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Metal-free radical selenothiocyanation of terminal and internal alkynes†

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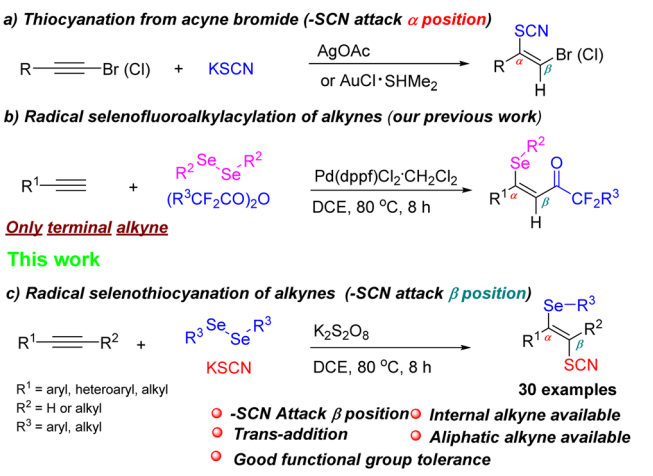
We report herein a synthetic strategy for the generation of direct selenothiocyanation from both terminal and internal alkynes *via* a radical process. Alkynes derived from bioactive molecules, such as L(−)-borneol and L-menthol, are suitable for selenothiocyanation reaction. This method features metal-free conditions and readily available reagents.

Direct difunctionalisation of alkenes/alkynes has attracted considerable interest because it features high atomic economy and allows for late-stage chemical transformations. Significantly, radical-mediated difunctionalization of unsaturated C–C bonds is one of the most promising ways to establish valuable transformations, but it remains a challenge due to the difficulties in decent substrate activation and selectivity control. In this context, the search for new strategies enabling selective construction of valuable and sophisticated compounds *via* difunctionalization of unsaturated hydrocarbons still remains a highly demanding goal, as they are expected to introduce two distinct functional groups in one simple operation by forming two new chemical bonds.[1–3]

Organic thiocyanates (R-SCN) are widely studied and useful in natural products, and medicinal chemistry such as antiparasitic compounds, fasicularin, and inhibitors of *Trypanosoma cruzi* proliferation, due to their unique biochemical properties.[4,5] Furthermore, thiocyanates are precursors for synthesizing valuable sulfur derivatives, including trifluoromethyl sulfides, gold-thiolates, and sulfur-containing heterocycles.[6] Therefore, their synthesis and late-functionalisation have been extensively explored, and considerable effort has been directed toward the preparation of thiocyanates and their derivatives.[7–9] On the other hand, vinyl selenides are highly valuable structures involved in many biological activities and often serve as important synthetic intermediates and therapeutic entities.[10,11] In the last few decades, various synthetic methods for vinyl selenide skeletons have been developed through the selenation of alkenes and alkynes.[12]

Recently, Jiang and Xu demonstrated that the pioneer homogeneous catalyzed addition of sulfur nucleophiles to alkynes was developed to accomplish the prepared hydrothiocyanation from haloalkynes and KSCN/NH_4SCN by using Ag/Au as a catalyst, respectively (Scheme 1a).[9] We recently have disclosed the palladium-catalyzed radical selenotrifluoroacetylation of terminal alkynes with high regio- and stereoselectivity under mild conditions according to the elicitation by the previous literature (Scheme 1b).[10] However, to the best of our knowledge, strategies for introducing –SeR and –SCN functional groups into an alkyne have not yet been established.



Scheme 1 Protocols for thiocyanation/selenation of alkynes.

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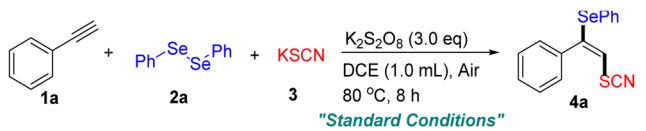
Therefore, novel general strategies that allow for this kind of transformation are needed. Potassium persulfate ($K_2S_2O_8$) is found to an effective oxidant, which is an inorganic salt, and it is a less expensive solid with strong oxidizing properties in nature and has emerged as an alternative for many of metal-catalyzed reactions in cleaner, and environment-friendly conditions.[13] With continuous interest in the radical-promoted difunctionalization of alkynes or transformation from alkynes,[3,10] we investigated whether both selenyl and SCN radicals are applicable to such a transformation. Herein, we presented a user-friendly strategy for the $K_2S_2O_8$-promoted radical selenothiocyanation by employing alkynes, diorganyl diselenide and KSCN as substrates under mild and metal-free conditions. The obtained products exhibited high regio- and stereoselectivity (Scheme 1d).

