

Solvent-Free Asymmetric Alkoxy-Selenylation of Styrenes Using I₂ / DMSO Catalytic System †

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† Presented at the 1st International Electronic Conference on Catalysis Sciences, 10–30 November 2020; Available online: <https://sciforum.net/conference/ECCS2020>.

Published: 10 November 2020

Abstract: Herein, we reported a study about the employment of the I₂/DMSO catalytic system in the asymmetric alkoxy-selenylation of styrenes by using chiral non-racemic reagents and how it influences on the diastereoisomeric excess of the corresponding β-alkoxy-selenides. The use of [(1S)-1-(methylthio)ethyl]phenyl diselenide provided products in satisfactory yields and diastereoisomeric excesses. Comparative study between microwave heating and room temperature was also performed.

Keywords: alkoxy-selenylation; asymmetric synthesis; green chemistry

1. Introduction

Organoselenium compounds have been widely studied in recent years due to the diverse therapeutic properties attributed to them, especially the antioxidant activity and the ability to mimic some enzymes [1–3]. Recently, the discovery that Ebselen showed important anti-viral activity against the main protease of the virus that causes COVID-19, has put selenium in an even greater level of prominence in the academic community [4]. From the synthetic point of view, these compounds are important building blocks since they can perform several organic transformations due to the particular reactivity of the selenium atom [5–7]. These reasons make the development of these compounds an area that has been attracting more and more researchers.

In this context, one of the most studied methods for the construction of the C-Se bond is the addition of electrophilic selenium species to olefins with the formation of the seleniranium intermediate, that is subsequently attacked by a nucleophile [8,9]. When the nucleophile is an alcohol, the reaction is called alkoxy-selenylation and the products, β-alkoxy-selenides, which are obtained mostly with Markonikov regiochemistry, have a stereogenic carbon that, without the control of the reaction conditions, will be obtained in a racemic mixture [10].

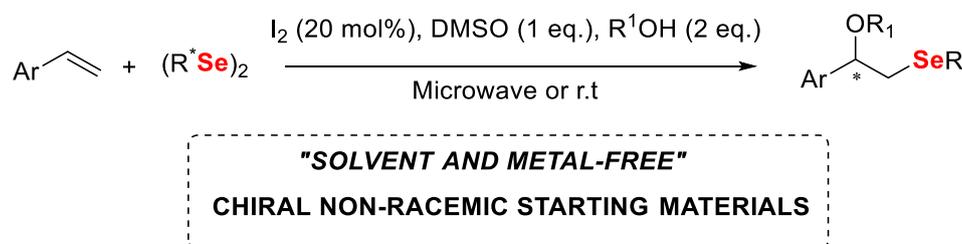
In order to control the formed chiral center, several optically active diselenides have been used as selenylation agents and chiral auxiliaries in the olefin alkoxy-selenylation reactions. Diselenides that contain nitrogen, oxygen and sulfur heteroatoms in the chiral portion of their structures [11] as well as diselenides derived from terpenes [12] are examples of the successful use of these reagents. Considering that these reactions lead to the formation of a new stereogenic center, it is possible to analyze the influence of the reagent in the induction of chirality, by determining the diastereoisomeric excess of the desired product.

On the other hand, the generation *in situ* of electrophilic selenium species is a very useful method since it avoids previous stages of preparation, which makes the synthesis more direct. Among the

methods for the alkoxy-selenylation of alkenes, the most used is the oxidation of dioganoyl diselenides in the presence of various oxidizing agents, such as, for example, ammonium persulfate [13], oxone [14], hypervalent iodine reagents [15] as well as inorganic metallic reagents like $Mn(OAc)_2$ [16], $CuSO_4$ [17] and $Ce(NH_4)_2(NO_2)_6$ [18]. Although all of these methods are efficient, they have some environmental disadvantages such as long reaction times, use of large amounts of solvents and / or metals as well as use of strong oxidizing agents. These particularities make the study of new environmentally methodologies for the alkoxy-selenylation of olefins be an important field of synthetic organic chemistry.

