On the use of seven-membered phosphorous heterocycles based on 2,2′-dihydroxy-1,1′-binaphthalene and 1,4:3,6-dianhydro-D-mannitol in the ^{31}P NMR analysis of the enantiomeric composition of chiral alcohols

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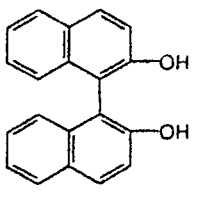
Some aspects of phosphorylation of 2,2′-dihydroxy-1,1′-binaphthalene (BINOL) and 1,4:3,6-dianhydro-D-mannitol (isomannide) were investigated. The possibility of using the corresponding cyclic chloro- and amidophosphites for the analysis of enantiomeric compositions of chiral primary and secondary alcohols by ^{31}P NMR was examined.

Key words: 2,2′-dihydroxy-1,1′-binaphthalene (BINOL); 1,4:3,6-dianhydro-D-mannitol; phosphorylation; chiral alcohols; chiral derivatizing agents; enantiomeric composition; ^{31}P NMR.

The problem of enantioselective synthesis occupies a prominent place in modern organic chemistry. Therefore, determination of the enantiomeric composition of final chemical products and reaction mixtures[1] and, hence, design of specific reagents that would permit[2] this analysis to be quickly carried out by NMR spectroscopy is an especially important task. It has been reported that phosphorus derivatives,[3] in particular, phosphorus-containing heterocycles[4—6] prepared from chiral organic molecules with C_2 axial symmetry, can be advantageously used for this purpose. The principle of using the C_2 symmetry to control enantioselective processes is well known and widely employed.[7] When molecules of this type form heterocycles incorporating a phosphorus atom, this atom does not act as a chiral center; therefore, the stereochemistry of substitution at the phosphorus atom has no effect on the isomeric composition of the adducts. This is a very important factor for the development of organophosphorus reagents for enantioselective analysis.

Among chiral molecules possessing a second-order axial symmetry, we chose 2,2′-dihydroxy-1,1′-binaphthalene (BINOL) (**1**) and 1,4:3,6-dianhydro-D-mannitol (isomannide) (**2**).



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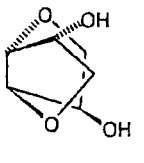

2

Both molecules possess clear-cut three-dimensionally distributed asymmetry; additional expectations are associated with the magnetically anisotropic aromatic rings present in molecule **1** and with rigid spatial arrangement of molecule **2**. Finally, pure enantiomers of both compounds are relatively easily accessible.

BINOL and its derivatives are widely used as inductors of chirality in enantioselective processes. In particular, BINOL has been used[8,9] as a specific solvating additive to control the enantiomeric composition of chiral organic substrates by ^{1}H NMR spectroscopy. The use of 1,1′-binaphthalene-2,2′-diylthiophosphoryl chloride as an organophosphorus reagent for enantioselective analysis has also been mentioned;[10] the authors claim that the interaction of this reagent with alcohols is accompanied by opening of the dioxaphosphepine ring.

In this work, we studied the reaction of cyclic chlorophosphites (**3**), prepared from binaphthalenediol **1** (Scheme 1), with chiral alcohols (**5a—h**) and the possibility of using the ^{31}P NMR spectra of the resulting phosphites (**6a—h**), phosphates (**7a—h**), and phosphothioates (**8a—h**) for the purposes of enantioselective analysis.

The reaction of 2,2′-dihydroxy-1,1′-binaphthalene with PCl_3 has been studied previously. It was shown[11,12] that, depending on the conditions, this reaction can yield both cyclic chlorophosphite **3** and phosphite **4** resulting[11] from the subsequent interaction of product **3** with the starting diol (see Scheme 1).