First, Pd(dppf)Cl_2·CH_2Cl_2 and Ru(OAc)$_3$ were employed as the precatalysts to test the possible transformation based on our previous experiments.[3b,11] We obtained the difunctionalisation product **4a** with 68% and 12% yields, respectively (Table 1, entries 1 and 2). Hence, phenylacetylene (**1a**) and PhSeSePh (**2a**) were selected as model substrates, suitable reaction conditions were determined, and the reactivity and selectivity of thiocyanate and selenyl groups toward different alkynes were investigated. Surprisingly, a catalyst-free condition is important to modern organic synthesis and improves the yield of **4a** (Table 1, entry 3). Next, a series of "SCN" sources were evaluated by using $K_2S_2O_8$ as a promoter for 8 h at 80 °C. We found that KSCN as a substrate gives the desired product in 93% isolated yield (Table 1, entries 4–6). Replacing the promoters with $(NH_4)_2S_2O_8$ and benzoyl peroxide resulted in a dramatic decrease in yield (Table 1, entries 7–8). When 1.0 mmol of $K_2S_2O_8$ was employed in this reaction, a low 25% yield of **4a** was obtained (Table 1, entry 9). Then, we optimized the solvent, and the yield of **4a** was decreased when *N*,*N*-dimethylacetamide (DMAc), *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, tetrahydrofuran (THF), or EtOH were used as the solvents under similar reaction conditions (Table 1, entries 10–14). Air plays an important role in this transformation, and little target product **4a** was detected under a N_2 atmosphere (Table 1, entry 15). The presence of O_2 might accelerate the generation of PhSe and SCN. Finally, this reaction can occur in the dark and lead to good yield (Table 1, entry 16).

Table 1 Optimization of the reaction conditions[a]

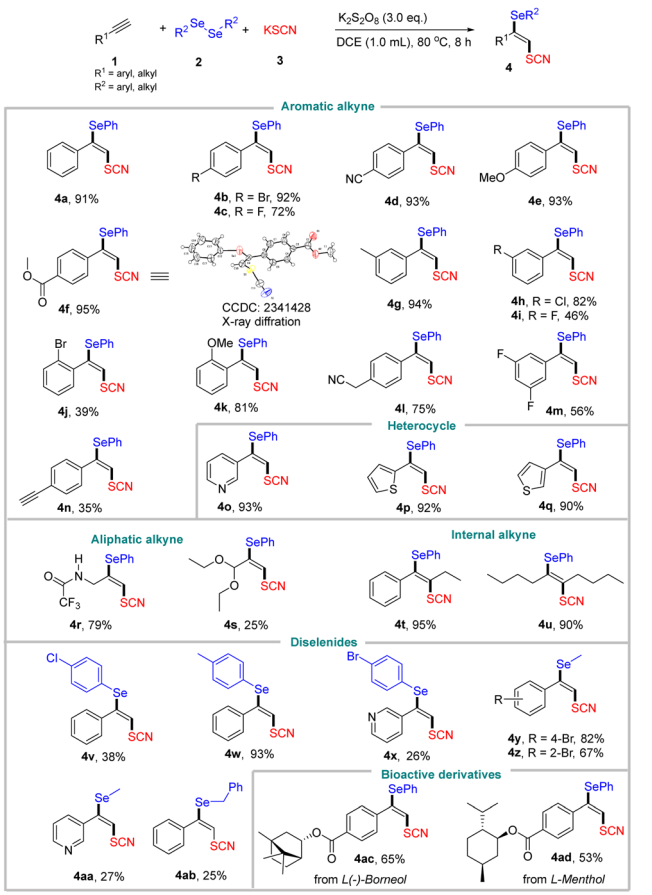


Entry	Deviation from standard conditions	Yield (%)
1	Pd(dppf)Cl_2·CH_2Cl_2 (5% mol)	49
2	Ru(OAc)$_3$ (5% mol)	12
3	None	93 (91)
4	NH_4SCN instead of KSCN	18
5	NaSCN instead of KSCN	35
6	AgSCN instead of KSCN	46
7	$(NH_4)_2S_2O_8$ instead of $K_2S_2O_8$	55
8	Benzoyl peroxide (BO) instead of $K_2S_2O_8$	38
9	1.0 mmol of $K_2S_2O_8$	25
10	DMAc instead of DCE	Trace
11	DMF instead of DCE	32
12	1,4-Dioxane instead of DCE	58
13	THF instead of DCE	45
14	EtOH instead of DCE	52
15	Under N_2 atmosphere	26
16	In the dark	90

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.3 mmol, 0.6 equiv.), **3** (0.6 mmol, 1.2 equiv.), [Pd] or [Ru] (5% mol), $K_2S_2O_8$ (1.5 mmol, 3.0 equiv.), Solvent (1.0 mL), 80 °C, air, 8 h. Isolated yields.

