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PAPER

Azetidines-derived dinuclear zinc catalyzed asymmetric phospha-Michael addition of dialkyl phosphite to α,β-unsaturated carbonyl compounds

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The asymmetric phospha-Michael addition of dialkyl phosphite to α,β-unsaturated carbonyl compounds by using azetidines-derived dinuclear zinc catalyst was described. The catalyst was proved to be general and efficient for a broad spectrum of enones and α,β-unsaturated *N*-acylpyrroles. A series of phosphonate-containing compounds were generated with excellent enantioselectivities (up to 99% *ee*) and chemical yields (up to 99%) under mild conditions without using additives. The products were obtained with more than 95% ee for 23 examples of α,β-unsaturated carbonyl compounds. A positive nonlinear effect was observed and the possible mechanism was proposed.

Introduction

The formation of C–P bonds is one of the most important transformations in the field of organic synthesis due to the wide application of organophosphorus compounds in the ligands synthesis[1] and pharmaceuticals.[2] The catalytic asymmetric phosphonylation of carbonyl compounds is one of the most useful methods to provide these kinds of compounds, mainly through the phospha-aldol reaction, phospha-Mannich reaction, as well as phospha-Michael reaction.[3] Asymmetric phospha-Michael addition is considered distinct not only because of its significant atom economy for asymmetric synthesis but also the adducts which are relevant chiral scaffolds for further conversion into β- or γ-substituted phosphonates.[4] Wang and co-workers has described the first enantioselective 1,4-addition of diphenyl phosphite to nitroalkenes in the presence of cinchona alkaloid catalyst.[5] Subsequently, the phospha-Michael addition of nitroalkenes has been also reported by using chiral guanidine catalyst[6] or chiral Al–Li–BINOL complex.[7] Jogensen[8a] and Melchiorre[8b–c] has demonstrated respectively phospha-Michael addition by employing α,β-unsaturated aldehydes as electrophiles. Ye presented an organocatalytic phospha-Michael reaction of cyclic α,β-unsaturated enones.[3b] A pincer-palladium complex catalyzed hydrophosphonylation of enones has been disclosed by Duan[9] and Leung,[10] respectively. An asymmetric hydrophosphonylation of chalcones has been described with high enantioselectivity in the presence of a chiral ytterbium silylamide.[11] Recently, the Wang group has achieved a dinuclear zinc catalyzed phosphonylation of a wide range of enones or α,β-unsaturated *N*-acylpyrroles. The proline-derived dinuclear zinc catalyst has proven effectively to afford products with good enantiomeric excess.[12–16] In this protocol, however, additives such as 4Å MS[12–13] or pyridine[14–16] are necessary to improve the reactivity and enantioselectivity. Pyridine has been found essential to prevent the deactivation of catalyst by inhabiting unfavorable binding between potential product and catalyst.[14] It is still highly desired to develop an effective and straightforward catalytic strategy for this transformation.

Based on our previous work, the azetidines-derived dinuclear zinc catalyst system has shown excellent performance on a number of efficient, catalytic, enantioselective transformations, including asymmetric domino Michael/Hemiketalization reaction,[17] Friedel–Crafts alkylation,[18] methylation,[19] alkynylation,[19] as well as enantioselective co-polymerization.[20] It is noteworthy that much higher enantioselectivity has been achieved by using our novel chiral catalyst than that of Trost's dinuclear zinc-ProPhenol catalyst in the asymmetric co-polymerization of cyclohexene oxide with carbon dioxide, which may attribute to the lower flexibility azetidine ring skeleton and appropriate sterically hindered microenvironment compared with that of pyrrolidine. We postulate that our azetidines-derived dinuclear zinc catalyst may be a well suitable catalytic system for the phospha-Michael reaction. Dialkyl phosphites, secondary phosphine oxides, and secondary phosphines are commonly used phosphorus nucleophiles towards this transformation. In view of the lowest pK_a of dialkyl phosphites among the phosphorus nucleophiles,[2b] therefore they are very prone to deprotonate and activate. Dialkyl phosphites are ideal substrates to be employed due to their readily available and more reactive toward a wide range of α,β-unsaturated carbonyl compounds. Herein, we elaborate an azetidines-derived dinuclear zinc catalyzed phospha-Michael addition of dialkyl phosphite to enones and α,β-unsaturated *N*-acylpyrroles.

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Electronic Supplementary Information (ESI) available: All chiral HPLC chromatograms data and spectra for phospha-Michael addition products and copies of NMR spectra for all products. See DOI: 10.1039/x0xx00000x

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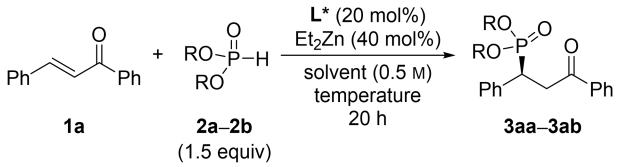
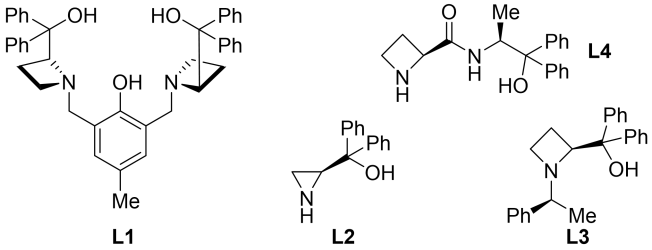
Table 1 Identification of the catalyst system for the catalytic asymmetric addition of dialkyl phosphite to chalcone derivatives.



Entry	L*	R	Et_2Zn	Solvent	$T_{activation}$ (°C)	$T_{reaction}$ (°C)	Yield (%)[a]	*ee* (%)[b]
1[c]	**L1**	Et	40	Toluene	30	25	76	67
2	**L2**	Et	40	Toluene	30	25	trace	0
3	**L3**	Et	40	Toluene	30	25	99	0
4	**L4**	Et	40	Toluene	30	25	65	0
5[d]	**L1**	Et	40	Toluene	30	25	90	77
6	**L1**	Et	40	Toluene	30	25	99	82
7	**L1**	Et	20	Toluene	30	25	62	0
8	**L1**	Et	80	Toluene	30	25	99	19
9	**L1**	Et	40	THF	30	25	78	51
10	**L1**	Et	40	DCM	30	25	trace	0
11	**L1**	Et	40	EtO_2	30	25	81	62
12	**L1**	Et	40	Toluene	25	25	95	74
13	**L1**	Et	40	Toluene	30	45	99	25
14	**L1**	Et	40	Toluene	30	17	99	99
15[e]	**L1**	Et	40	Toluene	30	17	85	80
16	**L1**	Me	40	Toluene	30	25	65	53

[a] Isolated yield reported. [b] The *ee* values were determined by HPLC analysis. In all cases, the product chromatograms were compared against a known racemic mixture. The absolute configurations were assigned by comparison to literature values. [c] 5 mol% of ligand was loaded. [d] 10 mol% of ligand was loaded. [e] 100 mg 4Å MS was introduced as additive.

