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Highly enantioselective 1,4-conjugate addition of diethylzinc to acyclic enones with chiral phosphite–pyridine ligands derived from H_8-NOBIN

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Abstract—A series of new phosphite–pyridine ligands, based on the H_8-binaphthyl backbone, were synthesized and employed in the copper-catalyzed enantioselective 1,4-conjugate addition of diethylzinc to acyclic enones. Ligands derived from (*S*)-H_8-NOBIN provided better results than their parent ligands in the reaction. Ligand **L1** provided excellent ees for *trans*-4-aryl-3-buten-2-ones (up to 97.8% ee) as substrates. Ligand **L2** was very efficient for various *para*-chalcones, and up to 97.2% ee was achieved.

1. Introduction

The enantioselective 1,4-conjugate addition of organometallic reagents to enones is an attractive method for carbon–carbon bond formation.[1] Although highly stereoselective 1,4-conjugate additions have been reported with the use of some chiral auxiliaries and stoichiometric reagents, the development of a stereoselective catalytic version of this transformation has recently gained much attention. The Cu-catalyzed enantioselective 1,4-conjugate addition of organozinc reagents to enones using chiral trivalent phosphorus ligands, originally introduced by Alexakis,[2] has therefore been investigated extensively.[3] A number of chiral phosphorus ligands, such as phosphoramidites,[4] phosphites,[5] aryl diphosphites,[6] MiniPHOS[7] and other chiral P,N ligands,[8] have been reported and successfully applied in the reaction. In recent years, phosphorus ligands have played very important roles in the successful applications of 1,4-conjugate addition of Et_2Zn to cyclic enones, where a few of them obtained good results for acyclic enones.[8d,f–j] However, very few ligands can provide high enantioselectivities for both chalcones and *trans*-4-aryl-3-buten-2-ones.[8i]

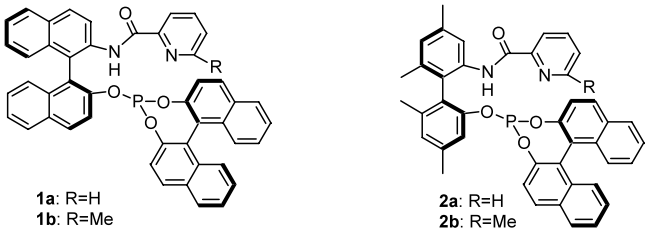

Figure 1.

Recently, we synthesized chiral phosphite–pyridine ligands of type 1, derived from (*S*)-2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) and (*S*)-2,2′-dihydroxy-1,1′-binaphthyl (BINOL), and obtained high enantioselectivities in the Cu(I)-catalyzed 1,4-conjugate additions of Et_2Zn to acyclic enones.[9] However, ligand **1** did not provide satisfactory enantioselectivities for 4′-methoxychalcone and 4′-methylchalcone. The substrate limitation has very recently been overcome by using relatively electron-rich phosphite–pyridine ligands **2** (Fig. 1).[10] The results from ligands **1** and ligands **2** showed that the electronic properties of the ligands played very important role in the Cu-catalyzed 1,4-conjugate addition. This prompted us to modify the electronic property of ligands **1**. Partial hydrogenation of binaphthyl rings was one of the most convenient and effective methods. In fact, some chiral catalysts based on 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (H_8-1,1′-binaphthyl) have exhibited higher catalytic ability than their parent ligands from 1,1′-binaphthyl in some asymmetric reactions.[6a,b,11–13]

We herein report the synthesis of a series of new phosphite–pyridine ligands **L1**–**6** derived from 2-amino-2′-hydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl

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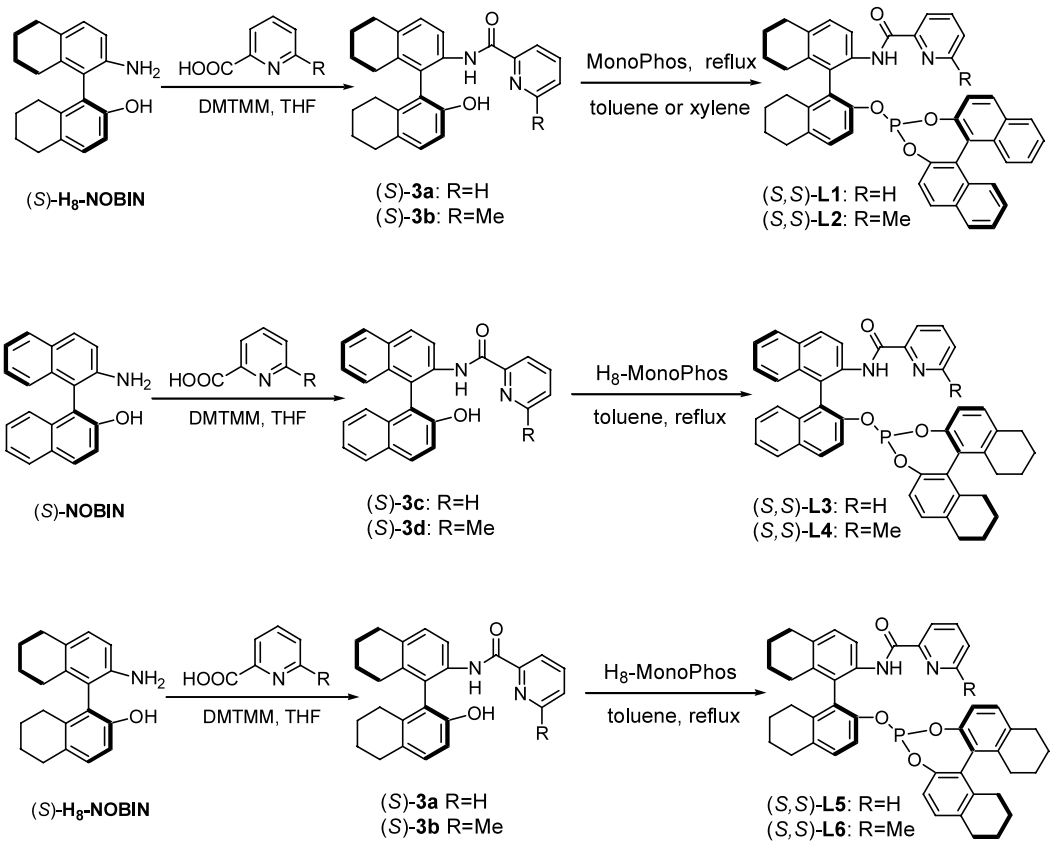


Scheme 1. Synthesis of phosphite–pyridine ligands **L1–6**.

(H_8-NOBIN) and/or 2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (H_8-BINOL). We envisioned that new ligands would be efficient for the 1,4-conjugate addition of Et_2Zn to acyclic enones due to the relatively electron-rich H_8-binaphthyl moieties.

2. Results and discussion

2.1. Synthesis of phosphite–pyridine ligands L1–6

In our previous study of the application of ligands **1** in Cu(I)-catalyzed enantioselective 1,4-addition of Et_2Zn to various enones, we found (*S*)-NOBIN and (*S*)-BINOL moieties were matched for high enantioselectivity[9] and a 6-methyl group of the pyridine moiety of the ligand was helpful for obtaining high enantioselectivities for chalcones but deleterious for *trans*-4-aryl-3-buten-2-ones.[9,10] Herein, we therefore focus on the syntheses and applications of new P,N ligands from (*S*)-H_8-NOBIN and/or (*S*)-H_8-BINOL with or without a 6-methyl group of the pyridine ring.

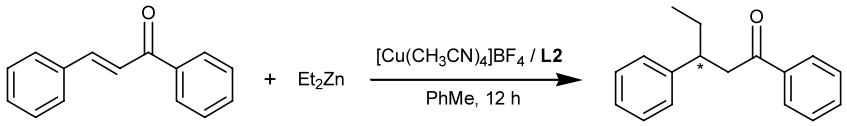
As shown in Scheme 1, ligands **L1–6** can be conveniently synthesized in two steps from (*S*)-NOBIN or (*S*)-H_8-NOBIN and (*S*)-MonoPhos or (*S*)-H_8-MonoPhos.[9] Amidation of (*S*)-H_8-NOBIN with 2-picolinic acids in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[14] as the condensation reagent proceeded smoothly to provide amides **3a** and **3b** in high yields, while the amides (*S*)-**3c** and (*S*)-**3d** had been described in previous report.[9] The phosphite–pyridine ligands (*S*,*S*)-**L1** and (*S*,*S*)-**L2** were subsequently obtained in high yields by refluxing the amide **3a** or **3b** and (*S*)-MonoPhos in toluene. Ligands **L3–6** were prepared with the similar method, but (*S*)-H_8-MonoPhos was prepared from (*S*)-H_8-BINOL and hexamethylphosphorous triamide (HMPT) and directly used.