Under the optimized conditions, we then investigated the generality of this selenothiocyanation reaction. As shown in Scheme 2, various terminal or internal alkynes and diorganyl diselenides exhibited good performance under the present reaction conditions, producing the corresponding selenothiocyanation products in moderate to excellent yields. First, this strategy can readily accommodate a range of aromatic acetylenes (**4b–4n**) with a good functional group tolerance, including electron-withdrawing and electron-donating groups (CN, CO_2Me, Ph, F, Cl, Br, Me, OMe, and CH_2CN).

When 1,4-diethynylbenzene was employed in this transformation, only mono-selenothiocyanation product **4n** was obtained with 35% isolated yield, but another alkynyl was retained. This result further illustrates the diversity and

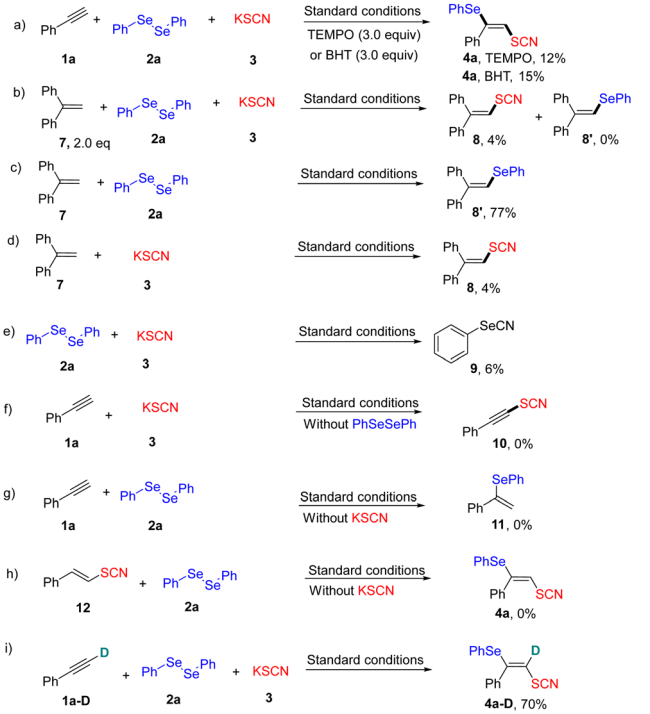


Scheme 2 Scope for selenothiocyanation of alkynes. Reaction conditions: **1** (0.5 mmol), **2** (0.3 mmol, 0.6 equiv.), **3** (0.6 mmol, 1.2 equiv.), DCE (1.0 mL), 80 °C, $K_2S_2O_8$ (1.5 mmol, 3.0 equiv.), air, 8 h. Isolated yield.

usefulness of this novel method. The structure of compound **4f** was confirmed by X-ray diffraction analysis (CCDC 2341428, Fig. S7, ESI†). Furthermore, terminal alkynes bearing heterocycles, such as 3-pyridine, 3-thiophene, or 2-thiophene motifs were tolerated, and the expected products (**4o–4q**) could be prepared in excellent yields (93%, 92%, and 90% yield, respectively). Next, this transformation was investigated using aliphatic alkynes. 2,2,2-Trifluoro-*N*-(prop-2-yn-1-yl)acetamide and 3,3-diethoxyprop-1-yne could afford the corresponding products **4r** (79%) and **4s** (25%), respectively. Significantly, internal alkynes, such as but-1-yn-1-ylbenzene and dec-5-yne, afforded the expected products **4t** and **4u** in good yields. When diphenyl diselenide was converted into other diorganyl diselenides in the same reaction, diaryl and dialkyl diselenides (**4v–4ab**) were converted in 25–93% yields. Notably, biologically active alkynes, such as L(−)-borneol and L-menthol derived from terpenes, were successfully used to generate the corresponding products **4ac** (65%) and **4ad** (53%), further illustrating the diversity and usefulness of this novel method.

