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PAPER

The asymmetric synthesis of chiral cyclic α-hydroxy phosphonates and quaternary cyclic α-hydroxy phosphonates†

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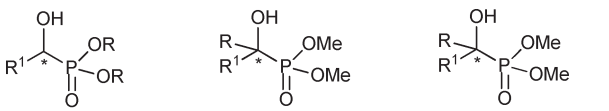
A highly practical, catalytic enantioselective cyclic phosphite addition to aldehydes and ketones was developed. The reaction rate of the asymmetric hydrophosphonylation was significantly enhanced by the addition of silver carbonate. Particularly, significant improvement has been achieved on the asymmetric hydrophosphonylation of unactivated ketones, giving quaternary α-hydroxy phosphonates with excellent enantioselectivity (up to 99% *ee*).

Introduction

The α-hydroxy phosphonates and α-hydroxy phosphonic acids are an important class of molecules that have exhibited intriguing biological activities,[1] and are widely applied in pharmaceutical chemistry, pesticide chemistry and enzyme inhibition. Numerous studies have demonstrated that the biological activity of these compounds depends largely on their stereo configurations,[1f–h] hence the synthesis of chiral α-hydroxy phosphonates with high enantioselectivity is focus of research interest.[2–5]

The base-catalysed hydrophosphonylation of aldehydes or imines (Pudovik reaction)[2a] is a convenient and widely used method for the synthesis of α-hydroxy phosphonates.[2] Since the pioneering work of Shibuya[3a] and Spilling,[3b] much attention has been paid to developing enantioselective catalysts for the synthesis of chiral α-hydroxy phosphonates **1**.[3] Chiral aluminium complexes are the most successful among the chiral catalysts.[4] Inspired by the tremendous success of Al(salen) and Al(salcyen) asymmetric catalysts, Al-Schiff base complexes[4f] have been developed for catalysing the asymmetric addition reaction.

Feng first prepared chiral quaternary α-hydroxy phosphonates **2** by hydrophosphonylation of α-ketoesters in the presence of organocatalysts.[5] The α-ketoesters could be converted to the chiral tertiary α-hydroxy phosphonates **2** in high yield and high enantioselectivity. The catalytic enantioselective addition of dialkyl phosphite with ketones was another approach to achieve the chiral quaternary α-hydroxy phosphonates **3**. Feng reported efficient Al-Schiff base complexes catalysing the asymmetric hydrophosphonylation of a simple ketone[4g] with moderate enantioselectivity (55% *ee*). It was the first example of the catalytic asymmetric hydrophosphonylation of an unactivated ketone. They later reported the catalytic enantioselective hydrophosphonylation of trifluoromethyl ketones[4h]. Takashi Ooi reported enantioselective hydrophosphonylation of ynones[4i] by using chiral tetraaminophosphonium phosphite as the catalyst and achieved high enantioselectivity. Despite these works, enantioselectivity for the asymmetric hydrophosphonylation of unactivated ketones have not been achieved so far. Because the carbonyl of the ketoester can be activated by the ester group, the reactivity of ketoesters is much higher than that of ketones, so their enantioselectivity is also higher than that for ketones. Therefore, there is still substantial room for improvement in terms of efficiency and substrate scope for asymmetric hydrophosphonylations. In order to find novel bioactive molecules, we have synthesized a series of α-substituted phosphonates and examined their biological activities. In this paper, we describe the catalytic asymmetric synthesis of chiral cyclic α-hydroxy phosphonates **7** and quaternary cyclic α-hydroxy phosphonates **8** *via* the enantioselective hydrophosphonylation of aldehydes and unactivated ketones using tridentate Schiff base Al(III) complexes as the catalyst (Scheme 1).



R^1= Aryl, Alkyl
Thiazolinyl
R = Me, Et

1

R^1= Aryl
R = COOMe

2

1) R^1= Aryl, R = Ph
2) R^1= CF_3, R = Aryl
3) R^1= Me, R = Alkynyl

3

Results and discussion

As excellent chiral scaffolds, tridentate Schiff base metal complexes, especially those of vanadium, chromium and iron,[6] have

