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Readily Prepared Chiral P,N Ligands and Their Applications in Cu-Catalyzed Enantioselective Conjugate Additions

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Abstract: A new type of phosphite−pyridine (P,N) ligand derived from (*S*)-NOBIN and (*S*)-BINOL was employed in Cu(I)-catalyzed conjugate addition of diethylzinc to chalcones. The new P,N ligands were highly efficient in the copper-catalyzed enantioselective 1,4-conjugate additions of diethylzinc to acyclic enones, and up to 97% ee was achieved.

Design and synthesis of chiral ligands play a very important role in the development of highly enantioselective asymmetric reactions.[1] Tunable and easily synthetic ligands are often desired for achieving high enantioselectivities because of strong substrate dependence in most cases. In fact, subtle changes in conformational, steric, and/or electronic properties of the chiral ligands can often lead to dramatic variation of the reactivity and enantioselectivity. The transition-metal-catalyzed 1,4-addition of organozinc reagents to conjugate enones is one of the most important methods of carbon−carbon bond formation.[1,2] In the past decade, great effort has been made to develop efficient chiral ligands for enantioselective catalytic conjugate additions.[3,4] The chiral P,N ligand−copper complexes have been proven to be efficient catalysts for 1,4-conjugate addition.[5] Among the P,N ligands, Zhang's phosphine−pyridine ligand (Figure 1) showed the best enantioselectivities in the Cu(I)-catalyzed 1,4-conjugate additions of diethylzinc to chalcones;[5f] however, the synthetic route was relatively long [six steps from chiral 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN **1**,[6] Scheme 1)], relatively lower chemical activity was observed, and electronic and steric properties were relatively difficult to adjust. We are particularly interested in exploring some new efficient chiral P,N ligands, which were easily synthesized and could be finely tuned, for asymmetric diethylzinc addition to acyclic enones. Therefore, we have designed and developed a new type of phosphite−pyridine ligand **4** by tethering a pyridine amido component and a phosphite component with a single chiral NOBIN.

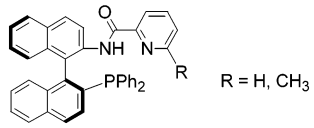
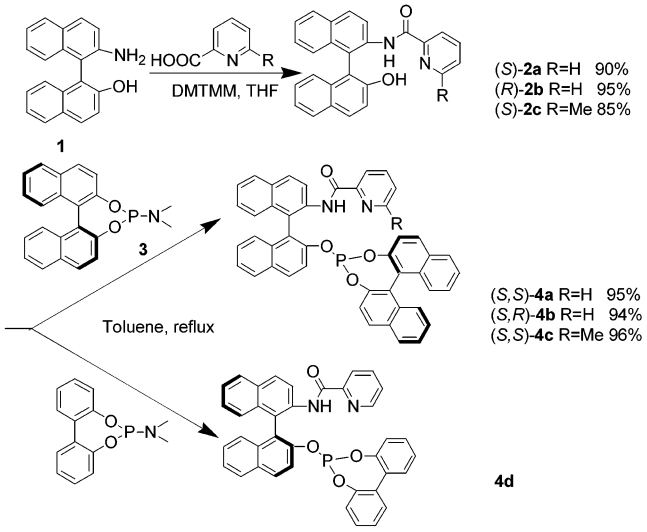


FIGURE 1. Zhang's phosphine−pyridine ligand.

SCHEME 1. Synthesis of Phosphite−Pyridine Ligands 4



Synthesis of the phosphite−pyridine ligands **4** can be accomplished from NOBIN in two steps (Scheme 1). Amidation of NOBIN with 2-picolinic acid in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[7] as the condensation reagent proceeded smoothly to afford the amides **2** in high yields.

