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Rabbit Gastric Lipase in Biocatalytic Resolution of 2-Hydroxyalkyldiphenylphosphines†

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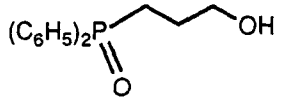
Abstract—Kinetic resolution of 2-hydroxyalkyldiphenylphosphines **4** by acylation with isopropenyl acetate was carried out under rabbit gastric lipase (RGL) catalysis to give optically active **4** and the corresponding acetate, the enantioselectivity factors *E* ranging from 10 to 20. 1-(2-Naphthyl)ethanol and 2-[*N*-(ethoxycarbonyl)amino]1-butanol **7** were also resolved.

Introduction

Use of lipases in organic synthesis has known an exponential growth during the last ten years.[1] This important development is the result of basic studies and the consequence of the commercial availability of many lipases.[2] A strong impulse for the use of lipases in organic synthesis has also been the possibility of working in organic solvents.[3]

We wish to report our results concerning a new mammalian lipase, the crude rabbit gastric lipase (RGL).[4]

Our purpose was to investigate the potential usefulness of the crude rabbit gastric lipase (RGL) in comparison with commercially available lipases, and to promote its use in the resolution of new substrates. As part of our activity in the search for new phosphorus ligands to be used in transition-metal enantioselective catalysis,[5] we looked at the resolution of hydroxyphosphines and their derivatives.[6] To the best of our knowledge, no phosphine or derivative has yet been resolved through lipase-catalyzed acylation reaction.



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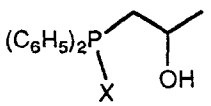

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a: X = O

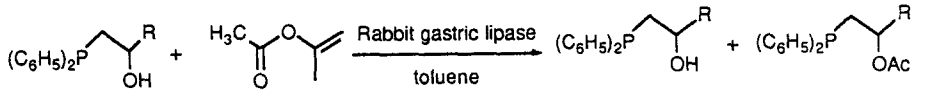
b: X = S

Results and Discussion

Crystalline 3-diphenylphosphinoylpropanol **1** is neither soluble in isopropenyl acetate **3** nor in benzene. No acylation was observed on stirring for 65 h a suspension of **1** or a 1:1 mixture of racemic-**2** and benzene in the presence of RGL (Table 1, runs 1 and 2). Substrate **1** dissolved in benzene on addition of cosolvents. With 6% DMSO, 80% conversion into acylated product was recorded within 18 h. DMSO is, however, detrimental to the activity of RGL since with 10% DMSO, 65 h was required to reach 50% conversion (runs 3 and 4). The enzyme was very active in THF, where it afforded a quantitative yield of acylated product in 8 h (run 5).

Racemic β-hydroxyphosphines of structure **2** were subjected to acylation by isopropenyl acetate (2 equiv.) in the presence of RGL, in toluene. The activity of the catalyst depended upon the size of the group on the phosphorus atom (Table 2). Interestingly, the β-hydroxyphosphine **4a** was acylated at a useful rate. We then turned to an examination of the resolution of β-hydroxyphosphines **4**, looking at the influences of the solvent, the substrate concentration, the nature of the acylating agent and the nature of the substituent α to the hydroxy group on the rate and enantioselectivity of the acylation.

A number of papers report that the nature of the solvent, in particular its hydrophobicity, influences both the activity and the enantioselectivity of acylation reactions.[7] For RGL-catalyzed acylation of **4a**, the rates of reaction carried out in pure isopropenyl acetate or in toluene (with 2 equiv. of isopropenyl acetate) were comparable. In hydroxylic solvents, however, both the activity of the catalyst and the enantioselectivity were low (Table 3).



racemic-4 + 3 → optically active-4 + optically active-5

racemic-4

a : R = -CH_3

b : R = -C_2H_5

c : R = -*n*-C_3H_7

3

d : R = -*i*-C_3H_7

e : R = -CH_2-O-CH_3

f : R = -C_6H_5

g: R = -CH_2-Ph

optically active-4

optically active-5

†Dedicated to Professor Charles J. Sih on the occasion of his 60th birthday.

