Enantioselective Methoxyselenenylation of α,β-Unsaturated Aldehydes

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Abstract: In this communication we propose a convenient methodology to effect the asymmetric methoxyselenenylation of β-aryl α,β-unsaturated aldehydes using as electrophilic reagent an optically pure sulfur-containing selenenyl chloride. Mechanistic aspects of the reaction were investigated and simple manipulations to prepare optically pure derivatives are reported.

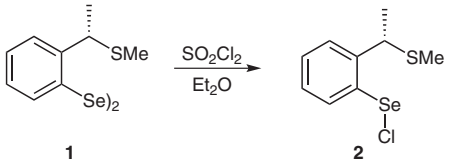
Key words: selenium, asymmetric synthesis, aldehydes, electrophilic addition

Organoselenium compounds are very useful reagents in organic synthesis and they have been extensively used in a wide range of reactions, varying from cationic, radical and anionic transformations, to rearrangements and eliminations.[1]

During the last decades the design of enantiomerically pure diselenides and their use as electrophilic reagents precursors have emerged as practical and powerful tools for the stereoselective preparation of chiral molecules.[1–3] We reported the synthesis of a new class of enantiopure sulfur-containing diselenides and their synthetic applications to promote enantioselective selenium addition reactions to unsaturated substrates.[4] Electrophilic reagents generated starting from diselenide **1** were successfully employed to prepare enantiomerically enriched alcohols,[5] ethers,[5] azides,[6] heterocycles[7] as well as for the kinetic resolution of allylic alcohols.[8] All the investigated reactions showed a very high facial selectivity, higher than those obtained with the corresponding nitrogen- or oxygen-containing reagents.[3]

We demonstrated also that the facial selectivity is strongly correlated to the nonbonding interaction established between the electrophilic selenium and the sulfur atom in compounds like **2**.[9] This compound is an air-stable solid that can be easily prepared starting from diselenide **1** by treatment with SO_2Cl_2 and crystallization from diethyl ether (Scheme 1). It can be successfully used in a large series of asymmetric conversions.[5–9]

In this communication the first efficient asymmetric methoxyselenenylation of α,β-unsaturated aldehydes is reported. Paulmier and co-workers have already described a methodology for the methoxyselenenylation of these substrates using PhSeCl in MeOH at –30 °C.[10] The authors claim that this process proceeds through a dimethylacetal intermediate, which undergoes electrophilic selenomethoxylation via seleniranium ion intermediate. This process, however, occurs with poor regio- and stereoselectivity and it is strongly conditioned by the nature of the substrate.

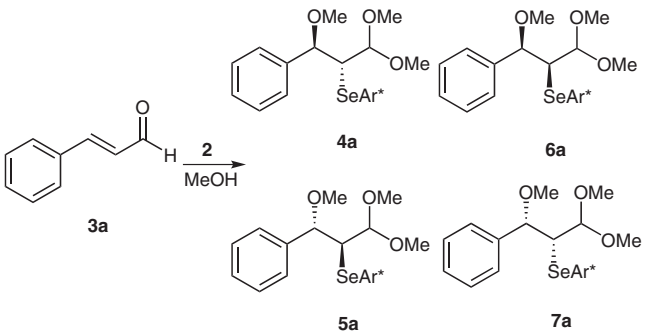


Scheme 1 Preparation of chiral electrophilic selenium reagent

In order to find the best reaction conditions preliminary experiments were carried out starting from cinnamaldehyde (**3a**) using the Ar*SeCl **2** as electrophilic selenenylating reagent at different temperatures and evaluating also the effect of $MgSO_4$ as an additive. The results are summarized in Table 1.

All of the reactions led to the formation of four enantiomerically pure diastereomers **4a**–**7a**, one of which in much higher yield (**4a**). Only this major isomer could be purified from the reaction mixture by flash chromatogra-

Table 1 Preliminary Investigation Starting from **3a**



Entry	Additive	Temp (°C)	Time (d)	Overall yield (%)[a]	Yield of **4a** (%)[a]	**4a/5a/6a/7a**[b]
1	–	0	6	20	8	34:16:25:25
2	–	–30	6	30	20	61:15:12:12
3	–	–30	10	83	55	61:15:12:12
4	$MgSO_4$	0	6	34	26	81:9:5:5
5	$MgSO_4$	0	10	91	65	81:9:5:5

[a] Isolated yields.
[b] Determined by ^1H NMR.

