The Stereochemistry of a Substitution Reaction *via* an Episelenonium Ion: Retention by a 2-Pyridylseleno Group *versus* Scrambling by a Phenylseleno Group[1]

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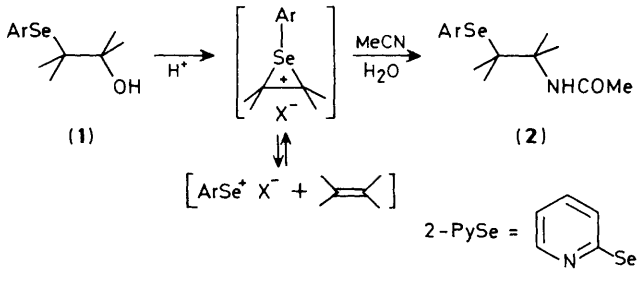
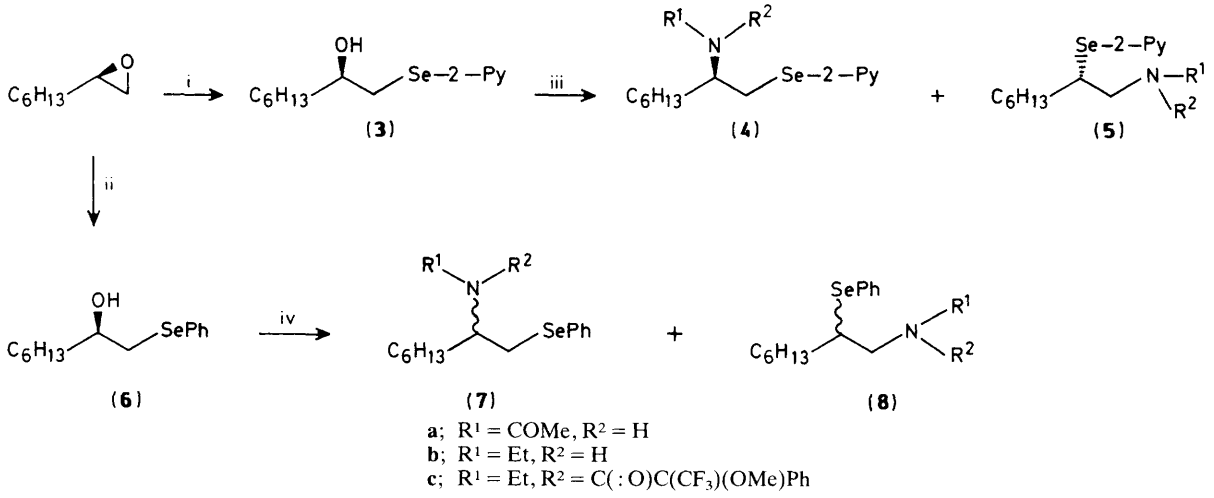
The first example of retention of configuration during substitution on a carbon atom situated β to an arylseleno group was discovered when using a 2-pyridylseleno (2-PySe) group.

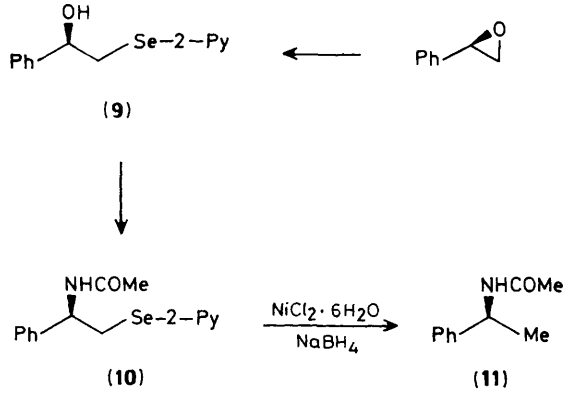
trans-Stereospecificity has been established during the electrophilic addition of an arylseleno group to alkenes, which proceeds through an episelenonium ion intermediate. A similar intermediate is expected during substitution on a carbon atom situated β to an arylseleno group. In fact, *erythro* → *erythro* and *threo* → *threo* stereospecificities have been reported during the conversion of β-hydroxyalkyl aryl selenides (**1**) to β-amidoalkyl aryl selenides (**2**)[1,2] (Scheme 1). However, it is not yet certain whether this reaction can be utilised in the preparation of optically active amine derivatives (**2**), as isomerisation of the episelenonium ion through the equilibrium shown in Scheme 1 has not been ruled out. By using a 2-pyridylseleno (2-PySe) group in this reaction we discovered for the first time that optical purity was not being lost. Another example of the usefulness of the 2-PySe moiety in organic synthesis is thus provided, since scrambling occurred to give a racemic amide when Ar = Ph.



