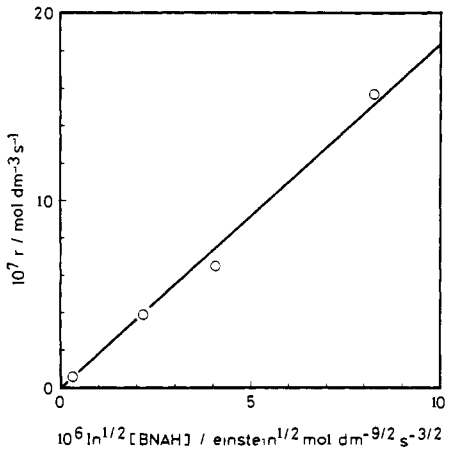

Figure 4. A plot of the rate of the photochemical reaction of BNAH with benzyl bromide in MeCN containing 1.11×10^{-1} M pyridine (r) as a function of $In^{1/2}$[BNAH]; see eq 12 and 22 in text.

where R_i is the initiation rate given by eq 12. From eqs 22 and 12 is derived eq 23,

$$\frac{1}{r^2} = C\left(\frac{1}{k_q\tau[PhCH_2Br]} + 1\right) \qquad (23)$$

where C is given as $2k_t[BNAH]^{-2}/(k_p^2\Phi_f^0 In)$. The validity of eq 23 is confirmed by the plots of $1/r^2$ against $1/[PhCH_2Br]$ which give a linear correlation under the conditions that the C value is constant (i.e., a fixed concentration of benzyl bromide and a constant light intensity), as shown in Figure 3a. The relation of eq 23 is applicable also for *p*-cyanobenzyl bromide by taking its concentration for $[PhCH_2Br]$ as shown in Figure 3b. From the slope and the intercept in Figure 3, parts a or b, the k_q values for the electron-transfer reactions from BNAH* to benzyl bromide and *p*-cyanobenzyl bromide (eq 7) have been determined as 4.2×10^9 and 1.4×10^{10} M^{-1} s^{-1}, respectively, which show excellent agreements with those determined independently from the fluorescence quenching of BNAH (4.9×10^9 and 1.3×10^{10} M^{-1} s^{-1}, respectively, see Table III). Such agreements clearly demonstrate that the electron transfer from the excited-state BNAH* to benzyl bromide or *p*-cyanobenzyl bromide (eq 7) is solely responsible for the photoinitiation of the chain reaction.

The validity of the rate formulation (eq 22) is further confirmed by the dependence of the reaction rate on the BNAH concentration as well as the light intensity absorbed by BNAH in the presence of a fixed amount of benzyl bromide in solution, as seen in Figure 4 which shows a linear relation between r and $In^{1/2}$[BNAH]. By substituting the reported value of k_t for the benzyl radical (1.8×10^9 M^{-1} s^{-1})[31] into eq 22, the propagation rate constant k_p of hydrogen transfer from BNAH to benzyl radical (eq 18) can be evaluated as 1.6×10^4 M^{-1} s^{-1}, which is the same order of magnitude as the rate constant of hydrogen transfer from BNAH to the hex-5-enyl radical (6.0×10^4 M^{-1} s^{-1}).[5c]

Registry No. BNAH, 952-92-1; benzyl bromide, 100-39-0; *p*-cyanobenzyl bromide, 17201-43-3; methyl iodide, 74-88-4; isopentyl nitrite, 110-46-3; *p*-dinitrobenzene, 100-25-4.

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Optically Active Phosphines. Facile Preparation of the Optically Active *n*-Propylmethylbenzyl- and Methylphenylbenzylphosphine Oxides as Precursors to the Corresponding Tertiary Phosphines

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Abstract: The optically active phosphine oxides $MePhP(O)CH_2Ph$ (**6**) and n-$PrMeP(O)CH_2Ph$ (**9**) are readily prepared by a new route from the easily available, essentially optically pure, *O*-isopropyl *S*-alkyl methylphosphonothioates **4** and **7**. Two successive Grignard reactions give **6** in 52–55% and **9** in 18–24% overall chemical yields. Reductions of **6** and **9** with $PhSiH_3$ afford the corresponding optically active phosphines $MePhCH_2Ph$ (**1**) and n-$PrMePCH_2Ph$ (**2**) of optical purities (45–70% and 53–57%, respectively) which are quite suitable for studies of the stereochemistries of reactions occurring at phosphorus. The relative ease of the procedure and the fact that both enantiomers are equally readily available especially recommend this route for the preparation of **1**. Moreover, no other experimentally detailed, published method for the preparation of an optically active trialkylphosphine such as **2** in reasonably high optical purity is available. The route to phosphine **1** depends on the use of a potentially tridentate ligand ($SCH_2CH_2OCH_2CH_2OCH_2CH_3$) on phosphorus which activates **4** toward reaction with PhMgBr and also allows $CH_3CH_2OCH_2CH_2OCH_2CH_2$ to be selectively displaced. Quite surprisingly, this displacement occurs with inversion of configuration at phosphorus by contrast to the retentive stereochemistry normally observed on reaction of *O*-alkyl *S*-alkyl methylphosphonothioates with Grignards. Evidence is also presented for the potential generality of this method for the preparation of optically active dialkylphenyl- and trialkylphosphines.

Optically active tertiary phosphines continue to be of interest for the study of the stereochemistries of reactions taking place at phosphorus and also as potential ligands in asymmetric catalysis.[1] The earliest practical preparations of optically active phosphines involved electrolysis of optically active phosphonium salts.[2] This approach was largely replaced by use of diastereomerically pure cholesteryl[3] and menthyl alkylarylphosphinates[4-6]

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(2) Horner, L. *Pure Appl. Chem.* **1964**, *9*, 225; Horner, L.; Winkler, H. *Justus Liebigs Ann. Chem.* **1965**, *685*, 1.

(3) Nudelman, A.; Cram, D. J. *J. Org. Chem.* **1971**, *36*. 335.

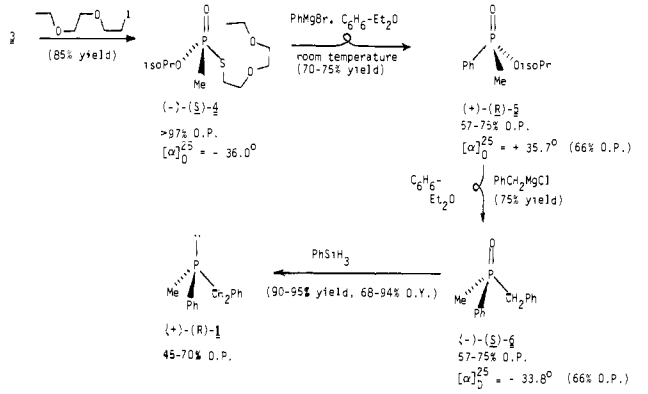
0002-7863/83/1505-4727$01.50/0

which undergo stereoselective reaction with Grignards to yield optically active phosphine oxides[3-6] whose stereospecific reductions[4,7] readily afford the corresponding phosphines. Hydrolyses of benzylphosphonium salts also give optically active phosphine oxides.[8,9] More recently, racemic tertiary phosphines have been resolved by the use of chiral palladium(II) complexes.[10] While the work we report here was in progress, a variety of tertiary phosphines, many of high optical purity, were reported to arise from the reaction of alkyl and aryl lithium compounds with diastereomerically reasonably pure cinchoninyl alkylphenyl- or arylphenylphosphonites.[11] The phosphonite precursor is formed from reaction of the requisite racemic chlorophosphine with optically pure cinchonine. The same sort of substitution reaction occurs with menthyl phosphinites[12] which are, however, much harder to prepare in high optical purity.

