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Design and synthesis of new chiral pyridine–phosphite ligands for the copper-catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones

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ABSTRACT

A series of new chiral pyridine–phosphite ligands have been prepared from (*R*)-pyridyl alcohols and BINOL-derived chlorophosphite, and successfully employed in the copper-catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones. Using the simple and inexpensive $CuBr_2$ as a precursor, the enantioselective additions to various substituted acyclic enones afforded products in high yields and good enantioselectivities (up to 92% ee).

1. Introduction

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated carbonyl substrates catalyzed by a chiral catalyst is one of the most useful synthetic methodologies for carbon–carbon bond formation in organic synthesis, which has been extensively investigated in recent years.[1] Following the pioneering work of Alexakis,[2] several groups have developed a number of effective chiral ligand systems for the Cu-catalyzed enantioselective addition of Et_2Zn to various structurally diverse enones.[3,4]

Among the many structures investigated, pyridine–phosphine ligand **1** reported by Zhang proved to be a particularly efficient ligand for the copper-catalyzed enantioselective conjugate addition of Et_2Zn to a wide range of acyclic enones as well as certain cyclic enones.[5] With the intention of mimicking the coordination sphere of this type of catalyst more closely and enabling an easier synthesis of those ligands, we have developed a series of pyridine–phosphite ligands such as **2** and **3**.[6] As expected, these ligands demonstrated a higher activity for the copper-catalyzed conjugate addition of Et_2Zn to acyclic enones than that of ligand **1**. Our previous studies also demonstrated that the bridge between the pyridine moiety and the chiral phosphate moiety in these ligands is important for achieving high activity and enantioselectivity. We reasoned that this may be attributed to the strong asymmetric induction ability imposed by the axial chiral bridge and the inherent appropriate steric and electronic features possessed by the BINOL-derived (BINOL = 1,1′-binaphthalene-2,2′-diol) phosphite moiety (Fig. 1). Despite the advantages of excellent enantioselectivities and high yields obtained for various substituted chalcones by this type of ligand, the synthetic procedure for the axial chiral bridge NOBIN (NOBIN = 2-amino-2′-hydroxy-1,1′-binaphthalene) and 2-amino-2′-hydroxy-6,6′-dimethyl-1,1′-biphenyl was somewhat tedious.[7] In an effort to develop low cost and easy-to-synthesize chiral pyridine–phosphorus ligands, which could still hold the advantage of high enantioselectivity and activity of **2** and **3**, as well as probing further the structural effect of chiral bridge which incorporated the pyridine and the phosphorus coordination sphere, we decided to extend our studies to introduce a stereogenic bridge to link the pyridine moiety and the phosphite moiety for preparing analogues of types **4–6** starting from **9** and **10** and BINOL. Herein, we report our results on the design and synthesis of a new class of modular pyridine–phosphite ligands **4–6**, as well as their applications in Cu-catalyzed asymmetric conjugate addition of Et_2Zn to enones.

2. Results and discussion

2.1. Synthesis of pyridine–phosphites 4–6

As shown in Scheme 1, ligands of this type are readily prepared from the corresponding pyridyl alcohols via commercially available **9** and easily accessible **10**.[8a] The acetate **11** was synthesized on a 0.1 molar scale in two steps according to the known procedure.[8] Hydrolysis of acetate **11** with KOH/EtOH afforded the corresponding racemic alcohol **13** in high yield. The racemic alcohol was transformed into chloroketone **15** in good yield by our own aerobic

