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NEW CHIRAL STATIONARY PHASES CONTAINING A PHOSPHORUS ATOM AS AN ASYMMETRIC CENTRE

I. SYNTHESIS AND FIRST CHROMATOGRAPHIC RESULTS

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SUMMARY

New chiral stationary phases with an asymmetric phosphorus atom have been prepared for the resolution of enantiomers. The synthesis was carried out by bonding an optically active phosphine oxide to a microparticulate γ-aminopropylsilanized silica gel via two different spacers. A baseline resolution of N-(3,5-dinitrobenzoyl) derivatives of α-amino esters and amines into their antipodes in a normal-phase system is often achieved, with resolution factors up to 4.3. Assignment of absolute configuration of the chiral phosphine oxides was established by chemical correlation. Additionally, NMR studies were made on the chemical shifts induced specifically on each enantiomeric form of the phosphine oxides in presence of the chiral solvating agent (*R*)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine.

INTRODUCTION

In a previous paper[1] we showed that some optically active tertiary phosphine oxides could be resolved with a selectivity as high as 1.56 by liquid chromatography on chiral stationary phases (CSPs) obtained by the ionic or covalent grafting of N-(3,5-dinitrobenzoyl) derivatives of α-amino acids to a γ-aminopropylsilanized silica gel. The role of the chiral moiety of the CSP and the chiral solute can be reversed because of the formal reciprocity of the diastereomeric interactions. It was therefore expected that the covalent bonding of chiral tertiary phosphine oxides to a γ-aminopropylsilanized silica gel would lead to new CSPs able to resolve racemic N-(3,5-dinitrobenzoyl)-α-amino esters, because the chiral moiety of these CSPs has simultaneously π-donor, basic and acidic sites complementary to the above solutes. Further, such CSPs were expected to separate amines and amino alcohols after an appropriate derivatization with 3,5-dinitrobenzoyl chloride.

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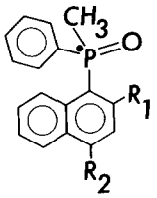
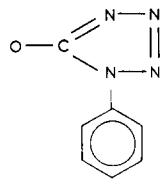
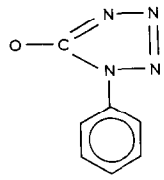
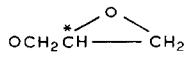
TABLE I

PHYSICAL DATA FOR THE CHIRAL TERTIARY PHOSPHINE OXIDES STUDIED



No.	R_1	R_2	*Absolute configuration**	$[\alpha]_D^{22}$ (°)**	*Melting point* (°C)
1	H	H	rac.	–	151–152
			S	+21	140–144
			R	−17.3	143–145
2	H	OCH_3	rac.	–	199–201
			S	−25.3	149–151
			R	+29.0	149–150
3	H	OH	rac.	–	221–223
			S	–	262–264
			R	–	250–252
4	H	$OCH_2CO_2C_2H_5$	rac.	–	127–129
			S	−26.6	152–153
			R	+33.7	154–156
5	H	OCH_2CO_2H	rac.	–	278–281
			–	–	–
			R	–	259–261
6	H		rac.	–	178–180
			S	+4.9	66–76
			–	–	–
7	OCH_3	H	rac.	–	130
			S	+124	131–132
			R	−120.5	130–132
8	OH	H	rac.	–	124–126
			S	–	–
			R	−23.0	179–182
9		H	rac.	–	211–213
			–	–	–
			R	+13.5	204–206
10	H		$(P)_{R,S}$–$(C)_{R,S}$	–	162–164
			$(P)_S$–$(C)_{R,S}$	−29.5	155–156

* The (*S*)-enantiomer was always the first eluted on the covalent Pirkle CSP (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine. The configuration refers to the phosphorus atom; rac. = racemate.

** Optical rotations were measured in methanol (c = 2) except for (*S*)-6 (c = 2, chloroform).

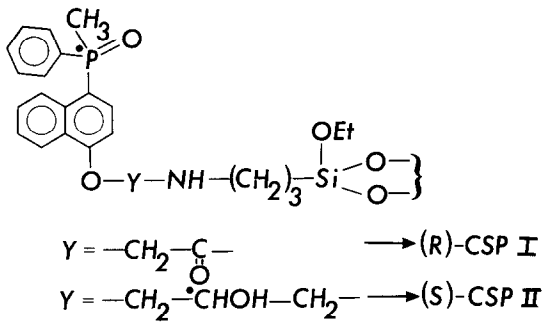


Fig. 1. Chiral stationary phases derived from chiral tertiary phosphine oxides.

(*R*)-CSP I and (*S*)-CSP II, containing an asymmetric phosphorus centre, were synthesized by grafting the chiral moieties (*R*)-5 and (*S*)-10 (Table I), respectively, to a γ-aminopropylsilanized silica gel (Fig. 1).

Preliminary chromatographic results obtained from some N-(3,5-dinitrobenzoyl) derivatives of α-amino esters and amines have shown great promise.

The assignment of the absolute configuration of (*R*)-5 and (*S*)-10 chiral moieties was deduced from the configuration of the enantiomers of the (4-methoxy-1-naphthalenyl)methylphenylphosphine oxide 2 (Table I), the latter being established by chemical correlation from the configurationally known[2] enantiomers (*S*)-1 and (*R*)-1.

Moreover, Dunach and Kagan[3] have recently reported that (*R*)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine could act as a chiral shift reagent (CSR) which allowed enantiomeric excess (e.e.) measurements for various phosphine oxides; we therefore intended to investigate whether a dependence of the absolute configuration of the phosphine oxide on the observed chemical displacements could be established.

EXPERIMENTAL

Apparatus

Analytical chromatography. Analytical chromatography was performed with a Model 8100 liquid chromatograph (Spectra Physics, Santa Clara, CA, U.S.A.) equipped with an SP-8400 variable-wavelength detector (190–600 nm), operating at 280 nm for the phosphine oxides on Pirkle-type CSP and 254 nm for the N-(3,5-dinitrobenzoyl)-α-amino esters and amines on CSP I or CSP II, and an SP-4200 dual-channel computing integrator. Chiral stationary phases (Pirkle type, CSP I and CSP II) were packed into 250 × 4.6 mm I.D. stainless-steel columns by the usual slurry technique at 400 bar with ethanol as pumping solvent. Chromatographic analysis of phosphine oxides was performed on Pirkle-type CSP columns [aminopropyl packing of 7-μm irregular particles modified covalently with (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine]. All chromatographic determinations were carried out at 40°C with *n*-hexane–ethanol as the mobile phase at a flow-rate of 2 ml min^{-1}.

