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Cesium-Catalyzed Regioselective Synthesis of Trisubstituted Heteroatom Alkenes: A New Strategy for the Preparation of Functional Alkenes

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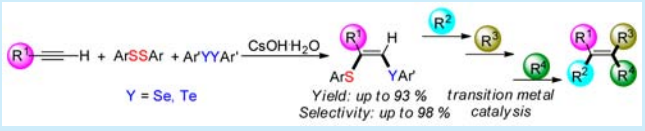
Supporting Information

ABSTRACT: A highly chemo-, regio-, and stereoselective method for the synthesis of (*Z*)-vinylic selenosulfides and (*Z*)-vinylic tellurosulfides in a one-pot reaction of terminal alkynes, diaryl disulfides, and diaryl diselenides (ditellurides) catalyzed by simple base cesium hydroxide monohydrate is described. Due to the different activities of the carbon−chalcogen bonds, the target products cleave selectively and act as a kind of readily available platform molecule for the synthesis of tetrasubstituted alkenes. The mechanism of thioselenation was studied by experimental and theoretical methods.



Since the report by Georg Witting on the transformation of ketone to olefin in 1953,[1] the use of alkenes for the construction of complex molecules has become strategically important.[2] For example, tri- and tetra-substituted alkenes are used in the syntheses of natural products such as Nileprost analogues[3] and Ratjadone,[4] as well as drugs such as Tamoxifen[5] and Roaccutane.[6] In addition, it is envisaged that there are potential uses of alkenes in polymer chemistry[7] and biochemistry.[8] But there are challenges, especially in terms of stereoselective synthesis of alkenes.

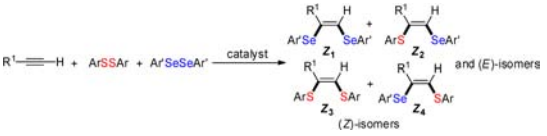
In general, it is difficult to attach reagents to double bonds due to the congested nature and eclipsing interactions of the products.[9] The carbon metalation of alkynes could be the most efficient method for the preparation of tri- and tetrasubstituted alkenes,[10] but the regio- and stereoselectivity of products is difficult to control. Recently, by using directing groups[10a] or employing symmetrical alkynes as substrates,[10f] the issue of regioselectivity is addressed partially, especially when symmetrical alkynes are used as substrates.[10g] However, the problem of structural flexibility still exists.

(*Z*)-Vinylic selenosulfides and (*Z*)-vinylic tellurosulfides are important platform molecules for stereoselective synthesis of tri- and tetrasubstituted alkenes (Figure 1). It is because the C−S, C−Se, and C−Te bonds can be readily cleaved in high selectivity.[11,10b] Due to the important functionality of (*Z*)-vinylic selenosulfides and tellurosulfides, efforts are devoted toward their generation.[12]

Figure 1. Preparation of tetrasubstituted alkenes using (*Z*)-diorganochalcogen alkenes as platform molecules.

Thioselenation of alkynes is one of the simplest, most efficient methods for the preparation of vinylic selenosulfides wherein alkynes, diaryl disulfides, and diaryl diselenides are reacted in one pot. In such a reaction, there are a total of eight products: Z_1, Z_2, Z_3, Z_4, and their relative *E*-stereoisomers (Scheme 1). Thus, the control of chemo- and regioselectivity of products is essential. Until now, the only two examples for such control are by means of photoirradiation[12a] and Rh catalysis[12b] (Scheme 2, a and b), but the approaches are limited for special or narrow substrates, and the chemo- and regioselectivity of products are poor. Therefore, it is necessary to develop a new method that can synthesize (*Z*)-vinylic selenosulfides regio-, chemo-, and stereoselectively under mild reaction conditions.

