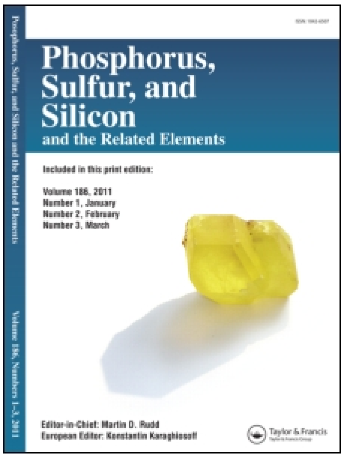

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Phosphoroselenoic Acid Derivatives Bearing a Binaphthyl Group as a Chiral Molecular Tool

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Phosphoroselenoic Acid Derivatives Bearing a Binaphthyl Group as a Chiral Molecular Tool

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New synthetic methods for phosphoroselenoic acid derivatives bearing 1,1′-bi-2-naphthyl group and their use as new chiral molecular tools have been described. Phosphoroselenoyl chloride is prepared in high yields from PCl_3, elemental selenium, and 1,1′-bi-2-naphthol. The conversion of the chloride to esters and amides are readily achieved by reacting with the corresponding alcohols and amines as electrophiles. The esters are obtained as a diastereomeric mixture in a ratio of almost 1:1. In ^{31}P and ^{77}Se NMR spectra, the diastereomers are discriminated even when two similar types of substituents are attached to the chiral carbon atom of the alcohols. The treatment of the amides with PBu_3 leads to phosphoramidites. The addition of H_2O to the chloride in the presence of Et_3N gives the phosphoroselenoic acid salt with high efficiency.

Keywords Amides; chiral molecular tools; esters; phosphoroselenoyl chlorides

INTRODUCTION

It is of great interest to develop new organoselenium compounds with applicability to a wide variety of fields of molecular engineering. During the course of our studies on P=Se bond-containing organoselenium compounds,[1] phosphoroselenoic acid derivatives bearing a binaphthyl group 1 (abbreviated as BISEP*) have been found to be available as a new chiral molecular tool.[2]

Initially, phosphoroselenoyl chloride **1a** was prepared from PCl_3, elemental selenium, and 1,1′-bi-2-naphthol in high yield (Scheme 1).[2a]

The formation of **1a** was confirmed by X-ray molecular structure analysis (Figure 1). Very recently, a wide range of syntheses of binaphthol bearing substituents at various positions have been developed.

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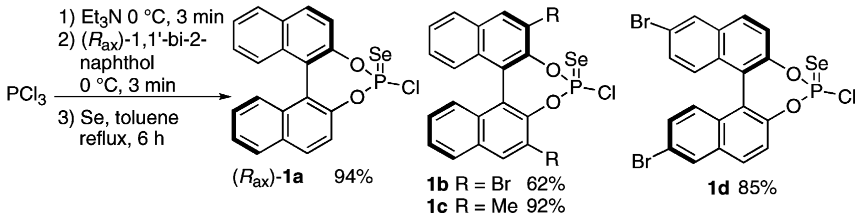
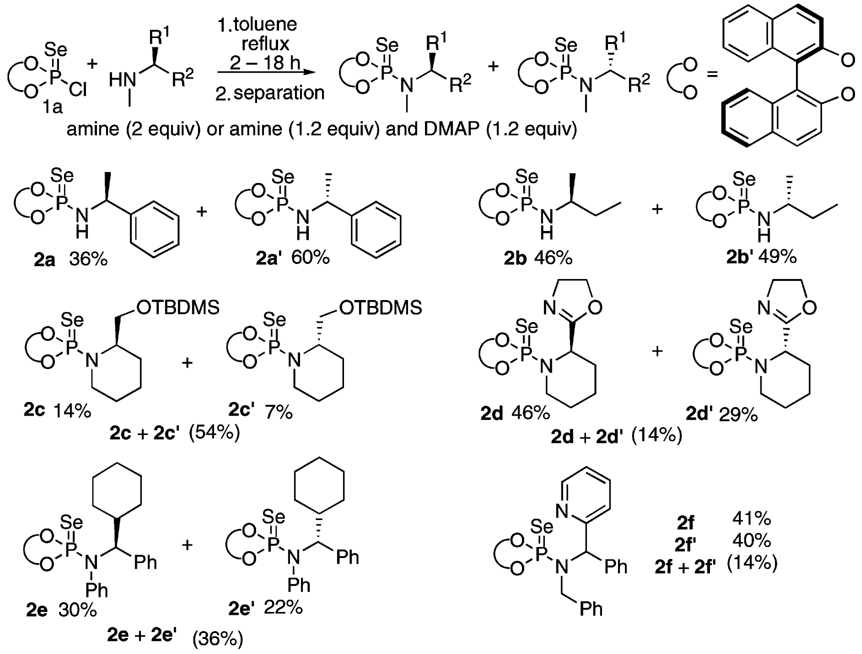


