Chiral Diamines for a New Protocol To Determine the Enantiomeric Composition of Alcohols, Thiols, and Amines by ^{31}P, ^{1}H, ^{13}C, and ^{19}F NMR

Alexandre Alexakis,* Juan C. Frutos, Stephane Mutti, and Pierre Mangeney

Laboratoire de Chimie des Organo-Eléments, CNRS UA 473, Université P. et M. Curie, 4, Place Jussieu, F-75252 Paris Cedex 05, France

Received January 7, 1994•

A new experimental protocol is described which greatly improves our recently reported method for the determination of the enantiomeric composition of alcohols, phenols, thiols, and amines. Thus, successive addition into the NMR tube of (1) a chiral fluorinated diamine (or any other chiral C_2 symmetrical diamine), (2) $CDCl_3$, (3) a tertiary amine, (4) PCl_3, and 5) the chiral alcohol, phenol, thiol, or amine allows a ^{31}P NMR spectrum of the diastereomeric derivatives to be recorded in 5 min. The method is accurate and very general, and no kinetic discrimination is observed. Sulfuration or selenation of the trivalent phosphorus derivatives, carried out in the NMR tube, allows for a second ^{31}P NMR determination, in addition to the ^{1}H, ^{13}C, and ^{19}F NMR spectra which may also be recorded.

Introduction

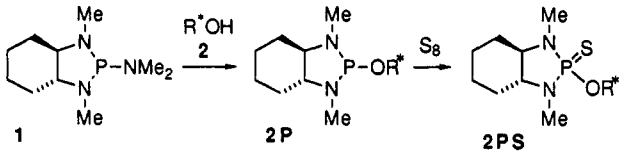
There are many ways to analyze the enantiomeric composition of chiral compounds.[1] Among them the transformation of enantiomers into diastereomers with a chiral derivatizing agent (CDA) and analysis by NMR techniques[2] occupy a prominent position. NMR spectra of nuclei other than ^{1}H and ^{13}C are particularly attractive, since they are devoid of the signals of the organic compound being analyzed.[3]

We recently disclosed a new chiral derivatizing reagent for the determination of the enantiomeric composition of chiral (primary, secondary, and tertiary) alcohols and thiols.[4] Reagent **1** reacts easily at room temperature within 1–12 h, without any adjuvant, with a chiral alcohol **2** to afford a trivalent (P^{III}) phosphorus derivative **2P** which can be analyzed by ^{31}P NMR, and also by ^{1}H and ^{13}C NMR. Derivative **2P** may be subsequently sulfurated with elemental sulfur, in the NMR tube, instantaneously and quantitatively. This new derivative **2PS** is again analyzed by ^{31}P, ^{1}H, and ^{13}C NMR, and also by gas chromatography (Scheme 1).

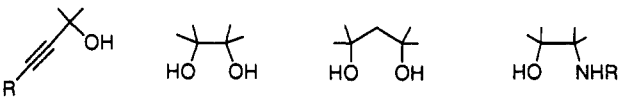
Primary, secondary, and tertiary alcohols react equally well, without any kinetic discrimination. There were, however, two limitations which concern propargylic alcohols and 1,2 or 1,3 diols and amino alcohols (Scheme 2).

We have modified our method to render it compatible with these classes of compounds. Moreover, *we describe a new experimental protocol, which does not require the prior formation of reagent 1 and allows the entire procedure to be run in the NMR tube in 5 min!* In addition, with this new procedure it is now possible to measure enantiomeric composition, not only of alcohols and thiols, but also of chiral phenols and primary and secondary amines.[5] It should also be noted that trimethylsilyl ethers can be directly derivatized, bypassing the need for the free alcohol itself.

Scheme 1



Scheme 2



A New Procedure with a New Reagent

The problems encountered with propargylic alcohols and polyols deal, in fact, mainly with the reactivity of reagent **1**. The basic idea was to replace the exocyclic-NMe_2 moiety by a better leaving group, such as a halide. Of course, such a reagent would be even more sensitive to moisture, and therefore a way was sought to prepare it *in situ*, directly in the NMR tube.

Thus, a chiral diamine **3**, containing a C_2 axis of symmetry was reacted with 1 equiv of PCl_3 in the presence of an excess of base (5–6 equiv) such as triethylamine, *N*-methylimidazole, pyridine, or diethylaniline leading to the desired very reactive derivatizing reagent **4** (see Scheme 3). This reaction is quantitative and instantaneous[6] and is performed in the NMR tube in $CDCl_3$ or CH_2Cl_2 (in this latter case a slight amount of C_6D_6 or $CDCl_3$ is needed for

• Abstract published in *Advance ACS Abstracts*, May 15, 1994.

(1) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1983; Vol. 1.

(2) 2. For a recent review see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.

(3) 3. Since the recent review by Parker (ref 2) some new CDA's based on ^{1}H, ^{19}F, or ^{31}P NMR have been reported: (a) Welch, C. J. *Tetrahedron: Asymmetry* **1991**, *2*, 1127–1132. (b) Brown, J. M.; Leppard, S. W.; Lloyd-Jones, G. C. *Tetrahedron:Asymmetry* **1992**, *3*, 261–266. (c) Brunel, J.-M.; Pardigon, O.; Maffei, M.; Buono, G. *Tetrahedron:Asymmetry* **1992**, *3*, 1243–1246. (d) Hulst, R.; Zijlstra, W. J.; Feringa, B. L.; de Vries, N. K.; ten Hoeve, W.; Wynberg, H. *Tetrahedron Lett.* **1993**, *34*, 1339–1342. (e) Takeuchi, Y.; Itoh, N.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1514–1515. (f) Takeuchi, Y.; Itoh, N.; Kawahara, S.-i.; Koizumi, T. *Tetrahedron* **1993**, *49*, 1861–1870. (g) Takeuchi, Y.; Itoh, N.; Satoh, T.; Koizumi, T.; Yamaguchi, K. *J. Org. Chem.* **1993**, *58*, 1812–1820. (h) Wang, X. *Tetrahedron Lett.* **1991**, *32*, 3651–3654.

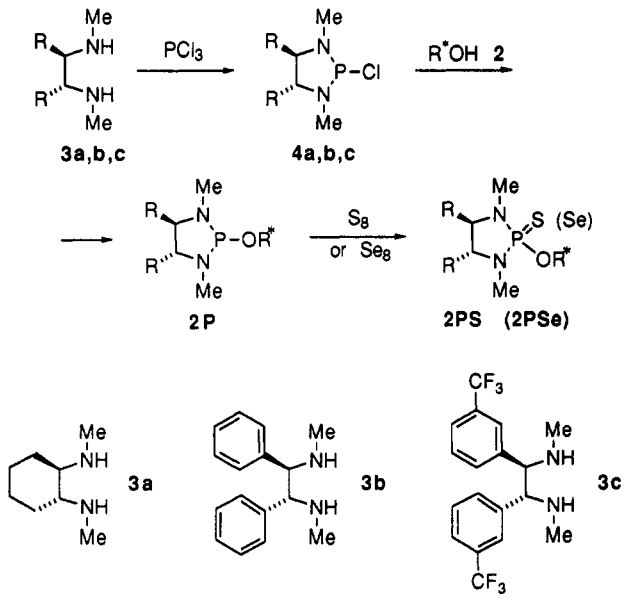
(4) 4. (a) Alexakis, A.; Mutti, S.; Mangeney, P.; Normant, J. F. *Tetrahedron:Asymmetry* **1990**, *1*, 437–441. (b) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224–1237.

