Tetrahedron: *Asymmetry* 26 (2015) 617–622

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric hydrogenation of α-keto phosphonates with chiral phosphine–phosphoramidite ligands

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ARTICLE INFO

Article history:
Received 12 March 2015
Accepted 8 May 2015
Available online 23 May 2015

ABSTRACT

Rh-catalyzed asymmetric hydrogenation of challenging α-keto phosphonates has been developed. With a new chiral phosphine–phosphoramidite ligand, a wide range of α-keto phosphonates were hydrogenated to afford the corresponding (*R*)-α-hydroxy phosphonates with moderate to good enantioselectivities (up to 87% ee).

1. Introduction

Optically active α-hydroxy phosphonic acids and phosphonates are an important class of compounds with intriguing biological activities, which have gained widespread applications in biological and pharmaceutical industries.[1] They have also served as convenient precursors for a variety of biologically significant chiral phosphonate derivatives, in particular, chiral α-amino phosphonates. Thus, much effort has been directed toward the development of the synthesis of chiral α-hydroxy phosphonates.[2] Among the numerous methods developed, the hydrophosphorylation of carbonyl compounds with phosphites (also known as the Pudovik reaction) is best elaborated.[3] Some other approaches include enzyme-catalyzed kinetic resolutions,[4] asymmetric reductions with catecholborane in the presence of chiral oxazaborolidine catalysts,[5] stereoselective hydroxylations of dialkyl benzylphosphonates,[6] Ru-catalyzed asymmetric transfer hydrogenations of acyl phosphonates,[7] and copper-catalyzed asymmetric O–H insertion of α-diazo phosphonates with alcohols using chiral spiro bisoxazoline ligands.[8] However, most of these methods require relatively high catalyst loadings and/or extended reaction times to obtain acceptable yields. Therefore, the development of a highly efficient catalytic system to synthesize chiral α-hydroxy phosphonates is still highly desirable.

Asymmetric hydrogenation has proven to be one of the most direct and convenient approaches to obtain a wide range of chiral compounds due to its inherent efficiency and atom economy. Over the past few decades, the asymmetric hydrogenation of β-keto phosphonates[9] and α-[10] or β-keto esters[11] with chiral Ru and Rh catalysts has achieved great success. However, the asymmetric hydrogenation of α-keto phosphonates remained scarsely explored probably due to the lability of α-keto phosphonates in the presence of some transition-metal complexes. Only one example was reported by Goulioukina et al.,[12] in which a $Pd(OCOCF_3)_2$/(*R*)-MeO-BIPHEP catalyst was applied to the asymmetric hydrogenation of diisopropyl α-keto phosphonates. However, very low to moderate enantioselectivities (33–55% ee) were obtained. On the basis of our research in developing chiral phosphine–phosphoramidite ligands[13] for asymmetric catalysis,[14] we herein report the first Rh-catalyzed asymmetric hydrogenation of α-keto phosphonates with chiral phosphine–phosphoramidite ligands, in which high yields and moderate to good enantioselectivities (up to 87% ee) were obtained.

2. Results and discussion

Chiral phosphine–phosphoramidite ligands have the advantages of easy accessibility, modularity, and stability toward air and moisture, which make them highly attractive for both academic and practical applications. These ligands have been found to be very useful in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins. We then decided to examine the efficiency of chiral phosphine–phosphoramidite ligands **1a–c** (Table 1) in the Rh-catalyzed asymmetric hydrogenation of α-keto phosphonates, a class of challenging substrates. Dimethyl benzoylphosphonate **2a** was selected as the model substrate for the screening process and the results are summarized in Table 1. The initial hydrogenation was carried out in the presence of 1 mol% of catalyst prepared in situ from $[Rh(COD)_2BF_4]$ and 1.1 equiv of chiral ligands under a H_2 pressure of 30 bar at room temperature