Preparative chromatography. Preparative chromatography was performed at room temperature with a Modulprep apparatus (Jobin-Yvon, Longjumeau, France). The Pirkle-type CSP (500 g) was packed into the column (80 mm I.D.) by axial

compression at 15 bar. UV detection was carried out at 325 nm with a Model SM-25 variable-wavelength detector (195–370 nm) (Jobin-Yvon). The eluent inlet pressure was about 9–10 bar, which gave a flow-rate of *ca.* 110 ml min^{-1}.

Nuclear magnetic resonance. ^1H NMR spectra were recorded at 500 MHz on a Bruker WM-500 spectrometer or at 200 MHz on a WP-200 spectrometer at 296 K, using tetramethylsilane (TMS) as internal standard and [^2H]chloroform as solvent; δ values and coupling constants are given in Hz.

Polarimetry. Optical rotations were measured on a Perkin-Elmer 141 micropolarimeter with a thermostated 1-dm quartz cell and using high-purity solvents [usually from Merck (Darmstadt, F.R.G.)]. The melting points were measured on a Büchi–Tottoli hot-stage apparatus and are uncorrected.

The compounds, listed with their empirical formulae, had elemental analyses consistent with the formula to within ±0.3% (Service Central de Microanalyse du CNRS).

Materials

For analytical chromatography, *n*-hexane and ethanol were of LiChrosolv grade, purchased from Merck. For preparative chromatography and packing of the columns, the solvents [*n*-hexane, ethanol and chloroform stabilized with 0.6% (w/w) of ethanol] were of analytical-reagent grade, purchased from Prolabo (Paris, France). γ-Aminopropylsilica gel LiChrosorb-NH_2 (particle diameter, d_p = 5 μm or 7 μm) was purchased from Merck.

Classical column chromatographic purifications were carried out on Merck H-60 silica gel (35 g of silica per gram of raw product for purification). Analytical thin-layer chromatography (TLC) was performed on Merck F-254 silica gel plates.

Syntheses of compounds

(4-Methoxy-1-naphthalenyl)methylphenylphosphine oxide (2). The preparation of the racemic and enantiomeric forms was carried out according to the general procedure described in ref. 1. Compound 2 was thus obtained by addition of methylphenyl phosphinyl chloride dissolved in tetrahydrofuran (THF) to the Grignard reagent, which was prepared from 1-bromo-4-methoxynaphthalene in THF under reflux[4]. The temperature was kept below 20°C. After the usual work-up, racemic 2, m.p. 199–201°C (toluene), was isolated in 62% yield. ^1H NMR data are given in ref. 4 and other physical data in Table I.

The enantiomers of (±)-2 were resolved by preparative chiral chromatography on a Pirkle-type CSP derived from (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine[4].

(4-Hydroxy-1-naphthalenyl)methylphenylphosphine oxide (3). A solution of (±)-(4-methoxy-1-naphthalenyl)methylphenylphosphine oxide (1.84 g, 4 mmol) in 40 ml of dichloromethane was treated dropwise with 10 ml of 1 *M* boron tribromide in dichloromethane (Aldrich, Milwaukee, WI, U.S.A.) at −15°C under nitrogen. The resulting mixture was stirred at −15°C for 1 h, then at 20°C overnight. The reaction mixture was hydrolysed by adding water, then neutralized with sodium hydrogencarbonate solution. The solid, collected by filtration under suction, was washed successively with water, water–ethanol (50:50) and diisopropyl ether, and finally dried under vacuum at 50°C. In this way, 1 g (88%) of pure (±)-(4-hydroxy-1-naphthalenyl)methylphenyl phosphine oxide (3) was obtained (m.p. 221–223°C).

^{1}H NMR ([$^2H_6$]dimethyl sulphoxide): 2.10 [d, ^2J(H, P) = 13.4 Hz; 3H, P–CH_3], 7.02 [d, ^4J(H, P) = 1.8 Hz; 1H, 3-naphthyl], 7.40–8.42 (m, 10 H), 11.09 (s; 1H, OH). Analysis (C, H, P): $C_{17}H_{15}O_2P$.

Each enantiomeric form of 3 was obtained likewise starting from the corresponding enantiomer of 2: (*R*)-3, m.p. 250–252°C; and (S)-3, m.p. 262–264°C; these were hardly soluble in the usual solvents, so their optical rotation was not measured.

(R)-(+)-Ethyl[(4-(1-methyl phenyl phosphinyl)naphthalenyl)oxy] acetate (4). This compound was synthesized from the optically pure (*R*)-3 enantiomer in 84% yield, in the same way as the racemate (±)-4 from (±)-3[5], after crystallization from diisopropyl ether–2-propanol (10:1, v/v), m.p. 154–156°C; $[\alpha]_D^{22} = +33.3°$ (c = 2, methanol); HPLC [*n*-hexane–ethanol (90:10)], 100% e.e. Analysis (C, H, P): $C_{12}H_{21}O_4P$.

(R)-Acetic [(4-(1-methyl phenyl phosphinyl)naphthalenyl)oxy] acid (5). Sodium hydroxide solution (1 *M*) (16.4 ml) was added to a solution of the ester (*R*)-(+)-4 (1.5 g, 4.1 mmol) in 60 ml of ethanol and the mixture was stirred for 10 h at room temperature. After acidification by successive additions of 4 ml of 6 *M* hydrochloric acid and 45 ml of water, the precipitate was collected by filtration under suction, washed with water until neutrality and then rinsed with ethanol. Yield, 1.25 g (90%) of acid (*R*)-5; m.p. 259–261°C. Analysis (C, H, P): $C_{19}H_{17}O_4P$. (*R*)-5 is hardly soluble in the usual solvents, so no measurement of its optical rotation was made. ^{1}H NMR ([$^2H_6$]dimethyl sulphoxide): 2.11 (d, J = 13.2, P–CH_3), 3.37 (CO_2 H), 4.99 (s, O–CH_2), 6.92–8.53 (m, 11 H aromatic).