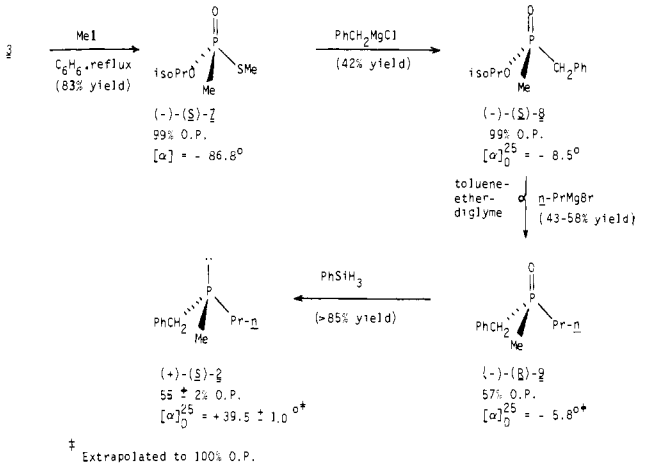
For our own research we needed to have tertiary phosphines of reasonably high optical purities with a benzyl substituent on phosphorus. It was also necessary that one of them be a phenylphosphine and the other a trialkylphosphine. $MePhPCH_2Ph$ (**1**) and *n*-$PrMePCH_2Ph$ (**2**) were chosen as suitable molecules. Both had been prepared previously, but no experimental procedure for optically active **2** was reported.[13] The optical purity of the reported **2**, it turns out, was actually only about 20%. The only other benzyl-substituted trialkylphosphine of which we are aware is *n*-$BuMePCH_2Ph$, obtained via the somewhat difficult-to-prepare optically active phosphonium hydrogen tartrate precursor.[8] The chemical yield and optical purity of the phosphine were not stated. The latter should now be easily measurable via the phosphine oxide by the use of (−)-*t*-BuPhP(S)OH as described later.

Each of the above methods as potential routes to **1** or **2** has certain disadvantages. The resolution of phosphonium salts is a very tedious process, and the electrolysis equipment is not routinely available in most laboratories. The hydrolysis of phosphonium salts is mostly limited to ones with a benzyl or allyl leaving group on phosphorus. The classical method based on menthyl alkylaryl- or dialkylphosphinates requires many very time-consuming recrystallizations of the phosphinate which then is not always optically pure and is obtained in low yields. The range of phosphine oxides obtainable in the subsequent Grignard reaction is limited[5] by the extreme sensitivity of the reaction of the phosphinates to variations of the groups on phosphorus and on oxygen and on the nature of the Grignard reagent, and yields of the phosphine oxides are quite variable. (We obtained **1** in only 30% yield, though 80% optically pure, in this final step.) Steric effects seem responsible for these limitations which can be somewhat overcome by the use of lithium reagents in place of the Grignards.[6] Also, with the menthyl methylphenylphosphinate, which is widely used for the preparation of **1**, only the S_p diastereomer is obtained in high optical purity. The method has seen only limited application and success in the preparation of trialkylphosphines.[6] The resolution of tertiary phosphines via palladium complexation[10] requires prior preparation of the optically active amines and their palladium complexes and may suffer unjustly from a reluctance of organic chemists to work with palladium compounds. Moreover, neither of the specific phosphines of interest to us has been prepared in this way previously. Finally, the method which employs the cinchoninyl phosphinites also has not been used to prepare trialkylphosphines,[11] and the (+)-$MePhCH_2Ph$ and (−)-$MePhPCH_2Ph$ made in this manner were reported[11] to have optical purities of only 18–20%.

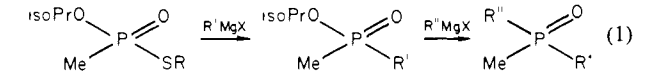
Scheme I



Scheme II



We report here an efficient new synthetic sequence for the preparations of $MePhPCH_2Ph$ (**1**) and *n*-$PrMePCH_2Ph$ (**2**) in good yields and optical purities suitable for stereochemical studies.[14] The method is based on the easily resolvable *O*-isopropyl methylphosphonothioic acid,[15] the amine salt of which, **3**, serves as the optically pure starting material. Unlike the preparation of **1** via menthyl methylphenylphosphinate (see above), either one of the enantiomers of **3** and thus of **1** and **2** can be obtained with equal ease. Phosphorothioate **3** is readily alkylated. Subsequent reaction with two different Grignard reagents in succession yields the required oxides of **1** and **2** according to the general sequence of eq 1. Reduction affords the phosphines. Preliminary indications that this approach may be reasonably general for the preparation of other phosphines will be given.



(1)

(4) Nauman, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.
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(7) Marsi, K. L. *J. Org. Chem.* **1974**, *39*, 265.
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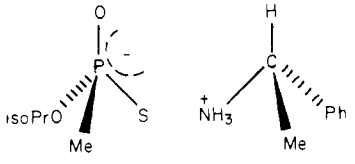
(12) Omelanczuk, J.; Perlikowska, W.; Mikolajczyk, M. *J. Chem. Soc., Chem. Commun.* **1980**, 24. Mikolajczyk, M.; Omelanczuk, J.; Perlikowska, W.; *Tetrahedron* **1979**, *35*, 1531. Mikolajczyk, M. *Pure Appl. Chem.* **1980**, *52*, 959.
(13) Horner, L.; Luckenbach, R.; Balzer, W. D. *Tetrahedron Lett.* **1968**, 3157. The phosphine in question was made by cathodic reduction of methyl-*n*-propylbenzylbenzhydrylphosphonium bromide and by the cyanolysis of methyl-*n*-propylallylbenzylphosphonium bromide (L. Horner, personal communication).
(14) A preliminary account of the preparation of **2** was published earlier. Moriyama, M.; Bentrude, W. G. *Tetrahedron Lett.* **1982**, 4547.
(15) Boter, H. L.; Platenburg, D. H. J. M. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 399.

The scope of the method is further widened by the known stereospecific replacement of the benzyl substituent of optically active tertiary benzylphosphines on nucleophilic attack by alkyl lithium reagents,[16] e.g.

$$MePhPCH_2Ph + t\text{-BuLi} \rightarrow MePhPBu\text{-}t + PhCH_2Li$$

Results and Discussion

O-Isopropyl methylphosphorothioic acid was easily prepared by a previously published method[17] from $MePCl_2$[18] and quickly resolved to 99% optical purity by the method of Boter and Platenburg[15] using commercially available, optically pure 1-phenylethylamine. Both enantiomers of salt **3** are available by employing in succession the (−)- and (+)-amines. Recovered, resolved acid accounts for 95% of the starting racemic material, and the resolution is accomplished in 2 days. The required 1-phenylethylamine is relatively inexpensive and is recovered as well. Salt **3** is readily converted in high yields (Schemes I and II) to the *S*-alkyl *O*-isopropyl methylphosphonothioates, **4** and **7**, nearly optically pure starting materials for the two-step sequence (eq 1 and Schemes I and II) to optically active phosphine oxide. The formation from (−)-**3** of (−)-(*S*)-**7**,[19] a compound of known con-



(−)-(S_P)-(S_C)-**3**

figuration,[20] confirms the configurations at phosphorus of the levorotatory (S_P, S_C) and dextrorotatory (R_P, R_C) enantiomers of **3**.[15] The reactions with RI of necessity proceed with retention of configuration at phosphorus.

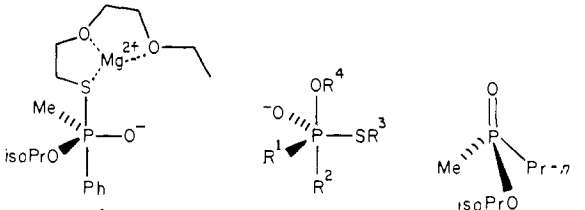
Of immense help in determining the optical purities of the intermediates and product phosphine oxides of Schemes I and II was the optically active phosphinothioc acid (−)-*t*-BuPhP(S)OH.[21] Addition of this material to mixtures of enantiomers resulted in nonequivalences of the MeP and/or POR proton resonances. In our experience this acid, easily obtainable in complete optical purity,[21] is a more effective shift reagent for use with P=O bond containing compounds than are the chiral lanthanide alternatives and has the added advantage of being reclaimable by extraction of collected samples by base.

Optically Active $MePhPCH_2Ph$, 1. The sequence of Scheme I was used to obtain the desired optically active phosphine. Overall chemical yields of **1** of 45–50%, based on **4**, were realized. Optical purity was 45–70%. Essential to the success of this sequence is the requirement that **4** be sufficiently reactive with PhMgBr under the reaction conditions that **5** not be converted further on reaction with PhMgBr to $Ph_2P(O)Me$. In an earlier report, Benschop and co-workers[20a] found **7** (Scheme II) to be converted in only 7% yield to (+)-(*R*)-**5**, isopropyl methylphenylphosphinate, though in 79% optical yield with retention of configuration. We were able to effect a greater conversion of phosphonothioate on reaction of racemic **7** with phenyl Grignard. Thus, in 28 h at room temperature, a 4.3/1 benzene/ether solution of PhMgBr and **7** (10/1 molar ratio, ca. 2 M in Grignard) led to 32% reaction of **7**. However, not only was **5** formed but an approximately equal amount of $Ph_2P(O)Me$ also was generated by obvious disubstitution. Shorter reaction times at reflux temperature using similar reaction mixtures resulted in greater conversion of **7** but also gave $Ph_2P(O)Me$ as the major product. Use of PhLi in place of PhMgBr and of various combinations of benzene with THF over a wide range of temperatures also was unsuccessful.

