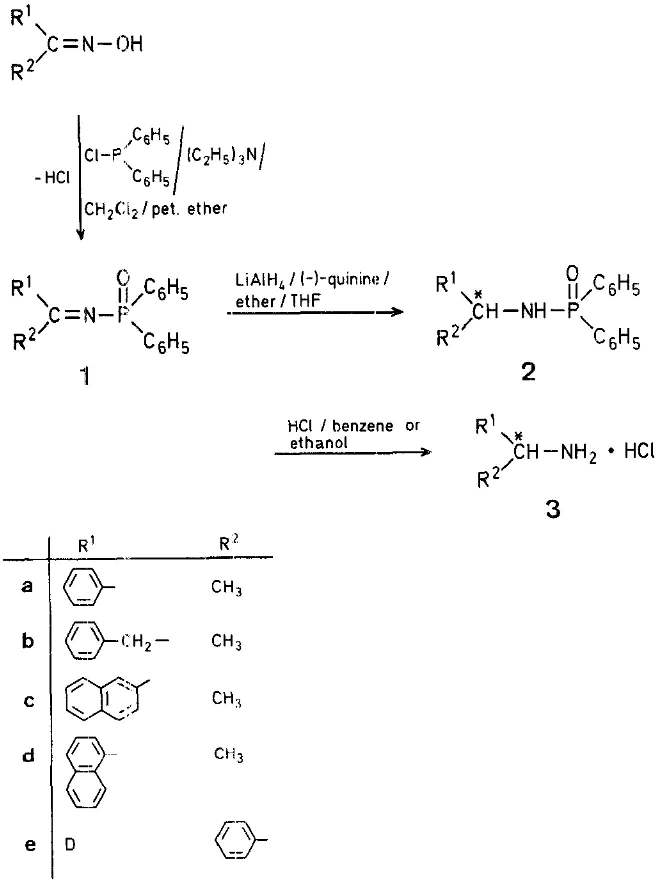
A Study of the Synthesis of Optically Active Amines from Prochiral *N*-Phosphinylimines

B. Krzyżanowska, W. J. Stec*

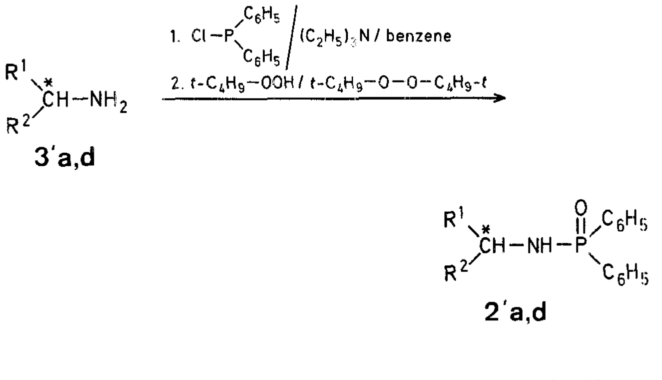
Department of Bioorganic Chemistry, Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Pl-90-362 Łódź, Boczna 5, Poland

N-(Diphenylphosphinyl)-alkanimines (*N*-alkylidenediphenylphosphinamides) obtained from benzaldoxime or cyclohexanone oxime and chlorodiphenylphosphine have been found to be appropriate substrates for the synthesis of *N*-diphenylphosphinyl compounds derived from primary aliphatic amines, 1-aminoalkanephosphonic esters, or 2-aminoalkanenitriles[1]. Reduction of the *N*-(diphenylphosphinyl)-imines with sodium borohydride under mild conditions affords the corresponding *N*-(diphenylphosphinyl)-amines (*N*-alkyldiphenylphosphinamides).



We report here that prochiral *N*-diphenylphosphinylimines (**1a–d**) can be conveniently reduced to optically active *N*-(diphenylphosphinyl)-amines (**2a–d**) by means of lithium alanate in the presence of an equimolar amount of (−)-quinine[2,3], the enantiomeric excess of (*R*)-**2a–d** being 8–34%. The optical purity of compounds **2** was determined by ^{31}P-N.M.R. spectrometry in the presence of Eu(tfc)$_3$ as shift reagent[4] and by comparison of the optical rotation of compounds **2a, d** with that of model compounds (**2′a, d**). Compounds **2** can be dephosphinylated by treatment with hydrogen chloride in benzene or ethanol to give the (*R*)-amine hydrochlorides **3** possessing comparable optical purity.

