions<sup>a</sup>


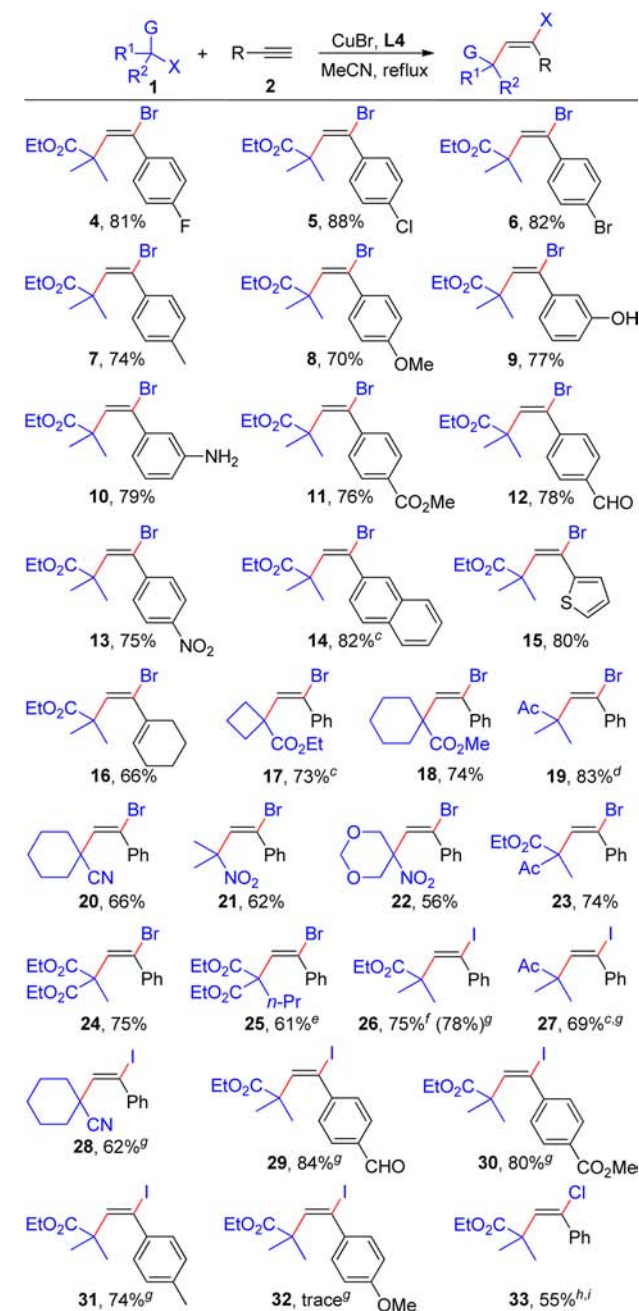
entry	[Cu]	ligand	solvent	yield <sup>b</sup> (%)	E/Z <sup>c</sup>
1	CuBr	L1	MeCN	72	94:6
2	CuI	L1	MeCN	64	91:9
3	CuCl	L1	MeCN	65	93:7
4	CuCl <sub>2</sub>	L1	MeCN	nr	/
5	CuBr <sub>2</sub>	L1	MeCN	nr	/
6	CuBr	L2	MeCN	8	28:72
7	CuBr	L3	MeCN	48	48:52
8	CuBr	L4	MeCN	85	>97:3
9	CuBr	L5	MeCN	80	>97:3
10	CuBr	L6	MeCN	nr	/
11	CuBr	L4	THF	83	>97:3
12	CuBr	L4	toluene	73	94:6
13	CuBr	L4	DMF	61	95:5
14	CuBr	L4	DMSO	80	96:4
15 <sup>d</sup>	CuBr	L4	MeCN	76	>97:3
16 <sup>e</sup>	CuBr	L4	MeCN	45	>98:2

<sup>a</sup>Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), [Cu] (10 mol %), ligand (30 mol %), solvent (1 mL), under N<sub>2</sub>, reflux, 10 h. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by GC. <sup>d</sup>**1a** (0.30 mmol) and **2a** (0.25 mmol) were used. <sup>e</sup>The reaction was run at room temperature for 16 h. nr = no reaction.



confirmed by X-ray diffraction analysis of **3'**,<sup>15</sup> a parent acid of **3**. The reaction proceeded efficiently in THF, whereas using toluene, DMF, or DMSO as the solvent slightly reduced the stereoselectivity (entries 11–14). Therefore, the optimum reaction conditions for the *trans*-addition of tertiary alkyl halides to terminal alkynes comprised 10 mol % of CuBr, 30 mol % of **L4**, and MeCN as the solvent at reflux for 10 h. It is worth mentioning that the stereoselectivity of **3** determined at 22%, 50%, and 71% conversion was uniformly >97% *E*, indicating that the selectivity is kinetically controlled.