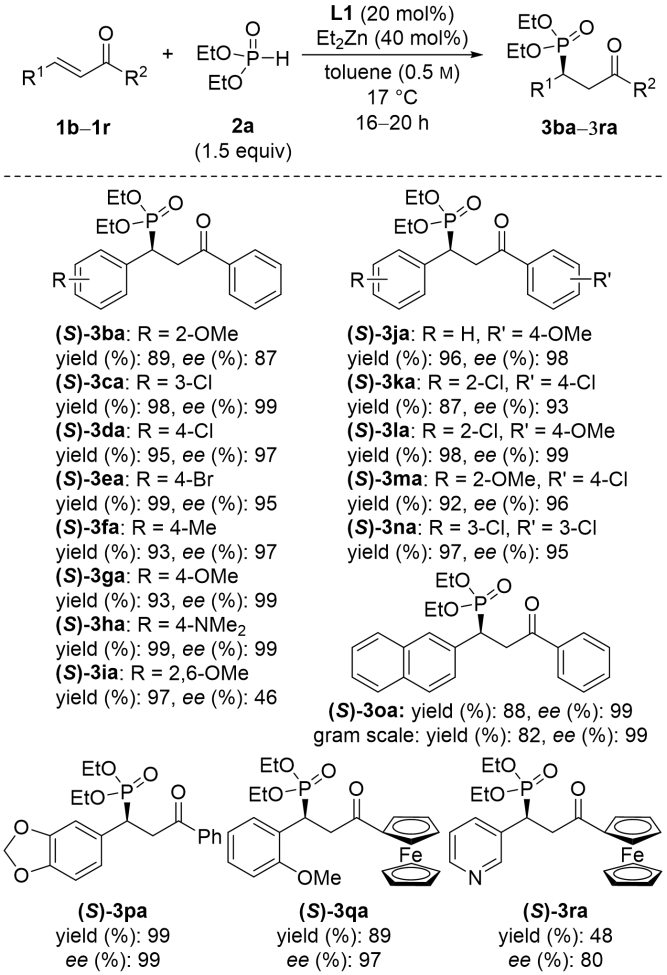


Scheme 1 Different kinds of chiral ligands involved.

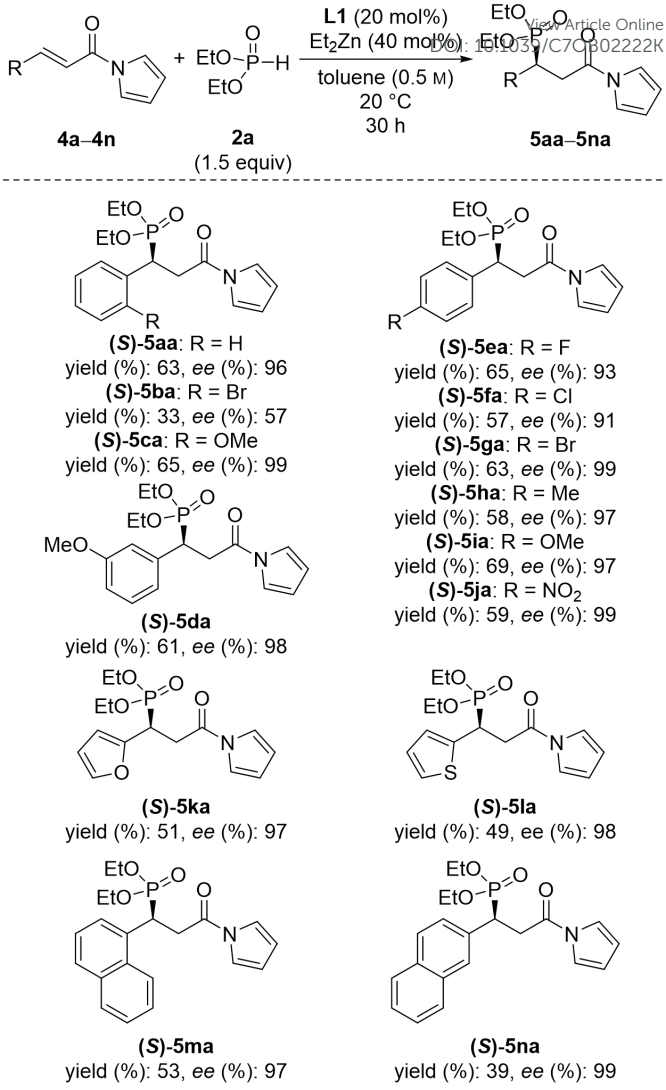
Results and discussion

Preliminary studies began with several chiral ligands and their loading screening in the model reaction between enone **1a** and diethyl phosphite **2a** (Table 1, entries 1–5). A trace amount of product **3aa** was isolated when chiral ligand **L2** was used. Chiral β-amino alcohols **L3–L4** gave desired products without showing enantioselectivity. Fortunately, our azetidines-derived ligand **L1** restored high enantioselectivity. In addition, an enhancement in enantioselectivity was observed with the increasing ligand loading (Table 1, entry 5). Dialkyl phosphite presented a tautomerism with the nucleophilic phosphinous acid tautomer, the equilibrium could shift towards the reactive phosphinous acid form under an appropriate basic environment.[14] An Et_2Zn was employed as a base to activate the phosphite, and its loading was investigated as well in the presence of 20 mol% of our ligand. We found that the racemic product was delivered when 20 mol% of Et_2Zn was used.

