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猪胰脂肪酶催化外消旋 *P*-手性 *α*-羟基磷酸酯类化合物的动力学拆分

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摘要 酶催化具有高效、高选择性以及反应条件温和等优点，已经成为有机合成领域的重要方法. 研究了 *P*-手性 *α*-羟基磷(膦)酸酯类化合物的合成方法. 在猪胰脂肪酶的催化作用下，外消旋 *α*-羟基磷(膦)酸酯与乙酸乙烯酯之间能够顺利地发生酯交换反应，以高达 49%的产率和 83%的 *ee* 值得到相应的手性产物，且该反应在非常温和的条件下就能够进行. 同时，在计算机的辅助下建立了酶-底物之间的结合模型，通过对接的方法揭示了反应中酶催化对映选择性的机理.
关键词 生物催化；动力学拆分；羟基磷酸酯；猪胰脂肪酶

Kinetic Resolution of Racemic *P*-Chiral *α*-Hydroxymethylphosphonates Catalyzed by Lipase from Porcine Pancreas

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Abstract The development of enzyme-catalyzed methods for the synthesis of *P*-chiral phosphine derivatives has important implications. Herein this work presents a direct biocatalytic transesterification of racemic *α*-hydroxyphosphonates and vinyl acetate, which provides a rapid access to *P*-chiral hydroxymethylphosphonates. Catalyzed by lipase from porcine pancreas (PPL), which is commercially available, the reactions proceed efficiently with a wide array of reaction partners to deliver various tertiary phosphine oxides in up to 49% yield and 83% *ee* under very mild conditions. The enzyme-substrate binding mode was established and the high enantioselectivity of PPL was revealed through docking simulations.
Keywords biocatalytic; kinetic resolution; hydroxymethylphosphonates; lipase from porcine pancreas

1 Introduction

Owing to their important applications in the field of medicinal chemistry,[1-3] chiral catalyst,[4-5] life and material science,[6] the synthesis of chiral phosphine compounds has attracted continuous and intense attention.[7] Compared to other chiral phosphine compounds, *P*-chiral phosphine compounds have important applications in many fields due to their unique structural characteristics. For example, they have seen widespread applications in the induction of chirality, and can be used as a ligand for metal catalysts[8-12] or directly as an organic catalyst (Figure 1A).[13-18] On the other hand, *P*-chiral phosphine oxide structural units are widely present in many natural products and bioactive molecules. These compounds possess anti-malarial[19] and antiproliferative[20] activities, and they are potent inhibitors of enzymes such as protein kinase (Figure 1B).[21-22]

So far, *P*-chiral organic phosphorus compounds are achieved either by chemical resolution[23-24] or asymmetric synthesis[25-27] using alcohols, diols[28-30], amines or amino alcohols[31-34] as auxiliaries. While many elegant synthetic strategies have been developed so far, the direct enantioselective syntheses from simple materials are rather few, the disadvantage of these synthetic methods is that they generally need to use equivalent or even excessive chiral reagents, and there is a problem of high economic cost. For the chiral auxiliary induction strategy, there are additional introductions and removal of cogroups, resulting in more reaction steps and low atomic economy.

Among the limited methodologies, biocatalytic synthesis is very appealing due to its significant advantages such as environment-friendly, excellent selectivity, and mild

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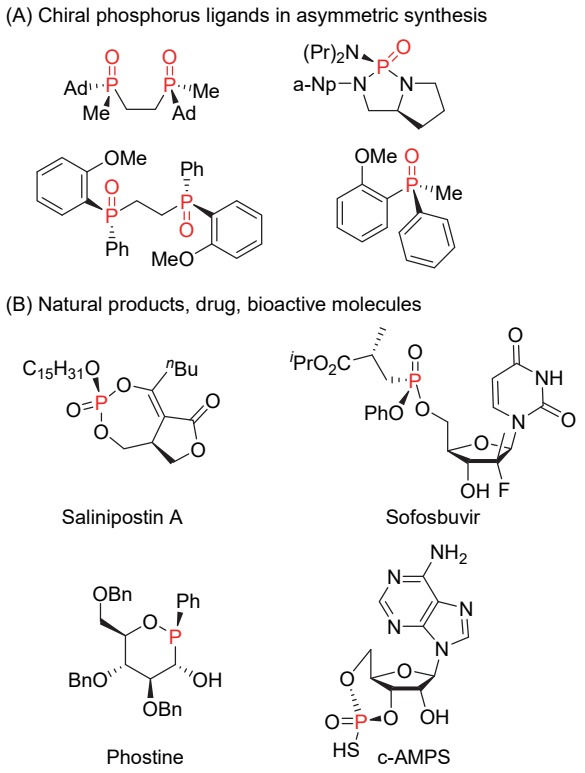


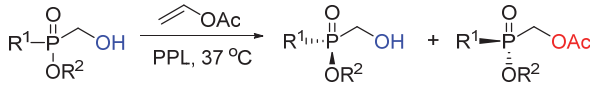
Figure 1 Selected catalysts featuring *P*-chiral phosphine oxides and natural products, drugs, bioactive molecules

reaction conditions. Amidase[35-41] and esterase-catalyzed[42-48] hydrolysis have become an important and powerful strategy in organic chemistry. Lipase [EC 3.1.1.3] is an important enzyme that catalyzes the conversion of alcohol into ester.[49] Resolution of racemates using lipases is a powerful method for obtaining enantiopure compounds.

Owing to the facile access of various lipases, a large number of them have been identified and commercialized, biotransformation of hydroxy catalyzed by lipases and microorganisms that contain lipases has been realized as a powerful and practical route to the synthesis of valuable enantioenriched *P*-chiral phosphonates compounds.

Kiełbasinski *et al.*[50] reported the enantioselective transesterification of racemic hydroxymethanephosphinates to an acylated product in 49% yield and 89% *ee* in the presence of lipase from *Pseudomonas fluorescens*, however the reaction must perform in ionic liquids (BMIM•PF_6 solutions). Soon afterwards, they disclosed the acetylation of the same substrates to corresponding acetates in the presence of lipase from *Candida antarctica* in supercritical carbon dioxide (sc-CO_2), which producted enantiopure and acetates in 46% yield and 27% *ee*.[51-52] Lipase from *Pseudomonas cepacia* is also an efficient biocatalyst of the resolution of racemic hydroxymethylphosphinates, resulting in 44% yield and 86% *ee*.[53]

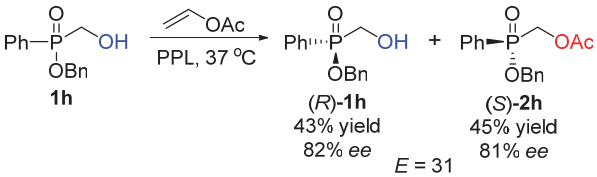
Herein we report the efficient synthesis of *P*-chiral hydroxymethylphosphonates through biocatalytic kinetic resolution (Scheme 1), catalyzed by lipase from porcine pancreas (PPL), which is commercially available and highly efficient, the reactions proceed efficiently with a wide array of reaction partners to deliver various tertiary phosphine oxides under very mild conditions. The aim of our present study was to determine the scope of the above reaction and to gain more data which would allow a general explanation of the stereoselectivity observed to be formulated. In addition, the origin of enantiopreference for PPL was revealed by docking simulations.



Scheme 1 PPL-catalyzed enantioselective acetylation of hydroxymethylphosphonates

2 Results and discussion

The starting substrates racemic *α*-hydroxymethylphosphonates **1** were readily synthesized from known compounds by means of simple and practical methods (supporting information), and the enzyme PPL is commercially available. The reaction was stopped at 50% conversion of **1**, which was determined by ^{31}P NMR. We initiated our study by investigating the biotransformation of *rac*-benzyl (hydroxymethyl)(phenyl)-phosphinate **1h**. As illustrated in Scheme 2, PPL was able to catalyze the transesterification of **1h** to corresponding ester product **2h** under mild conditions (*i.e.*, with vinyl acetate at 37 ℃). The reaction was efficient and complete in 24 h resulting in the acyl transfer product **2h** with 45% yield and 81% *ee*, while unreacted enantiopure alcohol **1h** with 43% yield and 82% *ee* (calculated with respect to its theoretical mass), the enantiomeric ratio *E* is 31. *E* was calculated on the basis of *ee* values, which offered a concise representation of the enantioselective properties of an enzyme in reactions that involve chiral compounds. In order to improve PPL's enantioselectivity toward substrate **1h**, decreasing or elevating reaction temperature was undertaken, resulting in a decrease in enantioselectivity. Beyond this, we also attempted to add organic solvent [such as toluene, benzene and *N*,*N*-dimethylformamide (DMF)] or ionic liquids (such as BMIM•PF_6 and BMIM•BF_4) to the reaction system, but they all ended in failure.