By comparison, reaction of (−)-(*S*)-**4** with PhMgBr, carried out in a 6/1 benzene/ether solution (PhMgBr/**4** molar ratio 10/1) at room temperature for 1.2 h, resulted in 52% consumption of **4** and formation of 51 GLC area % **5** along with only 1% of $Ph_2P(O)Me$. A greater consumption of **4** occurred on heating at about 70 °C for 1.2 h, but the major product was then $Ph_2P(O)Me$. Thus, although **4** reacts much more rapidly with PhMgBr than does **7**, it is still necessary to control the reaction time and conditions carefully to prevent formation of disubstitution product. This is easily done by monitoring the reaction at room temperature by GLC analysis of aliquots taken from time to time.

On a preparative scale (Scheme I), highly optically pure **4** is converted to **5** in 49% yield at about 50% consumption of **4**. Recovery of unreacted **4** and subsequent reaction raises the overall yield to 70–75%. The optical yields were determined from optical rotation based on a literature value of +54° for optically pure material.[22] Addition of (−)-(*R*)-*t*-BuPhP(S)OH did not result in sufficient peak separations to allow determination of optical purity by this means. Phosphinate **5** of optical purity 57–75% was obtained in this manner. The variation in observed yield is unexplained. Ranges of optical and chemical yields in Scheme I are composites from reactions of both (−)-(*S*)- and (+)-(*R*)-**4**.

What is surprising and notable about the stereochemistry of this reaction is the fact that it proceeds with predominant *inversion* of configuration about phosphorus. We suggest that the stereochemistry is a consequence of the same factor which makes **4** so reactive toward PhMgBr. This group was in fact designed to act as a potential intramolecular tridentate ligand to complex the Mg^{2+} and thus increase the nucleophilicity of the attacking phenyl group. At the same time the cation complex will be an electronegative ligand and thus understandingly more apicophilic than RS. The proposed intermediate in the conversion of **4** → **5** is depicted by **10**. RS displacements from phosphonothioates by Grignards



10 11 12

typically proceed with *retention* of configuration through initial adducts such as **11** which are presumed to undergo subsequent ligand exchange to place the RS apical prior to its departure.[21-23] Consistent with the Mg^{2+} complexation idea is the fact that the phosphonothioate equivalent to **4** but with RS = $SCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_3$ proved to be no more reactive than **7** and under forcing conditions gave predominantly $Ph_2P(O)Me$. It is significant, however, that the reaction of *n*-PrMgBr with (+)-(*R*)-**4** was found to proceed largely with *retention*, giving (*R*)-**12** (see below). Clearly, stereochemistry is susceptible to subtle factors, e.g., the structure of the Grignard[24] and the ease of dissociation of Mg^{2+} from the Grignard. The kinetic apicophilicity of RS and RO may well depend on subtle variations in the nature of the attacking nucleophile. Thus alkoxide ion attack on phosphonothioates, by contrast to reaction with RMgX, apparently is coaxial to the RS, resulting in overall inversion at phosphorus.[25]

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(18) Perry, B. J.; Reesor, J. B.; Ferron, J. L. *Can. J. Chem.* **1963**, *41*, 2299.
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(20) (a) van den Berg, G. R.; Platenburg, D. H. J. M.; Benschop, H. P. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 929. (b) Benschop, H. P.; van den Berg, G. R.; Boter, H. *Ibid.* **1968**, *87*, 387.
(21) Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1505; *Ibid.* **1978**, 326.
(22) DeBruin, K. E.; Johnson, D. M. *J. Chem. Soc., Chem. Commun.* **1975**, 753.
(23) Donohue, J.; Mandel, N.; Farnham, W. B.; Murray, R. K.; Mislow. K.; Benschop, H. P. *J. Am. Chem. Soc.* **1971**, *93*, 3792.
(24) Effects of solvent on Grignard composition are summarized in Parris. G. E.; Ashby, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 1206.
(25) See: De Bruin, K. E.; Ebersole, C. E.; Hughes. M. M.; Johnson, D. M. In "Phosphorus Chemistry"; Quin, L. D.; Verkade, J. G.; Eds.; American Chemical Society, Washington, DC, 1981; ACS Sym. Ser. No. 171. pp 543–550, and references cited therein.

The absolute configuration of **5** was based on literature precedent[22,23] and also on its conversion to known[4] (−)-(*S*)-**6** via a reaction which normally involves inversion of configuration.[5,6,20b] Similarly, $PhCH_2MgCl$ reacted with (*R*)-**12** to give known (−)-(*R*)-**9**, Scheme II. Presumed inversion accompanying **12** → **9** was used to establish the configuration of **12**.

Reaction of (+)-(*R*)-**5** (66% optical purity) with $PhCH_2MgCl$ in refluxing C_6H_6/Et_2O gave methylphenylbenzylphosphine oxide, (−)-(*S*)-**6**, of 66% optical purity in 75% isolated yield. The optical yield was 100%. The absolute configuration of (−)-(*S*)-**6** is well established, and the optical purity is based on the reported[4] specific rotation for optically pure **6** of −51.4°. Use of (−)-*t*-BuPhP(S)OH in $CDCl_3$ as the shift reagent resulted in concentration-dependent separations of the PMe doublets of 6.0–10.3 Hz (90 MHz). The average optical purity from integration of peak ratios was 70 ± 2%. In another reaction, purified (−)-(*S*)-**5** of undetermined optical purity was used. The isolated yield of pure (+)-(*R*)-**6** was 76%, and the optical purity was 75% based on its specific rotation. The range of optical yields of **6** in Scheme I is from a series of reactions of (*R*)- and (*S*)-**5**.

Reduction of **6** to the corresponding methylphenylbenzylphosphine, **1**, was accomplished by the method of Marsi, reported to proceed with complete retention of configuration at phosphorus.[7] When racemic **6** in gram quantities was used, pure **1** was isolated in 94% yield. Since the studies for which **1** was needed required only several-hundred-milligram quantities at a time, small-scale reductions were carried out in a one-piece apparatus described in the Experimental Section which allowed reduction, distillation, and manipulation of the very air sensitive product phosphine without transfers from flask to flask. In our hands this reduction was accompanied by minor amounts of racemization. This was minimized by keeping reaction times as short as possible and distilling the product phosphine quickly at minimum temperatures. Optical yields were 68–94%. We are not certain whether the racemizations noted with $PhSiH_3$ reductions occur during reaction or distillation. Furthermore, determinations of optical yield of reduction by comparisons of optical purities of **6** before reduction and after reoxidation with *t*-BuOOH assume the stereospecificity of the latter reaction as is found for **2** (below) and other phosphines.[7,26] Hexadichlorodisilane reductions (inversion) of optically active **6** have been reported to proceed in optical yields greater than 95%.[4,16] *This means that phosphine* **1** *of optical purity close to 75% can be realized.*

Optically Active *n*-PrMePCH$_2$Ph, 2. The sequence of Scheme II for (+)-(*S*)-**2** is illustrative. In this case the MeS of **7**, *O*-isopropyl *S*-methyl methylphosphothioate, was readily displaced; i.e., **7** was sufficiently reactive that formation of the product of double displacement, $(PhCH_2)_2P(O)Me$, was not a severe problem. Reasonable isolated yields of **8** of sufficient purity (94–100%) were obtained after 6–8 h of reflux. (The compound is very hygroscopic.) The stereospecificity of the reaction is very high. A purified sample was shown to 99% optically pure by use of (−)-*t*-BuPhP(S)OH.

