Asymmetric cyclization of unsaturated alcohols and carboxylic acids with camphor-based selenium electrophiles

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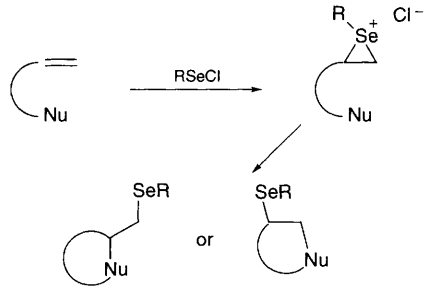
The diastereoselective cyclization of a series of unsaturated alcohols and carboxylic acids was achieved with chiral camphor-based selenenyl chlorides, of which the *spiro*-oxazolidinone 3c proved the most effective.

The additions of selenenyl chlorides (RSeCl) and related electrophiles to alkenes in the presence of external nucleophiles are known to afford the corresponding vicinally-functionalized selenides RSe–C–C–Nu.[1] Since these additions typically proceed *via* bridged seleniranium ions, *anti* addition is generally observed.[2] When the nucleophile is tethered to the alkene, the intramolecular version of this process affords cyclic products (Scheme 1).[3,4] Thus, unsaturated alcohols and carboxylic acids produce cyclic ethers and lactones, respectively. Since the process can be accompanied by the generation of new stereocentres, the opportunity exists for performing such reactions diastereoselectively by employing an electrophile R*SeX, where R* is a chiral auxiliary group. The subsequent oxidative or reductive removal of the selenium residue then permits the enantioselective preparation of selenium-free products. Several asymmetric cyclizations mediated by chiral selenium electrophiles have been reported recently,[5] generally employing aryl or organometallic auxiliaries. We recently developed a simple, one-step preparation of the camphor diselenide **1a** from (1*R*)-(+)-camphor and elemental selenium,[6] which can be conveniently performed on a 50–100 g scale. Moreover, both enantiomers of camphor are commercially available, and the ketone moiety provides the opportunity for further modification of the chiral auxiliary. We now report the results of a study of the selenenyl chlorides derived from **1a** and from the novel modified diselenides **1b** and **1c** in the stereoselective cyclizations of several alkenols and alkenecarboxylic acids.

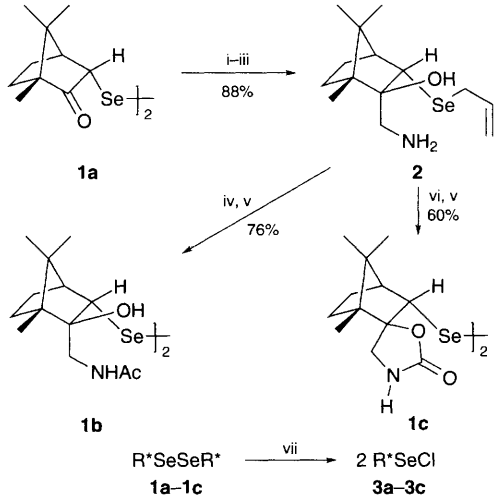
The preparation of the diselenides **1b** and **1c** is shown in Scheme 2. Since direct $LiAlH_4$ reduction of the cyanohydrin derivative of **1a** resulted in C–Se cleavage, the selenium moiety was first protected as an allyl selenide, affording **2**. The diselenides **1b** and **1c** were obtained from **2** by transformation of the amino alcohol moiety, followed by oxidation to the corresponding selenoxides and spontaneous [2,3]sigmatropic rearrangement to remove the protecting group and reductive workup with hydrazine to regenerate the diselenide linkage. The treatment of each diselenide in CH_2Cl_2 with sulfuryl chloride then produced the corresponding selenenyl chlorides **3a–3c** *in situ*.



Scheme 1

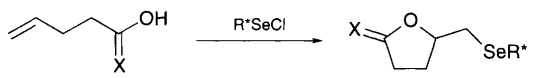
The cyclization of pent-4-en-1-ol and pent-4-enoic acid with each of **3a–3c** was effected at −78 °C in CH_2Cl_2 as shown in Table 1. Poor diastereoselectivity was observed with **3a**, which improved with **3b** and was highest with **3c**. Moreover, neither the use of diethyl ether, toluene or MeOH as solvent, nor the presence of triethylamine, provided any further improvement. Higher temperatures (0 °C) proved deleterious, while lower temperatures (−95 °C) gave comparable or slightly better stereoselectivities than those at −78 °C. We therefore chose **3c** in CH_2Cl_2 at −95 °C for further studies of cyclizations of other substrates.

The results are shown in Table 2. In general, monosubstituted and 1,2-disubstituted alkenes gave the best results, with 1,1-disubstituted (entry 5) and cyclohexenyl systems (entries 7 and 13) providing poor diastereoselectivity. In contrast to



Scheme 2 *Reagents*: i, $NaBH_4$, allyl iodide; ii, Me_3SiCN, ZnI_2; iii, $LiAlH_4$; iv, Ac_2O, pyridine; v, MCPBA, then NH_2NH_2; vi, *N*,*N*′-carbonylbis(imidazole); vii, SO_2Cl_2

Table 1 Cyclization of pent-4-en-1-ol and pent-4-en-1-oic acid[a]