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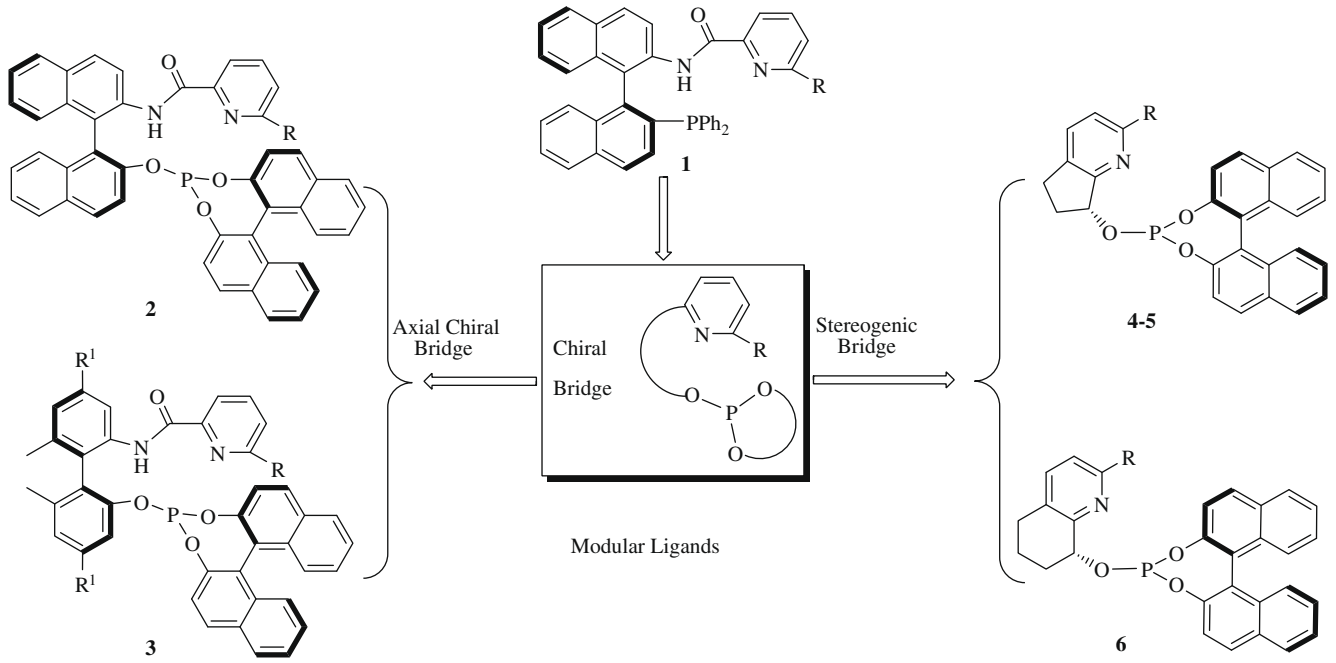
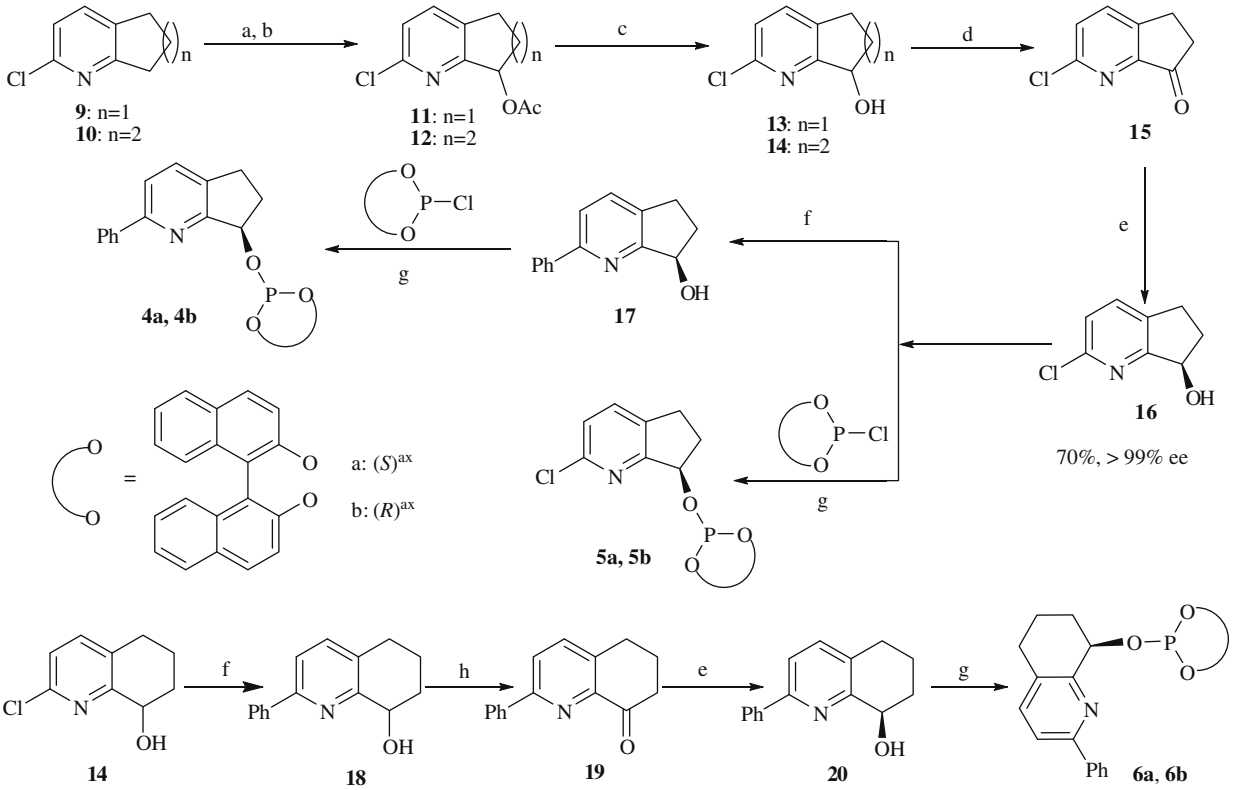


Figure 1. Design of the modular chiral phosphorus–pyridine ligands.



Scheme 1. Synthesis of pyridine–phosphite ligands **4**–**6**. Reagents and conditions: (a) CH_3COOH, H_2O_2, 82 °C, 17 h; (b) $(CH_3CO)_2O$, 85 °C, 5 h; (c) KOH/EtOH, rt, 3 h; (d) TEMPO/TBN/HBr/O_2, CH_2ClCH_2Cl, 80 °C; (e) (*S*)-Me-CBS (0.1 equiv), BH_3·THF, rt, 93% ee (for **16**, >99% after recrystallization), and 72% ee (for **20**, >99% ee after recrystallization); (f) $Pd(PPh_3)_4$, $PhB(OH)_2$, Na_2CO_3/H_2O, EtOH, $MeOCH_2CH_2OMe$, reflux, 12 h; (g) BINOL-chlorophosphite, Et_3N, THF, 0 °C to rt; (h) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C to rt.

oxidation procedure.[9] The commercially available CBS reagent was employed for catalyzing the enantioselective reduction to furnish the enantiopure pyridyl alcohols. Under optimal conditions, the catalytic enantioselective reduction of **15** with (*S*)-Me-CBS-borane[10] generated (*R*)-pyridyl alcohol **16** in quantitative yield with 93% ee, which was subjected to recrystallization from hexane/EtOAc to give enantiomerically pure chloroalcohol **16** with 50% yield. The residue in the mother liquor was subsequently crystallized two times in hexane/EtOAc to give the enantiomerically pure compound with 11.8% recovery. Chiral chloroalcohol **16** was subse-

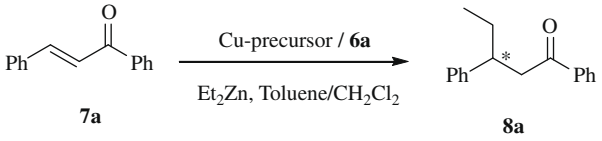
quently transformed into alcohol **17** by Suzuki coupling reaction with phenylboric acid in high yield. Using a similar procedure for preparing the five-membered chloroalcohol **16**, its six-membered analogue, enantiomerically pure (*R*)-alcohol **20**, was also successfully prepared in good yield. These enantiopure alcohols were converted into the corresponding phosphite ligands (R_c,S_a)-**4a**, (R_c,S_a)-**5a,** and (R_c,S_a)-**6a** in high yield by treatment with the (S_a)-BINOL-derived chlorophosphite[11] in THF at 0 °C in the presence of Et_3N. Besides their ready availability, these compounds are stable enough in air and can be conveniently purified by flash chromatography through silica gel in high yield. However, (R_c,R_a)-**4b** (R_c,R_a)-**5b,** and (R_c,R_a)-**6b**, which were accordingly prepared from their corresponding *R*-isomers of alcohol **16**, **17**, **20** and (R_a)-BINOL, are not stable and decomposed during the isolation procedure by column chromatography on either silica gel or alumina oxide, presumably due to the rigid conformation imposed by the bicycle ring of the pyridyl alcohols which is not matched with the (R_a)-BINOL. The structures of these ligands were deduced by their ^1H NMR, ^{13}C NMR, ^{31}P NMR spectra, and HRMS. In addition, the NMR-based structure was further confirmed by X-ray crystallographic analysis of **5a** (Fig. 2).[12]