Scheme 2 PPL-catalyzed enantioselective acetylation of **1h**

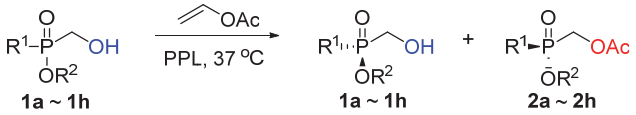
To investigate whether there is any general relationship between the substrate structure, a series of racemates of *α*-hydroxymethyl phosphonates were subjected to biocatalytic reactions. As shown in Table 1, all the substrates have achieved kinetic resolution (except for **1c**), and were transformed into acyl hydroxyethylphosphonates under the

same conditions, resulting in the acyl products **2a**～**2g** in 25%～48% yields and 64%～81% *ee* values (Table 1, Entry 1～7). In general, the catalytic performance of PPL is relevant to the substitution groups on the substrates, the greater the difference in steric hindrance between the two substituents of the substrate, the better the enantioselectivity of the reaction.

For example, the introduction of R^2 substituent group led to slightly slower conversion rate as the steric hindrance of R^2 increases, while the enantioselectivity of the reaction was improved. On the contrary, when replacing the substituent group of R^1 with smaller steric such as benzyl and methyl group, there were practically non-stereoselective (Table 1, Entry 1～3). It is obvious that the steric hindrance of the substituent has a great effect on the rate and enantioselectivity of the reaction from the experimental results.

The above experimental results show that the best substrate for the biotransformation reaction was obtained when the substituents were phenyl and benzyl, respectively. To further explore the biocatalytic efficiency of PPL on the steric and electronic effects of the substrates, a series of substrates that contain benzyl and phenyl were subjected to biocatalytic react ions. Among 11 different substrates, the catalyst did not exhibit strong preference toward specific electronic or steric features, high yields (36%～49%) and medium to good *ee* (33%～83%) were observed, and the position of the substituent on the substrates (*ortho*, *meta* or *para* position of the phenyl group) also has little effect on the reaction (Table 2, Entry 1～3). Substrates with electron withdrawing group such as halides and nitryl (Table 2, Entries 8～11), which can be used as prefunctionalities for further transformations, were accepted by the enzyme. The substrates with electron donating group showed the same reactivity and enantioselectivity (Table 2, Entries 1～7)

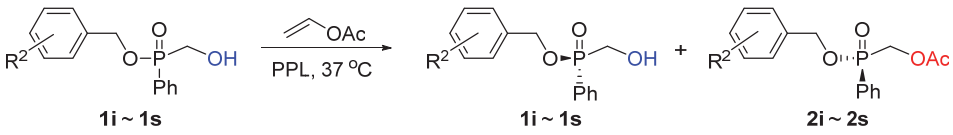
Table 1 PPL-catalyzed enantioselective acetylation of 1-hydroxyalkanephos-phonates [a]



Entry	Substrate	Time/h	R^1	R^2	1		2		E^d
					Yield[b]/%	*ee*[c]/%	Yield[b]/%	*ee*[c]/%	
1	**1a**	22	Ph	Et	38	68	44	64	10
2	**1b**	15	OBn	Et	47	9	43	18	2
3	**1c**	12	OMe	Et	—	—	82	0	—
4	**1d**	18	Ph	Me	45	63	47	74	16
5	**1e**	22	Ph	^{n}Pr	40	77	48	70	14
6	**1f**	96	Ph	^{i}Pr	62	63	25	80	29
7	**1g**	18	Ph	C_6H_{11}	42	80	45	74	18
8	**1h**	24	Ph	Bn	43	82	45	81	31

[a] Substrate (150 mg) was incubated with PPL (150 mg) in 5 mL of vinyl acetate without any organic solvent at 37 ℃. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] *E* is commonly used to characterize the enantioselectivity in enzyme-catalyzed kinetic resolution, the value was calculated according to Ref. [54～55].

Table 2 PPL-catalyzed enantioselective acetylation of 1-hydroxyalkanephos-phonates[a]



Entry	Substrate	Time/h	R^2	1		2		E^d
				Yield[b]/%	*ee*[c]/%	Yield[b]/%	*ee*[c]/%	
1	**1i**	35	2-Me	47	56	42	82	37
2	**1j**	17	3-Me	39	65	42	66	12
3	**1k**	24	4-Me	45	48	36	83	18
4	**1l**	9	4-Et	44	74	46	64	11
5	**1m**	48	4-^{i}Pr	47	30	43	69	9
6	**1n**	48	4-^{t}Bu	46	32	43	64	9
7	**1o**	24	4-Ph	45	67	48	59	7
8	**1p**	12	4-F	34	87	44	70	17
9	**1q**	17	4-Cl	45	7	38	68	3
10	**1r**	12	4-Br	26	91	49	73	17
11	**1s**	15	4-NO_2	32	60	49	59	8

[a] Substrate (150 mg) was incubated with PPL (150 mg) in 5 mL of vinyl acetate without any organic solvent at 37 ℃. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] *E* is commonly used to characterize the enantioselectivity in enzyme-catalyzed kinetic resolution, the value was calculated according to Ref. [54～55].

(except for *p*-Cl substituted substrate **1q**, which showed a lower biocatalytic enantioselectivity).

The absolute configuration of the biotransformation acetate products **2** and the slow reacting alcohols **1** were assigned through the literature in which the absolute configuration of compound **1a** is known.[53] To illustrating the enantioselectivity during enzyme-catalysis chiral separation, molecular dynamic and covalent docking were used to simulate the process. The catalysis pocket of Sus scrofa pancreatic triacylglycerol lipase which was same as PPL involves S153, D177 and H264 amino acid. Firstly, the S153 is acetylation by vinyl acetate. Subsequently, the hydroxy of substrates attacks the carbonyl and forms the carbon tetrahedron intermediate. In the end, the C—O bond is breakage and regains the serine and form the ester product. Considering all the substrates could participate in the reaction, we thought the rate-determining step is the formation of carbon tetrahedron intermediate instead of the diffusion of substrates into enzyme.

It was found that the phenyl in *S*-configuration substrates is vertical to the F216 residue and forms a T-shape π-stack (Figure 2, PPL-*S*). When the substrates are *R*-configuration, the phenyl inserts to the gap formed by A261-H264-F216, which block the entrance of phenyl group of substrate shown in the Figure 2 of PPL-(*R*)-**1h**, resulting in the *S*-**2h** as main product. On account of the orientation, the phenyl in *R*-configuration could not form the π-stack with F216, which results into the higher energy of intermediate and prevents the ester-exchange reaction. The higher (more negative covdock score) are consistence with if exist π-stack or not. The experiment results showed that there were more *S*-configuration products. For the substrates without the phenyl, such as **1c** (OR substrate), the enantioselectivity is almost disappear. For the substrates with benzyloxy but not phenyl, such as **1h** (OBn, OR substrate), the higher enantioselectivity is caused by R257, which could form π-π interaction for both *R*- and *S*-configuration substrates.

3 Conclusions

In conclusion, a versatile and efficient method to produce enantiopure *P*-chiral hydroxymethylphosphonates was demonstrated and its acyl transfer product uses PPL under mild conditions. The origin of enantiopreference of PPL has also been revealed using molecular docking. As a result, this study not only sheds light on the access to valuable chiral building blocks by biocatalysis, but also inspires the insights into kinetic resolution mechanism of PPL to racemic *P*-chiral phosphonates.