For preparation of the phosphine oxide (−)-(*R*)-**9**, several batches of (−)-(*S*)-**8** of 94–100% chemical and 72–93% optical purities were combined. Subsequent reaction with *n*-PrMgBr at a 100 °C bath temperature gave GLC-pure (−)-(*R*)-**9** in combined 52% isolated yield (range 43–58%), 46% following sublimation. Optical purity, determined by use of (−)-*t*-BuPhP(S)OH at 300 MHz, was 57 ± 2°. As noted earlier, reactions of Grignard with phosphinates typically proceed via inversion of configuration at phosphorus.[5,6,20b] The R_P absolute configuration of the (−)-**9** so prepared is in agreement with that assigned by Horner et al.,[13] as is that of the phosphine which is formed in the subsequent $PhSiH_3$ reduction of Scheme II. The absolute configuration of (−)-(*S*)-**8** of this sequence, a new optically active phosphinate, can thereby be assigned with confidence. The *S* assignment is fully consistent, as well, with the expected[20a,21,22] retentive stereochemistry of the conversion of (−)-(*S*)-**7** to (−)-(*S*)-**8** of Scheme II and the normal inversion pathway for reactions of phosphinates (**8** → **9**).[5,6,20b] The optical yield of the reaction **8** → **9** is actually better than that depicted in Scheme II since the 99% optical purity given for **8** is that of a highly purified material and not that used to prepare (−)-(*R*)-**9**.

(26) Denney, D. B.; Hanifin, J. W., Jr. *Tetrahedron Lett.* **1963**, 2177.

Table I. Effect of Diglyme on Stereochemistry of Conversion of 8 to 9[a]

diglyme, mL (mmol)[b]	reflux time, h	GLC area %[c] un-reacted 8	GLC area %[c] product 9	isolated 9[d] GLC purity, %[f]	isolated 9[d] % OP[e]
0.2 (1.4)	5	16	84	94	29
0.2 (1.4)	7	21	79	85	21
0.3 (2.1)	5	8	92	92	47
0.4 (2.8)	5	6	94	100	53
1.0 (7.0)	5.5	3	97	100	10

[a] One millimole of (−)-(*S*)-**8** (from a combined mixture of portions of 8, 72–93% optically pure) dissolved in 15 mL of toluene and 5 mL of ether to which was added 5 mL of 1 M Grignard solution. [b] Added to reaction mixture. [c] Other peaks neglected. Relative amounts of 8 and 9 given. [d] By preparative TLC. Isolated yields 30–40%. [e] Approximate optical purities from optical rotations corrected for GLC-detected impurities. [f] Area percentage, thermal conductivity instrument.

The addition of a proper amount of diglyme to the reaction mixture in the conversion of **8** to **9** is absolutely essential to the success of the reaction as shown in Table I. In the absence of any added diglyme (data not given in Table I), the major portion of **8** remained unreacted, and the product phosphine oxide was racemic. Addition of increasingly large amounts of diglyme (1–7 molar equiv relative to reactant **8**) led to progressively increased reaction rates. Addition of an excessive amount led to reduced optical yields, however. These effects are seen in the results of Table I. The diglyme may activate the Grignard by complexation of the metal and/or alteration of the Grignard structure.[24] Its role in determining the overall reaction stereochemistry is completely obscure. We were indeed quite surprised that the reaction did not proceed readily with high stereospecificity in toluene/ether by itself.

The $PhSiH_3$ reduction of (−)-(*R*)-**9** proceeded in completely straightforward fashion to give (+)-(*S*)-**2** in at least 85% isolated yield. Its reoxidation with *t*-BuOOH was completely stereospecific. The overall yield of **9** from readily prepared **7** is thus 24% and of **2** is 21%, both highly pure chemically and of reasonable optical purity. Optically pure (+)-(*S*)-**2** is expected by extrapolation to have a specific rotation of +38.5 to +40.5° as compared to that estimated earlier[13] of 20°. (The phosphine of the earlier preparation, $[\alpha]^{25}_D$ 7.3°, was thus 19% optically pure.)

Indications that the above preparations of optically active phosphine oxides via phosphonothioic acid salt **3** should prove to have general applicability comes from some preliminary studies using other Grignards or sequences of substitution. For example (eq 2), reaction of (+)-(*R*)-**4** of very high optical purity with

$$\text{(+)-(R)-4} \xrightarrow[\substack{\text{24\% yield (retention)}\\ \text{refluxing } C_6H_6/Et_2O}]{n\text{-PrMgBr}} \text{(R)-12} \xrightarrow[\substack{\text{refluxing } Et_2O/C_6H_6\\ \text{55\% yield (inversion)}}]{PhCH_2MgCl} \underset{(OP \simeq 50\%)}{\text{(−)-(R)-9}} \quad (2)$$

n-PrMgBr followed by $PhCH_2MgCl$ yielded (−)-(*R*)-**9** having an optical purity of about 50%. No effort was made to optimize reaction conditions. Isolated (*R*)-**12** was identified by its ^1H NMR and its GLC retention time, but a specific rotation was not measured. The mechanistic implications of the formation of (*R*)-**12** by retention of configuration were discussed earlier.

Racemic **4** also proved reactive with $PhCH_2MgCl$ (eq 3).

$$\text{(±)-4} \xrightarrow[\substack{\text{22\% yield}\\ \text{refluxing } C_6H_6/\text{ether}}]{PhCH_2MgCl} \text{(±)-8} \xrightarrow[\sim 60\% \text{ yield}]{n\text{-PrMgBr}} \text{(±)-9} \quad (3)$$

Subsequent reaction of (±)-**8** with *n*-PrMgBr gave racemic **9**. The isolated yield of (±)-**8** was only 22%. Here, however, as in the

preparation of (−)-(*R*)-**4** via eq 2, the reaction was a small-scale one, and product isolation was accomplished by preparative TLC methods. It has been our general finding that isolated yields on large-scale reactions run under similar conditions using normal column chromatography for product isolation provide higher product yields. Again, reaction conditions have not been optimized.

It is noteworthy that with the exception of PhMgBr, the reactions of **4** with Grignards required reflux conditions. This no doubt is related to the possible Mg^{2+}-complexing role of the leaving group of **4** and the peculiar stereochemistry of its displacement by PhMgBr.

Conclusions. In summary, the *O*-isopropyl *S*-alkyl methylphosphonothioates **4** and **7** are readily prepared in close to 100% optical purities by previously known methods. These form the precursors for the preparation of phosphine oxides **6** and **9** by subsequent Grignard reactions in 57–75% and 50–60% optical purities, respectively. Yields of each step are particularly good for the preparation of **6** and at least reasonable for **9**. $PhSiH_3$ reduction yields the corresponding optically active phosphines, **1** and **2**. The preparation of **2** is especially significant since it is not available in optically active form by methods for which details are available and has never before been reported in optical purity above about 20%. Since only a few examples of optically active trialkylphosphines are known, and no good method for their preparation exists, the route via essentially optically pure **8** provides the method of choice for such materials. It seems likely that a variety of not too sterically demanding Grignard reagents will undergo reaction with **8** to yield alkylmethylbenzylphosphines. Thus, on reaction with EtMgBr we obtained $MeEtP(O)CH_2Ph$ from racemic **8** in 65% isolated yield. The optical yield on the conversion of **8** to **9** is reasonably good (Scheme II) but may turn out to be even better with other Grignards, for example, EtMgBr.

Likewise, optically active **5** provides a convenient intermediate for the preparation of optically active alkylphenylmethylphosphines. Judging from the fact that **6** in optical purity as high as 75% was obtained from optically active **5**, it is evident that the latter can be made with optical purity at least that high. *Both enantiomers* of **5** and hence of widely used **1** and, potentially, similar phosphines are readily available by this approach. This route to optically active phenylphosphines should serve as useful, and at least in some cases superior, alternative to the method using optically active chinconinyl alkylphenylphosphonites of high diastereomeric purity.[11] For example, although optical purities of the tertiary phospines thus prepared are often high, that of **1**, as noted earlier, was only 18–20%.[11]

Finally, the further potential of this approach is emphasized by the fact that a whole series of *O*-alkyl alkylphosphonothioc acids, R(R′O)P(S)OH, have been resolved with R′ = Me, C_2H_5, isoPr, *n*-Bu, *n*-Pr, and *p*-$NO_2C_6H_5$ and R = Me, Et, isoPr, and *t*-Bu.[15,27] With these as chiral precursors, numerous sequences analogous to those of Schemes I and II can be devised which potentially can provide optically active phosphines with a variety of substituents on phosphorus. In preliminary work, we found that Me(EtO)P(O)SMe reacts with *n*-PrMgBr and EtMgBr to give Me(EtO)P(O)Pr-*n* and Me(EtO)P(O)Et in 40–50% isolated yields.

