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Sulfoxidation of alkenes and alkynes with NFSI as a radical initiator and selective oxidant†

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Sulfoxides are important functional molecules. We develop a short-route (one-pot) synthesis of this class of molecules by reacting thiols with alkenes or alkynes under mild and metal-free conditions. *N*-Fluorobenzenesulfonimide (NFSI) is used to play dual roles: as a radical initiator for a thiol–ene/–yne reaction to form sulfide adducts, and as efficient oxidant for conversion of the sulfides formed *in situ* to sulfoxides. Over-oxidation of the sulfoxides to sulfones is avoided in our approach.

The sulfoxide moiety is a functional group often found in pharmaceuticals and natural products, such as esomeprazole,[1] armodafinil[2] and alliin.[3] Sulfoxides are also used as ligands for metal catalysts with applications in a large set of reactions, including Pummerer[4] and Mislow–Evans rearrangements.[5] To date, the synthesis of sulfoxides typically involves oxidation of sulfides using peroxides[6] and hypervalent iodine reagent[7] as the oxidants with the assistance of transition metal catalysts.[8] One challenge of this otherwise widely used two-step protocol lies with over-oxidation of sulfoxides to sulfones.[6] Here we report a new method that selectively converts alkenes and alkynes to sulfoxides in a one-pot metal-free operation (Fig. 1). *N*-Fluorobenzenesulfonimide (NFSI), a shelf-stable reagent,[9] is used as a radical initiator and a selective oxidant. No over-oxidation of sulfoxides to sulfones was observed (Fig. 1).

Notably, Yadav[10] and Lei[11] have recently reported reactions of alkenes and thiols under dioxygen to form β-keto sulfoxides and β-oxy sulfoxides. In their reactions, oxidation of the alkene carbon by oxygen occurred concurrently. The NFSI reagent used in our reactions has often been employed as electrophilic fluorinating agent,[12] aminating reagent,[13] or a combined amino and fluorine source.[14] In radical reactions (SET reactions), it can generate aminyl radical for Cu-catalyzed radical amination of olefins, as reported by Kanai,[15] Zhang[16] and Studer.[17] Zhang and co-workers also developed radical aminofluorination of styrenes using NFSI.[18] In addition, Ritter reported Pd-catalyzed direct radical arene amination with NFSI,[19] and Studer developed radical aminooxygenation of alkenes with NFSI in combination with TEMPONa.[20]

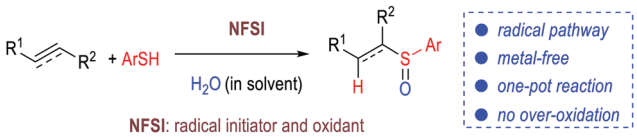

Fig. 1 Our strategy of NFSI-enabled selective one-pot access to sulfoxides from alkenes/alkynes and thiols.

Our initial design was to combine NFSI and thiol to generate thiyl and aminyl radicals for aminosulfidation of alkenes. We first studied reactions between alkene **1a** and thiol **2a** with NFSI as a potential radical generator in the presence of K_2CO_3 or K_3PO_4 as the base (Table 1, entry 1). The expected alkene aminosulfidation adduct was not formed. Instead, we found alkene sulfoxidation adduct **3a** as the product in 11% yield (entry 1). Additional evaluation of the base effects (Table 1, entries 2–6) indicated that 1,8-diazabicycloundec-7-ene (DBU) performed the best, giving **3a** in 72% yield (Table 1, entry 6). Several other solvents studied here did not work as well as toluene (Table 1, entries 7–10). The yield of **3a** (based on **1a**) could be further improved by increasing the loadings of thiol **2a** and NFSI (Table 1, entry 11).

With an acceptable condition (Table 1, entry 11) on hand, we proceeded to explore the scope of the reaction (Table 2). We first examined the reaction between various alkenes and thiol **2a** (**3a–3p**). Styrenes with different substituents or substitution patterns on the phenyl ring worked effectively (**3a–3l**). Internal alkenes, such as indene (**3m**), 1,2-dihydronaphthalene (**3n**), *trans*-β-methylstyrene (**3o**) were also effective substrates. Notably, no sulfoxidation products were obtained when aliphatic alkenes were used.