Table 1. Acylation of 3-diphenylphosphinoylpropanol **1** with isopropenyl acetate **3**, in the presence of RGL[a]

Run	Solvent composition (v:v)	Total solubility of the substrate	Reaction time, h	Substrate conversion, %
1	isopropenyl acetate **3**	no	65	0
2	benzene:**3** 50:50	no	65	0
3	benzene:DMSO 94:6	yes	18	86
4	benzene:DMSO 90:10	yes	65	50
5[b)]	benzene:THF 20:80	yes	2.3	100

[a]5 mL solution, 1 mmol substrate (concentration 0.2 M), 24 °C, 200 mg crude RGL.
[b]Substrate concentration 0.34 M (1.7 mmol/5 mL solvent), 100 mg crude RGL.

Table 2. Acylation of β-hydroxyphosphines **2** and **4a**[a]

Run	Substrate	Reaction time, h	Substrate conversion, %
1	**2a**	10	48
2	**2b**	4	0
3[b)]	**4a**	2.7	50

[a]5 mL toluene, 1.5 mmol substrate (concentration 0.3 M), 100 mg RGL, room temperature.
[b]Under argon.

Table 3. Influence of the solvent upon the activity and enantioselectivity of RGL in acylation of **4a**[a]

Run	Solvent	Reaction time (h)	Substrate conversion (%)	ee (%) of recovered **4a**	E[b)]
1	Isopropenyl acetate	4	53	83	12
2	toluene	4	51	89	13
3	2-methyl butan-2-ol	26	48	71	10
4	3-methyl pentan-3-ol	17	34	34	5

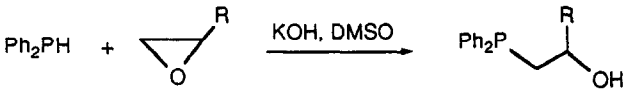
[a]5 mL toluene, 2 mmol substrate (concentration 0.4 M), 100 mg RGL, room temperature.
[b]Calculated from substrate's ee_s value at conversion c, taking $E = \ln [(1-c)\ (1-ee_s)] / \ln [(1-c)\ (1+ee_s)]$.[8]

The enantioselectivity ($E = 11 \pm 1$) for the acylation of **4a**, was constant for substrate concentrations ranging from 0.12–0.82 M, at the same catalyst concentration.

Several acylating agents have been tested for activity and selectivity in the RGL-catalyzed acylation of **4a**. It turned out that among vinyl acetate, isopropenyl acetate and vinyl valerate, isopropenyl acetate afforded the best results both in terms of activity and selectivity. The commercially available vinyl 2-ethylhexanoate was unreactive, probably due to the α-substitution of the acyl group. Acylations with succinic,[9] maleic and phthalic anhydride were also tried. Owing to the poor solubility of these compounds in ether and toluene, the reactions were carried out in THF. None of these anhydrides gave significant acylation. Since succinic anhydride proved to be a satisfactory acylating agent for 1-(2-naphthyl)ethanol *(vide infra)* and cyclo-alkylidenethanols,[9b] the lack of reactivity of **4a** indicates that this hydroxyphosphine cannot act as a nucleophile with the acylated-RGL.

A number of β-hydroxyphosphines of structure **4a-g** have been subjected to RGL-catalyzed acylations by isopropenyl acetate in toluene, under argon at room temperature. The acylated product and the recovered substrate were separated by flash chromatography, their optical rotations measured and their enantiomeric excesses reported in Table 4.

Racemic substrates **4** were prepared in good yield according to a slightly modified Kabachnik procedure,[12] involving regioselective ring opening of the appropriate epoxide by $(C_6H_5)_2PH$/KOH in DMSO. Racemic epoxides were either commercially available (giving access to **4a**, **4b**, **4e**, **4f**, **4g**) or prepared via the bromohydrin obtained through hydrobromination of the corresponding alkene (and used to yield **4c**, **4d**).[13]