(±)-Methyl [4-(2-phenyltetrazolyloxy)-1-naphthalenyl]phenylphosphine oxide (6). Potassium carbonate (0.478 g, 3.5 mmol) was added to a solution of (±)-3 (846 mg, 3 mmol) in acetonitrile (40 ml) and the resulting suspension was stirred magnetically for 1 h under nitrogen. Then 0.541 g (3 mmol) of 1-chloro-2-phenyltetrazole (Aldrich) was added and the mixture was stirred under reflux. Completion of the reaction was monitored by TLC with dichloromethane–ethyl acetate–methanol (65:30:5, v/v/v) as solvent; it took about 5 h. The precipitate was removed by filtration and washed with acetonitrile, the filtrate was evaporated and the organic material was extracted with dichloromethane, washed with water until neutrality and then washed with brine. Vacuum evaporation of the solvent led to crude (±)-6 in quantitative yield. Purification of the crude product was achieved by column chromatography [50 parts of silica gel; eluent, dichloromethane–ethyl acetate–methanol (65:30:5, v/v/v)]. After trituration with 7 ml of diisopropyl ether–2-propanol (6:1, v/v), 1.1 g of pure (±)-6 was obtained (86% yield); m.p. 178–180°C. Analysis (C, H, N, P): $C_{24}H_{19}N_4O_2P$.

(*S*)-6 was similarly obtained starting from (*S*)-3. The enantiomeric purity was monitored by HPLC [mobile phase, *n*-hexane–ethanol (75:25, v/v)]. ^{1}H NMR (500 MHz) (500 MHz, C^2HCl_3), 2.19 (d, J = 13.1 Hz, P–CH_3). (±)-9 and (*R*)-(+)-9 were prepared in the same way from (±)-8 and (*R*)-(+)-8, respectively. (±)-9, m.p. 211–213°C. (*R*)-(+)-9, m.p. 204–206°C. Analysis (C, H, N, P): $C_{24}H_{19}N_4O_2P$. HPLC: *n*-hexane–ethanol (80:20, v/v)]. (±)-8, ^{1}H NMR (C^2HCl_3); 2.33 (d, J = 13 Hz, P–CH_3), 7–8 (m, 11 H, aromatic), 13.10 (s, OH).

(2-Methoxy-1-naphthalenyl)methylphenylphosphine oxide (7). (±)-7 was synthesized according to the procedure described for (±)-2, starting from 1-bromo-2-methoxynaphthalene. The enantiomers (*R*)-7 and (*S*)-7 were obtained by preparative

chiral chromatography[4]. Some physical data are given in Table I.

(2-Hydroxy-1-naphthalenyl)methylphenylphosphine oxide (8). (±)-8 was obtained similarly to racemic (±)-3 starting from (±)-7. (*R*)-8 was synthesized in the same way from (*R*)-7. Some physical data are given in Table I.

Methyl [2-(2-phenyltetrazolyloxy)-1-naphthalenyl]phenylphosphine oxide (9). (±)-9 and its (*R*)-enantiomer were synthesized from (±)-8 and (*R*)-8, respectively, according to the procedure described for 6. Some physical data are given in Table I.

Hydrogenolysis of (±)-6, (±)-9, (S)-6 and (R)-9. The general procedure is given. A solution of (±)-6 (426 mg, 1 mmol) in dichloromethane–methanol (50:50, v/v) was stirred in the presence of 500 mg of 10% palladium on charcoal as catalyst under hydrogen at atmospheric pressure and room temperature. Completion of the reaction was monitored by HPLC of samples taken every hour. Hydrogenolysis was generally carried out for 5 h for (±)-9 and (*R*)-9, whereas about 10 h were necessary for (±)-6 and (*S*)-6. The catalyst was removed by filtration. The reaction led to pure methylnaphthylphenylphosphine oxides (monitored by HPLC).

*$(S)_p$-(S, R)$_c$-(−)-(4-Glycidyloxy-1-naphthalenyl)methylphenylphosphine oxide (10)**.* Potassium carbonate (1.0 g, 7.3 mmol) was added to a solution of (*S*)-3 (1.46 g, 5.2 mmol) in 50 ml of acetonitrile and the resulting suspension was stirred magnetically for 1 h under nitrogen, then 0.85 g (6.2 mmol) of epibromohydrin was added and the mixture was heated under reflux for 6 h. The precipitate was removed by filtration and washed with acetonitrile and the filtrate was evaporated. The organic material was extracted with dichloromethane and washed with water until neutrality and then washed with brine. The solvent was evaporated and 1.6 g of raw product was obtained, which was purified by chromatography on silica gel with dichloromethane–ethyl acetate–methanol (65:30:5, v/v/v) as eluent. Evaporation of the solvent and crystallization from diisopropyl ether–acetonitrile (95:5, v/v) gave 1.4 g (80%) of diastereomer (−)-10, m.p. 155–156°C; $[\alpha]_D^{22} = -29.5°$ (c = 2, methanol), 100% e.e. ^{1}H NMR (C^2HCl_3): 2.13 (d, J = 13.1, P–CH_3), 2.85 (m) and 2.98 (t) for the terminal methylene, 3.50 (m, CH glycidyloxy), 4.15 (ddd) and 4.48 (dt) for the other methylene, 6.8–8.3 (m, 11 H aromatic). Analysis (C, H, P): $C_{20}H_{19}O_3P$. There is no significant difference in the ^{1}H NMR spectra (200 MHz) between the racemic and the enantiomeric forms.

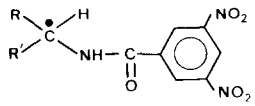
This diastereomeric mixture (with regard to the carbon atom configuration) was also obtained by chiral preparative chromatography from the diastereomer (R, $S)_p$-10 according to a previous method[4]. The composition of the mobile phase was determined from analytical optimization data: *n*-hexane–chloroform–ethanol (52:45.6:2.4, v/v/v). UV detection was carried out at 310 nm; other parameters were as mentioned previously[4]. The diastereomer (−)-10 with the (*S*)-configuration at the phosphorus atom was obtained after work-up: m.p. 152–154°C; $[\alpha]_D^{22} = -26.7°$ (c = 2, methanol). The diastereomer with the (*R*)-configuration at the phosphorus atom had m.p. 153–155°C and $[\alpha]_D^{22} = +33.7°$ (c = 2, methanol).