The researchers cited[11] dealt with pure (*R*)-BINOL and described the ^{31}P NMR spectrum of phosphite **4** as a singlet with δ_P 144.6. Naturally, the phosphite **4** that we prepared from (*S*)-BINOL exhibited an identical

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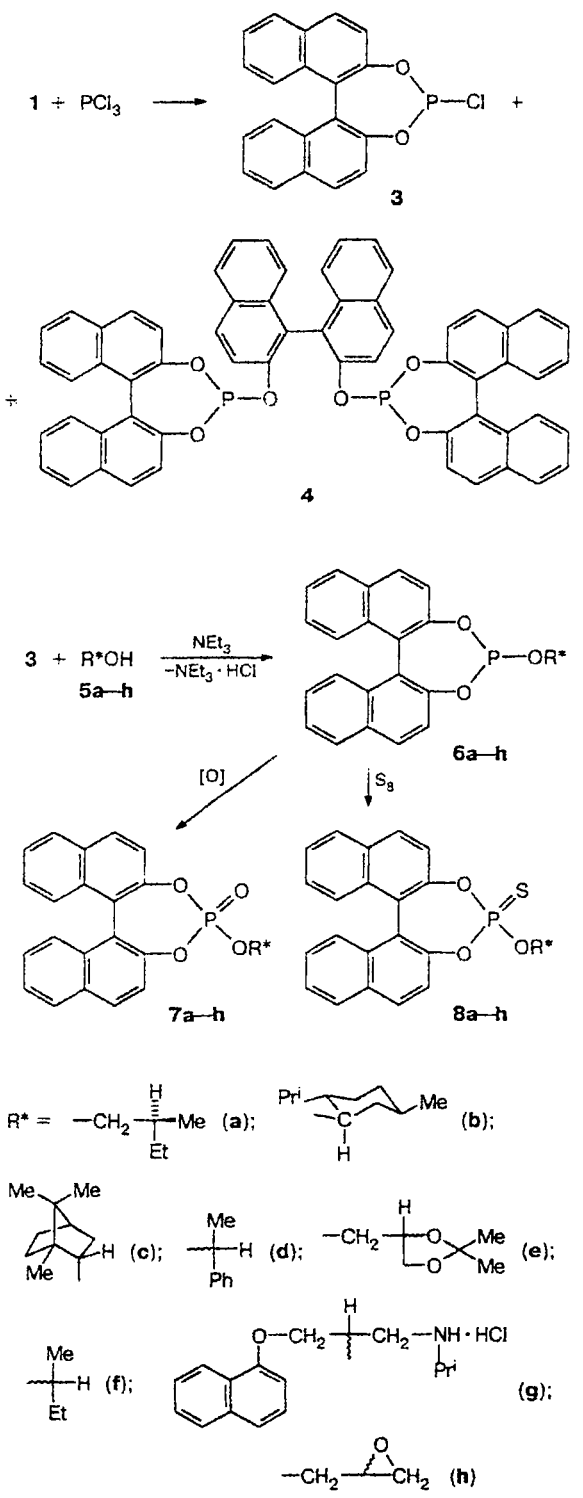
Scheme 1



^{31}P NMR spectrum (s, δ_P 144.3). However, when we used racemic (*R,S*)-**1** as the starting compound, the ^{31}P NMR spectrum of compound **4** contained a group of three signals with δ_P 143.7, 144.5, and 145.5; the ratio of their intensities was ~1 : 2 : 1.

"Triplets" of this sort are typical of compounds that exist as mixtures of isomers with chiral and pseudochiral phosphorus atoms.[3] A specific feature of this particular case is that the phosphorus atom in the axially symmetrical cyclic environment in any isomer of **4** is achiral and even does not act as a stereo-inducing center. However, being incorporated in various diastereomers, this atom possesses a sufficient anisochronicity to cause their discrimination. Thus, one of the weak signals of the "triplet" belongs to the pair of (*S,S,S*)- and (*R,R,R*)-isomers of **4**, the other weak signal characterizes the (*R,S,R*)- and (*S,R,S*)-isomers of **4**, whereas the central signal with the double intensity corresponds to the (*R,R,S*)- and (*S,R,R*)-diastereomers, which are degenerate owing to the axial symmetry of the central bridge in binaphthalenediol, and to a similar degenerate (*S,S,R*) and (*R,S,S*) enantiomeric pair. (The symbols *R* and *S* characterize the axial chirality of the BINOL fragments in compound **4** for movement along the chain of bonds of the molecule).