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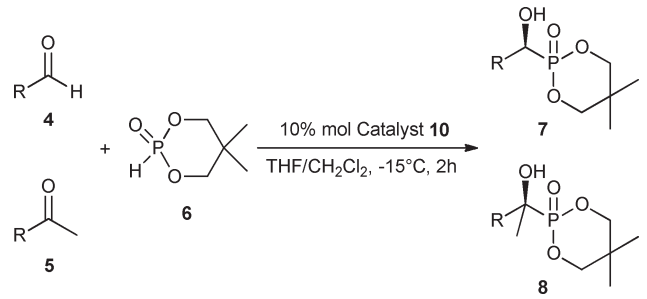
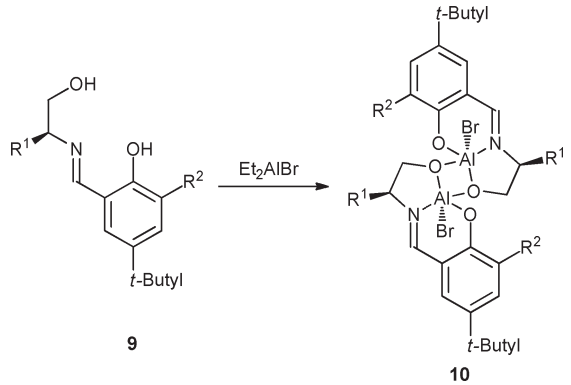


Scheme 1 Asymmetric hydrophosphonylation of aldehydes and ketones with Al(III) complexes **10** as catalyst.



Scheme 2 Synthesis of Al(III) complexes **10**.

been successfully applied in many asymmetric reactions. Al(III) complexes catalysed the asymmetric Pudovik reaction and the ligands can be synthesized easily.[7] Tridentate Schiff base ligands **9** reacted *in situ* with Et_2AlBr to form complexes **10** (Scheme 2) that effectively catalyse the asymmetric hydrophosphonylation of aldehydes and ketones.

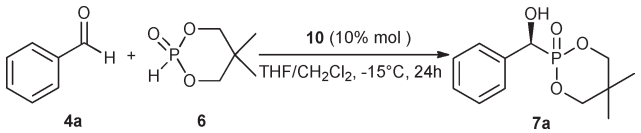
To improve the enantioselectivity of the reaction, the steric effects based on ligands **9** were examined (Table 1).

As shown in Table 1, the steric hindrance of substituent R^1 and R^2 affected the enantioselectivity principally. Ligands with bulky groups, such as R^1 = *tert*-butyl and R^2 = adamantyl, could achieve the highest enantioselectivity (99% *ee*; Table 1, entries 6 and 8). It is noteworthy that not only the size of substituent R^1, but also the distance between the bulky group and the chiral centre, had notable effect on the enantioselectivity. Although the size of phenyl is larger than that of isopropyl, the effect on enantioselectivity of both phenyl and isopropyl are almost the same (Table 1, entries 1 and 3). When R^1 was benzyl there was a methylene inserted between the phenyl and the chiral carbon, which put the phenyl far from the chiral centre, and accordingly the enantioselectivity significantly decreased (67% *ee*, Table 1, entry 2).

However, the steric hindrance of substituent R^1 and R^2 had no obvious effect on the reactivity (81–84% yield, Table 1, entries 1–8). The ligands **9** afforded the same absolute configuration of products. The *S* or *R* product with the same *ee* value could be obtained by changing the absolute configuration of (***S***)-**10** to (***R***)-**10** (Table 1, entries 5–8)

Dialkyl phosphonates undergo phosphite–phosphonate tautomerism and exist in two tautomeric forms: phosphonate and

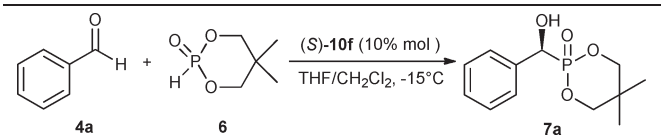
Table 1 Effects of complexes **10** on asymmetric hydrophosphonylation of benzaldehyde[a]



Entry	Catalyst	Ligands **9** R^1	Ligands **9** R^2	Yield[b] [%]	*ee*[c] [%]
1	(***S***)-**10a**	Isopropyl	Isobutyl	82	86 (*S*)
2	(***S***)-**10b**	Benzyl	Isobutyl	84	67 (*S*)
3	(***S***)-**10c**	Phenyl	Isobutyl	83	87 (*S*)
4	(***S***)-**10d**	Isobutyl	Isobutyl	83	91 (*S*)
5	(***S***)-**10e**	Isopropyl	Adamantyl	81	94 (*S*)
6	(***S***)-**10f**	Isobutyl	Adamantyl	82	99 (*S*)
7	(***R***)-**10e**	Isopropyl	Adamantyl	80	94 (*R*)
8	(***R***)-**10f**	Isobutyl	Adamantyl	82	99 (*R*)

[a] Reactions were carried out under nitrogen: benzaldehyde (10 mmol), cyclic phosphate (12 mmol), a mixture of 4 mL CH_2Cl_2 and 6 mL THF. [b] Isolated yield. [c] Determined by HPLC analysis.

