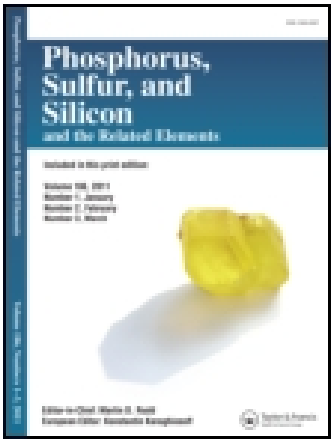


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# Kinetic Resolution of Allylic Alcohols Promoted by Electrophilic Selenium Reagents

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# Kinetic Resolution of Allylic Alcohols Promoted by Electrophilic Selenium Reagents

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*The first example of a kinetic resolution process promoted by an electrophilic selenium reagent is reported. Racemic allylic alcohols react with half equivalents of a selenenylating agent in methanol leading to the regiospecific formation of the corresponding addition products with a very high level of facial selectivity (98% de). The unreacted alcohol can be recovered in a optically enriched form (92% ee).*

**Keywords** Chiral diselenide; kinetic resolution; selenoadditions

## INTRODUCTION

During the last 10 years, several research groups have described the synthesis of a number of chiral nonracemic diselenides which can be transformed *in situ* into electrophilic selenenylating agents to effect efficient asymmetric synthesis.[1–3] A common characteristic of all these optically active diselenides is the close proximity of an oxygen or a nitrogen atom to the selenium atom. We recently reported a new class of chiral diselenides containing a sulphur atom in the chiral moiety. On the basis of several experimental evidences it was deduced that the

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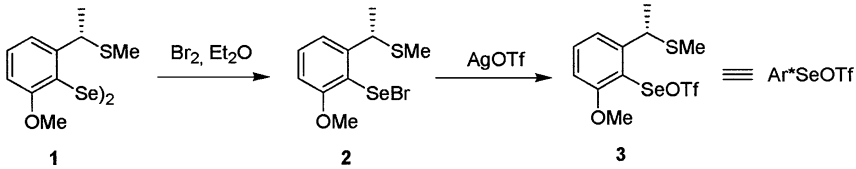
interaction of selenium with the sulphur atom probably could be more important than those with oxygen or nitrogen.[4–7]

The di-2-[methoxy-6-[(1S)-1-methylthio]ethyl]phenyl] diselenide **1** is a suitable precursor for very efficient electrophilic reagents.[5–6] Treatment of **1** with bromine in diethyl ether leads to the precipitation of the corresponding bromide **2** as a red-yellow solid that can be fully characterized by $^{1}$H-NMR $^{13}$C-NMR and $^{77}$Se-NMR experiments.

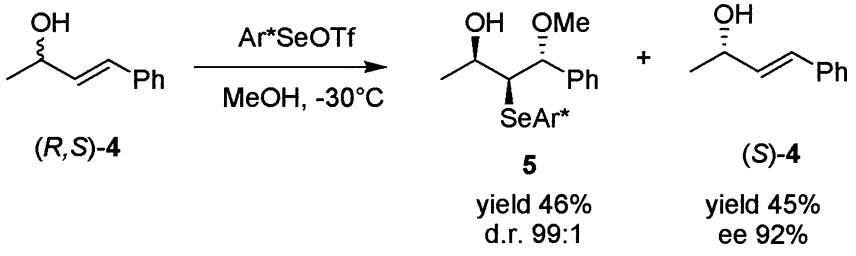



**1** **2** **3**

**SCHEME 1**

We now report that the electrophilic species aryl selenenyl triflate **3,** prepared from **2** by reaction with AgOTf in $CH_2Cl_2$ at 0°C, can be used to effect the kinetic resolution of racemic allylic alcohols (R,S)-**4** (Scheme 2) through a methoxyselenenylation reaction. To the best of our knowledge this is the first example of a kinetic resolution promoted by an organoselenium reagent from which a very common class of organic substrates can be obtained in an enantiomerically enriched form.

Two equivalents of the racemic allylic alcohol (R,S)-**4** react with 1 eq of the selenenylating reagent **3** in a mixture of $CH_2Cl_2$/MeOH (10:1) at −30°C, affording the addition product **5** with complete regioselectivity and a very high facial selectivity (45% de). From the reaction mixture the unreacted alcohol (S)-**4** can be recovered in 88% yield and in an enantiomerically enriched form (92% ee). The enantiomeric excess has been determined by recording the $^{1}$H-NMR spectra in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-antryl)-ethanol.




(*R,S*)-**4** **5** (*S*)-**4**

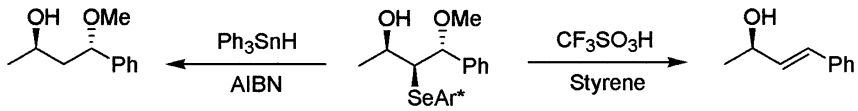
yield 46%
d.r. 99:1

yield 45%
ee 92%

**SCHEME 2**

The geometry and the absolute configuration of the adduct **5** were assigned by radical deselenenylation promoted by triphenyltin hydride and AIBN in refluxing benzene (Scheme 3) affording the derivative **6**.[8]

Furthermore, the resolution process can be completed by transforming the organoselenium compound **5** into the corresponding starting allylic alcohol (*R*)-**4** (98% ee) by treatment with $CF_3SO_3H$ and styrene at room temperature.