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http://dx.doi.org/10.1016/j.tetasy.2015.05.007
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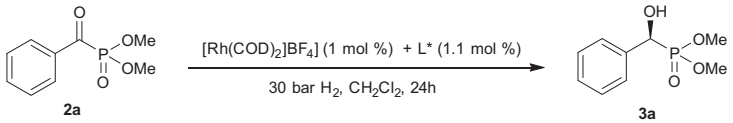
Table 1
Asymmetric hydrogenation of dimethyl benzoylphosphonate **2a** with ligands **1a–c** and monophos-**a–b**[a]



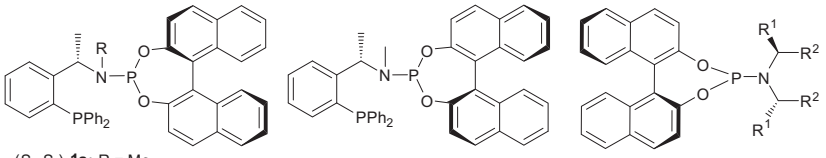
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	(S_c,S_a)-**1a**	92	81
2	(*S*)-Monophos-**a**	—[d]	—[e]
3	(*S*,*S*,*S*)-Monophos-**b**	—[d]	—[e]
4	(S_c,R_a)-**1b**	90	60
5	(S_c,S_a)-**1c**	91	59

[a] Hydrogenation was carried out with 0.5 mmol of substrate and 1.0 mol % of [Rh(COD)$_2$BF$_4$] and 1.1 mol % of chiral phosphine–phosphoramidite ligands in 2 mL CH_2Cl_2, 30 bar of H_2, at rt for 24 h.
[b] Yields of isolated product.
[c] Enantiomeric excesses were determined by HPLC using a chiral stationary phase.
[d] No reaction occurred by TLC.
[e] Not determined due to low conversion.

for 24 h. Ligand (S_c,S_a)-**1a** displayed a promising performance in this transformation, affording (*S*)-dimethyl (hydroxy(phenyl) methyl)phosphonate **3a** in 92% yield and with 81% ee (entry 1). In sharp contrast, the reaction did not occur when phosphoramidite ligands (*S*)-monophos-**a** and (*S*,*S*,*S*)-monophos-**b** were employed (entries 2 and 3). Meanwhile, (S_c,R_a)-**1b** with an (R_a)-axial chirality gave a low enantioselectivity of 60% ee (entry 4). These results indicated that the configuration of the two stereocenters in the phosphine–phosphoramidite ligands strongly influenced the enantioselectivity of the reaction and the matched ligand bearing (S_c)-central and (S_a)-axial configurations, which was in accordance with the results obtained in the asymmetric hydrogenation of olefins.[14] Ligand (S_c,S_a)-**1c** with a N–H proton on the amine unit showed poor performance, and gave lower enantioselectivity of 59% ee (entry 5). We concluded that the increased steric hindrance on the amine unit of the ligands may be crucial to achieve high stereocontrol in the hydrogenation of α-keto phosphonates. Thus new *N*-substituted phosphine–phosphoramidite ligands (R_c,R_a)-**1d–e** were prepared and subjected to this challenging hydrogenation reaction.