Next, we explored the synthetic utility of the developed chemistry. As shown in Scheme 3, we carried out a gram-scale reaction for the synthesis of (*E*)-phenyl(1-phenyl-2-thiocyanatovinyl)selanes, and performing the reaction of compound **1a** on a 5.0 mmol scale could proceed well to generate **4a** in 77% yield (Scheme 3a). Moreover, the desired compounds **6a–6c** were obtained in 38–53% yield through a Suzuki–Miyaura coupling of reactant **5a** phenylboronic acid through palladium and copper catalysis reaction (Scheme 3b).

To gain mechanistic insights into the newly developed alkyne difunctionalization reaction, we conducted a series of control experiments (Scheme 4). First, the yield of product **4a** dramatically decreased when 3.0 equivalents of radical-scavenging reagent TEMPO or BHT were added to the reaction mixture (Scheme 4a). Next, after **1a** was replaced with ethene-1,1-diyldibenzene **7** under standard reaction conditions, the (2-thiocyanatoethene-1,1-diyl)dibenzene **8** was obtained in only 4% yield (Scheme 4b). These results indicate that the reaction involves a radical process. Then, when ethene-1,1-diyldibenzene **7** was reacted with **2a** or **3**, the compound **8′** or **8** was obtained with 77% and 4% yield, respectively (Schemes 4c and d). When we employed **2a** and **3** in standard conditions, the compound **9** was detected (Scheme 4e). In addition, no reaction occurred to afford **10** between **1a** and **3** in the absence of **2a** under the standard reaction conditions (Scheme 4f). Product **11**

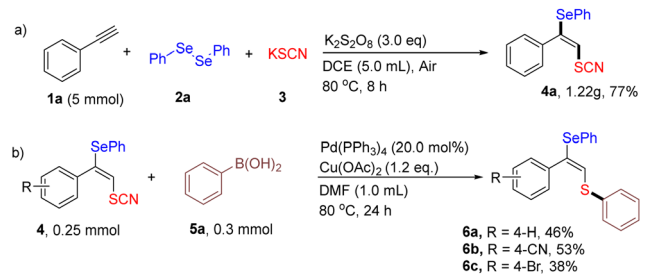


Scheme 4 Preliminary mechanistic experiments.

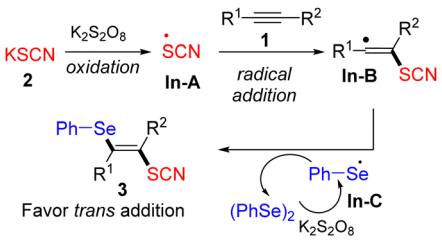
was not obtained when **2a** was removed under the standard conditions (Scheme 4g). Moreover, after the treatment of (*E*)-(2-thiocyanatovinyl)benzene **10** with **2a** without KSCN, the target molecule **4a** was not detected (Scheme 4h). These data reveal that compounds **10**, **11**, and **12** are not the reactive intermediates. Finally, changing **1a** with deuterated **1a-D** resulted in **4a-D** as the sole product in 70% yield (Scheme 4i).

Based on the above-mentioned results and the previous literature,[9a,11] a possible reaction pathway is depicted in Scheme 5. Initially, KSCN dissociated in DCE solution is oxidized by $K_2S_2O_8$ under air to produce thiocyanate radical intermediate **In-A**. Subsequently, the addition of radical **In-A** to alkyne **1** affords vinyl radical **In-B**. Finally, vinyl radical **In-B** is trapped by diorganyl diselenide **2** to afford (*E*)-phenyl(1-phenyl-2-thiocyanatovinyl)selane **3** because of the sterically less hindered factor. Meanwhile, the homocoupling of radical **In-C** PhSe• leads to the formation of PhSeSePh in the presence of $K_2S_2O_8$.

In summary, we have developed a regioselective selenothiocyanation of both terminal and internal alkynes with commercial



Scheme 3 Synthetic utility.



Scheme 5 Proposed mechanism.

diorganyl diselenides and potassium thiocyanate under metal-free conditions. Being different from the previously reported –SCN addition occurring at the α-site, the KSCN selectively reacts with the alkynes at the β-site in the present difunctionalization reaction. A series of selenothiocyano alkenes were obtained in moderate to excellent yields with high regio- and stereoselectivity. In addition, the striking features including good functionality and substrate tolerance, synthetic diversity, readily available feedstocks, and transition-metal free conditions highlight the practicality of the present work. In our laboratory, further study on the difunctionalization strategy and the applications of the products are currently in progress.

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Data availability

The data underlying this study are available in the published article and its ESI.†

Conflicts of interest

There are no conflicts to declare.

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