CHEMCOMM Communication
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First chiral selenium ylides used for asymmetric conversion of aldehydes into epoxides

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Received (in Cambridge, UK) 9th July 2001, Accepted 8th October 2001
First published as an Advance Article on the web 26th October 2001

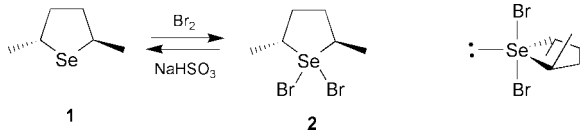
Enantioenriched selenonium ylides have been generated by addition of benzyl bromide to C_2 symmetric (2*R*,5*R*)-2,5-dimethylselenolane in the presence of NaOH, and subsequently reacted with a variety of aldehydes to give oxiranes with excellent enantiomeric excesses (a catalytic version has been achieved); also, an aliphatic cyclic hypervalent dibromoselenurane structure has been demonstrated by X-ray analysis.

The reaction of selenium ylides with carbonyl compounds provides epoxides.[1,2] Since the initial report by Krief and his group[3] in 1974, it has rarely been exploited[4,5] and, to our knowledge, no asymmetric version is available. We wished to introduce a chiral selenide for the conversion of aldehydes into oxiranes with absolute stereocontrol. This raises several challenges. Few enantioenriched selenides have been synthesized so far.[6] An interesting question is the stereochemical course: will it differ, due to the possible [2 + 2]cycloaddition for the key step, leading to 4-membered ring intermediates with a hypervalent selenium atom (oxaselenetanes),[7] or will it be similar to that of the sulfur analogue,[8] with classical betaines as intermediates?[9,10]

We anticipated favourable kinetics of the epoxidation sequence as compared to the sulfur series. For the first step, a high nucleophilicity of selenides towards benzyl halides has been reported.[11] Deprotonation of the selenonium salt will probably be facilitated,[12] as a result of the higher polarizability of selenium. For the third step, addition of the ylide to the carbonyl group, we found no accurate data in the literature, but a fair reactivity was hoped for in relation to polarizability, bond lengths and dissociation energies.

Our study has been based on our results[13,14] with C_2 symmetric sulfur ylides, prepared from (+)-(2*R*,5*R*)-2,5-dimethylthiolane and possible comparisons. Therefore we embarked on the synthesis of the selenium analogue and its use for the epoxidation reaction.

Enantiopure selenolane **1** has been prepared in two easy steps from commercially available (2*S*,5*S*)-hexanediol.† Activation of both hydroxy groups into mesylates and subsequent double nucleophilic substitution with lithium selenide[15,16] (generated *in situ* from selenium and $LiBEt_3H$) provided the crude selenolane quantitatively. Isolation of **1** proved problematic in relation to volatility and azeotrope formation with solvents. We converted **1** by addition of bromine into a stable crystalline 'dibromide'[17,18] **2** (Scheme 1). A selenurane structure was suggested by the single NMR signal observed for the two methyl groups. We were able to grow single crystals (mp: 93.5–94.5 °C) and the X-ray analysis demonstrated the Se^{IV} hypervalent[19] arrangement (Fig. 1). A trigonal bipyramid[20] was observed with the two electron withdrawing groups (bromine atoms) in apical positions, a reduced C–Se–C angle[21,22] of 89.9° and the lone pair in equatorial position. To our knowledge, this is the first structural determination of an aliphatic cyclic dibromoselenurane.



1 2

Scheme 1

Selenolane **1** was regenerated by reaction with aqueous sodium hydrogensulfite in 70% overall yield.

The expoxidation reaction was carried out in a very simple, one pot procedure. Selenolane **1**, benzyl bromide, an aldehyde, and sodium hydroxide were reacted at ambient temperature in a 9 : 1 mixture of Bu^tOH and water as solvent (Scheme 2).‡ With a stoichiometric amount of selenide (Table 1), the reaction time is shorter than for the corresponding sulfide: after 2 h, a 51% yield of stilbene oxide was isolated. After 24 h, oxiranes were obtained in 71–97% yields (Table 1, entries 2–4). Excellent enantiomeric excesses were attained: 92–93%.