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

Chalcone was chosen as the substrate to optimize the reaction temperature for the asymmetric 1,4-conjugate addition (Table 1). $[Cu(CH_3CN)_4]BF_4$ was selected as the metal precursor because of its high performance in the addition reaction.[9,10,15] The 1,4-conjugate additions of Et_2Zn to chalcone were conducted in the presence of 1 mol% of $[Cu(CH_3CN)_4]BF_4$ and 2.5 mol% of **L2**. As shown in Table 1, the reaction temperature between −30 to 0°C had slight effect on the enantioselectivity of the addition products, and the best ee (93.8%) was achieved when the reaction temperature was −20°C (entry 3).

The ligands **L1–6** were thus used in Cu(I)-catalyzed 1,4-conjugate additions of Et_2Zn to three types of enones: *para*-substituted chalcones, *trans*-aryl-3-buten-2-ones, and cyclic enones. In a typical procedure, 1 mol% of $Cu(CH_3CN)_4BF_4$ and 2.5 mol% of chiral

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



Entry	*T* [°C]	Yield (%)[b]	Ee (%)[c]	Config.[d]
1	0	67.4	91.0	*S*
2	−10	67.4	92.6	*S*
3	−20	71.5	93.8	*S*
4	−30	77.6	91.8	*S*

[a] The reaction was carried out for 12 h in 1.5 ml toluene, chalcone (0.5 mmol)/$[Cu(CH_3CN)_4]BF_4$/ligand **L2** = 1/0.01/0.025, Et_2Zn:substrate = 1.5:1.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD column.
[d] The absolute configuration was assigned by comparison of the specific rotation with reported data.

ligand were applied in the addition reactions of Et_2Zn to enones, with a ratio of 1.5:1 of Et_2Zn to enone substrate. The reactions were carried out in toluene at –20°C for 12 h.

The results of ligands **L1**–**6** in the 1,4-conjugate additions of Et_2Zn to various *para*-substituted chalcones (Table 2) showed the structure with partial hydrogenation in (*S*)-NOBIN unit was efficient. Ligand **L1** gave high enantioselectivities and the more sterically hindered ligand **L2** was better, which was consistent with previous report.[9,10] Compared with its parent ligand **1b**, ligand **L2** gave different results. When 4′-methoxy-chalcone was used as substrate, the ee of addition product was significantly improved from 73.6 to 92.2% although it provided a relatively lower ee (85.6 versus 95.3%) for 4′-chloro-chalcone. Ligand **L3** based on (*S*)-H_8-BINOL unit also provided good enantioselectivities for some chalcone substrates, but ligand **L4** gave only moderate enantioselectivities for all *para*-substituted chalcones. However, ligands **L5**–**6**, with both (*S*)-H_8-BINOL and (*S*)-H_8-NOBIN moieties, only showed poor to moderate activities and enantioselectivities. The results with ligand **L6** was similar to those from **L4**, while **L5** was nearly ineffective in the 1,4-conjugate additions.

Under the same reaction conditions, ligands **L1**–**6** were also employed in Cu(I)-catalyzed 1,4-conjugate additions of Et_2Zn to some *trans*-4-aryl-3-buten-2-ones (Table 3). As illustrated in Table 3, ligand **L1** showed good catalytic activity and enantioselectivity. When *trans*-(4-chloro-phenyl)-3-buten-2-one was used as substrate, up to 97.8% ee was achieved. To the best of our knowledge, this is the best result for the enantioselective 1,4-conjugate addition of Et_2Zn to *trans*-4-aryl-3-buten-2-one to date. The results from more sterically hindered ligand **L2** were accordance with the previous reports, only afforded moderate ees in low chemical yields.[9,10] Ligands **L3**–**6** with an (*S*)-H_8-BINOL moiety were much less efficient in the 1,4-conjugate addition of Et_2Zn to *trans*-4-aryl-3-buten-2-ones.

To expand the substrate scope of the 1,4-conjugate addition, we also applied these ligands in the reactions of Et_2Zn to 2-cyclohexen-1-one and 2-cyclohepten-1-one (Table 4). However, all ligands were not as efficient as in the reaction to acyclic enones.

3. Conclusion

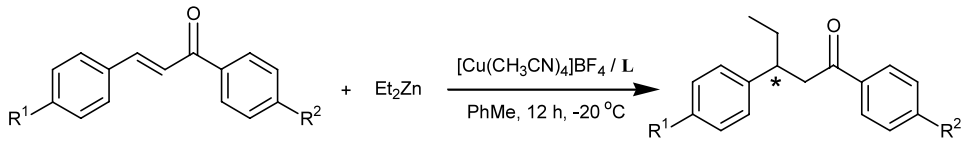
We have synthesized six new phosphite–pyridine ligands in two steps based on relative electron-rich H_8-binaphthyl backbone, and employed in the Cu(I)-catalyzed enantioselective 1,4-conjugate additions of diethylzinc to acyclic enones. The results showed the partial reduction in NOBIN backbone was helpful for obtaining high ee in the 1,4-conjugate addition reactions. Ligand **L2** was very efficient for various *para*-substitute chalcones (up to 97.2% ee), while **L1** showed high enantioselectivities for *trans*-4-aryl-3-buten-2-one as substrates (up to 97.8% ee). This is the best result for the enantioselective 1,4-conjugate additions of Et_2Zn to *trans*-4-aryl-3-buten-2-ones to date.