Scheme 1. Possible Products of Thioselenation



Herein, we demonstrate a highly chemo-, regio-, and stereoselective method for the synthesis of (*Z*)-vinylic selenosulfides using simple cesium hydroxide monohydrate ($CsOH·H_2O$) as a catalyst. First, propargyl alcohol was treated with a binary system of diphenyl disulfide and diphenyl diselenide, and a 71% yield of the desire product was obtained in Z_2-form (Scheme 3, **4a**). There is no detection of (*E*)-isomers

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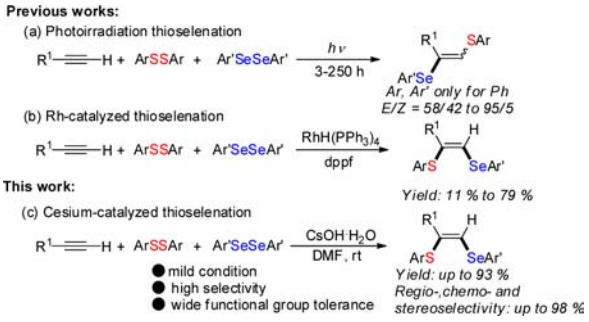
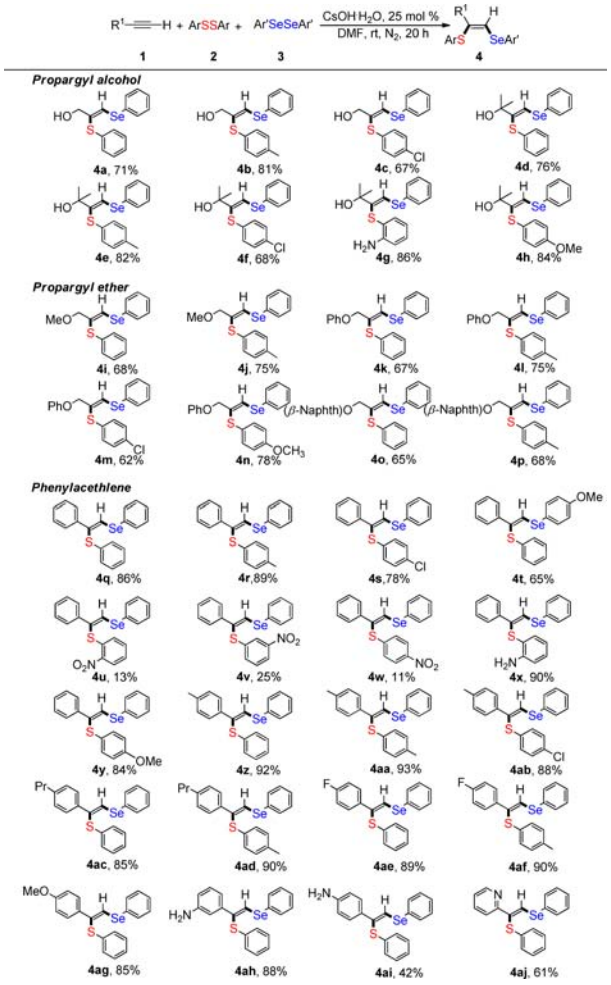
Scheme 2. Thioselenation of Alkynes via Three Main Routes



Scheme 3. Thioselenation of Alkynes with a Binary System of Diaryl Disulfides and Diaryl Diselenides[a,b]



[a]Reaction conditions: alkynes (**1**) (0.2 mmol), diaryl disulfides (**2**) (0.1 mmol), diaryl diselenides (**3**) (0.1 mmol), $CsOH{\cdot}H_2O$ (25 mol %), DMF (2 mL), rt, N_2, 20 h. [b]Isolated yields.

in ^1H NMR analysis of the crude product, exemplifying the idea of atom and step economy. After optimization of reaction conditions (Table S1), the most suitable parameters are alkynes, diaryl diselenides (0.5 equiv), diaryl disulfides (0.5 equiv), cesium hydroxide monohydrate (0.25 equiv), DMF, rt (25 °C), 20 h, and under N_2.

