Copper-Catalyzed Regioselective Chloroamination of Alkenes with Chlorotrimethylsilane and *N*-Fluorobenzenesulfonimide under Microwave-Assisted Conditions

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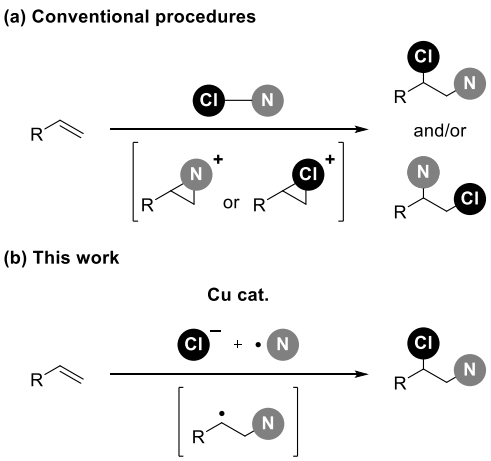
A copper-catalyzed chloroamination of alkenes with chlorotrimethylsilane and *N*-fluorobenzenesulfonimide has been developed. The reactions were complete within 1 h at 120 °C by means of microwave heating. The present chloroamination proceeds with a perfect regioselectivity and is compatible with various functional groups. The preliminary mechanistic investigation revealed that the reaction involves a radical process. The utility of the present method was demonstrated by scalable, operationally simple and safe system.

Keywords: Chloroamination, Copper catalyst, Alkenes

2-Chloroalkylamine derivatives are important scaffolds in synthetic organic chemistry, which can be found in nature as bioactive secondary metabolites.[1] In addition, some compounds of non-natural origin have also shown significant biological activities.[2] Moreover, such chlorinated alkaloids are regarded as versatile intermediates in organic synthesis since the chloro moiety can serve as a reactive functional group in substitution and cross-coupling reactions. As their ideal and straightforward synthetic method, vicinal chloroamination of alkenes has been known, in which both chloro and amino functionalities can be installed simultaneously.[3] *N*-Chloroamides having a Cl–N bond are well utilized for chloroamination of alkenes. The reactions are proposed to proceed through the activation of an alkene to form the aziridinium or chloronium intermediate, followed by nucleophilic attack of a counter anion (Scheme 1a). However, the substrate scope was strictly limited to the activated alkenes in most cases. Additionally, some reactions suffer from the control of the regioselectivity. Furthermore, the highly reactive *N*-chloroamides often cause the undesired side reactions.

Recently, *N*-fluorobenzenesulfonimide (NFSI) has been widely utilized as a radical amination reagent, which can provide a nitrogen-centered radical generated from single-electron reduction by transition-metal catalysts.[4] It should be noted that a sulfonimide moiety can be readily removed.[5] Therefore, NFSI can be considered as a formal amination reagent. Especially, NFSI has realized a variety of copper-catalyzed intermolecular vicinal difunctionalization of alkenes, such as aminoarylation,[6] aminocyanation,[7] aminoazidation,[8] diamination,[7a,9] aminofluorination,[10] aminothiolation,[11] aminooxygenation.[12] Our research group also focused on highly selective catalytic radical difunctionalization.[13] Given our interest in this chemistry, we paid attention to the corresponding chloroamination of alkenes with chlorosilanes as chlorination reagents by applying the copper-catalyzed radical amination strategy with NFSI. Herein, we report microwave-assisted copper-catalyzed regioselective chloroamination of alkenes with chlorotrimethylsilane and NFSI through a radical process (Scheme 1b).[14,15]

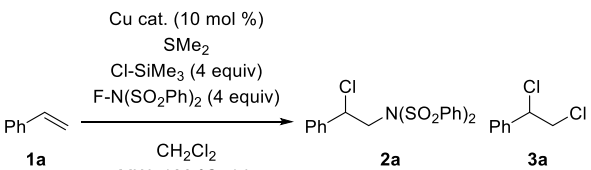


Scheme 1. Chloroamination of alkenes.

