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Enzymatic synthesis of optically active trifluoromethylated 1- and 2-hydroxyalkanephosphonates☆

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Abstract—Convenient enzymatic methods have been developed for the preparation of chiral 1- and 2-hydroxyalkanephosphonates bearing a trifluoromethyl moiety with high enantiomeric excess via *Candida antarctica* lipase B-, *Mucor miehei* lipase-catalyzed alcoholysis and *C. rugosa* lipase-catalyzed hydrolysis in organic media. The enantiomeric excess of such trifluoromethylated carbinols was determined using quinine as a chiral solvating agent. The catalytic preference was assigned according to the Kusumi–Ohtani method.

1. Introduction

Chiral 1- or 2-hydroxyalkanephosphonates have received more and more attention due to their biological and pharmaceutical properties.[1] Meanwhile, the unique behavior of fluorinated compounds makes them suitable for various applications.[2] Numerous biological and chemical studies have demonstrated that the introduction of fluorine to phosphonates exhibits excellent electronic and structural similarity to phosphate.[3] In particular, the lipophilicity attached to the trifluoromethyl moiety makes trifluoromethylated molecules of great interest, especially for biological purposes. There have been some synthetic routes to chiral hydroxyalkanephosphonates,[4] and the synthesis of optically active fluorinated compounds exhibiting biological activity has also aroused much interest during the past years. To the best of our knowledge, asymmetric synthesis of these interesting molecules bearing the trifluoromethyl moiety has not been reported yet, although the racemic compounds are easily attainable.[5]

It is known that the utility of lipases for efficient resolution of alcohols and related compounds is of great importance in organic synthesis.[6] Hammerschmidt has exploited such hydrolases for enantioselective hydrolysis of a series of 1-acyloxyphosphonates in an organic–buffer biphase system.[7] Biocatalysis in non-conventional media is well-established. Continuing our study on biotransformations of organophosphorus compounds,[8] we herein report a facile synthesis of trifluoromethylated 1-, or 2-hydroxyphosphonates via lipase-mediated resolution in organic media.

2. Results and discussion

The most commonly used method of lipase-catalyzed resolution in organic media is transesterification. *Candida antarctica* lipase B (CALB) has been proved effective in the enantioselective acetylation of some hydroxyalkanephosphonates[8] and trifluoromethylated carbinols.[9] Trifluoromethylated 1- or 2-hydroxyphosphonates, however, did not give any acetylated products under our experimental conditions. Among lipases (immobilized *Mucor miehei*, *Pseudomonas* sp, *C. rugosa*, *Porcine pancreatic*, *Geotrichum*, sp. etc.) screened, none proved effective in enzymatic acetylation. We ascribed the poor activity to the strong electron-withdrawing effect of the trifluoromethyl and phosphoryl groups, which may reduce the nucleophility of the oxygen atom. It is possible to reverse the unfavourable electronic effect by changing the enzymatic method. Enzymatic alcoholysis, i.e. acyloxyalkanephosphonates being attacked by alcohols as nucleophiles, seemed to be a practical alternative (Scheme 1 and Table 1).

Despite the fact that CALB showed poor activity in acetylation of such compounds, this widely used immobilized biocatalyst demonstrates satisfying activity and enantioselectivity in alcoholysis of their chloroacetyl derivatives using *n*-butanol as nucleophile in anhydrous benzene. This methodology provides both stereoisomers of trifluoromethylated 1- and 2-hydroxyalkanephosphonates with high enantiomeric excess. It should be noted that their acetyl or butyl derivatives led to poor conversion.

Among the lipases studied, immobilized *M. miehei* (IM)

☆ Studies on organophosphorus compounds 125.

Keywords: hydroxyalkanephosphonates; trifluoromethyl; lipase; organic media.

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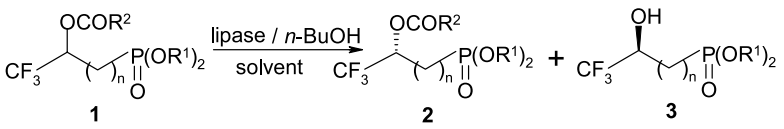


a:R^1=Et, R^2=$ClCH_2$, n=0;
b:R^1=*n*-Pr, R^2=$ClCH_2$, n=0;
c:R^1=*i*-Pr, R^2=$ClCH_2$, n=0;
d:R^1=Et, R^2=*n*-Pr, n=0;
e:R^1=*i*-Pr,R^2=*n*-Pr, n=0;
f:R^1=Me, R^2=$ClCH_2$, n=1;
g:R^1=Et, R^2=$ClCH_2$, n=1;
h:R^1=*n*-Pr, R^2=$ClCH_2$, n=1;
i:R^1=*i*-Pr, R^2=$ClCH_2$, n=1;

a: R^1=Et, n=0;
b:R^1=*n*-Pr, n=0;
c:R^1=*i*-Pr, n=0;
d:R^1=Me, n=1;
e:R^1=Et, n=1;
f:R^1=*n*-Pr, n=1;
g:R^1=*i*-Pr, n=1;

Scheme 1.

