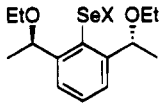
Asymmetric Ring Closure Reactions Mediated by a Chiral C_2 Symmetrical Organoselenium Reagent

Robert Déziel* and Eric Malenfant

Bio-Méga/Boehringer Ingelheim Research Inc., 2100 Cunard Street, Laval, Québec, Canada H7S 2G5

Received March 21, 1995

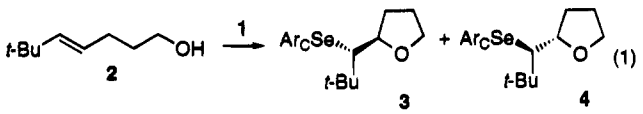
We recently reported the asymmetric selenomethoxylation of olefins involving the novel C_2 symmetrical organoselenium derivative **1**.[1] This reagent exhibited



1
X= OTf
(Ar_CSeOTf)

very high facial selectivity with several olefins to give the selenomethoxylated adducts in diastereoisomeric excess as high as 97%. Encouraged by these results we sought to expand the utility of this reagent further by investigating the diastereoselectivity of ring closure reactions to give five- and six-membered heterocycle derivatives (Scheme 1).

We initiated our investigation with *trans*-6,6-dimethyl-4-hepten-1-ol (**2**) and assessed the facial selectivity of **1** by measuring the ratio of the corresponding diastereoisomeric tetrahydrofuran derivatives **3** and **4** (eq 1).



Thus, when the unsaturated alcohol **2** was added to a dichloromethane solution of **1** (generated *in situ* from the corresponding diselenide[1]) at −78 °C, the cyclized products **3** and **4** were formed almost instantaneously but in a 2:1 ratio.

This poor selectivity contrasted with the excellent results we obtained for selenomethoxylation.[1] Upon further investigation we found that addition of a small amount of methanol dramatically improved the selectivity (Table 1). The best selectivity obtained so far with unsaturated alcohol **2** was 11.4:1 at −90 °C in the presence of 2.5% v/v methanol in dichloromethane.[2a] At higher temperatures selectivity decreased. Replacement of dichloromethane by ether or toluene gave poorer selectivity. Interestingly, we observed that the methanol does not compete with the internal nucleophile.[3] However, at higher concentrations of methanol, we observed a decrease in selectivity. We speculate that, in the presence of methanol, the reactive species may be the selenoester Ar_cSeOMe that for some reason exerts better facial selectivity than the corresponding trifluoromethanesulfonate reagent.[2b]

Scheme 1

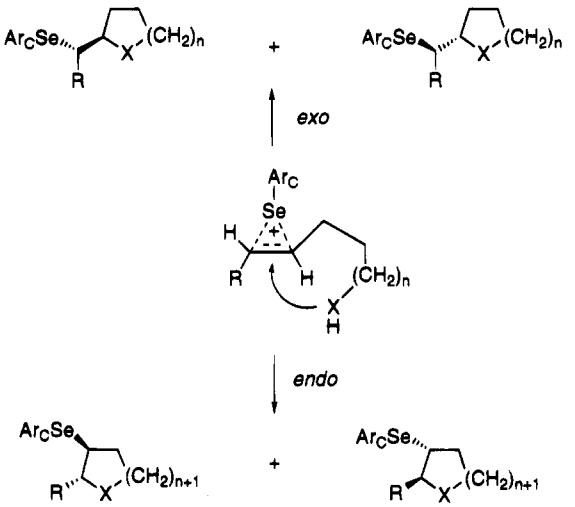


Table 1. Asymmetric Selenoetherification: Effect of Solvent and Temperature on Selectivity

entry	solvent	cosolvent[a] (2.5% v/v)	temp (°C)	ratio[b] **3**:**4**	yield[c] (%)
1	CH_2Cl_2	THF	−78	2:1	85
2	CH_2Cl_2	MeOH	−78	9:1	89
3	CH_2Cl_2	MeOH	−90	11.4:1	86
4	CH_2Cl_2	MeOH	0	4:1	
5	$PhCH_3$	THF	−78	2:1	
6	$PhCH_3$	MeOH	−78	3:1	
7	Et_2O	THF	−78	1:1	
8	Et_2O	MeOH	−78	4:1	88

[a] Solvent used to make a 2 M silver trifluoromethanesulfonate solution. [b] All ratios were measured from the crude reaction mixture. [c] Yields of **3** and **4** mixture obtained after purification by column chromatography on silica gel. Products from entries 4–7 were not purified, and the NMR spectrum of the crude mixture indicated an almost quantitative conversion.