(5) 5. Part of the present work was recently presented by Frutos, J. C. Diplôme d'Etudes Approfondies, Université Pierre et Marie Curie, Paris, 1992.

(6) Organische Phosphorverbingungen. In *Methoden der Organischer Chemie (Houben Weyl)*; Sasse, K., Ed.; Georg Thieme Verlag: Stuttgart, 1963–1964.

0022-3263/94/1959-3326$04.50/0

Scheme 3



locking). In these solvents, the formed hydrochlorides are usually soluble. Immediately after, 0.7 equiv of the chiral alcohol R*OH **2** is then added in order to insure complete consumption. The formation of the diastereomeric derivatives **2P** is again quantitative and instantaneous. A first ^{31}P NMR spectrum of this trivalent phosphorus derivative (P^{III}) may be recorded and the enantiomeric composition determined. Depending on the alcohol and on the base, ^{1}H and ^{13}C NMR spectra may also be recorded, when the NMR signals of these bases do not interfere with those of the derivatized alcohol in the analysis. The best bases are the mild ones *N*-methylimidazole or diethylaniline; stronger bases such as triethylamine, or most often pyridine, lead sometimes to byproducts such as formation of the corresponding chloride of the starting alcohol.

In a second step, it is possible to form new (pentavalent phosphorus) derivatives such as **2PS** and **2PSe** by addition, directly in the NMR tube, of excess molecular sulfur or selenium, both as the commercial powder (see Scheme 3). The advantage of adding selenium lies in the larger separation of the ^{31}P NMR signals, probably due to the greater steric requirements of the Se atom as compared to S. In addition, selenium derivatives open new perspectives on the use of ^{77}Se NMR,[7] a topic we are, presently, actively studying.

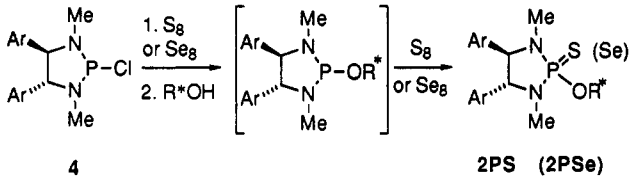
Derivatives **2PS** and **2PSe** are stable compounds and can be isolated after slightly acidic aqueous washings of the contents of the NMR tube, extraction, and evaporation, in order to remove the excess amine and the hydrochlorides. Alternatively, the contents of the NMR tube may be filtered through a short pad of silica gel. It is then possible to analyze these derivatives by ^{1}H and ^{13}C NMR where many signals (particularly the NMe groups) could differentiate the two diastereomers. However, most often, the ^{31}P, ^{1}H, and ^{13}C NMR spectra were immediately recorded without isolation of the **2PS** and **2PSe** derivatives. The excess S_8 or Se_8 settled down in the NMR tube without perturbation of the NMR analysis. A short survey of three available optically pure diamines (**3a**[8], **3b**,[8,9] and **3c**[10]) was made, with 1-phenylethanol **5**, in order to establish the best one for our purpose. As shown in Table 1, diamine **3a** is again the most effective; the separation of the diastereomeric signals is even better than in our previous procedure[4] which was performed in C_6D_6 solvent instead of $CDCl_3$! However, although slightly less efficient than diamine **3a**, diamine **3c** was mainly used in this study for the following reasons: (a) diamine **3c** is presently commercialy available, (b) the presence of the CF_3 groups allows for an additional measurement by ^{19}F NMR, (c) the two aromatic chromophores should facilitate an HPLC analysis. In all cases, the new protocol can be used with diamine **3a** (or any other new chiral diamine) when **3c** gives low or no separation of the diastereomeric signals.

Table 1. Evaluation, by ^{31}P NMR, of Diamines 3a–c under the new Procedure with 1-Phenylethanol (5)

diamine	Δδ of P^{III} in ppm	Δδ of PS in ppm	comments
3a: according to the previous procedure	**5aP**: 1.750	**5aPS**: 0.404	solvent: C_6D_6
3a: new procedure[a]	**5aP**: 2.600	**5aPS**: 0.501	solvent: $CDCl_3$
3b: new procedure[a]	**5bP**: 0.571	**5bPS**: 0.045	solvent: $CDCl_3$
3c: new procedure[a]	**5cP**: 1.131	**5cPS**: 0.337	solvent: $CDCl_3$

[a] Reactions performed with *N*-methylimidazole as base.

Scheme 4



In some sensitive cases (see below) or when the P^{III} derivative is not required, a variation of the standard protocol is also possible. Reagent **4** is not sufficiently nucleophilic to react with elemental sulfur or selenium, whereas the trivalent derivative **2P**, obtained after reaction with an alcohol, is reactive enough.[11] Introduction in the NMR tube of S_8 or Se_8 *prior* to the addition of the alcohol allows the immediate transformation of the **2P** derivative, as soon as it is formed, into the more stable sulfurated or selenated derivative **2PS** or **2PSe** (Scheme 4). By contrast, this reverse technique variation was not possible with the preformed reagent **1**, since it was also sulfurated.[4]

Lastly, it should be noted that the ^{31}P NMR spectra were recorded on a 16 year-old 90-MHz instrument. A better separation of the diastereomeric signals should be achieved on a more modern higher field instrument.

Scope and Limitations

As we did in our previous study with reagent **1**,[4] we screened a variety of alcohols with reagent **4c**. Many of the alcohols listed in the following tables were compounds

(7) ^{77}Se NMR of diastereomeric derivatives was shown to be a novel and useful tool for measuring the enantiomeric excess of (1) alcohols: Michelsen, P.; Annby, U.; Gronowitz, S. *Chem. Scripta* **1984**, *24*, 251–252; acids (a) Silks, L. A., III; Dunlap, R. B.; Odom, J. D. *J. Am. Chem. Soc.* **1990**, *112*, 4979–4982; (b) Silks, L. A., III; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Org. Chem.* **1991**, *56*, 6733–6736.

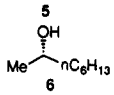
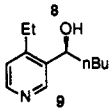
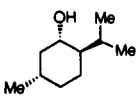
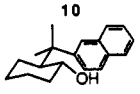
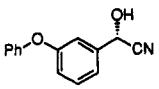
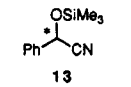
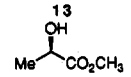
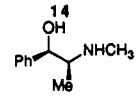
(8) 8. Fiorini, M.; Giongo, G. M. *J. Mol. Cat.* **1979**, *5*, 303–310. See also ref 4b for experimental details.

(9) 9. (a) Mangeney, P.; Tejero, T.; Alexakis, A.; Grojean, F.; Normant, J. F. *Synthesis* **1988**, 255–257. (b) Mangeney, P.; Alexakis, A.; Grojean, F.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 2675–2676.