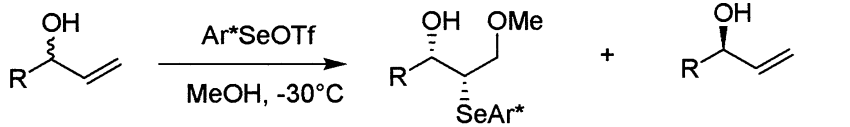

**6**
yield 95%
ee 98%

**5**
d.r. 99:1

(*R*)-**4**
yield 77%
ee 98%

**SCHEME 3**

In order to investigate the regioselectivity of the process we repeated the reaction starting from the mono substituted alkenes **7a–b** (Scheme 4). Even if in these substrates the facial selectivity was very low, in both cases the addition to the double bound resulted completely regiospecific and only the anti-Markovnicov regioisomers were obtained in a diasteroisomeric ratios of 60:40.




(*R,S*)-**7**

**7a** R=$C_4H_9$

**7b** R=$C_6H_5$

**8**
yield 35% dr 60:40
yield 20% dr 60:40

(*R*)-**7**
yield 20% ee 20%
yield 22% ee 20%

**SCHEME 4**

These results seem to indicate an active participation of the hydroxy group in governing the attack of the electrophilic reagents to the double bond by giving rise to a Se—O stabilizing interaction. Carrying out the reaction of **7a** in the presence of silica gel the intramolecular Se—O interaction becomes less important and the regioselectivity decreases, the Markovnicov and the anti Markovnicov regioisomers are in fact formed in a ratios of 30:70. In conclusion we report a simple procedure to effect efficient kinetic resolution of allylic alcohols using an organoselenium

reagent under very mild conditions. The application of the present procedure to other kind of substrates is under investigation.

## EXPERIMENTAL

Starting allylic alcohols (R,S)-**7a** and (R,S)-**7b** were commercial products and were used without further purification. Compound (R,S)-**4** was prepared starting from the corresponding ketone by reduction with $LiAlH_4$ in $Et_2O$ at 0°C.

The kinetic resolution experiments were carried out as follows: 0.5 mmol of AgOTf were added to a solution of the bromide **2** in $CH_2Cl_2$ (3mL) at 0°C and the mixture was cooled at −30°C. The allylic alcohol (1 mmol), dissolved in 0.3 mL of methanol was added. The reaction was stirred for 12 h at the same temperature and then poured into a 10% solution of $NaHCO_3$. The crude product was purified by flash chromatography on a silica gel column using a mixture of dichloromethane methanol (99:1) as eluant. All the compounds were fully characterized by $^1$H-NMR, $^{13}$C-NMR experiments, and by GC-MS analysis. Selected physical and spectral data are reported below. $^1$H- and $^{13}$C-NMR were recorded in a Bruker Advance DRX-400 spectrometer. Optical rotations were measured with a JASCO DIP-1000 digital polarimeter.

**(2*R*,3*S*,4*R*)-4-Methoxy-3-(2-methoxy-6-[(1*R*)-1-(methylsulfanyl)ethyl]phenylselanyl)-4-phenylbutan-2-ol (5):** Oil, $^1$H NMR ($CDCl_3$)$\delta$ 7.34–7.25 (m, 4H), 7.18–7.13 (m, 3H), 6.80 (dd, 1H, $J = 1.1$ and 8.2 Hz), 4.75 (q, 1H, $J = 7.0$ Hz), 4.52 (d, 1H, $J = 5.1$ Hz), 4.20 (dq, 1H, $J = 1.5$ and 6.2 Hz), 3.91 (s, 3H), 3.73 (s, 1H), 3.60 (dd, 1H, $J = 1.5$ and 5.1 Hz), 3.31 (s, 3H), 1.93 (s, 3H), 1.52 (d, 3H, $J = 7.0$ Hz),1.35 (d, 3H, $J = 6.2$ Hz); $^{13}$C NMR ($CDCl_3$)$\delta$ 160.2, 149.1, 139.9, 129.8, 128.7, 128.5, 128.2, 127.1, 119.8, 109.7, 87.3, 67.4, 58.3, 57.3, 56.4, 44.5, 22.2, 21.6, 14.3

**(2*S*,3*E*)-4-Phenyl-3-buten-2-ol (*S*)-4:** Oil $[\alpha]_D^{20.8} = -7.8$ (c = 0.52, $CHCl_3$)[9]

**(3*R*)-1-hepten-3-ol (*R*)-7:** Oil, $[\alpha]_D^{23.3} = -7.2$ (c = 0.25, $CH_3CH_2$-OH). Enantiomeric excess was determined by gaschromatography using an HP 5890 gas chromatograph with a 25 m Chirasilidex capillary column. The absolute configuration is reported in the literature.

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