Organic & Biomolecular Chemistry

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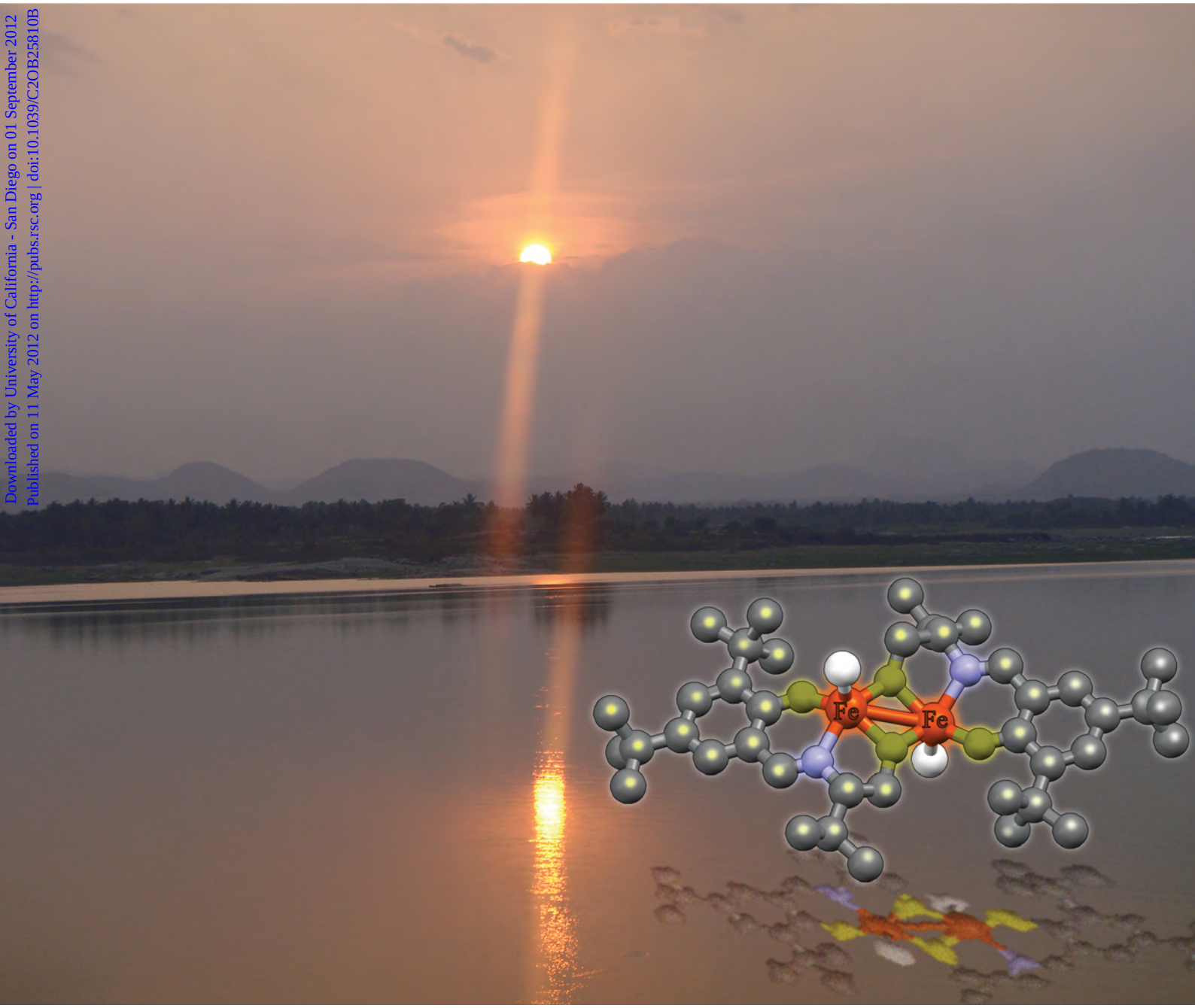
Volume 10 | Number 28 | 28 July 2012 | Pages 5317–5472



ISSN 1477-0520

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COMMUNICATION

Synthesis of an unusual dinuclear chiral iron complex and its application in asymmetric hydrophosphorylation of aldehydes†

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Received 27th April 2012, Accepted 9th May 2012
DOI: 10.1039/c2ob25810b

An unusual dinuclear chiral iron complex has been synthesized and effectively utilized in the asymmetric hydrophosphorylation of aldehydes to synthesize optically active α-hydroxy phosphonates with excellent yield and good enantioselectivity.

Introduction

Development of iron catalysts has been one of the primary long-term goals in synthetic organic chemistry. While iron is inexpensive, non-toxic, more abundant and environmental friendly, iron based catalysts are underutilized in organic synthesis, especially in the field of asymmetric synthesis.[1] On the other hand, optically active α-hydroxy phosphonates have proven to be an efficient structural unit in the pharmaceutical industry. Also, they are part of several biologically important molecules such as renin inhibitors, agonists of calcium transfer, inhibitors of HIV protease, anti-viral drugs and anti-cancer drugs.[2] Among the available methods, the asymmetric addition of phosphite to aldehyde is the most straightforward method for the synthesis of optically active α-hydroxy phosphonates.[3] In recent years, a set of different catalytic systems has emerged for this purpose which includes chiral bases,[4] Ti,[4b,5] La,[5a,6] and Yb[7] complexes. In addition, chiral Al complexes[8] have been widely utilized as effective catalysts for this reaction. However, most of these chiral complexes are either derived from rare metal salts like $Yb(OTf)_3$ and $LaCl_3$ or metal salts that are highly sensitive to handle such as $Ti(O^iPr)_4$ and Et_2AlCl. Therefore, an iron complex with a readily available chiral ligand, which is easily tunable by means of steric and electronic factors, will be a highly desirable catalyst for the synthesis of optically active α-hydroxy phosphonates.

