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FULL PAPER

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Iridium-catalyzed asymmetric hydrogenation of β-ketophosphonates with chiral ferrocenyl P,N,N-ligands

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The asymmetric hydrogenation of β-ketophosphonates with chiral Ir/P,N,N-ligands catalyst has been developed. A series of β-ketophosphonates were hydrogenated, and the corresponding β-hydroxyphosphonates were obtained in high yields with good or excellent enantioselectivities under mild condition.

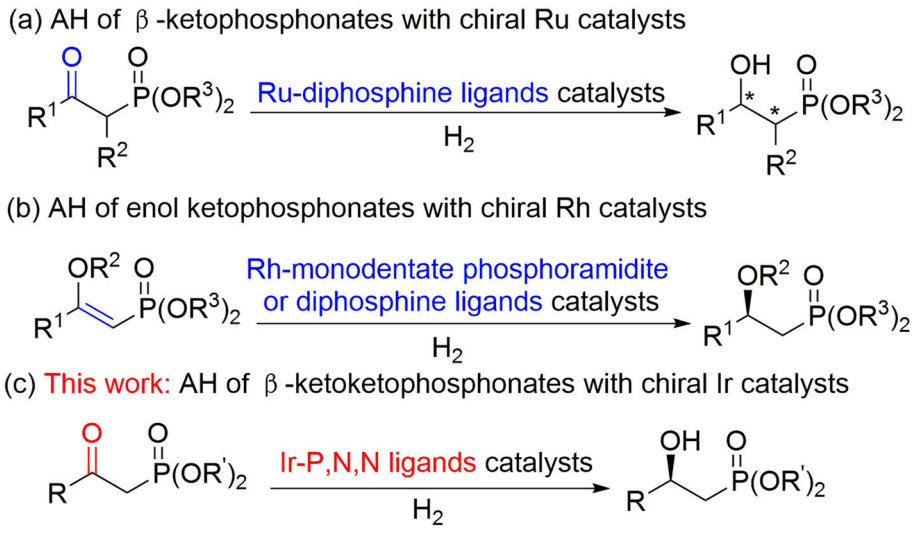
KEYWORDS
asymmetric hydrogenation, iridium, P,N,N-ligands, β-hydroxyphosphonates, β-ketophosphonates

1 | INTRODUCTION

Optical β-hydroxyphosphonates have received much attention in the past decades due to their wide variety of biological applications, such as antibacterial agents, enzyme inhibitors, peptide analogues, and phosphonic acid-based antibiotics.[1] Moreover, these compounds are also useful intermediates for a variety of organophosphorus derivatives, such as β-aminophosphonates.[2] For these reasons, several routes for the synthesis of chiral β-hydroxyphosphonates have been developed,[3] which involved the resolution, asymmetric reduction of the corresponding β-ketophosphonates, asymmetric C–C and C–P bond formation reactions. For instance, they can be prepared by resolution with MPA ((*S*)-methoxyphenylacetic acid)[4] and enzymatic[5] and non-enzymatic[6] kinetic resolutions. The asymmetric reduction of β-ketophosphonates for the preparation of chiral

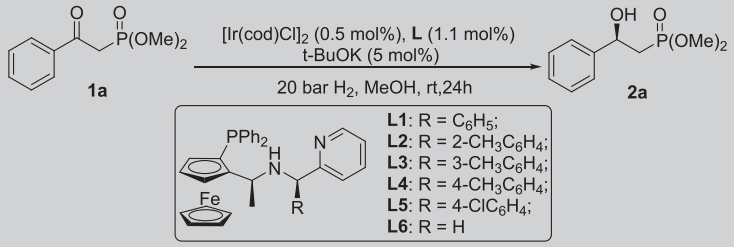
β-hydroxyphosphonates has also been reported with chiral modified metal hydrides[7] or biocatalysts.[8] In addition, the enantiomerically enriched α-substituted β-hydroxyphosphonates derivatives have also been prepared by stereoselective addition[9] of organophosphorous esters with chiral aldehydes or organocatalyzed enantioselective addition[10] of phosphonates with aldehydes.