2.2. Enantioselective 1,4-conjugate addition of Et_2Zn to enones

With ligands **4–6** in hand, we next examined their asymmetric induction ability in the Cu-catalyzed asymmetric conjugate addition of Et_2Zn to enones. In order to optimize the reaction conditions, ligand **6a** was chosen as a representative ligand, and chalcone **7a** was taken as a typical substrate in order to find an appropriate copper precursor. Based on our previous studies, the conjugate addition of Et_2Zn to chalcone was carried out in the presence of 1 mol % of copper source and 2.5 mol % of chiral ligand in 1/1 toluene/CH_2Cl_2 as solvent at room temperature (15–20 °C in our laboratory). Both copper(I) and copper(II) were examined and the results are summarized in Table 1. The first attempt, using $Cu(OTf)_2$ and $[Cu(OTf)]_2C_6H_6$ (entries 1 and 2) as catalyst precursors, which were the most popular precursors for this reaction in prior reports,[4] afforded the desired addition product in low yield with poor enantiomeric excess. Unfortunately, all our efforts to improve the reactivity and selectivity with the two copper salts as precursors proved unsuccessful. Thus, we turned our attention to the use of other copper salts as precursors for this reaction. The results showed that good yields with moderate enantioselectivities were obtained when a number of copper halides were employed in this reaction except CuF_2 (entries 3–8). Other kinds of copper salts, such as $Cu(OAc)_2{\cdot}H_2O$ also showed comparable results. As for the reactivity and enantioselectivity, $CuBr_2$ was the best candidate as the catalyst precursor. To the best of our knowledge, this is the first time that a simple and less expensive copper halide has shown superior catalytic performance to that of those expensive copper triflate salts in this type of reaction.[4l]

With $CuBr_2$ as the catalyst precursor and **6a** as ligand, we thoroughly investigated the solvent effect (Table 2). The results in Table 2 show a significant solvent effect in this copper-catalyzed conjugate addition. Reaction in solvents, such as CH_2Cl_2 and toluene, which were usually proper solvents for this reaction in the literature, showed lower enantioselectivities and reactivities for the conjugate addition (entries 1 and 2); unsatisfactorily results were also obtained in EtOAc (entry 3). However, the catalyst $CuBr_2$/**6a** performed well in a number of ethers, such as diethyl ether, methyl

Table 1
Enantioselective conjugate addition of diethylzinc to chalcone with different copper precursors[a]



7a **8a**

Entry	Cu precursor	Yield[b] (%)	ee[c] (%)	Config[d]
1	$Cu(OTf)_2$	41	13	(*R*)
2	$[Cu(OTf)]_2C_6H_6$	39	15	(*R*)
3	CuCl	51	50	(*R*)
4	$CuCl_2$	50	45	(*R*)
5	CuBr	72	45	(*R*)
6	**$CuBr_2$**	**79**	**50**	(*R*)
7	CuI	35	35	(*R*)
8	CuF_2	27	0	—
9	$Cu(OAc)_2{\cdot}H_2O$	65	40	(*R*)
10	$CuSO_4{\cdot}5H_2O$	19	0	(*R*)

[a] The reaction was carried out in 2 mL of toluene/CH_2Cl_2 = 1/1, chalcone (0.5 mmol)/Cu-precursor/**6a** = 1/0.01/0.025, 0.70 mL of Et_2Zn (1.1 M in toluene).
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD-H column.
[d] The absolute configuration was assigned by comparison of the specific rotation with reported data.

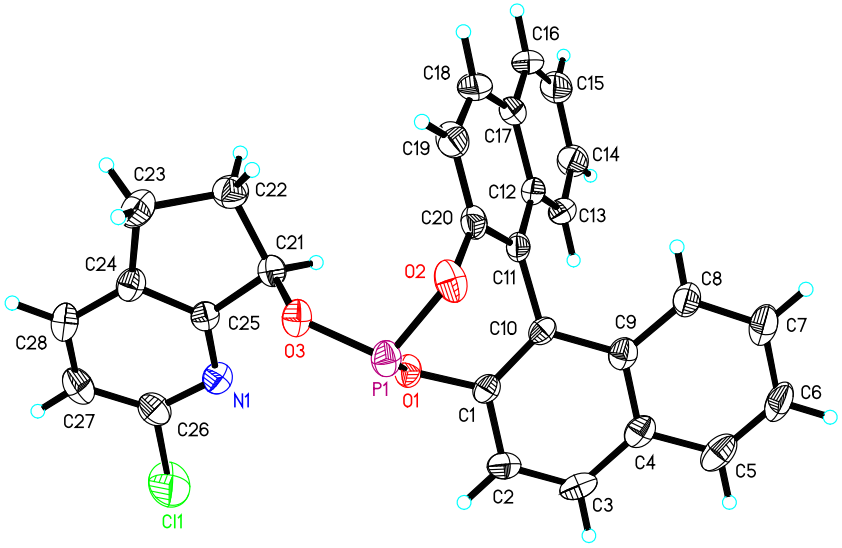
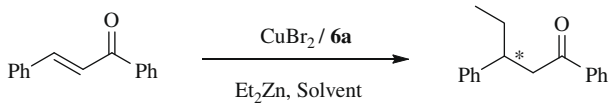


Figure 2. X-ray structure of ligand **5a**.

Table 2
Solvent effect in enantioselective conjugate addition of diethylzinc to chalcone[a]



7a **8a**

Entry	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)	Config[d]
1	CH_2Cl_2	14	39	15	(*R*)
2	Toluene	14	63	35	(*R*)
3	EtOAc	24	41	36	(*R*)
4	Et_2O	4	94	66	(*R*)
5	MTBE	4	86	67	(*R*)
6	*n*-Bu_2O	4	80	65	(*R*)
7	THF	14	0	—	—

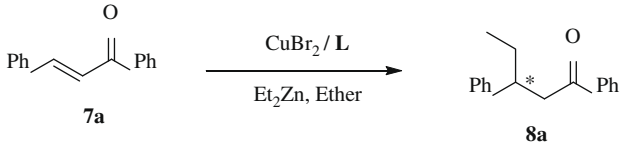
[a] The reaction was carried out in 2 mL of solvent, chalcone (0.5 mmol)/$CuBr_2$/**6a** = 1/0.01/0.025, 0.70 mL of Et_2Zn (1.1 M in toluene).
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD-H column.
[d] The absolute configuration was assigned by comparison of the specific rotation with reported data.

tert-butyl ether (MTBE), to give the conjugate addition product in high yield and good enantioselectivities at room temperature. Satisfactory results were obtained when the reaction was carried out in Et_2O. These results indicate that the ether solvent, possesses appropriate coordinating ability, and may be involved in the catalytic cycle acting as a hemilabile ligand to change the structure of the active catalyst. However, when THF was employed as the reaction solvent, no positive results were observed (entry 7), most likely due to its strong coordinating ability.