Table 1. CALB and IM catalyzed enantioselective alcoholysis of trifluoromethylated acyloxyalkanephosphonates

Entry	*n*	R^1	R^2	Lipase	Time (h)	Yield of **2** (%)[a]	ee of **2** (%)[b]	Yield of **3** (%)[a]	ee of **3** (%)[c]	E[d]
1	0	Et	$ClCH_2$	CALB	33	38	94	44	79	30
2	0	*n*-Pr	$ClCH_2$	CALB	49	39	>95	43	82	>37
3	0	*i*-Pr	$ClCH_2$	CALB	30	37	>95	45	80	>35
4[e]	0	Et	*n*-Pr	IM	30	–	–	41	>95	>25
5[e]	0	*i*-Pr	*n*-Pr	IM	55	–	–	44	>95	>41
6	1	Me	$ClCH_2$	CALB	28	44	82	42	>95	>100
7	1	Et	$ClCH_2$	CALB	40	43	93	44	>95	>100
8	1	*n*-Pr	$ClCH_2$	CALB	35	44	94	39	>95	>100
9	1	*i*-Pr	$ClCH_2$	CALB	43	44	90	39	>95	>94
10	1	*i*-Pr	$ClCH_2$	IM	43	44	75	39	>95	>88

Reactions were generally performed on 1 mmol scale.
[a] Isolated yield after column chromatography.
[b] ee Value was determined after its chemical conversion to the corresponding alcohol.
[c] ee Value determined by ^{19}F NMR (adding quinine), single peak was observed as ee>95%.
[d] 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).10
[e] The ee of **2** not determined due to the partial racemization during conversion of **2** to the corresponding alcohols; E was caculated according to yield and ee of **3**.

also showed high enantioselectivity. IM can alcoholyse acetyl, butyryl and chloroacetyl derivatives of 1-hydroxyalkanephosphonates, and the butyryl derivatives ensure both satisfying activity and enantioselectivity. As to 2-hydroxyalkanephosphonates, only their chloroacetyl derivatives give the best activity. This may be ascribed to that the electron-withdrawing phosphoryl moiety is comparably far away from the chiral center. Both CALB and IM show high enantioselectivity in benzene or toluene.

Quinine was adopted as a chiral solvating agent for direct simple ^{19}F NMR enantiomeric excess determination of chiral hydroxyalkanephosphonates bearing trifluoromethyl moiety. Quinine efficiently discriminates between the enantiomers of different classes of compounds because of the simultaneous presence of different and suitable functional groups in the molecule.[11] It has been used to determine the enantiomeric excess of binaphthyl derivatives, alkylarylcarbinols[11] and 2-hydroxyesters[12] via ^1H NMR spectroscopy and that of 1 or 2-hydroxyalkanephosphonates via ^{31}P NMR spectroscopy.[13] We found that quinine can also be used to accurately determine the ee values of those trifluoromethylated carbinols using ^{19}F NMR spectroscopy. The enantiomeric excess values thus obtained fits quite well with those obtained by the ^{19}F NMR spectroscopy of their Mosher's esters.

The configuration of the trifluoromethylated carbinols was tentatively assigned according to the refined Mosher's method, known as the Kusumi–Ohtani method.[14] It was established that this method is applicable for many types of secondary alcohols in which the absolute configuration of the chiral center was determined by comparing the $\Delta\delta$ values of the protons on the molecules. Takagi[15] and Hammschmidt[16] had respectively extended the scope of Kusumi–Ohtani method to those bearing different nuclei such as ^{19}F and ^{31}P. Here we also assigned the configuration of the molecule bearing ^{19}F on one side and ^1H and ^{31}P on the other side according to this rule. A typical example is shown in Figure 1.

The configuration assignment confirmed that the catalytic preference is in accordance with the Kaslauskas' rule (Fig. 2).[17]

In our previous paper, we reported crude *C. rugosa* lipase (CRL)-catalyzed enantioselective hydrolysis in diisopropyl ether for preparing optically pure 2-hydroxy-2-arylethanephosphonates.[8b] We found CRL also proved effective for preparing chiral 3,3,3-trifluoro-2-hydroxypropanephosphonates (Scheme 2 and Table 2).

Compared to IM and CALB, CRL showed opposite

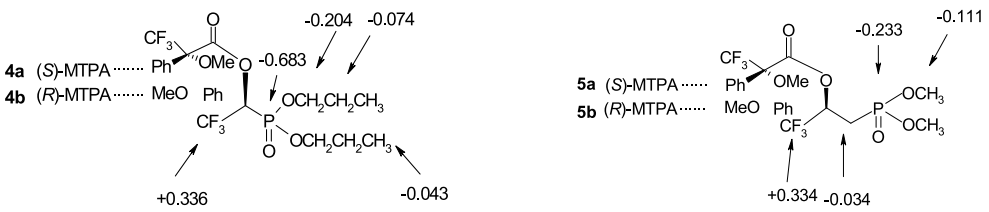


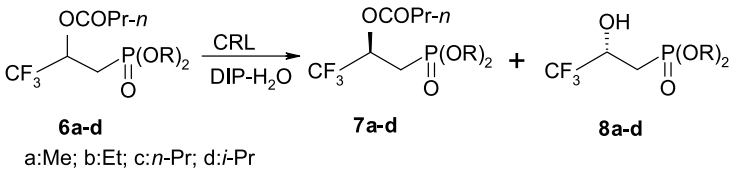
Figure 1. Configurational assignment of the trifluoromethylated carbinols based on the NMR $\Delta\delta$ values obtained for their (*S*)- and (*R*)-MTPA esters. $\Delta\delta$ Values (δS-δR) are expressed in ppm.