The asymmetric hydrogenation (AH) has always been one of the most important approach to synthesize many chiral compounds because of its atom economy and inherent efficiency. However, the AH reactions for the synthesis of chiral β-hydroxyphosphonates still remain less explored, and there are very few successful examples reported. In 1995, Noyori et al.[11] reported the first AH of β-ketophosphonates using Ru/BINAP catalysts and applied it to the preparation of fosfomycin (Scheme 1a). Later, Genet et al.[12] explored the AH reactions of β-ketophosphonates and β-ketothiophosphonates using Ru-MeO-Biphep catalysts (Scheme 1a). Zhang et al.[13] reported the AH reactions of α-substituted β-ketothiophosphonates with Ru-SunPhos catalysts (Scheme 1a). In addition, Pizzano et al.[14] reported the AH of enol phosphonates for the synthesis of chiral β-hydroxyphosphonates using Rh/phosphane-phosphite ligands system (Scheme 1b). The Rh complex of chiral



SCHEME 1 Ru, Rh, or Ir-catalyzed AH reactions for the preparation of β-hydroxyphosphonates

TABLE 1 Screening of ligands in asymmetric hydrogenation of **1a**[a]



Entry	Ligand	Conv. (%)[b]	Ee (%)[c]
1	($S_c R_p R_c$)-**L1**	>99	92
2	($S_c R_p R_c$)-**L2**	>99	93
3	($S_c R_p R_c$)-**L3**	>99	95
4	($S_c R_p R_c$)-**L4**	>99	94
5	($S_c R_p R_c$)-**L5**	>99	94
6	($S_c R_p$)-**L6**	16	90

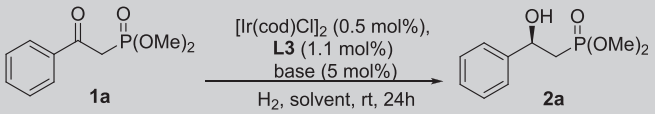
[a]Carried out with 0.5 mol% of [Ir (cod)Cl]$_2$, 1.1 mol% of P,N,N-ligands, and 5 mol% of *t*-BuOK under an H_2 pressure of 20 bar for 24 h at room temperature.
[b]Determined by ^{1}HNMR analysis of crude products.
[c]Determined by HPLC with chiral columns.

monodentate phosphoramidite ligands[15] had also been proved to be efficient for the AH of enol phosphonates (Scheme 1b). Despite these developments, the catalysts used are based on chiral diphosphorus or monophosphorus ligands combined with ruthenium or rhodium as the transition metal. In contrast to chiral ruthenium or rhodium catalysts, there are no reported examples of AH of β-ketophosphonates with chiral iridium catalysts, although the chiral iridium catalysts are most commonly used in the AH of ketones, olefins, and imines.[16] As a result, herein, we report our studies on the iridium-catalyzed AH of β-ketophosphonates, which provides the chiral β-hydroxyphosphonates with excellent enantioselectivities under mild conditions (Scheme 1c).

2 | RESULTS AND DISCUSSION

Recently, our group developed an efficient Ir-catalyzed AH of ketones and β-ketoesters with novel chiral ferrocene-based P,N,N-ligands.[17] More importantly, with the chiral Ir/P,N,N ligand system, a series of α-alkyl-β-aryl-β-ketoesters could be easily hydrogenated, and the corresponding chiral β-hydroxyesters were obtained with excellent enantioselectivity and diastereoselectivity.[18] Encouraged by the previous results, we envisioned that this Ir/P,N,N ligand system should also be suitable for the AH of β-ketophosphonates. Thus, we evaluated the ligands' (**L1**–**L6**) efficiency in the AH of dimethyl (2-oxo-2-phenylethyl) phosphonate (**1a**). The

TABLE 2 Optimization of base, solvent, and hydrogen pressure[a]