4 Experimental section

4.1 General

All the reagents are of analytical purity and used as received without further purification. Solvents were used in per analysis grade for reaction mixtures and industrial grade for chromatography. Anhydrous solvents were obtained following standard procedures. All other comer-

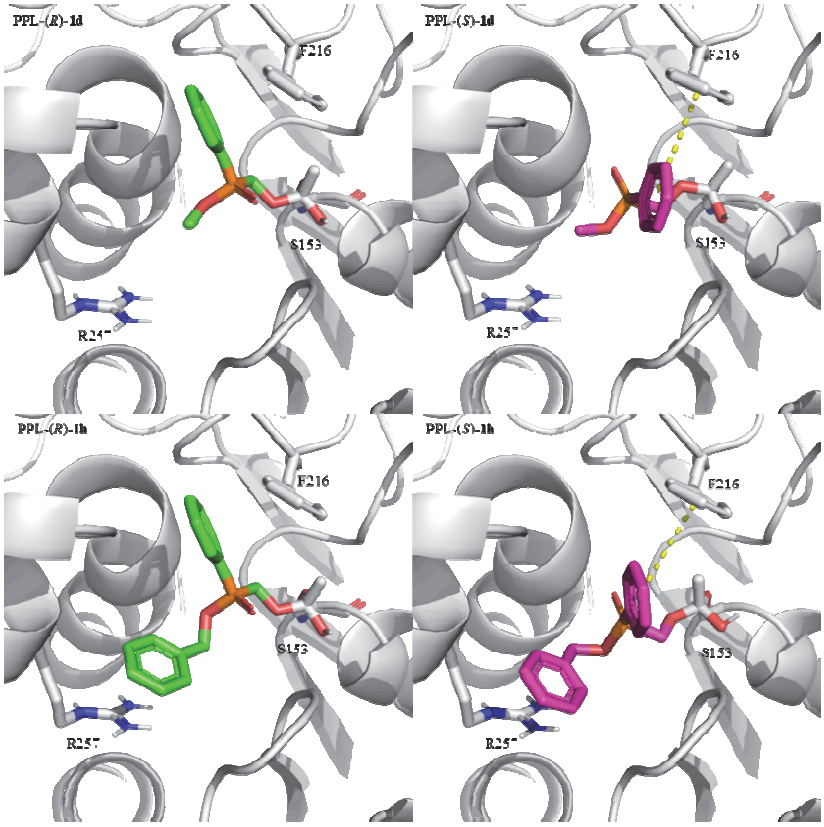


Figure 2 Covalent docking results for PPL with phosphates

cial chemicals were used without further purification.

Thin-layer chromatography (TLC) analysis was performed on pre-coated, glass-backed silica gel plates and visualized with UV light and $KMnO_4$. Column chromatography was performed on silica gel (100～200 mesh). ^1H NMR, ^{31}P NMR and ^{13}C NMR spectra were recorded on 300 MHz, 400 MHz, 500 MHz or 600 MHz NMR spectrometers of Bruker. Chemical shifts are reported with either tetramethylsilane or the residual solvent resonance used as an internal standard. Optical rotations were performed on a Rudolph Autopl VI. ESI mass spectra were determined on a Thermo Fisher Exactive Mass Spectrometer. High performance liquid chromatography (HPLC) was performed on a Shimadzu SCL-20AVP. Infrared spectra were recorded using a Nicolet-6700 FT-IR spectrometer with KBr pellets in the 4000～400 cm^{-1} region. Melting points were determined on a Mettler Toledo MP70 and uncorrected.

4.2 Synthesis of racemic substrates **1**

A dried 250 mL flask was Ar filled (3×) and then charge with corresponding dichlorophosphane (25 mmol) and toluene (18 mL). A solution of alcohol (54 mmol) and pyridine (2.6 mL) in toluene (3.6 mL) was then added dropwise over 30 min. Then the mixture was further stirred at room temperature for several hours, and then let it sit for about a day. The reaction was quenched with saturated sodium bicarbonate solution (100 mL). The mixture was extracted with dichloromethane (100 mL×3), the combined organic phase was washed with saturated salt solution, dried over anhydrous $MgSO_4$ and concentrated, the crude product **S1** was used for the following reaction without purified.

In a 15 mL pressure flask, **S1**, paraformaldehyde and triethylamine were added, and then the mixture was stirred at 100 ℃ for several hours. The reaction process was monitored using TLC method. After a period of time, the reaction was cooled to room temperature. The mixture was chromatographed on a silia gel column using ethyl acetate as the mobile phase to afford *α*-hydroxyphosphonate **1a**～**1s**.

Ethyl (hydroxymethyl)(phenyl)phosphinate (**1a**): Colourless oil (3.25 g, 65%). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 7.96～7.69 (m, 2H), 7.65～7.40 (m, 3H), 4.28～3.86 (m, 4H), 3.02 (brs, 1H), 1.33 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 132.85 (d, *J*=2.1 Hz), 131.99 (d, *J*=9.6 Hz), 128.74 (d, *J*=12.4 Hz), 61.64 (d, *J*=6.6 Hz), 60.32 (d, *J*=114.0 Hz), 16.53 (d, *J*=5.6 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) *δ*: 39.01; IR (KBr) *v*: 3272, 2984, 2902, 1720 cm^{-1}; HRMS (ESI^+) calcd for $C_9H_{14}O_3P$ $[M+H]^+$ 201.0675, found 201.0680.

Benzyl ethyl (hydroxymethyl)phosphonate (**1b**): Colourless oil (4.20g, 73%). ^1H NMR (500 MHz, $CDCl_3$) *δ*: 7.48～7.27 (m, 5H), 5.13 (d, *J*=8.5 Hz, 2H), 4.24～4.00 (m, 2H), 3.91 (d, *J*=5.8 Hz, 2H), 3.45 (brs, 1H), 1.40～1.19 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ*: 136.14 (d, *J*=5.5 Hz), 128.65, 128.57, 128.02, 68.06 (d, *J*=6.7 Hz), 62.81 (d, *J*=7.0 Hz), 57.26 (d, *J*=160.9 Hz), 16.39 (d, *J*=5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) *δ*: 24.75; IR (KBr) *v*: 3307, 3066, 2983, 2904, 1722 cm^{-1}; HRMS (ESI^+) calcd for $C_{10}H_{15}NaO_4P$ $[M+Na]^+$ 253.0600, found 253.0603.

Ethyl methyl (hydroxymethyl)phosphonate (**1c**): Colourless oil (2.16 g, 56%). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 4.26～4.10 (m, 2H), 4.01～3.89 (m, 2H), 3.82 (dd, *J*=10.6, 3.6 Hz, 3H), 2.63 (brs, 1H), 1.44～1.27 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 62.84 (d, *J*=6.8 Hz), 56.82 (d, *J*=161.3 Hz), 53.00 (d, *J*=6.7 Hz), 16.48 (d, *J*=5.5 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) *δ*: 25.37; IR (KBr) *v*: 3309, 2959, 1730, 1447 cm^{-1}; HRMS (ESI^+) calcd for $C_4H_{12}O_4P$ $[M+H]^+$ 155.0468, found 155.0468.

Methyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1d**): Colourless oil (3.16 g, 68%). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 7.98～7.70 (m, 2H), 7.70～7.40 (m, 3H), 4.23～3.94 (m, 2H), 3.75 (d, *J*=10.6 Hz, 3H), 3.67(brs, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 133.00 (d, *J*=2.5 Hz), 132.08 (d, *J*=9.9 Hz), 128.81 (d, *J*=12.5 Hz), 60.03 (d, *J*=114.5 Hz), 51.89 (d, *J*=6.9 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) *δ*: 40.82; IR (KBr) *v*: 3293, 2850, 2311, 1592 cm^{-1}; HRMS (ESI^+) calcd for $C_8H_{12}O_3P$ $[M+H]^+$ 187.0519, found 187.0525.

Propyl (hydroxymethyl)(phenyl)phosphinate (**1e**): Colourless oil (4.01 g, 75% yield). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 7.97～7.70 (m, 2H), 7.65～7.40 (m, 3H), 4.20～3.96 (m, 3H), 3.96～3.77 (m, 1H), 3.71(brs, 1H), 1.69 (p, *J*=7.1 Hz, 2H), 0.93 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 132.83 (d, *J*=2.5 Hz), 131.97 (d, *J*=9.8 Hz), 128.72 (d, *J*=12.4 Hz), 67.07 (d, *J*=7.1 Hz), 60.15 (d, *J*=114.4 Hz), 23.92 (d, *J*=5.9 Hz), 10.05; ^{31}P NMR (121.5 MHz, $CDCl_3$) *δ*: 39.16; IR (KBr) *v*: 3271, 2984, 2900, 1592 cm^{-1}; HRMS (ESI^+) calcd for $C_{10}H_{15}NaO_3P$ $[M+Na]^+$ 237.0651, found 237.0653.

