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α-Phenylethylamine based chiral phospholidines; new agents for the determination of the enantiomeric excess of chiral alcohols, amines and thiols by means of ^{31}P NMR

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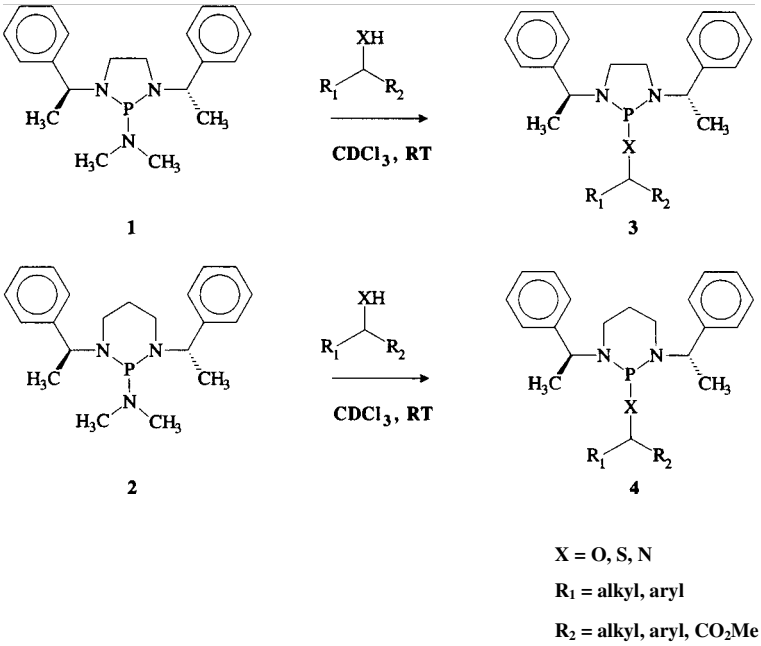
Abstract: The synthesis and application of two new trivalent phosphorus derivatizing agents, based upon (*S*)-α-phenylethylamine, for the enantiomeric excess determination of alcohols, amines and thiols using ^{31}P NMR, is presented.

The tremendous effort in asymmetric synthesis and the rapidly increasing use of enantiomerically pure compounds as chiral building blocks, auxiliaries or chiral ligands require the development of fast and accurate methodologies for the determination of the enantiomeric composition[1]. The enantiomeric ratio of various classes of compounds can be determined by a number of analytical techniques, although chromatographic and NMR methods are routinely most frequently used[2,3]. Despite the rapid progress that has been made in the development of resolution on GC and HPLC[4], NMR is an attractive technique as it is usually fast and relatively simple to perform[5]. Moreover, NMR offers the possibility to measure various nuclei. The enantiomeric excess (*e.e*) determination by means of NMR can be performed using chiral lanthanide shift reagents[6], chiral complexing agents[7] and through the use of chiral non-racemic derivatizing agents[8]. Furthermore, efficient methods using achiral derivatizing agents, based upon Horeau's principle[9], were developed in our laboratory for the determination of the enantiomeric excess of amines, alcohols and thiols[10].

More recently, ^{31}P NMR methods have become very popular due to the attractive features of this nucleus in the analysis of chiral compounds. Several derivatizing agents have been developed in our group, among which are trivalent and pentavalent *achiral* phosphorus reagents[10] like PCl_3 or $MePOCl_2$ and *chiral* phosphoric acid chlorides[11] or phosphorinane reagents[12]. Trivalent phosphorus reagents based on 1,2-N,N'-(dimethylamino)-cyclohexane probably give the most pronounced diastereomeric shift dispersion in the decoupled ^{31}P NMR spectra of their derivatives with chiral substrates, as was shown by Alexakis and co-workers[13]. The lack of availability of the chiral cyclohexyl-based diamines and the sensitivity of the derivatizing reagents towards hydrolysis and oxidation in practice, urged us to

develop alternative chiral phospholidine based derivatizing agents.

We now wish to report a simple and efficient ^{31}P NMR method for the *e.e.* determination of chiral alcohols, amines, amino acid esters, thiols and α-thiol acids and α-thiol acid esters, based on new chiral derivatizing agents **1** and **2** (Scheme **1**).