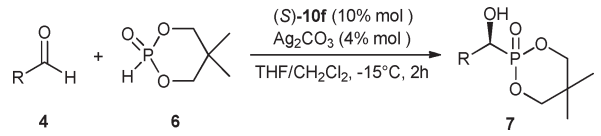
Table 2 Effects of inorganic salts on asymmetric hydrophosphonylation of benzaldehyde[a]



Entry	Salt	[mol%]	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	K_2CO_3	10	2/6/12	40/68/80	99
2	K_2CO_3	20	2/6/12	45/76/82	99
3	K_2CO_3	30	2/6/12	67/82/82	99
4	K_2CO_3	40	2/6/12	75/81/83	99
5	Ag_2CO_3	1	2/4/8	30/58/79	99
6	Ag_2CO_3	2	2/4/8	44/60/78	99
7	Ag_2CO_3	3	2/4	71/82	99
8	Ag_2CO_3	4	2/4	82/82	99
9	Ag_2CO_3	5	2/4	82/81	99
10	$AgNO_3$	1	2/12/24	20/61/80	99
11	$AgNO_3$	2	2/12/24	23/67/79	99
12	$AgNO_3$	3	2/12/24	23/68/80	99
13	$AgNO_3$	4	2/12/24	24/69/78	99
14	$AgNO_3$	5	2/12/24	23/67/79	99

phosphite.[8] There is now substantial agreement among chemists that the accepted mechanism for the Pudovik reaction involves deprotonation of the dialkyl phosphonate by a base to form the catalytically active dialkyl phosphite anion.[3e] Inorganic bases, such as potassium carbonate, which have a relatively weak basicity and low solubility in organic solvents, would generate an active phosphite anion at an appropriate rate and enhance the hydrophosphonylation without reducing the enantioselectivity.[4e] We expected to determine the role of the inorganic salts. Potassium carbonate, silver carbonate and silver nitrate were employed for experiment (Table 2). Indeed, the addition of 0.30–0.40 equivalents of potassium carbonate could effectively increase the reaction rate (Table 2, entries 3–4). It was most surprising that the addition of 0.04 equivalents of silver carbonate could significantly speed up the reaction. The reaction was completed in 2 h

Table 3 Asymmetric hydrophosphonylation of aldehydes[a]

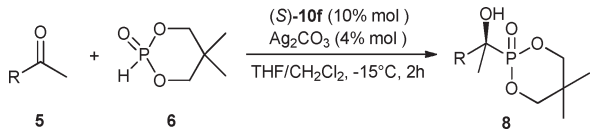


4 6 7

Entry	Product	R	Yield[b] [%]	*ee*[c] [%]	Conf[d]
1	**7a**	Ph	82	99	*S*
2	**7b**	4-MeC_6H_4	84	99	*S*
3	**7c**	3-MeC_6H_4	83	99	*S*
4	**7d**	4-ClC_6H_4	75	99	*S*
5	**7e**	4-BrC_6H_4	82	96	*S*
6	**7f**	4-MeOC_6H_4	79	92	*S*
7	**7g**	2,4-diClC_6H_3	77	99	*S*
8	**7h**	2,3-diClC_6H_3	72	99	*S*
9	**7i**	3,4-diClC_6H_3	76	99	*S*
10	**7j**	2-Furyl	68	99	*S*
11	**7k**	2-Thienyl	79	99	*S*

[a] Reactions were run under the conditions of entry 8 in Table 2. [b] Isolated yield. [c] Determined by HPLC analysis. [d] **7g** was confirmed by the crystal structure and others were determined by comparison with **7g**.

Table 4 Asymmetric hydrophosphonylation of ketones[a]



5 6 8

Entry	Product	R	Yield[b] [%]	*ee*[c] [%]	Conf[d]
1	**8a**	4-ClC_6H_4	68	98	*S*
2	**8b**	3-ClC_6H_4	70	97	*S*
3	**8c**	2-ClC_6H_4	68	99	*S*
4	**8d**	4-BrC_6H_4	70	95	*S*
5	**8e**	3-BrC_6H_4	71	95	*S*
6	**8f**	4-FC_6H_4	70	96	*S*
7	**8g**	4-MeOC_6H_4	67	98	*S*
8	**8h**	2-Thienyl	68	97	*S*

[a] Reactions were run under the conditions of entry 8 in Table 2. [b] Isolated yield. [c] Determined by HPLC analysis. [d] **8d** was confirmed by the crystal structure and others were determined by comparison with **8d**.

