New chiral electrophilic selenium reagents: synthesis and structural investigation

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Abstract: The synthesis of new optically pure diselenides has been realized in one pot, starting from 2, 2′- diselenobisbenzoic acid and naturally occurring chiral alcohols through a Mitsunobu reaction. They were used to promote electrophilic methoxyselenenylation of styrene, affording moderate to poor diastereoselectivity. The reason of the low stereoselection has been investigated on the basis of ^{77}Se-NMR experiments, evidencing an alternate double coordination with the oxygens of the carboxylic moiety. Some theoretical implications of these interactions in the GPx – like activity of the diselenides will be discussed.

Introduction

During last decades the interest in organoselenium compounds is continuously increased. Nowadays they are currently used as intermediates or catalysts in organic synthesis as well as objects of deep investigations for their biological activity especially as antiviral, anticancer, anti-inflammatory, antimicrobial and GPx- mimetics. [1]

We have described a number of asymmetric synthesis, by means of reagent-controlled or substrate-controlled addition reactions and cyclofunctionalizations of alkenes, promoted by electrophilic organoselenium reagents and, for these purposes several chiral non-racemic selenium containing reagents have been introduced in the literature to effect efficient asymmetric reagent controlled reactions.[2]

A common characteristic of all these reagents is the close proximity of the selenium atom to an oxygen, nitrogen or sulfur heteroatom that is linked to a chiral carbon atom. It was demonstrated that Se–N, Se–O and Se–S interactions play an important role not only in the catalytic antioxidant activity of these compounds but also in their use as reagents in synthetic organic chemistry. [3]

Very recently Wirth and co-workers reported the synthesis of some new diselenides through the Mitsunobu reaction between a phenoxy based diselenide and a chiral scaffold of commercially available compounds with ester moieties as substituents of a stereogenic center. They demonstrated that these diselenides can be efficiently used as precursors of the corresponding electrophilic selenenyl triflate and stereoselectively employed in the selenenylation of non activated alkenes.[4]

In this communication we report that, starting from the antranilic acid **1** is possible to prepare in *one pot* and using water as solvent the 2-2' diselenobenzoic acid. This latter represents an useful core structure for the synthesis of optically pure diselenides (**3a,b**) by the combination with naturally occurring optically pure alcohols and their derivatives using the Mitsunobu procedure.

The application of some electrophilic reagents, prepared starting from these diselenides, in the asymmetric methoxyselenenylation of styrene is here reported, discussing the observed

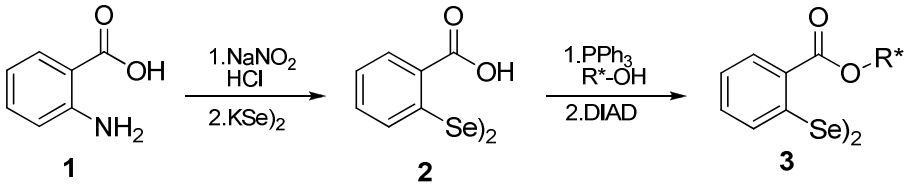
steroselectivity in terms of orbital interactions between the oxygen lone pair and the low-lying antibonding orbital of selenium investigated by NMR spectroscopy.

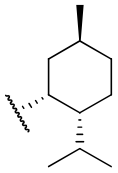
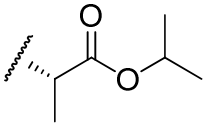
Results and discussion

The synthesis of enantiomerically pure diselenides are usually a complicated process, involving multi-steps procedures and not simple chromatographic purifications with a large use of organic solvents and a consequent considerable production of wastes. Looking for more efficient procedure our attention was attracted by the synthesis of 2, 2′- diselenobisbenzoic acid **2** that can be easily prepared from 2-amino benzoic acid **1** via a diazonium salt intermediated, by treatment in aqueous solution with potassium diselenide, prepared by melting of elemental selenium and potassium hydroxide. [5]

The diselenide **2** was purified by crystallization and easily converted into 2,2′-diselenobisbenzoates **3a,b** by treatment in the stereospecific Mitsunobu conditions with two optically pure alcohols, the menthol, and the isopropyl-lactate respectively (Table 1). [6]