The above-noted finding can be used to check additionally the quality of binaphthalenediol **1**; for this purpose, a slight excess of this compound should be used in the synthesis of chlorophosphite **3**. The ^{31}P NMR signals of isomeric compounds **4** do not overlap with the signals of **3** (singlets with δ_P 177.8 for all isomers); the presence of a set of signals in the 143—145 ppm region would indicate that the enantiomeric purity of the initial **1** is insufficient. On the other hand, if the reaction is carried out[12] by slow addition of BINOL to an excess of PCl_3, individual chlorophosphite **3** can be obtained as the only phosphorus-containing product, as indicated by the NMR spectra. 1,3,2-Dioxaphosphepine heterocyclic derivatives are believed to be unstable; however, we found that a solution of individual chlorophosphite **3** in toluene stored at a temperature of about 0 °C undergoes no changes for at least 6 months. Thus, in principle, this compound can serve as a convenient organophosphorus reagent for enantioselective analysis.

Derivatizing reagents used to determine enantiomeric compositions of chiral substrates by NMR spectroscopy should meet several requirements. First, the reaction between the reagent and the substrate should be fast and quantitative. The difference between the chemical shifts of diastereomeric adducts should be large enough to ensure correct integration of individual signals. Finally, the reaction between the reagent and substrate should not exhibit pronounced diastereoselectivity.

In this work, we used the chiral primary and secondary alcohols **5a—h** shown in Scheme 1 as substrates, whose enantiomeric composition was studied. It should be mentioned that (*S*)-(−)-2-methylbutanol (**5a**), *l*-(−)-menthol (**5b**), and *d*-(+)-borneol (**5c**) were used as pure enantiomers, whereas 1-phenylethanol (**5d**), butan-2-ol (**5f**), 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (**5e**),

and propranolol (**5g**) were racemates. Glycidol (**5h**) was used both as a racemic sample and as mostly the (*S*)-isomer. In the case of enantiomerically pure alcohols **5a—c**, the differences between the chemical shifts of diastereomeric phosphites **6a—c** and products of their subsequent transformations were estimated using racemic chlorophosphite **3**; in the case of alcohols **5d—h**, the spectra of the adducts based on (*R*)-BINOL were analyzed.

Chlorides **3** smoothly react with alcohols **5** in the presence of Et_3N without heating. Solutions of the corresponding phosphates **7** and phosphothioates **8** were obtained by treatment of aliquot portions of solutions of phosphites **6** with a slight excess of Bu^tOOH or elemental sulfur. The oxidation and thionylation do not necessarily proceed unambiguously; however, the pairs of signals that belong to the main products can usually be easily identified in the final spectrum.

The ^{31}P NMR chemical shifts of the diastereomeric phosphites, phosphates, and phosphothioates, the differences between the chemical shifts ($\Delta\delta$), and the relative integral intensities of some signals are presented in Table 1.

Table 1. Chemical shifts (δ ^{31}P), differences between the chemical shifts ($\Delta\delta$ ^{31}P), and relative integral intensities (I_{rel} (%)) of the signals of diastereomeric cyclic phosphites **6a—h**, phosphates **7a—h**, and phosphothioates **8a—h**

R*	Phosphites **6a—h**		Phosphates **7a—h**		Phosphothioates **8a—h**	
	δ ^{31}P ($\Delta\delta$)	I_{rel}	δ ^{31}P ($\Delta\delta$)	I_{rel}	δ ^{31}P ($\Delta\delta$)	I_{rel}
a	138.6, 138.5 (0.1)	99 100	2.1 (~0)		74.0 (~0)	
b	154.7, 149.2 (5.5)	87 100	1.6, 1.5 (0.1)	100 89	73.1, 72.8 (0.3)	83 100
c	145.6, 142.6 (3.0)	100 98	2.4, 2.3 (0.1)	100 91	73.9, 73.4	100 96
d	144.7, 137.6 (7.1)	52 100	1.6, 0.8 (0.8)	56 100	73.0, 72.1 (0.9)	53 100
e	138.8, 137.9 (0.9)	98 100	2.1, 1.9 (0.2)	100 97	73.7, 73.3 (0.4)	100 94
f	144.2, 144.1 (0.1)	98 100	1.4, 1.3 (0.1)		72.8, 72.6 (0.2)	100 99
g	150.0, 147.6 (2.4)	100 83			73.7, 73.1 (0.6)	100 80
h	138.0, 136.0 (2.0)	100 96	2.0 (~0)		73.9, 73.8 (0.1)	100 95

