Candida rugosa Lipase-catalyzed Kinetic Resolution of Hydroxyalkanephosphonates‡†

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An efficient lipase-catalyzed enantioselective hydrolysis of butyryloxyalkanephosphonates in water-equilibrated diisopropyl ether was developed. The relationship between the substrates' structure and the reactivity, as well as the enantioselectivity of this enzymatic transformation was studied. The catalytic preference of crude *Candida rugosa* lipase toward such molecules was assigned according to modified Mosher's method and X-ray crystallographic analysis. Optically pure 2-hydroxy-2-arylethanephosphonates, 3-hydroxy-3-phenylpropanephosphonate, and 3,3,3-trifluoro-2-hydroxypropanephosphonates were conveniently prepared in this manner.

Keywords *Candida rugosa* lipase, hydrolysis, hydroxyalkanephosphonate

Introduction

Chiral 1- or 2-hydroxyalkanephosphonates have received much attention due to their unique biological properties and synthetic utilities.[1] Several methods for preparing such molecules have been documented. 1-Hydroxyalkanephosphonates can be prepared by $TiCl_4$-catalyzed opening of homochiral 1,3-dioxane acetals with trimethyl phosphite,[2] diastereoselective addition of homochiral phosphorus derivatives to aldehydes,[3] enantioselective reduction of ketoalkanephosphonates,[4] enantioselective addition of dialkyl phosphites to aldehydes[5] and even chemical or enzymatic resolutions.[6] Comparably, only few reports dealt with the asymmetric synthesis of 2-hydroxyalkanephosphonates,[7] among which Noyori's asymmetic hydrogenation using BINAP-Ru catalyst seemed to be one of the most successful.[7j]

Nowadays, biocatalysts are widely used in synthetic chemistry due to their high chemo-, regio- and stereoselectivity.[8] Furthermore, enzyme-catalyzed reactions are non-hazardous, less energy-consuming and polluting compared to the conventional chemical process. The use of lipases for efficient resolution of alcohols and related compounds is of great importance in organic synthesis. These readily available hydrolases do not require cofactors and exhibit broad substrate specificity. More importantly, they are well suited to retain a high degree of activity in organic media. It was not until 1980s did the true blossom of the study of nonaqueous enzymology took place with Martinek's article in *Science* as the milestone.[9] Enzymatic reactions performed in a nonaqueous solvent system is now, indeed, a standard procedure in most synthetic laboratories worldwide. In this paper, we wish to report in detail our study on *Candida rugosa* lipase (CRL)-catalyzed enantioselective hydrolysis in organic media for the preparation of hydroxyalkanephosphonates.

Results and discussion

It was noticed that *Candida rugosa* lipase, probably the most widely used lipase in synthetic chemistry, could hydrolyze a series of bulky substrates.[10] Hammerschmidit had screened *Candida cylindracea* lipase for the enantioselective hydrolysis of diisopropyl 1-acyloxybenzylphosphonate but pitifully failed.[6c] This result was further confirmed by our experiments. On the other hand, diethyl or dimethyl butyryloxyl-1-benzylphosphonate could be hydrolyzed to its (*S*)-alcohol with satisfactory activity but poor enantioselectivity (Scheme 1 and Table 1). The dimethylphosphoryl moiety ensured better activity and selectivity.

Our further study showed that CRL-catalyzed acylation of hydroxyalkanephosphonates using vinyl acetate as acyl donor exhibited poor reactivity. Considering that CALB and immobilized *mucor miehei* lipase (IM)-catalyzed alcoholysis served as an efficient methodology in the resolution of some hydroxyalkanephosphonates,[11] we then examined CRL-catalyzed alcoholysis of their chloroacetyl derivatives, to our surprise, no desired products were observed. However, alcoholysis of their butyryloxy derivatives took place with poor enantioselectivity (Scheme 2).

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Scheme 1

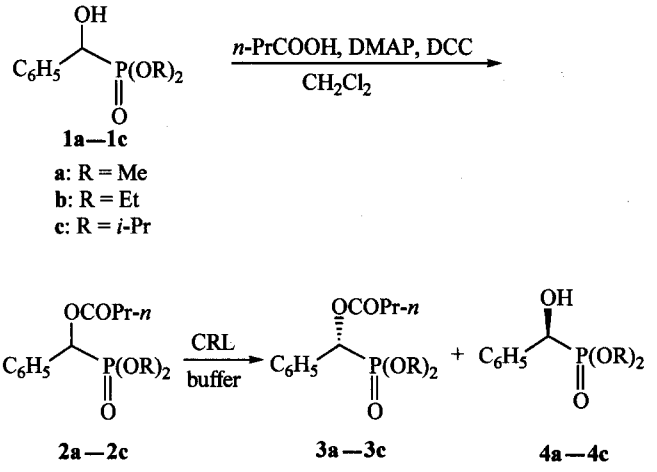
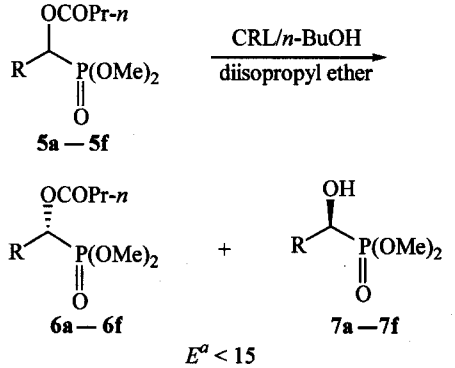


Table 1 CRL-catalyzed hydrolysis of 1-butyryloxylbenzylphosphonates **2a—2c**[a]

Entry	R	reaction time (h)	Conversion (%)	*ee* of **4a—4c** (%)
1	Me	4	33	75
2	Et	4	14	59
3	*i*-Pr		no reaction	

[a] Reaction conditions: 1 mmol of substrate, 100 mg of crude CRL, 4 mL of phosphate buffer, 30 ℃.

Scheme 2



$E^a < 15$

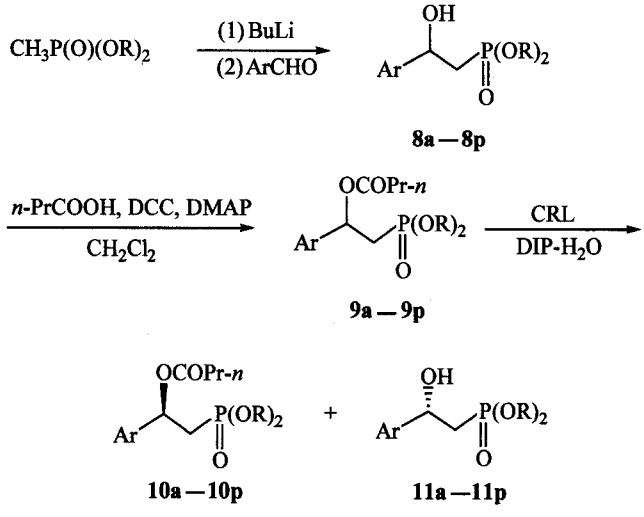
R = C_6H_5, 2-$NO_2C_6H_4$, 2-ClC_6H_4, 2,6-$Cl_2C_6H_3$, 4-EtC_6H_4, 4-$MeOC_6H_4$

[a] *E*, the enantiomeric ratio, $E = \ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)] = \ln[1-c(1+eep)]/\ln[1-c(1-eep)]$, $c = ees/(ees+eep)$

The failure of CRL-mediated resolution of 1-hydroxyalkanephosphonates may be partially ascribed to the substrates' rigidity, which was not favourable for some CRL-mediated reactions. Bearing this in mind, we extended the substrates scope to 2-hydroxyalkanephosphonates. Alcoholysis of diethyl 2-butyryloxy-2-arylethanephosphonates did not give any product. Then we turned our attention to CRL-catalyzed hydrolysis because water acted as stronger nucleophile, which may be helpful to enhance the enzymatic activity. Indeed, reaction performed in buffer system showed high activity and good enantioselectivity ($E = 65$). To avoid the extraction procedure and take the advantages of enzymatic reactions in organic media, we wished to perform the hydrolysis in a water-saturated organic solvent.