N-(3,5-Dinitrobenzoyl)methylamino esters and N(3,5-dinitrobenzoyl)amines. A general procedure for the derivatization is given. Derivatization of the amino group was developed from the procedure according to Pirkle and Hyun[6]. The preparation

* Subscripts p and c refer to phosphorus and carbon atoms, respectively.

TABLE II

PHYSICAL DATA FOR THE N-(3,5-DINITROBENZOYL) DERIVATIVES OF THE α-AMINO ESTERS AND AMINES STUDIED



No.	*R*	*R'*	*Configuration*	$[\alpha]_D^{22}$ (°)	*Melting point (°C)*	
					This work	*Lit.*[7]
11	CH_3	CO_2CH_3	rac.	–	95–96	–
			S	+10.93	119–120	70–72
12	$CH(CH_3)_2$	CO_2CH_3	rac.	–	164–165	180–182
			S	−1.26	122–123	113–115
13	$CH_2CH(CH_3)_2$	CO_2CH_3	rac.	–	141–142	–
			S	−12.17	109–110	80–82
14	$(CH_2)_2CO_2CH_3$	CO_2CH_3	rac.	–	130–131	–
			S	−1.83	107–109	–
15	CH_2-C_6H_5	CO_2CH_3	rac.	–	184–186	172–174
			S	−32.45	141–142	–
16	C_6H_5	CO_2CH_3	rac.	–	170–172	–
			R	−95	179–181	–
17	CH_2-C_6H_5	CH_3	rac.	–	145–146	–
			S	+80.3	145–147	–
18	C_6H_5	CH_3	*R*	−40.5	153–155	158–160
			S	+51.5	153–154	–

of (±)-N-(3,5-dinitrobenzoyl)leucine methyl ester is described as an example; some data are summarized in Table II for the other solutes. The ^1H NMR spectra were in accordance with their expected structure.

(±)-N-(3,5-Dinitrobenzoyl)leucine. 3,5-Dinitrobenzoyl chloride (11.5 g, 50 mmol) and propylene oxide (8.7 g, 150 mmol) were added simultaneously and in small portions to a slurry of 6.5 g (50 mmol) of (±)-leucine in 25 ml of dry THF. The mixture became slightly warm (40°C) as the reaction proceeded. After 2 h, the solution was filtered under suction in order to remove any traces of residual amino acid and was then evaporated to dryness *in vacuo* to yield 11.6 g (71.3%) of (±)-N-(3,5-dinitrobenzoyl)leucine after crystallization from acetonitrile; m.p. 198–199°C. Analysis (C, H, N): $C_{13}H_{15}N_3O_7$.

(±)-N-(3,5-Dinitrobenzoyl)leucine methyl ester (13). Gaseous hydrogen chloride was bubbled into methanol and the preceding derivatized amino acid was allowed to react for 8 h under reflux. Completion of the reaction was monitored by TLC [*n*-hexane–ethyl acetate (80:20, v/v)]. The methanol was evaporated and the resulting product was dissolved in chloroform and then washed successively with 1 *M* sodium hydroxide solution, water until neutrality and brine. Evaporation of the solvent *in vacuo* gave a crude product in quantitative yield. A sample (2 g) was purified by means of column chromatography [50 parts of silica gel; eluent, *n*-hexane–ethyl acetate (85:15, v/v)]. Crystallization from ethanol afforded the ester, m.p. 141–142°C. Analysis (C, H, N): $C_{14}H_{17}N_3O_7$. ^1H NMR (200 MHz, C^2HCl_3):

1.01 [d, $-CH(CH_3)_2$, 6 H), 1.80 (m, $-CH_2CH(CH_3)_2$, 3 H], 3.83 (s, OCH_3, 3 H), 4.91 (dt, $-CHCO_2CH_3$, 1 H), 7–7.5 (d, NH, 1 H), 8.95 (d, 2 H aromatic at 2- and 6-position), 9.19 (t, 1 H aromatic at 4-position).

Syntheses of chiral stationary phases

Synthesis of (R)-CSP I. Dichloromethane (40 ml) was slowly added, with magnetic stirring and under nitrogen pressure, to a mixture of 8 g of LiChrosorb-NH_2 (7 μm), 1.08 g (3.2 mmol) of acid (*R*)-5 and 0.95 g (3.84 mmol) of N-ethoxy carbonyl 2-ethoxy 1,2-dihydroquinoline (EEDQ); the stirring was then maintained for 2 h. The modified silica gel was isolated by filtration and washed repeatedly with methanol and diethyl ether. CSP I (8.6 g) was obtained after drying in air. Analysis: found, C 24.94, H 3.78, N 1.05, P 1.28, Si 23.65%; calculated, 0.40 mmol of chiral moiety per gram of chiral phase (based on P).

Synthesis of (S)-CSP II. Anhydrous benzene (50 ml), triethylamine (0.2 ml) and 0.65 g (1.92 mmol) of (*S*)-10 were added to 5 g of LiChrosorb-NH_2 (5 μm); the mixture was then stirred magnetically and refluxed under nitrogen. Advancement of the reaction was monitored by TLC with dichloromethane–ethyl acetate–methanol (65:30:5, v/v/v) as eluent until (*S*)-10 had disappeared; a further 0.2 g of (*S*)-10 was added three times successively. Complete refluxing was maintained for 44 h. CSP II was isolated by filtration, washed repeatedly with benzene, methanol and diethyl ether and dried in air; 5.9 g of CSP II were thus obtained. Analysis: found, 26.39, H 3.47, N 0.75, P 1.0, Si 22.60%; calculated, 0.32 mmol of chiral moiety per gram of chiral phase (based on P).

