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Stereospecific Reduction of Phosphine Oxides to Phosphines by the Use of a Methylation Reagent and Lithium Aluminum Hydride

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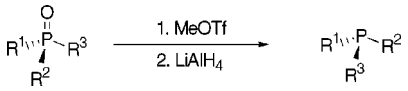
ABSTRACT



Various phosphine oxides are efficiently reduced by the use of a methylation reagent and lithium aluminum hydride. Optically active P-chirogenic phosphine oxides are also reduced with inversion of configuration at phosphorus atom by treatment with methyl triflate, followed by reaction with $LiAlH_4$.

Optically active phosphines possessing their chiral centers at phosphorus atoms have become increasingly important not only in the stereochemical studies of organophosphorus compounds but also as the chiral ligands in transition metal-catalyzed asymmetric reactions.[1−3] These phosphines are usually synthesized by the stereospecific reduction of optically active phosphine oxides with silane reagents[4−7] or by deboranation of the corresponding phosphine−boranes.[8] The former method is frequently employed, but in most cases it is accompanied by partial racemization of the products. On the other hand, $LiAlH_4$ is a powerful reducing reagent and it is often used for the reduction of achiral phosphine oxides.[9] However, the reduction of optically active phosphine oxides by $LiAlH_4$ leads predominantly to the racemized phosphines owing to pseudorotation of the pentacoordinate intermediates.[10] The utilities of optically active P-chirogenic phosphines and the powerful reducing ability of $LiAlH_4$ led us to develop a convenient method for the stereospecific reduction of phosphine oxides.

At first we chose triphenylphosphine oxide as a model substrate, and its reduction with $LiAlH_4$ was examined using

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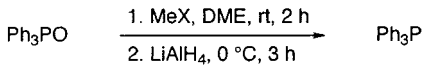
several methylation reagents as the activators. Thus, to a stirred solution of triphenylphosphine oxide in DME was added 1.1 equiv of a methylation reagent at room temperature. After 2 h, 2.5 equiv of $LiAlH_4$ was added in one portion at 0 °C. The reaction mixture was worked up in the usual manner, and the product was isolated by flash column chromatography. The results are shown in Table 1. The

Table 1. Reduction of Triphenylphosphine Oxides with MeXand $LiAlH_4$



entry	MeX	yield (%)[a]
1	MeOTf	97
2	MeOTs	94
3	MeOMs	96
4	MeI	96
5	*b*	4

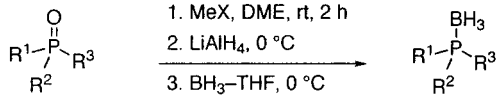
[a] Isolated yield. [b] No methylation reagent was added.

reactions readily proceeded regardless of the type of the methylation reagents (entry 1−4), in sharp contrast to the reaction in the absence of a methylation reagent (entry 5). It is noted that the use of methyl trifluoromethanesulfonate (methyl triflate) afforded the best-isolated yield (97%).

Gratified by the partial success achieved, we studied the reaction with a series of phosphine oxides. In these experiments, the products were isolated as air-stable borane adducts by treatment of the reaction mixture with BH_3−THF complex.[11] The results are summarized in Table 2. Various phosphine oxides including aliphatic ones were smoothly reduced in high yield by the use of methyl iodide or methyl triflate, with exception of some bulky phosphine oxides such as *tert*-butyldiphenylphosphine oxide. In general, the use of methyl triflate provided higher product yields than methyl iodide.

On the basis of these results, we tried the stereospecific reduction of enantiomerically pure phosphine oxides. (*S*)-Methyl(1-naphthyl)phenylphosphine oxide was chosen as the model substrate, because the enantiomeric excess of the reduction product was readily determined by HPLC analysis using a chiral column.[12] First, this phosphine oxide was reduced by the use of methyl iodide/$LiAlH_4$ under the conditions mentioned above to afford the corresponding phosphine in 94% yield, but its enantiomeric excess was

Table 2. Reduction of Phosphine Oxides with MeX and $LiAlH_4$



entry	R^1	R^2	R^3	MeX	yield (%)[a]
1	Ph	Ph	Me	MeOTf	95
2				MeI	97
3	Ph	Ph	Et	MeOTf	93
4				MeI	94
5	Ph	Ph	*i*-Pr	MeOTf	91
6				MeI	85
7	Ph	Ph	*t*-Bu	MeOTf	60
8				MeI	40
9	*n*-Bu	*n*-Bu	*n*-Bu	MeOTf	80
10				MeI	60
11	c-C_6H_{11}	c-C_6H_{11}	c-C_6H_{11}	MeOTf	83
12				MeI	<1
13	Ph	Ph	$CH_2CH_2P(O)Ph_2$	MeOTf	86[b]
14				MeI	72[b]
15		(*R*)-BINAPO[c]		MeOTf	90[b]
16				MeI	66[b]

[a] Isolated yield. [b] The reaction mixture was worked up without treatment with BH_3−THF to obtain the corresponding diphosphine. [c] (*R*)-BINAPO = (*R*)-2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl.

