Kinetic Resolution of Phosphines and Phosphine Oxides with Phosphorus Stereocenters by Hydrolases

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Lipase from *Candida rugosa* (CRL) and cholesterol esterase (CE) catalyzed the enantioselective hydrolysis of pendant acetates in chiral phosphines and phosphine oxides. The enantioselectivity for most substrates was modest (E = 1.5–4.8), but both hydrolases showed high enantioselectivity for one substrate, ArPhMeP=O (Ar = 1-(2-acetoxy)naphthyl, **4c**), E = 81 (CRL) and 32 (CE). Preparative-scale resolution of (±)-**4c** (1.0 g) catalyzed by CRL yielded enantiomerically-enriched starting acetate, (*S*)-(+)-**4c**, 0.48 g, 90% ee as well as product alcohol, (*R*)-(−)-**4b** (Ar = 1-(2-hydroxy)-naphthyl), 0.39 g, 88% ee. Recrystallization of **4b** from toluene raised the enantiomeric purity to >95% ee. Standard chemical steps followed by stereospecific reduction gave both enantiomers of phosphine ArPhMeP (Ar = 1-(2-methoxy)naphthyl) with 96–97% ee. This phosphine is an analog of PAMP (Ar = 2-methoxyphenyl), a chiral phosphine used in asymmetric synthesis.

Introduction

Organic chemists use enantiomerically-pure phosphines and phosphine oxides to control enantioselectivity in asymmetric syntheses. Phosphines are usually used as chiral ligands in transition metal catalyzed reactions.[1] Examples include: hydrogenation of olefins, ketones and imines,[2] hydrosilation of ketones, hydroformylation or isomerization of olefins, coupling of olefins, and allylic alkylation.[3]

Phosphine oxides are used as chiral auxiliaries in stoichiometric reactions. The phosphoryl moiety stabilizes anions α to the phosphorus and the substituents on phosphorus control the enantioselectivity. Examples include: alkylation,[4] amination,[5] Wittig-type olefination,[6] and carbanion-accelerated Claisen rearrangement.[7] In addition, chiral phosphine oxides direct conjugate additions to an allylic carbanion[8] and polar cycloadditions to olefins.[9]

Chiral phosphines and phosphine oxides can contain either phosphorus or carbon stereocenters. Carbon stereocenters are easier to make, but the phosphorus stereocenters lie closer to the reaction center and may be more effective at directing the formation of new stereocenters. Since better synthetic routes to phosphorus stereocenters could speed the discovery of new asymmetric syntheses, several research groups are trying to invent easier routes to phosphorus stereocenters.[10]

The classical route to enantiomerically pure phosphine oxides, developed by Mislow, starts with a fractional crystallization to separate diastereomers of PhMeP(O)-(*O*-menthyl).[11] Subsequent displacement of menthol from *O*-menthylphosphinates by Grignard reagents yields phosphine oxides containing the PhMeP(O)– group and stereospecific reduction yields the corresponding phosphines. Other workers developed similar methods using phosphine-boranes[12] and dialkylphosphinothioic acids.[13] Two disadvantages of these methods are the difficult separation of diastereomers by fractional crystallization and the limited range of phosphines accessible from resolved phosphorus stereocenters that contain only one displaceable group. Resolution of phosphinates and phosphine oxides by cocrystallisation with binaphthol[14] is also limited to a few compounds.

To widen the range of accessible phosphines, recent syntheses use several stereospecific displacements at phosphorus to introduce the substituents. For example,

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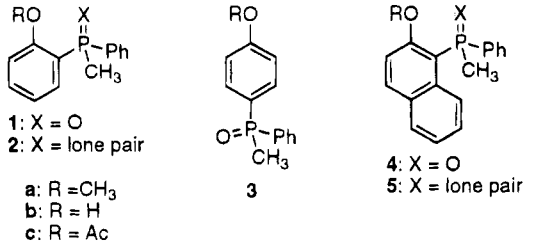
Jugé's[15] and Brown's groups[16] developed methods using oxazaphospholidines derived from ephedrine, while Corey's group used an oxathiophospholidine derived from a camphor derivative.[17] One disadvantage of these methods is that they require careful control of reaction conditions to ensure that each displacement is stereospecific.

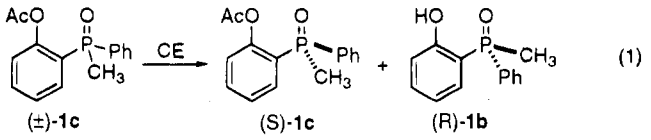
In this paper we report an alternate synthetic route to enantiomerically pure phosphines and phosphine oxides with phosphorus stereocenters: kinetic resolution by esterases and lipases. These enzymes did not act directly on the phosphorus stereocenters. Instead, they catalyzed the enantioselective hydrolysis of the pendant acetate in **1c**–**5c**. Using this method we demonstrated the preparation of enantiomerically pure phosphine oxides **4a** and **4c**, and an enantiomerically pure phosphine **5a**.



Other workers resolved sulfoxides with a stereogenic sulfur[18] and organometallics with a stereogenic metal[19] by lipase-catalyzed reactions of pendant ester groups, but no one has efficiently resolved phosphorus stereocenters with this approach. Several groups reported enzymic resolutions of phosphines and phosphine oxides containing carbon stereocenters[20] and Baba *et al.* reported an inefficient resolution of an antitumor metabolite containing a phosphorus stereocenter.[21] Duman and Zerner resolved a phosphate triester with a phosphorus stereocenter by enantioselective hydrolysis with horse serum.[22]

Results

An initial screening of commercial hydrolases using (±)-**1c**, identified cholesterol esterase (CE) as the most active and most enantioselective enzyme, eq 1, Table 1.



Cholesterol esterase-catalyzed hydrolysis of this unnatural substrate was seven times faster than hydrolysis of the natural substrate, cholesterol acetate, under the same conditions (1.2 vs 0.17 units/mg). The higher chemical reactivity of a phenyl ester as compared to a cholesteryl ester may account for this faster rate.