Our optimization studies commenced with the reaction of styrene (**1a**) with chlorotrimethylsilane and NFSI as a model reaction. We tested several copper catalysts in dichloromethane under microwave irradiation (Table 1). While the reaction did not proceed in the absence of a catalyst (entry 1), the desired chloroamination product **2a** was obtained in 46% yield in the presence of a catalytic amount of CuCl (entry 2). The reaction proceeded with a perfect regioselectivity, not giving other regioisomer. The structure of **2a** was unambiguously determined by X-ray diffraction analysis.[16] Instead, dichlorinated byproduct **3a** was obtained in 8% yield, in which vicinal dichlorination of **2a** with silyl chloride occurred under oxidative conditions by NFSI.[17] Among other copper(I) catalysts screened (entries 3–6), CuBr•SMe_2 was found to be the best (entry 6). In addition, copper(II) catalysts also showed the catalytic activity, except for $Cu(OTf)_2$ (entries 7–11). When $Cu(acac)_2$ (acac = acetylacetonate) was employed as a catalyst, **2a** was obtained in 78% yield (entry 11). The addition of dimethyl sulfide might help to form the active monomeric copper species (entries 3 and 6). Indeed, the combination of CuBr with dimethyl sulfide provided the comparable yield (entries 6 and 12). However, an excess amount of dimethyl sulfide decreased the product yield (entry 13). The further precise screening of the reaction

conditions revealed that **2a** was obtained in 89% isolated yield when $Cu(acac)_2$ catalyst was used with 5 mol % of dimethyl sulfide (entries 14 and 15).[18] Even when the reaction was conducted for 20 min, **2a** was obtained in 95% yield (entry 16). It should be noted that nearly equal amount of **2a** was obtained by heating in an oil bath (entry 17). The present microwave-assisted copper-catalyzed chloroamination can be scalable in practical synthesis. The desired product **2a** (1.3 g) was obtained in 89% yield by simply performing the reaction on 10-fold scale (4 mmol) (entry 18).

Table 1. Optimization for regioselective chloroamination of styrene (**1a**) with chlorotrimethylsilane and *N*-fluorobenzenesulfonimide[a]

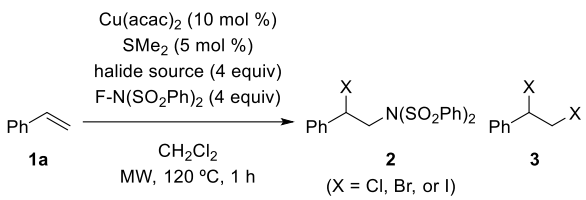


Entry	Cu cat.	SMe_2 (mol %)	Yield (%)[b]	
			2a	**3a**
1	none	0	0	0
2	CuCl	0	46	8
3	CuBr	0	57	11
4	CuI	0	30	9
5	CuOAc	0	27	25
6	CuBr•SMe_2	0	84	13
7	$CuCl_2$	0	20	20
8	$CuBr_2$	0	66	10
9	$Cu(OAc)_2$	0	18	19
10	$Cu(OTf)_2$	0	0	0
11	$Cu(acac)_2$	0	78	8
12	CuBr	10	82	17
13	CuBr•SMe_2	10	48	17
14	$Cu(acac)_2$	10	90	10
15	$Cu(acac)_2$	5	100 (89)	0
16[c]	$Cu(acac)_2$	5	95	0
17[d]	$Cu(acac)_2$	5	93 (85)	0
18[e]	$Cu(acac)_2$	5	(89)	0

[a]Reactions were carried out with **1a** (0.4 mmol), chlorotrimethylsilane (1.6 mmol), *N*-fluorobenzenesulfonimide (1.6 mmol), Cu cat. (0.04 mmol), and SMe_2 in CH_2Cl_2 (2 mL) under microwave irradiation at 120 °C for 1 h. [b]^{1}H NMR yield. Isolated yields are given in parentheses. [c]Performed for 20 min. [d]Performed by conventional heating in an oil bath. [e]Performed on 4 mmol scale.