Using the conditions of entry 2 in Table 1, we next determined if selectivity would depend on the mode of cyclization (*i.e.* 5,6-*endo*-*exo*). The results of entries 1, 3, and 5 (Table 2) indicate that 5-*endo*, 5-*exo*, and 6-*exo* pathways of cyclization occur with more or less the same degree of facial selectivity. However, replacing the *tert*-butyl group by a phenyl group (*cf.* entries 1 and 2, Table 2) results, surprisingly, in a reversal of facial selectivity. The reasons for this reversal of facial selectivity are not clear to us, and we are presently conducting experiments to gain some insight into this phenomenon. The 6-*endo* mode of cyclization (entry 4, Table 2) gives the highest selectivity. Cyclizations with terminal olefins or olefins substituted with a small alkyl group proceed with poorer selectivity (entries 6 and 7, Table 2). The regioselectivity observed for these cyclizations is consistent with what has already been observed with achiral electrophilic reagents.[4]

We also investigated the cyclization reaction involving carboxylic acids and a carbamate as internal nucleophiles (Table 3). In both cases, cyclization can occur with excellent facial selectivity and good yields. As observed

(1) Déziel, R.; Goulet, S.; Grenier, L.; Bordeleau, J.; Bernier. J. *J. Org. Chem.* **1993**, *58*, 3619.

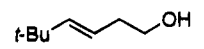
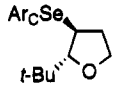
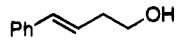
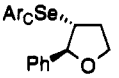
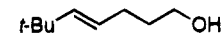
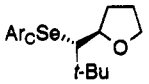
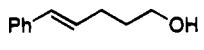
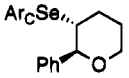
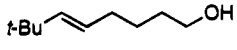
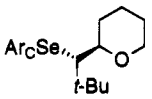
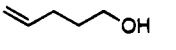
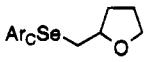
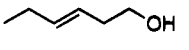
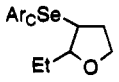
(2) (a) We found that the presence of a small amount of alcohol is essential for good selectivity and methanol could also be replaced by 2-propanol. (b) Experiments are currently in progress to validate this hypothesis.

(3) Harring, S. R.; Edstrom, E. D.; Livinghouse, T. In *Advances in Heterocyclic Natural Product Synthesis*; JAI Press: 1992; Vol. 2, p 313.

(4) For pertinent discussions on this topic, see: (a) *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: London, 1987; Chapter 2. (b) *Selenium Reagents and Intermediates in Organic Synthesis;* Paulmier, C., Ed.; Pergamon Press: Oxford, U.K., 1986; Chapter 8. (c) Reference 3, pp 300–305.

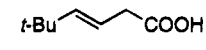
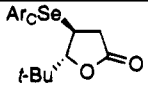
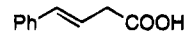
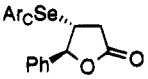
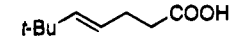
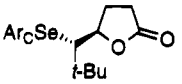
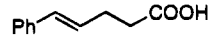
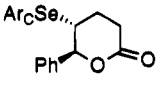
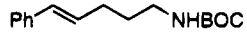
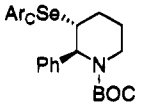
0022-3263/95/1960-4660$09.00/0 © 1995 American Chemical Society

Table 2. Asymmetric Selenoetherification: Mode of Cyclization vs Selectivity

Entry[a]	Olefin	Major Product	Ratio	Yield (%)
1			12:1	77
2			12:1	92
3			9:1	89
4			29:1	95
5			8:1	77
6			2.3:1	96
7			2:1	73

[a] Reactions carried out at -78 °C (see Experimental Section).

