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Highly Enantioselective Conjugate Addition of Diethylzinc to Acyclic Enones with Fine-Tunable Phosphite–Pyridine Ligands

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Abstract: A new series of fine-tunable phosphite–pyridine (P,N) ligands derived from (*S*)-2-amino-2'-hydroxy-6,6'-dimethyl-1,1'-biphenyl and (*S*)-2-amino-2'-hydroxy-4,4',6,6'-tetramethyl-1,1'-biphenyl was employed in Cu(I)-catalyzed conjugate addition of diethylzinc to acyclic enones. Excellent enantioselectivities (up to 98% ee) and highly catalytic activities were achieved for a variety of acyclic enones.

The 1,4-addition of organometallic reagents to conjugate enones is one of the most important methods for carbon–carbon bond formation.¹ The Cu(I)-catalyzed enantioselective addition of Et₂Zn to enones has attracted much attention in the past decade, and a number of efficient copper catalysts with chiral ligands have been reported.² Among those successful chiral ligands, phosphorus amidites by Feringa et al.³ and TADDOL-derived phosphites and biphenyl-derived phosphorus amidites by Alexakis et al.⁴ have shown remarkable enantioselectivities in the reaction of Et₂Zn addition to cyclic enones. Some diphosphine,⁵ diphosphite,⁶ P,N ligands,⁷ spiro-phosphoramidites,⁸ and aminophosphine⁹ are also ef-

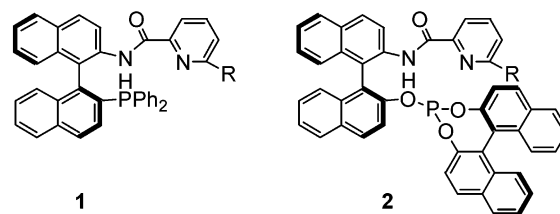


FIGURE 1. Chiral P,N ligands for Cu-catalyzed conjugate addition of Et₂Zn to chalcones.

ficient for this transformation. In contrast to the many successful chiral ligands for Et₂Zn addition to cyclic enones, only a few chiral ligands are reported to be efficient for Et₂Zn addition to acyclic enones.¹⁰ Recently, Hoveyda et al.¹¹ have developed peptidic phosphines which have shown high enantioselectivities for various enone substrates. However, high enantioselectivities (>95% ee) are rarely reported for Et₂Zn addition to chalcones (**1**^{10c} and **2**^{10a} in Figure 1).

In our previous paper, we developed chiral phosphite–pyridine ligands derived from (*S*)-2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN) and (*S*)-2,2'-dihydroxy-1,1'-binaphthyl (BINOL) for Cu(I)-catalyzed Et₂Zn addition to chalcones.^{10a} High enantioselectivities and yields are obtained for a set of chalcones except for some electron-rich substrates such as 4'-methyl and 4'-methoxy chalcones. The substrate limitation could probably be ascribed to the electron-deficiency of chiral phosphite–pyridine ligands at the NOBIN moiety, which implied that the limitation could be improved by an electron-rich and electronic tunable ligand. In this paper, we synthesize a new series of phosphite–pyridine ligands **L1–4**, derived from relatively electron-rich biphenyl backbones, for Cu(I)-catalyzed Et₂Zn additions to acyclic enones in order to overcome the substrate limitation and verify the subtle alternating effects of electronic property of the chiral ligands. The new phosphite-pyridine ligands **L1–4** can be conveniently synthesized from our newly developed chiral biphenyl backbones **3**¹² in two steps (Scheme 1).^{10a}

Our previous studies showed that toluene is an appropriate solvent for the Cu(I)-catalyzed enantioselective conjugate additions of Et₂Zn to chalcones (**1**).^{10a} Thus **L1** and chalcone were chosen to optimize the reaction conditions. The conjugate addition of Et₂Zn to chalcone was