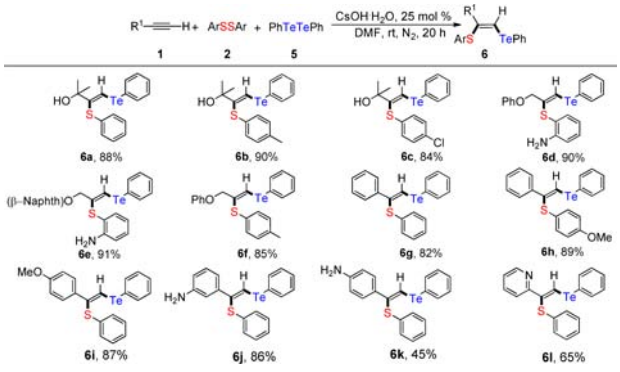
To demonstrate the efficiency and generality of the reaction, we applied the method to various terminal alkynes (**1**) and different diaryl disulfides (**2**) and diaryl diselenides (**3**). The results are summarized in Scheme 3.

As shown in Scheme 3, both propargylic alcohols and ethers and aromatic alkynes give the desired products in good to excellent yields. And the steric hindrance of the proparyl alcohols affects the stereoselectivity slightly (**4a**, 71%; **4d**, 76%). When the hydroxyl of proparyl alcohols is substituted by methoxyl, phenoxyl, and naphthoxyl, there is still a good yield for (*Z*)-vinylic selenosulfides (**4i**–**4p**, 62%–78%). The efficiency may be related to the electrostatic interaction of the cesium ion with the O-atom of alcohols and ethers and the promotion effect of the benzene ring on the reactions.

In addition, the reactions show good tolerance toward various phenyl acetylenes with electron-donating (e.g., *p*-methyl, *p*-(*n*-Pr), *p*-OMe, *m*-NH_2, except for *p*-NH_2) and -withdrawing groups (e.g., fluoro), leading to corresponding products in excellent yields (**4z**–**4ah**, 85%–92%). But it is not suitable for the phenyl acetylenes with a strong electron-withdrawing group (eg., *p*-NO_2, *p*-CN). The thioselenation of 2-ethynylpyridine with diphenyl diselenide and diphenyl disulfide also gives the desired product in moderate yield (**4aj**, 61%). Furthermore, there is also tolerance toward different functional groups in disulfides (**2**) and diselenides (**3**). For example, in the case of diaryl diselenide with an electron-donating group (e.g., methoxyl), the desire product is obtained in 65% yield (**4t**). For diaryl disulfides, the attachment of an electron-withdrawing group to the phenyl ring results in a good yield and regioselectivity (**4s**, 78%), and the same applies to the attachment of electron-donating groups to the ring (**4r**, 89% and **4x**, 90%, **4y**, 84%). The attachment of a NO_2 group to the phenyl ring of disulfides (**2**) gives the desired products in poor yields (**4u**–**4w**, 11–25%), and the yields of (*Z*)-vinylic disulfides increase, plausibly because of the high reactivity of the disulfides. As for 1-hexyne, the generation of desired products as detected in TLC analysis is low, and most of the reactants can be recovered.

We extended the procedure for the synthesis of (*Z*)-vinylic tellurosulfides and telluroselenides (Scheme 4). It was found that

Scheme 4. Thiotelluration of Alkynes with a Binary System of Diaryl Disulfides and Diaryl Ditellurides[a,b]



[a]Reaction conditions: alkynes (**1**) (0.2 mmol), diaryl disulfides (**2**) (0.1 mmol), diaryl ditellurides (**5**) (0.1 mmol), $CsOH{\cdot}H_2O$ (25 mol %), DMF (2 mL), rt, N_2, 20 h. [b]Isolated yields.

the method is not suitable for the synthesis of (*Z*)-vinylic telluroselenides mainly because the two heteroatoms Se and Te are rather similar in chemical and physical features. In the case when S and Te are heteroatoms, (*Z*)-vinylic telluroselenides are obtained in excellent yield (**6d**, 90%). Furthermore, both electron-donating (**6b**, 90%, **6d**, 90% and **6e**, 91%, **6f**, 85%, **6h**,