(10) Cuvinot, D.; Mangeney, P.; Alexakis, A.; Normant, J. F.; Lellouche, J.-P. *J. Org. Chem.* **1988**, *54*, 2420–2425.

(11) Organische Phosphorverbingungen II. In *Methoden der Organischer Chemie (Houben Weyl)*; Sasse, K., Ed.; Georg Thieme Verlag: Stuttgart, 1964; see pp 593, 617, and 757.

Table 2. Derivatization of Secondary Alcohols with Reagent 4c, Derived from Diamine 3c (unless otherwise noted)

alcohol	conditions[a] S: solvent B: base A: diamine	^{31}P NMR[b] chem shift ($\Delta\delta$) P^{III}	^{31}P NMR[b] chem shift ($\Delta\delta$) PS	^{31}P NMR[b] chem shift ($\Delta\delta$) PSe	^{1}H NMR	^{13}C NMR	^{19}F NMR chem shift	ee% found (known)
 5	S: A	139.657	80.429	–	PS	PS	PS = 0.238, 0.195, 0.164	
	B: 2	138.445	80.092		(++)	(–)		racemic
	A: (*S*,*S*)**3c**	(1.212)	(0.337)					
 6	S: A	140.860	81.707	–	PS	PS	PS = *0.066*, 0.059, *0.050*, –0.059	39.9[c]
	B: 2	*139.110*	*81.371*		(++)	(–)		(40)
	A: (*R*,*R*)**3c**	(1.750)	(0.336)					
 7	S: A	138.715	80.227	–	PS	PS	–	
	B: 2	137.772	79.823		(+)	(–)		racemic
	A: (*S*,*S*)**3c**	(0.943)	(0.404)					
 8	S: A	142.282	82.381	–	–	–	–	18[d]
	B: 2	*141.003*	*82.252*					(18)
	A: (*S*,*S*)**3c**	(1.279)	(0.129)					
 9	S: A	*142.484*	80.967	–	PS	PS	PS = *0.156*, 0.113, *0.073*, 0.000	80[e]
	B: 1	139.657	(–)		(+++)	(–)		(80)
	A: (*S*,*S*)**3c**	(2.827)						
 10	S: A	*142.820*	*81.977*	*82.012*	PS	PS	P^{III} = 0.259, *0.117*, 0.103	79.6[f]
	B: 2	140.061	81.304	81.301	(+++)	(+)	PS = *0.073*, 0.059, –0.015	(80)
	A: (*S*,*S*)**3c**	(2.759)	(0.673)	(0.711)			PSe = 0.049, 0.039, *0.024*, *–0.029*	
 11	S: A	144.100	80.833	79.960	P^{III}	PSe	–	racemic
	B: 4	137.430	80.160	78.610	(++)	(+)		
	A: (*R*,*R*)**3b**	(6.670)	(0.673)	(1.150)	PSe (+++)			
 12	S: A	148.474	–	86.083	PSe	PSe	PSe = 0.138, *0.121*, 0.098, *0.045*	34.7[f]
	B: 3	*145.984*		(–)	(+++)	(+)		(34.7)
	A: (*S*,*S*)**3c**	(2.490)						
 13	S: A	148.003	84.467	–	–	–	–	racemic
	B: 2	145.445	84.265					
	A: (*R*,*R*)**3c**	(2.558)	(0.202)					
 14	S: A	*143.426*	–	*83.794*	PSe	PSe	–	25.8[f]
	B: 1	141.744		83.188	(++)	(++)		(26)
	A: (*S*,*S*)**3c**	(1.682)		(0.606)				
 15	S: B	*143.022*	–	*83.929*	–	–	–	60[f]
	B: 3	141.945		81.371				(60)
	A: (*S*,*S*)**3c**	(1.077)		(2.558)				

[a] Conditions: Solvent A = $CDCl_3$, B = CH_2Cl_2 + ε $CDCl_3$, C = CH_2Cl_2 + ε C_6D_6. Base 1 = triethylamine, 2 = *N*-methylimidazole, 3 = *N*,*N*-diethylaniline, 4 = pyridine. [b] The values in italic are those of the major diastereomer. [c] Enantiomeric excess known by mixing a given amount of each enantiomer of the alcohol. [d] Enantiomeric excess known by polarimetry. [e] Enantiomeric excess known by derivatization with methoxymandelic acid. [f] Enantiomeric excess known by mixing a given amount of each enantiomer of the diamine.

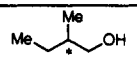
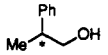
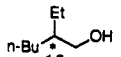
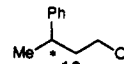
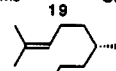
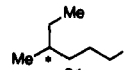
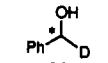
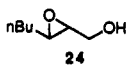
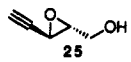
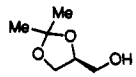
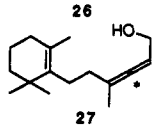
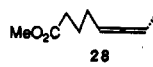
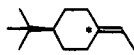
provided by colleagues which were difficult to analyze by other methods; some others were already analyzed with our previous reagent **1** and tested only for comparative purposes. In all the tables are mentioned (1) the experimental conditions under which this analysis was done, (2) the chemical shifts of the P^{III} and **PS** (or **PSe**) derivatives by ^{31}P NMR, (3) the efficiency of signal differentiation by ^{1}H,^{13}C according to an arbitrary scale (+++ excellent separation, ++ good separation, + no baseline separation, – no separation at all), (4) the chemical shifts by ^{19}F NMR, (5) the accuracy of the measurement as compared to a known enantiomeric composition. This accuracy depends mainly on the quality of NMR instrumentation. Due to usually complete baseline separation of peaks, the accuracy is higher by ^{31}P NMR where only singlets have to be integrated. However, depending on the structure of the alcohol and on the separation of the signals, ^{19}F and ^{1}H NMR may provide a quite high accuracy. Although we did not study explicitly this accuracy, we may estimate it (from all the data we have collected) to be at least ±1%.

An optically pure diamine **3c** was used with racemic and enantiomerically enriched alcohols. On the other hand, in order to be able to see the two diastereomeric signals with optically pure alcohols, a known mixture of diamines (*R*,*R*)**3c** and (*S*,*S*)**3c** was used.

Secondary Alcohols. The secondary alcohols tested in this study are listed in Table 2. In all cases a very good separation of ^{31}P NMR signals occurred with the P^{III} derivative ($\Delta\delta$ always >1.0 ppm). Although with the **PS** or **PSe** derivatives the separation ($\Delta\delta$) is smaller, the ^{31}P NMR signals of these pentavalent phosphorus compounds are much sharper and no problems were encountered. The accuracy of the measurements of the enantiomeric excesses (ee's) is always excellent and in agreement with the known enantiomeric composition. Benzylic as well as allylic alcohols are well distinguished.

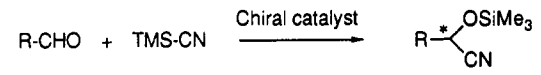
As we already observed with reagent **1**, there was no kinetic resolution during these experiments. Anyhow, since all of the alcohol was consumed within minutes, we may believe that from these exploratory and qualitative studies there does not seem to be any problem with kinetic resolution. Thus, the derivatization of the particularly crowded alcohol **11** was over in less than 5 min and the $\Delta\delta$ on the P^{III} derivative is exceedingly high (7 ppm!).

