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A NEW METHOD FOR THE SYNTHESIS OF OPTICALLY PURE PHOSPHINE OXIDES

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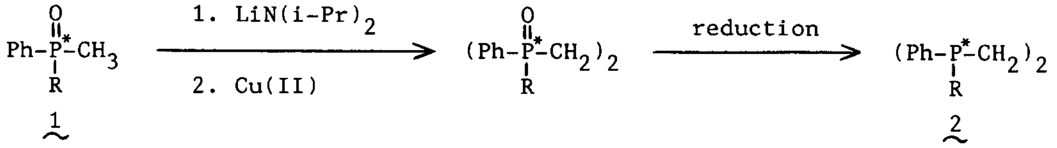
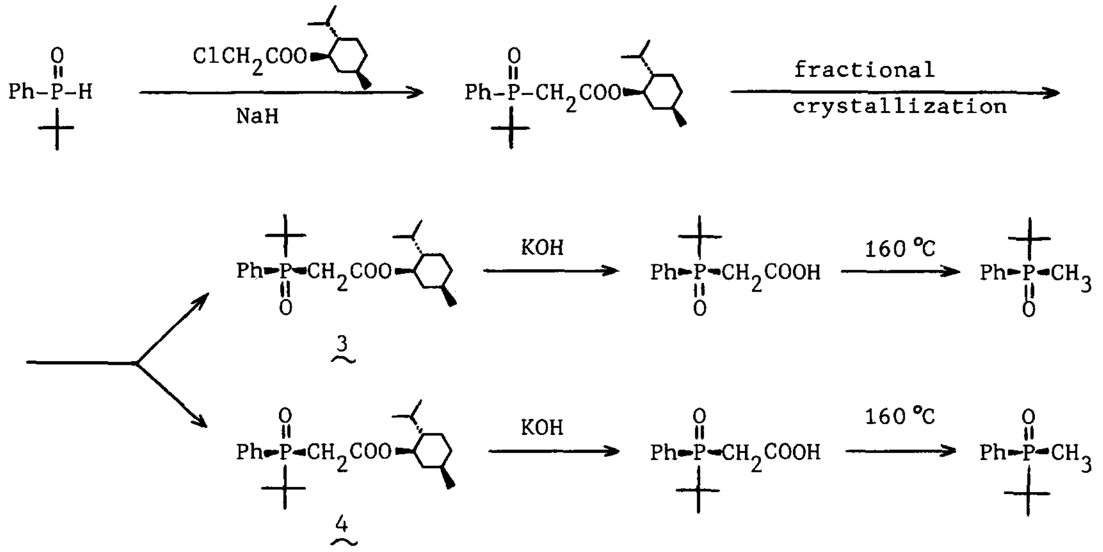
Summary: Tertiary phosphine oxides have been prepared with high enantiomeric excesses via intermediate menthyl 2-phosphinylacetates.

Optically active phosphine oxides **1** are key intermediates in the synthesis of bidentate phosphine ligands **2** useful for catalytic asymmetric homogeneous hydrogenation.1) These phosphine oxides can be prepared by the reaction of diastereomerically pure menthyl methylphenylphosphinate with Grignard reagents.2) However, this methodology is not applicable to the preparation of the phosphine oxides having a bulky group such as *t*-butyl or 2,4,6-triisopropylphenyl group. The use of organolithium reagents in place of the Grignard reagents permits preparation of the phosphine oxides, but the products are obtained in a significantly lower state of optical purity.3,4)



$$\underset{\mathbf{1}}{\mathrm{Ph}\text{-}\overset{O}{\underset{R}{P^{*}}}\text{-}CH_3} \xrightarrow[\text{2. Cu(II)}]{\text{1. LiN(i-Pr)}_2} (\mathrm{Ph}\text{-}\overset{O}{\underset{R}{P^{*}}}\text{-}CH_2)_2 \xrightarrow{\text{reduction}} \underset{\mathbf{2}}{(\mathrm{Ph}\text{-}\underset{R}{P^{*}}\text{-}CH_2)_2}$$