4. Experimental

4.1. General

Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). Optical rotations were measured on a JASCO 1200 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX 400 system with TMS as an internal standard. ^{31}P NMR spectra were recorded with 85% phosphoric acid as the external standard. The ee values were determined by HPLC with a Daicel ChiralPak-AD column or by GC with a Supelco γ-DEX 225 column. High resolution mass spectra (HRMS) were recorded on ABMS 5303 (ESI). All experiments were carried out under an argon atmosphere using standard Schlenk techniques. All solvents were dried before use according to standard procedures and stored under argon. (*S*)-BINOL was purchased from Nanjing University, NOBIN,[16] (*S*)-H_8-NOBIN[17] and (*S*)-H_8-BINOL[18] were prepared according to literature procedure. (*S*)-MonoPhos[19] was synthesized and isolated according to literature proce-

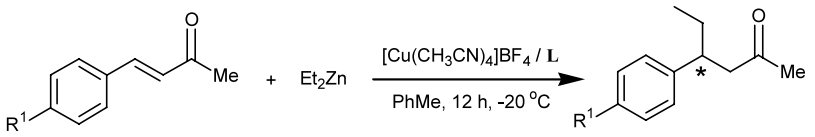
Table 2. Cu-catalyzed enantioselective 1,4-conjugate addition of Et_2Zn to chalcones[a]



Entry	R^1	R^2	L1		L2		L3		L4		L5		L6		Config.[d]
			Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	
1	H	H	90.7	92.8	71.5	93.8	53.9	90.8	39.9	86.1	37.3	48.8	49.7	81.0	*S*
2	Cl	H	85.8	97.2	60.7	96.4	66.4	94.9	54.2	83.2	22.6	50.3	37.1	85.3	+[e]
3	Me	H	92.3	93.3	93.3	97.2	69.8	94.0	51.2	80.5	30.1	47.2	45.5	81.0	+[e]
4	MeO	H	81.8	93.0	74.9	96.7	14.0	70.0	25.4	75.0	21.7	50.0	30.1	79.1	*S*
5	H	Cl	80.1	86.2	85.1	85.6	70.6	91.8	56.6	65.5	26.8	44.0	38.8	60.0	–[e]
6	H	Me	76.1	84.4	58.7	91.0	5.0	24.0	36.5	50.7	17.8	32.8	26.2	74.4	+[e]
7	H	MeO	41.4	66.7	47.8	92.2	7.5	47.7	14.2	41.0	–	–	12.7	46.2	–[e]

[a] The reaction was carried out at −20°C for 12 h in 1.5 ml of toluene, substrate (0.5 mmol)/$[Cu(CH_3CN)_4]BF_4$/**L** = 1/0.01/0.025, Et_2Zn:substrate = 1.5:1.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a ChiralPak-AD column.
[d] The absolute configuration was assigned by comparison of the specific rotation data.
[e] Sign of the optical rotation of the addition product.

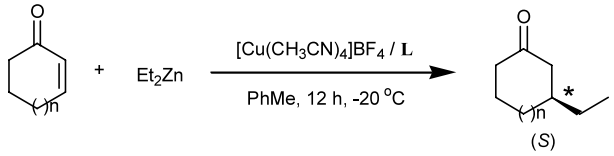
Table 3. Cu-catalyzed enantioselective 1,4-addition of Et_2Zn to *trans*-4-aryl-3-buten-2-ones[a]



Entry	R^1	L1		L2		L3		L4		L5		L6		Config.[d]
		Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	Yield (%)[b]	Ee (%)[c]	
1	H	67.9	91.5	28.4	64.0	24.3	72.2	15.3	19.5	39.8	39.1	20.4	17.0	*S*
2	Cl	81.2	97.8	42.6	85.0	64.2	90.9	14.5	50.0	26.8	58.6	13.3	28.7	+[e]
3	Me	58.9	93.4	22.8	68.7	28.9	79.3	7.4	29.7	14.7	22.3	8.1	rac.	+[e]
4	MeO	43.5	89.0	15.0	70.0	19.2	73.6	6.5	35.8	14.4	24.6	19.1	rac.	+[e]

[a] The reaction was carried out at –20°C for 12 h in 1.5 ml of toluene, substrate (0.5 mmol)/[$Cu(CH_3CN)_4BF_4$/**L**=1/0.01/0.025, Et_2Zn:substrate=1.5:1.
[b] Isolated yield.
[c] The ee value was determined by GC with a Chiral capillary gamma-225 column.
[d] The absolute configuration was assigned by comparison of the specific rotation data.
[e] Sign of the optical rotation of addition product.