Although there were several papers dealing with CRL-catalyzed hydrolysis in water-saturated diisopropyl ether,[12] we found that the aggregation (or allogation) of the reaction mixture was unavoidable. In many cases, salts were used for the control of water activity in organic solvent.[13] We finally found that diisopropyl ether saturated with 1.2 mol/L $MgCl_2$ could greatly inhibit agrregation. It showed that CRL-catalyzed hydrolysis served as an efficient methodology for the preparation of optically pure 2-hydroxy-2-arylethanephosphonates (Scheme 3 and Table 2).

Scheme 3



The choice of the acyl component was quite important for practical purposes as the acetyl group led to lower reaction rates under our experimental conditions. Butyryloxyarylethanephosphonates can be hydrolyzed easily.

The configuration of the hydrolyzed alcohols was assigned as (*S*) based on the refined Mosher's method, *i.e.* the Kusumi-Ohtani method.[14] Typical examples was shown in Fig. 1.

The absolute configuration of the hydrolyzed alcohol was also confirmed by X-ray structure of compound **11i** since it bears a bromine atom in the molecule (Fig. 2).

It was found by us that CRL-catalyzed hydrolysis of the 3-butyryloxyl-3-arylpropanephosphonate afforded (*R*)-alcohol with high optical purity (Scheme 4).

Table 2 *Candida rugosa* lipase-catalyzed enantioselective hydrolysis of 1-butyryloxylarylethylphosphonates in diisopropyl ether [a]

Substrate **9**	Ar	R	Time (h)	**10a—10o**		**11a—11o**		*E*
				Yield[b] (%)	*ee*[c] (%)	Yield[b] (%)	*ee*[d] (%)	
a	C_6H_5	Me	30	41	> 95	42	> 95	> 100
b	C_6H_5	Et	40	44	> 95	45	> 95	> 100
c	C_6H_5	*n*-Pr	40	43	> 95	44	> 95	> 100
d	C_6H_5	*i*-Pr	48	41	> 95	42	> 95	> 100
e	4-FC_6H_4	Et	39	41	> 95	42	> 95	> 100
f	4-$NO_2C_6H_4$	Et	44	43	> 95	44	> 95	> 100
g	4-MeC_6H_4	Me	30	45	> 95	40	> 95	> 100
h	4-BrC_6H_4	Et	30	41	> 95	42	> 95	> 100
i	2-BrC_6H_4	Et	28	42	> 95	42	> 95	> 100
j	2,4-$Cl_2C_6H_3$	Et	15	42	> 95	45	> 95	> 100
k	3-ClC_6H_4	Et	27	41	> 95	44	> 95	> 100
l	4-$EtOC_6H_4$	Me	35	42	> 95	43	> 95	> 100
m	2-$CF_3C_6H_4$	Et	40	44	> 95	42	> 95	> 100
n	2-Furyl	Et	20	45	88.7	40	93.8	93
o	2-Naphthyl	Et	35	41	> 95	39	> 95	> 100

[a] All reactions were performed on 100 mg scale with 100 mg of crude lipase and 4 mL of diisopropyl ether saturated with 1.2 mol/L $MgCl_2$ at 38 ℃. [b] Isolated yield after column chromatography. [c] Determined by ^{31}P NMR with quinine as the solvating agent after chemical conversion into alcohols using K_2CO_3/MeOH. [d] Determined by ^{31}P NMR with quinine as the solvating agent, a single peak was judged as > 95% *ee*.

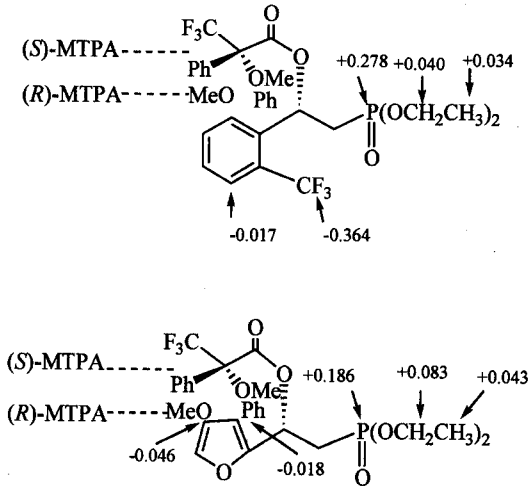


Fig. 1 Configurational assignment of the hydrolyzed hydroxyalkanephosphonates based on the NMR $\Delta\delta$ ($\delta S - \delta R$) values obtained for their (*S*)- and (*R*)-MTPA esters.

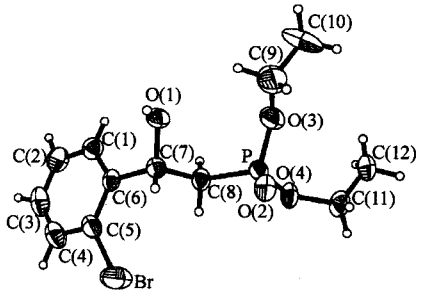
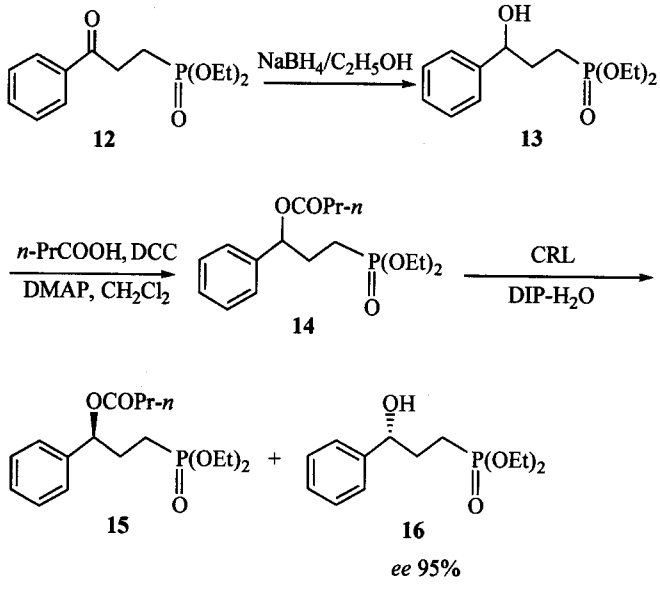


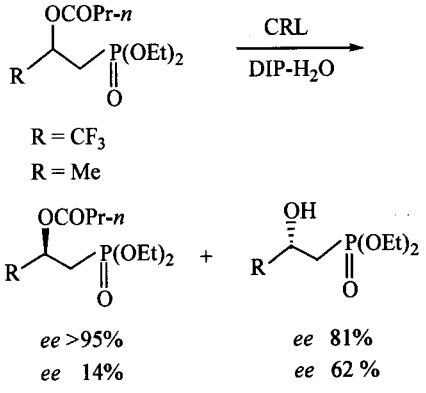
Fig. 2 X-Ray structure of compound **11i**.

Scheme 4



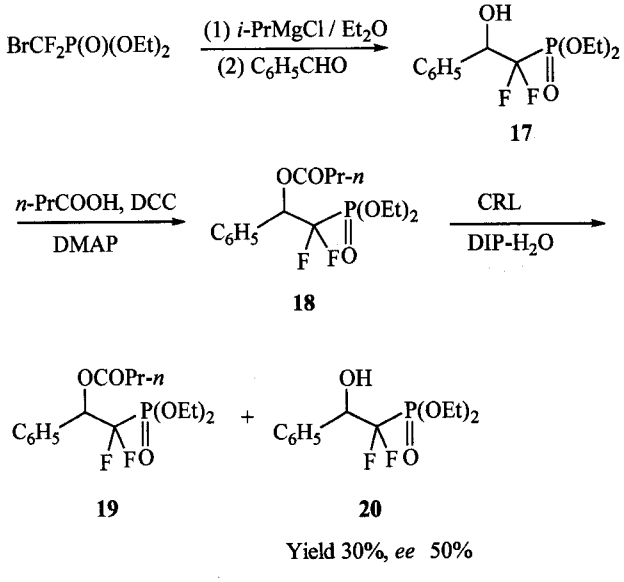
Our experimental results demonstrated that not only the steric but also the electronic effect, particularly the lipophilicity of the group in the substrate's molecule plays an important role. This can be demonstrated by that CRL-catalyzed enantioselectice hydrolysis of 2-butyryloxy-3,3,3-trifluoropropanephosphonates with high reactivity and enantioselectivity, as already shown by us (Scheme 5).[15]

Scheme 5



In contrast, introduction of fluorine atom at the carbon atom located between phosphoryl and hydroxy groups of the substrate reduced both the reactivity and selectivity significantly (Scheme 6).