As part of our continuing interest in the development of cost effective and easily accessible catalysts for the synthesis of optically active α-hydroxy ketones and α-hydroxy esters,[9] herein we report the synthesis of an unusual dinuclear chiral iron complex and its application as a catalyst in asymmetric hydrophosphorylation of aldehydes for the synthesis of optically active α-hydroxy phosphonates. To the best of our knowledge, this report uses a chiral iron complex as a catalyst for the first time in asymmetric hydrophosphorylation of aldehydes.

Results and discussion

Recently, we have used $Fe(OAc)_2$ in combination with salen ligand **L1** as an effective catalyst for the synthesis of optically active α-hydroxy ketones through oxidative kinetic resolution (OKR).[10] To extend the application of this catalyst, we went on to use the same catalyst for the asymmetric hydrophosphorylation of aldehydes by reacting 10 mol% of $Fe(OAc)_2$ and 10 mol% of salen ligand **L1** with 4-nitrobenzaldehyde and diethyl phosphite in THF at room temperature. The reaction provided the corresponding α-hydroxy phosphonate as a racemic product with 22% yield and the starting material remained unconsumed even after 2 days (Table 1, entry 1).

The low yield and longer duration of the reaction could be attributed to the less availability of nucleophilic phosphite in dialkyl phosphite, which exists in equilibrium with phosphate. We envisaged that the efficiency of the reaction can be increased by addition of base, which in turn will shift the equilibrium in favour of active nucleophilic phosphite (Scheme 1). True to our presumption, addition of 1 equivalent of Na_2CO_3 increased the yield to 78% albeit there was no asymmetric induction (Table 1, entry 2).

When the ligand **L1** was replaced with valinol derived salen ligand **L2**, the reaction provided the corresponding α-hydroxy phosphonate with 16% ee (entry 3). In the reaction medium, $Fe(OAc)_2$ and ligand **L2** may form chiral Fe complex **1** which might catalyze the reaction through activation of electrophile leading to partial destruction of the chiral environment in a catalyst (Scheme 1, path I, **TS-1**) and this could be the reason for low enantioselectivity.

To overcome this problem, we planned to synthesize chiral Fe complex **2** to trap a phosphite anion by replacing the chloride ligand. Thereby the catalyst can activate both the electrophile and nucleophile, so that the reaction can proceed in a more enantioselective fashion (Scheme 1, path II, **TS-2**). To synthesize

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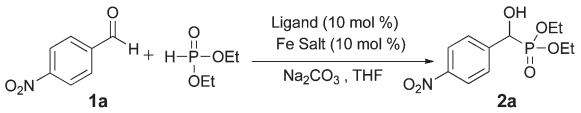
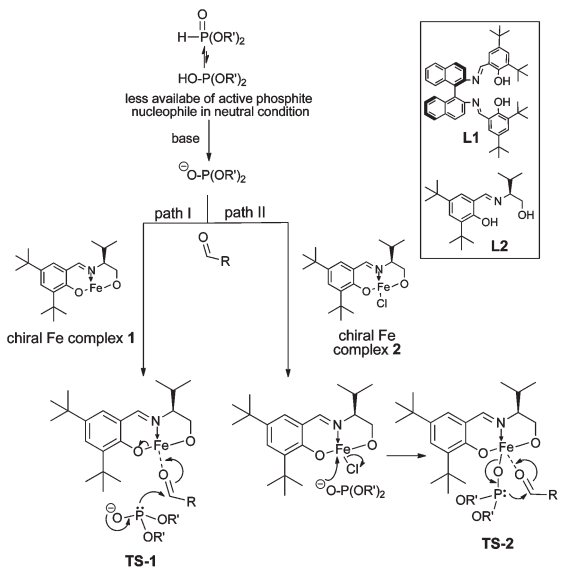
† Electronic supplementary information (ESI) available: HPLC chromatogram, copy of ^1H and ^{13}C NMR spectra for all compounds. CCDC 843428. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25810b

