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Assignment of the Absolute Configurations of 1-Aryl-2-propanols with the Use of Phosphoroselenoyl Chlorides as Chiral Derivatizing Agents

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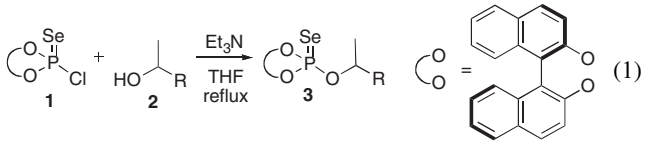
Phosphoroselenoyl chloride bearing a 1,1′-bi-2-naphthyl group was reacted with racemic 2-alkanols to give the corresponding esters. Based on the multiple combination of their NMR spectra, a method for the assignment of the absolute configuration of 1-aryl-2-propanols was established. The solid-state conformations of the esters were confirmed by X-ray structure analyses.

Determination of the absolute configurations of chiral secondary alcohols by NMR spectroscopy is one of the most important issues in chemistry.[1] This method stems from Mosher and co-workers' development of MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) as a chiral derivatizing agent (CDA).[2] Chiral alcohols are converted to acid esters by reacting with CDA. The original Mosher's method used ^{1}H and ^{19}F NMR spectra of these esters. Later, Kusumi and co-workers developed the modified Mosher's method, in which the general trends of the chemical shifts in the ^{1}H NMR spectra are analyzed as much as possible, and the absolute configurations of chiral alcohols are then estimated.[3] Several applications of MTPA esters for assigning absolute configurations have been reported.[4] Additionally, as CDA, other carboxylic acids with a chiral center at the position α to the carboxyl groups have also been developed.[5–9] ^{31}P and ^{77}Se NMR spectra are also available as probes to determine the absolute configuration, but they have been used only for chiral discrimination.[1c] To enhance the reliability of the determination of absolute configurations, the development of CDA other than those with carboxylic acid structures is also desirable.

Very recently, we found that phosphoroselenoyl chlorides (BISEPCl) **1** can be readily prepared from PCl_3, optically active 1,1′-bi-2-naphthol, and elemental selenium, and **1** react with secondary alcohols to give phosphoric acid esters as a diastereomeric mixture in a nearly equal ratio.[10] Therefore, these esters can be used as a tool to determine the enantiomeric purity of chiral secondary alcohols with ^{31}P and ^{77}Se NMR spectra. The NMR data of the esters have been evaluated further. We report here the use of **1** as a CDA and its application to the determination of the absolute configurations of 1-aryl-2-propanols.

Initially, a variety of 2-alkanols **2** were derivatized with (R_{ax})-phosphoroselenoyl chloride **1** in the presence of Et_3N in THF (eq 1).



(1)

The reaction went to completion within 3 h, and the corresponding esters **3** were obtained as diastereomeric mixtures. The yields of the esters **3** are shown in Table 1 along with their ^{1}H, ^{13}C, ^{31}P, and ^{77}Se NMR spectra.

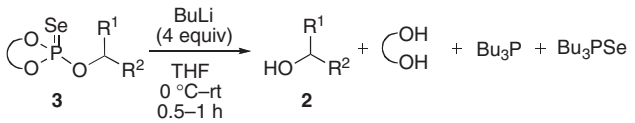
Table 1. Synthesis of esters **3**[a] and their NMR spectra[b]

