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Asymmetric Selenomethoxylation of Alkenes with Camphorselenenyl Sulfate

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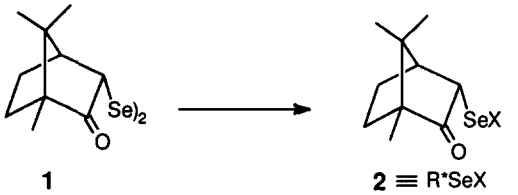
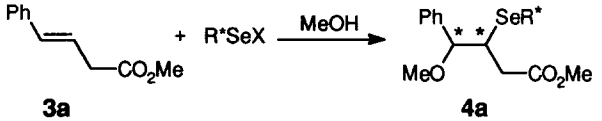
Abstract: By reaction with ammonium persulfate the easily available diselenide derived from (1*R*)-(+)-camphor was converted into the camphorselenenyl sulfate. This chiral electrophilic selenium reagent reacted at room temperature with alkenes in the presence of methanol to afford selenomethoxylated adducts in good yields and with moderate to good facial selectivity. The two diastereomeric addition products could be separated in most cases.

The use of organoselenium reagents to effect asymmetric syntheses has recently attracted the attention of several research groups. New chiral diselenides have been prepared and transformed *in situ* into electrophilic chiral selenenylating agents which were allowed to react with alkenes in the presence of external or internal nucleophiles.[1-5] Moderate to high asymmetric inductions were observed in the formation of the corresponding addition products. The camphor diselenide **1** can be easily prepared in one-step from (1*R*)-(+)-camphor and elemental selenium.[5b] The corresponding selenenyl chloride **2a** has been employed to promote seleno-etherification and seleno-lactonization reactions with very poor diastereoselectivity. However, good results could be obtained with a modified diselenide in which the carbonyl group was converted into an oxazolidinone ring.[5a] We now report that camphorselenenyl sulfate **2d**, which is produced *in situ* by the reaction of **1** with ammonium persulfate, according to the procedure described for the phenylselenenyl sulfate,[6] can be conveniently employed to effect the asymmetric selenomethoxylation of alkenes with moderate to good facial selectivity.



1 **2** ≡ R*SeX

2a : X = Cl
2b : X = Br
2c : X = OTf
2d : X = OSO_3H



3a **4a**

R*SeX	°C	h	Yield	D.r.
2a	0	4	49%	40:60
2b	0	2	56%	35:65
2c	0	5	77%	42:58
2d	25	24	94%	85:15

Preliminary esperiments were carried out on the methyl styrylacetate **3a** using camphorselenenyl chloride **2a**, bromide **2b**, triflate **2c** or sulfate **2d**. The reactions proceeded regioselectively in every case and afforded **4a** as a mixture of the two possible diastereomers deriving from a stereospecific *anti* addition.[7] Low chemical yields and poor diastereoselectivities were observed in the reactions of **2a** and **2b**. Chemical yields were improved with the use of the triflate **2c** but the diastereomeric ratio was still very low (D. r. = 42:58).

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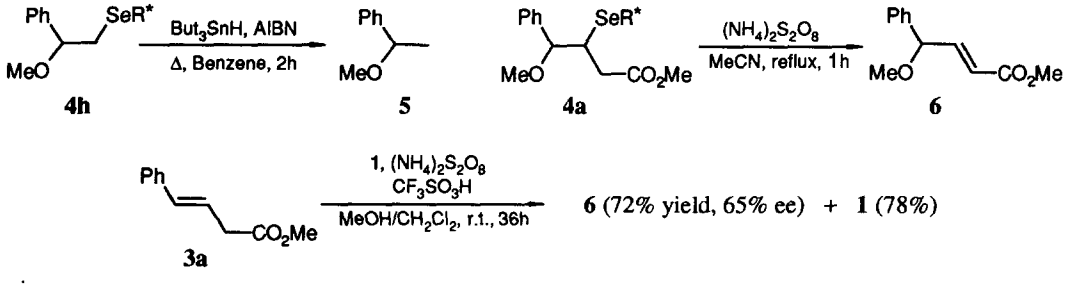
No substantial differences were observed when these reactions were run at 0 °C or at -30 °C. Good results were instead obtained when the sulfate **2d** was employed as the selenenylating agent (D. r. = 85:15, yield 94%). In this case the reaction was much slower and it was therefore carried out at room temperature for 24 h. These results indicate that the nature of the counter anion has a marked effect on the course of these asymmetric selenomethoxylation reactions. A similar effect was observed in other cases also[1a] but it was not so important as that produced by the sulphate in the present case. A further interesting point is that with the sulfate **2d** the addition occurs with a facial selectivity different from that observed with **2a**, **2b** and **2c**.[8]