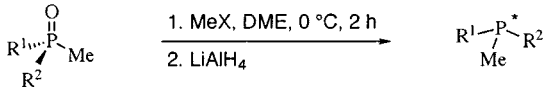
disappointedly low (18% ee (*R*)) (entry 1 in Table 3).[13] In contrast, the reaction with methyl triflate/$LiAlH_4$ provided the product with higher enantiomeric excess (77% ee (*S*)) (entry 4). When the reaction temperature was decreased, the enantioselectivity was significantly improved. Thus, the reduction using methyl triflate at −60 °C resulted in virtually net inversion of configuration at the phosphorus atom (98%

(11) **General Procedure for Reduction of Phosphine Oxides.** To a stirred solution of phosphine oxide (1.0 mmol) in DME (1 mL) was added methyl trifluoromethanesulfonate (1.1 mmol) at room temperature under an Ar atmosphere. After 2 h, the flask was immersed in an ice bath and lithium aluminum hydride (2.5 mmol) was added in one portion. The mixture was monitored by TLC for 2−5 h and then quenched by addition of 1 M aqueous HCl (5 mL) or BH_3−THF complex (1.5 mmol). The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined extracts were dried over $MgSO_4$, and evaporated under reduced pressure. The residue was passed through a column of basic alumina using degassed ether. The eluent was evaporated to leave practically pure phosphine or phosphine−borane.

(12) Watanabe, T.; Gridnev, I. D.; Imamoto, T. *CHIRALITY* **2000**, *12*, 346−351. **Enantiomeric Excess Determination.** The following list describes conditions used for separation of racemic products: **methyl(1-naphthyl)phenylphosphine oxide** (HPLC, Daicel Chiralcel OJ, flow rate 1.0 mL/min, 10% 2-PrOH/hexane, (S_p) t_1 = 33.5 min, (R_p) t_2 = 37.9 min); **methyl(1-naphthyl)phenylphosphine** (HPLC, Daicel Chiralcel OJ, flow rate 1.0 mL/min, 10% 2-PrOH/hexane, (S_p) t_1 = 11.7 min, (R_p) t_2 = 16.4 min); **cyclohexylmethyl(1-naphthyl) phosphine-borane** (HPLC, Daicel Chiralcel OJ, flow rate 0.5 mL/min, 3.2% 2-PrOH/hexane, (R_p) t_1 = 21.8 min, (S_p) t_2 = 25.1 min); **2-methoxyphenyl(methyl)phenylphosphine oxide** (HPLC, Daicel Chiralcel OJ, flow rate 0.5 mL/min, 10% ethanol/hexane, (S_p) t_1 = 14.3 min, (R_p) t_2 = 16.3 min); **2-methoxyphenyl(methyl)-phenylphosphine−borane** (HPLC, Daicel Chiralcel OJ, flow rate 2.0 mL/min, 10% 2-PrOH/hexane, (S_p) t_1 = 10.7 min, (R_p) t_2 = 22.7 min); **cyclohexyl(2-methoxyphenyl)methylphosphine−borane** (HPLC, Daicel Chiralcel OJ, flow rate 0.5 mL/min, 10% 2-PrOH/hexane, (S_p) t_1 = 14.0 min, (R_p) t_2 = 15.8 min); **2-isopropylphenyl(methyl)phenylphosphine−borane** (HPLC, Daicel Chiralcel AS, flow rate 0.5 mL/min, 3.2% 2-PrOH/hexane, (R_p) t_1 = 13.9 min, (S_p) t_2 = 17.0 min); ***tert*-butyl(2-phenylethyl)-methylphosphine−borane** (HPLC, Daicel Chiralcel OD-H, flow rate 0.5 mL/min, 10% 2-PrOH/hexane, (R_p) t_1 = 10.0 min, (S_p) t_2 = 10.9 min); **cyclohexyl(2-phenylethyl)methylphosphine−borane** (HPLC, Daicel Chiralcel OD-H, flow rate 0.5 mL/min, 10% 2-PrOH/hexane, (R_p) t_1 = 11.7 min, (S_p) t_2 = 13.3 min); **1,2-bis(boranato(*tert*-butyl)methylphosphino)ethane** (HPLC, Daicel Chiralcel OD-H, flow rate 0.5 mL/min, 10% 2-PrOH /hexane, (*R*,*R*) t_1 = 9.9 min, (*S*,*S*) t_2 = 14.1 min).

(13) The racemization barrier energy of methyl(1-naphthyl)phenylphosphine in toluene was measured to obtain the following kinetic data: E_a = 28.9 kcal/mol, ln A = 29.1, $\tau_{1/2}$(95 °C) = 6.9 h, $\tau_{1/2}$(20 °C) = 9.7 y. These results indicate that the formed phosphine itself is stereochemically stable under these reaction conditions in the reaction system.