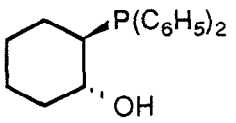
4

Both the activity and the enantioselectivity of RGL were satisfactory in the acylation of β-hydroxyphosphines **4a–4c**, **4e**. Replacement of a CH_2 group by an oxygen atom as in **4e** does not affect significantly the enantio-selectivity, although the rate of the reaction is slowed down. Substrates with sterically demanding R groups (**4f**, **4g**) were not transformed. Substrate **4d** was slowly acylated (44% conversion after 8 days); however, the reaction required a high concentration of lipase. Moreover, the formation of small amounts of phosphine oxide rendered the separation and purification somewhat tedious. The cyclic β-hydroxyphosphine **6** was poorly reactive, affording only 12% conversion after 9 days. As a comparison, cyclohexanol yielded 34% acetate within 16 h under the same conditions. Thus, steric hindrance by a substitution on the carbon bearing the phosphorus atom in the substrate appears to play a crucial role.

Table 4. RGL-catalyzed resolution of **4a–4g**[a]

Substrate	Time, h	Conversion, %[b]	**4** ee, %[c]	**5** ee, %[f]	E value[g]
4a	1.5	56	88[d,e]	69	34 ± 5
4b	3.5	38	47	76	12 ± 2
4c	8	44	66	84	20 ± 3
4d	8 days	44	- [h]	- [h]	
4e	26	51	80	77	18 ± 3
4f	6	0			
4g	36	0			

[a] 1 mmol **4**, with 0.25 g RGL in 0.8 mL toluene, 200 mL isopropenyl acetate, room temperature.
[b] Determined by glc, by comparison with an internal standard.
[c] Determined from the $[\alpha]_D$ of the enantiomers obtained through successive resolutions until constant (< 1% variation) value: $[\alpha]_D^{25}$ (c 2, AcOEt) **4a**: -7.0; **4b**: +9.8; **4c**: +3.9; **4e**: +8.5.
[d] Determined by ^1H NMR and HPLC measurement of the diastereomeric ratio of the urethane derivative made from (*R*)-(–)-1-(1-naphthyl)ethyl isocyanate.[10]
[e] Determined by ^1H NMR of the Mosher's esters.[11]
[f] Determined on the alcohol obtained from saponification of the ester.
[g] See Table 3.
[h] Not determined.



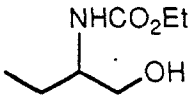
(±)-6

Common commercially available lipases showed much lower catalytic activity than RGL, even when used in large amounts. A 54% conversion was attained in 4 h for the RGL-catalyzed acylation of **4a**. After 6 h reaction, only 0.7% and 1.5% of **4a** was converted by *Candida cylindracea* lipase (CCL) and pig pancreatic lipase (PPL) catalysis, respectively. With *Pseudomonas fluorescens* lipase (PFL), 6.5% conversion was reached in 40 h.

All the resolutions described in this paper were carried out with a crude preparation of RGL. Surprisingly, a purified sample of RGL[4] gave very low activity in **4a** acylation. Comparison of rates of acylation of 2-octanol with purified RGL, crude RGL or crude PPL revealed that for roughly comparable activities of enzyme involved (expressed as unit of enzyme per mg of substrate), crude RGL was far more active than the other two lipases (Table 5). Reasons accounting for the loss of activity of purified RGL have not yet been elucidated.

Crude RGL was active in acylation of 1-(2-naphthyl)-ethanol with succinic anhydride to give unreacted (*S*)-(–)-alcohol in 98% ee after 16 h at 53% conversion ($E = 60 \pm 5$). The (*R*)-(+)-alcohol isolated after saponification of the hemiester product showed 86% ee. Thus, RGL is as efficient as lipase Amano Sam 2 in this kinetic resolution.[9c]

Crude RGL was also very active in acylation of 2-[*N*-(ethoxycarbonyl)amino]1-butanol **7** with isopropenyl acetate. High conversions were recorded in less than one hour. The enantioselectivity was dependent upon the nature of the solvent (Table 6). Acylation of **7** by ethyl acetate has already been reported in the presence of steapsine, pancreatine and Amano P lipase.[14]



7

Table 5. Crude or purified RGL as catalysts in the acylation of 2-octanol

Lipase	Lipase (mg)	Lipase activity[a] (U/mg substrate)	Reaction time (h)	Conversion (%)
Purified RGL	17	62	23	21
Crude RGL	60	60	5	73
Crude PPL	300	66	25	23

[a]Crude RGL, purified RGL: activity measured on tributyrin; crude PPL, activity measured on triacetin.