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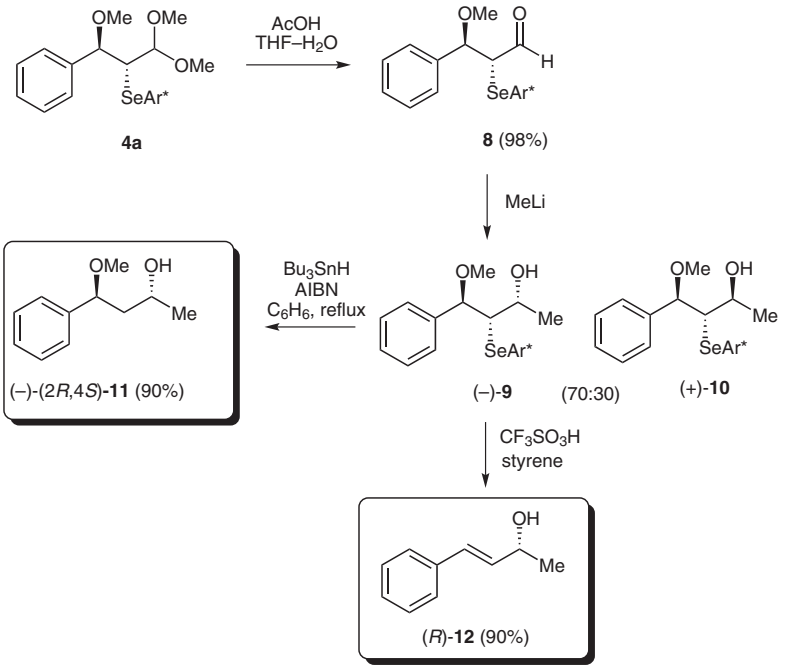


Scheme 2 Assignment of the absolute configuration of **4a**

phy on silica gel. Unfortunately the mixture of the minor products **5a**–**7a** could not be separated and the structures, as well as the ratios, were assigned by the NMR analysis of the crude.

A 'one-pot' carbonyl protection as dimethylacetal and methoxyselenenylation occurred.[10] In a typical optimized procedure, to one equivalent of aldehyde **3**, one equivalent of Ar*SeCl **2**, dissolved in a CH_2Cl_2–MeOH mixture was added, and the reaction mixture was stirred in the conditions shown in Table 1.

The reaction carried at 0 °C (entry 1) was slow and afforded the products **4a**–**7a** in very poor yields and with low selectivity. Moreover several unidentified by products were formed. Using lower temperature (–30 °C, entries 2 and 3) we observed an increase in yield as well as in diastereoselectivity. An unexpected improvement in yield and selectivity was also observed at 0 °C in the presence of one equivalent of $MgSO_4$ (entries 4 and 5).

In order to determine the absolute and relative configurations of the addition products, the pure isomer **4a** was hydrolyzed by treatment with acetic acid in THF–H_2O affording the corresponding aldehyde **8** that was treated with MeLi to give **9**[8] and **10**[11] in a 70:30 diastereoisomeric ratio. After chromatographic purification (–)-**9** was subjected to radical deselenenylation that furnished the enantiomerically pure β-methoxy alcohol **11**[12] (Scheme 2). The comparison of the experimental optical rotation of **11** with the value reported in literature[8] allowed us to assign the *R* configuration to the benzylic carbon. Taking into consideration that the methoxyselenenylation is a stereospecific *anti* addition we could assign *R* configuration to the selenium-binding carbon.

Furthermore treatment of (–)-**9** with a catalytic amount of CF_3SO_3H in the presence of styrene (2 equiv) afforded the corresponding enantiomerically pure (*R*)-allylic alcohol **12**.[8]

The relative configuration of derivatives similar to **4** can be also assigned on the basis of the value of the ^1H NMR coupling constants of the vicinal protons. The *anti* derivatives show larger *J* values (7–10 Hz) than the *syn* ones.[13,14]

This assessment has been confirmed by evaluation of the coupling constants measured for **4a** between ArSeC**H** and PhC**H** (J = 9.1 Hz), which is very similar to that measured by Paulmier[10] in the analogous compound obtained with PhSeCl (J = 8.7 Hz; Figure 1).

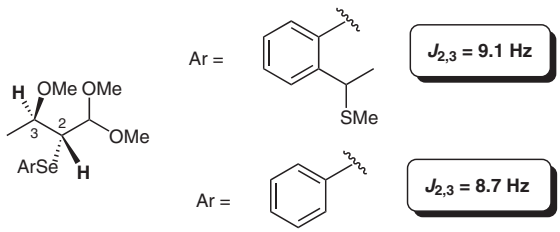
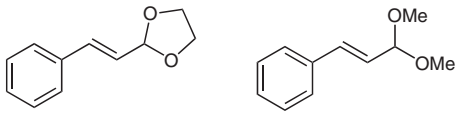


Figure 1 The vicinal *J* coupling values confirm the relative configuration

The experimental conditions reported in entry 4 were applied on acetals **13** and **14** (Figure 2) in order to evaluate the effect of different protections at the carbonyl function.