(Table 2, entry 8). But silver nitrate, which has a weak acidity, had a slight negative effect on the reactivity (Table 2, entries 10–14). This evidence supports the suggestion that basic conditions are favourable for the formation of phosphite anion. However, the addition of all three inorganic salts had no negative effect on the enantioselectivity (Table 2).

Under the optimized conditions, a series of aldehydes were examined, and the corresponding products **7** were given in high yields with excellent enantioselectivities by the asymmetric hydrophosphonylation of aldehydes **4** with cyclic phosphite **6** (Table 3).

As shown in Table 3, the disubstituted aldehydes could react smoothly with cyclic phosphite **6** and the corresponding products were given with 99% *ee* (Table 3, entries 7–9). *p*-Methoxybenzaldehyde showed a slightly reduced reactivity and enantioselectivity (Table 3, entry 6). Excellent enantioselectivities were also achieved in the asymmetric hydrophosphonylation of heteroaromatic aldehydes (up to 99% *ee*; Table 3, entries 10 and 11). It can be noted that both the electronic properties and the steric hindrance of the substitution at the aromatic ring of aldehydes had no obvious effect on the enantioselectivities (Table 3). The absolute configuration of compound **7g** was confirmed by the single-crystal X-ray analysis[9a] and others were determined by comparison with **7g**.

To expand the application of the present synthetic strategy, we examined the asymmetric hydrophosphonylation of unactivated ketones under the same catalytic reaction system. The quaternary cyclic α-hydroxy phosphonates **8** were obtained in good yields with high enantioselectivities (Table 4).

Although the ketones showed a slightly reduced reactivity (Table 4 *vs.* Table 3), it is noteworthy that excellent enantioselectivities were achieved for the first time in the asymmetric hydrophosphonylation of unactivated ketones by the use of chiral tridentate Schiff base Al(III) complexes **10** as the catalyst (up to 99% *ee*; Table 4). The absolute configuration of compound **8d** was confirmed by the single-crystal X-ray analysis[9b] and others were determined by comparison with **8d**.

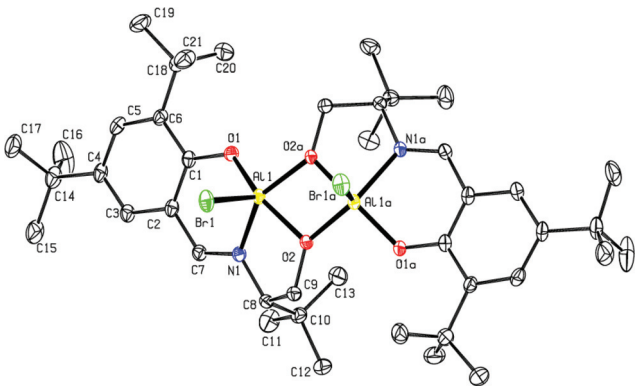


Fig. 1 Molecular structure of catalyst (*S*)-**10d**.

The relationship between the enantiomeric excess of Schiff base ligand and the product was tested by Feng and coworkers.[4f] The results indicated a strong positive nonlinear effect, which implied that the reaction occurred in the presence of a polymeric aluminium active species. Additionally the presence of dimeric aluminium species was observed by HR-MS analysis. However, the configuration of the catalyst was still unclear.

Fortunately, we obtained single crystals of catalyst (*S*)-**10d**[9c] (Fig. 1). As shown in Fig. 1, the oxygen atom of the alcohol group acts as a bridge in the dimeric aluminum species. Though the exact transition state for the reaction is unclear, the crystal structure may provide us some valuable information to understand the catalytic mechanism of the reaction. The two Br ions of the dimer are substituted by the phosphite ions. Consequently, the possibility might be that reaction proceeds *via* two pathways: monometallic catalysis or bimetallic catalysis. Perhaps the catalyst is capable of bringing both substrate and reagent together at a single metal centre or one metal centre may activate the phosphorus reagent whilst the other metal centre activates the carbonyl. The steric hindrance of substituent R^2 could force the carbonyl towards the chiral centre of the ligand, and the larger substituent R^1 would provide a more favourable chiral

environment. Therefore, ligands with bulkier groups could achieve higher enantioselectivities.