Subsequently, we applied the optimized reaction conditions to a variety of acetylenes (Scheme 2). The *trans*-carbromination process occurred smoothly with halogen-containing alkynes, thus providing possibilities for further synthetic manipulations (**4**–**6**). Satisfactory yields as well as excellent regio- and stereoselectivity were observed regardless of the electronic nature of substituents on the aryl ring of alkynes, including Me, OMe, CHO, and NO<sub>2</sub> groups (**7**, **8**, **12**, and **13**). The introduction of free alcohol and amine had no detrimental effect on the reaction (**9** and **10**). Furthermore, the reaction functioned well with thiophene, delivering **15** in 80% yield. 1-Ethynylcyclohexene (**2n**), an alkenyl alkyne, was also a competent coupling partner for this transformation (**16**). Conversely, no reaction occurred when aliphatic terminal alkynes or internal alkynes were employed as the substrates.

Scheme 2. Scope of *trans*-Carbohalogenation of Alkynes<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1** (0.25 mmol), **2** (0.30 mmol), CuBr (10 mol %), **L4** (30 mol %), MeCN (1 mL), under N<sub>2</sub>, reflux, 10 h. Unless otherwise noted, the desired products were obtained with >97% *E*-selectivity, and no regioisomers were detected. <sup>b</sup>Isolated yield. <sup>c</sup>E/Z = 95:5. <sup>d</sup>E/Z = 94:6. <sup>e</sup>**L4** (60 mol %) was used. <sup>f</sup>Ethyl 2-iodo-2-methylpropanoate (**1k**) was used instead of **1a**. <sup>g</sup>NaI (0.5 mmol) was added to the standard conditions. <sup>h</sup>Ethyl 2-chloro-2-methylpropanoate (**1l**) was employed instead of **1a**. <sup>i</sup>CuCl was used instead of CuBr.

Meanwhile, various functionalized tertiary alkyl bromides proved to be effective carbohalogenation reagents. For instance,  $\alpha$ -bromocyclic esters **1b** and **1c** coupled with **2a** to produce **17** and **18** in satisfactory yields. The reaction was also applicable to  $\alpha$ -bromoketone and  $\alpha$ -bromonitrile (**19** and **20**). Notably, tertiary alkyl bromides bearing a nitro group added efficiently to **2a** and furnished the corresponding products in good yields (**21** and **22**). The transformation of 2-bromo-2-methylmalonate (**1i**)

formed **24** in 75% yield, while a low conversion (<20%) was observed in the case of 2-bromo-2-propylmalonate (**1j**), presumably as a result of increased steric hindrance of **1j**. Pleasingly, after some trials, increasing the amount of **L4** (60 mol %) considerably accelerated the addition and gave **25** in a reasonable yield. On the contrary, functionalized secondary and primary alkyl halides only gave the desired products in low yields under the reaction conditions.

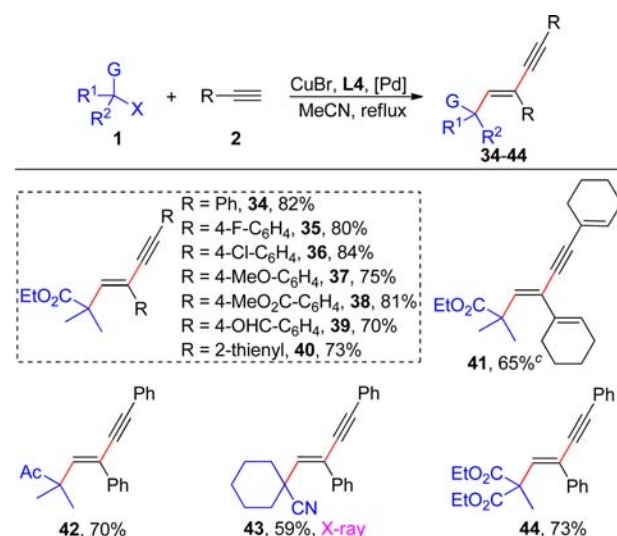
An important extension of this protocol was achieved with the use of ethyl 2-iodo-2-methylpropanoate (**1k**) instead of **1a**, leading to the production of alkenyl iodide **26** in 75% yield. In contrast, by simply adding 2 equiv of NaI to the standard conditions, the reaction between **1a** and **2a** produced **26** in 78% yield, thus allowing a more simple and practical procedure to perform *trans*-carboiodination of alkynes. Indeed, under the modified reaction conditions (with 2 equiv of NaI), alkyl bromides with ester, ketone, and nitrile substituents were well-suited substrates for this *trans*-carboiodination reaction (**26**–**28**). Alkynes having electron-withdrawing groups were transferred in particularly good yields, while *p*-methoxyphenylacetylene (**2f**), an electron-rich substrate, only afforded traces of **32** under identical conditions (**29**–**32**), implying that the electronic effect of alkynes has an obvious impact on the *trans*-carboiodination reaction. The *trans*-carbochlorination of terminal alkynes was also investigated. The combination of tertiary alkyl bromides with chloride sources such as LiCl or NaCl resulted in no formation of alkenyl chlorides. Gratifyingly, with ethyl 2-chloro-2-methylpropanoate (**1l**) acting as the carbohalogenation reagent, vinylic chloride **33** was synthesized successfully in a reasonable yield.