Figure 2. Configuration of the preferential enantiomer of alcoholyzed hydroxyalkanephosphonate catalyzed by CALB.

enantiopreference. It is also interesting to note that CRL showed quite different enantioselectivity toward non-trifluormethylated carbinols, as shown in Scheme 3.

4. 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 (300 MHz),^{31}P NMR (160 MHz) and ^{19}F NMR (282 MHz) spectra were taken on a Mercury spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard) and 80% phosphorus acid (external standard) in phosphorus spectra, trifluroacetic acid, respectively. Racemic 2,2,2-trifluoro-1-hydroxyethanephosphonates were synthesized from the starting material trifluoroacetalaldehyde ethyl



Scheme 2.

Table 2. CRL-catalyzed enantioselective hydrolysis of **6a–d**

Entry	Substrate	Time (h)	R	**7a–d**[a]		**8a–d**		*E*
				Yield (%)	ee (%)	Yield (%)	ee (%)	
1	**6a**	35	Me	43	93	44	>95	>100
2	**6b**	30	Et	43	>95	42	81	>100
3	**6c**	48	*n*-Pr	46	84	42	>95	>100
4	**6d**	50	*i*-Pr	41	>95	47	80	>100

[a] ee was determined after its chemical conversion to the corresponding alcohols using ^{19}F NMR spectroscopy (adding quinine).

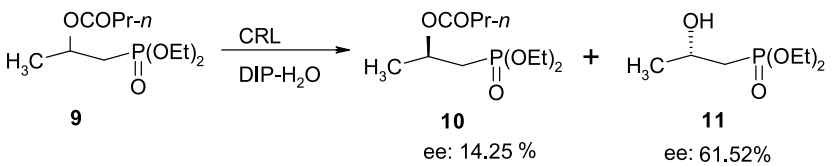
3. Conclusion

In conclusion, we have developed IM- and CALB-catalyzed alcoholysis and CRL-catalyzed hydrolysis in organic media for the convenient preparation of chiral trifluoromethylated 1- or 2-hydroxyalkanephosphonates. The high enantioselectivity and simplicity of the work-up procedure, combined with the ready availability of the starting material make our methodology a quite practical route to these potentially important compounds.

hemiacetal as reported by Shen.[5a] The racemic 3,3,3-trifluoro-2-hydroxypropanephosphonates were prepared via reduction of corresponding ketophosphonates.[5b] Their acyl derivatives were prepared via reaction with corresponding acids, DCC, and DMAP in a standard procedure. CALB (Novozym 435), *M. miehei* lipase (LIPOZYME IM) were gifts from Novo Norvodisk Co. Solvents used for enzymatic reactions were purified by standard methods and stored over 4 Å sieves before use. General procedure for ^{19}F NMR determination of ee value: to 20 mg hydroxyalkanephosphonates was added 1.5 equiv. quinine and 0.5 mL $CDCl_3$.

4.1. General procedure for CALB- and IM-catalyzed alcoholysis

To a solution of acyloxyalkanephosphonate (1 mmol) in benzene (1 mL) or toluene (1 mL) was added *n*-butanol (0.3 mL). The reaction was started by addition of CALB (100 mg). The mixture was maintained at 30°C. When the reaction proceeded to certain conversion, the enzyme was filtered off, washed with acetone (3 mL). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish



Scheme 3.

acyloxyalkanephosphonates and alcoholyzed products (eluent: $CHCl_3$/EtOAc 4:1, 1-hydroxyphosphonates series; petroleum ether/EtOAc 3:2, 2-hydroxyphosphonates series). The following is the data of CALB-catalyzed alcoholysis. Analogously, the alcoholysis can be catalyzed by IM in the same manner.

4.1.1. (*R*)-Diethyl 2,2,2-trifluoro-1-chloroacetyloxyethanephosphonate (2a). Colorless oil; yield=119 mg (38%); ee=94%; $[\alpha]_D^{20}=-40$ (*c* 0.9, $CHCl_3$); ν_{max}(liquid film) 2991, 1791, 1773, 1346, 1269, 1190, 1145, 1123, 1043, 1023, 576 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.60–5.79 (1H, m, C*H*P), 4.24–4.29 (6H, m, $ClCH_2$+$P(OCH_2CH_3)_2$), 1.35–1.41 (6H, m, $P(OCH_2CH_3)_2$); δ_F (282 MHz, $CDCl_3$) 6.88; *m/z* (EI) 313 (M^++1) (34), 285 (42), 257 (46), 239 (91), 109 (100%); HRMS (EI) Calcd for $C_8H_{13}F_3O_5P$ (M^+−Cl): 277.0453; found: 277.0453.