Table 6. RGL-catalyzed acylation of **7** with isopropenyl acetate[a]

Solvent	Reaction time (h)	Conversion (%)	Recovered **7** ee (%)[b]	E value
isopropenyl acetate	0.7	61	38	2.5
1:1 isopropenyl acetate : benzene	0.7	79	99	7
1:1 isopropenyl acetate : THF	0.7	44	41	4.5

[a]Substrate, 3 mmol; solvent 2 mL; 28 °C; lipase activity: 700 U/mg substrate.
[b]Calculated from the maximum specific rotation for (*S*)-(–)-**7** $[\alpha]_D^{21}$ -49.6 (c 2, AcOEt).

Conclusion

The crude mammalian lipase rabbit gastric lipase (RGL) displays high activity and enantioselectivity in catalysis of acylation of 1-(2-naphthyl)ethanol. It was very active in acylation of 2-[*N*-(ethoxycarbonyl)amino]-1-butanol with isopropenyl acetate. It also proved to be superior to other commonly used lipases in acylation of various β-hydroxyphosphines. This constitutes the first resolution of phosphines carried out through lipase-catalyzed acylation. RGL is an additional enzyme which deserves to be considered when a specific problem has not yet been solved by conventional lipases.

Experimental Section

General

NMR spectra were recorded in $CDCl_3$ with a Bruker WP 200 FT spectrometer. Chemical shifts were reported in δ with TMS (internal, for ^1H NMR) or 85% H_3PO_4 (external, for ^{31}P NMR) references. Mass spectra were obtained on a Ribermag 10-10 spectrometer. GLC analyses were performed on a 25 m capillary column of CP SIL19 CB, i.d. 0.33 mm. The retention times are given in min at the given temperature, for an H_2 flow of 5 mL·min^{-1}.

Materials

1,2-Epoxy propane, 1,2-epoxy butane, vinyl acetate, isopropenyl acetate, vinyl 2-ethylhexanoate were obtained from commercial sources. The following materials were prepared according to reported procedures: 3-methyl-1,2-epoxy butane,[13] vinyl valerate,[16] 2-[*N*-(ethoxycarbonyl)-amino]1-butanol **7**.[14]

1,2-Epoxypentane

It was synthesized through a reported procedure[17] which was slightly modified. A two-phase mixture of 1-butene (33 g, 0.47 mol), *N*-bromosuccinimide (84 g, 0.47 mol) and 200 mL of H_2O was rapidly stirred until the solid dissolved in the aqueous phase and the upper organic phase (1,2-epoxypentane) is replaced by a lower organic phase (bromhydrin). The reaction temperature increased up to 50 °C during the reaction. After 1 h stirring the solution was extracted with Et_2O, and the combined extracts were evaporated under reduced pressure (30 °C). The crude product was a colorless liquid (85 g) which was used without further purification. It was mixed with KOH (28 g, 1 equiv.) and H_2O (150 mL) and stirred for 45 min. The resulting solution was extracted with 3 portions of Et_2O, dried ($MgSO_4$) and concentrated under vacuum. The residue was distilled to give 1,2-epoxypentane (20 g, 0.23 mol, 49%); *Eb* = 89–90 °C; ^1H NMR δ 0.95 (t, 3H), 1.5–1.6 (m, 4H), 2.45 (dd, 1H), 2.75 (dd, 1H), 2.9 (m, 1H).

3-Diphenylphosphinoylpropanol (1)

This was prepared according to Kabachnik's procedure[12] from diphenylphosphine oxide and 3-chlorobutanol in 78% yield; m.p. 101–103 °C. ^1H NMR δ 1.85–1.95 (m, 2H), 2.3–2.4 (m, 2H), 3.45 (broad s, OH, 1H), 3.7 (t, 2H), 7.3–7.5 (m, 6H), 7.6–7.75 (m, 4H); ^{31}P NMR δ 35.