Isopropyl (hydroxymethyl)(phenyl)phosphinate (**1f**): Colourless oil (4.28 g, 80% yield). ^1H NMR (300 MHz, $CDCl_3$) *δ*: 7.93～7.75 (m, 2H), 7.69～7.41 (m, 3H), 4.74～4.54 (m, 1H), 4.17～3.92 (m, 2H), 3.51(brs, 1H), 1.40 (d, *J*=6.1 Hz, 3H), 1.23 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 132.64 (d, *J*=2.7 Hz), 131.94 (d, *J*=9.7 Hz), 129.36 (d, *J*=123.9 Hz), 128.59 (d, *J*=12.6 Hz), 70.79 (d, *J*=7.1 Hz), 60.46 (d, *J*=114.6 Hz), 24.45 (d, *J*=3.3 Hz), 24.09 (d, *J*=4.5 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) *δ*: 37.76; IR (KBr) *v*: 3274, 2979, 2933, 2878, 1439 cm^{-1}; HRMS (ESI^+) calcd for $C_{10}H_{15}NaO_3P$ $[M+Na]^+$ 237.0651, found 237.0655.

Cyclohexyl (hydroxymethyl)(phenyl)phosphinate (**1g**): White solid (5.33 g, 84%), m.p. 125～127 ℃; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 7.94～7.74 (m, 2H), 7.66～7.42 (m, 3H), 4.48～4.25 (m, 1H), 4.16～3.90 (m, 2H), 1.87～1.08 (m, 10H); ^{13}C NMR (126 MHz, Chloroform-*d*) *δ*: 132.62 (d, *J*=2.6 Hz), 131.93 (d, *J*=9.8 Hz), 129.61 (d, *J*=124.2 Hz), 128.59 (d, *J*=12.6 Hz), 75.60 (d, *J*=7.2 Hz), 60.63 (d, *J*=114.2 Hz), 34.01 (dd, *J*=46.3, 3.5 Hz), 25.09, 23.67 (d, *J*=4.2 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) *δ*: 37.53; IR (KBr) *v*: 3275, 2936, 2859, 1592 cm^{-1}; HRMS

(ESI$^+$) calcd for $C_{13}H_{19}NaO_3P$ $[M+Na]^+$ 277.0964, found 277.0971.

Benzyl (hydroxymethyl)(phenyl)phosphinate (**1h**): Colourless oil (4.65 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95～7.78 (m, 2H), 7.60 (dd, J=7.5, 1.4 Hz, 1H), 7.57～7.43 (m, 2H), 7.43～7.31 (m, 5H), 5.18 (dd, J=11.7, 7.1 Hz, 1H), 4.95 (dd, J=11.6, 7.3 Hz, 1H), 4.20～4.07 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 136.06 (d, J=6.1 Hz), 132.95 (d, J=2.5 Hz), 132.03 (d, J=9.7 Hz), 128.80, 128.72, 128.63, 128.52, 128.06, 66.78 (d, J=6.5 Hz), 60.03 (d, J=121.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 39.55; IR (KBr) ν 3335, 3063, 2889, 1743 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{14}H_{15}O_3NaP$ $[M+Na]^+$ 285.0651, found 285.0662.

2-Methylbenzyl (hydroxymethyl)(phenyl)phosphinate (**1i**): White solid (4.69 g, 68%), m.p. 141～143 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93～7.74 (m, 2H), 7.67～7.39 (m, 3H), 7.37～7.05 (m, 4H), 5.19 (dd, J=11.7, 6.5 Hz, 1H), 4.93 (dd, J=11.8, 6.5 Hz, 1H), 4.70 (brs, 1H), 4.23～3.98 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 136.82, 134.17 (d, J=6.6 Hz), 132.80 (d, J=2.8 Hz), 132.00 (d, J=9.9 Hz), 130.37, 128.95, 128.71, 128.63, 128.50 (d, J=122.3 Hz) 126.06, 65.03 (d, J=6.6 Hz), 60.20 (d, J=114.3 Hz), 18.80; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 40.12; IR (KBr) ν: 3278, 3062, 2890, 1438 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{15}H_{17}NaO_3P$ $[M+Na]^+$ 299.0808, found 299.0827.

3-Methylbenzyl (hydroxymethyl)(phenyl)phosphinate (**1j**): White solid (4.28 g, 62%), 137～139 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94～7.74 (m, 2H), 7.66～7.40 (m, 3H), 7.32～7.06 (m, 4H), 5.21～5.01 (m, 1H), 4.98～4.83 (m, 1H), 4.71 (brs, 1H), 4.29～4.00 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 138.28 , 136.01 (d, J=6.4 Hz), 132.81 (d, J=2.7 Hz), 132.07 (d, J=9.9 Hz), 129.21 , 128.83, 128.67 (d, J=12.4 Hz), 128.51 (d, J=123.8 Hz) 128.50, 125.16, 66.80 (d, J=6.7 Hz), 60.24 (d, J=114.0 Hz), 21.33; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 40.10; IR (KBr) ν: 3319, 3058, 2922, 2311, 1738 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{15}H_{17}NaO_3P$ $[M+Na]^+$ 299.0808, found 299.0826.

4-Methylbenzyl (hydroxymethyl)(phenyl)phosphinate (**1k**): Colourless oil (5.45 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83～7.65 (m, 2H), 7.57～7.30 (m, 3H), 7.25～6.96 (m, 4H), 5.10～4.95 (m, 1H), 4.88～4.70 (m, 1H), 4.23 (brs, 1H), 4.12～3.88 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 138.37, 133.12 (d, J=6.2 Hz), 132.79 (d, J=2.5 Hz), 132.05 (d, J=9.9 Hz), 129.28, 128.68 (d, J=12.3 Hz), 128.24, 66.72 (d, J=6.7 Hz), 60.34 (d, J=113.5 Hz), 21.22; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 39.78; IR (KBr) ν: 3298, 3056, 2925, 2318, 1739 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{15}H_{17}NaO_3P$ $[M+Na]^+$ 299.0808, found 299.0825.

4-Ethylbenzyl (hydroxymethyl)(phenyl)phosphinate (**1l**): Colourless oil (5.22 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93～7.78 (m, 2H), 7.66～7.43 (m, 3H), 7.35～7.23 (m, 2H), 7.23～7.10 (m, 2H), 5.14 (dd, J=11.5, 7.1 Hz, 1H), 4.92 (dd, J=11.5, 7.4 Hz, 1H), 4.15～3.99 (m, 2H), 2.78 (brs, 1H), 2.66 (q, J=7.6 Hz, 2H), 1.24 (t, J=7.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 144.80 , 133.27 (d, J=6.2 Hz), 132.85 (d, J=2.6 Hz), 132.05 (d, J=9.9 Hz), 128.71 (d, J=12.4 Hz), 128.34, 128.13, 66.77 (d, J=6.6 Hz), 60.42 (d, J=112.9 Hz), 28.62, 15.54; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 39.39; IR (KBr) ν: 3253, 2963, 230, 2873, 1438 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{16}H_{19}NaO_3P$ $[M+Na]^+$ 313.0964, found 313.0961.

4-Isopropylbenzyl (hydroxymethyl)(phenyl)phosphinate (**1m**): Colourless oil (4.79 g, 63%). ^{1}H NMR (300 MHz, CDCl3) δ: 7.93～7.74 (m, 2H), 7.66～7.55 (m, 1H), 7.55～7.41 (m, 2H), 7.36～7.10 (m, 4H), 5.14 (dd, J=11.5, 7.2 Hz, 1H), 4.92 (dd, J=11.5, 7.2 Hz, 1H), 4.20～4.00 (m, 2H), 2.98～2.83 (m, 1H), 2.14～2.03 (m, 1H), 1.30～1.14 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 149.42, 133.33 (d, J=6.6 Hz), 132.89 (d, J=2.7 Hz), 132.03 (d, J=10.0 Hz), 128.71 (d, J=12.4 Hz), 128.35, 126.70, 66.86 (d, J=6.7 Hz), 62.06～58.65 (m), 33.91, 23.94 (d, J=3.7 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 39.67; IR (KBr) ν: 3271, 3057, 2958, 2872, 1515, 1461 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{17}H_{21}NaO_3P$ $[M+Na]^+$ 327.1121, found 327.1108.

