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Copper-catalyzed aminooxygenation of styrenes with *N*-fluorobenzenesulfonimide and *N*-hydroxyphthalimide derivatives

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Letter

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Abstract

A copper-catalyzed aminooxygenation reaction of styrenes with *N*-fluorobenzenesulfonimide and *N*-hydroxyphthalimide derivatives has been developed. The aminooxygenation product could be converted into the corresponding alcohol or free amine through the cleavage of the N–O or C–N bond of the *N*-hydroxyphthalimide moiety.

Findings

Direct aminooxygenation of alkenes provides a straightforward and powerful approach to construct the 1,2-aminoalcohol skeleton [1], which is ubiquitous in bioactive compounds (such as the drugs bestatin (**1**) and tamiflu (**2**), the natural products Al-77-B (**3**) and hapolosin (**4**); Figure 1) [2] and has also been widely used as chiral ligands and auxiliaries in asymmetric synthesis [3]. Therefore, the development of a new aminooxygenation reaction is still highly attractive [4]. Most of the existing aminooxygenation reactions involve an intramolecular cyclization step [5-33] to provide various valuable cyclic compounds. Comparatively, methods for an intermolecular three-component aminooxygenation reaction are considerably less established. In 2006, Stahl and co-workers reported a Pd-catalyzed aminooxygenation reaction of alkenes with phthalimide and (diacetoxyiodo)benzene through *cis*-aminopalladation and S_N2 C–O bond formation [34]. In 2013, Zhu and co-workers described an *n*-Bu_4NI-catalyzed aminooxygenation of inactive alkenes with benzotriazole and water which underwent a nitrogen-centred radical addition and a nucleophilic oxygen attack [35]. Very recently, Studer and co-workers presented an aminooxygenation of alkenes with *N*-fluorobenzenesulfonimide (NFSI) and sodium 2,2,6,6-tetramethylpiperidine-1-olate (TEMPONa) via nitrogen-centred radical addition to the alkene followed by trapping of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) [36].

NFSI is a very interesting reagent. Besides classic electrophilic fluorination reagent [37], it has been used not only as fluoride-

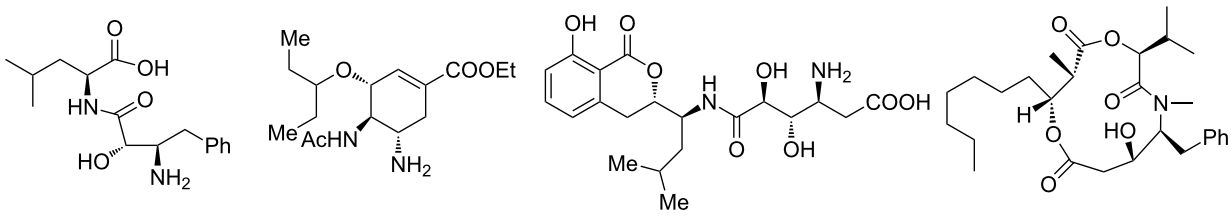
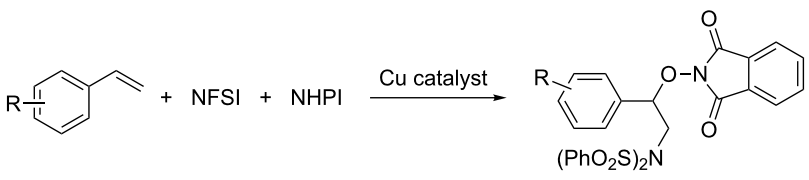


Figure 1: Bioactive compounds containing 1,2-aminoalcohol motif.

atom transfer reagent [38-40] but also as nucleophilic/radical amination reagent [41]. We are highly interested in the multiple reaction modes of NFSI [37-41], especially as a nitrogen-centred radical. In this context, we have realized copper-catalyzed benzylic sp^3 C–H amination [42], aminative multiple functionalization of alkynes [43], diamination, aminocyanation [44] and aminofluorination of alkenes [45], as well as amination of allenes [46]. Encouraged by these results, we try to develop copper-catalyzed aminooxygenation of alkenes by using NFSI. Herein, we report a simple and efficient copper-catalyzed three-component aminooxygenation reaction of styrenes with NFSI and *N*-hydroxyphthalimide (NHPI) derivatives (Scheme 1).