Analysis of the data listed in Table 1 leads to the following conclusions. First, as has been repeatedly noted previously, the differences between the chemical shifts of diastereomeric derivatives of tricoordinated phosphorus are normally larger than the corresponding values for P^V derivatives. Only when the $\Delta\delta$ values for P^{III} derivatives are small, as is the case with compound **6f**, can transition to thiophosphoryl analogs (but not to phosphates!) result in a slight increase in $\Delta\delta$. Second, the average $\Delta\delta$ value over the whole set of compounds **6a—h** amounts to ~2.3 ppm, *i.e.*, the difference between the chemical shifts of diastereomeric phosphites is quite pronounced, which enables the enantiomerism in the initial alcohols to be detected easily and reliably. Finally, the intensities of the signals of the phosphites given in Table 1 make it possible to judge the diastereoselectivity of the reaction of chiral alcohols with chiral compound **3**. Whereas in the case of alcohols **5a,c,e,f,h**, the diastereoselectivity is not clearly defined, and the resulting diastereomeric ratio is close to unity, the same cannot be said of alcohols **5b,d,g**. The stereoselectivity, *i.e.*, the predominant formation of one of the two possible diastereomers, which is clearly manifested in the latter two cases, compels one to treat with caution the general prospects for using compound **3** as a versatile reagent for the quantitative control of enantiomeric compositions of organic substrates.

Nevertheless, we checked the possibility of using compound **3** for the quantitative determination of the enantiomeric excess (*ee*) in glycidol samples. For racemic **5h** (see Table 1), the estimate of the *ee* by virtue of (*R*)-**3** gives 2.0%, which is sufficiently close to the true value equal to 0.0%. The *ee* values that we measured for two different samples of non-racemic (*S*)-**5h** using 2-chloro-4(*R*),5(*R*)-bis(*N*,*N*-dimethylcarbamoyl)-1,3,2-dioxaphospholane as the derivatizing reagent[6] were 87.2% and 91.5%. The *ee* values found for the same samples of (*S*)-glycidol by means of (*R*)-**3** are equal to 87.1% and 90.4%. The convergence of the data for this substrate should be considered to be satisfactory.

Like BINOL, dianhydromannitol **2** is a diol and, therefore, its phosphorylation occurs ambiguously. This has also been noted previously.[13,14] We studied the reaction between equimolar amounts of PCl_3 and dianhydromannitol in THF without a base at a very low temperature (−78 °C). It can be seen from Fig. 1 that the $^{31}P—\{^1H\}$ NMR spectrum of the reaction mixture recorded immediately after mixing the reactants exhibits five main signals, which can be assigned to P^{III} derivatives according to their chemical shifts. Thus the lowest-field signal (δ_P 218) corresponds to PCl_3; the following two closely spaced signals (δ_P 178.3 and 177.7) correspond to compounds containing $—OPCl_2$ fragments; the next signal is due to the O_2PCl fragment (δ_P 164.4), and the last signal (δ_P 136.1) belongs to the fully substituted phosphite. At ~−20 °C, the signal with δ_P 177.7 disappears, and the intensities of the signals with δ_P 218 and 136.1 decrease. Simultaneously, the signal with δ_P 164.4