Table 1. Enantioselectivity of Several Commercial Hydrolases toward Phosphines and Phosphine Oxides

substrate	enzyme[a]	activity[b] (units/mg)	convn[c] (%)	ee_p[d] (%) config	ee_s[e] (%)	E[f]
1c	CE	1.2	52	53 (*R*)	49	4.8
1c	CRL	0.0076	51	19 (*R*)	12	1.6
1c	PCL	0.0006	24	7 (*S*)	1	1.2
1c	K-10	0.0002	31	0	nd	1
1c	RML	0.016	64	7 (*S*)	24	1.4
1c	ANL	0.018	49	21 (*S*)	14	1.7
2c	CE	5.9	40	49 (*S*)[g]	33[g]	4.0
3c[h]	CE	3.2	40	7 (*S*)[i]	7[j]	1.3
4c	CE	0.96	42	89 (*R*)	61	32
4c	CRL	0.0059	51	95 (*R*)	69	81
4c	PCL	0.023	32	4 (*R*)	6	1.3
4c	PPL	0.0028	33	10 (*S*)	5	1.3
5c	CE	0.41	51	43 (*S*)[g]	44[g]	3.8
5c	CRL	0.0007	42	15 (*S*)[g]	11[g]	1.5

[a] CE = cholesterol esterase; CRL = lipase from *Candida rugosa*; PCL = lipase from *Pseudomonas cepacia* (Amano P30); K-10 = lipase from *Pseudomonas* sp. (Amano K-10); RML = lipase from *Rhizomucor miehei* (Amano MAP-10), ANL = lipase from *Aspergillus niger* (Amano AP-6); PPL = lipase from porcine pancreas. [b] Unit/mg = (μmol ester hydrolyzed/min)/mg of solid. [c] The percent conversion was determined either from the amount of base consumed during hydrolysis or from the enantiomeric excess of the starting material (ee_s) and product (ee_p) using conv = $ee_s/(ee_s + ee_p)$. [d] Determined by ^{1}H NMR in the presence of (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine. [e] Determined by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$. [f] E = enantiomeric ratio which measures the preference of the enzyme for one enantiomer over the other (see ref 23). The E listed is an average of at least two reactions. The values of ee and % convn are for one of these reactions and may not give exactly the E shown. [g] The phosphines were oxidized to phosphine oxides with H_2O_2 before analysis. [h] CRL, PCL, K-10, RML, and ANL also catalyzed hydrolysis of **3c** with low enantioselectivity (E < 2.0). [i] The product was treated with methyl iodide and the resulting enantiomers of **3a** were separated using a Chiralpak OT HPLC column. [j] The remaining **3c** was hydrolyzed to give **3b** and then treated with methyl iodide and analyzed as described in note *i*.

Another enzyme, lipase from *Candida rugosa* (CRL), also catalyzed the hydrolysis of (±)-**1c** faster than hydrolysis of cholesterol acetate (0.0076 vs 0.0005 units/mg, a factor of 15). However, CRL catalyzed hydrolysis of another natural substrate, triglyceryl esters in olive oil, was faster than either of these substrates with a specific activity of 0.30 units/mg.

The 160-fold lower specific activity of CRL as compared to CE is largely because commercial CE contained more protein. Commercial CE contained >50 wt % protein, while crude CRL contained only 2–4 wt % protein. We calculated specific activity based on the amount of solid powder added, so the higher amount of protein accounts for a 10–30-fold difference in activity.

The enantioselectivity of the CE-catalyzed hydrolysis of **1c**, measured by the enantiomeric ratio, E,[23] was modest, 4.8, while the enantioselectivity of the CRL-catalyzed hydrolysis was only 1.6. The four other lipases

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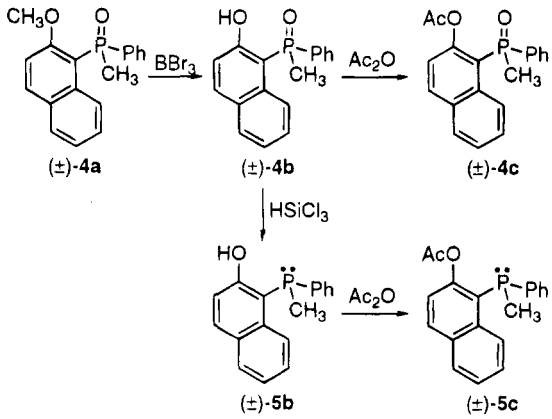
Scheme 1



tested were slow catalysts and none showed an enantioselectivity greater than 2.

To find a more enantioselective reaction, we examined a series of related substrates, **2c-5c**. Reduction of methoxyphosphine oxide **1a**[11c] with trichlorosilane followed by removal of the methyl group and acetylation yielded acetoxyphosphine **2c**. A similar removal of the methyl group and acetylation yielded acetoxyphosphine oxides **3c** and **4c** from the known methoxyphosphine oxides **3a** and **4a**,[11a] as shown in Scheme 1 for **4c**. Reduction of hydroxyphosphine oxide **4b** with trichlorosilane to **5b** followed by acetylation yielded **5c**, Scheme 1.

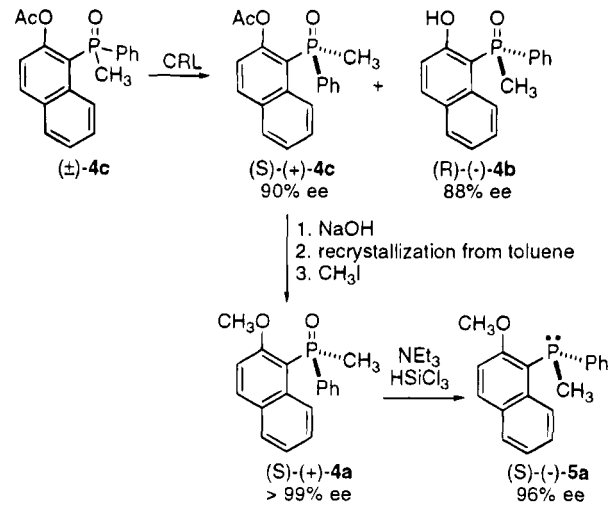
The enantioselectivity of the CE-catalyzed hydrolysis of these new substrates ranged from 1.3 for **3c** to 32 for **4c**, Table 1. Hydrolysis of both phosphine oxide **1c** and phosphine **2c** was moderately enantioselective, $E = 4.8$ and 4.0, respectively. Moving the acetoxy group further from the stereocenter, as in **3c**, decreased the enantioselectivity, $E = 1.3$, while replacing the phenyl group in phosphine oxide **1c** with a naphthyl group in **4c** increased the enantioselectivity by a factor of seven to $E = 32$. However, the same replacement of phenyl with naphthyl in the phosphines **2c** to **5c** did not increase the enantioselectivity, rather, a small decrease from 4.0 to 3.8 was observed. Thus, only **4c** was resolved with high enantioselectivity, suggesting that high enantioselectivity required both the P=O moiety and the naphthyl group.