Table 1. Synthesis of diselenides **3a** and **3b**



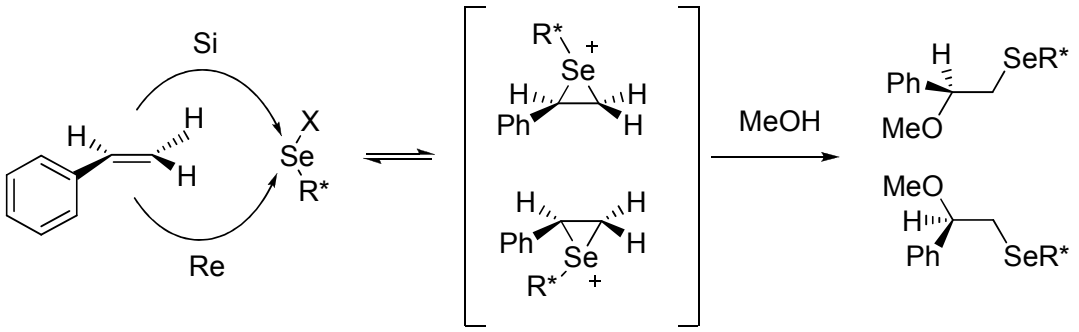
entry	R*	Yield %
a		70
b		60

Also the optically pure diselenides **3a,b** can be purified by crystallization from methanol and the overall yields, calculated on the amount of isolated products, resulted to be good in both the cases. (Table1)

The methoxyselenenylation reaction of styrene is commonly considered the probe reaction for the comparison of the stereoselectivity of different electrophilic selenium reagents as well as different reaction conditions. It has been well established that the selenium electrophile reacts with carbon-carbon double bond through a stereospecific *anti*- addiction passing through the initial formation of a seleniranium ion intermediate. This three membered ring is opened by an external nucleophile,

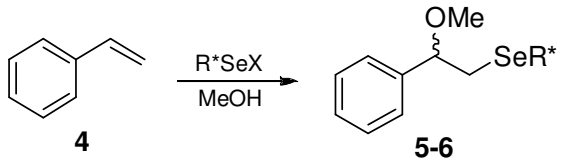
usually the solvent, leading the formation of a couple of diastereoisomers in a ratio that reflects the facial selectivity of the addition process (Scheme 1). [2]

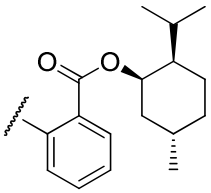
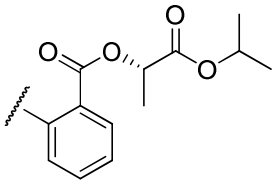
Scheme 1. Mechanism of asymmetric methoxyselenylation of olefins



Diselenides **3a** and **3b** were converted into the corresponding bromides by treatment with a stoichiometric amount of Br_2 (1M solution in CCl_4) and these latter were *in situ* reacted with styrene (**4**) and methanol at room temperature for 1h. The reactions, after the usual workup, afforded a mixture of diastereoisomers **5** and **6** in good yields and moderate diastereomeric excesses (Table 2, entries **a** and **f**).

Table 2. Asymmetric methoxyselenenylation of styrene



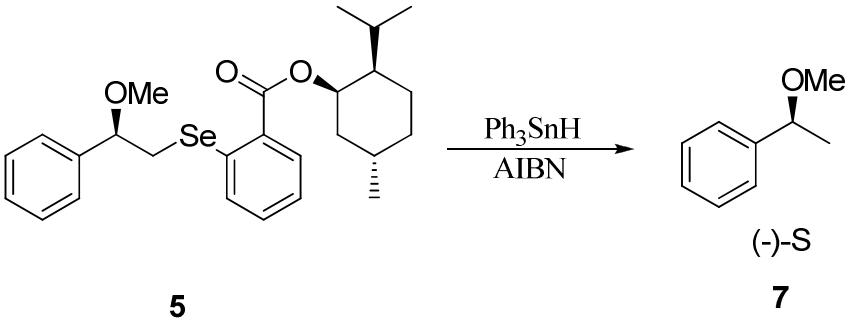
Entry	R*	X	T(°C)	d.r.	Yield(%)
a		Br	23	60:40	99
b		Br	-15	70:30	90
c		Br	-50	--	--
d		Cl	23	60:40	60
e		OTf	-78[a]	67:33	60
f		Br	23	57:43	70

a) After 3 hours at room temperature the reaction was warmed up at 23°C

Wirth and co-workers demonstrated that the formation of seleniranium ion is reversible process and, consequently, lower temperatures will favourite the formation of the kinetically controlled intermediate rather than the thermodynamic one, generally increasing the final diastereoisomeric ratio. [7] For this reason we investigated the effect of the temperature on the methoxyselenenylation of **4** starting from diselenide **3a**. At -15°C the diastereomeric ratio increased passing from 60:40 to 70:30 obtaining after 3h 90% of yield. Unfortunately at lower temperature the reactivity of the selenenyl bromide resulted to be strongly reduced and the reaction at -50°C did not afford appreciable results in terms of yields. We tried to enhance the reactivity as well the selectivity changing the counteranion. Selenenyl chloride (entry **d**) reacted only at room temperature affording moderate yields (60%) and a diastereomeric excess similar to those obtained with bromide (*de* 20%), selenenyl triflate (entry **f**) at -78 °C reacted very slowly and after 3 hours was warmed up at room temperature producing a *de* of 34%.