RESULTS AND DISCUSSION

Nowadays there is great interest in the development of new CSPs as they may lead to an extension of the scope of applications of liquid chromatography for the resolution of racemic mixtures, particularly in the pharmaceutical field[8]. We therefore studied the synthesis of new CSPs derived from chiral phosphine oxides which have been previously successfully resolved on various CSPs[1] and especially on a CSP obtained by covalent bonding of (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine on a γ-aminopropylsilica gel and developed by Pirkle *et al.*[9]. These new chiral grafts display several sites of interaction that are different in nature so that various combinations of them may provide CSP with possible chiral recognition power towards suitably derivatized amino acids, amines and amino alcohols. The P=O functional group

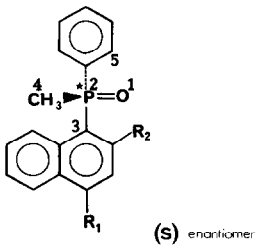


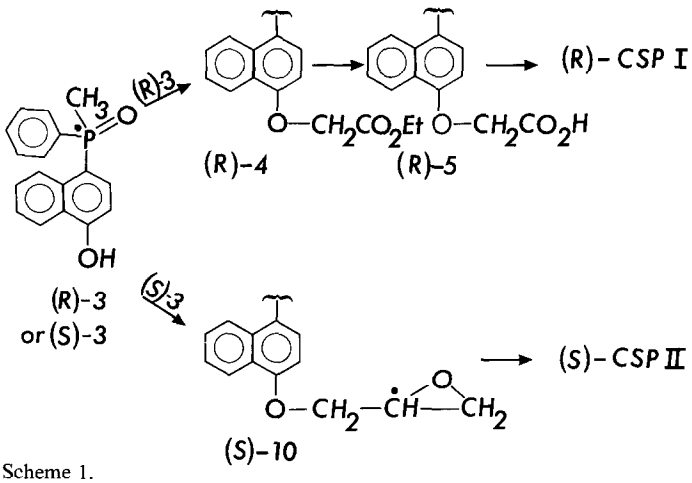
Fig. 2. Possible sites of interaction of a chiral tertiary phosphine oxide with another chiral moiety.

is essential because of its dipolar character[10]; two interactions can be generated by the oxygen atom (site 1, Fig. 2) which can act as a basic site, available for hydrogen bonding, and the phosphorus atom (site 2), which acts as an acidic site. A third interaction occurs through the formation of a π–π charge-transfer adduct between the naphthyl group of the phosphine oxide (site 3) and the π-acid group of the solute. Finally, a repulsive interaction is provided by the steric hindrance of either the methyl (site 4) or the phenyl (site 5) group of the phosphine oxide.

We were led to choose the enantiomers of (±)-(4-methoxy-1-naphthalenyl) methylphenylphosphine oxide (2) (Table I) as the chiral precursor for the synthesis of CSPs derived from phosphine oxides. The preparation of racemic and enantiomeric forms of 2 has been described previously[4]. This compound appeared to be the most suitable precursor among the series of phosphine oxides studied (Table I), for the following reasons: it can be easily prepared in reasonable yield (62%) by the reaction of methylphenylphosphinyl chloride on the Grignard reagent derived from 1-bromo-4-methoxynaphthalene; the racemic mixture is resolved with the highest selectivity on a Pirkle-type phase, which allowed the isolation of each enantiomer on a preparative scale by liquid chromatography on the same CSP[4]; and the absolute configuration of each enantiomer could be readily deduced by chemical correlation from those of (*S*)-1 and (*R*)-1, which have been established by Luckenbach[2].

Synthesis and absolute configuration of the CSPs

In a first approach, two modes of linkage were examined for covalently grafting the phosphorus chiral moieties on a γ-aminopropylsilica gel (Scheme 1, Fig. 1).

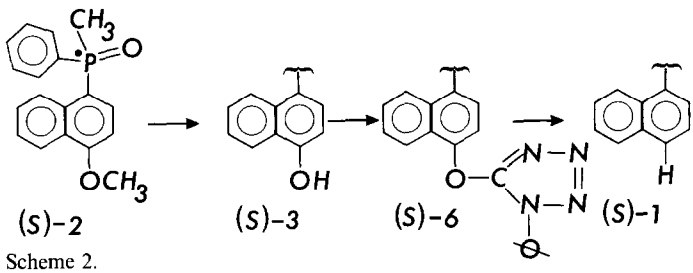


Scheme 1.

The chiral phenols (*R*)-3 and (*S*)-3, which constitute the key products in the synthesis of CSP I and CSP II, were obtained in good yield by demethylation with boron tribromide of the corresponding ethers (*R*)-2 and (*S*)-2, themselves resolved by means of chiral preparative chromatography[4]. The condensation of the enantiomeric phenol (*R*)-3 with ethyl bromoacetate gives the ester (*R*)-4, which is then hydrolysed into the acid (*R*)-5. Finally, (*R*)-5 is allowed to react with a γ-aminopro-

pylsilica gel in dichloromethane with EEDQ at room temperature so as to give CSP I (Scheme I, Fig. 1). It should be noted that the whole synthesis of the chiral graft can be also carried out from a racemic mixture of 2 until the ester (±)-4 is obtained, the antipodes of which are then separated by preparative liquid chromatography on a Pirkle-type CSP by analogy with the method described previously[4]; however, the selectivity is then lower than that for the racemic methoxy derivative 2. In another route, (*S*)-3 condensed with epibromohydrin gives the ether (*S*)-10, which is allowed to react with a γ-aminopropylsilica gel to lead to (*S*)-CSP II (Scheme 1, Fig. 1).

The absolute configuration of the enantiomers of (±)-2 were determined by chemical correlation from the configurationally established enantiomers (*S*)-1 and (*R*)-1: the successive chemical steps are depicted in Scheme 2. The conversion of the enantiomers (*S*)-2 and (*R*)-2 into the enantiomers (*S*)-1 and (*R*)-1, respectively, is achieved with retention of configuration in each step. The major interest in this conversion lies in the stereoselective substitution of the phenolic group in 3 by a hydrogen atom via the tetrazolyl ether 6, itself obtained in good yield. The last step, which leads to (*S*)-1, was carried out according to Canceill *et al.*[11], who modified the original procedure of Musliner and Gates[12,13] by using dichloromethane–methanol instead of benzene or ethanol as the solvent. The hydrogenolysis is carried out smoothly at 20°C under a hydrogen pressure of 1 bar with 10% of palladium on charcoal as catalyst. Starting from the tetrazolyl ether (*S*)-6, the reaction was completed in about 10 h; it was faster when one started with the tetrazolyl ether (*R*)-9 (4 h).