4-(*tert*-Butyl)benzyl (hydroxymethyl)(phenyl)phosphinate (**1n**): Colourless oil (5.41 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90～7.78 (m, 2H), 7.65～7.43 (m, 3H), 7.43～7.21 (m, 5H), 5.15 (dd, J=11.5, 7.1 Hz, 1H), 4.92 (dd, J=11.5, 7.1 Hz, 1H), 4.15～4.00 (m, 2H), 2.96 (brs, 1H), 1.33 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 151.65, 133.01 (d, J=6.5 Hz), 132.85 (d, J=2.6 Hz), 132.06 (d, J=9.9 Hz), 128.70 (d, J=12.6 Hz), 128.05, 125.56, 66.68 (d, J=6.7 Hz), 60.40 (d, J=113.0 Hz), 34.63, 31.29; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 39.43; IR (KBr) ν: 3269, 3059, 2960, 2869, 1515, 1462, 1438 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{18}H_{23}NaO_3P$ $[M+Na]^+$ 341.1277, found 341.1283.

[1,1'-Biphenyl]-4-ylmethyl (hydroxymethyl)(phenyl)-phosphinate (**1o**): Colourless oil (5.49 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96～7.79 (m, 2H), 7.65～7.32 (m, 12H), 5.29～5.14 (m, 1H), 5.08～4.93 (m, 1H), 4.21～4.03 (m, 2H), 2.73 (brs, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 141.03 (d, J=139.6 Hz), 135.04 (d, J=6.5 Hz), 132.93 (d, J=2.7 Hz), 132.05 (d, J=9.9 Hz), 128.82, 128.80, 128.72, 128.60, 128.04, 127.51, 127.37, 127.13, 66.54 (d, J=6.6 Hz), 60.47 (d, J=112.8 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 39.52; IR (KBr) ν: 3238, 2882, 1487, 1439, 1409 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{20}H_{19}NaO_3P$ $[M+Na]^+$ 361.0964, found 361.0958.

4-Fluorobenzyl (hydroxymethyl)(phenyl)phosphinate (**1p**): Colourless oil (3.92 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92～7.71 (m, 2H), 7.67～7.54 (m, 1H), 7.54～7.39 (m, 2H), 7.39～7.24 (m, 2H), 7.12～6.91 (m, 2H), 5.18～4.99 (m, 1H), 4.99～4.78 (m, 1H), 4.33 (brs, 1H), 4.21～3.96 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 162.73 (d, J=247.5 Hz), 132.93 (d, J=2.6 Hz), 131.97 (d, J=9.9 Hz), 130.07 (d, J=8.3 Hz), 128.74 (d, J=12.7 Hz), 127.97, 115.51 (d, J=21.6 Hz), 66.08 (d, J=6.6 Hz),

60.28 (d, J=113.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 40.06; IR (KBr) ν: 3270, 2888, 1604, 1512 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{14}H_{14}FNaO_3P$ $[M+Na]^+$ 303.0557, found 303.0566.

4-Chlorobenzyl (hydroxymethyl)(phenyl)phosphinate (**1q**): Colourless oil (4.65 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91～7.72 (m, 2H), 7.68～7.53 (m, 1H), 7.53～7.40 (m, 2H), 7.40～7.15 (m, 4H), 5.19～5.00 (m, 1H), 4.96～4.82 (m, 1H), 4.77 (brs, 1H), 4.22～3.97 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 134.65 (d, J=5.6 Hz), 134.29, 132.97, 131.97 (d, J=9.4 Hz), 129.36, 128.76 (d, J=12.1 Hz), 128.74 , 65.94 (d, J=6.0 Hz), 60.19 (d, J=114.1 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 40.63; IR (KBr) ν: 3284, 2888, 2324, 1734 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{14}H_{14}ClNaO_3P$ $[M+Na]^+$ 319.0261, found 319.0268.

4-Bromobenzyl (hydroxymethyl)(phenyl)phosphinate (**1r**): Colourless oil (5.18 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94～7.72 (m, 2H), 7.69～7.42 (m, 5H), 7.27～7.15 (m, 2H), 5.11 (dd, J=11.9, 7.2 Hz, 1H), 4.90 (dd, J=11.9, 7.1 Hz, 1H), 4.21～4.00 (m, 2H), 3.57 (brs, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 135.11 (d, J=6.0 Hz), 133.03 (d, J=2.4 Hz), 131.96 (d, J=9.7 Hz), 131.75 , 129.67 , 128.80 (d, J=12.6 Hz), 122.55, 65.98 (d, J=6.5 Hz), 60.38 (d, J=113.0 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 40.12; IR (KBr) ν: 3270, 2888, 1593, 1489 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{14}H_{14}BrNaO_3P$ $[M+Na]^+$ 362.9756, found 362.9763.

4-Nitrobenzyl (hydroxymethyl)(phenyl)phosphinate (**1s**): Colourless oil (5.21 g, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29～8.12 (m, 2H), 7.96～7.74 (m, 2H), 7.72～7.58 (m, 1H), 7.58～7.43 (m, 4H), 5.37～5.17 (m, 1H), 5.15～4.96 (m, 1H), 4.18 (s, 2H), 3.21 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 147.79, 143.33, 133.34, 131.96, 128.98, 128.11, 127.00, 123.81, 65.29, 60.49 (d, J=111.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 40.84; IR (KBr) ν: 3278, 2922, 2852, 1607, 1521 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{14}H_{15}NO_5P$ $[M+H]^+$ 308.0682, found 308.0688.

4.3 The biotransformations of substrates **1** catalyzed by PPL

General procedure for the biotransformations of substrates **1** catalyzed by PPL (150 mg) in an Erlenmeyer flask (20 mL) with a screw cap a suspension of PPL in vinyl acetate (10 mL) was activated at 37 ℃, substrates **1** (150 mg) was added in one portion, and the resulting mixture was incubated at 37 ℃ with orbital shaking (250 r/min). The reaction process was monitored using TLC and ^{31}P NMR method. After a period of time, the reaction was quenched by removing enzyme through filtration. The filtration cake was washed consecutively with dichloromethane (5 mL×3), the combined filtrate was removed under reduced pressure. After then, the residue was purified by silica gel chromatography using ethyl acetate as mobile phase to give product **2** and unreacted **1**. All products were fully characterized by means of spectroscopic data. Enantiomeric excess values were obtained from HPLC analysis using columns coated with chiral stationary phases.

(*S*)-(Ethoxy(phenyl)phosphoryl)methyl acetate (**2a**): Colourless oil (80 mg, 44% yield). $[\alpha]_D^{25}$ −33.02 (*c* 2.01, CH_3OH); *ee*=64%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93～7.71 (m, 2H), 7.66～7.56 (m, 1H), 7.56～7.42 (m, 2H), 4.67～4.38 (m, 2H), 4.28～3.97 (m, 2H), 2.05 (s, 3H), 1.37 (t, J=7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.90 (d, J=7.8 Hz), 133.05 (d, J=2.8 Hz), 132.00 (d, J=10.0 Hz), 128.70 (d, J=12.9 Hz), 128.43 (d, J=132.3), 61.64 (d, J=6.3 Hz), 59.88 (d, J=119.7 Hz), 20.49, 16.50 (d, J=6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 34.10; IR (KBr) ν: 3469, 3059, 2984, 2931, 1753 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{11}H_{15}O_4NaP$ $[M+Na]^+$ 265.0600, found 265.0627.

Ethyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1a**): Colourless oil (57 mg, 38% yield). $[\alpha]_D^{25}$ +7.46 (*c* 1.77, CH_3OH); *ee*=68%.