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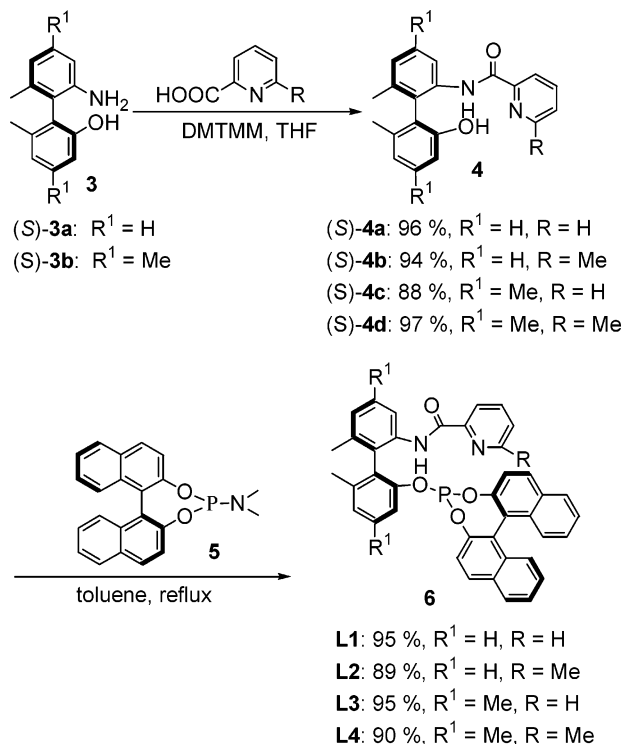
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SCHEME 1. Synthesis of Phosphite–Pyridine Ligands L1–4

TABLE 1. Cu-Catalyzed Enantioselective 1,4-Conjugate Addition of Et₂Zn to Chalcone^a

entry	T (°C)	time (h)	yield ^b (%)	ee ^c (%)	config ^d
1	10	12	79	79	S
2	0	12	71	87	S
3	-10	12	73	90	S
4	-20	12	83	93	S
5	-30	12	75	88	S
6	-20	6	82	93	S
7	-20	3	80	94	S

^a The reaction was carried out for 1.5 mL of toluene, chalcone (0.5 mmol)/[Cu(CH₃CN)₄]BF₄/L1 = 1/0.01/0.025, 0.70 mL of Et₂Zn (1.1 M in toluene). ^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 optical rotation with reported data.

carried out in toluene in the presence of Cu(CH₃CN)₄BF₄ (1 mol %) and L1 (2.5 mol %). The results are summarized in Table 1. As can be seen, the reaction temperature has a remarkable influence on the enantioselectivity of the reaction (entries 1–5). The best ee and yield are obtained when the reaction proceeded at -20 °C. The reaction time has a marginal effect on the yield as little difference is observed when the time varies from 3 to 12 h (entries 4, 6, and 7).

We thus used L1–4 as the ligands for Cu-catalyzed enantioselective conjugate addition of Et₂Zn to para-substituted (Me, MeO, Cl) chalcones (**2**) (entries 1–7, Table 2). The reactions were carried out at -20 °C in toluene with 1.5 equiv of Et₂Zn as the reagent. As shown in Table 2, ligands L1–4 provided over 95% ee for 4-substituted and electron-deficient 4'-substituted (Cl)

chalcones (entries 2, 4, 6, and 7, Table 2). Ligand L4 gave the best enantioselectivities for all chalcone substrates. Although a 6-methyl group of the pyridine moiety of the ligand was helpful for obtaining high enantioselectivities in most cases (column L2 vs column L1, column L4 vs column L3, Table 2), methyl groups at 4,4'-positions of biphenyl moiety were beneficial to improve enantioselectivity for 4'-methoxy chalcone as substrate (entry 5, Table 2, 95% ee from L4 and 87% ee from L2 vs 74% ee from ligand 2^{10a}). The different behaviors of ligands L1–4 and ligand 2^{10a} suggested the effects of the tunable electronic property of chiral ligands on the conjugate additions.