SCHEME 1

Among them, 3,3′- and 6,6′-substituted derivatives were subjected to the reaction in scheme 1 to give **1b–1d** in good yields. All the chlorides **1** obtained are stable under air and are purified by column chromatography on silica gel. The chloride 1a was inert toward water even at high temperatures unlike phosphoryl chlorides bearing 1,1′-bi-2-naphthyl group.[3]

Then, the reactivity of the chlorides **1** was tested. The chlorides **1** showed high stability under the neutral conditions, but show high reactivity toward amines (Scheme 2).[2b]



SCHEME 2

The reaction of **1a** with primary and cyclic secondary amines went to completion within 3 h to give phosphoroselenoic amides **2a–2d**, whereas

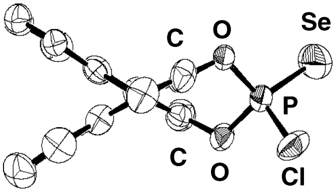
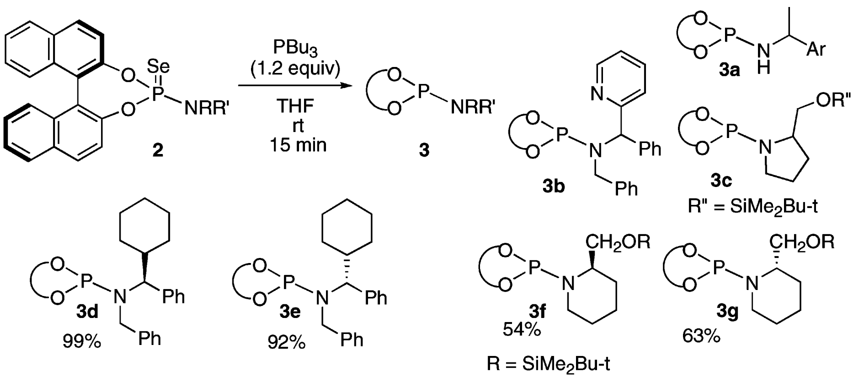


FIGURE 1 ORTEP drawing of **1a**.

the reaction with acyclic secondary amines required more than 12 h to give **2e** and **2f** probably because of the steric congestion around the nucleophilic nitrogen atom. In all cases, the substitution reaction at the phosphorus atom took place to give phosphoroselenoic amides **2** as two diastereomers in different ratios, but most of them were separated by simple recrystallization, by column chromatography on silica gel, or by HPLC. Crystallization of amides **2** obtained occurs readily, and this enabled us to determine the absolute configuration of chiral centers in amino moieties by X-ray structure analyses.[2b] Since the first synthesis of phosphoramidites by Ferringa and coworkers in 1994,[4] a range of derivatives **3** have been prepared and applied as optically active ligands. The syntheses of phosphoramidites are generally achieved by using trivalent phosphates, e.g., amine exchange reaction of *N*,*N*-dimethyl phosphoramidite[5] and amination of chlorophosphite bearing binaphthyl group.[6] In contrast, no routes via the reduction of pentavalent phosphorus compounds are known. Then, extrusion reaction of selenium atom from our amides **2** was tested to lead to phosphoramidites **3** (Scheme 3).