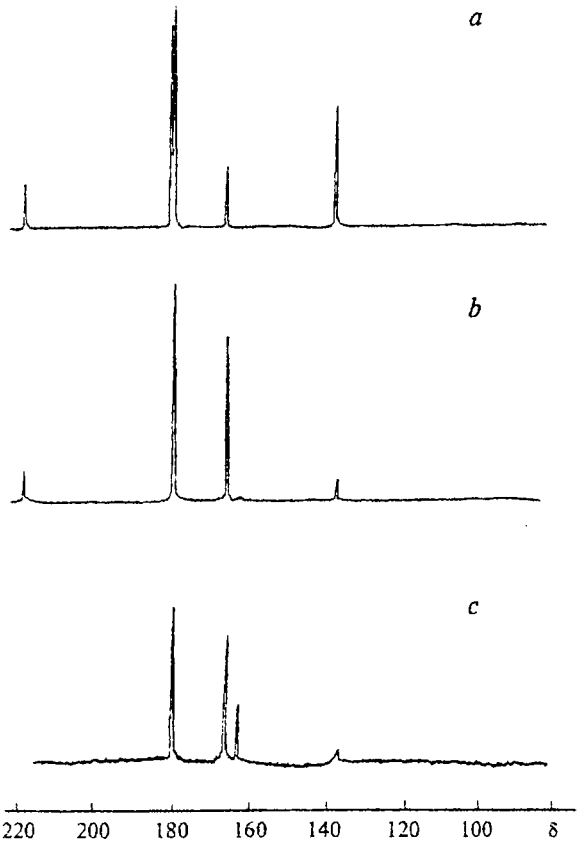


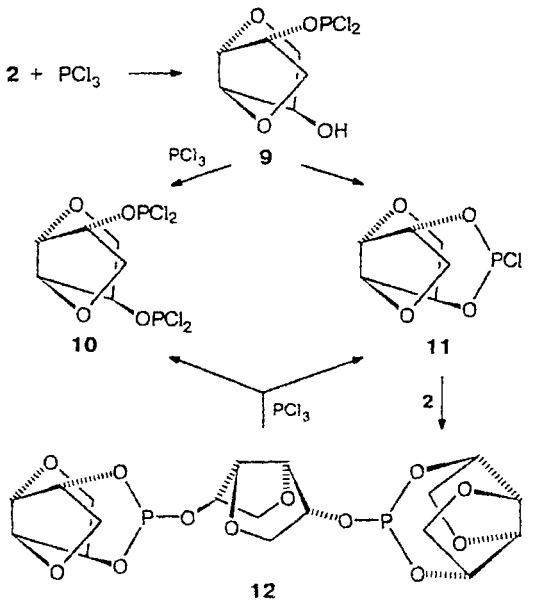
Fig. 1. ^{31}P NMR spectrum of the reaction mixture consisting of 1,4:3,6-dianhydro-D-mannitol (**2**) and PCl_3 at −78 (*a*), ~−20 (*b*) and ~20 °C (*c*).

becomes more intense, and a weak signal with δ_P 162.0 appears. Further heating of the mixture to ~20 °C is accompanied by intense formation of an insoluble phosphorus-containing polymer of unknown composition. This is manifested in the spectrum as a decrease of the integrated intensity of the signals, almost complete disappearance of the signals for PCl_3 and for the fully substituted phosphite, and simultaneous increase in the relative intensity of the signal with δ_P 162.0.

In our opinion, the spectral changes are consistent with the following scheme of chemical transformations (Scheme 2):

Hydroxy dichlorophosphite **9**, which is necessarily formed at the first stage and which is responsible, in our opinion, for the signal at 177.7 ppm, either reacts with excess PCl_3 to give bis(dichlorophosphite) **10** (δ_P 178.3) or undergoes intramolecular cyclization to give chlorophosphite **11** (δ_P 164.4). By analogy with the above-discussed reaction of PCl_3 with BINOL, two molecules of **11** can be linked by a free dianhydromannitol molecule to yield phosphite **12**, which is an analog of phosphite **4**. Compound **12** (δ_P 136.1) reacts, in turn, with PCl_3; this leads to the recovery of

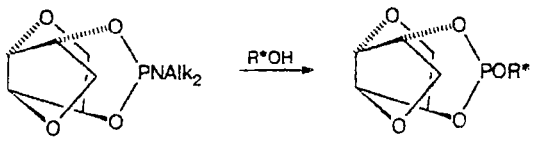
Scheme 2



compounds **10** and **11**. All the organic phosphorus chlorides arising during this reaction are relatively unstable and are converted on heating into oligomeric and polymeric products. One of the intermediate soluble oligomers might be responsible for the signal with δ_P 162.0.

