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AMINOMETHYLATION OF PHOSPHINES BY ALKOXYMETHYLAMINES AND DIAMINOMETHANES

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Most of the known methods for the synthesis of aminomethylphosphines (AMP) are essentially modifications of the Mannich reaction [1-4]. The simplest variant consists in the reaction of a secondary amine, formalin, and phosphine [3]. However, in our attempts to synthesize dimethylaminomethyldiisopropylphosphine (I) according to [3], the yield did not exceed 47%. The main difficulty was, apparently, that by carrying out the reaction in aqueous medium, it was not possible to exclude the extraction stage, at which the readily oxidizable aliphatic phosphine was lost. We therefore developed methods for aminomethylation of phosphines in a nonaqueous medium by the action of accessible and readily purified tetraalkyldiaminomethanes and alkoxymethylamines (briefly described in [5]). The former have already been used for the preparation of AMP under fairly drastic conditions [5]. The addition of the acid catalyst made it possible to appreciably lower the reaction temperature, and the yields of the products varied within 65-95% (Table 1).

$$(Me_2N)_2CH_2 + HPRR' \xrightarrow[CF_3COOH\ (cat.)]{80^\circ} Me_2NCH_2PRR'$$

R = R′ = *i*-Pr (I); R = *i*-Pr, R′ = $PhCH_2$ (II);
R = *t*-Bu, R′ = $PhCH_2$ (III); R = *t*-Bu, R′ = Ph (IV)

Alkoxymethylamines have already been successfully used for the aminomethylation of aziridines [6]. The reactions with phosphines are known only for similar, but more active reagents, tetraalkyldiaminoalkoxymethanes [7].

TABLE 1. Properties of Aminomethylphosphines

Compound	Formula	Yield, %	bp, °C (p, mm Hg)	M+, *m/e*
(I)	$Me_2NCH_2P(i\text{-}Pr)_2$	81	69(8)	175
(II)	$Me_2NCH_2P(i\text{-}Pr)CH_2Ph$	87	101–103(1,5)	223
(III)	$Me_2NCH_2P(t\text{-}Bu)CH_2Ph$	95	120–121(4)	237
(IV)	$Me_2NCH_2P(t\text{-}Bu)Ph$	65	130(10)	223
(V)	$O(CH_2CH_2)_2NCH_2P(i\text{-}Pr)_2$	86	87(3)	217
(VI)	$O(CH_2CH_2)_2NCH_2P(i\text{-}Pr)CH_2Ph$	79	135(3)	a
(VII)	$O(CH_2CH_2)_2NCH_2P(t\text{-}Bu)Ph$	65	158(6)	b
(VIII)	$MeOOCCH(CH_2)_3NCH_2P(i\text{-}Pr)_2$ c	94	100–104(2)	245
(IX)	$MeOOCCH(CH_2)_3NCH_2P(i\text{-}Pr)CH_2Ph$ d	63	150–152(1)	e
(X)	$MeOOCCH(CH_2)_3NCH_2P(t\text{-}Bu)Ph$ f	78	149–150(1,5)	g

a) M^+ is absent, characteristic peaks at m/e 166 and 100.
b) M^+ is absent, characteristic peaks at m/e 166, 100, and 57.
c) $[\alpha]_{546}^{20}$ −76.8° (C 9.45, MeOH).
d) $[\alpha]_{546}^{20}$ −22.3° (C 0.5, MeOH).
e) M^+ is absent, characteristic peaks at m/e 166, 141, and 91.
f) $[\alpha]_{546}^{20}$ −57° (C 1.9, MeOH).
g) M^+ is absent, characteristic peaks at m/e 166, 141, 110, and 57.

