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Organo-Selenium Mediated Regio- and Stereoselective Iodoselenylation of Alkynes in an Aqueous Medium: Simple Access to (*E*)-*β*-Iodoalkenyl Selenides

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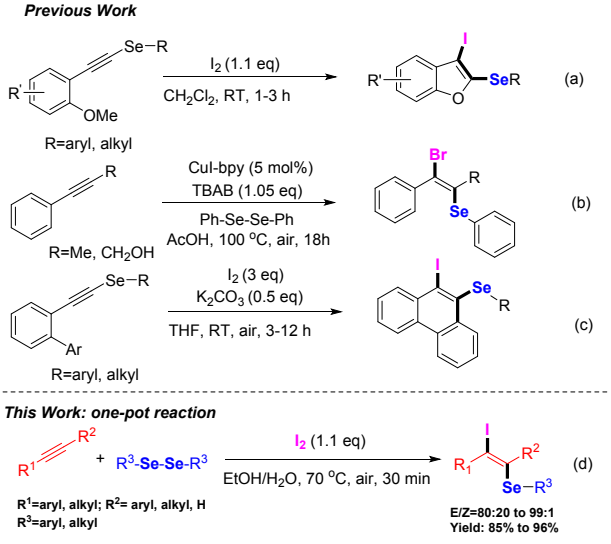
A method for the simple and efficient iodoselenylation of simple alkynes under mild conditions using commercially available molecular iodine (I_2) and diorganoyldiselenides as starting materials has been developed. A broad range of alkynes can be employed to afford (*E*)-*β*-iodoalkenyl selenides in good to excellent yields and with high regio- and stereoselectivity without the need for any protecting groups.

Hetero-atom functionalized aromatic and heteroaromatic structural motifs are present in numerous natural products and medicines, thus the synthesis of structures containing these skeletons is of high importance [1]. A number of synthetic strategies have been developed to synthesize hetero-atom functionalized compounds. For example, compounds bearing alkenyl heteroatoms can be prepared *via* the simultaneous introduction of two heteroatom groups into an alkyne bond [2]. Organoselenium compounds exhibit anti-oxidant activities, and may play a role in certain diseases such as cancer, heart diseases, inflammatory processes and arthritis, etc [3]. Although significant progress has been made towards the halogen-functionalization of alkynes, the halogen-selenylation of alkynes has not been widely reported [4]. Substituted *β*-haloalkenyl selenides are of particular importance because they are not only found in the structures of bioactive and drug molecules, but are also important building blocks in organic synthesis. In this context, numerous synthetic methods towards the preparation of halofunctionalized vinyl selenides have been developed [5-8]. In 2009, Zeni and co-authors reported the use of 2-chalcogenealkynylanisoles for the preparation of 3-iodo-2-chalcogen-benzo[b]furans in CH_2Cl_2 at room temperature (Scheme 1a) [9]. In 2010, the Nishiyama group prepared β-bromo alkenyl phenyl selenides *via* a CuI-bpy-catalyzed reaction between various alkynes and diphenyl diselenide under air (Scheme 1b) [10]. In 2016, Zeni and co-workers employed biphenyl-2-alkyne derivatives as common starting materials for the preparation of both 9-iodo-10-organochalcogen-phenanthrenes and 9-organochalcogen-phenanthrenes *via* electrophilic cyclization and iron(III) chloride and diorganyl diselenide-mediated intramolecular cyclization, respectively (Scheme 1c) [11].

Scheme 1 Synthetic strategy for the formation of *β*-haloalkenyl selenides



Based on our previous reports [12] and as part of our efforts aimed at developing new synthetic methodologies for the preparation of heterocycles and heteroatom-containing compounds [13]. We herein divulge a highly regio- and stereoselective synthesis of (*E*)-*β*-iodoalkenyl selenides via the reaction of various alkynes with molecular iodine and diorganoyldiselenides under mild conditions using