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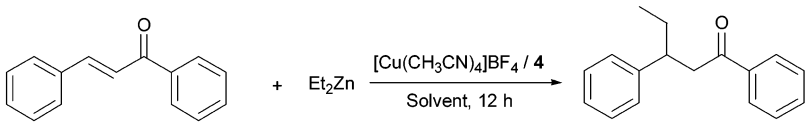
TABLE 1. Cu-Catalyzed Enantioselective 1,4-Conjugate Addition of Et_2Zn to Chalcone[a]



entry	ligand	solvent	*T* (°C)	Et_2Zn/chalcone	yield[b] (%)	ee[c] (%)	config[d]
1	**4a**	toluene/$ClCH_2CH_2Cl$ (2/1)	−10	1/1	35	85	S
2	**4a**	toluene/$ClCH_2CH_2Cl$ (1/1)	−10	1/1	47	77	S
3	**4a**	toluene/CH_2Cl_2 (1/1)	−10	1/1	46	81	S
4	**4a**	$ClCH_2CH_2Cl$	−10	1/1	52	26	S
5	**4a**	CH_2Cl_2	−10	1/1	27	37	S
6	**4a**	toluene	−10	1/1	75	92	S
7	**4a**	toluene	−20	1/1	63	91	S
8	**4a**	toluene	0	1/1	65	90	S
9	**4a**	toluene	10	1/1	63	83	S
10	**4a**	toluene	20	1/1	62	75	S
11	**4a**	toluene	−10	1.2/1	80	92	S
12	**4a**	toluene	−10	1.5/1	92	91	S
13	**4b**	toluene	−10	1.5/1	15	54	S
14	**4c**	toluene	−10	1.5/1	73	96	S
15	**4d**	toluene	−10	1.5/1	14	34	R

[a] Reaction was carried out for 12 h in 3 mL of solvent, chalcone (0.5 mmol)/$[Cu(CH_3CN)_4]BF_4$/ligand **4** = 1/0.01/0.025. [b] Isolated yield. [c] ee values were determined by HPLC with a ChiralPak-AD column. [d] Absolute configuration was assigned by comparison of optical rotation with reported data.

Synthesis of the desired phosphites **4** from **2** could be done through several methods.[8] We prepared optically pure phosphite−pyridine ligand **4** in high yields (>90%) by refluxing the mixture of the amide **2** and Feringa's phosphorus−amidite **3** in toluene. The advantage of this method is the convenience of its workup procedure. The obtained ligands **4** are quite stable in the solid state. Because the structure of **4** can be easily tuned by changing the phosphite component or the steric bulk of R, we can envision that new phosphite−pyridine ligands could be efficient for copper-catalyzed 1,4-conjugate additions.

Chalcone was chosen as a typical substrate to optimize the reaction conditions for the asymmetric conjugate addition (Table 1). $[Cu(CH_3CN)_4]BF_4$ was selected as the metal precursor for its high performance in the conjugate addition.[5f] The conjugate additions of diethylzinc to chalcone were conducted in the presence of 1 mol % of $[Cu(CH_3CN)_4]BF_4$ and 2.5 mol % of ligand **4**. The results summarized in Table 1 showed that pure toluene is advantageous over halogen-containing solvents or mixed solvents for achieving high enantioselectivity (entries 1−6). The reaction product was obtained in 92% ee with toluene as the solvent and **4a** as the ligand (entry 6). A decrease in the reaction temperature from −10 to −20 °C did not give a favorable ee, whereas the enantioselectivity dropped dramatically when the temperature was increased from −10 to 20 °C (entries 8−10). The reaction yield was enhanced to 92% when 1.5 equiv of diethylzinc was used, whereas the ee did not drop (entries 11 and 12 versus entry 6). Replacing ligand (*S*,*S*)-**4a** with its diastereomer **4b** [derived from (*R*)-NOBIN and (*S*)-1,1′-bi-2-naphthol (BINOL)] led to the addition product in a much lower ee (entry 13 versus entry 12). The result demonstrated that the two chiral configurations of ligand (*S*,*S*)-**4a** are matched for the high enantioselectivity of the reaction. When (*S*,*S*)-**4c**, a more sterically hindered ligand, was used instead of (*S*,*S*)-**4a**, the reaction product was obtained in 73% yield and in 96% ee. This enantioselectivity is comparable to the result obtained with the Cu(I)−phosphine−pyridine system.[5f] It is noteworthy that the absolute configuration of the addition product is dependent on the absolute configuration of the BINOL moiety of the ligand. To study the influence of the BINOL moiety of the ligand on the enantioselectivity of the reaction, structural flexible ligand **4d** with an achiral biphenyl group at the phosphite component was tested for the reaction. When **4d** was employed for the enantioselective conjugate addition, the configuration of the product was reversed and the obtained ee was only 34% (entry 15).