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



Entry	Ligand	$n=1$		$n=2$	
		Conv. (%)[b]	Ee (%)[c]	Conv. (%)[b]	Ee (%)[c]
1	**L1**	76.0	22.2	44.0	8.3
2	**L2**	53.3	29.3	50.2	13.9
3	**L3**	38.3	30.7	56.0	23.7
4	**L4**	60.0	65.3	22.0	49.3
5	**L5**	77.8	23.8	47.5	19.4
6	**L6**	67.3	14.2	33.5	18.6

[a] The reaction was carried out at −20°C for 12 h in 1.5 ml of toluene, substrate (0.5 mmol)/[$Cu(CH_3CN)_4BF_4$/**L**=1/0.01/0.025, Et_2Zn:substrate=1.5:1.
[b] Isolated yield.
[c] The ee value was determined by GC with a Chiral capillary gamma-225 column.

dure. (*S*)-H_8-MonoPhos was prepared according to the same method as for the synthesis of (*S*)-MonoPhos and directly used for the synthesis of ligands.

4.2. Synthesis of phosphite–pyridine ligands

4.2.1. Synthesis of amides

4.2.1.1. (*S*)-(–)-2-(2-Pyridinylcarboxamido)-2′-hydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl 3a. A mixture of picolinic acid (1.230 g, 10.0 mmol) and (*S*)-H_8-NOBIN (0.877 g, 3.0 mmol) in 25 ml of THF was stirred at room temperature for 10 min. Condensation agent DMTMM (0.910 g, 3.3 mmol) was added to the mixture and stirred at room temperature. After the reaction was complete (detected by TLC), 20 ml of water was added into the reaction mixture. The two layers were seperated, and the aqueous layer was extracted with diethyl ether (3×20 ml). The combined organic layers were subsequentially washed with 5 ml of saturated $NaHCO_3$, brine, 5% HCl and brine, then dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. The residue was chromatographed on a silica gel column (eluted with CH_2Cl_2) to afford 1.154 g (96%) of amide **3a** as a white solid: mp 187–189°C; $[\alpha]_D^{21}=-113.9$ (*c* 0.5, $CHCl_3$); ^1H NMR (CD_2Cl_2) δ 1.57–1.78 (m, 8H), 2.12–2.26 (m, 3H), 2.34–2.41 (m, 1H), 2.76–2.82 (m, 4H), 5.06–5.10 (m, 1H), 6.82 (d, $J=8.4$ Hz, 1H), 7.10 (d, $J=8.4$ Hz, 1H), 7.17 (d, $J=8.4$ Hz, 1H), 7.31–7.34 (m, 1H), 7.76–7.80 (m, 1H), 8.10 (d, $J=7.6$ Hz, 1H), 8.25 (d, $J=4.4$ Hz, 1H), 8.37 (d, $J=8.4$ Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 23.61, 23.85, 27.92, 30.08, 30.29, 113.83, 118.26, 121.94, 122.53, 125.29, 126.85, 130.64, 130.89, 131.10, 134.86, 137.04, 137.54, 138.17, 148.60, 150.71, 151.58, 162.56; HRMS (*m*/*z*): (M^++1) calcd for $C_{26}H_{27}N_2O_2$ 399.2067; found 399.2074.

4.2.1.2. (*S*)-(–)-2-(6-Methyl-2-pyridinylcarboxamido)-2′-hydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl 3b. Following the same method for the synthesis of **3a**, amide **3b** (0.961 g, 95%) was prepared from 6-methylpicolinic acid (0.411 g, 3.0 mmol) and (*S*)-H_8-NOBIN (0.714 g, 2.4 mmol) as a white solid: mp 227–229°C; $[\alpha]_D^{22}=-119.1$ (*c* 0.5, $CHCl_3$); ^1H NMR (CH_2Cl_2) δ 1.61–1.77 (m, 8H), 2.16–2.35 (m, 7H), 2.78–2.80 (m, 4H), 4.90 (s, 1H), 6.83 (d, $J=8.4$ Hz, 1H), 7.12 (d, $J=8.4$ Hz, 1H), 7.18 (d, $J=8.0$ Hz, 2H), 7.65 (t, $J=7.6$ Hz, 1H), 7.89 (d, $J=7.6$ Hz, 1H), 8.45 (d, $J=8.4$ Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (CH_2Cl_2) δ 23.46, 23.69, 24.09, 27.75, 29.93, 30.09, 113.58, 117.35, 119.15, 121.69, 124.19, 126.24, 130.57, 131.10, 134.32, 134.91, 137.07, 137.30, 138.08, 149.68, 151.45, 157.60, 162.25; HRMS (*m*/*z*): (M^++1) calcd for $C_{27}H_{29}N_2O_2$ 413.2224; found, 413.2210.