Table 1 Optimization of asymmetric hydrophosphorylation reaction

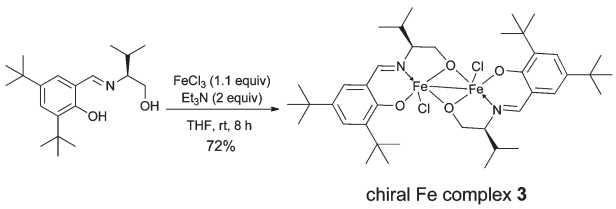


Entry	Catalyst	Ligand	Na_2CO_3	Temp.	Time	Yield[a]	Ee
1	$Fe(OAc)_2$	**L1**	—	rt	2 days	22%	0
2	$Fe(OAc)_2$	**L1**	1 equiv.	rt	26 h	78%	0
3	$Fe(OAc)_2$	**L2**	1 equiv.	rt	26 h	90%	16%
4[b]	Chiral Fe complex **3**	—	1 equiv.	rt	26 h	92%	57%
5	$FeCl_3$	**L2**	1 equiv.	rt	26 h	95%	56%
6	$FeCl_2$	**L2**	1 equiv.	rt	26 h	89%	28%
7	$FeBr_3$	**L2**	1 equiv.	rt	38 h	76%	38%
8	$FeCl_3$	**L2**	0.5 equiv.	rt	26 h	93%	52%
9	$FeCl_3$	**L2**	0.25 equiv.	rt	48 h	64%	27%
10	$FeCl_3$	**L2**	0.5 equiv.	10 °C	26 h	41%	18%
11	$FeCl_3$	**L2**	0.5 equiv.	45 °C	26 h	94%	49%
12	$FeCl_3$	**L2**	0.5 equiv.	55 °C	10 h	96%	64%
13	$FeCl_3$	**L2**	0.5 equiv.	60 °C	10 h	98%	52%

[a] Isolated yield. [b] 5 mol% of chiral Fe complex **3** was used.



Scheme 1



Scheme 2 Synthesis of a chiral iron complex.

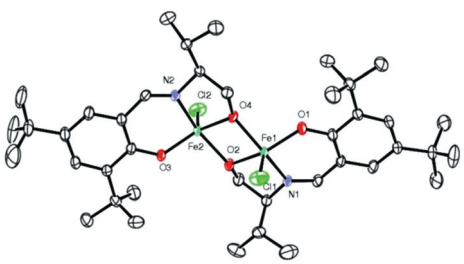


Fig. 1 ORTEP diagram of chiral Fe complex **3**. Ellipsoids represent 30% probability level (CCDC No. 843428). Hydrogen atoms are omitted for clarity.

chiral Fe complex **2**, $FeCl_3$ was reacted with ligand **L2** in the presence of Et_3N in THF at room temperature. Surprisingly, chiral Fe complex **2** did not form but intriguingly we isolated an unusual dinuclear chiral Fe complex **3** (Scheme 2). The complex formation was confirmed by paramagnetic ^1H NMR and high-resolution mass spectrometry. The single crystal X-ray analysis showed that chiral Fe complex **3** was crystallized in an orthorhombic manner with space group $P2_12_12_1$ (Fig. 1). The two iron atoms (Fe1 and Fe2) are separated by a distance of 3.1115(7) Å and bridged by two oxygen atoms (O2 and O4) of valinol through a two electron three centred bond by an average distance of 1.977(2) Å. This is longer than the Fe–O bond length (1.860(2)) where the oxygen atom (O1) is from the phenolic part of the ligand.

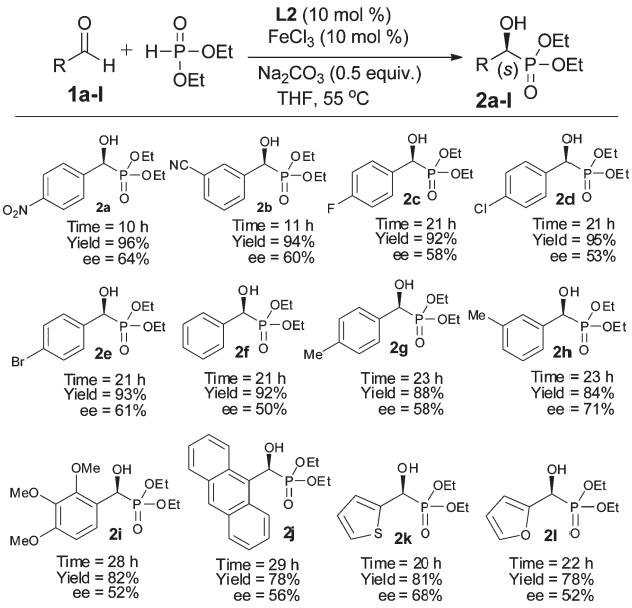
The geometry parameter $\tau = (\beta - \alpha)/60$ was used to deduce the structure of the five coordinated complex where $\tau = 0$ means square pyramidal and $\tau = 1$ means trigonal bipyramidal geometry.[8a,11] While the bond angles for O1–Fe1–O2 and N1–Fe1–O4 are 143.3(β) and 142.8(α), those for O4–Fe2–O3 and O2–Fe2–N2 are 135.0(α) and 148.7(β). Calculated τ values of chiral Fe complex **3** showed that iron (Fe1) in one part of the complex has adopted perfect square pyramidal geometry with $\tau = 0.008$ and iron (Fe2) in another part of the complex has adopted distorted square pyramidal geometry with $\tau = 0.23$. A chloride ligand occupies the axial position of each iron in their square pyramidal geometry but pointing towards opposite directions to each other with a bond length of 2.212 Å which is longer than the Fe1–O1 bond. The weaker Fe–Cl bond may help the catalyst to trap the phosphite anion by replacing the chloride ligand so that better enantioselectivity can be achieved.