Entry	Base	P (bar)	Solvent	Conv. (%)[b]	ee (%)[c]
1	*t*-BuOK	20	MeOH	>99	95
2	*t*-BuONa	20	MeOH	>99	93
3	*t*-BuOLi	20	MeOH	>99	90
4	KOH	20	MeOH	>99	91
5	NaOH	20	MeOH	>99	91
6	K_2CO_3	20	MeOH	>99	90
7	Na_2CO_3	20	MeOH	>99	88
8	*t*-BuOK	20	EtOH	>99	89
9	*t*-BuOK	20	*i*-PrOH	72	84
10	*t*-BuOK	20	Toluene	NR	_
11	*t*-BuOK	20	THF	NR	_
12	*t*-BuOK	20	Et_2O	NR	_
13	*t*-BuOK	20	CH_2Cl_2	NR	_
14	*t*-BuOK	30	MeOH	>99	91
15	*t*-BuOK	40	MeOH	>99	90
16	*t*-BuOK	50	MeOH	>99	90
17[d]	*t*-BuOK	20	MeOH	57	87
18[e]	*t*-BuOK	20	MeOH	21	87
19[f]	*t*-BuOK	20	MeOH	<5	_

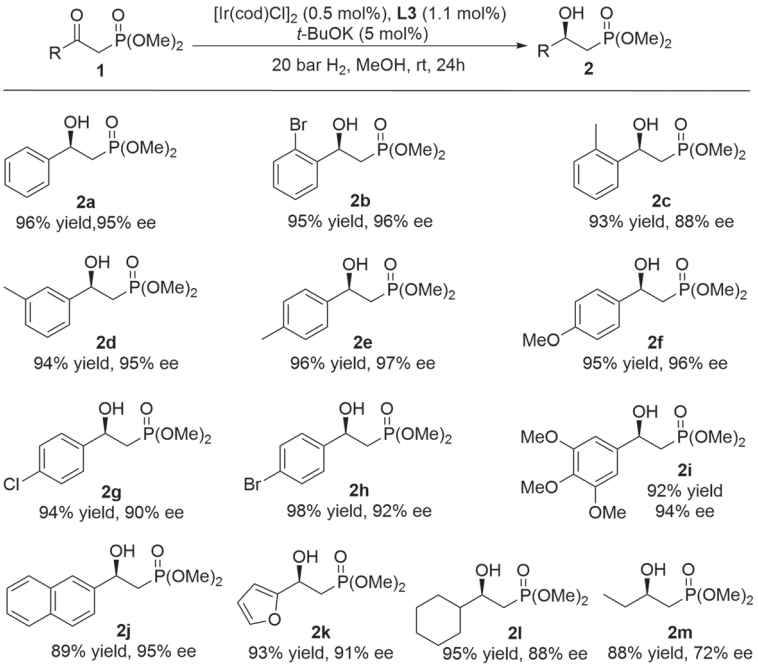
[a]Carried out with 0.5 mol% of [Ir (cod)Cl]$_2$, 1.1 mol% of ligand (S_c,R_p,R_c)-**L3** and 5 mol% of *t*-BuOK at room temperature for 24 h.
[b]Determined by ^{1}HNMR analysis of crude products.
[c]Determined by HPLC with chiral columns.
[d]S/C = 1000.
[e]S/C = 2000.
[f]S/C = 5000.

reactions were carried out in methanol under an H_2 atmosphere of 20 bar with 1.0 mol% iridium catalyst prepared from $[Ir(cod)Cl]_2$ and ligands **L1**–**L6**. To our delight, as shown in Table 1, the Ir/P,N,N ligands catalyst showed good performance and afforded the dimethyl (*R*)-(2-hydroxy-2-phenylethyl)phosphonate (**2a**) with >99% conversion and excellent enantioselectivities (entries 1–5). The ligand (S_c,R_p,R_c)-**L3** with 3-methyl phenyl substituent at pyridinylmethyl position afforded the best result of 95% ee (entry 3). In contrast, ligand (S_c,R_p)-**L6** with one chiral center showed disappointing reactivity (entry 6), which was similar as the AH of ketones and β-ketoesters.[17,18] On the basis of above results, (S_c,R_p, R_c)-**L3** was selected as the ligand for further optimization.