We thus used **4c** as the ligand for Cu-catalyzed enantioselective conjugate addition of diethylzinc to various substituted chalcones (Table 2). The reactions were carried out at −10 °C in toluene with 1.5 equiv of diethylzinc as the reagent. As shown in Table 2, excellent enantioselectivities (up to 97% ee) and yields were obtained for a variety of substituted chalcones. To our best knowledge, 97% ee values for chalcone and 4-chlorochalcone (entries 1 and 2) are the best results of copper-catalyzed conjugate additions to date. For 4′-substituted chalcones, a major electronic effect was observed. Electronic-deficient substrates appeared to be beneficial for the enantioselectivity of the reaction, as >95% ee was obtained for a 4′-Cl substrate (entry 5), whereas the result for an electronic-rich substrate was much less enantioselective (entry 7). In contrast, there was no electronic effect for 4-substituted chalcones, because all of the 4-substituted chalcones gave excellent enantioselectivities (entries 2−4). A simple acyclic enone, *trans*-4-phenyl-3-buten-2-one, was also used as the substrate for the conjugate additions (entries 8 and 9). Ligand **4a**

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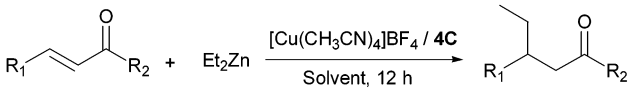
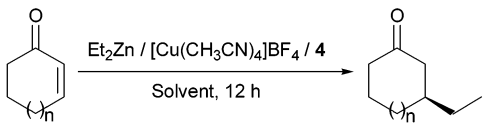
TABLE 2. Enantioselective 1,4-Conjugate Addition of Et_2Zn to Acyclic Enones[a]



entry	R_1	R_2	yield[b] (%)	ee[c] (%)	config[d]
1	Ph	Ph	82	97	*S*
2	4-Cl−C_6H_4	Ph	76	97	+[e]
3	4-Me−C_6H_4	Ph	86	97	+[e]
4	4-MeO−C_6H_4	Ph	80	97	*S*
5	Ph	4-Cl−C_6H_4	75	95	−[e]
6	Ph	4-Me−C_6H_4	71	89	+[e]
7	Ph	4-MeO−C_6H_4	31	74	−[e]
8	Ph	Me	48	58[f]	*S*
9[g]	Ph	Me	64	90[f]	*S*

[a] Reaction was carried out at −10 °C for 12 h in 3 mL of toluene [substrate (1.0 mmol)]/[$Cu(CH_3CN)_4$]BF_4/ligand **4c** = 1/0.01/0.025. [b] Isolated yield. [c] ee values were determined by HPLC with a ChiralPak-AD column. [d] Absolute configuration was assigned by comparison of optical rotation with reported data. [e] Sign of the optical rotation of addition product. [f] ee values were determined by GC with a capillary Gamma-DEX-225 column. [g] Reaction was carried out with **4a** as the ligand.

TABLE 3. Asymmetric Conjugate Additions of Et_2Zn to Cyclic Enones[a]



entry	*n*	ligand	conv[b] (%)	ee[b] (%)	config[c]
1	1	**4a**	90	53	*S*
2	1	**4c**	79	45	*S*
3	2	**4a**	90	31	*S*
4	2	**4c**	33	33	*S*

[a] Reaction was carried out at −10 °C for 12 h in 3 mL of toluene [substrate (1.0 mmol)]/[$Cu(CH_3CN)_4$]BF_4/ligand **4** = 1/0.01/0.025. [b] Conversions and ee values were determined by GC with a capillary Gamma-DEX-225 column. [c] Absolute configuration was assigned by comparison of optical rotation with reported data.

afforded a 90% ee for the addition product, which was much better than that obtained from **4c**.