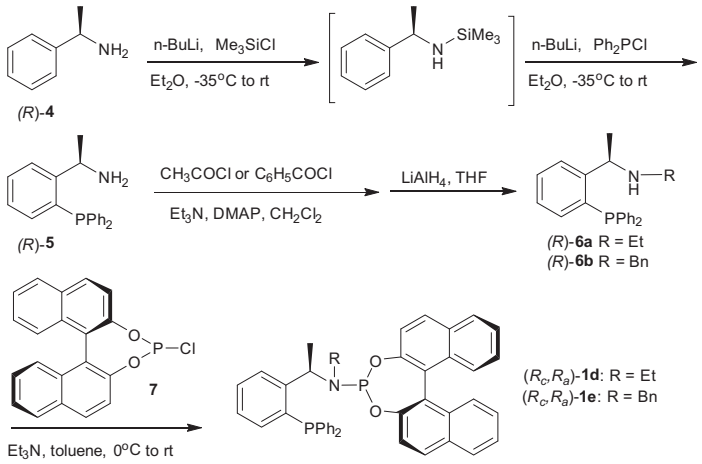
With these newly developed ligands (R_c,R_a)-**1d–e** in hand, we next investigated their efficiency in the hydrogenation of **2a**; the results are summarized in Table 2. As expected, ligand (R_c,R_a)-**1d** with an ethyl group on the amino moiety provided a good enantioselectivity of 87% ee (entry 1). However, ligand (R_c,R_a)-**1e** with a more sterically hindered benzyl group on the amino moiety did not increase the enantioselectivity (entry 2). The solvent effect was next investigated with ligand (R_c,R_a)-**1d**, and an obviously solvent dependency was observed. Results suggested that CH_2Cl_2 was the best choice while other solvents such as toluene, THF, MeOH, or EtOAc showed very low yield or ee value (entries 3–6).

Under the optimal reaction conditions, the scope of α-keto phosphonates for this hydrogenation was investigated, and the results are shown in Table 3. Results disclosed that the ester functional group had an important influence on the enantioselectivity. Although the change from a methyl ester **2a** to an ethyl ester **2b** showed the same enantioselectivities (entries 1 and 2), the introduction of a bulkier *i*-Pr ester functional group resulted in a greatly decreased enantioselectivity (entry 3). Thus a variety of dimethyl



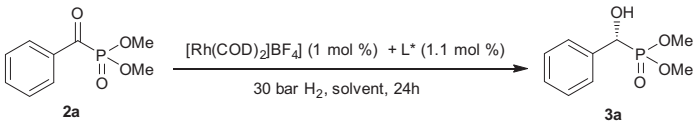
The phosphine–phosphoramidite ligands (R_c,R_a)-**1d–e** were prepared from commercially (*R*)-α-phenylethylamine (Scheme 1). Thus (*R*)-α-phenylethylamine **4** was treated successively with *n*-BuLi, TMSCl and Ph_2PCl to give diphenylphosphino-amine (*R*)–5. The resulting compound (*R*)-**5** can be ethylated or benzylated to give the corresponding (*R*)-**6a** and (*R*)-**6b**, which in turn can be easily converted to the desired phosphine–phosphoramidite ligands (R_c,R_a)-**1d–e**. Similar to the parent ligand **1a**, these new ligands (R_c,R_a)-**1d–e** also showed excellent stability toward air and moisture, and tolerance of various hydrogenation conditions.

α-keto phosphonates **2** were hydrogenated to afford the corresponding dimethyl (*R*)-α-hydroxy phosphonate **3** in good yields and enantioselectivities. All substrates with both electron-donating and -withdrawing groups at the *para*- or *meta*-position of the phenyl ring showed satisfactory enantioselectivities (entries 4–8). Furthermore, for alkyl substrate **2i**, a dramatic decrease in enantioselectivity (50% ee) was observed (entry 9). These results demonstrated that the present catalytic system was highly efficient for the asymmetric hydrogenation of a broad range of challenging α-keto phosphonate substrates.



Scheme 1. Synthesis of phosphine–phosphoramidite ligands (R_c,R_a)-**1d**–**e**.

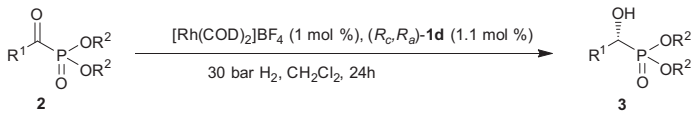
Table 2
Asymmetric hydrogenation of dimethyl benzoylphosphonate **2a** with ligands **1d**–**e**[a]



Entry	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	(R_c,R_a)-**1d**	CH_2Cl_2	93	87
2	(R_c,R_a)-**1e**	CH_2Cl_2	90	80
3	(R_c,R_a)-**1d**	Toluene	—[d]	—[e]
4	(R_c,R_a)-**1d**	THF	—[d]	—[e]
5	(R_c,R_a)-**1d**	MeOH	—[d]	—[e]
6	(R_c,R_a)-**1d**	EtOAc	65	62