With $CuBr_2$ as the copper precursor and diethyl ether as the reaction solvent, the remaining pyridine–phosphite ligands **4–6** were subsequently investigated to identify the most efficient ligand. The results are summarized in Table 3. Ligand screening tests showed that chiral induction ability and reaction activity of chiral catalysts for this conjugate addition were closely related to the structures of the ligands in this system. Firstly, the reactivities and enantioselectivities depended strongly on the moiety of the P/O heterocycle in the chiral ligands. Higher activities and enantioselectivities were observed with ligands **4a**, **5a**, and **6a**, which contained (*S*)-BINOL in the P/O heterocycle (entries 1, 3, 5). In marked contrast, ligands **4b**, **5b,** and **6b** derived from (*R*)-BINOL gave lower yields with lower ee values of less than 35% (entries 2, 4, and 6). These data indicated that (*S*)-BINOL had matched cooperativity to the corresponding chiral bicycle pyridine alcohols prepared in our system. Secondly, the reactivities and enantioselectivities induced by these ligands were significantly affected by the ring size contained in the ligands, which bridged the pyridine moiety and the phosphite moiety. For example, although at room temperature, both ligands **4a** and **5a** derived from the five-membered ring pyridine alcohol and ligand **6a** prepared from the six-membered ring pyridine alcohol demonstrated almost the same high activity, decreasing the reaction temperature from room temperature to −20 °C and −40 °C caused the reactivity of the catalysts with ligands **4a** and **5a** to decrease to a certain extent, although the chiral induction ability increased. In contrast, the catalyst with ligand **6a** provided a high yield along with high enantioselectivity at lower temperature due to its high reactivity (90% yield with 90% ee was obtained at −40 °C in 4 h, entry 10). The different behavior of these ligands could be explained by the conformational analysis of their structures. Ligands **4a** and **5a** contain a five-membered ring pyridine moiety which causes their Cu-complexes to become more congested and rigid than that of **6a**, thus the catalyst with **6a** should be expected to demonstrate much higher reactivities even at lower temperatures.

With ligand **6a** being identified as the most effective ligand, a survey of the reaction scope was then undertaken (Table 4). As shown in Table 4, in the case of chalcone **7a** and the electron-deficient-substituted chalcones **7b**, **7c**, and **7d**, the catalyst formed in situ with ligand **6a** and $CuBr_2$ proceeded well to give high yield (76–93% yield) with good to excellent enantioselectivity (up to 92% ee) at −40 °C (Table 4, entries 1–4). Unfortunately, using the same reaction condition for the conjugate additions of diethylzinc to the electron-rich-substituted chalcone **7e** gave the desired addition product in 37% chemical yield due to its lower solubility in Et_2O

Table 3
Enantioselective conjugate addition of diethylzinc to chalcone with different ligands[a]

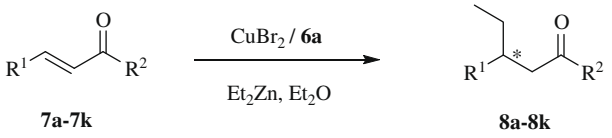


7a **8a**

Entry	Ligand	*T* (°C)	*t* (h)	Yield[b] (%)	ee[c] (%)	Config[d]
1	**4a**	rt	4	95	66	(*R*)
2	**4b**	rt	12	59	19	(*S*)
3	**5a**	rt	4	90	71	(*R*)
4	**5b**	rt	12	27	33	(*S*)
5	**6a**	rt	4	94	66	(*R*)
6	**6b**	rt	12	28	28	(*S*)
7	**6a**	0	4	91	74	(*R*)
8	**6a**	−10	4	92	76	(*R*)
9	**6a**	−20	4	93	84	(*R*)
10	**6a**	−40	**4**	**90**	**90**	(*R*)
11	**4a**	−20	4	87	78	(*R*)
12	**5a**	−20	4	93	83	(*R*)
13	**4a**	−40	8	75	85	(*R*)
14	**5a**	−40	8	70	85	(*R*)

[a] The reaction was carried out in 2 mL of Et_2O, chalcone (0.5 mmol)/$CuBr_2$/**L** = 1/0.01/0.025, 0.70 mL of Et_2Zn (1.1 M in toluene).
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD-H column.
[d] The absolute configuration was assigned by comparison of the specific rotation with reported data.

Table 4
Cu-catalyzed enantioselective 1,4-conjugate addition of Et_2Zn to acyclic enones[a]



7a-7k **8a-8k**

Entry	Enone (R^1, R^2)	*T* (°C)	*t* (h)	Yield[b] (%)	ee[c] (%)	Config[d]
1	**7a** (Ph, Ph)	−40	4	93	**90**	(*R*)-(−)
2	**7b** (4-ClPh, Ph)	−40	8	76	88	(−)
3	**7c** (Ph, 4-ClPh)	−40	8	80	87	(*R*)-(**+**)
4	**7d** (2-ClPh, Ph)	−40	6	84	**92**	(+)
5	**7e** (4-MeOPh, Ph)	−40	8	37	86	(−)
6	**7e** (4-MeOPh, Ph)	−20	6	74	82	(−)
7	**7f** (4-MePh, Ph)	−20	4	88	84	(−)
8	**7g** (Ph, 4-MeOPh)	−20	4	56	**91**	(+)
9	**7h** (Ph, Me)	−20	12	67	78	(−)
10	**7i** (4-MePh, Me)	−20	12	63	81	(−)
11	**7j** (4-ClPh, Me)	−20	12	91	76	(−)
12	**7k** (4-MeOPh, Me)	−20	12	61	77	(−)

[a] The reaction was carried out in 2 mL of Et_2O, enone (0.5 mmol)/$CuBr_2$/**6a** = 1/0.01/0.025, 0.70 mL of Et_2Zn (1.1 M in toluene).
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD-H column or GC with Supelco-Gamma-DEX-225 column (30 m × 0.25 mm (i.d.)).
[d] The absolute configuration was assigned by comparison of the specific rotation with reported data.

at lower temperature, although with comparable ee (86%). Indeed, the lower yield could be compensated (up to 74% chemical yield with 82% ee) when the reaction was carried out at −20 °C (Table 4, entry 5 vs entry 6). At this temperature, a variety of electron-rich-substituted chalcones **7e**, **7f**, and **7g** were successfully transformed to yield their corresponding 1,4-addition product with good yield and enantiomeric excess values (Table 4, entries 6–8). In addition, a series of *trans*-4-aryl-3-buten-2-one substrates, could also be transformed into their corresponding 1,4-addition products in good yields and enantiomeric excess values under these reaction conditions (Table 4, entries 9–12).

