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Direct access to β-seleno sulfones at room temperature through selenosulfonylation of alkenes

Kai Sun[1,2*], Yunhe Lv[1], Zuodong Shi[1], Fangfang Fu[1], Chong Zhang[1] & Zhiguo Zhang[3*]

[1]*College of Chemistry and Chemical Engineering, Anyang Normal University, Anyang 455000, China*
[2]*Henan Province Key Laboratory of New Opto-Electronic Functional Materials, Anyang 455000, China*
[3]*School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China*

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A new protocol has been developed for the formation of C−Se and C−S bonds by the direct selenosulfonylation of alkenes. This protocol is operationally simplistic, has a wide substrate scope, uses readily available seleno and sulfonyl sources, and is amenable to gram-scale synthesis. This reaction represents a significant addition to the limited number of reactions available for the intermolecular selenide difunctionalization of alkenes and would be useful for the synthesis of sulfur- and selenium-containing molecules.

alkenes, selenosulfonylation, difunctionalization, metal-free conditions, β-seleno sulfones

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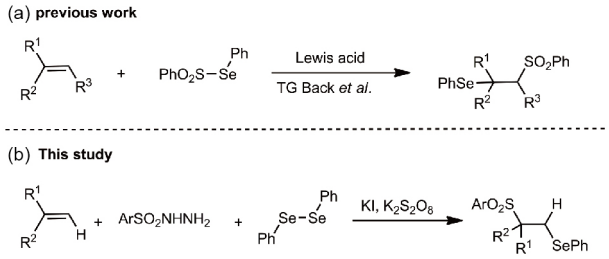
Selenium-containing structures can be found in a diverse range of drug candidates, biologically active compounds, and functional organic materials [1]. Moreover, the facile conversion of selenides to other functional groups and their ability to favor or even facilitate further synthetic transformations represent additional assets that render selenation reactions indispensable [2]. The development of new synthetic routes for the introduction of selenium groups into organic compounds would therefore be of significant synthetic value. Alkenes are simple and abundant bulk commodities, and the vicinal difunctionalization of these feedstock materials is of great importance for the introduction of molecular complexity in a single procedure [3]. However, compared with the well-established transition metal-catalyzed reactions for the difunctionalization of specific substrates [4], further research is still needed for the discovery of complementary organocatalyst-mediated difunctionalization approaches. Furthermore, the development of sustainable approaches for the synthetic introduction of selenium-containing functional groups via the organocatalyst-mediated seleno-difunctionalization of alkenes is an attractive topic.

The sulfonyl group has attracted considerable interest from researchers working in a variety of different fields, including medical chemistry, photovoltaic materials, nonlinear optics, and synthetic chemistry [5]. Significant progress has recently been made towards exploring the difunctionalization of alkenes using a sulfonylation-based transformation, such as an oxysulfonylation reaction [6]. The difunctionalization of alkenes to incorporate selenium and sulfone groups in a single step represents an attractive transformation, which could provide a unique and convenient method for the introduction of two synthetically versatile functionalities into an unsaturated substrate. However, a review of the literature revealed that very few reactions have been reported for the selenosulfonylation of alkenes (Scheme 1(a)) [7]. Based on the nucleophilic attack to a seleniranium intermediate, we recently achieved the highly regioselective selenoamination of

*Corresponding authors (email: sunk468@nenu.edu.cn; zhangzg@htu.cn)



Scheme 1 Selenosulfonylation reactions of alkenes.

alkenes [8]. Inspired by this result, and as part of our ongoing interest in the development of new methods for the formation of C–X (X=N, S, I) bonds [9], we herein disclose our latest work on the KI/$K_2S_2O_8$-mediated selenosulfonylation of alkenes under mild conditions (Scheme 1(b)). This new approach avoids the need for pre-prepared S–Se regents and exhibits wide substrate scope, high functional group tolerance, making it a useful tool with numerous potential applications in synthetic chemistry.

All reagents were used as received from commercial sources, unless otherwise specified or prepared as described in the literature. All reagents were weighed and handled in air.

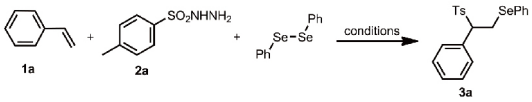
^{1}H and ^{13}C NMR spectra were respectively recorded at 400 and 100 MHz, using tetramethylsilane as an internal reference. Chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz, respectively.

