

Asymmetric Methoxyselenenylations with Chiral Selenium Electrophiles

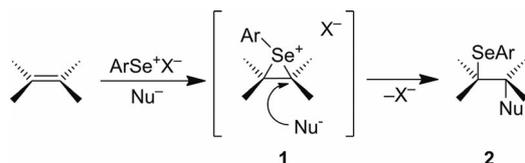
Liwei Zhao,^[a,b] Zhong Li,^[a] and Thomas Wirth*^[b]**Keywords:** Electrophilic addition / Alkenes / Selenium / Diastereoselectivity

Very simple, chiral, non-racemic diselenides were prepared and their corresponding selenium electrophiles were used for the stereoselective functionalization of alkenes. The influ-

ence of different alkenes on the outcome of the selenenylation reaction was investigated.

Introduction

The functionalization of alkenes with selenium compounds offers attractive possibilities for synthetic organic chemistry. Selenium electrophiles are quite powerful and can easily react with double bonds to generate the corresponding addition products after reaction with a nucleophile.^[1] The general reaction is illustrated in Scheme 1. A variety of nucleophiles have been used to open seleniranium intermediates **1**, and addition products **2** can be used for many subsequent reactions (Scheme 1). The reaction exhibits *anti* stereoselectivity with the nucleophile attacking usually at the more highly substituted carbon atom. In a stereoselective approach to this reaction, other research groups and we have investigated stereoselective reactions of alkenes with chiral selenium electrophiles,^[2,3] and also several computational approaches have been made on these reactions.^[4] However, the syntheses of chiral diselenides can be complex, involving many steps or expensive reagents with often low overall yields.



Scheme 1. Selenenylation of alkenes.

Recently, we have reported optically active diselenides with sulfoxides or ethers as chiral moieties.^[5] Herein, we describe new chiral diselenides prepared from readily avail-

able, cheap starting materials in a very short synthesis and the addition reactions of their corresponding selenium electrophiles to alkenes.

Results and Discussion

Non-bonding interactions between selenium and heteroatoms play a remarkable role in methoxyselenylation, especially Se \cdots O, Se \cdots N, and Se \cdots S non-bonding interactions.^[6] In many cases the heteroatom is connected to an adjacent benzylic position, and intermediate species such as **3** are generated (Figure 1). We have proven such interactions by various experiments and also by calculations.^[4a-4c,7] The success of larger ring intermediates in related iodine-based reagents^[8] prompted us to investigate similar structures that can form seven-membered intermediates of type **4**, as shown in Figure 1, by increasing the distance between the heteroatom and the selenium.

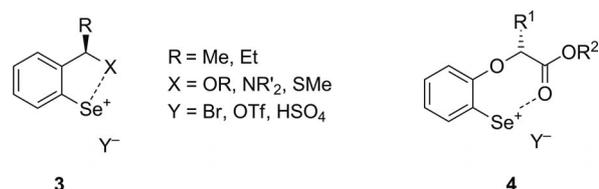


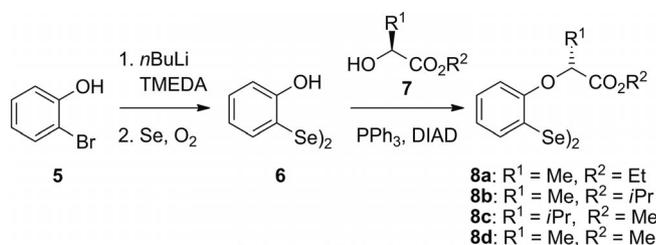
Figure 1. Interaction of heteroatoms with selenium electrophiles.

The starting material for the one-step synthesis is bis(2-hydroxyphenyl) diselenide (**6**), which is easily prepared from 2-bromophenol (**5**).^[9] A subsequent Mitsunobu reaction can be successfully used with different chiral alcohols **7** under very mild conditions to generate the required diselenides **8** in high yields (Scheme 2). This reaction proceeds with clean inversion of the stereocenter, as no diastereomeric diselenide was detected by NMR spectroscopy. Unfortunately, mandelic acid ester derivatives **7** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$) were found to be oxidized under the reaction conditions and did not lead to reaction products **8**.^[10]

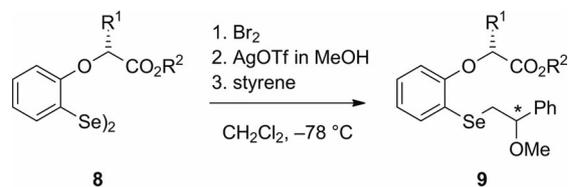
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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ejoc.201101373>.

Scheme 2. Synthesis of diselenides **8**.

A typical methoxyselenenylation with the use of diselenides **8** proceeds through the generation of the corresponding selenenyl bromides by addition of bromine to the diselenide, followed by treatment with silver triflate in methanol. Then the alkene (styrene) is added to yield the methoxyselenenylated products, as shown in Scheme 3. Typically, these reactions are performed at $-78\text{ }^{\circ}\text{C}$ in dry dichloromethane and are complete after a reaction time of 2 h. The mixtures of diastereomers can usually not be separated, and sometimes they are enriched during flash chromatography. The diastereomeric ratio (*dr*) was therefore determined by integration of the ^1H NMR signals in the crude reaction mixture. All chiral diselenides **8** were converted into the addition products **9** in reasonable yields and with high selectivities, as shown in Table 1.