4.2.2. Synthesis of the ligands

4.2.2.1. (*S*,*S*)-(+)-L1. Amide **3a** (438.0 mg, 1.1 mmol), (*S*)-MonoPhos (514.0 mg, 1.4 mmol) and 10 ml of xylene were added to 50 ml air-free Schlenk flask with a reflux condenser under an argon atmosphere. The mixture was heated to reflux. After the reaction was complete (detected by TLC), the reation solution was cooled to room temperature and purified by flash chromatograghy on a silica gel column (eluted with hexanes/CH_2Cl_2 (1/1)) to afford 744.0 mg (95%) of (*S*,*S*)-**L1** as a white foamy solid: mp 252–255°C; $[\alpha]_D^{22}=+177.3$ (*c* 0.5, THF); ^1H NMR (CD_2Cl_2) δ 1.64–1.78 (m, 8H), 2.16–2.46 (m, 4H), 2.84–2.86 (m, 4H), 6.78 (d, $J=8.4$ Hz, 1H), 7.14–7.31 (m, 8H), 7.36–7.43 (m, 3H), 7.71–7.74 (m, 1H), 7.79 (d, $J=8.8$ Hz, 1H), 7.86–7.96 (m, 3H), 8.10 (d, $J=7.6$ Hz, 1H), 8.18 (d, $J=4.4$ Hz, 1H), 8.47 (d, $J=8.4$ Hz, 1H), 9.69 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 23.55, 23.66, 23.83, 28.05, 28.67, 30.33, 30.38, 117.99, 119.28, 119.36, 122.38, 122.68, 123.28, 124.92, 125.60, 125.84, 126.63, 126.75, 126.88, 126.99, 127.28, 127.45, 128.40, 129.07, 130.04, 130.40, 130.94, 131.02, 131.93, 132.30, 132.98, 133.40, 134.33, 134.72, 135.70, 136.87, 138.01, 138.69, 147.86, 148.29, 148.47, 150.86, 162.21; ^{31}P NMR δ +145.77; HRMS (*m*/*z*):

(M^++1) calcd for $C_{46}H_{38}N_2O_4P$ 713.2564; found, 713.2590.

4.2.2.2. (*S*,*S*)-(+)-L2. Following the similar method for the synthesis of **L1**, Ligand **L2** (704.3 mg, 97%) was prepared from amide **3b** (411.0 mg, 1.0 mmol) and (*S*)-MonoPhos (467.1 mg, 1.3 mmol) as a white foamy solid: mp 211–212°C; $[\alpha]_D^{22}=+173.5$ (*c* 0.5, THF); ^{1}H NMR (CD_2Cl_2) δ 1.63–1.75 (m, 8H), 2.18–2.45 (m, 7H), 2.85 (br. m, 4H), 6.70 (d, $J=8.8$ Hz, 1H), 7.10–7.30 (m, 8H), 7.33–7.41 (m, 3H), 7.61 (t, $J=7.6$ Hz, 1H), 7.76 (d, $J=8.8$ Hz, 1H), 7.84–7.95 (m, 4H), 8.54 (d, $J=8.4$ Hz, 1H), 9.90 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 23.36, 23.48, 23.63, 24.06, 27.85, 28.50, 30.16, 117.02, 118.99, 119.14, 119.22, 122.20, 122.51, 123.05, 124.67, 125.38, 125.62, 126.02, 126.14, 126.53, 126.78, 127.05, 127.25, 128.24, 128.87, 129.89, 130.17, 130.82, 131.73, 132.10, 132.75, 133.20, 133.80, 134.71, 135.39, 136.57, 137.94, 138.66, 147.69, 148.07, 149.81, 157.37, 161.94; ^{31}P NMR δ +145.81; HRMS (*m*/*z*): (M^++1) calcd for $C_{47}H_{40}N_2O_4P$ 727.2720; found, 727.2765.