The model compounds **2′a, d** were prepared from the (*S*)-amines **3′a, d** by reaction with chlorodiphenylphosphine and oxidation of the resultant aminophosphine with *t*-butyl hydroperoxide/di-*t*-butyl peroxide.



Since compounds chiral by virtue of the presence of different isotopes of the same element at the chiral center of a molecule are of actual interest[5–8], we investigated if the reduction of prochiral *N*-(diphenylphosphinyl)-aldimines with lithium aluminium deuteride in the presence of (−)-quinine affords optically active 1-deuterioalkanamines. We found that the reduction of *N*-benzylidenediphenylphosphinamide[1] (**1e**) with LiAlD$_4$ in the presence of 1–3 mol equivalents of (−)-quinine leads to the formation of *N*-(benzyl-*α*-*d*)-diphenylphosphinamide (**2e**) with the specific optical rotation $[\alpha]_D^{20}$: +0.05 to +0.2° (methanol). Removal of the diphenylphosphinyl group afforded benzylamine-*α*-*d*, D enrichment amounting to >95%, but unmeasurable optical rotation. From this result it can be concluded that (−)-quinine is not an asymmetry-inducing agent potent enough to modify the LiAlD$_4$ reduction satisfactorily.

In the four successful examples described in the present communication, asymmetric induction is not high; however, it is worth mentioning that in all four cases studied the formation of an excess of the *R* enantiomer is observed.

All melting points are uncorrected. Solvents and commercial reagents were purified by conventional methods before use. I.R. spectra were taken on a Zeiss-Jena Specord 71 IR spectrometer. ^{1}H-N.M.R. spectra were recorded at 60 MHz using a Perkin-Elmer R-12 B spectrometer. ^{31}P-N.M.R. spectra were obtained at 24.3 MHz on a FT Jeol FX-60 spectrometer. Negative chemical shift values are reported for compounds absorbing at lower field than H$_3$PO$_4$. Mass spectra were measured on a LKB 2091 Mass spectrometer at 70 eV ionising energy. Optical activity measurements were performed with a Perkin-Elmer 241 MC photopolarimeter in methanol or water solution. T.L.C. analyses

0039-7881/82/0432-0270 $ 03.00

Table 1. *N*-Alkylidenediphenylphosphinamides (**1**)

1	Yield [%]	m.p. [°C]	R_F	Molecular formula	M.S. *m/e* (rel. int. %)	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]	^{31}P-N.M.R. ($CHCl_3$/H_3PO_{4ext}) δ [ppm]
a	58	135-137°	0.43	$C_{20}H_{18}NOP$[a] (319.3)	319 (M^+, 14.5), 242 (5.1), 201 (100), 125 (21.1), 77 (94), 41 (29.8)	3045 (m), 1635 (s), 1500 (w), 1190 (s)	2.9 (d, 3H, $C\underline{H}_3$, $^4J_{P,H}=1.5$ Hz); 7.2-8.2 (m, 15 H_{arom})	−18.5
b	75	153-155°	0.45	$C_{21}H_{20}NOP$ (333.4)	333 (M^+, 24.2), 201 (100), 125 (7.5), 91 (8.9), 77 (31.5), 41 (11.4)	3050 (m), 1640 (s), 1595 (w), 1190 (s)	2.4 (d, 3H, $C\underline{H}_3$, $^4J_{P,H}=1.5$ Hz); 3.9 (s, 2H, $Ar—C\underline{H}_2$); 7.0-8.1 (m, 15 H_{arom})	−17.4
c	51	174-176°	0.43	$C_{24}H_{20}NOP$ (369.4)	369 (M^+, 601); 292 (19.4), 201 (100), 168 (3.9), 127 (19.2), 125 (34.9), 77 (39)	3045 (m), 1625 (s), 1190 (s)	3.1 (d, 3H, $C\underline{H}_3$, $^4J_{P,H}=1.5$ Hz); 7.2-8.6 (m, 17 H_{arom})	−17.4
d	61	123-125°	0.52	$C_{24}H_{20}NOP$ (369.4)	369 (M^+, 105), 201 (66), 168 (100), 127 (21.1), 125 (10.2), 77 (47.7)	3030 (m), 1635 (s), 1195 (s)	3.0 (d, 3H, $C\underline{H}_3$, $^4J_{P,H}=1.5$ Hz); 7.2-8.7 (m, 17 H_{arom})	−18.4