Conclusions

In conclusion, we have developed an efficient method for the synthesis of chiral cyclic α-hydroxy phosphonates and quaternary cyclic α-hydroxy phosphonates in good yields with excellent enantioselectivity. We found that the addition of silver carbonate significantly enhanced the reaction rate of the Al-Schiff base complexes catalysed asymmetric hydrophosphonylation. Particularly, significant improvement has been achieved on the asymmetric hydrophosphonylation of unactivated ketones, giving quaternary α-hydroxy phosphonates with excellent enantioselectivity (up to 99% *ee*).

Experimental

General

Melting points were recorded on a hot-plate microscope apparatus and uncorrected. ^{1}H NMR spectra were measured on Varian-Mercury 600 (600 MHz) spectrometers. Chemical shifts were recorded in δ (ppm) relative to tetramethylsilane (TMS) or residual solvent signals as the internal standard ($CHCl_3$, δ = 7.26, DMSO-d_6, δ = 2.50). Spectra were reported as follows: Chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR spectra were collected on Varian-Mercury 600 (150 MHz) spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from TMS with the solvent resonance as internal standard (DMSO-d_6, δ = 39.5). Infrared spectra were obtained as a KBr disc on a Perkin-Elmer PE-983 infrared spectrometer. The X-ray diffraction data were collected on a Bruker SMART AXS CCD diffractometer. Mass spectra were measured on a Finnigan Trace MS spectrometer. Elementary analyses were taken on a Vario EL III elementary analysis instrument. Optical rotations were measured on JASCO P-1020 polarimeter and reported as follows: $[\alpha]_D^T$ (c = g per 100 mL, solvent). The enantiomeric excesses (*ee*) of the products were determined by HPLC analysis on a chiral DAICEL CHIRALPAK AS-H column at 254 nm unless specially indicated. All reagents are commercial reagents and were used as received. Solvents were purified by standard techniques. The chiral ligands **9a–f** were prepared according to literature reported.[7b,c] The progress of reaction was monitored by TLC.

Asymmetric hydrophosphonylation of aldehydes

Et_2AlBr (1 mmol) was added to a solution of ligand (***S***)-**9f** (1 mmol) in CH_2Cl_2 (4 mL) under nitrogen. After stirring at room temperature for 30 min, the aldehyde **4** (10 mmol) in THF (6 mL) and silver carbonate (0.4 mmol) were added and stirred for a further 30 min. The cyclic phosphite **6** (12 mmol) was added at −15 °C, and the reaction solution was stirred for 2 h. The reaction were quenched by diluted hydrochloric acid (v/v = 1/15). The pure α-hydroxy phosphonate **7** was afforded by column chromatography on silica gel (acetone : petroleum ether = 1 : 2).

7a: **(*S*)-2-[Hydroxy(phenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 82% (99% *ee*); mp 154.1–155.3 °C; $[\alpha]_D^{20}$ = −78.3° (c = 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.80 (s, 3H), 1.11 (s, 3H), 3.97–4.06 (m, 4H), 5.16 (d, J = 11.4 Hz, 1H), 7.31–7.38 (m, 3H), 7.50 (d, J = 7.2 Hz, 2H). The ^{1}H NMR data were consistent with literature data.[10a]

7b: **(*S*)-2-[Hydroxy(4-methylphenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 84% (99% *ee*); mp 170.3–172.1 °C; $[\alpha]_D^{20}$ = −60.7° (c = 0.49, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (s, 3H), 1.11 (s, 3H), 2.34 (s, 3H), 3.98–4.05 (m, 4H), 5.12 (d, J = 10.8 Hz, 1H), 7.18 (d, J = 7.2 Hz, 2H), 7.38 (d, J = 6.6 Hz, 2H). The ^{1}H NMR data were consistent with literature data.[10a]

7c: **(*S*)-2-[Hydroxy(3-methylphenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 83% (99% *ee*); mp 175.9–176.9 °C; $[\alpha]_D^{20}$ = −59.2° (c = 0.39, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.83 (s, 3H), 1.12 (s, 3H), 2.36 (s, 3H), 3.99–4.07 (m, 4H), 5.11 (d, J = 11.4 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.28 (m, 3H). The ^{1}H NMR data were consistent with literature data.[10a]

