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Copper-Catalyzed Chloroamination of Alkynes: Highly Regio- and Stereoselective Synthesis of (*E*)-β-Chloro-Enesulfonamides

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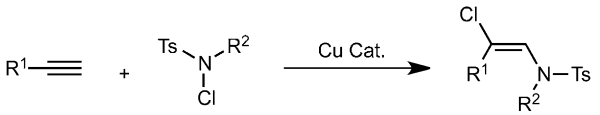
Abstract: An efficient copper catalysis system for the chloroamination of alkynes with chlorosulfonamide at room temperature is described, providing a highly regio- and stereoselective procedure for the synthesis of (*E*)-β-chloro-enesulfonamides in moderate to good yields.

Keywords: addition reaction; alkynes; chloroamination; copper; enesulfonamides

The transition metal-catalyzed addition reactions of X–Y-type substrates to an alkyne are very useful and attractive strategies in organic systhesis because a C–X bond and a C–Y bond are formed simultaneously from simple alkynes with high atom-economy. Among these transformations, the carbohalogenation reactions of alkynes including the addition of acid chlorides,[1] allyl halides,[2,3] haloalkynes[4] and cyanogen bromide[5] are of continued interest due to the facile access to vinyl-halogen and vinyl-carbon bonds, both of which can be used to construct complex structures. However, the application of heteroatom-halogen bonds in the addition reactions of alkynes is very limited,[6] and the addition reactions to alkynes with nitrogen-halogen bonds still remains a challenge.[7]

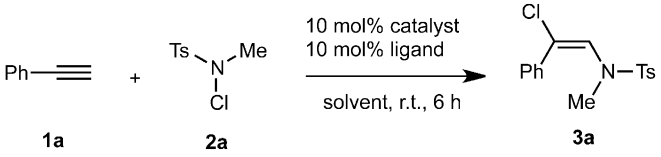
Enesulfonamides are valuable synthetic intermediates in asymmetric addition reactions and can also serve as pronucleophiles in metal-catalyzed reactions.[8] In general, enesulfonamides are synthesized from the corresponding ketones *via* the *N*-sulfonylimine intermediates.[8a] Herein, we report a new copper catalysis system for the chloroamination of alkynes with chlorosulfonamides at room temperature, providing an efficient route to (*E*)-β-chloro-enesulfonamides in a highly regio- and stereoselective fashion (Scheme 1). Although the utilization of chloroamides and chloroamines has been disclosed as electrophilic nitrogen sources in amination reactions,[9] they have been scarcely reported in addition reactions.



Scheme 1. Copper-catalyzed chloroamination of alkynes.

The initial development and optimization of the reaction was performed with *N*-chloro-*N*,4-dimethylbenzenesulfonamide (**2a)** (1.0 mmol) and phenylacetylene (**1a**) (0.5 mmol). We were pleased to observe that the addition product **3a** was obtained in moderate yield when a $Cu(acac)_2$ catalyst was used in the presence of a 2,2′-bipyridine (bpy) ligand in CH_2Cl_2 at room temperature (Table 1, entry 1). It should be noted that only (*E*)-adduct **3a** was obtained, whose configuration was confirmed by a single-crystal X-ray diffraction study (Figure 1).[10] After extensive screening of solvents, CH_2Cl_2 was a better reaction medium than 1,2-dichloroethane and toluene, while other solvents such as DMF, THF and dioxane were ineffective (entries 1–6). We further investigated the reaction parameters and found that nitrogen-based ligands exerted an important effect on the reaction outcome. For example, 1,10-phenanthroline (phen) allowed an improved yield of 75% over 6 h compared to bpy, and ultimately the addition product **3a** could be obtained in 83% isolated yield with 6,6′-dimethyl-1,10-phenanthroline (dmphen) (entries 7 and 8). However, the use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*′-dimethylethylenediamine (DMEDA) and benzotriazole (BTA) gave no positive effects (entries 9–11). Other copper species were also examined, the use of $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$ and CuI as the catalyst precursors was less effective (entries 12–14). Lowering

Table 1. Optimization of the reaction conditions for the chloroamination of alkynes.[a]

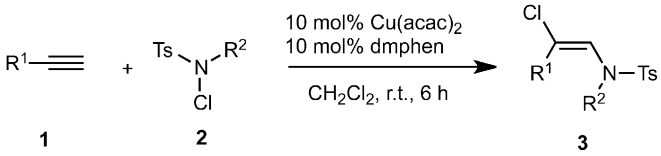


1a 2a 3a

Entry	Catalyst	Ligand	Solvent	Yield[b] [%]
1	$Cu(acac)_2$	bpy	DCM	40
2	$Cu(acac)_2$	bpy	DCE	32
3	$Cu(acac)_2$	bpy	toluene	14
4	$Cu(acac)_2$	bpy	DMF	0
5	$Cu(acac)_2$	bpy	THF	0
6	$Cu(acac)_2$	bpy	dioxane	0
7	$Cu(acac)_2$	phen	DCM	75
8	**$Cu(acac)_2$**	**dmphen**	**DCM**	**83**
9	$Cu(acac)_2$	TMEDA	DCM	26
10	$Cu(acac)_2$	DMEDA	DCM	18
11	$Cu(acac)_2$	BTA	DCM	42
12	$CuCl_2$	dmphen	DCM	45
13	$CuBr_2$	dmphen	DCM	51
14	$Cu(OAc)_2$	dmphen	DCM	32
15	CuI	dmphen	DCM	18
16[c]	$Cu(acac)_2$	dmphen	DCM	71
17	$Cu(acac)_2$	–	DCM	0
18	–	dmphen	DCM	0