We wish to report herein a new synthetic sequence for the preparation of tertiary phosphine oxides **1** in high enantiomeric purity. The preparations of (*S*)- and (*R*)-*t*-butylmethylphenylphosphine oxides provide typical examples of our method. Thus, (-)-menthyl chloroacetate5) (35.0 g, 0.15 mol) was added dropwise to a mixture of *t*-butylphenylphosphine oxide6) (27.3 g, 0.15 mol) and sodium hydride (0.36 mol) in tetrahydrofuran (150 mL) at 5~15 °C under nitrogen. After stirring at ambient temperature for 12 h, the reaction mixture was quenched with a saturated NH_4Cl solution, followed by extraction with hexane. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to leave a pasty oil (56 g). This crude diastereomeric mixture was dissolved in hexane (150 mL) and the solution was kept in a refrigerator (5 °C) for 3 days.

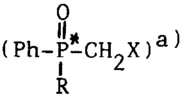


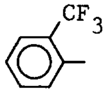
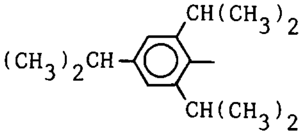
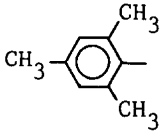
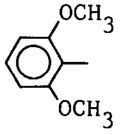
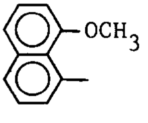
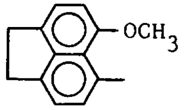
The crystalline solid was collected and fractionally recrystallized to afford diastereomer 3 7) (15.8 g, 28%) and diastereomer 4 8) (11.4 g, 20%). Diastereomer 3 (1.89 g, 5 mmol) was hydrolyzed with KOH (855 mg) in MeOH (5 mL) for 6 h at room temperature to yield the corresponding acid (mp 166-168 °C(dec), 1.19 g, 99%) and *l*-menthol (0.78 g, 100%). The acid (1.08 g, 4.5 mmol) was heated in bromobenzene (10 mL) at 160 °C for 2 h to afford the desired (*S*)-*t*-butylmethylphenylphosphine oxide 9) (0.86 g, 97%). Similarly, the other diastereomer 4 was converted into (*R*)-phosphine oxide 10,11) in 89% yield. Enantiomeric excesses of both enantiomers were found to be 100% by the ^{1}H-NMR (270 MHz) measurement using optically active phosphinothioic acid (-)-*t*-BuPhP(S)OH. 12,13)

In a similar manner, several other unsymmetrical secondary phosphine oxides were converted into the corresponding menthyl esters. The diastereomeric mixtures were then fractionally recrystallized from hexane to afford the diastereomeric esters of high optical purity. The subsequent hydrolysis and decarboxylation proceeded smoothly without any loss of optical purity to yield tertiary phosphine oxides 1. These results are summarized in Table 1.

By the present method, sterically crowded phosphine oxides, which are difficultly prepared by the previously existing methods, were obtained in exceedingly high enantiomeric purity. This method, consequently, provides a new synthetic route to a variety of chiral bidentate phosphine ligands 2.

Further studies on the application of the present method to asymmetric synthesis are currently underway.

Table 1. Optically Active Phosphine Oxides  $(Ph-\overset{O}{\overset{\|}{P}}{}^{*}(R)-CH_2X)$[a]

R	X	mp °C	$[\alpha]_D^{25}$ (MeOH)	Yield (%)[b,c]
$\underline{t}$-C_4H_9	COOMen	116.5-117.5	+9.4°(c 1.0)	28[d]
	COOH	166-168(dec)	————[e]	99
	H[f]	99-100	-21.8°(c 1.0)	97
"	COOMen	75-76	-85.7°(c 1.0)	20[d]
	COOH	————[g]		
	H[h]	99-100	+22.7°(c 1.0)	89[i]
	COOMen	113.5-114.0	-42.4°(c 1.0)	21[d]
	COOH	170-171(dec)	-6.7°(c 1.0)	91
	H	67-68	-9.4°(c 1.0)[j]	95
	COOMen[k]	139.5-140.0	+42.8°(c 1.0)	10[d]
	COOH	————[g]		
	H	108-109	+42.9°(c 1.0)[l]	87[i]
	COOMen	101-103	-72.7°(c 1.0)	13[d]
	COOH	158-160(dec)	-43.6°(c 2.0)	98
	H	oil	-10.4°(c 2.4)	99
	COOMen	114-115	-67.2°(c 1.0)	41[d]
	COOH	199-200(dec)	-79.2°(c 1.2)	94
	H	188-190	-119° (c 1.0)	95
	COOMen[m,n]	79-80	+55.5°(c 1.0)	25[d]
	COOH	207-208(dec)	+29.3°(c 1.0)	95
	H	177-178	+21.5°(c 1.0)	92
	COOMen	131-133	+64.0°(c 1.9)	16[d]
	COOH	205-207(dec)	+38.7°(c 1.0)	97
	H	149-151	+21.2°(c 1.2)	79