Scheme 6



Based on above study, we demonstrated that the catalytic preference of crude CRL-catalyzed hydrolysis of butyryloxyalkanephosphonates is not in accordance with the Kaslauskas' rule (Fig. 3), which was drawn based on the bulkiness of the functional groups.[16]

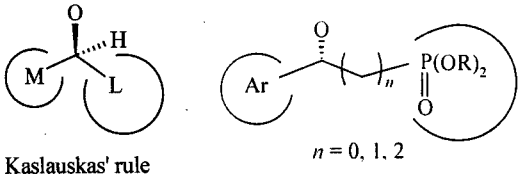


Fig. 3 Configuration of the preferential enantiomer of hydrolyzed hydroxyalkanephosphonates catalyzed by CRL.

Conclusion

CRL-mediated hydrolysis can be used successfully in asymmetric synthesis of hydroxyalkanephosphonates based on the rational design of the substrate structure. It was found that chiral δ-hydroxy-β-ketoarylbutanephosphonates, formed by lipase-catalyzed resolution, could be used as chirons for the synthesis of optically pure enones[17] and THF derivatives. Its further application in synthesis of chiral functionalized phosphonates and their carboxylic counterparts will be reported in due course.

Experimental

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were given downfield relative to TMS (internal standard); ^{31}P NMR spectra were taken on the same spectrometer using 80% phosphorus acid as external standard. The melting points were uncorrected. *Candida rugosa* lipase (901 units/mg) was purchased from Sigma Chemical Co. The enantiomeric excess value was determined by ^{31}P NMR and the typical procedure is as follows: To 20 mg of hydroxyalkanephosphonates was added 1.5 equiv. quinine and 0.5 mL of $CDCl_3$.

The racemic 1-hyroxyalkanephosphonates were prepared from corresponding aldehyde and dialkyl phosphite in the presence of KF according to the reported procedure.[18]

General procedure for the preparation of 1-butyryloxyalkanephosphonates

In a 100 mL bottle was added substrates (10 mmol), *n*-butyric acid (1.06 g, 12 mmol) and DCC (2.48 g, 12 mmol), methylene chloride (60 mL), the mixture was cooled to 0 ℃ and DMAP (50 mg) was added. After the starting material was consumed, ethyl ether (50 mL) was added, and the precipitate was filtered off. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the corresponding butyryl derivatives.

Dimethyl 1-butyryloxybenzylphosphonate (**1a**) Corlorless oil; yield 2.43 g, 85%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.48 (m, 5H, PhH), 6.20 (d, J = 13.5 Hz, 1H, CHP), 3.60—3.71 (m, 6H, P(OCH$_3$)$_2$), 2.38—2.43 (t, J = 7.6 Hz, 2H, CH$_3$CH$_2$-C**H$_2$**CO), 1.61—1.73 (m, 2H, CH$_3$C**H$_2$**CH$_2$CO), 0.89—0.94 (t, J = 7.3 Hz, 3H, C**H$_3$**CH$_2$CH$_2$CO); IR (film) ν: 2961, 1749, 1496, 1456, 1266, 1185, 1162, 1032 cm^{-1}. Anal. calcd for $C_{13}H_{19}O_5P$: C 54.55, H 6.69; found C 54.72, H 6.69.

Diethyl 1-butyryloxybenzylphosphonate (**1b**) Colorless oil; yield 2.86 g, 91%; ^{1}H NMR ($CDCl_3$, 300

MHz) δ: 7.42—7.45 (m, 5H, PhH), 6.12 (d, J = 13.6 Hz, 1H, CHP), 3.97—4.03 (m, 4H, P(OC**H**$_2$-CH$_3$)$_2$), 2.34—2.37 (m, 2H, $CH_3CH_2C\mathbf{H}_2CO$), 1.59—1.68 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 1.15—1.21 (m, 6H, P(OCH$_2$C**H**$_3$)$_2$), 0.89—0.92 (t, J = 7.3 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); IR (film) ν: 2975, 1749, 1262, 1164, 1053, 1026, 972, 699, 556 cm^{-1}.

Diisopropyl 1-butyryloxybenzylphosphonate (**1c**) Corlorless oil; yield 3.87 g, 88%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.50 (m, 5H, PhH), 6.12 (d, J = 13.9 Hz, 1H, CHP), 4.56—4.69 (m, 2H, P(OC**H**-(CH$_3$)$_2$)$_2$), 2.30—2.43 (t, J = 7.5 Hz, 2H, CH_3CH_2-$C\mathbf{H}_2CO$), 1.64—1.72 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 1.07—1.30 (m, 12H, P(OCH(C**H**$_3$)$_2$)$_2$), 0.91—0.96 (t, J = 7.2 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); IR (film) ν: 2980, 1750, 1259, 1164, 933, 698 cm^{-1}. Anal. calcd for $C_{17}H_{27}O_5P$: C 59.64, H 7.95; found C 59.41, H 7.84.

General procedure for the CRL*-catalyzed hydrolysis of* **1a**—**1c** *in buffer system*

To 4 mL of phosphate buffer was added 1 mmol of substrate, 100 mg of crude *Candida rugosa* lipase. The mixture was vigorously stirred at 30 ℃ for 4 h, and then was extracted with CH_2Cl_2 (20 mL) and concentrated. 20 mg of the concentrated oil was used for the ^{31}P NMR (adding 50 mg of quinine) determination of the conversion and *ee* of **4a**—**4c**: R = Me: ^{31}P NMR ($CDCl_3$, 120 MHz) δ: **3a** 20.768 (1.00), **4a** 24.742 (0.060), 24.607 (0.425); R = Et: ^{31}P NMR ($CDCl_3$, 120 MHz) δ: **3b** 18.315 (30.76), **4b** 22.520 (1.00), 22.434 (3.84).

General procedure for the CRL*-catalyzed alcoholysis of the dimethyl 1-butyryloxyarylmethylphosphonates* (**5a**—**5f**)

To the mixture of substrate (100 mg), anhydrous diisopropyl ether (1 mL), *n*-butanol (0.3 mL) was added crude CRL (100 mg), and the mixture was stirred at 35 ℃. The conversion and *ee* of **7a**—**7f** was determined by ^{31}P NMR (adding quinine) as described above. The *E* value was roughly caculated based on the conversion and *ee* of **7a**—**7f**.

The racemic **5a**—**5f** was prepared as above.

Dimethyl 1-butyryloxy-1-(2-nitrophenyl)-methylphosphonate (**5b**) Yield 85%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.51—8.06 (m, 4H, PhH), 7.27 (d, J = 8.7 Hz, 1H, CHP), 3.69—3.82 (dd, J = 11.4, 27.3 Hz, 6H, P(OCH$_3$)$_2$), 2.43—2.49 (m, 2H, CH_3CH_2-$C\mathbf{H}_2CO$), 1.67—1.74 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 0.93—0.98 (t, J = 7.8 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); IR (film) ν: 2964, 1751, 1533, 1353, 1263, 1033 cm^{-1}; EIMS m/z (%): 262 (8.54), 109 (31.91), 79 (19.51), 71 (100). Anal. calcd for $C_{13}H_{18}NO_7P$: C 47.13, H 5.48, N 4.23; found C 47.20, H 5.49, N 4.97.