[a] The microanalyses showed the following maximum deviations from the calculated values: C ±0.60, H ±0.21, N ±0.15, P ±0.15.

Table 2. *N*-Alkyldiphenylphosphinamides (**2**)

2	Yield [%]	m.p. [°C]	$[\alpha]_D^{20}$ (*c*, CH_3OH)	Optical purity [% e.e.]	Molecular formula[g]	M.S. *m/e* (rel. int. %)	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]	^{31}P-N.M.R. ($CHCl_3$/H_3PO_{4ext}) δ [ppm]
a	75	145-147°[a]	+14.7°[a] (1)	28-29[b]	$C_{20}H_{20}NOP$ (321.3)	321 (M^+, 3.4), 306 (43.3), 201 (68.6), 120 (100), 77 (32.3)	3120 (m), 3020 (m), 1600 (w), 1500 (w), 1190 (s)	1.3 (d, 3H, $C\underline{H}_3$, $^3J_{HH}=7$ Hz); 3.3 (m, 1H, $H_3C—C\underline{H}$); 4.1 (m, 1H, $N\underline{H}$); 6.9-7.9 (m, 15 H_{arom})	−22.4
b	21[c]	118-123°	−27° (2.1)	34-36[d]	$C_{21}H_{22}NOP$ (335.4)	335 (M^+, 1), 244 (100), 201 (92.6), 91 (30.4), 77 (35.9)	3150 (m), 3050 (w), 1490 (w), 1590 (w), 1190 (s)	1.25 (d, 3H, $C\underline{H}_3$, $^3J_{HH}=6$ Hz); 2.85 (d, 2H, $C\underline{H}_2$, $^3J_{HH}=6$ Hz); 3.4 (m, 1H, $C\underline{H}$); 7.1-8.2 (m, 15 H_{arom})	−22.0
c	41	135-137°	+23.3° (1.5)	20-22[e]	$C_{24}H_{22}NOP$ (371.4)	371 (M^+, 6.1), 356 (9.3), 201 (51.2), 170 (100), 155 (17.9), 127 (24), 77 (35.8)	3150 (m), 3040 (w), 1505 (w), 1595 (w), 1185 (s)	1.63 (d, 3H, $C\underline{H}_3$, $^3J_{HH}=7$ Hz); 3.65 (m, 1H, $H_3C—C\underline{H}$); 4.6 (m, 1H, $N\underline{H}$); 7.2-8.2 (m, 17 H_{arom})	−22.5
d	54	194-196°	−1.7° (1.1)	8-10[f]	$C_{24}H_{22}NOP$ (371.4)	371 (M^+, 3.6), 356 (11.7), 201 (37.1), 170 (100), 155 (6.5), 127 (4.7), 77 (12.3)	3160 (m), 3040 (w), 1505 (w), 1595 (w), 1185 (s)	1.7 (d, 3H, $C\underline{H}_3$, $^3J_{HH}=7$ Hz); 3.4 (m, 1H, $H_3C—C\underline{H}$); 5.25 (m, 1H, $N\underline{H}$); 7.2-8.3 (m, 17 H_{arom})	−22.6

[a] Two recrystallizations of **2a** from benzene raised the m.p. to 169-175 °C and the optical rotation to $[\alpha]_D^{20}$: +29.5°.