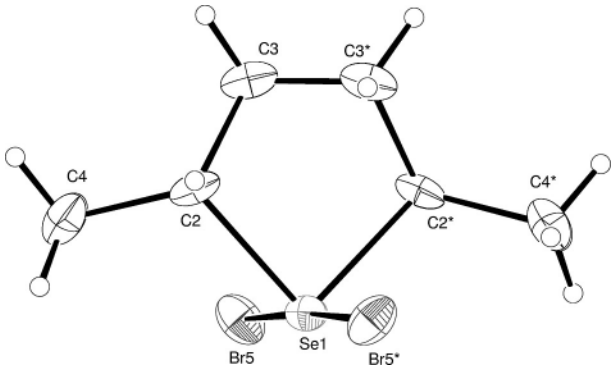
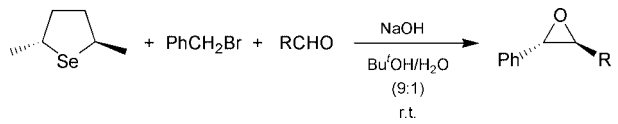


Fig. 1 X-Ray crystal structure of selenurane **2**.§ Selected interatomic distances (Å), bond angles (°) and torsion angles (°): Br–Se(1) 2.570(1), Se(1)–C(2) 2.013(7), C(2)–C(3) 1.53(1); Br–Se(1)–Br 176.4, Br–Se(1)–C(2) 93.4, Br–Se(1)–C(2) 89.2, C(2)–Se(1)–C(2) 89.9(4), Se(1)–C(2)–C(3) 103.0(5), C(2)–C(3)–C(3) 109.3(6).



Scheme 2

Table 1 Asymmetric synthesis of epoxides from aldehydes[a]

Entry	Aldehyde	Conditions	Yield (%)	dr *trans* (%)	ee (*S*,*S*) (%)
1	Benzaldehyde	2 h	51	1 : 1.4	92
2	Benzaldehyde	24 h	71	1 : 2	92
3	4-Tolualdehyde	24 h	86	1 : 1.4	93
4	2-Naphthaldehyde	24 h	97	1 : 1	92

[a] All reactions were performed with selenolane **1** (0.20 mmol), benzyl bromide (0.40 mmol), aldehyde (0.20 mmol) and NaOH (0.40 mmol).

 DOI: 10.1039/b106063p

Table 2 Catalytic asymmetric benzylidenation of various aldehydes[a]

Entry	Aldehyde	Yield (%)	dr *trans* (%)	ee[b] (*S*,*S*) (%)
1	Benzaldehyde	91	1 : 1	91
2	4-Tolualdehyde	97	1 : 1	92
3	2-Naphthaldehyde	97	1 : 1	92
4	4-Chlorobenzaldehyde	97	1 : 1	76
5	4-Trifluoromethylbenzaldehyde	76	1 : 1	83
6	(*E*)-Cinnamaldehyde	66	1 : 1	94
7	2-Furaldehyde	67	1 : 1	93
8		65[c]	1 : 1	92
9	2-Thiophenecarboxaldehyde	72	1 : 1	94
10		86[c]	1 : 1	94

[a] All reactions were performed with selenolane **1** (0.020 mmol, 20 mol% to aldehyde), benzyl bromide (0.40 mmol), aldehyde (0.20 mmol) and NaOH (0.40 mmol) at rt for 7 days. [b] Enantiomeric excesses were determined by chiral HPLC using a Daicel AD column. [c] Reaction time: 4 h.

These results led us to achieve a catalytic procedure.[23–25] Using 0.2 equivalent of selenolane **1** and eight aldehydes, at ambient temperature for a maximum of 7 days, good to excellent yields of oxiranes (65–97%) were obtained (Table 2). For the more reactive heteroaromatic aldehydes (entries 8, 10) the reaction time could be optimized to 4 h. Enantiomeric excesses were 91–94% (entries 1–3, 6–10), except for aldehydes bearing electron-withdrawing groups (entries 4, 5).

As compared to the sulfur analogues,[13,14] this series leads to enhanced reactivity and higher asymmetric induction, with the same absolute configuration.

