Asymmetric Azidoselenenylation

Asymmetric Azidoselenenylation of Alkenes: A Key Step for the Synthesis of Enantiomerically Enriched Nitrogen-Containing Compounds**

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Organic azides are versatile starting materials for the synthesis of a variety of nitrogen-containing compounds. The azido group can react with both nucleophilic and electrophilic reagents and can be used in 1,3-dipolar cycloaddition reactions.[1] One of the most convenient ways to produce organic azides is the electrophilic addition to alkenes of an appropriate reagent, such as hydrazoic acid,[2] mercuric azide,[3] or iodine azide.[4] Considerably improved results were obtained by using organoselenium reagents. The first example of the azidoselenenylation of alkenes was reported by Hassner and Amarasekara.[5] The reaction was effected with PhSeCl and sodium azide in DMSO and proceeded through the formation of a cyclic seleniranium ion intermediate, which then underwent ring opening by nucleophilic attack of the azide anion. The addition products therefore resulted from a stereospecific *trans* addition. However, the reaction was not regiospecific. Similarly, the reaction of exocyclic alkenes with *N*-(phenylseleno)phthalimide and azidotrimethylsilane gave rise to a mixture of regioisomers.[6] More recently we reported that the stereospecific azidoselenenylation of alkenes can be carried out more conveniently with phenylselenenyl triflate and sodium azide in acetonitrile.[7] We have also reported the use of an azido radical to promote the azidoselenenylation of olefins. The reaction is, of course, not stereospecific in this case, and the anti-Markownikoff addition products are formed.[8]

We report the first example of a remarkable asymmetric electrophilic azidoselenenylation of olefins that occurs with a very high level of facial selectivity. This process is made possible by the use of chiral, nonracemic selenium reagents. During the last 10 years several research groups have developed simple and efficient procedures for the preparation of chiral, nonracemic diselenides.[9] These compounds have been employed in various asymmetric reactions, mainly as precursors of electrophilic reagents,[9] but also as catalysts[10] or as a source of chiral selenium anions.[11] A common characteristic of all chiral diselenides studied is the close proximity of a heteroatom (oxygen or nitrogen) that can interact with selenium. We recently described the synthesis of the sulfur-containing diselenides di-2-[(1*S*)-1-(methylthio)ethyl]phenyl diselenide (**1**)[12] and di-2-methoxy-6-[(1*S*)-1-(methylthio)ethyl]phenyl diselenide (**2**).[13] Electrophilic reagents derived from these diselenides were used to effect asymmetric hydroxyselenenylation,[12,13] methoxyselenenylation,[12,13] and cyclofunctionalization reactions,[14] which proceeded with very high facial selectivity under very mild experimental conditions.

Preliminary experiments on asymmetric azidoselenenylation were carried out on styrene with the chiral diselenides **1**–**5**. Upon treatment with bromine and silver triflate, **1**–**5** were converted into the corresponding electrophilic selenenyl triflate reagents **6**–**10**. These reacted with styrene (**11**) in the presence of 1 equivalent of sodium azide to afford a mixture of the corresponding diastereomeric addition products **12**–**16** (Scheme 1).

The observed diastereomeric ratios and chemical yields are summarized in Table 1. The excellent selectivity observed

Table 1: Asymmetric azidoselenenylation of styrene.

Diselenide	*t* [h]	Yield [%]	d.r.
1	22	90	91:9
2	21	90	97:3
3	20	70	52:48
4	21	10	87:13
5	30	28	75:25

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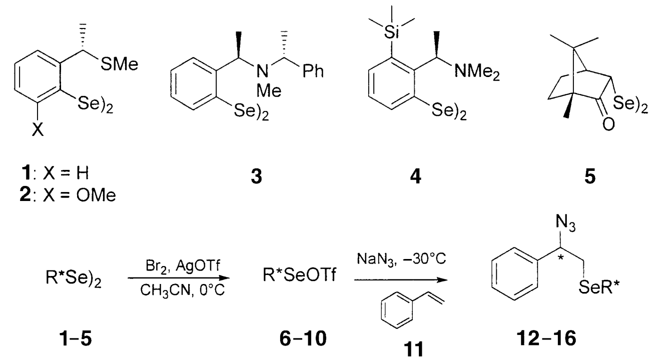
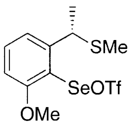


Scheme 1. Asymmetric azidoselenenylation of styrene.

with the diselenides **1** and **2** seems to indicate that the interaction of the selenium atom with the sulfur atom is stronger than its interaction with the other heteroatoms (oxygen or nitrogen) used in previous investigations.



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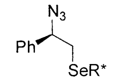
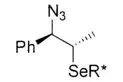
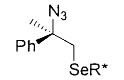
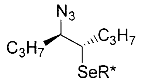
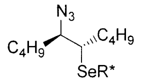
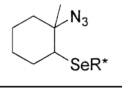
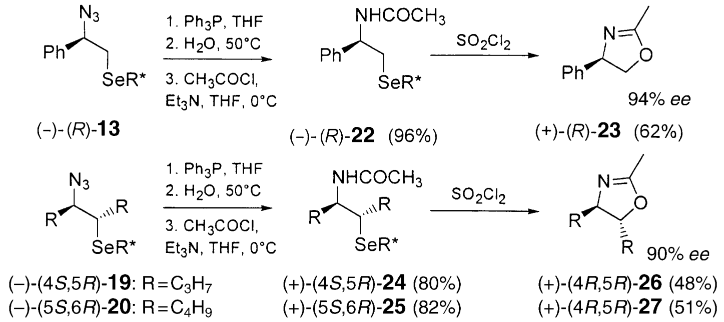
On the basis of these results all further reactions were carried out with the diselenide **2** as precursor to the electrophilic arylselenenyl triflate **7**. Experimental conditions, chemical yields, and diastereomeric ratios for the reactions of **7** with a variety of alkenes are reported in Table 2.