7d: **(*S*)-2-[Hydroxy(4-chlorophenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 75% (99% *ee*); mp 175.3–176.8 °C; $[\alpha]_D^{20}$ = −60.4° (c = 0.56, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (s, 3H), 1.10 (s, 3H), 3.99–4.11 (m, 4H), 5.14 (d, J = 12.0 Hz, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.2 Hz, 2H). The ^{1}H NMR data were consistent with literature data.[10a]

7e: **(*S*)-2-[Hydroxy(4-bromophenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 82% (96% *ee*); mp 189.1–191.6 °C; $[\alpha]_D^{20}$ = −59.6° (c = 0.39, $CHCl_3$); IR (KBr): 3233, 2978, 1483, 1247, 1202, 1180, 826 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (s, 3H), 1.10 (s, 3H), 3.99–4.12 (m, 4H), 5.12 (d, J = 12 Hz, 1H), 7.36 (d, J = 7.2 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.5, 32.1, 68.8, 68.9, 69.9, 77.4, 78.0, 120.8, 129.4, 131.0, 138.1; MS (EI) (m/z): 334 (M^+); Anal. Calcd. for $C_{12}H_{16}BrO_4P$: C 43.01, H 4.81; Found: C 43.20, H 4.67.

7f: **(*S*)-2-[Hydroxy(4-methoxyphenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 79% (92% *ee*); mp 186.4–187.9 °C; $[\alpha]_D^{20}$ = −59.6° (c = 0.42, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.86 (s, 3H), 1.12 (s, 3H), 3.81 (s, 3H), 4.03–4.05 (m, 4H), 5.10 (d, J = 10.2 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H). The ^{1}H NMR data were consistent with literature data.[10a]

7g: **(*S*)-2-[Hydroxy(2,4-dichlorophenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 77% (99% *ee*); mp 188.4–189.2 °C; $[\alpha]_D^{20}$ = −63.1° (c = 0.52, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (s, 3H), 1.10 (s, 3H), 3.96–4.10 (m, 4H), 5.62 (d, J = 12.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.39 (s, 1H), 7.70 (d, J = 7.2 Hz, 1H). The ^{1}H NMR data were consistent with literature data.[10a]

7h: **(*S*)-2-[Hydroxy(2,3-dichlorophenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 72% (99% *ee*); mp 193.1–194.5 °C; $[\alpha]_D^{20} = -61.8°$ (c = 0.51, $CHCl_3$); IR (KBr): 3221, 2970, 1375, 1237, 1185, 749, 683 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.87 (s, 3H), 1.10 (s, 3H), 3.98–4.11 (m, 4H), 5.71 (d, J = 12.0 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 19.9, 21.3, 32.0, 67.3, 68.4, 77.8, 78.0, 128.0, 128.3, 129.7, 131.4, 138.9, 139.0; MS (EI) (m/z): 324 (M^+); Anal. Calcd. for $C_{12}H_{15}Cl_2O_4P$: C 44.33, H 4.65; Found: C 44.36, H 4.59.

7i: **(*S*)-2-[Hydroxy(3,4-dichlorophenyl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 76% (99% *ee*); mp 189.8–191.5 °C; $[\alpha]_D^{20} = -60.2°$ (c = 0.48, $CHCl_3$); IR (KBr): 3273, 2967, 1466, 1247, 1193, 885, 822 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.88 (s, 3H), 1.12 (s, 3H), 4.04–4.15 (m, 4H), 5.14 (d, J = 12.6 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 19.9, 21.5, 32.2, 68.1, 69.2, 77.6, 78.0, 127.5, 129.0, 130.2, 130.3, 130.8, 139.9; MS (EI) (m/z): 324 (M^+); Anal. Calcd. for $C_{12}H_{15}Cl_2O_4P$: C 44.33, H 4.65; Found: C 44.56, H 4.68.

7j: **(*S*)-2-[Hydroxy(furan-2-yl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 68% (99% *ee*); mp 202.4–203.4 °C; $[\alpha]_D^{20} = -64.1°$ (c = 0.53, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 0.89 (s, 3H), 1.21(s, 3H), 4.00–4.04 (m, 2H), 4.24–4.25 (m, 2H), 5.20 (d, J = 13.2 Hz, 1H), 6.38 (s, 1H), 6.52 (s, 1H), 7.43 (s, 1H). The ^1H NMR data were consistent with literature data.[10b]