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† Electronic supplementary information (ESI) available: Experimental procedures, mechanistic details, spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra. CCDC 1497084 and 1497085. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc08631d

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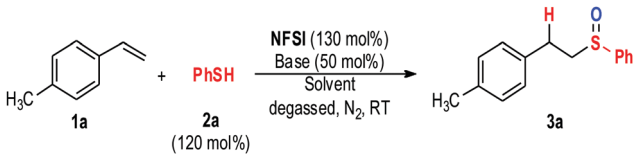
Table 1 Screening of reaction conditions for the reaction of **1a** with **2a** in the presence of NFSI[a]



Entry	Base	Solvent	Yield[b] [%]
1	K_2CO_3 or K_3PO_4	Toluene	11
2	KOMe	Toluene	23
3	NaO*t*Bu	Toluene	29
4	DIPEA	Toluene	43
5	DABCO	Toluene	66
6	**DBU**	**Toluene**	**72**
7	DBU	THF	52
8	DBU	Dioxane	31
9	DBU	CH_3CN	26
10	DBU	EA	48
11[c]	**DBU**	**Toluene**	**87**

[a] Conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.2 equiv.), NFSI (130 mol%) and base (50 mol%) in 3.0 mL of solvent at rt for 2–5 h. [b] Isolated yield based on **1a**. [c] **2a** (0.4 mmol, 2.0 equiv.), NFSI (0.36 mmol, 1.8 equiv.).

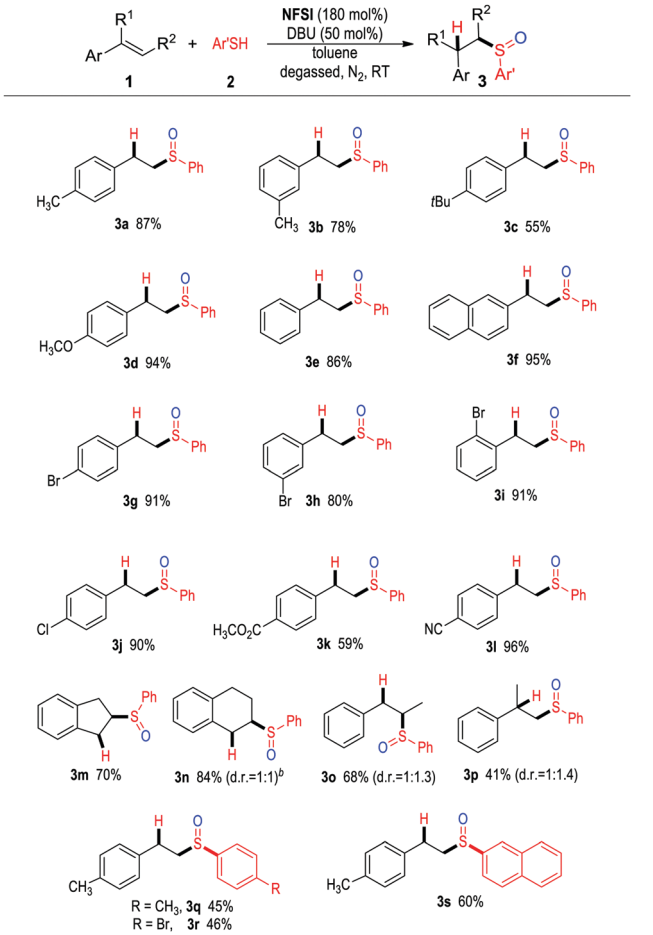
Substituents (*e.g.*, CH_3 and Br) could be placed on the phenyl unit of thiol **2a** (**3q**, **3r**), while 2-napthyl thiol (**3s**) was also tolerated.

We next found that alkynes could be used as substrates (to replace alkenes) under the same condition, affording unsaturated sulfoxides as the products (Table 3). The reactions proceeded smoothly for aryl alkynes with either electron-withdrawing or electron-donating substituents present on the aromatic ring (**4a–4e**) to afford the desired products (**5a–5e**) in moderate to excellent yields. Alkyl alkynes (**4f**, **4i–j**) and alkynes bearing an ester (**4g**) or silyl (**4h**) moiety were also effective substrates.[21] The structures of two vinylsulfoxide products (***E*-5a**, ***E*-5d**) were unambiguously assigned *via* X-ray crystallography.