(*S*)-((Benzyloxy)(ethoxy)phosphoryl)methyl acetate (**2b**): Colourless oil (76 mg, 43% yield). $[\alpha]_D^{25}$ −19.00 (*c* 2.64, CH_3OH); *ee*=18%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49～7.30 (m, 5H), 5.16 (d, J=8.7 Hz, 2H), 4.37 (d, J=8.8 Hz, 2H), 4.28～4.04 (m, 2H), 2.10 (s, 3H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 174.75 , 169.94 (d, J=8.9 Hz), 135.90 (d, J=5.6 Hz), 128.64 (d, J=3.5 Hz), 128.01 , 68.15 (d, J=6.1 Hz), 62.96 (d, J=6.5 Hz), 57.05 (d, J=170.2 Hz), 20.52 (d, J=20.3 Hz), 16.35 (d, J=5.8 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 19.92; IR (KBr) ν: 2984, 2936, 1753, 1498 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{12}H_{17}O_5NaP$ $[M+Na]^+$ 295.0706, found 295.0722.

Benzyl ethyl (*R*)-(hydroxymethyl)phosphonate (**1b**): Colourless oil (71 mg, 47% yield). $[\alpha]_D^{25}$ +15.11 (*c* 1.20, CH_3OH); *ee*=9%.

(Ethoxy(methoxy)phosphoryl)methyl acetate (**2c**): Colourless oil (157 mg, 82% yield), *ee*=0%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.39 (dd, J=8.7, 1.7 Hz, 2H), 4.26～4.14 (m, 2H), 3.82 (dd, J=11.0, 1.7 Hz, 3H), 2.19～2.10 (m, 3H), 1.42～1.29 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.98 (d, J=8.6 Hz), 63.08 (d, J=6.2 Hz), 56.49 (d, J=169.8 Hz), 53.06 (d, J=6.3 Hz), 20.49, 16.40 (d, J=5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.60; IR (KBr) ν: 3481, 2986, 2856, 1753 cm^{-1}; HRMS (ESI$^+$) calcd for $C_6H_{13}O_5NaP$ $[M+Na]^+$ 219.0393, found 219.0398.

(*S*)-(Methoxy(phenyl)phosphoryl)methyl acetate (**2d**): Colourless oil (88 mg, 47% yield). $[\alpha]_D^{25}$ −17.65 (*c* 0.34, CH_3OH); *ee*=74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93～7.75 (m, 2H), 7.72～7.45 (m, 3H), 4.70～4.35 (m, 2H), 3.78 (d, J=11.0 Hz, 3H), 2.06 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.85 (d, J=7.7 Hz), 133.19 (d, J=2.8 Hz), 132.07 (d, J=10.0 Hz), 128.78 (d, J=13.1 Hz), 127.72 (d, J=132.1 Hz), 59.54 (d, J=119.8 Hz), 51.78 (d, J=6.2 Hz), 20.47; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 35.97; IR (KBr) ν: 3470, 3059, 2952, 2850, 1753 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{10}H_{13}O_4NaP$ $[M+Na]^+$ 251.0444, found 251.0455.

Methyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1d**): Colourless oil (68 mg, 45% yield). $[\alpha]_D^{25}$ +6.74 (*c* 0.92, CH_3OH); *ee*=63%.

(*S*)-(Phenyl(propoxy)phosphoryl)methyl acetate (**2e**): Colourless oil (86 mg, 48% yield). $[\alpha]_D^{25}$ −22.41 (*c* 1.99, CH_3OH); *ee*=70%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92～7.76 (m, 2H), 7.68～7.43 (m, 3H), 4.63～4.35 (m, 2H), 4.26～3.98 (m, 2H), 2.05 (s, 3H), 1.36 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.90 (d, *J*=7.8 Hz), 133.03 (d, *J*=2.8 Hz), 132.01 (d, *J*=10.0 Hz), 128.69 (d, *J*=13.0 Hz), 128.5(d, *J*=132.3 Hz) 61.59 (d, *J*=6.4 Hz), 60.39, 59.44, 20.51, 16.51 (d, *J*=6.2 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 34.15; IR (KBr) *v*: 3469, 3059, 2984, 2931, 1752 cm^{-1}; HRMS (ESI^+) calcd for $C_{12}H_{17}O_4NaP$ $[M+Na]^+$ 279.0757, found 279.0767.

Propyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1e**): Colourless oil (60 mg, 40% yield). $[\alpha]_D^{25}$ +11.72 (*c* 1.80, CH_3OH); *ee*=77%.

(*S*)-(Isopropoxy(phenyl)phosphoryl)methyl acetate (**2f**): Colourless oil (45 mg, 25% yield). $[\alpha]_D^{25}$ −22.98 (*c* 1.18, CH_3OH); *ee*=80%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.95～7.72 (m, 2H), 7.66～7.43 (m, 3H), 4.80～4.61 (m, 1H), 4.60～4.32 (m, 2H), 2.04 (s, 3H), 1.41 (d, *J*=6.2 Hz, 3H), 1.28 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.94 (d, *J*=8.1 Hz), 132.88 (d, *J*=2.8 Hz), 131.97 (d, *J*=10.0 Hz), 129.80, 128.58 (d, *J*=13.0 Hz), 70.96 (d, *J*=6.5 Hz), 60.29 (d, *J*=120.0 Hz), 24.28 (dd, *J*=27.9, 4.1 Hz), 20.51; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 32.62; IR (KBr) *v*: 3471, 3060, 2980, 2933, 1753 cm^{-1}; HRMS (ESI^+) calcd for $C_{12}H_{17}O_4NaP$ $[M+Na]^+$ 279.0757, found 279.0778.

Isopropyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1f**): Colourless oil (93 mg, 62% yield). $[\alpha]_D^{25}$ +4.68 (*c* 2.25, CH_3OH); *ee*=63%.

(*S*)-((Cyclohexyloxy)(phenyl)phosphoryl)methyl acetate (**2g**): Colourless oil (79 mg, 45% yield). $[\alpha]_D^{25}$ −28.00 (*c* 0.5, CH_3OH); *ee*=74%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92～7.78 (m, 2H), 7.67～7.46 (m, 3H), 4.62～4.30 (m, 2H), 4.14～3.93 (m, 1H), 2.14～2.04 (m, 3H), 1.90～1.08 (m, 10H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.96 (d, *J*=8.0 Hz), 132.86 (d, *J*=2.8 Hz), 131.97 (d, *J*=8.4 Hz), 129.48 (d, *J*=123.2 Hz), 128.58 (d, *J*=12.6 Hz), 75.71 (d, *J*=6.6 Hz), 60.41 (d, *J*=120.0 Hz), 33.95 (d, *J*=34.8 Hz), 25.08, 23.57 (d, *J*=5.9 Hz), 20.52; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 37.27; IR (KBr) *v*: 3282, 2936, 2859, 1753 cm^{-1}; HRMS (ESI^+) calcd for $C_{15}H_{21}O_4NaP$ $[M+Na]^+$ 319.1070, found 319.1083.

Cyclohexyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1g**): White solid (63 mg, 42% yield), m.p. 125～127 ℃; $[\alpha]_D^{25}$ +3.8 (*c* 0.85, CH_3OH); *ee*=80%.

(*S*)-((Benzyloxy)(phenyl)phosphoryl)methyl acetate (**2h**): Colourless oil (78 mg, 45% yield). $[\alpha]_D^{25}$ −0.51 (*c* 1.395, CH_3OH); *ee*=81%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.95～7.78 (m, 2H), 7.69～7.45 (m, 3H), 7.45～7.31 (m, 5H), 5.27～4.93 (m, 2H), 4.72～4.35 (m, 2H), 2.02 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.84 (d, *J*=7.8 Hz), 135.86 (d, *J*=6.6 Hz), 133.15 (d, *J*=2.8 Hz), 132.03 (d, *J*=10.1 Hz), 128.77, 128.67 (d, *J*=3.1 Hz), 128.63, 128.56, 127.99, 66.74 (d, *J*=6.0 Hz), 59.93 (d, *J*=118.5 Hz), 20.45; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 35.17; IR (KBr) *v*: 3463, 3063, 3034, 2930, 1751 cm^{-1}; HRMS (ESI^+) calcd for $C_{16}H_{18}O_4P$ $[M+H]^+$ 327.0757, found 327.0778.

Benzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1h**): Colourless oil (65 mg, 43% yield). $[\alpha]_D^{25}$ +10.74 (*c* 0.61, CH_3OH); *ee*=82%.