2-Diphenylphosphinoylethanol (2a)

This was prepared by the same procedure from 2-chlorobutanol (45%); ^1H NMR δ 2.5–2.6 (m, 2H), 3.7 (broad s, OH, 1H), 4–4.1 (m, 2H), 7.3–7.5 (m, 6H), 7.6–7.75 (m, 4H); ^{31}P NMR δ 34.5; MS, *m/e* 228 (100), 227 (78), 201 (44), 183 (56), 77 (44).

Preparation of β-hydroxyphosphines 4

The synthesis used Kabachnik's method.[12] To a stirred solution of diphenylphosphine (9.8 g, 50 mmol) in 20 mL of dimethylsulfoxide (DMSO) under argon was added at 20 °C an aqueous solution of 56% potassium hydroxide (6 mL, 60 mmol). The reaction mixture turned red. A solution of the epoxide (60 mmol, 1.2 equiv.) in 20 mL of DMSO was added dropwise with stirring in an ice-bath, the temperature being maintained between 20–25 °C. After 30 min stirring at 20 °C, the solution was diluted with saturated NH_4Cl aqueous solution, extracted with toluene or AcOEt (3 x 20 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude colorless residual oil was purified by filtration through a silica gel column (with toluene or 70/30 cyclohexane/AcOEt as eluent). Evaporation of the solvent left an oil. **4b**, **4g**, **4f** are known compounds.[12]

1-Diphenylphosphinopropan-2-ol (4a)

(95% yield); ^1H NMR δ 1.3 (dd, 3H), 2.3–2.4 (m, 2H), 2.8–3.3 (broad s, 1H), 3.8–3.9 (m, 1H), 7.3–7.4 (m, 6H), 7.5–7.6 (m, 4H). ^{31}P NMR δ -22.5. MS, *m/e* 244 (M^+, 89), 202 (29), 201 (13), 200 (20), 199 (88), 186 (67), 185 (20), 184 (11), 165 (15), 155 (17), 121 (100), 108 (79), 107 (25), 91 (24), 78 (13), 77 (30), 51 (15), 47 (15). Anal. calcd for $C_{15}H_{17}OP$: C, 73.77; H, 6.96. Found C, 73.47; H, 6.96. GLC (215 °C) 4.9.

(S)-(–)-1-Diphenylphosphinopropan-2-ol (4a)

This was prepared by the above procedure from (*S*)-(+)-1,2-epoxypropane and showed $[\alpha]_D^{20}$ -7.2 (c 2, AcOEt).

1-Diphenylphosphinobutan-2-ol (4b)

(95% yield); ^1H NMR δ 0.9 (t, 3H), 1.6–1.7 (m, 2H), 1.85 (s, 3H), 2.3–2.4 (m, 1H), 2.6–2.62 (m, 1H), 4.9–5 (m, 1H), 7.3–7.5 (m, 6H), 7.4–7.5 (m, 4H). ^{31}P NMR δ -23.2. MS, *m/e* 258 (M^+, 37), 200 (37), 199 (100), 186 (32), 185 (16), 183 (53), 121 (37), 108 (37), 107 (16), 91 (21), 77 (21). Anal. calcd for $C_{16}H_{19}OP$: C, 74.42; H, 7.36. Found C, 74.49; H, 7.41. GLC (215 °C) 5.8.

1-Diphenylphosphinopentan-2-ol (4c)

(95% yield); ^1H NMR δ 0.85 (t, 3H), 1.45–1.55 (m, 4H), 2–2.1 (broad s, 1H), 2.3–2.4 (m, 2H), 3.7 (1H), 7.4–7.6 (m, 10H). ^{31}P NMR δ -22.5. MS, *m/e* 272 (M^+, 38), 255

(15), 229 (23), 200 (32), 199 (100), 186 (64), 185 (17), 183 (57), 121 (62), 108 (85), 107 (28), 91 (33), 78 (18), 77 (31). Anal. calcd for $C_{17}H_{21}OP$: C, 75.0; H, 7.72. Found C, 74.84; H, 7.78. GLC (215 °C) 7.0.