We next explored the halogenation reagents in the haloamination of **1a** (Table 2). In addition to chlorotrimethylsilane, other silyl chlorides, such as chlorotriethylsilane, chlorotriphenylsilane, and dichlorodimethylsilane, can also be applicable to the reaction, providing **2a** in comparable yields (entries 1–4). On the other hand, the reaction with a sterically hindered chlorotri(*i*-propyl)silane gave a modest yield, which might suppress the transmetalation step (entry 5). Instead of silyl chlorides, inorganic chloride salts were examined. Although lithium chloride gave an acceptable yield (entry 6), sodium, potassium, and cesium salts gave poor results probably due to their low solubility in dichloromethane (entries 7–9). The reactions with bromotrimethylsilane and iodotrimethylsilane gave complex mixtures (entries 10 and 11).

Table 2. Screening of halide sources[a]



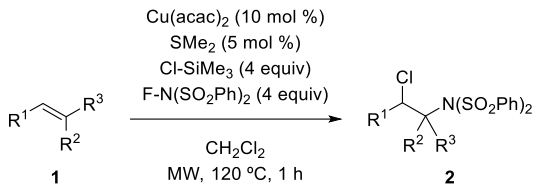
Entry	Halide source	Yield (%)[b]	
		2	**3**
1	Cl-$SiMe_3$	100 (89)	0
2	Cl-$SiEt_3$	87	11
3	Cl-$SiPh_3$	84	0
4	Cl-$SiMe_2Cl$	76	14
5	Cl-Si^iPr_3	7	0
6	LiCl	81	12
7	NaCl	11	0
8	KCl	8	0
9	CsCl	5	0
10	Br-$SiMe_3$	0	0
11	I-$SiMe_3$	0	0

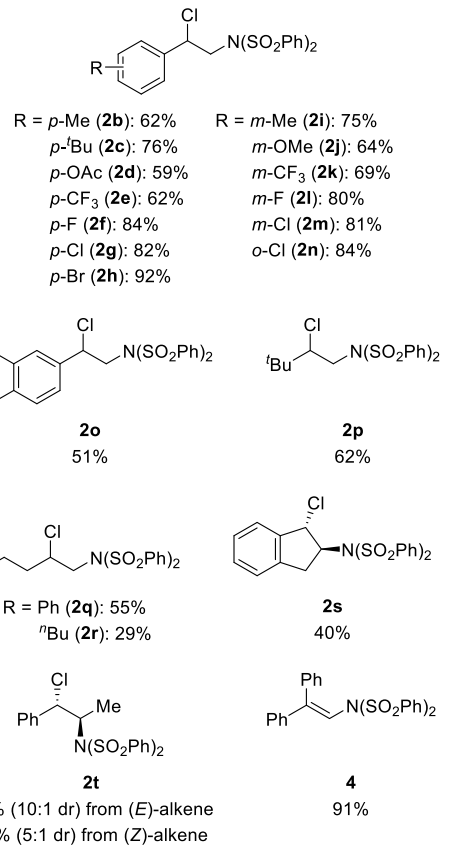
[a]Reactions were carried out with **1a** (0.4 mmol), halide source (1.6 mmol), *N*-fluorobenzenesulfonimide (1.6 mmol), $Cu(acac)_2$ (0.04 mmol), and SMe_2 (0.02 mmol) in CH_2Cl_2 (2 mL) under microwave irradiation at 120 °C for 1 h. [b]^{1}H NMR yield. An isolated yield is given in parentheses.

The present copper-catalyzed chloroamination was found to be applicable to various alkenes (Table 3). The reactions of styrene derivatives bearing electron-donating and electron-deficient functional groups in either *para*, *meta*, or *ortho* position proceeded with a perfect regioselectivity to provide the corresponding chloroamination adducts **2b**–**2o** in moderate to good yields. Each reaction was complete within 1 h regardless of the electronic and steric properties of styrenes employed. It is noteworthy that various functionalities were compatible even at a high reaction temperature. In addition to aromatic alkenes, aliphatic alkenes participated in the reaction, affording the products **2p**–**2r** in moderate yields. Moreover, the regioselective chloroamination proceeded even with unsymmetrical internal alkenes. The reactions of indene furnished the corresponding adducts **2s** with a high diastereoselectivitiy.

