New and efficient selenium reagents for stereoselective selenenylation reactions

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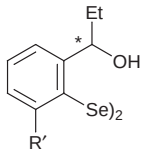
The simple substitution of an aryl proton by a methoxy substituent improves the selectivity of the stereoselective selenenylation reaction dramatically, leading to addition products with diastereomeric ratios up to 50 : 1 in the methoxyselenenylation reaction of styrene.

Stereoselective reactions using chiral selenium compounds have been investigated recently by us[1] and other research groups.[2] These reagents can be employed in asymmetric selenenylation reactions or as ligands in metal-catalyzed transformations. For this purpose we have developed readily available chiral diselenides of type **1**. Diselenide **1a** (R' = H),



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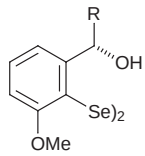

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which can be synthesized *via* a two-step procedure, has already been used in many stereoselective reactions with good results. We have shown that an oxygen atom in the chiral side chain in close proximity to the selenium is responsible for the efficient transfer of chirality.[3]

C_2-Symmetrical chiral diselenides with an additional chiral side chain at the second *ortho*-position are also very efficient reagents in selenenylation reactions, however, they have to be prepared by multistep synthesis.[2a] Because an additional simple substituent in **1** (R' = Me, CF_3) does not improve the selectivity in the selenenylation reaction,[4] we decided to prepare compounds **2** with heteroatom-containing substituents such as the methoxy group.

Diselenides **2a**,**b** were synthesized from the optically active alcohols **3a**,**b**, respectively (Scheme 1). Alcohol **3a** was obtained by chiral reduction of 3-methoxyacetophenone with (−)-*B*-chlorodiisopinocampheylborane in 97% ee.[5] Through diethylzinc addition to 3-methoxybenzaldehyde catalyzed by (*R*,*R*)-bis{2-[1-(pyrrolidin-1-yl)ethyl]phenyl} diselenide,[6] alcohol **3b** was obtained in 97% ee. The alcohols **3a**,**b** were first deprotonated with Bu^{n}Li in the presence of TMEDA and then lithiated in the *ortho*-position with an excess of PhLi.[7] Successive reaction with selenium and oxidative work-up yields the diselenides **2a**,**b** in 63 and 47% overall yield, respectively.‡

3a R = Me
b R = Et

2a R = Me
b R = Et

Scheme 1 *Reagents and conditions*: i, Bu^{n}Li, TMEDA; ii, PhLi; iii, Se, O_2

From diselenide **2a** crystals suitable for X-ray analysis were obtained. The structure of **2a** (Fig. 1)§ is substantially different from other diselenides bearing heteroatom-containing sidechains. In other structures we found a strong interaction between the heteroatom of the sidechain and the selenium atom. In the structure of **2a** a strong interaction with the oxygen of the methoxy group is observed [Se–O (mean): 2.977 Å] while the distance from the selenium to the oxygen in the side chain (4.22 Å) is clearly greater than the sum of the van der Waals radii (3.40 Å).

As a consequence of these interactions the smallest substituent, namely the hydrogen atom, is placed in the plane of the benzene ring. Because solid state geometries may not be adopted in solution, further structural investigations have been performed.

The structure in solution has been determined through NOE measurements of diselenide **2a** in [$^2H_6$]DMSO. Irradiation at the frequency of the proton in the 5-position (the proton *ortho* to the side chain) showed a strong NOE with the protons of the methyl group and the proton of the hydroxy group. No interaction could be detected with the benzylic proton. Therefore, we suggest that the structure is similar to that in the solid state.

To analyze the substrate efficiency in stereoselective synthesis, we employed these two diselenides in the methoxyselenenylation of styrene. The diselenides **2a**,**b** were transformed *in situ* into the electrophilic triflates **4a**,**b** by bromination and exchange of the bromine ion with AgOTf (Scheme 2). The reaction with **4a** yielded β-methoxy selenide **5a** with a diastereomeric ratio of 50 : 1 in 55% yield.¶ By carrying out the reaction with **4b** bearing an ethyl substituent in the side chain the addition product **5b** was obtained with a diastereomeric ratio of only 11.5 : 1 and 60% yield. This is in