A rescreening of the enzymes with the best substrate, **4c**, showed that CRL was even more enantioselective, $E = 81$, but the rate of CRL-catalyzed hydrolysis was approximately 160 times slower than the CE-catalyzed reaction.

We established the absolute configurations of the preferred enantiomers by comparing the optical rotations to known rotations in the literature, see Experimental Section. The three-dimensional shape of the preferred enantiomer for the CRL and CE resolutions was the same for all the 2-acetoxy substrates: (*R*)-phosphine oxides and (*S*)-phosphines were hydrolyzed. The phosphine and phosphine oxides have opposite stereochemical descriptors because the nomenclature is based on the atomic number of the substituents. Hydrolysis of substrate **3c**, which has the acetoxy group in the 4-position, favored the opposite enantiomer, but with low enantioselectivity.

We evaluated both CRL and CE for a synthetic scale resolution of (±)-**4c**. A 1 g scale resolution of **4c** catalyzed by CRL gave unreacted substrate (*S*)-**4c** 0.48 g, 90% ee and product (*R*)-**4b** 0.39 g, 88% ee, corresponding to an enantiomeric ratio of 44 for this resolution. Recrystallization raised the enantiomeric purity of (*R*)-**4b** to >95% ee according to ^{1}H-NMR in the presence of a chiral shift reagent. Hydrolysis of (*S*)-**4c** gave (*S*)-**4b** with >95% ee after recrystallization. Based on later HPLC analysis of the methoxyphosphines **4a** derived from these samples, we believe the enantiomeric purity was probably ≥99% ee.

Scheme 2



A 1.0 g scale resolution catalyzed by CE gave unreacted substrate (*S*)-**4c** (0.5 g) with 84% ee and product (*R*)-**4b** (0.47 g) with 76% ee, corresponding to an enantiomeric ratio of 19 for this resolution. Recrystallization as above raised the enantiomeric purity >95% ee. The enantiomeric ratio for the large scale reactions (44 and 19) was significantly lower than that measured for the same reactions on a smaller scale (81 and 32). We do not know what caused this drop,[24] but both hydrolases are still sufficiently enantioselective to prepare enantiomerically-pure material. We favor CRL because it is the more selective. The cost of the two hydrolases is similar after taking into account the lower specific activity of CRL.

To prepare enantiomerically pure phosphine **5a**, a potential ligand for asymmetric synthesis, we first added a methyl group to the hydroxyphosphine oxides (*R*)- and (*S*)-**4b** yielding (*R*)- and (*S*)-**4a**, Scheme 2. The enantiomeric purity of **4a** was ≥99% ee by HPLC analysis, suggesting that the starting material **4b** also had ≥99% ee. Reduction of (*S*)-**4a** (≥99% ee) with triethylamine/trichlorosilane proceeded with inversion to give (*S*)-**5a** with 96% ee. Similarly, reduction of (*R*)-**4a** (99% ee) yielded (*R*)-**5a** with 97% ee. The most likely cause of the small loss in enantiomeric purity is a small amount of retention of configuration during reduction.

Discussion

By screening commercially-available hydrolases, we found two—CRL and CE—that enantioselectively hydrolyzed pendant acetates in chiral phosphines and phosphine oxides. The enantioselectivity ranged from low to good even though the phosphorus stereocenters lay four or more atoms from the reacting carbonyl. Other researchers have also reported efficient resolutions of distant stereocenters. Remote sulfur and metal stereocenters were mentioned in the introduction; in addition, carbon stereocenters four and even eight atoms from the

(24) Slow chemical hydrolysis of the starting acetate during long reactions may lower the apparent enantioselectivity.

ester have been resolved by lipases or aldolases.[25] This ability to resolve distant stereocenters with hydrolases suggests that their synthetic potential may be larger than previously thought.

We demonstrated a preparative resolution of (±)-**4c** which yielded both enantiomers of hydroxyphosphine oxide **4b** in 88–90% ee, >95% ee after recrystallisation. Methylation yielded the methoxyphosphine oxides **4a** with ≥99% ee. These phosphine oxides may serve as starting points for chiral Wittig reagents and other reagents that require a stabilized methylene anion in a chiral environment. Further, chelation of a counterion by the methylene anion and the hydroxyl group in **4b** may create a more rigid and more enantioselective reagent.

Stereospecific reduction of **4a** gave both enantiomers of phosphine **5a** in 96–97% ee. Chemists have used similar monophosphines as ligands for transition metals in asymmetric syntheses. More often however, chemists favor chelating diphosphines because they often give higher enantioselectivity. One route to diphosphines starts from the monophosphines or monophosphine oxides containing a methyl as one of the phosphorus substituents.[26] Oxidative coupling joins the two phosphorus stereocenters by a $-CH_2CH_2-$ link. Thus, **4a** and **5a** may also serve as starting materials for synthesis of diphosphines.

Both CRL and CE showed similar enantioselectivity toward substrates **1c-5c** suggesting that the structures of their active sites may be similar. A comparison of the amino acid sequences of bovine CE[27] and CRL[28] shows significant similarities, especially in the regions containing the catalytic machinery.[29]

The common three-dimensional shape for the preferred enantiomers of the acetoxyphosphines **2c** and **5c** and the acetoxyphosphine oxides **1c** and **4c** suggests that shape determines enantioselectivity. Further, since only **4c** was resolved with high enantioselectivity, both the naphthyl moiety and the phosphine oxide probably contribute to enantiorecogntion. An examination of the X-ray crystal structure of CRL[30] suggest that the phosphorus stereocenter binds in the large hydrophobic pocket, but identification of the molecular interactions that determine enantioselectivity is still in progress. We hope that these calculations will aid design of new efficiently-resolved phosphines, especially phosphines with displaceable substituents so that a wider range of phosphines are accessible from enzymic resolutions.