(*S*)-(((2-Methylbenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2i**): Colourless oil (73 mg, 42% yield). $[\alpha]_D^{25}$ −0.23 (*c* 1.75, CH_3OH); *ee*=82%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.95～7.78 (m, 2H), 7.70～7.44 (m, 3H), 7.40～7.11 (m, 4H), 5.22 (dd, *J*=11.8, 6.6 Hz, 1H), 5.03 (dd, *J*=11.8, 7.2 Hz, 1H), 4.70～4.37 (m, 2H), 2.37 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.82 (d, *J*=8.1 Hz), 136.85, 133.89 (d, *J*=6.7 Hz), 133.11 (d, *J*=2.8 Hz), 131.97 (d, *J*=10.0 Hz), 130.43, 128.84 (d, *J*=4.2 Hz), 128.70 (d, *J*=13.1 Hz), 128.34(d, *J*=131.4 Hz) 126.11, 65.06 (d, *J*=6.0 Hz), 59.94 (d, *J*=118.3 Hz), 20.43, 18.80; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 34.82; IR (KBr) *v*: 3475, 3058, 3025, 2929, 1751 cm^{-1}; HRMS (ESI^+) calcd for $C_{17}H_{19}O_4NaP$ $[M+Na]^+$ 341.0913, found 341.0932.

2-Methylbenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1i**): White solid (71 mg, 47% yield); m.p. 141～143 ℃; $[\alpha]_D^{25}$ +10.68 (*c* 1.84, CH_3OH); *ee*=56%.

(*S*)-(((3-Methylbenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2j**): Colourless oil (73 mg, 42% yield). $[\alpha]_D^{25}$ −3.95 (*c* 1.22, CH_3OH); *ee*=66%; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93～7.79 (m, 2H), 7.71～7.57 (m, 1H), 7.57～7.45 (m, 2H), 7.28～7.24 (m, 1H), 7.21～7.11 (m, 3H), 5.15 (dd, *J*=11.6, 7.3 Hz, 1H), 4.98 (dd, *J*=11.6, 7.7 Hz, 1H), 4.59 (dd, *J*=14.3, 7.1 Hz, 1H), 4.47 (dd, *J*=14.3, 5.9 Hz, 1H), 2.37 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.85 (d, *J*=7.8 Hz), 138.35, 135.75 (d, *J*=6.5 Hz), 133.10 (d, *J*=3.0 Hz), 132.04 (d, *J*=10.0 Hz), 129.30, 129.00, 128.76 (d, *J*=2.0 Hz), 128.58 (d, *J*=8.6 Hz), 127.69, 125.10, 77.23, 66.78 (d, *J*=6.1 Hz), 59.98 (d, *J*=118.6 Hz), 20.89 (d, *J*=90.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 34.86; IR (KBr) *v*: 3474, 3058, 2927, 1751 cm^{-1}; HRMS (ESI^+) calcd for $C_{17}H_{19}O_4NaP$ $[M+Na]^+$ 341.0913, found 341.0933.

3-Methylbenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1j**): White solid (59 mg, 39% yield), m.p. 137～139 ℃; $[\alpha]_D^{25}$ +11.03 (*c* 0.73, CH_3OH); *ee*=65%.

(*S*)-(((4-Methylbenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2k**): Colourless oil (62 mg, 36% yield). $[\alpha]_D^{25}$ −3.4 (*c* 0.24, CH_3OH); *ee*=83%; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.97～7.75 (m, 2H), 7.71～7.44 (m, 3H), 7.36～7.12 (m, 4H), 5.23～4.86 (m, 2H), 4.68～4.34 (m, 2H), 2.37 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.85 (d, *J*=7.8 Hz), 138.49, 133.08 (d, *J*=2.8 Hz), 132.85 (d, *J*=6.6 Hz), 132.05 (d, *J*=10.1 Hz), 129.31, 128.69 (d, *J*=13.1 Hz), 128.21, 127.88, 66.76 (d, *J*=5.9 Hz), 59.96 (d, *J*=118.7 Hz), 20.60, 20.84 (d, *J*=117.2 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 34.99; IR

(KBr) ν: 3421, 3056, 2927, 1752, 1618 cm^{-1}; HRMS (ESI^+) calcd for $C_{17}H_{19}O_4NaP$ $[M+Na]^+$ 341.0913, found 341.0930.

4-Methylbenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1k**): Colourless oil (68 mg, 45% yield). $[\alpha]_D^{25}$ +4.24 (*c* 0.43, CH_3OH); *ee*=48%.

(*S*)-(((4-ethylbenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2l**): Colourless oil (79 mg, 46%). $[\alpha]_D^{25}$ −22.05 (*c* 0.71, CH_3OH); *ee*=64%. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.93～7.76 (m, 2H), 7.67～7.44 (m, 3H), 7.38～7.15 (m, 3H), 5.15 (dd, *J*=11.5, 7.3 Hz, 1H), 4.99 (dd, *J*=11.5, 7.7 Hz, 1H), 4.58 (dd, *J*=14.3, 7.1 Hz, 1H), 4.45 (dd, *J*=14.3, 6.0 Hz, 1H), 2.67 (q, *J*=7.6 Hz, 2H), 2.02 (s, 3H), 1.25 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.87 (d, *J*=7.8 Hz), 144.85, 133.09 (d, *J*=3.0 Hz), 133.03, 132.04 (d, *J*=10.0 Hz), 128.69 (d, *J*=12.9 Hz), 128.21 (d, *J*=22.2 Hz), 127.87, 66.78 (d, *J*=6.1 Hz), 59.96 (d, *J*=118.8 Hz), 28.62, 20.45, 15.54; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 34.90; IR (KBr) ν: 3444, 2964, 2931, 1750, 1439 cm^{-1}; HRMS (ESI^+) calcd for $C_{18}H_{21}O_4NaP$ $[M+Na]^+$ 355.1070, found 355.1062.

4-Ethylbenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1l**): Colourless oil (66 mg, 44% yield). $[\alpha]_D^{25}$ −23.22 (*c* 0.46, CH_3OH); *ee*=74%.

(*S*)-(((4-Isopropylbenzyl)oxy)(phenyl)phosphoryl)-methyl acetate (**2m**): Colourless oil (73 mg, 43%). $[\alpha]_D^{25}$ −8.86 (c 0.25, CH_3OH); *ee*=69%. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.92～7.76 (m, 2H), 7.67～7.56 (m, 1H), 7.56～7.43 (m, 2H), 7.32～7.16 (m, 4H), 5.23～4.90 (m, 2H), 4.64～4.36 (m, 2H), 3.01～2.84 (m, 1H), 2.01 (s, 3H), 1.26 (d, *J*=6.9 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.87 (d, *J*=7.9 Hz), 149.46, 133.16 (d, *J*=6.6 Hz), 133.09 (d, *J*=2.8 Hz), 132.04 (d, *J*=10.0 Hz), 128.68 (d, *J*=13.1 Hz), 128.28, 126.70, 66.78 (d, *J*=6.1 Hz), 59.95 (d, *J*=118.8 Hz), 33.91, 23.93, 20.44; ^{31}P NMR (300 MHz, $CDCl_3$) δ: 34.92; IR (KBr) ν: 3435, 2959, 1750, 1653, 1439 cm^{-1}; HRMS (ESI^+) calcd for $C_{19}H_{23}O_4NaP$ $[M+Na]^+$ 369.1226, found 369.1229.

4-Isopropylbenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1m**): Colourless oil (71 mg, 47% yield). $[\alpha]_D^{25}$ +3.68 (*c* 0.48, CH_3OH); *ee*=30%.

(*S*)-(((4-(*tert*-Butyl)benzyl)oxy)(phenyl)phosphoryl)-methyl acetate (**2n**): Colourless oil (73 mg, 43%). $[\alpha]_D^{25}$ −17.22 (*c* 0.41, CH_3OH); *ee*=64%. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.96～7.76 (m, 2H), 7.68～7.57 (m, 1H), 7.57～7.45 (m, 2H), 7.43～7.36 (m, 2H), 7.36～7.29 (m, 2H), 5.29～4.85 (m, 2H), 4.66～4.35 (m, 2H), 2.02 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.87 (d, *J*=7.8 Hz), 151.71, 133.08 (d, *J*=2.8 Hz), 132.80 (d, *J*=6.6 Hz), 132.05 (d, *J*=10.0 Hz), 128.68 (d, *J*=12.9 Hz), 128.31 (d, *J*=131.9 Hz), 127.98, 125.56, 66.67 (d, *J*=6.0 Hz), 59.97 (d, *J*=118.8 Hz), 34.64, 31.29, 20.46; ^{31}P NMR (300 MHz, $CDCl_3$) δ: 34.89; IR (KBr) ν: 3467, 2961, 2869, 1751, 1439 cm^{-1}; HRMS (ESI^+) calcd for $C_{20}H_{25}O_4NaP$ $[M+Na]^+$ 383.1383, found 383.1388.