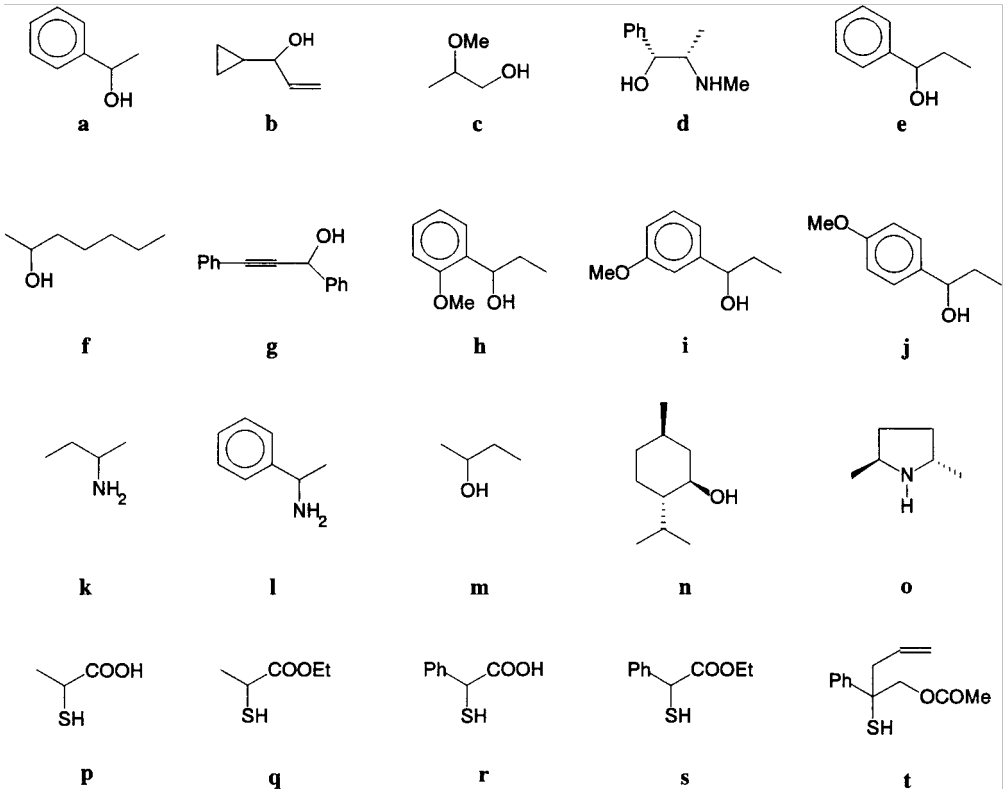


Scheme 1

The *C2*-symmetrical chiral reagents **1** and **2** are readily obtained from enantiomerically pure (*S*)-α-phenylethylamine via reaction with 1,2-dichloroethane or 1,3-dichloropropane [14] in 62 and 84 % yields, respectively. Subsequent diamine exchange with hexamethylphosphorus triamide (*HMPT*) in benzene or chloroform affords nearly quantitatively reagents **1** and **2** as air stable, colourless oils, that are purified by means of column chromatography. Moreover, the reagents **1** and **2** appear to be quite resistant towards moisture and can be stored as such or as a stock solution for at least 6 months.

The diastereomeric derivatives **3** and **4** are quantitatively prepared by amine exchange of the dimethylamine moiety in **1** or **2**, by reaction with alcohols, amines or thiols in benzene-d_6 or $CDCl_3$ at room temperature in an NMR tube (Scheme **1**). The decoupled ^{31}P NMR spectra of these derivatives are obtained directly without the need of further purification. The derivatives of type **3** or **4** afford excellent diastereomeric peak separation in the decoupled ^{31}P NMR spectra, allowing accurate integration and quantitative determination of the diastereomeric ratios. ^{1}H NMR analysis might also be used although the spectra are much more complex due to *P-H* and *H-H* coupling. Analysis by ^{31}P NMR has the great

advantage that no signals other than two singlets due to the diastereomeric derivatives **3** and **4** are observed in the spectra. In scheme **2** several of the chiral alcohols, amines and thiols that were analyzed using the new derivatizing agents **1** and **2** are shown. The results of the NMR measurements with the diastereomeric derivatives **3** and **4** are given in tables **1** and **2**, respectively.



Scheme 2 Representative alcohols, amines and thiol acid derivatives used for *e.e.* determination. The indices are also used in tables **1** and **2**.

As can be seen, sufficient diastereomeric shift dispersion is obtained in all the described cases, although large differences were found for the different chiral substrates. In fig. **1** the decoupled ^{31}P NMR spectra are shown of reagent **2** coupled to racemic and enantiomerically pure (-)-*cis*-exo-3-(1-azetidinyl)isoborneol.