To extend the range of substrates for these catalysts, the conjugate additions of Et_2Zn to cyclic enones were also examined (Table 3); however, ligands **4a** and **4c** did not show their enantioselectivities like the reaction of chalcones. These results showed that the new P,N ligand−copper complexes were not proper catalysts for conjugate additions of cyclic enones.

In summary, a new type of phosphite−pyridine ligand **4** derived from (*S*)-NOBIN and (*S*)-BINOL has been developed. Ligand **4c** has been successfully applied in Cu-catalyzed conjugate addition of Et_2Zn to chalcones, and up to 97% ee has been obtained. Less sterically hindered ligand **4a** showed good results, up to 90% ee, for *trans*-4-phenyl-3-buten-2-one as the substrate. Further study will be focused on the applications of the new P,N ligands **4** in other asymmetric catalytic reactions and progress will be reported in due course.

Experimental Section

General. All reactions were carried out in an argon atmosphere using standard Schelenk techniques. All solvents were dried before use according to standard procedures and stored under argon. Feringa's phosphorus amidite **3** was prepared according to a literature procedure.[9]

Synthess of Amides: (*S*)-(−)-2-(2-Pyridinylcarboxamido)-2′-hydroxyl-1,1′-binaphthyl (2a). Typical Procedure. A mixture of 0.740 g of picolinic acid (6.0 mmol) and 1.428 g of (*S*)-NOBIN (5.0 mmol) in 25 mL of THF was stirred at room temperature for 10 min; 1.522 g of condensation agent DMTMM (5.5 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. Separated layers and aqueous layer were extracted with diethyl ether (3 × 20 mL). The combined organic layers were successively washed with 5 mL of saturated sodium bicarbonate, brine, and 5% of HCl and brine and then dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. The residue was chromatographed on silica gel and eluted with CH_2Cl_2 to afford 1.751 g (90%) of amide **2a** as a white solid: mp 202−203 °C; $[\alpha]^{25}_D$ −175.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 6.84 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.17−7.32 (m, 3H), 7.43−7.52 (m, 3H), 7.94−8.19 (m, 7H), 8.80−8.83 (m, 1H), 9.95 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 112.65, 118.37, 118.49, 119.65, 121.86, 122.13, 122.94, 123.57, 124.78, 125.48, 126.49, 126.86, 127.02, 128.08, 128.30, 130.45, 130.54, 132.73, 133.57, 134.10, 138.32, 148.17, 148.85, 153.30, 153.46, 161.22; HR-MS, calcd for $C_{26}H_{18}N_2O_2$ 390.1368, found 390.1362.

(*R*)-(+)-2-(2-Pyridinylcarboxamido)-2′-hydroxyl-1,1′-binaphthyl (2b). The amide **2b** (1.845 g, 95%) was prepared from 0.738 g of picolinic acid (6.0 mmol) and 1.428 g of (*R*)-NOBIN (5.0 mmol) according to the same procedure as used for **2a** and isolated as a white solid: mp 202−203 °C; $[\alpha]^{25}_D$ +174.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 6.85 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H) 7.18−7.32 (m, 3H), 7.43−7.53 (m, 3H), 7.94−8.19 (m, 7H), 8.82 (d, J = 9.2 Hz, 1H), 9.97 (s, 1H), 10.05 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 112.68, 118.40, 118.52, 119.68, 121.88, 122.16, 122.95, 123.59, 124.80, 125.50, 126.50, 126.87, 127.02, 128.10, 128.32, 130.47, 130.56, 132.76, 133.59, 134.14, 138.31, 148.17, 148.87, 153.33, 153.49, 161.24; HR-MS, calcd for $C_{26}H_{18}N_2O_2$ 390.1368, found 390.1374.

