Enantiomerically pure P-chiral phosphinoselenoic chlorides: inversion of configuration at the P-chirogenic center in the synthesis and reaction of these substances†

Tsutomu Kimura and Toshiaki Murai*

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Reaction of diastereomerically pure phosphinoselenoic acid salts with oxalyl chloride leads to enantiomerically pure P-chiral phosphinoselenoic chlorides with inversion of configuration at phosphorus; one of these chlorides is converted to a phosphinoselenothioic acid salt with a high degree of enantioselectivity.

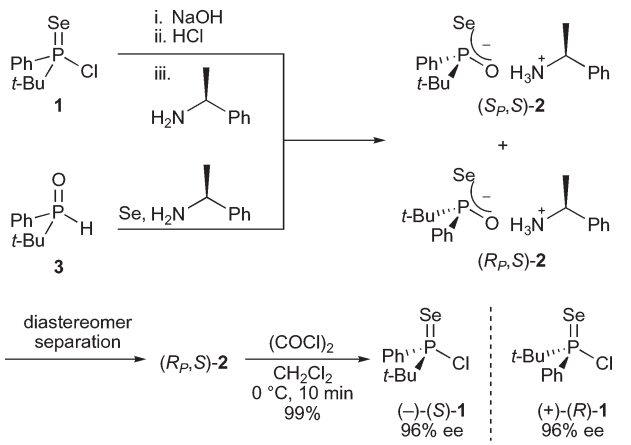
Knowledge of the stereochemical course of reactions at P-chirogenic centers is important because of the wide applicability of optically active P-chiral organophosphorus compounds in synthetic-organic and biochemical studies.[1] A number of optically active organophosphorus halides of high enantiomeric purity have been used previously as intermediates in synthetic routes to P-chiral organophosphorus compounds. However, P-chiral chlorophosphines racemize over a *ca.* 20 h period,[2] and their reactions are often accompanied by racemization of their P-chirogenic centers.[3] Chlorophosphine boranes[4] and organophosphorus halides containing pentavalent phosphorus atoms, such as phosphinoic halides[5] and phosphinothioic halides,[6] have been prepared and the stereochemistry of substitution reactions at their P-chirogenic centers evaluated. The stereochemical outcome of these processes has been found to depend on the type of nucleophile used and the nature of substituents attached to the phosphorus atom.

Recently, we reported a highly efficient synthetic method for preparation of racemic P-chiral phosphinoselenoic chlorides.[7] We observed that these substances tolerate chromatographic purification on silica gel and that, unlike phosphinoic chlorides, they do not decompose in the presence of neutral water. We also demonstrated the utility of phosphinoselenoic chlorides as precursors to selenium-containing, organophosphorus compounds.[8] The current investigation grew out of a postulation that optically active P-chiral phosphinoselenoic chlorides would serve as key intermediates in sequences leading to the preparation of various optically active, P-chiral organophosphorus compounds. Herein, we report the first synthesis of enantiomerically pure P-chiral phosphinoselenoic chlorides and the reaction of one of these substances with a sulfur nucleophile that takes place with inversion of configuration at the P-chirogenic center.

In the first step of the initial route we developed for the synthesis of enantiomerically pure P-chiral phosphinoselenoic chlorides, racemic phosphinoselenic chloride, **1**, is converted to the corresponding phosphinoselenoic acid sodium salt by reaction with NaOH (Scheme 1).[9] Acidolysis of this sodium salt with HCl gives a phosphinoselenoic acid, which is then subjected to an acid–base reaction with (*S*)-1-phenylethylamine to yield a mixture of the diastereomeric phosphinoselenoic acid phenylethylammonium salts, **2**. An alternative method for the one-pot synthesis of phosphinoselenoic acid ammonium salts, **2**, involves reaction of the racemic secondary phosphine oxide, **3**, with elemental selenium and (*S*)-1-phenylethylamine. The (R_P,*S*) diastereomer of **2** is less soluble in Et_2O and, as a result, can be readily separated. Attempts to chlorinate (R_P,*S*)-**2**, by reaction with PCl_3, PCl_5, $SOCl_2$ or HCl, failed. However, treatment of the ammonium salt with oxalyl chloride leads to the generation in high yield of the optically active P-chiral phosphinoselenoic chloride (−)-**1**; $[\alpha]_D^{20}$ −25 (*c* 1.0, $CHCl_3$, where *c* represents concentration in grams per 100 ml). The antipodal phosphinoselenoic chloride, (+)-**1**, was obtained by reaction of the diastereomeric salt (S_P,*R*)-**2** with oxalyl chloride.

In their CD spectra, (+)-(*R*)-**1** and (−)-(*S*)-**1** show negative and positive Cotton effects at 224 nm respectively (Fig. 1).

The optical purities of the chlorides (+)-**1** and (−)-**1** were determined by HPLC analysis using a Chiralcel OD column. This analysis showed that the chlorides were formed in 96% ee. The absolute configuration at the P-chiral center in chloride (−)-**1** was assigned as *S* by using X-ray crystallographic analysis and anomalous dispersion methods (Fig. 2).‡ The results show that the reaction of (R_P,*S*)-**2** with oxalyl chloride proceeds with inversion of configuration at phosphorus.§ The enantiomerically pure P-chiral phosphinoselenoic chlorides show a high degree of



Scheme 1 Synthesis of optically active P-chiral phosphinoselenoic chlorides (−)-(*S*)-**1** and (+)-(*R*)-**1**.