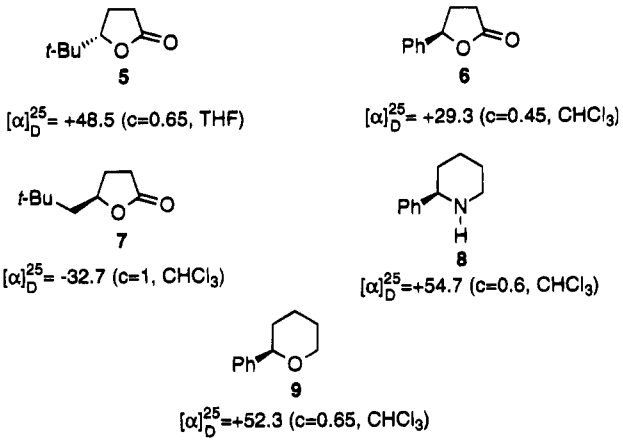
Table 3. Asymmetric Selenolactonization and Carbamate Cyclization

Entry	Olefin	Major Product	Ratio	Yield (%)
1			20:1	72
2			13:1	72
3			10:1	84
4			40:1	65[9]
5			25:1	89

for the selenoetherifications, the 6-*endo* pathways of cyclization gave the highest facial selectivity (entries 4 and 5, Table 3). It appears that the nature of the internal nucleophile (OH, COOH, R_2NH) has little influence on the facial selectivity.

The absolute stereochemistries of the major products of entries 1–3 from Table 3 and the tetrahydropyran derivative of entry 4 in Table 2 were assessed by removal of the chiral organoselenium moiety and comparison of the optical rotation of the resulting substituted heterocycles with literature values[5] or with values obtained by synthesizing the compounds via an alternative route.[6] Thus, reduction with triphenyltin hydride in the presence of a catalytic amount of AIBN in refluxing toluene[7] gave the corresponding substituted heterocycles **5**, **6**, **7**, **8**, and **9** in 78%, 81%, 87%, 50%,[8] and 48% yield, respectively (Scheme 2). The absolute configuration of the chiral center in compounds **6**–**9** was found to be *R*, and the *S* configuration was assigned for the lactone **5**.

Scheme 2



The assignment of the relative configuration of the centers bearing the organoselenium moiety as depicted in Tables 2 and 3 was based on NMR analysis of the adducts and on ample literature precedent for *anti* attack of nucleophiles to episelenonium ions.[4] The assignment of the absolute configuration of the cyclic ether derivatives of entries 1–5 in Table 2 was made by analogy with the corresponding compounds in Table 3 since the facial selectivity should be dictated by the chiral selenium reagent and the olefins, not by the nature of the nucleophile.

In conclusion, we have extended the application of the chiral organoselenium reagent **1** to asymmetric ring closure reactions. This has led to the preparation of enantiomerically enriched substituted heterocycle derivatives.

Experimental Section

General Procedure for the Cyclizations (Entry 3, Table 3). 5-(*R*)-[(*S*)-2,6-Bis(1-(*R*)-ethoxyethyl)phenylseleno]-2,2-dimethylpropyl)-2(3*H*)-dihydrofuranone. To a solution of the chiral diselenide[1] (30 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) cooled to −78 °C was added a 1 M solution of bromine in CCl_4 (54 μL, 0.054 mmol). After 5 min, a 2 M MeOH solution of silver trifluoromethanesulfonate (55 μL, 0.11 mmol) was added. The

(5) (a) For a recent enantiomeric synthesis of the lactone **6** ($[\alpha]^{25}_D$ +35.5 (*c* 2.52, $CHCl_3$)) and the enantiomer of **5** ($[\alpha]^{25}_D$ −44.6 (*c* 2.00, THF)), see: Brown, H. C.; Kulkarni, S.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365. (b) Piperidine **8** ($[\alpha]^{25}_D$ +35.3 (neat): Vetuschi, C.; Ottolino, A.; Tortorella, V. *Gazz. Chim. Ital.* **1975**, *105*, 935.