Dimethyl 1-butyryloxy-1-(2-chlorophenyl)-methylphosphonate (**5c**) Yield 87 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.19—7.58 (m, 4H, PhH), 6.60 (d, J = 13.5 Hz, 1H, CHP), 3.57—3.76 (dd, J = 10.8, 46.2 Hz, 6H, P(OCH$_3$)$_2$), 2.31—2.37 (m, 2H, CH_3CH_2-$C\mathbf{H}_2CO$), 1.57—1.64 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 0.84—0.89 (t, J = 7.2 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); IR (film) ν: 2963, 1753, 1565, 1469, 1446, 1265, 1188, 1158, 1036 cm^{-1}; EIMS m/z (%): 320 (30.58), 285 (27.99), 233 (30.66), 71 (100), 43 (61.26). Anal. calcd for $C_{13}H_{18}ClO_5P$: C 48.69, H 5.66; found C 48.53, H 5.89.

Dimethyl 1-butyryloxy-1-(2, 6-dichlorophenyl)-methylphosphonate (**5d**) Yield 81%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.19—7.35 (m, 3H, PhH), 6.92 (d, J = 17.7 Hz, 1H, CHP), 3.75—3.86 (dd, J = 10.8, 22.2 Hz, 6H, P(OCH$_3$)$_2$), 2.42—2.48 (t, J = 8.4 Hz, 2H, $CH_3CH_2C\mathbf{H}_2CO$), 1.66—1.73 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 0.92—0.97 (t, J = 7.2 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); IR (film) ν: 2962, 1751, 1580, 1564, 1275, 1180, 1160, 1097, 1037 cm^{-1}; EIMS m/z (%): 357 (M^+ + 3) (35.69), 355 (M^+ + 1, 54.64), 354 (M^+, 51.83), 319 (24.82), 285 (32.09), 110 (29.71), 71 (100), 43 (59.10). Anal. calcd for $C_{13}H_{17}Cl_2O_5P$: C 43.97, H 4.82; found C 43.963, H 4.94.

Dimethyl 1-butyryloxy-1-(4-ethylphenyl)-methylphosphonate (**5e**) Yield 88%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.19—7.41 (m, 4H, PhH), 6.18 (d, J = 13.2 Hz, 1H, CHP), 3.64—3.74 (dd, J = 10.5, 21.3 Hz, 6H), 2.63—2.66 (q, J = 7.2 Hz, 2H, $CH_3C\mathbf{H}_2$-Ar), 2.40—2.44 (t, J = 7.8 Hz, 2H, $CH_3CH_2C\mathbf{H}_2$-CO), 1.65—1.73 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 1.20—1.25 (t, J = 7.8 Hz, 3H, $C\mathbf{H}_3CH_2Ar$), 0.92—0.97 (t, J = 7.2 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); IR (film) ν: 2965, 1749, 1515, 1456, 1266, 1162, 1034 cm^{-1}; EIMS m/z (%): 314 (M^+, 19.16), 244 (30.67), 205 (10.19), 133 (44.32), 71 (100). Anal. calcd for $C_{15}H_{23}O_5P$: C 57.31, H 7.38; found C 57.15, H 7.39.

Dimethyl 1-butyryloxy-1-(4-methoxylphenyl)-methylphosphonate (**5f**) ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.87—7.43 (m, 4H, PhH), 6.12 (d, J = 13 Hz, 1H, CHP), 3.80 (s, 3H, $C\mathbf{H}_3OAr$), 3.61—3.75 (dd, J = 12, 27.7 Hz, 6H, P(OCH$_3$)$_2$), 2.35—2.41 (t, J = 7.4 Hz, 2H, $CH_3CH_2C\mathbf{H}_2CO$), 1.62—1.69 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 0.89—0.94 (t, J = 7.5 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); IR (film) ν: 2962, 1747, 1612, 1515, 1463, 1253, 1177, 1162, 846 cm^{-1}; EIMS m/z (%): 316 (M^+, 11.22), 245 (12.84), 229 (83.00), 137 (100), 135 (64.53), 71 (57.22), 43 (60.12). Anal. calcd for $C_{14}H_{21}O_6P$: C 53.16, H 6.69; found C 53.14, H 6.54.

The racemic 2-hydroxy-2-arylethanephosphonates were prepared according to the reported procedure.[18] Their butyryloxy derivatives were synthesized as above.

General procedure for CRL-*catalyzed enantioselective hydrolysis*

To 1.2 mol/L $MgCl_2$-saturated isopropyl ether (4 mL) was added butyryloxyalkanephophosnates (100 mg) and crude CRL (100 mg). The reaction mixture was vigorously stirred at 38 ℃. After the reaction proceeded to certain conversion, enzyme was filtered off and washed with ethyl acetate (5 mL). The concentrated oil was subjected to flash chromatography to furnish the corresponding butyryloxy derivatives and alcohols (general eluent Petro : EtOAc = 2:1).

Dimethyl (R)-2-butyryloxy-2-phenylethanephosphonate (**10a**) Colorless oil, yield 42%, *ee* > 95%. $[\alpha]_D^{23}$ − 21 (*c* 1.2, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.39 (m, 5H, PhH), 6.05—6.13 (m, 1H, C**H**CH_2P), 3.61—3.67 (d, *J* = 16 Hz, 6H, $P(OCH_3)_2$), 2.28—2.65 (m, 2H, CH_2P), 2.29—2.31 (m, 2H, $CH_3CH_2CH_2CO$), 1.61—1.66 (m, 2H, $CH_3CH_2CH_2CO$), 0.89—0.94 (t, *J* = 7.4 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 28.721; IR (film) ν: 2962, 1739, 1458, 1257, 1775, 1032, 972, 817, 700 cm^{-1}; EIMS *m/z* (%): 300 (M^+, 0.25), 230 (20.23), 229 (100), 213 (34.22), 197 (16.01), 109 (24.50).

Dimethyl (S)-2-hydroxy-2-phenylethanephosphonate (**11a**) Colorless oil; yield 41%; *ee* > 95%; $[\alpha]_D^{23}$ +27 (*c* 0.9, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.25—7.41 (m, 5H, PhH), 5.08—5.16 (m, 1H, C**H**OH), 3.66—3.75 (m, 6H, $P(OCH_3)_2$), 2.04—2.34 (m, 2H, CH_2P); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 32.393; IR (film) ν: 3302, 1496, 1240, 1215, 1089, 1069, 1040 cm^{-1}; EIMS *m/z* (%): 230 (M^+, 28.34), 124 (100), 111 (24.22), 94 (60.70), 79 (36.53).

Diethyl (R)-2-butyryloxy-2-phenylethanephosphonate (**10b**) Colorless oil; yield 45%; *ee* > 95%; $[\alpha]_D^{23}$ −21.9 (*c* 4.8, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.39 (m, 5H, PhH), 6.05—6.13 (m, 1H, C**H**CH_2P), 3.95—4.06 (m, 4H, $P(OCH_2CH_3)_2$), 2.23—2.58 (m, 2H, CH_2P), 2.23—2.36 (m, 2H, $CH_3CH_2CH_2CO$), 1.60—1.67 (m, 2H, $CH_3CH_2CH_2CO$), 1.21—1.28 (m, 6H, $P(OCH_2CH_3)_2$), 0.88—0.93 (t, *J* = 6.8 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.966; IR (film) ν: 2927, 1740, 1255, 1174, 1027, 975 cm^{-1}; EIMS *m/z* (%): 329 (M^+ + 1, 2.03), 241 (59.40), 229 (33.79), 201 (50.89), 109 (17.29), 43 (23.17). Anal. calcd for $C_{16}H_{25}O_5P$: C 58.53, H 7.67; found C 58.50, H 7.65.

Diethyl (S)-2-hydroxy-2-phenylethanephosphonate (**11b**) Pale yellow oil; yield 44%; *ee* > 95%; $[\alpha]_D^{22}$ +29.5 (*c* 2.8, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.42 (m, 5H, PhH), 5.09—5.17 (m, 1H, C**H**OH), 4.04—4.20 (m, 4H, $P(OCH_2CH_3)_2$), 3.84 (sr, 1H, OH), 2.13—2.33 (m, 2H, CH_2P), 1.24—1.42 (m, 6H, $P(OCH_2CH_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 29.63; IR (film) ν: 3276, 1637, 1225, 1031, 974 cm^{-1}.