[b] Assigned on the basis of the ^{31}P-N.M.R. spectrum [0.031 g **2a** + 0.22 g $Eu(tfc)_3$ in 2 ml $CHCl_3$] and by comparison with enantiomerically pure **2'a**.

[c] Product **2b** is accompanied by side products of unknown structure. The crude, dark-brown oily product was purified by column chromatography [silica gel, 60-230 mesh, benzene/acetone/chloroform (4/2/1)].

[d] Assigned on the basis of the ^{31}P-N.M.R. spectrum [0.04 g **2b** + 0.15 g $Eu(tfc)_3$ in 2 ml benzene].

[e] Assigned on the basis of the ^{31}P-N.M.R. spectrum [0.040 g **2c** + 0.27 g $Eu(tfc)_3$ in 2 ml tetrachloromethane].

[f] Assigned on the basis of the ^{31}P-N.M.R. spectrum [0.045 g **2d** + 0.28 g $Eu(tfc)_3$ in 2 ml tetrachloromethane] and by comparison with enantiomerically pure **2'd**.

[g] The microanalyses were not performed because of the changes of enantiomeric composition during purification for analytical purposes.

Table 3. Amines **3** obtained by Cleavage of the *N*-Alkyldiphenylphosphinamides **2**

Amine	Yield[a] [%]	m.p. [°C]		$[\alpha]_D^{20}$ (*c*, water)	
		found	reported	found	reported
(*R*)-(+)-**3a**[16]	70	169–170°	171–173°[16]	+2.3° ±0.2 (2.9)	+ 8° (2.1)[16]; −8.27°[17]
(*R*)-(−)-**3b**[22]	75	150–153°	156°[17]	−8.4° ±0.2 (1.3)	+24.8°[17]; +21.6° (9)[16]
(*R*)-(+)-**3c**[18, 19]	76	215–217°	219°[17]	+1.2° ±0.2 (3.4)	− 6°[17]; +5.4°[17]
(*R*)-(+)-**3d**[19, 20, 21]	72	carbonization at ~216 °C (cf. Ref.[14])		+0.4° ±0.2 (1.4)	− 3.9°[17]

[a] The mass spectra (molecular ion and fragmentation) were in agreement with the structure.

were performed on silica gel plates (Art. 5715, Merck) using chloroform/acetone (10/3) as solvent system.

N-(1-Phenylethylidene)-diphenylphosphinamide (1a); Typical Procedure:

To a stirred solution of acetophenone oxime (6.75 g, 0.05 mol) and triethylamine (5.05 g, 0.05 mol) in petroleum ether/dichloromethane or ether or toluene (1/1, 150 ml), a solution of chlorodiphenylphosphine (11.0 g, 0.05 mol) in dichloromethane (15 ml) is added dropwise at −45 to −40 °C. The cooling bath is not removed until the rearrangement reaction[9-12] is complete (violent increase of temperature from −40 to −15 °C). When room temperature is reached the precipitated triethylamine hydrochloride is filtered off, the solvents are evaporated, and the solid residue is recrystallised from benzene/petroleum ether (10/1); yield: 9.3 g (58%); m.p. 135–137 °C.

Asymmetric Reduction of *N*-(1-Phenylethylidene)-diphenylphosphinamide (1a); Typical Procedure:

A suspension of lithium aluminium hydride (0.46 g, 0.012 mol) and (−)-quinine (3.56 g, 0.011 mol, $[\alpha]_D^{20}$: −118° ±2, *c* 1.5 in chloroform; Fluka AG) in dry ether (120 ml) is stirred at 30–35 °C for 20–30 min. Then, a solution [in the analogous reduction of **1b**: a suspension] of *N*-(1-phenylethylidene)-diphenylphosphinamide (**1a**; 3.2 g, 0.01 mol) in dry tetrahydrofuran (50 ml) is added dropwise at room temperature and the mixture is allowed to stand for 24 h. Water (10 ml) is then added with stirring followed by 10–15% hydrochloric acid (15 ml). The ether layer is separated, washed with dilute hydrochloric acid (3 × 15 ml) and with water (15 ml), dried with magnesium sulfate, and evaporated to give *N*-(1-phenylethyl)-diphenylphosphinamide **(2a)**; yield: 2.4 g (75%); m.p. 145–147 °C; m.p. after two recrystallisations from benzene: 169–175 °C.