(*S*)-(−)-2-(6-Methyl-2-pyridinylcarboxamido)-2′-hydroxyl-1,1′-binaphthyl (2c). The amide **2c** (1.714 g, 85%) was prepared from 0.826 g of 6-methylpicolinic acid (6.0 mmol) and 1.428 g of (*S*)-NOBIN (5.0 mmol) according to the same procedure as used for **2a** and isolated as a white solid: mp 272−274 °C; $[\alpha]^{25}_D$ −190.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H), 6.87 (d, J = 8.0 Hz, 1H), 7.15−7.54 (m, 7H), 7.78−8.15 (m, 6H), 8.93 (d, J = 9.2 Hz, 1H), 9.90 (s, 1H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.22, 112.70, 118.52, 118.67, 121.41, 122.96, 123.48, 124.63, 125.43, 126.40, 126.52, 126.93, 128.10, 128.29, 128.48, 130.42, 132.78, 133.60, 134.14, 134.22, 138.35, 148.02, 153.45, 153.60, 156.64, 160.98; HR-MS, calcd for $C_{27}H_{20}N_2O_2$ 404.1525, found 404.1542.

Synthesis of the Ligands: (*S*,*S*)-(+)-4a. Typical Procedure. Amide **2a** (390.4 mg, 1.0 mmol), 467.2 mg of (*S*)-Feringa's phosphorus−amidite ligand **3** (1.3 mmol), and 15 mL of toluene were added to a 50 mL air-free Schlenk flask with a reflux condenser under an argon atmosphere. The mixture was heated to reflux; initially the mixture turned into a colorless solution, and then precipitation occurred in a few hours. After 24 h of refluxing, the reaction mixture was cooled to room temperature. The resulting white solid was collected by filtration under argon, washed with toluene (2 × 2 mL), and dried in vacuo to afford 667.2 mg of ligand **4a** (95%) as a white solid: mp 292−294 °C; $[\alpha]^{25}_D$ 174.9 (*c* 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 6.72 (d, J = 8.8 Hz, 1H), 7.00−7.10 (m, 4H), 7.30−7.47 (m, 10H), 7.79 (d, J = 9.2 Hz, 1H), 7.86−8.18 (m, 9H), 8.30−8.36 (m, 2H), 8.88−8.92 (m, 1H), 9.86 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 121.16, 124.66, 125.04, 125.37, 125.62, 125.86, 126.37, 126.62, 126.76, 126.90, 127.71, 128.21, 128.54, 129.39, 129.77, 130.71, 131.31, 138.02,

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147.87; ^{31}P NMR δ +144.86; HR-MS, calcd for $C_{46}H_{29}N_2O_4P$ 704.1865, found 704.1857.

(*S*,*R*)-(+)-4b. Ligand **4b** (663.8 mg, 94%) was prepared from 390.4 mg of amide **2b** (1.0 mmol) and 466.3 mg of **3** (1.3 mmol) according to the same procedure as used for **4a** and isolated as a white solid: mp 220−222 °C; $[\alpha]^{25}_D$ 116.1 (*c* 0.5, THF); ^{1}H NMR (DMSO-d_6) δ 6.21 (d, J = 8.8 Hz, 1H), 7.04−7.15 (m, 4H), 7.25−7.59 (m, 11H), 7.75 (d, J = 8.8 Hz, 1H), 7.90−8.37 (m, 10H), 8.94 (d, J = 8.8 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 119.59, 119.95, 121.12, 121.26, 121.67, 121.82, 124.66, 125.24, 125.49, 125.75, 125.82, 125.89, 126.57, 126.81, 127.11, 127.95, 128.36, 128.43, 128.65, 129.54, 129.71, 130.60, 130.88, 131.11, 131.18, 131.40, 131.58, 131.81, 132.82, 134.81, 138.33, 146.05, 146.56, 147.85, 148.03, 148.44, 161.15; ^{31}P NMR δ +144.83; HR-MS, calcd for $C_{46}H_{29}N_2O_4P$ 704.1865, found 704.1852.