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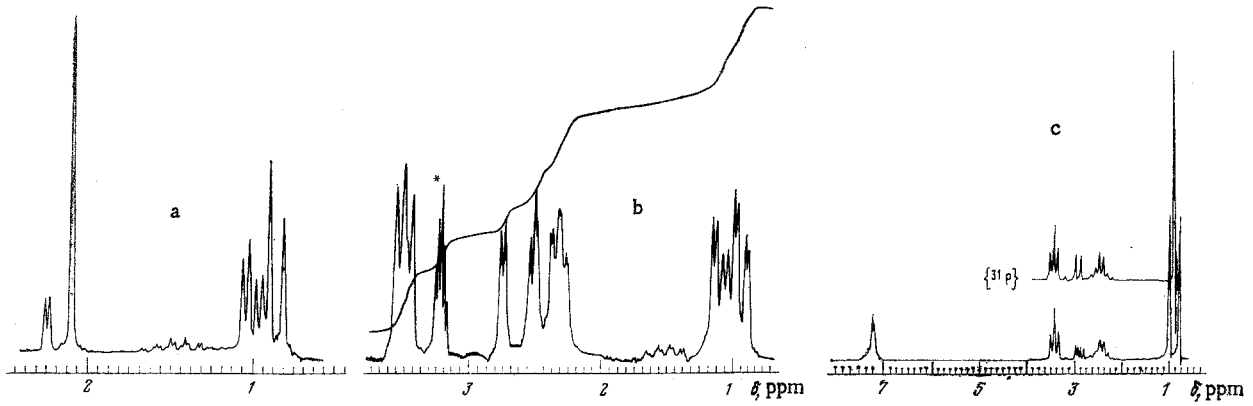

Fig. 1. PMR spectra of (I) in C_6H_6 (a), (VI) in CD_3OD (b), and (VII) in C_6F_6 (c). The nonequivalency of the diastereotopic Me groups and i-Pr substituents observed for (I) and (VI), and of the diastereotopic methylene protons of the CH_2P group observed for (VII), indicate a pyramidal configuration of the P atom. In the case of (VII), the experiment with decoupling from the spin–spin coupling with P shows that the additional multiplicity of the CH_2N ring signal [which is not present in the spectrum of (V)] is caused by the asymmetric induction of the phosphoric chiral center.

We carried out the aminomethylation of secondary phosphines with N-methoxymethyl derivatives of morpholine and S-(–)-methyl ester of proline by mixing the reagents without a solvent (with evolution of heat), followed by removal of methanol by distillation and short-term heating of the residue at 125-140°C

$$R_2NCH_2OMe + HPRR' \xrightarrow[-MeOH]{} R_2NCH_2PRR'$$

With $R_2N = O(CH_2CH_2)_2N$ $R = R' = i$-Pr (V);

R = i-Pr, R′ = $PhCH_2$ (VI); R = t-Bu, R′ = Ph (VII).

With $R_2N = MeO_2CCH(CH_2)_3N$ R = R′ = i-Pr (VIII);

R = i-Pr, R′ = CH_2Ph (IX); R = t-Bu, R′ = Ph (X)

The yields are practically the same as in the preceding case, 63-94% (see Table 1). All the AMP are colorless, mobile or viscous liquids; compound (II) crystallizes on storage in a refrigerator. The structure of all the AMP was confirmed by the NMR spectra (Table 2, Figs. 1 and 2) and mass spectra (see Table 1). The AMP (I) was characterized in the form of oxide (Ia), oxide iodomethylate (Ib), and hydrochloride (Ic), and (V) in the form of oxide (Va). The oxidation of (I) and (V) by a current of dry air is complete after 3-4 h to give yields of 83 and 85%. The AMP oxides are viscous colorless liquids, soluble in organic solvents.

We synthesized the aminomethyl derivatives of asymmetric secondary phosphines (II)-(IV), (VI), (VII), and (IX), (X), and optically active AMP, C-chiral (VIII), and C- and P-chiral (IX) and (X). The diastereomers (IX) and (X) are formed in the ratio ~1:1 (see, for example, Fig. 2). Compounds of this type can be readily obtained from available chiral amines, and therefore they may be interesting as polydentate ligands for building complex catalysts of asymmetric reactions. In the asymmetric reactions, for example, hydrogenation on rhodium complexes with optically active phosphines, optical yields of 96% have recently been obtained [8].