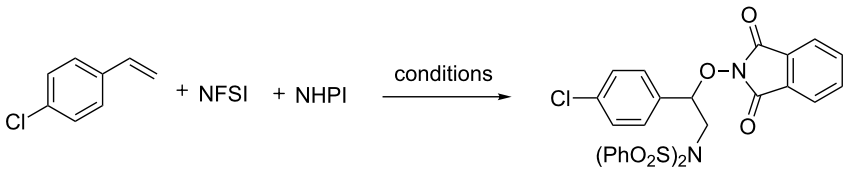
Initially, we conducted the three-component amnooxygenation of styrene **1a** with NFSI and NHPI (**2a**). After the reaction of **1a** (0.3 mmol), NFSI (0.3 mmol, 1.0 equiv) and **2a** (0.45 mmol, 1.5 equiv) was performed in the presence of $Cu(OTf)_2$ (10 mol %) in dichloromethane (DCM, 2 mL) under nitrogen atmosphere at 70 °C for 10.0 h, the desired aminooxygenation product **3a** was obtained in 39% yield (Table 1, entry 1). A variety of copper salts such as CuCl, CuBr, CuI, $[(CH_3CN)_4Cu]PF_6$, CuCN, $Cu(acac)_2$, $Cu(OAc)_2$, $CuBr_2$ and $CuCl_2$ were examined (Table 1, entries 2–10). We found that $CuCl_2$ was the most effective catalyst, affording **3a** in 55% yield (Table 1, entry 10). No reaction was observed in the absence of copper salts (Table 1, entry 11). Next, the reaction solvents were scanned. 1,2-Dichloroethane (DCE) and CH_3CN were not efficient solvents, providing **3a** in 9% and 20% yields, respectively (Table 1, entries 12 and 13). Using $CHCl_3$ as the solvent, only a trace amount of **3a** was observed (Table 1, entry 14). No reaction occurred in the solvents DMF, DMSO and THF (Table 1, entries 15–17). A relatively lower temperature (45 °C) only afforded a trace amount of **3a** (Table 1, entry 18). Increasing the temperature to 90 °C or 110 °C, **3a** was obtained in 45% and 40% yields, respectively (Table 1, entries 19 and 20). The ratio of substrates distinctly influenced the reaction (Table 1, entries 21–23). Changing the ratio from 1:1:1.5 (**1a**:NFSI:**2a**) to 1:2:2 or 1:2:3 (**2a**:NFSI:**1a**) led to much better yields (Table 1, entries 21 and 22). To our delight, when the ratio was 1:4:3 (**2a**:NFSI:**1a**), **3a** was obtained in 76% yield (Table 1, entry 23).

With the optimized reaction conditions in hand (Table 1, entry 23), the scope of this copper-catalyzed aminooxygenation reaction was examined (Figure 2). Styrenes with electron-withdrawing (**1a**–**f**) or electron-donating (**1h** and **1i**) groups were viable, providing the corresponding 1,2-aminoalcohol derivatives in good yields. It is worth noting that functionalities such as F, Cl, Br, CN, and NO_2 groups, which could easily undergo further transformations, were intact after the reaction (**3a**–**e**). The structure of **3e** was confirmed by X-ray crystallographic analysis [47]. The substituent at the *ortho* (**3j** and **3k**) or *meta* (**3l**) position of the aromatic ring did not hinder the reaction (41–55% yields). Similarly, for disubstituted (**1m**) and trisubstituted (**1n**) substrates, the aminooxygenation underwent smoothly, providing the corresponding products **3m** (51%) and **3n** (53%). The *trans*-β-methylstyrene (**1o**) afforded the desired



Scheme 1: Copper-catalyzed radical aminooxygenation reaction of styrenes.

Table 1: The optimization of reaction conditions[a].



1a **2a** **3a**

Entry[a]	Catalyst	Solvent	Temp (°C)	Yield[b] (%)
1	$Cu(OTf)_2$	DCM	70	39
2	CuCl	DCM	70	48
3	CuBr	DCM	70	43
4	CuI	DCM	70	30
5	$[(CH_3CN)_4Cu]PF_6$	DCM	70	50
6	CuCN	DCM	70	16
7	$Cu(acac)_2$	DCM	70	48
8	$Cu(OAc)_2$	DCM	70	51
9	$CuBr_2$	DCM	70	54
10	$CuCl_2$	DCM	70	55
11	none	DCM	70	NR[c]
12	$CuCl_2$	DCE	70	9
13	$CuCl_2$	CH_3CN	70	20
14	$CuCl_2$	$CHCl_3$	70	trace
15	$CuCl_2$	DMF	70	NR[c]
16	$CuCl_2$	DMSO	70	NR[c]
17	$CuCl_2$	THF	70	NR[c]
18	$CuCl_2$	DCM	45	trace
19	$CuCl_2$	DCM	90	45
20	$CuCl_2$	DCM	110	40
21[d]	$CuCl_2$	DCM	70	70
22[e]	$CuCl_2$	DCM	70	73
23[f]	**$CuCl_2$**	**DCM**	**70**	**76**