4.1.2. (*S*)-Diethyl 2,2,2-trifluoro-1-hydroxyethanephosphonate (3a).[5a] Colorless oil; yield=104 mg (44%); ee=79%; $[\alpha]_D^{20}=-4.70$ (*c* 1.5, $CHCl_3$); ν_{max}(liquid film) 3223, 2991, 1269, 1229, 1175, 1025 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.96 (1H, br, s, O*H*), 4.20–4.33 (5H, m, C*H*OH+$(P(OCH_2CH_3)_2)$), 1.38 (6H, t, *J*=7.2 Hz, $P(OCH_2CH_3)_2$); δ_F (282 MHz, $CDCl_3$) 4.42; δ_P (120 MHz, $CDCl_3$) 15.56; *m/z* (EI) 209 (10), 181 (18), 129 (28), 109 (100), 101 (62), 81 (92%).

4.1.3. (*R*)-Dipropyl 2,2,2-trifluoro-1-chloroacetyloxyethanephosphonate (2b). Colorless oil; yield=132 mg (39%); ee>95%; $[\alpha]_D^{20}=-37.5$ (*c* 0.85, $CHCl_3$); ν_{max}(liquid film) 2976, 1791, 1739, 1467, 1345, 1270, 1189, 1126, 1056, 1012, 576 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.69–5.76 (1H, m, C*H*P), 4.25 (2H, s, $ClCH_2CO$), 4.11–4.21 (4H, m, $P(OCH_2CH_2CH_3)_2$), 1.71–1.79 (4H, m, $P(OCH_2CH_2CH_3)_2$), 0.99 (6H, t, *J*=7.4 Hz, $P(OCH_2CH_2CH_3)_2$); δ_P (120 MHz, $CDCl_3$) 11.61; δ_F (282 MHz, $CDCl_3$) 6.83; *m/z* (EI) 344 (M^++4) (29), 342 (M^++2) (32), 341 (M^++1) (84), 299 (56), 257 (100), 181 (54), 123 (52). Anal. calcd for $C_{10}H_{17}ClF_3O_5P$: C, 35.26; H, 5.03; found: C, 32.50; H, 5.25.

4.1.4. (*S*)-Dipropyl 2,2,2-trifluoro-1-hydroxyethanephosphonate (3b).[5a] Colorless oil; yield=104 mg (43%); ee=82%; $[\alpha]_D^{20}=-4.40$ (*c* 1.0, $CHCl_3$); ν_{max}(liquid film) 3240, 2976, 1467, 1269, 1230, 1173, 1122, 1063, 1015 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.09–4.20 (6H, m, C*H*OH+$(OCH_2CH_2CH_3)_2$), 1.69–1.76 (4H, m, $(OCH_2CH_2CH_3)_2$), 0.98 (6H, t, *J*=7.5 Hz); δ_F (282 MHz, $CDCl_3$) 4.33; *m/z* (EI) 265 (M^++1) (7), 181 (26), 167 (41), 83 (100), 43 (91%).

4.1.5. (*R*)-Diisopropyl 2,2,2-trifluoro-1-chloroacetyloxyethanephosphonate (2c). Colorless oil; yield=125 mg (37%); ee>95%; $[\alpha]_D^{20}=-36.52$ (*c* 0.5, $CHCl_3$); ν_{max}(liquid film) 2987, 1791, 1772, 1456, 1479, 1390, 1345, 1270, 1188, 1145, 1125, 1103, 1053, 1002, 937 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.61–5.68 (1H, m, C*H*P), 4.81–4.88 (2H, m, $P(OCHMe_2)_2$), 4.23 (2H, s, $ClCH_2CO$), 1.35–1.39 (12H, m, $P(OCHMe_2)_2$); δ_F (282 MHz, $CDCl_3$) 7.04; δ_P (120 MHz, $CDCl_3$) 9.39; *m/z* (EI) 342 (M^++2) (6), 340 (M^+) (0.35), 299 (19), 257 (83), 239 (100), 181 (52), 123 (93), 43 (74). Anal. calcd for $C_{10}H_{17}ClF_3O_5P$: C, 35.26; H, 5.03; found: C, 35.39; H, 5.31.

4.1.6. (*S*)-Diisopropyl 2,2,2-trifluoro-1-hydroxyethanephosphonate (3c).[5a] Colorless oil; yield=109 mg (45%); ee=80%; $[\alpha]_D^{20}=-5.10$ (*c* 1.3, $CHCl_3$); ν_{max}(liquid film) 3260, 2987, 1469, 1390, 1370, 1269, 1232, 1174, 1120, 1004 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.69–4.87 (2H, m, $P(OCHMe_2)_2$), 4.20–4.27 (1H, m, C*H*OH), 1.38 (12H, t, *J*=6.2 Hz, $P(OCHMe_2)_2$); δ_F (282 MHz, $CDCl_3$) 4.29; δ_P (120 MHz, $CDCl_3$) 13.50; *m/z* (EI) 265 (M^++1) (78), 223 (75), 207 (21), 181 (100), 167 (413), 123 (28), 43 (100%).