[a] *Reaction conditions:* **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (0.05 mmol), ligand (0.05 mmol), in solvent (2 mL) was stirred at room temperature for 6 h under an argon atmosphere.
[b] Yields of isolated product.
[c] 0.75 mmol **2a** was used. Bpy = 2,2′-bipyridine, Phen = 1,10-phenanthroline, dmphen = 6,6′-dimethyl-1,10-phenanthroline, BTA = benzotriazole.

Table 2. Copper-catalyzed chloroamination of alkynes.[a]



1 2 3

Entry	1	R^1	2	R^2	Yield[b] [%]
1	**1a**	Ph	**2a**	Me	83 (**3a**)
2	**1b**	4-MeC_6H_4	**2a**	Me	85 (**3b**)
3	**1c**	4-$MeOC_6H_4$	**2a**	Me	84 (**3c**)
4	**1d**	4-FC_6H_4	**2a**	Me	82 (**3d**)
5	**1e**	3-FC_6H_4	**2a**	Me	80 (**3e**)
6	**1f**	3-ClC_6H_4	**2a**	Me	77 (**3f**)
7[c]	**1g**	4-$CF_3C_6H_4$	**2a**	Me	74 (**3g**)
8	**1h**	1-cyclohexenyl	**2a**	Me	70 (**3h**)
9	**1i**	6-MeO-2-naphthyl	**2a**	Me	68 (**3i**)
10	**1a**	Ph	**2b**	Et	82 (**3j**)
11	**1a**	Ph	**2c**	*n*-Pr	76 (**3k**)
12	**1a**	Ph	**2d**	*n*-Bu	73 (**3l**)
13[c]	**1a**	Ph	**2e**	*n*-Hept	63 (**3m**)
14[d]	**1a**	Ph	**2f**	*i*-Pr	15 (**3n**)
15	**1c**	4-MeC_6H_4	**2d**	*n*-Bu	77 (**3o**)
16	**1h**	1-cyclohexenyl	**2c**	*n*-Pr	64 (**3p**)
17	**1d**	4-FC_6H_4	**2b**	Et	80 (**3q**)
18[c]	**1f**	4-$CF_3C_6H_4$	**2b**	Et	70 (**3r**)
19	**1a**	Ph	**2g**	Ph	0

[a] *Reaction conditions:* **1** (0.5 mmol), **2** (1.0 mmol), $Cu(acac)_2$ (10 mol%), dmphen (10 mol%) in dry CH_2Cl_2 (2 mL) was stirred at room temperature for 6 h under an argon atmosphere.
[b] Yields of isolated product.
[c] Reaction time: 12 h.
[d] Reaction time: 24 h.

the amount of **2a** to 1.5 equivalents resulted in lower yield (entry 16).[11] The control experiments indicated that no reaction took place in the absence of the catalysts or the ligands (entries 17 and 18). Thus, the reaction efficiently proceeded when 10 mol% of $Cu(acac)_2$ was used in combination with dmphen (10 mol%) in CH_2Cl_2 at room temperature.

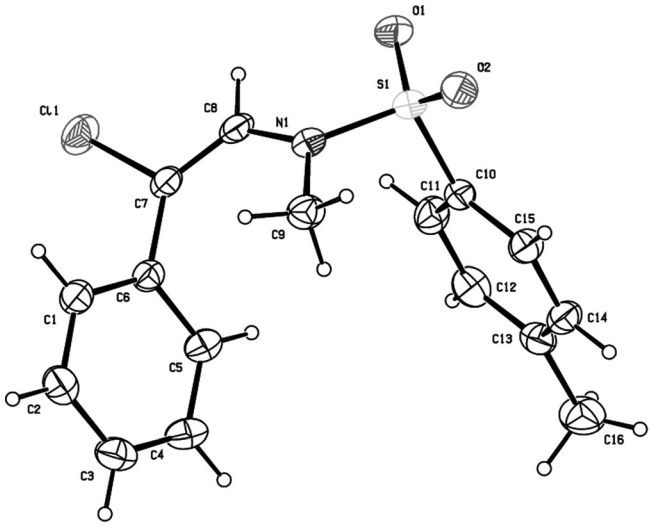
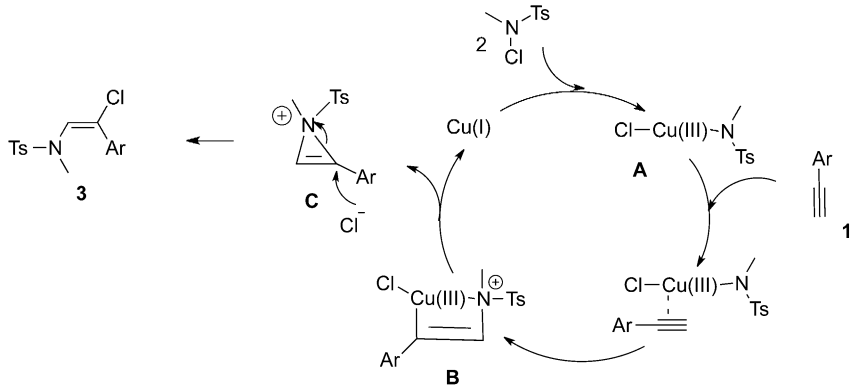