Scheme 2.

NMR studies

Dunach and Kagan[3] reported that the recording of ^{1}H NMR spectra at high resolution (400 MHz) induces a splitting of the methyl group (P–CH_3) signal in some tertiary methylphenylphosphine oxides with a magnitude varying from 3 to 7 Hz when registration is made in the presence of (*R*)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine as chiral solvating reagent (CSR) in a C^2HCl_3–CCl_4 mixture. They suggested using this result for the determination of the enantiomeric excess of some tertiary phosphine oxides. As we knew the absolute configuration of the enantiomers corresponding to (±)-1, (±)-2, (±)-4 and (±)-7, we were interested in recording the ^{1}H NMR spectra of enantiomeric and racemic forms of these compounds at high resolution (500 MHz) and under conditions similar to those described by Dunach and Kagan[3] (Table III). The spectra of (±)-1 and of its enantiomers showed that the CSR induces a splitting of 4.6 Hz for the P–CH_3 signal. Moreover, it is interesting that the (*R*)-form is more shielded (−21.6 Hz) than the (*S*)-form (−17.0 Hz), whereas opposite results are observed for racemic 2, 4 and 7 (Table III). These results showed

TABLE III

RESOLUTION OF SOME ^1H NMR SIGNALS (500 MHz) OF RACEMIC PHOSPHINE OXIDES IN PRESENCE OF ONE EQUIVALENT OF (*R*)-N-(3,5-DINITROBENZOYL)-α-PHENYLETHYLAMINE AS CSR IN C^2HCl_3 (c = 0.2 mol l^{-1}) AT 296 K

Compound	*Group*	*Chemical shift* (Hz)*		*Absolute difference (ΔR − ΔS)* (Hz)*
		ΔR	*ΔS*	
(±)-1	P–CH_3	−21.6	−17.0	4.6
(±)-2	P–CH_3	−21.7	−30.9	9.2
	O–CH_3	+9.8	+6.8	3.0
(±)-4	P–CH_3	−20.1	−26.1	6.0
	O–CH_2	+27.7	+22.2	5.5
(±)-7	P–CH_3	−24.6	−27.2	2.6
	O–CH_3	+51.1	+72.8	21.7

* Chemical shifts are given in Hz from internal TMS. *ΔR* and *ΔS* refer to the difference in the values of the chemical shifts measured on the one hand for the solute alone and on the other hand for the solute in the presence of the CSR. A negative value indicates shielding and a positive value deshielding. Values given were obtained on the racemic compounds; the assignment of configuration was deduced from the registration of the configurationally known enantiomers.

that no correlation can be established between the absolute configuration and the sign of *ΔR* and *ΔS* induced by the CSR. Splittings were also observed for methyl and methylene groups of the ether function of racemic 2, 4 and 7 with inverted signs compared with those of the P–CH_3 group. Coupling constants for the P–CH_3 group and some chemical shifts for some typical functional groups in 1–4, 6 and 7 are summarized in Table IV.

Preliminary chromatographic results

As expected, the new CSPs are able to resolve some racemic mixtures of N-(3,5-dinitrobenzoyl) derivatives of α-amino esters and amines (Table II). Table V

TABLE IV

HIGH-FIELD 500 MHz ^1H NMR SPECTRA OF RACEMIC 1–4, 6 AND 7

Chemical shifts in Hz from internal TMS, in C^2HCl_3 (c = 0.2 mol l^{-1}) at 296 K. Racemates and enantiomers showed identical spectra. Aromatic protons are omitted.

Compound	*P–CH_3 (J, Hz)*	*O–CH_3*	*O–CH_2*	*CO_2–CH_2CH_3*
(±)-1	1084.6 (d) (13.1)	–	–	–
(±)-2	1062.1 (d) (13.1)	2018.7 (s)	–	–
(±)-3	1038.0 (d) (13.2)	–	–	–
(±)-4	1063.2 (d) (13.4)	–	2429.0 (s)	2152.9 (q) 657.3 (t)
(±)-6	1096.4 (d) (13.1)	–	–	–
(±)-7	1109 (d) (14.0)	1831.4 (s)	–	–

TABLE V

SEPARATION OF THE ENANTIOMERS OF N-(3,5-DINITROBENZOYL) DERIVATIVES OF α-AMINO ESTERS AND AMINES

No.	*R*	*R'*	*(R)-CSP I**				*(S)-CSP II***			
			k'_2***	α§	R_S§§	*Absolute configuration*§§§	k'_2***	α§	R_S§§	*Absolute configuration*§§§
11	CH_3	CO_2CH_3	9.8	1.18	2.6	*S*	9.0	1.29	2.9	*R*
12	$CH(CH_3)_2$	CO_2CH_3	6.6	1.33	4.3	*S*	7.1	1.45	4.1	*R*
13	$CH_2CH(CH_3)_2$	CO_2CH_3	6.3	1.25	3.4	*S*	6.6	1.33	3.1	*R*
14	$(CH_2)_2CO_2CH_3$	CO_2CH_3	13.0	1.18	2.7	*S*	13.3	1.31	3.1	*R*
15	CH_2-C_6H_5	CO_2CH_3	11.6	1.28	3.95	*S*	12.6	1.43	4.1	*R*
16	C_6H_5	CO_2CH_3	10.7	1.06	0.8	*S*	10.1	1	–	–
17	CH_2-C_6H_5	CH_3	6.9	1.06	0.9	*R*	6.1	1.10	1.1	*S*
18	C_6H_5	CH_3	10.85	1.19	2.85	*S*	9.5	1.27	2.7	*R*

* Mobile phase: *n*-hexane–ethanol (90:10).

** Mobile phase: *n*-hexane–ethanol (83:17).

*** k'_2 is the capacity factor of the second eluted enantiomer, $k'_2 = (t_{r2}/t_0)^{-1}$, where t_{r2} is the retention time of the second eluted enantiomer and t_0 the retention time of a non-retained solute.

§ The selectivity, α, between two enantiomers is the ratio of their respective capacity factors (k'_2/k'_1).

§§ R_s (resolution factor) = 2 (distance of the two enantiomer peak positions/sum of the bandwidth of the two peaks at their bases): $R_s = 2(t_{r2} - t_{r1})\ (w_2 + w_1)$.