Comparatively, up to 82% *ee* was obtained by the employment of 40 mol% of Et_2Zn (Table 1, entry 6). However, very poor *ee* was observed when the loading increased to 0.8 equivalent (Table 1, entry 8). The results indicated diethylzinc in combination with chiral ligands with a ratio of 2:1 might lead to the best asymmetric induction for the current transformation, 20 mol% of ligand and 40 mol% of Et_2Zn was found out optimal. A survey of various solvents revealed that toluene was the choice of solvent to provide product with 99% yield and 82% *ee*. With these results in hand, we further investigated the influence of dialkyl phosphites nucleophiles (Table 1, entries 6 and 16), a comparatively better reactivity and enantioselectivity was obtained when diethyl phosphite (**2a**) was used. We found out the reactivity and enantioselectivity was sensitive to both the activation temperature and reaction temperature. A decrease in activation temperature resulted in reduction of *ee* (Table 1, entry 12), while an increase in reaction temperature led to a diminishment of the enantioselectivity (Table 1, entry 13). A 99% yield and 99% *ee* was achieved when diethyl phosphite (**2a**) was activated at 30°C and the reaction was carried out at 17°C (Table 1, entry 14). However, an obvious decrease in the enantiomeric excess was observed when 4Å MS was added (Table 1, entry 15). This result was contrary to the report of Wang,[12–13] in which the 4Å MS was necessary to significantly enhance the conversion and enantioselectivity, suggesting the superior of our catalytic system.



Scheme 2 Substrate scope for the catalytic asymmetric addition of diethyl phosphite to chalcone derivatives. Reaction conditions: **1b–1r** (0.5 mmol), **2a** (2.0 equiv), **L1** (20 mol%), Et_2Zn (40 mol%), activation temperature (30°C), reaction temperature 17°C) in toluene. Unless otherwise noted, all reactions were processed under argon for indicated reaction time. Isolated yield reported. The *ee* values were determined by HPLC analysis. In all cases, the product chromatograms were compared against a known racemic mixture. The absolute configuration of **3aa** was assigned by comparison of optical rotation and chiral HPLC traces with the literature.[12] The other products were tentatively assigned by analogy.



Scheme 3 Substrate scope for the catalytic asymmetric addition of diethyl phosphite to α,β-unsaturated *N*-acylpyrroles. Reaction conditions: **4a–4n** (0.5 mmol), **2a** (2.0 equiv), **L1** (20 mol%), Et_2Zn (40 mol%), activation temperature (35°C), reaction temperature (20°C) in toluene. Unless otherwise noted, all reactions were processed under argon for indicated reaction time. Isolated yield reported. The *ee* values were determined by HPLC analysis. In all cases, the product chromatograms were compared against a known racemic mixture. The absolute configurations were assigned by analogy.

Therefore, the optimal reaction conditions were finally identified as follows: 20 mol% of **L1**, 40 mol% of Et_2Zn, and diethyl phosphite (**2a**) in toluene, the mixture was activated at 30°C for 0.5 h and then the subsequent reaction was performed at 17°C for 16 h.

A series of substituted enones **1b–1r** were examined under the optimized conditions, excellent yields and enantioselectivities were achieved by employing a broad range of aromatic and heteroaromatic substrates (Scheme 2). The electronic properties of the substituents on the both aryls had no obvious effect on the enantioselectivities of the products (**1c–1h** → **3ca–3ha**). In addition, the enones with substitutions on the different positions of phenyl ring showed similar reactivity and enatioselectivity. Notably, the steric effect was crucial with respect to the enantioselectivity (**1b** → **3ba**, **1i** → **3ia**). The enone **1i** with substituents on the 2,6-positions of the phenyl ring afforded the corresponding product **3ia** with poor *ee* probably due to the bilateral steric hinderance. 2-Naphthyl **1o**, 2-piperonyl **1p** and ferrocenoyl substituted enone **1q** were undergoing hydrophosphonylation with high enantioselectivity. However, the products with poor yield and relatively low enantiomeric excess was obtained when the enones bearing a pyridyl on the α position was introduced (**1r** → **3ra**) because the catalyst might be poisoned by pyridine ring binding to the catalyst. It is worthy to mention that when the reaction was scaled up to 4 mmol of chalcone substrate **1o**, product **(*S*)-3oa** was obtained in

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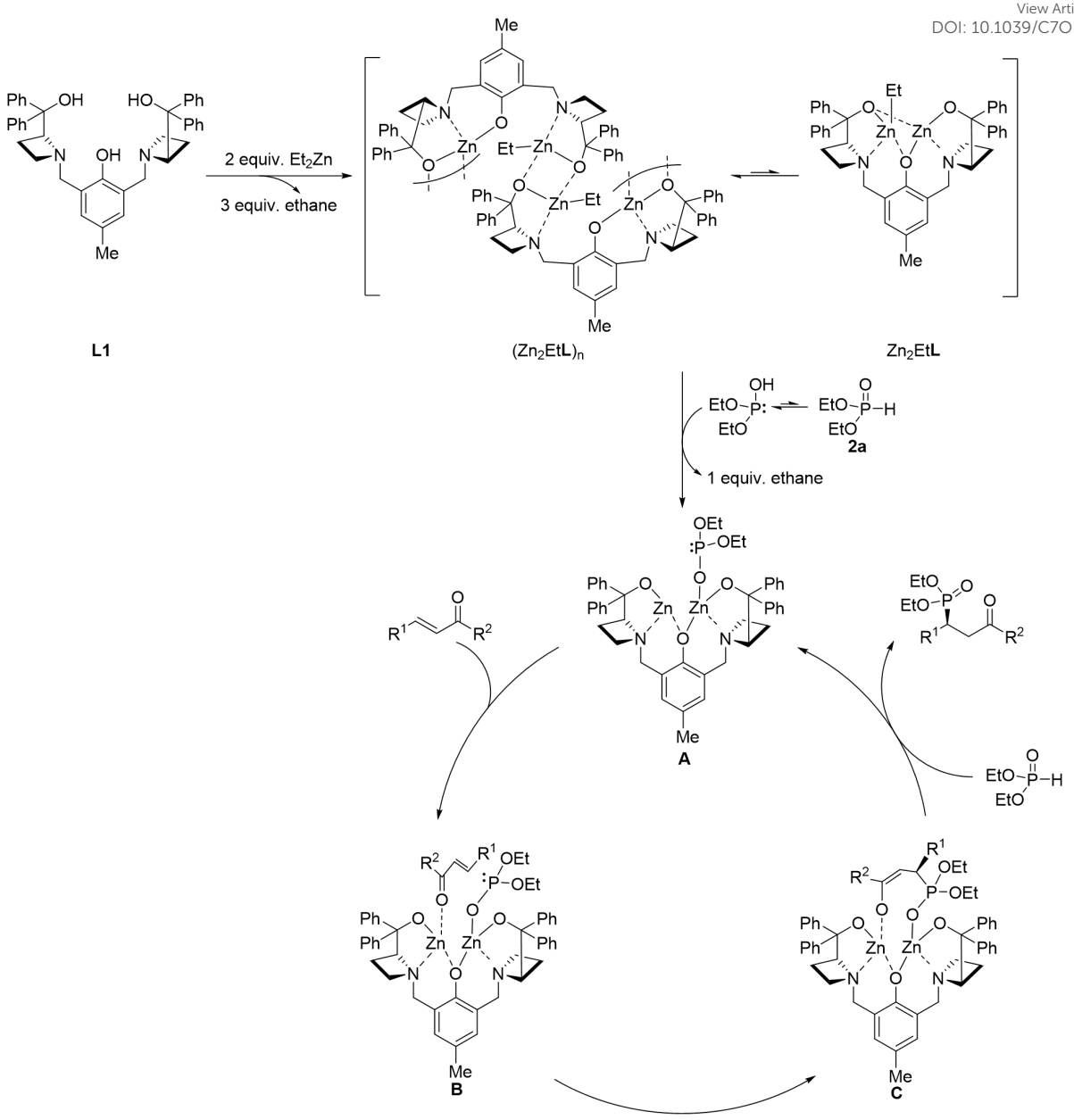