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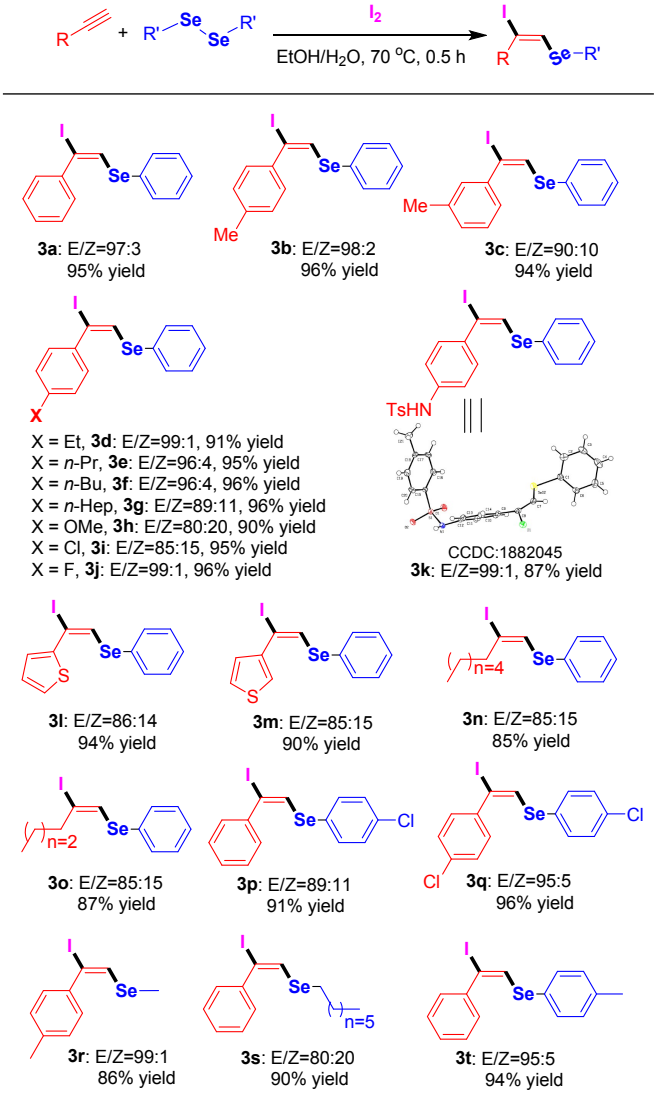
environmentally friendly aqueous media. Initially, we focused on developing a more efficient protocol in vitue of the reaction of **1a** and **2a** as a model system. After the screening reaction, an optimal yield (95%) and the ratio of *E:Z* to 97:3 of **3a** was obtained (See Table S1 in Supporting Information I (SI)). Under the optimized reaction conditions (Table S1, entry 10), we examined the scope and limitations of the iodoselenylation, the results for which are shown in Table 1. More specifically, 1-ethynyl-4-methylbenzene and 1-ethynyl-3-methylbenzene underwent iodoselenation successfully to afford the corresponding *β*-iodoalkenyl selenides in 94-96% yields and with excellent stereoselectivities (Table 1, **3b** and **3c**). We next employed the electron-rich compounds 1-ethyl-4-ethynylbenzene, 1-ethynyl-4-propylbenzene, 1-butyl-4-ethynylbenzene, 1-ethynyl-4-heptylbenzene and 1-ethynyl-4-methoxybenzene as substrates, and the corresponding products were obtained with excellent regioselectivity and stereoselectivity (Table 1, **3d**-**3h**).

Table 1 Substrate scope of terminal alkynes [a,b]

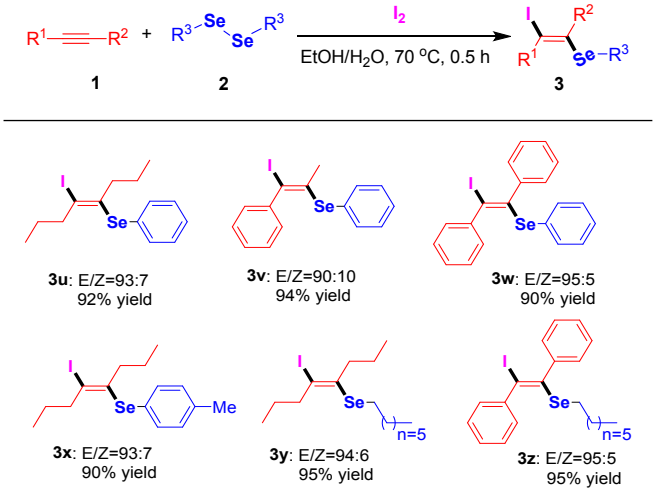


[a] Reaction conditions: Unless otherwise stated, alkynes (0.50 mmol), diselane (0.25 mmol), I_2 (0.275 mmol) in EtOH/H_2O (2:1, 1.5 mL) at 70 °C for 30 min under air atmosphere. [b] isolated yield.

Additionally, we also investigated the influence of electron-deficient substituents, including –Cl and –F groups, at the para-position of the aryl ring. The desired products were obtained in satisfactory yields (Table 1, **3i** and **3j**). The results show that the electronic character of the aryl ring does not have a significant influence on this transformation. The use of N-(4-ethynylphenyl)-4-methylbenzenesulfonamide as a substrate gave product **3k** in 87% yield; the stereochemistry and precise configuration of (*E*)-*β*-Iodoalkenyl selenide were unambiguously confirmed by single-crystal X-ray analysis. Interestingly, heteroaryl acetylenes, including 2-ethynylthiophene and 3-ethynylthiophene, also served as effective coupling partners and generated their corresponding *β*-iodoalkenyl selenides in high yields (Table 1, **3l** and **3m**).