Experimental Section

General. Cholesterol esterase (CE) from porcine pancreas was purchased from Genzyme, Boston, MA. Lipase from *Candida rugosa* (L-1754, 0.16 units/mg solid using olive oil, also known as *C. cylindracea*;[31] unit = μmol of ester group hydrolyzed per min) was purchased from Sigma Chemical Co., St. Louis, MO. Lipase from *Pseudomonas cepacia* (lipase P-30, 0.05 units/mg solid using olive oil), lipase from *Rhizomucor miehei* (MAP-10, 0.05 units/mg solid using olive oil, synonym *Mucor miehei*[31]) and lipase from *Aspergillus niger* (AP-6, 2 units/g solid using ethyl butyrate) were purchased from Amano International Enzyme Co., Troy, VI. Silica gel 70–230 mesh, 60A (Aldrich, Milwaukee, WI) was used for flash chromatography. Methylphenylphosphinic chloride was purchased from Alfa Chemical Co., Brampton, ON. All other reagents were purchased from Aldrich Chemical Company. Melting points are uncorrected. Tetrahydrofuran and benzene were dried by distillation from sodium under nitrogen with benzophenone as an indicator. Triethylamine was dried by distillation from sodium hydroxide under nitrogen. Trichlorosilane was purified by distillation from quinoline under nitrogen. Analytical TLC was performed on a 0.25 mm silica gel plates (Whatman) with G-UV-254 indicator. Chemical shifts for NMR were assigned using tetramethylsilane as an internal standard for ^{1}H NMR, chloroform (77.0 ppm) or dichloromethane (53.4 ppm) as an internal standard for ^{13}C NMR, and 85% phosphoric (0 ppm) as an external reference for ^{31}P NMR. Elemental combustion analyses were performed by Guelph Chemical Laboratories Ltd, Guelph, ON. The following compounds were prepared by literature methods: racemic methoxy phosphine oxides **1a**, **3a**,[11] and **4a**, **4b**[32] the methoxy phosphine, **2a**.[33]

Enzyme Reactions. Sodium taurocholate (30 mg), substrate (typically 50 mg) and CE (typically 0.5 mg) were added to a biphasic mixture of toluene (10 mL) and buffer (pH 7.0, 10 mL, 10 mM phosphate). Sodium taurocholate activates CE and helps form an emulsion. Sodium taurocholate was omitted from reactions catalyzed by other enzymes. The mixture was stirred rapidly at room temperature and the amount of NaOH (0.10 N) required to maintain the pH at 7.0 was measured as a function of time using a pH stat. Under these conditions CE had an activity of 0.17 units/mg solid with cholesterol acetate (~60 mg) as the substrate (unit = μmol ester hydrolyzed/min). When the consumption of base indicated that the reaction had reached approximately 40% conversion, the reaction mixture was extracted with 9: 1 ethyl acetate: ethanol (6 × 10 mL). The ethanol helps break up the emulsion and inactivates the enzyme. The combined extracts were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The alcohol and acetate were separated by silica gel column chromatography (1 cm dia × 15 cm) eluted with ethyl acetate.

Enantiomeric Purity. (a) Chiral Shift Reagents. The enantiomeric purity of **1b** and **4b** were determined by ^{1}H NMR ($CDCl_3$, 200 MHz) in the presence of 1.1 equiv of (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-phenylethylamine,[34] which separated the methyl resonances of each enantiomer by 4 Hz. The enantiomeric purity of **1c** and **4c** were determined by ^{1}H NMR ($CDCl_3$, 200 MHz) in the presence of approximately 1.5 equiv of Eu(hfc)$_3$ which separated the acetyl methyl resonances by 10 Hz.

Phosphines **2b**, **2c**, **5b**, and **5c** were oxidized to **1b**, **1c**, **4b** and **4c**, respectively, and analyzed as above. A sample was dissolved in acetone (5 mL) containing H_2O_2 (1.5 equiv) and stirred for 15 min at room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel.

(b) HPLC. Enantiomers of **3a** were separated on a Chiralpak OT column (Daicel Chemical Industries, Ltd. Fort Lee, NJ) eluted with methanol at 4 °C, α = 1.32. The S enantiomer eluted first. Compounds **3b** and **3c** were converted into **3a**

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for analysis. A sample of **3b** was dissolved in acetone (5 mL) containing CH_3I (10 equiv) and K_2CO_3 (1.5 equiv). The mixture was heated to reflux for 24–48 h until TLC indicated that the reaction was complete. The solvent was removed by rotary evaporation and the residue was dissolved in ethyl acetate (10 mL) and washed with $Na_2S_2O_4$ (10 mL of 10 w/v%), water (10 mL), and satd NaCl solution (10 mL). The ethyl acetate solution was dried over sodium sulfate, filtered, and concentrated under vacuum. A sample of **3c** was hydrolyzed to **3b** as described below for (*S*)-(+)-**4c**, then treated as for **3b**.

Enantiomers of **4a** were separated on a Chiralcel OD column (Daicel) eluted with 7: 3 hexane: 2-propanol, $\alpha = 1.27$. The *S* enantiomer eluted first.

Absolute Configuration. The isolated hydroxy phosphines and phosphine oxides were converted to the corresponding methoxy phosphine oxides by methylation and oxidation as described above. The oxidation of phosphines to phosphine oxides proceeds with retention of configuration.[11b] (*R*)-**1a** from (*R*)-**1b**, 49% ee: $[\alpha]_D$ (obsd) = +16 (*c* 0.12, MeOH) [lit.[35] (*R*)-(+), $[\alpha]_D$ = +26 (*c* 1.0, MeOH)]; (*R*)-**1a** from (*S*)-**2b**, 17% ee: $[\alpha]_D$ (obsd) = +4.5 (*c* 0.32, MeOH); (*R*)-**3a** from (*R*)-**3b**, 10% ee: $[\alpha]_{405}$ (obsd) = +5.0 (*c* 0.5, MeOH) [lit.[11a] (*S*)-(−), $[\alpha]_D$ = −8.0 (*c* 1.0–3.0, MeOH)]; (*R*)-**4b**, 88% ee: $[\alpha]_D$ (obsd) = −28 (*c* 1.3, MeOH) [lit.[32] (*R*)-(−), $[\alpha]_D$ = −23 (*c* 2, MeOH)]; (*R*)-**4b** from (*S*)-**5b**, 43% ee: $[\alpha]_D$ (obsd) = −12 (*c* 0.48, MeOH).