4.1.7. (*R*)-Dimethyl 3,3,3-trifluoro-2-chloroacetyloxypropanephosphonate (2f). Colorless oil; yield=131 mg (44%); ee=82%; $[\alpha]_D^{20}=-8.6$ (*c* 0.5, $CHCl_3$); ν_{max}(liquid film) 2963, 1788, 1263, 1185, 1139, 1057, 1032 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.71–5.75 (1H, m, $CHCH_2P$), 4.19 (2H, s, $ClCH_2CO$), 3.76–3.80 (6H, dd, *J*=2.4, 10.8 Hz, $P(OMe)_2$), 2.20–2.31 (2H, m, CH_2P); δ_F (282 MHz, $CDCl_3$) −1.21; *m/z* (EI) 298 (M^+) (1), 223 (50), 221 (69), 205 (20), 153 (21), 109 (100), 77 (41%). Anal. calcd for $C_7H_{11}ClF_3O_5P$: C, 28.16; H, 3.71; found: C, 35.34; H, 3.74.

4.1.8. (*S*)-Dimethyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (3d).[5b] Colorless oil; yield=93 mg (42%); ee=98%; $[\alpha]_D^{20}=-21$ (*c* 0.9, $CHCl_3$); ν_{max}(liquid film) 3271, 2964, 1258, 1237, 1165, 1129, 1108, 1059, 1039 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.5 (1H, br, s, O*H*), 4.36–4.39 (1H, m, C*H*OH), 3.75–3.81 (6H, m, $P(OMe)_2$), 2.04–2.21 (2H, m, CH_2P); δ_F (282 MHz, $CDCl_3$) −4.60 (d, *J*=6 Hz); *m/z* (EI) 223 (M^++1) (0.76), 221 (M^+−1) (1), 153 (100), 124 (23), 110 (39), 109 (53), 95 (29), 79 (57%).

4.1.9. (*R*)-Diethyl 3,3,3-trifluoro-2-chloroacetyloxypropanephosphonate (2g). Colorless oil; yield=140 mg (43%); ee=93%, $[\alpha]_D^{20}=-10$ (*c* 0.7, $CHCl_3$); ν_{max}(liquid film) 2988, 1798, 1277, 1258, 1185, 1139, 1051, 1027, 971 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.62–5.81 (1H, m, C*H*CH_2P), 4.10–4.18 (6H, m, $ClCH_2CO$+$P(OCH_2CH_3)_2$), 2.07–2.14 (2H, m, CH_2P), 1.34 (6H, t, *J*=7.2 Hz, $P(OCH_2CH_3)_2$); δ_F (282 MHz, $CDCl_3$) −1.25; *m/z* (EI) 299 (44), 249 (43), 233 (43), 205 (34), 195 (100), 177 (48), 77 (29%). Anal. calcd for $C_9H_{15}ClF_3O_5P$: C, 33.09; H, 4.63; found: C, 33.09; H, 4.73.

4.1.10. (*S*)-Diethyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (3e).[5b] Colorless oil; yield=110 mg (44%); ee>95%; $[\alpha]_D^{20}=-20$ (*c* 1.05, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.53 (1H, s, OH), 4.33–4.43 (1H, m, C*H*OH), 4.07–4.19 (4H, m, $P(O)(OCH_2CH_3)_2$), 2.03–2.25 (2H, m, CH_2P), 1.27–1.35 (6H, *J*=7.9 Hz, $P(O)(OCH_2CH_3)_2$); δ_F (282 MHz, $CDCl_3$) −3.43; *m/z* (EI) 251 (64), 223 (40), 195 (100), 177 (53), 138 (40), 125 (65), 81 (50%).

4.1.11. (*R*)-Dipropyl 3,3,3-trifluoro-2-chloroacetyloxypropanephosphonate (2h). Colorless oil; yield=156 mg (44%); ee=94%; $[\alpha]_D^{20}=-8.7$ (*c* 0.5, $CHCl_3$); ν_{max}(liquid film) 2973, 1789, 1278, 1260, 1184, 1139, 1062, 1008 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.74–5.77 (1H, m, C*H*CH_2P), 4.21 (2H, s, $ClCH_2CO$), 4.00–4.07 (4H, m, $P(OCH_2CH_2CH_3)_2$), 2.22–2.31 (2H, m, CH_2P), 1.67–1.78 (4H, m, $P(OCH_2CH_2CH_3)_2$), 0.98 (6H, t, *J*=6.9 Hz, $P(OCH_2CH_2CH_3)_2$); δ_F (282 MHz, $CDCl_3$) −1.24 (d, *J*=5.7 Hz); δ_P (120 MHz, $CDCl_3$) 28.54; *m/z* (EI) 357 (M^++2) (8), 355 (M^++1) (25), 271 (45), 195 (100), 177 (26), 77

(34%). Anal. calcd for $C_9H_{15}ClF_3O_5P$: C, 37.25; H, 5.40; found: C, 37.19; H, 5.56.