Styrene **1a** (0.3 mmol), 4-methyl benzene sulfonyl hydrazine **2a** (0.6 mmol), diphenyl diselenide (0.3 mmol), $K_2S_2O_8$ (0.6 mmol), KI (0.2 equiv.), and CH_3CN (2.0 mL) at 20 °C for 12 h (monitored by thin-layer chromatography (TLC)), quenched with water, extracted with dichloromethane (5×3 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by a shot flash silica gel column chromatography (EtOAc/petro ether=1:8) to give compound **3a** as a white solid (111.1 mg, 89%).

For our initial study, we chose styrene **1a** and diphenyl diselenide as model substrates, which were reacted with various sulfonyl reagents, including 4-methylbenzenesulfon-hydrazide **2a**, sodium *p*-toluenesulfonate **4**, and tosyl chloride **5**. Pleasingly, this reaction proceeds as anticipated with 4-methylbenzenesulfonhydrazide **2a** in the presence of $(NH_4)_2S_2O_8$ in tetrahydrofuran (THF) at 60 °C, affording the desired product **3a** in 29% yield (Table 1, entry 1). In contrast, only trace quantities of the desired product **3a** were obtained when **4** and **5** were used as the sulfonyl reagents (Table 1, entries 2 and 3). Encouraged by this result, we also tested $K_2S_2O_8$, oxone, and *t*-butylhydroperoxide (TBHP) as oxidizing agents in the reaction. The yield of **3a** improved to 36% when $K_2S_2O_8$ was added to the reaction (Table 1, entry 4), whereas oxone and TBHP proved to be much less effective (Table 1, entries 5 and 6). After detailed additive screening, we found that 20% KI led to marked improvements in the transformation, with the isolated yield of **3a** increasing to 71% (Table 1, entry 7). In a separate experiment, we noted that the addition of Na_2CO_3 had an adverse impact on the outcome of the reaction (Table 1, entry 8). We also evaluated the effects of several different solvents. We found that CH_3CN was the best solvent for this transformation (Table 1, entry 9). EtOAc also performed well, whereas the non-polar solvent DCE failed to afford any of the desired product (Table 1, entries 10 and 11). The reaction temperature was determined to be critical to the success of this reaction. Pleasingly, decreasing the temperature of the reaction to 20 °C led to a considerable increase in the yield of **3a** to 89% when the reaction was conducted in CH_3CN with KI and $K_2S_2O_8$ (Table 1, entry 13). The optimal catalytic system for the selenosulfonylation of styrene was therefore determined to be as follows: **1a** (0.3 mmol), **2a** (0.6 mmol), KI (0.06 mmol), and $K_2S_2O_8$ (0.6 mmol) in CH_3CN (2.0 mL) at 20 °C under air for 12 h.

With the optimized reaction conditions in hand (Table 1, entry 13), we turned our attention to the scope with respect to the alkenes and sulfonyl hydrazides. As shown in Table 2, various substituents on the benzene ring of styrene were well tolerated, including electron-withdrawing (–F, –Cl, –Br, and $–NO_2$) and -donating groups ($–CH_3$, $–CH_2Cl$, and –*t*-butyl). Some of these functional groups are useful for further syn-