(6) The lactone **7** was also synthesized from pure *S*-(−)-γ-methylleucine (99% ee, Bachem) via nitrous acid deamination, $[\alpha]^{25}_D$ −41.2 (*c* 1.2, $CHCl_3$). The cyclic ether **9** was also prepared from *R*-(+)-3-chloro-1-phenyl-1-propanol (99% ee, Aldrich Chemical Co.), $[\alpha]^{25}_D$ +55.8° (*c* 1.3, $CHCl_3$).

(7) Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Keil, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438.

(8) The (*R*)-2-phenylpiperidine **8** was obtained in 50% yield after removal of the *tert*-butoxycarbonyl (BOC) protecting group. NMR analysis of the Mosher amides of **8** indicated a 24:1 *R*:*S* ratio.

(9) We found that this lactone is somewhat unstable. Upon exposure to acidic conditions it rearranges to the corresponding 5-*exo*-cyclized product.

resulting yellowish heterogeneous solution of **1** was stirred for 5 min, and *trans*-6,6-dimethyl-4-heptenoic acid (20 mg, 0.13 mmol) was added. After 15 min of stirring at −78 °C, *s*-collidine (50 μL, 0.38 mmol) was added to neutralize the trifluoromethanesulfonic acid. The reaction mixture was diluted with ether, washed with 1 M citric acid solution, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography on silica gel gave the selenolactones in 84% yield (38 mg). Major diastereoisomer: ^{1}H NMR (C_6D_6, 400 MHz) δ 7.60 (d, J = 7.6 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 5.39 (q, J = 6.3 Hz, 2H), 4.33 (m, 1H), 3.44 (d, J = 5.7 Hz, 1H), 3.42−3.33 (m, 4H), 1.82 (ddd, J = 17.5 Hz, 9.2 Hz, 3.8 Hz, 1H), 1.72−1.60 (m, 1H), 1.55 (d, J = 6.3 Hz, 6H), 1.53−1.44 (m, 2H), 1.17 (t, J = 7.0 Hz, 6H), 1.06 (s, 9H); HRMS calcd for $C_{23}H_{36}O_4Se$ 456.1757, found 456.1828; $[\alpha]^{25}_D$ +16.0 (*c* 1.1, CCl_4); IR (CCl_4) 1770 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_4Se$: C, 60.65; H, 7.97. Found: C, 60.31; H, 8.24.

Minor diastereoisomer (distinct signals): ^{1}H NMR (C_6D_6, 400 MHz) δ 7.66 (d, 2H), 5.56 (q, 2H), 3.60 (q, 1H), 0.79 (s, 9H).

General Procedure for the Reductions. 5-(*R*)-(2,2-Dimethylpropyl)-2(3*H*)-dihydrofuranone (7). A mixture of the above selenolactones (34 mg, 0.075 mmol), AIBN (3 mg), and triphenyltin hydride (52 mg, 0.15 mmol) was refluxed in toluene (1 mL) for 4 h. The reaction mixture was directly flash chromatographed (silica gel, eluent pentane, then ether/pentane 30:70) to give the 2-(*R*)-neopentylbutyrolactone **7** in 87% yield (10 mg): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61−4.57 (m, 1H), 2.50 (dd, J = 10.0, 6.7 Hz, 2H), 2.36−2.28 (m, 1H), 1.88−1.78 (m, 1H), 1.71 (dd, J = 14.8, 8.5 Hz, 1H), 1.49 (dd, J = 14.8, 3.5 Hz, 1H), 0.98 (s, 9H); $[\alpha]^{25}_D$ −32.7 (*c* 1, $CHCl_3$); HRMS calcd for $C_9H_{16}O_2$ 157.1229, found 157.1219; IR (neat) 1775 cm^{-1}.

Acknowledgment. We thank Dr. Neil Moss for assistance in the preparation of the manuscript and Serge Valois and Nancy Shore for HPLC and elementary analysis. We are grateful to Drs. Yvan Guindon and Paul Anderson for support and encouragement of this work.

Supporting Information Available: Characterization data for (entry 1, Table 2), (E 2, T 2), (E 3, T 2), (E 4, T 2), (E 5, T2), (E 6, T 2), (E 7, T 2) (E 2, T 3), (E 3, T 3), (E 4, T 3), (E 5, T 3), and **6**−**9** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950540S