Table 3. Derivatization of Primary Alcohols with Reagent 4c, Derived from Diamine 3c (unless otherwise noted)

alcohol	conditions[a] S: solvent B: base A: diamine	^{31}P NMR[b] chem shift ($\Delta\delta$) pIII	^{31}P NMR[b] chem shift ($\Delta\delta$) PS	^{31}P NMR[b] chem shift ($\Delta\delta$) PSe	^{1}H NMR	^{13}C NMR	^{19}F NMR chem shift	ee% found (known)
 16	S: A B: 1 A: (*S,S*)3c	139.657 139.522 (0.135)	83.119 (–)	82.431 (–)	–	–	–	racemic
 17	S: C B: 2 A: (*R,R*)3c	141.370 (–)	83.736 (–)	83.601 83.537 (0.064)	–	–	p^{III} = 0.187, 0.122, 0.106 PSe = 0.033	racemic
 18	S: A B: 2 A: (*S,S*)3c	140.061 (–)	–	83.794 (–)	PSe (–)	PSe (–)	PSe = 0.150, 0.052	racemic
 19	S: A B: 1 A: (*S,S*)3c	141.231 (–)	83.741 (–)	–	–	–	–	racemic
 20	S: A B: 2 A: (*S,S*)3c	139.993 *139.791* (0.202)	83.185 *83.121* (0.064)	83.296 *83.231* (0.065)	PS (–)	PS (–)	p^{III} = *0.013, 0.000*, –0.056, –0.082 PS = 0.196, 0.127, *0.166*	59.8[f] (60)
 21	S: A B: 2 A: (*S,S*)3c	139.646 (–)	83.101 (–)	83.202 (–)	–	–	–	racemic
 22	S: B B: 2 A: (*S,S*)3c	141.205 (–)	–	83.323 (–)	PSe (++)	PSe (–)	–	racemic
CH_3-$(CH_2)_9$-CH_2-CHD-OH 23	S: A B: 1 A: (*S,S*)3a		see text		pIII (+++) see Figure 1	–	–	30
 24	S: A B: 1 A: (*S,S*)3c	143.358 142.753 (0.605)	83.929 83.859 (0.070)	–	PS (–)	PS (–)	PS = 0.048, 0.042, –0.000 PSe = –0.002, –0.025	racemic
 25	S: A B: 3 A: (*S,S*)3c	*144.907* 144.002 (0.905)	–	*85.275* 84.974 (0.301)	–	–	–	95.1
 26	S: A B: 1 A: (*S,S*)3c	141.878 *141.130* (0.748)	*83.861* 83.716 (0.145)	–	PS (++)	PS (–)	pIII = 0.011 PS = 0.035, 0.000	60.2[f] (60)
 27	S: A B: 3 A: (*S,S*)3c	140.936 140.599 (0.337)	–	84.063 84.020 (0.043)	–	–	–	racemic
 28	S: A B: 3 A: (*S,S*)3c	*140.868* 140.465 (0.403)	–	–	–	–	–	60[d] (60)
 29	S: A B: 3 A: (*S,S*)3a	–	–	86.823 (–)	PSe (–)	PSe (–)	–	racemic

[a–f] Same footnotes as in Table 2.

Scheme 5



Cyanohydrin **12**, just as other cyanohydrins, is known to easily racemize in basic media.[12] Under our conditions, the P^{III} derivative was stable for at least 3 days (in the NMR tube) without any detectable racemization. Particularly noteworthy is the reaction of trimethylsilyl ether **13** with reagents **4**. Silyl ethers are known to react with PCl compounds,[13] and this property is quite useful for alcohols obtained directly as silyl ethers such as in the following reaction (Scheme 5). To our knowledge, this is the first direct chiral derivatization of such protected alcohols, which avoids the potential racemization in the hydrolysis step.

α-Hydroxy esters such as methyl lactate **14** do not racemize under the derivatization conditions. Finally, the case of ephedrine **15** will be discussed in the amine section; it should be pointed out that, under the conditions used, the amine functionality is protonated, as the hydrochloride, and therefore does not react with the phosphorus reagent **4c**.

In addition to the ^{31}P NMR spectra, the ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in many instances. In most cases excellent to good separation of diastereomeric signals were observed. By ^{1}H NMR, these diastereomeric signals were usually the CHO protons, the CH_3N protons, and the benzylic ArCHN protons. Depending on the structure of the alcohol, some other signals may also be differentiated. Care should be taken upon analysis of the ^{1}H NMR spectrum, as J_{P-H} coupling constants may be quite large and sometimes confusing. By ^{19}F NMR, two signals are observed for each diastereomer, due to the nonequivalence of each aromatic group (one is cis to the RO- group, in the diazaphospholidine ring, and the other trans). It is better not to use $PhCF_3$ as an internal standard (or, if necessary, to add it after the first ^{19}F spectrum is recorded) since it often interferes with the desired signals. However, ^{19}F

(12) Ide, W. S.; Buck, J. S. *Org. React.* **1948**, *4*, 269–304.
(13) Fertig, J.; Gerrard, W.; Herbst, H. *J. Chem. Soc.* **1957**, 1488–1492.

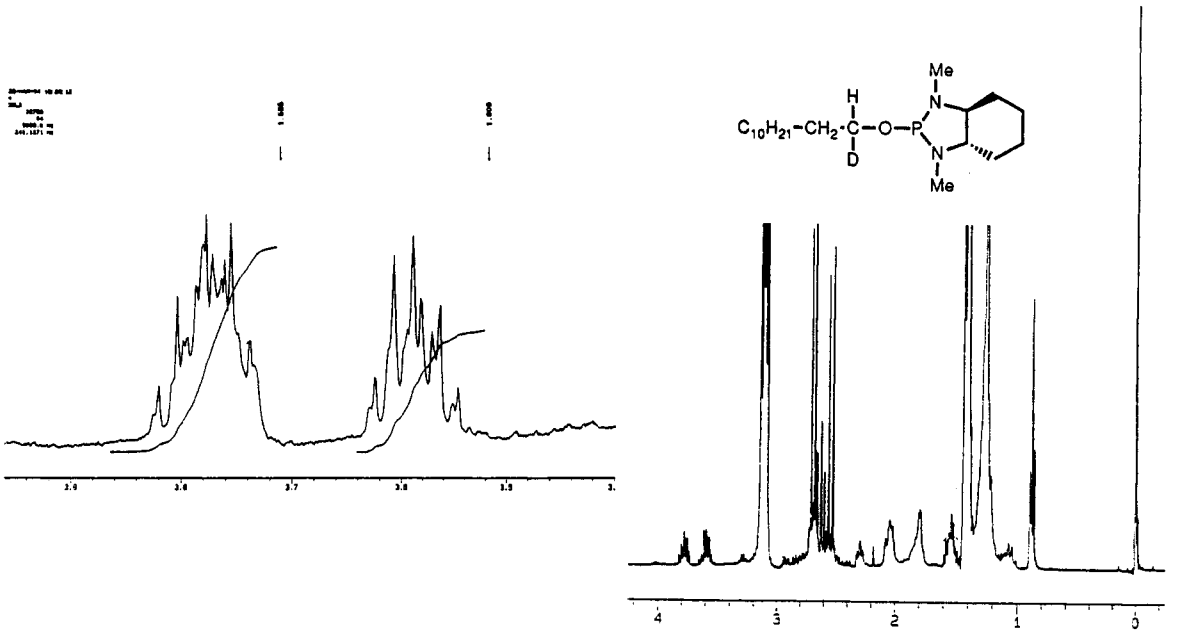


Figure 1. ^{1}H NMR spectrum (400 MHz) of racemic α-deuterated dodecanol (**23P** derivative, triethylamine as base). The enlargement corresponds to an enantiomerically enriched sample.