7k: **(*S*)-2-[Hydroxy(thiophen-2-yl)methyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** Yellowish solid; yield 79% (99% *ee*); mp 226.0–227.4 °C; $[\alpha]_D^{20} = -62.1°$ (c = 0.42, $CHCl_3$); IR (KBr): 3215, 2968, 1469, 1237, 1079, 825, 722 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.88 (s, 3H), 1.19 (s, 3H), 4.02–4.25 (m, 4H), 5.41 (d, J = 12.0 Hz, 1H), 7.01 (t, J = 4.2 Hz, 1H), 7.20 (s, 1H), 7.32 (d, J = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.6, 32.1, 65.8, 66.9, 77.6, 78.0, 125.6, 125.9, 126.8, 141.8; MS (EI) (m/z): 262 (M^+); Anal. Calcd. for $C_{10}H_{15}O_4PS$: C 45.80, H 5.76; Found: C 45.61; H 5.72.

Asymmetric hydrophosphonylation of ketones

Et_2AlBr (1 mmol) was added to a solution of ligand **(*S*)-9f** (1 mmol) in CH_2Cl_2 (4 mL) under nitrogen. After stirring at room temperature for 30 min, the ketone **5** (10 mmol) in THF (6 mL) and silver carbonate (0.4 mmol) were added and stirred for a further 30 min. The cyclic phosphite **6** (12 mmol) was added at −15 °C, and the reaction solution was stirred for 2 h. The reaction were quenched by diluted hydrochloric acid (v/v = 1/15). The pure α-hydroxy phosphonate **8** was afforded by column chromatography on silica gel (acetone : petroleum ether = 1 : 2).

8a: **(*S*)-2-[1-Hydroxy-1-(4-chlorophenyl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 68% (98% *ee*); mp 149.8–151.6 °C; $[\alpha]_D^{20} = -53.4°$ (c = 0.54, $CHCl_3$); IR (KBr): 3241, 2970, 1489, 1222, 1138, 829 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.86 (s, 3H), 1.07 (s, 3H), 1.88 (d, J = 15.6 Hz, 3H), 3.96–4.09 (m, 4H), 7.34 (d, J = 8.4 Hz, 2H), 7.57 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.4, 25.5, 32.0, 74.6, 75.6, 78.0, 78.5, 127.7, 128.1, 131.8, 142.0; MS (EI) (m/z): 304 (M^+); Anal. Calcd. for $C_{13}H_{18}ClO_4P$: C 51.24, H 5.95; Found: C 50.96, H 5.90.

8b: **(*S*)-2-[1-Hydroxy-1-(3-chlorophenyl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 70% (97% *ee*); mp 142.0.3–143.6 °C; $[\alpha]_D^{20} = -53.7°$ (c = 0.51, $CHCl_3$); IR (KBr): 3229, 2969, 1486, 1222, 1138, 787, 691 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 0.85 (s, 3H), 1.15 (s, 3H), 1.74 (d, J = 15.6 Hz, 3H), 3.89–3.93 (m, 1H), 4.03–4.08 (m, 1H), 4.39–4.40 (m, 1H), 4.47–4.49 (m, 1H), 7.37–7.43 (m, 2H), 7.54–7.60 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.4, 25.6, 32.0, 74.6, 75.6, 78.0, 78.5, 124.9, 125.8, 126.9, 129.7, 132.6, 145.5; MS (EI) (m/z): 304 (M^+); Anal. Calcd. for $C_{13}H_{18}ClO_4P$: C 51.24, H 5.95; Found: C 50.98, H 5.91.

8c: **(*S*)-2-[1-Hydroxy-1-(2-chlorophenyl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 68% (99% *ee*); mp 145.9–147.8 °C; $[\alpha]_D^{20} = -58.4°$ (c = 0.52, $CHCl_3$); IR (KBr): 3241, 2970, 1489, 1222, 1138, 768 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 0.85 (s, 3H), 1.14 (s, 3H), 1.74 (d, J = 15.6 Hz, 3H), 3.87–3.92 (m, 1H), 4.03–4.07 (m, 1H), 4.37–4.39 (m, 1H), 4.47–4.48 (m, 1H),7.44 (d, J = 7.8 Hz, 2H), 7.59 (m, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.4, 25.5, 32.0, 74.5, 75.6, 77.9, 78.4, 127.6, 128.0, 131.8, 141.9; MS (EI) (m/z): 304 (M^+); Anal. Calcd. for $C_{13}H_{18}ClO_4P$: C 51.24, H 5.95; Found: C 51.06, H 5.89.