In this context, molecular iodine (I_2) has been establishing itself as a versatile and sustainable reagent for the *in situ* preparation of electrophilic selenium species since it is solid, non-toxic, non-metallic and of low cost [19,20]. We demonstrated the efficiency of catalytic amounts of this reagent in association with stoichiometric amounts of DMSO in alkoxy-chalcogenylation reactions of olefins using non-chiral dichalcogenides [21]. This methodology allowed the preparation of a series of compounds using only equivalent amounts of the reagents, in the absence of solvents, besides being extremely energy efficient, forming the desired products in just 10 min in microwave.

As a continuation of this work, herein, we report a versatile and environmentally sustainable method for the asymmetric alkoxy-selenylation of styrenes using the catalytic system I_2 /DMSO in the presence of chiral non-racemic diselenides and alcohols in a solvent and metal-free reaction medium (Scheme 1).



Scheme 1. I_2 -catalyzed alkoxy-selenylation of styrenes under solvent-free conditions.

2. Materials and Methods

2.1. General Procedure for the Synthesis of Compounds 3a-i

The styrenes (0.5 mmol), diselenides (0.25 mmol), iodine (20% mol), respective alcohol (2 equiv.) and DMSO (1 equiv.) were placed in a dry microwave glass tube. The tube was sealed and placed into a CEM Discover microwave apparatus. Initially, an irradiation power of 100 W was applied. After the temperature reached 50 °C, the instrument was automatically adjusted to maintain a constant temperature. The reactions conducted at room temperature were performed using a Schlenk tube open to air for 24 h. After the corresponding time, the reactions were quenched with a solution of sodium thiosulfate 10% and the aqueous layer was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was completely removed under vacuum to give the crude products. Purification was carried out by flash chromatography using mixtures of hexane/ethyl acetate as eluent.

3. Results and Discussion

The studies were conducted using styrene and the chiral non-racemic diselenide in the presence of 2 equivalents of the corresponding alcohol, 20 mol% of I_2 and 1 equivalent of DMSO. For comparison purposes, the experiments were carried out using heating of 50 °C by microwave irradiation and 24 h at room temperature (Figure 1). Initially the reactions were carried out using methanol as alcohol. Using the [(1S)-1-(methylthio)ethyl]phenyl diselenide in microwave conditions, the corresponding product 3a was obtained with 95% yield and 68% diastereoisomeric excess (*d.e.*) in 10 min. The same reaction conducted at room temperature led to the formation of 3a in 75% yield and 80% of *d.e.* Using the camphor-derived diselenide, the corresponding product 3b was obtained in 36%

yield after 15 min and 20% of *d.e.* Similar results were obtained at room temperature, where after 24h, 3b was obtained in 41% and *d.e.* of 20%. Modest results, on the other hand, were obtained with the use of a chiral diselenide derived from amide. The corresponding product 3c was not obtained after 20 min of reaction in the microwave and at room temperature, after 24 h, it was obtained in 45% yield and only 11% *d.e.*