[a]Reaction conditions: **1a** (0.3 mmol), NFSI (0.3 mmol, 1.0 equiv), **2a** (0.45 mmol, 1.5 equiv), catalyst (10 mol %), solvent (2.0 mL), N_2, 10.0 h. [b]Isolated yields. [c]NR: no reaction. [d]**1a**:NFSI:**2a** = 2.0:2.0:1.0 [e]**1a**:NFSI:**2a** = 3.0:2.0:1.0. [f]**1a**:NFSI:**2a** = 3.0:4.0:1.0.

product **3o** in a low yield (15%). In addition, NHPI derivatives **2b** and **2c** were suitable nitrogen sources and the desired **3p** and **3q** were obtained in 56% and 64%, respectively. For 4-methoxystyrene (**1r**), no aminooxygenation reaction occurred.

Based on these experimental results and our previous investigations [42-46,48], a plausible mechanism for the copper-catalyzed three-component aminooxygenation of styrenes with NFSI an NHPI is shown in Scheme 2. Initially, the oxidation of Cu(I) with NFSI provided F–Cu(III)–N complex **I**, which could transform into a copper(II)-stabilized benzenesulfonimide radical **II** through a redox isomerization equilibrium. Next, the intermolecular radical addition of **II** to styrene **1g** took place, producing benzylic radical **III** and Cu(II)–F species **IV**. The combination of the intermediates **III** and **IV** gave the Cu(III) species **V** having a C–Cu bond, which reacted with **2a** to generate Cu(III)–O species **VI**, along with the loss of HF. Finally, the reductive elimination of **VI** afforded aminooxygenation product **3g**.

Finally, we tried to investigate the synthetic value of our new aminooxygenation method. Then, the selective reduction of **3g** was conducted (Scheme 3). The cleavage of the N–O bond in **3g** readily occurred with $Mo(CO)_6/Et_3N$ at 80 °C to give alcohol **4** [36] in 67% yield. Treatment of **3g** with $NH_2NH_2{\cdot}H_2O$ under mild conditions (25 °C) in $CHCl_3$/MeOH gave free amine **5** in 70% yield.

In summary, we have developed a novel copper-catalyzed three-component aminooxygenation reaction of styrenes with NFSI and NHPI derivatives. Furthermore, the aminooxygenation product could be easily converted into the corresponding