To extend the substrate scope of this transformation, the conjugate addition of Et₂Zn to *trans*-4-aryl-3-buten-2-one substrates has been studied (entries 8–11, Table 2). Interestingly, the more electron-rich but less sterically hindered ligand L3 gave the best ee's for all *trans*-4-aryl-3-buten-2-one substrates. Up to 96% ee has been obtained for conjugate addition of *trans*-4-(4-chlorophenyl)-3-buten-2-one (entry 11, Table 2). Compared to other ligands, L3 has also shown the best chemical yields for those substrates.

In summary, we have developed a new series of fine-tunable phosphite–pyridine ligands L1–4 from (S)-biphenyl backbones and (S)-BINOL. The electron-rich and sterically hindered ligand L4 has been successfully applied in Cu-catalyzed conjugate addition of Et₂Zn to various chalcone substrates and up to 98% ee has been obtained. An electron-rich but less sterically hindered ligand L3 provides best results for *trans*-4-aryl-3-buten-2-one substrates.

Experimental Section

Synthesis of the Amides:^{10a} (S)-(–)-2-(2-Pyridinylcarboxamido)-2'-hydroxy-6,6'-dimethyl-1,1'-biphenyl (**4a**). The amide **4a** (0.916 g, 96%) was prepared from 0.443 g of picolinic acid (3.6 mmol) and **3a** (0.639 g, 3.0 mmol) and isolated as a white solid: mp 150–151 °C; [α]_D²⁰ -16.2 (c 0.36, CHCl₃); ¹H NMR (DMSO-*d*₆) δ 1.83 (s, 3H), 1.97 (s, 3H), 6.85–6.90 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.50–7.54 (m, 1H), 7.96–8.00 (m, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 4.4 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 9.34 (s, 1H), 9.77 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 19.2, 19.64, 113.4, 116.7, 121.1, 121.8, 121.9, 125.3, 126.9, 127.4, 127.9, 129.1, 135.3, 136.9, 137.5, 138.3, 148.2, 149.1, 154.8, 161.0; HR-MS calcd for C₂₀H₁₈N₂O₂ 318.1369, found 318.1374.

(S)-(–)-2-(6-Methyl-2-pyridinylcarboxamido)-2'-hydroxy-6,6'-dimethyl-1,1'-biphenyl (**4b**). The amide **4b** (0.734 g, 94%) was prepared from 0.386 g of 6-methylpicolinic acid (2.8 mmol) and **3a** (0.500 g, 2.3 mmol) and isolated as a white solid: mp 157–158 °C; [α]_D²⁰ -17.3 (c 0.26, CHCl₃); ¹H NMR (DMSO-*d*₆) δ 1.85 (s, 3H), 1.99 (s, 3H), 2.23 (s, 3H), 6.88–6.93 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.83–7.89 (m, 2H), 8.44 (d, *J* = 8.0 Hz, 1H), 9.33 (s, 1H), 10.06 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 19.2, 19.7, 23.5, 113.4, 115.7, 118.6, 121.1, 121.9, 125.0, 126.4, 127.5, 129.1, 135.5, 136.9, 137.7, 138.4, 148.3, 154.9, 156.8, 160.9; HR-M, calcd for C₂₁H₂₀N₂O₂ 332.1526, found 332.1520.