4-(*tert*-Butyl)benzyl (*R*)-(hydroxymethyl)(phenyl)-phosphinate (**1n**): Colourless oil (69 mg, 46% yield). $[\alpha]_D^{25}$ +6.41 (*c* 0.41, CH_3OH); *ee*=32%.

(*S*)-(([1,1'-Biphenyl]-4-ylmethoxy)(phenyl)phosphoryl)-methyl acetate (**2o**): Colourless oil (81 mg, 48% yield). $[\alpha]_D^{25}$ −15.77 (*c* 0.77, CH_3OH); *ee*=59%. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.94～7.78 (m, 2H), 7.68～7.33 (m, 12H), 5.31～5.00 (m, 2H), 4.71～4.41 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.87 (d, *J*=7.8 Hz), 141.55, 140.54, 134.81 (d, *J*=6.6 Hz), 133.16 (d, *J*=2.8 Hz), 132.05 (d, *J*=10.1 Hz), 128.84, 128.79, 128.70, 128.54, 127.83, 127.54, 127.25 (d, *J*=38.7 Hz), 66.53 (d, *J*=6.0 Hz), 59.97 (d, *J*=118.7 Hz), 20.47; ^{31}P NMR (300 MHz, $CDCl_3$) δ: 35.13; IR (KBr) ν: 3445, 3030, 2929, 1750, 1488, 1438 cm^{-1}; HRMS (ESI^+) calcd for $C_{22}H_{21}O_4NaP$ $[M+Na]^+$ 403.1070, found 403.1062.

[1,1'-biphenyl]-4-ylmethyl (*R*)-(hydroxymethyl)-(phenyl)phosphinate (**1o**): Colourless oil (68 mg, 45% yield). $[\alpha]_D^{25}$ +30.31 (*c* 0.39, CH_3OH); *ee*=67%.

(*S*)-(((4-Fluorobenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2p**): Colourless oil (76 mg, 44% yield). $[\alpha]_D^{25}$ −1.05 (*c* 2.48, CH_3OH); *ee*=70%. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.86～7.66 (m, 2H), 7.63～7.48 (m, 1H), 7.48～7.34 (m, 2H), 7.34～7.23 (m, 2H), 7.11～6.74 (m, 2H), 5.05 (dd, *J*=11.7, 7.8 Hz, 1H), 4.91 (dd, *J*=11.7, 8.0 Hz, 1H), 4.59～4.43 (m, 1H), 4.43～4.29 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.83 (d, *J*=7.7 Hz), 162.80 (d, *J*=247.4 Hz), 133.20 (d, *J*=2.8 Hz), 131.97 (d, *J*=10.2 Hz), 131.72 (dd, *J*=6.4, 3.3 Hz), 130.07 (d, *J*=8.3 Hz), 128.75 (d, *J*=13.0 Hz), 115.59 (d, *J*=21.6 Hz), 66.05 (d, *J*=5.9 Hz), 59.91 (d, *J*=118.4 Hz), 20.45; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 35.12; IR (KBr) ν: 3474, 3060, 2931, 1751, 1604, 1513 cm^{-1}; HRMS (ESI^+) calcd for $C_{16}H_{16}FO_4NaP$ $[M+Na]^+$ 345.0662, found 345.0688.

4-Fluorobenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1p**): Colourless oil (51 mg, 34% yield). $[\alpha]_D^{25}$ +13.1 (*c* 1.59, CH_3OH); *ee*=87%.

(*S*)-(((4-Chlorobenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2q**): Colourless oil (77 mg, 45% yield). $[\alpha]_D^{25}$ −6.92 (*c* 0.80, CH_3OH); *ee*=68%. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.91～7.72 (m, 2H), 7.67～7.56 (m, 1H), 7.56～7.46 (m, 2H), 7.43～7.30 (m, 4H), 5.13 (dd, *J*=11.9, 7.7 Hz, 1H), 4.99 (dd, *J*=11.9, 7.9 Hz, 1H), 4.70～4.56 (m, 1H), 4.56～4.37 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.82 (d, *J*=7.6 Hz), 134.48, 134.38 (d, *J*=6.5 Hz), 133.25 (d, *J*=2.9 Hz), 131.97 (d, *J*=10.1 Hz), 129.37, 128.83, 128.73, 128.09 (d, *J*=131.9 Hz), 65.89 (d, *J*=6.0 Hz), 59.88 (d, *J*=118.3 Hz), 20.45; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 35.29; IR (KBr) ν: 3474, 3058, 2930, 1751, 1600 cm^{-1}; HRMS (ESI^+) calcd for $C_{16}H_{16}ClO_4NaP$ $[M+Na]^+$ 361.0367, found 361.0385.

4-Chlorobenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1q**): Colourless oil (75 mg, 38% yield). $[\alpha]_D^{25}$ +6.83 (*c* 0.62, CH_3OH); *ee*=7%.

(*S*)-(((4-Bromobenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2r**): Colourless oil (83 mg, 49% yield). $[\alpha]_D^{25}$ −8.42 (*c* 2.6, CH_3OH); *ee*=73%. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.91～7.76 (m, 2H), 7.71～7.59 (m, 1H),

7.59～7.44 (m, 4H), 7.34～7.18 (m, 2H), 5.12 (dd, J=11.9, 7.7 Hz, 1H), 4.97 (dd, J=12.0, 7.8 Hz, 1H), 4.67～4.55 (m, 1H), 4.55～4.39 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.82 (d, J=7.7 Hz), 134.89 (d, J=6.5 Hz), 133.26 (d, J=2.8 Hz), 131.97 (d, J=10.1 Hz), 131.79, 129.63, 128.79 (d, J=13.1 Hz), 128.07 (d, J=131.8 Hz), 122.63, 65.91 (d, J=5.9 Hz), 59.87 (d, J=118.3 Hz), 20.46; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 35.28; IR (KBr) ν: 3467, 3059, 2930, 1751, 1593 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{16}H_{17}BrO_4P$ $[M+H]^+$ 383.0042, found 383.0050.

4-Bromobenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1r**): Colourless oil (39 mg, 26% yield). $[\alpha]_D^{25}$ +20.97 (*c* 1.44, CH_3OH); *ee*=91%.

(*S*)-(((4-Nitrobenzyl)oxy)(phenyl)phosphoryl)methyl acetate (**2s**): Colourless oil (84 mg, 49% yield). $[\alpha]_D^{25}$ −4.88 (*c* 2.81, CH_3OH); *ee*=59%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.31～8.13 (m, 2H), 7.96～7.77 (m, 2H), 7.72～7.61 (m, 1H), 7.60～7.47 (m, 4H), 5.26 (dd, J=13.0, 7.7 Hz, 1H), 5.12 (dd, J=13.0, 7.7 Hz, 1H), 4.74～4.61 (m, 1H), 4.59～4.42 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.77 (d, J=7.4 Hz), 147.85, 143.09 (d, J=6.6 Hz), 133.52 (d, J=3.0 Hz), 131.92 (d, J=10.2 Hz), 128.93 (d, J=13.1 Hz), 127.67 (d, J=131.04 Hz), 128.08, 123.85, 65.11 (d, J=5.7 Hz), 59.77 (d, J=118.0 Hz), 20.46; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 36.12; IR (KBr) ν: 3467, 3063, 2931, 1752, 1608 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{16}H_{16}NO_6NaP$ $[M+Na]^+$ 372.0607, found 372.0625.

4-Nitrobenzyl (*R*)-(hydroxymethyl)(phenyl)phosphinate (**1s**): Colourless oil (48 mg, 32% yield); $[\alpha]_D^{25}$ +12.73 (*c* 1.71, CH_3OH); *ee*=60%.

Supporting Information Characterization data, copies of ^{1}H NMR, ^{31}P NMR and ^{13}C NMR spectra, IR spectra and MS spectra, HPLC of compounds **1a**～**1s** and **2a**～**2s**, docking simulations of compounds **1d** and **1h**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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