3. Conclusion

In conclusion, we have successfully developed a new class of modular pyridine–phosphite ligands from chiral pyridyl alcohol and (*S*)-BINOL, in which the pyridine and phosphite coordination spheres were incorporated by the central chiral bridge. These modular ligands have been applied in the copper-catalyzed asymmetric conjugate addition of Et_2Zn to acyclic enones. Excellent activities and high enantioselectivities were obtained under the optimal reaction conditions. Further studies to explore their applications in other transition metal-catalyzed asymmetric reactions are currently underway.

4. Experimental

4.1. General

Melting points were determined using a Metter FP5 melting apparatus in open capillaries and are uncorrected. NMR spectra were recorded on BRUKER DRX 400 or BRUKER DRX 500 spectrometers. Chemical shifts are reported in parts per million (ppm) down field from TMS with the solvent resonance as the internal standard. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplications. High resolution mass spectra (HRMS) were recorded on Agilent 6210-TOF. GC analysis was performed on an Agilent HP-6890 GC instrument with FID as detector. HPLC analysis was performed on an Agilent HP-1200. Optical rotations were measured on a PerkinElmer, Model 341LC polarimeter. Substituted chalcones and 4-*trans*-aryl-3-buten-2-ones were prepared according to a literature procedure.[13] Racemic conjugate addition products were prepared with acyclic enones and EtMgBr in THF. All non-aqueous reactions and manipulations were performed in a nitrogen atmosphere using standard Schlenk techniques. All solvents before use were dried and degassed by standard methods and stored under nitrogen.

4.2. Synthesis pyridine–phosphite ligands 4–6

4.2.1. General procedure for the preparation of the chloropyridine N-oxide and rearrangement of the corresponding chloropyridine N-oxide[8]

To a 250 mL three-necked jacketed flask, were added 2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine **9** (0.1 mol, 15.35 g) and 70 mL of glacial acetic acid. The mixture was warmed to a clear solution and then kept to 82 °C by a circulating hot water bath. To this solution, 15 mL of 30% aqueous hydrogen peroxide was slowly added. The reaction mixture was stirred at 82 °C for 5 h, after which another 2.5 mL of 30% aqueous hydrogen peroxide was added. The resulting reaction mixture was stirred for a further 12 h at this temperature, and then cooled to room temperature. The excess hydrogen peroxide was destroyed by adding a catalytic amount of manganese dioxide and stirred for another hour under room temperature. Water and acetic acid were removed under reduced pressure. The residue was poured into water (200 mL) and carefully neutralized by the slow addition of solid Na_2CO_3 and then extracted four times with CH_2Cl_2 (100 mL × 4). The combined organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the corresponding pyridine *N*-oxide as a yellowish oil, which was used directly for the next step without further purification. This crude pyridine *N*-oxide was dissolved in 130 mL of acetic anhydride, the resulting mixture was stirred at 85 °C for 5 h, cooled to room temperature, and then concentrated in vacuo to afford the crude product acetate as a dark brown oil. Flash chromatography using hexane/EtOAc (20:1–5:1) eluent afforded the desired compound **11** in 65.8% yield as an oil, which solidified during storage. An analytical sample was recrystallized by heptane to yield off-white crystalline-powdered solid.

4.2.1.1. 2-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-yl acetate 11. Mp: 67–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05–2.07 (m, 1H), 2.08 (s, 3H), 2.63–2.71 (m, 1H), 2.84–2.91 (m, 1H), 3.02–3.09 (m, 1H), 6.03 (dd, *J* = 4.4 Hz, 7.6 Hz 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 160.8, 150.5, 136.4, 135.6, 124.0, 76.6, 30.9, 27.2, 21.1; HRMS (APCI) calcd for $C_{10}H_{11}ClNO_2$ [M+1]: 212.0478, found: 212.0483.

4.2.1.2. 2-Chloro-5,6,7,8-tetrahydroquinoine-8-acetate 12. In a manner similar to that described for **11**, the compound **12** was prepared as a white solid in 65.5% yield over two steps, which is a known compound.[8a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85–2.03 (m, 3H), 2.10 (s, 3H), 2.15–2.18 (m, 1H), 2.68–2.72 (m, 1H), 2.73–2.86 (m, 1H), 5.85 (t, *J* = 3.6 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.56 (d, *J* = 6.4 Hz, 1H).

4.2.2. General procedure for preparation of the pyridyl alcohols 13 and 14[8]

To a stirred solution of acetate **11** (0.05 mol, 9.08 g) in 20 mL of EtOH, a solution of 3.22 g of KOH in 60 mL of EtOH was added. The resulting mixture was stirred at rt for 3 h and then the solvent was removed under reduced pressure to yield a dark solid, which was treated with 300 mL of water and extracted with CH_2Cl_2 (200 mL × 4). The combined organic phase was washed with brine and then dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography and a yellowish solid **13** was obtained in 89% yield.

4.2.2.1. 2-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-ol 13. Mp: 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04–2.11 (m, 1H), 2.54–2.60 (m, 1H), 2.78–2.84 (m, 1H), 2.99–3.05 (m, 1H), 3.05 (s, 1H), 5.20 (dd, *J* = 6.4 Hz, 16.4 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 148.3, 139.9, 130.6, 122.9, 68.4, 30.3, 27.8, 19.1. HRMS (APCI) calcd for C_8H_9ClNO [M+1]: 170.0372, found: 170.0365.

4.2.2.2. 8-Hydroxy-2-chloro-5,6,7,8-tetrahydroquinoine 14. In a manner similar to that described for **13**, the compound **14** was prepared as a white solid, which is a known compound.[8a] Mp: 53–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77–1.86 (m, 2H), 1.98–2.02 (m, 1H), 2.22–2.27 (m, 1H), 2.72–2.79 (m, 2H), 3.54 (br, 1H), 4.68 (dd, *J* = 4.0 Hz, 16.4 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 148.3, 139.9, 130.6, 122.9, 68.4, 30.3, 27.8, 19.1; HRMS (APCI) calcd for $C_9H_{11}ClNO$ [M+1]: 184.0529, found: 184.0523.