(±)-(2-Hydroxyphenyl)methylphenylphosphine Oxide, (±)-1b. A solution of BBr_3 in CH_2Cl_2 (5 mL of 1.0 M, 5.0 mmol) was added to a solution of **1a** (0.52 g, 2.1 mmol) in CH_2Cl_2 (15 mL) cooled to −23 °C (CO_2/CCl_4) under N_2. The reaction mixture was stirred for 1 h, allowed to warm to room temperature and stirred overnight. The reaction was quenched by the slow addition of H_2O (20 mL), washed with satd $NaHCO_3$ (20 mL), satd NaCl (20 mL), dried over sodium sulfate, filtered, and concentrated by rotary evaporation. Column chromatography on silica gel eluted with CH_2Cl_2: MeOH 19:1 afforded **1b** which was recrystallized from toluene-hexane to give a white powder (0.36 g, 1.6 mmol, 74%): mp 171–172 °C; MS (EI) *m*/*z* (rel int): 232 (93, $M^{\bullet+}$), 231 (100, $(M - H)^+$), 77 (14, $C_6H_5^+$); ^1H NMR ($CDCl_3$, 200 MHz) δ 11.15 (s, 1), 7.85–6.80 (m, 9), 2.10 (d, 3, $^2J_{P-H}$ = 12 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz, ^1H decoupled) δ 163.14, 163.11, 134.2, 132.9, 132.32, 132.28, 130.4, 130.23, 130.15, 130.0, 128.9, 128.8, 119.4, 119.3, 118.5, 118.4, 113.4, 112.1, 110.6 (aromatic carbons; some are split by phosphorus), 17.0 (d, $^1J_{P-C}$ = 73 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 42.9; Anal. Calcd for $C_{13}H_{13}O_2P$: C, 67.24 H, 5.64. Found: C, 67.54; H, 5.75

(±)-(2-Acetoxyphenyl)methylphenylphosphine Oxide, (±)-1c. Triethylamine (0.79 mL, 0.58 g, 5.7 mmol) followed by acetyl chloride (0.41 mL, 0.45 g, 5.7 mmol) were added to a solution of **1b** (0.88 g, 3.8 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred for 2 h at 25 °C. The organic layer was washed with satd $NaHCO_3$ (30 mL), satd NaCl (30 mL) and dried over sodium sulfate, filtered and concentrated by rotary evaporation. Column chromatography on silica gel eluted with CH_2Cl_2:ethyl acetate:MeOH 67:30:3 followed by recrystallization from toluene-hexane gave a white powder 0.67 g, 2.4 mmol, 64%: mp 73–74 °C; MS (EI) *m*/*z* (rel int): 274 (0.3, $M^{\bullet+}$), 233 (14), 232 (100, $(M - CH_2CO)^{\bullet+}$), 231 (64, $(M - CH_3CO)^+$), 77 (10, $C_6H_5^+$); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.02–7.14 (m, 9), 2.09 (d, 3, $^2J_{P-H}$ = 13 Hz), 1.90 (s, 3); ^{13}C NMR ($CDCl_3$, 67.8 MHz, ^1H decoupled) δ 168.1 (s, C=O), 151.51, 151.47, 134.8, 133.42, 133.39, 133.36, 133.2, 131.91, 131.88, 130.2, 130.0, 128.8, 128.6, 126.2, 126.1, 125.9, 124.7, 123.7, 123.6 (aromatic carbons; some are split by phosphorus), 20.6 (s, C(O)CH_3), 16.1 (d, $^1J_{P-C}$ = 75 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 28.1; Anal. Calcd for $C_{15}H_{15}O_3P$: C, 65.69; H, 5.51 Found: C, 65.76; H, 5.73

(±)-(2-Hydroxyphenyl)methylphenylphosphine, (±)-2b. A solution of **2a** (0.62 g, 2.7 mmol) in HBr (25 mL of a 48% solution) was refluxed for 12 h under N_2.[36] The solution was cooled, neutralized with 10% NaOH to pH 7. The product was extracted with CH_2Cl_2 (3 × 20 mL) and the combined extracts were washed with satd NaCl (25 mL), dried over sodium sulfate, filtered, and concentrated by rotary evaporation. Column chromatography on silica gel eluted with hexane:ethyl acetate 9:1 afforded an oil which solidified, 0.44 g, 2.0 mmol, 75%: mp 66–67 °C; MS (EI) *m*/*z* (rel int): 216 (100, $M^{\bullet+}$), 215 (46, $(M - H)^+$), 201 (22, $(M - CH_3)^+$), 199 (18), 183 (35), 77 (14, $C_6H_5^+$); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.41–6.87 (m, 9), 6.41 (br, s, 1), 1.64 (d, 3, $^2J_{P-H}$ = 2 Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz, ^1H decoupled) δ 159.2, 159.0, 138.5, 132.6, 131.3, 131.1, 128.6, 128.5, 128.4, 128.3, 122.8, 121.1, 115.3 (aromatic carbons; some are split by phosphorus), 10.9 (d, $^1J_{P-C}$ = 10 Hz); ^{31}P NMR ($CDCl_3$, 81 MHz) δ −52.6; Anal. Calcd for $C_{13}H_{13}OP$: C, 72.22; H, 6.06. Found: C, 71.91; H, 6.09.

(±)-(2-Acetoxyphenyl)methylphenylphosphine, (±)-2c. To a solution of **2b** (0.37 g, 1.7 mmol) in ethyl acetate (10 mL) was added Na_2CO_3 (0.23 g, 2.1 mmol), *N*,*N*-dimethyl-4-aminopyridine (21 mg, 0.17 mmol). Acetic anhydride (2.0 mL, 2.1 mmol) and stirred for 24 h at room temperature. The reaction mixture was washed with satd $NaHCO_3$ (10 mL), satd NaCl (10 mL), dried over sodium sulfate, filtered and concentrated by rotary evaporation to give a clear oil (0.39 g, 1.5 mmol, 88%). MS (EI) *m*/*z* (rel int): 258 (18, $M^{\bullet+}$), 244 (14), 243 (91, $M - CH_3)^+$), 216 (50, $(M - CH_2CO)^{\bullet+}$), 215 (100, $(M - CH_3CO)^+$), 201 (25), 77 (10, $C_6H_5^+$); HRMS (EI); exact mass 258.08050 ($C_{15}H_{15}O_2P$ requires 258.08096, 1.8 ppm error); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.00 (m, 9), 2.10 (s, 3), 1.55 (d, 3, $^2J_{P-H}$ = 4 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz, ^1H decoupled) δ 169.0 (s, C=O), 153.0, 152.6, 139.1, 138.8, 132.6, 132.3, 132.2, 132.1, 132.0, 131.8, 129.7, 128.5, 128.4, 128.3, 126.1, 122.4 (aromatic carbons; some are split by phosphorus), 20.5 (s, C(O)CH_3), 11.6 (d, $^1J_{PC}$ = 13 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 81 MHz) δ −36.5.