The absolute configuration of the major isomer **5** was established by reductive deselenenylation promoted by triphenyltin hydride and AIBN in refluxing benzene. As indicated in Scheme 2, the α-methoxyselenide **5** gave the enantiomerically enriched ether (-)-(*S*)-methoxyphenylethane (**7**). [8]

Scheme 2. Attribution of absolute configuration



5 **7**

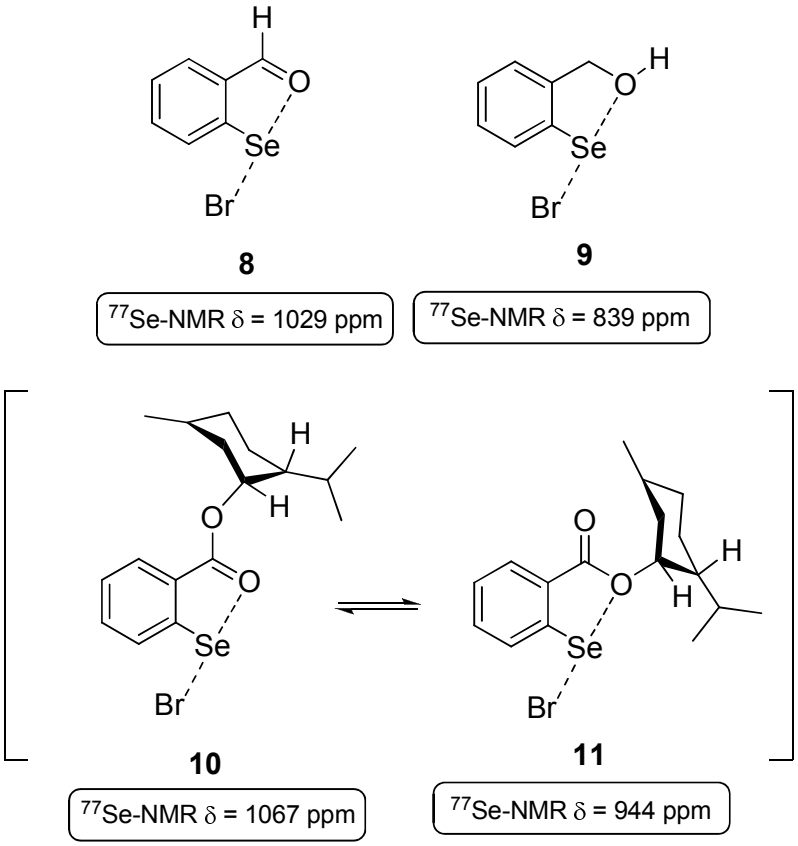
The non bonding interactions between selenium and heteroatoms were proved to be responsible of the high selectivity showed by some electrophilic selenium reagents and it was suggested that the role of this interaction in the stereoselection is to bring the chiral moiety near to the reactive selenium driving the attack of the olefin and affording more rigid transition states.

The Se-O non bonding interactions have been studied by Iwaoka and Tomoda, [9] who reported their physiochemical characterization in relation to the results obtained from their applications in asymmetric synthesis and to their enzyme-mimetic properties.

Previously, Baiwir et al. [10] demonstrated by X-ray analysis that the coordination between the carbonyl oxygen atom and the selenium atom produced T-shaped structures in which O-Se-Br are aligned with a distance between selenium and oxygen shorter than the sum of the respective Van der Waals radii.

In the cases of selenenyl bromides prepared starting from **3a** and **3b** two possible interactions should be envisioned deriving by the contacts between Selenium and the carbonyl or esteric oxygen respectively. The structure are depicted on Scheme 3 (**10** and **11**).

Scheme 3. Analysis of the nonbonding Se-O interactions by ^{77}Se-NMR



In order to explain the moderate stereoselectivity observed in our experiments we took in consideration the ^{77}Se-NMR chemical shifts of the selenenyl bromide deriving from **3a**. Using compounds **8** and **9** as references products.

The Se-O interaction in **8** is evidenced by an anisotropic deshielding effect produced by the aldehyde C=O bond when this moiety is coplanar with selenium atom. As result of this coordination the chemical shift of the selenium in **8** is 190 ppm higher than that in **9**.

By comparison of the ^{77}Se chemical shifts, we observed that in our case both coordinations are present in equilibrium (**10** and **11**) and it is reasonably to suppose that the intermediate **11** is the kinetic one and the responsible of the enantioselective induction. Unfortunately the scarce solubility of these reagents at low temperature does not allow to control kinetically its formation precluding the possibility to further increase the selectivity of the reaction.

In conclusion we reported here a general and efficient strategy for the preparation of enantiomerically pure diselenides starting from the easily accessible 2, 2′- diselenobisbenzoic acid unit. The low stereoselectivity of the electrophilic reagents generated by these diselenides has been interpreted on the basis of a competitive Se-O interaction. Further investigations are currently

ongoing in order to evaluate the effect of this double coordination to the biological activity of these compounds.

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