Next, the synthetic usefulness of this *trans*-carbohalogenation reaction was investigated. It is well-known that 1,3-enynes are versatile scaffolds in natural product synthesis and material science. As such, it is of great importance to explore simple and efficient methods for the synthesis of 1,3-enynes.<sup>16</sup> To this end, **1a** was treated with 2.2 equiv of **2a**, 10 mol % of CuBr, 1.5 equiv of **L4**, and 2 mol % of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> in MeCN at reflux for 10 h. Consequently, 1,3-enyne **34** was obtained in 82% yield. Meaningfully, it represents the first *trans*-carboalkynylation of C–C triple bonds. Next, the scope of this *trans*-carboalkynylation reaction was briefly investigated (Scheme 3). To our delight, a wide selection of aryl acetylenes displaying F, Cl, OMe, CO<sub>2</sub>Me, and CHO substituents were excellent substrates which provided stereodefined 1,3-enynes in high yields (**34**–**39**). Alkenyl alkyne **2n** also worked well for this reaction (**41**). The *trans*-addition selectivity was confirmed by the X-ray crystallographic analysis of **43**.<sup>15</sup>

Remarkably, the three-component coupling of **1a**, **2a**, and 1-octyne (**2o**) also occurred uneventfully to afford conjugated enyne **45** in reasonable yield. Likewise, triethylsilylacetylene (**2p**) and THP-protected propargyl alcohol (**2q**) were also amenable to this reaction, which leaves great room for later transformation. Moreover, by slowly adding **2a** to the reaction mixture containing **1a** and **2j**, polyfunctional 1,3-enyne **48** was isolated in 67% yield, while slow addition of **2j** to a mixture of **1a** and **2a** in the presence of Cu/Pd catalyst gave rise to **49** in 53% yield, thus significantly enhancing the scope and utility of this *trans*-carboalkynylation reaction (Scheme 4).

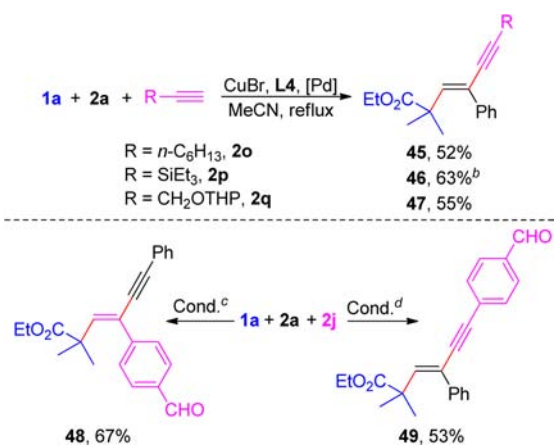
In summary, we have realized an unusual highly *trans*-selective Cu-catalyzed carbohalogenation, including carbobromination, carboiodination, and carbochlorination, of terminal alkynes for the first time, providing quaternary-carbon-containing alkenyl halides in good yields with excellent regio- and stereoselectivity.

### Scheme 3. Tandem Alkyne *trans*-Carbohalogenation/Sonogashira Coupling Reaction<sup>a,b</sup>



<sup>a</sup>Reaction conditions: **1** (0.25 mmol), **2** (0.55 mmol), CuBr (10 mol %), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2 mol %), **L4** (0.375 mmol), MeCN (1 mL), under N<sub>2</sub>, reflux, 10 h. <sup>b</sup>Isolated yield. <sup>c</sup>Pd(PPh<sub>3</sub>)<sub>4</sub> was used instead of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>.

### Scheme 4. Three-Component Coupling<sup>a</sup>



<sup>a</sup>Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), **2o** (0.75 mmol), CuBr (10 mol %), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2 mol %), **L4** (0.375 mmol), MeCN, under N<sub>2</sub>, reflux, 10 h; yields of isolated products were used. <sup>b</sup>Pd(PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> was used instead of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>. <sup>c</sup>**2a** (0.30 mmol) and **2j** (0.25 mmol) were used. <sup>d</sup>**2a** (0.25 mmol) and **2j** (0.30 mmol) were used. THP = 2-tetrahydropyranyl.

Meanwhile, a *trans*-carboalkynylation of C–C triple bonds has been developed as well via the tandem *trans*-carbohalogenation/Sonogashira coupling reaction, in which highly functionalized 1,3-enynes can be synthesized in a single synthetic step. Further investigations on the reaction mechanism<sup>17</sup> and synthetic application of this protocol are currently underway.

### ■ ASSOCIATED CONTENT

#### Supporting Information

Detailed experimental procedures, characterization data for products **3**–**49**, as well as the crystallographic data of **3'** and **43**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

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## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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