Department of Chemistry, Faculty of Engineering, Gifu University, Yanagido, Gifu, 501-1193, Japan. E-mail: mtoshi@cc.gifu-u.ac.jp
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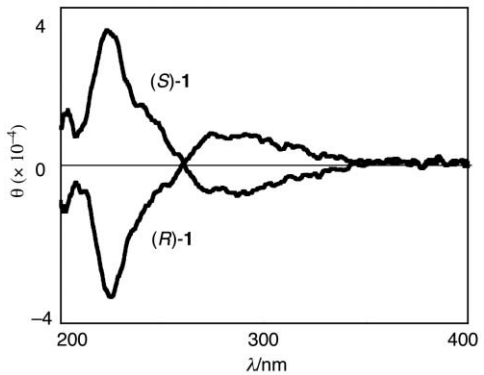


Fig. 1 CD spectra of optically active P-chiral phosphinoselenoic chlorides (−)-(*S*)-**1** and (+)-(*R*)-**1** in hexane.

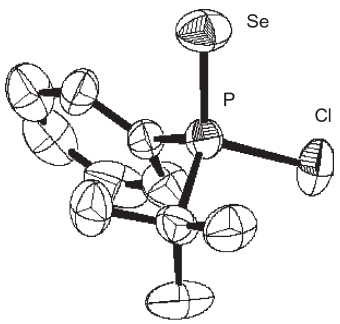
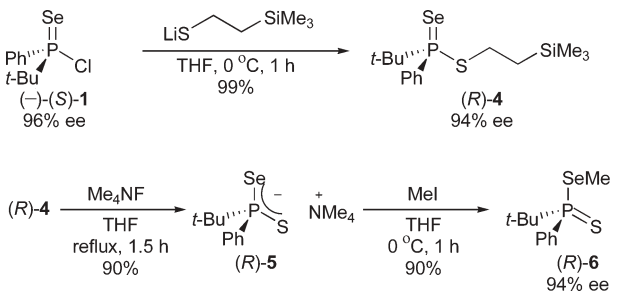


Fig. 2 ORTEP drawing of optically active P-chiral phosphinoselenoic chloride (−)-(*S*)-**1** with thermal ellipsoid plots of 50% probability. Hydrogen atoms are omitted for clarity. Two independent molecules were present in the asymmetric unit, only one of which is shown.

configurational stability; no racemization taking place during the purification of these substances by column chromatography on silica gel or when the chlorides are placed in refluxing toluene or THF. However, the enantiomeric purity of the chlorides gradually decreases when treated with a large excess of HCl.¶

The stereocontrolled conversion of enantiomerically pure P-chiral phosphinoselenoic chloride (*S*)-**1** to phosphinoselenothioic acid salt **5**,[8a,d] *via* phosphinoselenothioic acid *S*-[2-(trimethylsilyl)-ethyl] ester **4**, was examined (Scheme 2). In sharp contrast to the reaction of phosphinothioic chlorides with sulfur nucleophiles,[6a] reaction of (*S*)-**1** with lithium 2-(trimethylsilyl)ethanethiolate occurs over a 1 h period to form the corresponding phosphinoselenothioic acid *S*-ester, **4**. No significant loss of ee (96%) was observed in this process. Ester **4** reacts with Me_4NF to give phosphinoselenothioic acid tetramethylammonium salt **5** ($[\alpha]_D^{20}$ + 18) in 90% yield. Methylation of **5** with methyl iodide gives the phosphinoselenothioic acid *Se*-ester **6** in 90% yield and 94% ee. The absolute configuration at the P-chiral center in phosphinoselenothioic acid salt **5** was assigned as *R* by its transformation to the known triethylammonium salt.[11] Therefore, the reaction of the chloride (*S*)-**1** with the lithium thiolate proceeds with inversion of phosphorus configuration.



Scheme 2 Synthesis of optically active P-chiral phosphinoselenothioic acid salt (*R*)-**5**.

In summary, we have successfully synthesized and characterized enantiomerically pure P-chiral phosphinoselenoic chlorides by using the substitution reactions of phosphinoselenoic phenylethylammonium salts with oxalyl chloride. These processes, as well as the reaction of one of the chlorides with lithium thiolate, proceed with inversion of phosphorus configuration. Also, an enantiomerically pure P-chiral phosphinoselenothioic acid salt was prepared by reacting the selenothioic acid *S*-ester, formed in this nucleophilic substitution reaction, with Me_4NF. Further studies on the applications of this chemistry (*e.g.* the preparation of optically active ligands) are in progress.

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Notes and references

‡ Crystal data for (*S*)-**1**: $C_{10}H_{14}ClPSe$, M = 279.61, monoclinic, $P2_1$ (no. 4), a = 12.24(1), b = 7.629(8), c = 13.58(1) Å, β = 103.77(2)°, V = 1232(2) Å^3, D_c = 1.507 g cm^{-3}, Z = 4, T = 296 K, Mo-Kα (λ = 0.71070 Å), μ = 33.51 cm^{-1}, 9954 collected reflections, 3023 unique reflections (R_{int} = 0.049), $R1$ = 0.080 and $wR2$ = 0.203 ($I > 2.0\ \sigma\ (I)$). CCDC 274086. See http://dx.doi.org/10.1039/b507755a for crystallographic data in CIF or other electronic format.

§ The absolute configuration of the phosphinoselenoic acid salt (R_P,*S*)-**2** was determined on the basis of optical rotation measurements of the corresponding phosphinoselenoic acid. See ref. 10.

¶ The enantiomeric excess of the chloride (−)-(*S*)-**1** decreased in an exponential manner: ee = 96.0 × e$^{-0.0971t}$, where t represents reaction time in hours, (R^2 = 0.992). The rate constant, k, for the racemization was estimated to be 1.3 × 10^{-5} s^{-1}. The free energy of activation, $\Delta G^{\ddagger}$, for the racemization was calculated to be 6.5 kcal mol^{-1}.

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