Experimental Section

Methods and Materials. $MePCl_2$ was routinely prepared in 100-g quantities and 80% yields by a literature procedure[18] and is also commercially available (Strem Chemical). Highly optically pure 1-phenylethylamine (95% OP) was purchased from Aldrich Chemical. Diglyme was refluxed over CaH_2 and then distilled before use. *t*-BuOOH was neat material (Pfaltz and Bauer) used without purification, pure by ^1H NMR. Gas chromatography was done on a thermal conductivity Hewlett-Packard Model 5830 or 5840 instrument by using $^1/_4$ in. by 10 ft glass columns packed with 1–3% QF-1 on 80–100-mesh Gas-Chrom Q. Both the glass column and packing material were silanized. Preparative GLC plates were prepared by first shaking vigorously by hand for 5 min 20 g of silica gel (EM Laboratories, GF-254, type 60) with 45 mL of distilled water. The slurry was poured on a clean 20 cm × 20 cm glass plate and spread homogeneously by moving the plate from side to side and up and down. The plate was allowed to stand for 20 min and was then dehydrated in an oven at 110 °C for more than 2 h. ^1H NMR spectra were obtained on either a Varian EM-390 or SC-300 FT instrument.

Preparation of isoPrOMeP(S)OH. Following a procedure similar to that of Pelchowics and Leader,[17] $MePCl_2$[18] (76 g, 0.65 mol) was added dropwise over a 30-min period to stirred isoPrOH (312 g, 5.20 mol). Stirring was continued for 2 h after which powdered $NaHCO_3$ was slowly added until all foaming ceased. (Exit CO_2 was monitored.) Filtration removed the excess $NaHCO_3$ along with NaCl, and the remaining alcohol was distilled off under reduced pressure. Sublimed sulfur (21 g, 0.66 mol) was added after which dry ammonia was passed through the stirred solution over a 1-h period. Cooling was applied with a dry ice/acetone bath to keep the temperature of the reaction mixture in the range 5–20 °C. The NH_3 purge was continued for another hour after the reaction ceased to be exothermic. The resulting semisolid was dissolved in 150 mL of water. The filtered solution was acidified with concentrated HCl to pH 1. Extraction with ether (4 × 100 mL), drying over $MgSO_4$, ether evaporation, and distillation yielded isoPrOMeP(S)OH: 82 g (82%); bp 78–79 °C (0.4 mmHg), lit.[17] bp 75–76 °C (0.3 mmHg).

Resolution of isoPrOMeP(S)OH. Preparation of (−)-(S_P)-(S_C)-3. The following procedure for obtaining both enantiomers in high yields and high optical purity from a single bath of racemic acid is essentially that of Boter and Platenburg.[15] Racemic acid (120 g, 0.780 mol) and 1-phenylethylamine (47.2 g, 0.387 mol), $[\alpha]^{25}_D = -39.3°$ (neat), each in 750 mL of dry ether, were mixed slowly under ice-cooling conditions. The crude crystalline salt (85 g, 79%), isolated by filtration, was recrystallized from 1200 mL of hot EtOAc to give 66 g (62%) of pure material, (−)-(S_P)-(S_C)-**3**: mp 157.5–158.0 °C, lit.[15] mp 158 °C; $[\alpha]^{24}_D$ −10.6° (*c* 2.09, MeOH); lit. $[\alpha]^{25}_D$ −10.6°.[15] A second crop was also obtained (12 g, 11%).

To recover unresolved acid and the (−)-amine, the above mother liquors were evaporated. The combined residues were mixed with ice cooling with 100 mL of 25% aqueous NaOH. Following addition of 100 mL of water, the mixture was extracted with benzene (4 × 100 mL) from which the optically active amine was readily recovered. The basic aqueous solution was cooled by the addition of ice and with additional ice cooling of the reaction vessel was acidified by careful addition of 25 mL of concentrated H_2SO_4 to liberate the acid. The solution was saturated with NaCl and then ether extracted (5 × 100 mL) as was the liberated acid. The resulting ether solution was washed with saturated NaCl solution and then dried over $MgSO_4$.

The above filtrate (550 mL) was diluted with 250 mL of ether and then mixed with a solution of dextrorotatry 1-phenylethylamine (47.2 g, 0.387 mol), $[\alpha]^{25}_D$ +38.5° (neat), dissolved in 700 mL of ether. The crude amine salt was obtained in two crops of 87 g (81%) and 14 g (13%). Recrystallization from hot EtOAc (1300 mL) gave 73 g (69%) of purified material followed by another 6 g (6%). The former had a mp of 158.0–158.5 °C and an $[\alpha]^{25}_D$ of +10.3° (*c* 2.98, MeOH). The unisolated salt was recovered as amine and acid as described above. After distillation, the recovered acid amounted to 17 g (17%). The individual amine and salts and recovered acid accounted for 95% of the starting racemic acid. The above yields were based on a theoretical 100% yield of each enantiomeric salt.

Preparation of (−)-(*S*)-isoPrOMeP(O)SMe, 7. The salt formed from (−)-1-phenylethylamine, (−)-(S_P)-(S_C)-**3** (54 g, 0.196 mol), was added to 300 mL of benzene which was brought to reflux in order to dissolve most of the salt. Following the slow addition of MeI (57 g, 0.40 mol) dissolved in 50 mL of benzene, the reaction mixture was refluxed for 7.5 h. Removal of solvent and vacuum distillation gave product ester 7: 27.2 g (83%); bp 47–49 °C (0.7 mmHg), $[\alpha]^{25}_D$ −86.8° (*c* 1.87, benzene). By comparison to the reported rotation,[19] the 7 so prepared is 99% optically pure. The high optical purity was confirmed by use of the optically active (−)-*t*-BuPhP(S)OH,[21] 90-MHz ^1H NMR, C_6D_6, acid/ester ratio 1.3, $\Delta\delta$ 4.8 Hz, Me doublet.

Preparation of (−)-(*S*)-isoPrOMeP(O)S$(CH_2)_2O(CH_2)_2OC_2H_5$, 4. The above salt, (−)-(S_P)-(S_C)-**3** (35.0 g, 0.127 mol), and $EtOCH_2CH_2OCH_2CH_2I$ (34.0 g, 0.139 mol) were dissolved in 200 mL of benzene. After a 34-h reflux, the reaction mixture was washed with 100 mL of water. The organic layer was removed, and the aqueous layer was extracted with benzene (3 × 70 mL). The combined benzene solutions were shaken with a saturated aqueous NaCl solution and then dried over $MgSO_4$. Removal of solvent gave a residual oil, 91 area percent pure by GLC. After being subjected to 0.1-mmHg pressure at 60 °C for 1 h, the oil was 97% GLC pure (3% $EtOCH_2CH_2OCH_2CH_2I$): 29.2 g

(27) Aaron, H. S.; Braun, J.; Shryne, T. M.; Frack, H. F.; Smith, G. E.; Uyeda, R. T.; Miller, J. I. *J. Am. Chem. Soc.* **1960**, *82*, 596. Aaron, H. S.; Shryne, T. M.; Miller, J. I. *Ibid.* **1956**, *80*, 107. Krawiecka, B.; Michalski, *J. Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1971**, *19*, 373. Mikolajczyk, M.; Leitloff, M. *Russ. Chem. Rev. (Engl. Transl.)* **1975**, *44*, 670. Mikolazczyk, M.; Omelanczuk, J.; Para, M. *Tetrahedron* **1972**, *28*, 3855.