1,3-Dioxolane derivate **13** proved to be unstable and the acetal converted completely to the related dimethylacetal derivative. On the contrary the dimethylacetal **14** compared to the unprotected **3a** gave higher yields (overall



13 14

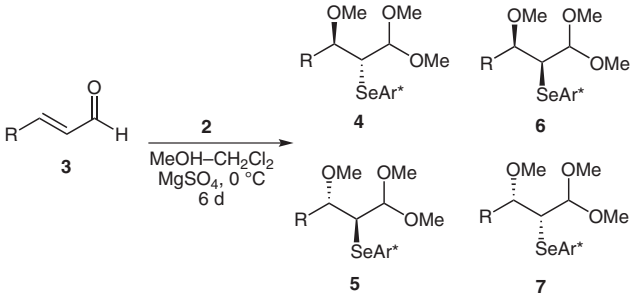
Figure 2 Acetals **13** and **14**

yield: 62%; yield of **4a**: 49%) but lower diastereo- and enantioselectivity (**4a/5a/6a/7a** = 47:13:20:20). This clearly suggests that starting from the aldehyde the reaction involves an intermediate different from **14** and that in the 'one-pot' reaction the formation of the dimethylacetal is not the first reaction step. We suppose that this intermediate is the hemiacetal **15** and that methoxyselenenylation occurs on it rather than on the acetal. In this way the stereocontrol of the process may be improved by a stronger nonbonding interaction between seleniranium ion and the hydroxy group in the allylic position (**16**; Scheme 3). We recently demonstrated that this coordination plays an important role in governing the stereochemistry of electrophilic addition reactions during the kinetic resolution of allylic alcohols.[8] Finally we performed the reaction in optimized conditions on some α,β-unsaturated aldehydes (Table 2). Substrates **3b–d** were prepared by Wittig reactions, while compound **3e** was prepared by refluxing 2-naphthaldehyde, vinyl acetate and $Ba(OH)_2$ in THF.[15]

With the exception of the reaction performed on (*E*)-3-(4-nitrophenyl)acrylaldehyde (**3d**) all processes showed good yields and good diastereo- and enantioselectivities. Moreover in each case the major isomer **4** could be recovered by chromatography on silica gel as a single diastereomer (de >99%).

Surprisingly no selectivity was observed in the formation of the diastereoisomers **6** and **7**. Presumably this data can be due to a match/mismatch effect during the addition to the couple of enantiomerically enriched isomers **17**. The results reported in entry 8 (Table 2) clearly indicate that in order to obtain a good diastereoselectivity, an aryl substit-

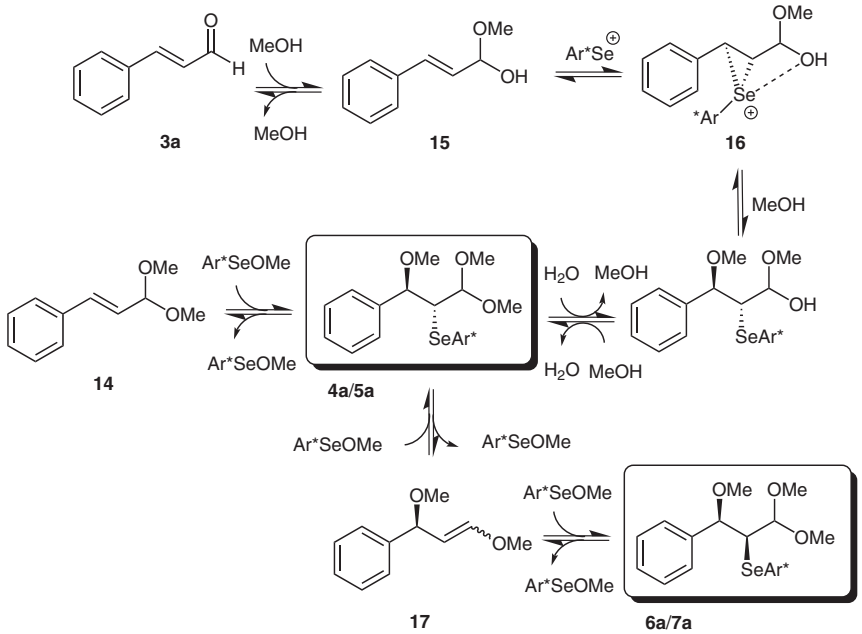
Table 2 Asymmetric Methoxyselenenylation of **3a–f**