For the syntheses of P-chiral AMP, we used their cleavage reaction by acid chlorides [5]. By the action of a half-molar amount of the chiral acid chloride, S-(–)tosylproline chloride [9], one dextrorotatory enantiomer is preferentially cleaved, and therefore, the residue becomes enriched with levorotatory (–)-(IV).

$$(IV) + {}^1/_2S\text{-}(-)\text{-}ClCOCH(CH_2)_3NTs \xrightarrow[-50°]{Et_2O} \underset{(-)\text{-}(IV)}{(-)\text{-}Me_2NCH_2P(t\text{-}Bu)Ph} \xrightarrow{PhCH_2Br} (-)\text{-}PhCH_2(Me_2)\overset{\oplus}{N}CH_2P(t\text{-}Bu)PhBr^{\ominus}(-)\text{-}(IVa)$$

The unreacted (–)-(IV) was extracted with n-heptane. According to the PMR spectrum, it is identical with (IV) and has an optical activity of $[\alpha]_{546}^{20}$ –8.2° (C 1.0, C_6H_6). To remove possible optically active admixtures, the product was converted into the N-bromobenzylate of (–)-(IVa), which after crystallization has $[\alpha]_{546}^{20}$ –3.4° (C 0.6, MeOH) (the PMR spectrum is given in Fig. 3).

EXPERIMENTAL

All the syntheses and physicochemical studies of AMP were carried out in an argon atmosphere and in absolute solvents. To remove air and moisture, before carrying out the experiments, the whole glass apparatus

TABLE 2. NMR Spectra of Aminomethylphosphines

Compound	Solvent	δ, ppm						J, Hz						$\delta^{31}P$ in Ph_2O (external standard 85% H_3PO_4), ppm
		Me_A (H_A)	Me_B (H_B)	HCP	MeN	CH_2	other	Me_ACH	Me_BCH	Me_AP (H_AP)	Me_BP (H_BP)	CH_2P	other	
(I)	C_6H_6	0,94	0,93	1,42	2,1	2,24	–	6,0	6,0	12,75	9,9	2,25	–	8,9
(II)	C_6F_6	0,97	0,93	1,32	2,1	2,64	CH_A=CH_B 2,31 Ph 7,05	6,2	7,0	13,0	12,0		H_AP 5,5 H_BP 3,0	18,6
(III)	C_6H_6	–	–	–	2,02	2,47 2,54	CMe_3 0,90 Ph 7,08	–	–	(2,0)	(3,0)		HCCP 12,0 H_AH_B 13,0 H_BH_A 16,5	9,7
(IV)	C_6F_6	(2,92)	(2,71)	–	2,1	–	CMe_3 0,87 Ph 7,29	–	–	(5,5)	(3,75)		HCCP 12,0 H_AH_B 13,8	11,5
(V)	CD_3OD	0,99	0,96	1,64	–	2,43	CH_2N 2,38 CH_2O 3,49	6,5	7,0	13,5	9,5			15,0
(VI)	CD_3OD	1,05	0,99	1,51	–	2,75	CH_2N 2,26 CH_2O 3,5 CH_A=CH_B 2,5 Ph 7,5	6,5	6,8	13,1	12,5	3,0	H_AP 4,5 H_BP 2,0	–
(VII)	C_6F_6	(3,17)	(2,68)	–	–	–	CMe_3 0,92 CH_2N 2,5 CH_2O 3,42 Ph 7,25	–	–	(3,0)	(5,0)		HCCP 12,0 H_AH_B 13,5	14,2
(VIII)	$CDCl_3$	1,2	1,1	1,72	MeO 3,75	2,92	$CH_{2\alpha}$ 3,3 $CH_{2\beta}$ 1,91	6,2	6,2	11,25	9,75		H_AP 2,5 H_BP 4,5 H_AH_B 12,5	–
(IX)	C_6F_6	1,06	0,98	–	MeO^1 3,5 MeO^2 3,66	–	$CH_{2\alpha}$ 2,69 $CH_{2\beta}$ 1,79 Ph 7,15	6,0	6,0	14,0	12,75			
(X)	C_2Cl_4	CMe_3^1 0,88	CMe_3^2 0,91	–	MeO^1 3,44 MeO^2 3,52	–	CH_2^1 3,18 CH_2^2 3,21 $CH_{2\alpha}$ 2,82 $CH_{2\beta}$ 1,66	–	–	(3,5)	(2,5)		HCCP 12,0 $H_AH_B^1$=$H_AH_B^2$ 13,0	–