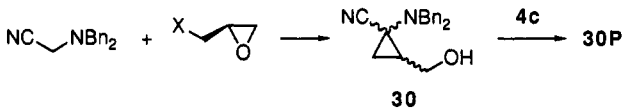
NMR has the same advantage as ^{31}P NMR: no signals other than those of the derivatizing agent are seen. The salient feature associated with the combination of all these NMR techniques lies in the fact that all these different measurements converge to an average enantiomeric composition giving a very accurate and precise value of the enantiomeric composition.

Primary Alcohols. No particular problems were encountered with a variety of primary alcohols (see Table 3). All α-substituted as well as β-substituted examples show usually baseline separation, either on the **P^{III}** or on the **PS** (or **PSe**) derivatives, or both. Exceptions include alcohol **19** which was correctly analyzed with our previous reagent **1**, the γ-substituted alcohol **21** where the chirality is too far away, and the α-substituted alcohol **18** where the differentiation of an Et from a Bu group is difficult.

α-Deuterated benzyl alcohol **22** gives a single signal by ^{31}P NMR; however, the two diastereotopic benzylic protons are clearly distinguished by ^{1}H NMR, exactly as in our previous study with reagent **1**.[4] A particularly spectacular case is α-deuterated 1-dodecanol **23** which was analyzed only by ^{1}H NMR on the **P^{III}** derivative with diamine **3a**. As shown in Figure 1, the two diastereotopic α-protons are extraordinarly well separated ($\Delta\delta > 0.2$ ppm) and integration of the two signals on an enantiomerically enriched sample allows the determination of its ee. With diamine **3b** or **3c** a slight overlap of the signals does not allow such an analysis. It should be recalled that such alcohols were analyzed previously by deuterium NMR or by a combination of MTPA esters *and* lanthanide shift reagents.[14]

Acetals (**26**) as well as epoxides (**24** and **25**) have been tested and no cleavage of these functionalities was observed. A series of α-allenic alcohols (**27** and **28**) was also successfully examined. This class of alcohols is known to be rather difficult to analyze, due to the axial chirality of such compounds.[15] However the non-allenic alcohol **29**, also having axial chirality, could not be analyzed.

Scheme 6



30

As stated in the previous study,[4] our method not only allows the determination of the enantiomeric purity but also the diastereomeric composition of a mixture. This possibility was recently used successfully by Aitken *et al.*[16] when all other ways failed. By ^{31}P NMR, four signals, two for each diastereomer and two for each enantiomer, were clearly distinguished (Scheme 6).

Tertiary Alcohols. Tertiary alcohols also react instantaneously with the in situ derivatizing reagent **4** (see Table 4). As with our previous reagent **1**, we did not observe any kinetic discrimination. Linalool (**33**) shows clearly two base line separated signals by ^{31}P NMR on both the **P^{III}** and the **PSe** derivatives. Even ^{19}F NMR gives acceptable separation of signals. However alcohol **31** could only be distinguished using diamine **3a** and only on the selenated derivative **PSe**. In our previous procedure, we have been unable to distinguish the diastereomers with the sulfurated derivative **PS**. This is clearly a situation where the advantages of selenation are highlighted.

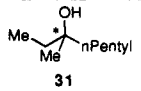
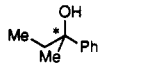
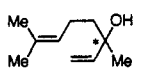
The tertiary benzylic alcohol **32** was more problematic, as some elimination (up to 5–20%) products (**34** and **35**) were detected (Scheme 7). The observed ^{31}P signal corresponds to the phosphorus compound **34**. When the reaction was performed with dimethyl(phenyl)carbinol (**36**), α-methylstyrene (**37**) was obtained, identified by comparison with an authentic sample.

(14) (a) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274–275. (b) Reich, C. J.; Sullivan, G. R.; Mosher, H. S. *Tetrahedron Lett.* **1973**, 1505–1508. (c) Parker, D. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 83–85. (d) Schwab, J. M. *J. Am. Chem. Soc.* **1983**, *103*, 1876–1878.

(15) See, for example, for alcohol **28**: Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083–1088.

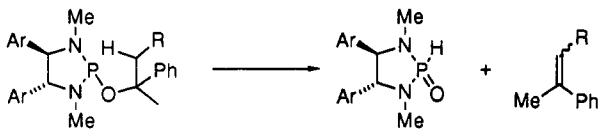
(16) Aitken, D. J.; Vergne, F.; Phimmanao, A. S.; Guillaume, D.; Husson, H.-P. *Synlett* **1993**, 599–601.

Table 4. Derivatization of Tertiary Alcohols with Reagent 4c, Derived from Diamine 3c (unless otherwise noted)

alcohol	conditions[a] S: solvent B: base A: diamine	^{31}P NMR[b] chem shift ($\Delta\delta$) **pIII**	^{31}P NMR[b] chem shift ($\Delta\delta$) **PS**	^{31}P NMR[b] chem shift ($\Delta\delta$) **PSe**	^{1}H NMR	^{13}C NMR	^{19}F NMR chem shift	ee% found (known)
 **31**	S: C B: 2 A: (*R,R*)**3c**	129.898 (-)	73.562 (-)	71.257 (-)	-	-	-	racemic
	S: A B: 3 A: (*R,R*)**3a**	-	-	73.967[g] 73.914 (0.053)	PSe (-)	PSe (-)	-	racemic
 **32**	S: C B: 2 A: (*S,S*)**3c**	131.782 130.705 (1.077)	73.698[g] (-)	71.208[g] 71.073 (0.135)	-	-	-	racemic
 **33**	S: A B: 2 A: (*S,S*)**3c**	131.648 131.176 (0.472)	-	71.343 71.141 (0.202)	-	-	pIII = 0.137, 0.128, 0.067	racemic

[a-f] Same footnotes as in Table 2. [g] Inverse technique used (addition of Se prior to the alcohol). See text.

Scheme 7



R = Me **32P** **34** R = Me **35**
R = H **36P** R = H **37**

Upon close examination, it was found that this elimination was not a fast process, being completed only after 15–30 min. The elimination problem could be circumvented by using the variation of our standard protocol. S_8 or Se_8 was added to CDA **4** in the NMR tube *prior* to the addition of alcohol **32** and, thus, the formed derivative **32P** is immediately trapped as the sulfurated or selenated derivative **32PS** or **32PSe**, without any detectable elimination product **35** (see Scheme 4).