3 **2** MeOH–CH_2Cl_2, $MgSO_4$, 0 °C, 6 d → **4**, **5**, **6**, **7**

Entry		Substrate	Overall yield (%)	Yield of **4**[11] (%)	Ratio[a] **4/5/6/7**
1	**3a**	R = Ph	34[b]	26[b]	81:9:5:5
2[c]	**3a**	R = Ph	91[b]	65[b]	81:9:5:5
3	**3b**	R = 4-ClC_6H_4	82[b]	39[b]	72:8:10:10
4	**3c**	R = 4-MeC_6H_4	66[b]	45[b]	73:13:7:7
5	**3d**	R = 4-$NO_2C_6H_4$	–	–	–
6	**3e**	R = 2-naphthyl	29[b]	18[b]	72:8:10:10
7[c]	**3e**	R = 2-naphthyl	67[b]	48[b]	72:8:10:10
8	**3f**	R = Me	64[b]	–	35:35:15:15

[a] Determined by ^1H NMR.
[b] Isolated yields.
[c] Reaction time was 10 d.



Scheme 3 Proposed mechanism

uent on the β-carbon of the α,β-unsaturated aldehydes is required.

In addition we observed that on increasing the reaction time the yields could be positively affected without a change in the diastereoisomeric ratios.

In conclusion we have reported the first methodology to effect the asymmetric methoxyselenenylation of β-aryl α,β-unsaturated aldehydes using easily prepared chiral electrophilic selenenylating reagents. The proposed synthetic approach leads to the formation of useful intermediates that can be manipulated in order to prepare other enantiomerically enriched derivatives.