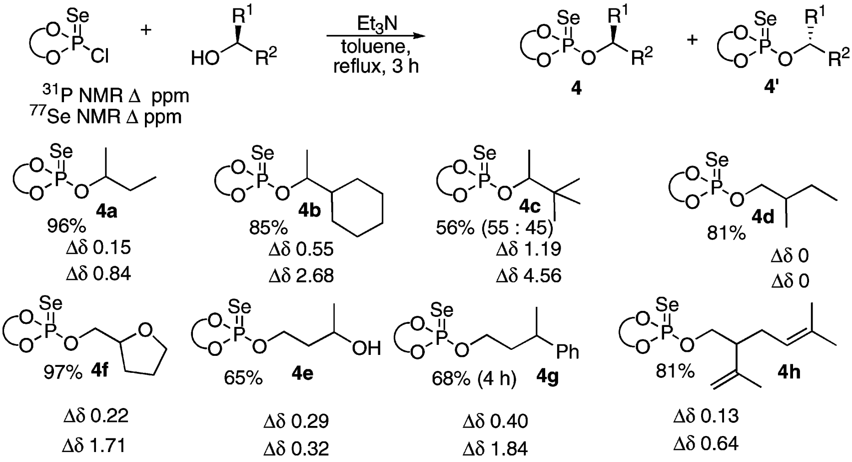
The extrusion reaction of the selenium atom in **2** proceeded successfully with the use of nucleophilic trivalent phosphorus compounds such as PBu_3 to give the desired phosphoramides **3** within 15 min along with



SCHEME 3

the formation of $Bu_3P{=}Se$. However, the stability of phosphoramidites **3** is highly dependent of the substitution on the alkyl groups attached to the nitrogen atom. Amidites **3** derived from primary amines such as **3a** were hard to be handled under the air to result in the formation of the complex mixture. Amidites **3b** and **3c** were also highly sensitive toward air, whereas **3d–3g** could be purified by column chromatography on silica gel.

Then, the reactivity of chloride **1a** toward alcohols was tested. The substitution reaction of **1a** with primary and secondary alcohols in the presence of Et_3N took place selectively at the phosphorus atom and was complete within 3 h to give phosphoroselenoic acid *O*-esters **4** in good to high yields, whereas the reaction with tertiary alcohols did not proceed to result in the recovery of the starting materials (Scheme 4).

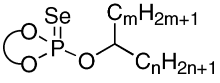
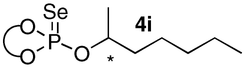
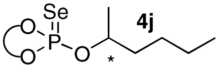
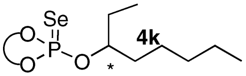
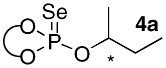
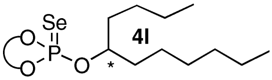
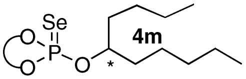
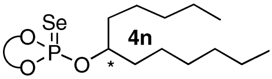


SCHEME 4

Two diastereomers of **4a**, **4b**, and **4d–4f** were obtained in equal ratios, and kinetic resolutions of enantiomers did not occur during the reaction. In ^{31}P NMR spectra, two diastereomers of **4a–4c** and **4e–4h** are discriminated, and ^{77}Se NMR spectra show larger chemical shift differences.

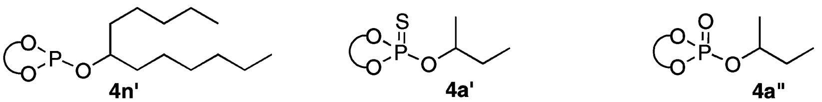
Further evaluation of the ability of our system to discriminate enantiomers was carried with esters derived from simple racemic alcohols. The differences of the chemical shifts of two diastereomers are listed in Table 1. The ratio of the lengths of the alkyl chains attached to chiral carbon centers are also shown as n/m. Generally, as the ratio n/m becomes small, the differences of chemical shifts become small. Nevertheless, two diastereomers of **4n** where n-pentyl and n-hexyl groups are attached to the chiral carbon center were discriminated by ^{31}P

TABLE I Relative Differences of Chemical Shifts of Diastereomers in ^{31}P and ^{77}se NMR Spctra

entry		n/m	^{31}P NMR $\Delta\delta$ ppm	^{71}Se NMR $\Delta\delta$ ppm
1	 **4i**	5	0.22	2.32
2	 **4j**	4	0.15	1.44
3	 **4k**	2.5	0.09	1.32
4	 **4a**	2	0.15	0.84
5	 **4l**	1.5	0.15	1.48
6	 **4m**	1.25	1.14	1.36
7	 **4n**	1.2	0.02	1.10

and ^{77}Se NMR spectra, although the peak separation begins to be incomplete.