Dipropyl (R)-2-butyryloxy-2-phenylethanephosphonate (**10c**) Colorless oil; yield 44%; *ee* > 95%; $[\alpha]_D^{17}$ − 27.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.43 (m, 5H, PhH), 5.12—5.17 (m, 1H, C**H**OH), 3.93—4.07 (m, 4H, $P(OCH_2CH_2CH_3)_2$), 2.19—2.29 (m, 2H, CH_2P), 1.63—1.75 (m, 4H, $P(OCH_2CH_2CH_3)_2$), 0.92—1.01 (m, 6H, $P(OCH_2CH_2CH_3)_2$); IR (film) ν: 3350, 2970, 1604, 1456, 1222, 1056, 1004 cm^{-1}; EIMS *m/z* (%): 286 (M^+, 8.38), 139 (46.19), 125 (14.52), 97 (100), 79 (18.96), 43 (21.79). Anal. calcd for $C_{14}H_{23}O_4P$: C 58.73, H 8.10; found C 58.78, H 7.94.

Dipropyl (S)-2-hydroxy-2-phenylethanephosphonate (**11c**) Colorless oil; yield 43%; *ee* > 95%; $[\alpha]_D^{17}$ +26.3 (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.287—7.431 (m, 5H, PhH), 5.117—5.167 (m, 1H, C**H**OH), 3.932—4.066 (m, 4H, $P(OCH_2CH_2CH_3)_2$), 2.189—2.285 (m, 2H, CH_2P), 1.634—1.749 (m, 4H, $P(OCH_2CH_2CH_3)_2$), 0.921—1.006 (m, 6H, $P(OCH_2CH_2CH_3)_2$); IR (film) ν: 3350, 2970, 1604, 1456, 1222, 1056, 1004 cm^{-1}; EIMS *m/z* (%): 286 (M^+, 8.38), 139 (46.19), 125 (14.52),97 (100),79 (18.96), 43 (21.79). Anal. calcd for $C_{14}H_{23}O_4P$: C 58.73, H 8.10; found C 58.78, H 7.94.

Diisopropyl (R)-2-butyryloxy-2-phenylethanephosphonate (**10d**) Colorless oil; yield 42%; *ee* > 95%; $[\alpha]_D^{22}$ − 22 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.31—7.41 (m, 5H, ArH), 6.10—6.14 (m, 1H, C**H**CH_2P), 4.64—4.71 (m, 2H, $P(OCH(CH_3)_2)_2$), 2.25—2.50 (m, 4H, $CH_2P + CH_3CH_2CH_2CO$), 1.62—1.70 (m, 2H, $CH_3CH_2CH_2CO$), 1.19—1.33 (m, 12H, $P(OCH(CH_3)_2)_2$), 0.88—0.95 (t, *J* = 7.5 Hz, 3H, $CH_3CH_2CH_2CO$); IR (film) ν: 2979, 1741, 1254, 1176, 987, 699 cm^{-1}; EIMS *m/z* (%): 356 (M^+, 9.64), 285 (21.22), 269 (53.41), 227 (100), 201 (76.17), 185 (76.23), 43 (43.55). Anal. calcd for $C_{18}H_{29}O_5P$: C 60.66, H 8.20; found C 60.60, H 7.98.

Diisopropyl (S)-2-hydroxy-2-phenylethanephosphonate (**11d**) Colorless oil; yield 41%; *ee* > 95%; $[\alpha]_D^{19}$ +27.3 (*c* 3.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.42 (m, 5H, PhH), 5.07—5.11 (m, 1H, C**H**OH), 4.67—4.81 (m, 2H, $P(OCH(CH_3)_2)_2$), 3.98 (s, 1H, OH), 2.05—2.20 (2H, m, CH_2P), 1.26—1.38 (12H, m, $P(OCH(CH_3)_2)_2$); IR (film) ν: 3333, 2979, 1224, 1014, 997, 971 cm^{-1}; EIMS *m/z* (%): 286 (M^+), 227 (9.90), 201 (32.48), 185 (27.27), 139 (56.39), 97 (100), 96 (69.03). Anal. calcd for $C_{14}H_{23}O_4P$: C 58.73, H 8.10; found C 58.15, H 8.26.

Diethyl (R)-2-butyryloxy-2-(4-fluorophenyl)-ethanephosphonate (**10e**) Colorless oil; yield 42%; *ee* > 95%; $[\alpha]_D^{27}$ − 26 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.97—7.36 (m, 4H, PhH), 5.91—6.10 (m, 1H, C**H**OH), 3.93—4.04 (m, 4H, $P(OCH_2CH_3)_2$), 2.01—2.48 (m, 2H, CH_2P), 2.01—2.31

(m, 2H, $CH_3CH_2CH_2CO$), 1.56—1.63 (m, 2H, $CH_3CH_2CH_2CO$), 1.18—1.25 (m, 6H, $P(OCH_2CH_3)_2$), 0.84—0.89 (t, J = 7.5 Hz, 3H, $CH_3CH_2CH_2CO$); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −36.328; ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.641; IR (film) ν: 2974, 1740, 1608, 1513, 1255, 1228, 1176, 1160, 1028, 973 cm^{-1}; EIMS m/z (%): 346 (M^+, 0.47), 275 (100), 259 (20.98), 247 (35.86), 219 (49.08).

Diethyl (S)-2-hydroxy-2-(4-fluorophenyl)-ethanephosphonate (**11e**) Colorless oil; yield 42%; *ee* >95%; $[\alpha]_D^{27}$ + 30.3 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.96—7.35 (m, 4H, PhH), 5.02—5.09 (m, 1H, CHOH), 4.00—4.12 (m, 4H, $P(OCH_2CH_3)_2$), 3.52 (s, 1H, OH), 2.01—2.19 (m, 2H, CH_2P), 1.17—1.46 (m, 6H, $P(OCH_2CH_3)_2$); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −38.10; ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 29.24; IR (film) ν: 3361, 2986, 1606, 1511, 1222, 1030, 966, 840 cm^{-1}; EIMS m/z (%): 276 (M^+, 19.74), 181 (12.30), 152 (42.86), 136 (31.74), 125 (100), 97 (62.88), 79 (27.28). HRMS calcd for $C_{12}H_{18}FO_4P$ 276.09268, found 276.09230.

Diethyl (R)-2-butyryloxy-2-(4-nitrophenyl)-ethanephosphonate (**10f**) Pale yellow oil; yield 42%; *ee* >95%; $[\alpha]_D^{19}$ − 20.1 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.16—8.19 (d, J = 7.0 Hz, 2H, PhH), 7.50—7.53 (d, J = 7.0 Hz, 2H, PhH), 6.04—6.12 (m, 1H, $CHCH_2P$), 3.95—4.08 (m, 4H, $P(OCH_2CH_3)_2$), 2.00—2.46 (m, 2H, CH_2P), 2.01—2.31 (m, 2H, $CH_3CH_2CH_2CO$), 1.56—1.64 (m, 2H, $CH_3CH_2CH_2CO$), 1.19—1.24 (m, 6H, $P(OCH_2CH_3)_2$), 0.84—0.90 (t, J = 7.3 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 24.81; IR (film) ν: 2974, 1743, 1608, 1525, 1348, 1265, 1168, 1027, 971 cm^{-1}; EIMS m/z (%): 374 (M^+ + 1, 22.27), 302 (44.91), 286 (100), 246 (31.40), 43 (20.40). Anal. calcd for $C_{16}H_{24}NO_7P$: C 51.47, H 6.48, N 3.75; found C 51.35, H 6.55, N 3.77.

Diethyl (S)-2-hydroxy-2-(4-nitrophenyl)-ethanephosphonate (**11f**) Pale yellow oil; yield 41%; *ee* >95%; $[\alpha]_D^{19}$ + 24.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.18—8.22 (d, J = 5 Hz, 2H, PhH), 7.56—7.59 (d, J = 8.7 Hz, 2H, PhH), 5.16—5.24 (m, 1H, CHOH), 4.54 (s, 1H, OH), 4.03—4.22 (m, 4H, $P(OCH_2CH_3)_2$), 2.12—2.24 (m, 2H, CH_2P), 1.22—1.41 (m, 6H, $P(OCH_2CH_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 28.602; IR (KBr) ν: 3265, 1606, 1521, 1343, 1234, 1214, 1081, 961 cm^{-1}; EIMS m/z (%): 303 (M^+, 0.65), 152 (100), 138 (9.41), 125 (86.07), 97 (34.16).