[a] Hydrogenation was carried out with 0.5 mmol of substrate and 1.0 mol% of $[Rh(COD)_2BF_4]$ and 1.1 mol % of chiral phosphine–phosphoramidite ligands in 2 mL solvent, 30 bar of H_2, at rt for 24 h.
[b] Yields of isolated product.
[c] Enantiomeric excesses were determined by HPLC using a chiral stationary phase.
[d] Trace reaction occurred by TLC.
[e] Not determined due to low conversion.

Table 3
Asymmetric hydrogenation of α-keto phosphonates **2**[a]



Entry	Substrate	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	**2a**	C_6H_5	Me	93	87 (*R*)
2	**2b**	C_6H_5	Et	92	87 (*R*)
3	**2c**	C_6H_5	^{i}Pr	94	80 (*R*)
4	**2d**	4-ClC_6H_4	Me	91	80 (*R*)
5	**2e**	4-$OMeC_6H_4$	Me	95	83 (*R*)
6	**2f**	4-MeC_6H_4	Me	93	85 (*R*)
7	**2g**	3-MeC_6H_4	Me	93	85 (*R*)
8	**2h**	3,4-$OMeC_6H_3$	Me	90	83 (*R*)
9	**2i**	Me	Me	92	50 (*R*)

[a] Hydrogenation was carried out with 0.5 mmol of substrates and 1.0 mol % of $[Rh(COD)_2BF_4]$ and 1.1 mol % of chiral phosphine–phosphoramidite ligand in 2 mL CH_2Cl_2, 30 bar of H_2, at rt for 24 h.
[b] Yields of isolated product.
[c] Enantiomeric excesses were determined by HPLC using a chiral stationary phase and the absolute configuration was determined by comparison of the sign of the specific rotation with the reported data.

3. Conclusion

In conclusion, we have developed novel and easily prepared chiral phosphine–phosphoramidite ligands that provided the first example of highly efficient Rh-catalyzed asymmetric hydrogenations of challenging α-keto phosphonate substrates. Results suggest that the substituents on the amine moiety of the ligand are crucial for this hydrogenation to obtain high enantioselectivity. Under the optimized conditions, a wide range of aryl α-keto phosphonates, which bear substituted groups such as methyl, methoxyl, and chloro at the *meta*- and *para*-positions of phenyl ring, as well as alkyl α-keto phosphonates, all worked well to afford the corresponding α-hydroxy phosphonates with moderate to good enantioselectivities. Further work on the hydrogenation of α-keto phosphonates with higher ee values and broader substrate scope is currently in progress.

4. Experimental

4.1. General

All reactions were carried out under a nitrogen atmosphere. Hydrogenation reactions were carried out in glove-box by use of a stainless steel autoclave. Solvents were purified by standard procedure before use. Commercial reagents were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are expressed in δ value (ppm) using tetramethylsilane (TMS) as an internal standard. HPLC analysis was performed on an Agilent 1100 series instrument with a chiralpak AS-H or chiralcel OD-H column. Optical rotations were recorded on a JASCO P-1020 polarimeter. The absolute configurations of the products were determined by comparing specific rotations with the reported data. The phosphine–phosphoramidite ligands **1a–c**[14c] and α-keto phosphonates **2**[12,15] were prepared according to the literature method.

