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

Masayuki Iwasaki,*1 Jie Xu,2 Yukari Tani,2 Liyan Fu,2 Yuichi Ikemoto,2 Yasuyuki Ura,3 and Yasushi Nishihara*1

1Research Institute for Interdisciplinary Science, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan
2Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan
3Department of Chemistry, Biology, and Environmental Science, Faculty of Science, Nara Women’s University, Kitauanishimi-machi, Nara 630-8506, Japan

E-mail: iwasa-m@okayama-u.ac.jp (M. Iwasaki), ynishiha@okayama-u.ac.jp (Y. Nishihara)

A copper-catalyzed chloroamination of alkenes with chlorotrimethylsilane and N-fluorobenzensulfonimide 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. In addition, some compounds of non-natural origin have also shown significant biological activities. 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. 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 azirinium 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-fluorobenzensulfonimide (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. It should be noted that a sulfonimide moiety can be readily removed. 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 aminoauration, aminocyanation, aminoazidation, diamination, aminofluorination, aminothiolation, and aminooxygenation. Our research group also focused on highly selective catalytic radical difunctionalization. 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).

(a) Conventional procedures

(b) This work

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, 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. Instead, dichlorinated byproduct 3a was obtained in 8% yield, in which vicinal dichlorination of 2a with silyl chloride occurred under oxidative conditions by NFSI. Among other copper(I) catalysts screened (entries 3–6), CuBr•SMe2 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 = acetylacetone) 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). 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% isolated yield when Cu(acac)₂ (0.4 mmol), Cu cat. (0.04 mmol), and SMe₂ (2 mL) under microwave irradiation at 120 °C for 1 h. ³¹H NMR yield. An isolated yield is given in parentheses.

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 due to their low solubility in dichloromethane (entries 7–9). The reactions with bromotrimethylsilane and iodotrimethylsilane gave complex mixtures (entries 10 and 11).

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 diastereoselectivity.
Both reactions of \((E)-\) and \((Z)-\beta\)-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\(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Radical scavenger</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>TEMPO</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1,1-diphenylethene</td>
<td>33</td>
</tr>
</tbody>
</table>

\(^{a}\)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 SM\(_2\) (0.02 mmol) in CH\(_2\)Cl\(_2\) (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 \(^1\)H and \(^19\)F 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).

![Scheme 2. Control experiments.](attachment:scheme_2.png)

Based on the above results and the literature precedents,\(^{1-12}\) we propose the reaction pathway for chloroamination of 1a as shown in Scheme 3. Initially, a
In summary, we have developed the copper-catalyzed chloroamination of alkenes with chlorotrimethylsilane and N-fluorobenzensulfonylimidamide. 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.****.

References and Notes


During preparation of this manuscript, a similar reaction was reported. See: G. C. Artega, J. Saavedra-Olavarria, S. Almendras, P. Hermosilla-Ibanez, I. Almndovarr, E. G. Pérez, *Tetrahedron Lett.* 2018, 59, 1091.


Crystallographic data for the structure of 2a have been deposited with The Cambridge Crystallographic Data Centre as the deposition number CCDC-1872871. This data can be obtained free of charge from an application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44) 01223 336033 or www.ccdc.cam.ac.uk/data_request/cif].


See the Supporting Information for more detailed optimization studies.


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

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Graphical Abstract

![Graphical Abstract Diagram]

- R¹ = aryl, alkyl
- R², R³ = H, alkyl
- Cu(diacac)_2 (10 mol %)
- SME_2 (5 mol %)
- CH_2Cl_2
- MW, 120 °C, 1 h

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