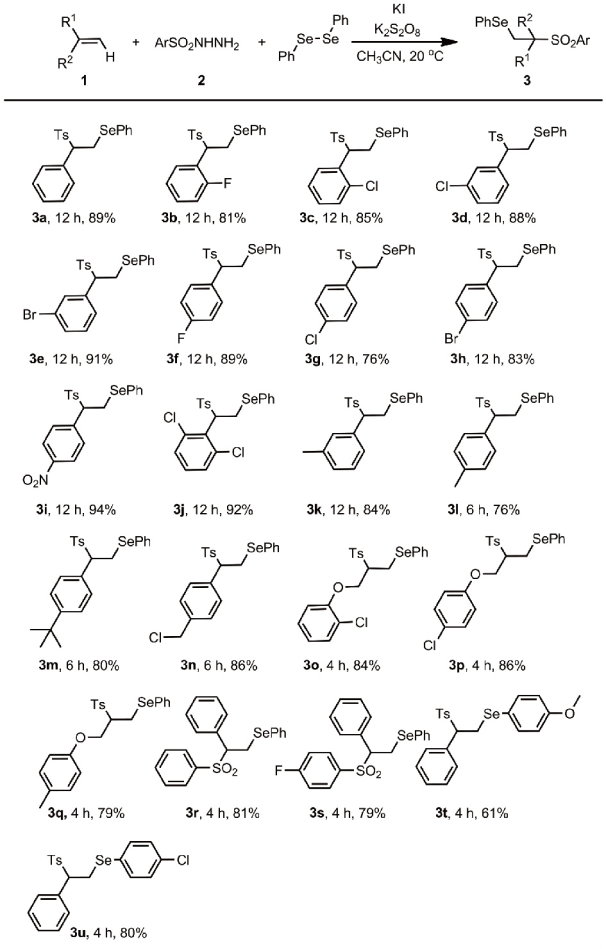
Table 1 Optimization of the reaction conditions [a]



Entry	Oxidant	Additive	Solvent	Yield (%) [b]
1	$(NH_4)_2S_2O_8$	no	THF	29
2	$(NH_4)_2S_2O_8$	no	THF	trace [c]
3	$(NH_4)_2S_2O_8$	No	THF	trace [d]
4	$K_2S_2O_8$	No	THF	36
5	Oxone	No	THF	0
6	TBHP	No	THF	17
7	$K_2S_2O_8$	KI	THF	71
8	$K_2S_2O_8$	Na_2CO_3	THF	22
9	$K_2S_2O_8$	KI	CH_3CN	78
10	$K_2S_2O_8$	KI	EtOAc	55
11	$K_2S_2O_8$	KI	DCE	0
12	$K_2S_2O_8$	KI	CH_3CN	72 [e]
13	$K_2S_2O_8$	KI	CH_3CN	89 [f]

a) Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), diphenyl diselenide (0.3 mmol), oxidant (0.6 mmol), and additive (0.2 equiv.) in solvent (2.0 mL) for 12 h. b) Yield of the isolated product. c) Sodium *p*-toluenesulfonate **4** was used as the sulfonyl reagent. d) Tosyl chloride **5** was used as the sulfonyl reagent. e) Reaction performed at 40 °C. f) Reaction performed at 20 °C.

Table 2 Scope of the alkenes and benzenesulfonyl hydrazides [a), b)]



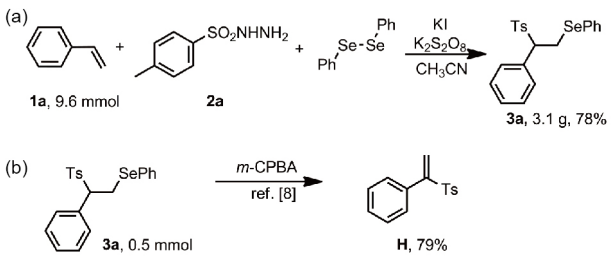
a) Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), diphenyl diselenide (0.3 mmol), $K_2S_2O_8$ (0.6 mmol), and KI (0.2 equiv.) in CH_3CN (2.0 mL) at 20 °C for 4–12 h. b) Yield of the isolated product.

thetic diversification. For example, the chloromethyl group ($–CH_2Cl$) in **1n** could be readily converted to a $–CH_3$, $–CH_2OH$, $–CH_2CN$, –CHO, or $–CH_2N(Me)_2$ group. Organo-chloro and -bromo substituents are reactive and can be difficult to retain during transition metal-catalyzed or organocatalytic reactions [10]. Therefore, these groups were well tolerated under our reaction conditions, further highlighting the synthetic utility of the current protocol. Substrates with substituents at different positions of their benzene ring, including *o*-chloro-, *m*-chloro-, and *p*-chloro-, all transformed smoothly to give the corresponding seleno-sulfonylated products **3c**, **3d**, and **3g**, respectively. Notably, the reaction of the sterically bulky substrate 1,6-dichloro-2-vinylbenzene **1j** also proceeded well to afford the corresponding β-iodo sulfone **3j** in 92% yield.