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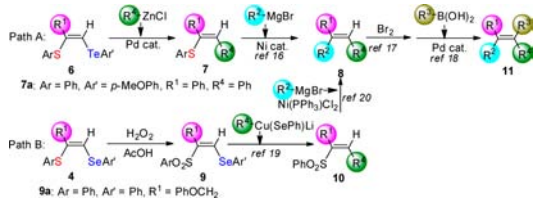
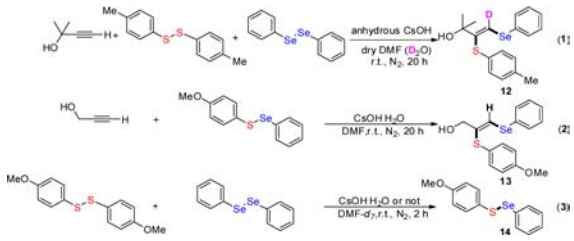
89%) and -withdrawing groups (**6c**, 84%) in the phenyl ring of diaryl disulfides lead to excellent yields of the corresponding products. Similar to thioselenation, thiotelluration works well with various phenyl acetylenes with an electron-donating group (e.g., *p*-OMe, *m*-NH_2) (**6i** and **6j**, 87% and 86%). The reaction gives the corresponding product in a moderate yield when 2-ethynylpyridine is used as a substrate (**6l**, 65%).

We also investigated the use of the products in the synthesis of tetrasubstituted alkenes. Recently, a number of methods for stereoselective synthesis of tetrasubstituted alkenes were reported,[13] but chemo- and regioselectivity are hard to control in some of these methods.[13b,d,e] Due to the different activities of C−S, C−Se, and C−Te bonds and the retention of configuration feature of the chalcogen atoms (S, Se, Te), the carbon−chalcogen bonds of (*Z*)-vinylic dichalcogenides can be cleaved readily with high stereoselectivity.[11,12d,14] For example, with **6h** and **4k**, we can easily obtain (*Z*)-vinylic monchalcogenides (**7a**, 62%; **9a**, 93%) through cleaving the C−Te bond[11a] and the transformation of the C−S bond,[15] respectively. Thus, the products can be efficiently transformed to the desired tetrasubstituted alkenes using the methods reported in the references (Scheme 5).[16−20]

Scheme 5. Possible Ways for the Synthesis of Tetrasubstituted Alkenes



To shed light on the mechanism of thioselenation, we treated 2-methylbut-3-yn-2-ol with a binary system of diphenyl diselenide and di(4-methylphenyl) disulfide in dry DMF/D_2O (eq 1) and obtained (*Z*)-vinylic selenosulfide (**12**). The result



indicates that the first step of thioselenation is the removal of acid hydrogen from terminal alkyne. We also found that cesium hydroxide monohydrate catalyzes the thioselenation of unsymmetrical diorganoyl dichalcogenide (RSSeR′) with a terminal alkyne for exclusive generation of (*Z*)-vinylic selenosulfide (**13**) (eq 2); the result suggests that unsymmetrical diorganoyl dichalcogenides (RSSeR′) have an active role to play in thioselenation. When diphenyl diselenide is treated with di(4-methoxyphenyl) disulfide in DMF-d_7 (eq 3), selenosulfide (**14**) is obtained in 20% yield, and a similar result is observed when diphenyl ditelluride is treated with di(4-methoxyphenyl) disulfide. In contrast, we do not obtain telluroselenide (RSeTeR′) when diphenyl diselenide is treated with diphenyl ditelluride in DMF-d_7 in the presence or absence of CsOH·H_2O. The overall results imply that the active species for thioselenation should be unsymmetrical diorganoyl dichalcogenides (RSSeR′) rather than diaryl disulfides or diselenides. An acetylenic anion is easily reacted with unsymmetrical diorganoyl dichalcogenides (RSSeR′) to form an acetylenic selenide intermediate, due to the stronger electronegativity of the S-atom then that of the Se-atom.