4.2.2.3. (*S*,*S*)-(+)-L3. (*S*)-H_8-BINOL (353.2 mg, 1.2 mmol), hexamethylphosphorustriamide (244.5 mg, 1.5 mmol), 2.5 mg of NH_4Cl and 5 ml of benzene were added to a 25 ml air-free Schlenk flask equipped with a reflux condenser under an argon atmosphere. The mixture was refluxed for 12 h, then the reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The residue in 15 ml toluene and (*S*)-**3c** (346.4 mg, 0.89 mmol) were added to a new dried 50 ml Schlenk flask under an argon atmosphere. The mixture was heated to reflux. After the reaction was complete (detected by TLC), the reation solution was cooled. White precipitation occurred. The resulting solid was collected by filtration under argon and washed with toluene (2×2 ml) to afford 477.0 mg of (*S*,*S*)-**L3** as a white solid. The filtrate was purified by flash chromatograghy on a silica gel column (eluted with CH_2Cl_2) to afford another 110.0 mg of (*S*,*S*)-**L3**, the yield was 92%: mp 282–285°C; $[\alpha]_D^{22}=+60.3$ (*c* 0.5, THF); ^{1}H NMR (CD_2Cl_2) δ 1.41–1.45 (m, 2H), 1.69–1.70 (m, 6H), 2.05–2.12 (m, 2H), 2.52–2.80 (m, 6H), 6.17 (d, $J=8.0$ Hz, 1H), 6.80 (d, $J=8.0$ Hz, 1H), 6.86 (d, $J=8.4$ Hz, 1H), 7.02 (d, $J=8.0$ Hz, 1H), 7.15–7.29 (m, 5H), 7.40–7.46 (m, 2H), 7.61 (d, $J=8.8$ Hz, 1H), 7.72 (t, $J=7.6$ Hz, 1H), 7.97–8.02 (m, 3H), 8.11–8.20 (m, 3H), 9.03 (d, $J=8.8$ Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 23.07, 23.26, 28.33, 29.74, 119.33, 119.47, 120.66, 121.22, 122.30, 122.37, 122.48, 123.00, 125.66, 126.16, 126.35, 126.83, 127.39, 128.08, 128.85, 129.04, 129.77, 130.01, 130.17, 131.57, 132.09, 134.03, 134.30, 134.91, 135.87, 136.18, 138.06, 139.18, 145.92, 146.25, 148.45, 149.21, 150.36, 162.47; ^{31}P NMR δ +136.87; HRMS (*m*/*z*): (M^++1) calcd for $C_{46}H_{38}N_2O_4P$ 713.2564; found, 713.2544.

4.2.2.4. (*S*,*S*)-(+)-L4. Following the same method for the synthesis of **L3**, ligand **L4** (694.7 mg, 80%) was prepared from amide (*S*)-**3d** (485.0 mg, 1.2 mmol) and 1.4 mmol of (*S*)-H_8-MonoPhos as a white foamy solid: mp 243–245°C; $[\alpha]_D^{22}=+57.1$ (*c* 0.5, THF); ^{1}H NMR (CD_2Cl_2) δ 1.40–1.43 (m, 2H), 1.66–1.69 (m, 6H), 1.96 (s, 3H), 2.02–2.11 (m, 2H), 2.49–2.74 (m, 6H), 6.06 (d, $J=8.0$ Hz, 1H), 6.76 (d, $J=8.0$ Hz, 1H), 6.83 (d, $J=8.0$ Hz, 1H), 7.00 (d, $J=8.0$ Hz, 1H), 7.06 (d, $J=7.6$ Hz, 1H), 7.18–7.30 (m, 4H), 7.39–7.46 (m, 2H), 7.57–7.61 (m, 2H), 7.87 (d, $J=7.6$ Hz, 1H), 7.96–8.02 (m, 2H), 8.12–8.18 (m, 2H), 9.09 (d, $J=9.2$ Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 22.88, 23.06, 23.87, 28.12, 29.52, 119.13, 119.22, 119.76, 120.28, 122.17, 122.24, 122.85, 125.30, 125.96, 126.04, 126.25, 127.19, 127.93, 128.66, 128.83, 129.53, 129.78, 130.04, 131.32, 132.00, 133.84, 134.17, 134.70, 135.66, 136.18, 137.83, 137.99, 138.98, 145.70, 146.06, 149.09, 149.32, 157.36, 162.15; ^{31}P NMR δ +136.87; HRMS (*m*/*z*): (M^++1) calcd for $C_{47}H_{40}N_2O_4P$ 727.2720; found, 727.2703.