a) Absolute configurations of all compounds have not yet been determined except the compounds having $\underline{t}$-butyl group (R=$\underline{t}$-Bu). b) Yield of isolated pure product. c) All compounds were confirmed by ^{1}H-NMR spectral analysis. d) Yield from secondary phosphine oxide. e) Optical rotation of this compound was not measured. f) ($\underline{S}$)-$\underline{t}$-butylmethylphenylphosphine oxide. g) This carboxylic acid was not isolated. h) ($\underline{R}$)-$\underline{t}$-butylmethylphenylphosphine oxide. i) Yield from the menthyl ester. j) Enantiomeric excess of this compound was determined to be 95% by ^{1}H-NMR measurement using (-)-$\underline{t}$-BuPhP(S)OH. k) Other diastereomer: mp 88-89 °C. l) 97% ee. m) Separated by medium pressure liquid chromatography (silica gel, dichloromethane/acetone= 10/1). n) Other diastereomer: mp 142-143 °C; $[\alpha]_D^{25}$ -93.5°(c 1.0, MeOH).

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References and Notes

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7) Colorless cubes; mp 116.5-117.5 °C; $[\alpha]_D^{25}$ +9.4°(c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 0.1~2.0 (18H, m), 1.17 (9H, d, J_{PCCH}=16Hz, t-C_4H_9), 3.23 (2H, d, J_{PCH}= 12Hz, -CH_2-), 4.3~4.9 (1H, m), 7.1~8.0 (5H, m); IR (KBr) 1720, 1175 cm^{-1}; Anal. Calcd for $C_{22}H_{35}O_3P$: C, 69.81; H, 9.32; P, 8.18. Found: C, 69.94; H, 9.29; P, 8.09.
8) Colorless long needles; mp 75-76 °C; $[\alpha]_D^{25}$ -85.7°(c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 0.3~2.0 (18H, m), 1.17 (9H, d, J_{PCCH}=16Hz, t-C_4H_9), 3.23 (2H, d, J_{PCH}= 12Hz, -CH_2-), 4.3~4.9 (1H, m), 7.2~8.0 (5H, m); IR (KBr) 1730, 1175 cm^{-1}; Anal. Calcd for $C_{22}H_{35}O_3P$: C, 69.81; H, 9.32; P, 8.18. Found: C, 69.93; H, 9.30; P, 8.27.
9) Colorless crystals; mp 99-100 °C; $[\alpha]_D^{25}$ -21.8°(c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 1.13 (9H, d, J_{PCCH}=15Hz, t-C_4H_9), 1.70 (3H, d, J_{PCH}=12Hz, CH_3), 7.2~7.9 (5H, m); IR (KBr) 1160 cm^{-1}; Anal. Calcd for $C_{11}H_{17}OP$: C, 67.33; H, 8.73. Found: C, 67.25; H, 8.67.
10) Colorless crystals; mp 99-100 °C; $[\alpha]_D^{25}$ +22.7°(c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 1.13 (9H, d, J_{PCCH}=15Hz, t-C_4H_9), 1.70 (3H, d, J_{PCH}=12Hz, CH_3), 7.2~7.9 (5H, m); IR (KBr) 1160 cm^{-1}; Anal. Calcd for $C_{11}H_{17}OP$: C, 67.33; H, 8.73. Found: C, 67.48; H, 8.69.
11) Mislow et al. prepared (R)-t-butylmethylphenylphosphine oxide ($[\alpha]_D$ +14.9° (MeOH), 71% ee) by the reaction of diastereomerically pure menthyl (S)-methylphenylphosphinate with t-butyllithium.[4)]
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