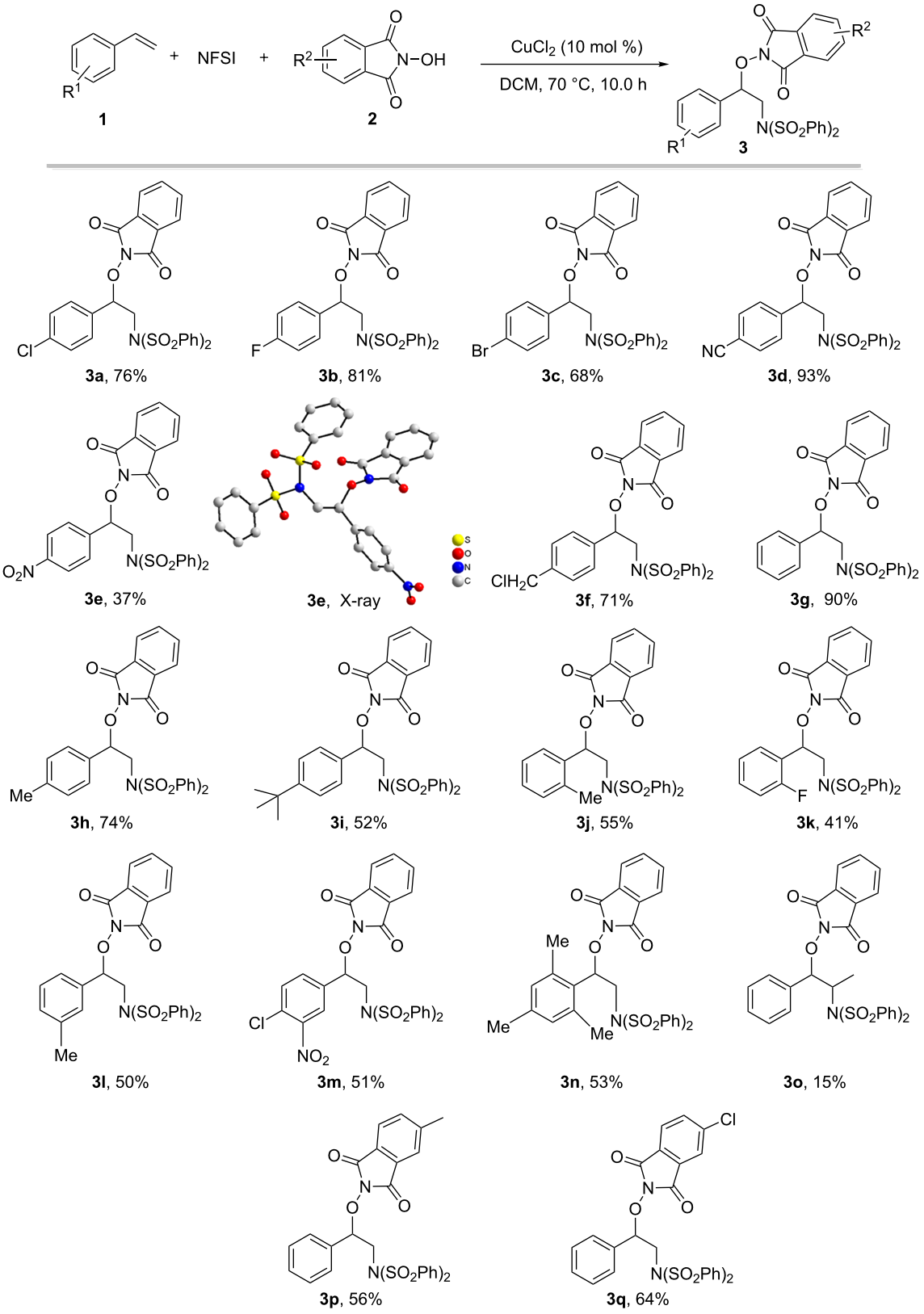
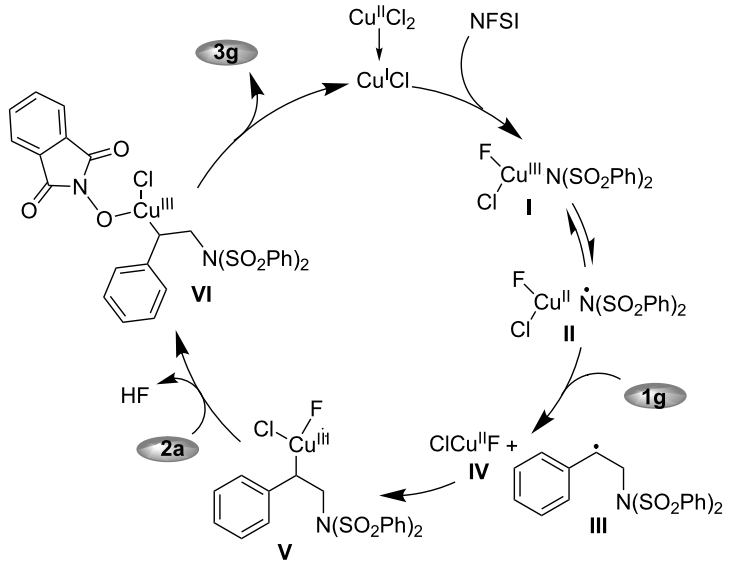
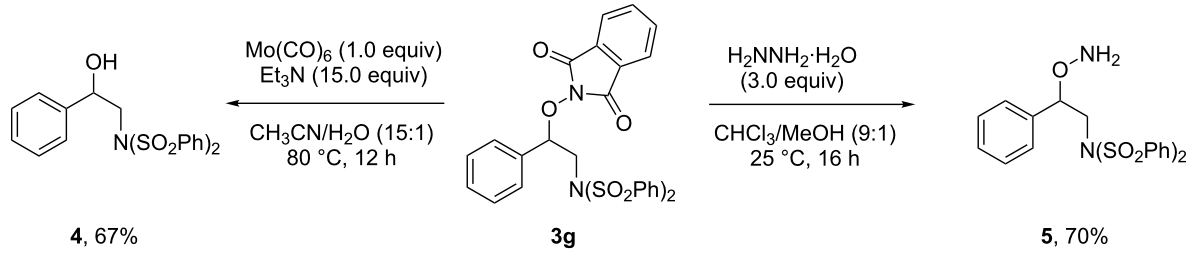


Figure 2: The copper-catalyzed three-component aminooxygenation of styrenes with NFSI and NHPI derivatives. Reaction conditions: **1** (0.9 mmol, 3.0 equiv), NFSI (1.2 mmol, 4.0 equiv), **2** (0.3 mmol, 1.0 equiv), $CuCl_2$ (10 mol %), DCM (2.0 mL), N_2, 70 °C, 10.0 h. Isolated yields.



Scheme 2: The plausible mechanism.



Scheme 3: Selective reduction of the aminooxygenation product.

alcohol or free amine through the cleavage of the N–O or C–N bond of the NHPI moiety. Further studies are underway in our lab.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-293-S1.pdf]

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