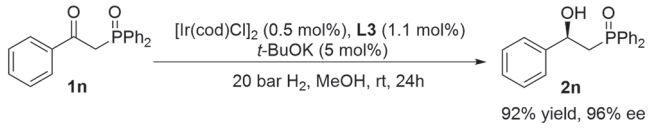
Results of the optimization of base, solvent, and hydrogen pressure were summarized in Table 2. Some bases were first screened for the AH of **1a** with Ir-**L3** catalyst. All the tested bases such as *t*-BuONa, *t*-BuOK, *t*-BuOLi, NaOH, KOH, K_2CO_3, and Na_2CO_3 gave good results (entries 1–7), and *t*-BuOK was selected as the best base with 95% ee (entry 1). The nature of the solvent dramatically affected the hydrogenation (entries 8–13). The alcohol solvent was proved to be suitable solvent, providing complete conversion of **1a** to **2a** with good to excellent enantioselectivities (entries 1, 8–9). Enantioselectivity in MeOH (entry 1) was superior to that in EtOH (entry 8) and *i*-PrOH (entry 9). No reaction occurred when toluene, THF, Et_2O, and CH_2Cl_2 were used as solvents (entries 10–13).[17b,19] The results showed that the ee value was depended on the hydrogen pressure, higher hydrogen pressure decreased the enantioselectivity (entries 1 and 14–16). The conversions and enantioselectivities decreased when the catalyst loading was reduced to 0.1 mol% and less (entries 17–19).

Based on these results, we therefore set the optimized conditions as follows: iridium complex of ligand (S_c,R_p, R_c)-**L3** as the catalyst (1 mol%), *t*-BuOK as the base (5 mol%), MeOH as the solvent and 20 bar H_2 at room temperature for 24 h.

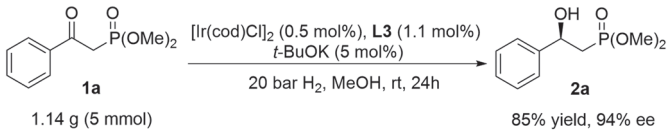
Under the optimized reaction conditions, the substrates' scope of β-ketophosphonates for the AH reaction was investigated, and results were summarized in Scheme 2. It disclosed that a variety of β-ketophosphonates could be hydrogenated smoothly and afforded the chiral β-hydroxyphosphonates with good or excellent enantioselectivities (**2a–m**). For the β-ketophosphonates with an *ortho* substituent on the phenyl ring, the results showed that the ee dropped dramatically for the substrate with electron-donating group (**2c**, 88% ee) than that with an electron-withdrawing group (**2b**, 96% ee). Substrates with different *para* substituents on the phenyl ring were also investigated, and it showed that electron density was important to the enantioselectivity. Higher ee can be obtained for the substrates having electron-donating substituents on the phenyl ring (**2e–f**) than that having electron-withdrawing groups (**2g–h**). Meanwhile, 2-naphthyl substrate also performed well, giving the corresponding hydrogenation product with 95% ee (**2j**). The heteroaryl group was also tolerated and good enantioselectivity (91% ee) was obtained (**2k**). Furthermore, aliphatic substrates **1l** and **1m** also reacted smoothly, affording the corresponding products **2l** and **2m** with good enantioselectivity.



SCHEME 2 Ir-catalyzed AH of β-ketophosphonates **1a–1m**. Isolated yields are given; the ee values are determined by HPLC with chiral columns and the absolute configurations are determined by the comparison of the specific rotations with reported data



SCHEME 3 Ir-catalyzed AH of β-ketophosphine oxide **1n**



SCHEME 4 Gram-scale experiment of **1a**

The β-ketophosphine oxide **1n** can also be hydrogenated with the Ir-**L3** catalyst, giving the corresponding chiral β-hydroxyphosphine oxide **2n** with excellent enantioselectivity (96% ee). In particular, the chiral β-hydroxyphosphine oxides could be converted to optically active β-aminophosphines,[20] which are important scaffolds for the construction of chiral ligands.

To further demonstrate the practicality of the methodology, a scale-up experiment of **1a** was carried out at gram scale. To our delight, the desired product **2a** was obtained with 85% yield and 94% ee without noticeable loss of reactivity and enantioselectivity (Scheme 4).

3 | CONCLUSION

In conclusion, we developed an efficient Ir-catalyzed AH of β-ketophosphonates with chiral ferrocene-based P,N, N-ligands. A wide range of β-ketophosphonates could be hydrogenated and the corresponding β-hydroxyphosphonates were obtained in high yields and with good or excellent enantioselectivities under mild condition. This reaction can provide an important method for the preparation of chiral β-hydroxyphosphonates.