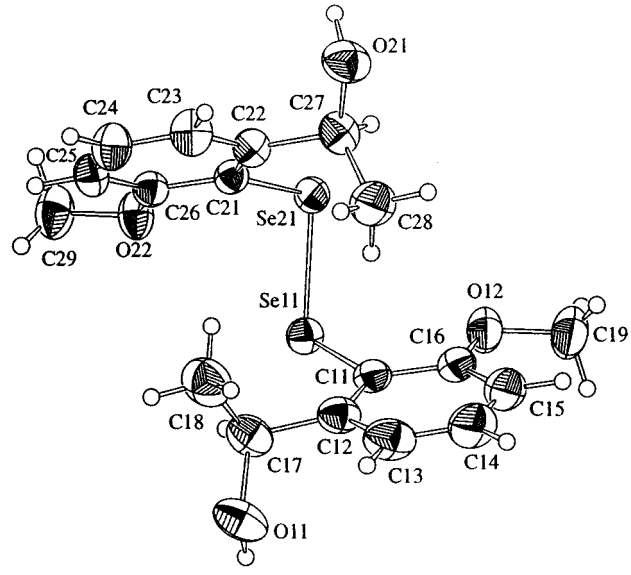
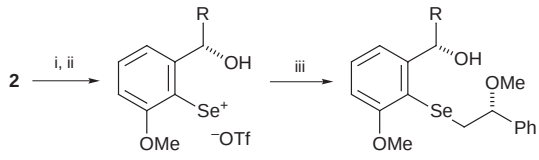
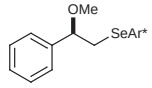
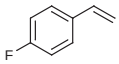
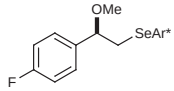
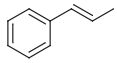
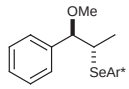
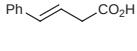
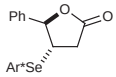
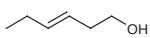
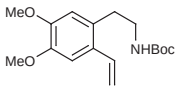
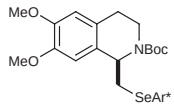


Fig. 1 ORTEP plot of the crystal structure of diselenide **2a**. Thermal ellipsoids are at the 30% probability level.



Scheme 2 *Reagents and conditions*: i, Br_2; ii, AgOTf; iii, styrene, MeOH

Table 1 Results of stereoselective reactions with selenium electrophiles generated from diselenides **2a** and **1**

Entry	Alkene	Product	Ratio (% yield) With **4a**	Ratio (% yield) With **6**
1			50:1 (55%)	16:1 (81%)
2			28:1 (45%)	5:1 (49%)
3			12:1 (51%)	9:1 (45%)
4			26:1 (54%)	6:1 (41%)
5			1.5:1 (42%)	1:1 (60%)
6			12:1 (66%)	9:1 (66%)

contrast to our previous observations where diselenides bearing ethyl substituents gave better selectivities than those with methyl substituents. Comparison of these results with those obtained using the arylselenenyl triflate **6** generated from diselenide **1a** (16 : 1) showed that selenenyl triflate **4a** represents a more efficient reagent for stereoselective selenenylation reactions (Table 1).

Encouraged by these results, we carried out further investigations with the electrophilic selenenyl triflate **4a** generated from diselenide **2a**. The methoxyselenenylation reaction of 4-fluorostyrene as well as β-methylstyrene showed increased facial selectivity compared to the reaction with the selenenyl triflate **6** derived from diselenide **1a** (entries 2 and 3). The selenolactonization of the unsaturated carboxylic acid (entry 4) was improved to a ratio of 26 : 1 by using the electrophile **4a**. The product of the cyclization of (*E*)-hex-3-enol and electrophile **6** (entry 5) was isolated as a racemate.[8] Cyclization with **4a** showed a modest facial selectivity of 1.5 : 1 in the resulting product. The stereochemistry of the major diastereomer could not be assigned in this case. The product of the cyclization of a carbamate (entry 6) is obtained with a diastereomeric ratio of 12 : 1. After radical removal of the selenium moiety and deprotection, (*S*)-salsolidine is obtained.[9] The absolute stereochemistry is in all cases the same as that observed with diselenide **1a**.

In summary, we present herein a new, readily available organoselenium reagent bearing a methoxy substituent *ortho* to the selenium. The electrophilic methoxyselenenylation of styrene was performed with a diastereomeric excess of 96%. The increased transfer of chirality is due to the forced interaction of the *ortho*-oxygen atom with the selenium. An X-ray diffraction structure and NOE measurements underline this assumption.