4.1.12. (*S*)-Dipropyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (3f). Colorless oil; yield=108 mg (39%); ee>95%, $[\alpha]_D^{20}=-23$ (*c* 1.4, $CHCl_3$); ν_{max}(liquid film) 3272, 2974, 1466, 1255, 1232, 1188, 1164, 1129, 1108, 1066, 1073 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.17 (1H, br, s, O*H*), 4.39–4.43 (1H, m, C*H*OH), 4.02–4.18 (4H, m, $PO(CH_2CH_2CH_3)_2$), 2.14–2.22 (2H, m, CH_2P), 1.69–1.81 (4H, m, $PO(CH_2CH_2CH_3)_2$), 0.96–1.03 (6H, t, *J*=7.2 Hz, $PO(CH_2CH_2CH_3)_2$); δ_F (282 MHz, $CDCl_3$) −3.48 (d, *J*=5.4 Hz); *m/z* (EI) 260 (M^+-18) (13), 237 (24), 195 (100), 177 (30), 125 (17),43 (55%). Anal. calcd for $C_9H_{18}F_3O_4P$: C, 38.66; H, 6.52; found: C, 39.03; H, 6.58.

4.1.13. (*R*)-Diisopropyl 3,3,3-trifluoro-2-chloroacetyloxypropanephosphonate (2i). Colorless oil; yield=156 mg (44%); ee=90%; $[\alpha]_D^{20}=-7.5$ (*c* 0.7, $CHCl_3$); ν_{max}(liquid film) 2984, 1790, 1388, 1378, 1278, 1255, 1183, 1140, 1008, 988 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.66–5.75 (1H, m, C*H*CH_2P), 4.65–4.76 (2H, m, $P(OCHMe_2)_2$), 4.18 (2H, s, $ClCH_2CO$), 2.09–2.22 (2H, m, CH_2P), 1.23–1.34 (12H, m, $P(OCHMe_2)_2$); δ_F (282 MHz, $CDCl_3$) −1.14; δ_P (120 MHz, $CDCl_3$) 18.39; *m/z* (EI) 355 (M^++1) (1), 295 (16), 271 (80), 253 (73), 195 (100), 177 (248), 77 (28%). Anal. calcd for $C_9H_{15}ClF_3O_5P$: C, 37.25; H, 5.40; found: C, 37.25; H, 5.40.

4.1.14. (*S*)-Diisopropyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (3g). Colorless oil; yield=108 mg (39%); ee>95%; $[\alpha]_D^{20}=-17$ (*c* 1.9, $CHCl_3$); ν_{max}(liquid film) 3260, 2987, 1469, 1390, 1370, 1269, 1232, 1174, 1120, 1004 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.2 (1H, br, s, O*H*), 4.71–4.78 (2H, m, $P(OCHMe_2)_2$), 4.34–4.36 (1H, m, C*H*OH), 2.04–2.13 (2H, m, CH_2P), 1.33–1.36 (6H, m, $P(OCHMe_2)_2$); δ_F (282 MHz, $CDCl_3$) −3.48 (d, *J*=6.3 Hz); *m/z* (EI) 221 (20), 195 (100), 177 (69), 125 (24), 77 (28), 43 (40%). Anal. calcd for $C_9H_{18}F_3O_4P$: C, 38.66; H, 6.52; found: C, 38.95; H, 6.39.

4.2. General procedure for the preparation of Mosher's ester of the corresponding hydroxyalkanephosphonates

To a dry 5 mL bottle was added anhydrous CH_2Cl_2 (1 mL), DCC (25 mg, 0.12 mmol), and Mosher's acid (28 mg, 0.12 mmol). The mixture was stirred at room temperature for 0.5 h, followed by addition of hydroxyalkanephosphonates (1 mmol) and DMAP (1 mg), and then stirred overnight. Ether (2 mL) was added, and precipitate was filtered off. After concentration under vacuum another 2 mL ether was added and the formed precipitate was removed. The concentrated oil was subjected to flash column chromatography (eluent: petroleum ether/EtOAc=3:1).

4.2.1. (*S*)-Mosher's ester of (*S*)-dipropyl-2,2,2-trifluoro-1-hydroxyethane phosphonate (4a). δ_H (300 MHz, $CDCl_3$) 7.56–7.58 (2H, m, Ph-*H*), 7.42–7.44 (3H, m, Ph-*H*), 5.81–5.87 (1H, m, C*H*P), 3.86–4.07 (4H, m, $P(OCH_2CH_2CH_3)_2$), 3.58 (3H, s, OCH_3), 1.57–1.68 (4H, m, $P(OCH_2CH_2CH_3)_2$), 0.81–0.89 (6H, m, $P(OCH_2CH_2\text{-}CH_3)_2$); δ_F (282 MHz, $CDCl_3$) 7.24 (d, *J*=12.4 Hz), 4.99 (s); δ_P (120 MHz, $CDCl_3$) 8.71.

4.2.2. (*R*)-Mosher's ester of (*S*)-dipropyl-2,2,2-trifluoro-1-hydroxyethane phosphonate (4b). δ_H (300 MHz, $CDCl_3$) 7.57–7.60 (2H, m, Ph-*H*), 7.43–7.45 (3H, m, Ph-*H*), 5.81–5.90 (1H, m, C*H*P), 4.03–4.20 (4H, m, $P(OCH_2CH_2CH_3)_2$), 3.59 (3H, s, OCH_3), 1.60–1.76 (4H, m, $P(OCH_2CH_2CH_3)_2$), 0.89–0.99 (6H, m, $P(OCH_2CH_2\text{-}CH_3)_2$); δ_F (282 MHz, $CDCl_3$) 6.84 (d, *J*=12.4 Hz), 5.07 (s); δ_P (120 MHz, $CDCl_3$) 9.39.