Dimethyl (S)-2-butyryloxy-2-(4-methylphenyl)-ethanephosphonate (**10g**) Colorless oil; yield 40%; *ee* >95%; $[\alpha]_D^{19}$ + 39.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.14—7.28 (m, 4H, PhH), 6.05—6.07 (m, 1H, $CHCH_2P$), 3.64—3.67 (dd, J = 3.3, 5.8 Hz, 6H, $P(OCH_3)_2$), 2.27—2.54 (m, 2H, CH_2P), 2.41 (s, 3H, CH_3Ar), 2.28—2.39 (m, 2H, $CH_3CH_2CH_2CO$), 1.60—1.67 (m, 2H, $CH_3CH_2CH_2CO$), 0.88—0.93 (t, J = 7.5 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 28.881; IR (film) ν: 2962, 1739, 1577, 1456, 1257, 1176, 1032, 827 cm^{-1}; EIMS m/z (%): 314 (M^+, 5.76), 243 (100), 227 (35.06), 211 (10.87), 151 (47.09), 43 (35.12). Anal. calcd for $C_{15}H_{23}O_5P$: C 57.32, H 7.38; found C 57.18, H 7.64.

Dimethyl (R)-2-hydroxy-2-(4-methylphenyl)-ethanephosphonate (**11g**) Colorless oil; yield 42%; *ee* >95%; $[\alpha]_D^{27}$ + 30.3 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.04—7.19 (m, 4H, PhH), 4.94—5.01 (m, 1H, CHOH), 3.57—3.63 (m, 6H, $P(OCH_3)_2$), 2.24 (s, 3H, CH_3Ar), 1.93—2.18 (m, 2H, CH_2P); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 32.514; IR (film) ν: 3360, 1515, 1457, 1224, 1034, 828 cm^{-1}; EIMS m/z (%): 244 (M^+, 6.76), 227 (100), 134 (33.02), 124 (33.72), 94 (38.53), 91 (27.66), 79 (22.24). Anal. calcd for $C_{11}H_{17}O_4P$: C 54.10, H 7.02; found C 54.09, H 6.97.

Diethyl (R)-2-butyryloxy-2-(4-bromophenyl)-ethanephosphonate (**10h**) Colorless oil; yield 42%; *ee* >95%; $[\alpha]_D^{27}$ − 17.8 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.23—7.49 (m, 4H, PhH), 5.98—6.05 (m, 1H, $CHCH_2P$), 3.96—4.12 (m, 4H, $P(OCH_2CH_3)_2$), 2.03—2.39 (m, 2H, CH_2P), 2.26—2.28 (m, 2H, $CH_3CH_2CH_2CO$), 1.61—1.66 (m, 2H, $CH_3CH_2CH_2CO$), 1.21—1.27 (m, 6H, $P(OCH_2CH_3)_2$), 0.87—0.92 (t, J = 7.5 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.465; IR (film) ν: 2971, 1741, 1489, 1255, 1171, 1027, 974, 824 cm^{-1}; EIMS m/z (%): 408 (M^+ + 2, 0.82), 406 (M^+, 0.74), 309 (33.75), 307 (36.25), 281 (44.48), 279 (44.09), 123 (23.52), 43 (30.13). Anal. calcd for $C_{16}H_{24}BrO_5P$: C 47.19, H 5.94; found C 47.25, H 5.98.

Diethyl (S)-2-hydroxy-2-(4-bromophenyl)-ethanephosphonate (**11h**) Colorless oil; yield 42%; *ee* >95%; $[\alpha]_D^{27}$ + 25 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.23—7.47 (m, 4H, PhH), 5.02—5.09 (m, 1H, CHOH), 4.01—4.16 (m, 4H, $P(OCH_2CH_3)_2$), 2.02—2.19 (m, 2H, CH_2P), 1.21—1.34 (m, 6H, $P(OCH_2CH_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 29.076; IR (film) ν: 3339, 2984, 1486, 1394, 1221, 1069, 1029, 964 cm^{-1}; EIMS m/z (%): 338 (M^+ + 2, 19.36), 336 (M^+, 17.86), 321 (25.77), 319 (24.41), 152 (51.46), 138 (45.82), 125 (100), 97 (54.40). Anal. calcd for $C_{12}H_{18}BrO_4P$: C 42.75, H 5.38; found C 42.79, H 5.45.

Diethyl (R)-2-butyryloxy-2-(2-bromophenyl)-ethanephosphonate (**10i**) Colorless oil; yield 41%; *ee* >95%; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.15—7.55 (m, 4H, PhH), 6.37—6.41 (m, 1H, $CHCH_2P$), 4.02—4.41 (m, 4H, $P(OCH_2CH_3)_2$), 2.34—2.41 (m,

2H, $CH_3CH_2CH_2CO$), 1.64—1.72 (m, 2H, $CH_3CH_2CH_2CO$), 1.23—1.35 (m, 6H, $P(OCH_2CH_3)_2$), 0.91—0.96 (t, J = 7.4 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.55; IR (film) ν: 2978, 1746, 1471, 1255, 1168, 1050, 1027, 985, 965, 758 cm^{-1}; EIMS m/z (%): 409 (M^+ + 3, 3.69), 407 (M^+ + 1, 4.11), 327 (78.56), 277 (29.93), 275 (29.02), 239 (100), 211 (46.81), 183 (86.19), 43 (47.11). Anal. calcd for $C_{16}H_{24}BrO_5P$: C 47.19, H 5.94; found C 47.00, H, 6.02.

Diethyl (S)-2-hydroxy-2-(2-bromophenyl)-ethanephosphonate (**11i**) White solid; m.p. 52—54 ℃; yield 42%; *ee* > 95%; $[\alpha]_D^{27}$ + 67.5 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.09—7.69 (m, 4H, PhH), 5.33—5.40 (m, 1H, CHOH), 4.02—4.26 (m, 4H, $P(OCH_2CH_3)_2$), 3.2—3.6 (s, 1H, OH), 1.94—2.42 (dm, J = 105 Hz, 2H, CH_2P), 1.21—1.46 (m, 6H, $P(OCH_2CH_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 29.440; IR (KBr) ν: 3261, 2986, 1464, 1442, 1226, 1079, 1054, 1026, 987, 803, 551 cm^{-1}; EIMS m/z (%): 257 (100), 211 (21.49), 183 (51.86), 152 (49.62), 125 (78.30), 108 (20.51), 97 (32.87). Anal. calcd for $C_{12}H_{18}BrO_4P$: C 42.75, H 5.38; found C 42.77, H 5.27.

Diethyl (R)-2-butyryloxy-2-(2,4-dichlorophenyl)-ethanephosphonate (**10j**) Colorless oil; yield 42%; *ee* > 95%; $[\alpha]_D^{27}$ - 14.9 (*c* 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.15—7.55 (m, 4H, PhH), 6.37—6.41 (m, 1H, $CHCH_2P$), 4.02—4.41 (m, 4H, $P(OCH_2CH_3)_2$), 2.34—2.41 (m, 2H, $CH_3CH_2CH_2CO$), 1.64—1.72 (m, 2H, $CH_3CH_2CH_2CO$), 1.23—1.35 (m, 6H, $P(OCH_2CH_3)_2$), 0.91—0.96 (t, J = 7.4 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.550; IR (film) ν: 2978, 1746, 1471, 1255, 1168, 1050, 1027, 985, 965, 758 cm^{-1}; EIMS m/z (%): 409 (M^+ + 3, 3.69), 407 (M^+ + 1, 4.11), 327 (78.56), 277 (29.93), 275 (29.02), 239 (100), 211 (46.81), 183 (86.19), 43 (47.11). Anal. calcd for $C_{16}H_{24}BrO_5P$: C 47.19, H 5.94; found C 47.00, H 6.02.