Figure 1. The crystal structure of **3a**.

Under the optimized conditions, the substrate scope toward this chloroamination reaction was further investigated. The results are summarized in Table 2. We examined the substrate scope of alkynes. Arylacetylenes having a range of aromatic rings underwent chloroamination of the alkyne moieties, affording the corresponding addition products in moderate to good yields with high regio- and stereoselectivity (entries 1–7). Phenylacetylenes bearing substituents with diverse electronic properties such as methyl, methoxy, chloro, fluoro and the trifluoromethyl group all showed the better reactivity. In addition, terminal alkynes such as 1-cyclohexenylacetylene (**1h**) and 2-ethynyl-6-methoxynaphthalene (**1i**), all smoothly reacted with **2a** to afford the desired products in 70% and 68% yields, respectively (entries 8 and 9). To further ascertain the scope of this methodology, *N*-substituted chlorosulfonamides were also investigated. *N*-



Scheme 2. Proposed mechanism for the addition reaction.

Alkyl-chlorosulfonamides showed the better reactivity and reacted with various terminal arylacetylenes to furnish the corresponding addition products in moderate to good yields (entries 10–13, 15–18). However, bulky chlorosulfonamides such as *N*-chloro-*N*-isopropyl-4-methylbenzenesulfonamide (**2f)** resulted in a low yield (entry 14). *N*-Phenyl-chlorosulfonamide did not undergo the addition reaction with phenylacetylene (**1a)** under these conditions, which may be due to steric hindrance (entry 19). Finally, all attempts to achieve chloroamination of the internal alkynes and alkylalkynes with **2a** under similar conditions have been unsuccessful.[12]

Although the precise mechanism of the addition reaction remains unclear at this moment, we assume that the reaction may involve the following key steps (Scheme 2). (i) The oxidative addition of the chlorosulfonamide to the Cu(I) would initially generate a Cu(III) intermediate **A**.[9a] (ii) The Cu(III) intermediate could coordinate with alkynes followed by the metal-insertion into the terminal alkynes to form a vinylic copper intermediate **B**. (iii) The reductive elimination of **B**, would deliver the intermediate **C** and reform the Cu(I) catalyst. Finally, the ring-opening of the intermediate **C** would furnish the *anti* addition product **3** *via* the attack of chlorine anion to the α-carbon of the aryl groups, the position of which is favorable for the formation of more stable carbenium cations.

In summary, we have developed a copper-catalyzed chloroamination of alkynes at room temperature. Chlorosulfonamides were employed as a novel addition partner to afford a series of (*E*)-β-chloro-enesulfonamides with high regio- and stereoselectivity. Further investigations in our laboratory will focus on expanding the scope of this reaction to include *N*-chloroamide and aliphatic alkynes as well as studying the mechanism of this transformation.

Experimental Section

Typical Procedure

Chlorosulfonamide **2** (1.0 mmol), $Cu(acac)_2$ (0.05 mmol) and dmphen (0.05 mmol) were added to an oven-dried Schlenk tube. Then the tube was evacuated and refilled with nitrogen, and alkyne **1** (0.5 mmol) in CH_2Cl_2 (2 mL) was added. The resulting mixture was stirred for 6 h at room temperature, quenched with 2 mL saturated aqueous sodium hyposulfite solution and extracted with ethyl acetate (3×20 mL). The organic phases were combined and dried over sodium sulfate. The mixture was concentrated under vacuum. Purification by silica gel column chromatography with hexane/ethyl acetate (v/v = 10/1) as eluent to afford the corresponding product **3**.

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[10] For the details of the X-ray crystal analysis of **3a**, CCDC 818988 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[11] The excess of *N*-chlorosulfonamide to alkynes was to improve the conversion of the reaction. The side products detected were mainly dechlorinated sulfonamides. For a similar report, see ref.[9c]

[12] The addition reaction with Chloramine-T or *N*-dialkylchloroamines such as *N,N*-dibutylchloroamine was unsuccessful.