Acidolysis of *N*-Alkyldiphenylphosphinamides (2):

The cleavage of compounds **2** to give the amines **3** is performed using the procedure described in Ref.[1, 13].

(*S*)-(−)-*N*-(1-Phenylethyl)-phosphinamide (2′a):

To a stirred solution of (*S*)-(−)-1-phenylethanamine (**3′a**; 1.21 g, 0.01 mol, $[\alpha]_D^{20}$: −38°, *c* 4.0, methanol) and triethylamine (1.01 g, 0.01 mol) in benzene (25 ml), a solution of chlorodiphenylphosphine (2.2 g, 0.01 mol) in benzene (5 ml) is added dropwise at 20–25 °C. The precipitated triethylamine hydrochloride is filtered off and a slight molar excess (10–15%) of an 80% solution of *t*-butyl hydroperoxide in di-*t*-butyl peroxide is added dropwise with cooling in such a manner as to maintain a temperature of 25–30 °C. The mixture is then concentrated to dryness and the solid residue is recrystallised from benzene; yield: 2.2 g (68.5%); m.p. 187–190 °C; $[\alpha]_D^{20}$: −50 ± 1° (*c* 1.8, methanol).

$C_{20}H_{20}NOP$	calc.	C 74.25	H 6.23	N 4.36	P 9.65
(321.4)	found	74.29	6.37	4.23	9.40

M.S.: *m/e* = 321 (M$^+$, 3.1), 306 (38.5), 201 (57), 120 (100), 77 (22.5%).

^{31}P-N.M.R. ($CDCl_3/H_3PO_{4\,ext}$): $\delta = -20.1$ ppm.

(*S*)-(+)-*N*-[1-(1-Naphthyl)-ethyl]-diphenylphosphinamide (2′d):

Prepared in the same manner as **2′a** from (*S*)-(−)-1-(1-aminoethyl)-naphthalene[19] (**3′d**; $[\alpha]_D^{20}$: −80.2°, neat; Ref.[14], $[\alpha]_D^{25}$: −80.8°, neat); yield: 62%; m.p. 162–163 °C (from dichloromethane/petroleum ether, 1/1); $[\alpha]_D^{20}$: +17° ±0.5° (*c* 1.7, methanol).

$C_{24}H_{22}NOP$	calc.	C 77.61	H 5.97	N 3.77	P 8.34
(371.4)	found	77.35	6.15	3.92	8.26

M.S.: *m/e* = 371 (M$^+$, 3.4), 356 (10.8), 201 (31.6), 170 (100), 155 (6.5), 127 (4.3), 77 (12%).

^{31}P-N.M.R. ($CHCl_3/H_3PO_{4\,ext}$): $\delta = -22.7$ ppm; ($CH_3OH/H_3PO_{4\,ext}$): $\delta = -25.0$ ppm.

Reduction of *N*-Benzylidenediphenylphosphinamide (1e) with $LiAlD_4$:

A suspension of lithium aluminium deuteride (0.55 g, 0.013 mol) and (−)-quinine (10 g, 0.031 mol) in dry benzene (250 ml) is stirred and refluxed for 1 h, then cooled to 20–25 °C, a solution of *N*-benzylidenediphenylphosphinamide[1] (**1e**; 3 g, 0.01 mol) in dry tetrahydrofuran (50 ml) is added dropwise with stirring, and the mixture is allowed to stand at room temperature for 24 h. Then, water (10 ml) and 10–15% hydrochloric acid (~50 ml) are added dropwise with stirring. The organic layer is separated, extracted with dilute hydrochloric acid (3 × 30 ml) and with water (50 ml), dried with magnesium sulfate, and evaporated. The oily residue solidifies when treated with a small amount of ether; yield of N-(*benzyl-α*-d)-*diphenylphosphinamide* **(2e)**: 1.4 g (45%); m.p. 110–111 °C; $[\alpha]_D^{20}$: +0.2° ±0.1° (*c* 2.1, methanol); $[\alpha]_{435}^{20}$: +0.4° ±0.1° (*c* 2.1, methanol).