In order to test the feasibility of our hypothesis, the chiral Fe complex **3** was used as a catalyst in the asymmetric hydrophosphorylation reaction. Interestingly, as we predicted, the enantiomeric excess was increased to 57% (Table 1, entry 4). To study the efficiency of *in situ* generated catalyst over synthesized chiral Fe complex **3**, $FeCl_3$ and ligand **L2** were employed to generate the *in situ* catalyst. The results obtained were comparable with synthesized chiral Fe complex **3** (entry 4 *vs.* 5), which encouraged us to move on with *in situ* generated catalyst for further optimization of reaction. The importance of the extra chloride ligand in the catalyst to enhance enantioselectivity was further realized by replacing $FeCl_3$ with $FeCl_2$ where enantiomeric excess was reduced to 28% (entry 5 *vs.* 6). The reaction with $FeBr_3$ in place of $FeCl_3$ provided the product with 38% ee (entry 5 *vs.* 7), which indicates that the enhancement in enantioselectivity also depends on the properties of the counterion.

The ligand **L2** was modified by means of the steric/electronic factor (Fig. 2) and the reaction was screened with these modified ligands to increase the enantiomeric excess but none of these ligands were superior to ligand **L2**. Similarly, the study of the reaction with different parameters such as solvents, bases and ratios of metal salt and ligand also failed to increase the enantiomeric excess. The use of 0.5 equivalent of base in the reaction was found to be as good as 1 equivalent of base (entry 5 *vs.* 8). However, the reactivity and enantioselectivity were decreased when 0.25 equivalent of base was used (entry 9). Likewise, the reaction at 10 °C diminished both reactivity and enantioselectivity (entry 10). Though the reaction at 45 °C decreased the selectivity (entry 11), the reaction at 55 °C amplified the enantioselectivity and offered the product with 64% ee (entry 8 *vs.* 12). Further rise in temperature only lessened the enantioselectivity (entry 13). Thus, 10 mol% of $FeCl_3$ and 10 mol% of ligand **L2** with 0.5 equivalent of Na_2CO_3 in THF at 55 °C became the optimized reaction condition for this hydrophosphorylation of aldehydes.

To explore the application of the catalytic system, the optimized condition was used for the asymmetric synthesis of different substituted α-hydroxy phosphonates and the results are summarized in Scheme 3. The reactions proceeded smoothly with all structurally varied aldehydes to afford the corresponding α-hydroxy phosphonates with excellent yield and good enantioselectivity. The rate of reaction was found to be higher in the case of aldehydes with stronger electron withdrawing substituents (**1a–b**) than in aldehydes with other substituents (**1c–h**). Very importantly, the reaction with highly electron rich aldehyde (**1i**), bulkier aldehyde (**1j**) and heterocyclic aldehydes (**1k–l**) also proceeded effortlessly to give the corresponding α-hydroxy phosphonates with good enantiomeric excess. All the substituted α-hydroxy phosphonates were obtained with excellent yield and good enantiomeric excess.[12] The absolute stereochemistry of the major enantiomer of all α-hydroxy phosphonates was found to be "*S*", which was determined from signs of specific rotation in comparison with the literature values. Enantiomeric excess was determined by HPLC using chiral columns.

The stereochemical outcome of chiral iron catalyzed asymmetric hydrophosphorylation of aldehydes can be explained as shown in Scheme 4. *In situ* generated chiral Fe complex **3** in the presence of aldehyde and phosphite leads to **TS-3** or **TS-4** where chloride is replaced with phosphite as mentioned in path II of Scheme 1. Subsequently, aldehyde coordinates with iron in such a way that the bulkier group is away from the tertiary butyl group of the ligand (**TS-3**), thereby generating a more favourable transition state which could be responsible for the major enantiomer. If the bulkier group of the aldehyde points towards the tertiary butyl group of the ligand (**TS-4**), the steric repulsion between these groups leads to the formation of a less favourable transition state which could be responsible for the minor enantiomer. It is also assumed that the reaction may take place at both



Scheme 3 Chiral iron catalyzed hydrophosphorylation of aldehydes.

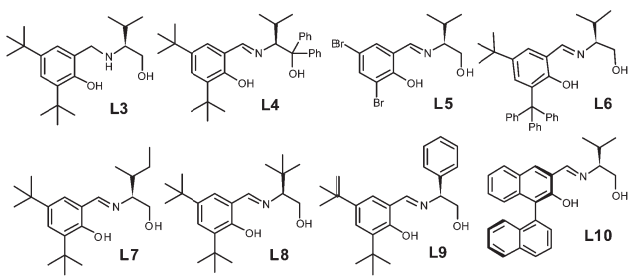
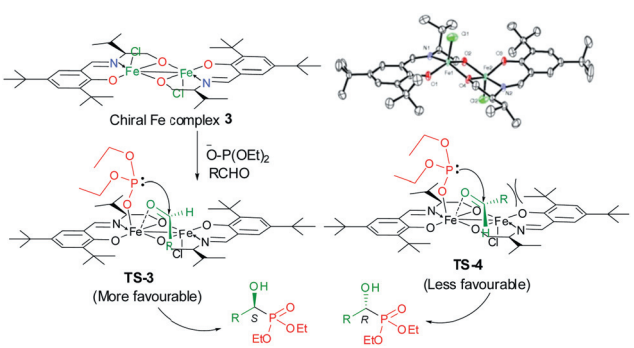


Fig. 2 Modified chiral ligands for asymmetric hydrophosphorylation.



Scheme 4 Elucidation of stereochemical outcome.

iron centers as 5 mol% of the chiral Fe complex **3** provided similar results compared with 10 mol% of $FeCl_3$ and 10 mol% of **L2** (Table 1, entry 4 *vs.* 5).