§§§ The absolute configuration of the most retained enantiomer was determined from chromatography of samples enriched in one configurationally known enantiomer.

summarizes the first results obtained on (*R*)-CSP I and (*S*)-CSP II (the configuration refers to the phosphorus atom). The elution orders determined on both CSPs for each solute are reversed from (*R*)-CSP I to (*S*)-CSP II, which is consistent with the inverted configuration of the chiral moieties grafted on these CSPs. The retention times are far longer on CSP II than on CSP I, so we had to use a higher concentration of polar solvent (ethanol) in the mobile phase on CSP II in order to work with close capacity factors, k', for each solute on both phases; ethanol contents of 10% and 17% in *n*-hexane were chosen for CSP I and CSP II, respectively, so that the retention times did not exceed 25 min.

The selectivities, α, measured on CSP II are markedly higher than those on CSP I except for the N-(3,5-dinitrobenzoyl)phenylglycine methyl ester 16, for which only a shoulder on the leading hedge of the peak is observed; on the other hand, CSP II gives lower efficiencies than CSP I, whereas the mean diameter of its silica beads is smaller (d_p = 5 μm for CSP II and 7 μm for CSP I); from the chromatographic data and applying the equation given by Foley and Dorsey[14] for the calculation of efficiencies of non-Gaussian peaks, we found average values of h (reduced theoretical plate height) of 13 and 25 for CSP I and CSP II, respectively (measured on 12 and 13); a second column filled with CSP II gave the same values of selectivities and efficiencies as the first column. We thus observed trailing on the leading edge of the peaks whatever the solute on CSP II; this peak shape, associated with high retention times, may suggest a low capacity of CSP II. Finally, the values of the resolution factor, R_s, are very similar on both CSPs for each racemic mixture; except for amphetamine and phenylglycine derivatives (17 and 16, respectively), baseline resolution is achieved.

From microanalytical results and correlation with the determination of the weight increase of the silica after the grafting step, we deduced that CSP I and CSP II contained 0.40 and 0.32 mmol, respectively, of chiral moiety per gram of chiral graft silica gel. Hence the increase in selectivity observed from CSP I to CSP II could not be ascribed to a higher grafting rate on CSP II. We can then assume that the spacer which connects the chiral phosphine oxide via its naphthyl group to γ-aminopropylsilica gel takes part in the chiral recognition mechanism; the spacer obtained from glycidyl ether 10 ($-OCH_2CHOHCH_2NH-$) displays a higher electron-donor character than that obtained from acid 5 (OCH_2CONH) and thus enhances the π-basicity of the naphthyl group to a larger extent: this can favour the π–π interaction with the π-acid group of the solute. We can also argue that the amide dipole of the spacer in CSP I may undergo a non-stereoselective dipole-stacking process with the amide function of the derivatized solutes (this interaction may compete with the interaction on P=O group); with CSP II, intramolecular hydrogen bonding between NH and OH groups may thus favour the interaction between P=O and the solute, leading to an increase in α. On CSP II we think that the chiral carbon is not responsible for the chiral recognition because we used the racemic epibromohydrin intermediate for the synthesis of the CSP. The introduction of a chiral carbon in the spacer during the grafting procedure should be avoided in order to understand the chiral recognition process at the phosphorus atom.

It was not easy to predict the elution orders for a racemic mixture between the two enantiomers and selectivity variations for various solutes from CPK models; in fact, it appeared that the phosphine oxides may have two possible preferential con-

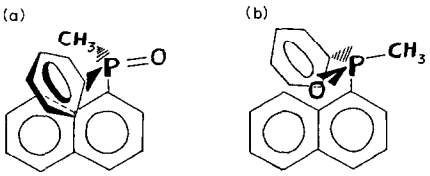


Fig. 3. Steric hindrance generated by the *peri* H atom at the 8-position of the naphthyl group on the free rotation around the P–naphthyl bond [compound: (*R*)-methyl 1-naphthylphenylphosphine oxide]. (a) Conformation with the oxygen atom "outside". (b) Conformation with the oxygen atom "inside".

formations (Fig. 3), depending on whether the oxygen atom of the P=O group is directed outside (Fig. 3a) or inside (Fig. 3b) with respect to the naphthyl group. It seemed to us that the more stable conformation, which is related to a planar naphthyl–(P=O) bond system, is associated with the oxygen atom in the "outside position". The conversion of this most stable conformation into the other is hindered by the *peri* hydrogen atom of the naphthyl group. Examination of the CPK models shows then that the most favourable approach of the π-acid group of the solute towards the naphthyl π-basic group should occur on the methyl side of the phosphine oxide. Fig. 4 depicts some stereospecific interactions between (*S*)-N-(3,5-dinitrobenzoyl)phenylalanine methyl ester 15 and the chiral phosphine oxide of (*R*)-CSP I. A dipolar interaction between the P=O group and the amide group is expected, in addition to a π–π interaction, but the steric discriminant interaction between the (*R*)- and (*S*)-forms of one solute is not clearly evidenced.

Considering the two pairs of solutes phenylalanine–phenylglycine (15–16) and amphetamine–phenylethylamine (17–18), a reversed selectivity order is observed

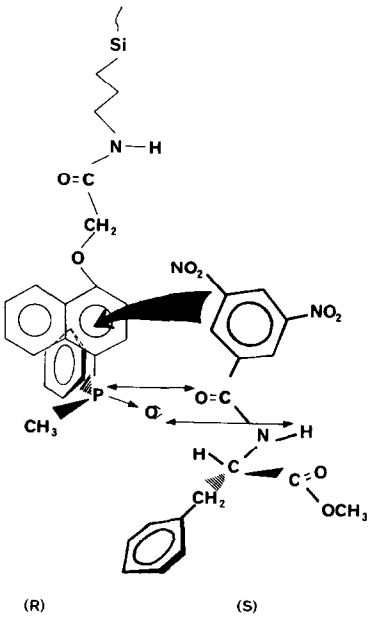


Fig. 4. Proposed interaction model between (*S*)-N-(3,5-dinitrobenzoyl)phenylalanine methyl ester and (*R*)-CSP I.