(S)-(–)-2-(2-Pyridinylcarboxamido)-2'-hydroxy-4,4',6,6'-tetramethyl-1,1'-biphenyl (**4c**). The amide **4c** (0.915 g, 88%) was prepared from 0.443 g of picolinic acid (3.6 mmol) and **3b** (0.723 g, 3.0 mmol) and isolated as a white solid: mp 118–119 °C; [α]_D²⁰ -3.0 (c 0.226, CHCl₃); ¹H NMR (DMSO-*d*₆) δ 1.79 (s, 3H), 1.92 (s, 3H), 2.29 (s, 3H), 2.34 (s, 3H), 6.67 (d, *J* = 7.2 Hz, 2H), 6.91 (s, 1H), 7.51–7.54 (m, 1H), 7.98 (t, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.19 (s, 1H), 8.31 (d, *J* = 4.0 Hz, 1H),

TABLE 2. Cu-Catalyzed Enantioselective 1,4-Conjugate Addition of Et₂Zn to Acyclic Enones^a

$$\text{R}^1\text{---}\text{CH}=\text{CH}\text{---}\text{C}(=\text{O})\text{---}\text{R}^2 \xrightarrow[\text{Et}_2\text{Zn, Toluene, -20 }^\circ\text{C, 6 h}]{[\text{Cu}(\text{CH}_3\text{CN})_4]\text{BF}_4 / \text{L1-L4}} \text{R}^1\text{---}\text{CH}_2\text{---}\text{CH}(\text{R}^*)\text{---}\text{C}(=\text{O})\text{---}\text{R}^2 \quad (2)$$

entry	R ¹	R ²	L1 ^{b,c}		L2 ^{b,c}		L3 ^{b,c}		L4 ^{b,c}		config ^d
			yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	
1	Ph	Ph	79	94	76	97	81	96	83	97	S
2	4-Me-C ₆ H ₄	Ph	88	95	77	97	90	96	84	97	+ ^e
3	Ph	4-Me-C ₆ H ₄	72	90	82	96	87	92	82	97	+ ^e
4	4-MeO-C ₆ H ₄	Ph	74	94	68	97	85	96	76	98	S
5	Ph	4-MeO-C ₆ H ₄	32	75	23	87	58	84	57	95	- ^e
6	4-Cl-C ₆ H ₄	Ph	74	96	57	94	85	97	77	97	+ ^e
7	Ph	4-Cl-C ₆ H ₄	87	96	77	96	85	97	78	97	- ^e
8	Ph	Me	20	81	14	20	67	90	24	52	+ ^e
9	4-Me-C ₆ H ₄	Me	24	88	12	54	47	90	28	53	+ ^e
10	4-MeO-C ₆ H ₄	Me	24	85	7	40	44	90	21	58	+ ^e
11	4-Cl-C ₆ H ₄	Me	7	93	4	56	70	96	34	75	+ ^e

^a The reaction was carried out at -20 °C for 6 h in 3 mL of toluene (substrate (1.0 mmol)/[Cu(CH₃CN)₄]BF₄/L1-L4/Et₂Zn = 1/0.01/0.025/1.5. ^b Isolated yield. ^c The ee values were determined by HPLC with a ChiralPak-AD column or by GC with a Supelco γ-DEX 225 column. ^d The absolute configuration was assigned by comparison of the optical rotation with reported data. ^e Sign of the optical rotation of addition product.

9.14 (s, 1H), 9.74 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 19.2, 19.6, 21.0, 21.2, 113.9, 117.2, 118.9, 121.7, 121.9, 125.1, 126.0, 126.9, 135.4, 136.3, 136.8, 137.3, 138.1, 138.3, 148.3, 149.2, 154.8, 160.9; HR-MS calcd for C₂₂H₂₂N₂O₂ 346.1682, found 346.1685.