Scheme 1. Ar = Ph or 2-Py.



Scheme 2. *Reagents and conditions:* i, 2-PySeNa, EtOH; ii, PhSeNa, EtOH; iii, MeCN, CF_3SO_3H–H_2O (1:1; 10 equiv.); iv, MeCN, CF_3SO_3H–H_2O (1:1; 1 equiv.).



Scheme 3

The reaction of (*R*)-1,2-epoxyoctane (enantiomeric excess, e.e., 92%) with sodium areneselenolate afforded the alcohols (**3**) and (**6**) (e.e. 93%)† in almost quantitative yields (Scheme 2).‡ The regioisomers of (**3**) and (**6**) were not detected in the product. When Ar = 2-Py, substitution of the hydroxy group by the nitrogen atom of a nitrile group required 10 equiv. of acid at reflux temperature to afford the β-amido selenide as a mixture of regioisomers [(**4a**) and (**5a**), 96%, 92:8].§ To determine the optical purity, either (**4a**) or (**5a**) was reduced by aluminium hydride to give (**4b**) or (**5b**) which was then converted to the amide (**4c**) or (**5c**) by reaction with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*R*)-MTPA-Cl].[3] The ratios of diastereoisomers were determined by the intensities of the methyl signals (N-CH_2CH_3)¶ in their 200 MHz ^{1}H n.m.r. spectra [(**4c**), diastereoisomeric excess (d.e.) 92%; (**5c**), d.e. 94%]. These results clearly show that optical purity at C-2 was not lost in the *ipso*-substitution product (**4a**) or in the migration product (**5a**), indicating that an episelenonium ion intermediate does not isomerise or 'racemise' during the reaction. In the case of Ar = Ph, substitution proceeded under much milder conditions (1 equiv. of acid, room temp., 5 h) to afford (**7a**) and (**8a**) (100%, 85:15). Similar procedures to those above revealed that both (**7a**) and (**8a**) consisted of racemic mixtures. We attempted the reaction of (**6**) with 1 equiv. of acid in dimethoxymethane as solvent (room temp., 5 h) and found that the β-hydroxy selenide was recovered as a racemic mixture, presumably *via* the trapping of the 'racemic' episelenonium ion by hydroxide. The reason why the episelenonium ion 'racemises' when Ar = Ph, but does not when Ar = 2-Py is not yet clear.

In order to confirm the retention of configuration during the conversion of (**3**) to (**4a**) [equal to the inversion in going from (**3**) to (**5a**)], we prepared β-amido selenide (**10**) (e.e. 80%) from (*R*)-styrene oxide *via* (*R*)-β-hydroxy selenide (**9**). Replacement of the 2-pyridylseleno group of (**10**) by a hydrogen atom (Scheme 3)[4] gave (**11**) ($[\alpha]_D^{26.8}$ −79.6 ± 0.3°, EtOH, *c* = 0.32) compared to the amide prepared from the commercially available (*S*)-methylbenzylamine ($[\alpha]_D^{30.4}$ −150.9 ± 0.3°, EtOH, *c* = 1.45). Although the reason for this partial loss of optical purity is not yet clear, we may conclude that the absolute configurattion of the major enantiomer of (**11**) is (*S*), and that of (**10**) is (*R*). These results clearly show that the conversion of (**9**) to (**10**) proceeded with retention of configuration. The application of this reaction to the synthesis of optically active amide derivatives is currently in progress.

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† Determined from intensities of methoxy signals (δ 3.54 and 3.59) in the 200 MHz ^{1}H n.m.r. spectrum of the (*S*)-MTPA ester.

‡ All new compounds gave satisfactory spectral and analytical data.

§ The amides (**4a**) and (**5a**) were easily separated by column chromatography [silica gel, hexane–ethyl acetate (2:1) as eluant].

¶ Chemical shifts of the methyl protons in both diastereoisomers were δ 0.39 and 0.52, 7.1 Hz.

References

1 For Part 5 of the series '2-Pyridylseleno Group in Organic Synthesis,' see A. Toshimitsu, G. Hayashi, K. Terao, and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2113.
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