(*S*,*S*)-(+)-4c. Ligand **4c** (686.7 mg, 96%) was prepared from 404.3 mg of amide **2c** (1.0 mmol) and 466.2 mg of **3** (1.3 mmol) according to the same procedure as used for **4a** and isolated as a white solid: mp 273−275 °C; $[\alpha]^{25}_D$ 164.7 (*c* 0.5, THF); ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H), 6.38 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 7.11−7.50 (m, 14H), 7.63 (d, J = 8.4 Hz, 2H), 7.75−8.16 (m, 8H), 9.13 (d, J = 8.8 Hz, 1H), 10.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.68, 118.72, 119.36, 119.92, 121.43, 121.51, 121.68, 121.74, 122.44, 124.30, 124.79, 124.94, 125.14, 125.61, 125.87, 126.27, 126.79, 126.84, 127.04, 127.57, 128.21, 128.31, 128.41, 129.67, 130.25, 130.75, 130.82, 131.16, 131.45, 131.54, 132.25, 132.77, 133.45, 133.81, 135.52, 137.29, 146.96, 147.38, 148.42, 148.49, 148.66, 156.47, 161.90; ^{31}P NMR δ +146.61; HR-MS, calcd for $C_{47}H_{31}N_2O_4P$ 718.2021, found 718.2050.

(*S*)-(−)-4d. 2,2′-Biphenol (286 mg, 1.0 mmol), 163 mg of hexamethylphosphorustriamide (1.0 mmol), 2.0 mg of NH_4Cl, and 5 mL of toluene were added to a 25 mL air-free Schlenk flask equipped with a reflux condenser under argon atmosphere. The mixture was heated to 90 °C for 12 h, and then the reaction mixture was filtered to remove NH_4Cl. The filtrate, 5 mL of toluene, and 195.2 mg of (*S*)-**2a** (0.5 mmol) were added to a new dried 50 mL Schlenk flask under an argon atmosphere. The mixture was heated to reflux. After 15 h of stirring, the reation solution was cooled to room temperature and purified by flash chromatograghy on silica gel and eluted with CH_2Cl_2 to afford 241.3 mg (80%) of (*S*)-**4d** as a white foamy solid: mp 79−82 °C; $[\alpha]^{15}_D$ −6.7 (*c* 1.2, THF); ^{1}H NMR (DMSO-d_6) δ 6.58 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 7.2 Hz, 1H), 7.05−7.54 (m, 13H), 7.77 (d, J = 8.8 Hz, 1H), 7.89−8.37 (m, 7H), 8.95 (d, J = 9.2 Hz, 1H), 9.96 (S, 1H); ^{13}C NMR (DMSO-d_6) δ 119.36, 119.77, 121.25, 121.54, 121.66, 124.53, 125.02, 125.53, 126.90, 127.71, 128.11, 128.51, 129.08, 129.19, 129.45, 129.60, 129.95, 130.36, 130.92, 131.34, 132.61, 132.71, 134.65, 138.11, 147.64, 147.83, 148.31, 160.94; ^{31}P NMR (DMSO-d_6) δ +148.89; HR-MS, calcd for $C_{38}H_{25}N_2O_4P$ 604.1552, found 604.1560.

General Procedure for Asymmetric 1,4-Conjugate Addition: Preparation of Catalyst. 4c (71.8 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 30 min of stirring at room temperature, the solvent was stripped off in vacuo, 6 mL of CH_2Cl_2 was added to the flask, and the catalyst solution was used for four separate conjugate addition reactions.

Asymmetric 1,4-Conjugate Addition. Chalcone substrate (1 mmol) and 1.5 mL of the above prepared catalyst solution were added to a flame-dried Schlenk tube under an argon atmosphere. After the solvent had been stripped off, 3 mL of toluene was added. The slurry was stirred at room temperture for 10 min and then cooled to the desired temperature. After the slurry had been stirred for 15 min, 1.4 mL of Et_2Zn (1.1 M in toluene, 1.5 mol equiv) was added slowly. The resulting mixture was stirred at that temperature for 12 h. Four milliliters of 5% hydrochloric acid 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 chromatagraphy on silica gel and eluted with EtOAc/hexanes (1/40−1/20) to afford the addition product. The ee values of the addition products were determined by chiral HPLC or capillary GC. The analytical conditions are given in the Supporting Information.

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Supporting Information Available: ee value determination conditions of HPLC and GC, spectra of **2a**−**c**, **4a**−**d** (^{1}H NMR, ^{13}C NMR, and ^{31}P NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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