Scheme 4 Proposed catalytic cycle of the phospha-Michael addition.

82% yield without losing enantioselectivit, demonstrating the utility on a preparative scale (**1o** → **3oa**, gram scal).

It is still highly demanded to improve the synthetic utility by extension the substrate scope of the α,β-unsaturated carbonyl compounds. α,β-Unsaturated *N*-acylpyrroles are desired substrates because they are highly reactive, monodentate ester surrogates and their adducts can be readily converted into alcohols, aldehydes/ketones, and carboxylic acid derivatives.[21] To our delight, a broad spectrum of aromatic α,β-unsaturated *N*-acylpyrroles **4a–4n** irrespective of electronic nature or positions of substituents on the phenyl ring were well applicable to the present catalyst with excellent enantioselectivity (Scheme 3). However, a relative lower yields were obtained compared to the enones due to the less reactivity of α,β-unsaturated *N*-acylpyrroles. Either electron donating methoxyl substituent or electron withdrawing nitro group led to high enantiomeric excess (**5ia** *vs* **5ja**). The *ortho*, *meta* or *para* methoxyl substituted *N*-acylpyrroles gave the corresponding products in comparable yield and enantioselectivity (**5ca**, **5da**, and **5ia**). We were pleased to find that the phosphonylation of *N*-acylpyrroles bearing furyl, thienyl, or naphthyl substituents on the β position were also highly enantioselective (**4k–4n** → **5ka–5na**). However, a bulkyl bromo substituent in the *ortho* position of the phenyl ring reduced both yield and enantioselectivity (**4b** → **5ba**).

To shed some light on reaction mechanism, a non-linear effect (NLE) was identified by measuring the correlation of the enantiomeric excess between product and chiral ligand.[22–26] The variation of *ee* values of the ligand generated asymmetric phosphonylation. A

positive non-linear effect was observed in the reaction of diethyl phosphite (**2a**) and α,β-unsaturated *N*-acylpyrrole **4a** catalyzed by azetidines-derived dinuclear zinc (Figure 1). The result suggested that the homochiral and heterochiral aggregates or dimeric form of the catalyst $(Zn_2Et\mathbf{L})_n$ would be involved in the catalytic cycle. The homochiral polymeric complex composed of the optically pure ligands dissociates more readily than the corresponding heterochiral one containing both (*S*,*S*) and (*R*,*R*) ligands to give monomeric enantiopure catalyst Zn_2Et**L1**, hence leading to a (+)-NLE.

Based on the above results and the previous reports,[12,18] the catalytic cycle would involve the formation of inactive species $(Zn_2Et\mathbf{L})_n$ by the coordination of chiral ligand to 2 equiv of Et_2Zn, the complex $(Zn_2Et\mathbf{L})_n$ is decomposed to the catalytically active species Zn_2Et**L** simultaneously. Subsequently, the diethyl phosphite (**2a**) is deprotonated by the catalyst to generate a zinc phosphonate intermediate **A**. Then the coordinating of α,β-unsaturated carbonyl compound to the other zinc atom from the most sterically accessible site leads to the formation of complexes **B** followed by undergoing the phospho-transfer (**B** → **C**). The catalytic cycle is regenerated by a proton exchange with another diethyl phosphite (**2a**) to release the product (Scheme 4).

Conclusions

In conclusion, we achieved an azetidines-derived dinuclear zinc catalyzed conjugate addition of dialkyl phosphite to α,β-unsaturated carbonyl compounds in the absence of additives. Our catalytic system was proved to be effective and general to provide the corresponding products in good yields with excellent enantioselectivity. Diethyl phosphite was found to be a highly reactive nucleophils, the phosphonylation of various α,β-unsaturated carbonyl compounds were highly enantioselective. a positive nonlinear effect was observed. On the basis of the experimental results and previous reports, a possible mechanism was proposed. Detailed reaction mechanism and applications of the phospha-Michael adducts are investigated in our ongoing studies.

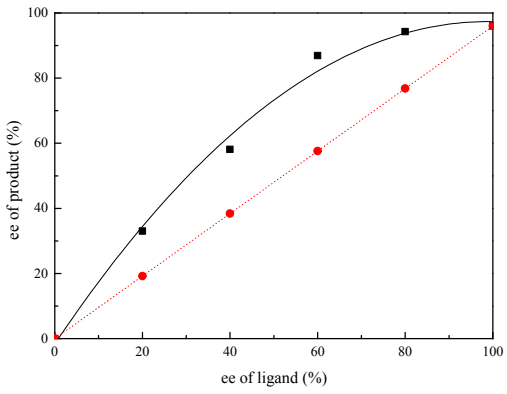

Figure 1 Correlation between the *ee* values of the ligand (*S*,*S*)-**L1** and the *ee* of product.