4.2.3. (*S*)-Mosher's ester of (*R*)-dimethyl-3,3,3-trifluoro-2-hydroxypropane phosphonate (5a). δ_H (300 MHz, $CDCl_3$) 7.57–7.60 (2H, m, Ph-*H*), 7.43–7.45 (3H, m, Ph-*H*), 5.85–5.93 (1H, m, C*H*CH_2P), 3.62–3.66 (6H, dd, *J*=11.4 Hz, $P(OCH_3)_2$), 3.59 (3H, s, OCH_3), 2.23–2.32 (2H, dd, *J*=6.3, 19.2 Hz, CH_2P); δ_F (282 MHz, $CDCl_3$) 5.44 (s), −0.51 (d, *J*=13.9 Hz); δ_P (120 MHz, $CDCl_3$) 26.21.

4.2.4. (*R*)-Mosher's ester of (*R*)-dimethyl-3,3,3-trifluoro-2-hydroxypropane phosphonate (5b). δ_H (300 MHz, $CDCl_3$) 7.57–7.60 (2H, m, Ph-*H*), 7.42–7.47 (3H, m, Ph-*H*), 5.85–5.95 (1H, m, C*H*CH_2P), 3.76–3.80 (6H, d, *J*=11.1 Hz, $P(OCH_3)_2$), 3.59 (3H, s, OCH_3), 2.29–2.38 (2H, m, CH_2P); δ_F (282 MHz, $CDCl_3$) 5.10 (s), −0.84 (d, *J*=7.9 Hz); δ_P (120 MHz, $CDCl_3$) 26.44.

4.3. General procedure for *C. rugosa*-catalyzed enantioselective hydrolysis of 3,3,3-trifluoro-2-butyryloxypropanephosphonate

To diisopropyl ether (4 mL) saturated with 0.75 M $MgCl_2$ solution was added 3,3,3-trifluoro-2-butyryloxypropanephosphonate (1 mmol) and crude *C. rugosa* lipase (100 mg). The mixture was stirred at 35°C. When the reaction proceeded to certain conversion, the enzyme was filtered, washed with 3 mL acetone. The volatile solvent was removed under reduced pressure and the residure was subjected to flash chromatography (eluent: petroleum ether/EtOAc 3:2).

4.3.1. (*S*)-Dimethyl 3,3,3-trifluoro-2-butyryloxypropanephosphonate (7a). Colorless oil; yield=126 mg (44%); ee=93%; $[\alpha]_D^{18}=+7.7$ (1.25, $CHCl_3$); ν_{max}(liquid film) 2966, 1766, 1280, 1183, 1137, 1105, 1055, 1033, 1004 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.69–5.74 (1H, m, C*H*CH_2P), 3.75–3.82 (6H, m, $P(OMe)_2$), 2.38–2.45 (2H, m, $CH_3CH_2CH_2CO$), 2.19–2.31 (2H, m, CH_2P), 1.67–1.77 (2H, m, $CH_3CH_2CH_2CO$), 0.97–1.03 (3H, m, $CH_3CH_2\text{-}CH_2CO$); δ_P (120 MHz, $CDCl_3$) 24.46; *m/z* (EI) 293 (M^++1) (1), 264 (14), 223 (100), 153 (37), 109 (28), 43 (31%). Anal. calcd for $C_9H_{16}F_3O_5P$: C, 37.00; H, 5.52; found: C, 37.30; H, 5.67.

4.3.2. (*R*)-Dimethyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (8a). Colorless oil; yield=98 mg (44%); ee>95%; $[\alpha]_D^{18}=+21.4$ (1.25, $CHCl_3$).

4.3.3. (*S*)-Diethyl 3,3,3-trifluoro-2-butyryloxypropanephosphonate (7b). Colorless oil; yield=138 mg (43%); ee>95%; $[\alpha]_D^{15}=+6.7$ (1.25, $CHCl_3$); ν_{max}(liquid film) 2978, 1766, 1278, 1182, 1137, 1102, 1052, 1028, 1006, 969 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.81–5.97 (1H, m, C*H*CH_2P), 4.06–4.26 (4H, m, $P(OCH_2CH_3)_2$), 2.44–2.50

(2H, t, J=7.4 Hz, $CH_3CH_2CH_2CO$), 2.25–2.38 (2H, m, CH_2P), 1.72–1.86 (2H, m, $CH_3CH_2CH_2CO$), 1.36–1.44 (6H, m, $P(OCH_2CH_3)_2$), 1.05 (3H, t, J=7.2 Hz, $CH_3CH_2CH_2CO$); δ_F (282 MHz, $CDCl_3$) −1.38 (J=4.8 Hz); m/z (EI) 321 (M^++1), 251 (100), 233 (35), 230 (86), 195 (61), 138 (26), 71 (34), 43 (38%). Anal. calcd for $C_{11}H_{20}F_3O_5P$: C, 41.26; H, 6.30; found: C, 41.11; H, 6.69.

4.3.4. (*R*)-Diethyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (8b). Colorless oil; yield=105 mg (42%); ee=81%; $[\alpha]_D^{15}$=+19 (1.1, $CHCl_3$).