It is possible to couple several unprotected amino acids under phase transfer conditions (solid phase-benzene-d_6), although only 20 % conversion was reached. Therefore, the new derivatizing agents **1** and **2** appear not to be particularly suitable for the enantiomeric excess determination of unprotected amino acids, although no kinetic resolution was observed and accurate *e.e.*'s were determined after partial conversion of a number of amino acids.

Substrate	δ(ppm)[a]	$\Delta\delta$(ppm)	ratio
d,l-Phe	96.9	0.49	49.5:50.5
d,l-Ala	97.0	0.45	49.5:50.5
d,l-PG[b]	122.5	0.19	49.5:50.5
e	124.1	0.39	49:51
c	125.3	1.05	49.5:50.5
f	125.0	1.98	49.5:50.5
a	124.2	0.20	49:51
g	114.2	5.21	49.5:50.5
l	94.4	0.15	50:50
k	94.6	5.21	50:50
d,l-heptylamine	93.7	0.29	49.6:50.4
t	123.9	0.08	49.1:50.9
r	136.5	1.21	48.5:51.5[c]
	133.5	0.75	50:50
p[d]	134.3	0.68	43:57[c]
	128.9	0.53	44:56
s	136.8	0.56	50:50
q[d]	135.6	0.54	44:56

Table 1 ^{31}P NMR data of derivatives **3** of racemic alcohols, amines, α-thiol acids, the corresponding esters and amino acids recorded in $CDCl_3$ [L]= 0.1 M at 30 °C.
a) Average of both signals given.
b) PG is Phenylglycine.
c) The additional absorption is due to *P-O* bond formation.
d) Enantiomerically enriched product was used.

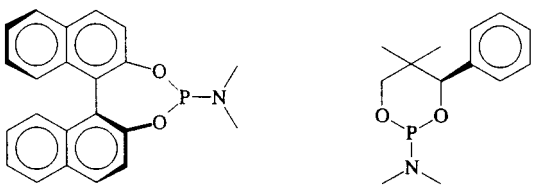
Several *e.e.* determinations were performed on partially enriched compounds. Comparison with the enantiomeric ratios as obtained by other methods, like the α-chloropropionylchloride[15] , chiral phosphorinane[12] and phosphoric acid chloride[11] methods, demonstrated that no racemization occurred during the formation of adducts **3** and **4** and that the enantiomeric ratios were in excellent agreement. Monitored reactions in benzene-d_6 showed that no kinetic resolution took place during the derivatization reactions. Furthermore, from the NMR studies it could be concluded that no side products are formed, except for the entries **g** in tables **1** and **2**. Using propargylic alcohol **g**, a rapid [2,3]-sigmatropic rearrangement was observed, in accordance with the observations by Alexakis and co-workers[13]. This reaction does, however, not affect the actual *e.e.* determination performed with the alcohol derivative.

Substrate	δ(ppm)[a]	$\Delta\delta$(ppm)	ratio
a	121.5	1.38	50:50
b	120.6	0.15	50:50
c	116.3	0.08	49.5:50.5
d	121.7	4.52	50:50
e	118.5	3.69	50:50
f	120.6	1.10	49.4:50.6
g	118.1	4.62	49.5:50.5
h	120.4	2.86	50:50
i	121.7	3.62	50:50
j	118.8	3.47	50:50
k	93.4	0.26	50:50
l	93.1	2.46	50:50
m	122.8	2.73	49.4:50.6
n	118.7	1.69	49.5:50.5
o	98.5	1.31	49.5:50.5
p	145.8	2.30	43:57[b]
q	152.5	0.23	42:58[b]
r	149.3	0.19	49.5:50.5
s	152.7	1.09	49.5:50.5
t	144.3	0.53	29.5:70.5[c]

Table 2 ^{31}P NMR data of derivatives **4** of racemic alcohols, amines and α-thiol acids and the corresponding esters recorded in $CDCl_3$ [L]= 0.1 M at 30 °C.
a) Average of both signals given.
b) Enriched compounds were used, *e.e.* unknown.
c) The *e.e.* determined by GC analysis was 41%; unpublished results, Hof, R.P., Kellogg, R.M., manuscript in preparation.

In order to compare chiral diamine based derivatizing agents **1** and **2** with chiral diol based reagents we also synthesized phosphorus derivatives **5** and **6** (Scheme **3**), based upon optically active bis-ß-naphthol and phencydiol [16], respectively.