(Table V and Fig. 5). This emphasizes the role of the ester function as a derivatizing group for amino acids that can undergo internal interaction with the amide group of the N-(3,5-dinitrobenzoyl)-derivatized amino acid, through hydrogen bonding for example, thus altering the diastereomeric interactions with the CSP in comparison with the methyl group of the corresponding amines. Concerning the elution orders between (*S*)- and (*R*)-forms, it should be noted that the change from an amino acid to the corresponding amine owing to the substitution of the acid group by a methyl group is accompanied by an inversion of conformation: the (*R*)-form of the amino acid can therefore be associated with the (*S*)-form of the amine. Hence the phenyl-

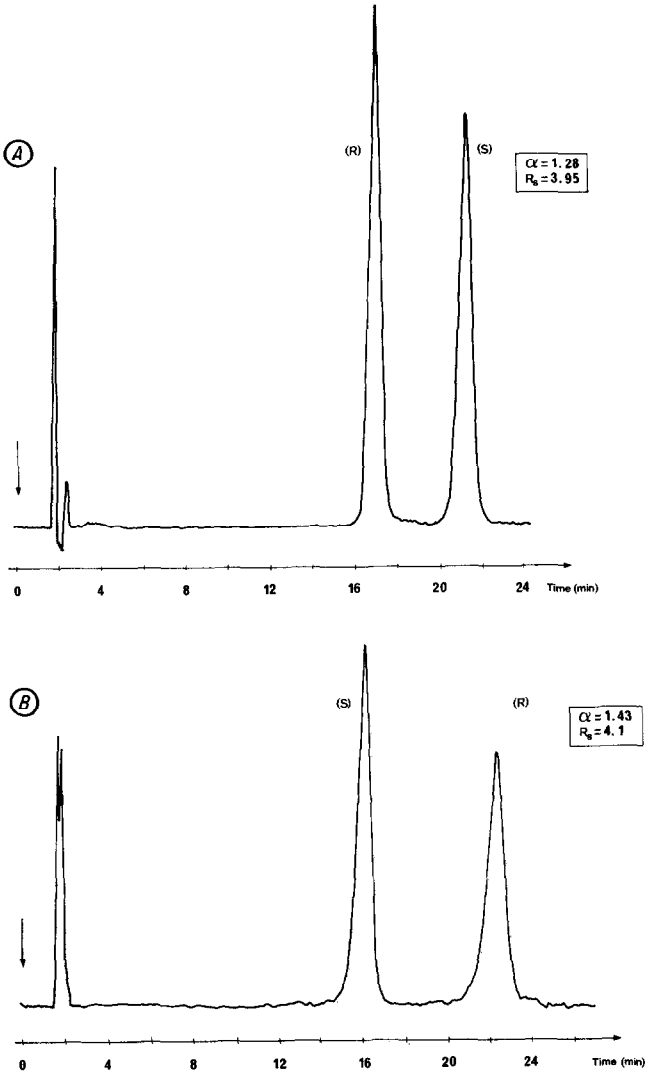


Fig. 5.

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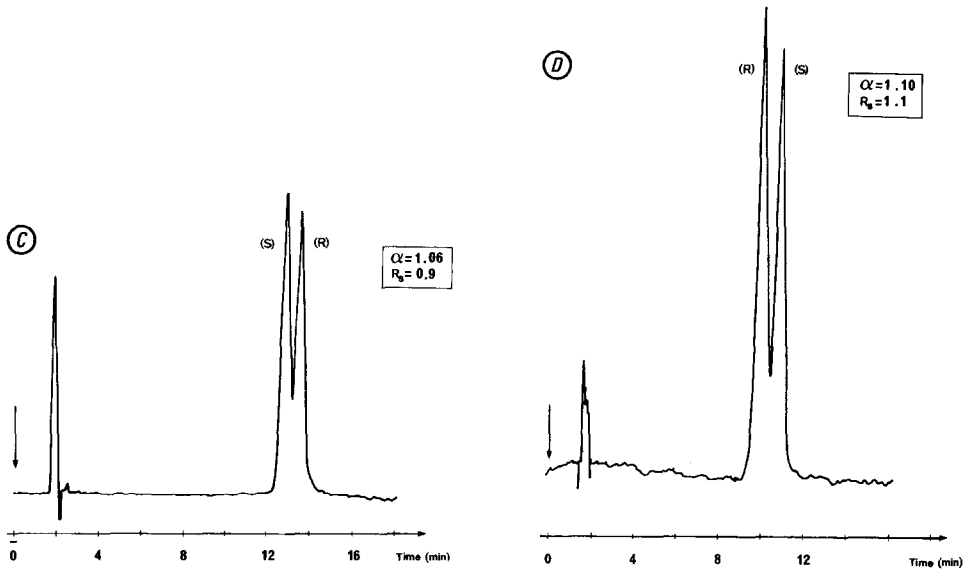

Fig. 5. Resolution of (±)-N-(3,5-dinitrobenzoyl)phenylalanine methyl ester (15) and (±)-N-(3,5-dinitrobenzoyl)amphetamine (17) on (*R*)-CSP I and (*S*)-CSP II. Solutes: (A) and (B), (±)-N-(3,5-dinitrobenzoyl)phenylalanine methyl ester (15); (C) and (D), (±)-N-(3,5-dinitrobenzoyl)amphetamine (17). Stationary phases: (A) and (C), (*R*)-CSP I (d_p = 7 μm); (B) and (D), (*S*)-CSP II (d_p = 5 μm).Mobile phases: (A) and (C), *n*-hexane–ethanol (90:10); (B) and (D), *n*-hexane–ethanol (83:17). Flow-rate: 2 ml min^{-1}. Columns: 250 × 4.6 mm I.D. UV detection at 254 nm.

ethylamine derivative 18 has an inverted elution order (whatever the CSP) compared with other solutes.

These first chromatographic results encouraged us to extend this study by means of further experiments including optimization of the composition and nature of the mobile phase and especially optimization of the synthesis of this new type of CSP with regard to the choice of the anchoring point of the phosphine oxide on the silica gel and of the nature of the spacing arm, and the reproducibility of grafting rates. Higher resolutions are expected. The extension of the scope of application of these CSPs is also under consideration (amino alcohols, etc.). Investigations of the modes of derivatization of the chiral solutes are also planned in order to understand better the chiral recognition mechanisms.

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