Experimental

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General remarks: All reactions were performed in flame-dried glassware using conventional Schlenk techniques under a static pressure of argon. Liquids and solutions were transferred with (micro)syringes. Solvents were purified and dried following standard procedures. Technical grade solvents for extraction and chromatography were distilled prior to use. Analytical thin-layer chromatography (TLC) and flash column chromatography were performed on silica gel using the indicated solvents. Infrared (IR) spectra were recorded on a *Nicolet IR 200* spectrophotometer in KBr pellets and are reported (br = broad, vw = very weak, w = weak, m = medium, s = strong) in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on *Bruker DPX 400* (400 MHz). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual solvent resonance as the internal standard (δ = 7.26 ppm for ^1H and δ = 77.16 ppm for ^{13}C). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. Optical rotations were recorded on a *Perkin-Elmer 341* polarimeter. Mass spectra were recorded on *VG-FAB* mass spectrometer. The *ee* value determination was carried out using chiral HPLC on a *Chiralcel AD, OD, or OD-H Column* (for all the columns: 4.6 mmϕ × 250 mm, Daicel Chemical Ind., LTD, Japan) combined with a *JASCO model PU-1580 intelligent HPLC pump* and a *JASCO model UV-1575 intelligent UV-vis detector*.

General procedure for the catalytic asymmetric addition of diethyl phosphite to enones: In a flame-dried Schlenk tube equipped with a magnetic stir bar, a solution of the chiral ligand **L1** (15.3 mg, 0.025 mmol, 20 mol%) in dry toluene (1.0 mL, 0.125 M) under nitrogen at 0 °C. Then diethylzinc (0.05 mL, 1.0 mol/L in hexane, 0.05 mmol, 40 mol%) and diethyl phosphite (**2a**, 0.19 mmol, 1.5 equiv) were added into the mixture successively. The system is stirred at 30°C for 30 min before cooled to 0°C. Then enone substrates (**1a**–**1r**, 0.125 mmol, 1.0 equiv) is added by a micro syringe to the mixture. The solution is stirred at 17°C for 16–20 h. After complete consumption of the starting material, as monitored by TLC analysis, the reaction mixture is allowed to cool to room temperature, quenched with 1M HCl (1.0 mL), and extracted with dichloromethane (3 × 5 mL). The combined organic phases are washed with brine (5.0 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, purification of the residue by column chromatography on silica gel using mixtures of petroleum ether and ethyl acetate as eluents (ethyl acetate: petroleum ether = 1:4 → 1:2) affords the analytically pure compounds **3aa**–**3ra**.

(*S*)-Diethyl 3-oxo-1,3-diphenylpropylphosphonate (**3aa**):[12] A colorless oil, 42.9 mg, 99% yield, 99% *ee*; $[\alpha]_D^{20}$ = –17.8 (*C* = 1.0, $CHCl_3$); determined by HPLC on a Chiralcel OD column (hexane/2-propanol = 90/10, flow rate = 0.3 mL/min, UV detection at 254 nm); retention time: $t_R(S)$ = 20.67 min, $t_R(R)$ = 22.46 min.

(*S*)-Diethyl 1-(2-methoxyphenyl)-3-oxo-3-phenylpropylphosphonate (**3ba**):[12] A colorless oil, 41.9 mg, 89% yield, 87% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: $t_R(S)$ = 15.94 min, $t_R(R)$ = 22.75 min.

(*S*)-Diethyl 1-(3-chlorophenyl)-3-oxo-3-phenylpropylphosphonate (**3ca**):[12] A colorless oil, 46.6 mg, 98% yield, 99% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 0.3 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 50.74 min, t_R(*R*) = 44.85 min.

(*S*)-Diethyl 1-(4-chlorophenyl)-3-oxo-3-phenylpropylphosphonate (**3da**):[12] A colorless oil, 45.2 mg, 95% yield, 97% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 19.76 min, t_R(*R*) = 23.39 min.

(*S*)-Diethyl 1-(4-bromophenyl)-3-oxo-3-phenylpropylphosphonate (**3ea**):[12] A colorless oil, 52.6 mg, 99% yield, 95% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 21.99 min, t_R(*R*) = 27.58 min.

(*S*)-Diethyl 3-oxo-3-phenyl-1-*p*-tolylpropylphosphonate (**3fa**):[12] A colorless oil, 41.9 mg, 93% yield, 97% *ee*; determined by HPLC on a Chiralcel OD column (hexane/2-propanol = 50/1, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 16.54 min, t_R(*R*) = 25.23 min.

(*S*)-Diethyl 1-(4-methoxyphenyl)-3-oxo-3-phenylpropylphosphonate (**3ga**):[12] A colorless oil, 43.8 mg, 93% yield, 99% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 17.49 min, t_R(*R*) = 21.88 min.

(*S*)-Diethyl 1-(4-dimethylamino)-3-oxo-3-phenylpropylphosphonate (**3ha**): A colorless oil, 48.2 mg, 99% yield, 99% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 29.43 min, t_R(*R*) = 23.48 min; $[\alpha]_D^{20}$ = –35.2 (*C* = 0.7, $CHCl_3$); IR (KBr): nu(tilde)/cm^{-1} = 3004, 2921, 1706, 1557, 1507, 1217, 897, 744, 524; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 7.94 (d, *J* = 7.2 Hz, 2H), 7.52 (dd, *J* = 7.2 Hz, *J* = 7.4 Hz, 1H), 7.42 (dd, *J* = 7.2 Hz, *J* = 7.4 Hz, 2H), 7.30–7.27 (m, 2H), 6.65 (d, *J* = 7.2 Hz, 2H), 4.08–4.06 (m, 2H), 3.91–3.89 (m, 2H), 3.71–3.62 (m, 3H), 2.88 (s, 6H), 1.26 (t, *J* = 6.6 Hz, 3H), 1.13 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 196.6 (d, *J* = 5.2 Hz), 149.6 (d, *J* = 2.4 Hz), 136.5, 133.0, 129.7 (d, *J* = 6.6 Hz), 128.4, 128.0, 123.1 (d, *J* = 7.2 Hz), 112.5 (d, *J* = 2.0 Hz), 62.8 (d, *J* = 7.0 Hz), 61.7 (d, *J* = 7.3 Hz), 40.4, 39.9 (d, *J* = 139.0 Hz), 29.6, 16.3 (d, *J* = 6.0 Hz), 16.2 (d, *J* = 5.8 Hz) ppm; HRMS m/z: calcd. for $C_{21}H_{29}NO_4P$ $[M+H]^+$ 390.1829, found 390.1826.