Propargylic Alcohols. Propargylic alcohols were a class of compound which could not be analyzed with reagent **1**.[4] As soon as the trivalent phosphorus derivative **2P** was formed, a *stereoselective* [2,3] sigmatropic shift afforded the corresponding allene.[17] In this reaction, 1 equiv of Me_2NH was also formed and this dimethylamine molecule added to the allenic system to destroy the axial chirality.[18] By using our new procedure (see Table 5), where no dimethylamine is formed, the allene is stable and analysis can be performed on this material (see Scheme 8).

This [2,3] sigmatropic shift is not always a fast process and, for example, in the case of the C-silylated propargylic alcohol **41** the trivalent phosphorus derivative is stable enough to be analyzed and then sulfurated. On the other hand, the reverse process variation (*vide supra*) can be applied to the case of this class of alcohols. Thus, when the propargylic alcohols **39** or **40** were added to reagent **4**, *in the presence of Se powder*, the formation of the **PSe** derivative is faster than the [2,3] sigmatropic shift (see Scheme 4).

Polyols and Amino Alcohols. 1,2 and 1,3 Diols were another class of alcohols which could not be analyzed by our previous method. The problem dealt with the intramolecular reaction of the formed trivalent phosphorus derivative which cyclized to form preferentially a dioxaphospholidine or a spirophospholidine ring.[6] The phosphorus atom now becomes a new stereogenic center, giving multiple signals by ^{31}P NMR. By contrast, with the more reactive *in situ* reagent **4**, the intermolecular reaction is faster than the intramolecular cyclization and the bis-derivatized compound is formed more rapidly (Scheme 9).

Dissymmetric racemic diols **43** and **44** (see Table 6) gave four sets of signals, each phosphorus atom being sensitive to the α or β stereogenic center. On the other hand, the C-2 symmetrical diol **45** gave only two signals. Clearly, in this case, as well as in the case of propargylic alcohols, the new protocol allows, now, the determination of their enantiomeric excess. Besides MTPA esters and chiral lanthanide shift reagents,[2] the best previous method to determine the ee of diols was through derivatization with camphanylboronic acid, and analysis by ^{13}C NMR.[19]

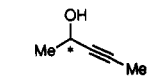
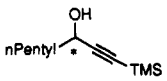
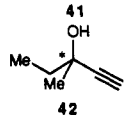
Atropisomers of phenolic-type biaryls have been successfuly tested without modification of our general procedure. Thus, binaphthol **46** could be analyzed (both phenolic functionalities were derivatized) and, by ^{31}P NMR, the two diastereomeric signals were clearly seen either on the $\mathbf{P^{III}}$ or the **PS** and **PSe** derivatives. ^{1}H NMR of these derivatives also allow a very accurate analysis; the CHN benzylic protons and the NCH_3 protons are very well distinguished. Additional examples have been done elsewhere.[20]

Ephedrine **15** could also be derivatized at both functional groups (under the conditions described in the amine section) and, using an enantiomerically enriched diamine **3c** (rather than optically pure material), four signals were obtained by ^{31}P NMR.

Amines. The higher reactivity of the *in situ* reagent **4** allows an extention of the range of its uses. The enantiomeric purity of primary or secondary amines can be determined by a variety of methods,[21] among which the derivatives as MTPA amides take an important place.[2] Recently, phosphorus derivatization reagents were also

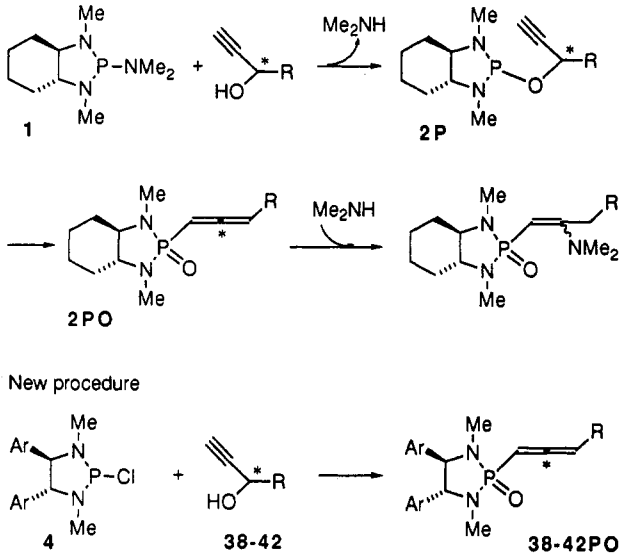
(17) (a) Landor, S. R. *The Chemistry of the Allenes*; Academic Press: London, 1982. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley: New York, 1984.
(18) Sturtz, G. *Bull. Soc. Chim. Fr.* **1967**, 1345–1353.
(19) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1988**, *29*, 6063–6066.
(20) Prof. A. I. Meyers informed us of his successful use of our new protocol on various biphenols.
(21) (a) Michalik, M.; Döbler, C. *Tetrahedron* **1990**, *46*, 7739–7744. (b) Parker, D.; Taylor, R. J. *Tetrahedron* **1987**, *43*, 5451–5456. (c) Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, *54*, 5826–5828. (d) Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. *J. Org. Chem.* **1988**, *53*, 5335–5341. (e) Calmes, M.; Daunis, Elyacoubi, R.; Jacquier, R. *Tetrahedron:Asymmetry* **1990**, *1*, 329–334.

Table 5. Derivatization of Propargylic Alcohols with Reagent 4c, Derived from Diamine 3c (unless otherwise noted)

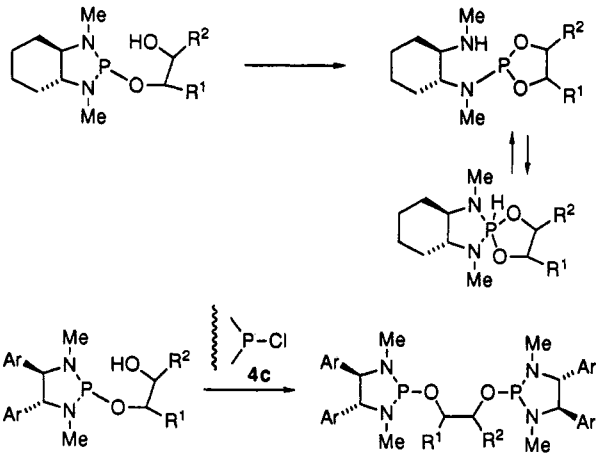
alcohol	conditions[a] S: solvent B: base A: diamine	^{31}P NMR[b] chem shift (Δδ) pIII	^{31}P NMR[b] chem shift (Δδ) PO	^{31}P NMR[b] chem shift (Δδ) PS or PSe	^{1}H NMR	^{13}C NMR	^{19}F NMR chem shift	ee% found (known)
 38	S: B B: 3 A: (*R,R*)3c	–	27.931 27.850 (0.081)	–	–	–	–	racemic
 39	S: A B: 3 A: (*R,R*)3c	–	–	**PSe**[g] 84.400 83.794 (0.606)	PSe (+++)	–	–	racemic
 40	S: A B: 1 A: (*S,S*)3c	–	31.902 31.859 (0.043)	**PSe**[g] 82.986 82.650 (0.336)	PSe (++)	–	–	racemic
 41	S: B B: 3 A: (*R,R*)3c	143.089 138.176 (4.913)	–	**PS** 83.794 83.054 (0.740)	PS (+)	PS (–)	–	racemic
 42	S: A B: 1 A: (*R,R*)3c	–	31.229 30.750 (0.479)	–	PO (+)	–	**PO** = 0.168, 0.145, 0.086	racemic

[a-f] Same footnotes as Table 2. [g] Inverse technique used (addition of Se prior to the alcohol). See text.