Detailed investigation of the phosphorylation of 1,4:3,6-dianhydro-D-mannitol was beyond the scope of the present work. Since molecule **11** is unstable, as had been reported previously[13] and confirmed in this study, it cannot be used as a routine organophosphorus reagent for enantioselective analysis. However, we carried out esterification of the reaction mixture that contained, according to ^{31}P NMR data, only compounds **10** and **11** and in which the latter predominated, with chiral racemic butan-2-ol and glycidol. The diastereomeric phosphites **13** (analogs of **6f** and **6h**) were readily identified in the spectra of the reaction products as pairs of signals with approximately equal intensities with δ_P 134.8 and 132.0 in the case of **5f** and δ_P 136.9 and 132.2 in the case of **5h**. Attention is attracted by the fact that the $\Delta\delta$ values for the signals of diastereomers are very large ($\Delta\delta$ = 2.7 and 4.7, respectively); this prompted us to introduce amides **14a,b**, whose dilute solutions were obtained by refluxing dianhydromannitol with hexaalkyltriamidophosphites in benzene as reported previously,[13] in the synthesis of phosphites **13** instead of chloride **11**. The ^{31}P NMR spectra of the final reaction mixtures exhibited actually only one signal corresponding to amide **14a** (δ_P 145.5) or **14b** (δ_P 146.8). Thus, these compounds might prove more convenient derivatizing reagents than chloride **11**.

Scheme 3



14a,b **13**

Alk = Me (**a**), Et (**b**)

Unfortunately, the replacement of the dialkylamino group by the chiral alkoxyl residue occurs only upon prolonged refluxing in benzene; moreover, in both cases, the ^{31}P NMR spectra of the final reaction mixtures contained numerous signals in the 130—145 ppm region, so that it was impossible to distinguish the signals belonging to diastereomers **13**.

To summarize the foregoing, it can be concluded that in the series of 2,2′-dihydroxy-1,1′-binaphthalene derivatives, cyclic chlorophosphites **3**, which are accessible in a pure state in any enantiomeric form and are stable in solution, are promising organophosphorus reagents for enantioselective analysis. However, it should be borne in mind that the use of these compounds as derivatizing reagents for ^{31}P NMR analysis of the enantiomeric composition of chiral organic substrates under the conditions studied here (moderate temperatures and an equimolar ratio of the reagent to the alcohol analyzed) can be complicated by the diastereoselectivity in the formation of the corresponding adducts discovered in this work.

When diastereomeric phosphites of chiral alcohols **13**, which contain a 1,4:3,6-dianhydro-D-mannitol fragment, can be identified, their chemical shifts δ_P prove to be appreciably different. However, the initial cyclic isomannide derivatives are either not stable enough in a pure state and cannot be isolated (chlorophosphite **11**) or, like amidophosphites **14**, do not react with chiral alcohols unambiguously enough; hence, they cannot be recommended as promising organophosphorus reagents for enantioselective analysis.

Experimental

$^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker MSL-400 spectrometer (161.92 MHz) using H_3PO_4 as the external standard and toluene, benzene, and THF as solvents.

The sample of racemic propranolol (**5g**) was prepared by a known procedure;[15] (*S*)-glycidol ((*S*)-**5h**) was synthesized by enantioselective epoxidation of allyl alcohol with cumene hydroperoxide according to Sharpless.[16] The rest of the chiral alcohols were commercial products.

1,4:3,6-Dianhydro-D-mannitol (2), 1,4:3,6-dianhydro-2,5-*O*-(dimethylaminophosphano)-D-mannitol (14a), and its diethyl analog (14b) were synthesized by procedures described previously.[13,17]

2,2′-Dihydroxy-1,1′-binaphthalene (1) was synthesized by oxidation of β-naphthol with ferric chloride by a known procedure.[18] Resolution of **1** into enantiomers was carried out, as described previously,[19] based on different solubilities of its complexes with (*R,R*)-1,2-diaminocyclohexane in toluene.

1,1′-Binaphthalene-2,2′-diyl chlorophosphite (3) was synthesized in solution similarly to a previously described procedure.[12] A suspension of racemic or enantiomerically pure **1** (5.18 g, 18.1 mmol) in toluene (100 mL) was slowly added at −78 °C under dry argon to a stirred mixture of PCl_3 (1.58 mL, 18.1 mmol) and Et_3N (5.05 mL, 36.2 mmol). The reaction mixture was stirred for 2 h at this temperature and allowed to stand for ~10 h in a refrigerator at −20 °C. Then the mixture was warmed up to ~20 °C under a dry inert atmosphere, separated from the precipitate of $Et_3N \cdot HCl$ using a syringe, and the total volume of the solution was measured. The content of **3** in 1 mL of the solution was calculated based on the ratio of the phosphorus-containing products found by ^{31}P NMR spectroscopy.