Another feature is the diastereoselectivity,[26] which has almost not been addressed so far in the selenium series.[1,2] Under stoichiometric conditions, the *trans* oxirane was the major isomer but to a much lesser extent than with sulfides (for the example of benzaldehyde: excess of 18–34% instead of 86%). The catalytic series provides an equal abundance of *trans* and *cis* oxiranes, for most cases. This trend towards the *cis* isomer is reminiscent of the reaction of unstabilized sulfur ylides with aliphatic aldehydes, and of the Wittig reaction of unstabilized phosphoranes with aldehydes. The higher reactivity observed here with selenonium ylides leads us to propose early transition states, and possible hypervalent oxaselenetane intermediates.[7,27]

In conclusion this first report of chiral selenium ylides demonstrates that they can provide efficient asymmetric induction for the synthesis of epoxides. They exhibit marked differences with sulfur ylides. The catalytic version is competitive with previous methods in the sulfur series.[23–25,28–30]

We thank CNRS and PunchOrga (‘Réseau inter-régional du Pôle Universitaire Normand de Chimie Organique’) for support.

Notes and references

† *Experimental data for* **1**: pale yellow oil; δ_H (250 MHz, $CDCl_3$) 1.45 (6H, d, *J* 6.6 Hz, 2 Me), 1.57–1.63 (2H, m), 2.25–2.30 (2H, m), 3.77–3.85 (2H, m, 2 CH); δ_C (62.9 MHz, CDCl3) 21.3, 38.2, 39.3; ν_{max} (NaCl)/cm^{-1} 2966, 2950, 2920, 1090, 1046, 1030, 1000, 990, 802; $[\alpha]_D^{22}$ +166 (*c* 1.31 in $CHCl_3$); HRMS (EI) *m*/*z* calcd. 164.0104, found 164.0131. **2**: yellow needles; mp 93.5–94.5 °C; δ_H (250 MHz, $CDCl_3$) 1.83 (6H, d, *J* 6.9 Hz, 2 Me), 2.29–2.36 (m, 2H), 2.67–2.76 (m, 2H), 4.85–4.93 (m, 2H); δ_H (250 MHz, C_6D_6) 1.49 (6H, d, *J* = 6.6 Hz, 2 Me), 1.65–1.71 (m, 2H), 1.96–2.04 (m, 2H), 4.40–4.47 (m, 2H); δ_C (62.9 MHz, $CDCl_3$) 20.1, 39.4, 78.7; δ_C (62.9 MHz, C_6D_6) 18.7, 39.8, 79.1; ν_{max} (KBr)/cm^{-1} 2920, 1440, 1370, 1090, 1046, 1030, 1000, 990, 802; $[\alpha]_D^{22}$ +64.4 (*c* 0.41 in CHCl3); HRMS (EI) *m*/*z* calcd. (M^+ − Br) 242.9287, found 242.9241.

‡ *Representative experimental procedure*: to a solution of selenolane **1** (0.020 mmol) in a 9 : 1 mixture of Bu^{t}OH and water (0.80 mL) were added benzyl bromide (48 μL, 0.40 mmol), benzaldehyde (20 μL, 0.20 mmol) and powdered NaOH (16 mg, 0.40 mmol). The reaction mixture was stirred at room temperature for 24 h then water was added. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and then concentrated to dryness. Purification by silica gel column chromatography (eluent diethyl ether–ethyl acetate) gave the expected oxirane. The ee was determined by HPLC analysis on a Daicel Chiralpak AD column (9 : 1 n-hexane–propan-2-ol).

§ *Crystal data for* **2**: $C_3H_6BrSe_{0.5}$. *M* = 161.46, tetragonal, space group $P4_32_12$, at 293.2 K, *a* = 9.009(3), *b* = 9.009(3), *c* = 12.21(1) Å, *V* = 991.0(7) Å 3 , *Z* = 8, *F*(000) = 608.00, μ(MoKα) = 0.7107 cm^{-1}, D_{calc} = 2.164 g cm^{-3}, final *R* values R_1 = 0.0452 (all data), wR_2 = 0.0358. CCDC 167809. See http://www.rsc.org/suppdata/cc/b1/b106063p/ for electronic files in .cif or other electronic format.

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