(S)-(-)-2-(6-Methyl-2-pyridinylcarboxamido)-2'-hydroxy-4,4',6,6'-tetramethyl-1,1'-biphenyl (4d). The amide **4d** (0.728 g, 97%) was prepared from 0.341 g of 6-methylpicolinic acid (2.5 mmol) and **3b** (0.500 g, 2.1 mmol) and isolated as a white solid: mp 178–179 °C; [α]_D²⁵ -1.6 (c 0.322, CHCl₃); ¹H NMR (DMSO-*d*₆) δ 1.80 (s, 3H), 1.96 (s, 3H), 2.23 (s, 3H), 2.29 (s, 3H), 2.34 (s, 3H), 6.70 (s, 2H), 6.89 (s, 1H), 7.36–7.41 (m, 1H), 7.83–7.87 (m, 2H), 8.27 (s, 1H), 9.12 (s, 1H), 10.03 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 19.2, 19.6, 21.0, 21.3, 23.2, 114.0, 116.2, 118.5, 119.0, 121.9, 124.6, 125.7, 126.3, 135.5, 136.4, 136.8, 137.5, 138.1, 138.4, 148.4, 154.9, 156.7, 160.7; HR-MS calcd for C₂₃H₂₄N₂O₂ 360.1839, found 360.1829.

Synthesis of the Ligands:^{10a} **L1. Typical Procedure.** Amide **4a** (318.4 mg, 1.0 mmol), 465.4 mg of (S)-Feringa's phosphorus–amidite ligand **5** (1.3 mmol), and 10 mL of toluene were added to a 50 mL air-free Schlenk flask with a reflux condenser under an argon atmosphere. After 12 h of refluxing, the reaction was complete (detected by TLC) and the mixture cooled to room temperature. The solvent was removed under reduced pressure, the residue was purified by column chromatography on 30 g of silica gel and eluted with EtOAc/hexanes (1/5–1/2) to afford white foamy solid. Recrystallization with CH₂Cl₂/heptane and drying in vacuo provided 601 mg of ligand **L1** (95%) as a white solid: mp 99–123 °C; [α]_D¹⁶ 302 (c 0.53, THF); ¹H NMR (CD₂Cl₂) δ 2.02 (s, 6H), 6.83 (d, *J* = 8.8 Hz, 1H), 7.14–7.28 (m, 8H), 7.33–7.47 (m, 5H), 7.72–7.78 (m, 2H), 7.84–7.95 (m, 3H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 4.8 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 9.72 (s, 1H); ¹³C NMR (CD₂Cl₂) δ 20.2, 20.8, 118.2, 119.6, 119.7, 122.4, 122.46, 122.53, 123.2, 124.9, 125.6, 125.9, 126.4, 126.8, 127.0, 127.3, 127.5, 127.6, 129.1, 129.3, 130.2, 130.5, 131.1, 132.0, 132.3, 133.0, 133.4, 137.2, 138.1, 138.4, 140.5, 147.7, 148.2, 148.5, 150.4, 150.6, 162.4; ³¹P NMR δ 145.34; HR-MS calcd for C₄₀H₂₉N₂O₄P 632.1866, found 632.1874.

L2. The ligand **L2** (577 mg, 89%) was prepared from amide **4b** (332.0 mg, 1.0 mmol) and **5** (465.4 mg, 1.3 mmol) according to the same procedure as used for **L1** and isolated as a white solid: mp 99–125 °C; [α]_D¹⁶ 305 (c 0.558, THF); ¹H NMR (CD₂Cl₂) δ 2.03 (s, 3H), 2.04 (s, 3H), 2.16 (s, 3H), 6.79 (d, *J* = 8.8 Hz, 1H), 7.09–7.28 (m, 8H), 7.34–7.48 (m, 5H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.83–7.95 (m, 4H), 8.65 (d, *J* = 8.0 Hz, 1H), 9.97 (s, 1H); ¹³C NMR (CD₂Cl₂) δ 20.2, 20.8, 24.4, 117.4, 119.3, 119.61, 119.62, 122.4, 122.6, 123.2, 124.9, 125.6, 125.9, 126.1, 126.4, 126.8, 127.0, 127.2, 127.5, 127.7, 129.1, 129.4, 130.2, 130.5, 131.1, 132.0, 132.3, 132.9, 133.4, 137.4, 138.2, 140.6, 147.7, 148.2, 149.8, 150.5, 157.7, 162.4; ³¹P NMR δ 145.42; HR-MS calcd for C₄₁H₃₁N₂O₄P 646.2023, found 646.2027.