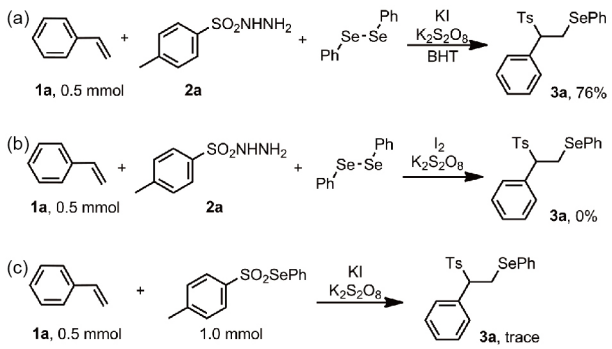
1-(Allyloxy)-2-chlorobenzene **1o**, 1-(allyloxy)-4-chlorobenzene **1p**, and 1-(allyloxy)-4-methyl-benzene **1q** also reacted well to give the desired products **3o**, **3p**, and **3q** with high yields of 84%, 86%, and 79%, respectively, thereby greatly expanding upon the substrate scope of this reaction. In addition, we also briefly tested the scope of sulfonyl hydrazides [11] and diphenyl diselenides. As expected, these reactions proceeded smoothly, affording the corresponding products **3r**–**3u** in good yields (61%–81%).

To demonstrate the synthetic utility of this selenosulfonylation reaction, we conducted a gram-scale reaction under the optimized conditions using **1a**, **2a**, and diphenyl diselenide, which gave the desired product **3a** in an isolated yield of 78% (Scheme 2(a)). We subsequently showed that **3a** could be converted to the corresponding vinyl sulfone H in 79% yield using known transformations (Scheme 2(b)) [7].

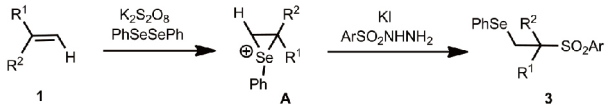
$K_2S_2O_8$ is a good initiator of free seleno radicals. To determine whether $K_2S_2O_8$ was acting as a radical initiator in this reaction, we added 2 equiv. of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) to the reaction of **1a**, **2a**, and diphenyl diselenide under the standard conditions. After 3 h, the desired selenosulfonylation product **3a** was obtained in 76% yield, which argues against the possibility of a pathway involving the initial addition of a free seleno radical to alkenes pathway (Scheme 3(a)). It is likely that the $K_2S_2O_8$ will oxidize the iodide ion to I_2, which could easily reacted with the tosylhydrazine to give an *N*-iodo-*N*-tosyldiazene. Nucleophilic attacked by the PhSe portion of the phenyldiselenide to *N*-iodo-*N*-tosyldiazene will generate Back's reagent ($TsSO_2SePh$) *in situ*. However, when I_2 was introduced instead of KI, no reaction occurred (Scheme 3(b)). In addition, we prepared the $TsSO_2SePh$ according to Back's work and was then reacted with **1a**, only a small amount of **3a** could be detected (Scheme 3(c)). The pH of the reaction mixture was



Scheme 2 Gram-scale synthesis and functionalization of the selenosulfonylation product.



Scheme 3 Reactions determining the reaction mechanism.



Scheme 4 Proposed reaction mechanism.

tested during the selenosulfonylation the selenosulfonylation reaction and determined to be in the range of 4–5, which suggested the possibility of seleniranium intermediate would be relatively stable, and could undergo a rapid nucleophilic attack of the benzene sulfonyl anion. Based on the results described above, we proposed this reaction proceeds via a selenium cationic-species-induced mechanism, which is shown in Scheme 4. The regioselectivity of the final product was consistent with this electrophilic mechanism.

In conclusion, we have developed a facile approach for the selenosulfonylation of alkenes, providing a straightforward for KI/$K_2S_2O_8$-mediated electrophilic reaction. This approach avoids the need for pre-prepared S–Se regents, and therefore represents a significant addition to the limited number of existing strategies for the intermolecular selenide difunctionalization of alkenes. Notably, this reaction was compatible with a broad range of styrenes and (allyloxy)benzenes, providing facile access to a series of structurally diverse vicinal sulfonyl selenides. This reaction has therefore paved the way for new endeavors in organic synthesis involving the exploration of the synthetic potency of these intermediates.

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Conflict of interest The authors declare that they have no conflict of interest.

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