The ability to discriminate diastereomers by NMR is compared with those of phosphite derivatives with a binaphthyl group (Scheme 5).



4n' ^{31}P NMR Δ 0.00 ppm

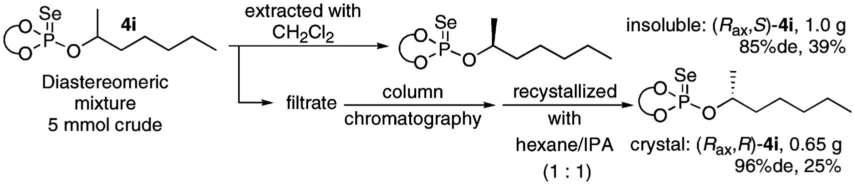
4a' ^{31}P NMR Δ 0.13 ppm

4a" ^{31}P NMR Δ 0.08 ppm

SCHEME 5

In the case of phosphite **4n**′, two diastereomers were observed as one signal in ^{31}P NMR spectra unlike the case of **4n**. Sulfur and oxygen isologues of **4a** were synthesized, and their ^{31}P NMR spectra were checked, also. Better peak separation was not observed for **4a**′ and **4a**″, when compared with those of **4a**. Therefore, our system involving a binaphthyl group and P=Se bond is more powerful to discriminate racemic alcohols.

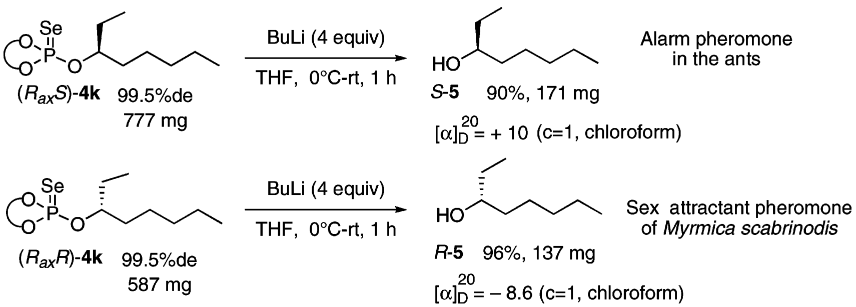
The separation of diastereomers of esters **4** was achieved by several methods. For example, crude ester **4i** derived from 2-heptanol was extracted with CH_2Cl_2, and the insoluble parts collected involved exclusively (*R*$_{\text{ax}}$,*S*)-**4i** (Scheme 6).



SCHEME 6

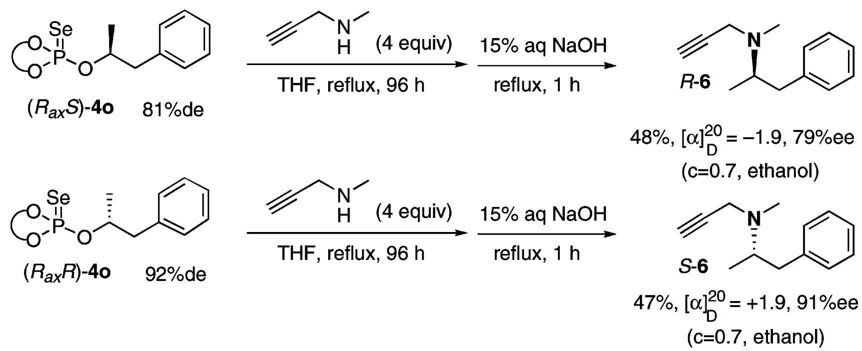
The filtrate was concentrated and purified by column chromatography followed by recrystallization to give exclusively (R_{ax},*R*)-**4i**.