4 | EXPERIMENTAL SECTION

4.1 | General methods

All the experiments were carried out under nitrogen (N_2) atmosphere. The asymmetric hydrogenation (AH) reactions were carried out in glovebox with a stainless-steel autoclave. All the solvents were purified according to standard procedure. The other commercial chemicals were used directly without any further purification. ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker 400 MHz spectrometer. Chemical shifts were reported in δ value (ppm) with tetramethyl silane (TMS) as the internal standard. HPLC analysis was performed using Agilent 1260 series instrument with chiralcel AD-H, chiralpak AS-H, or chiralcel OJ-H column. Copies of NMR spectra and HPLC analysis were given in the supporting information.

4.2 | General procedure for the asymmetric hydrogenation of β-ketophosphonates

In a N_2 filled glovebox, a stainless-steel autoclave was charged with [Ir (COD)Cl]$_2$ (1.7 mg, 0.005 mmol), **L3** (3.2 mg, 0.11 mmol), and dry MeOH (1.0 ml). After the solution was stirred for 1 h at room temperature, the β-ketophosphonates **1** (0.5 mmol), *t*-BuOK (2.8 mg, 0.025 mmol), and MeOH (2.0 ml) were added. The reaction was then performed under an H_2 pressure of 20 bar for 24 h at room temperature. The solvent was removed, and the obtained crude product was then purified by flash chromatography affording the corresponding product β-hydroxyphosphonates.

4.2.1 | Dimethyl (*R*)-(2-hydroxy-2-phenylethyl)phosphonate (2a)

The target compound was obtained as colorless oil in 96% yield and 95% ee. The ee value was determined by HPLC (chiralcel OJ-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 9.8 min, t_R (major) = 10.6 min. $[\alpha]_D^{20} = -16.3$ (c 1.13, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.32 (m, 4H), 7.31–7.26 (m, 1H), 5.17–5.08 (m, 1H), 3.77 (d, J = 11.0 Hz, 3H), 3.72 (d, J = 11.0 Hz, 3H), 2.33–2.13 (m, 2H).

4.2.2 | Dimethyl (*R*)-(2-(2-bromophenyl)-2-hydroxyethyl)phosphonate (2b)

The target compound was obtained as colorless oil in 95% yield and 96% ee. The ee value was determined by HPLC (chiralcel OJ-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 7.1 min, t_R (major) = 8.1 min. $[\alpha]_D^{20} = -53.8$ (c 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.58 (m, 1H), 7.45–7.38 (m, 1H), 7.30–7.23 (m, 1H), 7.09–7.00 (m, 1H), 5.42–5.24 (m, 1H), 4.50 (d, J = 3.1 Hz, 1H), 3.71 (d, J = 11.0 Hz, 3H), 3.65 (d, J = 11.0 Hz, 3H), 2.36–2.20 (m, 1H), 2.04–1.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (d, J = 17.1 Hz), 132.6, 129.0, 127.9, 127.2, 121.1, 67.7 (d, J = 4.8 Hz), 52.7

(d, $J = 6.4$ Hz), 52.6 (d, $J = 6.7$ Hz), 33.2 (d, $J = 136.0$ Hz). HRMS cal. for $C_{10}H_{15}BrO_4P$ ($[M + H]^+$): 308.9891, found: 308.9857.

4.2.3 | Dimethyl (*R*)-(2-hydroxy-2-(*o*-tolyl)ethyl)phosphonate (2c)

The target compound was obtained as colorless oil in 93% yield and 88% ee. The ee value was determined by HPLC (chiralcel OJ-H, 5% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 10.7 min, t_R (major) = 14.1 min. $[\alpha]_D^{20} = -35.0$ (c 1.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, $J = 7.6$ Hz, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.13 (d, $J = 7.4$ Hz, 1H), 5.33 (t, $J = 10.0$ Hz, 1H), 3.80 (d, $J = 11.0$ Hz, 3H), 3.76 (d, $J = 11.0$ Hz, 3H), 3.62 (br, 1H), 2.34 (s, 3H), 2.24–2.07 (m, 2H).