*1-Diphenylphosphino-3-methylbutan-2-ol (**4d**)*

(26% yield); ^{1}H NMR δ 0.95 (d, 6H), 1.8 (m, 1H), 2.15 (m, 1H), 2.5–2.6 (broad s, 1H), 3.5 (m, 1H), 7.3–7.4 (m, 6H), 7.4–7.5 (m, 4H). ^{31}P NMR δ -22.4. MS, *m/e* 272 (M^+, 18), 200 (74), 199 (100), 186 (16), 185 (20), 183 (33), 121 (28), 108 (45), 107 (21), 91 (34), 77 (19). GLC (245 °C) 3.7.

*1-Diphenylphosphino-1-methoxypropan-2-ol (**4e**)*

(95% yield); ^{1}H NMR δ 2.3–2.4 (m, 2H), 2.8–3 (broad s, 1H), 3.3 (s, 3H), 3.35 (dd, 1H), 3.5 (dd, 1H), 3.9–3.95 (m, 1H), 7.3–7.4 (m, 6H), 7.45–7.55 (m, 4H). ^{31}P NMR δ -22.4. MS, m/e 274 (M^+, 22), 259 (26), 257 (16), 229 (18), 200 (46), 199 (100), 185 (26), 183 (56), 121 (43), 108 (30), 71 (25), 45 (30). Anal. calcd for $C_{14}H_{19}O_2P$: C, 70.07; H, 6.93. Found C, 70.68; H, 6.92. GLC (215 °C) 7.3; (245 °C) 4.05.

*2-Diphenylphosphino-1-phenylethanol (**4f**)*

(52% yield); ^{1}H NMR δ 2.5–2.6 (m, 2H), 3.25 (broad s, 1H), 4.7–4.8 (m, 1H), 7.3–7.5 (m, 15H). ^{31}P NMR δ -22.5. GLC (245 °C) 7.46.

*1-Diphenylphosphino-3-phenylpropan-2-ol (**4g**)*

(34% yield); ^{1}H NMR δ 1.95 (broad s, 1H), 2.35–2.4 (m, 2H), 2.8, 2.95, 3.95 (3H, ABX system, Ph_2P $CH_AH_BCH_XOH$ (J_{AB} = 7.4 Hz, J_{AX} = 4 Hz, J_{BX} = 2 Hz), 7.2–7.4 (m, 15H). ^{31}P NMR δ -23; MS, *m/e* 320 (M^+, 12), 200 (33), 199 (100), 185 (11), 183 (36), 121 (11), 108 (11), 91 (44), 77 (14).

trans-*2-Diphenylphosphinocyclohexan-1-ol (**4f**)*

(86% yield); m.p. 138–140 °C; ^{31}P NMR δ -9.5; MS, *m/e* 284 (M^+, 30), 267 (13), 187 (23), 186 (55), 185 (14), 109 (21), 108 (100), 107 (29), 91 (11), 81 (20), 57 (10). Anal. calcd for $C_{18}H_{21}OP$: C, 76.06; H, 7.39. Found C, 75.80; H, 7.45.

*2-Diphenylphosphinothioylethanol (**2b**)*

This was prepared according to Aguiar and Daigle[19] by sulfuration of **4a**; a solution of phosphine **4a** (0.50 g, 2.05 mmol) and sulfur (65.6 mg, 2.05 mmol) in toluene (10 mL) was refluxed for 1 h. After cooling, the product **2b** crystallizes out. The crystals were filtered, washed with ether, to give the product **2b** (0.52 g, 97%) as colorless crystals; m.p. 58–59 °C. ^{1}H NMR δ 0.9 (t, 3H); 1.6 (m, 2H); 2.35 (m, 2H); 2.5–3.3 (1H, O*H*); 3.65 (m, 1H); 7.3 (m, 6H); 7.45 (m, 4H).