Conclusion

Asymmetric hydrophosphorylation of aldehydes using a chiral iron catalyst has been successfully achieved for the first time. An unusual dinuclear chiral Fe complex **3** was isolated and used as a catalyst in asymmetric synthesis of optically active α-hydroxy phosphonates. The additional chloride ligand in chiral Fe complex **3** enhanced the enantioselectivity by activating both electrophile and nucleophile. All the substituted α-hydroxy phosphonates were obtained with excellent yield and good enantiomeric excess.[12]

Experimental section

General considerations

$FeCl_3$ (reagent grade, 97%) and dialkyl phosphite were purchased from Aldrich Chemicals and used as received. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching. Silica gel for column chromatography (particle size 100–200 mesh) was purchased from SRL India. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. ^1H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CDCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were reported relative to $CDCl_3$ (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 4100 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on a Q-Tof Micro mass spectrometer. Optical rotations were measured with an Autopol IV – Rudolph Research Analytical Polarimeter. The enantiomeric excess (% ee) of all the compounds was determined by SHIMADZU HPLC using Daicel Chiral columns. ^1H and ^{13}C NMR and HRMS spectral data have been included for all compounds. The ligands **L1** and **L3–L10** were prepared using procedures available in the literature.[13–18]

Synthesis of ligand L2

A mixture of valinol (1 g, 10 mmol) and 2,5-di-*tert*-butylsalicylaldehyde (2.3 g, 10 mmol) in EtOH (50 mL) was refluxed for 12 h. The reaction mixture was then concentrated and the resulting residue was purified by silica gel column chromatography (eluents: hexanes–ethyl acetate) to give ligand **L2** in 78% yield. Yellow solid, Mp: 107–109 °C, R_f 0.21 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −30.9 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 6.4 Hz, 6H), 1.32 (s, 9H), 1.46 (s, 9H), 1.50–1.70 (m, 1H), 1.88–2.02 (m, 1H), 2.98–3.09 (m, 1H), 3.71–3.90 (m, 2H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 8.38 (s, 1H), 13.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 19.9, 29.4, 29.6, 30.2, 31.6, 34.3, 35.2, 64.9, 78.1, 117.8, 126.3, 127.3, 136.9, 140.3, 158.3, 167.2. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{34}NO_2$, 320.2590; found, 320.2578.

Synthesis of chiral Fe complex 3

Et_3N (137 μL, 0.99 mmol) was added dropwise to a mixture of $FeCl_3$ (81 mg, 0.5 mmol) and ligand **L2** (144 mg, 0.45 mmol) in THF (10 mL) solvent under a nitrogen atmosphere and stirred for 8 h at room temperature. The reaction mixture was then concentrated and water was added to the resulting residue. The aqueous mixture was extracted with CH_2Cl_2 and the combined organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give chiral Fe complex **3** in 62% yield. The single crystal suitable for X-ray analysis was obtained by recrystallization of chiral Fe complex **3** in a CH_2Cl_2–hexanes mixture. HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{40}H_{63}N_2O_4Cl_2Fe_2$, 817.2864; found, 817.2866.

General procedure for synthesis of optically active α-hydroxy phosphonates

To a mixture of chiral Fe complex **3** (5 mol%) or $FeCl_3$ (10 mol%), ligand **L2** (10 mol%) and Na_2CO_3 (0.5 equiv.) in THF (5 mL) were added diethyl phosphite (0.6 mmol) and aldehyde (0.5 mmol) at room temperature and further stirred for 10–29 h at 55 °C. The reaction mixture was then concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography (eluents: hexanes–ethyl acetate) to give optically active α-hydroxy phosphonate.

Diethyl hydroxy(4-nitrophenyl)methylphosphonate (2a). R_f 0.21 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −31.8 (*c* = 2.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–1.30 (m, 6H), 4.03–4.17 (m, 4H), 5.16 (d, *J* = 12.4 Hz, 1H), 7.66 (dd, *J* = 2.0, 9.8 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5 (t, *J* = 4.6 Hz), 63.5 (d, *J* = 7.5 Hz), 64.2 (d, *J* = 6.9 Hz), 70.2 (d, *J* = 156.9 Hz), 123.5, 127.8 (d, *J* = 4.9 Hz), 144.3, 147.7; IR (neat) 751, 1019, 1257, 3278 cm^{-1}; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{11}H_{17}NO_6P$, 290.0794; found, 290.0791. The enantiomeric excess (% ee) was determined to be 64% by HPLC using a Daicel ChiralPAK AS-H column (20% i-PrOH–hexanes, 1 mL min^{-1}, 254 nm): t_R (major, 10.915 min), t_R (minor, 8.577 min).

Diethyl (3-cyanophenyl)(hydroxy)methylphosphonate (2b). R_f 0.31 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −16.8 (*c* = 1.4 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.20–1.32 (m, 6H), 4.01–4.18 (m, 4H), 5.07 (d, *J* = 11.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 6.8 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 63.4 (d, *J* = 7.3 Hz), 64.0 (d, *J* = 7.1 Hz), 69.8 (d, *J* = 159.0 Hz), 112.4, 118.9, 129.0, 130.6 (d, *J* = 5.2 Hz), 131.6, 138.8; IR (neat) 732, 1038, 1230, 2236, 3252 cm^{-1}; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{12}H_{17}NO_4P$, 270.0895; found, 270.0899. The enantiomeric excess (% ee) was determined to be 60% by HPLC using a Daicel ChiralCEL OD-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 15.426 min), t_R (minor, 18.266 min).