Table 3. Reduction of Enantiomerically Pure Phosphine Oxides



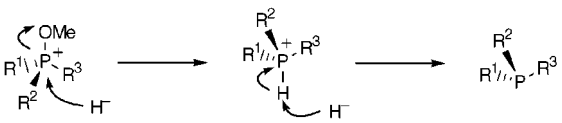
entry	R^1	R^2	MeX	temp (°C)	yield (%)[a]	% ee (config)
1	Np[b]	Ph	MeI	0	94	18 (*R*)
2	Np[b]	Ph	MeOMs	0	90	13 (*R*)
3	Np[b]	Ph	MeOTs	0	97	6 (*R*)
4	Np[b]	Ph	MeOTf	0	92	77 (*S*)
5	Np[b]	Ph	MeOTf	−50	92	97 (*S*)
6	Np[b]	Ph	MeOTf	−60	90	98 (*S*)
7	Ph	*o*-$MeOC_6H_4$	MeOTf	−60	85[c]	98 (*R*)
8	c-C_6H_{11}	*o*-$MeOC_6H_4$	MeOTf	−60	74[c]	95 (*R*)
9	c-C_6H_{11}	Np[b]	MeOTf	−60	81[c]	88 (*R*)
10	Ph	*o*-$iPrC_6H_4$	MeOTf	−60	97[c]	98 (*R*)
11	$(CH_2)_2Ph$	*t*-Bu	MeOTf	−60	55[c]	97 (*R*)
12	$(CH_2)_2Ph$	c-C_6H_{11}	MeOTf	−60	96[c]	92 (*R*)

[a] Isolated yield. [b] Np = 1-naphthyl. [c] Isolated as the phosphine−borane.

ee) (entry 6).[14] Several other enantiomerically pure phosphine oxides were subjected to reduction under the same conditions. The products were isolated as borane adducts by treatment of the reaction mixtures with borane−THF, because the produced phosphines were readily oxidized on contact with air. The chemical yields and the ee values of the products are described in Table 3. It is noted that (*R*)-2-methoxyphenyl(methyl)phenylphosphine oxide was converted to the borane adduct of (*R*)-2-methoxyphenyl(methyl)phenylphosphine ((*R*)-PAMP) in excellent stereospecificity (entry 7).[8b,15] Another notable fact is that trialkylphosphine oxides were also reduced with a high degree of stereospecificity, although the chemical yields were not always satisfactory (entries 11 and 12).

Although the detailed reaction mechanism has not yet been studied, we suppose that when methyl triflate/$LiAlH_4$ is employed as the reagent system the reaction proceeds through the following pathway. The phosphine oxide is methylated by methyl triflate, and the resulting phosphonium salt is subjected to hydride attack from the backside of the methoxy group to give the reduction product (Scheme 1).[16−18] On the

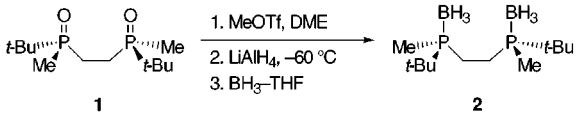
Scheme 1



other hand, very low stereospecificity was observed when methyl iodide, methyl methanesulfonate, and methyl *p*-toluenesulfonate were used. In these cases, the methylation of the phosphine oxide was not observed, although the reduction took place smoothly. The reduction probably proceeds in this case through the initial generation of alane by the reaction of methylation reagents with $LiAlH_4$ and subsequent reaction of phosphine oxides with alane.[19]

Previously, we reported that P-chirogenic trialkylphosphine ligands, (*S*,*S*)-1,2-bis(alkylmethyl phosphino)ethanes (BisP*), were effectively employed in the asymmetric hydrogenations of various α-(acylamino)acrylic acid and *β*-keto esters.[20] These phosphine ligands are prepared by the use of naturally occurring (−)-sparteine as a chiral source. However, the synthesis of (*R*,*R*)-enantiomers of the phosphine ligands was difficult mainly owing to the unavailability of (+)-sparteine as a chiral source.[21] Our method might provide an approach to the (*R*,*R*)-enantiomers by reduction of (*R*,*R*)-1,2-bis(alkylmethylphosphinyl)ethanes that are obtained by deboranation of (*S*,*S*)-BisP*, followed by oxidation with H_2O_2.[22] To examine this possibility, we carried out the reduction of (*R*,*R*)-1,2-bis(*tert*-buthylmethylphosphinyl)ethane (**1**). The reduction proceeded clearnly to give the expected product possessing almost 100% ee,[23] but the isolated yield was not high (24%) (Scheme 2).

Scheme 2



1 **2**

24% (>99% ee)

In summary, we have shown that phosphine oxides are readily converted to the corresponding phosphines in high

(14) Use of L-Selectride (lithium tri-*sec*-buthylborohydride) in place of $LiAlH_4$ under the same conditions resulted in recovery of the starting phosphine oxide.

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yields by the use of a methylation reagent and $LiAlH_4$. Enantiomerically pure phosphine oxides are reduced with inversion of configuration at the phosphorus atom by the use of this reagent system.

(23) A very small amount (<1%) of the meso isomer of **2** was detected by HPLC analysis.

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