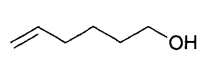
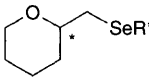
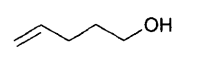
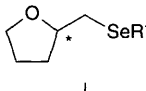
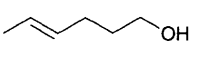
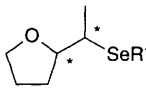
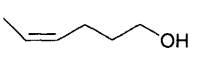
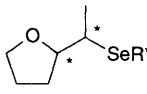
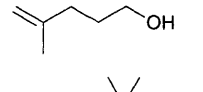
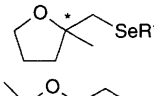
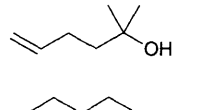
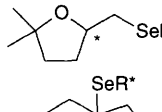
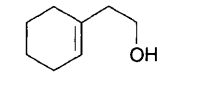
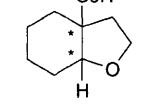
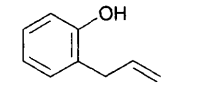
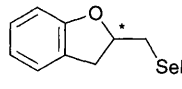
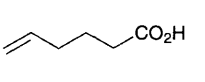
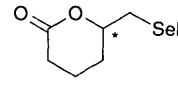
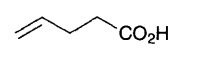
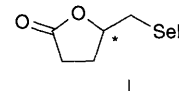
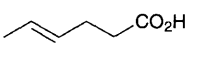
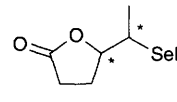
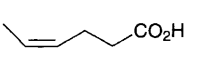
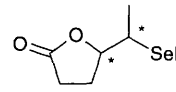
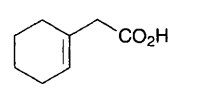
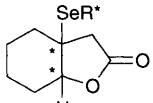
Entry	R*SeCl	X	Isolated yield (%)	Dr[b,c]
1	**3a**	H,H	57	58:42
2	**3a**	O	87	53:47
3	**3b**	H,H	66	71:29
4	**3b**	O	73	73:27
5	**3c**	H,H	89	90:10
6	**3c**	O	85	93:7

[a] All reactions were performed in CH_2Cl_2 at −78 °C. [b] Dr = diastereomeric ratio. [c] Measured by NMR integration.

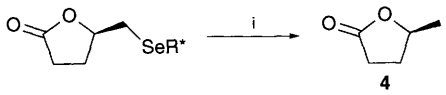
previous work reported with other chiral selenium electrophiles,[5b] *cis*-alkenes (entries 4 and 12) gave comparable stereoselectivity to their *trans* isomers (entries 3 and 11).

In a typical experiment (Table 2, entry 1), sulfuryl chloride (0.014 ml, 0.17 mmol) was added to a mixture of diselenide **1c** (99.5 mg, 0.17 mmol) and 4 Å molecular sieves (*ca.* 20 mg) in 5 ml of CH_2Cl_2, and stirring was continued for 15 min. The resulting orange mixture was cooled to −95 °C, and hex-5-en-1-ol (0.046 ml, 0.38 mmol) was added, which immediately discharged the orange colour. After 45 min at −95 °C, the mixture was warmed to room temperature, concentrated *in vacuo* and chromatographed over silica gel (elution with EtOAc) to afford 129 mg (96%) of the mixed diastereomers in the ratio of 87 : 13 (NMR integration). Longer reaction times were required for entries 7 (4 h at −95 °C) and 13 (8 h at −95 °C, followed by 12 h at room temperature) for complete consumption of the selenenyl chloride. In several instances, NMR analysis prior to chromatography indicated the initial presence of more complex mixtures, tentatively identified as containing both *exo* and *endo* cyclization products and uncyclized adducts of the selenenyl chloride to the alkene. These equilibrated during chromatography and/or upon standing for several days to provide the products shown in Table 2. In the case of entry 3, the initial products required stirring with a catalytic amount of toluene-*p*-sulfonic acid in order to achieve equilibrium. All diastereomer mixtures in Table 2 were consistent with their ^1H and ^{13}C NMR, IR and mass spectra, as well as exact mass measurements. The diastereomeric ratios were measured by NMR integration, except in the case of entry 7, where the individual diastereomers were separated by chromatography.

Table 2 Cyclizations of alkenols and alkenoic acids with **3c**[a]

Entry	Substrate	Product	Isolated yield (%)	Dr[b,c]
1			96	87 : 13
2			87	84 : 16
3			92	85 : 15
4			80	95 : 5
5			93	71 : 29
6			61	84 : 16
7			73	57 : 43
8			93	92 : 8
9			87	91 : 9
10			81	>95 : 5
11			80	89 : 11
12			78	91 : 9
13			66	67 : 33

[a] All reactions were performed in CH_2Cl_2 at −95 °C. [b] Dr = diastereomeric ratio. [c] Measured by NMR integration, except in entry 7 where the diastereomers were separated.



Scheme 3 *Reagents*: i, Bu_3SnH, AIBN, toluene, reflux

The nearly homogeneous lactone produced in entry 10 was subjected to deselenization with tributyltin hydride and azoisobutyronitrile (AIBN) to afford **4** (Scheme 3) with $[\alpha]_D$ −27.9, comparing favourably with the literature value[7] of $[\alpha]_D$ −29.6 for the *S*-enantiomer. This confirms its high optical purity and establishes its absolute stereochemistry. The absolute configurations of the other products in Table 2 have not yet been determined. We assume that the products containing two new chiral centres were formed by *anti* addition according to literature precedents.[2]

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Footnote

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