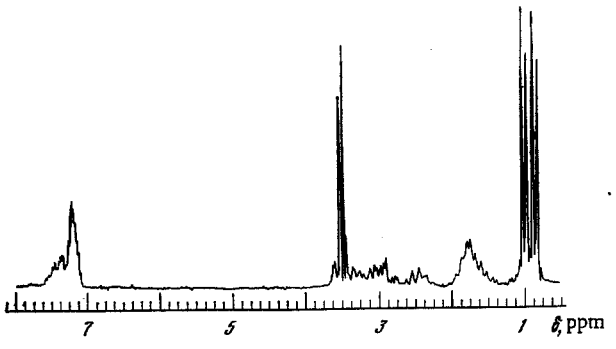

Fig. 2

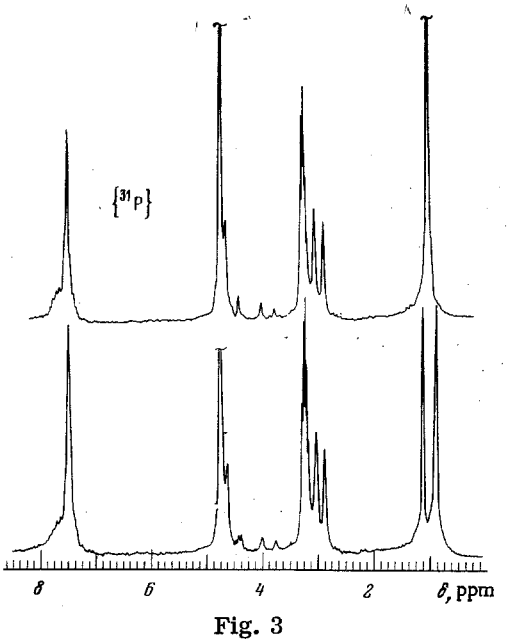

Fig. 3

Fig. 2. PMR Spectra of optically active (X) in C_2Cl_4. The two sets of signals of the MeO and t-Bu groups correspond to diastereomers, one of which predominates.

Fig. 3. PMR Spectra of (–)-(IVa) in CD_3OD. The nonequivalency of the diastereotopic methylene protons of the CH_2P group (the AB spectrum at decoupling from P atom) and of the methyl groups in Me_2N is caused by the asymmetric induction of the chiral P atom.

was evacuated (to 1 mm) with heating over an open flame of a burner, and was then filled with dry argon.

The PMR spectra were run on the "Jeol JNM-C-60HL" (60 MHz), "Tesla BS-487C" (80 MHz), and "Varian HA-100" (100 MHz) spectrometers. The chemical shifts were measured with reference to TMS and HMDS internal standards, depending on the chemical properties of the compounds studied. The ^{31}P NMR spectra were

run on the "Varian XL-100," "JNM-4H-100" (40.5 MHz), and "Brucker SXP-4/100" (36.44 MHz) apparatus, and the chemical shifts were measured in ppm with 85% H_3PO_4 used as external standard (into the stronger field, positive). The optical rotation was measured on "Polamat A" and "Perkin–Elmer-141" polarimeters.

The starting phosphines were prepared by the method described in [10]. The properties of the AMP described below are given in Tables 1 and 2.

Dimethylaminomethyldiisopropylphosphine (I). A) According to the procedure of [3], 2 g (44 mmoles) of dry dimethylamine was passed with cooling (bath temperature −30°C) through 7 g of a 37% aqueous solution of formaldehyde. The mixture was heated to 80°C, and 5 g (42 mmoles) of diisopropylphosphine were added. The mixture was then boiled for 2 h, and extracted with n-hexane (3 × 8 ml). The extract was dried over calcined $MgSO_4$, the solvent was distilled, and the residue distilled in vacuo. Yield, 3.5 g (47%) of (I).

B) A 3.8 g (32 mmoles) portion of diisopropylphosphine was placed in a distillation flask, and 3.4 g (34 mmoles) of bis-dimethylaminomethane (bp 84°C) were added at 20°C. The mixture spontaneously heated up to 50°C, and then 3 drops of CF_3COOH were added. It was further heated to 80°C, and left to stand overnight. After distillation, 4.66 g (yield 81%) of (I) were obtained.