Both reactions of (*E*)- and (*Z*)-*β*-methylstyrene gave the same diastereomer **2t**, which can be rationalized by a 1,3-allylic strain model.[19] Furthermore, the reaction of 1,1-diphenylethene gave the aminated product **4** in 91% yield instead of the expected chloroamination adduct.

Table 3. Copper-catalyzed chloroamination of alkenes **1** with chlorotrimethylsilane and *N*-fluorobenzenesulfonimide[a]

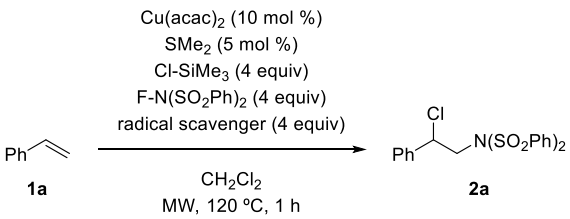




[a]Reactions were carried out with alkenes **1** (0.4 mmol), chlorotrimethylsilane (1.6 mmol), *N*-fluorobenzenesulfonimide (1.6 mmol), $Cu(acac)_2$ (0.04 mmol), and SMe_2 (0.02 mmol) in CH_2Cl_2 (2 mL) under microwave irradiation at 120 °C for 1 h.

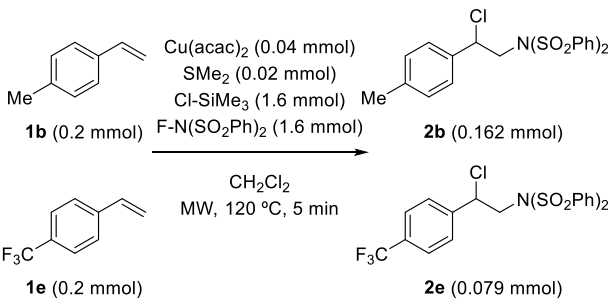
To gain mechanistic insights into the chloroamination reaction, some control experiments were performed (Scheme 2). The addition of a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl), or 1,1-diphenylethene, suppressed the formation of product **2a** (Scheme 2a). The radical adduct **4** was obtained in the reaction with 1,1-diphenylethene. These results suggest that the present reaction involves a nitrogen-centered radical generated from NFSI.[20] In addition, competition experiment was conducted with an equimolecular mixture of styrenes **1b** and **1e** to elucidate the electronic preference (Scheme 2b). As a result, the formation of **2b** was preferred to **2e**, indicating that the reaction can be categorized to the electrophilic radical addition. Moreover, the possible formation of *N*-chlorobenzenesulfonimide from chlorotrimethylsilane and NFSI was investigated by ^1H and $^{19}F\{^1H\}$ NMR spectra. However, no new signals appeared and their original signals remained even upon heating at 140 °C for 1 h. Furthermore, the reaction of **1a** with *N*-chlorobenzenesulfonimide instead of chlorotrimethylsilane and NFSI gave no formation of **2a**, indicating that the intermediacy of *N*-chlorobenzenesulfonimide is unlikely (Scheme 2c).