Entry	Ester **3** Yield/%[c]		^{1}H[d] NMR	^{13}C[e] NMR	^{31}P NMR	^{77}Se NMR
1	**3a** 82% (49:51)	R_{ax},S	1.34	82.01	78.16	–326.29
		R_{ax},R	1.52	81.77	78.03	–325.49
2	**3b** 82% (48:52)	R_{ax},S	1.32	80.80	78.19	–326.93
		R_{ax},R	1.51	80.56	78.12	–326.63
3	**3c** 86% (49:51)	R_{ax},S	1.27	81.03	78.12	–326.57
		R_{ax},R	1.52	80.72	77.99	–324.85
4	**3d** 64% (49:51)	R_{ax},S	1.34	81.08	78.10	–326.78
		R_{ax},R	1.52	80.75	77.88	–324.45
5	**3e** 91% (50:50)	R_{ax},S	1.34	80.36	78.01	–324.53
		R_{ax},R	1.56	79.96	77.83	–322.65
6	**3f** 85% (47:53)	R_{ax},S	1.27	84.84	79.01	–327.77
		R_{ax},R	1.51	84.54	78.49	–325.17
7	**3g** 56% (38:62)	R_{ax},S	1.27	88.25	79.62	–331.09
		R_{ax},R	1.52	87.68	78.48	–326.53
8	**3h** 94% (49:51)	R_{ax},S	1.35	80.63	77.75	–325.97
		R_{ax},R	1.45	80.26	77.21	–321.73
9	**3i** 67% (48:52)	R_{ax},S	1.36	80.49	77.70	–324.13
		R_{ax},R	1.47	80.39	77.50	–323.25
10	**3j** 92% (48:52)	R_{ax},S	1.33	80.80	77.72	–325.25
		R_{ax},R	1.43	80.39	77.21	–321.57
11	**3k** 86% (49:51)	R_{ax},S	1.34	80.10	77.61	–324.13
		R_{ax},R	1.46	79.54	77.15	–320.73
12	**3l** 87% (50:50)	R_{ax},S	1.38	79.83	77.83	–325.49
		R_{ax},R	1.50	79.41	77.35	–322.25

[a]The chloride **1** was reacted with **2** in the presence of Et_3N in THF for 3 h. [b]Measured by using $CDCl_3$ as a solvent. [c]The ratio of diastereomers (R_{ax},S:R_{ax},R) is shown in parentheses. [d]The signals due to methyl protons are shown. [e]The signals due to chiral carbon atoms are shown.

The absolute configurations of esters **3a**–**3e** and **3h** were determined by comparing the NMR data of the corresponding esters prepared from optically active alcohols **2**. Diastereomeric mixtures of **3f**, **3g**, and **3i**–**3l** were separated by recrystallization and/or recycle high-performance liquid chromatography to give

Table 2. Cleavage of phosphoroselenoic acid esters **3**[a]



3 **2**

Entry	Ester **3**	Alcohol **2** Yield[b]	$[\alpha]_D^{25}$
1	**3f** (85%de)	*R*-**2f** 40%	–2.47 (*c* 0.41, CCl_4)[11]
2	**3g** (76%de)	*R*-**2g** 40%	–1.62 (*c* 0.14, $CHCl_3$)[12]
3	**3i** (73%de)	*S*-**2i** 70%	+15.6 (*c* 0.28, $CHCl_3$)[13]
4	**3j** (82%de)	*S*-**2j** 62%	+18.9 (*c* 0.52, $CHCl_3$)[14]
5	**3k** (66%de)	*R*-**2k** 72%	–17.5 (*c* 0.63, $CHCl_3$)[14]
6	**3l** (82%de)	*S*-**2l** 33%	+16.8 (*c* 0.33, EtOH)[15]

[a]Esters **3** were treated with BuLi in THF. [b]Isolated yield.

the esters **3** in a different diastereomeric ratio. Esters **3** separated were then cleaved with excess BuLi to give optically active 2-alkanols **2f**, **2g**, and **2i**–**2l** along with Bu_3P, Bu_3PSe, and 1,1′-bi-2-naphthol (Table 2).