To further expand the substrate scope, we turned our attention to the application of terminal alkyl acetylenes. As illustrated in Table 1, substrates bearing alkyl chains, such as *n*-oct and *n*-butyl compounds, underwent efficient coupling to produce the desired products in 85-87% yield (Table 1, **3n** and **3o**). We then tested the reactivity of different diselanes with this protocol. 1,2-Bis(4-chlorophenyl)diselane, 1,2-dimethyldiselane, 1,2-dihexyldiselane and 1,2-di-p-tolyldiselane were all well tolerated, affording the corresponding products in 90-96% yield (Table 1, **3p**-**3t**).

Table 2 Substrate scope of internal alkynes [a,b]



[a] Reaction conditions: Unless otherwise stated, alkynes (0.50 mmol), diselane (0.25 mmol), I_2 (0.275 mmol) in EtOH/H_2O (2:1, 1.5 mL) at 70 °C for 30 min under air atmosphere. [b] isolated yield.

In addition to terminal alkynes, we also employed internal alkynes as substrates, including diaryl, arylalkyl and dialkyl compounds. Reaction with these substrates proceeded smoothly, affording the desired products in good yields (Table 2, **3u**-**3w**). In comparison with previously reported protocols, this represents the first example of the preparation of difunctionalized alkenes with internal alkynes. Furthermore, we

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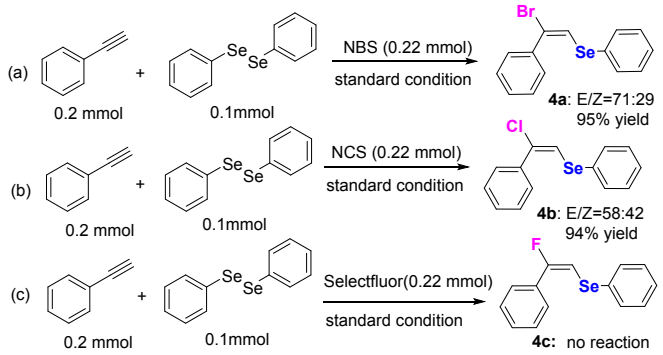
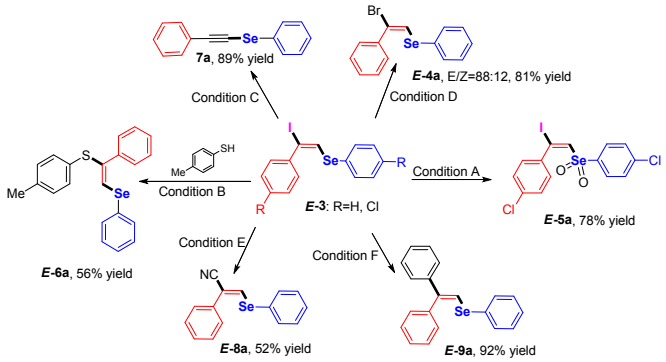
employed 1,2-di-p-tolyldiselane and 1,2-diheptyldiselane as substrates for reaction with oct-4-yne and 1,2-diphenylethyne, and the target products were obtained in high yields (Table 2, **3x**-**3z**).

Scheme 2 Synthesis of β-haloalkenyl selenides



To explore the generality of this protocol, we selected NBS and NCS as halogen sources to promote this transformation under the standard conditions. The expected bromoalkenyl and chloroalkenyl selenides were obtained, respectively, but with relatively poor *E:Z* selectivity (Scheme 2a and Scheme 2b). When we employed selectfluor as a halogen source in this model reaction, the expected product **4c** was not detected (Scheme 2c).