(85%), $[\alpha]^{25}_D$ −36.0° (c 2.65, C_6H_6). The product also may be distilled, bp 115–120 °C (0.30–0.35 mmHg), but at the risk of some decomposition. The optical purity of **4** was examined by use of (−)-*t*-BuPhP(S)OH in CCl_4, acid/ester ratio = 1.3/1, $\Delta\delta$ = 4.1 Hz at 90 MHz, Me doublet. No peak for a second enantiomer could be seen: optical purity ≥97%. A rapidly distilled sample was used for analysis: bp 117–119 °C (0.15 mmHg); ^{1}H NMR (CCl_4) δ 1.13 (3 H, t, J_{HH} = 6 Hz, CH_3CH_2O), 1.33 [6 H, 2 overlapping d, J_{HH} = 5.5 Hz, $\Delta\delta \simeq 6$ Hz, $(CH_3)_2CH$], 1.67 (3 H, d, J_{HP} = 14.8 Hz, MeP), 2.94 (2 H, m, SCH_2), 3.50 (8 H, m, CH_2O), 4.70 [1 H, d of sep, $J_{HH} = J_{HP}$ = 6 Hz, $(CH_3)_2CH$]. Anal. Calcd for $C_{10}H_{23}O_4PS$: C, 44.43; H, 8.58; P, 11.46. Found: C, 44.29; H, 8.72; P, 11.28.

Preparation of $EtOCH_2CH_2OCH_2CH_2I$. The corresponding chloride was refluxed in acetone with a half-molar excess of NaI for 2 days. Purification was effected by vacuum distillation. Filtration, solvent removal, and distillation gave $EtOCH_2CH_2OCH_2CH_2I$: 29 g (67%); bp 75–77 °C (16–17 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, t, OCH_2CH_3), 3.30 (2 H, q, CH_3CH_2O), 3.3–3.7 (8 H, m, CH_2O). The required chloride was readily prepared from diethylene glycol monoethyl ether, previously distilled from CaH_2. The alcohol (37.5 g, 0.28 mol), charcoal (0.8 g), and freshly distilled $SOCl_2$ (50 g, 0.42 mol), the latter added dropwise at 5–10 °C, were refluxed for 14 h, after which the product was isolated by vacuum distillation.

Preparation of (+)-(*R*)-Isopropyl Methylphenylphosphinate, 5. The required PhMgBr was prepared by the addition over a 30-min period of neat PhBr (69.2 g, 0.441 mol) to an ice-cooled mixture of Mg (10.6 g, 0.441 g mol) in 50 mL of ether. This mixture was stirred at about 40 °C for an additional 30 min. To it was slowly added a solution of (−)-(*S*)-**4** (20 g, 0.074 mol) in 800 mL of benzene. After being stirred at 25 °C for 2 h, the mixture was cooled to 5 °C and to it was slowly added 250 mL of a saturated aqueous NH_4Cl solution. The benzene/ether layer was separated, and the aqueous solution was extracted with benzene (2 × 250 mL). The combined organic fractions were washed with aqueous NaCl solution and dried over $MgSO_4$. The entire reaction mixture was vacuum distilled at 0.25 mmHg. The fraction boiling at 88–92 °C was chromatographed on 300 g of 60–200-mesh SiO_2 with first benzene and then 1% $EtOH/C_6H_6$. Products eluted in the order biphenyl, $EtOCH_2CH_2OCH_2CH_2SH$, **5**, unreacted **4**, and $Ph_2P(O)Me$. GLC showed **5** to be 99% pure: 7.2 g (49%); $[\alpha]^{25}_D$ +35.7° (c 2.3, C_6H_6); optical purity 66%.[22] Optical purity could not be determined for **5** by use of (−)-*t*-BuPhP(S)OH because of insufficient peak separations. Reisolated **4** was used in a second reaction to increase overall yield to 70–75%. The critical variable in this preparation is the reaction time. Beyond 2 h, the product mixture builds up more disubstitution product. At shorter reaction times, too much unreacted **4** remains. The benzene/ether ratio and temperature must also be strictly controlled. To check the extent of conversion at any given time in the reaction, an aliquot was removed and hydrolyzed with saturated aqueous NH_4Cl solution, dried over $MgSO_4$, and then analyzed by GLC.

Preparation of (+)-(*R*)-Methylphenylbenzylphosphine Oxide, 6. In a preparation analogous to the above, but starting with (+)-(R_P)-(R_C)-**3**, isolated (−)-(*S*)-isopropyl methylphenylphosphinate, **5** (4.2 g, 0.021 mol), in 120 mL of benzene was used. Its optical rotation had not been determined, but from the 75% optical purity of the product [(+)-(*R*)-**6**] must have been at least 75% optically pure. Benzyl chloride (10 g, 0.086 mol) in 100 mL of ether was added slowly to an argon-protected mixture of Mg (2.07 g, 0.086 g-atom) in 20 mL of ether stirred and cooled at 0–5 °C. After a 30-min reflux, the solution of phosphinate **5** was added to the above, stirred at room temperature. The reaction mixture was heated at reflux (ca. 75 °C) and the ether mostly driven off. Reflux was continued for another 5 h. Workup of an aliquot of the reaction mixture by treatment with saturated aqueous NH_4Cl and drying over $MgSO_4$ gave material which by GLC analysis showed the presence of only toluene, bibenzyl, and the product phosphine oxide. The entire reaction mixture was hydrolyzed with saturated NH_4Cl, extracted with several portions of $CHCl_3$ (total volume, 300 mL), $MgSO_4$-dried and column-chromatographed on 100 g of 60–200-mesh SiO_2. Eluting solvents were $CHCl_3$ (500 mL) and 1% EtOH in benzene (1000 mL). Product **6** was 99.9% pure by GLC: 3.7 g (76%); $[\alpha]^{25}_D$ +38.3° (c 2.61, MeOH); optical purity 75% (lit.[5] $[\alpha]^{25}_D$ +51.4° and 100% OP). Mp 124–135 °C after recrystalization from 90–120 °C of ligroin (lit.[5] mp 134–135 °C).

Preparation (−)-(*S*)-Methylphenylbenzylphosphine Oxide, 6. The above 66% optically pure (+)-(*R*)-**5** (0.240 g, 1.04 mmol), $[\alpha]^{25}_D$ +35.7°, in 10 mL of C_6H_6 was reacted as above with Grignard made from benzyl chloride (0.668 g, 5.30 mmol) and an equivalent amount of Mg using a total volume of 15 mL of ether. A similar workup to that above for (+)-(*R*)-**6** gave the phosphine oxide (−)-(*S*)-**6** in 75% yield: $[\alpha]^{25}_D$ −33.8° (c 2.16, MeOH); optical purity 66%; 100% optical yield (optically pure; $[\alpha]^{25}_D$ −51.4°, lit.[5]). Optical purity determination in $CDCl_3$ with (−)-*t*-BuPhP(S)OH at acid/oxide ratios of 0.6/1.0 to 1.15/1.0 had $\Delta\delta$ for the PMe of 6.0–10.2 Hz at 90 MHz. Average optical purity by integration was 70 ± 2%.

Preparation of (−)-(*S*)-Isopropyl Methylbenzylphosphinate, 8. To the starting ester, (−)-(*S*)-**7** (5.0 g, 30 mmol), in 450 mL of dry toluene was added 150 mL of an ether solution which was 1 M in $PhCH_2MgCl$. The mixture was brought to reflux, bp ca. 70 °C. After 8 h the ice-cooled reaction mixture was hydrolyzed with about 100 mL of saturated aqueous NH_4Cl. The toluene/ether layer was separated, and the aqueous layer was extracted several times with toluene. The combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. The residue from solvent removal was analyzed by GLC, which showed the presence of toluene, small amounts of unreacted **7**, bibenzyl, the product **8**, and two longer retention time materials, one of which is $(PhCH_2)_2P(O)Me$. Column chromatography of the residue on 160 g of 60–200-mesh SiO_2 in a 3 × 100 cm column was used to isolate 2.68 g of **8**, 94% pure by GLC, 42% yield. About 3 L of $CHCl_3$ was used as the eluting solvent.

In another experiment, the crude product was vacuum distilled, and the fraction boiling at 75–95 °C at 0.15–0.20 mmHg was chromatographed by using first benzene and then 1% EtOH in benzene with GLC as the monitor. Phosphinate **8**, 100% pure by GLC, was isolated and distilled (bp 92–95 °C, 0.2 mmHg) to give a low-melting solid: mp 50–51 °C; $[\alpha]^{25}_D$ −8.5° (c 1.95, C_6H_6). Anal. Calcd for $C_{11}H_{17}O_2P$: C, 62.65; H, 8.07; P, 14.59. Found: C, 62.35; H, 8.15; P, 14.65.