*Kinetic resolution of 1-diphenylphosphinopropan-2-ol (**4a**)*

To a solution of **4a** in toluene was added 2 equivalents of isopropenyl acetate (1.6 mL, 16.5 mmol) then 3 g of rabbit gastric lipase. The resulting suspension was stirred for the required time. The reaction was monitored by GLC analysis of aliquots (100 mL) that were filtered through diatomaceous earth, and washed with toluene (~1 mL). At the required conversion, the reaction mixture was filtered through Celite, (~1 g), which was washed with toluene (~ 40 mL). After evaporation of the solvent, the residue was purified on a silica gel column with 80:20 hexane:ethyl acetate as eluent. Two oily fractions were collected (conversion 0.56): 1-diphenylphosphinopropan-2-ol (**4a**) (0.78 g, 3.2 mmol, 39%) $[\alpha]_D^{20}$ -6.4 (c 2, AcOEt), 88% ee and 1-diphenylphosphinopropan-2-yl acetate (**5a**) (1.02 g, 3.6 mmol, 43 %) $[\alpha]_D^{20}$ +40.5 (c 2, AcOEt). A 0.1 g sample of **5a** was saponified under argon to give **4a** (68% ee)

*1-Diphenylphosphinopropan-2-yl acetate (**5a**)*

^{1}H NMR δ 1.3 (dd, 3H), 1.85 (s, 3H), 2.2–2.3 (m, 1H), 2.5–2.6 (m, 1H), 5–5.1 (m, 1H), 7.3–7.4 (m, 6H), 7.45–7.6 (m, 4H); ^{31}P NMR δ -22. GLC (215 °C) 5.8.

*1-Diphenylphosphinobutan-2-yl acetate (**5b**)*

^{1}H NMR δ 0.9 (t, 3H), 1.65–1.70 (m, 2H), 1.85 (s, 3H), 2.35 (broad s, 1H), 2.6–2.65 (m, 1H), 4.95–5 (m, 1H), 7.2–7.3 (m, 6H), 7.4–7.5 (m, 6H). GLC (215 °C) 6.5.

*1-Diphenylphosphinopentan-2-yl acetate (**5c**)*

^{1}H NMR δ 0.85 (t, 3H), 1.3–1.45 (m, 4H), 1.7–1.75 (m, 2H), 1.8 (s, 1H), 2.4–2.45 (m, 2H), 5 (m, 1H), 7.4–7.55 (m, 10H); ^{31}P NMR δ -22.5 GLC (215 °C) 7.8.

*1-Diphenylphosphino-3-methylbutan-2-yl acetate (**5d**)*

^{1}H NMR δ 0.9 (t, 6H), 1.8 (s, 3H), 2.05 (m, 1H), 2.35–2.4 (m, 1H), 4.9 (m, 1H), 7.2–7.3 (m, 6H), 7.4–7.5 (m, 4H). GLC (215 °C) 3.9.

*1-Diphenylphosphino-3-phenylpropan-2-yl acetate (**5g**)*

^{1}H NMR δ 1.9 (s, 3H), 2.45 (dd, 2H), 3.30 (s, 3H), 3.55 (d, 2H), 5.1 (m, 1H), 7.35–7.4 (m, 6H), 7.45–7.5 (m, 4H).

Kinetic resolution of 1-(2-naphthyl)ethanol

1-(2-Naphthyl)ethanol (0.86 g, 5 mmol), succinic anhydride (0.7 g, 7 mmol) and 100 mg of crude RGL in 10 mL of ethyl ether were stirred at room temperature. GLC analysis of an aliquot showed that after 16 h, 53% conversion was reached. The reaction was then stopped by filtering off the enzyme which was washed with 2 x 10 mL ether. The combined ethereal fractions were extracted with 3 x 20 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give the (*S*)-enriched unreacted alcohol, 3.8 g, (44%), $[\alpha]_D^{20}$ -41.1 (c 3, ethanol), 98% ee.[18] The aqueous phase was stirred for 5 h with 5 g NaOH, then extracted with 3 x 10 mL, ether. The combined ethereal fractions were dried ($MgSO_4$), and evaporated to give (*R*)-(+)-alcohol, 4.3 g (50%), $[\alpha]_D^{20}$ 36 (c 3, ethanol), 86% ee.

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