Dimethylaminomethyldiisopropylphosphine Oxide (Ia). Air was passed for 3 h through a tube filled with KOH into 0.71 g (41 mmoles) of (I) to yield 0.66 g of (Ia) (85%), colorless liquid, bp 82°C (2 mm), M^+ m/e 191. PMR spectrum (C_6H_6, δ, ppm, J. Hz): 0.95 (Me_A, J_{HH} = 6.15, J_{HP} = 13.7), 0.87 (Me_B, J_{HH} = 6.75, J_{HP} = 13.2), 1.55 (HCP), 2.05 (MeN), 2.16 (CH_2).

Diisopropylphosphinomethyltrimethylammonium Iodide Oxide (Ib). A solution of 0.3 g (excess) of CH_3I in 10 ml of ether was added to a solution of 0.2 g (1 mmole) of (Ia) in 10 ml of ether. The precipitate was separated, washed with ether (4 × 5 ml), and dried in vacuo to give a yield of 0.24 g (69%) of (Ib), white crystals, mp > 250°C (sublimation). Found: C 36.34; H 7.73; N 4.40; P 9.05%. $C_{10}H_{25}NOPI$. Calculated: C 36.03; H 7.51; N 4.20; P 9.31%. PMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.24 (Me_A, J_{HH} = 7.0, J_{HP} = 16.0), 1.20 (Me_B, J_{HH} = 7.0, J_{HP} = 16.0), 2.25 (HCP), 3.32 (MeN), 3.81 (CH_2, J_{HP} = 3.5).

Dimethylaminomethyldiisopropylphosphine Hydrochloride (Ic). From 0.8 g (4.2 mmoles) of (I) and 0.15 g of dry HCl in 20 ml of ether, 0.8 g of (Ic) (83%), mp 150–152°C, was obtained. Found: C 51.32; H 10.83; N 6.63; P 14.80%. $C_9H_{23}NPCl$. Calculated: C 51.18; N 10.90; N 6.63; P 14.69%. PMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.01 (Me_A, J_{HH} = 6.15, J_{HP} = 13.35), 0.99 (Me_B, J_{HH} = 6.15, J_{HP} = 12.0), 1.8 (HCP), 2.72 (MeN), 3.16 (CH_2, J_{HP} = 3.0).

Dimethylaminomethylisopropylbenzylphosphine (II). From 4.2 g (25 mmoles) of isopropylbenzylphosphine and 3.3 g (32 mmoles) of bis-dimethylaminomethane, by procedure B for the synthesis of (I), 4.9 g of (II) were obtained, yield 87%.

Dimethylaminomethyl-tert-butylbenzylphosphine (III). Similarly, from 3.7 g (20.5 mmoles) of tert-butylbenzylphosphine and 3 g (29 mmoles) of bis-dimethylaminomethane, 4.64 g of (III) were obtained. Yield 95%, colorless, viscous liquid.

Dimethylaminomethyl-tert-butylphenylphosphine (IV). Similarly, from 3 g (18 mmoles) of tert-butylphenylphosphine and 1.85 g (18 mmoles) of bis-dimethylaminomethane, 2.62 g of (IV) were obtained. Yield 65%, colorless, viscous liquid.

(−)-Dimethylaminomethyl-tert-butylphenylphosphine (−)-(IV). A solution of 0.72 g (2.5 mmoles) of N-tosylproline chloride (prepared by the method in [9]) in 15 ml of ether cooled to −50°C was added to a solution of 1.11 g (5 mmoles) of (IV) in 20 ml of ether cooled to the same temperature. A precipitate immediately formed. After 10 min, the cooling was discontinued, and after 20 min, the precipitate was separated, and washed with ether. After removal of ether from the filtrate, the residue was extracted thrice with n-heptane, and the solvent was evaporated from the extract to give a yield of 0.15 g of (−)-(IV), which according to PMR spectrum is identical with racemate of (IV), $[\alpha]_{546}^{20}$ −8.2° (C 1.0, C_6H_6).