Diethyl (S)-2-hydroxy-2-(2,4-dichlorophenyl)-ethanephosphonate (**11j**) Colorless oil; yield 42%; *ee* > 95%; $[\alpha]_D^{27}$ + 49.3 (*c* 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.21—7.35 (m, 3H, PhH), 6.29—6.37 (m, 1H, $CHCH_2P$), 3.98—4.12 (m, 4H, $P(OCH_2CH_3)_2$), 2.24—2.38 (m, 4H, $CH_3CH_2CH_2CO$ + CH_2P), 1.60—1.67 (m, 2H, $CH_3CH_2CH_2CO$), 1.20—1.31 (m, 6H, $P(OCH_2CH_3)_2$), 0.88—0.95 (t, J = 7.7 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 24.804; IR (film) ν: 2970, 1747, 1591, 1475, 1255, 1168, 1053, 1027, 968 cm^{-1}; EIMS m/z (%): 399 (M^+ + 3, 28.54), 398 (M^+ + 2, 28.21), 397 (M^+ + 1, 42.28), 361 (66.66), 311 (65.99), 309 (100), 273 (29.25). Anal. calcd for $C_{12}H_{17}Cl_2O_4P$: C 48.38, H 5.84; found C 48.18, H 6.03.

Diethyl (R)-2-butyryloxy-2-(3-chlorophenyl)-ethanephosphonate (**10k**) Colorless oil; yield 42%; *ee* > 95%; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.36 (s, 1H, 2-H of Ar), 7.26—7.29 (m, 3H, ArH), 6.00—6.08 (m, 1H, $CHCH_2P$), 3.98—4.05 (m, 4H, $P(OCH_2CH_3)_2$), 2.26—2.34 (m, 4H, $CH_3CH_2CH_2CO$ + CH_2P), 1.61—1.68 (m, 2H, $CH_3CH_2CH_2CO$), 1.23—1.29 (m, 6H, $P(OCH_2CH_3)_2$), 0.89—0.94 (t, J = 7.5 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.402; IR (film) ν: 2973, 1742, 1600, 1577, 1255, 1173, 1028, 971, 824, 789 cm^{-1}; EIMS m/z (%): 362 (M^+, 4.54), 291 (100), 263 (33.57), 235 (62.09), 138 (47.87), 109 (37.08). Anal. calcd for $C_{16}H_{24}ClO_5P$: C 52.97, H 6.67; found C 53.07, H 6.91.

Diethyl (R)-2-hydroxy-2-(3-chlorophenyl)-ethanephosphonate (**11k**) Colorless oil; yield 42%; *ee* > 95%; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (s, 1H, 2-H of Ar), 7.21—7.32 (m, 3H, ArH), 5.03—5.11 (m, 1H, CHOH), 4.02—4.19 (m, 4H, $P(OCH_2CH_3)_2$), 2.72—3.01 (s, 1H, OH), 2.12—2.19 (m, 2H, CH_2P), 1.24—1.41 (m, 6H, $P(OCH_2CH_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 29.114; IR (film) ν: 3298, 2992, 1213, 1071, 1021, 967, 817 cm^{-1}; EIMS m/z (%): 292 (M^+, 21.02), 152 (80.03), 138 (41.18), 125 (100), 111 (27.56), 97 (38.71), 77(20.40). Anal. calcd for $C_{12}H_{18}ClO_4P$: C 49.24, H 6.20; found C 49.15, H 6.22.

Diethyl (R)-2-butyryloxy-2-(4-ethoxyphenyl)-ethanephosphonate (**10l**) Colorless oil; yield 42%; *ee* > 95%; $[\alpha]_D^{19}$ - 34 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.36 (s, 1H, 2-H of Ar), 7.26—7.29 (m, 3H, ArH), 6.00—6.08 (m, 1H, $CHCH_2P$), 3.98—4.05 (m, 4H, $P(OCH_2CH_3)_2$), 2.26—2.34 (m, 4H, $CH_3CH_2CH_2CO$ + CH_2P), 1.61—1.68 (m, 2H, $CH_3CH_2CH_2CO$), 1.23—1.29 (m, 6H, $P(OCH_2CH_3)_2$), 0.89—0.94 (t, J = 7.5 Hz, 3H, $CH_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.402; IR (film) ν: 2973, 1742, 1600, 1577, 1255, 1173, 1028, 971, 824, 789 cm^{-1}; EIMS m/z (%): 362 (M^+, 4.54), 291 (100), 263 (33.57), 235 (62.09), 138 (47.87), 109 (37.08). Anal. calcd for $C_{16}H_{24}ClO_5P$: C 52.97, H 6.67; found C 53.07, H 6.91.

Diethyl (S)-2-hydroxy-2-(4-ethoxyphenyl)-ethanephosphonate (**11l**) Colorless oil; yield 42%; *ee* > 95%; $[\alpha]_D^{19}$ + 21 (*c* 1.4, $CHCl_3$); ^1HNMR ($CDCl_3$, 300 MHz) δ: 6.84—7.31 (m, 4H, ArH), 5.02—5.10 (m, 1H, CHOH), 3.98—4.05 (q, J = 7.0 Hz, 2H, CH_3CH_2OAr), 3.67—3.77 (m, 6H, $P(OCH_3)_2$), 3.66 (s, 1H, OH), 2.04—2.34 (m, 2H, CH_2P), 1.40—1.49 (t, J = 7.6 Hz, 3H, CH_3CH_2OAr); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 32.463; IR (film) ν: 3382, 2982, 1613, 1246, 1180, 1036, 833 cm^{-1}; EIMS m/z (%): 274 (M^+, 6.26), 257 (71.59), 164 (100), 124 (65.30), 94 (89.56), 79 (49.87).

Diethyl (R)-2-butyryloxy-2-(2-trifluoromethylphenyl)-ethanephosphonate (**10m**) Colorless oil;

yield 44%; *ee* > 95%; $[\alpha]_D^{19}$ - 29.4 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.36—7.64 (m, 4H, ArH), 6.43—6.50 (m, 1H, C**H**CH_2P), 4.03—4.18 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 2.15—2.37 (m, 4H, $C\mathbf{H}_2P + CH_3CH_2C\mathbf{H}_2CO$), 1.58—1.68 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 1.24—1.36 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$), 0.88—0.97 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.161; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: 18.120; (CF_3COOH as outerstandard); IR (film) ν: 2972, 1748, 1458, 1315, 1162, 1128, 1062, 1037, 1028 cm^{-1}; EIMS *m/z* (%): 397 (M^+ + 1, 31.72), 325 (89.25), 309 (100), 289 (29.86), 153 (41.91), 43 (41.29). Anal. calcd for $C_{13}H_{18}F_3O_4P$: C 47.86, H 5.56; found C 47.87, H 5.56.

Diethyl (S)-2-hydroxy-2-(2-trifluoromethylphenyl)-ethanephosphonate (**11m**) Colorless oil; yield 42%; *ee* > 95%; $[\alpha]_D^{15}$ + 35.5 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.32—7.95 (m, 4H, ArH), 5.52—5.58 (m, 1H, C**H**OH), 4.10—4.32 (m, 5H, OH + $P(OC\mathbf{H}_2CH_3)_2$), 2.07—2.27 (m, 2H, CH_2P), 1.27—1.52 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 28.986; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: 18.725; IR (film) ν: 3301, 1321, 1278, 1220, 1156, 1116, 1025, 989, 966 cm^{-1}; EIMS *m/z* (%): 326 (M^+, 6.42), 152 (69.85), 125 (100), 108 (27.12), 97 (49.01), 96 (21.13). Anal. calcd for $C_{13}H_{18}F_3O_4P$: C 47.86, H 5.56; found C 47.87, H 5.56.