Diethyl (4-fluorophenyl)(hydroxy)methylphosphonate (2c). R_f 0.27 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −15.5 (*c* = 2.6 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.16–1.31 (m, 6H), 3.93–4.12 (m, 4H), 4.53 (s, 1H), 4.99 (d, *J* = 10.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 2H), 7.40–7.52 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 16.5 (d, J = 5.1 Hz), 63.1 (d, J = 7.1 Hz), 63.6 (d, J = 6.9 Hz), 70.1 (d, J = 161.4 Hz), 115.2 (d, J = 21.3 Hz), 128.9 (t, J = 6.8 Hz), 132.7, 162.6 (d, J = 245.2 Hz); IR (neat) 747, 1026, 1223, 3264 cm^{-1}; HRMS (m/z): $[M + H]^+$ calcd for $C_{11}H_{17}O_4FP$, 263.0849; found, 263.0845. The enantiomeric excess (% ee) was determined to be 58% by HPLC using a Daicel ChiralPAK AS-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 17.492 min), t_R (minor, 14.155 min).

Diethyl (4-chlorophenyl)(hydroxy)methylphosphonate (2d). R_f 0.36 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −18.9 (c = 2.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.16–1.29 (m, 6H), 3.95–4.12 (m, 4H), 4.98 (d, J = 10.8 Hz, 1H), 7.30 (d, J = 7.2 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4 (d, J = 4.8 Hz), 63.2 (d, J = 7.2 Hz), 63.7 (d, J = 6.8 Hz), 70.0 (d, J = 160.2 Hz), 128.4, 128.5 (d, J = 5.4 Hz), 133.8, 135.6; IR (neat) 730, 1046, 1239, 3274 cm^{-1}; HRMS (m/z): $[M + H]^+$ calcd for $C_{11}H_{17}O_4ClP$, 279.0553; found, 279.0551. The enantiomeric excess (% ee) was determined to be 53% by HPLC using a Daicel ChiralPAK AS-H column (20% i-PrOH–hexanes, 1 mL min^{-1}, 254 nm): t_R (major, 5.878 min), t_R (minor, 4.907 min).

Diethyl (4-bromophenyl)(hydroxy)methylphosphonate (2e). R_f 0.29 (hexanes–ethyl acetate, 50 : 50 v/v); $[\alpha]_D$ = −17.4 (c = 1.4 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.18–1.29 (m, 6H), 3.95–4.12 (m, 4H), 4.86 (s, 1H), 4.97 (d, J = 11.2 Hz, 1H), 7.33 (dd, J = 2.4, 8.8 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5 (d, J = 5.4 Hz), 63.2 (d, J = 7.4 Hz), 63.7 (d, J = 7.4 Hz), 70.1 (d, J = 159.1 Hz), 122.0, 128.5 (d, J = 5.6 Hz), 131.4, 136.0; IR (neat) 758, 1020, 1237, 3254 cm^{-1}; HRMS (m/z): $[M + H]^+$ calcd for $C_{11}H_{17}O_4BrP$, 323.0048; found, 323.0041. The enantiomeric excess (% ee) was determined to be 61% by HPLC using a Daicel ChiralPAK AS-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 17.857 min), t_R (minor, 14.089 min).

Diethyl hydroxy(phenyl)methylphosphonate (2f). R_f 0.38 (hexanes–ethyl acetate, 50 : 50 v/v); $[\alpha]_D$ = −14.9 (c = 2.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.13–1.30 (m, 6H), 3.54 (s, 1H), 3.89–4.14 (m, 4H), 5.02 (d, J = 10.4 Hz, 1H), 7.27–7.40 (m, 3H), 7.42–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 63.2 (d, J = 7.2 Hz), 63.5 (d, J = 7.0 Hz), 70.8 (d, J = 158.4 Hz), 127.2 (d, J = 5.6 Hz), 128.1, 128.3, 136.8; IR (neat): 734, 1261, 3289 cm^{-1}; HRMS (m/z): $[M + Na]^+$ calcd for $C_{11}H_{17}O_4PNa$, 267.0762; found, 267.0768. The enantiomeric excess (% ee) was determined to be 50% by HPLC using a Daicel ChiralPAK AS-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 17.403 min), t_R (minor, 14.175 min).

Diethyl hydroxy(*p*-tolyl)methylphosphonate (2g). R_f 0.39 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −22.4 (c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 2.34 (s, 3H), 3.91–4.11 (m, 4H), 4.97 (d, J = 10.4 Hz, 1H), 7.17 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5 (t, J = 4.6 Hz), 21.3, 63.2 (d, J = 7.1 Hz), 63.4 (d, J = 6.8 Hz), 70.9 (d, J = 158.4 Hz), 127.1 (d, J = 5.9 Hz), 129.2, 133.5, 138.1; IR (neat) 743, 1029, 1232, 3283 cm^{-1}; HRMS (m/z): $[M + H]^+$ calcd for $C_{11}H_{17}NO_6P$, 290.0794; found, 290.0797. The enantiomeric excess (% ee) was determined to be 58% by HPLC using a Daicel ChiralPAK AS-H column (20% i-PrOH–hexanes, 1 mL min^{-1}, 254 nm): t_R (major, 5.679 min), t_R (minor, 4.794 min).