4.2.3. General procedure for the oxidation of pyridyl alcohols

4.2.3.1. Swern oxidation. To a stirred solution of oxalyl chloride (2.45 mL, 28.1 mmol) in dichloromethane (60 mL) was slowly added DMSO (3.98 mL, 56.1 mmol) at −78 °C, and the resulting mixture was stirred for 30 min at this temperature. A solution of

racemic pyridyl alcohol (25 mmol) in dichloromethane (45 mL) was added to this mixture slowly over 3 h, and then Et_3N (15.6 mL, 112 mmol) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature by stirring for 1 h at room temperature and then quenched with water (60 mL). After extraction with dichloromethane, the organic layer was washed successively with HCl (60 mL, 1 M), saturated aqueous Na_2CO_3, and then brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product. The crude product was purified by flash chromatography with hexane/EtOAc as the eluant to afford the desired compounds.

4.2.3.1.1. 2-Chloro-5,6-dihydrocyclopenta[*b*]pyridin-7-one 15. 34% yield, mp: 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (m, 2H), 3.16 (t, J = 5.6 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 154.1, 152.9, 148.5, 137.9, 128.6, 30.9, 23.1; HRMS (APCI) calcd for C_8H_7ClNO [M+1]: 168.0216, found: 168.0209.

4.2.3.1.2. 2-Phenyl-5,6,7,8-tetrahydroquinoine-8-one 19. In a manner similar to that described for **15**, the compound **19** was prepared as a white solid in 88% yield, which is known compound.[8c] Mp: 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18–2.52 (m, 2H), 2.81 (t, J = 6.0 Hz, 2H), 3.03 (t, J = 6.0 Hz, 2H), 7.40–7.49 (m, 3H), 7.70 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 156.6, 147.8, 139.2, 138.5, 138.4, 129.2, 129.0, 128.7, 127.1, 123.9, 39.9, 28.9, 22.7; HRMS (APCI) calcd for $C_{15}H_{14}NO$ [M+1]: 224.1075, found: 224.1069.

4.2.3.2. Aerobic oxidation for the oxidation of alcohol 13 to chloroketone 15[9]. To a Teflon-lines 316L stainless steel autoclave (300 mL), was added 17.0 g (100 mmol) of alcohol **13**, 312 mg (2 mmol, 2 mol %) of TEMPO, 480 μL (700 mg, 4 mmol, 4 mol %) of 48% HBr (d = 1.46), 460 μL (410 mg, 4 mmol, 4 mol %) of *tert*-butyl nitrite (TBN), 10 mL of glacial acetic acid, and 40 mL of CH_2ClCH_2Cl. The autoclave was then closed and charged with oxygen to 0.5 MPa. The autoclave was placed into an oil bath, which was preheated to 80 °C. When the barometer dropped to 0.25 MPa, it was charged with oxygen to 0.5 MPa again. The procedure was repeated until the barometer was constant to indicate that the reaction had finished. The autoclave was taken out from the heating bath, cooled to room temperature, and carefully depressurized. The mixture was diluted with CH_2Cl_2 and transferred to a separation funnel, then washed with water (100 mL × 2), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure. The residue was recrystallized from 400 mL of 1:1 toluene and heptane to afford 11.8 g (yield 70.2%) of a pale white solid. The ^{1}H NMR data were consistent with the result from the above Swern oxidation.

4.2.4. General procedure for (*S*)-Me-CBS reduction of ketones and preparation of optical pure (*R*)-alcohols[8b]

To a stirred solution of (*S*)-Me-CBS (5.1 mmol) in THF (20 mL) was added a solution of BH_3·THF (4 mL) under nitrogen protection at room temperature. After stirring for 30 min at room temperature, a solution of the ketone dissolved in THF (120 mL) and a solution of BH_3·THF (38 mL in 80 mL of THF) were added at the same time over a period of 1.5–2.5 h. After the addition, the reaction mixture was stirred for 1 h and quenched with MeOH. Concentration in vacuo gave a crude residue, which was extracted with CH_2Cl_2 (100 mL × 3). The extract was washed with brine and dried over anhydrous Na_2SO_4. Removing the solvent gave the crude product, which was purified by flash chromatography to afford the corresponding (*R*)-pyridyl alcohol in quantitative yield with 72% ee or 93% ee.

4.2.4.1. (R)-2-Chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-ol 16. The product of 93% ee (6.01 g) was recrystallized with hexane/EtOAc to give the crystalline white solid (3.72) in 61.8% recovery. $[\alpha]_D^{20} = -4.1$ (c 0.39, $CHCl_3$), >99% ee, HPLC analysis for racemic alcohol **13** (Chiralcel OB-H column, *i*-PrOH/hexane 5/95, 1.0 mL/min, 254 nm): $t(S)$ = 23.917 min, $t(R)$ = 16.208 min. ^{1}H NMR data were consistent with the racemic one.

4.2.4.2. (R)-8-Hydroxy-2-chloro-5,6,7,8-tetrahydroquinoine 20. The product of 72% ee (3.29 g) was subsequently crystallized four times with hexane/EtOAc to give the crystalline white solid (1.44 g) in 43.8% recovery. $[\alpha]_D^{20} = -140.4$ (c 0.31, $CHCl_3$), >99% ee, literature[8c] $[\alpha]_D^{20} = -131$ (c 1.07, $CHCl_3$) for (*R*)-isomer. HPLC analysis for racemic alcohol **14** (Chiralcel AD-H column, *i*-PrOH/hexane 15/85, 0.6 mL/min, 254 nm): $t(S)$ = 16.043 min, $t(R)$ = 20.504 min.

4.2.5. General procedure for Suzuki coupling reaction of pyridyl alcohols with the phenylboronic acid

A solution of alcohol (*R*)-**16** (6 mmol) and $Pd(PPh_3)_4$ (0.18 mmol) in 13 mL of ethylene glycol dimethyl ether was treated with a degassed solution of K_2CO_3 (12 mmol) in H_2O (13 mL), followed by a solution of phenylboronic acid (7.2 mmol) in EtOH (13 mL). The mixture was stirred at reflux for 12 h under N_2. After cooling to room temperature, the solvent was removed in vacuo, after which the residue was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product after removal of the solvent under reduced pressure was purified by silica gel chromatography to afford (*R*)-**17** in 96.5% yield.