The proposed reaction pathway is illustrated in Scheme 1. Initially, removal of one electron from thiol **2a** by oxidant NFSI[12a,b] generates radical cation **A** that can be subsequently transformed to thiyl radical **B** after a proton transfer (Scheme 1a). Thereafter, addition of radical **B** to alkene **1** forms radical intermediate **C**. A hydrogen atom transfer (HAT) from a molecule of **2a** converts **C** to sulfide **D** with the regeneration of the thiyl radical intermediate **B** which returns back into the propagation step (Scheme 1b). Finally, the sulfide **D** is oxidized to sulfoxide **3** by NFSI. One possible pathway (see ESI† for another possibility) for the oxidation of sulfide **D** involves nucleophilic addition of the sulfide to the electrophilic fluorine atom of NFSI to afford intermediate **E** (Scheme 1c). Substitution of the fluorine atom of **E** by water forms **G** that then transforms to sulfoxide **3** after a proton transfer process.

To investigate the reaction mechanism, we performed multiple experiments (Scheme 2). The addition of TEMPO inhibited the formation of **3a** (Scheme 2a). In the presence of 150 mol% TEMPO, the formation of sulfoxide product **3a** was completely suppressed. The aminooxygenation adduct **6** previously reported by Studer[20] was observed in about 5% yield. Adducts **7**, **8** and **9** (89% of

Table 2 Substrate scope for reactions of alkenes with thiols in the presence of NFSI[a]

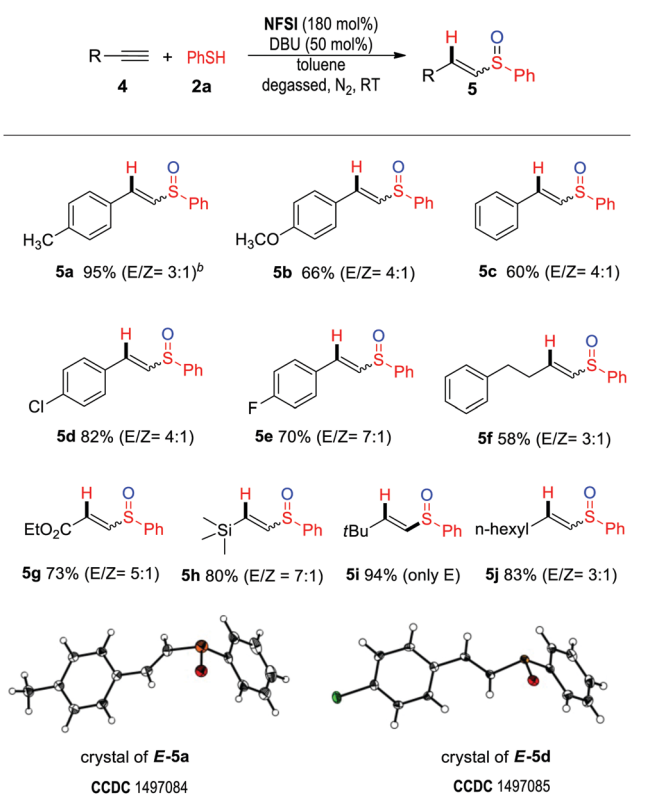


[a] Conditions as in Table 1, entry 11; yields (after SiO_2 chromatography purification) were based on olefin **1**. [b] Diastereoselective ratio (d.r.) was determined *via* ^{1}H NMR analysis of the product mixture.

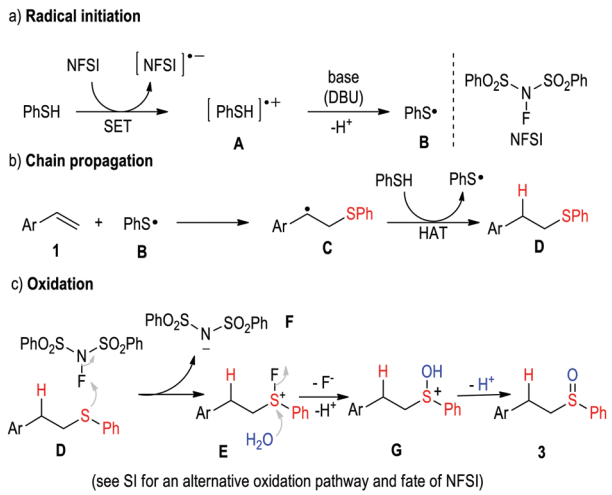
combined yields based on thiol **2a**) were previously reported by Greci and co-workers in a study on the reaction between **2a** and TEMPO.[22] The use of diphenyl disulfide **7** in place of thiophenol **2a** did not lead to desired product **3a** (Scheme 2b), suggesting that under the oxidative condition of NSFI the disulphide adduct did not convert to thiol. The oxygen atom in the sulfoxide product came from the trace amount of H_2O present in the solvent, as suggested by an ^{18}O isotope labelling experiment (Scheme 2c). Additional experiments by adjusting the loadings of NFSI (Scheme 2d) suggest that both the thiol–ene reaction and oxidation reaction are enabled by NFSI. When 30 mol% of NFSI was added, only sulfide adduct **10** was observed. Sulfide **10** could then be transformed under standard conditions to sulfoxide **3a**.[23] These experiments (Scheme 2a and b) support the formation of radical intermediate as proposed in Scheme 1a and b. The results (Scheme 2c and d) showed that the formation of sulfide (**D**, Scheme 1c) and its oxidation occurs in a stepwise process.