Scheme 3 Synthetic applications

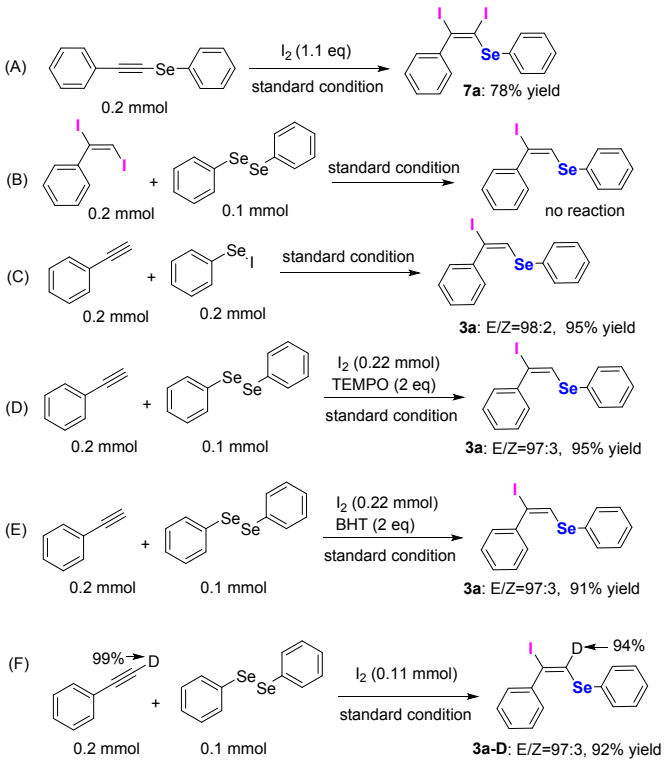


Reaction conditions: (A) **3q** (0.2 mmol), *m*CBPA (3 eq), CH_2Cl_2 (2mL), 40 °C, 12h, under N_2. (B) **3a** (0.2 mmol), *p*-toluenethiol (1.1 eq), CuI (0.1eq), Et_3N (2eq), 1,4-dioxane (2mL), 25 °C, 8h, under N_2. (C) **3a** (0.2 mmol), Cs_2CO_3 (2eq), H_2O (2mL), 100 °C, 12h, under N_2. (D) **3a** (0.2 mmol), $CuBr_2$ (2eq), THF (2mL), 40 °C, 24h, under N_2. (E) **3a** (0.2 mmol), Cu_2O (1eq), phenylacetonitrile (1.5eq), DMF (2mL), 130 °C, 12h, under air. (F) **3a** (0.2 mmol), phenylboronic acid (1.5 eq), $Pd(PPh_3)_4$ (0.1eq), K_2CO_3 (2eq), DMF/H_2O (2 mL/0.2 mL), 100 °C, 12h, under N_2.

The synthetic utility of the *β*-Iodoalkenyl selenide products was also explored. Selenide **3q** could be oxidized with *m*CPBA in dichloromethane solvent to give the corresponding compound ***E*-5a** in 78% yield. Furthermore, selenide **3a** was treated under standard Ullmann-type coupling[14], dehydroiodization, bromination[15], cyanation[16] and Suzuki[17] conditions, providing the corresponding coupling products **4a** and **6a**-**9a** in good yields (Scheme 3).

In order to gain mechanistic insight into the reaction, several control experiments were performed. First, we performed the reaction of phenyl(phenylethynyl)selane and I_2 under the optimal conditions and the unexpected disubstituted iodoalkenyl selenide **7a** was obtained (Scheme 4A). When (*E*)-(1,2-diiodovinyl)benzene was employed as a substrate under the standard conditions, the desired product **4a** was obtained (Scheme 4B). Next, we selected phenylacetylene and phenyl hypoiodoselenoite as starting materials for reaction under the standard conditions and the target product **4a** was obtained in good yield and stereoselectivity (Scheme 4, **C**).

Scheme 4 Control experiments

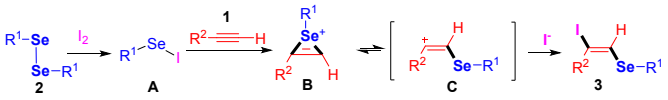


It was found that the addition of a radical scavenger (2 equiv of TEMPO or BHT) had no effect on the reaction outcome, suggesting that a single electron transfer process might not be involved in this iodoalkenyl selenide reaction (Scheme 4D, and 4E). Furthermore, by replacing phenylacetylene with deuterated phenylacetylene and carrying out the reaction under the optimal conditions with PhSeSePh and I_2, the corresponding *β*-iodoalkenyl selenide was obtained in 92% yield as a mixture of deuterated products with a ratio of 94:6 deuterated **3a**-D/non-deuterated **3a**-H. These results provide evidence that the reaction proceeds with hydrogen retention on the phenylacetylene starting material (Scheme 4F).

On the basis of the above findings, a plausible reaction pathway is depicted in Scheme 5. Initially, the presence of I_2 leads to electrophilic addition to the 1,2-diphenyldiselane to form phenyl hypoiodoselenoite **A,** which subsequently reacts with phenylacetylene to form intermediate **B** or **C** [6]. I^- then undergoes nucleophilic attack at the more substituted site of **B**

leading to ring opening *via* the possible intermediate **C**, affording difunctionalized product **3**.

Scheme 5 Proposed reaction mechanism



Conclusions

In summary, we have developed a new environmentally friendly, economical and straightforward approach to the synthesis of *β*-haloalkenyl selenides from readily available and inexpensive diselanes and I_2 with various aryl and alkyl alkynes. In comparison with previously reported protocols, the developed chemistry is also amenable to the transformation of internal alkynes, including halo-substituted compounds. The transformation proceeds in aqueous ethanol under mild conditions, furnishing the desired products in good to excellent isolated yields. The protocol is adaptable to a broad substrate scope with good functional group tolerance and provides an important foundation for the efficient preparation of functional alkenes from non-activated alkynes.

Acknowledgements

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