(*S*)-Diethyl 1-(2,6-dimethoxyphenyl)-3-oxo-3-phenylpropylphosphonate (**3ia**): A colorless oil, 49.3 mg, 97% yield, 46% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 11.53 min, t_R(*R*) = 13.39 min; $[\alpha]_D^{20}$ = –9.2 (*C* = 0.2, $CHCl_3$); IR (KBr): nu(tilde)/cm^{-1} = 2924, 2850, 1687, 1594, 1398, 1163, 957, 781, 568; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 7.95 (d, *J* = 7.4 Hz, 2H), 7.53 (dd, *J* = 7.3 Hz, *J* = 7.3 Hz, 1H), 7.42 (dd, *J* = 7.5 Hz, *J* = 7.5 Hz, 2H), 7.15 (m, 1H), 6.52 (d, *J* = 7.8 Hz, 2H), 4.86–4.77 (m, 1H), 4.12–4.08 (m, 3H), 4.17–4.05 (m, 2H), 3.90 (s, 6H), 3.83–3.72 (m, 1H), 1.30 (t, *J* = 6.5 Hz, 3H), 1.13 (t, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 198.0 (d, *J* = 13.5 Hz), 158.4, 137.0, 132.7, 129.3, 128.2, 112.7, 112.6, 104.3, 62.0 (d, *J* = 6.8 Hz), 61.7 (d, *J* = 6.7 Hz), 55.9, 29.3, 22.7, 16.4 (d, *J* = 6.3 Hz), 16.2 (d, *J* = 6.3 Hz) ppm; HRMS m/z: calcd. for $C_{21}H_{28}O_6P$ $[M+H]^+$ 407.1618, found 407.1620.

(*S*)-Diethyl 3-(4-methoxyphenyl)-3-oxo-1-phenylpropylphosphonate (**3ja**):[12] A white solid, 45.2 mg, 96% yield, 98% *ee*; determined by HPLC on a Chiralcel OD column (hexane/2-propanol = 90/10, flow rate = 0.5 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 20.21 min, t_R(*R*) = 19.30 min.

(*S*)-Diethyl 1-(2-chlorophenyl)-3-(4-chlorophenyl)-3-oxopropylphosphonate (**3ka**): A yellow solid, 45.2 mg, 87% yield, 93% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 24.59 min, t_R(*R*) = 22.13 min; $[\alpha]_D^{20}$ = –27.2 (*C* = 0.4, $CHCl_3$); m.p. = 77.1–77.6 °C; IR (KBr): nu(tilde)/cm^{-1} = 2982, 2928, 1690, 1589, 1477, 1246, 1093, 967, 748, 566; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 8.86 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.40–7.37 (m, 3H), 7.18–7.11 (m, 2H), 4.61–4.54 (m, 1H), 4.14–4.09 (m, 2H), 3.89–3.86 (m, 1H), 3.78–3.69 (m, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 194.7 (d, *J* = 15.1 Hz), 139.7, 135.1 (d, *J* = 8.6 Hz), 134.5, 133.8 (d, *J* = 6.4 Hz), 129.6 (d, *J* = 2.3 Hz), 129.4, 128.9 (d, *J* = 4.5 Hz), 128.8, 128.2 (d, *J* = 3.1 Hz), 126.8 (d, *J* = 3.0 Hz), 62.9 (d, *J* = 7.0 Hz), 62.2 (d, *J* = 7.0 Hz), 34.5 (d, *J* = 140.0 Hz), 29.5, 16.2 (d, *J* = 6.1 Hz), 16.0 (d, *J* = 5.7 Hz) ppm; HRMS m/z: calcd. for $C_{19}H_{22}Cl_2O_4P$ $[M+H]^+$ 415.0627, found 415.0624.

(*S*)-Diethyl 1-(2-chlorophenyl)-3-(4-methoxyphenyl)-3-oxopropylphosphonate (**3la**): A colorless oil, 50.3 mg, 98% yield, 99% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 90/10, flow rate = 0.15 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 99.78 min, t_R(*R*) = 96.19 min; $[\alpha]_D^{20}$ = –25.2 (*C* = 0.7, $CHCl_3$); IR (KBr): nu(tilde)/cm^{-1} = 2981, 2926, 1680, 1597, 1511, 1394, 1246, 1172, 968, 757, 547;^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 7.93 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.20–7.14 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.66–4.60 (m, 1H), 4.17–4.11 (m, 2H), 3.90–3.84 (m, 1H), 3.84 (s, 3H), 3.75–3.68 (m, 3H), 1.30 (t, *J* = 6.6 Hz, 3H), 1.09 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 194.4 (d, *J* = 15.3 Hz), 163.6, 135.2 (d, *J* = 8.7 Hz), 134.1 (d, *J* = 6.5 Hz), 130.3, 129.7 (d, *J* = 2.5 Hz), 129.4, 129.1 (d, *J* = 4.6 Hz), 128.1 (d, *J* = 3.2 Hz), 126.8 (d, *J* = 3.2 Hz), 113.7, 62.9 (d, *J* = 7.0 Hz), 62.2 (d, *J* = 7.0 Hz), 55.4, 34.6 (d, *J* = 139.7 Hz), 29.6, 16.3 (d, *J* = 6.2 Hz), 16.1 (d, *J* = 5.8 Hz) ppm; HRMS m/z: calcd. for $C_{20}H_{25}ClO_5P$ $[M+H]^+$ 411.1123, found 411.1118.