The azidoselenenylation products were obtained in every case as an inseparable mixture of the two possible diastereomers. The results reported in Table 2 indicate that this azidoselenenylation reaction is a stereospecific *trans* addition (Table 2, entries 2, 4, and 5) that occurs regioselectively (Table 2, entries 1, 2, 3, and 6) with Markownikoff orientation. The diastereomeric ratios were determined from the ^{1}H NMR spectra of the crude reaction mixtures and confirmed after purification by column chromatography. Excellent levels of diastereoselectivity were obtained in all cases. The major isomers of the azidoselenides **13** and **18**–**20** are depicted in Table 2. In the cases of **13**, **19**, and **20** these were determined after conversion into the known oxazolines[15] **23**, **26**, and **27** (Scheme 2). For this purpose the azides were reduced to the corresponding amines, which were then treated in situ with CH_3COCl at 0°C. The acetamido selenides **22**, **24**, and **25** thus obtained underwent a stereospecific S_N2 intramolecular deselenenylation upon treatment with SO_2Cl_2 to afford the oxazolines **23**, **26**, and **27**, respectively.[15] The absolute configurations of compounds **17** and **18** were assigned by analogy.

Table 2: Asymmetric azidoselenenylation of alkenes with the diselenide **2**.[a]

Entry	Alkene	Azidoselenide	*t* [h]	Yield [%]	d.r.
1	styrene (**11**)	 **13**	21	90	97:3
2	β-methylstyrene	 **17**	20	70	98:2
3	α-methylstyrene	 **18**	18	60	99:1
4	(*E*)-4-octene	 **19**	24	95	95:5
5	(*E*)-5-decene	 **20**	20	95	95:5
6	1-methyl-1-cyclohexene	 **21**	20	70	95:5

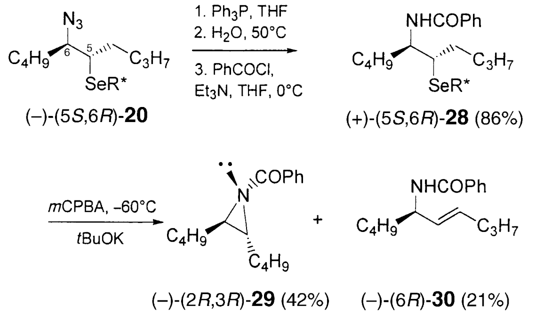
[a] In a typical experiment, bromine (0.5 mmol) and silver triflate (1.1 mmol) were added to a solution of the diselenide **2** (0.5 mmol) in MeCN (2.5 mL) at 0°C. After 15 min the mixture was cooled to −30°C and sodium azide (1.0 mmol) was added. The reaction mixture was stirred for 30 min, then the alkene (1.0 mmol) was added, and the mixture was allowed to warm to room temperature gradually. Upon completion of the reaction (monitored by TLC and GC–MS), the mixture was filtered through anhydrous K_2CO_3, and the filtrate was concentrated under vacuum.



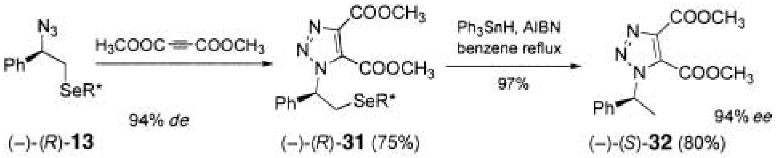
Scheme 2. Conversion of azidoselenides into optically active oxazolines.

To highlight the importance of these compounds as synthetic intermediates, some of the azidoselenides were then transformed into other enantiomerically enriched nitrogen-containing compounds. The benzoyl derivative **28** was prepared from **20** as indicated in Scheme 3. The corresponding selenoxide, obtained by treatment of **28** with *meta*-chloroperbenzoic acid (*m*CPBA),[16] underwent spontaneous deselenenylation to afford the optically active aziridine **29** by an intramolecular nucleophilic substitution, and the α,β-unsaturated amide **30** by an elimination process.

Enantiomerically enriched azides can be also conveniently employed in 1,3-dipolar cycloadditions to allow the synthesis of triazoles.[17] Thus, as indicated in Scheme 4, the azide **13** was treated with dimethyl acetylenedicarboxylate to give the triazole **31**.[17] Deselenenylation of **31** with triphenyltin hydride and AIBN (azobisisobutyronitrile) then afforded the triazole **32**. The enantiomeric excess of **32**



Scheme 3. Preparation of optically active aziridines.



Scheme 4. Conversion of azidoselenides into optically active triazoles.

was identical to the diastereomeric excess of the starting azide.

In conclusion, we have reported the first example of the highly enantioselective addition of a nitrogen nucleophile to a carbon–carbon double bond, which was made possible by the use of chiral, nonracemic electrophilic selenium reagents. An important aspect of this new reaction lies in the synthetic applications of the resulting azidoselenides. These products can be conveniently used in the synthesis of a variety of nitrogen-containing derivatives of very high optical purity.

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