Although these new chiral phosphorus compounds appear to be interesting chiral ligands[17], they are not very reactive towards nucleophilic attack by alcohols or amines. Reagent **5** did not react at all in benzene-d_6 (not even at elevated temperatures) with amines or alcohols or water as solvent !.



5 **6**

Scheme 3

The method for *e.e.* determination presented here compares favourably with other known methods, for instance broad scope and large diastereomeric shift dispersion of the derivatives are observed compared to pentavalent based phosphorus derivatizing methods. Besides these advantages, it should be emphasized that compared to previously reported trivalent phosphorus derivatizing agents, reagents **1** and **2** appear to be very resistant towards hydrolysis and oxidation. Moreover, these reagents are easily accessible and based upon inexpensive (*R*)- or (*S*)-α-phenylethylamine and are complementary to cyclohexane-diamine based phosphorus reagents.

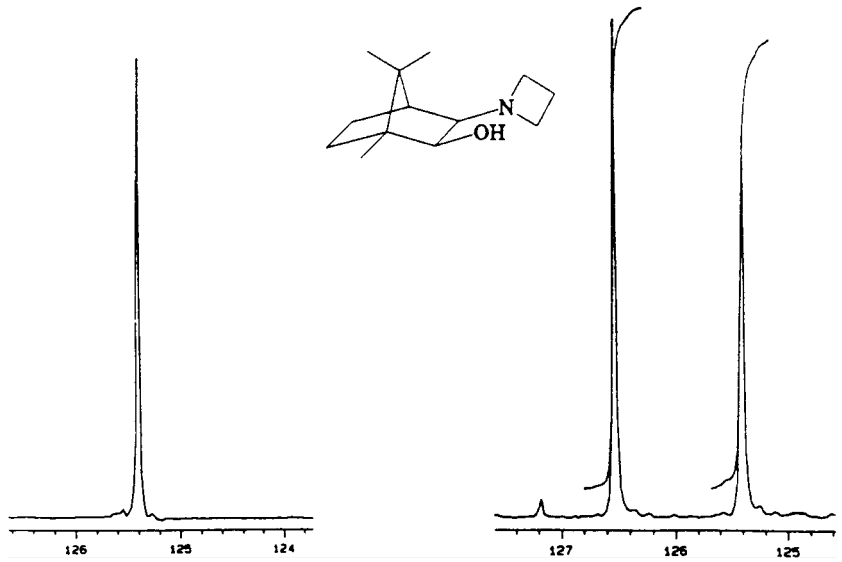


Figure 1 ^{31}P NMR spectra of derivatives of **3** of enantiomerically pure (*a*) and racemic (*b*) *cis*-exo-3-(1-azetidinyl)isoborneol.

In conclusion, the new chiral derivatizing agents **1** and **2** give excellent results in *e.e.* determinations by ^{31}P NMR, allowing broad structural variation in substrates, including certain unprotected amino acids.

Experimental

^{31}P, ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 instrument thermostatted at 30 °C. The chemical shifts are expressed relative to $CDCl_3$ for ^{1}H NMR (at δ 7.26 ppm) or ^{13}C NMR (at δ 76.91 ppm) and to $(NPCl_2)_3$ (at δ 19.91 ppm) for ^{31}P NMR spectra. All solvents were dried according to literature procedures. Deuterated solvents were dried over an Al_2O_3 (activity I) column just prior to use. (*S*)-α-Phenylethylamine ($[\alpha]_D^{20}$= -39 (neat)) was purchased from Janssen Chimica.

N,N'-bis(1-(S)-Phenylethyl)-1,2-ethylenediamine ***(7)*** was prepared analogous to the method described by Horner and Dickerhof[14].

(*S*)-α-Phenylethylamine (72.0 g, 059 mole) was heated to 100 °C and 1,2-dichloroethane (22.5 g, 0.23 mole) was added to the stirred solution over 2h. Stirring of the mixture was continued for another 16 h at 100 °C. The mixture was cooled to 60 °C and 150 mL of a saturated KOH solution was added with constant stirring. After cooling to room temperature the mixture was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were washed with brine and dried on Na_2SO_4. After evaporation of the solvent unreacted (*S*)-α-phenylethylamine was removed by vacuum distillation. The product was distilled (149-150 °C, 0.5 mm Hg)(lit[14] 110 °C, 0.02 mm Hg), yielding a colourless oil. Yield 37.51 g (0.15 mol), 62 %. $[\alpha]_D^{20}$= -69.4 (c 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.35 (d, ^{3}J= 7.45 Hz, 6H), 1.50 (s, br, 2H), 2.54 (m, 4H), 3.65 (q, ^{3}J= 7.45 Hz, 2H), 7.20-7.41 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 24.31 (CH_3), 47.22 (CH_2), 58.01 (CH), 126.40 (CH), 126.58 (CH), 127.99 (CH), 145.71 (C); HRMS calcd 268.194, found 268.193.