4.2. General procedure for the preparation of chiral phosphine–phosphoramidite ligands

4.2.1. Synthesis of (*R*)-1-(2-(diphenylphosphino)phenyl) ethanamine 5[14c]

To a solution of (*R*)-α-phenylethylamine **4** (1.21 g, 10.0 mmol) in dry ether (10 mL) at −35 °C was added dropwise *n*-BuLi (4.0 mL, 2.5 M in hexane, 10.0 mmol). The resulting solution was stirred at −35 °C for 15 min, after which TMSCl (1.39 mL, 11.0 mmol) was added slowly at the same temperature. The reaction mixture was stirred for 1 h and then *n*-BuLi (12 mL, 2.5 M in hexane, 30.0 mmol) was added dropwise. After the addition was completed, the reaction mixture was stirred at −35 °C for 3 h. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction mixture was cooled at −35 °C again, and a solution of chlorodiphenylphosphine (1.8 mL, 10.0 mmol) in ether (10 mL) was added dropwise over 1 h. The reaction mixture was then stirred for another 3 h at the same temperature, and then warmed to room temperature. After stirring for another 4 h, a solution of 1 M HCl was added slowly until the reaction mixture became clear in both phases. The aqueous phase was extracted with ether. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83–7.59 (m, 14H), 4.90 (m, 1H), 1.38 (s, 2H), 1.23 (d, J = 6.8 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −16.3.

4.2.2. Synthesis of (*R*)-1-(2-(diphenylphosphino)phenyl)-*N*-ethylethanamine 6a and (*R*)-*N*-benzyl-1-(2-(diphenylphosphino)-phenyl)ethanamine 6b

To a stirred solution of (*R*)-**5** (1.53 g, 10 mmol), Et_3N (4.2 mL, 30 mmol) and DMAP (0.24 g, 2 mmol) in CH_2Cl_2 was added dropwise acetyl chloride (0.85 mL, 12 mmol) or benzoyl chloride (1.38 mL, 12 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature, and then 5% $NaHCO_3$ aqueous solution was added. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product, which was used directly for the next step.

In a 100 mL freshly oven-dried three-neck flash containing $LiAlH_4$ (0.46 g, 12 mmol) in THF (10 mL) was added a solution of the above crude product in THF (10 mL) under a nitrogen atmosphere. The reaction mixture was refluxed for 5 h, and then cooled to 0 °C, after which 10% aqueous KOH was added slowly. The reaction mixture was filtered and the solid was washed with THF. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography.

6a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.54 (m, 1H), 7.36–7.25 (m, 11H), 7.17–7.09 (m, 1H), 6.90–6.83 (m, 1H), 4.69–4.57 (m, 1H), 2.40–2.25 (m, 2H), 1.21 (d, J = 5.9 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −16.99; ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 23.4, 41.9, 54.8, 126.0, 126.9, 128.5, 128.6, 128.7, 129.4, 133.5, 133.9, 134.0, 134.2, 135.1, 136.8, 137.1, 150.3; HRMS calcd for $C_{22}H_{25}NP$ $(M+H)^+$: 334.1725, found: 334.1738.

6b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.69 (m, 1H), 7.43–7.38 (m, 1H), 7.37–7.12 (m, 16H), 6.95–6.84 (m, 1H), 4.84–4.64 (m, 1H), 3.54–3.36 (m, 2H), 1.63 (br, 1H), 1.30–1.21 (m, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −17.35; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 51.7, 54.9, 126.0, 126.7, 126.9, 128.0, 128.2, 128.4, 128.5, 128.6, 128.7, 129.5, 133.5, 133.8, 134.0, 134.2, 135.1, 136.7, 137.1, 140.9, 150.1; HRMS calcd for $C_{27}H_{27}NP$ $(M+H)^+$: 396.1881, found: 396.1884.

4.2.3. Synthesis of chiral phosphine–phosphoramidite ligands 1d–e

To a stirred solution of (R_a)-chlorophosphite **7** (0.35 g, 1.0 mmol) in dried toluene (4.0 mL) at 0 °C was added dropwise a solution of (*R*)-**6a** (0.33 g, 1 mmol) or (*R*)-**6b** (0.40 g, 1.0 mmol) and Et_3N (0.42 mL, 3.0 mmol) in dried toluene (4.0 mL) within 30 min. The resulting mixture was stirred overnight at room temperature. The precipitate was filtered, and the solid was washed with toluene. The filtrate was collected, and concentrated under reduced pressure to give a crude product, which was further purified by column chromatography.