Diethyl (R)-2-butyryloxy-2-(2-furyl)-ethanephosphonate (**10o**) Pale yellow oil; yield 45%; *ee* > 95%; $[\alpha]_D^{15}$ - 68 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (m, 1H, 5-H of Furyl), 6.16—6.39 (m, 2H, 3, 4-H of Furyl), 4.01—4.08 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 2.49—2.57 (m, 2H, CH_2P), 2.25—2.31 (m, 2H, $CH_3CH_2C\mathbf{H}_2CO$), 1.60—1.68 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 1.22—1.31 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 0.87—0.93 (t, *J* = 7.2 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.55; IR (film) ν: 2973, 1741, 1251, 1170, 1027, 972, 748 cm^{-1}; EIMS *m/z* (%): 318 (M^+, 10.63), 248 (38.63), 247 (100), 219 (28.10), 191 (28.10), 151 (31.85), 123 (36.08), 94 (30.95). Anal. calcd for $C_{14}H_{23}O_6P$: C 52.82, H 7.28; found C 52.81, H 7.32.

Diethyl (S)-2-hydroxy-2-(2-furyl)-ethanephosphonate (**11o**) Pale yellow oil; yield 40%; *ee* > 95%; $[\alpha]_D^{15}$ + 20 (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.39—7.40 (m, 1H, 5-H of Furyl), 6.32—6.36 (m, 2H, 4,5-H of Furyl), 5.14—5.17 (m, 1H, C**H**OH), 4.08—4.19 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 2.33—2.44 (m, 2H, CH_2P), 1.30—1.39 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 29.13; IR (film) ν: 3340, 2986, 1394, 1226, 1163, 1027, 965, 742 cm^{-1}; EIMS *m/z* (%): 248 (23.04), 231 (100), 123 (25.45), 110 (44.52), 97 (34.71). Anal. calcd for $C_{10}H_{17}O_5P$: C 48.39, H 6.90; found C 47.94, H 7.34.

Diethyl (R)-2-butyryloxy-2-(2-naphthyl)-ethanephosphonate (**10p**) Colorless oil; yield 39%; *ee* > 95%; $[\alpha]_D^{15}$ - 31.4 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.45—7.85 (m, 7H, ArH), 6.23—6.30 (m, 1H, C**H**CH_2P), 3.95—4.07 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 2.30—2.67 (m, 4H, $C\mathbf{H}_2P + CH_3CH_2C\mathbf{H}_2CO$), 1.61—1.68 (m, 2H, $CH_3C\mathbf{H}_2CH_2CO$), 1.18—1.25 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$), 0.88—0.96 (t, *J* = 7.3 Hz, 3H, $C\mathbf{H}_3CH_2CH_2CO$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 25.998; IR (film) ν: 2972, 1739, 1255, 1174, 1099, 1027, 966, 821, 757 cm^{-1}; EIMS *m/z* (%): 378 (M^+, 5.14), 308 (62.70), 307 (100), 279 (29.91), 251 (27.40), 170 (27.22). HRMS calcd for $C_{20}H_{27}O_5P$ 378.15961, found 378.16104.

Diethyl (S)-2-hydroxy-2-(2-naphthyl)-ethanephosphonate (**11p**) Colorless oil; yield 41%; *ee* > 95%; $[\alpha]_D^{15}$ + 26.9 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.44—7.85 (7H, ArH), 5.24—5.30 (1H, m, C**H**OH), 4.02—4.15 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 3.80 (s, 1H, OH), 2.24—2.32 (m, 2H, CH_2P), 1.22—1.32 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 29.608; IR (film) ν: 3342, 2984, 1602, 1240, 1222, 1028, 965, 820 cm^{-1}; EIMS *m/z* (%): 308 (M^+, 32.37), 170 (45.94), 152 (32.93), 125 (100), 108 (55.30), 97 (100), 79 (100). HRMS calcd for $C_{18}H_{29}O_4P$: 308.11775; found 308.11453.

Mosher's ester of **11n** and **11o**

(*R*)-*Mosher's ester of* **11n** ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.70—7.62 (m, 1H, 5-H of Ar), 7.35—7.59 (m, 9H, ArH), 6.66—6.74 (m, 1H, C**H**CH_2P), 3.97—4.14 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 3.53 (s, 3H, OCH_3), 2.26—2.60 (m, 2H, CH_2P), 1.22—1.31 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 23.88; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: - 53.682.

(*S*)-*Mosher's ester of* **11n** ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.85—7.88 (m, 1H, 5-H of Ar), 7.18—7.438 (m, 9H, ArH), 6.55—6.63 (m, 1H, C**H**CH_2P), 4.03—4.18 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 3.61 (s, 3H, OCH_3), 2.14—2.52 (m, 2H, CH_2P), 1.26—1.34 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 24.158; ^{19}F NMR ($CDCl_3$, 282 MHz) δ: - 54.046.

(*R*)-*Mosher's ester of* **11o** ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.44 (m, 6H, 1H of Furyl + 5H of Phenyl), 6.521—6.535 (dd, *J* = 0.9, 3.3 Hz, 1H, (1)H), 6.348—6.393 (m, 2H, C**H**CH_2P + (2) H), 3.895—4.062 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 3.431 (s, 3H, OCH_3), 2.423—2.729 (m, 2H, CH_2P), 1.188—1.250 (m, 6H, $P(OCH_2C\mathbf{H}_3)_2$); ^{31}P NMR ($CDCl_3$, 120 MHz) δ: 22.099.

(*S*)-*Mosher's ester of* **11o** ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.333—7.371 (m, 6H, 1H of Furyl + 5H of Phenyl), 6.476—6.488 (dd, *J* = 0.3, 3.3 Hz, 1H, (1)H), 6.316—6.395 (m, 2H, C**H**CH_2P + (2)H), 3.954—4.102 (m, 4H, $P(OC\mathbf{H}_2CH_3)_2$), 3.541 (s,

3H, OCH_3), 2.514—2.729 (m, 2H, CH_2P), 1.228—1.298 (m, 6H, $P(OCH_2CH_3)_2$); ^{31}P NMR (120 MHz, $CDCl_3$) δ: 22.285.

CRL-catalyzed hydrolysis of diethyl 3-butyryloxy-3-arylpropanephosphonate (**14**)

Racemic diethyl 3-hydroxy-3-arylpropanephosphonate (**13**) was prepared via reduction of the corresponding ketoalkanephosphonates. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.32—7.36 (m, 5H, ArH), 4.69—4.07 (m, 1H, CHOH), 3.98—4.07 (m, 4H, $P(OCH_2CH_3)_2$), 3.72 (s, 1H, OH), 1.80—2.02 (m, 4H, CH_2CH_2P), 1.26—1.30 (t, J = 7.2 Hz, 6H, $P(OCH_2CH_3)_2$); IR (film) ν: 3368, 2984, 1452, 1231, 1058, 1029, 967 cm^{-1}; EIMS m/z (%): 272 (M^+, 7.13), 166 (100), 152 (63.35), 139 (35.31), 138 (66.55), 125 (57.57), 111 (52.05). Anal. calcd for $C_{13}H_{21}O_4P$: C 57.34, H 7.77; found C 56.80, H 7.89.

Diethyl 3-butyryloxy-3-arylpropanephosphonate (**14**) ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.30—7.39 (m, 5H, ArH), 5.76—5.81 (m, 1H, $CHCH_2P$), 4.04—4.14 (m, 4H, $P(OCH_2CH_3)_2$), 2.32—2.37 (t, J = 7.5 Hz, 2H, $CH_3CH_2CH_2CO$), 1.63—2.16 (m, 6H, $CH_2CH_2P + CH_3CH_2CH_2CO$), 1.30—1.37 (t, J = 7.0 Hz, 6H, $P(OCH_2CH_3)_2$), 0.92—0.98 (t, J = 7.5 Hz, 3H, $CH_3CH_2CH_2CO$); IR (film) ν: 2970, 1737, 1456, 1392, 1369, 1247, 1176, 1057, 1028, 963 cm^{-1}; EIMS m/z (%): 343 (M^+, 1.03), 271 (30.40), 255 (100), 197 (6.11). Anal. calcd for $C_{17}H_{27}O_5P$: C 59.64, H 7.95; found C 59.53, H 7.91.

CRL-catalyzed hydrolysis of **14** is as above.

(R)-Diethyl-3-hydroxy-3-arylpropanephosphonate (**15**) Colorless oil; yield 35%; $[\alpha]_D^{15}$ + 26.7 (*c* 0.8, $CHCl_3$).

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