L3. The ligand **L3** (949 mg, 95%) was prepared from amide **4c** (519.0 mg, 1.5 mmol) and **5** (698.1 mg, 2.0 mmol) according to the same procedure as used for **L1** and isolated as a white solid: mp 92–133 °C; [α]_D¹⁶ 261 (c 0.508, THF); ¹H NMR (CD₂Cl₂) δ 1.981 (s, 3H), 1.984 (s, 3H), 2.43 (s, 3H), 2.52 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 1H), 7.00–7.07 (m, 3H), 7.16–7.29 (m, 5H), 7.34–7.43 (m, 3H), 7.72–7.78 (m, 2H), 7.85–7.96 (m, 3H), 8.10 (d, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 4.0 Hz, 1H), 8.44 (s, 1H), 9.71 (s, 1H); ¹³C NMR (CD₂Cl₂) δ 20.2, 20.8, 21.7, 22.3, 118.7, 120.2, 120.3, 122.4, 122.5, 122.7, 123.3, 124.4, 124.9, 125.6, 125.9, 126.7, 126.8, 127.0, 127.3, 127.5, 128.4, 129.1, 130.4, 131.1, 132.0, 132.3, 133.0, 133.4, 137.2, 138.1, 138.3, 139.2, 140.1, 140.4, 147.8, 148.3, 148.6, 150.5, 150.8, 162.3; ³¹P NMR δ 145.25; HR-MS calcd for C₄₂H₃₃N₂O₄P 660.2180, found 660.2173.

L4. The ligand **L4** (606 mg, 90%) was prepared from amide **4d** (360.3 mg, 1.0 mmol) and **5** (465.4 mg, 1.3 mmol) according to the same procedure as used for **L1** and isolated as a white solid: mp 91–132 °C; [α]_D¹⁶ 262 (c 0.474, THF); ¹H NMR (CD₂Cl₂) δ 1.99 (s, 3H), 2.02 (s, 3H), 2.17 (s, 3H), 2.43 (s, 3H), 2.52 (s, 3H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.99–7.12 (m, 4H), 7.16–7.30 (m, 4H), 7.34–7.43 (m, 3H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.84–7.96 (m, 4H), 8.52 (s, 1H), 9.96 (s, 1H); ¹³C NMR (CD₂Cl₂) δ 20.2, 20.8, 21.6, 22.3, 24.2, 117.9, 119.3, 120.3, 122.4, 122.7, 123.3, 123.9, 124.9, 125.6, 125.9, 126.3, 126.8, 127.0, 127.2, 127.5, 128.5, 129.1, 130.4, 131.1, 132.0, 132.3, 133.0, 133.4, 137.4, 138.2, 139.3, 140.4, 147.8, 148.3, 149.9, 150.6, 157.6, 162.2; ³¹P NMR δ 145.39; HR-MS calcd for C₄₃H₃₅N₂O₄P 674.2336, found 674.2354.

General Procedure for Asymmetric 1,4-Conjugate Addition: Preparation of Catalyst. **L1** (126.4 mg, 0.20 mmol), 25.2 mg of [Cu(CH₃CN)₄]BF₄ (0.08 mmol), and 16 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, 8 mL of CH₂Cl₂ was added to the flask, and the catalyst solution was used for eight separated conjugate addition reactions.

Asymmetric 1,4-Conjugate Addition. Chalcone substrate (1 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 stripped off, 3 mL of toluene 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, 1.4 mL of Et₂Zn (1.1 M in toluene, 1.5 mol equiv) was added slowly. The resulting mixture was stirred at that temperature for 6 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 NaHCO₃ and 5 mL of brine and then dried over anhydrous Na₂SO₄. 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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Supporting Information Available: General Experimental Section, HPLC and GC conditions for ee values, and spectra of **4a–d**, **L1–4** (^1H 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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