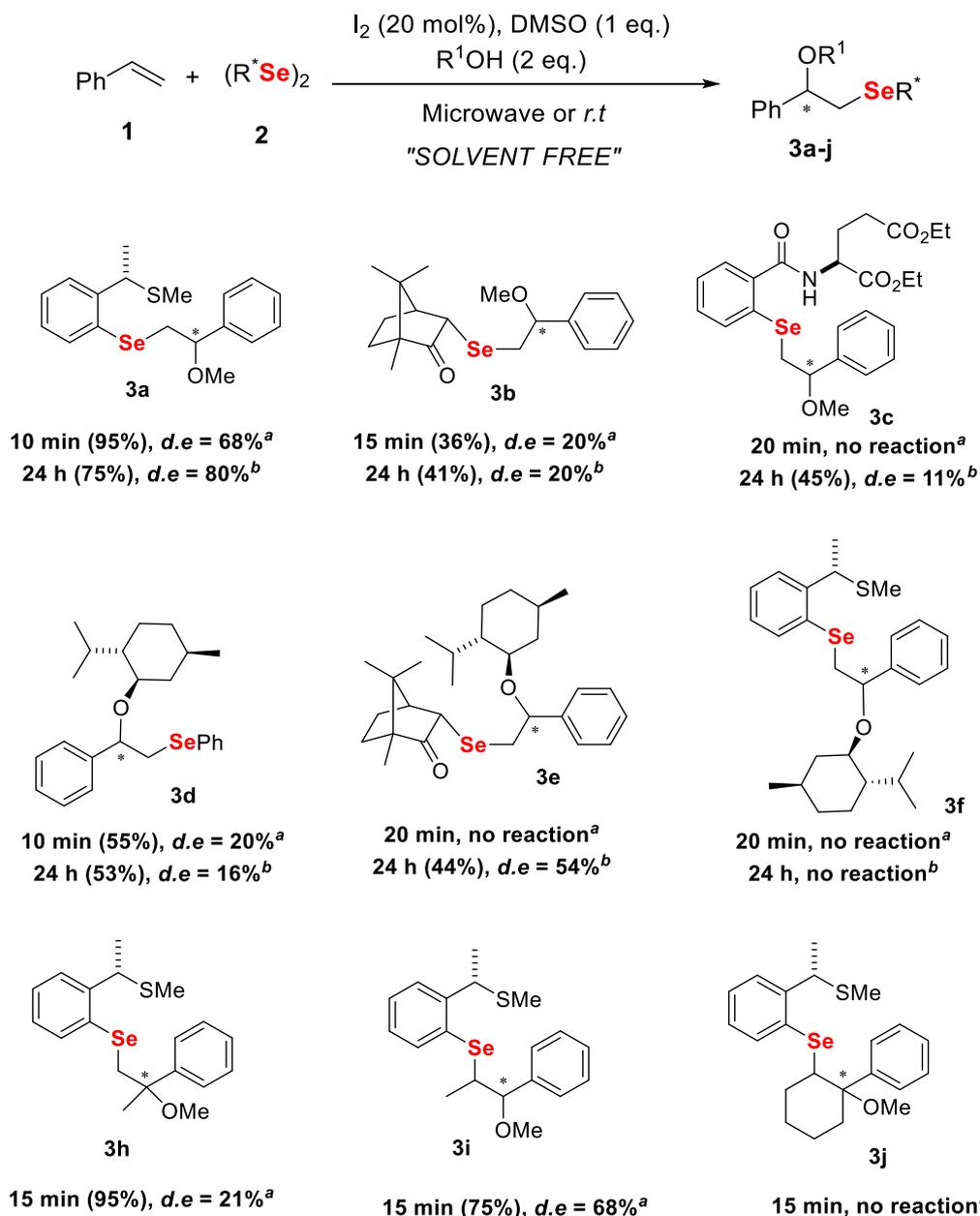


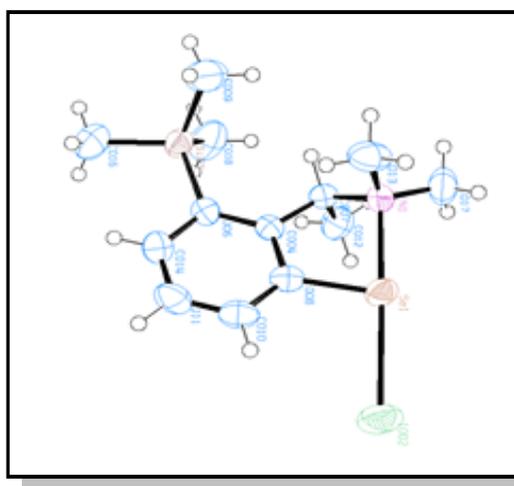
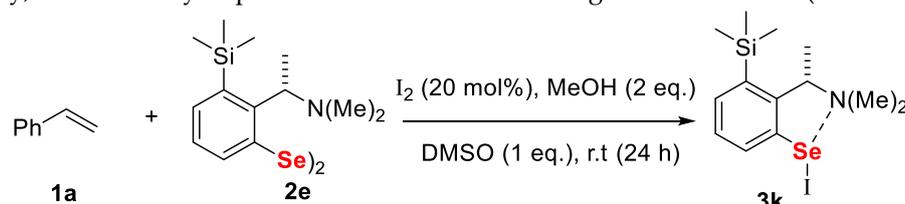
Figure 1. Target molecules in the alkoxy-selenylation protocol. ^a Microwave, 100 W, 50 °C; ^b r.t. Isolated yields. *d.e.* determined by ¹H or ⁷⁷Se NMR.