(*S*)-Diethyl 3-(4-chlorophenyl)-1-(2-methoxyphenyl)-3-oxopropylphosphonate (**3ma**): A colorless oil, 47.2 mg, 92% yield, 96% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 23.08 min, t_R(*R*) = 32.42 min; $[\alpha]_D^{20}$ = –18.9 (*C* = 0.47, $CHCl_3$); IR (KBr): nu(tilde)/cm^{-1} = 2923, 2850, 1688, 1589, 1511, 1394, 1246, 1172, 968, 757, 571; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 7.87 (d, *J* = 8.2 Hz, 2H), 7.41–7.38 (m, 3H), 7.19 (dd, *J* = 7.5 Hz, *J* = 7.5 Hz, 1H), 6.88 (dd, *J* = 7.6 Hz, *J* = 8.2 Hz, 2H), 4.61–4.54 (m, 1H), 4.10–4.07 (m, 2H), 3.93–3.88 (m, 1H), 3.87 (s, 3H), 3.78–3.72 (m, 1H), 3.68–3.64 (m, 2H), 1.36–1.25 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 195.5 (d, *J* = 14.9 Hz), 157.3 (d, *J* = 7.0 Hz), 139.4, 134.9, 129.5, 128.8, 128.6 (d, *J* = 4.9 Hz), 128.2 (d, *J* = 3.2 Hz), 124.3 (d, *J* = 6.9 Hz), 120.6 (d, *J* = 3.0 Hz), 110.9 (d, *J* = 2.2 Hz), 62.6 (d, *J* = 7.0 Hz), 61.9 (d, *J* = 7.0 Hz), 55.8, 30.5 (d, *J* = 140.5 Hz), 29.6, 16.3 (d, *J* = 6.2 Hz), 16.1 (d, *J* = 6.0 Hz) ppm; HRMS m/z: calcd. for $C_{20}H_{25}ClO_5P$ $[M+H]^+$ 411.1123, found 411.1120.

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(*S*)-Diethyl 1,3-bis(3-chlorophenyl)-3-oxopropylphosphonate (**3na**): A colorless oil, 50.4 mg, 97% yield, 95% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 0.8 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 18.15 min, t_R(*R*) = 16.60 min; $[\alpha]_D^{20}$ = –35.2 (*C* = 0.47, $CHCl_3$); IR (KBr): nu(tilde)/cm^{-1} = 2980, 2925, 1689, 1596, 1246, 1163, 965, 755, 585; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 7.95 (d, *J* = 7.5 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.35–7.33 (m, 1H), 7.31–7.21 (m, 2H), 4.11–4.07 (m, 2H), 3.99–3.94 (m, 2H), 3.82–3.78 (m, 1H), 3.72–3.67 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 195.9 (d, *J* = 14.9 Hz), 138.1 (d, *J* = 6.7 Hz), 136.3, 134.2 (d, *J* = 2.9 Hz), 133.4, 129.6 (d, *J* = 2.4 Hz), 129.2, 129.2, 128.6, 128.0, 127.4, 127.4, 127.4, 62.9 (d, *J* = 6.9 Hz), 62.1 (d, *J* = 7.1 Hz), 38.9, 29.6, 16.3 (d, *J* = 6.0 Hz), 16.1 (d, *J* = 5.7 Hz) ppm; HRMS m/z: calcd. for $C_{19}H_{22}Cl_2O_4P$ $[M+H]^+$ 415.0627, found 415.0622.

(*S*)-Diethyl 1-(naphthalen-3-yl)-3-oxo-3-phenylpropylphosphonate (**3oa**):[12] A white solid, 43.6 mg, 88% yield, 99% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 9.29 min, t_R(*R*) = 10.82 min.

(*S*)-Diethyl 1-(benzo[*d*][1,3]dioxol-6-yl)-3-oxo-3-phenylpropylphosphonate (**3pa**): A white solid, 48.3 mg, 99% yield, 99% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 38.91 min, t_R(*R*) = 35.08 min; $[\alpha]_D^{20}$ = –16.7 (*C* = 0.4, $CHCl_3$); IR (KBr): nu(tilde)/cm^{-1} = 2981, 1688, 1597, 1489, 1245, 1163, 1099, 964, 755, 572; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = δ 7.94 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.98 – 6.82 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 2H), 4.19 – 4.03 (m, 2H), 4.02 – 3.75 (m, 3H), 3.73 – 3.54 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 196.4 (d, *J* = 15.2 Hz), 147.6 (d, *J* = 2.6 Hz), 146.8 (d, *J* = 3.0 Hz), 136.6, 133.3, 130.0 (d, *J* = 7.2 Hz), 128.6, 128.1, 122.7(d, *J* = 7.8 Hz), 109.9 (d, *J* = 6.1 Hz), 108.0 (d, *J* = 2.1 Hz), 101.0, 62.9(d, *J* = 7.1 Hz), 61.9(d, *J* = 7.3 Hz), 39.2, 37.8, 29.6, 16.4 (d, *J* = 5.9 Hz) 16.3 (d, *J* = 5.7 Hz) ppm; HRMS m/z: calcd. for $C_{20}H_{23}O_6P$ $[M+H]^+$ 391.1305, found 391.1307.

(*S*)-Diethyl 3-(ferrocene)-1-(2-methoxyphenyl)-3-oxopropylphosphonate (**3qa**): A brown solid, 53.9 mg, 89% yield, 97% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 22.35 min, t_R(*R*) = 17.59 min; $[\alpha]_D^{20}$ = –35.2 (*C* = 0.35, $CHCl_3$); m.p. = 102.1 –103 °C; IR (KBr): nu(tilde)/cm^{-1} = 2921, 2850, 1677, 1494, 1451, 1398, 1250, 1106, 964, 755, 571; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 7.45 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.8 Hz, *J* = 7.8 Hz, 1H), 6.91 (dd, *J* = 7.5 Hz, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.74 (s, 2H), 4.63–4.55 (m, 1H), 4.43 (s, 2H), 4.11–4.06 (m, 2H), 3.99 (s, 5H), 3.89–3.85 (m, 3H), 3.85–3.83 (m, 1H), 3.71–3.69 (m, 1H), 3.50–3.47(m, 1H), 3.36–3.33 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 200.2 (d, *J* = 16.3 Hz), 157.5 (d, *J* = 7.1 Hz), 128.7 (d, *J* = 5.0 Hz), 128.1 (d, *J* = 3.2 Hz), 124.6 (d, *J* = 6.6 Hz), 120.5 (d, *J* = 3.1 Hz), 111.0 (d, *J* = 3.2 Hz), 78.4, 72.1 (d, *J* = 5.1 Hz), 69.5 (d, *J* = 4.9 Hz), 69.1, 69.0, 62.5 (d, *J* = 6.9 Hz), 61.6 (d, *J* = 7.0 Hz), 55.9, 39.9, 29.5 (d, *J* = 140.4 Hz), 16.3 (d, *J* = 6.2 Hz), 16.0 (d, *J* = 5.9 Hz) ppm; HRMS m/z: calcd. for $C_{24}H_{30}FeO_5P$ $[M+H]^+$ 485.1164, found 485.1162.