The *E*/*Z* diastereoselectivity of the products is mainly driven by the addition reaction of an arylthio anion (ArS^-) with the acetylenic selenide intermediate. Various cesium intermediates (I_1−I_7) should be formed during the addition. The structures and relative energies of the cesium intermediates at the B3LYP/6-311G(d,p) and B3LYP/6-311++G(d,p) level using the Gaussian 09 B.01 package[21] show that the I_1 intermediate is more stable than the other isomers (I_2−I_7), because of the lower relative energies (Figure 2). The stability of the I_1-form structure may be

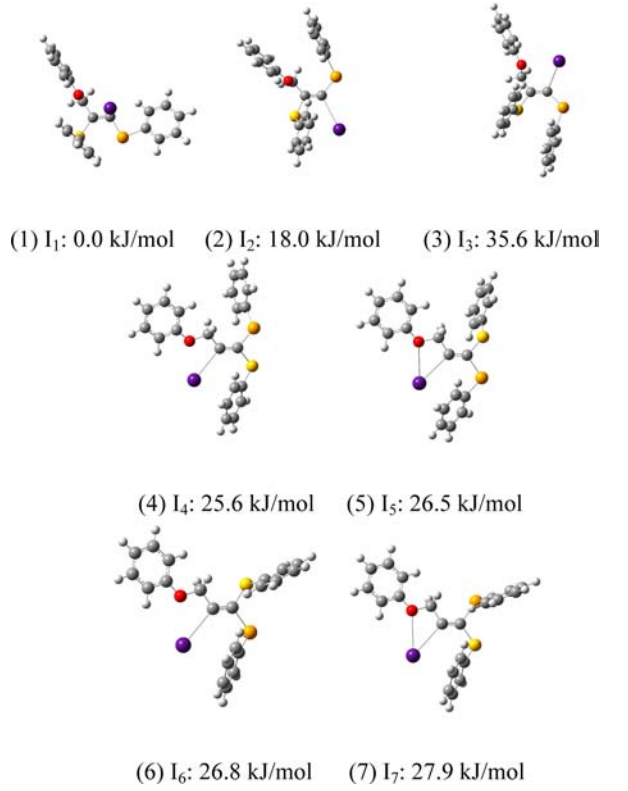


Figure 2. Structures and relative energies of the various isomers of the cesium intermediates at B3LYP/6-311++G(d,p)//B3LYP/6-311G-(d,p) level.

a result of the cation interaction between Cs^+ and the benzene ring as well as interaction between the O- and Cs-atoms (see Figure S9 of SI). In addition, the Se-atom can also stabilize the carbanions bonding to it, which contributes to the stability of the I_1 intermediate.[22]

On the basis of the calculation and experimental results, a plausible mechanism is brought forward (Figure 3a). First, there is the removal of acid hydrogen from terminal alkyne **1** giving the cesium intermediate **a** as a result. Second, selenosulfides (tellurosulfides) **15** obtained via the exchange reaction of **2** and **3**(**5**) react readily with cesium intermediate **a**, giving species **b** and **c**. Finally, there is nucleophilic addition of species **c** with **b** to give cesium intermediate **d** and hydrogen addition by water to give the desired products **4** or **6**. The configuration is confirmed by X-ray (Figure 3b) and NOE analyses (see Figures S2 and S3).

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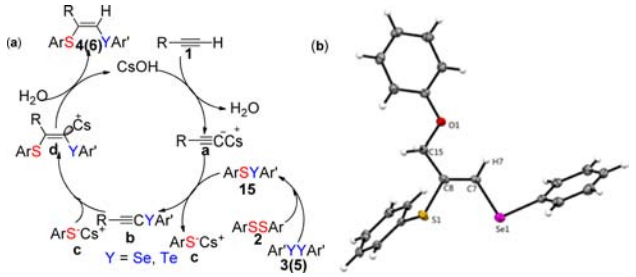

Figure 3. (a) A plausible mechanism of thioselenation or thiotelluration. (b) X-ray crystal structure of **4j**.

In summary, we developed a convenient and green method for the synthesis of (*Z*)-vinylic dichalcogenides regio-, chemo-, and stereoselectively from alkynes using a binary system of diaryl disulfides and diaryl diselenides (ditellurides) catalyzed by $CsOH{\cdot}H_2O$. These (*Z*)-vinylic dichalcogenides can be used as platform molecules for the synthesis of tetrasubstituted alkenes such as (*Z*)-tamoxifen which is an important drug for the treatment of breast cancer.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data, and copies of ^1H, ^{13}C, and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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