In summary, we have developed a facile synthesis of sulfoxides from alkenes and alkynes in the presence of NFSI. Sulfoxides are useful structural moieties for construction of natural products

Table 3 Substrate scope for reactions of alkynes with thiols in the presence of NFSI[a]

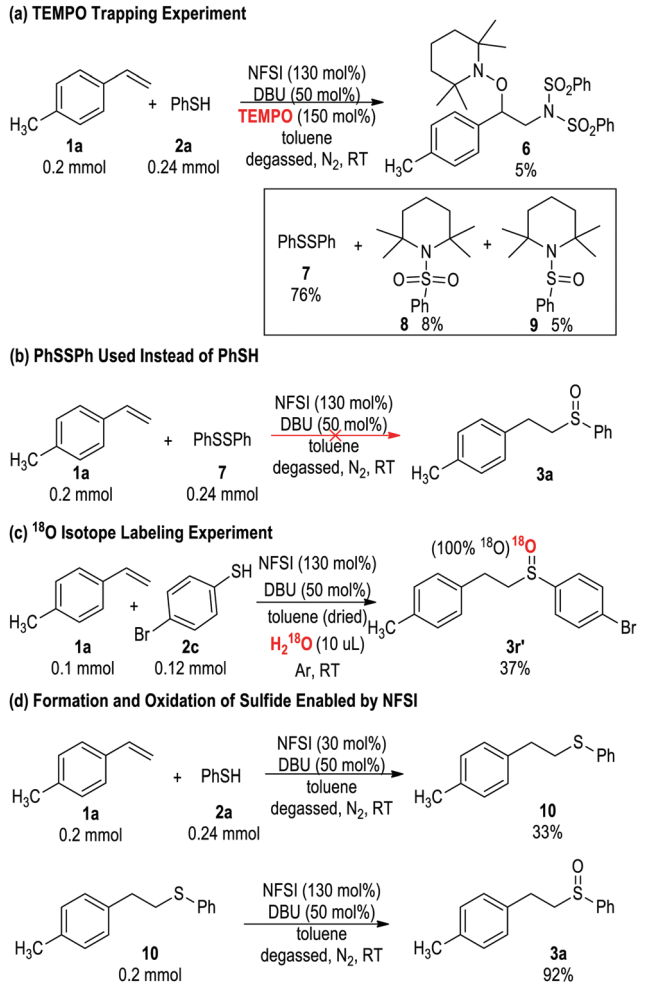


[a] Alkyne (0.2 mmol), **2a** (0.4 mmol), NFSI (0.36 mmol) and DBU (50 mol%), in toluene (3 mL) at rt for 16 h; yields (after SiO_2 chromatography purification) were based on alkyne. [b] The ratio of *E*/*Z* was determined by the weight of isolated *E* and *Z* products.



Scheme 1 Proposed reaction pathway.

and other functional molecules. Our approach provides a metal-free and concise synthesis of this class of molecules. The substrates and reagents used in our approach are either inexpensive or readily available with reasonable cost. NFSI is used as a radical initiator (to initiate the sulfide formation) and a selective oxidant



Scheme 2 Experiments to probe mechanism.

(to transform sulfides to sulfoxides). The oxygen atom in the sulfoxide products was determined to originate from trace water in the reaction mixture, providing a simple way for the incorporation of ^{18}O isotope to sulfoxide-containing molecules. Further development of related radical reactions, including catalytic versions mediated by carbene organic catalysts, is in progress.

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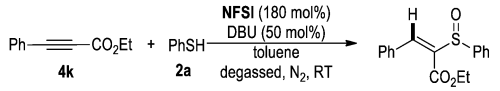

33% (E/Z = 5:1)

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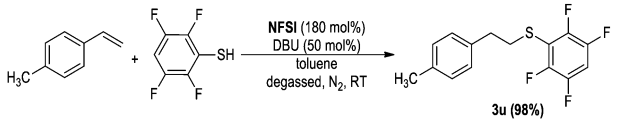

3u (98%)