(±)-(4-Hydroxyphenyl)methylphenylphosphine oxide, (±)-3b. A solution of **3a** (1.4 g, 5.8 mmol) in HBr (30 mL of a 48% solution) was refluxed for 2.5 h.[36] The solution was cooled to room temperature, neutralized by addition of 2 N NaOH and the pH was adjusted to 7.0. The product was extracted with ethyl acetate (7 × 50 mL). The combined extracts were washed with satd $NaHCO_3$ (100 mL), H_2O (100 mL), dried over $MgSO_4$, filtered, concentrated by rotary evaporation and recrystallized from ethyl acetate to give a white powder (0.92 g, 4.0 mmol, 68%), mp 161–162 °C; MS (EI) *m*/*z* (rel int): 232 (55, $M^{\bullet+}$), 217 (100, $(M - CH_3)^+$); ^1H NMR ($CDCl_3$, 200 MHz) δ 10.45 (s, 1), 7.80–6.90 (m, 9), 2.10 (d, 3, $^2J_{P-H}$ = 13 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz, ^1H decoupled) δ 161.7, 161.6, 134.5, 132.4, 132.2, 131.9, 131.8, 130.6, 130.7, 128.8, 128.6, 122.2, 120.0, 116.4, 116.2 (aromatic carbons; some are split by phosphorus), 16.6 (d, $^1J_{P-C}$ = 74 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 81 MHz) δ 34.4; Anal. Calcd for $C_{13}H_{13}O_2P$: C, 67.24; H, 5.64. Found: C, 67.36; H, 5.68.

(±)-(4-Acetoxyphenyl)methylphenylphosphine oxide, (±)-3c, was prepared by acetylation of **3b** as described for **1c**: 66% yield of a white powder: mp 105–106 °C (CH_2Cl_2-hexane); MS (EI) *m*/*z* (rel int): 274 (14, $M^{\bullet+}$), 232 (90, $(M - CH_2CO)^{\bullet+}$), 217 (100), 77 (12, $C_6H_5^+$); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.85–7.23 (m, 9), 2.32 (s, 3), 2.03 (d, 3, $^2J_{P-H}$ = 14 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz, ^1H decoupled) δ 168.9 (s, C=O), 153.4, 153.3, 134.4, 133.0, 132.3, 132.2, 132.0, 131.93, 131.90, 130.8, 130.6, 130.4, 128.8, 128.6, 122.1, 121.9 (aromatic carbons; some are split by phosphorus), 21.1 (s, C(O)CH_3), 16.7 (d, $^1J_{P-C}$ = 74 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 30.0; Anal. Calcd for $C_{15}H_{15}O_3P$: C, 65.69; H, 5.51. Found: C, 65.56; H, 5.60.

(±)-(2-Methoxy-1-naphthyl)methylphenylphosphine oxide, (±)-4a, was synthesized from a literature procedure.[32] 80% yield of white crystals: mp 128–129 °C (toluene-hexanes) [lit.[32] 130 °C]; MS (EI) m/z (rel int): 297 (6, $(M + 1)^{\bullet+}$), 296 (37, $M^{\bullet+}$), 295 (100, $(M - H)^+$), 265 (18, $(M - OCH_3)^+$); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.58 (d, 1, *J* = 8 Hz), 8.03–7.12 (m, 10), 3.96 (s, 3), 2.23 (d, 3, $^2J_{P-H}$ = 14 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, ^1H decoupled) δ 159.2, 159.1, 138.3, 136.9, 136.3, 136.2, 135.2, 130.7, 129.4, 129.3, 128.2, 128.0, 127.7, 126.1, 124.2, 113.3, 112.5, 112.4, 112.0 (aromatic carbons; some are split by phosphorus), 55.8 (s, OCH_3), 19.0 (d, $^1J_{P-C}$ = 76 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 35.5.

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(±)-(2-Hydroxy-1-naphthyl)methylphenylphosphine oxide, (±)-4b, was prepared in the same manner as described for **1b** except that the column was eluted with CH_2Cl_2:ethyl acetate:MeOH 67:30:3, 75% yield of white crystals: mp 147–148 °C (toluene-hexane) [lit.[32] 124–126 °C]; MS (EI) *m/z* (rel int): 283 (13, $(M + 1)^{\bullet+}$), 282 (77, $M^{\bullet+}$), 281 (100, $(M - H)^+$), 139 (14, $(M - C_{10}H_7O)^+$); ^1H NMR ($CDCl_3$, 200 Hz) δ 7.88–7.12 (m, 11), 2.32 (d, 3, $^2J_{P-H}$ = 12 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz, ^1H decoupled) δ 166.47, 166.44, 135.90, 135.87, 134.9, 133.4, 132.9, 132.8, 132.6, 132.5, 130.1, 129.9, 129.4, 129.3, 129.1, 128.4, 128.3, 127.2, 123.6, 123.5, 123.0, 121.2, 121.1, 100.5, 99.0 (aromatic carbons; some are split by phosphorus), 16.5 (d, $^1J_{P-C}$ = 74 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 45.7; Anal. Calcd for $C_{17}H_{15}O_2P$: C, 72.41 H, 5.36. Found: C, 72.13; H, 5.54

(±)-(2-acetoxy-1-naphthyl)methylphenylphosphine oxide, (±)-4c, was prepared by acetylation of **4b** as described for **2c**. A recrystallization from toluene afforded white crystals (1.95 g, 6.02 mmol, 84%): mp 131–132 °C (toluene-hexane); MS (EI) *m/z* (rel int): 324 (8, $M^{\bullet+}$), 283 (15), 282 (100, $(M - CH_2CO)^{\bullet+}$), 139 (17, $(M - C_{10}H_7O)^+$); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.38 (d, 1, J = 10 Hz), 8.05–7.15 (m, 10), 2.26 (d, 3, $^2J_{P-H}$ = 14 Hz), 1.94 (s, 3); ^{13}C NMR ($CDCl_3$, 67.8 MHz, ^1H decoupled) δ 168.5 (s, C=O), 151.2, 151.1, 137.0, 135.5, 135.4, 134.54, 134.51, 132.0, 131.9, 131.7, 131.6, 129.5, 129.3, 128.9, 128.7, 128.6, 127.8, 127.1, 127.0, 126.2, 121.8, 121.7, 118.8, 117.4 (aromatic carbons; some are split by phosphorus), 20.9 (s, C(O)CH_3), 18.8 (d, $^1J_{P-C}$ = 76 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 33.5; Anal. Calcd for $C_{19}H_{17}O_3P$: C, 70.37; H, 5.28. Found: C, 70.58; H, 5.40