Analysis of the enantiomeric compositions of alcohols using (*R*)-3 (general procedure). A solution of chloride **3** (10.0 mL, ~2.07 mmol) prepared as described above was placed into a flask equipped with a magnetic stirrer in an atmosphere of dry argon, and Et_3N (0.57 mL, 4.14 mmol) was added at 5—10 °C. The mixture was stirred for 10 min, then the alcohol to be analyzed (2.07 mmol) was slowly added. The mixture was stirred for an additional 10 min, warmed up to ~20 °C, and the solution was filtered and divided into two portions. The first portion was placed in a tube (10 mm in diameter), and the ^{31}P NMR spectrum was recorded. Enantiomeric excess was calculated from the formula *ee* (%) = $100 \cdot (I_1 - I_2)/(I_1 + I_2)$, where I_1, I_2 are integral intensities of the signals of the corresponding diastereomeric phosphites **6**. After the spectrum had been recorded, the contents of the tube were cooled with ice, a 5.56 *M* solution of Bu^tOOH (0.15 mL) in CH_2Cl_2 was added, and the ^{31}P NMR spectrum of phosphates **7** was recorded in a similar way. Elemental sulfur (0.05 g, 1.56 mmol) was added to the second portion of the solution of phosphites **6**, and the mixture was stirred for several hours and left for ~10 h. The excess of sulfur was filtered off, the solution was placed in a tube (10 mm in diameter), and the ^{31}P NMR spectrum of phosphothioates **8** was recorded.

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References

1. *Asymmetric Synthesis. I. Analytical methods*, Ed. J. D. Morrison, Academic Press, New York, 1983.
2. D. Parker, *Chem. Rev.*, 1991, **91**, 1441.
3. R. Hulst, R. M. Kellogg, and B. L. Feringa, *Rec. Trav. Chim.*, 1995, **114**, 115.
4. R. C. Anderson and M. J. Shapiro, *J. Org. Chem.*, 1984, **49**, 1304.
5. J.-M. Brunel, O. Pardigon, M. Maffei, and G. Buono, *Tetrahedron: Asymmetry*, 1992, **3**, 1243.
6. A. A. Bredikhin, E. I. Strunskaya, N. M. Azancheev, and Z. A. Bredikhina, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 172 [*Russ. Chem. Bull.*, 1998, **47**, 174 (Engl. Transl.)].
7. J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.

8. F. Toda, K. Mori, J. Okada, M. Node, A. Itoh, K. Oomine, and K. Fuji, *Chem. Lett.*, 1988, 131; F. Toda, K. Mori, and A. Sato, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4167.
9. O. V. Mikhalev, O. R. Malyshev, M. G. Vinogradov, G. V. Chel'tsova-Bebutova, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 900 [*Russ. Chem. Bull.*, 1995, **44**, 873 (Engl. Transl.)].
10. C. R. Johnson, R. C. Elliott, and T. D. Penning, *J. Am. Chem. Soc.*, 1984, **106**, 5019.
11. M. J. Baker and P. G. Pringle, *J. Chem. Soc., Chem. Commun.*, 1991, 1292.
12. N. Greene and T. P. Kee, *Synth. Commun.*, 1993, **23**, 1651.
13. E. E. Nifant'ev, O. M. Plotnikova, N. G. Ruchkina, L. K. Vasyanina, and A. R. Bekker, *Zh. Obshch. Khim.*, 1992, **62**, 2456 [*Russ. J. Gen. Chem.*, 1992, **62** (Engl. Transl.)].
14. M. K. Grachev, K. L. Anfilov, A. R. Bekker, and E. E. Nifant'ev, *Zh. Obshch. Khim.*, 1995, **65**, 1946 [*Russ. J. Gen. Chem.*, 1995, **65** (Engl. Transl.)].
15. J. S. Farina, S. A. Jackson, and C. L. Cumming, *Org. Prep. Proced. Int.*, 1989, **21**, 173.
16. R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, Ed. I. Ojima, VCH Publishers, New York, 1993, 103.
17. R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 1948, 2204.
18. R. Pummerer, E. Prell, and A. Rieche, *Ber.*, 1926, **59**, 2159.
19. M. Kawashima and R. Hirata, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2002.

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