The optical purity of the above analytically pure material was shown to be greater than 99% by use of the (−)-*t*-BuPhP(S)OH shift reagent in CCl_4 at 90 MHz, acid/ester ratio = 1.2. Each peak of the MeP doublet was observed to be a single signal. (When 6% of the other enantiomer was added, the peak separation was 3 Hz.) Addition of just 1% of racemic **8** gave a detectable upfield shoulder. The material is very hygroscopic.

Preparation of (−)-(*R*)-$PrMePhCH_2PO$, 9. A 1 M *n*-PrMgBr solution was prepared by adding *n*-PrBr (6.2 g, 50 mmol) in dropwise fashion over a 20-min period to a mixture of Mg (1.44 g, 60 mmol) in 5 mL of ether, stirred at ice temperatures. The mixture was stirred at room temperature for another hour and then stored overnight in a refrigerator. Some material precipitated on the bottom of the flask. The clear supernatant was used for subsequent reactions, all under argon. Three reactions were run by utilizing 3.00-g (14.2 mmol), 4.00-g (18.9 mmol), and 4.10-g (19.3 mmol) portions of (−)-(*S*)-**8**, taken from a mixture of several preparations of **8**, 94–100% chemically pure and 72–93% optically pure. The esters were dissolved in respectively 210/5.5, 300/7.3, and 300/7.5 toluene/diglyme solvent mixtures (ratio in milliliters) at room temperature. Enough 1 M *n*-PrMgBr in ether solution was slowly added to make the Grignard/ester molar ratio 5/1. The three reaction mixtures were heated at reflux (bath temperatures about 100 °C) for 5.2, 6.5, and 7.5 h, respectively, and then quenched with the addition of about 250 mL of saturated aqueous NH_4Cl after first cooling the reaction mixtures to ice temperature. The organic layer was then separated and the aqueous layer extracted in each case with $CHCl_3$ (3 × 300 mL). Following a wash with saturated NaCl, drying over $MgSO_4$, and evaporation of solvent, each residue was column chromatographed on SiO_2 by using $CHCl_3$ followed by 50/1 $CHCl_3$/MeOH. The chromatography was monitored by GLC. Phosphine oxide **9** was isolated in 98–100% GLC purity from the respective reactions in 43, 53, and 58% yields (average 52%): $[\alpha]^{25}_D$ −3.0, −3.2, and −2.9°, respectively (c 3.9–4.3, MeOH). The combined product phosphine oxide (5.3 g, 52%) was sublimed in four equal batches. The more volatile impurities were removed first at a 60–80 °C bath temperature in about 3 min at 0.15 mmHg. The pure oxide (4.7 g total) was obtained subsequently in 30–60 min, bath temperature 90–100 °C. An ice-water-cooled condenser was used throughout. Sublimed product was dissolved in $CHCl_3$ and dried over $MgSO_4$. Solvent removal left an oil which crystallized on standing: mp 54–59 °C; $[\alpha]^{25}_D$ −3.2° (c 4.14, MeOH).

A 150-mg portion of the above sublimed material was recrystallized from hot 60–90 °C ligroin to give 85 mg of crystals: mp 57–63 °C; $[\alpha]^{25}_D$ −3.0° (c 4.3, MeOH). The residue from removal of solvent was an oil: $[\alpha]^{25}_D$ −3.5° (c 3.67, MeOH). Racemic material recrystallized from *n*-hexane, mp 65.5–66.0 °C, was used for analysis. Anal. Calcd for $C_{11}H_8OP$: C, 67.33; H, 8.73; P, 15.78. Found: C, 67.20; H, 8.78; P, 15.89.

Optical purity determination by ^{1}H NMR using the thio acid (−)-*t*-BuPhP(S)OH was made on a sublimed sample [$[\alpha]^{25}_D$ −3.3° (c, 3.04, MeOH)]. A sample in C_6D_6, cooled in ice water just before the spectrum was taken, thioacid/phosphine oxide ratio about 1.2, showed a 3-Hz separation of the MeP doublet signals. Six measurements based on relative peak heights gave an average optical purity of 57% with a range of 54–60%. For the same solution at 300 MHz, $\Delta\delta$ 10.6 Hz, the left-hand peak of the lower field (minor) doublet and the upfield peak of the major, higher field doublet were clear of other signals. Integration gave an

optical purity value of 57 ± 2%. One predicts, thereby, optically pure phosphine oxide to have an $[\alpha]^{25}_D$ of 5.8 ± 0.2°. The optical purities of the above phosphine oxide batches prepared above, therefore, range from 50 to 55%, based on $[\alpha]^{25}_D$ values.

Effect of Diglyme on Preparation of 9. Reactant **8** (0.210 g, 0.99 mmol) was dissolved in 15 mL of toluene under argon. To this solution was added a measured amount of diglyme and then 5 mL of a 1 M solution of *n*-PrMgBr. Each reaction mixture was refluxed (bath temperature about 100 °C) for a period of 5–7 h (Table I) and then hydrolyzed by the addition of 10 mL of saturated aqueous NH_4Cl with ice cooling. The organic layer was separated, and the aqueous layer was extracted 3 times with 15-mL portions of $CHCl_3$. After the combined organic products were washed with saturated aqueous NaCl and dried over $MgSO_4$, they were subjected to GLC analysis to determine the relative proportions of **8** and **9**. Solvent and diglyme were removed under vacuum (50–70 °C, 0.15 mmHg, 10 min). The oily product residue was purified by preparative TLC using $CHCl_3$/MeOH, 24/1, as the developing solvent. The band on SiO_2 containing the desired **9** was extracted by stirring with 1/1 MeOH/$CHCl_3$ for 1 h. The extraction solvent was evaporated. Benzene was added, and the solution was dried over $MgSO_4$. The residues were analyzed by GLC. For each an $[\alpha]^{25}_D$ value was determined in benzene.

Preparation of (+)-(*S*)-Methyl-*n*-propylbenzylphosphine, 2. The following is typical. According to the method of Marsi,[7] (−)-(*R*)-**9** (0.300 g, 1.53 mmol) and $PhSiH_3$ (0.184 g, 1.70 mmol) were heated under argon at 90 °C for a 4-h period. Following addition of 1 mL of benzene, the volatile materials were removed at 0.15 mmHg and room temperature (2–4 h). The bath temperature was then raised to about 60–80 °C to cause the distillation of the product phosphine, **2**, collected in a dry ice/acetone-cooled portion of the apparatus. Isolated **2** weighed 0.230 g (1.28 mmol), 85%. The apparatus most useful for preparation of small amounts of phosphine and manipulating it under argon consisted of a simple S-shaped tube with 14/20 joints at each end. The reaction flask was then attached at one end and a three-way stopcock at the other. During distillation of **2**, the ascending portion of the tube was wrapped with heating tape, and the phosphine was trapped in the other loop of the tube cooled in dry ice/acetone.

As an example of the stereochemistry of the reaction, a sample of (−)-(*S*)-**9**, $[\alpha]^{25}_D$ −3.2° (*c* 4.4, MeOH), OP = 55% [^{1}H NMR with (−)-*t*-BuPhP(S)OH], gave (+)-(*S*)-**2**, 98% purity by GLC, $[\alpha]^{25}_D$ + 21.5° (*c* 0.97, MeOH), OP 53–56% [^{1}H NMR, P(O)Me, from several *t*-BuOOH oxidations (yields approximately 90%) of the above **2** sample, acid/**2** ratios, 1.0–1.4, C_6D_6 solvent, $\Delta\delta$ = 2.5–3.0 Hz, 90-MHz integration of relative areas]. The $[\alpha]^{25}_D$ value of **2** was corrected for the amount (usually 1–2%) of **9** found in the GLC of the solution in the polarimeter after optical rotation determination. The air oxidation of **2** to **9** was independently determined to proceed with retention of configuration at phosphorus. $[\alpha]^{25}_D$ for optically pure **2** is thereby estimated to be 38.5–40.5° (lit.[13] $[\alpha]^{25}_D$ 20°, MeOH). The sequence of reduction of **9** to **2** and reoxidation to **9** of the same optical purity is strong evidence for the stereospecific, retentive nature of both steps. The reduction of **9** was in some cases found to be less stereospecific if benzene was added as solvent, longer reduction times were used, or high distillation temperatures were employed. Because of this uncertainty, however, it is necessary to check the optical purity of **2** in each preparation.