4.3.5. (*S*)-Dipropyl 3,3,3-trifluoro-2-butyryloxypropanephosphonate (7c). Colorless oil; yield=160 mg (46%); ee=84%; $[\alpha]_D^{15}$=+8.7 (0.5, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.60–5.74 (1H, m, $CHCH_2P$), 3.98–4.05 (4H, m, $P(OCH_2CH_2CH_3)_2$), 2.39–2.42 (2H, J=7.5 Hz, $CH_3CH_2CH_2CO$), 2.18–2.28 (2H, m, CH_2P), 1.64–1.77 (6H, m, $CH_3CH_2CH_2CO$+$P(OCH_2CH_2CH_3)_2$), 0.94–1.00 (9H, m, $CH_3CH_2CH_2CO$+$P(OCH_2CH_2CH_3)_2$); δ_F (282 MHz, $CDCl_3$) −1.56; m/z (EI) 261 (13), 237 (63), 219 (23), 195 (100), 177 (22%). Anal. calcd for $C_{13}H_{24}F_3O_5P$: C, 44.83; H, 6.95; found: C, 44.36; H, 6.77.

4.3.6. (*R*)-Dipropyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (8c). Colorless oil; yield=117 mg (42%); ee=84%, $[\alpha]_D^{15}$=+8.7 (0.5, $CHCl_3$).

4.3.7. (*S*)-Diisopropyl 3,3,3-trifluoro-2-butyryloxypropanephosphonate (7d). Colorless oil; yield=143 mg (41%); ee>95%; $[\alpha]_D^{20}$=+7.5 (1.0, $CHCl_3$); ν_{max}(liquid film) 2982, 1766, 1469, 1387, 1378, 1279, 1260, 1187, 1137, 1108, 1008 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.66–5.75 (1H, m, $CHCH_2P$), 4.67–4.76 (2H, m, $P(OCHMe)_2$), 2.38–2.43 (2H, J=7.5 Hz, $CH_3CH_2CH_2CO$), 2.09–2.23 (2H, m, CH_2P), 1.64–1.77 (2H, m, $CH_3CH_2CH_2CO$), 1.31–1.35 (4H, m, $P(OCH_2CH_3)_2$), 0.98 (3H, t, J=7.5 Hz, $CH_3CH_2CH_2CO$); δ_F (282 MHz, $CDCl_3$) −1.44 (d, J=5.7 Hz); m/z (EI) 348 (M^+) (10), 307 (17), 265 (50), 247 (79), 197 (100), 71 (74%). Anal. calcd for $C_{13}H_{24}F_3O_5P$: C, 44.83; H, 6.95; found: C, 44.80; H, 7.02.

4.3.8. (*R*)-Dipropyl 3,3,3-trifluoro-2-hydroxypropanephosphonate (8d). Colorless oil; yield=131 mg (47%); ee>95%; $[\alpha]_D^{15}$=+20 (1.05, $CHCl_3$).

4.4. CRL-catalyzed hydrolysis of diethyl 2-butyryloxypropanephosphonate

The procedure is similar to the above. Silical gel flash chromatography (eluent: petroleum ether/EtOAc 1:1) furnished (**10**) and (**11**).

4.4.1. (*R*)-Diethyl 2-butyryloxypropanephosphonate (10). Colorless oil; yield=35 mg (13%); ee=62%; $[\alpha]_D^{25}$=+9.4 (1.5, $CHCl_3$); ν_{max}(liquid film) 2982, 1735, 1460, 1382, 1254, 1184, 1054, 1025, 963 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.15–5.23 (1H, m, $CHCH_2P$), 4.09–4.14 (4H, m, $P(OCH_2CH_3)_2$), 2.24–2.29 (2H, t, J=7.5 Hz, $CH_3CH_2CH_2CO$), 1.93–2.25 (2H, CH_2P), 1.59–1.72 (2H, m, $CH_3CH_2CH_2CO$), 1.31–1.40 (9H, m, $P(OCH_2CH_3)_2$+CH_3CHCH_2P), 0.95 (3H, t, J=7.2 Hz, $CH_3CH_2CH_2CO$); m/z (EI) 266 (6), 195 (42), 179 (90), 151 (48), 123 (67), 59 (100%). Anal. calcd for $C_{11}H_{23}O_5P$: C, 49.62; H, 8.71; found: C, 49.26; H, 8.48.

4.4.2. (*S*)-Diethyl 2-hydroxypropanephosphonate (11).[8a] Colorless oil; yield=104 mg (53%); ee=14.2%; $[\alpha]_D^{25}$=+1.3 (0.6, $CHCl_3$); ν_{max}(liquid film) 3399, 2983, 1234, 1048 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.08–4.23 (5H, m, CH_3CHOH+$P(OCH_2CH_3)_2$), 3.66 (1H, br, s, OH); 1.96 (2H, dd, J=6.3, 17.1 Hz, CH_2P), 1.36–1.38 (6H, m, $P(OCH_2CH_3)_2$); 1.31 (3H, dd, J=2.4, 5.9 Hz, CH_3CH); δ_P (120 MHz, $CDCl_3$) 30.44.

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