(±)-(2-Acetoxy-1-naphthyl)methylphenylphosphine, (±)-5c. A solution **4b** (0.28 g, 1.0 mmol) and $HSiCl_3$ (1.0 mL, 9.9 mmol) in dry benzene (40 mL) was placed in a heavy-walled tube closed by a Teflon needle valve. The solution was degassed by two freeze-pump-thaw cycles, then heated to 110 °C for 6 h.[37] The solution was cooled and the benzene was removed by rotary evaporation. The residue was dissolved in $CHCl_3$ (20 mL) and H_2O (20 mL), filtered through a celite pad and the organic phase was separated. The aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated by rotary evaporation to a green oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.87–7.13 (m, 9), 1.88 (d, 3, $^2J_{P-H}$ = 2 Hz). This compound reoxidized readily in air; therefore, it was immediately converted to the more stable acetyl derivative using the procedure described for preparation of **2c**. Purification by column chromatography on neutral alumina eluted with 1: 1 hexane:ethyl acetate afforded an oil which solidified to a green-white solid: 0.14 g, 0.45 mmol, 45%; mp 96–97 °C; MS (EI) *m/z* (rel int): 308 (21, $M^{\bullet+}$), 294 (15), 293 (80, $(M - CH_3)^+$), 266 (26, $(M - CH_2CO)^{\bullet+}$), 265 (100, $(M - CH_3CO)^+$), 77 (6, $C_6H_5^+$); ^1H NMR (C_6D_6, 200 MHz) δ 8.90 (m, 1 aromatic H), 7.53–6.94 (m, 8), 1.66 (d, 3, $^2J_{P-H}$ = 4 Hz), 1.57 (s, 3); ^{13}C NMR ($CDCl_3$, 75 MHz, ^1H decoupled) δ 169.1 (s, C=O), 153.02, 153.0, 141.2, 141.0, 137.2, 137.0, 132.0, 131.9, 129.4, 129.2, 128.6, 128.3, 128.28, 127.5, 127.0, 126.8, 126.7, 126.6, 125.5, 125.4, 125.0, 122.3 (aromatic carbons; some are split by phosphorus), 20.4 (s, C(O)CH_3), 9.7 (d, $^1J_{C-P}$ = 14 Hz, PCH_3); ^{31}P NMR ($CDCl_3$, 81 MHz) δ −43.1; Anal. Calcd for $C_{19}H_{17}O_2P$: C, 74.02; H, 5.56. Found: C, 74.24; H, 5.59.

(*R*)-(−)-2-Hydroxy-1-naphthylmethylphenylphosphine Oxide, (*R*)-(−)-4b, and (*S*)-(+)-2-Acetoxy-1-naphthylmethylphenylphosphine Oxide, (*S*)-(+)-4c. Lipase from *Candida rugosa* (300 mg) was dissolved in phosphate buffer (100 mL, pH 7.0, 10 mM), and the pH was readjusted to pH 7.0. The substrate **4c** (1.00 g, 3.10 mmol) was dissolved in toluene (75 mL) and added to the enzyme solution. The reaction mixture was rapidly stirred and the pH was maintained at pH 7.0 by a Radiometer RTS822 pH stat which controlled the addition of 0.105 N NaOH. After 42 h, 14.9 mL of base had been consumed, 51% conversion. The products were extracted with 10:1 EtOAc:EtOH (4 × 55 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to an oil by rotary evaporation. The alcohol and acetate were separated by silica gel column chromatography (4 × 15 cm) eluted with 67:30:3 CH_2Cl_2:EtOAc:MeOH. The alcohol eluted first (R_f = 0.80) followed by the acetate (R_f = 0.33). Concentration under vacuum gave an oil, (*S*)-(+)-**4c**, 0.48 g, 1.48 mmol, 48% yield, 90% ee, $[\alpha]_D$ (obsd) = +73.6 (*c* 0.47, MeOH) and a white solid, (*R*)-(−)-**4b**, 0.39 g, 1.38 mmol, 45% yield, 88% ee. The resolution had an enantiomeric ratio of 44. Recrystallization of (*R*)-(−)-**4b** from toluene gave white crystals with an increased enantiomeric purity of >95% ee (0.32 g, 1.08 mmol, 35%). mp 186–187 °C; $[\alpha]_D$ = −38.0 (*c* 1.0, MeOH). The TLC and ^1H NMR of (*S*)-(+)-**4c** and (*R*)-(−)-**4b** were identical to those for (±)-**4b** and (±)-**4c**.

(*S*)-(+)-(2-Hydroxy-1-naphthyl)methylphenylphosphine oxide, (*S*)-(+)-4b: Sodium hydroxide (2 mL of 1.0 N) was added to (*S*)-(+)-**4c** (0.48 g, 1.48 mmol) obtained from the resolution above and dissolved in methanol (30 mL). After stirring for 1 h at room temperature, the reaction mixture was neutralized to pH 7 with the addition of 1.0 N HCl (pH paper). The solvents were removed by rotary evaporation and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with satd $NaHCO_3$ (25 mL), satd NaCl (25 mL), dried over sodium sulfate, filtered, concentrated by rotary evaporation, and recrystallized from toluene to give white crystals. This recrystallization increased the enantiomeric purity to >95% ee (0.31 g, 1.11 mmol, 75% yield). mp 185–186 °C, $[\alpha]_D$ = +40.0 (*c* 1.0, MeOH) [lit.[32] (*R*)-(−), $[\alpha]_D$ = −23.0 (*c* 2, MeOH)]. The TLC and ^1H NMR were identical to those for (±)-**4b**.