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Notes and References

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‡ Alcohol **3a** (1.37 g, 9 mmol) and TMEDA (1.86 g, 9.6 mmol) were dissolved in dry pentane (12 ml) under argon, cooled to 0 °C, treated slowly with Bu^nLi (9 mmol, 1.6 M solution in hexane) and allowed to stir for 15 min. Then PhLi (27 mmol, 3.0 M solution in cyclohexane–Et_2O) was added and the mixture was stirred for 14 h. After cooling to 0 °C, selenium powder (54 mmol, 4.32 g) was added. The mixture was allowed to warm up to room temperature and stirred for an additional 5 h, then 1 M HCl (50 ml) was added. After extraction of the resulting mixture with Bu^tOMe (3 × 50 ml) and drying of the combined organic phases with $MgSO_4$, powdered KOH (100 mg) was added. The solvent was removed under vacuum and the residue purified by flash chromatography (silica gel, Bu^tOMe–pentane 1 : 2) and recrystallized from EtOH to yield **2a** (1.37 g, 66%) as orange crystals: mp 146–148 °C (Calc. for $C_{18}H_{22}O_4Se_2$: C, 46.98; H, 4.82. Found: C, 46.80; H, 4.90%); $[\alpha]$ +914.5 (*c* 0.96, $CHCl_3$); $\delta_H(CDCl_3)$ 1.26 (t, *J* 6.5, 6H), 2.22 (br s, 2H), 3.83 (s, 6H), 5.06 (q, 6.5 Hz, 2H), 6.84 (d, *J* 8.2, 2H), 7.18 (d, *J* 7.8, 2H), 7.36 (t, *J* 8.0, 2H); $\delta_C(CDCl_3)$ 24.2 (q, 2C), 56.3 (q, 2C), 69.3 (d, 2C), 110.0 (d, 2C), 118.0 (d, 2C), 118.7 (s, 2C), 131.3 (d, 2C), 151.4 (s, 2C), 159.7 (s, 2C); $\delta_{Se}(CDCl_3)$ 365.6; *m/z* (EI) 462 ([M^+], 54%), 230 (60), 214 (100), 214 (100), 198 (28), 182 (16), 134 (35), 107 (22), 91 (26), 77 (21); $\nu(CHCl_3)/cm^{-1}$ 3478, 3376, 3005, 2939, 1568, 1464, 1422, 1136, 1051, 1016.

§ *Crystal data* for **2a**: $C_{18}H_{22}O_4Se_2$, M = 460.29, monoclinic, space group $P2_1$, a = 8.1601(5), b = 13.8981(22), c = 16.5883(13) Å, β = 99.903(6)°, U = 1853.2(3) Å^3, Z = 4, T = 293 K, λ = 1.54180 Å^3, D_c = 1.65 g cm^{-3}, μ = 5.28 mm^{-1}, for 7767 observed reflections, R_1 = 0.0258, wR_2 = 0.0313. CCDC 182/957.

¶ The methoxyselenenylations and selenocyclizations were performed as described in refs. 4 and 8. *Selected data* for **5a**: $[\alpha]$ −1.2 (*c* 0.55, $CHCl_3$); $\delta_H(CDCl_3)$ 1.48 (d, *J* 6.5, 3H), 1.65 (br s, 1H), 3.13 (d, *J* 5.3, 1H), 3.14 (d, *J* 8.1, 1H), 3.21 (s, 3H), 3.88 (s, 3H), 4.29 (dd, *J* 8.1, 5.3, 1H), 5.41 (q, *J* 5.8, 1H), 6.79 (d, *J* 8.0, 1H), 7.14 (dd, *J* 7.8, 0.8, 1H), 7.22–7.35 (m, 6H); $\delta_C(CDCl_3)$ 24.1 (q), 34.9 (t), 56.1 (q), 56.8 (q), 69.8 (d), 83.4 (d), 109.9 (d), 117.1 (s), 118.2 (d), 126.6 (d, 2C), 128.0 (d), 128.5 (d, 2C), 129.7 (d), 141.0 (s), 150.0 (s), 162.8 (s). MS(EI): *m/z* (%) 366 (18) [M^+], 230 (37), 184 (30), 151 (27), 135 (21), 121 (100), 103 (14), 91 (18), 77 (15); $\nu(CHCl_3)/cm^{-1}$ 3666, 3382, 3005, 2937, 2838, 1570, 1464, 1431, 1136, 1103, 1052, 1016 (HRMS found: 366.0747. Calc. for $C_{18}H_{22}O_3Se$: 366.0734).

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