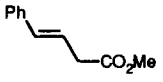
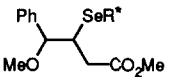
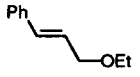
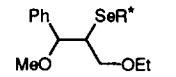
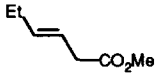
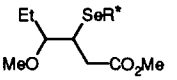
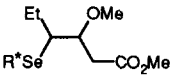
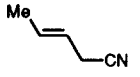
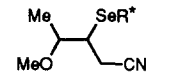
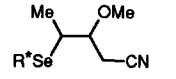
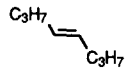
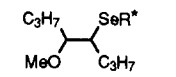
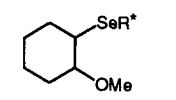
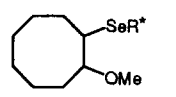
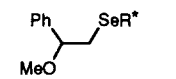
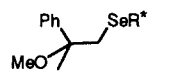
Thus the camphorselenenyl sulfate **2d** proved to be more efficient than the other camphor-based selenenylating agents investigated and it was therefore employed for the experiments with other alkenes. The results of the selenomethoxylations of the alkenes **3a-3i** are collected in Table 1. In a typical experiment the diselenide **1** (0.5 mmol) was dissolved in dichloromethane (2.5 ml) and ammonium persulfate (0.5 mmol) and trifluoromethanesulfonic acid (1 mmol) were added. The mixture was stirred at room temperature for 15 min and then a solution of the alkene (1 mmol) in methanol (2.5 ml) was added. The progress of the reaction was monitored by TLC and GC-MS. The reaction mixture was poured in water and worked up in the usual way. GC-MS and ^{1}H-NMR analyses of the reaction mixture indicated that the addition products **4a-4i** were formed as a mixture of two diastereomers in the ratios indicated in Table 1. The reaction products were isolated by medium pressure column chromatography. In most cases the two diastereomers were separated and were fully characterized by GC-MS, ^{1}H- and ^{13}C-NMR. In the case of the reactions of **3c** and **3d** (entries 3 and 4) small amounts of the regioisomers **4c'** and **4d'** were also formed together with **4c** and **4d**. In all the other cases (entries 1, 2, 8, and 9) the adducts were obtained as single regioisomers. Moderate diastereoselectivity was observed in the selenomethoxylation of ethyl cinnamyl ether, cyclohexene, styrene and α-methylstyrene (entries 2, 6, 8 and 9). Good facial selectivity was instead observed in all the other cases.

Absolute configuration was established only in the case of the addition products **4h** deriving from styrene. Reductive deselenenylation with tributyltin hydride and AIBN in refluxing benzene was carried out on the two separated diastereomers. The major isomer afforded the (+)-(*R*)-**5** (86%) and the minor isomer gave the (-)-(*S*)-**5** (82%).[9] In both cases the enantiomeric excess[10] was greater than 95%. The removal of the selenium moiety could also be effected by oxidative elimination using ammonium persulfate. This procedure was applied to the two separated diastereomers deriving from **3a**. The major isomer of **4a** gave the allylic ether (+)-**6** (87%, ee >95%) and the minor isomer gave the (-)-**6** (80%, ee >95%).[10]



Finally, we used the diselenide **1** and $(NH_4)_2S_2O_8$ to effect the catalytic one-pot conversion of the β,γ-unsaturated ester **3a** into the allylic ether **6** according to our recent selenenylation-elimination procedure.[11]

Table1. Selenomethoxylation of Alkenes with Camphorselenenyl sulfate **2d** at Room Temperature.

Entry	Alkenes, 3		Reaction Time (h)	Addition Products, 4		Yield (%)[a]	D. r.
1		**3a**	24		**4a** [b]	94	85:15 [e]
2		**3b**	40		**4b** [b]	77	73:27 [e,f]
3		**3c**	21		**4c** [b]	72	90:10 [f]
					**4c'** [c]	7	90:10 [f]
4		**3d**	36		**4d** [d]	64	88:12 [e,f]
					**4d'** [c]	12	75:25 [f]
5		**3e**	22		**4e** [b]	78	86:14 [e,f]
6		**3f**	29		**4f** [b]	73	75:25 [e,f]
7		**3g**	22		**4g** [b]	82	83:17 [e]
8		**3h**	18		**4h** [b]	91	65:35 [e]
9		**3i**	22		**4i** [b]	86	75:25 [f]

a) Based on isolated products after column chromatography. *b*) The two diastereomers were separated and identified by ^{1}H, ^{13}C-NMR and GC-MS. *c*) The two diastereomers were detected by GC-MS. *d*) The minor isomer could not be obtained in a pure form. *e*) Determined by ^{1}H-NMR. *f*) Determined by GC-MS.

The reaction was first carried out in methanol and dichlorometane (1:1), in the presence of trifloromethanesulfonic acid, using catalytic amounts of **1** and an excess of ammonium persulfate. Under these conditions conversion was very low even after several days. The reaction was therefore repeated using stoichiometric amounts of **1**. After 36 h at room temperature the allylic ether **6** was obtained in 72% yield and

with 66% ee (in good agreement with the diastereomeric ratio observed for **4a**). Moreover, most of the diselenide **1** can be recovered (78%) at the end of the reaction.[12]

The results here presented indicate that the camphorselenenyl sulfate **2d** can be conveniently employed to effect asymmetric selenomethoxylation of alkenes.[12] In view of the easy availability of the diselenide **1** the present procedure favourably compare with other methods which employ more complex chiral diselenides.[1-4]

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7. *Anti* addition is assumed on the basis of literature precedents.[6]
8. Similar changes in facial selectivity on passing from the bromide **2b** to the sulfate **2d** were also observed with styrene, α-methylstyrene and with the *trans* alkenes β-methylstyrene, 4-octene and methyl 3-hexenoate. No changes were observed with cyclohexene and cyclooctene. This effect of the counter anion on the facial selectivity of the addition reaction is presently under further investigation.
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10. The ee was determined by ^{1}H-NMR in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.
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12. Further investigations on this selenenylation-elimination procedure, as well as on other asymmetric intermolecular and intramolecular addition reactions promoted by **2d**, are presently under way.