Scheme 8



Scheme 9



disclosed.[3d 22] We now report that the same procedure which allows the derivatization of alcohols is applicable, with slight modifications, to the above classes of amines.

During the *in situ* preparation and derivatization procedure, the formed HCl is trapped as the hydrochloride of a tertiary amine. When this amine is not sufficiently basic (*N*-methylimidazole or *N,N*-diethylaniline), the primary or secondary amine to be analyzed may form hydrochloride, which does not react further (Scheme 10). At this point, addition of a more basic amine, such as triethylamine, reverses the equilibrium and the primary or secondary amine to be analyzed is able to react with reagent 4 (see Table 7). A striking example is illustrated with ephedrine 15: before the addition of triethylamine, only the alcohol derivative is formed (see Table 2) whereas *both* the alcohol *and* the amine functionalities are derivatized upon addition of triethylamine (see Table 6).

Our method was succesfully applied to α-amino esters, an important class of chiral compounds. For practical reasons only the **PSe** derivative was formed using the reverse technique variation (*vide supra*). The derivatives formed from valine **49PSe** and tryptophan **50PSe** could be analyzed not only by ^{31}P NMR but also by ^{1}H NMR where the diastereomeric MeO groups of the ester functionality were perfectly separated.

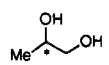
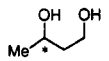
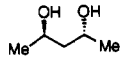
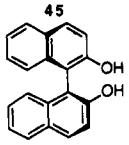
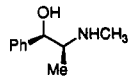
Thiols. The same thiols as in our previous study were tested under the standard derivatization conditions (Table 7). In both cases the separation of the ^{31}P signals was excellent. With the secondary thiol **52**, ^{1}H NMR of the **PSe** derivative clearly showed differentiated sets of signals.

Conclusion

The new *in situ* protocol, described herein, is not only very efficient but it also allows a *very fast* derivatization into diastereomeric phosphorus products for the determination of enantiomeric excesses. The scope of functional groups amenable to be analyzed by this technique include, now, all types of alcohols and phenols, as well as amines and thiols. It should be pointed out, again, that we never observed any kinetic discrimination during the derivati-

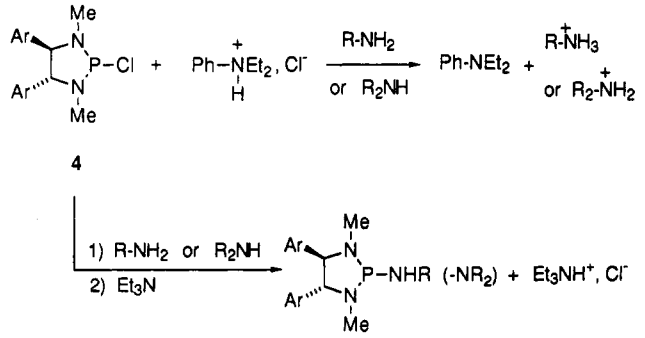
(22) (a) Feringa, B. L.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 5484–5486. (b) Hulst, R.; de Vries, N. K.; Feringa, B. L. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1092–1093.

Table 6. Derivatization of Diols (and amino alcohol) with Reagent 4c, Derived from Diamine 3c (unless otherwise noted)

alcohol	conditions[a] S: solvent B: base A: diamine	^{31}P NMR[b] chem shift ($\Delta\delta$) pIII	^{31}P NMR[b] chem shift ($\Delta\delta$) PS	^{31}P NMR[b] chem shift ($\Delta\delta$) PSe	^{1}H NMR	^{13}C NMR	^{19}F NMR chem shift	ee% found (known)
 43	S: C B: 3 A: (*R*,*R*)**3c**	140.195 139.993 (0.202) 139.522 139.051 (0.471)	84.332 84.292 (0.040) 82.582 82.488 (0.094)	84.736 84.661 (0.075) 82.650 82.537 (0.113)	–	–	–	racemic
 44	S: A B: 2 A: (*S*,*S*)**3c**	139.388 139.302 (0.086) 138.782 138.545 (0.237)	81.753 81.640 (0.113) 80.286 80.092 (0.194)	84.265 84.063 (0.202) 82.313 (–)	PS (++)	PS (–)	PS = 0.112, 0.103, 0.091, 0.031, 0.010, 0.000	racemic
 45	S: B B: 3 A: (*R*,*R*)**3c**	140.936 140.734 (0.212)	–	80.025 (–)	–	–	–	racemic
 46	S: A B: 3 A: (*S*,*S*)**3c**	*139.053* 138.851 (0.202)	*80.093* 78.747 (1.346)	80.833 79.286 (1.548)	PS (+++)	PS (+)	PSe = 0.166, *0.109*, 0.070	32.3[c] (30)
 15	S: A B: 2 + 1 A: (*S*,*S*)**3c**	*143.291* 139.993 (3.298) *128.215* 126.196 (2.019)	81.842 (–) 79.890 (–)	–	–	–	pIII = *0.171*, 0.132, *0.096*, 0.015 PSe = *0.142*, 0.114, *–0.020*, –0.075	60[f] (60)

[a-f] Same footnotes as Table 2.

Scheme 10



zation process. Although this study was mainly done with the fluorinated diamine **3c**, it is noteworthy that any other chiral C_2 diamine (the ones depicted herein as well as any new one) may be used, particularly diamine **3a** for its larger discrimination of diastereomeric signals. Besides ^{31}P NMR, the ^{1}H, ^{13}C, and ^{19}F NMR spectra may be recorded, giving additional support to the first analysis and confirmation of the enantiomeric excess. Finally, except for PCl_3, which is handled by microsyringe, no toxic materials are used.

Experimental Section

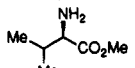
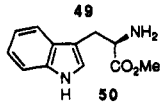
^{31}P NMR spectra were recorded at 36.22 MHz, ^{19}F at 234.16 MHz, ^{13}C at 22.5, 50.25 or 100.5 MHz, and ^{1}H at 200 or 400 MHz. Chemical shifts are expressed as δ values with TMS or CF_3Ph (for ^{19}F NMR) as internal standard, or H_3PO_4 as external standard. Optically pure chiral diamines **3a–3c** may be purchased from Aldrich, Janssen, or Fluka, or may be prepared according to described procedures: ref 4b for **3a**, ref 9 for **3b**, and ref 10 for **3c**. Phosphorous trichloride is distilled and stored on 4-Å molecular sieves. Triethylamine, *N*-methylimidazole, *N*,*N*-diethylaniline, and pyridine were distilled and stored on 4-Å molecular sieves. Commercial $CDCl_3$ and C_6D_6 are used as received, and CH_2Cl_2 is distilled on CaH_2 and stored over 4-Å molecular sieves. Sulfur and selenium powder are purchased from Aldrich and used as received. All NMR experiments were carried out in well dried ∅ 5-mm NMR tubes equipped with rubber septa.