$C_{19}H_{17}DNOP$ (308.3)

M.S.: *m/e* = 308 (M$^+$, 5.5), 307 (1.1), 201 (18.5), 155 (7.3), 107 (100), 92 (28), 77 (37.7), 47 (23%).

I.R. (film): $\nu = 3160$ (m), 3040 (w), 1500 (w), 1190 (s) cm^{-1}.

^{31}P-N.M.R. ($CHCl_3/H_3PO_{4\,ext}$): $\delta = -23.5$ ppm.

This work was financially supported by the Polish Academy of Sciences, Grant No MR-I-12.1.7.10. The authors are indebted to Prof. H. Hoffmann, Bayer AG., Wuppertal, for the generous gift of optically active amines.

Received: June 30, 1980
(Revised form: August 21, 1981)

---

* Address for correspondence.

[1] B. Krzyżanowska, W. J. Stec, *Synthesis* **1978,** 521.
[2] O. Cervinka, *Collect. Czech. Chem. Commun.* **30,** 1684 (1965).
[3] O. Cervinka, V. Suchan, O. Kotynek, V. Dudek, *Collect. Czech. Chem. Commun.* **30,** 2484 (1965).
[4] A. F. Cockerill, G. L. O. Davies, R. C. Harden, D. M. Rackham, *Chem. Rev.* **73,** 553 (1973).
[5] D. Nasipuri, C. K. Ghosh, R. J. L. Martin, *J. Org. Chem.* **35,** 657 (1970).
[6] J. W. Lown, M. H. Akhtar, *J. Chem. Soc. Chem. Commun.* **1973,** 511.
[7] A. R. Battersby, J. Staunton, M. C. Summers, *J. Chem. Soc. Perkin Trans. 1* **1976,** 1052.

[8] M. Kajiwara, S. F. Lee, A. I. Scott, *J. Chem. Soc. Chem. Commun.* **1978**, 967.

[9] Y. L. Kruglyak et al., *Zh. Obshch. Khim.* **38**, 943 (1968); *C. A.* **69**, 58784 (1968).

[10] Y. L. Kruglyak et al., *Zh. Obshch. Khim.* **39**, 215 (1969); *C. A.* **70**, 105743 (1969).

[11] C. Brown, R. F. Hudson, A. Maron, K. A. F. Record, *J. Chem. Soc. Chem. Commun.* **1976**, 663.

[12] L. Lopez, J. Barrans, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1806.

[13] A. Zwierzak, J. Brylikowska-Piotrowicz, *Angew. Chem.* **89**, 109 (1977); *Angew. Chem. Int. Ed. Engl.* **16**, 107 (1977).

[14] E. Samuelsson, *Thesis*, University of Lund, 1923; *C. A.* **18**, 1833 (1924).

[15] H. Gerlach, *Helv. Chim. Acta* **51**, 1587 (1968).

[16] H. E. Smith, M. E. Warren, L. I. Katzin, *Tetrahedron* **24**, 1327 (1968).

[17] *Dictionary of Organic Compounds*, Eyre & Spottiswoode Publishers Ltd., London, 1965.

[18] V. M. Potapov, V. M. Demyanovich, A. P. Terentev, *Zn. Obshch. Khim.* **35**, 1538 (1965); *J. Gen. Chem. USSR* **35**, 1541 (1965).

[19] W. H. Pirkle, T. G. Birlingame, S. D. Beare, *Tetrahedron Lett.* **1968**, 5849.

[20] H. Wolf, E. Bunnenberg, L. Djerassi, *Chem. Ber.* **97**, 533 (1964).

[21] M. E. Warren, Jr., H. E. Smith, *J. Am. Chem. Soc.* **87**, 1757 (1965).

[22] W. Klyne, J. Buckingham, *Atlas of Stereochemistry*, Oxford University Press, New York, 1974.

0039-7881/82/0432-0273 $ 03.00