Diethyl hydroxy(*m*-tolyl)methylphosphonate (2h). R_f 0.36 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −16.1 (c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.03–1.17 (m, 6H), 2.24 (s, 3H), 3.79–4.04 (m, 4H), 4.87 (d, J = 11.6 Hz, 1H), 5.31 (s, 1H), 6.99 (d, J = 6.8 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 7.14–7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4 (t, J = 4.0 Hz), 21.5, 63.1 (d, J = 7.2 Hz), 63.5 (d, J = 7.0 Hz), 70.7 (d, J = 158.6 Hz), 124.3 (d, J = 5.9 Hz), 127.8 (d, J = 5.9 Hz), 128.1, 128.9, 136.6; IR (neat): 786, 1021, 1238, 3323 cm^{-1}; HRMS (m/z): $[M + H]^+$ calcd for $C_{12}H_{20}O_4P$, 259.1099; found, 259.1094. The enantiomeric excess (% ee) was determined to be 71% by HPLC using a Daicel ChiralPAK AS-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 14.567 min), t_R (minor, 12.819 min).

Diethyl (2,3,4-trimethoxyphenyl)(hydroxy)methylphosphonate (2i). R_f 0.35 (hexanes–ethyl acetate, 20 : 80 v/v); $[\alpha]_D$ = −9.4 (c = 2.4 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 3.82–3.92 (m, 4H), 3.92–4.04 (m, 1H), 4.04–4.16 (m, 2H), 5.22 (d, J = 11.6 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5 (d, J = 5.8 Hz), 16.6 (d, J = 5.8 Hz), 56.0, 60.8, 61.5, 63.0 (d, J = 7.0 Hz), 63.2 (d, J = 6.9 Hz), 65.5 (d, J = 162.6 Hz), 107.4, 122.6, 123.4 (d, J = 4.6 Hz), 141.7, 151.7 (d, J = 7.3 Hz), 153.8; IR (neat) 746, 1021, 1269, 3285 cm^{-1}; HRMS (m/z): $[M + H]^+$ calcd for $C_{14}H_{24}O_7P$, 335.1260; found, 335.1259. The enantiomeric excess (% ee) was determined to be 52% by HPLC using a Daicel ChiralCEL AS-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 21.322 min), t_R (minor, 17.296 min).

Diethyl (anthracen-9-yl)(hydroxy)methylphosphonate (2j). R_f 0.38 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −3.3 (c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 6.8 Hz, 3H), 1.16 (t, J = 6.8 Hz, 3H), 3.57–3.73 (m, 1H), 3.74–4.15 (m, 4H), 6.59 (d, J = 16.0 Hz, 1H), 7.38–7.58 (m, 4H), 7.98 (d, J = 8.0 Hz, 2H), 8.07–8.54 (m, 2H), 9.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2 (d, J = 5.6 Hz), 16.5 (d, J = 5.8 Hz), 63.0 (d, J = 7.2 Hz), 63.3 (d, J = 7.0 Hz), 68.3 (d, J = 162.8 Hz), 125.0, 125.9, 127.4, 129.1, 129.4 (d, J = 4.3 Hz), 130.5, 131.6; IR (neat) 738, 1046, 1230, 3281 cm^{-1}; HRMS (m/z): $[M + H]^+$ calcd for $C_{19}H_{21}O_4PNa$, 367.1075; found, 367.1069. The enantiomeric excess (% ee) was determined to be 56% by HPLC using a Daicel ChiralPAK AS-H column (20% i-PrOH–hexanes, 1 mL min^{-1}, 254 nm): t_R (major, 13.141 min), t_R (minor, 8.383 min).

Diethyl (thiophen-2-yl)(hydroxy)methylphosphonate (2k). R_f 0.28 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D$ = −13.3 (c = 1.6 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14–1.26 (m, 6H), 3.94–4.11 (m, 4H), 4.78 (s, 1H), 5.16 (d, J = 10.8 Hz, 1H), 6.92 (t, J = 3.6 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.16–7.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 63.5 (d, J = 7.1 Hz), 63.8 (d, J = 7.0 Hz), 67.1 (d, J = 166.1 Hz), 125.8 (d, J = 3.0 Hz), 126.2 (d, J = 7.3 Hz), 126.9, 139.7; IR (neat): 731, 1037, 1219,

3272 cm^{-1}; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_9H_{16}O_4SP$, 251.0507; found, 251.0516. The enantiomeric excess (% ee) was determined to be 68% by HPLC using a Daicel ChiralPAK AS-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 20.268 min), t_R (minor, 15.147 min).

Diethyl (furan-2-yl)(hydroxy)methylphosphonate (2l). R_f 0.44 (hexanes–ethyl acetate, 40 : 60 v/v); $[\alpha]_D = -11.3$ (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, *J* = 6.8 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 3.98–4.24 (m, 4H), 4.99 (d, *J* = 13.2 Hz, 1H), 6.37 (d, *J* = 1.6 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5 (t, *J* = 6.8 Hz), 63.5 (d, *J* = 6.9 Hz), 63.6 (d, *J* = 6.6 Hz), 64.9 (d, *J* = 165.4 Hz), 109.5 (d, *J* = 6.3 Hz), 110.9, 142.9, 150.1; IR (neat) 729, 1028, 1215, 3274 cm^{-1}; HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_9H_{15}O_5PNa$, 257.0555; found, 257.0554. The enantiomeric excess (% ee) was determined to be 52% by HPLC using a Daicel ChiralCEL OD-H column (10% i-PrOH–hexanes, 0.5 mL min^{-1}, 254 nm): t_R (major, 17.126 min), t_R (minor, 12.569 min).