1d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.01 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.64–7.56 (m, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.43–7.26 (m, 15H), 7.22–7.16 (m, 3H), 7.06–6.97 (m, 1H), 5.68–5.39 (m, 1H), 2.77–2.58 (m, 1H), 2.11–1.93 (m, 1H), 1.66–1.55 (m, 3H), 0.79-0.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.7, 39.5, 54.0, 122.1, 122.5, 124.4, 124.7, 125.4, 125.9, 126.0, 127.1, 127.2, 127.4, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.1, 129.7, 130.0, 130.3, 130.5, 131.4, 132.7, 133.8, 133.9, 134.0, 134.1, 135.5, 136.8, 137.9, 149.5, 149.7, 150.0, 150.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 146.86, −18.27; HRMS calcd for $C_{42}H_{36}NO_2P_2$ $(M+H)^+$: 648.2221 found: 648.2201.

1e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30–8.22 (m, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.88–7.78 (m, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.47–7.33 (m, 7H), 7.32–7.17 (m, 10H), 7.15–7.05 (m, 7H), 5.33–5.13 (m, 1H), 4.04 (d, J = 15.2 Hz, 1H), 3.10 (d, J = 15.0 Hz, 1H), 1.54–1.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 47.9, 54.0, 117.0, 120.7, 121.4, 123.5, 123.7, 125.0, 125.7,

126.0, 126.1, 126.3, 126.9, 127.1, 127.3, 127.4, 127.5, 127.6, 128.8, 129.1, 129.2, 129.5, 130.4, 131.5, 131.8, 132.4, 132.6, 132.8, 133.5, 134.3, 134.5, 136.1, 137.4, 148.3, 148.6, 149.2, 151.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 142.60, −20.19; HRMS calcd for $C_{47}H_{38}NO_2P_2$ $(M+H)^+$: 710.2378, found: 710.2349.

4.3. General procedure for the Rh-catalyzed asymmetric hydrogenation

In a nitrogen-filled glovebox, a stainless steel autoclave was charged with $[Rh(COD)_2]BF_4$ (2.0 mg, 0.005 mmol) and (R_c,R_a)-**1d** (3.6 mg, 0.0055 mmol) in 1.0 mL of degassed CH_2Cl_2. After stirring for 10 min at room temperature, a solution of α-keto phosphonates **2** (0.5 mmol) in 1.0 mL of CH_2Cl_2 was added to the reaction mixture, after which the hydrogenation was performed at room temperature under an H_2 pressure of 30 bar for 24 h. The solvent was then evaporated and the residue was purified by flash column chromatography to give the corresponding hydrogenation product.

4.3.1. (*R*)-Dimethyl(hydroxy(phenyl)methyl)phosphonate 3a[3e]

87% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, 0.8 mL/min, 215 nm, 40 °C); t_1 = 11.3 min, t_2 = 13.9 min; $[\alpha]_D^{25}$ = +41.1 (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.46 (m, 2H), 7.43–7.29 (m, 3H), 5.06 (d, *J* = 10.9 Hz, 1H), 3.71 (d, *J* = 10.4 Hz, 1H), 3.67 (d, *J* = 10.4 Hz, 1H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.46.

4.3.2. (*R*)-Diethyl(hydroxy(phenyl)methyl)phosphonate 3b[3h]

87% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 215 nm, 40 °C); t_1 = 13.6 min, t_2 = 18.3 min; $[\alpha]_D^{25}$ = +29.3 (*c* 1.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2H), 7.40–7.28 (m, 3H), 5.02 (d, *J* = 10.9 Hz, 1H), 4.10–3.93 (m, 4H), 3.68 (br, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.38.

4.3.3. (*R*)-Diisopropyl(hydroxy(phenyl)methyl)phosphonate 3c[3e]

80% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, 0.8 mL/min, 215 nm, 40 °C); t_1 = 6.6 min, t_2 = 7.7 min; $[\alpha]_D^{25}$ = +20.4 (*c* 1.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2H), 7.39–7.27 (m, 3H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.69–4.57 (m, 2H), 3.50 (br, 1H), 1.30–1.24 (m, 9H), 1.13 (d, *J* = 6.2 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.80.