N,N'-bis(1-(S)-Phenylethyl)-1,3-propylenediamine ***(8)*** was prepared analogous to the method described by Horner and Dickerhof[14].

Yield 84 %, colourless oil after distillation (148-151 °C, 0.01 mm Hg)(lit[14] 115 °C, 0.02 mm Hg). $[\alpha]_D^{20}$= -66.3 (c 0.55, $CHCl_3$)(lit[14] $[\alpha]_D^{20}$= -66.4); ^{1}H NMR ($CDCl_3$): δ 1.38 (d, ^{3}J= 6.65 Hz, 6H), 1.43 (s, br, 2H), 1.62 (m, 2H), 2.52 (m, 2H), 3.78 (q, ^{3}J= 6.65 Hz, 2H), 7.21-7.40 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 24.28 (CH_3), 30.28 (CH_2), 46.32 (CH_2), 58.30 (CH), 126.42 (CH), 126.66 (CH), 128.31 (CH), 145.68 (C); HRMS calcd 282.210, found 282.210.

N,N'-bis(1-(S)-Phenylethyl)-1,2-ethylenediamino-N,N'-diaza-N'',N''-dimethylphospholidine ***(1)***

A mixture of bisamine **9** (2.50 g, 9.33 mmole), hexamethylphosphorus triamide (3.05 g, 18.7 mmole) and a catalytic amount of dry NH_4Cl was gently refluxed in 50 mL of dry benzene for 96 h. During the reaction a stream of N_2 was passed through the flask in order to remove the formed dimethyl amine. Benzene and excess $P(NMe_2)_3$ were removed under vacuum (0.01 mm) at 50 °C. The resulting oil was purified by chromatography over Al_2O_3 (benzene) and used as such. *Attempts to distill the products at temperatures above 75 °C were not successful, and sometimes resulted in violent explosions.* The product appeared to be 98 % pure, based upon ^{31}P and ^{1}H NMR data. Yield 2.86 g (8.40 mmole, 90 %), colourless oil. ^{1}H NMR (C_6D_6): δ 1.55 (d, ^{3}J= 7.20 Hz, 3H), 1.58 (d, ^{3}J= 7.18 Hz, 3H), 2.54 (d, $^{3}J_{PH}$= 9.00 Hz, 6H), 2.62 (m, 1H), 2.76 (m, 1H), 3.02 (m, 1H), 3.09 (m, 1H), 4:18 (dq, $^{3}J_{PH}$= 7.15 Hz, ^{3}J= 7.20 Hz, 1H), 4.23 (dq, $^{3}J_{PH}$= 7.15 Hz, ^{3}J= 7.18 Hz, 1H), 7.18-7.39 (m, 10H); ^{13}C NMR (C_6D_6): δ

21.34 (d, $^3J_{PC}$= 13.10 Hz, CH_3), 21.91 (d, $^3J_{PC}$= 12.09 Hz, CH_3), 37.13 (d, $^2J_{PC}$= 17.21 Hz, CH_3), 46.82 (d, $^2J_{PC}$= 7.05 Hz, CH_2), 47.13 (d, $^2J_{PC}$= 8.18 Hz, CH_2), 56.76 (d, $^2J_{PC}$= 22.16 Hz, CH), 57.12 (d, $^2J_{PC}$= 18.13 Hz, CH), 126.65 (CH), 126.69 (CH), 127.42 (CH), 127.93 (CH), 128.03 (CH), 128.03 (CH), 128.33 (CH), 145.29 (d, $^3J_{PC}$= 5.02 Hz, C), 145.43 (d, $^3J_{PC}$= 5.03 Hz, C); ^{31}P NMR (C_6D_6): δ 105.62; HRMS calcd 341.202, found 341.202.