4.2.4 | Dimethyl (*R*)-(2-hydroxy-2-(*m*-tolyl)ethyl)phosphonate (2d)

The target compound was obtained as colorless oil in 94% yield and 95% ee. The ee value was determined by HPLC (chiralcel OJ-H, 5% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 12.7 min, t_R (major) = 13.8 min. $[\alpha]_D^{20} = -15.5$ (c 1.01, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 2H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 7.3$ Hz, 1H), 5.07 (td, $J = 10.2$, 2.8 Hz, 1H), 3.94 (br, 1H), 3.74 (d, $J = 7.2$ Hz, 3H), 3.71 (d, $J = 7.2$ Hz, 3H), 2.34 (s, 3H), 2.31–2.10 (m, 2H).

4.2.5 | Dimethyl (*R*)-(2-hydroxy-2-(*p*-tolyl)ethyl)phosphonate (2e)

The target compound was obtained as colorless oil in 96% yield and 97% ee. The ee value was determined by HPLC (chiralcel OJ-H, 5% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 15.8 min, t_R (major) = 16.2 min. $[\alpha]_D^{20} = -16.6$ (c 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, $J = 8.2$ Hz, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 5.09 (t, $J = 10.2$ Hz, 1H), 3.77 (d, $J = 11.0$ Hz, 3H), 3.73 (d, $J = 11.0$ Hz, 3H), 3.57 (d, $J = 2.5$ Hz, 1H), 2.34 (s, 3H), 2.29–2.12 (m, 2H).

4.2.6 | Dimethyl (*R*)-(2-hydroxy-2-(4-methoxyphenyl)ethyl)phosphonate (2f)

The target compound was obtained as colorless oil in 95% yield and 96% ee. The ee value was determined by HPLC (chiralcel OJ-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 16.8 min, t_R (major) = 17.6 min. $[\alpha]_D^{20} = -10.3$ (c 1.09, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, $J = 8.5$ Hz, 2H), 6.89 (d, $J = 8.5$ Hz, 2H), 5.08 (t, $J = 10.1$ Hz, 1H), 3.80 (s, 3H), 3.77 (d, $J = 11.0$ Hz, 3H), 3.74 (d, $J = 11.0$ Hz, 3H), 3.58 (br, 1H), 2.31–2.11 (m, 2H).

4.2.7 | Dimethyl (*R*)-(2-hydroxy-2-(4-chlorophenyl)ethyl)phosphonate (2g)

The target compound was obtained as colorless oil in 94% yield and 90% ee. The ee value was determined by HPLC (chiralcel OJ-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 9.4 min, t_R (major) = 10.2 min. $[\alpha]_D^{20} = -14.8$ (c 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 4H), 5.10 (t, $J = 10.0$ Hz, 1H), 3.91 (d, $J = 2.3$ Hz, 1H), 3.77 (d, $J = 11.0$ Hz, 3H), 3.73 (d, $J = 11.0$ Hz, 3H), 2.25–2.10 (m, 2H).

4.2.8 | Dimethyl (*R*)-(2-hydroxy-2-(4-bromophenyl)ethyl)phosphonate (2h)

The target compound was obtained as colorless oil in 98% yield and 92% ee. The ee value was determined by HPLC (chiralcel OJ-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 10.2 min, t_R (major) = 11.2 min. $[\alpha]_D^{20} = -13.6$ (c 1.01, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.6$ Hz, 2H), 5.09 (t, $J = 9.1$ Hz, 1H), 3.93 (br, 1H), 3.79 (d, $J = 10.8$ Hz, 3H), 3.74 (d, $J = 10.8$ Hz, 3H), 2.30–2.08 (m, 2H).

4.2.9 | Dimethyl (*R*)-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl) phosphonate (2i)

The target compound was obtained as colorless oil in 92% yield and 94% ee. The ee value was determined by HPLC (chiralcel OJ-H, 15% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 12.2 min, t_R (major) = 13.6 min. $[\alpha]_D^{20} = -14.2$ (c 1.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 2H), 5.11–5.01 (m, 1H), 3.87 (s, 6H), 3.79 (dd, $J = 21.0$, 9.8 Hz, 9H), 2.31–2.11 (m, 2H).