Acknowledgements

We thank CSIR (Project No. CHY/10-11/264/CSIR/GSEK), New Delhi for the financial support. PM thanks UGC, New Delhi for a senior research fellowship. We thank DST, New Delhi for the funding towards the 400 MHz NMR instrument to the Department of Chemistry, IIT Madras under the IRPHA scheme and ESI-MS facility under the FIST programme.

Notes and references

1 For review, see: (*a*) C. Bolm, J. Legros, J. L. Paih and L. Zani, *Chem. Rev.*, 2004, **104**, 6217; (*b*) S. Enthaler, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2008, **47**, 3317 and references therein; (*c*) *Iron Catalysis*, ed. B. Plietker, Wiley-VCH, Weinheim, 2008.
2 O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry*, 2005, **16**, 3295.
3 H. Gröger and B. Hammer, *Chem.–Eur. J.*, 2000, **6**, 943.
4 (*a*) F. Yang, D. Zhao, J. Lan, P. Xi, L. Yang, S. Xiang and J. You, *Angew. Chem., Int. Ed.*, 2008, **47**, 5646; (*b*) D. Uraguchi, T. Ito and T. Ooi, *J. Am. Chem. Soc.*, 2009, **131**, 3836.
5 (*a*) T. Yokomatsu, T. Yamagishi and S. Shibuya, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1527; (*b*) K. V. Zaitsev, M. V. Bermeshev, A. A. Samsonov, J. F. Oprunenko, A. V. Churakov, J. A. L. Howard, S. S. Karlov and G. S. Zaitsevaa, *New J. Chem.*, 2008, **32**, 1415.
6 (*a*) C. Qian, T. Huang, C. Zhu and J. Sun, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2097; (*b*) A. J. Wooten, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2008, **130**, 7407.
7 W. Chen, Y. Hui, X. Zhou, J. Jiang, Y. Cai, X. Liu, L. Lin and X. Feng, *Tetrahedron Lett.*, 2010, **51**, 4175.
8 (*a*) J. P. Duxbury, J. N. D. Warne, R. Mushtaq, C. Ward, M. Thornton-Pett, M. Jiang, R. Greatrex and T. P. Kee, *Organometallics*, 2000, **19**, 4445; (*b*) B. Saito, H. Egami and T. Katsuki, *J. Am. Chem. Soc.*, 2007, **129**, 1978; (*c*) B. Saito and T. Katsuki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4600; (*d*) S. Gou, X. Zhou, J. Wang, X. Liu and X. Feng, *Tetrahedron*, 2008, **64**, 2864; (*e*) X. Zhou, X. Liu, X. Yang, D. Shang, J. Xin and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 392; (*f*) A. C. Gledhill, N. E. Cosgrove, T. D. Nixon, C. A. Kilner, J. Fisher and T. P. Kee, *Dalton Trans.*, 2010, **39**, 9472; (*g*) K. Suyama, Y. Sakai, K. Matsumoto, B. Saito and T. Katsuki, *Angew. Chem., Int. Ed.*, 2010, **49**, 797.
9 (*a*) S. K. Alamsetti, S. Mannam, P. Muthupandi and G. Sekar, *Chem.–Eur. J.*, 2009, **15**, 1086; (*b*) S. K. Alamsetti, P. Muthupandi and G. Sekar, *Chem.–Eur. J.*, 2009, **15**, 5424; (*c*) S. K. Alamsetti and G. Sekar, *Chem. Commun.*, 2010, 7235.
10 P. Muthupandi, S. K. Alamsetti and G. Sekar, *Chem. Commun.*, 2009, 3288.
11 (*a*) A. W. Addison, T. N. Rao, J. Reedijk, J. Rijn and G. C. Verschoor, *J. Chem. Soc., Dalton Trans.*, 1984, 1349; (*b*) T. Kurahashi, K. Oda, M. Sugimoto, T. Ogura and H. Fujii, *Inorg. Chem.*, 2006, **45**, 7709.
12 Though enantiomeric excess using our chiral iron catalyst for asymmetric hydrophosphorylation is moderate compared to the chiral aluminum and titanium catalytic systems reported by Katsuki[8] and You[4] in which more than 90% ee were obtained, this is the first chiral iron catalytic system developed for asymmetric hydrophosphorylation which will pave the way for better selectivity in the near future.
13 M. J. McKennon and A. I. Meyers, *J. Org. Chem.*, 1993, **58**, 3568.
14 S. Ay, M. Nieger and S. Brase, *Chem.–Eur. J.*, 2008, **14**, 11539.
15 K. Alexander, S. Cook, C. L. Gibson and A. R. Kennedy, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1538.
16 Y. N. Belokon, D. Chusov, D. A. Borkin, L. V. Yashkina, P. Bolotov and T. Skrupskaya, *Tetrahedron: Asymmetry*, 2008, **19**, 459.
17 J. Chin, D. C. Kim, F. Panosyan and K. M. Kim, *Org. Lett.*, 2004, **6**, 2593.
18 S. Zhu, C. Wang, L. Chen, R. Liang, Y. Yu and H. Jiang, *Org. Lett.*, 2011, **13**, 1146.