Preparation of Reagent 4. Into a dried NMR tube were placed the chiral diamine **3a**, **3b**, or **3c** (0.15 mmol), and $CDCl_3$ (800 μL) or CH_2Cl_2 (800 μL and a few drops of $CDCl_3$ for locking). The tube was shaken until complete dissolution. The base (0.75 mmol) (usually *N*,*N*-diethylaniline or *N*-methylimidazole; triethylamine or pyridine in special cases) was added with a microsyringe, followed by slow addition of PCl_3 (12.8 μL, 0.15 mmol) also with a microsyringe. The NMR tube was shaken and an exothermic reaction took place. The in situ solution of reagent **4** was ready for further use. A ^{31}P NMR spectrum can be recorded to check the formation of the reagent. NMR data of **4** ($CDCl_3$, pyridine as base): ^{1}H NMR 7.4–7.6 (m, 8H), 4.27 (d, 2H, J_{HP} = 6 Hz), 2.54 (d, 6H, J_{HP} = 14.8 Hz); ^{13}C NMR 137.6, 131.1, 130.8 (q, J_{CF} = 33 Hz),129.2, 125.0, 124.3 (arom), 123.4 (q, CF_3, J_{CF} = 272 Hz), 31.6 (d, ArCHN, J_{CP} = 20.3 Hz), 31.5 (d, NCH_3, J_{CP} = 20.3 Hz); ^{31}P NMR 173.11; ^{19}F NMR –0.036.

Normal Procedure for Derivatization of Alcohols, Phenols, and Thiols. Into the above NMR tube where reagent **4** was prepared (0.15 mmol) was added the alcohol or the thiol (0.1 mmol; for diols or biphenols: 0.05 mmol) to be analyzed. The NMR tube was shaken and the ^{31}P spectrum was recorded. Spectra of other nuclei (^{1}H, ^{13}C, and ^{19}F) can also be recorded with the same tube.

Sulfuration and Selenation. After the first spectra were recorded, S_8 (32 mg; 1 mmol) or Se_8 powder (79 mg; 1 mmol) was added in the NMR tube. This tube was shaken, and excess S_8 or Se_8 was deposited in the bottom of the tube. Usually the solid deposit did not disturb the NMR analysis. However, if this was the case, the supernatant liquid was filtered through a wool plug and then transferred into another NMR tube. The **PS** or **PSe** derivatives are stable to air and may be handled conveniently under the hood. ^{31}P (as well as other nuclei) NMR spectra may then be recorded. If the base disturbs the ^{1}H or the ^{13}C analysis, the contents of the NMR tube are partitioned in 50 mL of Et_2O and 50 mL of aqueous 0.5 N HCl. The organic phase was dried (Na_2SO_4) and then evaporated and analyzed by NMR. Alternatively, the contents of the NMR tube were flash chromato-

Table 7. Derivatization of Amines and Thiols with Reagent 4c, Derived from Diamine 3c (unless otherwise noted)

amines/thiols	conditions[a] S: solvent B: base A: diamine	^{31}P NMR[b] chem shift ($\Delta\delta$) **pIII**	^{31}P NMR[b] chem shift ($\Delta\delta$) **PS**	^{31}P NMR[b] chem shift ($\Delta\delta$) **PSe**	^{1}H NMR	^{13}C NMR	^{19}F NMR chem shift	ee% found (known)
 **47**	S: B	111.322	–	68.650	PSe	PSe	–	39.8
	B: 2 + 1	*110.514*		*67.843*	(+++)	(++)		(40)
	A: (*R*,*R*)**3c**	(0.808)		(0.807)				
 **48**	S: B	124.446	–	80.092	PSe	PSe	–	60
	B: 2 + 1	*123.167*		*79.828*	(++)	(–)		(60)
	A: (*R*,*R*)**3c**	(1.279)		(0.264)				
 **49**	S: A	–	–	72.151[g]	PSe	PSe	PSe = 0.240, *0.109*, 0.074, *0.019*	27.8
	B: 3 + 1			*70.737*	(+++)	(+++)		(28)
	A: (*S*,*S*)**3c**			(1.414)				
 **50**	S: A	–	–	70.468[g]	PSe	PSe	PSe = 0.220, 0.103, *0.074*	36.4
	B: 3 + 1			*69.795*	(++)	(–)		(36.6)
	A: (*S*,*S*)**3c**			(0.673)				
 **51**	S: B	170.213	–	88.371	PSe	PSe	–	racemic
	B: 3	169.877		88.101	(–)	(–)		
	A: (*R*,*R*)**3c**	(0.336)		(0.270)				
 **52**	S: B	165.906	–	86.755	PSe	PSe	–	racemic
	B: 3	164.762		86.082	(+++)	(+)		
	A: (*R*,*R*)**3c**	(1.144)		(0.673)				

[a-f] Same footnotes as Table 2. [g] Inverse technique used (addition of Se prior to the amine). See text.

graphed through a short pad of silica gel, with cyclohexane/EtOAc as eluent (the choice of the mixture of solvents was determined after TLC assay; usually 90/10 to 95/5).

Reverse Technique Variation. Into the NMR tube containing the reagent 4 was *first* added S_8 (32 mg; 1 mmol) or Se_8 powder (79 mg; 1 mmol) and immediately after the alcohol (0.1 mmol) to be analyzed. The tube was vigorously shaken, the solid was left to deposit, and the NMR spectra were recorded as above.

Procedure for Amines. Into the above NMR tube containing the reagent 4 was added first the amine to be analyzed (0.1 mmol) and then Et_3N (104 μL, 0.75 mmol). The tube was shaken and the ^{31}P spectrum recorded. Sulfuration or selenation were done as described above for the alcohols.

Alternatively, the inverses technique variation can be used, and this procedure is particularly recommanded for α-amino esters. Thus, S_8 (32 mg; 1 mmol) or Se_8 powder (79 mg; 1 mmol) was first added to the NMR tube containing reagent 4, followed by addition of the amine (0.1 mmol) and, then, addition of Et_3N (104 μL, 0.75 mmol).

Acknowledgment. The authors wish to thank Dr. R. Burgada for his helpful comments in organophosphorus chemistry. We are grateful to Rhône-Poulenc Co. for a grant to S.M. We also aknowledge Dr. D. Aitken, I. Aujard, Dr. J. P. Demoute, Dr. F. Dumas, Dr. J. C. Fiaud, Dr. R. Gosmini, S. Klein, I. Koenig, Dr. C. Larpent-Petrignani, Dr. I. Marek, and Dr. R. Snowden for providing samples of alcohols to be analyzed.

Supplementary Material Available: Copies of the NMR spectra (^{31}P for all compounds; for ^{19}F, ^{1}H, and ^{13}C see Tables 2–7 for availability; 58 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.