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(11) Physical and spectral data for selected new compounds are reported below: Compound **4a** ($C_{21}H_{28}O_3SSe$): oil; $[\alpha]_D^{18.0}$ –40.9 (*c* = 1.38, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.35 (dd, 1 H, *J* = 1.4, 7.7 Hz), 7.15–7.25 (m, 6 H), 7.10 (dd, 1 H, *J* = 1.2, 7.5 Hz), 6.95 (dt, 1 H, *J* = 1.4, 7.5 Hz), 4.84 (d, 1 H, *J* = 2.9 Hz), 4.36 (d, 1 H, *J* = 9.1 Hz), 4.19 (q, 1 H, *J* = 6.9 Hz), 3.60 (dd, 1 H, *J* = 2.9, 9.1 Hz), 3.58 (s, 3 H), 3.56 (s, 3 H), 3.17 (s, 3 H), 1.87 (s, 3 H), 1.35 (d, 3 H, *J* = 6.9 Hz). ^{13}C NMR (100.62 MHz): δ = 145.9, 139.5, 136.1, 132.6, 128.6 (2 × CH_{Ar}), 128.2, 128.1 (2 × CH), 127.7, 127.3, 126.3, 105.7, 84.8, 57.7, 57.02, 57.01, 56.4, 43.7, 21.4, 13.9. GC–MS: *m*/*z* (%) = 442 (5), 440 (20) [M^+], 438 (10), 436 (4), 231 (100), 215 (2), 183 (71), 121 (72), 91 (19), 75 (69). Compound **4b** ($C_{21}H_{27}O_3ClSSe$): oil. ^1H NMR (400 MHz): δ = 7.35 (d, 1 H, *J* = 7.3 Hz), 7.15–7.20 (m, 2 H), 7.05–7.13 (m, 3 H), 6.95–7.00 (m, 2 H), 4.85 (d, 1 H, *J* = 2.6 Hz), 4.33 (d, 1 H, *J* = 9.4 Hz), 4.10 (q, 1 H, *J* = 6.9 Hz), 3.60 (s, 3 H), 3.59 (s, 3 H), 3.58 (dd, 1 H, *J* = 2.6, 9.4 Hz), 3.15 (s, 3 H), 1.90 (s, 3 H), 1.41 (d, 3 H, *J* = 6.9 Hz). ^{13}C NMR (100.62 MHz): δ = 145.2, 137.6, 135.6, 133.5, 132.0, 129.5 (2 × CH), 127.7 (2 × CH), 127.2, 126.9, 125.9, 105.2, 83.9, 57.4, 56.6, 56.4, 56.3, 43.2, 20.6, 13.2. GC–MS: *m*/*z* (%) = 476 (6), 474 (12) [M^+], 472 (6), 470 (2), 231 (100), 215 (9), 183 (68), 155 (45), 135 (8), 91 (16), 75 (60). Compound **4c** ($C_{22}H_{30}O_3SSe$): oil. ^1H NMR (400 MHz): d = 7.38 (dd, 1 H, *J* = 1.3, 7.8 Hz), 7.19 (dd, 1 H, *J* = 1.7, 7.8 Hz), 7.14 (ddd, 1 H, *J* = 1.3, 7.3, 7.8 Hz) 7.04–7.08 (m, 2 H), 6.94–6.98 (m, 3 H), 4.83 (d, 1 H, *J* = 2.9 Hz), 4.32 (d, 1 H, *J* = 9.2 Hz), 4.15 (q, 1 H, *J* = 6.9 Hz), 3.58 (s, 3 H), 3.57 (dd, 1 H, *J* = 2.9, 9.2 Hz), 3.56 (s, 3 H), 3.16 (s, 3 H), 2.28 (s, 3 H), 1.87 (s, 3 H), 1.34 (d, 3 H, *J* = 6.9 Hz). ^{13}C NMR (100.62 MHz): δ = 145.4, 137.3, 136.0, 135.8, 132.3, 128.4 (2 × CH), 128.0 (2 × CH), 127.1, 126.8, 125.8, 105.3, 84.2, 57.4, 56.9, 56.5, 56.1, 43.3, 21.1, 20.9, 13.4. GC–MS: *m*/*z* (%) = 454 (21) [M^+], 452 (10), 231 (72), 229 (37), 215 (11), 183 (49), 135 (100), 105(6), 91 (14), 75 (52). Compound **4e** ($C_{25}H_{30}O_3SSe$): oil. ^1H NMR (400 MHz): δ = 7.70–7.75 (m, 2 H), 7.69 (s, 1 H), 7.53 (d, 1 H, *J* = 8.5 Hz), 7.45–7.50 (m, 2 H), 7.33 (d, 1 H, *J* = 7.8 Hz), 7.19 (d, 1 H, *J* = 8.6 Hz), 7.00 (dd, 1 H, *J* = 7.6, 8.0 Hz), 6.92 (d, 1 H, *J* = 7.5 Hz), 6.80 (t, 1 H, *J* = 7.5 Hz), 4.93 (d, 1 H, *J* = 2.5 Hz), 4.52 (d, 1 H, *J* = 9.6 Hz), 3.83 (q, 1 H, *J* = 6.9 Hz), 3.71 (dd, 1 H, *J* = 2.5, 9.6 Hz), 3.63 (s, 3 H), 3.62 (s, 3 H), 3.25 (s, 3 H), 1.78 (s, 3 H), 0.88 (d, 3 H, *J* = 6.9 Hz). ^{13}C NMR (100.62 MHz): δ = 145.5, 136.9, 136.1, 133.6, 133.1, 132.7, 128.5, 128.4, 128.3, 127.9, 127.8, 127.4, 127.1, 126.3, 126.0, 125.7, 105.8, 85.2, 57.9, 57.0, 56.7, 43.6, 30.7, 20.3, 13.6. Compound **10** ($C_{20}H_{26}O_2SSe$): oil; $[\alpha]_D^{18.0}$ = 19.9 (*c* = 1.11, $CHCl_3$). ^1H NMR (400 MHz): δ = 7.40 (d, 1 H, *J* = 8.0 Hz), 7.10–7.30 (m, 7 H), 7.00–7.05 (m, 1 H), 4.35 (d, 1 H, *J* = 9.5 Hz), 4.25–4.30 (m, 1 H), 4.03 (q, 1 H, *J* = 7.0 Hz), 3.72 (dd, 1 H, *J* = 4.5, 9.5 Hz), 3.18 (s, 3 H), 3.07 (d, 1 H, *J* = 9.1 Hz), 1.89 (s, 3 H), 1.41 (d, 3 H, *J* = 7.0 Hz), 1.38 (d, 3 H, *J* = 6.3 Hz). ^{13}C NMR (100.62 MHz): δ = 144.5, 139.3, 134.8, 132.0, 128.6, 127.91 (2 × CH), 127.88 (2 × CH), 127.4, 127.2, 125.9, 86.2, 67.4, 63.6, 56.9, 43.1, 21.1, 20.1, 13.0. GC–MS: *m*/*z* (%) = 410 (7) [M^+], 408 (3), 231 (82), 229 (40), 215 (13), 194 (31), 183 (100), 181 (57), 147 (13), 121 (36), 105 (28), 91 (45), 77 (21), 51 (4).

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