8d: **(*S*)-2-[1-Hydroxy-1-(4-bromophenyl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 70% (95% *ee*); mp 148.5–150.2 °C; $[\alpha]_D^{20} = -64.8°$ (c = 0.56, $CHCl_3$); IR (KBr): 3239, 2970, 1486, 1222, 1138, 830 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.84 (s, 3H), 1.06 (s, 3H), 1.85 (d, J = 15.6 Hz, 3H), 4.00–4.01 (m, 4H), 7.49 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 19.8, 21.3, 25.4, 31.8, 74.5, 75.5, 77.8, 78.3, 120.3, 128.3, 130.4, 142.2; MS (EI) (m/z): 348 (M^+); Anal. Calcd. for $C_{13}H_{18}BrO_4P$: C 44.72, H 5.20; Found: C 44.51; H 5.31.

8e: **(*S*)-2-[1-Hydroxy-1-(3-bromoophenyl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 71% (95% *ee*); mp 162.3–163.5 °C; $[\alpha]_D^{20} = -74.0°$ (c = 0.41, $CHCl_3$); IR (KBr): 3233, 2969, 1477, 1225, 1139, 777, 690 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.87 (s, 3H), 1.10 (s, 3H), 1.89 (d, J = 15.6 Hz, 3H), 3.96–4.11 (m, 4H), 7.27 (m, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.4, 25.7, 32.0 (d, J = 8.55 Hz), 74.5, 75.6, 78.0, 78.6, 121.3, 125.2, 128.7, 129.8, 130.0, 145.8; MS (EI) (m/z): 348 (M^+); Anal. Calcd. for $C_{13}H_{18}BrO_4P$: C 44.72, H 5.20; Found: C 44.39, H 5.48.

8f: **(*S*)-2-[1-Hydroxy-1-(4-fluorophenyl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 70% (95% *ee*); mp 168.7–169.9 °C; $[\alpha]_D^{20} = -65.0°$ (c = 0.64, $CHCl_3$); IR (KBr): 3220, 2974, 1510, 1374, 1223, 1135, 828 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.86 (s, 3H), 1.07 (s, 3H), 1.89 (d, J = 15.6 Hz, 3H), 3.92–4.10 (m, 4H), 7.06 (m, 2H), 7.61 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.4, 25.6, 31.9, 74.4,

75.5, 78.3(m), 114.4(d, J = 6.9 Hz), 128.1, 139.0, 160.5, 162.1; MS (EI) (m/z): 288 (M^+); Anal. Calcd. for $C_{13}H_{18}FO_4P$: C 54.17, H 6.29; Found: C 54.19, H 6.51.

8g: **(*S*)-2-[1-Hydroxy-1-(4-methoxyphenyl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 67% (98% *ee*); mp 155.6–156.3 °C; $[\alpha]_D^{20}$ = −48.1° (c = 0.48, $CHCl_3$); IR (KBr): 3329, 2969, 1513, 1251, 1230, 1137, 830 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.88 (s, 3H), 1.10 (s, 3H), 1.90 (d, J = 15.6 Hz, 3H), 3.82 (s, 3H), 3.90–4.08 (m, 4H), 6.93 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.1, 21.5, 25.6, 32.0 (d, J = 7.05 Hz), 55.1, 74.4, 75.5, 77.7, 78.2, 113.1, 127.4, 134.7, 158.3; MS (EI) (m/z): 300 (M^+); Anal. Calcd. for $C_{14}H_{21}O_5P$: C 56.00, H 7.05; Found: C 55.72, H 7.28.

8h: **(*S*)-2-[1-Hydroxy-1-(thiophen-2-yl)ethyl]-5,5-dimethyl-1,3,2-dioxaphosphinane-2-one.** White solid; yield 68% (97% *ee*); mp 152.0–153.8 °C; $[\alpha]_D^{20}$ = −63.0° (c = 0.57, $CHCl_3$); IR (KBr): 3234, 2967, 1468, 1372, 1224, 1128, 1064, 836 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 0.84 (s, 3H), 1.17 (s, 3H), 1.78 (d, J = 15.6 Hz, 3H), 3.92–4.05 (m, 2H), 4.43–4.45 (m, 2H), 6.70 (d, J = 18 Hz, 1H), 7.04 (d, J = 18 Hz, 2H), 7.47 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.0, 21.4, 26.3, 32.0, 73.9, 75.0, 78.1, 78.5, 124.4, 125.2, 126.9, 147.8; MS (EI) (m/z): 276 (M^+); Anal. Calcd. for $C_{11}H_{17}O_4PS$: C 47.82, H 6.20; Found: C 47.72, H 6.02.

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