These mixtures were initially purified by column chromatography on silica gel to give the desired alcohols contaminated with a small amount of 1,1′-bi-2-naphthol. They were further purified by bulb-to-bulb distillation. Based on a comparison of the specific optical rotations of these alcohols with those in the literature, the absolute configurations of the alcohols, and eventually those of esters **3**, were determined. For the ^{1}H NMR spectra in Table 1, the signals due to methyl protons adjacent to the carbon atom bearing an oxygen atom are listed. For ^{13}C NMR spectra, the signals due to the carbon atom bearing an oxygen atom are listed. In all cases, the signals observed in relatively higher fields are shown in blue. In ^{1}H NMR spectra, the signals of R_{ax},*S*-isomers are at higher fields, whereas those in ^{13}C NMR spectra are at lower fields. Differences in the chemical shifts were also observed in ^{31}P and ^{77}Se NMR spectra. In the former spectra, the signals of R_{ax},*R*-isomers were at higher fields, whereas those were at lower fields in the latter spectra. All of the spectra in Table 1 showed exactly the same patterns. Therefore, multiple combinations of NMR spectra can be reliably used to determine the absolute configurations of 2-alkanols bearing similar carbon skeletons. To further ensure the identical trend in the ^{1}H NMR spectra of the esters **3**, values of $\Delta\delta^{SR}$ (ppm) and the sign distribution for **3** are shown in Figure 1. The difference in the chemical shifts of the methyl groups of **3** is negative, whereas that of the alkyl groups of **3** is positive.[16] This implies

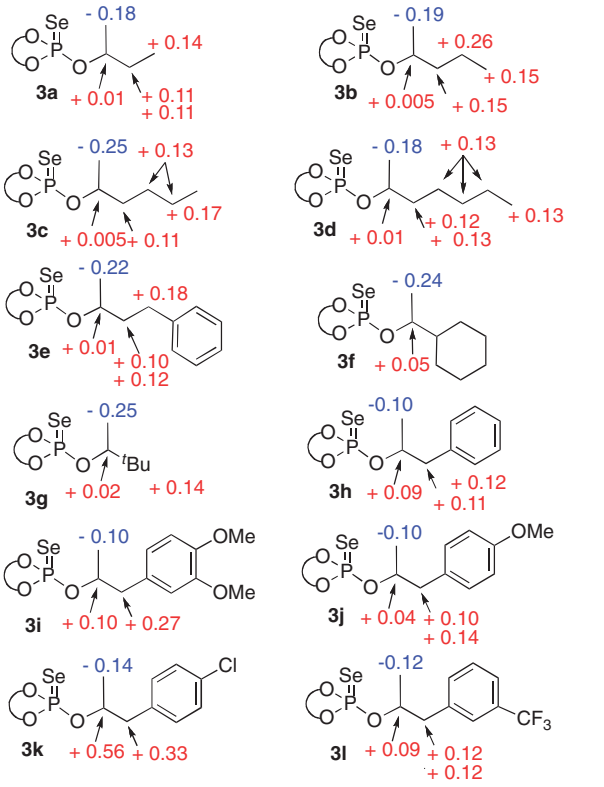


Figure 1. $\Delta\delta$ values for esters **3** in ^{1}H NMR spectra. $\Delta\delta$ values = $\delta(R_{ax},S) - (R_{ax},R)$.

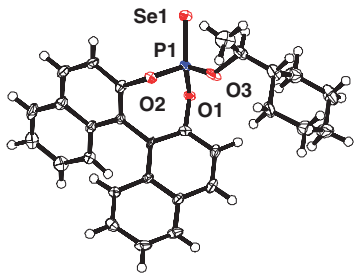


Figure 2. ORTEP drawing of phosphoroselenoic acid ester **3f**. Selected bond lengths (Å): P1–O1, 1.599(6); P1–O2, 1.606(6); P1–O3, 1.510(6). Selected bond angles (°): Se–P–O1, 112.1(2); Se–P–O2, 116.5(2), Se–P–O3, 118.3(2).

that all the esters adopt similar conformations and that the methyl groups of *R*-isomers are deshielded rather that those of *S*-isomers.