N,N'-bis(1-(S)-Phenylethyl)-1,3-propylenediamino-N,N'-diaza-N'',N''-dimethylphospholidine ***(2)***

Prepared as described for **1**, using bisamine **8** (2.50 g, 8.86 mmole). Yield 2.99 g (8.42 mmole, 95 %) of **2**, colourless oil, 98 % pure. ^{1}H NMR (C_6D_6): δ 1.48 (d, ^{3}J= 6.05 Hz, 3H), 1.49 (m, 1H), 1.50 (d, ^{3}J= 5.90 Hz, 3H), 1.51 (m, 1H), 2.48 (d, $^3J_{PH}$= 9.05 Hz, 6H), 2.53 (m, 1H), 2.62 (m, 1H), 2.90 (m, 1H), 2.90 (m, 1H), 3.10 (m, 1H), 4.31 (dq, $^3J_{PH}$= 3.00 Hz, ^{3}J= 6.05 Hz, 1H), 4.45 (dq, $^3J_{PH}$= 4.10 Hz, ^{3}J= 5.90 Hz, 1H0, 7.18-7.42 (m, 10H); ^{13}C NMR (C_6D_6): δ 17.87 (d, $^3J_{PC}$= 6.05 Hz, CH_3), 19.75 (d, $^3J_{PC}$= 13.09 Hz, CH_3), 26.66 (CH_2), 38.48 (d, $^2J_{PC}$= 18.13 Hz, CH_3), 38.97 (d, $^2J_{PC}$= 5.03 Hz, CH_2), 40.81 (D, $^2J_{PC}$= 3.02 Hz, CH_2), 58.14 (d, $^2J_{PC}$= 38.27 Hz, CH), 59.82 (d, $^2J_{PC}$= 35.26 Hz, CH), 126.36 (CH), 126.44 (CH), 127.24 (CH), 127.92 (CH), 127.96 (CH), 128.00 (CH), 144.63 (d, $^3J_{PC}$= 9.06 Hz, C), 145.15 (d, $^3J_{PC}$= 5.04 Hz, C); ^{31}P NMR (C_6D_6): δ 107.41; HRMS calcd 355.218, found 355.217.

2,2'-O,O-(1,1'-Binaphtyl)-O,O'-dioxo-N,N-dimethylphospholidine ***(5)***

(+)-bis-ß-Napthol (2.00 g, 7.50 mmole), hexamethylphosphorustriamide (1.40 g, 9.50 mmole), 0.01 g NH_4Cl and 10 mL of dry benzene were heated to reflux for 12 h. The mixture was concentrated under reduced pressure affording an oil. The oil was stirred with 25 mL of dry ether, upon which crystals were formed spontaneously. The crystals were recrystallized from dry ether. Yield 2.65 g (7.38 mmole, 98 %). $[\alpha]_D^{20}$= 579 (c 0.06, $CHCl_3$); Mp[10-191 °C; ^{1}H NMR ($CDCl_3$): δ 2.75 (d, $^3J_{PH}$= 9.20 Hz, 6H), 7.25-8.00 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 35.81 (d, $^3J_{PC}$= 22.00 Hz, CH_3), 121.83 (d, $^3J_{PC}$= 1.01 Hz, CH), 123.02 (d, $^3J_{PC}$= 84.00 Hz, C), 124.53 (d, $^4J_{PC}$= 15.13 Hz, CH), 125.94 (s, CH), 126.78 (d, $^4J_{PC}$= 6.04 Hz, CH), 128.14 (d, $^7J_{PC}$= 6.01 Hz, CH), 130.01 (d, $^6J_{PC}$= 36.03 Hz, CH), 130.80 (d, $^4J_{PC}$= 47.38 Hz, C), 132.67 (d, $^3J_{PC}$= 2.01 Hz, C), 149.51 (d, $^2J_{PC}$= 38.31 Hz, C): ^{31}P NMR ($CDCl_3$): δ 148.72; Analysis calcd for $C_{22}H_{18}NO_2P$, C: 73.53, N: 3.90, P: 8.62, H: 5.05. Found C: 73.39, N: 3.74, P: 8.39, H: 4.97; HRMS calcd 359.107, found 359.108.

Procedure for derivatization with ***1*** *and* ***2***

Into an NMR tube is placed 0.11 mmole of **1** or **2**, 0.1 mmole alcohol, amine or thiol to be analyzed and 1.5 mL of $CDCl_3$ or C_6D_6. The mixture is stirred for 8 h, and a ^{1}H decoupled ^{31}P NMR spectrum is recorded directly at 30 °C. After the 8 h reaction time all the monitored reactions were completed.

Acknowledgement

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