Scheme 3. Methoxyselenenylation of styrene with diselenides **8**.Table 1. Methoxyselenenylation of styrene with the use of diselenides **8**.

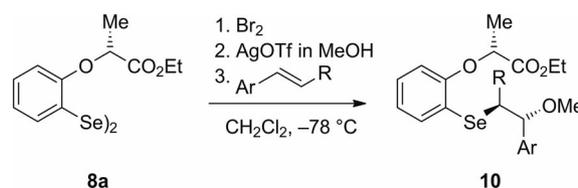
Entry	Diselenide	Yield 9 [%]	<i>dr</i> ^[a]
1	8a	62	93:7 ^[b]
2	8b	55	92:8
3	8c	46	80:20
4	8d	78	83:17

[a] The diastereomeric ratios were determined from the ^1H NMR spectra of the crude reaction mixtures and confirmed after purification by column chromatography. [b] 95:5 after flash column chromatography.

Diselenide **8c** with an isopropyl substituent at the stereogenic carbon atom (R¹ = *i*Pr) gave methoxyselenenylated product **9c** with the lowest diastereomeric ratio. The increased size of the isopropyl substituent over that of a methyl substituent (i.e., **8a** and **8b**) slightly disturbs the selenium–oxygen interaction. Also, the change of the R² substituent from isopropyl (**8c**) to methyl (**8d**) does not lead to a large increase in selectivity. A similar behavior has already been observed with the size of the R substituent in electrophiles of type **3**.^[11] Comparing the reaction products by using diselenides **8a** and **8b** revealed that the nature of the ester (R² = Et vs. *i*Pr) does not influence the selectivity.

The reaction of the selenium electrophile generated from diselenide **8a** showed the highest selectivity of 93:7 (Table 1, Entry 1), which could be enriched to 95:5 after flash chromatography.

Then the reactivity towards other alkene substrates was investigated by using diselenide **8a** (Scheme 4). Yields of the methoxyselenenylation reaction and the diastereomeric ratios of the products are presented in Table 2. In contrast to other recent results,^[5a] 2-chlorostyrene produced a low yield of the methoxyselenenylated product. 3-Methylstyrene and β -methylstyrene gave good yields and diastereomeric ratios. The result using β -methylstyrene is important, because this means that, unlike other recently investigated compounds,^[5b] the electrophile generated from diselenide **8a** will react with disubstituted alkenes and can be used in the future for selenium-mediated cyclizations.

Scheme 4. Methoxyselenenylation of alkenes with diselenide **8a**.Table 2. Methoxyselenenylation of alkenes with diselenide **8a**.

Entry	Alkene Ar	R	10 , % yield	<i>dr</i> ^[a]
1	2-ClC ₆ H ₄	H	10a , 25	89:11
2	3-MeC ₆ H ₄	H	10b , 59	91:9
3	Ph	Me	10c , 56	92:8

[a] The diastereomeric ratios were determined from the ^1H NMR spectra of the crude reaction mixtures and confirmed after purification by column chromatography.

The selectivities observed in the asymmetric methoxyselenenylations mentioned above prove the existence of non-bonding interactions between the selenium electrophile and the oxygen in the ester moieties in the chiral selenium electrophiles.

Conclusions

Four new diselenides have been synthesized in only very few steps from cheap commercial compounds with ester moieties as substituents of a stereogenic center. The selenium electrophiles, generated from these diselenides, have been successfully applied in methoxyselenenylation reactions with good yields and diastereomeric ratios. Further experiments to improve the stereoselectivity of these reactions and related processes and to gain additional insight into the observed selectivities are in progress.

Experimental Section

General Procedure for the Addition of Selenium Electrophiles to Alkenes: Diselenide **8** (0.1 mmol) was dissolved in dry dichloromethane (2.5 mL) under an atmosphere of argon, cooled to $-78\text{ }^{\circ}\text{C}$,

and treated with bromine (1 M in CCl₄, 0.11 mL, 0.11 mmol). After 20 min, a solution of silver triflate (72 mg, 0.28 mmol) in dry methanol (0.1 mL) was added, and the mixture was stirred for 30 min at -78 °C. The alkene derivative (0.4 mmol) was added. After the mixture had been stirred for 2 h at -78 °C, saturated NaHCO₃ (2 mL) was added followed by water (2 mL). After extraction of the reaction mixture with dichloromethane (3 × 10 mL), the combined organic phases were dried with MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, yielding the addition products as colorless oils. The diastereomers could not be separated by column chromatography (ethyl acetate/hexane, 5:1).

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures; characterization data; and ¹H and ¹³C NMR spectra for compounds **8**, **9**, and **10**.

Acknowledgments

We thank the China Scholarship Council (CSC) (L.Z.) and the School of Chemistry, Cardiff University, for support and the EPSRC National Mass Spectrometry Service Centre, Swansea, for mass spectrometric data.

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Received: September 20, 2011

Published Online: November 4, 2011