4.2.5.1. (R)-2-Phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-ol 17. White solid, which is known compound. 96.5% yield. Mp: 119–120 °C; $[\alpha]_D^{20} = -36.7$ (c 0.28, $CHCl_3$), >99% ee, literature[8c] $[\alpha]_D^{20} = -31$ (c 0.95, $CHCl_3$) for the (*R*)-isomer. HPLC (Chiralcel AD-H column, *i*-PrOH/hexane 15/85, 0.6 mL/min, 254 nm): $t(S)$ = 11.645 min, $t(R)$ = 14.222 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00–2.08 (m, 1H), 2.48–2.55 (m, 1H), 2.75–2.83 (m, 1H), 2.96–3.03 (m, 1H), 4.47 (br, 1H), 5.26 (t, J = 6.4 Hz, 1H), 7.35–7.47 (m, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 156.4, 139.3, 135.0, 134.8, 133.7, 128.6, 128.3, 127.0, 126.6, 120.0, 74.5, 32.9, 27.1; HRMS (APCI) calcd for $C_{14}H_{14}NO$ [M+1]: 212.1075, found: 212.1070.

4.2.5.2. 8-Hydroxy-2-phenyl-5,6,7,8-tetrahydroquinoine 18. In a manner similar to that described for **17**, the compound **18** was prepared as a white solid in 94.9% yield. Mp: 84–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74–1.87 (m, 2H), 1.96–2.04 (m, 1H), 2.31–2.38 (m, 1H), 2.76–2.87 (m, 1H), 4.44 (br, 1H), 4.72 (t, J = 6.0 Hz, 1H), 7.36–7.46 (m, 4H), 7.53 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.0, 138.8, 137.6, 129.8, 128.7, 128.6, 128.3, 126.8, 126.6, 119.3, 69.0, 30.6, 27.9, 19.5; HRMS (APCI) calcd for $C_{15}H_{16}NO$ [M+1]: 226.1231, found: 226.1220.

4.2.6. General procedure for synthesis of the pyridine–phosphite ligands 4–6

To a stirred solution of pyridyl alcohol (2 mmol) in THF (10 mL) was added Et_3N (10 mmol, 1.5 mL). The mixture was then cooled to 0 °C and BINOL-derived chlorophosphite was slowly added. The reaction mixture was allowed to warm to room temperature and stirred overnight prior to dilution with diethyl ether. The solid was removed by filtration through a pad of Celite, the solvent was removed in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane: 1/20–1/10), and furnished the title ligand as white foamy solid in 29–90% yield.

4.2.6.1. (*R*)-7-*O*-((*S*)-2,2′-*O*,*O*-(1,1′-Binaphthyl)-dioxo-phosphite)-2-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 4a. White solid, 65.0% yield, mp: 117 °C (dec). $[\alpha]_D^{20} = +78.1$ (*c* 0.19, $CHCl_3$). ^1H NMR (400 MHz, CD_3COCD_3) δ 2.13–2.18 (m, 1H), 2.53–2.57 (m, 1H), 2.80–2.91 (m, 1H), 3.01–3.04 (m, 1H), 5.84–5.87 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.24–7.31 (m, 4H), 7.37–7.43 (m, 2H), 7.46–7.52 (m, 3H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.72–7.82 (m, 2H), 7.88–7.92 (m, 2H); 8.01–8.05 (m, 1H), 8.12–8.15 (m, 1H), 8.30 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 162.4, 156.9, 149.1, 149.0, 148.7, 140.0, 136.5, 134.9, 133.6, 133.2, 132.5, 132.0, 131.4, 130.3, 129.7, 129.6, 129.4, 129.3, 127.6, 127.3, 127.2, 127.1, 127.0, 126.0, 125.7, 125.0, 124.9, 123.6, 123.1, 122.7, 120.8, 79.9, 32.9, 23.3; ^{31}P NMR (DMSO-d_6) δ 153.4; HRMS (APCI) calcd for $C_{34}H_{25}NO_3P$ [M+1]: 526.1572, found: 526.1584.

4.2.6.2. (*R*)-7-*O*-((R)-2,2′-*O*,*O*-(1,1′-Binaphthyl)-dioxo-phosphite)-2-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 4b. White solid, 55.1% yield. $[\alpha]_D^{20} = -221.5$ (*c* 0.42, $CHCl_3$). ^1H NMR (400 MHz, CD_3COCD_3) δ 2.15–2.21 (m, 1H), 2.48–2.54 (m, 1H), 2.74–2.81 (m, 1H), 2.95–3.01 (m, 1H), 5.70–5.75 (m, 1H), 7.22–7.34 (m, 4H), 7.38–7.48 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.04 (t, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 162.3, 156.9, 149.5, 148.6, 140.1, 136.4, 134.8, 133.6, 133.3, 132.5, 132.0, 131.5, 130.8, 129.7, 129.6, 129.5, 129.4, 127.8, 127.6, 127.4, 127.3, 127.2, 127.1, 126.1, 125.8, 125.1, 125.0, 123.4, 123.3, 122.7, 120.8, 79.6, 33.3, 27.9; ^{31}P NMR (DMSO-d_6) δ 145.4; HRMS (APCI) calcd for $C_{34}H_{25}NO_3P$ [M+1]: 526.1572, found: 526.1547.

4.2.6.3. (*R*)-7-*O*-((S)-2,2′-*O*,*O*-(1,1′-Binaphthyl)-dioxo-phosphite)-2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 5a. White solid, 78.4% yield, mp: 123 °C (dec). $[\alpha]_D^{20} = +231.0$ (*c* 0.16, $CHCl_3$). ^1H NMR (400 MHz, CD_3COCD_3) δ 2.13–2.18 (m, 1H), 2.51–2.57 (m, 1H), 2.81–2.89 (m, 1H), 2.97–3.03 (m, 1H), 5.74–5.79 (m, 1H), 7.29–7.35 (m, 4H), 7.39–7.52 (m, 4H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.97–8.00 (m, 2H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CD3COCD3) δ 162.9, 150.7, 148.9, 148.5, 137.4, 137.2, 133.6, 133.2, 132.6, 132.1, 131.5, 130.5, 129.5, 129.3, 127.4, 127.3, 127.2, 127.0, 126.1, 125.8, 124.9, 124.8, 123.5, 123.4, 122.6, 78.7, 33.3, 27.5; ^{31}P NMR (DMSO-d_6) δ 150.3; HRMS (APCI) calcd for $C_{28}H_{20}ClNO_3P$ [M+1]: 484.0869, found: 484.0880. Crystal data for **5a**. M_w = 483.86, *T* = 293(2) *K*, λ = 0.71073 Å, monoclinic, *P*2(1), *a* = 9.0228(19) Å, *b* = 12.6596 (13) Å, *c* = 10.0940(10) Å, α = 90° (3), β = 94.861° (2), γ = 90° (2), *V* = 1148.8(2) Å^3, *Z* = 2, D_{calcd} = 1.399 mg/m^3, μ = 0.268 mm^{-1}, *F*(0 0 0) = 500. Crystal size 0.202 × 0.147 × 0.086 mm, independent reflections 4549 [R_{int} = 0.0451], reflections collected 6834, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 0.917, final *R* indices [$I > 2\sigma(I)$] R_1 = 0.0491, wR_2 = 0.0975, *R* indices (all data) R_1 = 0.0726, wR_2 = 0.1052, absolute structure parameter was −0.13 (9), largest diff. peak and hole 0.269 and −0.235 e Å^{-3}.