4.2.2.5. (*S*,*S*)-(+)-L5. Following the same method for the synthesis of **L3**, ligand **L5** (510.0 mg, 64%) was prepared from amide (*S*)-**3a** (437.9 mg, 1.1 mmol) and 1.4 mmol of (*S*)-H_8-MonoPhos as a white foamy solid: mp 170–712°C; $[\alpha]_D^{22}=+45.9$ (*c* 0.5, THF); ^{1}H NMR (CD_2Cl_2) δ 1.49–1.74 (m, 16H), 2.14–2.18 (m, 6H), 2.73–2.85 (m, 10H), 6.21 (d, $J=8.4$ Hz, 1H), 6.85–6.90 (m, 2H), 7.06 (t, $J=8.0$ Hz, 2H), 7.22 (d, $J=8.0$ Hz, 1H), 7.26–7.30 (m, 2H), 7.77 (t, $J=7.6$ Hz, 1H), 8.11 (d, $J=8.0$ Hz, 1H), 8.21 (d, $J=4.8$ Hz, 1H), 8.44 (d, $J=8.4$ Hz, 1H), 9.65 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 23.16, 23.33, 23.56, 23.68, 23.85, 28.02, 28.41, 28.65, 29.79, 30.31, 30.38, 117.87, 119.30, 119.39, 119.54, 119.67, 122.38, 126.66, 126.94, 128.32, 129.79, 129.95, 129.99, 130.84, 134.24, 134.60, 134.84, 135.45, 135.79, 136.75, 138.05, 138.57, 139.16, 146.18, 146.59, 147.91, 148.00, 148.51, 150.96, 162.16; ^{31}P NMR δ +137.49; HRMS (*m*/*z*): (M^++1) calcd for $C_{46}H_{46}N_2O_4P$ 721.3190; found, 721.3175.

4.2.2.6. (*S*,*S*)-(+)-L6. Following the same method for the synthesis of **L3**, ligand **L6** (589.3 mg, 80%) was prepared from amide (*S*)-**3b** (412.0 mg, 1.0 mmol) and 1.4 mmol of (*S*)-H_8-MonoPhos as a white foamy solid: mp 264–267°C; $[\alpha]_D^{22}=+37.7$ (*c* 0.5, THF); ^{1}H NMR (CD_2Cl_2) δ 1.46–1.73 (m, 16H), 2.11–2.42 (m, 9H), 2.53–2.84 (m, 10H), 6.13 (d, $J=8.0$ Hz, 1H), 6.85 (t, $J=8.4$ Hz, 2H), 7.05 (t, $J=8.4$ Hz, 2H), 7.14 (d, $J=7.6$ Hz, 1H), 7.21–7.26 (m, 2H), 7.64 (t, $J=7.6$ Hz, 1H), 7.88 (d, $J=7.6$ Hz, 1H), 8.49 (d, $J=8.4$ Hz, 1H), 9.88 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 22.94, 23.11, 23.37, 23.50, 23.65, 24.08, 27.81, 28.20, 28.49, 29.57, 30.15, 116.91, 118.98, 119.15, 119.30, 119.51, 126.02, 126.21, 128.08, 128.19, 129.57, 129.77, 130.75, 133.69, 134.58, 134.65, 135.14, 135.58, 136.42, 137.80, 137.96, 138.55, 138.97, 145.95, 146.40, 147.96, 149.90, 157.38, 161.88; ^{31}P NMR δ +137.53; HRMS (*m*/*z*): (M^++1) calcd for $C_{47}H_{48}N_2O_4P$ 735.3346; found, 735.3307.

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

4.3.1. Preparation of the catalyst. **L1** (71.2 mg, 0.10 mmol), 12.6 mg of $[Cu(CH_3CN)_4]BF_4$ (0.04 mmol) and 10 ml of toluene were added to a 50 ml air-free Schlenk flask under an argon atmosphere. After stirring 30 min at room temperature, the solvent was stripped off in vacuo, 8 ml of CH_2Cl_2 was added to the flask and the

catalyst solution was used for eight separate conjugate addition reactions.

4.3.2. Asymmetric 1,4-conjugate addition. Substrate (0.5 mmol) and 1.0 ml of the above prepared catalyst solution were added to a flame-dried Schlenk tube under an argon atmosphere. After stripping off the solvent, 1.5 ml of toluene was added. The slurry was stirred at room temperture for 10 min and then cooled to –20°C. After the slurry was stired for 15 min, 0.7 ml of Et_2Zn (1.1 M in toluene, 1.5 mol equiv.) was added slowly. The resulting mixture was stired at –20°C for 12 h. 2 ml of 5% HCl 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 orgnic 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, the residue was purified by column chromatagraphy on silica gel and eluted with EtOAc/hexanes (1/40–1/20) to afford the addition product. The ees of the addition products were determined by chiral HPLC or capillary GC, which were detailed described in the supporting information of Refs. 9 and 10.

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