4.3.4. (*R*)-Dimethyl((4-chlorophenyl)(hydroxy)methyl)phosphonate 3d[3e]

80% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, 0.8 mL/min, 215 nm, 40 °C); t_1 = 11.7 min, t_2 = 15.3 min; $[\alpha]_D^{25}$ = +39.7 (*c* 1.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 5.04 (d, *J* = 10.9 Hz, 1H), 3.73 (d, *J* = 6.0 Hz, 3H), 3.70 (d, *J* = 5.9 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.92.

4.3.5. (*R*)-Dimethyl(hydroxy(4-methoxyphenyl)methyl)phosphonate 3e[3g]

83% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, 0.8 mL/min, 215 nm, 40 °C); t_1 = 19.2 min, t_2 = 27.0 min; $[\alpha]_D^{25}$ = +38.9 (*c* 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.7, 2.0 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.92 (d, *J* = 10.1 Hz, 1H), 3.74 (s, 3H), 3.65 (d, *J* = 10.4 Hz, 3H), 3.59 (d, *J* = 10.3 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.78.

4.3.6. (*R*)-Dimethyl(hydroxy(*p*-tolyl)methyl)phosphonate 3f[3e]

85% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, 0.8 mL/min, 215 nm, 40 °C); t_1 = 13.0 min, t_2 = 16.4 min; $[\alpha]_D^{25}$ = +48.4 (*c* 1.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.1, 2.0 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 5.01 (d, *J* = 10.5 Hz, 1H), 3.71 (d, *J* = 10.5 Hz, 3H), 3.67 (d, *J* = 10.3 Hz, 3H), 2.35 (d, *J* = 1.6 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.73.

4.3.7. (*R*)-Dimethyl(hydroxy(*m*-tolyl)methyl)phosphonate 3g[3e]

85% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, 0.8 mL/min, 215 nm, 40 °C); t_1 = 9.7 min, t_2 = 12.3 min; $[\alpha]_D^{25}$ = +33.2 (*c* 1.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.29–7.25 (m, 2H), 7.14 (d, *J* = 6.3 Hz, 1H), 5.01 (d, *J* = 10.9 Hz, 1H), 3.72 (d, *J* = 10.5 Hz, 3H), 3.67 (d, *J* = 10.4 Hz, 3H), 3.35 (br, 1H), 2.37 (s, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.63.

4.3.8. (*R*)-Dimethyl((3,4-dimethoxyphenyl)(hydroxy)methyl) phosphonate 3h[16]

83% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/*i*-PrOH = 80/20, 0.8 mL/min, 215 nm, 40 °C); t_1 = 11.7 min, t_2 = 18.8 min; $[\alpha]_D^{25}$ = +25.5 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.91 (d, *J* = 10.3 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.67 (d, *J* = 10.4 Hz, 3H), 3.59 (d, *J* = 10.3 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.74.

4.3.9. (*R*)-Dimethyl(1-hydroxyethyl)phosphonate 3i[4b]

50% ee was determined after conversion into the corresponding benzoate by chiral HPLC (chiralcel OD-H, *n*-hexane/*i*-PrOH = 98/2, 0.8 mL/min, 230 nm, 40 °C); t_1 = 34.2 min, t_2 = 37.4 min; $[\alpha]_D^{25}$ = −4.4 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (br, 1H), 4.12–4.06 (m, 1H), 3.83 (d, *J* = 4.9 Hz, 3H), 3.80 (d, *J* = 5.0 Hz, 3H), 1.45 (dd, *J* = 17.7, 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.03.

Acknowledgments

The authors are grateful for the financial support from the National Natural Science Foundation of China (21403022) and Program for Liaoning Excellent Talents in University (LJQ2013059).

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