To prove the usefulness of the synthetic routes to optical pure alcohols via the esters **4**, one of biologically important alcohols, i.e. 3-octanol,[7] was isolated (Scheme 7).



SCHEME 7

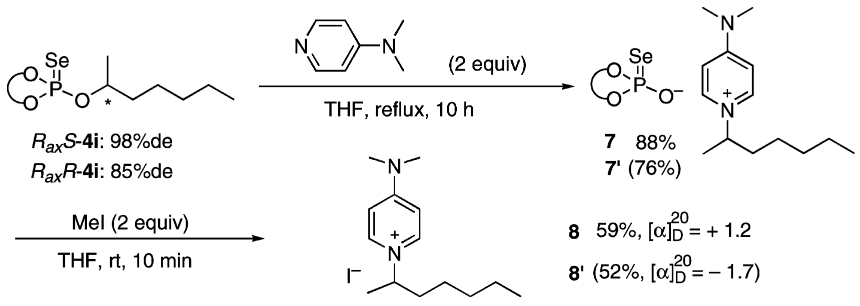
To lead to these alcohols, the diastereomerically pure esters **4k** were initially obtained by recrystallization and further purification with HPLC. To recover the alcohols **5**, attempts to hydrolyze **4k** were carried out under acidic and basic conditions. No reactions took place under mild hydrolytic conditions, and the reaction under harsh conditions gave complex mixtures. After several disappointing results, the reaction of the esters **4k** with excess butyllithium (BuLi) took place selectively at the phosphorus atom to give optically active alcohols **5** with high enantiomeric excess. The diastereomeric excess of the staring esters **4k** was retained in the enantiomeric excess of the products **5**. The absolute configuration of the alcohol moiety of **4k** was also reflected in **5**. These results have suggested the direct substitution reaction of **4k** with BuLi proceeds at the phosphorus atom.



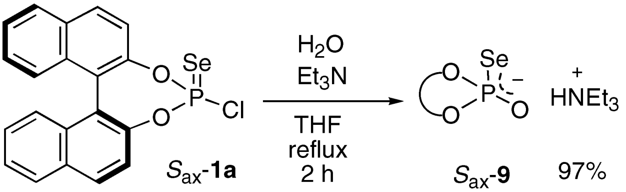
SCHEME 8

During further elucidation of the reactivity of esters **4**, the reaction with amines was found to proceed at the chiral carbon center, unlike the reaction with BuLi. For example, (R_{ax},S)-**4o** was treated with *N*-methyl propargylamine under reflux in THF, followed by the alkaline hydrolysis to give selegiline *R*-**6**, which has been known as monoamine oxygenase inhibitor (Scheme 8).[8] In contrast, the use of (R_{ax},R)-**4o** gave amine *S*-**6**. The enantiomeric excess of both products is in accordance with the diastereomeric excess of the starting esters **4o**. The absolute configuration of **6** was opposite to that of the chiral center of alkoxy moiety of **4o**. Therefore, the substitution reaction of **4o** with amines proceeds with inversion of configuration at the chiral carbon center.

The ester **4** was also reacted with tertiary amine such as 4-methyldimethylaminopyridine. A similar substitution reaction of **4i** took place at the chiral carbon center to give the phosphoroselenoic acid pyridinium salts **7** in high yields (Scheme 9). Then, methylation of the salts **7** gave pyridinium iodide **8** as a product. The ammonium salts derived from the different diastereomers showed the specific rotations



SCHEME 9



SCHEME 10

with opposite signs, which is indicative of the formation of enantiomers **8** and **8**′ in each reaction.

Finally, phosphoroselenoic acid salt **9** was prepared. The chloride **1a** was inert toward water under neutral conditions, but the reaction of S_{ax}-**1a** with water in the presence of triethylamine proceeded smoothly to give the corresponding salt S_{ax}-**9** as a stable compound (Scheme 10).

In summary, a series of phosphoroselenoic acid derivatives bearing a binaphthyl group (BISEP*) were synthesized by using the chlorides (BISEPCl) as key starting compounds and were used as chiral molecular tools. They were applied to discriminate simple alcohols, and to provide less accessible alcohols and amines. Finally, phosphoroselenoic acid salts were isolated as stable compounds.

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