The conformation of esters **3** was unequivocally determined by X-ray molecular structure analyses of the esters (R_{ax},*S*)-**3f**[17] and (R_{ax},*S*)-**3h**,[17] whose ORTEP drawings are shown in Figures 2 and 3, respectively. Although the shielding effect of binaphthyl groups cannot be predicted based on the data at the present stage, these proved that esters **3** have a similar conformation in a solid state. The phosphorus atoms adopt a tetrahedral structure with a slight deviation. They adopt an anti-periplanar conformation with a chiral carbon atom–cyclohexyl or –phenylmethyl group and P=Se groups close to anti-periplanar. Methyl groups are oriented at the synclinal position of the selenium atom.

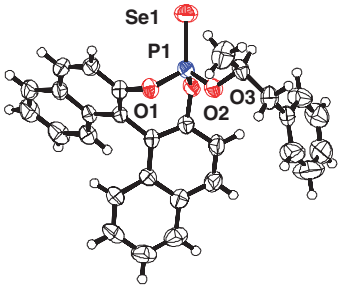
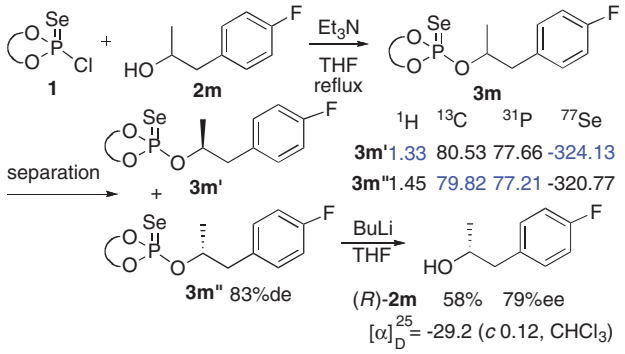


Figure 3. ORTEP drawing of phosphoroselenoic acid ester **3h**. Selected bond lengths (Å): P1–O1, 1.600(3); P1–O2, 1.595(3); P1–O3, 1.558(3). Selected bond angles (°): Se–P–O1, 117.92(11); Se–P–O2, 103.23(14), Se–P–O3, 119.23(12).



Scheme 1.

Finally, multiple combinations of NMR spectra were used to determine the absolute configuration of the alcohol **2m**. Initially, the alcohol **2m** was derivatized with (R_{ax})-**1** to give a diastereomeric mixture of **3m** (Scheme 1). Diastereomers of the ester **3m** were then separated by recrystallization to obtain **3m″** with 83%de. The ^{1}H, ^{13}C, ^{31}P, and ^{77}Se NMR spectra of **3m** are also listed in Scheme 1. Based on these data in comparison to those in Table 1, the absolute configuration of **3m″** was determined to be R_{ax},*R*. Finally, the ester **3m″** was cleaved with BuLi to give optically active alcohol (*R*)-**2m** with 79%ee in 58% yield. The alcohol (*R*)-**2m** showed a specific optical rotation with a negative sign, as did those of the *R* isomers in Table 2.

In summary, we have demonstrated a multiple-NMR combination method for determining the absolute configurations of 1-aryl-2-propanols. In the application of this method to 2-alkanols with unknown absolute configurations, the tendencies of all the spectra should match those of 2-alkanols with known absolute configurations. In contrast, this system should not be applied if even one of them is not consistent. Additionally, the sequential manipulation from racemic 1-aryl-2-alkanols, i.e., synthesis, separation, and cleavage of esters **3**, provides the method for the preparation of optically active 1-aryl-2-propanols. Further application of the present method to chiral compounds is in progress.[18,19]

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16 These trends of the aromatic protons in **3** could not be evaluated since their signals were partly overlapped with those of the binaphthyl group.
17 The details of crystallographic data for **3f** and **3h** are in Supporting Information. CCDC for **3f**: 764817, CDC for **3h**: 764816.
18 Preliminary results of the application of the present method for 3-alkanols are shown in Supporting Information.
19 Supporting Information is available electronically on the CSJ Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