4.2.6.4. (*R*)-7-*O*-((R)-2,2′-*O*,*O*-(1,1′-Binaphthyl)-dioxo-phosphite)-2-chloro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 5b. White solid, 79.7% yield, mp: 121 °C (dec). $[\alpha]_D^{20} = -206.1$ (*c* 0.16, $CHCl_3$), ^1H NMR (400 MHz, CD_3COCD_3) δ 2.21–2.26 (m, 1H), 2.57–2.63 (m, 1H), 2.83–2.87 (m, 1H), 2.99–3.05 (m, 1H), 5.64–5.69 (m, 1H), 7.30–7.36 (m, 5H), 7.44–7.53 (m, 2H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.71–7.42 (m, 2H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 161.4, 149.1, 147.4, 146.8, 136.8, 136.3, 132.0, 131.7, 131.2, 130.8, 130.6, 130.1, 128.6, 128.5, 126.7, 126.5, 125.9, 125.8, 125.3, 125.1, 124.0, 123.4, 123.3, 121.9, 121.6, 78.4, 32.1, 26.5; ^{31}P NMR (DMSO-d_6) δ 148.2; HRMS (APCI) calcd for $C_{28}H_{20}ClNO_3P$ [M+1]: 484.0869, found: 484.0888.

4.2.6.5. (*R*)-8-*O*-((S)-2,2′-*O*,*O*-(1,1′-Binaphthyl)-dioxo-phosphite)-2-phenyl-5,6,7,8-tetrahydroquinoine 6a. White solid, 90.1% yield, mp: 109 °C (dec). $[\alpha]_D^{20} = +72.9$ (*c* 0.20, $CHCl_3$), ^1H NMR (400 MHz, CD_3COCD_3) δ 1.74–1.97 (m, 2H), 2.09–2.14 (m, 2H), 2.76–2.85 (m, 2H), 5.55–5.59 (m, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 7.22–7.30 (m, 4H), 7.35–7.39 (m, 2H), 7.40–7.47 (m, 3H), 7.61–7.72 (m, 3H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H); 8.02 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 155.3, 154.6, 149.1, 149.0, 139.8, 139.2, 133.6, 133.3, 132.7, 132.4, 131.9, 131.3, 130.0, 129.7, 129.5, 129.4, 129.2, 127.6, 127.3, 127.2, 127.1, 126.9, 125.9, 125.6, 125.1, 125.0, 123.8, 123.0, 122.8, 120.5, 74.6, 31.9, 23.3, 14.3; ^{31}P NMR (DMSO-d_6) δ 154.4; HRMS (APCI) calcd for $C_{35}H_{27}NO_3P$ [M+1]: 540.1728, found: 540.1698.

4.2.6.6. (*R*)-8-*O*-((*R*)-2,2′-*O*,*O*-(1,1′-Binaphthyl)-dioxo-phosphite)-2-phenyl-5,6,7,8-tetrahydroquinoine 6b. White solid, 29.3% yield, mp: 104 °C (dec). $[\alpha]_D^{20} = -290.7$ (*c* 0.35, $CHCl_3$). ^1H NMR (400 MHz, CD_3COCD_3) δ 1.81–1.90 (m, 2H), 2.13–2.29 (m, 1H), 2.26–2.30 (m, 1H), 2.72–2.88 (m, 2H), 5.54–5.58 (m, 1H), 7.25–7.35 (m, 4H), 7.37–7.54 (m, 5H), 7.58–7.61 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.89–8.08 (m, 4H), 8.30 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 155.1, 154.8, 149.5, 149.4, 148.9, 139.9, 139.0, 133.6, 133.3, 133.1, 132.4, 132.3, 132.0, 131.2, 130.4, 129.8, 129.5, 129.4, 129.3, 127.7, 127.3, 127.2, 127.1, 127.0, 125.9, 125.6, 125.2, 125.1, 123.6, 123.5, 122.7, 120.2, 73.9, 31.9, 28.5, 19.6; ^{31}P NMR (CD_3COCD_3) δ 153.4; HRMS (APCI) calcd for $C_{35}H_{27}NO_3P$ [M+1]: 540.1728, found: 540.1759.

4.3. General procedure for asymmetric 1,4-conjugate addition

4.3.1. Preparation of catalyst

To a 25 mL air-free Schlenk tube, were added 53.9 mg of **6a** (0.10 mmol), 8.8 mg of $CuBr_2$ (0.04 mmol), and 8 mL of CH_2Cl_2 under nitrogen atmosphere. After the mixture was stirred at 40 °C for 45 min, the catalyst solution was used for eight separated conjugate addition reactions.

4.3.2. Asymmetric 1,4-conjugate addition

Chalcone substrate (0.5 mmol) and 1 mL of the above prepared catalyst solution were added to a flame-dried Schlenk tube under an argon atmosphere. After the solvent had been removed, 2 mL of diethyl ether was added. The slurry was stirred at room temperature for 10 min and then cooled to the desired temperature. After the slurry had been stirred for 15 min at the desired temperature, 0.7 mL of Et_2Zn (1.1 M in toluene, 1.5 mol equiv) was added slowly. The resulting mixture was stirred at this temperature for the time indicated. Dilute hydrochloric acid (4 mL, 5%) was added to quench the reaction. The mixture was allowed to warm to room temperature, and then 15 mL of diethyl ether was added. The organic layer was washed with 5 mL of saturated $NaHCO_3$ and 5 mL of brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel and eluted with EtOAc/hexanes (1/40–1/20) to afford the addition product.

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