4.2.10 | Dimethyl (*R*)-(2-hydroxy-2-(naphthalen-2-yl)ethyl)phosphonate (2j)

The target compound was obtained as colorless oil in 89% yield and 95% ee. The ee value was determined by HPLC

(chiralpak AS-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 21.9 min, t_R (major) = 24.0 min. $[\alpha]_D^{20} = -11.5$ (c 1.02, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.65 (m, 4H), 7.46–7.29 (m, 3H), 5.19 (td, J = 10.4, 2.9 Hz, 1H), 4.08 (br, 1H), 3.63 (t, J = 10.4 Hz, 6H), 2.32–2.11 (m, 2H).

4.2.11 | Dimethyl (*R*)-(2-(furan-2-yl)-2-hydroxyethyl)phosphonate (2k)

The target compound was obtained as colorless oil in 93% yield and 91% ee. The ee value was determined by HPLC (chiralpak OJ-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 23.6 min, t_R (major) = 24.4 min. $[\alpha]_D^{20} = -8.8$ (c 1.11, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.31 (d, J = 10.9 Hz, 2H), 5.19–5.03 (m, 1H), 4.39 (br, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 2.49–2.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2 (d, J = 17.0 Hz), 142.2, 110.3, 106.2, 62.8 (d, J = 4.1 Hz), 52.7 (d, J = 6.3 Hz), 52.5 (d, J = 6.6 Hz), 31.5 (d, J = 139.6 Hz). HRMS cal. for $C_8H_{13}NaO_5P$ ($[M + Na]^+$): 243.0367, found: 243.0365.

4.2.12 | Dimethyl (*R*)-(2-cyclohexyl-2-hydroxyethyl)phosphonate (2l)

The target compound was obtained as colorless oil in 95% yield and 88% ee. The ee value was determined after converting to the corresponding *p*-nitrobenzoyl derivative by HPLC (chiralcel AD-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (major) = 18.0 min, t_R (minor) = 20.1 min. $[\alpha]_D^{20} = -9.8$ (c 1.03, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (d, J = 2.6 Hz, 3H), 3.74 (d, J = 2.6 Hz, 3H), 3.10 (s, 1H), 2.04–1.80 (m, 3H), 1.79–1.71 (m, 2H), 1.70–1.60 (m, 2H), 1.44–1.32 (m, 1H), 1.30–1.12 (m, 3H), 1.10–0.95 (m, 2H).

4.2.13 | Dimethyl (*R*)-(2-hydroxybutyl) phosphonate (2m)

The target compound was obtained as colorless oil in 88% yield and 72% ee. The ee value was determined after converting to the corresponding *p*-nitrobenzoyl derivative by HPLC (chiralcel AD-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 20.1 min, t_R (major) = 21.6 min. $[\alpha]_D^{20} = -14.7$ (c 1.12, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 4.01–3.92 (m, 1H), 3.82 (d, J = 4.4 Hz, 3H), 3.79 (d, J = 4.5 Hz, 3H), 2.53 (br, 1H), 2.06–1.89 (m, 2H), 1.69–1.51 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H).

4.2.14 | (*R*)-(2-Hydroxy-2-phenylethyl) diphenylphosphine oxide (2n)

The target compound was obtained as colorless oil in 92% yield and 96% ee. The ee value was determined by HPLC (chiralpak AD-H, 10% *i*-PrOH/*n*-hexane, 0.8 ml/min, 40°C, 210 nm): t_R (minor) = 32.9 min, t_R (major) = 35.0 min. $[\alpha]_D^{20} = -15.9$ (c 1.10, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.78 (m, 2H), 7.78–7.68 (m, 2H), 7.65–7.50 (m, 4H), 7.50–7.44 (m, 2H), 7.39–7.29 (m, 4H), 7.28–7.23 (m, 1H), 5.18 (t, J = 8.0 Hz, 1H), 5.03 (s, 1H), 2.86–2.72 (m, 1H), 2.66–2.55 (m, 1H).

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AUTHOR CONTRIBUTIONS

Yin-Feng Ma: Data curation; investigation; methodology. **Chuan-Jin Hou:** Conceptualization; supervision. **De-Quan wei:** Data curation; investigation; methodology; validation. **Ting-Ting Chu:** Formal analysis; supervision. **Xiu-Shuai Chen:** Data curation; investigation; methodology; validation. **Xiang-Ping Hu:** Conceptualization; supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

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