Subsequently, methanol was replaced by the natural product menthol in order to evaluate the influence of chiral centers present in the alcohol portion of the β -alkoxy-selenides on the diastereoisomeric excesses. In the reaction of menthol with diphenyl diselenide, the desired product **3d** was obtained in 55% yield and 20% *d.e.* after 15 min. Similarly, at room temperature, 53% yield and 16% *d.e.* were found. Using menthol in association with the camphor-derived diselenide, the corresponding product **3e** was obtained only at room temperature, after 24 h, with 44% yield and 54% *d.e.* Menthol in association with [(1*S*)-1-(methylthio)ethyl]phenyl diselenide did not lead to the formation of the corresponding product **3f** under any of the conditions. Although the results have

been modest, the products are of great relevance since they add the properties of natural products with the selenium.

As the best results were obtained with the [(1*S*)-1-(methylthio)ethyl]phenyl diselenide and methanol as alcohol, it was performed the variation of the styrenes in the reaction under microwave irradiation conditions. Using α -methylstyrene, a high yield and a low diastereoisomeric excess was observed, since the desired product **3h**, was obtained in 95% after 15 min and *d.e.* of only 21%. A more satisfactory result was obtained when *trans*- β -methylstyrene was used. In that case, after 15 min, the corresponding product **3i** was achieved in 75% yield and 68% of *d.e.* When the hindered styrene 1-phenyl-1-cyclohexene was used, there was no formation of the desired product **3j**.

The good results obtained with the use of the [(1*S*)-1-(methylthio)ethyl]phenyl diselenide can be explained by the proximity of the sulfur atom with the selenium atom. It is already known that there may be an interaction between these atoms as a result of the orbital interaction between the heteroatom non-ligand electron pair and the low-energy anti-ligand orbital of the SeR portion [22,23]. This would bring the stereogenic center closer to the reaction center during the selenylation, resulting in asymmetric induction. This interaction could be proven with the use of the chiral diselenide **2e**, with the presence of a nitrogen atom. When we trying to perform the methoxy-selenylation with styrene, a complex was obtained where the selenium makes a bond with iodine and a strong interaction with the nitrogen atom. The stability of product **3k** allowed it to be isolated and subsequently, ORTEP analysis proved the link between nitrogen and selenium (Scheme 2).



Scheme 2. N-Se-I interactions, detected by ORTEP analysis of **3k**.

4. Conclusions

As conclusion, a continuation of the protocol developed for the alkoxy-selenylation of styrenes employing the sustainable system I₂/DMSO was carried out. Equivalent amounts of reagents and oxidant were used avoiding the use of solvent and metallic reagents in its process. This method was used in the asymmetric synthesis of β -alkoxy-selenides, using non-racemic chiral diselenides to evaluate the application of this reaction system to obtain diastereoisomerically enriched compounds. In addition, the chiral terpene menthol was also target of study. It was also, demonstrated the viability of this protocol using two different energy sources, microwave irradiation and room temperature conditions, where similar results were obtained in both methods.

Among the diselenides used, the [(1*S*)-1-(methylthio)ethyl]phenyl diselenide was the one that presented the best results in terms of yield and diastereoisomeric excess. These results confirm that

the presence of heteroatoms in the vicinity of the selenium atom and the ability to induce chirality resulting from this asymmetry. To our surprise, the use of diselenide **2e**, led to the formation of crystals where X-ray structures confirmed that it is a complex formed by the atoms of N-Se-I, showing the formation of the species R-Se-I and the interaction of selenium with the heteroatom. Additional studies are still ongoing in our laboratory.

Author Contributions: Conceptualization, C.S. and A.L.B.; methodology, J.B.A. formal analysis, J.B.A.; investigation, J.B.A.; resources, C.S.; writing—original draft preparation, J.B.A.; writing—review and editing, C.S. and A.L.B.; visualization, C.S. and A.L.B.; supervision, C.S. and A.L.B.; project administration, C.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors kindly acknowledge CAPES for a fellowship to J.B.A (7706-13-8). CNPq is also acknowledged for the doctorate fellowship received by J.B.A.

Conflicts of Interest: The authors declare no competing financial interest.

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