(−)-Dimethylaminomethyl-tert-butylphenylphosphine N-Bromobenzylate (−)-(IVa). A 0.15 g (0.84 mmole) portion of benzyl bromide was added to a solution of 0.11 g (0.49 mmole) of (−)-(IV) in 15 ml of ether. After 15 min, the solution became turbid, and a precipitate formed. After 2 h this was separated, washed with ether and dried in vacuo. After crystallization from an acetonitrile–ether mixture, 0.10 g of (IVa) was obtained. Yield 40%, $[\alpha]_{546}^{20}$ −3.4° (C 0.6, MeOH). PMR spectrum (CD_3OD, δ, ppm, J, Hz): 1.05 (Me_3C, J_{HCCP} = 13.5), 3.02 and 2.94 (Me_AN and Me_BN),* 4.2 (CH_2P, AB spectrum, $\Delta\nu$ = 36 Hz, J_{H_AP} = 1.5, J_{H_BP} = 5.0, $J_{H_AH_B}$ = 15.0), 4.65 ($PhCH_2N$), 7.5 (Ph).

*A similar nonequivalency of the diastereotopic methyl groups bound to the heteroatom, was observed in [11].

N-Morpholinomethyldiisopropylphosphine (V). A 3.7-g (28 mmoles) portion of N-methoxymethylmorpholine [bp 43°C (4 mm)] was added at 20°C to 3.3 g (28 mmoles) of diisopropylphosphine. The mixture was heated up to 50°C, methanol was distilled off, and heating was continued on a water bath at 125-140°C. The residue was distilled in vacuo to give 5.2 g of (V), yield 86%.

N-Morpholinomethyldiisopropylphosphine Oxide (Va). Air was passed for 4 h through a tube containing alkali into 0.55 g (2.5 mmoles) of (V) to yield 0.48 g of (Va) (83%), bp 105°C (3 mm); n_D^{26} 1.4702, M^+ m/e 233. PMR spectrum (C_6H_6, δ, ppm, J, Hz): 1.01 (Me_A, J_{HH} = 6.2, J_{HP} = 13.8), 0.96 (Me_B, J_{HH} = 7.0, J_{HP} = 14.5), 2.32 (CH_2P, J_{HP} = 5.5), 2.42 (CH_2N), 3.44 (CH_2O).

N-Morpholinomethylisopropylbenzylphosphine (VI). Similarly to the synthesis of (V), from 2.4 g (14.4 mmoles) of isopropylbenzylphosphine and 1.9 g (14.5 mmoles) of N-methoxymethylmorpholine, 3 g of (VI) were obtained. Yield 79%, colorless mobile liquid.

N-Morpholinomethyl-tert-butylphenylphosphine (VII). Similarly, from 1.75 g (10.5 mmoles) of tert-butylphenylphosphine and 1.44 g (14.1 mmoles) of N-methoxymethylmorpholine, 1.81 g of (VII) was obtained, yield 65%; the compound crystallizes on standing in a refrigerator.

S-(−)-Methyl Ester of N-(Diisopropylphosphinomethyl)proline (VIII). Similarly, from 1.11 g (9.4 mmoles) of diisopropylphosphine and 1.63 g (9.4 mmoles) of S-(−)-methyl ester of N-methoxymethylproline (prepared by the method in [6], bp 65°C (2 mm), n_D^{20} 1.4553, $[\alpha]_{546}^{20}$ − 75.1° (9.45, MeOH)), 2.18 g of (VIII) were obtained, yield 94%.

S-(−)-Methyl Ester of N-(Isopropylbenzylphosphinomethyl)proline (IX). Similarly, from 1.2 g (7.2 mmoles) of isopropylbenzylphosphine and 1.4 g (8.8 mmoles) of S-(−)-methyl ester of N-methoxymethylproline, 1.34 g of (IX) was obtained, yield 63%.

S-(−)-Methyl Ester of N-(tert-Butylphenylphosphinomethyl)proline (X). Similarly, from 3.57 g (21.5 mmoles) of tert-butylphenylphosphine and 3.72 g (21.7 mmoles) of S-(−)-methyl ester of N-methoxymethylproline, 4.9 g of (X) were obtained, yield 78%.

CONCLUSIONS

1. Methods for the aminomethylation of phosphines with alkoxymethylamines and diaminomethanes were developed.

2. Aminomethyl derivatives of asymmetric phosphines and optically active C-chiral and diastereomeric C- and P-chiral aminomethylphosphines were prepared.

3. An enatiomerically enriched (−)-dimethylaminomethyl-tert-butylphenylphosphine, with an asymmetric center at the P atom was synthesized.

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