(*R*)-(−)-(2-Hydroxy-1-naphthyl)methylphenylphosphine Oxide, (*R*)-(−)-4b, and (*S*)-(+)-(2-acetoxy-1-naphthyl)methylphenylphosphine Oxide, (*S*)-(+)-4c, from a CE Catalyzed Resolution. Cholesterol esterase (4.7 mg) was added to a biphasic solution of toluene (50 mL) and phosphate buffer (75 mL, pH 7.0, 10 mM) containing **4c** (1.03 g, 3.18 mmol) and sodium taurocholate (150 mg). The reaction mixture was rapidly stirred and the pH was maintained at 7.0 by a Radiometer RTS822 pH stat which controlled the addition of 0.105 N NaOH. After 27 h, 14.7 mL of base had been consumed, 48% conversion. The reaction mixture was worked up in the same manner as described above. Concentration under vacuum gave an oil, (*S*)-(+)-**4c**, 0.50 g, 1.54 mmol, 50% yield, 76% ee and a white solid, (*R*)-(−)-**4b**, 0.47 g, 1.67 mmol, 52% yield, 84% ee, corresponding to an enantiomeric ratio of 19 for the reaction. Recrystallization of (*R*)-(−)-**4b** from hot toluene increased the enantiomeric purity to >95% ee (0.31 g, 1.1 mmol, 35%). mp 186–187 °C; $[\alpha]_D$ = −38.0 (*c* 1.0, MeOH). (*S*)-(+)-**4c** was hydrolyzed (*S*)-(+)-**4b** and recrystallized as above: >95% ee (0.27 g, 1.0 mmol, 32%). mp 185–186 °C, $[\alpha]_D$ = +40.0 (*c* 1.0, MeOH). The TLC and NMR of (*S*)-(+)-**4c**, (*S*)-(+)-**4b** and (*R*)-(−)-**4b** were identical to those for (±)-**4b** and (±)-**4c**.

(*S*)-(+)-(2-Methoxy-1-naphthyl)methylphenylphosphine Oxide, (*S*)-(+)-4a. (*S*)-**4b** (0.24 g, 0.85 mmol) was dissolved in acetone (15 mL) containing CH_3I (0.11 mL, 1.7 mmol) and suspended K_2CO_3 (0.15 g, 1.1 mmol). The mixture was refluxed for 48 h while additional CH_3I (1.0 mL) was added in 200 μL aliquots to replace what was lost by evaporation. When TLC showed that the reaction was complete, the acetone was removed by rotary evaporation and the residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with H_2O (15 mL), $Na_2S_2O_3$ (15 mL of 10 w/v%), satd NaCl (15 mL), dried over sodium sulfate, filtered, concentrated by rotary evaporation, and recrystallised from toluene to give white needles: (0.19 mg, 0.64 mmol, 75%, >99% ee), mp 133–134 °C (toluene) [lit.[32] 131–132 °C], $[\alpha]_D$ = +128 (*c* 1.0, MeOH) [lit.[32] (*S*)-(+), $[\alpha]_D$ = +124.0° (*c* 2, MeOH)]. The TLC and NMR were identical to those for (±)-**4a**.

(*R*)-(−)-(2-Methoxy-1-naphthyl)methylphenylphosphine Oxide, (*R*)-(−)-4a, was synthesized in the same manner as (*S*)-**4a**, but starting from (*R*)-**4b** (0.18 g, 0.64 mmol). The reaction afforded (*R*)-(−)-**4a** as white needles with 99% ee (0.15 g, 0.51 mmol, 80%). mp 134–135 °C (toluene) [lit.[3] 130–132 °C], $[\alpha]_D$ = −126.0 (*c* 1.0, MeOH) [lit.[32] (*R*)-(−), $[\alpha]_D$

(37) A similar procedure was used to reduce other phosphine oxides: Okada, Y.; Minami, T.; Umezu, Y.; Nishikawa, S.; Mori, R.; Nakayama, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 667–682

= −120.5 (*c* 2, MeOH)]. The TLC and NMR were identical to those for (±)-**4a**.

(*S*)-(−)-(2-Methoxy-1-naphthyl)methylphenylphosphine, (*S*)-5a. To a solution of dry benzene (5 mL) was added (*S*)-(+)-**4a** (0.14 g, 0.47 mmol, 99% ee) and Et_3N (0.28 mL, 2.0 mmol). After stirring for 5 min $HSiCl_3$ (0.19 mL, 1.9 mmol) was added and the reaction mixture was stirred another 45 min at room temperature. The reaction was quenched with the addition of NaOH (2 mL of 10 w/v%) and stirred until both phases became clear. The aqueous phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were washed with water (3 × 20 mL), dried over sodium sulfate, filtered, concentrated by rotary evaporation. Purification by column chromatography on neutral alumina (2 × 15 cm) eluted with 9:1 hexane:ethyl acetate gave a clear oil which crystallized from a few drops of methanol: 96 mg, 0.34 mmol, 72% yield; 96% ee (*S*) by HPLC; $[\alpha]_D$ = −116.0 (*c* 0.55, CH_2Cl_2); mp 60−61 °C; MS (EI) m/z (rel int): 280 (100, $M^{\bullet+}$), 279 (76, $(M - H)^+$), 249 (30, $(M - OCH_3)^+$), 233 (18), 202 (12), 189 (28), 187 (18), 125 (13), 115 (10), 91 (14), 77 (9, $C_6H_5^+$); HRMS (EI); exact mass 280.10170 ($C_{18}H_{17}O_1P$ requires 280.10140, 1.1 ppm error); ^1H NMR (C_6D_6, 200 MHz) δ 9.45 (m, 1), 7.67−6.70 (m, 10), 2.99 (s, 3), 1.80 (d, 3, $^2J_{P-H}$ = 4 Hz); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 161.6, 161.5, 142.9, 142.8, 139.2, 138.8, 132.7, 130.1, 129.9, 128.7, 129.6, 128.6, 128.1, 128.07, 127.2, 127.0, 126.9, 126.6, 123.9 (aromatic carbons; some are split by phosphorus), 56.3 (s, OCH_3), 9.3 (d, $^1J_{P-C}$ = 12 Hz, PCH_3); ^{31}P (C_6D_6, 121 MHz) δ −44.2.

(*R*)-(+)-(2-Methoxy-1-naphthyl)methylphenylphosphine, (*R*)-(+)-5a, was synthesized and purified in the same manner starting from (*R*)-**4a** (0.26 g, 0.88 mmol, >99% ee) to give (*R*)-**5a**; 0.19 g, 0.68 mmol, yield 77%; 97% ee (*R*) by HPLC; $[\alpha]_D$ = 113.0 (*c* 0.50, CH_2Cl_2); mp 50−51 °C. The TLC and NMR were identical to those for (*S*)-**5a.**

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Note added in proof: Kiełbasiński et al. efficiently resolved phosphinoyl acetates with pig liver esterase: Kiełbasiński, P.; Żurawiński, R.; Pietrusiewicz, K. M.; Zablocka, M.; Mikołajczyk, M. *Tetrahedron Lett.* **1994**, *35*, 7081−7084.