(*S*)-Diethyl 3-(ferrocene)-1-(2-pyridinyl)-3-oxopropylphosphonate (**3ra**): A brown oil, 27.3 mg, 48% yield, 80% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 27.73 min, t_R(*R*) = 16.71 min; $[\alpha]_D^{20}$ = –27.2 (*C* = 0.3, $CHCl_3$); IR (KBr): nu(tilde)/cm^{-1} = 2924, 1688, 1633, 1542, 1509, 1398, 1399, 1256, 1161, 1025, 968, 561; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major + minor) = 8.52 (s, 1H), 7.58–7.53 (m, 1H), 7.47–7.41 (m, 1H), 7.20–7.09 (m, 1H), 4.75–4.70 (m, 2H), 4.42–4.37(m, 2H), 4.09–4.00 (m, 11H), 3.27–3.25 (m, 1H), 1.24 (t, 3H), 0.84 (t, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ (major + minor) = 200.8 (d, *J* = 16.2 Hz), 155.9 (d, *J* = 7.4 Hz), 149.0, 136.3, 125.4, 122.0, 78.4, 72.2, 69.8, 69.4, 69.0, 62.5 (d, *J* = 6.9 Hz), 62.3 (d, *J* = 6.5 Hz), 40.4 (d, *J* = 137.1 Hz), 29.6, 16.4 (d, *J* = 5.8 Hz), 16.2 (d, *J* = 5.7 Hz) ppm; HRMS m/z: calcd. for $C_{22}H_{27}FeNO_4P$ $[M+H]^+$ 456.1022, found 456.1018.

General procedure for the catalytic asymmetric addition of diethyl phosphite to α,β-unsaturated *N*-acylpyrroles: In a flame-dried Schlenk tube equipped with a magnetic stir bar, a solution of the chiral ligand **L1** (15.3 mg, 0.025 mmol, 20 mol%) in dry toluene (1.0 mL, 0.125 M) under nitrogen at 0 °C. Then diethylzinc (0.05 mL, 1.0 mol/L in hexane, 0.05 mmol, 40 mol%) and diethyl phosphite (**2a**, 0.19 mmol, 1.5 equiv) were added into the mixture successively. The system is stirred at 35°C for 30 min before cooled to 0°C. Then α,β-unsaturated *N*-acylpyrrole substrate (**4a**–**4n**, 0.125 mmol, 1.0 equiv) is added by a micro syringe to the mixture. The solution is stirred at 20°C for 30 h. After complete consumption of the starting material, as monitored by TLC analysis, the reaction mixture is allowed to cool to room temperature, quenched with 1M HCl (1.0 mL), and extracted with dichloromethane (3 × 5 mL). The combined organic phases are washed with brine (5.0 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, purification of the residue by column chromatography on silica gel using mixtures of petroleum ether and ethyl acetate as eluents (ethyl acetate: petroleum ether = 1:4 → 1:2) affords the analytically pure compounds **5aa**–**5ma**.

(*S*)-Diethyl 1-phenyl-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5aa**):[13] A colorless oil, 41.3 mg, 63% yield, 96% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 0.5 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 25.83 min, t_R(*R*) = 29.04 min.

(*S*)-Diethyl 1-(2-bromophenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ba**):[13] A colorless oil, 17.1 mg, 33% yield, 57% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 15.03 min, t_R(*R*) = 18.01 min.

(*S*)-Diethyl 1-(2-methoxyphenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ca**):[13] A colorless oil, 29.8 mg, 65% yield, 99% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 19.76 min, t_R(*R*) = 22.38 min.

(*S*)-Diethyl 1-(3-methoxyphenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5da**):[13] A colorless oil, 27.8 mg, 61% yield, 98% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 19.24 min, t_R(*R*) = 22.83 min.

(*S*)-Diethyl 1-(4-fluorophenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ea**):[13] A white solid, 28.7 mg, 65% yield, 93% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 13.46 min, t_R(*R*) = 20.10 min.

(*S*)-Diethyl 1-(4-chlorophenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5fa**):[13] A white solid, 26.3 mg, 57% yield, 91% *ee*; determined by HPLC on a Chiralcel AD column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 47.81 min, t_R(*R*) = 64.54 min.

(*S*)-Diethyl 1-(4-bromophenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ga**):[13] A white solid, 32.6 mg, 63% yield, 99% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 17.48 min, t_R(*R*) = 20.73 min.

(*S*)-Diethyl 1-(4-methylphenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ha**):[13] A colorless oil, 25.3 mg, 58% yield, 97% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 12.09 min, t_R(*R*) = 17.02 min.

(*S*)-Diethyl 1-(4-methyoxylphenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ia**):[13] A colorless oil, 31.5 mg, 69% yield, 97% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 20.45 min, t_R(*R*) = 24.67 min.

(*S*)-Diethyl 1-(4-nitrophenyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ja**):[13] A pale yellow solid, 28.1 mg, 59% yield, 99% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 7.45 min, t_R(*R*) = 8.55 min.

(*S*)-Diethyl 1-(furan-2-yl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ka**):[13] A colorless oil, 20.7 mg, 51% yield, 97% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 0.5 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 42.68 min, t_R(*R*) = 45.48 min.

(*S*)-Diethyl 1-(thiophen-2-yl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5la**):[13] A colorless oil, 20.5 mg, 48% yield, 98% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 0.5 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 18.60 min, t_R(*R*) = 20.56 min.

(*S*)-Diethyl 1-(1-naphthyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5ma**):[13] A colorless oil, 25.5 mg, 53% yield, 97% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 18.98 min, t_R(*R*) = 21.43 min.

(*S*)-Diethyl 1-(2-naphthyl)-3-oxo-3-pyrrol-1-yl-propylphosphonate (**5na**):[13] A colorless oil, 18.8 mg, 39% yield, 99% *ee*; determined by HPLC on a Chiralcel OD-H column (hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV detection at 254 nm); retention time: t_R(*S*) = 8.20 min, t_R(*R*) = 13.98 min.

Conflicts of interest

There are no conflicts of interest to declare.

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