(a) Reaction in the presence of radical scavengers

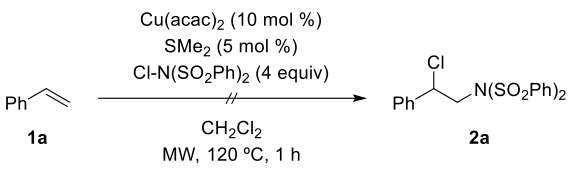


entry	radical scavenger	yield (%)
1	none	89
2	TEMPO	0
3	1,1-diphenylethene	33

(b) Competition Experiment



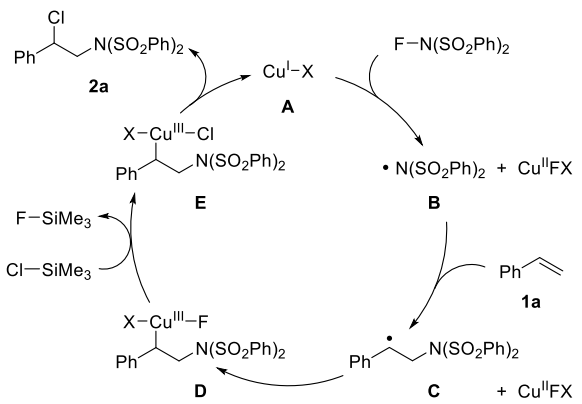
(c) Reaction with *N*-chlorobenzenesulfonimide



Scheme 2. Control experiments.

Based on the above results and the literature precedents,[4–12] we propose the reaction pathway for chloroamination of **1a** as shown in Scheme 3. Initially, a

nitrogen-centered radical **B** is generated from single-electron reduction of NFSI by a copper catalyst **A**. The detailed reaction mechanism of this step was revealed by means of DFT calculation.[21] The formed imidyl radical **B** attacks at the terminal position of **1a** to afford the thermodynamically stable benzyl radical intermediate **C**. After recombination of **C** with copper(II) gives a benzylcopper species **D**, transmetalation with chlorotrimethylsilane affords a copper intermediate **E** with a release of fluorotrimethylsilane, which might be accelerated by the strong affinity between Si and F. The following reductive elimination provides **2a**, regenerating the initial copper species **A**. As an alternative pathway for carbon–chlorine bond formation, direct reaction of the generated benzyl radical **C** with copper(II) chloride after transmetalation with chlorotrimethylsilane can also be conceivable.



Scheme 3. A Proposed Reaction Pathway.

In summary, we have developed the copper-catalyzed chloroamination of alkenes with chlorotrimethylsilane and *N*-fluorobenzenesulfonimide. The reaction proceeds with a perfect regioselectivity. A proposed radical pathway is supported by a series of mechanistic studies. The present method was applicable to the practical large-scale synthesis. Further investigation of the mechanistic details and the development of vicinal difunctionalization of alkenes are currently underway in our laboratory.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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20 A radical clock experiment with α-cyclopropylstyrene or 2-phenyl-1,6-heptadiene gave a complex mixture.

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NOTE *The diagram is acceptable in a colored form. Publication of the colored G.A. is free of charge.*
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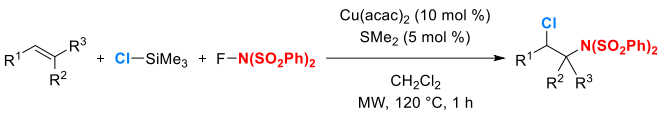
You are requested to put a brief abstract (50-60words, one paragraph style) with the graphical abstract you provided, so that readers can easily understand what the graphic shows.

Graphical Abstract

Textual Information

A brief abstract (required)	A copper-catalyzed chloroamination of alkenes with chlorotrimethylsilane and *N*-fluorobenzenesulfonimide has been developed. The reactions were complete within 1 h at 120 °C by means of microwave heating. The present chloroamination proceeds with a perfect regioselectivity and is compatible with various functional groups. The preliminary mechanistic investigation revealed that the reaction involves a radical process. The utility of the present method was demonstrated by scalable, operationally simple and safe system.
Title(required)	Copper-Catalyzed Regioselective Chloroamination of Alkenes with Chlorotrimethylsilane and *N*-Fluorobenzenesulfonimide under Microwave-Assisted Conditions
Authors' Names(required)	Masayuki Iwasaki, Jie Xu, Yukari Tani, Liyan Fu, Yuichi Ikemoto, Yasuyuki Ura, and Yasushi Nishihara

Graphical Information



R^1 = aryl, alkyl
R^2, R^3 = H, alkyl

- ✓ copper-catalyzed chloroamination of alkenes
- ✓ microwave-assisted scalable synthesis
- ✓ perfect regioselectivity
- ✓ radical pathway