Preparation of Racemic 1. $PhSiH_3$ (0.5 mL, 435 mg, 4.0 mmol) was added to oxide **6** (0.230 g, 1.00 mmol) along with 1 mL of benzene in the apparatus described earlier for the preparation of **2**. In a typical reaction the mixture was then heated to reflux for 15 h under argon. Volatile materials were removed at 0.15 mmHg and 90–95 °C over a 1-h period. Short-path distillation gave pure **1** (0.204 g, 0.95 mol) in 95% yield. In a typical reoxidation experiment, the phosphine (0.080 g, 0.035 mmol) was dissolved in 6 mL of argon-flushed MeOH cooled to 10–20 °C with an ice bath. *t*-BuOOH (0.90 g, 0.010 mol) in 5 mL of MeOH was then slowly added. Solvent and volatile materials were removed at room temperature at 0.15 mmHg to give a solid, 85 mg, but which by ^{1}H NMR contained about 30% of entrapped *t*-BuOH (or unreacted *t*-BuOOH). Corrected yield, ~85%. No peaks other than those of **6** were noted by GLC.

Preparation of Optically Active 1. Using the previously described one-piece reaction apparatus and procedure analogous to the one above for racemic *1*, less than 1-g quantities of optically active **6** were readily reduced in greater than 90% isolated yields. Overall optical yields of 68–94%, based on *t*-BuOOH reoxidation, were obtained. Low reaction temperatures and rapid, low-temperature distillation were required for high optical yields. Optical purity of the resulting phosphine was established by reoxidation with *t*-BuOOH and determination of the optical purity of the re-formed **6** by ^{1}H NMR using (−)-*t*-BuPhP(S)OH.

Preparation of (*R*)-*n*-PrMeP(O)OPriso, 12. A solution of (+)-(*R*)-**4** (1.0 g, 3.7 mmol) in 420 mL of benzene was stirred at ice temperatures. To it was added 48 mL of a 1 M solution of *n*-PrMgBr in ether. The mixture was refluxed for 2.3 h and then hydrolyzed with about 80 mL of saturated aqueous NH_4Cl solution. The benzene solution was separated and the aqueous layer extracted 3 times with 50-mL portions of $CHCl_3$. The combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. The residue from solvent removal was quickly distilled at about 80 °C (0.1 mm) and then purified by chromatography on SiO_2 using in order as eluting solvents benzene, benzene/1% EtOH, and benzene/2% EtOH to yield 144 mg of product **12** (24% yield) which was 100% pure by GLC.

Preparation of (−)-(*R*)-*n*-PrMeP(O)CH_2Ph, 9, from (*R*)-12. $PhCH_2MgCl$ (2 mmol) in 2 mL of ether was added at room temperature to a solution of (*R*)-**12** (0.050 g, 0.30 mmol) in 30 mL of benzene. After 30 h at reflux, the mixture was hydrolyzed with 20 mL of saturated aqueous NH_4Cl, and the benzene layer was separated. The aqueous layer was extracted 3 times with 20-mL portions of $CHCl_3$, and the combined organic layers were shaken with saturated aqueous NaCl and dried over $MgSO_4$. The residual oil from solvent removal was purified by preparative TLC (R_f = 0.2) on SiO_2 by elution with $CHCl_3$/MeOH (24/1). Isolated (−)-(*R*)-**9**, 30 mg (50% yield), was 97% pure by GLC. Its optical purity determined on an approximately 1% solutions in C_6D_6 on addition of (−)-*t*-BuPhP(S)OH was about 50% (ester/acid ratio about 1.0/1.2).

Reaction of Racemic 4 with $PhCH_2MgCl$. $PhCH_2MgCl$ (5.0 mmol) in 2 mL of ether solution was added to a solution of **4** (0.270 g, 1.0 mmol) in 15 mL of benzene. After a 1.5-h reflux, the reaction mixture was worked up in the usual manner (see above) by treatment with saturated NH_4Cl, extraction with benzene, and drying over $MgSO_4$. Removal of the benzene and then at 80 °C and 0.3-mmHg pressure the volatile products left an oil which was purified by preparative TLC using a 24/1 $CHCl_3$/MeOH developing solvent. Product **8**, 0.047 g (22% yield), was 96% pure by GLC analysis. Its structure was confirmed by GLC retention time and ^{1}H NMR comparisons with an authentic sample.

Reaction of Racemic 8 with EtMgBr. A 3.6 M solution of EtMgBr in 4 mL of ether was prepared in the usual manner and added at room temperature to racemic **8** (0.10 g, 0.47 mmol) dissolved in 25 mL of benzene to which had been added diglyme (0.200 g, 1.4 mmol). After a 24-h reflux, workup of a small portion of the reaction was followed by GLC analysis which showed product MeEtP(O)CH_2Ph and reactant **8** to be present in ratio 97/2. Workup of the entire reaction mixture in the usual way with saturated NH_4Cl, extraction with $CHCl_3$, aqueous NaCl wash, and drying over $MgSO_4$, followed by preparative TLC with 24/1 $CHCl_3$/MeOH eluant, gave the isolated phosphine oxide [MeEtP(O)CH_2Ph] (0.056 g) in 65% yield, 99% pure by GLC: ^{1}H NMR (CCl_4) δ 1.00 (3 H, t, J_{HH} = 6.9 Hz, CH_3CH_2), 1.22 (3 H, d, J_{HP} = 12 Hz, CH_3P), 1.52 (2 H, m, CH_3CH_2), 3.00 (2 H, d, J_{HP} = 15 Hz. $PhCH_2$), 7.27 (5 H, m, C_6H_5).

Reaction of Me(EtO)P(O)SMe with EtMgBr and *n*-PrMgBr. Me(EtO)P(S)OH was prepared in the same fashion as Me(isoPrO)P(S)OH (see above) and converted to the amine salt on reaction with racemic 1-phenylethylamine. The salt was recrystallized from ethyl acetate, mp 90–93 °C, 65% yield. The salt was routinely coverted by MeI treatment to Me(EtO)P(O)SMe. The Grignard reactions were carried out as previously in refluxing 25/1 benzene/ether with a molar ratio of Grignard/Me(EtO)P(O)SMe of 1.1/1.0, reaction time 1 h. Workup with NH_4Cl, benzene extraction, NaCl wash, drying over $MgSO_4$, and TLC isolation using 24/1 $CHCl_3$/MeOH gave the two phosphinates: Me(EtO)P(O)Pr-*n* [47 mg (45% yield); 87% GLC purity; ^{1}H NMR (C_6D_6) δ 0.77 (3 H, t, J_{HH} = 7.6 Hz, $CH_3CH_2CH_2$), 0.99 (3 H, d, J_{HP} = 13.5 Hz, MeP), 1.02 (3 H, t, J_{HH} = 7.2 Hz CH_3CH_2O), 1.37 (4 H, m, $CH_3CH_2CH_2$), 3.79 (2 H, d of t, J_{HH} = 7.2 Hz)] and Me(EtO)P(O)Et [40 mg (42% yield); 100% GLC purity; ^{1}H NMR (CCl_4) δ 0.98 (1.5 H, half of a d of t, J_{HH} = 6 Hz, other half-obscured CH_3CH_2P), 1.23 (3 H, t, J_{HH} = 6 Hz, CH_3CH_2O), 1.26 (3 H, d, J_{HP} = 11.5 Hz, CH_3P), 1.32 ≃ 1.70 (2 H, m, CH_3CH_2P), 3.94 (2 H, quintet, $J_{HH} \simeq J_{HP} \simeq$ 6 Hz, CH_3CH_2O)].

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Registry No. (±)-(*R*)-**1**, 25140-53-8; (+)-(*S*)-**2**, 85248-81-3; (−)-(S_P)-(S_C)-**3**, 85202-34-2; (−)-(*S*)-**4**, 85185-98-4; (+)-(*R*)-**5**, 18944-66-6; (−)-(*S*)-**6**, 1515-98-6; (−)-(*S*)-**7**, 18878-84-7; (−)-(*S*)-**8**, 85185-99-5; (−)-(*R*)-**9**, 85186-00-1; (*R*)-**12**, 85186-02-3; $EtOCH_2CH_2OCH_2CH_2I$, 20133-15-7; MeEtP(O)CH_2Ph, 85186-01-2; Me(EtO)P(O)SMe, 51865-09-9; Me(EtO)P(O)Pr-*n*, 85186-03-4; Me(EtO)P(O)Et, 19929-33-0.